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

SYNTHESIS OF NEW THIAZOLOPYRIMIDINE, THIAZOLO (IMIDAZOLO) PYRIDINONE DERIVATIVES VIA MULTICOMPONENT REACTIONS

MASTER OF SCIENCE

DERYA ÇELİKEL

BOLU, JUNE 2015

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APPROVAL OF THE THESIS

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June 9, 2015

Prof. Dr. Duran KARAKAŞ ....

Director, **Graduate School of Natural and Applied Sciences**

To my parents and my sweatheart,

DECLARATION

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

Derya ÇELİKEL

ABSTRACT

SYNTHESIS OF NEW THIAZOLOPYRIMIDINE, THIAZOLO (IMIDAZOLO) PYRIDINONE DERIVATIVES VIA MULTICOMPONENT REACTIONS

MSC THESIS
DERYA ÇELİKEL
ABANT IZZET BAYSAL UNIVERSITY GRADUATE SCHOOL OF NATURAL AND APPLIED SCIENCES
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(SUPERVISOR: ASSIST. PROF. DR. MUHAMMET YILDIRIM)
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Generally thiazolopyrimidines, specifically thiazolo[4,5-*d*]- and [3,2-*a*] pyrimidines have great importance due their diverse biological activities (anticancer, antimicrobial, anti-HIV, antiparkinsonian etc.) and they have been prepared with various synthetic ways up to the date. Another important derivative of them, thiazolo[3,2-*c*]pyrimidines is scarcely studied one and this thesis work mostly describes the efficient synthetic ways to access them through multicomponent strategy utilising Mannich cyclisations. To achieve this goal;

In the first part of the work, suitable precursors have been prepared and characterized. Later on, in the second and third part of this work, double-Mannich cyclisations of the precursors, 2-(nitromethylene)thiazolidine and (Z)-ethyl 2-(5-methyl-4-oxothiazolidin-2-ylidene) acetate with primary amines and formaldehyde afforded, new 6-nitrothiazolo[3,2-*c*]pyrimidines by microwave-assisted chemistry and new 3-oxothiazolo[3,2-*c*]pyrimidine-8-carboxylates by conventional heating, respectively. Developed synthetic methodologies for the preparation of thiazolo[3,2-*c*]pyrimidines are the first examples in the literature to the best of our knowledge.

Another important heterocycle which covers the rest of our synthetic work is 2-pyridone containing fused heterocyclic molecules such as camptothecin or pilicide-based antibiotics. Fourth part of our work describes an efficient access to thiazolo[3,2-*a*]- and imidazolo[1,2-*a*]pyridones through base-catalysed Michael cyclisations utilizing nitroenamines and 2-substituted acryloyl chlorides. Thus, a new library of 2-pyridones have been accessed by a simple and efficient one-pot methodology.

The last part covers the results of anticancer and antibacterial activity studies of new thiazolo[3,2-*c*]pyrimidines. These derivatives only showed moderate to good anticancer activities over human breast cancer cell lines but however, they do not have any significant antibacterial properties.

KEYWORDS:
2-(nitromethylene)thiazolidine, Heterocyclic secondary enamines, Acryloyl chlorides, Mannich and Michael cyclisations, One-pot, Microwave synthesis, Anticancer.

ÖZET

YENİ TİYAZOLOPİRİMİDİN, TİYAZOLO (İMİDAZOLO) PİRİDİNON TÜREVLERİNİN ÇOK BİLEŞENLİ REAKSİYONLAR ARACILIĞIYLA SENTEZİ

YÜKSEK LISANS TEZI
DERYA ÇELİKEL
ABANT İZZET BAYSAL ÜNİVERSİTESİ FEN BİLİMLERİ ENSTİTÜSÜ
KIMYA ANABILIM DALI
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Genel olarak tiyazolopirimidinler, özellikle de tiyazolo[4,5-*d*]- ve [3,2-*a*]-pirimidinler, çeşitli biyolojik aktivitelerinden (antikanser, antimikrobial, anti-HIV, antiparkinson vb.) dolayı çok büyük öneme sahiptirler ve bugüne kadar birçok sentetik yolla elde edilmişlerdir. Diğer önemli türevlerinden birisi, tiyazolo[3,2-*c*] pirimidinler, çok az çalışılmış olanıdır ve bu tez çalışması çoğunlukla Mannich halkalaşmalarını içeren çok bileşenli reaksiyon stratejisiyle bu bileşiklerin elde edildiği etkili bir sentetik yolu açıklamaktadır. Bu hedefe ulaşmak için;

Çalışmanın ilk kısmında, uygun başlangıç bileşiklerinin hazırlanıp karakterize edilmiştir. Sonrasında, bu çalışmanın ikinci ve üçüncü kısımlarında, başlangıç maddeleri, 2-(nitrometilen)tiyazolidin ve (Z)-etil 2-(5-metil-4-oksotiyazolidin-2-iliden) asetat'ın primer aminler ve formaldehitle çift-Mannich halkalaşması, sırasıyla yeni 6-nitrotiyazolo[3,2-*c*]pirimidinleri mikrodalga destekli kimya yoluyla ve 3-oksotiyazolo[3,2-*c*]pirimidin-8-karboksilatları da geleneksel ısıtma koşullarında vermiştir. Tiyazolo[3,2-c]pirimidinlerin hazırlanması için geliştirilen sentetik yöntemler, bilgimiz dahilinde literatürdeki ilk örneklerdir.

Sentetik çalışmamızın kalan kısmını kapsayan diğer önemli heterohalka ise, kamptotesin ve pilisid-tabanlı antibiyotikler gibi 2-piridon içeren bitişik heteohalkalı bileşiklerdir. Çalışmamızın dördüncü kısmı, tiyazolo[3,2-*a*]- ve [1,2-*a*]-piridinonlara, nitroenaminler ve 2-sübstitüe akriloil klorürlerin baz-katalizli Michael halkalaşmaları üzerinden etkili şekilde elde edilmesini anlatmaktadır. Bu şekilde, 2-piridonların yeni bir kütüphanesi, basit ve etkili bir tek-kap yöntemi ile elde edilmiştir.

Son kısım, yeni tiyazolo[3,2-*c*]pirimidinlerin antikanser ve antibakteriyel aktivite çalışma sonuçlarını içermektedir. Bu türevler sadece, insan meme kanseri hücre serileri üzerinde ortadan iyiye doğru antikanser aktiviteler göstermiş olup, buna karşın önemli bir antibakteriyel özellikleri yoktur.

ANAHTAR KELİMELER:
2-(nitrometilen)tiyazolidin, Heterohalkalı sekonder enaminler, Akriloil klorürler, Mannich ve Michael halkalaşmaları, Tek-kap, Mikrodalga sentezi, Antikanser.

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LIST OF ABBREVIATIONS AND SYMBOLS

Ac_2O	:	Acetic anhydride
AcOH	:	Acetic acid
$APCI^+$	:	Atmospheric pressure chemical ionization (positive)
Ar	:	Aryl
ATR	:	Attenuated Total Reflectance
b.p.	:	Boiling point
Bmim	:	1-butyl-3-methylimidazolium
Bn	:	Benzyl
Boc	:	*tert*-Butoxycarbonyl
Bpy	:	2,2’-bipyridine
Btz	:	Phenylbutazone
Bu	:	Butyl
cat.	:	Catalyst
$CDCl_3$	:	Deuterated chloroform
CSA	:	Camphorsulfonic acid
d	:	Doublet (NMR)
DCM	:	Dichloromethane
dd	:	Doublet of doublets (NMR)
ddd	:	Doublet of doublet of doublets (NMR)
de	:	Diastereomeric excess
DMF	:	*N*,*N*-Dimethylformamide
DMS	:	Dimethylsulfide
DMSO	:	Dimethylsulfoxide
dq	:	Doublet of quartets (NMR)
dt	:	Doublet of triplets (NMR)
EDG	:	Electron-donating group
ee	:	Enantiomeric excess
ENG	:	Electron-neutral group

eq.	:	Molar equivalents
ESI^-	:	Electrospray ionisation (negative)
ESI^+	:	Electrospray ionisation (positive)
Et	:	Ethyl
Et_2O	:	Diethyl ether
EtOAc	:	Ethyl acetate
EtOH	:	Ethanol
EW	:	Electron-withdrawing
EWG	:	Electron-withdrawing group
HDMS	:	Bis(trimethylsilyl)amide
HRMS	:	High resolution mass spectrometry
Hz	:	Hertz
IL	:	Ionic liquids
IR	:	Infrared spectroscopy
J	:	Coupling constant (NMR)
LDA	:	Lithium diisopropyl amide
m	:	Multiplet (NMR)
m.p.	:	Melting point
MCR	:	Multicomponent reactions
Me	:	Methyl
MeCN	:	Acetonitrile
MeOH	:	Methanol
min	:	Minutes
MS	:	Mass spectrometry
MW	:	Microwave radiation
NMR	:	Nuclear magnetic resonance
OAc	:	Acetate
OTf	:	Triflate
p	:	Pentet (NMR)
Ph	:	Phenyl
ppm	:	Parts per million (NMR)
pTSA	:	Para-toluenesulfonic acid
q	:	Quartet (NMR)

Rf	**:**	Retardation Factor
rt	**:**	Room temperature
s	**:**	Singlet (NMR)
Selectfluor^{TM}	**:**	1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)
t	**:**	Triplet (NMR)
td	**:**	Triplet of doublets (NMR)
Tf		Trifluoromethanesulfonyl
TFA	**:**	Trifluoroacetic acid
THF	**:**	Tetrahydrofuran
TLC	**:**	Thin layer chromatography
TMS	**:**	Tetramethylsilane
TOF	**:**	Time of flight
Ts	**:**	Tosyl
tt	**:**	Triplet of triplets (NMR)
δ	**:**	Chemical shift (NMR)
Δ	**:**	Heat

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During the interval of completing thesis, I shared a lot of things with people, whom contribute to my education and me. It is not possible to write all names and events in this short part, however, I have to mention the unforgettable milestones.

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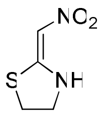
FORMULAE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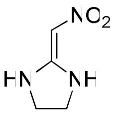
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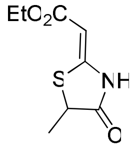
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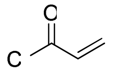
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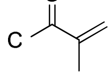
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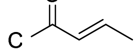
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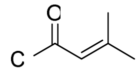
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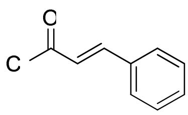
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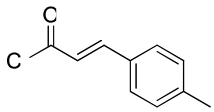
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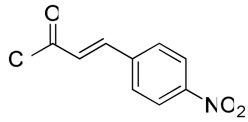
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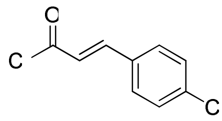
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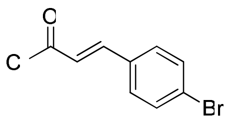
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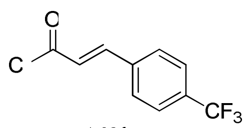
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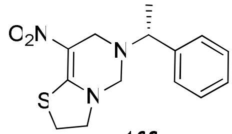
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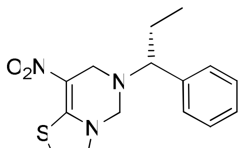
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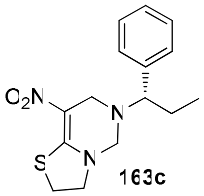
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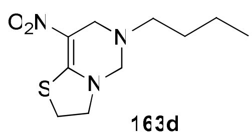
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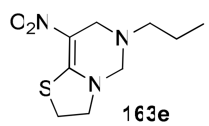
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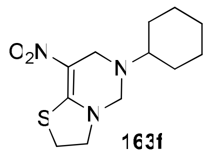
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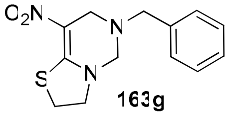
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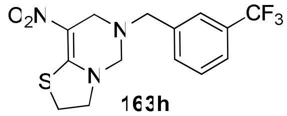
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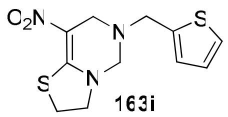
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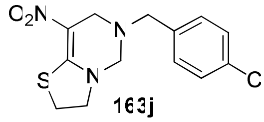
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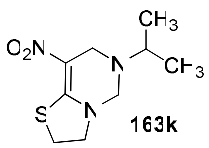
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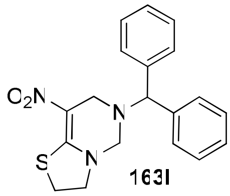
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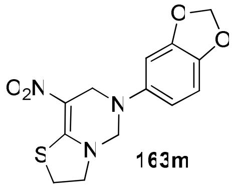
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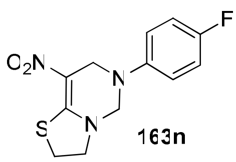
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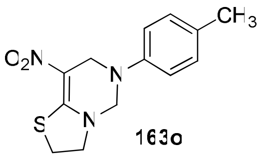
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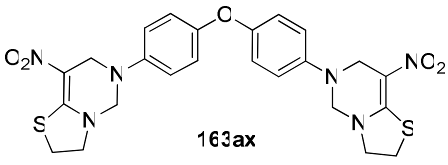
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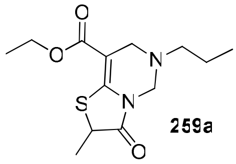
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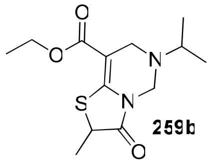
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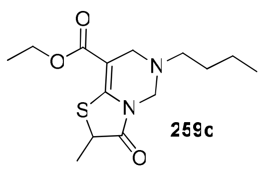
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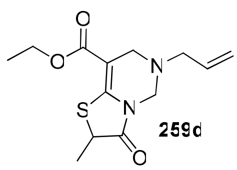
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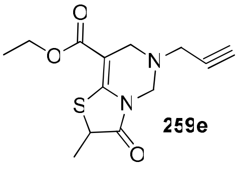
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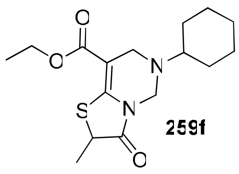
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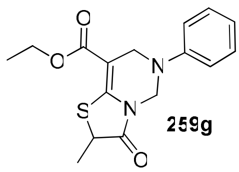
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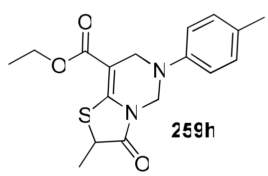
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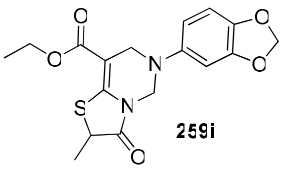
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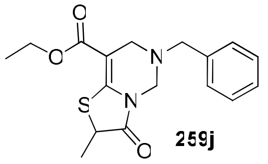
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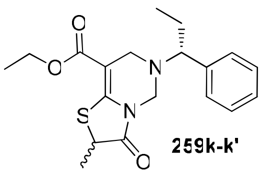
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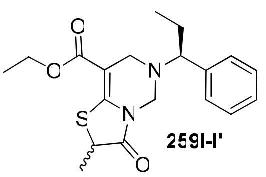
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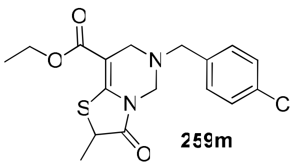
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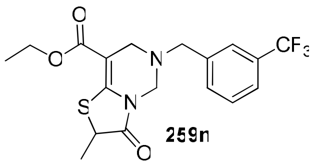
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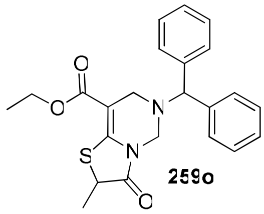
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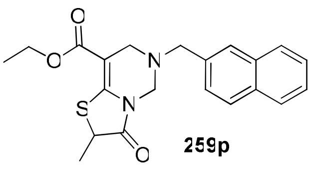
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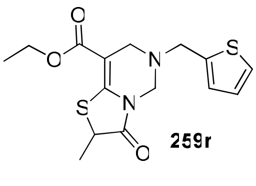
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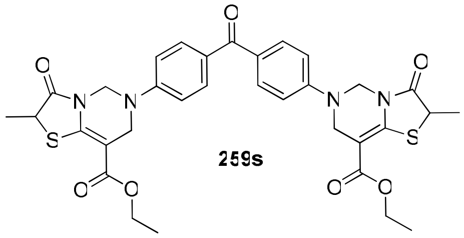
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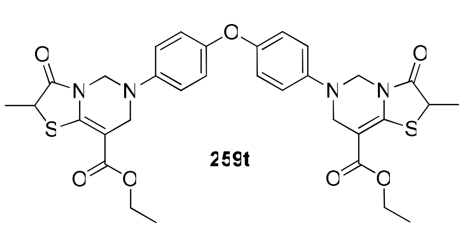
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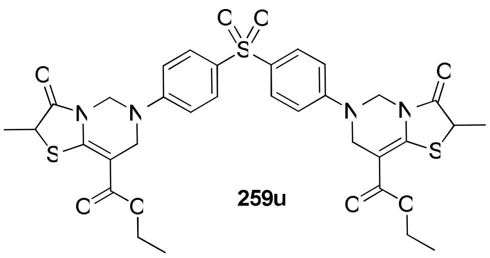
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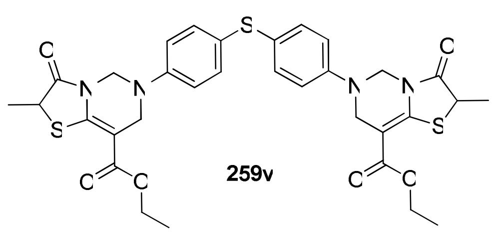
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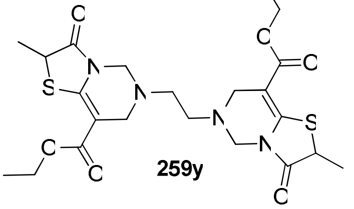
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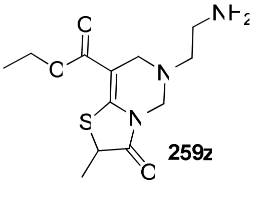
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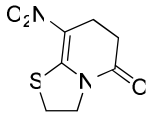
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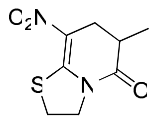
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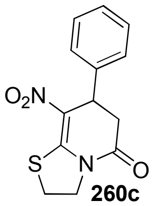
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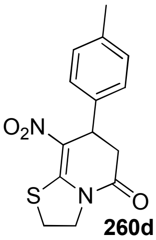
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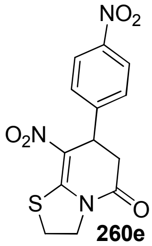
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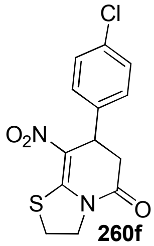
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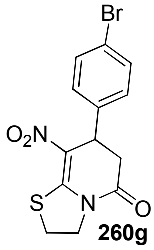
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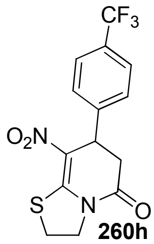
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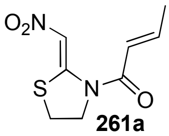
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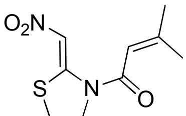
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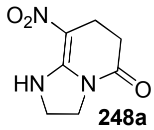
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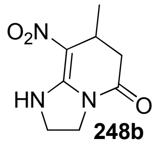
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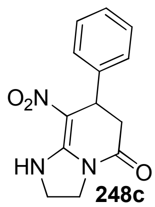
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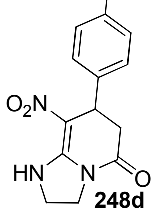
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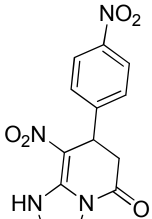
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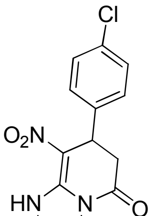
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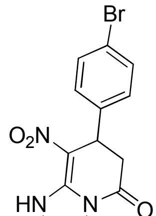
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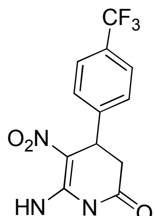
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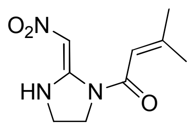
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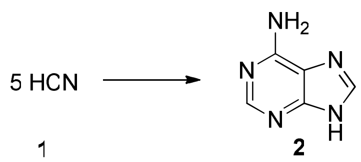
1. INTRODUCTION

1.1 CHAPTER 1

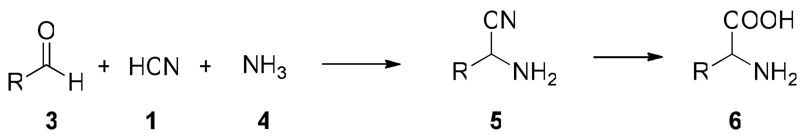
1.1.1 Multicomponent Reactions

MCR is defined as a one-pot reaction which three or more reactants used to synthesize a product. The reactants can be either different compounds or different functional groups of the same compound (Ugi et al., 1994). Many examples of MCR can be encountered in nature. For instance, it was assumed that adenine **2** might be formed via addition of five molecules of isocyanic acid **1** (Scheme 1.1) (Ugi et al., 1994). It is important to consider that each of isocyanic acid molecules constitutes different part of adenine molecule.



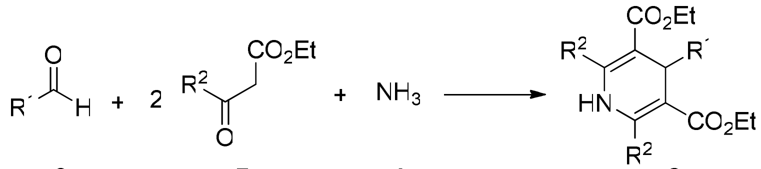
Scheme 1. 1 Synthesis of adenine in early age.

In organic chemistry, MCR has been used for more than 150 years. The first report of MCR in literature was Strecker synthesis of α-amino nitrile **6** (Scheme 1.2) (Strecker, 1850).



Scheme 1. 2 Strecker synthesis of α-amino acids.

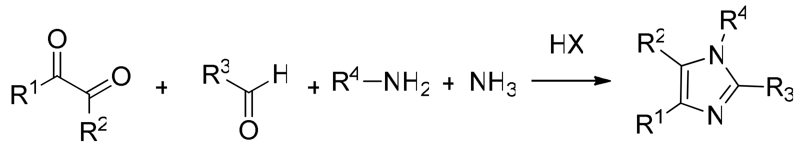
Hantszch (1882) discovered formation of dihydropyridine **8** from β-ketoesters **7**, aldehydes **3** and ammonia **4** (Scheme 1.3).



3 7 4 8

Scheme 1. 3 Hantzsch synthesis of dihydropyridines.

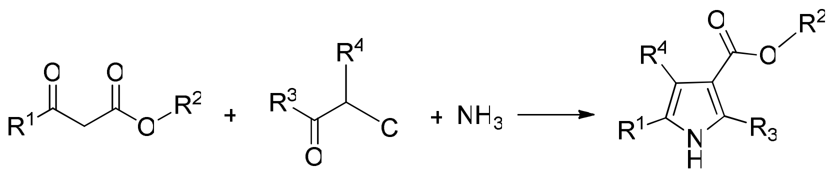
Radziszewski (1882) reported synthesis of imidazole **11** from a dicarbonyl compound **9**, an aldehyde **3**, and ammonia **4** via MCR (Scheme 1.4).



9 3 10 4 11

Scheme 1. 4 Radziszewski synthesis of imidazole.

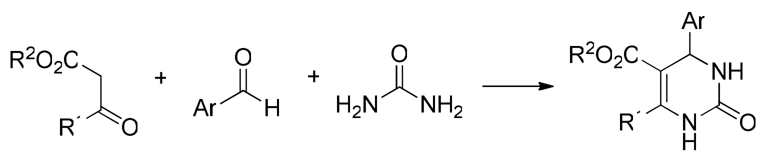
Hantzsch (1890) introduced formation of pyrrole (**13**) as a result of the reaction of β-ketoesters (**7**) with ammonia **4** and α-haloketones **12** (Scheme 1.5).



7 12 4 13

Scheme 1. 5 Hantzsch synthesis of pyrroles.

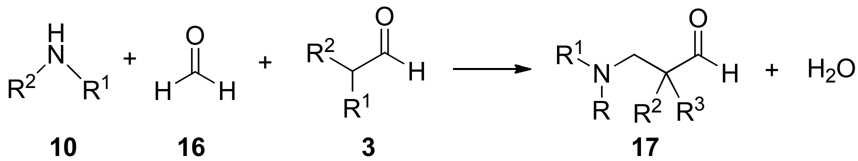
Biginelli (1891) discovered multiple-component reaction synthesis of substituted dihydropyrimidines **15** from ethyl *β*-ketoesters **7**, an aryl aldehyde **3** and urea **14** (Scheme 1.6).



7 3 14 15

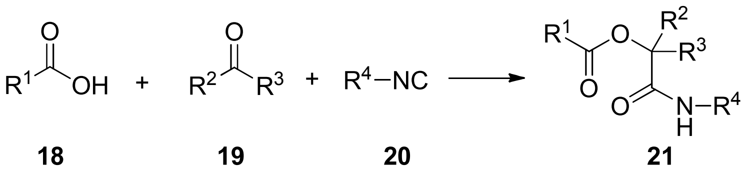
Scheme 1. 6 Biginelli synthesis of dihydropyrimidines.

One of the most utilized MCRs was discovered by Mannich and Krosche (1912). They discovered a MCR for methylation of amines (Scheme 1.7). Mannich reaction comprises reaction of primary or secondary amines **10** or ammonia with formaldehyde **16** and carbonyl compound having at least one α-hydrogen (**3**) (Tramontini and Angiolini, 1994).



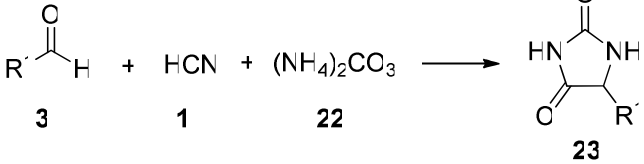
Scheme 1. 7 Mannich reaction.

Passerini (1921) reported the first MCR with isocyanides. In this MCR, α-acyloxy carboxamides **21** by the reaction of carboxylic acids **18**, carbonyl compounds **19** and isocyanides **20** (Scheme 1.8).



Scheme 1. 8 Passerini reaction of isocyanides.

Bucherer (1934) and Bergs (1929) were the first to report a four-component reaction. They discovered synthesis of hydantoins **23** by the reaction of aldehydes **3**, hydrogen cyanide **1** and ammonia and carbondioxide (Scheme 1.9). The products can be easily converted into α-amino acids by hydrolysis. It is the main method to prepare the starting materials of many α-amino acids (Ugi et al., 1994).

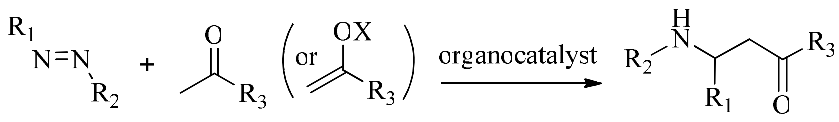


Scheme 1. 9 Bucherer-Bergs synthesis of hydantoins.

1.2 CHAPTER 2

1.2.1 Mannich Reactions

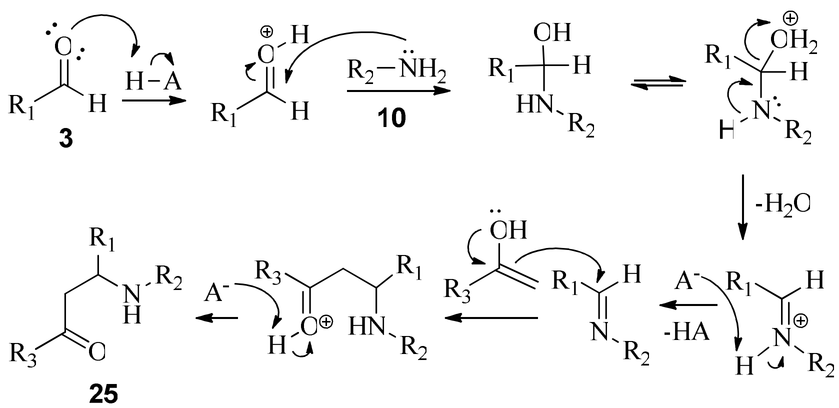
The Mannich reaction was discovered by German chemist Carl Ulrich Franz Mannich in 1912 (Mannich and Krosche, 1912). Mannich reaction, also called amine methylation reaction, is a reaction of primary or secondary amines or ammonia with formaldehyde and carbonyl compound having at least one α-hydrogen.(Tramontini and Angiolini, 1994). The resultant product is a *β*-amino-carbonyl compound (**24**) which is known as a Mannich base (Scheme 1.10) (Akiyama, 2012).



24 **19** **25**

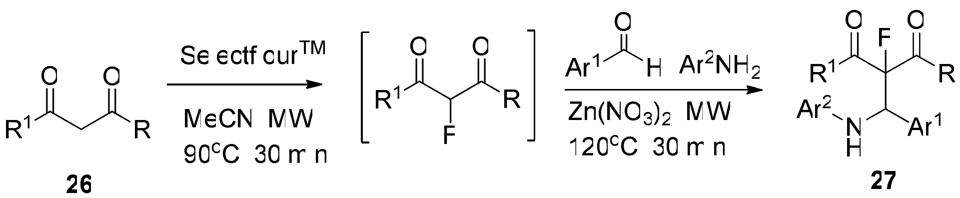
Scheme 1. 10 Mannich and Mannich-type reaction.

The general mechanism of the Mannich reaction was shown in Scheme 1.11 (Ramella, 2013). Firstly, aldehyde **3** is activated by protonation (a) and then amine **10** attacks the electrophilic carbonyl carbon of aldehyde (b) and forms protonated carbinolamine (c). Imine forms by elimination of water from tautomeric form of protonated carbinolamine (d). Enol is added to the imine via attack of double bond of enol to the carbon of imine (e). Finally, deprotonation of resultant product gives *β*-amino ketone (**25**).



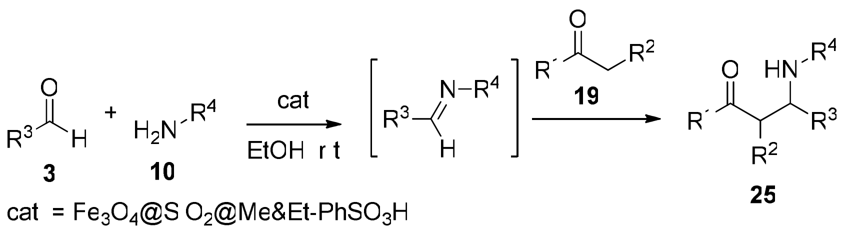
Scheme 1. 11 General mechanism of the Mannich Reaction.

The Mannich reaction is an important part of many multicomponent reactions in synthetic chemistry and there are many useful applications such as the Betti, Pictet-Spengler and Kabachnike-Fields reactions (Mitsumori et al., 2006; Lehmann et al., 2003). Mannich reaction is very common and efficient way for the construction of new C-C bond. There are various applications of Mannich and Mannich-type reactions in literature. In 2015, Pham et al. reported Mannich reactions of 1,3-dicarbonyl compounds (Pham et al., 2015). In this study, a one-pot and two-step reaction process including electrophilic fluorination of an enolizable 1,3-dicarbonyl compound **26** followed by the Mannich reaction with anilines and benzaldehydes is developed for the synthesis of α-fluoro-aminomethylated 1,3-dicarbonyl compounds **27** (Scheme 1.12).



Scheme 1. 12 One-pot fluorination and Mannich reactions of 1,3-dicarbonyl compounds.

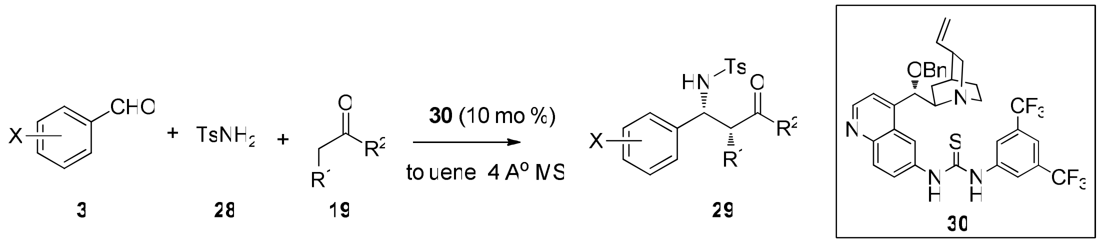
Movassagh et al. (2015) developed catalytic amount of the magnetic solid sulfonic acid catalyst, Fe_3O_4@SiO_2@Me&Et-$PhSO_3H$ which is used for the Mannich-type reactions of a series of aldehydes, ketones, and amines, at room temperature (Scheme 1.13). The catalyst can be reused four times without loss of activity.



Scheme 1. 13 Mannich reaction of enolates with imines using solid-phase catalyst.

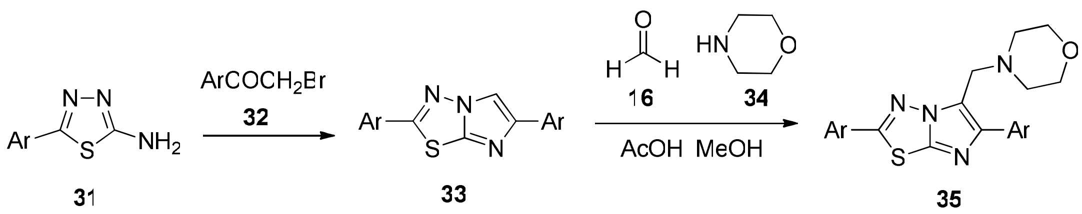
Guo and Zhao (2013) reported enantioselective three-component direct Mannich reactions of unfunctionalized ketones catalyzed by bifunctional organocatalysts. They performed through an enolate mechanism for the first time with a bifunctional quinidine thiourea catalyst **30** (Scheme 1.14). The corresponding

N-tosylated *β*-aminoketones **29** were obtained in high yields and high diastereo- and enantioselectivities (up to >99:1 dr and >99% ee).



Scheme 1. 14 A catalytic double-Mannich reaction

Da et al. (2012) synthesized a series of 2,5,6-trisubstituted imidazo[2,1-b][1,3,4]thiadiazoles **35** via Mannich reaction of imidazo[2,1-b][1,3,4]thiadiazoles **33** with morpholine **34** and formaldehyde **16** (Scheme 1.15) (Da et al., 2012).



Scheme 1. 15 Synthesis of 2,5,6-trisubstituted imidazo[2,1-*b*][1,3,4]thiadiazole derivatives.

1.2.2 Mannich cyclizations

One of the most general methods in order to synthesize *N*-heterocyclic compounds is Mannich cyclizations of iminium cations (Overman and Ricca, 1991; Enholm and Prasad, 1989). Figure 1.1 shows the different types of Mannich cyclization reactions (Waterson, 1999). All of these reactions are based on attack of a nucleophile (Y) onto an iminium ion. A variety of monocyclic and fused heterocyclic compounds can be obtained by Mannich cyclization reactions.

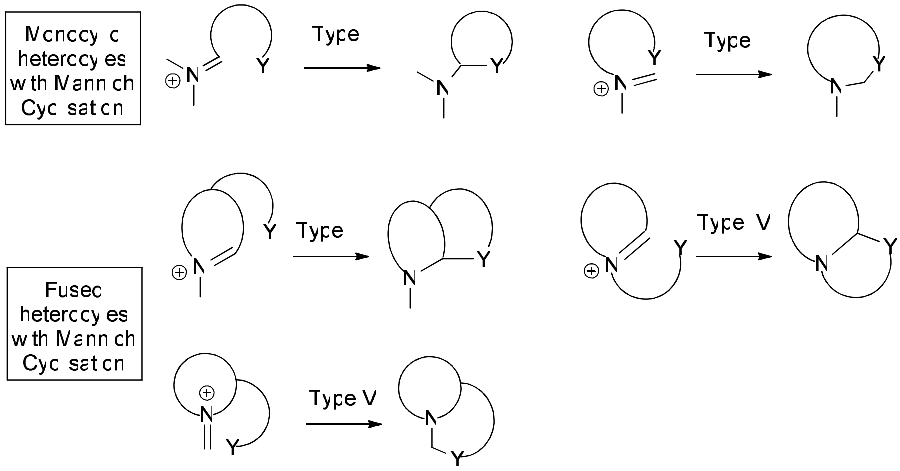
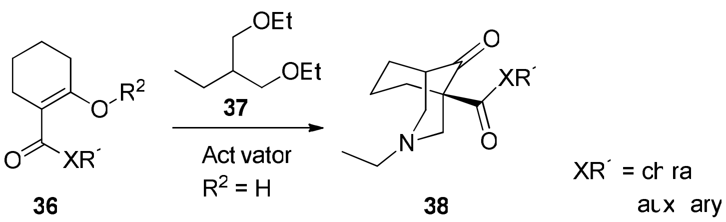


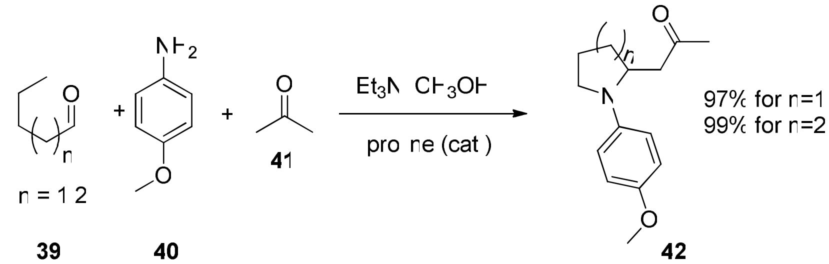
Figure 1. 1 Various types of Mannich Cyclizations (Waterson, 1999).

Sparrow et al. (2015) developed an asymmetric synthesis of azabicyclo[3.3.1]nonanes by utilizing double-Mannich reactions. For this purpose, a range of chiral ester and chiral imide derivatives of 2-oxocyclohexanecarboxylic acid were used in double-Mannich reactions with bis(aminol)ethers (Scheme 1.16). The use of oxazolidinone auxiliaries afforded the high yields and diastereoselectivities enabling separation of the resulting diastereomers of the azabicyclo[3.3.1]nonanes.



Scheme 1. 16 A catalytic double-Mannich reaction leading to bicyclic product.

Chacko and Ramapanicker (2015) reported that proline-catalyzed one-pot three component Mannich reaction of 4-bromobutanal or 5-bromopentanal **39**, acetone **41**, and *p*-anisidine **40**. Mannich reaction was followed by cyclization leading to the synthesis of 2-substituted pyrrolidine and piperidine derivatives **42** (Scheme 1.17). This method gave the products with high yields.

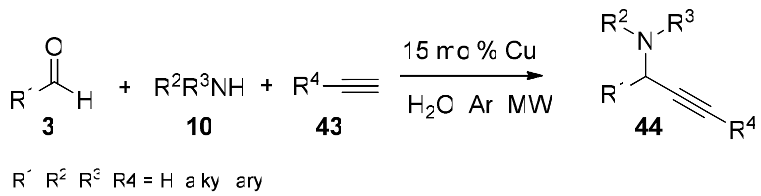


Scheme 1. 17 One-pot three component reaction leading to 2-substituted piperidine and pyrrolidine derivatives.

1.2.3 Microwave-assisted Mannich additions and cyclizations

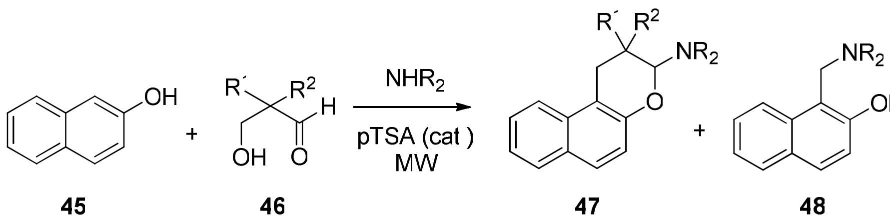
Microwave energy was first introduced for the heating of food products. However, in the 1980s, microwave heating was found to significantly accelerate many organic transformations (Gedye et al, 1986; Giguere et al., 1986). For such microwave-induced organic syntheses, many reaction media and conditions have been employed, including neat reactions or reactions in the presence of a phase transfer catalyst (e.g., alumina, clayfen, Aliquat 336), (Shabani, 1998; Varma et al., 1993; Varma et al., 1997) under an open atmosphere, in a closed cup (Strohmeier and Kappe, 2002; Vasudevan and Verzal, 2004; Vallin et al., 2002; Dubreuil and Bazureau, 2000) or under pressure, (Kaval et. al., 2004; Andappan et al., 2004) in water, ionic liquids or various organic solvents. In the last decade, the number of MW-assisted organic reactions has increased exponentially due to the many advantages associated with its use, the most important of which are arguably greater speed and enhanced efficiency with formation of cleaner products than ones formed via conventional heating.

Shi et al. (2004) reported MW-promoted three-component coupling of aldehyde, alkyne **43**, and amine via C−H activation. The reaction was performed under microwave irradiation in water by using CuI as catalyst (Scheme 1.18). Besides this, the study which is applied by using (*S*)-proline methyl ester as a chiral source showed that it could be developed to be a direct diastereoselective technique to construct chiral propargylamines **44**.



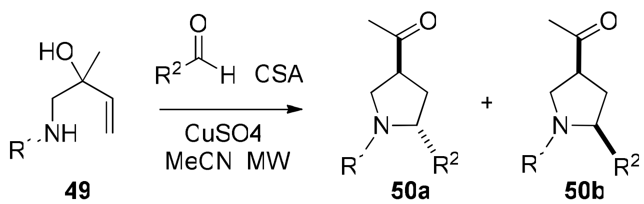
Scheme 1. 18 Microwave-assisted three-component coupling of aldehyde, alkyne, and amine via C–H activation.

Microwave irradiation is an applicable method for also the Mannich cyclisation reactions. In literature, there are few approaches for the MW-assisted Mannich cyclisation reactions. Huang et al. (2009) reported formation of 2,2-dialkyl-3-dialkylamino-2,3-dihydro-*1H*-naphtho[2,1-*b*]pyrans **48**. They were synthesized from 2-naphthol **45** and 3-hydroxy-2,2-dialkylpropanal **46** in the presence of p-TSA as catalyst along with 2-naphthol via solvent-free MW-assisted Mannich reaction (Scheme 1.19).



Scheme 1. 19 MW-assisted synthesis of 2,2-dialkyl-3-dialkylamino-2,3-dihydro-1*H*-naphtho[2,1-*b*]pyrans

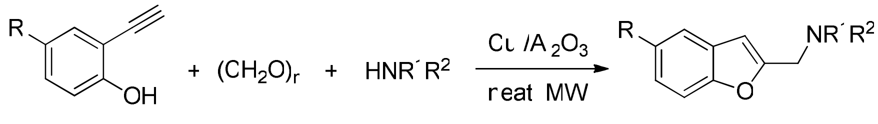
The first MW-assisted tandem aza-Cope rearrangement-Mannich cyclization was developed by using aldehydes, *β*-vinyl secondary amines **49** in the presence of Cu(II) catalyst under MW conditions leading to monosubstited acylpyrrolidines **50a-b** in a single synthetic step (Johnson et al., 2007).



Scheme 1. 20 MW-assisted synthesis of monosubstituted acylpyrrolidines.

A MW-enhanced, solventless Mannich condensation-cyclization sequence involving the reaction of *o*-ethynylphenol **51** with secondary amines and *para*-

formaldehyde **52** on CuI-doped alumina has been developed by Kabalka et al. (2001) leading to 2-(dialkylaminomethyl)benzo[*b*]furans **53** in good yields (Scheme 1.21).

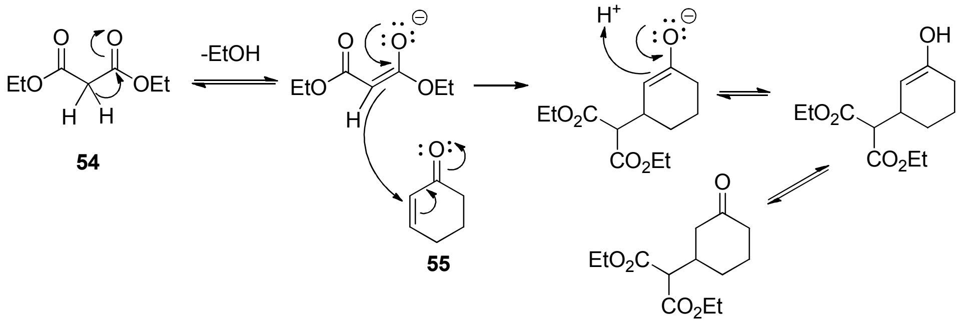


Scheme 1. 21 MW-assisted synthesis of benzo[*b*]furan derivatives.

1.3 CHAPTER 3

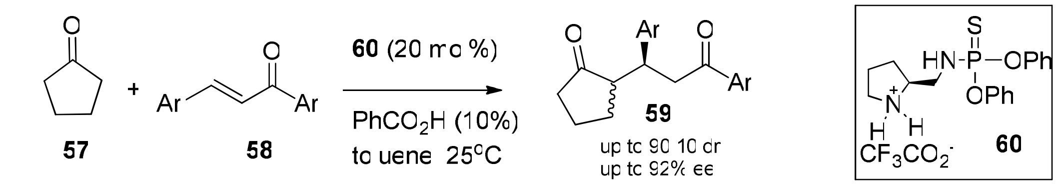
1.3.1 Michael Reactions

Michael reaction, which is also known as Michael addition, is the addition of nucleophile to *β*-position of an α,*β*-unsaturated compound. As primarily defined by American organic chemist Arthur Michael, the reaction covers the addition of an enolate ion of a ketone or aldehyde to an α,*β*-unsaturated carbonyl compound at the *β*-carbon (Michael, 1887). A general mechanism of the Michael reaction was given in Scheme 1.22. The reaction is initiated by the deprotonation of nucleophile **54** by a strong base. This nucleophile, called as *Michael donor*, reacts with α,*β*-unsaturated compound **55** named as a *Michael acceptor*. Finally, protonation of the product occurred by protonated base or solvent. Michael acceptors are the α,*β*-unsaturated compounds including ketones, esters, nitriles and sulfones having activated double bonds.



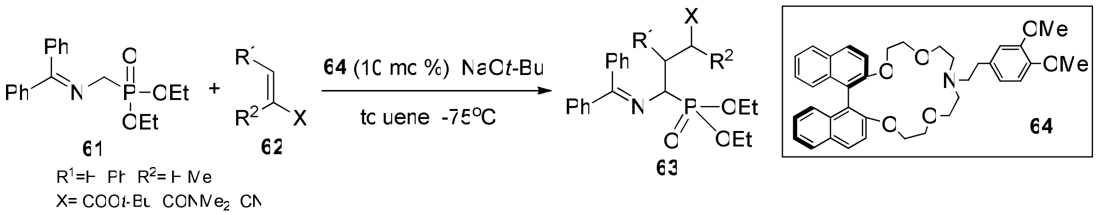
Scheme 1. 22 General mechanism of the Michael addition reaction.

In literature, different type of Michael donors and acceptors have been utilized to synthesize various types of products. Liu et al. (2011) reported asymmetric Michael reaction of cyclopentanone **57** with various chalcones **58** (Scheme 1.23). They found that thiophosphoramide **60** is an effective bifunctional organocatalyst for this reaction in good yields with moderate to high diastereo- (up to 90/10 dr) and enantioselectivities (up to 92% ee).



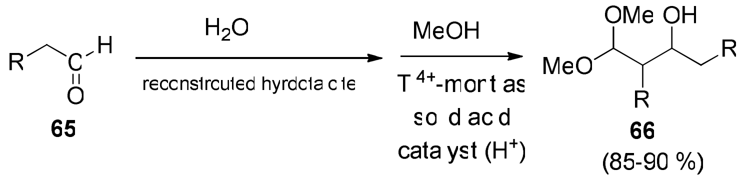
Scheme 1. 23 Michael reaction of cyclopentanone with chalcones in the presence of thiophosphoramide catalyst.

Pham et al. (2011) used azacrowns **64** as catalysts for the reaction of *N*-protected aminomethylenephosphonate **61** with acrylonitriles **62** to synthesize α-aminophosphonates **63** by the asymmetric Michael reaction (Scheme 1.24).



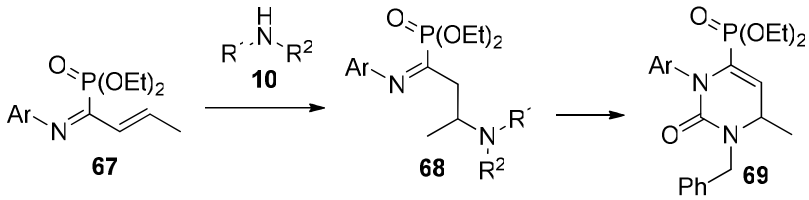
Scheme 1. 24 Michael addition of *N*-protected aminomethylenephosphonate onto acrylonitriles catalyzed by azacrowns.

Ebitani et al. (2006) used reconstructed hydrotalcite as a heterogeneous base catalyst for C-C bond formations (Scheme 1.25). Reconstructed hydrotalcites, which is obtained by treating the Mg-Al mixed oxide with water, catalyzes the aldol reaction of carbonyl compounds in the presence of water. This catalyst supplies a unique acid-base bifunctional surface capable of promoting Michael reactions of nitriles with carbonyl compounds.



Scheme 1. 25 Michael reactions of carbonyl compounds are efficiently catalyzed in the presence of water by reconstructed hydrotalcites as solid base catalysts.

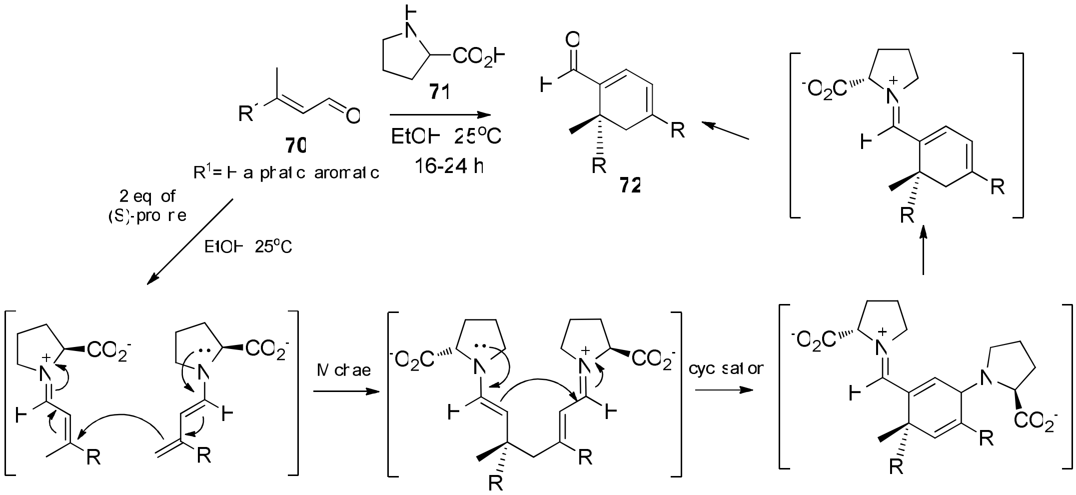
Vicario et al. (2009) reported synthesis of γ-amino-α-dehydroaminophosphonates **68**. They performed conjugate addition of amines to an α,β-unsaturated imine **67** derived from α-aminophosphonate (Scheme 1.26). Resulting γ-amino-(*R*)-dehydroaminophosphonates **69** can be used for the preparation of phosphorylated pyrimidine derivatives.



Scheme 1. 26 Conjugate addition of amines to α,*β*-unsaturated imine.

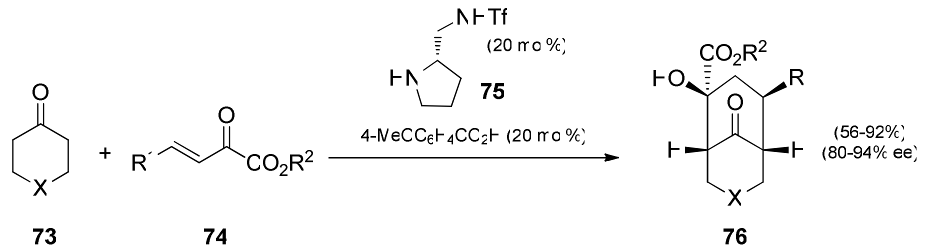
1.3.2 Michael cyclizations

Michael addition is commonly used in cyclisation processes. Various types of examples of this process exist in literature. Bench et al. (2006) described an (*S*)-proline-catalysed dimerization of enals to produce cyclohexadiene carbaldehydes via Michael-like imine addition (Scheme 1.27). It is showed that use of proline **71** promotes asymmetric self-condensation of α,β-unsaturated aldehydes **70** to form trisubstituted cyclohexadiene products **72**. They also reported that the reaction conditions are mild and suitable for different type of substrates which yield molecules from simple precursors via complex scaffolds.



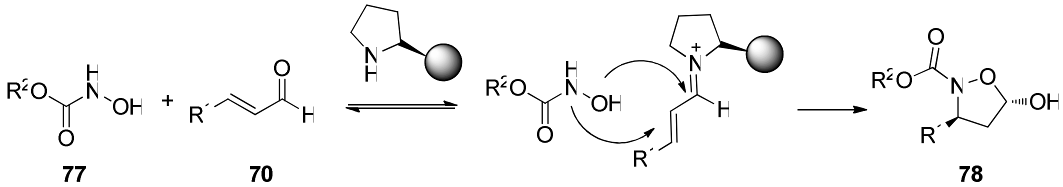
Scheme 1. 27 Self-condensation of *β*-methyl substituted α,*β*-unsaturated aldehydes to give 1,2,4-trisubstituted cyclohexadienals via Michael-like imine addition and cascade Michael-cyclization processes catalyzed by (*S*)-proline.

Cao et al. (2012) reported an enantioselective formal cyclization reaction including a Michael-Aldol sequence catalysed by (*S*)-pyrrolidine trifluoromethanesulfonamide (Scheme 1.28). Reaction of cyclic ketones **73** with enone esters **74** in the presence of 20 mol% of pyrrolidine-thiourea or *N*-(pyrrolidin-2-ylmethyl)trifluoromethanesulfonamide **75** with no solvent at rt furnished bicyclic adducts (**76**) in moderate to good yields under mild conditions.



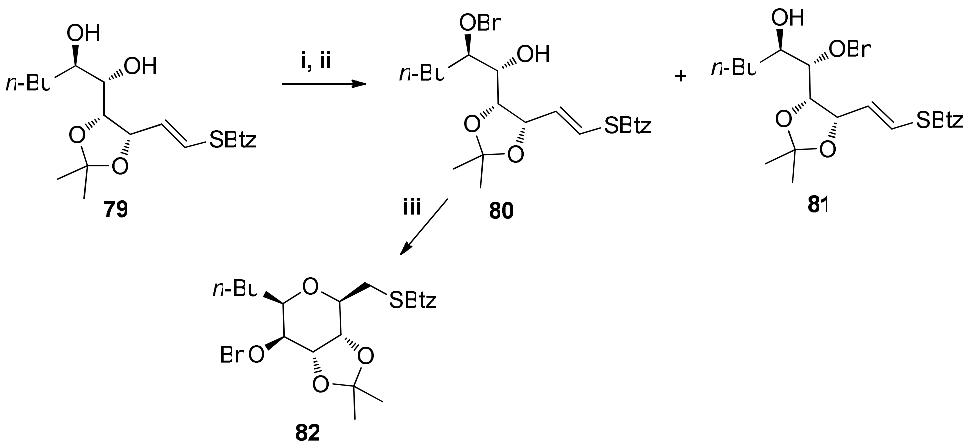
Scheme 1. 28 Asymmetric formal [3+3] cyclisation reaction catalysed by (*S*)-pyrrolidine sulfonamide.

Ibrahem et al. (2007) reported that the chiral pyrrolidines catalyze the formation of 5-hydroxyisoxazolidines **78** via an asymmetric tandem aza-Michael/cyclization reaction pathway (Scheme 1.29). The reaction supplies access to 5-hydroxyisoxazolidines in high yields with 90–99% ee.



Scheme 1. 29 Chiral pyrrolidines catalyze the formation of 5-hydroxyisoxazolidines via an asymmetric tandem aza-Michael/cyclization reaction pathway.

Aucagne et al. (2005) focused on moderate EW-thiofunctions like heteroaryl vinyl sulfides and vinyl dithiocarbamates. Hence, they studied on regioselective Michael-induced cyclisation of γ- and *δ*-hydroxyvinyl sulfides and vinyl dithiocarbamates (Scheme 1.30). Michael cyclisation, the diol **79** was mono-*O*-benzylated and a mixture of regio-isomers of *δ*-hydroxy heteroaryl vinyl sulfides **80** (45%) and **81** (38%) was resulted. The *δ*-hydroxy heteroaryl vinyl sulfide **80** was subjected to give the *C*-glycopyranoside **82** as a single diastereoisomer (72%) through the phase-transfer conditions.

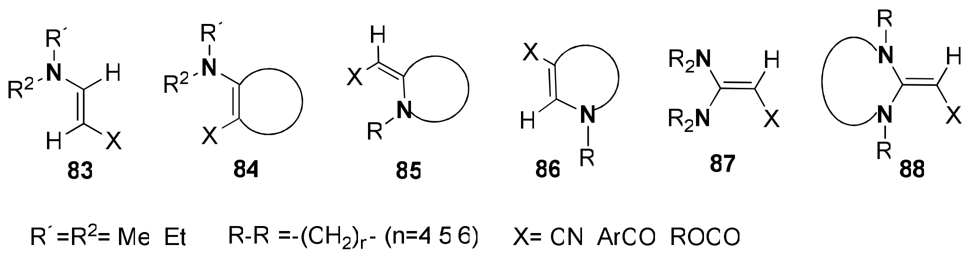


Scheme 1. 30 Hetero-Michael cyclisation of a *δ*-hydroxy heteroaryl vinyl sulfide into a pyrano derivative. (i) Bu_2SnO, toluene, Δ; (ii) BnBr, n-Bu_4NBr; (iii) Aliquat 336®, NaOH 50%, CH_2Cl_2.

1.4 CHAPTER 4

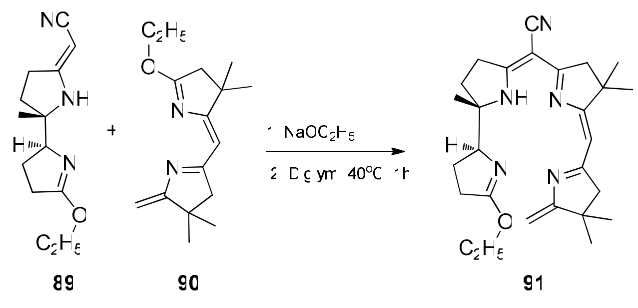
1.4.1 Heterocyclic Secondary Enamines

The nitrogen analogs of enols were named as "*enamine*" by Wittig and Blumenthal (1927). Enamine is a resultant product of the aldehydes or ketones with a secondary amine. It is a versatile synthetic precursors in order to synthesize heterocycles and natural products (Shawali and Edrees, 2006). Furthermore, enamine derivatives have an important role as asymmetric catalysis for alkylation and also used as blocking groups (Friary et al., 1973). Enamines can be classified as acyclic enamines **83**, endocyclic enamines **84**, exocyclic enamines **85** and heterocyclic enamines **86** (Sheme 1.31) (Shawali and Edrees, 2006).



Scheme 1. 31 Main types of enamines.

Heterocyclic secondary enamines can be called with various names in respect to their EWG. For instance, they are named as exo-cyclic *enamino esters* if EWG is ester; they are *enaminonitriles* if EWG is cyano; and if EWG is acyl, then they are known as *enaminones* (Cheng et al, 2002). In 1960s, study of Eschenmoser et al. (1964) about a synthetic route to the corrin system can be counted as the spearheading study for the chemistry of heterocyclic enamines. In this study, they reacted enaminonitrile **89** with iminoether **90** (Scheme 1.32).

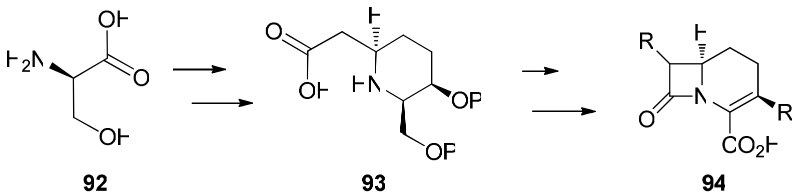


Scheme 1. 32 Synthesis of Corrin system over enaminonitrile-iminoester

1.4.1.1 Synthesis of Heterocyclic Secondary Enamines

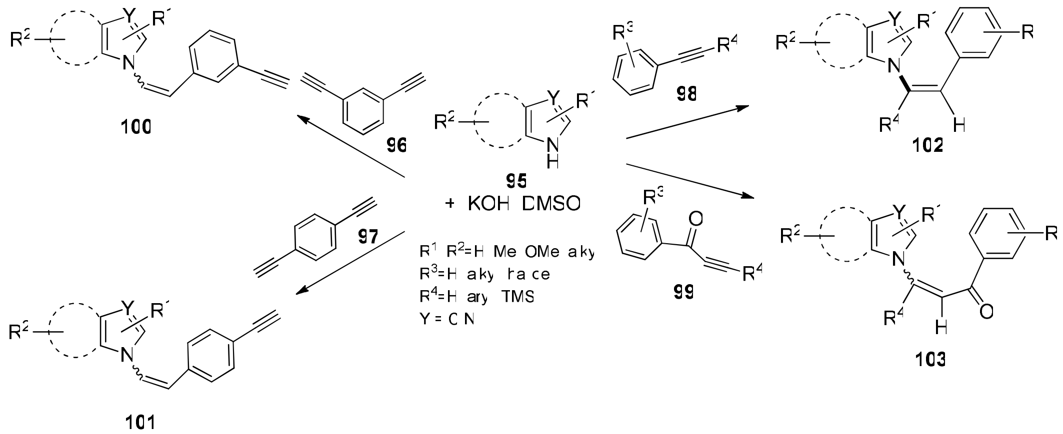
Heterocyclic secondary enamines are effective intermediates for the synthesis of fused heterocyclic compounds and natural products. Due to important functions of heterocyclic secondary enamines in organic chemistry as explained beforehand, there are many studies about synthesis of heterocyclic secondary enamines by especially using *N*-heterocyclic compounds as starting materials (Wang et al, 2003).

Folmer et al. (1998) discovered the synthesis of carbacephems **94** from *D*-serine **92** by reducing the double bond of exo-cyclic enaminoesters **93** followed by cyclization (Sheme 1.33).



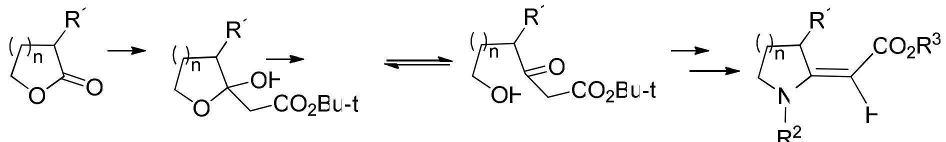
Scheme 1. 33 Synthesis of carbacephems from *D*-serine.

Joshi et al. (2012) reported base-mediated synthesis of diversely substituted *N*-heterocyclic enamines (**100-102**) and enaminones (**103**) by the hydroamination of alkynes (**96-99**) (Sheme 1.34). Regio- and stereoselective alkynylation of various *N*-heterocycles **95** was performed by using potassium and cesium salts in DMSO.



Scheme 1. 34 Regio- and stereoselective alkynylation of various *N*-heterocycles using potassium and cesium salts in DMSO.

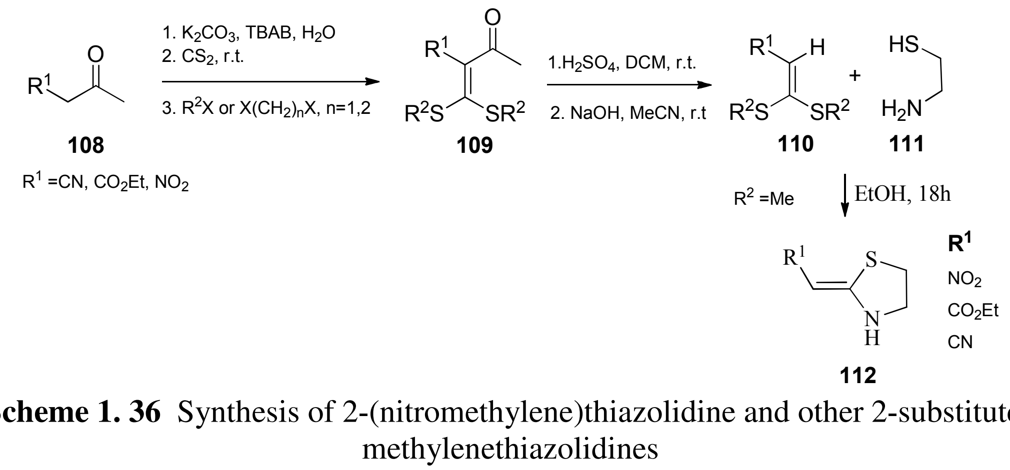
Wang et al. (2003) reported preparation of heterocyclic enamines **107** via formal ring transformation reaction of lactones **104** (Sheme 1.35). The synthesis consists of Reformatsky reaction of lactones and mesylation of the resulting mixture of ring-chain tautomers (**105**,**106**) in a one-pot reaction, followed by cyclocondensation reaction with primary amines.



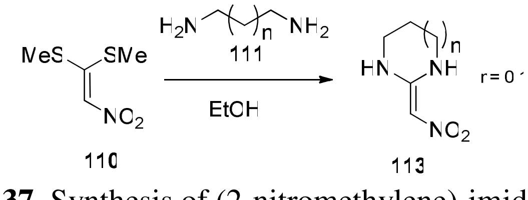
104 105 106 107

Scheme 1. 35 Synthesis of heterocyclic enamines by the ring transformation of lactones.

Rajappa and Advani, (1982) reported the preparation of 2-(nitromethylene)thiazolidine **112** bearing electron withdrawing group belongs the heterocyclic enamine class that having two reactive sides by reacting 1,1-bis (methylmercapto)-2-nitroethylene **110** with cysteamine **111** in EtOH. Besides, Yuan et.al (2010) reported the efficient preparation of methylenethiazolidines (bearing different EWG on exocyclic methylene carbon) over the synthesis of ketene dithioacetals **109** in good yields (Scheme 1.36). In similar fashion, Kalisiak et.al (2012) prepared (2-nitromethylene)- imidazolidines and -hexahydropyrimidines (**113**) by a straightforward cyclisation of 1,1-bis(methylthio)-2-nitroethylene **110** with suitable diamines **111** in refluxing ethanol (Scheme 1.37).

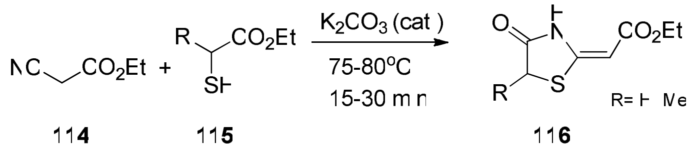


Scheme 1. 36 Synthesis of 2-(nitromethylene)thiazolidine and other 2-substituted methylenethiazolidines



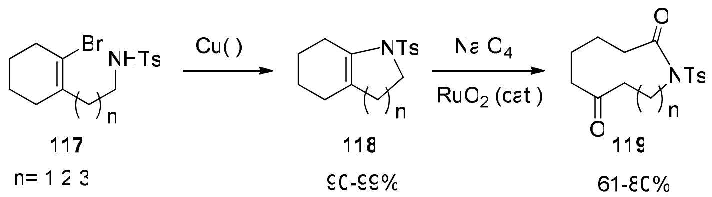
Scheme 1. 37 Synthesis of (2-nitromethylene)-imidazolidines or hexahydropyrimidines

However, methylene-4-oxothiazolidines **116** were simply prepared by the base-catalyzed reaction of ethyl cyanoacetate **114** and α-mercapto esters **115**, without using a solvent in almost quantitative yields (Stojanovic et al., 2011) (Scheme 1.38).



Scheme 1. 38 Synthesis of methylene-4-oxothiazolidines

Lu et al. (2008) reported synthesis of heterocyclic enamines by *N*-vinylation of sulfonamides in the presence of copper as catalyst. Intramolecular C–N coupling between sulfonamides **117** and vinyl halides was achieved and then, synthesis of 5-, 6-, 7-, and even 8-membered heterocyclic enamines **118** in both *exo*- and *endo*-modes were performed with high yields (Sheme 1.39).

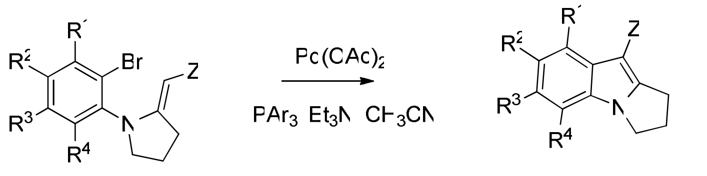


Scheme 1. 39 Synthesis of heterocyclic enamines from sulfonamides.

1.4.1.2 Reactions of Heterocyclic Secondary Enamines

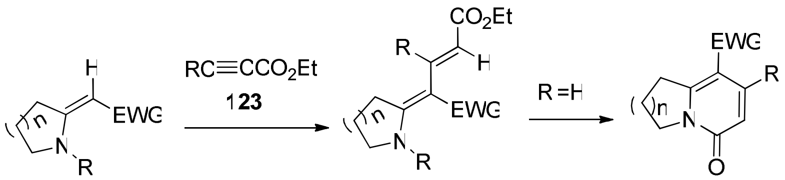
Heterocyclic secondary enamines are unique compounds owing to fact that nucleophilic reaction can occur at the enaminic carbon and/or the secondary amino nitrogen of these compounds (Liu et al., 2003). Therefore regioselectivity in the reaction can occur with monoelectrophiles and biselectrophiles and leads to various types of heterocyclic compounds (Cheng et al., 2004).

Michael et al. (1993) synthesized pyrrolo[1,2-*a*]indoles by intramolecular Heck reaction of *N*-(2-bromoaryl)enaminones. Treatment of *N*-(2-bromoaryl) enaminones **120** with palladium (II) acetate, triarylphosphine and triethylamine in boiling acetonitrile resulted with the product pyrrolo[1,2-*a*]indoles **121** with yields of 50-100% (Sheme 1.40).



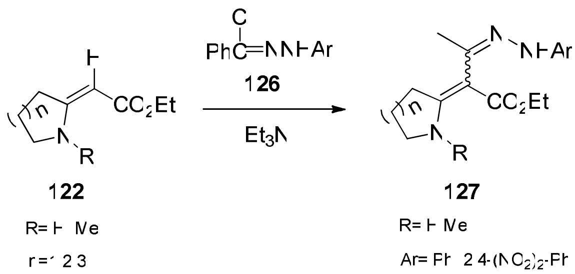
Scheme 1. 40 Synthesis of from pyrrolo[1,2-*a*]indoles from *N*-(2-bromoaryl) enaminones.

Wang et al. (1999) reported a study about reaction of heterocyclic enamines with electrophilic alkynes (Sheme 1.41). Heterocyclic enamines **122** reacted with electrophilic alkynes **123** via the Michael addition pathway followed by cyclocondensation to produce 2-pyridinone-fused heterocycles **125** in good to excellent yield.



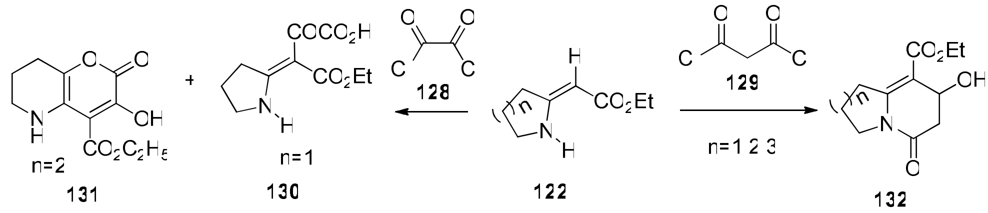
Scheme 1. 41 Synthesis of 2-pyridinone-fused heterocycles from heterocyclic enamines.

Miao et al. (2000) reported nucleophilic addition reaction of heterocyclic enamines **122** with nitrilimine 1,3-dipoles **126** to form *C*-hydrazidoyl-substituted heterocyclic enamines **127** (Sheme 1.42).



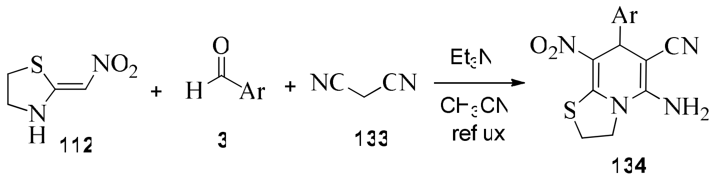
Scheme 1. 42 Nucleophilic reaction of heterocyclic enamines with nitrile imine 1,3-dipoles.

Cheng et al. (2001) studied on annulation of heterocyclic secondary enamines **122** with dicarboxylic acid dichlorides and discovered an unexpected ring size effect of heterocyclic secondary enamines. Heterocyclic secondary enamines react with malonyl chloride **129** to give hydroxylated 2-pyridinone-fused heterocycles **132** whereas the reactions of enamines with oxalyl chloride **128**, result different products (**130**,**131**) with respect to the heterocyclic structure of the enamine (Sheme 1.43).



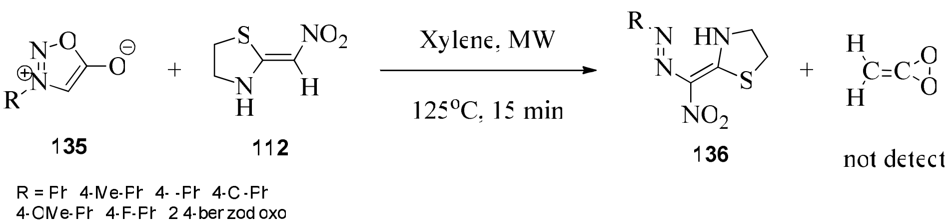
Scheme 1. 43 Annulation of heterocyclic secondary enamines with both malonyl chloride and oxalyl chloride.

Altuğ et al., (2011) successfully prepared of thiazolo[3,2-*a*]pyridines **134** by means of one pot multicomponent cyclisation between 2-(nitromethylene)thiazolidine **112**, aromatic aldehydes **3** and nitriles bearing active metylene group **133** in the presence of triethylamine (Scheme 1.44).



Scheme 1. 44 Multicomponent reaction for the formation of thiazolo[3,2-*a*]pyridines.

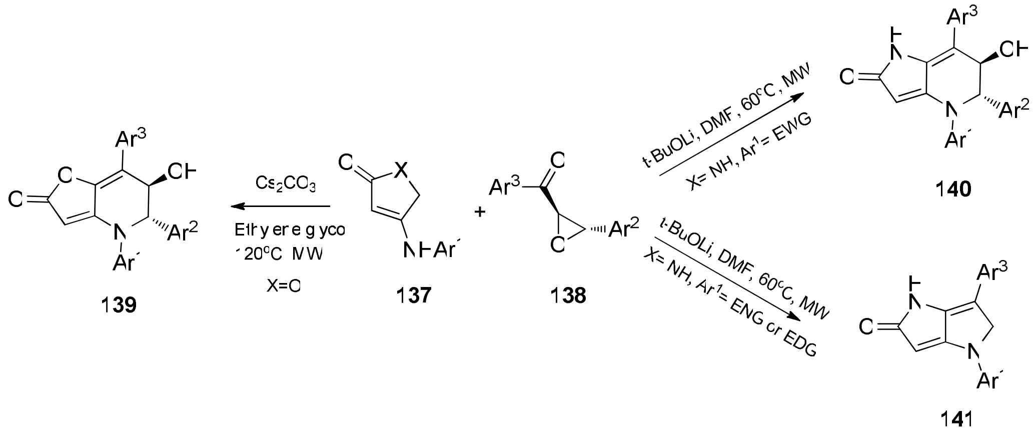
Dürüst and Sağırlı (2014) reported that the coupling reactions of mesoionic sydnones **135** with 2-(nitromethylene)thiazolidine **112,** under microwave conditions affording novel (*Z*)-2-(nitro((*E*)-*p*-substitutedphenyldiazenyl)methylene) thiazolidines **136** (Scheme 1.45).



Scheme 1. 45 Reaction of *N*-aryl sydnones with 2-nitromethylenethiazolidine affording diazenyl thiazolidines

Yang et al. (2015) newly reported base-promoted transannulation of heterocyclic enamines and 2,3-epoxypropan-1-ones **138** in order to synthesize fused pyridines and pyrroles with regio- and stereoselectivity. The *N*-aryl 4-aminopyrrol-

2(5H)-ones **137** bearing an electron-withdrawing group (EWG) formed pyrrolo[3,2-*b*]pyridines **140**, while their counterparts with an ENG or an EDG gave pyrrolo[3,2-*b*]pyrroles **141** through C–C bond cleavage (Sheme 1.46).

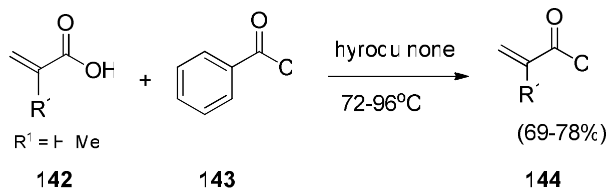


Scheme 1. 46 Transannulation of heterocyclic enamines bearing EWG or ENG/EDG and 2,3-epoxypropan-1-ones.

1.4.2 Acryloyl and cinnamoyl chlorides

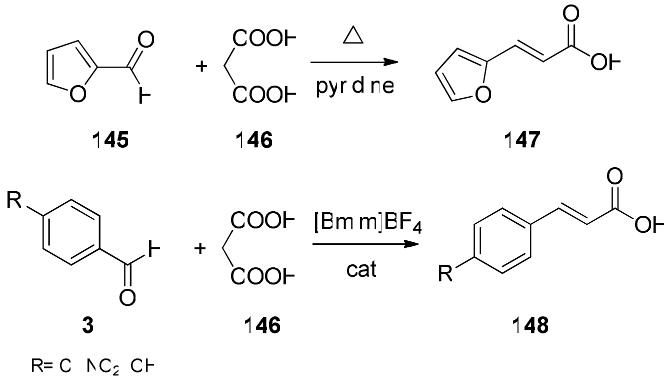
1.4.2.1 Synthesis of Acryloyl and Cinnamoyl chlorides

Acryloyl and methacryloyl chlorides **144** have been prepared by Stampel et al. (1950) by heating a mixture of acrylic acid (or metahcrylic acid) **142**, benzoyl chloride **143** and hydroquinone at 72-76°C and they were simply isolated by fractional distillation. In order to prevent polymerization of acrylic acid, hydroquinone was used (Scheme 1.47).



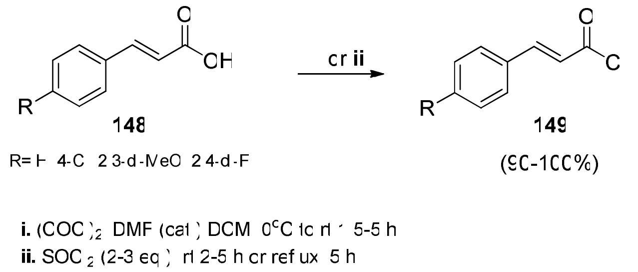
Scheme 1. 47 Synthesis of acryloyl and methacryloyl chlorides from acrylic acid derivatives

Aryl substituted acryloyl chlorides or cinnamoyl chlorides can be prepared by two-step and efficient synthetic method in which the first step covers the preparation of corresponding cinnamic acids **147**, **148** with Doebner condensation of aldehydes **3** (or **145**) and malonic acids **146** using pyridine or ethanol (Rajagopalan and Raman, 1955) or ILs such as [Bmim]BF_4, [Bpy]BF_4 (Jiang et.al, 2009) as solvent (Scheme 1.48).



Scheme 1. 48 Synthesis of cinnamic acid derivatives

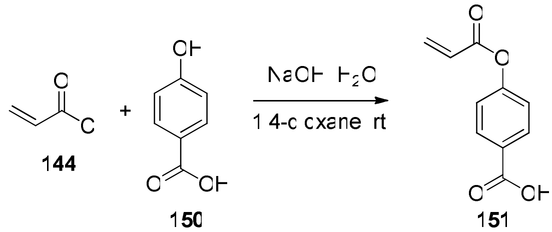
Thus, in the second step of the synthesis, easily prepared propenoic acids **148** reacted with oxalyl chloride in the presence of catalytic amounts of DMF to give the corresponding propenoic acid chlorides **149** (Burja et.al, 2009) or the cinnamic acids reacted with thionyl chloride in different equivalents to afford acid chlorides **149** (Li et.al, 2009) (Scheme 1.49).



Scheme 1. 49 Preparation of cinnamic acid chloride derivatives

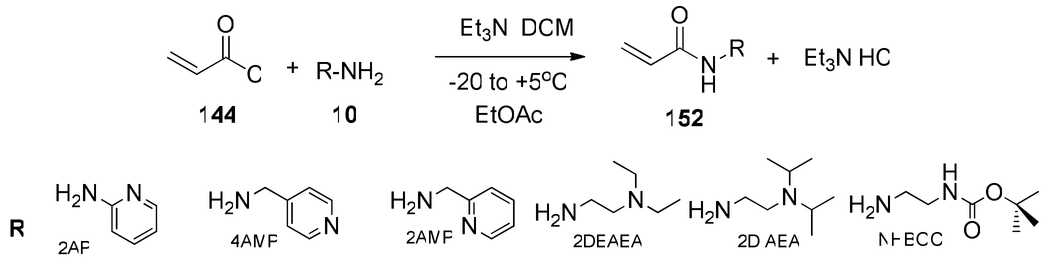
1.4.2.2 Reactions of Acryloyl and Cinnamic acid chlorides

Acrylic or cinnamic acid chloride derivatives are usually reactive and useful sythons in the preparation of different polymeric materials, amides by *N*-acylation, esters by *O*-acylation or different heterocycles by ring-closing methathesis (RCM) reactions. Bharathi et.al (2010) reported the base-catalysed condensation of acryloyl chloride **144** with *p*-hydroxy benzoic acid **150** in very mild conditions to afford *p*-carboxy phenyl acrylate **151** to be used in the production of poly(carboxy phenyl acrylate) homopolymers (Scheme 1.50).



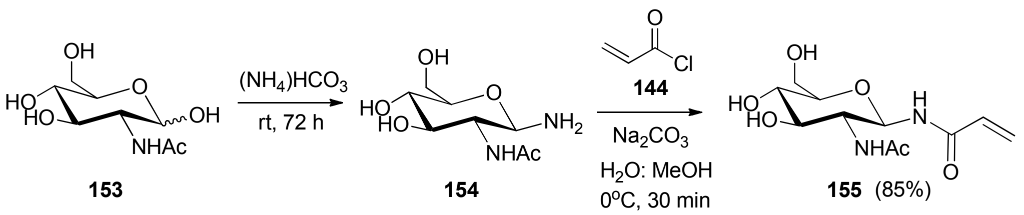
Scheme 1. 50 Preparation of *p*-carboxy phenyl acrylate monomer

Saez et.al. (2006) reported synthesis of the functionalized monomers (**152**), the commercial monomers, 4AMP, 2AMP, 2AP, 2DIPAEA, 2DEAEA and NHBOC by the addition reaction of acryloyl chloride **144** with different amine (**10**) functionalities (Scheme 1.51).



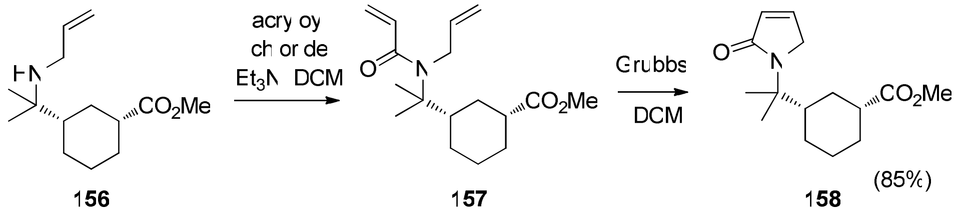
Scheme 1. 51 Preparation of functionalized acryl amide monomers

In a similar fashion, *N*-acryloyl group can be introduced by adding acryloyl chloride **144** in THF to the mixture of compound **154** and sodium carbonate in aqueous methanol at 0^{o}C to yield 2-acetamido-*N*-acryloyl-2-deoxy-*β*-D-glucopyranosylamine (**155**) (Kim et.al, 2001) (Scheme 1.52).



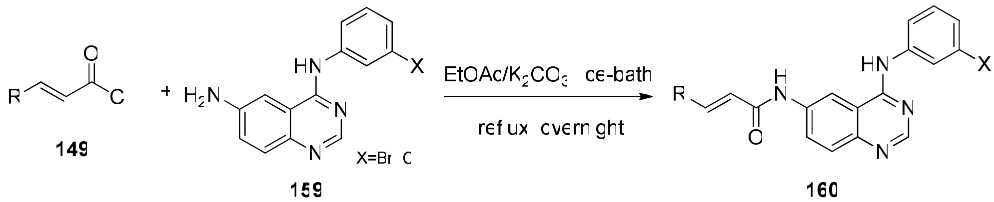
Scheme 1. 52 Preparation of *N*-acryloyl-2-deoxy-*β*-D-glucopyranosylamine

Ring-closing metathesis (RCM) reactions are often applied to the synthesis of medium and large sized rings. Use of acryloyl chloride in RCM reactions reported by Daly (2012). The sysnthesis starts with alkylation with allyl bromide followed by acylation with acryloyl chloride afforded the diene precursor **157**. In the last step, Grubbs 1st generation catalyst mediated RCM then afforded the unsaturated γ-lactam intermediate **158** in good yield (Scheme 1.53).



Scheme 1. 53 RCM in the synthesis of BACE-1 inhibitor

Li et al. (2011) reported the synthesis of novel type cinnamic acid quinazoline amide derivatives (**160**) by the combination of quinazoline and various substituted cinnamic acid chlorides **149** as the side chain (Scheme 1.54).



Scheme 1. 54 Synthesis of cinnamic amide derivatives.

1.5 CHAPTER 5

1.5.1 Thiazolopyrimidines

Thiazolopyrimidines are one of the common heterocyclic cores of many important *N*,*S*-containing molecules having diverse biological activities (Kashyap et al., 2011). They are formed by different combinations of thiazole and pyrimidine rings (Figure 1.2).

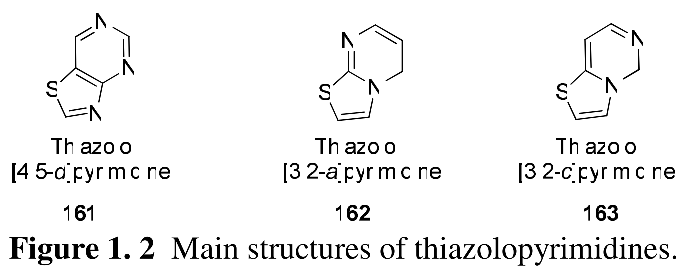
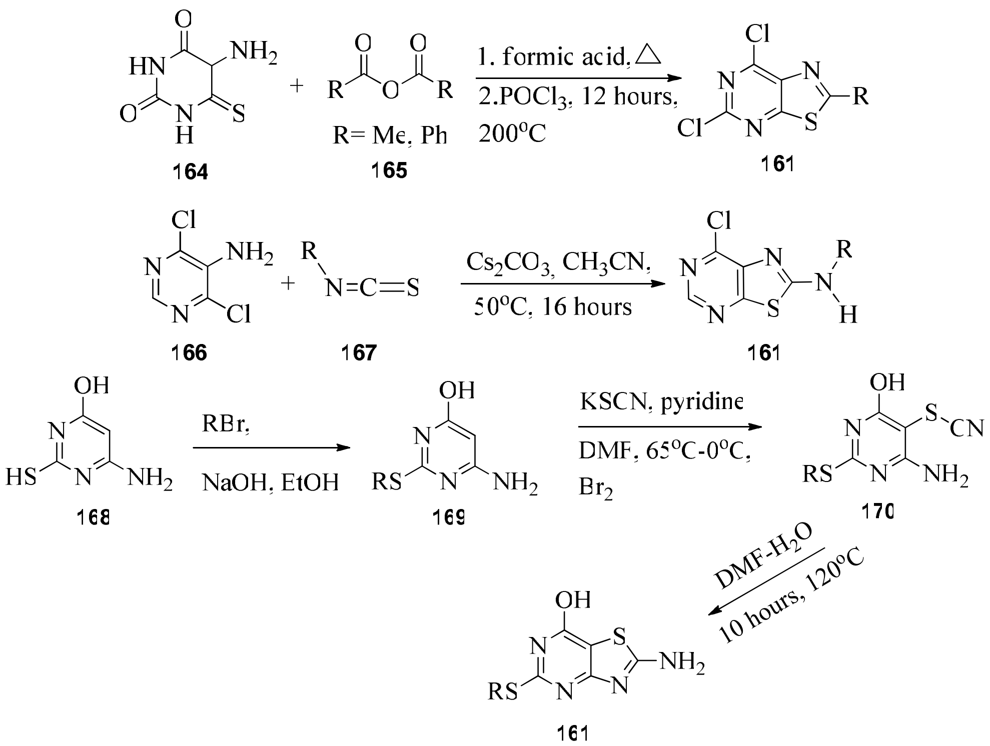


Figure 1. 2 Main structures of thiazolopyrimidines.

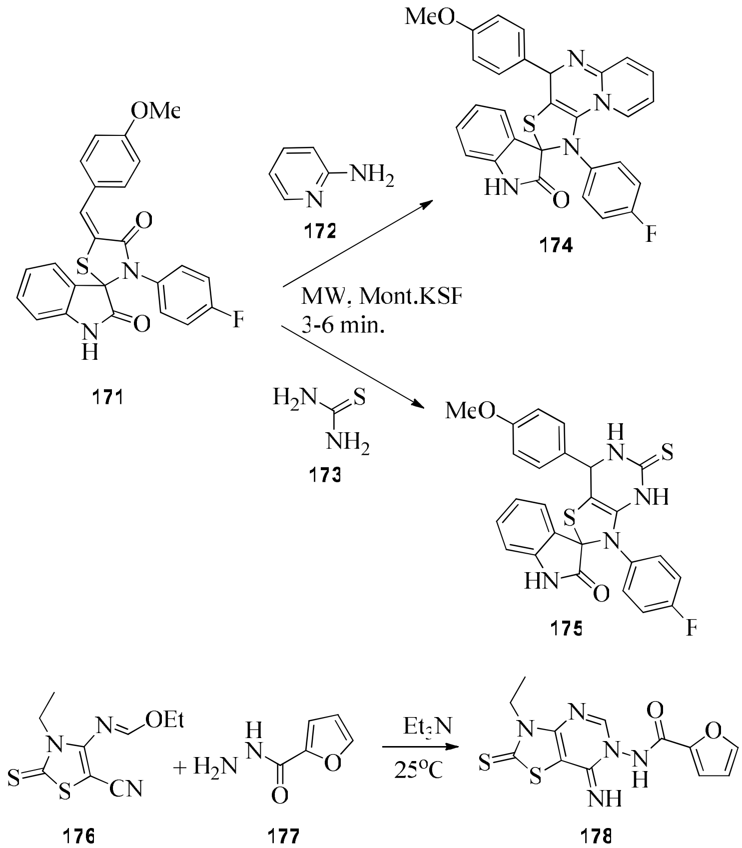
1.5.1.1 Synthesis of Thiazolopyrimidines

Due to the broad diverse biological activities of thiazolo[4,5-*d*]- and thiazolo[3,2-*a*]pyrimidines, many examples for their preparation have been reported in the literature up to date. Thiazolo[4,5-*d*]pyrimidines (**161**) can be prepared either from thiouracil **164** by using formic acid and some anhydrides **165** followed by phosphorus oxychloride oxidation or from one-pot reaction of 4,6-dichloro-5-aminopyrimidine **166** with isothiocyanates **167** in the presence of solid-phase transfer catalysts or through the transformation of 6-aminothiouracil in a stepwise manner (Scheme 1.55) (Childress and McKee, 1951; Liu et al., 2005; Singh et al., 2013; Baxter et al., 2006; Hunt et al., 2007).



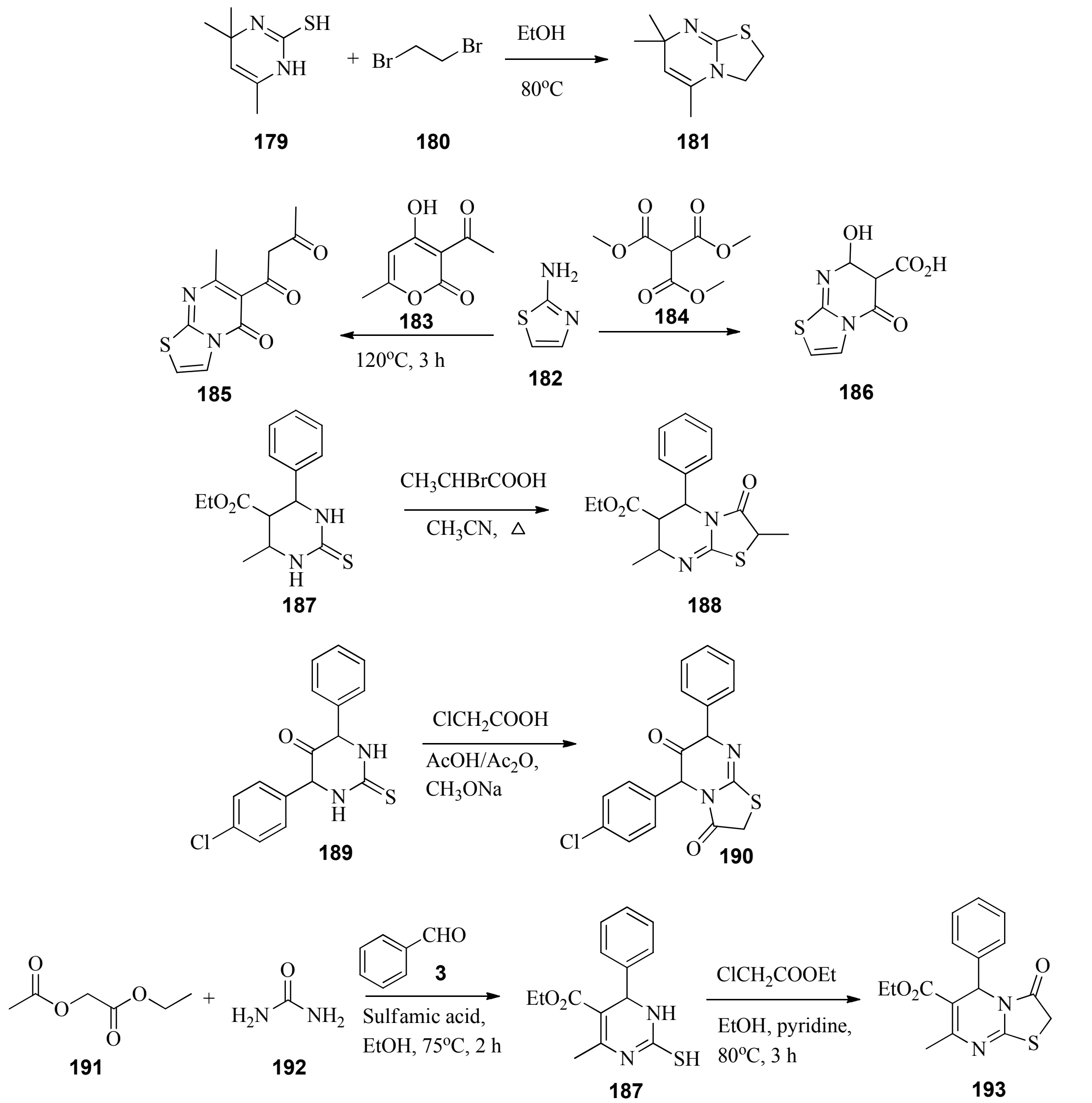
Scheme 1. 55 Synthesis of 2-amino substituted thiazolo[4,5-*d*]pyrimidines.

Besides, some fluorinated spiro- and iminothioxo- analogs (**174**, **175**) can be prepared by the reaction of spirothiazolidines **171** with thiourea **173** and 2-aminopyridines **172** under microwave irradiation conditions and by the reaction of imino-ethers **176** with semicarbazide or furoic acid hydrazides **177**, respectively (Scheme 1.56) (Arya, and Dandia, 2007; Luthra et al., 2010).



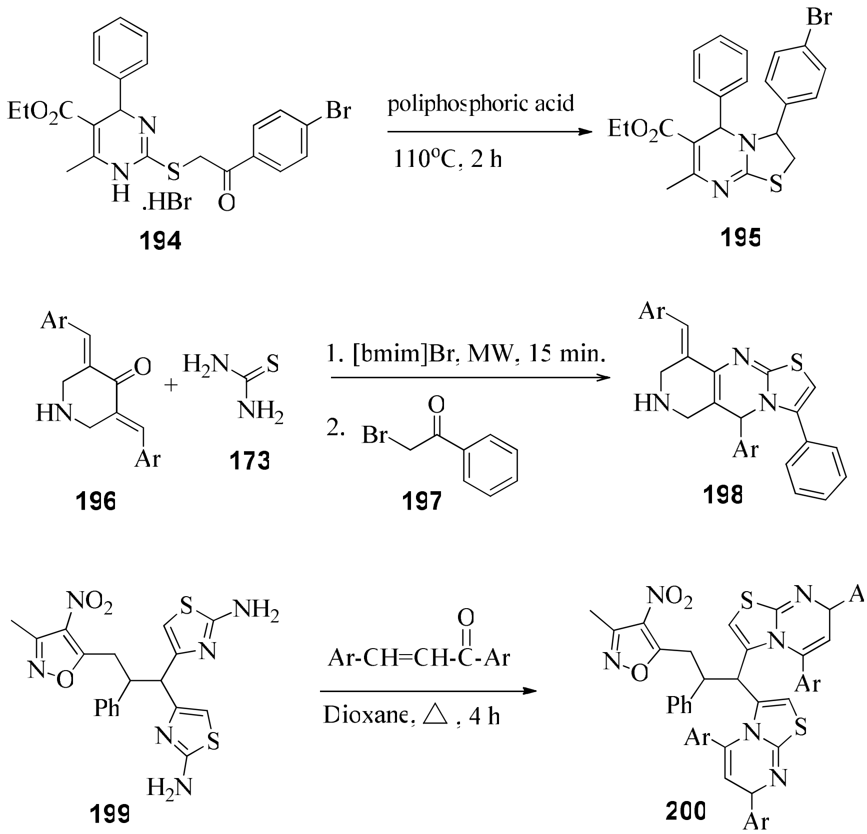
Scheme 1. 56 Synthesis of spiro- and iminothioxo-substituted thiazolo[4,5-*d*] pyrimidines.

Nonetheless, simple methyl-substituted thiazolo[3,2-*a*]pyrimidines **181** can be easily prepared by the condensation of ethylenedibromide **180** and 2-mercaptopyrimidine **179** in good yields (Gill et al., 1961). Also, thiazolo[3,2-*a*]pyrimidinones (**185**, **186**, **188**, **190**) can be obtained either by the ring opening reaction of dehydroacetic acid with 2-aminothiazole **182** at 120°C or by cyclocondensation reaction of 2-thioxopyrimidinones **189** with chloroacetic acid under acidic conditions or from a one-pot Biginelli reaction of ethyl acetylacetate **191**, thiourea **192**, and benzaldehyde **3** in the presence of sulfamic acid catalyst (Scheme 1.57) (Dijerrari et al., 2002; Mohammed at al., 2010; Hu et al., 2013).



Scheme 1. 57 Synthesis of various aryl and alkyl substituted thiazolo[3,2-*a*] pyrimidines and pyrimidinones.

More recently, some related carboxylate analogs **195** were prepared by intramolecular cyclisation of 2-phenacylthiodihydropyrimidine hydrobromides **194** using polyphosphoric acid (Moty et al., 2013). Besides, pyrido- and isoxazoyl-substituted analogs (**198**, **200**) have been obtained by domino reaction of diarylidenepiperidinones **196**, thiourea **173**, and α-bromoacetophenones **197** in ionic liquids or through cyclisations of bis-aminothiazoles **199** with chalcone derivatives, respectively (Scheme 1.58) (Basiri et al., 2014; Al-Omary et al., 2012; Rajanarendar et al., 2012).

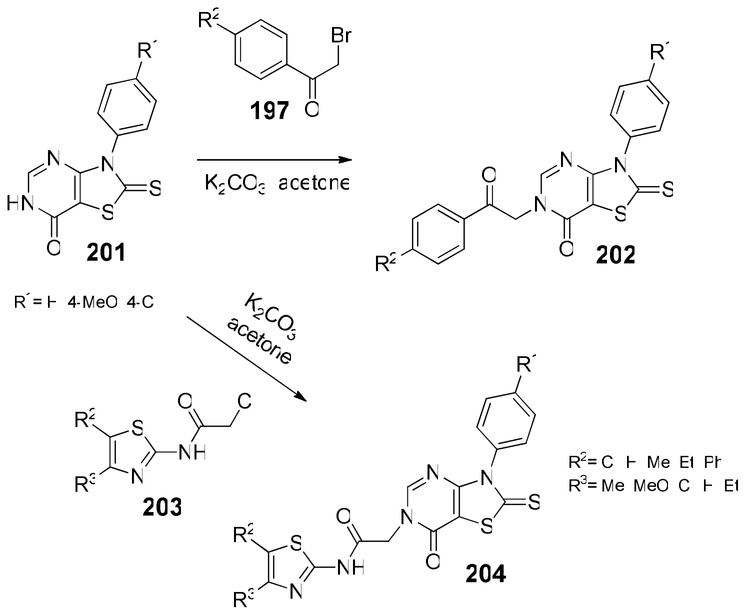


Scheme 1. 58 Synthesis of various aryl- and pyrido thiazolo[3,2-*a*]pyrimidines and isoxazoyl- substituted thiazol[3,2-*a*]pyrimidines.

As it was explained above, there are two many ways and examples for the preparation of thiazolo[4,5-*d*]- and [3,2-*a*]pyrimidines in recent literature, however, to the best of our knowlegde, only one example can be found for the preparation of thaziolo[3,2-*c*]pirimidine containing heterocycles (Heravi et al., 1998).

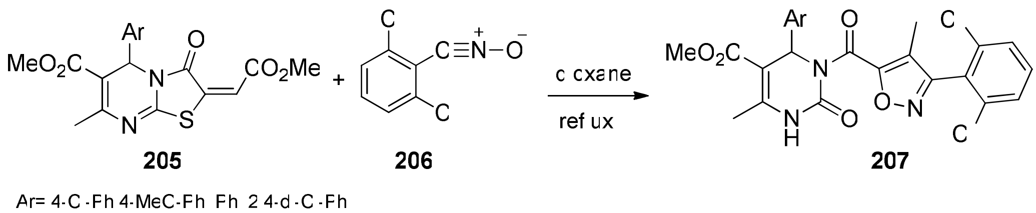
1.5.1.2. Reactions of Thiazolopyrimidines

Various reactions of thiazolopyrimidines are encountered in the literature. Demirayak et al. (2007) synthesized some 6-substituted 3-aryl-7-oxothiazolo[4,5-*d*]pyrimidin-2(3H)-thione derivatives **202** by reacting thiazolo[4,5-d]pyrimidines **201** with ω-bromo-acetophenones **197** or 2-chloro-*N*-(2-thiazolyl) acetamides **203**. **202** were obtained with the 61–78% yield and **204** with 54–86% yield (Sheme 1.59).



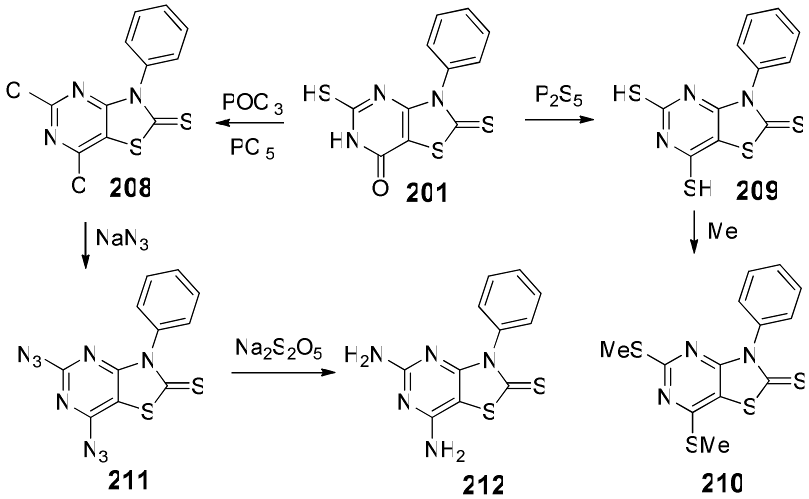
Scheme 1. 59 Reacting thiazolo[4,5-*d*]pyrimidines with ω-bromo-acetophenones or 2-chloro-*N*-(2-thiazolyl)acetamides.

Li et al. (2010) published a reaction of thiazolo[3,2-*a*]-pyrimidine derivatives, ethyl 2-[(methoxycarbonyl)methylidene]-2,3-dihydro-6-methyl-3-oxo-4 phenyl-5*H*-thiazolo-[3,2-*a*]pyrimidine-5-carboxylate (**205**) and nitrile oxide (**206**) to form *N*-substituted 1,2,3,6-tetrahydropyrimidin-2-ones (**207**) (Sheme 1.60).



Scheme 1. 60 Synthesis of *N*-substituted 1,2,3,6-tetrahydropyrimidin-2-ones via reaction of thiazolo[3,2-*a*]pyrimidine derivatives and nitrile oxide.

Habib et al. (1997) reported synthesis of 5,7-disubstituted thiazolo[4,5-*d*] pyrimidines (**210**,**212**) by starting with chlorination of 5-mercapto-thiazolopyrimidine **201** with a mixture of phosphorous pentachloride and phosphorous oxychloride (Sheme 1.61). The yields of the reaction is in the range of 50-71%.



Scheme 1. 61 Chlorination, thiation and methylation of 2,3-dihydro-5-mercapto-3-phenyl-2-thioxothiazololo[4,5-*d*]pyrimidin-7(6*H*)-one.

1.5.1.3. Biological Importance of Thiazolopyrimidines

Thiazolo[4,5-*d*]pyrimidines are the thia-analogs of purine bases (adenine, guanine) and so they have received great attention by the pharmaceutical industry and researchers working on the development of new therapeutics in the field of medicinal chemistry for many years. Also, thiazolo[3,2-*a*]pyrimidines can be considered as another important derivative of thiazolopyrimidines. Both types exhibit a variety of biological properties, such as antitumor and cytotoxic (**213**) (Abu-Hashem et al., 2011), immunomodulatory (Doria et al., 1985), antimicrobial (Youssef and Amin, 2012; Youssef et al., 2008), antipsychotic (Van Laar et al., 2001), antiinflammatory (Tozkoparan et al., 1999; Tozkoparan et al., 1998; Amr et al., 2007), calcium antagonist (Balkan et al. 1992), antiviral (Danel et al., 1998), antiparkinsonian (Abdel-Latif et al., 2007), antiarrhythmic (Shalaby et al., 2007), antidepressant (**216**) (Amr and Abdulla, 2002), anticancer (Amr et al., 2006; Selvam et al. 2012), and analgesic (**214**) (Amr et al., 2003) activities (Figure 1.3).

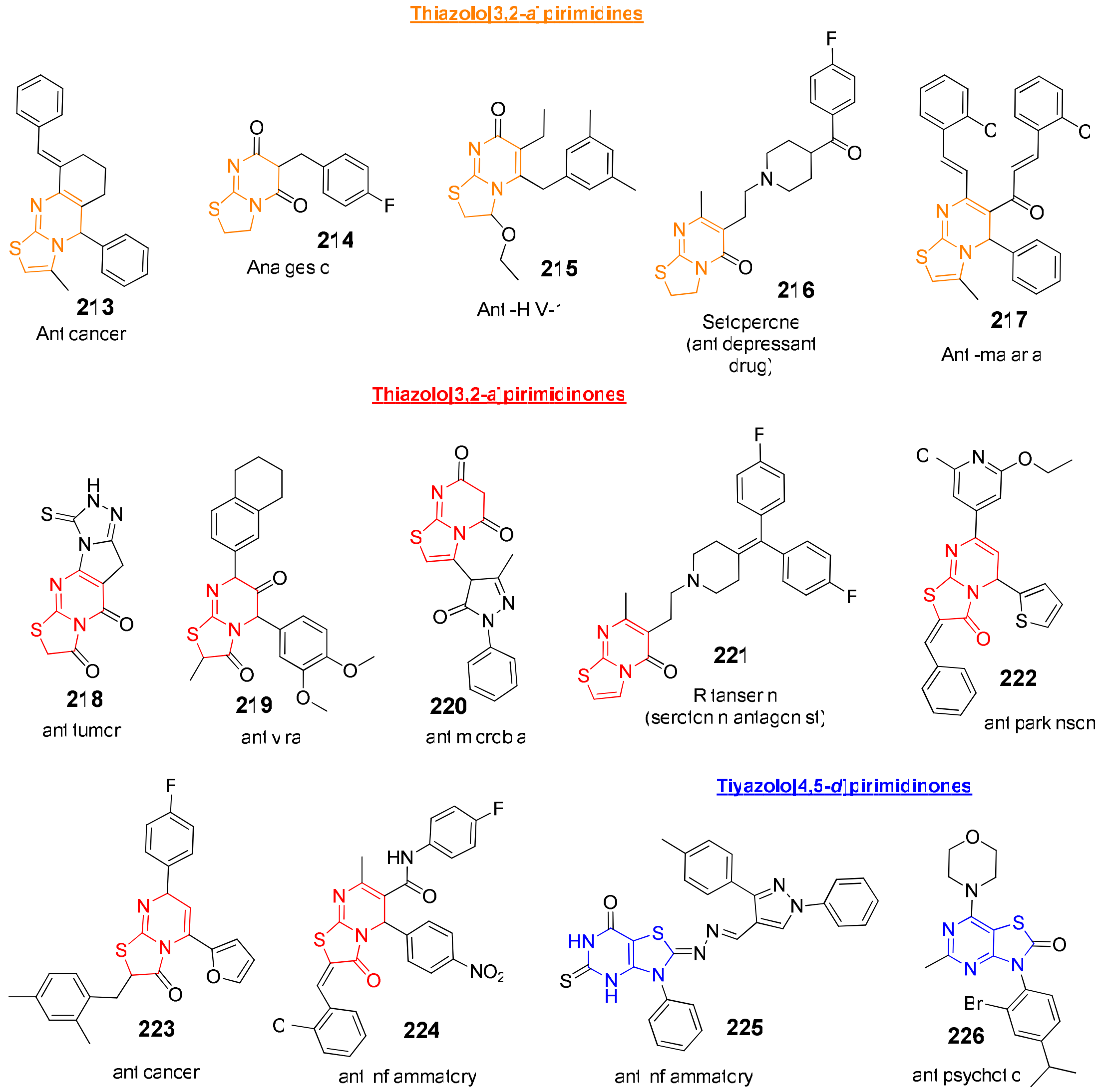


Figure 1. 3 Biologically active thiazolo- and oxothiazolo-pyrimidinone derivatives.

1.5.2 Thiazolo (imidazolo)pyridinones

Fused *N*-heterocyclic compounds (especially those containing 2-pyridone residues) can be seen in many biologically important natural products such as the multiring-fused natural product Camptothecin **228** and Nauclefine **227** and bicyclic molecules including the 2-pyridone acid A58365A (**229**,**230**), the ACE inhibitor (Chorell et al., 2007) Moreover, the thiazolo[3,2-*a*]pyridinone structure is the key part of pilicide-based antibiotic derivatives (**231**) (Figure1.4).

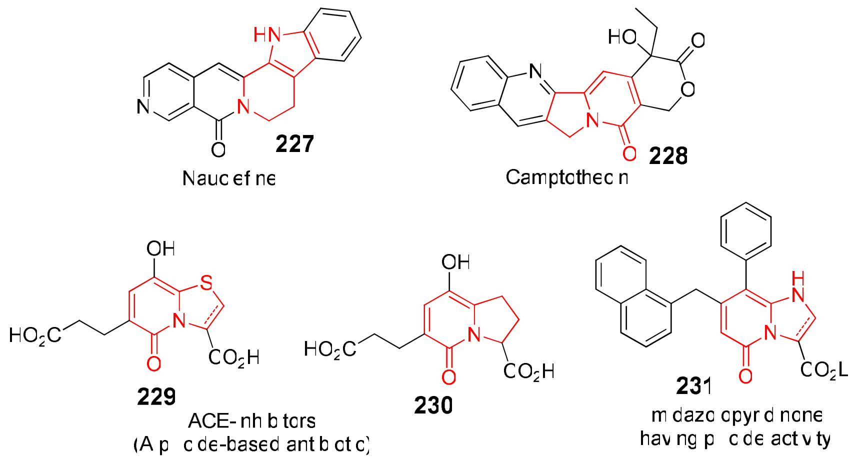
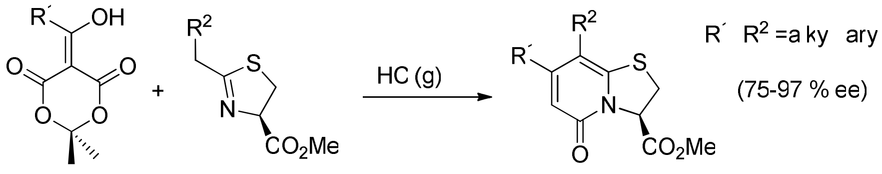


Figure 1. 4 Examples of 2-pyridone or thiazolo- (or imidazolo-) pyridinone containing natural products and biologically active compounds.

Thiazolopyridinones and imidazolopyridinones have shown a wide variety of biological activities including antihypertensive, antihepatic, antiviral, antifungal, vasodilatory and some insecticidal properties (Adachi et al., 1988; Hasegawa et al., 1995; Krauze et al., 1988; Shao et al., 2008; Tian et al., 2007).

1.5.2.1. Synthesis of thiazolo (imidazolo)pyridinones

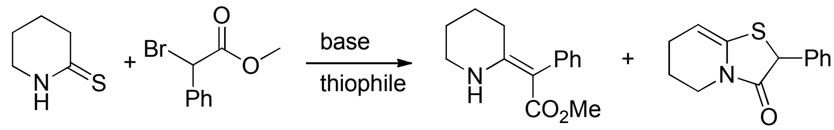
Recently, thiazolopyridin-2-ones have been prepared by starting from 2*H*- or 2-alkyl-substituted Δ^2-thiazolines and Meldrum's acid derivatives or by using 2-piperidinethione under a modified Eschenmoser sulfur contraction reaction with DBU in moderate yields. However, tetrahydroimidazolopyridinones were prepared in moderate to good yield through a multicomponent Michael cyclisation of β-nitroketeneaminal, aldehydes and Meldrum's acid (Taguchi et al., 1977). For example, Emtenäs et al. (2001) synthesized of substituted ring-fused 2-pyridinones via an enantioselective ketene–imine cycloaddition method. 2-alkyl-Δ^2-thiazolines **233** and Meldrum's acid derivatives **232** were treated with $HCl_{(g)}$ in benzene at 5 → 78°C. Then, 1,2-dichloroethane used as solvent at 0 → 64 °C led to the desired 2-pyridinones **234** with 63-86% yields (Sheme 1.62).



232 **233** **234** 63-86%

Scheme 1. 62 Synthesis of substituted ring-fused 2-pyridinones via an enantioselective ketene-imine cycloaddition method**.**

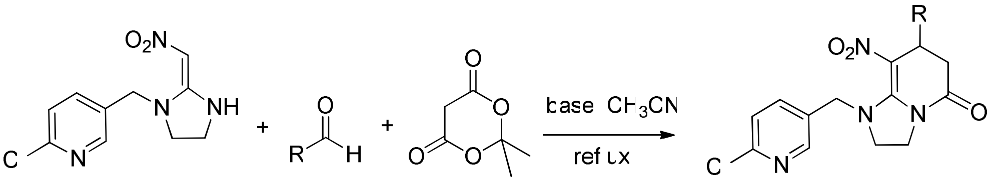
Russowsky and da Silveira (2004) investigated the influence of the ring size of thiolactams in the Eschenmoser coupling reaction in presence of DBU and discovered formation of bicyclic thiazolidinones. The reaction of the piperidin-2-thione (**235**) with the α-bromoester **236**, through the Eschenmoser protocol, formed **237** and a variable quantity of the unexpected thiazolidinone **238**, depending on the base employed (Sheme 1.63).



235 **236** **237** **238**

Scheme 1. 63 Formation of *β*-enaminocarbonyl and the thiazolidinone.

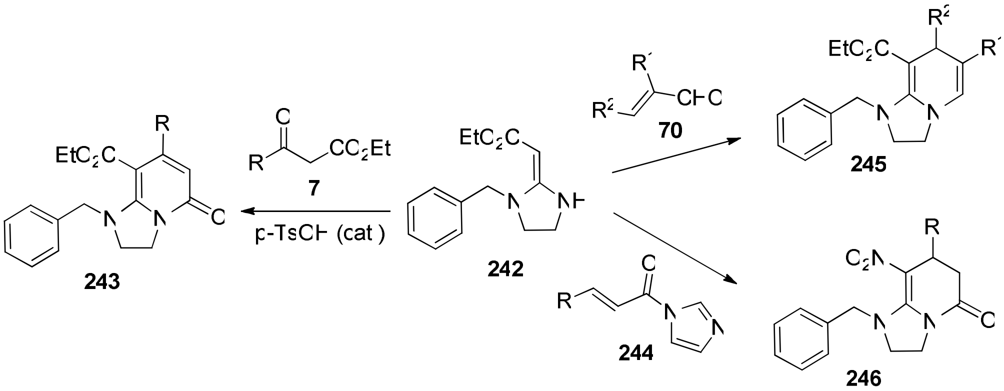
Hu et al. (2011) reported synthesis of tetrahydroimidazolpyridinones via an MCR involving 6-Cl-PMNI **239**, aldehydes **3**, and Meldrum's acid **240**. Et_3N or K_2CO_3 are used as catalysis in anhydrous CH_3CN at refluxing temperature and tetrahydroimidazolpyridinones **241** were obtained with 30–96% (Sheme 1.64).



239 **3** **240** **241**

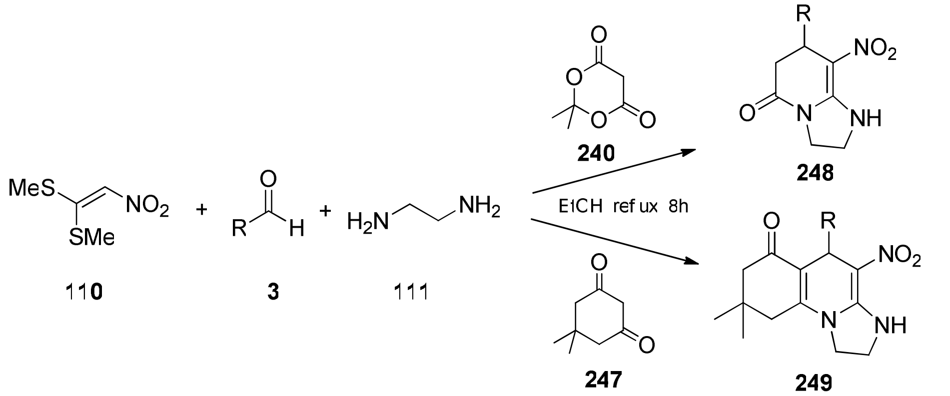
Scheme 1. 64 Three-component reaction of various aldehydes, Meldrum's acid, and **239**.

In similar fashion, the preparation of some imidazolopyridinone carboxylic acids by the azaannulation of itaconic anhydride with α-nitro -*N*,*N*-ketene acetals and the preparation of imidazolopyridinones by annulation of 2-(ethoxycarbonylmethylene)tetrahydroimidazoles **242** with different 1,3-bis-electrophiles (**70**, **244**) have been found as good examples in recent literature (Jones et al., 1998; Chakrabarti et al., 2005).

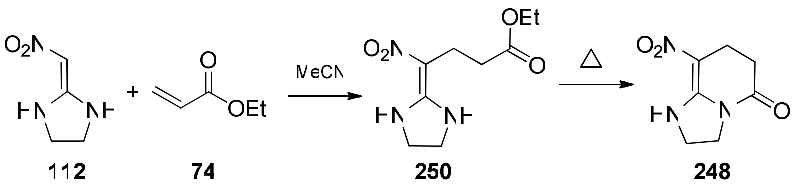


Scheme 1. 65 Preparation of imidazolopyridinones using different electrophiles

Besides, imidazo[1,2-*a*]pyridinones (**248**) can be prepared by either one-pot four-component condensation reaction of ethane-1,2-diamine **111**, 1,1-bis(methylthio)-2-nitroethene **110**, aldehydes **3** and activated methylene compounds (**240**, **247**) in moderate yields or by stepwise cyclisation of α,*β*-unsaturated esters **74** with 2-(nitromethylene)imidazolidine **112** in good yields (Tokumitsu, 1990; Movahed et al., 2013) (Scheme 1.66-67).



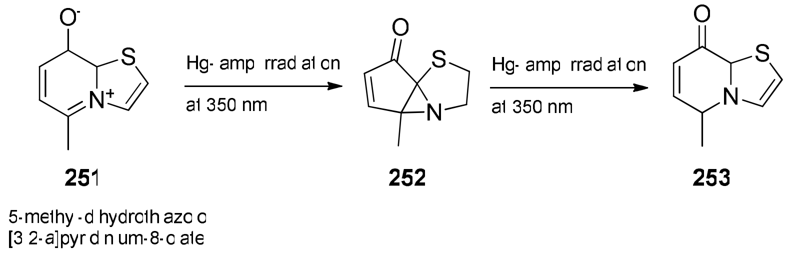
Scheme 1. 66 Preparation of imidazolopyridinones by one-pot four-component reaction



Scheme 1. 67 Two-step preparation of nitroimidazolo[1,2-*a*]pyridinone using ethyl acrylate

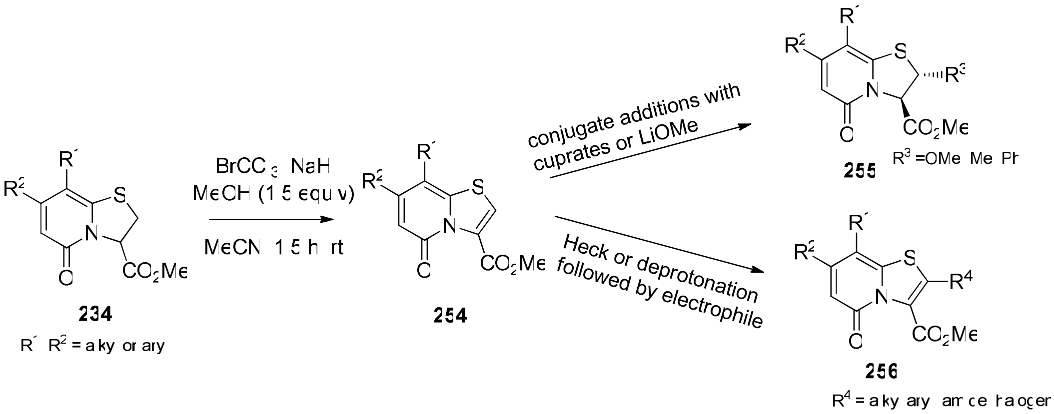
1.5.2.2 Reactions of thiazolo (imidazolo)pyridinones

Since ring-fused 2-pyridones exhibit biologically active functions, there are various studies about them in order to synthesize derivatives and investigate their biological activities. Laerum and Undheim (1979) studied on *N*-quaternary compounds and investigated photochemically induced valence bond isomerism and rearrangement to pyridinones of thiazolo[3,2-*a*]pyridinium-8-olate derivatives. Irradiation of derivatives of thiazolo[3,2-*a*]pyridinium-8-olate caused a rearrangement into derivatives of the isomeric thiazolo[3,2-*a*]pyridin-5-ones. Furthermore, irradiation of 5-methyldihydrothiazolo[3,2-*a*]pyridinium-8-olate **251** resulted with the valence isomeric structure 6-methyl-2-thia-5-azatricyclo-[4.3.0.0^{1,5}]non-7-en-9-one **252** which on and further irradiation gave the corresponding rearranged dihydrothiazolo[3,2-*a*]pyridin-5-one **253** (Scheme 1.68).



Scheme 1. 68 Photochemical reactions of thiazolo[3,2-*a*]pyridinium-8 olates

Chorell et al. (2010) designed and synthesized C-2 substituted thiazolo- and dihydrothiazolo- ring-fused 2-pyridones. The α,*β*-unsaturated methyl ester **254** substituents were introduced by conjugate additions resulting in an addition with complete *trans*-selectivity (**255**). Substituents were also introduced with a retained double bond by the use of Heck couplings or deprotonation using LDA and subsequently react the lithiated scaffold with various electrophilic reagents (**256**). These unique techniques enable introducing a different type substituents with varying size, electronic properties, and spatial arrangement (Sheme 1.69).



Scheme 1. 69 Different techniques were improved to introduce substituents in position C-2 on the scaffold from the oxidized scaffold**.**

1.6 CHAPTER 6

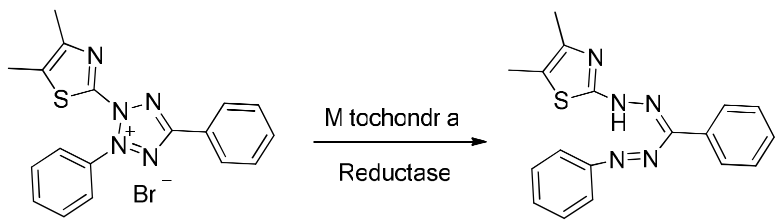
1.6.1 Cytotoxicity and Cell Viability Tests

Cytotoxicity is the degree of being toxic of an agent on the cells. Experimental toxicological studies are carried out in order to determine and investigate structural and functional changes depending on the chemical agent on living cells. It is necessary to determine the amount of cell populations in a meaningful way for high performance of measuring, success of repeatability or comparison of the studies. Therefore, some methods have been developed to investigate cell viability and proliferation in cell populations (Doyle, and Griffiths, 1998).

There are many specific methods suitable for particular circumstances or for certain experimental purposes. These methods involves Tritium-Labeled Thymidine Uptake method, Crystal Violet method, Colony Formation method, MTT, and WST methods, which are used for counting the number of live cells. They are based on various cell functions including enzyme activity, cell adherence, ATP production, cell membrane permeability, nucleotide uptake activity and co-enzyme production (Dojindo Molecular Technologies, Inc).

1.6.1.1. MTT Assay

The MTT assay is a colorimetric assay which was primarily defined by Mossman (1983) for assessing cell viability (Mosmann, 1983). The assay is based on the capacity of mitochondrial dehydrogenase enzymes in living cells to convert the yellow water-soluble substrate 3-(4,5-dimethylthiazol-2-y1)-2,5-diphenyl tetrazolium bromide (**257**) into a dark blue, water-insoluble formazan product (**258**) (Scheme 1.70) (Doyle, and Griffiths, 1998).



257 3-(4 5-d methy th azo -2-y)-2 5-d pheny tetrazo um brom de **(MTT)**

258 (*E Z*)-1-(4 5-d methy th azo -2-y)-3 5-d pheny formazan **(Formazan)**

Scheme 1. 70 Molecular structure of MTT, and its corresponding reaction product, formazan.

Since reduction of MTT to formazans can be performed by only cells having metabolic activity, this assay detects only living cells. Because cells which proliferate shows more metabolic activity than ones which does not proliferate, not only cell viability and cytotoxicity but also cell activation and proliferation by this method (Doyle, and Griffiths, 1998; Mosmann, 1983).

1.6.2 Antibacterial Assay

Antimicrobial susceptibility tests are the tests performed to determine the in vitro activity of an antimicrobial agent against a particular bacterial species. Susceptibility tests must be applied to all agents which led to an infectious disease required antimicrobial chemotherapy and whose antibiotic susceptibility cannot be known precisely by the description of type strains (Türkiye Halk Sağlığı Kurumu Mikrobiyoloji Referans Laboratuvarları Daire Başkanlığı, 2015).

In order to measure the *in vitro* susceptibility of bacteria, a variety of laboratory methods including disc diffusion method, antimicrobial gradient method, e-test, dilution methods, and genotype methods are used (Reller et al., 2009). Disc diffusion among these methods is a common test in clinical laboratories easy to use and can be applied to partially lack of breeding of bacteria (Türkiye Halk Sağlığı Kurumu Mikrobiyoloji Referans Laboratuvarları Daire Başkanlığı, 2015).

1.6.2.1. Disc diffusion method

Disk diffusion test, or Kirby-Bauer antibiotic test (KB test) with the names of its developer, is a test which uses commercially prepared disks, each of which are pre-impregnated with a standard concentration of a particular antibiotic in order to test if bacteria are affected by antibiotics (Michigan State University College of Veterinary Medicine, 2015). After a while, discs diffuses towards dissolved agar, inoculated microorganisms begins to multiply. After a certain incubation time, growth is not observed around the discs which inhibitory concentration of the drug is provided. The more sensitive microorganisms are to drug, the larger inhibition zone formed around the disc. The diameter of the inhibition zone is measured in mm and is evaluated by standard zone tables and then susceptibility of microorganism is determined against antimicrobial agents used (Demirpek U, 2012).

2. AIM AND SCOPE OF THE STUDY

This thesis describes the work that establishes the discovery of new fused *N*-heterocyclic compounds and their ability to exhibit cytotoxic and antibacterial activities. The general aims of the current research work were to found new synthetic methods for the efficient preparation of these potential cytotoxic and antibacterial agents. More specifically, the objectives were to apply Mannich and Michael cyclisations, examples of MCRs, for the efficient synthesis of thiazolopyrimidines, 4-oxothiazolopyridimines and thiazolo-(imidazolo-)pyridinones, respectively. To achieve these objectives and to attain new fused *N*-heterocylic compounds;

Primarily, as the starting materials, 2-(nitromethylene)thiazolidine, 2-(nitromethylene)imidazolidine and methylene-4-oxothiazolidine carboxylates were prepared by using literature methods through versatile precursors (Rajappa and Advani,1982; Kalisiak et.al, 2012, Stojanovic et al., 2011). Also, some 2-aryl substituted acryloyl chlorides have been accessed through a two-step synthetic route (Rajagopalan and Raman, 1955; Burja et.al, 2009).

- In the second part of the work, MW-assisted efficient preparation of new thiazolo[3,2-*c*]pyrimidines was achieved using the double-Mannich cyclisations of a nitroenamine through iminium formation in aqeous solution.
- In the third part of the work, in order to widen the scope and limitations of the Mannich cyclisations of heterocyclic enamines, 4-oxothiazolidines were used. This provided us an easy access to a library of new oxothiazolo[3,2-*c*]pyrimidine carboxylates using conventional heating methods.
- The fourth part of the study was aimed to describe the base-catalysed one-pot preparation of thiazolo-(imidazolo-) [3,2-c]pyridinones through the Michael-type cyclisation of nitroenamines with acryloyl chloride derivatives.
- In the last part of our work, it was aimed to screen the cytotoxic and antibacterial properties of title compounds produced in cyclisation reactions in the synthetic parts.

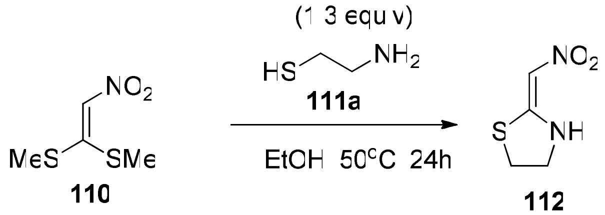
3. MATERIALS AND METHODS

All reagents and solvents were commercially available with analytical grade (Merck, Sigma-Aldrich) and used as received. ^{1}H- and ^{13}C- NMR spectra were recorded on VARIAN spectrometers (400 MHz for proton and 100 MHz for carbon) and a BRUKER Ultrashield (300 MHz for proton and 75 MHz for carbon) spectrometer at ambient temperature. All chemical shifts (δ) are reported in parts per million (ppm) downfield from TMS; *J* values are given in Hz. The abbreviations used for NMR signals are: s = singlet, d = doublet, t = triplet, q = quartet, sep = septet and m = multiplet. IR spectra were recorded on a SHIMADZU FTIR-8400S instrument (KBr pellet or NaCl discs) and a Shimadzu FT-IR Spectormeter with ATR system. High resolution mass spectra were run on a Waters Lct Premier XE oa-TOF Mass Spectrometer, on an orthogonal acceleration-TOF mass spectrometer and a FTMS (4.7T) mass spectrometer. Single crystal X-ray Diffraction measurements were run on an EnrafeNonius CAD-4 Diffractometer. Specific rotations were run by a Rudolph Research Analytical Autopol I Automatic polarimeter. A Single-mode Microwave reactor (CEM Discover Explorer SP) were used for microwave-mediated reactions. Melting points were determined on a MELTEMP apparatus and are uncorrected. TLC was carried out using precoated plates with fluorescent indicator (Merck 5735) for monitoring the reactions. Column chromatographic separations were performed on silica gel (Merck, 230–400 mesh ASTM) and the eluent was a mixture of ethyl acetate (EA) and hexanes (H) or only ethyl acetate. Staining solutions of permanganate, phosphomolybdic acid (PMA) and iodine were used for visualization of the TLC spots.

3.1 EXPERIMENTAL

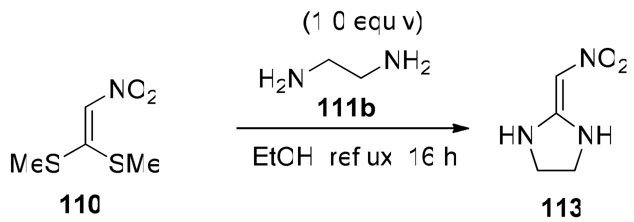
3.1.1 PREPARATION OF STARTING MATERIALS

3.1.1.1 Preparation of 2-(nitromethylene)thiazolidine (112) (Rajappa and Advani, 1982)



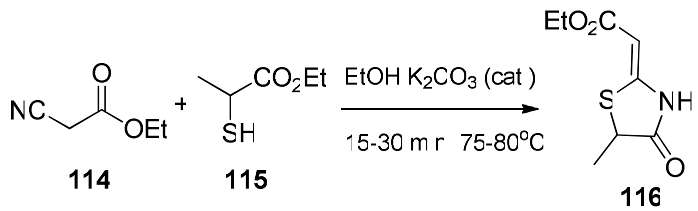
To a stirred suspension of 1,1-bis(methylthio)-2-nitroethylene (**110**) (3.3 g, 20.0 mmol) in ethanol (20 mL) under nitrogen, 2-aminoethanethiol (**111a**) (2.0 g, 26.0 mmol) was added at room temperature and resulting mixture was warmed up to 50^{o}C and left for 24 hours. After the consumption of starting compound, the reaction was quenched. The solid was filtered and washed with water (10 mL) and ethanol (10 mL), successively and the solution part was discarded. Resulting pale yellow solid was dried under high vacuum for 3 hours and obtained in dry and pure state without needing any chromatography, to provide **112** (2.46 g), yield 84%, pale yellow solid.

3.1.1.2 Preparation of 2-(nitromethylene)imidazolidine (113) (Kalisiak et.al, 2012)



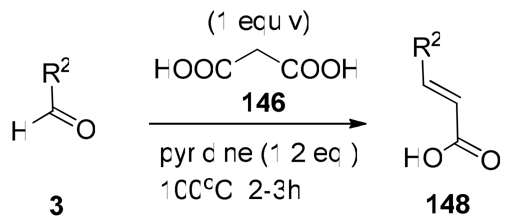
The mixture of 1,1-bis(methylthio)-2-nitroethylene (**110**) (3.3 g, 20.0 mmol) and 1,2-diaminoethane (**111b**) (1.35 mL, 1.2 g, 20.0 mmol) in anhydrous ethanol (50 mL) was stirred for overnight at reflux. The mixture was cooled to 0 °C in an ice-water bath and the product **113** collected by filtration and dried under high vacuum for 2 hours as a very pale yellow solid (2.32 g, 90%).

3.1.1.3 Preparation of (Z)-ethyl 2-(5-methyl-4-oxothiazolidin-2-ylidene) acetate (116)



The starting material **116** was prepared efficiently according to literature (Stojanovic et al., 2011).

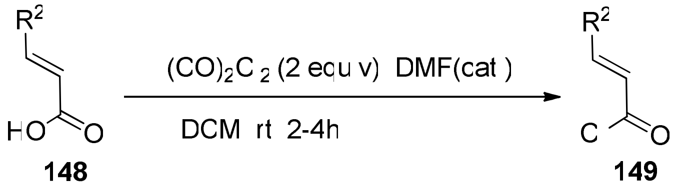
3.1.1.4 General procedures for preparation of cinnamic acids (148) (Rajagopalan and Raman, 1955)



To a mixture of corresponding aldehyde **3** (10 mmol) and malonic acid **146** (1.04 g, 10 mmol) in a round-bottomed flask, pyridine (0.96 mL, 12 mmol) was added and reaction mixture was heated to 100°C for 2-3 hours. After completion, the reaction mixture was cooled and diluted with 40 mL of water. The formed acid was dissolved by the addition of concentrated aqueous NH_3, the solution was filtered and washed with water (2x10 mL). The combined filtrates were acidified with an excess of dilute (1:1) HCl, then cooled and allowed to stand in an ice bath for 1 h. It was filtered, washed with water and dried to afford the corresponding cinnamic acids (**148**) in good yields.

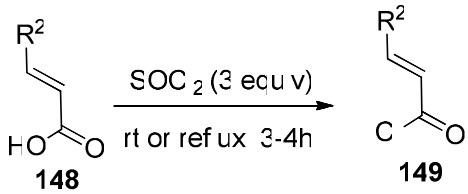
3.1.1.5 General procedures for preparation of cinnamoyl chlorides (149)

<u>**Method A:**</u> (Burja et.al, 2009)



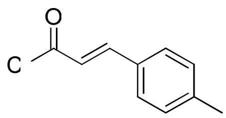
Oxalyl chloride (0.86 mL, 1.27 g, 10.0 mmol) was added dropwise to a mixture of corresponding cinnamic acid **148** (5 mmol) and *N*,*N*-dimethylformamide (3-4 drops) in dry CH_2Cl_2 (25 mL) at 0°C under N_2 atmosphere. Resulting mixture was stirred at ambient temperature for 2-5 hours and after completion of reaction, it was evaporated to dryness to afford corresponding cinnamic acid chlorides (**149**) as solid or crystalline form in quantitative yields.

<u>**Method B:**</u> (Li et.al, 2009)



Corresponding cinnamic acid **148** (3 mmol) was mixed with thionyl chloride (0.4 mL, 0.65 g, 9 mmol) under N_2 atmosphere. The resulting mixture was either stirred in CH_2Cl_2 at room temperature or refluxed in CH_3CN for 3-4 hours**.** The reaction mixture was cooled and evaporated to afford corresponding cinnamic acid chlorides **149** as powder or crystals.

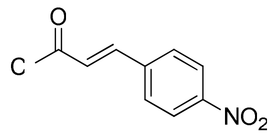
(*E*)-*p*-methylcinnamoyl chloride (149b):



Following the general procedure **II** (**d, method B**), treating thionyl chloride (0.70 mL, 1.08 g, 15.0 mmol) with (*E*)-*p*-methylcinnamic acid (0.81 g, 5 mmol) in dry CH_2Cl_2 (25 mL) at 25°C under N_2 atmosphere for 4 hours to give **149b** (0.94 g), yield: quantitative. pale yellow crystals. m.p. 127-128°C. R_f: 0.80 (33% -hexane/ethyl acetate). IR (KBr): ν_{max}/cm^{-1} = 3059 (-C=CH), 3034 (arom. C-H), 2995

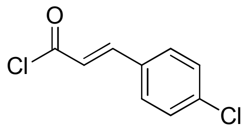
(C-H), 1739 (C=O), 1600 (C=C), 1510, 1413, 1267, 1105, 974, 806, 644 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.57 (d, 2H, *J* = 7.6 Hz), 7.55 (d, 1H, *J* = 15.2 Hz), 7.23 (d, 2H, *J* = 8.0 Hz), 6.47 (d, 1H, *J* = 16.0 Hz), 2.32 (s, 3H, $-CH_3$). ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.6, 118.7, 128.8, 130.1, 132.1, 140.8, 144.5, 168.3.

(*E*)-4-nitrocinnamoyl chloride (149c):



Following the general procedure **II** (**d, method A**), treating oxalyl chloride (1.72 mL, 2.54 g, 20.0 mmol) with a mixture of (*E*)-*p*-nitrocinnamic acid (1.93 g, 10 mmol) and *N*,*N*-dimethylformamide (5-6 drops) in dry CH_2Cl_2 (40 mL) at 0°C under N_2 atmosphere for 2.5 hours to give **149c** (2.00 g), yield: quantitative. bright yellow crystals. m.p. 293-294˚C. R_f: 0.90 (50% ethyl acetate/hexane). IR (KBr): ν_{max}/cm^{-1} = 3107 (-C=CH), 3061 (arom. C-H), 2922, 1753 (C=O), 1626 (C=C), 1518, 1344, 1265, 1101, 1026, 977, 840, 748, 665 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.21 (d, 2H, *J* = 8.8 Hz), 7.95 (d, 2H, *J* = 9.2 Hz), 7.67 (d, 1H, *J* = 16.0 Hz), 6.73 (d, 1H, *J* = 16.0 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 124.3, 124.6, 129.9, 141.4, 142.0, 148.6, 167.7.

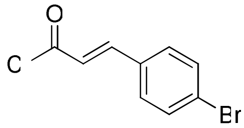
(*E*)-4-chlorocinnamoyl chloride (149d):



Following the general procedure **II** (**d, method A**), treating oxalyl chloride (1.72 mL, 2.54 g, 20.0 mmol) with a mixture of (*E*)-*p*-chlorocinnamic acid (1.83 g, 10 mmol) and *N*,*N*-dimethylformamide (5-6 drops) in dry CH_2Cl_2 (40 mL) at 0°C under N_2 atmosphere for 4 hours to give **149d** (2.05 g), yield: quantitative. white-yellow solid. m.p. 79-80˚C. R_f: 0.80 (33% hexane/ethyl acetate). IR (KBr): ν_{max}/cm^{-1} = 3086 (-C=CH), 3061 (arom. C-H), 1751 (C=O), 1610 (C=C), 1491, 1408, 1263, 1112, 1089, 976, 812, 640 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.74 (d, 2H, *J* = 8.4 Hz), 7.59 (d, 1H, *J* = 16.0 Hz), 7.48 (d, 2H, *J* = 8.4 Hz), 6.57 (d, 1H, *J* = 16.0

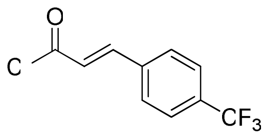
Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 120.7, 129.6, 130.6, 133.8, 135.4, 143.2, 168.1.

(*E*)-4-bromocinnamoyl chloride (149e):



Following the general procedure **II** (**d, method A**), treating oxalyl chloride (0.86 mL, 1.27 g, 10.0 mmol) with a mixture of (*E*)-*p*-bromocinnamic acid (1.13 g, 5 mmol) and *N*,*N*-dimethylformamide (3-4 drops) in dry CH_2Cl_2 (25 mL) at 0^{o}C under N_2 atmosphere for 3 hours to give **149e** (1.24 g), yield: quantitative. light brown solid. m.p. 249-250˚C. R_f: 0.70 (33% hexane/ethyl acetate). IR (KBr): ν_{max}/cm^{-1} = 3051 (-C=CH), 2969 (arom. C-H), 2924, 1739 (C=O), 1620 (C=C), 1483, 1402, 1263, 1111, 1072, 974, 806, 638 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.63 (d, 2H, *J* = 8.8 Hz), 7.58 (d, 2H, *J* = 8.8 Hz), 7.54 (d, 1H, *J* = 16.0 Hz), 6.54 (d, 1H, *J* = 16.0 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 120.5, 123.9, 130.5, 132.2, 133.9, 143.0, 167.8 (C=O).

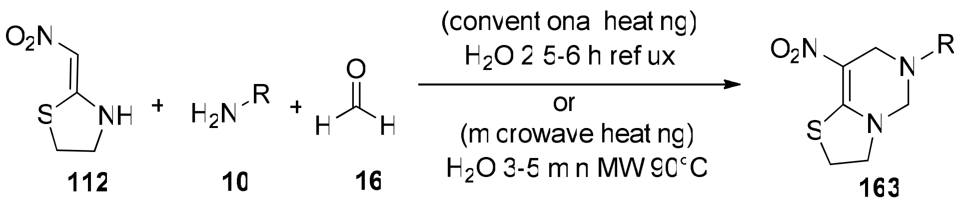
(*E*)-(4-(trifluoromethyl)cinnamoyl chloride (149f):



Following the general procedure **II** (**d, method A**), treating oxalyl chloride (0.91 mL, 1.34 g, 10.6 mmol) with a mixture of (*E*)-*p*-bromocinnamic acid (1.15 g, 5.31 mmol) and *N*,*N*-dimethylformamide (3-4 drops) in dry CH_2Cl_2 (25 mL) at 0^{o}C under N_2 atmosphere for 4 hours to give **149f** (1.26 g), yield: quantitative. green-yellow solid. m.p. 229-230˚C. R_f: 0.50 (ethyl acetate-n-hexane; 2:1). IR (KBr): ν_{max}/cm^{-1} = 3064 (-C=CH), 2920 (arom. C-H), 1739 (C=O), 1621 (C=C), 1415, 1323, 1166, 1118, 1066, 977, 825, 655 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): *δ* 7.74 (dd, 2H, *J* = 8.8, 5.6 Hz), 7.56 (d, 1H, *J* = 16.0 Hz), 7.22 (t, 2H, *J* = 8.8 Hz), 6.47 (d, 1H, *J* = 16.0 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): *δ* 116.2, 116.4, 119.5, 130.9, 131.3, 143.1, 162.3-164.8 (C-F carbon, *J*=246.6 Hz), 167.9 (C=O).

3.1.2 SYNTHESIS OF TARGET PRODUCTS

3.1.2.1 General Procedures for the Preparation of Thiazolo[3,2-*c*] pyrimidine Derivatives (163)



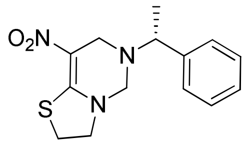
3.1.2.1.1 General Procedure (conventional heating)

2-(Nitromethylene)thiazolidine **112** (0.5 mmol, 1.0 equiv) and a primary amine **10** (0.5 mmol, 1.0 equiv.) were dissolved in water (20 mL) and the resulting suspension was stirred for 5 min. Formaldehyde **16** (37 % v/v solution in water, 1.0 mmol, 2.0 equiv.) was added dropwise by syringe and the resulting mixture was refluxed for 2-6 h under an argon atmosphere. The reaction progress was followed by TLC and upon completion, the reaction mixture was cooled to ambient temperature. The resulting precipitate was filtered off using a sintered funnel and washed with water (2 x 10 mL). After drying, the crude products were purified by flash column chromatography on silica gel, using the mixtures of EtOAc and hexanes specified, to afford the title compound **163** in a pure state.

3.1.2.1.2 General Procedure (microwave heating)

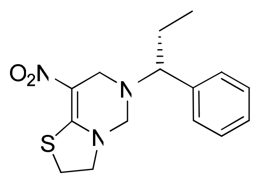
2-(Nitromethylene)thiazolidine **112** (0.5 or 0.25 mmol, 1.0 equiv), a primary amine **10** (0.5 or 0.25 mmol, 1.0 equiv.) and formaldehyde **16** (37 % v/v solution in water, 1.0 or 0.5 mmol, 2.0 equiv.) were mixed in water (2 mL) and the resulting suspension was pre-stirred for 1 min in a microwave reactor prior to reaction. Then the reaction mixture was heated at exactly 90 °C in the dynamic mode for 4-6 min. The reaction progress was followed by TLC every 2 minutes and upon completion, reaction was stopped by cooling the microwave system to 50°C by external vacuum system. The same work-up procedure as in the conventional heating reactions was applied and products **163** were isolated in a pure state.

(R)-(+)-8-Nitro-6-(1-phenylethyl)-3,5,6,7-tetrahydro-*2H*-thiazolo[3,2-*c*] pyrimidine (163a)



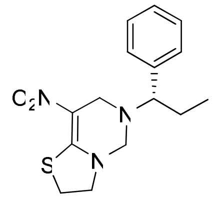
Flash chromatography (50% hexane/EtOAc) afforded yellow crystals. (135 mg, 100 % with MW; 124 mg, 92% with conv. heating), m.p. 156 - 157 °C; R_f (50% EtOAc/hexane) 0.60; $[\alpha]_D^{20}$ +24.3 (*c* 1.0, $CHCl_3$);ν_{max}(KBr) 3026 (arom. C-H), 2972 (C-H), 2854, 1552 (C=C-NO_2), 1452, 1350, 1253, 1190, 1149, 1020, 748, 702 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.27 - 7.36 (5H, m, Ph), 4.20 (1H, d, *J* 12.0 Hz) , 4.12 (1H, d, *J* 16.4 Hz), 3.95 (2H, dd, *J* 18.8, 12.4 Hz), 3.67-3.74 (2H, m), 3.59 (1H, quartet, *J* 8.7 Hz), 3.15 (2H, t, *J* 7.6 Hz), 1.42 (3H, d, *J* 6.4 Hz); δ_C (100 MHz, $CDCl_3$) 21.7, 28.1, 46.4, 54.1, 59.5, 65.2, 115.1, 127.4, 128.0, 129.0, 143.4, 162.2; *m/z* (TOF-MS ES^+) 292 (100, MH^+), 291 (1), 235 (3), 134 (3%); HRMS (TOF-MS ES^+): MH^+, found 292.1120. $C_{14}H_{18}N_3O_2$ Srequires 292.1120.

(R)-(+)-8-Nitro-6-(1-phenylpropyl)-3,5,6,7-tetrahydro-*2H*-thiazolo[3,2-*c*] pyrimidine (163b)



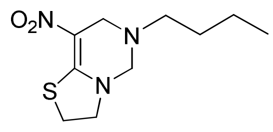
Flash chromatography (33% hexane/EtOAc) afforded yellow crystals. (144 mg, 95% with MW; 106 mg with conv. heating), m.p. 184-185°C; R_f (50% EtOAc/hexane) 0.55; $[\alpha]_D^{20}$ +33.5 (*c* 1.0, $CHCl_3$); ν_{max}(KBr) 3026 (arom. C-H), 2964 (C-H), 2874, 1552 (C=C-NO_2), 1483, 1352, 1257, 1180, 1147, 1091, 956, 916, 868, 743, 704 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.23 - 7.36 (5H, m, Ph), 4.18 (1H, dd, *J* 16.0, 1.2 Hz), 4.16 (1H, d, *J* 12.0 Hz), 3.95 (2H, dd, *J* 14.0, 1.6 Hz), 3.64 (1H, dt, *J* 10.8, 8.0 Hz), 3.50 (1H, dt, *J* 10.4, 8.0), 3.45 (1H, q, *J* 4.6 Hz), 3.10 (2H, t, *J* 8.0 Hz), 1.96 - 2.00 (1H, m), 1.69 - 1.80 (1H, m), 0.67 (3H, t, *J* 7.4 Hz);δ_C (100 MHz, $CDCl_3$) 10.8, 26.9, 28.0, 46.3, 54.0, 65.4, 66.3, 115.2, 128.1, 128.4, 128.8, 140.7, 162.1; *m/z* (TOF-MS ES$^+$) 305 (100, MH$^+$), 243 (1), 159 (2), 148 (5), 119 (2%); HRMS (TOF-MS ES$^+$): MH$^+$, found 306.1276. $C_{15}H_{20}N_3O_2S$ requires 306.1268.

(S)-(-)-8-Nitro-6-(1-phenylpropyl)-3,5,6,7-tetrahydro-*2H*-thiazolo[3,2-*c*] pyrimidine (163c)



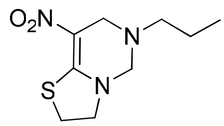
Flash chromatography (33% hexane/EtOAc) afforded yellow crystals. (79 mg, 100 % with MW; 143 mg, 94 % with conv. heating).m.p. 187-188°C; R_f (50% hexane/EtOAc) 0.45; $[\alpha]_D^{20}$ -32.8 (*c* 1.0, $CHCl_3$);ν_{max}(KBr) 3030 (arom. C-H), 2962 (C-H), 2850, 1550 (C=C-NO_2), 1481, 1383, 1253, 1176, 1150, 1012, 740, 703 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.23 - 7.36 (5H, m, Ph), 4.16 (2H, dd, *J* 16.4, 8.4 Hz), 3.96 (2H, dd, *J* 13.2, 2.4 Hz), 3.64 (1H, dt, *J* 10.8, 8.0 Hz), 3.51 (1H, dt, *J* 10.8, 8.0 Hz), 3.44 (1H, dd, *J* 9.6, 4.4 Hz), 3.10 (1H, t, *J* 8.0 Hz), 1.94 - 2.01 (1H, m), 1.69 - 1.80 (1H, m), 0.67 (3H, t, *J* 7.2 Hz);δ_C (100 MHz, $CDCl_3$) 10.5, 26.7, 27.8, 46.1, 53.7, 65.1, 66.1, 114.9, 127.8, 128.1, 128.6, 140.4, 161.8; *m/z* (TOF-MS ES$^+$) 306 (100, MH$^+$), 297 (5), 148 (5%); HRMS (TOF-MS ES$^+$): MH$^+$, found 306.1256. $C_{15}H_{20}N_3O_2S$ requires 306.1276.

6-Butyl-8-nitro-3,5,6,7-tetrahydro-*2H*-thiazolo[3,2-*c*]pyrimidine (163d)



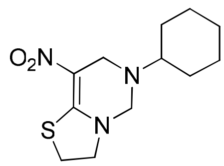
Flash chromatography (25% hexane/EtOAc) afforded a yellow powder. (78 mg, 65% with MW; 49 mg with conv.heating). m.p. 124-125°C; R_f (50% hexane/EtOAc) 0.40; ν_{max}(KBr) 2949, 2926 (C-H), 2854, 1552 (C=C-NO_2), 1462, 1359, 1280, 1188, 1151, 1128, 1018, 985, 958, 744, 665, 607 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 4.15 (2H, s), 3.89 (2H, s), 3.81 (2H, t, *J* 8.0 Hz), 3.19 (2H, t, *J* 8.0 Hz), 2.54 (2H, t, *J* 7.4 Hz), 1.51 (2H, p, *J* 7.4 Hz), 1.35 (2H, sextet, *J* 7.6 Hz), 0.92 (3H, t, *J* 7.2 Hz); δ_C (100 MHz, $CDCl_3$) 14.1, 20.5, 28.0, 30.2, 48.3, 53.1, 54.3, 67.7, 115.1, 162.1; *m/z* (TOF-MS ES$^+$) 244 (100, MH$^+$), 228 (1), 159 (8), 61 (1%); HRMS (TOF-MS ES$^+$): MH$^+$, found 244.1125. $C_{10}H_{18}N_3O_2S$requires 244.1120.

8-Nitro-6-propyl-3,5,6,7-tetrahydro-*2H*-thiazolo[3,2-*c*]pyrimidine (163e)



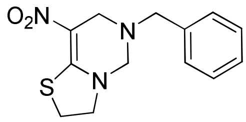
Flash chromatography (25% hexane/EtOAc) afforded a yellow solid. (38 mg, 65% with MW; (0.5 mmol) 40 mg, 35% with conv. heating). m.p. 132-133°C; R_f (50% hexane/EtOAc) 0.30; ν_{max}(KBr) 2960 (C-H), 2933, 2874, 1550 (C=C-NO_2), 1383, 1359, 1249, 1186, 1130, 1018, 744, 665 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 4.16 (2H, s), 3.89 (2H, s), 3.81 (2H, t, *J* 7.6 Hz), 3.19 (2H, t, *J* 8.0 Hz), 2.51 (2H, t, *J* 7.2 Hz), 1.55 (2H, p, *J* 7.6 Hz), 0.93 (3H, t, *J* 7.2 Hz); δ_C (100 MHz, $CDCl_3$) 11.6, 21.1, 27.8, 48.0, 54.1, 55.0, 67.6, 115.0, 161.4; *m/z* (TOF-MS ES^+) 230 (100, MH^+), 159 (10%); HRMS (TOF-MS ES^+): MH^+, found 230.0954.$C_9H_{16}N_3O_2S$requires 230.0963.

6-Cyclohexyl-8-nitro-3,5,6,7-tetrahydro-2H-thiazolo[3,2-*c*]pyrimidine (163f)



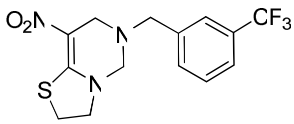
Flash chromatography (33% hexane/EtOAc) afforded a yellow solid. (67.5 mg, 100 % with MW; (0.5 mmol) 110 mg, 82% with conv. heating). m.p. 138-139 °C; R_f (50% hexane/EtOAc) 0.30; ν_{max}(KBr) 2931 (C-H), 2856, 1550 (C=C-NO_2), 1450, 1357, 1263, 1188, 1153, 1020, 738, 665 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 4.26 (2H, s), 4.00 (2H, s), 3.81 (2H, t, *J* 7.6 Hz), 3.19 (2H, t, *J* 7.6 Hz), 2.50 - 2.58 (1H, m), 1.88 - 1.90 (2H, m), 1.78 - 1.81 (2H, m), 1.62 (1H, d, *J* 12.0 Hz), 1.12 - 1.31 (5H, m); δ_C (100 MHz, $CDCl_3$) 25.5, 25.9, 28.1, 31.0, 45.5, 54.0, 59.7, 64.6, 116.0, 162.6; *m/z* (TOF-MS ES^+) 270 (100, MH^+), 218 (3), 112 (5%); HRMS (TOF-MS ES^+): MH^+, found 270.1260. $C_{12}H_{20}N_3O_2S$requires 270.1276.

6-Benzyl-8-nitro-3,5,6,7-tetrahydro-*2H*-thiazolo[3,2-*c*]pyrimidine (163g)



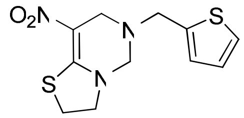
Flash chromatography (33% hexane/EtOAc) afforded a yellow powder. (65 mg, 95 % with MW; 90 mg, 65% with conv. heating).m.p. 132 - 133°C; R_f (50% hexane/EtOAc) 0.45; ν_{max}(KBr) 3028 (arom. C-H), 2922 (C-H), 2854, 1554 (C=C-NO_2), 1473, 1350, 1251, 1188, 1143, 1024, 742, 700 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.27- 7.37 (5H, m, Ph), 4.10 (2H, s), 3.96 (2H, s), 3.75 (2H, t, *J* 8.4 Hz), 3.72 (2H, s), 3.20 (2H, t, *J* 7.8 Hz); δ_C (100 MHz, $CDCl_3$) 28.1, 48.8, 54.2, 57.6, 66.3, 115.1, 128.1, 128.9, 129.2, 137.3, 161.6; *m/z* (TOF-MS ES^+) 278 (100, MH^+), 276 (1), 228 (2), 120 (3%); HRMS (TOF-MS ES^+): MH^+, found 278.0958. $C_{13}H_{16}N_3O_2S$ requires 278.0963.

8-Nitro-6-(3-(trifluoromethyl)benzyl)-3,5,6,7-tetrahydro-*2H*-thiazolo[3,2-*c*]pyrimidine (163h)



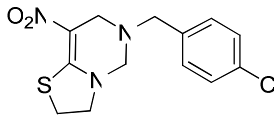
Flash chromatography (25% hexane/EtOAc) afforded yellow crystals. (84 mg, 98 % with MW; 133 mg, 77% with conv. heating). m.p. 181-182 °C; R_f (33% hexane/EtOAc) 0.50; ν_{max}(KBr) 2926 (C-H), 2856, 1552 (C=C-NO_2), 1489, 1460, 1357, 1327, 1286, 1251, 1188, 1118, 1147, 1072, 987, 792, 700 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 7.72 (1H, s), 7.65 (2H, d, *J* 7.2 Hz), 7.59 (1H, t, *J* 7.6 Hz), 4.29 (2H, s), 3.85 (2H, t, *J* 8.0 Hz), 3.80 (2H, s), 3.74 (2H, s), 3.23 (2H, t, *J* 8.0 Hz); δ_C (100 MHz, DMSO-d_6) 28.1, 47.9, 54.5, 56.3, 67.1, 112.8, 122.8, 124.0, 124.8, 125.5, 129.3, 132.5, 139.5, 161.5; *m/z* (TOF-MS ES^+) 346 (100, MH^+), 254 (10), 246 (3), 145 (1%); HRMS (TOF-MS ES^+): MH^+, found 346.0841. $C_{14}H_{15}F_3N_3O_2S$requires 346.0837.

8-Nitro-6-(thiophen-2-ylmethyl)-3,5,6,7-tetrahydro-*2H*-thiazolo[3,2-*c*] pyrimidine (163i)



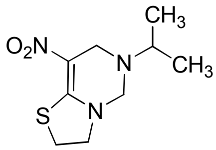
Flash chromatography (25-33% hexane/EtOAc)afforded a yellow solid. (56 mg, 80 % with MW; 99 mg, 70% with conv. heating). m.p. 173- 174 °C; R_f (33% hexane/EtOAc) 0.40; ν_{max}(KBr) 3097 (arom. C-H), 2922 (C-H), 2854, 1550 (C=C-NO_2), 1467, 1357, 1286, 1184, 1143, 1122, 1022, 977, 850, 742, 707 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.29 (1H, dd, *J* 5.2, 1.6 Hz), 6.94 - 6.97(2H, m), 4.15 (2H, s), 4.00 (2H, s), 3.93 (2H, s), 3.76 (2H, t, *J* 7.6 Hz), 3.20 (2H, t, *J* 7.8 Hz); δ_C (100 MHz, $CDCl_3$) 28.1, 48.5, 52.1, 54.2, 65.8, 114.9, 126.2, 127.0, 127.1, 140.6, 161.6; *m/z* (TOF-MS ES^+) 284 (100, MH^+), 231 (2), 159 (5%); HRMS (TOF-MS ES^+): MH^+, found 284.0525. $C_{11}H_{14}N_3O_2S$requires 284.0527.

6-(4-Chlorobenzyl)-8-nitro-3,5,6,7-tetrahydro-*2H*-thiazolo[3,2-*c*] pyrimidine (163j)



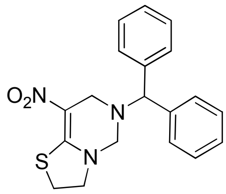
Flash chromatography (25% hexane/EtOAc) afforded a yellow solid. (63 mg, 80% with MW; 98 mg, 63% with conv. heating). m.p. 174-175 ^{o}C; R_f (33% hexane/EtOAc) 0.40; ν_{max}(KBr) 2922 (C-H), 2852, 1552 (C=C-NO_2), 1481, 1450, 1350, 1251, 1188, 1143, 1014, 802, 665 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.32 (2H, d, *J* 8.8 Hz), 7.26 (2H, d, *J* 8.8 Hz), 4.10 (2H, s), 3.92 (2H, s), 3.75 (2H, t, *J* 7.6 Hz), 3.70 (2H, s), 3.20 (2H, t, *J* 7.6 Hz); δ_C (100 MHz, $CDCl_3$) 28.0, 48.6, 54.2, 56.8, 66.4, 115.0, 129.1 130.4, 133.8, 135.8, 161.6; *m/z* (TOF-MS ES^+) 312 (100, MH^+), 257 (3), 230 (3), 156 (2%); HRMS (TOF-MS ES^+): MH^+, found 312.0563. $C_{13}H_{15}ClN_3O_2S$requires 312.0574

6-Isopropyl-8-nitro-3,5,6,7-tetrahydro-2H-thiazolo[3,2-*c*]pyrimidine (163k)



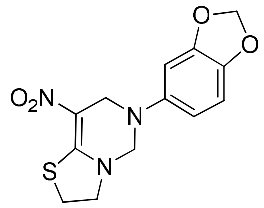
Flash chromatography (33% hexane/EtOAc) afforded a yellow solid. (58 mg, 100 % with MW;89 mg, 78% with conv. heating). m.p. 128- 129 °C; R_f (33% hexane/EtOAc) 0.10-0.20; ν_{max}(KBr) 2970 (C-H), 2926, 2868, 1550 (C=C-NO_2), 1460, 1377, 1278, 1255, 1188, 1151, 1122, 1014, 748, 693cm^{-1}; δ_H (400 MHz, $CDCl_3$) 4.23 (2H, s), 3.83 (2H, t, *J* 8.0 Hz), 3.75 (2H, s), 3.17 (2H, t, *J* 8.4 Hz), 2.80 (1H, septet, *J* 6.4 Hz), 1.00 (6H, d, *J* 6.0 Hz); δ_C (100 MHz, $CDCl_3$) 21.1, 28.1, 45.5, 51.0, 54.3, 64.7, 114.7, 162.9; *m/z* (TOF-MS ES$^+$) 230 (100, MH$^+$), 188 (1), 159 (2%); HRMS (TOF-MS ES$^+$): MH$^+$, found 230.0957. $C_9H_{16}N_3O_2S$ requires 230.0963.

6-Benzhydryl-8-nitro-3,5,6,7-tetrahydro-2H-thiazolo[3,2-*c*]pyrimidine (163l)



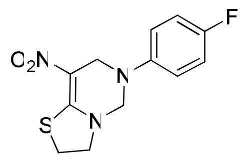
Flash chromatography (33% hexane/EtOAc) afforded yellow crystals. (89 mg, 100 % with MW;123 mg, 70% with conv. heating). m.p. 184- 185°C; R_f (EtOAc) 0.70-0.75; ν_{max}(KBr) 3026 (arom. C-H), 2922 (C-H), 2856, 1552 (C=C-NO_2), 1477, 1448, 1390, 1356, 1253, 1192, 1145, 1020, 748, 707 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.44 (4H, d, *J* 7.2 Hz), 7.29 (4H, t, *J* 7.2 Hz), 7.21 (2H, tt, *J* 7.2, 1.2 Hz), 4.67 (1H, s), 4.08 (2H, s), 3.77 (2H, s), 3.53 (2H, t, *J* 7.6 Hz), 3.19 (2H, t, *J* 8.0 Hz); δ_C (100 MHz, $CDCl_3$) 28.2, 46.9, 54.4, 64.8, 68.8, 113.5, 115.0, 128.1, 128.2, 129.4, 130.6, 142.4, 162.7; *m/z* (TOF-MS ES$^+$) 354 (100, MH$^+$), 278 (5), 258 (5), 250 (2), 193 (5%); HRMS (TOF-MS ES$^+$): MH$^+$, found 354.1262. $C_{19}H_{20}N_3O_2S$ requires 354.1276.

6-(Benzo[*d*][1,3]dioxol-5-yl)-8-nitro-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*] pyrimidine (163m)



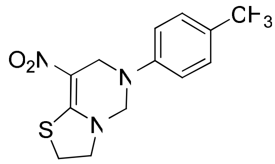
Flash chromatography (33% hexane/EtOAc) afforded yellow crystals. (55 mg, 72 % with MW; (64 mg, 42% with conv. heating). m.p. 182 - 183°C; R_f (33% hexane/EtOAc) 0.40-0.50; ν_{max}(KBr) 3015 (arom. C-H), 2928 (C-H), 2895, 1550 (C=C-NO_2), 1483, 1382, 1357, 1246, 1197, 1149, 1120, 1031, 950, 748, 665 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.77 (1H, d, *J* 5.6 Hz), 6.75 (1H, s), 6.35 (1H, dd, *J* 8.0, 2.4 Hz), 5.92 (2H, s, -O-CH_2-O-), 4.79 (2H, s), 4.32 (2H, s), 3.87 (2H, t, *J* 8.0 Hz), 3.16 (2H, t, *J* 8.4 Hz); δ_C (100 MHz, $CDCl_3$) 28.1, 48.0, 54.3, 65.3, 101.3, 101.6, 108.8, 110.3, 114.4, 142.6, 143.8, 148.7, 163.2; *m/z* (TOF-MS ES^+) 308 (100, MH^+), 255 (12), 235 (10), 227 (5), 150 (20%); HRMS (TOF-MS ES^+): MH^+, found 308.0693. $C_{13}H_{14}N_3O_4S$ requires 308.0705.

6-(4-Fluorophenyl)-8-nitro-3,5,6,7-tetrahydro-2H-thiazolo[3,2-*c*] pyrimidine (163n)



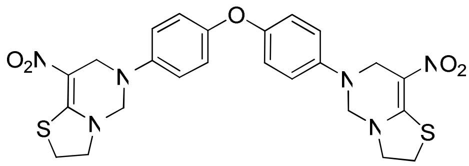
Flash chromatography (33% hexane/EtOAc) afforded a pale orange solid. (50 mg, 76 % with MW; 82 mg, 58% with conv. heating). m.p. 185 - 186°C; R_f (50% hexane/EtOAc) 0.35-0.40; ν_{max}(KBr) 3015 (arom. C-H), 2924 (C-H), 2852, 1548 (C=C-NO_2), 1508, 1356, 1280, 1251, 1201, 1147, 1122, 1068, 1006, 746, 665 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.04 - 7.13 (4H, m, Ph), 4.89 (2H, s), 4.14 (2H, s), 3.92 (2H, t, *J* 8.4 Hz), 3.19 (2H, t, *J* 8.0 Hz); δ_C (100 MHz, $CDCl_3$) 28.1, 47.7, 54.4, 64.8, 114.3, 116.3 - 116.5 (α-C to C- F, *Jortho* = 22 Hz), 119.8 -119.9 (β-C to C-F, *Jmeta* = 10 Hz), 145.13 - 145.15 (quarter.C in Ph ring, *Jpara* = 2.2 Hz), 158.5 - 158.9 (C-F carbon, *J* = 232 Hz), 163.3; *m/z* (TOF-MS ES^+) 282 (100, MH^+), 222 (35), 214 (12), 208 (3%); HRMS (TOF-MS ES^+): MH^+, found 282.0700. $C_{12}H_{13}FN_3O_2S$ requires 282.0713.

8-Nitro-6-(4-methylphenyl)-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*] pyrimidine (163o)



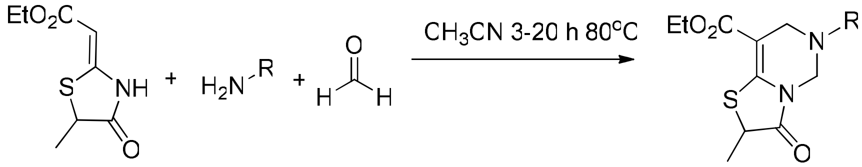
Flash chromatography (33% hexane/EtOAc) afforded bright yellow crystals. (35 mg, 55 % with MW; 44 mg, 32% with conv. heating).m.p. 194 - 195°C; R_f (EtOAc) 0.55 - 0.45; ν_{max}(KBr) 3032 (arom. C-H), 2922 (C-H), 2856, 1550 (C=C-NO_2), 1512, 1450, 1356, 1278, 1251, 1201, 1145, 1124, 1070, 815, 748 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.03 (2H, d, *J* 8. 0 Hz), 6.88 (2H, d, *J* 8.4 Hz), 4.84 (2H, s), 4.36 (2H, s), 3.87 (2H, t, *J* 8.0 Hz), 3.13 (2H, t, *J* 8.0 Hz), 2.16 (3H, s); δ_C (100 MHz, $CDCl_3$) 20.7, 28.1, 47.3, 54.4, 64.6, 114.4, 118.0, 130.4, 130.7, 146.1, 163.2; *m/z* (TOF-MS ES^+) 278 (100, MH^+), 207 (23), 173 (4), 143 (10), 122 (15%). HRMS (TOF-MS ES^+): MH^+, found 278.0956. $C_{13}H_{16}N_3O_2S$requires 278.0963

6,6'-(4,4'-Oxybis(4,1-phenylene))bis(8-nitro-3,5,6,7-tetrahydro-2H-thiazolo[3,2-*c*]pyrimidine) (163ax)



Flash chromatography (25% hexane/EtOAc) afforded bright yellow crystals. (135 mg, 100 % with MW; 256 mg, 95% with conv. heating).m.p. 188 °C (decomp.); R_f (33% hexane/EtOAc) 0.20 - 0.30; ν_{max}(KBr) 3053 (arom. C-H), 2987 (C-H), 2870, 1550 (C=C-NO_2), 1502 (C-O-C), 1450, 1356, 1263, 1203, 1149, 1122, 1068, 731, 665 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.03 (2x2H, d, *J* 9.2 Hz), 6.89 (2x2H, d, *J* 8.8 Hz), 4.86 (2x2H, s), 4.40 (2x2H, s), 3.92 (2x2H, t, *J* 8.0 Hz), 3.20 (2x2H, t, *J* 8.0 Hz). δ_C (100 MHz, $CDCl_3$) 28.1, 47.9, 54.3, 64.6, 114.4, 119.7, 119.9, 144.3, 152.0, 163.3; *m/z* (TOF-MS ES^+) 541 (100, MH^+), 331 (45), 302 (15), 174 (5%); HRMS (TOF-MS ES^+): MH^+, found 541.1317. $C_{24}H_{25}N_6O_5S_2$ requires 541.1328.

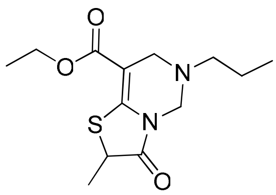
3.1.2.2 General procedure for the preparation of 6-substituted-3-oxothiazolo[3,2-*c*]pyrimidine-8-carboxylates (259)



116 10 16 259

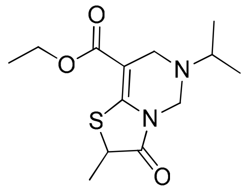
(*Z*)-ethyl 2-(5-methyl-4-oxothiazolidin-2-ylidene) acetate **116** (0.5 mmol), aliphatic or aromatic primary amine **10** (0.5 mmol, 1.0 equiv.) were dissolved in CH_3CN (15-20 mL) and the resulting mixture was stirred for 5 min at ambient temperature. Formalin **16** (37% v/v solution in water, 1.0 mmol, 2.0 equiv.) was added dropwise by syringe and the resulting mixture was refluxed for 3-20 h under inert atmosphere. The reaction progress was followed by TLC and upon completion, the solvent was concentrated under reduced pressure. The remaining pale yellow crude oil or solid was purified by flash column chromatography on silica gel, using the mixtures of EtOAc and hexanes specified, to afford the title compound **259** in a very pure state and good yields.

Ethyl 2-methyl-3-oxo-6-propyl-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*] pyrimidine-8-carboxylate (259a)



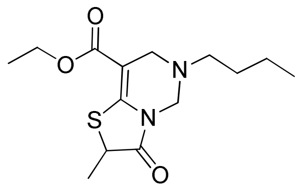
Pale yellow oil, 73(%), R_f (25% EtOAc / hexane) 0.50; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.50 (q, J = 12.4Hz, 2H, CH_2), 4.22 (q, J = 7.2Hz, 2H, CH_2), 3.89 (q, J = 7.6Hz, 1H, CH), 3.60 (s, 2H, CH_2), 2.43 (t, J =7.6Hz, 2H, CH_2), 1.62 (d, J = 7.2 Hz, 3H), 1.52 (q, J = 7.2Hz, 2H, CH_2), 1.30 (t, J = 7.2 Hz, 3H, CH_3), 0.91 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.5, 168.5, 147.5, 97.9, 63.2, 60.3, 54.2, 49.4, 41.3, 21.0, 19.1, 14.4, 11.6; IR (ATR-mode) υ: 2970, 2933, 2872, 1708, 1683, 1577, 1450, 1253, 1220, 1109, 1031, 761, 682 cm^{-1}; HRMS (ESI$^+$) Calcd. for $C_{13}H_{21}N_2O_3S$ ($[M+H]^+$): 285.1273. Found: 285.1279.

Ethyl 6-isopropyl-2-methyl-3-oxo-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*] pyrimidine-8-carboxylate (259b)



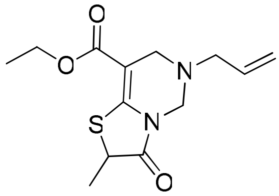
Pale yellow oil, 92(%), R_f (25% EtOAc / hexane) 0.63; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.55 (q, J = 12.4Hz, 2H, CH_2), 4.23 (q, J = 7.2Hz, 2H, CH_2), 3.88 (q, J = 7.2Hz, 1H, CH), 3.66 (s, 2H, CH_2), 2.85 (sep, J = 6.4Hz, 1H, CH), 1.59 (d, J = 7.2 Hz, 3H, CH_3), 1.30 (t, J = 7.2 Hz, 3H, CH_3), 1.12 (s, 3H, CH_3), 1.10 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.0, 166.3, 148.0, 98.9, 60.6, 60.3, 50.3, 46.6, 41.4, 20.5, 19.0, 14.4; IR (ATR-mode) υ: 2976, 2929, 1705, 1681, 1577, 1462, 1259, 1228, 1118, 1031, 761 cm^{-1}; HRMS (ESI$^+$) Calcd. for $C_{13}H_{21}N_2O_3S$ ($[M+H]^+$): 285.1273. Found: 285.1264.

Ethyl 6-butyl-2-methyl-3-oxo-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*]pyrimidine-8-carboxylate (259c)



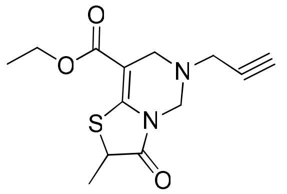
Pale yellow oil, 90(%), R_f (25% EtOAc / hexane) 0.45; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.50 (q, J = 12.4Hz, 2H, CH_2), 4.23 (q, J = 7.2Hz, 2H, CH_2), 3.89 (q, J = 7.6Hz, 1H, CH), 3.60 (s, 2H, CH_2), 2.46 (t, J = 7.2Hz, 2H, CH_2), 1.60 (d, J = 7.2 Hz, 3H), 1.47 (q, J = 7.6Hz, 2H, CH_2), 1.36-1.24 (m, 5H), 0.91 (t, J = 7.6 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.3, 166.5, 147.4, 97.9, 63.2, 60.3, 52.0, 49.4, 41.3, 29.8, 20.2, 19.1, 14.4, 13.8; IR (ATR-mode) υ: 2956, 2931, 2864, 1708, 1683, 1577, 1450, 1255, 1213, 1138, 1033, 763, 682 cm^{-1}; HRMS (ESI$^+$) Calcd. for $C_{14}H_{23}N_2O_3S$ ($[M+H]^+$): 299.1429. Found: 299.1416.

Ethyl 6-allyl-2-methyl-3-oxo-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*]pyrimidine-8-carboxylate (259d)



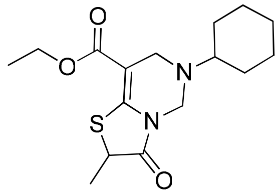
Colorless oil, 100(%), R_f (25% EtOAc / hexane) 0.70; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.88-5.80 (m, 1H, allylic H), 5.25-5.22 (m, 2H, allyl.H), 4.53 (d, J = 12.4Hz, 1H, CH), 4.49 (d, J = 12.0Hz, 1H, CH), 4.23 (q, J = 7.2Hz, 2H, CH_2), 3.89 (q, J = 7.2Hz, 1H, CH), 3.63 (s, 2H, CH_2), 3.12 (dt, J = 6.4, 1.2 Hz, 2H, CH_2) 1.61 (d, J = 7.5 Hz, 3H, CH_3), 1.29 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.4, 166.5, 147.5, 133.9, 119.1, 97.6, 62.6, 60.3, 55.6, 49.1, 41.3, 19.1, 14.4; IR (ATR-mode) υ: 3076, 2978, 2931, 1705, 1681, 1577, 1450, 1253, 1215, 1107, 1031, 925, 848, 763 cm^{-1}; HRMS (ESI$^+$) Calcd. for $C_{13}H_{19}N_2O_3S$ *(*[M+H]$^+$*)*: 283.1116. Found: 283.1123.

Ethyl 2-methyl-3-oxo-6-(prop-2-yn-1-yl)-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*]pyrimidine-8-carboxylate (259e)



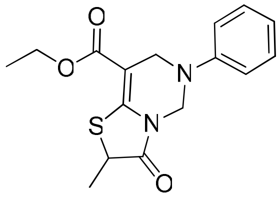
Colorless oil, 100(%), R_f (25% EtOAc / hexane) 0.69; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.58 (q, J = 11.6Hz, 2H, CH_2), 4.24 (q, J = 7.2Hz, 2H, CH_2), 3.90 (q, J = 7.2Hz, 1H, CH), 3.70 (s, 2H, CH_2), 3.43 (d, J = 6.4Hz, 1H, CH), 2.31 (t, J = 1.8Hz, 1H, acetylenic CH), 1.61 (d, J = 7.2 Hz, 3H, CH_3), 1.31 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.2, 166.2, 147.4, 97.4, 78.2, 73.6, 62.0, 60.4, 49.0, 42.2, 41.3, 19.0, 14.4; IR (ATR-mode) υ: 3263, 2976, 2931, 1705, 1680, 1577, 1328, 1251, 1215, 1109, 1031, 842, 763 cm^{-1}; HRMS (ESI$^+$) Calcd. for $C_{13}H_{17}N_2O_3S$ *(*[M+H]$^+$*)*: 281.0960. Found: 281.0958.

Ethyl 6-cyclohexyl-2-methyl-3-oxo-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*] pyrimidine-8-carboxylate (259f)



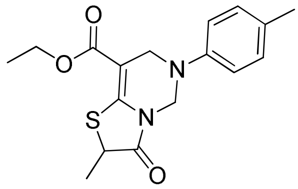
Pale yellow solid, 92(%), m.p. 86–87°C, R_f (33% EtOAc / hexane) 0.50; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.59 (q, J = 12.4Hz, 2H, CH_2), 4.23 (q, J = 7.2Hz, 2H, CH_2), 3.88 (q, J = 7.2Hz, 1H, CH), 3.70 (s, 2H, CH_2), 2.46-2.49 (m, 1H, CH), 1.84 (s, 2H, CH_2), 1.76 (s, 2H, CH_2), 1.59 (d, J = 7.6 Hz, 3H, CH_3), 1.30 (t, J = 7.2 Hz, 3H, CH_3), 1.24-1.07 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.0, 166.3, 148.1, 99.1, 60.4, 60.3, 58.4, 46.5, 41.4, 30.7, 25.7, 25.2, 19.0, 14.4; IR (ATR-mode) υ: 2976, 2929, 2854, 1705, 1673, 1581, 1477, 1259, 1105, 1031, 753, 732 cm^{-1}; HRMS (ESI$^+$) Calcd. for $C_{16}H_{25}N_2O_3S$ *([M+H]$^+$)*: 325.1586. Found: 325.1599.

Ethyl 2-methyl-3-oxo-6-phenyl-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*] pyrimidine-8-carboxylate (259g)



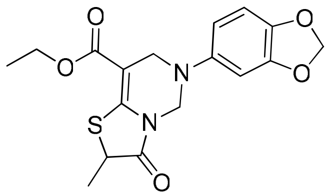
Pale yellow solid, 100(%), m.p. 89–90°C, R_f (25% EtOAc / hexane) 0.30; ^{1}H NMR (400 MHz, $CDCl_3$) δ : 7.28-7.24 (m, 2H, ArH), 6.96-6.93 (m, 3H, ArH), 5.17 (d, J = 13.2Hz, 1H, CH), 5.06 (d, J = 13.2Hz, 1H, CH), 4.29-4.23 (m, 4H, 2xCH_2), 3.87 (q, J = 7.2Hz, 1H, CH), 1.58 (d, J = 7.2 Hz, 3H, CH_3), 1.32 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.1, 165.9, 148.3, 147.4, 129.4, 121.7, 117.5, 98.9, 60.6, 60.5, 48.4, 41.3, 18.9, 14.4; IR (ATR-mode) υ: 2980, 2916, 1705, 1674, 1573, 1496, 1361, 1263, 1222, 1122, 1066, 1022, 887, 754 cm^{-1}; HRMS (ESI$^+$) Calcd. for $C_{16}H_{19}N_2O_3S$ *([M+H]$^+$)*: 319.1116. Found: 319.1108.

Ethyl 2-methyl-3-oxo-6-(p-tolyl)-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*] pyrimidine-8-carboxylate (259h)



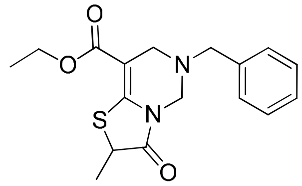
White solid, 82(%), m.p. 106–107°C, R_f (33% EtOAc / hexane) 0.81; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.06 (d, J = 8.4Hz, 2H, ArH), 6.84 (d, J = 8.8Hz, 2H, ArH), 5.13 (d, J = 12.8Hz, 1H, CH), 5.02 (d, J = 12.8Hz, 1H, CH), 4.29-4.19 (m, 4H, $2xCH_2$), 3.86 (q, J = 7.6Hz, 1H, CH), 2.26 (s, 3H, CH_3), 1.57 (d, J = 7.2 Hz, 3H, CH_3), 1.32 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.1, 166.0, 148.2, 145.1, 131.2, 129.9, 117.6, 98.9, 60.9, 60.4, 48.7, 41.3, 20.4, 18.9, 14.4; IR (ATR-mode) υ: 2980, 2922, 1708, 1672, 1577, 1512, 1265, 1226, 1124, 1024, 817, 769 cm^{-1}; HRMS (ESI^+) Calcd. for $C_{17}H_{21}N_2O_3S$ *(*$[M+H]^+$*)*: 333.1273. Found: 333.1277.

Ethyl 6-(benzo[d][1,3]dioxol-5-yl)-2-methyl-3-oxo-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*]pyrimidine-8-carboxylate (259i)



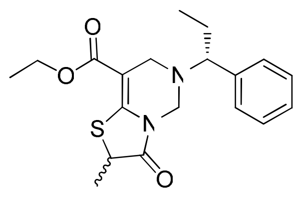
Light brown oil, 100(%), R_f (25% EtOAc / hexane) 0.90; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.67 (d, J = 8.4Hz, 1H, ArH), 6.53 (d, J = 2.4Hz, 1H, ArH), 6.34 (dd, J = 8.4, 2.4Hz, 1H, ArH), 5.90 (s, 2H, CH_2), 5.04 (d, J = 12.8Hz, 1H, CH), 4.94 (d, J = 12.8Hz, 1H, CH), 4.25 (q, J = 6.8Hz, 2H, CH_2), 4.16 (s, 2H, CH_2), 3.87 (q, J = 7.2Hz, 1H, CH), 1.58 (d, J = 7.2 Hz, 3H, CH_3), 1.31 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.1, 165.9, 148.4, 148.2, 142.8, 110.5, 108.3, 101.2, 101.1, 98.7, 90.7, 61.5, 60.8, 49.3, 41.3, 18.9, 14.4; IR (ATR-mode) υ: 2980, 2929, 1708, 1680, 1577, 1489, 1261, 1220, 1122, 1033, 798, 761, 732 cm^{-1}; HRMS (ESI^+) Calcd. for $C_{17}H_{19}N_2O_5S$ *(*$[M+H]^+$*)*: 363.1015. Found: 363.1022.

Ethyl 6-benzyl-2-methyl-3-oxo-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*] pyrimidine-8-carboxylate (259j)



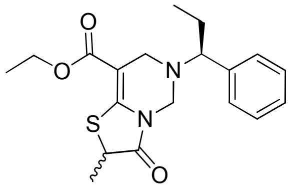
Pale yellow oil, 90(%), R_f (25% EtOAc / hexane) 0.70; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.34-7.25 (m, 5H, ArH), 4.51 (q, J = 12.3Hz, 2H, CH_2), 4.21 (q, J = 7.2Hz, 2H, CH_2), 3.91 (q, J = 7.2Hz, 1H, CH), 3.63 (s, 4H, CH_2), 1.62 (d, J = 7.5 Hz, 3H, CH_3), 1.27 (t, J = 7.2 Hz, 3H, CH_3) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 174.5, 166.5, 147.6, 137.1, 129.0, 128.5, 127.7, 97.6, 62.9, 60.3, 56.8, 49.1, 41.3, 19.1, 14.4; IR (KBr) υ: 2980, 2933, 2852, 1697, 1674, 1570, 1469, 1354, 1251, 1134, 1028, 746, 704, 682 cm^{-1}; HRMS (ESI$^+$) Calcd. for $C_{17}H_{21}N_2O_3S$([M+H]$^+$): 333.1273. Found: 333.1271.

1:1 mixture of two diastereomers: Ethyl 2-methyl-3-oxo-6-((*R*)-1-phenylpropyl)-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*]pyrimidine-8-carboxylate (259k)



Pale yellow oil, 70(%), R_f (20% EtOAc / hexane) 0.85; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.31-7.25 (m, 6H, ArH), 7.20-7.17 (m, 4H, ArH), 4.73 (d, J = 12.4Hz, 1H, CH), 4.62 (d, J = 12.3Hz, 1H, CH), 4.47 (d, J = 12.4Hz, 1H, CH), 4.39 (d, J = 12.3Hz, 1H, CH), 4.19 (q, J = 7.2Hz, 4H, 2xCH_2), 3.80 (q, J = 7.2Hz, 2H, 2xCH), 3.65 (q, J = 12.8Hz, 4H, 2xCH_2), 3.41 (dd, J = 4.8, 2.8Hz, 1H, CH), 3.39 (dd, J = 4.8, 2.8Hz, 1H, CH), 1.97-1.87 (m, 2H, CH_2), 1.80-1.70 (m, 2H, CH_2), 1.58 (d, J = 7.6 Hz, 3H, CH_3), 1.56 (d, J = 7.2 Hz, 3H, CH_3), 1.26 (t, J = 7.2 Hz, 3H, CH_3), 1.25 (t, J = 7.2 Hz, 3H, CH_3), 0.68 (t, J = 7.6 Hz, 3H, CH_3), 0.67 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.05, 174.04, 166.39, 166.38, 148.04, 148.02, 140.25, 140.20, 128.33, 128.31, 128.09, 128.06, 127.68, 127.66, 98.29, 98.26, 65.9, 65.8, 61.2, 61.1, 60.24, 60.20, 47.31,, 47.15, 41.33, 41.29, 26.36, 26.34, 18.99, 18.90, 14.45, 14.42 10.70, 10.65; IR (ATR-mode) υ: 2974, 2933, 2873, 1705, 1683, 1577, 1452, 1251, 1222, 1107, 1031, 763, 702 cm^{-1}; HRMS (ESI^+) Calcd. for $C_{19}H_{25}N_2O_3S$ ($[M+H]^+$): 361.1586. Found: 361.1585.

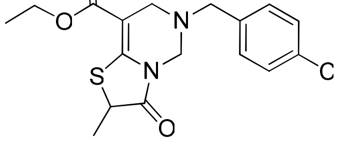
1:1 mixture of two diastereomers: Ethyl 2-methyl-3-oxo-6-((*S*)-1-phenylpropyl)-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*]pyrimidine-8-carboxylate (259l)



mixture of two diastereomers

Pale yellow oil, 65(%), R_f (25% EtOAc / hexane) 0.85; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.31-7.25 (m, 6H, ArH), 7.20-7.17 (m, 4H, ArH), 4.72 (d, J = 12.4Hz, 1H, CH), 4.62 (d, J = 12.8Hz, 1H, CH), 4.47 (d, J = 12.4Hz, 1H, CH), 4.39 (d, J = 12.4Hz, 1H, CH), 4.20 (q, J = 7.2Hz, 4H, $2xCH_2$), 3.80 (q, J = 7.2Hz, 2H, 2xCH), 3.65 (q, J = 16.0Hz, 4H, $2xCH_2$), 3.41 (dd, J = 4.8, 2.8Hz, 1H, CH), 3.39 (dd, J = 4.8, 2.8Hz, 1H, CH), 1.96-1.89 (m, 2H, CH_2), 1.78-1.71 (m, 2H, CH_2), 1.58 (d, J = 7.2 Hz, 3H, CH_3), 1.56 (d, J = 7.6 Hz, 3H, CH_3), 1.26 (t, J = 7.2 Hz, 3H, CH_3), 1.25 (t, J = 7.2 Hz, 3H, CH_3), 0.69 (t, J = 7.2 Hz, 3H, CH_3), 0.68 (t, J = 7.6 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.05, 174.04, 166.40, 166.39, 148.04, 148.02, 140.28, 140.24, 128.32, 128.30, 128.08, 128.07, 127.67, 127.66, 98.31, 98.28, 65.9, 65.8, 61.2, 61.1, 60.22, 60.20, 47.31, 47.16, 41.32, 41.30, 26.37, 26.35, 18.99, 18.90, 14.45, 14.41, 10.70, 10.65; IR (ATR-mode) υ: 2970, 2933, 2873, 1708, 1683, 1577, 1452, 1253, 1222, 1107, 1031, 763, 702 cm^{-1}; HRMS (ESI^+) Calcd. for $C_{19}H_{25}N_2O_3S$ ($[M+H]^+$): 361.1586. Found: 361.1581.

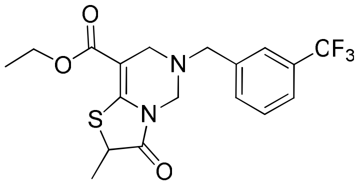
Ethyl 6-(4-chlorobenzyl)-2-methyl-3-oxo-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*] pyrimidine-8-carboxylate (259m)



White solid, 96(%), m.p. 97–98°C, R_f (33% EtOAc / hexane) 0.86; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.31-7.29 (d, J = 8.4Hz, 2H, ArH), 7.23-7.21 (d, J = 8.0Hz, 2H, ArH), 4.50 (q, J = 12.4Hz, 2H, CH_2), 4.23 (q, J = 7.2Hz, 2H, CH_2), 3.91 (q, J =

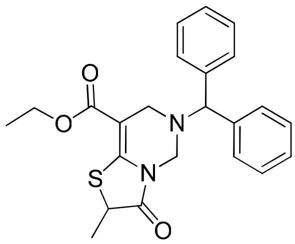
7.2Hz, 1H, CH), 3.61 (s, 2H, CH_2), 3.60 (s, 2H, CH_2), 1.63 (d, J = 7.6 Hz, 3H, CH_3), 1.27 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz,$CDCl_3$) δ: 174.5, 166.5, 147.5, 135.6, 133.5, 130.2, 128.7, 97.4, 62.9, 60.4, 56.0, 49.0, 41.3, 19.1, 14.4; IR (ATR-mode) υ: 2987, 2927, 2800, 1683, 1579, 1489, 1300, 1261, 1145, 1089, 1014, 806, 759 cm^{-1}; HRMS (ESI$^+$) Calcd. for $C_{17}H_{20}ClN_2O_3S$ ([M+H]$^+$): 367.0883. Found: 367.0894.

Ethyl 2-methyl-3-oxo-6-(3-(trifluoromethyl)benzyl)-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*]pyrimidine-8-carboxylate (259n)



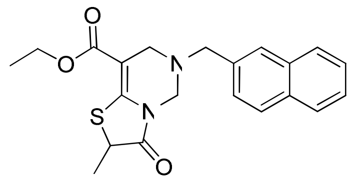
Pale yellow solid, 65(%), m.p. 93–94°C, R_f (50% EtOAc / hexane) 0.71; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.58-7.44 (m, 4H, ArH), 4.54 (q, J =12.4Hz, 2H, CH_2), 4.21 (q, J = 7.2Hz, 2H, CH_2), 3.92 (q, J = 7.2Hz, 1H, CH), 3.69 (s, 2H, CH_2), 3.62 (s, 2H, CH_2), 1.63 (d, J = 7.2 Hz, 3H, CH_3), 1.26 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz,$CDCl_3$) δ: 174.5, 166.4, 147.6, 138.2, 132.1, 132.0, 129.0, 128.9, 125.4, 124.5, 97.3, 63.1, 60.4, 56.2, 48.9, 41.3, 19.1, 14.3 (C-F coupling constants are not indicated, most intense peaks are reported); IR (ATR-mode) υ: 2995, 2908, 2858, 1708, 1676, 1573, 1452, 1327, 1253, 1163, 1120, 1070, 802, 698 cm^{-1}; HRMS (ESI$^+$) Calcd. for $C_{18}H_{20}F_3N_2O_3S$ ([M+H]$^+$): 401.1147. Found: 401.1121.

Ethyl 6-benzhydryl-2-methyl-3-oxo-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*] pyrimidine-8-carboxylate (259o)



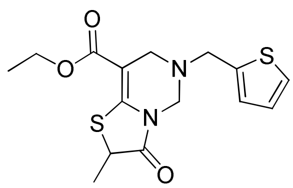
White solid, 94(%), m.p. 96–97°C, R_f (33% EtOAc / hexane) 0.72; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38-7.34 (m, 4H, ArH), 7.30-7.21 (m, 6H, ArH), 4.58 (s, 1H, CH), 4.49 (q, J = 12.4Hz, 2H, CH_2), 4.12 (q, J = 7.2Hz, 2H, CH_2), 3.87 (q, J = 7.2Hz, 1H, CH), 3.65 (s, 2H, CH_2), 1.61 (d, J = 7.2 Hz, 3H, CH_3), 1.15 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.9, 166.5, 148.0, 141.1, 128.7, 127.7, 127.6, 97.5, 68.0, 61.5, 60.1, 47.9, 41.2, 19.1, 14.3; IR (ATR-mode) υ: 3061, 2972, 2935, 1716, 1672, 1579, 1452, 1253, 1138, 1026, 763, 744 cm^{-1}; HRMS (ESI$^+$) Calcd. for $C_{23}H_{25}N_2O_3S$ *(*[M+H]$^+$*)*: 409.1586. Found: 409.1581.

Ethyl 2-methyl-6-(naphthalen-2-ylmethyl)-3-oxo-3,5,6,7-tetrahydro-2H-thiazolo[3,2-*c*]pyrimidine-8-carboxylate (259p)



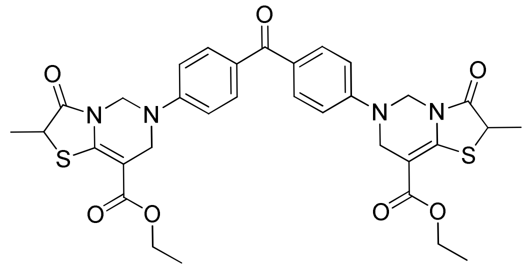
Colorless oil, 95(%), R_f (33% EtOAc / hexane) 0.40; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.20 (d, J = 8.0Hz, 1H, ArH), 7.89 (d, J = 7.6Hz, 1H, ArH), 7.84 (d, J = 7.6Hz, 1H, ArH), 7.57-7.50 (m, 2H, ArH), 7.42 (t, J = 7.2Hz, 1H, ArH), 7.31-7.27 (m, 1H, ArH), 4.59 (q, J = 12.4Hz, 2H, CH_2), 4.25 (q, J = 7.2Hz, 2H, CH_2), 4.08 (s, 2H, CH_2), 3.97 (q, J = 7.2Hz, 1H, CH), 3.74 (s, 2H, CH_2), 1.68 (d, J = 7.2 Hz, 3H, CH_3), 1.29 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.6, 166.6, 147.6, 133.9, 132.5, 132.2, 128.8, 128.6, 127.9, 126.1, 125.8, 125.2, 124.3, 97.5, 62.7, 60.3, 54.6, 49.2, 41.3, 19.2, 14.4; IR (ATR-mode) υ: 3047, 2978, 2929, 2856, 1705, 1681, 1573, 1450, 1253, 1201, 1107, 1031, 840, 777, 729 cm^{-1}; HRMS (ESI$^+$) Calcd. for $C_{21}H_{23}N_2O_3S$ *(*[M+H]$^+$*)*: 383.1429. Found: 383.1418.

Ethyl 2-methyl-3-oxo-6-(thiophen-2-ylmethyl)-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*]pyrimidine-8-carboxylate (259r)



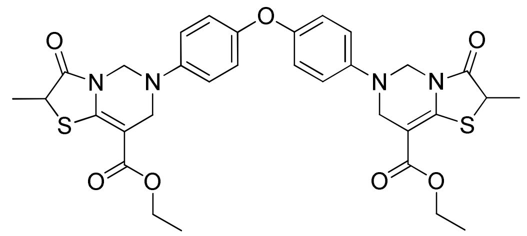
Yellow oil, 100(%), R_f (25% EtOAc / hexane) 0.46; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.27-7.25 (m, 1H), 6.94 (dd, J = 5.2, 3.6Hz, 1H), 6.87 (d, J = 3.6Hz, 1H), 4.55 (q, J = 14.4Hz, 2H, CH_2), 4.22 (q, J = 8.0Hz, 2H, CH_2), 3.91 (q, J = 7.2Hz, 1H, CH), 3.84 (s, 2H, CH_2), 3.69 (s, 2H, CH_2), 1.62 (d, J = 7.2 Hz, 3H, CH_3), 1.28 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.5, 166.4, 147.5, 140.3, 126.7, 126.6, 125.7, 97.4, 62.4, 60.3, 51.2, 48.9, 41.2, 19.1, 14.4; IR (ATR-mode) υ: 2970, 2929, 1705, 1680, 1573, 1369, 1255, 1226, 1130, 1031, 852, 763, 700 cm^{-1}; HRMS (ESI$^+$) Calcd. for $C_{15}H_{19}N_2O_3S_2$ *(*[M+H]$^+$*)*: 339.0837. Found: 339.0836.

Diethyl 6,6'-(carbonylbis(4,1-phenylene))bis(2-methyl-3-oxo-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*]pyrimidine-8-carboxylate) (259s)



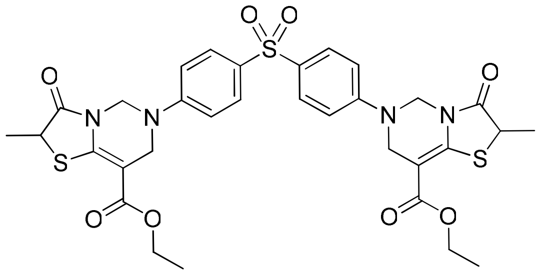
Yellow solid, 70(%), m.p. 97–98°C, R_f (50% EtOAc / hexane) 0.46; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.73 (d, *J* = 8.8Hz, 2x2H, ArH), 6.98 (d, *J* = 8.8Hz, 2x2H, ArH), 5.27 (d, *J* = 13.2Hz, 2x1H, 2xCH), 5.13 (d, *J* = 13.2Hz, 2x1H, 2xCH), 4.38 (s, 2H, CH_2), 4.36 (s, 2H, CH_2), 4.27 (q, *J* = 7.2Hz, 2x2H, 2xCH_2), 3.90 (q, *J* = 7.2Hz, 2x1H, 2xCH), 1.59 (d, *J* = 7.2 Hz, 2x3H, 2xCH_3), 1.34 (t, *J* = 7.2 Hz, 2x3H, 2xCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 193.7, 173.9, 165.7, 150.5, 148.4, 132.1, 130.7, 115.8, 98.6, 60.9, 59.4, 47.9, 41.3, 18.9, 14.4; IR (ATR-mode) υ: 2960, 2924, 2854, 1712, 1680, 1581, 1371, 1263, 1222, 1182, 1124, 1031, 927, 848, 769 cm^{-1}; HRMS (ESI$^+$) Calcd. for $C_{33}H_{35}N_4O_7S_2$ *(*[M+H]$^+$*)*: 663.1947. Found: 663.1921.

Diethyl 6,6'-(oxybis(4,1-phenylene))bis(2-methyl-3-oxo-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*]pyrimidine-8-carboxylate) (259t)



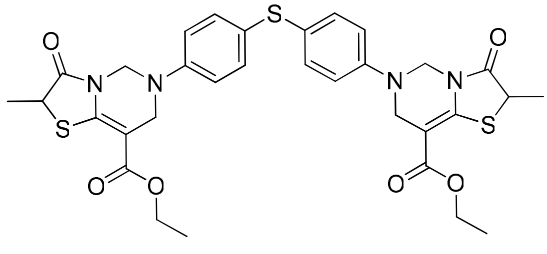
Yellow oil, 100(%), R_f (25% EtOAc / hexane) 0.68; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.88 (m, 8H, ArH), 5.10 (d, *J* = 12.8Hz, 2x1H, 2xCH), 4.99 (d, *J* = 12.8Hz, 2x1H, 2xCH), 4.25 (q, *J* = 7.2Hz, 2x2H, 2xCH_2), 4.22 (s, 2x2H, 2xCH_2), 3.88 (q, *J* = 7.2Hz, 2x1H, 2xCH), 1.58 (d, *J* = 7.2 Hz, 2x3H, 2xCH_3), 1.31 (t, *J* = 7.2 Hz, 2x3H, 2xCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.1, 165.9, 152.2, 148.3, 143.1, 119.5, 119.2, 98.7, 61.2, 60.5, 48.9, 41.3, 19.0, 14.4; IR (ATR-mode) υ: 2976, 2927, 2856, 1705, 1674, 1577, 1498, 1261, 1222, 1193, 1124, 1031, 829, 761 cm^{-1}; HRMS (ESI$^+$) Calcd. for $C_{32}H_{35}N_4O_7S_2$ *(*[M+H]$^+$*)*: 651.1947. Found: 651.1960.

Diethyl 6,6'-(sulfonylbis(4,1-phenylene))bis(2-methyl-3-oxo-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*]pyrimidine-8-carboxylate) (259u)



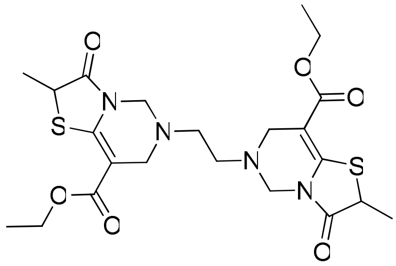
White solid, 45(%), m.p. 89–90 °C, R_f (50% EtOAc/ hexane) 0.70; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.78 (d, J = 8.8Hz, 2x2H, ArH), 6.96 (d, J = 8.8Hz, 2x2H, ArH), 5.20 (d, J = 12.8Hz, 2x1H, 2xCH), 5.06 (d, J = 12.8Hz, 2x1H, 2xCH), 4.32 (d, J = 8.8Hz, 2x2H, 2xCH_2), 4.24 (q, J = 7.2Hz, 2x2H, 2xCH_2), 3.87 (q, J = 7.2Hz, 2x1H, 2xCH), 1.57 (d, J = 7.2 Hz, 2x3H, 2xCH_3), 1.31 (t, J = 7.2 Hz, 2x3H, 2xCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.8, 165.5, 150.9, 148.9, 129.5, 129.3, 116.4, 98.4, 60.7, 58.9, 47.9, 41.3, 18.8, 14.4; IR (ATR-mode) υ: 2970, 2924, 2852, 1737, 1687, 1571, 1365, 1263, 1227, 1105, 1029, 806, 761 cm^{-1}; HRMS (ESI$^+$) Calcd. for $C_{32}H_{33}N_4O_8S_3$ *(*[M+H]$^+$-2H*)*: 697.1461. Found: 697.1448.

Diethyl 6,6'-(thiobis(4,1-phenylene))bis(2-methyl-3-oxo-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*]pyrimidine-8-carboxylate) (259v)



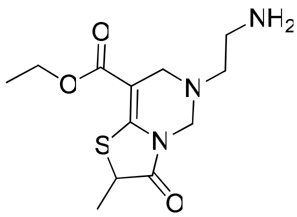
Dark yellow solid, 100(%), m.p. 80–81°C, R_f (33% EtOAc / hexane) 0.20; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.22 (d, J = 8.8Hz, 2x2H, ArH), 6.85 (d, J = 8.8Hz, 2x2H, ArH), 5.14 (d, J = 12.8, 2x1H, 2xCH), 5.02 (d, J = 12.8Hz, 2x1H, 2xCH), 4.30-4.20 (m, 8H), 3.87 (q, J = 7.2Hz, 2x1H, 2xCH), 1.57 (d, J = 7.6 Hz, 2x3H, 2xCH_3), 1.30 (t, J = 7.2 Hz, 2x3H, 2xCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.0, 165.8, 148.3, 146.6, 132.4, 128.1, 118.1, 98.7, 60.5, 60.2, 48.4, 41.3, 18.9, 14.4; IR (ATR-mode) υ: 2970, 2929, 2858, 1708, 1683, 1579, 1494, 1371, 1259, 1220, 1124, 1031, 821, 761 cm^{-1}; HRMS (ESI$^+$) Calcd. for $C_{32}H_{35}N_4O_6S_3$ *(*[M+H]$^+$*)*: 667.1719. Found: 669.1716.

Diethyl 6,6'-(ethane-1,2-diyl)bis(2-methyl-3-oxo-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*]pyrimidine-8-carboxylate) (259y)



White solid, 75(%), m.p. 168–169°C, R_f (50% EtOAc/ hexane) 0.30; ^{1}H NMR (400 MHz, CDCl$_3$) δ: 4.58 (dq, *J* = 12.8, 3.2Hz, 2x2H, 2xCH_2), 4.24 (q, *J* = 7.2Hz, 2x2H, 2xCH_2), 3.90 (q, *J* = 7.2Hz, 2x1H, 2xCH), 3.66 (s, 2x2H, 2xCH_2), 2.65 (s, 2x2H, 2xCH_2), 1.62 (d, *J* = 7.2 Hz, 2x3H, 2xCH_3), 1.31 (t, *J* = 7.2 Hz, 2x3H, 2xCH_3); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 174.6, 166.4, 147.5, 97.4, 63.3, 60.4, 50.2, 49.7, 41.3, 19.1, 14.4; IR (ATR-mode) υ: 2976, 2920, 2858, 1708, 1678, 1579, 1463, 1274, 1251, 1105, 1028, 759 cm^{-1}; HRMS (ESI$^+$) Calcd. for $C_{22}H_{31}N_4O_6S_2$ *(*[M+H]$^+$*)*: 511.1685. Found: 511.1656.

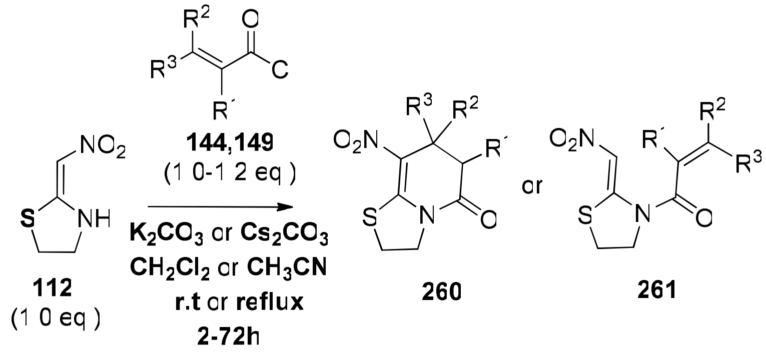
Ethyl 6-(2-aminoethyl)-2-methyl-3-oxo-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*]pyrimidine-8-carboxylate (259z)



Yellow solid, 25(%), m.p. 239–240°C, R_f (MeOH) 0.50; ^{1}H NMR (400 MHz, CDCl$_3$) δ: 5.29 (s, 2H, NH_2), 4.58 (d, *J* = 12.4Hz, 1H, CH), 4.49 (d, *J* = 12.4Hz, 1H, CH), 4.22 (q, *J* = 7.2Hz, 2H, CH_2), 3.89 (q, *J* = 7.2Hz, 1H, CH), 3.63 (s, 2H, CH_2), 2.64-2.58 (m, 4H, CH_2-CH_2), 1.60 (d, *J* = 7.2 Hz, 3H, CH_3), 1.30 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 174.5, 166.4, 147.5, 97.7, 63.4, 60.3, 51.7, 50.4, 49.8, 41.3, 19.1, 14.4; IR (ATR-mode) υ: 3350, 2970, 2935, 1705, 1678, 1573, 1409, 1255, 1109, 1028, 923, 761 cm^{-1}; HRMS (ESI$^+$) Calcd. for $C_{12}H_{20}N_3O_3S$ *(*[M+H]$^+$*)*: 286.1225. Found: 286.1210.

3.1.2.2 Preparation of thiazolo- or imidazolo-pyridinone(s)

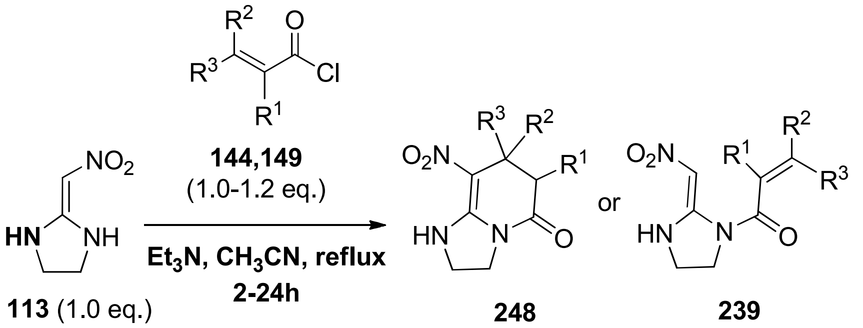
3.1.2.3.1 General procedure for preparation of 8-nitro-6,7-dihydro-2H-thiazolo[3,2-*a*]pyridin-5(3H)-one 260 or 1-(2-(nitromethylene) thiazolidin-3-yl)prop-2-en-1-one(s) 261.



To a stirred solution of heterocyclic nitroenamine **112** (73.0 mg, 0.5 mmol) and acryloyl chloride **144a** (50μL, 55 mg, 0.6 mmol) in CH_2Cl_2 (20 mL), 5 minutes later, K_2CO_3 (138 mg, 1 mmol) was added. The reaction mixture was stirred for 3 hours at 25°C and controlled by TLC. After consumption of compound **112**, the reaction was stopped and undissolved solid was removed by filtration. The remaining solution was evaporated to afford yellow crystalline solid. The crude product was purified by using flash chromatography on silica gel, with 50% hexane/ethyl acetate, to give desired product **260** (90 mg), yield 90%, yellow-green needless.

(P.S. By the same experimental procedure, some uncyclisation or retrocyclisation products **261** have been obtained.)

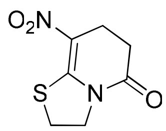
3.1.2.3.2 General procedure for preparation of 8-nitro-2,3,6,7-tetrahydroimidazo[1,2-*a*]pyridin-5(1*H*)-one 248 or 1-((Z)-2-(nitromethylene) imidazolidin-1-yl)but-2-en-1-one(s) 239.



To a stirred solution of heterocyclic nitroenamine 11**3** (64.5 mg, 0.5 mmol) and acryloyl chloride **144a** (50µL, 55 mg, 0.6 mmol) in CH_3CN (25 mL), 5 minutes later, triethylamine (135 µL, 101 mg, 1 mmol) was added. The reaction mixture was refluxed in CH_3CN for 3.5 hours and the completion of reaction was contolled by TLC. The reaction was stopped and the solvent was rotaevaporated to dryness. 20 mL of water was added into remaning crude product and stirred for 15 min at room temperature. The organic part was extracted using ethyl acetate (3x15 mL) and combined organic layers were dried over anhydrous $MgSO_4$ and filtered. Remaining brown solution was evaporated and the crude product was purified by using flash chromatography on silica gel, using ethyl acetate, to give desired product **248** (83 mg), yield 91%, yellow-white powder.

(P.S. By the same experimental procedure, few uncyclisation or retrocyclisation products **239** have been obtained.)

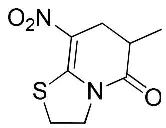
8-Nitro-6,7-dihydro-2*H*-thiazolo[3,2-*a*]pyridin-5(3*H*)-one (260a).



Following the general procedure, heterocyclic nitroenamine **112** (73.0 mg, 0.5 mmol), acryloyl chloride **144a** (50µL, 55 mg, 0.6 mmol) and K_2CO_3 (138 mg, 1 mmol) were stirred in CH_2Cl_2 (20 mL) at 25 ^oC for 3 hours and purified by flash chromatography (50% ethyl acetate/hexane) to afford **260a** (90 mg, 90%) as yellow-greenish crystals, m.p. 190-191 ˚C; R_f: (33% hexane/ethyl acetate) 0.70; ν_{max} (KBr)

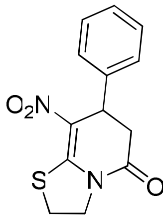
2922 (C-H), 2852, 1701 (amide C=O), 1577 (C=C-NO_2), 1369, 1274, 1180, 1089, 1035, 819, 740 cm^{-1}; δ_H (400 MHz, DMSO-d_6, Me_4Si) 4.12 (2H, t, *J* 7.6 Hz), 3.27 (2H, t, *J* 8.0 Hz), 2.96 (2H, t, *J* 7.6 Hz), 2.72 (2H, t, *J* 8.0 Hz); δ_C (100 MHz, DMSO-d_6, Me_4Si) 21.6, 28.8, 30.7, 49.0, 123.4, 156.2, 167.2; *m/z* (TOF-MS ES^+) 201 (100, MH^+), 189 (18), 181 (2), 55 (2%); HRMS (ESI^+): MH^+, found 201.0329. $C_7H_9N_2O_3S$ requires 201.0334.

7-Methyl-8-nitro-6,7-dihydro-2*H*-thiazolo[3,2-*a*]pyridin-5(3*H*)-one (260b).



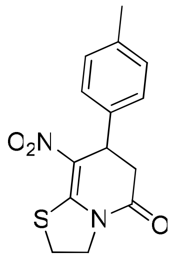
Following the general procedure, heterocyclic nitroenamine **112** (73.0 mg, 0.5 mmol), methacryloyl chloride **144b** (59µL, 63 mg, 0.6 mmol) and K_2CO_3 (138 mg, 1 mmol) were stirred in CH_3CN (25 mL) at reflux for overnight and purified by flash chromatography (50% ethyl acetate/hexane) to afford **260b** (85 mg, 79%) as orange-yellow crystals, m.p. 170-172 °C; R_f: (50% ethyl acetate/hexane) 0.65; ν_{max} (KBr) 2974 (C-H), 2916, 1701 (amide C=O), 1581 (C=C-NO_2), 1371, 1313, 1292, 1234, 1184, 1062, 995, 877, 717 cm^{-1}; δ_H (300 MHz, $CDCl_3$, Me_4Si) 4.42 (1H, pentet, *J* 6.0 Hz), 4.11 (1H, m), 3.35 (1H, q, *J* 6.0 Hz), 3.21 - 3.27 (2H, m), 2.67 - 2.85 (2H, m), 1.34 (3H, d, *J* 6.6 Hz); δ_C (75 MHz, $CDCl_3$, Me_4Si) 15.4, 28.7, 29.3, 35.4, 49.0, 122.7, 155.7, 170.2; *m/z* (TOF-MS AP^+) 215 (100, MH^+), 198 (80), 183 (15), 159 (25%); HRMS (AP^+): MH^+, found 215.0495. $C_8H_{11}N_2O_3S$ requires 215.0490.

8-Nitro-7-phenyl-6,7-dihydro-2*H*-thiazolo[3,2-*a*]pyridin-5(3*H*)-one (260c).



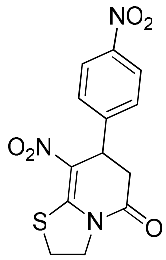
Following the general procedure, heterocyclic nitroenamine **112** (73.0 mg, 0.5 mmol), cinnamoyl chloride **149a** (83 mg, 0.5 mmol) and Cs_2CO_3 (163 mg, 0.5 mmol) were stirred in CH_3CN (25 mL) at 25 °C for overnight and purified by flash chromatography (33% ethyl acetate/hexane) to afford **260c** (123 mg, 89%) as yellow powder, m.p. 155-157 °C; R_f: (50% ethyl acetate/hexane) 0.47; ν_{max} (KBr) 3063 (arom. C-H), 2922 (C-H), 2854, 1703 (amide C=O), 1579 ($C=C-NO_2$), 1450, 1371, 1278, 1226, 1157, 1091, 952, 844, 700 cm^{-1}; δ_H (300 MHz, $CDCl_3$, Me_4Si) 7.26 - 7.34 (3H, m, Ph), 7.13 (2H, d, *J* 8.1 Hz, Ph), 4.76 (1H, dd, *J* 8.1, 1.2 Hz), 4.63 (1H, ddd, *J* 14.7, 6.9, 4.5 Hz), 4.00 (1H, dt, *J* 11.7, 9.3 Hz), 3.25 - 3.35 (2H, m), 3.17 (1H, dd, *J* 16.8, 8.1 Hz), 2.97 (1H, dd, *J* 16.8, 1.8 Hz); δ_C (75 MHz, $CDCl_3$, Me_4Si) 28.6, 38.1, 38.8, 48.9, 126.2, 127.8, 129.1, 129.2, 139.5($C=C-NO_2$), 156.5, 166.2 (C=O); *m/z* (TOF-MS APCI) 277 (100, MH^+), 260 (40), 243 (8), 215 (8), 181 (1%); HRMS (APCI): MH^+, found 277.0653. $C_{13}H_{13}N_2O_3S$ requires 277.0647.

8-Nitro-7-p-tolyl-6,7-dihydro-2*H*-thiazolo[3,2-*a*]pyridin-5(3*H*)-one (260d).



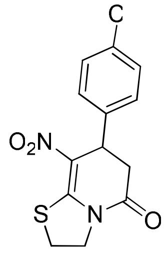
Following the general procedure, heterocyclic nitroenamine **112** (73.0 mg, 0.5 mmol), *p*-methylcinnamoyl chloride **149b** (90 mg, 0.5 mmol) and Cs_2CO_3 (326 mg, 1 mmol) were stirred in CH_3CN (25 mL) at 25 °C for overnight and purified by flash chromatography (50% ethyl acetate/hexane) to afford **260d** (97 mg, 67%) as yellow powder, m.p. 213-214 °C; R_f: (33% hexane/ethyl acetate) 0.67; ν_{max} (KBr) 3016 (arom.CH), 2916 (C-H), 2852, 1701 (amide C=O), 1581 ($C=C-NO_2$), 1444, 1367, 1282, 1226, 1192, 1087, 950, 848, 723 cm^{-1}; δ_H (300 MHz, $CDCl_3$, Me_4Si) 7.11 (2H, d, *J* 8.1 Hz), 7.01 (2H, d, *J* 8.1 Hz), 4.72 (1H, dd, *J* 7.8, 1.2 Hz), 4.62 (1H, ddd, *J* 11.7, 7.2, 4.5 Hz), 3.99 (1H, dt, *J* 12.0, 9.3 Hz), 3.24- 3.30 (2H, m), 3.15 (1H, dd, *J* 16.5, 8.1 Hz), 2.95 (1H, dd, *J* 16.5, 1.5 Hz), 2.31 (3H, s, $-CH_3$); δ_C (75 MHz, $CDCl_3$, Me_4Si) 21.0 ($-CH_3$), 28.6, 37.7, 38.8, 48.8, 126.1, 129.8, 136.4, 137.5, 148.4 ($C=C-NO_2$), 156.4, 166.4 (C=O); *m/z* (TOF-MS ES^+) 291 (100, MH^+), 239 (40), 196 (10), 140 (30), 102 (90%); HRMS (ESI^+): MH^+, found 291.0802. $C_{14}H_{15}N_2O_3S$ requires 291.0803.

8-Nitro-7-(4-nitrophenyl)-6,7-dihydro-2*H*-thiazolo[3,2-*a*]pyridin-5(3*H*)-one (260e).



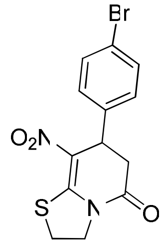
Following the general procedure, heterocyclic nitroenamine **112** (73.0 mg, 0.5 mmol), *p*-nitrocinnamoyl chloride **149c** (106 mg, 0.5 mmol) and K_2CO_3 (138 mg, 1 mmol) were stirred in CH_3CN (25 mL) at reflux for overnight and purified by flash chromatography (50% ethyl acetate/hexane) to afford **260e** (93 mg, 58%) as yellow powder, m.p. 204-206 ˚C; R_f: (33% hexane/ethyl acetate) 0.20; ν_{max} (KBr) 3074 (arom. C-H), 2906 (C-H), 2848, 1707 (amide C=O), 1572 (C=C-NO_2), 1450, 1348, 1284, 1228, 1188, 1157, 1087, 949, 856, 703 cm^{-1}; δ_H (300 MHz, $CDCl_3$, Me_4Si) 8.20 (2H, d, *J* 8.6 Hz), 7.32 (2H, d, *J* 9.0 Hz), 4.87 (1H, d, *J* 7.5 Hz), 4.64 (1H, ddd, *J* 11.7, 6.3, 5.1 Hz), 4.06 (1H, dt, *J* 12.0, 9.3 Hz), 3.30 - 3.36 (2H, m), 3.25 (1H, dd, *J* 16.8, 8.4 Hz), 2.97 (1H, dd, *J* 16.8, 1.6 Hz); δ_C (75 MHz, $CDCl_3$, Me_4Si) 28.7, 38.1, 38.2, 49.1, 100.0, 124.5, 127.4, 146.8, 147.5, (C=C-NO_2), 157.3, 165.3 (C=O); *m/z* (TOF-MS ES^+) 322 (55, MH^+), 239 (95), 196 (8), 140 (30), 102 (93%); HRMS (ESI^+): MH^+, found 322.0486. $C_{13}H_{12}N_3O_5S$ requires 322.0498.

7-(4-Chlorophenyl)-8-nitro-6,7-dihydro-2*H*-thiazolo[3,2-*a*]pyridin-5(3*H*)-one (260f).



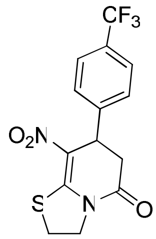
Following the general procedure, heterocyclic nitroenamine **112** (73.0 mg, 0.5 mmol), *p*-chlorocinnamoyl chloride **149d** (100.5 mg, 0.5 mmol) and K_2CO_3 (138 mg, 1 mmol) were stirred in CH_3CN (25 mL) at reflux for 6 hours and purified by flash chromatography (50% ethyl acetate/hexane) to afford **260f** (122 mg, 79%) as white solid, m.p. 162 ˚C (decomp.); R_f: (50% ethyl acetate/hexane) 0.82; ν_{max} (KBr) 3053 (arom. C-H), 2983 (C-H), 2916, 1701 (amide C=O), 1570 (C=C-NO_2), 1438, 1282, 1226, 1147, 1109, 950, 848, 736 cm^{-1}; δ_H (300 MHz, $CDCl_3$, Me_4Si) 7.28 (2H, d, *J* 8.1 Hz), 7.06 (2H, d, *J* 8.4 Hz), 4.73 (1H, dd, *J* 8.1, 1.5 Hz), 4.62 (1H, ddd, *J* 12.0, 6.9, 4.8 Hz), 4.01 (1H, dt, *J* 11.7, 9.3 Hz), 3.26 -3.31 (2H, m), 3.17 (1H, dd, *J* 16.8, 8.1 Hz), 2.93 (1H, dd, *J* 16.8, 1.5); δ_C (75 MHz, $CDCl_3$, Me_4Si) 28.6, 37.6, 38.6, 48.9, 127.7, 129.3, 133.7, 138.0, 144.7, 156.7, 165.9 (C=O); *m/z* (TOF-MS ES^+) 311 (100, MH^+), 239 (30), 196 (8), 140 (25), 102 (65%); HRMS (ESI^+): MH^+, found 311.0250. $C_{13}H_{12}ClN_2O_3S$ requires 311.0257.

7-(4-Bromophenyl)-8-nitro-6,7-dihydro-2*H*-thiazolo[3,2-*a*]pyridin-5(3*H*)-one (260g).



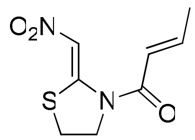
Following the general procedure, heterocyclic nitroenamine **112** (73.0 mg, 0.5 mmol), *p*-bromocinnamoyl chloride **149e** (122.5 mg, 0.5 mmol) and K_2CO_3 (138 mg, 1 mmol) were stirred in CH_3CN (25 mL) at reflux for 4 hours and purified by flash chromatography (50% ethyl acetate/hexane) to afford **260g** (100 mg, 57%) as yellow crystals, m.p. 145 ˚C (decomp.); R_f: (50% ethyl acetate/hexane) 0.63; ν_{max} (KBr) 3053 (arom. C-H), 2929 (C-H), 2858, 1701 (amide C=O), 1581 (C=C-NO_2), 1450, 1282, 1226, 1192, 1157, 1087, 952, 844, 763 cm^{-1}; δ_H (300 MHz, $CDCl_3$, Me_4Si) 7.42 (2H, d, *J* 8.4 Hz), 6.99 (2H, d, *J* 8.4 Hz), 4.71 (1H, dd, *J* 6.9, 0.9 Hz), 4.61 (1H, ddd, *J* 11.7, 6.6, 4.5 Hz), 3.99 (1H, dt, *J* 12.0, 9.3 Hz), 3.24 - 3.31 (2H, m), 3.16 (1H, dd, *J* 16.5, 8.1 Hz), 2.92 (1H, dd, *J* 13.5, 1.5 Hz); δ_C (75 MHz, $CDCl_3$, Me_4Si) 28.6, 37.7, 38.5, 48.9, 121.8, 125.5, 128.0, 132.3, 138.5 (C=C-NO_2), 156.8, 165.9 (C=O); *m/z* (TOF-MS ES^+) 354 (50, MH^+), 301 (25), 266(50), 239 (45), 140 (30), 102 (100%); HRMS (ESI^+): MH^+, found 354.9746. $C_{13}H_{12}BrN_2O_3S$ requires 354.9752.

8-Nitro-7-(4-(trifluoromethyl)phenyl)-6,7-dihydro-2*H*-thiazolo[3,2-*a*]pyridin-5(3*H*)-one (260h).



Following the general procedure, heterocyclic nitroenamine **112** (73.0 mg, 0.5 mmol), *p*-trifluoromethylcinnamoyl chloride **149f** (117 mg, 0.5 mmol) and K_2CO_3 (138 mg, 1 mmol) were stirred in CH_3CN (25 mL) at reflux for overnight and purified by flash chromatography (33% hexane/ethyl acetate) to afford **260h** (118 mg, 69%) as white crystals, m.p. 148-149 ˚C; R_f: (50% ethyl acetate/hexane) 0.70; ν_{max} (ATR-mode) 3051 (arom. C-H), 2897 (C-H), 1701 (amide C=O), 1581 (C=C-NO_2), 1448, 1369, 1284, 1226, 1192, 1157, 1085, 950, 837, 727 cm^{-1}; δ_H (300 MHz, $CDCl_3$, Me_4Si) 7.10 (2H, dd, *J* 9.0, 5.4 Hz), 7.00 (2H, t, *J* 8.6 Hz), 4.75 (1H, dd, *J* 8.1, 1.5 Hz), 4.63 (1H, ddd, *J* 11.6, 6.8, 4.4 Hz), 4.01 (1H, dt, *J* 12.0, 9.6 Hz), 3.26 - 3.32 (2H, m), 3.17 (1H, dd, *J* 16.5, 8.1 Hz), 2.94 (1H, dd, *J* 16.8, 1.6 Hz); δ_C (75 MHz, $CDCl_3$, Me_4Si) 28.4, 37.2, 38.5, 48.6, 115.6, 115.9, 125.6, 127.6, 135.0, 156.4, 160.3, 163.5, 165.7 (C=O); *m/z* (TOF-MS ES^+) 295 (100, MH^+-CF_2), 239 (40), 196 (5), 140 (20), 102 (60%); HRMS (ESI^+): MH^+, found 295.0539. $C_{13}H_{12}FN_2O_3S$ requires 295.0553.

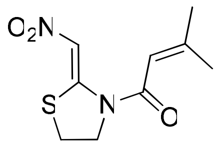
2-(Nitromethylene)thiazolidin-3-yl)but-2-en-1-one (261a).



Following the general procedure, heterocyclic nitroenamine **112** (73.0 mg, 0.5 mmol), crotonoyl chloride **144c** (58µL, 63 mg, 0.6 mmol) and Cs_2CO_3 (163 mg, 0.5 mmol) were stirred in CH_3CN (25 mL) at 25 ^oC for 1.5 hour or K_2CO_3 (138 mg, 1 mmol) in CH_3CN (25 mL) at reflux for 16 hours and purified by flash chromatography (25% ethyl acetate/hexane) to afford **261a** (80 mg, 70%) as yellow crystals, m.p. 112-114 ˚C; R_f: (50% ethyl acetate/hexane) 0.42; ν_{max} (KBr) 3174 (C=$CHNO_2$), 2960 (C-H), 2937, 1685 (C=C(CH_3)$_2$, 1629(C=C-NO_2), 1533, 1453, 1388, 1321, 1290, 1203, 1176, 1101, 1012, 956, 779, 665 cm^{-1}; δ_H (300 MHz,

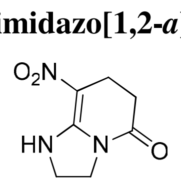
$CDCl_3$, Me_4Si) 8.42 (1H, s, C=CHNO$_2$), 7.15 (1H, septet, *J* 7.2 Hz), 6.26 (1H, dq, *J* 15.0, 1.5 Hz), 4.30 (3H, t, *J* 7.2 Hz), 3.15 (3H, t, *J* 7.2 Hz), 2.00 (3H, dd, *J* 6.9, 1.6 Hz); δ_C (75 MHz, $CDCl_3$, Me_4Si) 18.6, 27.7, 52.4, 122.8, 148.1, 158.6, 164.5; *m/z* (TOF-MS AP$^+$) 215 (15, MH$^+$), 170 (8), 129 (15), 95.0 (12), 83.0 (100%); HRMS (AP$^+$): MH$^+$, found 215.0490. $C_8H_{11}N_2O_3S$ requires 215.0490.

3-Methyl-1-(2-(nitromethylene)thiazolidin-3-yl)but-2-en-1-one (261b).



Following the general procedure, heterocyclic nitroenamine **112** (73.0 mg, 0.5 mmol), 3,3-dimethylacryloyl chloride **144d** (55 µL,59 mg, 0.5 mmol) and Cs_2CO_3 (163 mg, 0.5 mmol) were stirred in CH_3CN (25 mL) at 25 ^oC for overnight and purified by flash chromatography (33% ethyl acetate/hexane) to afford **261b** (70 mg, 61%) as pale yellow crystals, m.p. 98-99 ˚C; R$_f$: (50% ethyl acetate/hexane) 0.54; ν_{max} (KBr) 3174 (C=CHNO$_2$), 2941 (C-H), 2916, 1685 (C=O), 1631 (C=C(CH$_3$)$_2$, 1545 (C=C-NO$_2$), 1444, 1365, 1323, 1232, 1165, 1143, 1062, 864, 777, 665 cm^{-1}; δ_H (400 MHz, $CDCl_3$, Me_4Si) 8.43 (1H, s, C=CHNO$_2$), 5.93 (1H, t, *J* 1.2 Hz), 4.26 (3H, t, *J* 7.2 Hz), 3.12 (3H, t, *J* 14.8 Hz), 2.13 (3H, d, *J* 1.2 Hz), 1.99 (3H, d, *J* 1.2 Hz); δ_C (100 MHz, $CDCl_3$, Me_4Si) 21.2, 27.8, 27.9, 52.9, 117.6, 121.9, 158.7, 159.1, 165.2; *m/z* (TOF-MS AP$^+$) 229 (100, MH$^+$), 215 (8), 173 (25), 156 (60%); HRMS (AP$^+$): MH$^+$, found 229.0641. $C_9H_{13}N_2O_3S$ requires 229.0647.

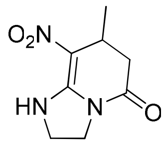
8-Nitro-2,3,6,7-tetrahydroimidazo[1,2-*a*]pyridin-5(1*H*)-one (248a).



Following the general procedure, heterocyclic nitroenamine **113** (64.5 mg, 0.5 mmol), acryloyl chloride **144a** (50µL, 55 mg, 0.6 mmol) and Et_3N (68 µL, 50 mg, 0.5 mmol) were stirred in CH_3CN (25 mL) at reflux for 3.5 hours and purified by flash chromatography (ethyl acetate) to afford **248a** (88 mg, 96%) as yellowish-white powder, m.p. 208 ˚C (decomp.); R$_f$: (ethyl acetate) 0.10; ν_{max} (KBr) 3355 (N-H), 2956 (C-H), 2918, 1701 (C=O), 1647 (C=C-NO$_2$), 1489, 1400, 1350, 1315, 1286, 1217, 1174, 1147, 1022, 933, 661, 555 cm^{-1}; δ_H (400 MHz, DMSO-d$_6$, Me_4Si) 9.59

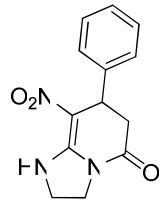
(1H, s, -NH), 3.85 (2H, t, *J* 7.6 Hz), 3.72 (2H, t, *J* 7.2 Hz), 2.82 (2H, t, *J* 8.0 Hz), 2.61 (2H, t, *J* 7.6 Hz); δ_C (100 MHz, DMSO-d$_6$, Me$_4$Si) 20.9, 31.0, 43.1, 43.8, 103.8, 153.2, 168.8; *m/z* (TOF-MS ES$^+$) 184 (100, MH$^+$), 173 (35), 167 (5%); HRMS (ESI$^+$): MH$^+$, found 184.0724. $C_7H_{10}N_3O_3$ requires 184.0722.

7-Methyl-8-nitro-2,3,6,7-tetrahydroimidazo[1,2-*a*]pyridin-5(1*H*)-one (248b).



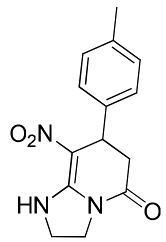
Following the general procedure, heterocyclic nitroenamine **113** (64.5 mg, 0.5 mmol), crotonoyl chloride **144c** (58µL, 63 mg, 0.6 mmol) and Et$_3$N (135 µL, 101 mg, 1 mmol) were stirred in CH$_3$CN (25 mL) at reflux for 3.5 hours and purified by flash chromatography (ethyl acetate) to afford **248b** (72 mg, 74%) as yellowish-white solid, m.p. 186-187 ˚C; R$_f$: (ethyl acetate) 0.30; ν_{max} (KBr) 3347 (N-H), 2956 (C-H), 2924, 2854, 1701 (C=O), 1631 (C=C-NO$_2$), 1485, 1450, 1348, 1309, 1286, 1172, 1147, 1030, 935, 765, 665 cm^{-1}; δ_H (400 MHz, DMSO-d$_6$, Me$_4$Si) 9.53 (1H, s, -NH), 3.80 - 3.93 (3H, m), 3.70 - 3.74 (2H, m), 2.86 (1H, dd, *J* 16.4, 6.8 Hz), 2.34 (1H, dd, *J* 16.8, 2.0 Hz), 1.00 (3H, d, *J* 6.4 Hz); δ_C (100 MHz, DMSO-d$_6$, Me$_4$Si) 18.9, 27.6, 38.8, 43.1, 43.9, 108.8, 152.5, 168.4; *m/z* (TOF-MS ES$^+$) 196 (40, M$^+$-H), 187(5%); HRMS (ESI$^-$): M$^+$-H, found 196.0729. $C_8H_{10}N_3O_3$ requires 196.0722.

8-Nitro--7-phenyl-2,3,6,7-tetrahydroimidazo[1,2-*a*]pyridin-5(1*H*)-one (248c).



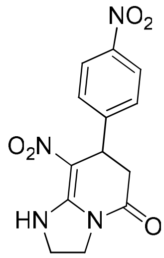
Following the general procedure, heterocyclic nitroenamine **113** (64.5 mg, 0.5 mmol), cinnamoyl chloride **149a** (83 mg, 0.5 mmol) and Et$_3$N (135 µL, 101 mg, 1 mmol) were stirred in CH$_3$CN (25 mL) at reflux for 4 hours and purified by flash chromatography (ethyl acetate) to afford **248c** (114 mg, 88%) as yellow powder, m.p. 228-229 ˚C; R$_f$: (ethyl acetate) 0.43; ν_{max} (KBr) 3279 (N-H), 3026 (arom. CH), 2922 (C-H), 1697 (C=O), 1631 (C=C-NO$_2$), 1485, 1444, 1284, 1213, 1180, 1143, 1028, 937,756, 698 cm^{-1}; δ_H (400 MHz, DMSO-d$_6$, Me$_4$Si) 9.73 (1H, s, -NH), 7.29 (2H, t, *J* 7.2 Hz), 7.22 (1H, t, *J* 6.8 Hz), 7.15 (2H, d, *J* 7.2 Hz), 4.54 (1H, d, *J* 6.8 Hz), 3.76 - 3.96 (4H, m), 3.21 (1H, dd, *J* 15.6, 8.0 Hz), 2.58 (1H, d, *J* 15.6 Hz); δ_C (100 MHz, DMSO-d$_6$, Me$_4$Si) 37.8, 40.8, 43.2, 44.1, 106.8, 127.0, 127.5, 129.3, 143.1, 153.3, 168.0; *m/z* (TOF-MS ES$^+$) 260 (100, MH$^+$), 231.5 (30), 203.0 (12), 167 (5%); HRMS (ESI$^+$): MH$^+$, found 260.1028. $C_{13}H_{14}N_3O_3$ requires 260.1035.

8-Nitro-7-p-tolyl-2,3,6,7-tetrahydroimidazo[1,2-*a*]pyridin-5(1*H*)-one (248d).



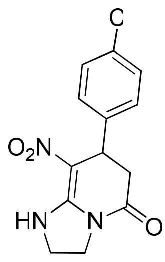
Following the general procedure, heterocyclic nitroenamine **113** (64.5 mg, 0.5 mmol), *p*-methylcinnamoyl chloride **149b** (90 mg, 0.5 mmol) and Et_3N (135 µL, 101 mg, 1 mmol) were stirred in CH_3CN (25 mL) at reflux for 3 hours and purified by flash chromatography (ethyl acetate) to afford **248d** (93 mg, 68%) as white powder, m.p. 275 °C (decomp.); R_f: (ethyl acetate) 0.33; ν_{max} (KBr) 3358 (N-H), 2920 (C-H), 2852, 1701 (C=O), 1620 (C=C-NO_2), 1444, 1344, 1325, 1282, 1213, 1180, 1143, 1028, 810, 767, 665 cm^{-1}; δ_H (400 MHz, DMSO-d$_6$, Me$_4$Si) 9.71 (1H, s, -NH), 7.09 (2H, d, *J* 8.4 Hz), 7.02 (2H, t, *J* 7.6 Hz), 4.49 (1H, d, *J* 6.8 Hz), 3.75 - 3.97 (4H, m), 3.18 (1H, dd, *J* 16.8, 7.6 Hz), 2.58 (1H, d, *J* 16.4 Hz), 2.24 (3H, s); δ_C (100 MHz, DMSO-d$_6$, Me$_4$Si) 20.4, 30.2, 36.6, 42.4, 43.3, 106.2, 126.1, 129.1, 135.8, 139.2, 152.5, 167.3; *m/z* (TOF-MS ES$^+$) 274 (100, MH$^+$), 238 (10), 218.0 (5), 161 (2%); HRMS (ESI$^+$): MH$^+$, found 274.1183. $C_{14}H_{16}N_3O_3$ requires 274.1192.

8-Nitro-7-(4-nitrophenyl)-2,3,6,7-tetrahydroimidazo[1,2-*a*]pyridin-5(1*H*)-one (248e).



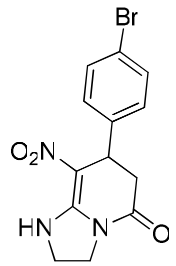
Following the general procedure, heterocyclic nitroenamine **113** (64.5 mg, 0.5 mmol), *p*-nitrocinnamoyl chloride **149c** (106 mg, 0.5 mmol) and Et_3N (135 μL, 101 mg, 1 mmol) were stirred in CH_3CN (25 mL) at reflux for 2 hours and purified by flash chromatography (ethyl acetate) to afford **248e** (92 mg, 60%) as yellow powder, m.p. 208 ˚C (decomp.); R_f: (ethyl acetate) 0.30; ν_{max} (KBr) 3358 (N-H), 3072, 2983(C-H), 2926, 1707 (C=O), 1639 (C=C-NO_2), 1597 (-NO_2), 1491, 1452, 1344, 1313, 1286, 1174, 1147, 1026, 933, 856, 771, 665 cm^{-1}; δ_H (400 MHz, DMSO-d$_6$, Me_4Si) 9.81 (1H, s, -NH), 8.15 (2H, d, *J* 8.4 Hz), 7.47 (2H, d, *J* 8.4 Hz), 4.71 (1H, d, *J* 7.6 Hz), 3.78 - 3.97 (4H, m), 3.29 (1H, dd, *J* 16.8, 8.4 Hz), 2.62 (1H, d, *J* 16.4 Hz); δ_C (100 MHz, DMSO-d$_6$, Me_4Si) 30.2, 37.1, 42.5, 43.5, 105.2, 123.7, 127.8, 146.4, 150.2, 152.5, 166.7; *m/z* (TOF-MS ES$^+$) 305 (100, MH$^+$), 254(45), 225.0 (20), 123 (2%); HRMS (ESI$^+$): MH$^+$, found 305.0883. $C_{13}H_{13}N_4O_5$ requires 305.0886.

7-(4-Chlorophenyl)-8-nitro-2,3,6,7-tetrahydroimidazo[1,2-*a*]pyridin-5(1*H*)-one (248f).



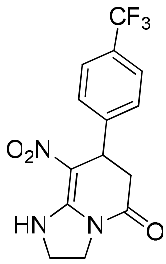
Following the general procedure, heterocyclic nitroenamine **113** (64.5 mg, 0.5 mmol), *p*-chlorocinnamoyl chloride **149d** (100.5 mg, 0.5 mmol) and Et_3N (135 μL, 101 mg, 1 mmol) were stirred in CH_3CN (25 mL) at reflux for 5 hours and purified by flash chromatography (ethyl acetate) to afford **248f** (112 mg, 76%) as white powder, m.p. 250 ˚C (decomp.); R_f: (ethyl acetate) 0.83; ν_{max} (KBr) 3219 (N-H), 2922 (C-H), 2852, 1701 (C=O), 1620 (C=C-NO_2), 1485, 1448, 1369, 1344, 1319, 1282, 1215, 1180, 1143, 1028, 933, 819, 767, 665 cm^{-1}; δ_H (400 MHz, DMSO-d$_6$, Me$_4$Si) 9.72 (1H, s, -NH), 7.31 (2H, d, *J* 8.4 Hz), 7.15 (2H, d, *J* 8.4 Hz), 4.52 (1H, d, *J* 6.8 Hz), 3.73 - 3.92 (4H, m), 3.18 (1H, dd, *J* 16.8, 8.0 Hz), 2.54 (1H, dd, *J* 16.8, 1.6 Hz); δ_C (100 MHz, DMSO-d$_6$, Me$_4$Si) 37.3, 39.5, 43.3, 44.2, 106.5, 129.0, 129.2, 132.1, 142.1, 153.2, 167.8; *m/z* (TOF-MS ES$^+$) 294 (100, MH$^+$), 248.0 (5), 220.0 (2), 156 (1%); HRMS (ESI$^+$): MH$^+$, found 294.0631. $C_{13}H_{13}ClN_3O_3$ requires 294.0645.

7-(4-Bromophenyl)-8-nitro-2,3,6,7-tetrahydroimidazo[1,2-*a*]pyridin-5(1*H*)-one (248g).



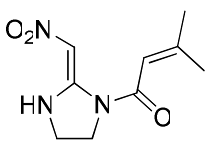
Following the general procedure, heterocyclic nitroenamine **113** (64.5 mg, 0.5 mmol), *p*-bromocinnamoyl chloride **149e** (122.5 mg, 0.5 mmol) and Et_3N (135 µL, 101 mg, 1 mmol) were stirred in CH_3CN (25 mL) at reflux for 24 hours and purified by flash chromatography (ethyl acetate) to afford **248g** (98 mg, 58%) as yellow powder, m.p. 200 ˚C (decomp.); R$_f$: (ethyl acetate) 0.10; ν_{max} (ATR-mode) 3219 (N-H), 2953 (C-H), 2922, 2854, 1699 (C=O), 1622 (C=C-NO$_2$), 1485, 1446, 1371, 1342, 1317, 1280, 1213, 1180, 1145, 1028, 964, 821, 767, 642 cm^{-1}; δ_H (300 MHz, DMSO-d$_6$, Me$_4$Si) 9.74 (1H, s, -NH), 7.48 (2H, d, *J* 8.4 Hz), 7.12 (2H, d, *J* 8.4 Hz), 4.52 (1H, d, *J* 6.6 Hz), 3.77 - 3.97 (4H, m), 3.21 (1H, dd, *J* 16.8, 8.1 Hz), 2.57 (1H, dd, *J* 16.5, 1.5 Hz); δ_C (75 MHz, DMSO-d$_6$, Me$_4$Si) 32.0, 37.1, 43.1, 43.9, 106.3, 120.3, 129.1, 131.9, 142.3, 153.0, 167.5; *m/z* (TOF-MS ES$^+$) 338 (100, MH$^+$), 239.0 (10), 140.0 (5), 102 (15%); HRMS (ESI$^+$): MH$^+$, found 338.0128. $C_{13}H_{13}BrN_3O_3$ requires 338.0140.

8-Nitro-7-(4-(trifluoromethyl)phenyl)-2,3,6,7-tetra hydroimidazo[1,2-*a*]pyridin-5(1*H*)-one (248h).



Following the general procedure, heterocyclic nitroenamine **113** (64.5 mg, 0.5 mmol), *p*-trifluoromethylcinnamoyl chloride **149f** (117 mg, 0.5 mmol) and Et_3N (135 μL, 101 mg, 1 mmol) were stirred in CH_3CN (25 mL) at reflux for 24 hours and purified by flash chromatography (ethyl acetate) to afford **248h** (118 mg, 72%) as white crystals, m.p. 255-256 ˚C; R_f: (ethyl acetate) 0.10; ν_{max} (ATR-mode) 3246 (N-H), 2922(C-H), 2854, 1703 (C=O), 1622 (C=C-NO_2), 1508, 1485, 1446, 1342, 1315, 1284, 1180, 1143, 1028, 939, 837, 767, 686 cm^{-1}; δ_H (300 MHz, DMSO-d_6, Me_4Si) 9.71 (1H, s, -NH), 7.19 (2H, td, *J* 5.1, 2.5 Hz), 7.10 (2H, t, *J* 9.0 Hz), 4.54 (1H, d, *J* 7.2 Hz), 3.75 - 3.96 (4H, m), 3.20 (1H, dd, *J* 16.5, 7.8 Hz), 2.56 (1H, dd, *J* 16.5, 0.9 Hz); δ_C (75 MHz, DMSO-d_6, Me_4Si) 36.9, 43.0, 43.9, 106.6, 115.6, 115.9, 128.7, 139.0, 153.0, 159.9, 163.1, 167.7; *m/z* (TOF-MS ES^+) 278 (100, MH^+-CF_2), 239.0 (20), 140.0 (10), 102.1 (40%); HRMS (ESI^+): MH^+–CF_2, found 278.0937. $C_{13}H_{13}FN_3O_3$ requires 278.0941.

3-Methyl-1-(2-(nitromethylene)imidazolidin-1-yl)but-2-en-1-one (239a).



Following the general procedure, heterocyclic nitroenamine **113** (64.5 mg, 0.5 mmol), 3,3-dimethylacryloyl chloride **144d** (68 μL,71 mg, 0.6 mmol) and Et_3N (139 μL, 101 mg, 1 mmol) were stirred in CH_3CN (25 mL) at reflux for 5.5 hours and purified by flash chromatography (33% hexane/ethyl acetate) to afford **239a** (100 mg, 95%) as yellow solid, m.p. 171-172 ˚C; R_f: (50% ethyl acetate/hexane) 0.75; ν_{max} (ATR-mode) 3253 (-NH), 3178 (C=$CHNO_2$), 2922 (C-H), 2859, 1739(C=O), 1683 (C=C$(Me)_2$), 1585 (C=C-NO_2), 1436, 1355, 1307, 1205, 1182, 1126, 1083, 1051, 958, 823, 765, 684 cm^{-1}; δ_H (400 MHz, DMSO-d_6, Me_4Si) 9.65 (1H, s, -NH), 7.78 (1H, s, C=$CHNO_2$), 6.03 (1H, s, C=CHCO), 4.06 (2H, t, *J* 8.4), 3.65 (2H, t, *J* 8.4), 2.02 (3H, s), 1.90 (3H, s); δ_C (100 MHz, DMSO-d_6, Me_4Si) 20.2, 26.9, 42.4, 45.9, 101.4, 116.9, 154.5, 156.6, 165.0 (C=O); *m/z* (TOF-MS ES^+) 212 (100, MH^+), 190 (1), 130 (5%); HRMS (ESI^+): MH^+, found 212.1030. $C_9H_{14}N_3O_3$ requires 212.1035.

3.1.3 BIOLOGICAL ACTIVITY ASSAYS OF THIAZOLO- and 4-OXOTHIAZOLO-[3,2-*c*]PYRIMIDINES (163, 259)

3.1.3.1 Method for Anticancer (or cyctotoxic) Activity Assay

MCF-7 human breast cancer cells were planted into 96-well plates as $2x10^4$ cells/well. After 1 day, derivatives of **163** and **259** with 4 different concentrations (1, 10, 100, 1000 µM) 5-FU were applied onto cells for 72 hours. All of the substances were dissolved in DMSO and the solutions were diluted to be the last concentration of DMSO at 0.5%, and then they applied to cells. At the end of 72 hours, cell viability was measured with MTT test and cell viability was calculated with respect to control group.

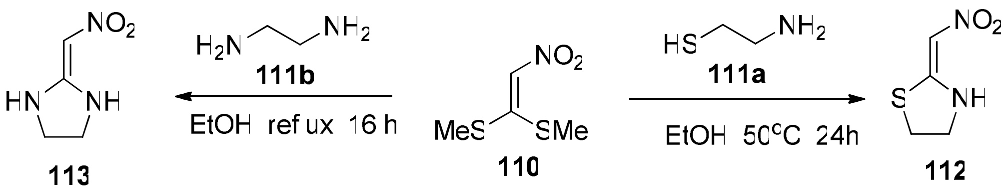
3.1.3.2 Method for Antibacterial Activity Assay

Disc diffusion technique (Kirby-Bauer method) was used in order to evaluate anti-microbial activity. Six types of Gram (-) bacteria (*Pseudomonas aeruginosa, Salmonella typhimurium, Serratia marcescens, Proteus vulgaris, Enterobacter cloacae and Klebsiella pneumoniae*), and two types of Gram (+) bacteria (*Staphylococcus aureus, Staphylococcus epidermidis*) were used in the tests. Stock microorganism suspensions (100-200 .mu.l) was transferred to a test tube containing 2 ml of TSB, and absorbance values adjusted according to the microorganism has been standardized. These cultures were then inoculated onto petri dishes containing Mueller-Hinton agar. 39 compounds (**163** and **259** derivatives) to be tested were dissolved separately in DMSO (20mg/mL), sterilized using 0.22-µm filter, and then the filter paper discs were immersed into the prepared solutions, placed on sterile towels and placed on inoculated petri dishes. Each pethri dish has filter paper discs containing 4 substances and 2 different petri dishes were used for each microorganism. 5 different antibiotic discs (erythromycin, ampicillin, carbenicillin, tetracycline and chloramphenicol) were used for positive control. The inoculated petri dishes were kept in incubator at 37°C for 16-18 hours and then the diameter of the inhibition zones were measured.

4. RESULTS AND DISCUSSIONS

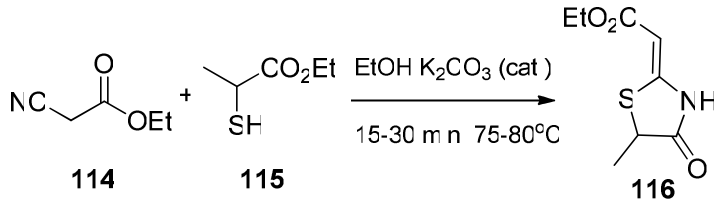
4.1 PART 1: SYNTHESIS AND CHARACTERIZATION OF HETEROCYCLIC SECONDARY ENAMINES (112, 113, 116) AND CINNAMOYL CHLORIDES (149a-f)

The starting material, 2-(nitromethylene)thiazolidine **112**, was easily and efficiently obtained by heating 1,1-bis(methylthio)-2-nitroethylene **110** and 2-aminoethanethiol **111a** together in ethanol at reflux. However, in the present work, we found that the nitroenamine **112** could also be obtained under microwave conditions with a considerably shorter reaction time (20 min) when compared with the reported method (30 h) (Rajappa and Advani, 1982). The structure of **112** was determined by C=C and NH stretching vibrations at 1562 and 3174 cm^{-1} in IR spectrum, respectively. Also, NH and C=CH protons appeared at 9.14 and 6.99 ppm in proton NMR spectrum, respectively. Similarly, two NH and C=C IR-stretchings of **113** have been at around 3226, 3241 and 1606 cm^{-1}, respectively. In proton NMR of **113**, a broad NH signal resonated around 8.4 ppm and the C=CH signal was slightly deshielded and resonated at 6.33 ppm. The yields for the syntheses of **112** and **113** were obtained good to excellent (Scheme 4.1).



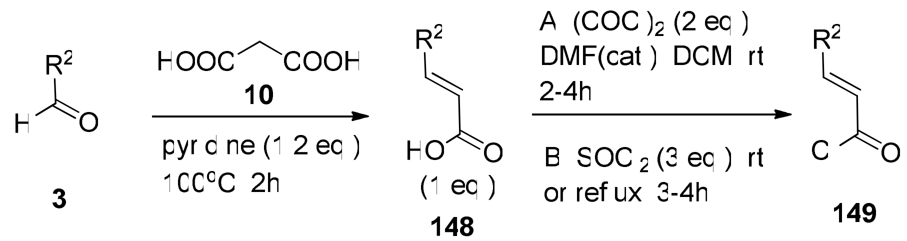
Scheme 4. 1 Preparation of 2-(nitromethylene)-thiazolidine or imidazolidine

The (*Z*)-ethyl 2-(5-methyl-4-oxothiazolidin-2-ylidene) acetate **116** was prepared in 83% yield following a reported procedure (Scheme 4.2). NH, ester C=O and amide C=O IR-strecthing vibrations appeared around 3151, 1722 and 1654 cm^{-1} and these spectral data were consistent with the literature (Stojanovic et al., 2011). In proton NMR, NH and C=CH proton signals resonated around 9.62 and 5.6 ppm, respectively.



Scheme 4. 2 Preparation of 4-oxothiazolidine carboxylates.

Also, some cinnamic acid chlorides **149** were prepared in excellent yields (95-100%) by using literature methods below (Scheme 4.3). Their structures were characterized by IR, proton and carbon NMR spectra. In IR spectra of products **149**, C=O stretchings appeared around 1739-1751 cm^{-1}. With the aromatic and olefinic proton signals resonate around 7.0-8.0 and 6.5 ppm, respectively, the structures of cinnamoyl chlorides **149** have been proved completely.



R^2

149a: 4-Me-Ph- **149b** 4-NO2-Ph- **149c** 4-C -Ph- **149d** 4-Br-Ph- **149e** 4-CF_3-Ph-
149f 4-F-Ph-

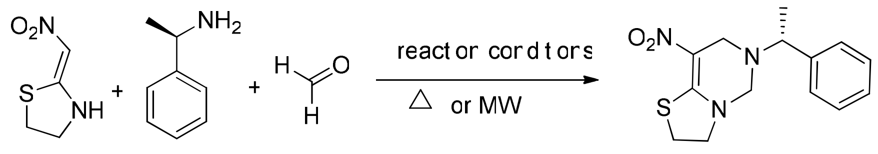
Scheme 4. 3 Preparation of derivatives **149a-f**

4.2 PART 2: MICROWAVE-ASSISTED SYNTHESIS OF 6-NITROTHIAZOLO [3,2-c]PYRIMIDINES (163)

First of all, some optimization experiments have been performed to find the most efficient method for the synthesis of thiazolo[3,2-*c*]pyrimidines, therefore, microwave irradiation (MW) was compared with conventional heating with or without additives using, as a model reaction, the combination of 2-(nitromethylene)thiazolidine (**112**), formaldehyde (**16**) and (*R*)-(+)-1-phenylethylamine (**10a**). These preliminary results are presented in (Table 4.1).

(R)-(+)-1-Phenylethylamine **10a** was reacted with equivalent quantities of the nitroenamine **112**, but varying stoichiometries of formaldehyde **16**. Several solvents and two heterogeneous catalysts have been tried in order to understand their effect on the formation of the product under MW conditions. However, we found that there were, at best, only very slight beneficial effects associated with adding the clays (Montmorillonite KSF and K10) and the total yields were found as low to moderate (Table 4.1, entry 1-6). However, more significantly, the reaction time for complete consumption of starting materials was lowered from 2 hours with conventional heating to a remarkable 5 minutes using MW irradiation (Table 4.1, entry 7). When more polar solvents such as ethanol or acetonitrile were used, a small increment was observed in terms of reaction yields, but there was no significant change in reaction times for either conventional or MW heating (Table 1, entry 8). Finally, we were pleased to find that the best results were obtained for the reaction in water without any catalyst at reflux temperature for conventional heating or around 90°C for MW heating (Table 4.1, entry 9). Of course, this was very convenient as the formaldehyde could simply be added as formalin solution.

Table 4.1. Optimization of reaction conditions to yield compound **163a**



112 10a 16 163a

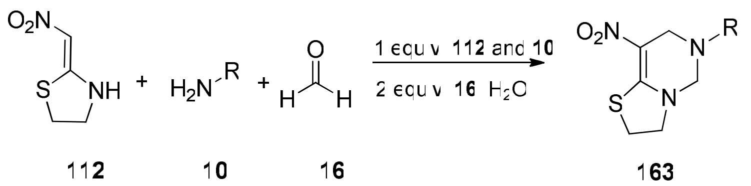
			Time		Yield (%)	
Entry	Reaction conditions	Additive*	Δ (h)	MW (min)	Δ	MW
1	EtOH,**112** (1eq), **10a** (1eq), **16** (1.5 eq)	1	5	3	32	40
2	Toluene,**112** (1eq), **10a** (1eq), **16** (1.5 eq)	1	3	3	25	36
3	CH_3CN,**112** (1eq), **10a** (1eq), **16** (1.5 eq)	2	4	4	45	52
4	Neat,**112** (1eq), **10a** (1eq), **16** (3.0 eq)**	2	2	3	40	34
5	CH_2Cl_2, **112** (1eq), **10a** (1eq), **16** (2.0 eq)	1	5	6	24	32
6	H_2O, **112** (1eq), **10a** (1eq), **16** (1.0 eq)	2	3	4	49	63
7	Neat, **112** (1eq), **10a** (1eq), **16** (2.5 eq)**	-	2	5	66	73
8	EtOH, **112** (1eq), **10a** (1eq), **16** (2.0 eq)	-	4	5	68	76
9	H_2O, **112** (1eq), **10a** (1eq),**16** (2.0 eq)	-	2.5	5	92	100

*1: Montmorillonite KSF 2: Montmorillonite K10, were used (0.5-1.0 g) during MW heating only; The reactions were performed at reflux temperature of the solvents specified. ** The reactions were carried out at 90°C.

After determining that the most suitable solvent was water, and optimizing the reaction conditions for the preparation of **163a**, a variety of amines (**10**) having alkyl or aryl substituents were reacted with formaldehyde **16** and 2-(nitromethylene)thiazolidine (**112**) (Yildirim et. al, 2014a).

We produced novel 6-substituted-8-nitro-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*]pyrimidine derivatives (**163**) in good to excellent yields (65-100%). An especially important outcome in terms of reaction yields was that at least 50% higher yields were often obtained under MW conditions when compared with conventional heating and the reaction times were reduced to minutes from several hours (Table 4.2).

Table 4. 2. Reaction conditions and yields of title compounds **163(a-z)**



Entry	Comp.	R	CH*	Yield (%)***	MW**	Yield (%)***
1	**163a**	(R)-(+)-1-phenylethyl	2.5h	92	5 min	100
2	**163b**	(R)-(+)-1-phenylpropyl	2.5h	70	4 min	95
3	**163c**	(S)-(-)-1-phenylpropyl	2h	94	4 min	100
4	**163d**	butyl	3h	41	4 min	65
5	**163e**	propyl	3.5h	35	4 min	65
6	**163f**	cyclohexyl	2.5h	82	4 min	100
7	**163g**	benzyl	4h	65	4 min	95
8	**163h**	3-trifluoromethylbenzyl	5h	77	4 min	98
9	**163i**	2-methylthienyl	4h	70	4 min	80
10	**163j**	4-chlorobenzyl	4h	63	4 min	80
11	**163k**	isopropyl	3.5h	78	4 min	100
12	**163l**	diphenyl	3h	70	4 min	100
13	**163m**	benzo[*d*][1,3]dioxol-5-yl	6h	42	7 min	72
14	**163n**	4-fluorophenyl	5h	58	4min	76
15	**163o**	p-tolyl	6h	32	4 min	55
16	**163p**	2-thiazoyl	3h	NR	4 min	NR
17	**163r**	2-mercaptobenzo[d]imidazol-5-yl	4h	NR	6 min	NR
18	**163s**	2-(1-piperazinyl)ethyl	5h	NR	4 min	NR
19	**163t**	1,2,4-triazoyl	4h	NR	6 min	NR
20	**163u**	6-methylpyridyl	8h	NR	6 min	NR
21	**163v**	6-nitroquinolin-5-yl	3h	NR	4 min	NR
22	**163y**	1-naphthyl	8h	NR	3 min	NR
23	**163z**	2,6-dichloro-4-nitrophenyl	16h	NR	5 min	NR

CH* 0.5 mmol reactants in 20 mL of water at reflux; **MW**** 0.5 mmol reactants in 2 mL of water at 90 °C. ***Total yields after column chromatographic separation **NR****** No reaction

On the other hand, the experiments showed that no cyclisation occurred with many heterocyclic (especially *N*-containing) amines or examples which were sterically hindered (Table 4.2, entries 16-23) under either conventional heating or MW irradiation. Even when the reaction times were extended to 16 hours (conventional) or 3-6 minutes (MW), no Mannich cyclisation products were observed or isolated. These results strongly suggest that if the amine **10** is insufficiently nucleophilic, for whatever reason, to allow formation of an imine as a first step, or subsequently an iminium ion at a later stage with formaldehyde (see Scheme 4.4 below) then the sequence will fail and only a few by-products will be obtained (Figure 4.1).

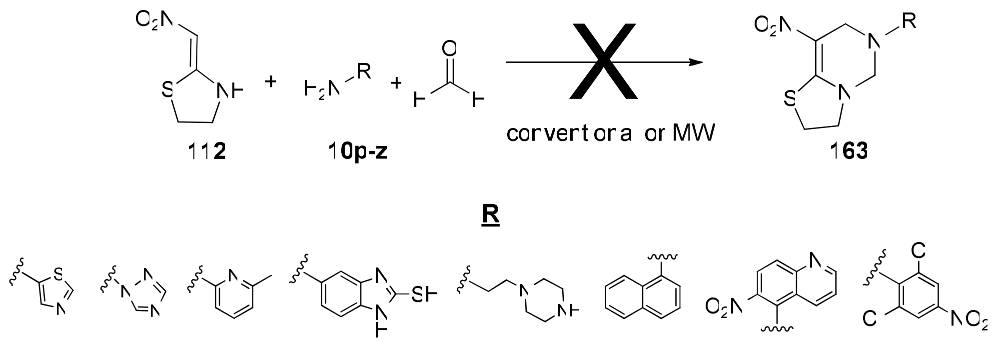
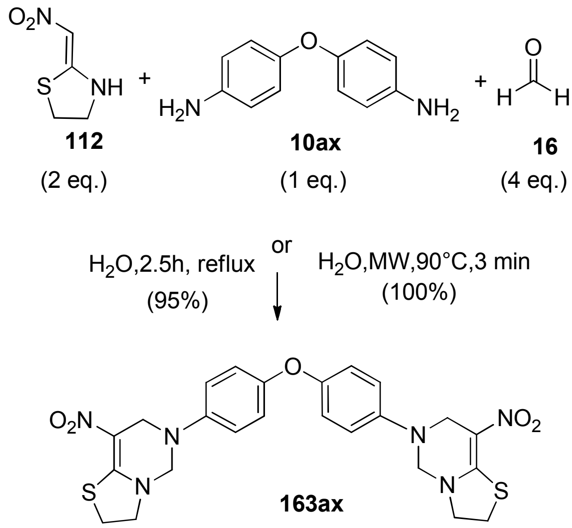


Figure 4. 1 Unreactive heterocyclic or bulky amine derivatives **10p-z** as Mannich substrate

However, the number of unsuccessful cyclisations are limited when compared with the number of successful examples (Table 4.2, entries 1-15). Based on these successful results, we can say that this Mannich-based three multicomponent cyclisation method was suitable for the efficient and green production of 6-substituted-8-nitro-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*]pyrimidines.

In order to expand the scope of this efficient microwave-mediated protocol, amines **10** were substituted by a diamine, 4,4'-oxydianiline **10ax**, which was reacted with two equivalents of nitroenamine **163** and four equivalents of formaldehyde **16** under both heating conditions (Scheme 4.4). The expected bicyclic product **163ax** was obtained in quantitative yield without any need for chromatographic separation, as it directly precipitated out of the cooled solution and only required washing and drying to secure the pure product. This result indicates that many other *bis*-amines could be used in this methodology leading to many types of bicyclic thiazolo[3,2-*c*] pyrimidines in a highly efficient manner. In addition, the microwave cyclisation protocol is especially ‘green’ and effective since no organic solvent or purification material is used.



Scheme 4. 4 Synthesis of bicyclic thiazolo[3,2-*c*]pyrimidine derivative **163ax**

The structures of all new compounds **163a-ax** were fully supported by means of IR, ^{1}H-NMR, ^{13}C-NMR and HRMS measurements. Also, the structures of **163g** and chiral, non-racemic products **163a-b** were further elucidated by X-ray crystallographic analysis (Figure 4.2).

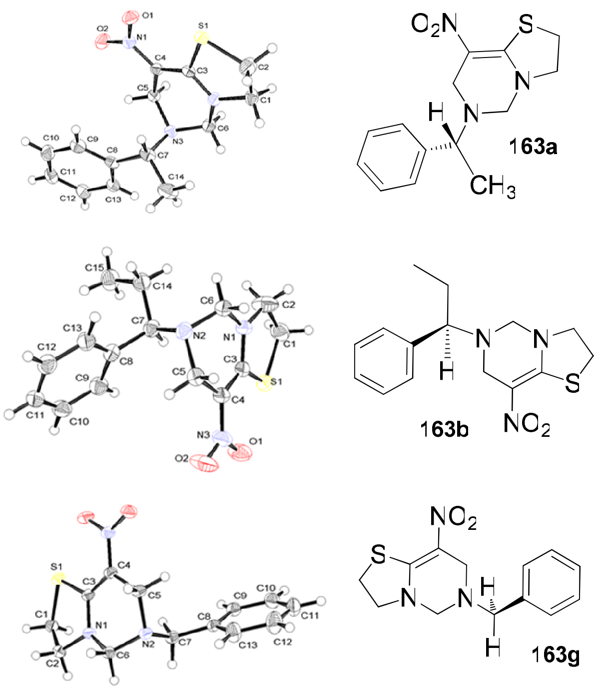
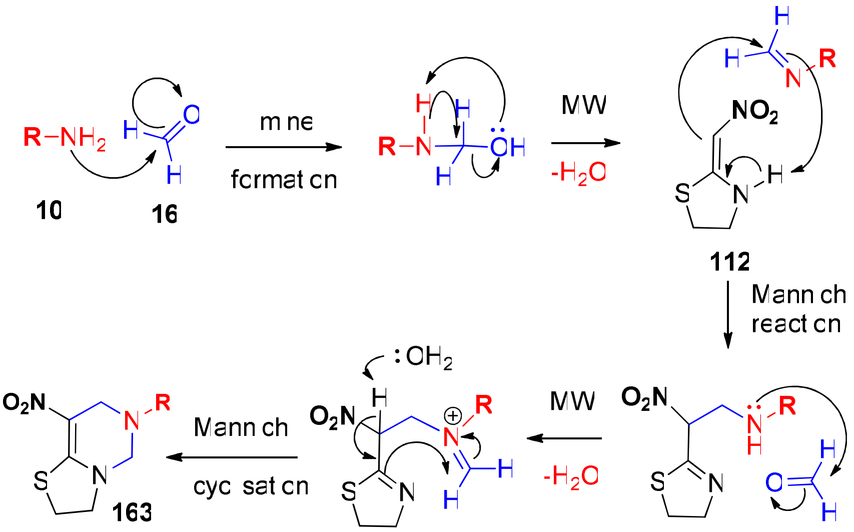


Figure 4. 2 X-ray crystal structures of **163a-b** and **163g**

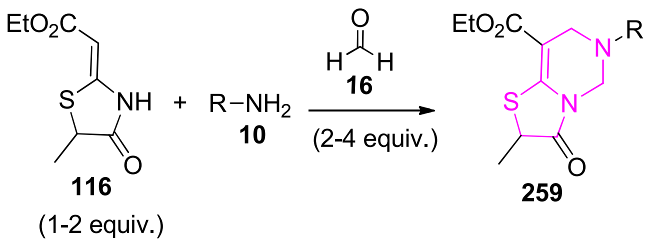
Given that the Mannich cyclisation takes place by imine formation, we can describe a mechanism in which first such an imine forms between the primary amine **10** and formaldehyde **16**. This then undergoes thermally-induced condensation with the nitroenamine **112** to give a *β*-amino-substituted nitroimine (or nitroenamine) which is the precursor of an iminium ion, following a second condensation with formaldehyde. Finally, an internal cyclisation of this iminium ion with the thiazoline C=N group results in formation of the 6-substituted-8-nitro-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*]pyrimidine products (Scheme 4.5).



Scheme 4. 5 Proposed microwave-mediated mechanism for the formation of derivatives **163**

4.3 PART 3: SYNTHESIS OF OXOTHIAZOLO[3,2-c]PYRIMIDINE CARBOXYLATES (259) BY CONVENTIONAL HEATING

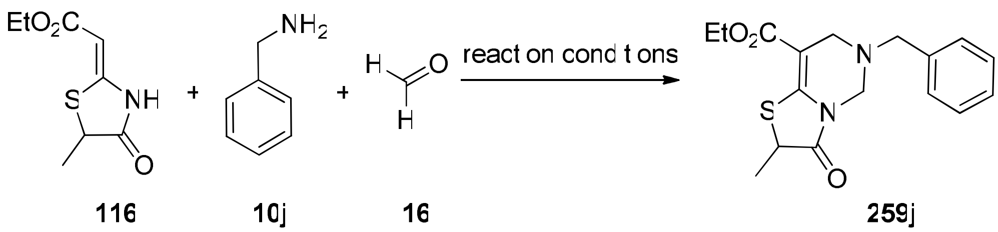
As a new example of our successful ongoing studies, herein we describe the one-pot Mannich cyclisation reactions of (*Z*)-ethyl 2-(5-methyl-4-oxothiazolidin-2-ylidene) acetate **116** with formaldehyde **16** and a variety of primary amines or bis-amines (**10**) and the successfully developed new efficient procedure for the preparation of novel and biologically interesting 3-oxothiazolo[3,2-*c*]pyrimidine carboxylates (**259**) under very mild conditions (Scheme 4.6).



Scheme 4. 6 Synthesis of starting material and novel 6-substituted 3-oxothiazolo[3,2-*c*]pyrimidine carboxylates via Mannich cyclisations

We tested a comprehensive set of reaction conditions using **116**, formaldehyde **16** and benzylamine **10j** in a model reaction for the synthesis of **259j** (summarized in Table 4.3). In all trials at least two equivalents of formaldehyde **16** were used in comparison with **116** and **10j**.

Table 4. 3. Optimization of reaction conditions for the synthesis of compound **259j**



Entry	Reaction conditions*	Catalyst	Time	Yield (%)
1	CH_2Cl_2, **116** (1eq), **10j** (1eq), **16** (2.0 eq)	Et_3N	7h	36
2	EtOH, **116** (1eq), **10j** (1eq), **16** (2.0 eq)	K_2CO_3	5h	42
3	EtOH, **116** (1eq), **10j** (1eq), **16** (2.0 eq)	Et_3N	4h	53
4	Neat,**116** (1eq), **10j** (1.5eq),**16** (3.0 eq)**	-	2h	27
5	H_2O, **116** (1eq), **10j** (1eq), **16** (2.0 eq)	-	3h	48
6	H_2O, **116** (1eq), **10j** (1eq), **16** (2.5 eq)	Et_3N	3h	40
7	H_2O, **116** (1eq), **10j** (1eq), **16** (2.5 eq)	MW	2-10 min	-[a]
8	CH_3CN, **116** (1eq), **10j** (1eq), **16** (2.0 eq)	Et_3N	3h	65
9	CH_3CN, **116** (1eq), **10j** (1eq), **16** (2.0 eq)	K_2CO_3	6h	63
10	CH_3CN, **116** (1eq), **10j** (1eq), **16** (2.0 eq)	**-**	**3h**	**90**
11	CH_3CN, **116** (1eq), **10j** (1eq), **16** (2.0 eq)	MW	2-10 min	-[a]

*The reactions were performed at reflux temperature of the solvents specified. ** The reactions were carried out at 100°C. [a] No product was seen or isolated.

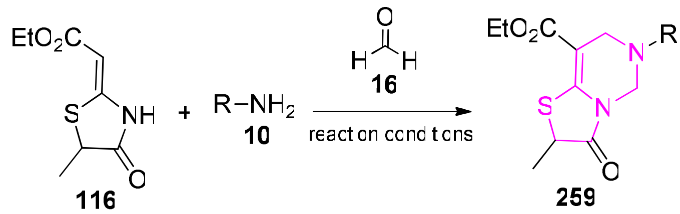
Best yields (90%) were attained when the reaction was performed in acetonitrile at reflux for 3 hours (entry 10, table 4.3) without using any base or catalyst. The reaction was not effective under solvent-free conditions even in the presence of 3 equivalents of formaldehyde solution (entry 4, table 4.3). Also, the use of triethylamine or potassium carbonate in acetonitrile did not increase the product yields (63-65%) (entry 8-9, table 4.3). As opposed to the results in our previous work (Yildirim et. al, 2014a), the use of water as a solvent did not provide any increase in product yields (40-48%) in the current work (entry 5-6, table 4.3). We also applied microwave irradiation (in dynamic mode, 80-90^{o}C) in variable reaction times (2-10 min), however, no product **259** was detected by TLC analysis of the crude reaction mixture, only some decomposition reactions were obtained in most of the trials (entry 7 and 11, table 4.3).

The cyclisation product **259j** was purified by flash column chromatography and the structure assigned on the basis of proton NMR chemical shifts of two methylenic groups in the tetrahydropyrimidine ring resonating at 3.63, 4.51 ppm, consistent with the NMR data and X-ray structures of their analogs described in our previously reported work (Yildirim et. al, 2014a).

In order to survey the scope and limitations of our cyclisation methodology, further reactions of 2-methylene-4-oxothiazolidine **116** with a variety of primary amines **10a-y** were carried out in the presence of 2-4 equivalents of formalin **16** in acetonitrile at reflux for 3-8 hours or overnight (Table 4.4) (Yildirim and Çelikel, 2015).

First, the Mannich cyclisations of **116** with primary amines **10a-r** in the presence of formalin **16** (2 equiv.) were studied. The reactions of amines bearing simple alkyl groups **10a-c** were completed within 3-6 hours and the product yields were good (73-90%) (entries 1-3, table 4.4). However, the reaction of **10f** with **116** was completed in good yields (entry 6) after overnight heating. Besides, the reactions of amines bearing allyl, propargyl, phenyl or substituted phenyl and naphthyl rings proceeded in good and excellent yields (82-100%) but required longer reaction times (entries 4,5,7,8,16) except the cyclisation of **10i** with **116** (entry 9). Otherwise, the cyclisations of benzylamine derivatives required quite short reaction times with good to excellent yields (65-94%) (entries 10-15) when compared with the cyclisations of other monoamines. Similarly, the cyclisation reaction of 2-thienylmethylamine **10r** with **116** was very rapid and the reaction yield was quantitative (entry 17). Our success in the formation of **259a-r** using monoamines **10a-r** through Mannich cyclisations encouraged us to use bis-amines **10s-y** with **116** (2 equiv.) in the presence of formalin **16** (4 equiv.) under similar reaction conditions (entries 18-22, table 2). Not suprisingly, double Mannich cyclisation products through both primary amine sides were obtained with all bis-amines in good to excellent yields under reflux overnight (entries 18,19,21,22). However, product **259u** was obtained by the reaction of 4,4'-sulfonyldianiline **10u** with **116** in moderate yields but in shorter reaction time (entry 20), however, the substitution of 3,3'- sulfonyldianiline with **10u** did not give any expected cyclisation product with **116** and **16**.

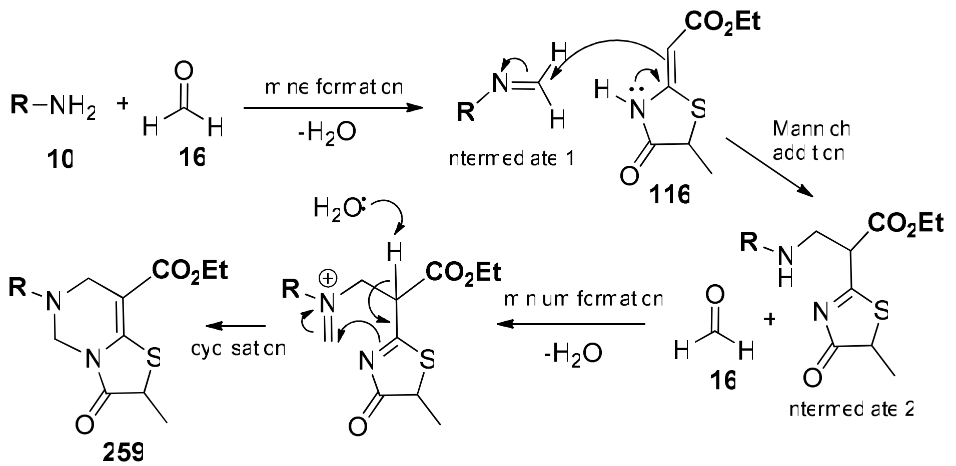
Table 4. 4. Reaction yields and conditions for the synthesis of 6-substituted 3-oxothiazolo[3,2-*c*]pyrimidine carboxylates **259a-z**



Entry	R	Equiv.of **16**	Time (h)	Product(s)	Yield (%)
1	propyl	2.0	6.0	**259a**	73
2	isopropyl	2.0	3.0	**259b**	92
3	butyl	2.0	6.0	**259c**	90
4	allyl	2.0	16	**259d**	100
5	propargyl	2.0	16	**259e**	100
6	cyclohexyl	2.0	20	**259f**	92
7	phenyl	2.0	16	**259g**	100
8	tolyl	2.0	16	**259h**	82
9	benzo[d][1,3]dioxol-5-yl	2.0	5.0	**259i**	100
10	benzyl	2.0	3.0	**259j**	90
11	(R)-1-phenylpropyl	2.0	5.0	**259k (isomer mixt.)**	70
12	(S)-1-phenylpropyl	2.0	4.5	**259l (isomer mixt.)**	65
13	p-chlorobenzyl	2.0	5.5	**259m**	96
14	3-trifluoro methylbenzyl	2.0	6.0	**259n**	65
15	diphenyl	2.0	3.5	**259o**	94
16	2-methyl naphthyl	2.0	16	**259p**	95
17	2-methylthienyl	2.0	8.0	**259r**	100
18	bis(4-aminophenyl) methanonyl	4.0	16	**259s**	70
19	4,4'-Oxydianilinyl	4.0	16	**259t**	100
20	4,4'-sulfonyldianilinyl	4.0	16	**259u**	45
21	4,4'-thiodianilinyl	4.0	16	**259v**	100
22	ethylenediamine	4.0	16	**259y** **259z**	75 25

Possibly due to the strong EW-effect of sulfonly groups resulting in a decrease in nucleophilicity of amine functionalities. Similar decrease in product yield can be observed in the synthesis of **259s** derivative. In the cyclisation reaction of **116** with 1,2-ethylenediamine **10y**, a Mannich cyclisation product **259z** through only one amine side was obtained along with the double Mannich cyclisation product **259y** in totally quantitative yield (entry 22). Both products **259y-z** were purified by flash column chromatography by eluting with ethyl acetate and methanol, respectively. The structure of **259z** was confirmed by infrared absorption peaks of NH_2 group in 3350 cm^{-1}, NH signal resonating at 5.29 ppm in proton NMR and HRMS data.

A plausible reaction mechanism for the formation of derivatives **259** is reported in Scheme 4.7. The first step is the formation of an imine intermediate, which reacts with **116** via a Mannich-type addition reaction. The resulting new intermediate forms an iminium ion by reacting with another formaldehyde molecule. The last step involves a new water-assisted intramolecular Mannich-type cyclisation reaction and results in the formation of derivatives **259**.

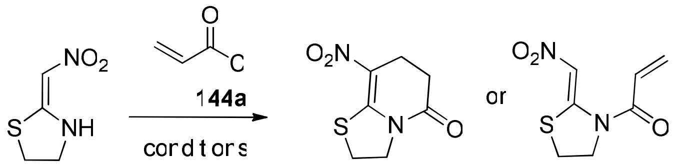


Scheme 4. 7 Plausible mechanism for the formation of 6-substituted 3-oxothiazolo[3,2-*c*]pyrimidine carboxylates **(259)**

4.4 PART 4: SYNTHESIS OF THIAZOLO[3,2-*a*]- and IMIDAZOLO[1,2-*a*]- PYRIDONES (260, 248) VIA MICHAEL CYCLISATIONS

Our initial experiments using **112** and **144a** in different solvents and conditions with different bases were focused to find the optimal reaction conditions for the cyclisations. So, we have tried a variety of bases and Lewis bases to determine their effects on the cyclisations (Table 4.5). First of all, no desired products (**260** or **261**) formed without using a base (entries 1-2).

Table 4. 5. Optimisation of reaction conditions



112 260 261

Entry	Bases (equiv.)^{b}	Conditions	Yield (%)^{c} 260	261
1	No base	DCM, r.t., 5 h	–^{a}	–^{a}
2	No base	CH_3CN, reflux, 3 h	–^{a}	–^{a}
3	pyridine (2 eq.)	DCM, r.t., 3 h	–	23
4	pyridine (2 eq.)	CH_3CN, reflux, 2 h	–	15
5	Et_3N (2.2 eq)	DCM, r.t., 4 h	21	36
6	Et_3N (2.5 eq)	CH_3CN, reflux, 2 h	–	25
7	piperidine (1.5 eq.)	CH_3CN, reflux, 2 h	–	53
8	CH_3NH_2 (2.0 eq.)	DCM, reflux, 3 h	–^{a}	–^{a}
9	DBU (2.0 eq.)	CH_3CN, reflux, 2 h	–	32
10	i-Pr_2NEt (1.5 eq.)	DCM, r.t., 8 h	–	48
12	$Ca(OH)_2$ (2.0 eq.)	DCM, r.t., 4 h	48	34
13	Cs_2CO_3 (2.0 eq.)	CH_3CN, r.t., 3 h	–	25
14	Cs_2CO_3 (1.2 eq.)	CH_3CN, reflux, 2 h	18	40
15	**K_2CO_3 (2.0 eq.)**	**DCM, r.t., 3 h**	**90**	–
16	K_2CO_3 (2.0 eq.)	CH_3CN, reflux, 3 h	50	–

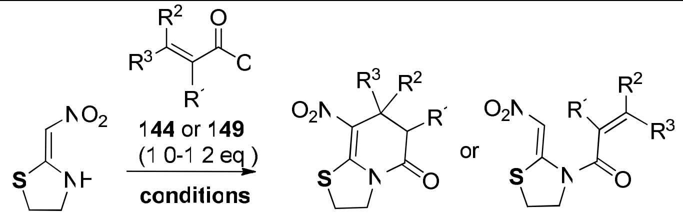
^{a} None of this product formed. ^{b} Equivalents of bases respect to nitroenamine. ^{c}All yields were calculated after purification by flash chromatography.

While most of the amine bases showed poor or no activity to induce the cyclisation (entries 3-10), inorganic bases were moderately active and facilitated the formation of cyclisation products (entries 12-16). However, addition of 2.2 equiv of Et_3N in DCM at room temperature led to formation of products **260a** in 21% and **261a** in 36% yields (entry 5). In the presence of $Ca(OH)_2$, better yields were obtained for formation of product **260a** (entry 12). Addition of Cs_2CO_3 was only effective at reflux, giving the products in low yields (entry 14). We were then pleased to find that use of 2 equiv of K_2CO_3 in DCM gave the cyclisation product **260a** in excellent yields (90%) at room temperature with no **261a** formation observed (entry 15). However, a low yield of **260a** was obtained when the same mixture was refluxed in acetonitrile (entry 16).

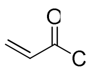
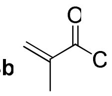
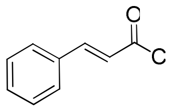
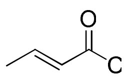
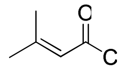
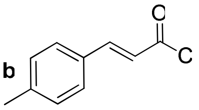
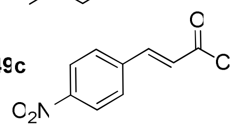
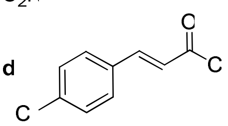
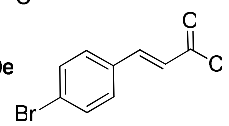
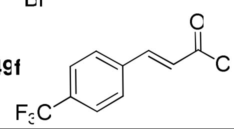
After finding the optimized conditions for the model reaction, we first studied the Michael cyclisations of some commercially available acryloyl chlorides **144a-b**,

144c-d and cinnamoyl chloride **149a** with **112** (Table 4.6) (Yildirim et al, 2014b). Thiazolopyridinones **260a-c** were obtained in good yields (entries 1-4) using K_2CO_3 or Cs_2CO_3 at room temperature or at reflux.

Table 4. 6. Formation of thiazolopyridinones **260** and *N*-enoyl-(2-nitromethylene)thiazolidines **261**



112 (1.0 eq.) **260** **261**

Entry	Substrate	Conditions	Product	Yield (%)[a]
1	**144a** 	A	**260a**	90
2	**144b** 	B	**260b**	79
3		C		35
4	**149a** 	C	**260c**	89
5	**144c** 	B	**261a**	62
6		C		70
7	**144d** 	C	**261b**	61
8	**149b** 	C	**260d**	67
9	**149c** 	B	**260e**	58
10	**149d** 	B	**260f**	79
11	**149e** 	B	**260g**	57
12	**149f** 	B	**260h**	69

Conditions: **A**: K_2CO_3 (2.0 eq.), 25˚C, DCM, 3-16h; **B**: K_2CO_3 (2.0 eq.), 80˚C, CH_3CN, 4-36h; **C**: Cs_2CO_3(1.0-2.0 eq.), 25˚C, CH_3CN, 1.5-16h;
[a] Yields after isolation by flash chromatography using hexane:ethyl acetate mixtures.

The title compounds **260e-h** have been obtained in moderate to good yields (entries 9-12) using mostly K_2CO_3 in CH_3CN at reflux. However, only using Cs_2CO_3 at 25^{o}C was effective in the formation of **260d** (entry 8), the use of K_2CO_3 did not lead any product formation either at rt or at reflux. The molecular structure of **260a** was determined by X-ray single crystal analysis (Figure 4.3).

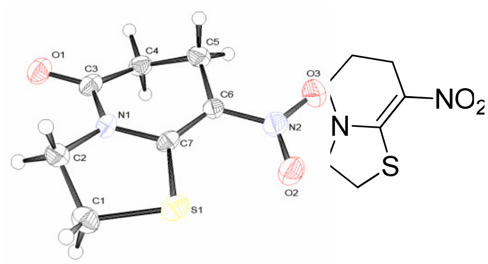
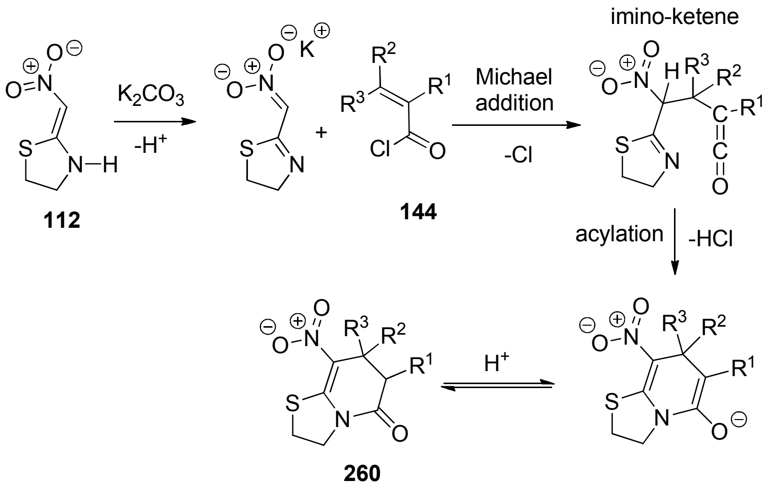


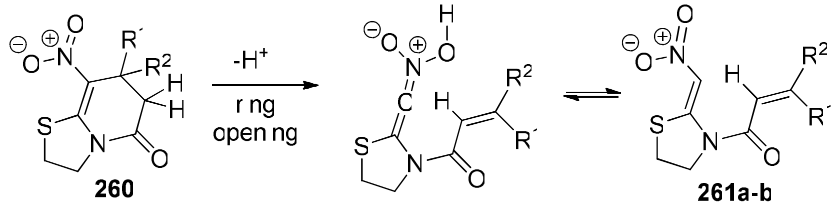
Figure 4. 3 X-ray structure of **260a**

We propose a plausible mechanism for the formation of thiazolo derivatives **260** in Scheme 4.8. First, in the presence of K_2CO_3 or Cs_2CO_3, **112** gives a nitronic acid salt intermediate by tautomerization. Then, Michael addition through the β-C atom of **144** with the nitronic acid gives an imino-ketene intermediate. Then follows an acylation of the imine nitrogen and a second tautomerization step, resulting in ring closure reactions affording thiazolopyridinones **260**.



Scheme 4. 8 Plausible mechanism for the formation of **260**

However, uncyclised addition products **261a-b** have been obtained by the reactions of compound **112** with **144c-d** in moderate yields under similar conditions (Table 4.6, entries 5-7). Since crotonoyl (**144c**) and 3,3-dimethylacryloyl (**144d**) chlorides have alkyl group(s) on the end of double bond, they are poor Michael acceptors and this may prevent the cyclisation. Alternatively, they may form by loss of a proton next to the C=O on **260** and retrocyclisation via an allenyl nitronate and tautomerism (Scheme 4.9). The structure of **261a** was demonstrated by X-ray crystallography (Figure 4.4).



Scheme 4. 9 Ring-opening mechanism for the formation of **261a-b**

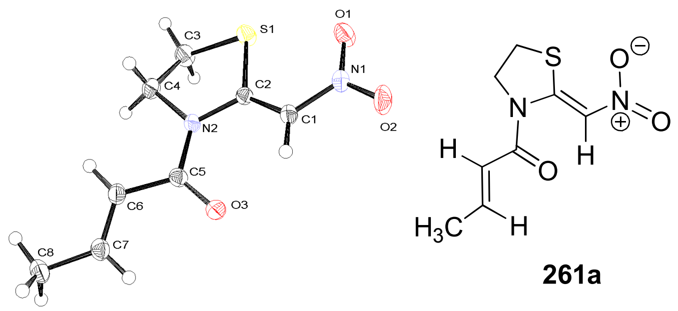
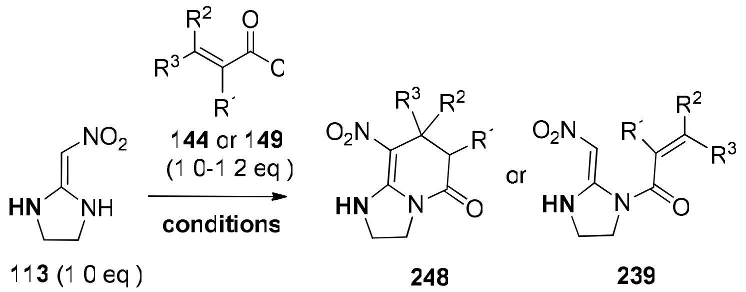
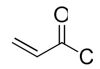
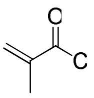
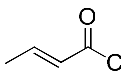
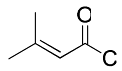
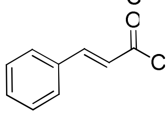
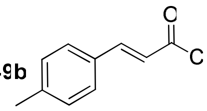
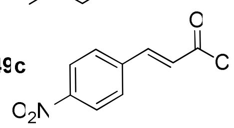
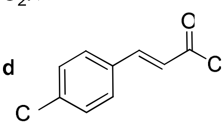
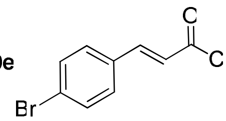
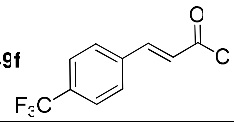


Figure 4. 4 X-ray structure of **261a**

Our success in the formation of derivatives **260** using compound **112** through Michael addition by this one-step transformation prompted us to investigate the behaviour of 2-(nitromethylene)imidazoline **113** with compounds **144a-d** and **149a-f** (Table 4.7). Perhaps surprisingly, no cyclisation product **248** was obtained in the reaction of **113** with **144a** in the presence of K_2CO_3 (or Cs_2CO_3) (entry 1). However, the title compound **248a** was obtained in excellent yield (96%) using 2 equiv of Et_3N in CH_3CN at reflux (entry 2). Suprisingly, the reaction of **144b** with **113** was unsuccessful in giving either product **248** or **239** (entry 3), but the reaction of **144c** with **113** did give the expected cyclisation product **248b** in good yield (entry 4). This contrast between the reactions of **112** and **113** with compounds **144b** and **144d** might be explained by the mechanistic difference in their cyclisation reactions (see schemes 4.8-9-10). However, **144d** with **113** afforded only addition product **239a** in excellent yields (entry 5). The reactions of cinnamic acid chlorides **149a-f** with **113** afforded the expected cyclisation products **248c-h** in the presence of triethylamine in good yields (entries 6-12) (Yildirim et al, 2014b).

Table 4. 7. Formation of imidazolopyridinones **248** and *N*-enoyl-(2-nitromethylene) imidazolidines **239**

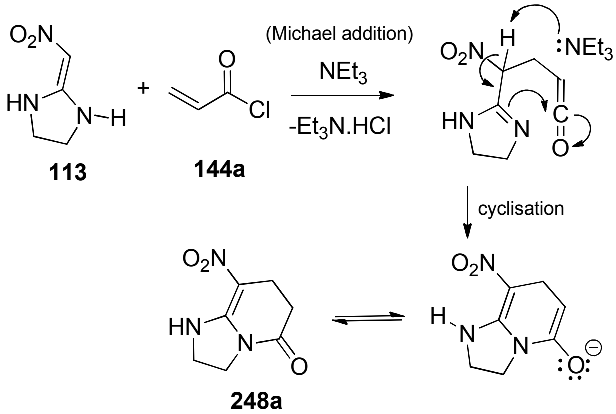


Entry	Substrate	Conditions	Product	Yield(%)[a]
1	144a 	A, C	–[b]	–[b]
2	**144a**	D	**248a**	96
3	144b 	B, D	–[b]	–[b]
4	144c 	D	**248b**	74
5	144d 	D	**239a**	95
6	149a 	B	**248c**	–[b]
7		D		89[c]
8	149b 	D	**248d**	68
9	149c 	D	**248e**	60
10	149d 	D	**248f**	76
11	149e 	D	**248g**	58
12	149f 	D	**248h**	72

Conditions: **A**: K_2CO_3 (2.0 eq.), 25 ˚C, DCM, 3-16 h; **B**: K_2CO_3 (2.0 eq.), 80 ˚C, CH_3CN, 4-36 h; **C**: Cs_2CO_3 (1.0-2.0 eq.), 25 ˚C, CH_3CN, 1.5-16 h; **D**: Et_3N (2.0 eq.), 80 ˚C, CH_3CN, 2-24 h.

[a] Yields after isolation by flash chromatography using ethyl acetate.[b] No product was observed in TLC. [c] Purified by recrystallization from ethyl acetate.

Likewise, we can propose a similar mechanism for the formation of derivatives **248**. First, in the presence of triethylamine, Michael addition through the β-C atom of **144a** with compound **113** gives an imino-ketene intermediate which undergoes an intramolecular cyclisation with a final tautomerization affording the title compound **248a** (Scheme 4.10).



Scheme 4. 10 Proposed mechanism for the formation of **248a**

4.5 PART 5: BIOLOGICAL ACTIVITY STUDIES OF THIAZOLO- and 4-OXOTHIAZOLO-[3,2-*c*]PYRIMIDINES (163, 259)

After preparation of new thiazolo[3,2-*c*]pyrimidine derivatives (**163** and **259**) with good yields and determination of their structures, biological activity studies have been started. As being the similar derivatives given in literature having a wide variety of biological activities, we also expected that the new thiazolo[3,2-*c*]pyrimidine derivatives would exhibit antibacterial and anticancer activities and hence, we completed their activity assays. The related results and followed methods are being given below.

4.5.1 Anticancer (cytotoxicity) Studies

First of all, this study was conducted by a researcher who is expert on his field, from A.I.B.U. Faculty of Medicine, Department of Pharmacology.

4.5.1.1 Results of anticancer activity studies

According to the obtained results, it was observed that cell viability of six of the **163** derivatives (**163a, 163c, 163j, 163k, 163l, 163m**) falls below 50% at their 1000 μM concentrations (Figures 4.5-4.9). Three substances (**163c, 163k, 163m**) among them were very close to the 5-FU dose-effect plot and exhibit a curve even under 5-FU's (Figure 4.7-4.9). Accordingly, it was suggested that these three substances demonstrating the effect close to the effect of 5-FU (particularly those containing different alkyl and aryl groups at the 6-position) (Figure 4.5) has a potential to be anticancer drugs and it was necessary to study in more detailed manner.

According to the results of the first anticancer study, a second dose-effect study was performed. Exactly the same method given above was used, but this time, with three different concentrations (1, 10, 100 μM) of 14 different **163** derivatives and with three different concentrations (1, 10, 100 μM) 23 different **259** derivatives synthesized and 5-FU were applied for 72 hours. At the end of 72-hour incubation, cell viability was measured by MTT test.

According to the results of the second study which was performed with lower doses, it was determined that proliferative effects (>100%) in 11 substances, weak anticancer effects (80-100%) in 17 substances, moderate and high anticancer effects (80-60%) in 6 substances (**163l-m, 259h, 259j, 259r, 259y**) and almost the same or effect more potent anticancer activity (60-40%) as compared with the reference drug (5-FU) in 5 substances (**163ax, 259g, 259i, 259m, 259n**) (Figure 4.10-4.14).

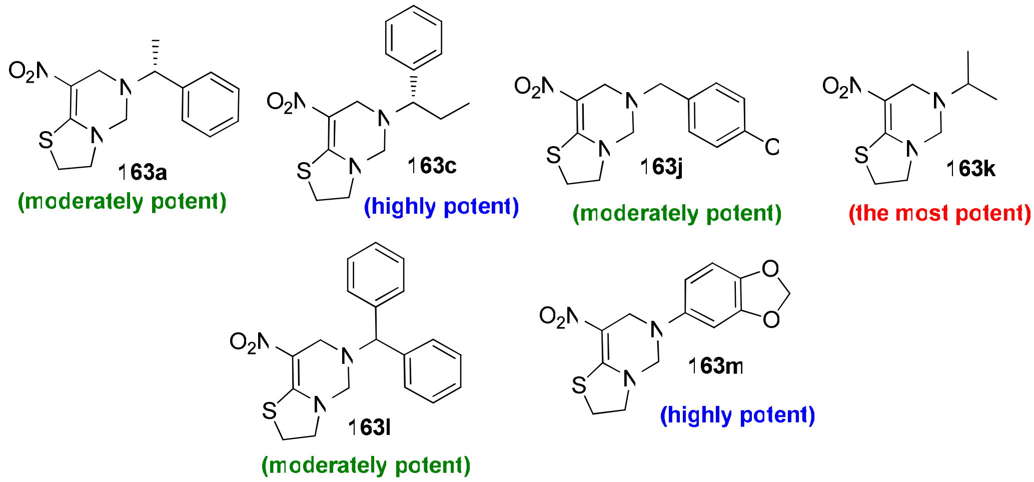


Figure 4. 5 **163** derivatives showing anticancer effect on MCF-7 breast cancer cells (in 1000 μm concentrations)

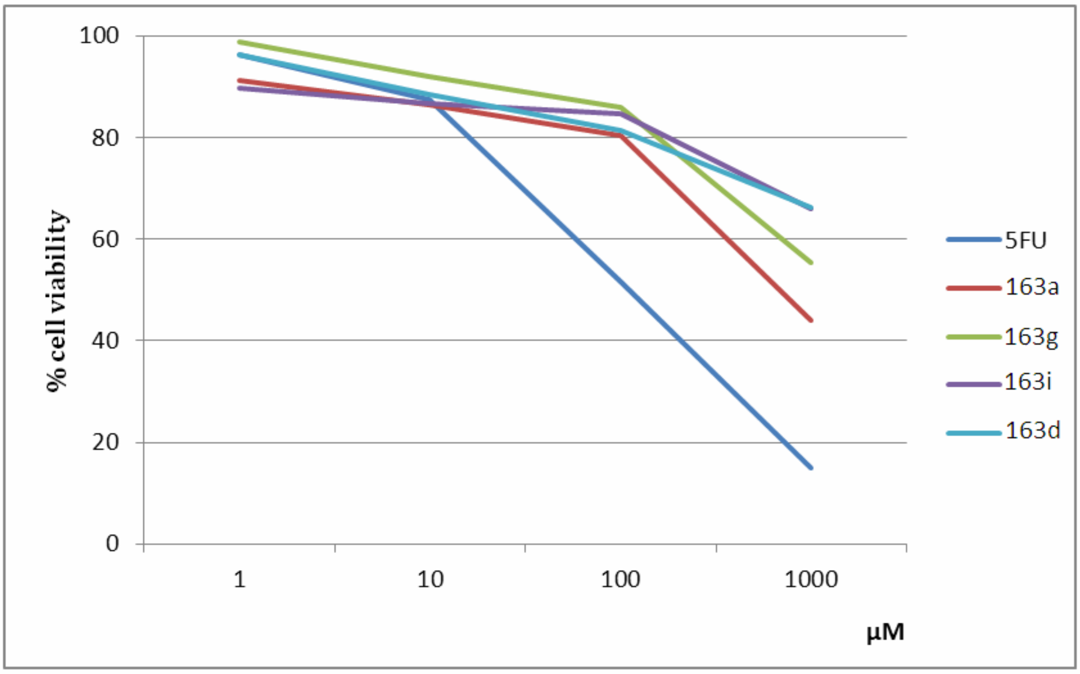


Figure 4. 6 Plot for 24-h-dose-dependent effect of 5-FU and **163a**, **163d**, **163g**, **163i** derivatives on MCF-7 breast cancer cells (first study)

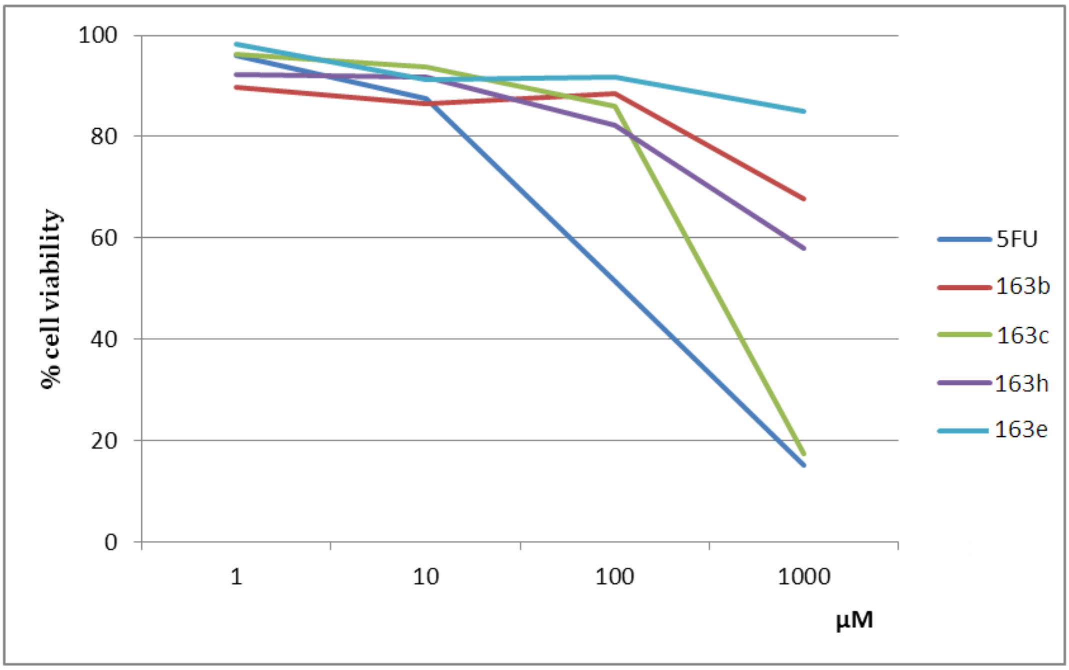


Figure 4. 7 Plot for 24-hour-dose-dependent effect of 5-FU and **163b, 163c, 163e, 163h** derivatives on MCF-7 breast cancer cells (first study)

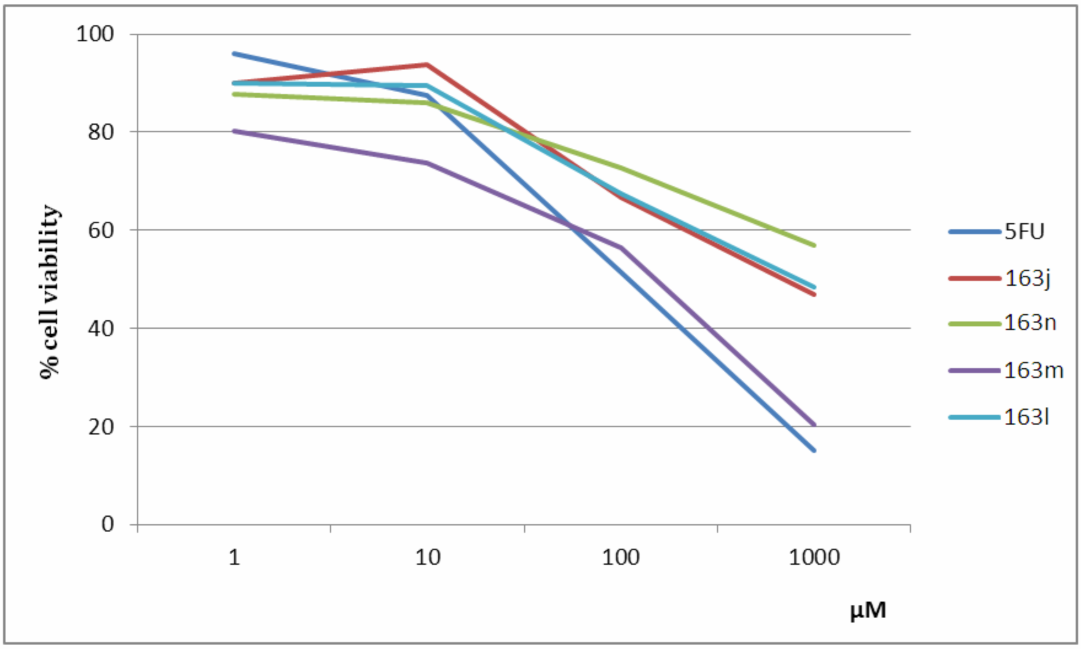


Figure 4. 8 Plot for 24-hour-dose-dependent effect of 5-FU and **163j**, **163l**, **163m**, **163n** derivatives on MCF-7 breast cancer cells (first study)

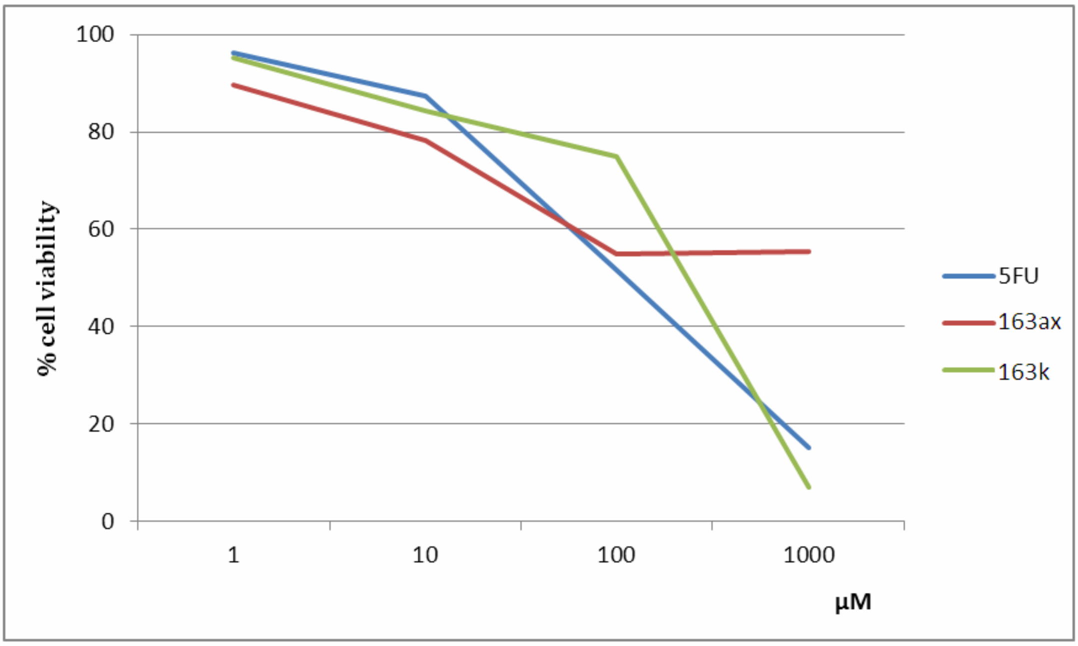


Figure 4. 9 Plot for 24-hour-dose-dependent effect of 5-FU and **163k**, **163ax** derivatives on MCF-7 breast cancer cells (first study)

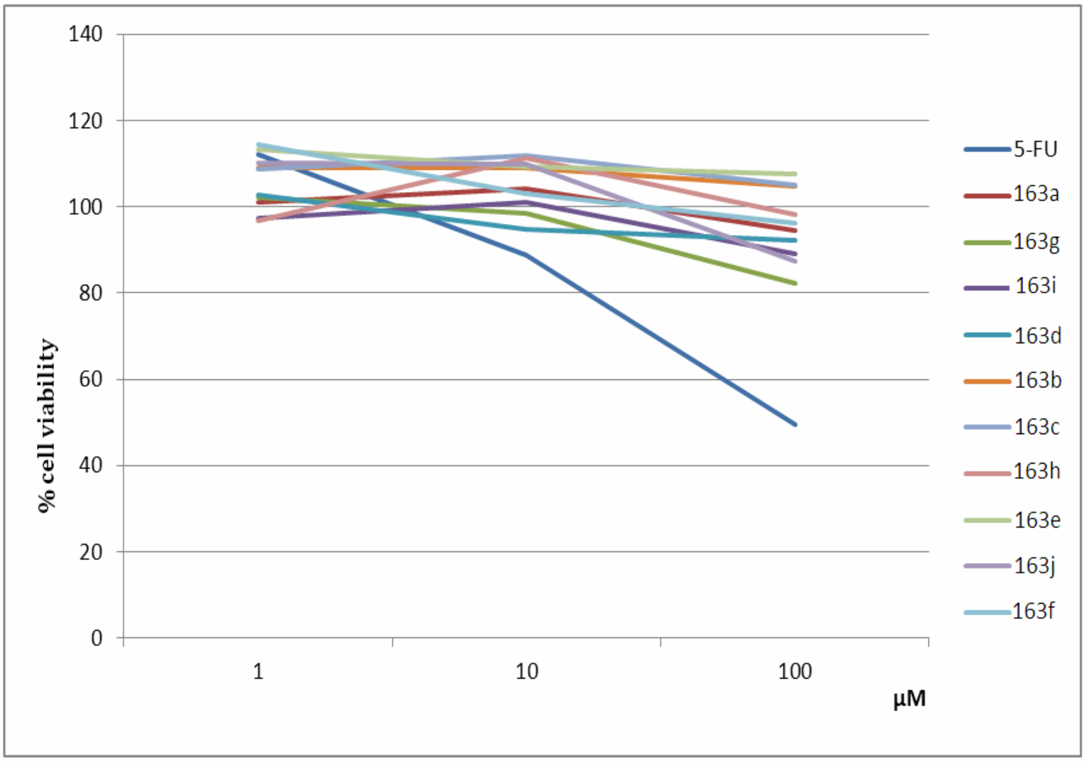


Figure 4. 10 Plot for 24-hour-dose-dependent effect of 5-FU and **163a-j** derivatives on MCF-7 breast cancer cells (second study)

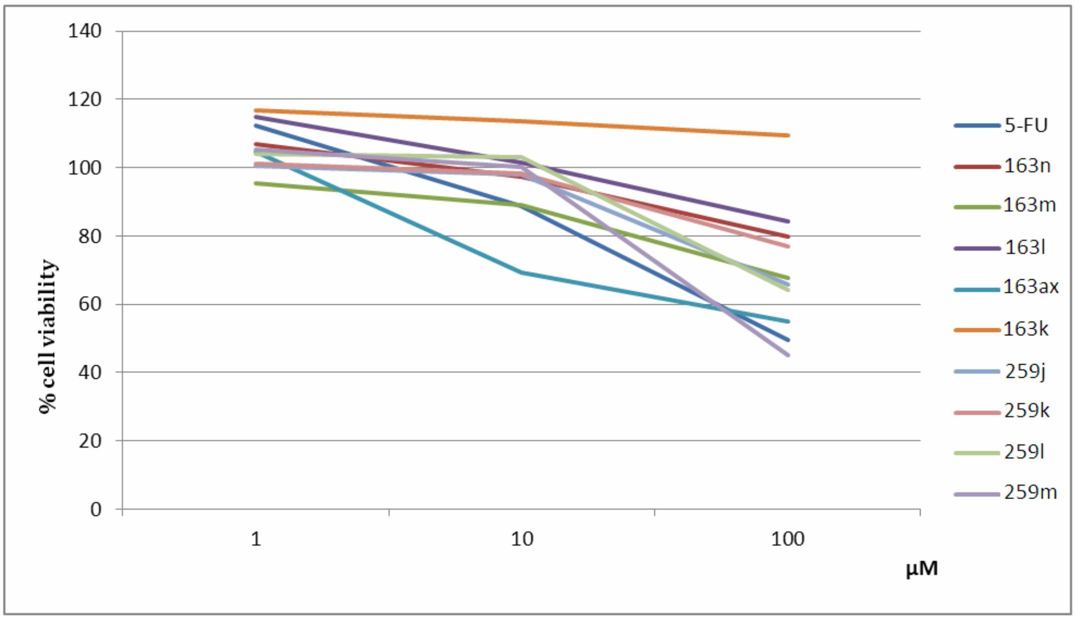


Figure 4. 11 Plot for 24-hour-dose-dependent effect of 5-FU and **163k-m**, **163ax**, **163j-m** derivatives on MCF-7 breast cancer cells (second study)

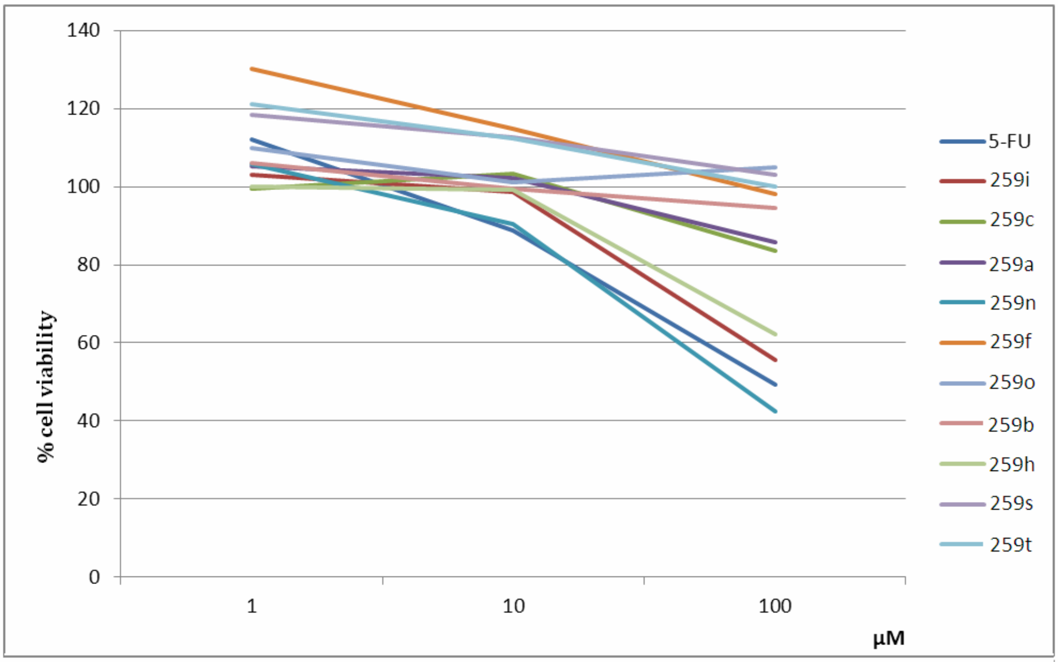


Figure 4. 12 Plot for 24-hour-dose-dependent effect of 5-FU and **259a-c**, **259f**, **259h-i**, **259n-o**, **259s-t** derivatives on MCF-7 breast cancer cells (second study)

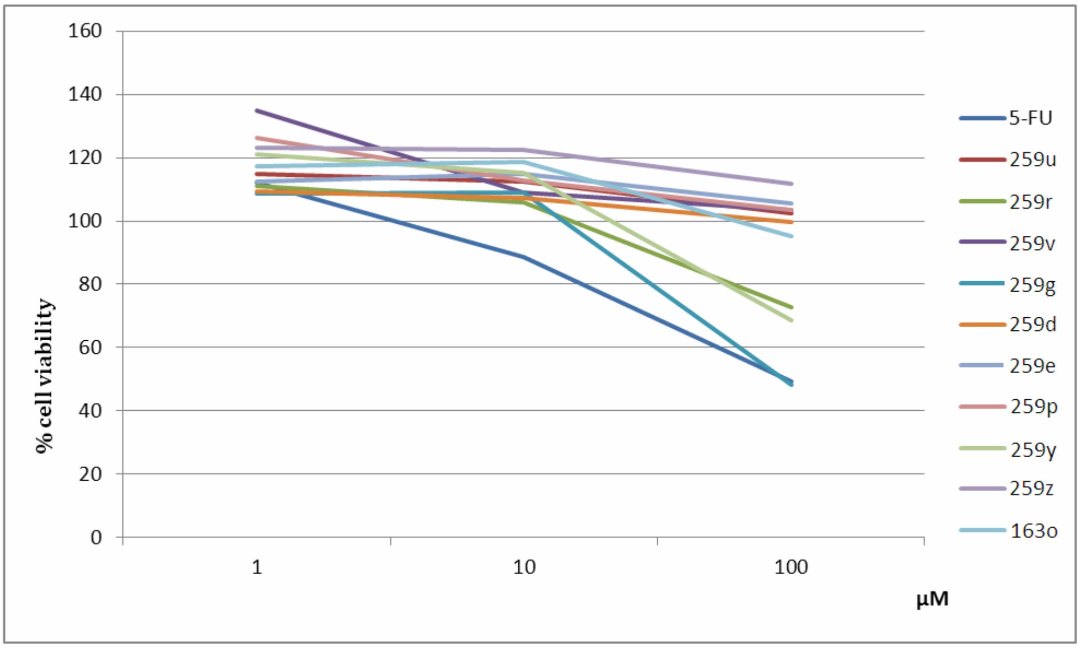


Figure 4. 13 Plot for 24-hour-dose-dependent effect of 5-FU and **163o**, **259d-e**, **259g**, **259p-r**, **259u-z** derivatives on MCF-7 breast cancer cells (second study)

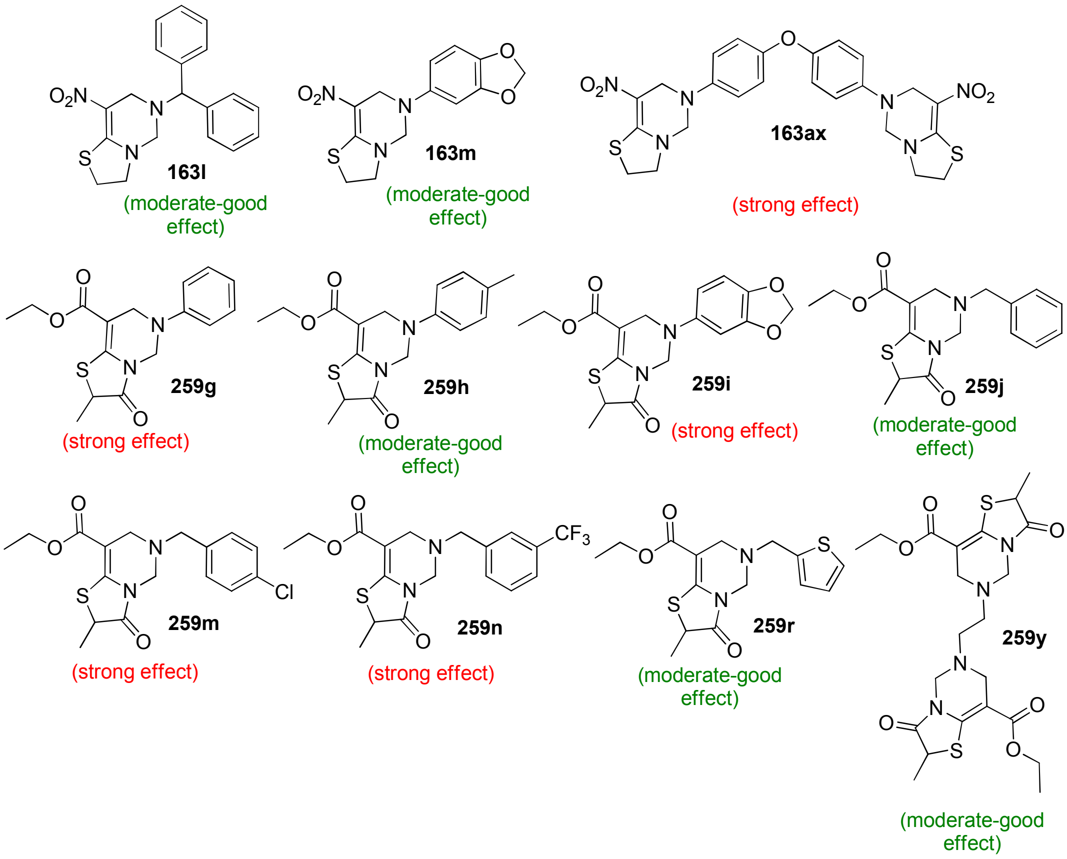


Figure 4. 14 163 and **259** derivatives showing anticancer effect on MCF-7 breast cancer cells (in 100µM concentrations)

4.5.2 Antibacterial Activity Studies

As given in the literature examples of thiazolo[3,2-*a*]- and [4,5-*d*]pyrimidines, the derivatives having thiazolopyrimidine structure may show antimicrobial or antibacterial effects. Therefore, antibacterial studies of thiazolo[3,2-*c*]pyrimidine derivatives (**163** and **259**) were performed by researchers who are specialist in this field, in A.I.B.U. Faculty of Arts and Sciences, Department of Biology. The followed methods and the corresponding results are given below.

4.5.2.1 Results of Antibacterial Activity Studies

According to the obtained results, the high inhibitory effects of tested thiazolo[3,2-*c*]pyrimidine derivatives were not observed against bacteria used. According to the results obtained by the zone of inhibition measurements, it was observed that only bacteriostatic effect of **163a** and **163g** derivatives against *P.vulgaris* bacteria (Figure 4.15); **259r** derivative showed moderate against *S.epidermidis* and weak antibacterial effect against *S.aureus*; **259r** derivative shows bacteriostatic effect against S.aureus; and **259z** derivative shows weak antibacterial effect against *P.vulgaris, K.pneumonia, S.marcescens, E.cloacae* and bacteriostatic effect against *S.typhimurium*. It was not found a good antibacterial effect in the other compounds tested. The inhibition zones of the **259z** derivatives, gives results very close to the zone of inhibition of the antibiotic erythromycin, but compared with the results given by the inhibition of other antibiotics, it is understood that these results are quite low. Therefore, the effect of the **259z** derivative was defined as poor (in compound 39, Table 4.8)

Table 4. 8. The inhibition effect by the synhesized **163** and **259** derivatives against bacteria used and the zones of inhibition produced.

	Compound	**Bacteria and inhibition zones**							
		SA	***SE***	***PV***	***PA***	***KP***	***ST***	***SM***	***EC***
1	**163a**	-	-	bs	-	-	-	-	-
2-6	**163b-f**	-	-	-	-	-	-	-	-
7	**163g**	-	-	bs	-	-	-	-	-
8-16	**163h-p**	-	-	-	-	-	-	-	-
17-27	**259a-k**	-	-	-	-	-	-	-	-
28	**259l**	8	15	-	-	-	-	-	-
29-32	**259m-p**	-	-	-	-	-	-	-	-
33	**259r**	bs							
34-38	**259s-y**	-	-	-	-	-	-	-	-
39	**259z**	-	-	7-8	-	8-9	bs	7-8	8
Positive controls (Antibiotics)	erythromycin	29	39	13	0	13	11	11	9
	ampicillin	42	33	30	0	8	29	15	28
	carbenicillin	43	38	38	20	8	30	29	33
	tetracycline	30	8	35	15	29	24	23	30
	chloramphenicol	26	33	28	9	30	28	27	30

SA**: **S.aureus**; **SE**: **S.epidermidis**; **PV: P.vulgaris**; **PA: P.aureginos; KP: K.pneumoni;ST: S.typhimurium; SM: S.marcescens; EC: E.cloacea. bs: bacteriostatic effect

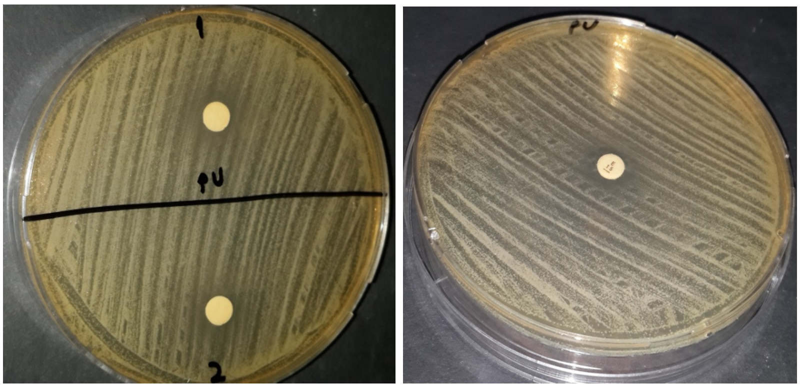


Figure 4. 15 Inhibition zones of **163a** and **163g** derivatives showing comparative bacteriostatic effects with erythromycin

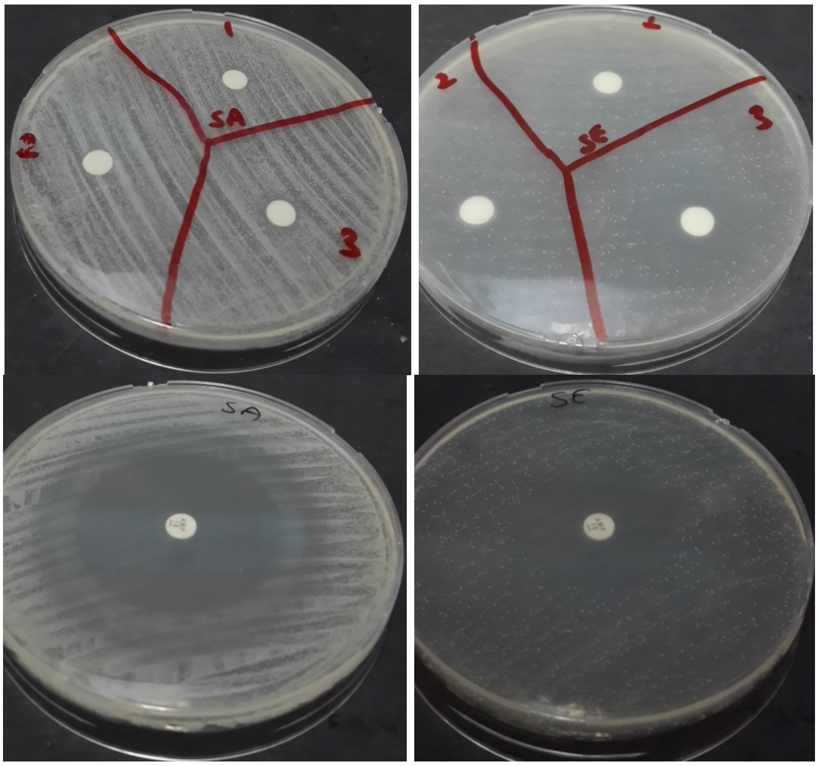


Figure 4. 16 Inhibition zones of **259 l** derivatives showing comparative bacteriostatic effects with ampicillin

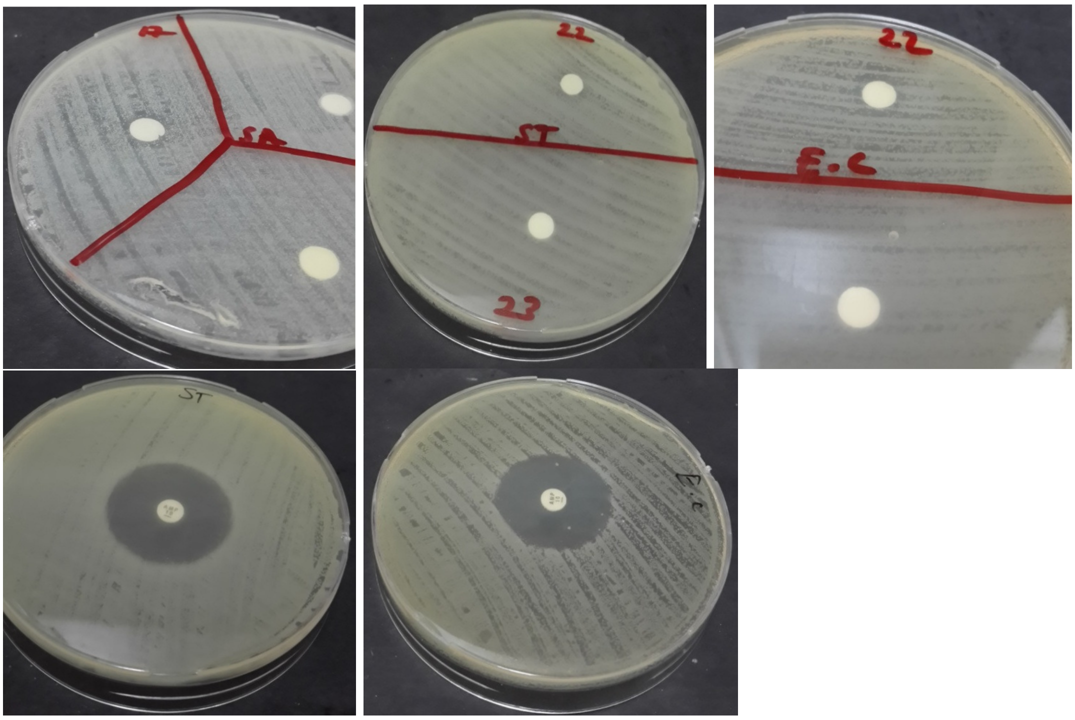


Figure 4. 17 Inhibition zones of **259r** and **259z** derivatives showing comparative bacteriostatic and weak effects with ampicillin

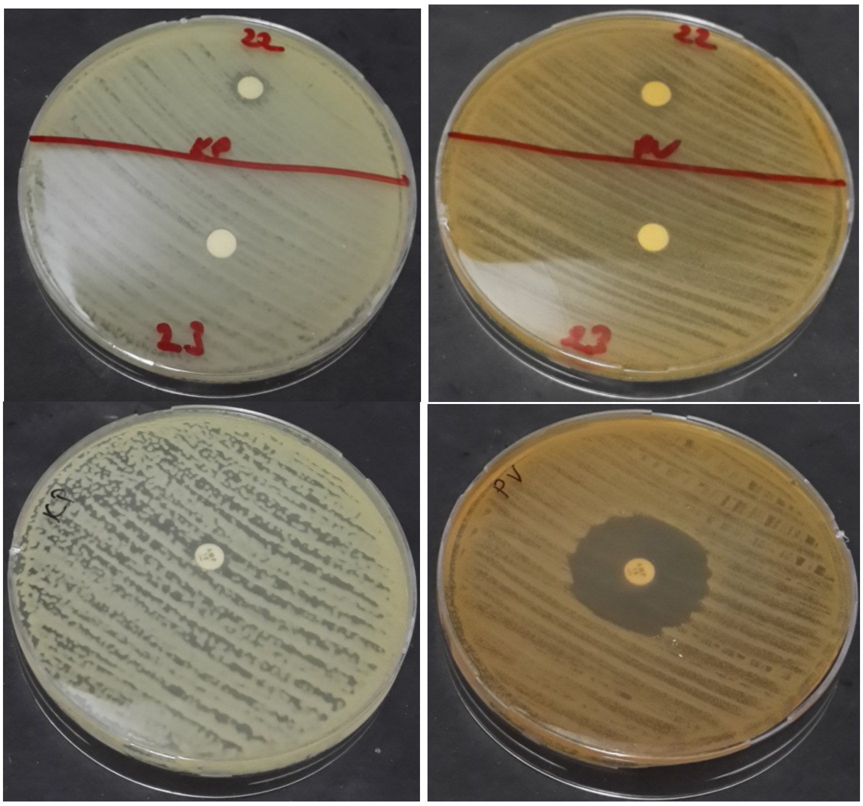
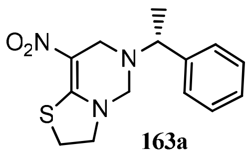
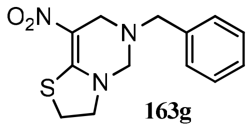


Figure 4. 18 Inhibition zones of **259z** derivative showing comparative weak effects with ampicillin



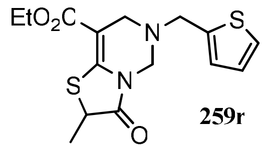
163a

(*P vulgaris*: bacteriostatic)



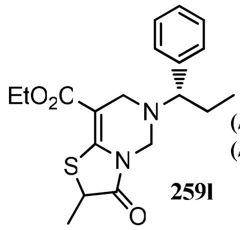
163g

(*P vulgaris*: bacteriostatic)



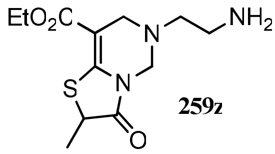
259r

(*S aureus*:bacteriostatic)



259l

(*S aureus*: 8)
(*S epidermidis*: 15)



259z

(*S typhimurium*: bacteriostatic)
(*S marcences*: 7-8)
(*E cloacae*: 8)
(*K pneumonia*: 8-9)
(*P vulgaris*: 7,8)

Figure 4. 19 Thiazolo[3,2-*c*]pyrimidine derivatives showing antibacterial activity.

According to the obtained antibacterial activity results, it was understood that the applied dose (20 mg/mL) of the compounds were insufficient and only bacteriostatic effect against certain bacteria was observed. It's possible that the compounds which shown bacteriostatic effect might exhibit better antibacterial activity at higher doses (50-100 mg/mL).

5. CONCLUSIONS

To sum up the works done and their outcomes in this dissertation briefly,

- ✓ In the first part of the study, three literaturally known heterocyclic secondary enamines (**112**, **113**, **116**) and five 2-phenyl substituted acryloyl chlorides (**149b-f**) have been prepared according to literature methods and their structure have been characterized by means of IR, NMR measurements.
- ✓ In the second part of the study, we have developed a new, efficient and environmentally friendly approach for the synthesis of 16 novel 6-nitrothiazolo[3,2-*c*]pyrimidines (**163**) using Mannich reactions under microwave irradiation. The structures of derivatives **163** have been fully determined by IR, NMR, HRMS and X-ray single crystal measurements. This method is very effective for accessing such heterocycles having a diverse range of substituents. The protocol is the first example of green chemistry since water is used as the solvent and often no other (organic) solvent is required at any stage. We also believe that this efficient microwave synthesis of thiazolo[3,2-*c*]pyrimidines is remarkable in terms of microwave-based synthetic chemistry and is a new and first example in this area.
- ✓ In the third part of experiments, we described another efficient synthetic route for the preparation of 23 novel oxothiazolo[3,2-*c*]pyrimidine carboxylates (**259**) bearing alkyl, aryl or heteroaryl groups from various mono- or bis-primary amines (**10**) and ethyl 4-oxomethylenethiazolidine carboxylate (**116**) in the presence of formaldehyde (**16**) under conventional heating conditions. Unfortunately, the MW-assisted synthesis of derivatives **259** was unsuccessful to access any cyclisation product. The structures of the derivatives **259** have been fully characterized by means of IR, NMR and HRMS measurements. The main basis of this synthetic protocol was double inter- and intramolecular Mannich-type cyclisation reactions as first described in the second part of the study, hence the limitation and applicability of this synthetic method were extended by the newly synthesized derivatives of **259**.

- ✓ In the fourth part of the study, we have described a practical, rapid and very efficient one-pot protocol for the preparation of thiazolo[3,2-*a*]- and imidazolo[1,2-*a*]-pyridinones (**260** and **248**) in good yields through the Michael cyclisation reactions of 2-(nitromethylene)thiazolidine (or imidazolidine) (**112** and **113**) with *β*-substituted acryloyl chlorides (**144** and **149**) using homogenous or heterogenous bases under mild conditions. The structures of title compounds **260** and **248** were elucidated based on the IR, NMR, HRMS and X-ray single crystal analysis techniques. Since various biologically important molecules containing thiazolo (or imidazolo) pyridinone cores are of interest in a pharmaceutical context, our synthetic process would provide a new contribution to the preparation of industrially relevant molecules.
- ✓ Finally, 39 newly synthesized thiazolo[3,2-*c*]pyrimidines (**163** and **259**) were screened for their biological activities (anticancer and antibacterial). The screening for potential anticancer activities of these derivatives on MCF-7 cell lines showed that five of products (**163ax**, **259g**, **259i**, **259m-n**) had strong cytotoxic effect on breast cancer cell lines, besides, six of products (**163l-m**, **259h**, **259j**, **259r** and **259y**) had moderate to good cytotoxic effects on breast cancer cell lines. In antibacterial activity assay of the products (**163** and **259**), no significant bacterial inhibition have been observed, only the bacteriostatic effect has been obtained with five of the products (**163a**, **163g**, **259r**, **259l**, **259z**) on different pathogenic bacterial strains.

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7. APPENDICES

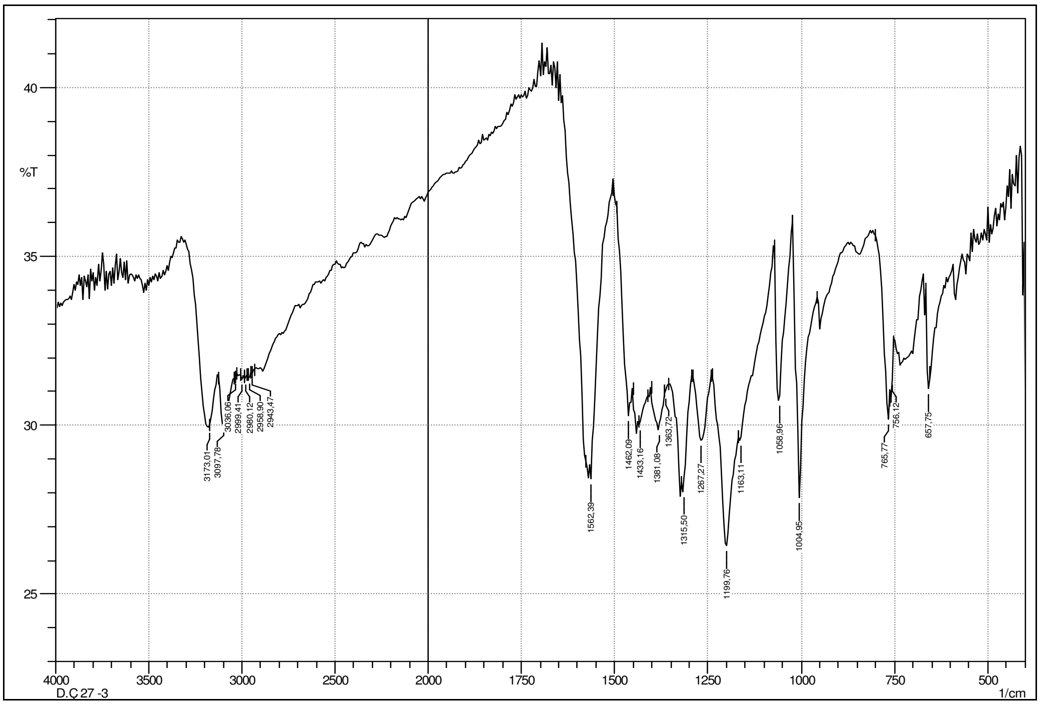


Figure 7. 1. IR spectrum of compound **112**

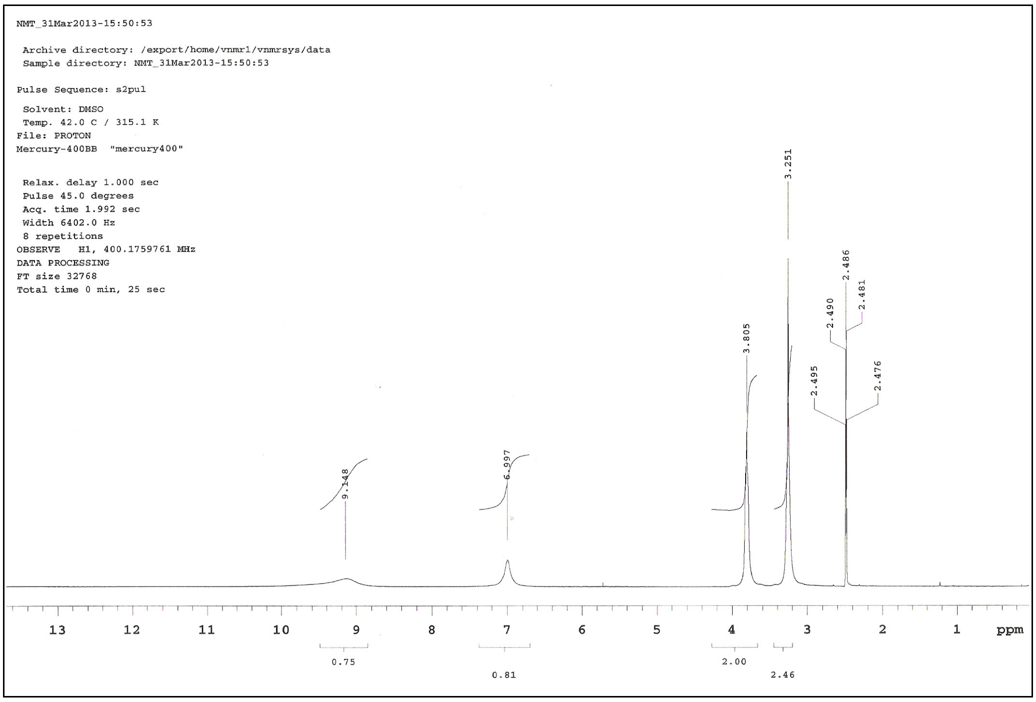


Figure 7. 2. ^{1}H NMR (400 MHz, DMSO-d$_6$) spectrum of compound **112**

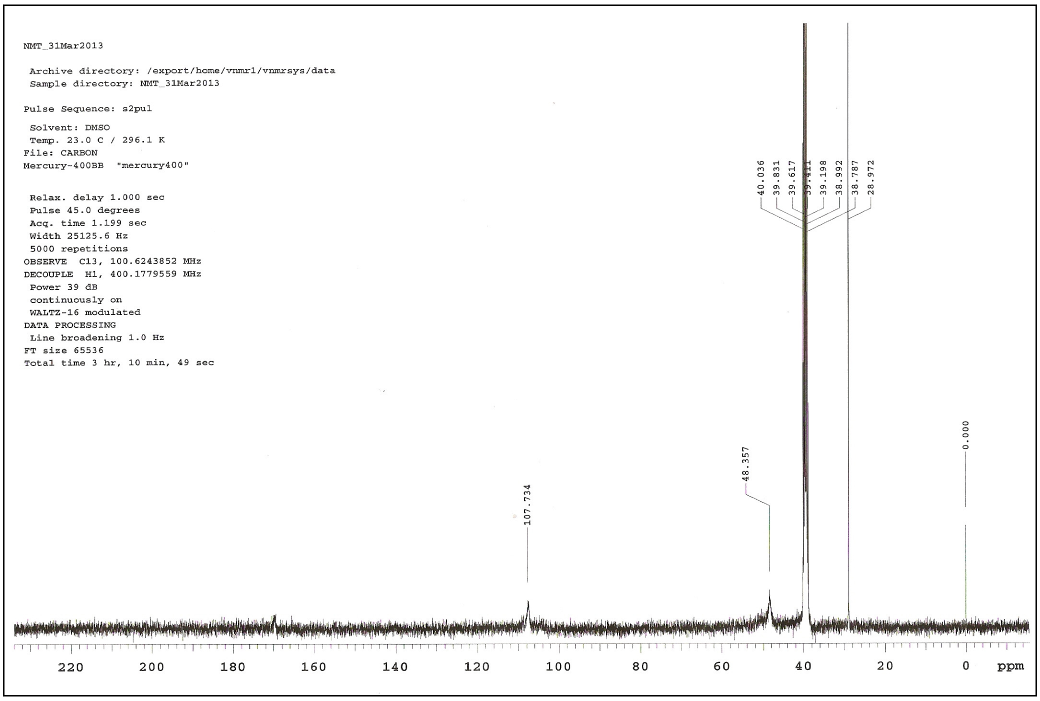


Figure 7. 3. ^{13}C NMR (100 MHz, DMSO-d_6) spectrum of compound **112**

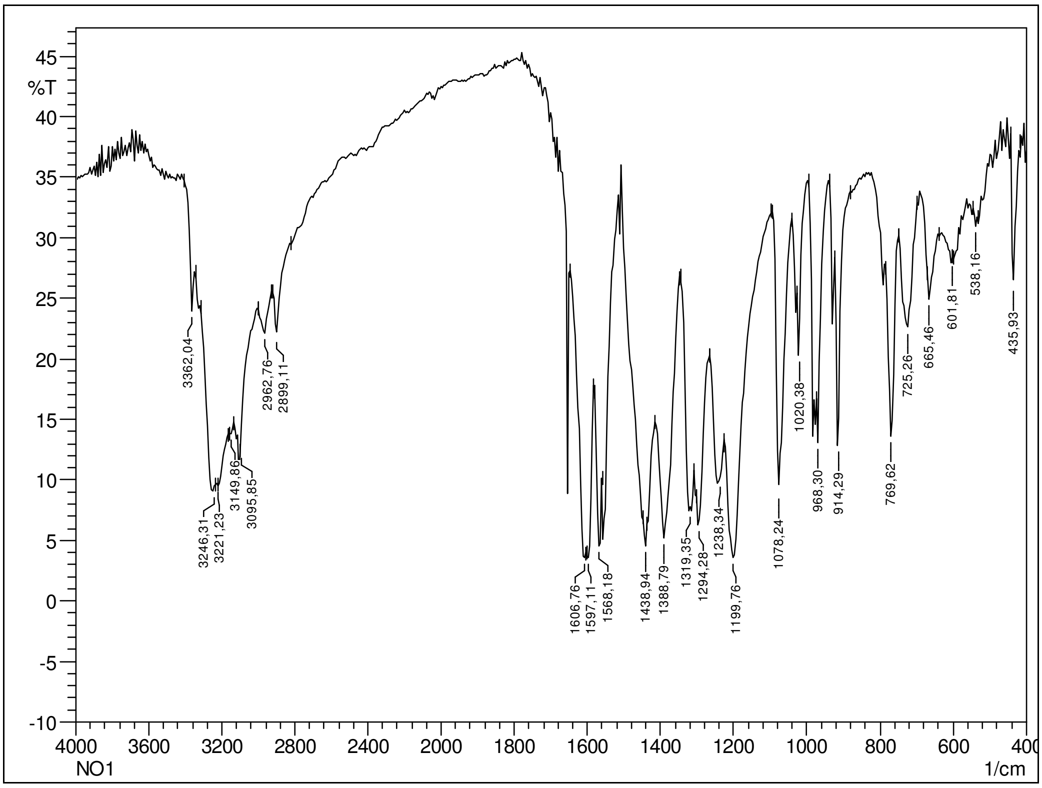


Figure 7. 4. IR spectrum of compound **113**

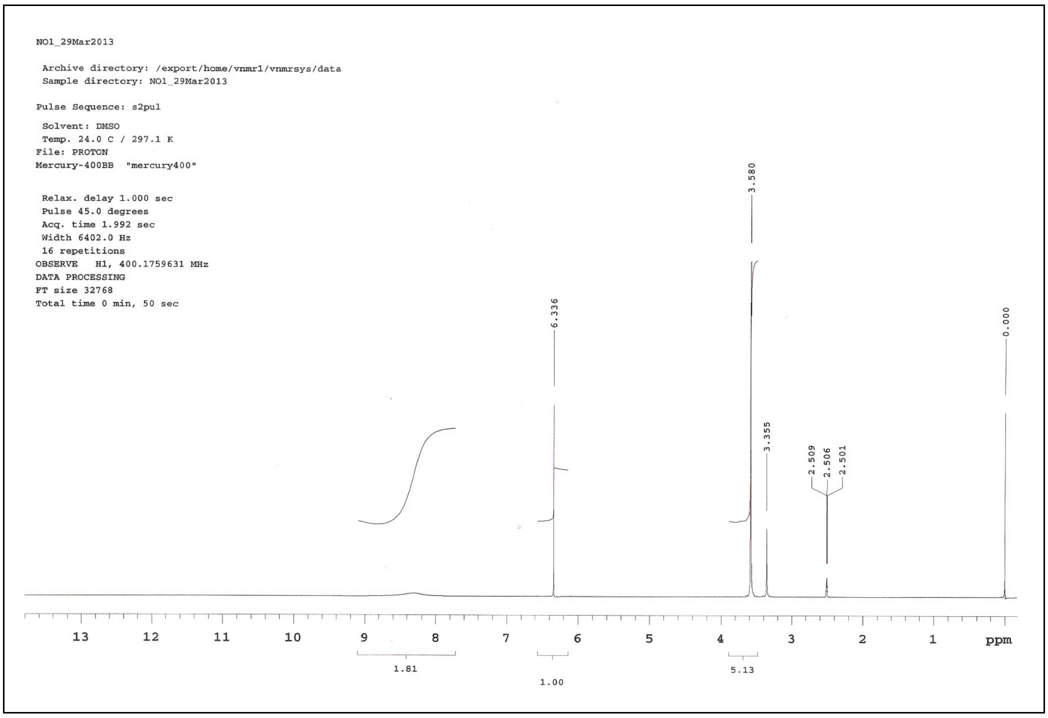


Figure 7. 5. ^{1}H NMR (400 MHz, DMSO-d6) spectrum of compound **113**

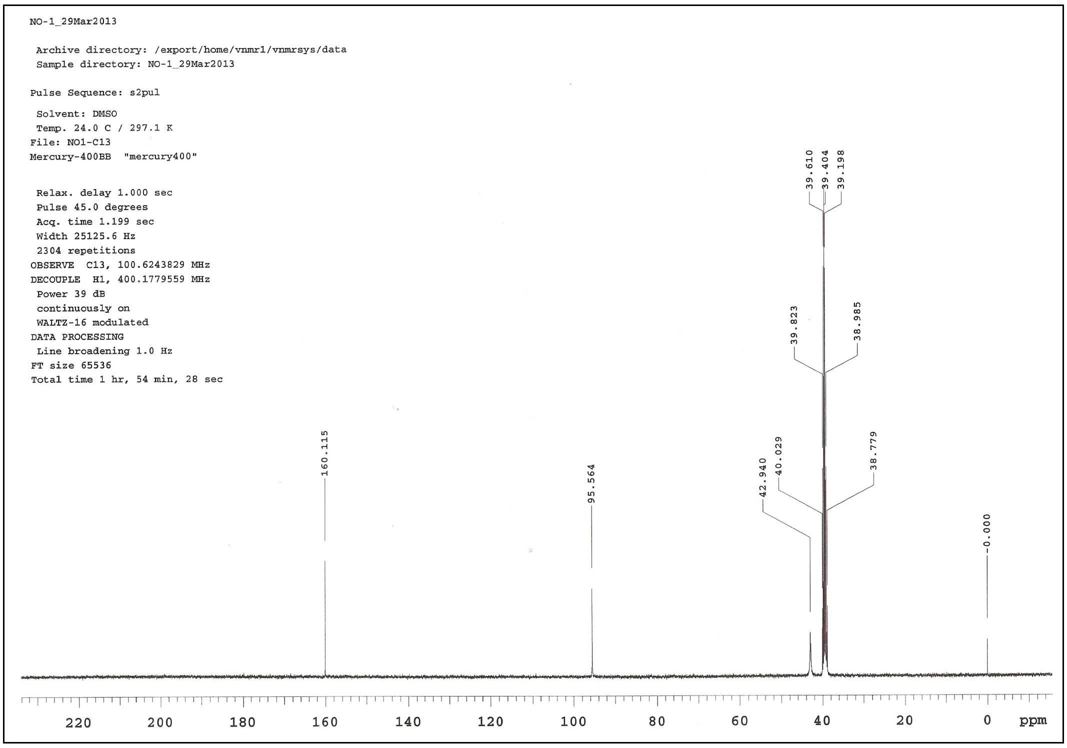


Figure 7. 6. ^{13}C NMR (100 MHz, DMSO-d6) spectrum of compound **113**

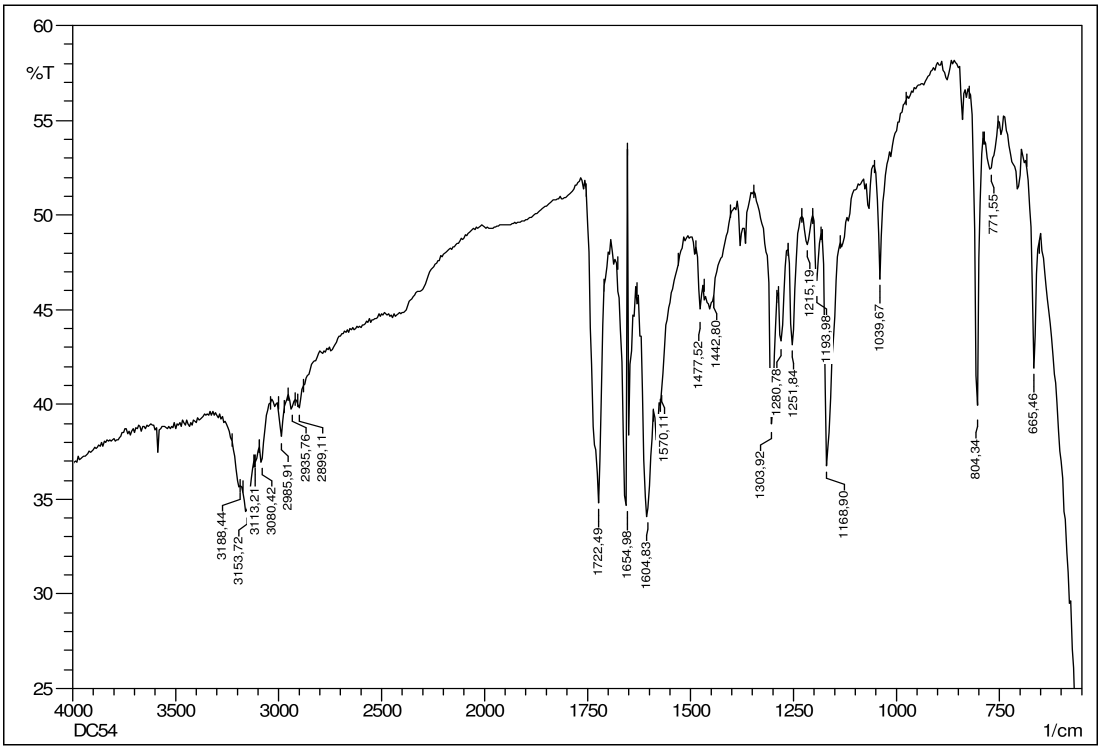


Figure 7. 7. IR spectrum of compound **116**

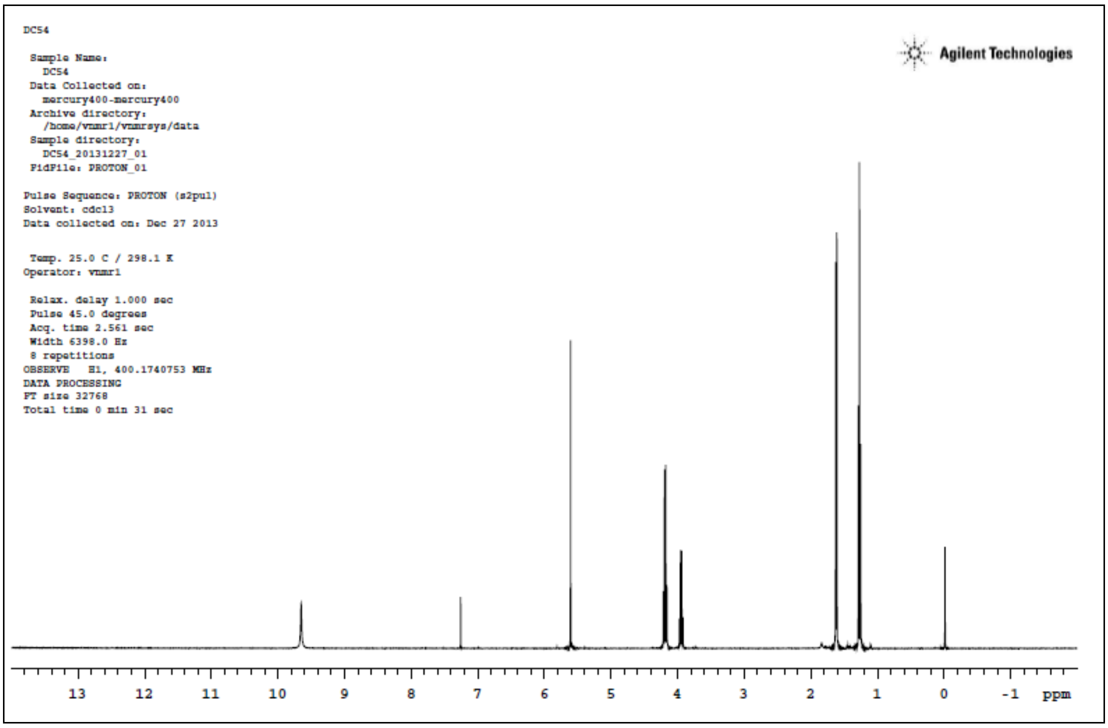


Figure 7. 8. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **116**

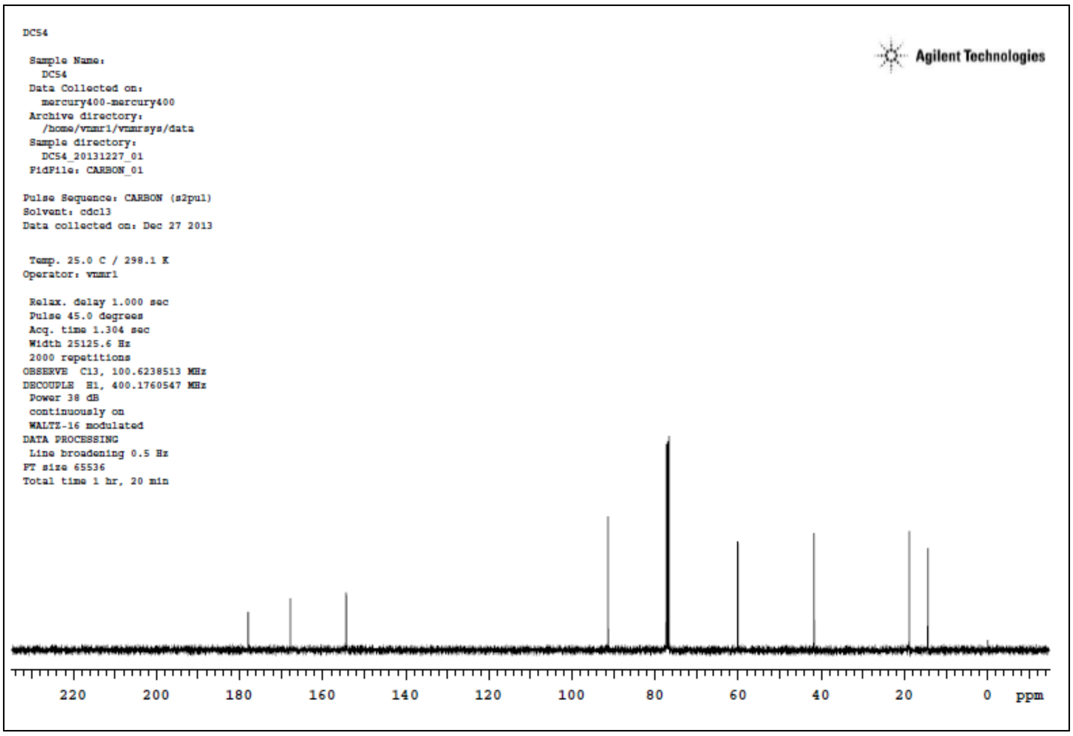


Figure 7. 9. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **116**

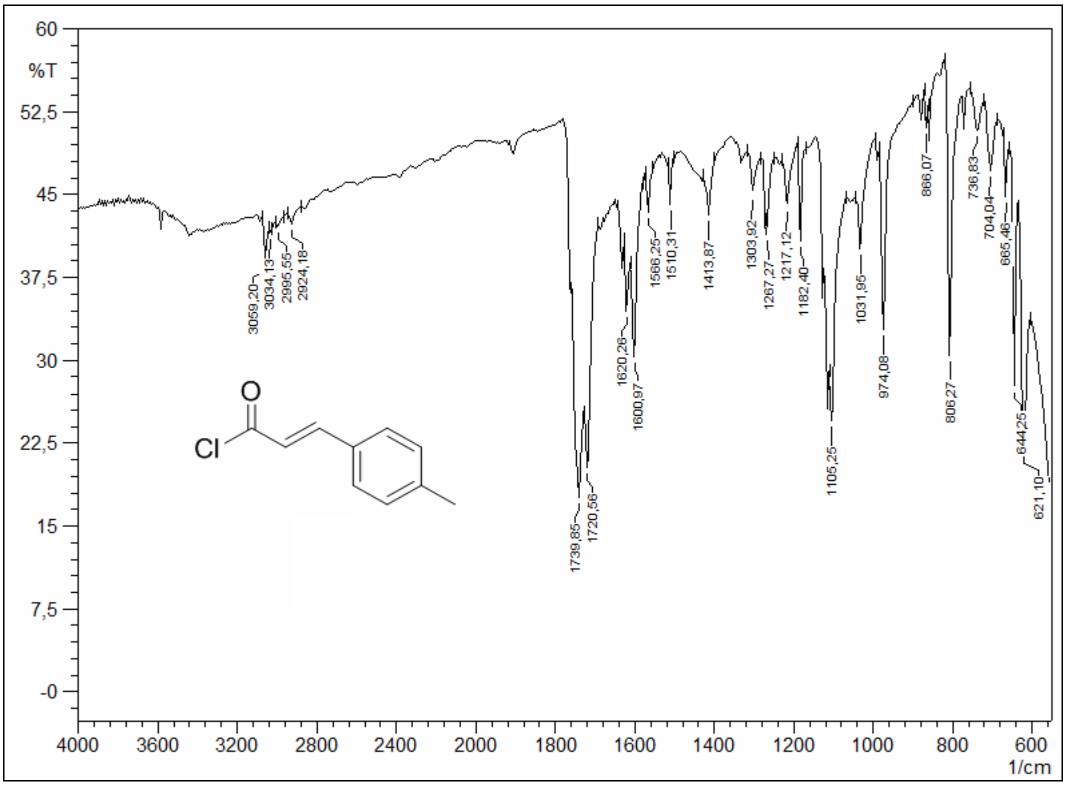


Figure 7. 10. IR spectrum of compound **149b**

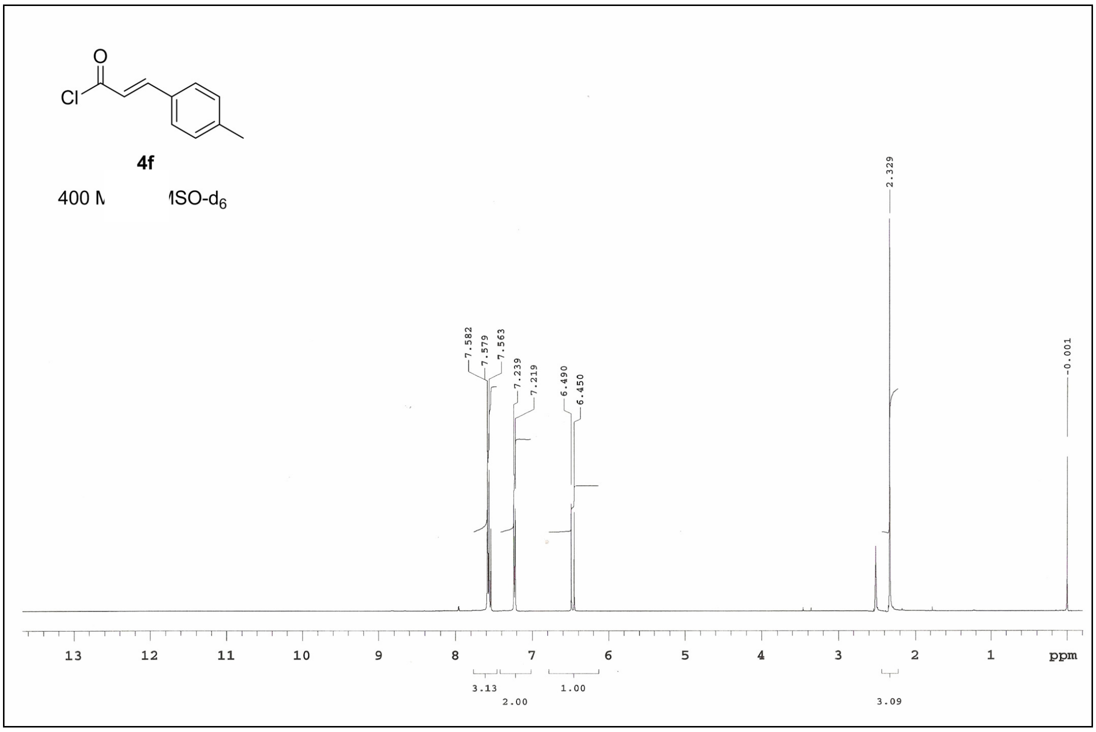


Figure 7. 11. ^{1}H NMR (400 MHz, DMSO-d$_6$) spectrum of compound **149b**

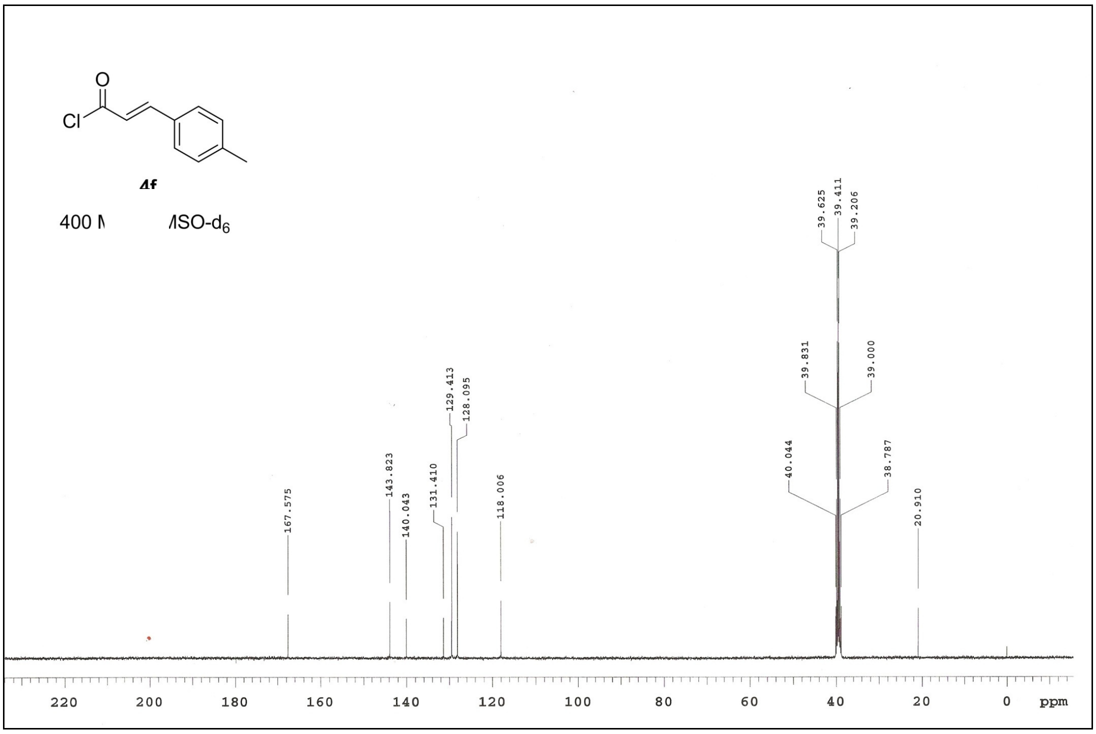


Figure 7. 12. ^{13}C NMR (100 MHz, DMSO-d$_6$) spectrum of compound **149b**

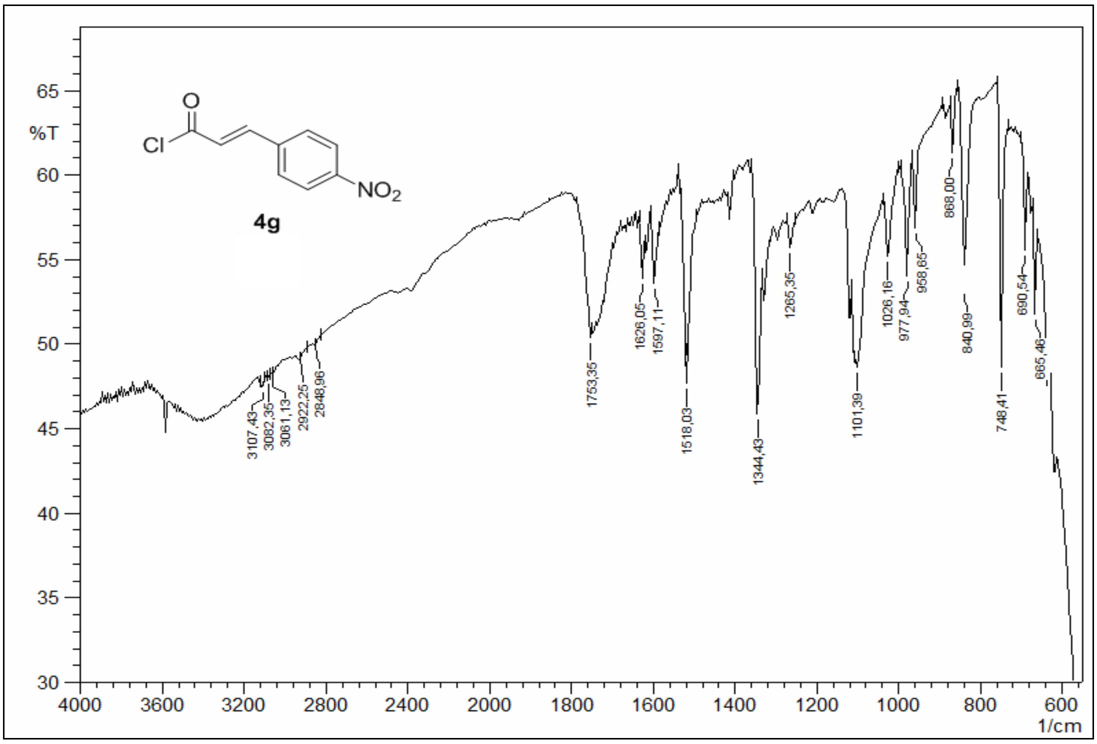


Figure 7. 13. IR spectrum of compound **149c**

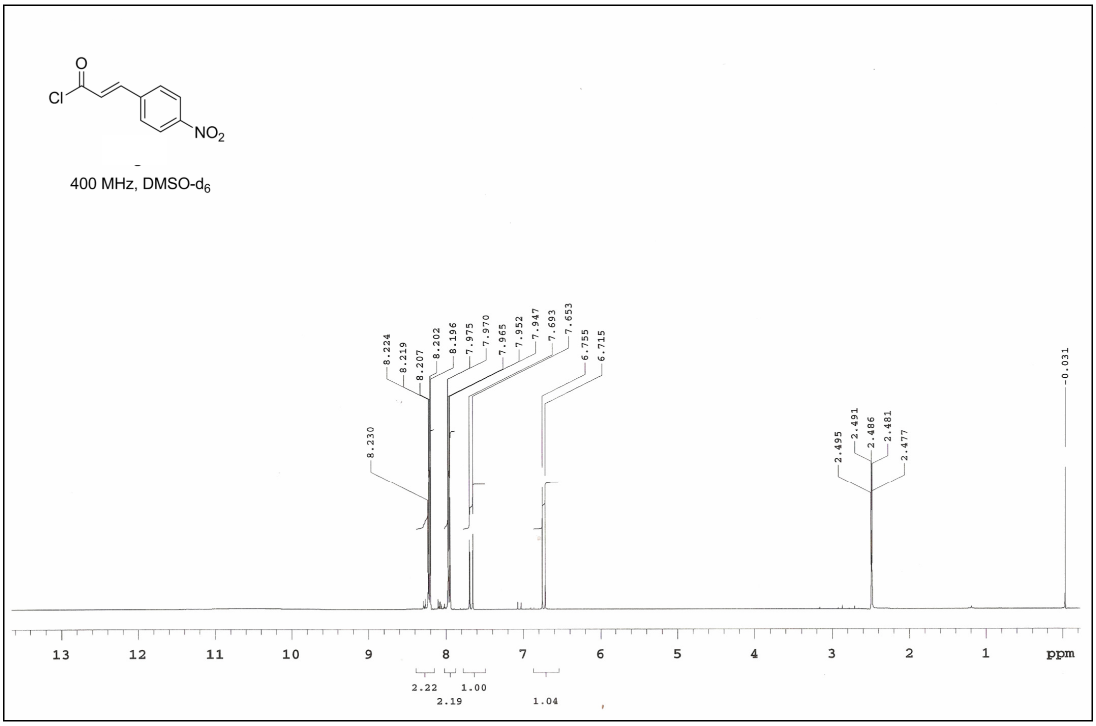


Figure 7. 14. ^{1}H NMR (400 MHz, DMSO-d$_6$) spectrum of compound **149c**

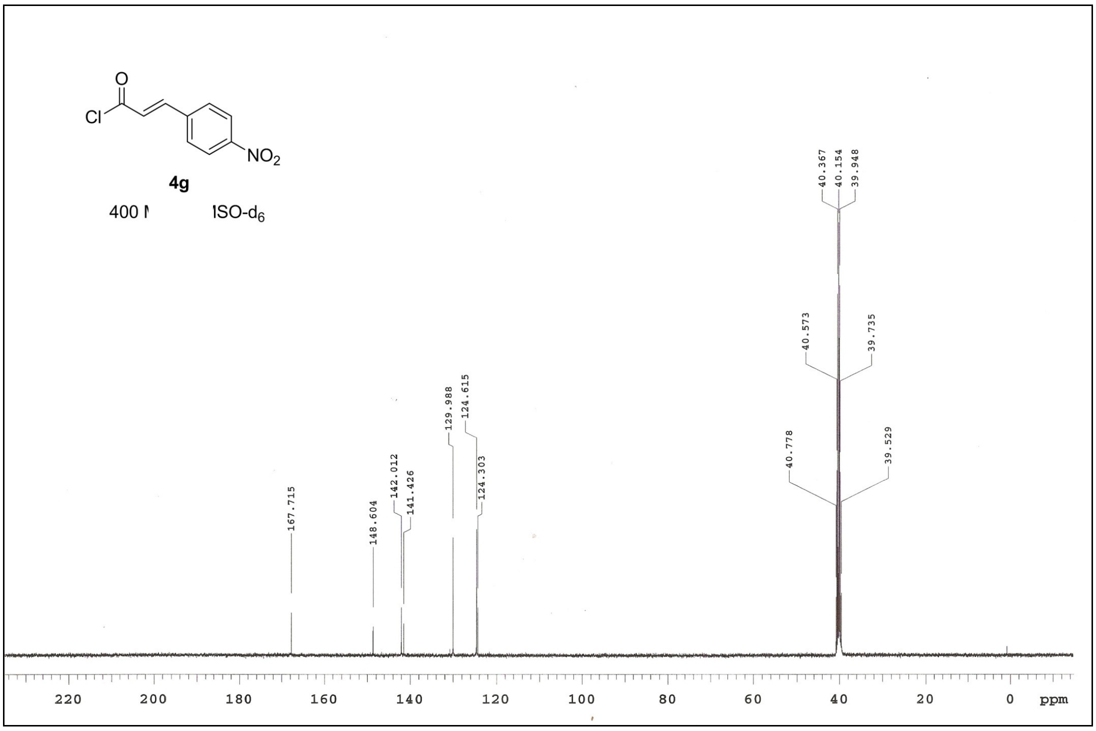


Figure 7. 15. ^{13}C NMR (100 MHz, DMSO-d6) spectrum of compound **149c**

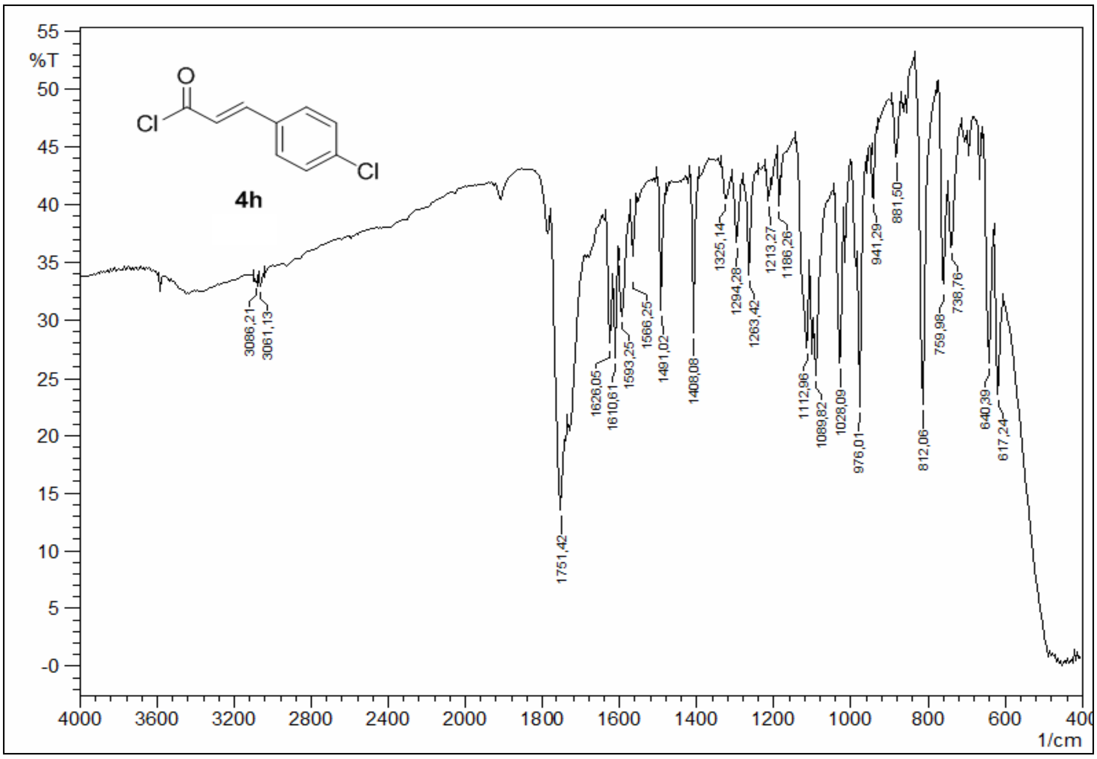


Figure 7. 16. IR spectrum of compound **149d**

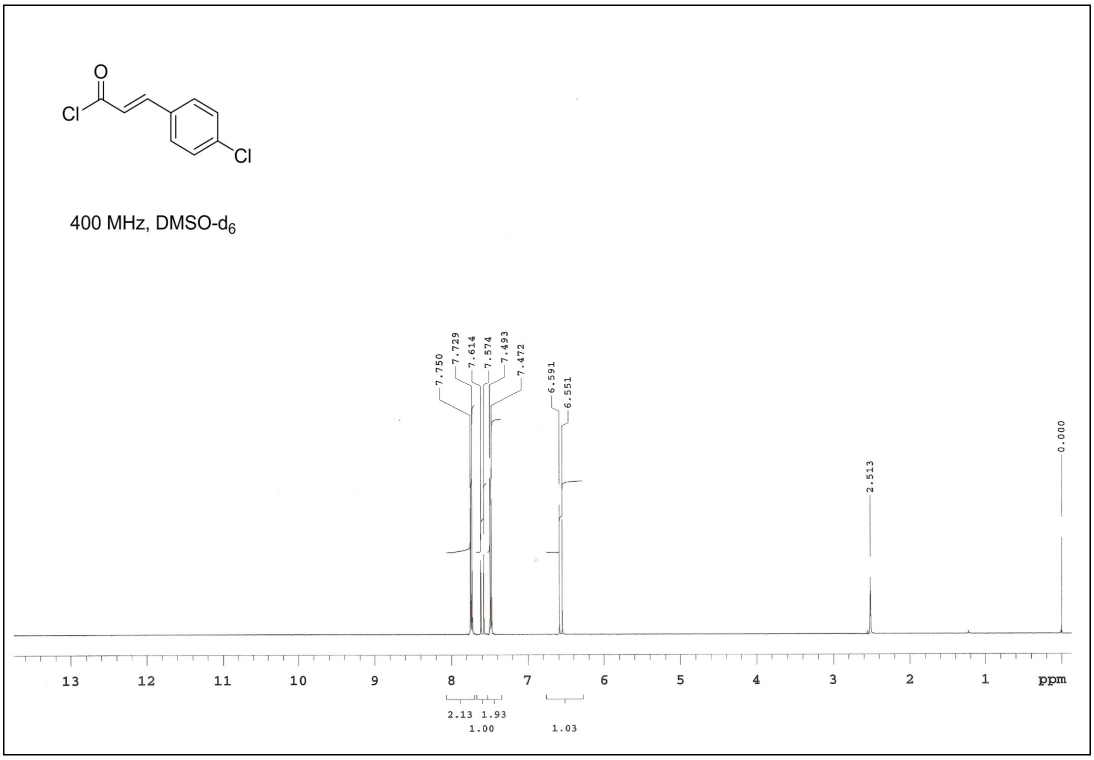


Figure 7. 17. ^{1}H NMR (400 MHz, DMSO-d6) spectrum of compound **149d**

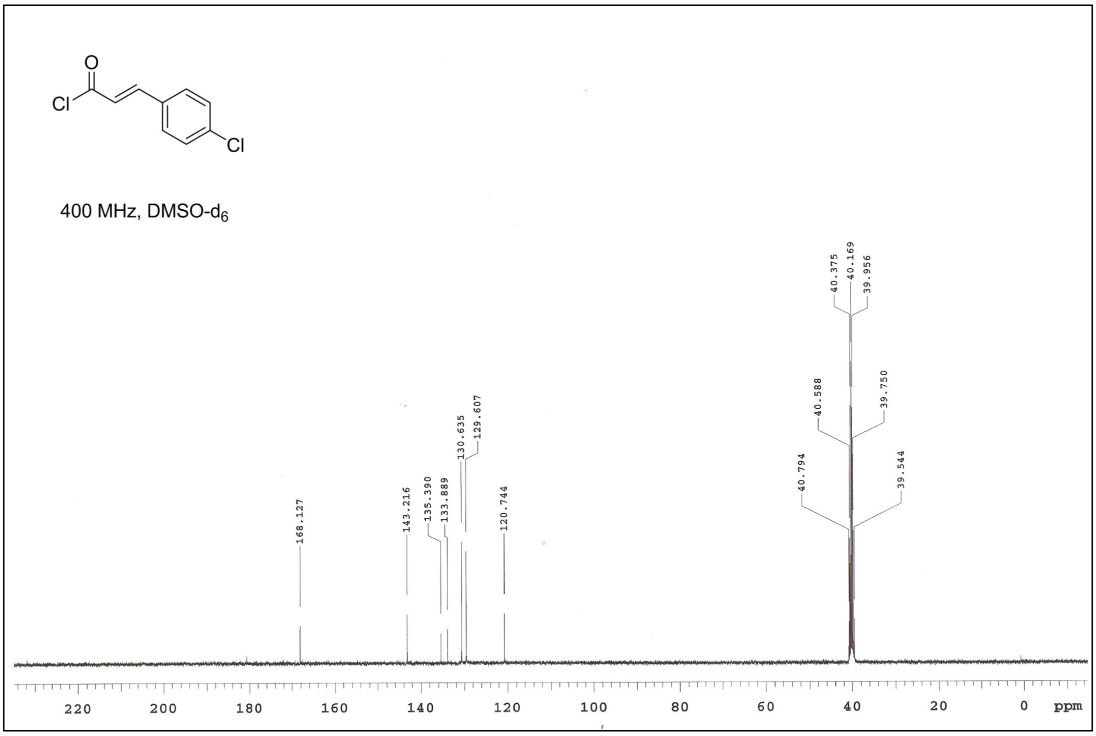


Figure 7. 18. ^{13}C NMR (100 MHz, DMSO-d6) spectrum of compound **149d**

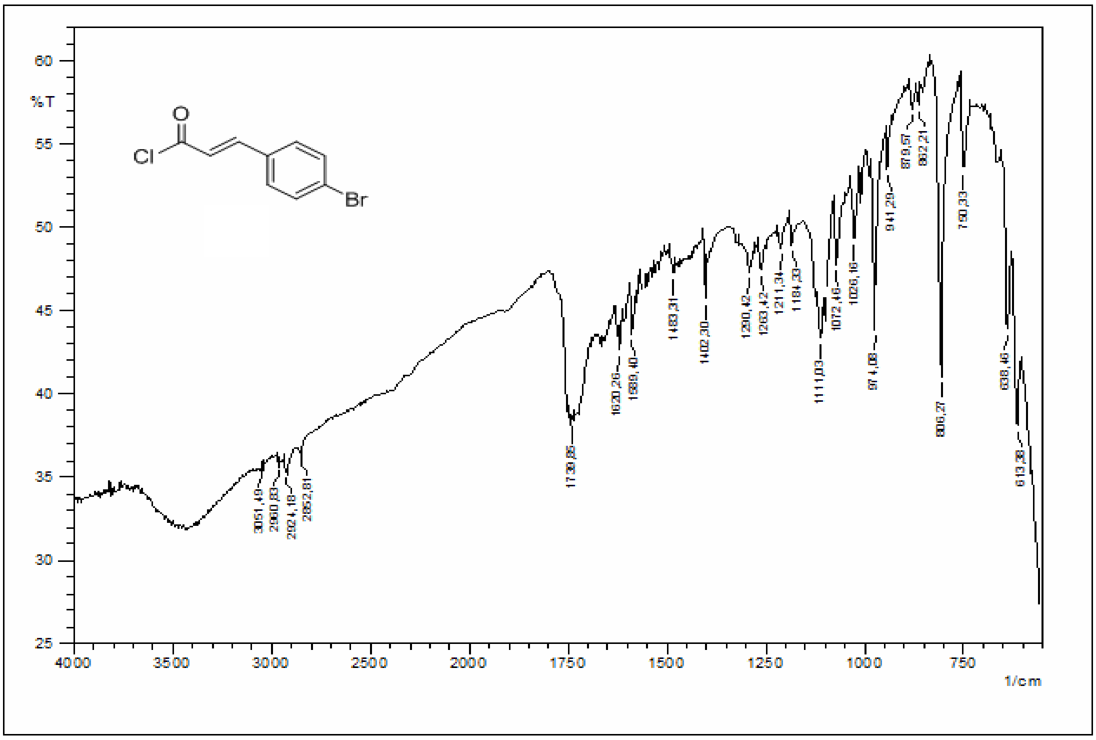


Figure 7. 19. IR spectrum of compound **149e**

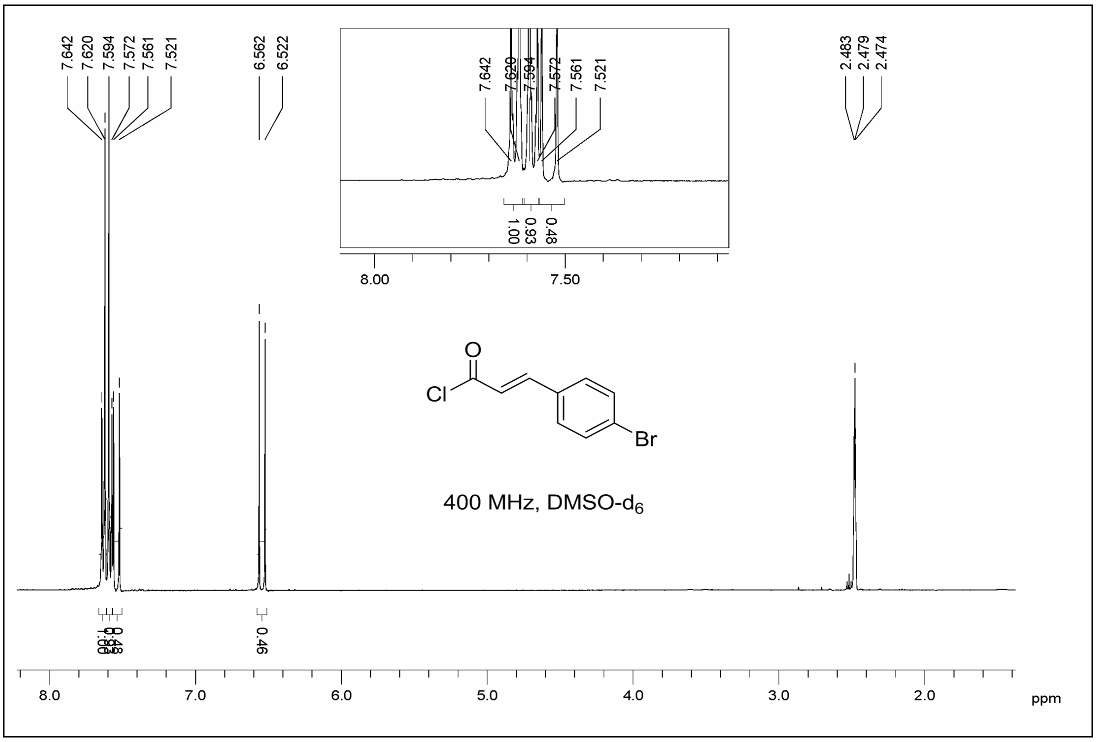


Figure 7. 20. [1]H NMR (400 MHz, DMSO-d6) spectrum of compound **149e**

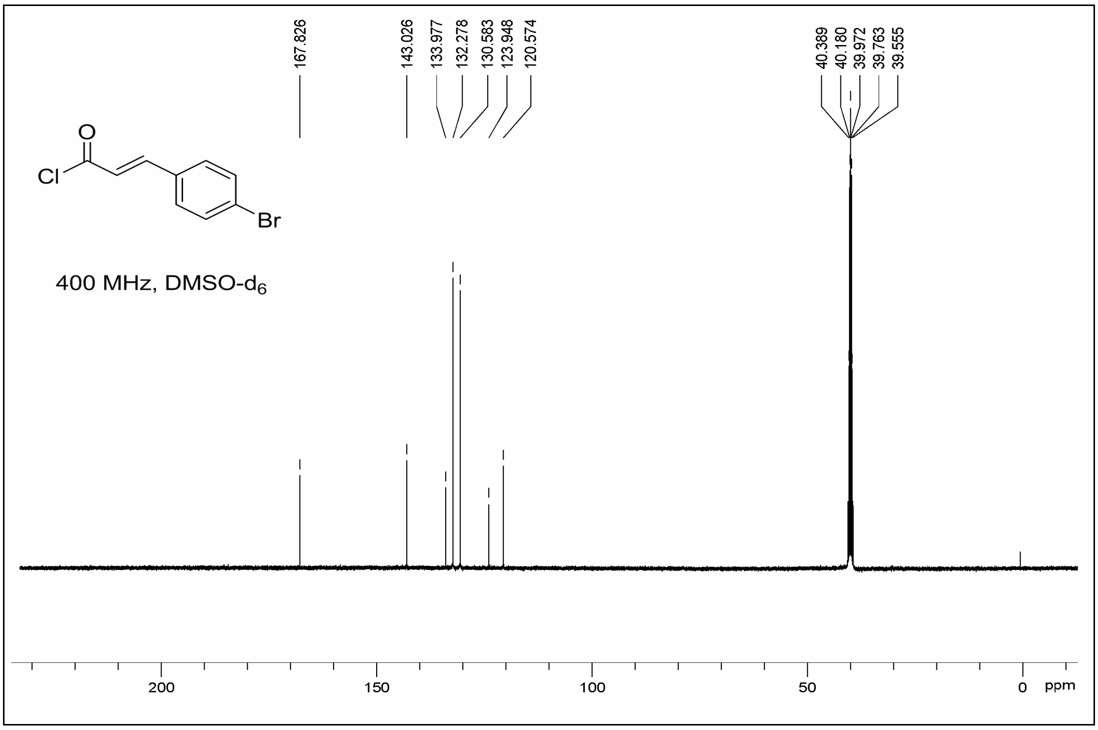


Figure 7. 21. ^{13}C NMR (100 MHz, DMSO-d6) spectrum of compound **149e**

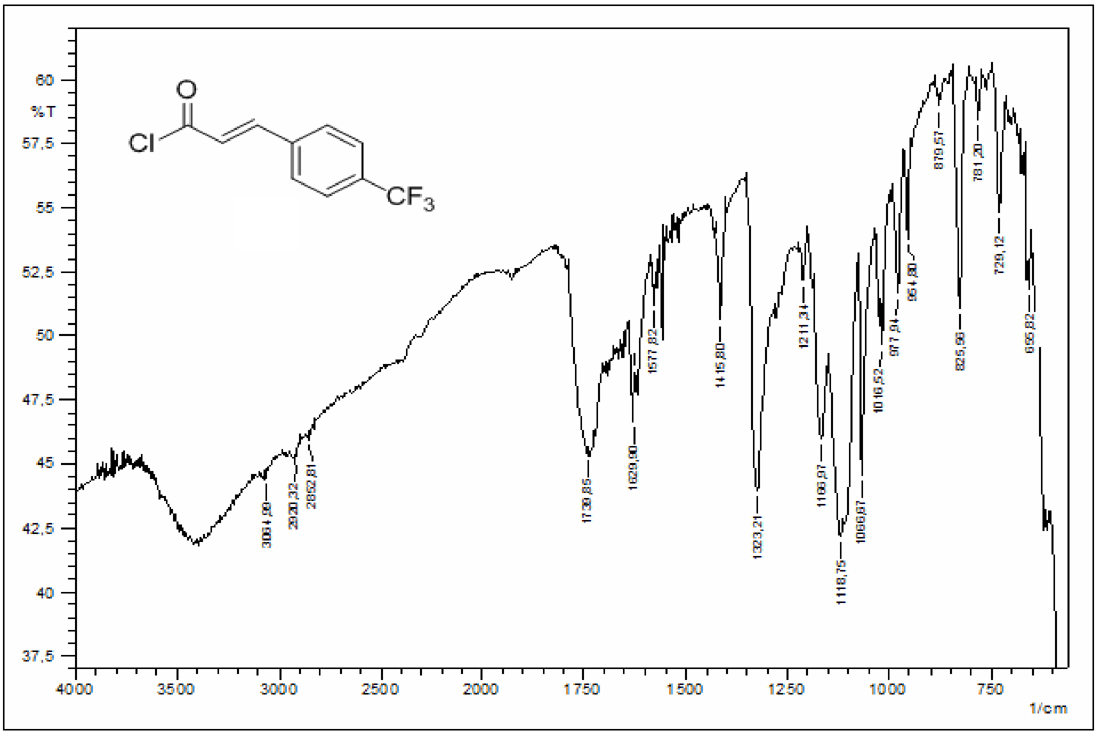


Figure 7. 22. IR spectrum of **149f**

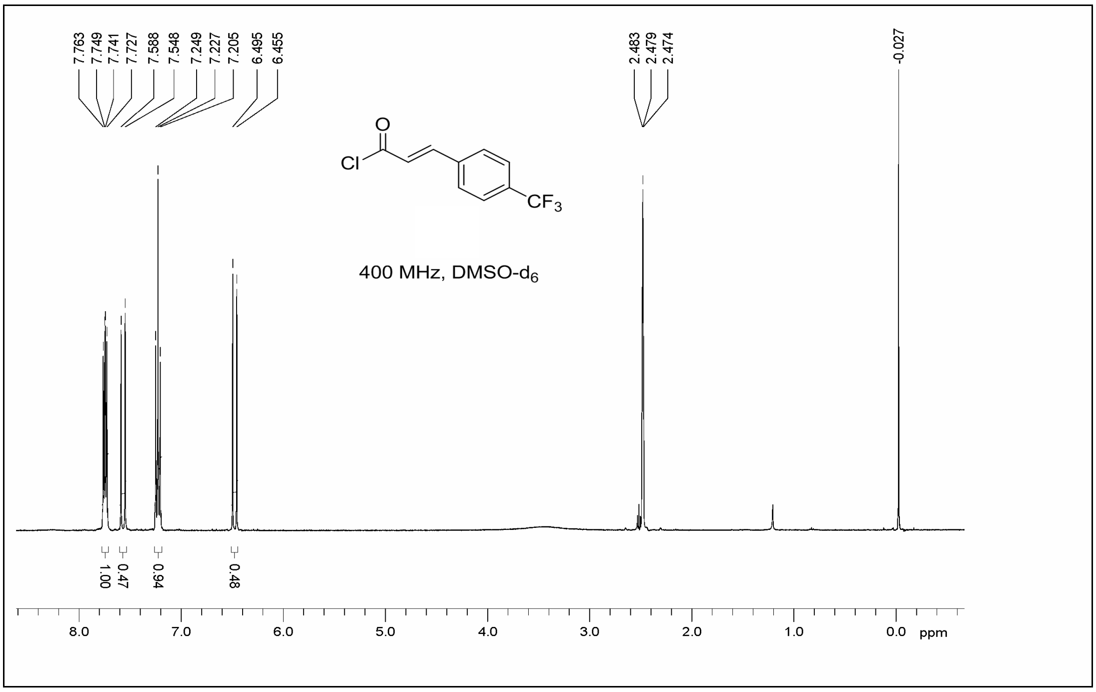


Figure 7. 23. ^{13}C NMR (100 MHz, DMSO-d6) spectrum of compound **149f**

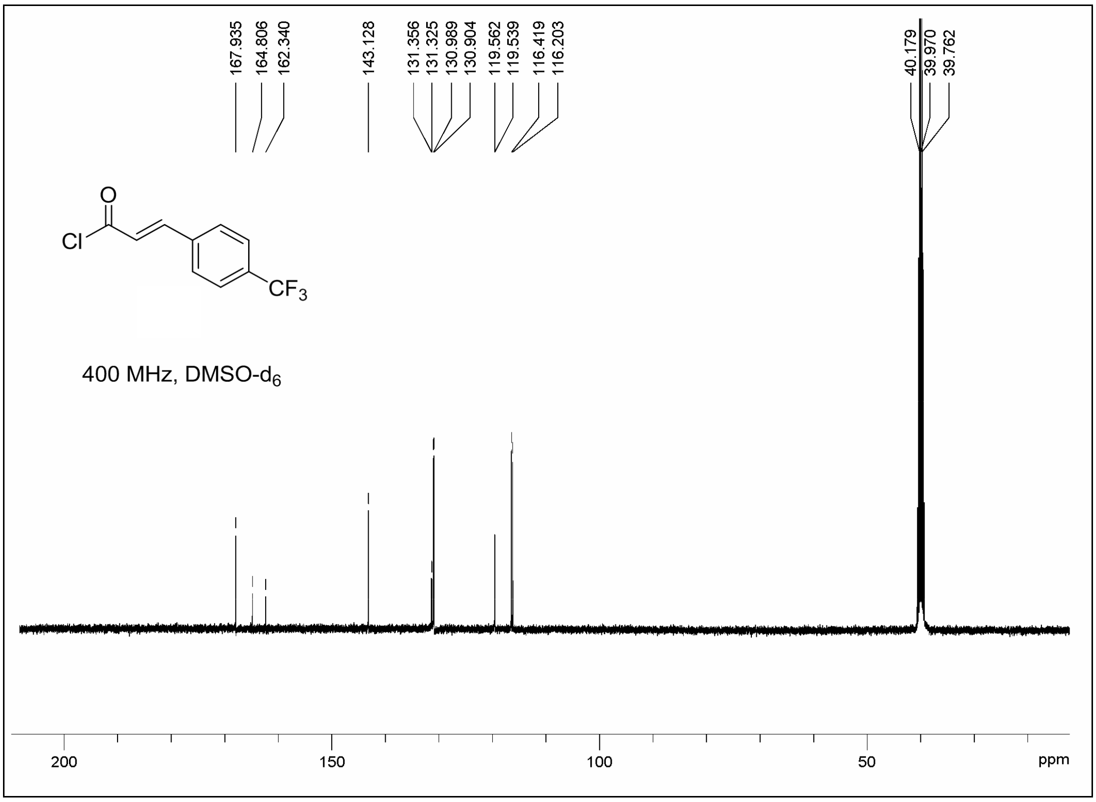


Figure 7. 24. ^{13}C NMR (100 MHz, DMSO-d6) spectrum of compound **149f**

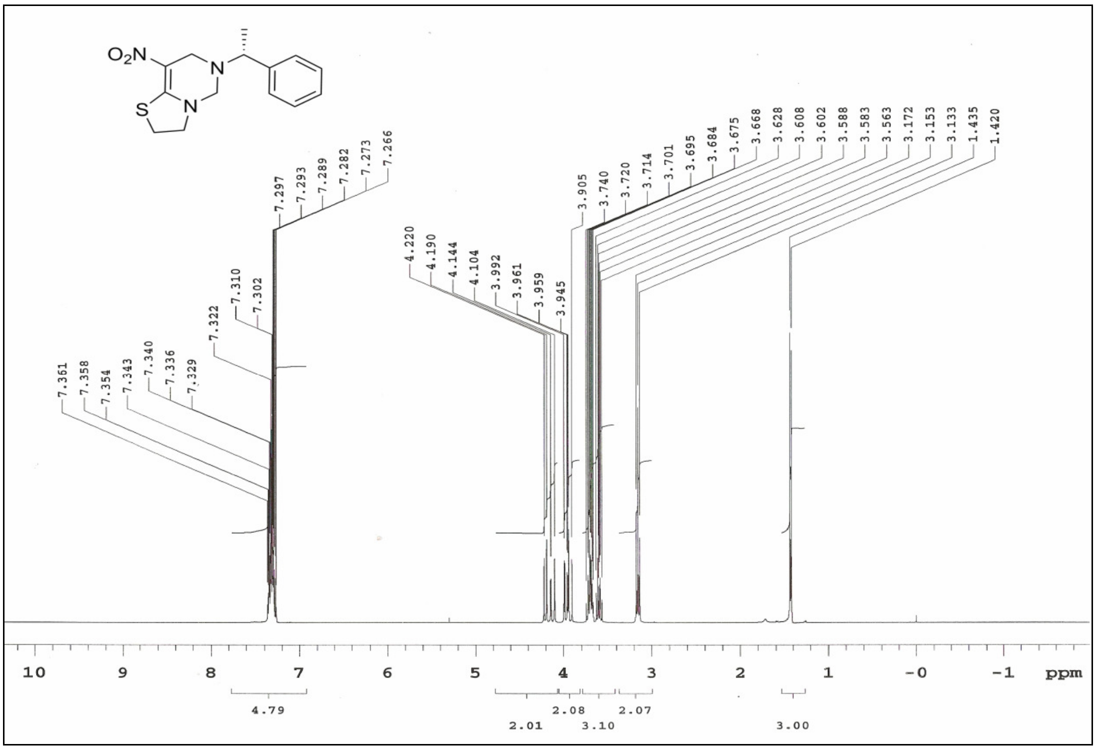


Figure 7. 25. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **163a**

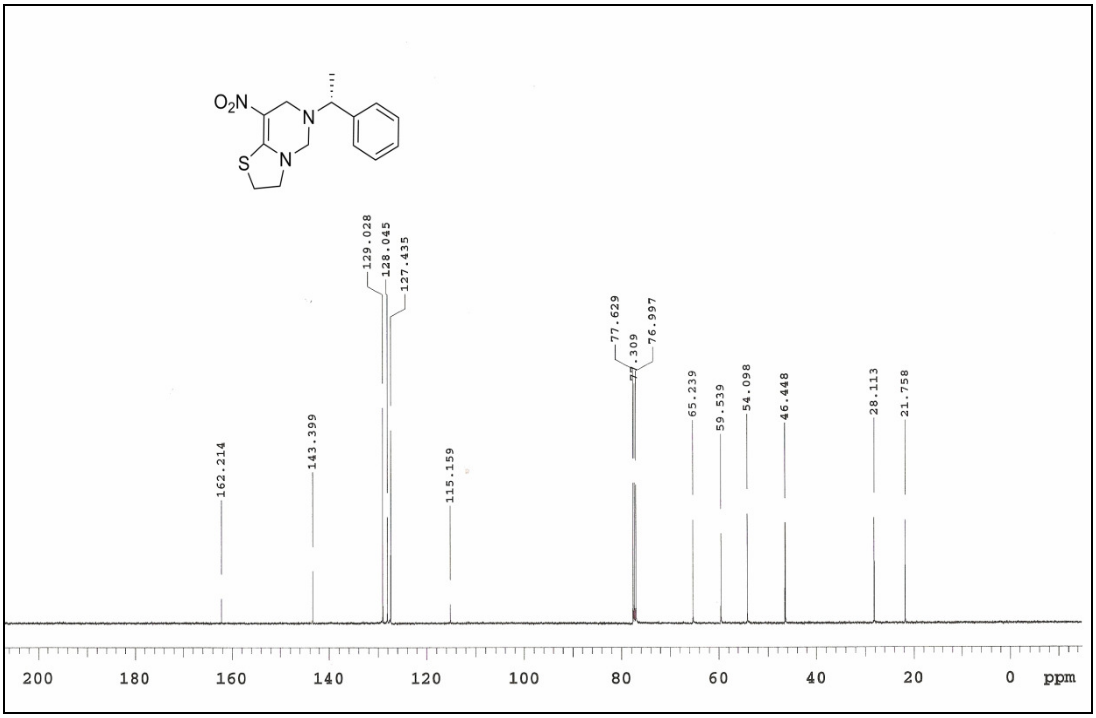
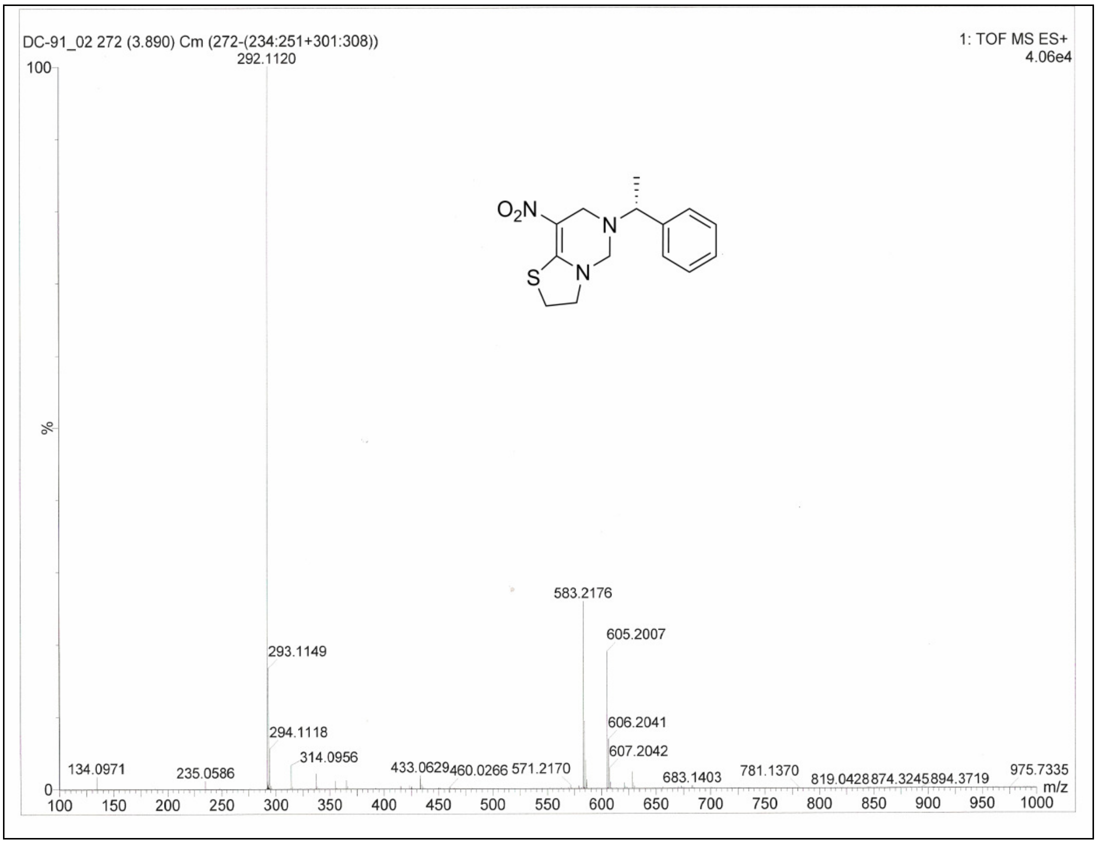


Figure 7. 26. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **163a**

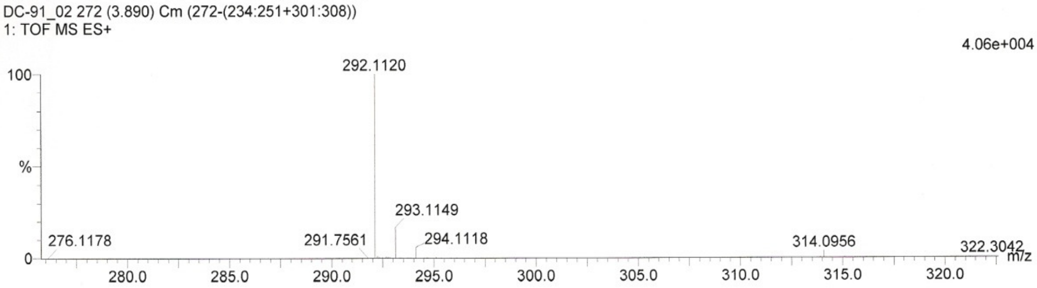


Elemental Composition Report

Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
21 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 1-14 H: 1-18 N: 1-5 O: 1-2 S: 1-2



Minimum:				-1.5			
Maximum:		5.0	5.0	50.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
292.1120	292.1120	0.0	0.0	7.5	211.7	0.0	C14 H18 N3 O2 S

Figure 7. 27. HRMS and elemental composition of compound **163a**

X-ray Structure and Data for 163a

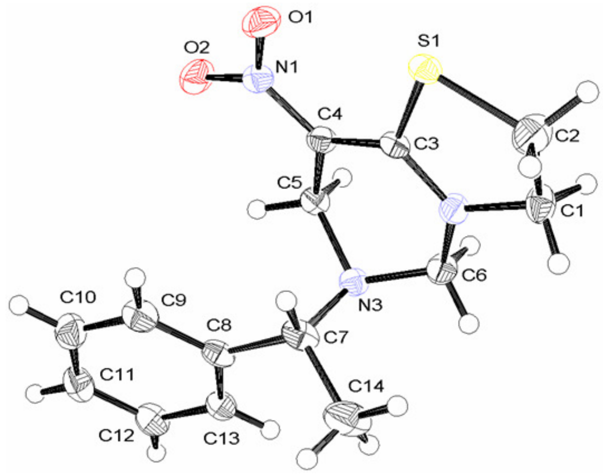


Figure 7. 28. X-ray Crystal Structure of **163a**

Table 7. 1. Crystal data and structure refinement for **163a**

Empirical formula	C14 H17 N3 O2 S	
Formula weight	291.37	
Temperature	150(2) K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	P21	
Unit cell dimensions	a = 5.41030(10) Å	α= 90°.
	b = 6.67940(10) Å	β= 92.983(2)°.
	c = 19.1411(4) Å	γ = 90°.
Volume	690.78(2) $Å^3$	
Z	2	
Density (calculated)	1.401 Mg/m^3	
Absorption coefficient	2.133 mm^{-1}	
F(000)	308	
Crystal size	0.28 x 0.20 x 0.04 mm^3	
Theta range for data collection	4.63 to 73.02°.	
Index ranges	-5<=h<=6, -8<=k<=8, -23<=l<=19	
Reflections collected	4467	
Independent reflections	2633 [R(int) = 0.0160]	
Completeness to theta = 73.02°	97.4 %	
Max. and min. transmission	0.9203 and 0.5892	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2633 / 1 / 182	
Goodness-of-fit on F^2	1.029	
Final R indices [I>2sigma(I)]	R1 = 0.0253, wR2 = 0.0656	
R indices (all data)	R1 = 0.0256, wR2 = 0.0657	
Absolute structure parameter	0.019(12)	
Largest diff. peak and hole	0.207 and -0.192 e.$Å^{-3}$	

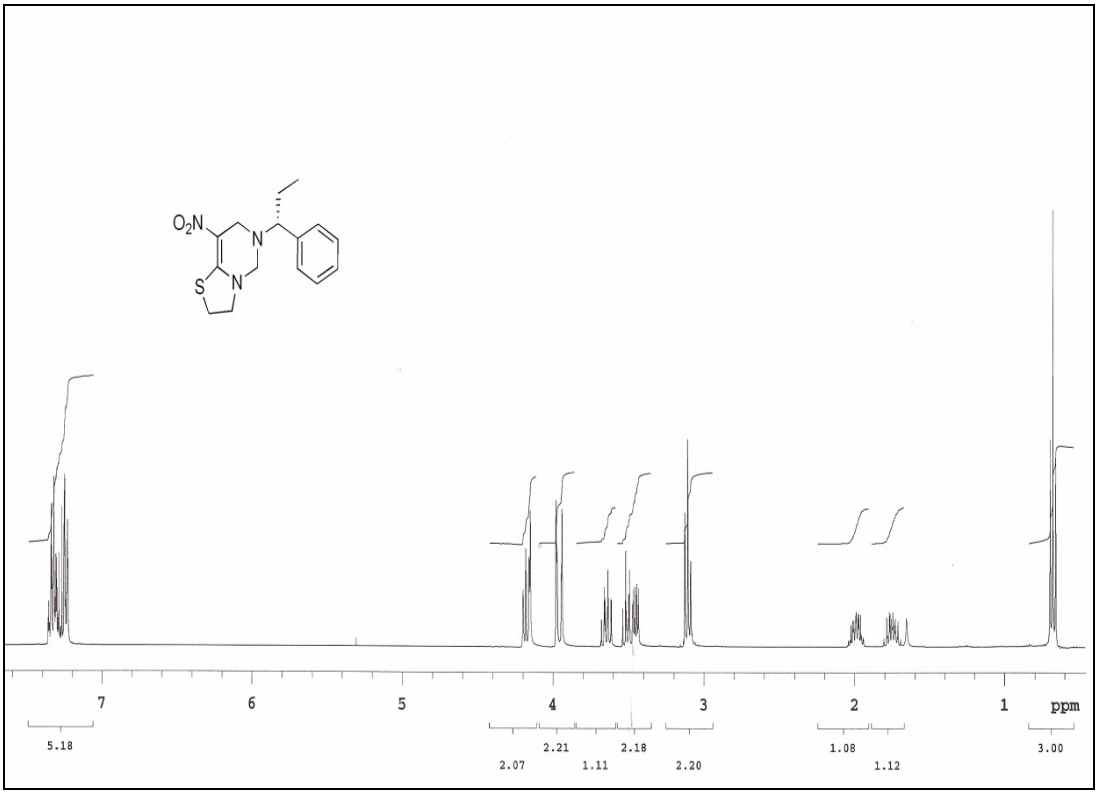


Figure 7. 29. ^{1}H NMR (400 MHz, CDCl3) spectrum of compound **163b**

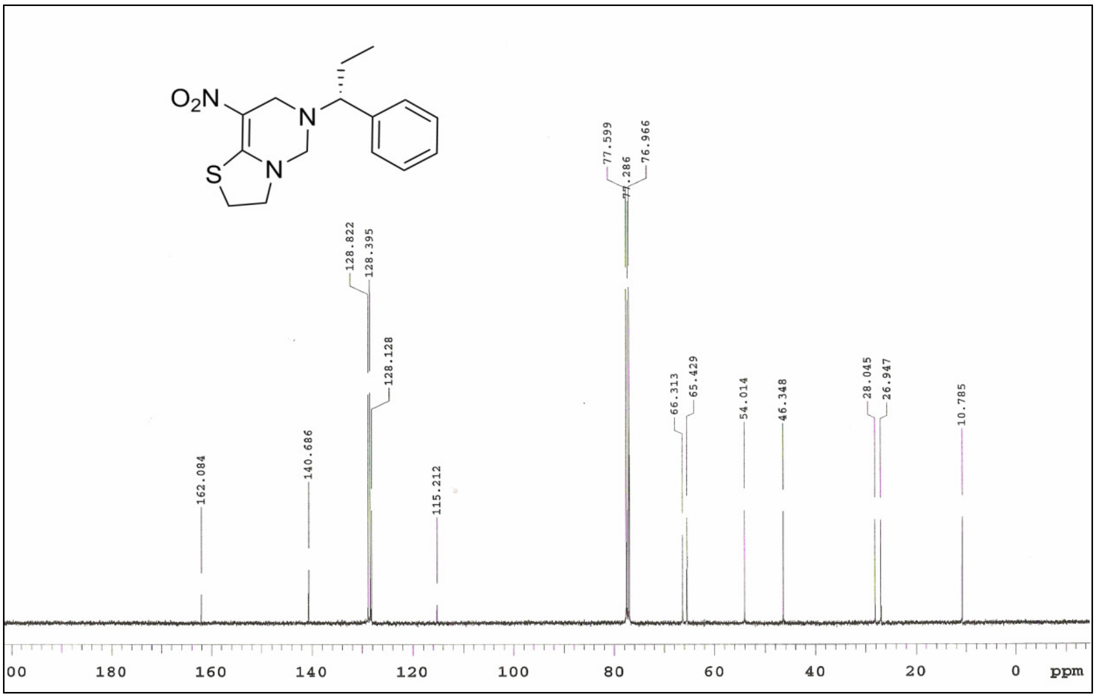
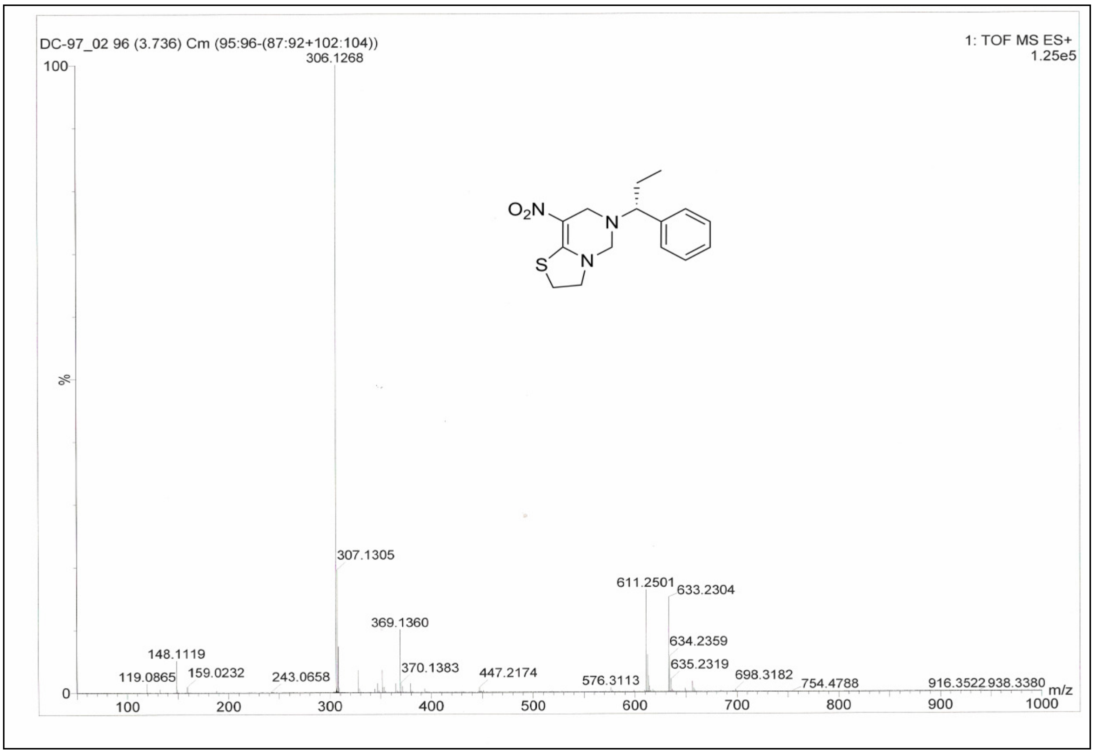
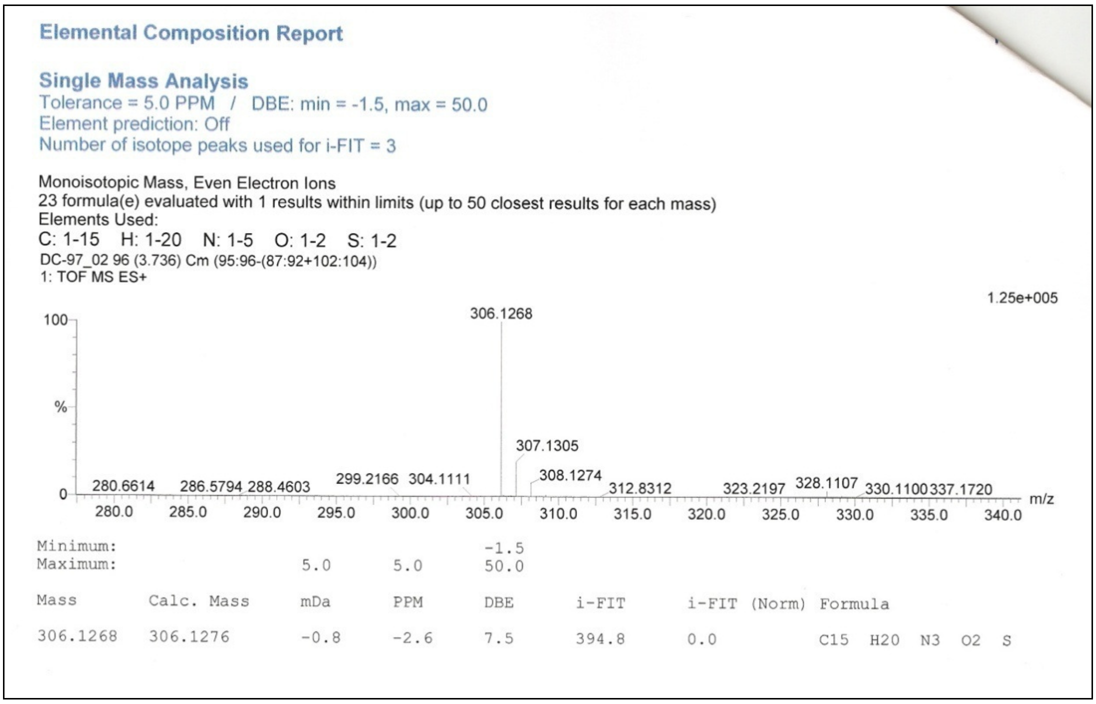


Figure 7. 30. ^{13}C NMR (100 MHz, CDCl3) spectrum of compound **163b**





Elemental Composition Report

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
23 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 1-15 H: 1-20 N: 1-5 O: 1-2 S: 1-2
DC-97_02 96 (3.736) Cm (95:96-(87:92+102:104))
1: TOF MS ES+

Minimum:				-1.5			
Maximum:		5.0	5.0	50.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
306.1268	306.1276	-0.8	-2.6	7.5	394.8	0.0	C15 H20 N3 O2 S

Figure 7. 31. HRMS and elemental composition of compound **163b**

X-ray Structure and Data for 163b

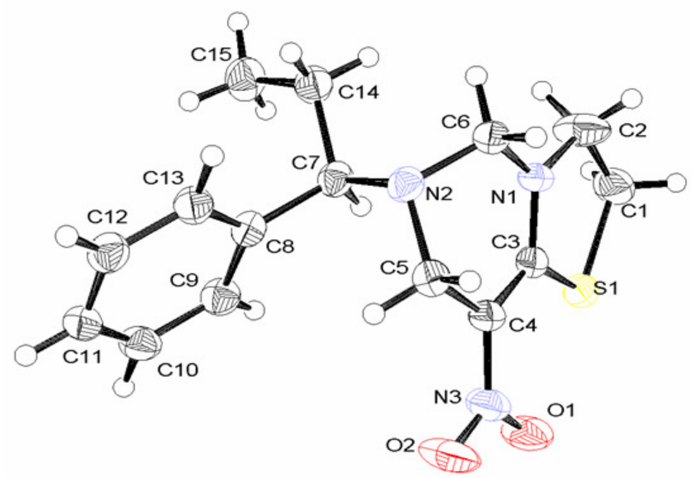


Figure 7. 32. X-ray Crystal Structure of **163b**

Table 7. 2. Crystal data and structure refinement for **163b**

Empirical formula	C15 H19 N3 O2 S	
Formula weight	305.39	
Temperature	150(2) K	
Wavelength	1.54180 Å	
Crystal system	Monoclinic	
Space group	C2	
Unit cell dimensions	a = 14.6114(3) Å	α= 90°.
	b = 5.4269(2) Å	β= 93.109(3)°.
	c = 18.8409(6) Å	γ = 90°.
Volume	1491.78(8) $Å^3$	
Z	4	
Density (calculated)	1.360 Mg/m^3	
Absorption coefficient	2.000 mm^{-1}	
F(000)	648	
Crystal size	0.24 x 0.16 x 0.05 mm^3	
Theta range for data collection	4.70 to 73.23°.	
Index ranges	-17<=h<=11, -6<=k<=6, -23<=l<=22	
Reflections collected	4909	
Independent reflections	2894 [R(int) = 0.0307]	
Completeness to theta = 73.23°	98.8 %	
Max. and min. transmission	0.9066 and 0.6454	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2894 / 1 / 191	
Goodness-of-fit on F^2	1.041	
Final R indices [I>2sigma(I)]	R1 = 0.0379, wR2 = 0.0966	
R indices (all data)	R1 = 0.0398, wR2 = 0.0986	
Absolute structure parameter	-0.024(18)	
Largest diff. peak and hole	0.252 and -0.220 e.$Å^{-3}$	

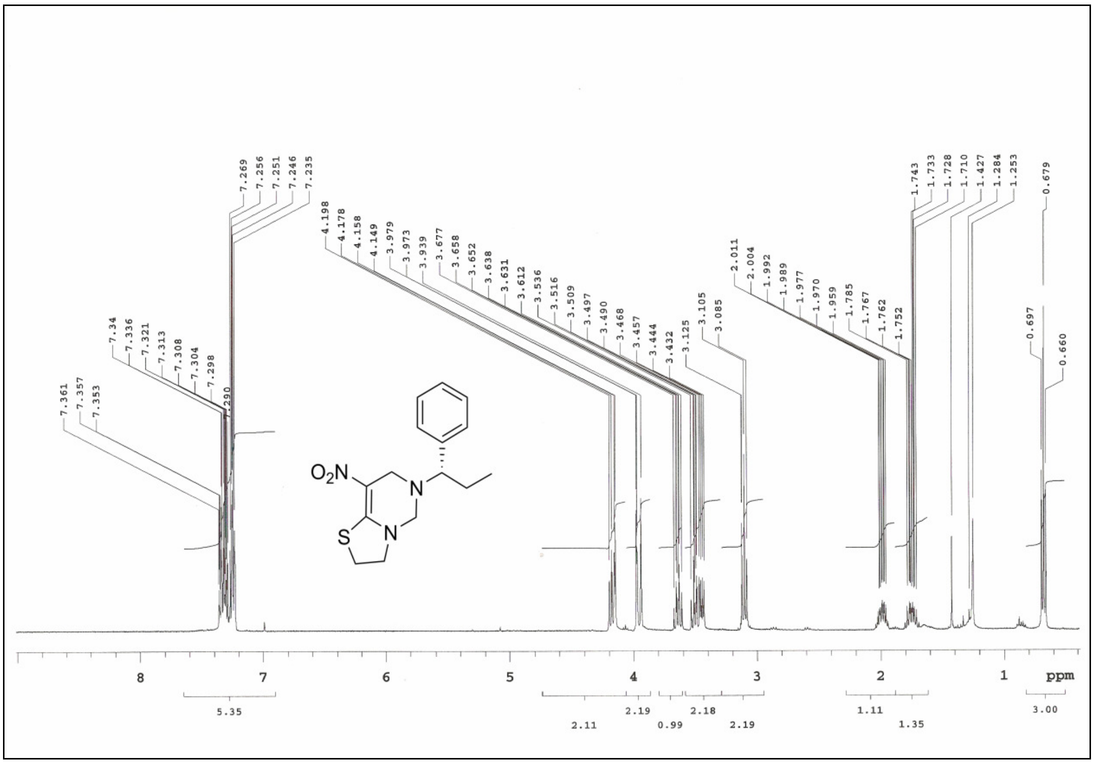


Figure 7. 33. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **163c**

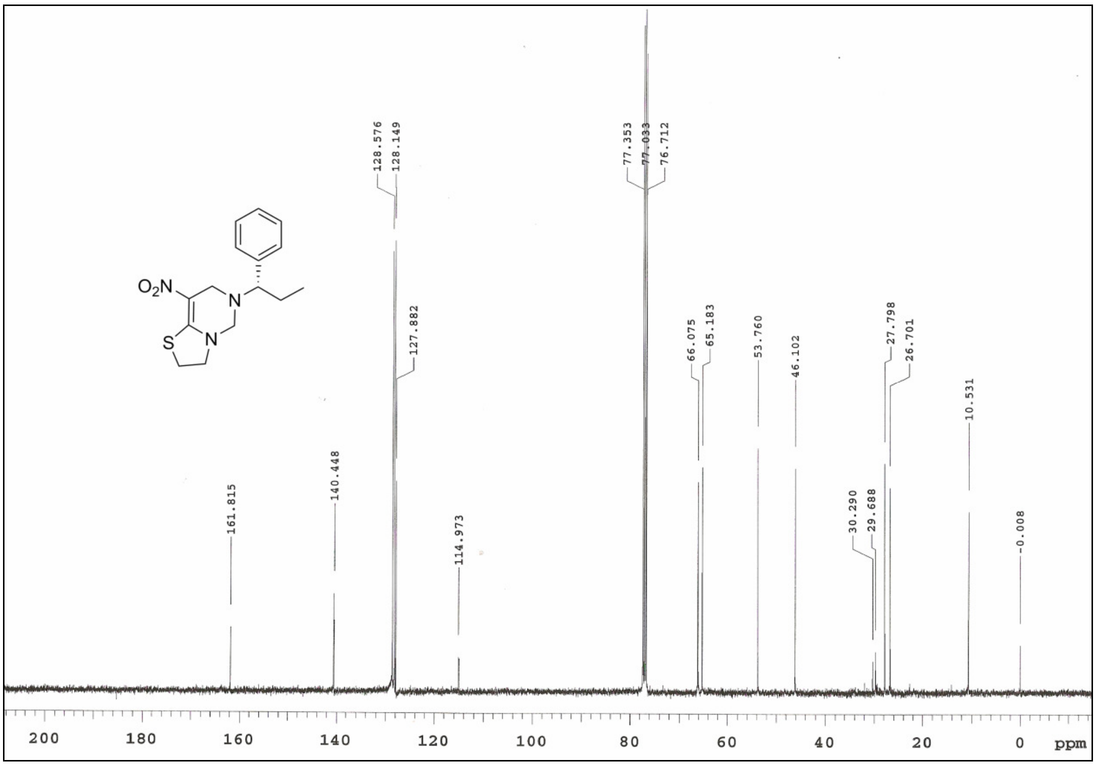
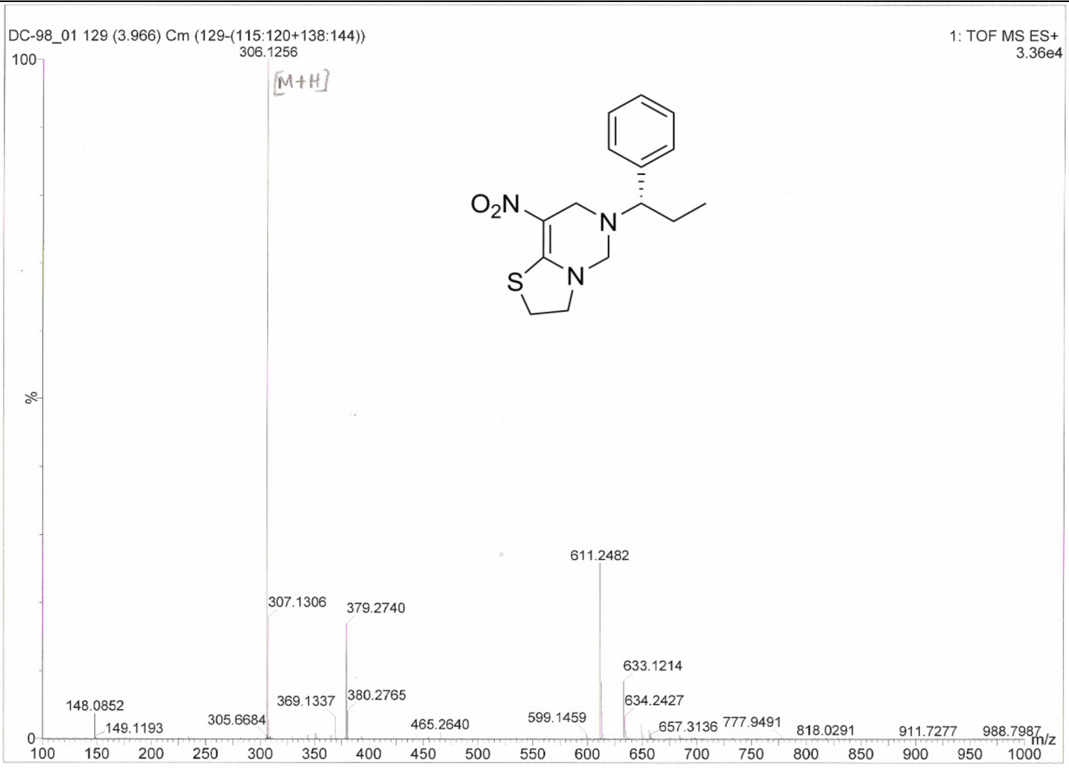


Figure 7. 34. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **163c**



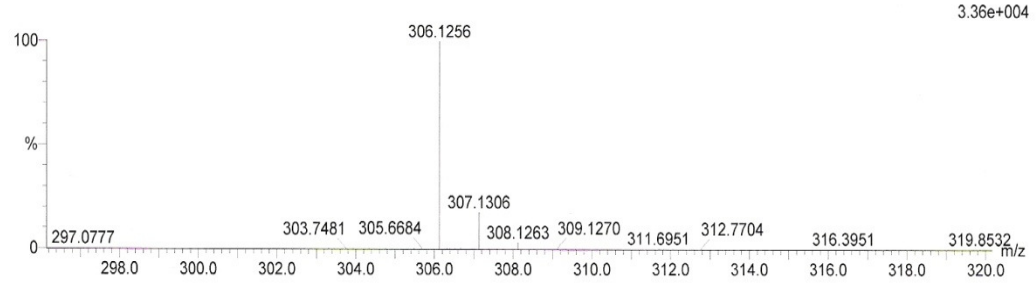
Elemental Composition Report

Page 1

Single Mass Analysis

Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
63 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 1-15 H: 1-20 N: 1-3 O: 1-3 S: 1-5
DC-98_01 129 (3.966) Cm (129-(115:120+138:144))
1: TOF MS ES+



Minimum:				-1.5			
Maximum:		5.0	10.0	50.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
306.1256	306.1276	-2.0	-6.5	7.5	108.8	0.0	C15 H20 N3 O2 S

[M+H]

Figure 7. 35. HRMS and elemental composition of compound **163c**

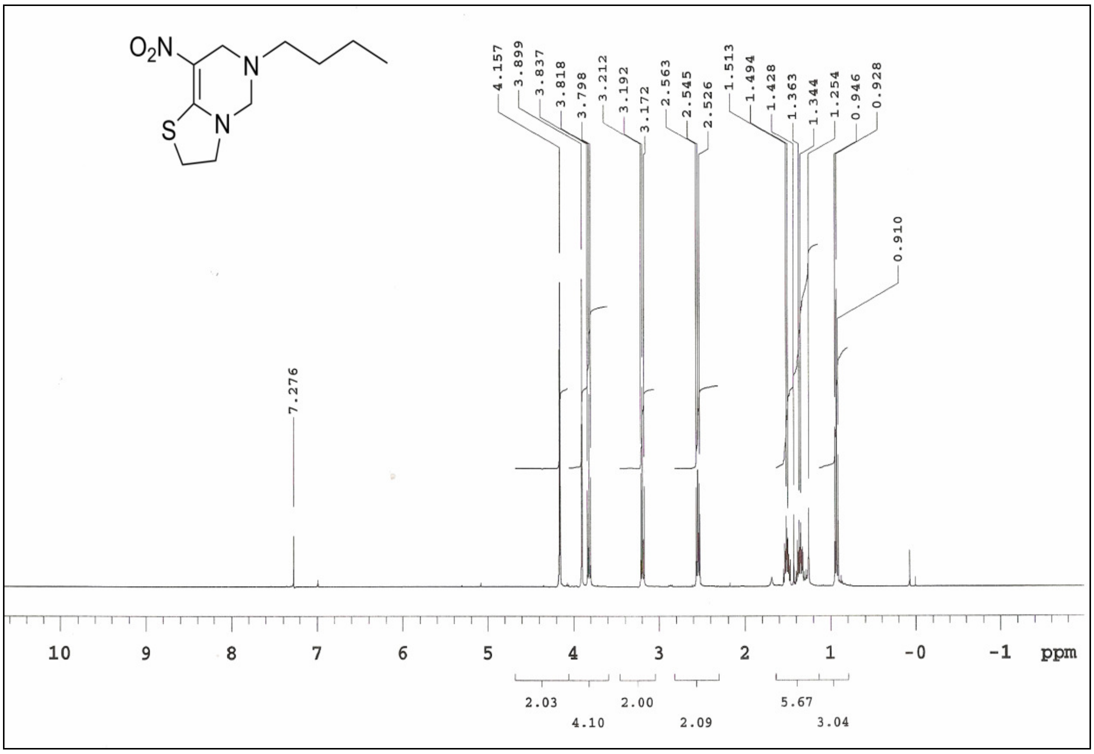


Figure 7. 36. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **163d**

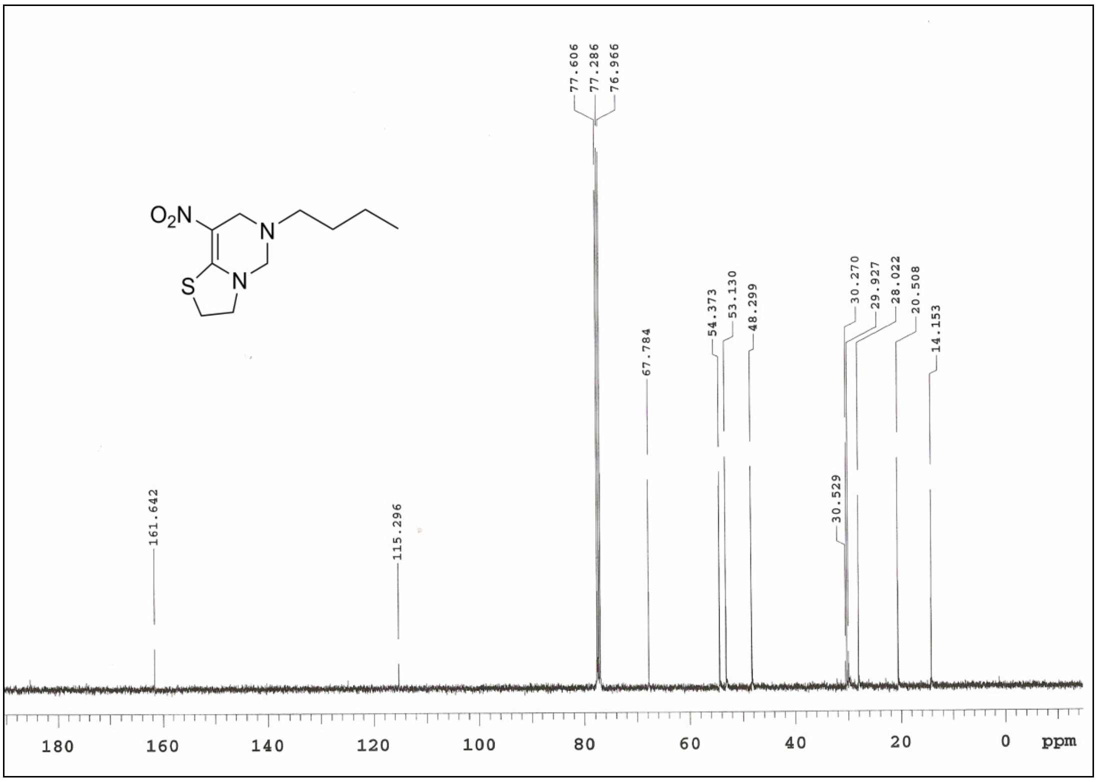
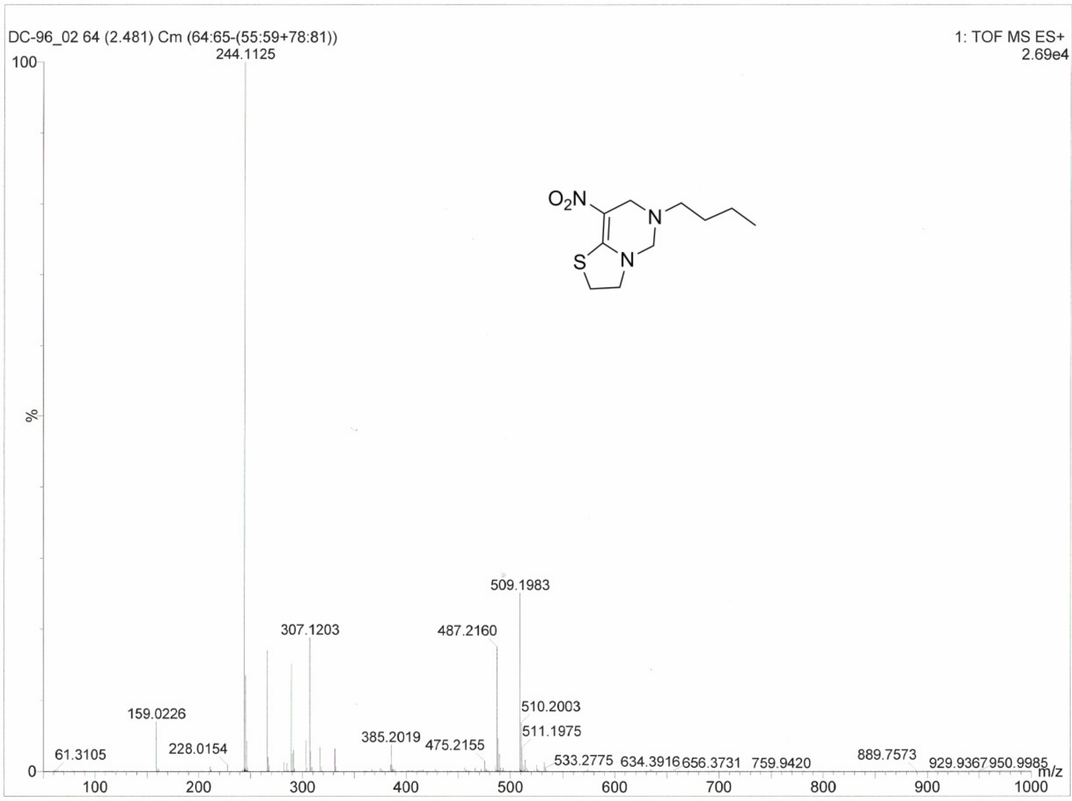


Figure 7. 37. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **163d**



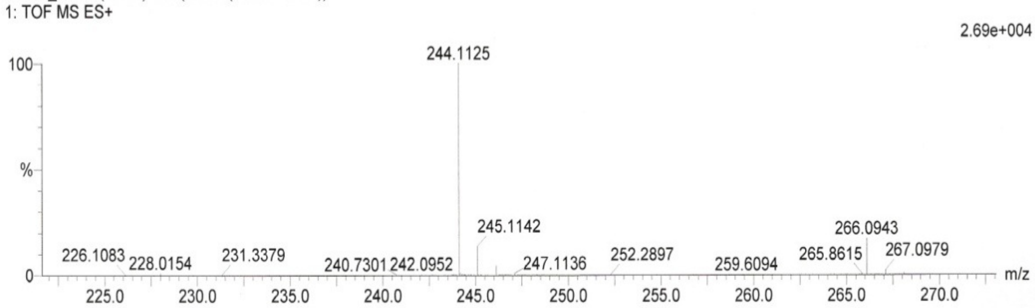
Elemental Composition Report

Pa

Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
29 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 1-14 H: 1-18 N: 1-5 O: 1-2 S: 1-2
DC-96_02 64 (2.481) Cm (64:65-(55:59+78:81))
1: TOF MS ES+



Minimum:				-1.5			
Maximum:		5.0	5.0	50.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
244.1125	244.1120	0.5	2.0	3.5	197.6	0.0	C10 H18 N3 O2 S

Figure 7. 38. HRMS and elemental composition of compound **163d**

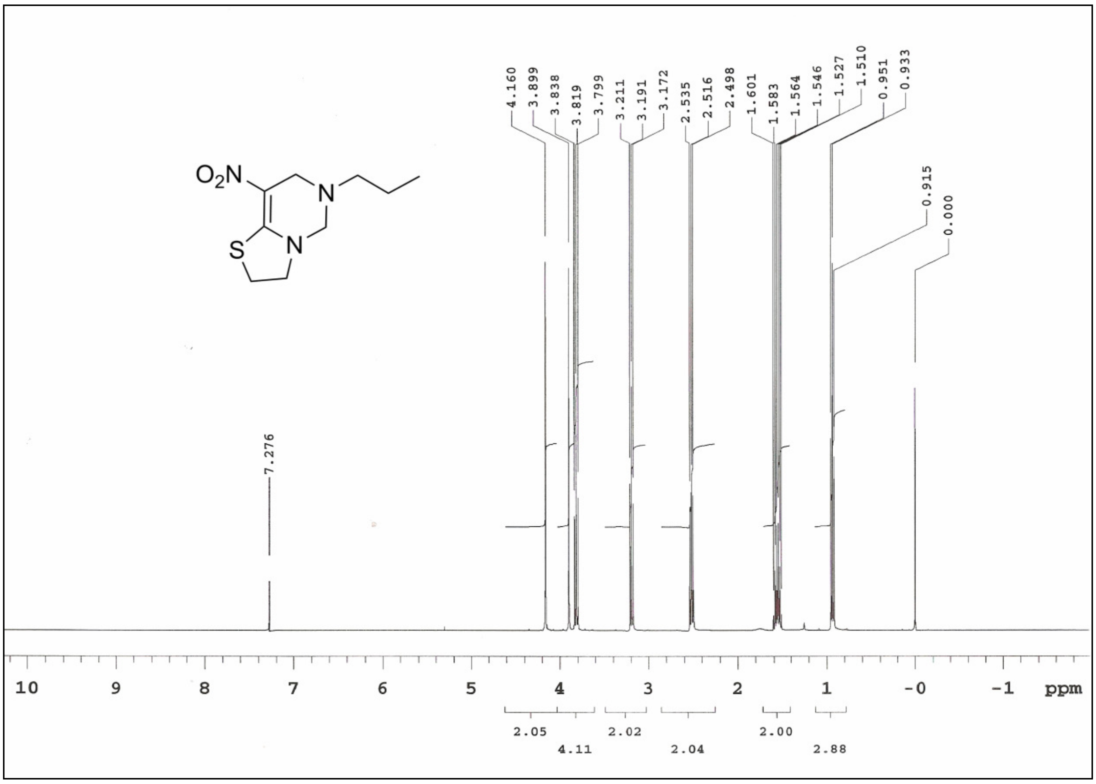


Figure 7. 39. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **163e**

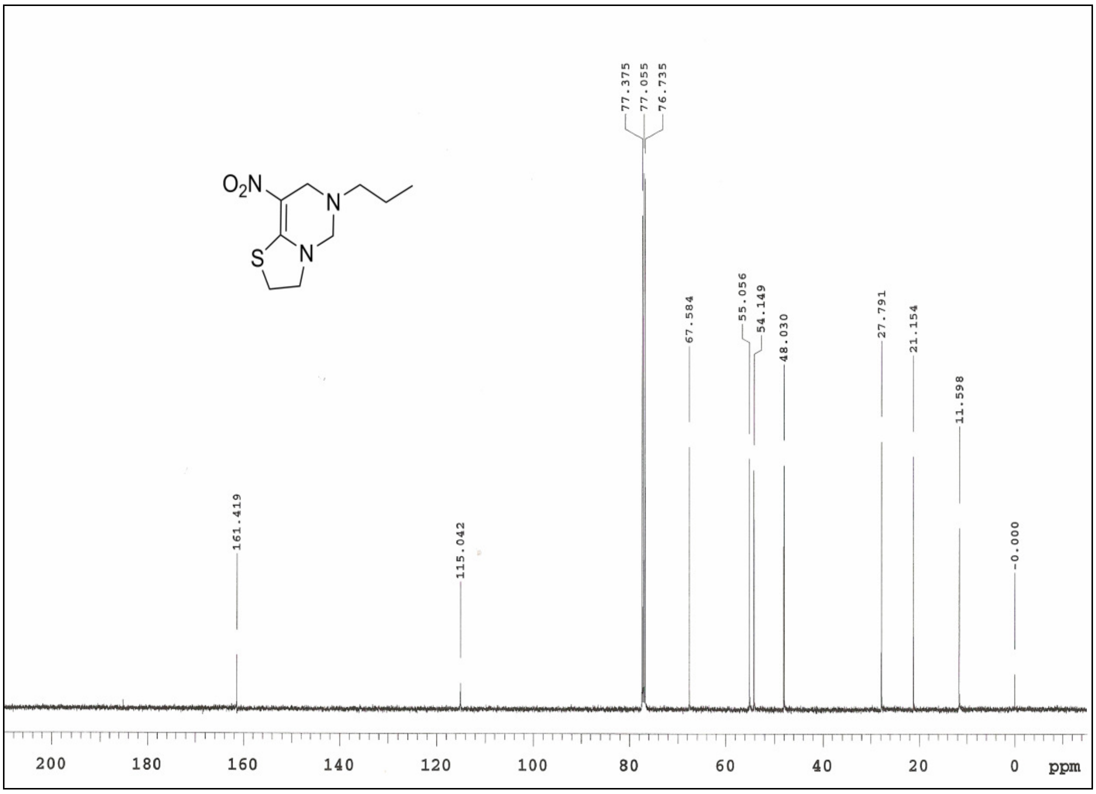
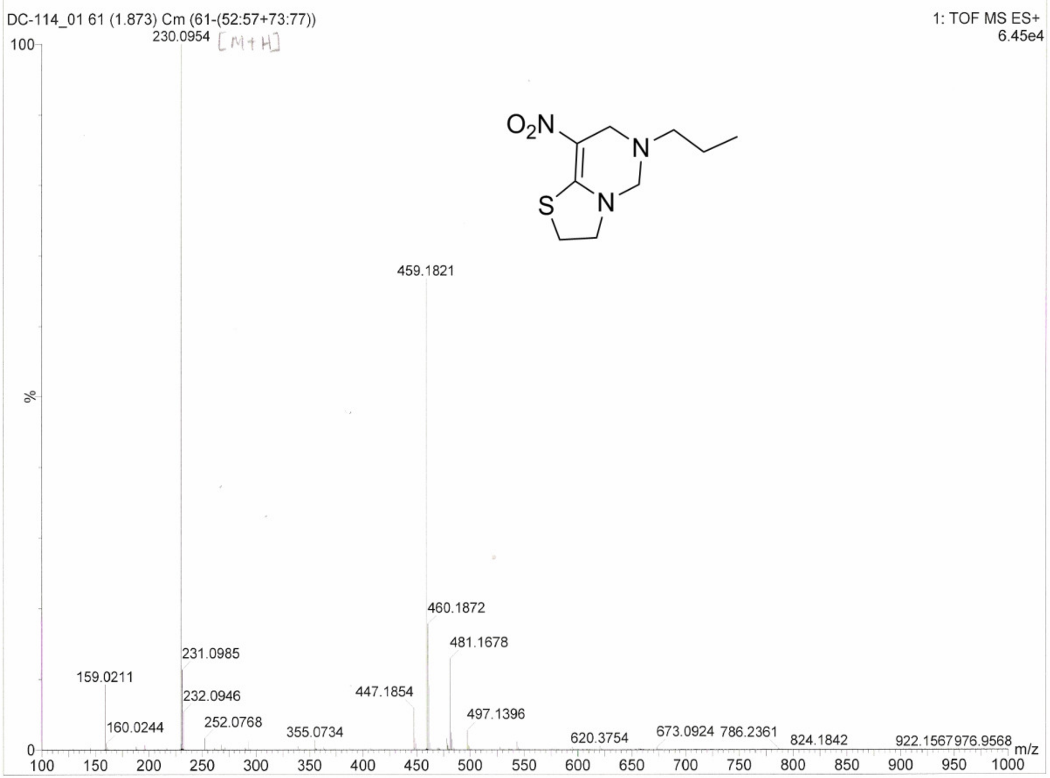


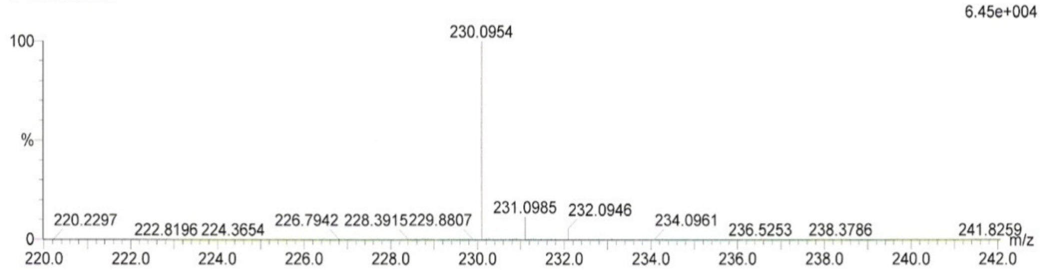
Figure 7. 40. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **163e**



Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
52 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 1-14 H: 1-16 N: 1-3 O: 1-3 S: 1-5
DC-114_01 61 (1.873) Cm (61-(52:57+73:77))
1: TOF MS ES+



Minimum:				-1.5			
Maximum:		5.0	10.0	50.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
230.0954	230.0963	-0.9	-3.9	3.5	236.1	0.0	C9 H16 N3 O2 S

[M+H]

Figure 7. 41. HRMS and elemental composition of compound **163e**

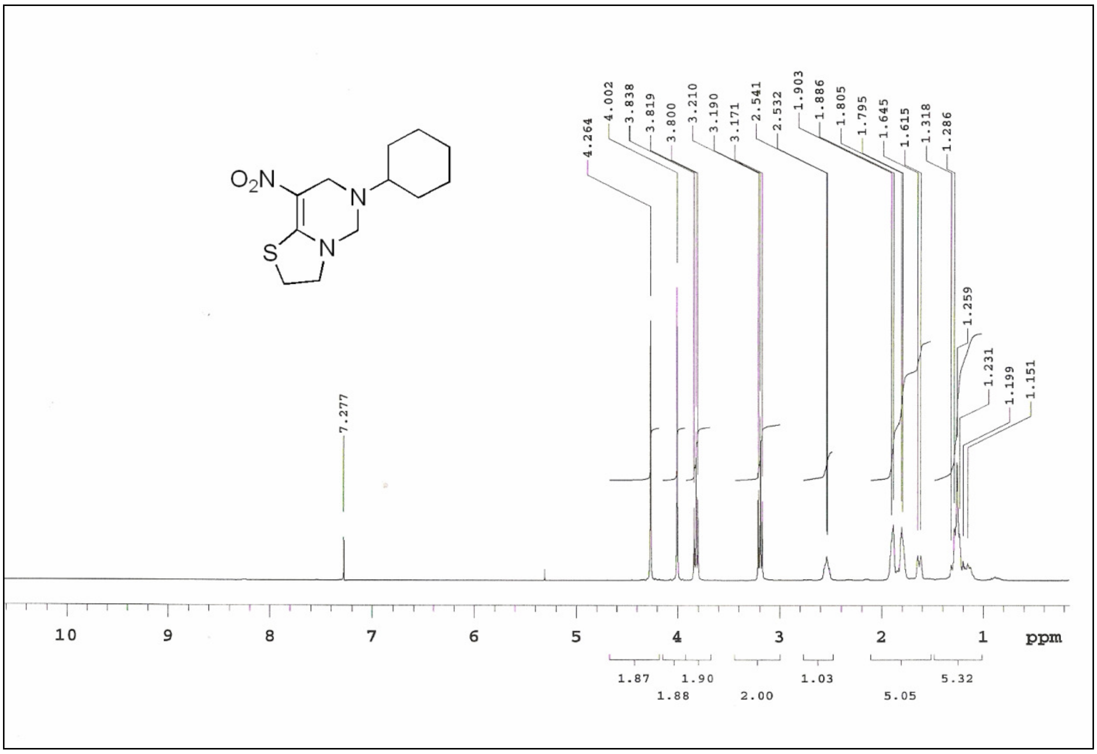


Figure 7. 42. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **163f**

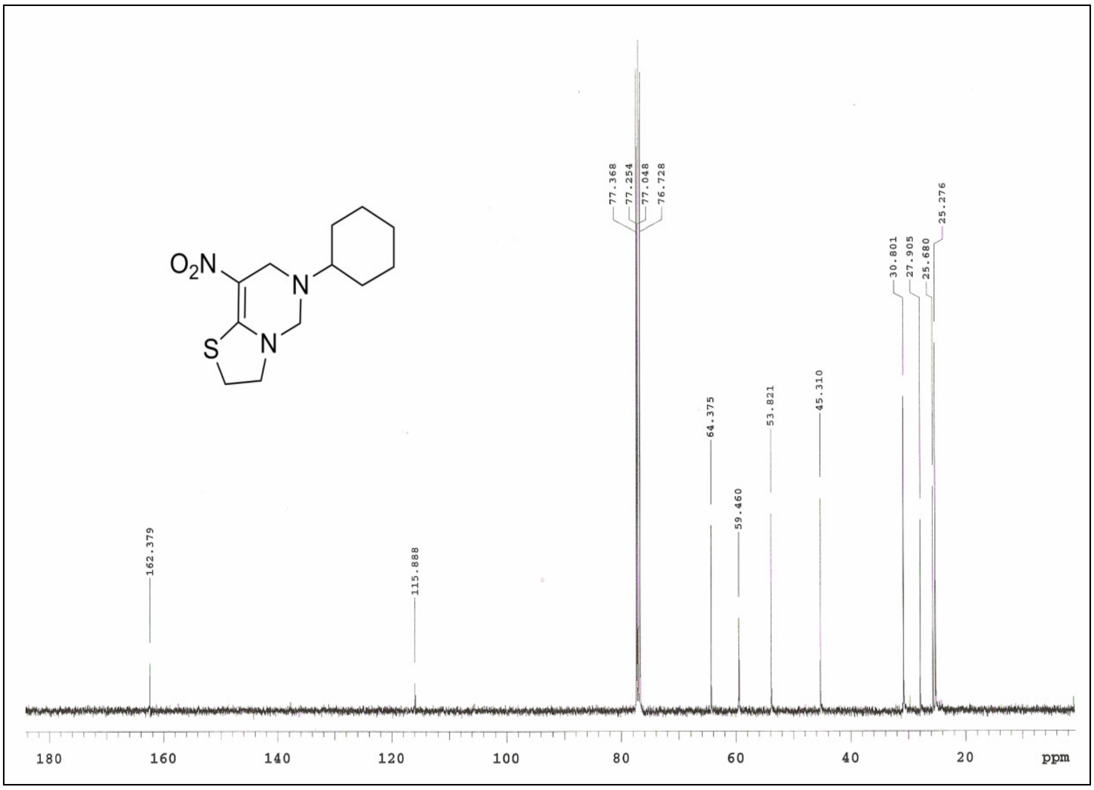
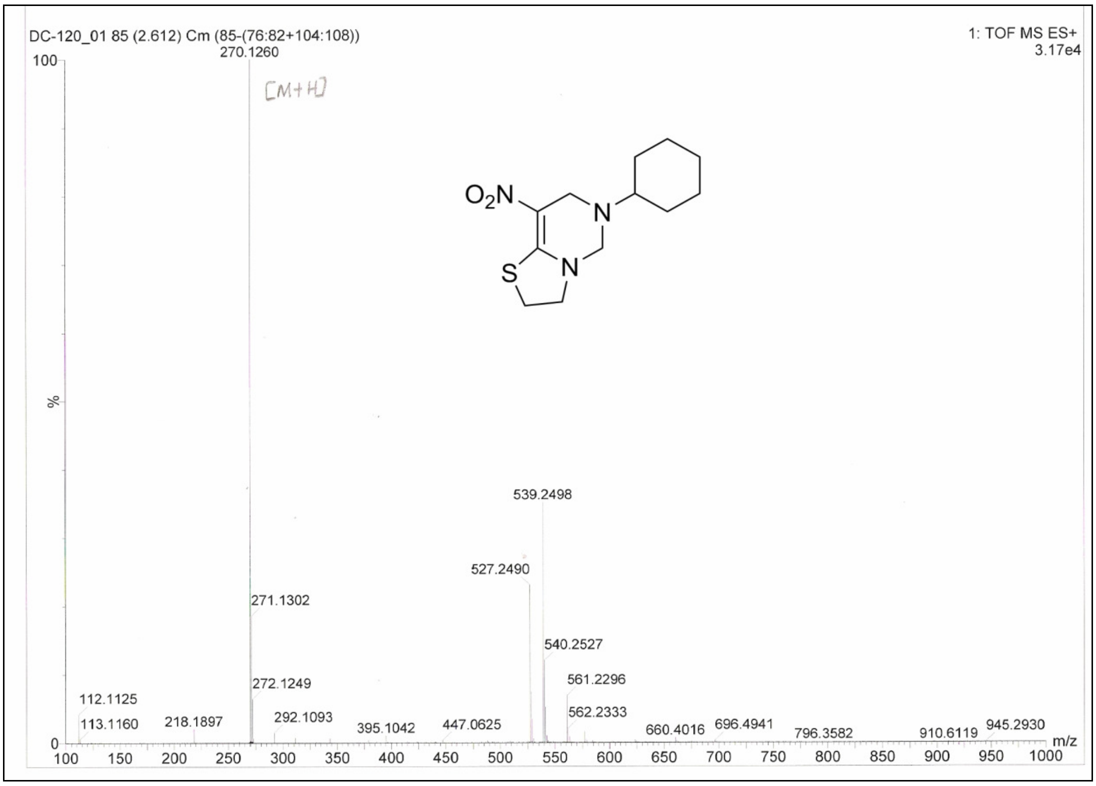


Figure 7. 43. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **163f**



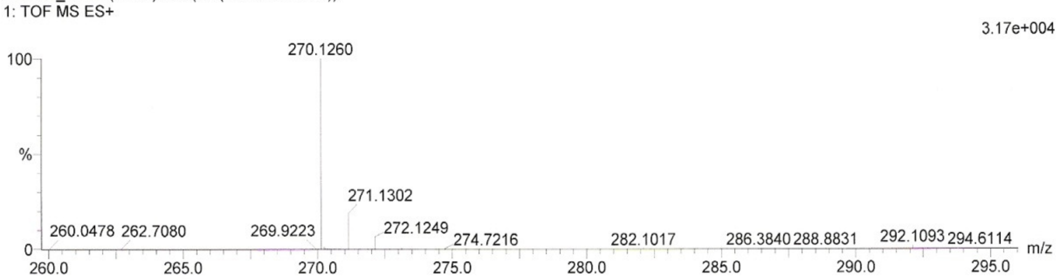
Elemental Composition Report

Page 1

Single Mass Analysis

Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
69 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 1-14 H: 1-20 N: 1-3 O: 1-3 S: 1-5
DC-120_01 85 (2.612) Cm (85-(76:82+104:108))
1: TOF MS ES+



Minimum:				-1.5			
Maximum:		5.0	10.0	50.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
270.1260	270.1276	-1.6	-5.9	4.5	157.5	0.0	C12 H20 N3 O2 S

[M+H]

Figure 7. 44. HRMS and elemental composition of compound **163f**

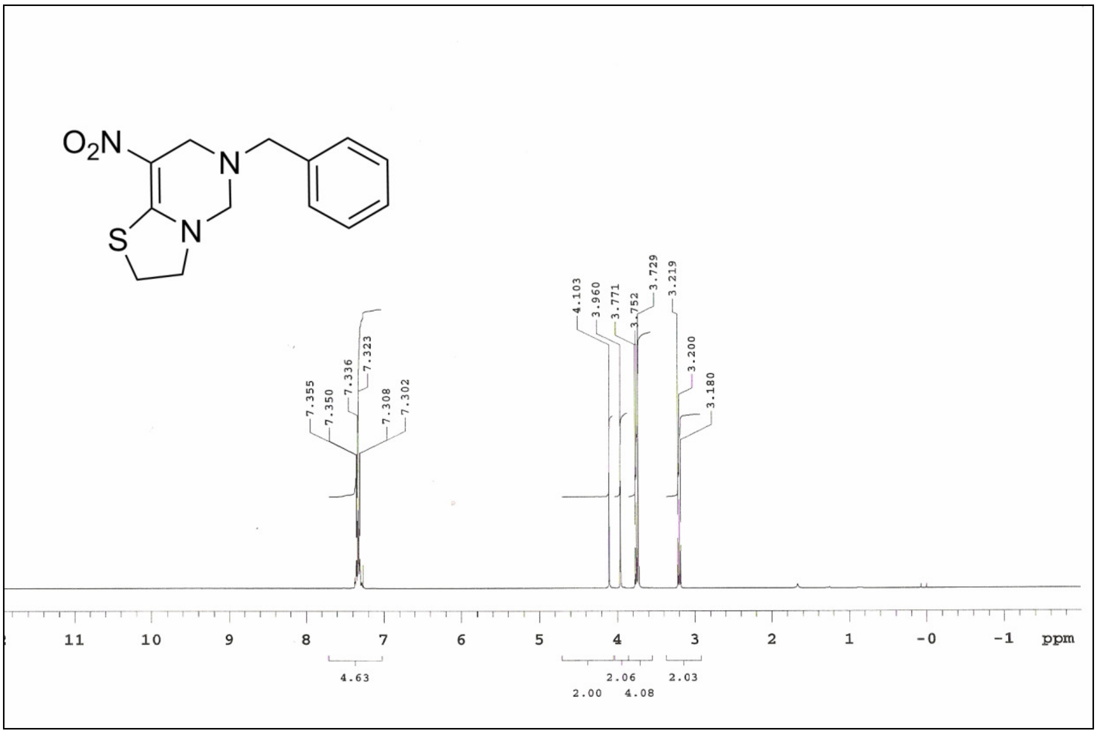


Figure 7. 45. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **163g**

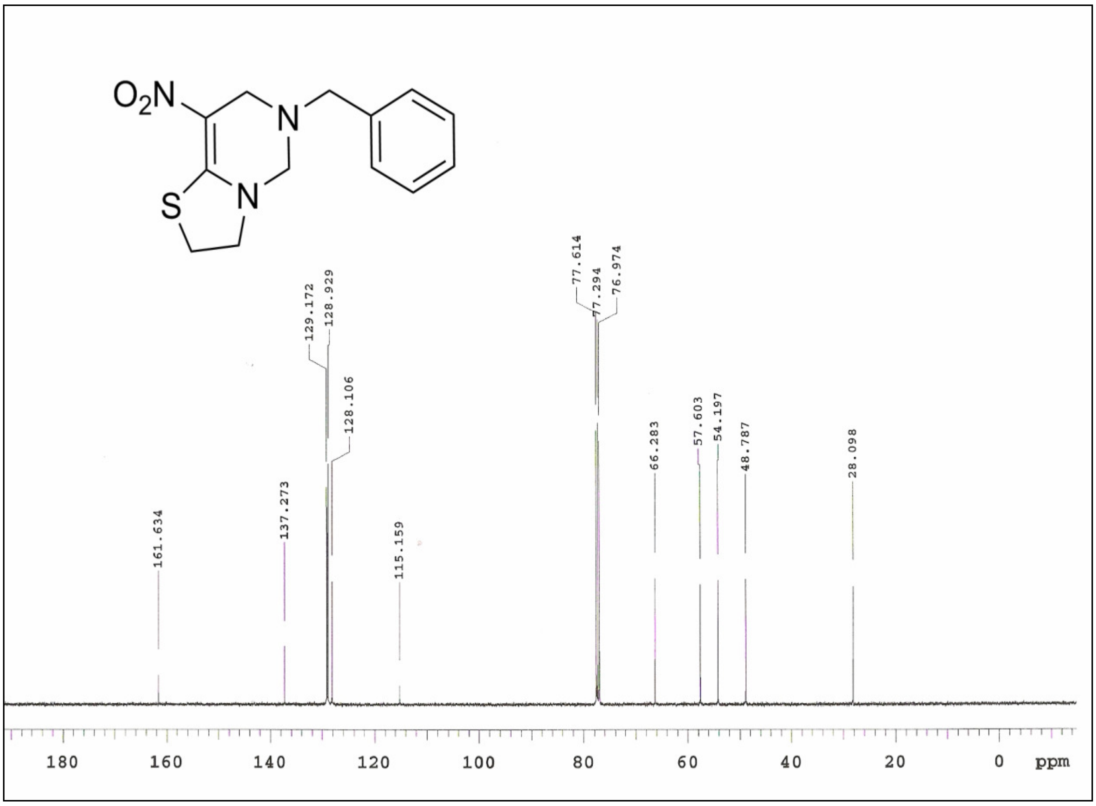
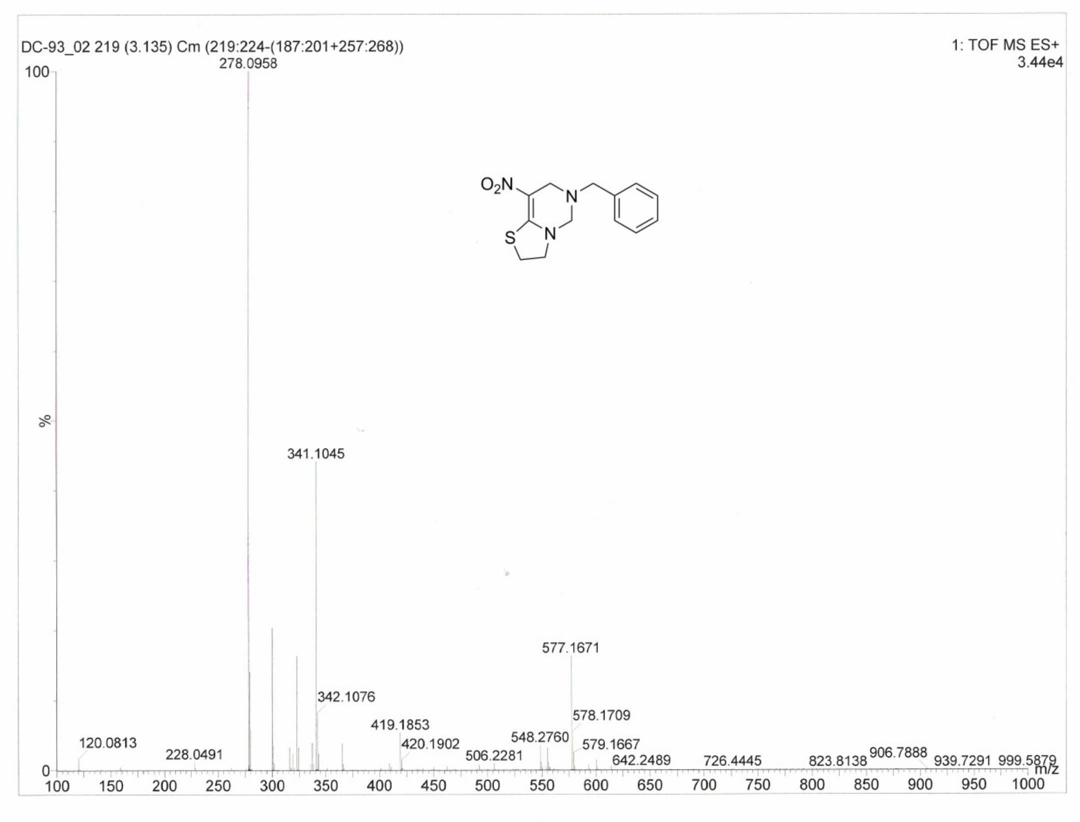


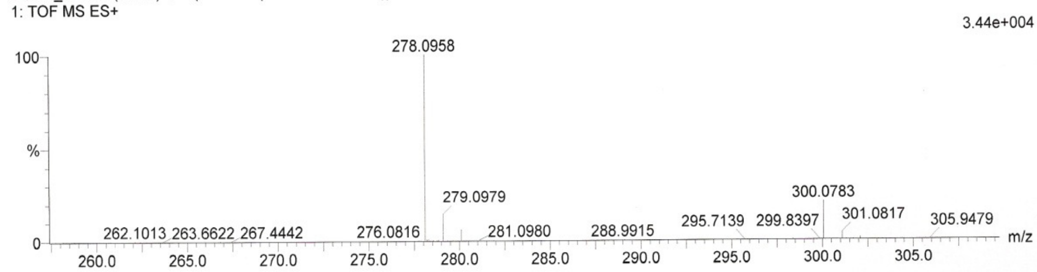
Figure 7. 46. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **163g**



Elemental Composition Report

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
24 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 1-14 H: 1-18 N: 1-5 O: 1-2 S: 1-2
DC-93_02 219 (3.135) Cm (219:224-(187:201+257:268))
1: TOF MS ES+



Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
Minimum:				-1.5			
Maximum:		5.0	5.0	50.0			
278.0958	278.0963	-0.5	-1.8	7.5	160.5	0.0	C13 H16 N3 O2 S

Figure 7. 47. HRMS and elemental composition of compound **163g**

X-ray Structure and Data for 163g

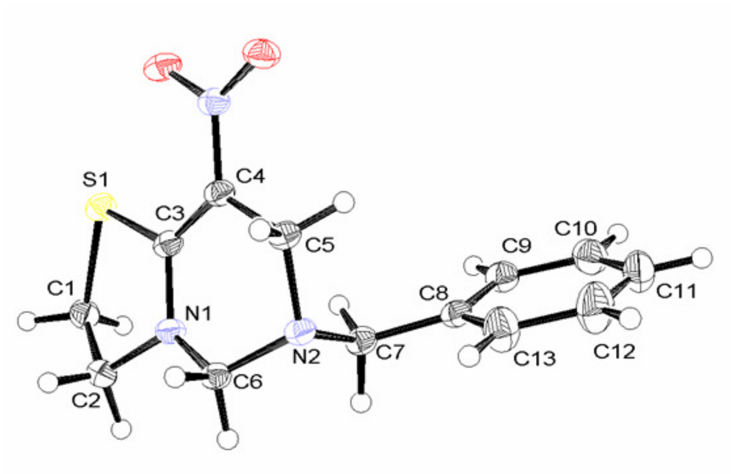


Figure 7. 48. X-ray Crystal Structure of **163g**

Table 7. 3. Crystal data and structure refinement for **163g**

Empirical formula	C13 H15 N3 O2 S	
Formula weight	277.34	
Temperature	150(2) K	
Wavelength	1.54180 Å	
Crystal system	Monoclinic	
Space group	C2/c	
Unit cell dimensions	a = 22.1403(12) Å	α= 90°.
	b = 7.4116(3) Å	β= 96.477(4)°.
	c = 15.9650(6) Å	γ= 90°.
Volume	2603.1(2) Å^3	
Z	8	
Density (calculated)	1.415 Mg/m^3	
Absorption coefficient	2.236 mm^{-1}	
F(000)	1168	
Crystal size	0.23 x 0.14 x 0.03 mm^3	
Theta range for data collection	4.02 to 73.38°.	
Index ranges	-27<=h<=24, -9<=k<=9, -19<=l<=17	
Reflections collected	8554	
Independent reflections	2568 [R(int) = 0.0366]	
Completeness to theta = 73.38°	98.1 %	
Max. and min. transmission	0.9360 and 0.6273	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2568 / 0 / 172	
Goodness-of-fit on F^2	1.050	
Final R indices [I>2sigma(I)]	R1 = 0.0381, wR2 = 0.0951	
R indices (all data)	R1 = 0.0453, wR2 = 0.1022	
Largest diff. peak and hole	0.263 and -0.465 e.Å^{-3}	

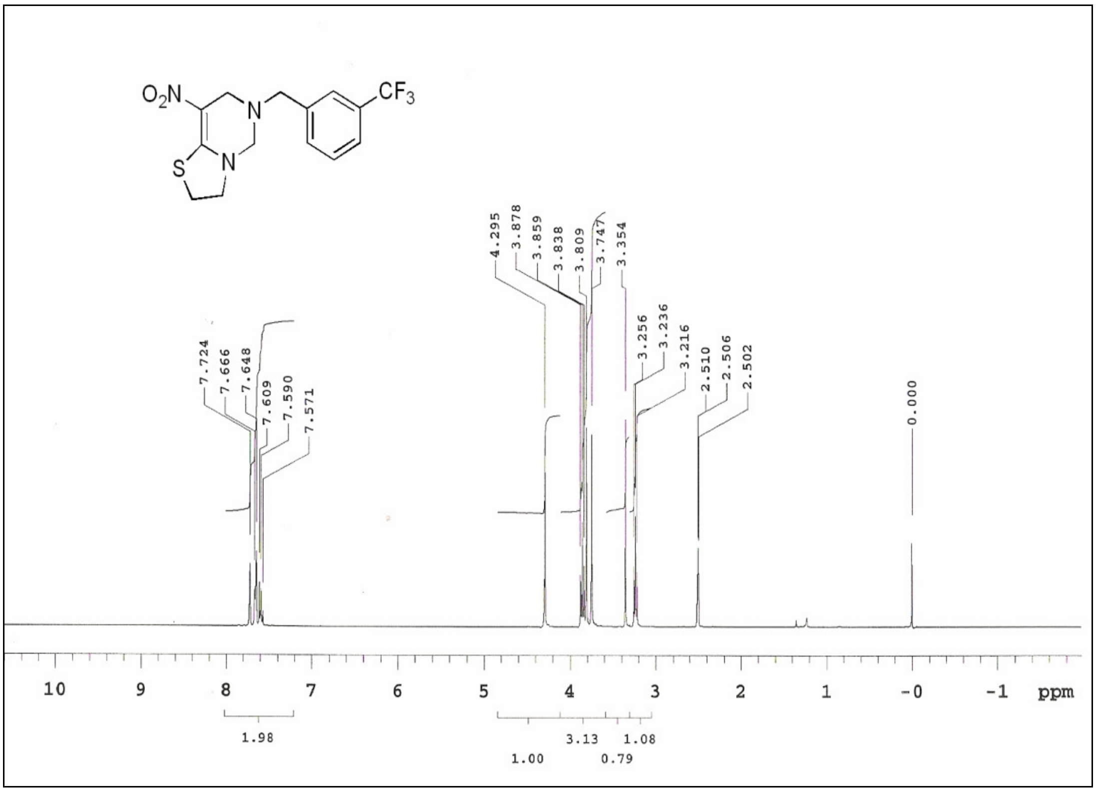


Figure 7. 49. ^{1}H NMR (400 MHz, DMSO-d6) spectrum of compound **163h**

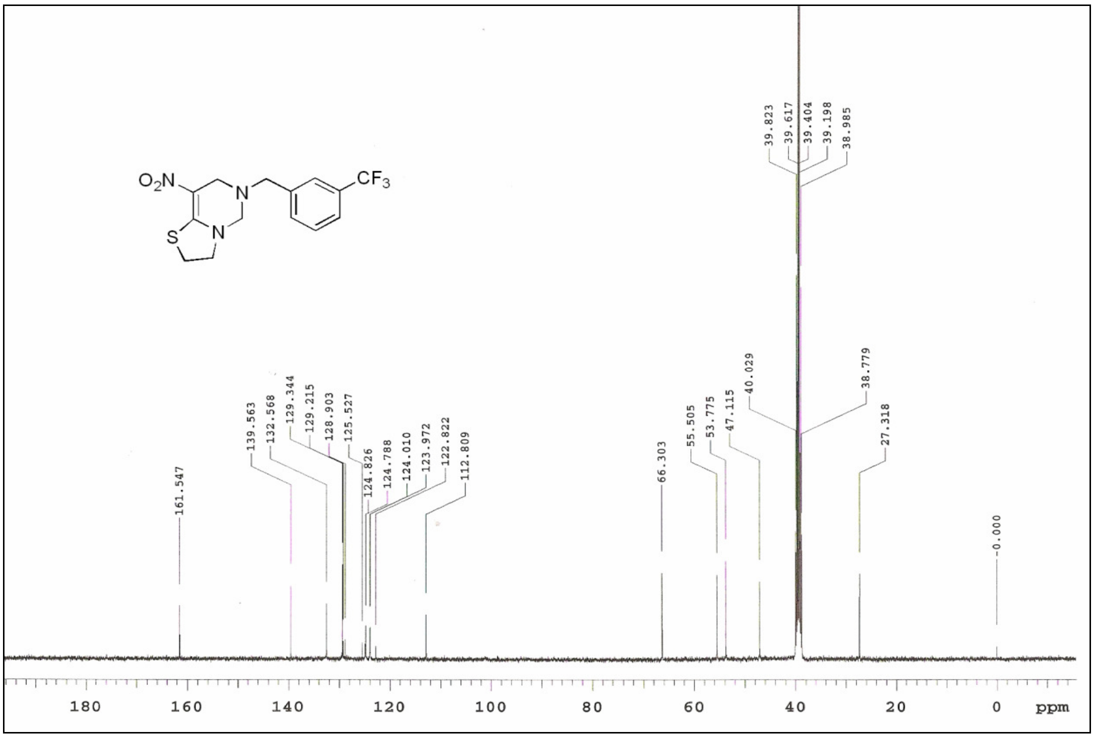
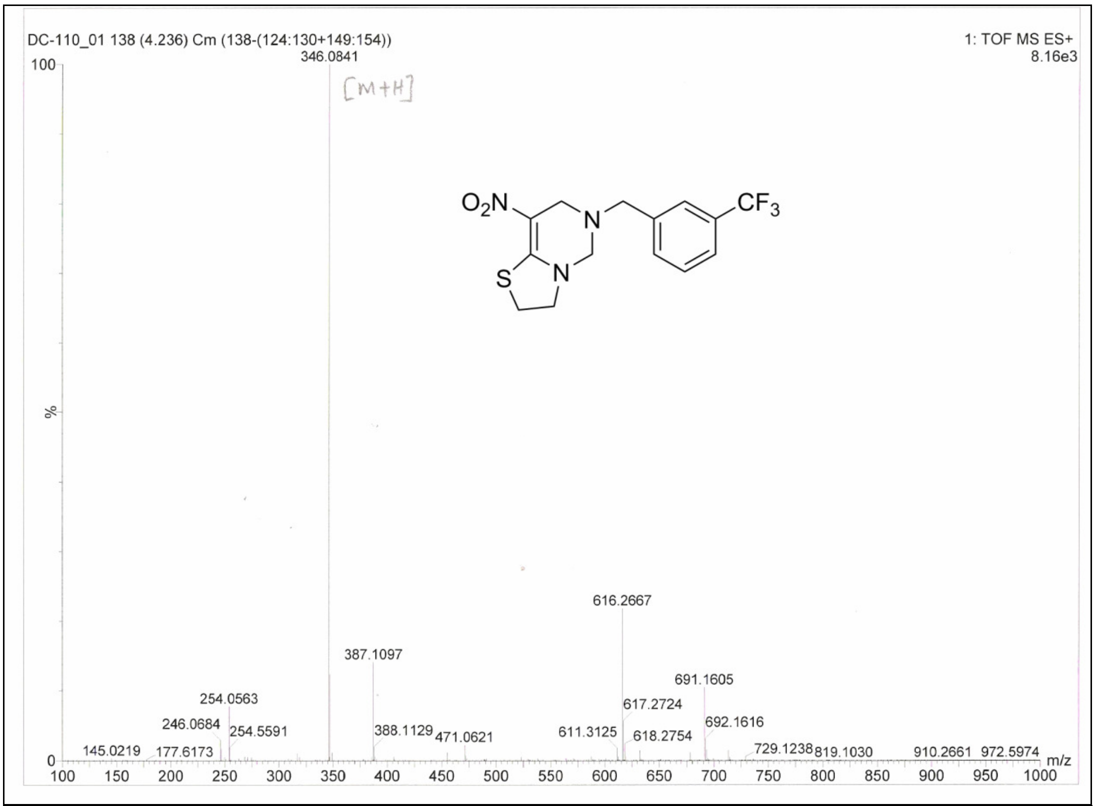


Figure 7. 50. ^{13}C NMR (100 MHz, DMSO-d6) spectrum of compound **163h**



Elemental Composition Report

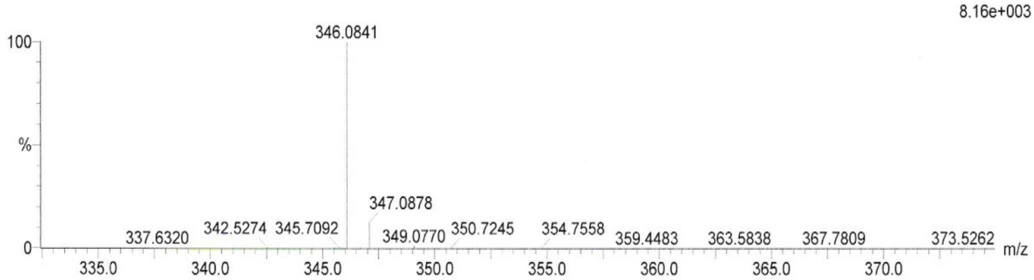
Page 1

Single Mass Analysis

Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
140 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 1-14 H: 1-15 N: 1-3 O: 1-3 S: 1-5 F: 1-3

DC-110_01 138 (4.236) Cm (138-(124:130+149:154))
1: TOF MS ES+



Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
Minimum:				-1.5			
Maximum:		5.0	10.0	50.0			
346.0841	346.0837	0.4	1.2	7.5	33.2	0.0	C14 H15 N3 O2 S F3

[M+H]

Figure 7. 51. HRMS and elemental composition of compound **163h**

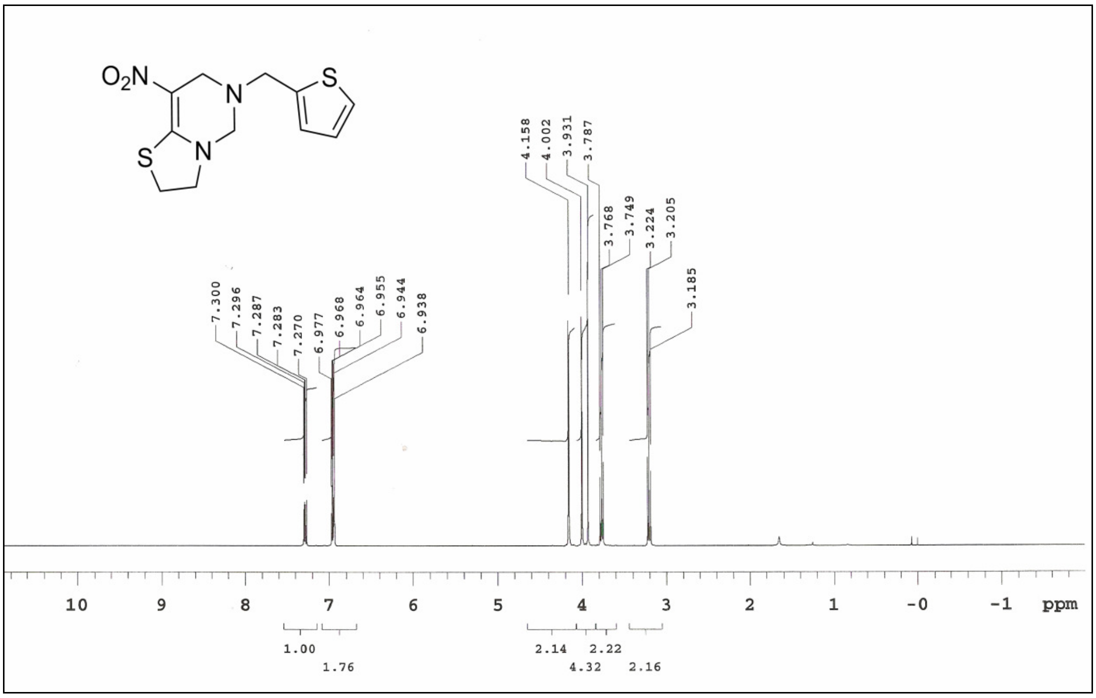


Figure 7. 52. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **163i**

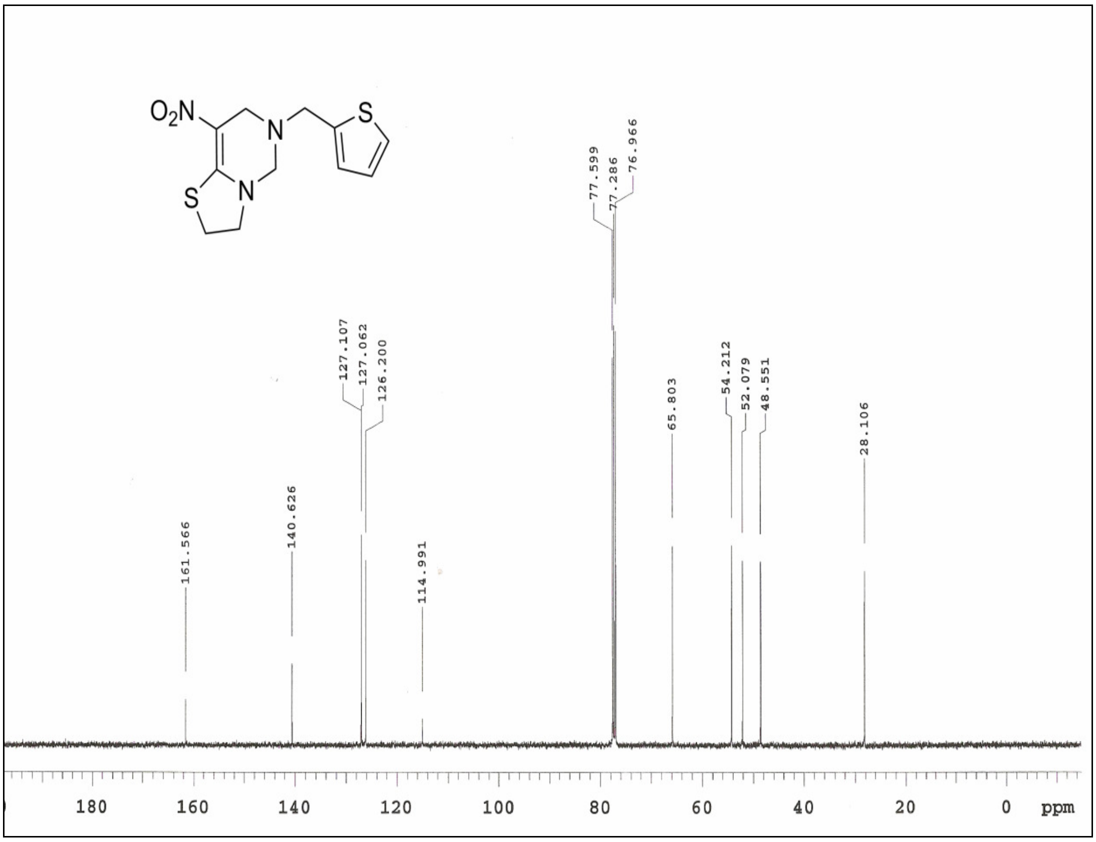
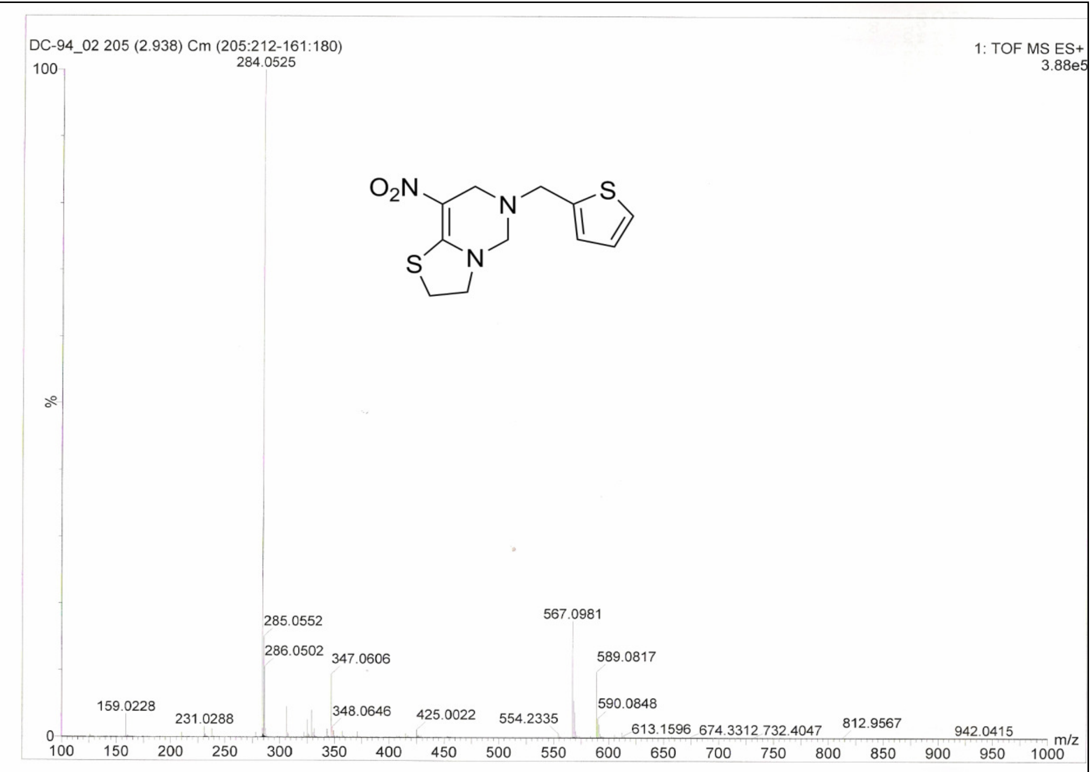


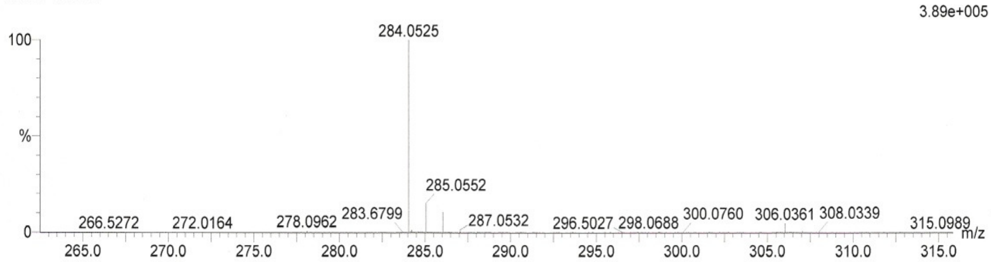
Figure 7. 53. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **163i**



Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
22 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 1-14 H: 1-18 N: 1-5 O: 1-2 S: 1-2
DC-94_02 205 (2.938) Cm (205:212-161:180)
1: TOF MS ES+



Minimum:				-1.5			
Maximum:		5.0	5.0	50.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
284.0525	284.0527	-0.2	-0.7	6.5	637.1	0.0	C11 H14 N3 O2 S2

Figure 7. 54. HRMS and elemental composition of compound **163i**

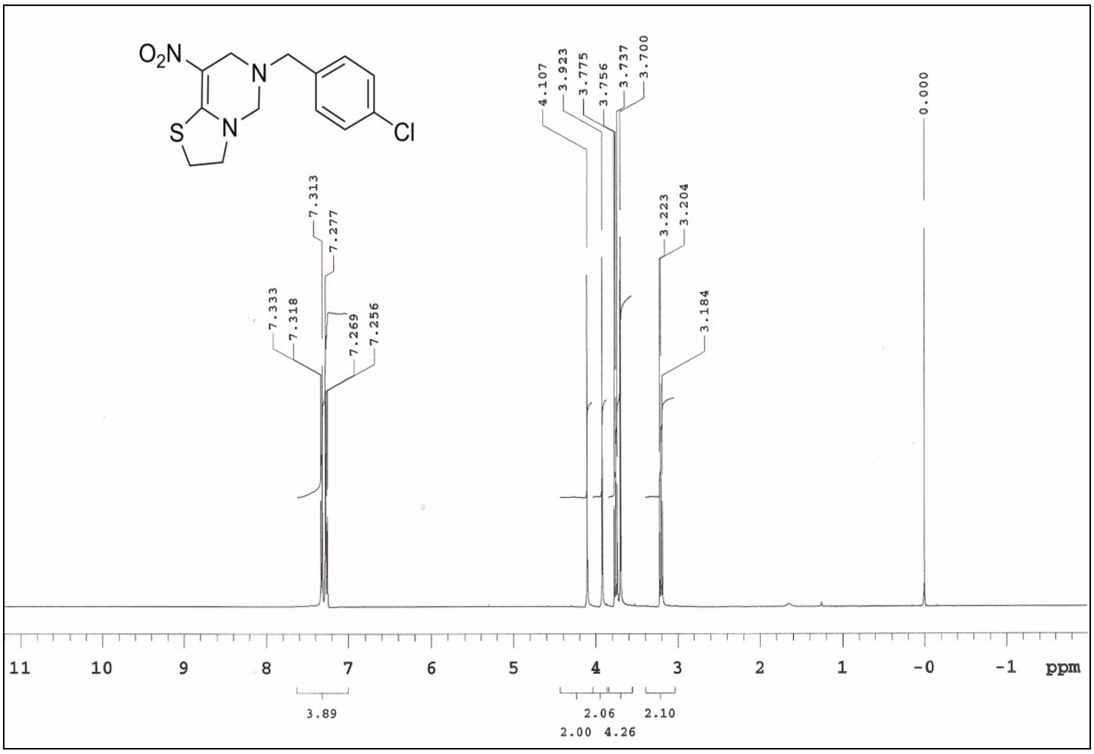


Figure 7. 55. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **163j**

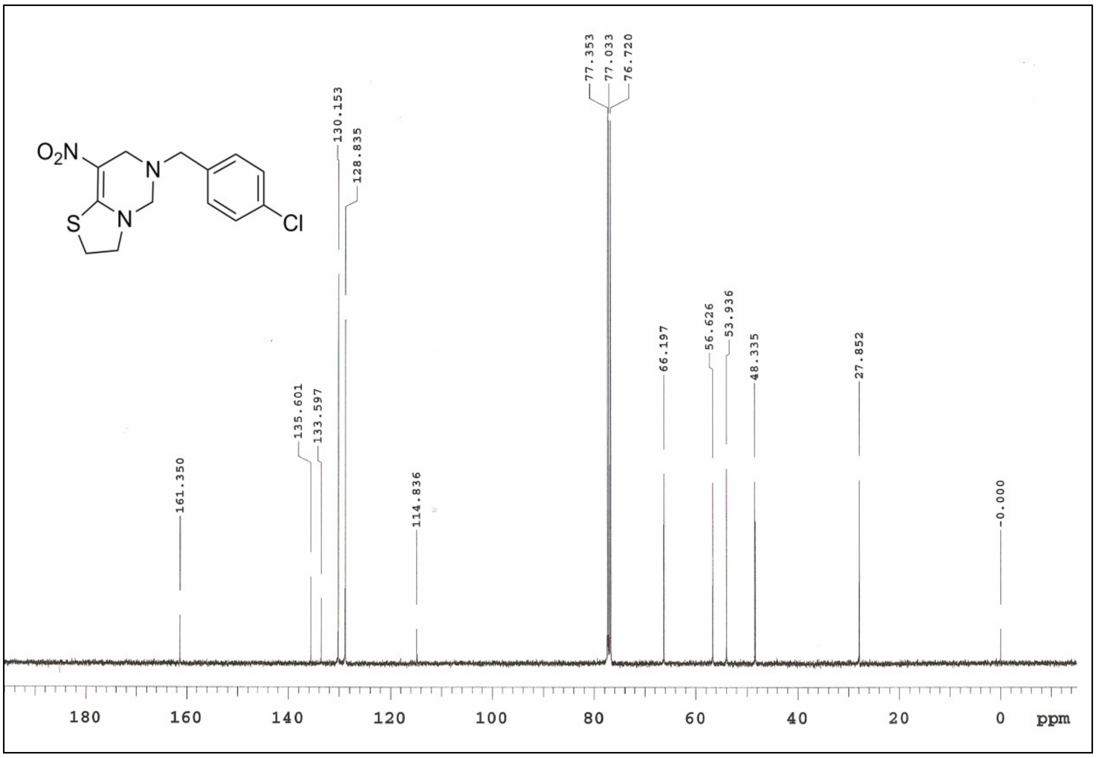
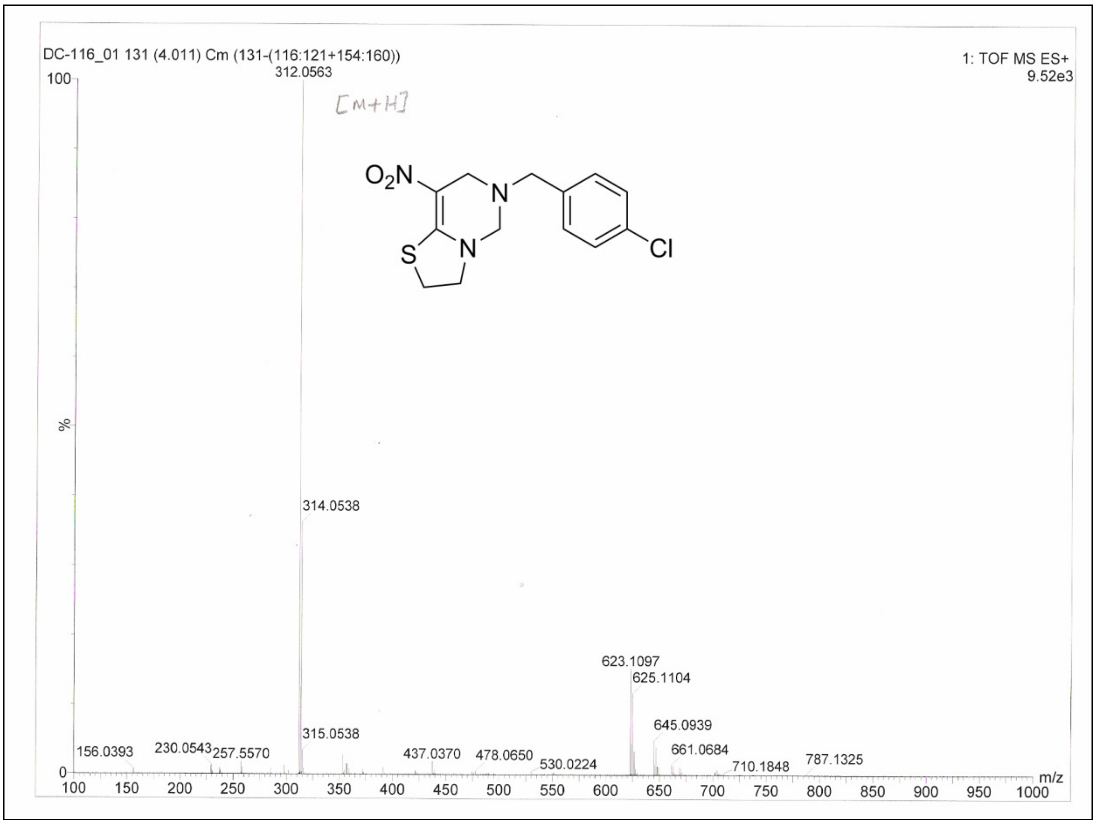


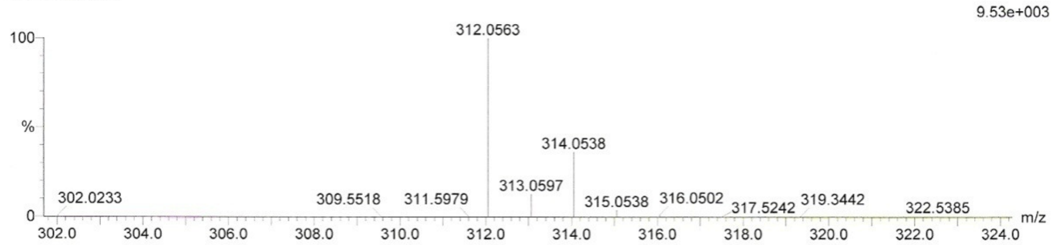
Figure 7. 56. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **163j**



Elemental Composition Report | **Page 1**

Single Mass Analysis
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
101 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 1-14 H: 1-16 N: 1-3 O: 1-3 S: 1-5 Cl: 0-1
DC-116_01 131 (4.011) Cm (131-(116:121+154:160))
1: TOF MS ES+



Minimum:				-1.5			
Maximum:		5.0	10.0	50.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
312.0563	312.0574	-1.1	-3.5	7.5	49.3	0.0	C13 H15 N3 O2 S Cl

[M+H]

Figure 7. 57. HRMS and elemental composition of compound **163j**

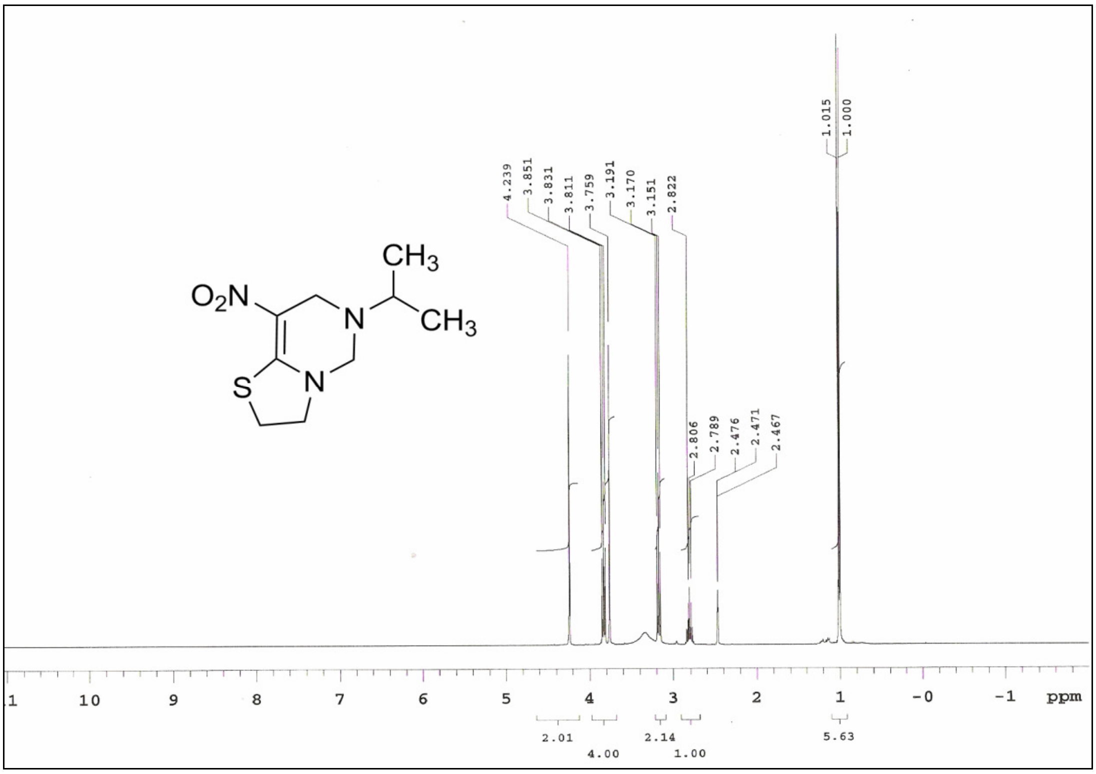


Figure 7. 58. ^{1}H NMR (400 MHz, DMSO-d$_6$) spectrum of compound **163k**

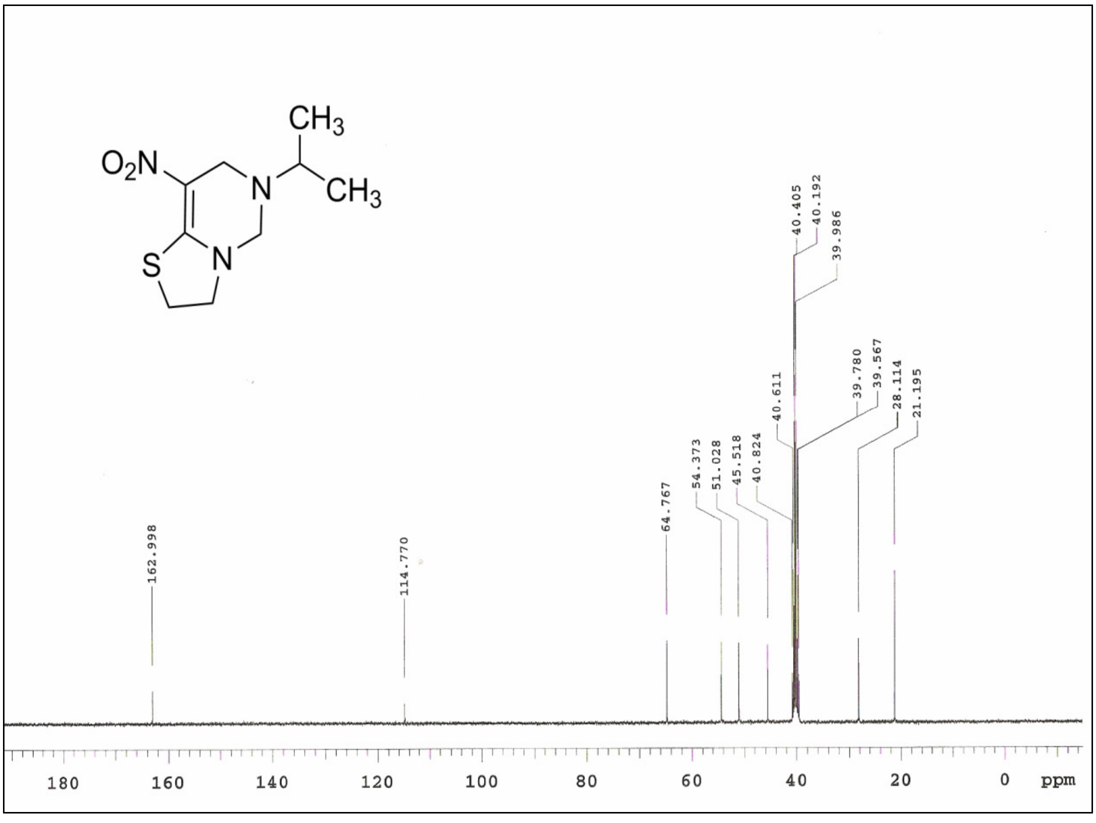
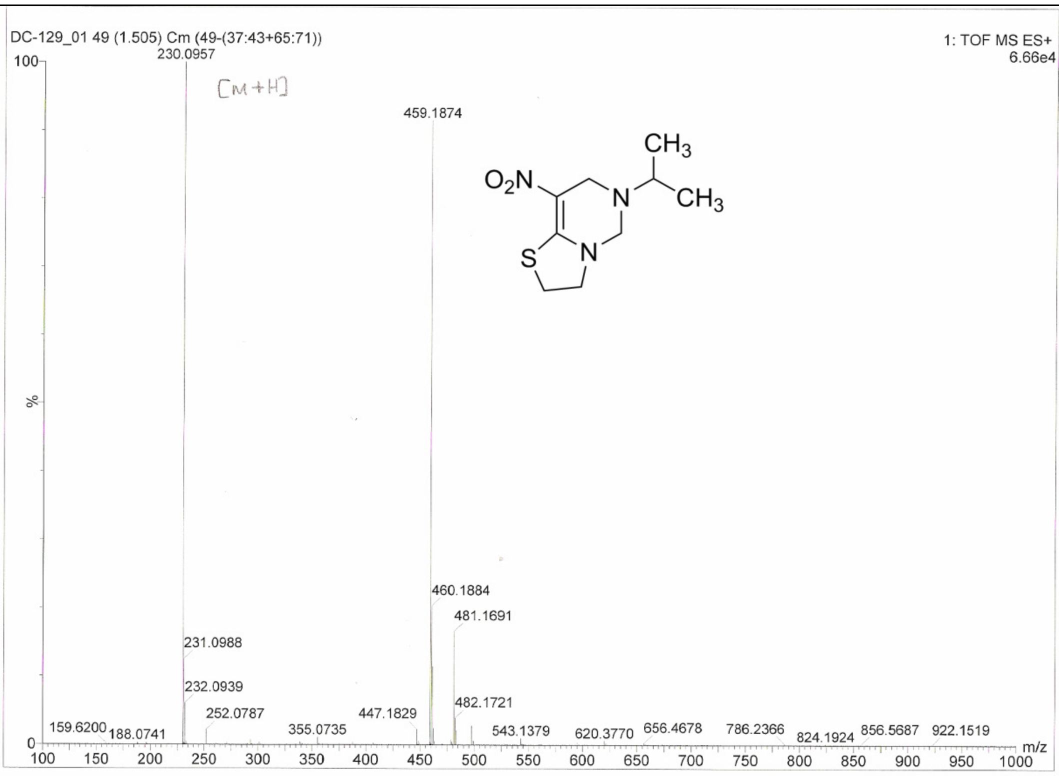


Figure 7. 59. ^{13}C NMR (100 MHz, DMSO-d$_6$) spectrum of compound **163k**



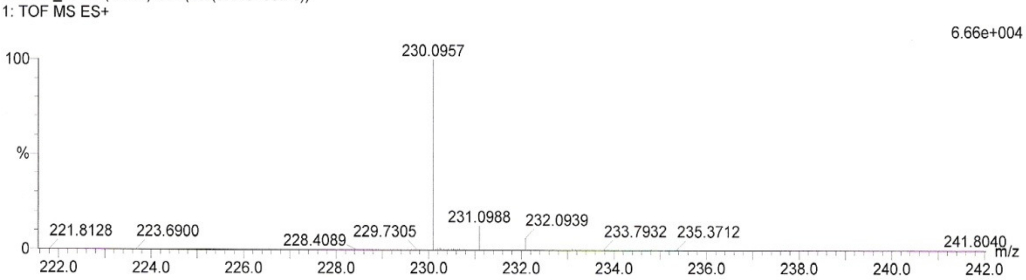
Elemental Composition Report

Page 1

Single Mass Analysis

Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
94 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 1-19 H: 1-20 N: 1-4 O: 1-4 S: 1-5
DC-129_01 49 (1.505) Cm (49-(37:43+65:71))
1: TOF MS ES+



Minimum:				-1.5			
Maximum:		5.0	10.0	50.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
230.0957	230.0963	-0.6	-2.6	3.5	254.4	0.0	C9 H16 N3 O2 S

[M+H]

Figure 7. 60. HRMS and elemental composition of compound **163k**

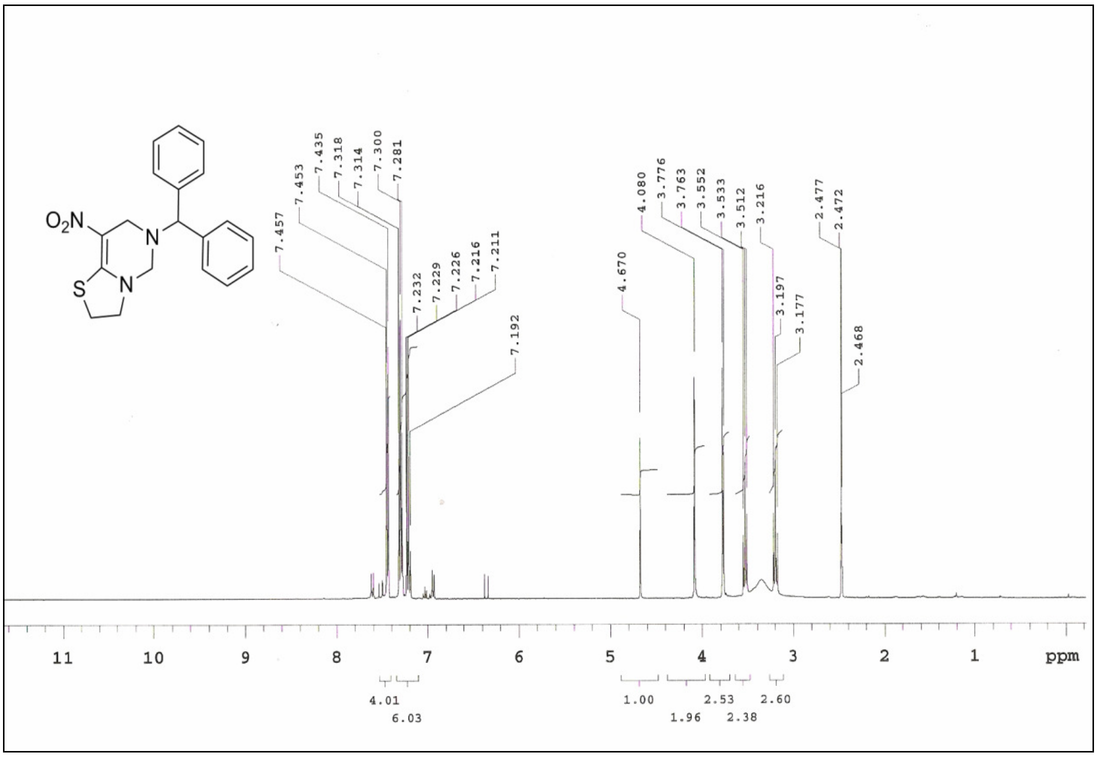


Figure 7. 61. ^{1}H NMR (400 MHz, DMSO-d$_6$) spectrum of compound **163l**

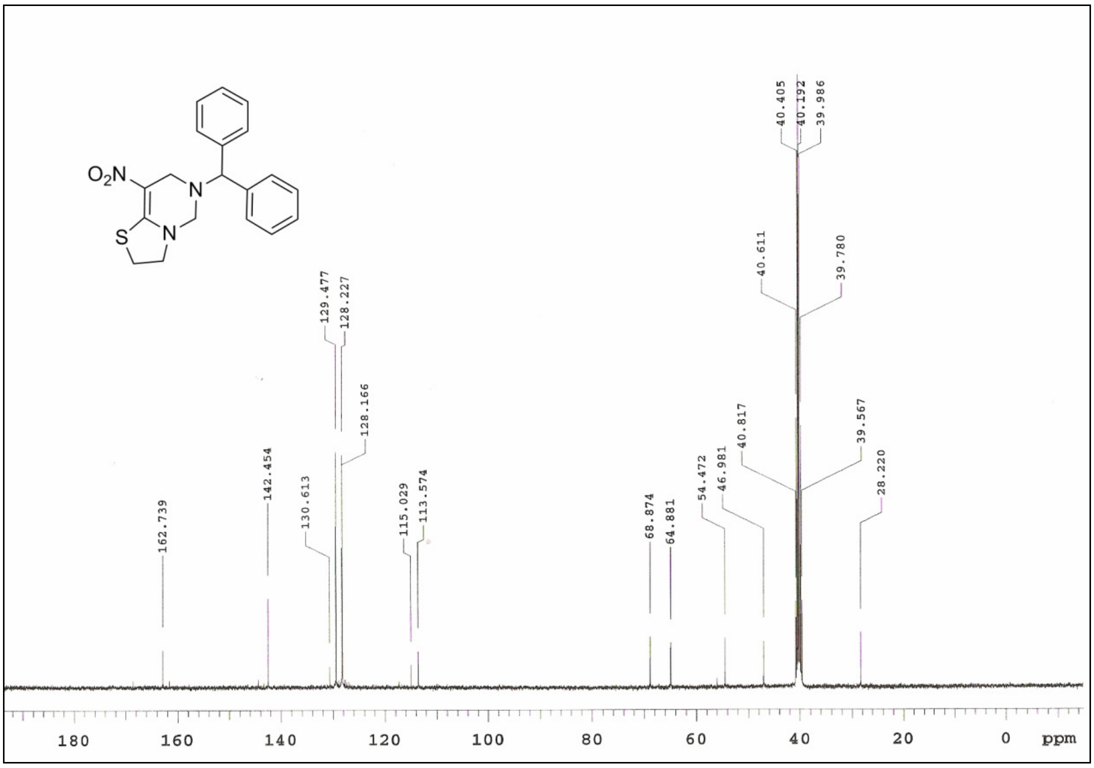
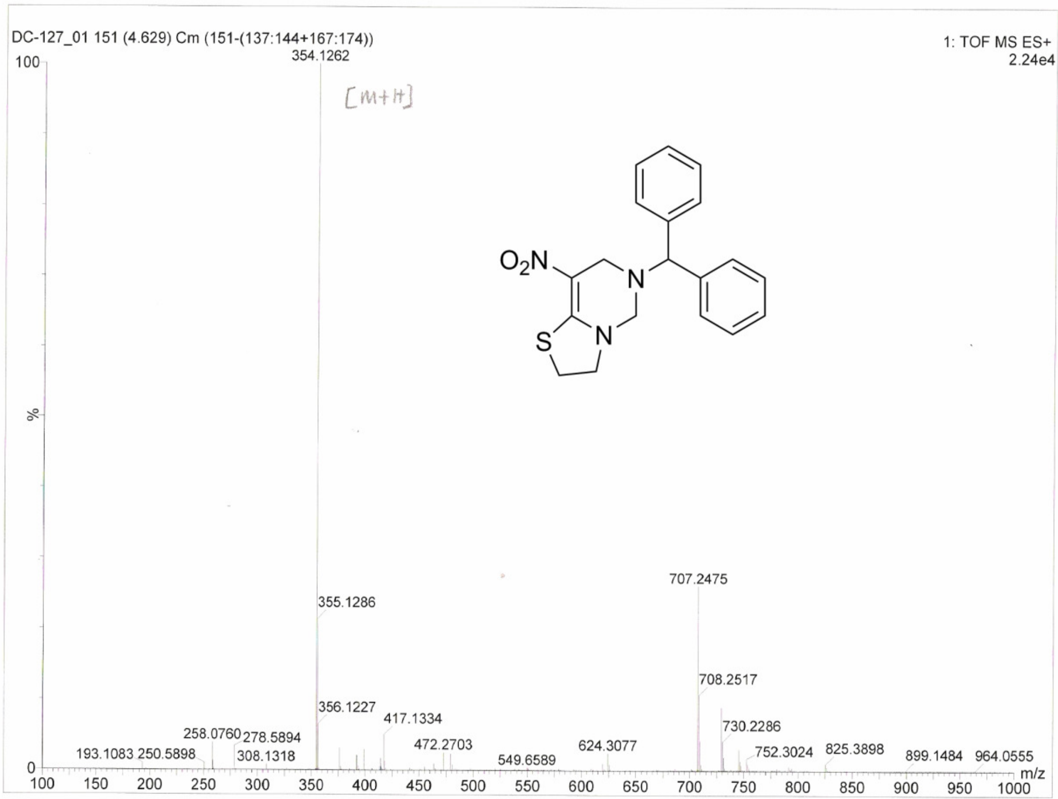


Figure 7. 62. ^{13}C NMR (100 MHz, DMSO-d$_6$) spectrum of compound **163l**



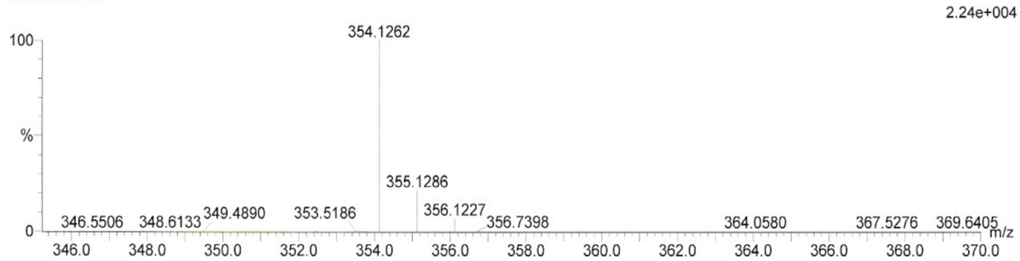
Elemental Composition Report

Page 1

Single Mass Analysis

Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
118 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 1-19 H: 1-20 N: 1-4 O: 1-4 S: 1-5
DC-127_01 151 (4.629) Cm (151-(137:144+167:174))
1: TOF MS ES+



Minimum:				-1.5			
Maximum:		5.0	10.0	50.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
354.1262	354.1276	-1.4	-4.0	11.5	50.2	0.0	C19 H20 N3 O2 S
	[M+H]						

Figure 7. 63. HRMS and elemental composition of compound **163l**

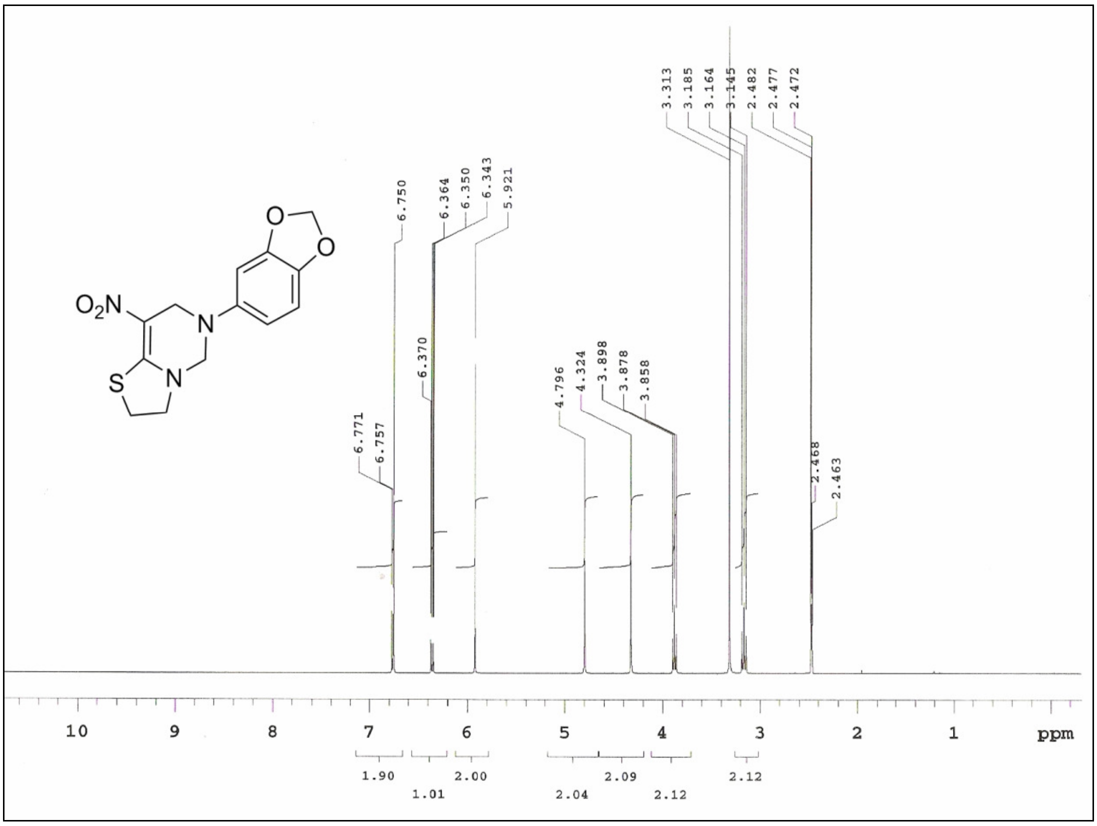


Figure 7. 64. ^{1}H NMR (400 MHz, DMSO-d6) spectrum of compound **163m**

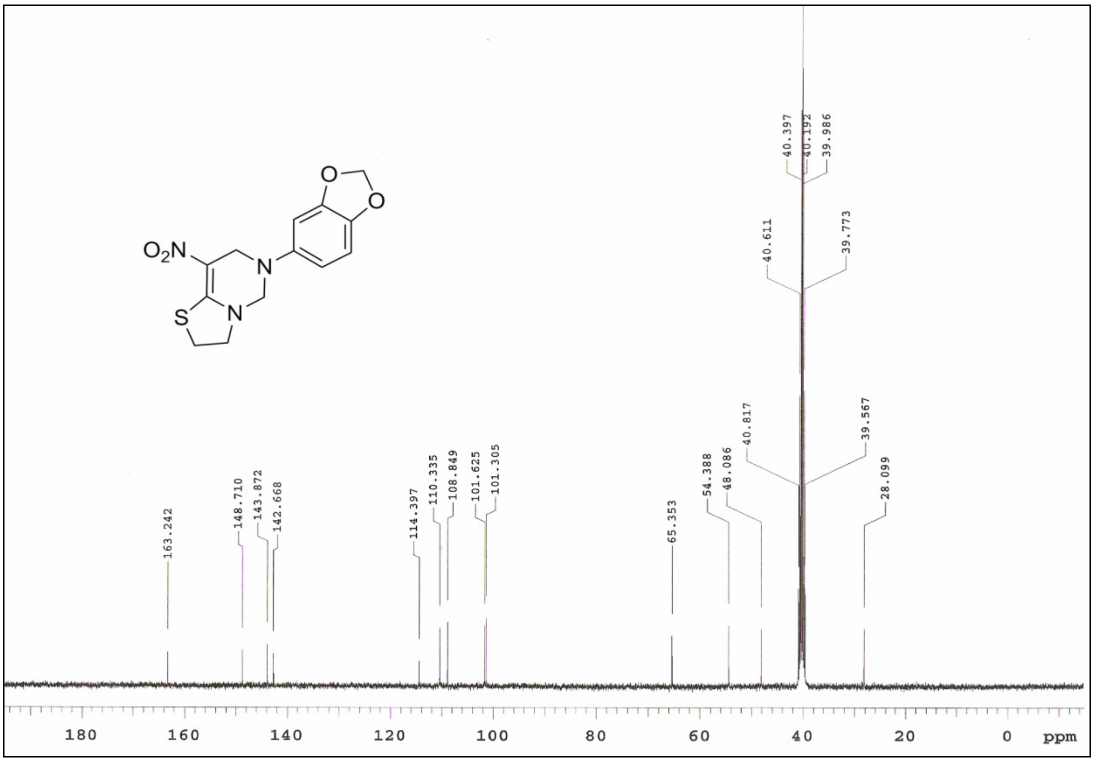
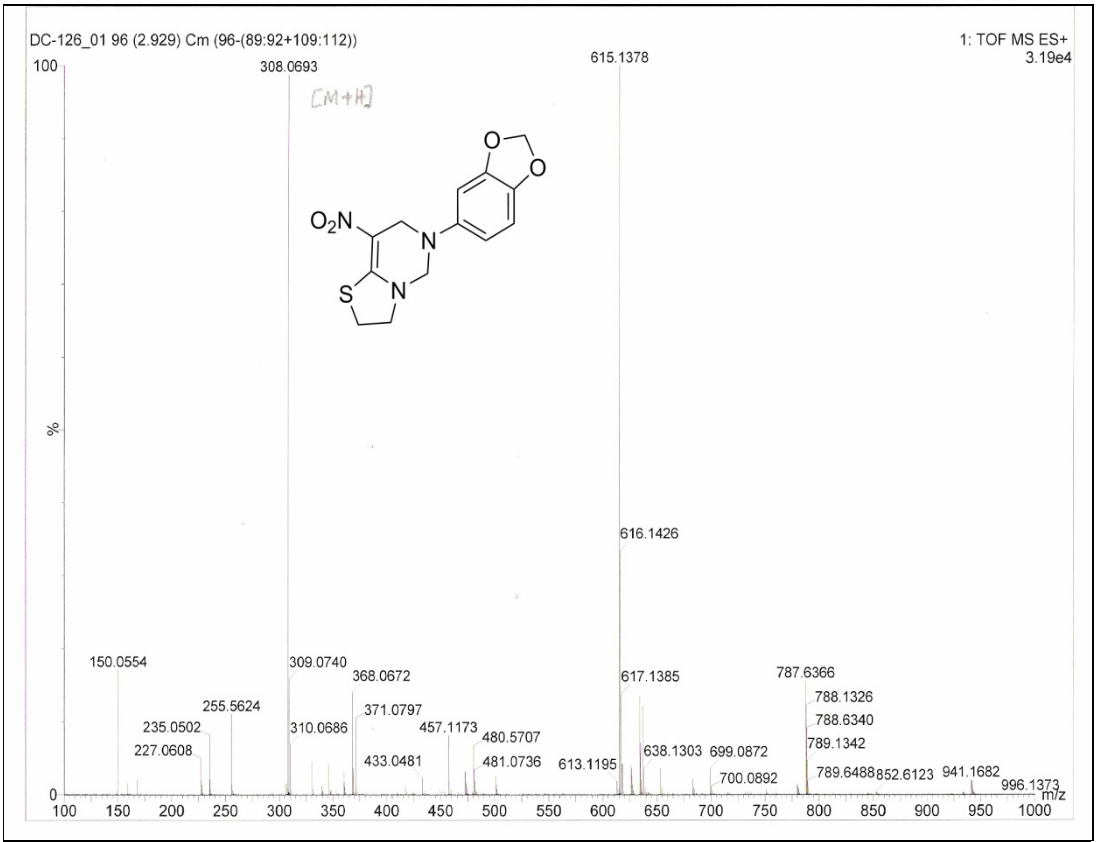


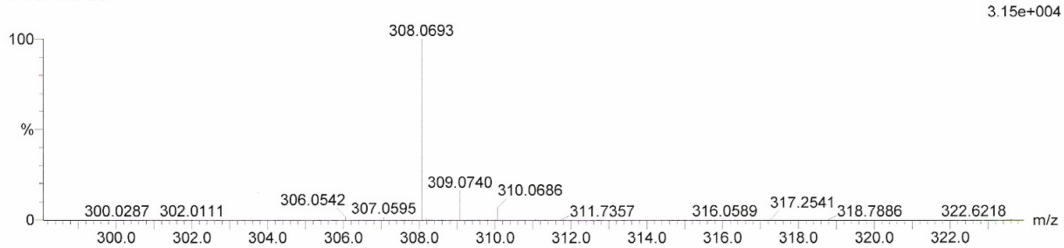
Figure 7. 65. ^{13}C NMR (100 MHz, DMSO-d6) spectrum of compound **163m**



Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
78 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 1-14 H: 1-14 N: 1-4 O: 1-4 S: 1-5
DC-126_01 96 (2.929) Cm (96-(89:92+109:112))
1: TOF MS ES+



Minimum:				-1.5			
Maximum:		5.0	10.0	50.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
308.0693	308.0705	-1.2	-3.9	8.5	115.9	0.0	C13 H14 N3 O4 S

Figure 7. 66. HRMS and elemental composition of compound **163m**

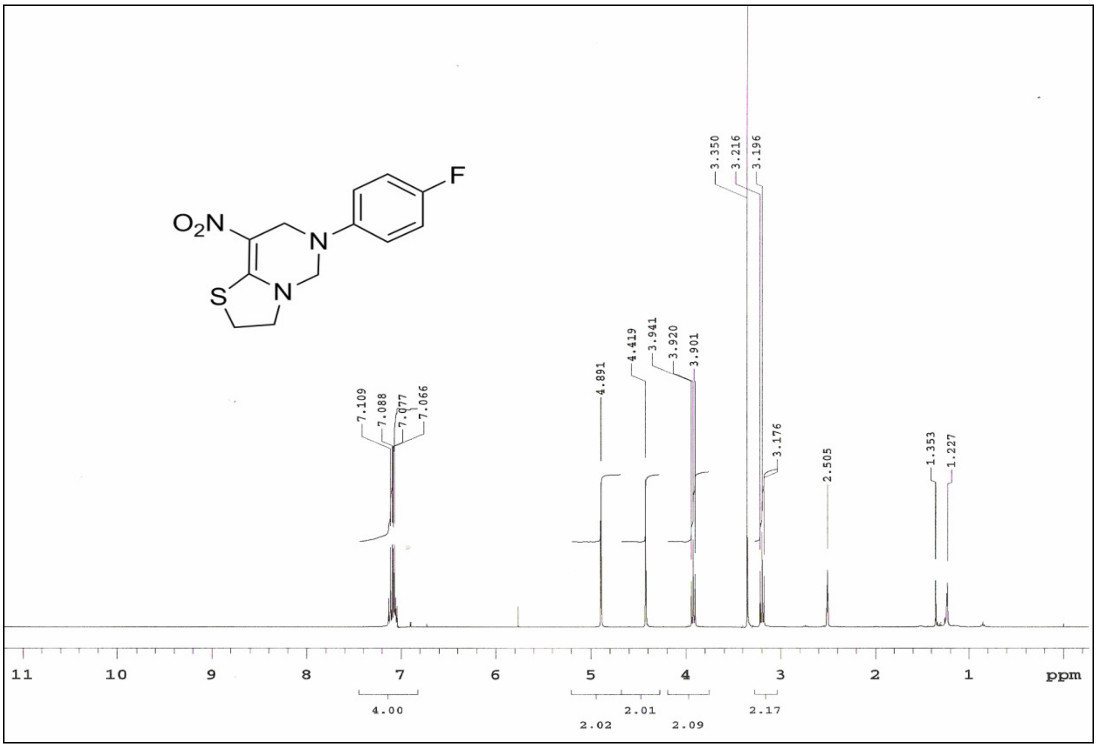


Figure 7. 67. ^{1}H NMR (400 MHz, DMSO-d6) spectrum of compound **163n**

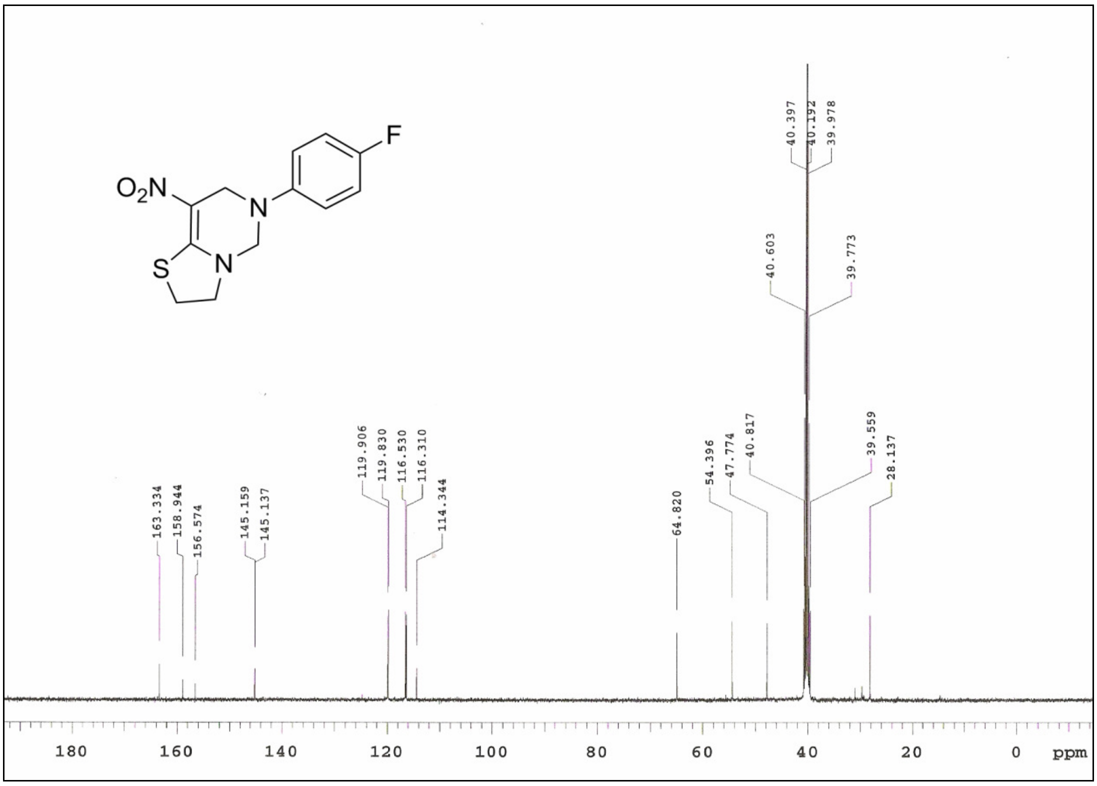
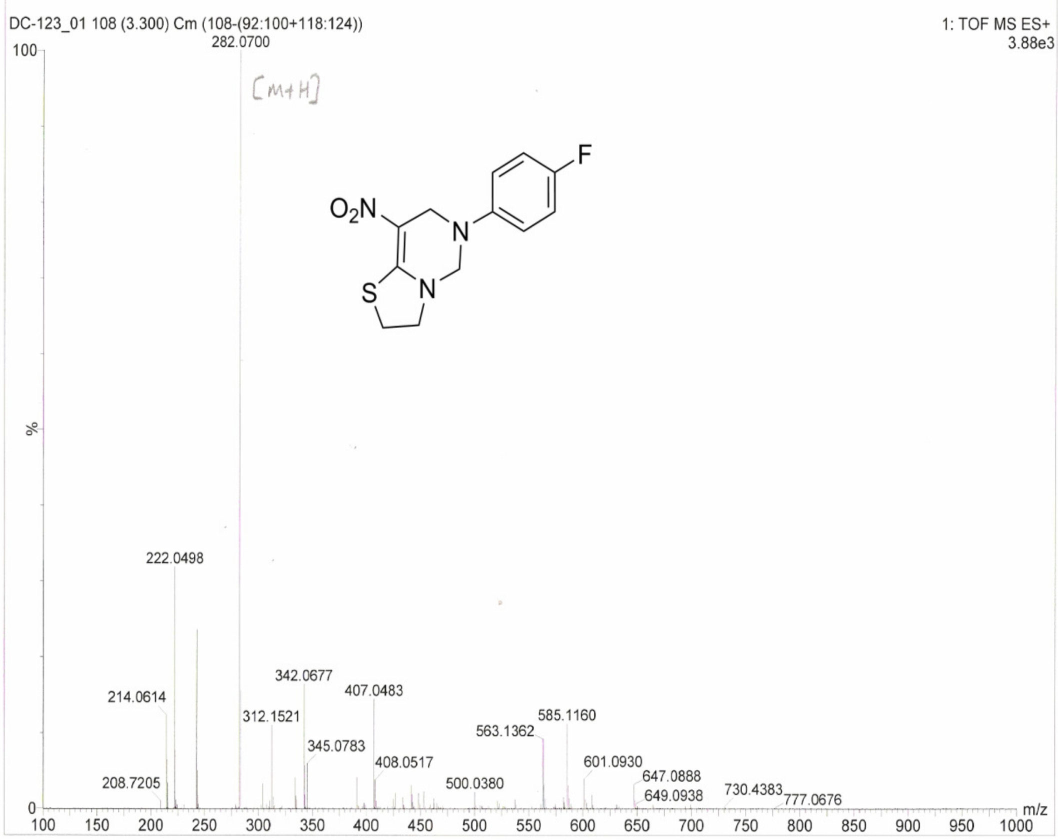


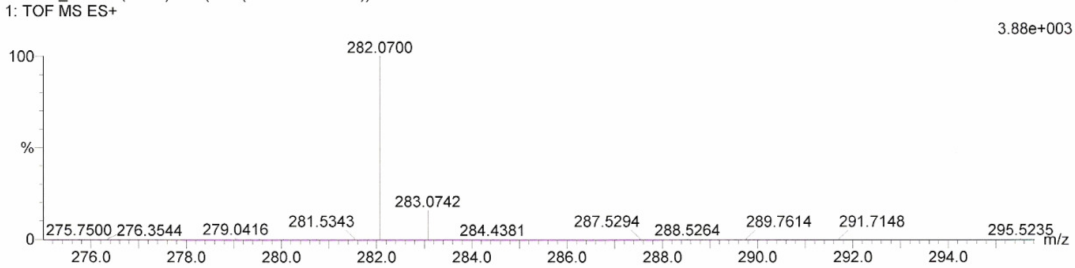
Figure 7. 68. ^{13}C NMR (100 MHz, DMSO-d6) spectrum of compound **163n**



Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
136 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 1-14 H: 1-13 N: 1-3 O: 1-3 F: 1-3 S: 1-5
DC-123_01 108 (3.300) Cm (108-(92:100+118:124))
1: TOF MS ES+



Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
Minimum:				-1.5			
Maximum:		5.0	10.0	50.0			
282.0700	282.0713	-1.3	-4.6	7.5	24.9	0.0	C12 H13 N3 O2 F S

Figure 7. 69. HRMS and elemental composition of compound **163n**

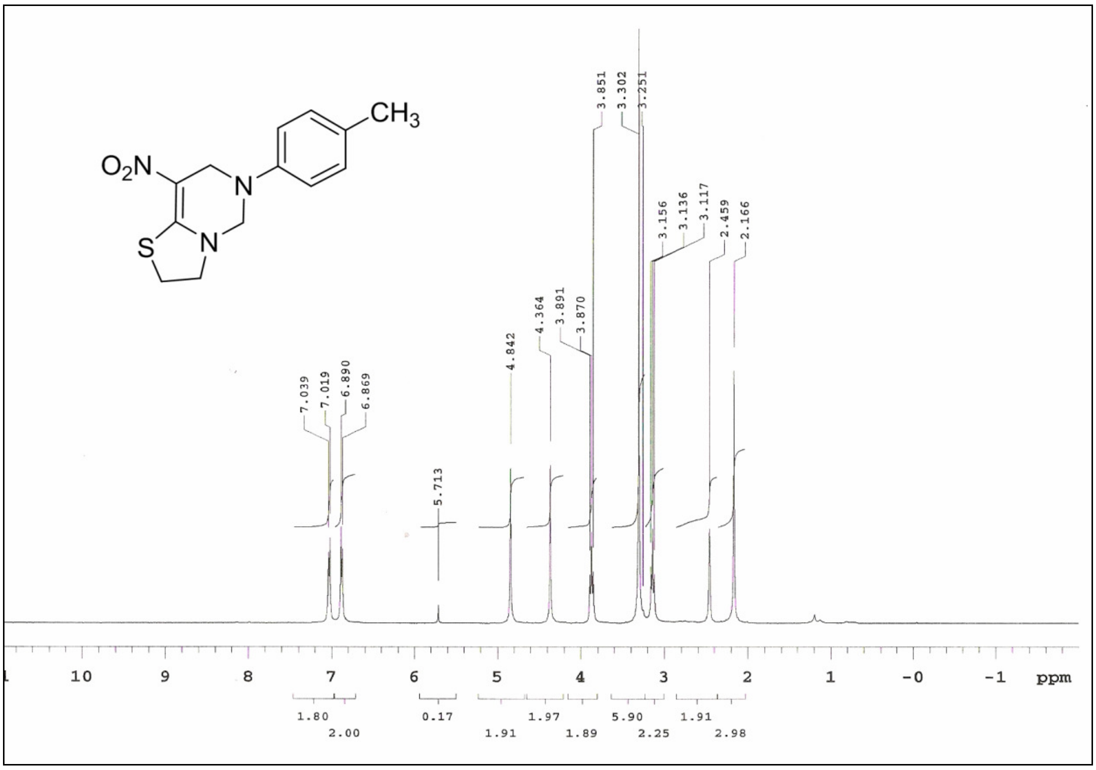


Figure 7. 70. ^{1}H NMR (400 MHz, DMSO-d6) spectrum of compound **163o**

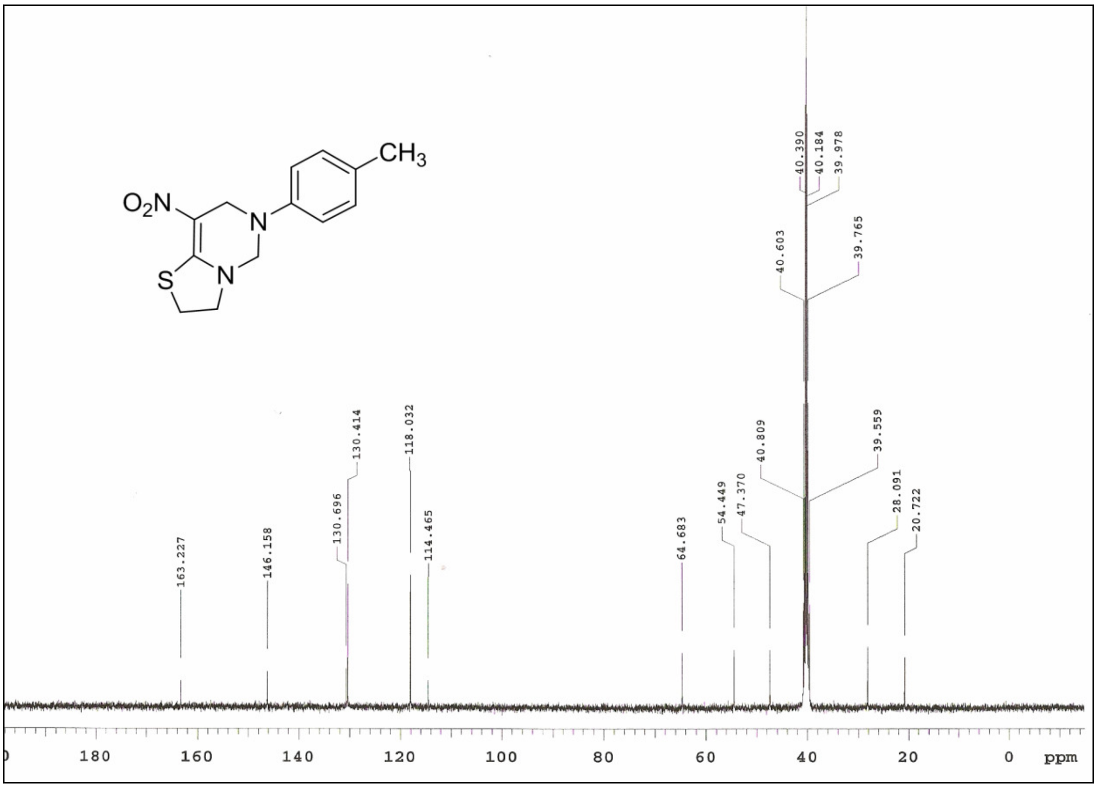
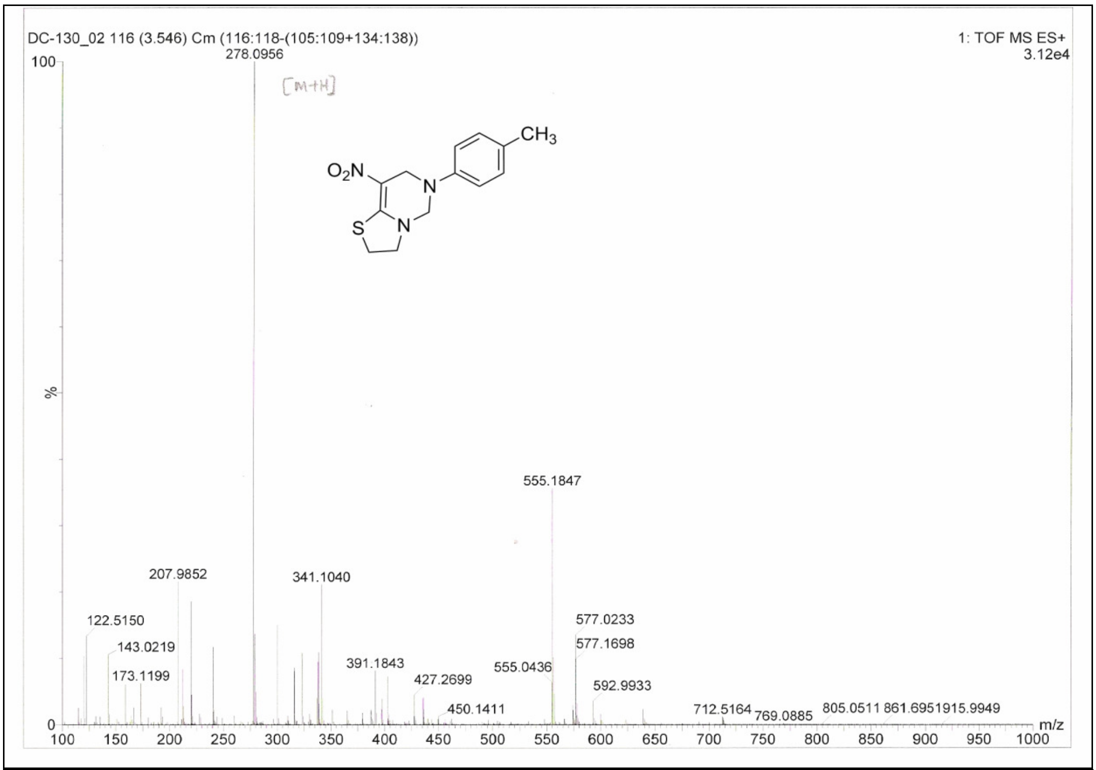


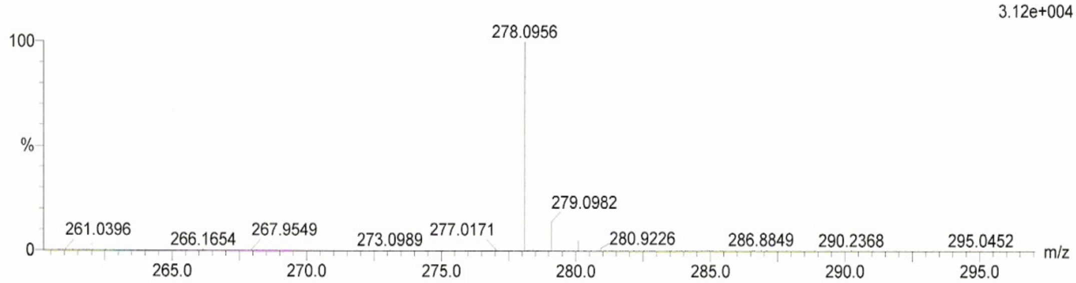
Figure 7. 71. ^{13}C NMR (100 MHz, DMSO-d6) spectrum of compound **163o**



Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
171 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 1-13 H: 1-16 N: 1-6 O: 1-5 S: 1-5
DC-130_02 116 (3.546) Cm (116:118-(105:109+134:138))
1: TOF MS ES+



Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
Minimum:				-1.5			
Maximum:		5.0	10.0	50.0			
278.0956	278.0963	-0.7	-2.5	7.5	127.1	0.0	C13 H16 N3 O2 S

Figure 7. 72. HRMS and elemental composition of compound **163o**

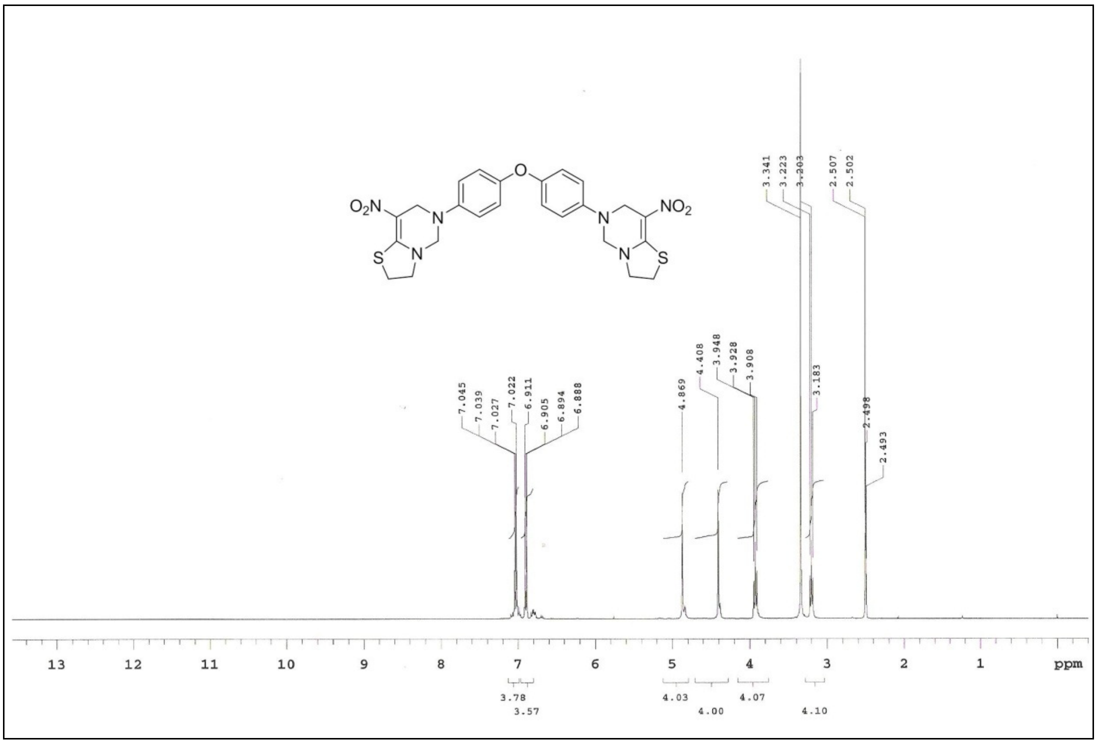


Figure 7. 73. [1]H NMR (400 MHz, DMSO-d6) spectrum of compound **163ax**

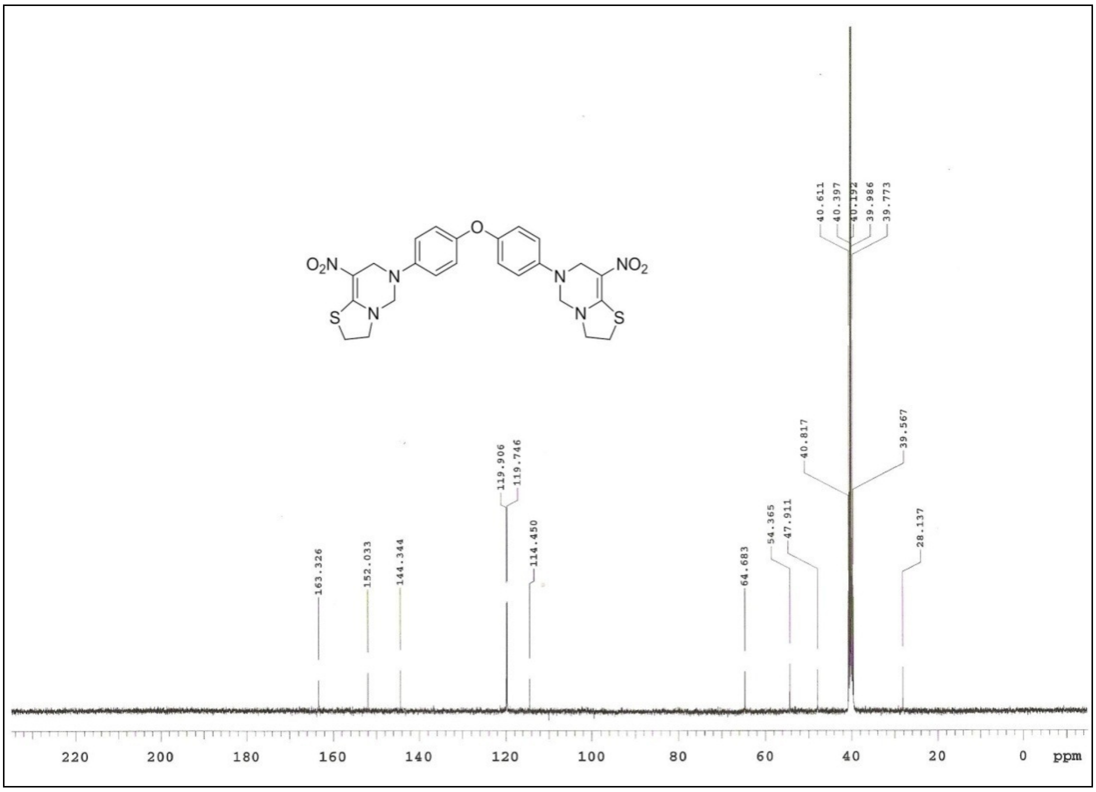
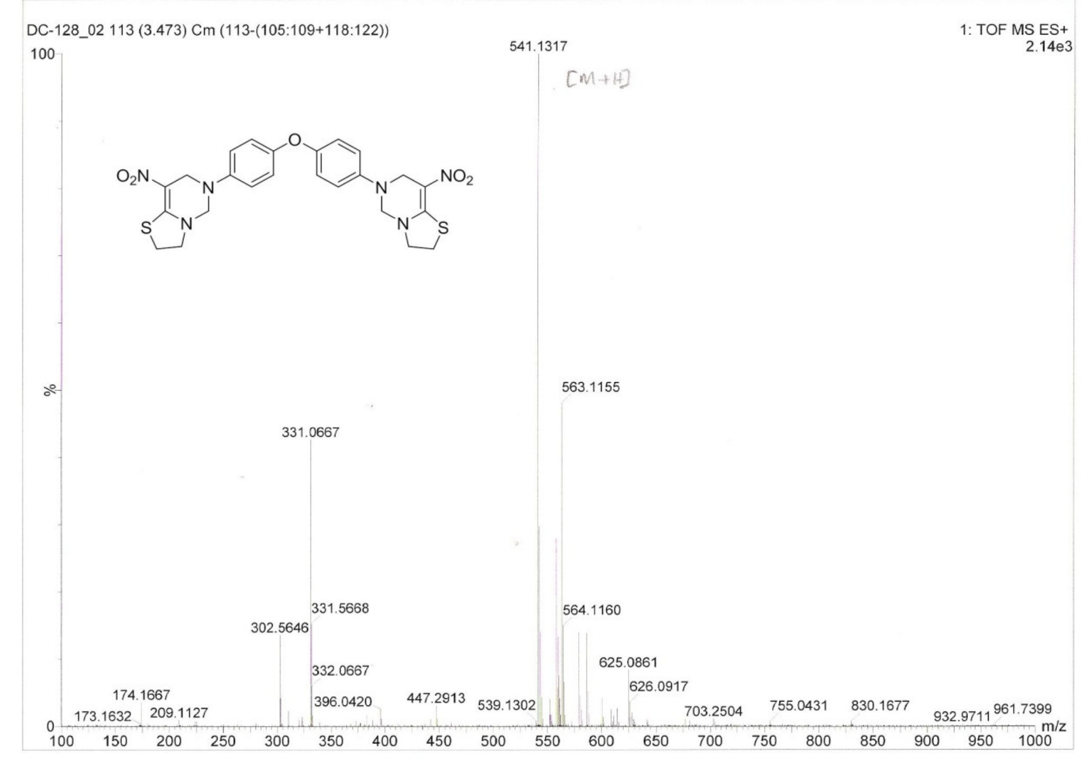


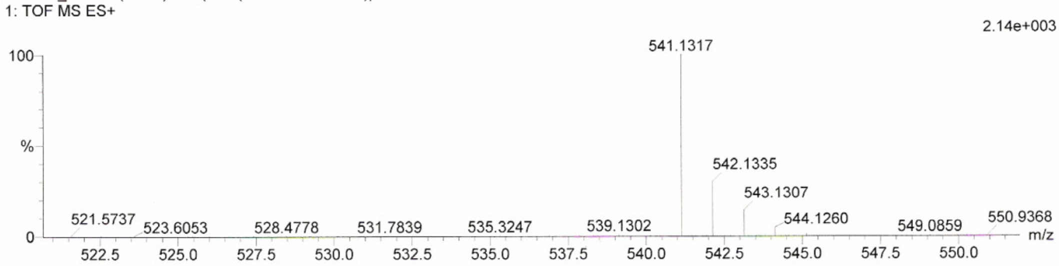
Figure 7. 74. [13]C NMR (100 MHz, DMSO-d6) spectrum of compound **163ax**



Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
160 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 1-24 H: 1-25 N: 1-6 O: 1-5 S: 1-5
DC-128_02 113 (3.473) Cm (113-(105:109+118:122))
1: TOF MS ES+



Minimum:				-1.5			
Maximum:		5.0	10.0	50.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
541.1317	541.1328	-1.1	-2.0	15.5	35.8	0.0	C24 H25 N6 O5 S2

[M+H]

Figure 7. 75. HRMS and elemental composition of compound **163ax**

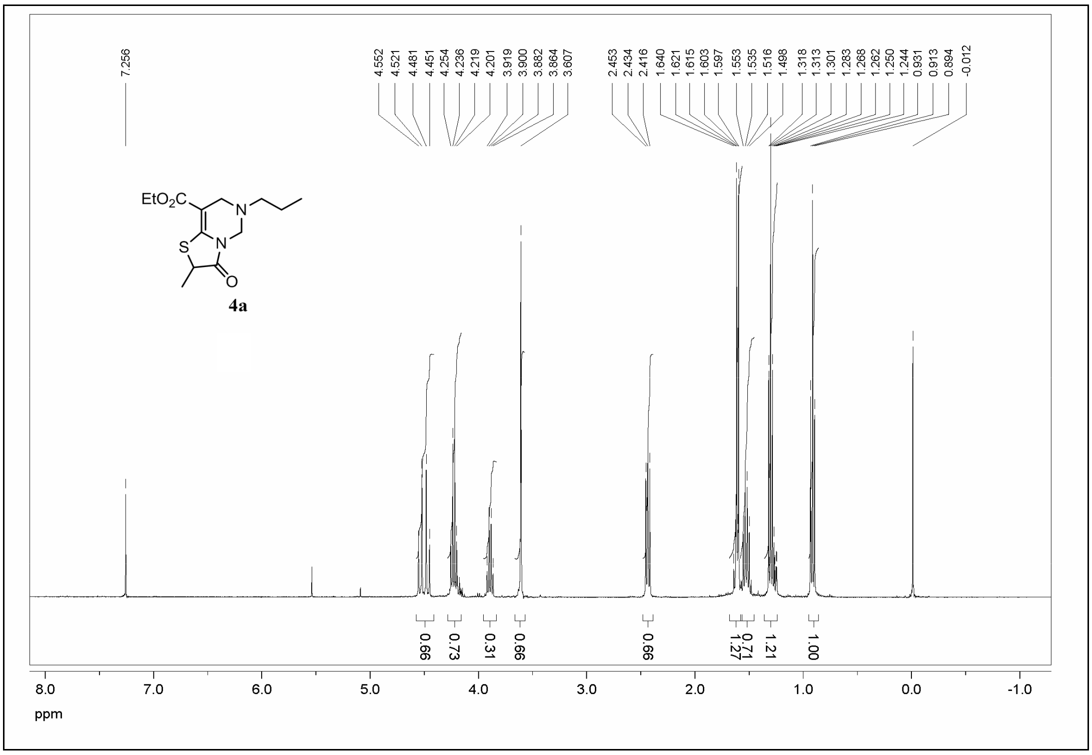


Figure 7. 76. ^{1}H NMR (400 MHz, CDCl3) spectrum of compound **259a**

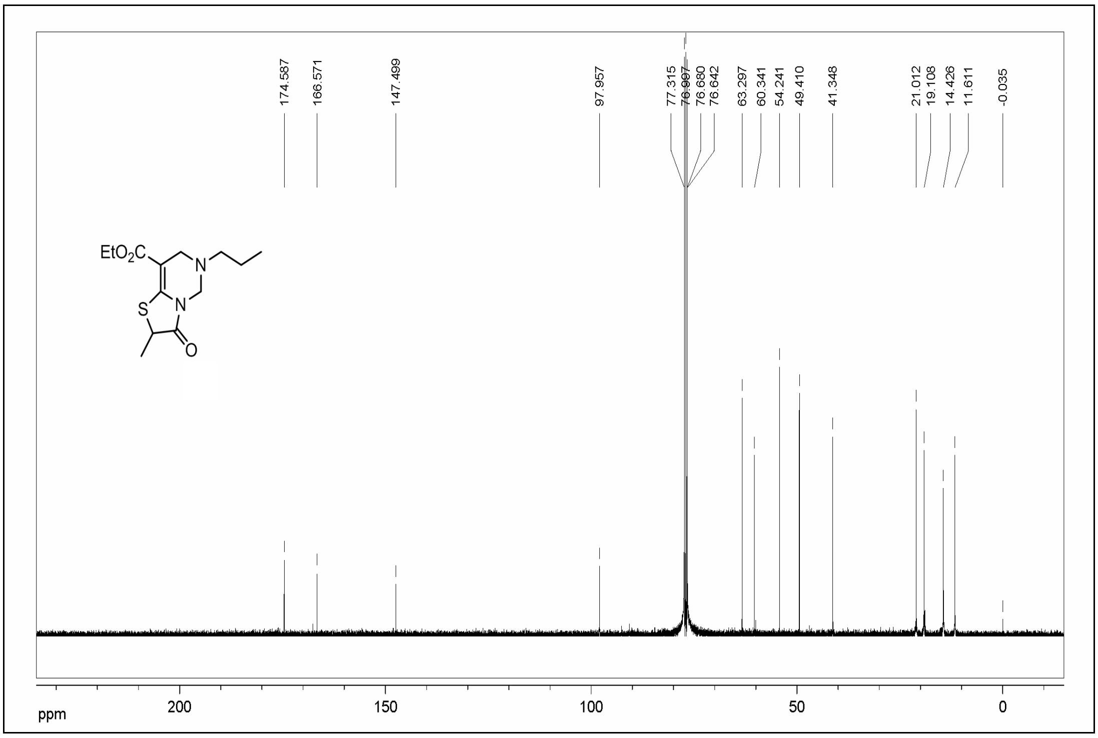
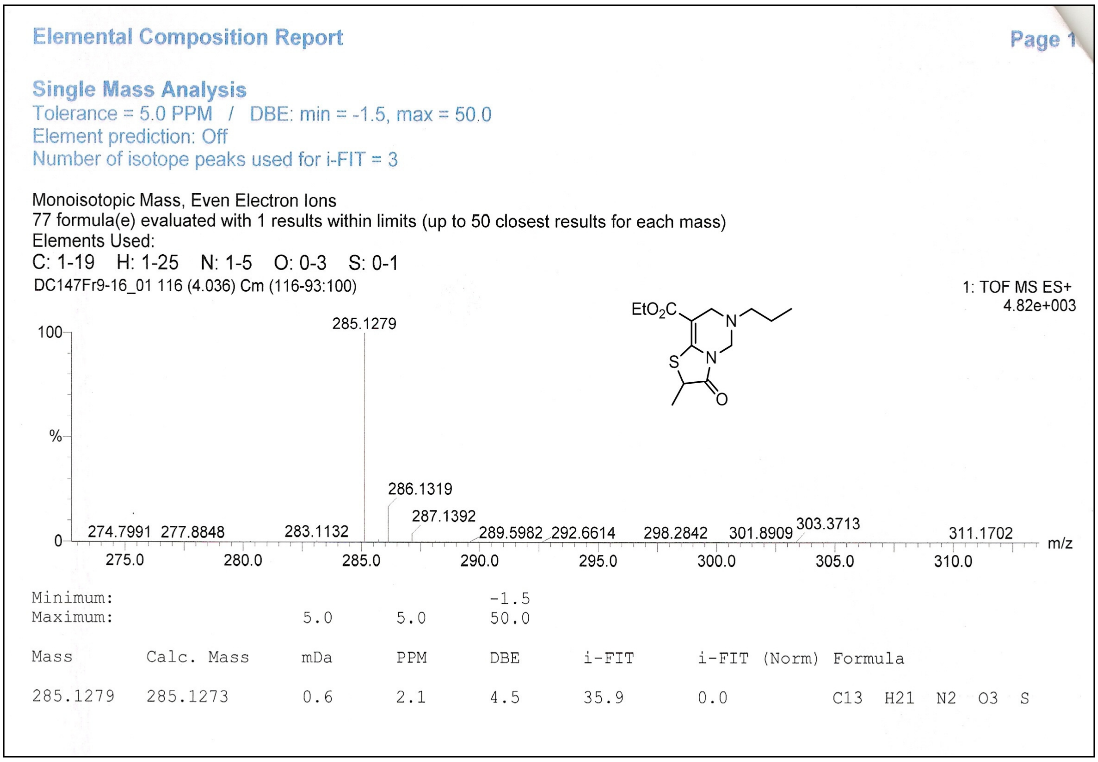


Figure 7. 77. ^{13}C NMR (100 MHz, CDCl3) spectrum of compound **259a**



Elemental Composition Report

Page 1

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
77 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 1-19 H: 1-25 N: 1-5 O: 0-3 S: 0-1

Minimum:				-1.5			
Maximum:		5.0	5.0	50.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
285.1279	285.1273	0.6	2.1	4.5	35.9	0.0	C13 H21 N2 O3 S

Figure 7. 78. HRMS and elemental composition of compound **259a**

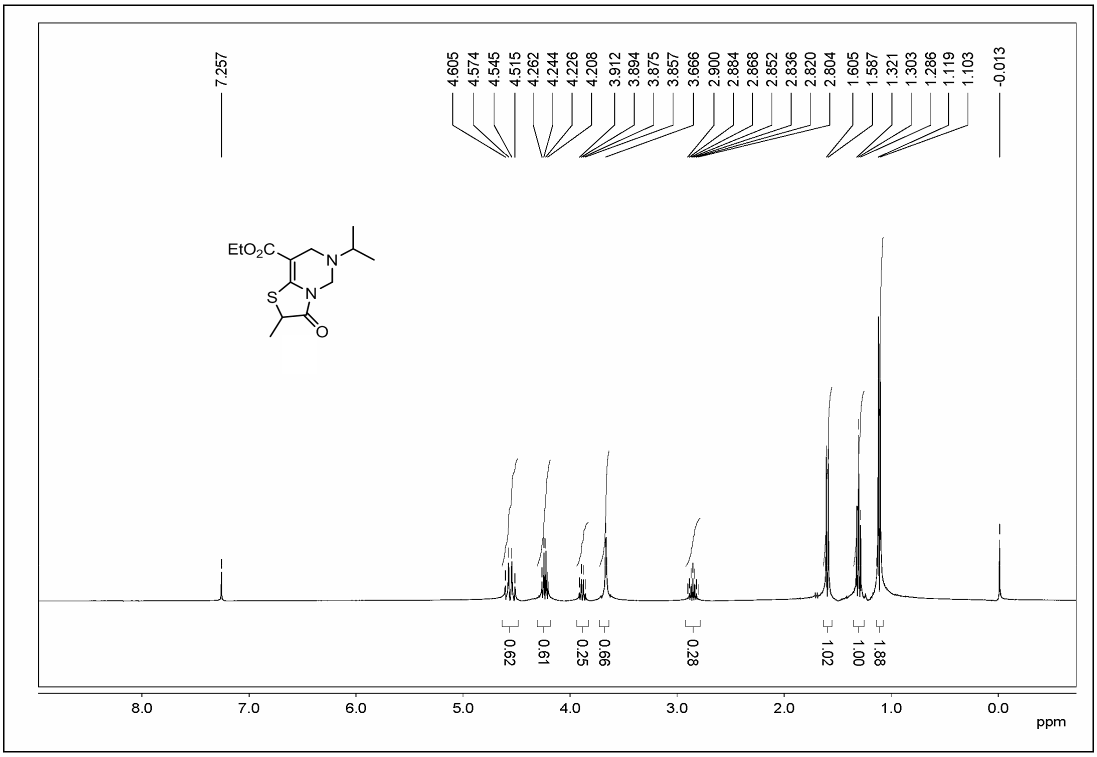


Figure 7. 79. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **259b**

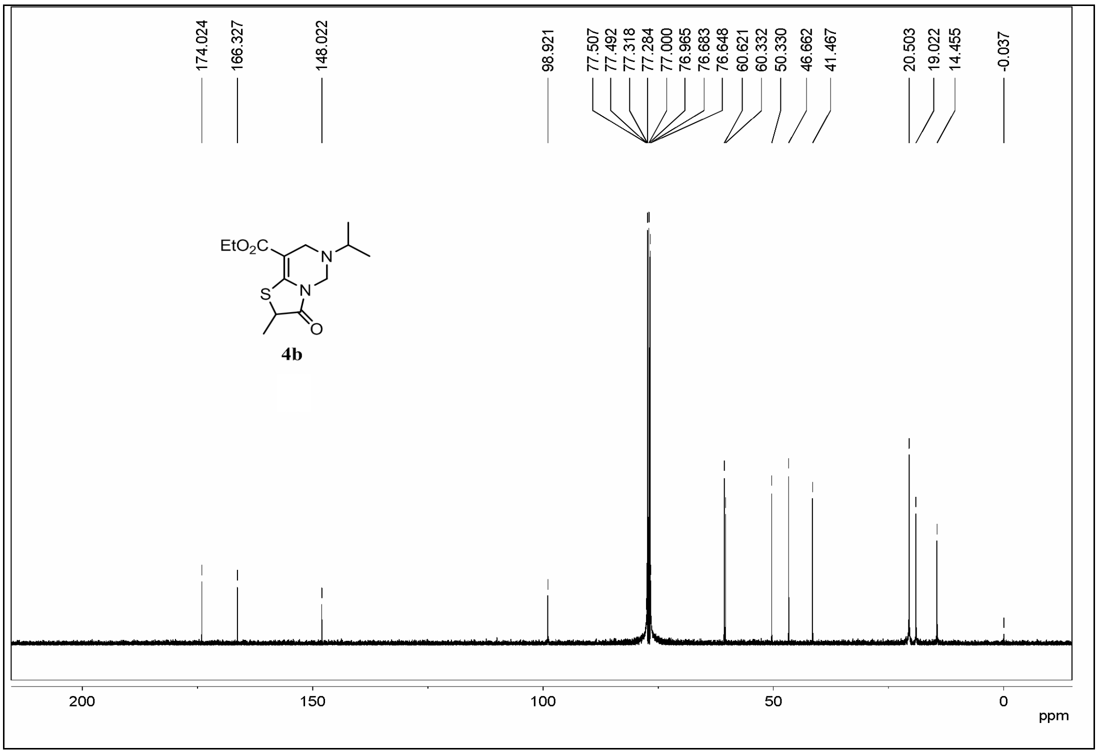
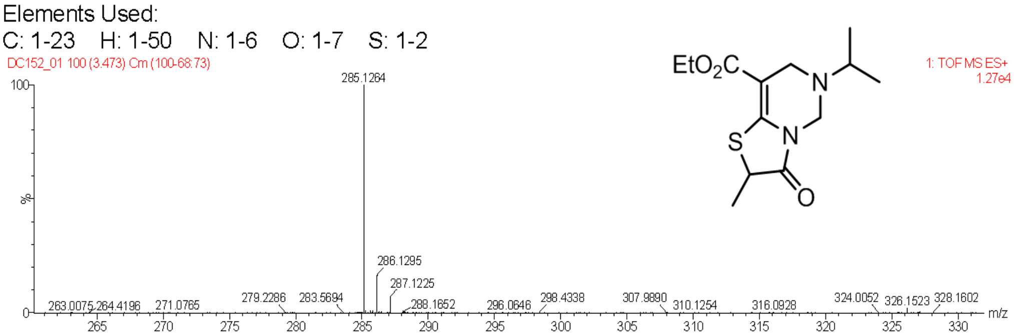


Figure 7. 80. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **259b**

Elemental Composition Report

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
215 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 1-23 H: 1-50 N: 1-6 O: 1-7 S: 1-2



Minimum:				-1.5			
Maximum:		5.0	5.0	50.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
285.1264	285.1273	-0.9	-3.2	4.5	111.1	0.0	C13 H21 N2 O3 S

Figure 7. 81. HRMS and elemental composition of compound **259b**

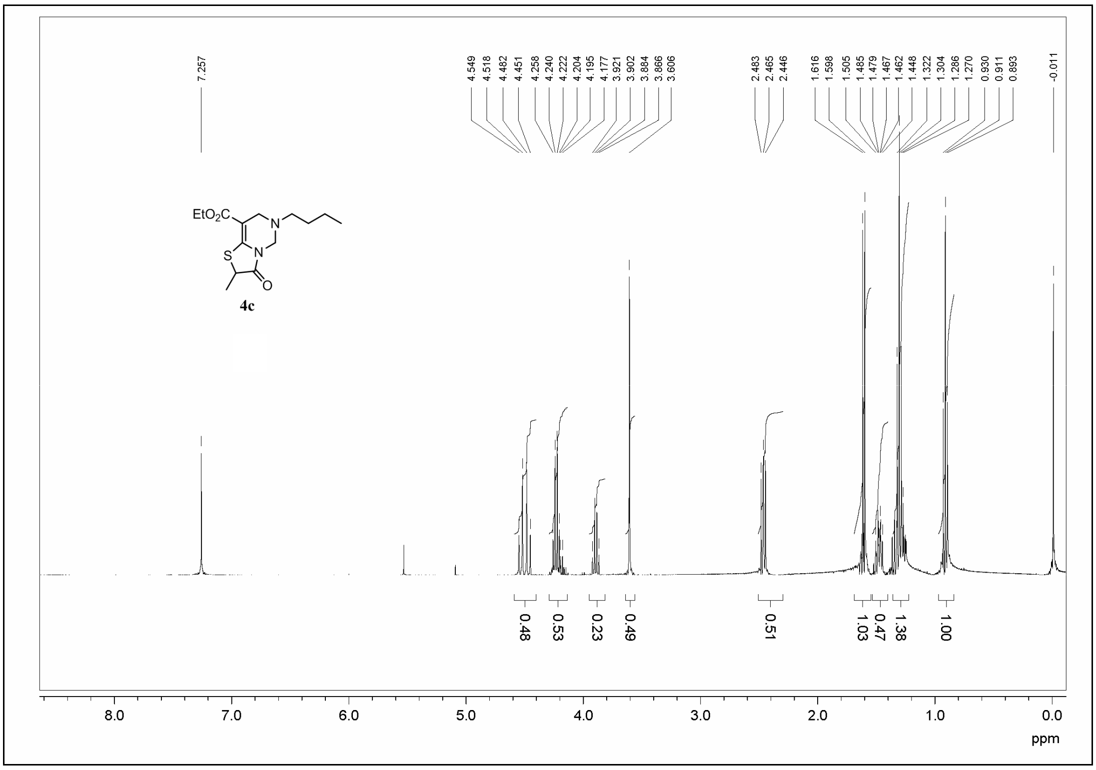


Figure 7. 82. ^{1}H NMR (400 MHz, CDCl3) spectrum of compound **259c**

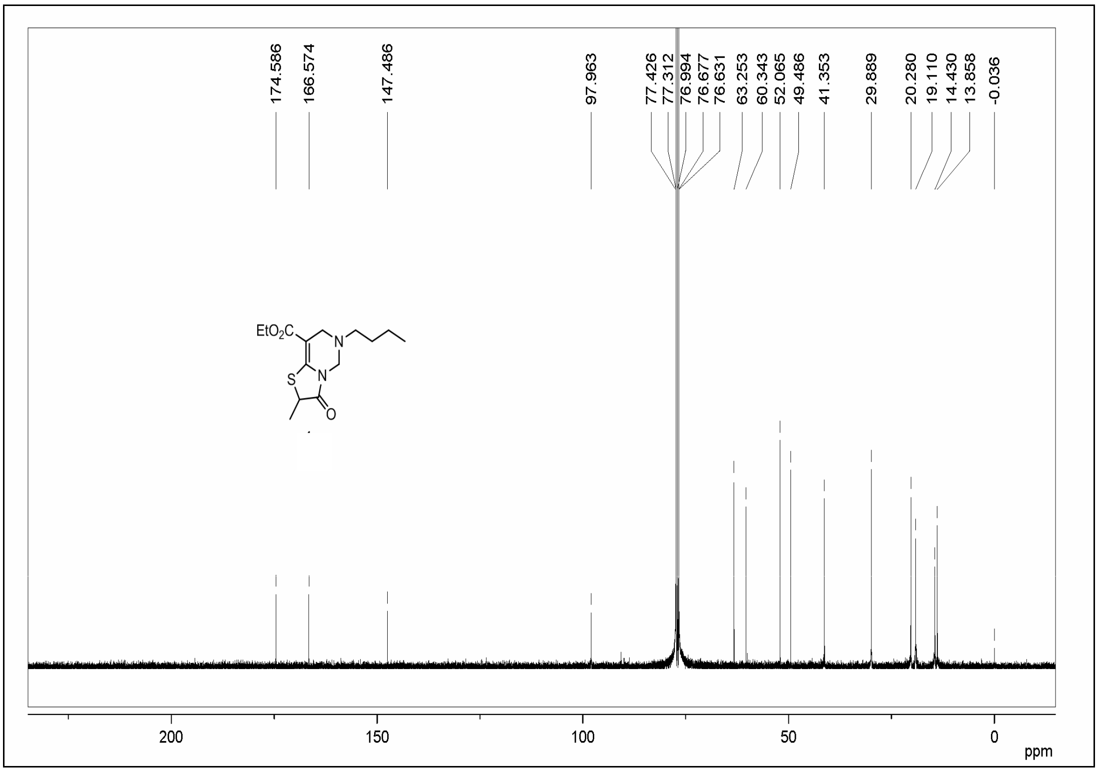
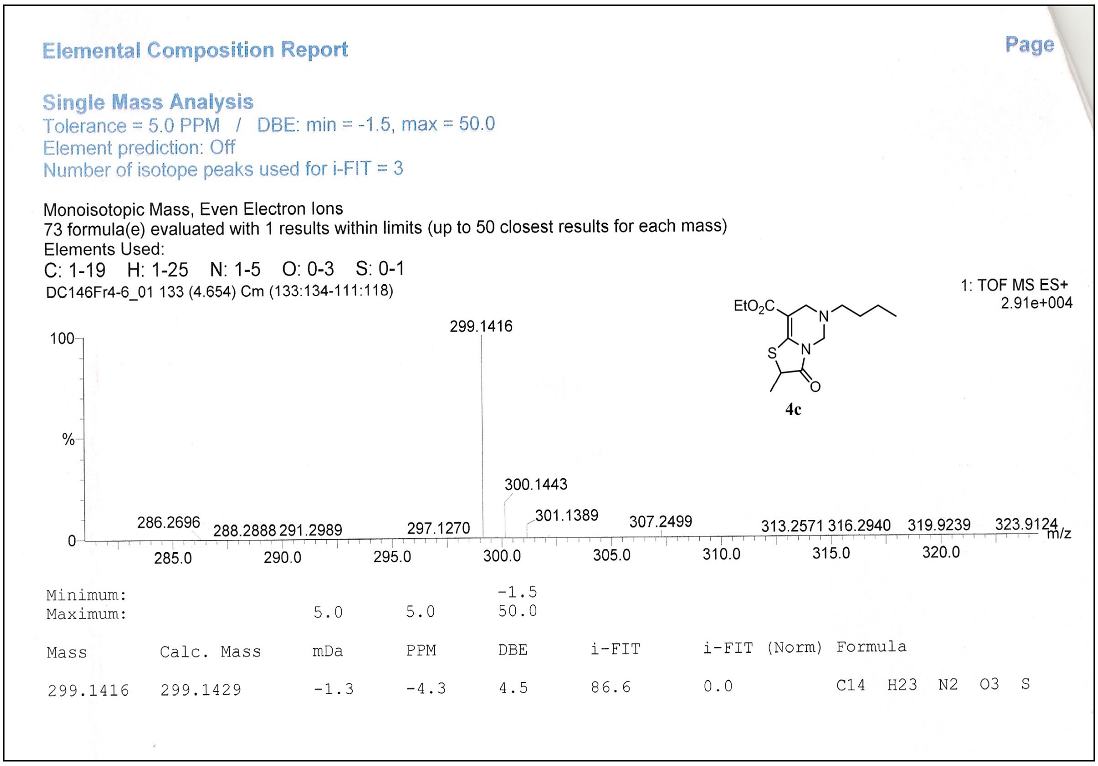


Figure 7. 83. ^{13}C NMR (100 MHz, CDCl3) spectrum of compound **259c**


Elemental Composition Report

Page

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
73 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 1-19 H: 1-25 N: 1-5 O: 0-3 S: 0-1
DC146Fr4-6_01 133 (4.654) Cm (133:134-111:118)

Minimum:				-1.5			
Maximum:		5.0	5.0	50.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
299.1416	299.1429	-1.3	-4.3	4.5	86.6	0.0	C14 H23 N2 O3 S

Figure 7. 84. HRMS and elemental composition of compound **259c**

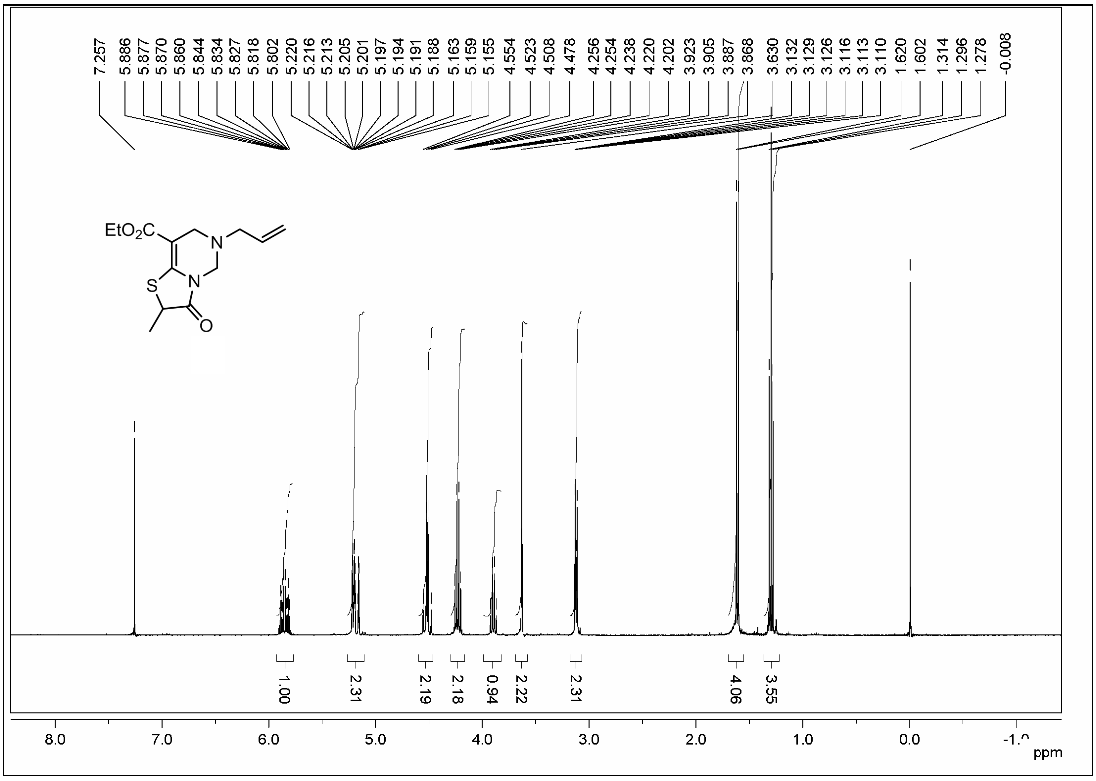


Figure 7. 85. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **259d**

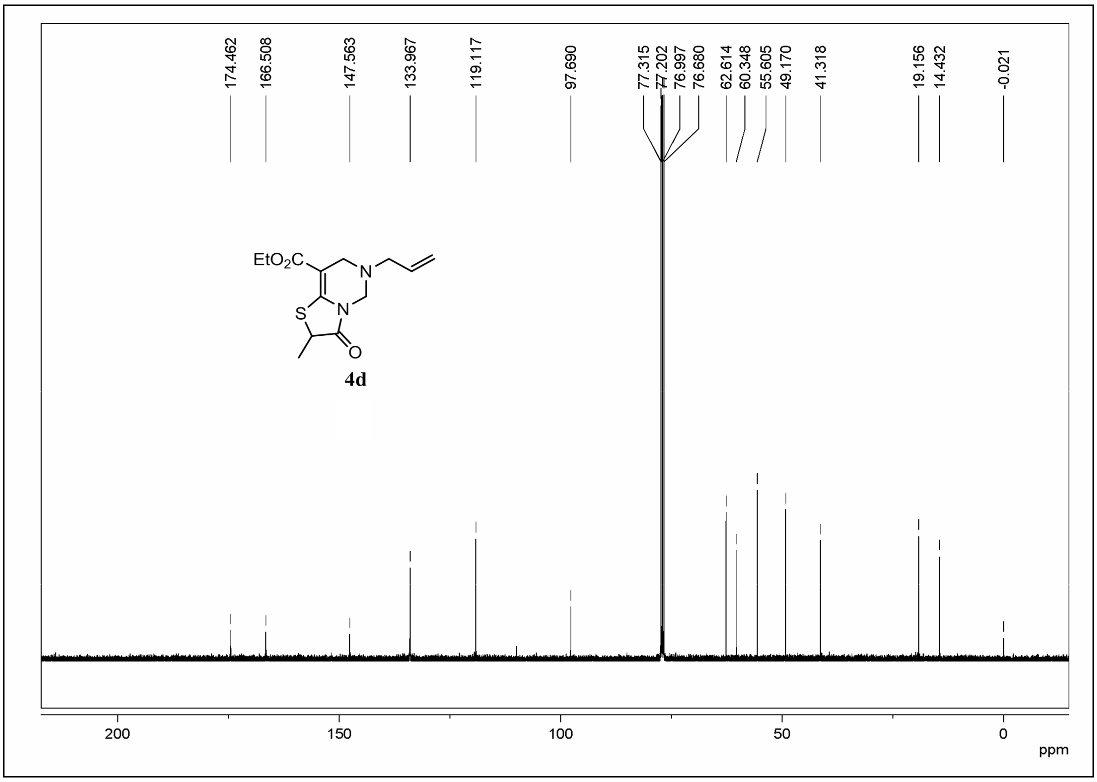
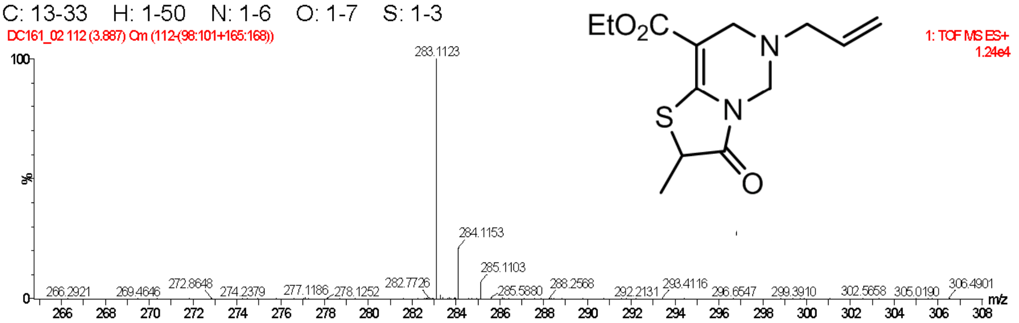


Figure 7. 86. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **259d**

Elemental Composition Report

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
148 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 13-33 H: 1-50 N: 1-6 O: 1-7 S: 1-3



Minimum:				-1.5			
Maximum:		5.0	5.0	50.0			
Mass	Calc. Mass	mDa	PM	DBE	i-FIT	i-FIT (Norm)	Formula
283.1123	283.1116	0.7	2.5	5.5	96.2	0.0	C13 H19 N2 O3 S

Figure 7. 87. HRMS and elemental composition of compound **259d**

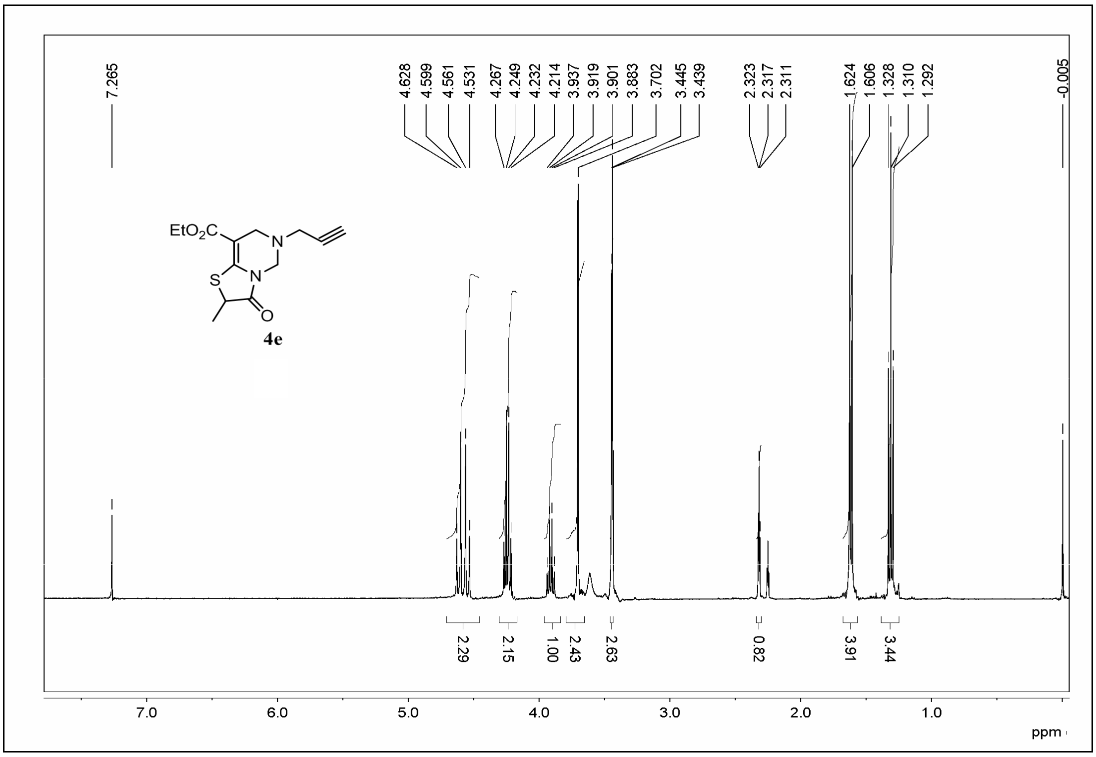


Figure 7. 88. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **259e**

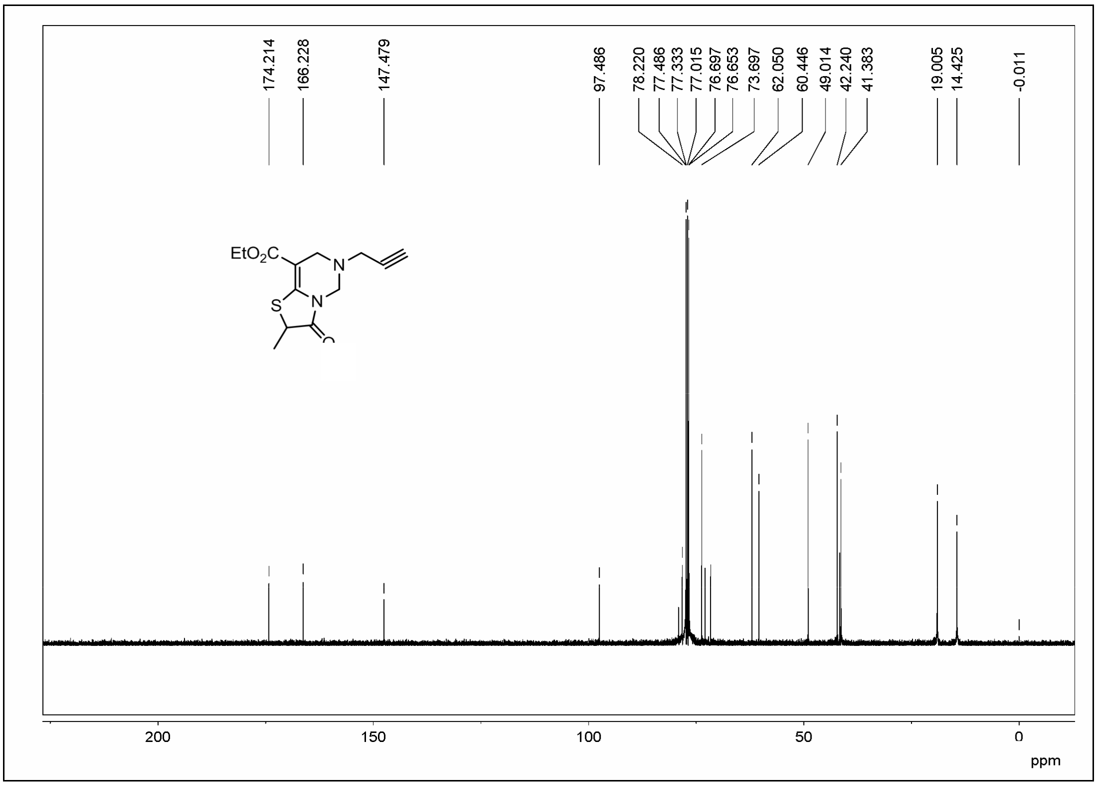
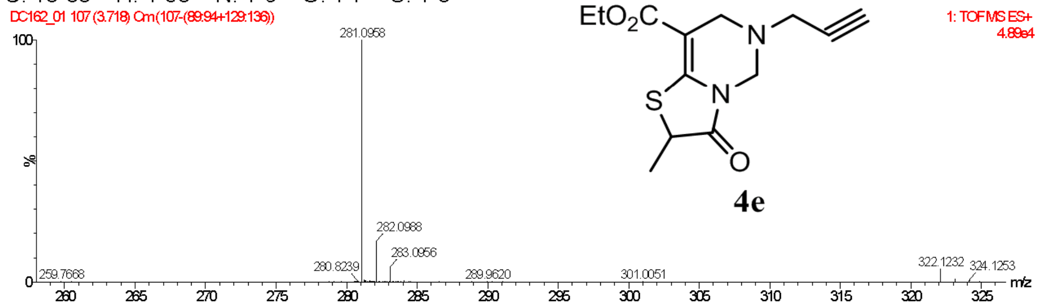


Figure 7. 89. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **259e**

Elemental Composition Report

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
144 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 13-33 H: 1-50 N: 1-6 O: 1-7 S: 1-3



Minimum:				-1.5			
Maximum:		5.0	5.0	50.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
281.0958	281.0960	-0.2	-0.7	6.5	242.4	0.0	C13 H17 N2 O3 S

Figure 7. 90. HRMS and elemental composition of compound **259e**

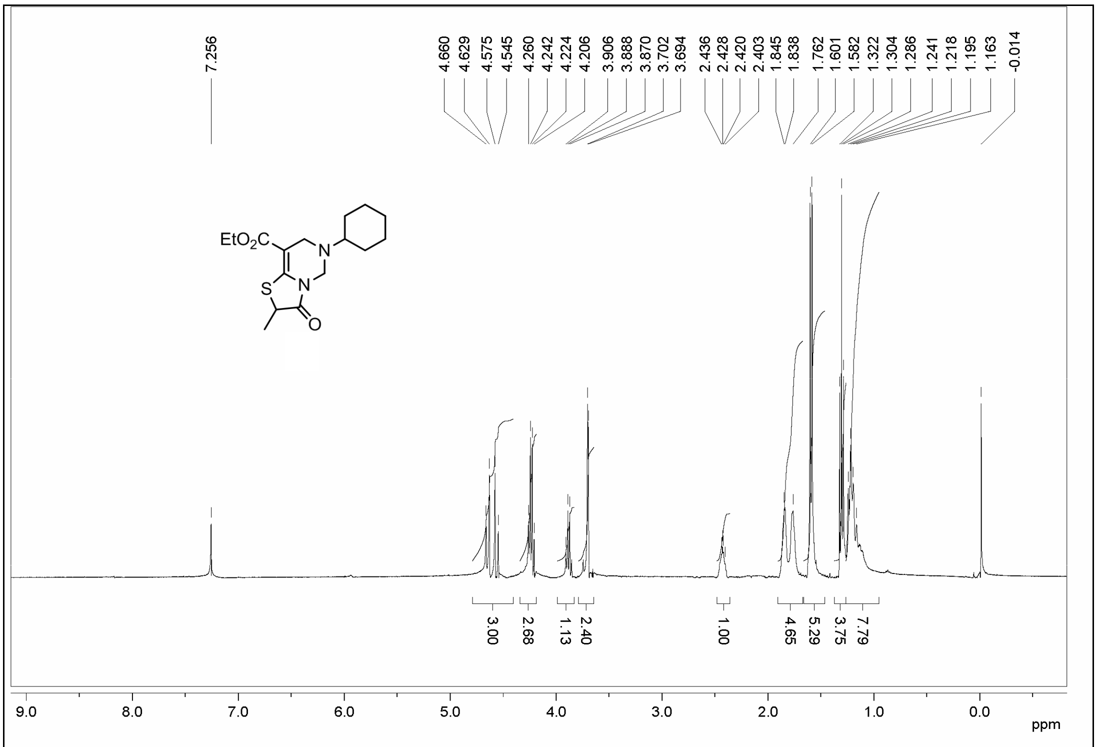


Figure 7. 91. [1]H NMR (400 MHz, $CDCl_3$) spectrum of compound **259f**

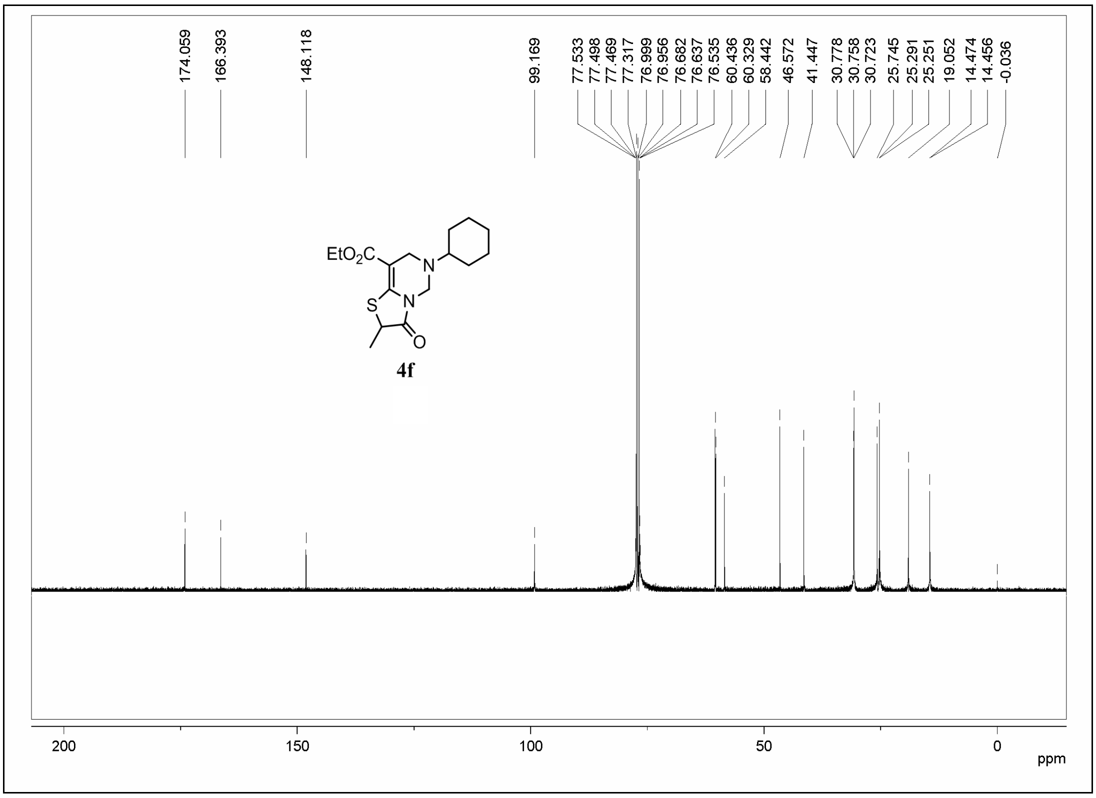


Figure 7. 92. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **259f**

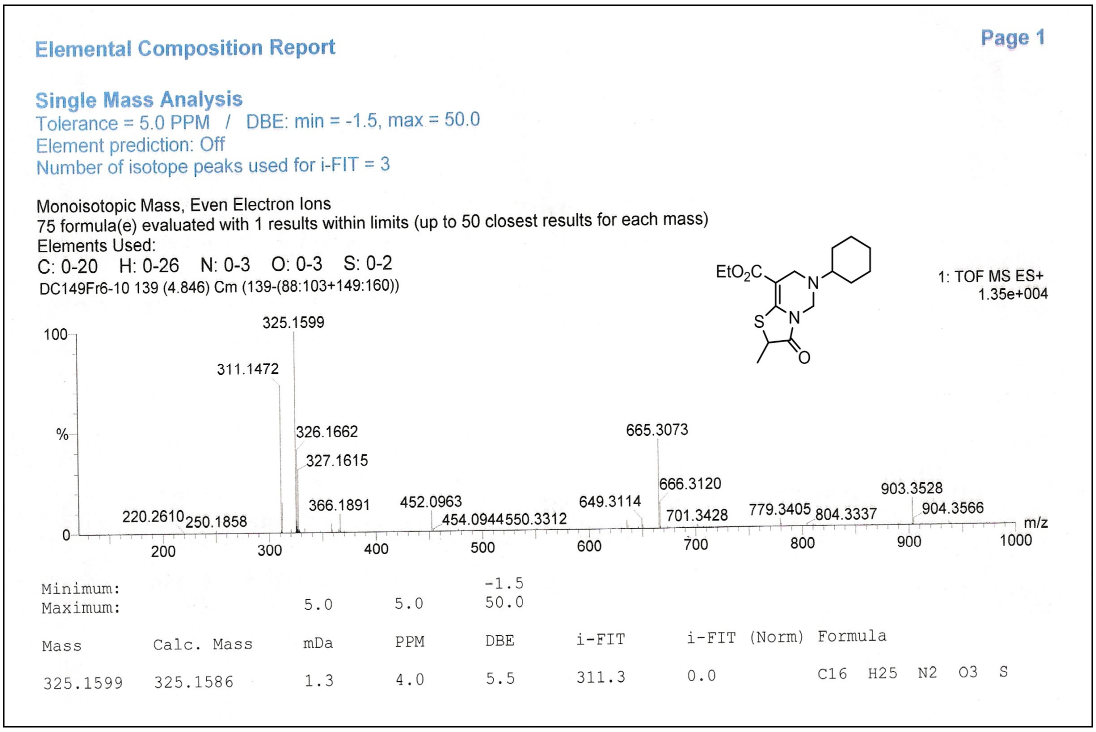


Figure 7. 93. HRMS and elemental composition of compound **259f**

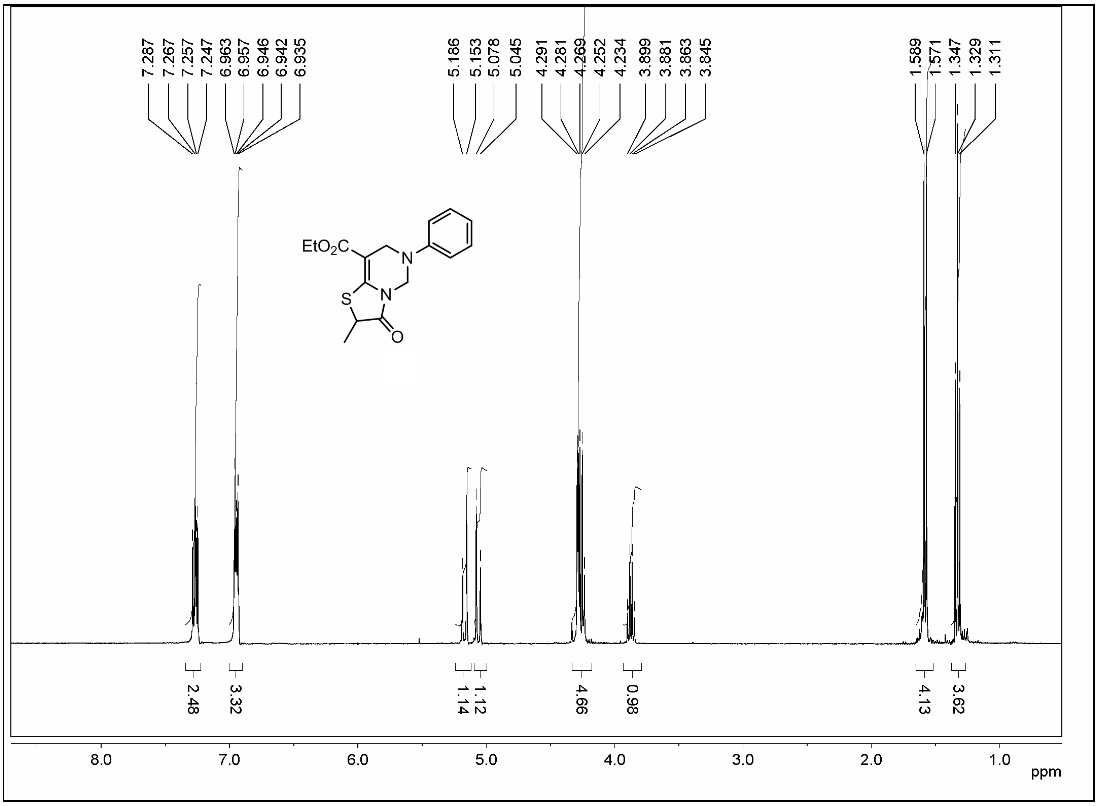


Figure 7. 94. ^{1}H NMR (400 MHz, CDCl3) spectrum of compound **259g**

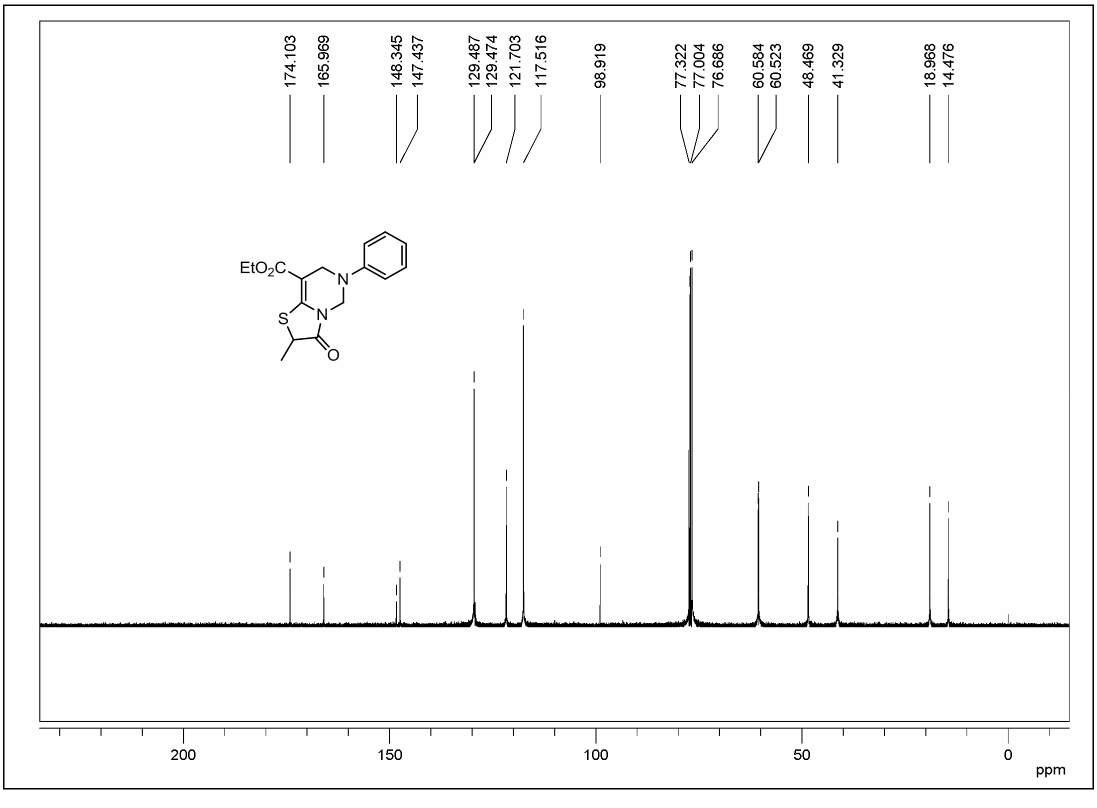
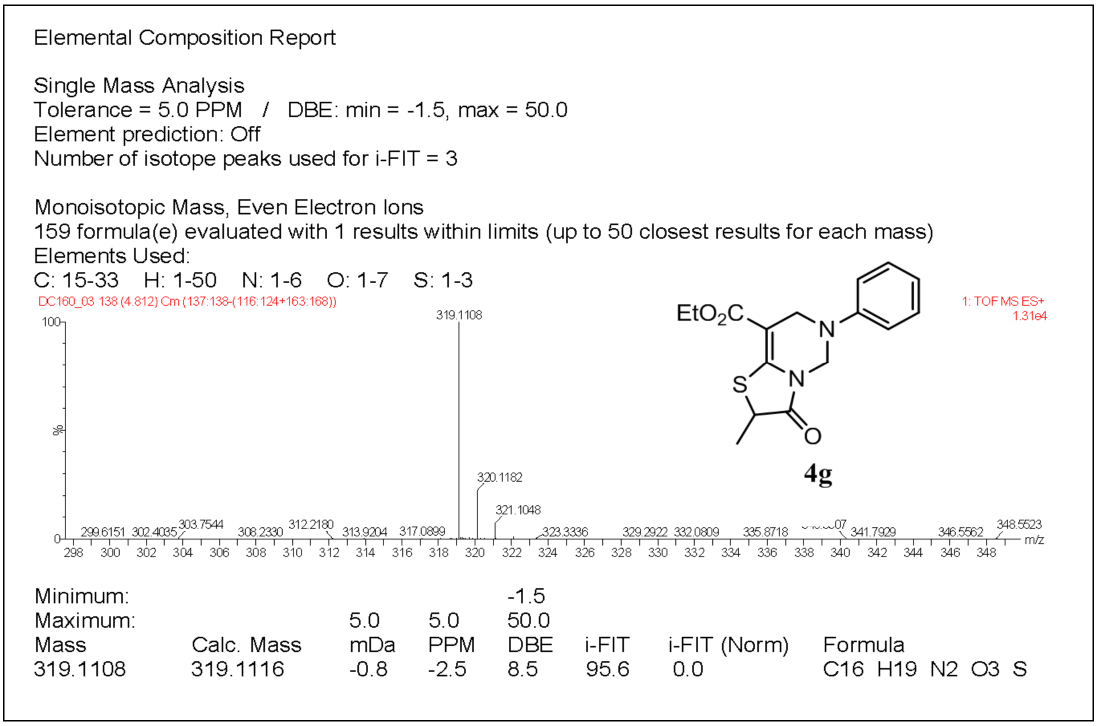


Figure 7. 95. ^{13}C NMR (100 MHz, CDCl3) spectrum of compound **259g**


Elemental Composition Report

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
159 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 15-33 H: 1-50 N: 1-6 O: 1-7 S: 1-3

Minimum:				-1.5			
Maximum:		5.0	5.0	50.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
319.1108	319.1116	-0.8	-2.5	8.5	95.6	0.0	C16 H19 N2 O3 S

Figure 7. 96. HRMS and elemental composition of compound **259g**

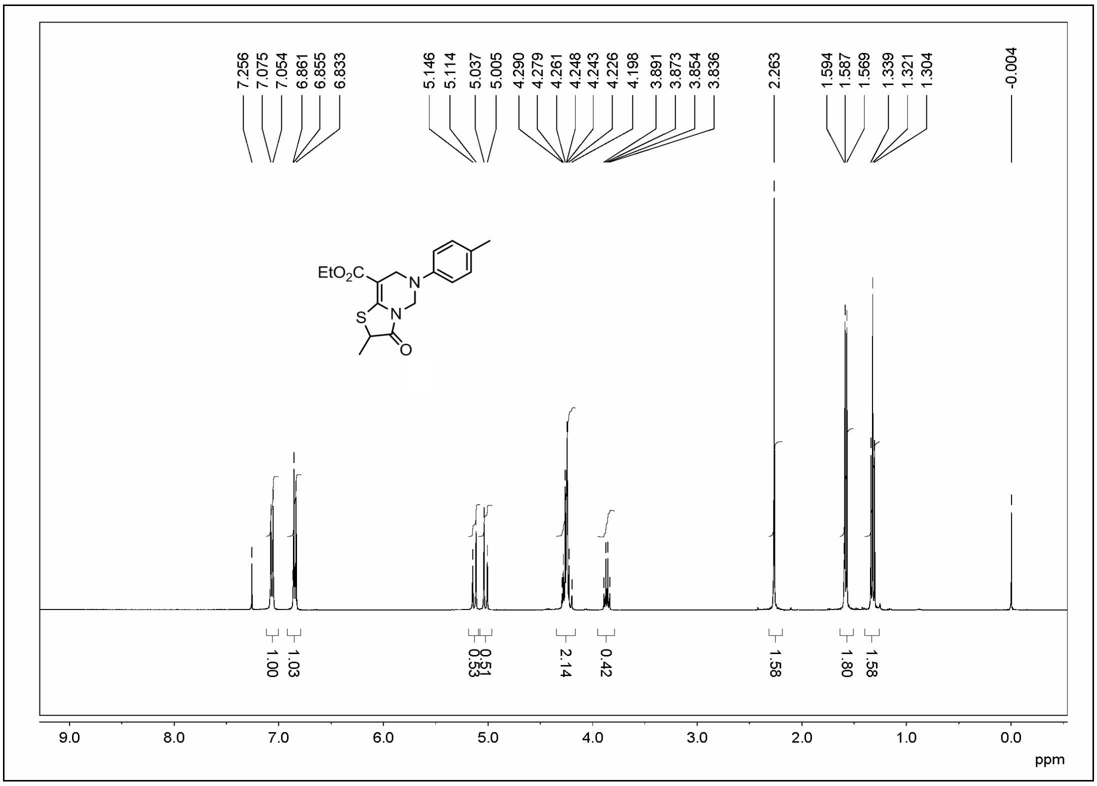


Figure 7. 97. [1]H NMR (400 MHz, CDCl3) spectrum of compound **259h**

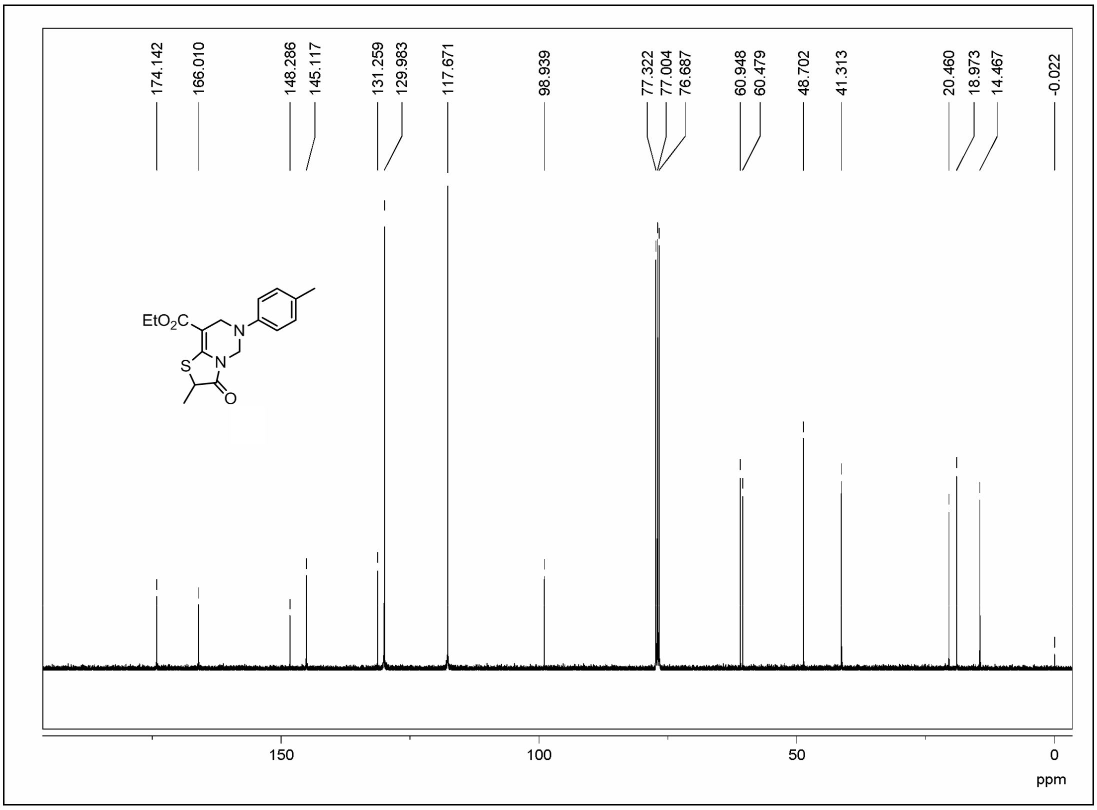
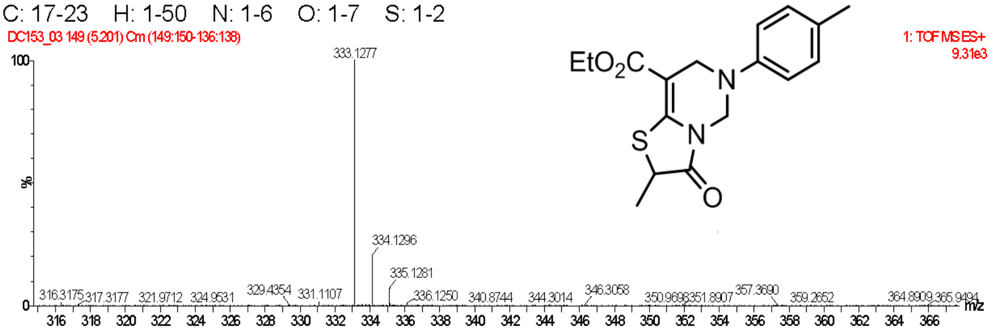


Figure 7. 98. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **259h**

Elemental Composition Report

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
108 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 17-23 H: 1-50 N: 1-6 O: 1-7 S: 1-2



Minimum:				-1.5			
Maximum:		5.0	5.0	50.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
333.1277	333.1273	0.4	1.2	8.5	124.3	0.0	C17 H21 N2 O3 S

Figure 7. 99. HRMS and elemental composition of compound **259h**

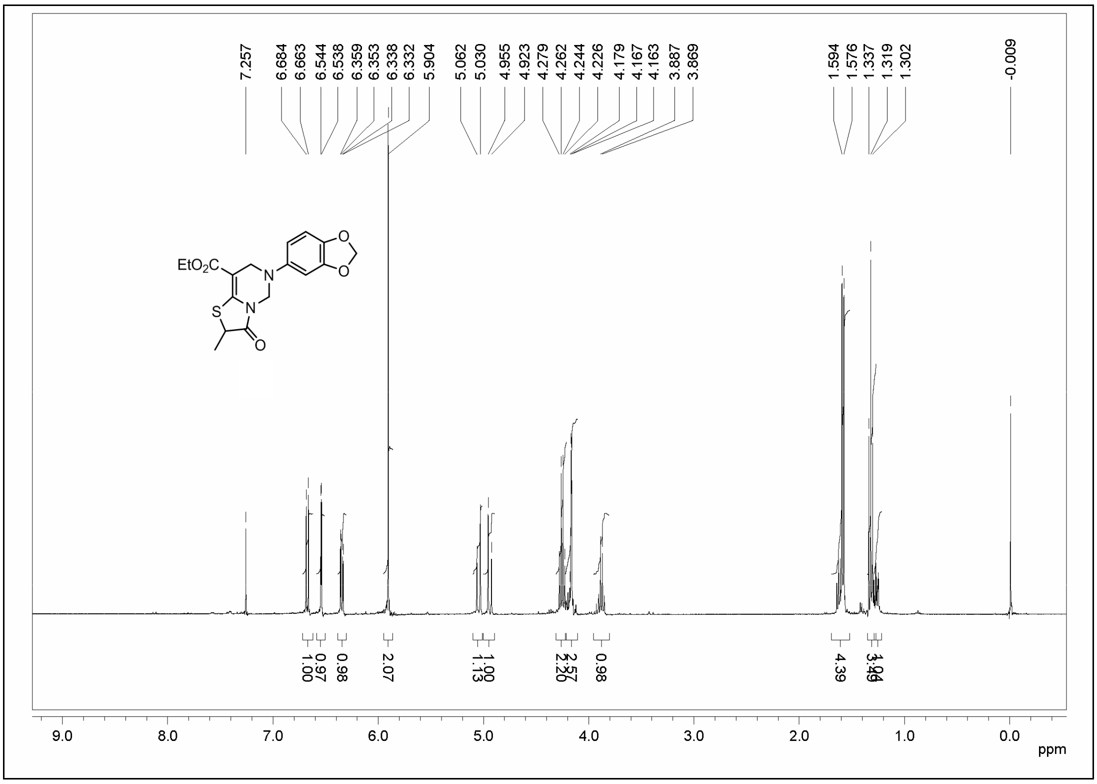


Figure 7. 100. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **259i**

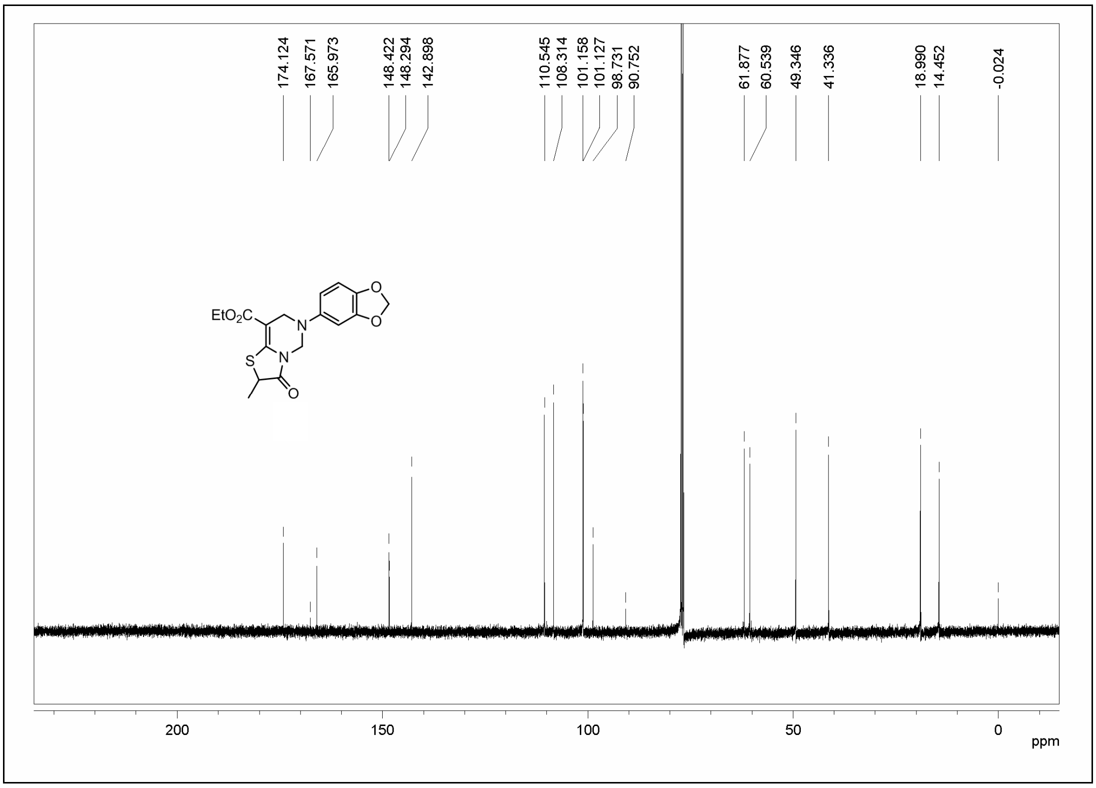


Figure 7. 101. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **259i**

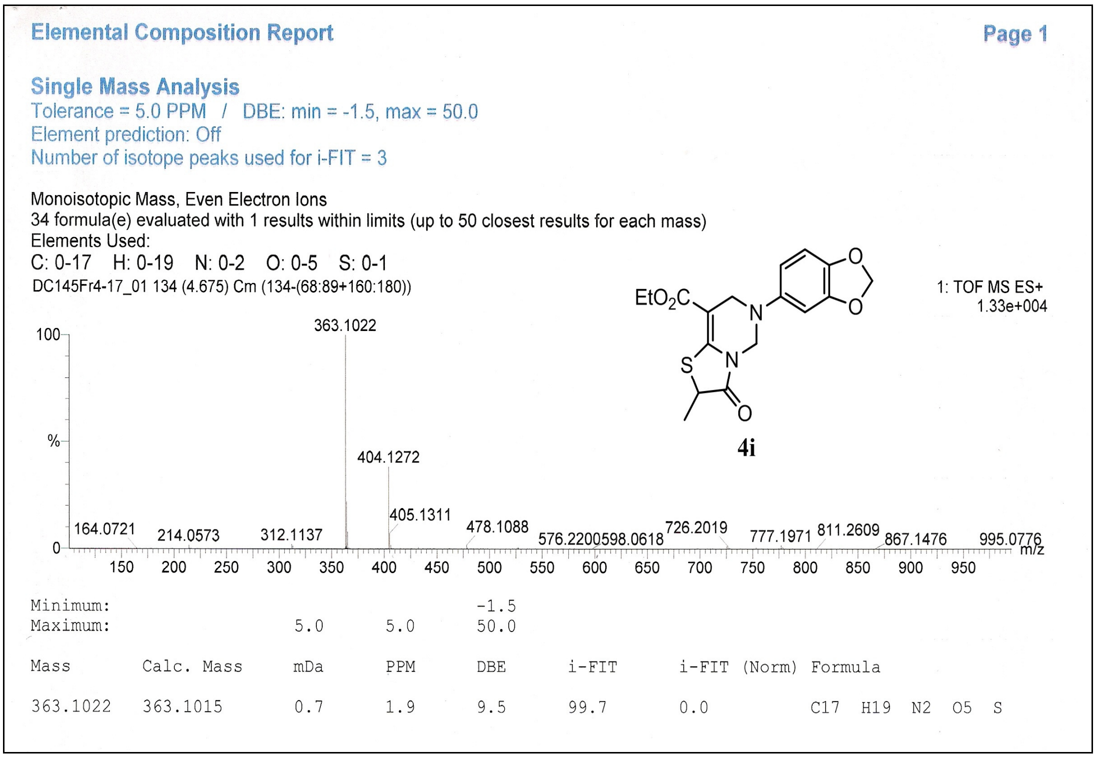


Figure 7. 102. HRMS and elemental composition of compound **259i**

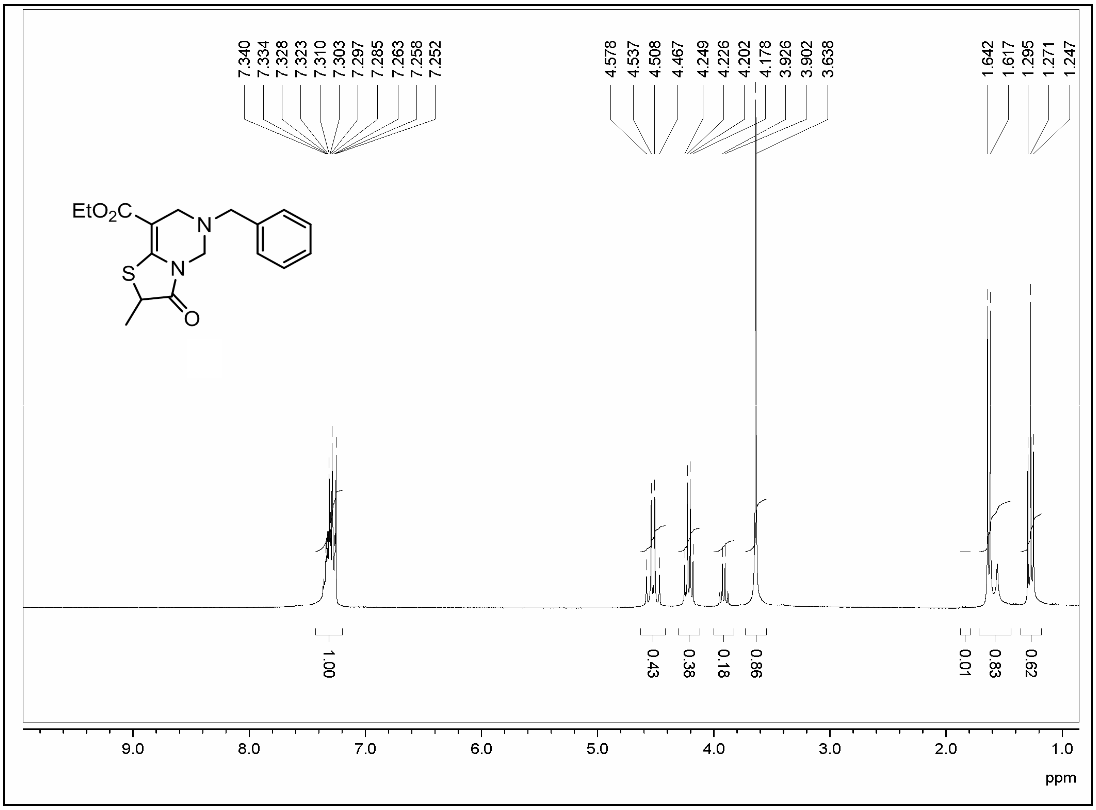


Figure 7. 103. ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of compound **259j**

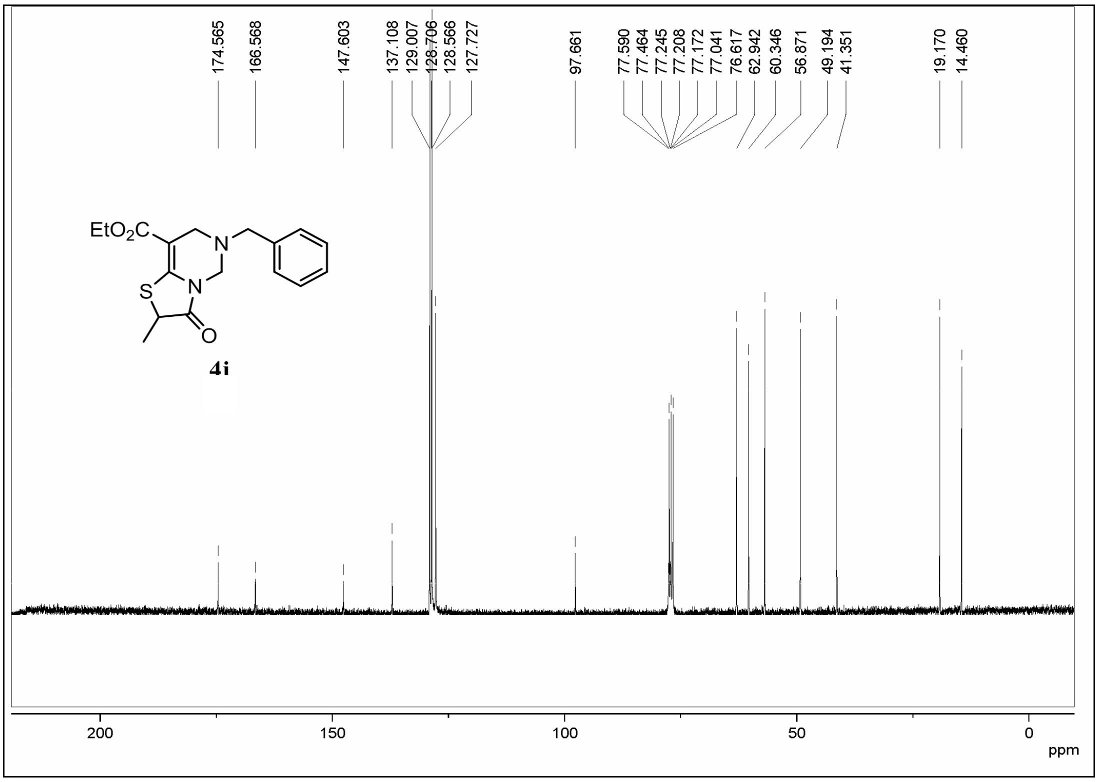


Figure 7. 104. ^{13}C NMR (75 MHz, CDCl$_3$) spectrum of compound **259j**

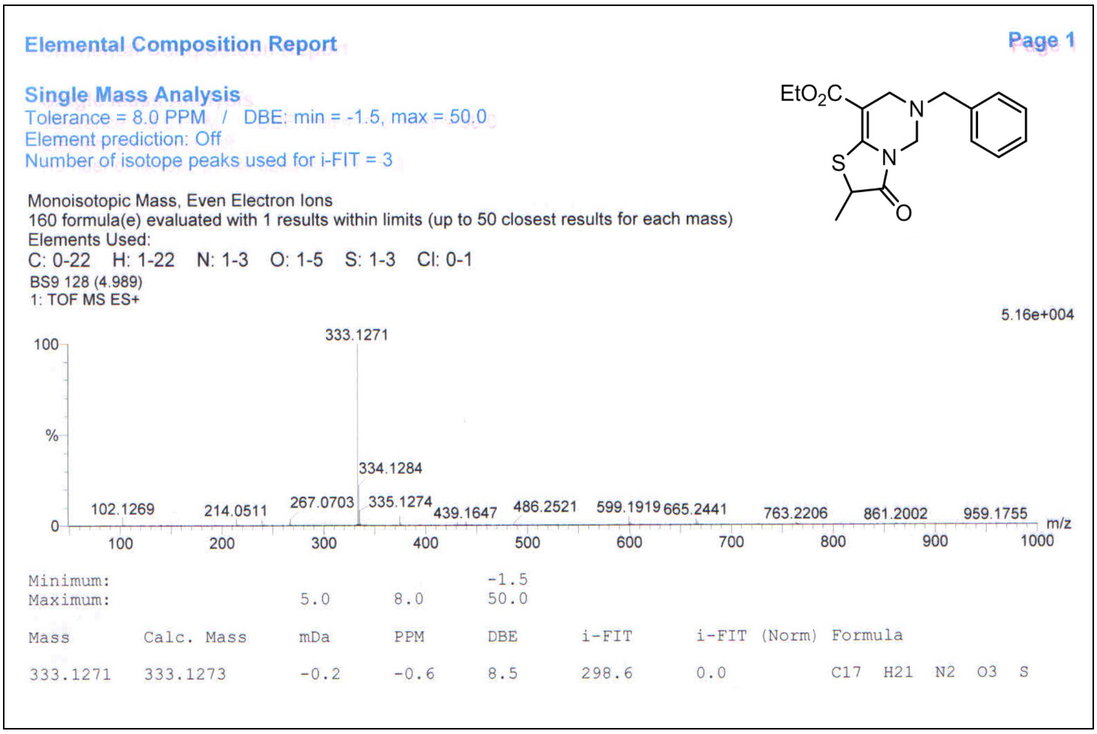


Figure 7. 105. HRMS and elemental composition of compound **259j**

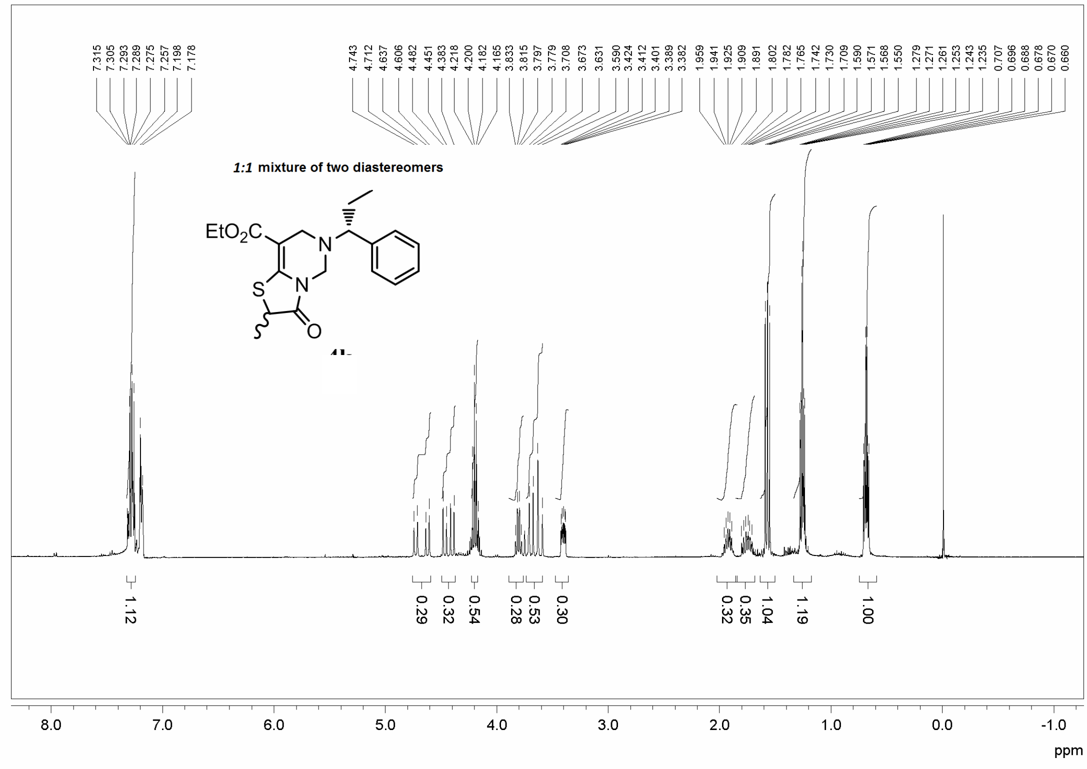


Figure 7. 106. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **259k**

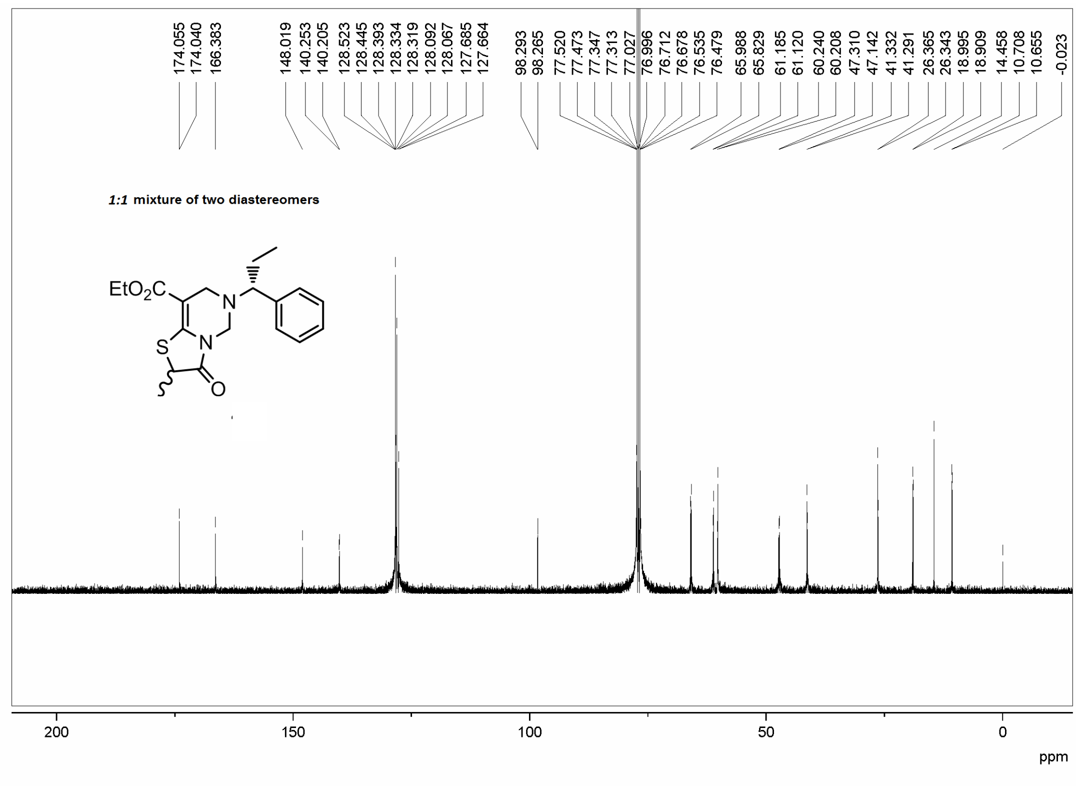
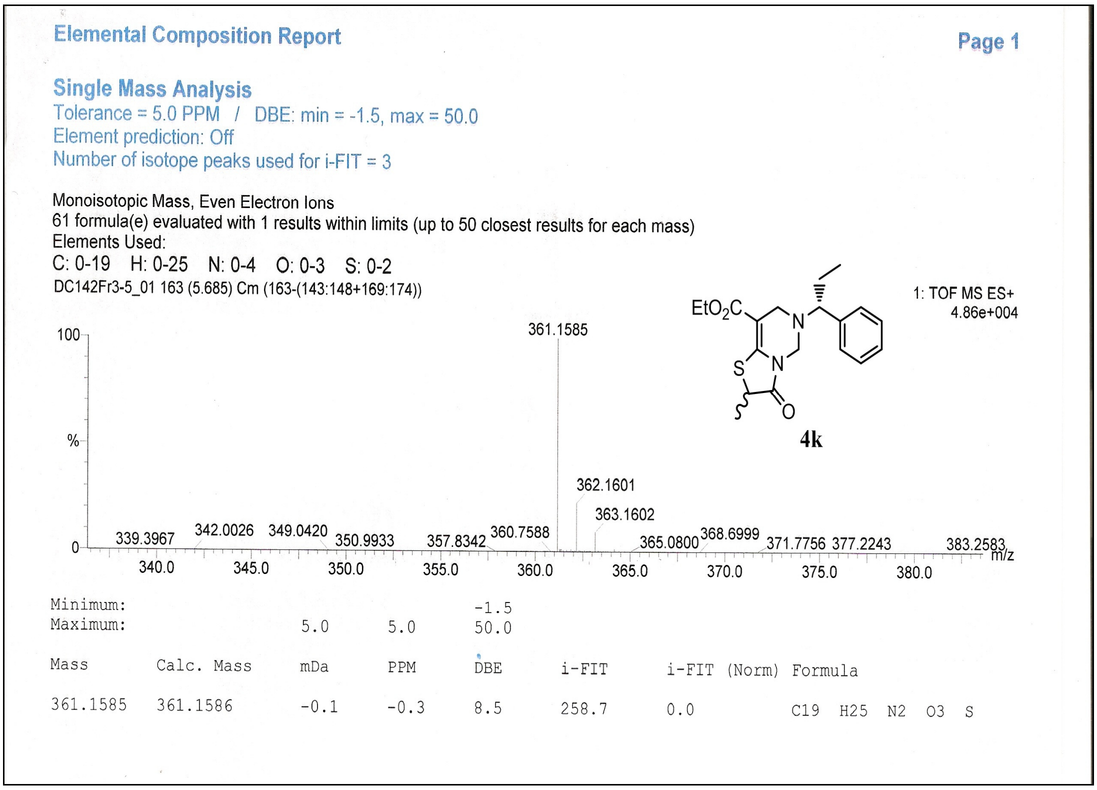


Figure 7. 107. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **259k**


Elemental Composition Report

Page 1

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
61 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-19 H: 0-25 N: 0-4 O: 0-3 S: 0-2
DC142Fr3-5_01 163 (5.685) Cm (163-(143:148+169:174))

Minimum:				-1.5			
Maximum:		5.0	5.0	50.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
361.1585	361.1586	-0.1	-0.3	8.5	258.7	0.0	C19 H25 N2 O3 S

Figure 7. 108. HRMS and elemental composition of compound **259k**

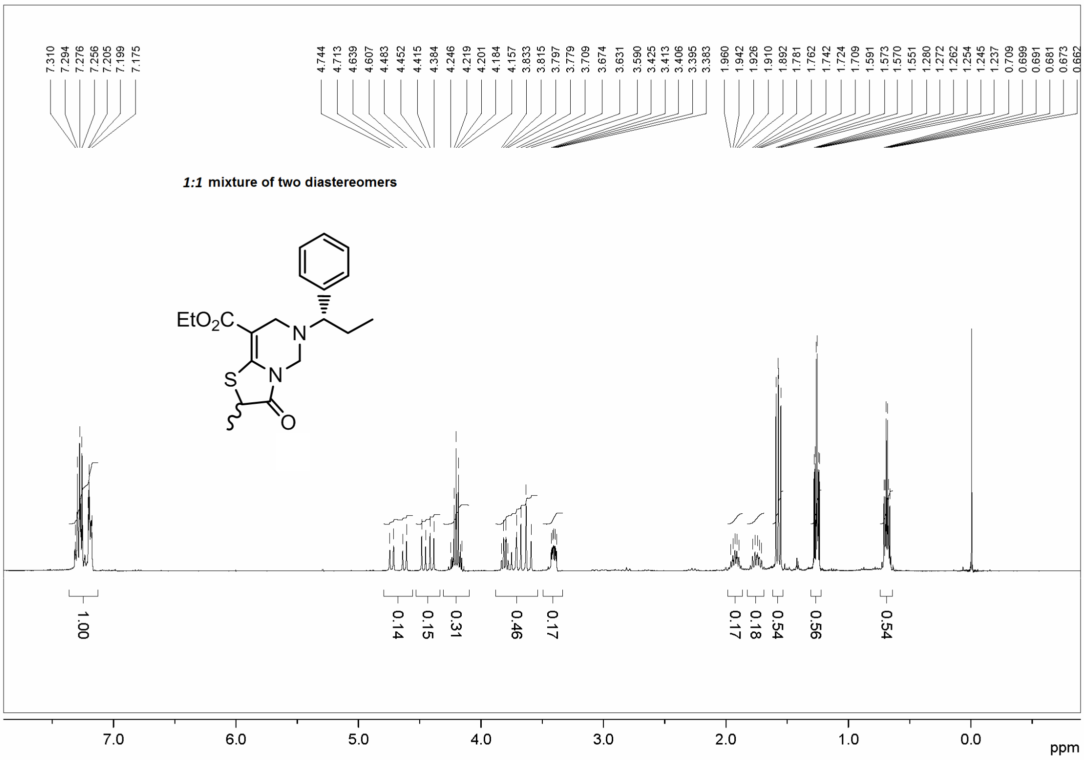


Figure 7. 109. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **259l**

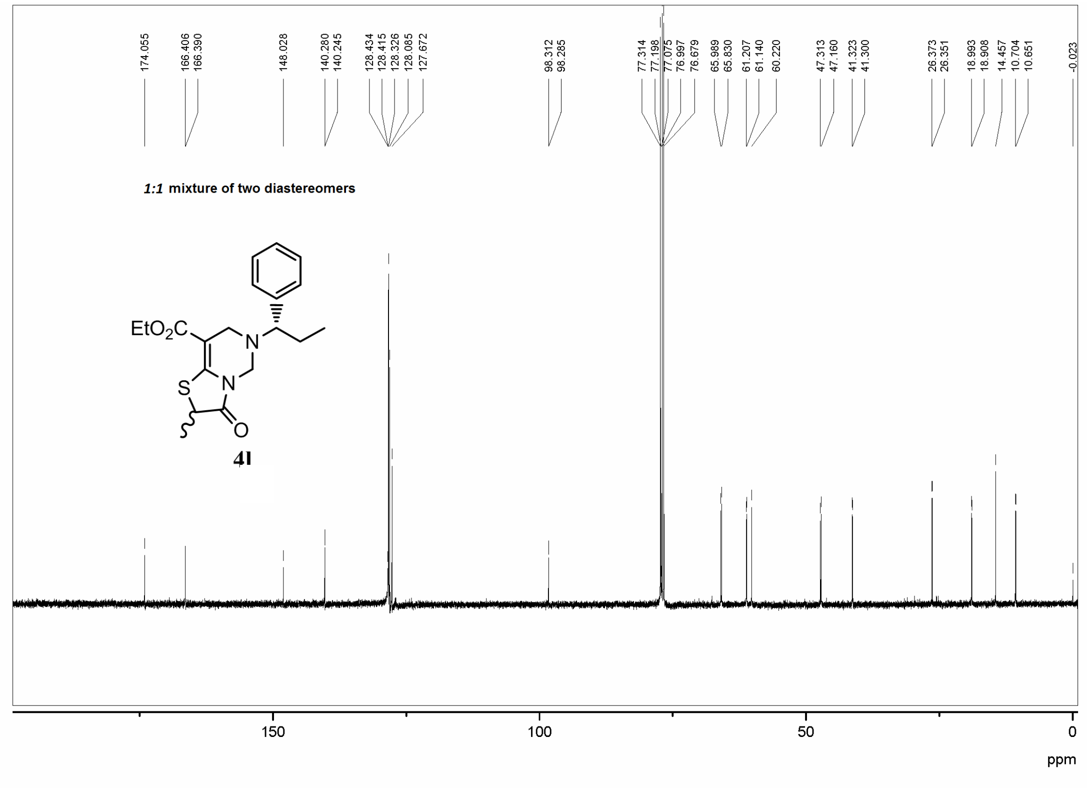


Figure 7. 110. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **259l**

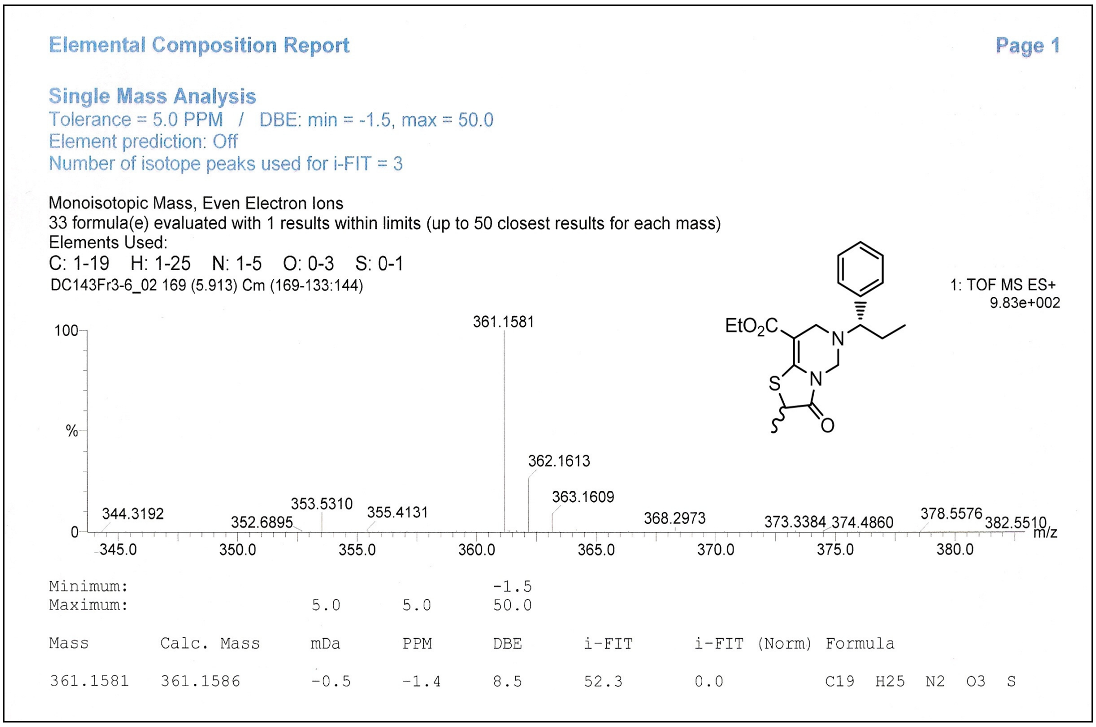


Figure 7. 111. HRMS and elemental composition of compound **259l**

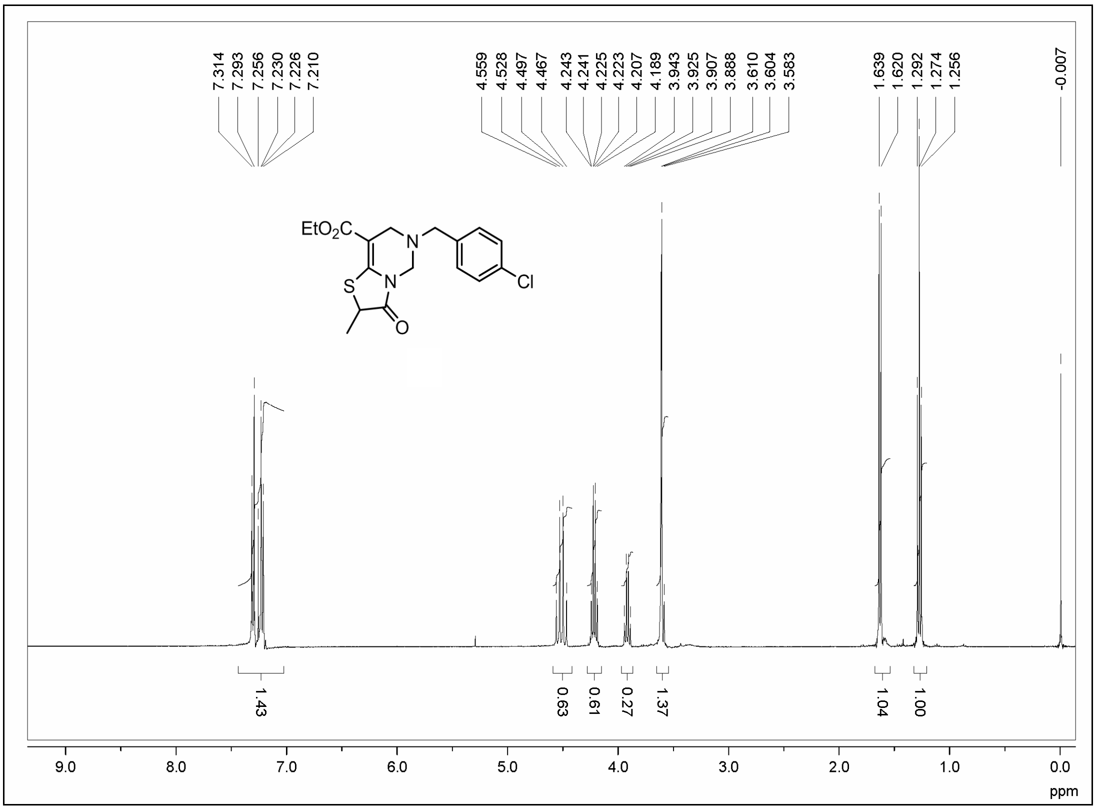


Figure 7. 112. ^{1}H NMR (400 MHz, CDCl3) spectrum of compound **259m**

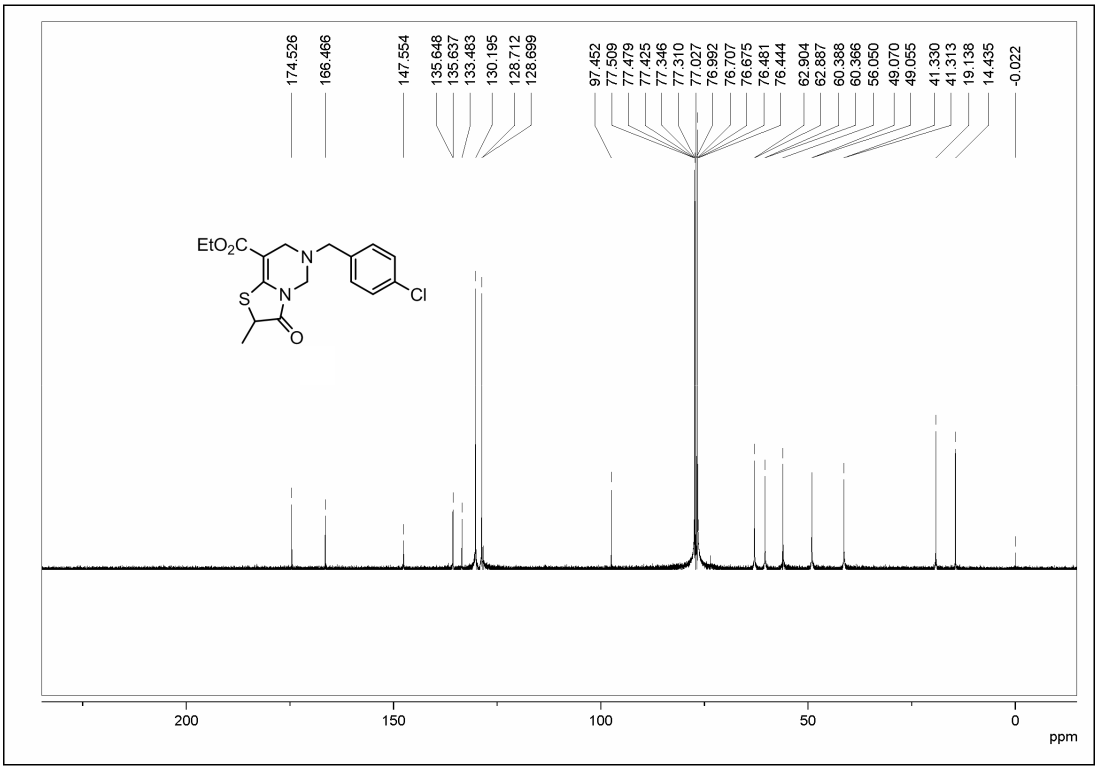
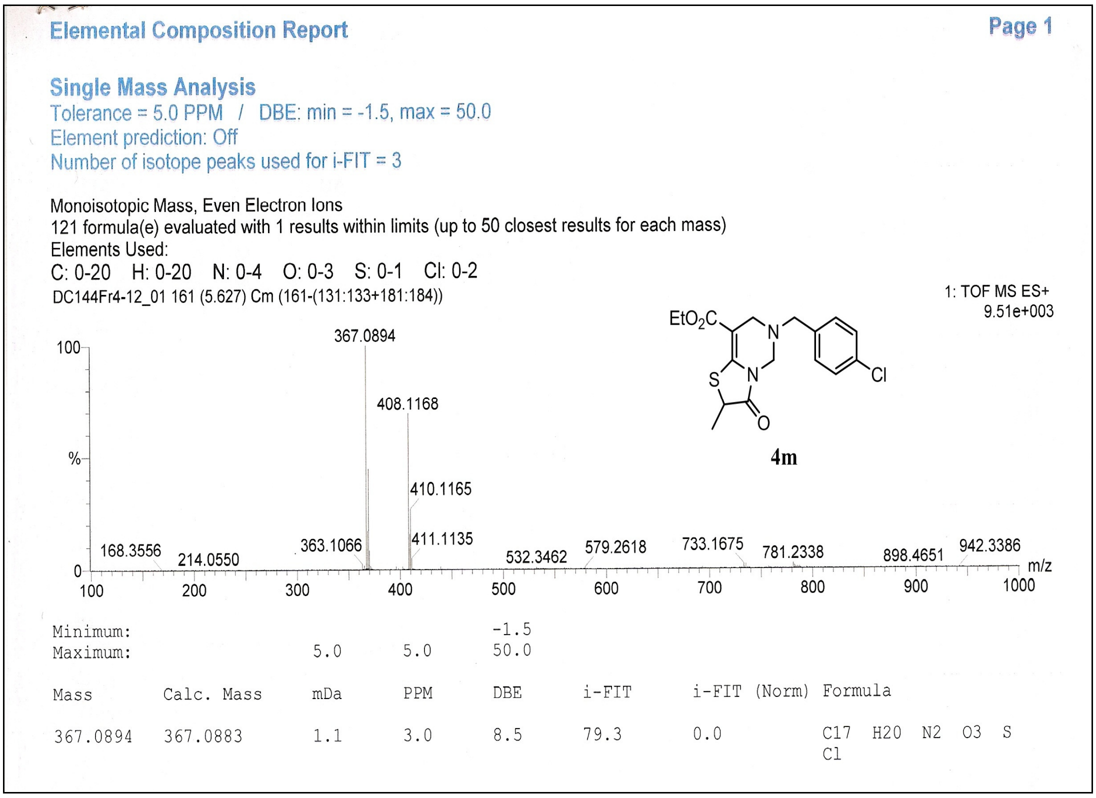


Figure 7. 113. ^{13}C NMR (100 MHz, CDCl3) spectrum of compound **259m**



Minimum:				-1.5			
Maximum:		5.0	5.0	50.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
367.0894	367.0883	1.1	3.0	8.5	79.3	0.0	C17 H20 N2 O3 S Cl

Figure 7. 114. HRMS and elemental composition of compound **259m**

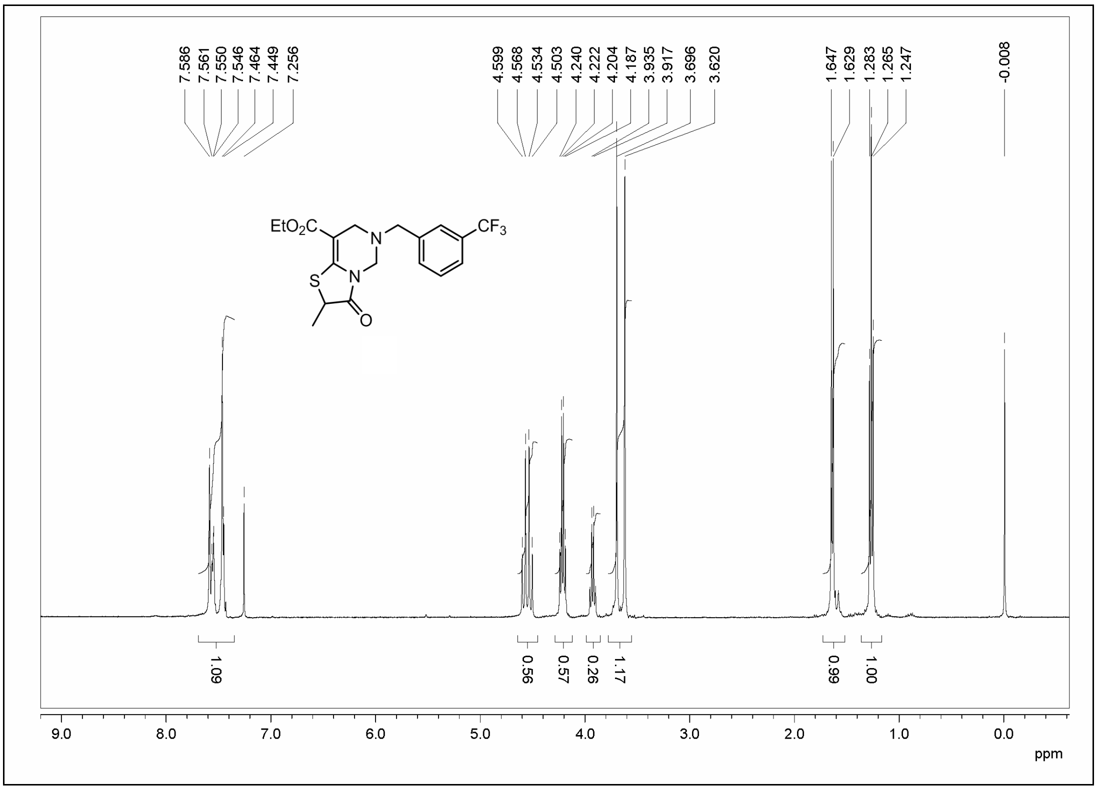


Figure 7. 115. [1]H NMR (400 MHz, CDCl3) spectrum of compound **259n**

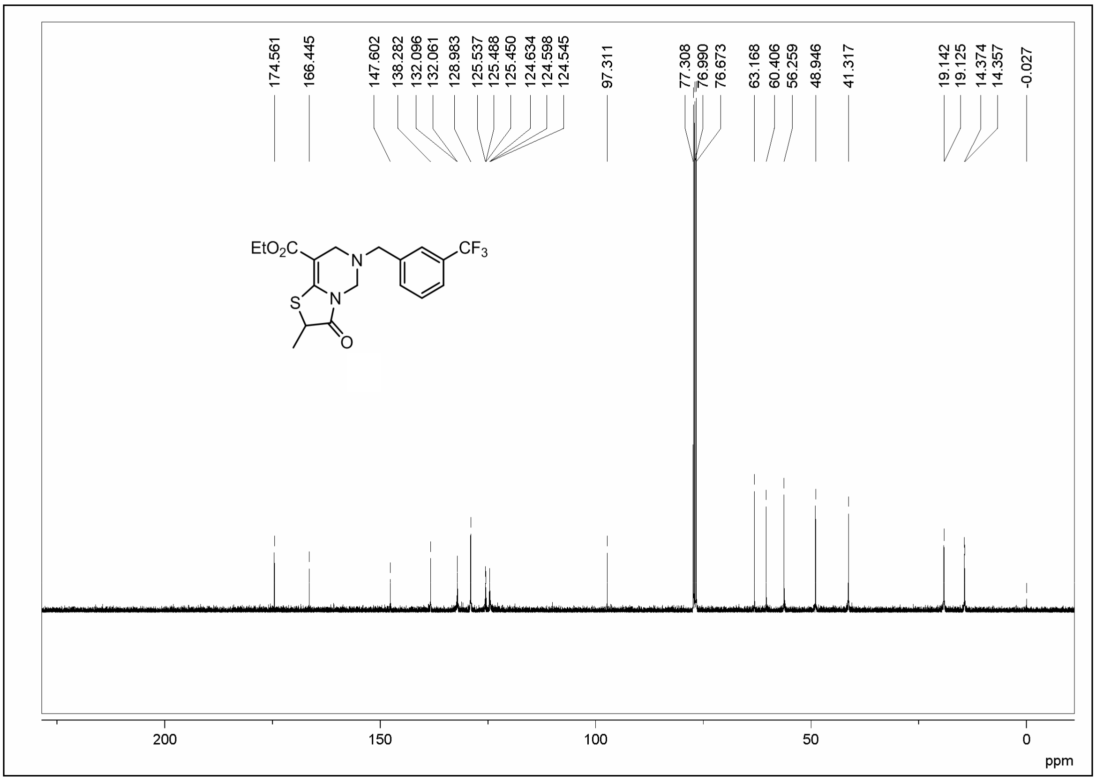
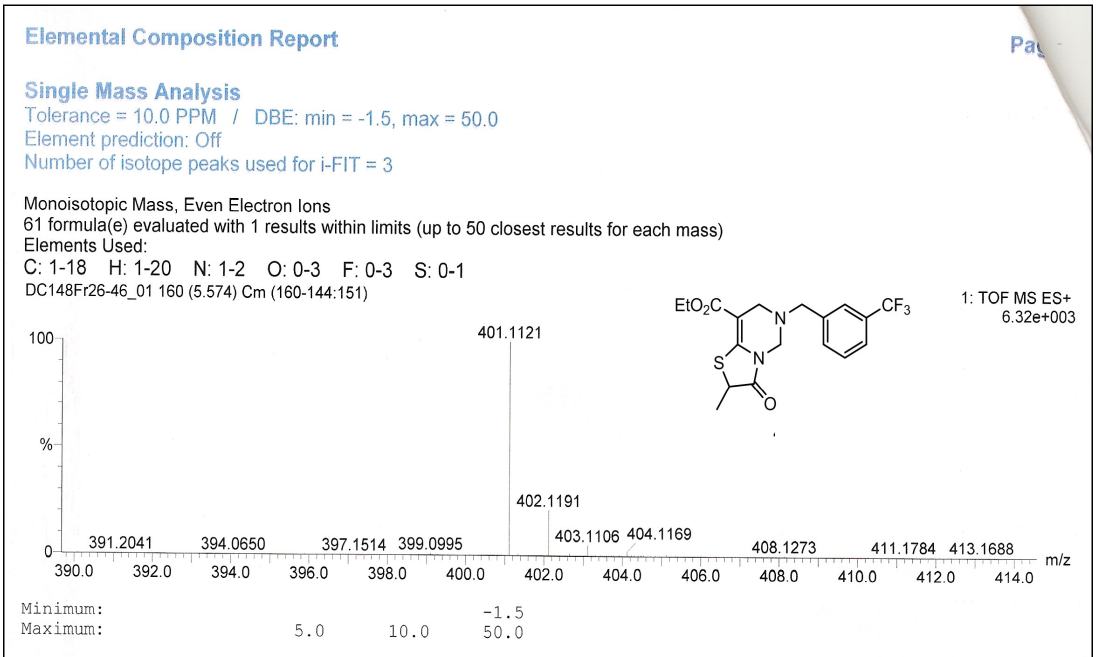


Figure 7. 116. ^{13}C NMR (100 MHz, CDCl3) spectrum of compound **259n**



Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
401.1121	401.1147	-2.6	-6.5	8.5	49.7	0.0	C18 H20 N2 O3 F3 S

Figure 7. 117. HRMS and elemental composition of compound **259n**

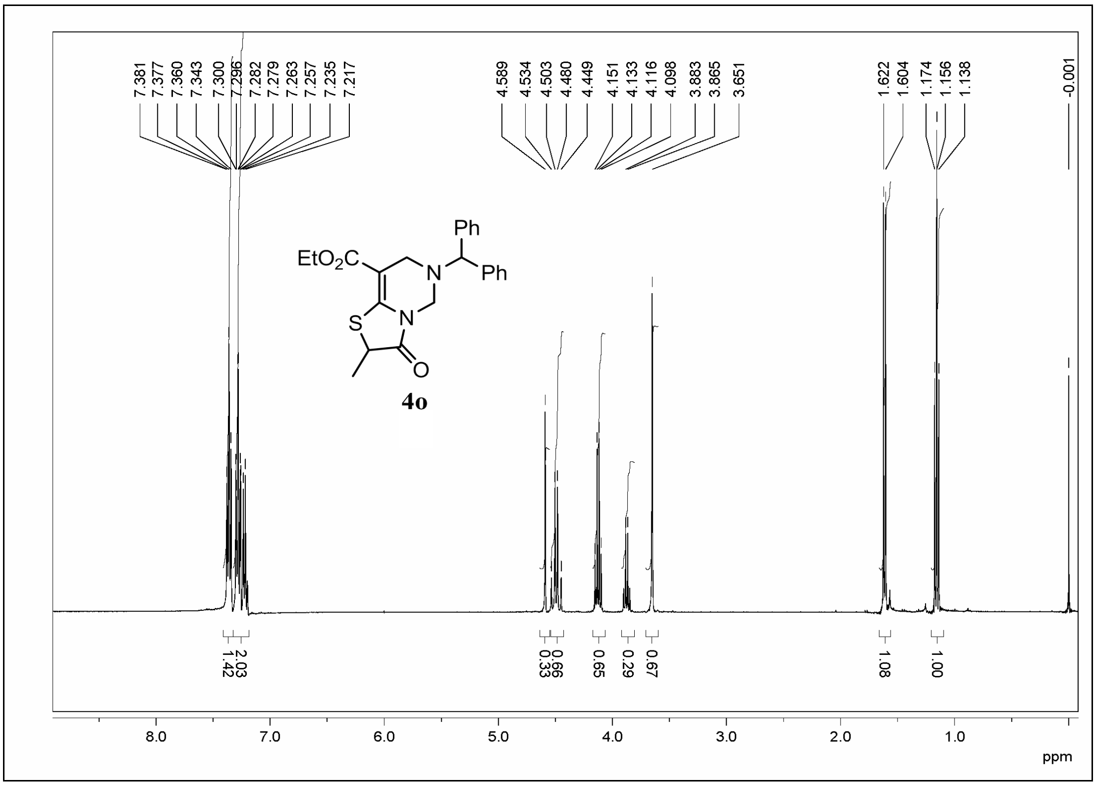


Figure 7. 118. ^{1}H NMR (400 MHz, CDCl3) spectrum of compound **259o**

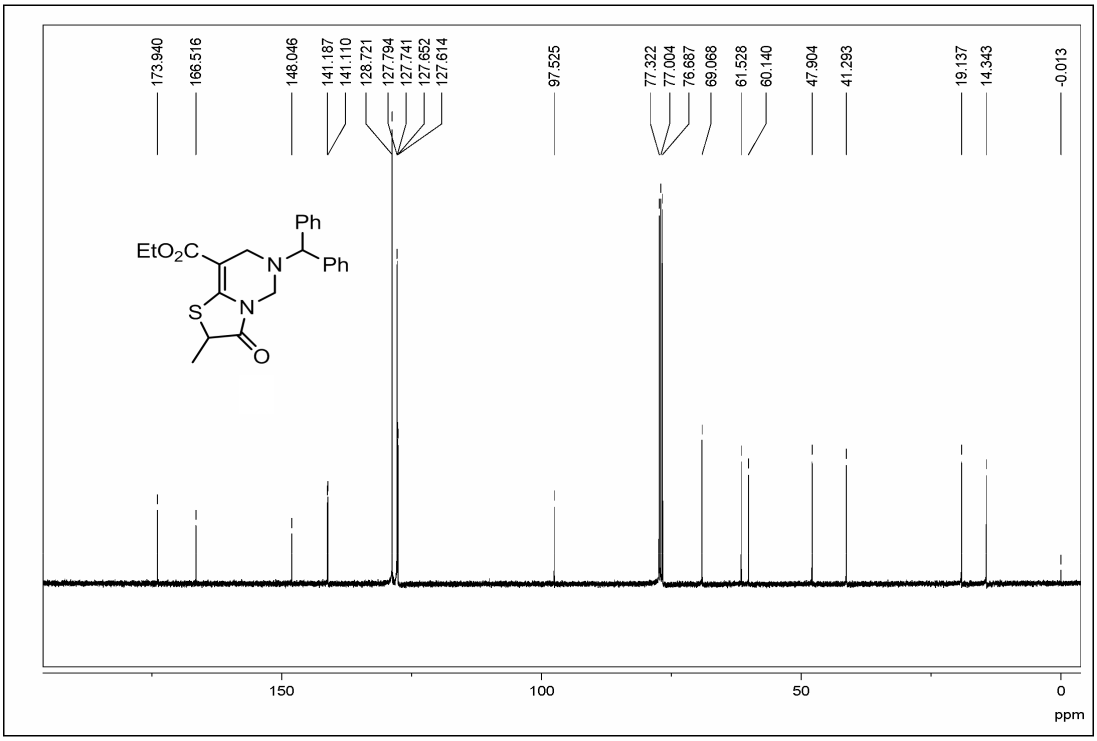


Figure 7. 119. ^{13}C NMR (100 MHz, CDCl3) spectrum of compound **259o**

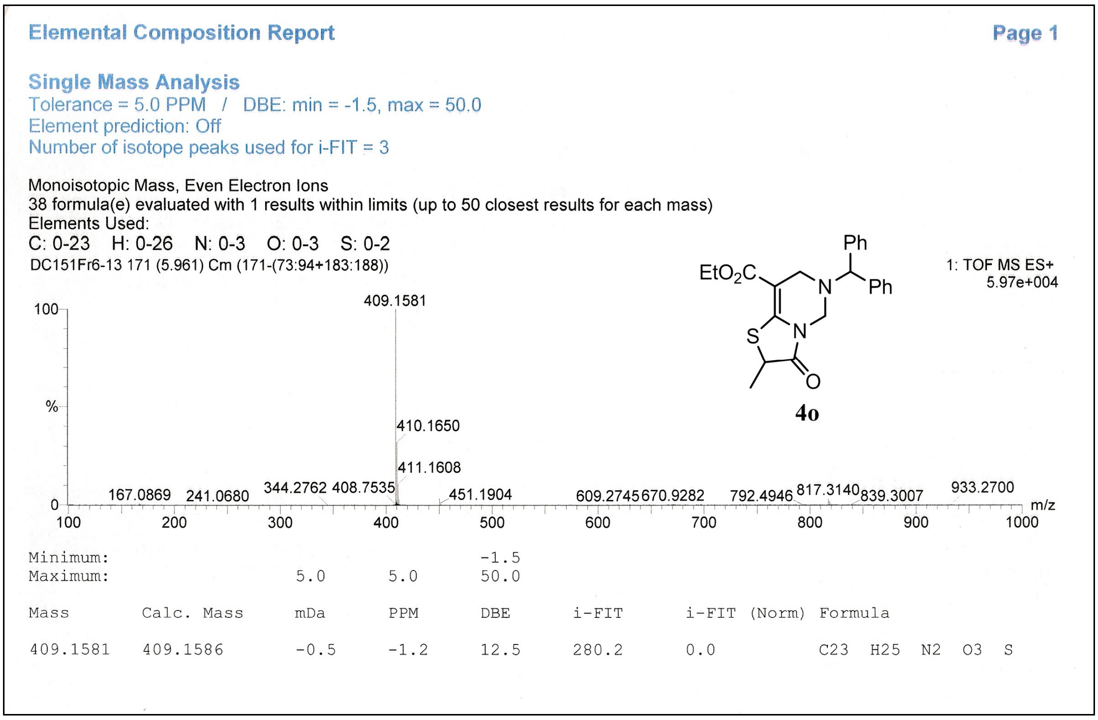


Figure 7. 120. HRMS and elemental composition of compound **259o**

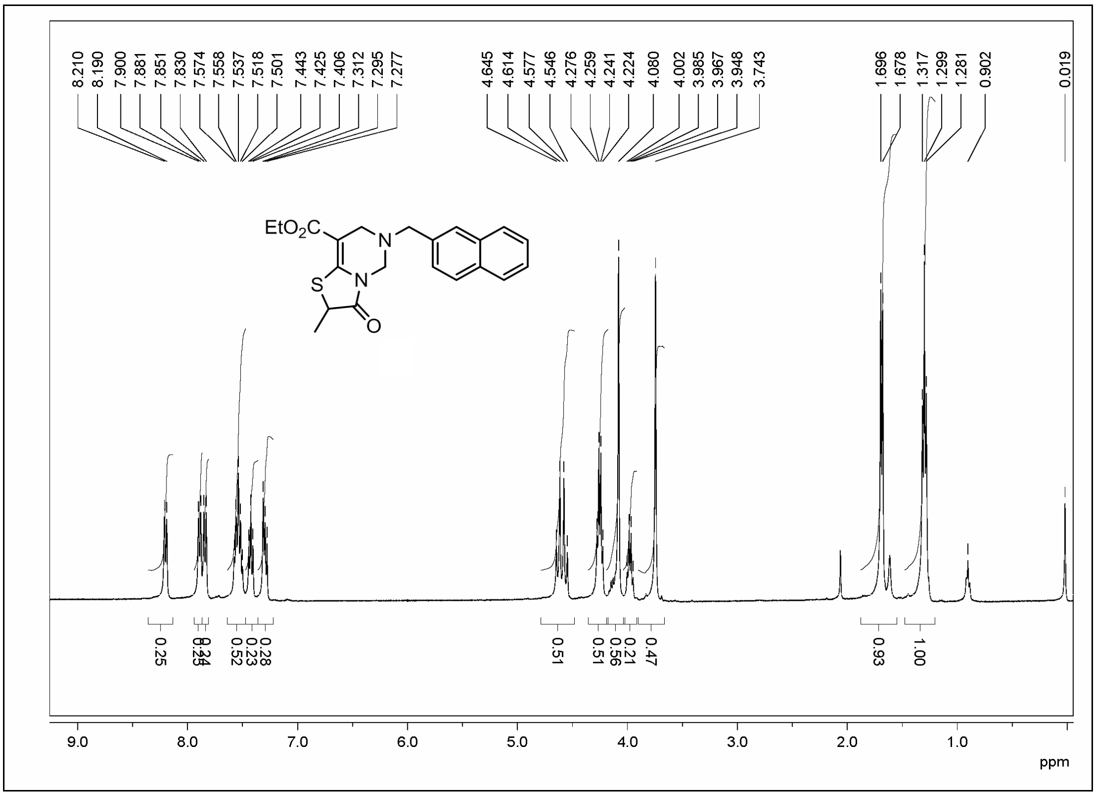


Figure 7. 121. [1]H NMR (400 MHz, CDCl3) spectrum of compound **259p**

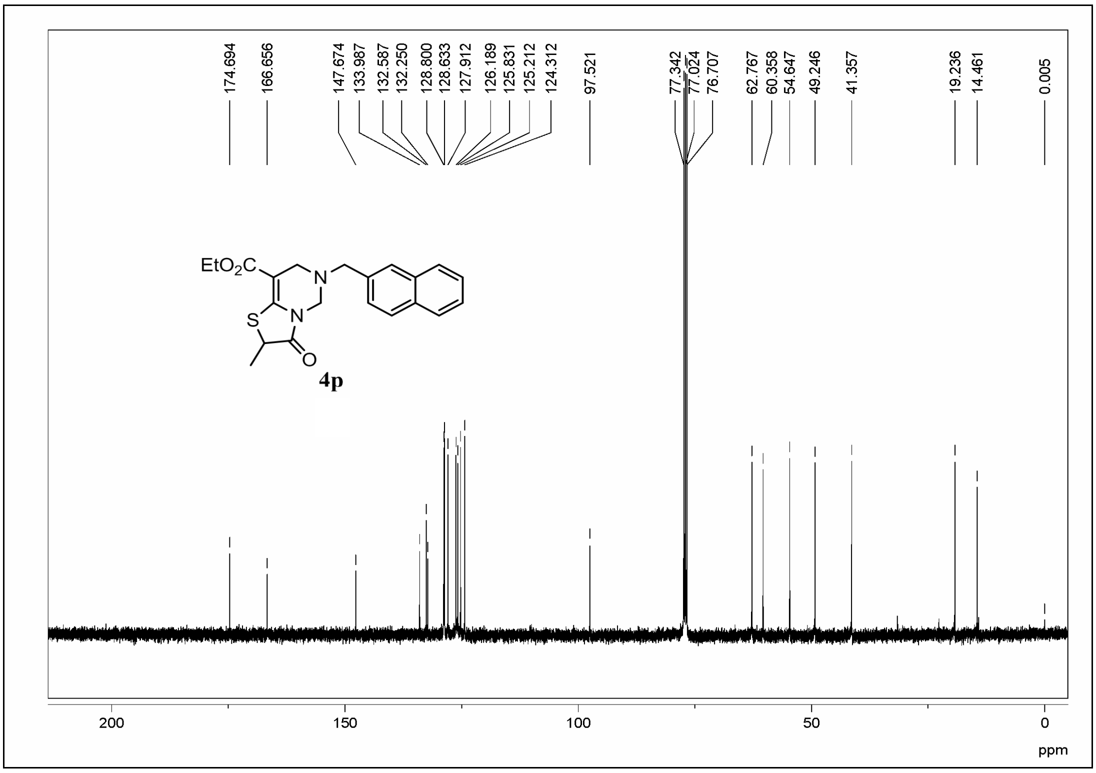
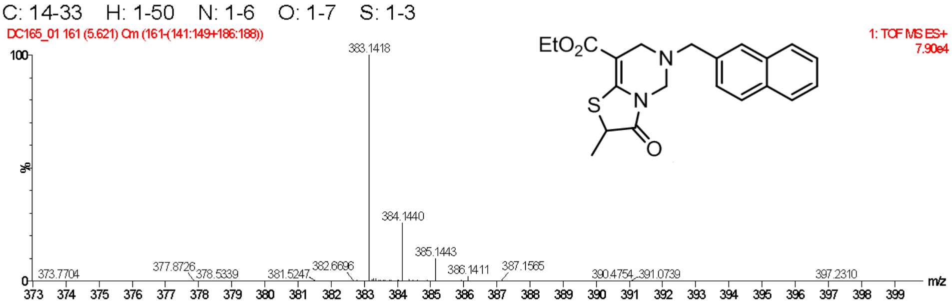


Figure 7. 122. ^{13}C NMR (100 MHz, CDCl3) spectrum of compound **259p**

Elemental Composition Report

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
340 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 14-33 H: 1-50 N: 1-6 O: 1-7 S: 1-3



Minimum:				-1.5			
Maximum:		5.0	5.0	50.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
383.1418	383.1429	-1.1	-2.9	11.5	238.3	0.0	C21 H23 N2 O3 S

Figure 7. 123. HRMS and elemental composition of compound **259p**

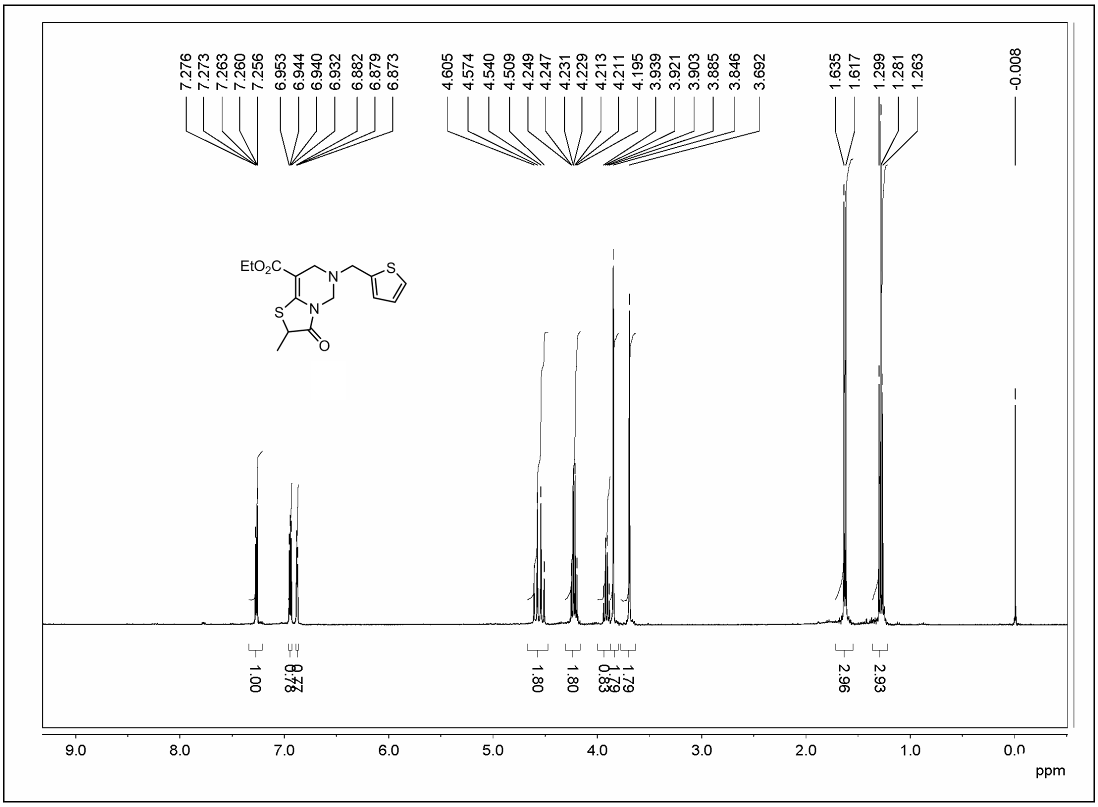


Figure 7. 124. ^{1}H NMR (400 MHz, CDCl3) spectrum of compound **259r**

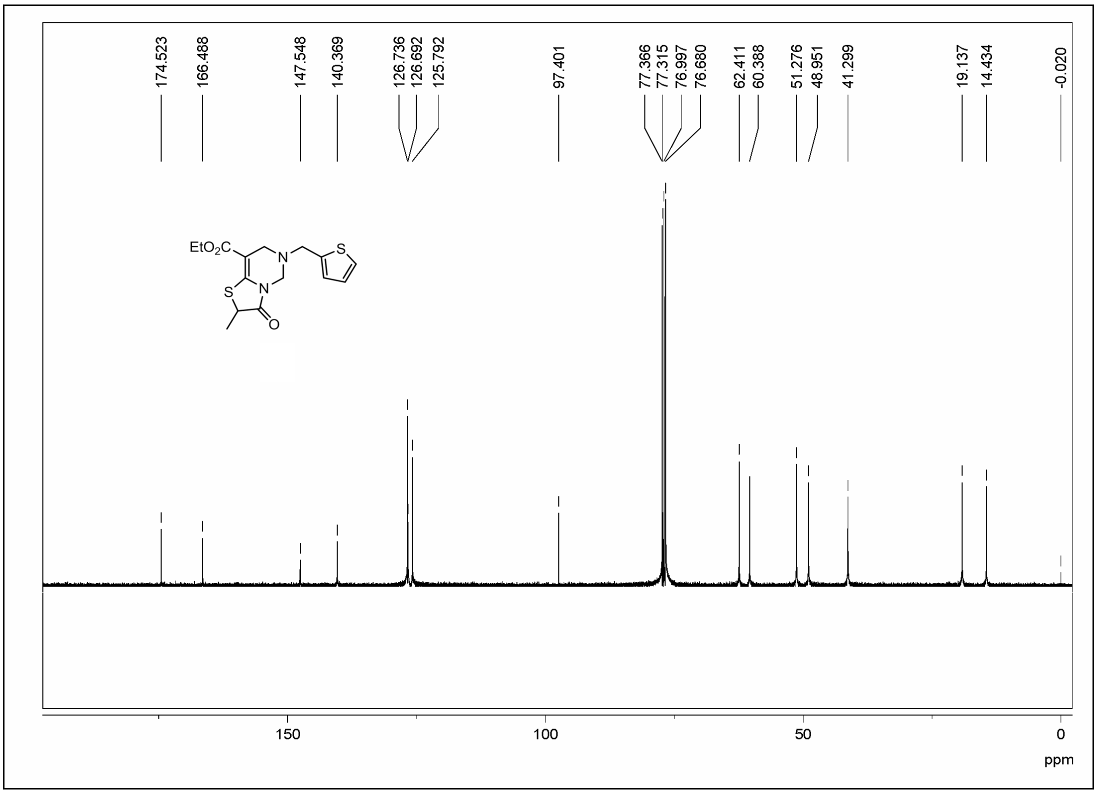
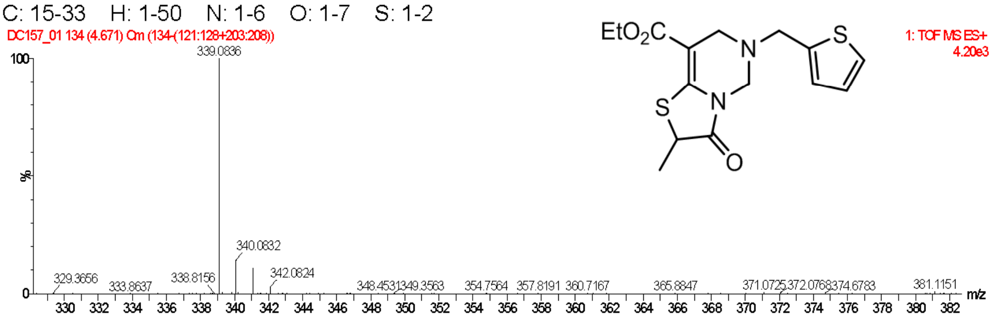


Figure 7. 125. ^{13}C NMR (100 MHz, CDCl3) spectrum of compound **259r**

Elemental Composition Report

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
154 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 15-33 H: 1-50 N: 1-6 O: 1-7 S: 1-2



	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
Minimum:				-1.5			
Maximum:		5.0	5.0	50.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
339.0836	339.0837	-0.1	-0.3	7.5	41.5	0.0	C15 H19 N2 O3 S2

Figure 7. 126. HRMS and elemental composition of compound **259r**

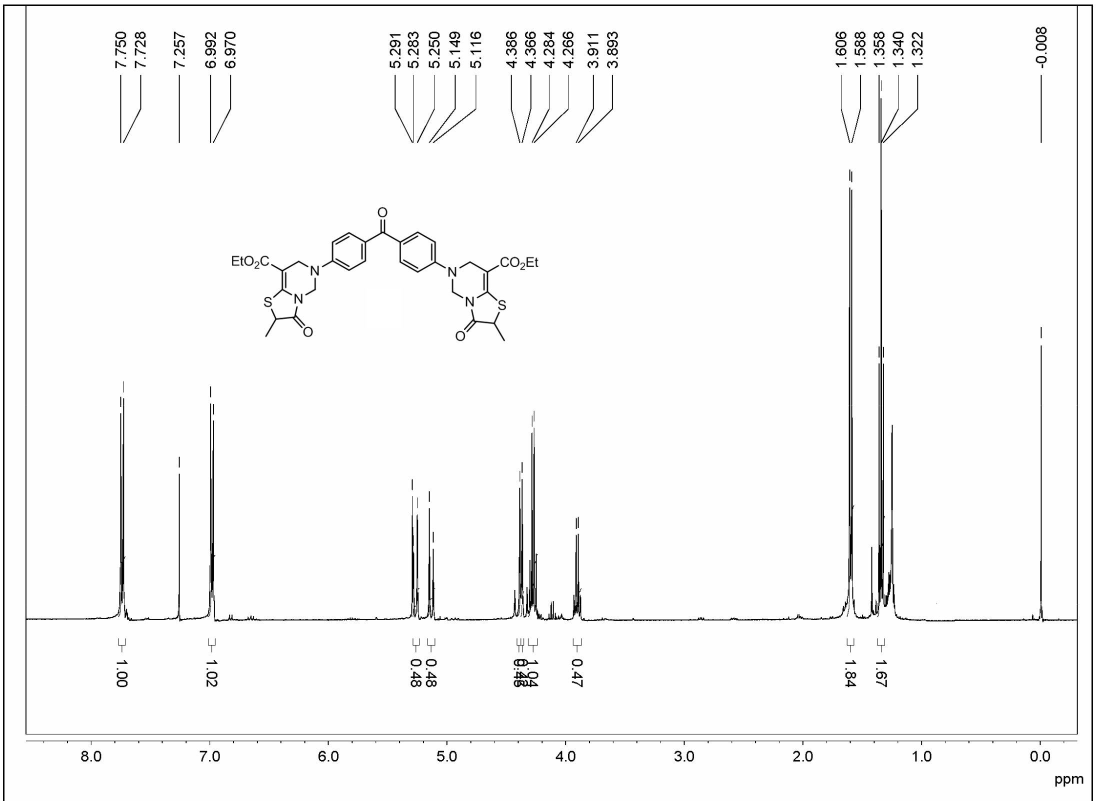


Figure 7. 127. ^{1}H NMR (400 MHz, CDCl$_3$) spectrum of compound **259s**

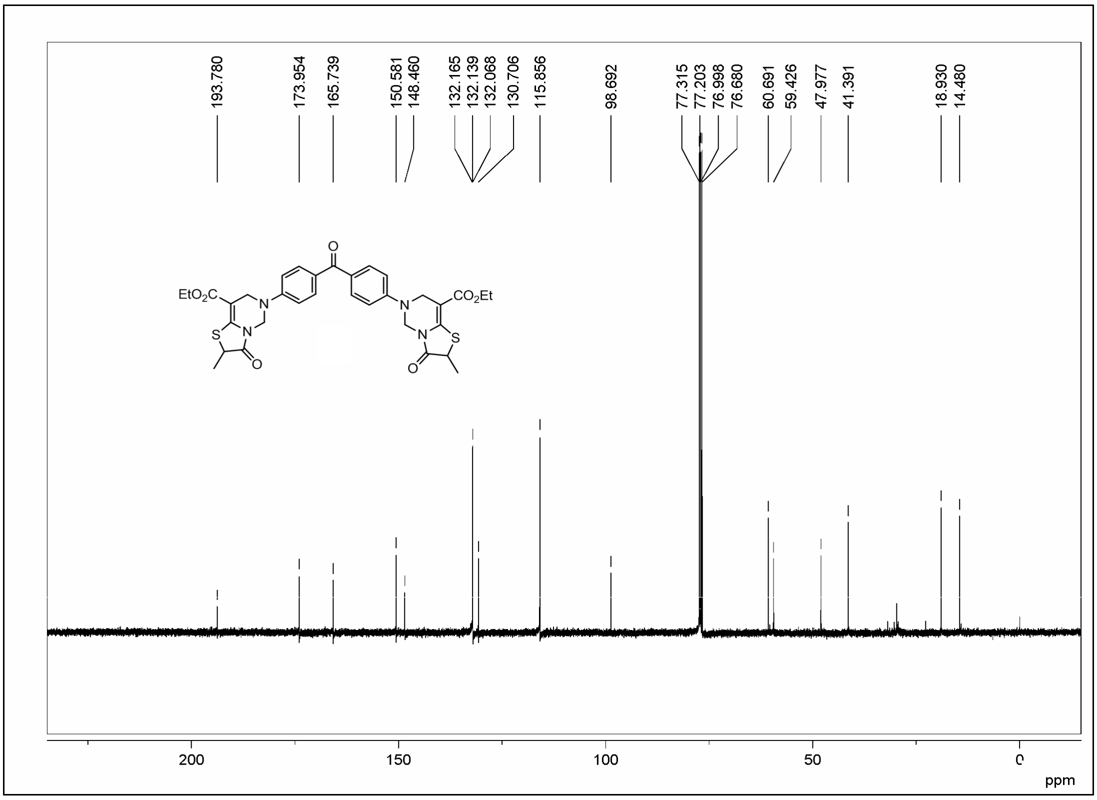
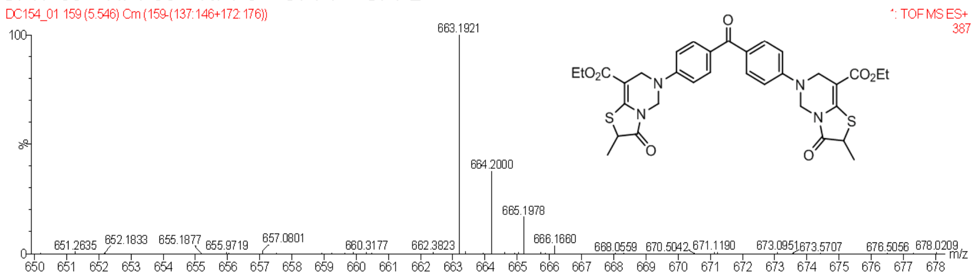


Figure 7. 128. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **259s**

Elemental Composition Report

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
76 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 17-33 H: 1-50 N: 1-6 O: 1-7 S: 1-2



Minimum:				-1.5			
Maximum:		5.0	5.0	50.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
663.1921	663.1947	-2.6	-3.9	18.5	16.2	0.0	C33 H35 N4 O7 S2

Figure 7. 129. HRMS and elemental composition of compound **259s**

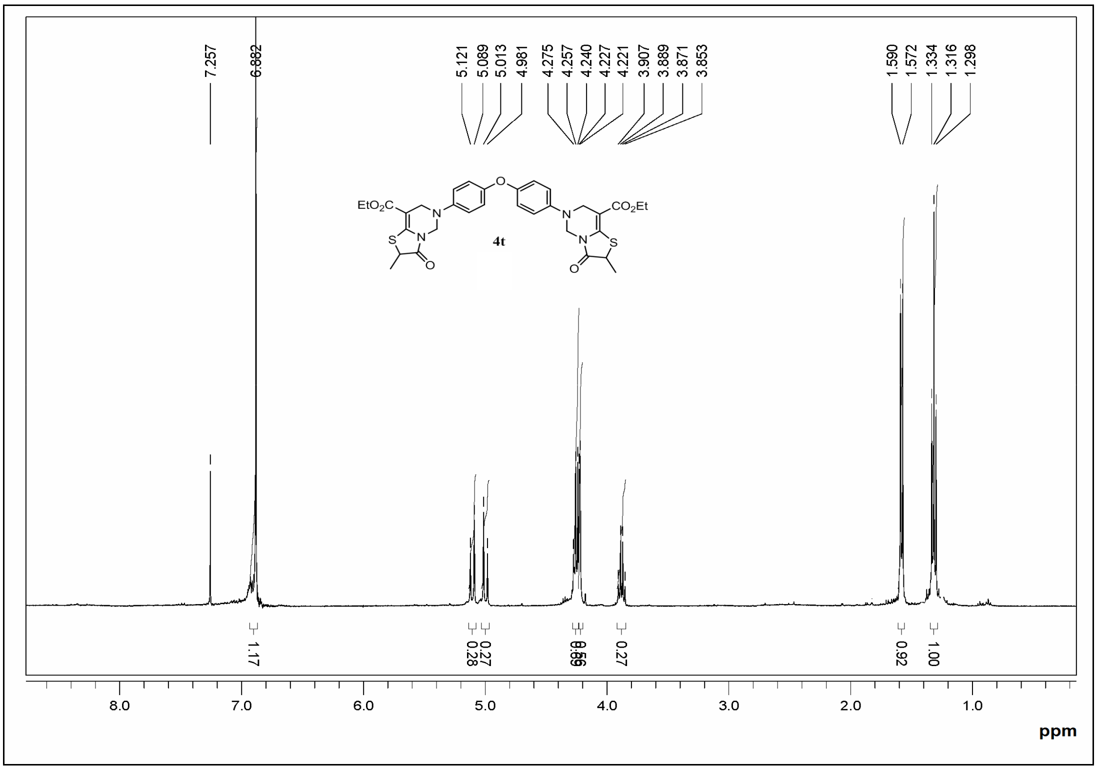


Figure 7. 130. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **259t**

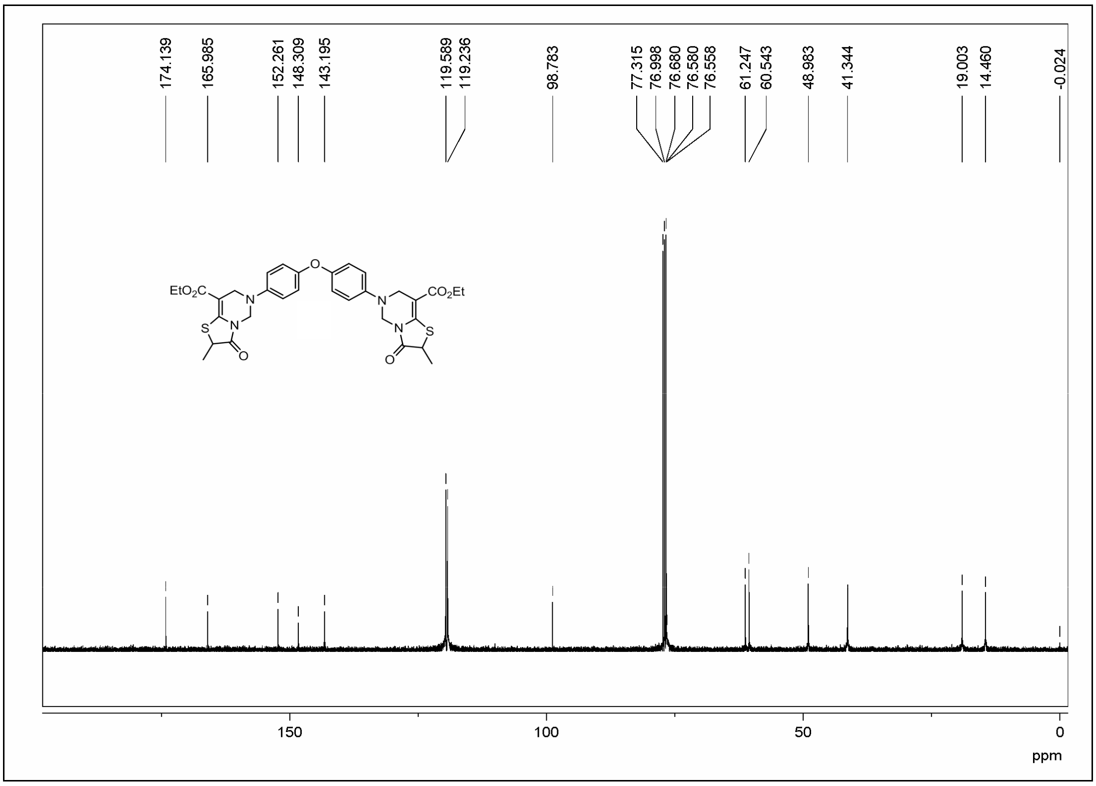
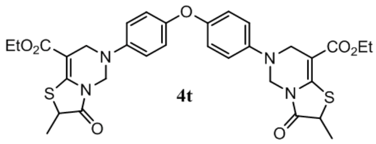


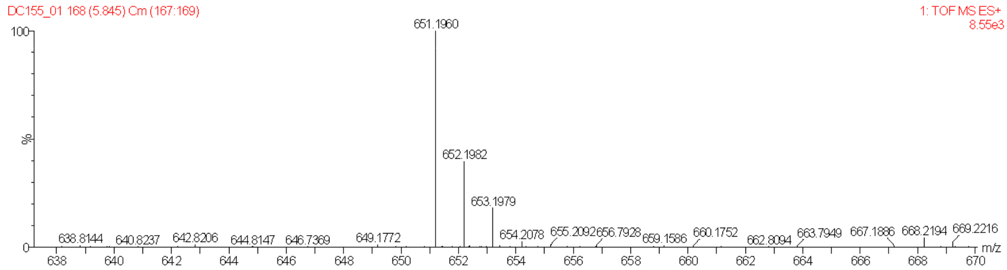
Figure 7. 131. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **259t**

Elemental Composition Report

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3



Monoisotopic Mass, Even Electron Ions
117 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 32-33 H: 1-50 N: 1-6 O: 1-7 S: 1-3



Minimum:				-1.5			
Maximum:		5.0	5.0	50.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
651.1960	651.1947	1.3	2.0	17.5	125.8	0.0	C32 H35 N4 O7 S2

Figure 7. 132. HRMS and elemental composition of compound **259t**

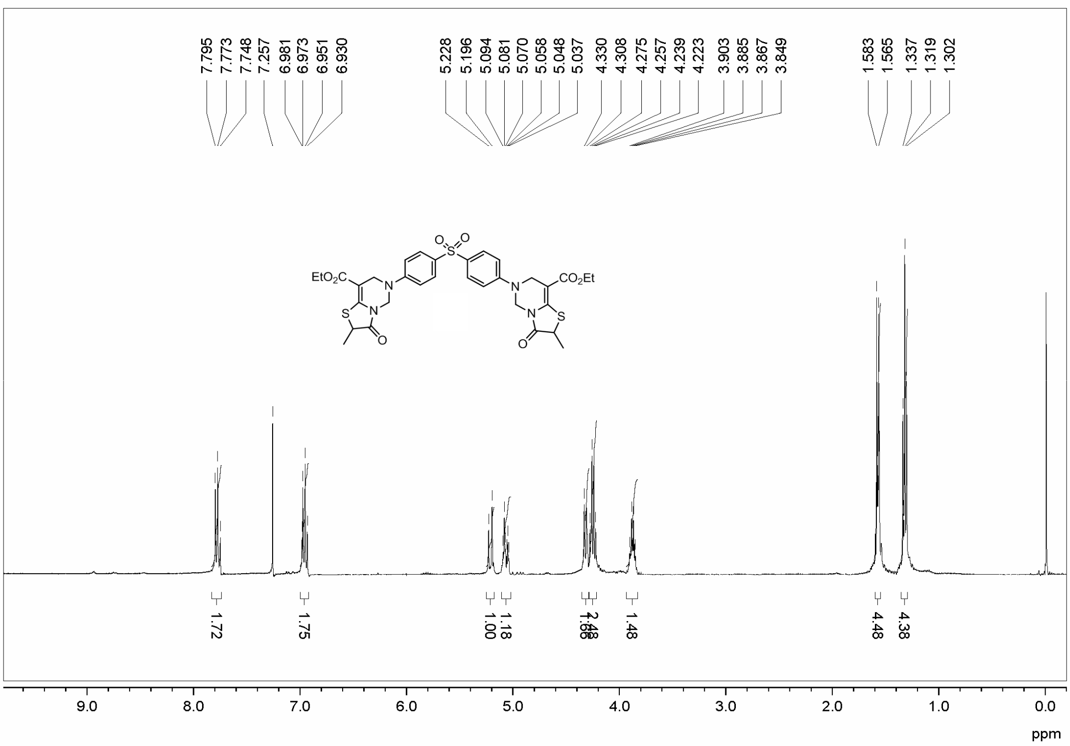


Figure 7. 133. ¹H NMR (400 MHz, $CDCl_3$) spectrum of compound **259u**

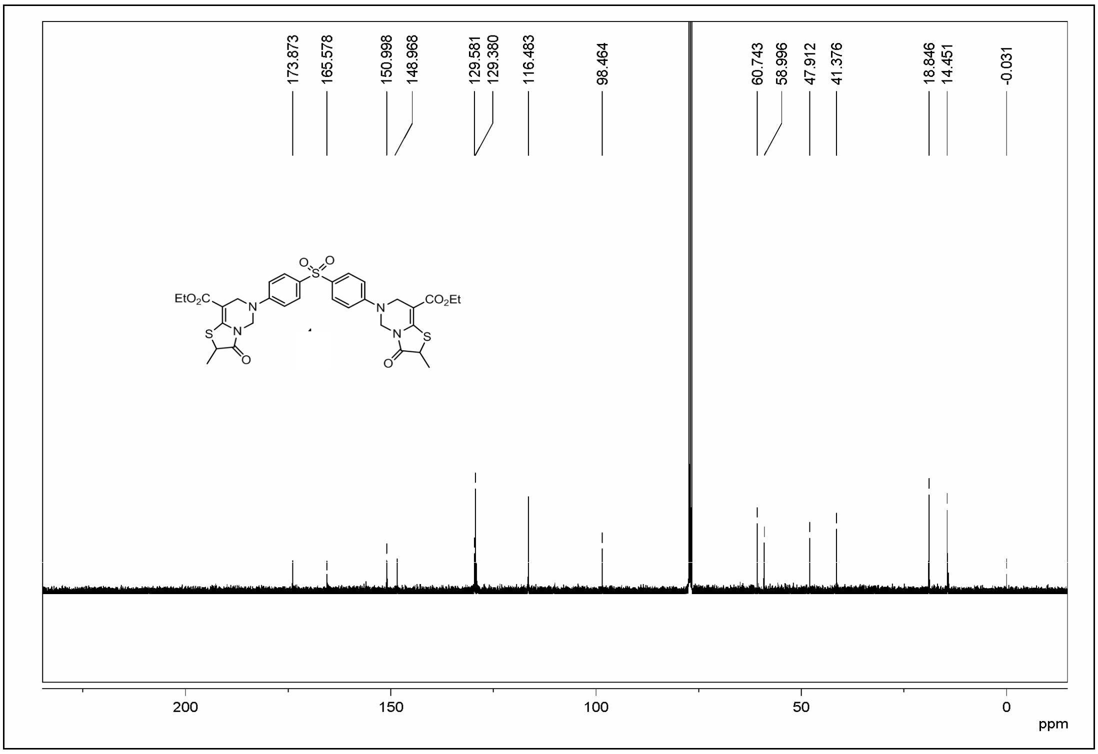


Figure 7. 134. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **259u**

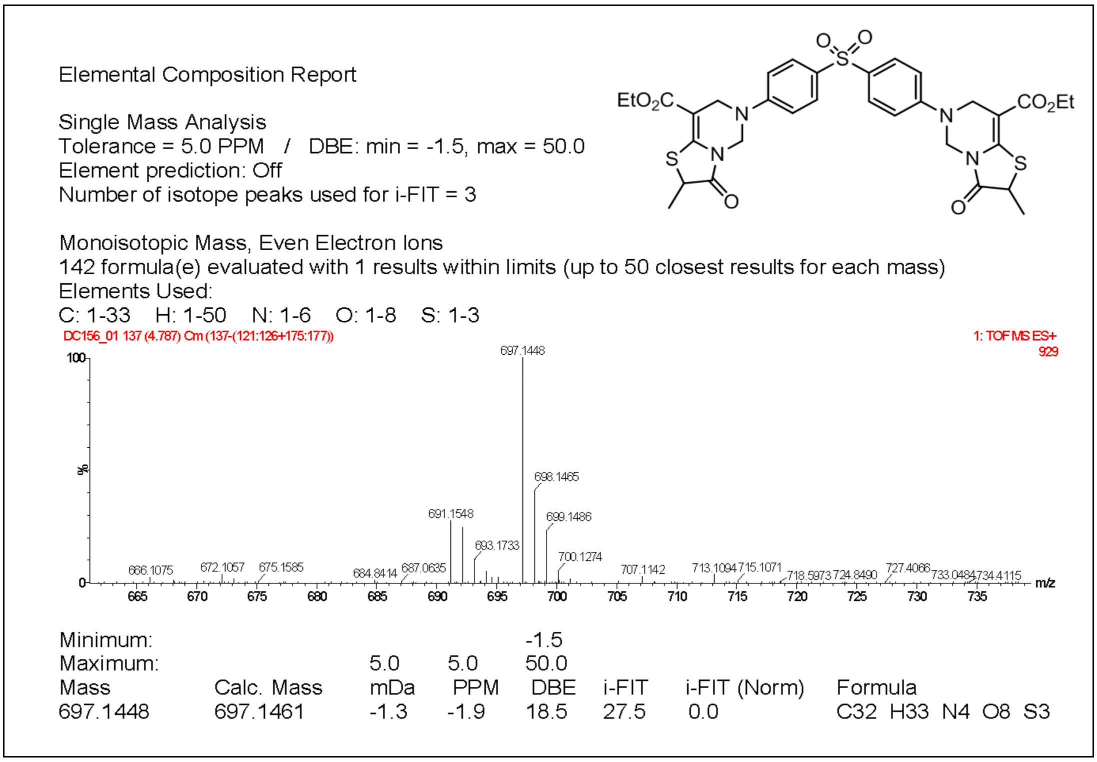


Figure 7. 135. HRMS and elemental composition of compound **259u**

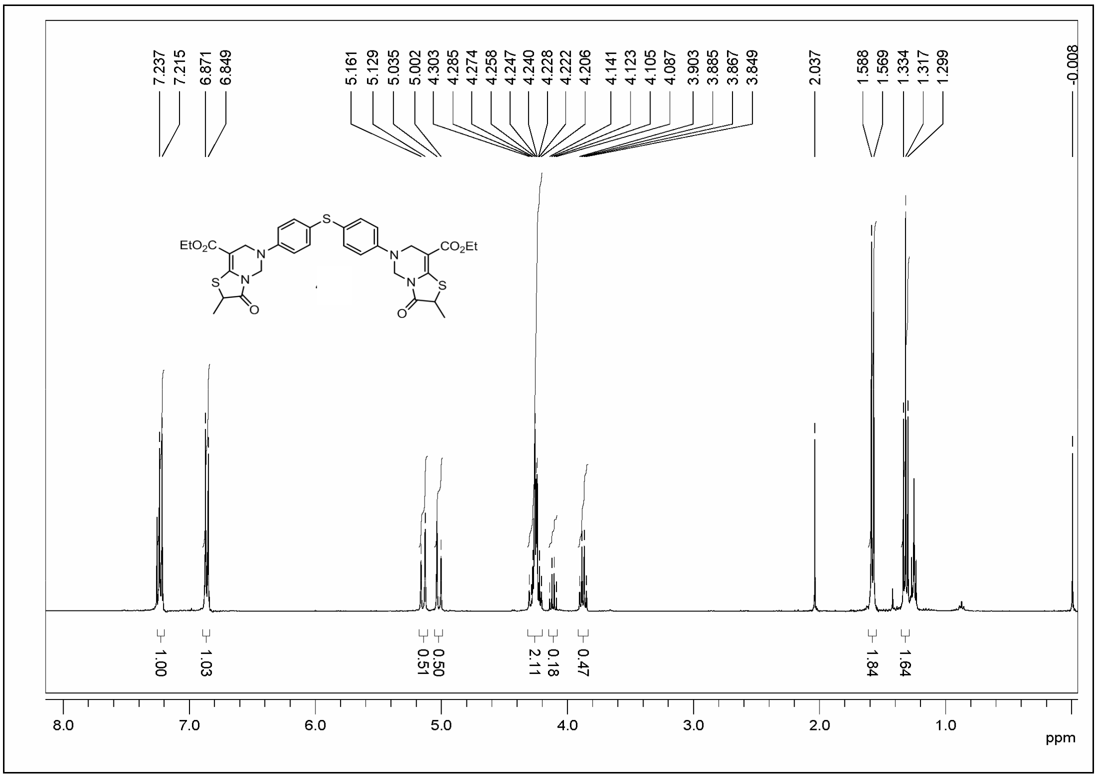


Figure 7. 136. ^{1}H NMR (400 MHz, CDCl3) spectrum of compound **259v**

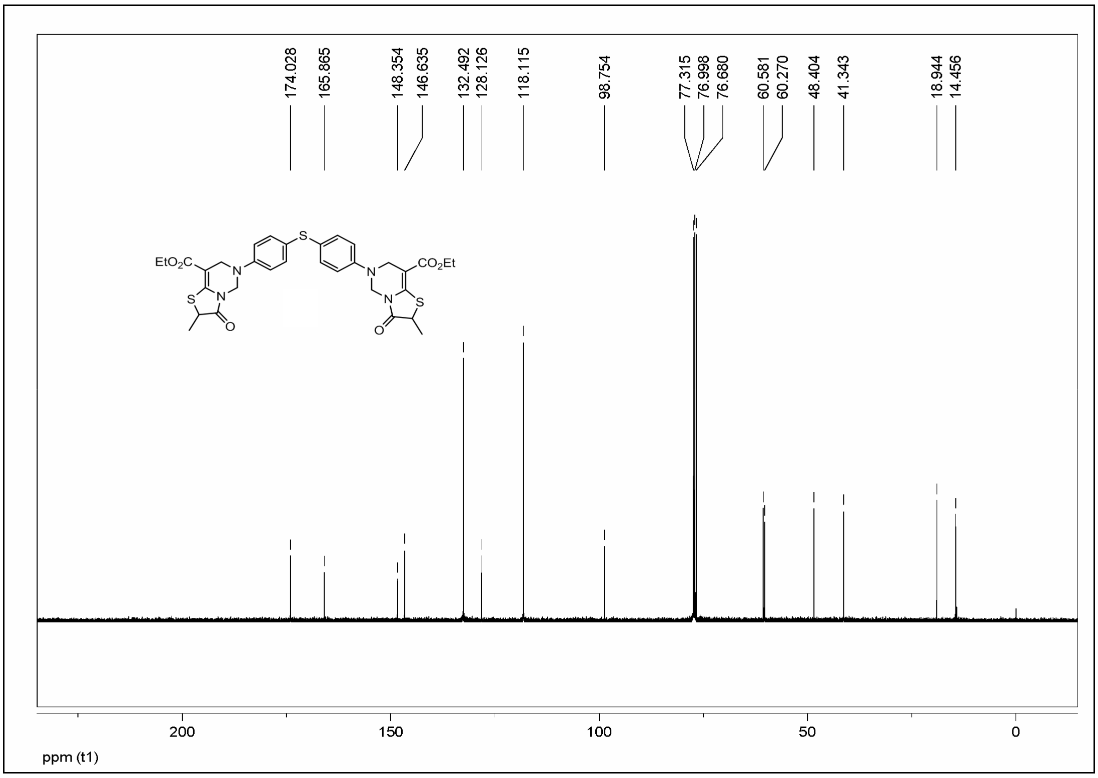


Figure 7. 137. ^{13}C NMR (100 MHz, CDCl3) spectrum of compound **259v**

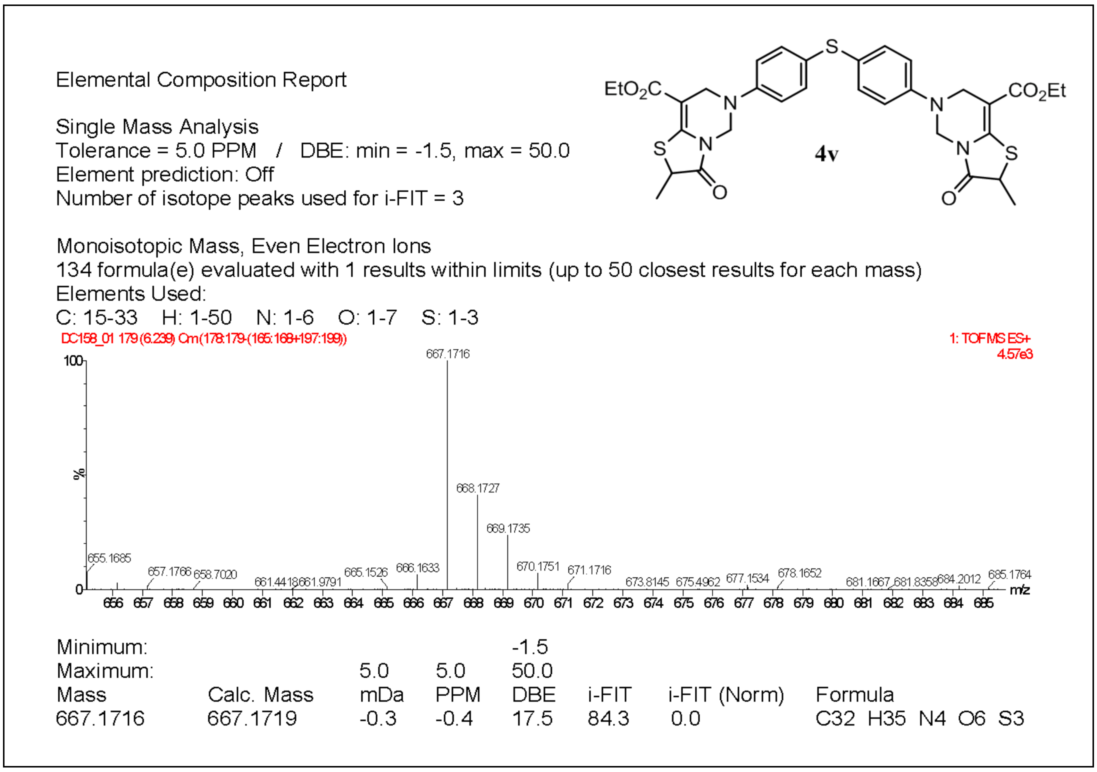


Figure 7. 138. HRMS and elemental composition of compound **259v**

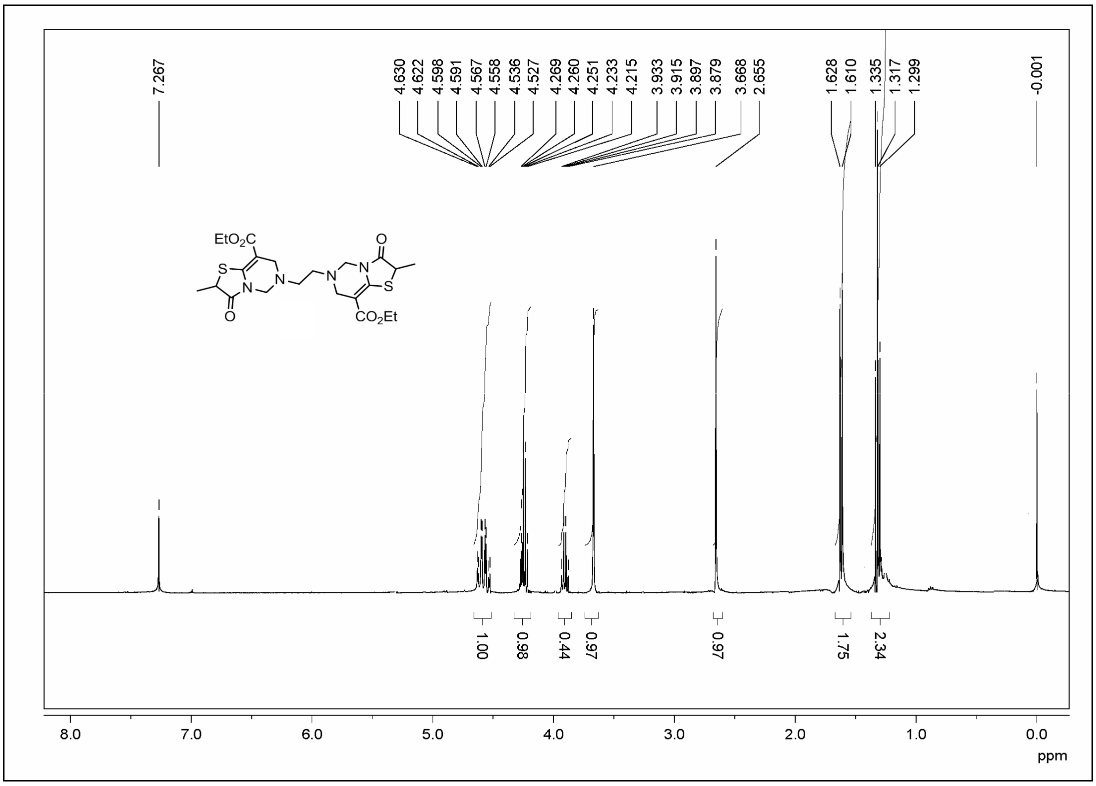


Figure 7. 139. [1]H NMR (400 MHz, CDCl3) spectrum of compound **259y**

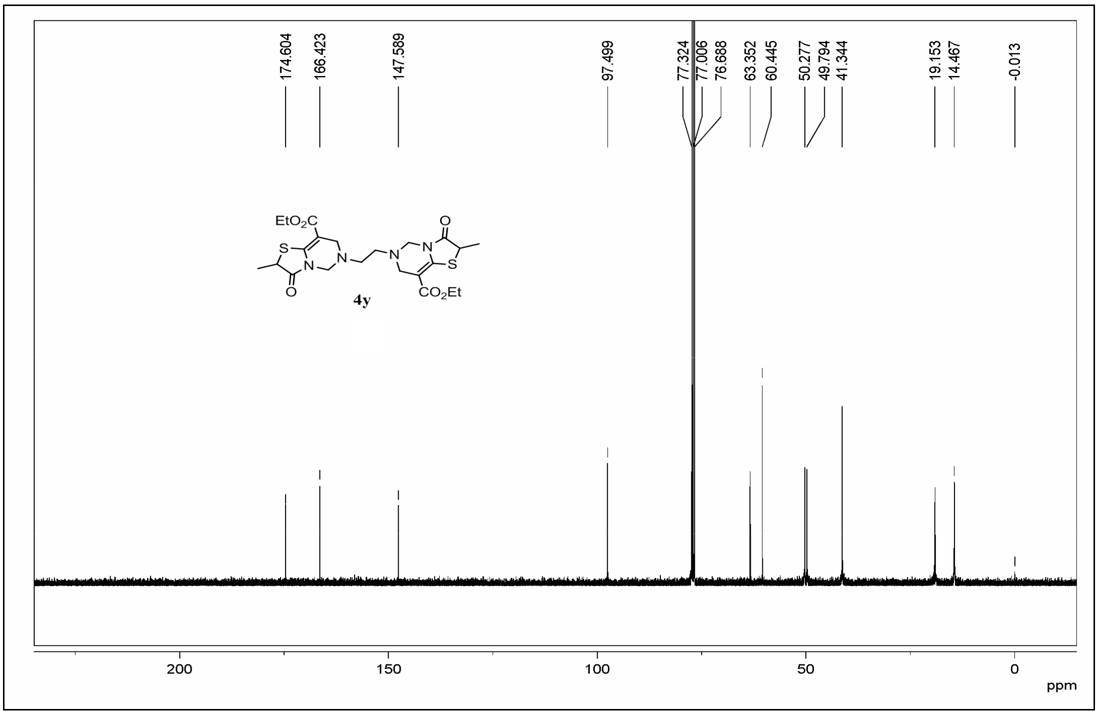
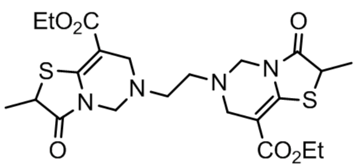


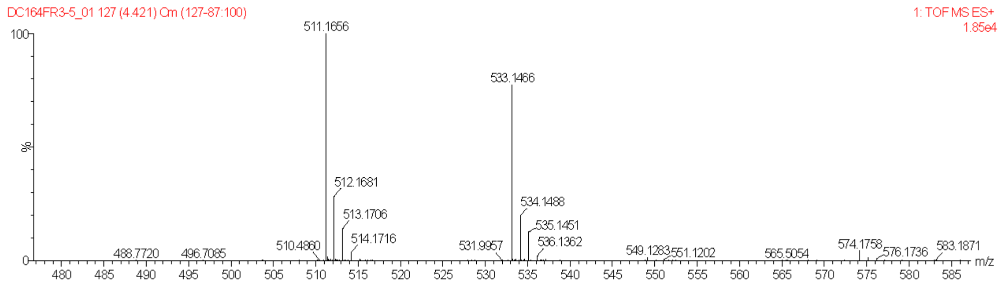
Figure 7. 140. ^{13}C NMR (100 MHz, CDCl3) spectrum of compound **259y**

Elemental Composition Report



Single Mass Analysis
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
135 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 22-22 H: 1-50 N: 1-6 O: 1-8 S: 1-3



Minimum:				-1.5			
Maximum:		5.0	10.0	50.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
511.1656	511.1685	-2.9	-5.7	9.5	108.7	0.0	C22 H31 N4 O6 S2

Figure 7. 141. HRMS and elemental composition of compound **259y**

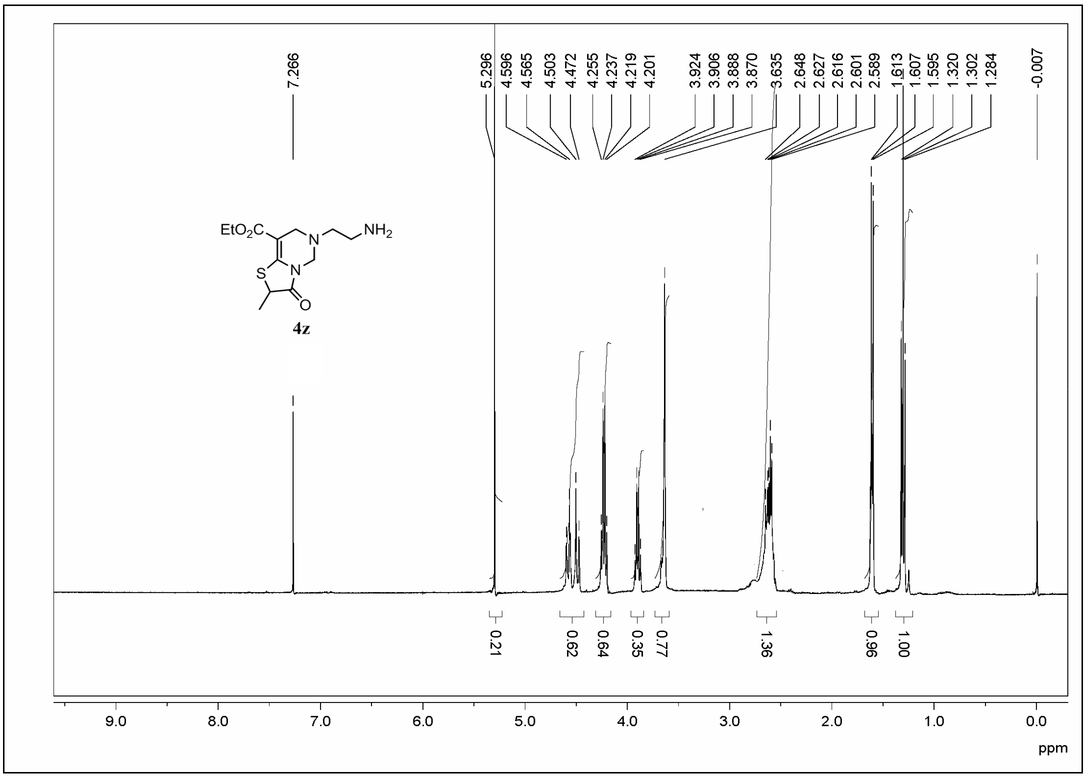


Figure 7. 142. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **259z**

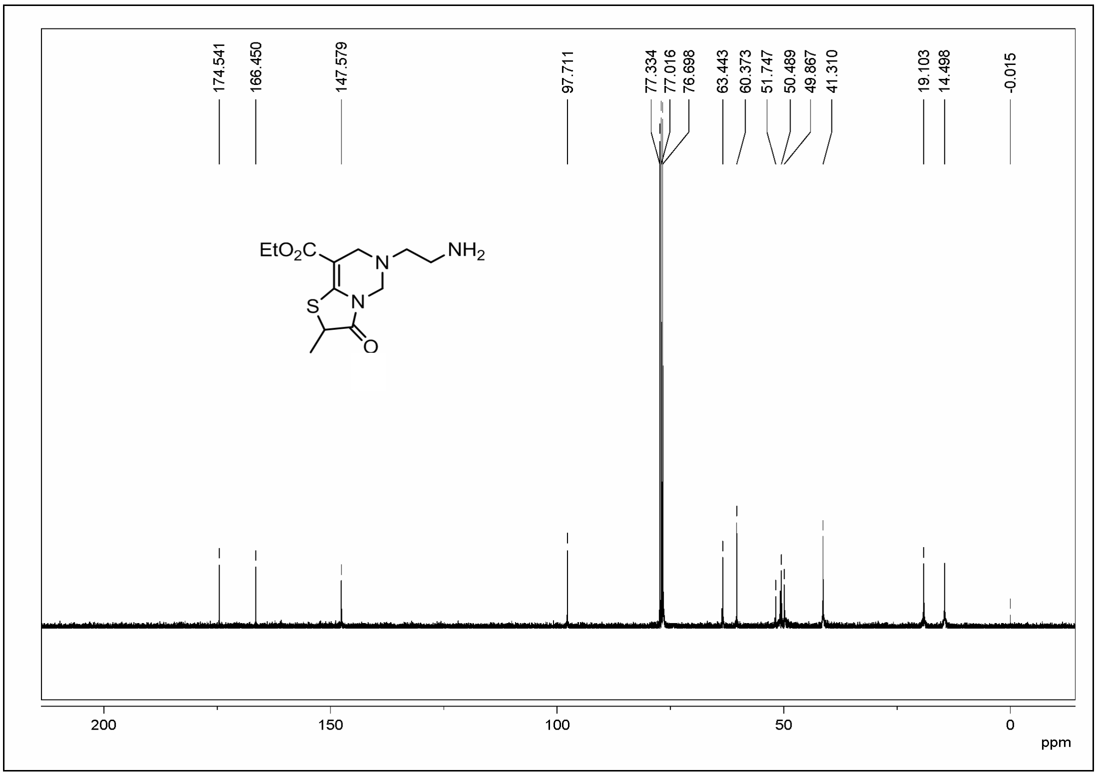


Figure 7. 143. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **259z**

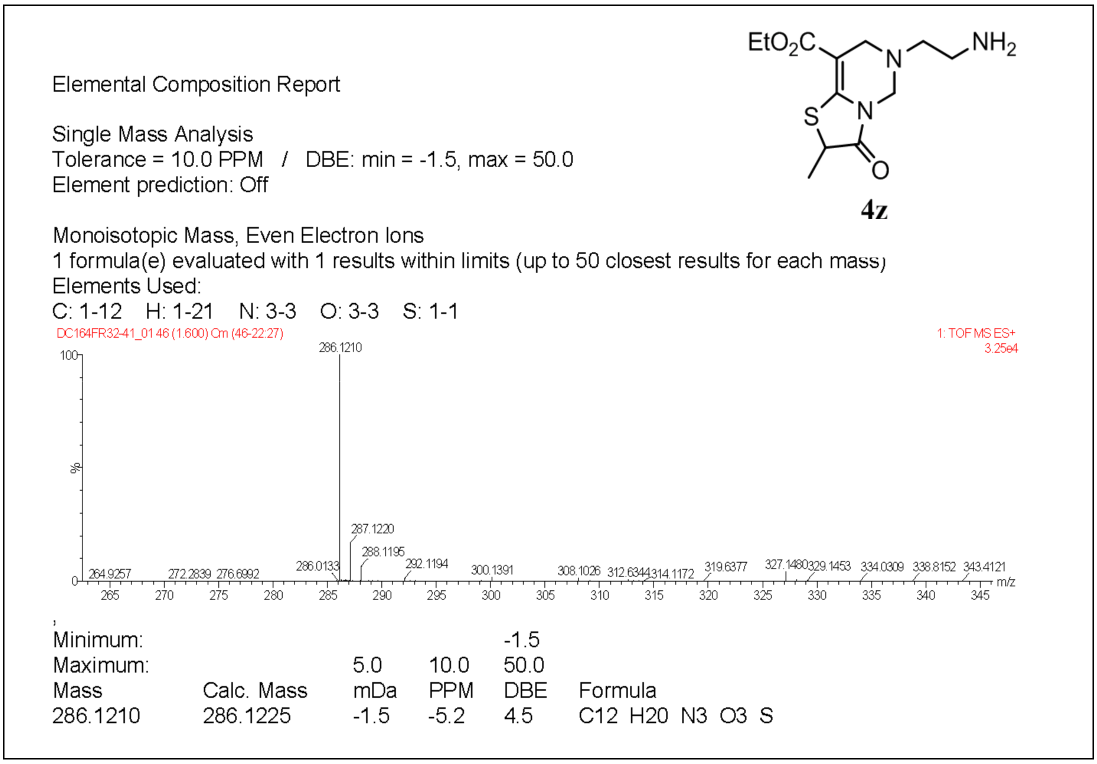


Figure 7. 144. HRMS and elemental composition of compound **259z**

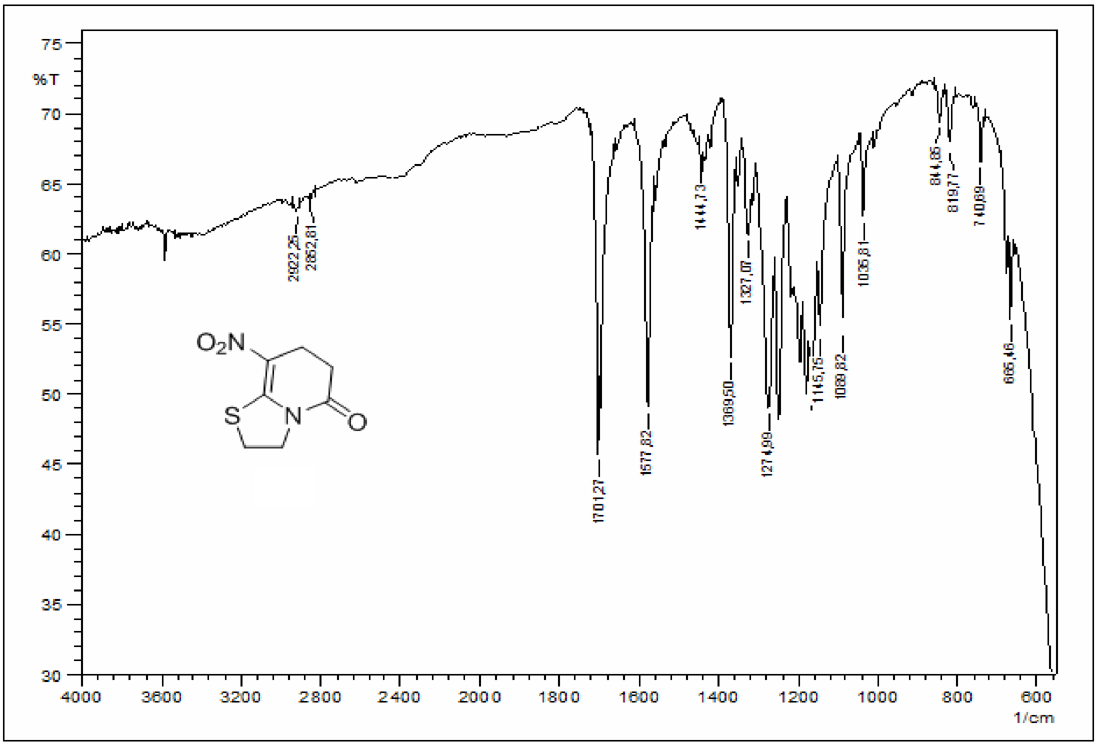


Figure 7. 145. IR spectrum of compound **260a**

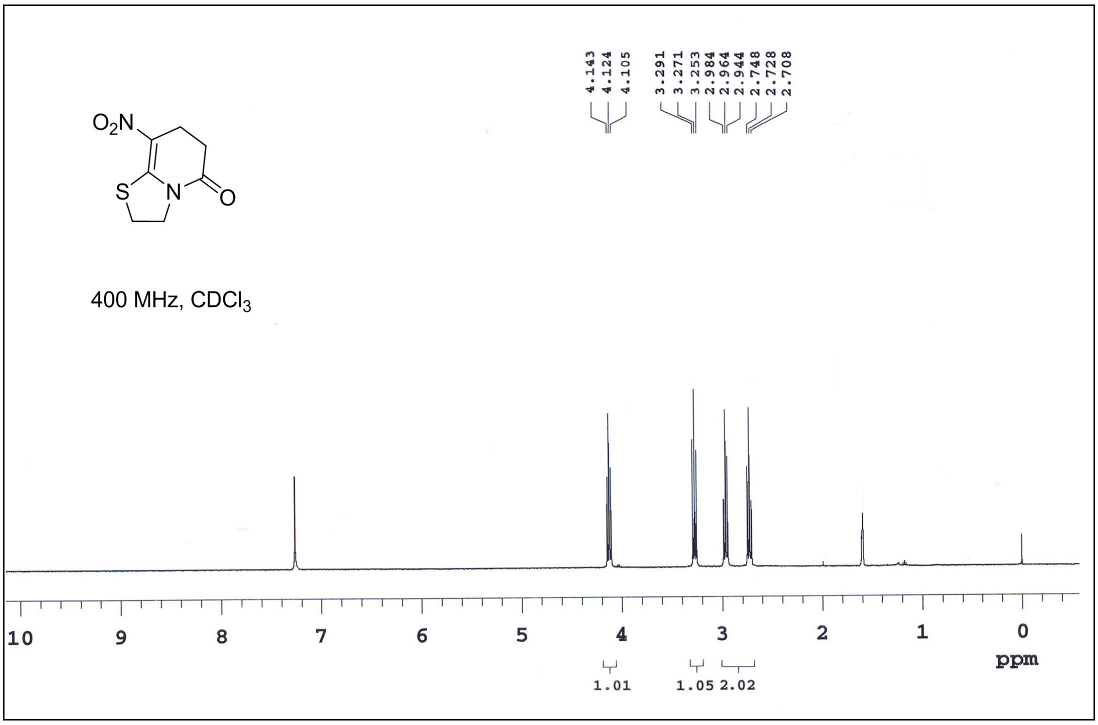


Figure 7. 146. ^{1}H NMR (400 MHz, CDCl3) spectrum of compound **260a**

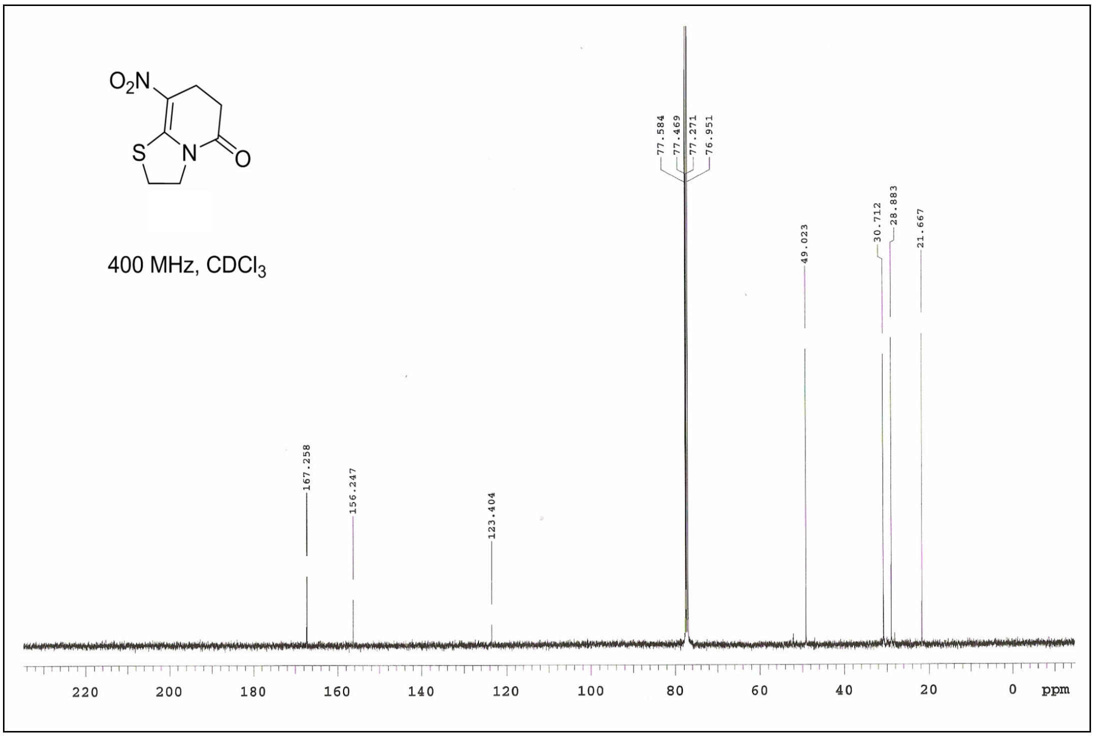
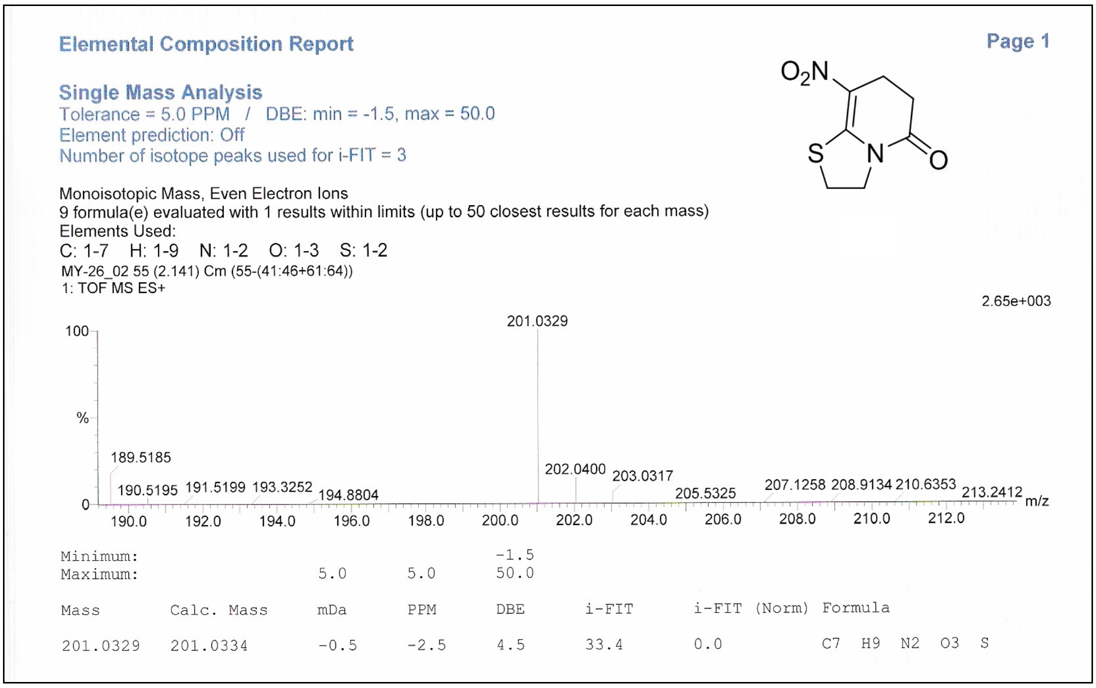


Figure 7. 147. ^{13}C NMR (100 MHz, CDCl3) spectrum of compound **260a**


Elemental Composition Report

Page 1

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
9 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 1-7 H: 1-9 N: 1-2 O: 1-3 S: 1-2
MY-26_02 55 (2.141) Cm (55-(41:46+61:64))
1: TOF MS ES+

Minimum:				-1.5			
Maximum:		5.0	5.0	50.0			

Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
201.0329	201.0334	-0.5	-2.5	4.5	33.4	0.0	C7 H9 N2 O3 S

Figure 7. 148. HRMS and elemental composition of compound **260a**

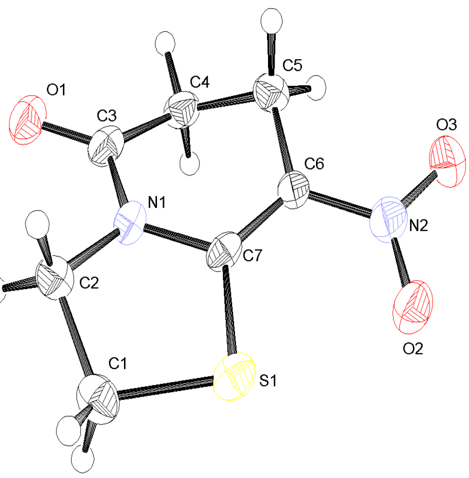


Figure 7. 149. X-ray structure of **260a**

Table 7. 4. Crystal data and structure refinement for **260a**.

Identification code	dwk1201	
Empirical formula	C7 H8 N2 O3 S	
Formula weight	200.21	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P21/a	
Unit cell dimensions	a = 10.2058(17) Å	α= 90°.
b = 5.8378(14) Å	β = 107.347(11)°.	
c = 14.398(2) Å	γ = 90°.	
Volume	818.8(3) $Å^3$	
Z	4	
Density (calculated)	1.624 Mg/m^3	
Absorption coefficient	0.368 mm^{-1}	
F(000)	416	
Crystal size	0.40 x 0.40 x 0.02 mm^3	
Theta range for data collection	2.96 to 27.50°.	
Index ranges	-13<=h<=13, -6<=k<=7, -18<=l<=18	
Reflections collected	2574	
Independent reflections	1609 [R(int) = 0.0645]	
Completeness to theta = 25.00°	95.5 %	
Absorption correction	Empirical	
Max. and min. transmission	0.9927 and 0.8666	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1609 / 0 / 118	
Goodness-of-fit on F^2	1.059	
Final R indices [I>2sigma(I)]	R1 = 0.0607, wR2 = 0.1314	
R indices (all data)	R1 = 0.0962, wR2 = 0.1508	
Largest diff. peak and hole	0.435 and -0.373 e.$Å^{-3}$	

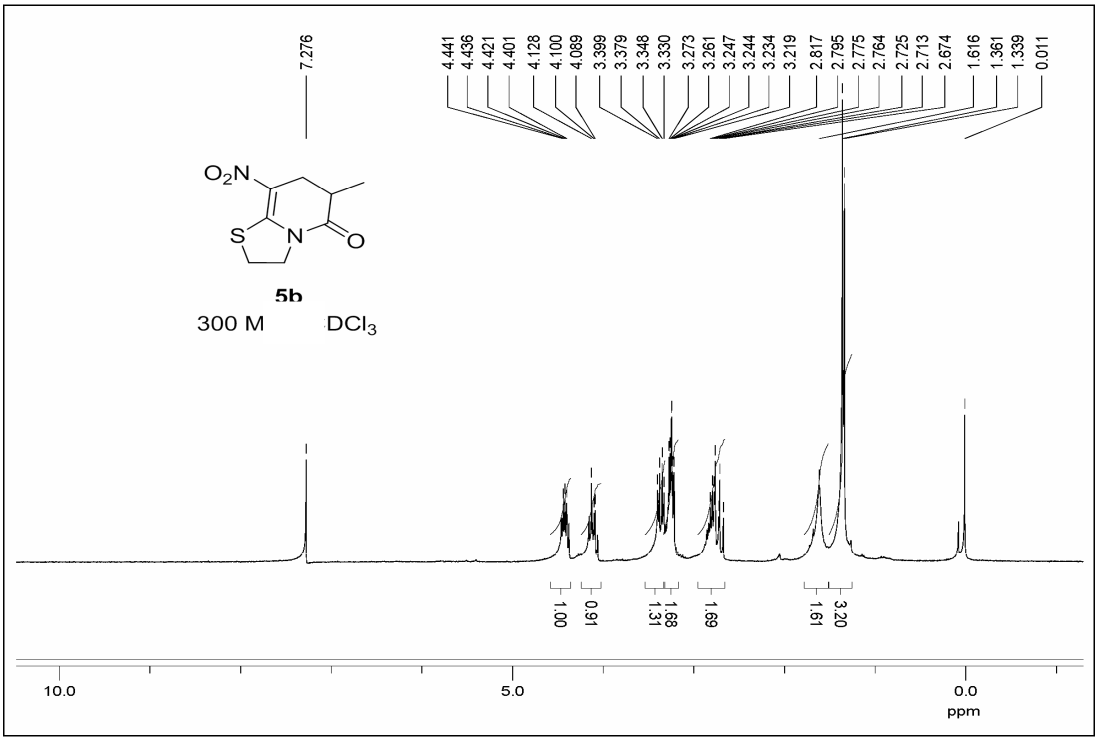


Figure 7. 150. ^{1}H NMR (400 MHz, CDCl3) spectrum of compound **260b**

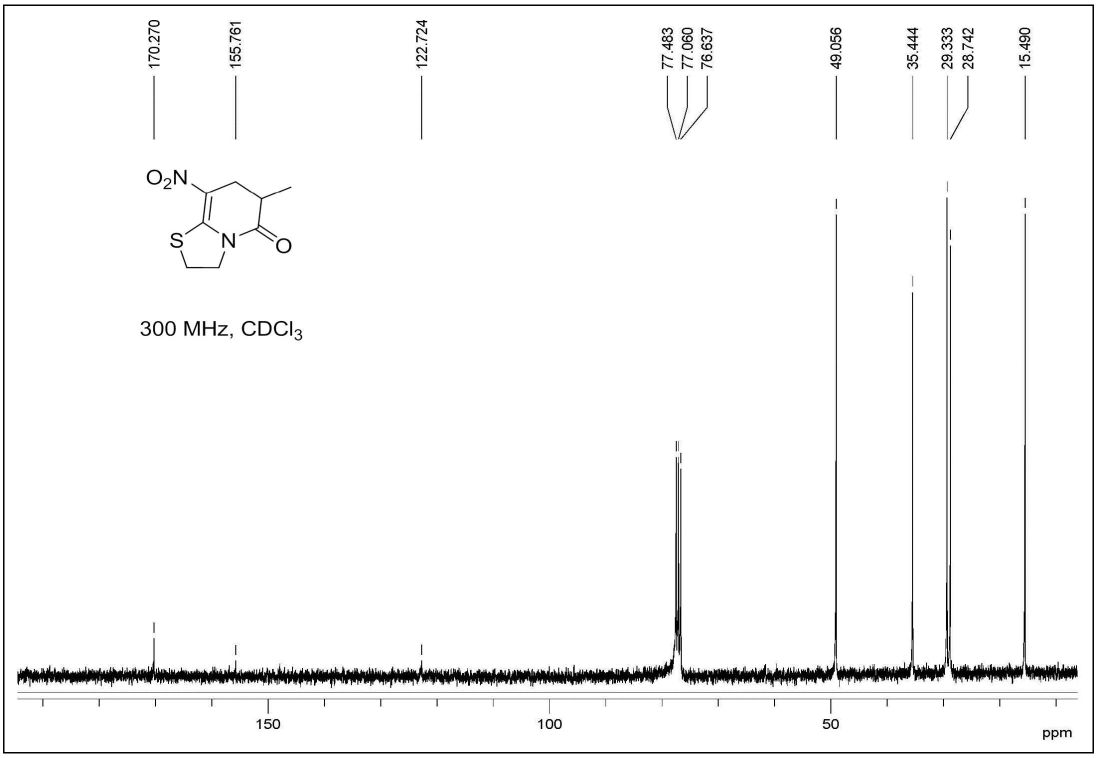
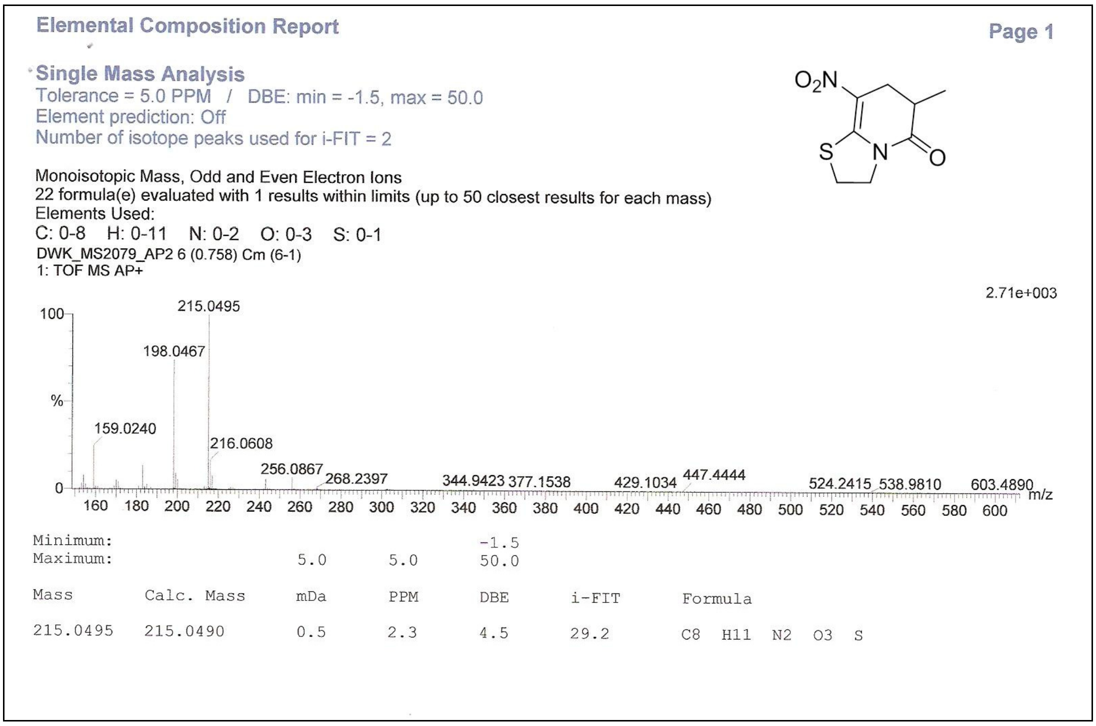


Figure 7. 151. ^{13}C NMR (100 MHz, CDCl3) spectrum of compound **260b**



Elemental Composition Report

Page 1

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 2

Monoisotopic Mass, Odd and Even Electron Ions
22 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-8 H: 0-11 N: 0-2 O: 0-3 S: 0-1
DWK_MS2079_AP2 6 (0.758) Cm (6-1)
1: TOF MS AP+

Minimum:				-1.5		
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
215.0495	215.0490	0.5	2.3	4.5	29.2	C8 H11 N2 O3 S

Figure 7. 152. HRMS and elemental composition of compound **260b**

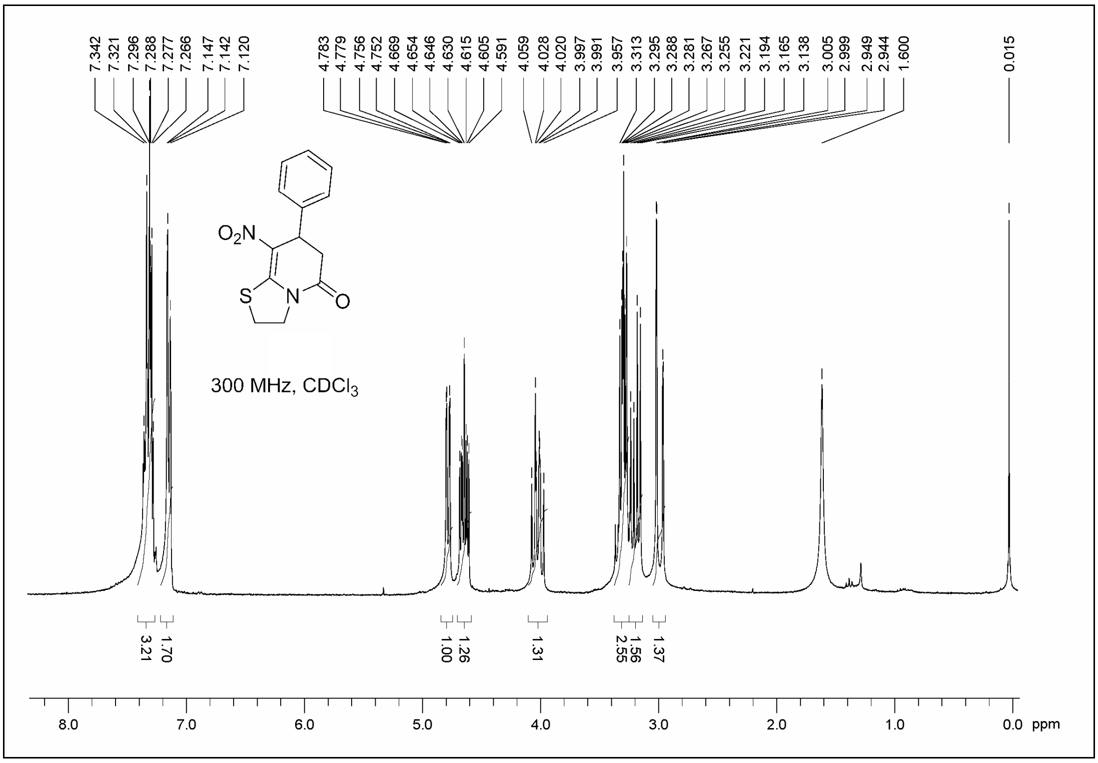


Figure 7. 153. [1]H NMR (400 MHz, CDCl3) spectrum of compound **260c**

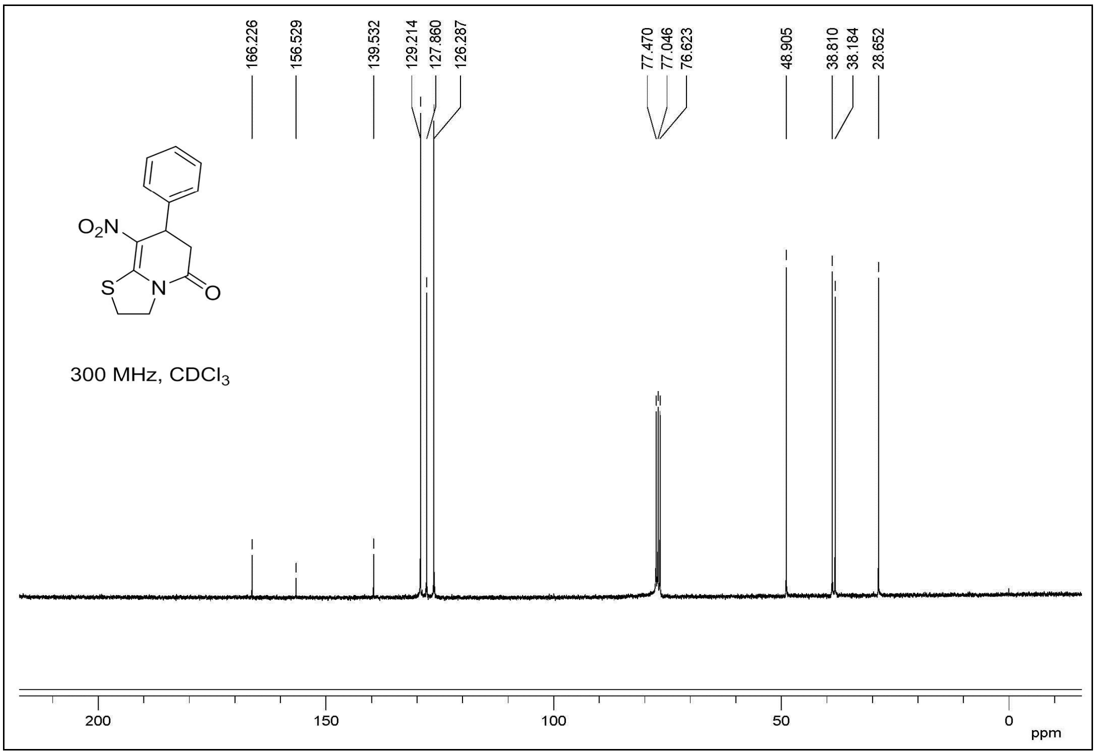


Figure 7. 154. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **260c**

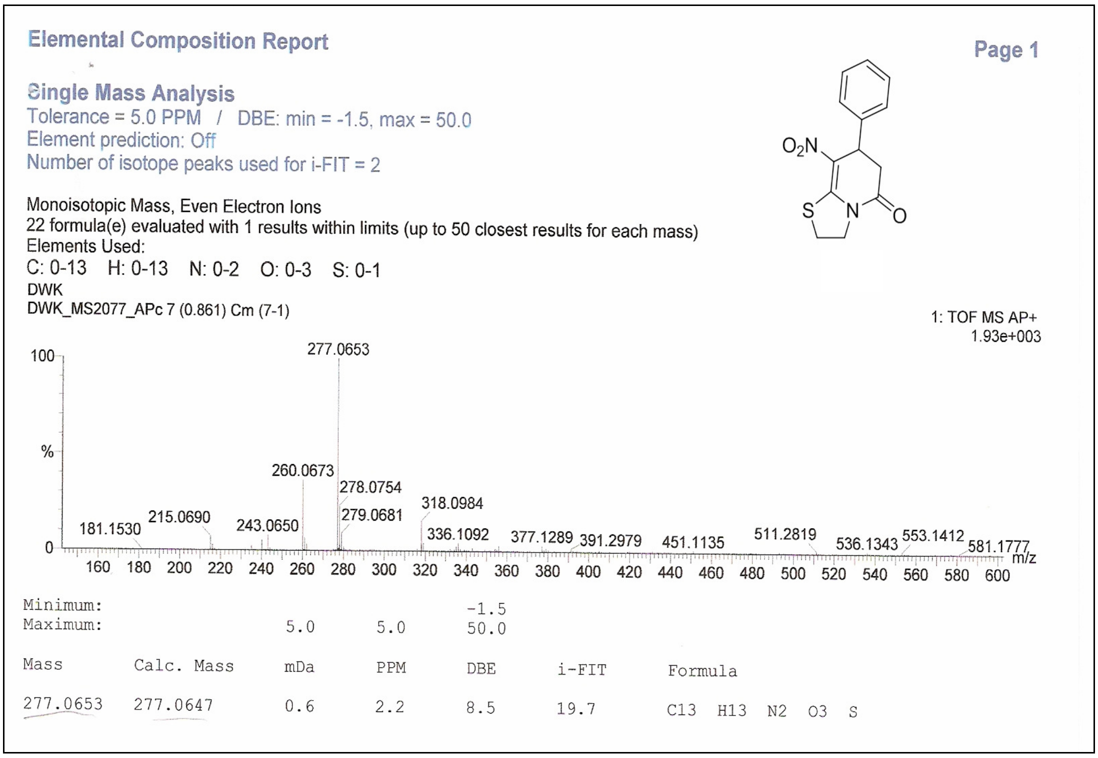


Figure 7. 155. HRMS and elemental composition of compound **260c**

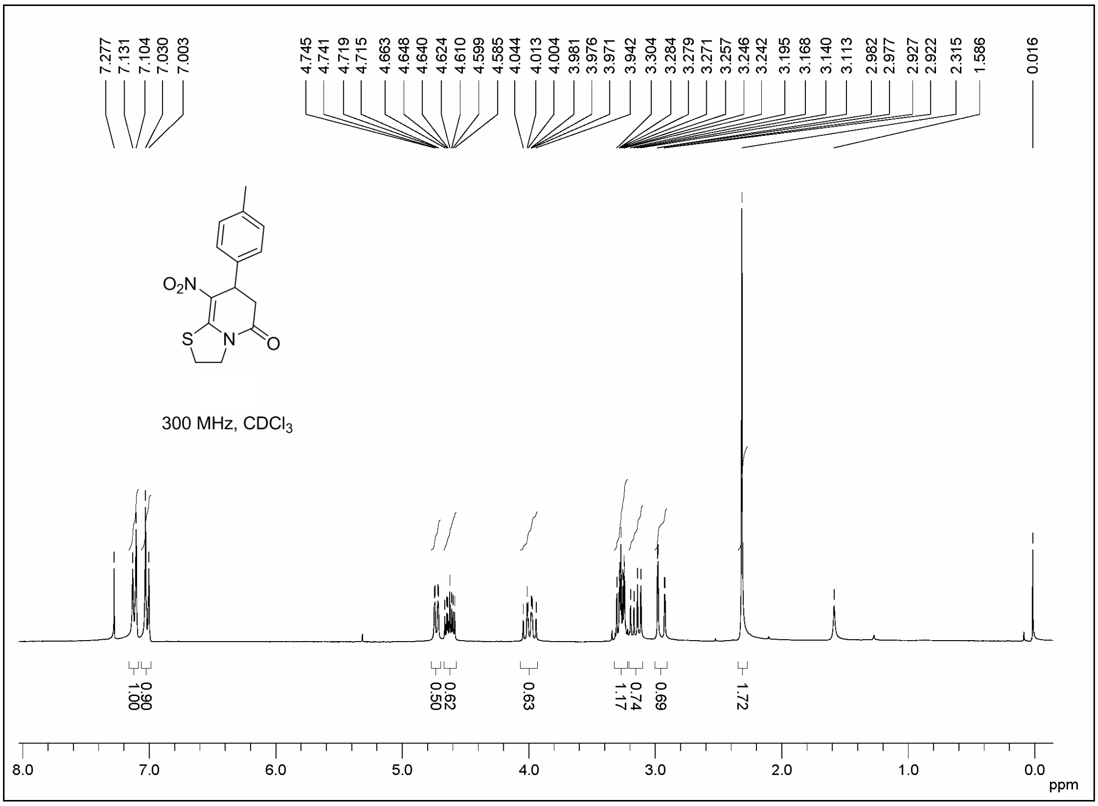


Figure 7. 156. ^{1}H NMR (400 MHz, CDCl3) spectrum of compound **260d**

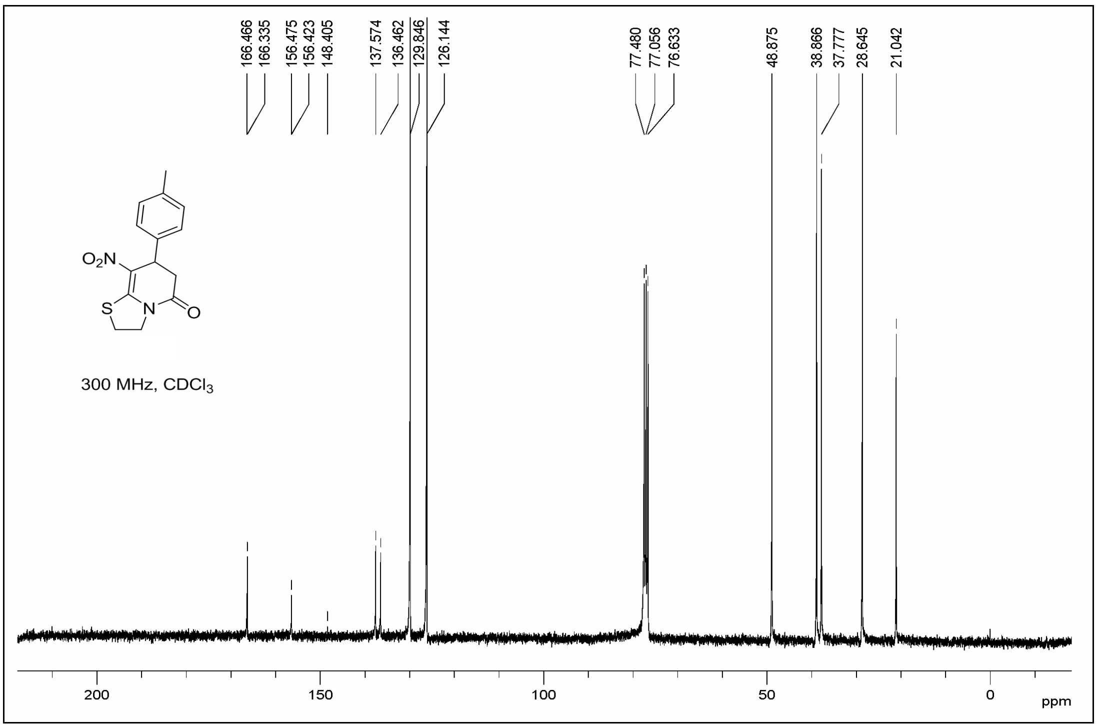


Figure 7. 157. ^{13}C NMR (100 MHz, CDCl3) spectrum of compound **260d**

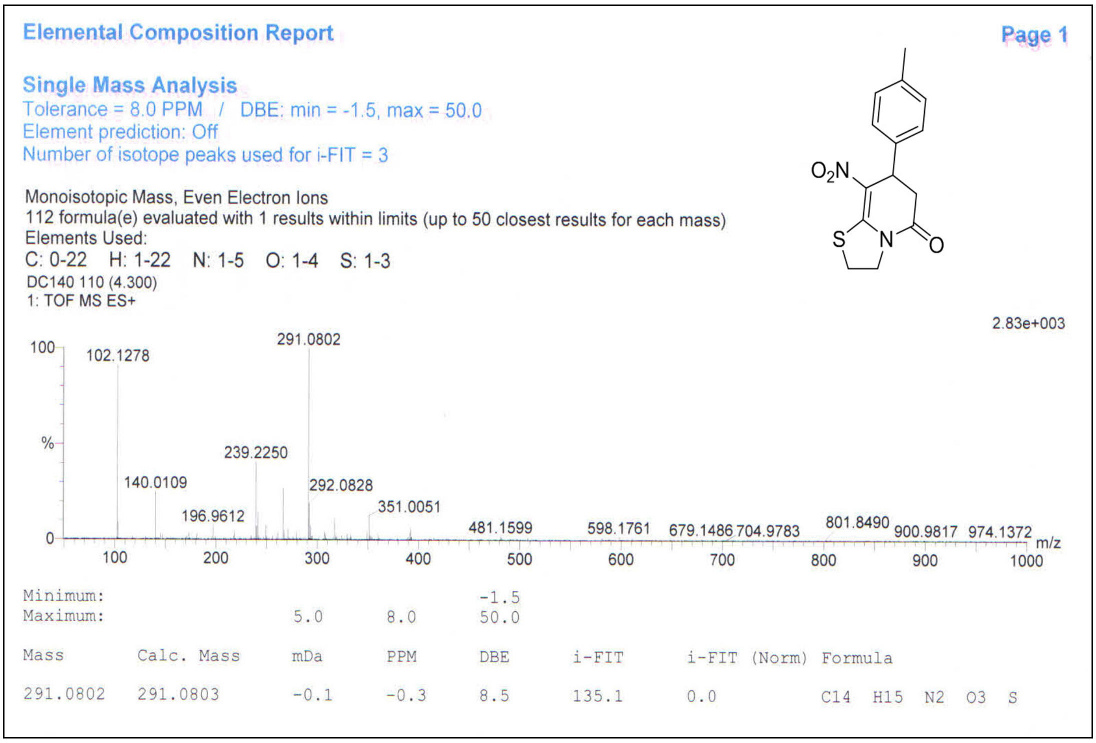


Figure 7. 158. HRMS and elemental composition of compound **260d**

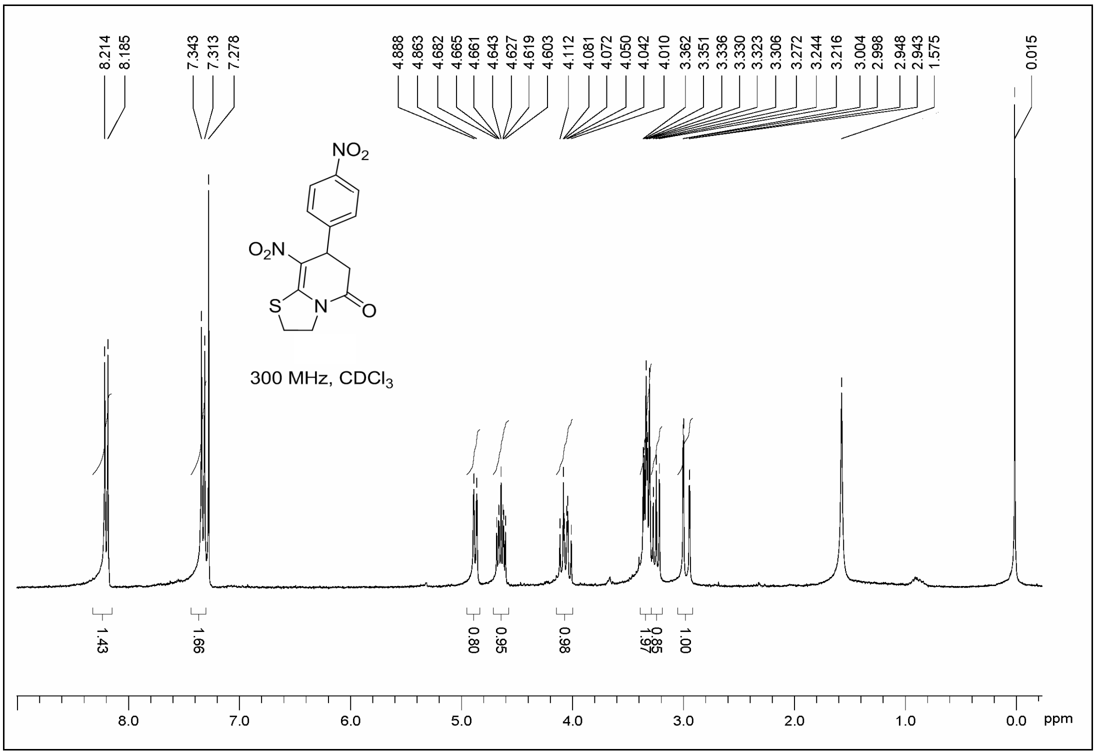


Figure 7. 159. [1]H NMR (400 MHz, $CDCl_3$) spectrum of compound **260e**

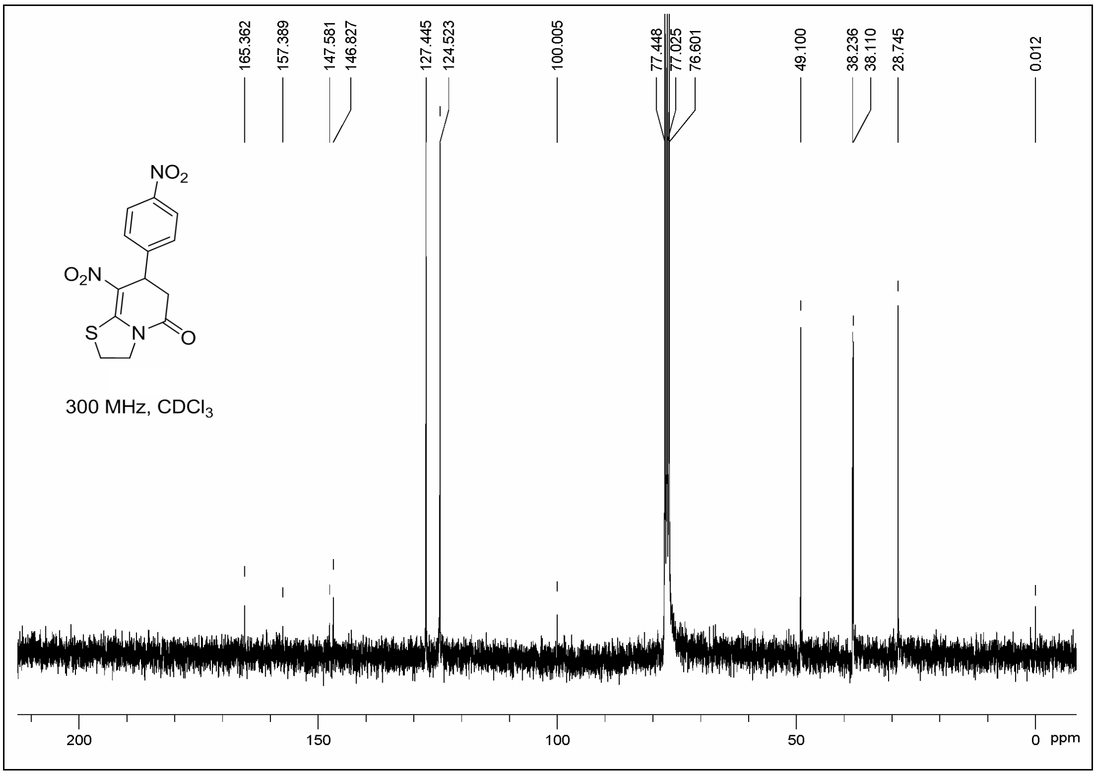


Figure 7. 160. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **260e**

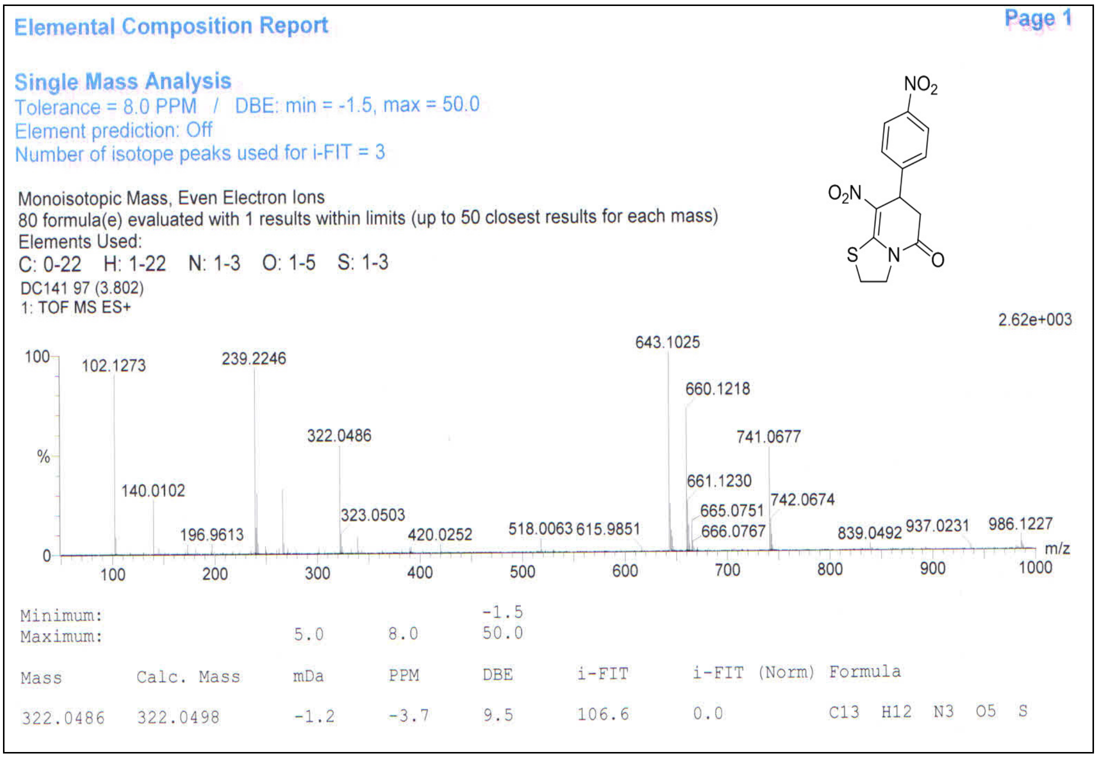


Figure 7. 161. HRMS and elemental composition of compound **260e**

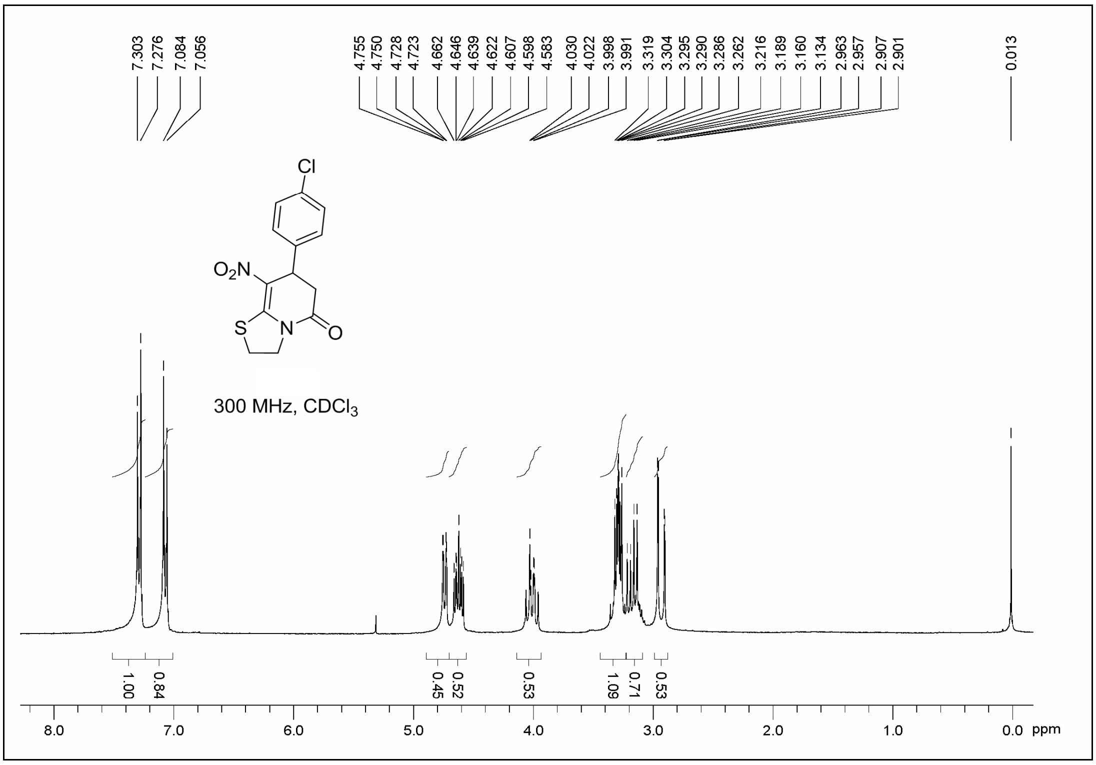


Figure 7. 162. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **260f**

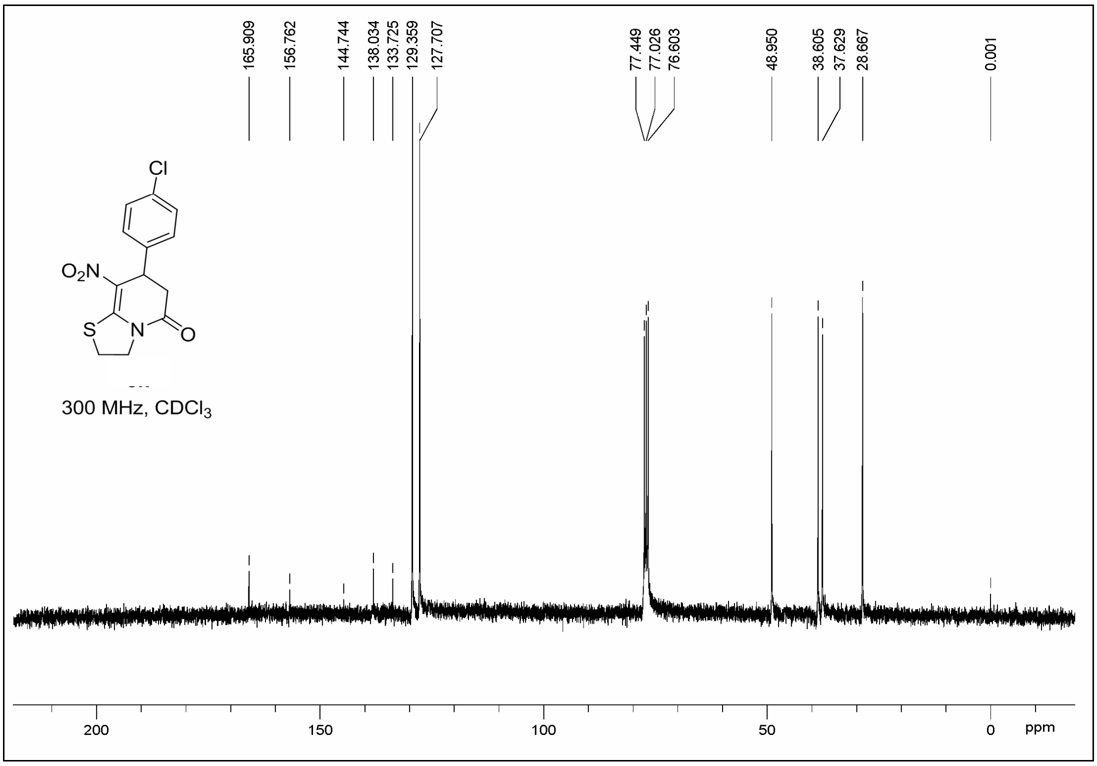


Figure 7. 163. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **260f**

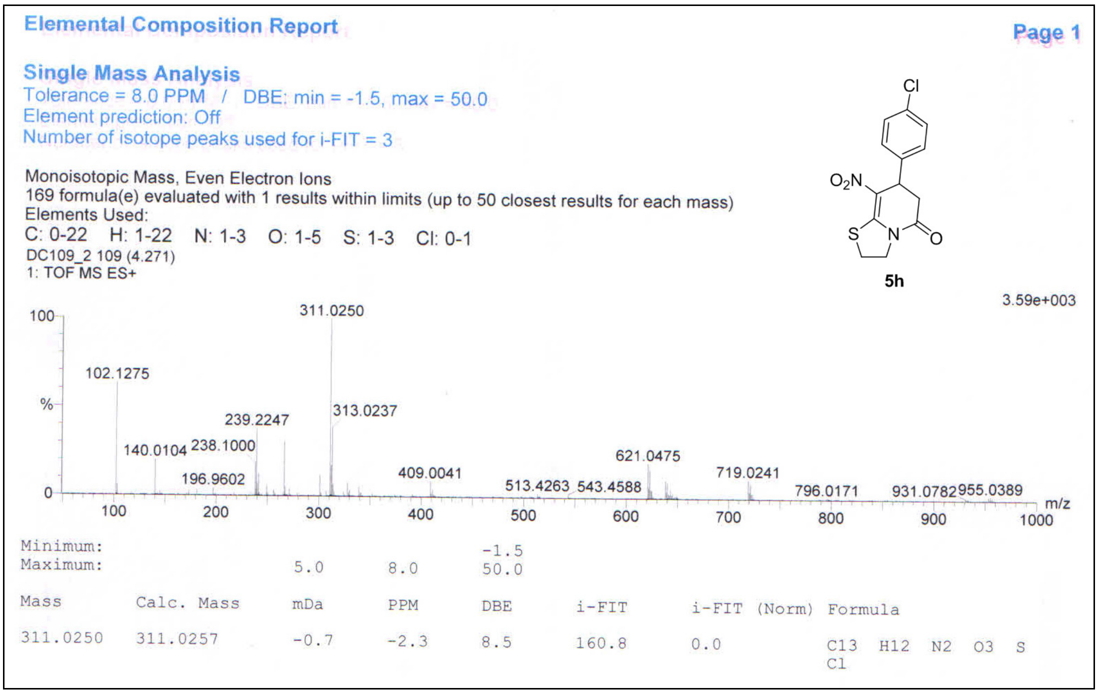


Figure 7. 164. HRMS and elemental composition of compound **260f**

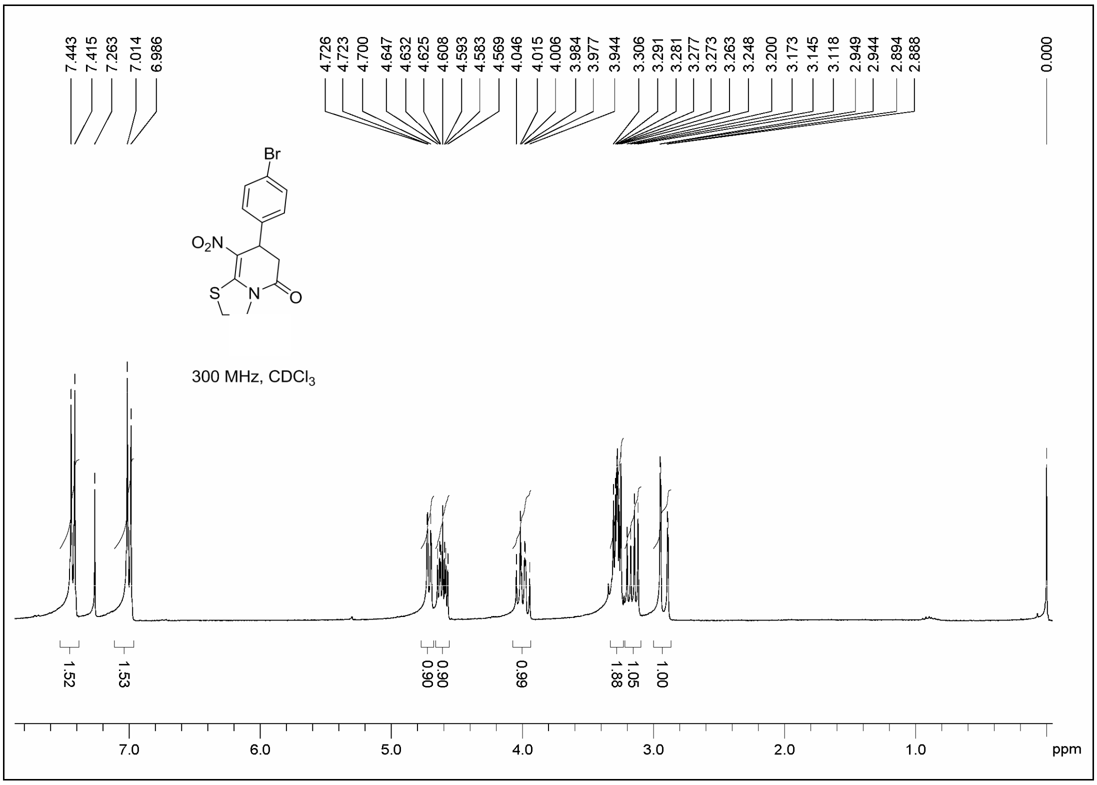


Figure 7. 165. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **260g**

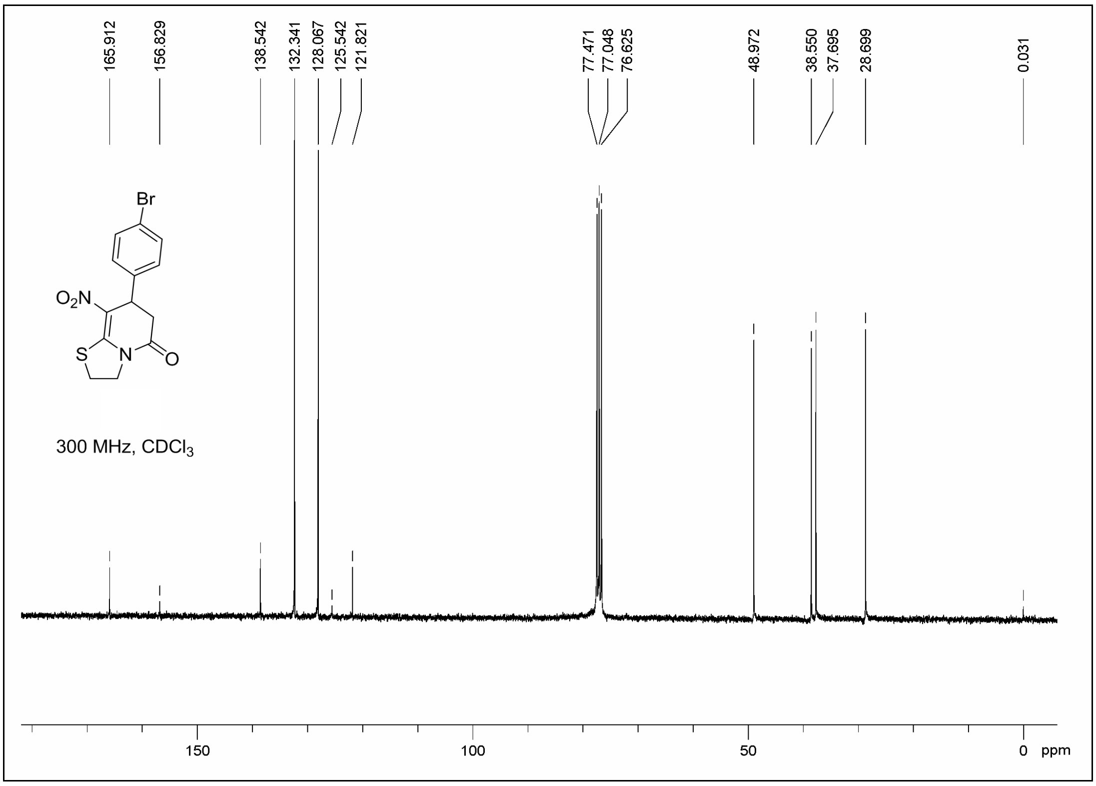
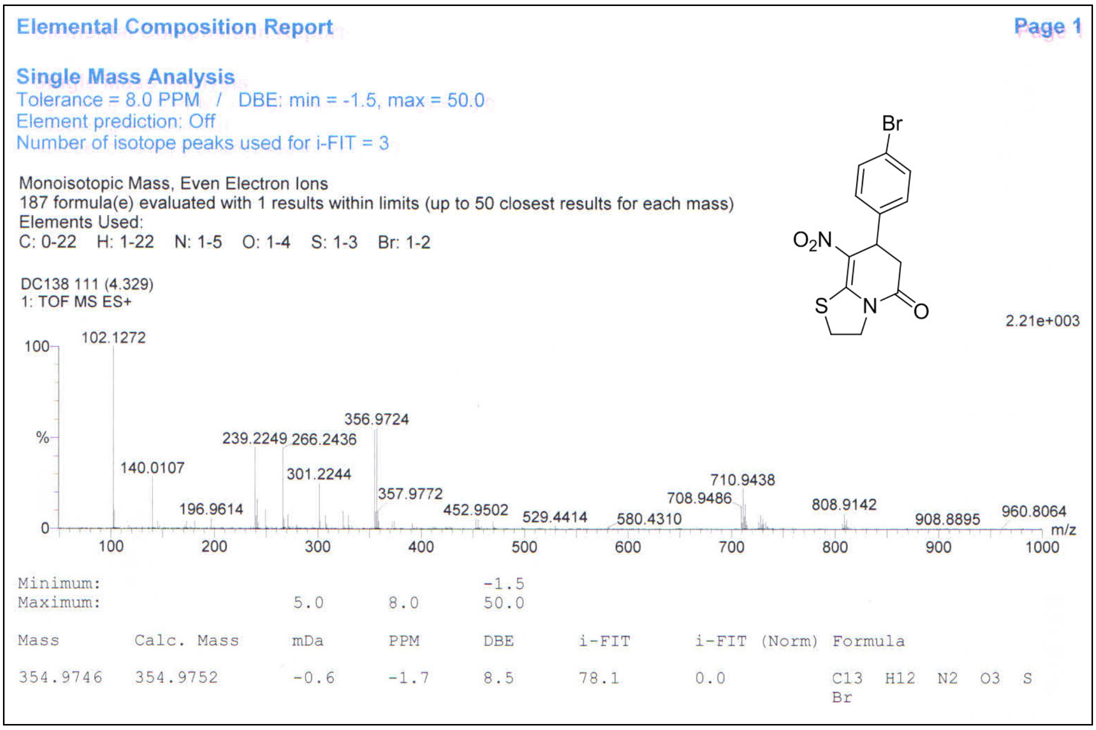


Figure 7. 166. ^{13}C NMR (100 MHz, CDCl3) spectrum of compound **260g**



Elemental Composition Report

Page 1

Single Mass Analysis
Tolerance = 8.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
187 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-22 H: 1-22 N: 1-5 O: 1-4 S: 1-3 Br: 1-2

DC138 111 (4.329)
1: TOF MS ES+

Minimum:				-1.5			
Maximum:		5.0	8.0	50.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
354.9746	354.9752	-0.6	-1.7	8.5	78.1	0.0	C13 H12 N2 O3 S Br

Figure 7. 167. HRMS and elemental composition of compound **260g**

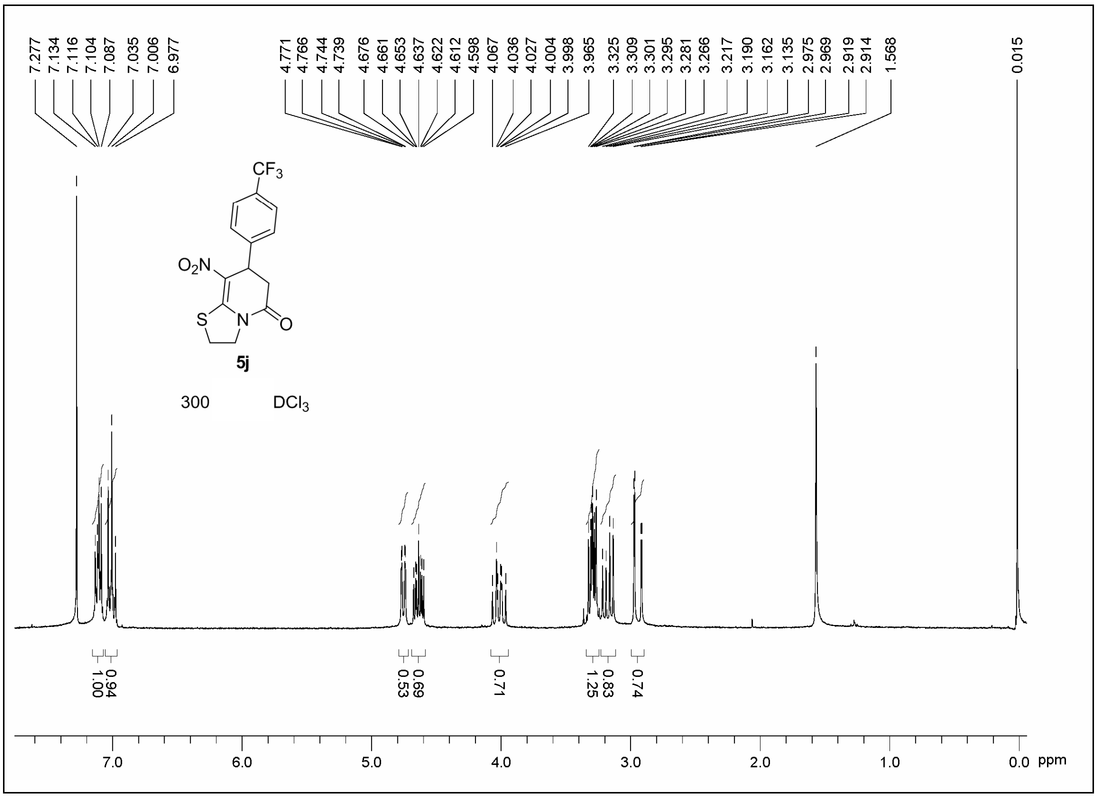


Figure 7. 168. ^{1}H NMR (400 MHz, CDCl3) spectrum of compound **260h**

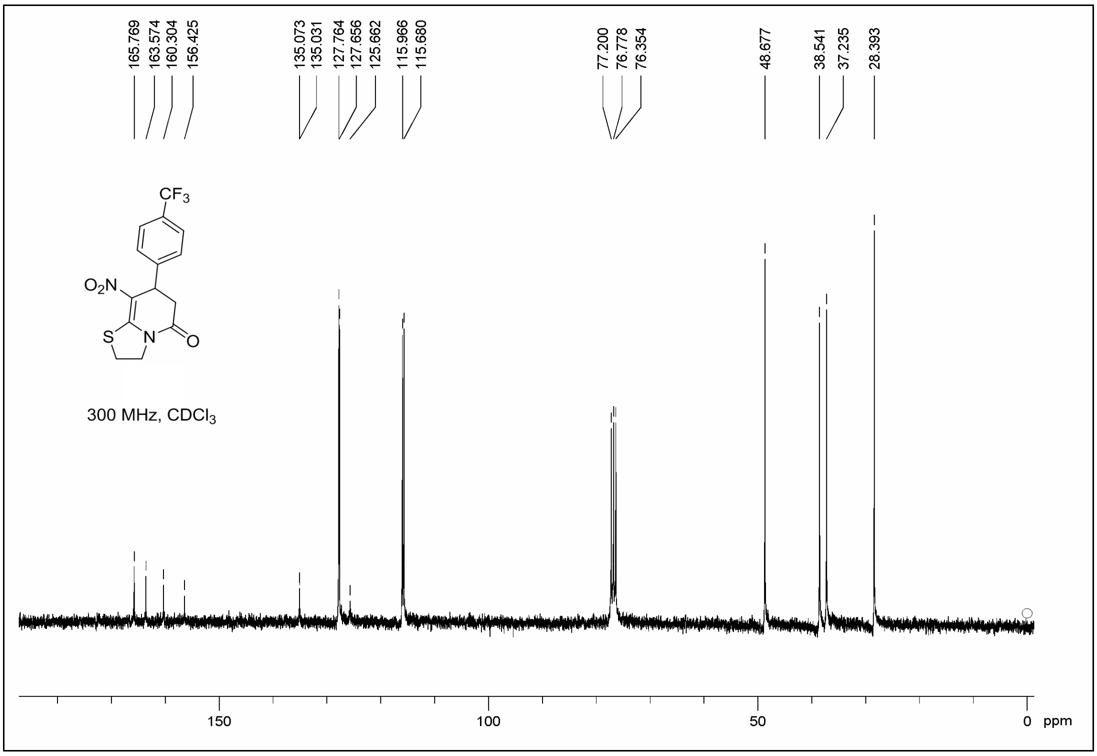


Figure 7. 169. ^{13}C NMR (100 MHz, CDCl3) spectrum of compound **260h**

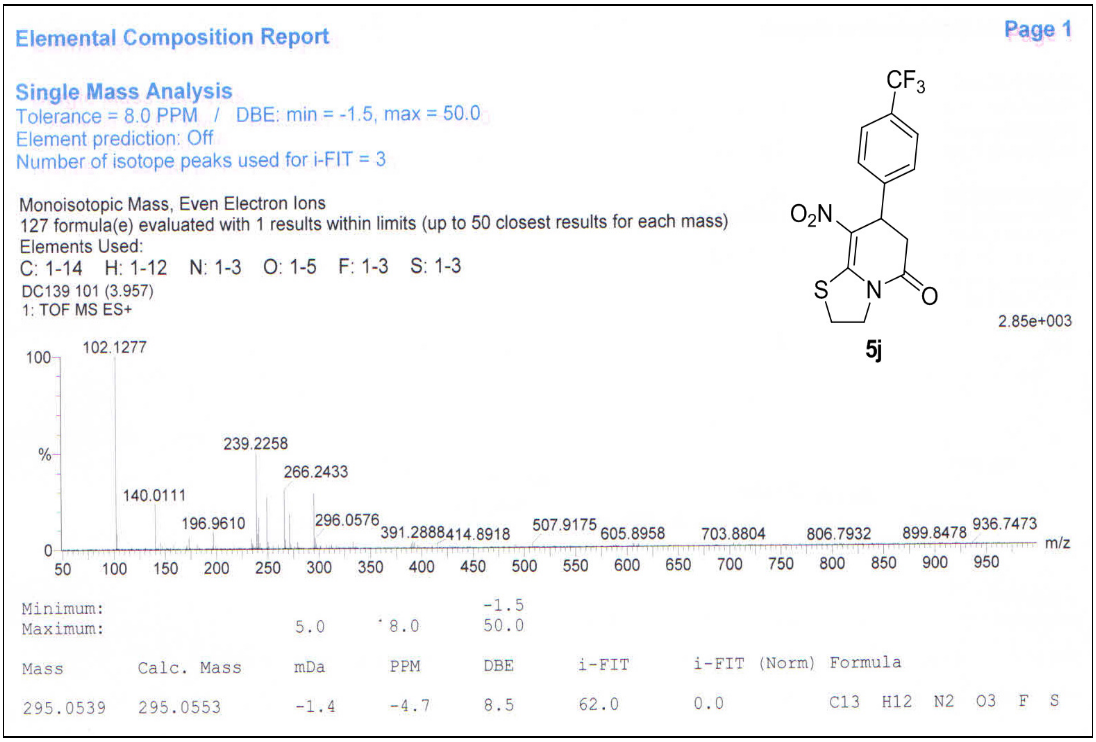


Figure 7. 170. HRMS and elemental composition of compound **260h**

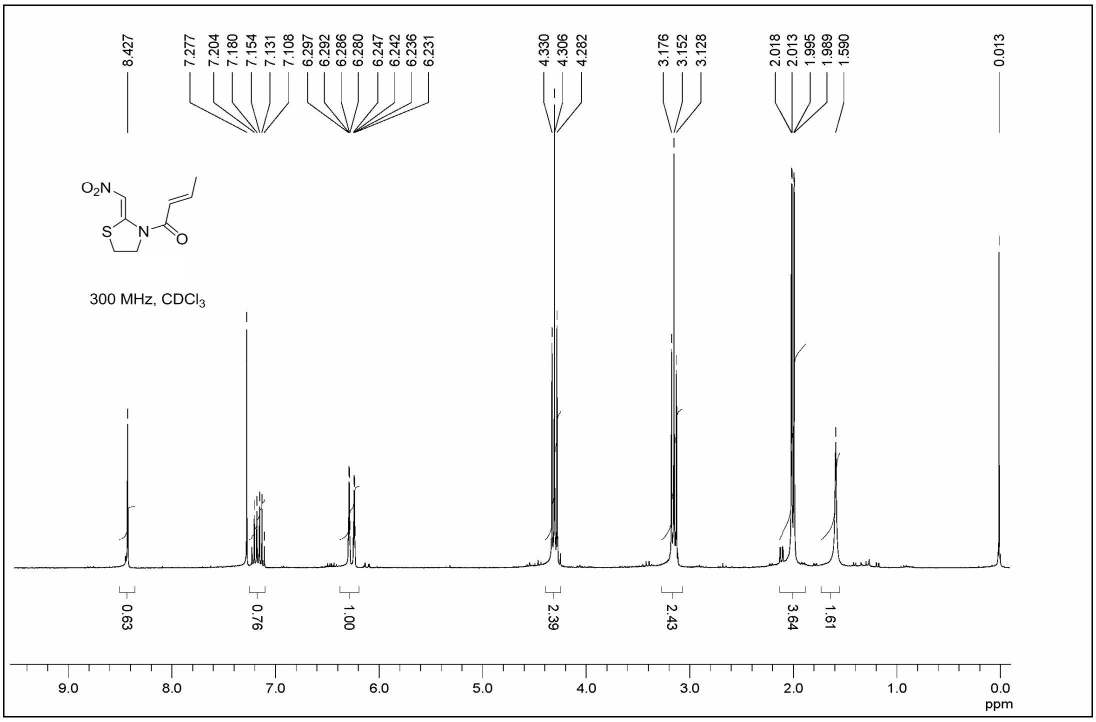


Figure 7. 171. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **261a**

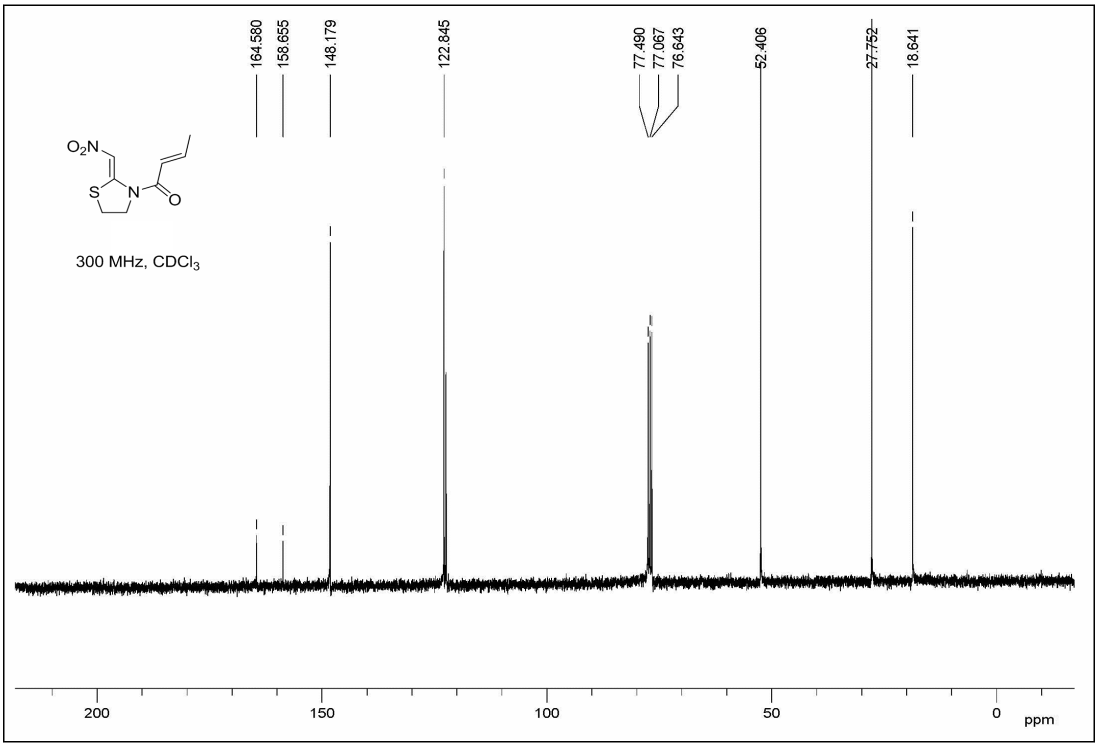


Figure 7. 172. ^{13}C NMR (100 MHz, CDCl3) spectrum of compound **261a**

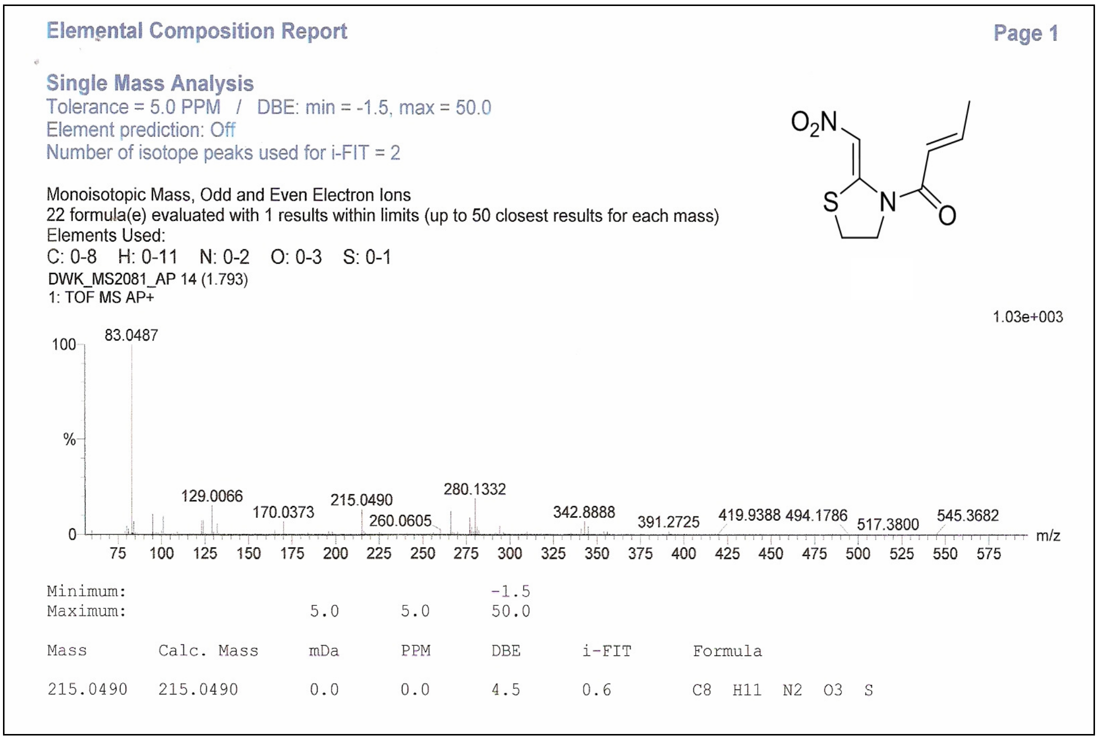


Figure 7. 173. HRMS and elemental composition of compound **261a**

Figure 7. 174 X-ray Structure of **261a**

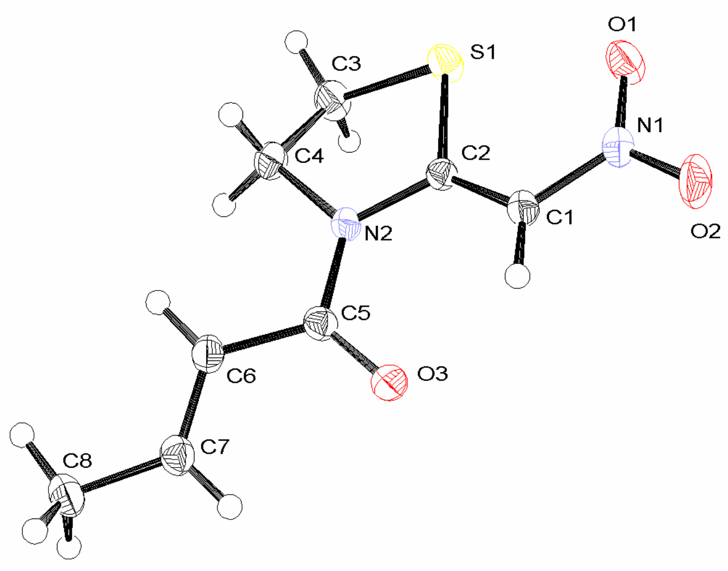


Table 7. 5. Crystal data and structure refinement for **261a**.

Identification code	dwk1207	
Empirical formula	C8 H10 N2 O3 S	
Formula weight	214.24	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P21/n	
Unit cell dimensions	a = 8.5327(4) Å	α = 90°.
	b = 12.8521(6) Å	β = 105.727(2)°.
	c = 8.9035(3) Å	γ = 90°.
Volume	939.83(7) $Å^3$	
Z	4	
Density (calculated)	1.514 Mg/m^3	
Absorption coefficient	0.326 mm^{-1}	
F(000)	448	
Crystal size	0.24 x 0.23 x 0.12 mm^3	
Theta range for data collection	2.86 to 30.49°.	
Index ranges	-12<=h<=12, -15<=k<=17, -12<=l<=12	
Reflections collected	3921	
Independent reflections	2492 [R(int) = 0.0271]	
Completeness to theta = 25.00°	98.5 %	
Absorption correction	Empirical	
Max. and min. transmission	0.9619 and 0.9258	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2492 / 0 / 128	
Goodness-of-fit on F^2	1.041	
Final R indices [I>2sigma(I)]	R1 = 0.0368, wR2 = 0.0843	
R indices (all data)	R1 = 0.0465, wR2 = 0.0904	
Largest diff. peak and hole	0.316 and -0.341 e.$Å^{-3}$	

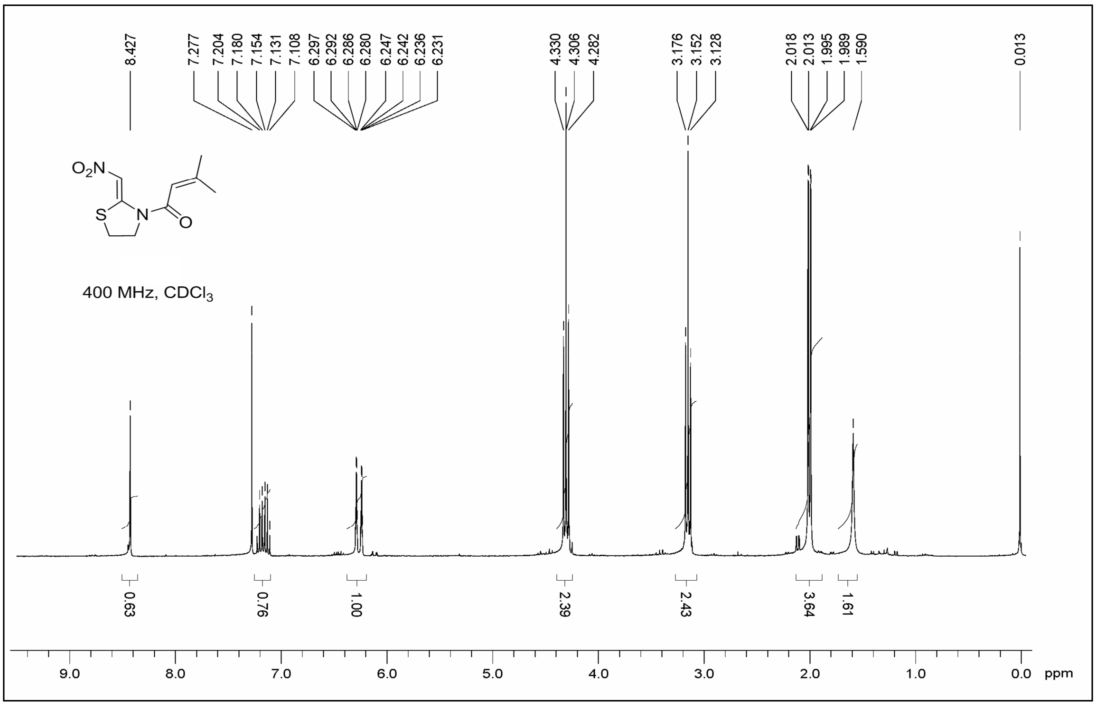


Figure 7. 175. ^{1}H NMR (400 MHz, CDCl3) spectrum of compound **261b**

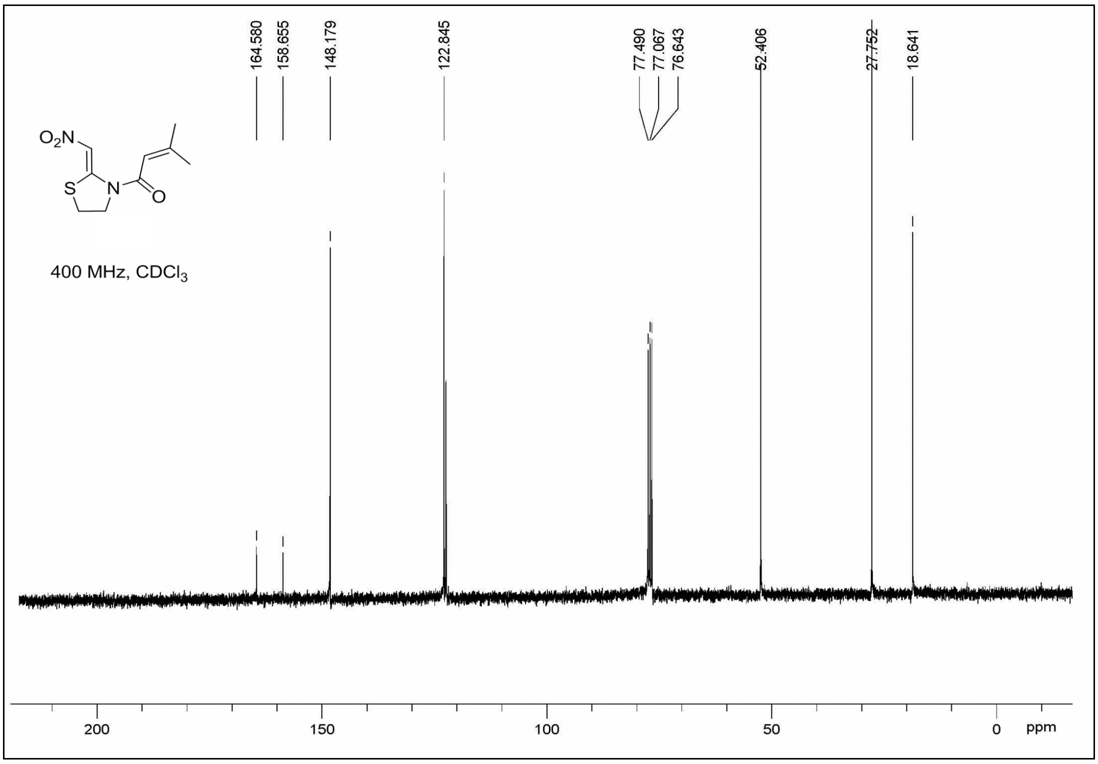
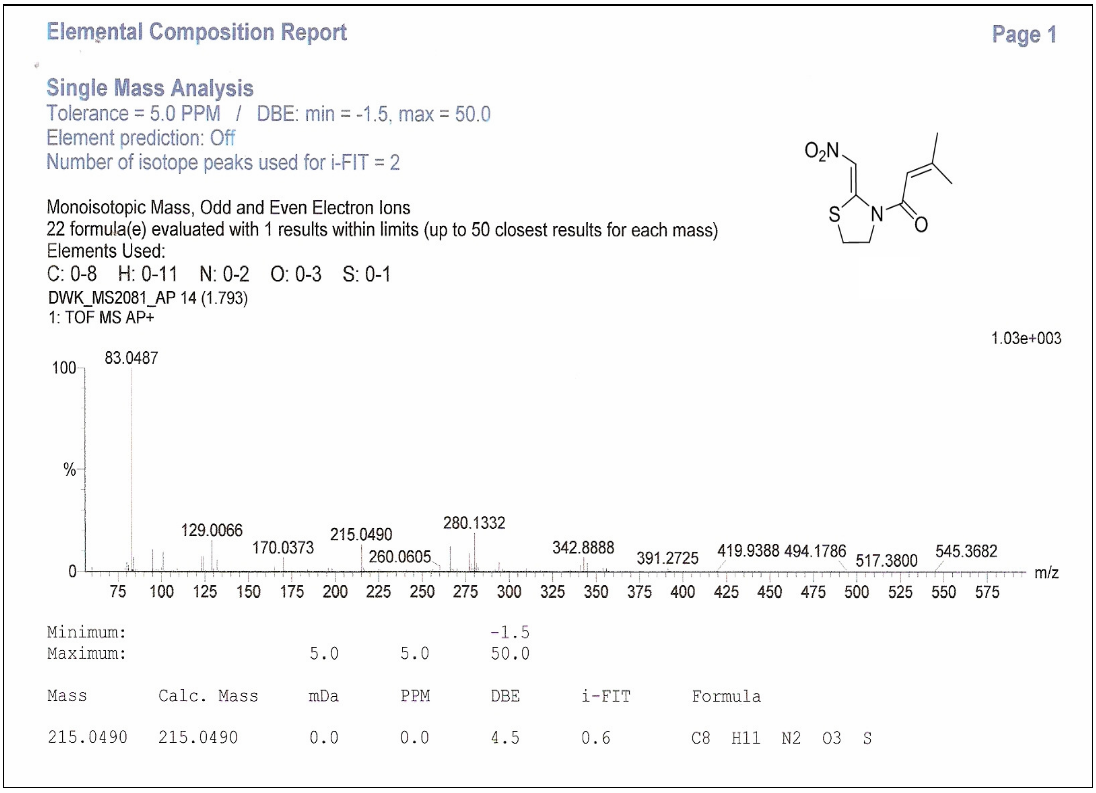


Figure 7. 176. ^{13}C NMR (100 MHz, CDCl3) spectrum of compound **261b**



Minimum:				-1.5		
Maximum:		5.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
215.0490	215.0490	0.0	0.0	4.5	0.6	C8 H11 N2 O3 S

Figure 7. 177. HRMS and elemental composition of compound **261b**

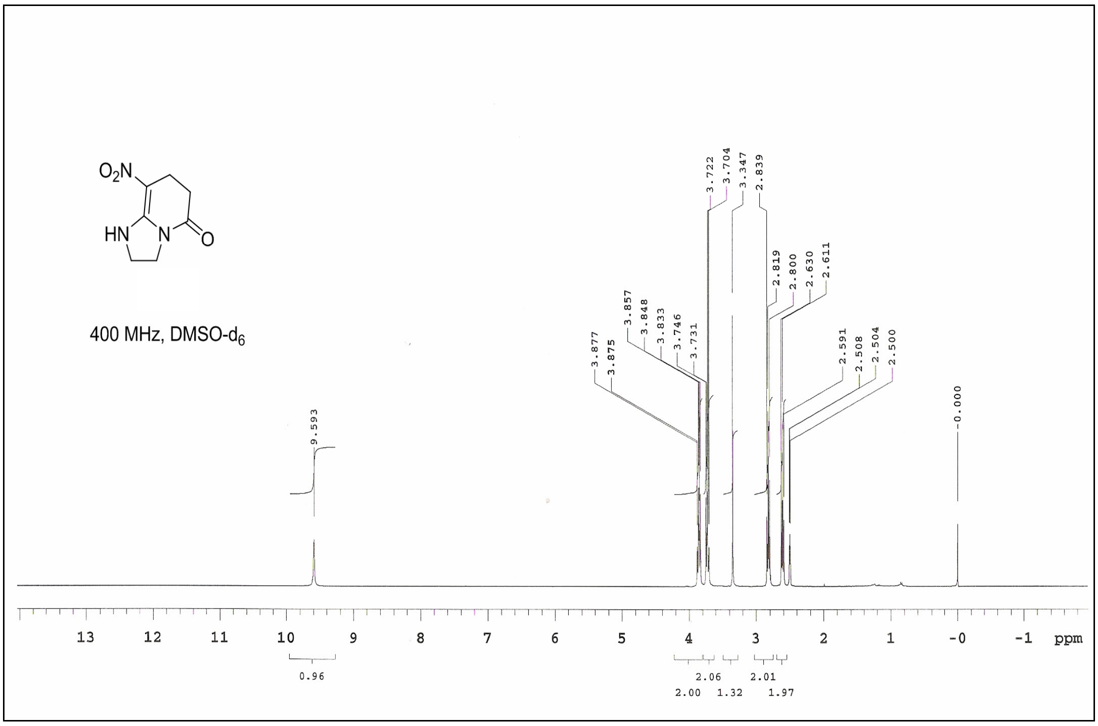


Figure 7. 178. ^{1}H NMR (400 MHz, DMSO-d6) spectrum of compound **248a**

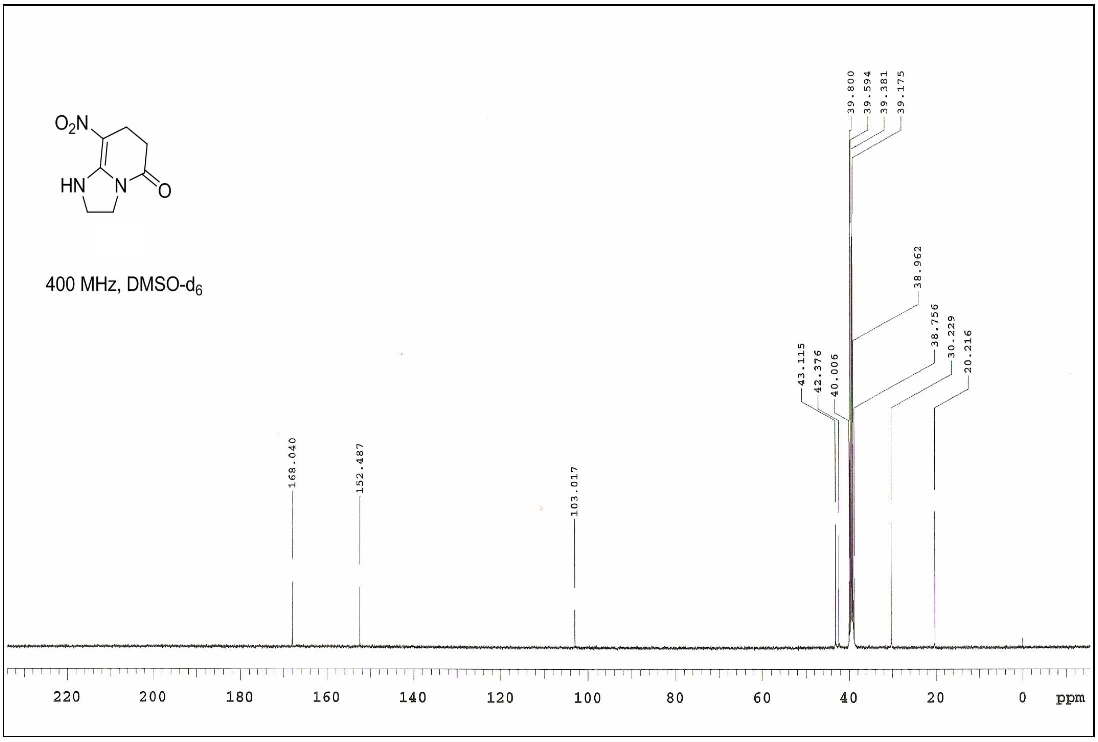
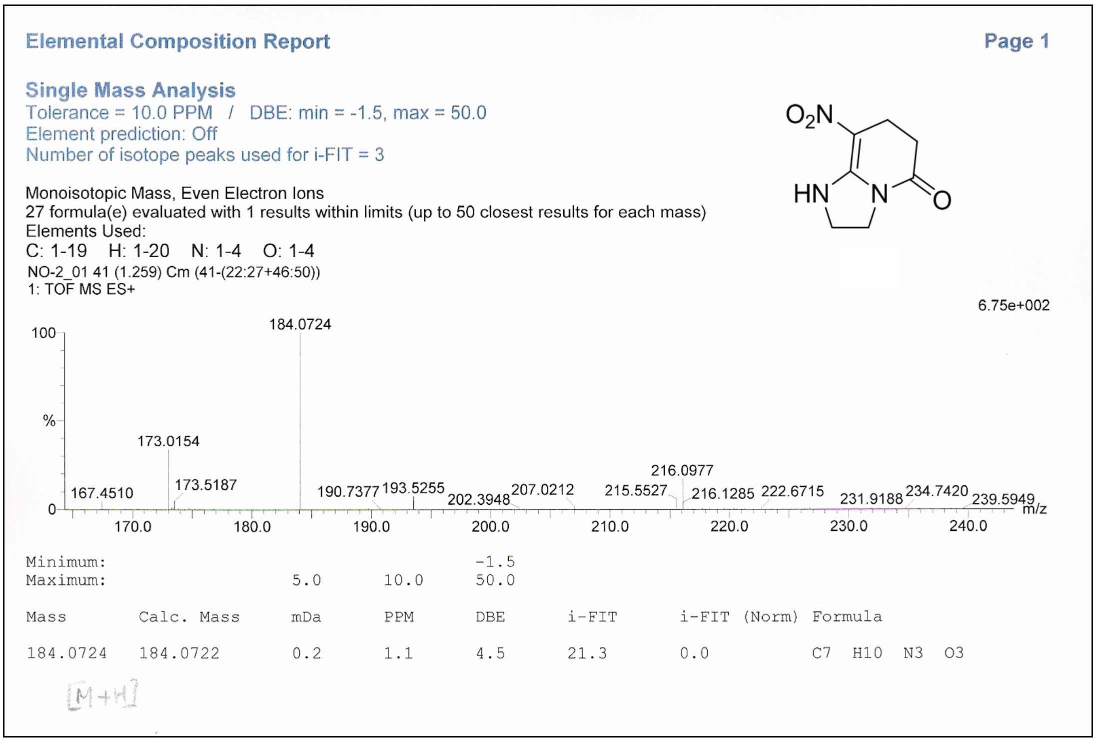


Figure 7. 179. ^{13}C NMR (100 MHz, DMSO-d6) spectrum of compound **248a**



Elemental Composition Report Page 1

Single Mass Analysis
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
27 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 1-19 H: 1-20 N: 1-4 O: 1-4
NO-2_01 41 (1.259) Cm (41-(22:27+46:50))
1: TOF MS ES+

Minimum:				-1.5			
Maximum:		5.0	10.0	50.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
184.0724	184.0722	0.2	1.1	4.5	21.3	0.0	C7 H10 N3 O3

[M+H]

Figure 7. 180. HRMS and elemental composition of compound **248a**

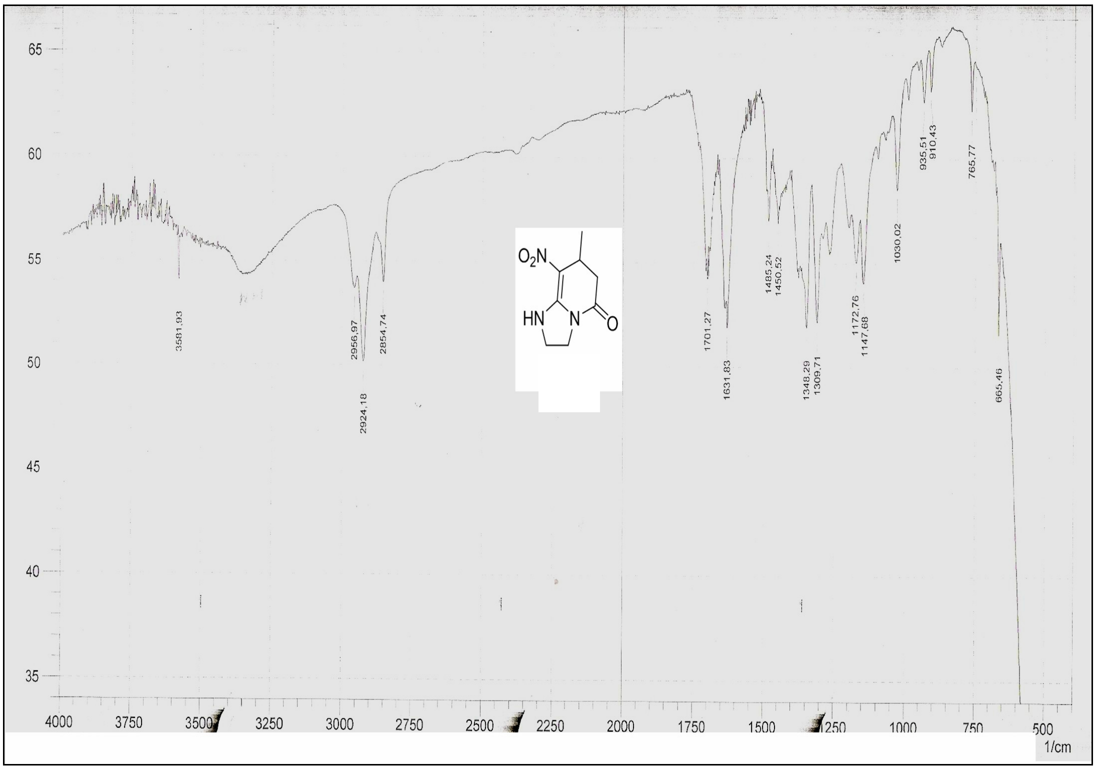


Figure 7. 181. IR spectrum of compound **248b**

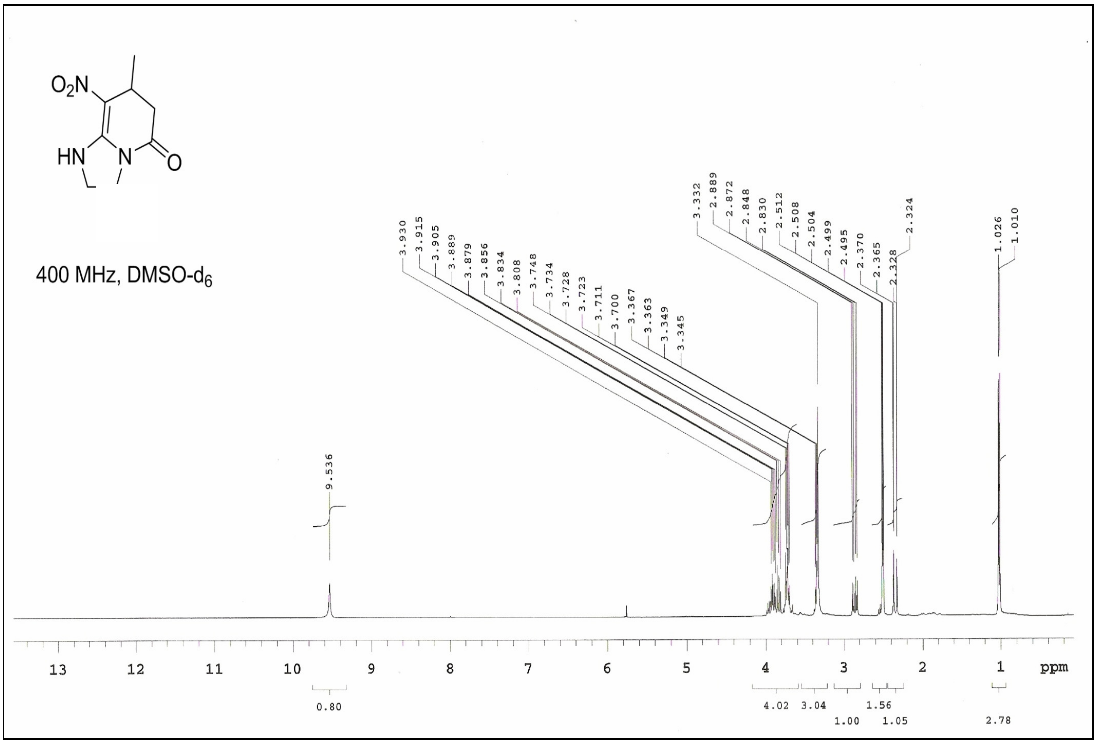


Figure 7. 182. ^{1}H NMR (400 MHz, DMSO-d$_6$) spectrum of compound **248b**

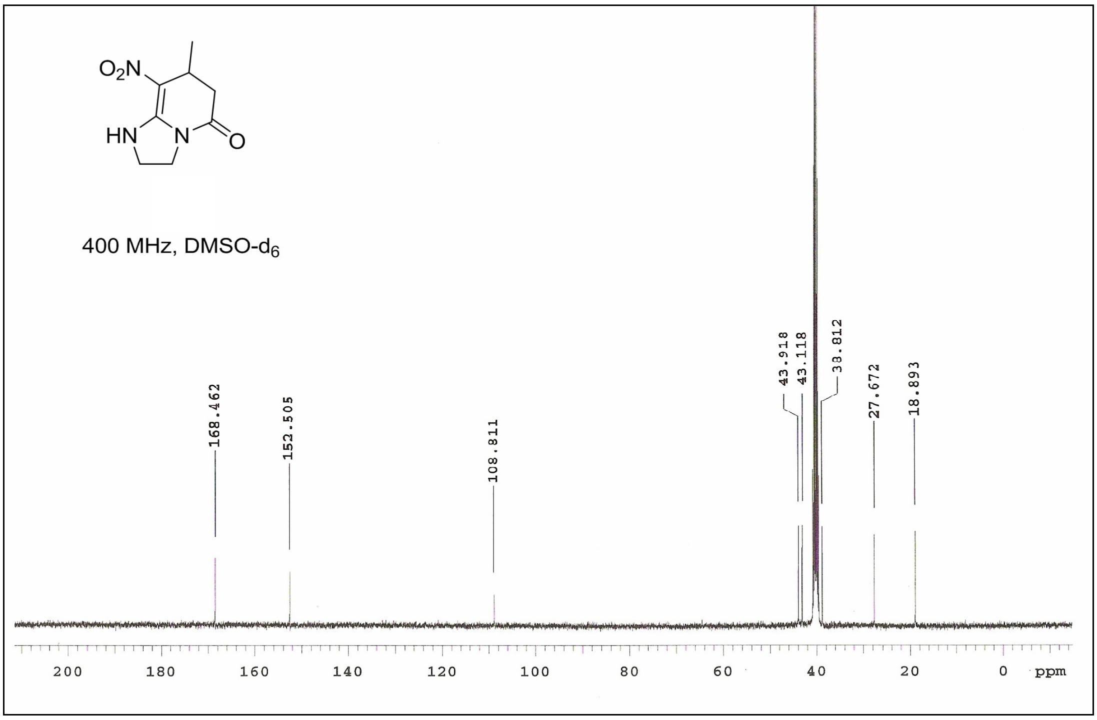
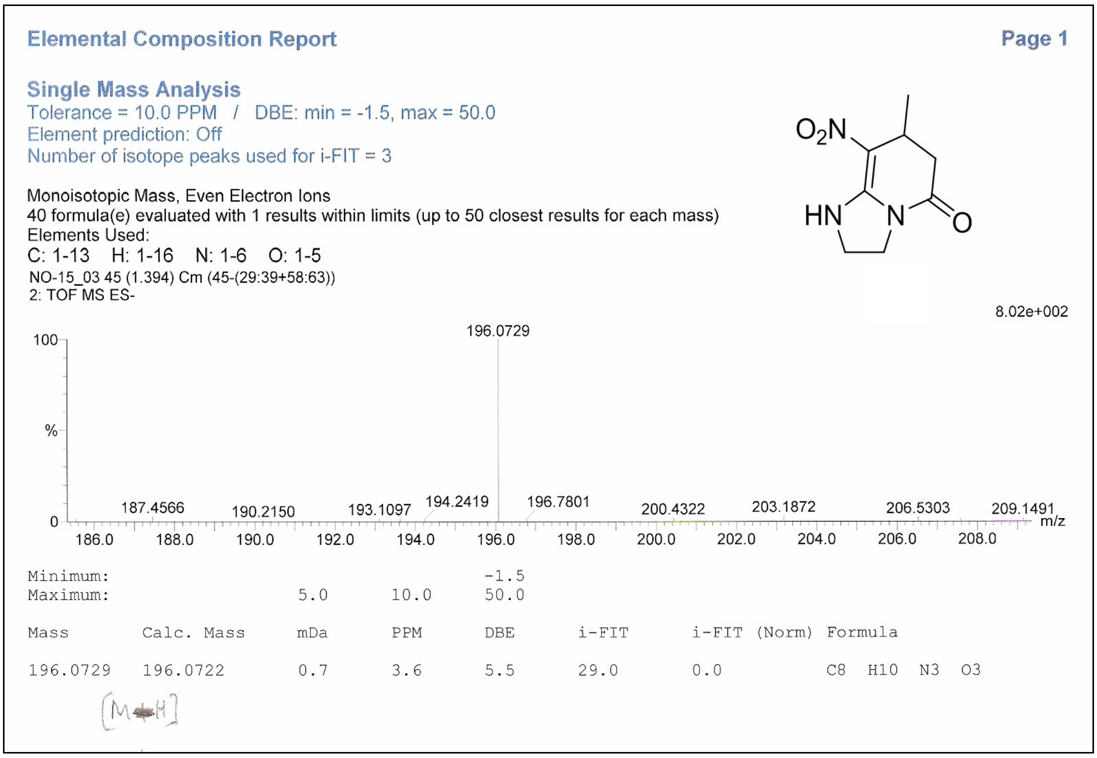


Figure 7. 183. ^{13}C NMR (100 MHz, DMSO-d6) spectrum of compound **248b**


Elemental Composition Report

Page 1

Single Mass Analysis
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
40 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 1-13 H: 1-16 N: 1-6 O: 1-5
NO-15_03 45 (1.394) Cm (45-(29:39+58:63))
2: TOF MS ES-

Minimum:				-1.5			
Maximum:		5.0	10.0	50.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
196.0729	196.0722	0.7	3.6	5.5	29.0	0.0	C8 H10 N3 O3

[M-H]

Figure 7. 184. HRMS and elemental composition of compound **248b**

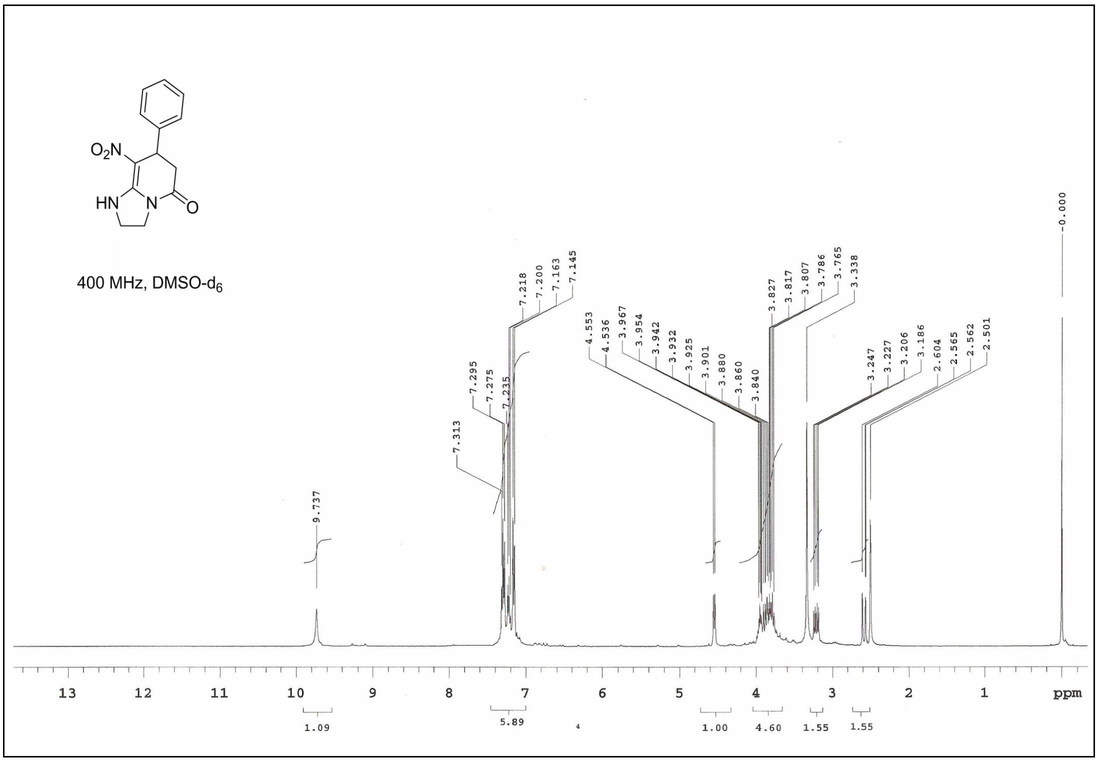


Figure 7. 185. ^{1}H NMR (400 MHz, DMSO-d6) spectrum of compound **248c**

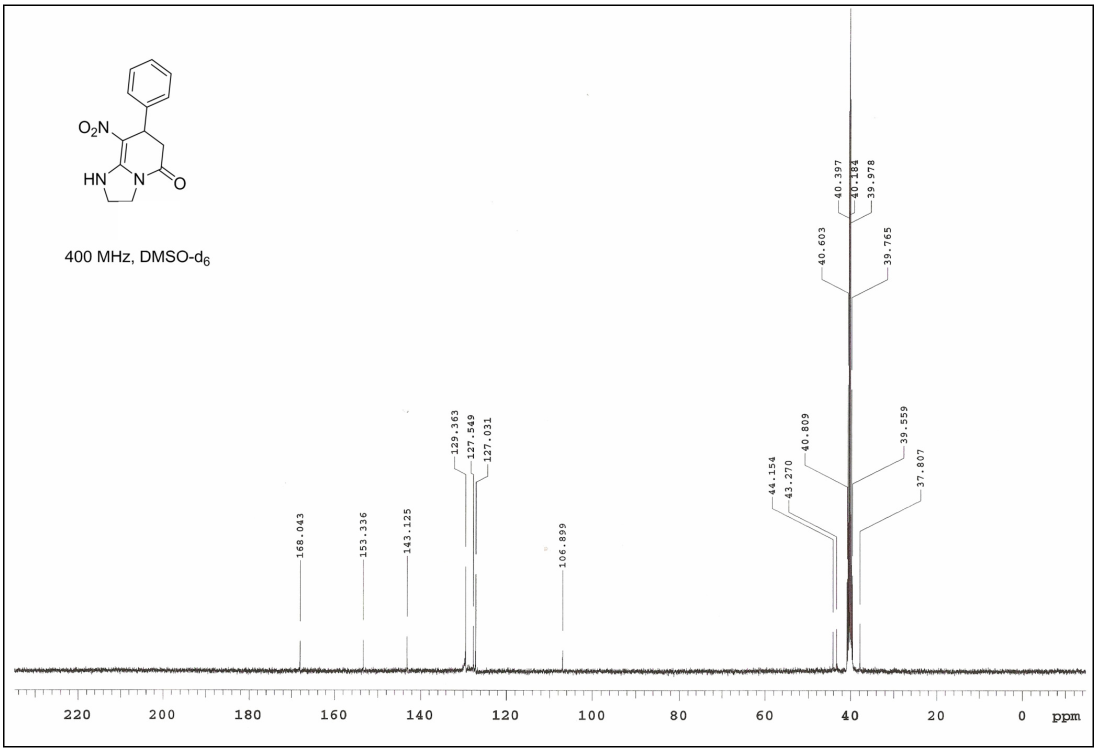


Figure 7. 186. ^{13}C NMR (100 MHz, DMSO-d6) spectrum of compound **248c**

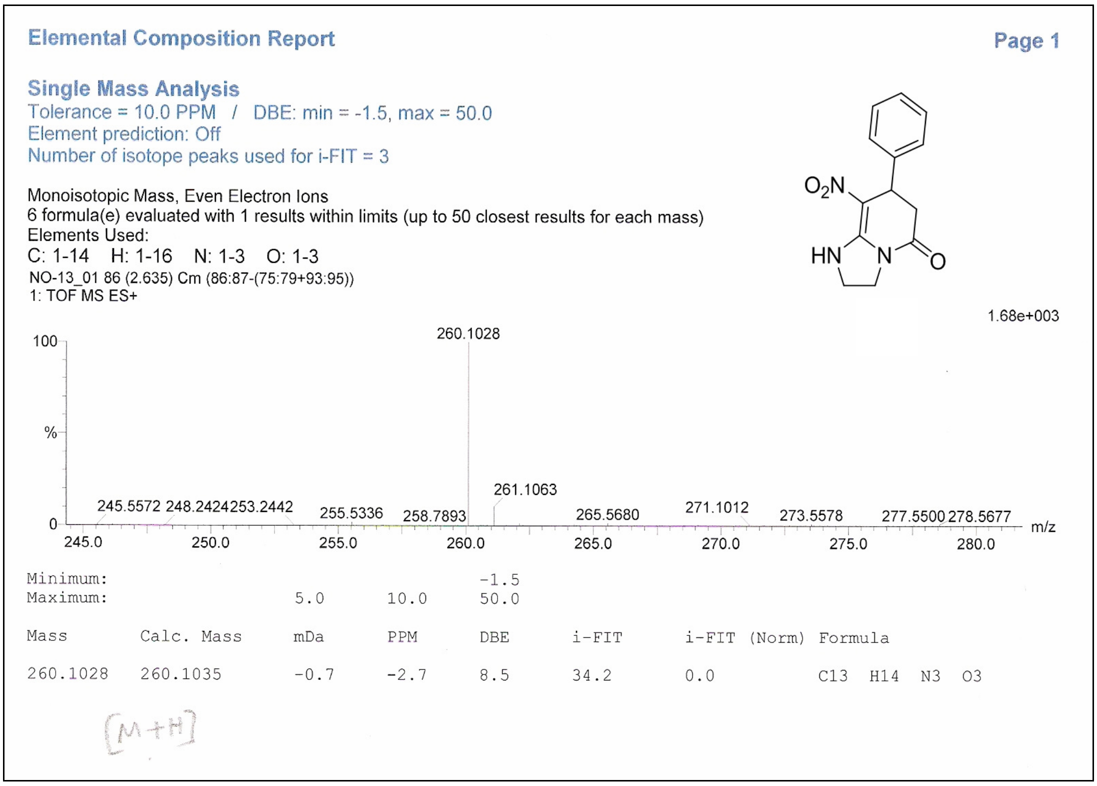


Figure 7. 187. HRMS and elemental composition of compound **248c**

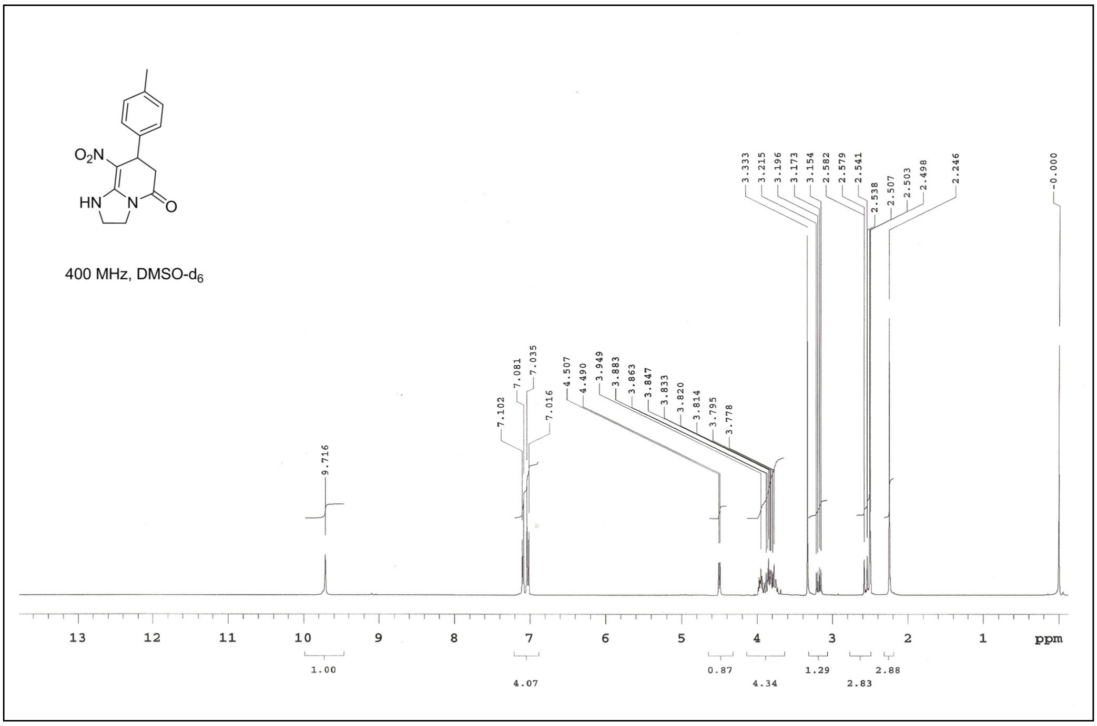


Figure 7. 188. ^{1}H NMR (400 MHz, DMSO-d6) spectrum of compound **248d**

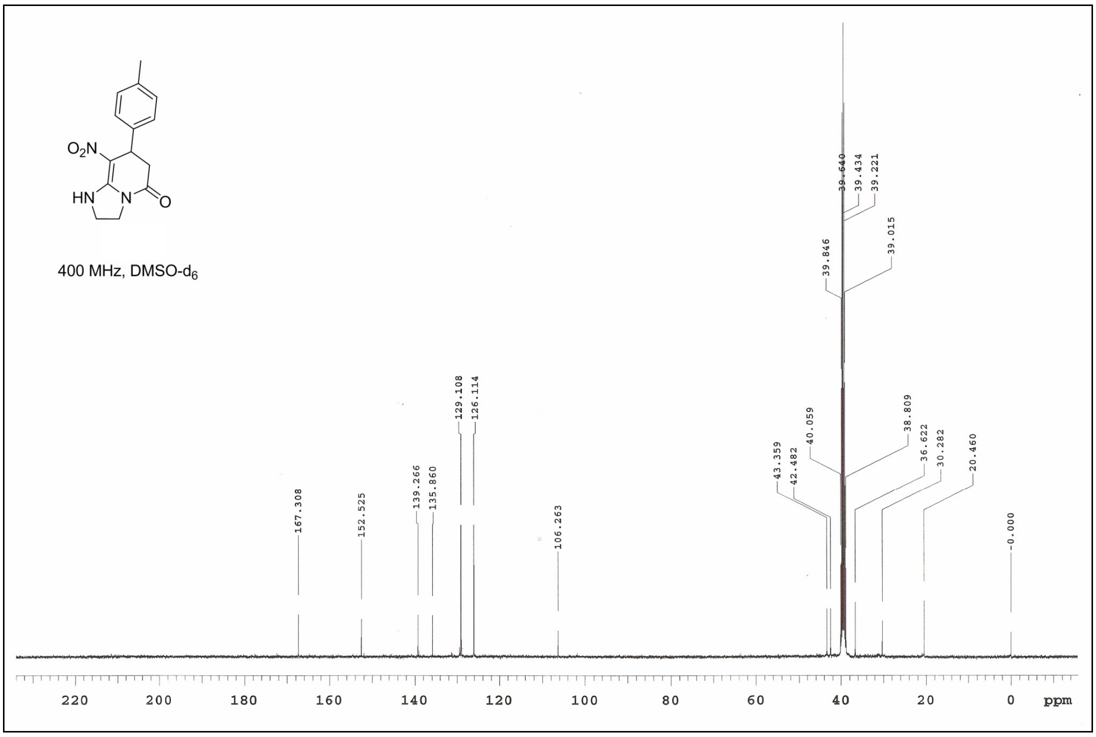


Figure 7. 189. ^{13}C NMR (100 MHz, DMSO-d6) spectrum of compound **248d**

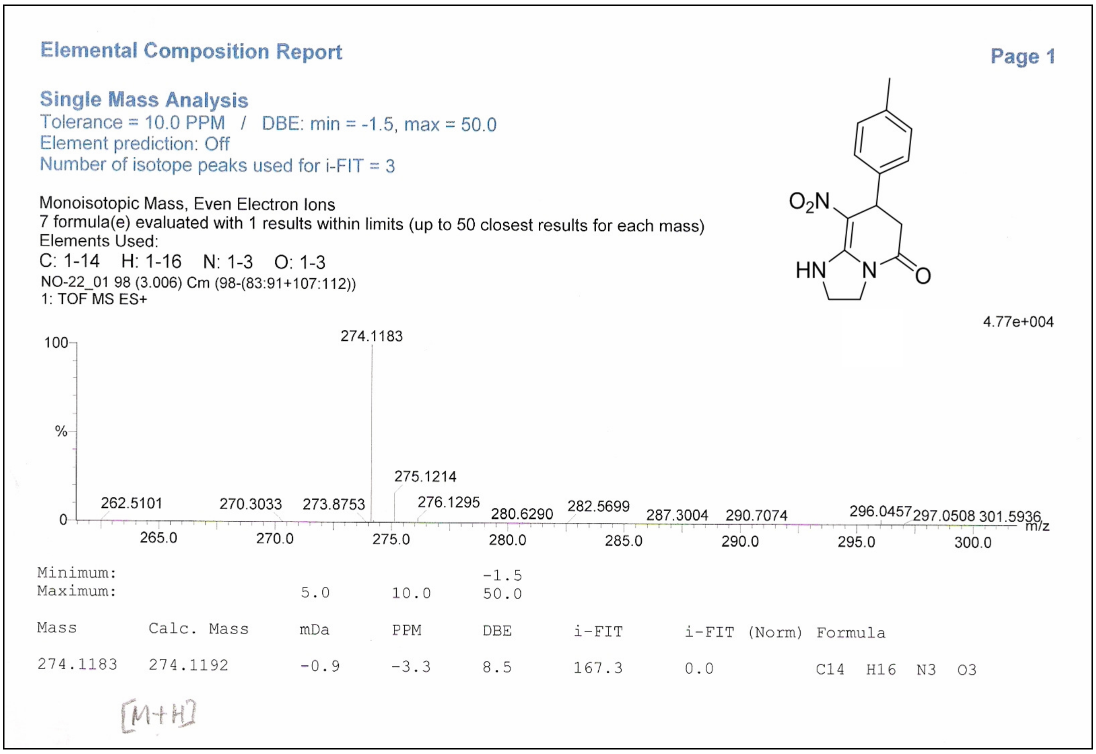


Figure 7. 190. HRMS and elemental composition of compound **248d**

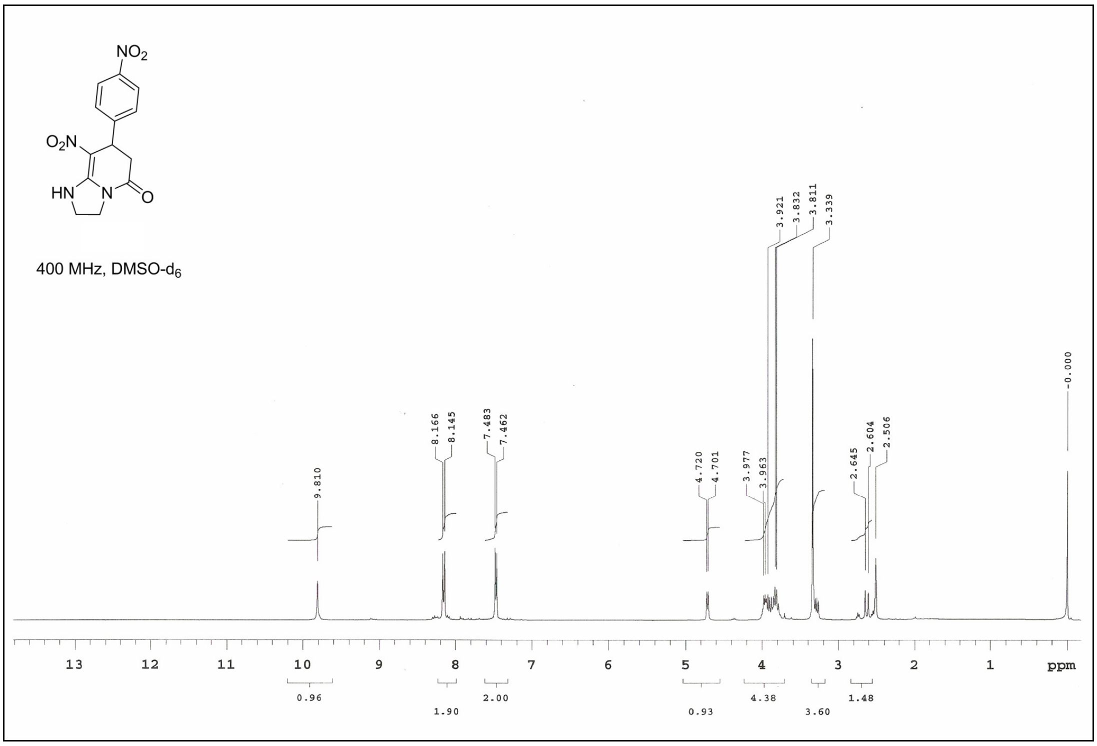


Figure 7. 191. ^{1}H NMR (400 MHz, DMSO-d6) spectrum of compound **248e**

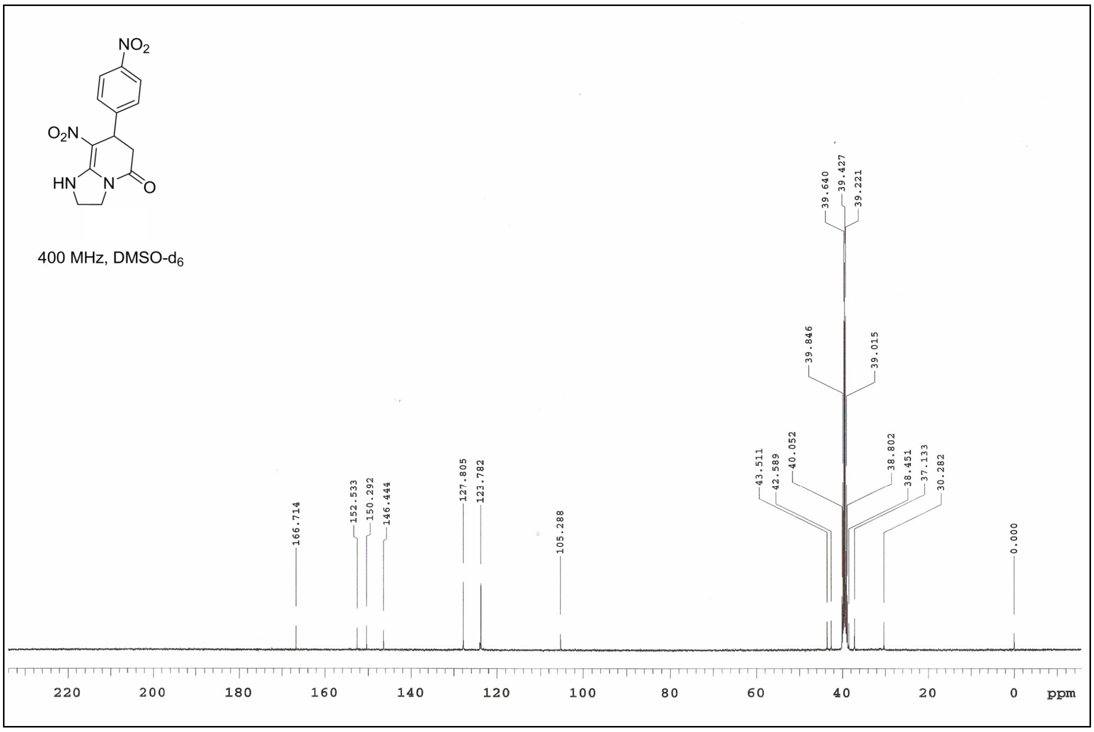


Figure 7. 192. ^{13}C NMR (100 MHz, DMSO-d6) spectrum of compound **248e**

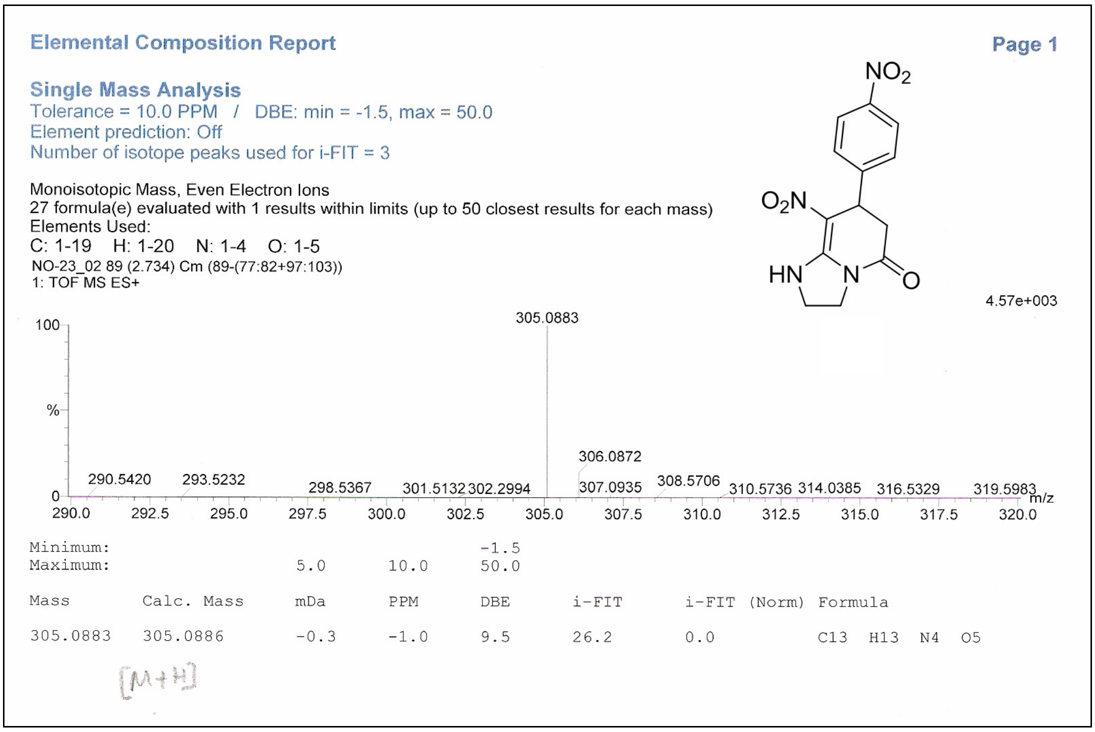


Figure 7. 193. HRMS and elemental composition of compound **248e**

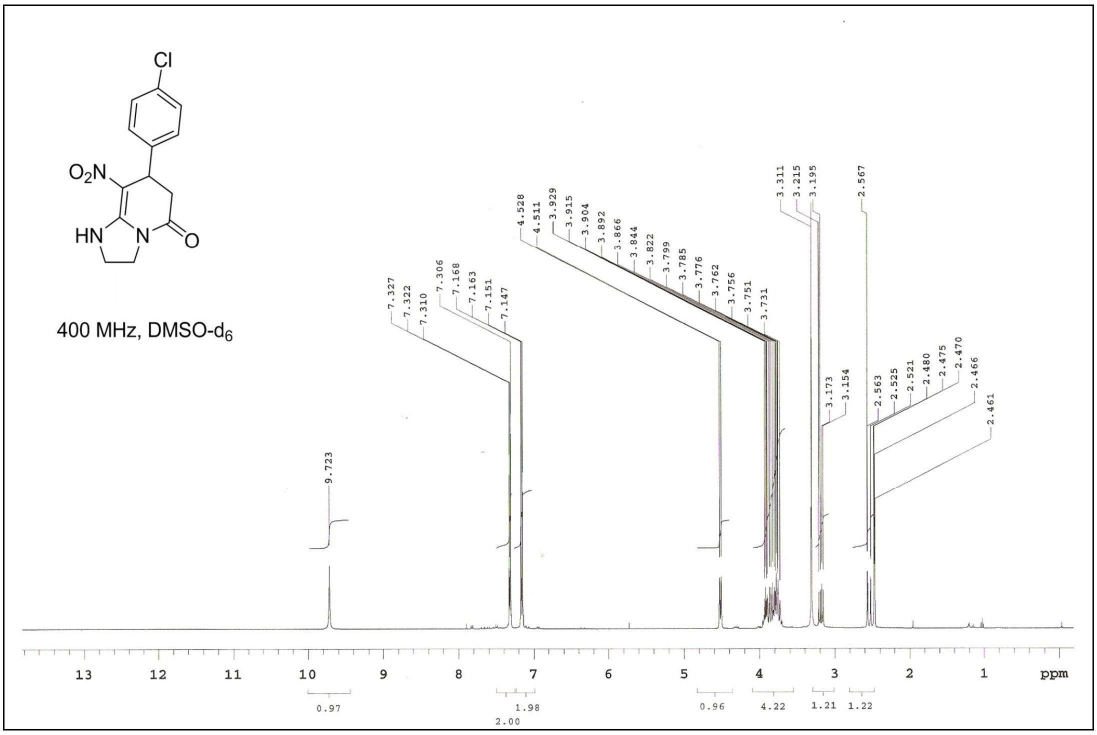


Figure 7. 194. ^{1}H NMR (400 MHz, DMSO-d$_6$) spectrum of compound **248f**

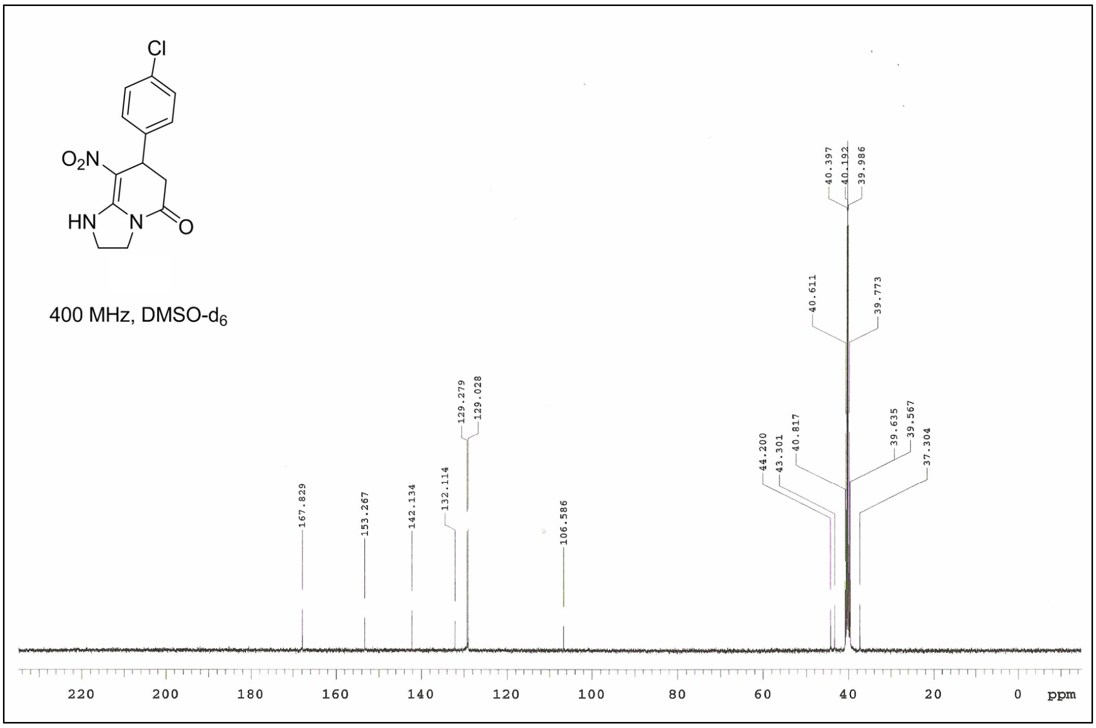


Figure 7. 195. ^{13}C NMR (100 MHz, DMSO-d6) spectrum of compound **248f**

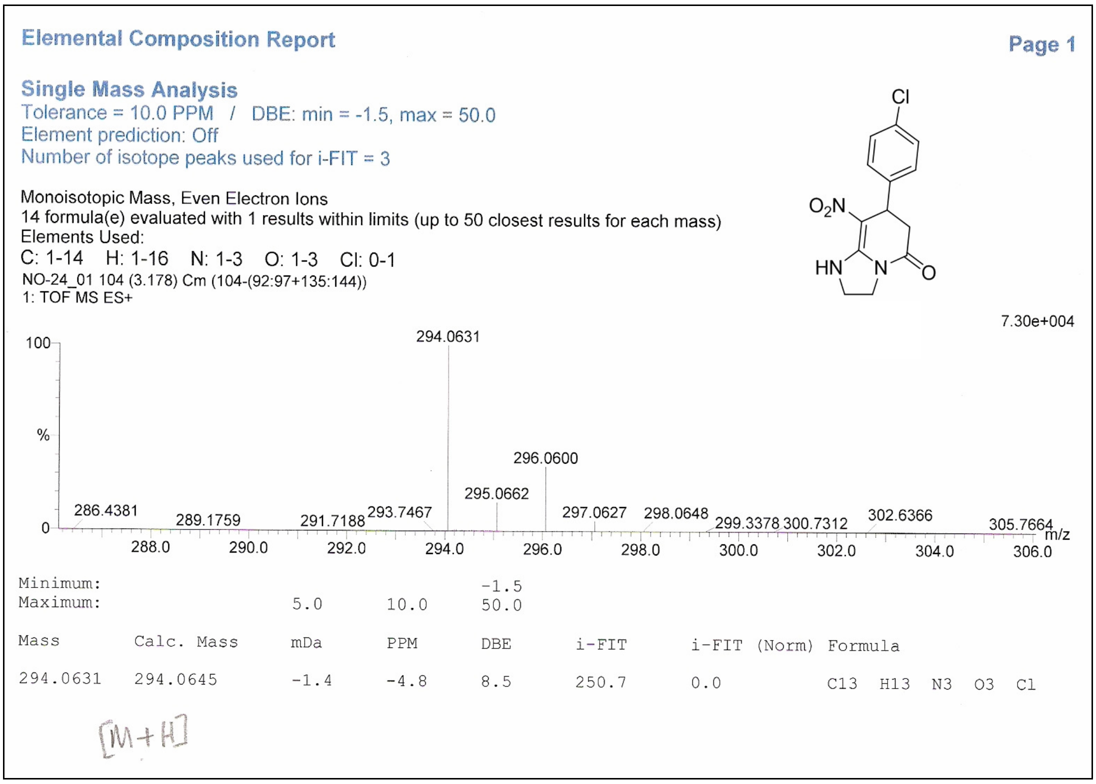


Figure 7. 196. HRMS and elemental composition of compound **248f**

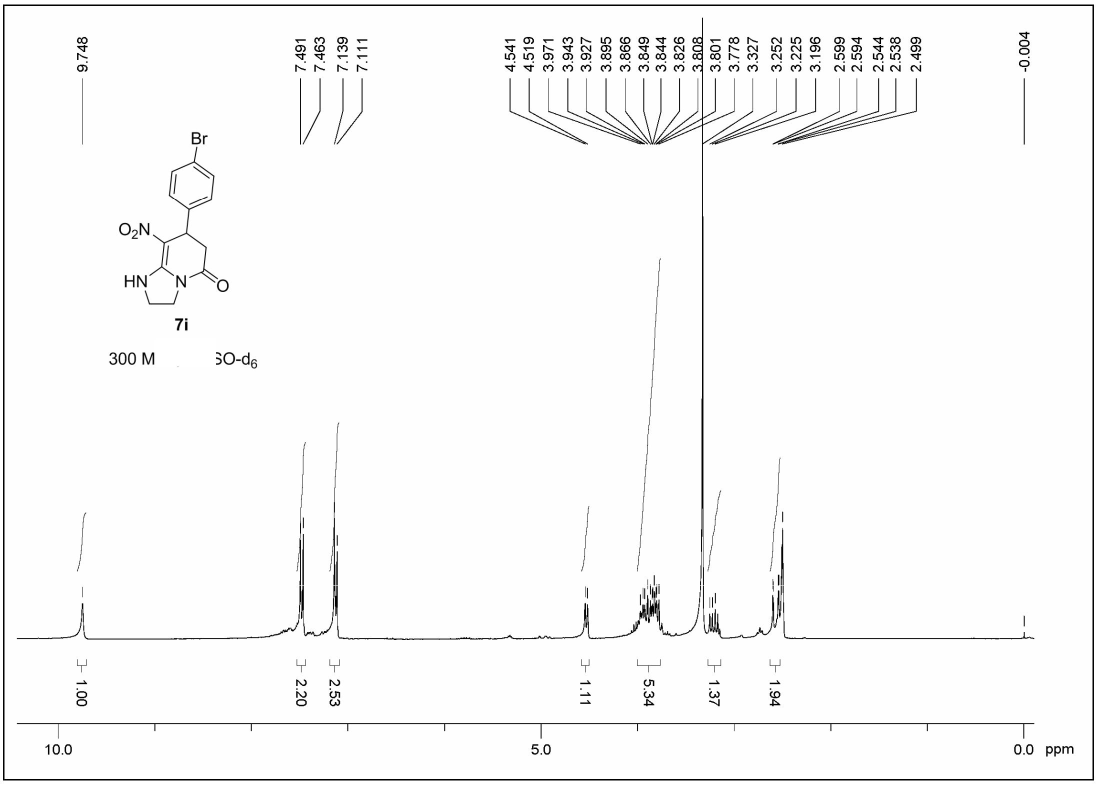


Figure 7. 197. ^{1}H NMR (400 MHz, DMSO-d6) spectrum of compound **248g**

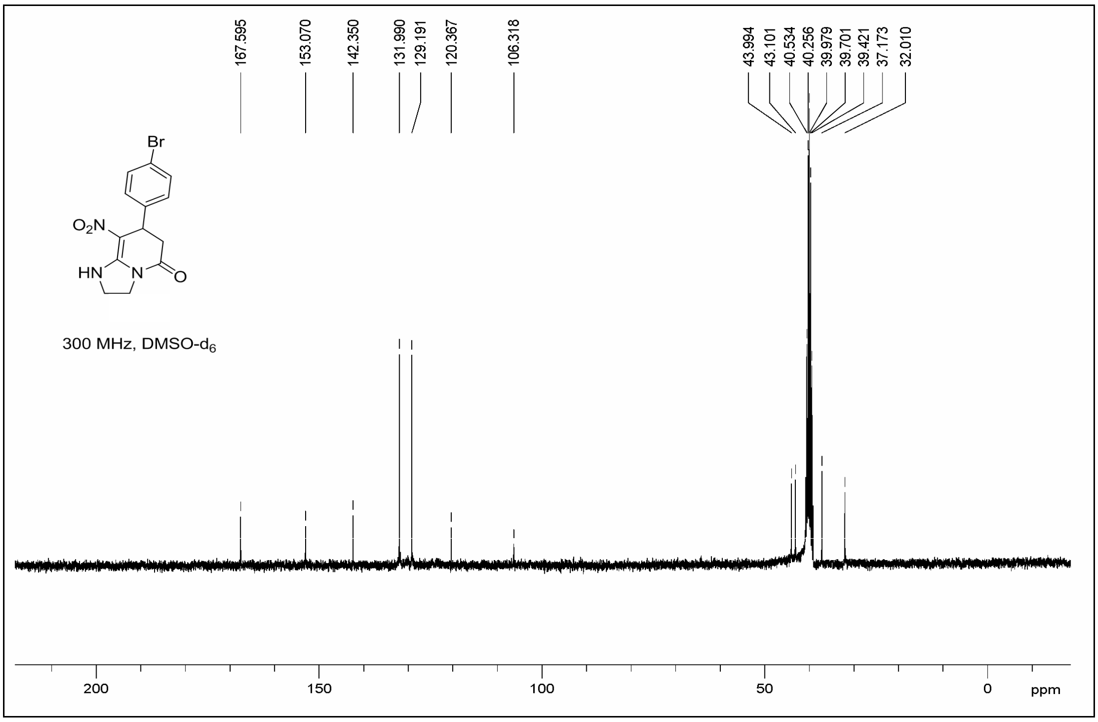


Figure 7. 198. ^{13}C NMR (100 MHz, DMSO-d6) spectrum of compound **248g**

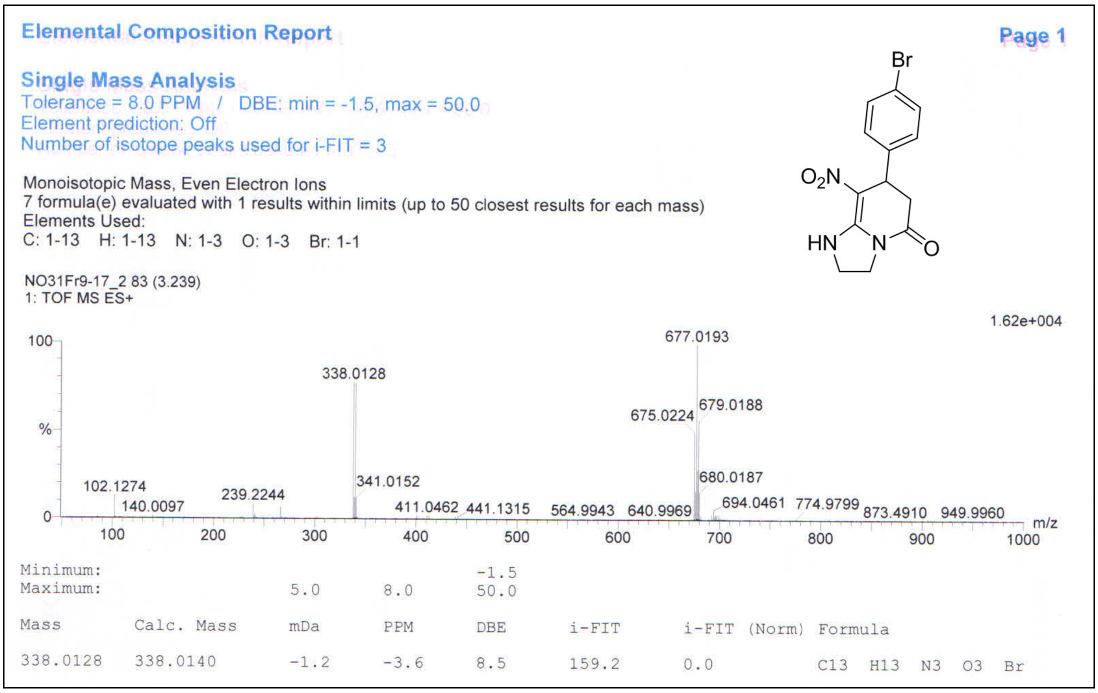


Figure 7. 199. HRMS and elemental composition of compound **248g**

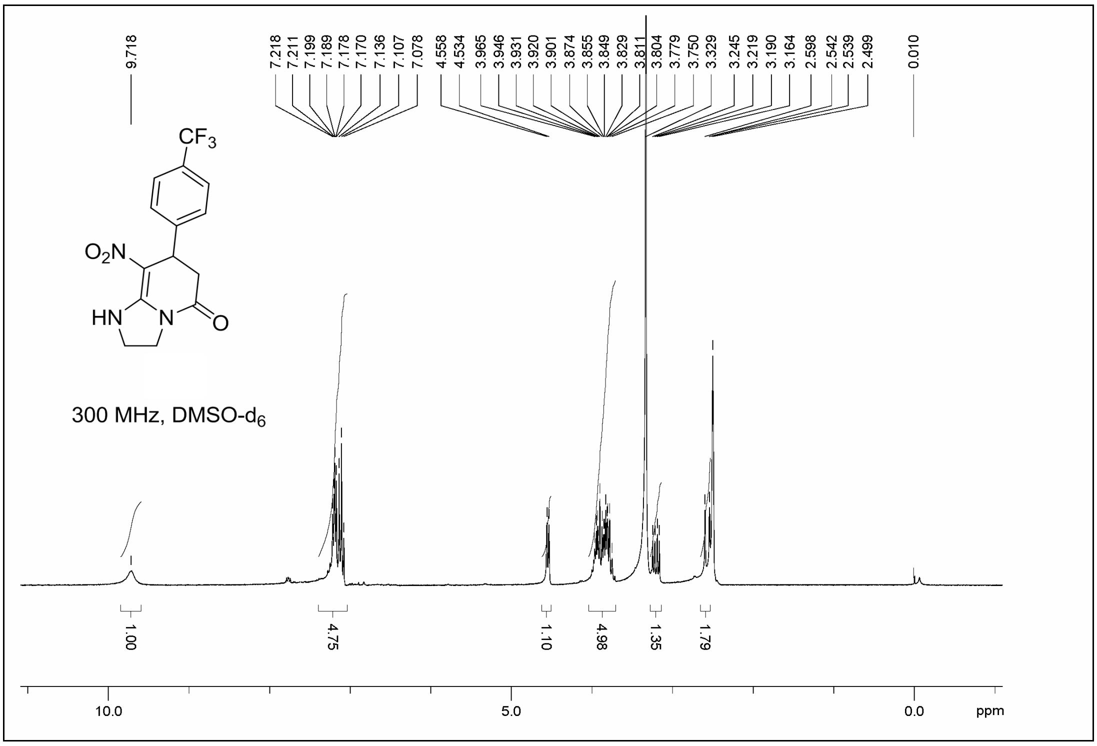


Figure 7. 200. ^{1}H NMR (400 MHz, DMSO-d6) spectrum of compound **248h**

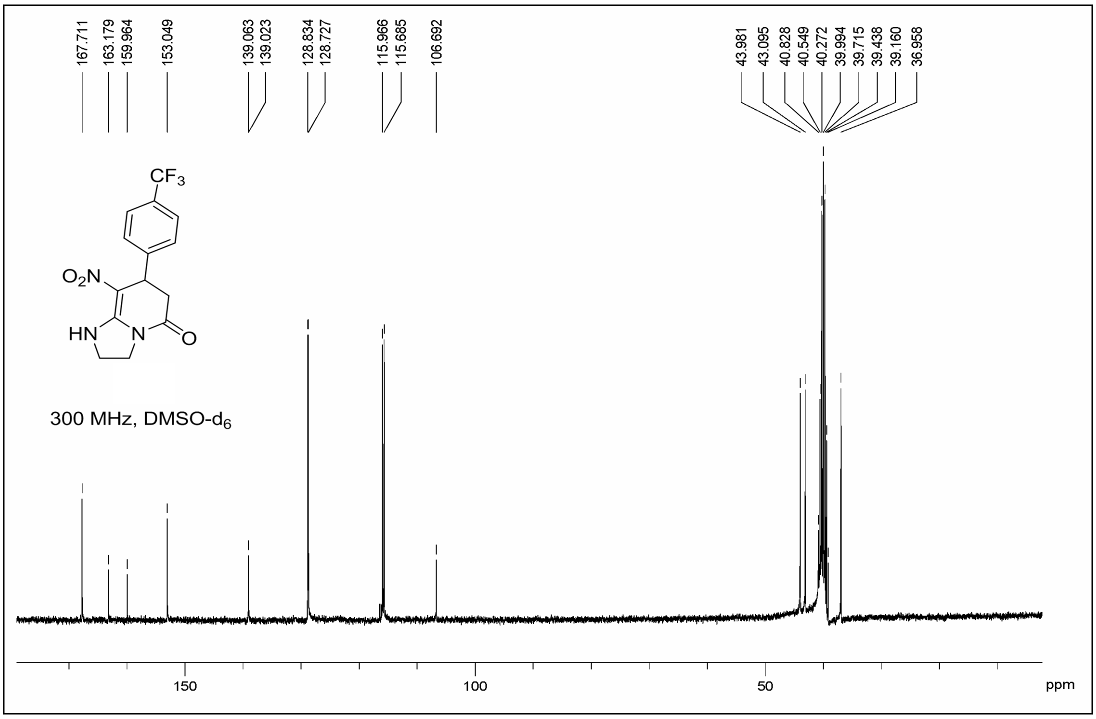


Figure 7. 201. ^{13}C NMR (100 MHz, DMSO-d6) spectrum of compound **248h**

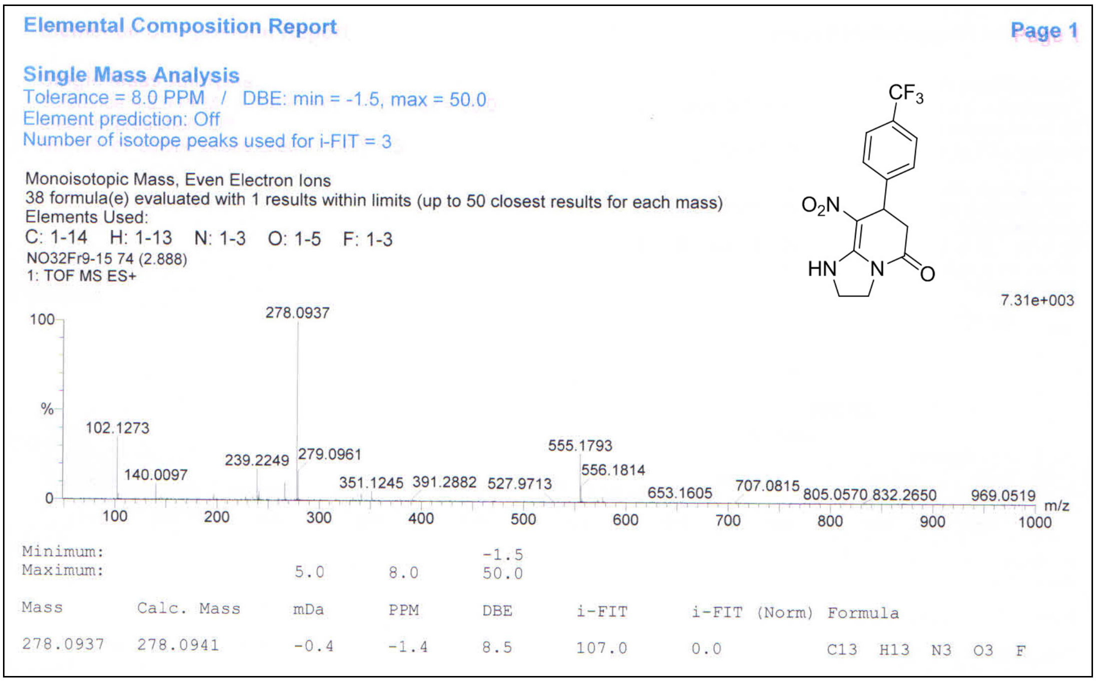


Figure 7. 202. HRMS and elemental composition of compound **248h**

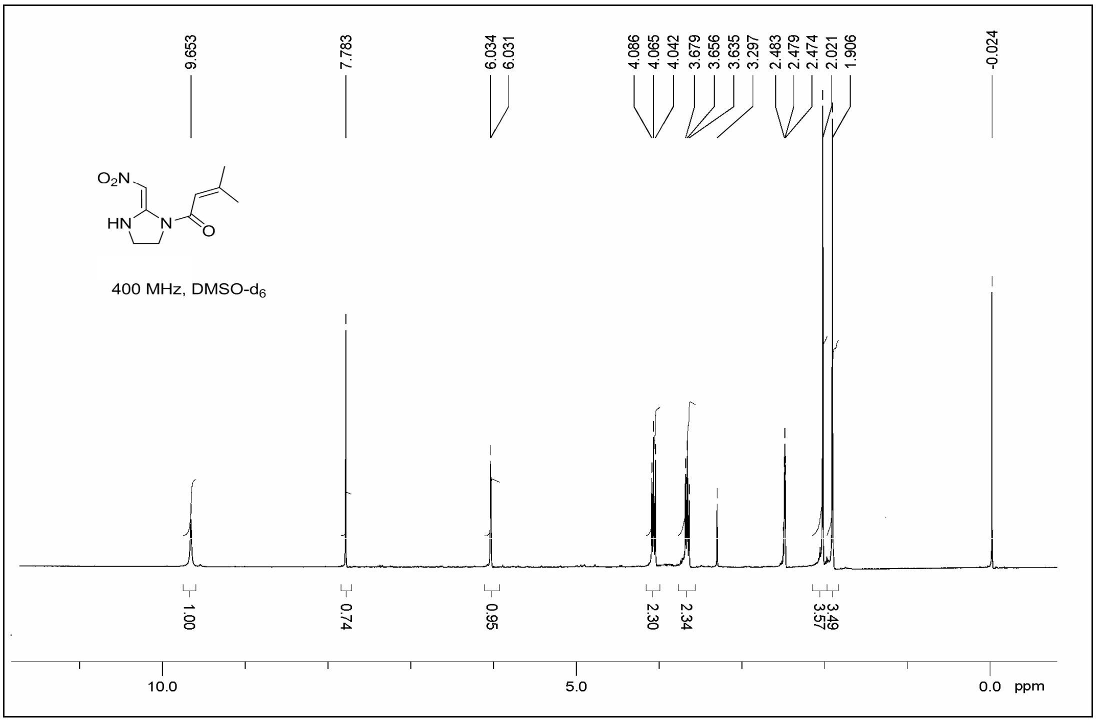


Figure 7. 203. ^{1}H NMR (400 MHz, DMSO-d6) spectrum of compound **239a**

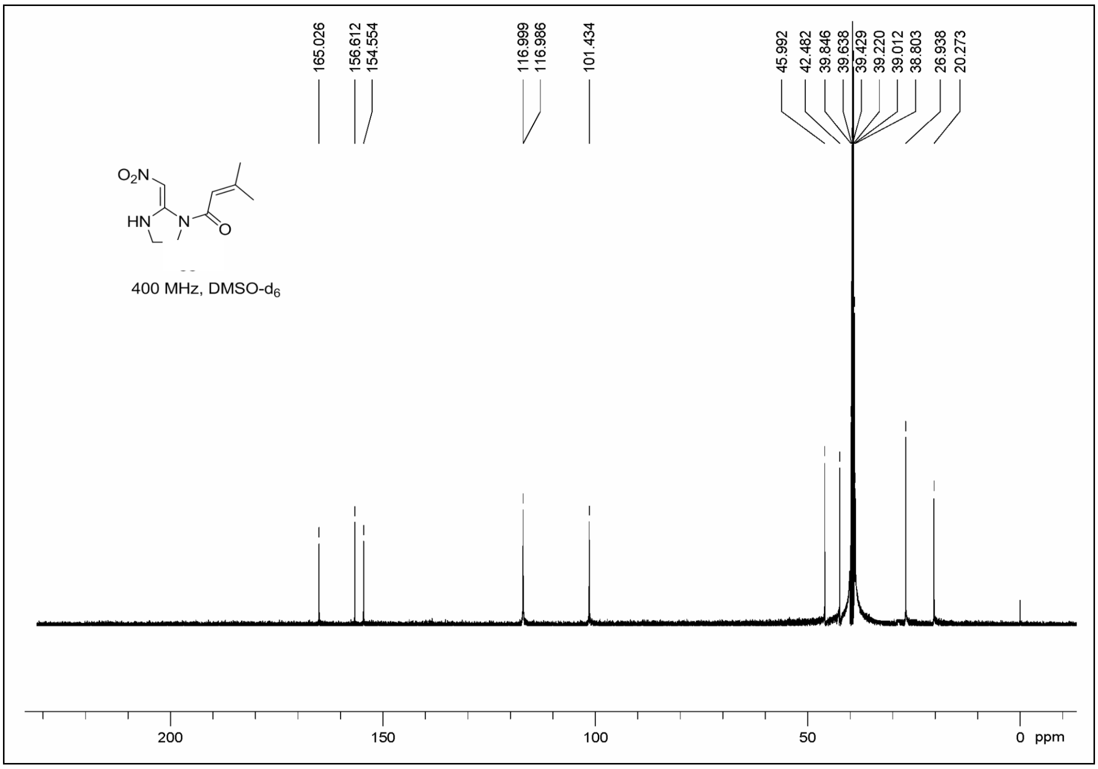
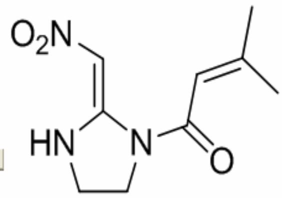


Figure 7. 204. ^{13}C NMR (100 MHz, DMSO-d6) spectrum of compound **239a**

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3
Monoisotopic Mass, Even Electron Ions
14 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:

Mass	Calc. Mass	mDa	PPM	DBE	Formula	i-FIT	i-FIT (Norm)	C	H	N	O
212.1030	212.1035	-0.5	-2.4	4.5	C9 H14 N3 O3	370.7	0.0	9	14	3	3



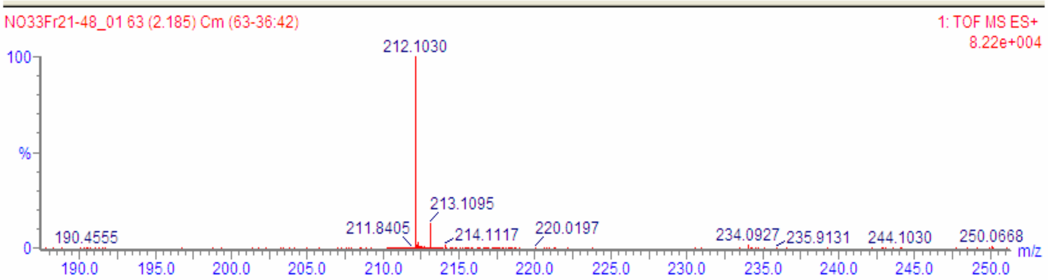


Figure 7. 205. HRMS and elemental composition of compound **239a**