BOLU ABANT IZZET BAYSAL UNIVERSITY

THE GRADUATE SCHOOL OF NATURAL AND APPLIED SCIENCES

DEPARTMENT OF CHEMISTRY

SYNTHESIS AND STRUCTURAL IDENTIFICATION OF SOME NEW BENZOTHIADIAZINE-RELATED DERIVATIVES

MASTER OF SCIENCE

ZEYNEP GEDİK ÖZŞENTÜRKLÜ

BOLU, AUGUST 2019

APPROVAL OF THE THESIS

SYNTHESIS AND STRUCTURAL IDENTIFICATION OF SOME NEW BENZOTHIADIAZINE-RELATED DERIVATIVES submitted by **Zeynep GEDİK ÖZŞENTÜRKLÜ** in partial fulfillment of the requirements for the degree of **Master of Science** in **Department of Chemistry, The Graduate School of Natural and Applied Sciences of BOLU ABANT IZZET BAYSAL UNIVERSITY in 08/04/2019** by

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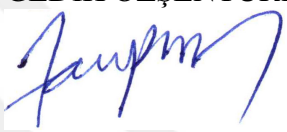
To my family

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.

Zeynep GEDİK ÖZŞENTÜRKLÜ



ABSTRACT

SYNTHESIS AND STRUCTURAL IDENTIFICATION OF SOME NEW BENZOTHIADIAZINE-RELATED DERIVATIVES
MSC THESIS
ZEYNEP GEDİK ÖZŞENTÜRKLÜ
BOLU ABANT IZZET BAYSAL UNIVERSITY GRADUATE SCHOOL OF NATURAL AND APPLIED SCIENCES
DEPARTMENT OF CHEMISTRY
(SUPERVISOR: PROF. DR. YAŞAR DÜRÜST)

BOLU, AUGUST 2019

The aim of this work is to synthesize some new 4H-1,2,4-benzothiadiazine 1,1-dioxide derivatives with a new aproach and identify their structures by means of spectral and physical data.

This research work has been constructed primarily based on the synthesis of some 3-aryl-4H-1,2,4-benzothiadiazine-1,1-dioxide derivatives and then determination of their structures. Novelty of the chemistry can be described as follows; benzothiadiazine 1,1-dioxide derivatives exhibit various important biological activities and some of them are currently being used as medicines containing benzothiadiazine 1,1-dioxide skeleton. For this reason, major purpose is to obtain these compounds by incorporating chloromethyl oxadiazoles by means of microwave irradiation or otherwise classical methods. The new compounds to be obtained will be elucidated by means of spectroscopic and physical methods.

In summary, within this work, despite the difficulties encountered during the experiments, we succesfully synthesized 8 new benzothiadiazine-1,1-dioxide derivatives carrying 1,2,4-oxadiazolylmethyl group at 4-position of the benzothiadiazine ring. Synthesis of amidoximes and chloromethyl oxadiazoles as starting materials were carried out and their nucleophilic substitution reaction with benzothiazines dioxides were performed leading to target N-substituted products.

All of these compounds are new and original and they are considered to make a remarkable contribution to the literature of synthetic organic chemistry. It is strongly possible that the compounds are potentially bioactive due to having the main skeleton and substituents. But, unfortunately, at the moment, we were not able to conduct a bioactivity screening of the compounds due to the low amounts of them and, in addition, regarding unrecoverable from DMSO-d_6 NMR solutions.

KEYWORDS:
Benzothiadiazine 1,1-dioxide, amidoxime, aminosulfonamide, aldoxime, oxadiazole, microwave, spectroscopy.

ÖZET

BAZI YENİ BENZOTİYADİAZİN TÜREVLERİNİN SENTEZİ VE YAPILARININ BELİRLENMESİ
YÜKSEK LİSANS TEZİ
ZEYNEP GEDİK ÖZŞENTÜRKLÜ
BOLU ABANT İZZET BAYSAL ÜNİVERSİTESİ
FEN BİLİMLERİ ENSTİTÜSÜ
KİMYA ANABİLİM DALI
(TEZ DANIŞMANI: PROF. DR. YAŞAR DÜRÜST)

BOLU, AĞUSTOS - 2019

Bu tez çalışmasının amacı, bazı yeni 4H-1,2,4-benzotiadiazin 1,1-dioksit türevlerini yeni bir yaklaşımla sentezlemek ve yapılarını spektral ve fiziksel verilerle tanımlamaktır.

Bu araştırma çalışması, temel olarak bazı 3-aril-4H-1,2,4-benzotiadiazin-1,1-dioksit türevlerinin sentezine ve daha sonra yapılarının belirlenmesine dayanarak yapılmıştır. Kimyadaki yeniliği şöyle düşünülebilir; benzotiadiazin 1,1-dioksit türevleri çeşitli önemli biyolojik aktiviteler sergilerler ve bazıları şu anda benzotiadiazin 1,1-dioksit iskeleti içeren ilaçlar olarak kullanılmaktadır. Bu nedenle amacımız, bu bileşikleri, klorometil oksadiazollerle, mikrodalga ışıması ya da klasik ısıtma yöntemleri kullanarak birleştirerek elde etmektir. Elde edilen yeni bileşiklerin yapıları, spektroskopik ve fiziksel yöntemlerle aydınlatıldı.

Özet olarak, bu çalışma içerisinde, deneyler sırasında karşılaşılan zorluklara rağmen, benzotiyadiazin halkasının 4-konumunda 1,2,4-oksadiazolilmetil grubu taşıyan 8 yeni benzotiadiazin-1,1-dioksit türevi başarıyla sentezlendi. İlk olarak başlangıç bileşikleri para substitue benzamidoksimler ve klorometil oksadiazoller sentezlendi ve benzotiyazinler dioksitlerle etkileştirildi.

Bu bileşiklerin tümü yeni ve orijinaldir ve sentetik organik kimya literatürüne kayda değer bir katkı sağladığı düşünülmektedir. Bileşiklerin taşıdıkları gruplara göre potansiyel olarak biyolojik olarak aktif olmaları beklenmektedir. Ancak, ne yazık ki, şu anda, düşük miktarlarda olmaları ve DMSO-d_6 NMR çözeltilerinden geri kazanılamaz olmalarından dolayı bileşiklerin biyoaktivite taraması gerçekleştirilememiştir.

ANAHTAR KELİMELER:
Benzotiyadiazin 1,1-dioksit, amidoksim, aminosulfonamid, aldoksim, microdalga, spektroskopi.

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^{13}C	**:** Carbon-13
^{1}H	**:** Proton
AcOH	**:** Acetic acid
Ar	**:** Aryl
CDI	**:** Carbonyldiimidazole
$Ca(NTf_2)_2$	**:** Calcium(II) bis(trifluoromethanesulfonimide)
$CDCl_3$	**:** Deuterated chloroform
$CH(OEt)_3$	**:** Triethyl orthoformate
DABCO	**:** 1,4-Diazabicyclo[2.2.2]octane
DABSO	**:** Bis(Sulfur Dioxide)-1,4-diazabicyclo[2.2.2]octane Adduct
DMAD	**:** Dimethylacetylene dicarboxylate
DMF	**:** Dimethyl formamide
DMSO-d_6	**:** Deuterated dimethylsulfoxide
EA	**:** Ethyl acetate
eq.	**:** Equivalent
Et	**:** Ethyl
Et_3N	**:** Triethylamine
EtOH	**:** Ethanol
EtOAc	**:** Ethyl acetate
FTIR	**:** Fourier-transform infra-red
g	**:** Gram
H	**:** Hexane
h	**:** Hour
LC-MS	**:** Liquid chromatography- mass spectrometry
Hz	**:** Hertz
IR	**:** Infra-red
J	**:** Coupling constant
$K_2S_2O_8$	**:** Potassium persulfate
KBr	**:** Potassium bromide
m.p.	**:** Melting point
m/z	**:** Mass to charge ratio

M^+ : Molecular ion

Me : Methyl

MeO : Methoxy

MeOH : Methanol

mg : Miligram

MHz : Megahertz

min : Minute

ml : Mililiter

mmol : Milimole

MW : Microwave

NaOH : Sodium hydroxide

Na_2SO_4 : Sodium sulfate

NH_2 : Amine

NCS : N-chlorosuccinimide

NMR : Nuclear magnetic resonance

NO_2 : Nitro

OH : Hydroxyl

$PhSO_2F$: Fluorobenzenesulfonamide

Ph : Phenyl

R : Radical group

R_f : Retention factor

RT : Room temperature

SmI_2 : Samarium(II) iodide

SO_2 : Sulfur dioxide

TMS : Tetramethylsilane

TLC : Thin Layer Chromatography

UV : Ultra-violet

v/v : Volume per volume

δ : Chemical shift

Δ : Heat

υ : Wavenumber

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Firstly, I would like to express my very great appreciation to my supervisor Prof. Dr. Yaşar DÜRÜST for his valuable support, encouragements, advice and immense knowledge. His guidance helped me at all stages of this work including writing the thesis and he allowed me reach whenever I needed and directed me in a correct manner within whole period of research. I will always be grateful for having the opportunity to carry out research work under his supervision.

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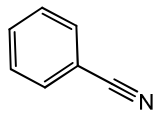
Finally, my deep and sincere gratitude to my family and to my husband Erhan ÖZŞENTÜRKLÜ for their continuous and unparalleled love, help and support through the process of research work and writing this thesis. This achievement would not have been possible without them, and I dedicate this work to them.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

FORMULAE



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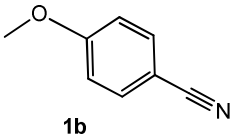

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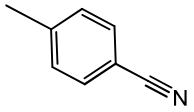

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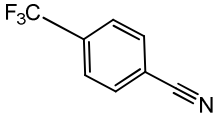

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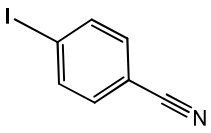

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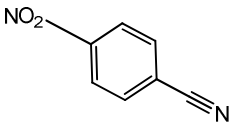

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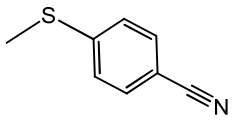

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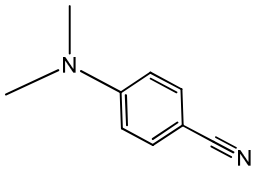

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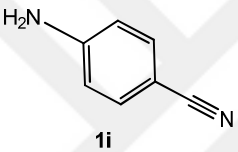

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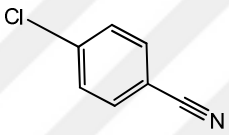

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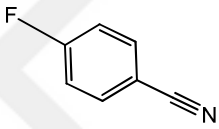

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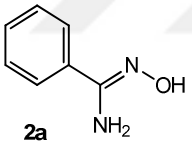

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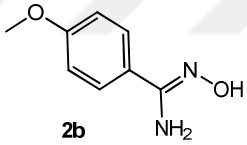

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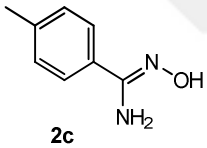

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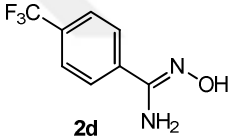

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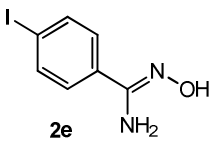

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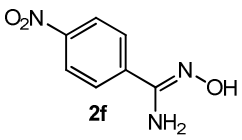

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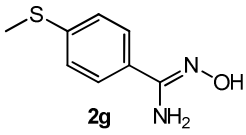

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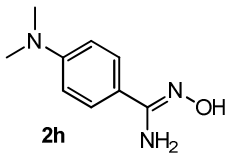

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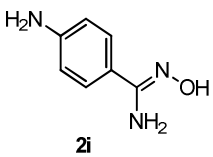

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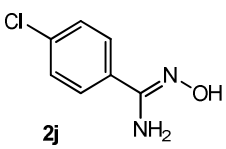

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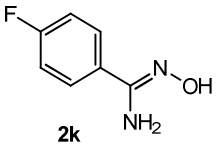

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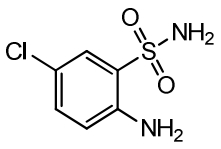

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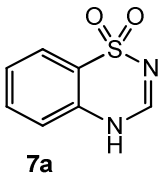

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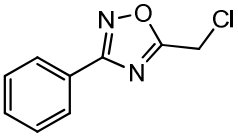

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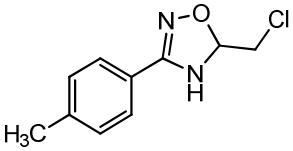

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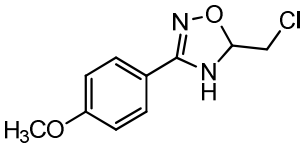

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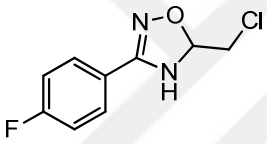

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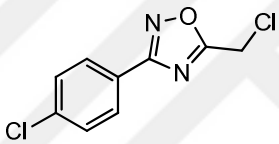

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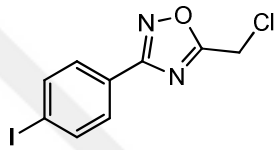

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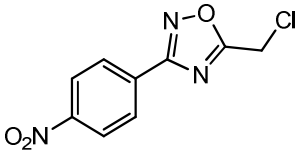

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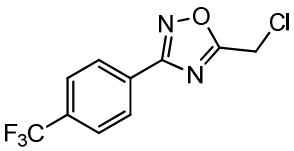

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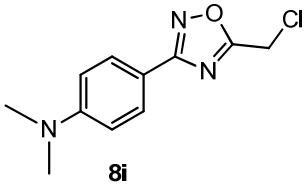

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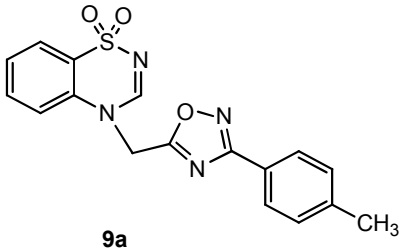

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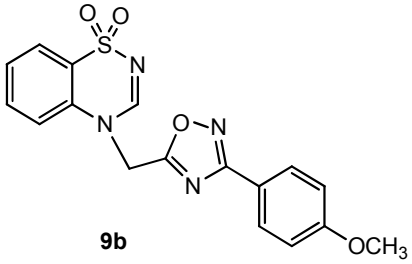

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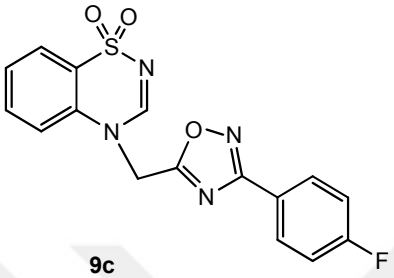

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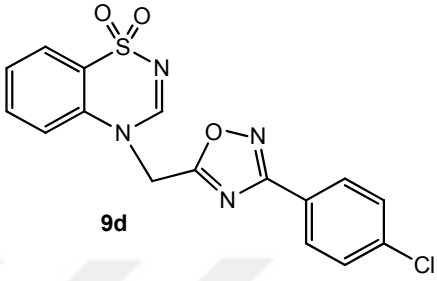

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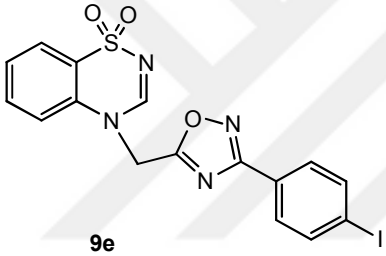

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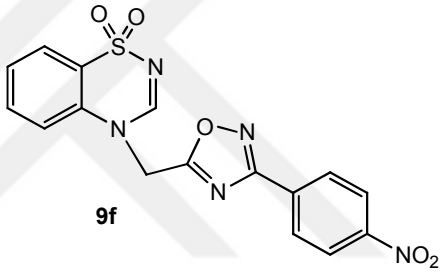

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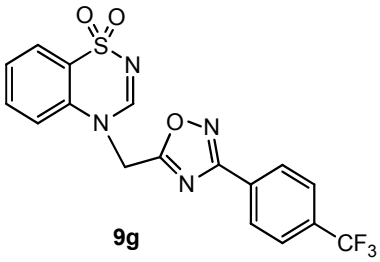

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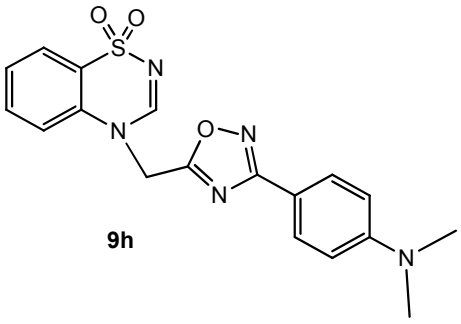


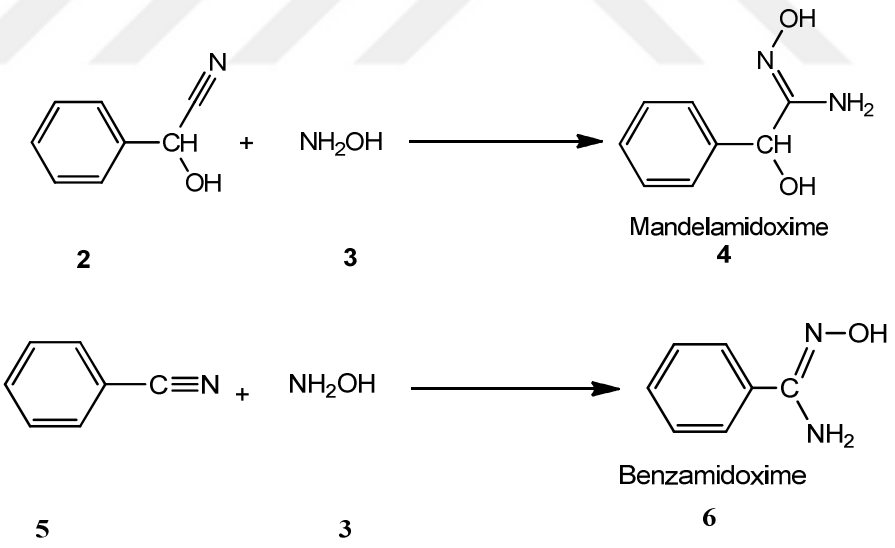
9h

1. INTRODUCTION

1.1 AMIDOXIMES

Amidoximes which are one of the major starting materials for this work, in general, are useful precursors for the construction of a great number of O, N containing heterocyclic scaffolds and have been found to unveil many engrossing biological activities against various species. The amidoxime group was reported to act as a prodrug for the amidine structure (De Morais, Hallwass, Malvestiti, & Srivastava, 2006).

Tiemann described firstly the name "amidoxime" and prepared two compounds through the addition of hydroxylamine to benzaldehyde cyanohydrin and to benzonitrile (Eloy & Lenaers, 2002) (Scheme 1.1).



Scheme 1.1. Mandelamidoxime and benzamidoxime reactions

Although the first synthesis of an amidoxime compound was managed by Lossen and Schifferdecker (1873) via HCN and NH_2OH interaction, they were not able to identify real structure, and they called "isuretin" (Figure 1.1).

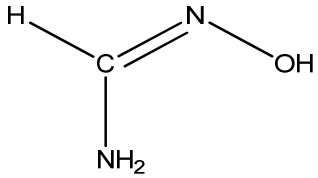


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Figure 1.1. Structure of isuretin (formamidoxime)

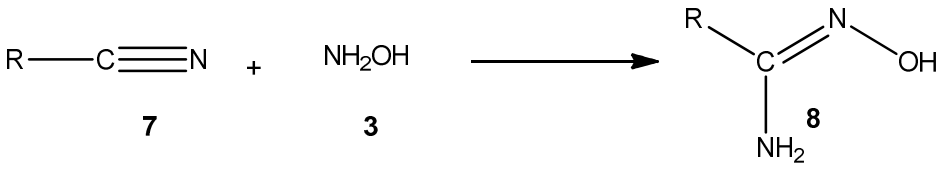
Some amidoxime derivatives have been reported to have shown anti-leukemic, bactericidal and fungicidal, local anesthetics, and fibrinogen receptor antagonist activities (Nagahara & Nagahara, 2014; Srivastava et al., 1997).

There have been an increasing interest in the synthesis of amidoximes over the decades by development of new methods (Sanguineti et. al., 2011;Voros et. al., 2014).

1.1.1. Synthesis of Amidoximes

1.1.1.1 Action of Hydroxylamine on Nitriles

The preparation of amidoximes from nitriles by the action of hydroxylamine was utilized by Tiemann and Krüger (1884) (Scheme 1.2).



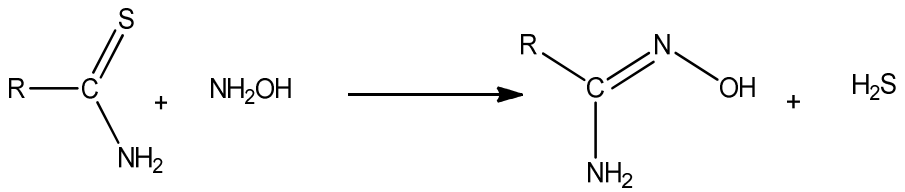
7 **3**

Scheme 1.2. Action of hydroxylamine on nitriles

They recommended a method involving the addition of the equivalent amount of nitrile in enough alcohol (generally ethanol) to hydroxylamine hydrochloride accompanying a base (sodium carbonate, triethylamine, sodium hydroxide, potassium hydroxide) leading amidoximes at 60–80˚C within a couple of hours. The highest yields were reported in the case of an excess hydroxylamine in butanol (Eloy & Lenaers, 2002).

1.1.1.2 Action of Hydroxylamine on Amides or Thioamides

Thioamides were also used to prepare some aromatic amidoximes by the action of hydroxylamine (Scheme 1.3).



Scheme 1.3. Action of hydroxylamine on thioamides

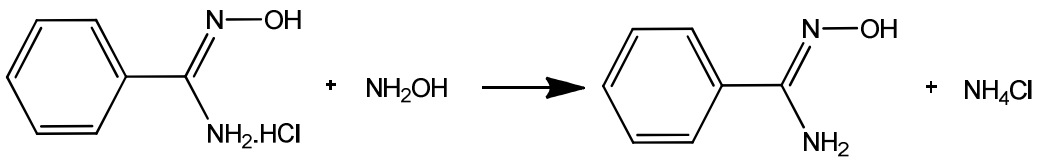
1.1.1.3 Reduction of Nitrosolic Acids

Benzonitrosolic and nitrolic acids have been reduced with hydrogen sulfide to give amidoximes (Brady & Peakin, 1929).

Scheme 1.4. Reduction of nitrosolic acids to give amidoxime

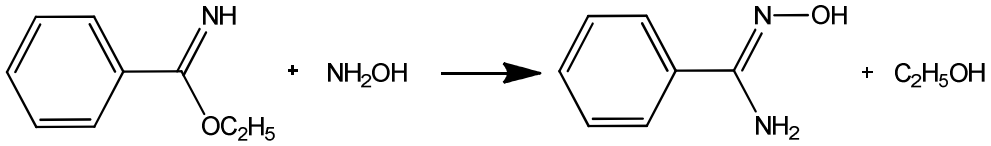
1.1.1.4 Action of Hydroxylamine on Amidine Hydrochlorides and Iminoethers

Pinner also developed a method involving the interaction of hydroxylamine and amidine hydrochlorides and iminoethers to yield benzamidoxime (Scheme 1.5).



Scheme 1.5. Synthesis of benzamidoxime by Pinner

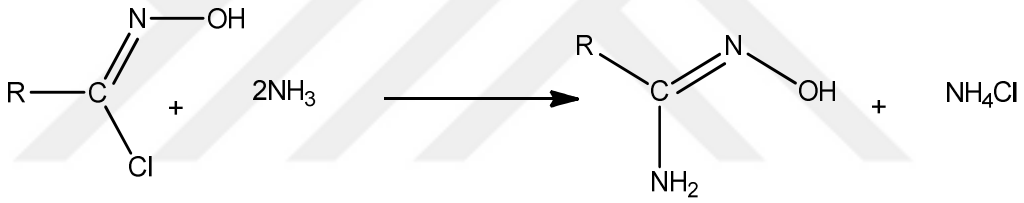
According to Pinner and Lossen's method, benzamidoxime was obtained straightforward manner by interacting ethyl iminobenzoate with hydroxylamine accompanying ethanol release (Scheme 1.6).



Scheme 1.6. Synthesis of benzamidoxime by Pinner and Lossen

1.1.1.5 Action of Ammonia on Hydroxamic Acid Chlorides

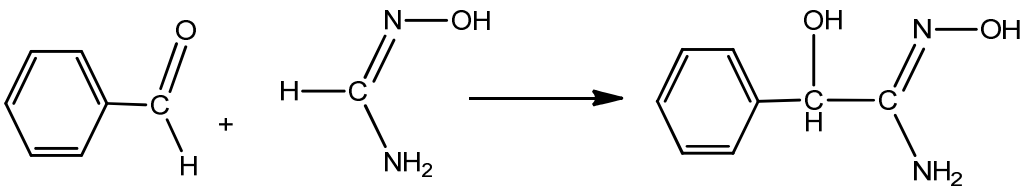
Direct chlorination of aldoximes leaded to chloroximes or hydroxamic acid chlorides. Further, these compounds reacts straightforwardly with ammonia or other primary or secondary amines to yield amidoximes (Werner&Buss,1894).



Scheme 1.7. Action of ammonia on chloroxime

1.1.1.6 Action of Formamidoxime on Aromatic Aldehydes

Conduché (1908) carried out a reaction where formamidoxime reacted with benzaldehyde ending up to an aldol type condensation product.



Scheme 1.8. Interaction of benzaldehyde with formamidoxime

1.1.2 Physical Properties of Amidoximes

As they are usually obtained in fine crystals, amidoximes, especially aromatic ones, display sharp melting points.They can be decomposed by heating over the melting point. They tend to be soluble in lower amounts in water and higher in alcohols and also in some polar organic solvents. In addition, aromatic ones are more stable than aliphatic ones in terms of decomposing tendency. The aqueous solubilities of aliphatic amidoximes decrease with increasing molecular weight. The amidoximes are considered to be O–H acids, not N–H acids which can be accounted for the remarkable higher pK_{HA} of O-methyl derivative of benzamidoxime (pK_{HA} value is 26.0). The pK_{HA} value of benzamidoxime itself is 23.0 (Bordwell & Ji,1992). Acidity measurements have been performed for a variety of amidoximes (Dürüst et. al., 2002; Dürüst, et. al. 2000; Akay et. al., 1999).

Tautomerism, conformation, and configuration are important characteristics observed in amidoximes (Figure 1.2) (Novikov & Bolotin, 2018;Eloy & Lenaers, 2002).

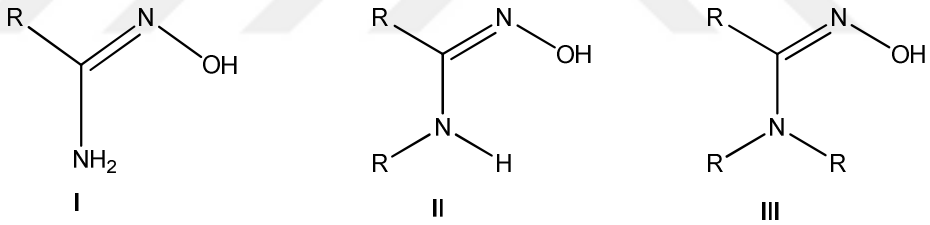


Figure 1.2. Amidoximes

IR and NMR data of the O-acyl derivatives of amidoximes reveal that they exist in solutions in the amino oxime form (Bauer et al.,1964). In the IR spectra of amidoximes, two distinct absorption bands are mostly observed; the first one is a doublet at (3484–3412 cm^{-1}) and (3378–3300 cm^{-1}) which can be assigned to NH_2 stretching vibrations; the second one (1680 and 1644 cm^{-1}) is considered as of C=N absorption. Very broad NOH stretching band which is attributed to strong both intra and intermolecular hydrogen bonding interactions, appears at approximately 3125 cm^{-1} (Field et. al., 2008).

1.2 OXADIAZOLES

In the oxadiazole ring there are two nitrogens and one oxygen atom, totally five atoms and suffix –ole stands for a five-membered heterocycle according to IUPAC nomenclature system. According to IUPAC numbering recommendations, oxadiazoles may be depicted as 1,2,4-, 1,2,5-, 1,2,3- and 1,3,4-oxadiazoles. The numbers are indicating the locations of heteroatoms with their compatible priority (State et al., 1995) (Figure 1.3).

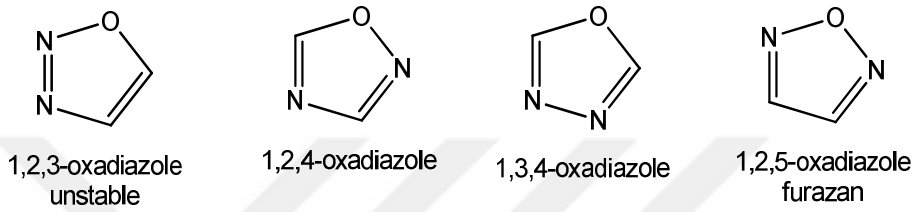


Figure 1.3. Representation of simple oxadiazoles

Depending on the ring composition and position of the heteroatoms they have been reported to exhibit diverse bioactivities against various species such as fungi, bacteria, gastric ulcer, cancer, etc. (Bishayee et al., 1997;Chitamber and Wereley, 1997). As a representative example, 1,3,4-oxadiazoles bearing substitution at 3 and 5 positions display activities regarding antibacterial, , antimalarial, antiinflammatory antifungal and anticonvulsant (Silvestrini&Pagatti, 1961;Sharma&Bahel, 1982;Jain et al., 2009;Hutt et al., 1970;Modi & Modi, 2012).

Generally speaking of oxadiazole itself, the ring is a very weak base due to the lone pairs of nitrogens which are sp^2-hybridized. Incorporation of two -CH= groups in furan by two sp^2-hybridized nitrogens reduces aromaticity of resulting oxadiazole.The aromaticity degree of oxadiazoles was being determined by Bird unified aromaticity index I_A. In this regard, 1,2,4-oxadiazole having I_A of 48 is lower than that of 1,2,5-oxadiazole with a I_A value of 52 (Balaban et. al., 2004; Joule &Mills, 2004).

1.2.1 1,2,4-Oxadiazoles

Namely, 1,2,4-oxadiazoles are composed of five ring atoms three of which are nitrogens and oxygen. They can have also substitutions at 3 and 5 positions depicted as in (Figure 1.4).

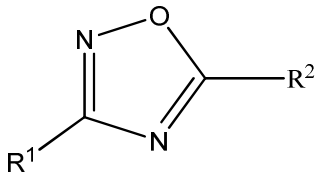


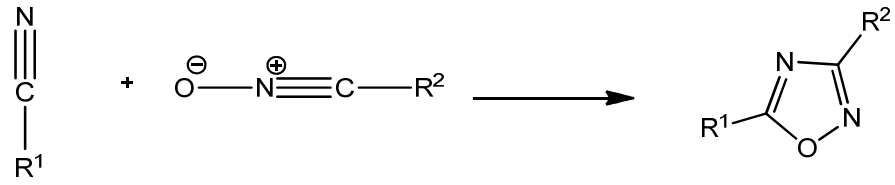
Figure 1.4. A disubstituted 1,2,4-oxadiazole

As a presentation of the general properties of these heterocycles, mechanical interpretations of the thermal and photochemical reactivity of 1,2,4-oxadiazoles have been published recently. Further, their usage in different area of life sciences and chemistry was compiled (Pace, Buscemi, Piccionello, & Pibiri, 2015).

1.2.2 Synthesis of 1,2,4-Oxadiazoles

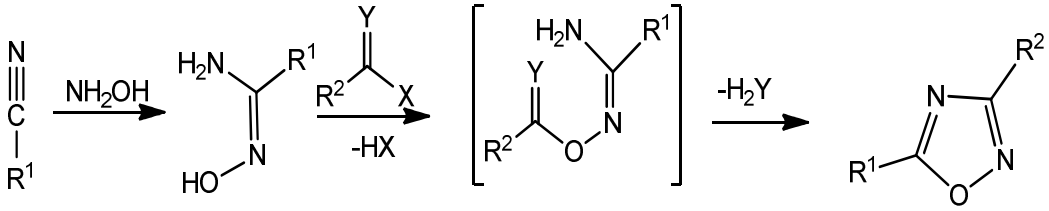
1.2.2.1 Classical methods of synthesis 1,2,4-Oxadiazole

The classical methods to construct 1,2,4-oxadiazole ring utilize different starting reagents and precursors. Among them, cycloaddition strategy is based on the 1,3-dipolar cycloaddition of a nitrile and a nitrile oxide which is mostly generated *in situ* from hydroxamoyl halides, and heterocyclization process via amidoxime-and acid derivative. Both strategies involve a nitrile moiety, the corresponding substituent (R^1) terminating at the final oxadiazole product, in the case of 1,3-dipolar cycloaddition (Scheme 1.9) or at the target oxadiazole position in the amidoxime route (Scheme 1.10) (Pace et al., 2015).



Scheme 1.9. Cycloaddition route leading to oxadiazoles

The intermediate O-acylamidoxime may be isolated before proceeding to the final cyclization step in some transformations depending on reaction and purification conditions.



Scheme 1.10. The amidoxime-acid derivative route leading to oxadiazoles

A recent synthetic protocol for 1,2,4-oxadiazoles carrying ferrocenyl units was reported by Zora et. al., (2014).

1.2.2.2 Reactive Sites in the 1,2,4-Oxadiazole Ring

The 1,2,4-oxadiazole ring can be classified as electron-poor azole due to being the furan-type heterocycle and the two sp^2-hybridized nitrogens. Impact of nitrogens may be considered to resemble the effect exposed by a NO_2 or CN group. Furthermore, due to its asymmetric structure, the electron-withdrawing effect of the 1,2,4-oxadiazole ring is much more sensed in the 5-position than in the 3-position. Induced reactivity by oxadiazole ring and reactive sites in the ring were shown below (Figure 1.5) (Pace et al., 2015).

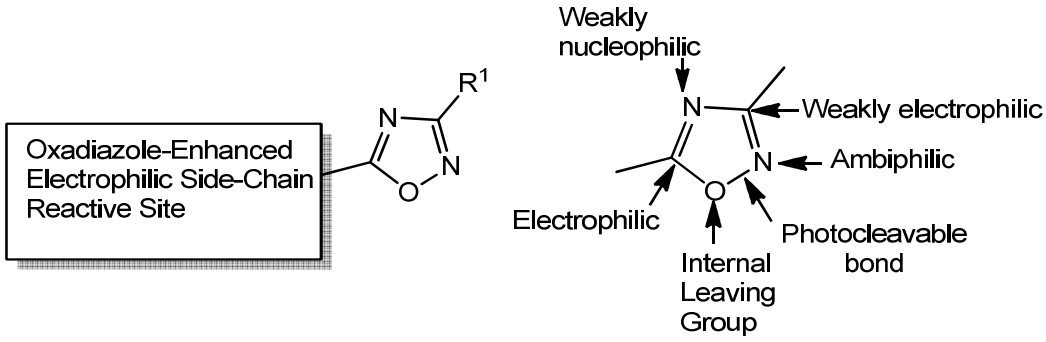
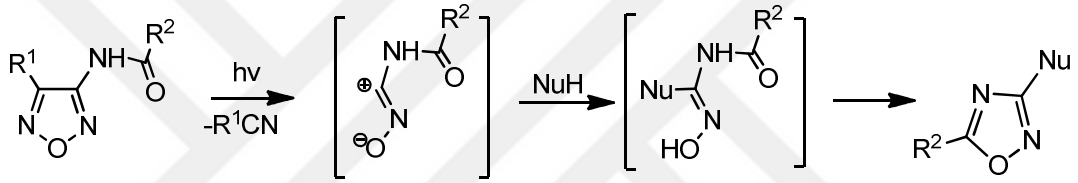


Figure 1.5. Reactivity sites in oxadiazole

1.2.2.3 Contemporary Synthetic Routes to 1,2,4-Oxadiazoles

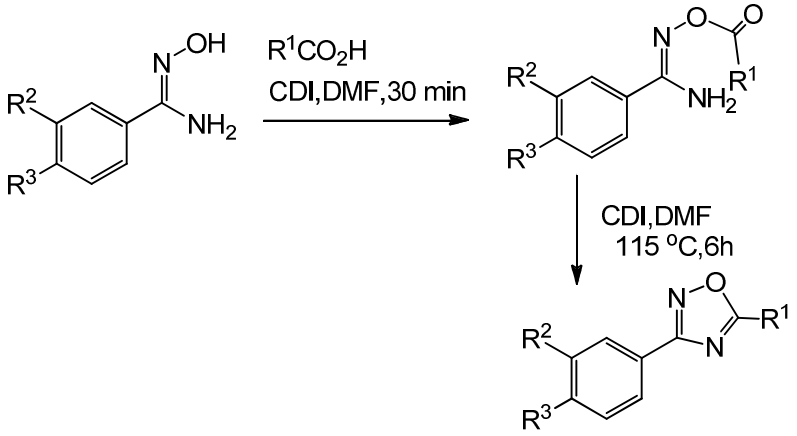
A great number of recent syntheses of 1,2,4-oxadiazole derivatives are based one of the two classical transformations described above (Schemes 1.9 and 1.10). Protected precursors, where a sensitive group which can be affected by reaction medium and conditions is attached to the main oxadiazole skeleton are sometimes used. In some combinatorial cases, reactive precursors are particularly generated *in situ*; as an example, acylamino furazan is being converted into the 1,3-dipolar intermediate through a photoinduced reverse cycloaddition pathway, then sequentially it is attacked by the nucleophile (Nu) and turns into open-chain intermediate and finally cyclizes into 1,2,4-oxadiazole (Scheme 1.11) (Pace et al., 2015).



Nu = NH, NR, OR.

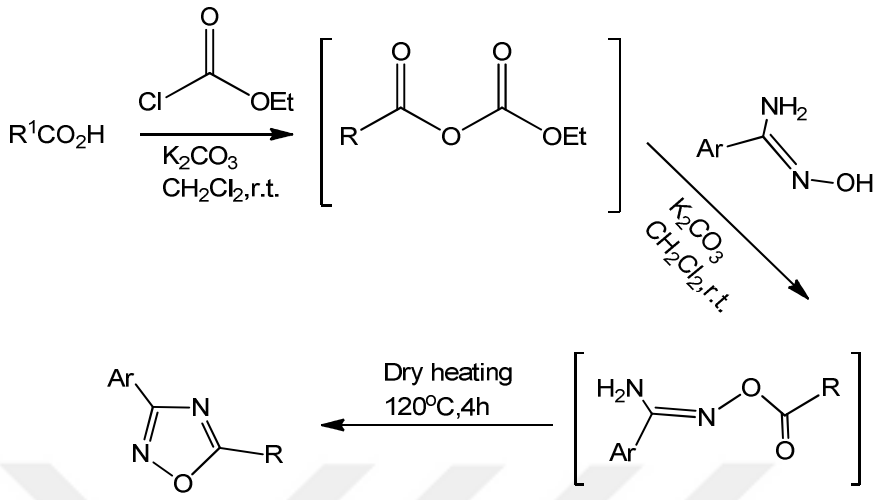
Scheme 1.11. Retro-cycloaddition reaction of acylamino furazan leading to 1,2,4-oxadiazole

Another method uses carbonyl diimidazole (CDI) activation involving an acyl amidoxime intermediate then cyclization to 1,2,4-oxadiazole end product (Scheme 1.12) (Deegan, et. al.,1999).



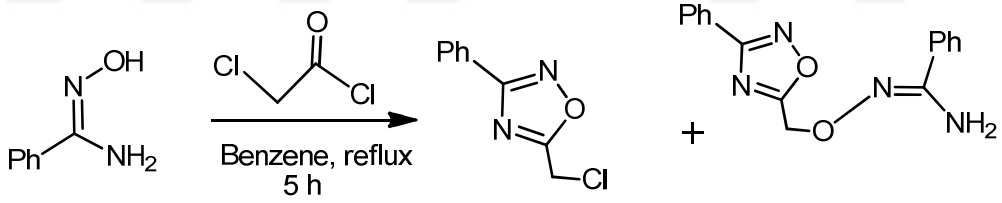
Scheme 1.12. Carbonyl diimidazole route to 1,2,4-oxadiazole

Starting from carboxylic acid, 1,2,4-oxadiazoles have been synthesized using ethyl chloroformate then cyclization of intermediate (Filho et. al., 2009).



Scheme 1.13. Ethyl chloroformate and acid route to 1,2,4-oxadiazole

Ağırbaş et. al., (1992) reported a synthesis where end products are a mixture of 5-chloromethyl oxadiazole and O-amidoximate mixture, being predominantly the compound 40**.**



Scheme 1.14. Chloroacetyl chloride and amidoxime reaction

1.3 SULFONAMIDES

Upon the recognition of the importance of sulfonamides in the early 1930s, thanks to them, many bacterial diseases have been treated. Sulfonamides are now widely used in pharmaceutical preparations, agrochemicals. Penoxsulam, Probenecid and Sulfadiazine which are on the pharmaceutical market as best selling drugs belong to sulfonamide carrying molecules (Figure 1.6). Sulfonamide formation usually takes place within a reaction of corresponding amines and sulfonyl chlorides. However, the synthetic routes for sulfonyl chlorides are often carried out in

extremely dry reaction medium and need special precations due to hazardous chemicals, contaminants or oxidants (Zhang et al., 2018).

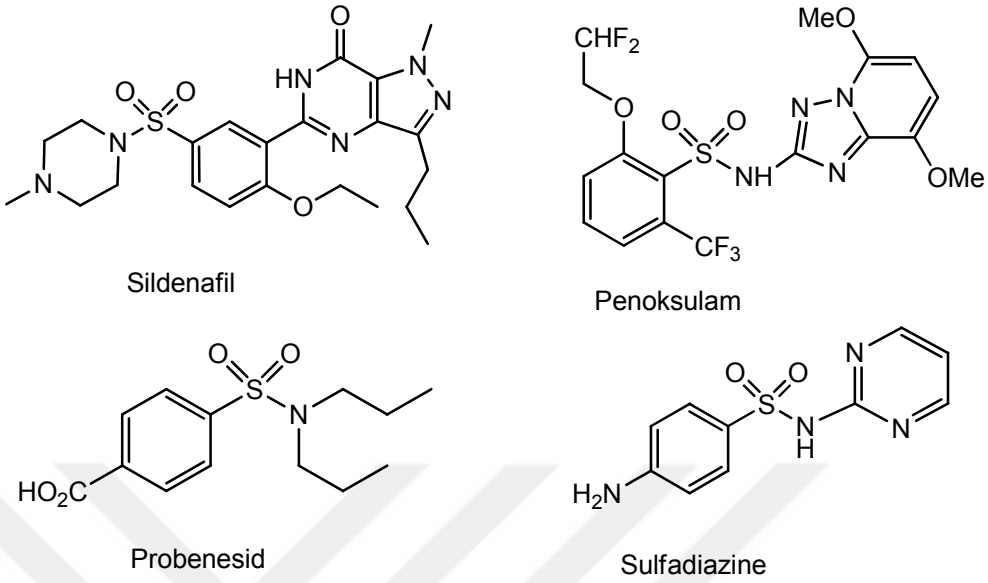
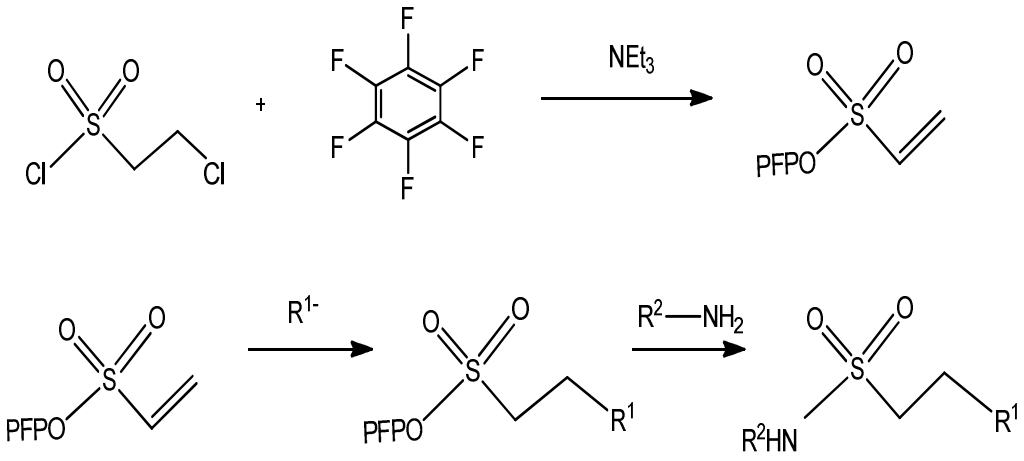


Figure 1.6. Some sulfonamide drugs in pharmaceutical market

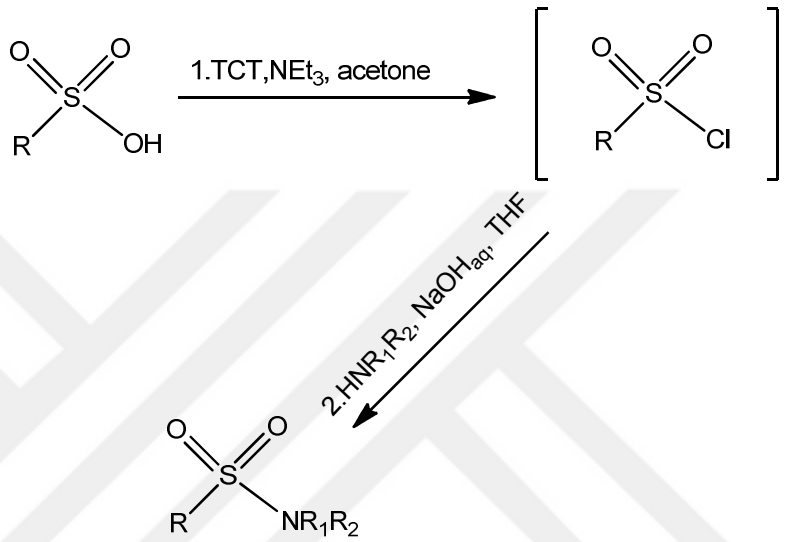
1.3.1 Synthesis of Sulfonamides

Aromatic sulfonamides carrying chiral centers have been found to be effective carbonic anhydrase inhibitors. In general, sulfonamides are formed by reaction of sulfonyl chloride and ammonia or amines. Caddick et. al., (2002) reported a method involving an intermolecular radical addition to pentafluorophenyl vinylsulfonate and sequential aminolysis (Scheme 1.15).

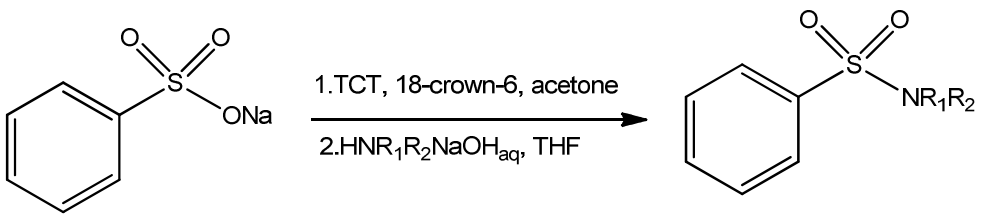


Scheme 1.15. Sulfonamide synthesis via radical addition method

There are two synthetic methodologies to obtain compounds of medicinal importance containing a sulfonamide group exhibiting significant therapeutic role from a sulfonic acid. First one uses TCT or cyanuric chloride as chlorinating agent for sulfonic acid and then triethylamine added to yield sulfonyl chloride. Successively, a secondary amine is added to the reaction mixture. Second method starts with sodium sulfonate salt and uses a crown ether as catalyst (De Luca & Giacomelli, 2008) (Schemes 1.16 and 1.17).



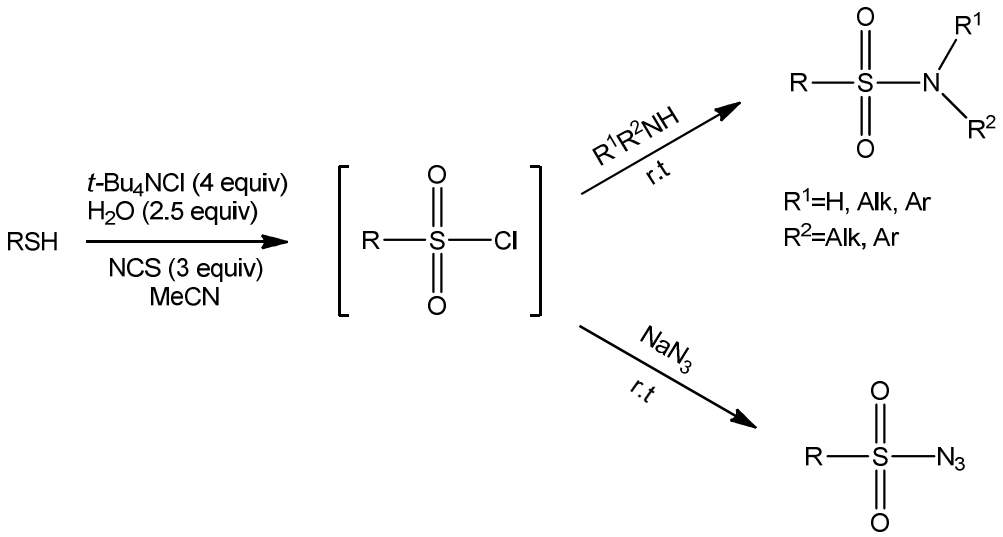
Scheme 1.16. Sulfonamide synthesis from sulfonic acids



Scheme 1.17. Sulfonamide synthesis from sulfonic acid sodium salts

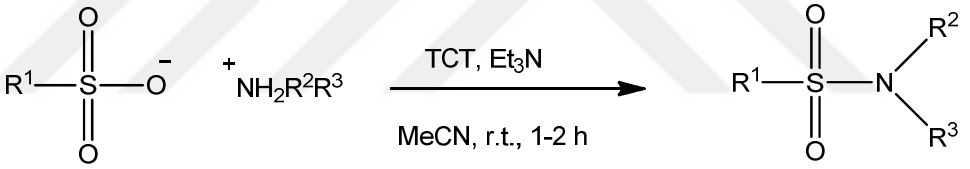
Sulfonamide synthesis was managed by reacting sulfonic acid with isocyanide at room temperature (Shaabani et. al., 2007).

A transformation using ionic liquid as medium leading to sulfonamides and sulfonyl azides directly from thiols using NCS was reported (Veisi, Ghorbani-Vaghei, Hemmati, & Mahmoodi, 2011) (Scheme 1.18).



Scheme 1.18. Sulfonamides and sulfonyl azides directly from thiols using *N*-chlorosuccinimide (NCS) in ionic liquids

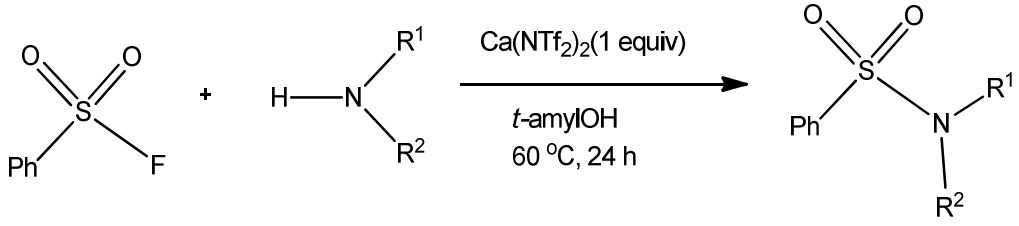
Preparation of sulfonamides from various primary and secondary amine sulfonate salts using triethylamine as base and cyanuric chloride or TCT in acetonitrile (Rad et al., 2009) (Scheme 1.19).



R^1=Alk, Ar
R^2, R^3 =H, Alk, Ar,Allyl, Benzyl, Heterocycle

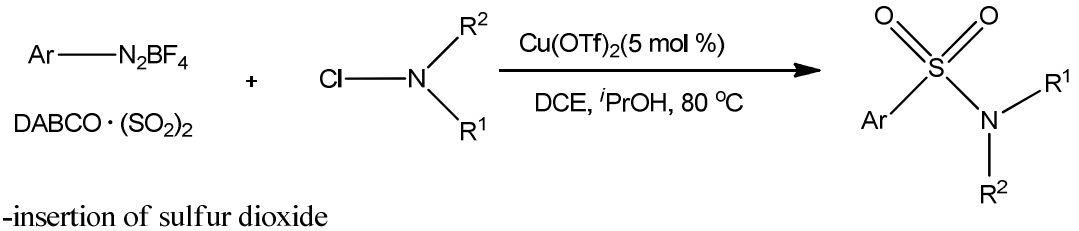
Scheme 1.19. Sulfonamide preparation from an dialkylamino–sulfonate salt

Ca $(NTf_2)_2$ was utilized as catalyst to perform disubstituted sulfonamide synthesis via the reaction between benzene sulfonyl fluoride and aromatic (or heteroaromatic) amines with high yields (Scheme 1.20) (Mukherjee et al., 2018).



Scheme 1.20. Sulfonamides from $PhSO_2F$ by the effect of triflate catalyst

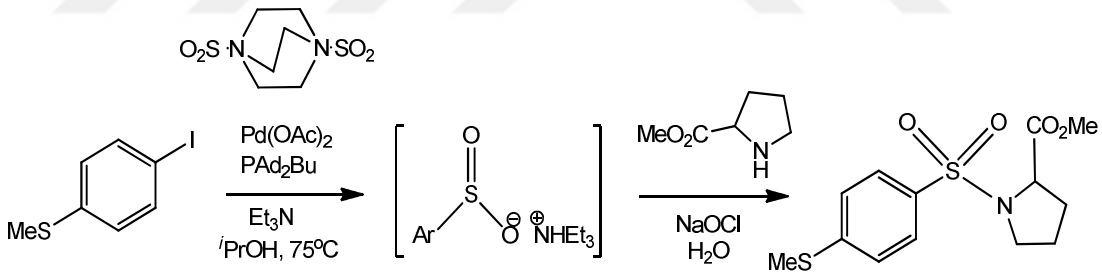
Zhang et al., (2018) reported a multicomponent synthetic protocol incorporating aryl diazotetrafluoroborate bicyclic base, SO_2 and chloroamine with accompanying a triflate salt (Scheme 1.21).



-insertion of sulfur dioxide
-mild condition and broad substrate scope
-construction of valuable sulfonamides

Scheme 1.21. A multicomponent generation of sulfonamides with aryldiazotetrafluoroborate, DABCO·$(SO_2)_2$, and N-chloroamine

Under the action of a palladium catalyst, the aryl ammonium sulfates conveniently were prepared from aryliodides and DABSO and then intermediate sulphinate salt underwent a reaction with pyrrolidine carboxylate in the presence of sodium hypochlorite to give sulfonamide (Flegeau et. al., 2016) (Scheme 1.22).



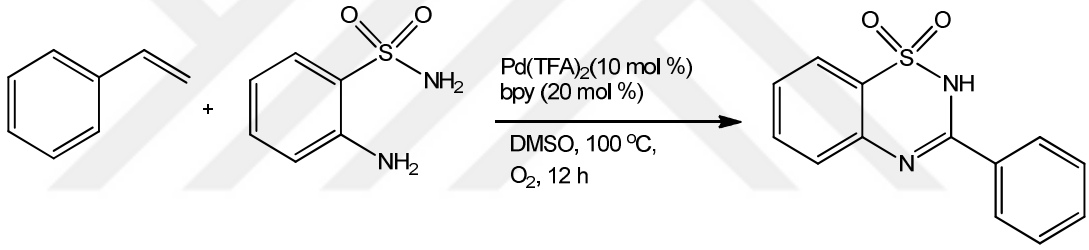
Scheme 1.22. Palladium-catalyzed sulfination of aryl iodides for sulfonamide synthesis

1.4 BENZOTHIADIAZINES

Benzothiadiazine-1,1-dioxides are important scaffolds in heterocyclic chemistry due to their various biological activities as diuretics, antihypertensive, anticancer, antimicrobial (Karpe et. al., 2019). Literature survey reveals that first synthesis was accomplished by Parke &Williams in 1950.

Over the last few decades, a number of different methods have been introduced related to benzothiadiazine-1,1-dioxides that is a compilation of literature citations of the specific and representative syntheses can be given as follows; Restrepo et.al., (2011) used synthetic sequence through aminobenzenesulfonamide and aldehyde or carboxylic acids by means of microwave heating.

Iwakawa et. al., (1991) reported a cycloaddition pathway to afford sulfonamides. Yang et al., (2009) used transition metal catalyzed reactions to synthesize 1,2,4-benzothiadiazine-1,1-dioxide. In this regard, iron catalyst provided the combination of 2-bromobenzenesulfonamide with amidine hydrochloride. Among the most recently published studies, Karpe et. al., (2019) have studied palladium-catalyzed cleavage initiated by oxygen and subsequent cyclization reaction of aminosulfonamides with styrene leading to 3-substituted benzothiadiazine-1,1-dioxide (Scheme 1.23).



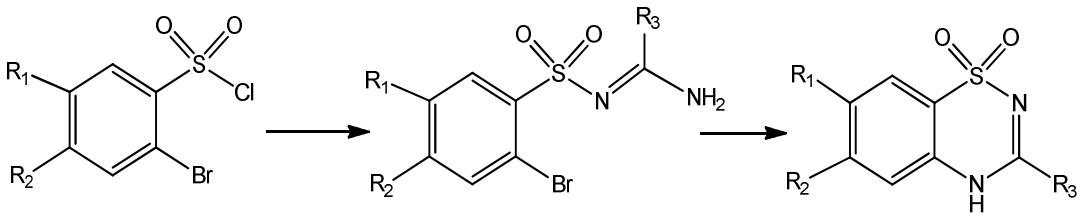
Scheme 1.23. Phenyl substituted benzothiadiazine-1,1-dioxide from styrene and amino sulfonamide

1.4.1 Synthesis of Benzothiadiazine Derivatives

1.4.1.1 Synthesis of 4H-1,2,4-benzothiadiazine-1,1-dioxide

Some of the antihypertensive, antiviral (including anti-HIV) and antimicrobial compounds have the common structural 1,2,4-benzothiadiazine-1,1-dioxide moiety. So-called ring is generally constructed by incorporating the *o*-aminobenzenesulfonamides with orthoesters or acylating reagents. The main disadvantage of this method is the difficulties encountered in the synthesis and availability of *o*-aminosulfonamides. An alternative way is presented by Cherepakha et. al., (2011) who developed a one-pot approach based on ring closure under

Friedel-Crafts conditions through a conjugate addition (Michael) of chlorosulfonyl isocyanate to anilines. This group also performed a successful transformation in a combination of *o*-bromobenzylsulfonyl azide with highly substituted terminal acetylene in the presence of NH_4Cl (Scheme 1.24).



Scheme 1.24. 4H-1,2,4- benzothiadiazine-1,1-dioxides synthesis

2. AIM AND SCOPE OF THE STUDY

The core 1,2,4-benzothiadiazine ring having sulfone group can be found in the structure of many bioactive substances; especially in anti-Alzheimer, anti-hypertensive, anti-microbial, anti-viral and anti-scizophrenia agents (Parenti et al.,1988).

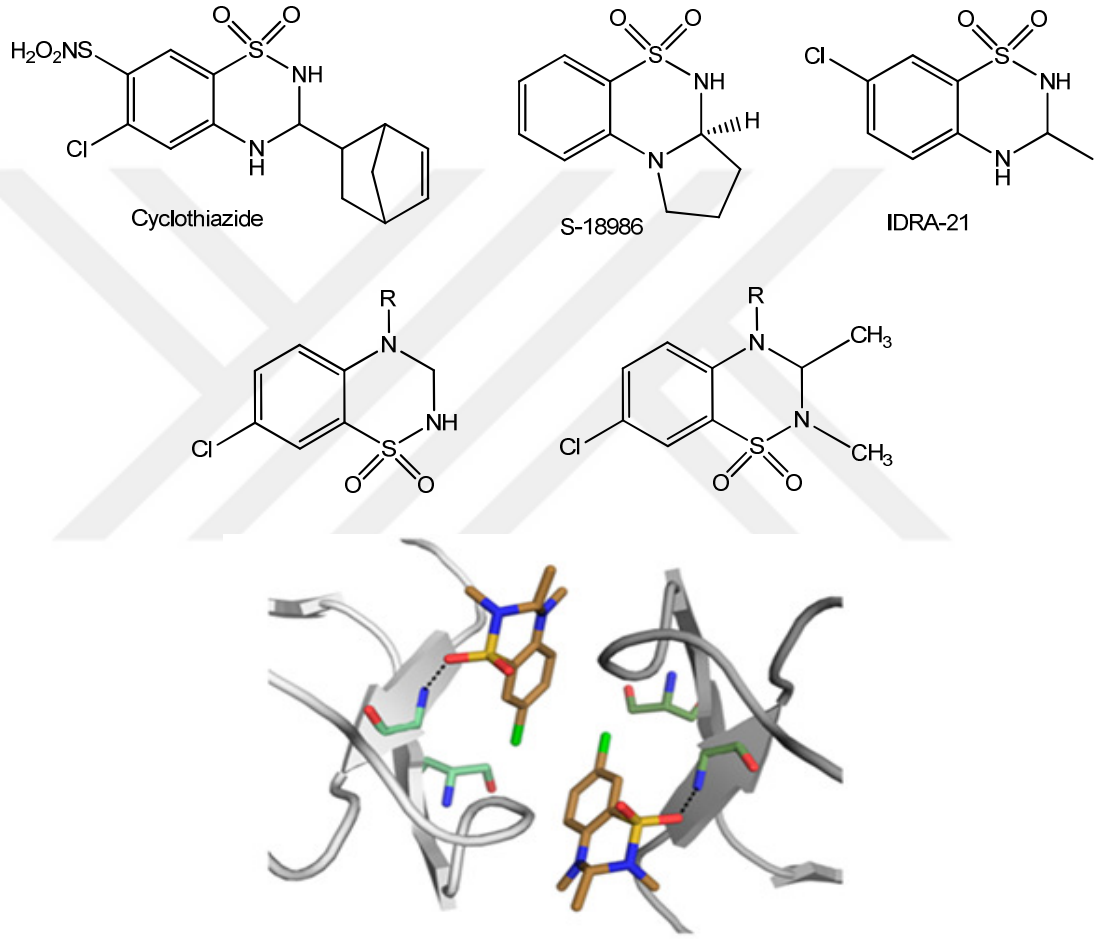


Figure 2.1. Some benzothiadiazine drugs with chiral centers as potent AMPA transmission (Cyclothiazide), AMPA receptor modulator (S-18986) and cognition-enhancing activity (IDRA-21) and used against Alzhemier's disease and sczophrenia

.

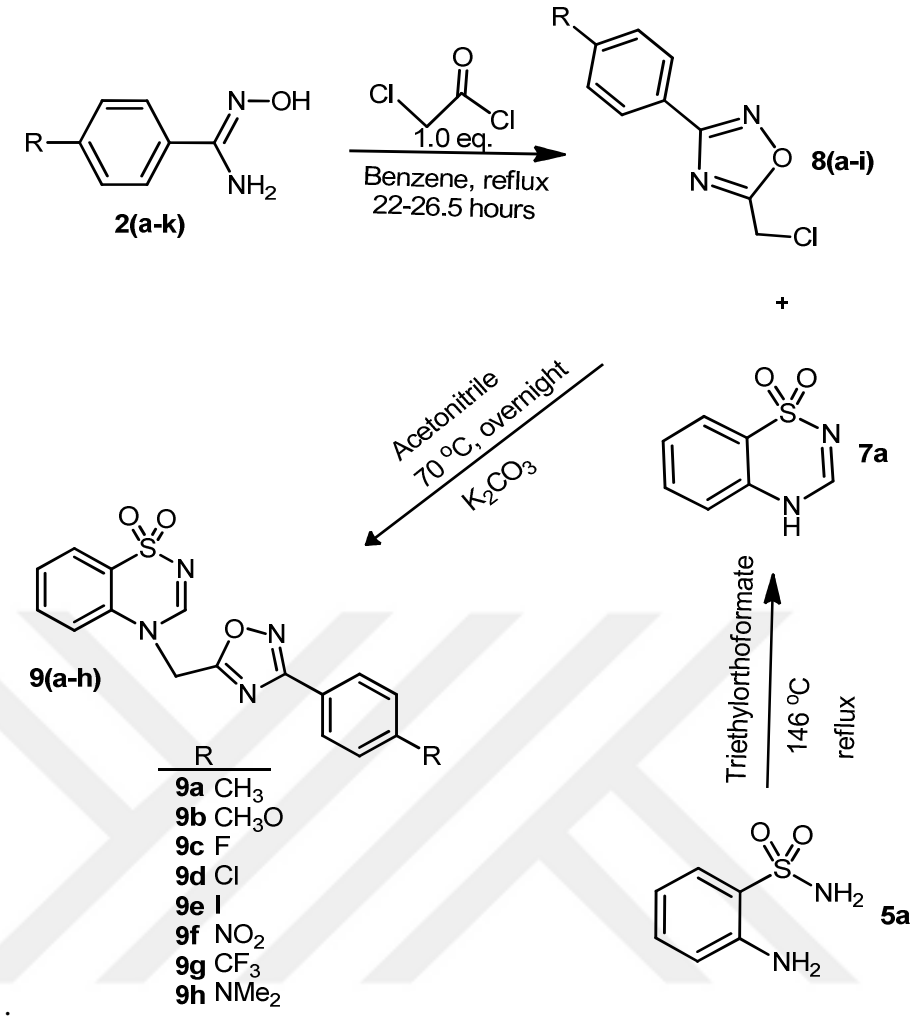
Amidoximes and aldoximes which are also among the key starting substances are prepared according to methods previously published in literature (Nicolaides et. al.,1998;Dürüst et.al., 2002) and they are selected to have electron-withdrawing and electron-releasing substituents. These derivatives were synthesized starting from the substituted aromatic aldehydes or nitriles.

Since it is the key precursor for the thesis, substituted 2-amino benzene sulfonamides were prepared by reacting the substituted amino benzenes with chlorosulfonyl isocyanates and successive ring opening with acid according to previously reported publications.

On the other hand, as oxygen and nitrogen containing heterocycles, 1,2,4-oxadiazoles and their derivatives have been drawing an increasing attention over the recent decades. In this regard, many synthetic protocols were developed. In addition to synthesis, bioactivity screening was performed for a variety of biological activities such as Nrf2 activators, inhibitors of EthR, antitumor agents and anti-protozoal agents (Spink et. al., 2015; Dürüst et al.,2012).

Chen et. al. (2010) described the major 1,2,4-benzothiadiazine skeleton which is generally constructed by reacting 2-aminoarylsulfonamides with orthoester or acylating reagents.To the best of our literature knowledge, there is no 1,2,4-oxadiazole substituted benzothiadiazine core structures in the 3-position of the ring reported so far.

The major purpose of this work is to construct benzothiadiazine-1,1-dioxide skeletone carrying para-substituted 1,2,4-oxadiazole moiety on the N4 nitrogen atom (thiadiazine ring numbering). In order to achieve this ultimate goal, first, para-substituted benzamidoximes (**2a-k**) have been obtained by using para substituted benzonitriles. Subsequently, these compounds were transformed into 5-chloromethyl 1,2,4-oxadiazoles (**8a-i**). Interaction of oxadiazoles with the benzothiadiazine-1,1-dioxide (**7a)** which was prepared from aminosulfonamide (**5a**) gave the target heterocycles (**9a-h**) (Scheme 2.1).



Scheme 2.1. Synthesis of new benzothiadiazine-related derivatives

3. MATERIALS AND METHODS

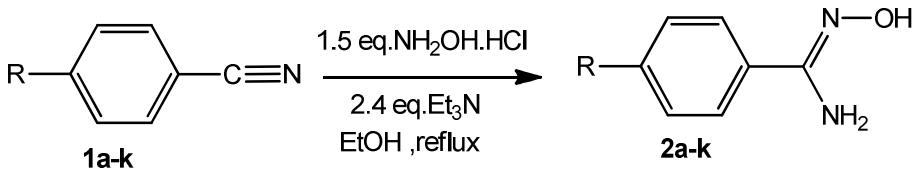
All reagents and solvents were supplied from commercial sources in analytical grade (Merck, Sigma-Aldrich). A computer-controlled single-mode microwave reactor (CEM Discover Explorer SP) were used for microwave heating. NMR spectra were recorded on a JEOL ECS 400 spectrometer (400 MHz for proton and 100 MHz for carbon) in $CDCl_3$ or DMSO-d_6 at room temperature. All chemical shifts (δ) were reported in parts per million (ppm) downfield from TMS; *J* values are given in Hz. The abbreviations used for NMR signals are: br s= broad singlet, s = singlet, d = doublet, t = triplet, q = quartet, hept = heptet, m = multiplet, dd=doublet of doublets, dt=doublet of triplets, ddd=doublet of doublet of doublets. IR spectra were recorded on a SHIMADZU FTIR-8400S instrument using KBr pellets. LC-MS spectra were run on a Agilent instrument. Melting points were determined on a MELTEMP apparatus and they are uncorrected. TLC analyses were carried out to monitor the reaction progress using precoated plates with fluorescent indicator (Merck 5735). Column chromatographic separations were performed on silica gel (Merck, 230–400 mesh ASTM) and the eluents were mostly mixtures of ethyl acetate and hexanes. Staining solutions of $KMnO_4$ and UV-(254 or 366 nm) light were used to detect the TLC spots.

3.1 EXPERIMENTAL

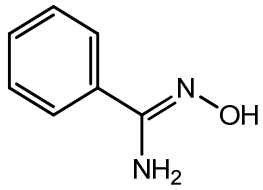
3.1.1 PREPARATION OF STARTING MATERIALS

3.1.1.1 Preparation of para substituted benzamidoximes

To a solution of *p*-substituted benzonitrile (1 eq.) and triethylamine in ethanol, $NH_2OH.HCl$ (1.5 eq.) was added slowly by stirring until all of hydroxylamine hydrochloride was dissolved. The mixture was stirred at 80–85°C for 0.5–24 h. During this time interval, reactions were monitored on TLC plate. When the reaction was finished, the reaction mixture was cooled to room temperature. When the temperature reduced to RT, white or yellow precipitate form in ethanol mixture. Ethanol was evaporated with a rotary evaporator. Then, water was added to these white or yellow precipitate in remaining ethanol mixture. The resulting precipitate was filtered off and it was washed with a plenty of distilled water. The resulting solid was thoroughly dried under vacuo. (Ağırbaş et.al., 1992; Dürüst & Karakuş, 2017; Dürüst et. al., 2017; Dürüst et. al, 2015; Dürüst et. al., 2014; Sağırlı & Dürüst, 2018).



Benzamidoxime (2a):

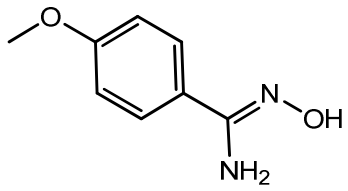


2a

Benzonitrile **(1a)** (3.094 g, 30 mmol), triethylamine (10 ml), hydroxylamine hydrochloride (3.132 g, 45 mmol), EtOH (30 ml). After cooling the reaction mixture to room temperature, white precipitate formation was not observed.

After evaporation of most of ethanol from the mixture, a white solid was observed, but with addition of water to the remaining part, white solid dissolved. Extraction was performed with EtOAc and water only. The organic layer was dried with anhydrous Na_2SO_4. Yield: 2.042 g (50%). M.p. : 74–75°C. R_f : 0.425 (2:1 ; EtOAc :n-Hexane).IR (KBr: cm^{-1}): 3454, 3362 (N–H), 1651 (C=N).

4-Methoxybenzamidoxime (2b):

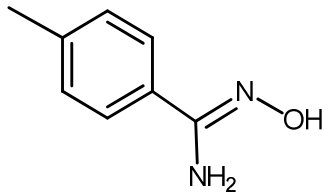


2b

4-Methoxybenzonitrile **(1b)** (3.995 g, 30 mmol), triethylamine (10 ml), hydroxylamine hydrochloride (3.132 g, 45 mmol), EtOH (30 ml). Yield: 3.00 g (60%).

M.p. : 118–119°C. R_f : 0.125 (1:1 ; EtOAc :n-Hexane). IR (KBr: cm^{-1}): 3443, 3354 (N–H), 1647 (C=N).

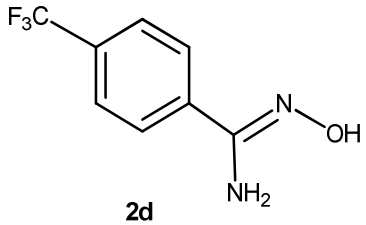
4-Methylbenzamidoxime (2c):



2c

4-Methylbenzonitrile **(1c)** (5.272 g, 45 mmol), triethylamine (15 ml), hydroxylamine hydrochloride (4.697 g, 67.5mmol), EtOH (40 ml).Yield: 5.315 g (79%).M.p. : 145–146°C. R_f : 0.325 (1:1 ; EtOAc :n-Hexane).IR (KBr, ν: cm^{-1}): 3500, 3369 (N–H), 1662 (C=N).

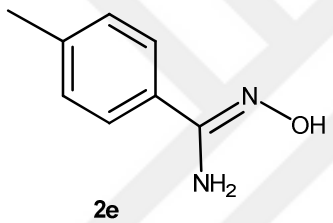
4-Trifluoromethylbenzamidoxime (2d):



2d

4-Trifluoromethylbenzonitrile **(1d)** (2.567 g, 15 mmol), triethylamine (5 ml), hydroxylamine hydrochloride (1.564 g, 22.5 mmol), EtOH (15 ml).Yield: 2.124g (69%). M.p. : 128–130°C. R_f : 0.400 (1:1 ; EtOAc :n-Hexane).IR (KBr, ν: cm^{-1}): 3489, 3367 (N–H), 1666 (C=N).

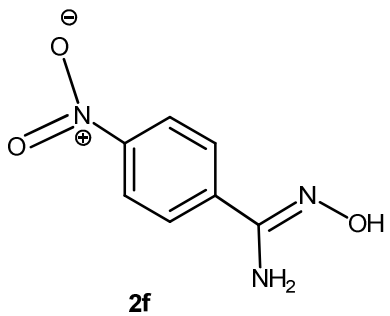
4-Iodobenzamidoxime (2e):



2e

4-Iodobenzonitrile **(1e)** (1.603 g, 7 mmol), triethylamine (2.3 ml), hydroxylamine hydrochloride (0.731 g, 10.5 mmol), EtOH (7 ml).Yield: 1.660 g (90%). M.p. : 158–160°C. R_f: 0.375 and 0.1875 (1:1 ; EtOAc :n-Hexane).
IR (KBr, ν: cm^{-1}): 3483, 3371 (N–H), 1662 (C=N).

4-Nitrobenzamidoxime (2f):

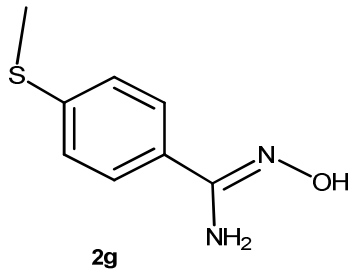


2f

4-Nitrobenzonitrile **(1f)** (4.444 g, 30 mmol), triethylamine (10 ml), hydroxylamine hydrochloride (3.132 g, 45 mmol), EtOH (30 ml).Yield: 4.679 g (86%).

M.p. : 163–165°C. R_f: 0.725 and 0.400 (3:1 ; EtOAc :n-Hexane).IR (KBr, ν: cm^{-1}): 3462, 3358 (N–H), 1663 (C=N).

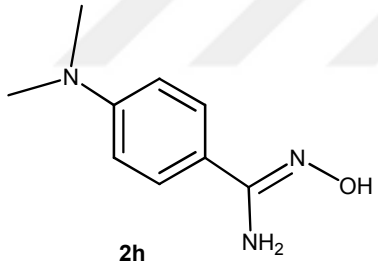
4-Methylthiobenzamidoxime (2g):



2g

4-Methylthiobenzonitrile **(1g)** (3.730 g, 25 mmol), triethylamine (8.3 ml), hydroxylamine hydrochloride (2.610 g, 37.5 mmol), EtOH (25 ml).Yield: 4.184 g (92%).M.p. : 125–127°C. R_f : 0.250 (1:1; EtOAc:*n*-Hexane).IR (KBr, ν: cm^{-1}): 3476, 3450, 3358 (N–H), 1655 (C=N).

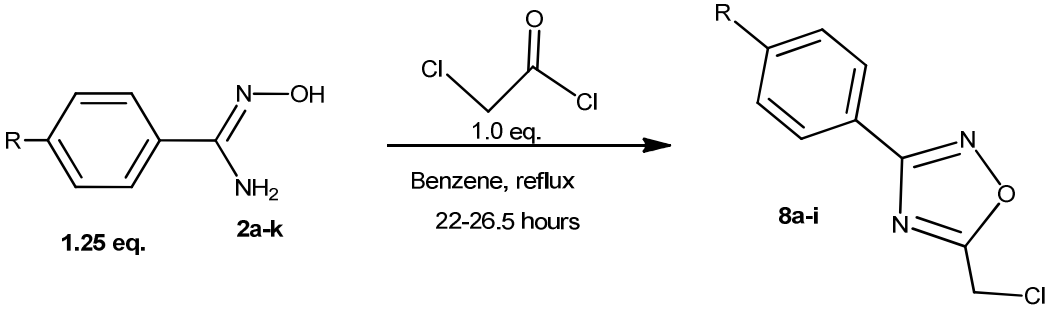
4-*N,N*-Dimethylaminobenzamidoxime (2h):



2h

4-*N,N*-dimethylaminobenzonitrile **(1h)** (1.608 g, 11.0 mmol), triethylamine (3.7 ml), hydroxylamine hydrochloride (1.147 g, 16.5 mmol), EtOH (30 ml).Yield: 0.496 g (25%). M.p. : 127–128°C. R_f : 0.200 (3:1 ; EtOAc :*n*-Hexane).IR (KBr, ν: cm^{-1}): 3505, 3404 (N-H), 3188-2814 (C-H)**,** 1654, 1612 (C=N), 1582, 1365.

3.1.1.2 General Procedures for Preparation of 5-(chloromethyl)-3-aryl-1,2,4-oxadiazoles



To a solution of para-substituted benzamidoxime (1.25 eq.) in benzene, chloroacetyl chloride (1.0 eq.) dissolved in 5 ml of benzene was added dropwise by stirring and the mixture was refluxed overnight. Benzene was evaporated under the reduced pressure. The remaining crude product was purified with flash column chromatography in silica gel. In general, 5- (chloromethyl)-3-aryl-1,2,4-oxadiazoles were obtained as a solid product except 5-(chloromethyl)-3-(4-fluorophenyl)-1,2,4-oxadiazole which was a colorless liquid (Ağırbaş et.al., 1992; Dürüst & Karakuş, 2017; Dürüst et. al., 2017; Dürüst et. al, 2015; Dürüst et. al., 2014; Sağırlı & Dürüst, 2018).

5-(Chloromethyl)-3-phenyl-1,2,4-oxadiazole (8a):

Benzamidoxime **(2a)** (0.545 g,4.0 mmol) in benzene (200 ml), 0.362 g (3.2 mmol) of chloroacetyl chloride in benzene (5 ml).Yield: 529 mg (85%). M.p. : 40–42°C. R_f :0.825 (2:1; EtOAc :n-Hexane). IR (KBr, ν: cm^{-1}): 3069-2967 (C-H), 1597, 1583 (C=N).

5-(Chloromethyl)-3-(*p*-tolyl)-1,2,4-oxadiazole (8b):

4-Methylbenzamidoxime **(2c)** (0.375 g, 2.5 mmol) in benzene (200 ml), 0.226 g (2.0 mmol) of chloroacetyl chloride in benzene (5 ml).Yield: 298 mg (71%).M.p. : 41–44°C. R_f : 0.8125 (1:1 ; EtOAc :*n*-Hexane). IR (KBr, ν: cm^{-1}): 3034-2854 (C-H), 1597, 1577 (C=N).

5-(Chloromethyl)-3-(4-methoxyphenyl)-1,2,4-oxadiazole (8c):

4-Methoxybenzamidoxime **(2b)** (0.499 g, 3 mmol) in benzene (115 ml), chloroacetyl chloride (0.271 g, 2.4 mmol) in benzene (5 ml).Yield: 448 mg (83%).M.p. : 40–41°C. R_f : 0.8125 (1:1 ; EtOAc :*n*-Hexane). IR (KBr, ν: cm^{-1}): 3020–2841 (C-H), 1612, 1597,1573 (C=N).

5-(Chloromethyl)-3-(4-chlorophenyl)-1,2,4-oxadiazole (8e) :

4-Chlorobenzamidoxime **(2j)** (0.342 g, 2.0 mmol) in benzene (50 ml), chloroacetyl chloride (0.110 g, 0.974 mmol) in benzene (5 ml).Yield: 194 mg (87%).M.p. : 60–61°C. R_f: 0.725 (1:1;EtOAc :*n*-Hexane). IR (KBr, ν: cm^{-1}): 3020-2972 (C-H), 1591,1568 (C=N).

5-(Chloromethyl)-3-(4-iodophenyl)-1,2,4-oxadiazole (8f):

4-Iodobenzamidoxime **(2e)** (0.524 g, 2.0 mmol) in benzene (200 ml), chloroacetyl chloride (0.181 g, 1.6 mmol) in benzene (5 ml).Yield: 510 mg (99%). M.p. : 71–73°C. R_f : 0.825 (1:1; EtOAc :*n*-Hexane).IR (KBr, ν: cm^{-1}): 3069–2987 (C-H), 1595, 1560 (C=N).

5-(Chloromethyl)-3-(4-nitrophenyl)-1,2,4-oxadiazole (8g):

4-Nitrobenzamidoxime **(2f)** (0.544 g, 3.0 mmol) in benzene (275 ml), chloroacetyl chloride (0.271 g, 2.4 mmol) in benzene (5 ml).Yield: 356 mg (62%). M.p. : 89–90°C. R_f : 0.775 (2:1; EtOAc :*n*-Hexane).IR (KBr, ν: cm^{-1}): 3099–2960 (C-H), 1612, 1578 (C=N).

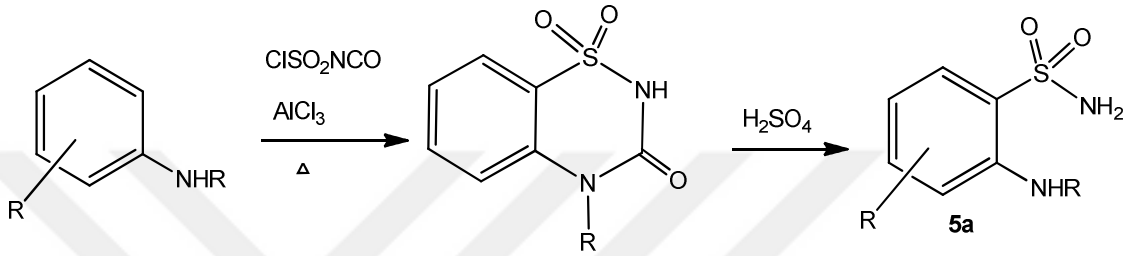
5-(Chloromethyl)-3-(4-(trifluoromethyl)phenyl)-1,2,4-oxadiazole (8h):

4-Trifluoromethylbenzamidoxime **(2d)** (0.510 g, 2.5 mmol) in benzene (90 ml), chloroacetyl chloride (0.226 g, 2.0 mmol) in benzene (5 ml).Yield: 380 mg (72%). colorless oil. R_f: 0.850 (2:1; EtOAc : *n*-Hexane). IR (KBr, ν: cm^{-1}): 1597, 1577 (C=N).

(5-Chloromethyl)-3-(4-N,N-dimethylaminophenyl)-1,2,4-oxadiazole (8i):

4-*N,N*-Dimethylaminobenzamidoxime **(2h)** (0.448 g, 2.50 mmol) in benzene (225 ml), chloroacetylchloride (0.226 g, 2.0 mmol) in benzene (5 ml).Yield: 139 mg (29%). M.p. : 63–66°C. R_f : 0.775 (2:1; EtOAc : *n*-Hexane). IR (KBr, ν: cm^{-1}): 3010–2816 (C-H), 1608 (C=N).

3.1.1.3 Preparation of substituted 2-aminobenzene sulfonamides



Chlorosulfonyl isocyanate (26 ml, 300 mmol) in nitroethane (200 ml) was cooled to –40 ° C (dry ice-acetone), and 4-chloroaniline (270 mmol) in nitroethane (100 m) was added dropwise with stirring. At the end of the addition, the reaction mixture was stirred for a further 30 min and aluminium chloride (39 g, 300 mmol) was added. The mixture was heated at 110 ° C for 1 h. The product was poured onto ice and the precipitate was filtered off in vacuum, washed with cold water and dry ether. The residue was taken up in 50% aqueous sulfuric acid solution (320 ml) and heated at 140 ^{o}C for 8 h. The solution was taken up on ice and neutralized with saturated aqueous sodium hydroxide at 0 °C. The precipitate was filtered off under vacuum, washed with cold water and dried in vacuum. The desired compound was obtained. Spectral data are found to be consistent with the literature values (Cherepakha et al., 2011).

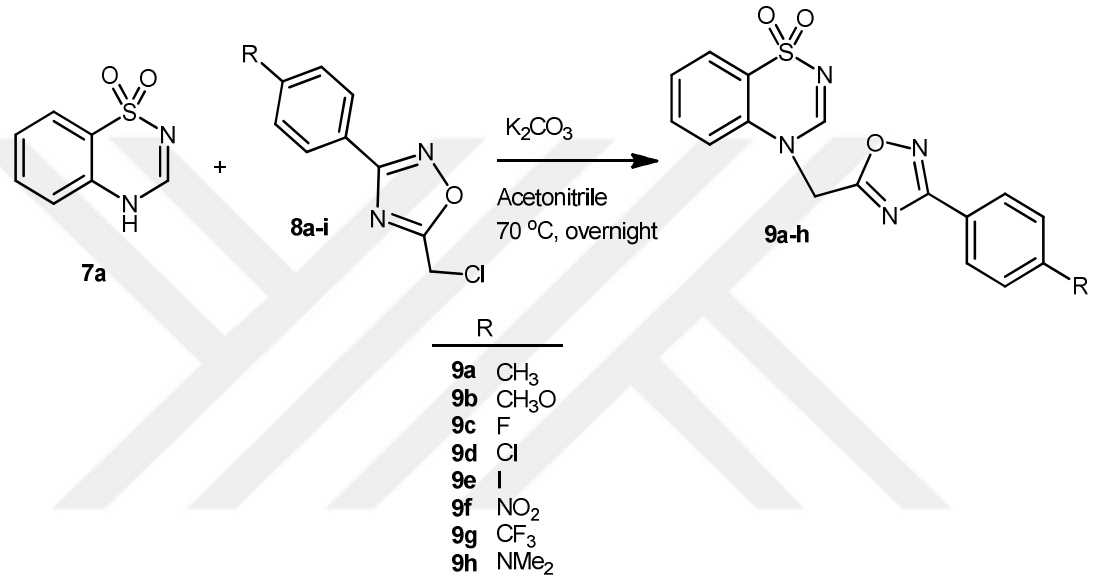
3.1.1.4 General Procedures for Preparation of 4*H*-1,2,4-benzothiadiazine-1,1-dioxide

2-Aminobenzenesulfonamide (1.754 g, 100 mmol) and triethylorthoformate (155 mL) were refluxed for 2 h (146 ^{o}C).The mixture was cooled to room

temperature, the white precipitate was filtered, washed with ether and dried in vacuum. Yield: 1.200 g (65%).

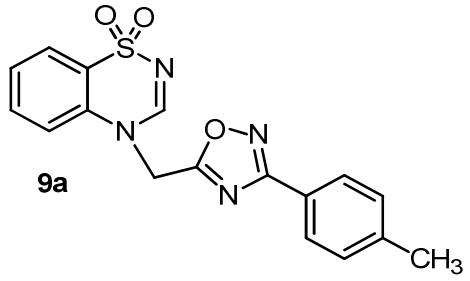
3.1.2 SYNTHESIS OF TARGET PRODUCTS

3.1.2.1 Preparation of 4 - ((3- (*p*-substitutedphenyl) -1,2,4-oxadiazol-5-yl) methyl) -4H-1,2,4-benzothiadiazine-1,1-dioxides (9a-h)



Anhydrous potassium carbonate (1.0 g) was added to an acetonitrile (20 mL) solution of benzothiadiazine 1,1-dioxide (96.59 mg, 0.5301 mmol) and p-tolyl 5-chloromethyl-1,2,4-oxadiazole (131 mg, 0.583 mmol) and the mixture was heated in oil bath at 70 ° C overnight. The progress of the reaction was monitored by thin layer chromatography The mixture was filtered, the solvent was removed under reduced pressure. The crude product was purified by column chromatography (n-hexane: ethyl acetate; 1: 1).

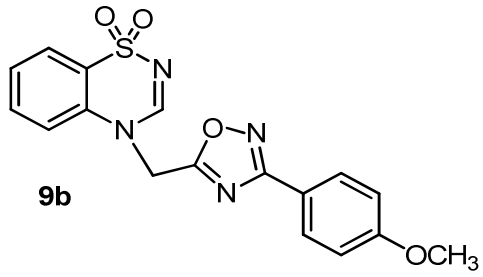
4-((3-(4-Methylphenyl)-1,2,4-oxadiazol-5-yl)methyl)-4H-1,2,4-benzothiadiazine-1,1-dioxide (9a)



9a

White solid. M.p.: 155–157 °C yield : %38: IR (KBr, cm^{-1}): 3053, 1622, 1265 (SO_2 asym), 1172 (SO_2-sym), 1030, 738. ^1H NMR (400 MHz,$CDCl_3$) δ 8.15 (s, 1H), 7.91–7.87 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 2H), 7.58–7.52 (dt, *J* = 7.6, 1.2 Hz, 1H), 7.46–7.37 (dd, *J* = 16.4, 7.8 Hz, 1H), 7.20–7.16 (dd, *J* = 8.4, 3.6 Hz, 4H), 5.58 (s, 2H), 2.31 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$+DMSO-d_6) δ 173.17, 168.64, 150.72, 142.08, 134.99, 133.35, 129.61, 127.36, 125.31, 122.89, 115.31, 45.69, 29.52. LC-MS (ESI) $C_{17}H_{14}N_4O_4S$: m/z 355.36 (M + H).

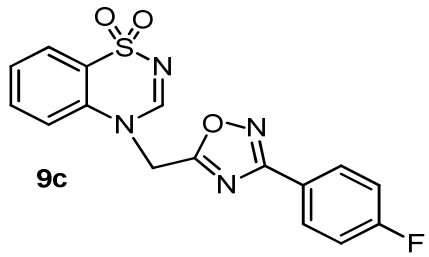
4-((3-(4-Methoxyphenyl)-1,2,4-oxadiazol-5-yl)methyl)-4*H*-1,2,4-benzothiadiazine-1,1-dioxide (9b)



9b

White solid. M.p.: 145–147 °C. Yield : 48%: IR (KBr, cm^{-1}): 3078, 2928, 1620, 1257 (SO_2 asym), 1176 (SO_2-sym), 1022, 775. ^1H NMR (400 MHz, $CDCl_3$) δ 8.10–8.04 (dd, *J* = 9.4, 2.0 Hz, 1H), 7.99–7.93 (d, *J* = 12.0 Hz, 2H), 7.90 (s, 1H), 7.70–7.60 (dt, *J* = 8.0, 2.0 Hz, 1H), 7.54–7.48 (t, *J* = 8.0 Hz, 1H), 7.20 (d, *J* = 11.2 Hz, 1H), 6.98 (d, *J* = 12.0 Hz, 3H), 5.34 (s, 2H), 3.87 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$+DMSO-d_6) δ 173.28, 168.25, 162.23, 150.97, 135.03, 133.43, 129.09, 127.31, 125.19, 123.57, 118.06, 115.54, 114.39, 55.42, 45.72. LC-MS (ESI) $C_{17}H_{14}N_4O_4S$: m/z 371.24 (M + H).

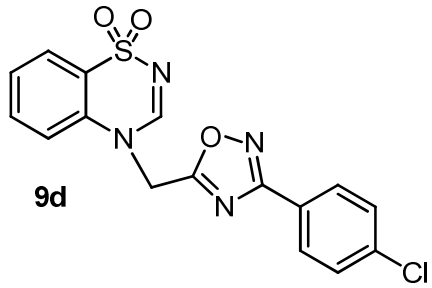
4-((3-(4-Fluorophenyl)-1,2,4-oxadiazole-5-yl)methyl)-4H-1,2,4-benzothiadiazine-1,1-dioxide (9c)



9c

White solid. M.p.: 112–114 ^{o}C. Yield : 64%: IR (KBr, cm^{-1}): 3066, 2985, 1624, 1265 (SO_2 asym), 1172 (SO_2-sym), 895. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.95–7.90 (dt, *J* = 7.2, 2.0 Hz, 1H), 7.88–7.84 (d, *J* = 8.0, 1.6 Hz, 1H), 7.61–7.55 (dt, *J* = 7.2, 1.2 Hz, 1H), 5.72 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$+DMSO-d_6) δ 174.20, 167.63, 165.82, 163.32, 151.23, 135.11, 133.47, 129.82, 129.74, 127.32, 125.06, 123.55, 122.23, 122.20, 116.37, 116.15, 115.86, 45.76. LC-MS (ESI) $C_{16}H_{11}FN_4O_3S$: m/z 359.48 (M + H).

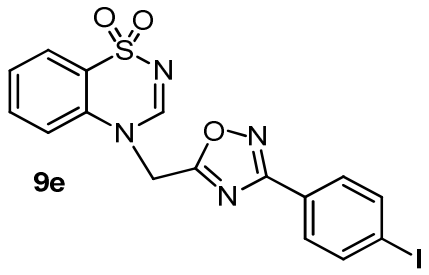
4-((3-(4-Chlorophenyl)-1,2,4-oxadiazole-5-yl)methyl)-4H-1,2,4-benzothiadiazine-1,1-dioxide (9d)



9d

White solid. M.p.: 132–135 ^{o}C. Yield : 55%: IR (KBr, cm^{-1}): 2924, 1620, 1311 (SO_2 asym), 1170 (SO_2-sym), 1018, 825, 761. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.95–7.89 (dt, *J* = 5.6, 1.6 Hz, 2H), 7.59–7.53 (dt, *J* = 7.2, 1.2 Hz, 1H), 7.44–7.39 (t, *J* = 8.0 Hz, 1H), 7.38–7.34 (dt, *J* = 9.2, 2.4 Hz, 1H), 5.65 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$+DMSO-d_6) δ 173.92, 167.77, 150.94, 137.61, 134.99, 133.45, 129.26, 128.85, 127.35, 125.23, 124.35, 123.57, 115.49, 45.68. LC–MS (ESI) $C_{16}H_{11}ClN_4O_3S$: m/z 375.30 (M + H).

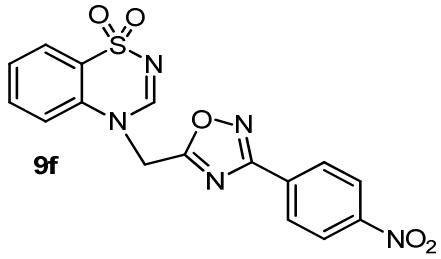
4-((3-(4-Iodophenyl)-1,2,4-oxadiazol-5-yl)methyl)-4*H*-1,2,4-benzothiadiazine-1,1-dioxide (9e)



9e

White solid. M.p.: 119–120 ^{o}C. Yield : 48%: IR (KBr, cm^{-1}): 3051, 2982, 1624, 1267 (SO_2 asym), 1172 (SO_2-sym), 1030, 819, 731. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.88–7.86 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.76–7.73 (t, *J* = 3.6 Hz, 2H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.60–7.56 (dt, *J* = 8.4, 1.6 Hz, 1H), 7.43 (t, *J* = 8.0 Hz, 1H), 7.29 (d, *J* = 8.4 Hz, 1H), 5.74 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$+DMSO-d_6) δ 174.40, 167.95, 151.23, 138.22, 135.15, 133.43, 129.00, 127.29, 125.44, 125.05, 123.65, 115.89, 98.62, 45.77. LC–MS (ESI) $C_{16}H_{11}IN_4O_3S$: m/z 467.25 (M + H).

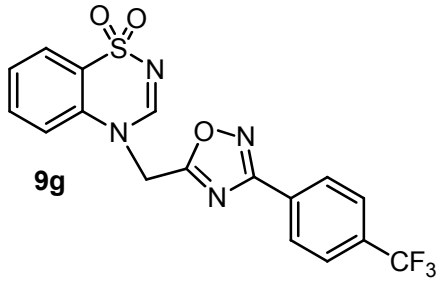
4-((3-(4-Nitrophenyl)-1,2,4-oxadiazol-5-yl)methyl)-4H-1,2,4-benzothiadiazine-1,1-dioxide (9f)



9f

Light brown solid. M.p.: 162–165 ^{o}C. Yield : 37%: IR (KBr, cm^{-1}): 1662, 1616, 1047, 1024, 827, 765. ^{1}H NMR (400 MHz, $CDCl_3$+DMSO-d_6) δ 8.35 (d, *J* = 8.8 Hz, 2H), 8.29 (s, 1H), 8.16 (d, *J* = 8.8 Hz, 2H), 7.96–7.92 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.76–7.69 (dt, *J* = 8.4, 1.2 Hz, 1H), 7.58–7.51 (dt, *J* = 11.6, 7.6 Hz, 2H), 5.92 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$+DMSO-d_6) δ 176.22, 166.94, 152.14, 149.77, 135.36, 134.01, 131.69, 129.34, 128.97, 127.83, 125.04, 123.40, 117.05, 46.26. LC–MS (ESI) $C_{16}H_{11}N_5O_5S$: m/z 386.35 (M + H).

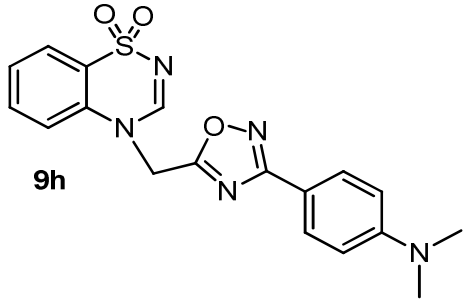
4-((3-(4-Trifluoromethylphenyl)-1,2,4-oxadiazol-5-yl)methyl)-4H-1,2,4-benzothiadiazine-1,1-dioxide (9g)



9g

White solid. M.p: 98–101 ^{o}C. Yield : 47%: IR (KBr, cm^{-1}): 1643, 1624, 1168, 1049, 1026, 827. ^{1}H NMR (400 MHz, $CDCl_3$+DMSO-d_6) δ 8.22 (s, 1H), 8.07 (d, *J* = 8.0 Hz, 2H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 2H), 7.57 (t, *J* = 8.4 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.27 (d, *J* = 8.4 Hz, 1H), 5.74 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$+DMSO-d_6) δ 174.26, 167.53, 151.12, 135.11, 133.41, 132.68, 129.47, 128.00, 127.31, 125.99, 125.95, 125.13, 123.67, 115.73, 45.74. LC–MS (ESI) $C_{17}H_{11}F_3N_4O_3S$: m/z 409.52 (M + H).

4-((3-(4-Dimethylaminophenyl)-1,2,4-oxadiazol-5-yl)methyl)-4H-1,2,4-benzothiadiazine-1,1-dioxide (9h)



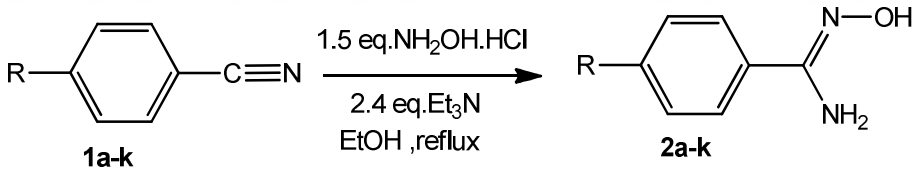
9h

Beige solid. M.p.: 126–128 ^{o}C. Yield : 59%: IR (KBr, cm^{-1}): 2922, 1654, 1612, 1313, 1170, 1026, 825, 763. ^{1}H NMR (400 MHz, $CDCl_3$+DMSO-d_6) δ 8.20 (s, 1H), 7.86 (dd, *J* = 7.6, 1.2 Hz, 1H), 8.07 (d, *J* = 8.0 Hz, 2H), 7.70 (d, *J* = 8.8 Hz, 2H), 7.58–7.53 (dt, *J* = 8.8, 1.2 Hz, 1H), 7.41 (t, *J* = 7.2 Hz, 1H), 6.61 (d, *J* = 8.8 Hz, 2H), 5.61 (s, 2H), 2.93 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$+DMSO-d_6) δ 172.82, 168.62, 152.39, 151.10, 135.09, 133.43, 128.62, 127.28, 125.09, 123.54, 115.71, 112.44, 111.59, 61.15, 45.80. LC–MS (ESI) $C_{18}H_{17}N_5O_3S$: m/z 384.34 (M + H).

4. RESULTS AND DISCUSSION

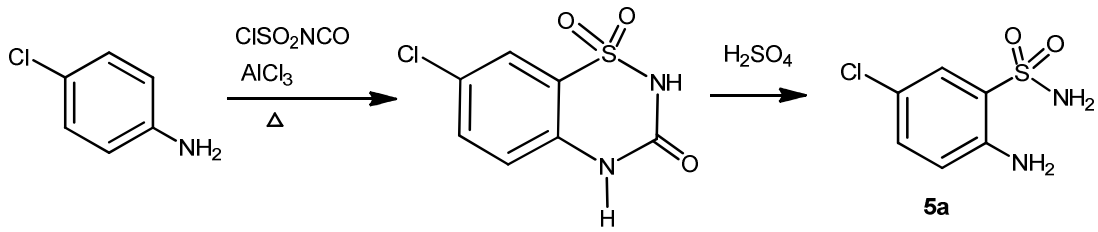
4.1 SYNTHESIS AND CHARACTERIZATION OF STARTING MATERIALS

In order to achieve the project objectives, a series of *para* substituted benzamidoximes (9 compounds) and chloro substituted 2-amino benzenesulfonamide were synthesized. The physical constants (melting points, R_f values) in the literature and the IR spectra were found to be in accord with those values we obtained (Scheme 4.1). Most indicative absorption bands for benzamidoximes **2a-i** are C=N stretching vibrations at around 1640 cm^{-1} and NH_2 stretching vibrations at around 3300–3400 cm^{-1} (two peaks). Hydrogen-bonded strong and wide NOH absorption appears in the region 2400–3200 cm^{-1}. In addition, disappearance of C≡N absorption at around 2250 cm^{-1} , which is core signal for nitrile group, is another confirmative physical evidence for amidoximes.



Scheme 4.1. Synthesis of *para* substituted benzamidoximes from corresponding nitriles

Synthesis of 2-amino-5-chlorobenzenesulphonamide which is the main starting material of the procedure, from the 4-chloroaniline and chlorosulphonyl isocyanate, was performed according to literature method and its structure was verified (Scheme 4.2).



Scheme 4.2. Synthesis of 2-amino-5-chlorobenzenesulfonamide **5a**.

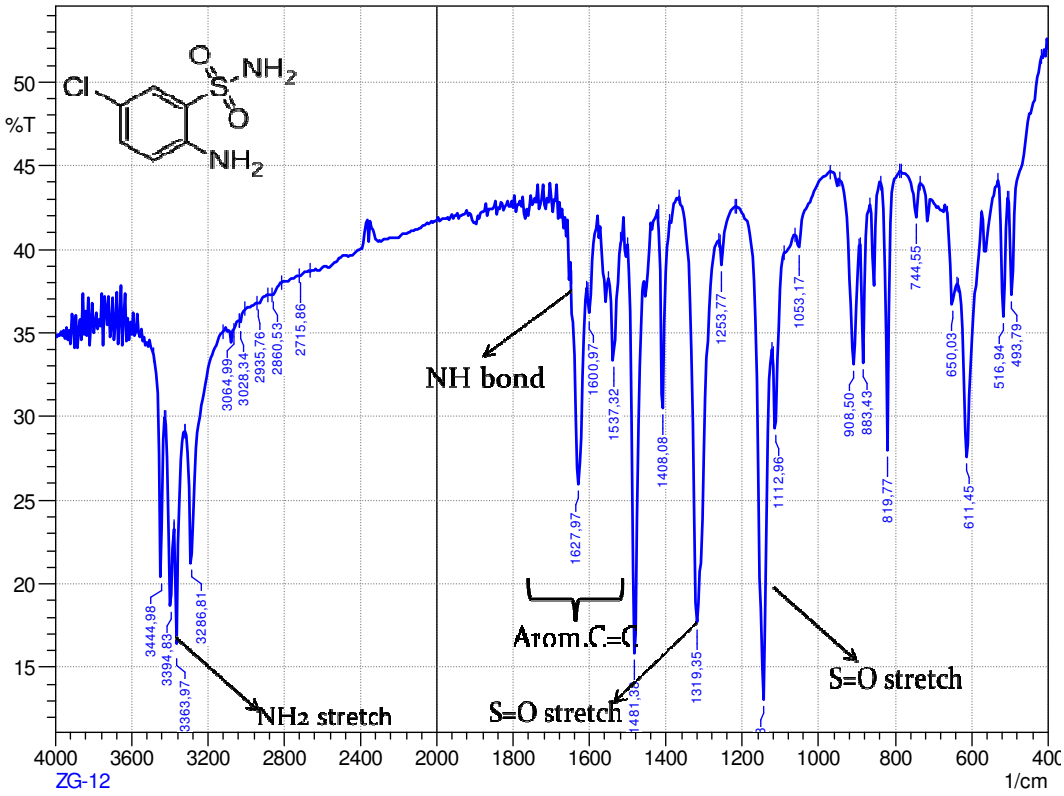


Figure 4.1. IR spectrum of 2-amino-5-chlorobenzenesulfonamide **5a**.

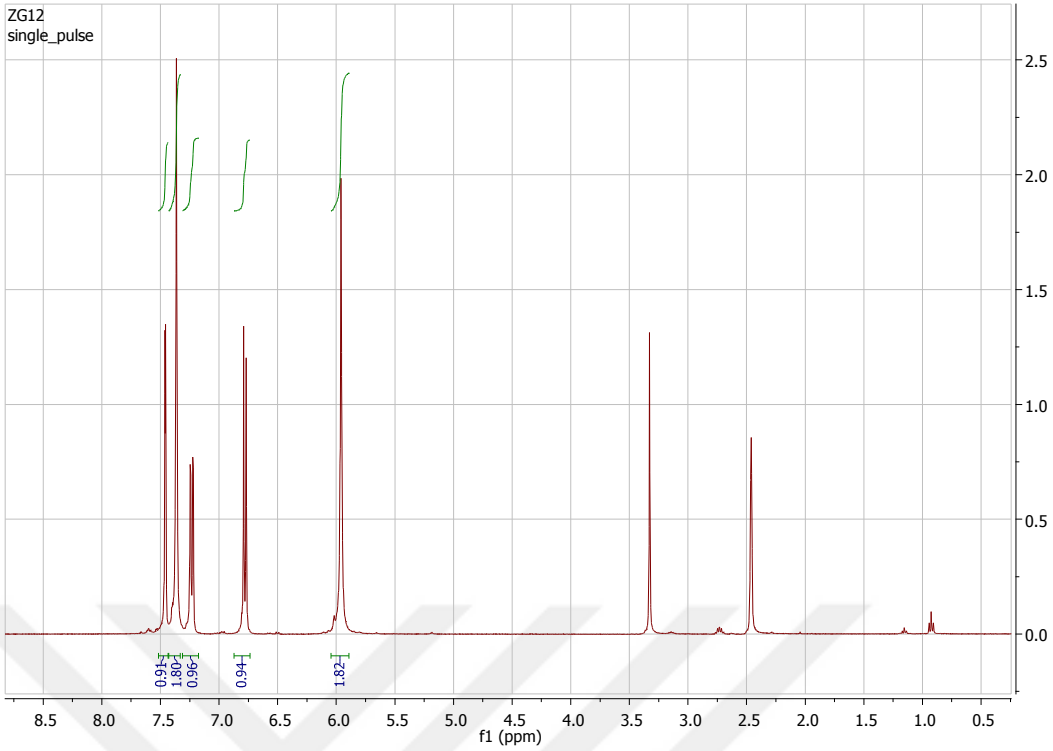


Figure 4.2. ^{1}H NMR (DMSO-d_6) spectrum of 2-amino-5-chlorobenzenesulphonamide **5a**.

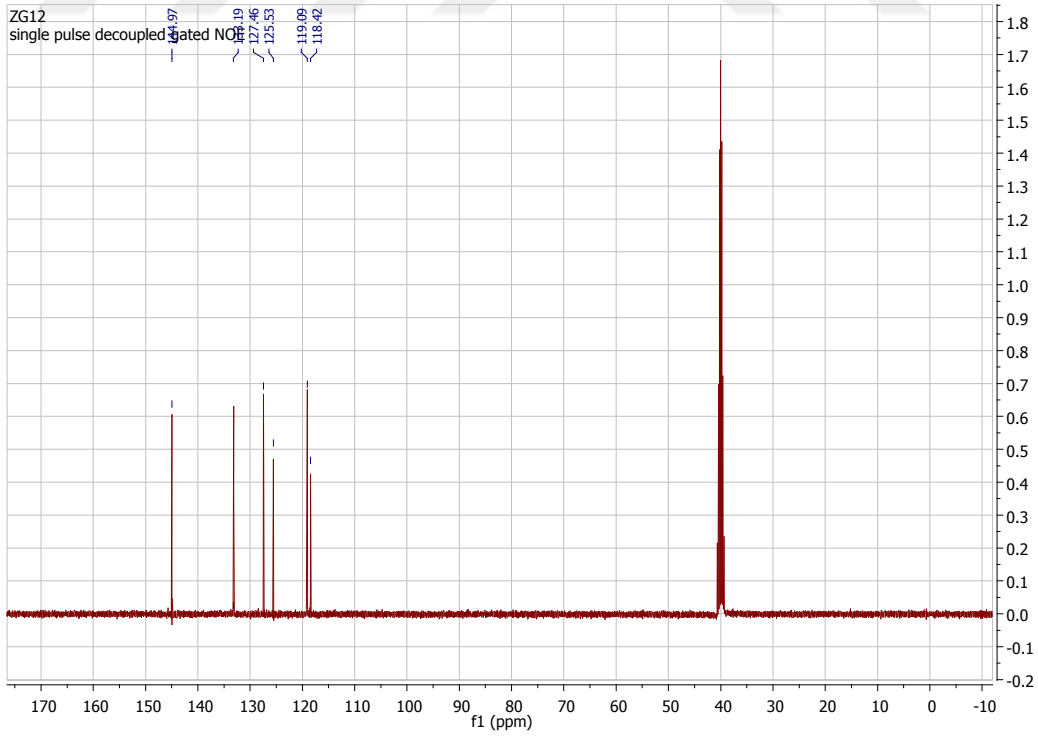
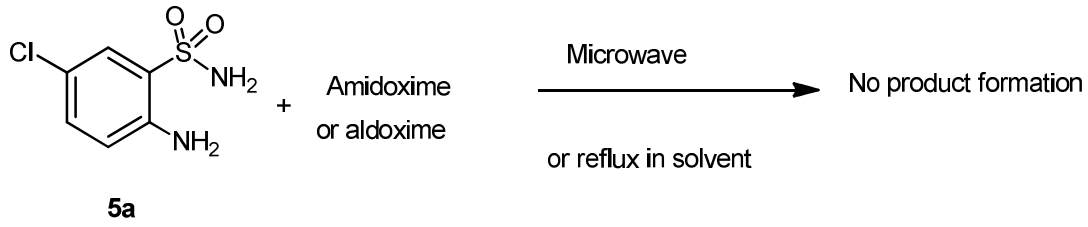


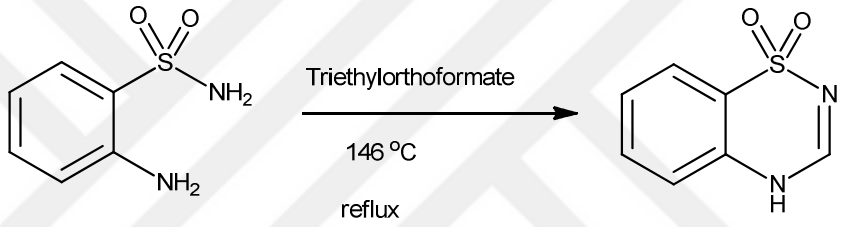
Figure 4.3. ^{13}C NMR (DMSO-d_6) spectrum of 2-amino-5-chlorobenzenesulphonamide **5a**

Although the reactions between chloroaminosulfonamide and various amidoximes/or aldoximes were attempted under the different reaction conditions, especially, no product formation could be observed in the microwave heating.



5a

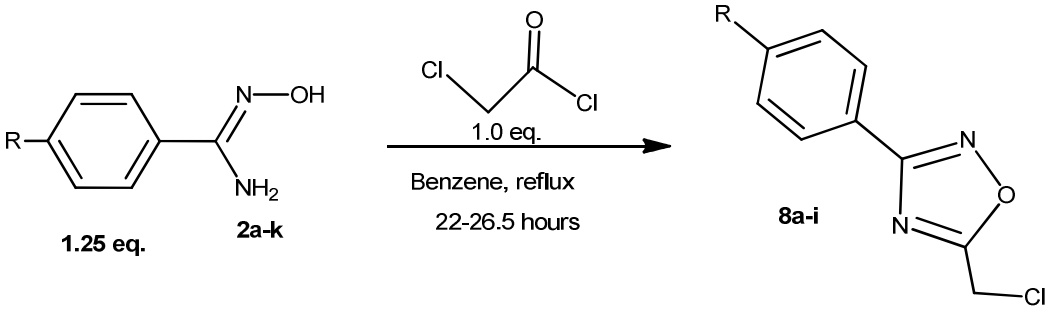
Then, in order to obtain a structure which resembles heterocycle bearing benzothiazine dioxide scaffold, benzothiadiazinedioxide was synthesized from sulfonamide using triethyl orthoformate (Scheme 4.3).



5b **7a**

Scheme 4.3. Synthesis of benzothiadiazine dioxide **7a**

In order to obtain 3-p-(substitutedphenyl)-5-chloromethyl-1,2,4-oxadiazoles which are the most important components of the work, para substituted benzamidoximes were reacted with chloroacetylchloride in refluxing benzene and the structures were confirmed by the literature data published previously (Scheme 4.4) (Ağırbaş et. al., 1992).

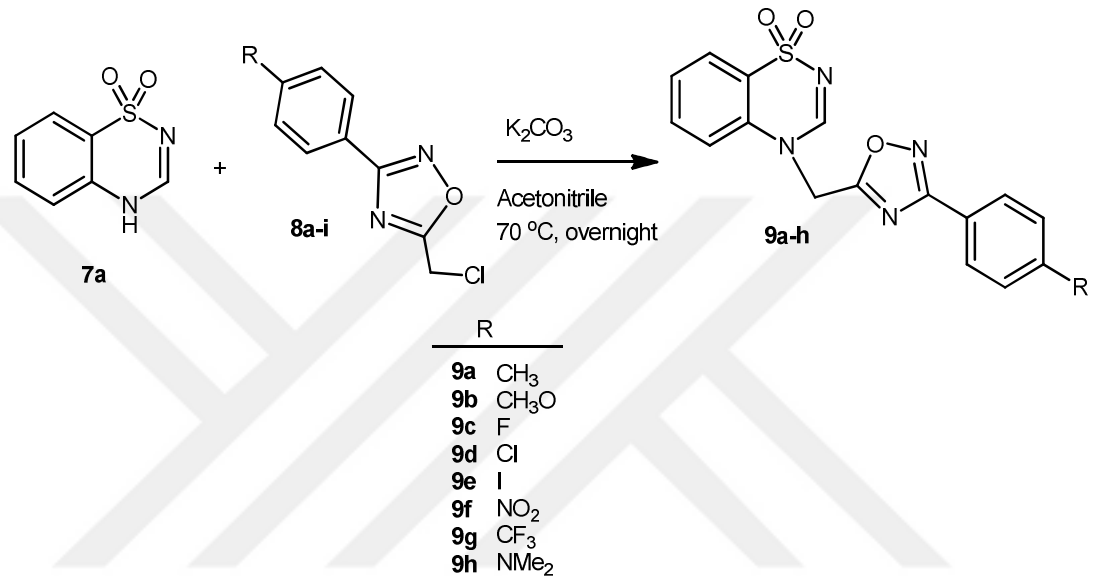


1.25 eq. **2a-k** **8a-i**

Scheme 4.4. Synthesis of 5-chloromethyl-1,2,4-oxadiazoles

4.2 SYNTHESIS OF 4 - ((3- (p-SUBSTITUTEDPHENYL) -1,2,4-OXADIAZOL-5-YL) METHYL)-4H-1,2,4-BENZOTHIADIAZINE-1,1-DIOXIDES (9)

The *N*-substituted target compounds were successfully obtained from the reaction of benzothiadiazine dioxide with 3-(p-substitutedphenyl)-5-chloromethyl-1,2,4-oxadiazoles (Scheme 4.5).



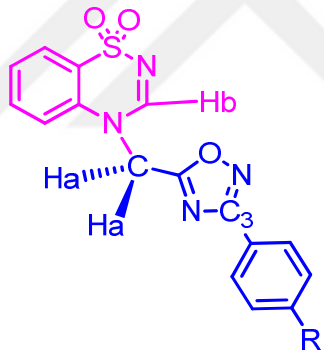
Scheme 4.5. Synthesis of 4 - ((3- (p-substitutedphenyl) -1,2,4-oxadiazol-5-yl) methyl) -4H-1,2,4-benzothiadiazine-1,1-dioxides **9a-h**

These novel compunds have been elucidated by spectral and physical methods. IR, NMR and mass spectra shown below (Figures 4.10–4.13). Molecular ion peak of each compounds is clearly seen in the LC-mass spectra. Further, the asymmetric and symmetric vibration bands of the sulfone group being the most prominent absorption bands in the IR spectra of the compounds arose at 1260 and 1170 cm^{-1}, respectively. C = N stretching absorption band arose at 1620 cm^{-1} .

In the proton NMR spectra, the most indicative proton signals were CH_2 protons from the initial oxadiazoles at about 5.5 ppm, and the iminic protons from benzothiadiazine-1,1-dioxide at about 8.5 ppm as singlets. In the ^{13}C NMR spectra, oxadiazole iminic carbons appeared at about 172 and 170 ppm, and benzothiazine ring carbon at about 150 ppm. The oxadiazole methylene carbon appears to be around 45 ppm. Both proton and carbon chemical shifts observed show a distinctive

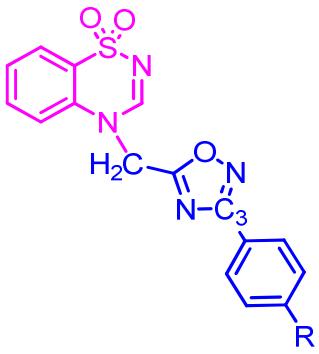
feature depending on the nature of substituents attached at para positions of the phenyl ring of oxadiazole moiety. In this regard, we see more deshielded protons and carbons especially for NO_2 and F substitution due to strong electron withdrawing effect. Thus, in compound **9f**, oxadiazole bridge methylene protons (Ha) resonated at most deshielded region (5.92 ppm) and also oxadiazole ring C3 carbon at 176.22 ppm. Lowest value for these carbons is that of compound **9h** where electron releasing $N(CH_3)_2$ group is attached at para position. In addition, as an unexpected manner, iminic proton of benzothiadiazine ring have been found to be affected by the substituents also.These variations in chemical shifts may be considered as a result of field-spatial effects of the substituents. Another observation we have noticed is that substituents exposing electron-releasing or electron-withdrawing effect by resonance have much higher impact on the chemical shift values than that of inductive effects. These are tabulated and shown below (Tables 4.1 and 4.2).

Table 4.1. Chemical Shift (δ ppm) values of Typical Protons of 9a-h



Compound	R	δ (ppm) (N-CH_2-oxadiazole, Ha)	δ (ppm) (C3-H-benzothiadiazine, Hb)
9a	CH_3	5.58	8.15
9b	CH_3O	5.34	7.90
9c	F	5.72	8.23
9d	Cl	5.65	8.18
9e	I	5.74	8.22
9f	NO_2	5.92	8.29
9g	CF_3	5.74	8.22
9h	$N(CH_3)_2$	5.61	8.20

Table 4.2. Chemical Shift (δ ppm) values of Typical Carbons of 9a-h



Compound	R	δ (ppm) (C3-oxadiazole)	δ (ppm) (N-CH_2-oxadiazole)
9a	CH_3	45.77	173.17
9b	CH_3O	45.72	173.28
9c	F	45.76	174.20
9d	Cl	45.68	173.92
9e	I	45.77	174.40
9f	NO_2	46.26	176.22
9g	CF_3	45.74	174.26
9h	$N(CH_3)_2$	45.80	172.82

The Hammett equation (linear free energy relationship) has been one of the most widely used means for the study and interpretation of organic reactions and their mechanisms. It was basically established for the acidities of the substituted benzoic acids and given by the following equation, but, later, it has been used to analyze various organic reactions in terms of substituent effects (Hammett, 1937 & 1938; Hansch et. al., 1991) (Figure 4.4).

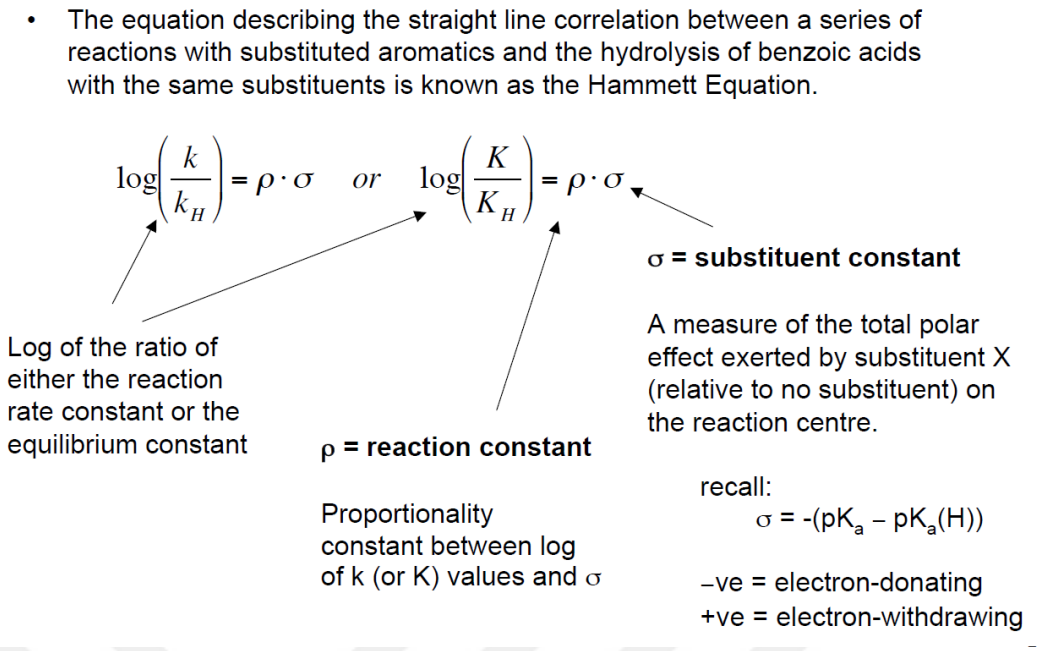


Figure 4.4. Hammett equation and descriptions of its elements

The Hammett equation, or its extended form is one of the most useful tool to interprete too many different types of organic reactions. Hammett's successs can be seen especially in taking account of the electronic effects of substituents on the reaction rates and equilibria. That is why organic chemists or experts in other chemical fields use this equation in their research studies over the decades.

Based on the above considerations, we have already performed Hammett correlations between the chemical shifts of the typical protons, carbons related to the benzothiadiazine-1,1-dioxide derivatives **9a-h** and sigma para substituent constants ($\boldsymbol{\sigma_p}$) (Figures 4.5–4.8).

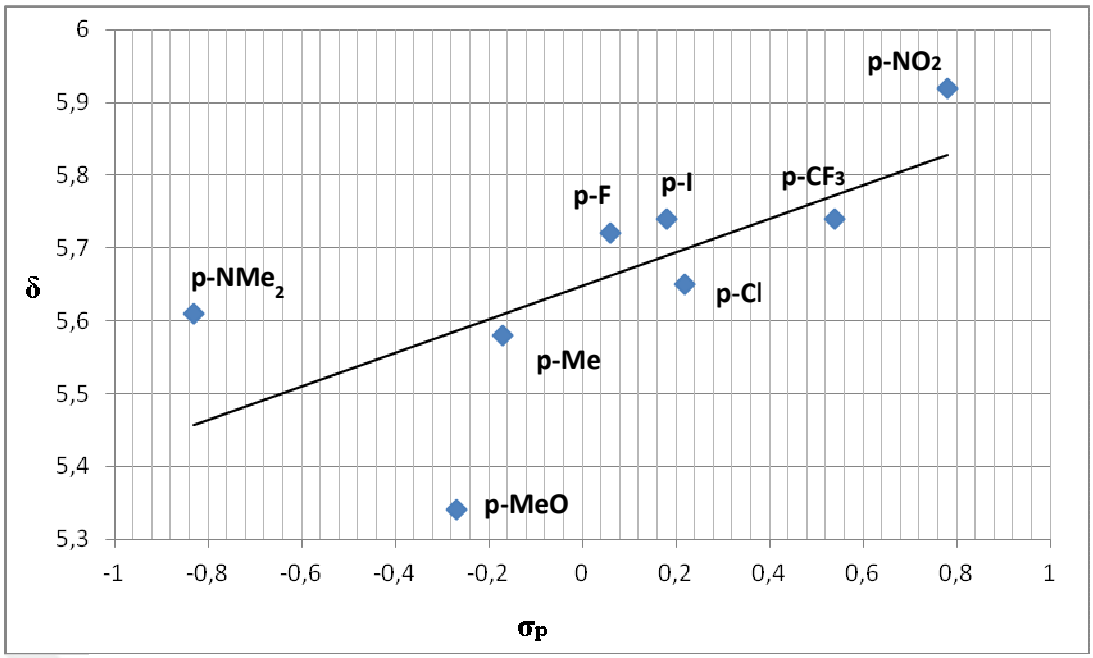


Figure 4.5. Hammett correlation of bridge methylene (**Ha**) protons

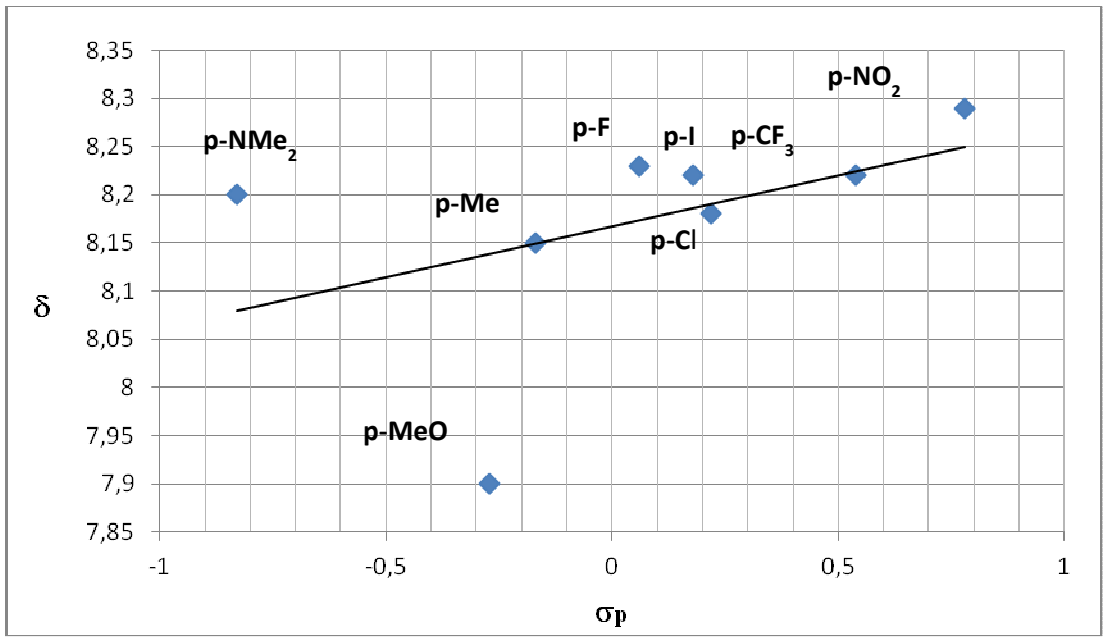


Figure 4.6. Hammett correlation of iminic protons (**Hb**) of benzothiadiazine ring.

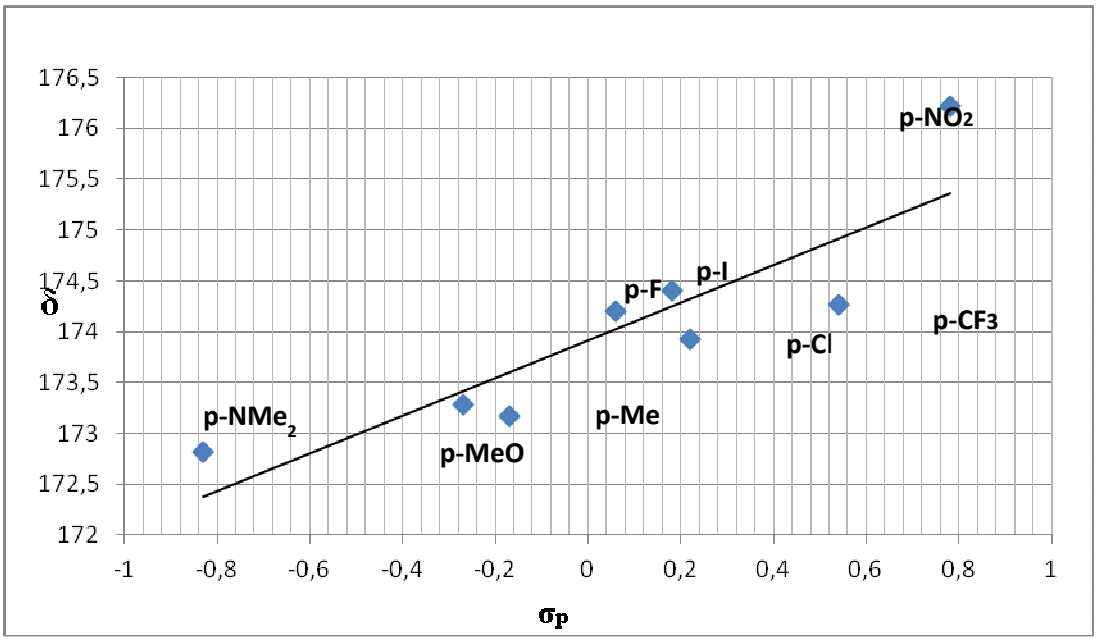


Figure 4.7. Hammett correlation of C3 iminic carbons of oxadiazole ring.

Upon examination of the above plots, we may conclude that most coinciding one is that of the iminic carbon correlation with the Hammett sigma substituent constants. This can be interpreted by taking account of being closure to the electron with-drawing and electron releasing subtituents.

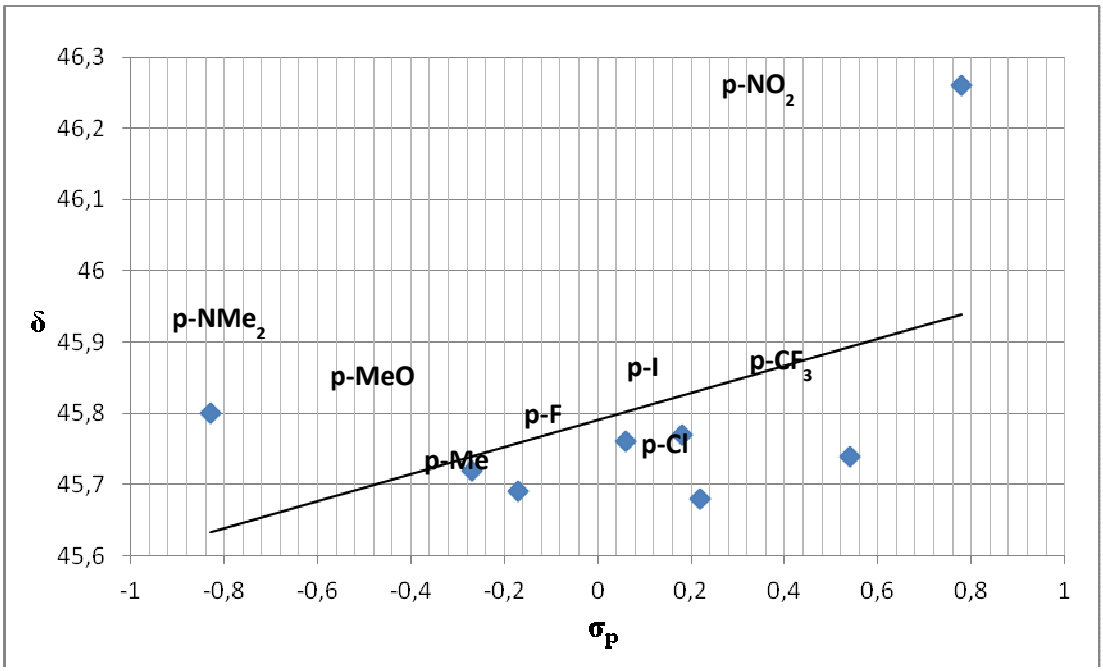


Figure 4.8. Hammett correlation of bridge methylene carbons

In general, the graphs given above tell us about the higher chemical shift values which are an indication of deshielding effect of strongly electron-withdrawing substituent like NO_2.The lower chemical shift values was related to the more shielded protons or carbons distinctive for electron-releasing substituent such as a dimethylamino. In summary, minus values of sigma para constants coincide with the electron-donating substituents appearing in left lower side of the graph. Reversely, plus sigma para constant values appear in the right upper side of the graph.These results are in accord with theoretically established calculations.

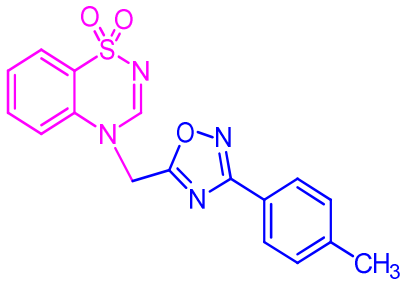


Figure 4.9. Structure of 4-((3-(4-methylphenyl)-1,2,4-oxadiazol-5-yl) methyl)-4H-1,2,4- benzothiadiazine-1,1-dioxide **9a**

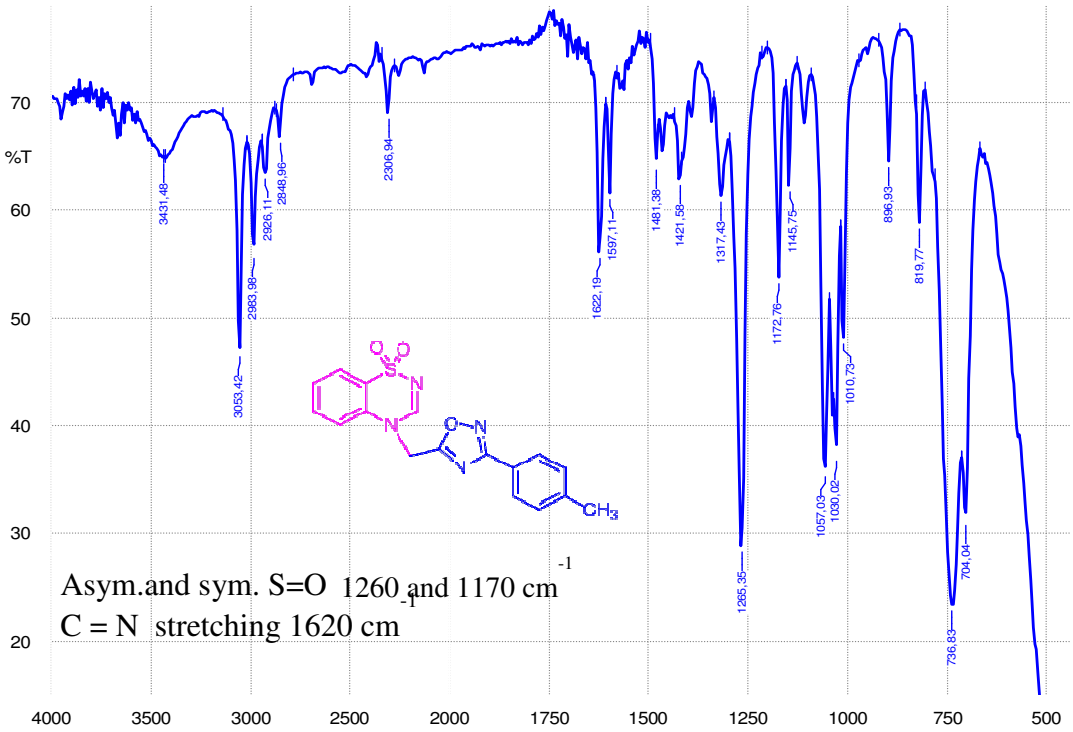


Figure 4.10. IR spectrum of **9a**

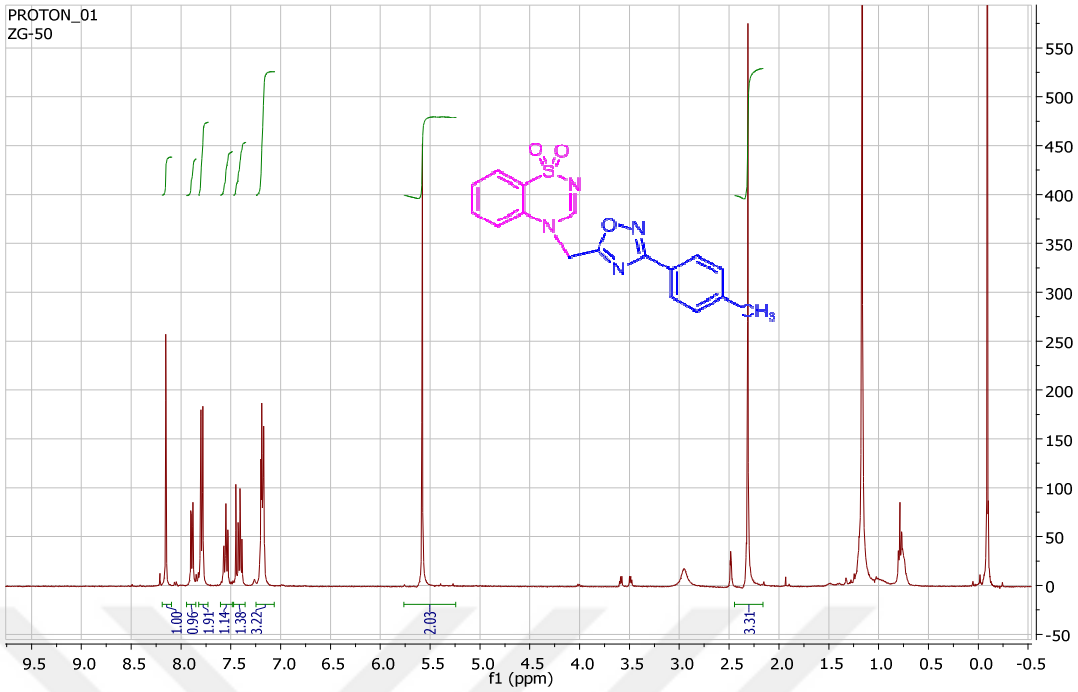


Figure 4.11. ^{1}H NMR spectrum of **9a**

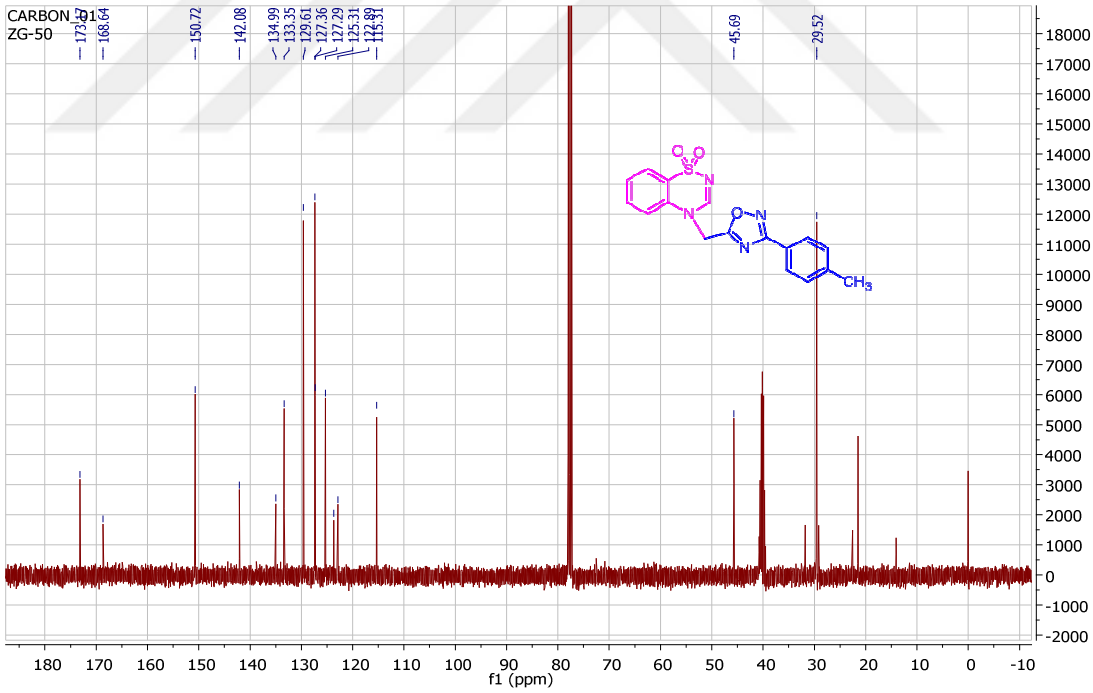


Figure 4.12. ^{13}C NMR spectrum of **9a**

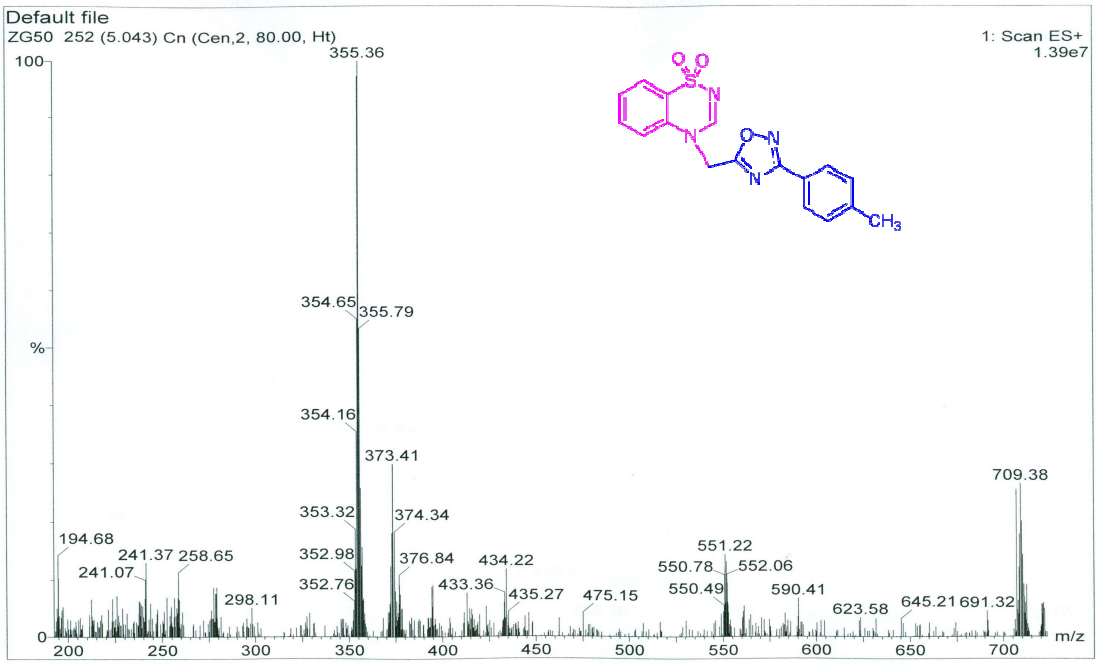


Figure 4.13. LC-MS spectrum of **9a**

5. CONCLUSIONS

In summary, within this study, despite the difficulties encountered during the experiments, we succesfully synthesized 8 new benzothiadiazine-1,1-dioxide derivatives carrying 1,2,4-oxadiazolylmethyl group at 4-position of the benzothiadiazine ring. Synthesis of amidoximes and chloromethyl oxadiazoles as starting materials were carried out and their interaction with benzothiazine-1,1-dioxide were performed. Amidoximes and aminosulfonamides did not undergo an anticipated reaction which would lead to target compounds even if we tried under too many conditions including microwave or classical heating methods.

All of these compounds are new and original and makes a remarkable contribution to the literature of synthetic organic chemistry. It is strongly possible that the compounds are potentially bioactive according to the groups they carry. But, unfortunately, at the moment, we are not able to conduct a bioactivity screening of the compounds due to the low amounts of them and being unrecoverable from DMSO-d_6 NMR solutions.

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APPENDICES

7. APPENDICES

IR, ^{1}H NMR, ^{13}C NMR and LC-MS Spectra of the precursors and products

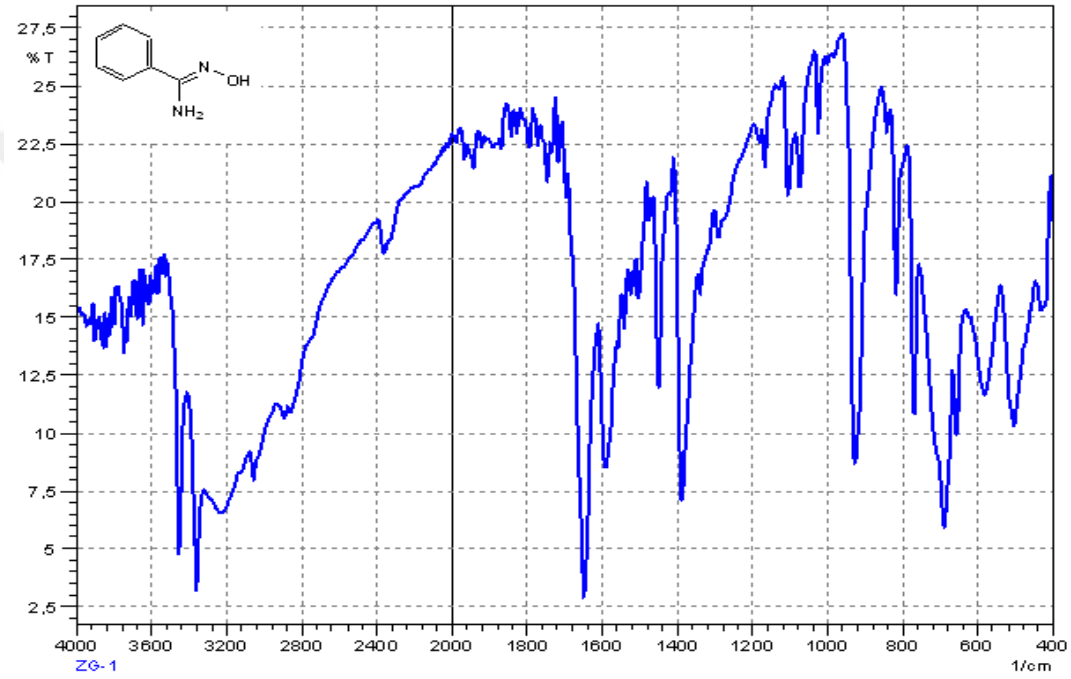

Figure 7.1. IR spectrum of benzamidoxime **2a**

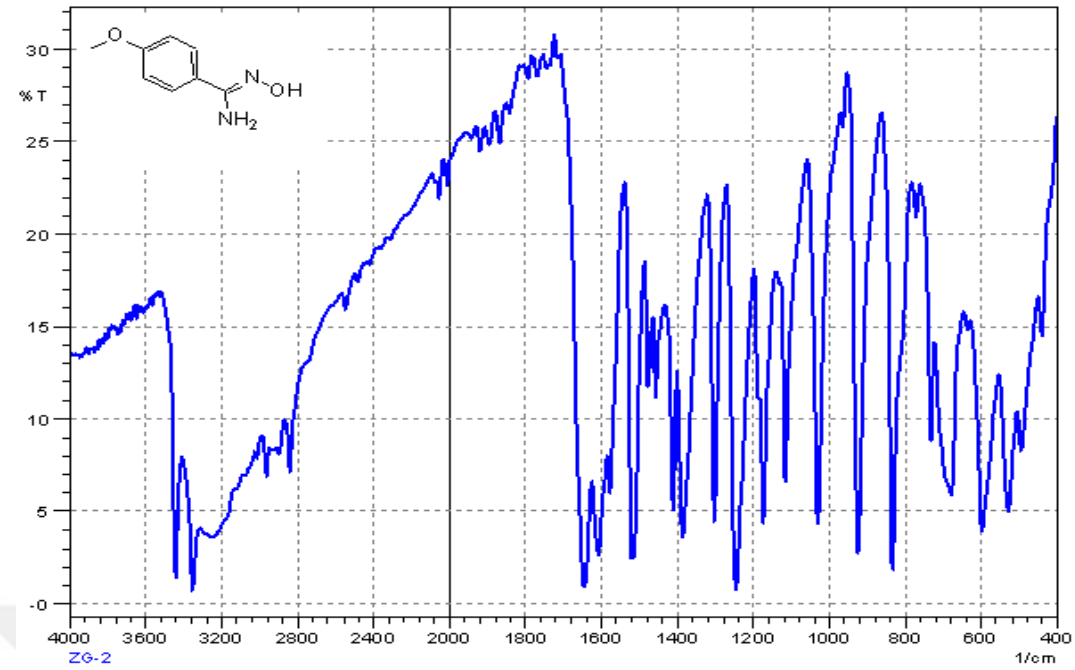

Figure 7.2. IR spectrum of 4-methoxybenzamidoxime **2b**

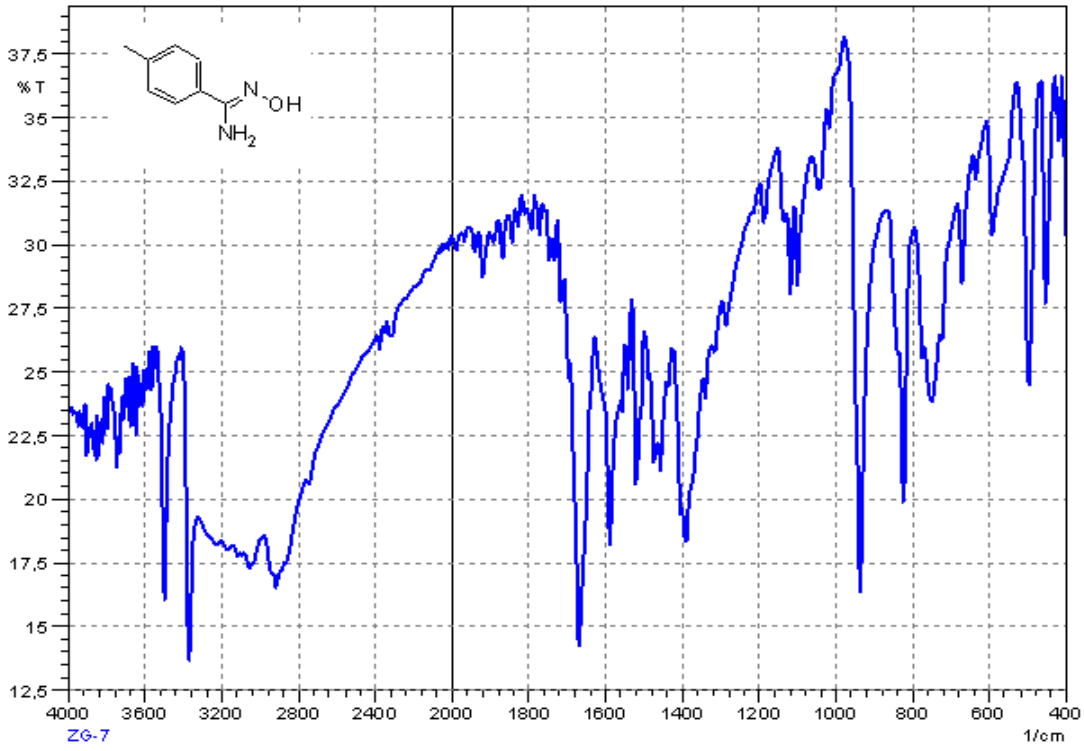

Figure 7.3. IR spectrum of 4-methylbenzamidoxime **2c**

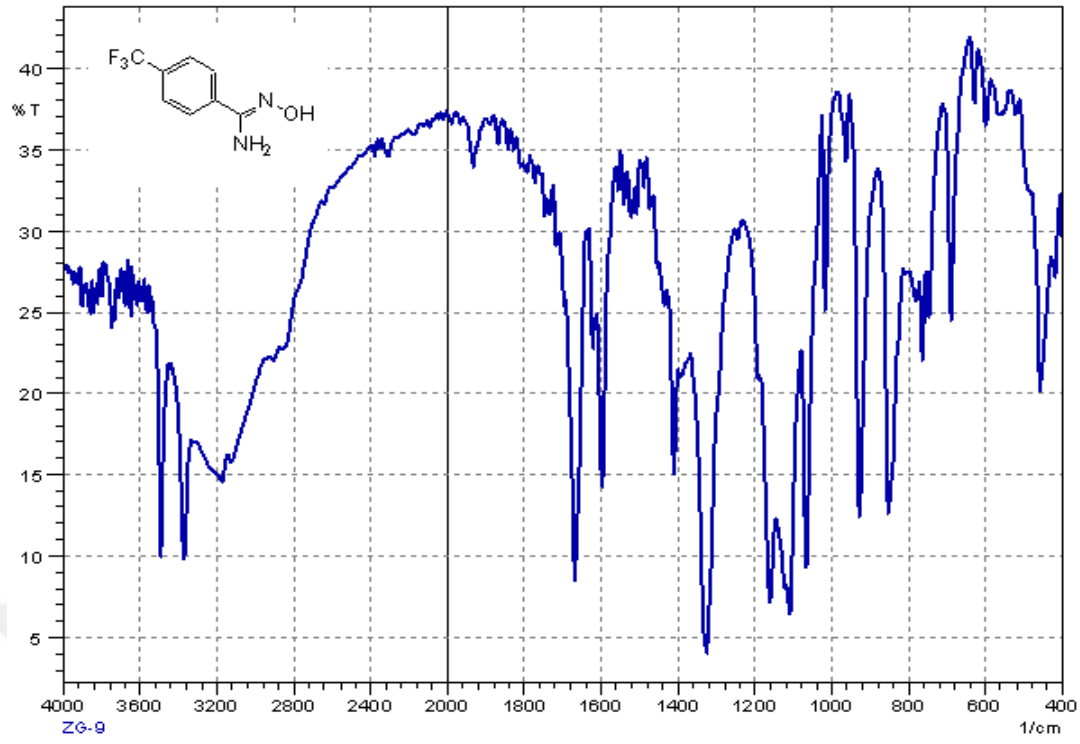

Figure 7.4. IR spectrum of 4-trifluoromethylbenzamidoxime **2d**

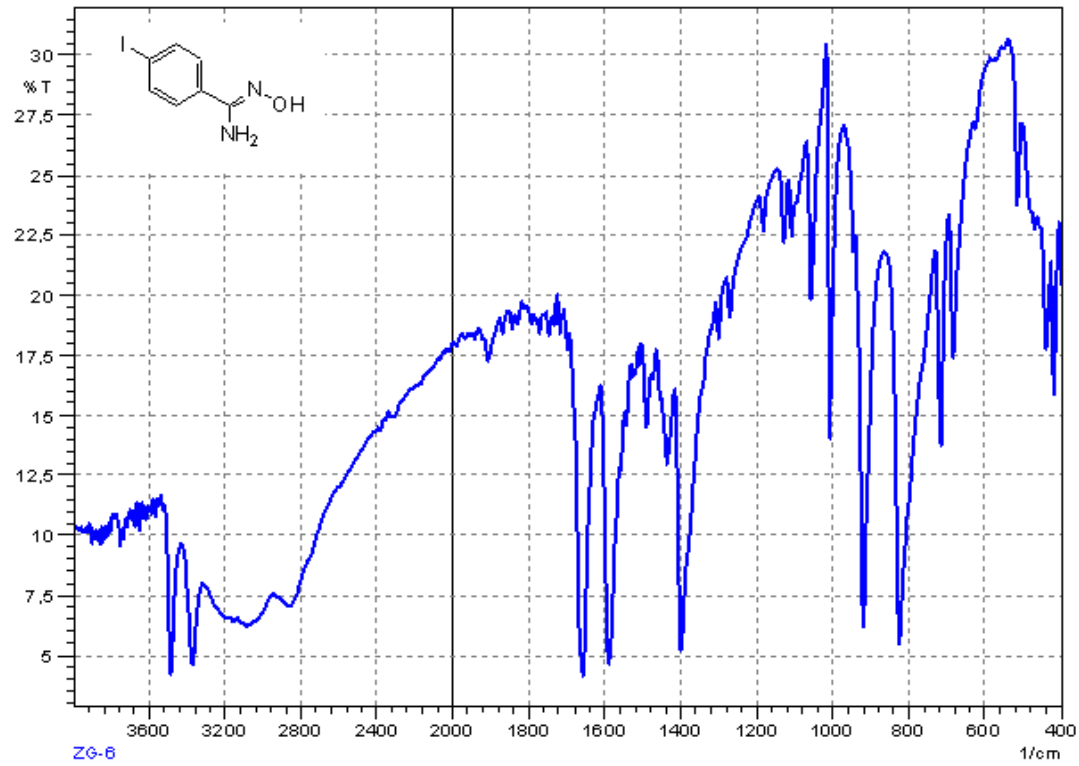

Figure 7.5. IR spectrum of 4-iodobenzamidoxime **2e**

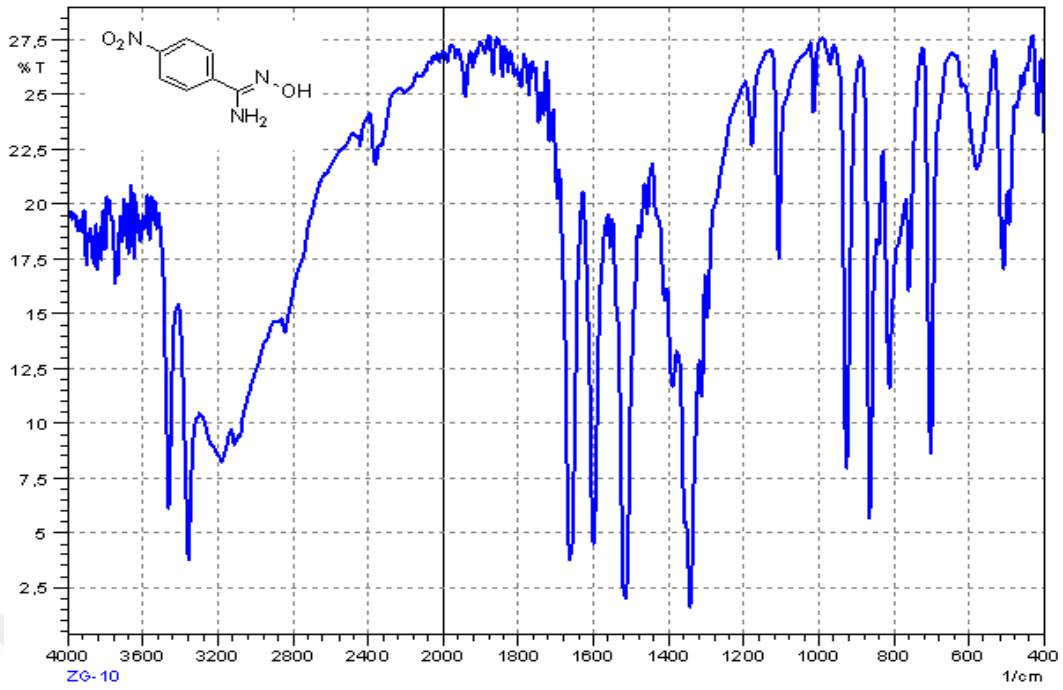

Figure 7.6. IR spectrum of 4-nitrobenzamidoxime **2f**

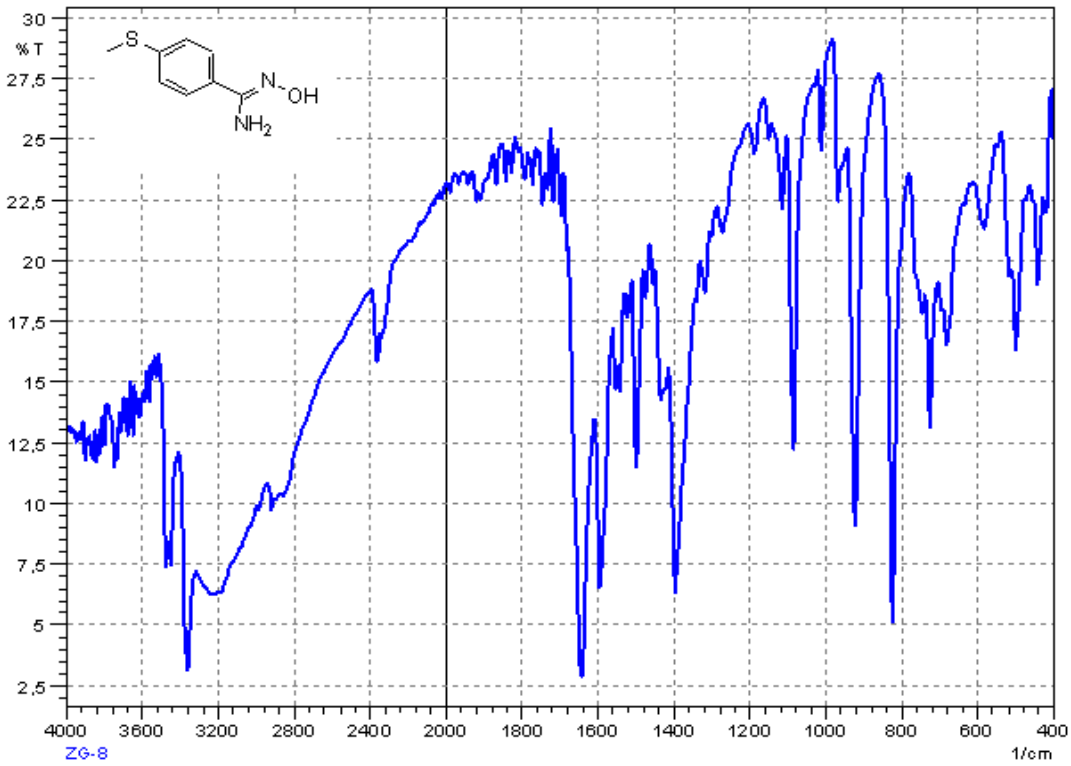

Figure 7.7. IR spectrum of 4-methylthiobenzamidoxime **2g**

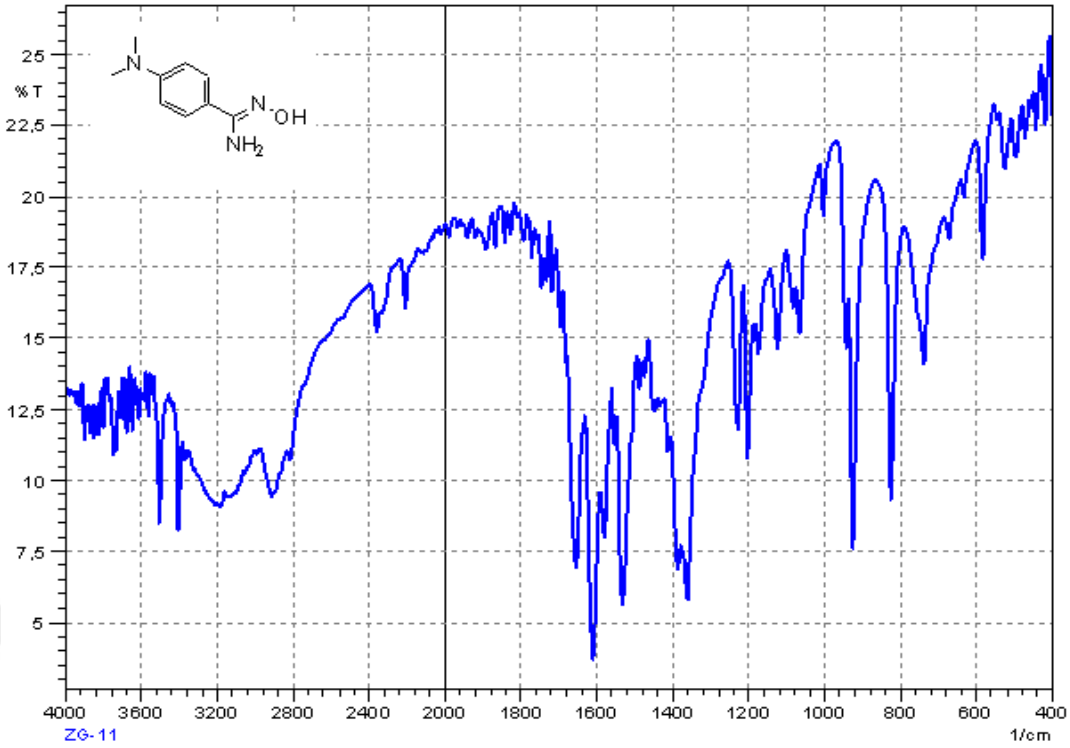

Figure 7.8. IR spectrum of 4-dimethylaminobenzamidoxime **2h**

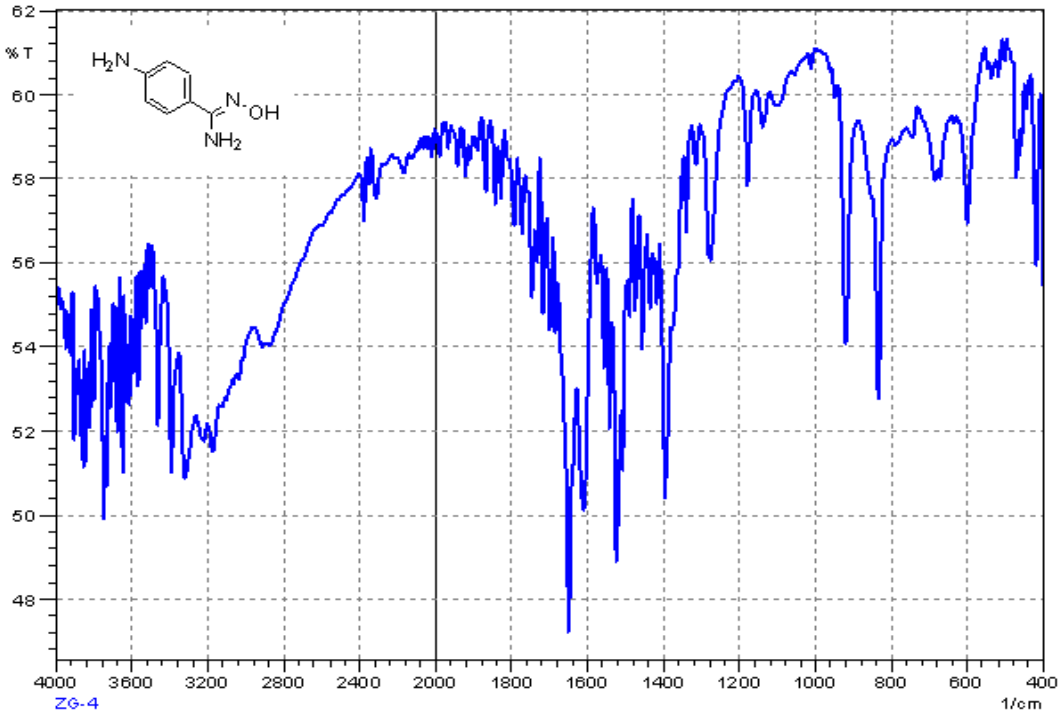

Figure 7.9. IR spectrum of 4-aminobenzamidoxime **2i**

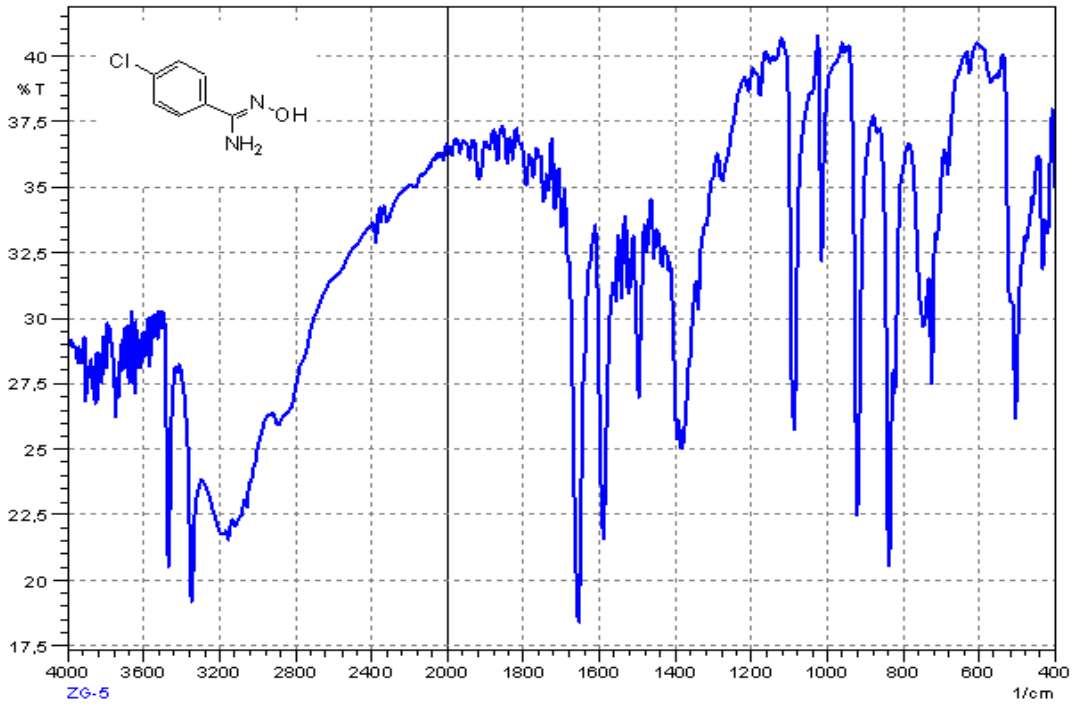

Figure 7.10. IR spectrum of 4-chlorobenzamidoxime **2j**

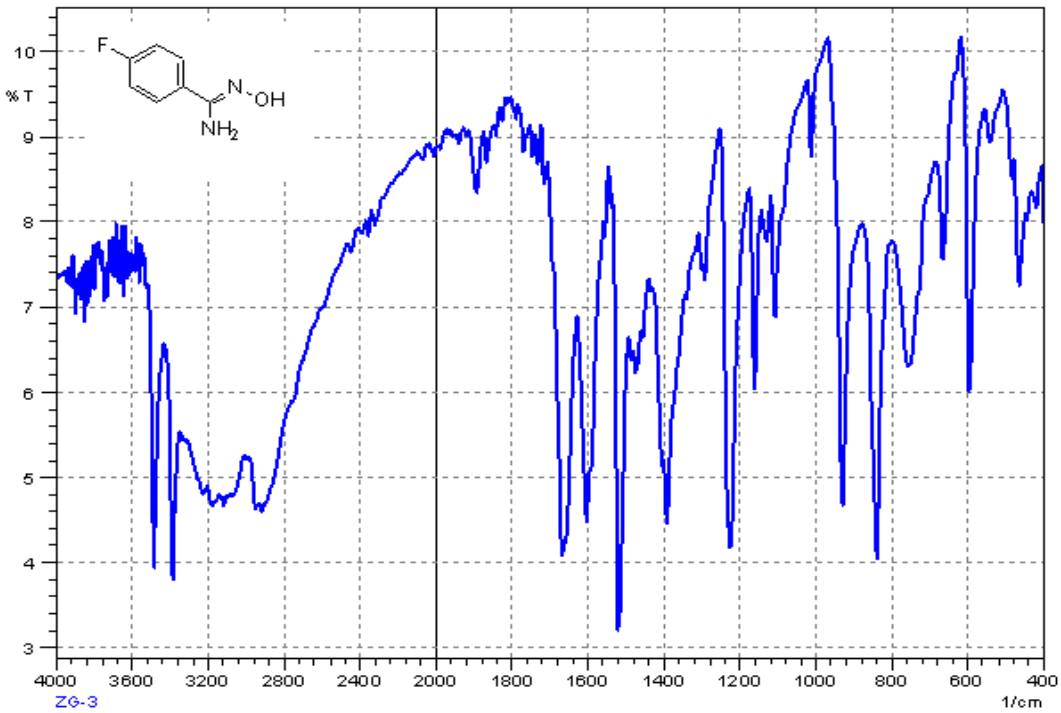

Figure 7.11. IR spectrum of 4-fluorobenzamidoxime **2k**

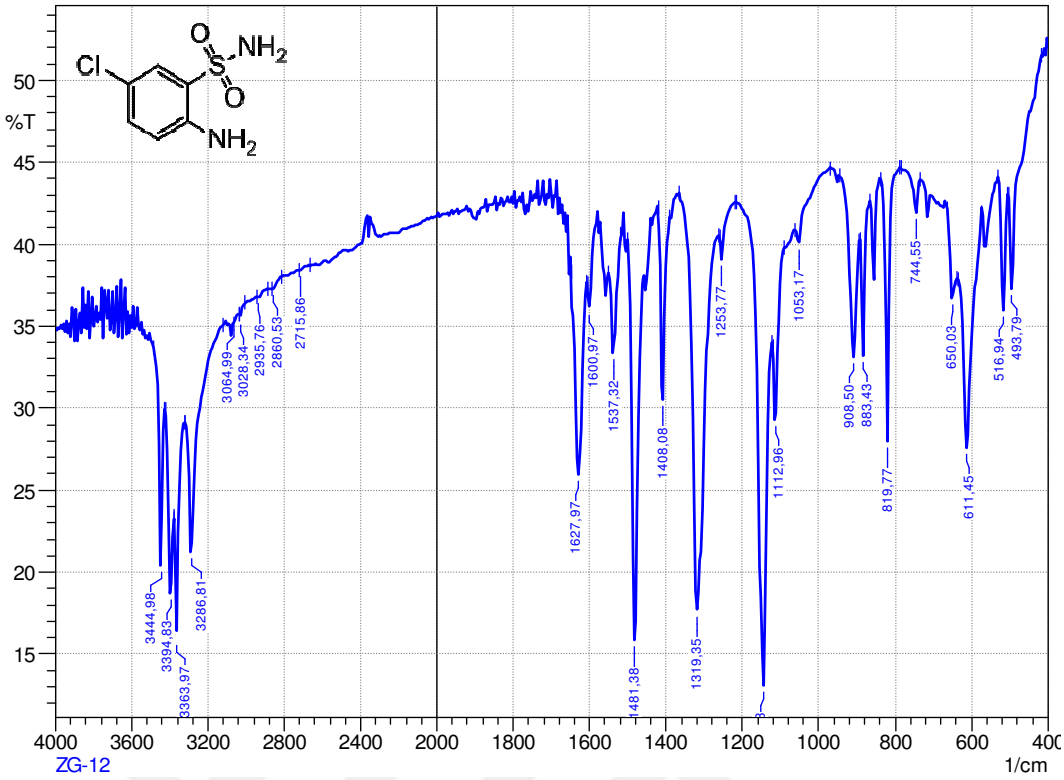

Figure 7.12. IR spectrum of 2-amino-5-chlorobenzenesulfonamide **5a**

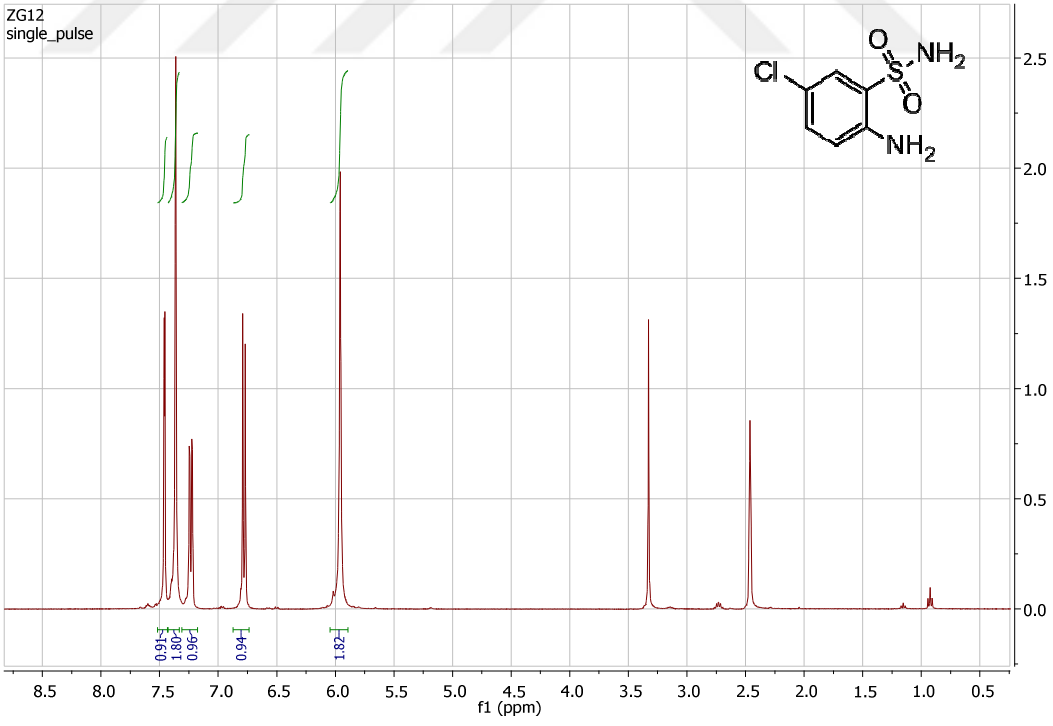

Figure 7.13. ^{1}H NMR spectrum of 2-Amino-5-chlorobenzenesulphonamide **5a**

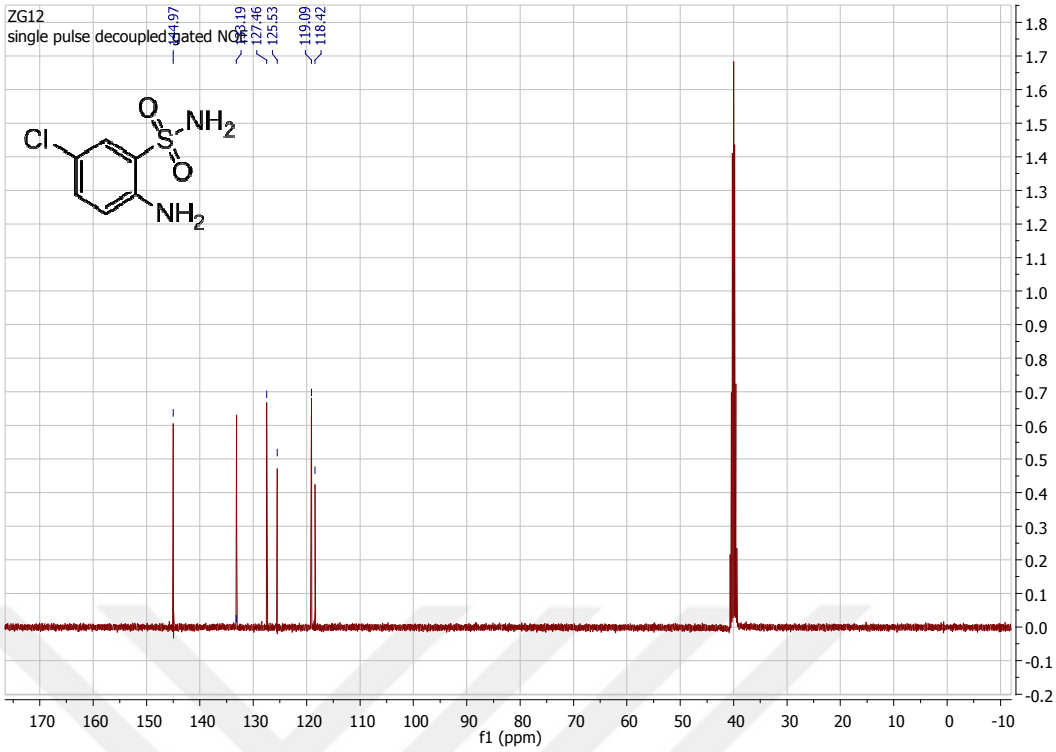

Figure 7.14. ^{13}C NMR spectrum of 2-amino-5-chlorobenzenesulphonamide **5a**

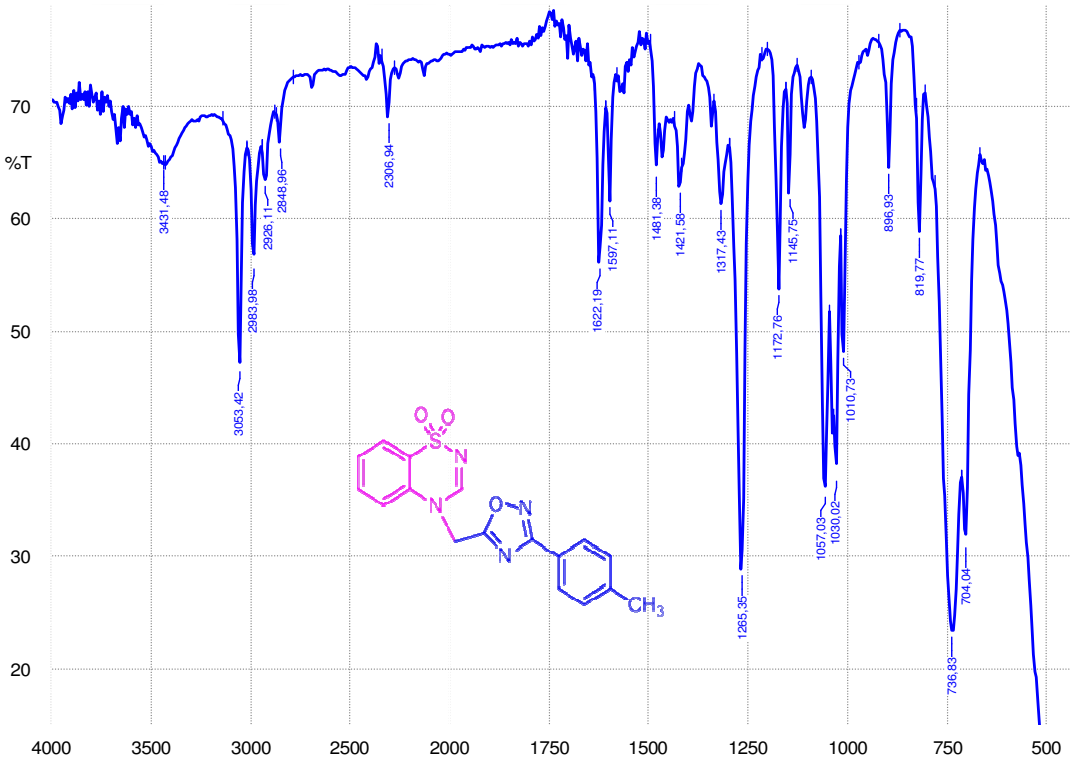

Figure 7.15. IR spectrum of compound **9a**

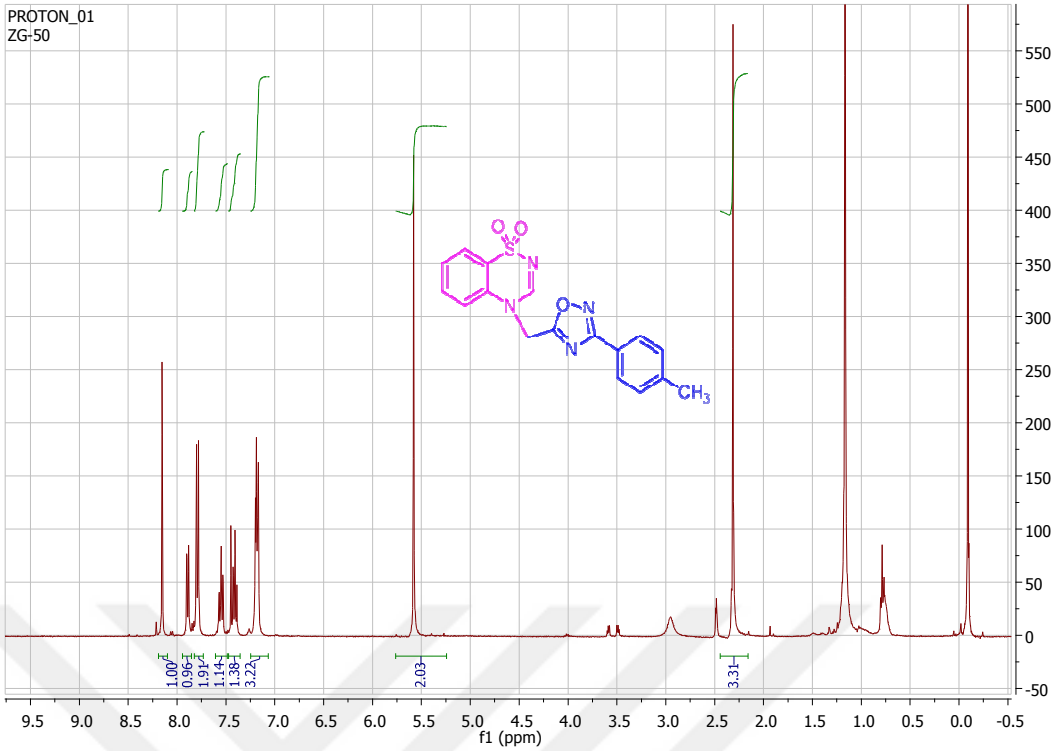

Figure 7.16. ^{1}H NMR spectrum of compound **9a**

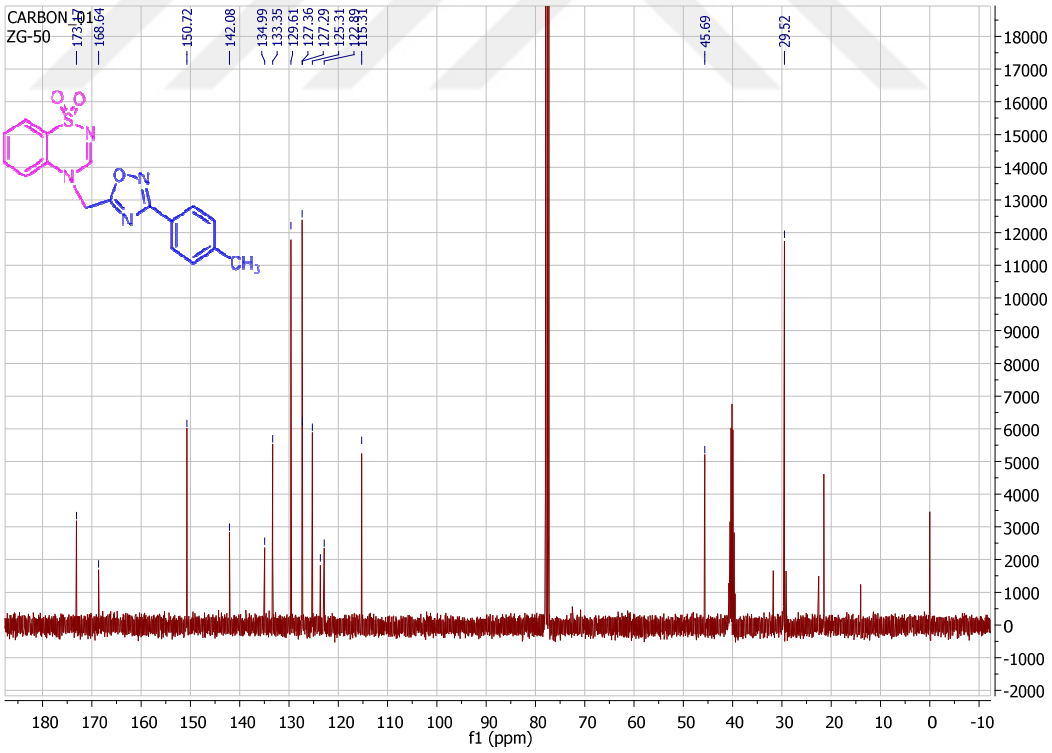

Figure 7.17. ^{13}C NMR spectrum of compound **9a**

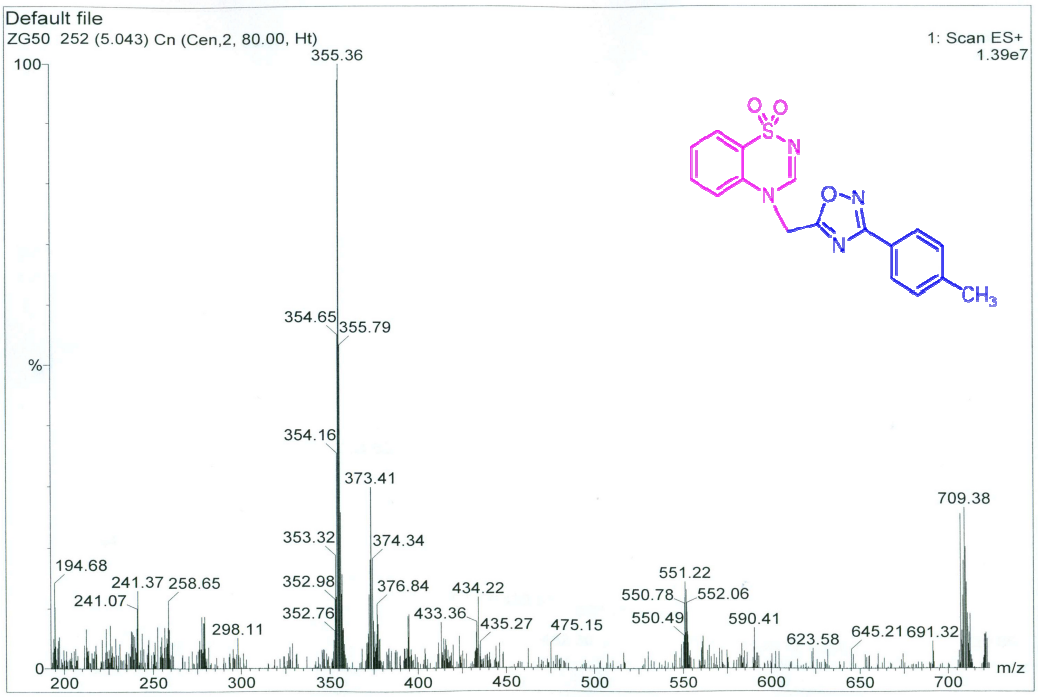

Figure 7.18. LC-MS spectrum of compound **9a**

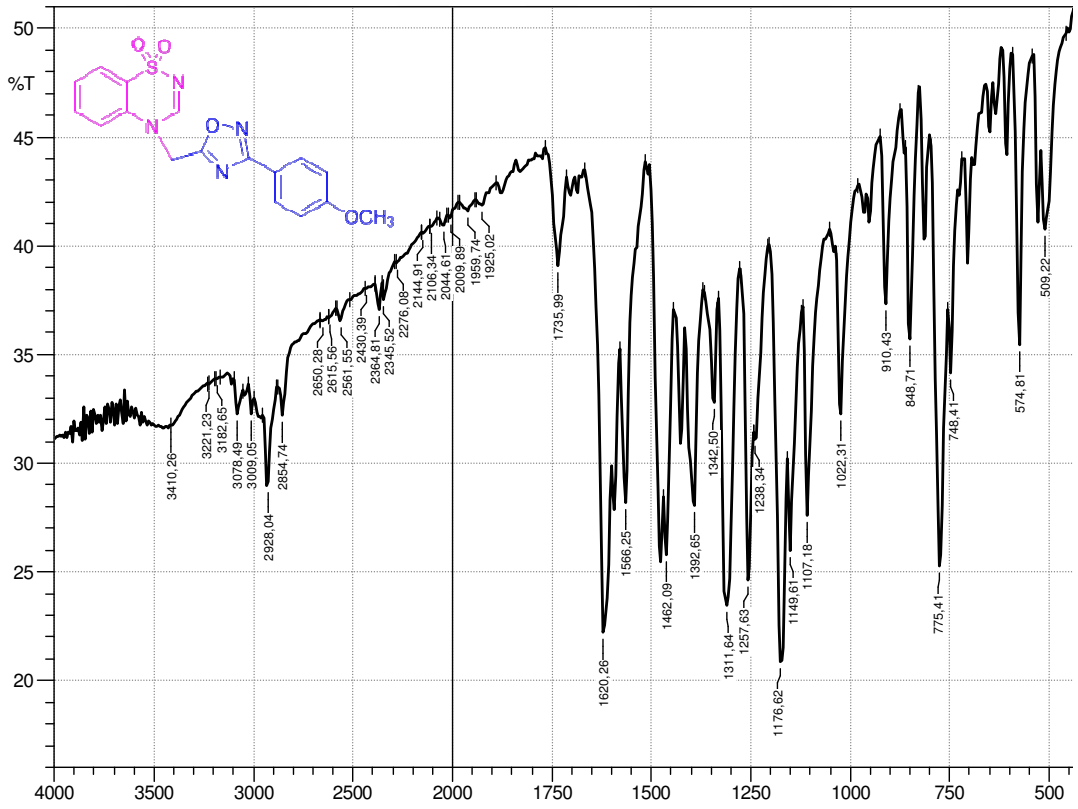

Figure 7.19. IR spectrum of compound **9b**

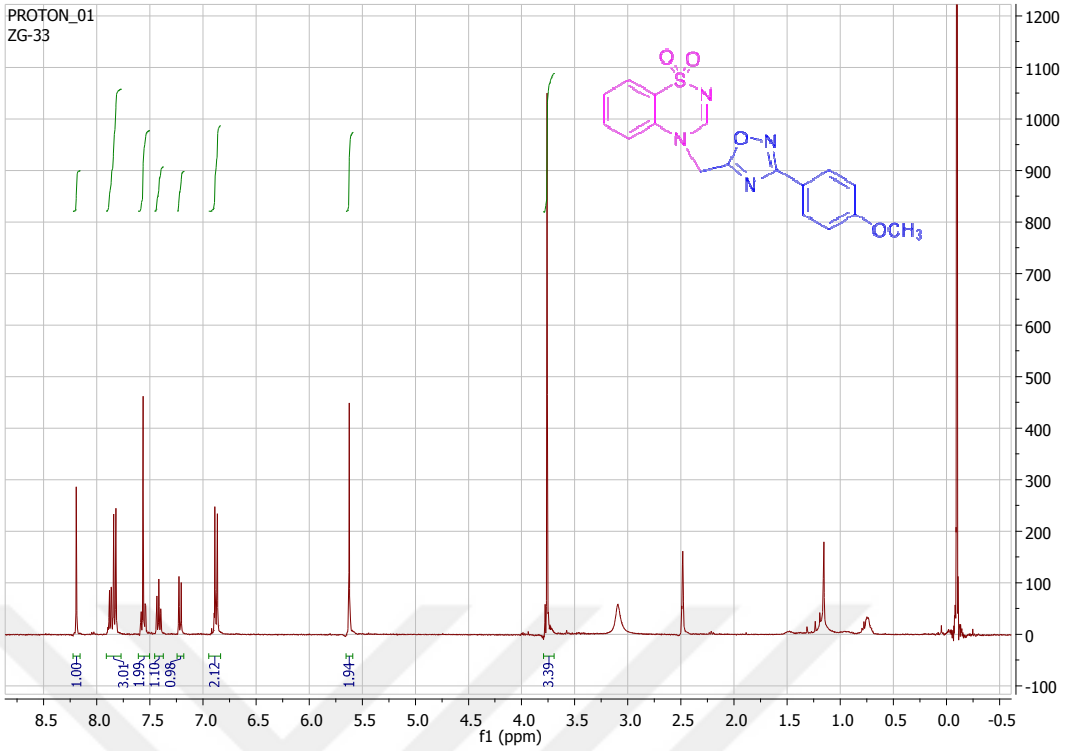

Figure 7.20. ^{1}H NMR spectrum of compound **9b**

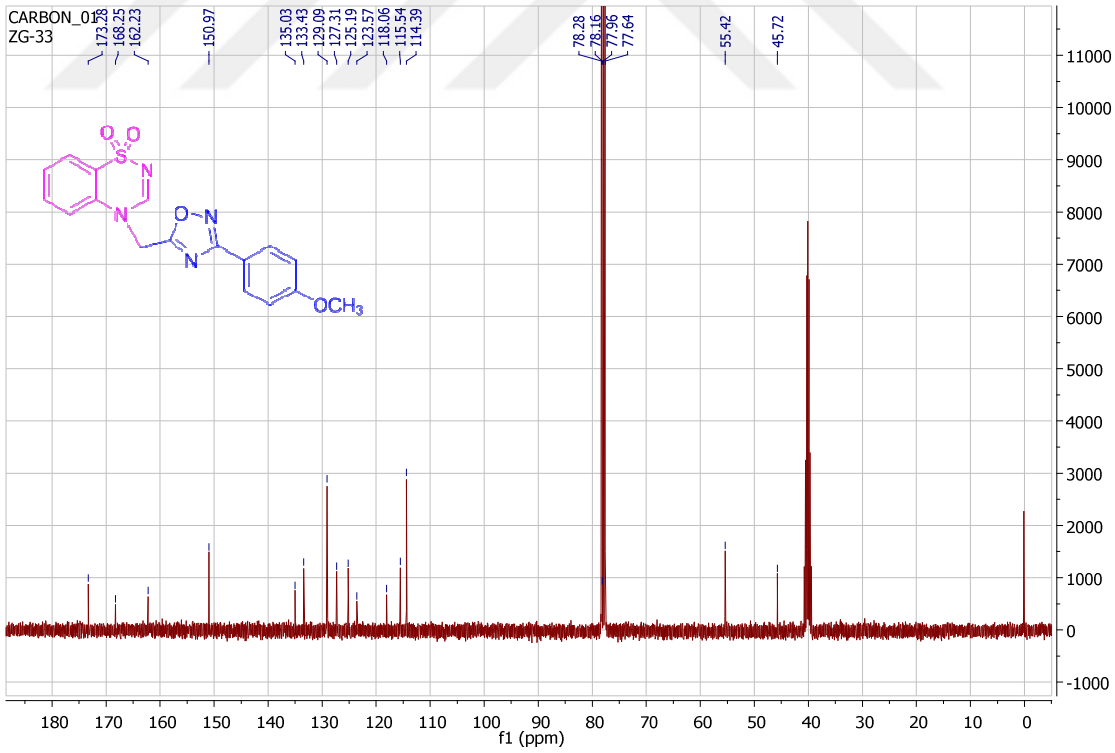

Figure 7.21. ^{13}C NMR spectrum of compound **9b**

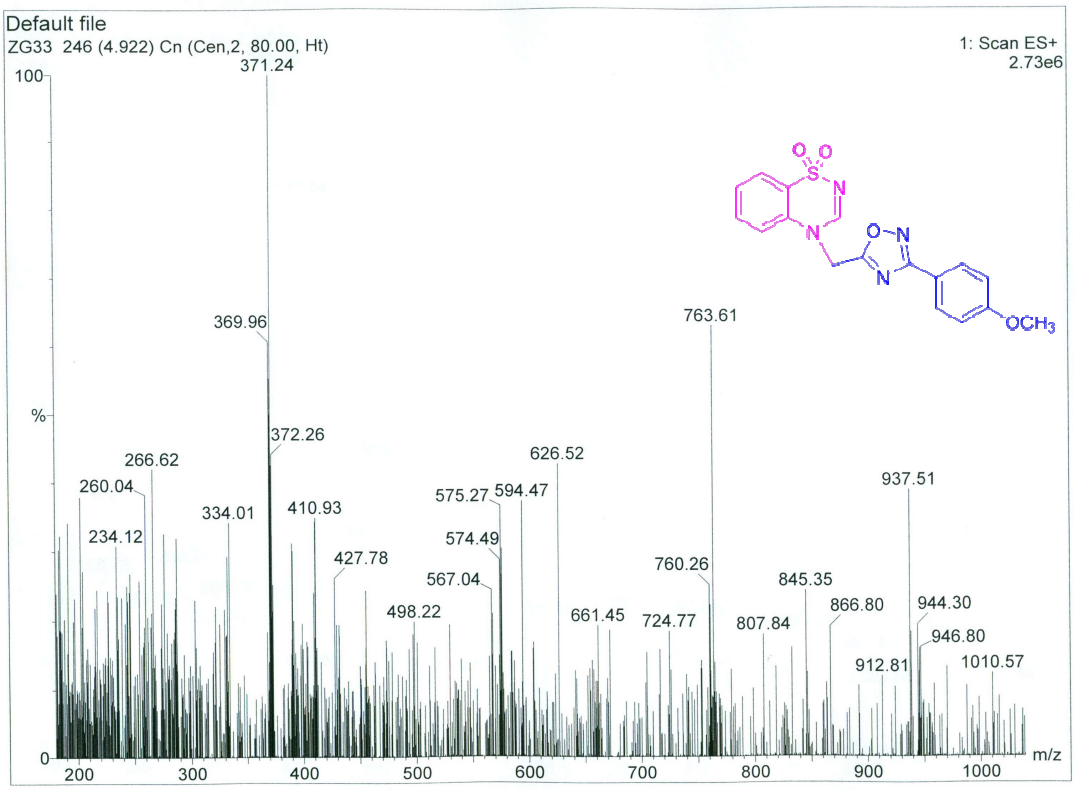

Figure 7.22. LC-MS spectrum of compound **9b**

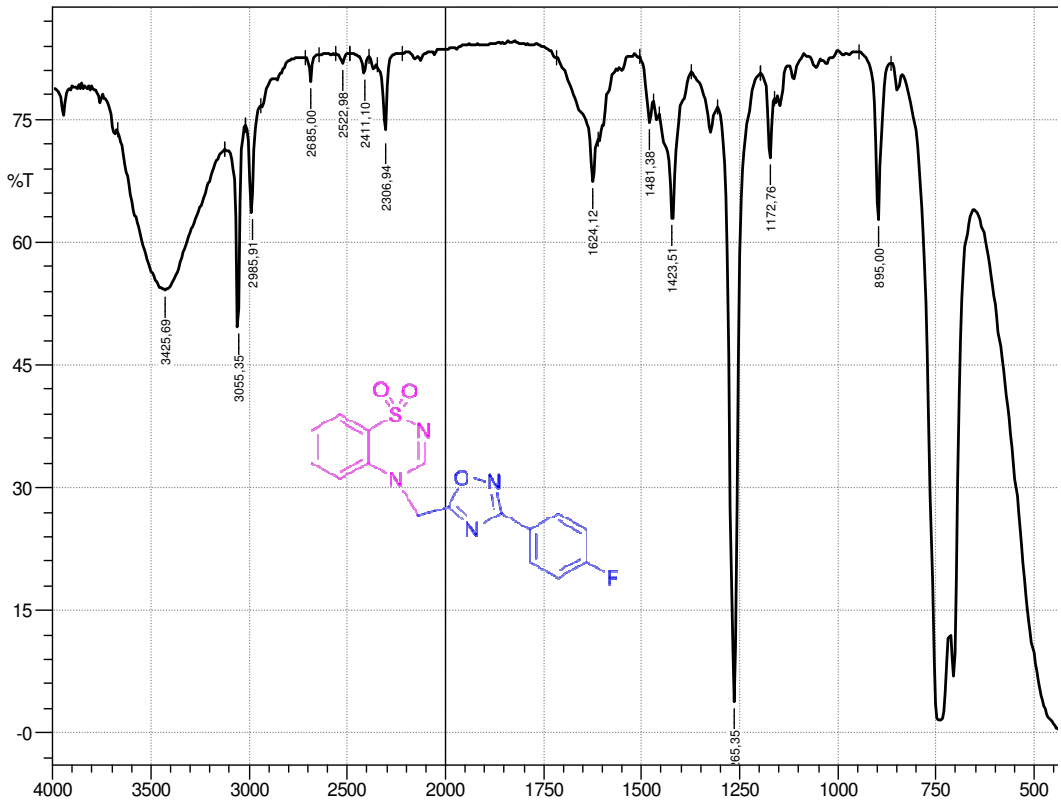

Figure 7.23. IR spectrum of compound **9c**

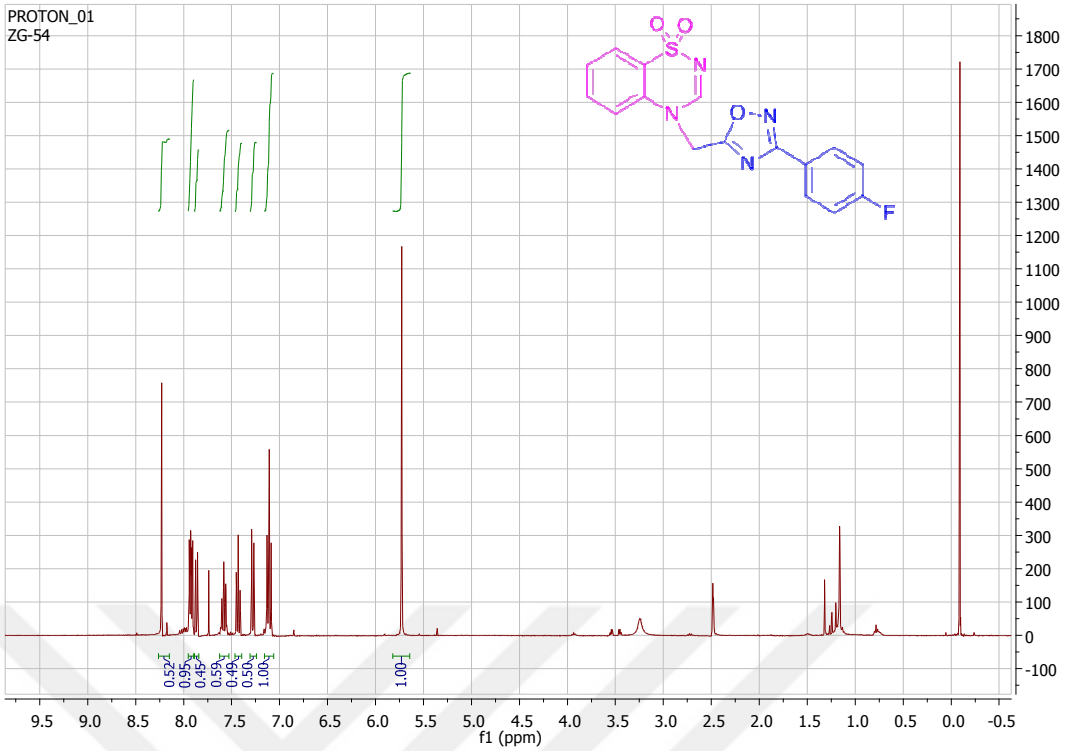

Figure 7.24. ^{1}H NMR spectrum of compound **9c**

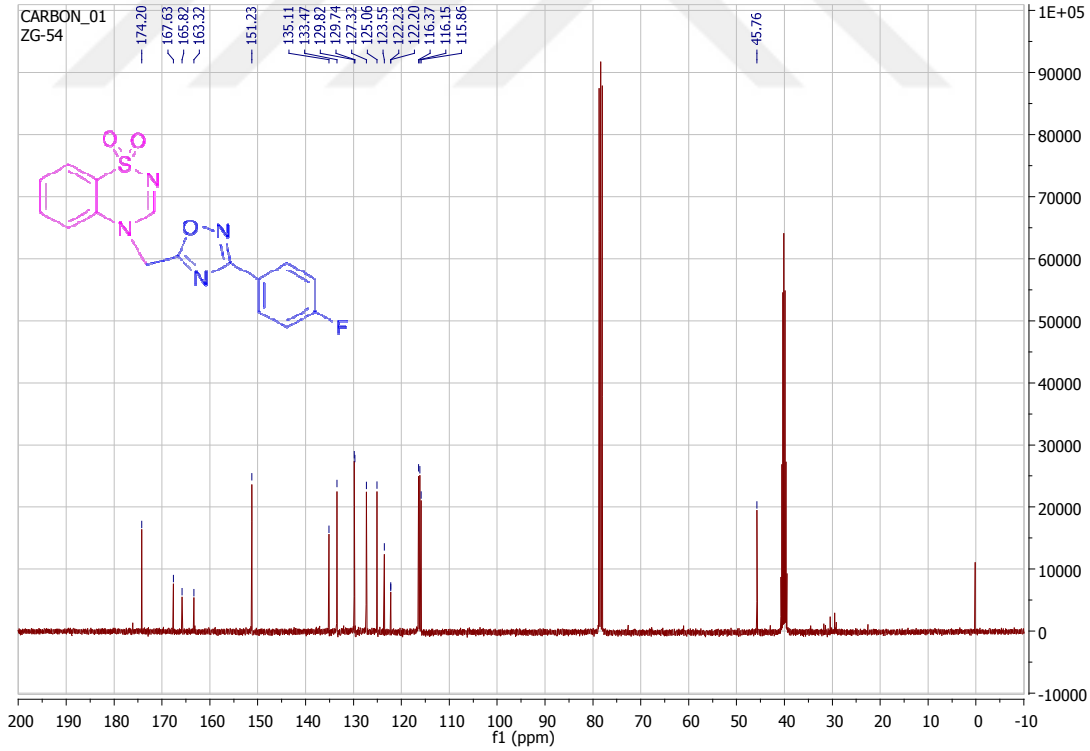

Figure 7.25. ^{13}C NMR spectrum of compound **9c**

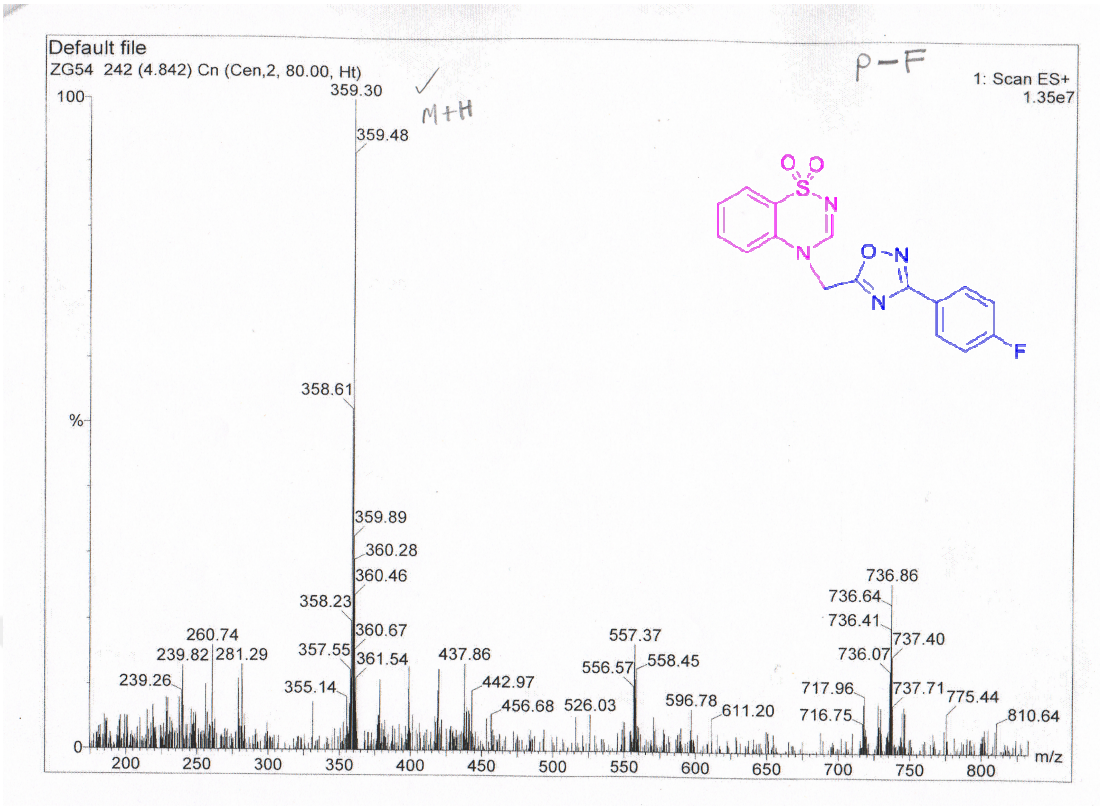

Figure 7.26. LC-MS spectrum of compound **9c**

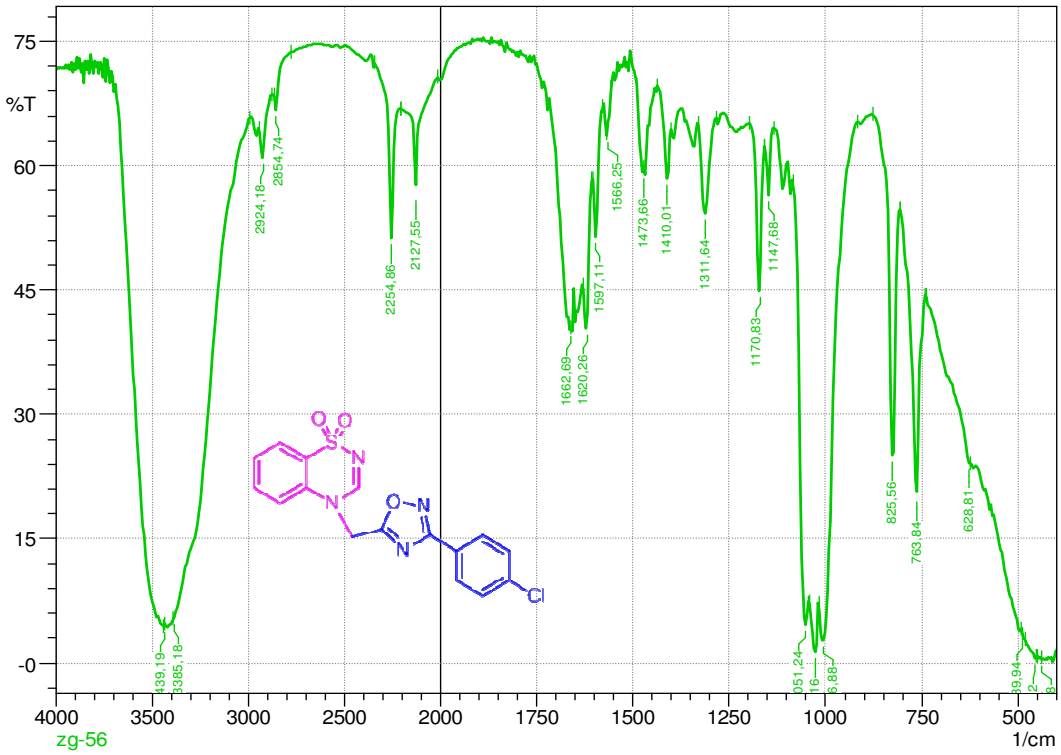

Figure 7.27. IR spectrum of compound **9d**

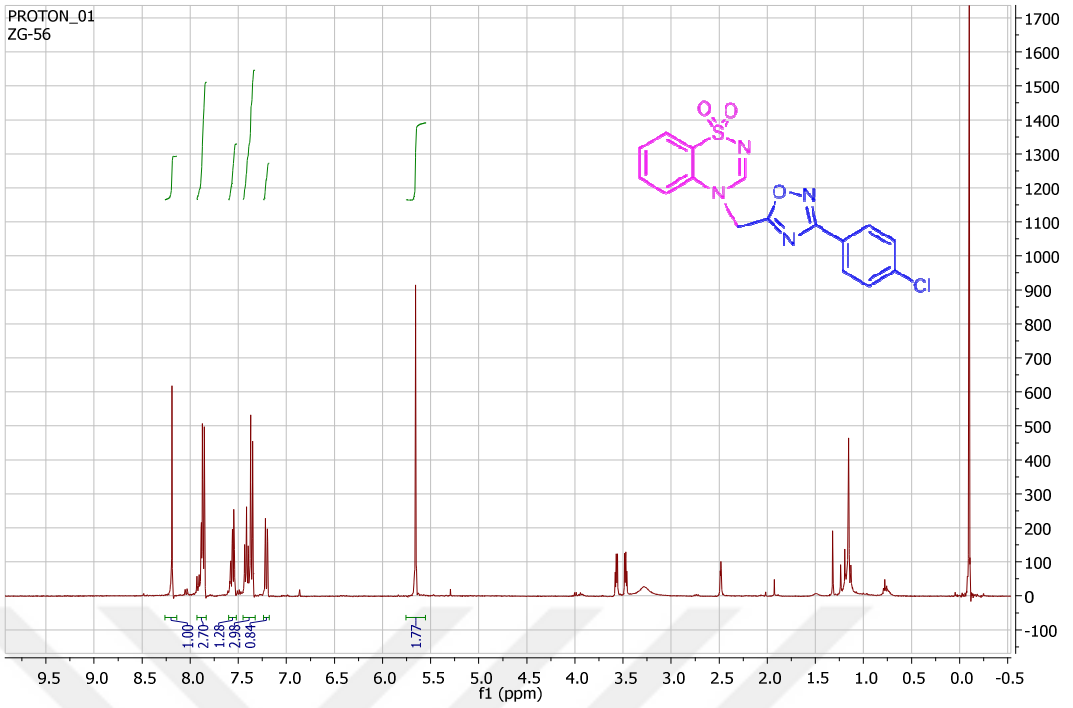

Figure 7.28. ^{1}H NMR spectrum of compound **9d**

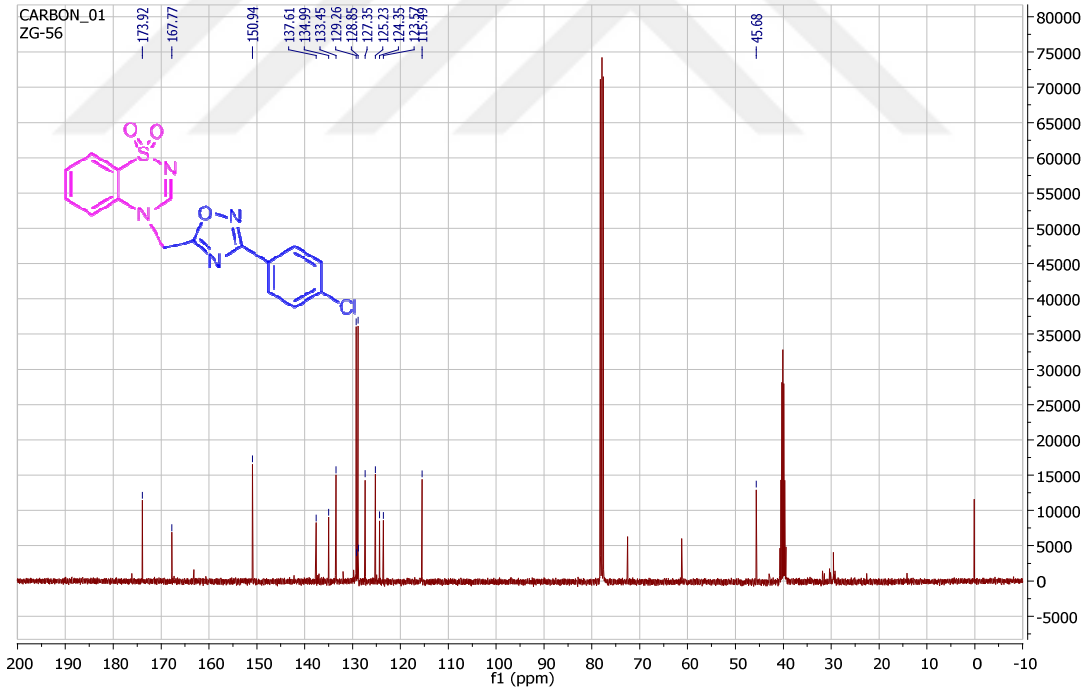

Figure 7.29. ^{13}C NMR spectrum of compound **9d**

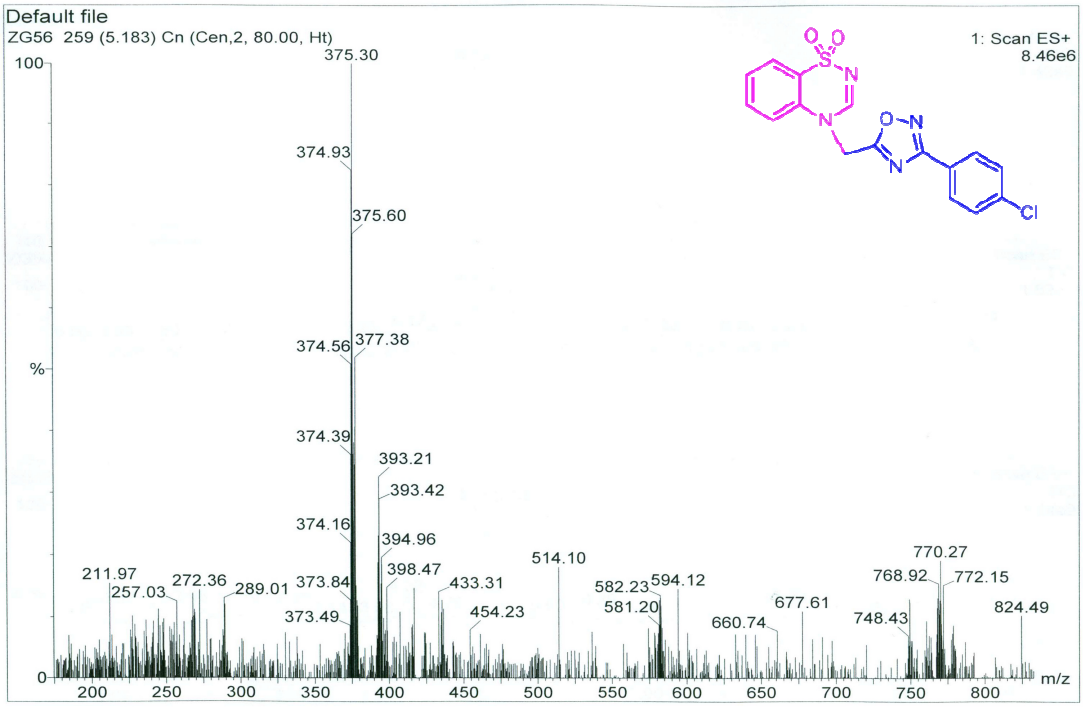

Figure 7.30. LC-MS (ES+) spectrum of compound **9d**

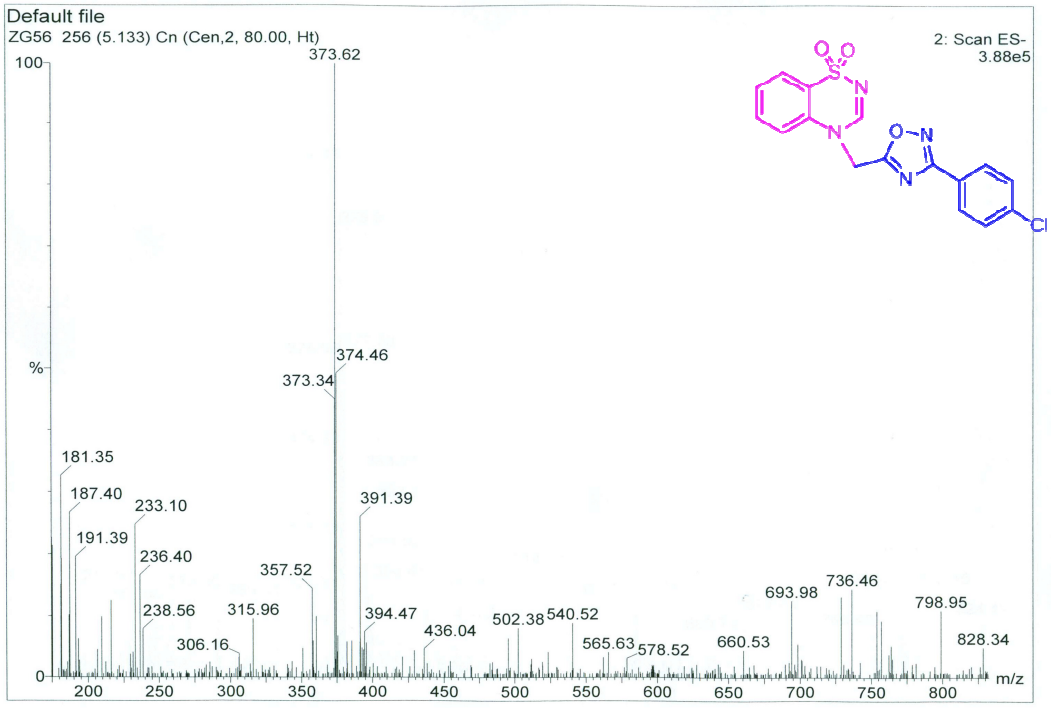

Figure 7.31. LC-MS (ES-) spectrum of compound **9d**

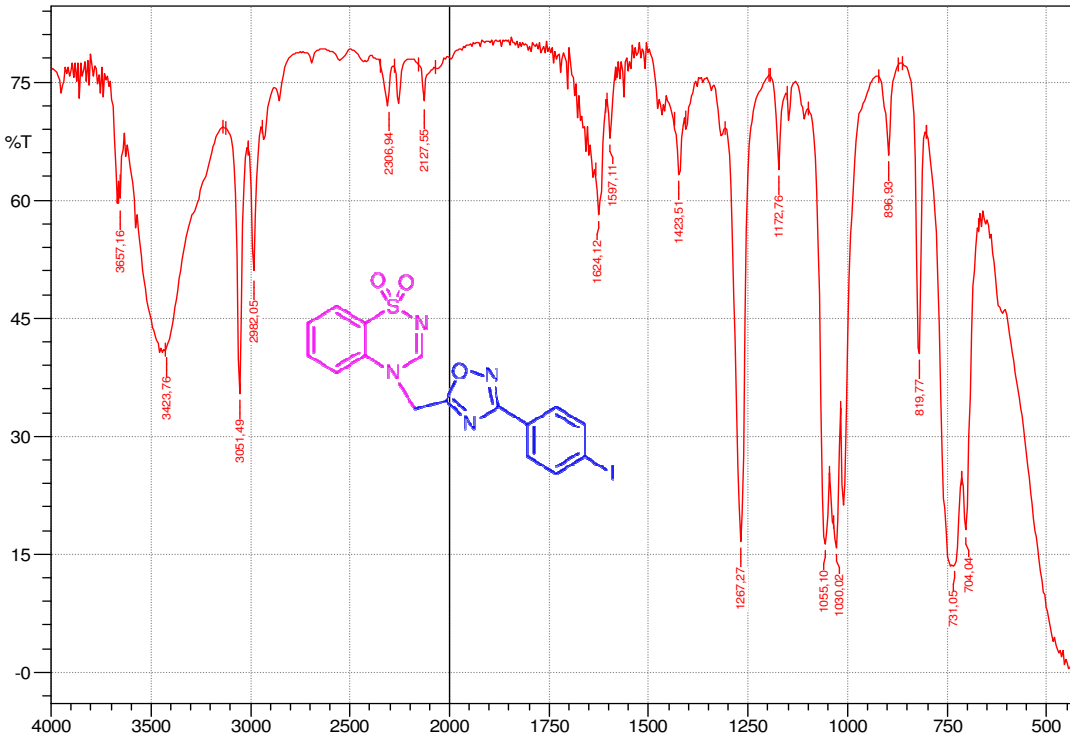

Figure 7.32. IR spectrum of compound **9e**

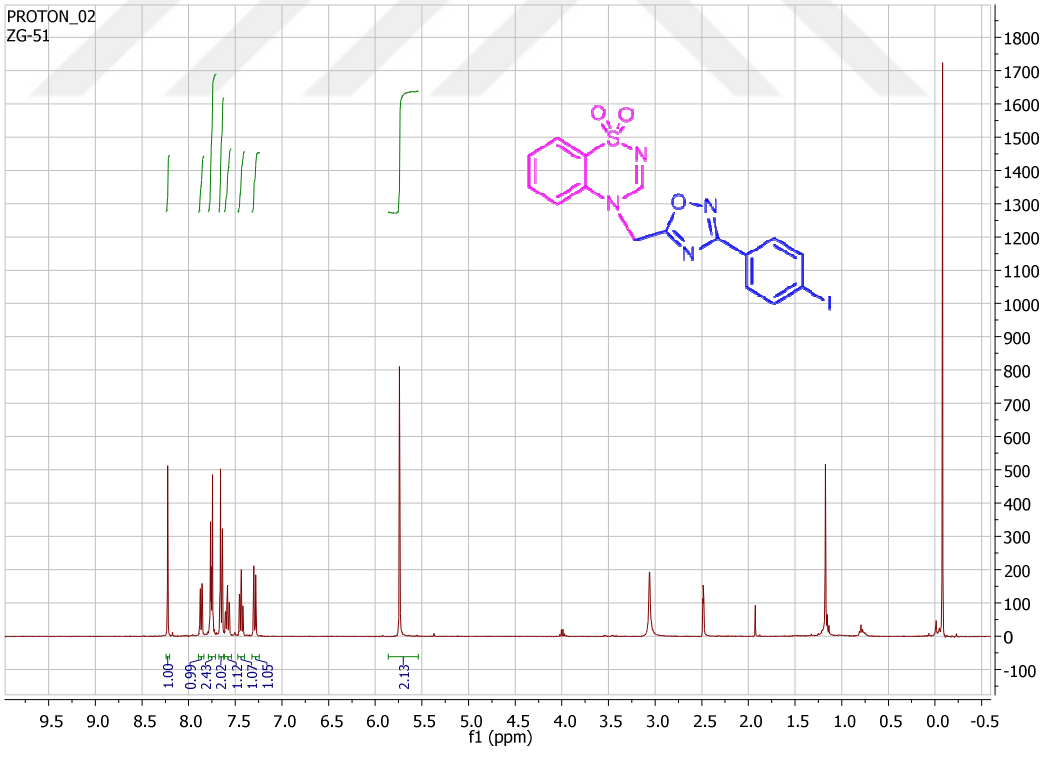

Figure 7.33. ^{1}H NMR spectrum of compound **9e**

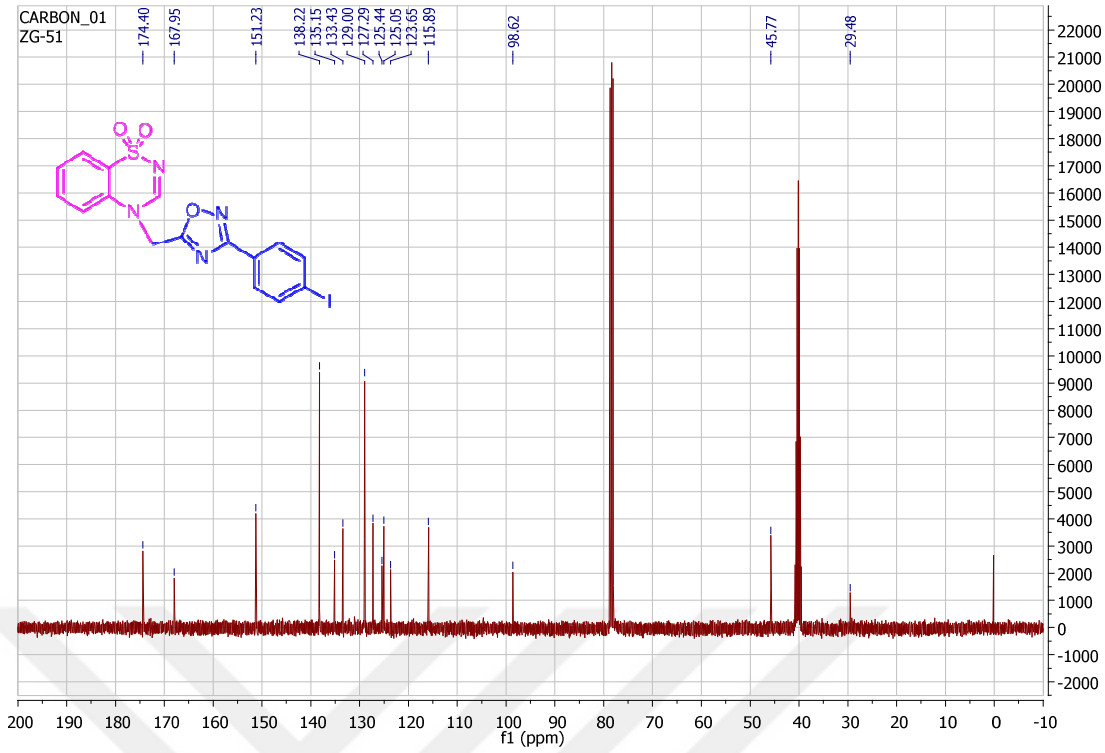

Figure 7.34. ^{13}C NMR spectrum of compound **9e**

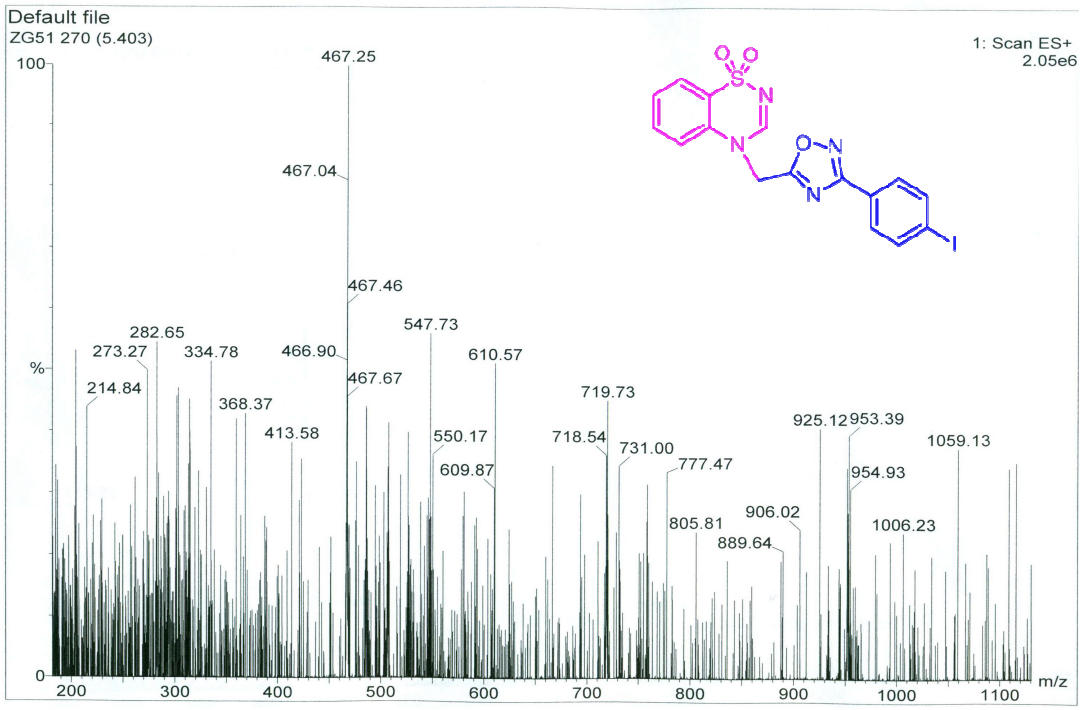

Figure 7.35. LC-MS (ES+) spectrum of compound **9e**

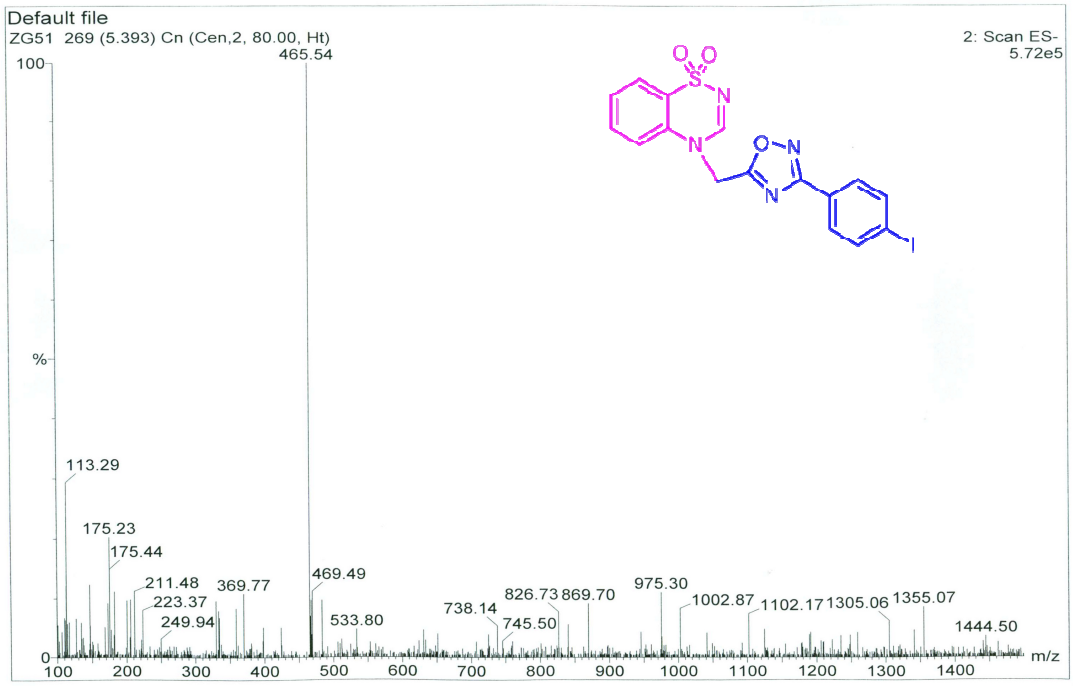

Figure 7.36. LC-MS (ES-) spectrum of compound **9e**

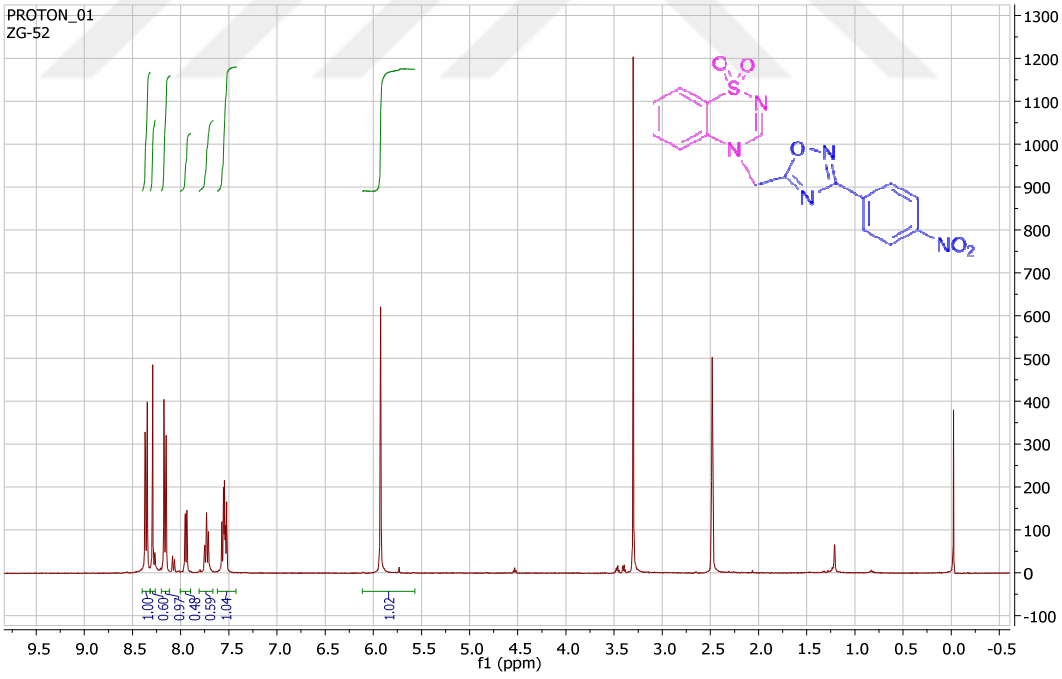

Figure 7.37. ^{1}H NMR spectrum of compound **9f**

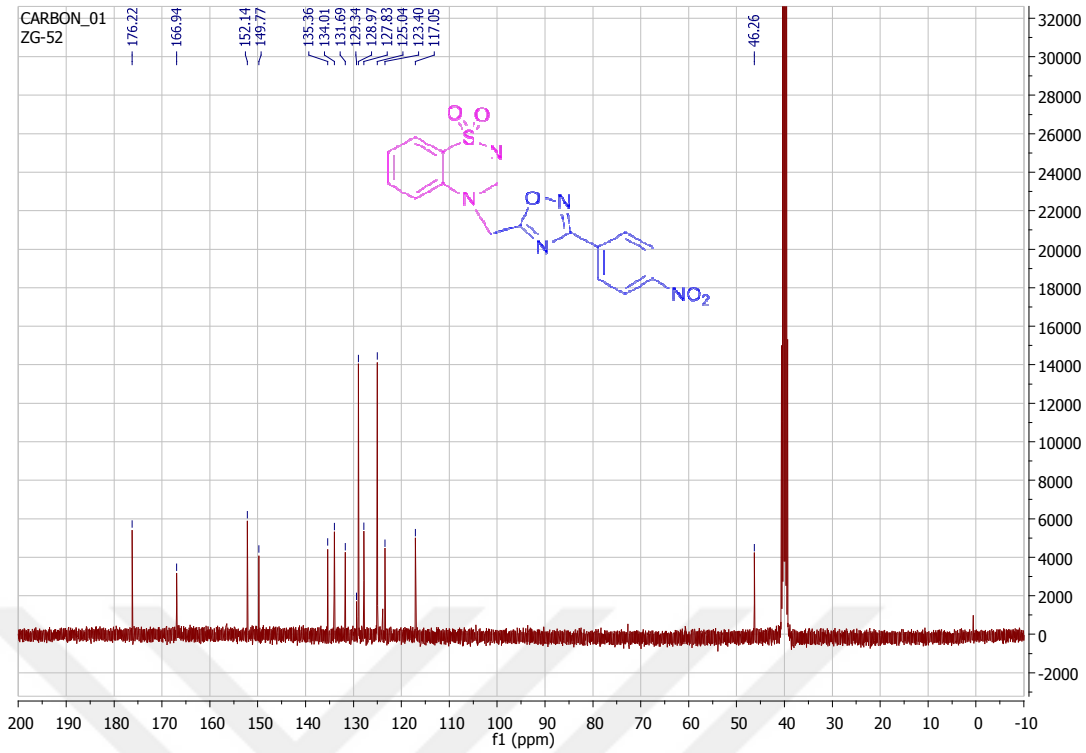

Figure 7.38. ^{13}C NMR spectrum of compound **9f**

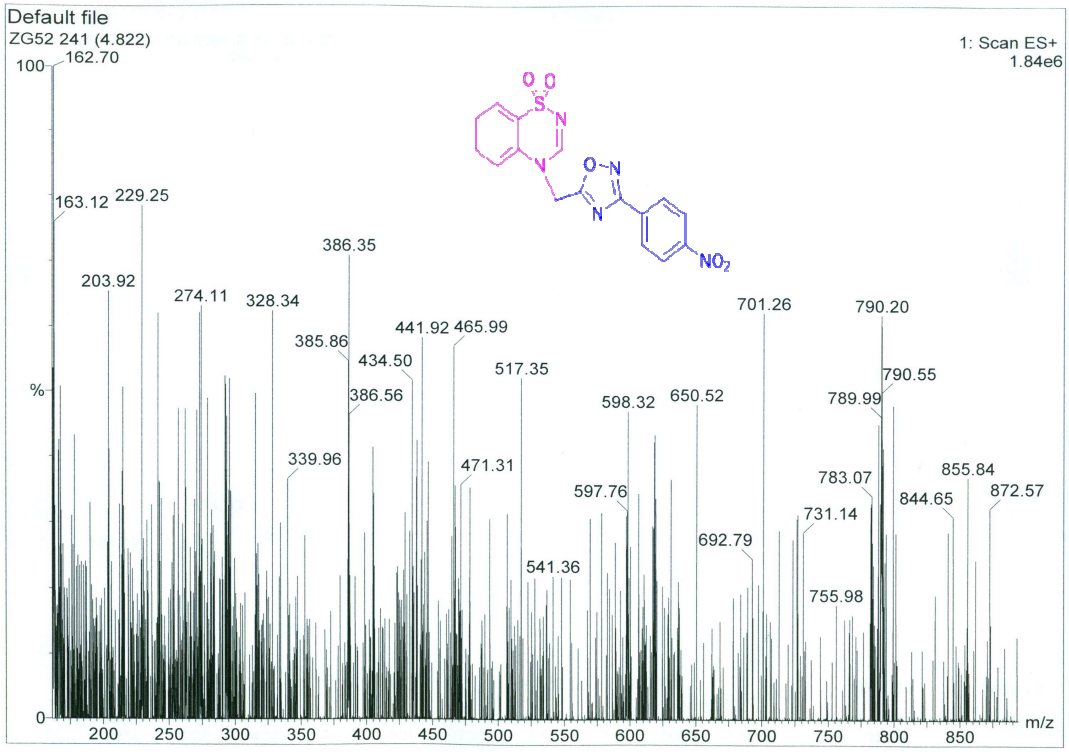

Figure 7.39. LC-MS (ES+) spectrum of compound **9f**

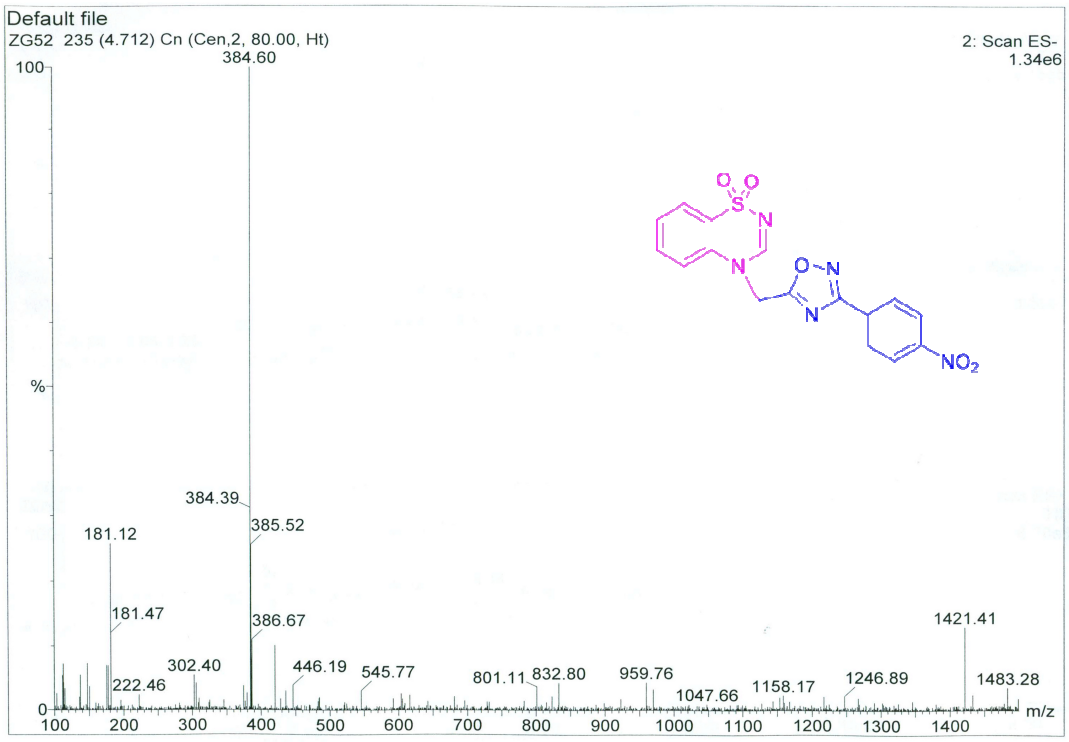

Figure 7.40. LC-MS (ES-) spectrum of compound **9f**

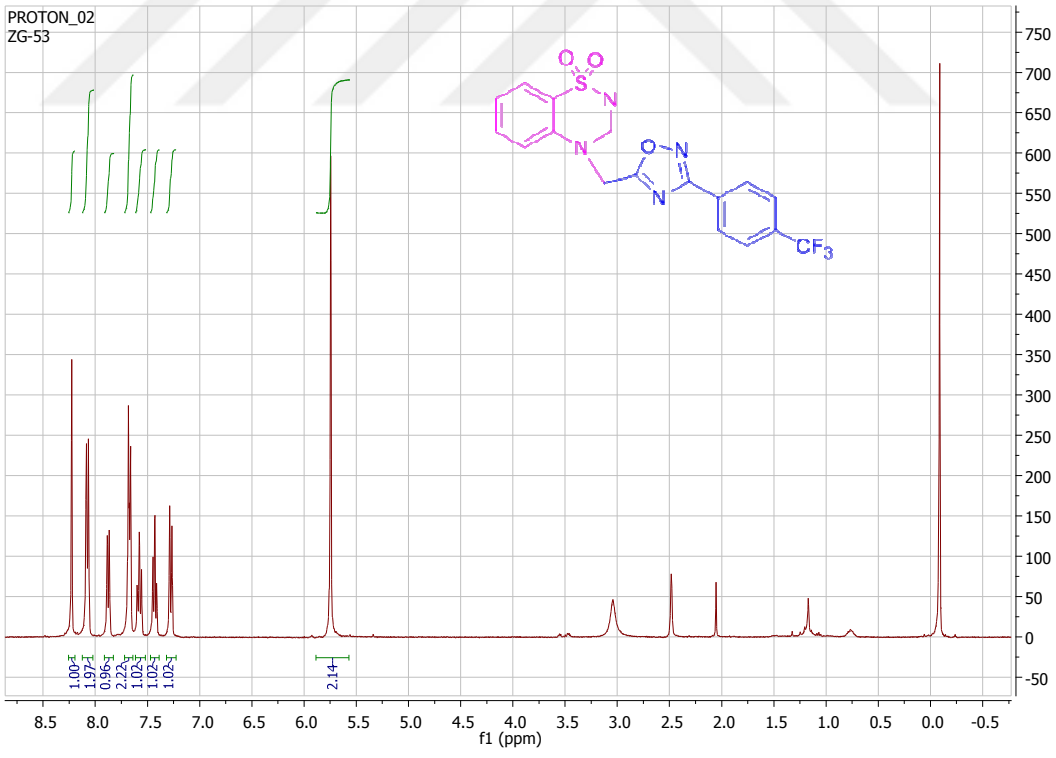

Figure 7.41. ^{1}H NMR spectrum of compound **9g**

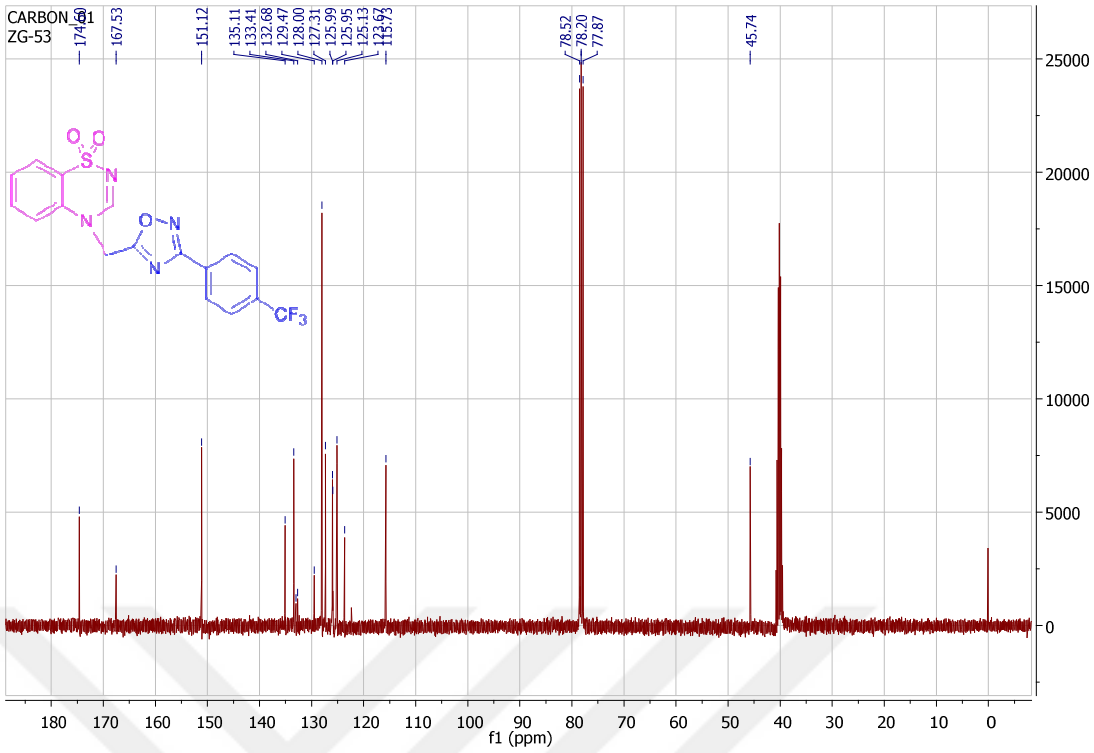

Figure 7.42. ^{13}C NMR spectrum of compound **9g**

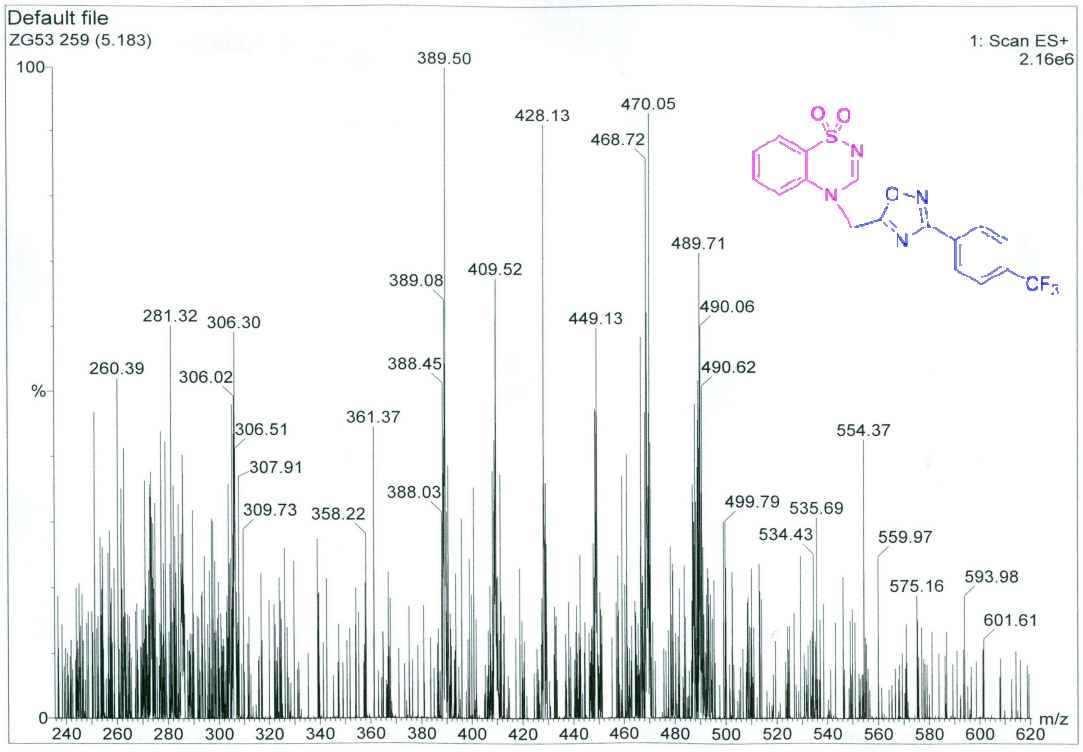

Figure 7.43. LC-MS (ES+) spectrum of compound **9g**

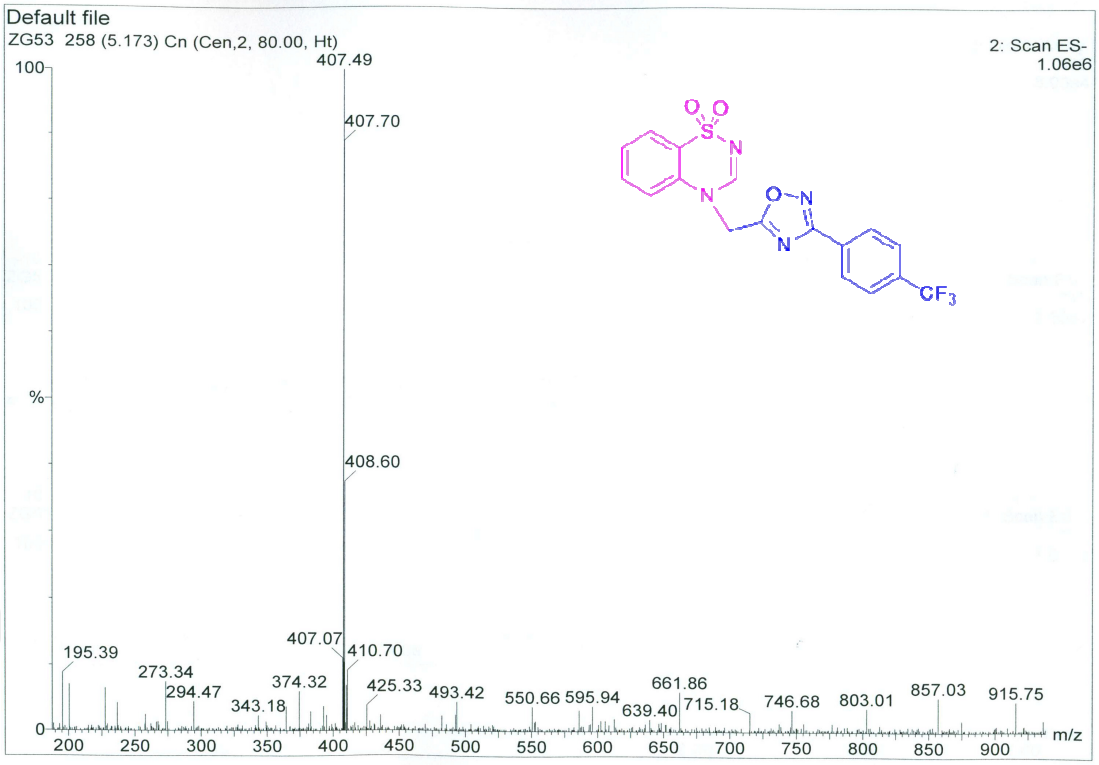

Figure 7.44. LC-MS (ES-) spectrum of compound **9g**

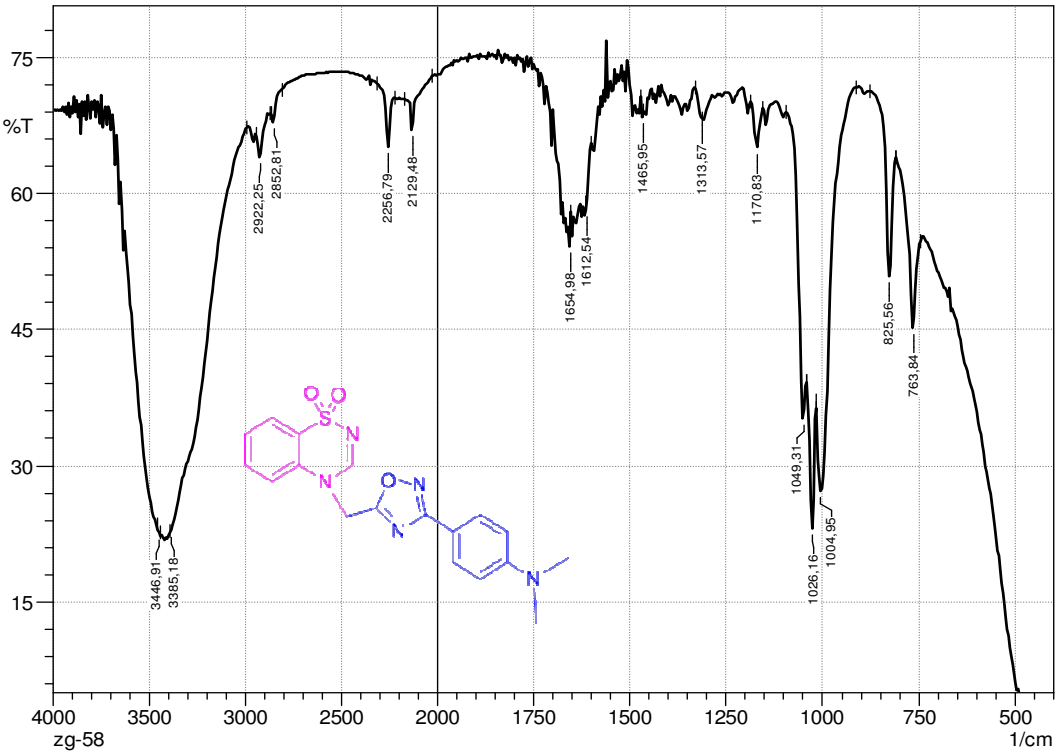

Figure 7.45. IR spectrum of compound **9h**

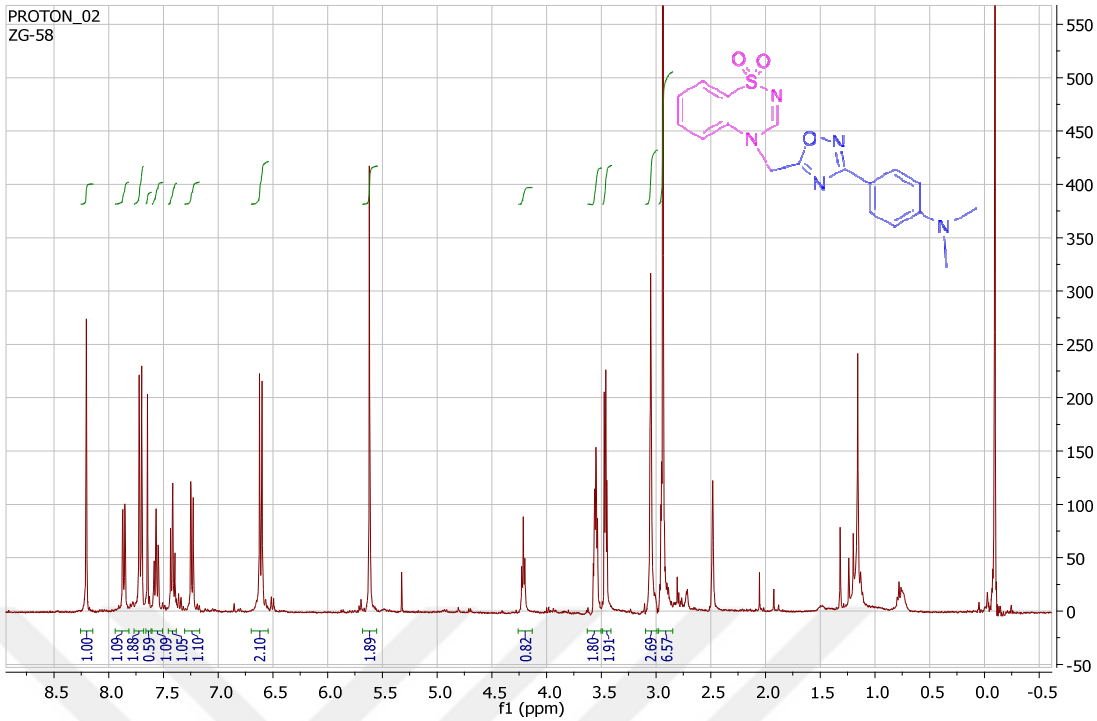

Figure 7.46. ^{1}H NMR spectrum of compound **9h**

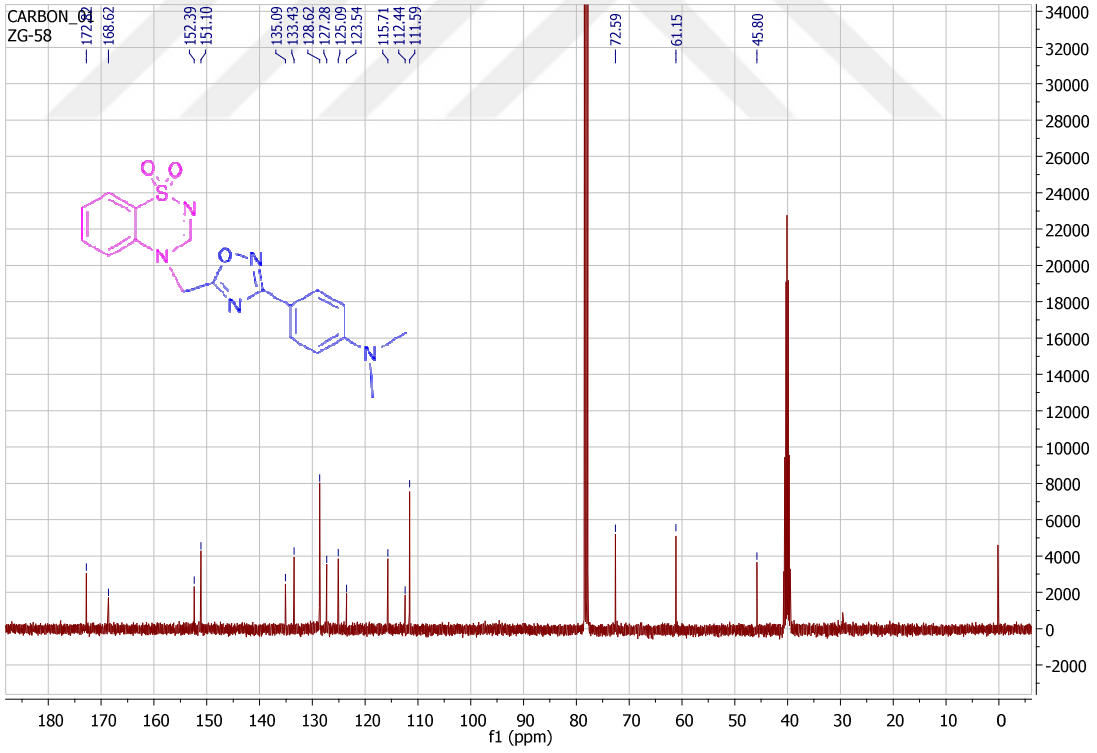

Figure 7.47. ^{13}C NMR spectrum of compound **9h**

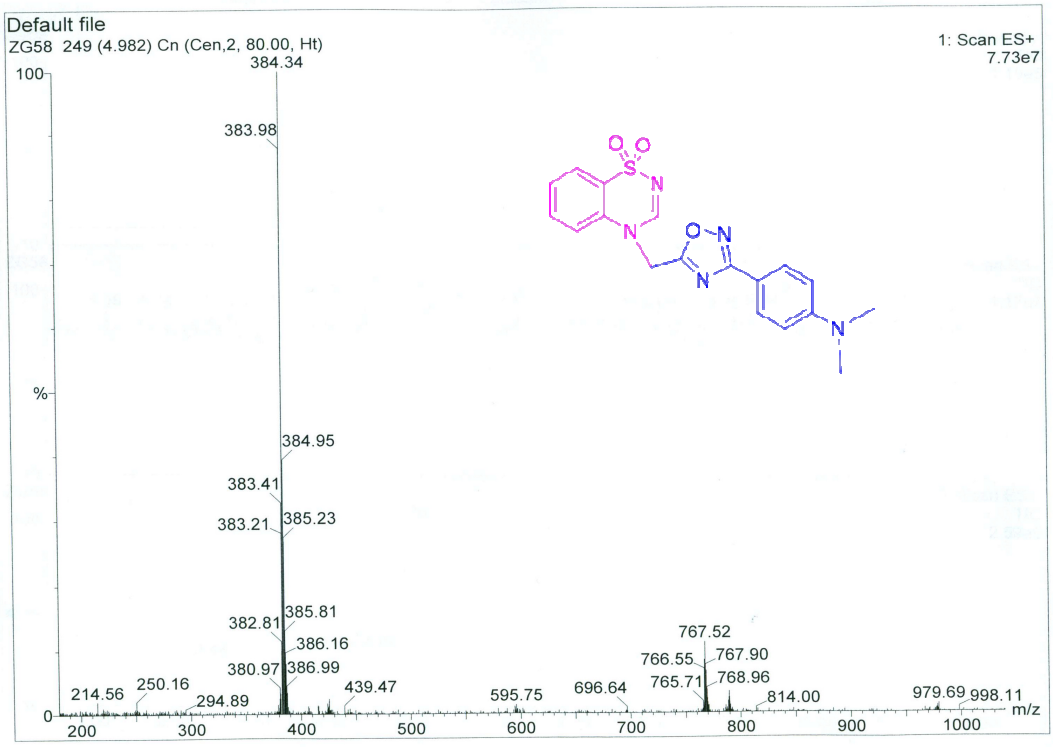

Figure 7.48. LC-MS spektrum of compound **9h**

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