ACYLATION AND STRUCTURAL CHARACTERIZATION OF 5-(2,6-DICHLOROBENZYL)-1,3,4-THIADIAZOLE-2-AMINE

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ACYLATION AND STRUCTURAL CHARACTERIZATION OF 5-(2,6-DICHLOROBENZYL)-1,3,4-THIADIAZOLE-2-AMINE

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Karabük University

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Department of Chemistry

Master's Thesis

KARABÜK

March 2018

I certify that in my opinion the thesis submitted by Ali Hasin BAWAH titled "ACYLATION AND STRUCTURAL CHARACTERIZATION OF 5-(2,6-DICHLOROBENZYL)-1,3,4-THIADIAZOLE-2-AMINE" is fully adequate in scope and in quality as a thesis for the degree of Master of Science.

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This thesis is accepted by the examining committee with a unanimous vote in the Department of Chemistry as a master thesis. March 18, 2018

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Ali Hasin BAWAH

ABSTRACT

M. Sc. Thesis

ACYLATION AND STRUCTURAL CHARACTERIZATION OF 5-(2,6-DICHLOROBENZYL)-1,3,4-THIADIAZOLE-2-AMINE

Ali Hasin BAWAH

Graduate School of Natural and Applied Sciences
The Department of Chemistry

Thesis Advisor:
Prof. Dr. Mustafa ER
March 2018, 91 pages

Thiadiazole is a five-membered heterocyclic aromatic compound containing two nitrogens and one sulfur heteroatoms. Its molecular formula is $C_2H_2N_2S$. Compounds containing thiadiazole are known to have special importance in heterocyclic chemistry as they possess biological activities. 1,3,4-thiadiazole and its derivatives have become the focus of attention in drug, agriculture and material chemistry due to their high activity in 2' and 5' positions against nucleophilic substitution reactions. The –N=C-S group in the structure allows for great structural stability and is known to be the part responsible for biological activity. In addition to their anti-inflammatory, antidepressant, and antibacterial properties, thiadiazole derivatives are known to be effective against herbicides and fungicides.

Acetazolamide, an acyl derivative of 1,3,4-thiadiazole, has been widely used in medicine and in treatment of glaucoma, heart failure, and epilepsy. Researchers focus on possible new properties in hetero ring thanks to new compounds obtained by means of adding various substitute groups in thiadiazoles, which may contribute to medicine and industry. The main objective of this thesis is to carry out synthesis and characterization of new compounds containing substitute thiadiazole ring and their substitute acyl groups, which have potential biological activity. Firstly, 5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-amine **(2)** was synthesized with high yields. Then, the target compounds N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-yl)-3,4,5-substitute benzamide derivatives **(4a-n)** were synthesized from reactions of these compounds with various acyl chloride derivatives with medium-high yields (76-91%).

The obtained compounds were characterized using IR, ^{13}C-NMR, ^{1}H-NMR, MS, and Elemental Analysis.

Key Words **:** Thiadiazole, acylation, heterocyclic.
Science Code **:** 201.1.112

ÖZET

Yüksek Lisans Tezi

5-(2,6-DİKLOROBENZİL)-1,3,4-TİYADİAZOL-2-AMİN BİLEŞİĞİNİN AÇİLASYONU VE YAPISAL KARAKTERİZASYONU

Ali Hasin BAWAH

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Prof. Dr. Mustafa ER
Mart 2018, 91 sayfa

Tiyadiazol, iki azot ve bir kükürt heteroatomu içeren, molekül formülü $C_2H_2N_2S$ olan beş üyeli heterosiklik aromatik bir bileşiktir. Tiyadiazol halkası içeren bileşikler heterosiklik kimyada önemli bir yere sahiptir. Bu bileşiklerin çeşitli biyolojik aktivite gösterdiği uzun yıllardır bilinmektedir. Nükleofilik sübstitüsyon reaksiyonlarına karşı 2' ve 5' pozisyonları çok aktif olduğu için 1,3,4-tiyadiazol ve türevleri ilaç, tarım ve malzeme kimyasında son derece önem arz eden yapılar olarak son yıllarda ilgi odağı haline gelmiştir. Yapısında bulunan –N=C-S grubu, yapıya büyük bir kararlılık sağlar ve biyolojik aktiviteden sorumlu olan kısım olarak bilinir. Tiyadiazol türevleri antienflammatuar, antidepresif, antibakteriyal özelliklerinin yanı sıra bazı türevlerinin herbisitlere ve fungisitlere karşıda etkin olduğu bilinmektedir. Tıp alanında yaygın olarak kullanılan asetazolamid, 1,3,4-tiyadiazolün açil türevidir ve glakom, kalp yetmezliği ve epilepsi tedavisinde kullanılır. Bu özelliklerinden dolayı, çeşitli sübstitüe gruplarının tiyadiazollere ilavesiyle, elde edilecek yeni bileşiklerin hetero halkaya sağlayacağı özelliklerden dolayı, tıp ve endüstri dünyasına

sağlanabilecek katkılar üzerinde çalışılmaktadır. Bu tezin ana amacı, potansiyel biyolojik aktiviteye sahip olan sübstitüe tiyadiazol halkası ve bunların sübstitüe açil grupları içeren yeni bileşiklerin sentezi ve karakterizasyonudur. Bu amaç için, ilk olarak 5-(2,6-diklorobenzil)-1,3,4-tiyadiazol-2-amin **(2)** yüksek verimlerle (%88) sentezlendi. Ardından bu bileşiklerin çeşitli açil klorür türevleriyle olan reaksiyonlarından orta-yüksek verimlerle (%76-91) hedef bileşikler N-(5-(2,6-diklorobenzil)-1,3,4-tiyadiazol-2-yl)-3,4,5-sübstitüe benzamid türevleri **(4a-n)** sentezlendi.

Sentezlenen bileşiklerin yapıları IR, ^{13}C-NMR, ^{1}H-NMR, MS ve Elemantel Analiz kullanılarak karakterize edilmiştir.

Anahtar Kelimeler : Tiyadiazol, açilleme, heterosiklik.
Bilim Kodu **:** 201.1.112

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I'm highly grateful to the teachers of the chemistry department, who spent the time to offer me guidance. Also I would like to thank my family, my wife, my children, and all of my close friends. Finally, this thesis is dedicated to the soul of my mother and father.

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SYMBOLS AND ABBREVITIONS INDEX

°C	: Centigrade
OH	: Hydroxyl
O	: Oxygen
N	: Nitrogen
H	: Hydrogen
S	: Sulfur
R	: Alkyl
C	: Carbon
Ar	: Aryl
EtOH	: Ethyl alcohol
H_2O	: Water
HCl	: Hydrochloric acid
P_2S_5	: Phosphorus pentasulfide
H_2S	: Hydrogen sulfide
H_2SO_4	: Sulfuric acid
CH_3OH	: Methyl alcohol
NH_2NH_2	: Hydrazine
NaOH	: Sodium hydroxide
TFA	: Trifluoroacetic acid
DMF	: Dimethyl formamide
g	: Gram
ml	: Milliliter
$CHCl_3$	: Chloroform
K_2CO_3	: Potassium carbonate
cm	: Centimeter
ppm	: Parts per million
KBr	: Potassium bromide
DMSO	: Dimethyl sulfoxide

$CDCl_3$: Deuterated chloroform

TMS : Trimethylsilane

D_2O : Deuterium oxide

Tyd : Thiadiazole

CF_3COOH : Trifluoroacetic acid

ABBREVIATIONS

NMR : Nuclear Magnetic Resonance

IR : Infrared

MS : Mass Spectrometry

DNA : Deoxyribonucleic acid

IUPAC : International Union of Pure and Applied Chemistry

HIV : Human Immunodeficiency Virus

PART 1

INTRODUCTION

Heterocyclic molecules are widespread in nature and are used in many fields. Among these, hetero ring compounds containing nitrogen and sulfur are known to have various biological activities. They have an important place in our live due to their biological activities. These compounds can be found in nature, but it is also possible to obtain them quickly and easily using synthetic methods, which increases their significance even more. In addition to pharmaceutics, these compounds are used in many other industries including the paint industry.

Thiadiazoles have an important place among compounds with hetero rings containing nitrogen and sulfur hetero and extensively used in pharmaceutics due to their biological activity. Fungicidal properties enabled by the –N=C-S bond contribute to drug and paint industries in particular.

Schiff bases containing thiadiazole show high coupling properties and widely used in dyestuff synthesis. Also, such dyestuffs gain antibacterial properties without any further treatments as they contain thiadiazole ring. Moreover, Schiff bases obtained from 2,5-disubstitute-1,3,4-thiadiazoles have been found to show anti-inflammatory and antidepressant properties. Many studies show that some 1,3,4 thiadiazoles have antiallergic properties.

Furthermore, several thiadiazole derivatives are known to have extensive activities against fungicides and herbicides.

Various studies show that addition of different groups in the thiadiazole molecule lead to different biological activities.

1,3,4 thiadiazoles are also used in the polymer industry, which is one of the noteworthy industries of our time. Thermal behaviors of N and S atoms play a significant role in conductivity, hence 1,3,4 thiadiazoles are used for semi-conductivity and coating in polymer applications with electrical conductivity.

Commonly used in medicine, acetazolamide is a derivative of 1,3,4-thiadiazole and used in treatment of glaucoma, heart failure, and epilepsy.

Acid solutions are used to remove rust in industrial processes. A controlled rust removing operation requires inhibitors. Sulfuric acid and hydrochloric acid are used to remove the oxide layer on steel and alloys containing iron. Most organic inhibitors cling on the metal surface by adsorption. Organic compounds containing sulfur, nitrogen, and oxygen atoms are widely used as acid inhibitors. Thiadiazoles are known to be commonly used as such inhibitors.

For the reasons mentioned above, researchers focus on possible new properties in hetero ring enabled by new compounds obtained by means of adding various substitute groups in thiadiazoles, which may contribute to medicine and industry.

Overall, this thesis consists of two parts: a literature review and experimental trials. These two sections are also divided into sub-sections. Structure formulas of compounds synthesized in experimental trials can be seen in the Table of Formulas.

The second part of the study presents general information related to thiadiazole and derivatives, earlier and recent studies, and synthesis methods based on a review of the literature.

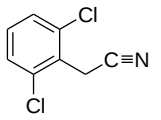
The third part of the study involving experimental trials explains how 2-amino-1,3,4-thiadiazole compounds were obtained from reactions of appropriate nitrile compounds with thiosemicarbazide, and acylation reactions of these compounds.

Since the yield calculation for synthesized compounds was performed after the purification process, yields are given as pure yield.

The four part involving experimental results and discussion presents the spectral data for all compounds in charts and interprets the data based on literature data.

The fifth section containing the results presents reactions mechanisms for synthesized compounds in equations.

Table 1.1. Formulas Table



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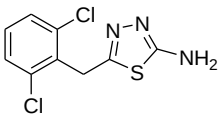

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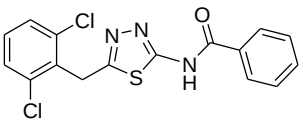

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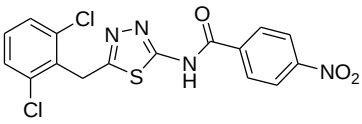

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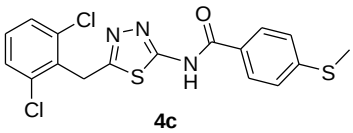

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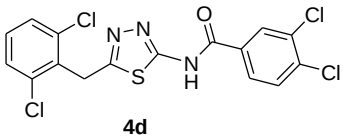

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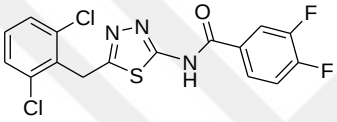

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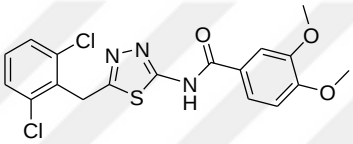

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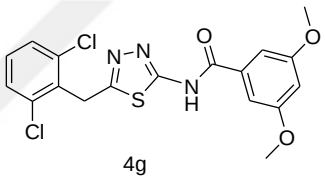

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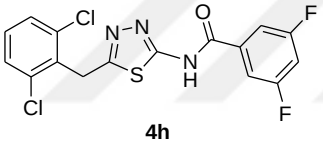

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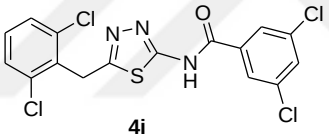

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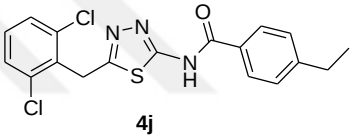

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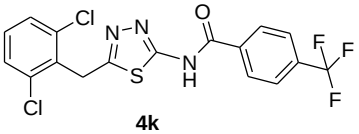

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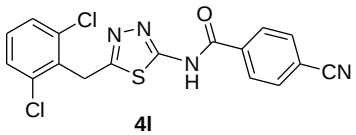

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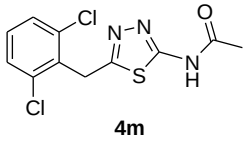

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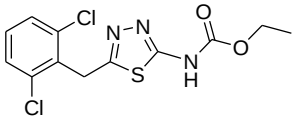

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PART 2

GENERAL INFORMATION

2.1. THIADIAZOLES

2.1.1. Structure and Characteristics

Heterocyclic compounds are known to involve one or more heteroatoms other than carbon and hydrogen such as oxygen, nitrogen, or sulfur and have the maximum number of conjugated double bonds. Systems containing two nitrogen atoms and one sulfur atom in a five-membered heterocyclic ring are referred to as thiadiazole ring in Hantzch Windman nomenclature. Thiadiazole has four isomers depending on the position of heteroatom in the ring: 1,2,3-thiadiazole(1), 1,2,4-thiadiazole(2), 1,2,5-thiadiazole(3), and 1,3,4-thiadiazole(4).

Figure 2.1. Thiadiazole isomers.

1,3,4-thiadiazole is a colorless substance with aromatic character. It has a melting point of 45 ^{o}C and boiling point of 203 ^{o}C. It is quite resistant against acids. It can be decomposed in 30% hydrogen peroxide and diluted alkaline zinc.

We will mostly address 2-amino-1,3,4-thiadiazole derivatives in detail in this study.

2.1.2. Spectral Properties of 2-Amino-1,3,4-Thiadiazoles

2.1.2.1. IR Spectra

IR spectroscopy using KBr tablets in studies on 2-amino-1,3,4-thiadiazole derivatives show absorption bands for C=N stretching vibration in the 1665-1672 cm^{-1} range, C-N stretching vibration in the 1300-1280 cm^{-1} range, N-H deflection in the 1620-1600 cm^{-1} range, and amino group N-H stretching vibration in the 3350-3100 cm^{-1} range [1].

2.1.2.2. ^{1}H-NMR Spectra

According to the structure of the substituents at the amino nitrogen of 2-amino-1,3,4-thiadiazoles, ^{1}H-NMR spectra of the protons in secondary amine are in the 10.20-10.30 ppm range [2].

2.1.3. Methods Used to Obtain Thiadiazole

The first compound known to contain a 1,3,4-thiadiazole ring is the 2-phenylamino-1,3,4-thiadiazole compound synthesized by Pulvermacher in 1894 by formic acid treatment of 4-phenyl-thiosemicarbazide [3].

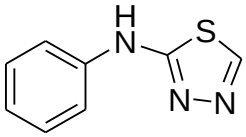


Figure 2.2. Synthesis of 2-phenylamino-1,3,4-thiadiazole

2.1.3.1. From Thiosemicarbazides

1,3,4-thiadiazoles are usually formed as a result of cyclization reactions. Many syntheses of thiadiazoles occur in the form of cyclization reaction of thiosemicarbazide or substitute thiosemicarbazide.

2-amino-5-substitute-1,3,4-thiadiazole is obtained as a result of cyclization from the reaction of thiosemicarbazide with acetly chloride [4].

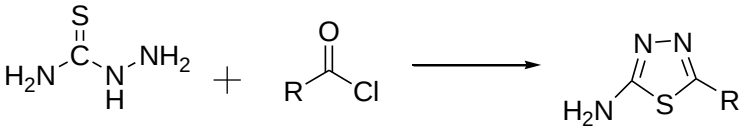


Figure 2.3. Synthesis of 2-amino-5-substitute-1,3,4-thiadiazole from thiosemicarbazides.

2-Amino-1,3,4-thiadiazole, 2-amino-5-phenyl-1,3,4-thiadiazole, and 2-phenylamino-5-phenyl-1,3,4-thiadiazole were synthesized by Freund and Meinecke (1896) and Markwald and Bott (1896) using the Pulvermacher's method (from thiosemicarbazides) [5,6].

Arnold synthesized 2-norhydnocarpyl-5-amino-1,3,4-thiadiazoles from the reaction of thiosemicarbazide with hydnocarpic acid chloride in 1942.

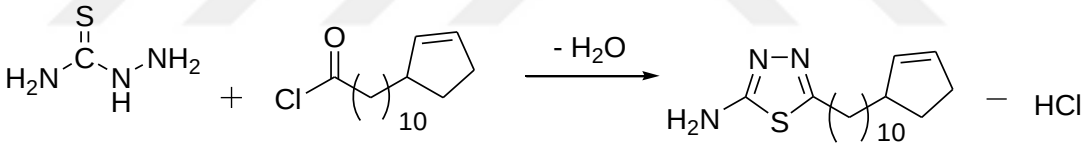


Figure 2.4. Synthesis of 2-norhydnocarpyl-5-amino-1,3,4-thiadiazole.

Clark et al. obtained ethyl-2-amino-1,3,4-thiadiazole-5-acetate/butyrate derivatives by heating thiosemicarbazides with carbethoxyacetyl/butyryl chloride in 1946 [7].

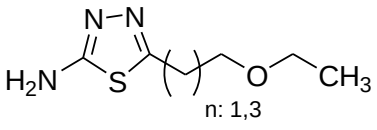
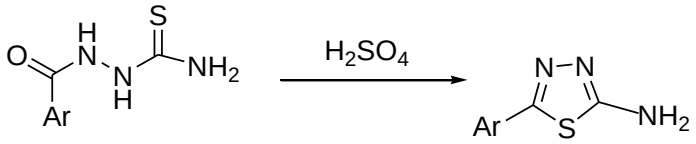


Figure 2.5. Synthesis of ethyl-2-amino-1,3,4-thiadiazole-5-acetate/butyrate.

In 1949, Hoggarth obtained 2-amino-5-aryl-1,3,4-thiadiazoles from the reaction of 1-(benzoyl/substitutedbenzoyl)thiosemicarbazides with phosphoric acid. Using

concentrated sulfuric acid instead of phosphoric acid to obtain this compound yielded the same result [8].



Ar: -C_6H_5, p-C_6H_4, p-CH_3-OC_6H_4, p-$NO_2C_6H_4$

Figure 2.6. Synthesis of 2-amino-5-aryl-1,3,4-thiadiazole.

In 1973, Coburn and Bhoosman used a different method and obtained 2,5-disubstituted-1,3,4-thiadiazole from the reaction of thiosemicarbazide with orthoesters such as triethyl orthoformate and triethyl orthoacetate in media containing ethyl alcohol using acid as catalyst [9].

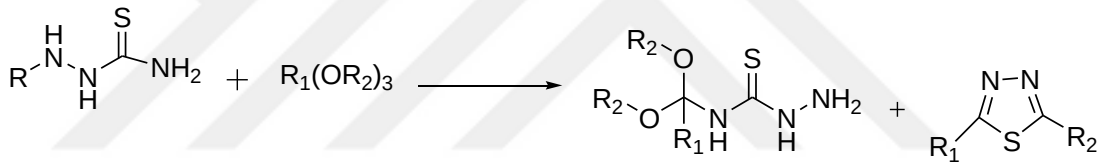


Figure 2.7. Synthesis 2,5-disubstituted-1,3,4-thiadiazole derivatives.

Doğan et al. (2002) obtained 1,3,4-thiadiazoles by adding sulfuric acid to thiosemicarbazide, stirring the reaction mixture in magnetic stirrer, transferring the mixture into iced water, and finally washing the mixture [10].

In 2006, Matsiak et al. synthesized N-substituted-2-amino-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazole from the reaction of sulfinyl bis(2,4-dihydroxy)thiobenzoyl (STB) with 4-substituted-3-thiosemicarbazide [11].

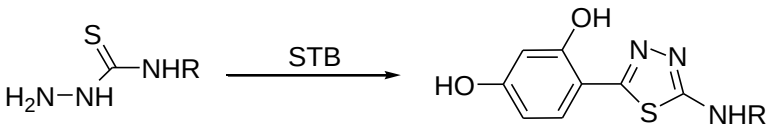


Figure 2.8. N-substituted-2-amino-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazole derivatives.

In 2001, Wang et al. synthesized 2-(2-furoylamido)-5-aryloxymethyl-1,3,4-thiadiazoles from the reaction of 1-aryloxymethyl-4-furoyl-thiosemicarbazides with glacial acetic acid using the microwave method, which allows for a quick synthesis with high yield [12].

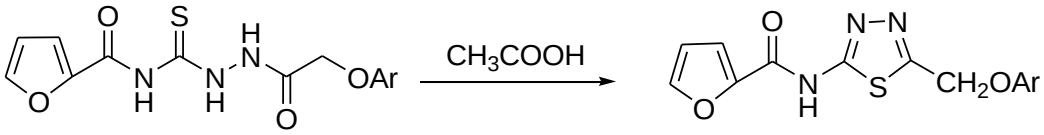


Figure 2.9. 2-(2-furoylamido)-5-aryloxymethyl-1,3,4-thiadiazole derivatives.

1,3,4-thiadiazole was synthesized from the cyclization of thiosemicarbazides or oxidation cyclization of thiosemicarbazones catalyzed by ferric ammonia sulphate or ferric chloride [13].

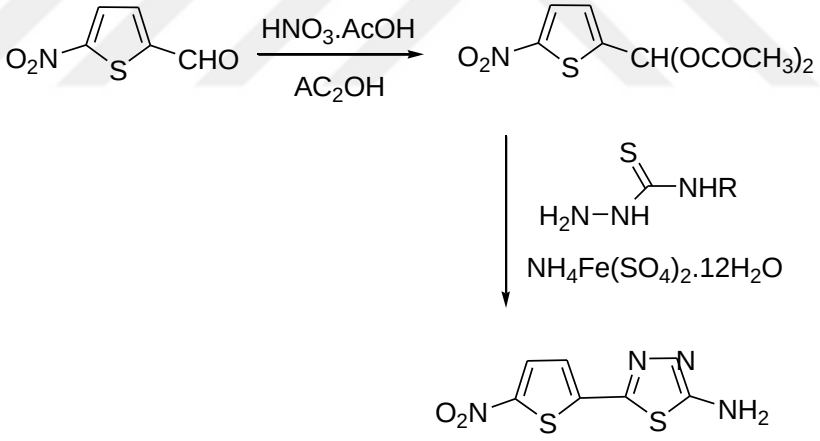


Figure 2.10. 2-Amino-1,3,4-thiadiazole derivatives from oxidation cyclization catalyzed by ferric ammonia sulphate or ferric chloride.

2.1.3.2. From Thiosemicarbazones

In 1901, Compounds containing 1,3,4-thiadiazole ring from the reaction of thiosemicarbazones with iron(III) chloride were synthesised by Young and Eyre [14].

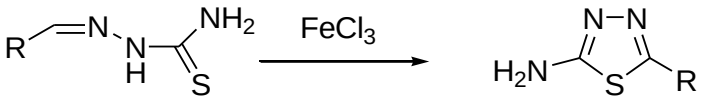


Figure 2.11. Synthesis of 2-amino-5-substitute-1,3,4-thiadiazole.

2.1.3.3. From hydrazines

Disubstituted-1,3,4-thiadiazoles are obtained from the reaction of diacetyl hydrazines with diphosphorus pentasulfide [15].

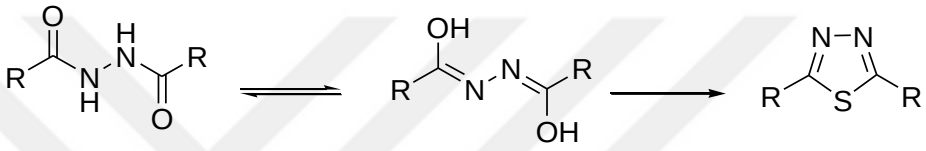


Figure 2.12. Synthesis of 2,4-dialkyl 1,3,4-thiadiazole from diacetyl hydrazines.

1,3,4-thiadiazoles are obtained from the reaction of hydrazine with sodium dithioformate [16].

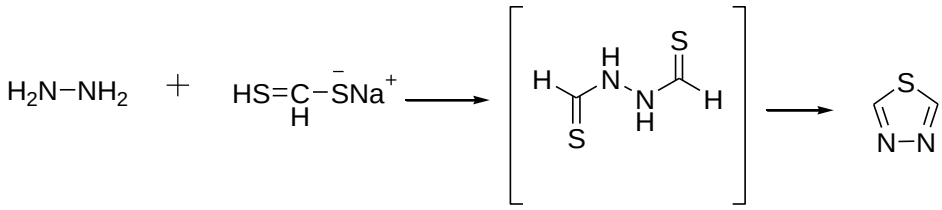


Figure 2.13. Synthesis of 1,3,4-thiadiazole from hydrazine.

In 1985, Rollas synthesized 2-(4-aminophenyl)-5-alkyl/arylamino-1,3,4-thiadiazole derivatives for the first time from the reduction of 2-alkyl/arylamino-5-[p-(1-phenyl-3,5-dimethyl-4-(1*H*)-pyrazylyl-azo)phenyl-1,3,4-thiadiazoles with hydrazinehydrate in ethyl alcohol medium without catalyst [17].

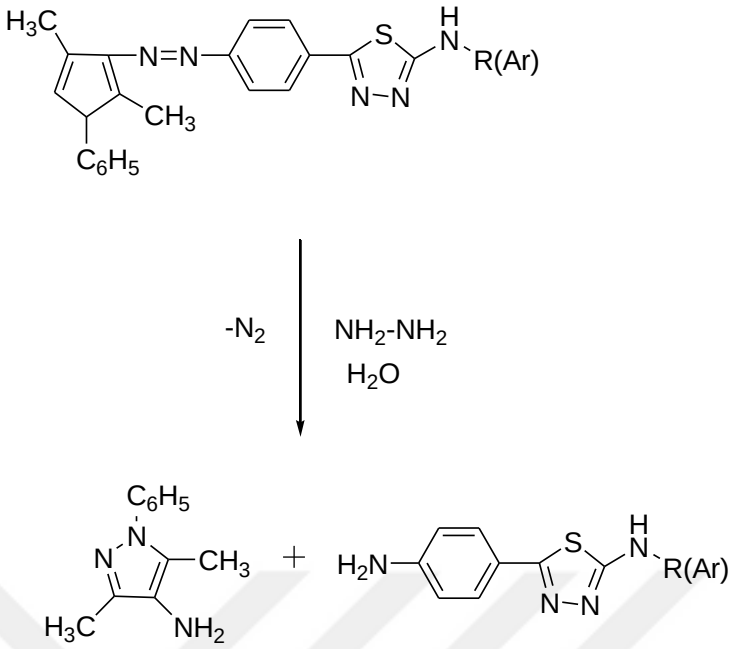


Figure 2.14. Synthesis of 2-(4-aminophenyl)-5-alkyl/arylamino-1,3,4-thiadiazole.

2.1.3.4. Other Methods

In 1961, Huisgen et al. obtained 1,3,4-thiadiazole derivatives by heating tetrazoles with electrophilic reagents such as isothiocyanate and thiocarboxylic acid chloride [18].

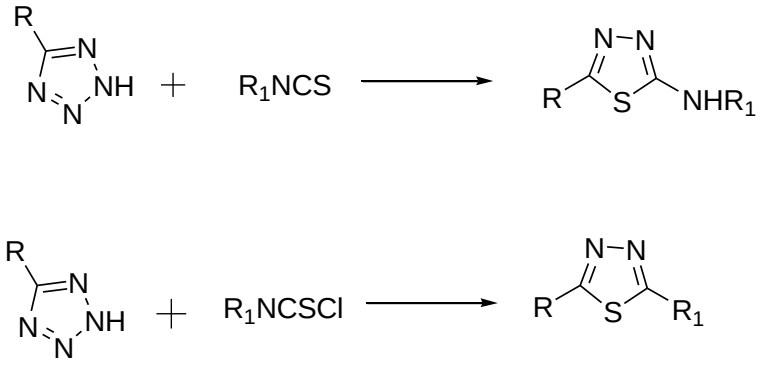


Figure 2.15. Synthesis of 1,3,4-thiadiazole derivatives.

In 1961, Kurzer synthesized N-thiobenzoaminoguanidine by treating aminoguanidine with carboxymethyl dithiobenzoate and obtained 2-amino-5-phenyl-1,3,4-thiadiazole

from its reaction with hydrochloric acid and 2-amino-5-phenyl-1,3,4-thiadiazole from its reaction with acetic anhydride [19].

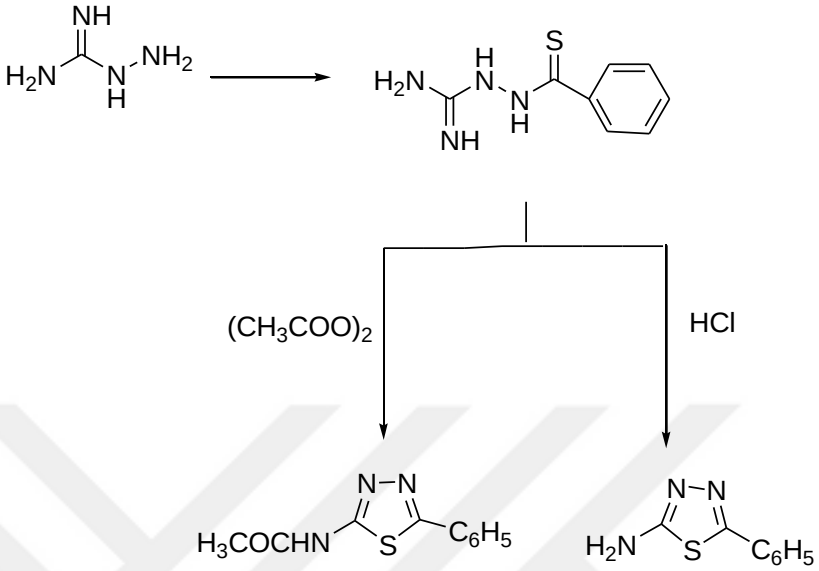


Figure 2.16. 2-Amino-5-phenyl-1,3,4-thiadiazole and 2-amino-5-phenyl-1,3,4-thiadiazole synthesis.

In 2009, Efimova et al. obtained 2-aryl(heteroaryl)-5-phenylamino-1,3,4-thiadiazole derivatives from 5-aryl(hetaryl)-tetrazoles and phenyl isothiocyanate with high yields using the microwave method [20].

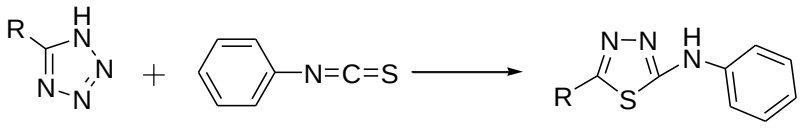
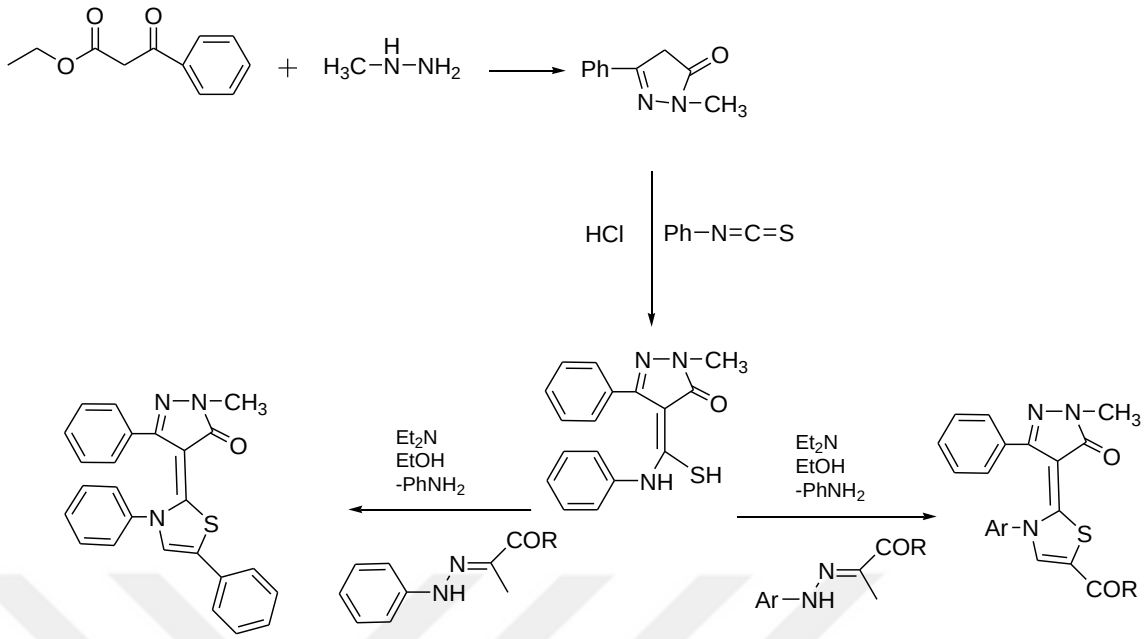


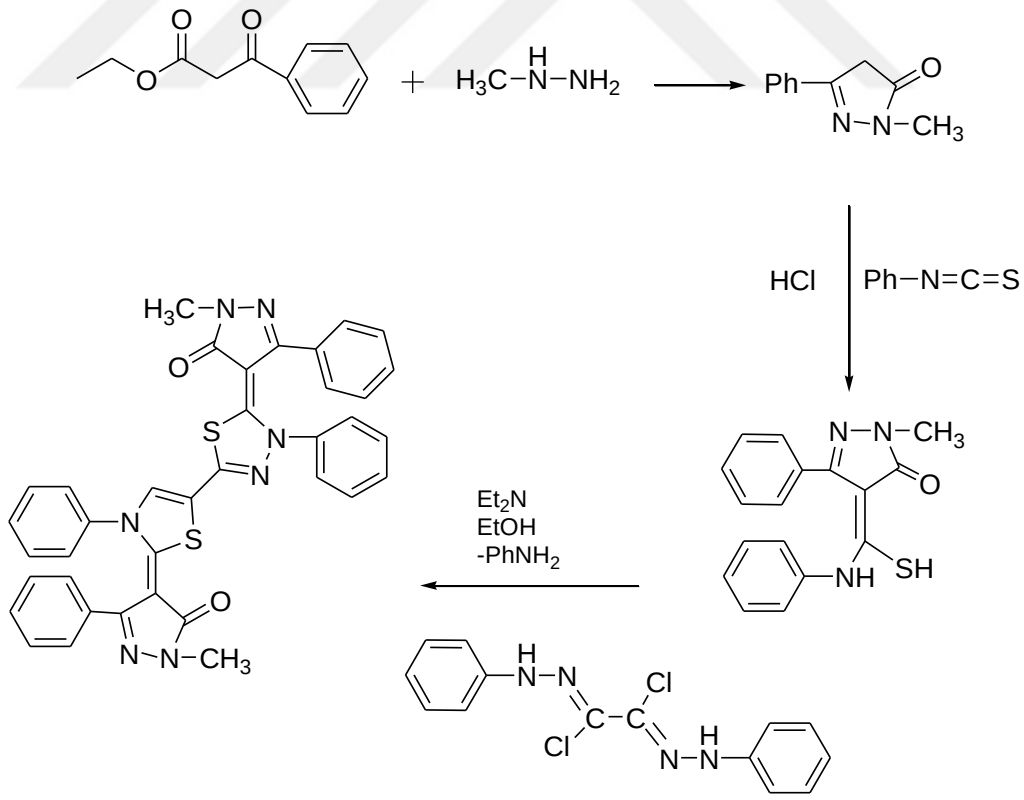
Figure 2.17. Synthesis of 2-aryl(heteroaryl)-5-phenylamino-1,3,4-thiadiazole.

In 2009, El-Rahman et al. obtained 1,3,4-thiadiazole and bis(1,3,4-thiadiazole) derivatives under conventional and ultrasonic irradiation conditions by treating 1-methyl-5-oxo-3-phenyl-2-pyrazoline-4-thiocarboxyanilide with triethylamine, hydrogen halide, or N,N'-diphenyloxelo hydrazonile dichloride in ethyl alcohol medium [21].



Me: -CH_3, Ph: -C_6H_5, Et: -C_2H_5, X: Cl, Br, R: C_6H_5, C_6H_4Cl

Figure 2.18. 1,3,4-Thiadiazole derivatives.



Me: -CH_3, Ph: -C_6H_5, Et: -C_2H_5

Figure 2.19. Bis-(1,3,4-thiadiazole) derivatives.

2.1.4. Significance of 1,3,4-Thiadiazole and Derivatives

Biological activity of a compound essentially depends on its molecular structure. Heterocyclic compounds show high biological activity due to their structure. Thiadiazole having N=C-S structure in the ring is a versatile compound that can be used a wide rang of applications. It has become a significant heterocyclic class due to its wide range of biological activities. Commercially available drugs containing 1,3,4-thiadiazole nucleus include acetazolamide, methazolamide, butazolamide, sulfamethazole, and megazol. Also, other analogs of thiadiazole are used for paints, pesticides, lubricants, and conductive polymers [22].

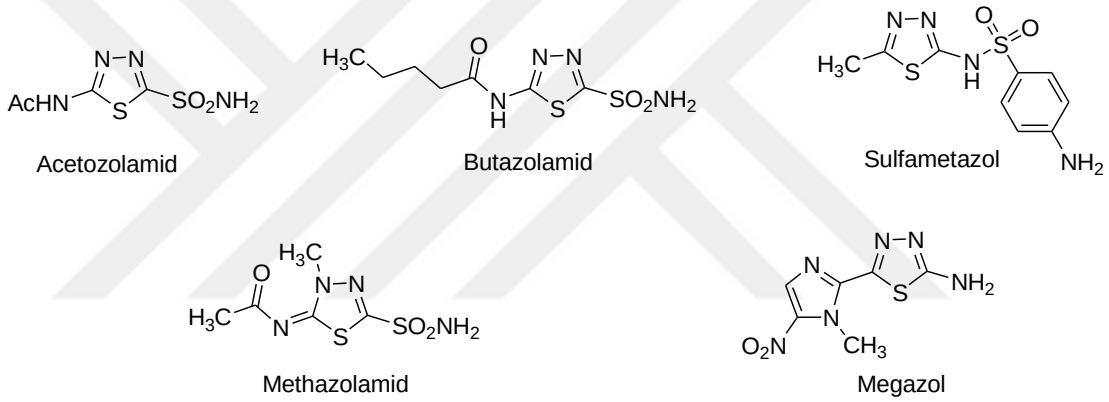


Figure 2.20. Some drugs containing 1,3,4-thiadiazole ring.

Rapidly developing resistance against available drugs has become a serious problem throughout the world. The need for designing new compounds to deal with this problem has become a priority in drug research in today's world. Thiadiazoles have been receiving constant attention from researchers for development of new drugs. In both pharmaceutical and agricultural chemistry, researchers have firmly established the importance of thiadiazole's biological properties. Studies in the literature have shown that compounds with thiadiazole nucleus have a broad spectrum of pharmacological activities including antimicrobial, antitubercular, anti-inflammatory, analgesic, CNS depressant, anticonvulsant, anticancer, antioxidant, antidiabetic, molluscicidal, antihypertensive, and diuretic activities.

Antimicrobial activity

Arun Kumar et al. demonstrated that the cyclization reaction of thiosemicarbazide with different aromatic carboxylic acids using $POCl_3$ yielded 1,3,4-thiadiazole. The resulting compounds were identifed using elemental analysis, IR, 1H-NMR, and mass spectrum. The researchers found that the 1,3,4-thiadiazole derivatives had significant antimicrobial activities [23].

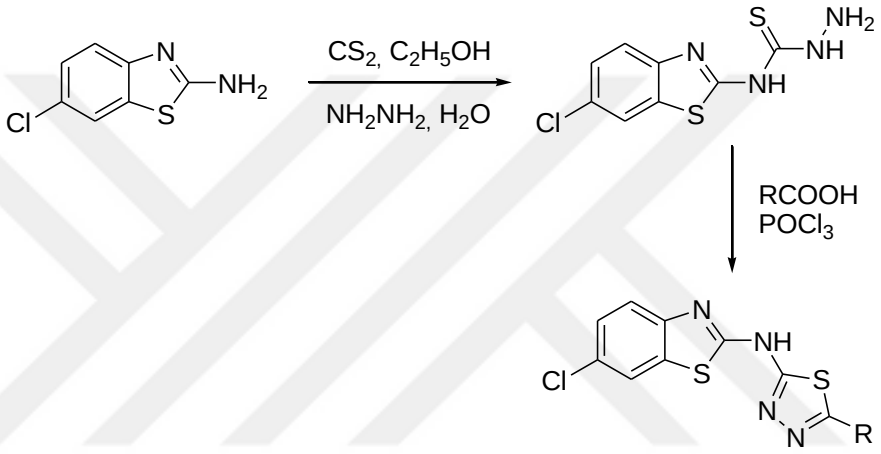


Figure 2.21. 1,3,4-thiadiazole derivatives obtained by Arun Kumar.

Sherman synthesized a series of nitrfhurylamino thiadiazole derivative derivatives and examined their antimicrobial activities. The researchers found that antimicrobial activity increased when phenylamino, ethylamino, and methylamino groups bonded to 1,3,4-thiadiazole ring, respectively [24].

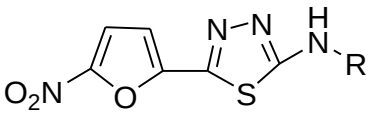


Figure 2.22. 2-aminoalkyl/aryl-5-(5-nitro)furan-1,3,4-thiadiazole derivatives.

Mishra synthesized 5-substitutedphenoxymethyl-2-[N-(2-alkyl-1,3,4-thiadiazole-5il)carbamoylmethylthio] -1,3,4-oxadiazole derivatives and tested them for antimicrobial, insecticidal, and acetylcholine esterase inhibitor activities. The

derivative containing methyl at the 2-position of the 1,3,4-thiadiazole ring was found to be the most active compound for activities tested in the study [25].

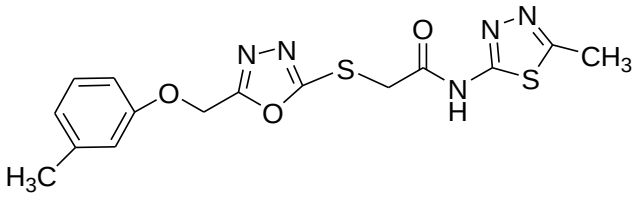


Figure 2.23. 5-methyl-phenoxymethyl-2-[N-(2-alkyl-1,3,4-thiadiazole-5-yl) carbamoyl methyl-thio]-1,3,4-oxadiazole derivatives.

Asato and Berkelhammer reported that, compared to 2-amino-5-(1-methyl-5-nitro-2-imidazolyl)-1,3,4-thiadiazole, the corresponding 2-nitro isomer was inactive in terms of antibacterial activity [26].

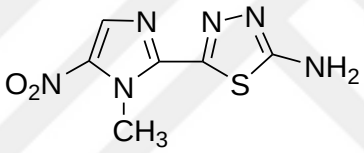


Figure 2.24. 2-Amino-5-(1-methyl-5-nitro-*1H*-imidazole-2-yl)-1,3,4-thiadiazole.

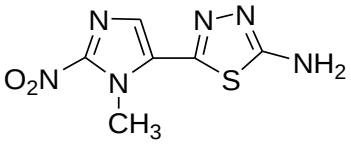
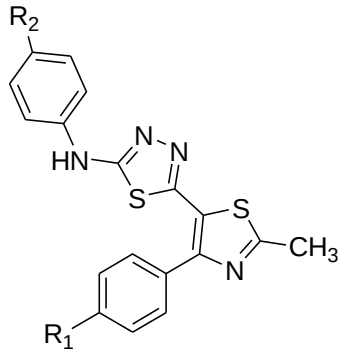


Figure 2.25. 2-Amino-5-(1-methyl-2-nitro-*1H*-imidazole-5-yl)-1,3,4-thiadiazole.

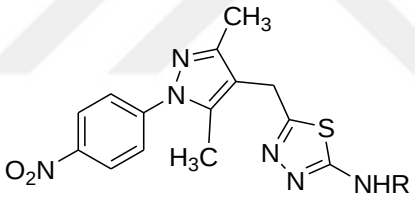
Gawande and Shingare determined that 5-arylamino-2-(4-aryl-2-methylthiazole-5-yl)-1,3,4-thiadiazole derivatives showed antifungal activity against *Penicillium notatum* [27].



R_1: H, Br, Cl, CH_3, OCH_3 R_2: H, Br, Cl, OCH_3, OC_2H_5

Figure 2.26. 5-Arylamino-2-(4-aryl-2-methylthiazole-5-yl)-1,3,4-thiadiazole derivatives.

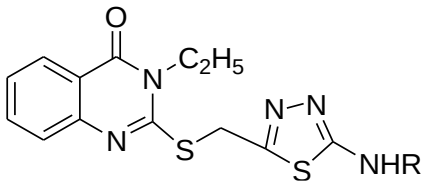
Patel and Fernandes obtained a series of compounds by binding [3,5-dimethyl-1-4-nitrophenyl)*1H*-pyrazole-yl]methylene to the 2- position of thiadiazole and found that the compound with amino group at 5-position was effective on *E. Coli*, while other compounds did not show any significant activity [28].



R: H, C_6H_5, 4-$CH_3C_6H_4$, 4-ClC_6H_4

Figure 2.27. 2-Amino/arylamino-[3,5-dimethyl-1-4-nitrophenyl)*1H*-pyrazole-yl] methylene-1,3,4-thiadiazole derivatives.

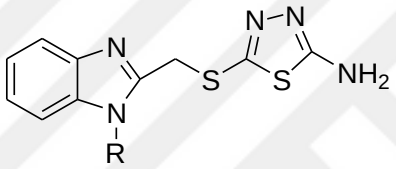
Terzioğlu et al. synthesized 2-[(3-ethyl-4-(*3H*)quinazolinone-2-yl)mercaptomethyl-5-alkyl/arylamino-1,3,4-thiadiazole derivatives and found that all compounds were inactive against bacteria and showed varying degrees of inhibition against fungi [29].



R: 4-Br/Cl/F/CH_3/$NO_2C_6H_4$

Figure 2.28. 2-[(3-ethyl-4-(*3H*)quinazolinone-2-yl)mercaptomethyl-5-alkyl/aryl amino -1,3,4-thiadiazole derivatives.

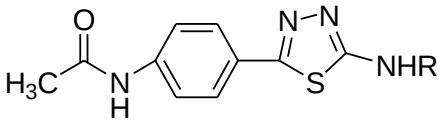
Ashour et al. synthesized 1-ethyl or benzyl-2-(2-amino-1,3,4-thiadiazole-5-yl)thiomethyl benzimidazole derivatives and found that the compounds showed antimicrobial activity against *E. Coli* [30].



R: C_2H_5, $CH_2C_6H_4$

Figure 2.29. 2–Ethyl/benzyl-2-(2-amino-1,3,4-thiadiazole-5-yl)thiomethyl benzimidazole.

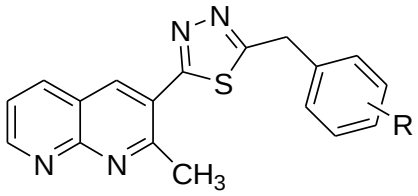
Gülerman et al. synthesized 2-(substitutedamino)-5-[4-(acetylamino)phenyl]-1,4-thiadiazole derivatives. The derivative containing ethylamino at the 2-position of the thiadiazole ring was found to have a MIC value equal to that of tobramycin, which is used as a standard, against *M. Fortuitum* strain. The thiadiazole derivatives in the series were found to be inactive against *M. Tuberculosis*, and had lower antibacterial activity than antifungal activity [31].



R: H, CH_3, C_2H_5, C_3H_7, $CH_2CH{=}CH_2$, C_6H_5

Figure 2.30. 2-(Substitutedamino)-5-[4-(acetylamino)phenyl]-1,4-thiadiazole derivatives.

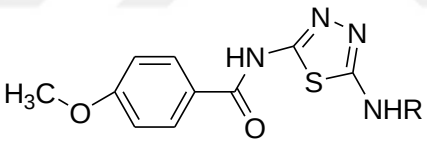
Reddy et al. tested antifungal activities of 3-(5-anilino-1,3,4-thiadiazole-2-yl)-2-methyl-1,8-naphthyridine derivatives against *Fusarium Oxysporum* and *Drechslera Rostrata*, and found that the compounds had a minimum inhibitor concentration (MIC) of 100 and 500 mg/mL [32].



R: H, 4-Br, 4-CH_3, 3-CH_3O, 4-CH_3O

Figure 2.31. 3-(5-Anilino-1,3,4-thiadiazole-2-yl)-2-methyl-1,8-naphthyridine derivatives.

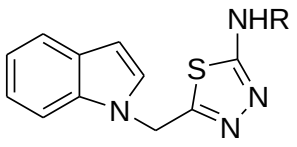
Rollas et al. synthesized 2-(4-methoxybenzoylamino)-5-alkyl/arylamino-1,3,4-thiadiazole derivatives, and found the compound containing cyclohexyl group was active against *Candida Albicans* ATCC 1021 [33].



R: CH_3, C_2H_5, C_3H_7, $CH_2CH{=}CH_2$, C_6H_{11}, C_6H_5

Figure 2.32. 2-(4-methoxybenzoylamino)-5-alkyl/arylamino-1,3,4-thiadiazole derivatives.

Tsotinis et al. synthesized 1-[(5-substitutedamino-1,3,4-thiadiazole-2-yl)methyl]indol derivatives, and found that the compound containing 1-naphthylamino at the 5-position showed antibacterial activity against *Straphylococcus Aureus* [34].



R: C_6H_5, 4-$CH_3C_6H_4$, 1-naftil

Figure 2.33. 1-[(5-substitutedamino-1,3,4-thiadiazole-2-yl)methyl]indol derivatives.

Doğan et al. obtained acetlythiadiazoles by acylating 2-(alkyl/arylamino)-5-(3-hydroxy-2-naphthyl)-1,3,4-thiadiazole derivatives with acetic anhydride, and found that the trifluoromethyl to be active against penicillin [10].

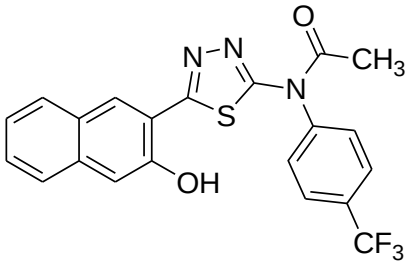


Figure 2.34. 2-(4-Trifluoromethyl)acetamide-5-(3-hydroxy-2-naphthyl)-1,3,4-thiadiazole.

Anti-inflammatory Activity

Non-steroidal anti-inflammatory drugs (NSAIDs) are known as important therapeutically active compounds that can be used to treat acute and chronic inflammation, pain, and fever.

In the survey literature, it was demonstrated that various heterocyclic compounds containing thiadiazole group have anti-inflammatory activity. Most of thiadiazole derivatives have anti-inflammatory activity.

Labanauskas et al. reported that 2-acetlyamino and 4-fluoro benzoylamino derivatives of 2-amino-5-(3,4-dimethoxyphenyl)-1,3,4-thiadiazoles had an anti-inflammatory activity equal to that of acetly salicylic acid and ibuprofen, and lower toxicity compared to acetly salicylic acid [35].

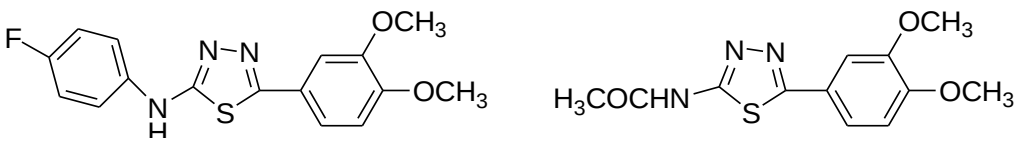


Figure 2.35. 2-Acetlyamino and 4-fluoro benzoylamino 1,3,4-thiadiazole derivatives.

Mullican et al. synthesized a series of 1,3,4-thiadiazole derivatives, which were orally active and had non-ulcerogenic anti-inflammatory activity. Especially the derivatives with amino and thione at the 2-position were found to be orally active [36].

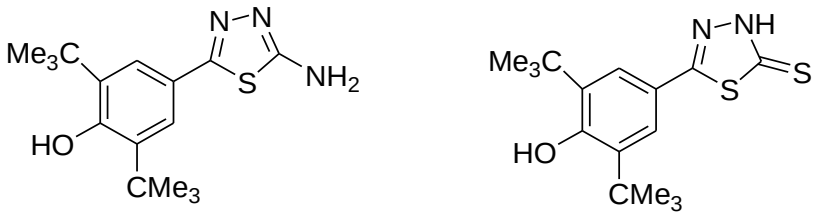
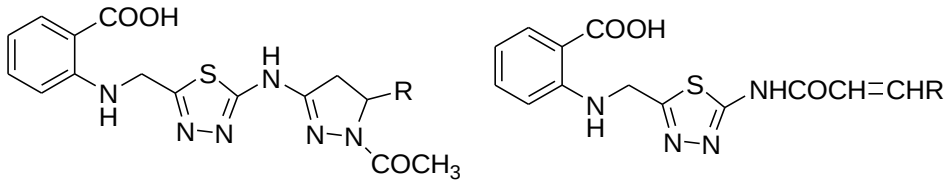


Figure 2.36. 2-Amino and 2-thione 1,3,4-thiadiazole derivatives.

Sharma et al. obtained anthranilic acid derivatives with 1,3,4-thiadiazole ring at the 2-position. Among the compounds synthesized, those containing phenyl group had 30% anti-inflammatory activity, while those containing 4-methoxyphenyl group had 40% anti-inflammatory effect. Also, the researchers found that the 3-methoxy-4-hydroxyphenyl group led to a considerable increase in anti-inflammatory activity, the 4-methoxy derivative was more active compared to the 3-methoxy derivative, and N-[2'-amino-(1''-acetly -5- substituted -2''-pyrazoline-3''-yl)1',3',4',- thiadiazole-5'ylmethyl] anthranilic acid had higher anti-inflammatory activity compared to phenylbutazone [37].



R: C_6H_5, 4-$CH_3OC_6H_4$, 3-OH-4-$CH_3OC_3H_8$, 4-OH-C_6H_4, $(CH_3)_2N$-C_8H_4

Figure 2.37. N-[2'-amino-(1''-acetly -5- substituted -2''-pyrazoline-3''-yl)1',3',4',-thiadiazole-5'ylmethyl] anthranilic acid derivatives.

Disubstituted thiadiazole derivatives were synthesized with the reaction between salicylic acid and thiosemicarbazide using concentrated H_2SO_4 by Shiv K. Gupta et al.. The researchers assessed in vivo anti-inflammatory activity, and found all

compounds to have moderate anti-inflammatory activity compared to the standard drug, ibuprofen [38].

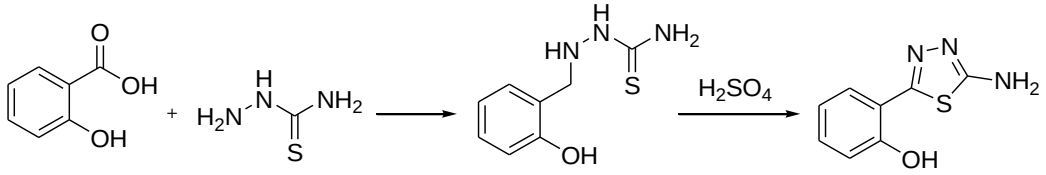
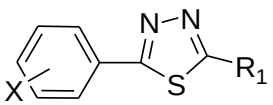


Figure 2.38. Disubstituted 1,3,4-thiadiazole derivatives.

Anticonvulsant Activity

Epilepsy is a clinical picture which occurs as a result of temporary abnormal electrical discharges in the brain. The patient presents deficiencies in consciousness, behavior, movement, or perception functions for a clinically limited time period. The pharmacotherapy of epilepsy has been archived in the last ten years. In spite of the addition of new antiepileptic drugs to the clinical practice in the last twenty years, the maximal electroshock (MES) test and the subcutaneous pentylenetetrazole (scPTZ) test are the most commonly used animal models to characterize anticonvulsant activity in epilepsy.

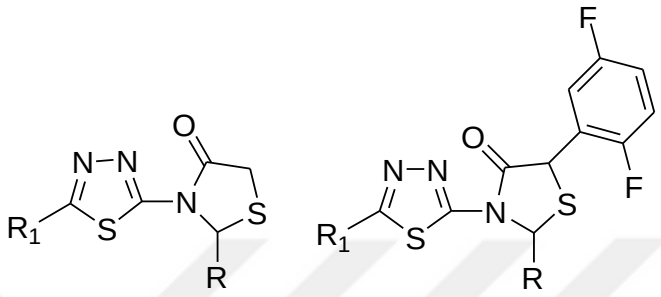
Foroumadi et al. synthesized 2,5-disubstituted-1,3,4-thiadiazole derivatives with –Cl, $-NH_2$, -SH, $-SCH_3$ and $–SO_2CH_3$ groups at the 2-position and fluorophenyl group at the 5-position. In terms of the anticonvulsant activity of the compound containing fluorophenyl group at the 5-position, the fluorine atom was found to have no effect on the activity, while the derivatives containing amino group at the 2-position showed anticonvulsant activity [39].



R_1: NH3, SH, SCH_3, SO_2CH_3 X: 2-F, 3-F, 4-F

Figure 2.39. 2.5-Disubstituted-1, 3, 4-thiadiazole derivatives.

Chimmiri et al. synthesized a new series of 2-substituted-3-(1,3,4-thiadiazole-2-yl)thiazolidine-4-on derivatives and examined anticonvulsant activity of these compounds to find antiepilectic compounds with less side effects. The researchers found that the anticonvulsant activity when the fluorine atom was bonded to the 2-position and the 5-postion of the phenyl ring [40].



R: H, SH R_1: C_2H_5, $C3H_7$, C_6H_{11}, C_6H_5, 2-Br/Cl/F/OHC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 3,4-$Cl_2C_6H_3$, 2,5-$F_2C_6H_3$, 4-C_6H_5-$C6H_4$, 2-Cl-$NO_2C_6H_3$

Figure 2.40. 2-Substituted-3-(1,3,4-thiadiazole-2-yl)thiazolidine-4-on derivatives.

Doğan et al. synthesized 2,5-disubstituted-1,3,4-thiadiazole derivatives, and found that 2-ethylamino-5-(3-hydroxy-2-naphthyl)-1,3,4-thiadiazole had 90% more anticonvulsant activity compared to pentylenetetrazole and 80% more anticonvulsant activity compared to sodium valproate [10].

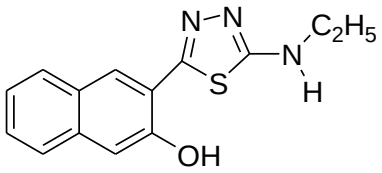


Figure 2.41. 2-Ethylamino-5-(3-hydroxy-2-naphthyl)-1,3,4-thiadiazole derivative.

Masi Hasmin. H et al. designed and synthesized a series of carboxamide derivatives with substituted 1,3,4-thiadiazole. The anticonvulsant activity of these compounds was assessed using the PTZ model (60 mg/kg) and the reference drug, carbamazepine (100 mg/kg). None of the compounds caused sedation as a side effect compared to the standard drug (carbamazepine). The researchers proved that such compounds were strong candidates for prospective anticonvulsant research [41].

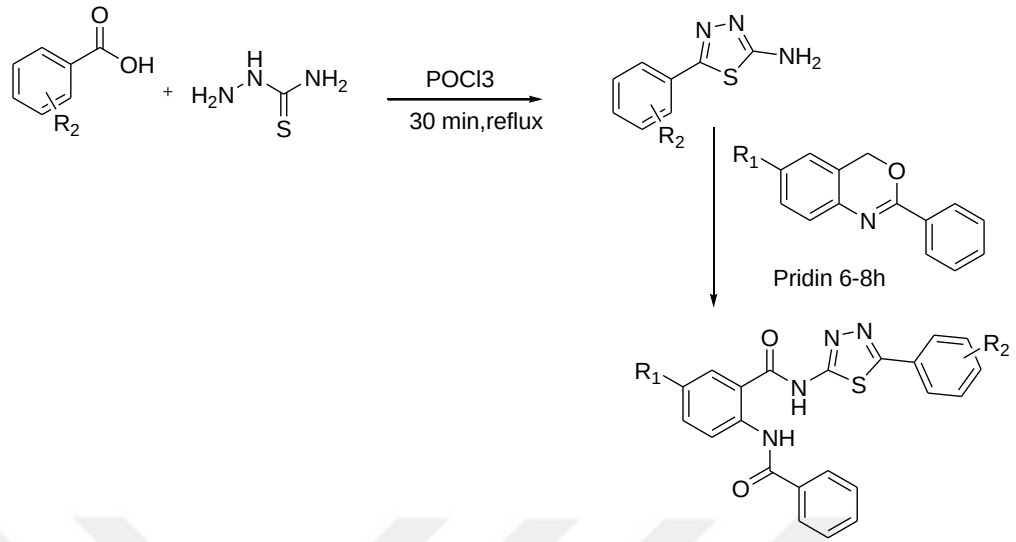
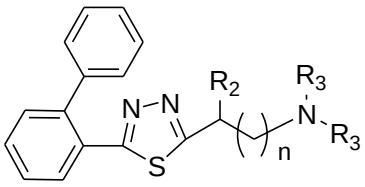


Figure 2.42. The 1,3,4-thiadiazole derivative synthesized by Masi Hasmin. H.

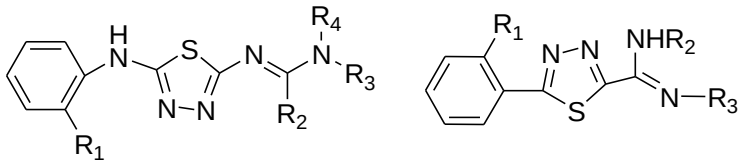
Stilling et al. synthesized alkylamino derivatives with alkyl group instead of nitrogen at the 2-position, and investigated their anticonvulsant activity. The researcher determined that the aryl substitution or the elongation of the alkyl ring led to a decrease in anticonvulsant effect. Also, the biphenyl ring replaced by phenyl or benzyl at the 5-position of the thiadiazole ring led to a decrease as well [42].



R_2=R_3: H, CH_3 R_4: H, CH_3, $C_6H_5CH_2$, $CH(CH_3)_2$

Figure 2.43. 1,3,4-Thiadiazole derivatives containing alkylamino group in the 2-position.

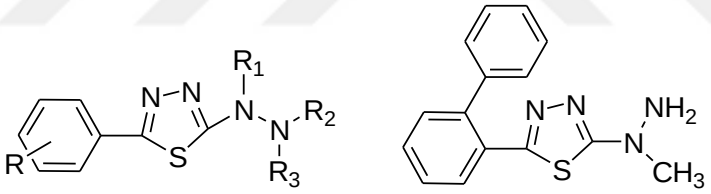
Chapleo et al. synthesized 2-aryl-1,3,4-thiadiazole amide derivatives with 2-methylphenyl and 2-(trifluoromethyl)phenyl at the 5-position of the 1,3,4-thiadiazole ring, and examined their anticonvulsant activity. The authors found that the 2-(trifluoromethyl)phenyl derivatives were the most active, but showed side effects such as sedation and neurotoxicity [43].



R_1: H, CF_3, C_6H_5 R_2: H, CH_3, n-C_3H_7, $C_6H_5CH_2$ R_1: CH_3, C_6H_5 R_2: n-C_4H_9 R_3: H
R_3: H, C_2H_5, n-C_4H_9, $C_6H_5CH_2$ R_4: H, C_2H_5

Figure 2.44. 2-Aryl-1,3,4-thiadiazole amide derivatives.

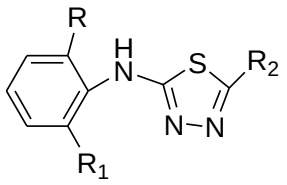
Chapleo et al. synthesized 2-aryl-5-hydrazine-1,3,4-thiadiazole derivatives, compared these to standard anticonvulsant drugs such as phenobarbital, carbamazepine, and phenytoin, and aimed to develop 5-(2-biphenyl)-2-(1-methylhydrazine)-1,3,4-thiadiazole as a new class of anticonvulsant agents. The researchers found these compounds to have antihypertensive effects. The derivatives containing chlorine, methyl, phenyl, and hexyloxy at the 2-position of the aromatic ring as a substituent were found to have high anticonvulsant activity, but low antihypertensive activity [44].



R: H, 2-Cl, 2-CH_3, 2-C_6H_5, 2-$C_6H_{11}O$ R_1: H, CH_3, i-C_3H_7, n-C_4H_9, CH2OCH_3, C6H_5CH_2, $C_6H_5CH_2CH_2$
R_2: H, CH_3, i-C_3H_7, c-C_5H_9, C_6H_5, $CH(C_6H_5)_2$ R_3: CH_3, i-C_3H_7, C_6H_5

Figure 2.45. 2-Aryl-5-hydrazine-1,3,4-thiadiazole derivatives.

Vio et al. synthesized 2-arylamino-1,3,4-thiadiazole derivatives, and found that the 2,6-dimethylphenylamino derivative had higher antihypertensive activity compared to the other compounds in the series. A decrease was observed in antihypertensive activity when the hydrogen at the 5-position of the thiadiazole ring was replaced with pyridyl group [45].



R	R_1	R_2
CH_3	CH_3	H
Cl	Cl	H
Cl	CH_3	H
Cl	Cl	
CH_3	CH_3	

Figure 2.46. 2-arylamino-1,3,4-thiadiazole derivatives.

Antitubercular Activity

Tuberculosis is one of the oldest known infections and still poses a serious health risk throughout the world. It may affect lungs and several other systems. There is a high number of studies on the subject in the literature.

Karakuş and Rollas synthesized a series of N-phenyl-N-[4-(5-alkyl/arylamino-1,3,4-thiadiazole-2-yl)phenyl]thiourea derivatives, and found that the compound containing cyclohexyl had the highest antitubercular activity, whereas the derivative containing 2-fluorophenylamino had no antitubercular activity at all [46].

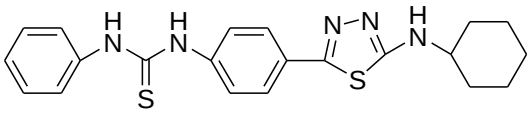


Figure 2.47. N-phenyl-N-[4-(5-cyclohexylamino-1,3,4-thiadiazole-2-yl)phenyl] thiourea.

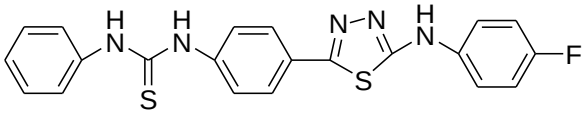


Figure 2.48. N-phenyl-N-[4-(5-(4-fluorophenylamino)-1,3,4-thiadiazole-2-yl)phenyl] thiourea.

Karigar Asif A. et al. synthesized a series of thiadiazole derivatives. The structure of each compound was confirmed with FTIR.

The NMR and mass spectrum data and anti-tubercular activity against *Mycobacterium tuberculosis* were examined using microplate Alamar Blue Assay (MABA). All of the compounds showed good anti-tubercular activity [47].

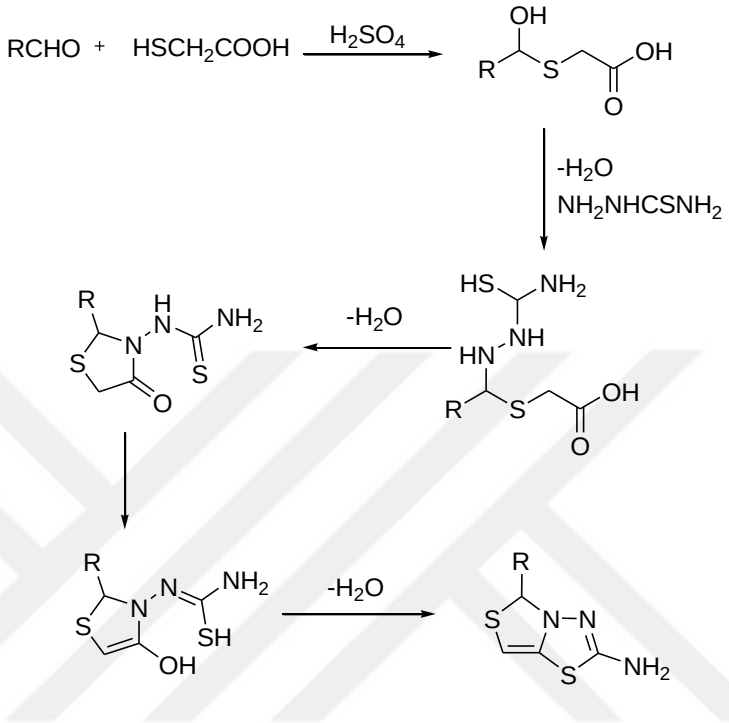


Figure 2.49. A series of thiadiazole derivatives synthesized by Karigar Asif A. et al.

Antidiabetic Activity

Prasanna A Datar et al. designed thiadiazole derivatives as antidiabetic substances using the docking technique. The researchers synthesized these thiadiazole derivatives by microwave irradiation of the product in presence of aldehyde. The product itself was obtained from the cyclization of aromatic acid and thiosemicarbazide in presence of H_2SO_4. In vitro studies to assess antidiabetic activity were carried out using α-amylase inhibition and in vivo studies were carried out on alloxan induced diabetes rat model. Molecular docking revealed that synthesized derivatives and target proteins were actively involved in binding and had significant correlation with biological activity [48].

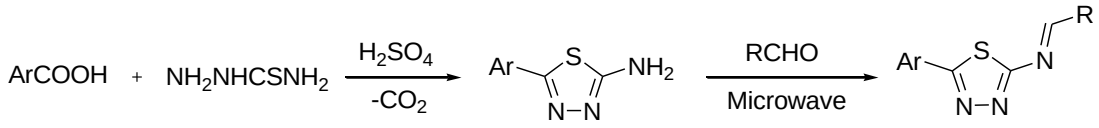
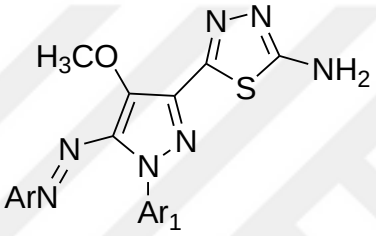


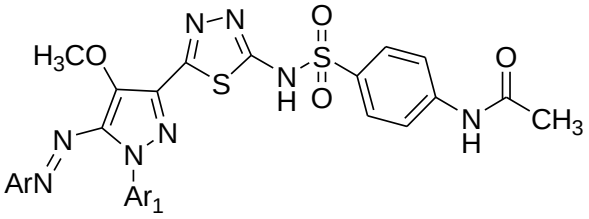
Figure 2.50. The thiadiazole derivative designed by Prasanna A Datar et al.

Hanna et al. synthesized a series of thiadiazole derivatives and found that 2-amino-5-(5'-arylazo-1'-phenyl-4'-methoxy-pyrazole-3'-yl)1,3,4-thiadiazoles decreased blood glucose level by 15-16% and 2-(4-acetly-aminobenzenesulfuonamido) derivatives decreased blood glucose level by 18% [49].



Ar: 3-ClC_6H_4 Ar_1: 4-$(CH_3)_2NC_6H_4$, C_6H_5, 4-$NO_2C_6H_4$

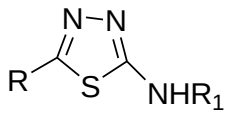
Figure 2.51. 2-amino-5-(5'-arylazo-1'-phenyl-4'-methoxy-pyrazole-3'-yl)1,3,4-thiadiazole derivatives.



Ar: 3-ClC_6H_4 Ar_1: 4-$(CH_3)_2NC_6H_4$, C_6H_5, 4-$NO_2C_6H_4$

Figure 2.52. 2-(4-acetly-aminobenzenesulphonamido)-5-(5'arylazo-1'-phenyl-4'-methoxy-pyrazole-3'-yl)1,3,4-thiadiazole derivatives.

Mhasalkar et al. assessed hypoglycemic activity of 2-aryl/pyridyl-5-alkyl/arylamino-1,3,4-thiadiazole derivatives, and determined that the presence of 4-nitrophenyl, 4-pyridyl, and *p*-sulfamoylphenyl at the 2-position was necessary for hypoglycemic activity. Isopropylamino, phenylamino, and cyclohexylamino groups at the 5-position were also found to increase activity [50].



R	R_1
4-$NH_2SO_2C_6H_4$	i-C_3H_7
4-$NH_2SO_2C_6H_4$	C_6H_{11}
4-piridil	C_6H_5
4-$NH_2C_6H_4$	i-C_3H_7

Figure 2.53. 2-aryl/pyridyl-5-alkyl/arylamino-1,3,4-thiadiazole derivatives.

Anticancer Activity

Arun Naskar et al. synthesized 2-amino-5-aryl-1,3,4-thiadiazole derivatives through oxidative cyclization of thiosemicarbazones using $FeCl_3$ as catalyst, and Schiff bases by concentrating these with aldehydes. The researchers assessed the anticancer activity of the derivatives using Ehrlich's ascites carcinoma cells, and all compounds presented significant anticancer activity [51].

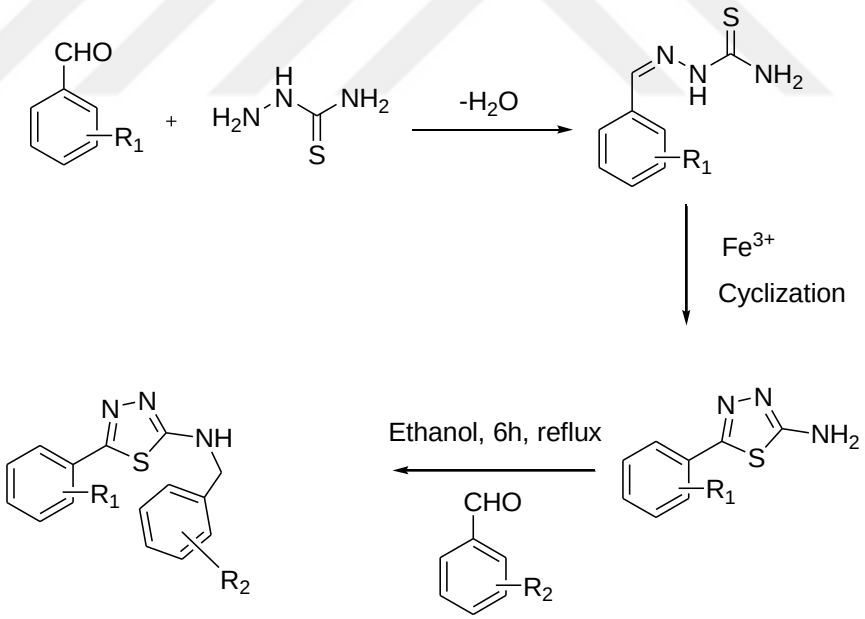


Figure 2.54. Thiadiazole derivatives designed by Arun Naskar et al.

Chou et al. examined the human lung cancer cell A549 activity of (*E*,*E*)-2,5-bis[4-(3-dimethylaminopropoxy)styryl]-1,3,4-thiadiazole and found that the compound had anticancer activity [52].

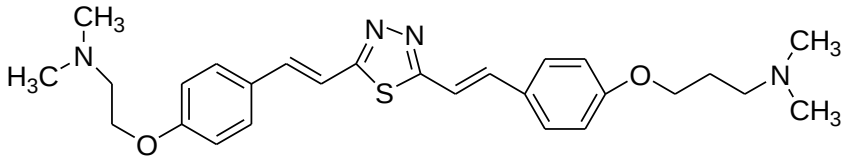


Figure 2.55. (*E,E*)-2,5-bis[4-(3-dimethylaminopropoxy)styryl]-1,3,4-thiadiazole.

Suddasatwa Banerjee et al. synthesized thiadiazole derivatives by refluxing furan-2-carboxylic acid and thiosemicarbazide in presence of concentrated H_2SO_4, and then reacted these compounds with various substituted aldehydes in presence of a few drops of acetic acid to prepare different Schiff bases. The researchers tested the compounds for in vitro anticancer activity on HT-29 colorectal cancer cell line using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assay. The compounds showed significant activity even in very low concentrations [53].

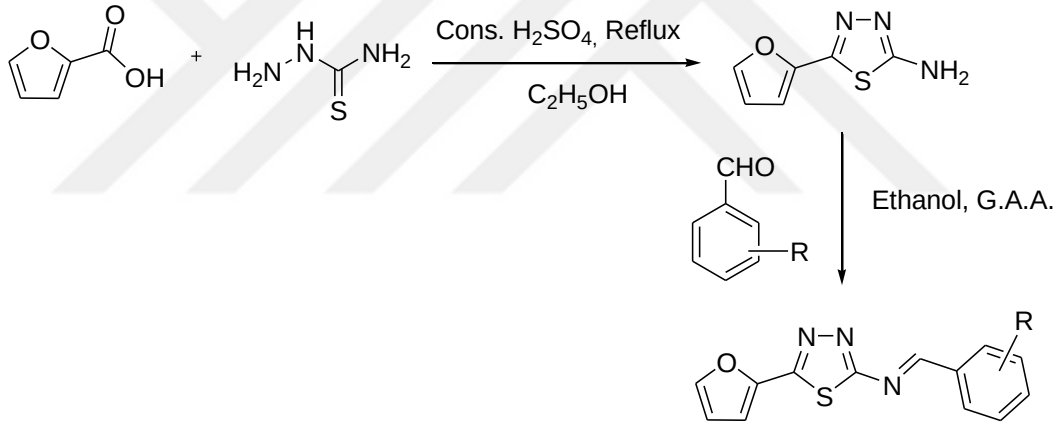


Figure 2.56. Thiadiazole derivatives designed by Suddasatwa Banerjee et al.

Sancak et al. synthesized 1,3,4-thiadiazole derivatives, and tested their growth inhibition properties on 3 human tumor cell lines, breast cancer (MCF7), non-small cell lung cancer (NCI-H460), and CNS (8SF-268). The researchers found that thiadiazole derivatives containing acetly and ethoxy carbonyl groups had anticancer activity [54].

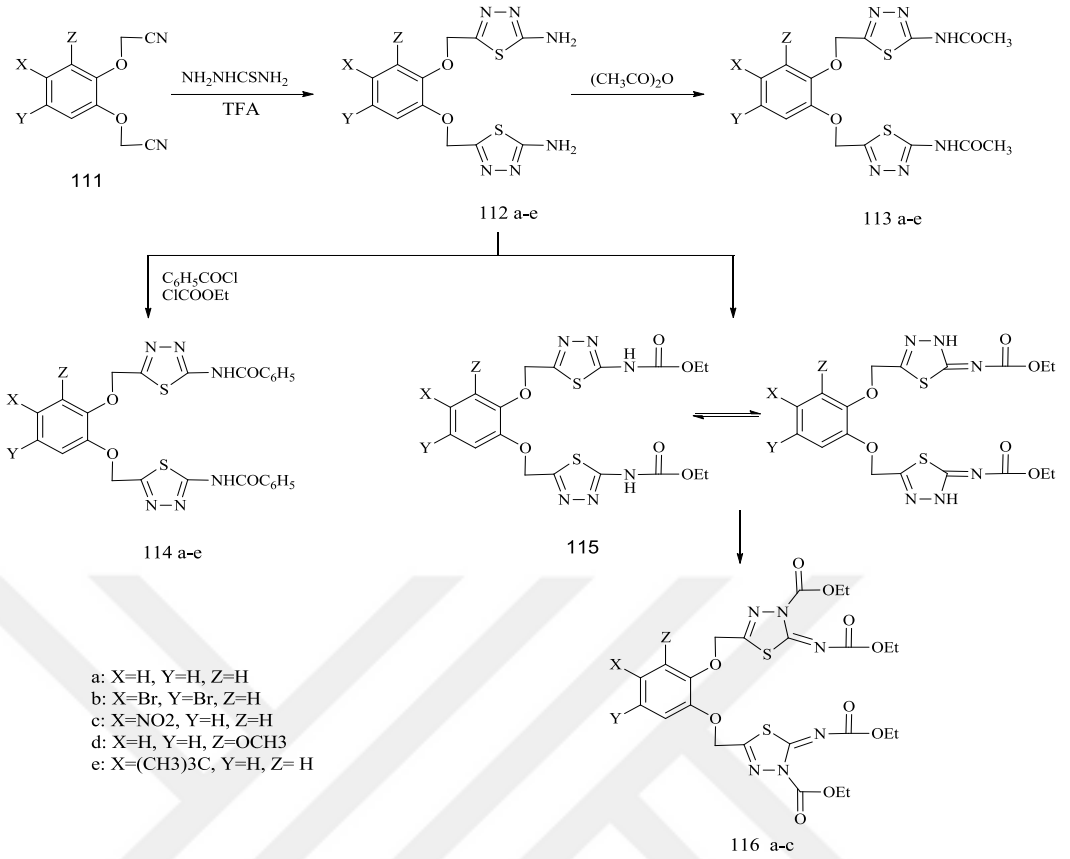


Figure 2.57. Thiadiazole derivatives containing acetly and ethoxy carbonyl groups.

Miyamolo et al. synthesized 2-N and/or 5-substituted-2-amino-1,3,4-thiadiazole derivatives. Among the compounds synthesized, 2-amino-1,3,4-thiadiazole, 2-formamide-1,3,4-thiadiazole, and 2-trifluoroacetamido were found to have antitumor activity, whereas 5-substituted, 2-urethane, and 2-carbamate derivatives were found to be inactive [55].

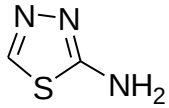


Figure 2.58. 2-Amino-1,3,4-thiadiazole.

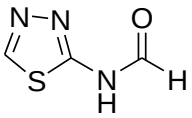


Figure 2.59. 2-Formamide-1,3,4-thiadiazole.

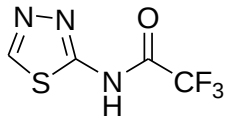
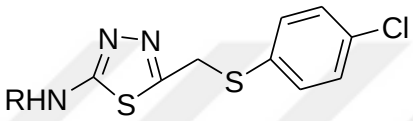


Figure 2.60. 2-Trifluoroacetamide-1,3,4-thiadiazole.

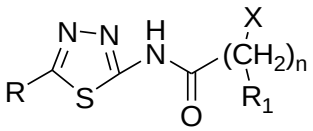
Bahadur et al. determined that 2-arylamino-5-(4'-chlorophenylthiomethyl)-1,3,4-thiadiazole derivatives showed antiviral activity against the virus of Ranikhet disease [56].



R: C_6H_5, 4-$CH_3C_6H_4$, 4-ClC_6H_4

Figure 2.61. 2-Arylamino-5-(4'-chlorophenylthiomethyl)-1,3,4-thiadiazole derivatives.

Mazzone et al. synthesized a series of 2-acylamino substituted thiadiazole derivatives. The researchers found that the local anesthetic effect of the derivative containing trialcoxyphenyl at the 5-position of the 1,3,4-thiadiazole ring was lower compared to dialcoxy derivatives. Also, 2-(3-piperidinopropionyl)amino-5-(3,4-methylenedioxy phenyl) and 2-(3-N-methylpiperazinopropionyl)amino-5-(3,5-dimethoxy-4-ethoxy phenyl-1,3,4-thiadiazole had the highest local anesthetic effect compared to the standard substance, lidocain [57].

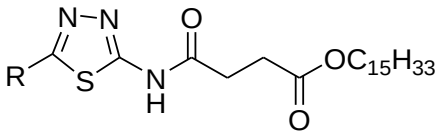


R: 3,4,5-$(OCH_3)C_6H_2$, 3,4-$(OCH_2O)C_6H_3$, 3,5-(OCH_3)-4-$OC_2H_5C_6H_2$
X: Br, Cl n:1 R_1: H, CH_3, C_2H_5, C_6H_5 n:2,3 R_1: H

Figure 2.62. 2-Acylamino-5-aryloxy-1,3,4-thiadiazole derivatives.

Habib et al. investigated antihyperlipidemic and antihypercholesterolemic activities of 5-substituted-2-(hexadecyloxycarbonylpropionylamino)-1,3,4-thiadiazole and 5-

isopropylthio-2-(cyclohexyloxycarbonylpropionylamino)-1,3,4-thiadiazole derivatives, and found that the thiadiazole derivative containing isopropylthio group at the 5-position had antihyperlipidemic activity [58].



R: CH_3, C_6H_5, $(CH_3)_2CHS$

Figure 2.63. 5-Substituted-2-(hexadecyloxycarbonylpropionylamino)-1,3,4-thiadiazole derivatives.

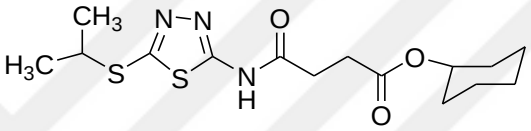


Figure 2.64. 5-Isopropylthio-2-(cyclohexyloxycarbonylpropionylamino)-1,3, 4-thiadiazole.

PART 3

EXPERIMENTAL STUDIES

This study was supported by the Scientific Research Fund of Karabük University (Project No: KBU-BAP-16/2-YL-090)

The ^{1}H-NMR and ^{13}C-NMR spectra of the compounds were assessed using an Agilent Annual Refill (400 MHz) device in the Central Research Laboratory of Recep Tayyip Erdoğan University. Mass spectrum was determined by the ESI (+) method using a Thermo TSQ Quantum Access device in the Central Research Laboratory of Recep Tayyip Erdoğan University. The elemental analysis of the compounds was performed using a LECO 932 CHNS (Leco-932, St. Joseph, MI, USA) device in the Central Research Laboratory of Recep Tayyip Erdoğan University. The melting points of the compounds were determined using a Thermo Scientific IA9000 device.

3.1. SYNTHESIS OF 2-AMINO-1,3,4-THIADIAZOLE DERIVATIVES (2)

The solution of the compound 1 (0.075 mol) in 40 ml trifluoroacetic acid is added thiosemicarbazide (0.100 mol) in a flask with a round bottom and then the mixture is heated at 60 ^{o}C for 4 hours on a condenser with the drying tube attached. At the end of 4 hours, the reaction mixture is poured on 200 ml ice-water mixture and neutralized with diluted ammonia. The resulting substance is filtered through a funnel. The solid substance obtained is rinsed with pure water, ethyl alcohol, and diethyl ether, respectively. Then, the substance is purified by crystallizing with an appropriate solvent or solvent mixture.

The pure substance is dried with P_2O_5 vacuum oven. Finally, structures of the synthesized compounds are illuminated with FT-IR, ^{1}H NMR, ^{13}C NMR, mass spectroscopy, and elemental analysis.

The physical properties and the spectral data of the products are listed below.

3.1.1. 5-(2,6-dichlorobenzyl)-1,3,4-thiadiazol-2-amine (2)

White solid, yield: 15.79 g (81%), m.p. 219-220 °C (DMF-EtOH, 1:15). IR (ATR, cm^{-1}): 3258-3098 (-NH_2), 3080 (Ar-CH), 2976 (Aliphatic CH), 1582 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 4.40 (s, 2H, -CH_2), Arom-H [7.49 (d, *J*=8.0 Hz, 2H), 7.36 (t, *J*=8.0, 7.6 Hz, 1H)], 7.69 (bs, 2H, NH_2). ^{13}C NMR (400 MHz, DMSO-d_6, δ ppm): 32.16 (-CH_2), Arom-C [129.09 (CH), 130.49 (CH), 133.40 (C), 135.44 (C)], Thiadiazole-C [154.37 (C), 169.39 (C)]. *Anal.* Calcd. for $C_9H_7Cl_2N_3S$: C, 41.55; H, 2.71; N, 16.15. Found: C, 41.43; H, 2.76; N, 15.99. MS: *m/z* 260 (M^+, 74); 261 (M+1, 51).

3.2. GENERAL ACYLATION REACTIONS OF 2-AMINO-1,3,4-THIADIAZOLE DERİVATIVES (4a-n)

In a two-necked flask, compound (2) (0.004 mol) was suspended in dry benzene (40 mL) and pyridine (1 mL). Acyl chloride derivatives (0.004 mol) were added drop-wise to this solution at room temperature with the assistance of a dropping funnel. The mixture was then refluxed and stirred for 4-6 h. The progress of the reaction was monitored by TLC at appropriate time intervals. After completion of the reaction, the solution was filtered and the solid matter was obtained. It was washed with deionized water, ethanol and diethyl ether, respectively. The solid matter was recrystallized from the appropriate solvent. All physical properties and spectral data derived from the obtained products are given in the Supplementary Material Section.

3.2.1. N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazol-2-yl)benzamide (4a)

White solid, yield: 1.14 g (78%), m.p. 279-280 °C (DMF-EtOH, 1:1). IR (ATR, cm^{-1}): 3169 (-NH-), 3061 (Ar-CH), 2983 (Aliphatic CH), 1667 (C=O), 1582 (C=N). ^{1}H

NMR (400 MHz, DMSO-d_6) δ (ppm): 4.62 (s, 2H, -CH_2), Arom-H [8.06 (d, *J*=6.4 Hz, 2H), 7.61 (d, *J*=6.0 Hz, 1H), 7.54 (bs, 2H), 7.52 (bs, 2H), 7.39 (t, 2H)], 12.99 (s, 1H, NH). ^{13}C NMR (400 MHz, DMSO-d_6, δ ppm): 31.80 (-CH_2), Arom-C [128.80 (CH), 129.08 (CH), 129.22 (CH), 130.64 (CH), 131.90 (CH), 133.41 (C), 134.64 (C), 135.52 (C)], Thiadiazole-C [159.86 (C), 160.84 (C)], 165.53 C=O. *Anal.* Calcd. for $C_{16}H_{11}Cl_2N_3OS$: C, 52.76; H, 3.04; N, 11.54. Found: C, 52.68; H, 3.00; N, 11.49. MS: *m/z*: 363.68 (M-1, 100), 365.85 (M+1, 84).

3.2.2. N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazol-2-yl)-4-nitrobenzamide (4b)

White solid, yield: 1.21 g (74%), m.p. 320-321 °C (DMF-EtOH, 1:15). IR (ATR, cm^{-1}): 3133 (-NH-), 3044 (Ar-CH), 2930 (Aliphatic CH), 1677 (C=O), 1596 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 4.62 (s, 2H, -CH_2), Arom-H [8.39 (d, 4H), 7.54 (bs, 2H), 7.53 (bs, 2H), 7.39 (bs, 1H)], 13.40 (s, 1H, NH). ^{13}C NMR (400 MHz, DMSO-d_6, δ ppm): 31.80 (-CH_2), Arom-C [124.09 (CH), 126.64 (CH), 129.23 (CH), 130.41 (CH), 133.57 (C), 135.51 (C), 139.82 (C), 150.33 (C)], Thiadiazole-C [159.88 (C), 160.81 (C)], 165.40 C=O. *Anal.* Calcd. for $C_{16}H_{10}Cl_2N_4O_3S$: C, 46.96; H, 2.46; N, 13.69. Found: C, 46.88; H, 2.59; N, 13.56. MS: *m/z*: 408.93 (M^+, 100), 410.96 (M+1, 93).

3.2.3. N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazol-2-yl)-4-(methylthio)benzamide (4c)

White solid, yield: 1.13 g (69 %), m.p. 282-283 °C (DMF-EtOH, 1:1). IR (ATR, cm^{-1}): 3132 (-NH-), 3035 (Ar-CH), 2921 (Aliphatic CH), 1674 (C=O), 1595 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.48 (t, 3H, -CH_3), 4.61 (s, 2H, -CH_2), Arom-H [8.00 (d, *J*=8.0 Hz, 2H), 7.54 (d, *J*=8.4 Hz, 2H), 7.37 (m, 3H)], 12.90 (s, 1H, NH). ^{13}C NMR (400 MHz, DMSO-d_6, δ ppm): 14.95 (CH_3), 31.79 (-CH_2), Arom-C [125.32 (CH), 127.54 (CH), 129.22 (CH), 130.64 (CH), 133.66 (C), 135.52 (C), 139.63 (C), 145.70 (C)], Thiadiazole-C [160.46 (C), 163.66 (C)], 165.63 C=O. *Anal.* Calcd. for $C_{17}H_{13}Cl_2N_3OS_2$: C, 49.76; H, 3.19; N, 10.24. Found: C, 49.68; H, 3.06; N, 10.12. MS (ESI-*m/z*): 411,38 (M+1, 26), 413,34 (M+2, 48).

3.2.4.N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazol-2-yl)-3,4-dichlorobenzamide (4d)

White solid, yield: 1.25 g (73 %), m.p. 295-296 °C (DMF-EtOH, 1:15). IR (ATR, cm^{-1}): 3142 (-NH-), 3084 (Ar-CH), 2967 (Aliphatic CH), 1682(C=O), 1560 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 4.62 (s, 2H, -CH_2), Arom-H [8.30 (s, 1H), 7.99 (d, *J*=8.0 Hz, 1H), 7.80 (d, *J*=8.4 Hz, 1H), 7.53 (d, *J*=8.0 Hz, 2H), 7.38 (t, *J*=8.0, 7.2 Hz, 1H)], 13.15 (s, 1H, NH). ^{13}C NMR (400 MHz, DMSO-d_6, δ ppm): 31.84 (-CH_2), Arom-C [129.05 (CH), 129.22 (CH), 129.97 (CH), 130.68 (CH), 130.76 (CH), 131.42 (C), 131.98 (C), 133.54 (C), 135.51 (C), 136.16 (C)], Thiadiazole-C [159.85 (C), 160.96 (C)], 166.16 C=O. *Anal.* Calcd. for $C_{16}H_9Cl_4N_3OS$: C, 44.37; H, 2.09; N, 9.70. Found: C, 44.23; H, 2.01; N, 9.57. MS (ESI-*m/z*): 433.71 (M+1, 100).

3.2.5. N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazol-2-yl)-3,4-difluorobenzamide (4e)

White solid, yield: 1.30 g (80 %), m.p. 304-305 °C (DMF-EtOH, 1:15). IR (ATR, cm^{-1}): 3142 (-NH-), 3087 (Ar-CH), 2941 (Aliphatic CH), 1663 (C=O), 1563 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 4.61 (s, 2H, -CH_2), Arom-H [8.13 (t, 1H), 7.95 (s, 1H), 7.60 (q, 1H), 7.53 (d, *J*=8.4 Hz, 2H), 7.38 (t, *J*=8.0, 8.0 Hz, 1H)], 13.09 (s, 1H, NH). ^{13}C NMR (400 MHz, DMSO-d_6, δ ppm): 31.82 (-CH_2), Arom-C [118.32 (CH), 126.65 (CH), 129.21 (CH), 130.65 (CH), 133.54 (CH), 135.51 (C), 148.33(C), 150.91 (C), 151.47 (C), 154.11 (C)], Thiadiazole-C [159.80 (C), 161.90 (C)], 163.80 C=O. *Anal.* Calcd. for $C_{16}H_9Cl_2F_2N_3OS$: C, 48.02; H, 2.27; N, 10.50. Found: C, 48.11; H, 2.12; N, 10.36. MS (ESI-*m/z*): 400.00 (M^+, 74), 402.26 (M+2, 54).

3.2.6. N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazol-2-yl)-3,4-dimethoxybenzamide (4f)

White solid, yield: 1.07 g (64 %), m.p. 252-253 °C (DMF-EtOH, 1:1). IR (ATR, cm^{-1}): 3155 (-NH-), 3047 (Ar-CH), 2941 (Aliphatic CH), 1661 (C=N), 1587 (C=N). ^{1}H

NMR (400 MHz, DMSO-d_6) δ (ppm): 3.82 (s, 6H, -OCH_3), 4.60 (s, 2H, -CH_2), Arom-H [7.71 (s, 2H), 7.52 (s, 2H), 7.37 (s, 1H), 7.08 (s, 1H)], 12.82 (s, 1H, NH). ^{13}C NMR (400 MHz, DMSO-d_6, δ ppm): 31.76 (-CH_2), 56.10 (-OCH_3), 56.17 (-OCH_3), Arom-C [111.59 (CH), 122.85 (CH), 123.66 (CH), 129.19 (CH), 130.59 (C), 133.68 (CH), 135.51 (C), 148.81 (C), 153.17 (C), 160.13 (C)], Thiadiazole-C [160.59 (C), 162.74 (C)], 164.73 C=O. *Anal.* Calcd. for $C_{18}H_{15}Cl_2N_3O_3S$: C, 50.95; H, 3.56; N, 9.90. Found: C, 50.78; H, 3.46; N, 9.78. MS (ESI-*m/z*): 423.91 (M^+, 100), 425.87 (M+2, 66).

3.2.7. N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazol-2-yl)-3,5-dimethoxybenzamide (4g)

White solid, yield: 1.00 g (59 %), m.p. 204-205 °C (DMF-EtOH, 1:1). IR (ATR, cm^{-1}): 3138 (-NH-), 3032 (Ar-CH), 2959 (Aliphatic CH), 1683 (C=O), 1596 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 3.76 (s, 6H, -OCH_3), 4.39 (s, 2H, -CH_2), Arom-H [7.49 (d, *J*=8.0 Hz, 2H), 7.34 (t, *J*=8.0, 7.6 Hz, 1H), 7.04 (s, 2H), 6.71 (s, 1H)], 13.01 (bs, 1H, NH). ^{13}C NMR (400 MHz, DMSO-d_6, δ ppm): 31.76 (-CH_2), 56.09 (-OCH_3), 56.16 (-OCH_3), Arom-C [107.89 (CH), 109.73 (CH), 129.17 (CH), 130.59 (CH), 133.64 (C), 135.53 (C), 146.41 (C), 160.48 (C)], Thiadiazole-C [153.18 (C), 162.75 (C)], 164.33 C=O. *Anal.* Calcd. for $C_{18}H_{15}Cl_2N_3O_3S$: C, 50.95; H, 3.56; N, 9.90. Found: C, 50.79; H, 3.50; N, 9.81. MS (ESI-*m/z*): 423.91 (M^+, 100).

3.2.8. N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazol-2-yl)-3,5-difluorobenzamide (4h)

White solid, yield: 1.18 g (74%), m.p. 270-271 °C (DMF-EtOH, 1:1). IR (ATR, cm^{-1}): 3147 (-NH-), 3044 (Ar-CH), 2928 (Aliphatic CH), 1679 (C=O), 1595 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 4.62 (s, 2H, -CH_2), Arom-H [7.76 (s, 2H), 7.54 (bd, 3H), 7.39 (t, 1H)], 13.16 (s, 1H, NH). ^{13}C NMR (400 MHz, DMSO-d_6, δ ppm): 31.84 (-CH_2), Arom-C [108.80 (CH), 112.24 (CH), 112.43 (C), 129.22 (CH), 130.68 (CH), 133.51 (C), 135.51 (C), 163.80 (C)], Thiadiazole-C [161.35 (C), 161.48 (C)], 164.93 C=O. *Anal.* Calcd. for $C_{16}H_9Cl_2F_2N_3OS$: C, 48.02; H, 2.27; N,

10.50. Found: C, 47.96; H, 2.20; N, 10.56. MS (ESI-*m/z*): 399.80 (M-1, 100), 401.83 (M+1, 74).

3.2.9. N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazol-2-yl)-3,5-dichlorobenzamide (4i)

White solid, yield: 1.33 g (77 %), m.p. 260-261 °C (DMF-EtOH, 1:1). IR (ATR, cm^{-1}): 3147 (-NH-), 3070 (Ar-CH), 2969 (Aliphatic CH), 1663 (C=O), 1563 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 4.62 (s, 2H, -CH_2), Arom-H [8.06 (s, 2H), 7.89 (s, 1H), 7.54 (d, *J*=8.0 Hz, 2H),7.39 (t, *J*=8.0, 7.6 Hz, 1H)], 13.16 (s, 1H, NH). ^{13}C NMR (400 MHz, DMSO-d_6, δ ppm): 31.87 (-CH_2), Arom-C [127.60 (CH), 129.22 (CH), 130.69 (C), 132.50 (CH), 133.50 (C), 134.90 (C), 135.47 (C), 135.52 (C)], Thiadiazole-C [160.08 (C), 162.54 (C)], 163.93 C=O. *Anal.* Calcd. for $C_{16}H_9Cl_4N_3OS$: C, 44.37; H, 2.09; N, 9.70. Found: C, 44.22; H, 2.18; N, 9.52. MS (ESI-*m/z*): 431.79 (M-1, 56).

3.2.10. N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazol-2-yl)-4-ethylbenzamide (4j)

White solid, yield: 1.02 g (65 %), m.p. 275-276 °C (DMF-EtOH, 1:1). IR (ATR, cm^{-1}): 3184(-NH-), 3059 (Ar-CH), 2964 (Aliphatic CH), 1662 (C=O), 1576 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.17 (t, 3H, -CH_3), 2.65 (q, 2H, -CH_2-), 4.61 (s, 2H, -CH_2), Arom-H [7.99 (d, *J*=8.0 Hz, 2H), 7.54 (d, *J*=8.4 Hz, 2H), 7.36 (m, 3H)], 12.87 (s, 1H, NH). ^{13}C NMR (400 MHz, DMSO-d_6, δ ppm): 15.61 (-CH_3), 28.58 (-CH_2-), 31.79 (-CH_2), Arom-C [128.47 (CH), 128.95 (CH), 129.01 (CH), 129.21 (CH), 130.62 (C), 133.66 (C), 135.52 (C), 149.83 (C)], Thiadiazole-C [159.65 (C), 160.72 (C)], 165.40 C=O. *Anal.* Calcd. for $C_{18}H_{15}Cl_2N_3OS$: C, 55.11; H, 3.85; N, 10.71. Found: C, 55.02; H, 3.79; N, 10.63. MS (ESI-*m/z*): 393.77 (M+1, 53).

3.2.11. N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazol-2-yl)-4-(trifluoromethyl) benzamide (4k)

White solid, yield: 1.07 g (62 %), m.p. 274-275 °C (DMF-EtOH, 1:1). IR (ATR, cm^{-1}): 3152 (-NH-), 3041 (Ar-CH), 2943 (Aliphatic CH), 1680(C=O), 1531 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 4.63 (s, 2H, -CH_2), Arom-H [8.23 (d, *J*=8.0 Hz, 2H), 7.90 (d, *J*=8.4 Hz, 2H), 7.54 (d, *J*=8.4 Hz, 2H), 7.39 (t, *J*=7.6, 7.6 Hz, 1H)], 13.26 (s, 1H, NH). ^{13}C NMR (400 MHz, DMSO-d_6, δ ppm): 31.84 (-CH_2), 122.84 (CF_3), Arom-C [125.56 (CH), 125.99 (CH), 126.03 (CH), 129.22 (CH), 129.78 (C), 130.68 (C), 133.56 (C), 135.52 (C)], Thiadiazole-C [159.86 (C), 160.84 (C)], 165.53 C=O. *Anal.* Calcd. for $C_{17}H_{10}Cl_2F_3N_3OS$: C, 47.24; H, 2.33; N, 9.72. Found: C, 47.36; H, 2.26; N, 9.65. MS (ESI-*m/z*): 431.86 (M-1, 82).

3.2.12. N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazol-2-yl)-4-cyanobenzamide (4l)

White solid, yield: 1.26 g (81%), m.p. 334-335 °C (DMF-EtOH, 1:1). IR (ATR, cm^{-1}): 3142 (-NH-), 3094 (Ar-CH), 2921 (Aliphatic CH), 2235 (CN), 1684 (C=O), 1542 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 4.63 (s, 2H, -CH_2), Arom-H [8.18 (d, *J*=8.4 Hz, 2H), 8.01 (d, *J*=8.0 Hz, 2H), 7.54 (d, *J*=8.4 Hz, 2H), 7.38 (t, *J*=8.0, 8.0 Hz, 1H)], 13.27 (s, 1H, NH). ^{13}C NMR (400 MHz, DMSO-d_6, δ ppm): 31.86 (-CH_2), 118.56 (CN), Arom-C [115.40 (C), 125.54 (CH), 129.23 (CH), 129.61 (CH), 130.70 (CH), 133.03 (C), 133.53 (C), 135.52 (C)], Thiadiazole-C [159.88 (C), 160.86 (C)], 165.80 C=O. *Anal.* Calcd. for $C_{17}H_{10}Cl_2N_4OS$: C, 52.45; H, 2.59; N, 14.39. Found: C, 52.36; H, 2.46; N, 14.50. MS (ESI-*m/z*): 385.22 (M-4, 100).

3.2.13. N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazol-2-yl)acetamide (4m)

White solid, yield: 1.03 g (83%), m.p. 284-285 °C (DMF-EtOH, 1:15). IR (ATR, cm^{-1}): 3158 (-NH-), 3052 (Ar-CH), 2976 (Aliphatic CH), 1698 (C=O), 1563 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.12 (s, 3H, -CH_3), 4.56 (s, 2H, -CH_2), Arom-H [7.59 (d, *J*=7.6 Hz, 2H), 7.36 (t, *J*=8.4, 8.0 Hz, 1H)], 13.26 (s, 1H, NH). ^{13}C NMR (400 MHz, DMSO-d_6, δ ppm): 22.77 (CH_3), 31.75 (-CH_2), Arom-C [129.15 (CH), 130.56 (CH), 133.63 (C), 135.48 (C)], Thiadiazole-C [159.99 (C), 160.26 (C)], 169.01 C=O. *Anal.* Calcd. for $C_{11}H_9Cl_2N_3OS$: C, 43.72; H, 3.00; N, 13.91. Found: C, 43.76; H, 3.09; N, 13.86. MS (ESI-*m/z*): 302.01 (M^+, 55).

3.2.14. Ethyl 5-(2,6-dichlorobenzyl)-1,3,4-thiadiazol-2-ylcarbamate (4n)

White solid, yield: 0.76 g (56%), m.p. 217-218 °C (DMF-EtOH, 1:5). IR (ATR, cm^{-1}): 3160 (-NH-), 3022 (Ar-CH), 2982 (Aliphatic CH), 1720 (C=O), 1569 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.23 (t, 3H, $-CH_3$), 4.17 (q, 2H, $-OCH_2-$), 4.41 (s, 2H, $-CH_2$), Arom-H [7.51 (d, 2H), 7.36 (t, 1H)], 12.08 (s, 1H, NH). ^{13}C NMR (400 MHz, DMSO-d_6, δ ppm): 14.65 ($-CH_3$), 27.00 ($-CH_2-$), 62.60 ($-OCH_2-$), Arom-C [129.20 (CH), 130.37 (CH), 133.83 (C), 135.42 (C)], Thiadiazole-C [160.63 (C), 161.48 (C)], 162.49 C=O. *Anal.* Calcd. for $C_{12}H_{11}Cl_2N_3O_2S$: C, 43.39; H, 3.34; N, 12.65. Found: C, 43.33; H, 3.36; N, 12.56. MS (ESI-*m/z*): 331.14 (M-1, 43).

PART 4

FINDINGS, DISCUSSION, AND CONCLUSION

4.1. SYNTHESIS AND CHARACTERIZATION OF SOME NEW N-(5-(2,6-DICHLOROBENZYL)-1,3,4-THIADIAZOLE-2-YL)-3,4,5-SUBSTITUTED BENZAMIDE COMPOUNDS

In this study, the target compounds N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-yl)-3,4,5-substituted benzamide derivatives **(4a-n)** were synthesized using the synthetic pathway shown in Figure 4.1.

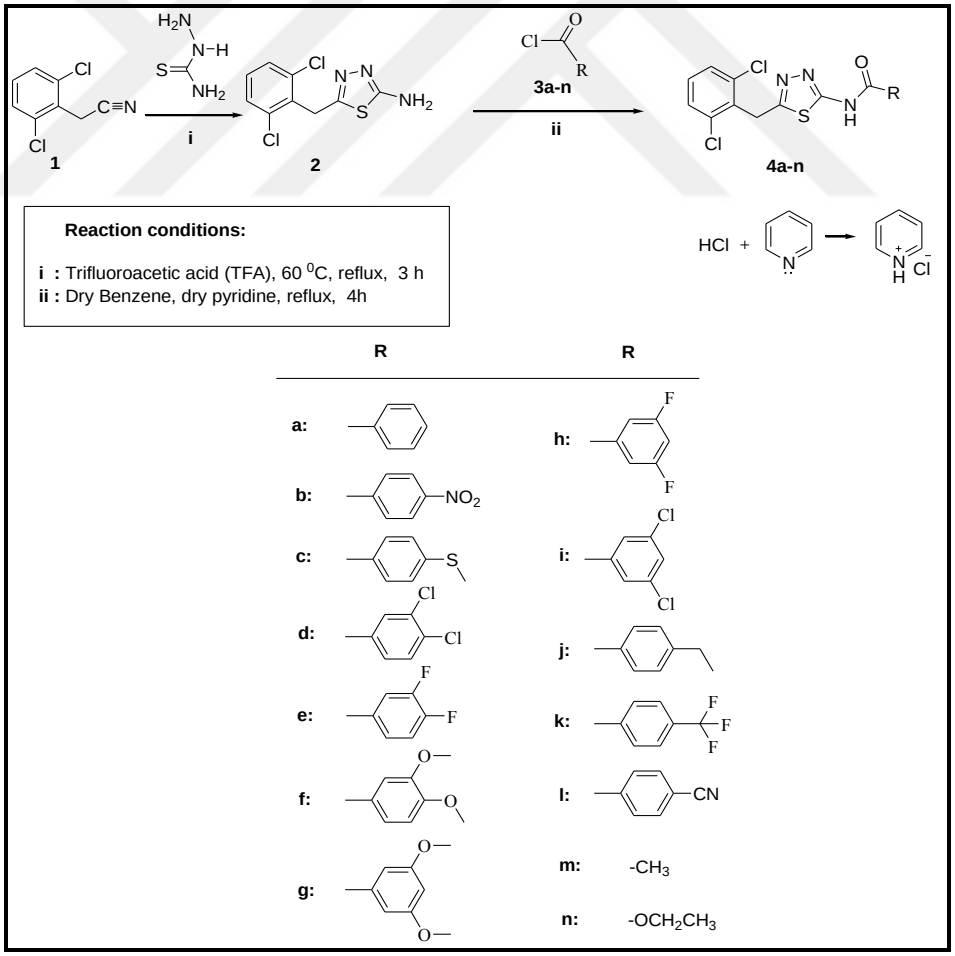


Figure 4.1. The synthetic pathway used to synthesize N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-yl)-3,4,5-substituted benzamide derivatives **(4a-n)**.

In our study on synthesis and acylation of some new compounds containing 2-amino-1,3,4-thiadiazole ring, a total of 15 substances were synthesized, 1 recorded in the literature and 14 originals. 2-amino-1,3,4-thiadiazole derivatives and acylation reactions of these compounds were examined in this study, and 5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-amine (**(2)** was obtained from the reaction of 2-(2,6-dichlorophenyl)acetonitryl **(1)** with thiosemicarbazide in TFA.

In this reaction, an addition occurs as a result of the thiosemicarbazide's nucleophilic attack on the positively charged iminium carbon, which forms under the catalytic effect of trifluoroacedic acid according to the literature data, from the hydrazine end, which is more basic. Although an intermediate stable product is not observed in the reaction, in parallel with the intermediate products observed in similar reactions, the elimination of the ammonia ion following the addition and then the nucleophilic attack of the sulfur atom on the carbon atom where the elimination occurs addition gives a 2-amino-1,3,4-thiadiazole derivative **(2)** as a result of heterocyclization [59].

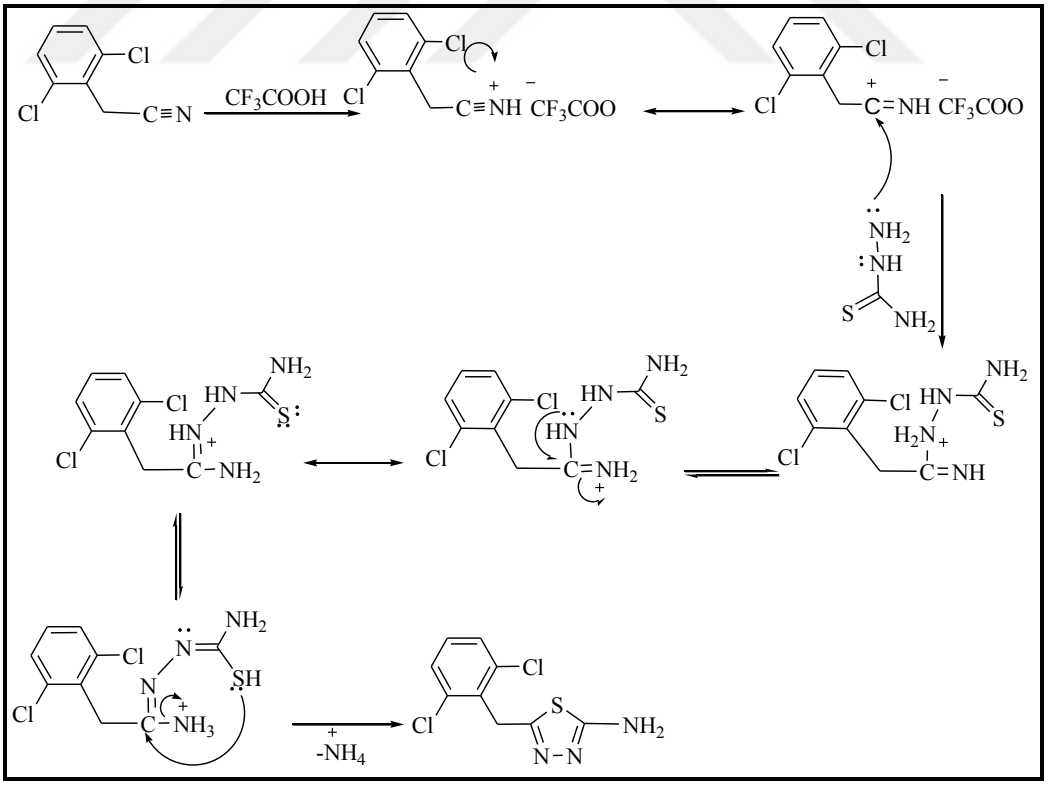


Figure 4.2. Formation mechanism of 2-amino-1,3,4-thiadiazole derivative **(2)**.

IR, ^{1}H-NMR, ^{13}C-NMR and MS spectra of the 2-amino-1,3,4-thiadiazole derivative **(2)** synthesized to illuminate its structure. The spectral data can be found in the experimental part of the article (Part 3) and relevant spectra can be seen in the Annotations section.

In the second part of our experimental trials, the target compound N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-yl)-3,4,5-substituted benzamide derivatives **(4a-n)** were obtained from the reaction of 5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-amine **(2)** with substituted acyl derivatives **(3a-n)** in dry benzene accompanied by pyridine (Figure 4.1). The suggested reaction mechanism related to the formation of these compounds is shown in Figure 4.3.

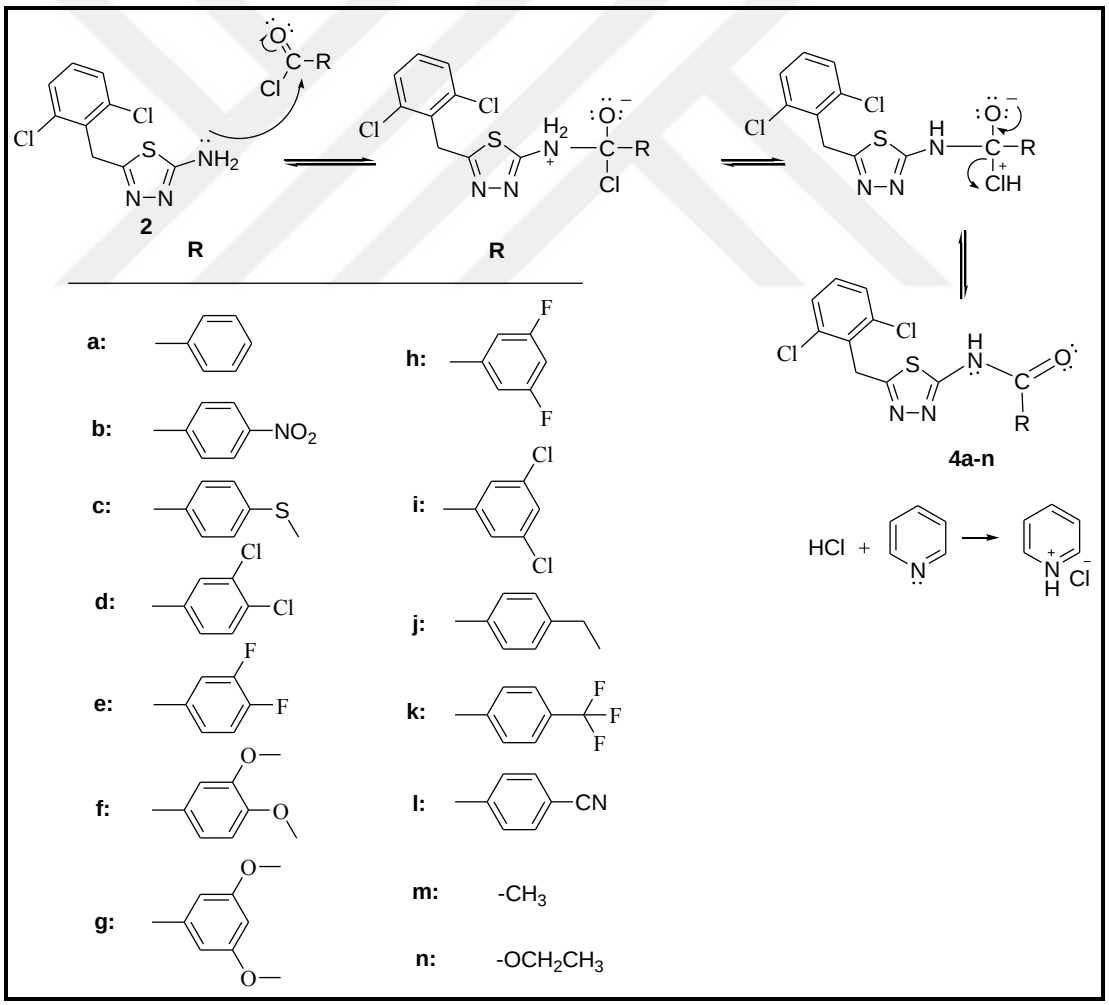


Figure 4.3. Formation mechanism of the target compounds **(4a-n)**.

This reaction is a typical nucleophilic acyl substitution reaction which occurs through nucleophilic addition to and elimination from the carbonyl group. Acyl compounds give displacement reactions as expected, because it is a group bonded to the chloride carbonyl carbon and has sufficient ease of elimination (or turns into a group that eliminates well by protonation). Acyl chlorides usually give reactions by losing the chloride ion. The chloride ion is a very weak base and thus eliminates very well. Lone electron pairs on the nitrogen atom in the amino group of 2-amino-1,3,4-thiadiazole engage in nucleophilic attack on the acyl carbonyl as a nucleophile, and the carbonyl group in the sp^2 hybridized trigonal planar structure turns into a sp^3 hybridized tetrahedral structure with the opening of the double bond on the oxygen atom. Thus, the nucleophilic addition is completed. One of the protons in the amino group passes on to the chloride to facilitate the elimination. Then, the load on the oxygen atom attacks the carbon atom to form a double bond, and eliminate together with hydrogen chloride bond electrons. Hydrogen chloride are kept as pyridinium chloride by pyridin, which is the weak base in the environment.

Structures of the target compounds **(4a-n)** were revealed with FT-IR, ^{1}H NMR, ^{13}C NMR, elemental analysis, and mass spectroscopy. The results can be found in the experimental part of the article (Part 3) and relevant spectra can be seen in the Annotations section.

All of the compounds synthesized were solid and the IR spectra of the original compounds were determined with ATR. ^{1}H-NMR spectra of the compounds synthesized were determined in DMSO-d_6 due to resolution problems. In ^{1}H-NMR spectra, methyl peaks due to DMSO-d_6 were approximately in the 2.50-2.60 ppm range, and water peaks were observed in the 3.20-3.40 ppm range. TMS used in deuterium solvents was taken as the standard chemical slip point in ^{1}H-NMR spectra.

The fact that 2-amino-1,3,4-thiadiazole derivative's **(2)** sharp absorption bands belonging to the -C≡N group observed in the 2200-2250 cm^{-1} range in nitrile derivatives in IR spectrum disappeared and symmetric and asymmetric absorption

bands corresponding to the $–NH_2$ group emerged as two separate bands in the 3258-3098 cm^{-1} range shows that the ring was closed (cyclization).
The stretching band of the -C=N group in the thiadiazole ring was observed at 1582 cm^{-1}. Values for other azomethine stretching bands and aromatic aliphatic stretching bands of 2-amino-1,3,4-thiadiazole compounds and deformation bands of the aromatic ring can be seen in the experimental part.

The structure of the 2-amino-1,3,4-thiadiazole derivative **(2)** was confirmed with ^1H NMR spectroscopy as well. The $–NH_2$ group proton signals of compound **2** bonded to 1,3,4-thiadiazole ring from C-2 position in ^1H NMR spectra were recorded as a singlet corresponding to two protons in the 7.69 ppm range. Proton peaks belonging to the $–NH_2$ group of these compound **(2)** disappeared as a result of proton-deuterium exchange performed with D_2O. The methylene ($–CH_2$) protons bonding the phenyl group to the thiadiazole ring from the 5-position were observed as a singlet corresponding to 2 protons in the 4.40 ppm range. CH protons bonded to the phenyl ring were observed as a doublet corresponding to 2H-proton at 7.49 and a triplet corresponding to 1H-proton at 7.36. This is the most important evidence for the formation of compound 2.

The structure of the 2-amino-1,3,4-thiadiazole derivative **(2)** was confirmed with ^{13}C NMR spectrum as well. The most significant data related to the formation of the 2-amino-1,3,4-thiadiazole ring is the similarity between ^{13}C-NMR data and resonance values of the carbons at thiadiazole C-2 and C-5 positions in these compounds and similar compounds [68]. C-2 carbon signals of the 2-amino-1,3,4-thiadiazole ring in these compounds were recorded at 154.37 ppm and C-5 carbon signals were recorded at 169.39 ppm. Other spectral data belonging to the carbon skeleton of the molecule fully support the suggested structures.

In the second part of our study, the target compounds **(4a-n)** were obtained from the reaction of acetylchloride with 2-amino-1,3,4-thiadiazole derivatives in presence of pyridine within dry benzene solvent.

In terms of IR spectrum values of these compounds, symmetrical and asymmetrical stretching bands corresponding to the $–NH_2$ group of the initial compound and observed at two separate bands at 3258-3098 cm^{-1} were replaced by –NH stretching bands observed at 3186-3121 cm^{-1}, which is one of the most important evidences for the acylation of these compounds. Another evidence is C=O stretching band peaks observed at 1720-1661 cm^{-1} with the acylation of 2-amino-1,3,4-thiadiazole. The appearance of –NH and C=O stretching bands in IR spectra of compounds **(4a-n)** clearly shows that the amino group was acylated at the 2-position of 2-amino-1,3,4-thiadiazole. Peaks showing the bonding points of aromatic, aliphatic, azomethine, and substituted groups bonded to the aromatic ring can be seen in the experimental part.

Also, the ^{1}H-NMR spectrum data of the target compounds **(4a-n)** show that $–NH_2$ proton signals bonded to the 2-amino-1,3,4-thiadiazole ring at the C-2 position observed at 7.69 ppm disappeared.

Instead, the target compounds **(4a-n)** were observed as a singlet corresponding to a proton at 13.40-12.82 ppm indicating -NH signals, which is the most significant evidence for the acylation of 2-amino-1,3,4-thiadiazole **(2)** ring. This is consistent with the literature as well [59].

The peak of the 2-amino group observed at 7.69 ppm shifted to high values at 13.40-12.82 ppm due to electron attracting property of the carbonyl group, which is one of the considerable evidences for this structure. Other ^{1}H NMR spectrum data of these compounds is given in the experimental part of this study in detail.

C=O carbonyl group peaks are observed at 169.01-162.49 ppm in ^{13}C NMR spectrum of these compounds. The fact that this value was found in ^{13}C NMR spectrum is seen as an important evidence that the amino group at the 2-position of the thiadiazole ring was acylated. C-2 carbon peaks for the 1,3,4-thiadiazole ring in the target compounds **(4a-n)** were observed in the 159.65-161.47 ppm range, and C-5 carbon peaks were observed in the 160.72-163.66 ppm range. In these spectra, sp^3 hybridized S-CH_3 carbons appeared at 14.95 ppm in compound 4b, whereas $–OCH_3$

carbon peaks in compounds 4f and 4g resonated in the lower region due to the electronegativity of the oxygen atom and were observed in the 56.10-56.17 ppm range due to Sp^3 hybridized methylene carbons which bonds the thiadiazole ring to the aromatic ring in these compounds were observed in the 31.76-31.87 ppm range. These data belonging to the compounds are highly compatible with the literature.

The MS spectral data for compounds **2** and **4a-n** are as follows: 260 (M^+, 74) and 261 (M+1, 51) for compound **2**, 363.68 (M-1, 100) and 365.85 (M+1, 84) for compound **4a**, 408.93 (M^+, 100) and 410.96 (M+1, 93) for compound **4b**, 411,38 (M+1, 26) and 413,34 (M+2, 48) for compound **4c**, 433.71 (M+1, 100) for compound **4d,** 400.00 (M^+, 74) and 402.26 (M+2, 54) for compound **4e**, 423.91 (M^+, 100) and 425.87 (M+2, 66) for compound **4f**, 423.91 (M^+, 100) for compound **4g**, 399.80 (M-1, 100), 401.83 (M+1, 74) for compound **4h**, 431.79 (M-1, 56) for compound **4i**, 393.77 (M+1, 53) for compound **4j**, 431.86 (M-1, 82) for compound **4k**, 431.86 (M-1, 82) for compound **4l**, 302.01 (M^+, 55) for compound **4m** and 331.14 (M-1, 43) for compound **4n** which are compatible with the suggested structure.

ADDITIONAL EXPLANATIONS A COMPOUNDS' ^{1}H NMR SPECTRA

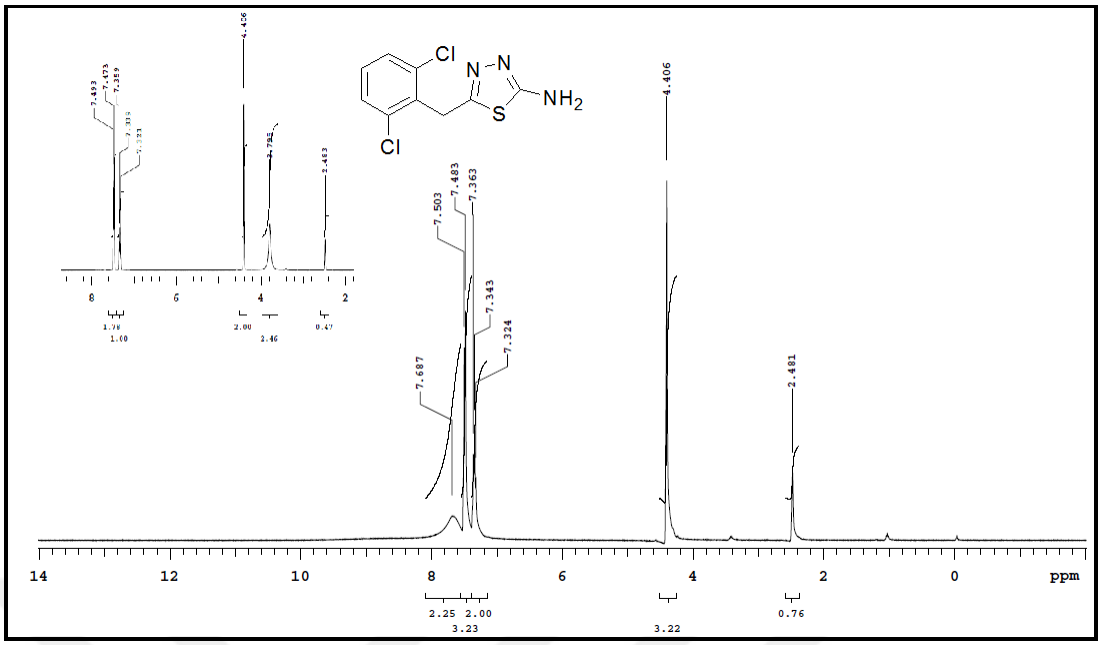


Figure Annex A.1. ^{1}H NMR spectra for 5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-amine **(2)** compound (DMSO-d_6)

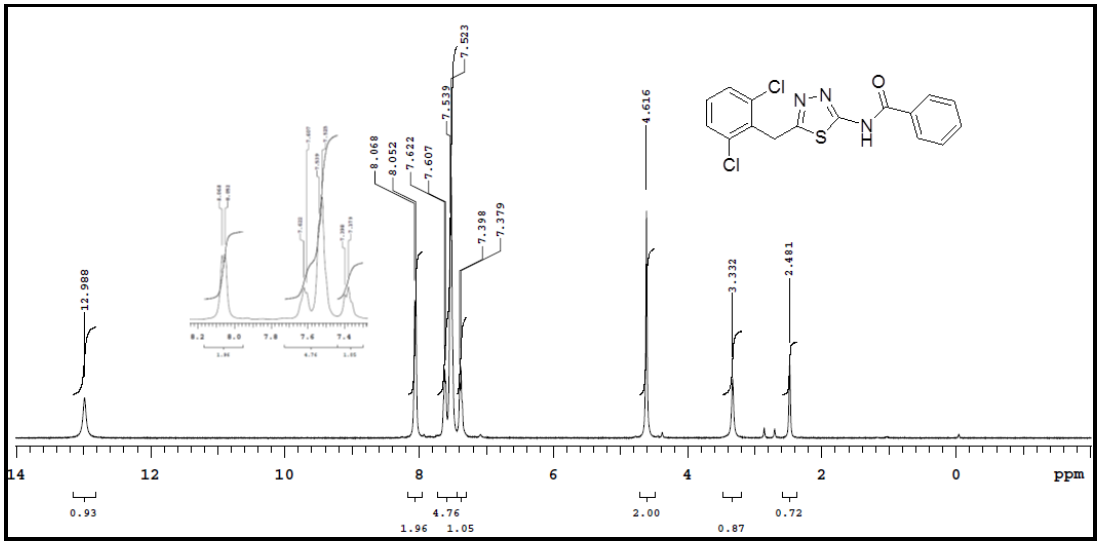


Figure Annex A.2. ^{1}H NMR spectra for N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-yl) benzamide **(4a)** compound (DMSO-d_6).

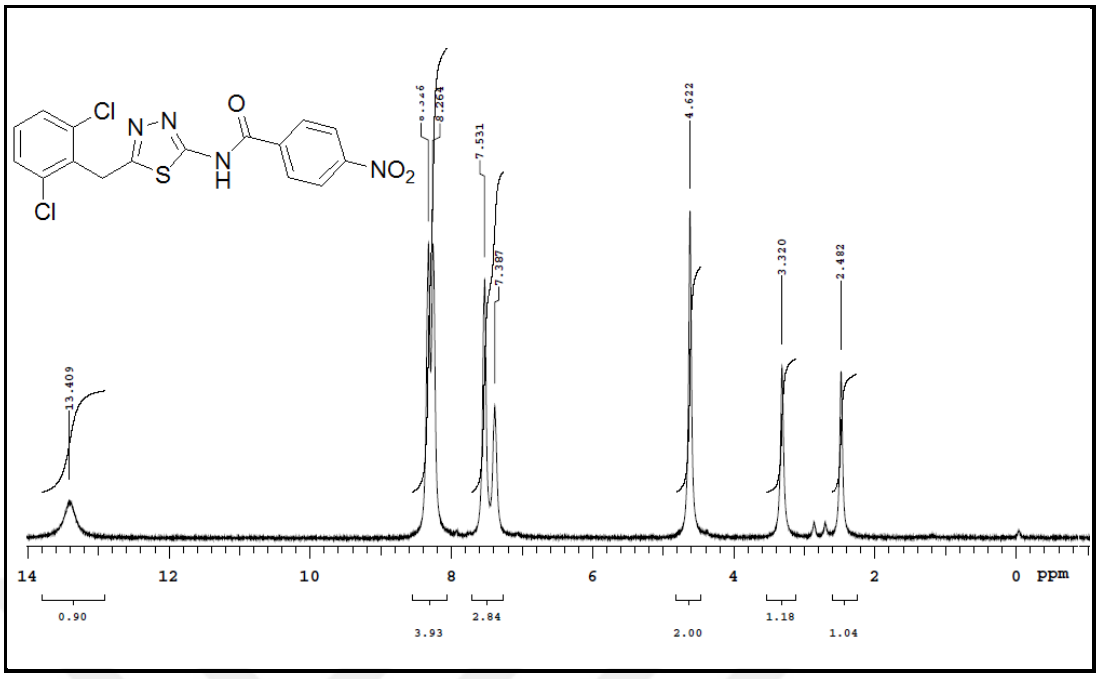


Figure Annex A.3. ^{1}H NMR spectra for N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-yl)-4-nitrobenzamide **(4b)** compound (DMSO-d_6)

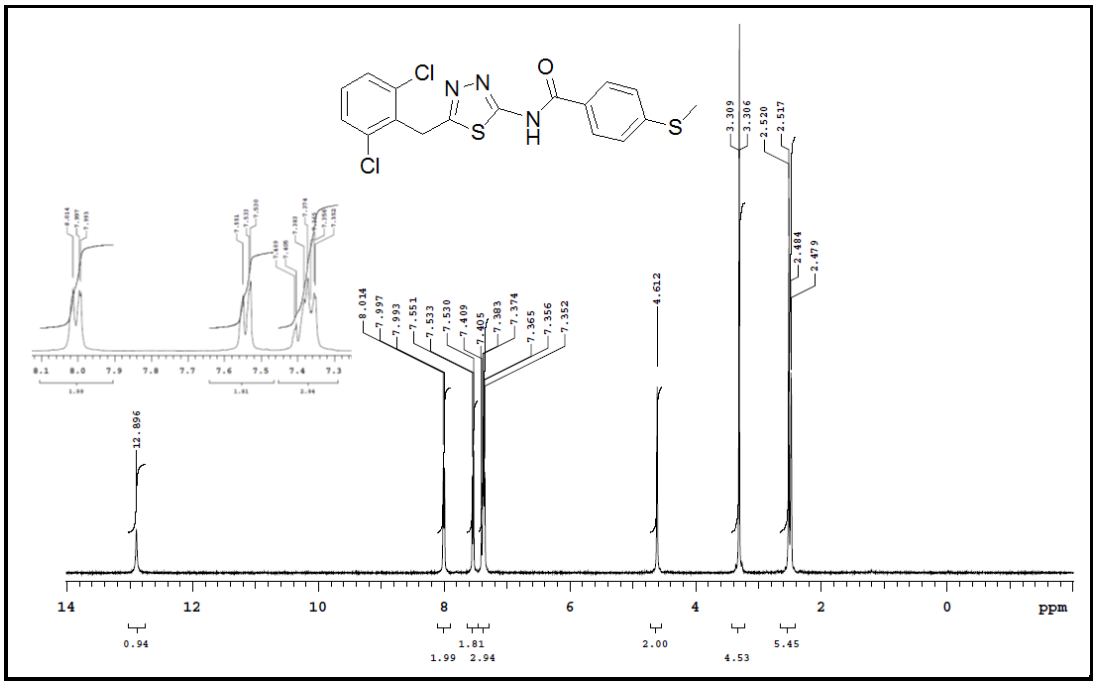


Figure Annex A.4. ^{1}H NMR spectra for N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-yl)-4-(methylthio) benzamide **(4c)** compound (DMSO-d_6).

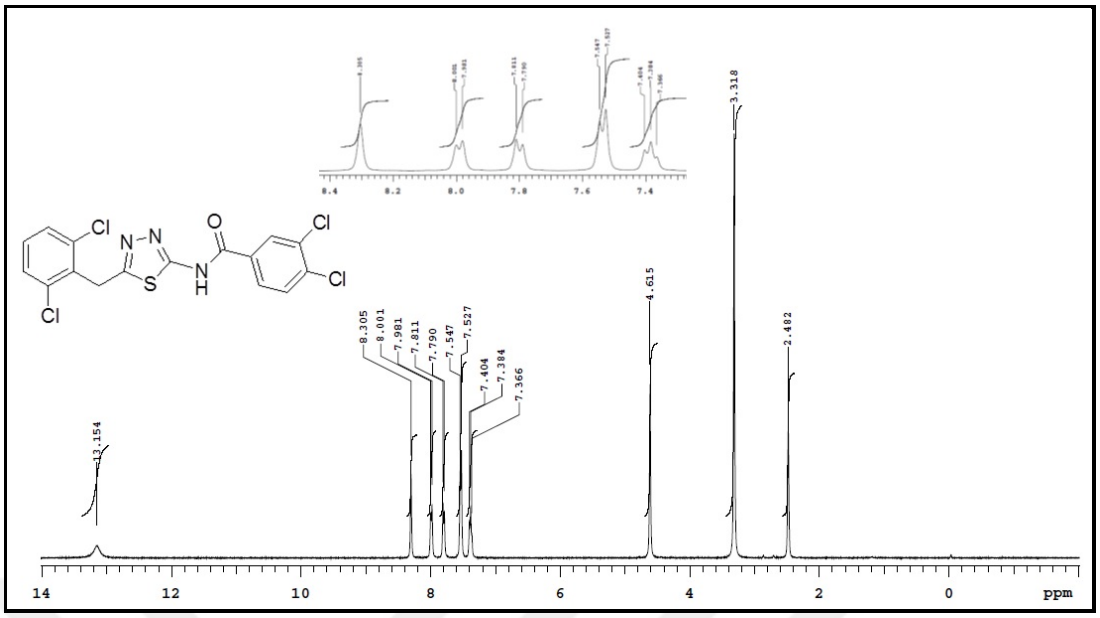


Figure Annex A.5. ^{1}H NMR spectra for N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-yl)-3,4-dichloro benzamide **(4d)** compound (DMSO-d_6).

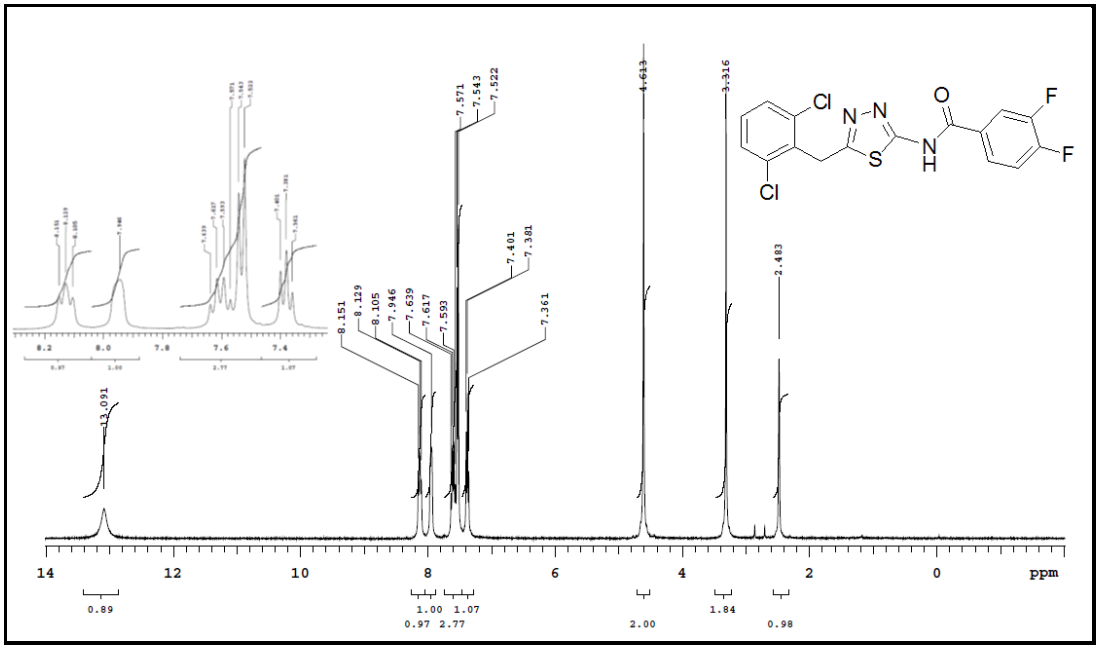


Figure Annex A.6. ^{1}H NMR spectra for N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-yl)-3,4-difluoro benzamide **(4e)** compound (DMSO-d_6).

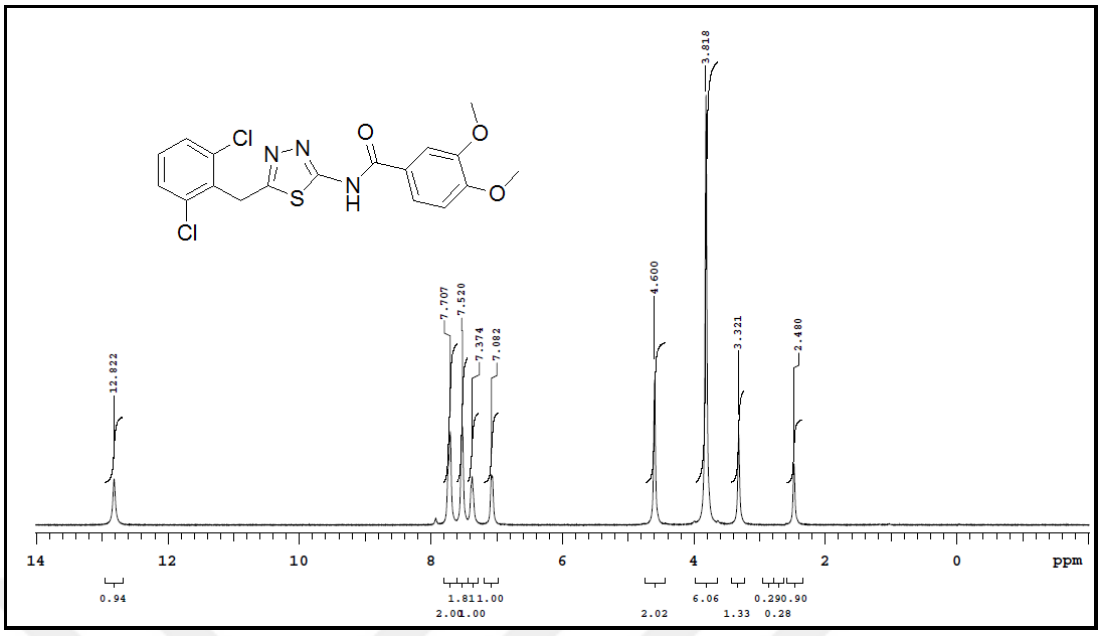


Figure Annex A.7. ^{1}H NMR spectra for N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-yl)-3,4-dimethoxy benzamide **(4f)** compound (DMSO-d_6).

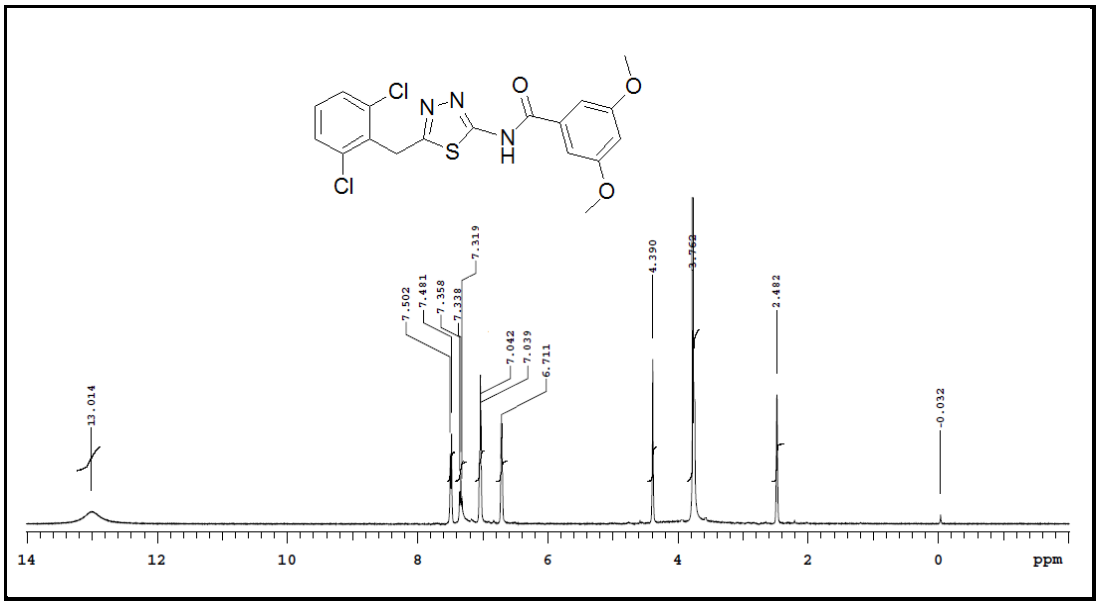


Figure Annex A.8. ^{1}H NMR spectra for N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-yl)-3,5-dimethoxy benzamide **(4g)** compound (DMSO-d_6).

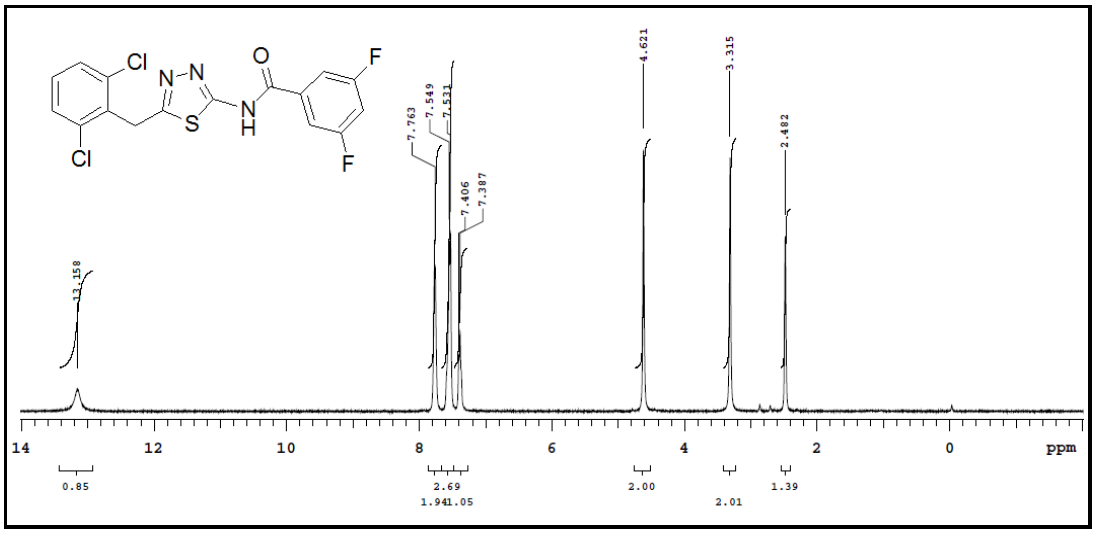


Figure Annex A.9. ^{1}H NMR spectra for N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-yl)-3,5-difluoro benzamide **(4h)** compound (DMSO-d_6).

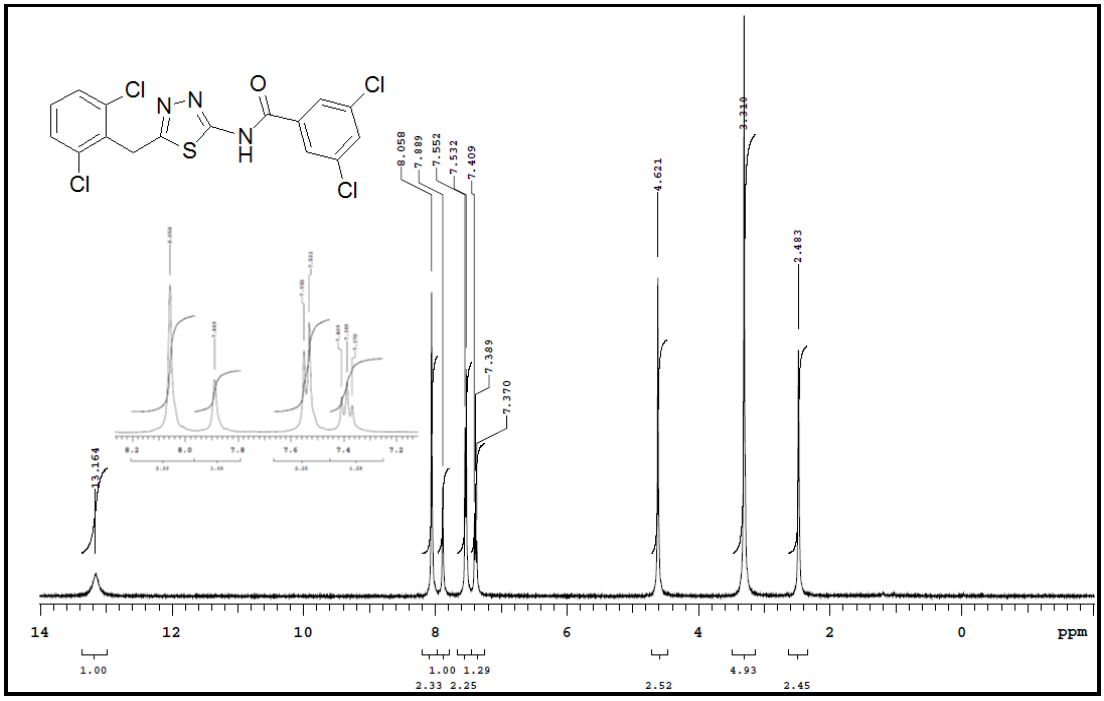


Figure Annex A.10. ^{1}H NMR spectra for N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-yl)-3,5-dichloro benzamide **(4i)** compound (DMSO-d_6).

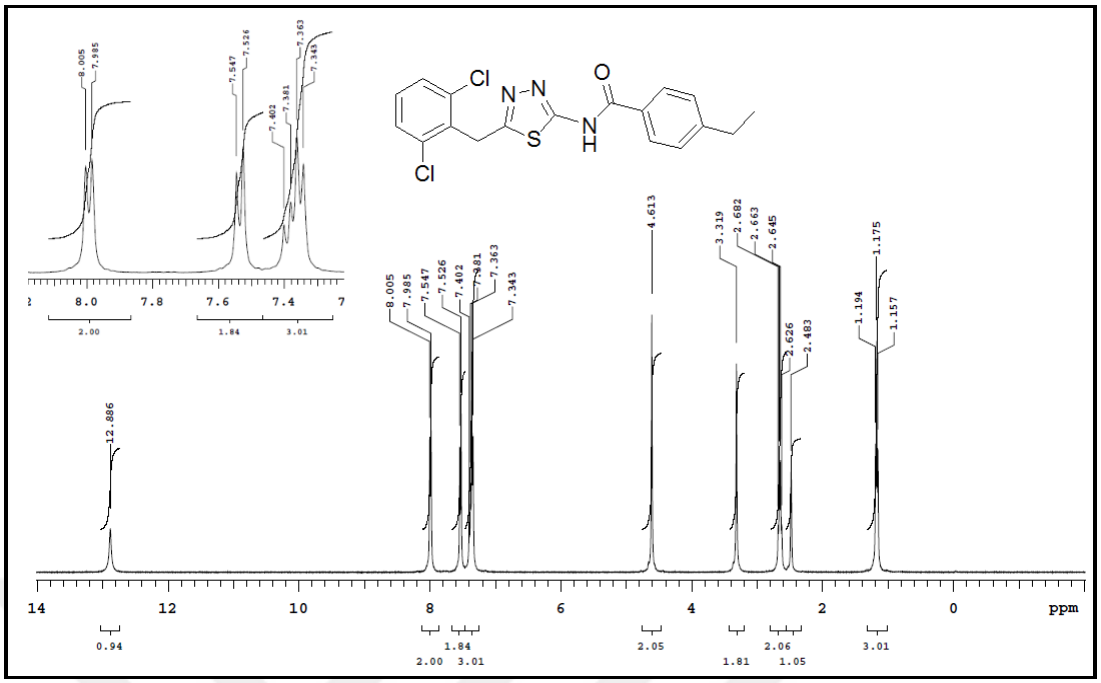


Figure Annex A.11. ^{1}H NMR spectra for N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-yl)-4-ethylbenzamide **(4j)** compound (DMSO-d_6).

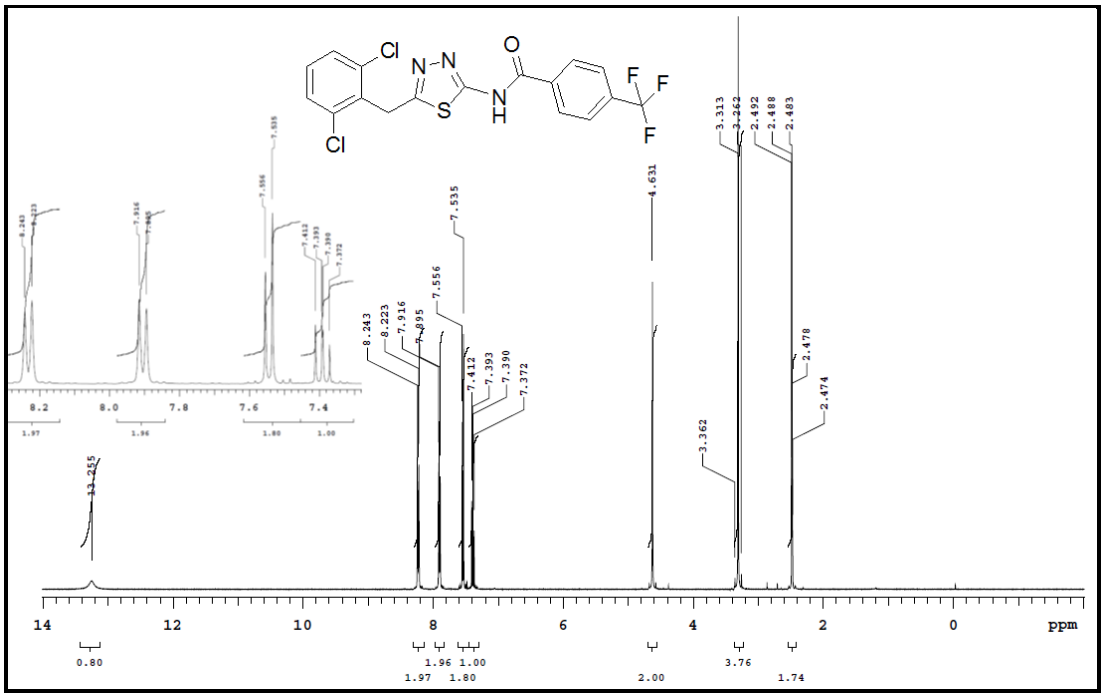


Figure Annex A.12. ^{1}H NMR spectra for N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-yl)-4-(trifluoromethyl) benzamide **(4k)** compound (DMSO-d_6).

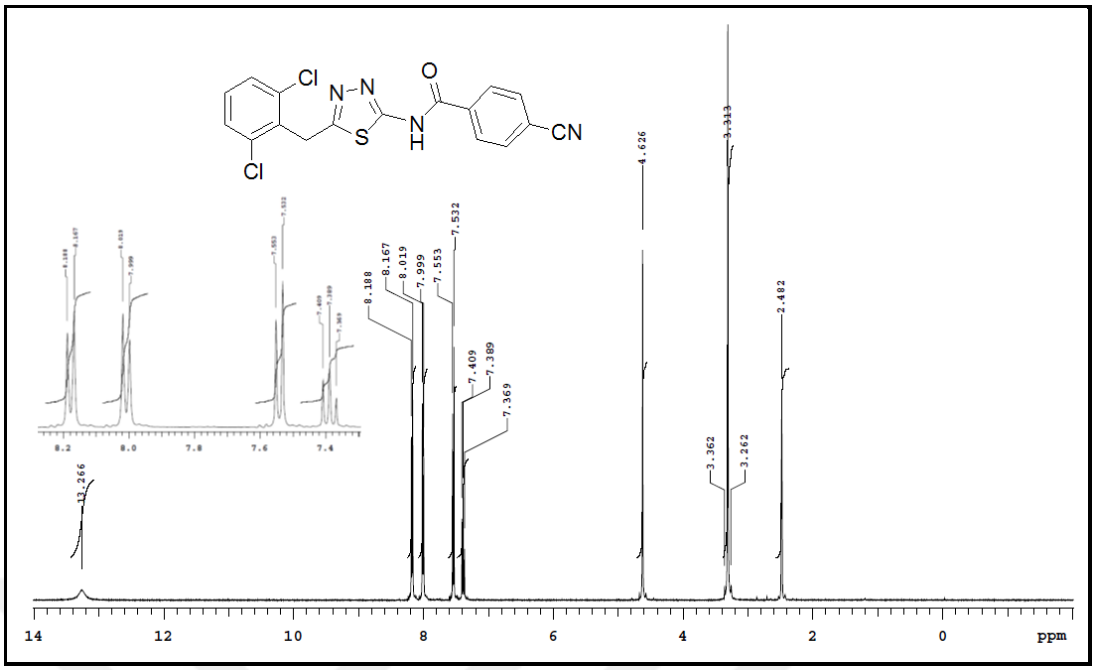


Figure Annex A.13. ^{1}H NMR spectra for N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-yl)-4-cyanobenzamide **(4l)** compound (DMSO-d_6).

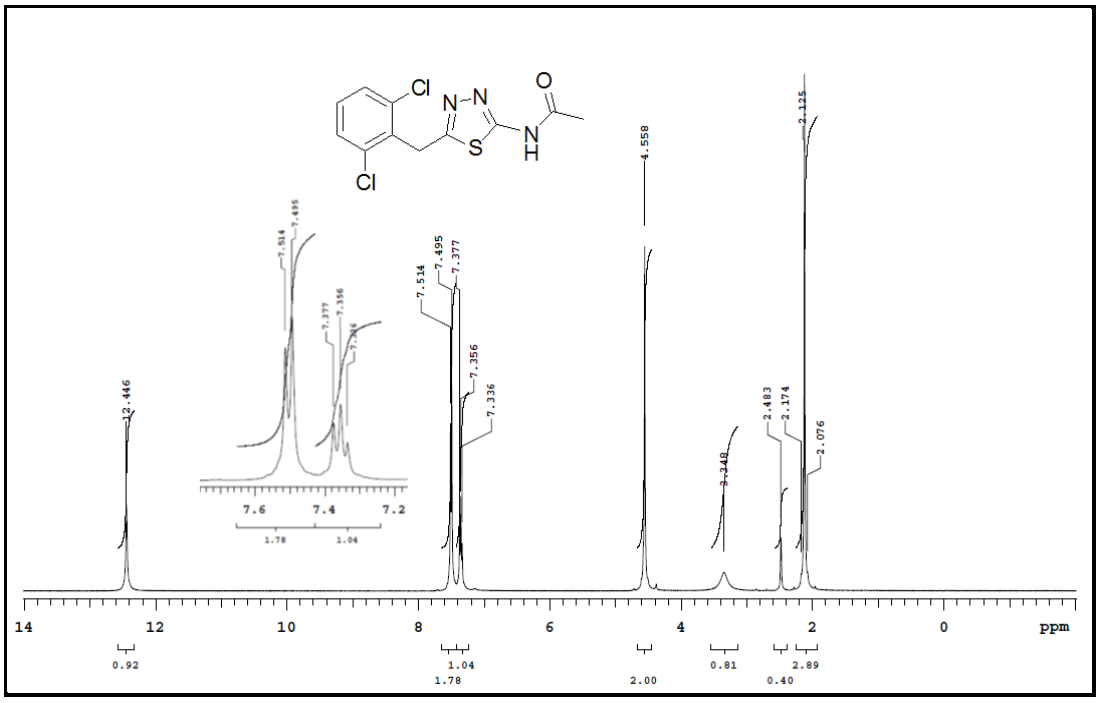


Figure Annex A.14. ^{1}H NMR spectra for N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-yl)acetamide **(4m)** compound (DMSO-d_6).

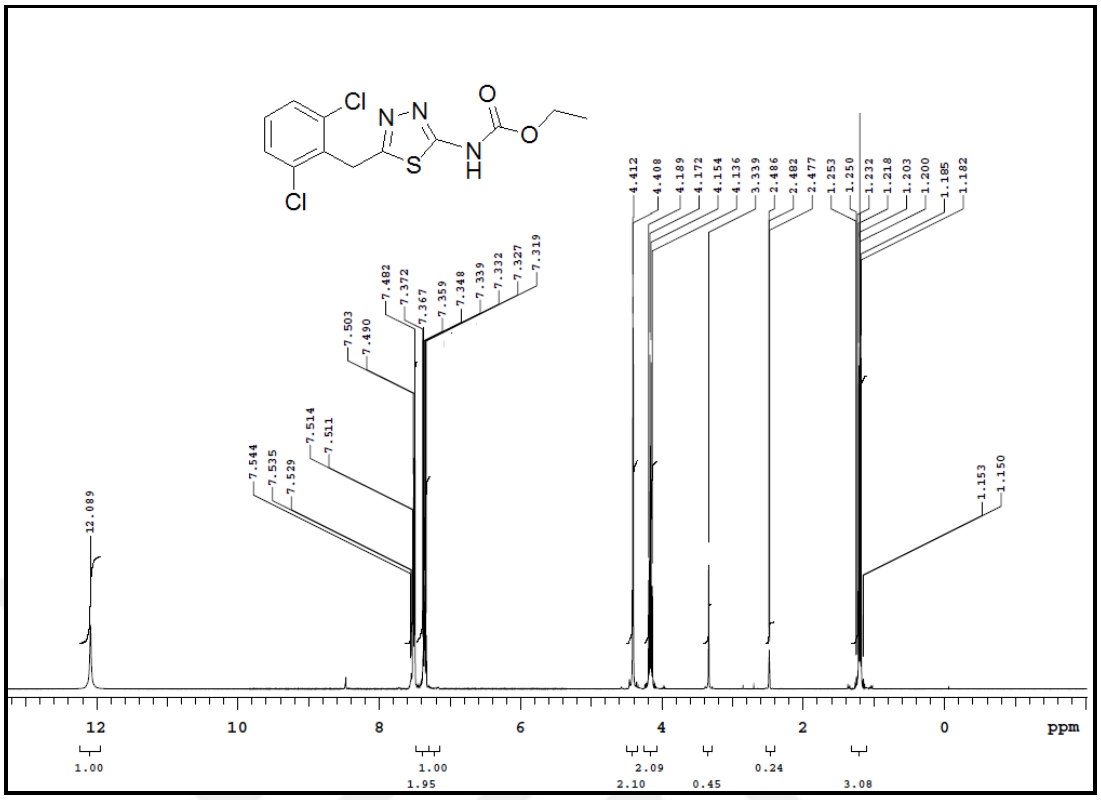


Figure Annex A.15. ^{1}H NMR spectra for Ethyl 5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-ylcarbamate **(4n)** compound (DMSO-d_6).

ADDITIONAL EXPLANATIONS B
COMPOUNDS' ^{13}C NMR SPECTRA

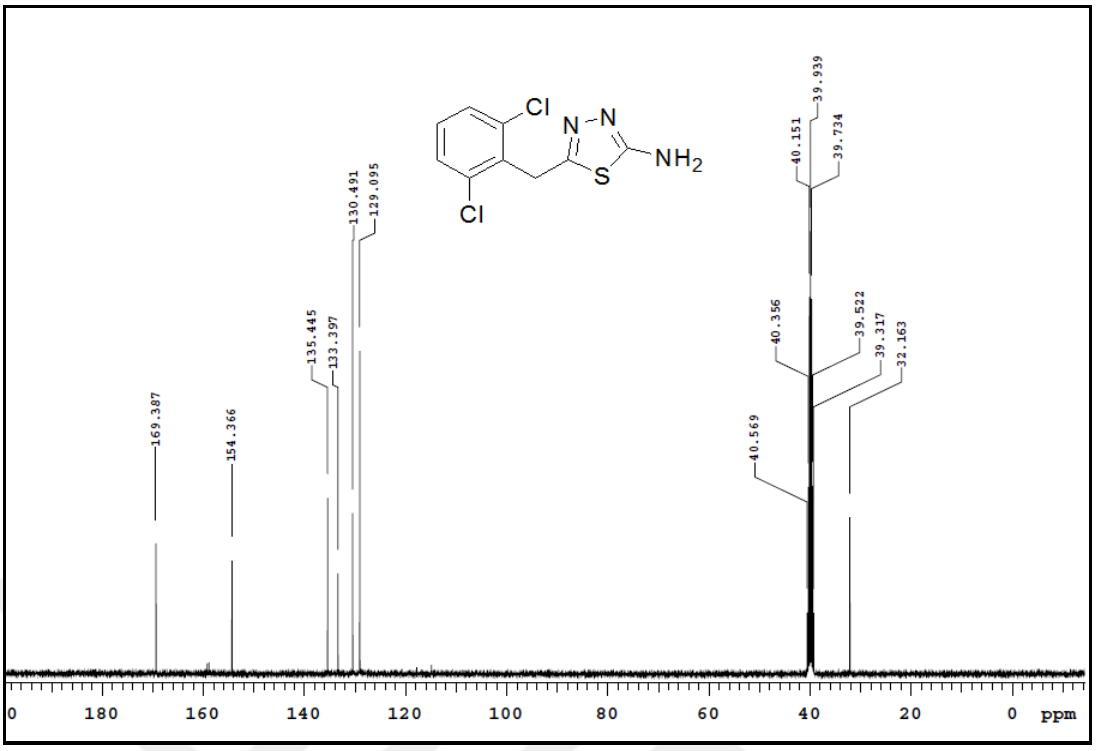


Figure Annex B.1. ^{13}C NMR spectra for 5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-amine **(2)** compound (DMSO-d_6).

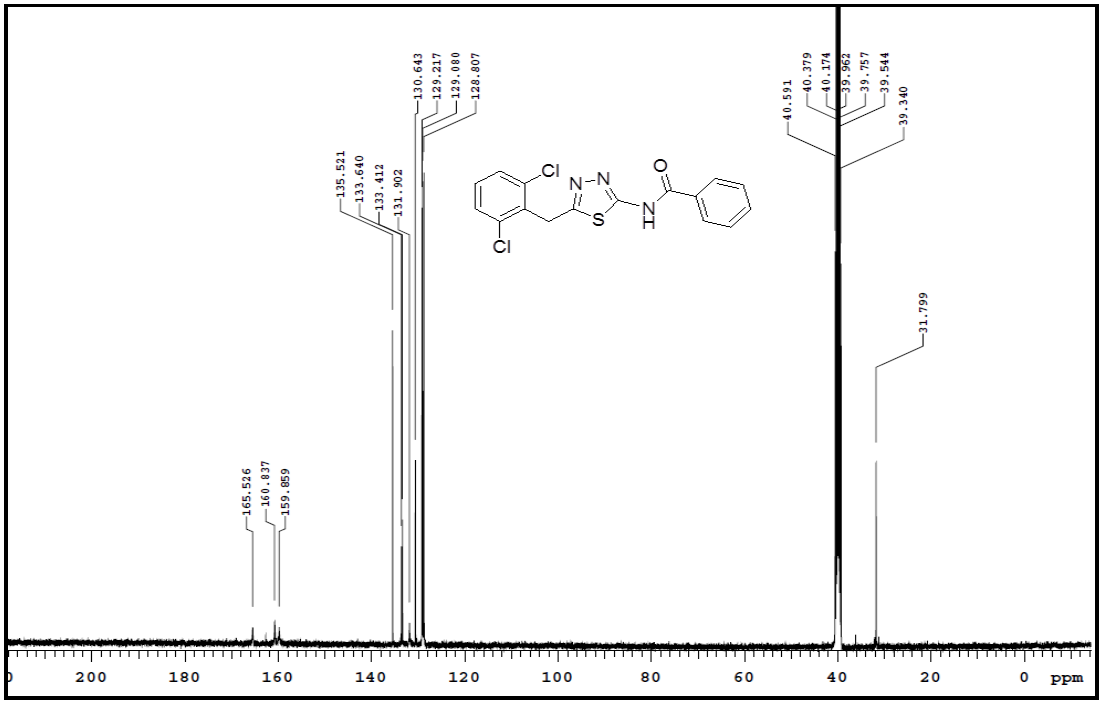


Figure Annex B.2. ^{13}C NMR spectra for N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-yl)benzamide **(4a)** compound (DMSO-d_6).

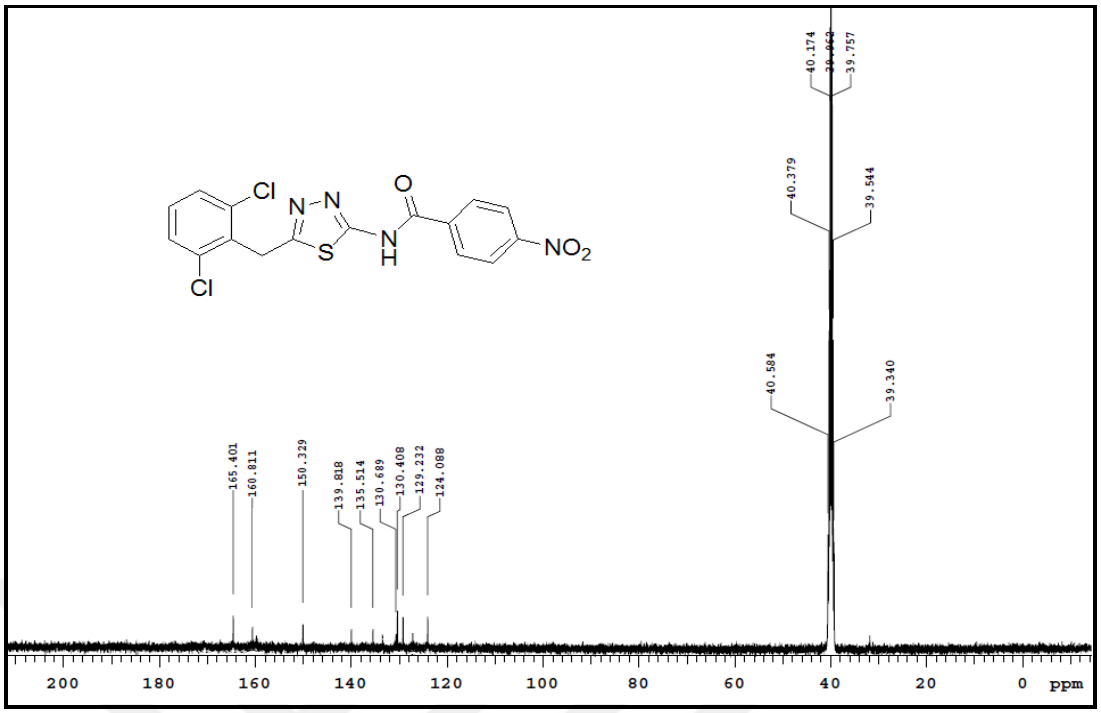


Figure Annex B.3. ^{13}C NMR spectra for N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-yl)-4-nitrobenzamide **(4b)** compound (DMSO-d_6).

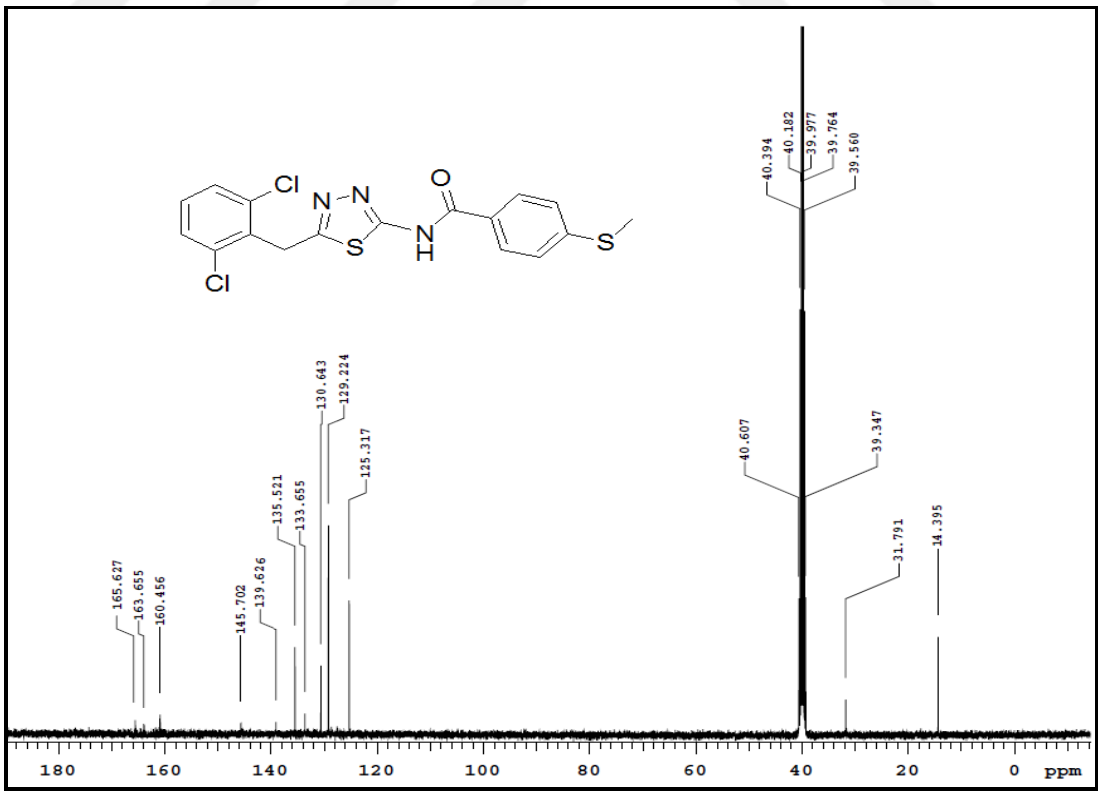


Figure Annex B.4. ^{13}C NMR spectra for N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-yl)-4-(methylthio) benzamide **(4c)** compound (DMSO-d_6).

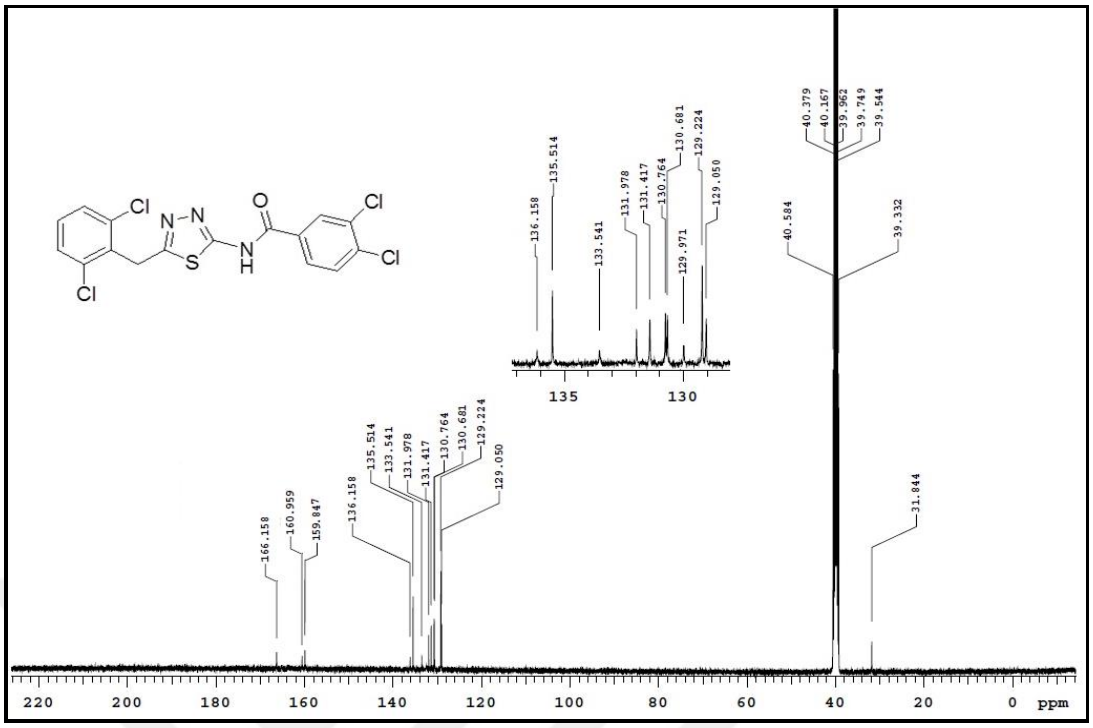


Figure Annex B.5. ^{13}C NMR spectra for N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-yl)-3,4-dichloro benzamide **(4d)** compound (DMSO-d_6).

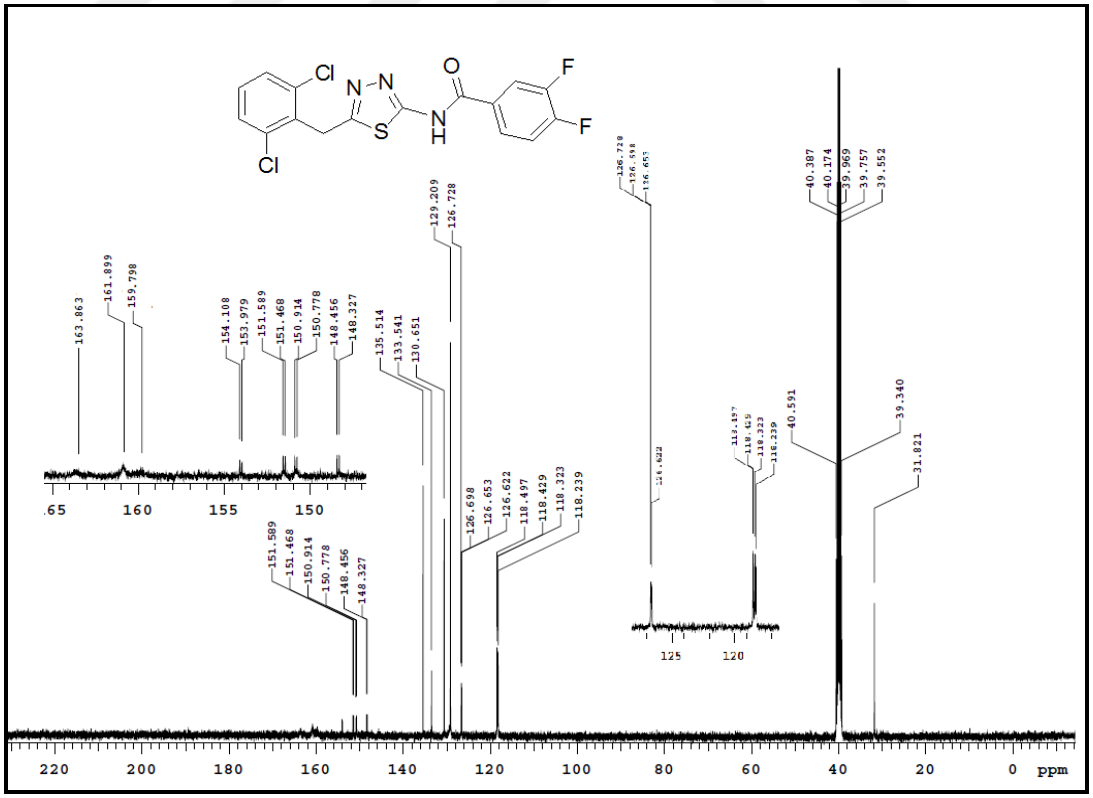


Figure Annex B.6. ^{13}C NMR spectra for N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-yl)-3,4-difluoro benzamide **(4e)** compound (DMSO-d_6).

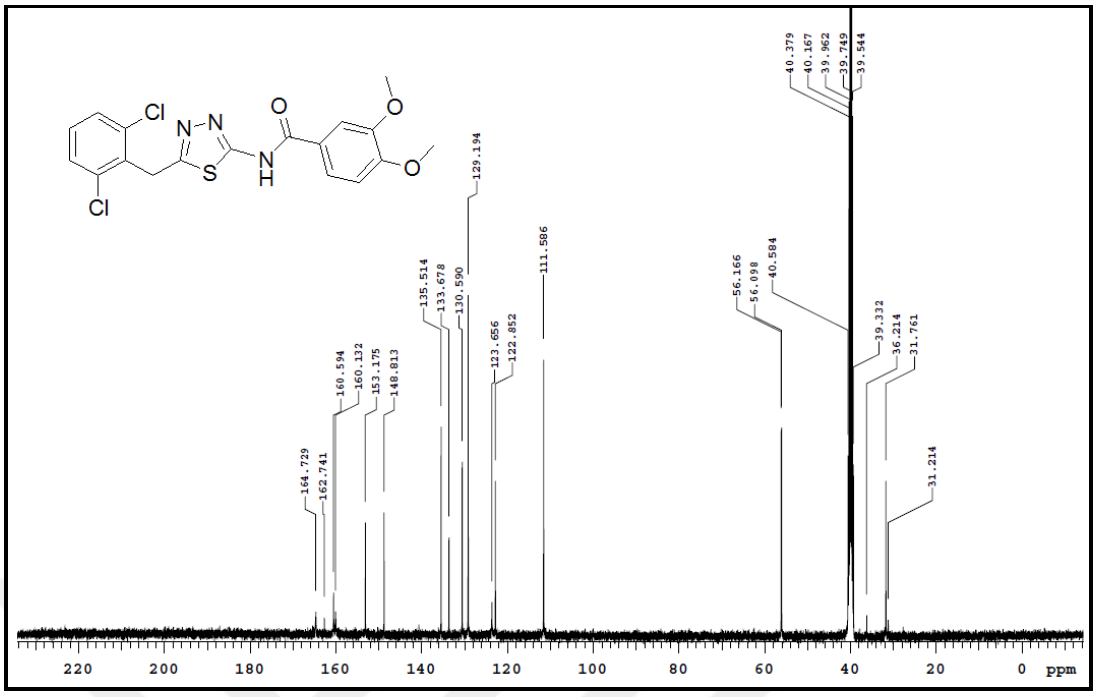


Figure Annex B.7. ^{13}C NMR spectra for N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-yl)-3,4-dimethoxy benzamide **(4f)** compound (DMSO-d_6).

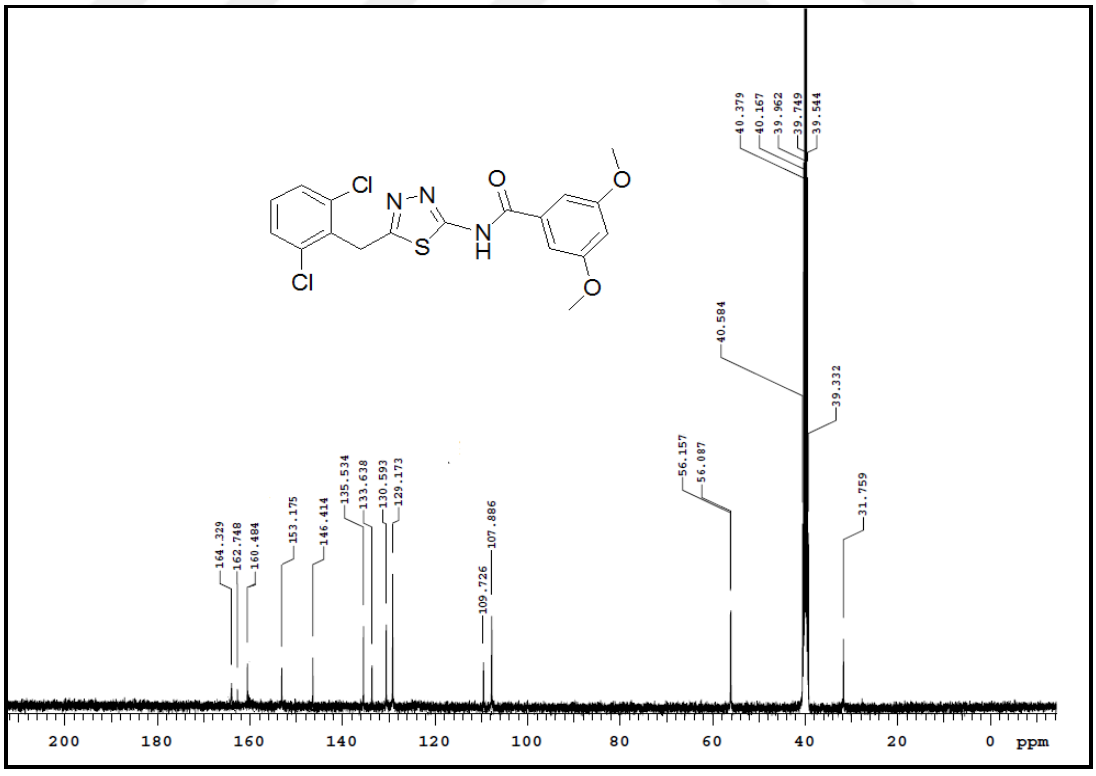


Figure Annex B.8. ^{13}C NMR spectra for N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-
2-yl)-3,5-dimethoxy benzamide **(4g)** compound (DMSO-d_6).

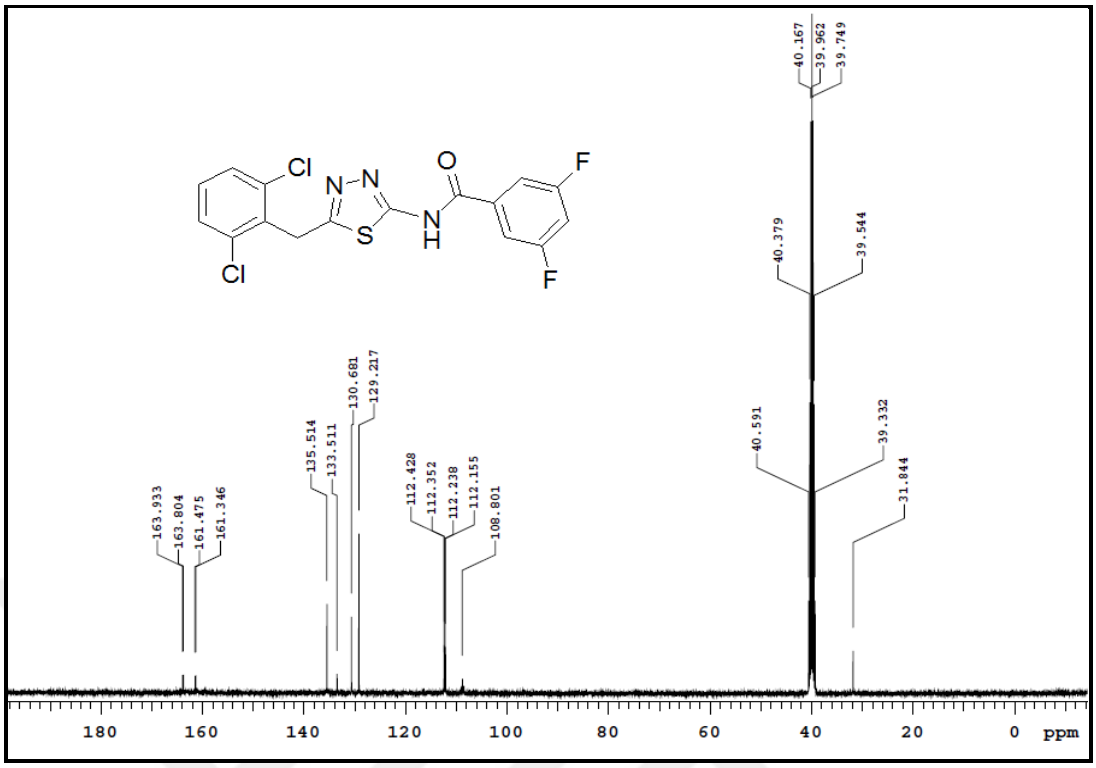


Figure Annex B.9. ^{13}C NMR spectra for N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-yl)-3,5-difluoro benzamide **(4h)** compound (DMSO-d_6).

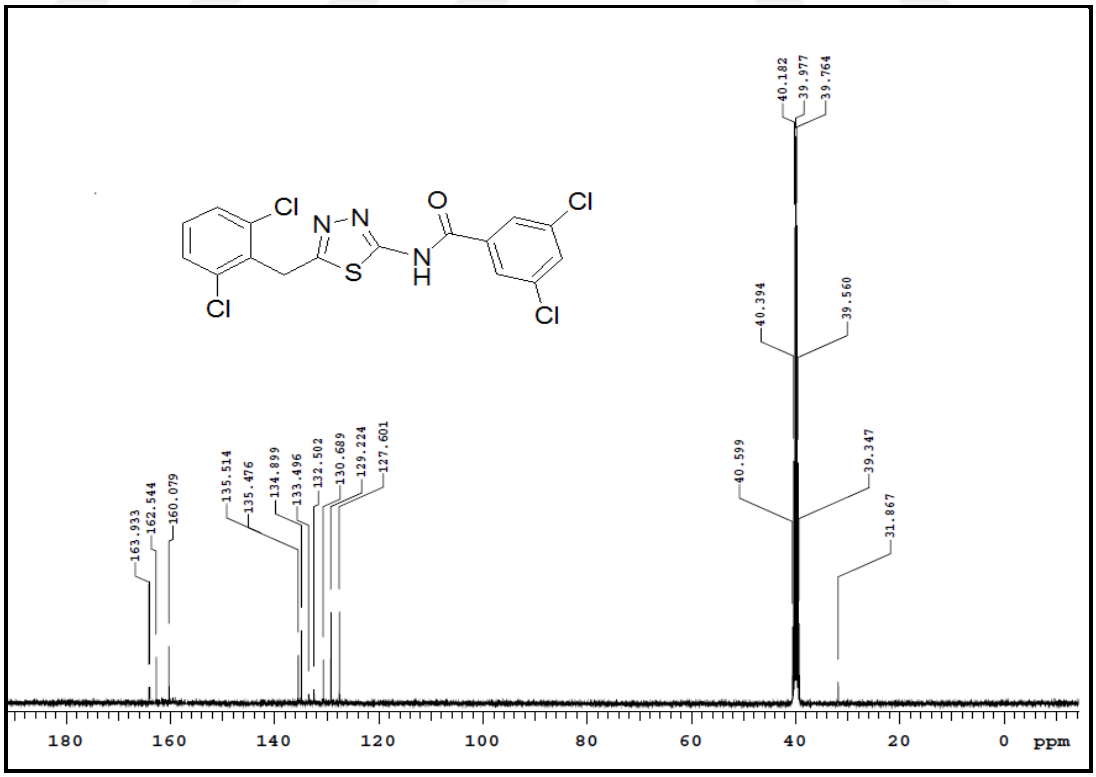


Figure Annex B.10. ^{13}C NMR spectra for N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-yl)-3,5-dichloro benzamide **(4i)** compound (DMSO-d_6).

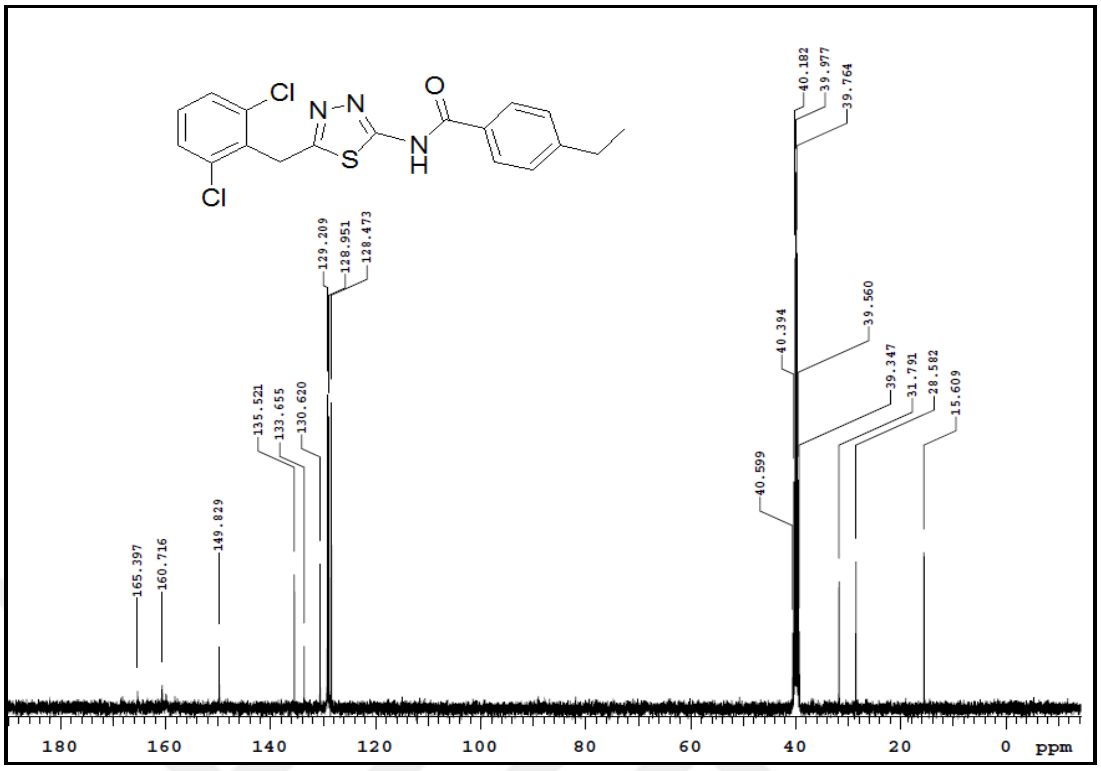


Figure Annex B.11. ^{13}C NMR spectra for N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-yl)-4-ethylbenzamide **(4j)** compound (DMSO-d_6).

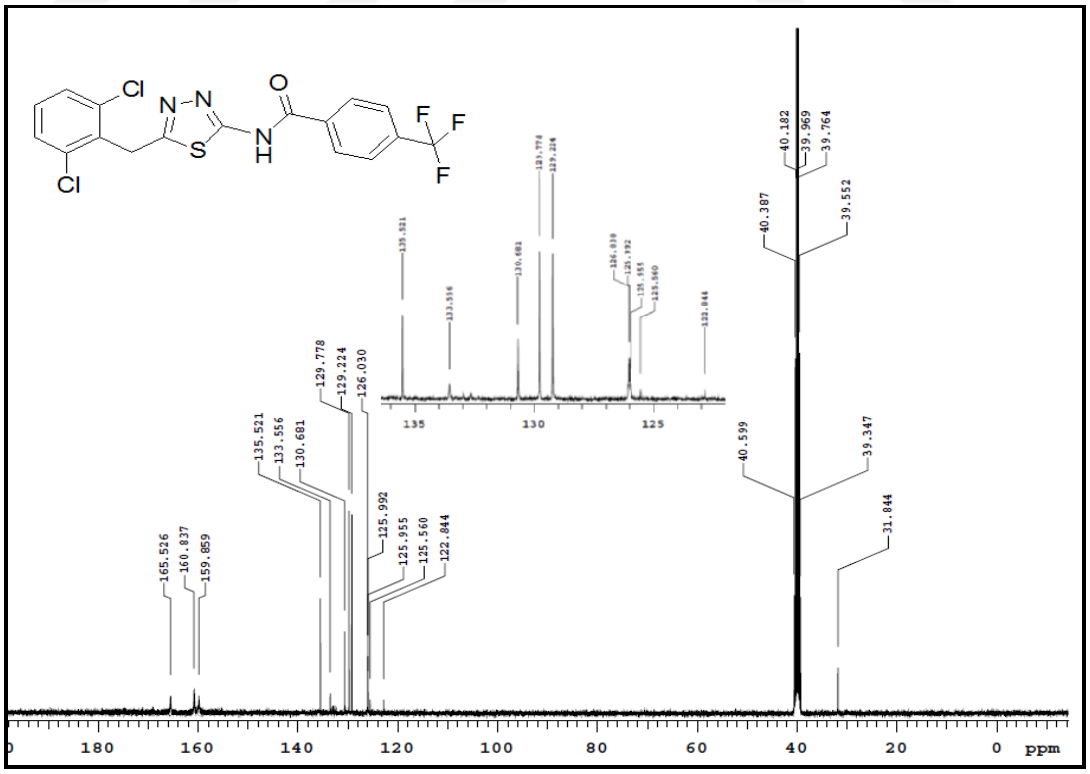


Figure Annex B.12. ^{13}C NMR spectra for N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-yl)-4-(trifluoromethyl) benzamide **(4k)** compound (DMSO-d_6).

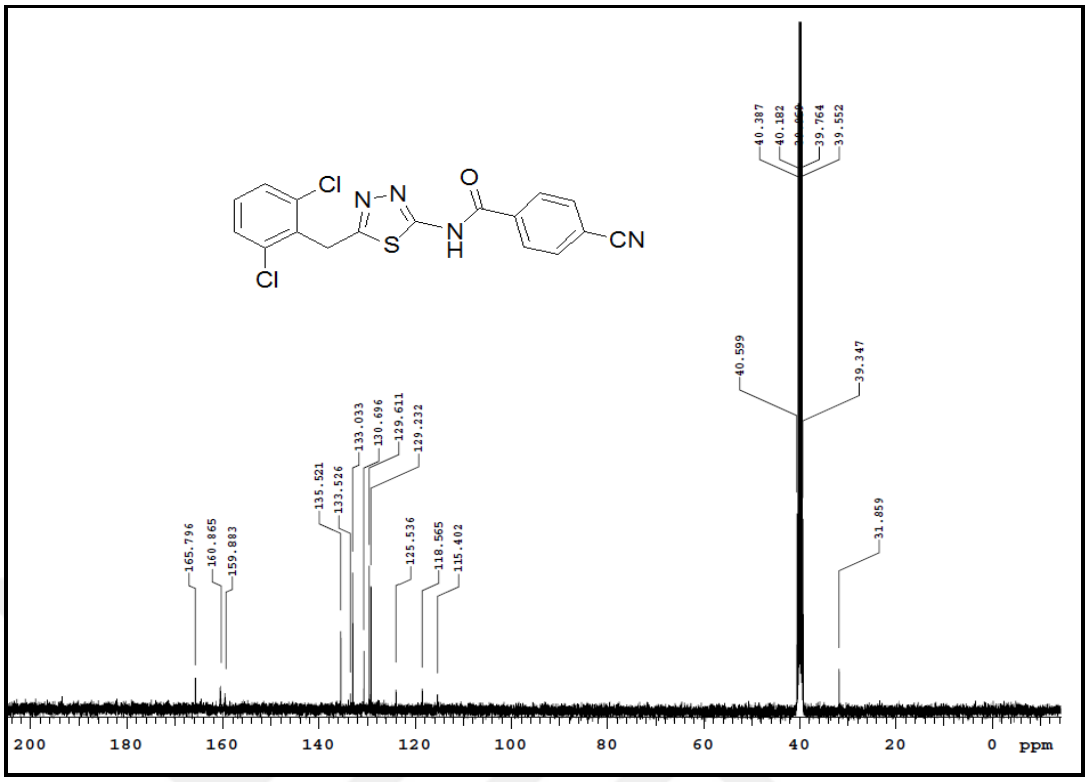


Figure Annex B.13. ^{13}C NMR spectra for N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-yl)-4-cyanobenzamide **(4l)** compound (DMSO-d_6).

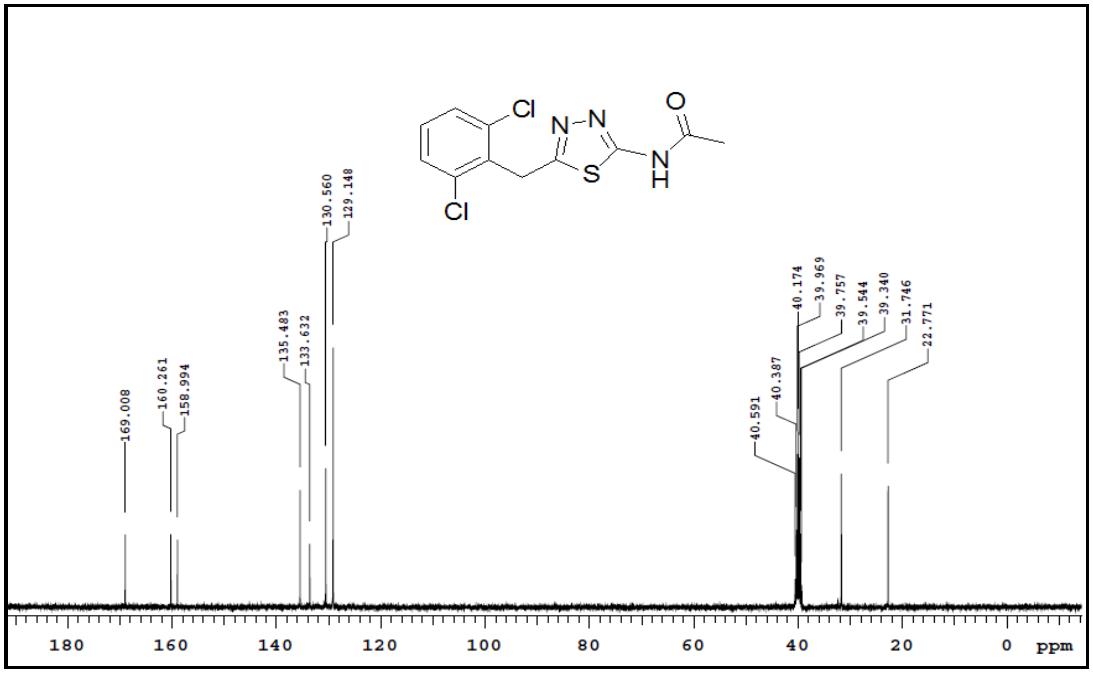


Figure Annex B.14. ^{13}C NMR spectra for N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-yl)acetamide **(4m)** compound (DMSO-d_6).

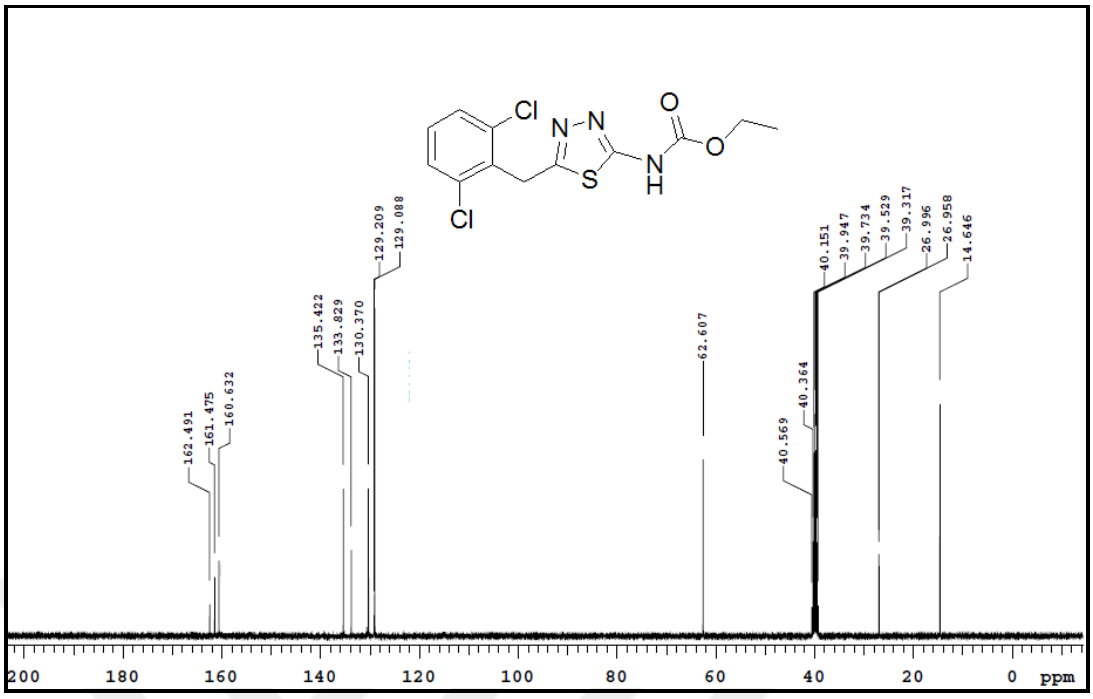


Figure Annex B.15. ^{13}C NMR spectra for Ethyl 5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-ylcarbamate **(4n)** compound (DMSO-d_6).

ADDITIONAL EXPLANATIONS C
COMPOUNDS' FT-IR SPECTRA

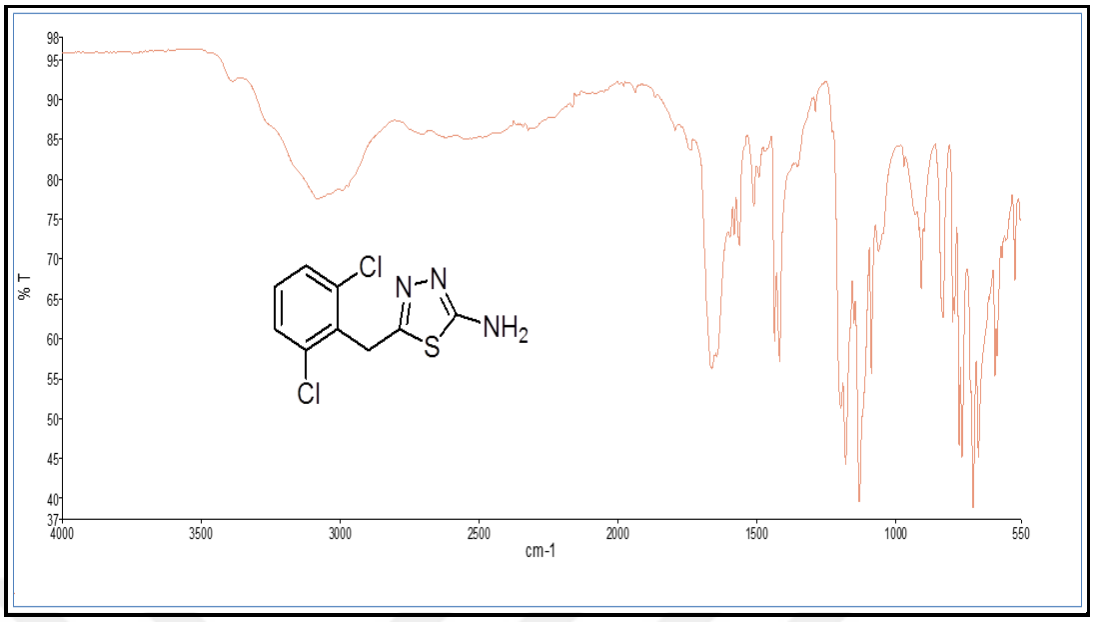


Figure Annex C.1. IR spectra for 5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-amine **(2)** compound.

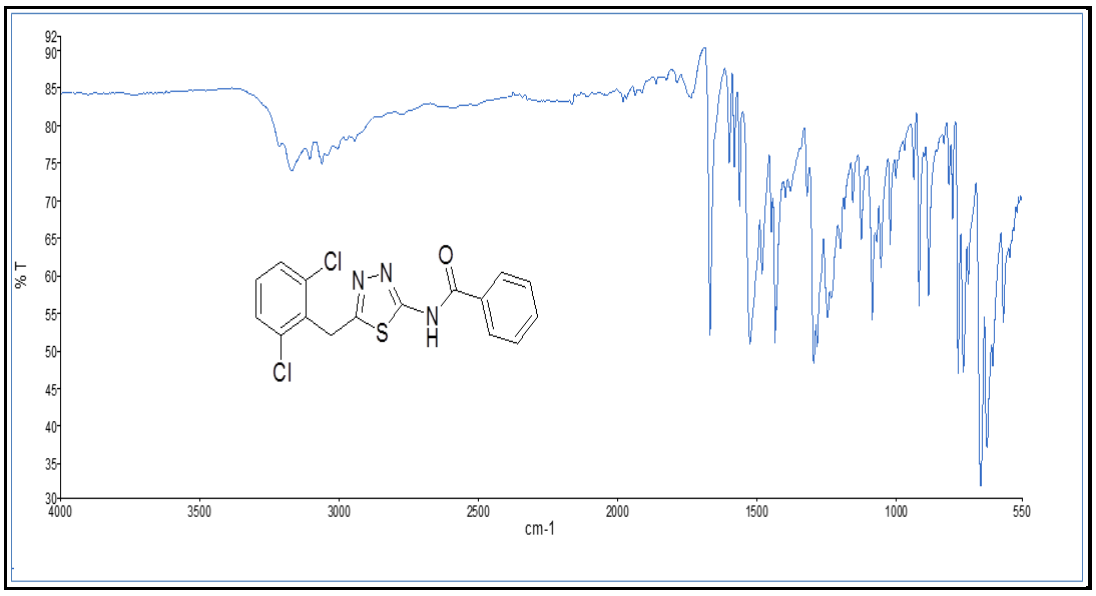


Figure Annex C.2. IR spectra for N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-yl)benzamide **(4a)** compound.

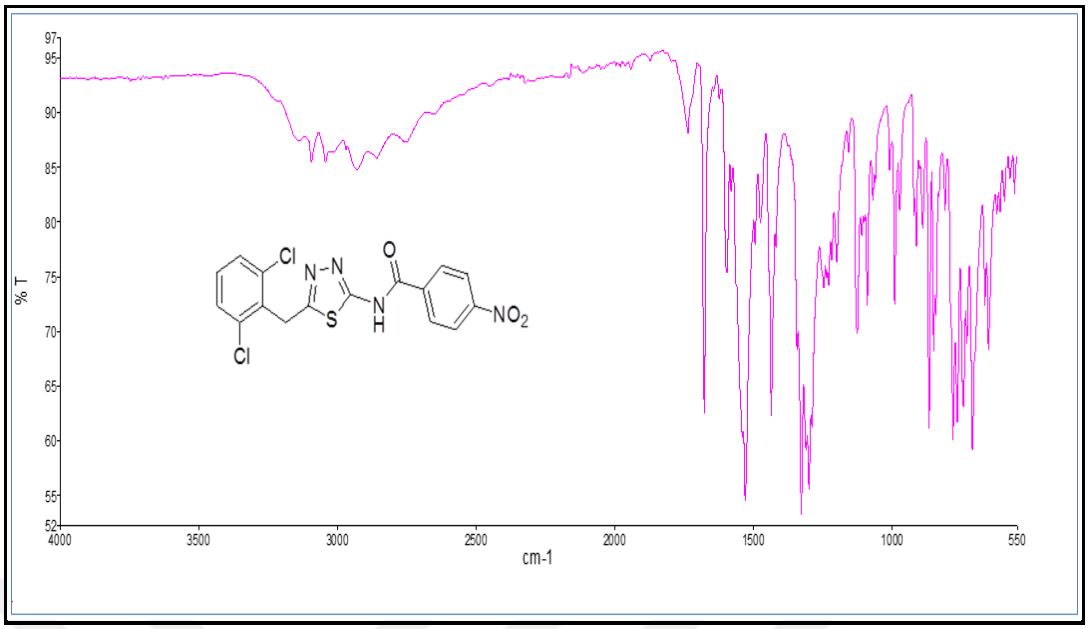


Figure Annex C.3. IR spectra for N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-yl)-4-nitrobenzamide **(4b)** compound.

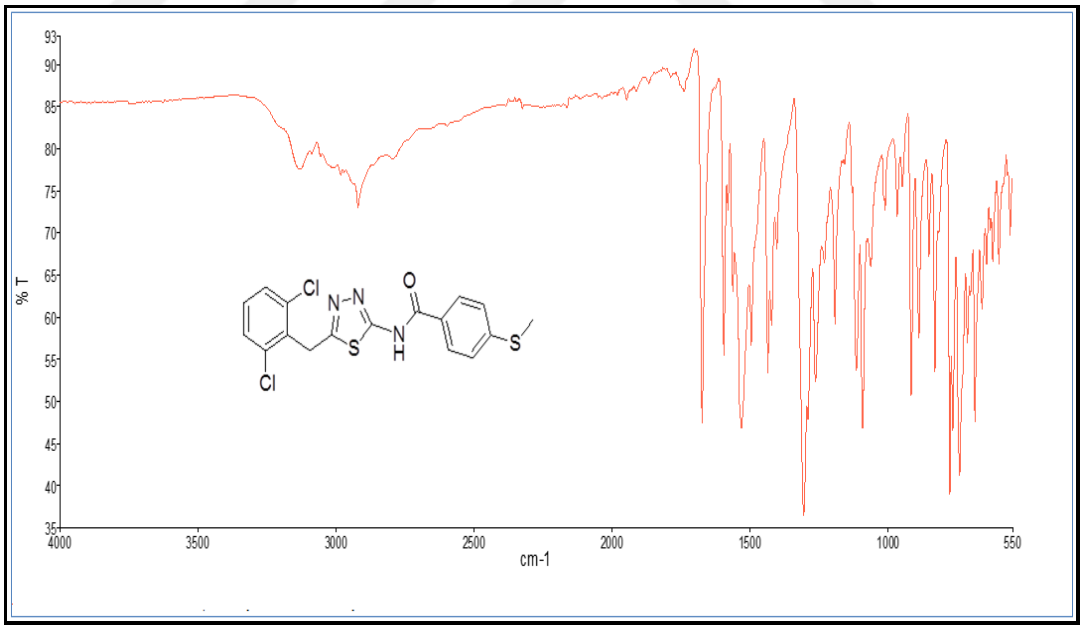


Figure Annex C.4. IR spectra for N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-yl)-4-(methylthio) benzamide **(4c)** compound.

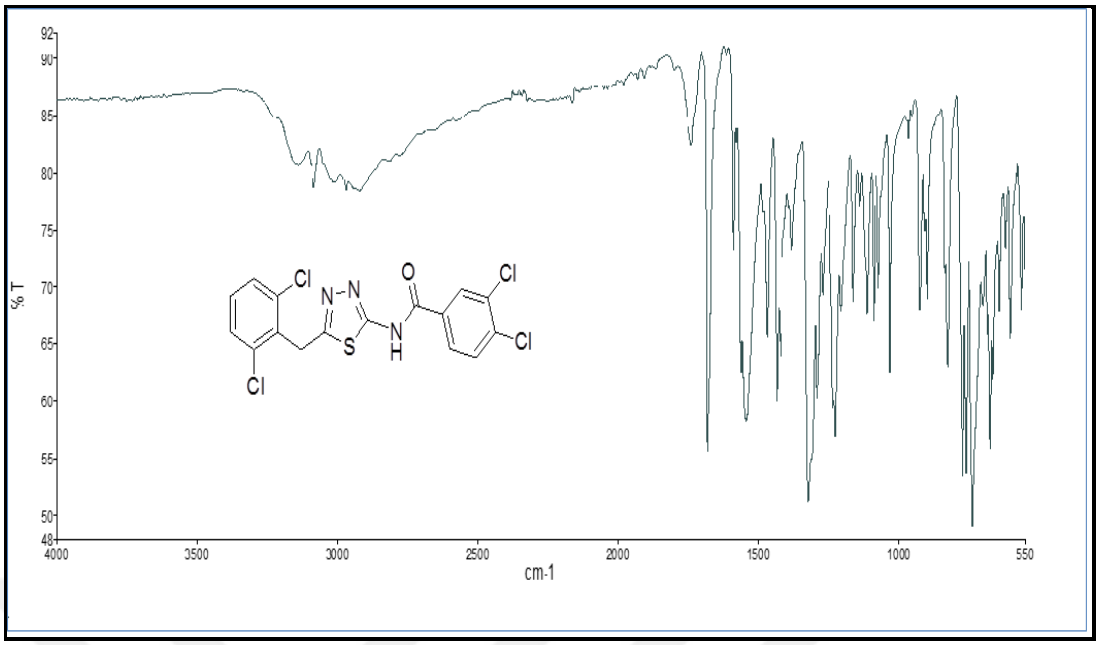


Figure Annex C.5. IR spectra for N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-yl)-3,4-dichlorobenzamide **(4d)** compound.

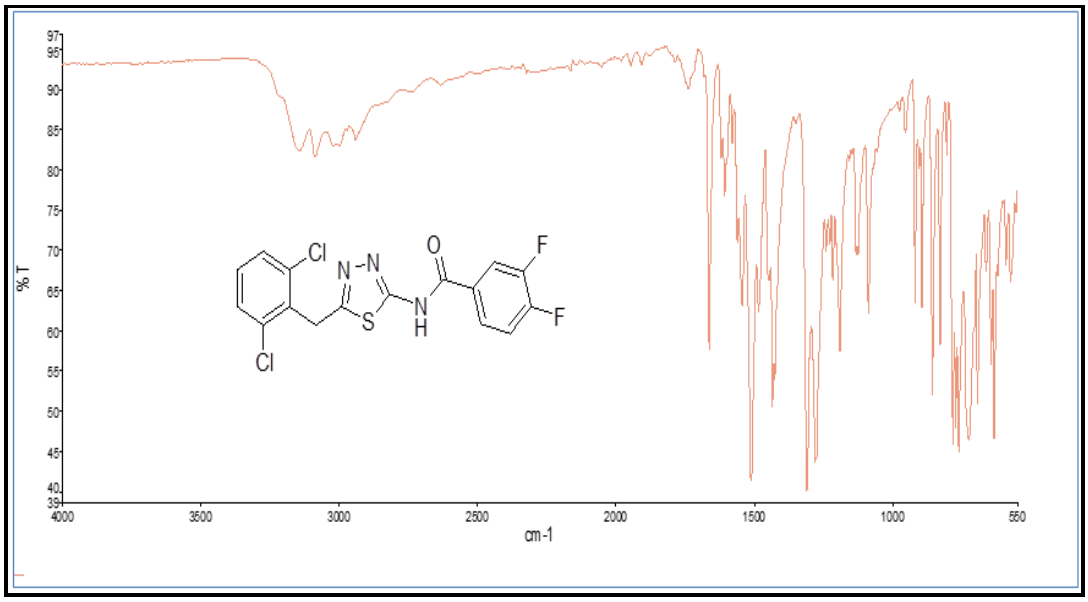


Figure Annex C.6. IR spectra for N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-yl)-3,4-difluorobenzamide **(4e)** compound.

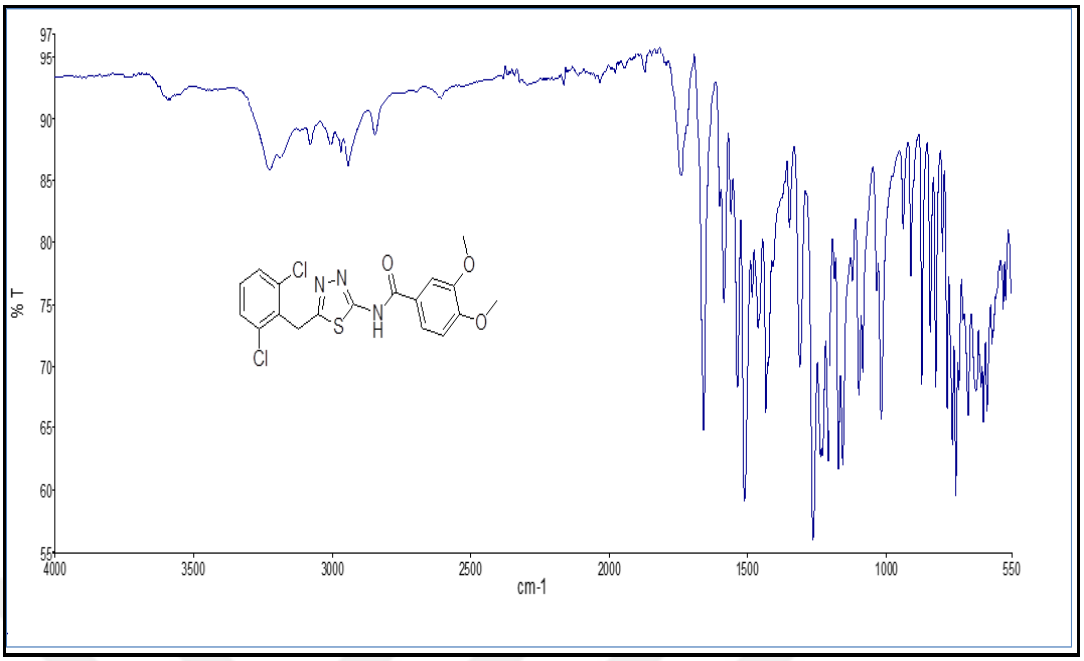


Figure Annex C.7. IR spectra for N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-yl)-3,4-dimethoxy benzamide **(4f)** compound.

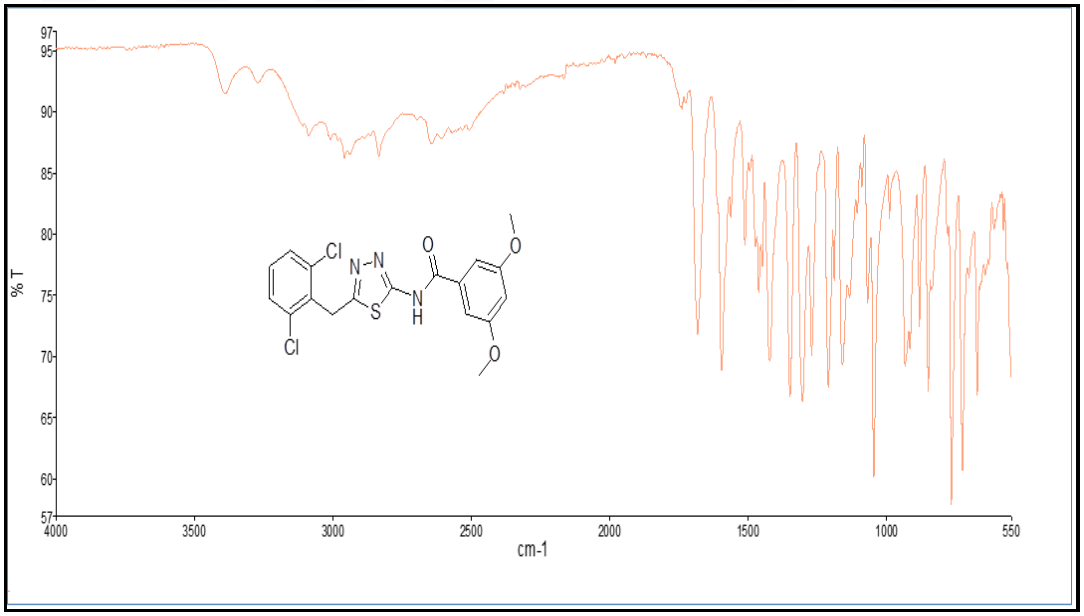


Figure Annex C.8. IR spectra for N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-yl)-3,5-dimethoxy benzamide **(4g)** compound.

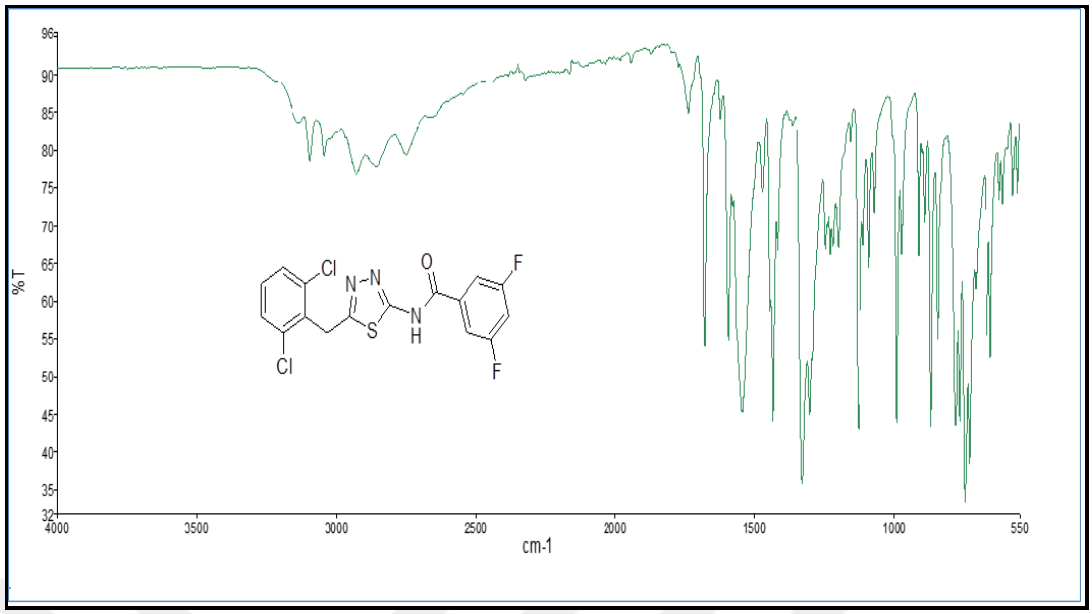


Figure Annex C.9. IR spectra for N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-yl)-3,5-difluorobenzamide **(4h)** compound.

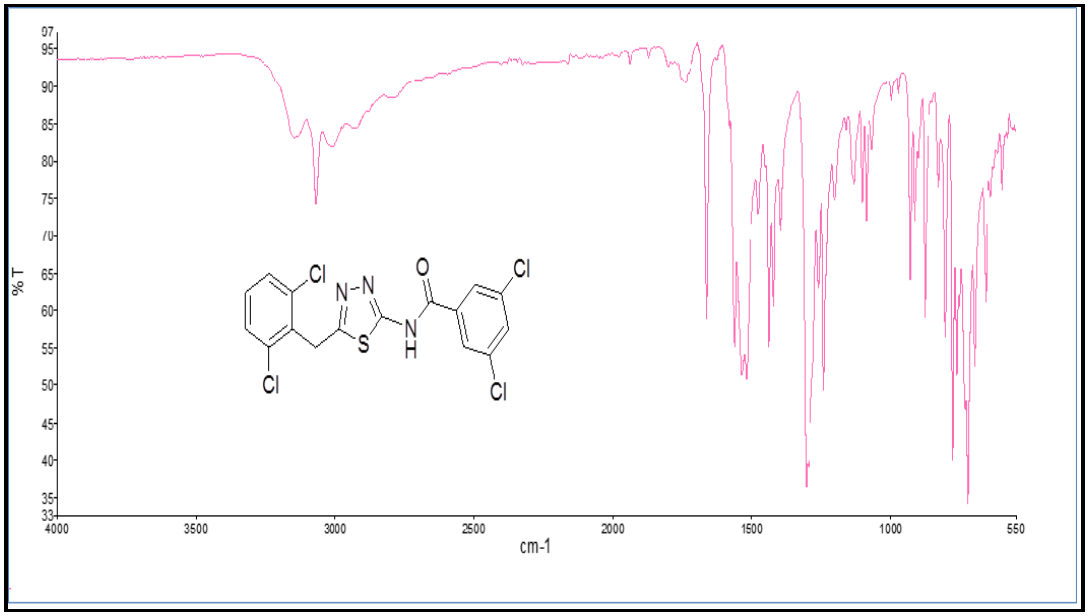


Figure Annex C.10. IR spectra for N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-yl)-3,5-dichloro benzamide **(4i)** compound.

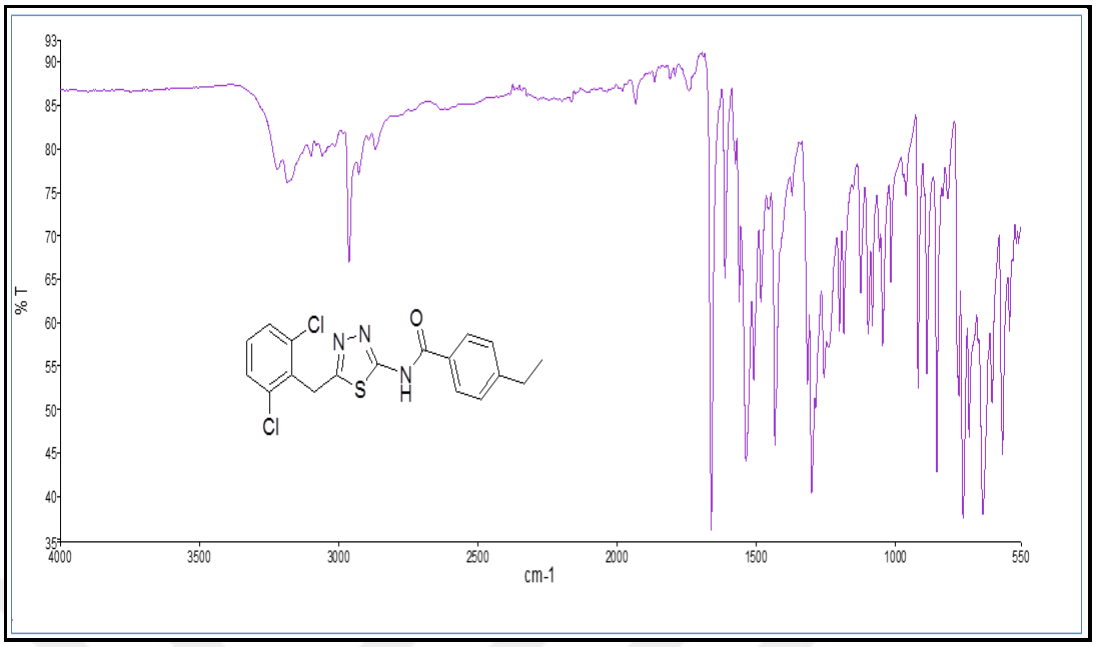


Figure Annex C.11. IR spectra for N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-yl)-4-ethylbenzamide **(4j)** compound.

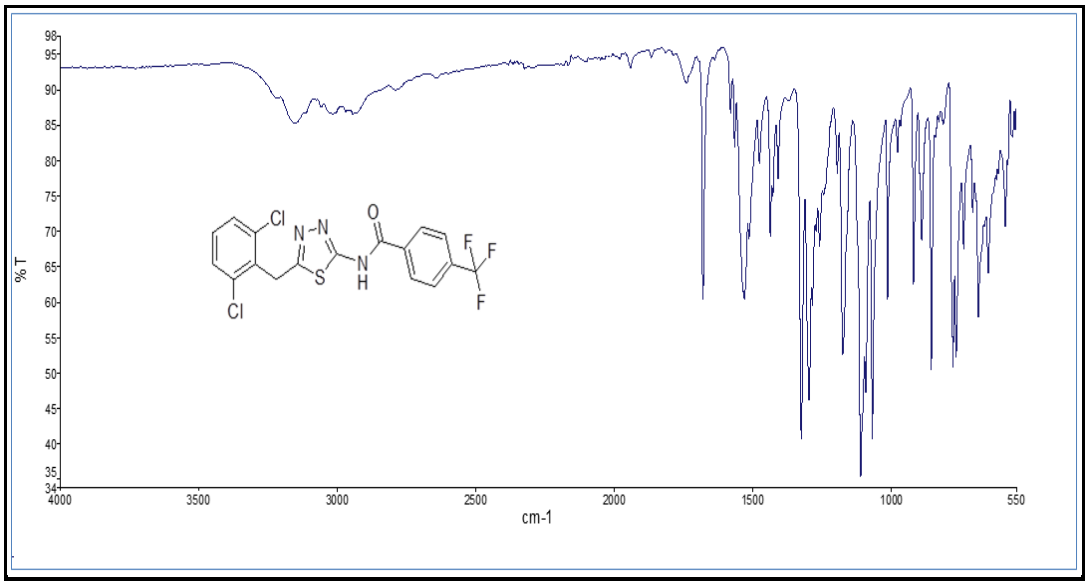


Figure Annex C.12. IR spectra for N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-yl)-4-(trifluoromethyl) benzamide **(4k)** compound.

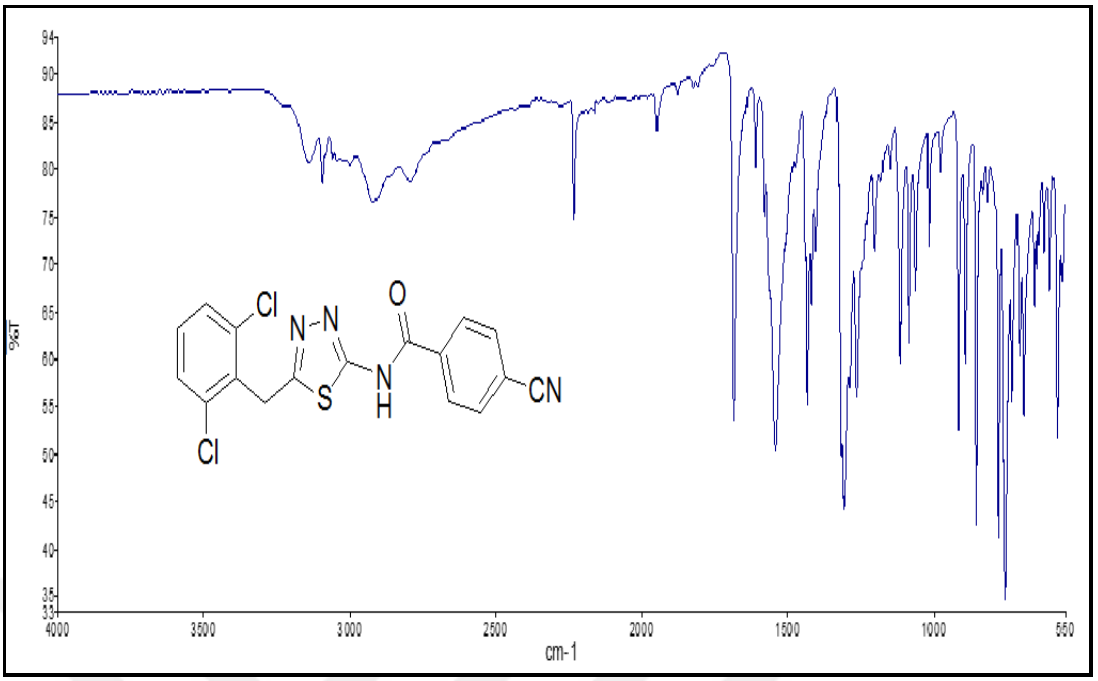


Figure Annex C.13. IR spectra for N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-yl)-4-cyanobenzamide **(4l)** compound.

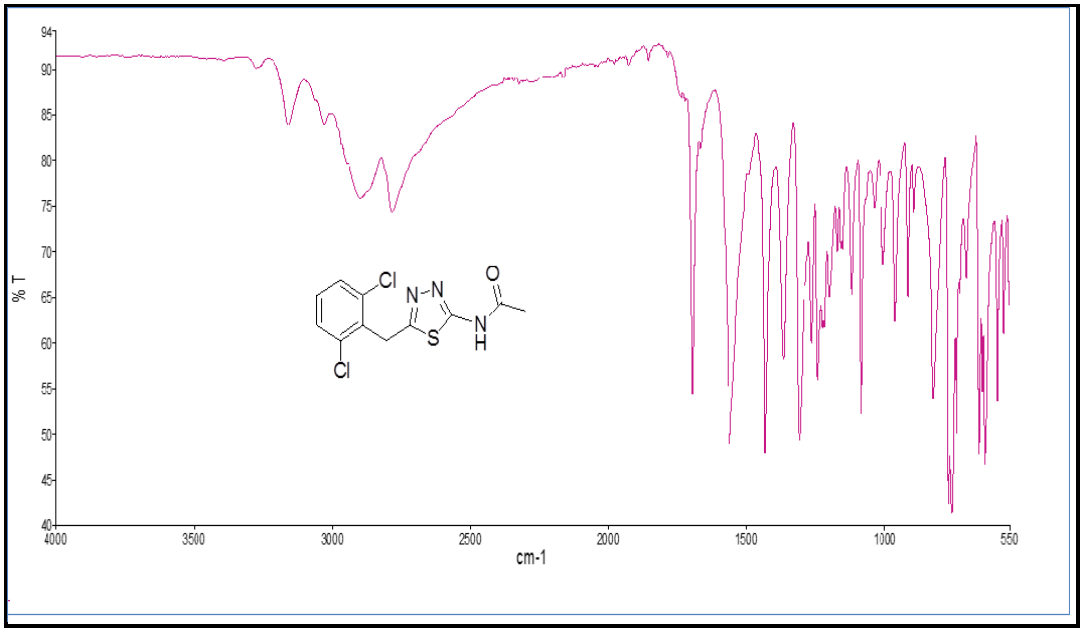


Figure Annex C.14. IR spectra for N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-yl)acetamide **(4m)** compound.

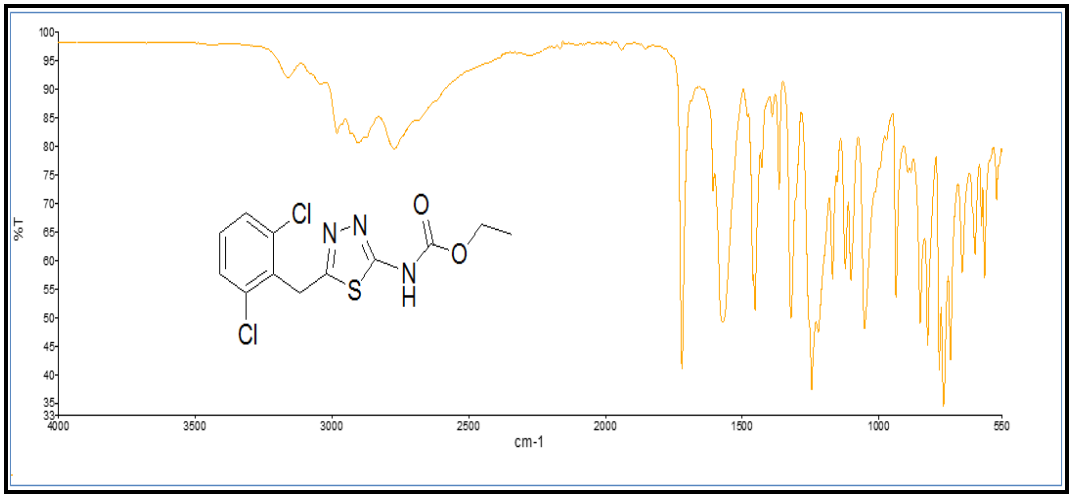


Figure Annex C.15. IR spectra for Ethyl 5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-ylcarbamate **(4n)** compound.

ADDITIONAL EXPLANATIONS D
COMPOUNDS' MS SPECTRA

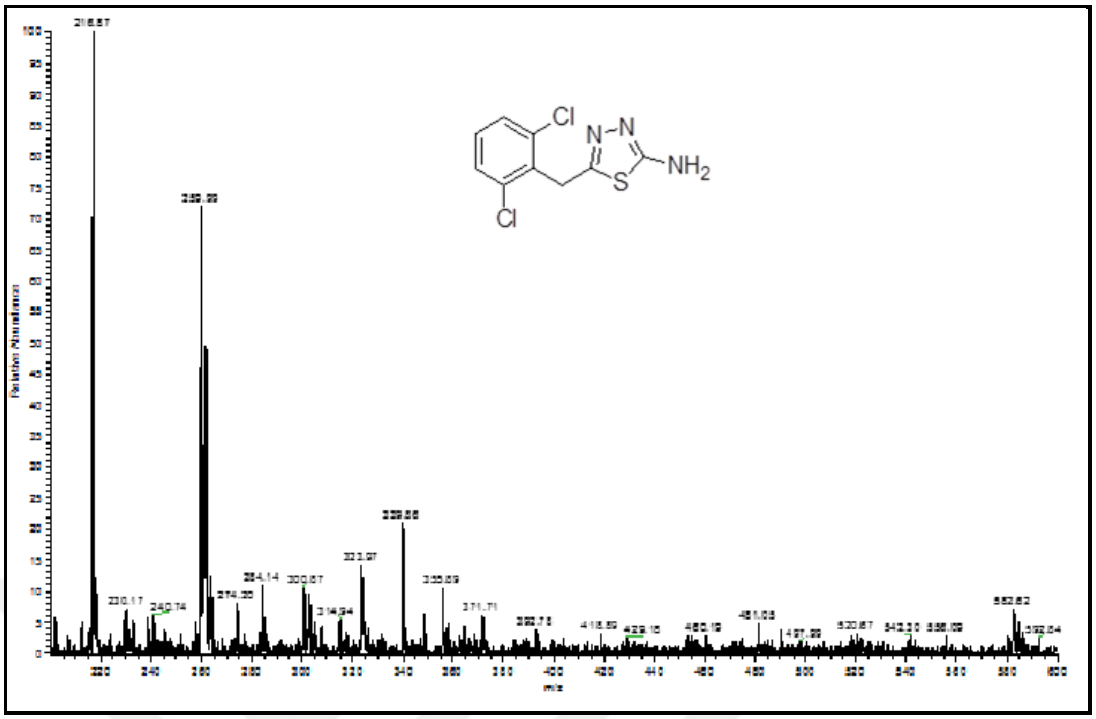


Figure Annex D.1. Mass spectrum for 5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-amine **(2)** compound.

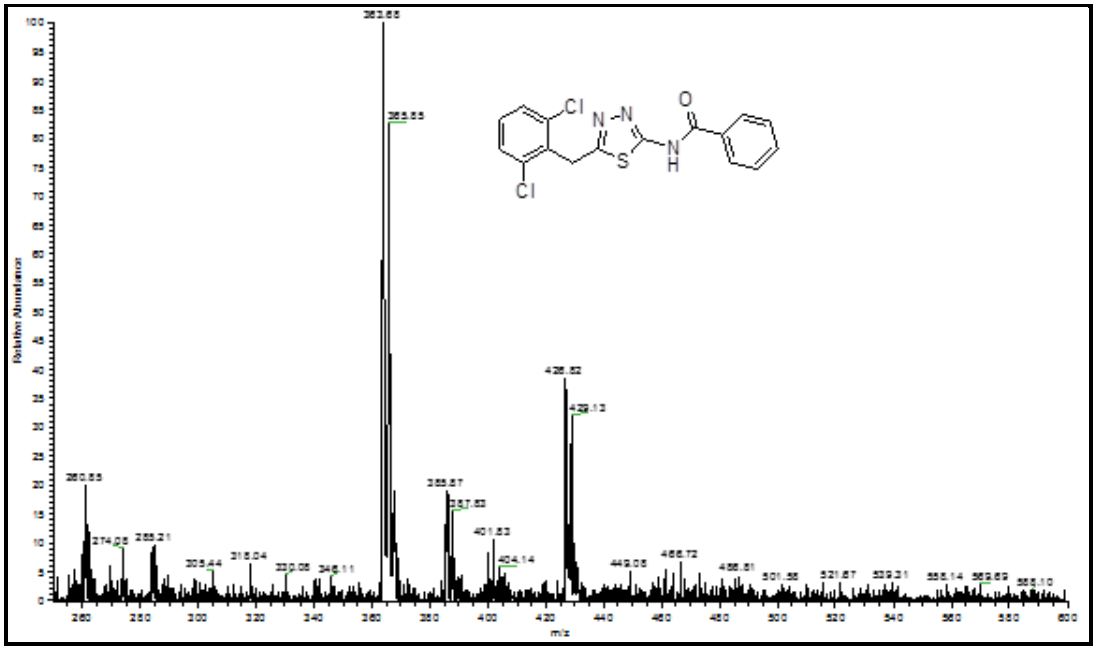


Figure Annex D.2. Mass spectrum for N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-yl)benzamide **(4a)** compound.

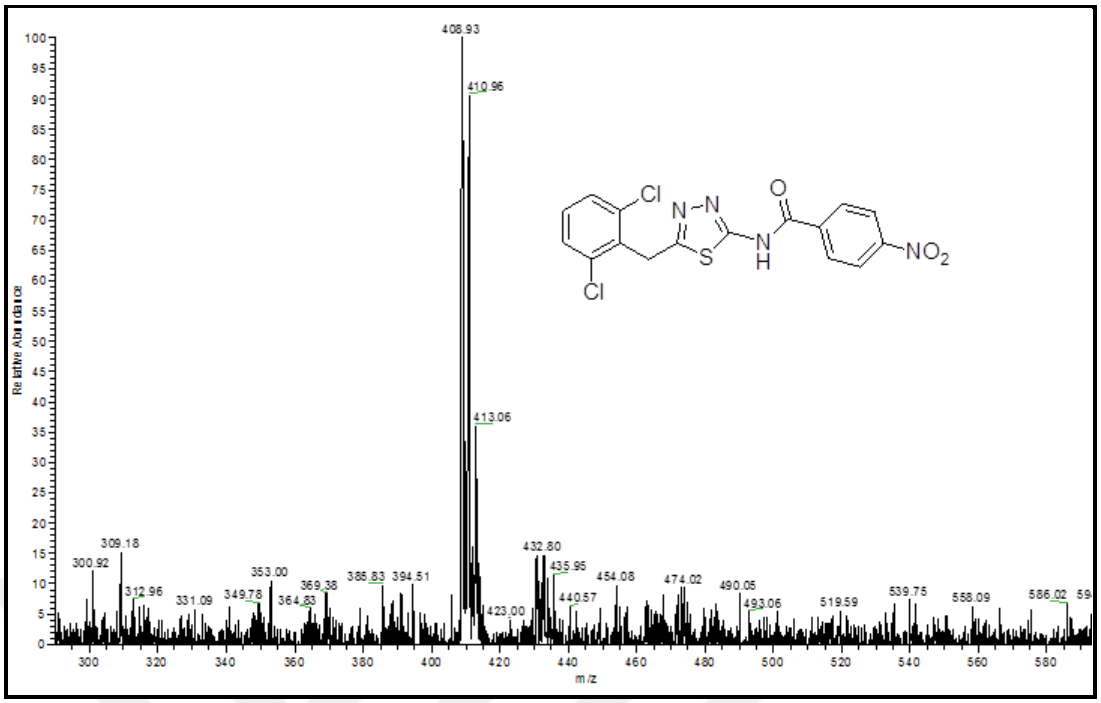


Figure Annex D.3. Mass spectrum for N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-yl)-4-nitrobenzamide **(4b)** compound.

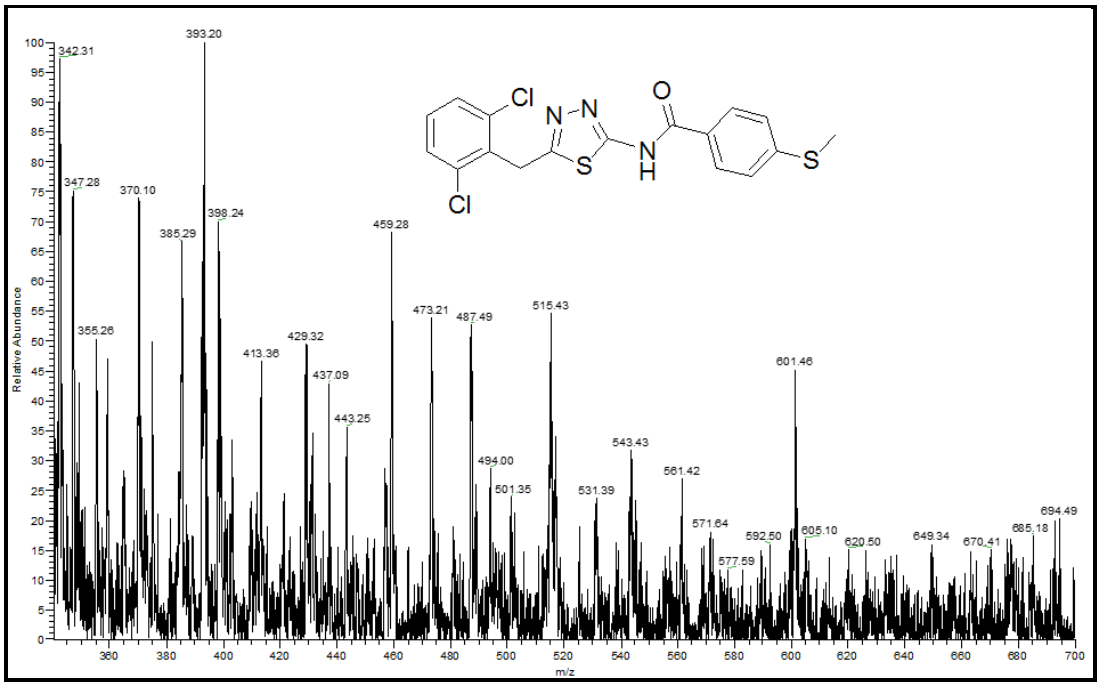


Figure Annex D.4. Mass spectrum for N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-yl)-4-(methylthio) benzamide **(4c)** compound.

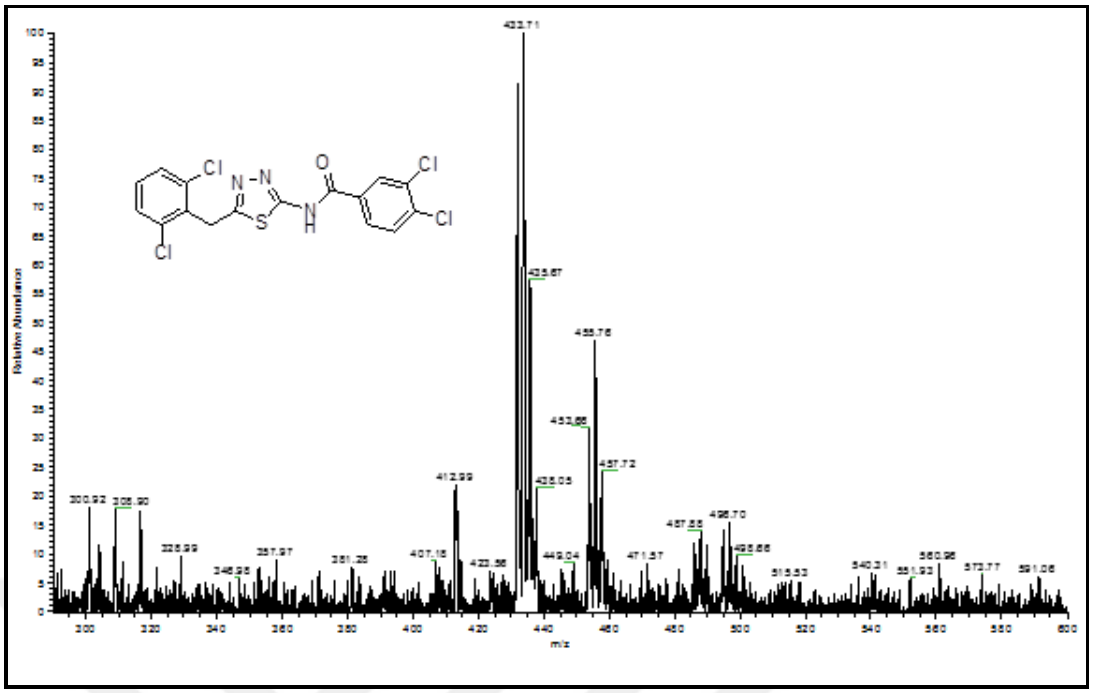


Figure Annex D.5. Mass spectrum for N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-yl)-3,4-dichlorobenzamide **(4d)** compound.

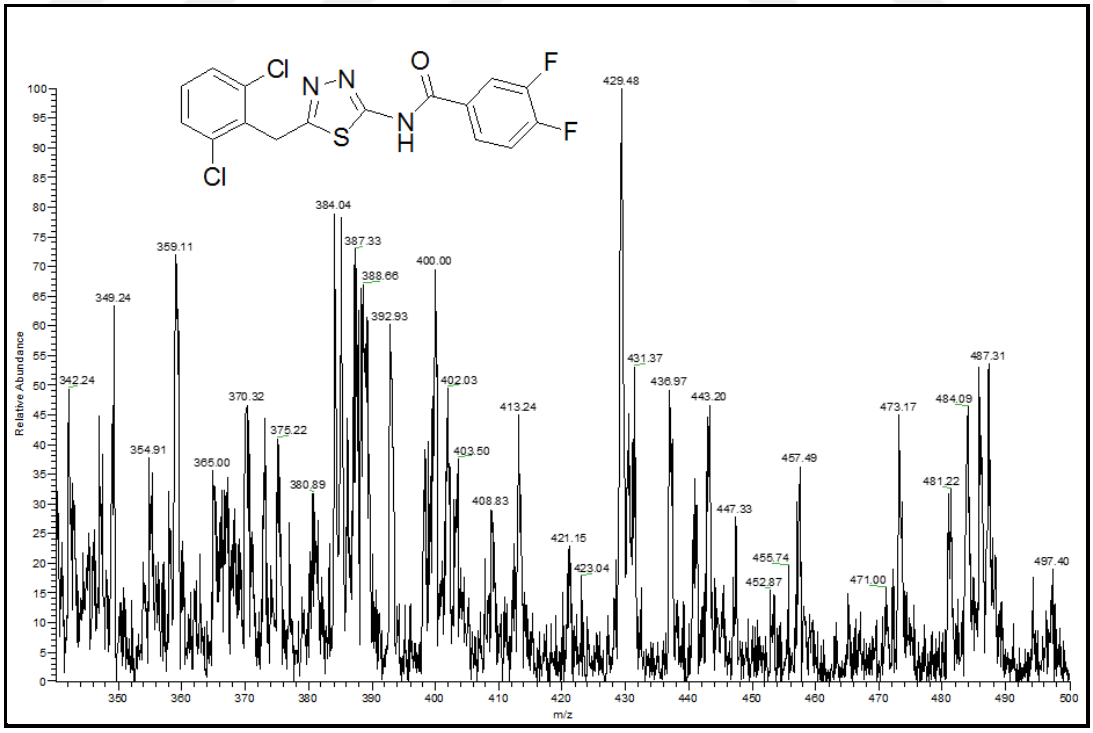


Figure Annex D.6. Mass spectrum for N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-yl)-3,4-difluorobenzamide **(4e)** compound.

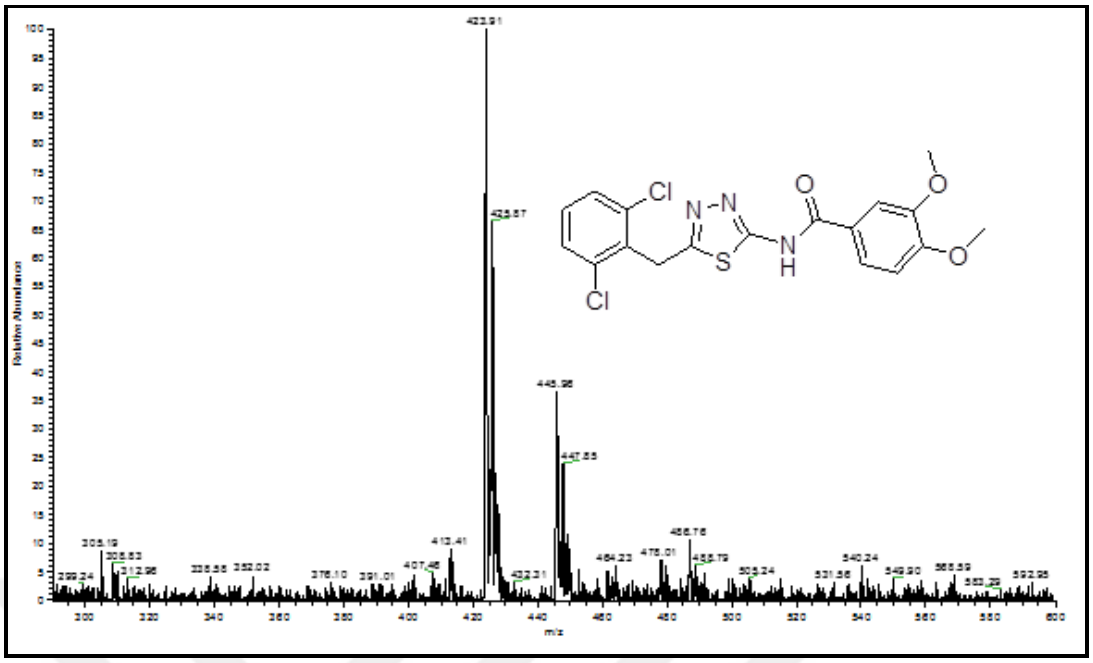


Figure Annex D.7. Mass spectrum for N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-yl)-3,4-dimethoxy benzamide **(4f)** compound.

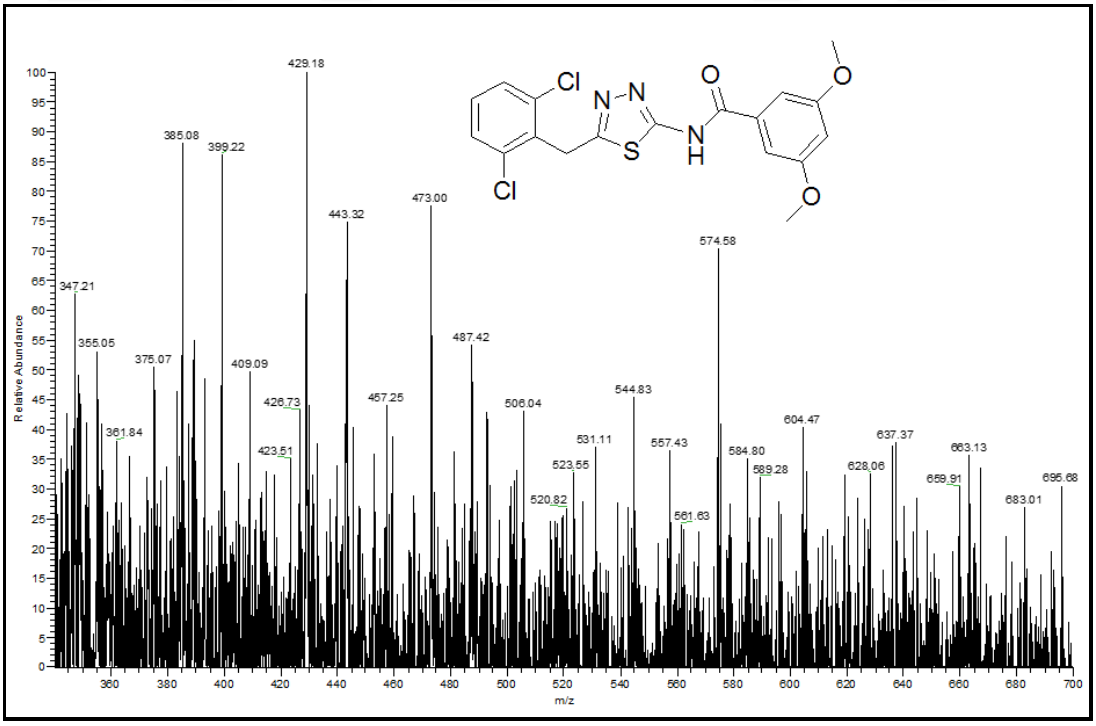


Figure Annex D.8. Mass spectrum for N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-yl)-3,5-dimethoxy benzamide **(4g)** compound.

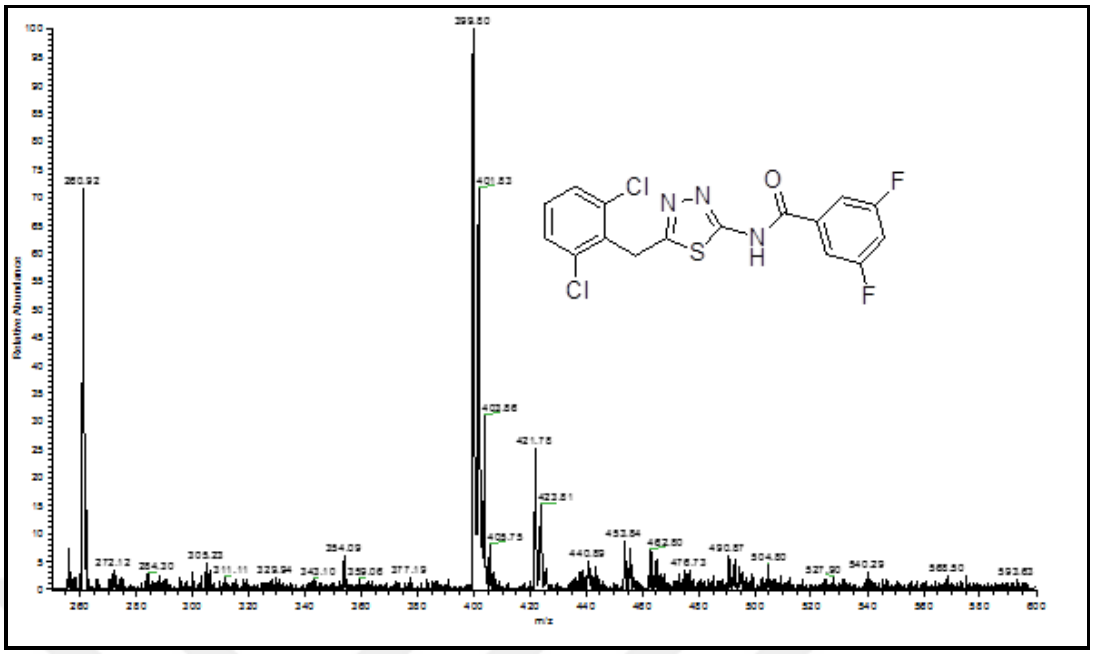


Figure Annex D.9. Mass spectrum for N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-yl)-3,5-difluorobenzamide **(4h)** compound.

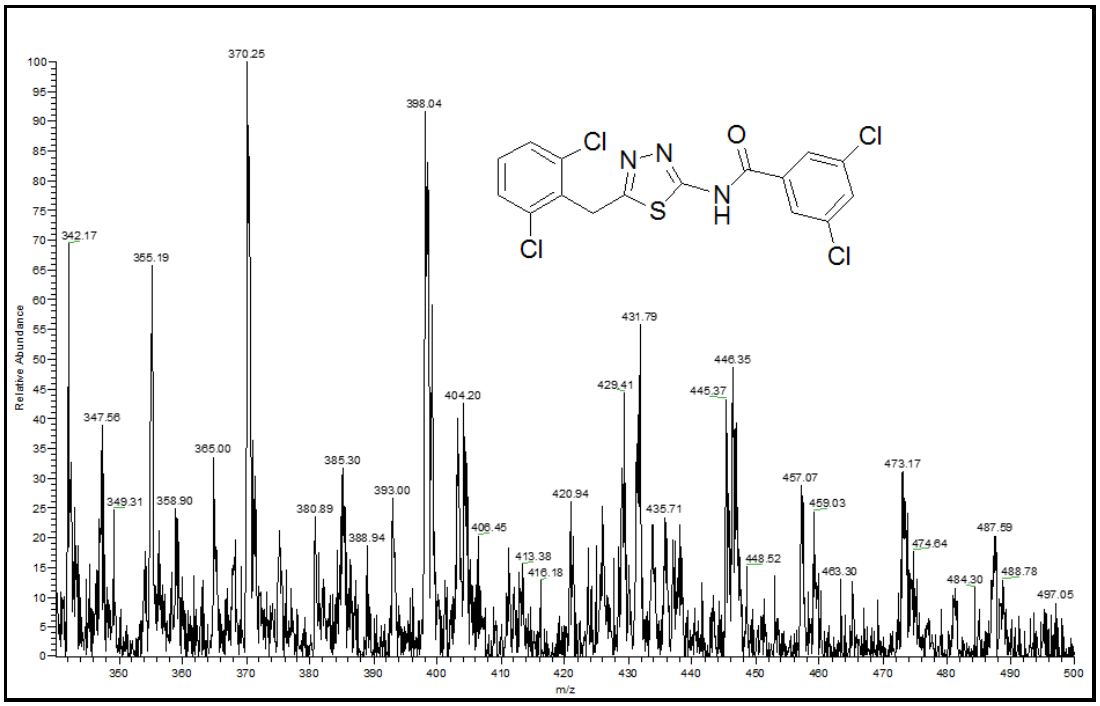


Figure Annex D.10. Mass spectrum for N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-yl)-3,5-dichloro benzamide **(4i)** compound.

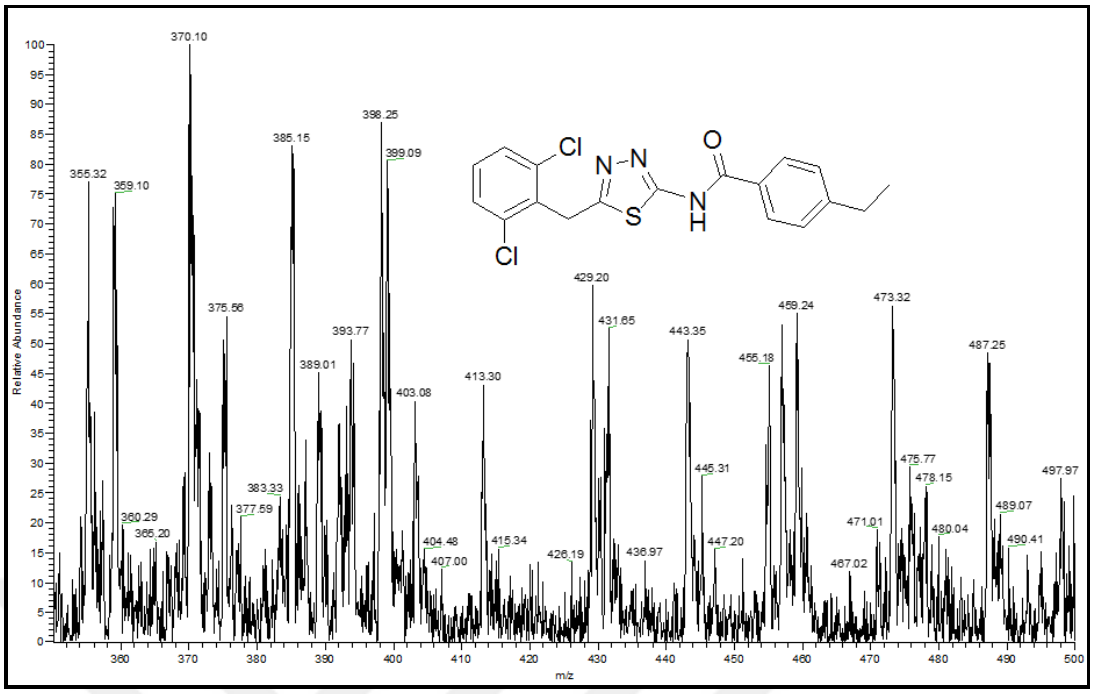


Figure Annex D.11. Mass spectrum for N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-yl)-4-ethylbenzamide **(4j)** compound.

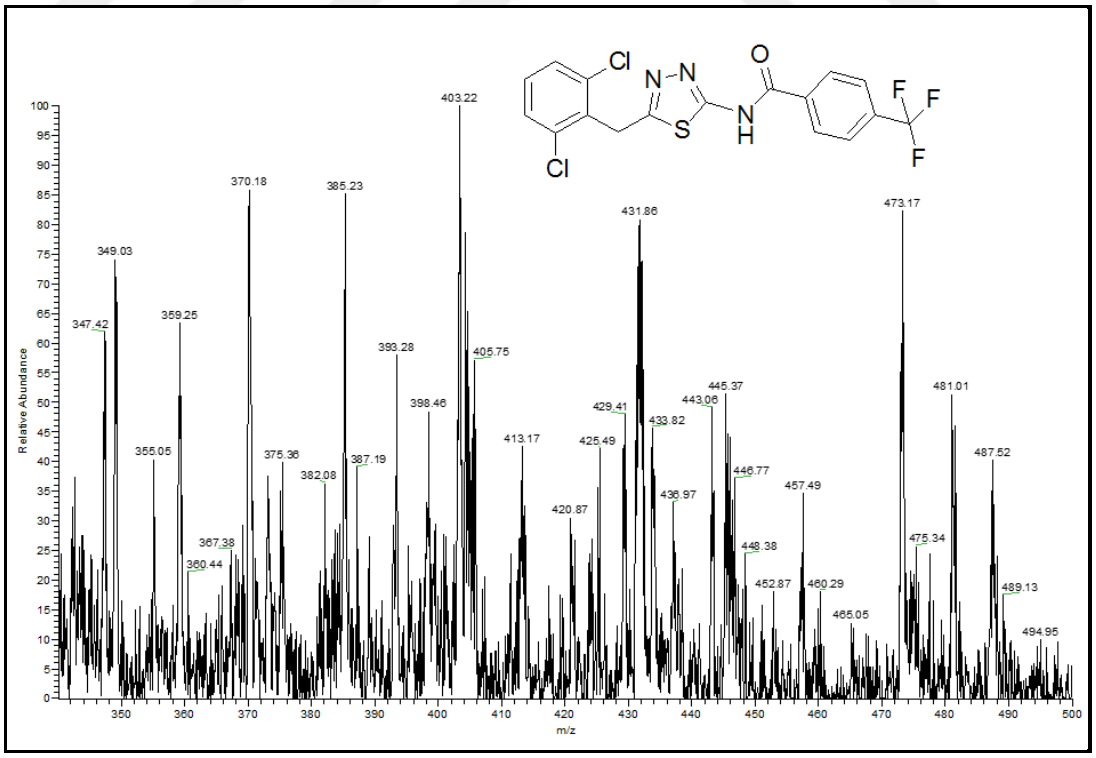


Figure Annex D.12. Mass spectrum for N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-yl)-4-(trifluoromethyl) benzamide **(4k)** compound.

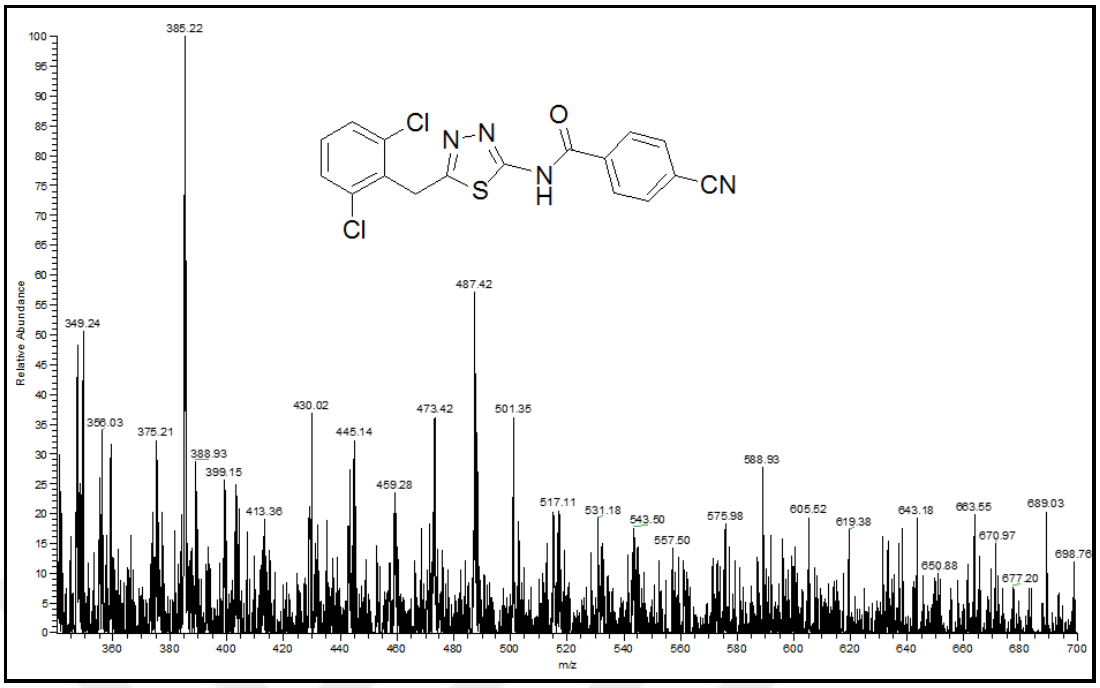


Figure Annex D.13. Mass spectrum for N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-yl)-4-cyanobenzamide **(4l)** compound.

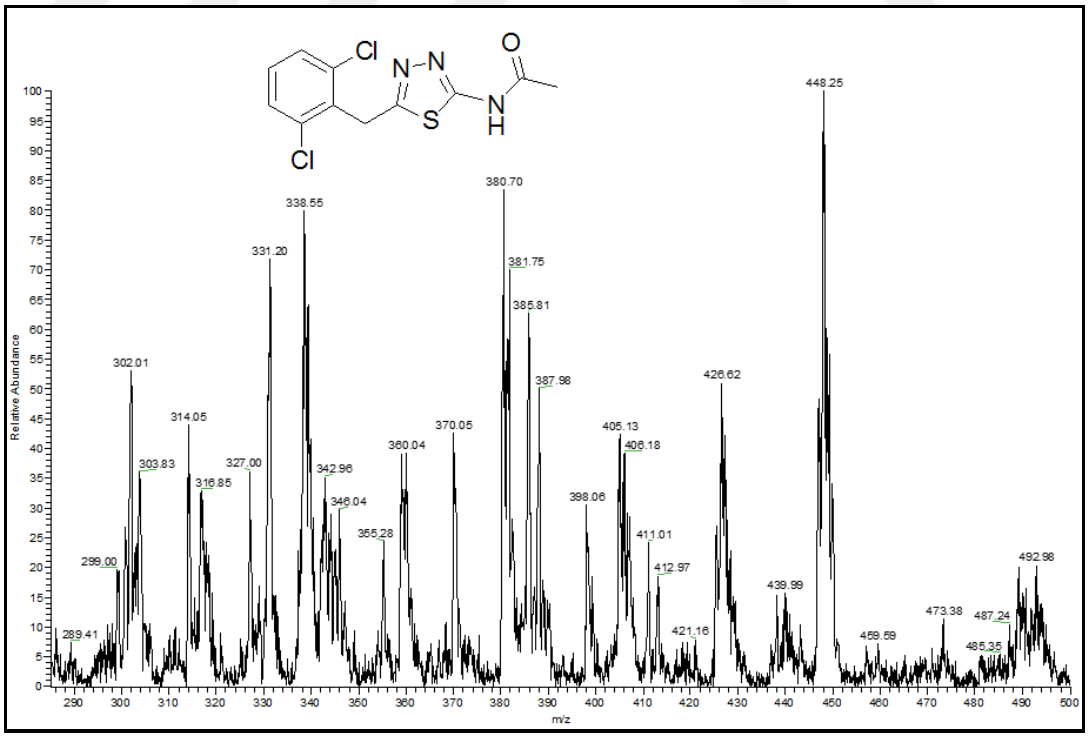


Figure Annex D.14. Mass spectrum for N-(5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-yl)acetamide **(4m)** compound.

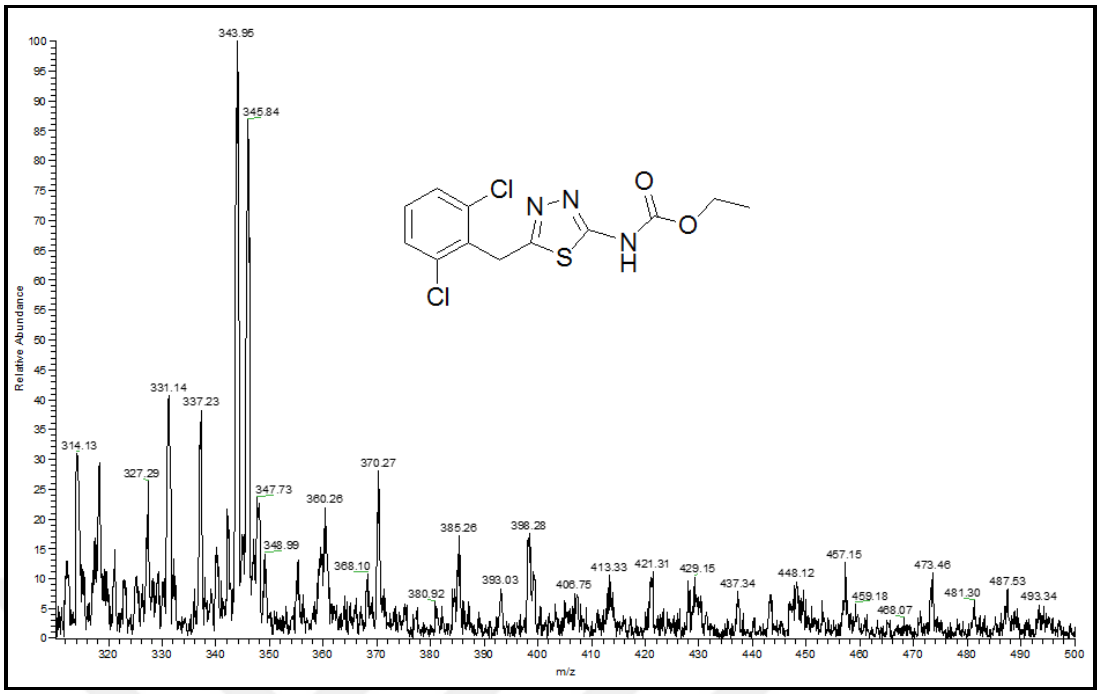


Figure Annex D.15. Mass spectrum for Ethyl 5-(2,6-dichlorobenzyl)-1,3,4-thiadiazole-2-ylcarbamate **(4n)** compound.

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RESUME

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