T.R.
KASTAMONU UNIVERSITY
INSTITUTE OF SCIENCE

SYNTHESIS AND CHARACTERIZATION OF SOME NEW 1,3,4-THIADIAZOLE COMPOUNDS DERIVED FROM CINNAMIC ACID AND DETERMINATION OF ANTIMICROBIAL ACTIVITY

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THESIS APPROVAL

The thesis study entitled "**Synthesis and Characterization of Some New 1,3,4-Thiadiazole Compounds Derived From Cinnamic Acid and Determination of Antimicrobial Activity**" submitted by **Maesm Ahmed Mohamed BEN HSIN**, has been argued in front of the following examining committee members and accepted as **THE DEGREE OF MASTER OF SCIENCE** in the Science Education Programme, Department of **Biology**, Institute of Sciences, in Kastamonu University by unanimity of votes.

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All information in this thesis have written according to the ethical behaviour and academic regulations of Kastamonu University, in addition what does not belong to me in this study was prepared in accordance with the rules of thesis in Kastamonu Uinversity, all kinds of statements and reports writing that fully referenced to the source of knowledge and commitment.

Signature
Maesm Ahmed Mohamed BEN HSIN

ABSTRACT

MSc. Thesis

SYNTHESIS AND CHARACTERIZATION OF SOME NEW 1,3,4-THIADIAZOLE COMPOUNDS DERIVED FROM CINNAMIC ACID AND DETERMINATION OF ANTIMICROBIAL ACTIVITY

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Supervisor: Asst. Prof. Dr. Halit MUĞLU

5-[2-(1,3-benzodioxol-5-yl)ethenyl]-*N*-phenyl-1,3,4-thiadiazol-2-amine (1), 5-[2-(1,3-benzodioxol-5-yl)ethenyl]-*N*-[2'-chlorophenyl]-1,3,4-thiadiazol-2-amine (2), 5-[2-(1,3-benzodioxol-5-yl)ethenyl]-*N*-[4'-chlorophenyl]-1,3,4-thiadiazol-2-amine (3), 5-[2-(1,3-benzodioxol-5-yl)ethenyl]-*N*-[2'-fluorophenyl]-1,3,4-thiadiazol-2-amine (4), 5-[2-(1,3-benzodioxol-5-yl)ethenyl] -*N*- [3'-fluorophenyl] -1,3,4- thiadiazol-2-amine (5), 5-[2-(1,3-benzodioxol -5- yl)ethenyl] -*N*- [4'-fluorophenyl] -1,3,4- thiadiazol-2-amine (6), 5-[2-(1,3-benzodioxol -5- yl)ethenyl] -*N*- [2'-methoxyphenyl] -1,3,4-thiadiazol-2-amine (7), 5-[2-(1,3-benzodioxol-5-yl)ethenyl] -*N*- [3'-methoxyphenyl]-1,3,4- thiadiazol -2- amine (8), 5- [2-(1,3-benzodioxol -5- yl)ethenyl]-*N*-[4'-methoxyphenyl]-1,3,4-thiadiazol-2-amine (9), 5-[2-(1,3-benzodioxol-5-yl)ethenyl]-*N*-[2',4'-dichlorophenyl]-1,3,4-thiadiazol-2-amine (10), 5-[2-(1,3-benzodioxol-5-yl) ethenyl]-*N*-[4'-nitrophenyl]-1,3,4-thiadiazol-2-amine (11), 5-[2-(1,3-benzodioxol-5-yl)ethenyl]-*N*-[2'-ethylphenyl]-1,3,4-thiadiazol-2-amine (12), 5-[2-(1,3-benzodioxol-5-yl)ethenyl]-*N*-[2'-methoxycarbonylphenyl]-1,3,4-thiadiazol-2-amine (13), 5-[2-(1,3-benzodioxol-5-yl)ethenyl]-*N-benzyl* -1,3,4- thiadiazol -2- amine (14), 5-[2-(1,3-benzodioxol-5-yl)ethenyl]-*N*-(2'-phenylethyl) -1,3,4- thiadiazol -2- amine (15) were synthesized by the reaction of phenylthiosemicarbazide derivatives and cynnamic acid derivatives with phosphorous oxychloride. Antibacterial activity was studied for selected bacteria. Compounds 1-15 synthesized and characterized with UV, FT-IR, ^{13}C-NMR, ^{1}H-NMR elemental methods. Compounds 1-15 were screened for five bacteria types. The newly synthesized compounds were investigated for their antimicrobial activities with disk diffusion method. Some of compounds were found to have moderate activities against test microorganisms. The compounds (5,7,10,13,14) showed inhibition zones on *Staphylococcus auries,* while compund (7) showed inhibition zones on *Enterococcus durans.* Compund (8) showed inhibition zones on *E.coli.* Compound (9) showed inhibition zones on *Enterobacter aerogenes.* Compound (13) showed inhibition zones on *Salmonella Kentucky*. But all compounds had no activity against on *Candida albicans, Salmonella infants, Salmonella typhimurium, Salmonella enteritidis* and *Bacillus subtilis.*

Key Words: 1,3,4-Thiadiazole, antimicrobial activity, IR, UV, NMR spectroscopies.
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ÖZET

Yüksek Lisans Tezi

BAZI YENİ SİNNAMİK ASİT TÜREVİ 1,3,4-TİYADİAZOL BİLEŞİKLERİNİN SENTEZİ, KARAKTERİZASYONU VE ANTİMİKROBİYAL AKTİVİTELERİNİN BELİRLENMESİ

Maesm Ahmed Mohamed BEN HSIN

Kastamonu Üniversitesi
Fen Bilimleri Enstitüsü
Biyoloji AnaBilim Dalı

Danışman: Yrd. Doç. Dr. Halit MUĞLU

Bu tez çalışmasında 3,4-(metilen dioksi) sinnamik asit ile N-fenil tiyosemikarbazit türevlerinin fosfor oksiklorür katalizörlüğündeki reaksiyonundan, 5-[2-(1,3-benzodioksol-5-il)etenil]-*N*-fenil-1,3,4-tiyadiazol-2-amin(1), 5-[2-(1,3-benzodioksol-5-il)etenil]-*N*-[2'-klorofenil]-1,3,4-tiyadiazol-2-amin (2), 5-[2-(1,3-benzodioksol-5-il)etenil]-*N*-[4'-klorofenil]-1,3,4- tiyadiazol-2-amin (3),5-[2-(1,3-benzodioksol-5-il) etenil]-*N*-[2'-florofenil]-1,3,4- tiyadiazol-2-amin (4),5-[2-(1,3-benzodioksol-5-il) etenil]-*N*-[3'-florofenil]-1,3,4- tiyadiazol-2-amin (5),5-[2-(1,3-benzodioksol-5-il) etenil]-*N*-[4'-florofenil]-1,3,4- tiyadiazol-2-amin (6),5-[2-(1,3-benzodioksol-5-il) etenil]-*N*-[2'-metoksifenil]-1,3,4-tiyadiazol-2-amin (7),5-[2-(1,3-benzodioksol-5-il) etenil]-*N*-[3'- metoksifenil]-1,3,4-tiyadiazol-2-amin (8),5-[2-(1,3-benzodioksol-5-il) etenil]-*N*-[4'- metoksifenil]-1,3,4-tiyadiazol-2-amin(9), 5-[2-(1,3-benzodioksol-5-il) etenil]-*N*-[2',4'-diklorofenil]-1,3,4- tiyadiazol-2-amin (10),5-[2-(1,3- benzodioksol-5-il)etenil]-*N*-[4'-nitrofenil]-1,3,4- tiyadiazol-2-amin (11),5-[2-(1,3- benzodioksol-5-il)etenil]-*N*-[2'-etilfenil]-1,3,4- tiyadiazol-2-amin (12),5-[2-(1,3-benzodioksol-5-il) etenil] -*N*- [2'-metoksikarbonilfenil] -1,3,4- tiyadiazol -2- amin(13),5-[2-(1,3-benzodioksol -5- il)etenil] -N- benzyl -1,3,4- tiyadiazol -2- amin (14),5-[2-(1,3-benzodioksol-5-il)etenil]-*N*-(2'-feniletil)-1,3,4-tiyadiazol-2-amin (15) bileşikleri sentezlendi.. Sentezlenen bileşikler UV, FT-IR, ^{13}C-NMR, ^{1}H-NMR elemental yöntemleri ile karakterize edildi. Bu bileşiklerin bazı bakteriler ve mantar üzerinde antimikrobiyal aktivitesi incelendi Bazı bileşiklerin test mikroorganizmalarına karşı orta düzeyde aktivite gösterdiği bulundu. 5, 7, 10, 13, 14 numaralı bileşikler *Staphylococcus auries* üzerinde inhibisyon zonu sergiliyor iken, bileşik 7 *Enterococcus durans* üzerinde inhibisyon zonu göstermiştir. Bileşik 8 *E. coli* üzerinde, bileşik 9 *Enterobacter aerogenes* üzerinde ve bileşik 13 *Salmonella Kentucky* üzerinde inhibisyon zonu göstermiştir Ancak bileşiklerin hiçbiri *Candida albicans, Salmonella infants, Salmonella typhimurium, Salmonella enteritidis* ve *Bacillus subtilis* üzerinde aktivite göstermemişlerdir.

Anahtar Kelimeler: 1,3,4-Tiyadiazol, antimikrobiyal aktivite, IR, NMR spektroskopileri.

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Maesm Ahmed Mohamed BEN HSIN
Kastamonu, July, 2017

CONTENTS

ABBREVIATIONS

IR	Inferred
UV-Spectroscopy	Ultraviolet-visible spectroscopy
NMR	Nuclear magnetic resonance
MP	Melting point
h	hour
G	Gram
mL	Milliliter
DH2O	Distilled Water
mmol	Millimole
mM	Millimolar
µL	Microliter
THF	(Tetrahydrofuran)

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1. INTRODUCTION

A heterocyclic compound is that which contain more than one kind of atoms if ring are only made up of the carbon atoms than that are named the homocyclic compounds but the heterocyclic circle contain more than one compounds as nitrogen, oxygen or sulfur for example pyrole, furon, thiophene [1]. The heterocyclic compounds that contain more than one heteroatom in there five membered ring are azole, pyrrole, thiazole, thiadiazole, oxadiazole, triazene etc [2].

The history of heterocyclic chemistry started in the 1800s, in stage with the development of organic chemistry. Some important developments:
1818: Brugnatelli separates alloxan from uric acid
1832: Dobereiner yields furfural (a furan) by treating starch with sulfuric acid
1834: Runge attains pyrrole ("fiery oil") by dry distillation of bones
1906: Friedlander makes indigo dye, allowing synthetic chemistry to displace a large agricultural industry
1936: Treibs separates chlorophyl derivatives from crude oil, explaining the biological origin of petroleum.
1951: Chargaff's rules are characterized, highlighting the role of heterocyclic compounds (purines and pyrimidines) in the genetic code [3].

Thiadiazole, a heterocyclic organic chemical compound, is a pentane ring with two nitrogen atoms and one sulfur atom. 1,2,3-thiadiazole, 1,2,5-thiadiazole, 1,2,4-thiadiazole and 1,3,4-thiadiazole (Figure 1.1).

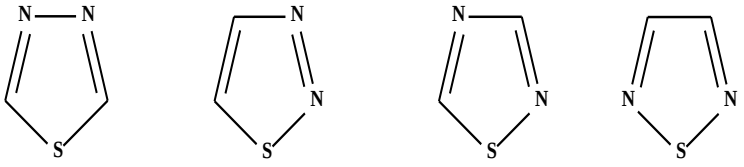


Figure 1.1. Thiadiazole Isomers

1,3,4-Thiadiazole is the most important isomer of thiadiazole. Pharmacological and biological activity is very high (Figure 1.1) [4]. Probably the group -N = C-S- is associated with the biological activities of 1,3,4-thiadiazoles [5].

When we consider the published data on 2,5-disubstituent-1,3,4-thiadiazole derivatives and their potent antimicrobial activities, we have led to the synthesis of novel compounds containing the substituent at the 5 and 2 position of the 1,3,4-thiadiazole core in order to be able to discover antimicrobial activities .

1.1. Thiadiazole

Thiadiazole is a pentagonal ring having two nitrogen atoms and one sulphur atom [6]. The wide spectrum activities of 1,3,4-thiadiazoles have make them one of the best chemical substances that have biological activities. Thiadiazole compounds have great important in agriculture, medicine, and many other technology areas. A lot of 1,3,4 thiadiazoles have been patented in the agricultural areas as bactericides and herbicides [7].

The parameter of 1,3,4-thiadiazole ring structure by X-ray analysis is shown in (Figure1.2, Figure 1.3 and Table 1.1).

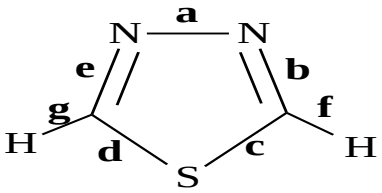
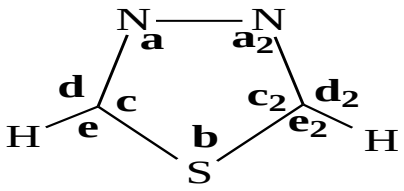


Figure 1.2. Bond length for 1,3,4-thiadiazole



a = 112.2 °; **b** = 86.4 °; **c** = 114.6°;
d = 123.5°; **e** = 121.9°

Figure 1.3. Bond angle 1,3,4-thiadiazole

Table 1.1. *1,3,4-Thiadiazole physical propertie*

Bond length		**Bond angle**	
Bond	˚A	Angle	(◦)
A	1.371	(a)(a2)	112.2
B	1.302	(b)	86.4
C	1.721	(c) (c2)	114.6
D	1.721	(d) (d2)	123.5
E	1.302	(e) (e2)	121.9
F	1.077		
G	1.077		

1.1.1. Chemistry of Thiadiazole

The 1,3,4-thiadiazole type has been heavily used in the medicals chemistry during the last years to show its biological actions. The discovery of hydrazine and phenylhydrazines in the last years of nineteenth century improved the development of 1,3,4-thiadiazole chemistry. In 1882 Fischer is the first one who defined 1,3,4-thiadiazole, and Freund and Kuh in 1890 discovered the true circle system nature and proved first [8].

1.1.2. 1,3,4-Thiadiazoles

In 1882 Fischer described 1,3,4-Thiadiazole and Bush and his coworkers developed 1,3,4-Thiadiazole, but Goerdler et al in 1956 proved the true nature of the ring order [9]. The latest discovery of mesoionic compound represents the sulphur drugs has achieved tremendous success. Thiadiazole carrying amino substituents, hydroxyl, and mercapto can occur in many forms.There are three subclasses of 1,3,4-thiadiazoles [10].

(a) The neutral thiadiazoles aromatic systems (Figure 1.4).

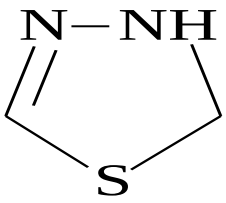


Figure 1.4. Structure of the neutral 1,3,4-thiadiazoles aromatic

(b) Mesoionic systems also identified fivemembered heterocycles circle which are not polar or covalent and have a sextet of electrons associated with the five atoms to comprise in the circle (Figure 1.5).

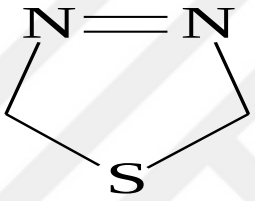


Figure 1.5. Structure of 1,3,4-thiadiazole mesoionic systems

(c) Nonaromatic order for example 1,3,4-thiadiazoles and tetrahydro 1,3,4-thiadiazoles (Figure 1.6).

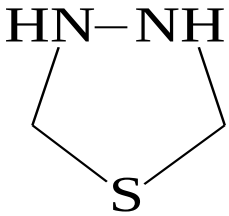


Figure 1.6. Structure of nonaromatic 1,3,4-thiadiazole

1.2. Method of Synthesis of 1,3,4-Thiadiazole

1.2.1. From Thiosemicarbazides

Frund and Meinecke have shown that thiosemicarbazide is cyclized directly to acetyl chloride to 2-amino-5-methyl-1,3,4-thiadiazole. This simple route of 2-amino 5-

substituted-1,3,4-thiadiazole appears quite general. In the illustrated example, R can be methyl [11], norhidnocarpyl [12], benzyl [13], cyclopropyl [14], and others (Figure 1.7).

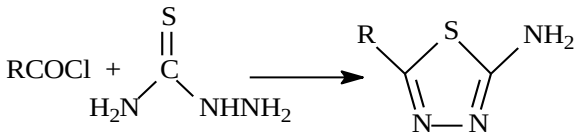


Figure 1.7. Synthesis of 1,3,4-Thiadiazole from Thiosemicarbazides

Hoggarth, has prepared a number of 2-amino-5-aryl-1,3,4-thiadiazole using phosphoric acid as the dehydrating agents. An example of smooth cyclization in high yield by phosphoric acid is the formation of 2- benzamido-5-phenyl-1,3,4-thiadiazole from 1,4-dibenzoylthiosemicarbazide (Figure 1.8) [15].

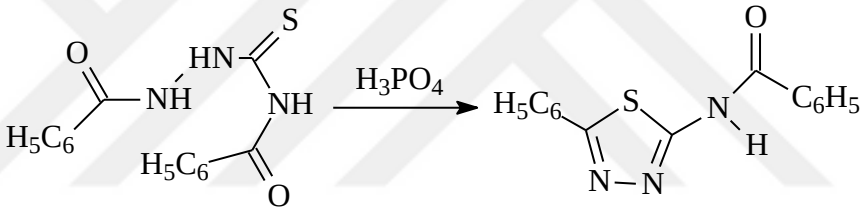


Figure 1.8. Synthesis of 1,3,4-Thiadiazole from Thiosemicarbazides

Pulvermacher, observed that formic acid could cyclize the alkanoyl halides by acylation. He found that by heating 4-phenylthiosemicarbazide with formic acid, 2-anilino-1,3,4-thiadiazole was formed (Figure 1.9) [16].

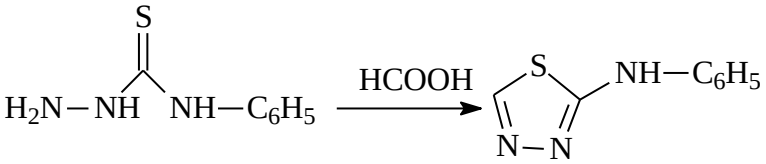


Figure 1.9. Synthesis of 1,3,4-Thiadiazole from Thiosemicarbazides

A useful preparative method for 2-amino-5-mercapto-1, 3, 4-thiadiazole was developed by Guha. When thiosemicarbazide is treated with carbon disulphide and potassium hydroxide, the potassium salt of thiosemicarbazide-4-dithiocarboxylic acid is formed. Heating this potassium salt of thiosemicarbazide-4- dithiocarboxylic

acid to 140°causes cyclization to the salt of 2-amino-5-mercapto-1, 3, 4-thiadiazole (Figure 1.10) [17].

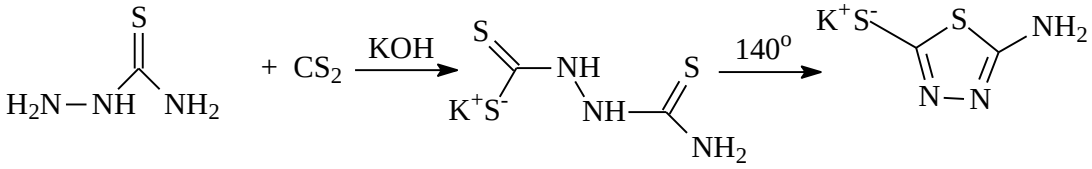


Figure 1.10. Synthesis of 1,3,4-Thiadiazole from Thiosemicarbazides

Young and Eyre. reported that benzalthiosemicarbazones could be oxidatively cyclize to form 2- amino-5-phenyl-1, 3, 4-thiadiazole by ferric chloride. A large number of 5-substituted 2-amino-1, 3, 4-thiadiazole have been prepared by De and Roy-Choudury25 by this procedure (Figure 1.11) [18].

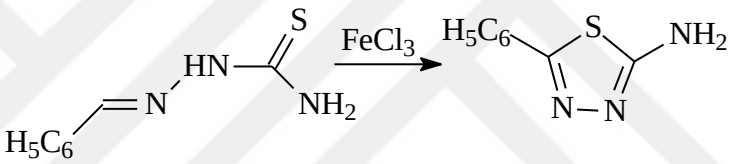


Figure 1.11. Synthesis of 1,3,4-Thiadiazole from Thiosemicarbazides

1.2.2. From Thiocarbazides

There are two ways in which 1,3,4-thiadiazole can be prepared from thiocarbazides.

Method 1. When 1-phenylthiocarbazide is heated with formic acid, 2-phenylhydrazino-1, 3,4-thiadiazole is converted (Figure 1.12) [19].

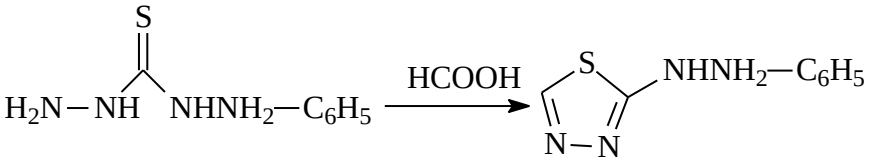


Figure 1.12. Synthesis of 1,3,4-Thiadiazole from Thiocarbazides

Method 2. This method is related to the oxidation of 1-phenylbenzalthiocarbazone to 2-phenyl-5-phenyl hydrazino-1, 3, 4-thiadiazole (Figure 1.13) [20].

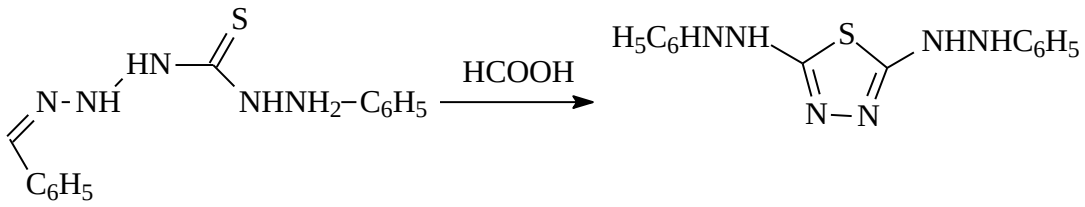


Figure 1.13. Synthesis of 1,3,4-Thiadiazole from Thiocarbazides

1.2.3. From Dithiocarbazides

Formation of 2,5-dimercapto-1,3,4-thiadiazole with carbon disulfidine interaction on hydrazine in basic medium (Figure 1.14) [21,22].

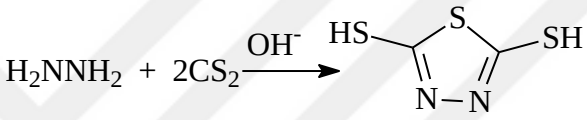


Figure 1.14. Synthesis of 2,5-dimercapto-1,3,4-thiadiazole from Dithiocarbazides

1.2.4. From Thioacylhydrazines

Thioacylhydrazines may often serves as starting materials for the preparation of 1, 3, 4-thiadiazole. If thiobenzoylhydrazine is heated with ethyl orthoformate , 2-phenyl-1, 3, 4-thiadiazole is formed.33 If ethyl orthoacetate is substituted for the orthoformate, 2-methyl-5-phenyl-1, 3, 4-thiadiazole is obtained (Figure 1.15) [23].

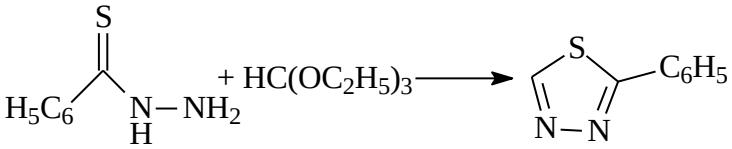


Figure 1.15. Synthesis of 1,3,4-Thiadiazole from Thioacylhydrazines

1.2.5. From Acylhydrazines

Stolle obtained 2,5-diphenylthiadizole by various methods. Benzoylhydrazine [24] or N, N'-dibenzoylhydrazines react with phosphorus pentasulfide to form 2,5-diphenyl-1,3,4-thiadiazole (Figure 1.16) [25].

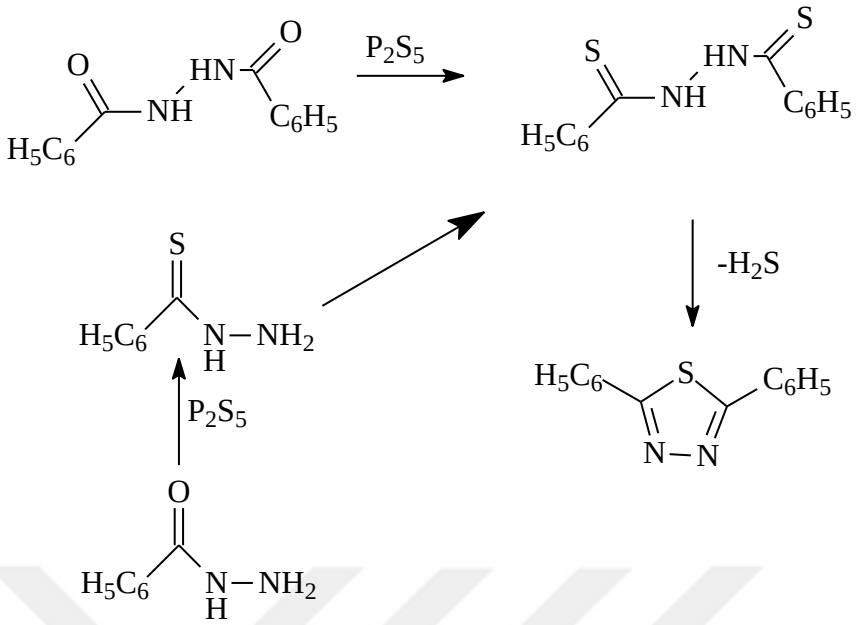


Figure 1.16. Synthesis of 1,3,4-Thiadiazole from Acylhydrazines

1.3. Biological Activity

Over the past decade, drug impedance has become an increasing problem in the therapy of infectious diseases caused bacteria, fungi and viruses. In particular, impedance of bacterial therapy pathogens to current antibiotics has emerged as a measure health problem. This is especially true in case of infectious diseases such as pneumonia, meningitis and tuberculosis, which would once have been easily treated with antibiotics, but is no longer so readily treated. Right now, all widely used antibiotics, counting some of the agents such as streptogramins and new generation flouroquinolones are subjected to bacterial resistance. The search for new antimicrobial agents is one of the most challenging tasks to the medicinal chemist. [26].

Antimicrobial drugs have important therapeutic role in the 20th century. Since the appearance explained the impact of these drugs on the disease, where some of them had a therapeutic result. Clarify one of the most greatly currently treatments are used even the misused drugs.

Drugs are designed to kill or inhibit the microbes and to have no effect or minimum effect on infected person. This chemical treatment is in general named

chemotherapy, which means “the specified chemical treatment that treats systemic infections by suppress the microorganism which have securely effect on the host” [27].

The biological activity of compounds mostly hinge on their molecular structure. Heterocyclic moieties can be found in a huge amount of compounds, which display big number of biological activity. Thiadiazole is a versatile moiety that exhibits a wide variety of activity due to the presence of N=C-S moiety in the ring. They have become an essential class of heterocycles of great interest of researches because of their broad types of biological activity. Some drugs containing 1,3,4- thiadiazole nucleus such us: acetazolamide, butazolamide. [28].

Among the hetero cyclic compounds have our attention is absorbed on 1,3,4-thiadiazole since it is used to develop the new drugs. The importance of 1,3,4-thiadiazol come from its biological activity where it expose some properties, including, anti-inflammatory, antioxidant, anticancer, anticonvulsants, antihypertensive carbonic anhydrase inhibitors, antimicrobial, antituberculosis and antifungalproperties. Structural distinctive shape of 1,3,4-thiadiazole has the ability to submit different chemical reactions, this essential feature for molecule planning and has extensive biological potential. As example the compounds that have 1,3,4-thiadiazole group in there structure and used in clinical treatment are: acetazolamide and methazolamide as carbonic anhydrase inhibitors [29].Thiadiazole can change with the thiazole since can act as the bio-isostatic for it and can use in antibiotic preparations. The biological activity of thiadiazole derivatives are due to robust aromaticity ring system, which it is stabile in vivo and generally. For higher vertebrates, counting humans’ thiadizole exhibited little or no toxicity effect. Functional groups in chemical drug interact with biological receptors through attaching to this circle, by this way the compounds yield notable properties [30].

1.3.1. Antimicrobial Activity

Arun Kumar et al. 1,3,4-thiadiazole derivatives synthesized and screened for their antimicrobial activity. Significant antimicrobial activities have been observed in studies (Figure 1.17) [31].

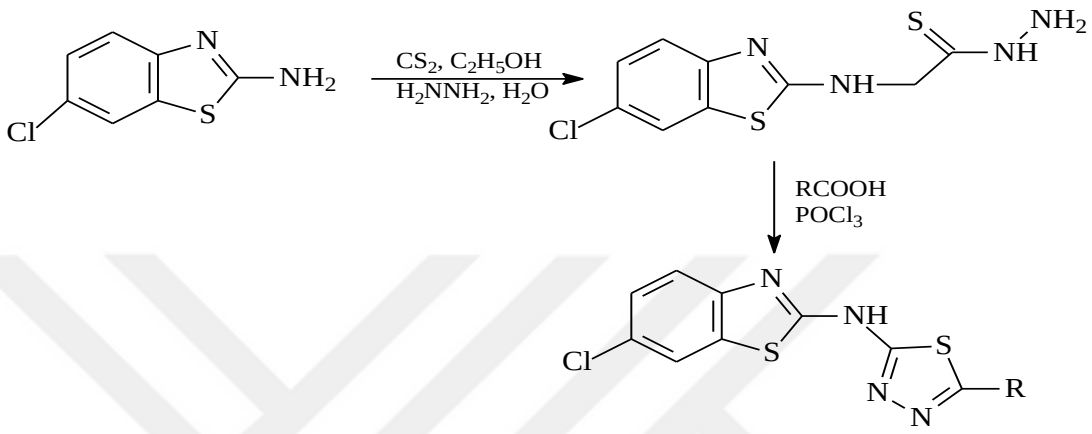


Figure 1.17. Antimicrobial activity of 1,3,4-thiadiazole

1.3.2. Anti Inflammatory Activities

Shiv K Gupta et al. synthesized disubstituted thiadiazole derivatives by reaction between salicylic acid and thiosemicarbazide in presence of conc. H2SO4.

In vivo anti-inflammatory activity was evaluated and compared with standard drug ibuprofen and all compounds showed moderate anti inflammatory activity (Figure 1.18) [32].

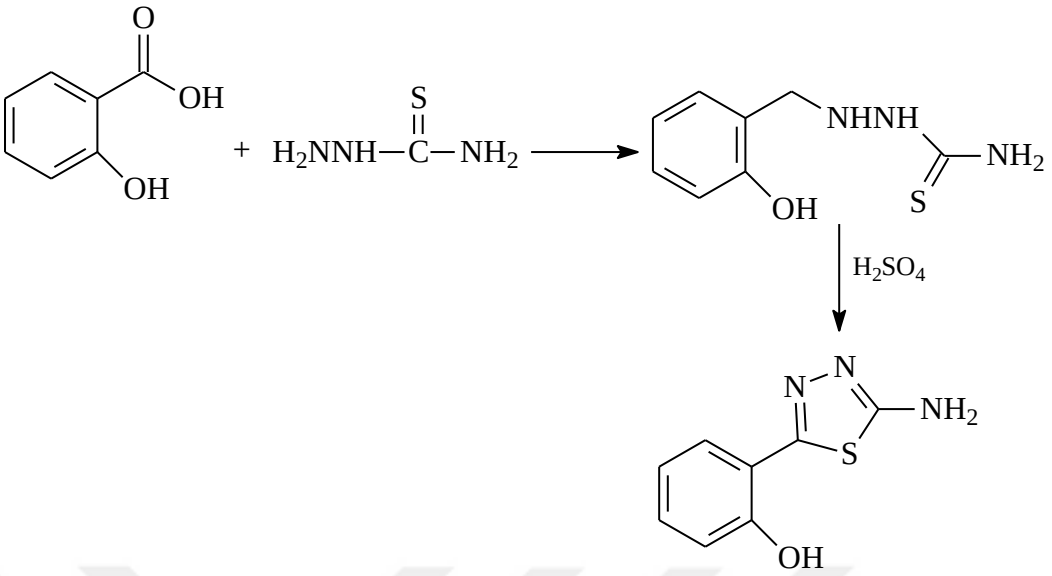


Figure 1.18. Anti inflammatory activity of 1,3,4-Thiadiazole

1.3.3. Anti Cancer Activity

Suddasatwa Banerjee vd. Thiadiazole derivatives, and noted that the compounds exhibited significant anti-cancer activity at much lower concentrations (Figure 1.19) [33].

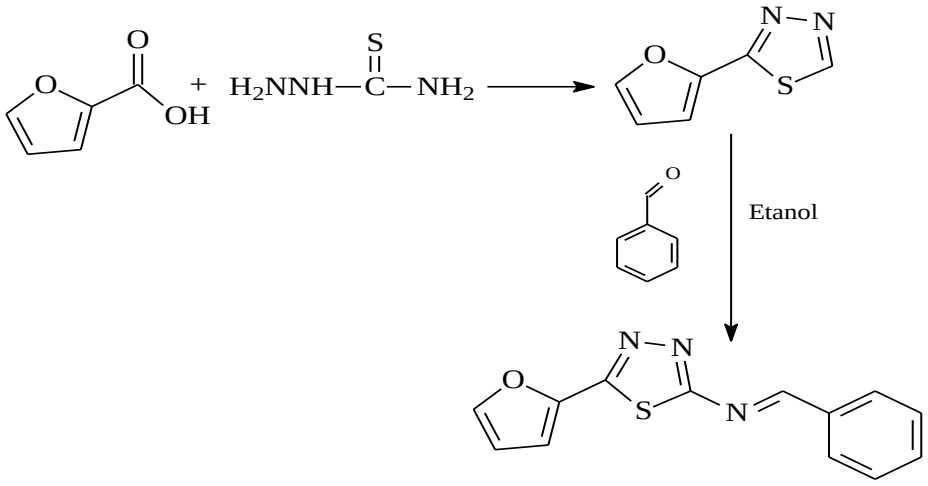


Figure 1.19. Anti cancer activity of 1,3,4-Thiadiazole

1.3.4. Antidiabetic activity

S. R. Patten et al. Synthesized thiadiazole derivatives and evaluated all compounds for anti-diabetic activity by the tail-tipping method which is alloxane-bound. In the study, it was reported that most of the compounds show promising activities (Figure 1.20) [34].

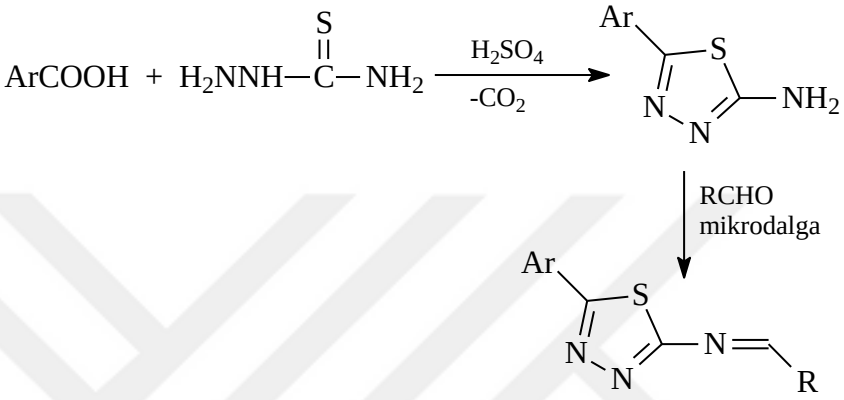


Figure 1.20. Anti Antidiabetic activity of 1,3,4-Thiadiazole

1.3.5. Anti Oxidant Activity

Brijendra Kumar Soni et al .synthesized thiadiazole derivative and evaluated for *in vitro* antioxidant activity by hydrogen peroxide and nitric oxide scavenging activity and lipid peroxidation inhibitory activity. Some of the compounds showed potent antioxidant activity (Figure 1.21) [35].

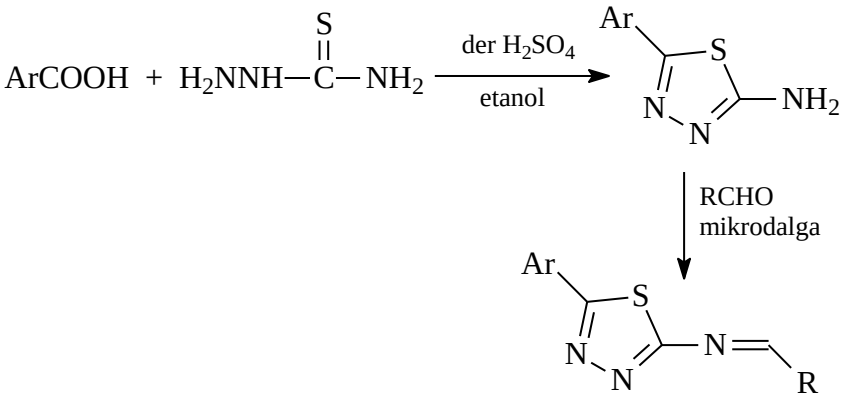


Figure 1.21. Anti oxidant activity of 1,3,4-Thiadiazole

1.3.6. Anticonvulsant Activity

Muhammed Shahar Yar et al. Five members of the heterocyclic compound sequence synthesized and tested for their anticonvulsant activity. Among the compounds synthesized, 2- (4-chlorophenyl) amino-5- (4-pyridyl) -1,3,4-thiadiazole series was found to be promising compound (Figure 1.22) [36].

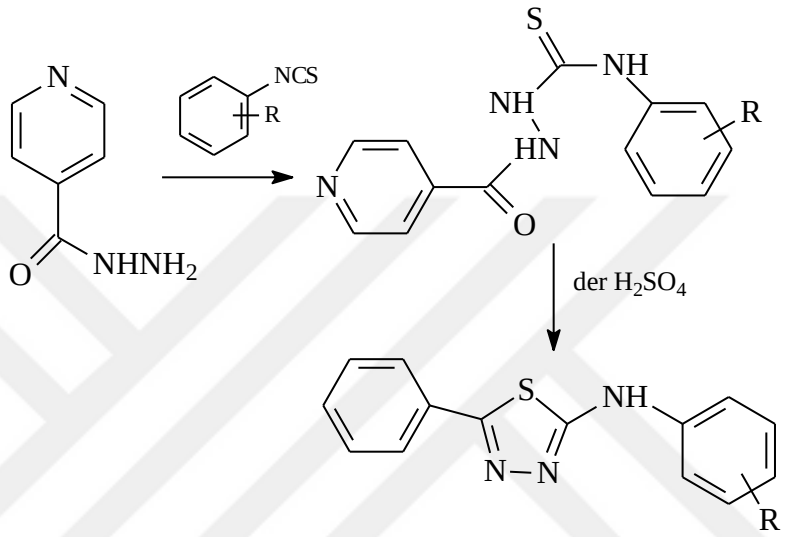


Figure 1.22. Anti convulsant activity of 1,3,4-Thiadiazole

1.3.7. Antituberculous Activity

Karigar Asifa et al. A series of thiadiazole derivatives synthesized and investigated antitubercular activities against Mycobacterium tuberculosis using microplate blue-blot analysis. All synthesized compounds showed good anti-tuberculosis activity (Figure 1.23) [37].

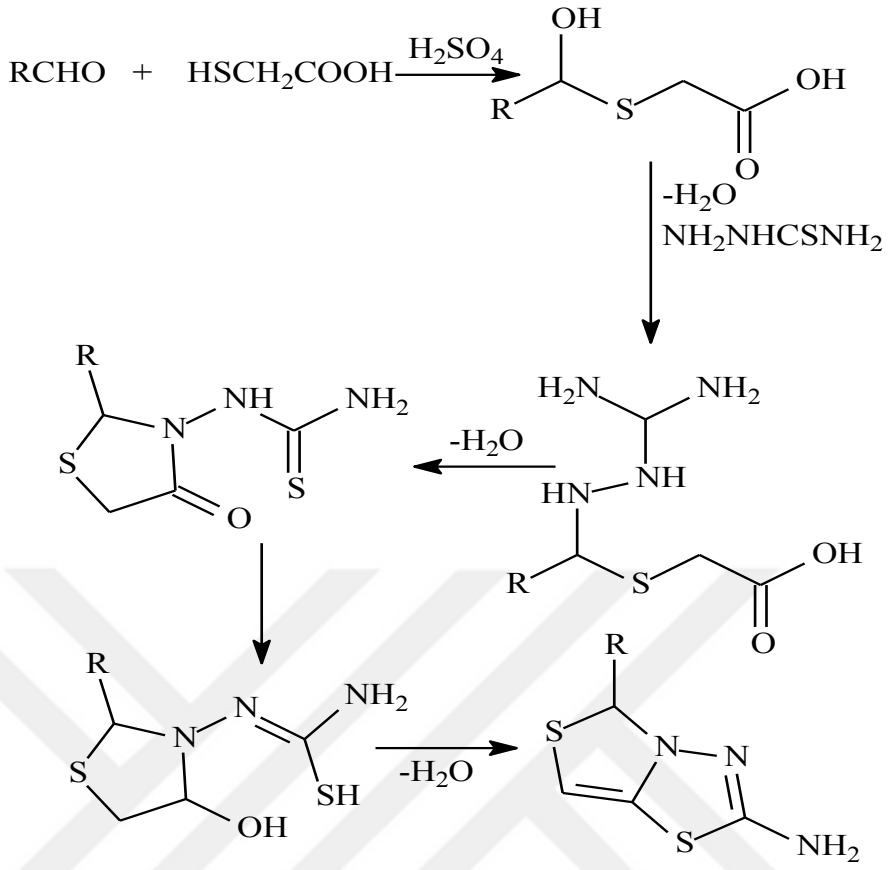


Figure 1.23. Antituberculous activity of 1,3,4-Thiadiazole

2. LITERATURE REVIEW

Ozturk et al synthesized 3-(1,3,4-thiadiazol-2-ylazo)quinoline-2,4-diol. And reported that compound had no antibacterial effect. [38].

Likewise, Bhatia et al synthesized imidazo [2, 1-b] [1,3,4] thiadiazole derivatives and screened for the antimicrobial activity and they reported they showed positive result against bacterial strains of *Shigella flexneri*, *Staphylococcus aureus* and *Candida albicans*. [39].

On the other hand, Kaur et al synthesized some of imidazole and 1,3,4-thiadiazole derivatives screened there antibacterial activity and reported that these compounds displayed good antibacterial activity against deffirent strains of bacteria with using Ampicillin as standard drug and also reported that the antifungal screening results showed mild activity against *Candida albicans* and *Aspergillus niger* strains using standard drug Amphotericin B to compare [40].

Ammen et al. synthesized 2-Amino-5-mercapto-1,3,4-Thiadiazole Derivatives. The result was the presence of some of the activities as antibacterial and antifungal [41].

In addition, Rezki et al. synthesizes novel 2, 5-disubstituted-1, 3, 4-thiadiazoles by IR, 1H-NMR, 13C-NMR, MS and elemental analyses. The result was the presence of some of the activities as antibacterial and antifungal.and antiproliferative activity [42].

On the other hand, Samee et al. synthesis of aseries of novel 2,5-dimercapto-1,3,4-thiadiazole derivatives. And anti-candida activity was determined by resazurin microplate assay (REMA). However, Some of the compounds were found to have good potency against *C. albicans* [43].

Salimon et al synthesis of 5-(*p*-substituted phenyl)-N-(3-(5-nitrofur-2-yl) allylidene)-1,3,4-thiadiazol-2-amine Derivatives. The synthesized compounds were screened for

their antimicrobial activities. Moreover, The preliminary results revealed that some of the compounds showed antimicrobial activities [44].

Purohit et al. Synthesis of Some New 1,3,4-Thiadiazoles and 1,3,4-Thiadiazines Containing 1,2,4-Triazolo Nucleus. All the synthesized compounds were screened for their antimicrobial activity. Furthermore, Some of the compounds exhibited significant inhibition on bacterial and fungal growth as compared to standard drugs [45].

Aly et al. Different condensed of N-[5-(3-Chlorobenzo[b]thiophen-2-yl)-1, 3, 4-thiadiazol-2-yl]-1H-benzo [d]imidazol-2-ylamine 3(a-c). Additionally, screened for antimicrobial activity against *E.coli (*gram negative) and other gram positive bacteria [46].

In contrast, Jalhan et al. synthesized and investigated biological activities and some Schiff bases of imidazo-[2, 1b]-1,3,4-thiadiazole derivatives. The purity of derivatives has been characterized by using IR, NMR and mass spectra.. The derivative has shown moderate to good activity when compared with standard antibiotic ampicillin. In addition, Schiff bases have different biological activities like ,antimicrobial [47].

3. MATIREAL AND METHOD

3.1. Experimental Chemistry

Solvents were dried and distilled prior to use. Infrared spectra were recorded on FT-IR Fourier Transform Infrared Spectroscopy Spectrum. ^{1}H-NMR and ^{13}C-NMR spectra were taken on Bruker AVANCE III 400 MHz NMR Spectrometer. The UV-Vis was carried out on Thermo Scientific MULTISKAN GO. Melting points were uncorrected and recorded on SMP30 melting point apparatus.

3.1.1. Synthesis of 1, 3, 4-Thiadiazole Derivatives

The mixture of 3,4 methylene dioxy cynnamic acide derivatives and phenylthiosemicarbazide derivatives were placed into refrigerator. And then phosphorous oxychloride was added drop-wise to a cold mixture with stirring, reflux was continued for three hours. After the reaction was completed, cooled in room temperature, added to stirred iced water and neutralized by add ammoniac solution. The precipitated product was filtered, washed with distillated water.

3.1.1.1. Synthesis of 5-[2-(1,3-benzodioxol-5-yl)ethenyl]-N-phenyl-1,3,4-thiadiazol -2-amine

The mixture of 3,4 methylene dioxy sinnmic asid (0.3 g ,0.00156 mole) and phenyl thiosemicarbazide (0.261 g ,0.00156 mole) were put into refrigerator to cold it and, then phosphorous oxychloride (1.5 ml) was added drop-wise to a cold mixture with stirring, reflux was continued for two hours. After the reaction was completed, cooled in room temperature, added to stirred iced water and neutralized by adding ammoniac solution. The precipitated product was filtered, washed with distillated water (Figure 3.1).

White solid, Yield: (90%), mp: 270ºC; **IR(cm^{-1}) υ_{max}:** 3218.00, 3188.80, 3138.52 (stretching, -NH), 3050.93 (Arbenzene, C-H), 2893.53 (Aliphatic, C-H), 1657.83 (-C=C-), 1601.04 (thiadiazole, C=N), 691.26 (C-S-C), 1124.77 (C-O-C); **^{1}H-NMR**

(DMSO-d_6) (ppm): 7.64 (d)(H1), 7.64 (d)(H2), 7.15 (s)(H3), 7.30 (H4), 7.04-7.01 (dd)(H5), 7.38 -7.30 (H6), 7.38 -7.30 (H7), 7.38 -7.30 (H8), 6,11(H9), 6,53 (d)(H10), 7,14 (d) (H11), 10,44 (H12); **^{13}C-NMR (DMSO-d_6) (ppm):** 122.52 (C1), 108.91 (C2), 148.53 (C3), 148.48 (C4), 106.32 (C5), 130.58 (C6), 141.03 (C7), 117.61 (C8), 129.56 (C9), 123.48 (C10), 129.56 (C11), 117.61 (C12), 101.81 (C13), 141.29 (C14), 118.07 (C15) 136.40(C16), 158.55(C17); **UV-Vis Absorptions(nm):** 293, 363.

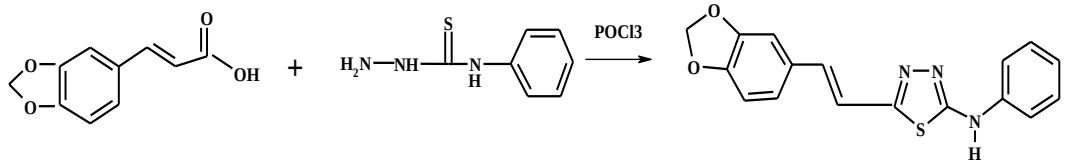


Figure 3.1. Synthesis of 5-[2-(1,3-benzodioxol-5-yl)ethenyl]-*N*-phenyl-1,3,4-thiadiazol-2-amine

3.1.1.2. Synthesis of 5-[2-(1,3-benzodioxol-5-yl)ethenyl]-N-[2'-chlorophenyl]-1,3,4-thiadiazol-2-amine

The mixture of 3,4 methylene dioxy sinnmic asid (0.285 g ,0.00148 mole) and 2-chloro phenyl thiosemicarbazide (0.3 g ,0.00148 mole) were put into refrigerator to cold it. And then phosphorous oxychloride (2 ml) was added drop-wise to a cold mixture with stirring, reflux was continued for two hours. After the reaction was completed, cooled in room temperature, added to stirred iced water and neutralized by add ammoniac solution. The precipitated product was filtered, washed with distillated water (Figure 3.2).

White solid, Yield: (99%), mp: 160ºC; **IR(cm^{-1}) υ_{max}:** 3161.32, 3130.00 (stretching, -NH), 3035.19 (Arbenzene, C-H), 2946.00, 2900.19 (Aliphatic, C-H), 1624.22 (-C=C-), 1593.86 (thiadiazole, C=N), 683.72 (C-S-C), 1090.61 (C-O-C); **^{1}H-NMR (DMSO-d_6) (ppm):** 7,52 (d)(H1), 7,52 (d)(H2), 7,31 (s)(H3), 8,22 (d)(H5), 7,41-7,35(m) (H6), 7,41-7,35(m) (H7), 7,17-7,11 (m)(H8), 6,07 (H9), 6,94 (H10), 7,17-7,11 (H11), 9,10 (H12); **^{13}C-NMR (DMSO-d_6) (ppm):** 123.95 (C1), 108.91 (C2), 148.56 (C3), 148.46 (C4), 106.31 (C5), 130.52 (C6), 104.76 (C7), 123.59 (C8), 128.43 (C9), 122.79 (C10), 130.23 (C11), 163.92 (C12), 101.81 (C13), 104.76 (C14), 117.55 (C15) 136.44 (C16), 148.84 (C17); **UV-Vis Absorptions(nm):** 276, 347.

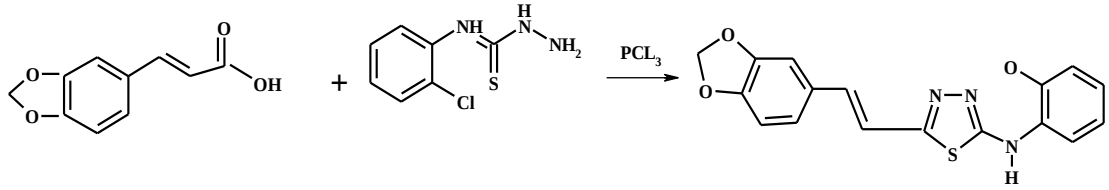


Figure 3.2. Synthesis of 5-[2-(1,3-benzodioxol-5-yl)ethenyl]-*N*-[2'-chlorophenyl]-1,3,4-thiadiazol-2-amine

3.1.1.3. Synthesis of 5-[2-(1,3-benzodioxol-5-yl)ethenyl]-N-[4'-chlorophenyl]-1,3,4-thiadiazol-2-amine

The mixture of 3,4 methylene dioxy sinnmic asid (0.285 g ,0.00148mole) and 4-chloro phenyl thiosemicarbazide (0.3 g ,0.00148 mole) were put into refrigerator to cold it. And then phosphorous oxychloride (2 ml) was added drop-wise to a cold mixture with stirring, reflux was continued for two hours. After the reaction was completed, cooled in room temperature, added to stirred iced water and neutralized by add ammoniac solution. The precipitated product was filtered, washed with distillated water (Figure 3.3).

White solid, Yield: (95%), mp: 294ºC; **IR(cm^{-1}) υ_{max}:** 3239.67 3164.96 (stretching, -NH), 3040.21, 2997.12 (Arbenzene, C-H), 2893.24 (Aliphatic, C-H), 1623.00 (-C=C-), 1604.52 (thiadiazole, C=N), 696.29 (C-S-C), 1093.06 (C-O-C); **^{1}H-NMR (DMSO-d_6) (ppm):** 7,41 (d)(H1), 7,41 (d)(H2), 7,18 (H3), 7,34 (d)(H4), 7,49 (d)(H5), 7,69 (d) (H7), 7,34(d)(H8), 6,07 (H9), 6,94 (H10), 10,63 (H12); **^{13}C-NMR (DMSO-d_6) (ppm):** 123.58 (C1), 108.91 (C2), 148.47 (C3), 148.48 (C4), 106.32 (C5), 130.51 (C6), 139.88 (C7), 117.48 (C8), 129.39 (C9), 125.88 (C10), 129.39 (C11), 117.48 (C12), 101.82 (C13), 139.88 (C14), 119.53 (C15) 136.73 (C16), 159.03 (C17); **UV-Vis Absorptions(nm):** 291, 363.

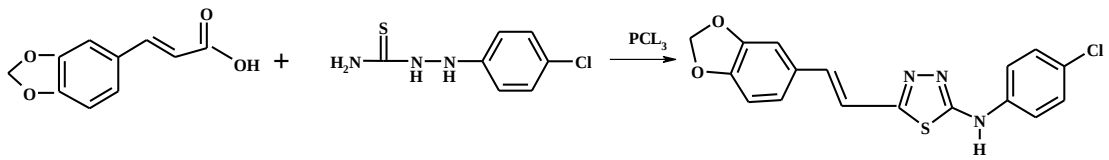


Figure 3.3. Synthesis of 5-[2-(1,3-benzodioxol-5-yl)ethenyl]-*N*-[4'-chlorophenyl]-1,3,4-thiadiazol-2-amine

3.1.1.4. Synthesis of 5-[2-(1,3-benzodioxol-5-yl)ethenyl]-N-[2'-fluorophenyl]-1,3,4-thiadiazol-2-amine

The mixture of 3,4 methylene dioxy sinnmic asid (0.3 g ,0.00156 mole) and 2-fluoro phenyl thiosemicarbazide (0.2892 g ,0.00156 mole) were put into refrigerator to cold it. And then phosphorous oxychloride (1.5 ml) was added drop-wise to a cold mixture with stirring, reflux was continued for two hours. After the reaction was completed, cooled in room temperature, added to stirred iced water and neutralized by add ammoniac solution. The precipitated product was filtered, washed with distillated water (Figure 3.4).

White solid, Yield: (98%), mp: 240ºC; **IR(cm^{-1}) υ_{max}:** 3186.65, 3138.90 (stretching, -NH), 3040.00 (Arbenzene, C-H), 2981.80, 2901.98 (Aliphatic, C-H), 1619.44 (-C=C-), 1604.53 (thiadiazole, C=N), 683.36 (C-S-C), 1089.04 (C-O-C); **^{1}H-NMR (DMSO-d_6) (ppm):** 7,26-7,21 (H1), 7,26-7,21 (H2), 7,19 (H3), 7,29(d)(H5), 7,10-7,05 (dd) (H6), 7,10-7,05(dd) (H7), 7,14 (H8), 6,07 (H9), 6,93 (H10), 6,95 (H11), 10,32 (H12); **^{13}C-NMR (DMSO-d_6) (ppm):** 121.24 (C1), 108.90 (C2), 148.56 (C3), 148.46 (C4), 106.32 (C5), 125.27 (C6), 136.55 (C7), 123.68 (C8), 123.58 (C9), 125.23 (C10), 115.64 (C11), 163.29 (C12), 101.81 (C13), 136.55 (C14), 117.54 (C15) 130.53 (C16), 153.67 (C17); **UV-Vis Absorptions(nm):** 294, 362.

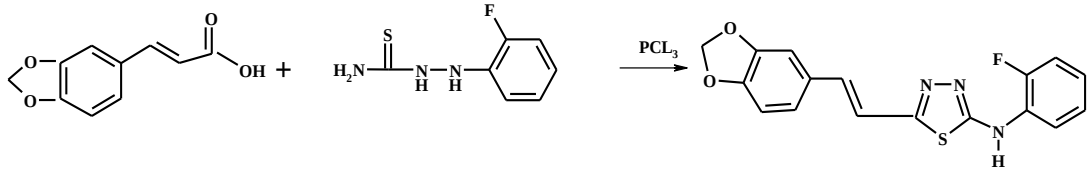


Figure 3.4. Synthesis of 5-[2-(1,3-benzodioxol-5-yl)ethenyl]-*N*-[2'-fluorophenyl]-1,3,4-thiadiazol-2-amine

3.1.1.5. Synthesis of 5-[2-(1,3-benzodioxol-5-yl)ethenyl]-N-[3'-fluorophenyl]-1,3,4-thiadiazol-2-amine

The mixture of 3,4 methylene dioxy sinnmic asid (0.3 g ,0.00156 mole) and 3-fluoro phenyl thiosemicarbazide (0.295 g ,0.00159 mole) were put into refrigerator to cold it and, then phosphorous oxychloride (2 ml) was added drop-wise to a cold mixture with stirring, reflux was continued for two hours. After the reaction was completed,

cooled in room temperature, added to stirred iced water and neutralized by adding ammoniac solution. The precipitated product was filtered, washed with distillated water (Figure 3.5).

White solid, Yield: (95%), mp: 264ºC; **IR(cm^{-1}) υ_{max}:** 3256.24, 3206.72 (stretching, -NH), 3040.00 (Arbenzene, C-H), 2902.41 (Aliphatic, C-H), 1617.13 (-C=C-), 1559.55 (thiadiazole, C=N), 678.60 (C-S-C), 1093.04 (C-O-C); **^{1}H-NMR (DMSO-d_6) (ppm):** 7,31(d)(H1), 7,31 (d)(H2), 7,20 (H3), 7,69 (d)(H4), 7,39 (d) (H6), 6,83 (m) (H7), 7,39 (d)(H8), 6,03 (H9), 6,94 (H10), 7,14 (H11), 10,76 (H12); **^{13}C-NMR (DMSO-d_6) (ppm):** 123.62 (C1), 108.60 (C2), 148.60 (C3), 148.48 (C4), 106.32 (C5), 131.06 (C6), 142.64 (C7), 117.40 (C8), 130.48 (C9), 108.81 (C10), 164.20 (C11), 113.87 (C12), 101.83 (C13), 142.53 (C14), 117.40 (C15) 136.85 (C16), 159.21 (C17); **UV-Vis Absorptions(nm):** 293, 306,275,350.

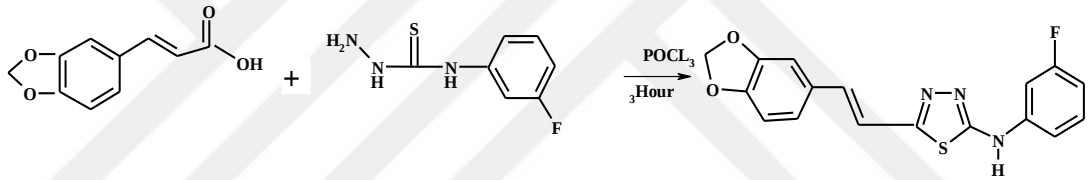


Figure 3.5. Synthesis of 5-[2-(1,3-benzodioxol-5-yl)ethenyl]-*N*-[3'-fluorophenyl]-1,3,4-thiadiazol-2-amine.

3.1.1.6. Synthesis of 5-[2-(1,3-benzodioxol-5-yl)ethenyl]-N-[4'-fluorophenyl]-1,3,4-thiadiazol-2-amine

The mixture of 3,4 methylene dioxy sinnmic asid (0.3 g ,0.00156mole) and 4-fluoro phenyl thiosemicarbazide (0.2892 g ,0.00156 mole) were put into refrigerator to cold it and, then phosphorous oxychloride (1.5 ml) was added drop-wise to a cold mixture with stirring, reflux was continued for two hours. After the reaction was completed, cooled in room temperature, added to stirred iced water and neutralized by adding ammoniac solution. The precipitated product was filtered, washed with distillated water (Figure 3.6).

White solid, Yield: (90%), mp: 285ºC; **IR(cm^{-1}) υ_{max}:** 3255.84, 3219.04, 3152.57 (stretching, -NH), 3051.69, 3015.97 (Arbenzene, C-H), 2906.232 (Aliphatic, C-H), 1618.96 (-C=C-), 1605.57 (thiadiazole, C=N), 681.37 (C-S-C), 1093.05 (C-O-C);

^{1}H-NMR (DMSO-d_6) (ppm): 7,22-7,12 (H1), 7,22-7,12 (H2), 7,22-7,12(H4), 7,69-7,66 (m) (H5), 7,69-7,66 (H7), 7,22-7,12 (H8), 6,06 (H9), 6,93 (d)(H10), 7,33 (H11), 10,52 (H12); **^{13}C-NMR (DMSO-d_6) (ppm):** 119.76 (C1), 108.89 (C2), 148.53 (C3), 148.46 (C4), 106.29 (C5), 130.55 (C6), 137.50 (C7), 116.21 (C8), 119.69 (C9), 158.97 (C10), 119.69 (C11), 116.21 (C12), 101.81 (C13), 137.50 (C14), 115.99 (C15) 136.48 (C16), 156.60 (C17); **UV-Vis Absorptions(nm):** 297,359.

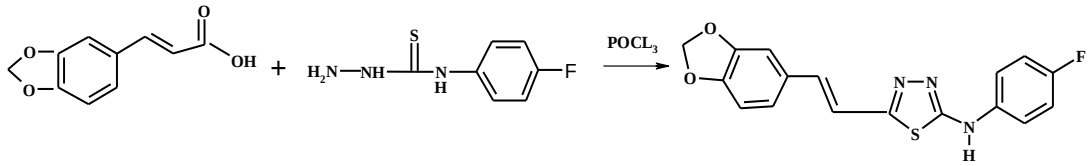


Figure 3.6. Synthesis of 5-[2-(1,3-benzodioxol-5-yl)ethenyl]-*N*-[4'-fluorophenyl]-1,3,4-thiadiazol-2-amine.

3.1.1.7. Synthesis of 5-[2-(1,3-benzodioxol-5-yl)ethenyl]-N-[2'-methoxyphenyl]-1,3, 4-thiadiazol-2-amine

The mixture of 3,4 methylene dioxy sinnmic asid (0.3 g ,0.00156 mole) and 2-methoxy phenyl thiosemicarbazide (0.31g , 0.00157 mole) were put into refrigerator to cold it and, then phosphorous oxychloride (0.5 ml) was added drop-wise to a cold mixture with stirring, reflux was continued for two hours. After the reaction was completed, cooled in room temperature, added to stirred iced water and neutralized by adding ammoniac solution. The precipitated product was filtered, washed with distillated water (Figure 3.7).

White solid, Yield: (96%), mp: 175ºC; **IR(cm^{-1}) υ_{max}:** 3377.67 (stretching, -NH), 3069.44 (Arbenzene, C-H), 2909.17 (Aliphatic, C-H), 1623.00 (-C=C-), 1604.40 (thiadiazole, C=N), 686.55 (C-S-C), 1094.98 (C-O-C); **^{1}H-NMR (DMSO-d_6) (ppm):** H1-H8 protons are overlapped between 7,4 and 6,89, 6,07 (H9), 9,76 (H12); **^{13}C-NMR (DMSO-d_6) (ppm):** 130.63 (C1), 108.89 (C2), 148.93 (C3), 148.45 (C4), 106.29 (C5), 126.65 (C6), 135.96 (C7), 123.43 (C8), 129.99 (C9), 119.76 (C10), 111.53 (C11), 159.08 (C12), 101.79 (C13), 134.13 (C14), 117.78 (C15), 135.95 (C16), 151.16 (C17), 56.18 (C of $-OCH_3$) (H19) ; **UV-Vis Absorptions(nm):** 280,,353.

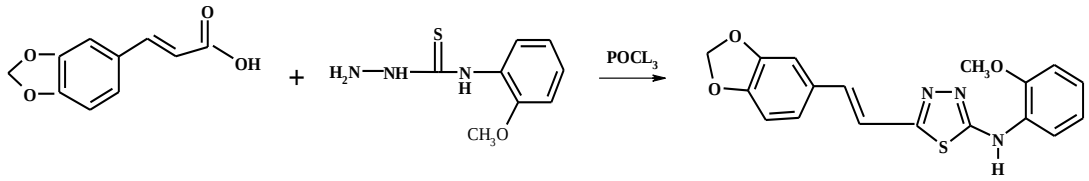


Figure 3.7. Synthesis of 5-[2-(1,3-benzodioxol-5-yl)ethenyl]-*N*-[2'-methoxyphenyl]-1,3,4-thiadiazol-2-amine

3.1.1.8. Synthesis of 5-[2-(1,3-benzodioxol-5-yl)ethenyl]-N-[3'-methoxyphenyl]-1,3, 4-thiadiazol-2-amine

The mixture of 3,4 methylene dioxy sinnmic asid (0.3 g ,0.00156 mole) and 3-methoxy phenyl thiosemicarbazide (0.31 g, 0.00157 mole) were put into refrigerator to cold it and, then phosphorous oxychloride (0.5 ml) was added drop-wise to a cold mixture with stirring, reflux was continued for two hours. After the reaction was completed, cooled in room temperature, added to stirred iced water and neutralized by adding ammoniac solution. The precipitated product was filtered, washed with distillated water (Figure 3.8).

White solid, Yield: (97%), mp: 225ºC; **IR(cm^{-1}) υ_{max}:** 3199.57, 3139.96 (stretching, -NH), 3040.00 (Arbenzene, C-H), 2907.13 (Aliphatic, C-H), -- (-C=C-), 1604.24 (thiadiazole, C=N), 682.20 (C-S-C), 1165.46, 1091.04 (C-O-C); **^{1}H-NMR (DMSO-d_6) (ppm):** 7,38 (d)(H1), 7,38 (d)(H2), 7,18 (H3), 7,14 (d)(H4), 7,34 (H6), 7,26 (t) (H7), 7,14 (d)(H8), 6,07 (H9), 6,61 (d)(H10), 6,94(d)(H11), 10,51 (H12); **^{13}C-NMR (DMSO-d_6) (ppm):** 123.53 (C1), 106.30 (C2), 148.53 (C3), 148.47 (C4), 104.09 (C5), 130.55 (C6), 142.10 (C7), 110.48 (C8), 130.39 (C9), 107.61 (C10), 160.41 (C11), 108.91 (C12), 101.81 (C13), 142.10 (C14), 117.54 (C15) 136.49 (C16), 158.63 (C17), 55.50 (C of $-OCH_3$) (H19) ; **UV-Vis Absorptions(nm):** 288,362 (very weak).

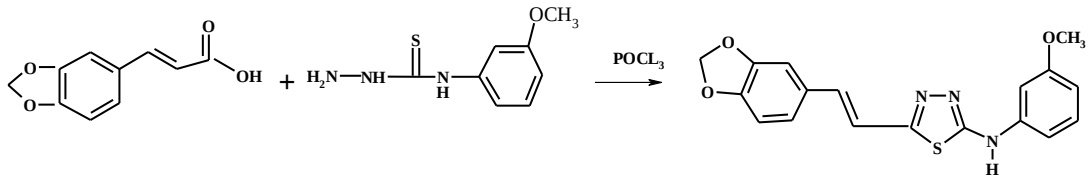


Figure 3.8. Synthesis of 5-[2-(1,3-benzodioxol-5-yl)ethenyl]-*N*-[3'-methoxyphenyl]-1,3,4-thiadiazol-2-amine.

3.1.1.9. Synthesis of 5-[2-(1,3-benzodioxol-5-yl)ethenyl]-N-[4'-methoxyphenyl]-1,3, 4-thiadiazol-2-amine

The mixture of 3,4 methylene dioxy sinnmic asid (0.3 g ,0.00156 mole) and 4-methoxy phenyl thiosemicarbazide (0.31g ,0.00157 mole) were put into refrigerator to cold it and, then phosphorous oxychloride (0.5 ml) was added drop-wise to a cold mixture with stirring, reflux was continued for two hours. After the reaction was completed, cooled in room temperature, added to stirred iced water and neutralized by adding ammoniac solution. The precipitated product was filtered, washed with distillated water (Figure 3.9).

White solid, Yield: (96%), mp: 257C; **IR(cm^{-1}) υ_{max}:** 3240.55, 3194.67, 3218.32 (stretching, -NH), 3038.74, 3012.27 (Arbenzene, C-H), 2981.98, 2962.99, 2906.97, 2834.27 (Aliphatic, C-H), -- (-C=C-), 1604.52 (thiadiazole, C=N), 680.17 (C-S-C), 1114.87, 1091.03 (C-O-C); **^{1}H-NMR (DMSO-d_6) (ppm):** 7,55 (d)(H1), 7,55 (d)(H2), 7,33 (d)(H3), 7,11 (H4), 7,34 (H5), 7,34 (H7), 7,11 (H8), 6,03 (H9), 6,93 (H10), 6,95 (H11), 10,29 (H12); **^{13}C-NMR (DMSO-d_6) (ppm):** 123.42 (C1), 108.90 (C2), 148.45 (C3), 148.45 (C4), 106.25 (C5), 130.63 (C6), 134.50 (C7), 119.96 (C8), 114.79 (C9), 163.88 (C10), 114.79 (C11), 119.96 (C12), 101.79 (C13), 136.06 (C14), 117.72 (C15) 136.06 (C16), 155.17 (C17), 55.71 (C of $-OCH_3$) (H19) ; **UV-Vis Absorptions(nm):** 286,360.

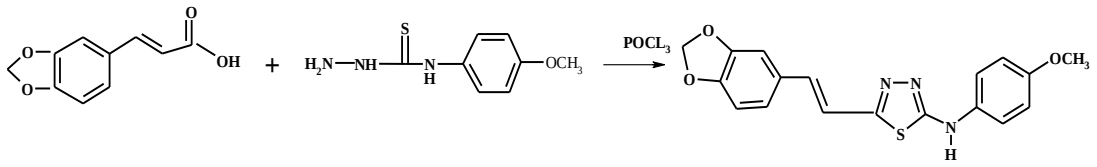


Figure 3.9. Synthesis of 5-[2-(1,3-benzodioxol-5-yl)ethenyl]-*N*-[4'-methoxyphenyl]-1,3,4-thiadiazol-2-amine

3.1.1.10. Synthesis of 5-[2-(1,3-benzodioxol-5-yl)ethenyl]-N-[2',4'-dichlorophenyl]-1,3,4-thiadiazol-2-amine

The mixture of 3,4 methylene dioxy sinnmic asid (0.2 g,0.00104 mole) and 2,4 dichloro phenyl thiosemicarbazide (0.246 g ,0.00104 mole)were put into refrigerator to cold it and, then phosphorous oxychloride (1.5 ml) was added drop-wise to a cold

mixture with stirring, reflux was continued for two hours. After the reaction was completed, cooled in room temperature, added to stirred iced water and neutralized by adding ammoniac solution. The precipitated product was filtered, washed with distillated water (Figure 3.10).

White solid, Yield: (98%), mp: 178ºC; **IR(cm^{-1}) υ_{max}:** 3240.00 (stretching, -NH),

3040.00 (Arbenzene, C-H), 2981.84, 2869.06 (Aliphatic, C-H), 1620.00 (-C=C-), 1591.30 (thiadiazole, C=N), 694.63 (C-S-C), 1098.09 (C-O-C); **^{1}H-NMR (DMSO-d_6) (ppm):** 7,34 (d)(H1), 7,34 (d)(H2), 7,20 (H3), 7,46 (s)(H5), 7,07 (H7), 7,06 (H8), 6,07 (H9), 6,84 (H10), 6,86 (H11), 9,82 (H12); **UV-Vis Absorptions(nm):** 280,363.

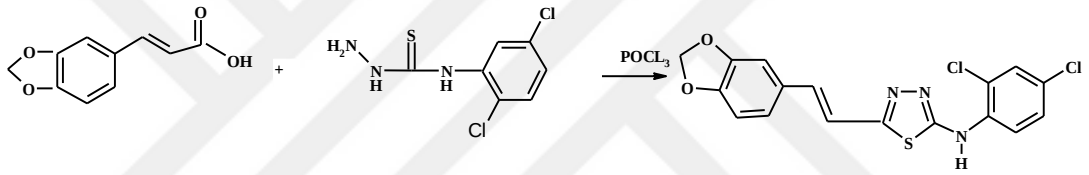


Figure 3.10. Synthesis of 5-[2-(1,3-benzodioxol-5-yl)ethenyl]-*N*-[2',4'-dichlorophenyl]-1,3, 4-thiadiazol-2-amine

3.1.1.11. Synthesis of 5-[2-(1,3-benzodioxol-5-yl)ethenyl]-N-[4'-nitrophenyl]-1,3, 4-thiadiazol-2-amine

The mixture of 3,4 methylene dioxy sinnmic asid (0.3 g ,0.00156 mole) and 4-nitro phenyl thiosemicarbazide (0.2717 g ,0.00128 mole) were put into refrigerator to cold it and, then phosphorous oxychloride (1.5 ml) was added drop-wise to a cold mixture with stirring, reflux was continued for two hours. After the reaction was completed, cooled in room temperature, added to stirred iced water and neutralized by adding ammoniac solution. The precipitated product was filtered, washed with distillated water (Figure 3.11).

White solid, Yield: (97%), mp: 335ºC; **IR(cm^{-1}) υ_{max}:** 3260.79, 3222.89, 3167.94 (stretching, -NH), 3058.86, 3024.81 (Arbenzene, C-H), 2981.91, 2916.39 (Aliphatic, C-H), 1621.52 (-C=C-), 1599.58 (thiadiazole, C=N), 686.45 (C-S-C), 1081.90 (C-O-C), 1575.26 and 1361.98 para-NO_2 ; **^{1}H-NMR (DMSO-d_6) (ppm):** 7,38-7,21 (H1),

7,38-7,21 (H2), 7,41 (H3), 7,89 (d)(H4), 8,26 (H5), 8,26 (d) (H7), 7,89 (d)(H8), 6,07 (s)(H9), 6,94 (d)(H10), 7,15 (d)(H11), 11,04 (H12); **^{13}C-NMR (DMSO-d_6) (ppm):** 123.82 (C1), 108.91 (C2), 148.73 (C3), 148.48 (C4), 106.36 (C5), 130.37 (C6), 146.0 (C7), 117.14 (C8), 125.95 (C9), 141.31 (C10), 125.95 (C11), 117.14 (C12), 101.86 (C13), 146.67 (C14), 117.51 (C15) 137.50 (C16), 160.61 (C17) ; **UV-Vis Absorptions(nm):** 307,346.

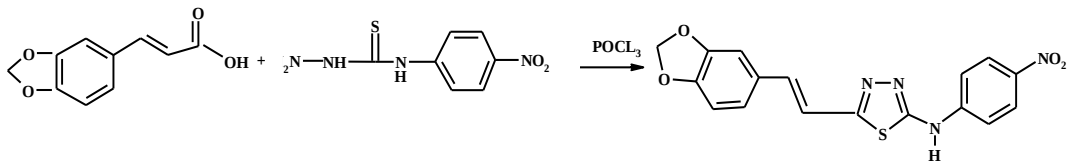


Figure 3.11. Synthesis of 5-[2-(1,3-benzodioxol-5-yl)ethenyl]-*N*-[4'-nitrophenyl]-1,3,4-thiadiazol-2-amine

3.1.1.12. Synthesis of 5-[2-(1,3-benzodioxol-5-yl)ethenyl]-N-[2'-ethylphenyl]-1,3,4-thiadiazol-2-amine

The mixture of 3,4 methylene dioxy sinnmic asid (0.2 g , 0.00104 mole) and 2-ethyl phenyl thiosemicarbazide (0.203 g ,0.001039 mole) were put into refrigerator to cold it and, then phosphorous oxychloride (1.5 ml) was added drop-wise to a cold mixture with stirring, reflux was continued for two hours. After the reaction was completed, cooled in room temperature, added to stirred iced water and neutralized by adding ammoniac solution. The precipitated product was filtered, washed with distillated water (Figure 3.12).

White solid, Yield: (94%), mp: 195ºC; **IR(cm^{-1}) υ_{max}:** --- (stretching, -NH), 3042.47, 2997.95 (Arbenzene, C-H), 2893.19 (Aliphatic, C-H); **^{1}H-NMR (DMSO-d_6) (ppm):** 7,34- 7,30 (H1), 7,34-7,30 (H2), 7,02 (H3), 6,92-6,91 (H6), 6,92-6,91 (H7), 7,11 (H8), 6,01 (H9), 6,95 (H12), 1.29-1.25 (t) (-CH_3), 2.78-2.72 (q) (-CH_2-); **^{13}C-NMR (DMSO-d_6) (ppm):** 123.80 (C1), 108.89 (C2), 148.41 (C3), 148.43 (C4), 106.23 (C5), 129.56 (C6), 138.60 (C7), 125.65 (C8), 130.64 (C9), 123.36 (C10), 127.24 (C11), 135.79 (C12), 101.77 (C13), 138.60 (C14), 117.78 (C15) 137.00 (C16), 159.08 (C17), 14.92 (-CH_3), 24.28 (-CH_2-) (H19) ; **UV-Vis Absorptions(nm):** 288,356.

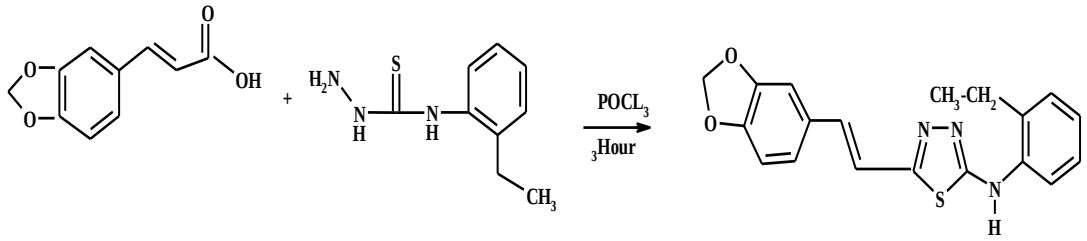


Figure 3.12. Synthesis of 5-[2-(1,3-benzodioxol-5-yl)ethenyl]-*N*-[2'-ethylphenyl]-1,3,4-thiadiazol-2-amine

3.1.1.13. Synthesis of 5- [2- (1,3- benzodioxol -5-yl)ethenyl] -N- [2'-methoxycarbonylphenyl]-1,3,4-thiadiazol-2-amine

The mixture of 3,4 methylene dioxy sinnmic asid (0.2 mg ,0.00104 mole) and 2-methoxy carbonyl phenyl thiosemicarbazide (0.246 g ,0.00109 mole)were put into refrigerator to cold it and, then phosphorous oxychloride (1,5 ml) was added drop-wise to a cold mixture with stirring, reflux was continued for two hours. After the reaction was completed, cooled in room temperature, added to stirred iced water and neutralized by adding ammoniac solution. The precipitated product was filtered, washed with distillated water (Figure 3.13).

White solid, Yield: (95%), mp: 312ºC; **IR(cm^{-1}) υ_{max}:** 3154.95 (stretching, -NH), 3067.62 (Arbenzene, C-H), 2981.86, 2964.12, 2869.73 (Aliphatic, C-H), 1611.00 (-C=C-), 1589.00 (thiadiazole, C=N), 681.07 (C-S-C), 1103.28 (C-O-C); **^{1}H-NMR (DMSO-d_6) (ppm):** 6,11 (H9), 9,28 (H12); **UV-Vis Absorptions(nm):** 282,292,298,302,357,371.

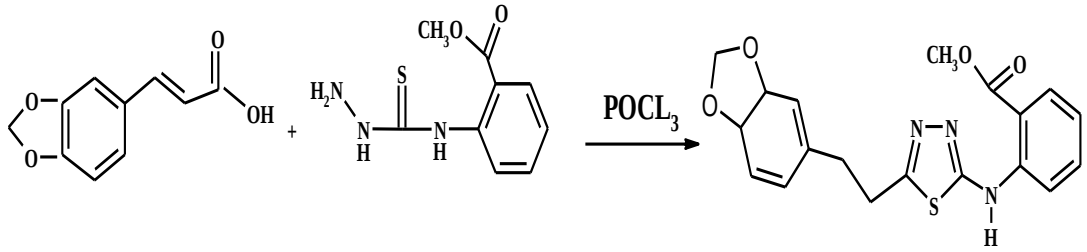


Figure 3.13. Synthesis of 5-[2-(1,3-benzodioxol-5-yl)ethenyl]-*N*-[2'-methoxycarbonylphenyl]-1,3,4-thiadiazol-2-amine

3.1.1.14. *Synthesis of 5-[2- (1,3- benzodioxol -5- yl)ethenyl] -N- benzyl -1,3,4-thiadiazol-2-amine*

The mixture of 3,4 methylene dioxy sinnmic asid (0.3 g , 0.00156 mole) and benzyl thiosemicarbazide (0.28298 g ,0.00156 mole) were put into refrigerator to cold it and, then phosphorous oxychloride (1.5 ml) was added drop-wise to a cold mixture with stirring, reflux was continued for two hours. After the reaction was completed, cooled in room temperature, added to stirred iced water and neutralized by adding ammoniac solution. The precipitated product was filtered, washed with distillated water (Figure 3.14).

White solid, Yield: (94%), mp: 218C; **IR(cm^{-1}) υ_{max}:** 3198.29 (stretching, -NH), 3040.00 (Arbenzene, C-H), 2981.80, 2869.83 (Aliphatic, C-H), 1620.00(-C=C-), 1601.16 (thiadiazole, C=N), 697.04 (C-S-C), 1094.98 (C-O-C); **^{1}H-NMR (DMSO-d_6) (ppm):** In the range of 7,38-6,93H1), In the range of 7,38-6,93 (H2), In the range of 7,38-6,93 (H3), In the range of 7,38-6,93 (H4), In the range of 7,38-6,93 (H6), In the range of 7,38-6,93 (H7), In the range of 7,38-6,93 (H8), 6,04 (H9), 8,44 (H12), 4,53(H13); **^{13}C-NMR (DMSO-d_6) (ppm):** 118.10 (C1), 108.88 (C2), 148.42 (C3), 148.28 (C4), 106.17 (C5), 130.72 (C6), 139.00 (C7), 128.01 (C8), 127.64 (C9), 128.88 (C10), 127.64 (C11), 128.01 (C12), 101.73 (C13), 139.00 (C14), 123.18 (C15) 135.02 (C16), 157.42 (C17), 48.45) (H18) ; **UV-Vis Absorptions(nm):** 279,353.

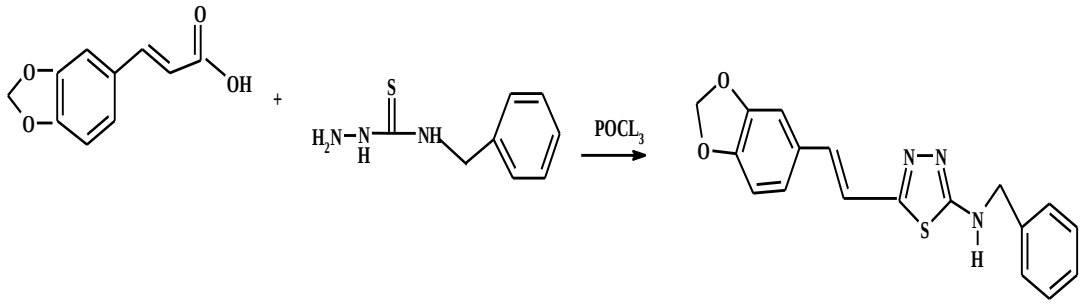


Figure 3.14. Synthesis of 5-[2-(1,3-benzodioxol-5-yl)ethenyl]-*N-benzyl*-1,3,4-thiadiazol-2-Amine

3.1.1.15. *Synthesis of 5-[2-(1,3-benzodioxol-5-yl)ethenyl]-N-(2'-phenylethyl)-1,3, 4-thiadiazol-2-amine*

The mixture of 3,4 methylene dioxy sinnmic asid (0.2 g , 0.00104 mole) and 2-phenyl ethyl thiosemicarbazide (0.2036 g ,0.00104 mole) were put into refrigerator to cold it and, then phosphorous oxychloride (1.5 ml) was added drop-wise to a cold mixture with stirring, reflux was continued for two hours. After the reaction was completed, cooled in room temperature, added to stirred iced water and neutralized by adding ammoniac solution. The precipitated product was filtered, washed with distillated water (Figure 3.15).

White solid, Yield: (96%), mp: 161ºC; **IR(cm^{-1}) υ_{max}:** 3176.01, 3127.19 (stretching, -NH), 3040.00 (Arbenzene, C-H), 2981.00, 2874.42 (Aliphatic, C-H), 1605.57 (-C=C-), 1584.65 (thiadiazole, C=N), 688.69 (C-S-C), 1093.81 (C-O-C); **^{1}H-NMR (DMSO-d_6) (ppm):** In the range of 7,30-7,23 (H1), In the range of 7,30-7,23 (H2), In the range of 7,30-7,23 (H3), In the range of 7,30-7,23 (H4), In the range of 7,30-7,23 (H6), In the range of 7,30-7,23 (H7), In the range of 7,30-7,23 (H8), 6,06 (H9), 8,05 (H12), 2,91 (CH_2-phenyl) and 3,5 (N-CH_2 under DMSO peaks) ; **^{13}C-NMR (DMSO-d_6) (ppm):** 118.19 (C1), 108.89 (C2), 148.42 (C3), 148.26 (C4), 106.17 (C5), 130.76 (C6), 134.90 (C7), 128.83 (C8), 129.18 (C9), 126.66 (C10), 129.18 (C11), 128.83 (C12), 101.73 (C13), 134.90 (C14), 123.13 (C15), 139.67 (C16), 157.04 (C17), 46.52 – 34.97 (H18) ; **UV-Vis Absorptions(nm):** 279,352.

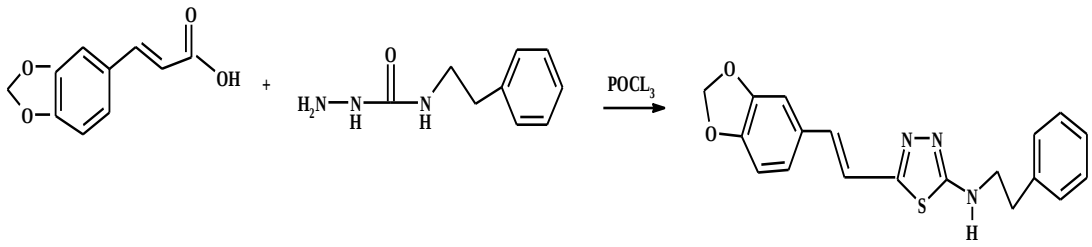


Figure 3.15. Synthesis of 5-[2-(1,3-benzodioxol-5-yl)ethenyl]-*N*-(2'-phenylethyl)-1,3,4-thiadiazol-2-amine

3.2. Antimicrobial Activity

3.2.1. Microorganism Strains

Gram negative (*Salmonella enteritidis, Salmonella typhimurium, Enterobacter aerogenes, Salmonella infantis, Salmonella kentucky, Escherichia coli*) and Gram positive (*Staphylococcus aureus, Bacillus subtilis, Enterococcus durans*) bacteria were chosen to test the antibacterial activity of 1,3,4-thiadiazole. The fungi *Candida albicans* was used to test the antifungal activity of 1,3,4-thiadiazole.

3.2.2. Microbial Activity Assay

The method used for microbial activity is disc diffusion method. In the study, 9 mm sized petri dishes containing 25 mL Mueller Hinton Agar were used. The newly synthesized thiadiazole derivative compounds were prepared at 5 mg / mL and 2.5 mg / mL concentrations. 5, 6, 7, 8, 10, 11, 12 and 14 were prepared at 5 mg / mL concentration and 13, 4, 17, 2, 9, 15 and 3 compounds at 2.5 mg / mL concentration. The compound (5- [2- (1,3-benzodioxol-5-yl) ethenyl] -N- [3'-chlorophenyl] -1,3,4-thiadiazol-2-amine in antimicrobial activity test due to the solubility problem has antimicrobial activity It was used. The prepared solvent was absorbed in sterile empty antimicrobial discs in different amounts and then allowed to dry overnight in the safety cabinet at room temperature.

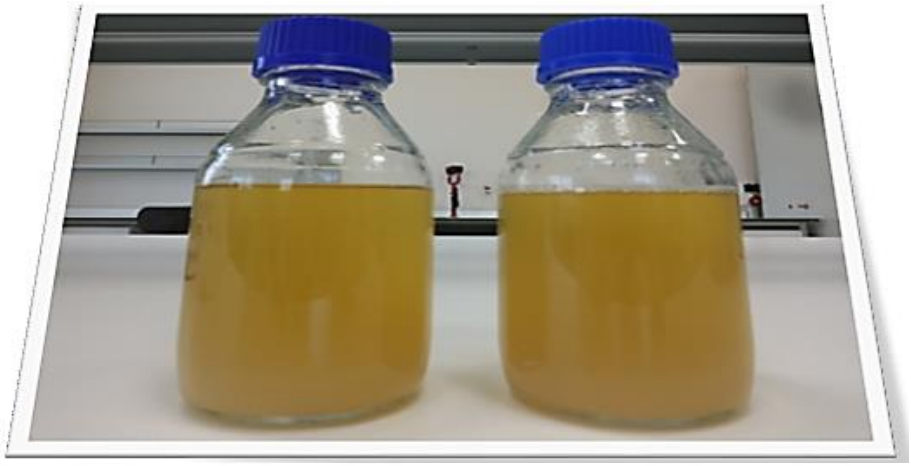
3.2.3. Preparation of Chemical Compounds

We've dissolving chemical compounds[0.2 g] in the solvent[THF] 40 ml.

All the paper disks were filled with the chemical in dishes where every dish contains 33 paper disks. Every chemical compound was prepared in three different concentrations (30 µ,50µ,80µ) Disks were kept at room temperature for 24 h in aseptic conditions.

3.2.4. Preparation of Media

The media were readied by including the parts according to maker's directions by measured 13,6 g of Hinton Agar in 400 ml of distilled water(DH_2O) , and disinfected in the autoclave at 121 ^{0}C and air weight for 20 min. Every medium was cooled to 45-60 ^{0}C and 25 ml of it was filled a Petri dish and allowed to solidify at room temperature in safety cabinet to avoid the contamination as shown in photograph.[48],[49],[50].



Photograph 3.1. Media preparatıon.

Photograph 3.2. Filling the media in petri dishes.

All types of bacteria that used in our work were mentioned in the Table 3.1.

Table 3.1. *List of different types of bacteria*.

Bacteria No	**Name of Bacteria**
1	***Salmonella enteritidis***
2	***Candida albicans***
3	***Staphylococcus aureus***
4	***Salmonella typhimurium***
5	***Enterobacter aerogenes***
6	***Salmonella infantis***
7	***Bacillus subtilis***
8	***Salmonella kentucky***
9	***Escherichia coli***
10	***Enterococcus durans***

THF,ethanol, chlorofrom paper disks were used as control negative for these trail by using the THF,ethanol and chlorofrom paper disks concentration 5 µl in the experiment agents all type of the bacteria tested.

A colony of the bacteria strain was inoculated into nutrient broth medium at 37 C° for 24 h. Prepare the bacterial concentration by add bacterial suspension to 0.9% sterile saline solution to get turbidity equal to 0.5 McFarland. The 1000 ml media was preperd and autoclaved at 120°C for 20min.The media was poured into sterilized Petri dishes. After the media rigidity, the bacterial strain was spread by the swab, then chemicals compounds were spread for each type of bacteria by using paper disc method. All plates were incubated at 37 ^{0}C for 24 h and checked for the growth of inhibition zones. The presence of clear zones around the disc indicated that both the ligand and complex if were active. We measure the diameter of inhibition zones [51, 52, 53, 54].

4. RESULTS

4.1. IR Spectroscopy Results

The IR absorption values for the whole of the obtained compounds

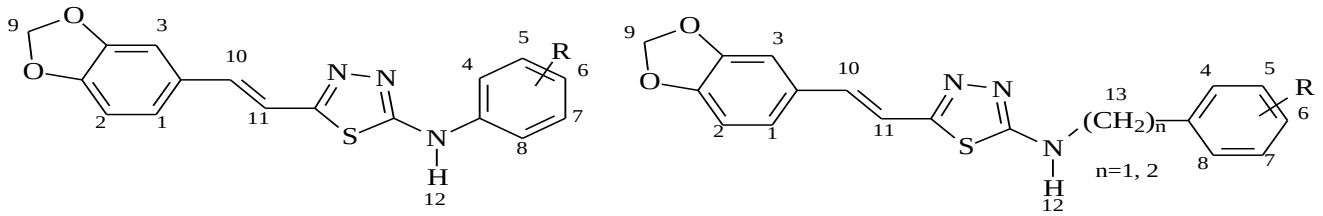
Table 4.1. *The IR absorption values of the obtained compounds*

	υ (-N(H)- vibration vibration	**υ C-H (Aromatic)**	**υ C-H (Aliphatic)**	**υ (C=C)**	**υ C=N (Thiadiazole)**	**υ C-S-C**	**υ (C-O-C)**	**υ (R grup)**
No	**IR absorptimoetry (cm^{-1})**							
1	3218 3188 3138	3050	2893	1657	1601	691	1124	-
2	3161 3130	3035	2946 2900	1624	1593	683	1090	*orto*-Cl
3	3239 3164	3040 2997	2893	1623	1604	696	1093	*para*-Cl
4	3186 3138	3040	2981 2901	1619	1604	683	1089	*orto*-F
5	3256 3206	3040	2902	1617	1559	678	1093	*meta*-F
6	3255 3219 3152	3051 3015	2906	1618	1605	681	1093	*para*-F
7	3377	3069	2909	1623	1604	686	1094	*orto*-OCH_3
8	3199 3139	3040	2907	-	1604	682	1165 1091	meta-OCH_3
9	3240 3194 3218	3038 3012	2981 2962 2906 2834	-	1604	680	1114 1091	*para*-OCH_3
10	3240	3040	2981 2869	1620	1591	694	1098	2,4dichloro
11	3260 3222 3167	3058 3024	2981 2916	1621	1599	686	1081	*money-NO2 1575.26 and 1361.98*
12	-	3042 2997	2893					
13	3154	3067	2981 2964 2869	1611	1589	681	1103	
14	3198	3040	2981 2869	1620	1601	697	1094	benzyl
15	3176 3127	3040	2981 2874	1605	1584	688	1093	2phenylethyl

4.2. 1H-NMR Spectroscopy Results

The 1H-NMR values of the whole compounds obtained are summarized in Table 4.2.

Table 4.2. *1H-NMR data of the obtained compounds*



Compound No.	H1	H2	H3	H4	H5	H6	H7	H8	H9	H10	H11	H12	H13	R
1	7.64d	7.64d	7.15s	7.30	7.04-7.01dd	7.38 - 7.30 between				6.53d	7.14d	10.44	---	H
2	7,52d	7,52d	7,31s	-	8,22d	7,41-7,35m 7,17-7,11m		7,17-7,11m	6.07	6.94	7,17-7,11m	9.10	---	2-c1
3	7,41d	7,41d	7,18	7,34d	7,4 d	7.10-7.05 dd		7.14	6,07	6,94	-	10,63	---	4-Cl
4	7,26-7,21		-7,19	---	7.29d	7,14	6,07	6,93	607	6.93	6.95	10.32	---	2-F
5	7,31d	7,31d	7,20	7,69d	-	7,39 d	6,83m	7,39 d	6,03	6,94	7,14	10,76	---	3-F
6	7,22-7,12 the range		7,22-7,12 the range	7,69-7,66m	--	7,69-7,66	7,22-7,12 the range	6,06	6.06	6.93d	7.33	10.52	---	4-F
7	H1-H8 Protons overlap at 7.4 and 6.8								6.07			9.76	---	o-OCH3
8	7,38d	7,38d	7,18	7,14d	-	7,34	7,26t	7,14d	6,07	6,61d	6,94d	10,51	---	m-OCH3

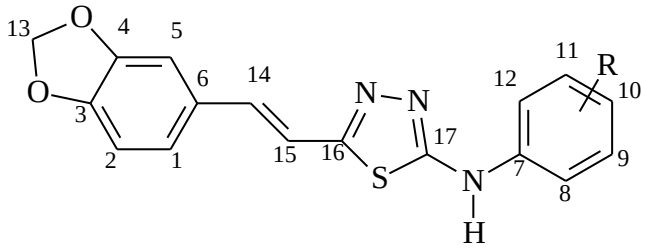
Table 4.2's Continue

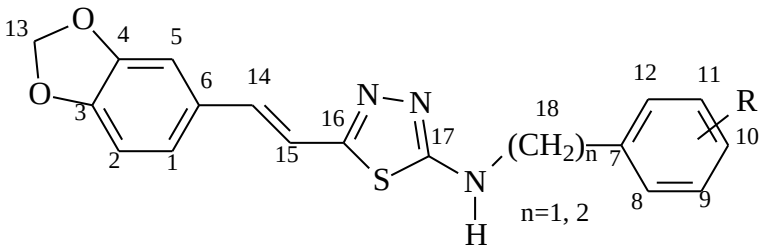
9	7,55d	7,55d	7,33 d	7,11	7,34	---	7,34	7,11	6,03	6,93	6,95	10,29	---	p-OCH3
10	7,34d	7,34d	7,20	-	7,46s	---	7,07	7,06	6,07	6,84	6,86	9,82	---	2,4-dichloro
11	H1 nad H2 protons 7,38-7,21 Coincidence	7,41	7,89 d	8,26 d	---		7,89d	6,07s	6,94 d	6.94d	7.15d	11.04	---	NO3
12	7,34-	-7,30	7,02			6,92-	-6,91	7,11	6,01			6,95	---	2-C2H5
13									6,11			9,28	---	---
14	7,386-7,93 the range							6,04			8,44	4,53		---
15	7,30-7,23 the range							6,06	7,30-7,23 the range	6,06	8,05		2,91 (CH2 phenyl) ve 3,5 (N CH2 DMSO Under the peaks)	--CH2-phenyl

4.3. 13C-NMR Spectroscopy Results

The 13C-NMR values of the whole of the obtained compounds are summarized in Table 4.3.

Table 4.3. *The 13C-NMR data of the obtained compounds*





R	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	C13	C14	C15	C16	C17	C18	C19	C atomu içeren R grupları
1	122.52	108.91	148.53	148.48	106.32	130.58	141.03	117.61	129.56	123.48	129.56	117.61	101.81	141.29	118.07	136.40	158.55	-	-	
2	123.95	108.91	148.56	148.46	106.31	130.52	104.76	123.59	128.43	122.79	130.23	163.92	101.81	104.76	117.55	136.44	148.84	-	-	
3	123.58	108.91	148.47	148.48	106.32	130.51	139.88	117.48	129.39	125.88	129.39	117.48	101.82	139.88	119.53	136.73	159.03	-	-	C7 veC14 çakıştı
4	121.24	108.90	148.56	148.46	106.32	125.27	136.55	123.68	123.58	125.23	115.64	163.29	101.81	136.55	117.54	130.53	153.67	-	-	C7 ve C14 çakıştı
5	123.62	108.60	148.60	148.48	106.32	131.06	142.64	117.40	130.48	108.81	164.20	113.87	101.83	142.53	117.40	136.85	159.21	-	-	C8 veC15 çakıştı
6	119.76	108.89	148.53	148.46	106.29	130.55	137.50	116.21	119.69	158.97	119.69	116.21	101.81	137.50	115.99	136.48	156.60	-	-	C7 ve C14

Table 4.3's Continue

7	130.63	108.89	148.93	148.45	106.29	126.65	135.96	123.43	129.99	119.76	111.53	159.08	101.79	134.13	117.78	135.95	151.16	-	56.18 (C in OCH3)	
8	123.53	106.30	148.53	148.47	104.09	130.55	142.10	110.48	130.39	107.61	160.41	108.91	101.81	142.10	117.54	136.49	158.63		55.50 C in OCH3)	C7 and C14 confluence
9	123.42	108.90	148.45	148.45	106.25	130.63	134.50	119.96	114.79	163.88	114.79	119.96	101.79	136.06	117.72	136.06	155.17	-	55.71 (C in OCH3)	C3 and C4; C14 and C16 coincidence
10	The spectrum can not be taken because it is insoluble in the solvent.																			
11	123.82	108.91	148.73	148.48	106.36	130.37	146.0	117.14	125.95	141.31	125.95	117.14	101.86	146.67	117.51	137.50	160.61	-	-	
12	123.80	108.89	148.41	148.43	106.23	129.56	138.60	125.65	130.64	123.36	127.24	135.79	101.77	138.60	117.78	137.00	159.08	-	14.92 (-CH_3), 24.28 (-CH_2-)	C7 and C14 confluence
13	The spectrum can not be taken because it is insoluble in the solvent.																			
14	118.10	108.88	148.42	148.28	106.17	130.72	139.00	128.01	127.64	128.88	127.64	128.01	101.73	139.00	123.18	135.02	157.42	48.45	-	C7 and C14 confluence
15	118.19	108.89	148.42	148.26	106.17	130.76	134.90	128.83	129.18	126.66	129.18	128.83	101.73	134.90	123.13	139.67	157.04	46.52 – 34.97	-	C7 and C14 confluence

4.4. UV-Vis Absorption Results

The synthesized compounds were analyzed by UV-Vis spectrophotometry of the solutions prepared with 10-5 M concentration in chloroform solvent. Absorption measurements were made at 200-700 nm in the spectrophotometer. According to the results obtained, double maximum wavelengths were observed for all compounds. UV-Vis Absorption values for all of the obtained compounds are summarized in Table 4.4. Looking at the table it is seen that the results are in the range of 276-371 nm. The appearance of the results in this range is compatible with the structure of the molecules.

Table 4.4. *UV-Vis Absorption data (nm) of the obtained compounds*

Compound No	**UV-Vis absorptimoetry**	
1	293	363
2	276	347
3	291	363
4	294	362
5	293 306 275	350
6	297	359
7	280	353
8	288	362
9	286	360
10	280	363
11	307	346
12	288	356
13	282 292 298	302 357 371
14	279	353
15	279	352

Table 4.5. *List of chemical compounds*

No	Name of Compounds
1	5-[2-(1,3-benzodioxol-5-yl)ethenyl]-N-[4'-nitrophenyl]-1,3,4-thiadiazol-2-amine
2	5-[2-(1,3-benzodioxol-5-yl)ethenyl]-N-phenyl-1,3,4-thiadiazol-2-amine
3	5-[2-(1,3-benzodioxol-5-yl)ethenyl]-N-[2'-methoxycarbonylphenyl]-1,3,4-thiadiazol-2-amine
4	5-[2-(1,3-benzodioxol-5-yl)ethenyl]-N-[4'-chlorophenyl]-1,3,4-thiadiazol-2-amine
5	5-[2-(1,3-benzodioxol-5-yl)ethenyl]-N-benzyl-1,3,4-thiadiazol-2-amine
6	5-[2-(1,3-benzodioxol-5-yl)ethenyl]-N-[2'-fluorophenyl]-1,3,4-thiadiazol-2-amine
7	5-[2-(1,3-benzodioxol-5-yl)ethenyl]-N-[2',4'-dichlorophenyl]-1,3,4-thiadiazol-2-amine
8	5-[2-(1,3-benzodioxol-5-yl)ethenyl]-N-(2'-phenylethyl)-1,3,4-thiadiazol-2-amine
9	5-[2-(1,3-benzodioxol-5-yl)ethenyl]-N-[4'-methoxyphenyl]-1,3,4-thiadiazol-2-amine
10	5-[2-(1,3-benzodioxol-5-yl)ethenyl]-N-[2'-ethylphenyl]-1,3,4-thiadiazol-2-amine
11	5-[2-(1,3-benzodioxol-5-yl)ethenyl]-N-[3'-fluorophenyl]-1,3,4-thiadiazol-2-amine thiadiazol-2-amine
12	5-[2-(1,3-benzodioxol-5-yl)ethenyl]-N-[3'-methoxyphenyl]-1,3,4-thiadiazol-2-amine
13	5-[2-(1,3-benzodioxol-5-yl)ethenyl]-N-[4'-fluorophenyl]-1,3,4-thiadiazol-2-amine
14	5-[2-(1,3-benzodioxol-5-yl)ethenyl]-*N*-[2'-methoxyphenyl]-1,3,4-thiadiazol-2-amine
15	5-[2-(1,3-benzodioxol-5-yl)ethenyl]-*N*-[2'-chlorophenyl]-1,3,4-thiadiazol-2-amine

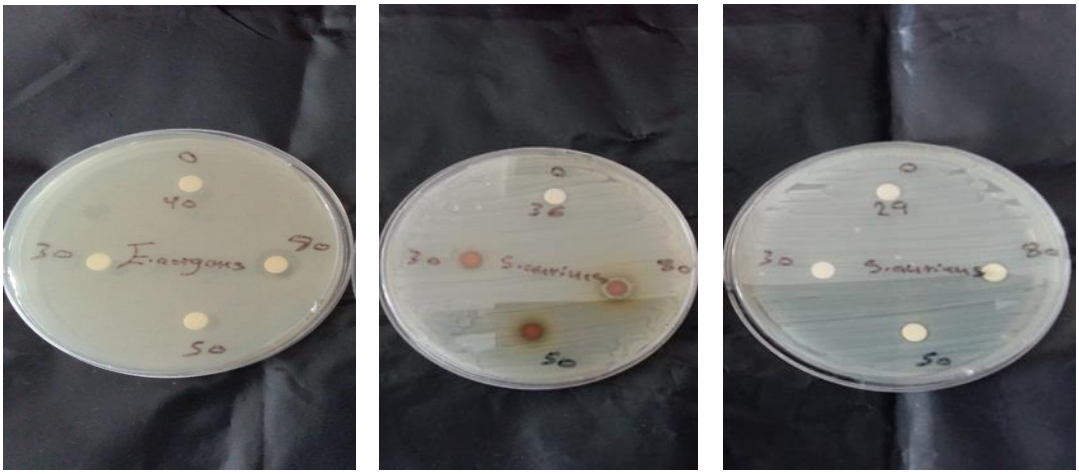
Table 4.6. *Antimicrobial activity of synthesized thiadiazole compounds*

Microorganisms	Synthesized Thiadiazole Compounds																							
	1			2			3			4			5			6			7			8		
	30	50	80	30	50	80	30	50	80	30	50	80	30	50	80	30	50	80	30	50	80	30	50	80
Candida albicans	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Enterobacter aerogenes	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Salmonella infants	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Staphylococcus aureus	-	-	-	-	-	-	-	-	-	-	-	-	-	7	8	-	-	-	-	-	7	-	-	-
Salmonella typhimurium	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Escherichia coli	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	8	9
Salmonella enteritidis	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Bacillus subtilis	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Salmonella kentucky	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		-	-
Enterococcus durans	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	7	7	8	-	-	-

*: not active

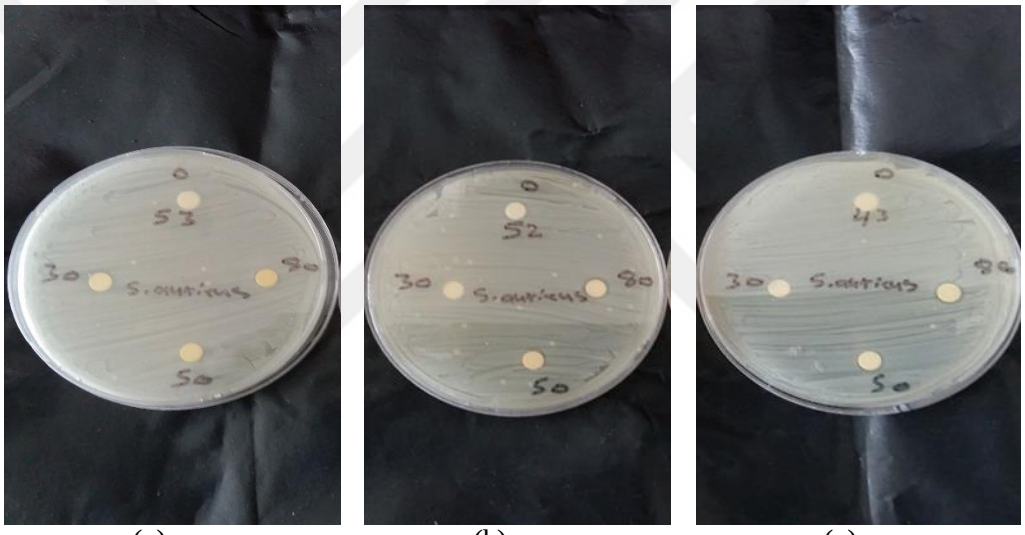
Table 4.7. *Antimicrobial activity of synthesized thiadiazole compounds*

Microorganisms	Synthesized Thiadiazole Compounds																							
	9			10			11			12			13			14			15					
	30 / 50 / 80			30 / 50 / 80			30 / 50 / 80			30 / 50 / 80			30 / 50 / 80			30 / 50 / 80			30 / 50 / 80					
Candida albicans	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
Enterobacter aerogenes	-	-	12	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
Salmonella infants	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
Staphylococcus aureus	-	-	-	-	-	7	-	-	-	-	-	-	-	7	8	-	-	7	-	-	-			
Salmonella typhimurium	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
Escherichia coli	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
Salmonella enteritidis	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
Bacillus subtilis	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
Salmonella kentucky	-	-	-	-	-	-	-	-	-	-	-	-	-	-	9	-	-	-	-	-	-			
Enterococcus durans	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			



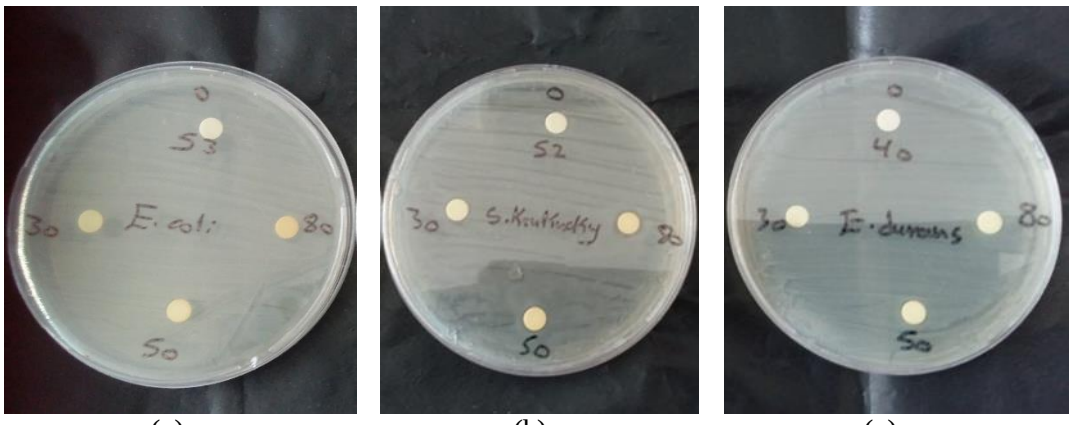
(a) (b) (c)

Photograph 4.1. Inhibition zone for (a) : *E. aerogenes*. ,(b) :S.aureus ,*(*c): *S.aureus*



(a) (b) (c)

Photograph 4.2. Inhibition zone for (a) : *S. aureus*. ,(b) :S.aureus ,*(*c): *S.aureus*



(a) (b) (c)

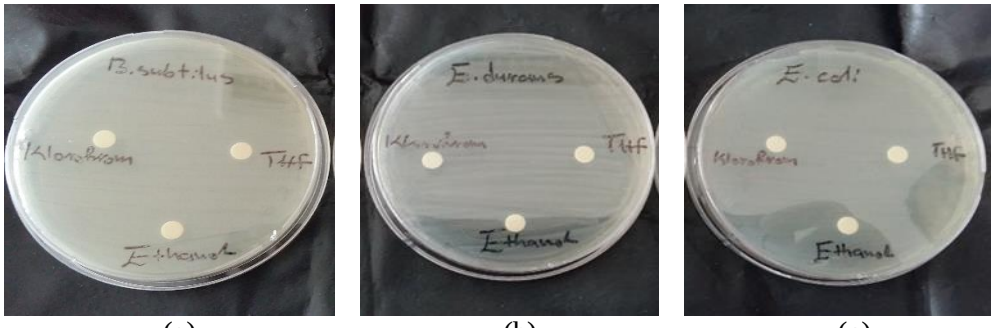
Photograph 4.3. Inhibition zone for (a) : *E.coli* ,(b) : *Salmonella kentucky* ,*(*c): *E.durans.*

4.5. Antimicrobial Activity Test Results

The antibacterial activity of 1,3,4-thiadiazoles was tested against 9 bacteria and 1 fungus strain. Bacteria were selected for Gram negative (Salmonella enteritidis, Salmonella typhimurium, Enterobacter aerogenes, Salmonella infantis, Salmonella kentucky, Escherichia coli) and Gram positive (Staphylococcus aureus, Bacillus subtilis, Enterococcus durans) to test for antibacterial activity. C. albicans was used to test for antifungal activity. Disc diffusion method was used in the antimicrobial test and three replications were studied.

Compounds showed inhibition zones on 5, 7, 10, 13, 14 Gram positive Staphylococcus aureus. Compound (5) showed 7 and 8 mM inhibition zone at 50, 80 mL concentrations on Staphylococcus aureus. Compounds 7, 10, and 14 showed the weakest effect on Staphylococcus aureus at 50 and 80 mL concentrations with small inhibition zones of about 7 mm. Compound (13) showed a 7 and 8 mM inhibition zone on Staphylococcus aureus at 50, 80 mL concentrations.

Compound (8) showed 8 and 9 mM inhibition zones on Gram negative E. coli at 50 and 80 µL concentrations. Compound (9) showed a 12 mM inhibition zone at 80 µl concentration on Gram negative Enterobacter aerogenes. Compound (13) showed a 9 mM inhibition zone at 80 µl concentration on Gram negative Salmonella Kentucky. Compound (7) showed inhibition zones of 7, 7 and 8 mm at 30, 50, and 80 µL concentrations on Gram positive Enterococcus durans, respectively. However, the synthesis compounds used in the whole experiment did not show antifungal activity on Candida albicans.



(a) (b) (c)

Photograph 4.4. No inhibition zone in THF, Ethanol, chloroform solvent.

THF, ethanol, chlorofrom paper disks were used as control negative for these trail by using the THF,ethanol and chlorofrom paper disks concentration 5 µl in the experiment agents all type of the bacteria tested.

Hussain et al [55] .were synthesized a new 4-amino-2-{5-[(4-substituted phenyl) amino]-1, 3, 4-thiadiazole-2-yl} phenol 2(a-g) and tested for antibacterial activity. The compounds display antibacterial activity against *E.coli* (gram negative) and *S. aureus* (gram positive) bacteria these result is agree with compounds (5,7,10,13,14) effects on *S. aureus* and compound (8) effect on *E.coli.*

In another study Barboiu et al. [56] examined antifungal activities against the group of 5- (2-aminoethyl) -2-amino-1,3,4-thiadiazole metal complexes against C. albicans [57]. It has been found that the compounds do not have antifungal activity on C. albicans.

In addition, Bhatia et al [58]. Synthesized novel derivatives of imidazo[2,1-b][1,3,4]thiadiazole containing biphenyl moiety. In the reactions we have reacted various substituted benzoic acids with thiosemicarbazide in the presence of Phosphorous Oxychloride The structures of the compounds were elucidated by spectral studies and screened for the antimicrobial activity against Bacterial strains of *Shigella flexneri, Staphylococcus aureus* and *Candida albicans.*

These result is agree with compounds (5,7,10,13,14) effects on *S. aureus*, but disagree with effect on *C. albicans*, because in our stydies compounds (1-15) don not have antifungal activity on *C. albicans.*

The variation between the results reported by previous works and my study could be due to differences in the concentration of compounds, concentration of strain of test microorganisms, materials and methods, volume and quantity, potion, environmental conditions, the area, and the weather.

5. DISCUSSION

5.1. Interpretation of IR Spectroscopy Results

The general structures of compounds, which were obtained, are indicated. The results were listed at Table 4.1 as the compounds' infrared spectrums in a solid form were received with a spectrometer device of Alpha FTIR spectrometer Bruker. When the skeletal structure of obtained compounds is considered, it is expected that the vibrations belonging to the aromatic C-H and C=C, C-O-C, -CH_2-, N=C (thiadiazole), C-S-C and N-H functional groups are observed. Moreover, it is expected that the vibrations' absorbtions are observed on the base of a substituted group on the benzene ring which is connected to NH group.

When it is generally considered at Table 4.1 it is seen for all the synthesized compounds that N-H stretching vibration bands are at the range of 3377,67-3127,19 cm^{-1} , the aromatic C-H stretching vibration bands are at the range of 3090,00-2997,12 cm^{-1} , the aliphatic C-H stretching vibration bands are at the range of 2981,98-2834,27 cm^{-1} , the aliphatic C=C bond's stretching vibrations are at the range of 1657,83-1605,57 cm^{-1} , the stretching vibrations belonging to C=N bond on the thiadiazole ring are at the range of 1605,57-1559,55 cm^{-1} , the stretching vibrations belonging to C-S-C bond are at the range of 694,63-678,60 cm^{-1} , the stretching vibrations belonging to C-O-C bond are at the range of 1165,46-1073,46 cm^{-1} .

5.2. Interpretation of 1H-NMR Spectroscopy Results

The general structures of synthesized compounds are indicated at the above-stated The compounds' NMR spectrums were taken in DMSO with 400 MHz Bruker NMR spectrometer and the results were listed at Table 4.2.

When Table 4.2 was reviewed, it was observed for all the synthesized compounds that H1-H3 and H9 protons on the 1,3 dehydroisobenzofuran ring; H1 and H2 protons are at the range of 7,64-7,21 ppm, H3 proton is at the range of 7,41-7,02 ppm

and H9 proton is at the range of 6,01-6,11 ppm. H4-H8 protons on the benzene ring which is visinal to NH group; H4 proton is at the range of 7,89-7,11 ppm,H5, H6, H7 and H8 protons overlap generally at the range of 8,26-6,83 ppm. It was observed that the alkene H10 proton is at the range of 6,94-6,61 ppm and the alkene H11 proton is at the range of 7,33-6,86 ppm generally as doublete. H12 which is a NH proton was observed as singlet at the range of 11,04-8,05. The methylene proton on 14 numbered compound was observed at 4,53 ppm, –CH2CH2- protons on 15 numbered compound were observed at 2,91 and 3,5 ppm (under DMSO peak). The metoxy-group protons (compounds were observed 8, 9 and 10) were observed as singlet at 2,51 ppm.

5.3. 13C-NMR Spectroscopy Results

The compounds' ^{13}C-NMR spectrums were indicated at Table 1,5 When Table 4.3 was reviewed, for all the synthesized compounds, C1,-C6 and C13 carbons on 1,3-dehydroisobenzofuran ring; C1 carbon was observed at the range of 118,10-130,63 ppm, C2 carbon was observed at the range of 106,30-108,91 ppm, C3 carbon was observed at the range of 148,71-148,93 ppm, C4 carbon was observed at the range of 148,26-148,48 ppm, C5 carbon was observed at the range of 104,09-106,32 ppm, C6 carbon was observed at the range of 125,27-130,76 ppm, C13 carbon was observed at the range of 114,79-130,64 ppm. C13 carbon which was exposed to the electronegative impact of two O atom was rebounded at very inferior site rather than the aliphatic C atoms. Similarly, C3 and C4 atoms were affected from O atom, and they were rebounded at very inferior site rather than the other aromatic C atoms on 1,3- dehydroisobenzofuran ring. The places of carbon atoms (C7-C12) on the benzene ring which carries substituent on it change substantially with the substituent changing Especially, the decrease in the electron's density in the presence of -NO_2 and -F causes that the carbons are rebounded at very inferior site. C7 carbon was observed at the range of 134,50-146,00 ppm and C8 carbon was observed at the range of 108,91-163,92 ppm. It arises that such a wide range slides the resonance to the inferior site due to the decrease in the electron's density of groups such as F Cl and O atoms in position 2. C8 carbons were rebounded at the range of 113,87-119,96 ppm on the compounds which don't carry any substituent at position 2. C9

carbon was observed at the range of 111,53-160,41 ppm. C9 carbon was rebounded at the range of 111,53-130,23 ppm on the compounds which don't carry any substituent at position 3. C10 carbon was rebounded at the range of 107,61-163,88 ppm. C10 carbon resonated in the range of 107.61-163.88 ppm. The C10 carbon atom carrying the -F (compound 4) and -NO2 (compound 12) in the 4-position resonated below the others. Compound 10 has resonated in the uppermost field under the influence of the electronegative O atom. C11 carbon atom resonance occurred in the range of 114,79-130,64 ppm, C12 carbon was found in the range of 110,48-128,83 ppm, in the range of 110,48-128,83 ppm.

The C atoms in the thiadiazole ring resonate in two different places. The electron density of the C atom, to which the N atom is bound, is somewhat lower because it is reduced by the inductive effect. C17 carbon atoms in the range of 148.84-160.61 ppm, and C15 in the higher range in the range of 135.02-139.67 ppm. The methylene carbon atom in the compound 14 was determined to be 48.54 ppm while the other compound was determined to be 46.52 ppm, which is azotane-bonded to the -CH2CH2-carbons of 15 compounds, to 34.97 ppm. In the compounds 7-10, It was observed in the range of 50-56,18 ppm.

6. CONCLUSION

The main focus of this study was to synthesize, purify, characterize and evaluate the antimicrobial activity of newly synthesized 1, 3, 4-thiadiazole.

The synthesis of thiadiazole derivatives (1–15) was carried out with the mixture of methoxy cynnamic acide derivatives and phenylthiosemicarbazide derivatives using phosphorous oxychloride.

Structural elucidation of synthesized compounds was done by using various analytical techniques like IR, NMR and UV Spectroscopy.The physical properties like melting point, solubility etc.

were also evaluated to support the identity of the compounds. Further to evaluate the antimicrobial activity of newly synthesized compounds with disk diffusion method. Some of compounds were found to have moderate activities against test microorganisms The compounds (5,7,10,13,14) shown inhibition zones on *Staphylococcus auries* while compund (7) shown inhibition zones on *Enterococcus durans.* compund (8) shown inhibition zones on E.coli .compound (9) shown inhibition zones on *Enterobacter aerogenes*.compound (13) shown inhibition zones on *Salmonella Kentucky*.but all compound have no activity against on *Candida albica.*

REFERENCE

1. Singh, A. K., Mishra, G., & Jyoti, K. (2011). Review on Biological Activities of 1,3,4-Tiyadiazole Derivatives. Research Journal of Applied Pharmaceutical Science 01, (05), 44-49.

2. Kalidhar, U & Kaur, A. (2011). 1, 3, 4-Tiyadiazole Derivatives and their Biological Activities: A Review. Research Journal of Pharmaceutical, Biological and Chemical Sciences, 2, (4), 1091 – 1106.

3. URL Arora, P., Arora, V., Lamba, H. S., & Wadhwa, D. (2012). Importance of heterocyclic chemistry: A Review. *International Journal of Pharmaceutical Sciences and Research*, *3*(9), 2947.

4. Sharma, B; Verma, A, Prajapati, S & Sharma. U. K. (2013). Synthetic Methods, Chemistry, and the Anticonvulsant Activity of Tiyadiazoles. International Journal of Medicinal Chemistry. Vol (2013) ,1-16.

5. Haider, S., Alam, M. S., & Hamid, H. (2015). 1, 3, 4-Tiyadiazoles: A potent multi targeted pharmacological scaffold. European journal of medicinal chemistry, (92), 156-177.

6. Kushwaha, N., Kushwaha, S. K., & Rai, A. K. (2012). Biological activities of tiyadiazole derivatives: a review. *Int J Chem Tech Res*, *4*(2), 517-531.

7. Wei, T. B. Liu ,H & Hu. , J. H. (2006). Microwave promoted efficient synthesis of 2,5-disubstituted 1,3,4-tiyadiazole. *Indian Journal of Chemistry B, (45),* 2754–2756.

8. Sharma, B; Verma, A, Prajapati, S & Sharma. U. K. (2013). Synthetic Methods, Chemistry, and the Anticonvulsant Activity of Tiyadiazoles. *International Journal of Medicinal Chemistry. Vol (2013)* ,1-16.

9. Goerdeler, J., Ohm, J., & Tegtmeyer, O. (1956). Darstellung und Eigenschaften des 1.2. 4- und des 1.3. 4- Thiodiazols. *European Journal of Inorganic Chemistry*, *89*(6), 1534-1543.

10. Bhawna, S; Amita, V; Sunil, P & Upendra, K. S. (2013). Synthetic Methods, Chemistry, and the Anticonvulsant Activity of Tiyadiazoles. *International Journal of Medicinal Chemistry, Vol(2013),* 1-16

11. Freund, M., & Schander, A. (1896). Zur Kenntniss des Thiourazols. *European Journal of Inorganic Chemistry*, *29*(3), 2506-2511.

12. Arnold, H. (1942). Über höher- C- alkylierte 2- Amino- 1.3. 4- thiodiazole und ihre Sulfanilamidderivate. *European Journal of Inorganic Chemistry*, *75*(1), 87.

13. Gupta, J. K.,Yadav, R. K., Dudhe, R., & Sharma, P. K. (2010). Radvancementsin the synthesis and pharmacological evaluation of substituted 1, 3,thiadiazole derivatives. *Int. J. Pharm. Tech. Res*, *2*(2), 1493-1507.

14. Gupta, J.K., Dudhey, R., & Sharma, P. K. (2010). Synthesis and pharmacological activity of substituted 1, 3, 4-thiadiazole derivatives. *Medichemonline, 1*, 1-9.

15. Hoggarth, E. (1949). 251. Compounds related to thiosemicarbazide. Part II. 1-Benzoylthiosemicarbazides. *Journal of the Chemical Society (Resumed)*, 1163-1167.

16. Pulvermacher, G. (1894). Ueber einige Abkömmlinge des Thiosemicarbazids und Umsetzungsproducte derselben. *European Journal of Inorganic Chemistry*, *27*(1), 613-630.

17. Guha, P. C. (1922). Constitution of the so-called dithio-urazole of martin freund. II. New methods of synthesis, isomerism and poly-derivatives. *Journal of the American Chemical Society*, *44*(7), 1510-1517.

18. Young.G.,&Eyre,W.(1901).III.—Oxidation of benzalthiosemicarbazone. *Journal of the Chemical Society, Transactions*, *79*, 54-60.

19. Gupta, J. K., Yadav, R. K., Dudhe, R., & Sharma, P. K. (2010). Recent advancements in the synthesis and pharmacological evaluation of substituted 1, 3, 4-thiadiazole derivatives. *Int. J. Pharm. Tech. Res*, *2*(2), 1493-1507.

20. Gupta, J. K., Dudhey,R., & Sharma, P. K. (2010). Synthesis and pharmacological activity of substituted 1, 3, 4-thiadiazole derivatives. *Medichemonline, 1*, 1-9.

21. Busch, M. (1894). Ueber eine neue Reaction zwischen Schwefelkohlenstoff und primären Hydrazinen. *European Journal of Inorganic Chemistry*, *27*(2), 2507-2520.

22. Losanitch,S. M. (1922). CCCIII.—Decomposition of dithiocarbazinates. *Journal of the Chemical Society, Transactions*, *121*, 2542-2545.

23. Losanitch, S. M. (1922). CCCIII.—Decomposition of dithiocarbazinates. *Journal of the Chemical Society, Transactions*, *121*, 2542-2545.

24. Eisner, U., & Kuthan, J. (1972). Chemistry of dihydropyridines. *Chemical Reviews*, *72*(1), 1-42.

25. Nesynov, E. P., & Grekov, A. P. (1964). The chemistry of 1, 3, 4-oxadiazole derivatives. *Russian Chemical Reviews*, *33*(10), 508.

26. Ameen, H. A., & Qasir, A. J. (2012). Synthesis and preliminary antimicrobial study of 2-amino-5-mercapto-1, 3, 4-tiyadiazole derivatives. *Iraqi J Pharm Sci*, *21*(1), 98-104.

27. Tripathi, K.D. (2006). Essentials of Medicinal Pharmacology, 6th edition. *Jaypee Brothers Medical Publishers, New Delhi,* 667.

28. Joseph, L., George, M., & Mathews, P. A Review on Various Biological Activities of 1, 3, 4-Tiyadiazole Derivatives. *Journal of Pharmaceutical, Chemical and Biological Sciences* , 3(3): 329-345

29. Khalilullah, H., Khan, M U., Mahmood, D., Akhtar, J., & Osman, G. (2014). 1,3,4-Tiyadiazole: a Biologically Active Scaffold. *International Journal of Pharmacy and Pharmaceutical Sciences, 6* (9), 8-15.

30. Kushwaha, N., Kushwaha, S. K., & Rai, A. K. (2012). Biological activities of tiyadiazole derivatives: a review. *Int J Chem Tech Res*, *4*(2), 517-531.

31. Kumar A, Amir M, Ali I, Khan SA. Synthesis of Pharmaceutically important 1, 3, 4- tiyadiazole and imidazolinone derivatives as antimicrobials. Indian J Chem 2009; 4813: 1288-1293.

32. Guptha SK, Sharma PK. Synthesis and anti-inflammatory activity of disubstituted 1,3,4- tiyadiazole. Int J Drug Formulation Res 2011; 2(2): 344-350.

33. Banerjee S, Swaroop TVSS, Ferdy IC, Singh A, lakshmi SM, Dr. Mohan, Dr. Saravunan J. Indo Am J Pharm Res 2014; 2(2): 1074-1082.

34. Pattan SR, Kittur BS, Sastry BS, Jadav SG, Thakum DK, Madamwar SA, Shinde HV. Synthesis and evaluation of some novel 1, 3, 4 – tiyadiazole for anti diabetic activity. Indian J Chem 2011; 50(B): 615-618.

35. Soni BK, Singh T, Bhalgat CM, Kamlesh B, Kumar SM, Pavani M. *In vitro* antioxidant studies of some 1, 3, 4 – tiyadiazole derivatives. Int J Res Pharm Biomed Sci 2011; 2: 1590-1592.

36. Masi HH, Gajjor AK, Savjani JK, Masi Inayal. Synthesis and anticonvulsant activity of novel 2,5-disubstituted 1, 3, 4- tiyadiazole derivatives. Int J Pharmtech Res 2011; 3(4): 2017-2024.

37. Rahman A, Shakya AK, Wahab S, Ansari NH. Synthesis of some new tiyadiazole derivatives and their anticonvulsant activity. Bulgarian Chem Commun 2014; 46(4): 750-756.

38. Öztürk, F., Acik, L., Şener, İ., Karci, F., & Kilic, E. (2012). Antimicrobial properties and DNA interactions studies of 3-hetarylazoquinoline-2, 4-diol compounds. *Turkish Journal of Chemistry*, *36*(2), 293-302.

39. Rohit Bhatia; Amandeep Kaur. (2014). Synthesis, spectral studies and antimicrobial activity of some imidazo [2,1-b][1,3,4] tiyadiazole derivatives , *Der Pharma Chemica,* 6(6):114-120.

40. Amandeep Kaur; Rajinder Kumar & Uday Kalidhar. (2012). Synthesis, spectral studies and biological activity of some novel bifenil imidazo[2,1-b][1,3,4]tiyadiazole derivatives. *Research Journal of Pharmaceutical, Biological and Chemical Sciences, 3(2),* 1084- 1096.

41. Ameen, H. A., & Qasir, A. J. (2012). Synthesis and preliminary antimicrobial study of 2-amino-5-mercapto-1, 3, 4-tiyadiazole derivatives. *Iraqi J Pharm Sci*, *21*(1), 98-104.

42. Rezki, N., Al-Yahyawi, A. M., Bardaweel, S. K., Al-Blewi, F. F., & Aouad, M. R. (2015). Synthesis of novel 2, 5-disubstituted-1, 3, 4-tiyadiazoles clubbed 1, 2, 4-triazole, 1, 3, 4-tiyadiazole, 1, 3, 4-oxadiazole and/or Schiff base as potential antimicrobial and antiproliferative agents. *Molecules*, *20*(9), 16048-16067.

43. Samee, W., & Vajragupta, O. (2011). Antifungal, cytotoxic activities and docking studies of 2, 5-dimercapto-1, 3, 4-tiyadiazole derivatives. *African journal of pharmacy and pharmacology*, *5*(4), 477-485.

44. Salih, N., Salimon, J., & Yousif, E. (2011). Synthesis and antimicrobial evaluation of 5-(p-substituted fenil)-N-(3-(5-nitrofur-2-yl) allylidene)-1, 3, 4-tiyadiazol-2-amin derivatives. *Oriental Journal of Chemistry*, *27*(2), 373

45. Purohit, D. H., Dodiya, B. L., Ghetiya, R. M., Vekariya, P. B., & Joshi, H. S. (2011). Synthesis and Antimicrobial Activity of Some New 1, 3, 4-Tiyadiazoles and 1, 3, 4-Thiadiazines Containing 1, 2, 4-Triazolo Nucleus. *Acta Chim. Slov*, (*58*) 53-59.

46. Aly, A. A., & El-Sayed, R. (2006). Synthesis and biological activity of new 1, 3, 4-tiyadiazole derivatives. *Chemical Papers*, *60*(1), 56-60.

47. Jalhan, S., Jindal, A., Gupta, A., & Hemraj, H. (2013). Synthesis, biological activities and chemistry of tiyadiazole derivatives and Schiff bases. *ChemInform*, *44*(16).

48. Venkatesha, K., Rayamb, P., Sekha, K. B. C., Mukkantia, K. (2016). Synthesis, Charachterization and Biological Activity of Some New Thiosemicarbazide Derivativies and their Transition Metal Complexes. *International Journal of Applied Biology and Pharmaceutical Technology,7* (1), 258-266.

49. Kandemirli, F., et al. (2012). Quantum Chemistry-Molecules for Innovations, Quantum chemical calculations for some isatin thiosemicarbazones. *Quantum Chemistry - Molecules for Innovations, 2* (3), 25-58.

50. Abu-Dief, A. M., & Nassr, L. A. E. (2015). Tailoring, Physicochemical Characterization, Antibacterial and DNA Binding Mode Studies of Cu (II) Schiff Bases Amino Acid Bioactive Agents Incorporating 5-Bromo-2-Hydroxybenzaldehyde. *Journal of the Iranian Chemical Society, 12,* 943-955.

51. Venkatesha, K., Rayamb, P., Sekha, K. B. C., Mukkantia, K. (2016). Synthesis, Charachterization and Biological Activity of Some New Thiosemicarbazide Derivativies and their Transition Metal Complexes. *International Journal of Applied Biology and Pharmaceutical Technology,7* (1), 258-266.

52. Kandemirli, F., et al. (2012). Quantum Chemistry-Molecules for Innovations, Quantum chemical calculations for some isatin thiosemicarbazones. *Quantum Chemistry - Molecules for Innovations, 2* (3), 25-58.

53. Prathima, B., Subba Rao, Y., Chalapathi, P.V., Reddy, Y. P., Varada Reddy, A. (2012). Spctral, Structural and Biological Analysis of Cr (III) Complex with Benziloxybenzaldehyde-4-Fenil-3-Thiosemicarbazone. *International Journal of Pharmacy and Pharmaceutical Sciences, 4* (3), 167-174.

54. Yidliz, M., Dulger, B., Yancu, S. Y. K., Yanpici, B. M. (2004). Synthesis and Antimicrobial Activity of Bis(imido) Schiff Bases Derived from Thiosemicarbazide with some 2-Hydroxyaldehydes and Metalcomplexes. *Journal of the Indian Chemical Society, 81*, 7-12.

55. Sabir Hussain; Jyoti Sharma & Mohd Amir. (2008). Synthesis and Antimicrobial Activities of 1,2,4-Triazole and 1,3,4-Tiyadiazole Derivatives of 5-Amino-2-Hydroxybenzoic Acid. *E-Journal of Chemistry, 5(4),* 963-968.

56. Mihai Barboiu; Marilena Cimpoesu; Cornelia Guran & Claudiu T, Supumn. (1996). 1,3,4- Tiyadiazole Derivatives Synthesis And Biological Activity Of Metal Complexes Of 5- (2-Aminoethyl)-2-Amino-1,3,4-Tiyadiazole. *Hindawi Publishing Corporation, 3 (5)* , 227-232.

57. Manvinder Kaur and Amandeep Kaur. (2015). A Review on Some Imidazo[2,1-b][1,3,4]Tiyadiazole Derivatives as a Potent Antimicrobial Agents. *World Journal of Pharmaceutical Research, 4(8)* 2472-2487.

58. Bhatia, R., & Kaur, A. Synthesis, spectral studies and antimicrobial activity of some imidazo [2, 1-b][1, 3, 4] tiyadiazole derivatives. *Scholars Research Library* 6(6):114-120.

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