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Ministry of Higher Education and Scientific Research
Baghdad University
College of Education for Pure Sciences - Ibn Al-Haitham
Department of Chemistry

Synthesis, Characterization of Fifth, Sixth Heterocyclic Compounds and Studying their Bacterial Properties

A Thesis submitted to the College of Education for Pure Science (Ibn-Al Haitham) / University of Baghdad in partial fulfillment of the requirements for the degree of Master of Science in Chemistry

By

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(B.Sc. 2012)

Supervised by
Prof. Dr. Ibtisam K.Jassim

2019 A.D. **1440 A.H.**

بِسْمِ اللهِ الرَّحْمنِ الرَّحِيمِ

((يَرْفَعُ اللَّهُ الَّذِينَ آمَنُوا مِنْكُمْ

وَالَّذِينَ أُوتُوا الْعِلْمَ دَرَجَاتٍ

وَاللَّهُ بِمَا تَعْمَلُونَ خَبِيرٌ))

صدق الله العلي العظيم

سورة المجادلة-الاية(11)

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I certify that this thesis was prepared under my supervision at the Department of Chemistry, College of of Education for Pure Science (Ibn-Al-Haitham), University of Baghdad, in partial fulfillment requirements for the Degree of Master in organic chemistry science .

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Date : 1 / 7 / 2019

In view of the avaliable recommendation, I forwared this thesis for debate by the Examining Committee.

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We, the examining committee, after reading this thesis **(Synthesis, Characterization of Fifth, Sixth Heterocyclic Compounds and studying their antibacterial properties)** and examining the student " **Ali Hatem Ahmeed** " in its contents, find that it is adequate as a thesis for the degree of Master of Science in Chemistry Organic.

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University of Baghdad

Dedication

- To the beacon of science and the master of mankind ..... Prophet Muhammad (peace be upon him) and the god of the good
- To those who sacrificed themselves and threw the earth with their blood ..... Martyrs of the popular crowd

"To whom did my happiness be wrought with woven threads from her heart?

.....My dear mother

- To his soul embraces me for life ..... My late father
- To the love of them being in my veins ..... My brothers and sisters
- To those who drafted for us their knowledge letters and ideas lighthouse ..... Our distinguished professors
- To those who like brotherhood and distinguished by loyalty and giving ..... My colleagues

Give them the fruit of my effort

Acknowledgments

You are the Lord of the heavens and the earth and all that is inside it ... You are the King of Praise, the Kingdom of the heavens and the earth and all that is inside it, and peace and blessings be upon the master of mankind, our beloved messenger, and his pure offspring: the Companions and all those who follow His path in charity until the Day of Judgment.

I would like to express my sincere gratitude and appreciation to Prof.Dr. Ibtisam K. Jassim for her guidance and encouragement throughout this work.

I would like to thank my family for their kindness, support and patience during my years of study.

My thanks to all my professors in the department of chemistry and staff of the faculty of Education for Pure Sciences _ Ibn Al-Haytham.

Finally, I thank my friends and colleagues for their support.

Ali

Abstract

This work consists of the preparation of heterocyclic ring compounds of five to six members starting from Mefenamic acid.

This work includes seven different parts as shown below .

Part One: Includes the preparation of pyrazole [4,7], phthalazine-1,4-dione [5] and pyridazine-3,6-dione[6,8]derivatives derived from hydrazide .

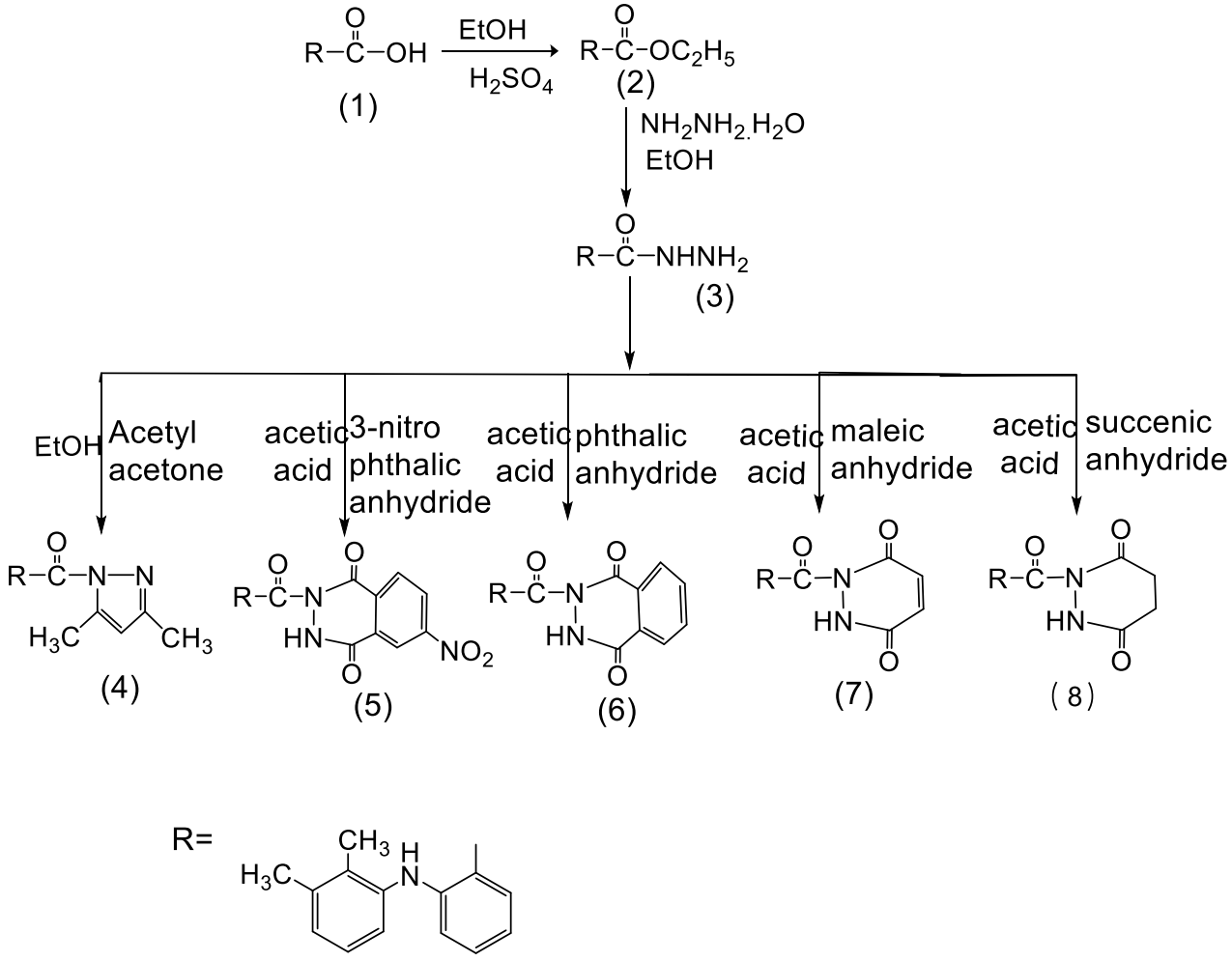
Part Two*:* Involvs the synthesis of oxazole [10] and thiazole derivative [12] via the reaction of 2-((2,3-dimethylphenyl)amino) benzamide with urea and thiourea and cyclization of the resulted products with *p*-phenyl phenacyl bromide .

Part Three : Includes the preparation of thiadiazole, triazole, thiazolidin and oxadiazin via the reaction of hydrazide compound [3] with phenyl isothiocyanate [13] and ammonium thiocyanate [17] in absolute ethanol and cyclization of the products with sulfuric acid [14], sodium hydroxide [15,18], *p*-phenyl phenacyl bromide [16], and reaction of hydrazide compound [3] with chloro acetic acid and sodium acetate [19] .

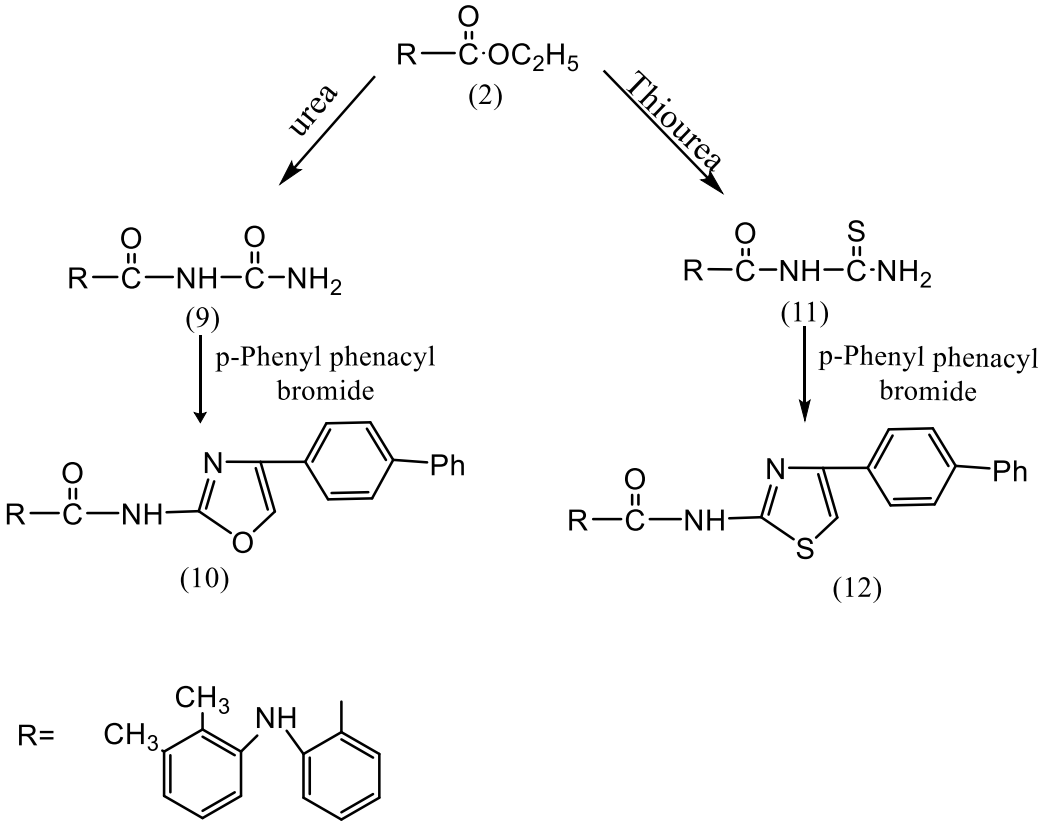
Part Four : Involvs the treatment of reacted hydrazide compound [3] with para nitro benzoic acid [20] and phenyl acetic acid [21] and 2-chloro benzoic acid[22] and benzoic acid [23] and mefenamic acid [24] and cynamic acid [25] . Then cyclization the of products with nitro benzoic acid and phenyl acetic acid and 2-chloro benzoic acid and benzoic acid and mefenamic acid and cynamic acid is to get oxadiazol rings [20,21,22,23,24,25] .

Part Five : Includes the preparation of schiff bases [29-33] by reacting amin [28] with different benzyldehyde and also **i**ncludes the preparation of tetrazol [34 – 38] by reacting schiff bases[29 -33] with sodium azid .

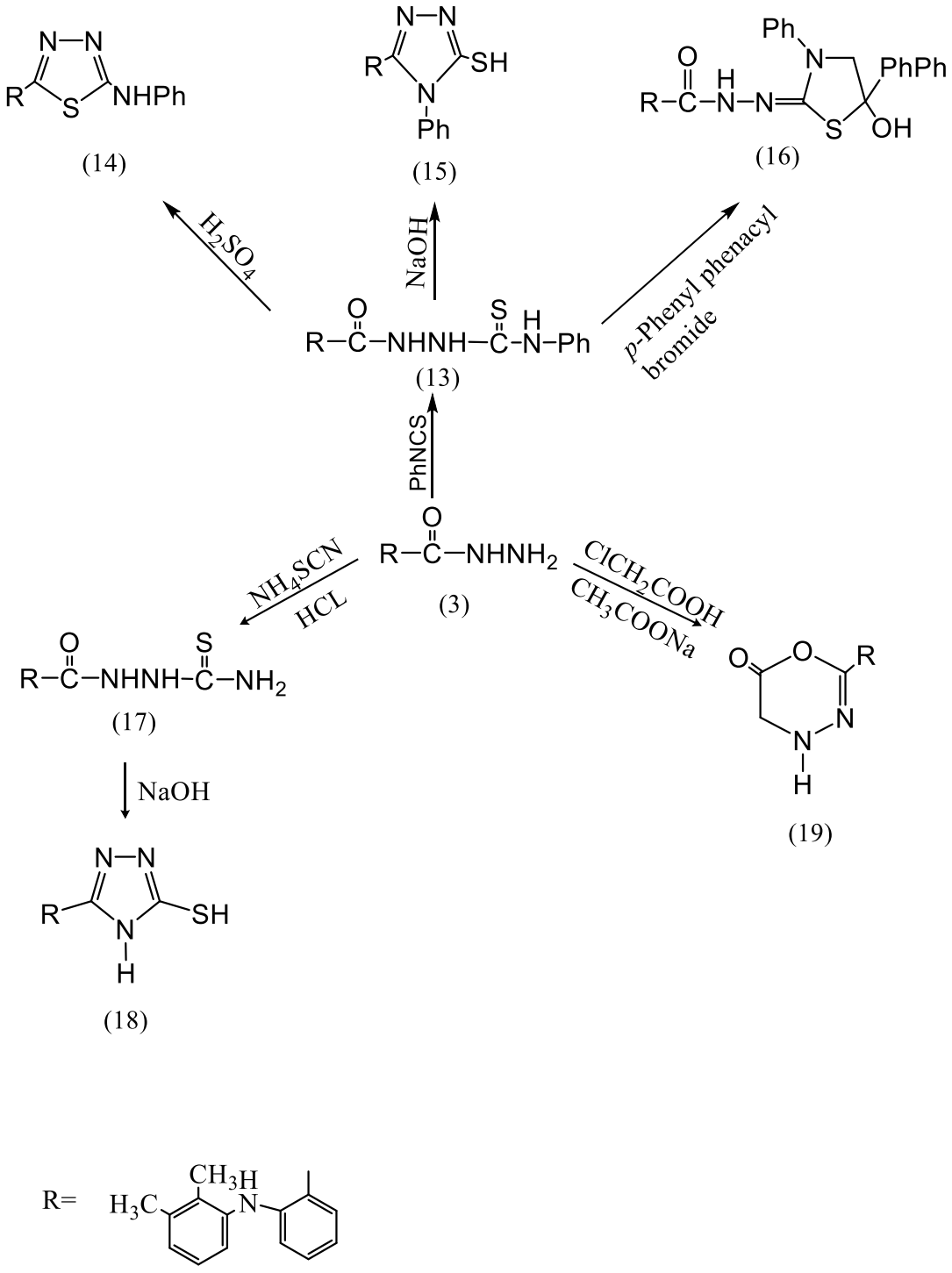
Part Six: Is focuced on studying the antibacterial activity of some prepared compounds using two types of bacteria *staphylococcus aureus. (G +), E.coli.(G -)* .



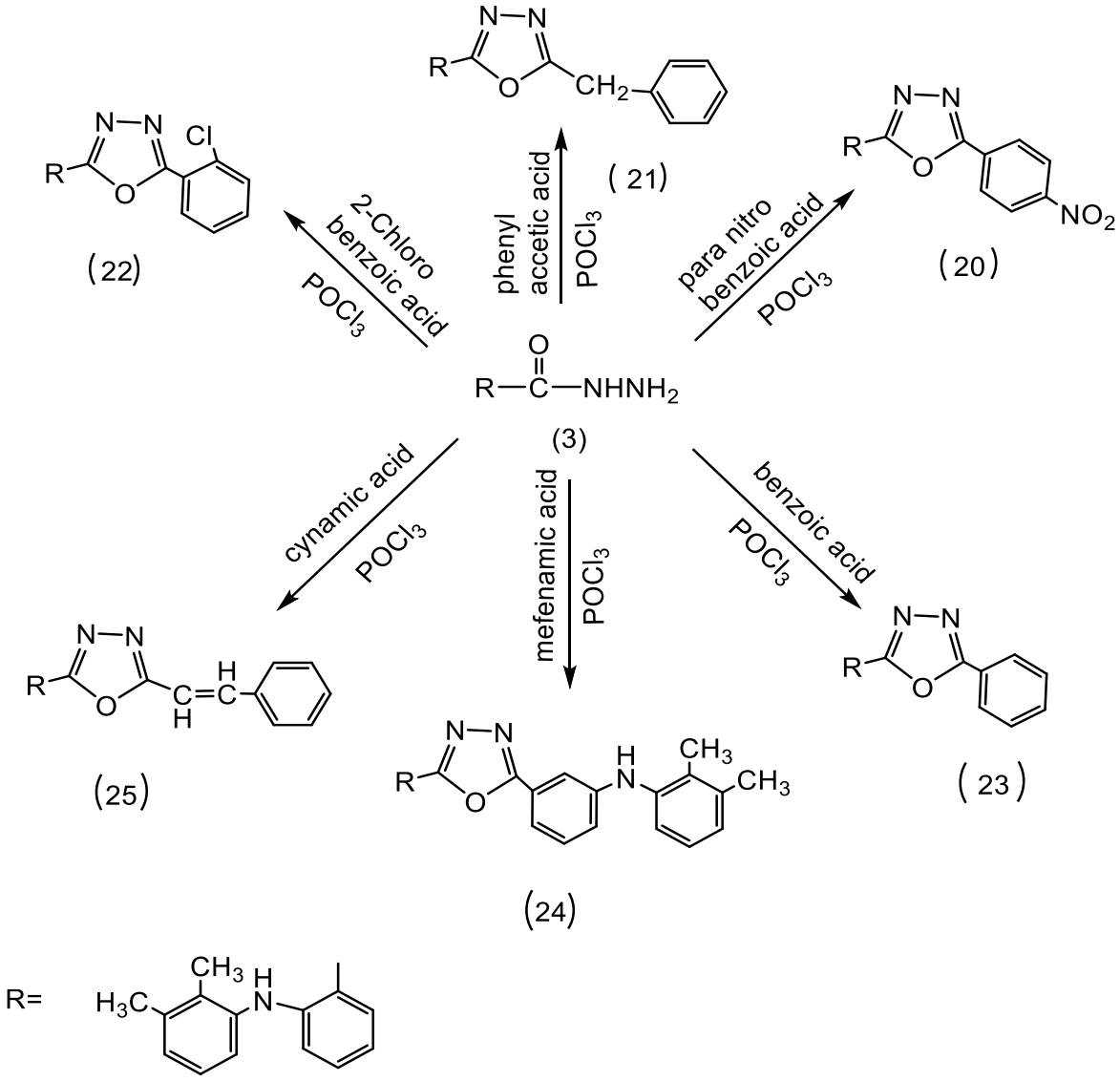
(Scheme I)


R—C·OC2H5
(2)
urea
Thiourea
R—C—NH—C—NH2
(9)
p-Phenyl phenacyl bromide
R—C—NH—C·NH2
(11)
p-Phenyl phenacyl bromide
Ph
(10)
(12)
R=
CH3
CH3
NH

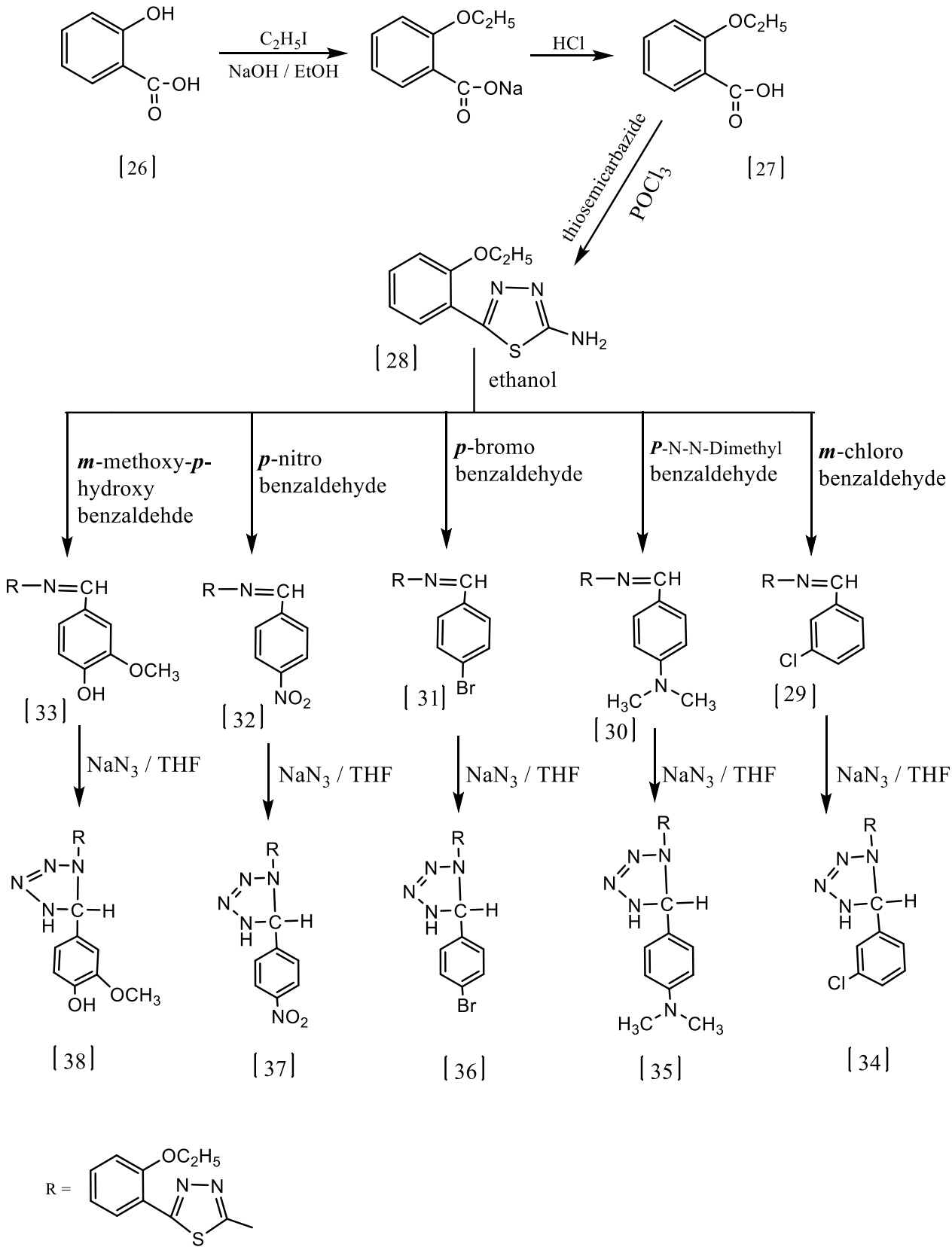
(Scheme II)


(14)
(15)
(16)
H_2SO_4
NaOH
p-Phenyl phenacyl bromide
(13)
PhNCS
NH_4SCN
HCL
(3)
$ClCH_2COOH$
CH_3COONa
(17)
NaOH
(19)
(18)
R=

(Scheme III)


R
N—N
O
CH2
(21)
phenyl accetic acid
POCl3
Cl
(22)
2-Chloro benzoic acid
POCl3
para nitro benzoic acid
POCl3
NO2
(20)
R—C(=O)—NHNH2
(3)
cynamic acid
POCl3
mefenamic acid
POCl3
benzoic acid
POCl3
(25)
(24)
(23)
CH3
H3C
H
N
R=

(Scheme IV)


C2H5I
NaOH / EtOH
HCl
thiosemicarbazide
POCl3
[26]
[27]
[28]
ethanol
m-methoxy-p-hydroxy benzaldehde
p-nitro benzaldehyde
p-bromo benzaldehyde
P-N-N-Dimethyl benzaldehyde
m-chloro benzaldehyde
[33]
[32]
[31]
[30]
[29]
NaN3 / THF
[38]
[37]
[36]
[35]
[34]
R =

(Scheme V)

List of Abbreviations

No.	Abbreviation	Full Name
1	Ar.	Aromatic
2	Abs.	Absolute
3	Aliph.	Aliphatic
4	Asym.	Asymmetrical
5	DMSO	Dimethyl sulfoxide
6	DMF	Dimethyl Formamide
7	EtOH	Ethanol
8	FT.IR	Fourier Transform Infra Red
9	^{1}H -NMR	Proton Nuclear Magnetic Resonance
10	M.P.	Melting point
11	M.WI	Micro Wave Irradiation
12	NSAID	a non-steroidal anti- inflammatory drug
13	Symm.	Symmetrical
14	THF	Tetra hydro furan
15	TLC	Thin Layer Chromatography
16	U.V	Ultra violet
17	CDI	carbonyl diimidazole

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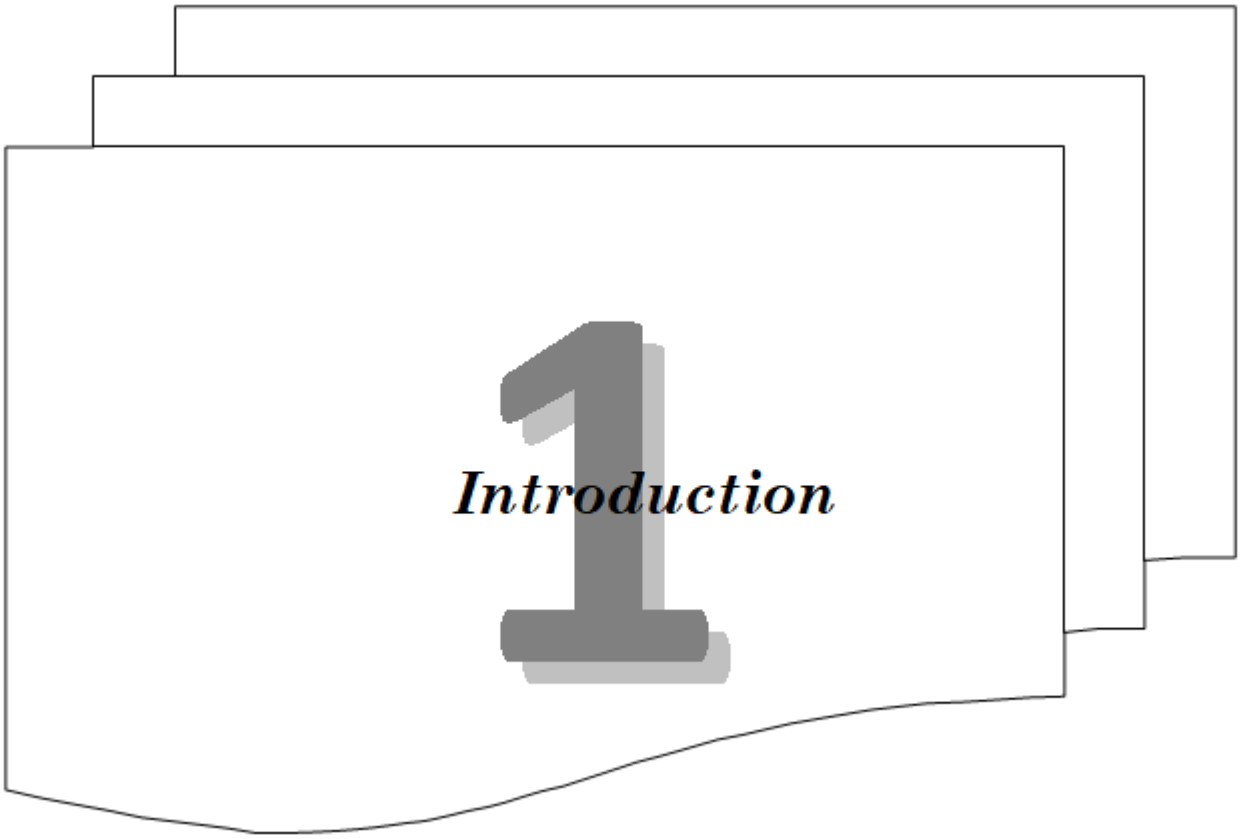
Chapter One

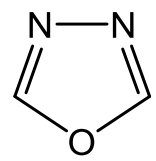


1. Introduction

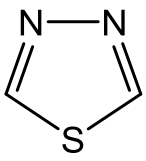
1.1. Hetrocyclic compounds

Heterocyclic organic chemistry is one of the important branches of organic chemistry, which has attracted the attention of scientific. organic compounds are heterocyclic compounds. A cyclic organic compound contains carbon atoms in the form of a ring to be assigned to a carbon composite ring. If the carbon does not represent at least one atom part of the ring, it will be chosen as a heterocyclic compound [(1)]. Hetrocyclic chemistry deals with the synthesis and properties and applications of heterocyclic ring compounds [(2)].

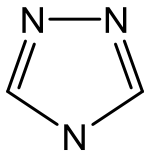
Hetrocyclic compounds were obtained as building blocks through many biological molecules [(3)], Most molecules containing five and six rings [(4)]. The heterocyclic compounds, sulfur, nitrogen and oxygen contain a heterocyclic compound that has maintained the interest of researchers through the development of organic synthesis[(5)].



oxadiazole



thiadiazole



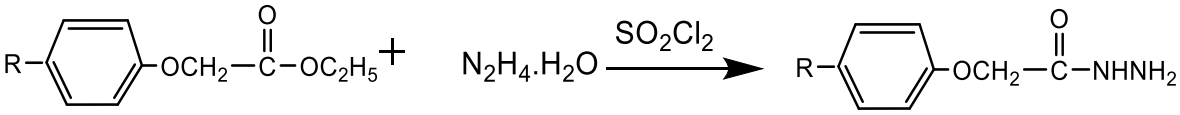
triazole

1.2.The Hydrazides:

Hydrazides are considered as intermediates to synthesis of many derivatives. The structur for this type of compound is (RCONHNH-)[(6)]. Hydrazide derivatives could exhibit various biological activities such as antiviral, anticancer , antidepressant, anti-inflammatory and anti-depressant [(7-8)] .

1.2.1 Synthesizing the hydrazides of derivatives :

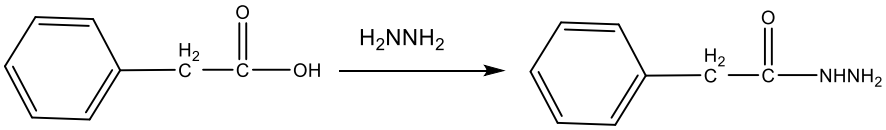
Many methods are available for the preparing of hydrazone derivatives. The importace of which is depends on the reaction of ester compound, with hydrazine hydrate, [9,10].



[1] [2]

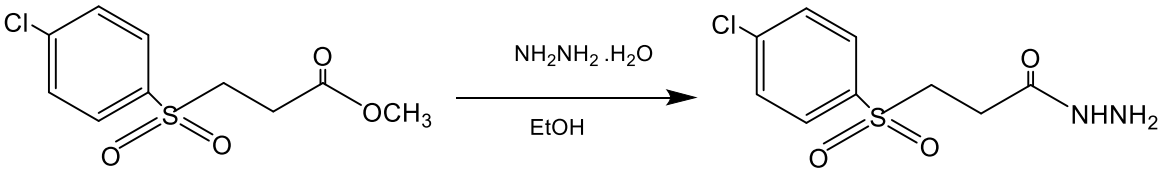
R=CH_3CONH

Acid hydrazone derivatives could also be synthesized using condensation reaction of carboxylic halide with hydrazine hydrate [10] .



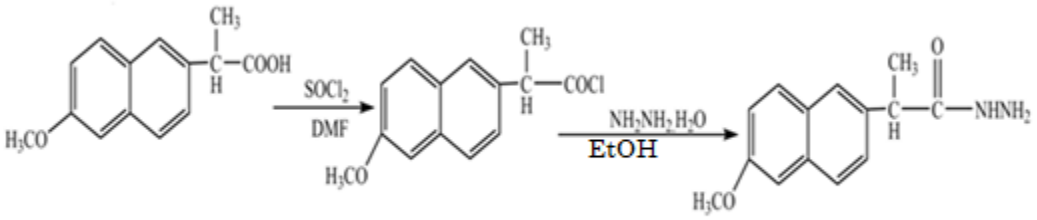
[3]

A novel hydrazide has been synthesized by Kumar et .al[11] by the reaction of 3-[4-chloro phenyl) sulfonyl] propanoate, with hydrazine hydrate in ethanol under reflux.



[4]

Moreover, Zena[13] has synthesized 2-(6-methoxy naphthaline-2-yl) propane hydrazide by the same way starting from naproxen .

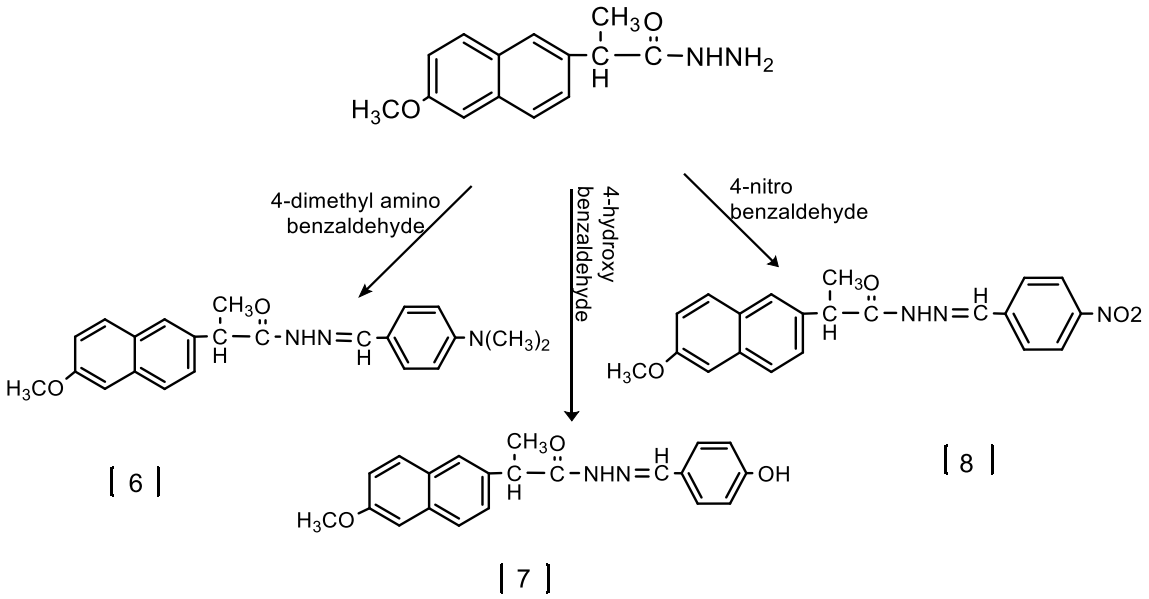


[5]

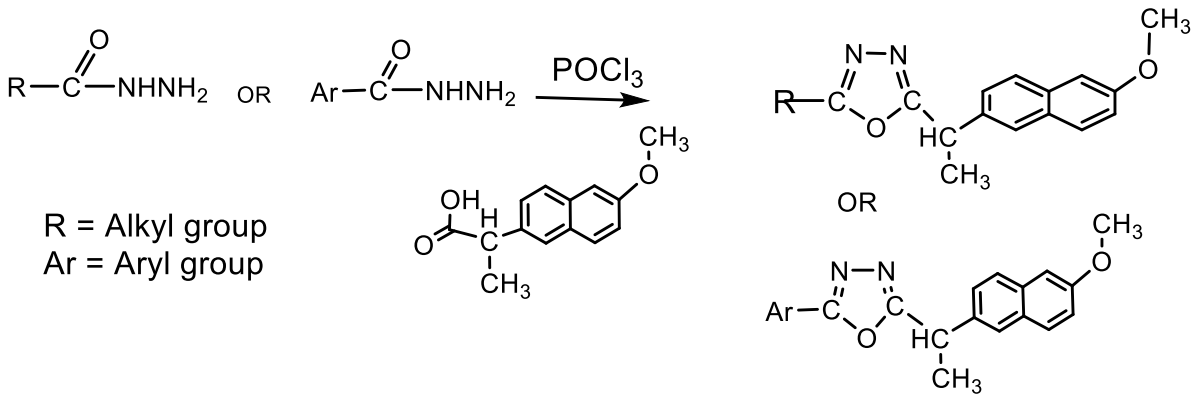
1.2.2 Reactions of acid hydrazides:

Acid hydrazides considered as a very important intermediate to synthesize new derivatives as follows:

a) The reaction of acid hydrazide with different aromatic aldehyde to produce schiff base[14].



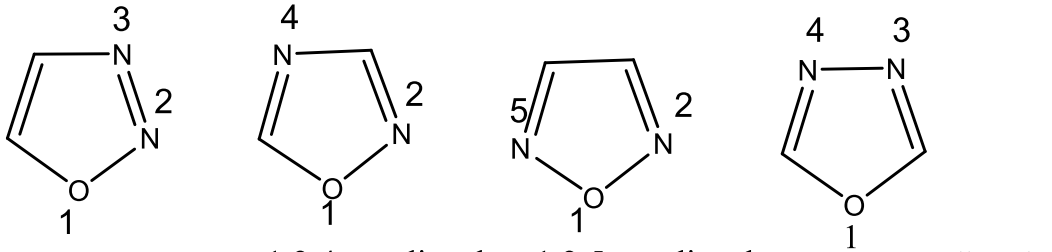
b) Ring closure of acid hydrazide with carboxylic acid in the presence of phosphorous oxychloride ($POCl_3$)[15].



[9]

1.3-Oxadiazole and its derivatives:

Oxadiazoles can be defined as a five - membered ring compounds which have three hetero atoms oxygen and two nitrogen atoms. The five-member oxadiazole ring contains four[16] isomers.



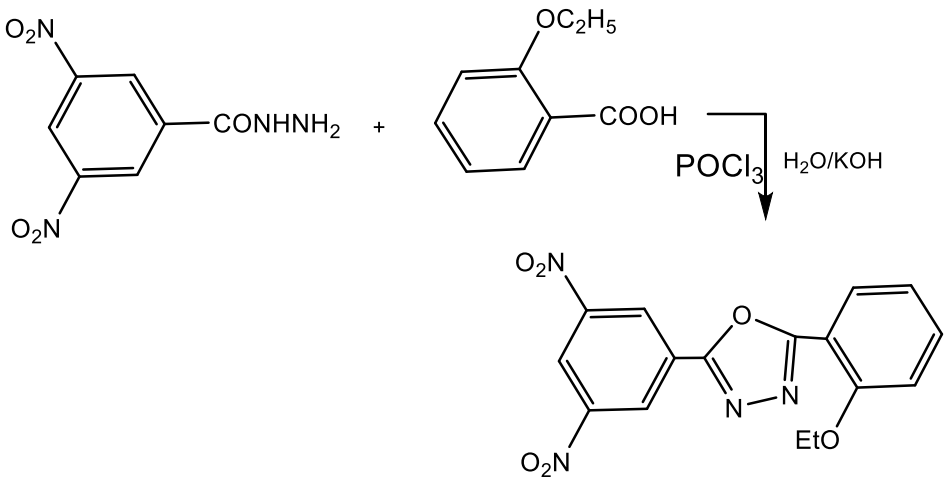
1,2,3-oxadiazole 1,2,4-oxadiazole 1,2,5-oxadiazole 1,3,4-oxadiazole

1,3,4 - Oxadiazole is the most stable isomer, which is of particular importance; this is due to the large number of uses as the biological agent as anticancer[17]and anti inflammatory [18].

1.3.1 Synthesis of Oxadiazoles:

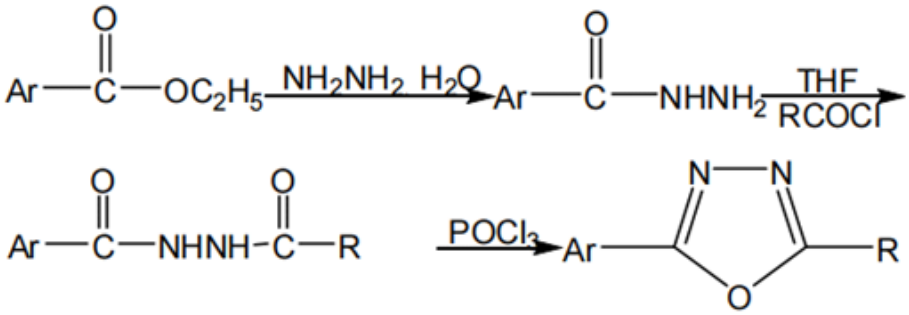
Ali et al. [19] synthesized 2-(3,5-dinitrophenyl)-5-(2-ethoxy-phenyl)-1,3,4-oxadiazole by the reaction of hydrazides with 2-ethoxy benzoic acid

and phosphorous oxychloride. Also, another compounds have prepared by this method[20].



[10]

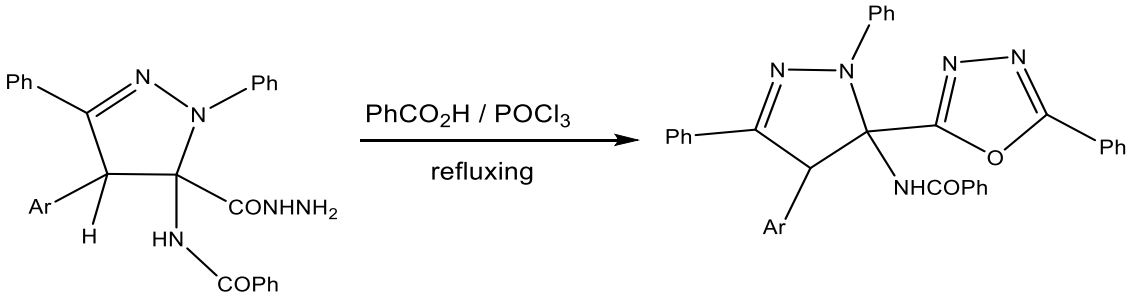
Cao [21], prepared 2-chloromethyl-5-aryl-1,3,4-oxadiaozles by cyclo dehydration of N -chloroacetyl- N -aryl hydrazines in boiled phosphorous oxychloride ($POCl_3$).



R = C_6H_5 , *p*-$C_2H_5C_6H_4$, *p*-ClC_6H_4 , *p*-FC_6H_4 , *o*-FC_6H_4 , Ar= $NO_2C_6H_4$

[12]

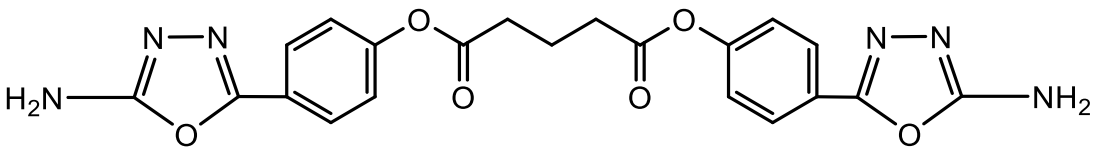
Mansour[22] prepared 2-(1, 3, 4-triphenyl pyrazole-5-yl)- 5-phenyl-1,3,4-oxadiazole by reacting 4-aryl-5-benzoylamino-1,3-diphenyl-2-pyrazdine-5-carbohydrazides with benzoic acid and phosphorus oxychloride. The reaction was found to proceed via concerted cyclocondensation and elimination of a benzamide molecule .



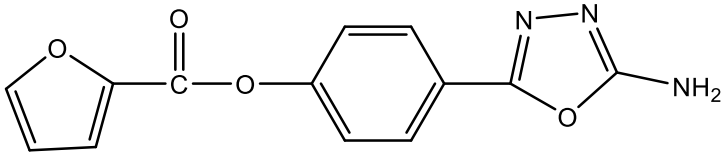
[13]

Ar = C_6H_5 . 2-OCH_3-C_6H_4

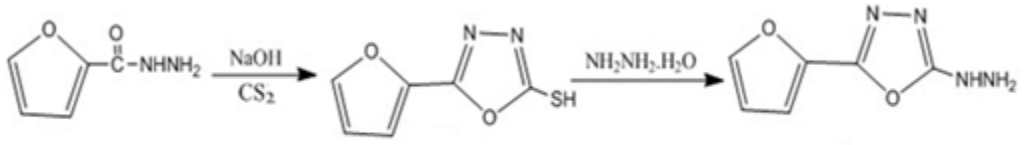
Another oxadiazol[23] (bis oxadiazole) was prepared by using Br_2 and acetic acid with sodium acetate.



Amal et. al[24]. have synthesized 2-amino -1,3,4-oxadiazole using bromine (Br_2) and sodium acetate with semicarbazide hydrochloride.

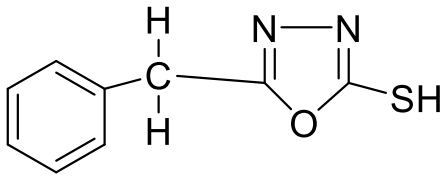


They also synthesized 2-(furan-2-yl)-5- hydrazineyl -1,3,4 oxadiazole using another method .



[14]

Aish[25] synthesized oxadiazole from phenyl acetic acid and CS_2 in presence of KOH .

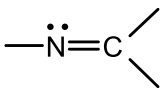


1.3.2 Biological Activity of 1,3,4-Oxadiazoles

The biological activity of oxadiazole ring is well documented in the literature. It has been shown that many substituted-1, 3, 4-oxadiazoles have biological and medical uses as antibacterial, antifungal, antimalarial and anti-inflammatory[26-29] .

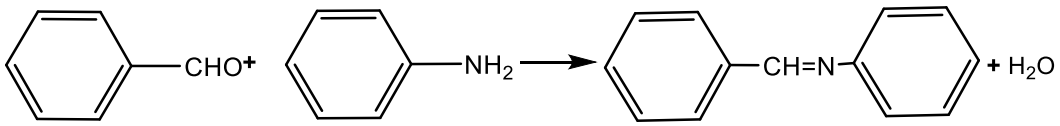
1.4 Schiff' Bases

Schiff bases are compounds that contain azomethine group. It was named after Hugo Schiff, who made a number of these compounds by reaction primary aromatic amines and primary aliphatic amines and amino acids.The formula below explain this:



Their nomenclature depends on the substituted groups R, R', R"[27]. The for example compound $C_6H_5–N=CH–C_6H_5$, is an aromatic Schiff base named as N-benzylidene aniline, or N-benzylidenebenzenamine while compound ($C_4H_9–N=CH–C_2H_5$) also is named as N-propylidenebutylamine but it is an

aliphatic Schiff's bases. Many raw materials include azomethine, anil, imine, ketimine, benzylideneaniline, benzanaline, benzaniline, benzalanil, or benzanil, as a base of benzaldehyde and aniline. Aromatic Schiff's base is considered as a chromophore due to conjucation of the electron pair on the nitrogen atom with the benzene ring of aniline and benzaldehyde [32].



[15]

Most aromatic schiff bases are soluble in water, and the solubility of units that contain carbohydrates is greater [33].

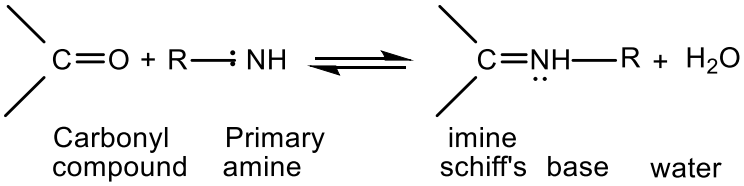
Biologically, Schiff's bases are important since they have biological activity against bacteria and fungi [34-38].

1.4.1 Synthesis of Schiff Bases

Generlly, Schiff base are synthesized by the reaction of aldehyde, or ketons with amin compounds .

A. **Primary Amines**

The reaction of primary amines with carbonyl compound will result in schiff bases and this is done by condensation [39] .



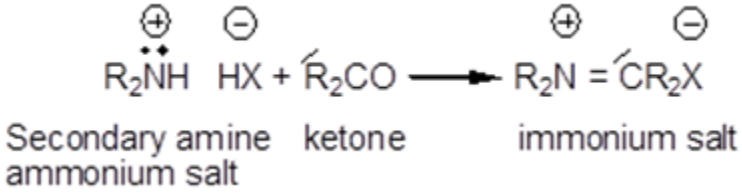
[16]

Often, it is recommended to remove the water, which is formed by distillation or by using a solvent to form the isotropic [40,41]. Aromatic aldehydes react readily in appropriate solvents under moderate conditions and low temperatures.

The condensation reaction of aromatic amines with aromatic aldehydes will reduce the alternatives that pull the electron in the position of the paragraph of amines rate of reaction, while reaction with aldehydes and ketones will increase, especially those with aromatic, and high temperatures and long reaction times are needed when removing water during its formation[42].

B. Secondary Amines

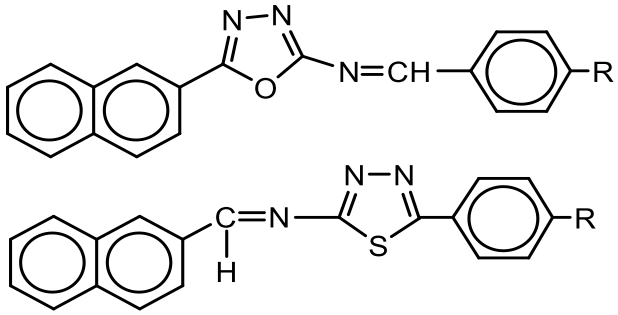
Interaction of secondary amines with carbonyl compounds by condensation without rearrangement not lead to Azomethine. However, immune globulin was obtained when the salt was treateded with aldehyde or ketone [43].



[17]

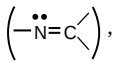
Emaad et. al.[44] prepared imines compounds containing heterocyclic ring with naphthyl rings. They found that these compounds have biological activity. They prepared the title compounds from the reaction between α,β-

naphthaldehyde and heterocyclic amines or different aldehydes with amine heterocyclic rings containing naphthyl ring by using absolute ethanol as a solvent and glacial acetic acid as catalyst.



R = H, OH, NO_2, $N(CH_3)_2$, Cl, CH_3
3,4-di OH

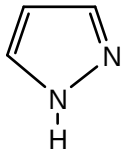
1.4.2 Reactions of Schiff's Bases:

addition ractions of the imine group; the reagents are added to a polarized double  bond, so the reactant in the azo methine bond attack the carbon atom[45] .Alkylhalide. Acid halides. Grignared Reagents. Hydrogenation. Anhydrides .

Anils react with maleic anhydride in the presence of water to form maleanilic acid and aldehydes[46,47].When an anil is heated with maleic anhydride in toluene, maleanilic acid is also obtained[48], whereas the formation of a condensation product has been reported when the mixture is heated without using the solvent (oxazepines).

1.5 Pyrazoles:

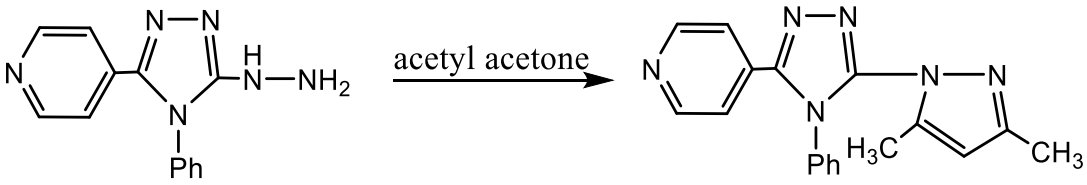
Pyrazole is unsaturated heterocyclic organic compounds charactarisezd by a five membered ring structure composed of three carbon atoms and two nitrogen atoms [49].



Few pyrazole derivatives occur naturally, this may be due to the difficulty for living organisms to consider the N-N bond. The most important derivatives of pyrazole are pyrazolones [50].

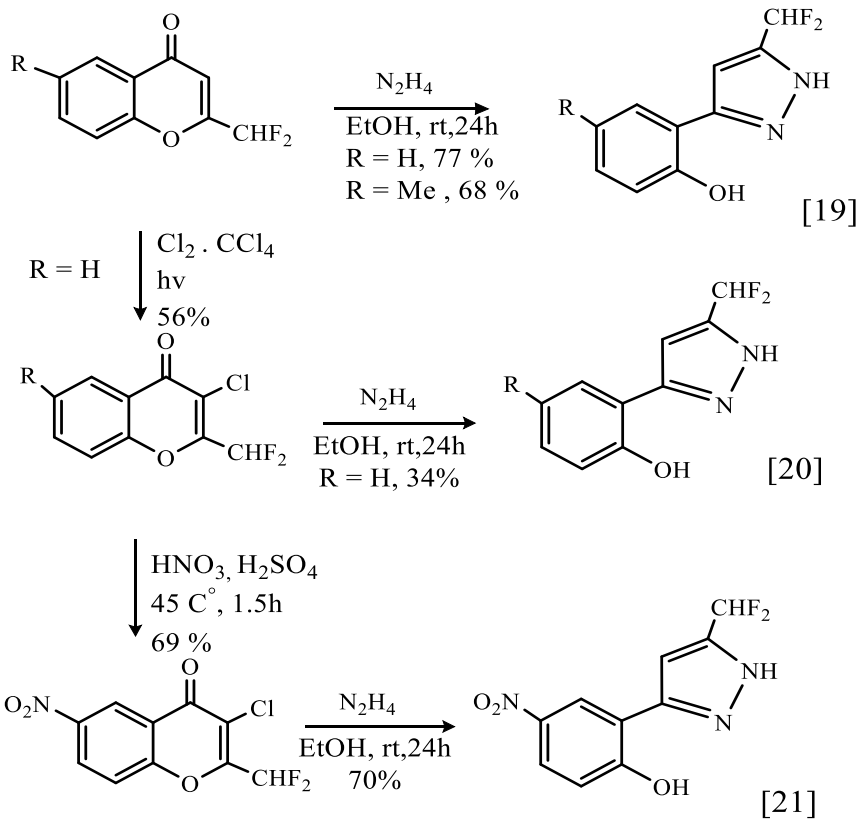
1.5.1 Synthesis of pyrazole:

Pyrazole ring derived from 4-(5-hydrazinyl-4-phenyl-4H-1,2,4-triazol-3-yl) pyridine were also prepared in presence of acetyl acetone [51,52].

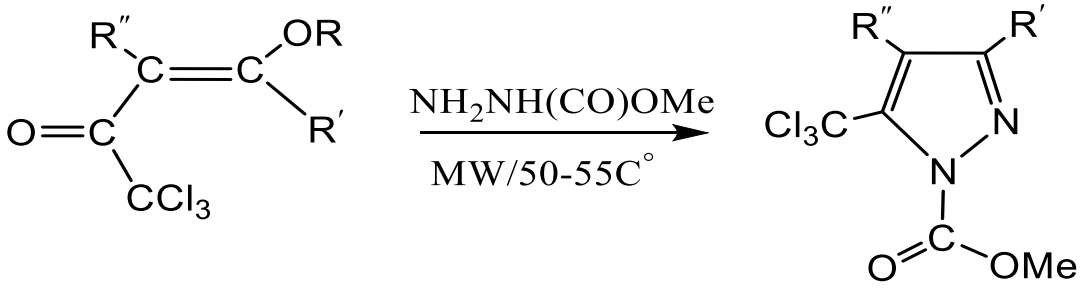


[18]

Chromones can be compared to ‘‘hidden’’ alkoxy enones, and they react easily with hydrazine to give fluoroalkyl pyrazoles containing an aryl group at the 3-position. The most study were focused on trifluorom pyrazoles, while a few examples with difluoromethyl substituents have been remambered. The desired pyrazoles were got in mild to good yields, attributing to the substituents on the aromatic rings [53].



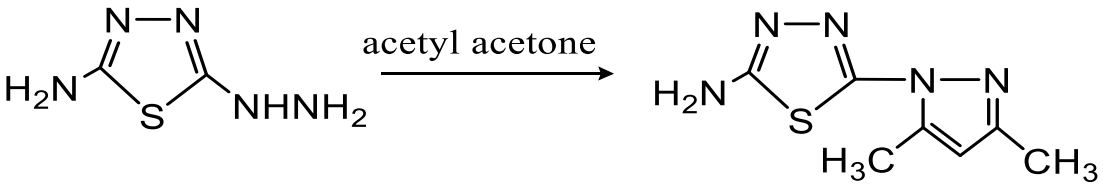
A number of 3,4-disubstituted-5-trichloromethyl-1H-1-pyrazole methyl ester have been synthesized under microwave irradiation conditions through the reaction of 1,1,1-trichloro-4-alkoxy-3-alken-2-one and methyl hydrazino carboxylate in presence of 10% HCl [(54)].



R =Et
R⁻ =H
R⁼ =H

[22]

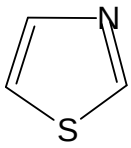
New azole heterocyclic 2-amino-5-(3,5-dimethyl-1H-pyrazole-1-yl)-1,3,4-thiadiazole have also been synthesized [55] .



[23]

1-6 Thiazoles :

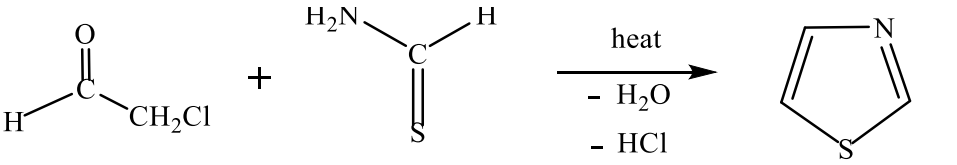
Thiazole is structurally related to thiophene and pyridine but in most of its properties, it resembles the pyridine [56].



In 1887 Huntsch Weber was first described thiazol. In 1889 Bob confirmed its structure. The numbering starts in the thiazol from the sulfur atom. Thiazol has been extensively studied and as a part of vitamin B, penicillin and antibacterial thiazol. Low thiazol is used in the study of peptides and proteins which occurs as structural units in compounds of biological importance[57].

1.6.1 Synthesis of Thiazoles :

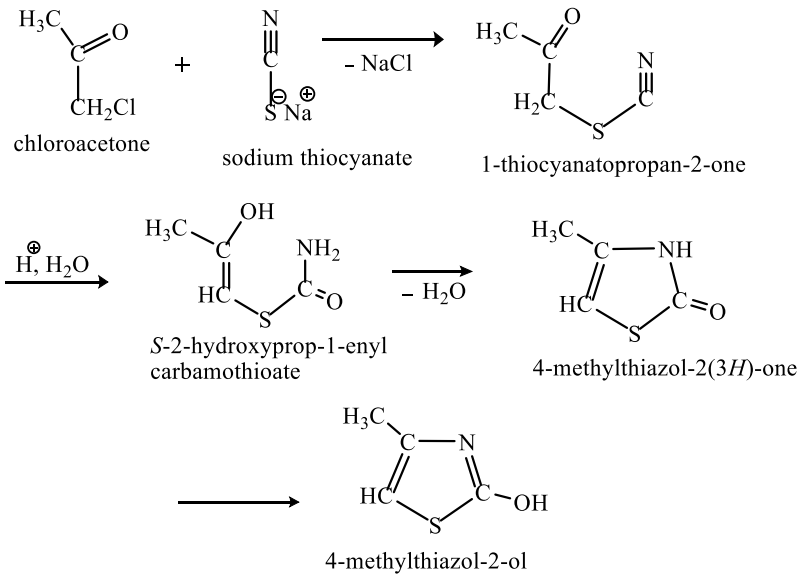
Thiazole are synthesized From α-Halocarbonyl compounds. It is an old but one of the most important methods for the preparation of thiazoles. In a general, α-halo ketone is react with an appropriate thioamide or thiourea. Chloroacetaldehyde, for instance, on condensation with thioformamide affords thiazole [58].



2-chloro acetaldehyde — methanethioamide — Thiazole 21%

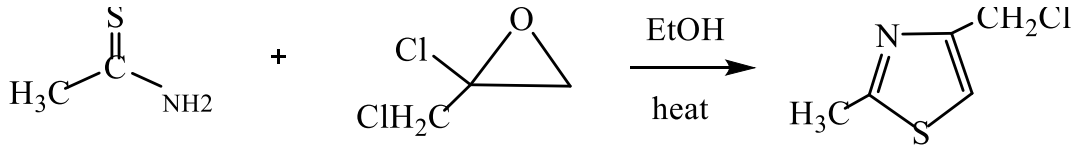
[24]

It can also be synthesized from α-thiocyanato ketone α-halocarbonyl compounds and metal thiocyanate react to give α-thiocyanato ketone which cyclized on treatment with acid or alkali, 2-hydroxy-4-methylthiazole has been obtained in about 60% yield from chloroacetone and sodium thiocyanate [59].



[25]

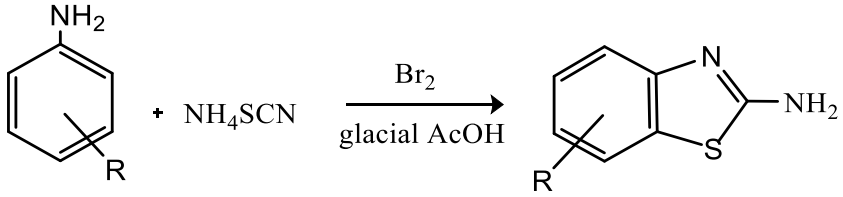
From α-halooxirane: Thiazole derivatives may also be obtained by reaction thioamide with substituted 2-chloro-2-(chloromethyl) oxirane [60].



ethanethioamide 2-chloro-2-(chloromethyl) oxirane 4-(chloromethyl)-2-methylthiazole

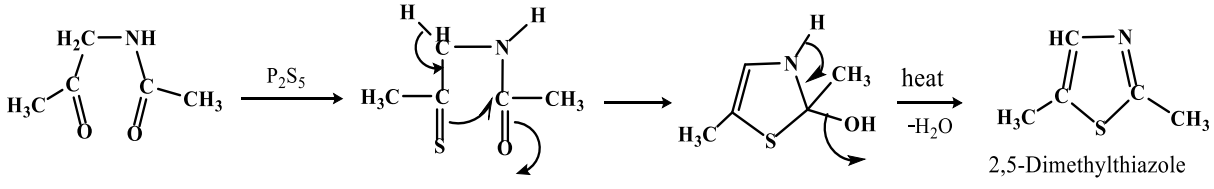
[26]

It was also found that thiazole derivatives were obtained from the reaction of ammonium thiocyanate with aniline derivatives [(61)].



R= *o*-H, *o*-CH_3, *p*-NO_2, *m*-OCH_3 [27]

The Gabriel synthesis method can also be used for preparation of thiazoles. The synthesis involves the heating of acylamine compounds with phosphorus pentasulfide as shown below to give thiazole derivatives. The carbonyl group is probably attacked first by P_2S_5, the oxygen atom is replaced by sulfur and the intermediate cyclized to thiazole. This method is similar to (Paal-Knorr) method for synthesis of thiophene. The driving force in this process results from the stabilization obtained in the formation of the aromatic heterocyclic [(62)].

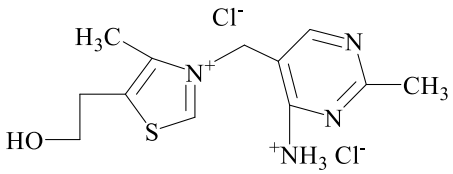


[28]

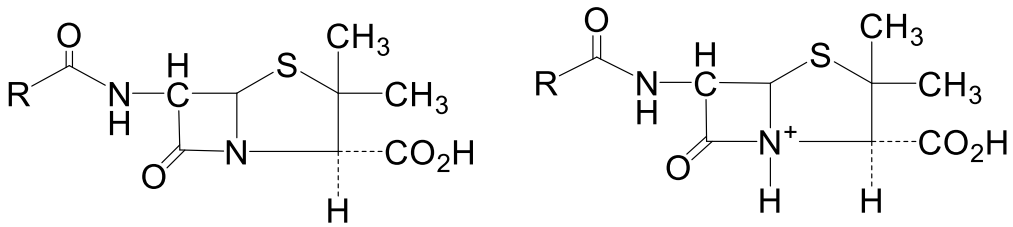
1.6.2 Biological activity of Thiazols:

Thiazole compounds are regarded as a class of heterocyclic compounds. It was found that numerous contained thiazole derivatives such as tomato, roasted coffee and roasted peanuts [63].

R.R.William and et. al. [64] demonstrated existence of simple thiazole ring in vitamin B_1 (thiamine) in 1935 .

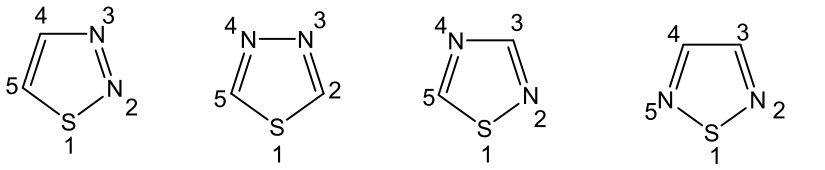


R.Mills recognized of cyanine dyes containing the ring as photographic sensitizers. It has also been proved that thiazolidine ring is considered as a part of penicillin structure and other derivatives which used as antibacterial agents[65].



1.7 1,3,4-Thiadiazoles:

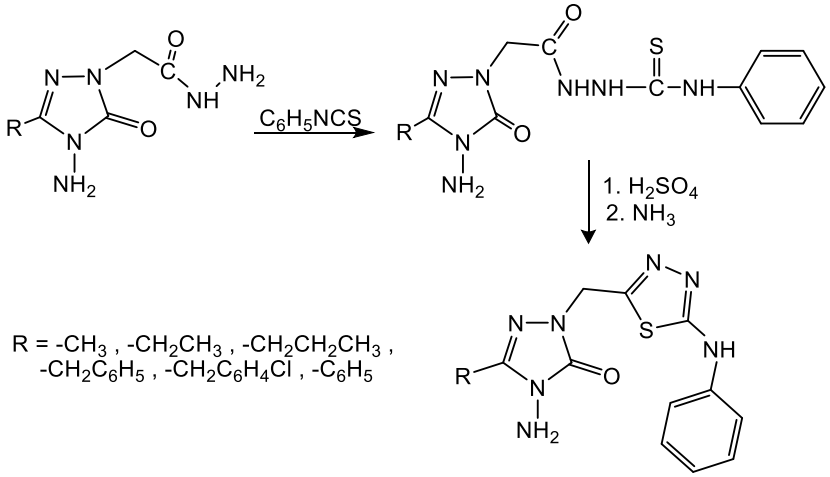
1,3,4-thiadazoles are the most important category of heterocyclic compounds and are of great importance in the study of research because of their broad types of biological activity. The thiazol is a five-ring system that contains a hydrogen binding field, a sulfur atom, and a dual-electron donor nitrogen system that provides a wide range of biological activity. It exists on four isomeric forms in nature and is. 1,2,3-thiadiazole. 1,2,5-thiadiazole. 1,2,4-thiadiazole. and 1,3,4 thiadizol [66] **.**



thiadiazole 1,3,4-thiadiazole 1,2,4-thiadiazole 1,2,5-thiadiazole

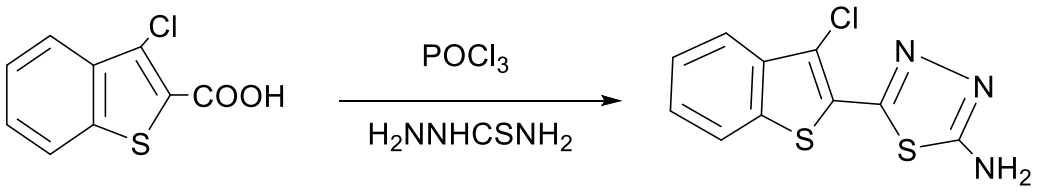
1.7.1 Synthesis of 1,3,4-thiadiazoles:

Derivatives of 1,3,4-thiadiazole are produced by reaction of 3-alternative 4-amino-5-oxo-4-dihydro-1H-1,2,4-triazole -1-yil) acetic acid hydrazide with phenyl isothocyanate and its products, using sulfuric acid (H_2SO_4), thiosymecarbazide derivatives were recycled[(67)] .



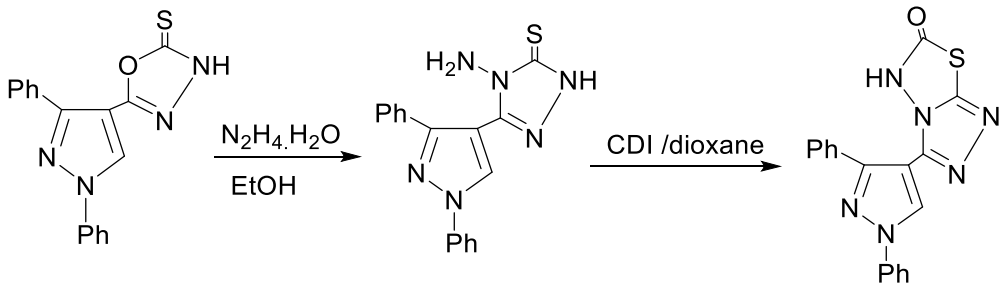
[29]

EL-Sayed et.al. synthesized 2-amino-5-(3-chlorobenzo [b]thiophen-2-yl)-1,3,4-thiadiazole through the condensation of 3-chlorobenzo[b]thiophene-2-carboxylic acid with thiosemicarbazide using phosphorous oxychloride as condensing agent [(68)].



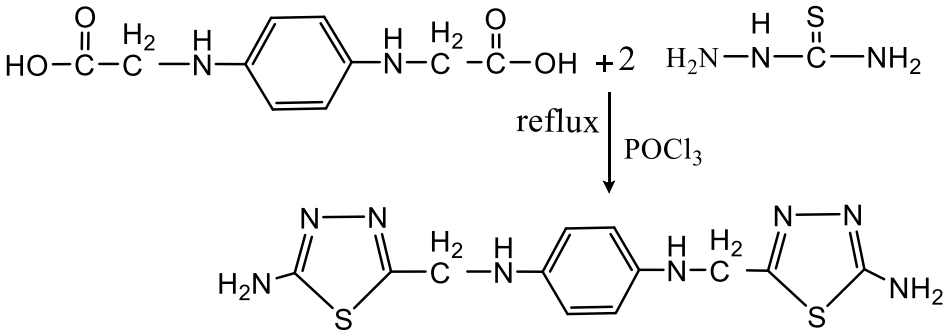
[30]

It was found that the reaction of oxadiazole thion with hydrazine hydrate afforded 4-amino-3- (1,3-diphenyl-1*H*-pyrazole-4-yl) 4,5-dihydro-[1,2,4] triazole -5(1*H*)-thione. Then the later reaction above compound with 1,1-carbonyl diimidazole (CDI) in dry dioxane gave 3-(1,3-diphenyl-1*H*-pyrazole-4-yl)5,6-dihydro-[1,2,4]trizolo[3,4-b][1,3,4]thiadiazol-5-one [(69)].



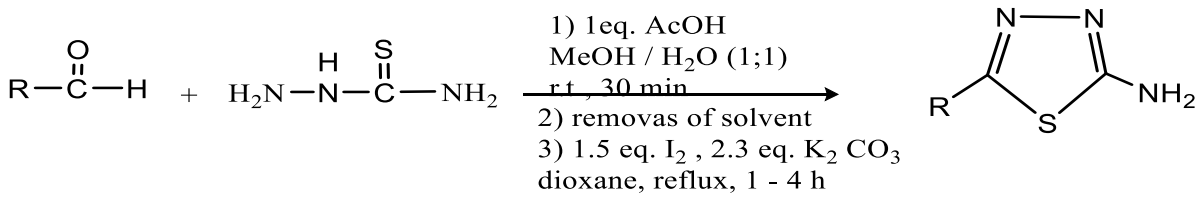
[31]

Derivatives of N,N'- Bis- [(5-amino -1,3,4- thiadiazol-2-yl) methyl] -*p*-phenylenediamine were also synthesized from the reaction of N,N'-Bis-(acetic acid)-*p*-phenylenediamine acetic acid with thiosemicarbazide in phosphorus oxychloride to give 1,3,4-thiadiazole ring [(70)].



[32]

A transition-metal-free condensation of semicarbazide/ thiosemicarbazide with aldehydes followed by 12-mediated oxidative C-O/C-S bond formation provides 2-amino-substituted 1,3,4-oxadiazoles and 1,3,4-thiadiazoles in an effective way[71].

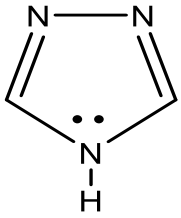


R= Ar, alkyl, vinyl

[33]

1.8. 1,2,4 -triazoles :

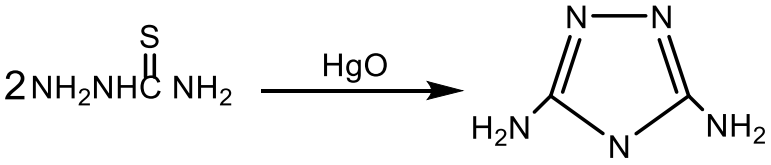
There are three nitrogen atoms in the five-ring system at 1,2 and 4-positions define an interesting class of compounds ,called 1,2,4-triazoles. The ring system 1,2,4-triazole is planar 6π-electron aromatic system with distortion of the π-system prompted by the annular nitrogen atoms[72].



A large number of 1,2,4-triazole compounds have been incorporated into a wide variety of therapeutically interesting drug candidates including anti-septic, analgesic, anti-convulsant[73,74] anti-biotic[74] ,anti-allergic[74] anti-inflammatory[75,76], diuretic[77,78], fungicidal[79,80] , insecticidal[75,80] , herbicidal [75,79], anti bacterial[76,78], anti-viral[79,80], anti-depressant[77] anti-microbial[74,79] anti-tumor[75,79] , and antihypertensive [77].

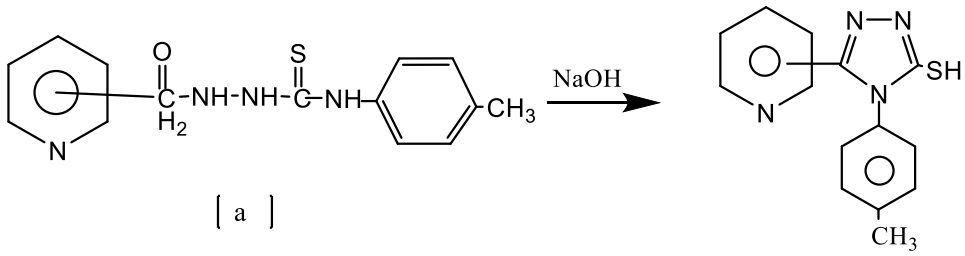
1.8.1 Synthesis of 1,2,4- triazoles:

A) 1,2,4 triazoles can be synthesized from the reaction of thiosemicarbazide, with HgO to yielded 3,5-diamino-1,2,4-triazole [81].



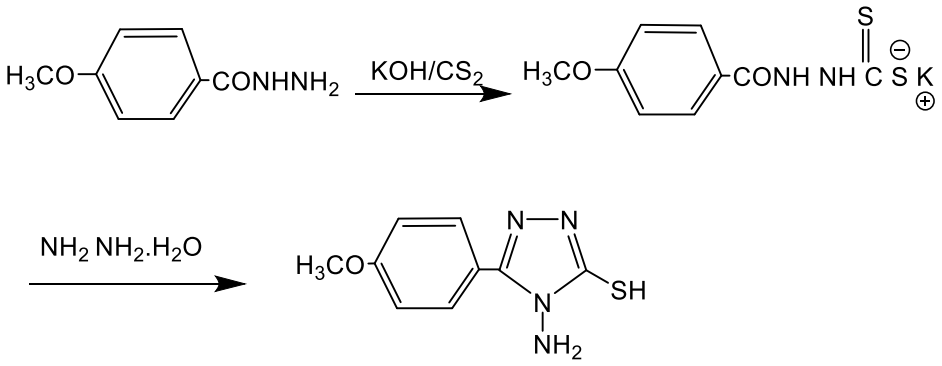
[34]

b) They can also be synthesized by ring closure reaction of compound [a] to give new triazole in NaOH medium [82] .



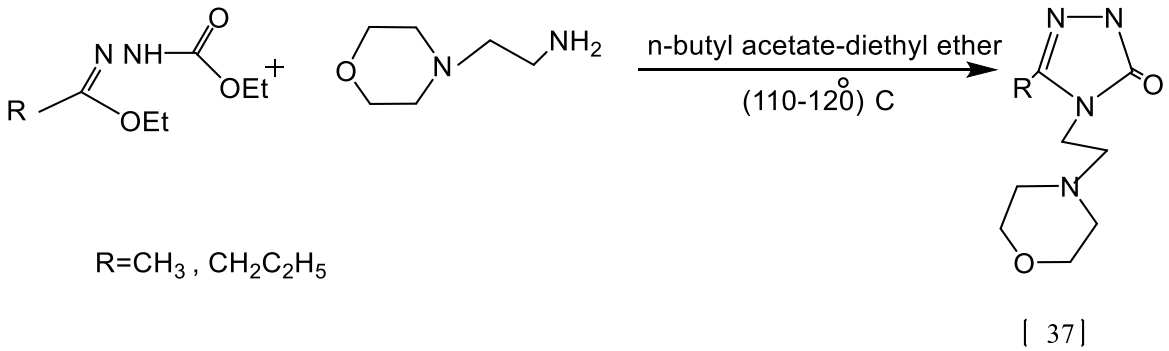
[a] [35]

c) Another method for the synthesis of 1,2,4 triazol from the reaction of 4-methoxy phenyl dithiocarbazates (which was synthesized from the reaction of aryl hydrazide with CS_2 in basic medium) with hydrazine hydrate to form new triazole, as follows[83] :



[36]

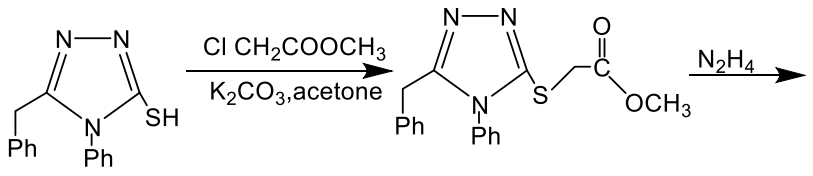
d) More over cyclocondensation method of ester ethoxy carbonyl hydrazones, with 2-morpholinoethan amine, in an oil bath for 2 hrs then n-butyl acetate-diethyl ether was added to yield triazol[84] was also used for the synthesis of 1,2,4 triazol



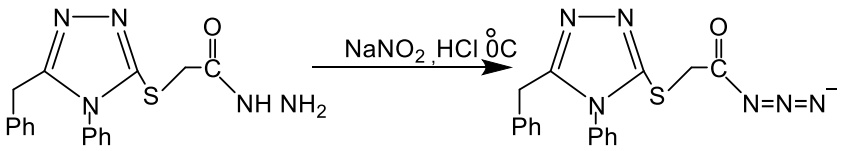
[37]

1.8.2 Reaction of 1,2,4-Triazoles and their 5-Thiol :

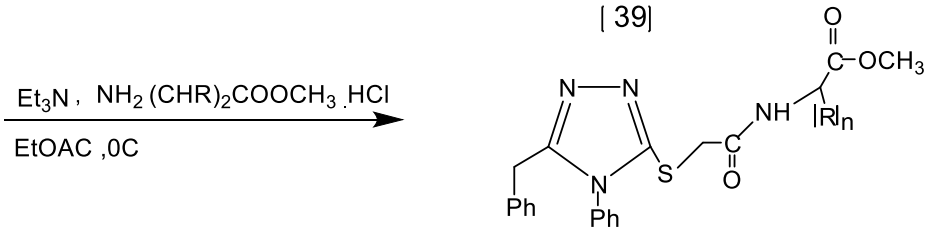
On the other hand, the reaction of 1,2,4- triazol -3-thiols, with methyl chloro acetate in basic medium to gave a corresponding new ester, which was undergone in different reactions, as follows[85] .



[38]



[39]

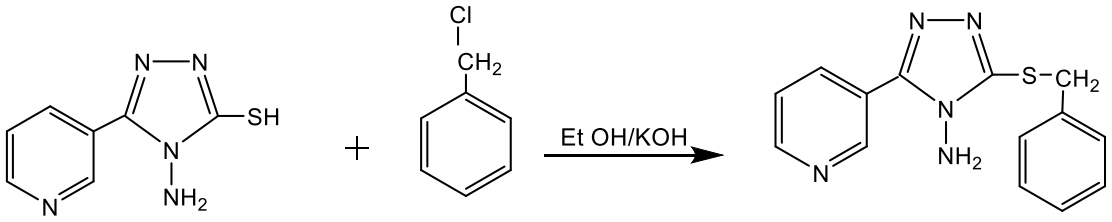


[40]

R= H,$CH_2CH(CH_3)_2$ and $CH_2CH_2SCH_3$

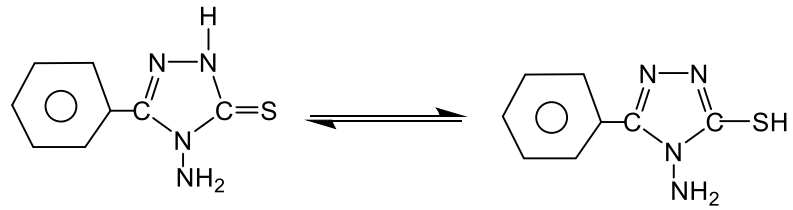
n=2 and 1

Jadhav et .al [86] synthesized of 5- (benzyl thio)-3-(pyridin-3-yl)-4-amino-1,2,4-triazole, from the reaction of 5-thiol-3-(pyridin-3-yl)-4-amino-1,2,4-triazole, with benzyl chloride, in ethanolic KOH .

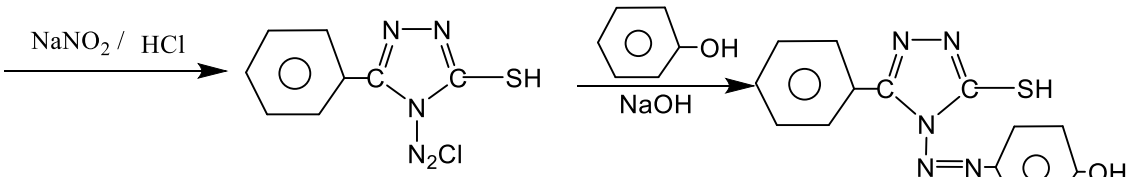


[41]

While, the treatment of 1,2,4-triazole, with HCl and $NaNO_2$ produce diozonium salt, this salt was added to cold solution of phenol (was coupled under alkaline condition) to obtain new azo compounds of 1,2,4- triazole, [87] .

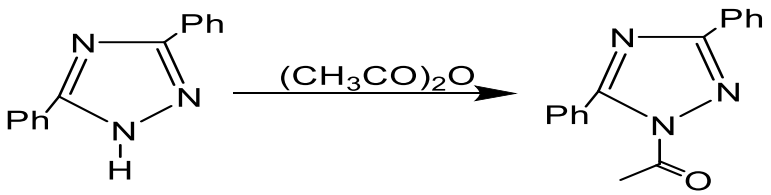


[42]



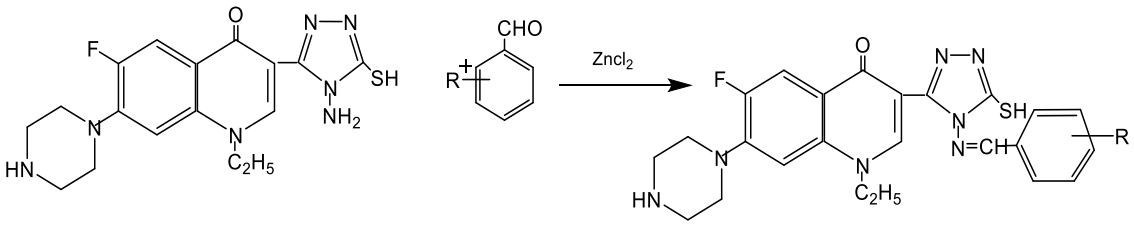
[43]

In addition, 3,5-diphenyl-1,2,4- triazole, was acylated by acetic anhydride to get 1-acetyl-3,5-diphenyl-1,2,4-triazole, [88] .



[44]

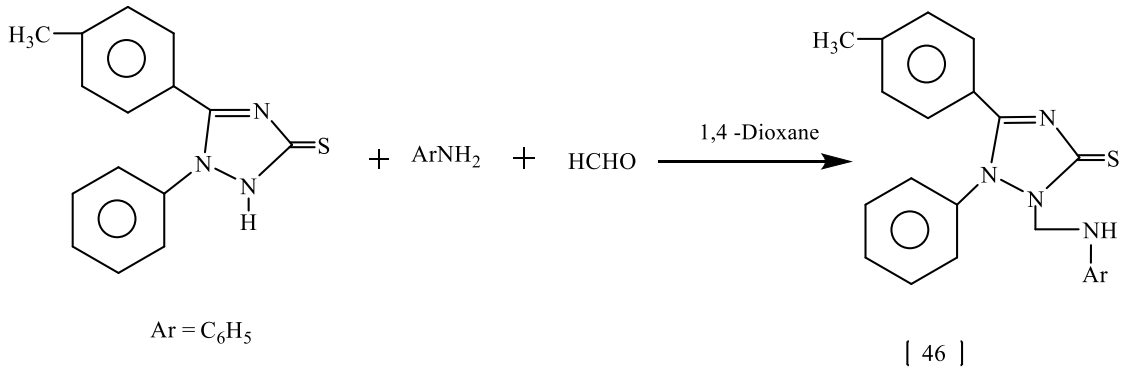
The condensation of 3-substitued -4-amino-5-mercapto -1,2,4-triazole, through aromatic aldehyde, and zinc chloride yielded new Schiff bases of 1,2,4-triazole, [89] .



[45]

R= *p*-Aminophenyl, *p*-Chlorophenyl, *p*-Hydroxyphenyl)

New derivative of 1,2,4- triazoles, was synthesized from the reaction of 1-Phenyl-5-p-tolyl-1,2-dihydro - [1,2,4] triazole-3-thion, with formaldehyde and aromatic amine in 1,4- dioxin[90] as a solvent.

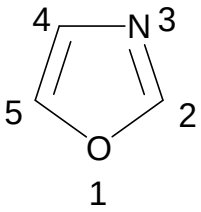


Ar = C_6H_5

[46]

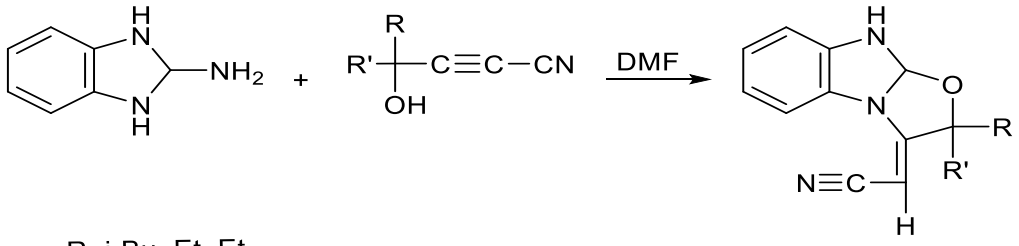
1.9 Oxazole :

Oxazole compound is a five –member ring heterocyclic compound, azafuran, by a molecular structure(C_3H_3ON) including one oxygen and nitrogen besides three carbon atoms. It is a yellowish liquid with a pyridine like odor [91].



1.9.1 Synthesize of Oxazole:

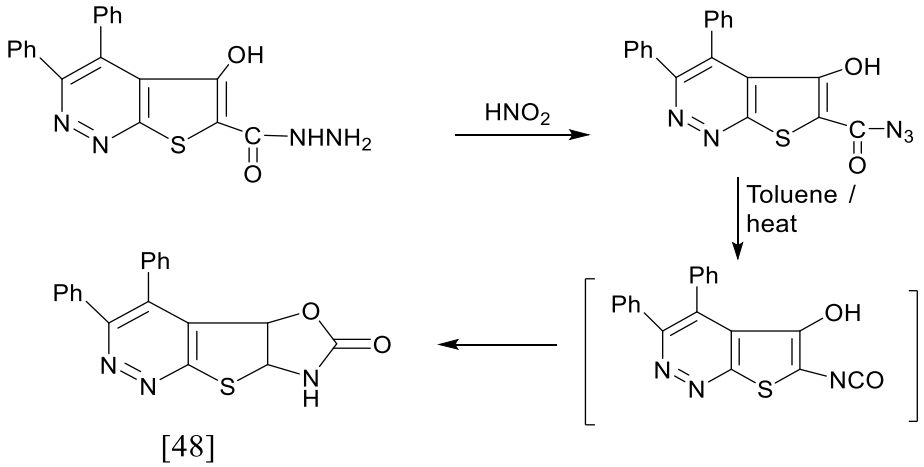
The literature revealed that the oxazole compounds are developed and got a wide interest,which is attributed to their uses in many fields. It was reported that when 4,4-dialkyl-4-hydroxyacetylenic nitrile was heated under reflux with 2-aminobenzimidazole in dimethylforamide (2,2-dialkyl-2, 3-dihydrooxazolo benzimidazolyl idene) ethannitrile could be formed [92].



R=i-Bu, Et, Et
R=' Me, Me, Et

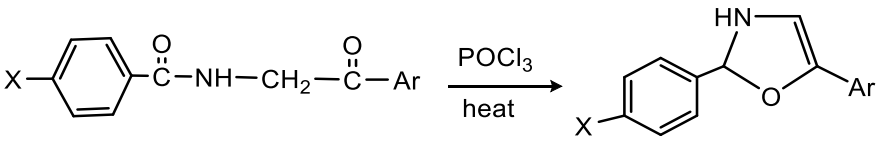
[47]

The reacting of carbohydrazide derivative and sodium nitrite in presence of glacial acetic acid gave the carboazide that heated with dry toluene to obtain furnish oxazolo, thieno and pyridazine via the isocyanate intermediate [93].



[48]

2-[4-(4-halobenzenesulphonyl) phenyl]-5-aryloxazoles was synthesized by cyclization of 2-aza-1-[4-(4-halo benzensulphonyl) -phenyl] -4-aryl-1,4-butanedione through the using of phosphorus oxychloride [94].

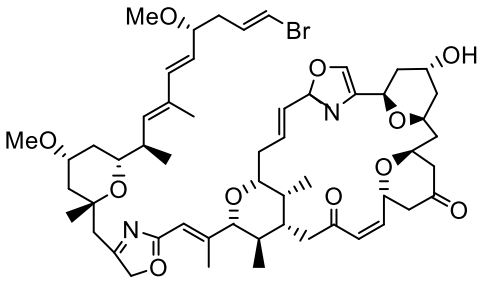


X=p-$BrC_6H_4SO_2$, Ar=Ph
X=p-$ClC_6H_4SO_2$, Ar=Ph
X=p-$BrC_6H_4SO_2$, Ar=p-$CH_3C_6H_4$
X=p-$BrC_6H_4SO_2$, Ar=2,4-$(CH_3)_2C_6H_3$
X=p-$ClC_6H_4SO_2$, Ar=2,4-$(CH_3)_2C_6H_3$

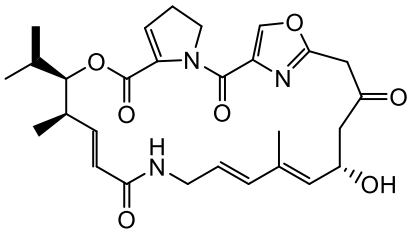
[49]

1.9.2 Biological activity of Oxazoles:

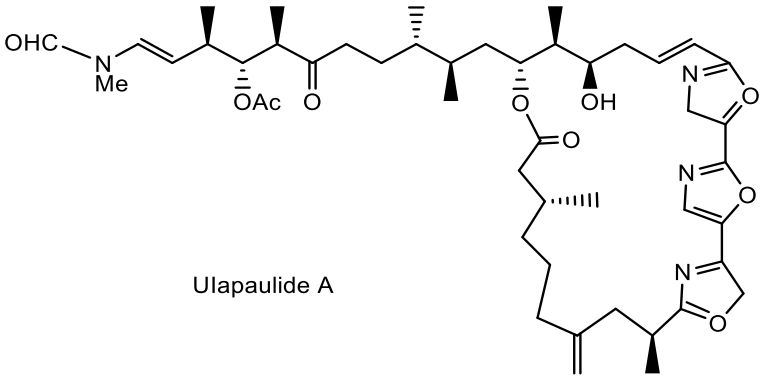
Oxazoles are found in many naturally occurring and biologically active materials as sub-structures within more complicated molecular groups. In particular, oxazole functionalized at both the 2-and 4-position have found important application in the synthesis of the more complex natural products including phorboxazoles, virginiamycins, and ulapualides[95] .



Phorboxazole A



Virginiamycine M



Ulapaulide A

Not surprisingly, a number of structures have therefore evolved for the construction and incorporation of disubstituted oxazole into complex synthetic target. Furthermore, oxazoles are important compounds for the synthesis of anti-inflammatory pharmaceuticals and vitamin for example, 5-ethoxy-4-methoxyoxazole used as a precursor for the synthesis of vitamin B_6 [91].

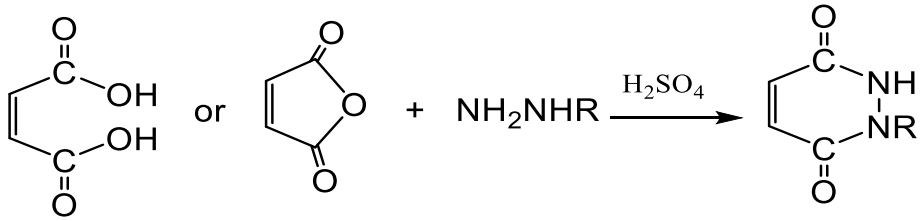
Vitamin B_6 is a naturally occurring, highly subsisted pyridine derivatives with comparable physiologic activity. Vitamin B_6 is a water soluble vitamin that is manufactured in bulk as pyridoxine hydrochloride (the predominant from of vitamin B_6, it is an important nutrient, and plays an essential role in the body's amino acid biochemical pathways [(93)].

1.10 Pyridazines :

Pyridazine is a heterocyclic organic compound with the molecular formula $(CH)_4N_2$. It contains a six-membered ring with two adjacent nitrogen atoms, and is aromatic. It is a colorless liquid with a boiling point of 208 °C. It is isomeric with two other $(CH)_4N_2$ rings, pyrimidine and pyrazine[(96)].

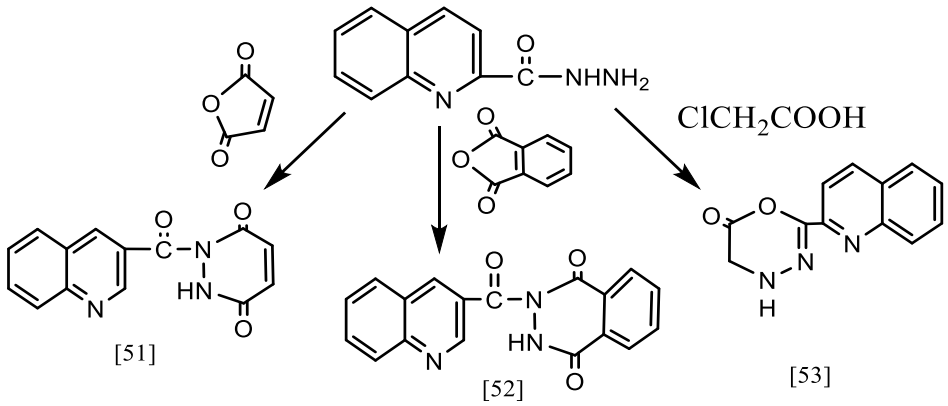
1.10.1 Synthesis of Pyridazine derivatives:

Pyridazine and number of its derivatives were prepared by different methods such as from the reaction of maleic acid or maleic unhydride with hydrazine or substituted hydrazine [(97)].



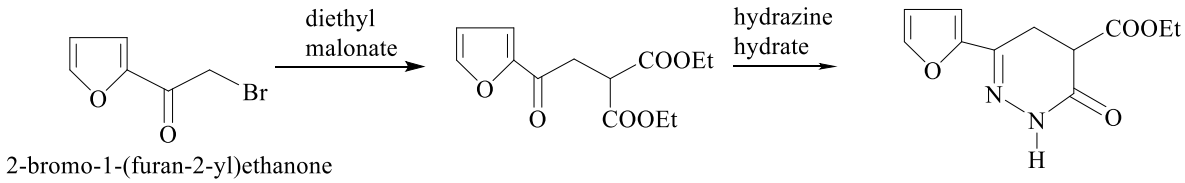
R = H , many different substituents [50]

Pyridazine was also produced from the reaction of 2-quinoline acid hydrazide with maleic anhydride or phthalic anhydride with chloroacetic acid in acetic acid [98].



[51] [52] [53]

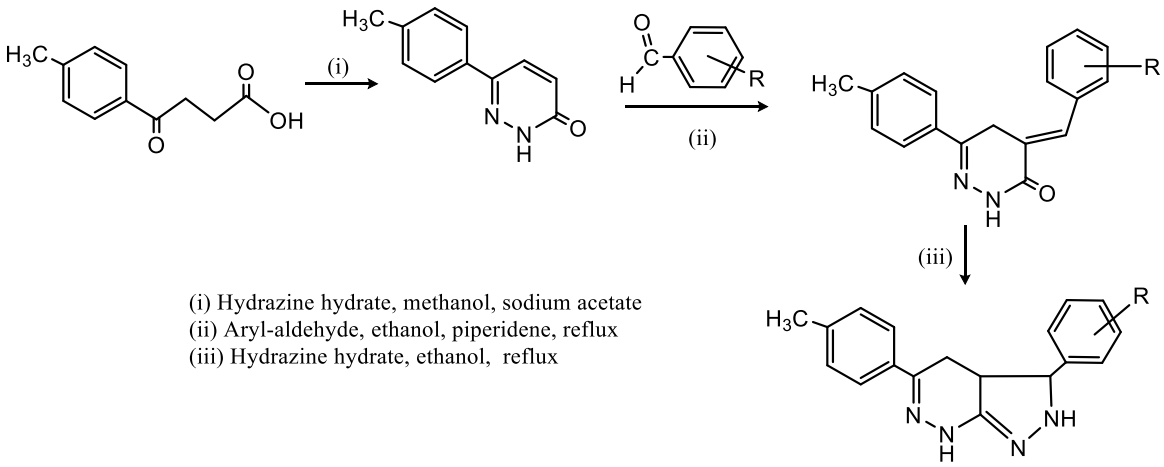
It was found that when diethyl malonate allowed to react with 2-bromo-1-(2-furyl) ethanone, diethyl 2-[2-(2-furyl)-2-oxoethyl] malonate would be formed. Reaction of the latter compound with hydrazine hydrate gave ethyl 6-(2-furyl)-3-oxo-2,3,4,5-tetrahydropyri-dazine-4-carboxylate [99].



2-bromo-1-(furan-2-yl)ethanone

[54]

A series of pyrazol-pyridazine derivatives was prepared by multi-step synthesis. Reaction of -4 oxo-4-p-tolylbutanoic acid with hydrazine hydrate gave 6-phenyl-2,3,4,5-tetrahydropyridazin-3- one, which on reaction with different aryl-aldehydes furnished pyridazinones. In the final step, pyridazinones were reacted with hydrazine hydrate to furnish the title compounds [100].



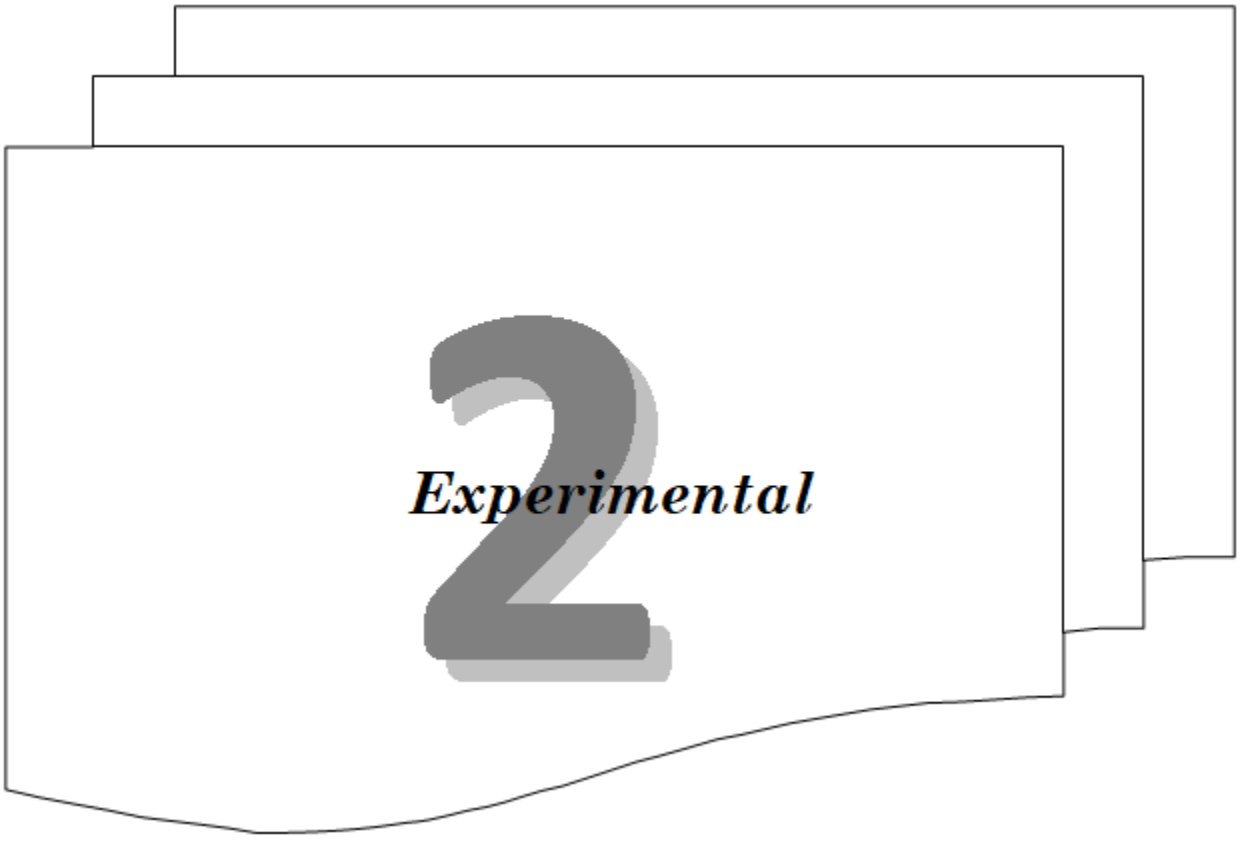
(i) Hydrazine hydrate, methanol, sodium acetate
(ii) Aryl-aldehyde, ethanol, piperidene, reflux
(iii) Hydrazine hydrate, ethanol, reflux

[55]

The aim of work:

The research includes the preparation of five, six and seven cyclic members heterocyclic compound and studing the biological activity. These compound including pyrazole, oxydiazole, thiadiazole, triazole, tetrazoles, oxazole, and pyrazadine starting from mefenamic acid(2-((2,3-dimethylphenyl)amino)benzoic acid).

Chapter Two



2.1 Chemicals : The chemicals used are and its supplier company are listed in table (2-1):

Table (2.1): Chemical materials used and its company.

No.	Chemicals	Company	Purty%
1	Aceton	Sigma-Aldrich	99
	Acetic acid	sigma	85
2	Acetyl aceton	Aldrich	95
3	Amonium thiocyanate	CDH	95
4	Benzene	Alpha chemika	99
5	Benzoic acid	Riedel-dehaen	99
6	Chloro acetic acid	CDH	98
7	Cynamic acid	Aldrich	98
8	Ethanol absolute	Scharlau	99
9	Ethyl scetate	Analar	98
10	Hydrazin hydrate (N_2H_5 .H_2O)	CDH	85
11	Hydrochloric acid (HCl)	CDH	99
12	Iodo ethan	Riedel dehaen	99
13	Maleic anhydride	Aldrich	98
14	*m*-nitrophthalicanhydride	BDH	90
15	*m*-chloro benzaldehyde	BDH	98
16	*m*-methoxy-*p*-hydroxybenzaldehyde	CDH	95
17	N,N-dimethyl amino benzyldehyde	BDH	95
18	*o*-chlorobenzoic acid	Romil	99
19	Phthalicanhydride	Fluka	99
20	Phenyl iso thiocyanate	Fluka	98

21	Phosphoryl chloride	CDH	99
22	Phenyl acetic acid	Merck	98
23	*p*-nitrobenzoic acid	Merck	98
24	*p*-phenyl phenacyl bromide	Aldrich	98
25	*p*-nitrobenzoic acid	Himedia	99
26	*p*-hydroxybenzaldehyde	Himedia	95
27	Sulfuric acid	Biosolvechime	99
28	Sodium hydroxide	Aldrich	99
29	Sodium azid	Fluka	99
30	Succenic anhydride	Merck	98
31	Sodium acetate	BDH	95
32	Thiourea	Merck	99
33	Thiosemicarbazide	BDH	99
34	Tetrahydrofuran(THF)	Solvocheme	99
35	Urea	Merck	98

2.2 Instruments:

1- Melting points are recorded using hot stage Gallen Kamp melting point apparatus.

2- Infrared spectra were recorded using Fourier Transform infrared SHIMADZU (8300) (FT.IR) infrared spectrophotometer, KBr disc was performed in chemistry department, Baghdad University- Ibn Alhatham and using Fourier Transform infrared SHIMADZU (8400) (F.T.IR) infrared spectrophotometer, KBr disc was performed in Al-Mustansryia Univrsity.

3- Thin layer chromatography (TLC) was carried out using Fertigfollen precoated sheets type polygram Silg, and the plates were developed with iodine vapour.

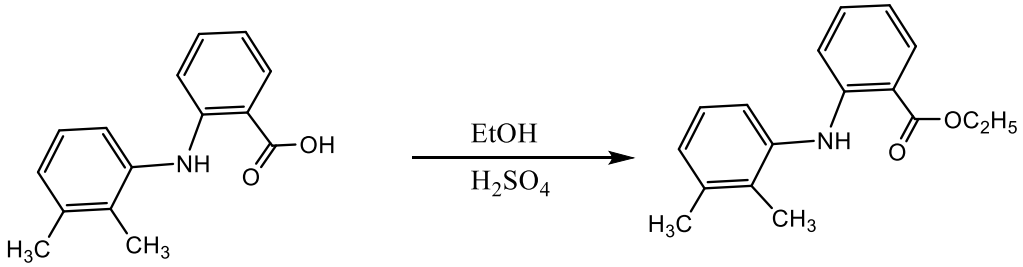
4- ^{1}H-NMR spectra were recorded on Foruier Transform Varian spectrometer, operating at 500 MHz with tetramethylsilane as internal standard in DMSO; Measurements were made at Chemistry Department, in Iran.

5- The mass spectra were recorded by MS model: 5975c VL MSD with tripe- Axis Detector University of Tehran, Center Lab. (in Iran).

6- Biological activity was studied at biology department, Baghdad University.

2.3. Methods :

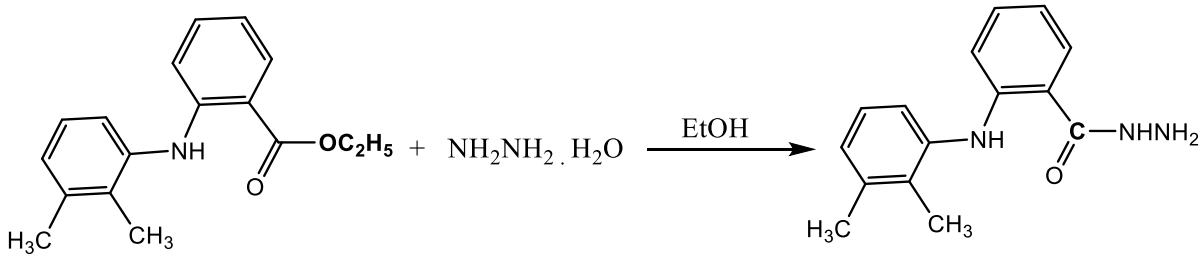
2.3.1. Characterization of ethyl 2-((2,3-dimethylphenyl)amino) benzoate[2]



[1] [2]

2- (2,3 - dimethyl phenyl) amine (benzoic acid) (10) gm, (0.041) mol was dissolve in (20 ml) of absolute ethanol and (10 ml) of Conc. sulfuric acid. Then, the mixture was refluxed for 6 hours, and after that cooled and extracted with ethyl acetate, washed with water, dried with sodium sulfate and finally, the solvent was evaporated[97] , m.p.(126-128), yield(80%) .

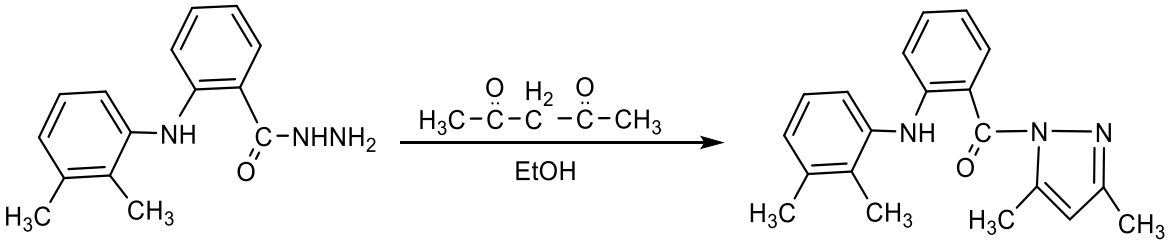
2.3.2. Characterization of 2-((2,3-dimethylphenyl)amino) benzohydrazide[3]



[2] [3]

Compound [3] was preparation from the reaction of compound [2] with hydrazine hydrazine (10 ml) to (0.01 mol, 3 g) in 30 ml of ethanol and then refluxing for 5 hours. The precipitate was filtered, washed with distilled water to give final product. [98], m.p.(176-178), yield(95%) .

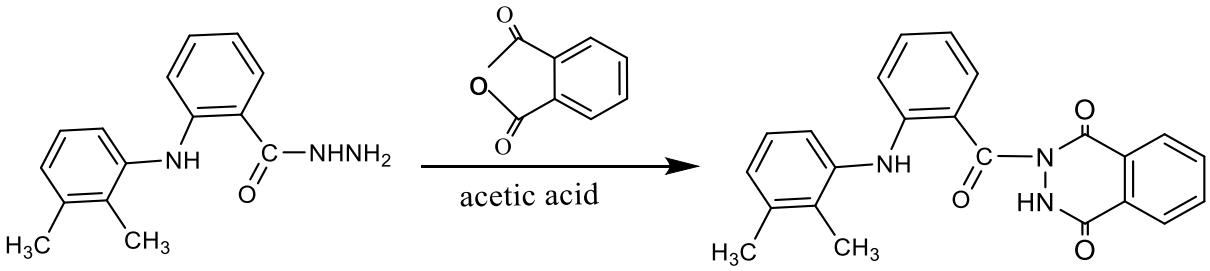
2.3.3 . Characterization of (3,5-dimethyl-1H-pyrazol-1-yl)(2-((2,3-dimethylphenyl)amino)phenyl)methanone [4] .



[3] [4]

Compound [4] was preparation from the reaction of compound [3] (0.00078 mol, 0.2g) with acetyl acetone (0.001 mol, 0.1 ml) in ethanol (15 ml) and then refluxing for 8 hours. The precipitate was filtered, washed with distilled water to give final product. [(99)].

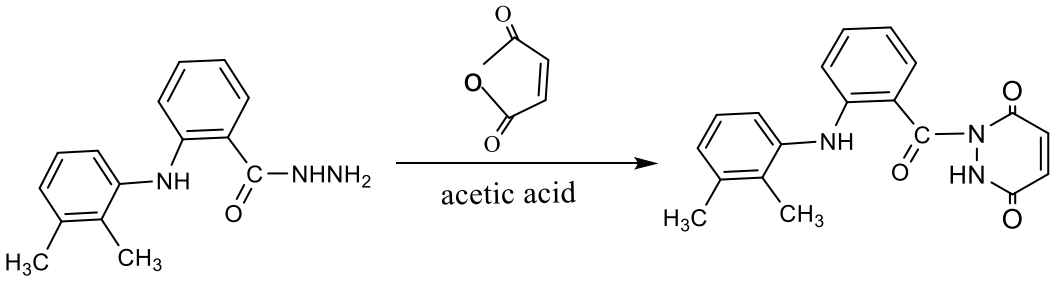
2.3.4 . Characterization of 2-(2-((2,3-dimethylphenyl)amino) benzoyl)-2,3-dihydrophthalazine-1,4-dione [5] .



[3] [5]

Compound [5] was prepared from the reaction of product [3] (0.00078 mol, 0.2g) with phthalic anhydride (0.00074 mol, 0.11g) in acetic acid (15 ml). The mixtures was refluxed for 8 hours then cooled and added to crushed ice. The precipitate was filtered, washed with distilled water to give final product.[(100)]

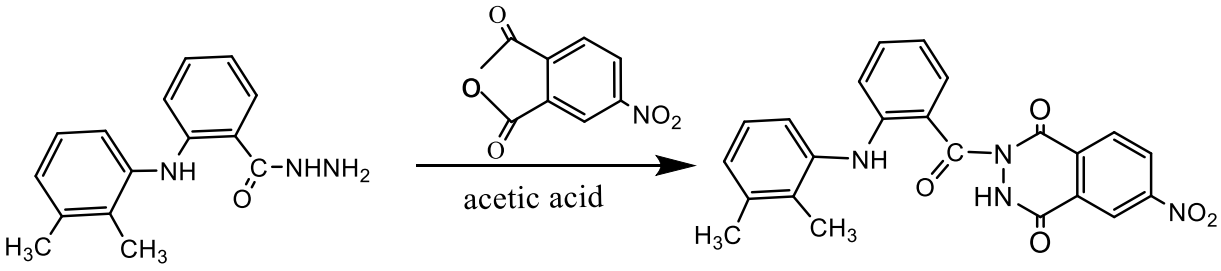
2.3.5 . Characterization of 1-(2-((2,3-dimethylphenyl)amino) benzoyl)-1,2-dihydropyridazine-3,6-dione [6] .



[3] [6]

Compound [6] was prepared from the reaction of product [3] (0.00078 mol, 0.2 g) with maleic anhydride(0.00077 mol, 0.076 g) in acetic acid (15ml). The mixture was refluxed for 7 hours then cooled and added onto crushed ice. The obtained precipitate was filtered, washed with distilled water to give the final product [6] [(101)].

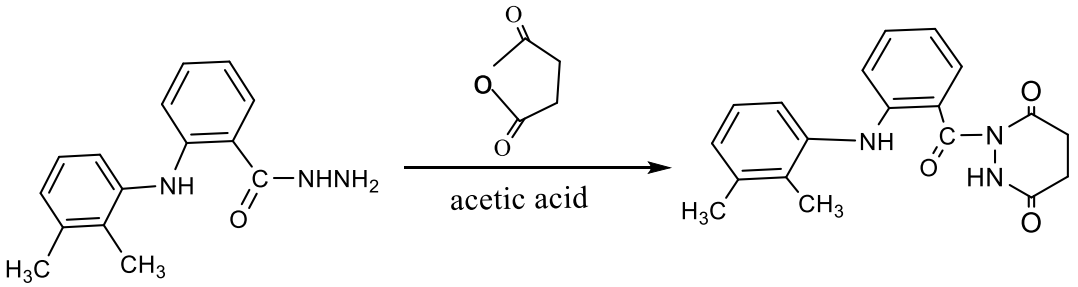
2.3.6 . Characterization of 2-(2-((2,3-dimethylphenyl)amino) benzoyl)-6-nitro-2,3-dihydrophthalazine-1,4-dione[7] .



[3] [7]

Compound [7] was prepared from the reaction of product [3] (0.00078 mole, 0.2g) with 3-nitro phthalic anhydride (0.00077 mol, 0.15 g) in acetic acid (15ml). The mixture was refluxed for 5 hours then cooled and added to crushed ice. The precipitate was filtered, washed with distilled water to give the final product[(102)].

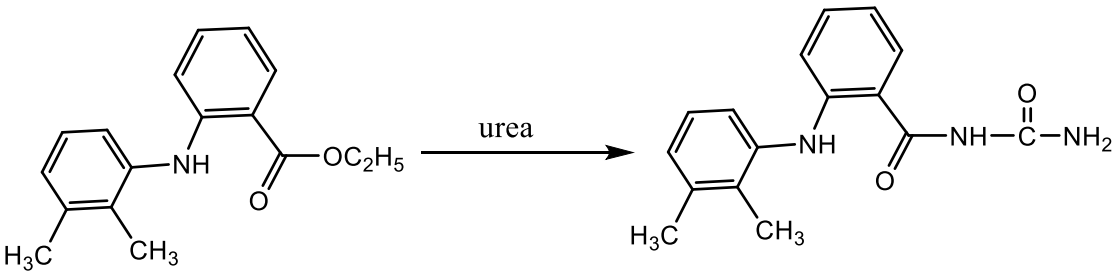
2.3.7 . Characterization of 1-(2-((2,3-dimethylphenyl)amino) benzoyl)-1,2-dihydropyridazine-3,6-dione[8].



[3] [8]

Compound [8] was prepared from the reaction of product [3] (0.00078 mol, 0.2 g) with succenic anhydride(0.001 mol, 0.1 g) in acetic acid (15ml). The mixture was refluxed for 7 hours then cooled and poured onto crushed ice. The obtained precipitate was filtered off and washed with distilled water to give the product [(103)].

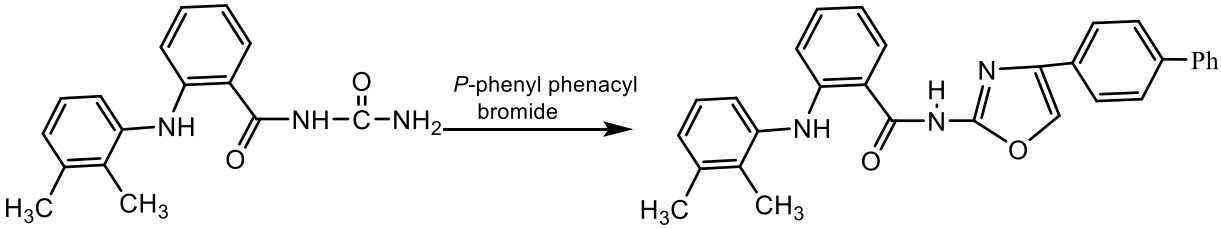
2.3.8 . Characterization of N-carbamoyl-2-((2,3-dimethyl phenyl)amino) benzamide[9] .



[2] [9]

Ester [2] (0.00063 mol , 0.170 g) in absolute ethanol (15ml) and urea (0.00061mol, 0.037g) were mixed to produce compound [9]. The mixture was refluxed for 6hours. After cooling and filtering, a solid product was obtained. [(104)].

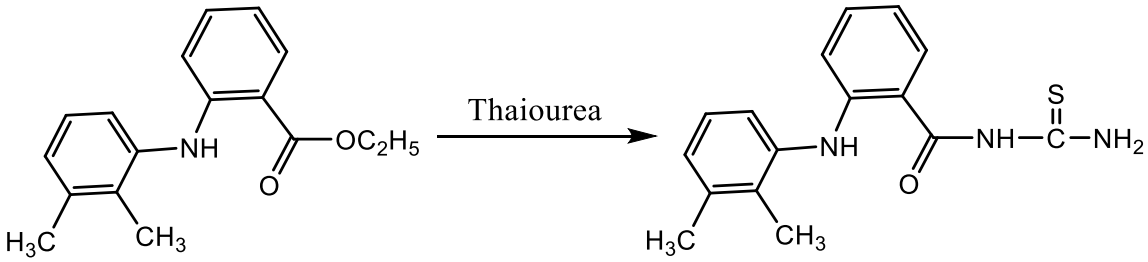
2.3.9 . Characterization of N-(4-([1,1'-biphenyl]-4-yl)oxazol-2-yl)-2-((2,3-dimethylphenyl)amino)benzamide[10] .



[12] [10]

Compound [12] (0.00012 mol, 0.04g) was dissolved absolute ethanol (10ml), *p*-phenyl phenacyl bromide (0.00012 mol, 0.035g) was mixed to produce compound [10]. The mixture was refluxed for 7 hours, cooled and neutralized with ammonium hydroxide solution. The precipitate was filtered and washed with water. Petroleum ether (80-100) was used for recrystallization[104].

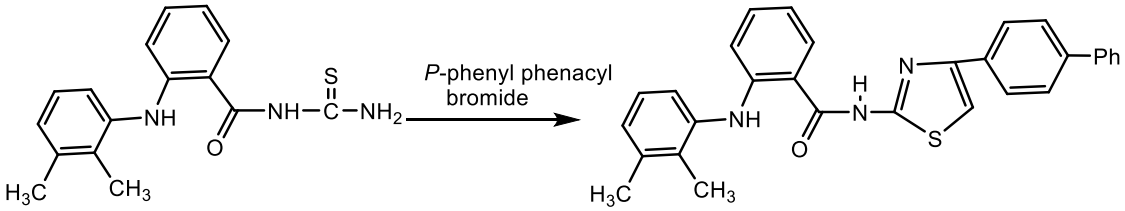
2.3.10. Characterization of N-carbamothioyl-2-((2,3-dimethyl phenyl) amino) benzamide[11] .



[2] [11]

Compound [11] was prepared following the same method described for the preparation of [9][104].

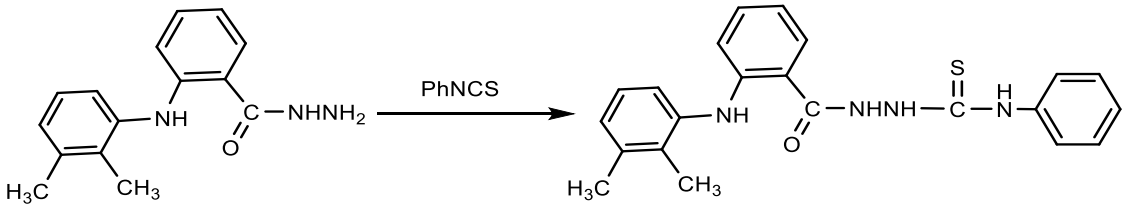
2.3.11. Characterization of N-(4-([1,1'-biphenyl]-4-yl)thiazol-2-yl)-2-((2,3-dimethylphenyl)amino)benzamide[12] .



[11] [12]

Compound [12] was prepared using the same method described for the compound [10](104).

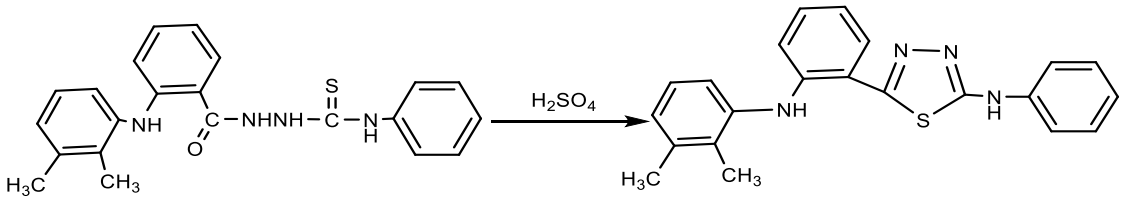
2.3.12. Characterization of 2-(2-((2,3-dimethylphenyl)amino) benzoyl)-N-phenylhydrazine-1-carbothioamide[13] .



[3] [13]

A mixuter of compound [3] (0.0039 mol, 1g) and phenyl isothiocyanate (0.0043 mol, 0.6 g) in (15ml) absolute ethanol was refluxed for 7 hours. The solid material obtained on cooling was filtered off and then recrystallized using (50:50) ethanol water(105).

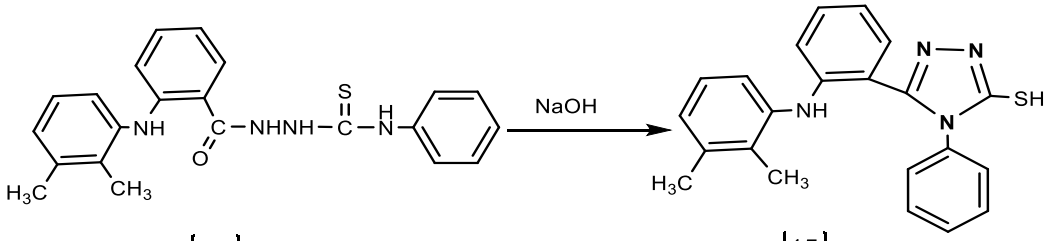
2.3.13. Characterization of 5-(2-((2,3-dimethylphenyl)amino) phenyl)-N-phenyl-1,3,4-thiadiazol-2-amine[14] .



[13] [14]

Compound [13] (0.00012 mol, 0.2g) was added dropwise to (2.5ml) of concentrated sulfuric acid at 0°C with continuous stirring. The reaction mixture was further stirred for 3 hours at room temperature and then allowed to stand overnight. Neutralization with diluted sodium hydroxide prepcipitated acrude solid, obtained which was filtered and washed with water(105).

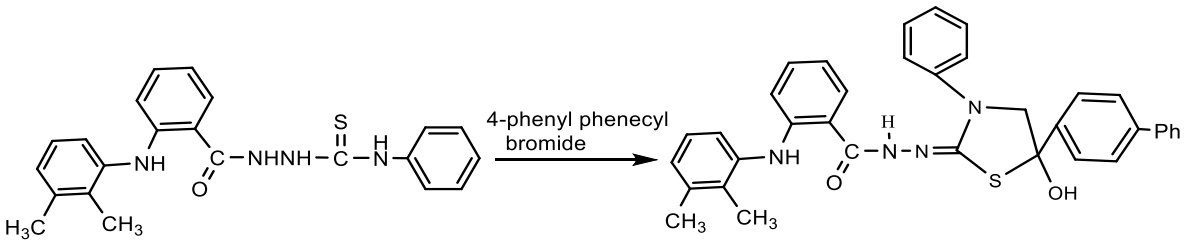
2.3.14. Characterization of 5-(2-((2,3-dimethylphenyl)amino) phenyl)-4-phenyl-4H-1,2,4-triazole-3-thiol[15] .



[13] [15]

A mixture of compound [13] (0.00012 mol, 0.2g) and (10ml) of (0.2 M) sodium hydroxide solution was refluxed with stirring for 8 hours. After cooling, the solution was acidified with hydrochloric acid and the precipitate was filtered(105).

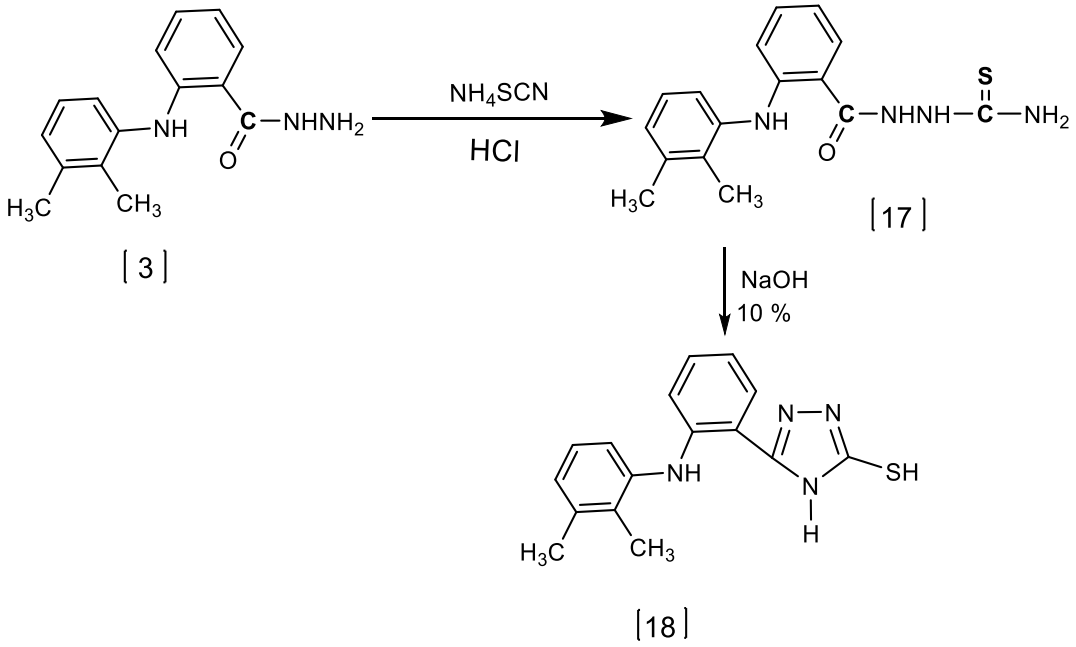
2.3.15. Characterization of 2-((2,3-dimethylphenyl)amino)-N'-(5-hydroxy-5-(4-hydroxyphenyl)-3-phenylthiazolidin-2-ylidene) benzohydrazide[16] .



[13] [16]

Compound [16] (0.00025mole, 0.1g) was prepare from the reaction of *P*-phenyl phenacyl bromide (0.00022 mol, 0.063g) in absolute ethanol (10 ml) was refluxed for 5 hours, cooled and neutralized with ammonium hydroxide solution. The precipitate was filtered and washed with water, and then dried[105].

2.3.16 . Characterization of 2-(2-((2,3-dimethylphenyl)amino) benzoyl) hydrazine-1-carbothioamide and (2-((2,3-dimethyl phenyl) amino) phenyl) (5-mercapto-4H-1,2,4-triazol-3-yl) methanone [17,18].

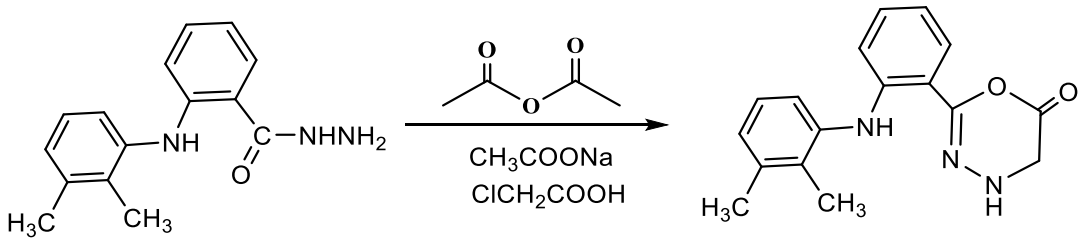


[3] [17] [18]

Compound [17] was prepare from the reaction of product [3] (0.00078 mol,0.2 g) with ammonium thiocyanate (0.00077 mol, 0.059g) and aqeous hydrochloric acid (1 ml). The mixture was refluxed for 6 hours. The brown solid compound [17] obtained on cooling and then filtered. The excess solvent was removed by vacuums evaporation, and the product [17] was refluxed in 10% NaOH solution (10 ml) for 4 hours. The brown solid compound [18]

obtained. The resulting solution was cooled and recrystallized from ethanol[106].

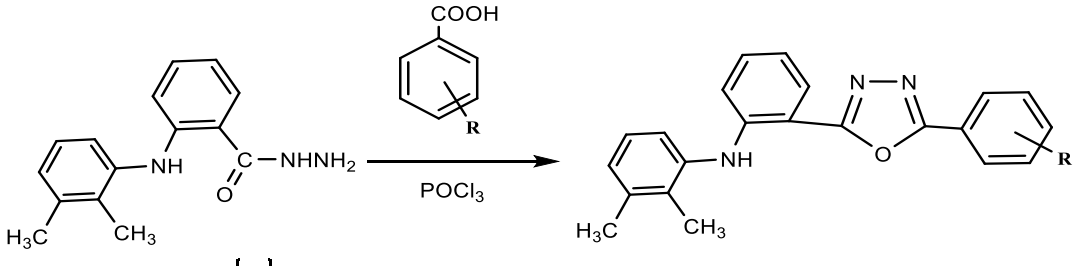
2.3.17 . Characterization of 2-(2-((2,3-dimethylphenyl)amino) phenyl)-4,5-dihydro-6H-1,3,4-oxadiazin-6-one [19] .



[3] [19]

Compound [19] (0.00078 mol, 0.2g) was prepare from the reaction of chloroacetic acid (0.00077 mol, 0.073g) in presence of sodium acetate (0.002 mol, 0.17g) and acetic anhydride was refluxed for 2 hours then poured on water to obtain a solid product [19][107].

2.3.18. Characterization of 2,3-dimethyl-N-(2-(5-(4-nitro and 2-phenyl) -1,3,4-oxadiazol-2-yl)phenyl)aniline[20 , 22] .

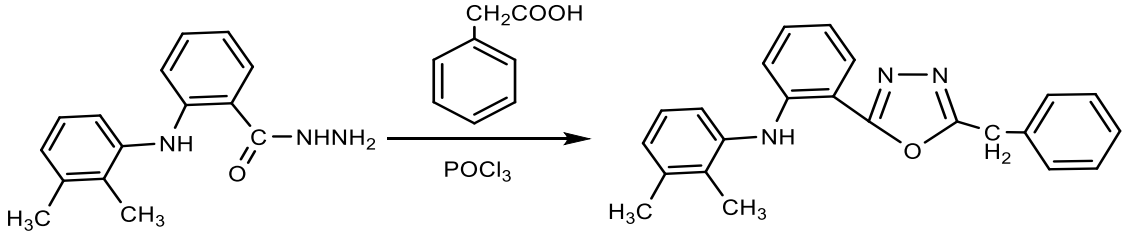


[3] [20,22]

R= *p*-NO_2 , *o*-Cl

Compound [20,22] (0.00078 mol,0.2g) was prepare from the reaction of (para nitro benzoic acid, Ortho benzoic acid) respectively (0.00077 mol) and phosphoryl chloride (5 ml). The mixture was then refluxed for 4 hours, then left to cool down then add water, equivalent to a basic solution(NaOH) then filtered weighed then re-crystallized[108].

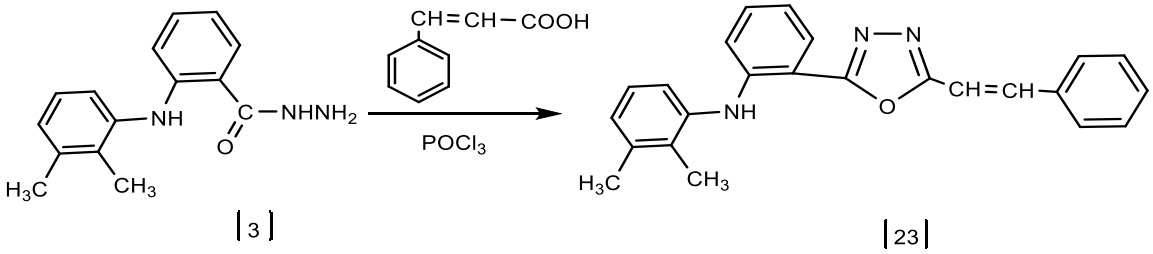
2.3.19. Characterization of N-(2-(5-benzyl-1,3,4-oxadiazol-2-yl)phenyl) -2,3-dimethylaniline[21] .



[3] [21]

Compound [21] (0.00078 mol,0.2g) was prepare from the reaction of phenyl acetic acid (0.00078 mol, 0.1g) and phosphoryl chloride (5 ml) , then the mixture mas refluxed for 4 hours. The mixture was left to cool down and then water, was added[(108)].

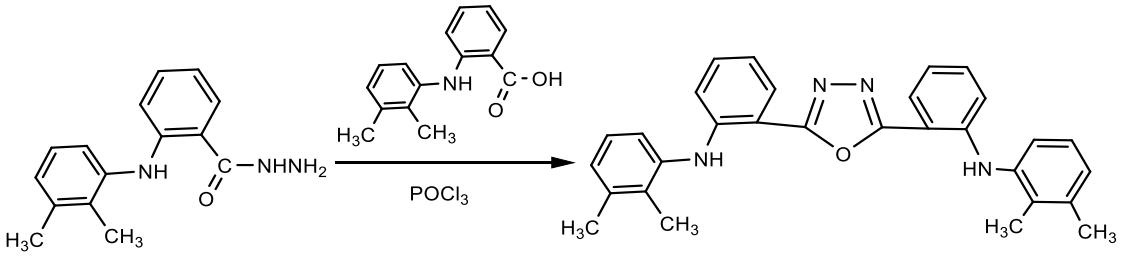
2.3.20. Characterization of 2,3-dimethyl-N-(2-(5-styryl-1,3,4-oxadiazol-2-yl)phenyl)aniline[23] .



[3] [23]

Compound [23] (0.00078 mol,0.2g) was prepare from the reaction of cinnamic acid (0.00074 mol, 0.11g) and phosphoryl chloride (5 ml), the mixture was refluxed for 4 hours[(109)].

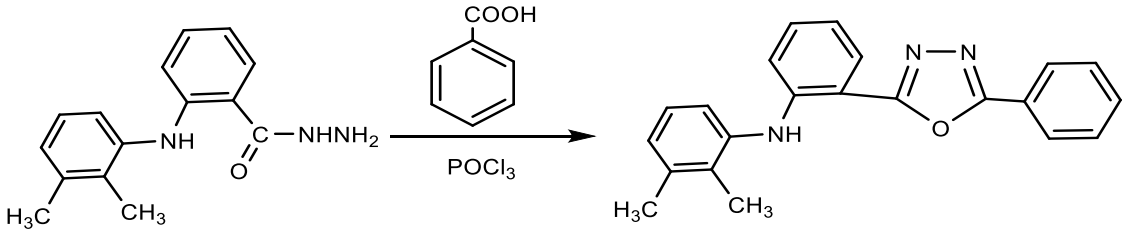
2.3.21. Characterization of N,N-((1,3,4-oxadiazole-2,5-diyl)bis (2,1-phenylene)) bis(2,3-dimethylaniline) [24] .



[3] [24]

Compound [24] (0.00078 mol,0.2g) was prepare from the reaction of mefenamic acid (0.00074 mol, 0.18g) and Phosphoryl chloride (5 ml) , then the mixture was refluxed for 4 hours[109].

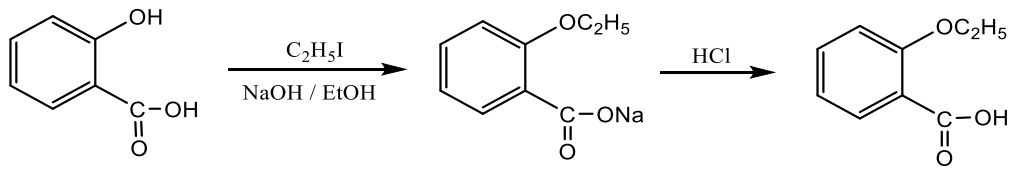
2.3.22. Characterization of 2,3-dimethyl-N-(2-(5-phenyl-1,3,4-oxadiazol-2-yl)phenyl)aniline[25] .



[3] [25]

Compound [25] (0.00078 mol,0.2g) was prepare from the reaction of benzoic acid (0.00078 mol, 0.09g) and Phosphoryl chloride (5 ml) , then the mixture was refluxed for 4 hours[109].

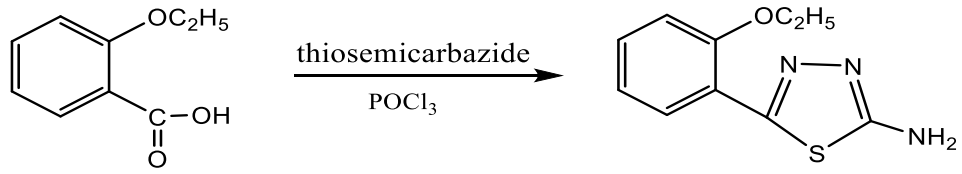
2.3.23. Preparation of 2-ethoxybenzoic acid[27] .



[26] [27]

Compound [27] (0.0724 mol,10g) was prepare from the reaction of Iodo ethan (0.0724 mol, 11.3g) and sodium hydroxide (2.8g). Then, the mixture was refluxed for 24 hours. After cooling, the solution was acidified with hydrochloric acid and the precipitate was filtered .

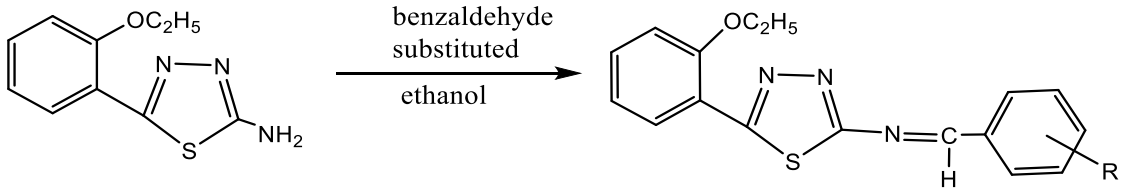
2.3.24. Characterization of 5-(2-ethoxyphenyl)-1,3,4-thiadiazol -2-amine[28].



[27] [28]

Compound [28] (0.031mol,5.2g) was prepare from the reaction of thiosemicarbazide (0.03 mol, 2.8g) and phosphoryl chloride (20 ml). Then, the mixture was refluxed for 4 hours. The mixture was left to cool down and then add water[(110)], m.p.(234-236), yield(81%) .

2.3.25. Characterization of 1-(3-chloro, *p*-N-N- dimethyl, *p*-bromo, *p*-nitro, *p*-hydroxy-2-ethoxyphenyl phenyl)-N-(5-(2-ethoxy phenyl) -1,3,4-thiadiazol-2-yl)methanimine [29,30,31, 32,33] .

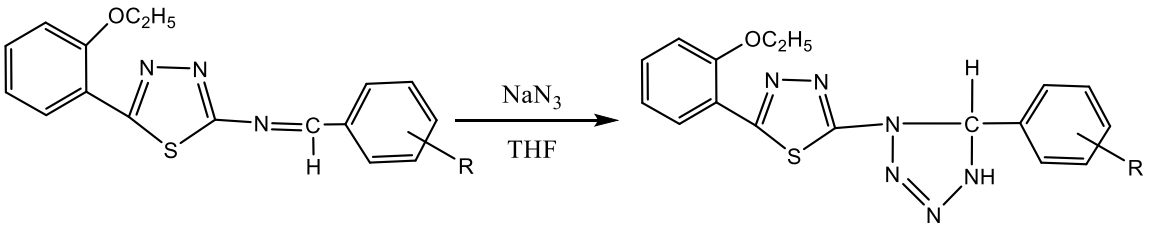


[28] [29,30,31,32,33]

R=*m*-Cl, *p*-Br, *p*-NO_2,(*p*-OH *m*-OCH_3), *p*-N-N-$(CH_3)_2$

Compound [29,30,31,32,33] (0.000451mol,0.1g) was prepare from the reaction of *m*-chloro, *p*-Br, *p*-bromo, *p*-nitro, *p*-hydroxy-2-ethoxyphenyl, or *p*-N-N- dimethyl phenyl respectively (0.00044 mol) and ethanol (20 ml). For 4 drops of acetic acid, were added then the mixture was refluxed for 30 hours then filtered, weighed and then re-crystallized[110].

2.3.26. Characterization of 2-(5-(3-chloro, *p*-N-N- dimethyl, *p*-bromo, p-nitro, *p*-hydroxy-2-ethoxyphenyl phenyl)-N-(5-(2-ethoxy phenyl)-4,5-dihydro-1H-tetrazol-1-yl)-5-(2-ethoxy phenyl)-1,3,4-thiadiazole[34,35,36,37,38] .



[29] [34,35,36,37,38]

R= *p*-Cl, *p*-Br, *p*-NO_2,(*p*-OH, *m*-OC_2H_5), *p*-N-N-$(CH_3)_2$

Compound [34,35,36,37,38] (0.00029mol, 0.1g) was prepare from the reaction of 0.00027mol of soduim azide in tetrahydrofuran (20 ml) and then refluxed for 5 h. After that, it was cooled and washed with water then obtained solid product was filtered and recrystallized from ethanol[111,112].

Tab. (2.2): Some of the physical properties and the yield and (R_f) for the prepared compounds.

Comp. No.	Molecular formula	M/wt (g/mole)	Yield (%)	M.P. (°C)	colour	R_f
1	$C_{15}H_{15}O_2$	241.29	-	230-232	Off white	0.90
2	$C_{17}H_{19}O_2$	269.34	80	126-128	white	0.89
3	$C_{15}H_{17}N_3O$	255.32	95	176-178	brown	0.86
4	$C_{20}H_{21}N_3O$	319.41	85	202-205	Pale yellow	0.91
5	$C_{23}H_{19}N_3O_3$	385.42	90	226-228	Pale yellow	0.84
6	$C_{19}H_{17}N_3O_3$	335.36	78	228-230	Off white	0.93
7	$C_{23}H_{18}N_4O_5$	430.42	83	226-228	Pale brown	0.95
8	$C_{19}H_{19}N_3O_3$	337-38	89	230-232	white	0.85
9	$C_{16}H_{17}N_3O_2$	283.33	88	194-196	white	0.92
10	$C_{30}H_{25}N_4OS$	459.55	94	Dec.	white	0.90
11	$C_{16}H_{17}N_3OS$	299.39	90	190-192	Pale yellow	0.84
12	$C_{30}H_{25}N_3OS$	475.61	85	188-190	white	0.88
13	$C_{22}H_{22}N_4OS$	390.51	90	190-192	Pale yellow	0.93
14	$C_{22}H_{20}N_4S$	372.49	94	202-204	white	0.95
15	$C_{22}H_{20}N_4S$	372.49	88	214-216	white	0.82
16	$C_{36}H_{32}N_4O_2S$	584.74	90	210-212	brown	0.86
17	$C_{16}H_{18}N_4OS$	314.41	85	232-234	white	0.89
18	$C_{17}H_{16}N_4OS$	324.40	87	Dec.	white	0.93
19	$C_{17}H_{17}N_3O_2$	295.34	82	130-132	brown	0.86
20	$C_{22}H_{18}N_4O_3$	386.41	79	110-112	brown	0.90
21	$C_{23}H_{21}N_3O$	355.44	89	113-115	brown	0.87
22	$C_{22}H_{19}ClN_3O$	375.86	78	110-112	yellow	0.89
23	$C_{22}H_{21}N_3O$	341.41	80	Dec.	brown	0.93
24	$C_{30}H_{28}N_4O$	460.58	84	220-222	brown	0.88
25	$C_{24}H_{18}N_3O$	367.45	90	250-252	Pale brown	0.85
26	$C_7H_6O_3$	138.12	95	159	yellow	0.94
27	$C_9H_{10}O_3$	166.18	85	162	Pale yellow	0.89
28	$C_{10}H_{11}N_3OS$	221.28	81	234-236	orange	0.95
29	$C_{17}H_{14}N_3OS$	308.38	92	204-206	yellow	0.91
30	$C_{19}H_{20}N_4OS$	352.46	88	228-230	orange	0.89
31	$C_{17}H_{14}BrN_3S$	388.28	78	206-208	yellow	0.92
32	$C_{17}H_{14}N_4O_3S$	354.38	87	Dec.	yellow	0.86

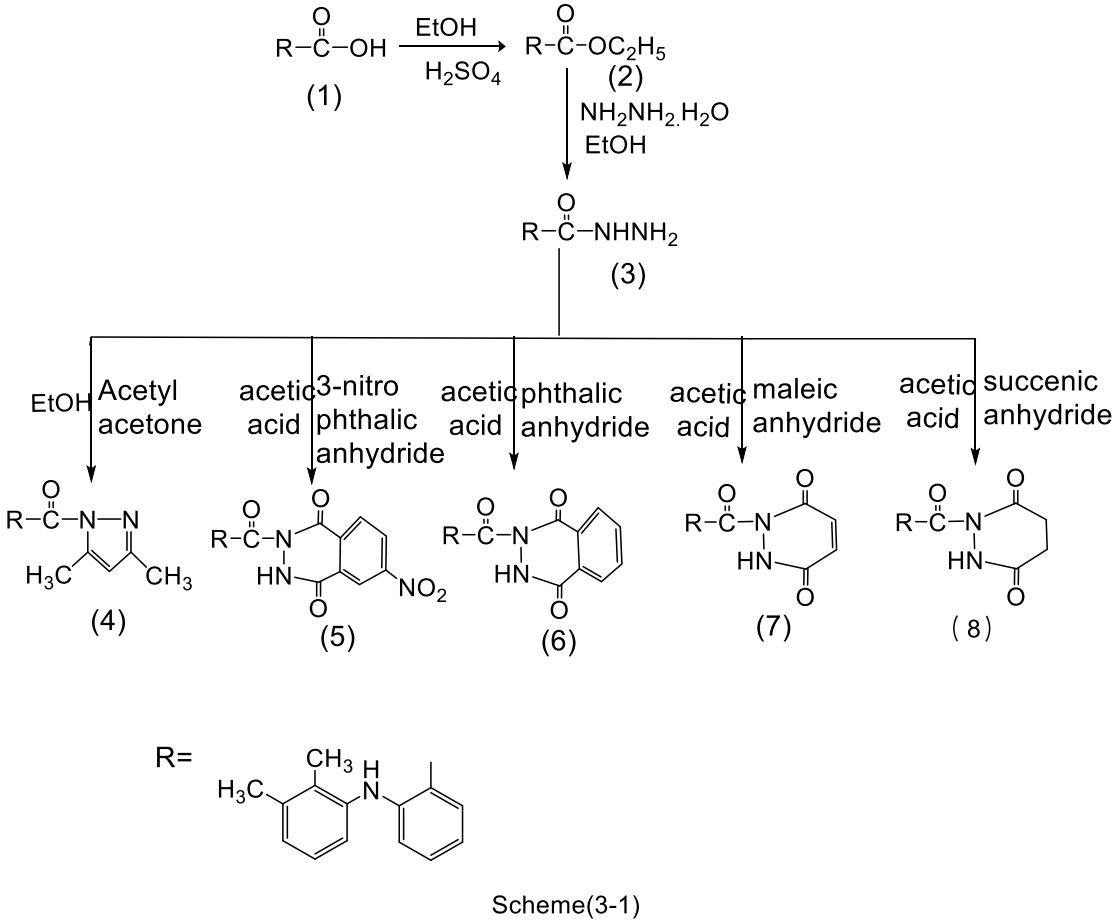
33	$C_{18}H_{17}N_3O_3S$	355.41	75	245-248	Darkyellow	0.94
34	$C_{17}H_{15}ClN_6S$	386.86	79	192-194	Pale yellow	0.91
35	$C_{19}H_{21}N_7OS$	395.49	89	230-232	orange	0.92
36	$C_{17}H_{15}BrN_6S$	431.31	92	206-208	yellow	0.94
37	$C_{17}H_{15}N_7O_3S$	397.41	81	258-260	yellow	0.90
38	$C_{18}H_{18}N_6O_3S$	398.44	92	238-240	brown	0.95

Chapter Three

This work is divided into six part as following .

3.1 The first part:

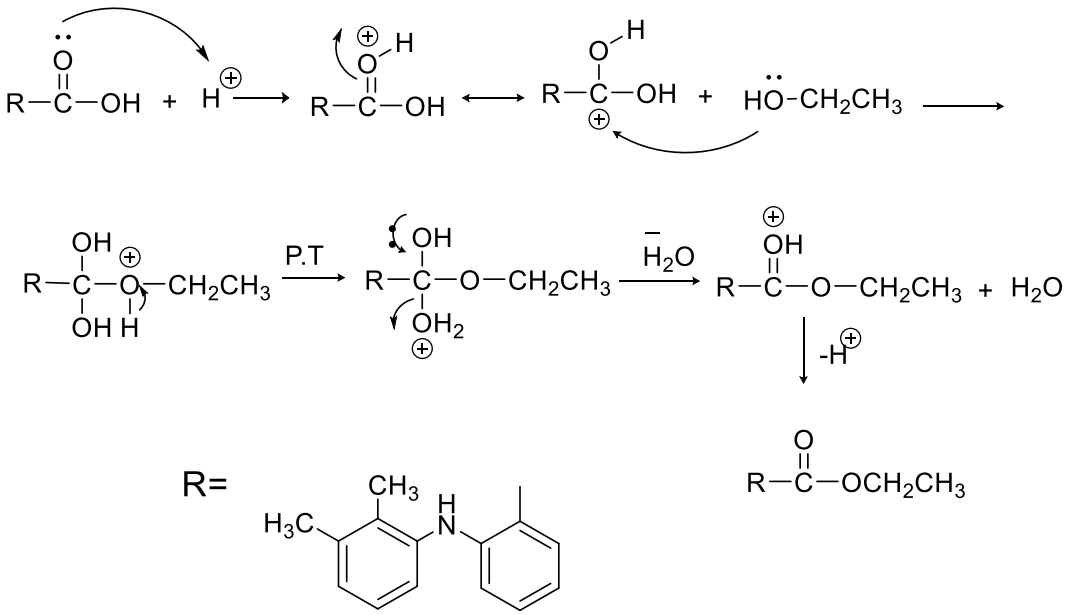
This part include the preparation of pyrazole [4], phthalazin-3,8-dione [5,6] and pyridazin-3,6-dione [7,8] derivatives, which were derived from hydrazide compound [3] as shown in scheme (3-1).



Scheme(3-1)

3.1.1. Synthesis of ethyl 2-((2,3-dimethylphenyl)amino) benzoate[2].

Ethyl 2-((2,3-dimethylphenyl)amino)benzoate[2] was prepared by reacting of 2-(6-methoxy naphthalene -2-yl) benzoic acid in absolute ethanol and presence of concentrated. H_2SO_4 as a catalyst. The structure of this compound was identified. The mechanism of this reaction is shown below:



Mechanism (1)

Compound [2] was identified by using FT-IR spectrum which showed bands at 3317 cm^{-1}, (2991, 2868) cm^{-1}, 1159 cm^{-1} 1710 cm^{-1} that may attributed to NH, CH (aliph.), C-O-C and C=O respectively.

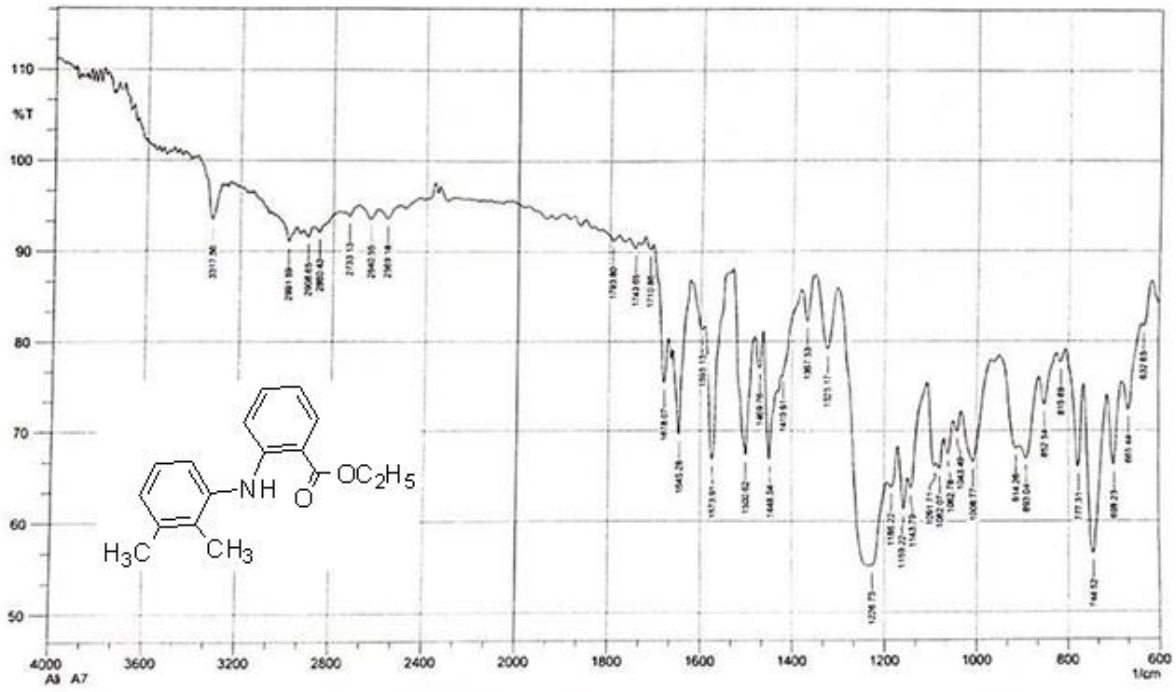
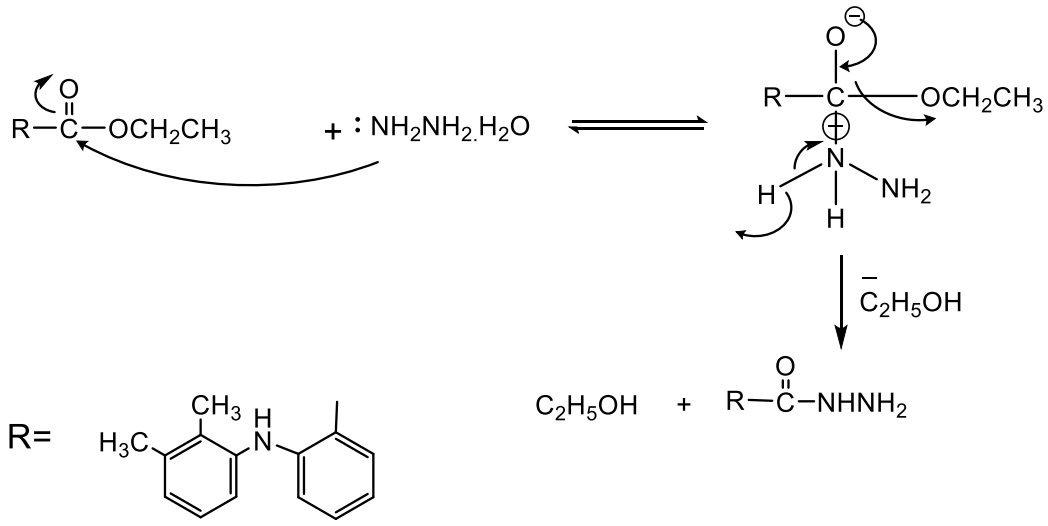


Figure (3.1) : FT.IR spectrum of compound (2)

3.1.2. Synthesis of 2-((2,3-dimethylphenyl)amino) benzo hydrazide[3].

Compound [3] was prepared using hydrazine hydrate to give the hydrazide [3]. The acid hydrazide was produced by the reaction of ester [2] with hydrazine hydrate in ethanol. The mechanism of the reaction[113] is shown below:

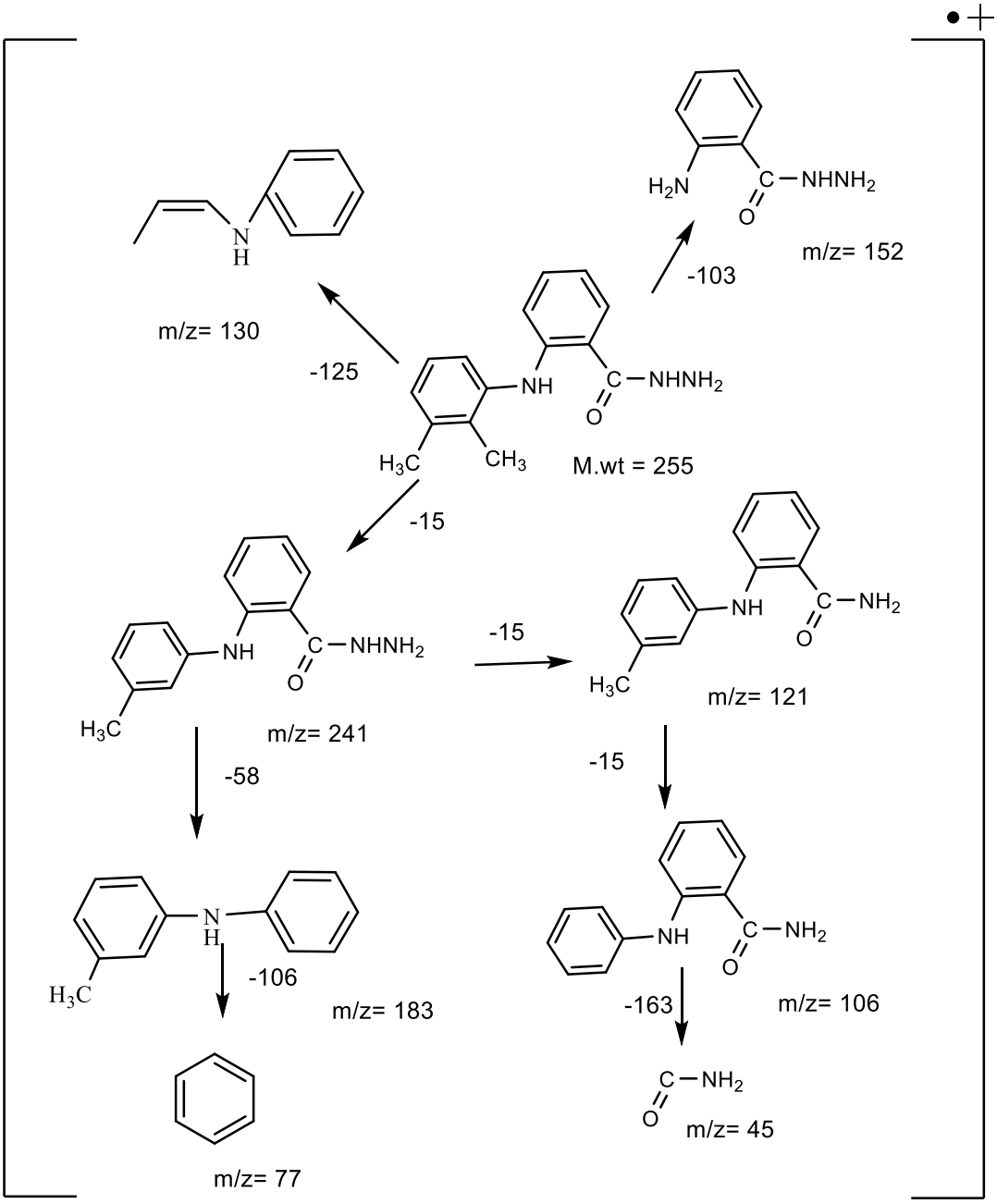


Mechanism (2)

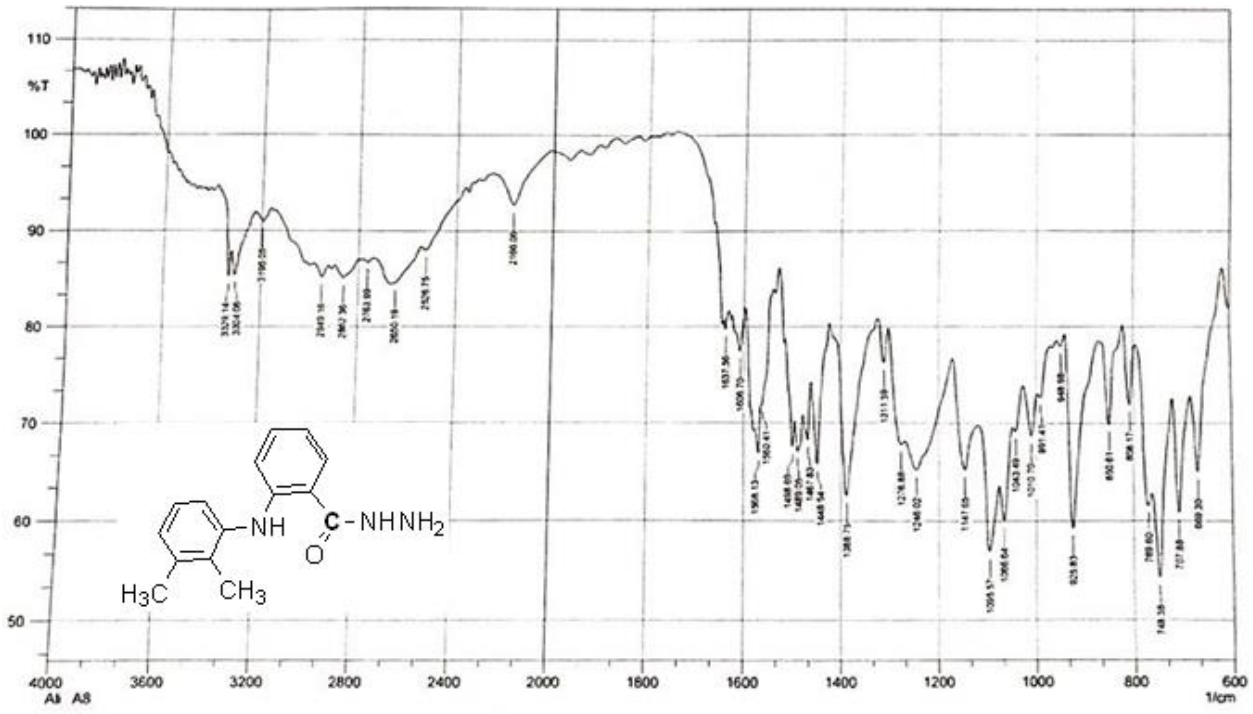
Compound [3] was identified using FT-IR spectrum which showed bands at 3329 cm^{-1}, 3304, 3196 cm^{-1}, (2949, 2862) cm^{-1} and 1637 cm^{-1} that many attributed to NH, NH_2, CH (aliph.) and C=O respectively.

The ^{1}H-NMR spectrum for [3] showed singlet signals at δ 2.1, 2.2 ppm for $2CH_3$ groups, other signals also appeared at 2.5 ppm for DMSO, as solvent and multiplet signals δ (6.5 - 7.1) ppm due to aromatic protons, singlet signals δ 6.8 ppm for NH_2 and signal at 7.9 ppm due to NH group.

The mass spectrum of compound [3] showed a characteristic fragmentation to the presence of hydrazide moiety at m\z = (255, 226, 208, 183, 152, 130, 102, 77 and 45), as in the scheme(3-1) below .


m/z= 130
-125
-103
m/z= 152
M.wt = 255
-15
m/z= 241
-15
m/z= 121
-58
-15
-106
m/z= 183
-163
m/z= 106
m/z= 77
m/z= 45

Scheme (3-1)



aFigure (3.2) : FT.IR spectrum of compound (3)

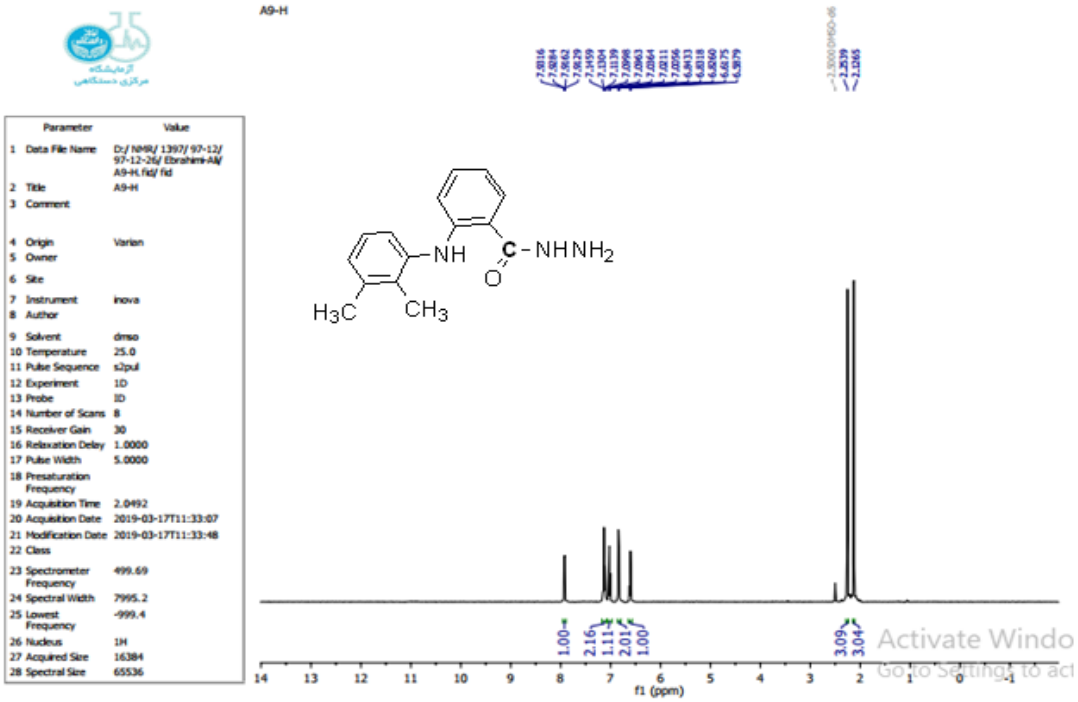


Figure (3.3) : ^{1}H-NMR spectrum of compound (3)

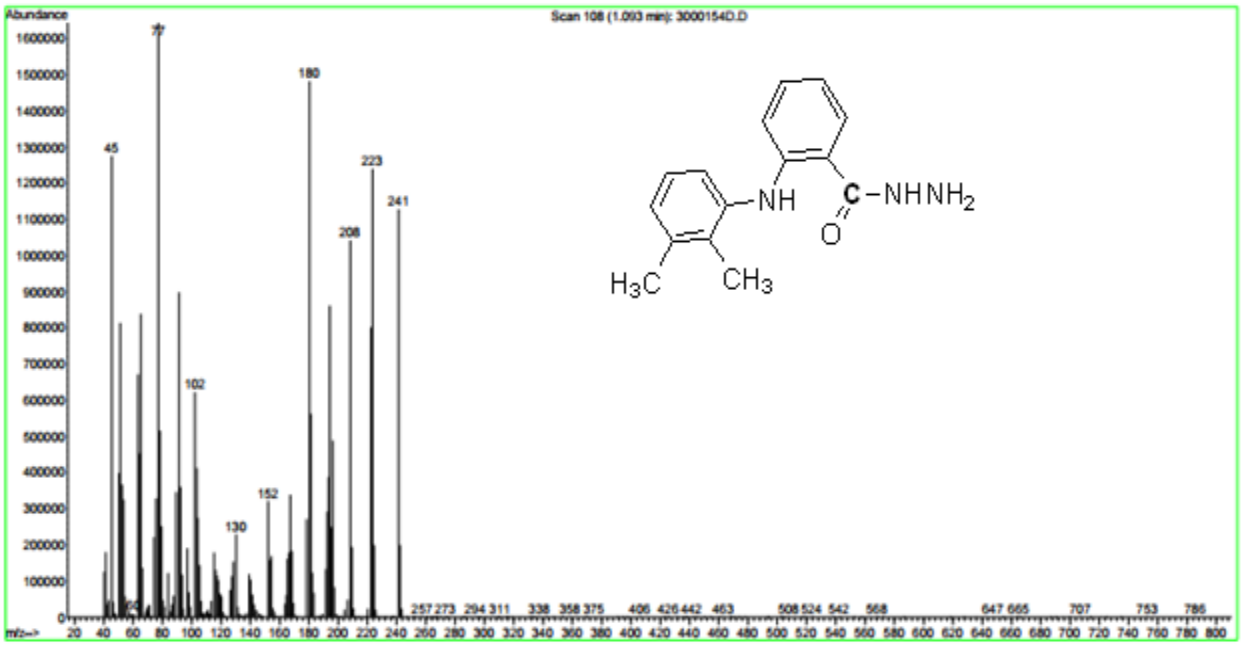
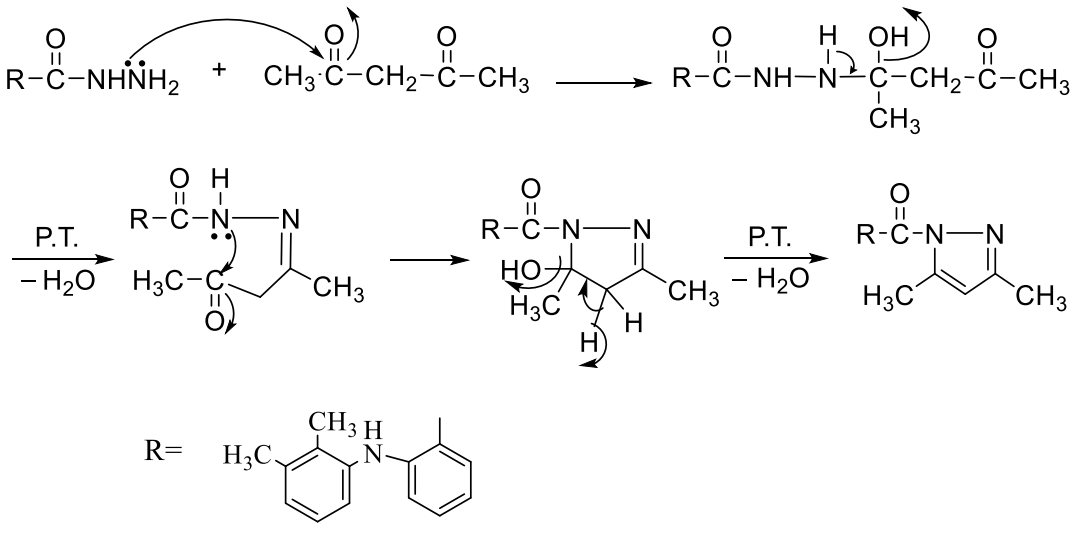


Figure (3.4) : Mass spectrum of compound (3)

3.1.3 . Synthesis of 1-(3,5-dimethyl-1H-pyrazol-1-yl)-2-(2-((2,3-dimethylphenyl)amino)phenyl)ethane-1,2-dione [4] .

For derivative of 3,5-dimethyl-1H-pyrazol-1-yl)(2-((2,3-dimethylphenyl) amino) phenyl)methanone[4] .

The suggested mechanism for formation of compound is as shown below[114]:



Mechanism(3)

Compound [4] was identified by using FT-IR spectrum which showed bands at 3308 cm^{-1}, 3036 cm^{-1}, (2974, 2872) cm^{-1}, 1708 cm^{-1}, 1647 cm^{-1} which are attributed to NH, CH (arom.), CH (aliph.), C=O and C=N respectively.

The ^{1}H-NMR spectrum for [4] showed singlet signals at δ 2.0 ppm, 2.1 ppm , 2.2 ppm and 2.5 ppm, the multiplet signals at δ (6.6 -7.8) ppm and at 9.4 ppm which are attributed to $4CH_3$ and DMSO, aromatic protons and for NH proton

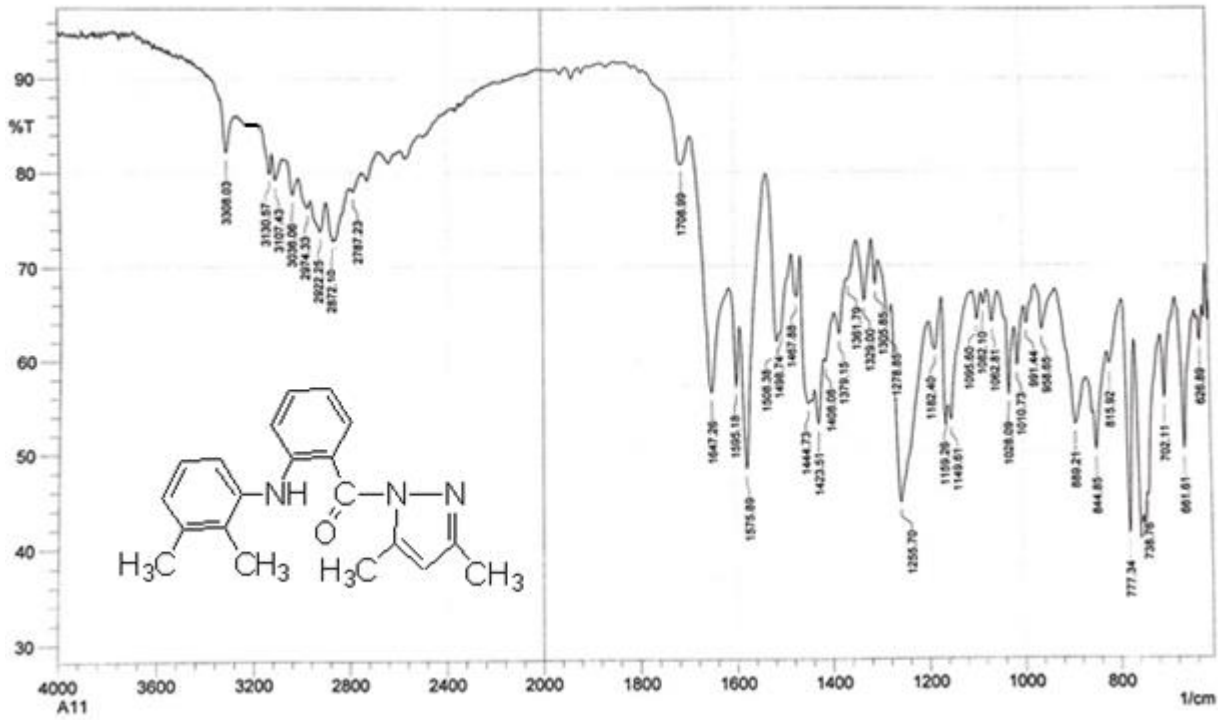


Figure (3.5): FT.IR spectrum of compound (4)

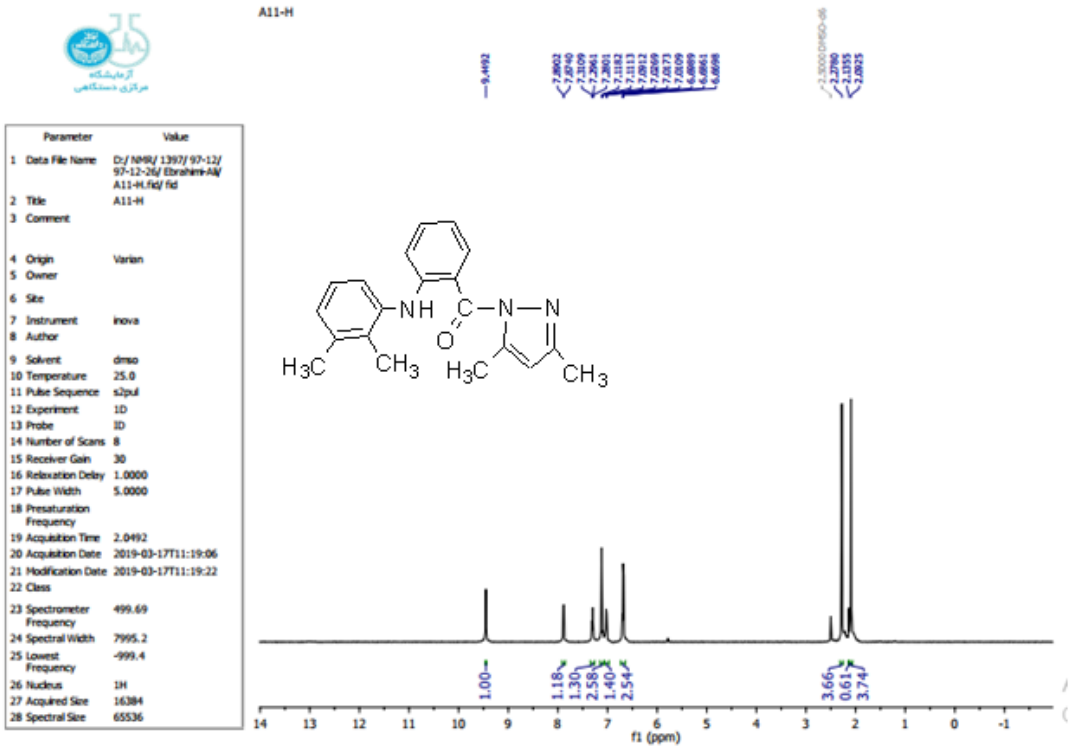


Figure (3.6) : ^{1}H-NMR spectrum of compound (4)

3.1.4 Synthesis of phthalazine and pyridazine [5,6,7,8].

Compound [5] was identified by using FT-IR spectrum which showed bands at 3344 cm^{-1}, 3078 cm^{-1}, (2928, 2860) cm^{-1} and 1651 cm^{-1} that may attributed to NH, CH (arom.), CH (aliph.) and C=O respectively.

The ^{1}H-NMR spectrum for [5] showed singlet signals at δ 2.0 , 2.2 ppm , 2.5 ppm, the multiplet signals at δ (6.6 -7.6) ppm and at δ 9.4 ppm which are attributed to $2CH_3$ and DMSO, aromatic protons and NH proton , respectively.

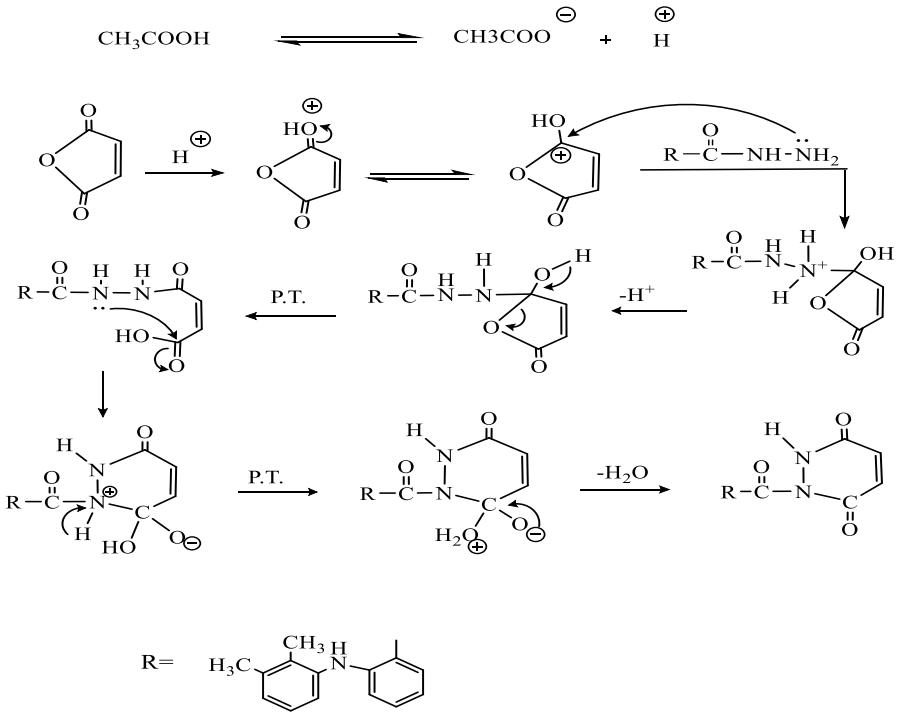
Compound [6] was identified using FT-IR spectrum at 3344 cm^{-1}, 3068 cm^{-1}, δ (2912, 2858) cm^{-1} and 1647 cm^{-1} which due to NH, CH (arom.), CH (aliph.) and C=O respectively.

Compound [7] was identified using FT-IR spectrum which showed bands at 3342 cm^{-1} , 3068 cm^{-1} , (2910, 2827) cm^{-1} and 1647 cm^{-1} that many attributed to NH, CH (arom.), CH (aliph.) and C=O respectively.

The ^{1}H-NMR spectrum for [7] showed singlet signals at δ 2.0, 2.2 ppm, 2.5 ppm, the multiplet signals at δ (6.6 - 7.8) ppm and at 9.4 ppm which attributed to $2CH_3$ and DMSO, aromatic protons and for NH proton respectively.

Compound [8] was identified using FT-IR spectrum which showed bands at 3344 cm^{-1} , 3068 cm^{-1} , (2976, 2858) cm^{-1} and 1647 cm^{-1} that may attributed to NH, CH (arom.), CH (aliph.) and C=O respectively.

The suggested reaction mechanism for reaction below is displayed in the diagram as well, the formation of compounds [5,6,8] followed the same mechanism [115] as in compound [7].



Mechanism(4)

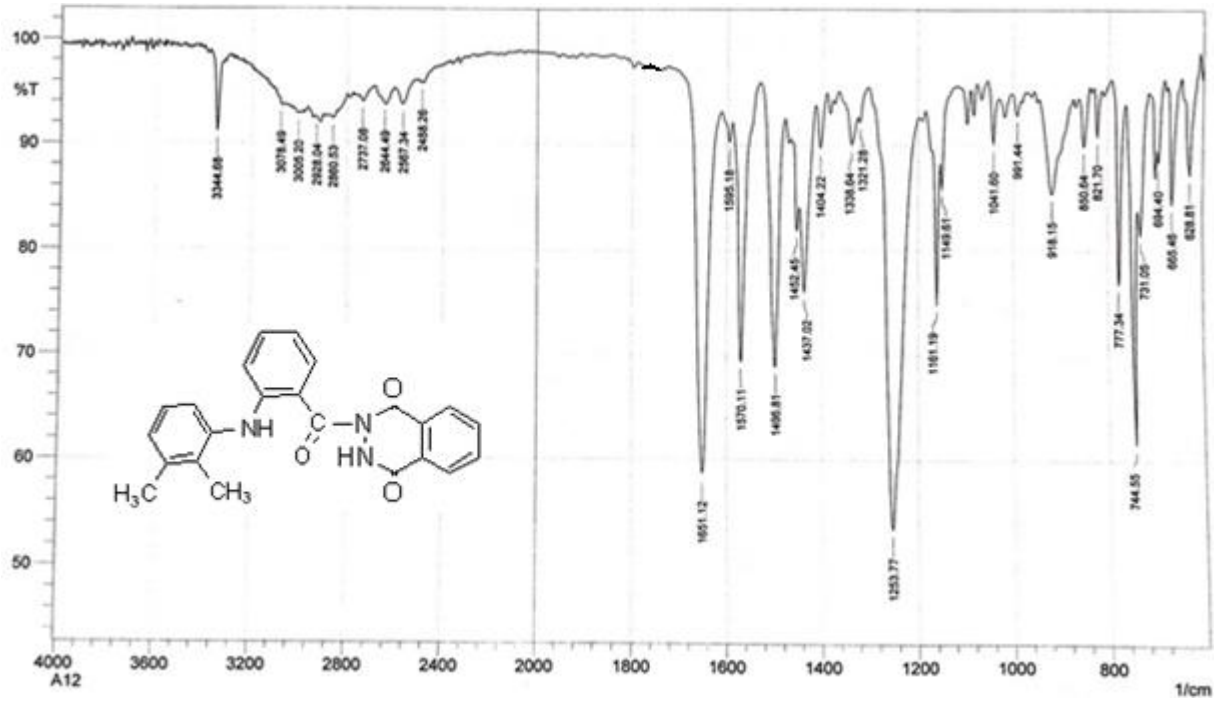


Figure (3.7) : FT.IR spectrum of compound (5)

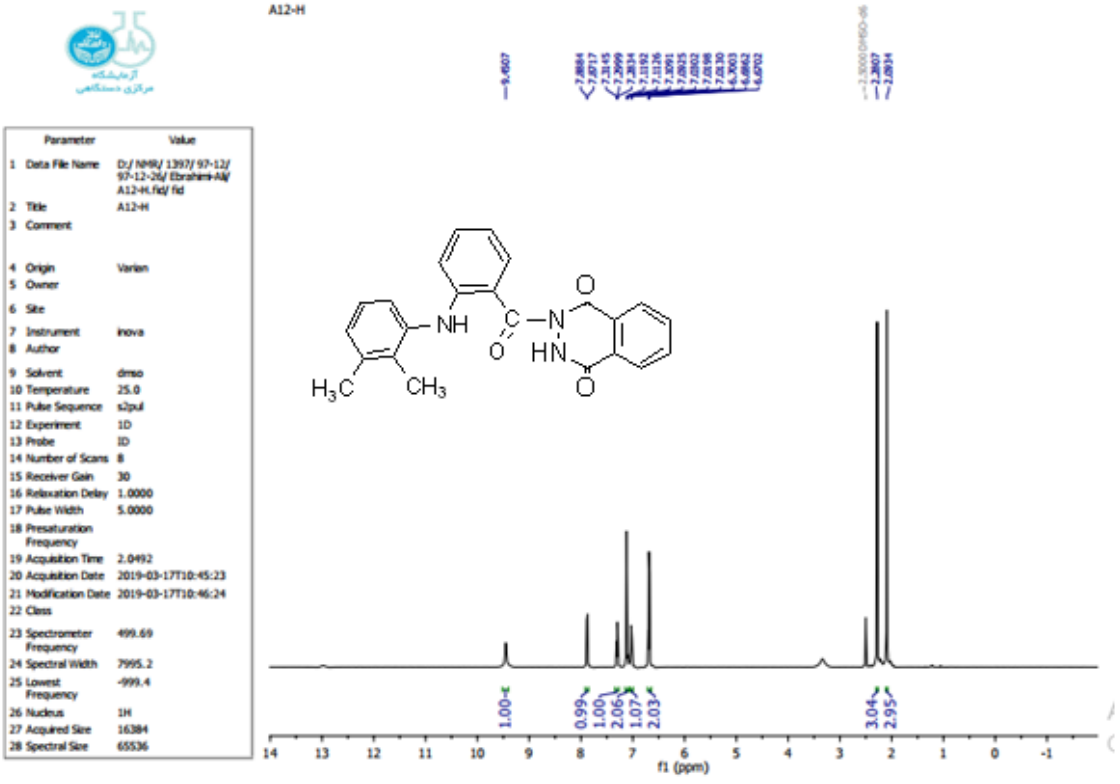


Figure (3.8) : ^{1}H-NMR spectrum of compound (5)

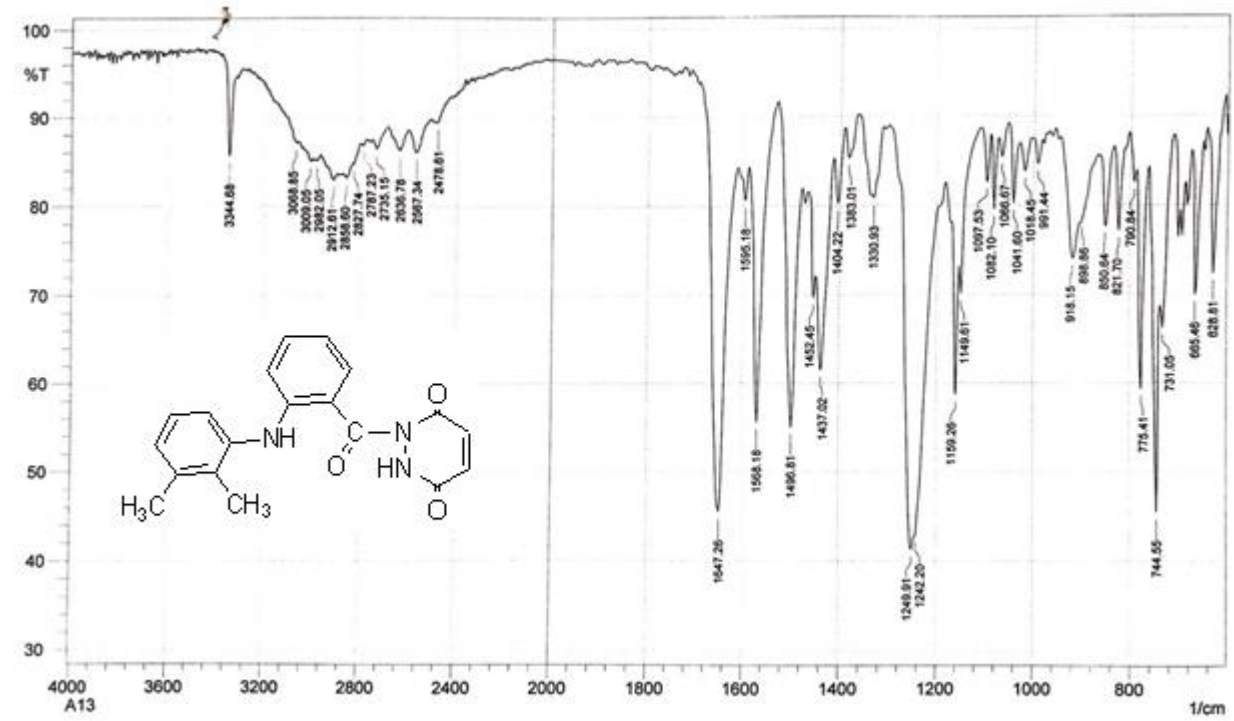


Figure (3.9) : FT.IR spectrum of compound (6)

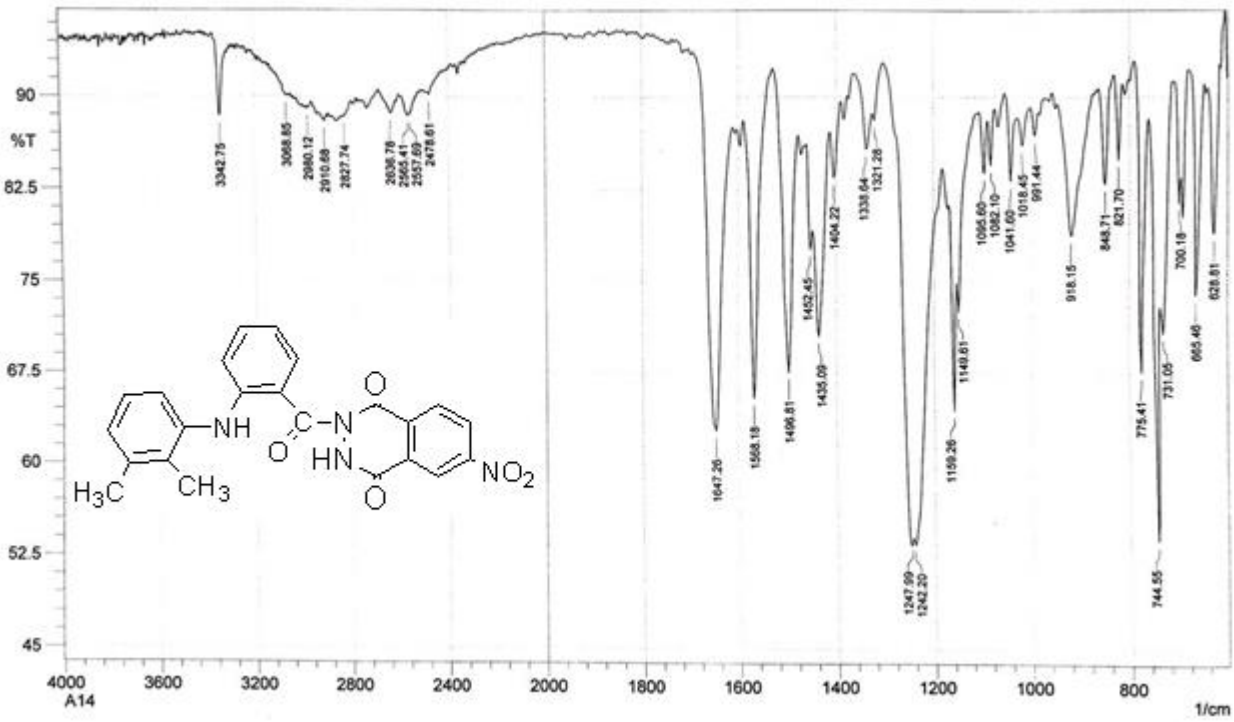


Figure (3.10) : FT.IR spectrum of compound (7)

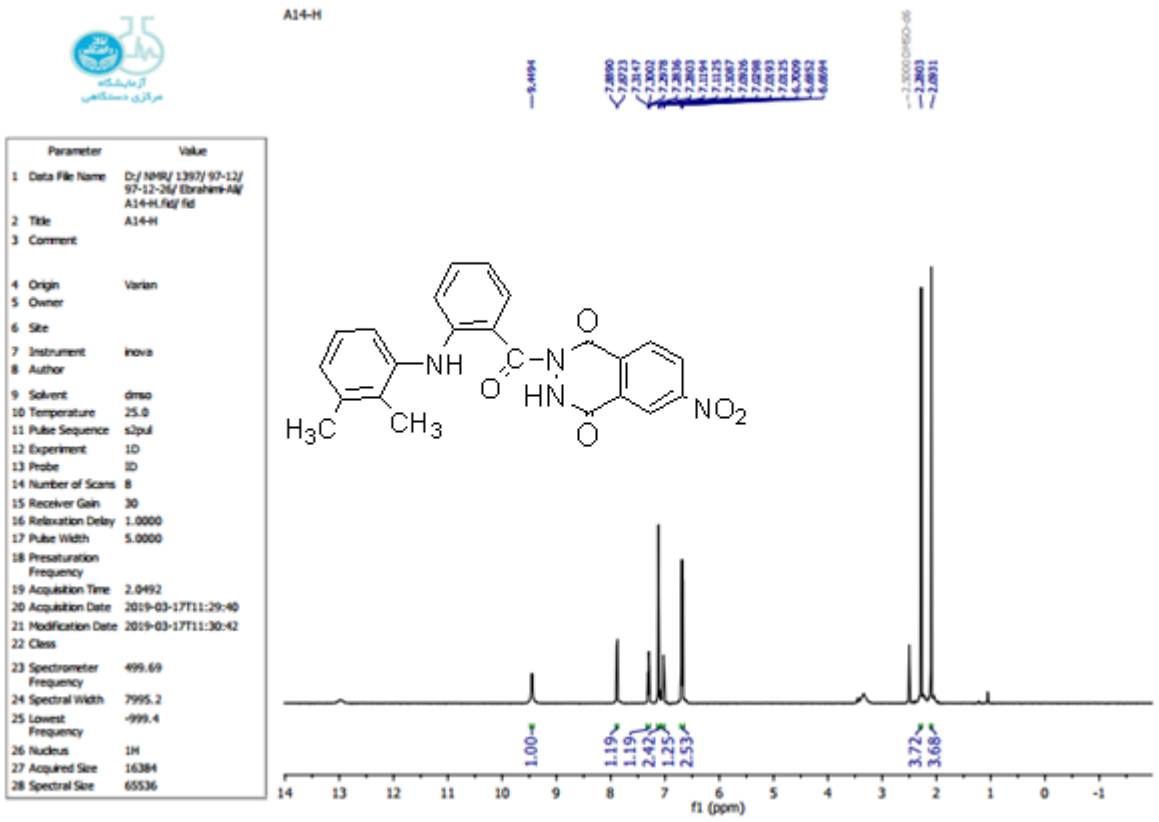


Figure (3.11) : ^{1}H-NMR spectrum of compound (7)

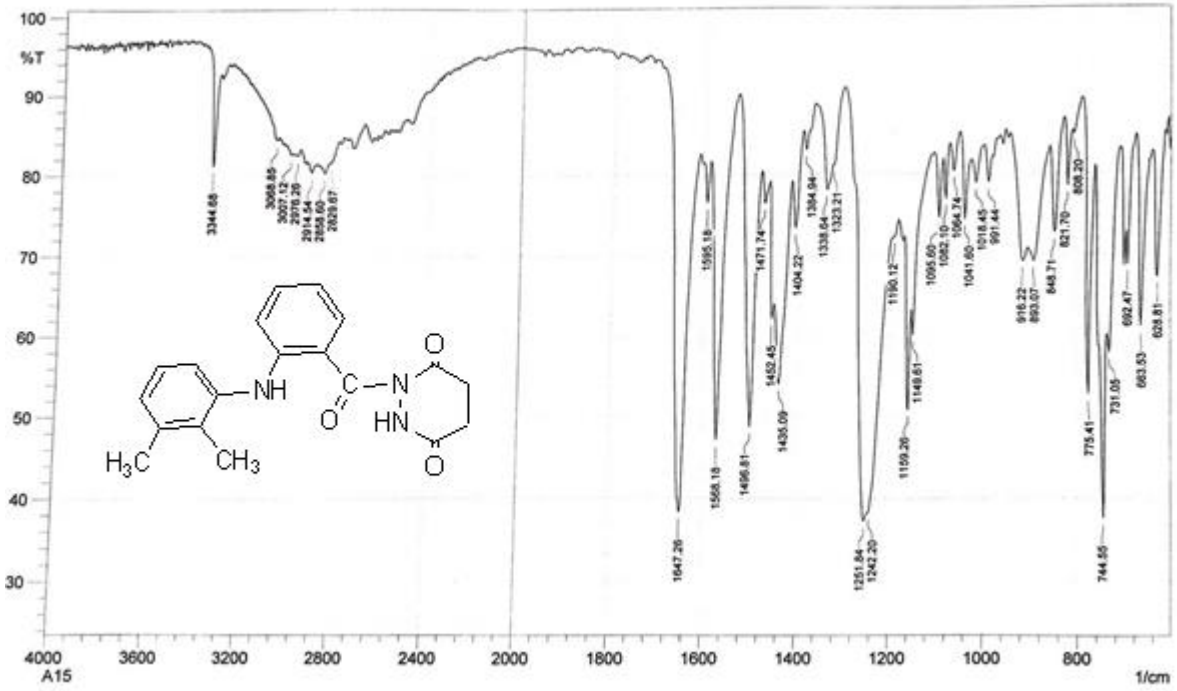
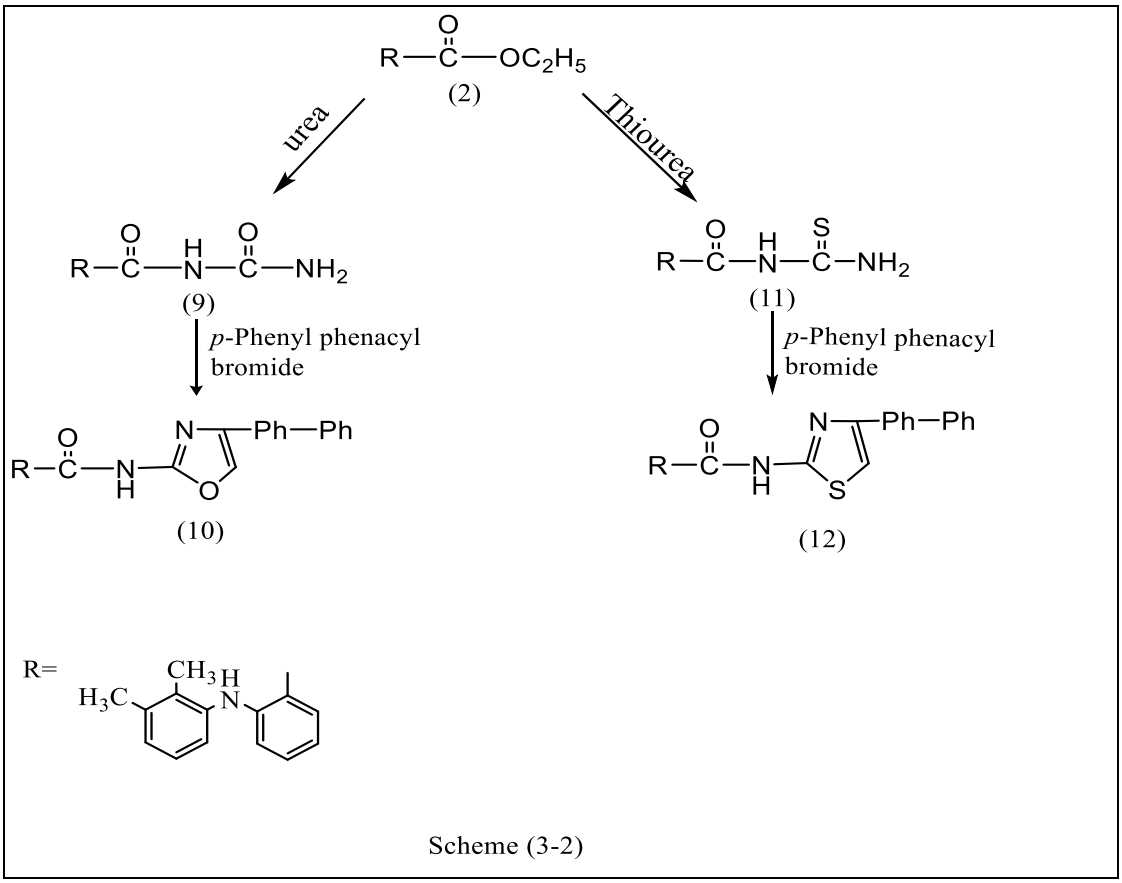


Figure (3.12) : FT.IR spectrum of compound (8)

3.2 The Second part :

This part includes the preparation of oxazole [10] and thiazole [12] derivatives via the reaction of ethyl 2-((2,3-dimethylphenyl)amino) benzoate with urea and thiourea and cyclization of the resulted products with p-phenyl phenacyl bromide, as shown in scheme (3-2).

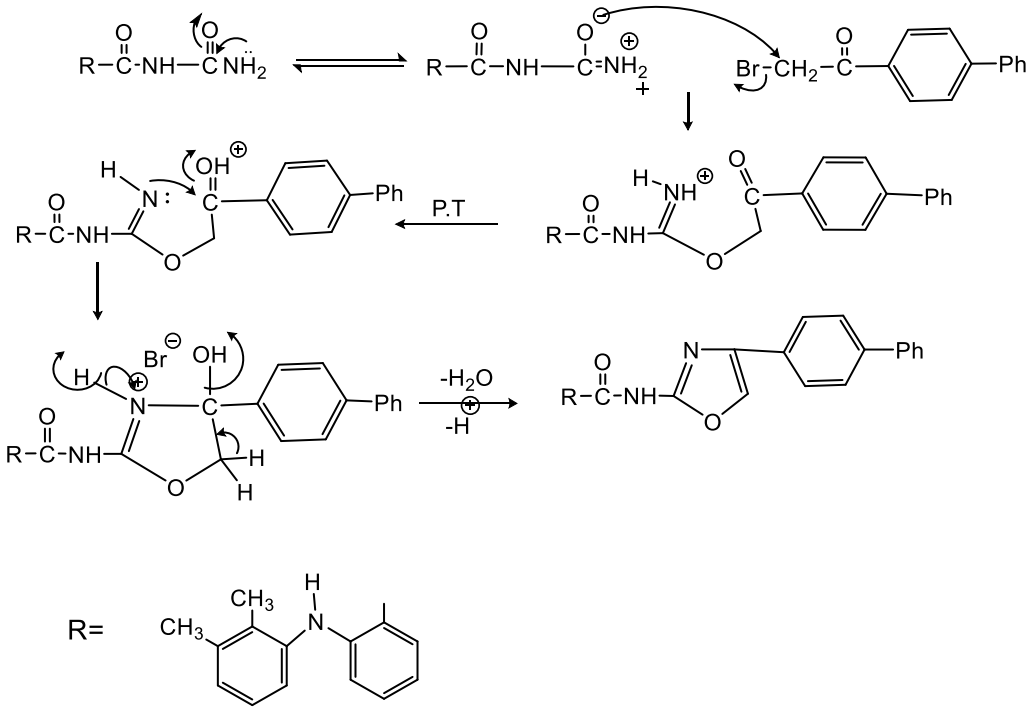


Scheme (3-2)

3.2.1 Synthesis of 2-(2-((2,3-dimethylphenyl)amino)benzoyl) hydrazine-1-carbothioamide and N-(4-([1,1'-biphenyl]-4-yl)oxazol-2-yl)-2-((2,3-dimethylphenyl)amino)benzamide [9,10].

The compound [9] was prepare from the reaction of ester compound [2] with urea and ethanol as a solvent, The reaction of the compound [9] with *p*-

phenylphenecyl bromide under reflux conditions gave the oxazole compound [10]. As the following mechanism [10][(116)].



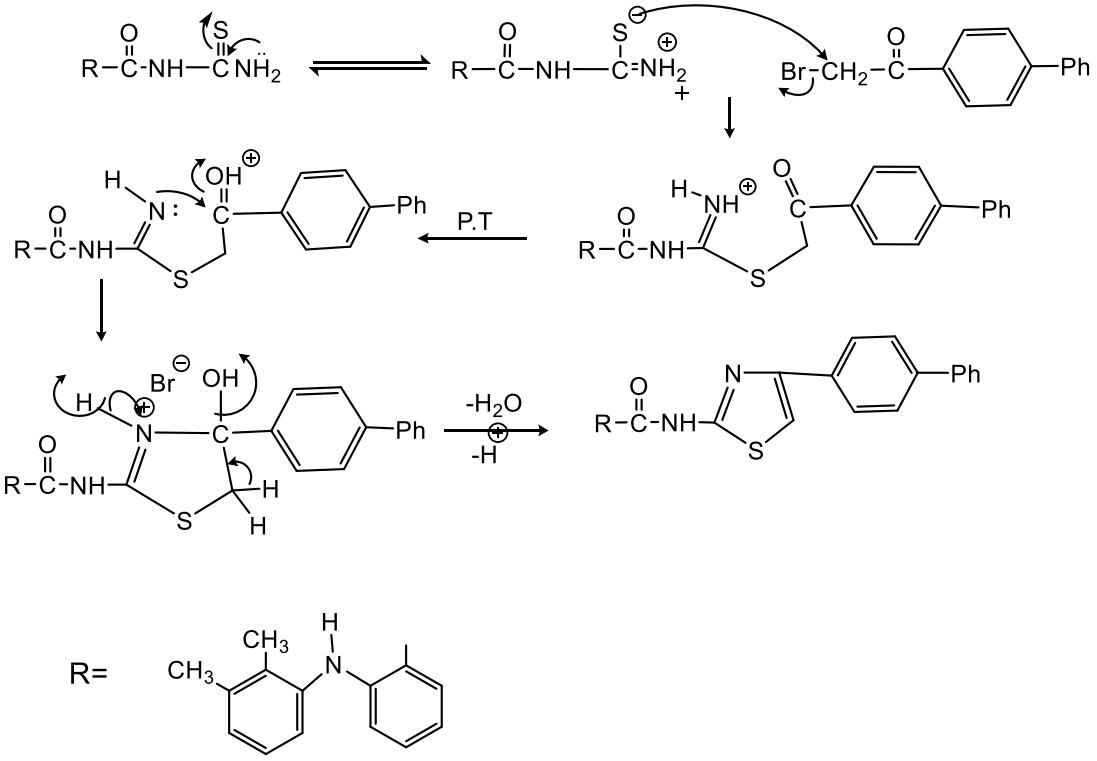
Mechanism(5)

Compound [9] was identified by using FT-IR spectrum which showed bands at 3433,3255 cm^{-1}, 3311 cm^{-1}, (2974,2866) cm^{-1} and 1647 cm^{-1} which are due to NH_2, NH, CH (arom.), CH (aliph.) and C=O, respectively.

Compound [10] was identified by using FT-IR spectrum which showed bands at 3313 cm^{-1}, 3043 cm^{-1}, (2983,2856) cm^{-1}, 1683 cm^{-1}, 1600 cm^{-1} and 1150 cm^{-1} which are due to NH, CH (arom.), CH (aliph.), C=O, C=N and C-O-C respectively.

3.2.2. Synthesis of N-carbamothioyl-2-((2,3-dimethylphenyl) amino) benzamide[11] and N-(4-([1,1'-biphenyl]-4-yl)thiazol-2-yl)-2-((2,3-dimethylphenyl)amino)benzamide [12] .

The refluxing of thiourea with ester compound [2] in ethanol resulted compound [11]. Compound [11] in its reaction with *p*-phenylphenecyl bromide and refluxing conditions produced thiazole derivative [12].



Mechanism(6)

Compound [11] was identified by using FT-IR spectrum which showed bands at 3435, 3284 cm^{-1}, 3201 cm^{-1}, (2931,2752) cm^{-1} and 1676 cm^{-1} which due to NH_2, NH, CH (aliph.) and C=O, respectively.

Compound [12] was identified by using FT-IR spectrum which showed bands at 3308 and 3010 cm^{-1}, (2974, 2856) cm^{-1}, 1647 cm^{-1} and 1595 cm^{-1} which are due to NH, CH (arom.), CH (aliph.), C=O and C=N respectively.

The ^{1}H-NMR spectrum for [12] showed the following singlet signals, at δ 2.2, 2.6 ppm , 2.5 ppm, the multiplet signals at δ (6.6 - 7.8) ppm and at 9.1 ppm which attributed to $2CH_3$, DMSO, aromatic protons and for NH proton .

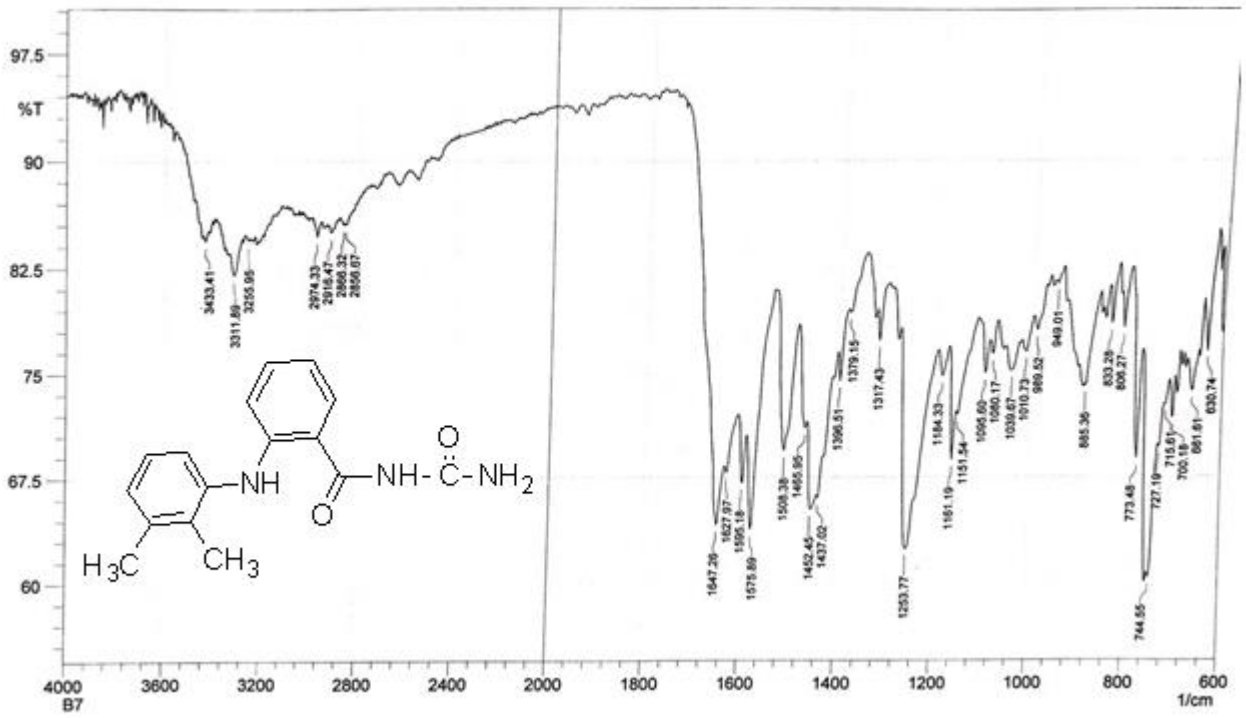


Figure (3.13) : FT.IR spectrum of compound (9)

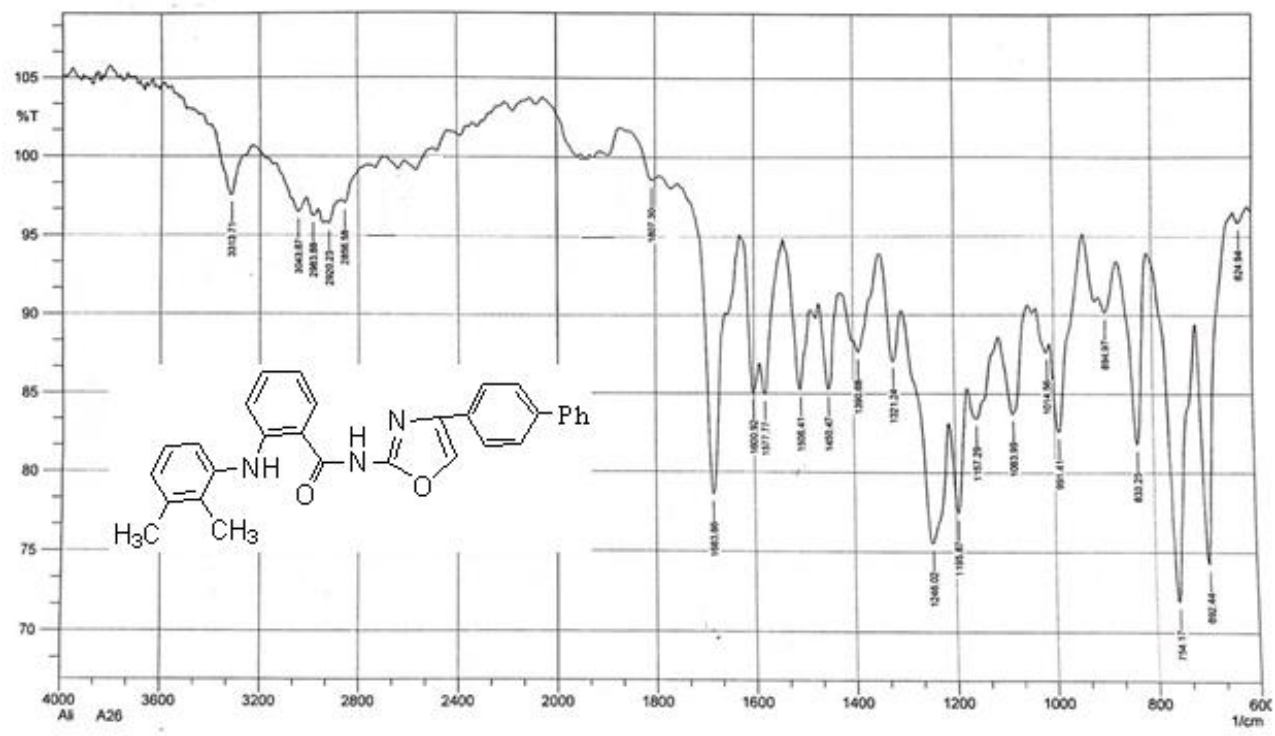


Figure (3.14) : FT.IR spectrum of compound (10)

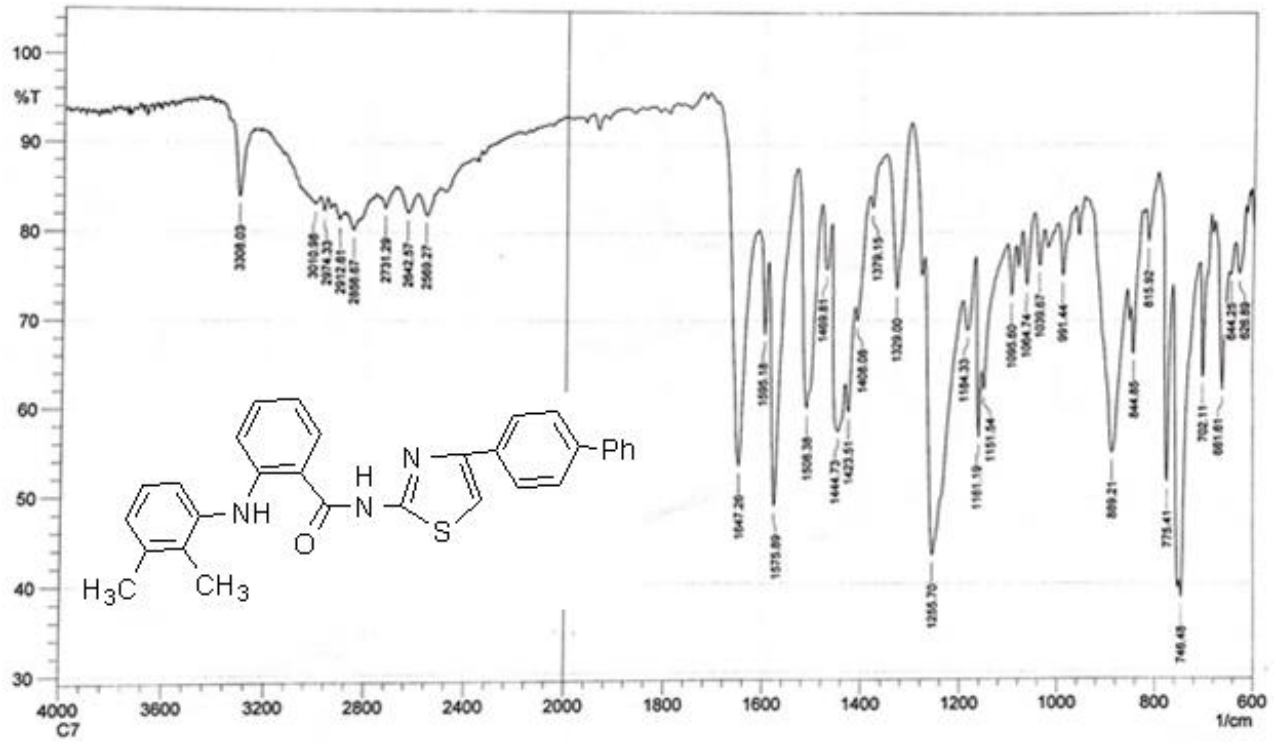


Figure (3.15) : FT.IR spectrum of compound (12)

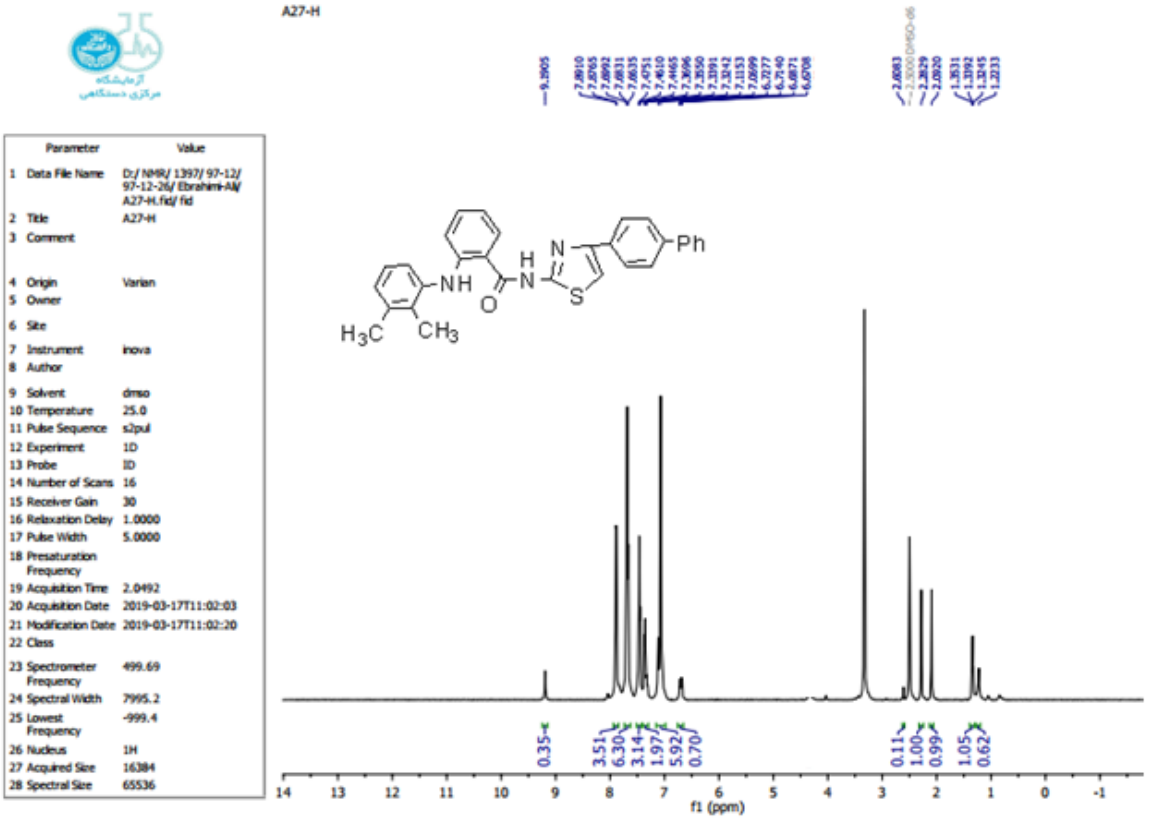
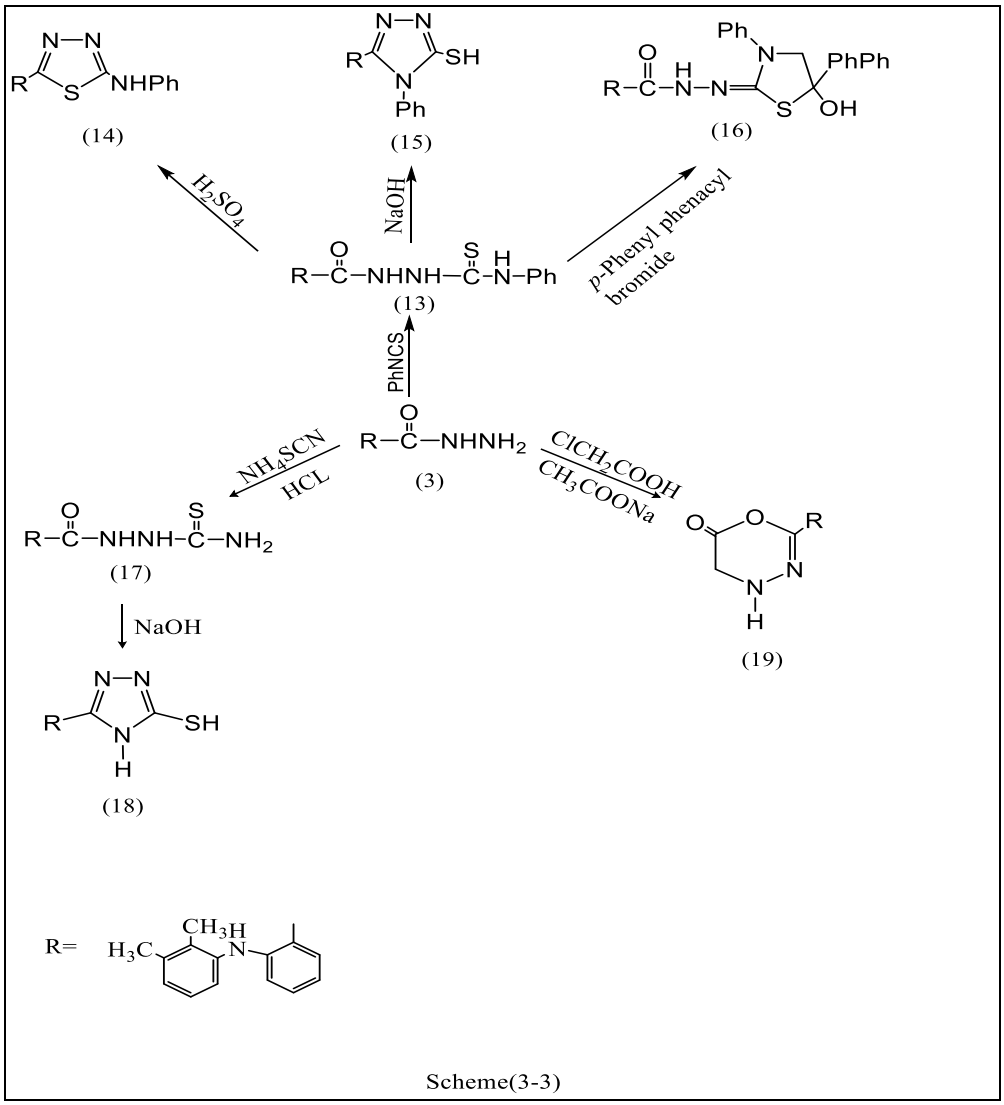


Figure (3.16) : ^{1}H-NMR spectrum of compound (12)

3.3 The part three:

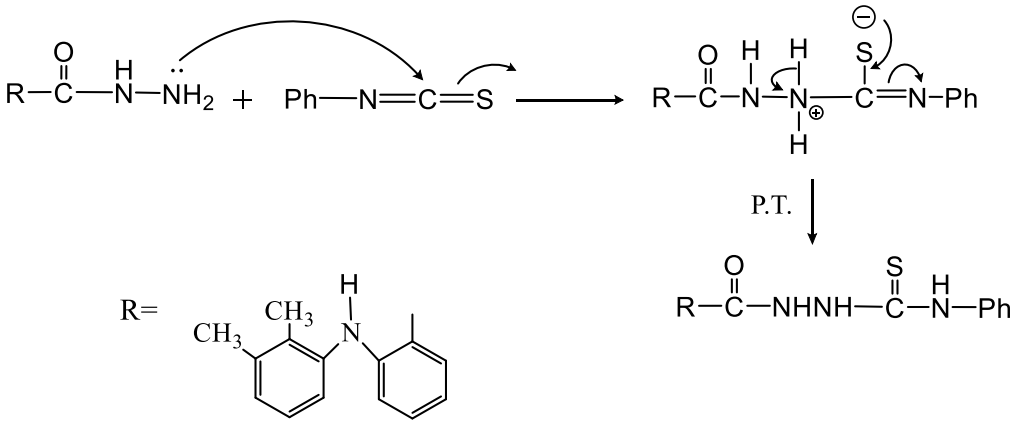
This part include preparation of thiadiazole, triazole, thiazolidin and oxadiazin via the reaction of hydrazide compound [3] with phenyl isothiocyanate [13]. ammonium thiocyanate [17] in ethanol, and cyclization of the products with sulfuric acid [14], sodium hydroxide [15,18], *p*-phenyl phenacyl bromide[16], and reaction of hydrazide. Compound [3] with chloro acetic acid and sodium acetate [19] as shown in scheme (3-3).



Scheme(3-3)

3.3.1 . Synthesis of N-(4-([1,1'-biphenyl]-4-yl)oxazol-2-yl)-2-((2,3-dimethylphenyl)amino)benzamide[13] .

The reaction of acid hydrazide with phenyl isothiocyanate in absolute ethanol gaveN-(4-([1,1'-biphenyl]-4-yl)oxazol-2-yl)-2-((2,3-dimethylphenyl) amino) benzamide [13] . The mechanism of the reaction is shown below:

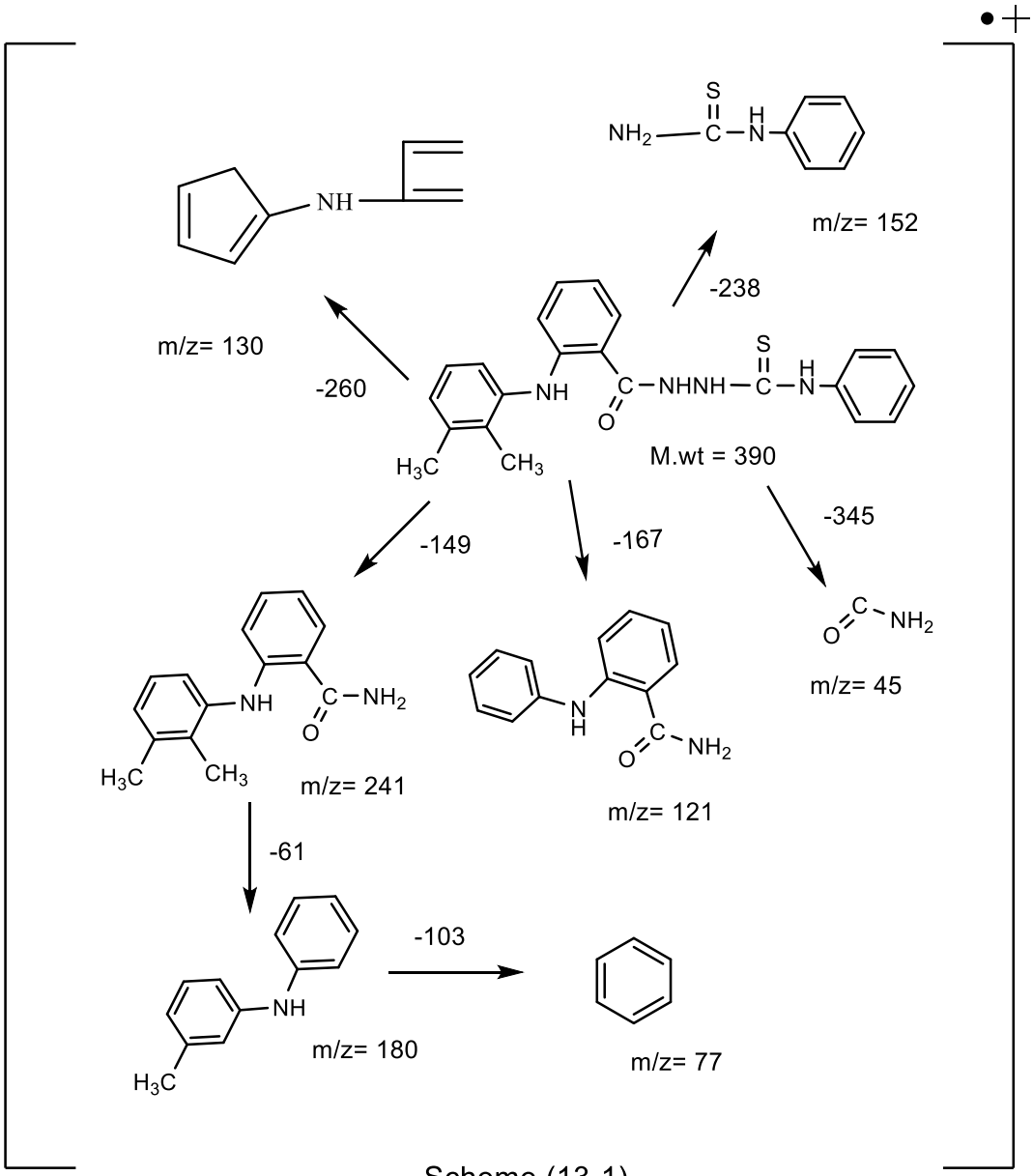


Mechanism(7)

Compound [13] was identified by using FT-IR spectrum which showed bands at 3207 cm^{-1}, 3066 cm^{-1}, (2989, 2868) cm^{-1} and 1651 cm^{-1} which due to NH, CH (arom.), CH (aliph.) and C=O respectively.

The ^{1}H-NMR spectrum for [13] showed the following singlet signals, at δ (2.0, 2.2) ppm, 2.5 ppm, the multiplet signals at δ (6.6 - 7.8) ppm and at 9.4 ppm which attributed to $2CH_3$, DMSO, aromatic protons and for NH proton.

The mass spectrum of compound [13] showed a characteristic fragmentation to the presence of quinazoline moiety at m\z = (390, 241, 223, 208, 180, 152, 130, 77 and 45), as in the Scheme(13-1) below .


m/z= 152
-238
m/z= 130
-260
M.wt = 390
-345
-149
-167
m/z= 45
m/z= 241
m/z= 121
-61
-103
m/z= 180
m/z= 77

Scheme (13-1)

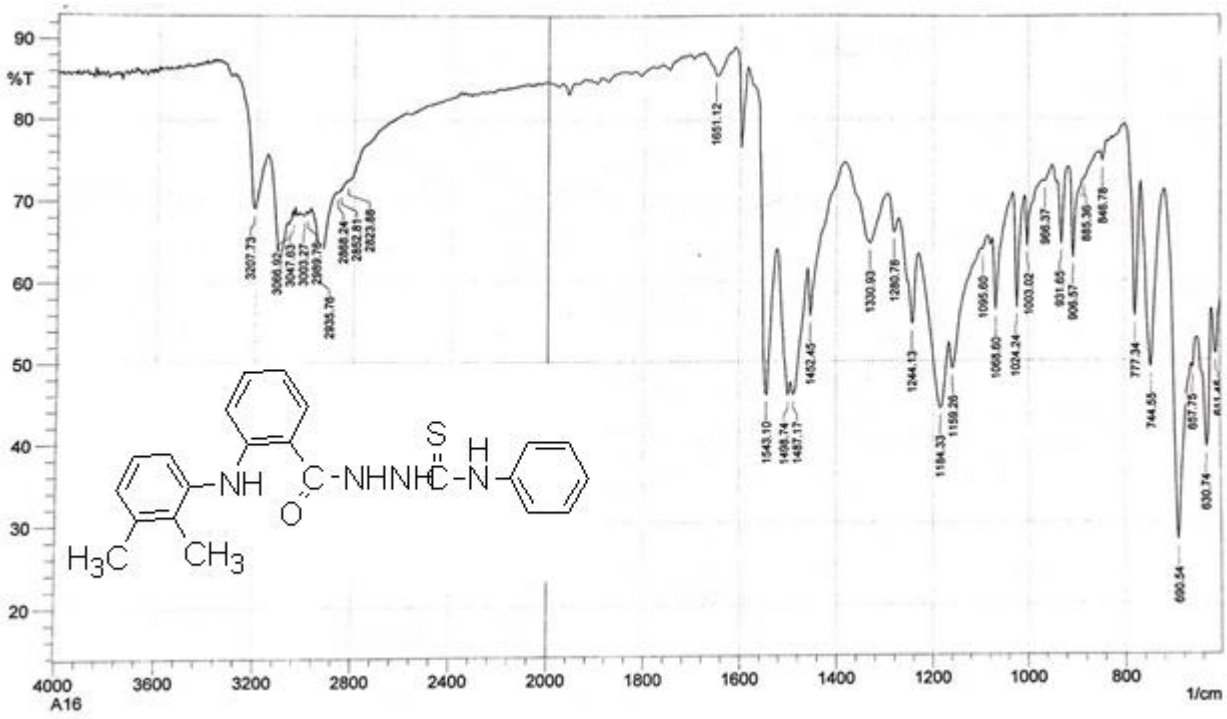


Figure (3.17) : FT.IR spectrum of compound (13)

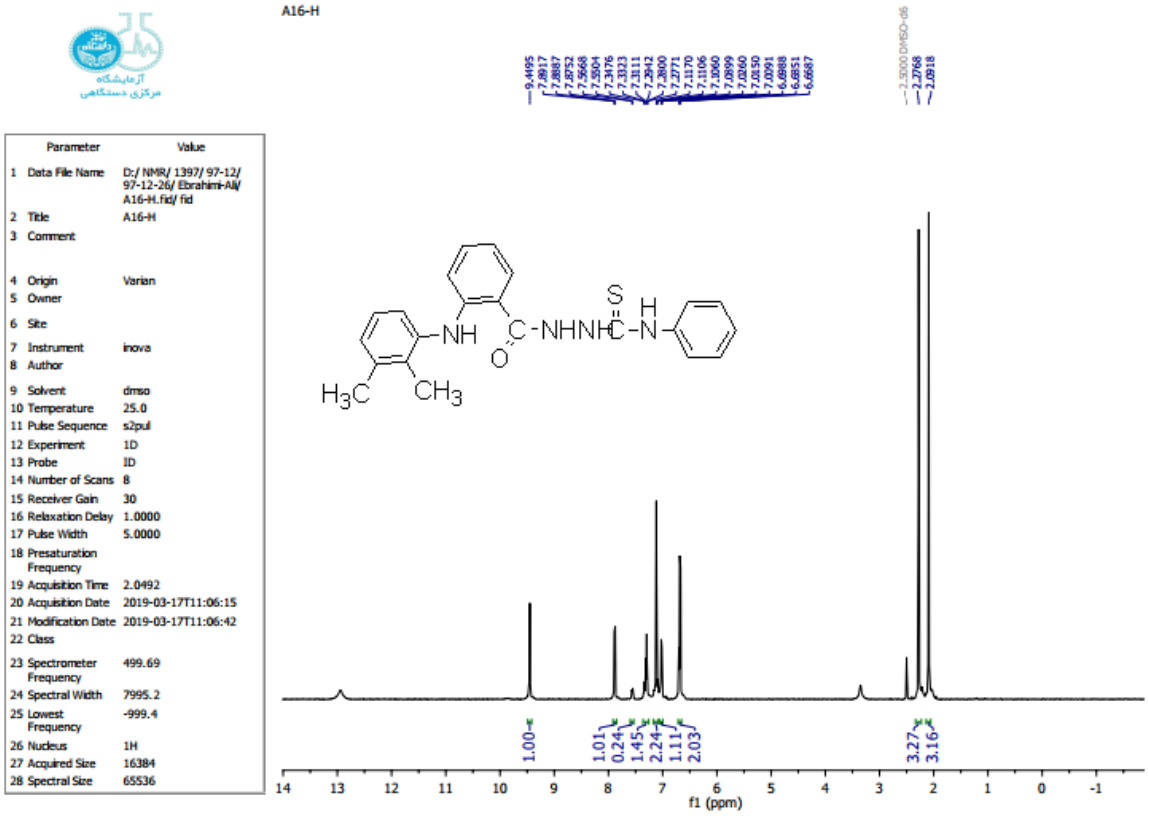


Figure (3.18) : ^{1}H-NMR spectrum of compound (13)

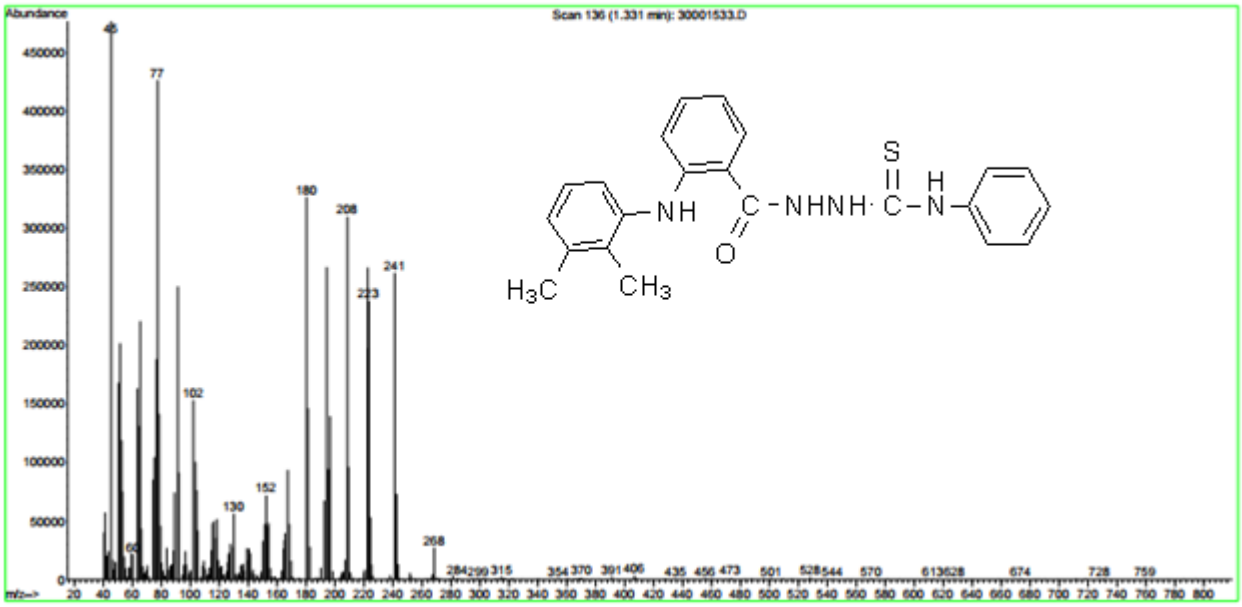
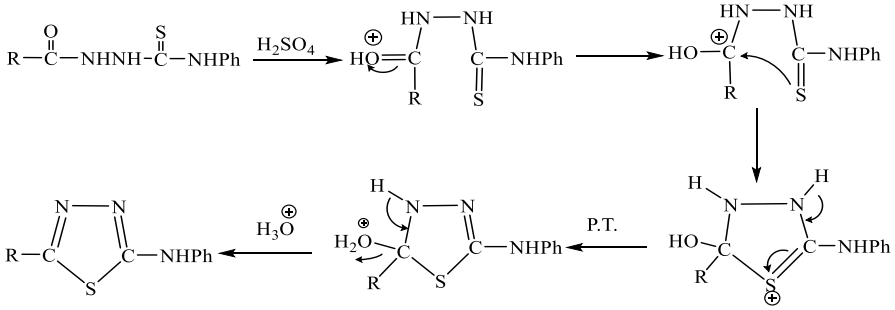


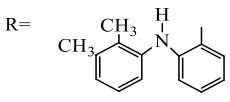
Figure (3.19) : Mass spectrum of compound (13)

3.3.2. Synthesis of 5-(2-((2,3-dimethylphenyl)amino)phenyl)-N-phenyl-1,3,4-thiadiazol-2-amine[14] .

1,3,4-Thiadiazole derivative [14] produced by reaction of thiosemicarbazide derivative with concentrated sulfuric acid at (0) ^{0}C.

The mechanism of the reaction was affected by intermolecular cyclization through the lossing of H_2O, as shown below [117]:





Mechanism(8)

Compound [14] was identified by using FT-IR spectrum which showed bands at 3344 cm^{-1}, 3066 cm^{-1}, (2912, 2729) cm^{-1} and 1651 cm^{-1} which are due to NH, CH (arom.), CH (aliph.) and C=N respectively.

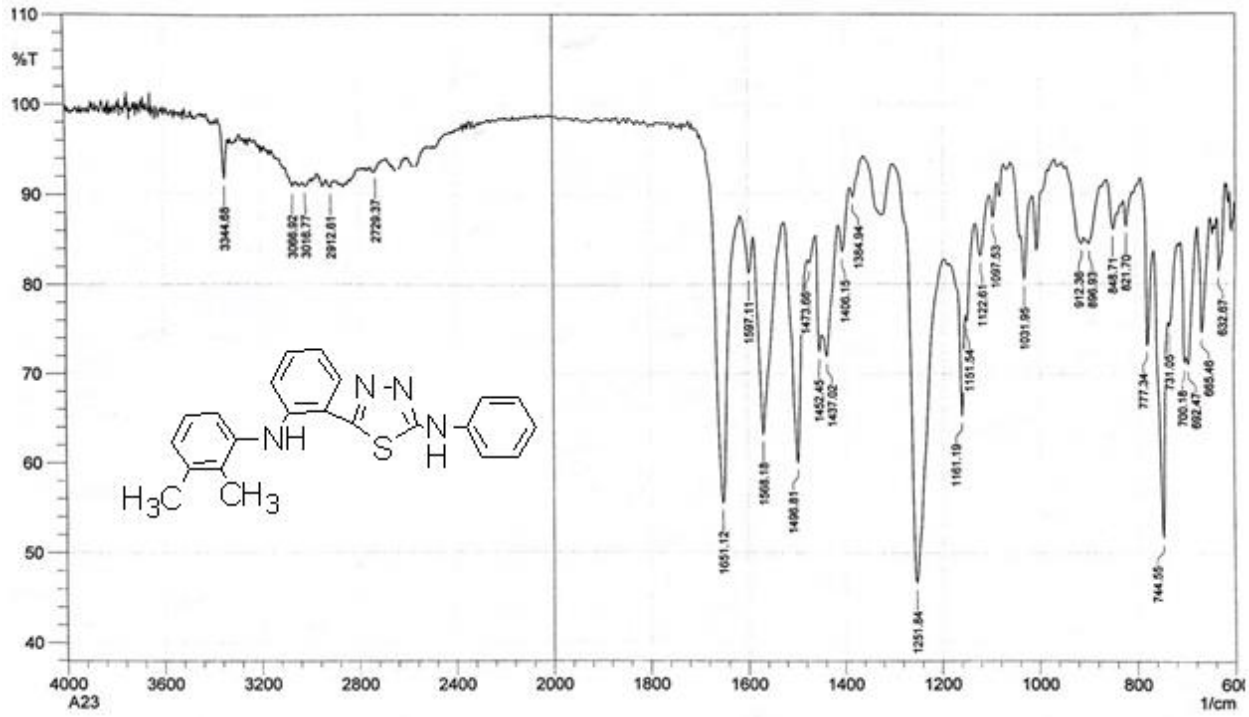
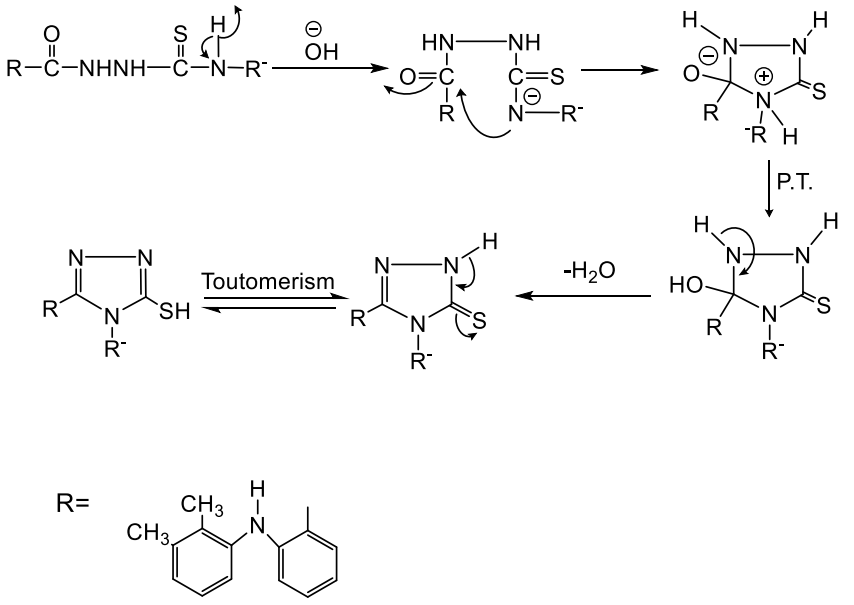


Figure (3.20) : FT.IR spectrum of compound (14)

3.3.3 Characterization 1,2,4-triazole [15], [18]:

Thiol-triazole prepared by the reaction of thiosemicarbazide derivative with NaOH under refluxing condition. The suggested mechanism for the reaction is [118]:



Mechanism(9)

Compound [15] was identified by using FT-IR spectrum which showed bands at 3346 cm^{-1}, 3068 cm^{-1}, (2941, 2858) cm^{-1} and 1651 cm^{-1} which are due to NH, CH (arom.), CH (aliph.) and C=N respectively.

The ^{1}H-NMR spectrum for [15] showed the following singlet signals, at δ 2.0, 2.2 ppm , 2.5 ppm, the multiplet signals at δ (6.6 - 7.8) ppm, 9.4 ppm and 12.8 ppm which attributed to $2CH_3$, DMSO, aromatic protons, NH and SH proton.

Compound [18] was identified by using FT-IR spectrum which showed bands at 3305 cm^{-1}, 3062 cm^{-1}, (2947, 2866) cm^{-1}, 2573 cm^{-1}, 1647, 1573 cm^{-1} which are due to NH, CH (arom.), CH (aliph.), SH, C=O and C=N respectively.

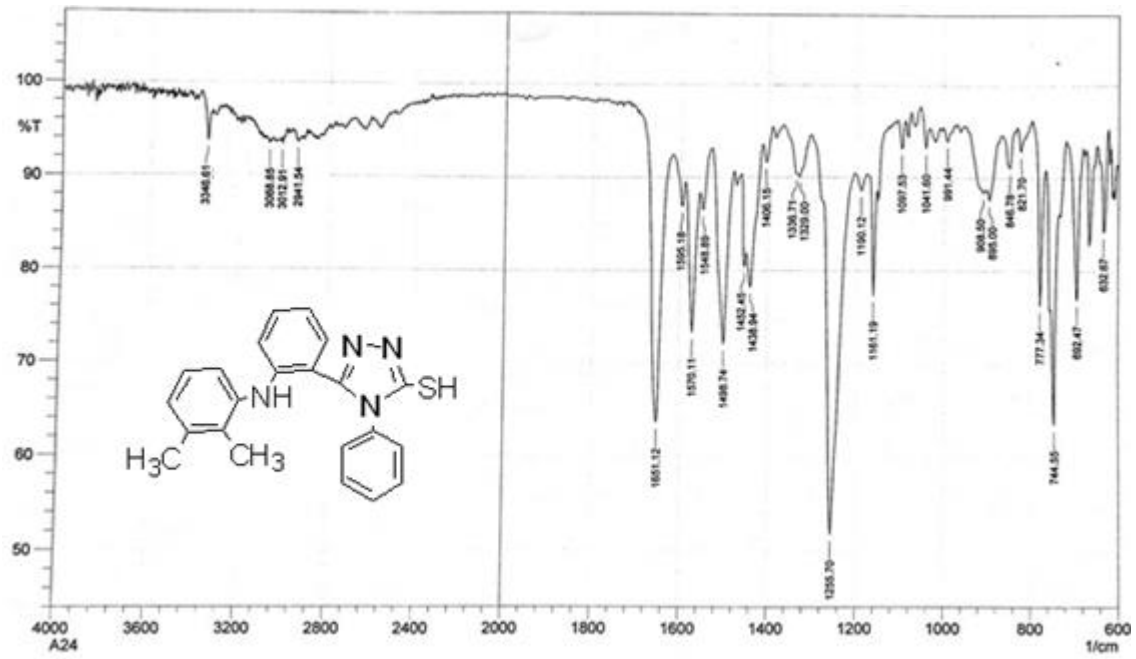


Figure (3.21) : FT.IR spectrum of compound (15)

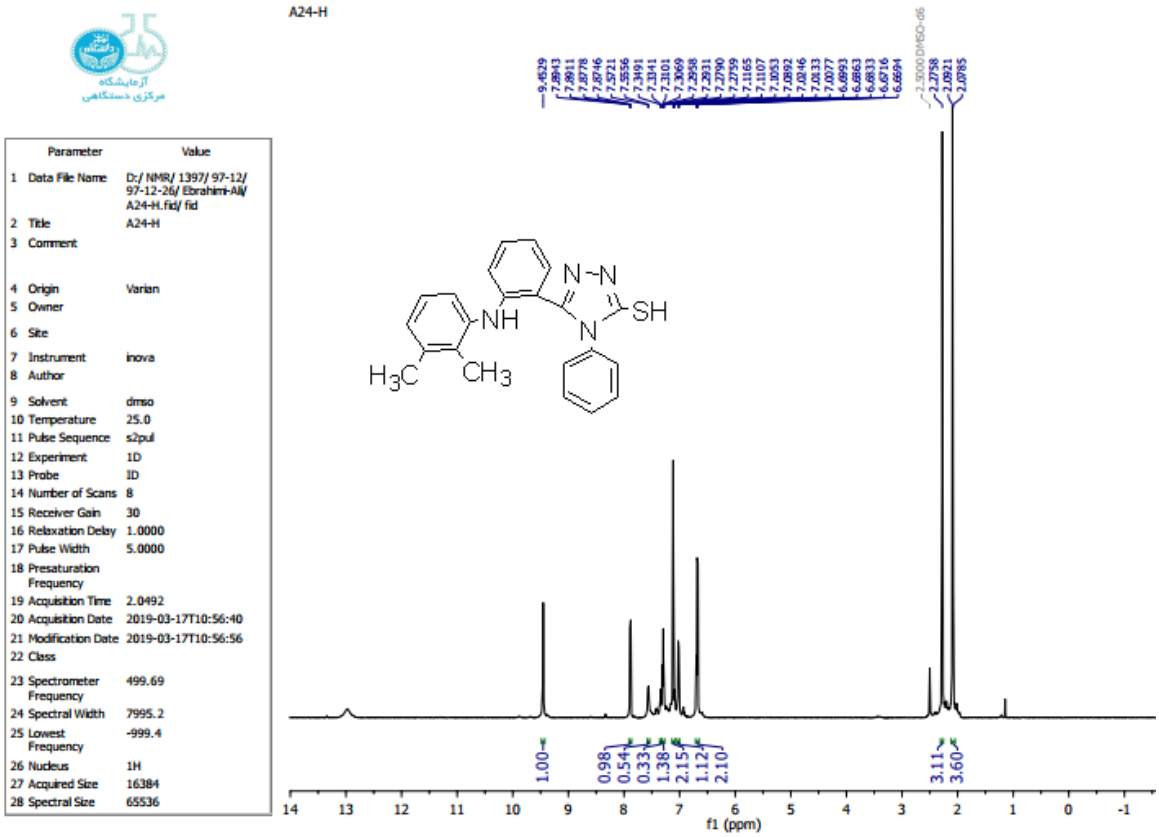


Figure (3.22) : ^{1}H-NMR spectrum of compound (15)

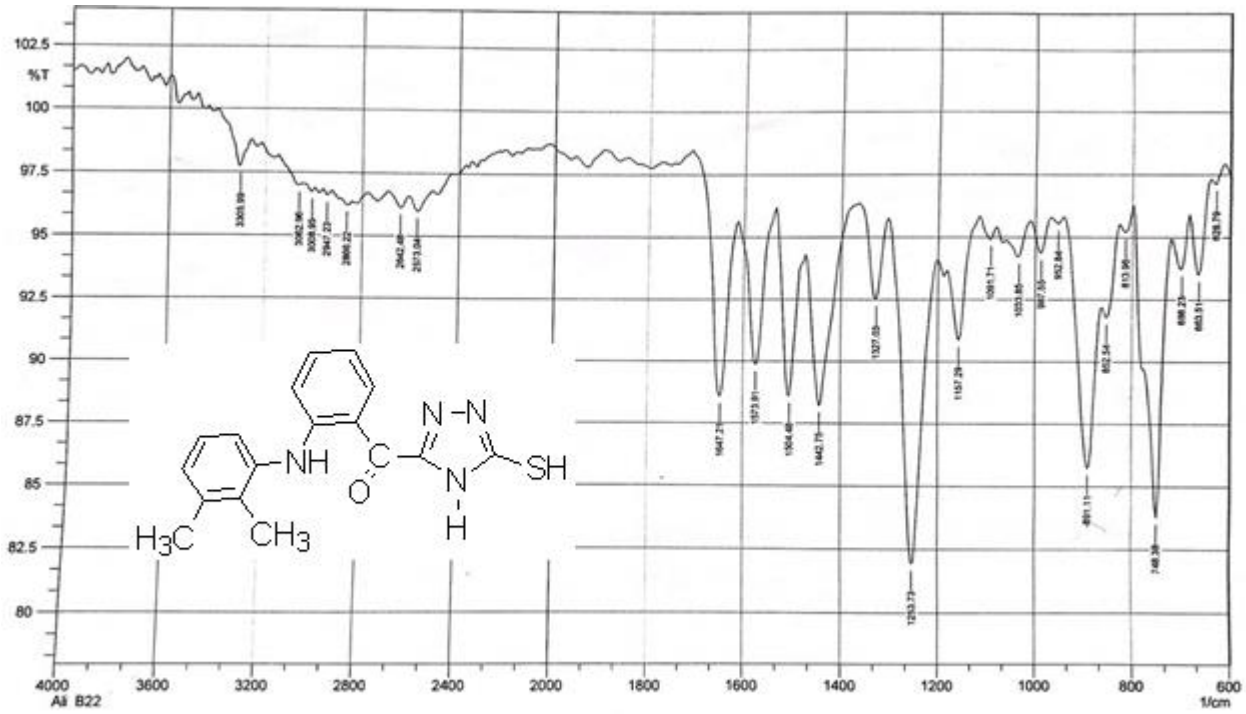
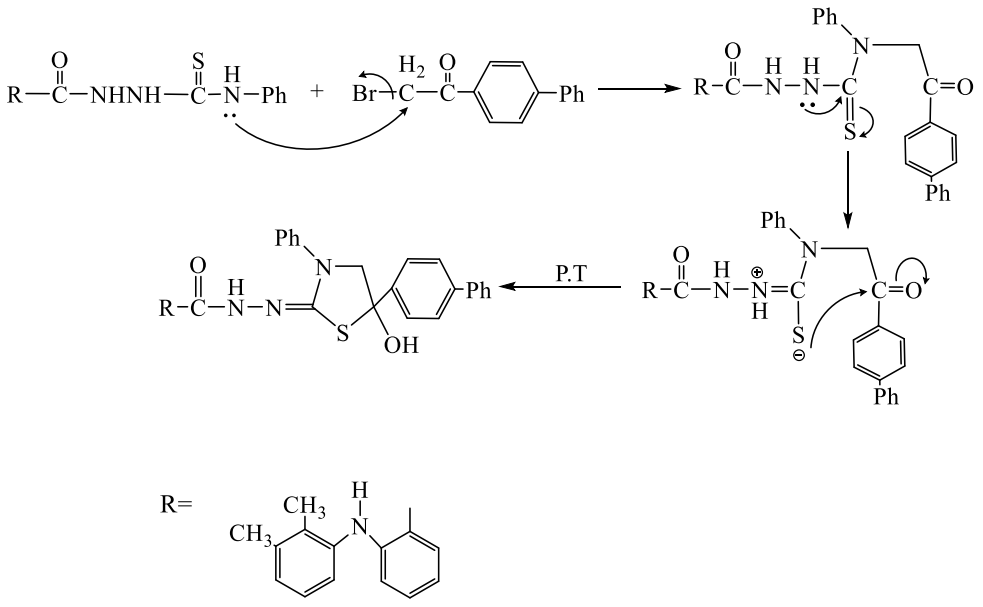


Figure (3.23) : FT.IR spectrum of compound (18)

3.3.4. Synthesis of 2-((2,3-dimethylphenyl)amino)-N'-(5-hydroxy-5-(4-hydroxyphenyl)-3-phenylthiazolidin-2-ylidene) benzohydrazide[16] .

Thiazolidine derivative [16] produced from the reaction of thiosemicarbazide derivative [13] with *p*-phenylphenacyl bromide which was used for cyclization of the previous compound. The mechanism of reaction is shown below [(119)]:



Mechanism(10)

Compound [16] was identified by using FT-IR spectrum which showed bands at 3380 cm^{-1}, 3317 cm^{-1}, 3059 cm^{-1}, (2916, 2858) cm^{-1}, 1674 cm^{-1}, 1593 cm^{-1} which due to OH, NH, CH (arom.), CH (aliph.), C=O and C=N, respectively.

The ^{1}H-NMR spectrum for [16] showed the following singlet signals, at δ 2.0, 2.2 ppm , 2.5 ppm, 2.6 ppm, 5.3 ppm, the multiplet signals at δ (6.7 - 8.2) ppm and 9.2 ppm which attributed to $2CH_3$, DMSO, CH_2, OH, aromatic protons and NH .

Compound [17] was identified by using FT-IR spectrum which showed bands at 3223,3170 cm^{-1}, 3059 cm^{-1}, (2933, 2856) cm^{-1}, 1645 cm^{-1} which due to NH_2, CH (arom.), CH (aliph.) and C=O respectively.

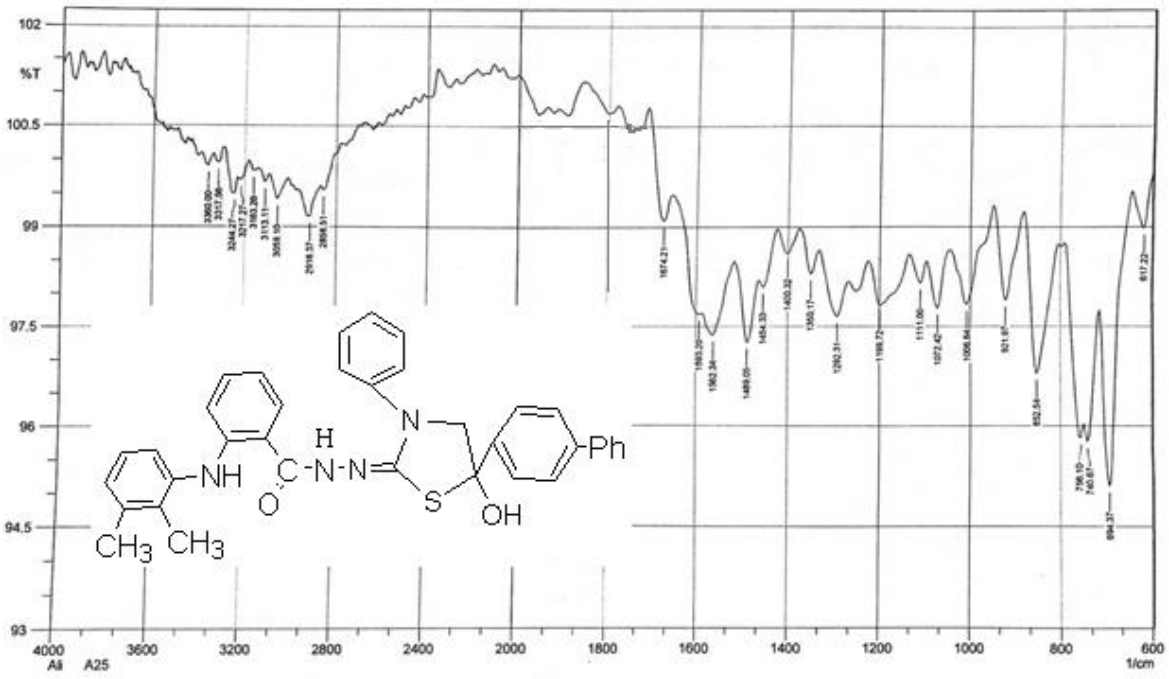


Figure (3.24) : FT.IR spectrum of compound (16)

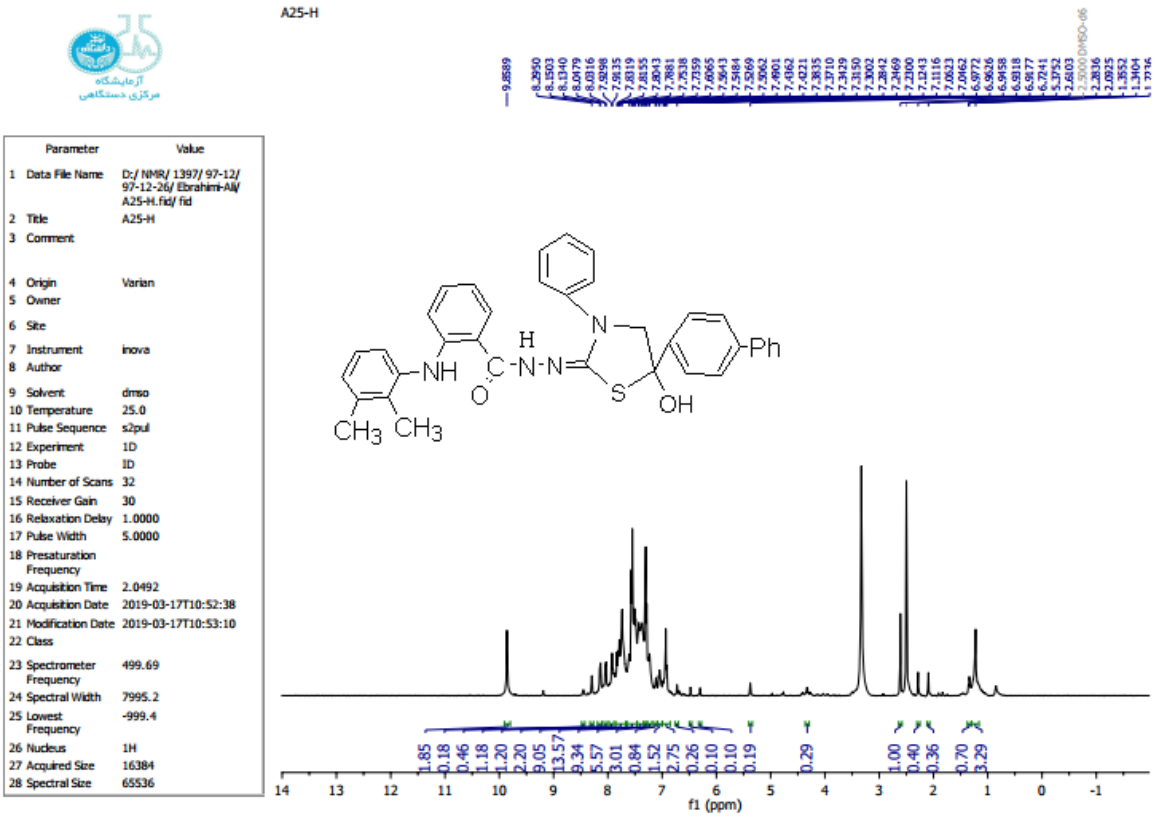


Figure (3.25) : ^{1}H-NMR spectrum of compound (16)

3.3.5 . Synthesis of 2-(2-((2,3-dimethylphenyl)amino)benzoyl) hydrazine-1-carbothioamide[17].

Reaction of acid hydrazide compound [3] with ammonium thiocyanate in presence of aqeous hydrochloric acid gave compound [17] .

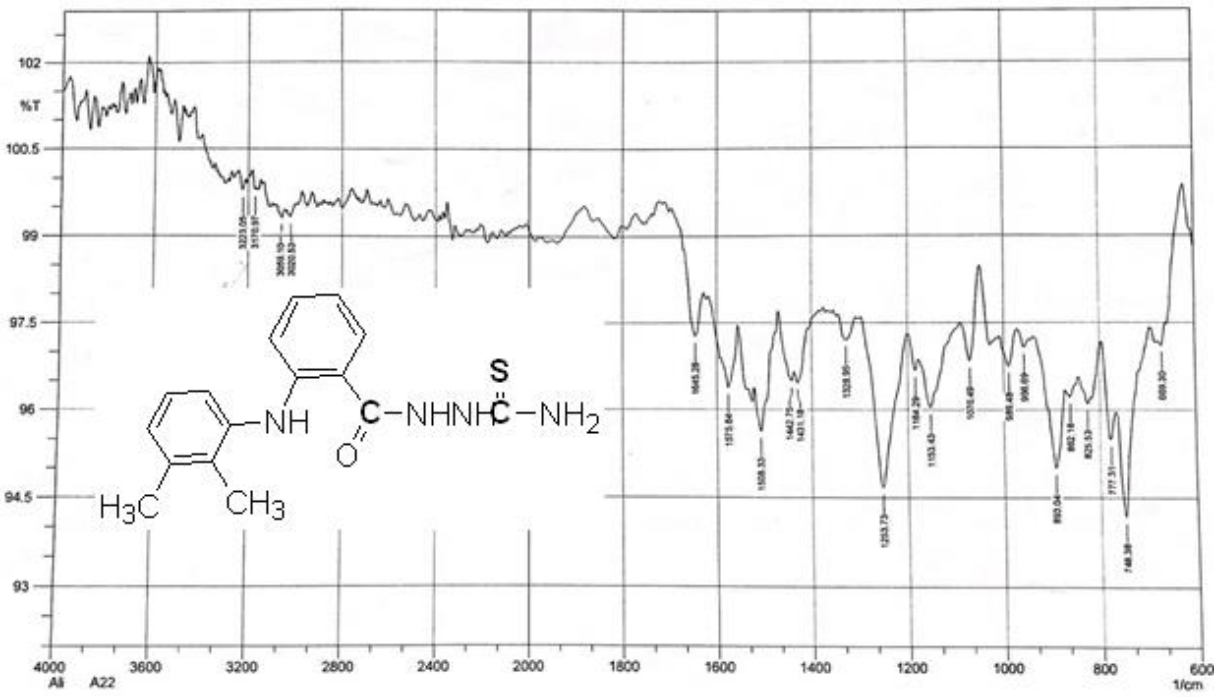
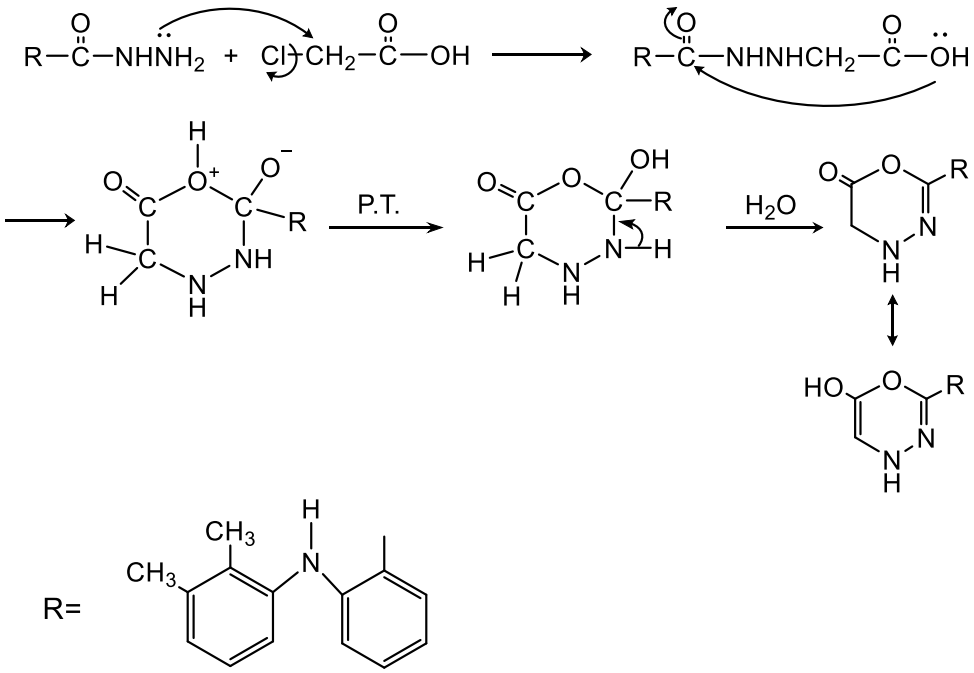


Figure (3.26) : FT.IR spectrum of compound (17)

3.3.6 . Synthesis of 2-(2-((2,3-dimethylphenyl)amino)phenyl)-4,5-dihydro-6H-1,3,4-oxadiazin-6-one [19] .

Reaction of acid hydrazide compound [3] with chloro acetic acid in presence of sodium acetate and acetic anhydride gave compound [19]. The mechanism of this reaction is shown below:



Mechanism(11)

Compound [19] was identified by using FT-IR spectrum which showed bands at 3383 cm^{-1}, 3090 cm^{-1}, (2993 , 2858) cm^{-1}, 1778 cm^{-1}, 1643 cm^{-1} and 1162 cm^{-1} which due to NH, CH (arom.), CH (aliph.), C=O, C=N and C-O-C respectively.

The ^{1}H-NMR spectrum for compound [19] showed the following singlet signals, at δ 2.2 ppm, 2.5, 2.6 ppm, 3.4 ppm, the multiplet signals at δ (6.7 - 8.2) ppm and 9.2 ppm which attributed to $2CH_3$, DMSO, CH_2, aromatic protons and NH .

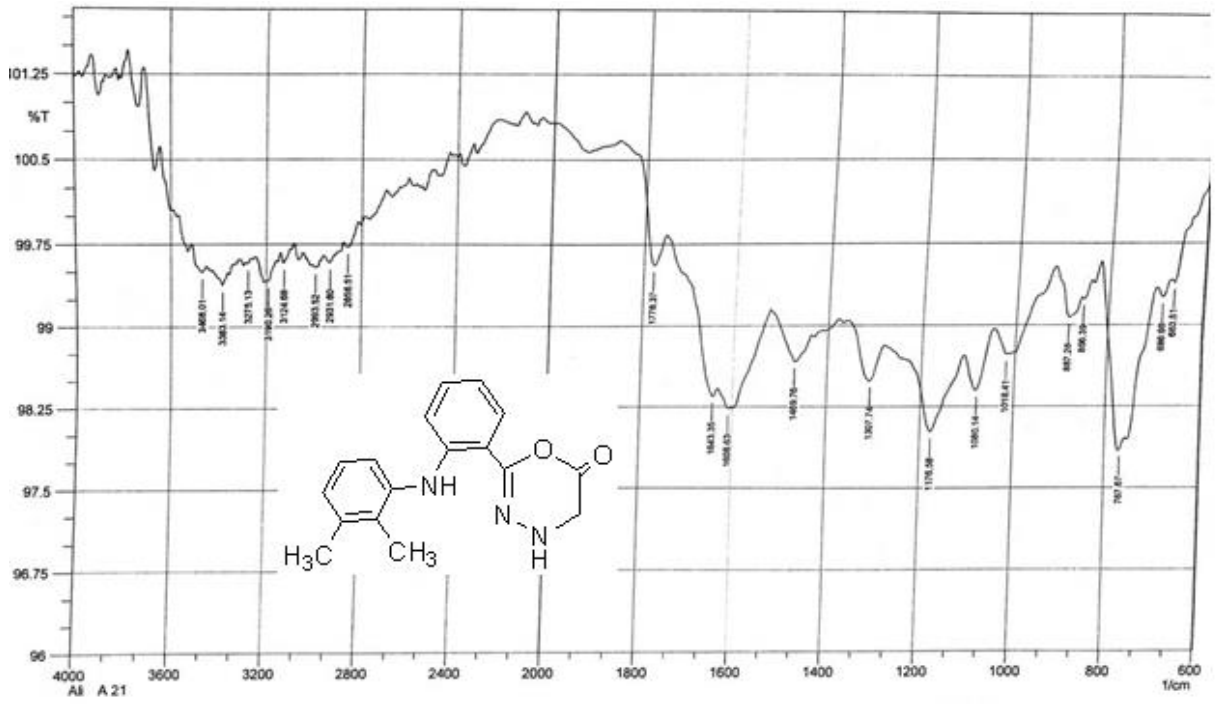


Figure (3.27) : FT.IR spectrum of compound (19)

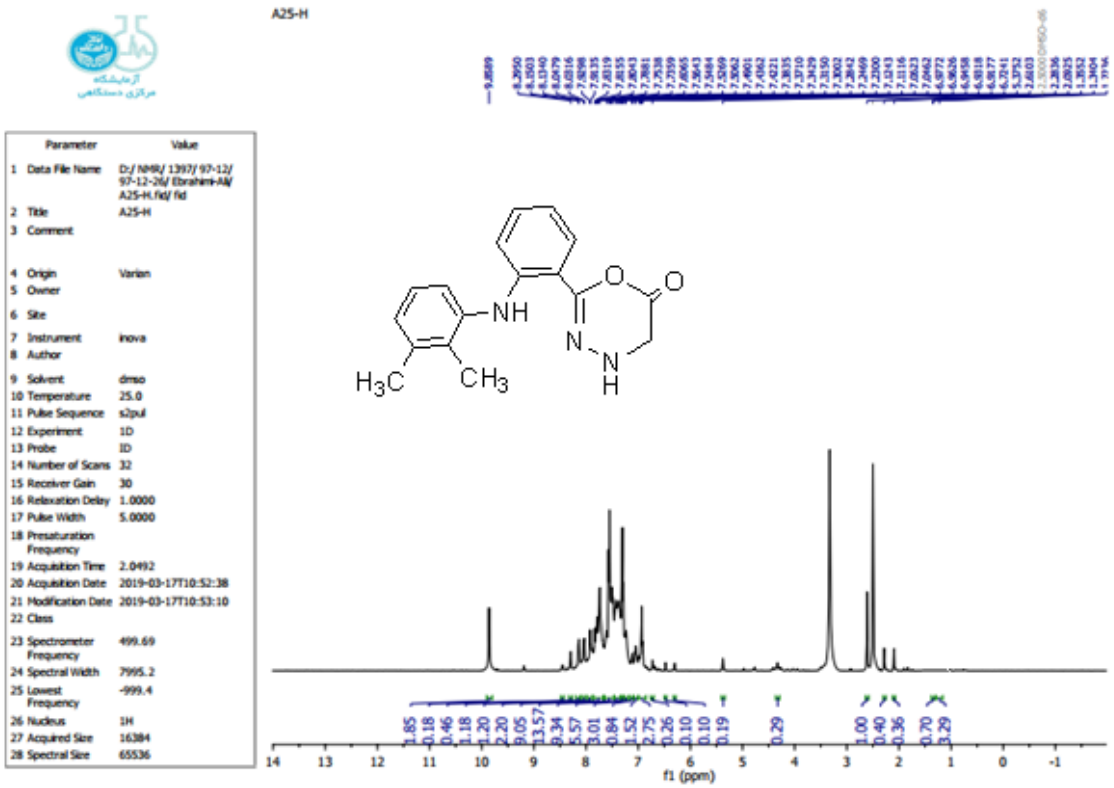
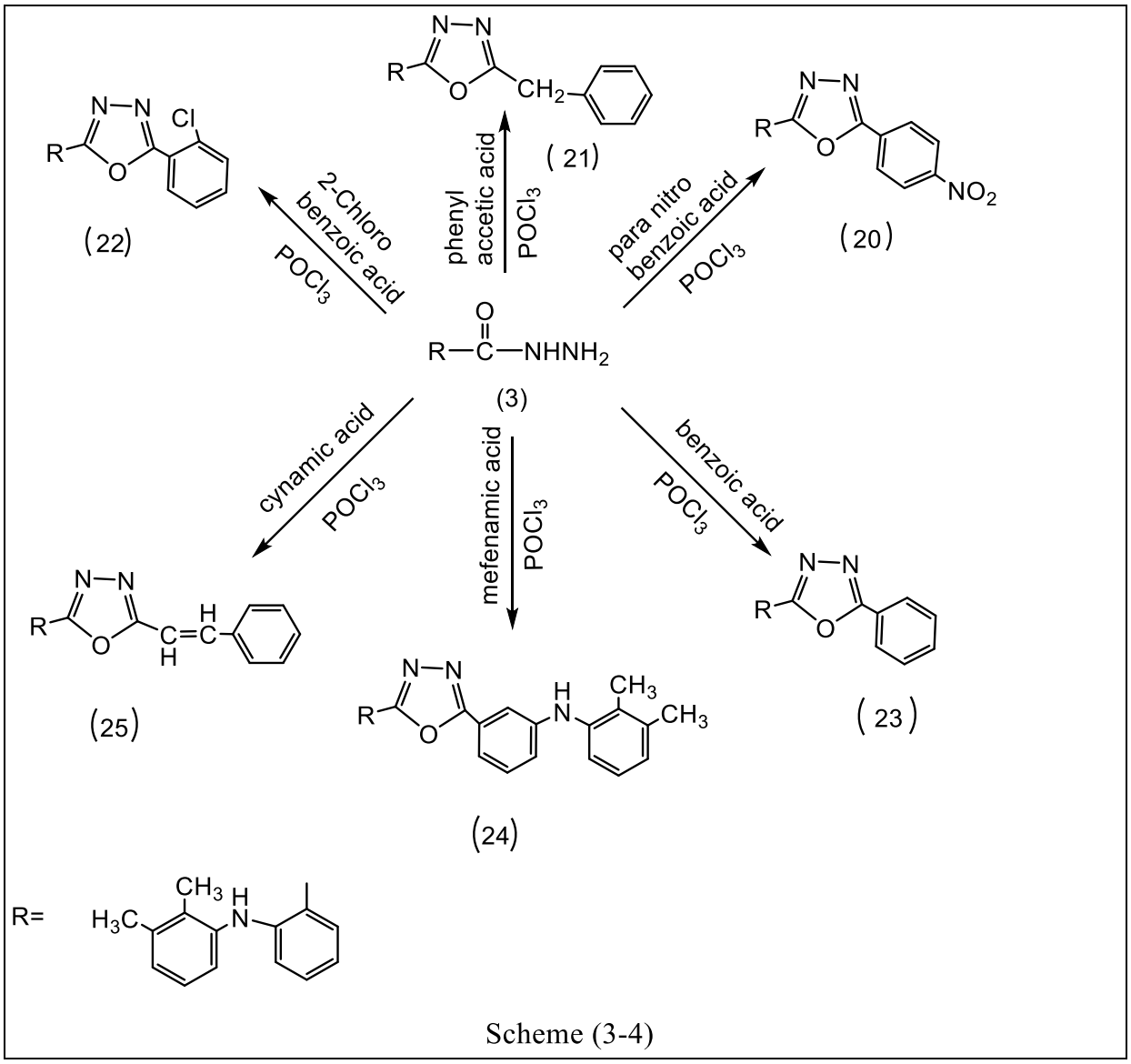


Figure (3.28) : ^{1}H-NMR spectrum of compound (19)

3.4. The Four Part:

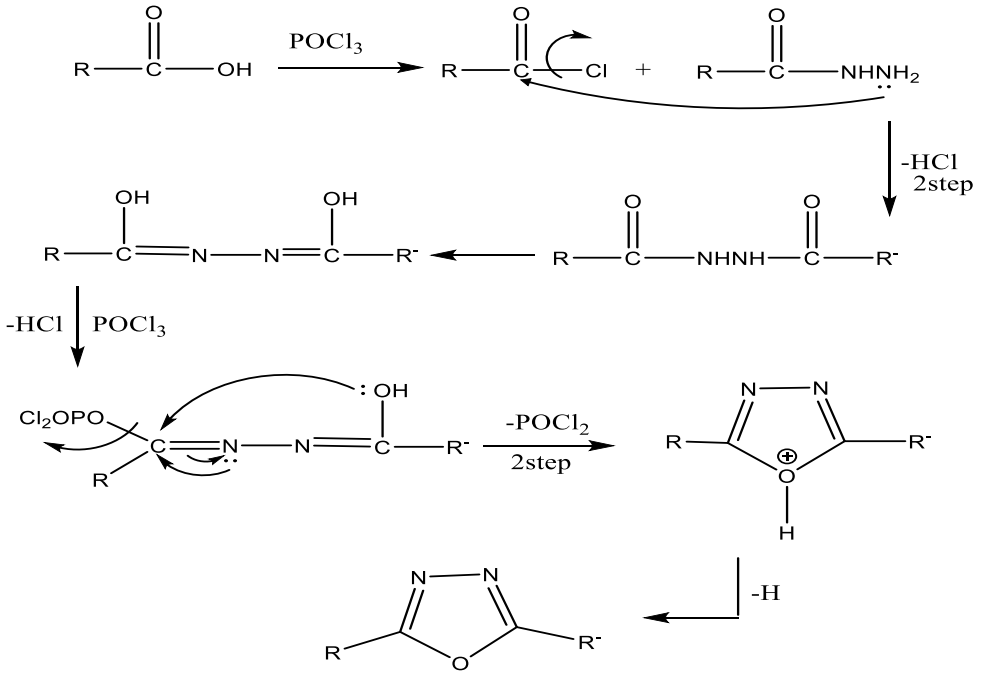
This part of describes synthesis of oxadiazole from the reaction of hydrazide compound [3] with phosphoryl chloride [20], [21], [22], [23], [24] and [25] as shown below:



Scheme (3-4)

3.4.1 Synthesis of oxadiazol [20],[21],[22],[23],[24],[25] :

Oxadiazol prepared by the reaction of benzoic acid, *P*-nitro benzoic acid, phenyl accetic acid, 2-chloro benzoic acid, cynamic acid and mefenamic acid, derivative with $POCl_3$ under refluxing condition . Below is the suggested interaction mechanism [118] :



Mechanism(12)

Compound [20] was identified by using FT-IR spectrum which showed bands at 3207 cm^{-1}, 2972, 2856 cm^{-1}, 1645 cm^{-1}, 1518 cm^{-1}, 1165 and 1317 cm^{-1}which due to NH, CH (aliph.), C=N, C-O-C and NO_2 respectively.

Compound [21] was identified by using FT-IR spectrum which showed bands at 3200 cm^{-1}, 3032 cm^{-1}, (2910, 2854) cm^{-1}, 1662 cm^{-1} and 1160 cm^{-1} which due to NH, CH (aliph.), C=N and C-O-C respectively.

Compound [22] was identified by using FT-IR spectrum which showed bands at 3209 cm^{-1}, 3053 cm^{-1}, (2974, 2854) cm^{-1}, 1645, 1162 cm^{-1} which due to NH, CH (arom.), CH (aliph.), C=N and C-O-C respectively.

Spectrum ^{1}H-NMR for [22] showed the following singlet signals, at δ 2.40, 2.47 ppm, 2.5 ppm, the multiplet signals at δ (6.6 - 8.1) ppm and at 10.4 ppm which attributed to $2CH_3$, DMSO, aromatic protons and for NH proton.

Compound [23] was identified by using FT-IR spectrum which showed bands at 3273 cm^{-1}, 3093 cm^{-1}, (2910, 2852) cm^{-1}, 1653 cm^{-1} and 1163 cm^{-1} which due to NH, CH (arom.), CH (aliph.), C=N and C-O-C respectively.

Compound [24] was identified by using FT-IR spectrum which showed bands at 3275 cm^{-1}, 3062 cm^{-1}, (2924, 2851) cm^{-1},1666 cm^{-1} and 1166 cm^{-1} which due to NH, CH (arom.), CH (aliph.), C=N and C-O-C respectively.

Compound [25] was identified by using FT-IR spectrum which showed bands at 3363 cm^{-1}, 3055 cm^{-1}, (2974, 2908) cm^{-1},1689 cm^{-1} and 1152 cm^{-1} which due to NH, CH (arom.), CH (aliph.), C=N and C-O-C respectively.

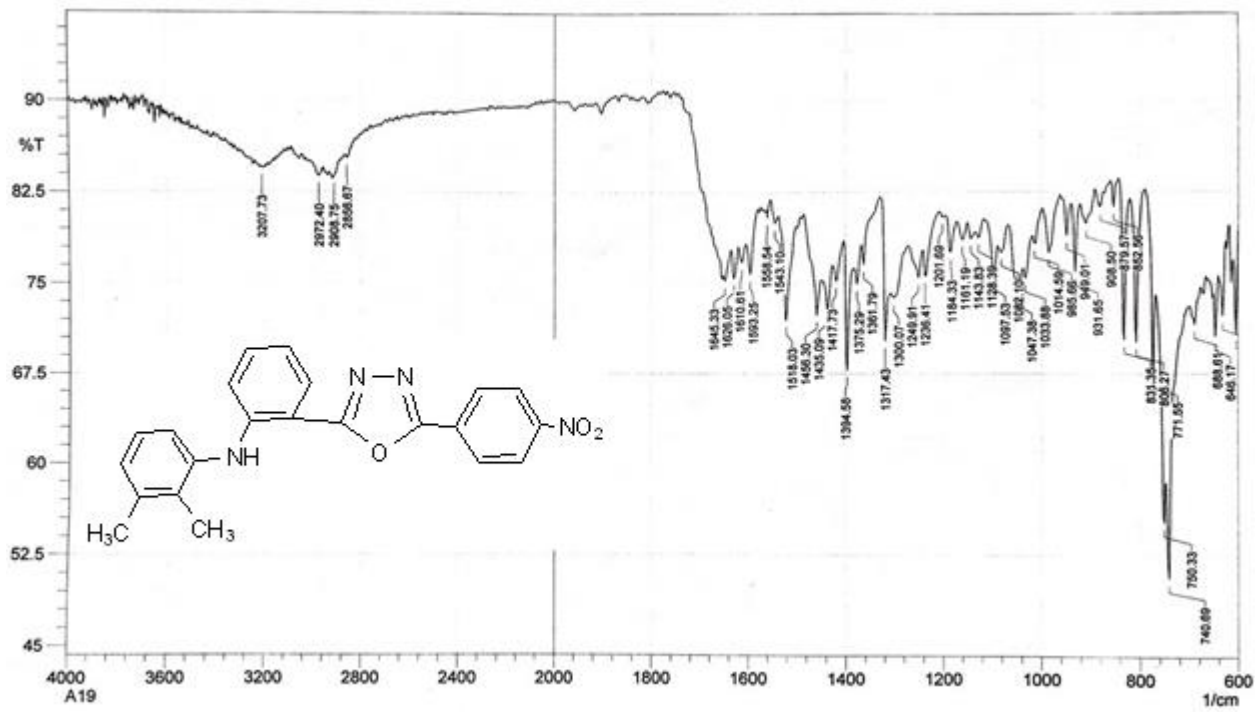


Figure (3.29) : FT.IR spectrum of compound (20)

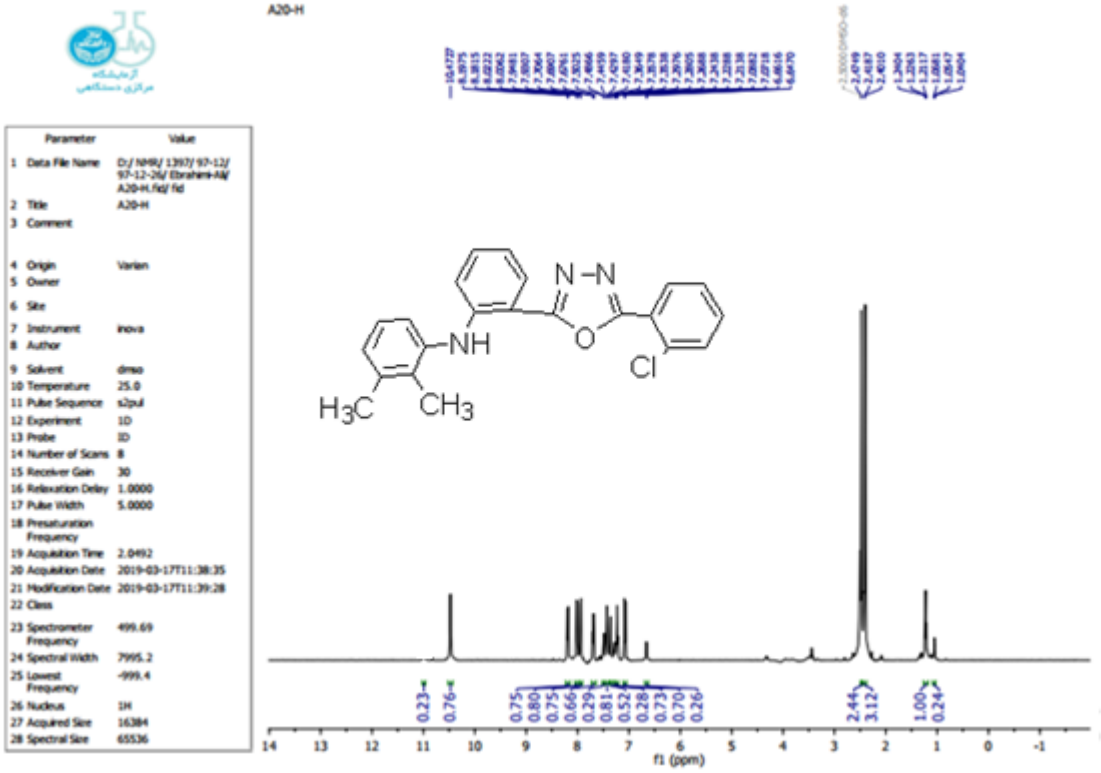


Figure (3.30) : ^{1}H-NMR spectrum of compound (22)

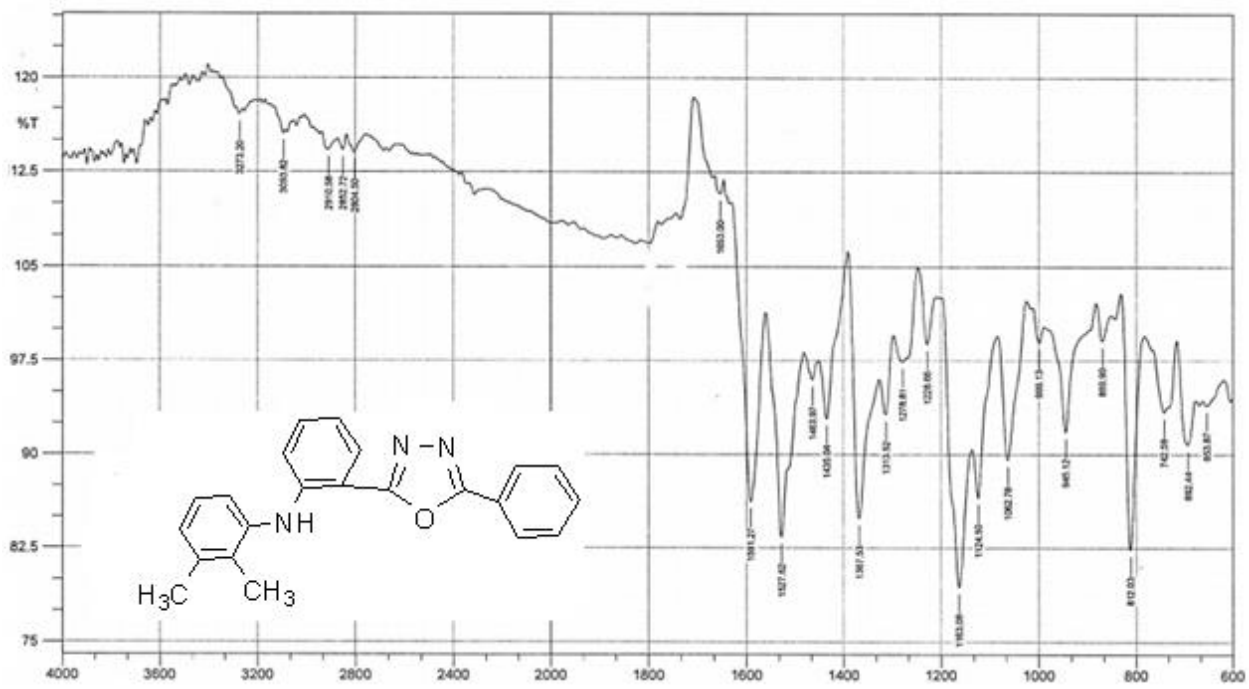


Figure (3.31) : FT.IR spectrum of compound (23)

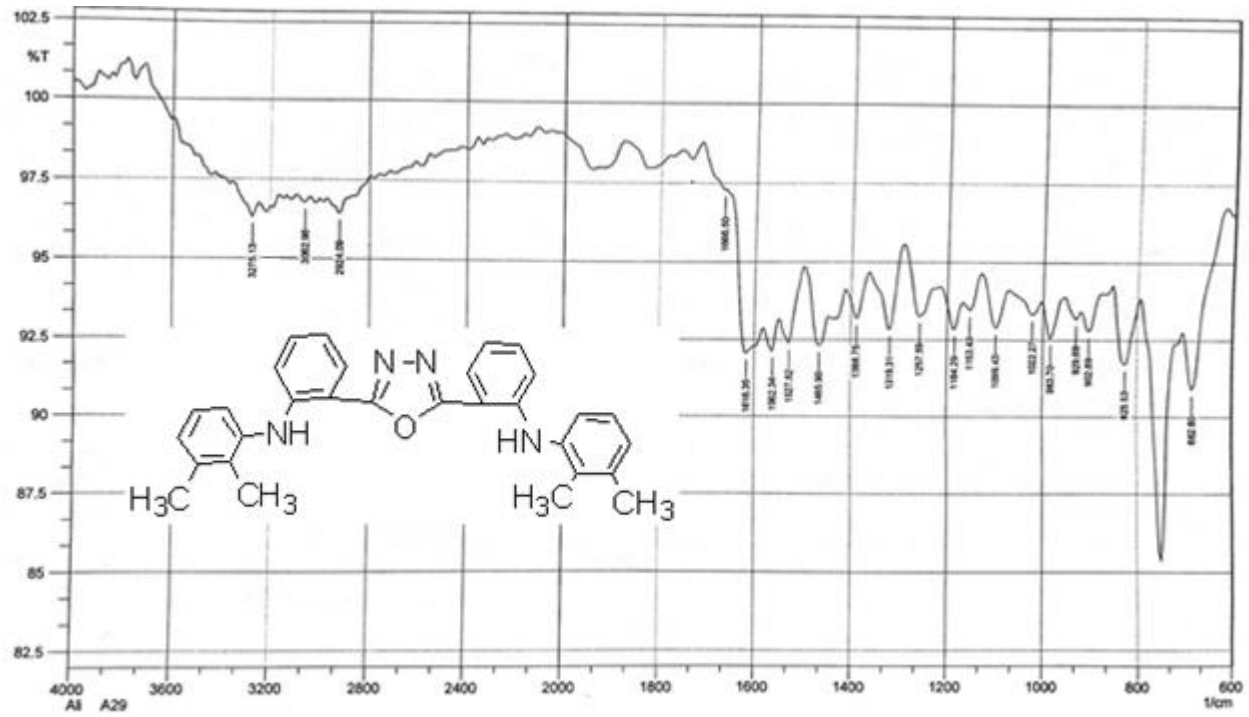


Figure (3.32) : FT.IR spectrum of compound (24)

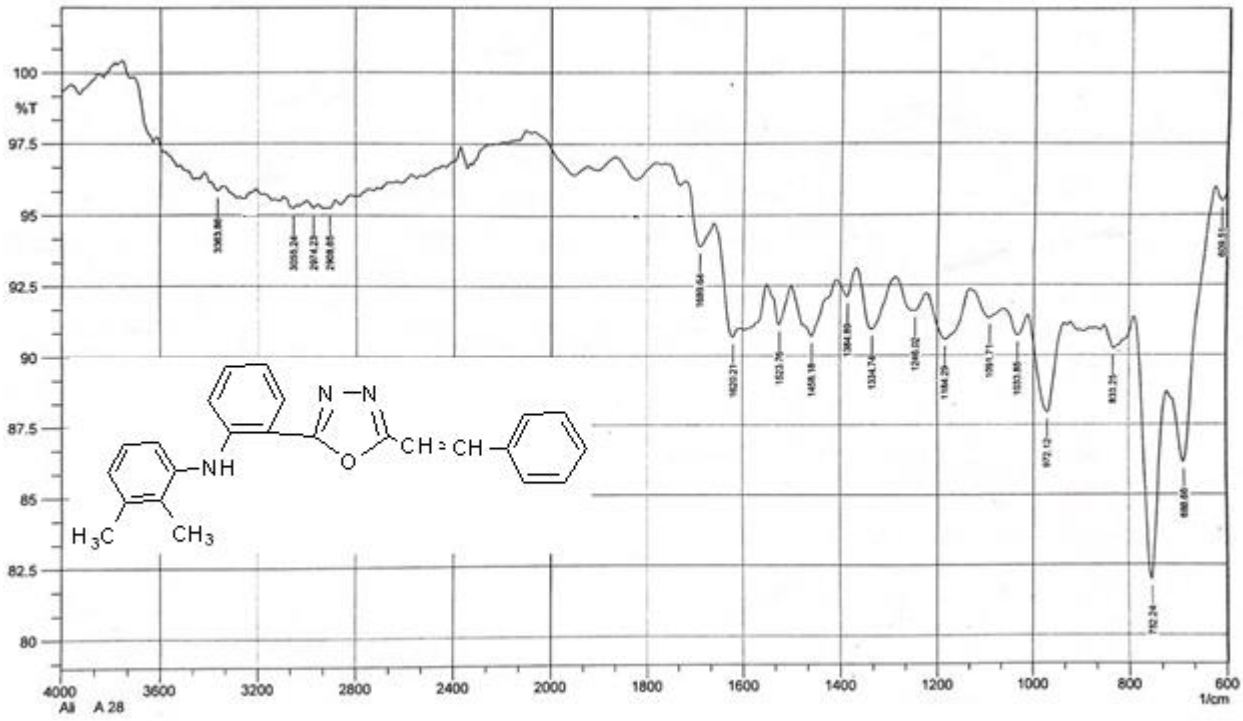
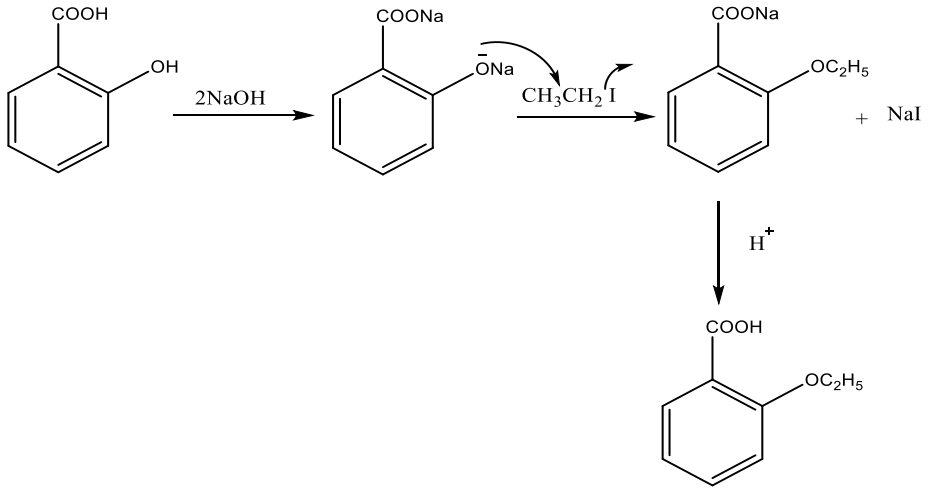


Figure (3.33) : FT.IR spectrum of compound (25)

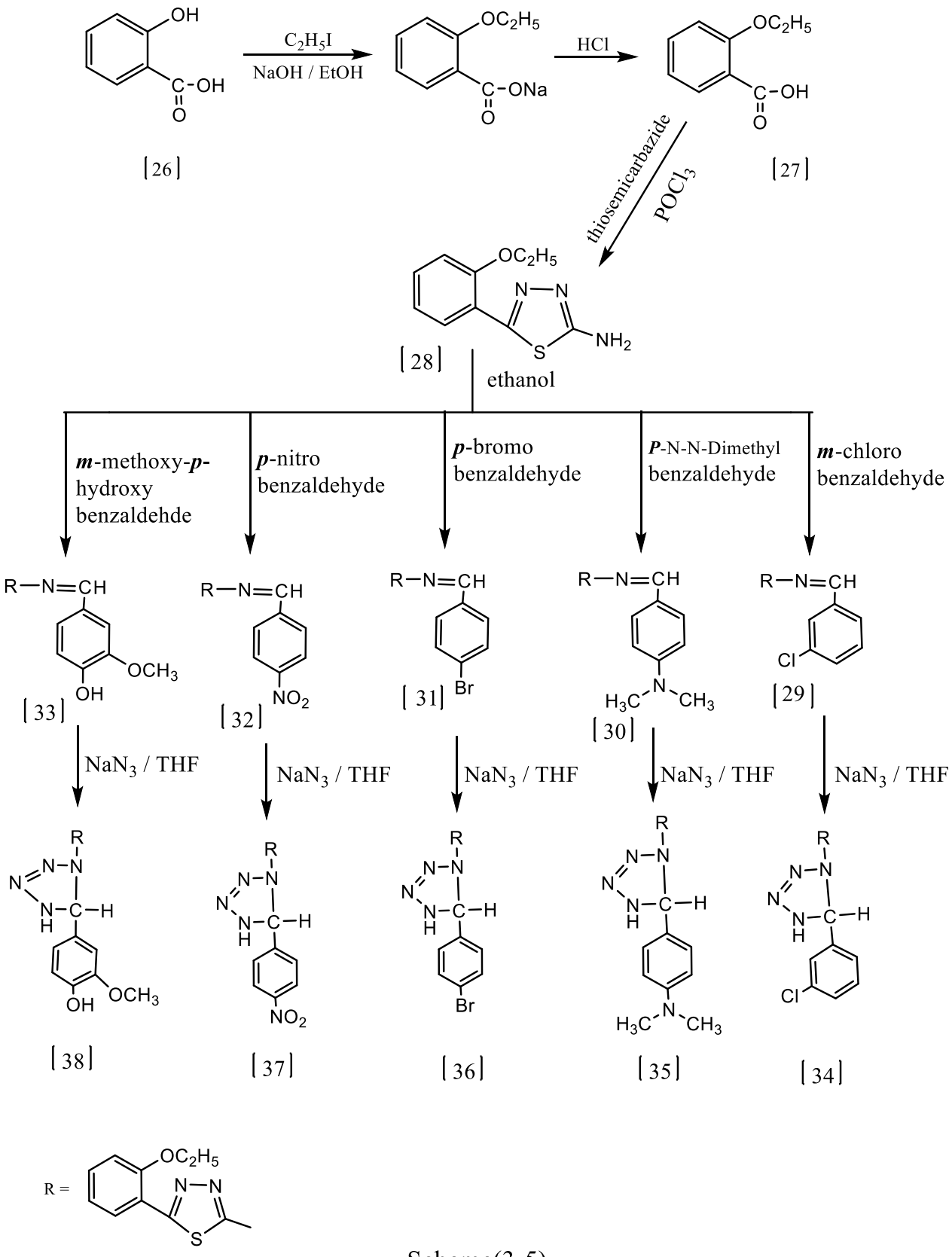
3.5. The Five Part:

3.5.1. Characterazation of 2-ethoxybenzoic acid[27] .

2-ethoxybenzoic acid [27] was prepared by reaction salcalyic acid with iodo ethan in present NaOH in absolute ethanol. The mechanism of this reaction is shown below:



Mechanism(13)


OH
C-OH
O
[26]
C_2H_5I
NaOH / EtOH
OC_2H_5
C-ONa
O
HCl
OC_2H_5
C-OH
O
[27]
thiosemicarbazide
$POCl_3$
OC_2H_5
N—N
S
NH_2
[28]
ethanol
m-methoxy-*p*-hydroxy benzaldehde
p-nitro benzaldehyde
p-bromo benzaldehyde
P-N-N-Dimethyl benzaldehyde
m-chloro benzaldehyde
R—N=CH
OCH_3
OH
[33]
NO_2
[32]
Br
[31]
H_3C N CH_3
[30]
Cl
[29]
NaN_3 / THF
NaN_3 / THF
NaN_3 / THF
NaN_3 / THF
NaN_3 / THF
R
N-N
N
N-C-H
H
[38]
[37]
[36]
[35]
[34]
R =
OC_2H_5
N—N
S

Scheme(3-5)

Compound [27] was identified by using FT-IR spectrum which showed bands at 3226 cm^{-1}, (2993, 2850) cm^{-1}, 1743 cm^{-1}, 1162 cm^{-1} which due to OH, CH (aliph.), C=O, and C-O-C respectively.

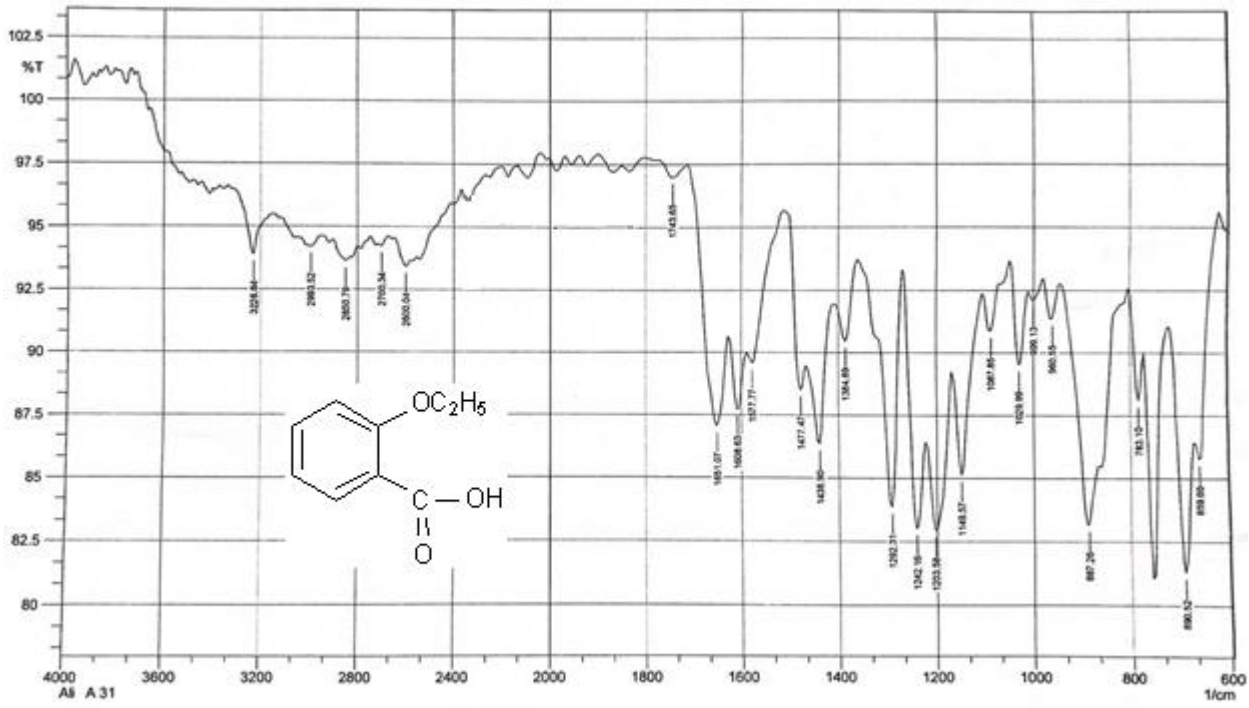
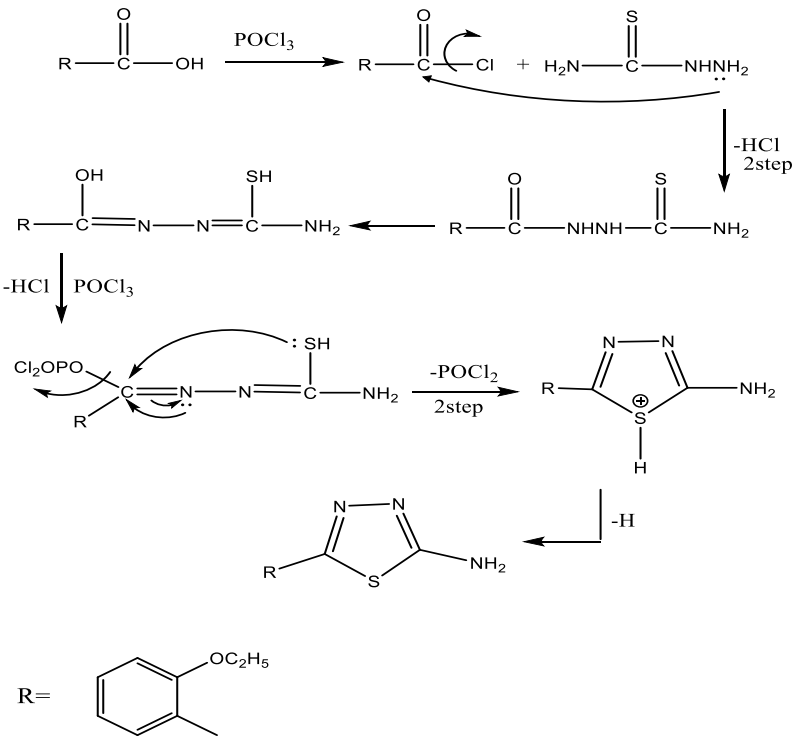


Figure (3.34) : FT.IR spectrum of compound (27)

3.5.2. Charctrazation of 5-(2-ethoxyphenyl)-1,3,4-thiadiazol-2-amine[28].

1,3,4-thiadiazol [28] was prepared by reaction 2-ethoxybenzoic acid with thiosemicarbazide in present phosphoryl chloride . The mechanism of this reaction is shown below:

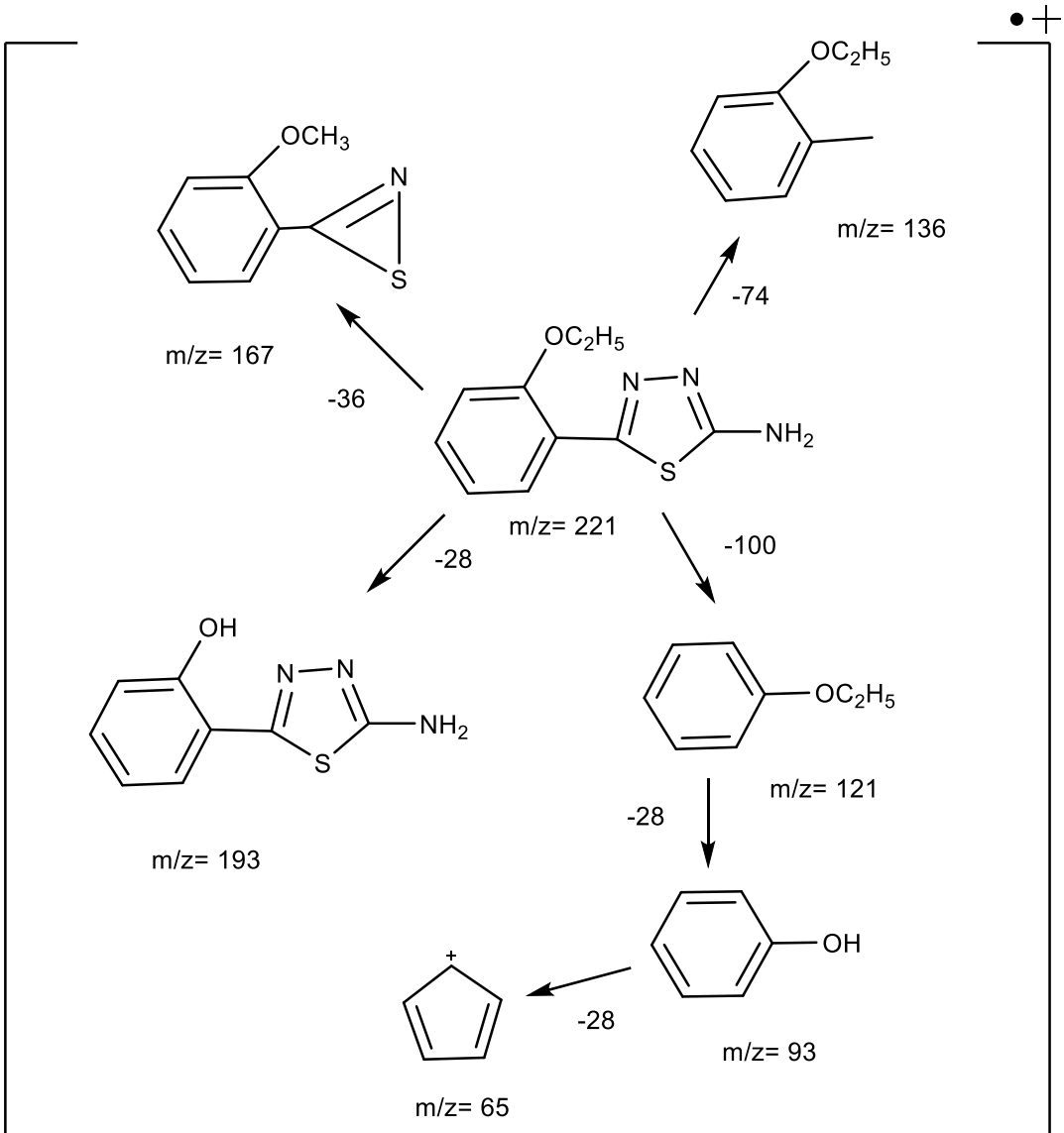


Mechanism(14)

Compound [28] was identified by using FT-IR spectrum which showed bands at 3387, 3282 cm^{-1}, 3088 cm^{-1}, (2966, 2850) cm^{-1},1624 cm^{-1} and 1164 cm^{-1} which due to NH_2, CH (arom.), CH (aliph.), C=N and C-O-C respectively.

The ^{1}H-NMR spectrum for [28] showed the following singlet signals, at δ 1.0 ppm, 2.5 ppm, 3.4 ppm, the multiplet signals at δ (6.8 - 7.8) ppm and at 10.9 ppm which attributed to CH_3, DMSO, CH_2 aromatic protons and for NH_2 proton.

The mass spectrum of compound [28] showed a characteristic fragmentation at m\z = (221, 193, 167, 136, 121, 93 and 65), as in the Scheme(28-1) below .


OCH3
N
S
m/z= 167
-36
OC2H5
m/z= 136
-74
OC2H5
N
N
NH2
S
m/z= 221
-28
-100
OH
N
N
NH2
S
m/z= 193
OC2H5
m/z= 121
-28
OH
m/z= 93
-28
m/z= 65

Scheme (28-1)

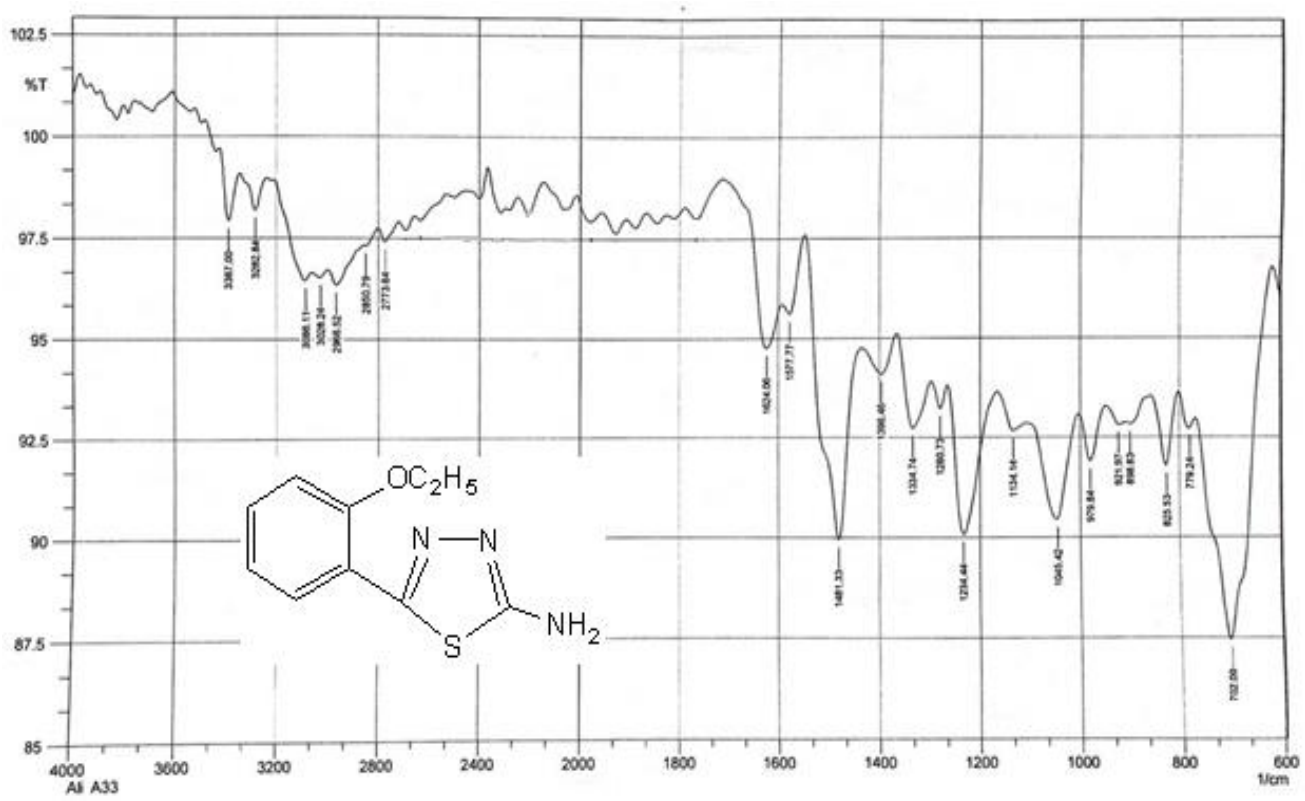


Figure (3.35) : FT-IR spectrum of compound (28)

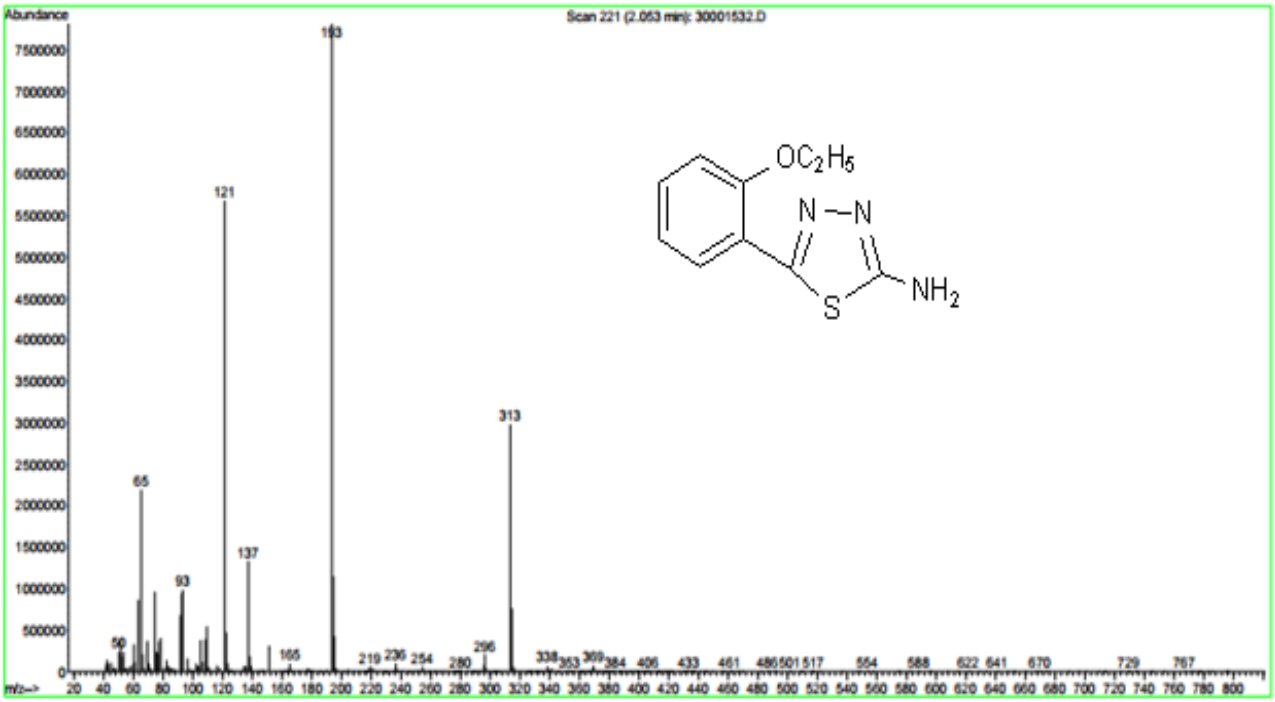
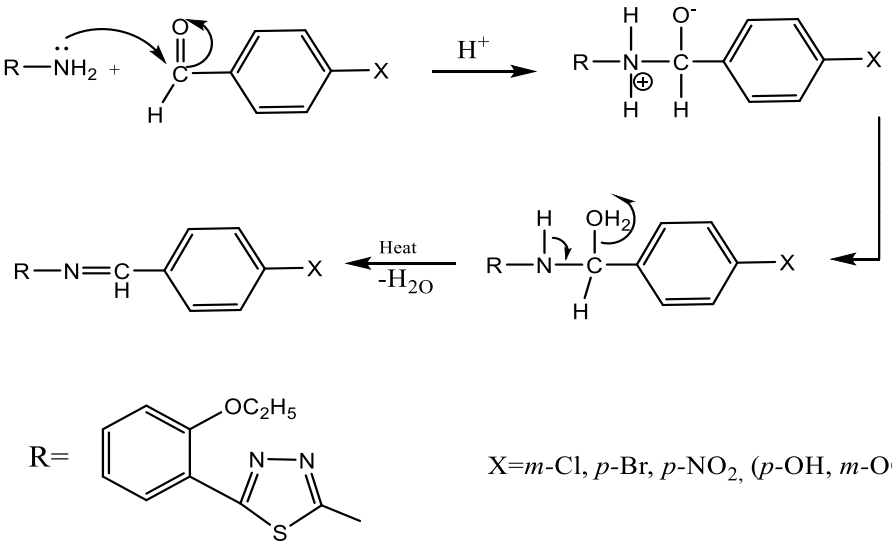


Figure (3.36) : Mass spectrum of compound (28)

3.5.3 Characterization of Schiff bases [29],[30],[31],[32],[33]:

Schiff bases was prepared by the reaction of m-chlorobenzaldehyde, P-N-N-Dimethylbenzaldehyde, p-bromobenzaldehyde, *p*-nitrobenzaldehyde, m-methoxy-p-hydroxybenzaldehyde, derivative with $POCl_3$ under refluxe condition . Below is the suggested reaction mechanism :



X=*m*-Cl, *p*-Br, *p*-NO_2, (*p*-OH, *m*-OCH_3, *p*-N-$(CH_3)_2$

Mechanism(15)

Compound [29] was identified by using FT-IR spectrum which showed bands at 3061 cm^{-1}, (2918, 2854) cm^{-1}, 1608 cm^{-1} and 1579 cm^{-1} which due to CH (arom.), CH (aliph.) and C=N (exo and endo) respectively.

Compound [30] was identified by using FT-IR spectrum which showed bands at 3049 cm^{-1}, (2914, 2860) cm^{-1}, 1614 cm^{-1} and 1575 which due to CH (arom.), CH (aliph.), and C=N (exo and endo) respectively.

Compound [31] was identified by using FT-IR spectrum which showed bands at 3053 cm^{-1}, (2951, 2866) cm^{-1}, 1693 cm^{-1} and 1683 cm^{-1} which due to CH (arom.), CH (aliph.) and C=N (exo and endo) respectively.

Compound [32] was identified by using FT-IR spectrum which showed bands at 3107 cm^{-1}, (2920, 2848) cm^{-1}, 1695 cm^{-1} and 1618 cm^{-1} which due to CH (arom.), CH (aliph.) and C=N (exo and endo) respectively.

The ^{1}H-NMR spectrum for [32] showed the following singlet signals, at δ 1.0 ppm, 2.50 ppm, δ 6.9 ppm, the multiplet signals at δ (7.0 – 8.4) ppm and 7.3 ppm which attributed to CH_3, DMSO, O-CH_2, aromatic protons and =CH respectively.

Compound [33] was identified by using FT-IR spectrum which showed bands at 3282 cm^{-1}, 3091 cm^{-1}, (2966, 2856) cm^{-1} , 1635 cm^{-1} , 1614 cm^{-1} and 1157 cm^{-1} which due to OH, CH (arom.), CH (aliph.), C=N (exo and endo) and C-O-C respectively.

The ^{1}H-NMR spectrum for [33] showed the following singlet signals, at δ 3.0 ppm, 2.5 ppm, 6.8 ppm, 6.9 ppm, the multiplet signals at δ (6.8 – 8.0) ppm, 8.7 ppm, 11.1 ppm which attributed to CH_3, DMSO, O-CH_2-CH_3, aromatic protons, =CH and OH respectively.

Compound [34] was identified by using FT-IR spectrum which showed bands at 3427 cm^{-1}, 3095 cm^{-1}, (2956, 2870) cm^{-1} and 1672 cm^{-1} which due to NH, CH (arom.), CH (aliph.), and C=N respectively.

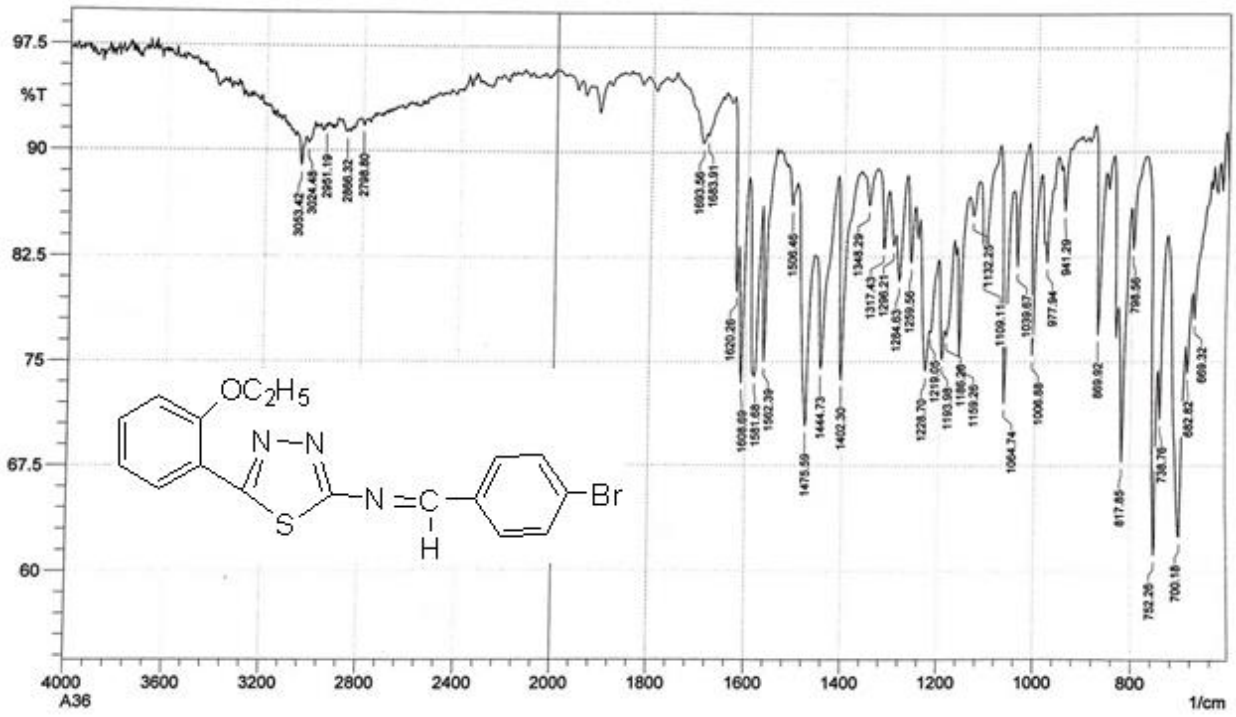


Figure (3.37) : FT.IR spectrum of compound (31)

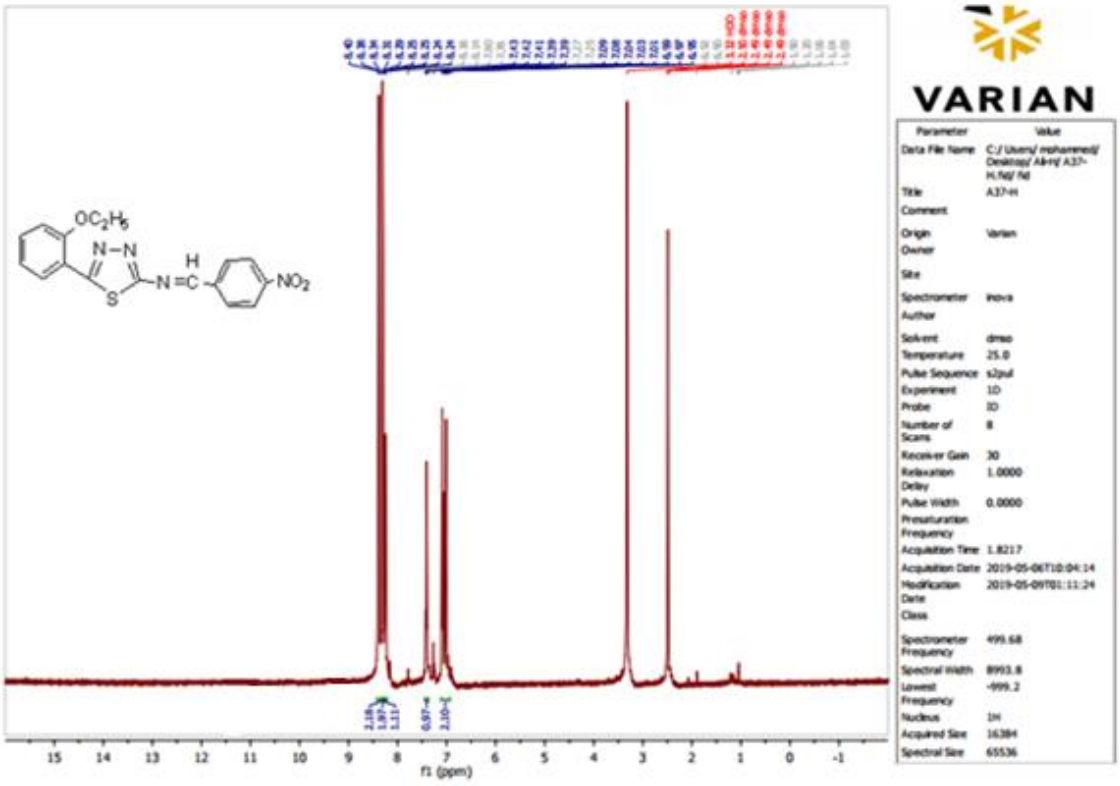


Figure (3.38) : ^{1}H-NMR spectrum of compound (32)

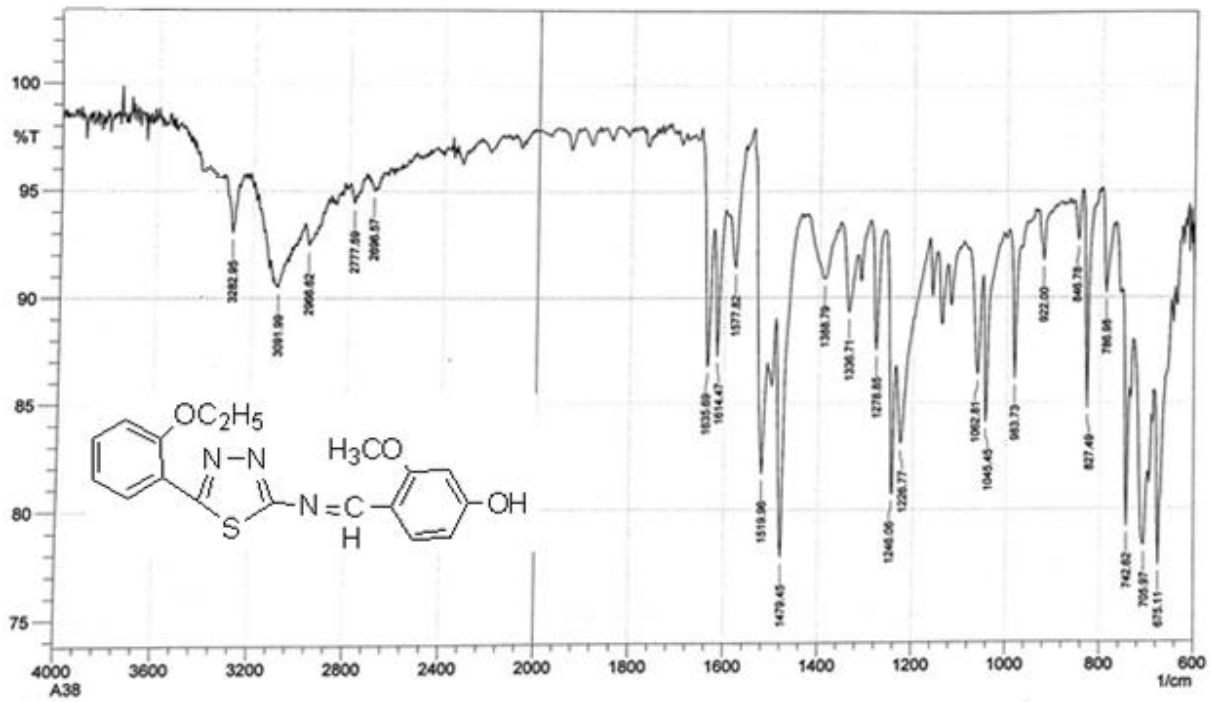


Figure (3.39) : FT.IR spectrum of compound (33)

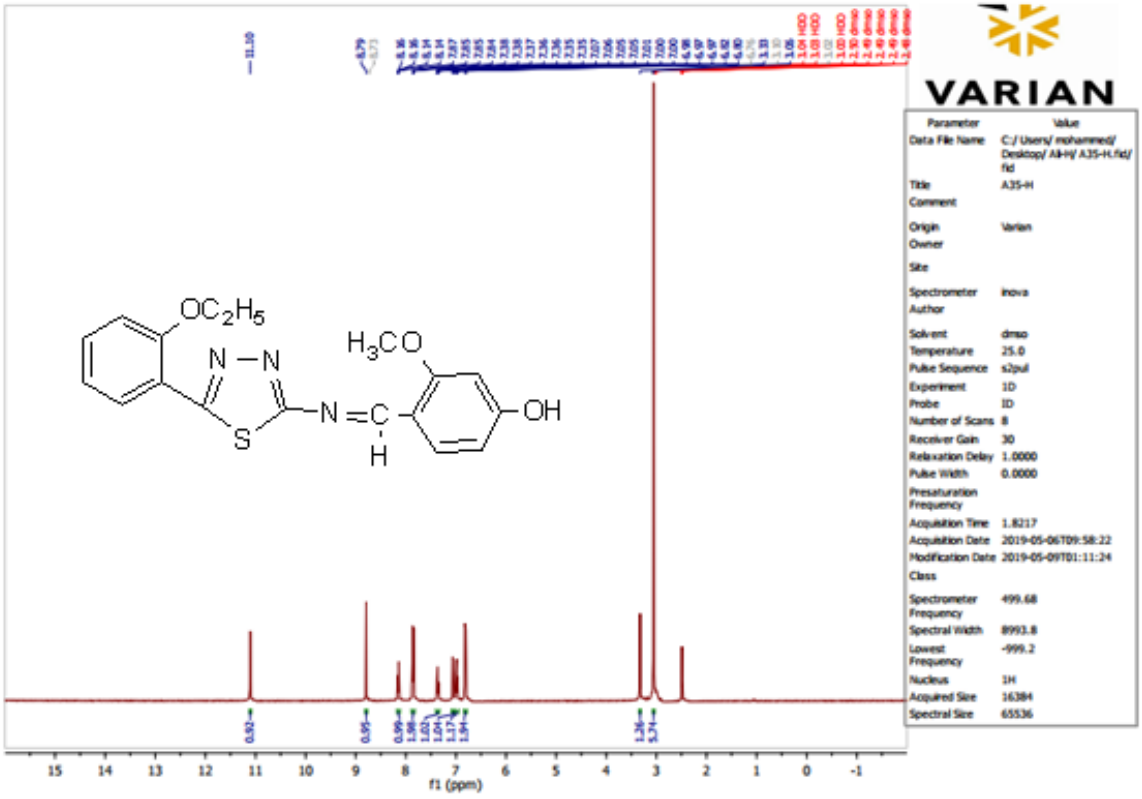
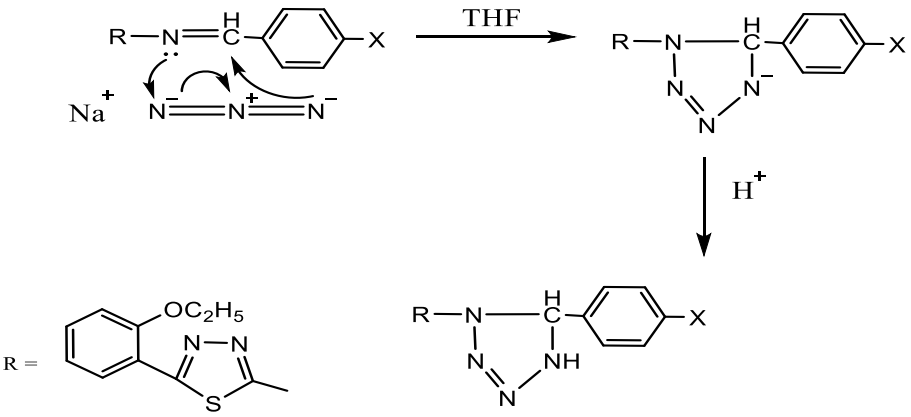


Figure (3.40) : ^{1}H-NMR spectrum of compound (33)

3.5.4 Characterization tetrazol [34],[35],[36],[37],[38]:

The following compounds [34-38] prepared by reaction of compounds [29-33] with sodium azide in THF. The suggested mechanism for the reaction is



Mechanism(16)

Compound [34] was identified by using FT-IR spectrum which showed bands at 3362 cm^{-1}, 3065 cm^{-1}, (2956, 2870) cm^{-1} and 1672 cm^{-1} which due to NH, CH (arom.), CH (aliph.), and C=N respectively.

Compound [35] was identified by using FT-IR spectrum which showed bands at 3171 cm^{-1}, 3049 cm^{-1}, (2918, 2800) cm^{-1} and 1614 cm^{-1} which due to NH, CH (arom.), CH (aliph.), and C=N respectively.

Compound [36] was identified by using FT-IR spectrum which showed bands at 3396 cm^{-1}, 3055 cm^{-1}, (2926, 2854) cm^{-1} and 1635 cm^{-1} which due to NH, CH (arom.), CH (aliph.), and C=N respectively.

Compound [37] was identified by using FT-IR spectrum which showed bands at 3103 cm^{-1}, 3057 cm^{-1}, (2922, 2848) cm^{-1} and 1618 cm^{-1} which due to NH, CH (arom.), CH (aliph.), and C=N respectively.

Compound [38] was identified by using FT-IR spectrum which showed bands at 3394 cm^{-1}, 3288 cm^{-1}, 3091 cm^{-1}, (2922, 2854) cm^{-1} and 1633 cm^{-1}, which due to OH, NH, CH (arom.), CH (aliph.), and C=N, respectively.

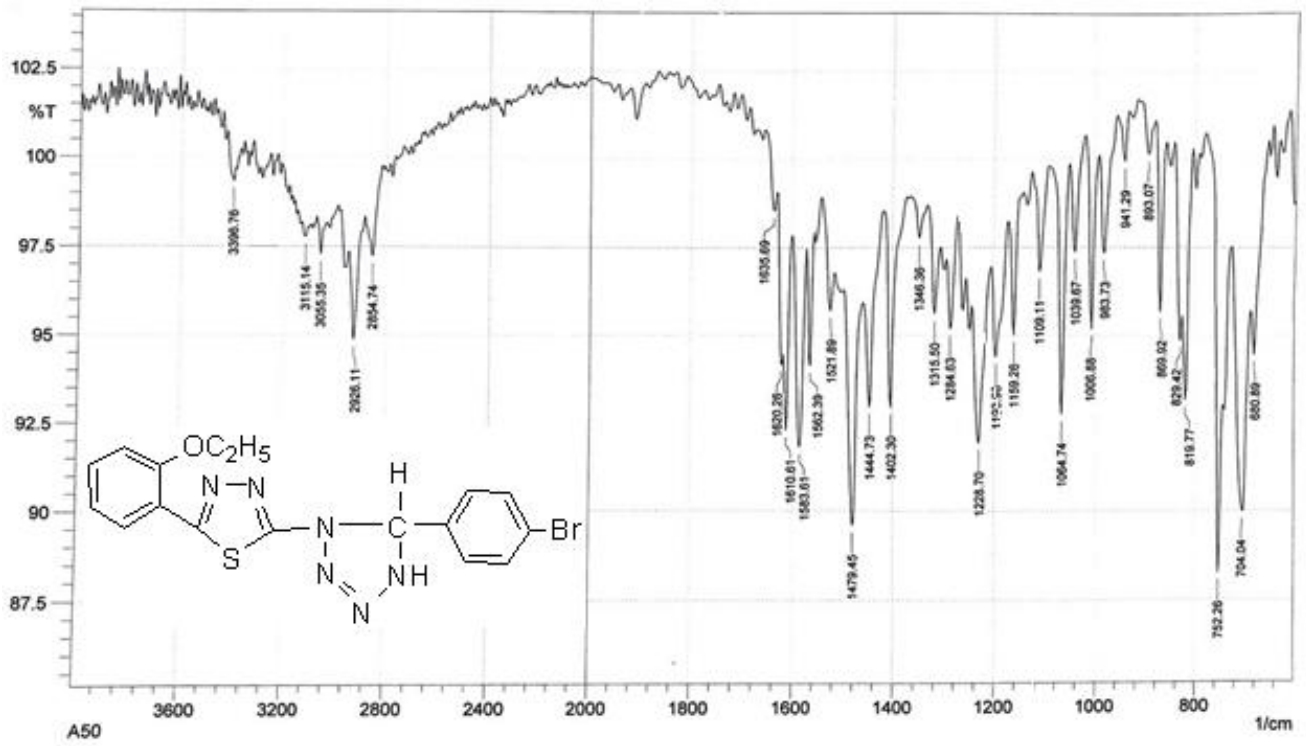


Figure (3.41) : FT.IR spectrum of compound (36)

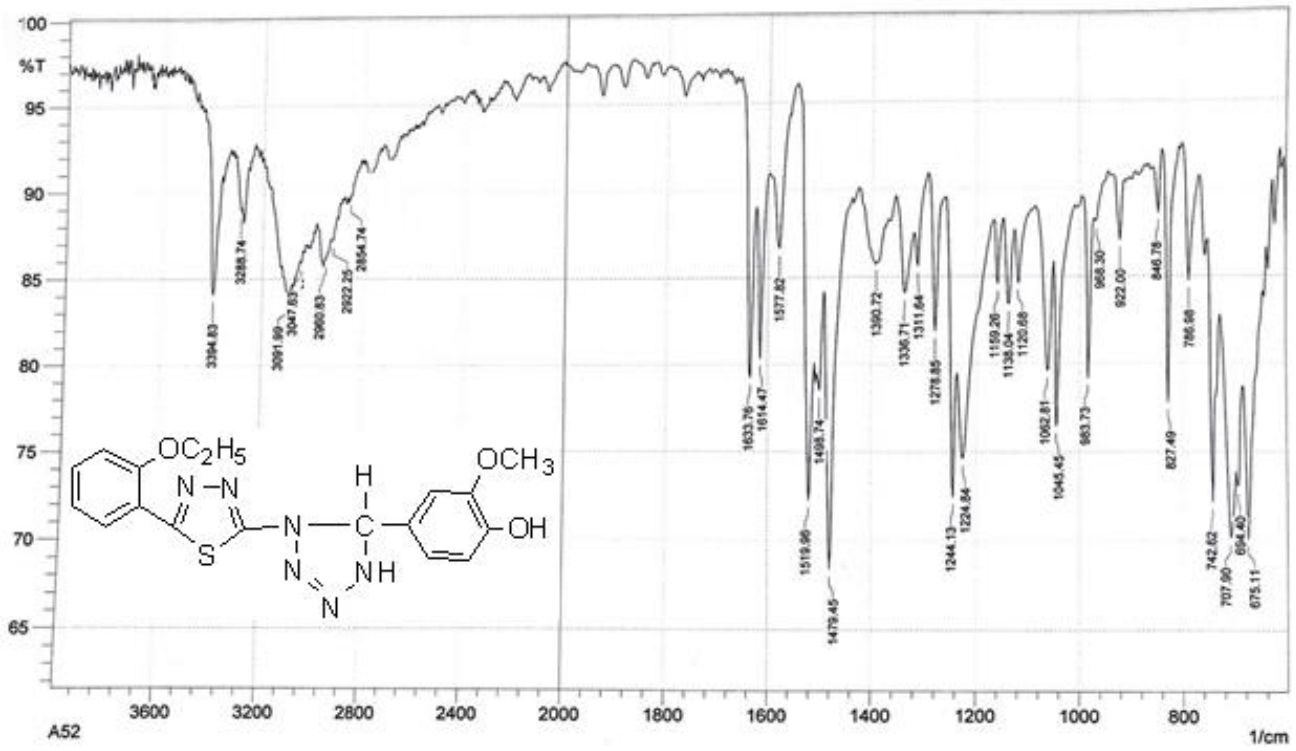


Figure (3.42) : FT.IR spectrum of compound (38)

3.7. Tables IR and ^{1}H-NMR for some of the prepared compounds:

Table (3.1) The IR characteristic bands of compounds (2 - 4)

Comp. No.			IR, KBr, υ, cm^{-1}				
	(NH)	(N-H_2)	(C-H) Ar.	(C-H) Aliph. Asy./sy.	(C=O)	C=N	(C=C) Asy./sy.
2	3317	---	Over lap	2991,2868	1710 ester	---	1645,1469
3	3329	3304, 3196	3096	2949,2862	1637 amid	---	1606,1467
4	3308	---	3036	2928,2872	1708 amid	1647	1595,1498

Table (3.2) The IR characteristic bands of compound (5 - 8)

Comp. No	IR, KBr, υ, cm^{-1}					
	(N-H)	(C-H) Ar.	(C-H) Aliph. asy. /sy.	(C=O)	C=C Ar.	Other Band
5	3344	3078	2928,2860	1651 amid	1570,1496	----
6	3344	3068	2912,2858	1647 amid	1568,1496	----
7	3342	3068	2910, 2827	1647 amid	1595,1496	1568,1384 C-NO_2
8	3150	3050	2975,2915	1725 amid	1568,1471	----

Table (3.3) The IR characteristic bands of compound (9 - 12)

Comp. No	IR, KBr, υ, cm^{-1}							
	N-H_2	**(N-H)**	**(C-H) Ar.**	**(C-H) Aliph. asy. /sy.**	**(C=O)**	**(C=N)**	**(C=C)**	**(C=S)**
9	3446	3311	3067	2916,2866	1647	----	1595,1452	----
10	-----	3313	3043	2983,2856	1683	1600	1577,1450	
11	3435	3113	Over lap	2931,2752	1678	----	1629,1477	1149
12	----	3308	3010	2974,2856	1647	1595	1575,1469	----

Table (3.4) The IR characteristic bands of compound (13 - 19)

Comp. No	IR, KBr, υ, cm^{-1}								
	(OH)	**(NH_2)**	**(N-H)**	**(C-H) Ar.**	**(C-H)Aliph. asy. /sy.**	**(C=O)**	**(C=N)**	**(C=C) Ar.**	Other Bands
13	---	----	3207	3066	2989,2868	1651 amid	----	1600,1452	1184 C=S
14	---	----	3344	3066	2912,2729	----	1651	1597,1473	----
15	---	----	3346	3068	2941,2858	----	1651	1595,1452	----
16	3380	----	3317	3059	2916, 2858	1774 amid	1593	1562,1489	----
17	----	3223, 3170	Over lap	3059	2933,2856	1645 amid	----	1575,1442	1184 C=S
18	----	----	3305	3062	2947,2866	1647 keton	1573	1504,1442	2573 S-H
19	----	----	3383	3098	2993,2858	1778 ester	1643	1608,1469	----

Table (3.5) The IR characteristic bands of compound (20 - 25)

Comp. No	IR, KBr, υ, cm^{-1}					
	(N-H)	(C-H) Ar.	(C-H)Aliph. asy. /sy.	(C=N)	(C=C) Ar.	Other Bands
20	3207	Over lap	2972,2856	1645	1626,1456	1518,1317 C-NO_2
21	3200	3032	2910,2854	1662	1608,1456	----
22	3209	3053	2974,2854	1645	1626,1456	740 C-Cl
23	3273	3093	2910, 2852	1653	1591,1483	----
24	3275	3062	2924,2851	1666	1616,1465	----
25	3363	3055	2974,2808	1689	1523,1485	1620 (C=C)aliph.

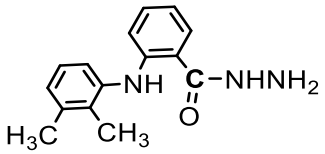
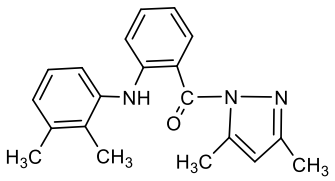
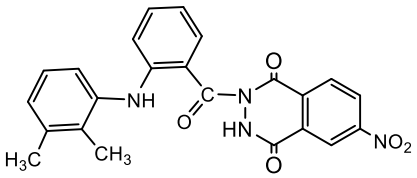
Table (3.6) The IR characteristic bands of compound (27 - 33)

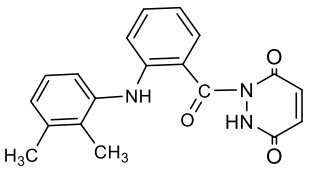
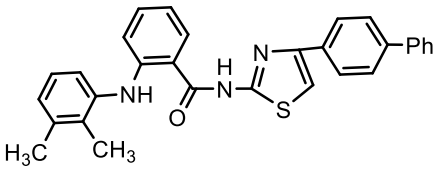
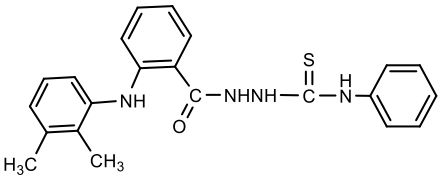
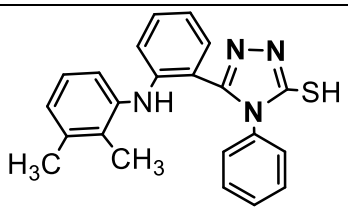
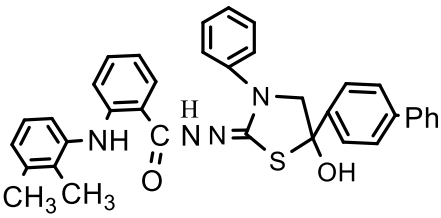
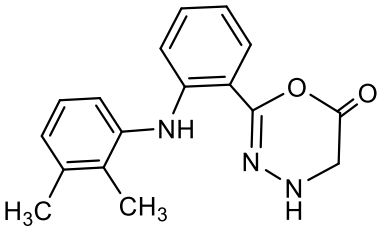
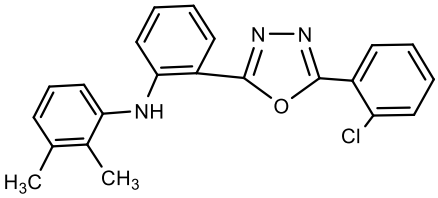
Comp. No	IR, KBr, υ, cm^{-1}							
	(N-H_2)	(O-H)	(C-H) Ar.	(C-H)Aliph. asy. /sy.	(C=O)	(C=N)	(C=C) Ar.	Other Bands
27	----	3226 Carbo.	Over lap	2966,2850	1743 Carbo.	-----	1651,1477	----
28	3387, 3282	----	3088	2966,2850	---	1624	1577,1481	----
29	----	---	3061	2918, 2854	---	1608(exo) 1579(endo)	1506,1473	698 C-Cl
30	----	---	3049	2914,2860	---	1614(exo) 1575(endo)	1533,1471	----
31	----	---	3053	2951,2866	---	1693(exo) 1683(endo)	1620,1475	682 C-Br
32	----	---	3097	2920,2848	---	1695(exo) 1618(endo)	1593,1473	1514,1342 C-NO_2
33	----	3282	3091	2966,2852	---	1635(exo) 1614(endo)	1577,1479	----

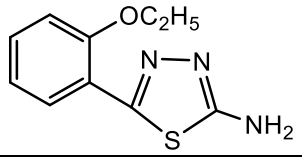
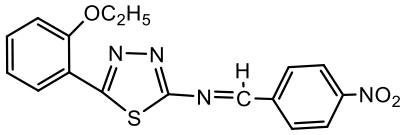
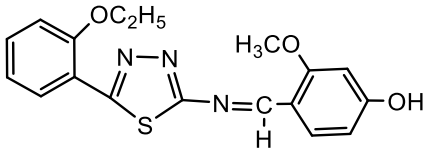
Table (3.7) The IR characteristic bands of compound (34 - 38)

Comp. No	IR, KBr, υ, cm^{-1}						
	(O-H)	(N-H)	(C-H) Ar.	(C-H)Aliph. asy. /sy.	(C=N)	(C=C) Ar.	Other Bands
34	---	3362	3065	2956,2870	1672	1650,1473	744 C-Cl
35	---	3171	3049	2918,2800	1614	1573,1469	----
36	---	3396	3055	2926, 2854	1635	1583,1479	680 C-Br
37	---	3103	3057	2922,2848	1618	1593,1473	1514,1334 $C-NO_2$
38	3394	3288	3091	2960,2854	1633	1577,1498	1120,1159 C-O

The following table (3.8) shows the spectrum of ^{1}H-NMR for some of the prepared compounds.

Comp. No.	Structure	^{1}H-NMR Spectrum, δ ppm, 500MHz
3		2.12, ppm (s,3H,CH_3), 2.2 ppm (s,3H,CH_3), 6.5 - 7.1 ppm (m,7H,H-Ar), 6.8 ppm (s,2H,NH_2),7.9 ppm(s,1H, NH)
4		2.0 ppm (s,3H, CH_3), 2.1 ppm (s,3H,CH_3), 2.2 ppm (s,3H,CH_3) , 6.6 - 7.8 ppm (s,8H,H-Ar), 9.4 ppm (s,1H, NH)
5		2.0, ppm (s,3H,CH_3), 2.2 ppm (s,3H,CH_3), 6.6 - 7.6 ppm (m,10H,H-Ar), 9.4 ppm (s,1H,NH)

7		2.0, ppm (s,3H,CH_3), 2.2 ppm (s,3H,CH_3), 6.6 - 7.6 ppm (m,9H,H-Ar), 9.4 ppm (s,1H,NH)
12		2.2, ppm (s,3H,CH_3), 2.6 ppm (s,3H,CH_3), 6.6 - 7.8 ppm (m,11H,H-Ar), 9.1 ppm (s,1H,NH)
13		2.0, ppm (s,3H,CH_3), 2.2 ppm (s,3H,CH_3), 6.6 - 7.8 ppm (m,12H,H-Ar), 9.4 ppm (s,1H,NH)
15		2.0, ppm (s,3H,CH_3), 2.2 ppm (s,3H,CH_3), 6.6 - 7.8 ppm (m,11H,H-Ar), 9.4 ppm (s,1H,NH), 12.8 ppm (s,1H,SH)
16		2.0, ppm (s,3H,CH_3), 2.2 ppm (s,3H,CH_3), 2.6 ppm (s,2H,CH_2), 5.3 ppm (s,1H,OH), 6.7 - 8.2 ppm (m,21H,H-Ar), 9.2 ppm (s,1H,NH)
19		2.2, ppm (s,3H,CH_3), 2.6 ppm (s,3H,CH_3), 3.4 ppm (s,2H,CH_2) 6.7 - 8.2 ppm (m,8H,H-Ar), 9.8 ppm (s,1H,NH)
22		2.40, ppm (s,3H,CH_3), 2.47 ppm (s,3H,CH_3), 6.6 - 8.1 ppm (m,11H,H-Ar), 10.4 ppm (s,1H,NH)

28		1.0, ppm (s,3H,CH_3), 3.4 ppm (d,2H,O-CH_2), 6.8 - 7.8 ppm (m,4H,H-Ar), 10.9 ppm (s,2H,NH_2)
32		1.0, ppm (s,3H,CH_3), 6.9 ppm (t,2H,OCH_2), 7.0 – 8.4 ppm (m,8H,H-Ar), 7.3 ppm (s,1H,=CH)
33		3.0, ppm (s,3H,CH_3), 6.8 ppm (s,2H,OCH_3), 6.9 ppm (m,2H,OCH_2), (6.8 - 8.0) ppm (m,7H,H-Ar), 8.7 ppm (s,1H,=CH), 11.1 (s,1H, OH)

3.8. Biological Activity:

This section includes the antibacterial activity of some prepared compounds. Using a good propagation method in the laboratory against two types of pathogenic strains of bacteria, these activities were identified for Staphylococcus (G+), E.coli (G-). The results obtained showed that some of these compounds have a measurable activity, Table (3-10).

Table (3.3) below: Some antibacterial activities of measured compounds.

Comp. No.	**Sample No. (In image)**	***E.coli* *(G-)/mm***	***Staphylococcus* *(G+)/mm***
6	**5**	20	15
8	**3**	18	17
13	**4**	20	20
14	**6**	15	25
20	**2**	15	15

24	**7**	15	15
25	**1**	15	22

Key to symbols:

Highly active = (20 – 25) mm . / Moderately active = (15-20 mm).

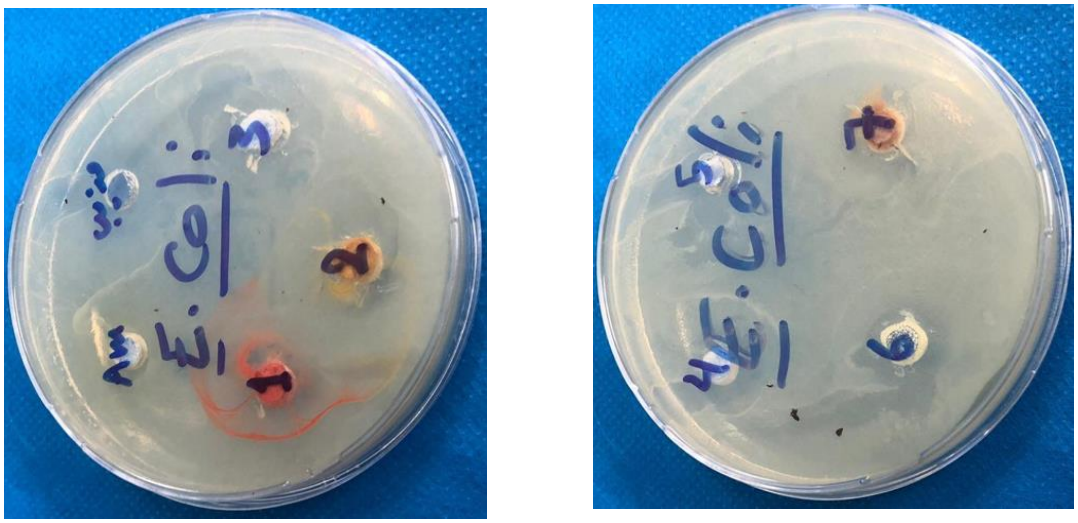


Figure (3.4) shows the effect of some prepared compounds (8,20,25,13,6,14,24) gainst E.coli

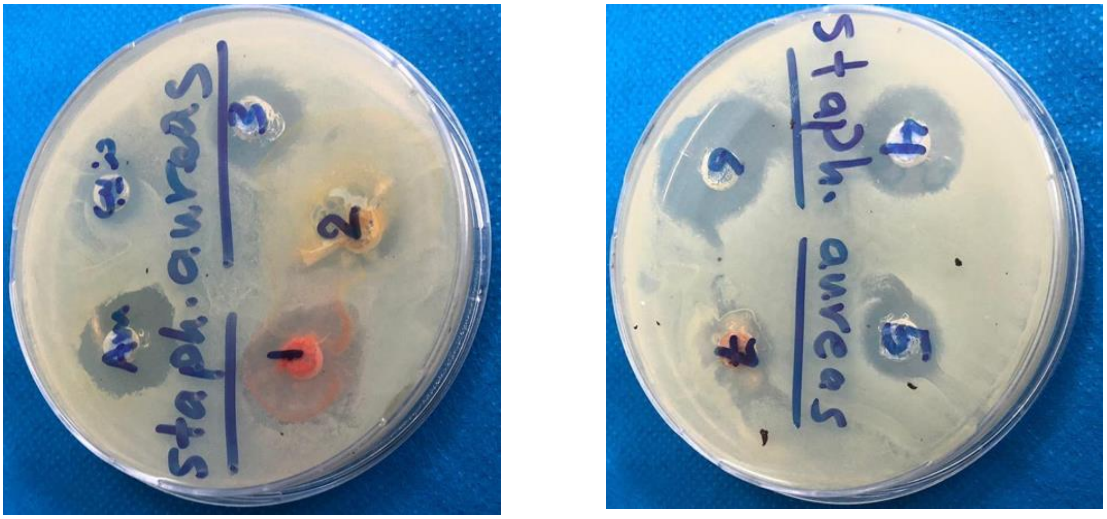


Figure (3.5) shows the effect of some prepared compounds (8,20,25,13,6,14,24) against Staphylococcus aureus

Conclusions

In this study, was prepared heterocyclic compounds five and six rings from the reaction of mefenamic acid and salicylic acid with aldehyde derivatives. Both the analytical with spectral data (FT-IR, ^{1}H-NMR and Mass spectrum) prepared derivatives fully consistent with the proposed structure; the biological activity of some prepared compounds, As well :

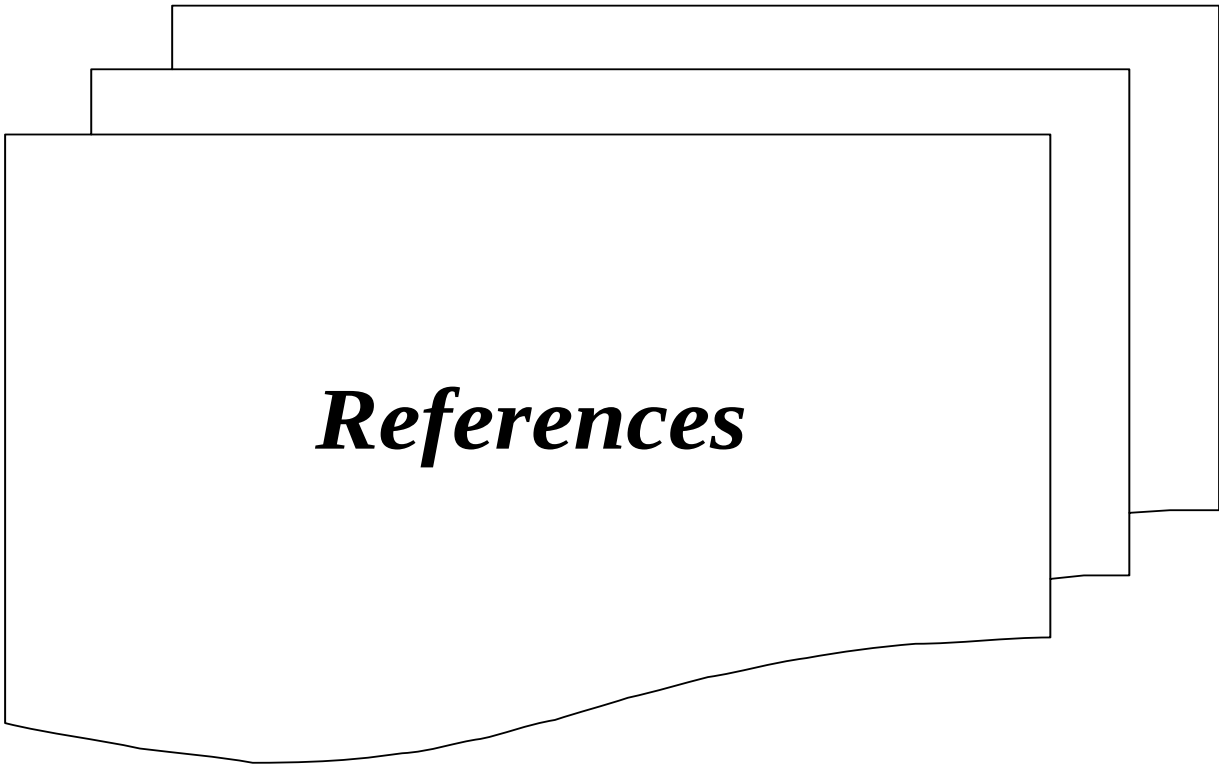
1- The new hetrocyclic compound with aromatic units are high melting points then the other .

2- Some compounds (8,20,25,13,6,14,24) are hightly effective against staphylococcus while no effect agains E.coli.

Recomendations for future work:

- Pharmaceutical study of the synthesized compounds in vivo.
- Study of toxicity of the synthesized compounds.
- Study of the liquid crystalline of the synthesized compounds.
- Study of the superficially of the synthesized compounds.
- Study of mutations polymeric of the synthesized compounds.

The Study of the conductivity of the synthesized compounds



References

1- F. Russo, G. Romeo, and N. Santagati, Eur. J. Med. Chem. 29, 569(1994).

2- B. Vashti, D. Mehta, and D. Shah, Indian J. Chem. 34B, 802 (1995);(b)

3- K. Patel and A. Mehta, Eur. J. Chem. 3, 267(2006).

4- P. Y. Bruise , "Organic Chemistry", 2nd ed., Viacom company (1998).

5- R. M. Acheson, "An Introduction to the Chemistry of Heterocyclic Compounds", 2nd Ed., Wiley International Edition, New York, London (1990).

6- Campaign E. ; J . Chemical Education . ,Vol. 6,p. 860 (1986) .

7- E. pomarnacka and A.kornicka , Acta poloniae pharmaccutica-Durg Researsh ,55(4) ,297-304 (1998).

8- R.paprocka , B. modzelewska-banachiewics , M.wiese ,A. eljaszewicz and J.michalkiewicz , Acta poloniae pharmaccutica-Durg Researsh ,69(6) , 1390-1394 (2012).

9- N.Verma, B.S.Verma, V.chawla and O.P.Malik, Ind . J.Chem, 35B,688-691 (1996).

10- Ibtisam khalifa Jassim and Aisha mohammed Ali, Jornal Education scientific studies – chem. sci. vol. 12, N. 3, IssN 2413- 4759(2018)

11- G.R.Rania , K.Mogilaiah and Screenivasula ,Ind.J.Chem, 35B, 339-344 (1996).

12- L. Vinay Kumar , P. Jagan Naik , T. Chandrasekhar, A. Babul Reddy, M. Karuna sree N. Penchalaiah and G. Narayana Swamy, Der Pharma Chemica ,4(2) , 676-677 (2012).

13- Zena A.Razak, Msc. Thesis. Baghdad University (2016) .

14- Sara .salam, Msc. Thesis . Tikrit University (2016) .

15- Enaam F, Msc. and Ibtisam k.jassim, j. pharma. Sci &Res, vol. 10(12), 3036-3040 (2018) .

16- J. A. Joule, K. Mills, and G.F. Smith, "Heterocyclic Chemistry" 3rd ed, Wiley p 452 (2003).

17- X.Ouyang, E.L.Piatniksi, and P.Vatee., J.Biorg and Med.Lett 16,iss 5,1191-1196 (2005).

18- H.R.Ajak,D.K.Murli, and P.Mishra.,J.Phama,Soc.Japan., 127(10) 1757 -1764 (2007).

19- Ali. Talib, ph,D. Thesis, Baghdad University, (2019) .

20- Enaam F, Msc. and Ibtisam k.jassim, j. pharma. Sci &Res, vol. 10(9), 2297-2304 (2018).

21- S. Cao, Journal of Fluorine Chemistry, 117, 63-66 (2002).

22- A. K. Mansour , Molecules, 8, 744-755 (2003).

23- Gabriel A.jaber and Ibtisam k.jassim, j. pharma. Sci of Res, vol. 11(3), 688-691 (2019) .

24- Amal Abd Al-Rada, Ibtisam khalifa Jassim, Journal of Global pharma Technology, vol. 11, Issue 02 (314-320) (2019).

25- Maysoon Tariq Tawfiq, Ibtisam k. Jassim and Fatell Aoliewe Hadi, Journal of Education and scientific studies – chem. Sci. vol. 12, No. 3, ISSN 2413-4759 (2018) .

26- A.N.Mayekar.,International, of chem.,2No1,38-49 (2010).

27- A.Almasirad., J.Acta.Chem.Slov 54,317-324 (2007).

28- A.O.Maslat, and M.Abusaad J.pharmacology,54,55-59 (2002).

29- Y.Zhang,R.Qiao, and R.Feixu.,J.Chinese,Chem. Soc,4,369-374 (2002).

30- H. Sciff., Ann., 131, 118 (1864).

31- R. W. Layer, Chem. Rev., 63, 489 (1963).

32- S. Patai. "The Chemistry of the Carbon-Nitrogen Double Bond", John Wiley and Sons, New York, PP. 149, 64, 67, (1970).

33- D. Gargiulo, N. Ikemoto, J. Odingo, N. Bozhkova T. Iwashita, N. Berova and K. Nakanishi., J. Am. Chem.Soc., 116, 3760 (1994).

34- Y. Ali, M. J. A. Habib and K.W. Al-Janabi, Iraqi J. Chem., 21, 104 (1996).

35- E. M. Hodnett and J. Taim., J. Med. Chem., 14, 115(1971).

36- J. D. Roberts and M. C. Casserio, "Basic Principles of Organic Chemistry", W.A. Benjamin P. 335, (1965).

37- A. Varshney and J. P. Tenden, Proc. Indian Acad. Sci. Chem., 97, 141, (1986).

38- V. Mishra, D. K. Saksenaad and M. C. Jatn, Synth. React. Inorg. Met-Org. Chem., 17, 987, (1987).

39- prof.Dr.Ibtisam Khalifa Jassim and Aisha Mohammed, Journal of Education and Scientific Studies-Chem. Sci.Vol.12,3 (2018) .

40- a) R. B. Moffett and W.M. Hoehn., J. Am. Chem. Soc., 69, 1792(1947); b) M. Freifelder., J. Org. Chem., 31, 3875, (1966).

41- R. Grewe, R. Hamann, G. Jacobsen, E. Nolte and K. Riecke, Ann. Chem., 581, 85 (1953).

42- Muhanned T. Mahmoud, Ibtisam k. Jassim and Mohanned A. Mahmoud, J. Baghdad for science, 10(3) (2013) .

43- M. M. Sprung, Chem. Rev., 26, 297, (1940).

44- E. T. Bakir, I. K. Jassim and Wissan. K. Jassim., J. of Al-Nahrain University Science, 9 (1), PP. 21-28 (2006).

45- Ali T. Bader, Basim I. Al-Abdaly and Ibtisam k. Jassim, J. pharm,sci& Res. Vol. 11(5), 2062-2073 (2019) .

46- F. Bergman., J. Am. Chem., Soc., 60, 2811, (1938).

47- M. R. Snyder, R.B. Hasbrouck and J. F. Richardson., J. Am. Chem., Soc., 61, 3558, (1939).

48- Ranen HashimRida, Maysoon Tariq Taefiq and Ibtisam k. Jassim,J. pharma, sci &Res. Vol.11(14), 1548-1557 (2019) .

49- N. B. Ahasan and Md. R. Islam, Bangladesh J. Pharm., 2, PP. 81-87 (2007).

50- V. V. Dabholkar and R. P. Gavande, J. Serb. Chem. Soc., 68, 10, P. 723 (2003).

51- Asif M, Singh A, Lakshmayya B, "In-vivo Anticonvulsant and In-vitro Antitubercular Activity of methyl Indole Derivative of some 6-aryl-4, 5-Dihydropyridazin-3(2H)-ones and their Expected Anticonvulsant Mechanisms", Iranian Journal of Pharmaceutical Sciences, 9(1), 67-80, (2013).

52- I. K.Jassim , J. of Kerbala of Pharmaceutical Sciences , Number 2, (2011).

53- F. Giornal , S. Pazenok , L. Rodefeld , N. Lui , J. P. Vors and F. R. Leroux , Journal of Fluorine Chemistry, 152 (2013)

54- M. A. P. Martins, P. Beck, P. Machado, S. Brondans, S. Moura, N. Zanatta, H. H. Bonacorso and A. F. C. F'lores, J. Braz. Chem. Soc., Vol. 17, No. 2, PP. 408-411 (2006).

55- N. A. Salih, Turk. J. Chem., 32, PP. 229-235 (2008).

56- B. Iddon, and P. A. Lowe, Spec. Period. Rep., "Organic Compounds", Chapter 12 (1977).

57- K. Bansal, "Heterocyclic Chemistry", 4th ed., New Delhi, Vol. 10, P. 483 (2007).

58- Kawther A. Alheety, Wissam Kalifa Jassim and Ibtisam Kalifa Jassim, J. pharma. Sci . & Res. Vol. 11(9), 1582-1588 (2019) .

59- L. Forlani, L. Lunazzi, and A. Medici, Tet. Letters, P. 4525 (1977).

60- T. S. Jagodzinski, Chem. Rev., Vol. 103, P. 197 (2003).

61- A. M. Al-Azzawi and K. K. Hammud, Department of Chemistry, College of Science, University of Baghdad, Kerbala Journal of Pharmaceutical Sciences, Number 5, (2013).

62- R. M. Ansidei, and G. Travagli, Gazz. Chem. Ital., Vol. 31, P. 680 (1941).

63- J. V. Metzger, "Thiazole and its Derivatives", John Wiley and Sons, New York, PP. 395-399 (1958).

64- Kawther A. Al heety, Wessam K. J. and Ibtisam K. J, J. Pharm. Sci & Res. Vol. N(9), 1582-1588 (2019) .

65- R.Mills, J. Am. Chem. Soc.,80, 3719 (1959).

66- Y. Iizawa, K. Okonogi, R. Hayashi, T.Iwahi, T.Yamazaki, A.Imada , Therapeutic effect of cefozopran (SCE-2787), a new parenteral cephalosporin, against experimental infections in mice. Antimicrob Agents Chemother;37:100–105,(1993) .

67- N. Demirbas, European Journal of Medicinal-Chemistry, 39, 793 (2004).

68- A. A. Aly and R. EL-Sayed, Chem. Pap. 60 (1), 56-60 (2006).

69- A. Farghaly, E. D. Clercq and H. El-Kashef, ARKIVOC, (X) 137-151 (2006).

70- A. A. Ahmed, College of Education (Ibn Al-Haitham) of the University of Baghdad , (2011).

71- P. Niu, J. Kang, X. Tian, L. Song, H. Liu, J. Wu, W. Yu, J. Chang, J. Org. Chem., 80, 1018-1024, (2015).

72- D. Barton and W.D. Oills, "Comprehensive Organic Chemistry" ed. P. G. Sammes, 4, 357 (1979).

73- H. E El Ashry , A. A. Kassem and M. H. Abdel Hameed , Carbohydr. Res., 344,725-733(2009).

74- M. A. Isloor, B. Kalluraya and P.Shetty, Eur. J. Med. Chem., 44, 3784-3787 (2009).

75- N. Foroughifar , A. Mobinikhaledi , S.Ebrahimi , H.Moghanian, B. A. M. Fard and M. Kalhor, Tetrahedron Lett., 50, 836-839 (2009).

76- B. Chai , X. Qian, S.Coa, H. Lui and G. Song, ARKIVOC, (ii), 141-145 (2003) .

77- M. Sztanke , T. Tuzimski , J. Rzymowska , K. Pasternak and M.Kandefer-Szerszen, Eur. J.Med. Chem. 43, 404-419 (2008).

78- J. Liu, L.Li, H. Dai, Z. Liu and J. Fang, J. Organomet. Chem., 691, 2686-2690 (2006).

79- X. Qian, H. Yu, J.Liu, B. G.Dai, Z.Qin, X. Zhang, T.Wang and J. Fang, Arkivoc , (ii), 201-210 (2009).

80- M. Nath, Sulaxn, X.Song, G. Eng and A. Kumar, Spectrochim. Acta, Part A, 70,766 -774(2008).

81- H. Emilsson, J. Heterocyclic Chem., 26, 1077 (1989).

82- K. Zamani , K. Faghihi, M. Reza Sangi and J. Zolgharnein . Turk J Chem , 27 , 119 – 125 (2003).

83- S. Chandaa, Y. Baravaliaa and S. Balujab , Scholars Research Library Archives of Applied Science Research, , 2 (3), 117-126 (2010).

84- D. Sahin, H. bayrak , A. dem˙irbas and N. dem˙irbas¸ Turk J Chem 36, 411 – 426 (2012).

85- S. M. El Rayes, 13rd international Electronic conferenceone synthetic chemistry (ECSOC-13) ,1-7 (2009).

86- S. Jadhav , M. rai, L. Khillare and A. Durrani , Asian Journal of Chemistry , 22(6), 4245-4248 (2010).

87- H . Kumar and Neena ,J. Chem. & Cheml. Sci. ,1 (1) , 1-19 (2010).

88- S. Khanage, P .Mohite , R. Pandhare and A. Raju. Marmara Pharmaceutical Journal 16 134-140 (2012).

89- M. R. Shivanand , T.B.Nayanbhai , Bheemachari and R. H. Udupi, Journal of Chemical and Pharmaceutical Research, 4(2),1151-1159 (2012).

90- D. R. Godhani , D. B. Sanja and A. M. Sanghani , Journal of Chemical and Pharmaceutical Research, 5(1), 240-243 (2013).

91- A. W. Erian, S. M. Sherif and H. .M. Gaber , Molecules, 8, 112 (2003).

92- A. Wahe , H. Goker , S. Ozden, H. Karatas and S. Yildiz , Arch. Pharm. Pharm. Med. Chem.,337,556 (2004).

93- H. Bakhite, S. Ozden, H. Karatas and S. Yildiz, Arch. Pharm. Pharm. Med. Chem.,337,556 (2004).

94- H. Balaan, A. Chimirri, S. Ferro and P. Monfort, ARKIVOC, V, 147 (2006).

95- A.W. Hoffmann, Ber. , 13, 8 (1880).

96- S.Gumus, "A computational study on substituted diazabenzenes". Turk J Chem 35: 803–808. (2011).

97- Mansur Nassiri Koopaeia, Mohammad Javad Assarzadeh, Ali Almasirad, Seyedeh Farnaz Ghasemi-Niri, Mohsen Aminic, Abbas Kebriaeezadeh, Nasser Nassiri Koopaeib, Maryam Ghadimi and Arash Tabei, "Synthesis and Analgesic Activity of Novel Hydrazide and Hydrazine Derivatives", Iranian Journal of Pharmaceutical Research, 12 (4) (2013).

98- Ahmad Walid Mohammed, M.Sc. Thesis, "Synthesis of new heterocyclic compounds and evaluation of biological activity for some of them", Education for women Tikrit University, Iraq, (2015).

99- Ibtisam Khalifa Jassim and Aisha Mohammed, Journal of Education and Scientific Studies-Chem. Sci.Vol.13,2,November (2018).

100- S.S.Khalel, MSc. Thesis, University of Tikrit,for Women,College of Education (2016).

101- Asif M, "Analgesic Activity of Some 6-Phenyl-4-Substituted Benzylidene Tetrahydro Pyridazin-3(2H)-Ones", Global J. Pharmacol, 5(1)18-22 (2011).

102- prof.Dr.Ibtisam Khalifa Jassim and Aisha Mohammed, Journal of Education and Scientific Studies-Chem. Sci.Vol.12,3 (2018).

103- Ibtisam Khalifa Jassim,Intisar Yahyia Mohamme, Zena Razak and Wissam Khalifa Jassim,International Journal of Chemical Environmental & Biolojical Sciences Volume 6 Issue 1, (2018).

104- Sahar Balkit Hussein, M.Sc.Thesis, College of Science,AL-Nahrain University (2007).

105- A. H. Mohammad, M.Sc.Thesis, College of Science,AL-Nahrain University (2007).

106- N. Abdel-Razaak,M.Sc.Thesis, College of Science,AL-Nahrain University (2007).

107- I. K.Jassim , S. A. Jabbar and A. W. Mohammed, Kerbala Journal of Pharmaceutical Sciences, No. 10 , (2015).

108- Enaam F.M., Prof. Dr. Ibtisam K.J., J. pharm. sci, Res. vol.10(9) (2018).

109- I. K. Jassim , S.A. Jabbar and A.W. Mohammed, , Kerbala Journal of Pharmaceutical Science, No.10, (2015).

110- Malak, N. S. MSc.Thesis, Baghdad University,Iraq."Synthesis and Characterization of New Monemers and Polymers Containing Hetero-

cyclic Rings and Studying Their Conducting Properties and Biological Activity" (2012).

111- A. W. Mohammed, M.Sc. Thesis, Tikrit University, College of Education for women , (2015).

112- M. A. Al-Nemi, Ph.D. Thesis, Baghdad,Iraq, (2012).

113- J. Anderson and Dovid, C. A., Vol. 112, 178982r (1990).

114- A. S. Shubrem, M. Sc. Thesis College of Science, Al-Nahrain University, Iraq (2006).

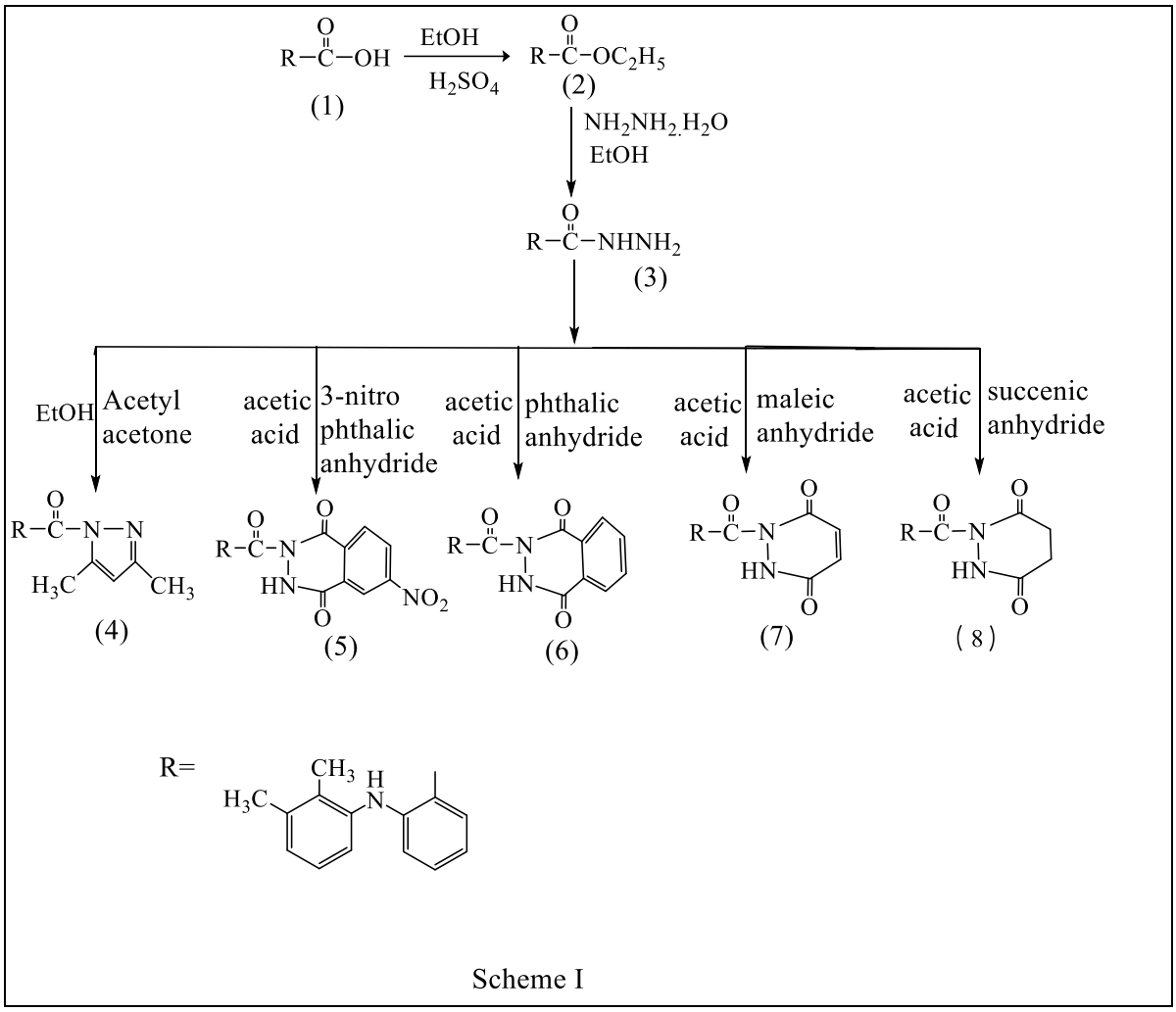
115- S. S. Hassan, M. Sc. Thesis College of Science, Al-Nahrain University, Iraq (2006).

116- E. S. El-Tamaty, M. E. Abdel-Fattah and I. M. El-Deen, Indian J. Chem., 35B, 1067 (1997).

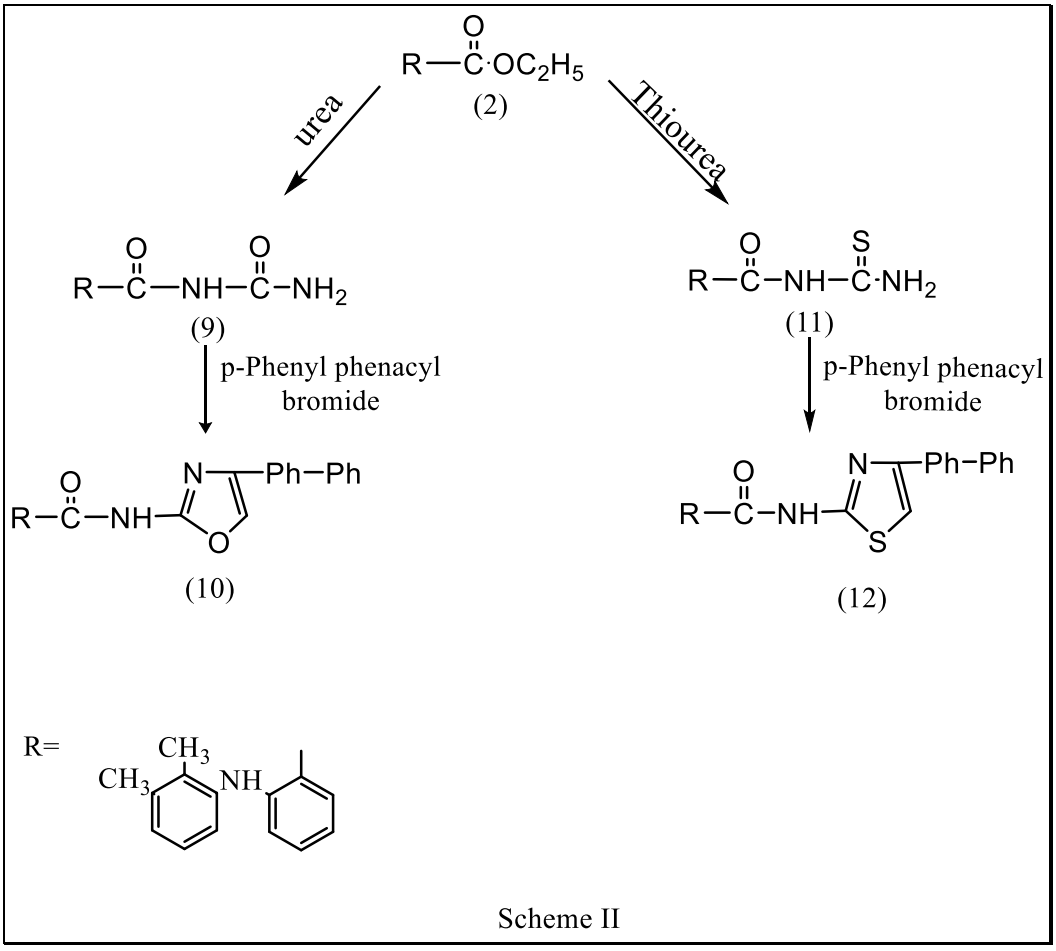
117- Z. S. Al-Taie, M. Sc. Thesis College of Science, Al-Nahrain University, Iraq (2005).

118- A. Sener, Turk. J. Chem., 28, 39 (2000).

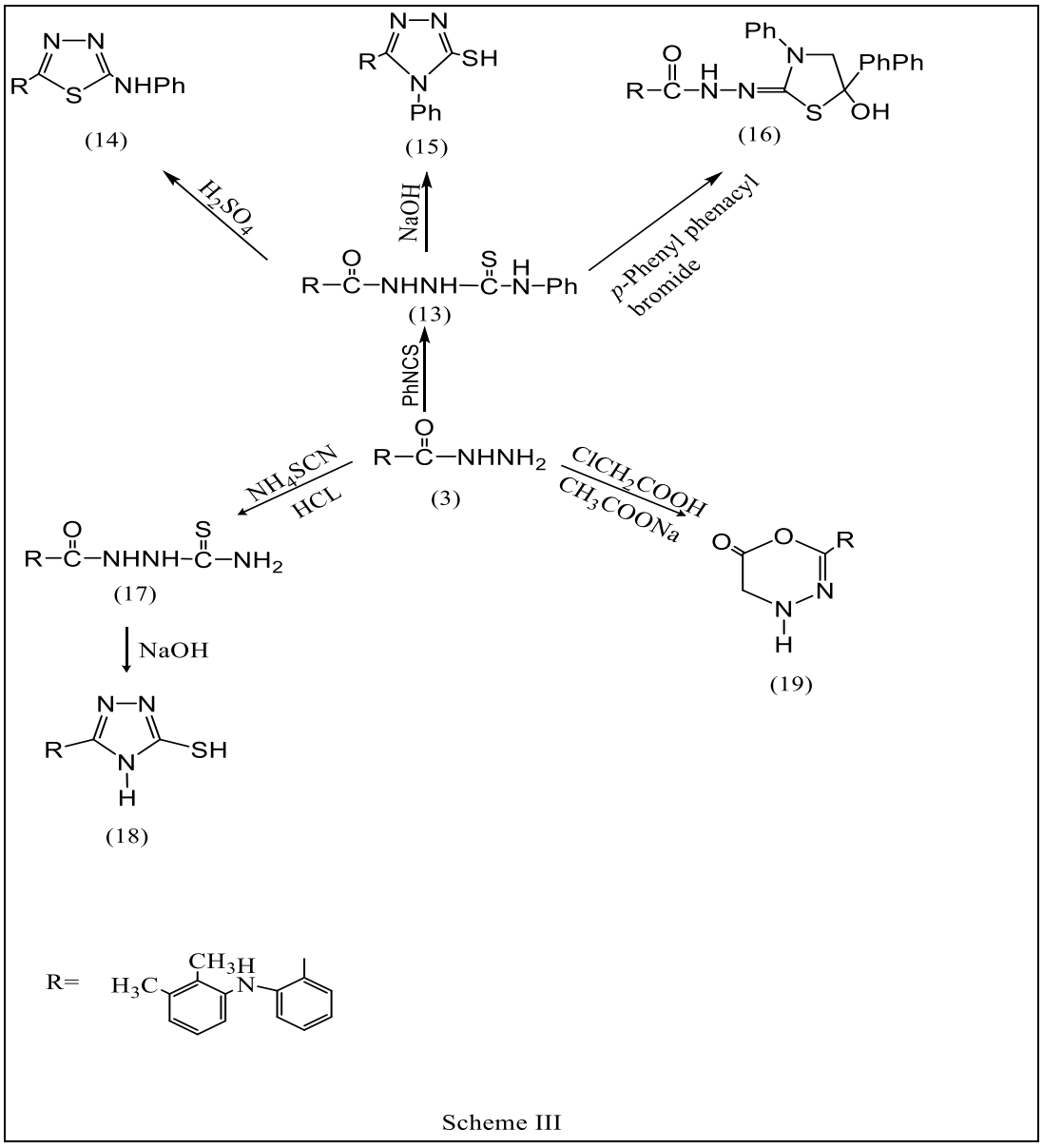
119- A. Yu. Dodroumov, A. V. K. G. Soedin, Chem. Heterocyclic. Compd. (Engl. Transl.), 825 (2000).


EtOH
H2SO4
(1)
(2)
NH2NH2.H2O
EtOH
(3)
EtOH
Acetyl acetone
acetic acid
3-nitro phthalic anhydride
acetic acid
phthalic anhydride
acetic acid
maleic anhydride
acetic acid
succenic anhydride
(4)
(5)
(6)
(7)
(8)
R=

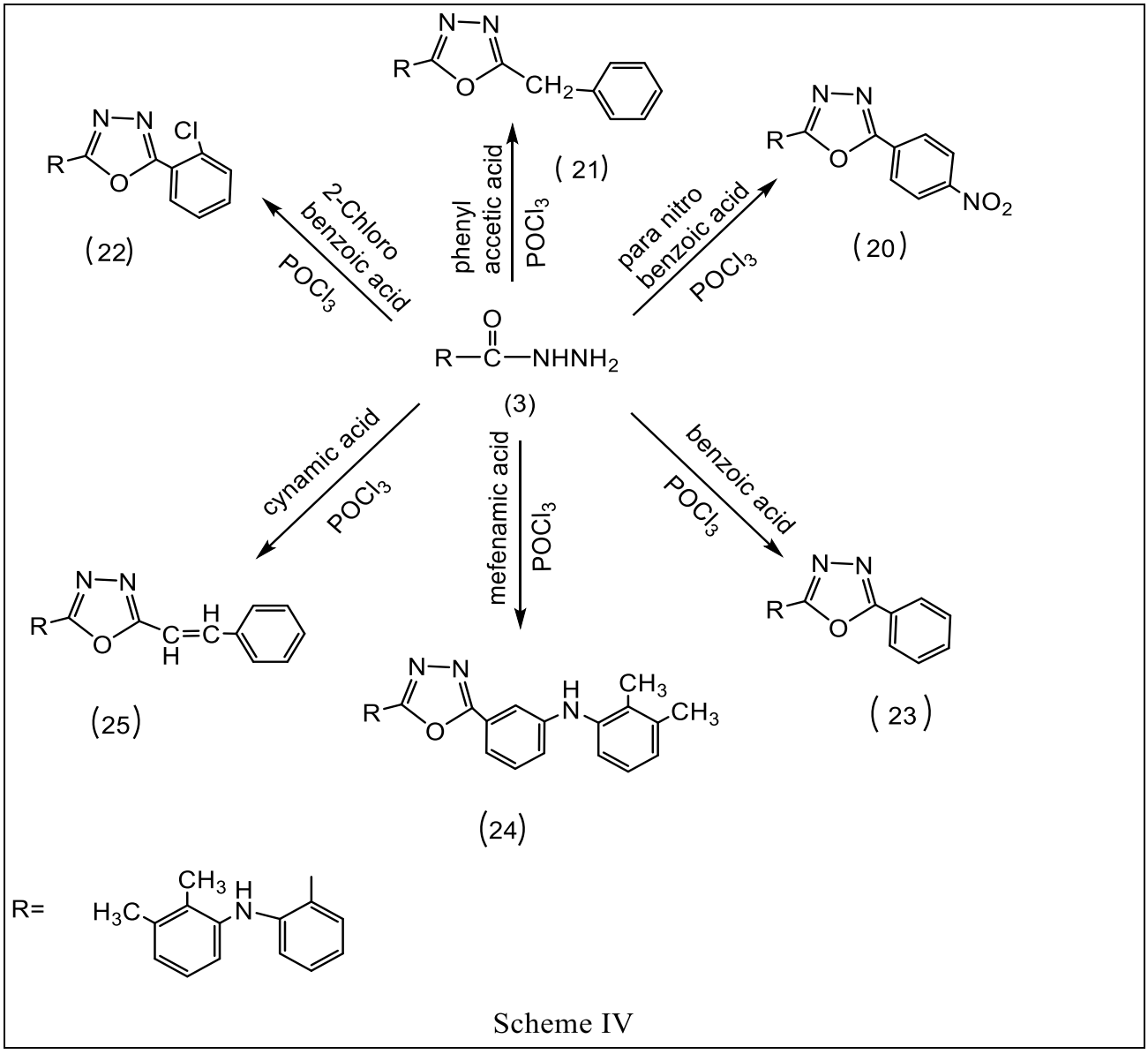
Scheme I


R—C·OC2H5
(2)
urea
Thiourea
R—C—NH—C—NH2
(9)
p-Phenyl phenacyl bromide
R—C—NH—C·NH2
(11)
p-Phenyl phenacyl bromide
(10)
(12)
R=
CH3
CH3
NH

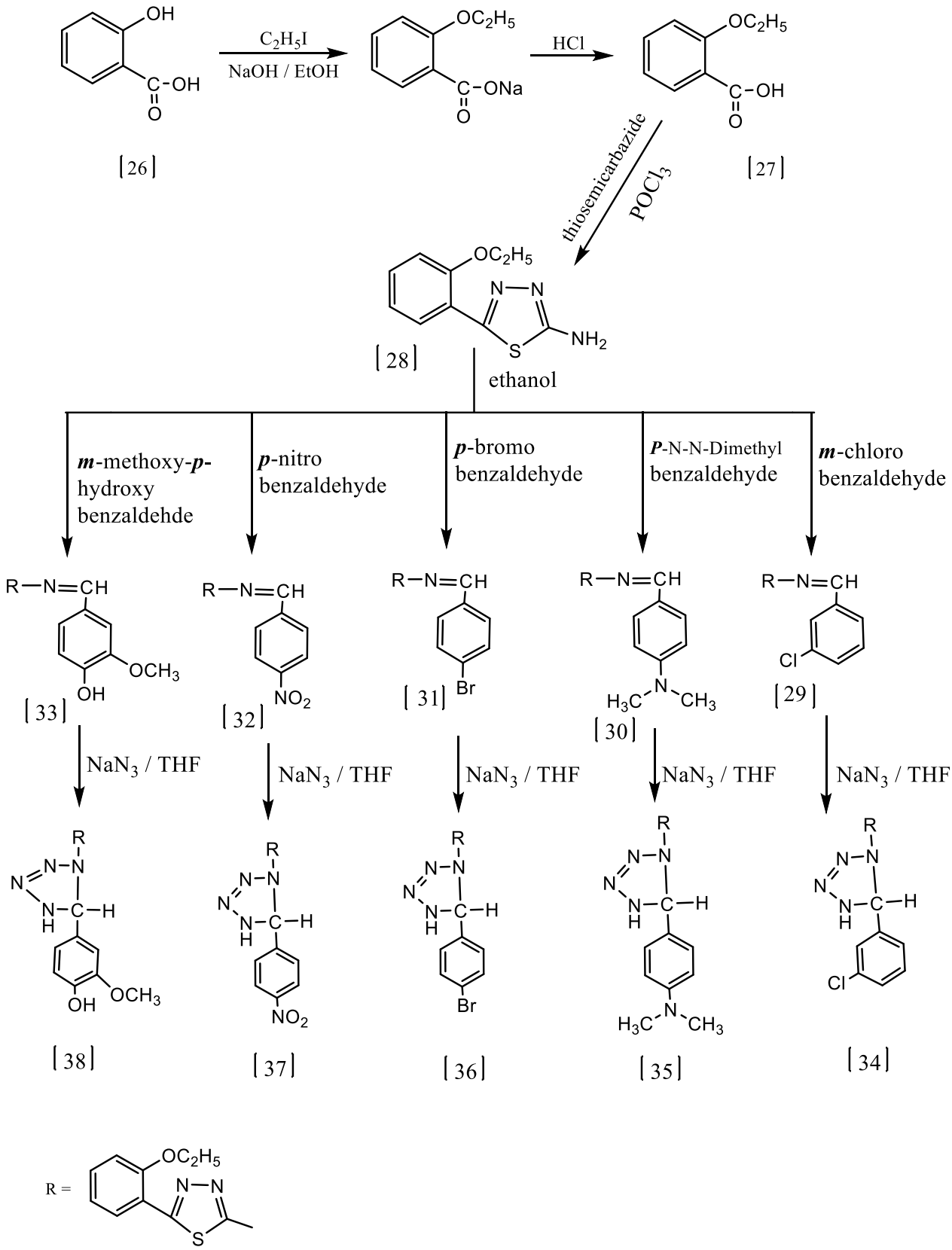
Scheme II


(14)
(15)
(16)
H_2SO_4
NaOH
p-Phenyl phenacyl bromide
(13)
PhNCS
(3)
NH_4SCN
HCL
$ClCH_2COOH$
CH_3COONa
(17)
NaOH
(18)
(19)
R=

Scheme III


(22)
2-Chloro benzoic acid
POCl3
phenyl accetic acid
POCl3
(21)
para nitro benzoic acid
POCl3
(20)
(3)
cynamic acid
POCl3
mefenamic acid
POCl3
benzoic acid
POCl3
(25)
(24)
(23)
R=

Scheme IV


C2H5I
NaOH / EtOH
HCl
thiosemicarbazide
POCl3
[26]
[27]
[28]
ethanol
m-methoxy-p-hydroxy benzaldehde
p-nitro benzaldehyde
p-bromo benzaldehyde
P-N-N-Dimethyl benzaldehyde
m-chloro benzaldehyde
[33]
[32]
[31]
[30]
[29]
NaN3 / THF
[38]
[37]
[36]
[35]
[34]
R =

(Scheme V)

الخلاصة

هذا العمل يتضمن تحضير مركبات حلقية خماسية وسداسية غير متجانسة ابتداءا" من عقار الميفينامك .

ويقسم هذا العمل الى سبعة اجزاء :

الجزء الاول: يتضمن هذا الجزء تحضير البايرزول (4,7) , الفثالزين 1,4- دايون(5) والبايرزدين3,6-دايون(6,8) من مشتقات الهيدرزايد (3) .كما موضح في الشكل I

الجزء الثاني: يتضمن هذا الجزء تحضير الاوكسازول (10) ومشتقات الثايزول(12) عن طريق تفاعل (2) 3-داي مثيل فنيل)امينو) بنزمايد مع كل من اليوريا والثايوريا ثم حولقة المركبات الناتجة مع بارا فنيل فنيسيل بروماید كما موضح في مخطط II

الجء الثالث: يتضمن هذا الجزء تحضير الثاياديازول والترايزول والثايوزولدين والاوكساديازين عن طريق مفاعلة المركب الهيدرزايد (3) مع فنيل ايزو ثايو سيانات (14) ومع امونيوم ثايوسيانيت (17) بالايثانول المطلق وحولقة المركبات بحامض الكبريتيك (14),هيدروكسيد الصوديوم (15,18) ومع بارا فنيل فنيسيل بروماید (16) ومفاعلة المركب الهيدرزايد(3) مع كلورو حامض الخليك وكلورات الصوديوم(19) كما موضح في مخطط III

الجزء الرابع: يتضمن الجزء مفاعلة مركب الهيدرزايد (3) مع بارانايترو حامض البنزويك(20) وفنيل حامض الخليك (21) و2-كلورو حامض البنزويك(22) وحامض البنزويك(23) وحامض الميفينامك (24) وحامض السينامك (25) . ثم حولقة النواتج مع نايترو حامض البنزويك وفنيل حامض الخليك (21) و2-كلورو حامض البنزويك(22) وحامض البنزويك(23) وحامض الميفينامك (24) وحامض السينامك للحصول على حلقات الاوكساديازول من (20-25) كما موضح في المخطط IV

الجزء الخامس : يتضمن هذا تحضير قواعد شف (29-33) بواسطة تفاعل الامين(28) مع الديهايدات مختلفة كما موضح في المخطط V

الجزء السادس: يتضمن هذا الجزء تحضير التيتترازول (34-38) بواسطة تفاعل قواعد شف (29-33) ازيد الصوديوم كما موضح في مخطط VI

الجزء السابع: تم التركيز في هذا الجزء على الفعالية المضادة للبكتيريا لبعض المركبات المحضرة وذلك باستخدام نوعين من البكتيريا كما موضح في الجدول (3)

جمهورية العراق
وزارة التعليم العالي والبحث العلمي
جامعة بغداد
كلية التربية للعلوم الصرفة - ابن الهيثم
قسم الكيمياء

تخليق وتشخيص مركبات خماسية وسداسية غير متجانسة ودراسة خواصها البكتيرية

هذه الرسالة مقدمة إلى مجلس كلية التربية للعلوم الصرفة / جامعة بغداد
وهي جزء من متطلبات نيل درجة الماجستير في علوم الكيمياء

من قبل

علي حاتم احمد العنبكي

جامعة بغداد / بكالوريوس كيمياء

٢٠١٢ م

بإشراف

ا.د- ابتسام خليفة جاسم

٢٠١٩ م **١٤٤٠هـ**