Chapter One

Introduction

1.1-Heterocyclic Compounds:

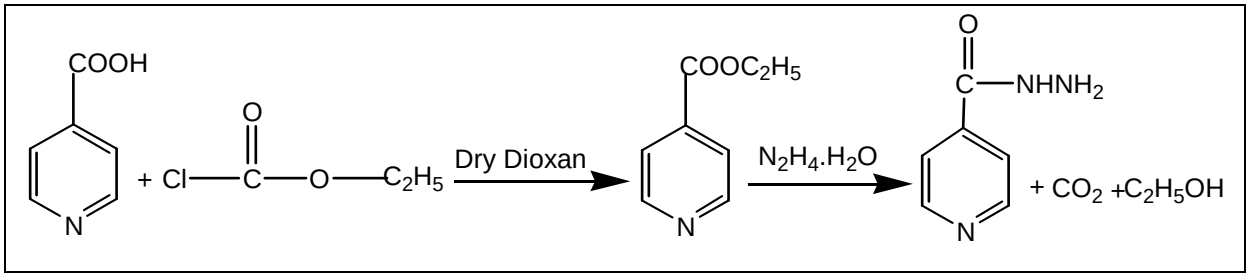
Heterocyclic compounds are considered one of important types of organic compounds due to their applications in drug and industrial studies. Heterocyclic compounds are cyclic compounds in which one or more of the atoms of the ring are hetero atoms. The name comes from the Greek word heteros, which means "different". A variety of atoms such as (N, O, S, Se, P, Si, B and As) can be incorporated into the ring structure[1].

1.1.0- Hydrazide derivatives:

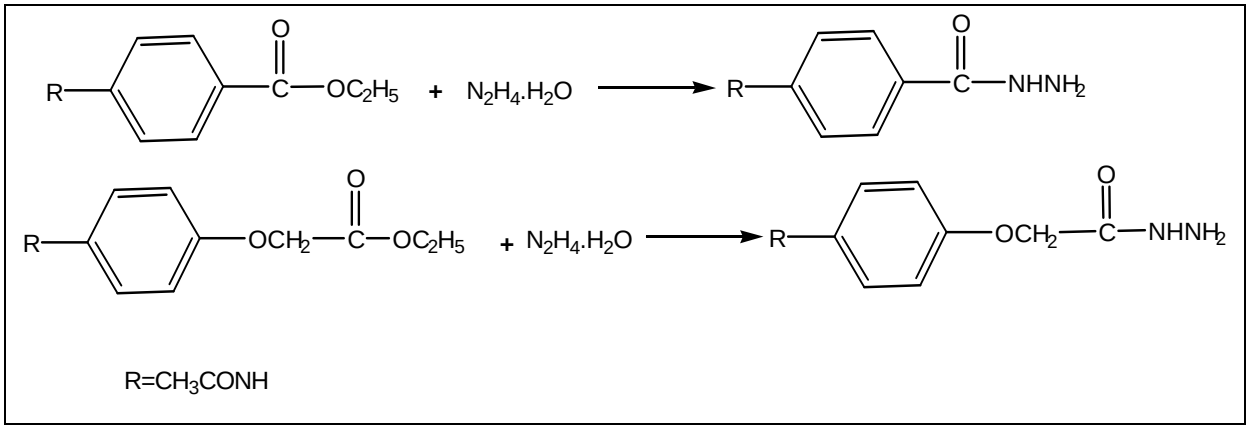
Hydrazide and thiosemicarbazide derivatives attracted a lot of attention because they are considered as intermediates to synthesize several compounds such as ***Schiff*** bases, thiadiazole [2], oxadiazole [3] and triazole[4] derivatives which all were reported to possess biological activities. The structural formula for this type of compounds is (RCONHNH-).

1.1.1- Synthesis of hydrazide derivatives:

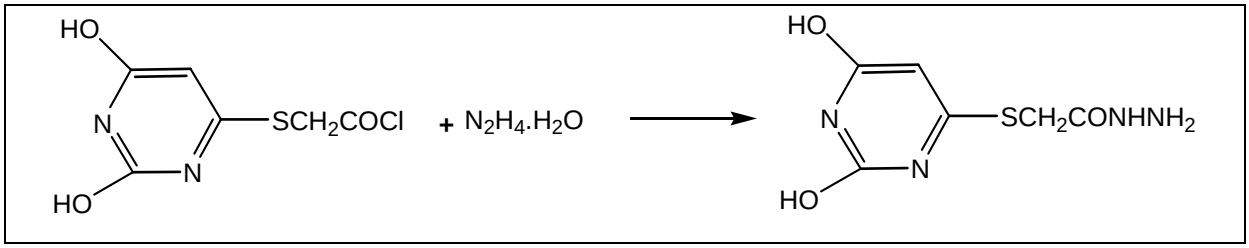
Rinder Kenecht [5] found that the isonicotinic acid reacted with ethylchloro formate to afford asymmetrical anhydride Further reaction with hydrazine hydrate led to formation of isonicotinic acid hydrazide:



Several methods are available for the synthesis of hydrazide derivatives, the most important of which is based on the reaction of esters with hydrazine hydrate [6] as shown below:



Acid hydrazide derivatives can also be synthesized from condensation reaction of carboxylic acid chloride with hydrazine hydrate [7].



1.1.2- Hydrazide derivatives uses:-

Hydrazides and related compounds have been described as useful building blocks for the assembly of various heterocyclic rings. A large number of aliphatic, alicyclic, aromatic and heterocyclic carbohydrazides, their derivatives and related compounds are reported to have a plethora of biological activities [8].

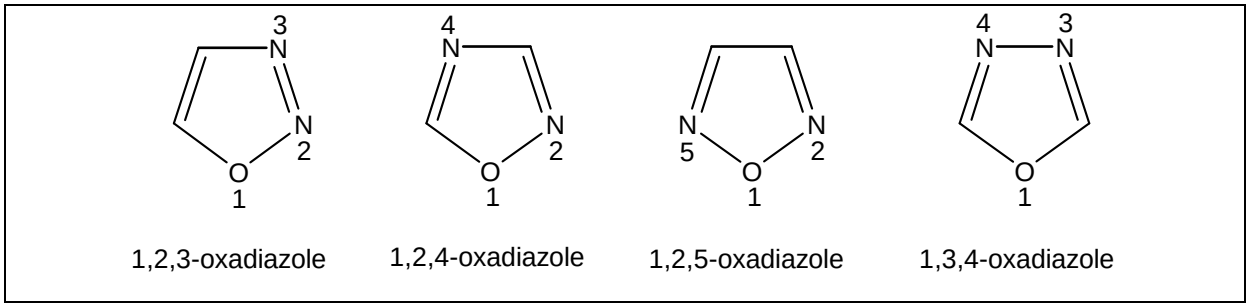
Mycobacterium tuberculosis infects over one-third of world's population and causes almost three million deaths every year. Isonicotinic acid hydrazide (isoniazid) is one of the primary drugs used in the treatment of tuberculosis [9].

Thus, different carbohydrazides were found to be useful as medicaments specially in the treatment of inflammatory and autoimmune disease, osteoarthritis, respiratory diseases, tumors, cachexia, cardiovascular diseases, fever, hemorrhage and sepsis [10].

Some heterocyclic carbohydrazides are useful as antifertility agents in rats and pigeons. Other carbohydrazides were reported to be components of deodorant compositions that can be used for removal of offensive odor components [11].

1.2-0- Oxadiazoles:

Oxadiazoles are five-membered ring compounds with three hetero atoms one oxygen atom and two nitrogen. The oxadiazole ring has four[12] isomers as shown below:



1,3,4-Oxadiazole is the most thermally stable isomer which has attracted special attention, this is primarily due to the large number of uses in many diverse areas, including drugs, scintillation materials, dyes[13] and surface active agents [14].

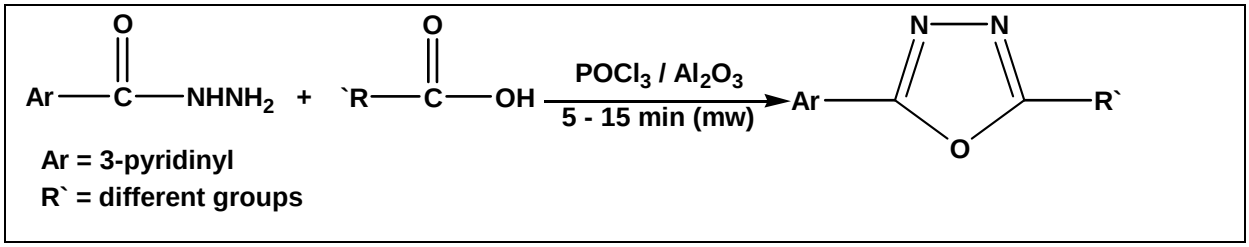
1.2.1-Synthesis of oxadiazoles:

Several methods have been used to synthesize 1,3,4-oxadiazoles. Among these the following are most important methods:

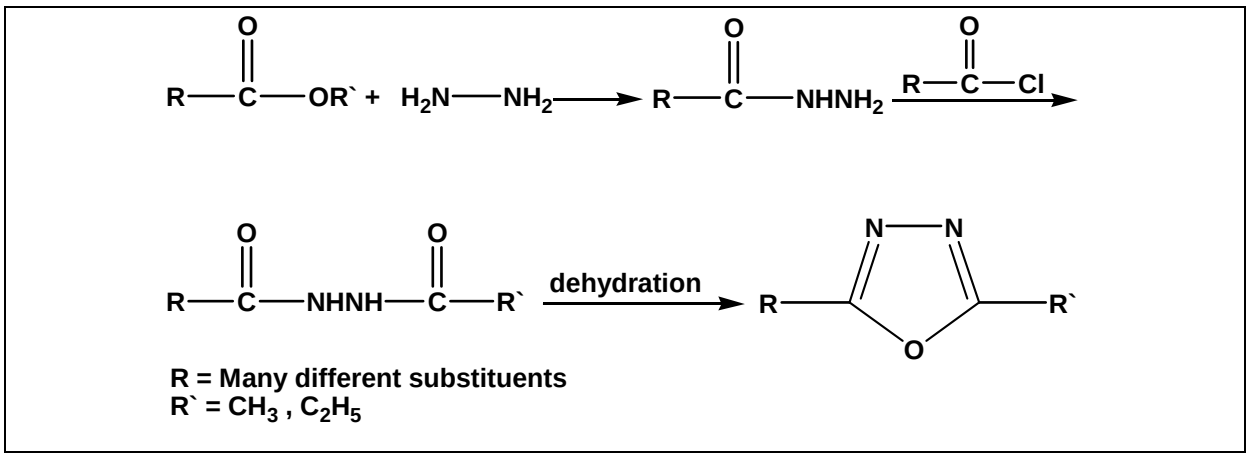
Dehydration of acid hydrazides:

Carlson and ***Jorgensen*** [15] synthesized a number of 2,5-disubstituted-1,3,4-oxadiazole under microwave irradiation through the reaction of variable

hydrazides with different carboxylic acids in the presence of phosphorous oxychloride. This method provides an excellent approach for the safe, rapid, inexpensive and simple synthesis medically important 2,5-disubstituted-1,3,4-oxadiazole.

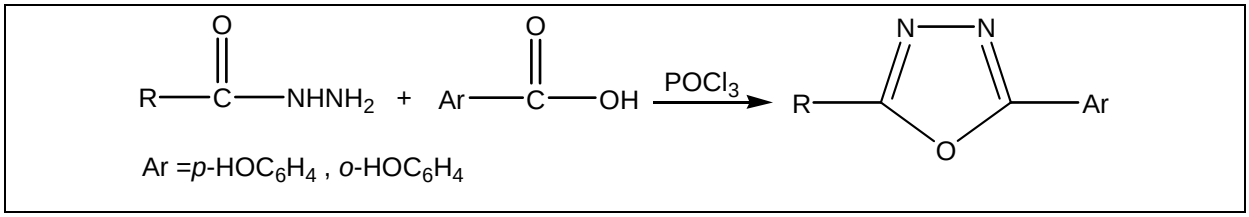


Acid hydrazides are usually prepared from the reaction of corresponding esters with hydrazine hydrate. These hydrazides are converted to di-acid hydrazides through their reaction with appropriate acid chlorides. The di-acid hydrazides are established to be the most convenient precursors for the synthesis of substituted 1,3,4-oxadiazole[16].



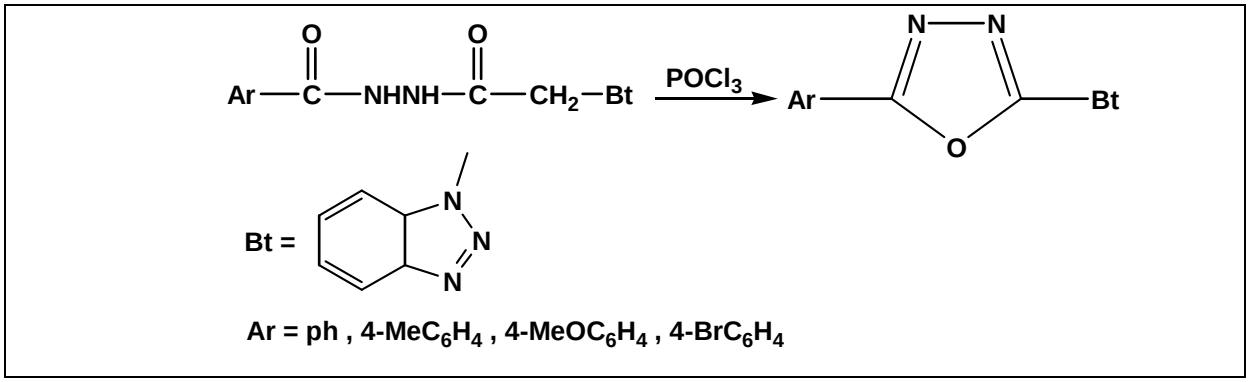
Variant conditions influence the dehydration reaction, typically the reaction is promoted by heat and anhydrous agents including thionyl chloride or phosphorous oxychloride.

Recently 2,5-disubstituted-1,3,4-oxadiazoles have been synthesized by a route in which acid hydrazide was condensed with appropriate aromatic acid and phosphorous oxychloride.

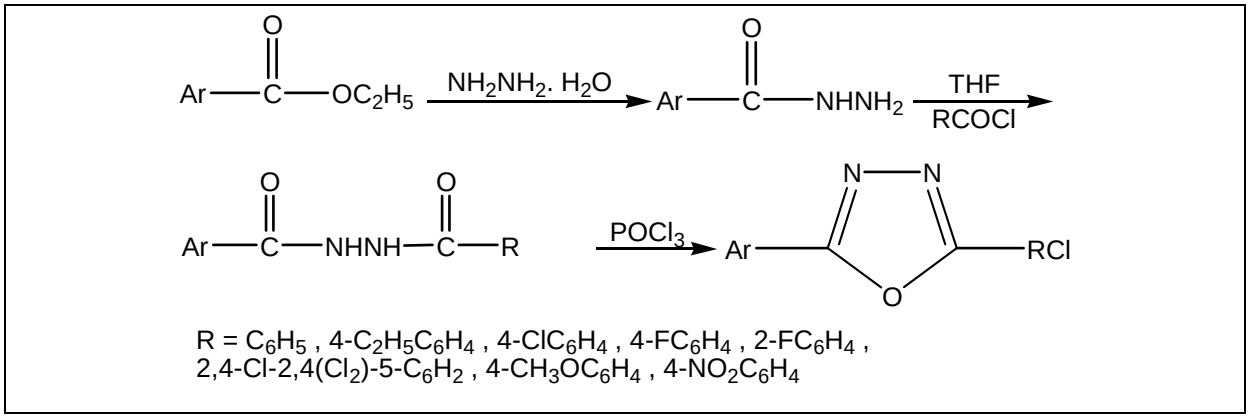


In the last few years, a great number of 1,3,4-oxadiazole derivatives were synthesized, the following examples include some of these compounds.

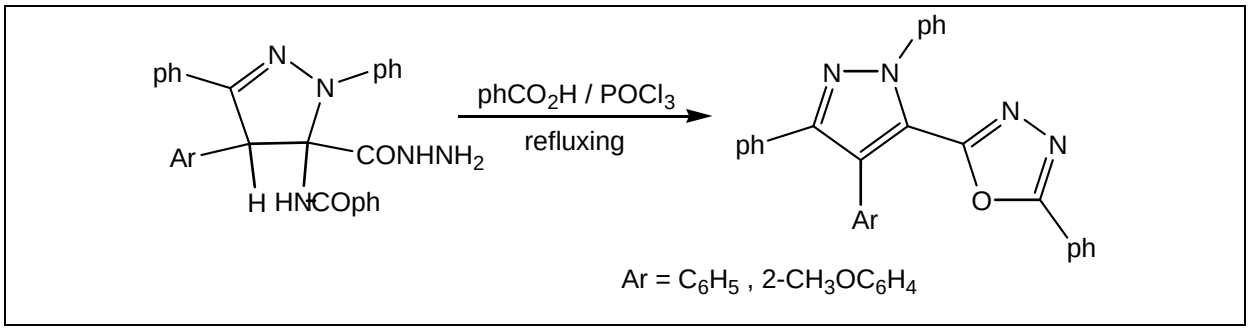
Katritzky [17] synthesized 1-[5-aryl(1,3,4-oxadiazole-2-yl) methyl]-1H-benzotriazole by reaction of unsymmetrical diacylhydrazines with phosphorous oxychloride.



Cao [18] synthesized 5-aryl-2-chloromethyl-1,3,4-oxadiaozles by cyclodehydration of N-chloroacetyl-N-aryl hydrazines in boiling $POCl_3$.



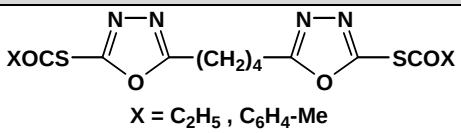
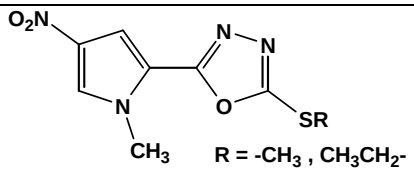
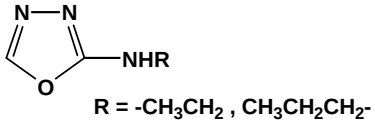
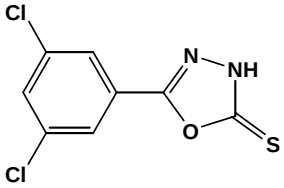
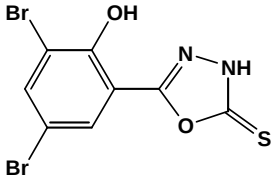
Mansour [19] prepared 5-phenyl-2-(1,3,4-triphenyl pyrazole-5-yl)-1,3,4-oxadiazole by treatment of 4-aryl-5-benzoylamino-1,3-diphenyl-Δ^2-pyrazdine-5-carbohydrazides with benzoic acid and phosphorus oxychloride. The reaction was found to proceed via concurrent cyclocondensation and elimination of a benzamide molecule.



1.2.2- Biological activity of 1,3,4-oxadiazoles:

The biological significance of oxadiazole ring is well documented in the literature [20]. Thus, it has been shown that many substituted-1,3,4-oxadiazoles have biological and medical uses as antibacterial [20], antifungal [21], antimalarial [22,23] and anti-inflammatory [24] activities when probably substituted in (2) and (5) positions. Further, it was suggested that (-SH) group attached to a heterocyclic nucleus may include fungicidal activity [25]. Table (1-1) shows the biological activity of some derivatives of 1,3,4-oxadiazoles.

Table (1-1): Biological activity of some oxadiazole derivatives.

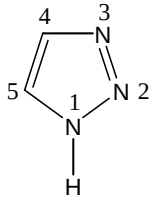
No.	Name	Structure	Biological activity	Ref.
1	5,5`-(1,4`-Butane)bis-[1,3,4-oxadiazole-2-thiol substituent]		Antimicrobial activity	26
2	2-(1-Methyl-4`-nitro pyrrayl)-5-alkylthio-1,3,4-oxadiazole		Effective drugs against tropical diseases	27
3	N-Alkylated-2-amino-1,3,4-oxadiazole		Antimitotic activity	28
4	5`(2`,4-Dichlorophenyl)-1,3,4-oxadiazol-2-thione		Fungi toxic activity	29
5	5-(2`-Hydroxy-3`,5`-dibromophenyl)-1,3,4-oxadiazol-2-thione		Monomine oxidase and succinate dehydrogenase inhibitory	30

1.3.0- 1, 2, 4-Triazoles: General description

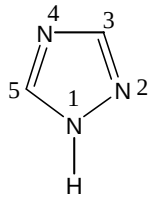
1, 2, 4-Triazole is one of a class of organic heterocyclic compounds containing a five membered di-unsaturated ring structure composed of three nitrogen atoms and two non adjacent carbon atoms. 1, 2, 4-Triazole is a white to pale yellow crystalline solid with a weak odor, soluble in water and alcohol, melts at 120^{o}C [31].

Triazole ring is planar with 6π-electron aromatic system with distortion of the π-system induced by the annular nitrogen.

There are two possible combinations of the three nitrogen and two carbon atoms.

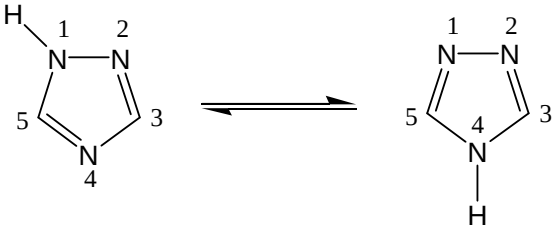


1,2,3-triazole



1,2,4-triazole

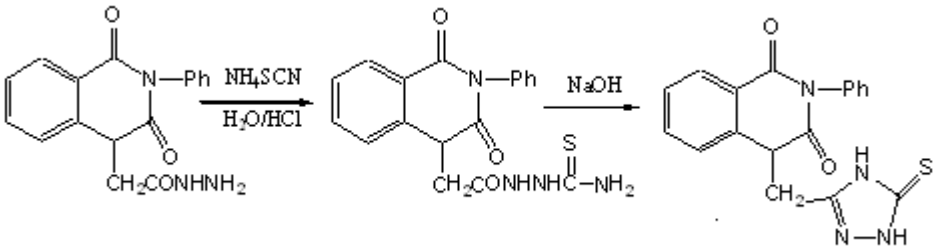
1, 2, 3-Triazole was originally called ʋic-(vicinal) triazoles, and 1, 2, 4-triazole known as sym-(symmetrical) triazoles [32] .



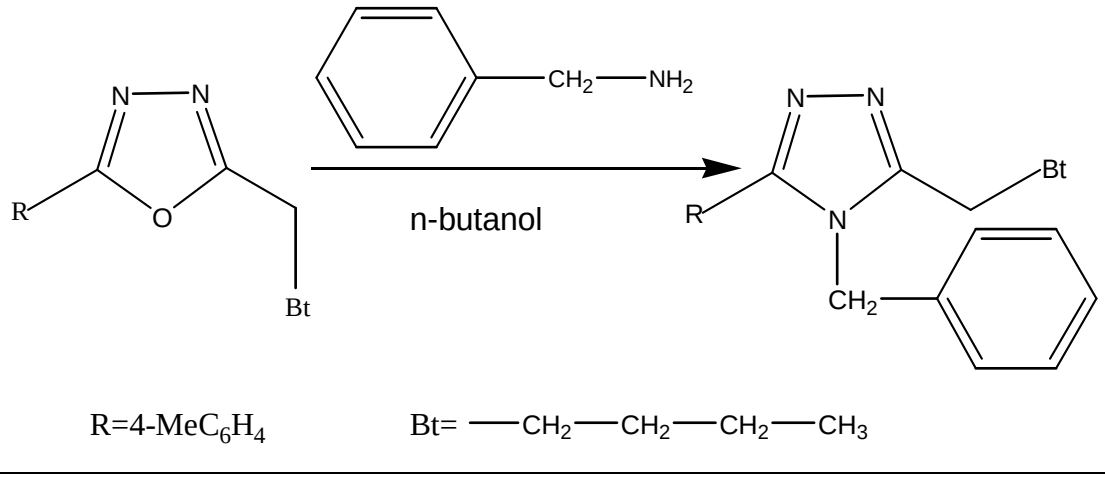
1H-1,2,4-triazole 4H-1,2,4-triazole

1.3.1- Synthesis of 1, 2, 4-triazoles:

El-Tamany et.al., [33] found that the reaction of (3-benzyl-2,4-quinazolin-1-yl)acetylhydrazine with ammonium thiocyante in aqueous acidic medium afforded the thiosemicarbazide derivative which cyclized in alkaline medium to 3'-[(3-benzyl-2,4-quinazolinon-1-yl)-1',2',4'-triazole - 5'thion :

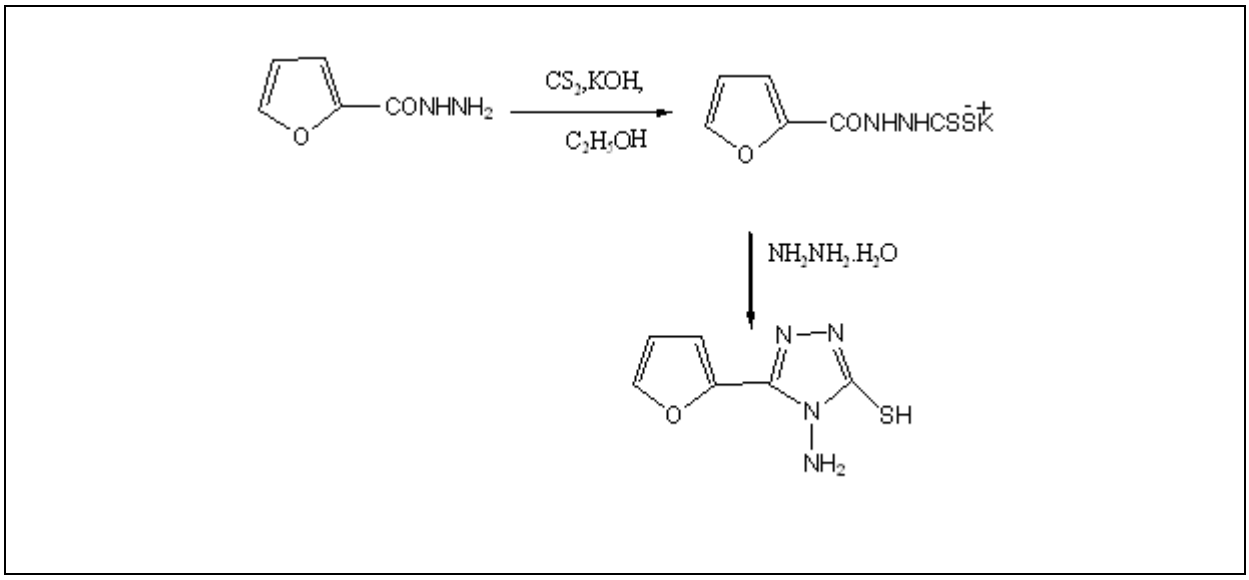


Katritzky et.al., [34] synthesized [(4-Benzyl-3-(4-methyl phenyl)-5-pentyl-1,2,4-triazole] from the reaction of [5-(4-(methyl phenyl)-2-pentyl-1,3,4-oxadiazole] with benzyl amine in the presence of n-butanol:

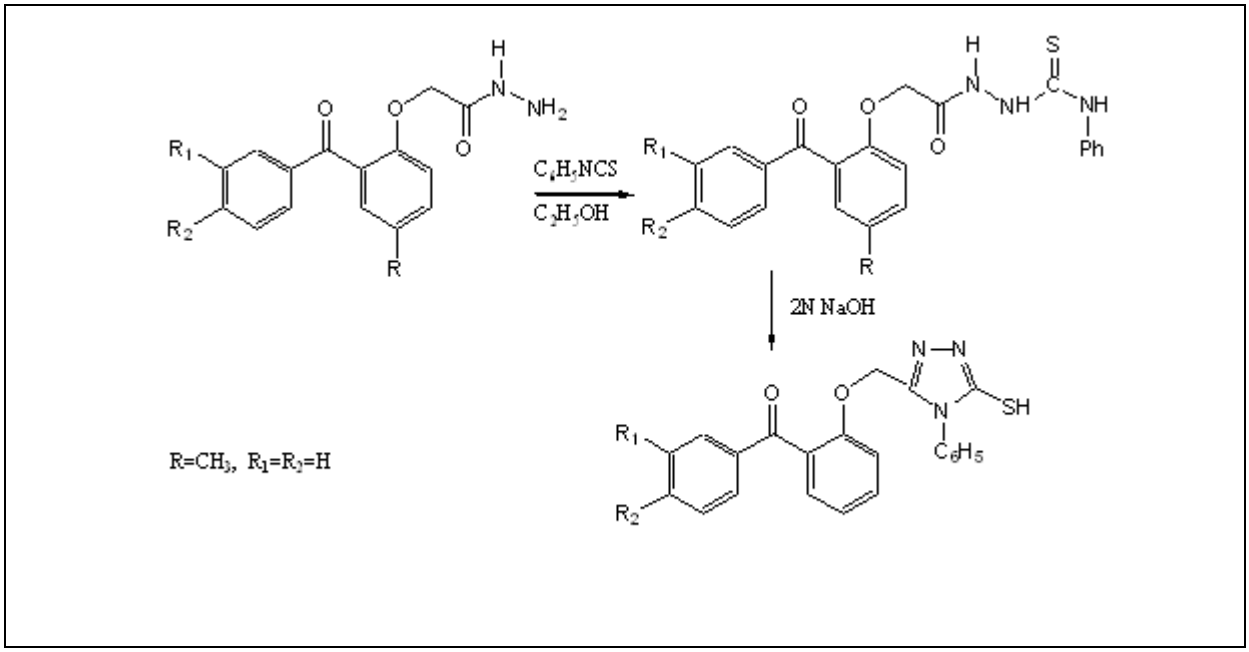


R=4-MeC_6H_4 Bt= —CH_2—CH_2—CH_2—CH_3

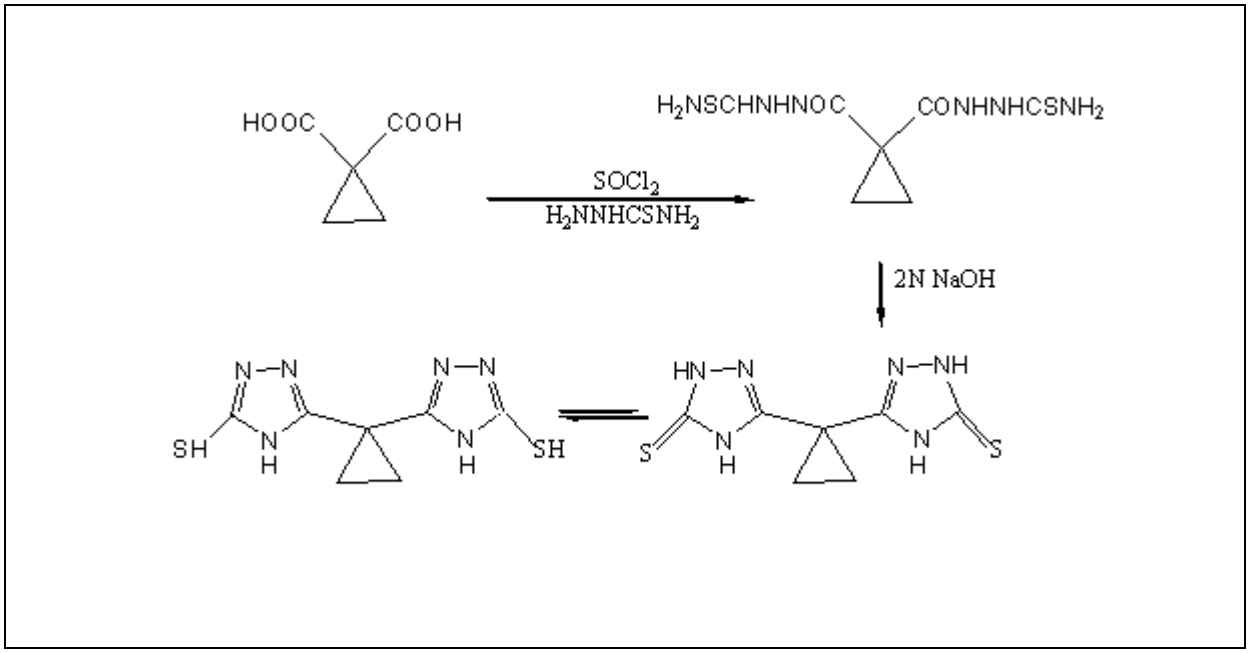
Zhang et.al., [35] found that the the reaction of furylhydrazide with CS_2 and potassium hydroxide in absolute ethanol gave potassium 2-furylhydrazidedithiocarbazate. Further cyclization of pottassium 2-furylhydrazidedithiocarbazate with 85% hydrazine hydrate led to formation of 3-(2-furyl)-4-amino-5-mercapto-1, 2, 4-triazole:



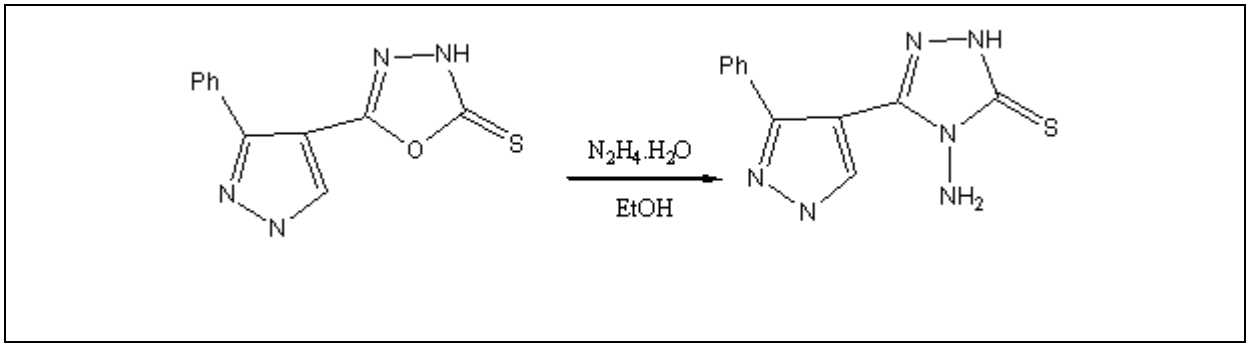
Khanum et.al., [36] found that the reaction of 2-(2-aroylaryloxy) acetohydrazide with phenylisothiocyante in the presence of absolute ethanol gave 2-[2-(aroylaryloxy) acetyl]-N-phenylhydrainecarbothioamide . Further cyclization of 2-[2-(aroylaryloxy) acetyl]-N-phenylhydrainecarbothioamide with 2N NaOH led to formation of 3-(2-aroylaryloxy)methyl-5-mercapto-4-phenyl-1,2,4-triazoles:



Sharba et.al.,[37]found that the reaction of cyclopropane dicarboxylic acid afforded the respective thiosemicarbazide.Further cyclization of the respective thiosemicarbazide in the presence of 2N NaOH leds to the formation of 1,1-bis (3-mercapto-1,2,4-triazol-5-yl)cyclopropane:



Farghaly et.al., [38] synthesized 4-amino-3-(1, 3-diphenyl-1H-pyrazol-4-yl)-4, 5-dihydro-[1, 2, 4] triazole-5(1H)-thione by reaction oxadiazolethione with hydrazine hydrate in the presence of ethanol:



1.3.2- 1, 2, 4-Triazole uses:

Epilepsy is neurological disorder that affects at least 50 million people worldwide. There is continuing demand for new anticonvulsant agents as it has

not been possible to control every kind of this disease with the currently available antiepileptic drugs. Loreclezole and Estazolam, Figure (1-1), are anticonvulsant drugs containing 1,2,4-triazole ring[39,40].

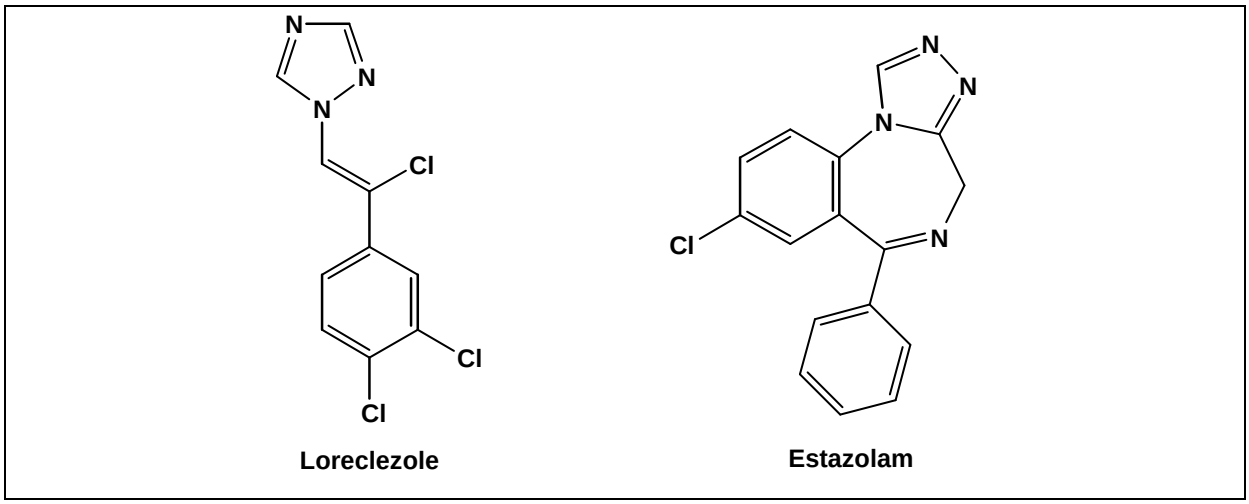


Figure (1-1):

In addition, it was reported that, compounds having triazole moieties, such as vorozole, letrozole and anastrozole, Figure (1-2), appeared to be very useful for preventing breast cancer [41]:

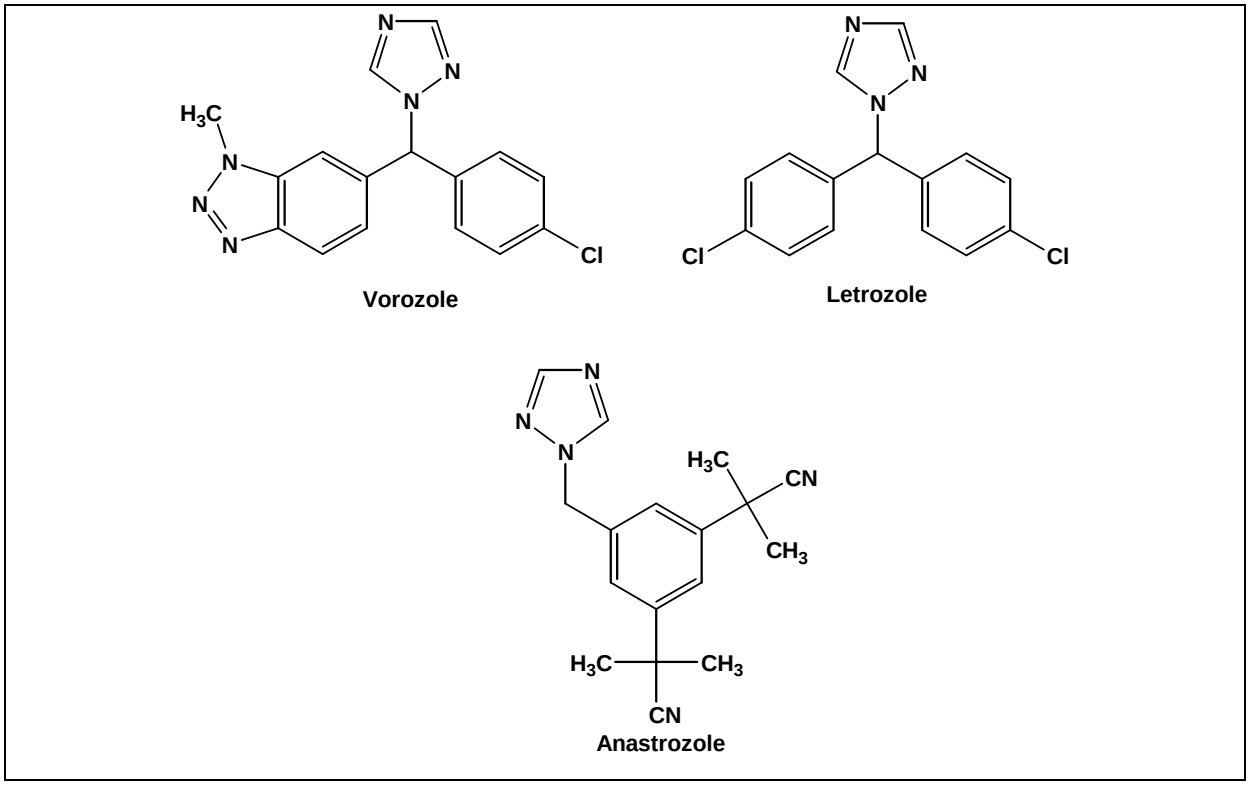


Figure (1-2):

Fungal infections remain a significant cause of morbidity and mortality despite advances in medicine and the emergence of new antifungal agents. Voriconazole, Fluconazole and Itraconazole, Figure (1-3), are triazole antifungal agents that are widely used for treating human infections [(42)].

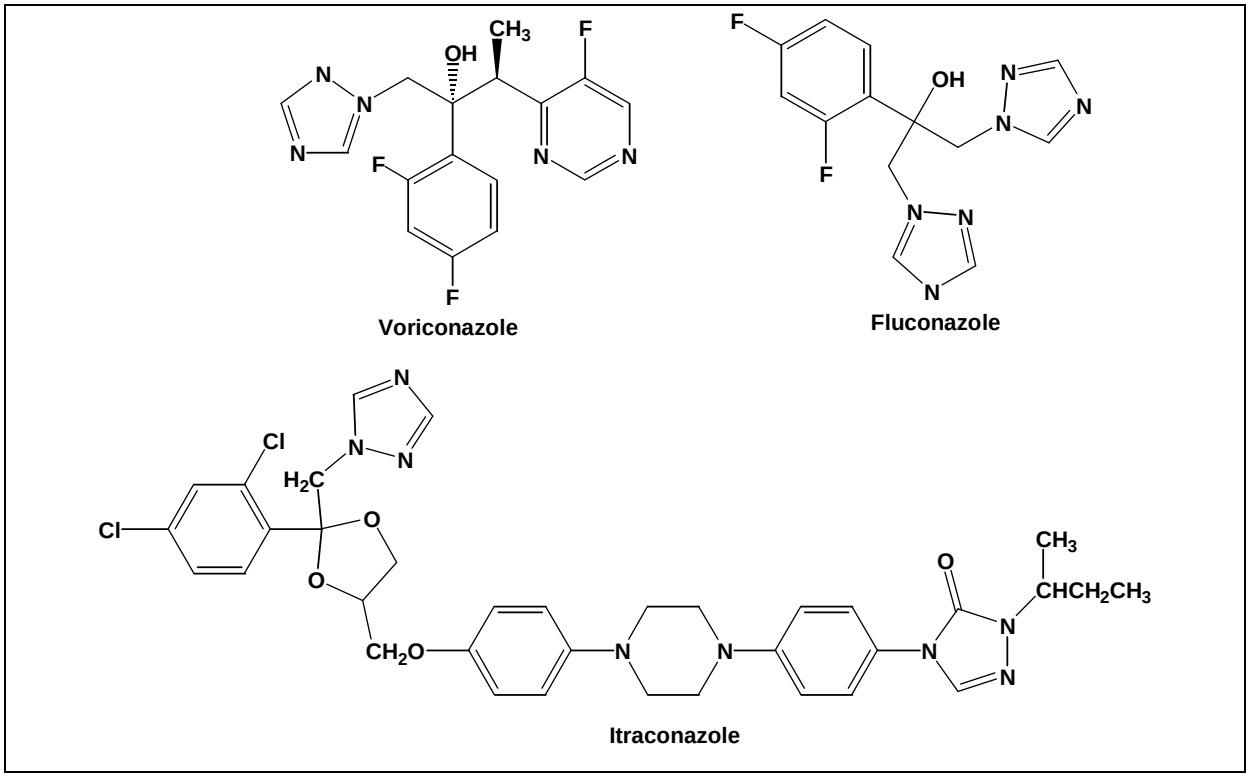


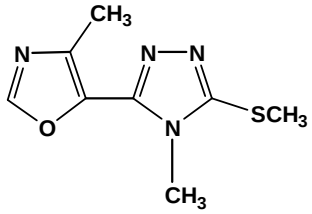
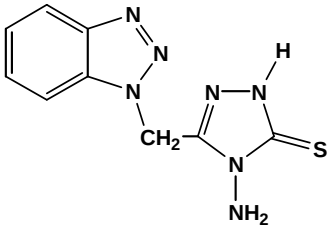
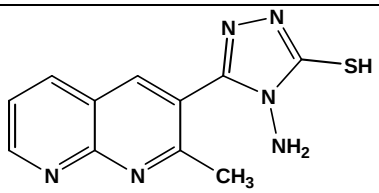
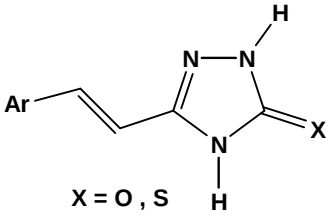
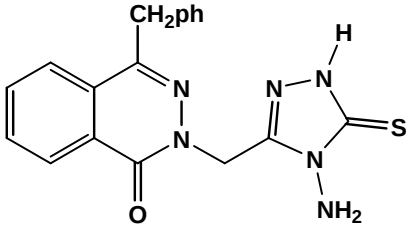
Figure (1-3):

Voriconazole is the newest agent in the armamentarium against fungal infections. It inhibits fungal ergosterol biosynthesis with a structure related to that of Fluconazole and a spectrum of activity comparable to that of Itraconazole[(43)]. Furthermore, some reported mercapto triazole derivatives showed potent activity [(44)] more than Streptomycin against Candida albicans. Thus, among an important type of fungicides, triazole compounds are highly efficient, low poisonous and inward absorbent [(45)].

Since the discovery of the biological importance of these compounds, the aim of many research projects was to synthesize many different substituted triazoles,

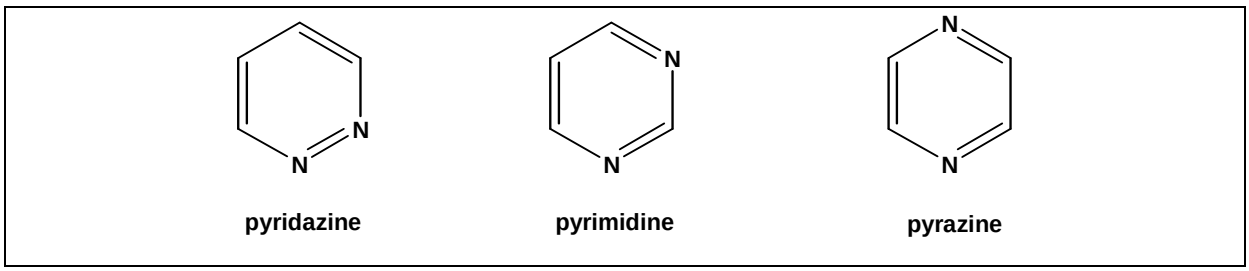
and their biological activity was a subject of many studies. Table (1-2) includes some of these compounds.

Table (1-2): Biological activity of 1, 2, 4-triazole compounds.

Comp. No.	Comp. Name	Structure	Biological Activity	Ref.
1	3-(4-methyl-5-oxazolyl)-4-methyl-5-methylthio-4H-1,2,4-triazole		Potential biological activity	46
2	1-(4-amino-4H-1,2,4-triazol-3-thione-5-yl)methyl-1H-benzotriazole		Potential biological activity	47
3	4-amino-5-mercapto-3-(2'-methyl-1',8'-naphthyridin-3'-yl)-1,2,4-triazole		Anti microbial activity	48
4	Styryl triazoles		Anti inflammatory agent	49
5	4-benzyl-2-(1-amino-2-thioxo-1,3,4-triazol-5-yl-methyl)phthalazin-1-(2H)-one		Anti fungal activity	50

1.4.0- Pyridazines:

Pyridazine is a member of a diazine group. There are three possibly isomeric diazines with the nitrogen atoms in a 1,2-, 1,3- or 1,4-relationship:

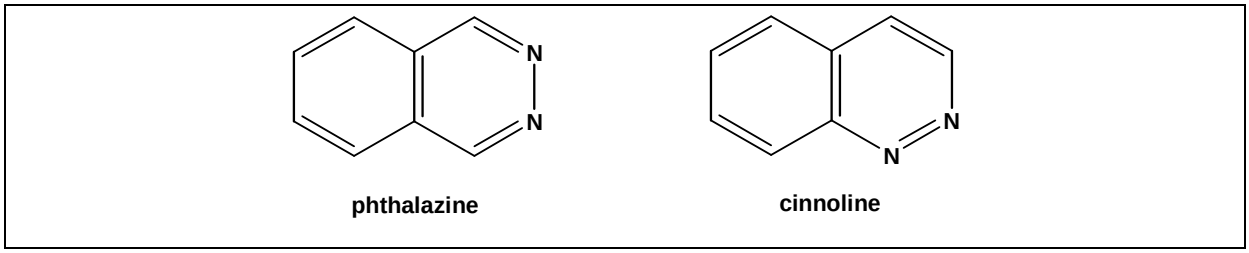


pyridazine **pyrimidine** **pyrazine**

No naturally occurring pyridazines have been reported and indeed this comes as no surprise because of the paucity of chemical compounds containing two nitrogen atoms bonded to one another in nature.

Pyridazines is a colorless liquid, its boiling point is equal to (207.4 ^{o}C) and it is considered a weak base (pKa = 2.331).

Pyridazine ring can be fused on to a benzene ring in two ways giving phthalazine or cinnoline [51].

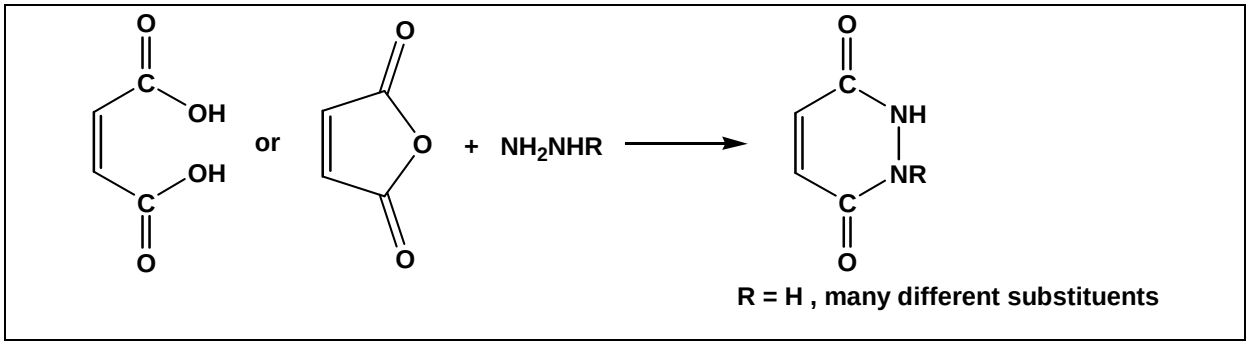


phthalazine **cinnoline**

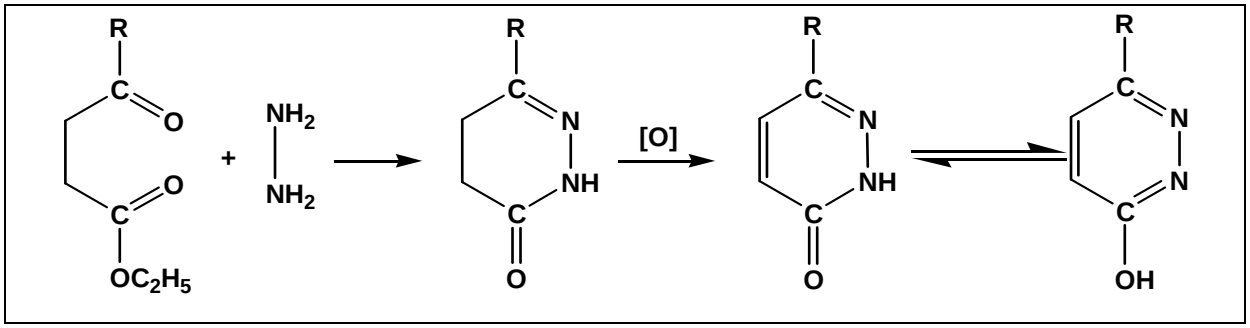
1.4.1- Synthesis of Pyridazine derivatives:

Pyridazine and number of its derivatives were prepared by different methods [51,52] such as.

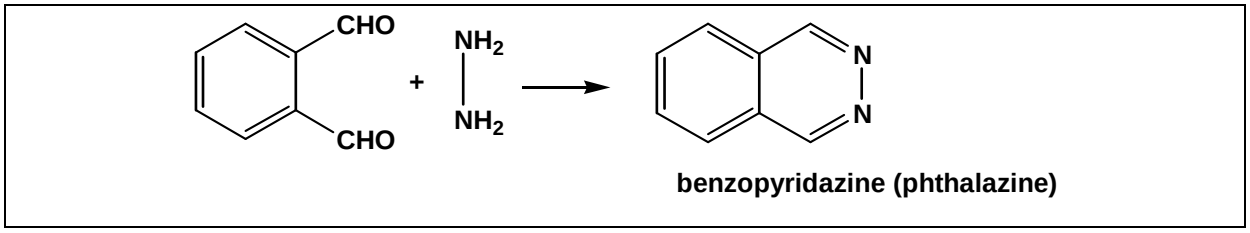
From the reaction of maleic acid or maleic unhydride with hydrazine or substituted hydrazine.



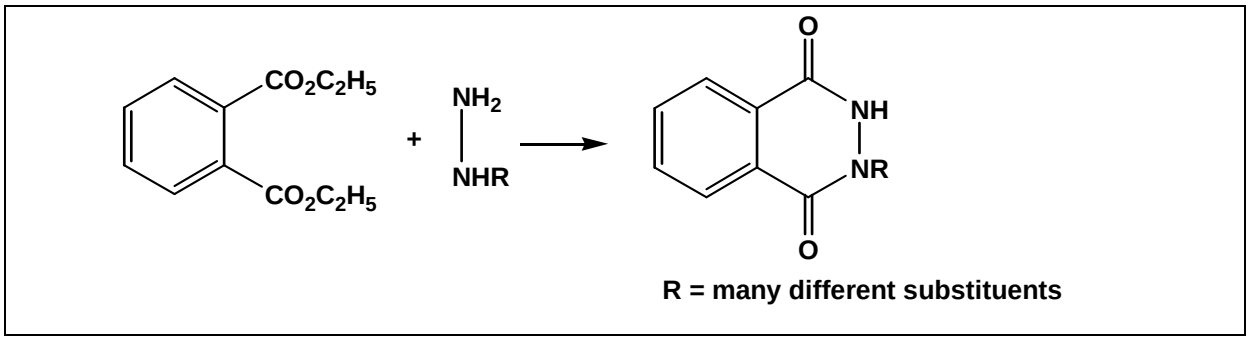
From the reaction of γ-keto carboxylic acid or their esters with hydrazine.



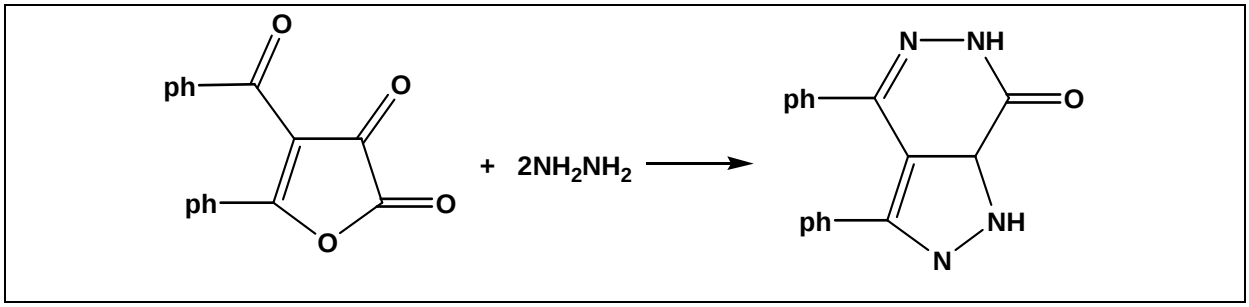
From the reaction of phthaldehyde with hydrazine.



From the reaction of phthalic acid or one of its derivatives (ester, anhydride and imide) with the hydrazine or substituted hydrazine.



Sener [53] found that 3,4-diphenyl-2H-pyrazol [3,4-d] pyridazin-7-one was obtained from the reaction of hydrazine with 4-benzoyl-5-phenyl-1,2,3-dihydro-2,4-furandione.



1.4.2- pyridazine uses:

Some imidazole [1,2-b] pyridazine derivatives are reported to possess antiasthmatic and analgesic activities [54]. It has been reported that a considerable number of 3(2H)-pyridazine derivatives bear analgesic activity as Emorfazone (4-ethoxy-2-methyl-5-morpholino-3(2H) pyridazinone [55].

Hydrazine-pyridazines continue to be an object of interest for improving medicinal drugs for blood pressure control such as hydralazine, which has been used for many years in the treatment of essential hypertension [56].

On the other hand, substituted pyridazine are often used in medicine field to their pronounced bactericidal and fungicidal effects[57] and consequently 4-phenylfuro [2,3-d] pyridazine-7-one is being used as intermediate for cardiovascular agents.

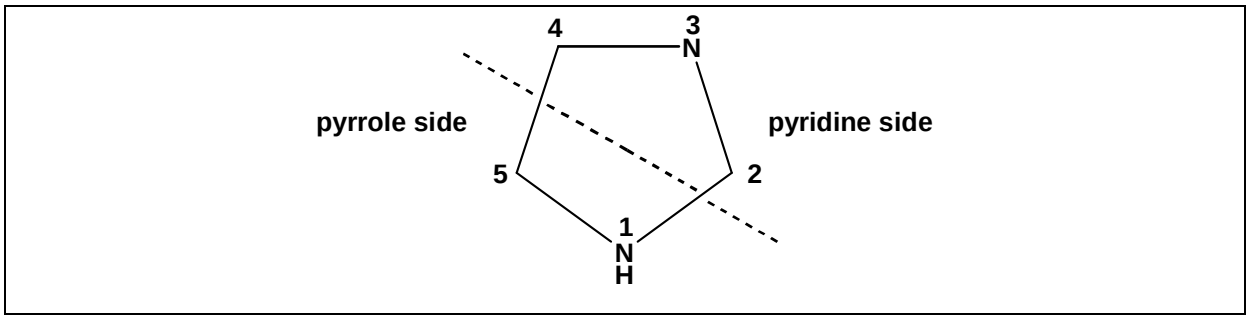
Pyridazine and condensed pyridazines are reported to have good biological activities. The discovery [58] of a natural antifungal antibiotic, containing this heteroarene system stimulated even broader interest in 1,2-diazine chemistry [59].

Therapeutic interest in this kind of drug has increased considerably due to their cytotoxic activity, notable decreasing blood flow in the tumors [60].

From their structure-activity relationship, it may be expected that hydrazinepyrazoleo [3,4-d] pyridazines, which are formed by replacement of the benzene ring in hydrazine with a pyrazole nucleus can exhibit interesting biological activity [57].

1.5.0- Imidazoles and Pyrazoles:

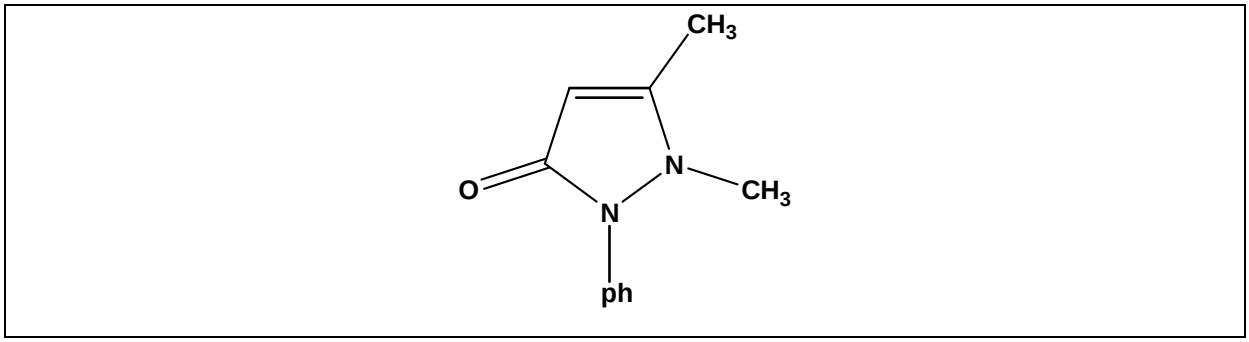
Imidazole is an aromatic compound because it is cyclic, planar and conjugated associated with 6π-electrons; one from each carbon one from the "pyridine" nitrogen and two from the "pyrrole" nitrogen:



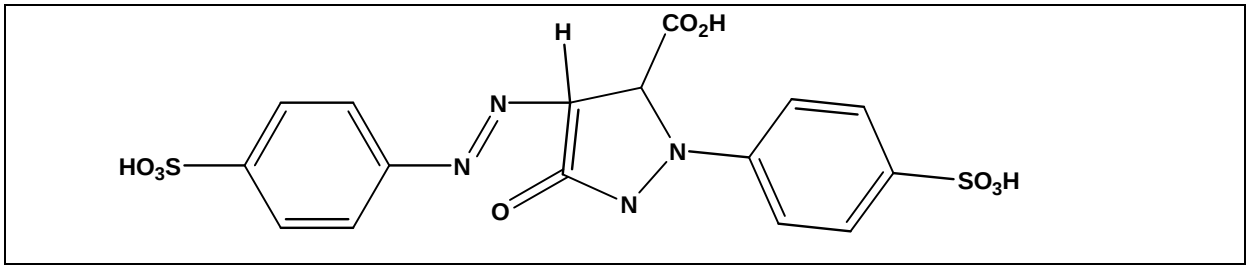
The emido hydrogen atom in imidazole is tautomeric and in practice the two nitrogen atoms are indistinguishable [61].

This is one of the reasons why histidine, the imidazole containing amino acid, is an important component of serine protease enzymes: these are family of closely related enzymes that contain uniquely reactive serine residue at the active site. They are called protease because they catalyze the hydrolysis of peptide bonds in polypeptides and proteins [(62)].

Antipyrine 2,3-dimethyl-1-phenyl-5-pyrazolone and its derivatives exhibit a wide variety of potentially useful applications including biological, clinical and pharmaceutical [(63)].



Tartrazine is a yellow dye for wool; this dye has been gaining commercial importance [(63)] because they are also used for the artificial coloring of foods:



However very 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 in fact pyrazolones [(64)].

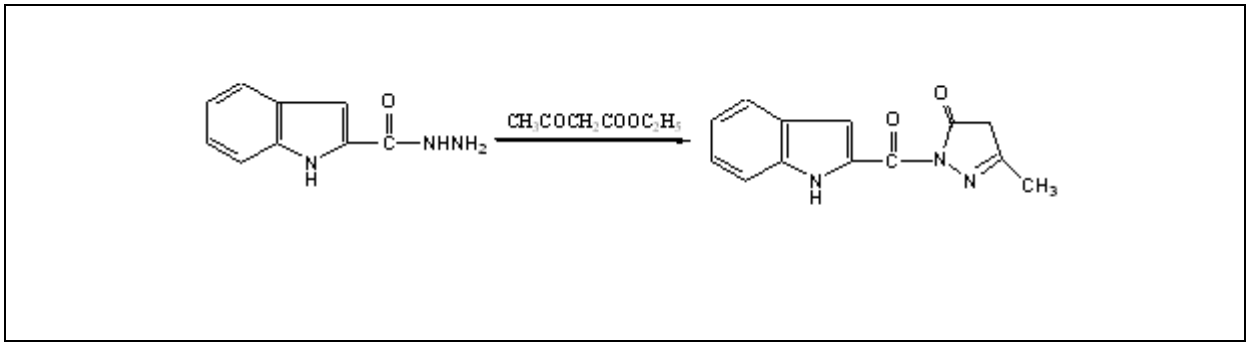
Pyrazole and imidazole are heterocyclic compounds of five membered diunsaturated ring structure composed of three carbon atom and two nitrogen

atoms, if pyrazole is 1,2-diazole while imidazole is 1,3-diazole. Pyrazole derivatives play a vital role in many biological processes and synthetic drugs [65].

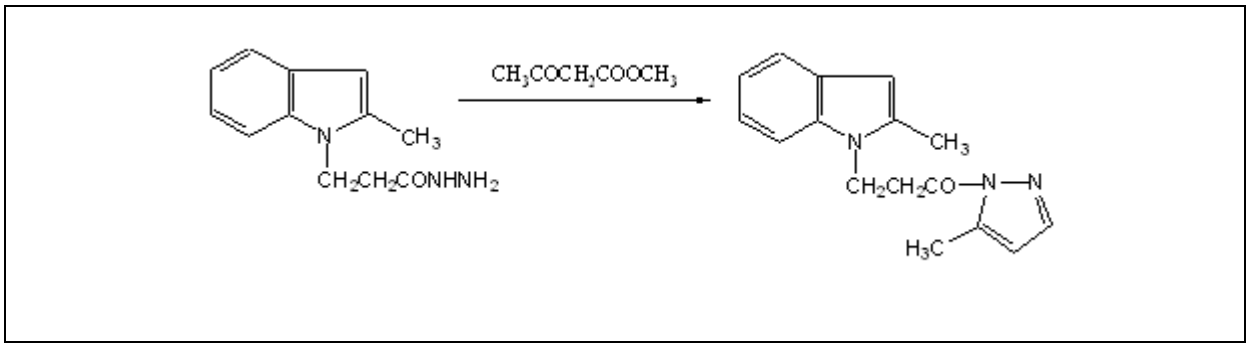
1.5.1- Synthesis of Imidazole and pyrazole:

Pyrazolones are biologically interesting compounds and their chemistry has received considerable attention. These variable activities have led to intensive research on their synthesis.

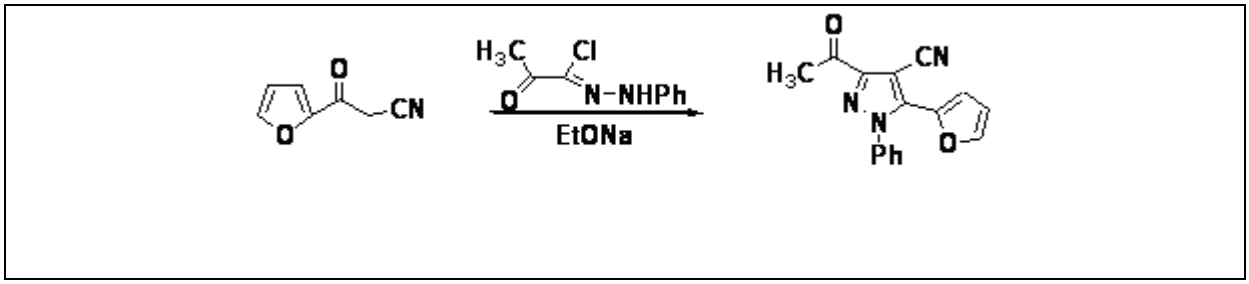
Fahmy et.al., [66] found that the reaction of 2-indol carbohydrazide with ethyl acetoacetate gave 2-[3-methyl-5-oxo-pyrazolin-1-yl]carbonyl indole :



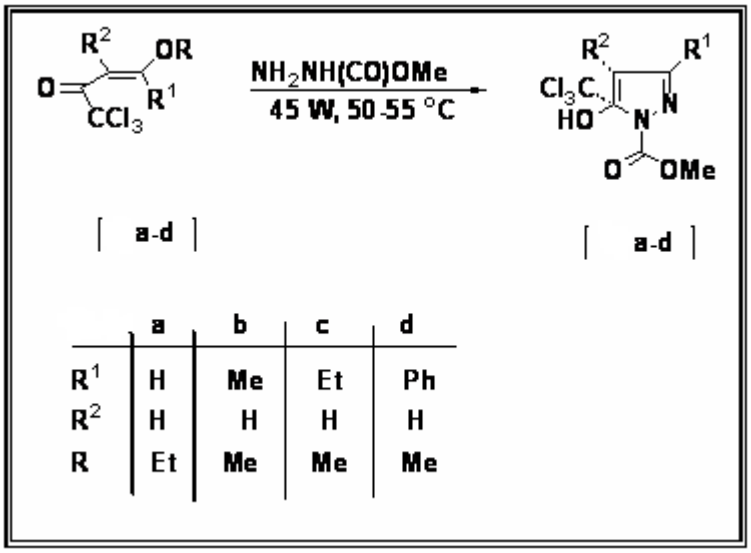
El-Masry et.al.,[67] found that the reaction of 3-(2-methylbenzi midazol-1-yl) propanoic acidhydrazide with acetylacetone to afford the 1-[3(2-methylbenzimidazol-1-yl]-3, 5-dimthylpyrazole :



Dawood et. al., [68] have synthesized through reaction of 3-(2-furyl)-3-oxo-propanitrile with ethanolic sodium ethoxide followed by addition of hydrazonyl halide:



Martins et. al., [69] prepared a number of 3,4-disubstituted-5-trichloromethyl-5-dihydro-1*H*-1-pyrazole methyl ester [a-d] under microwave irradiation through the reaction of 1,1,1-trichloro-4-alkoxy-3-alken-2-one [a-d] and methyl hydrazino carboxylate in presence of 10 ٪ HCl :



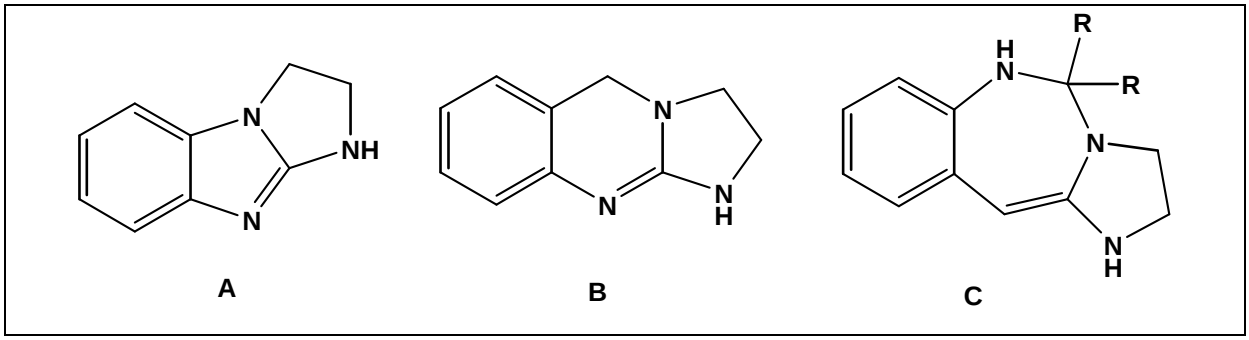
	a	b	c	d
R^1	H	Me	Et	Ph
R^2	H	H	H	H
R	Et	Me	Me	Me

1.5.2- Biological activity of pyrazoles and imidazoles:

Imidazole drugs have been a broad spectrum in remedying various dispositions in clinical medicine[70].

It was found that interconnecting the imidazoline and phenyl ring, as was achieved in 2,3-dihydroimidazol [1,2-a] benzimidazole (A) or 1,2,3,5-tetrahydro-imidazo [2,1-b] quinazoline (B) afford agents capable of lowering the blood pressure of experimental animals.

On the other hand, it was recently found that certain 2,3,5,6-tetrahydro imidazo-[2,1-b][1,3,5] benzothiazepines of type (C) exhibit have been broad spectrum vasocontractile activity in isolated rabbit aortic [71].



Benzimidazole derivatives are of wide interest because of their diverse biological activity and clinical applications. They have a broad antifungal spectrum as they inhibit the action of certain microorganisms[70,71].

The incorporation of the imidazole nuclei is an important synthetic strategy in drug discovery [72]. The high therapeutic properties of the related drugs have encouraged the medicinal chemists to synthesize a large number of novel chemotherapeutic agents [73].

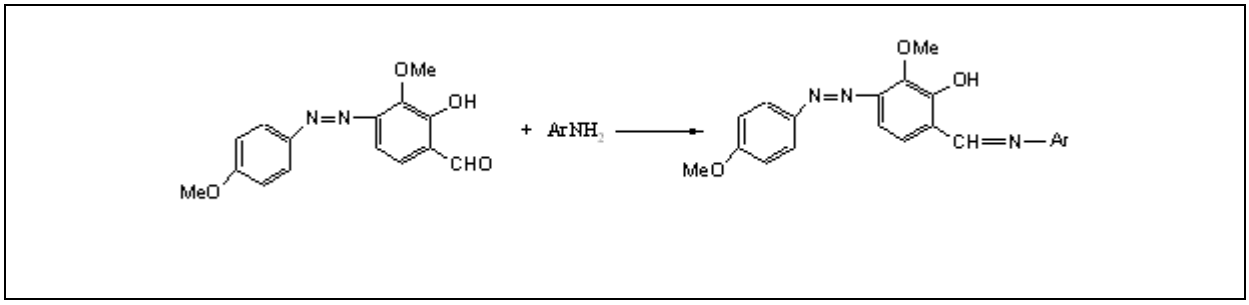
1.6.0- Schiff bases:

Schiff bases, so called since their synthesis was first reported by German chemist H. Schiff, result from condensation of primary amines with aldehydes or ketones.

Schiff bases are characterized by the –N=CH- (imine) group which is important in elucidating the mechanism of transformation in biological systems. Due to great flexibility and diverse structural aspects, a wide range of Schiff bases have been synthesized and their complexation behavior studied [(74)]. Furthermore, Schiff bases are reported to show a variety of interesting biological activities, including antibacterial [(75)], antifungal [(76)], anti mouse hepatitis virus (MHV) [(77)], anticancer [(78)] and herbicidal activities [(79)].

It is also known that the presence of an azo moiety in different types of Schiff bases can lead them to exhibit pesticidal activities. Both Schiff bases and azo compounds are important structures in the medicinal and pharmaceutical fields [(80)] and it has been suggested that the azomethine linkage might be responsible for biological activities displayed by Schiff bases.

In the light of the interesting variety of biological activities seen in compounds containing azo and azomethine linkage, ***Jarrahpour*** et.al.,[(81)] prepared eight new azo Schiff bases via condensation of different aromatic amines and new azoaldehydes:



Ar = C_6H_5, $CH_2C_6H_5$, *m*-HOC_6H_4, *m*-$CH_3C_6H_4$, *o*-$CH_3C_6H_4$, *p*-MeC_6H_4,

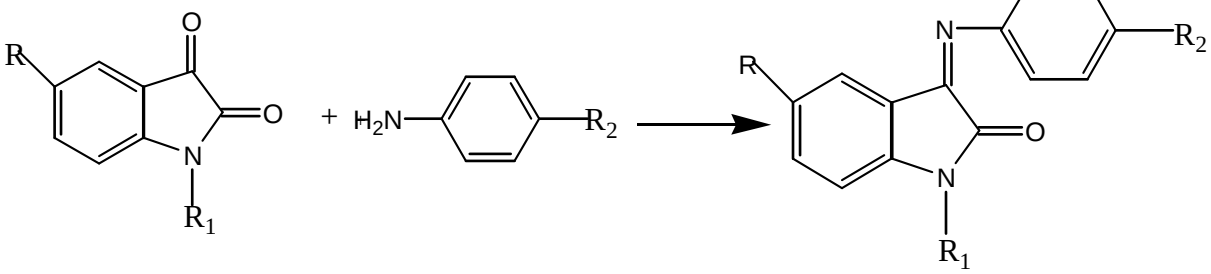
m-MeC_6H_4, *o*-$MeOC_6H_4$

The antifungal and antibacterial activities of these compounds were also determined.

Aldimines have generally used in the formation of a large number of industrial compounds via cycloaddition, ring closure and replacement reactions [82,83].In addition, the ketimines of heterocyclic carbaldehydes, which are widely used in the production of pharmaceuticals, have taken an important place among the compounds of biological interest because of the conjugation and the groups that they might contain within their molecules.

Epilepsy is a disease of complex nature and of different etiology. A large number of populations of different age groups and sex are affected by this disease.

Verma et.al, [84] synthesized Schiff bases of N-methyl and N- acetyl isatin derivatives, the synthesized compounds have been screened for anticonvulsant activities:



R=Br,NO_2

R_1=CH_3,$COCH_3$

R_2=NO_2,COOH,OCH_3,Cl,F

All the synthesized compounds show anticonvulsant activities , the compound N- methyl-5- bromo -3-(*p*-chlorophenylimino)isatin showing better activity than

the standard drugs thus it may be chosen as a prototype for development of new anticonvulsants [85].

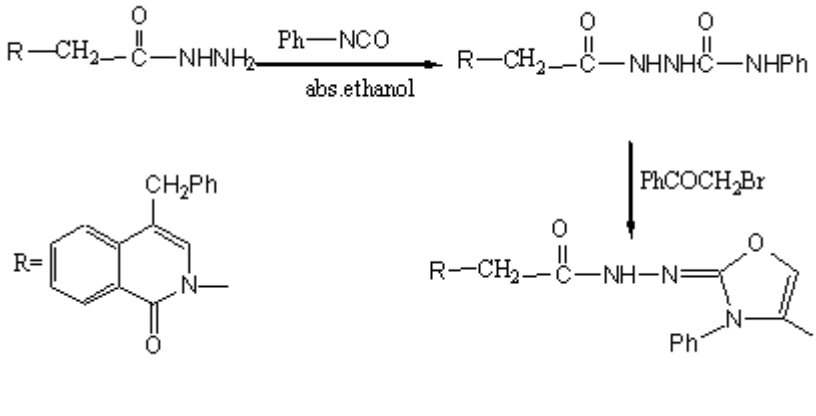
1.7.0- Oxazolines:

Oxazoline is one of a class of organic heterocyclic compounds containing a five member one unsaturated ring structure composed of one oxygen atom and one nitrogen atom, oxazoline can be represented by two forms [86].

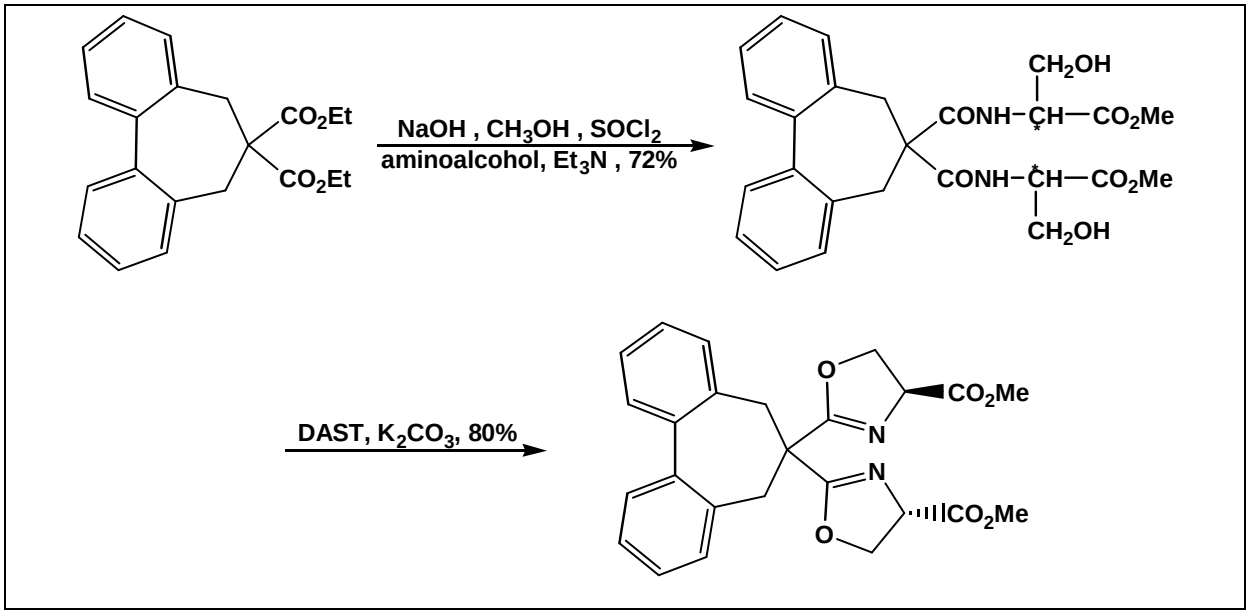
1,3-Oxazoline

1.7.1- *Synthesis of oxazoline:*

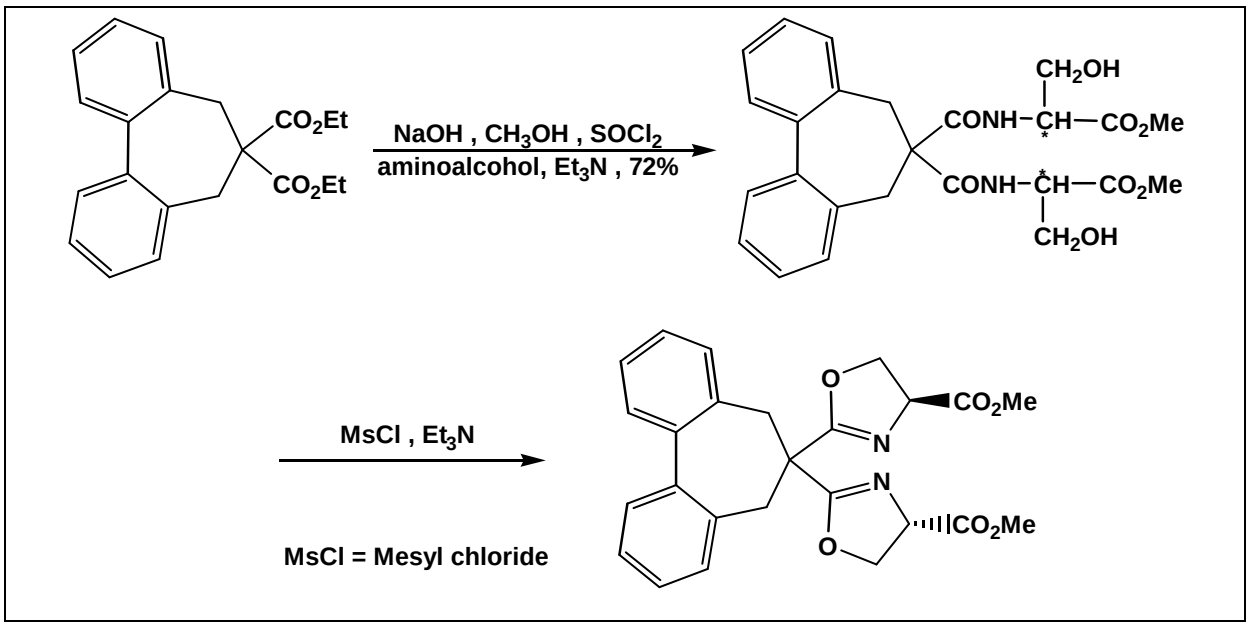
El-Tamaty et.al., [87] found that the reaction of 4-Benzyl-1(2H)-oxa phthalazine-2-yl acetic hydrazide with phenylisocynate afforded the respective semicarbazides. Further cyclization of the respective semicarbazides with phenacyl bromide led to formation 4-Benzyl-2- (3,4-diphenyloxazole-5-yliden hydrazidecarboxymethyl) phthalazine-1 (2H)-one :



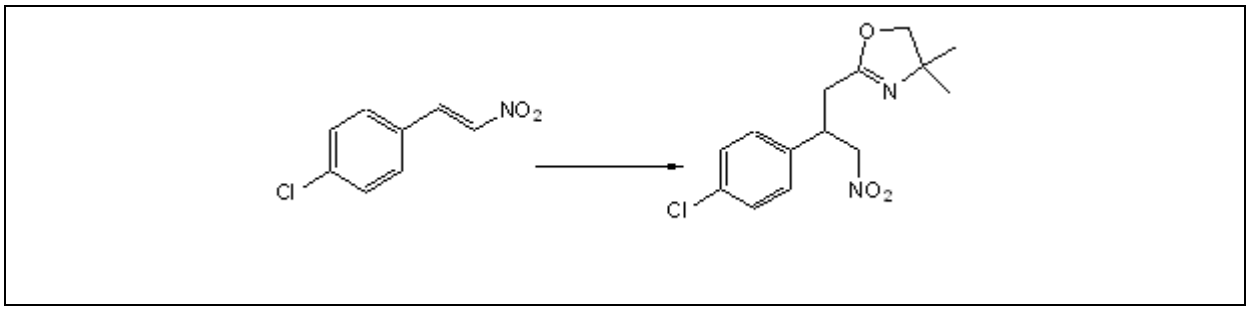
Williams et. al. [88], synthesize bis (oxazoline) biscarboxylate in high yield from treatment of dihydroxy diamide with a slight excess of the dehydrating agent, dimethylaminosulfur trifluoride (DAST) at -78 ^{o}C in CH_2Cl_2 followed by addition of K_2CO_3 and warming to room temperature.



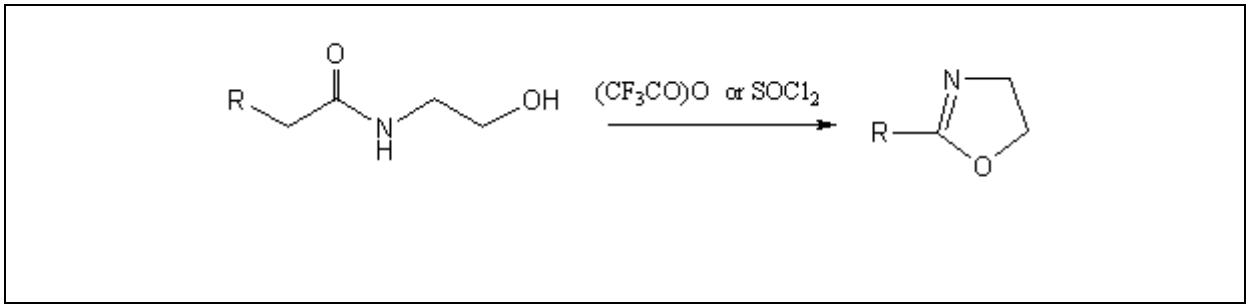
The compound below which bear tert-butyl on the oxazoline ring was also synthesized following the same procedure using MsCl, Et_3N instead.



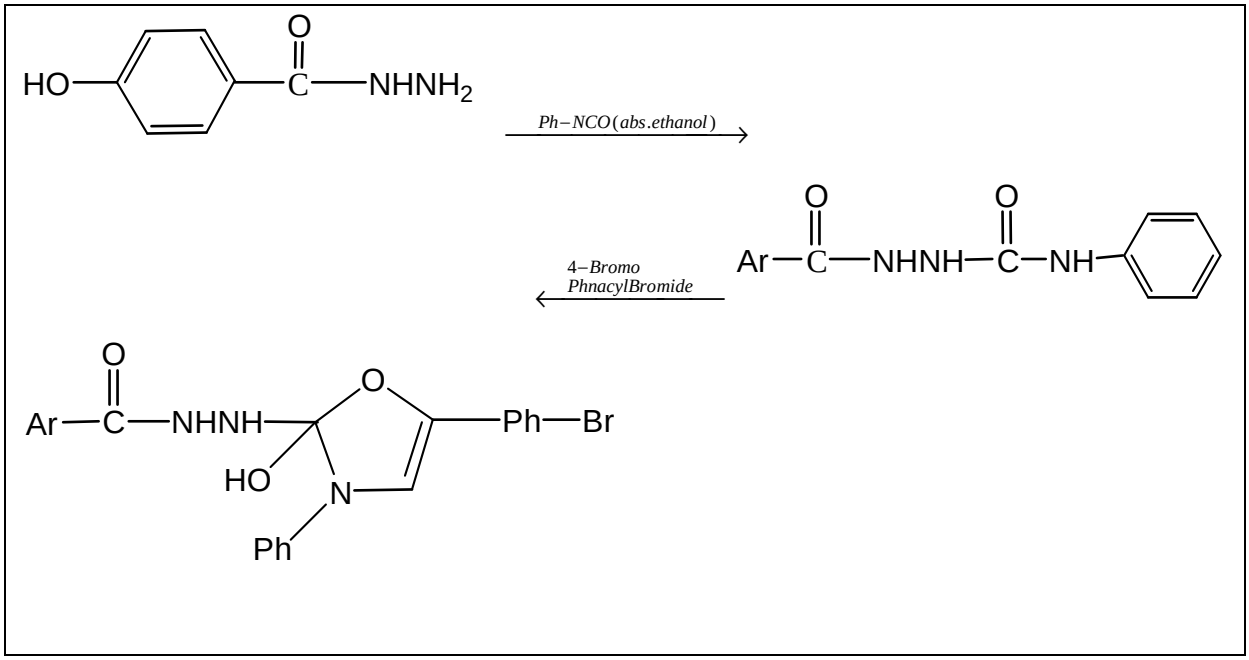
Santos et.al., [89] synthesized γ-nitro oxazoline by reaction of p-chloro-β-nitrostyrene with oxazolinecyanocuprate :



Kuklev and Smith [90] reported that the reaction of dienoic with trienoic fatty acids yielded 2-acyloalines :



R.M.Fowzi[91] et.al, found that the reaction of p-hydroxy benzoic hydrazide with phenyl isocyanate afforded to the respective semicarbazide . Further cyclization of the respestive semicarbazide with 4-bromophenacylbromide led to formation of N-[(2)-5-(p-bromophenyl)-3-phenyl-1,3-oxazol-2-(3H)-ylidine]-aryl-hydrazide.



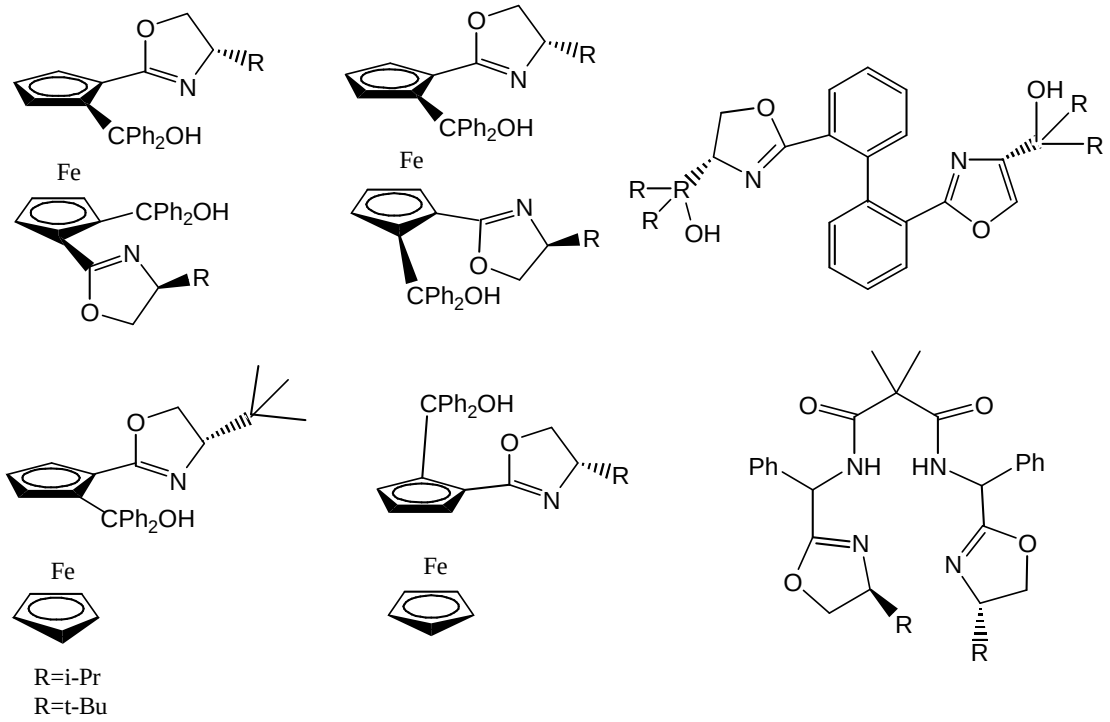
1.6.1 Oxazoline uses:

Chiral oxazolines, especially chiral bis(oxazoline), have been widely applied in many catalytic asymmetric reactions as versatile ligands[92,93].

Oxazoline-base ligands were also found to be effective for the asymmetric addition of diethyl zinc to aldehydes [94,95]. In particular, the ligand combining the oxazoline ring and hydroxy group or an amino group have been reported to show execllent catalytic activity in the asymmetric addition of diethyl zinc to aldehydes[96,97].

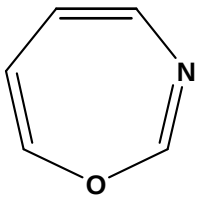
For example, ***Zhang*** et.al., [98] developed the ligands for the asymmetric addition of diethyl zinc to aldehydes and high enantioselectivities were obtained.

Ligands and that explored by ***Bolm*** et.al., [99] and ligands designed by ***Pastor*** and ***Adolfsson***[100], respectively, also showed good catalytic activity. In these ligands, the oxazoline unit and adjacent hydroxy group function together to control the catalytic process.



1.8.0- Oxazepines:

Oxazepine belongs taking non-homologous structure which has 7-membered that contains 2-non-homologous atoms (oxygen and nitrogen) and structure formula compounds:



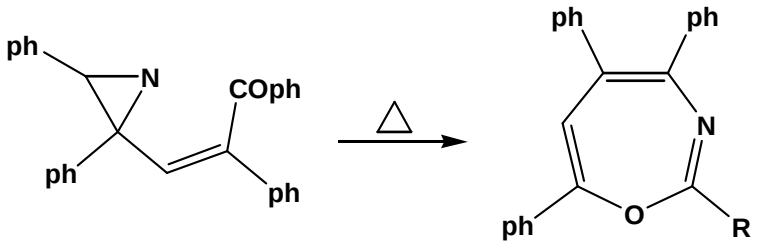
1,3-oxazepine

H. Abid et. al. [101,102] prepared new ways to build up this 7-membered heterocyclic ring system.

1.8.1- Synthesis of oxazepines:

Oxazepine and number of its derivatives were prepared by different methods such as:

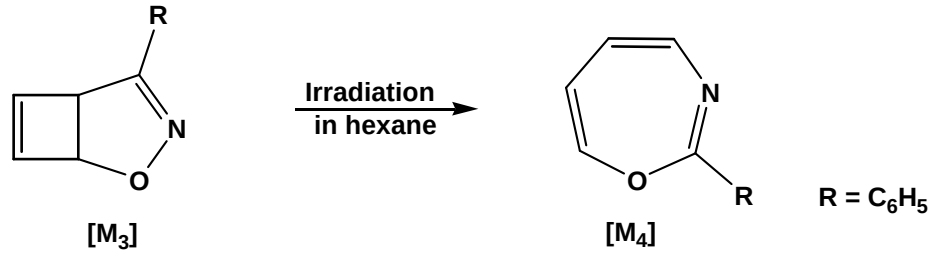
Le Roux et. al. [103], synthesized oxazepines in 90% [M_2] through heating of [M_1] in 100 ^{o}C.



[M_1] **[M_2]**

Tetraphenyl (Z) keto vinylazine **4,5,7-tetraphenyl-2-sub-1,3-oxazepine**

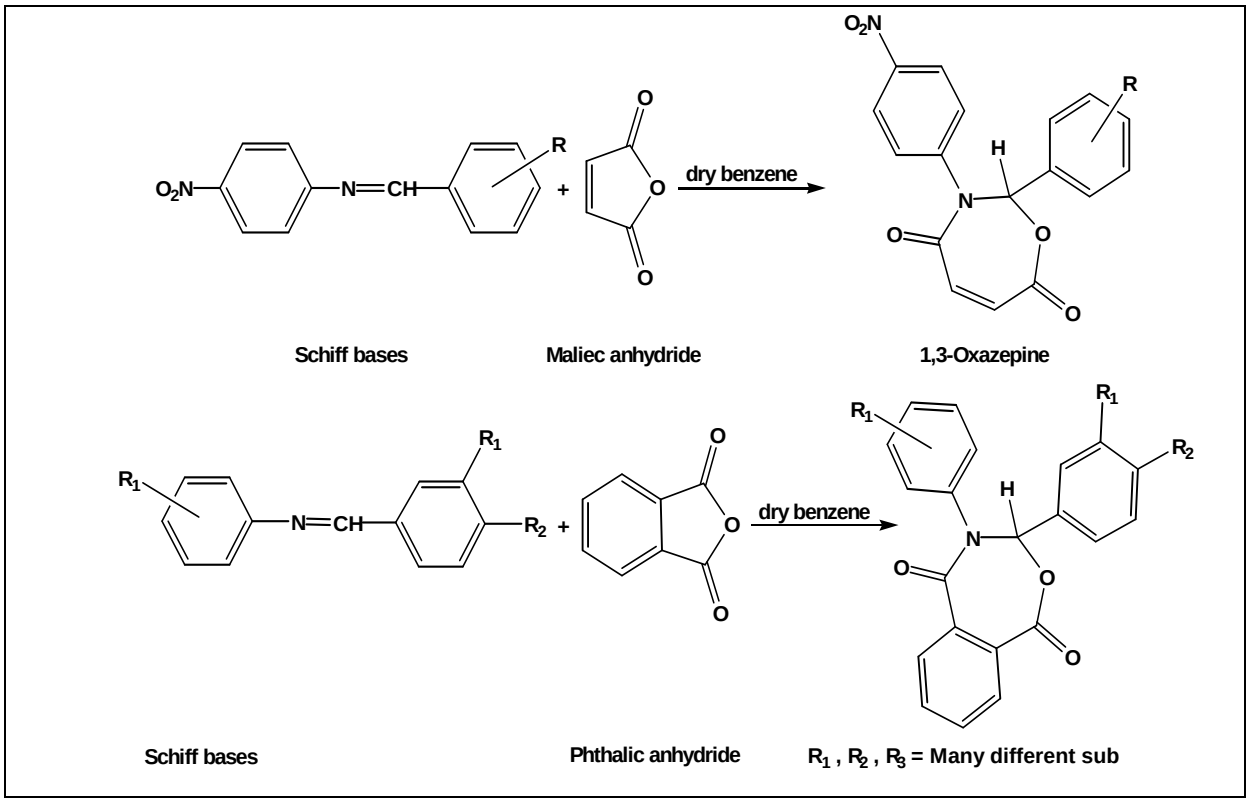
Kumagai et. al. [104], synthesized oxazepines through photochemical reaction of [M_1] as shown in the following equation:



[M_3] **[M_4]**

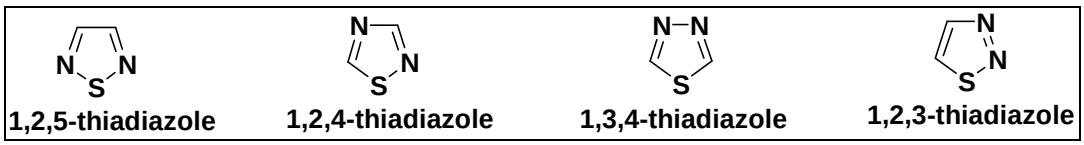
2-oxa-3-azabicyclo [3.2.0] hepta-3,6-dione **2-Sub-1,3-oxazepine 80% yield**

Hussein and ***Obaid*** [101,102] prepared oxazepindione from the reaction of Schiff bases with maleic or phthalic anhydride in dry benzene.



1.9.0- Thiadiazole:

Thiadiazole compounds are classes of five membered rings containing two nitrogen atoms and one sulfar atom and exist with different structure formulas:



The development of 1,3,4-thiadiazole chemistry is linked to the discovery of hydrazine and phenyl hydrazine. The first 1,3,4-thiadiazole was prepared by J.Sand in 1882 [105].

Bak et. al., [106] made a careful analysis of the microwave spectrum of 1,3,4-thiadiazole, they could determine the structure of the molecule as shown in figure (1 -4)

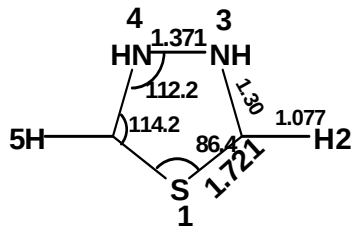
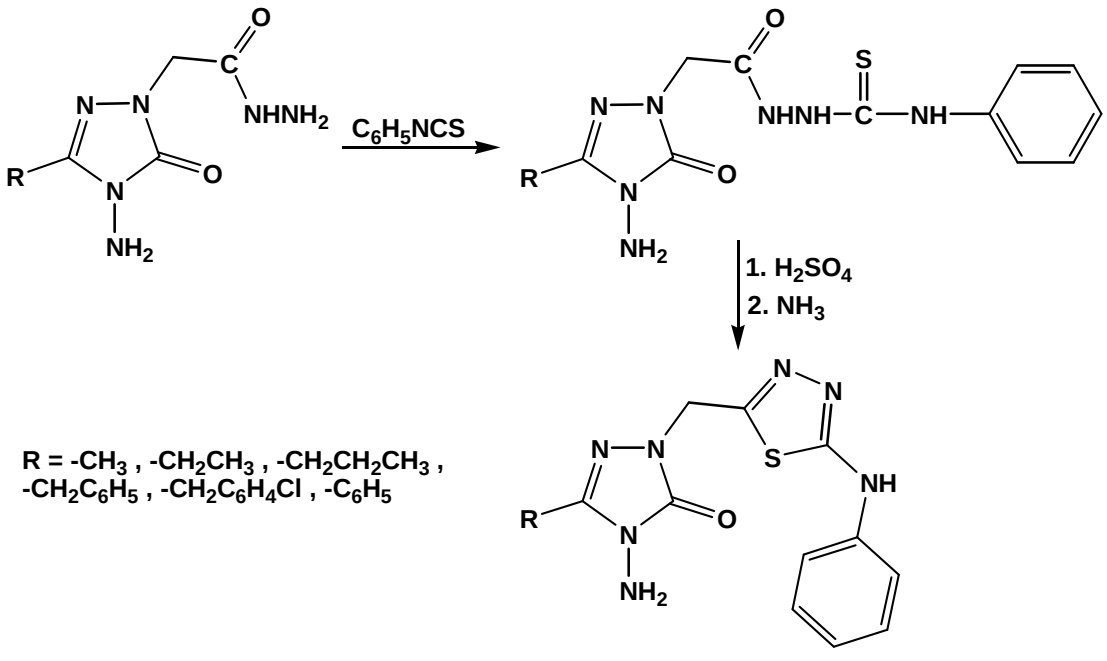


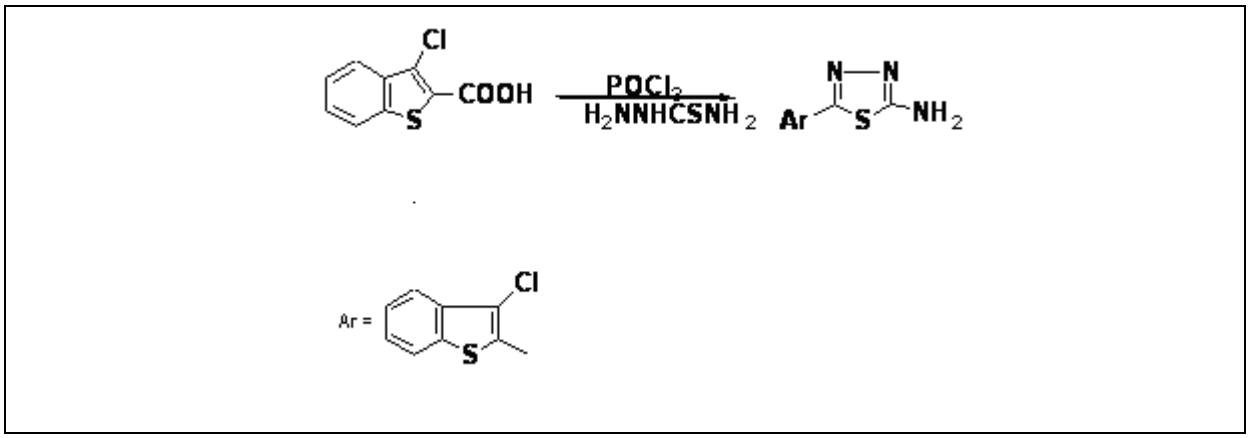
Figure (1-4)

1.9.1- Synthesis of 1,3,4- Thiadiazole:

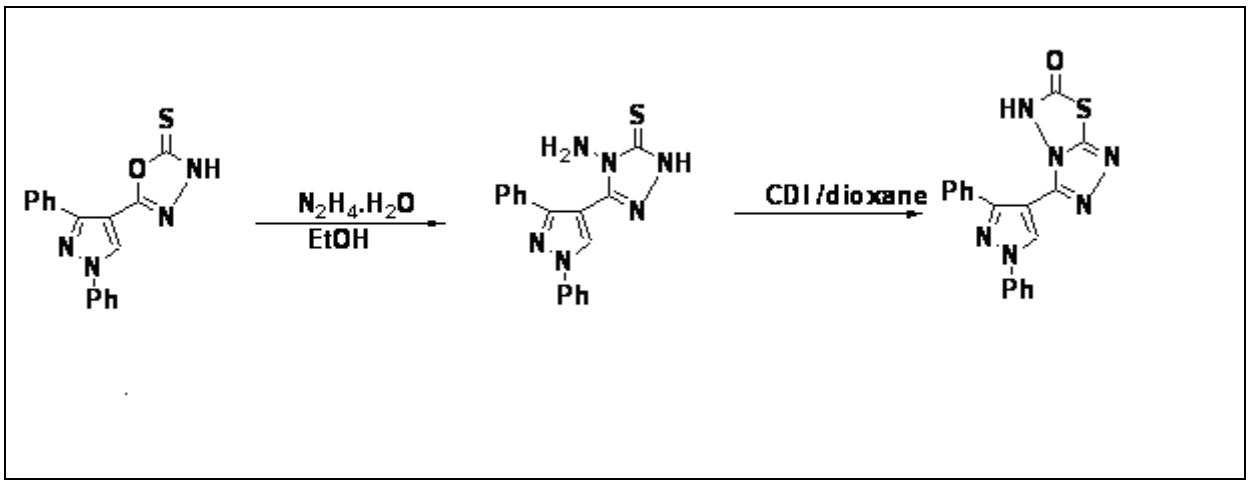
Neslihan Demirbas [107] synthesized derivatives of 1,3,4-thiadiazole from the reaction of (4-amino-3-substituted-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl) acetic acid hydrazide with phenyl isothiocyanate and the resulting thiosemicarbazide derivatives were cyclized using sulfuric acid.



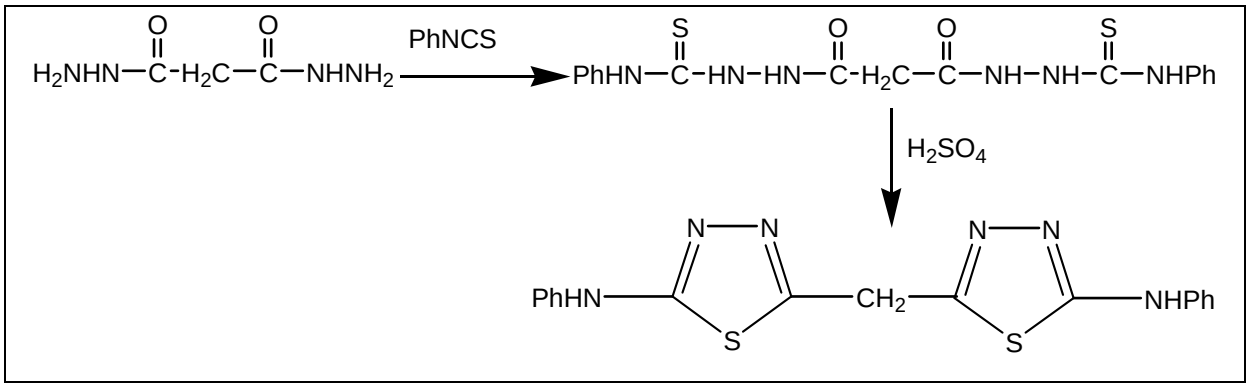
Aly and El-Sayed [108] have synthesized 2-amino-5-(3-chlorobenzo [b]thiophen-2-yl)-1,3,4-thiadiazole through condensation of 3-chlorobenzo[b]thiophene-2-carboxylic acid with thiosemicarbazide by using phosphorous oxychloride as condensing agent:



Farghaly et. al., [109] found that the reaction of oxadiazole thione 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. Reacted of with 1,1-carbonyldiimidazole (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-6-one



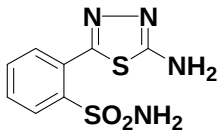
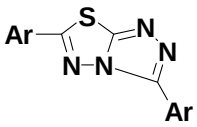
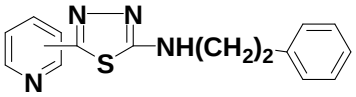
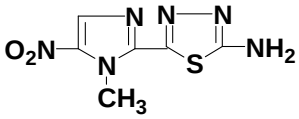
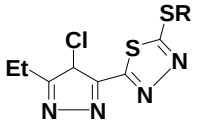
Sh.S.Hassan [110] found that the reaction of malonic acid hydrazide with phenyl isothiocyanate afforded to the respective thiosemicarbazide.Further cyclization of the respective thiosemicarbazide with conc. sulfuric acid led to formation of bis-[5-phenyl amino-2-yl-1,3,4-thiadiazole] methane.



1.9.2- Biological activity of 1,3,4-thiadiazole :

1,3,4-thiadiazoles are known for their broad-spectrum of biological activity such as antifungal [111, 112], antibacterial [113], herbicidal [114], antiviral [115], and analgesic effect [116, 117].

Table (1-3): Biological activity of some thiadiazole.

No.	Compound name	Structure	Biological activty	Ref
1.	2-amino-5-(2-sulfamoylphenyl)1,3,4-thiadiazole		antiviral activity	115
2.	2,5-disubstituted-s-triazolo[3,4-b][1,3,4]thiadiazole		antibactrial	118
3.	2-benzylamino-5-(2-pyridyl)1,3,4-thiadiazole		antibactrial	118
4.	[2-amino-5(1-methyl-5-nitro-2-imidazolyl)1,3,4-thiadiazole		antibacterial and anti-parastic compound	120
5.	5-(4-chloro-3-ethyl-1-methyl-1-pyrazol-5-yl)-2-alkylthio-1,3,4-thiadiazole	 R = H, CH_3 , CH_3CH_2 , C_3H_7 , C_6H_{11}	fungicidal	121

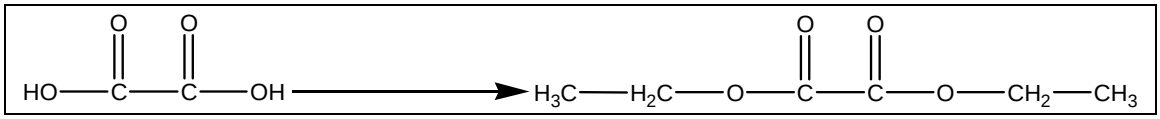
The aim of the Work:

Five, six and seven membered heterocyclic compounds have been of great interest on account of their variety of applications particularly in the field of chemotherapeutic, antimicrobial, pesticidal, agriculture and fungicide, therefore, the present work was directed toward the synthesis of new derivatives containing heterocyclic ring, starting from oxalic acid. Such derivatives are expected to have biological activity.

Chapter Three

Results and Discussion

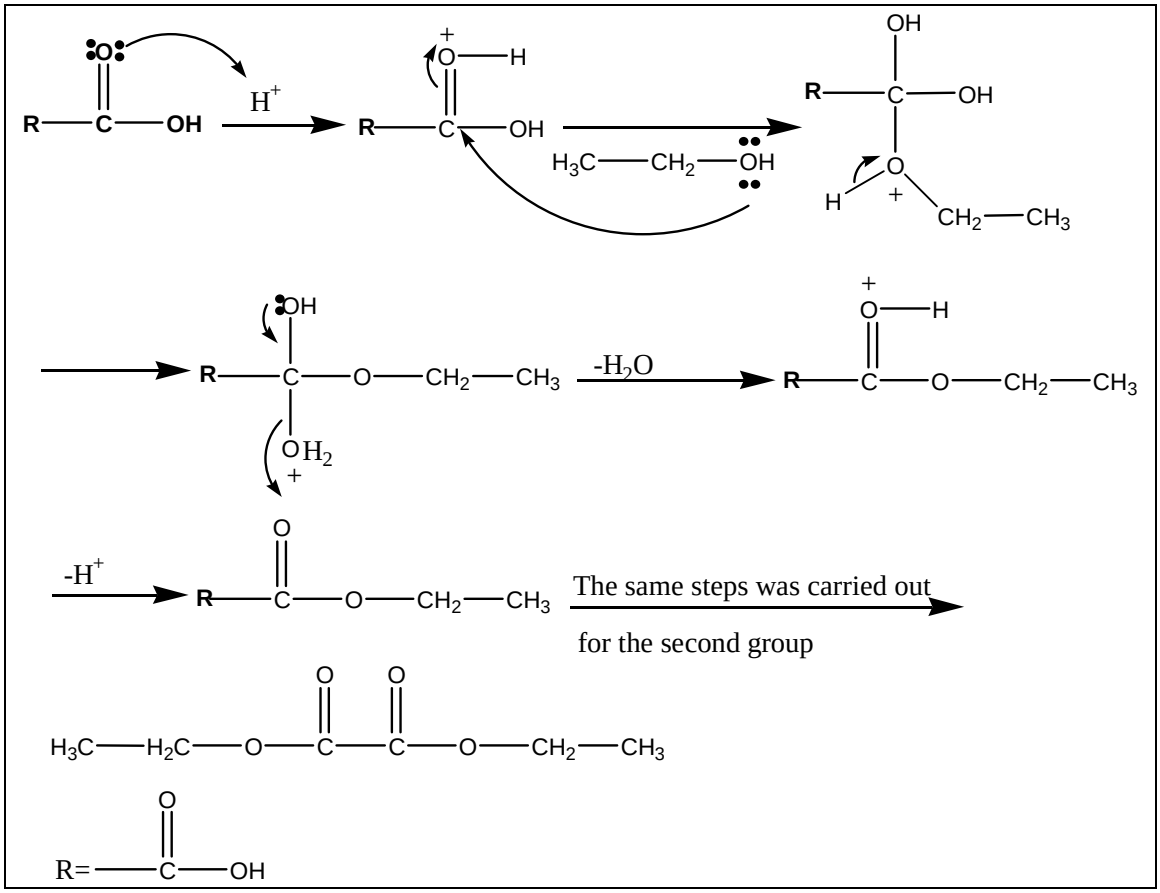
3.1 Synthesis of Diethyl oxalate [1]:



Scheme (3-1) Reagents and Conditions:abs.EtOH, H_2SO_4 ,Reflux (6) hrs.

The FTIR spectrum in figure (3-1) shows the appearance of the C=O carbonyl band of oxalic acid at (1697.2) cm^{-1} ,and appearance of band due to (-OH) group at (3431.1) cm^{-1} .
The FTIR spectrum in figure (3-2) shows the disappearance of the C=O carbonyl band of oxalic acid at (1697.2) cm^{-1} , also disappearance of (OH) of acid at (3431.1) cm^{-1} , appearance of band at (1743.5) cm^{-1} due to the stretching vibration of the C=O of the formed ester, aliphatic C-H appeared in the region (2925.8-2858.3) cm^{-1} , (C-H) bending vibration appeared at (1417.6) cm^{-1} ,and (-OH) band appeared at (3450) cm^{-1} due to the presence of excess ethanol with diethyl oxalate.

The mechanism of formation of [1] is shown below :



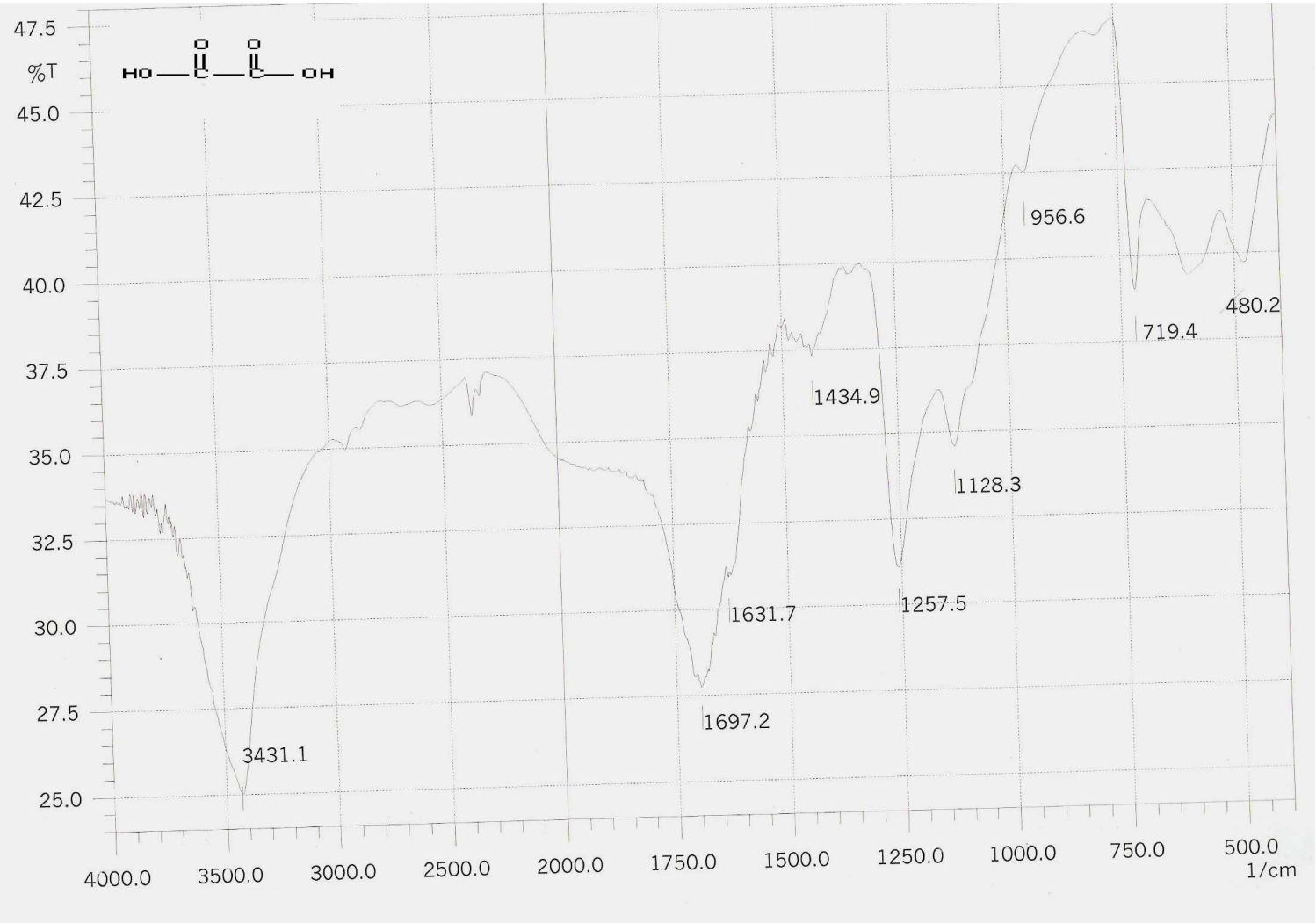


Figure (3-1) FTIR spectrum of compound [oxalic acid] [I]

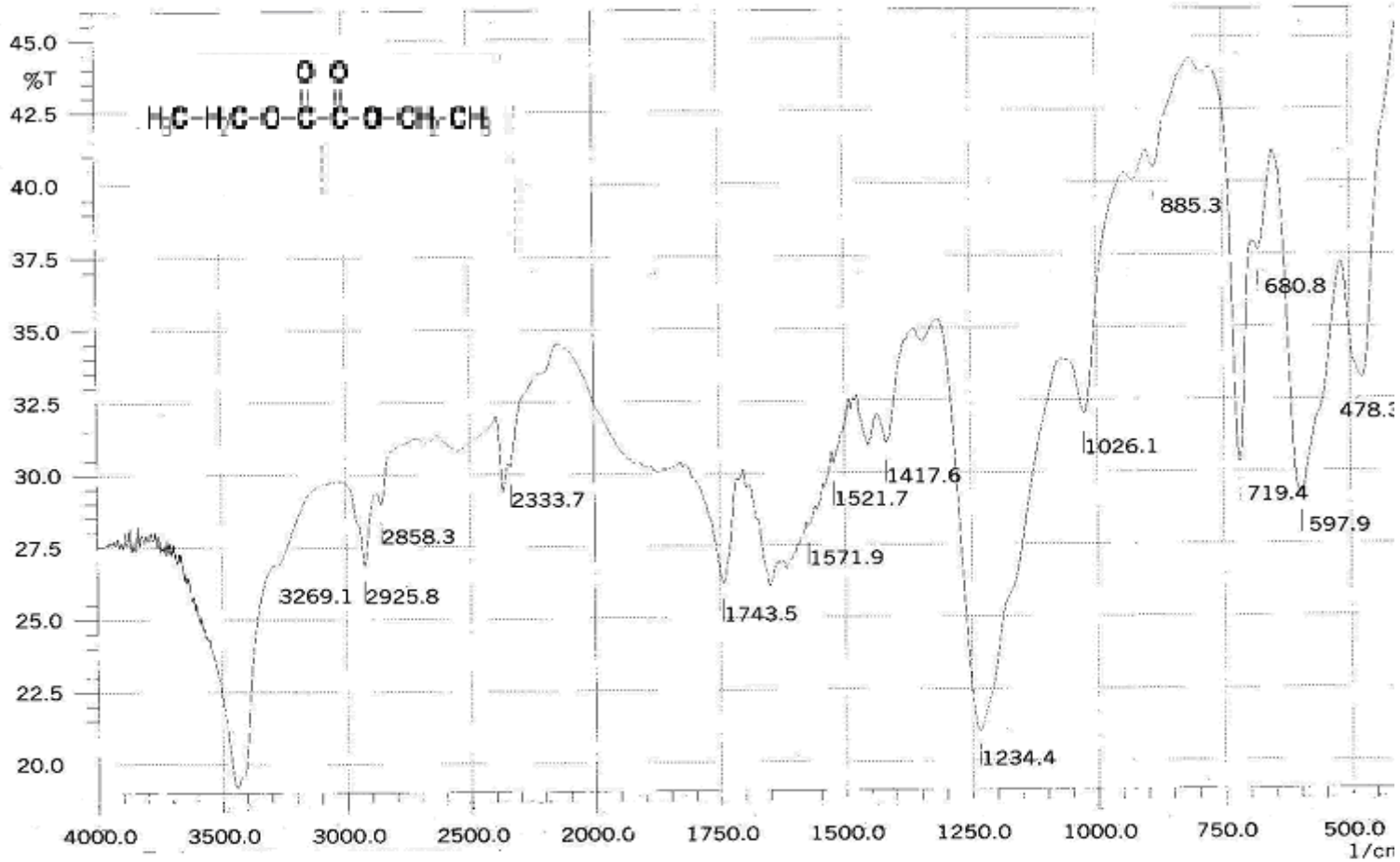


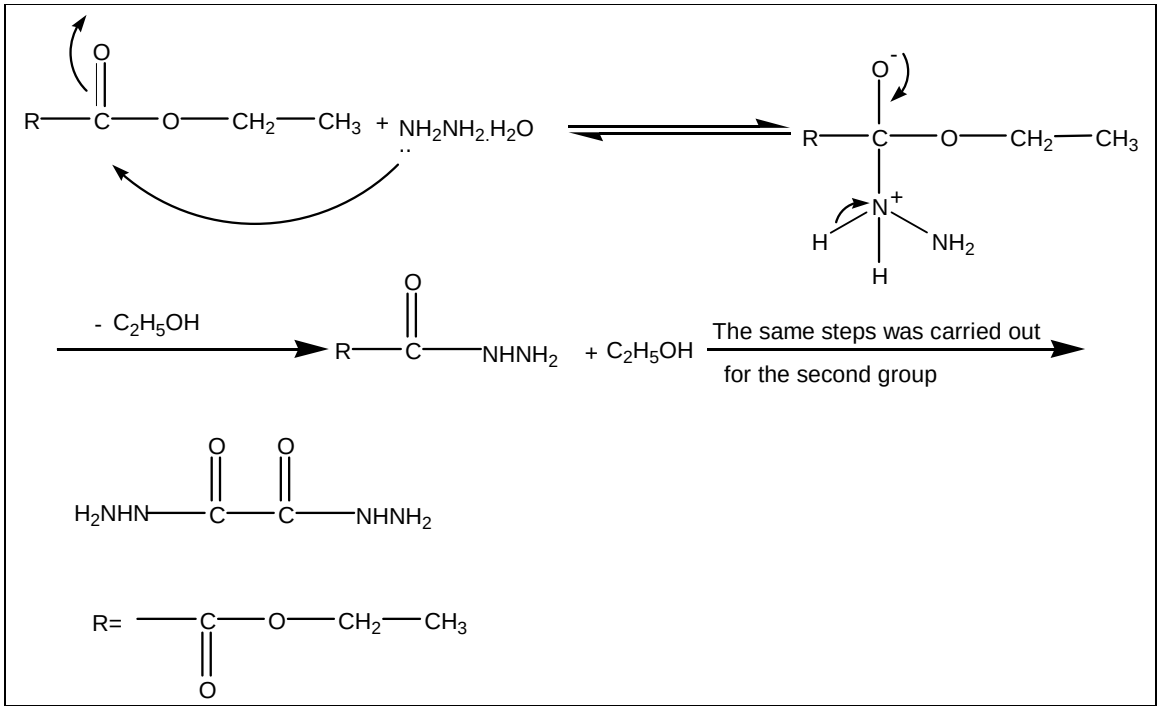
Figure (3-2) FTIR spectrum of compound [diethyl oxalate] [1]

3.2 Synthesis of oxalic acid dihydrazide [2]:

The acid hydrazide was synthesized by the reaction of ester [1] with hydrazine hydrate in absolute ethanol.

The reaction of hydrazine hydrate with ester is one of the most common reactions to synthesize the acid hydrazide derivatives; it is a tetrahedral nucleophilic substitution reaction [(134)]. The FTIR spectrum in figure (3-3) shows the appearance of the characteristic absorption bands in the region (3292.3-3190) cm^{-1} due to asymmetric and symmetric stretching vibration of the ($NH-NH_2$) group, disappearance of absorption band in the region (1743.5) cm^{-1} for [1] due to the stretching vibration of the carbonyl group of ester, a new band appeared at (1662.5) cm^{-1} due to the stretching vibration of amide I and appearance of amide II bending vibration band at for (-NH) group at (1502) cm^{-1}.

The mechanism of the reaction [135] is shown below:



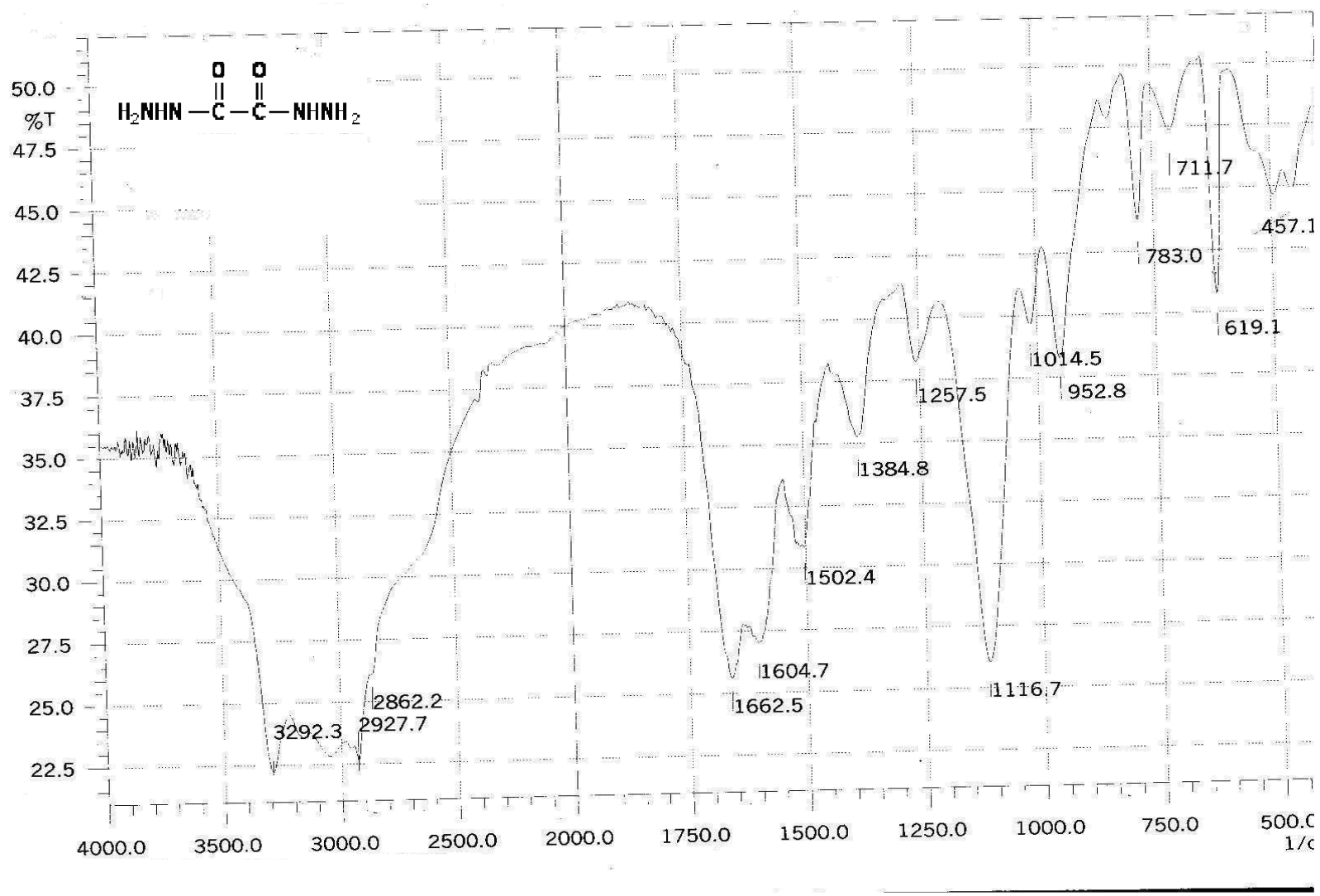
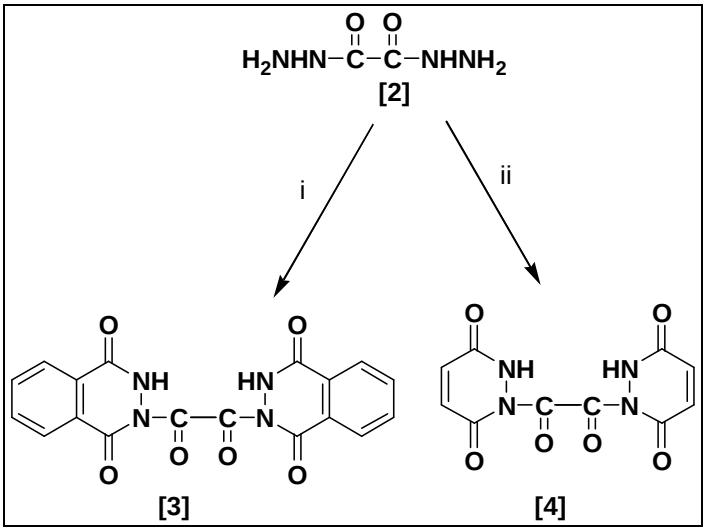


Figure (3-3) FTIR spectrum of compound [oxalic acid hydrazide] [2]

3.3 Synthesis of pyridazin-dione and phthalazin derivative [3,4] :



Scheme (3-2) Reagents and Conditions: i- phthalic anhydride, acetic acid, reflux (7) hrs. ii- maleic anhydride, acetic acid, reflux (7) hrs.

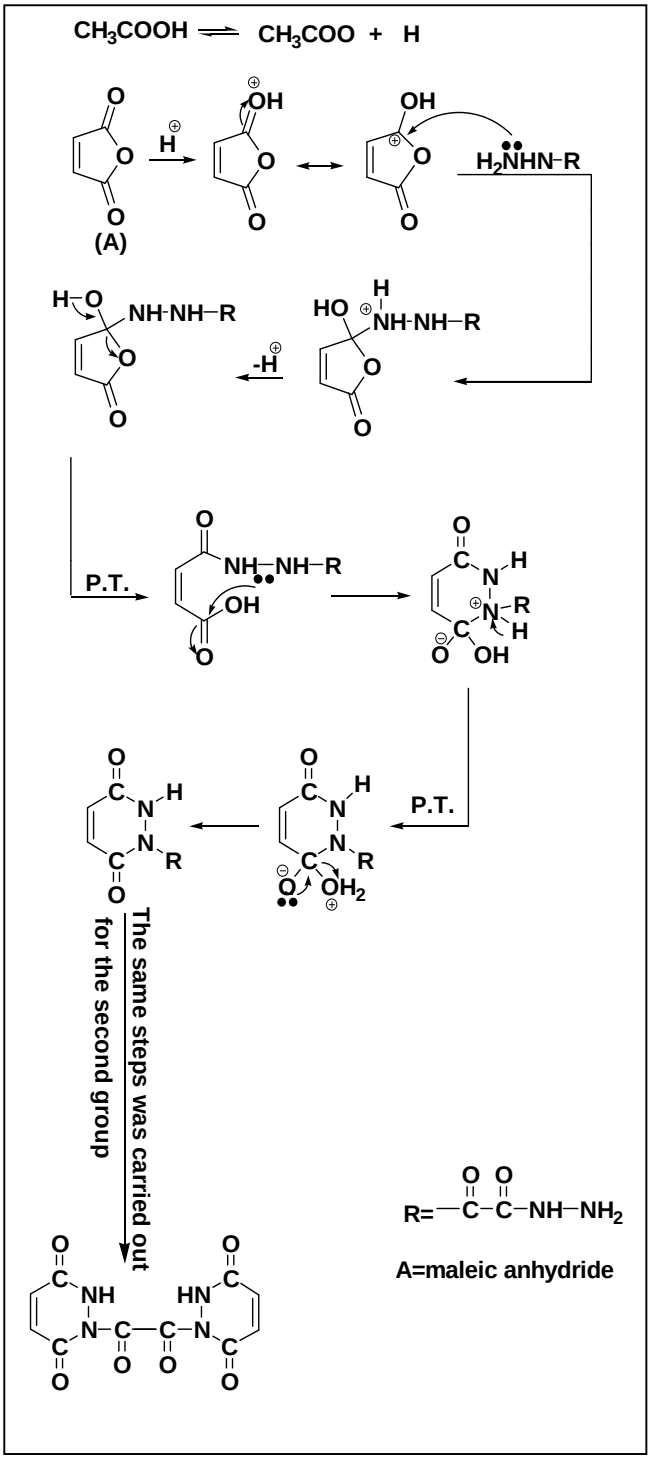
Pyridazin-3,6-dione and phthalazin-3,8-dione derivatives were synthesized by the reaction of hydrazide derivative with maleic anhydride and phthalic anhydride respectively in the presence of acetic acid as a solvent and catalyst.

The FTIR spectra of compounds [3,4] in figures (3-4) and (3-5)show the disappearance of the bands of NH–NH_2 group in the region (3292.3-3190) cm^{-1} , appearance of a band due to (N-H) group at the range (3250-3190) cm^{-1}, two carbonyl groups of compounds [3,4] appeared at (1660.6) cm^{-1} , aromatic (CH) appeared at (3025) cm^{-1},and (-CH) alkene appeared at (3178.47) cm^{-1}.The characteristic bands of compounds [3,4] is shown in table (3-1).

Table (3-1):Characteristic bands of compounds [3] and [4]:

Comp. No.	***υ(C-H) alkene cm^{-1}***	***υ(N-H) cm^{-1}***	***υ(C-H) arom. cm^{-1}***	***υ(C=O) cm^{-1}***	***υ(C=C) cm^{-1}***	***δ(N-H) cm^{-}***
3	***------***	***3190***	***3025***	***1660.6***	***1604.7***	***1556.4***
4	***3178.47***	***3250***	***------***	***1660.6***	***1544.88***	***1407.94***

The mechanism of this reaction is shown below[136] :



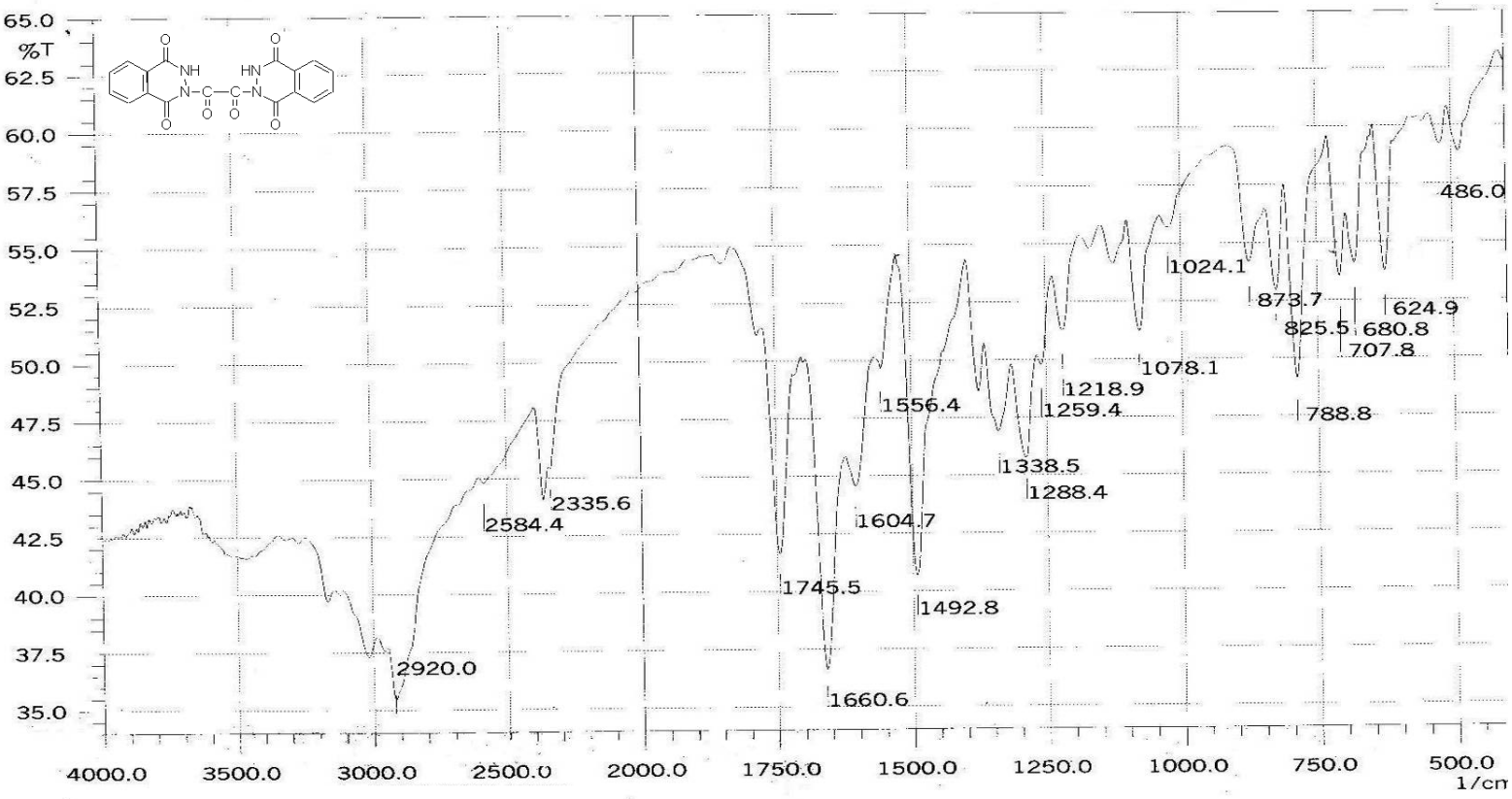


Figure (3-4) FTIR spectrum of compound [bis-(1-(formyl)-1,2-dihydrophthalazin-3,8-dione] [3]

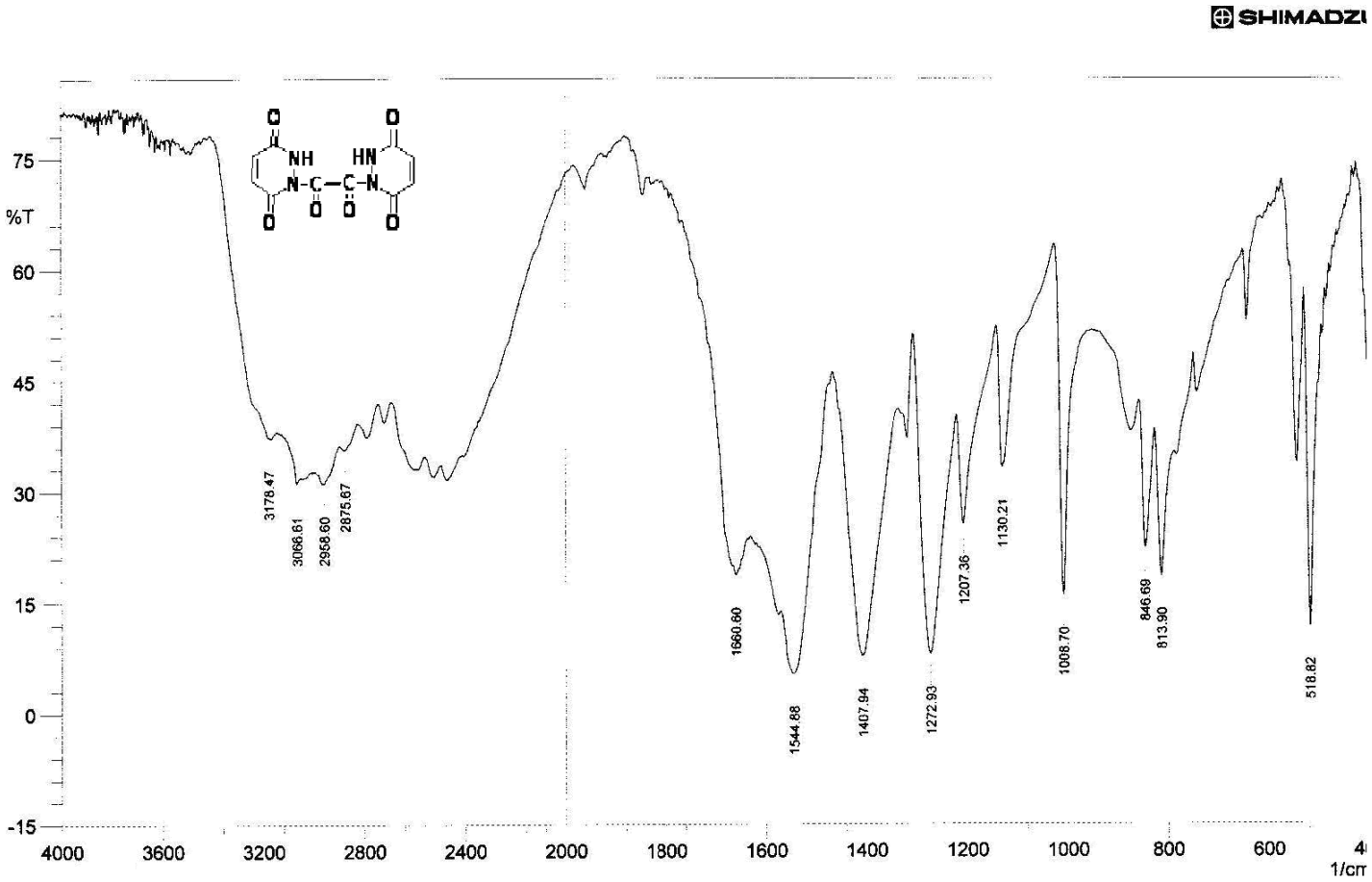
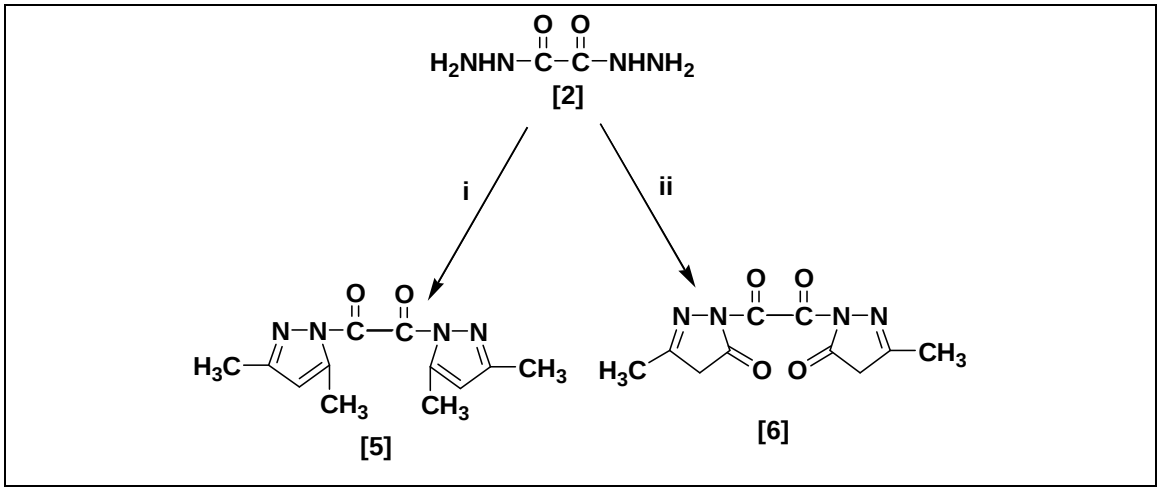


Figure (3-5) FTIR spectrum of compound (bis-1-(formyl)-1,2-dihydropyridazin-3,6-dione) [4]

3.4 Synthesis of pyrazol derivatives [5,6] :



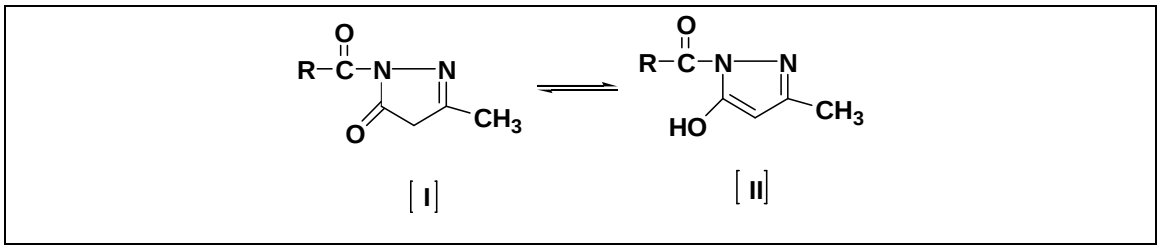
Scheme (3-3) Reagents and Conditions: i-$CH_3COCH_2COCH_3$, abs. EtOH, reflux (5) hrs. ii-$CH_3COCH_2COOCH_2CH_3$, abs. EtOH, reflux (5) hrs.

The pyrazol derivatives were prepared through the reaction of hydrazide derivative [2] with acetyl acetone or ethyl aceto acetate.

FTIR spectrum of compound [5] in figure (3-6) shows the disappearance of NH_2 and NH bands in the region (3292.3, 3190) cm^{-1} , appearance of C-H aliphatic at (2950) cm^{-1}, amide C=O appeared at (1675) cm^{-1}, C=C appeared at (1600) cm^{-1} (-CH) bending vibration appeared at (1400)cm^{-1},and appearance of band at (1650) cm^{-1} assignable to υ (C=N) of pyrazole ring. While FTIR spectrum of compound [6] in figure (3-7)shows the disappearance of NH_2 and NH bands in the region (3392.3-3190) cm^{-1} ,appearance of OH band at (3440) cm^{-1} of enol form , C=O band at

(1735.81) cm^{-1} of the keto form in addition to the amide C=O at (1660) cm^{-1} and appearance of band at range(1620.09) cm^{-1} assignable to υ (C=N) of pyrazole ring.

From the above mentioned facts, we can indicate compound [6] through the equilibrium between keto [I] and enol [II] forms:

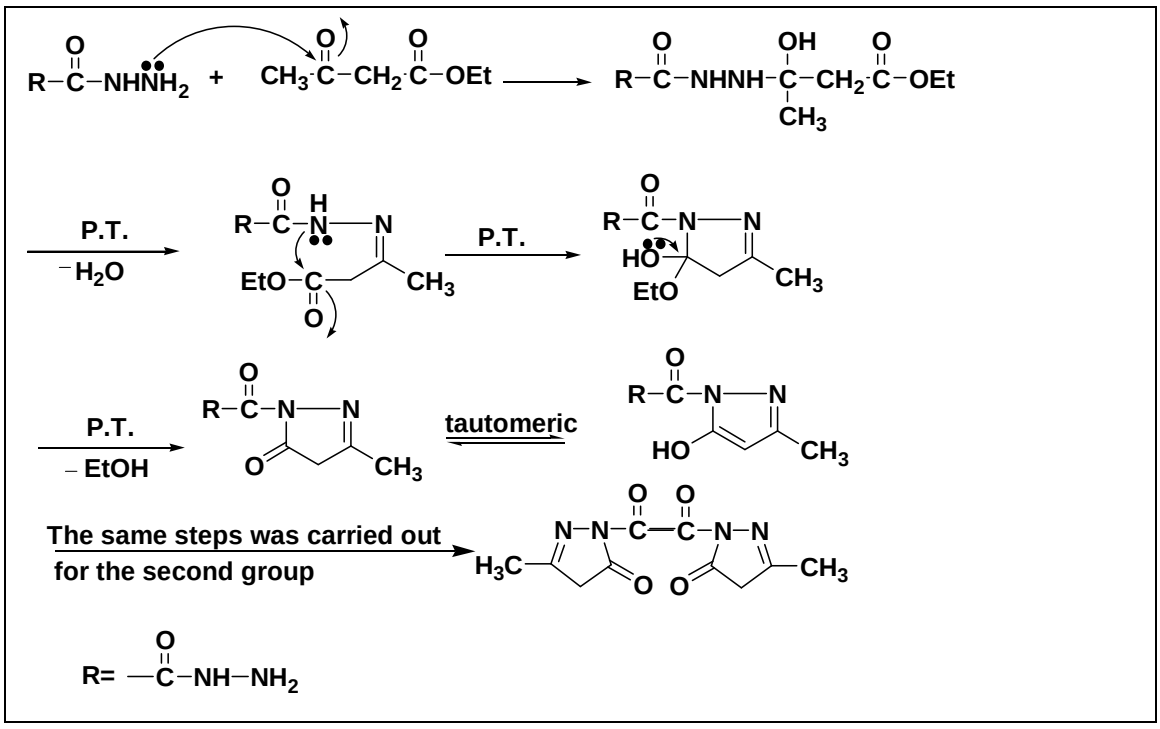


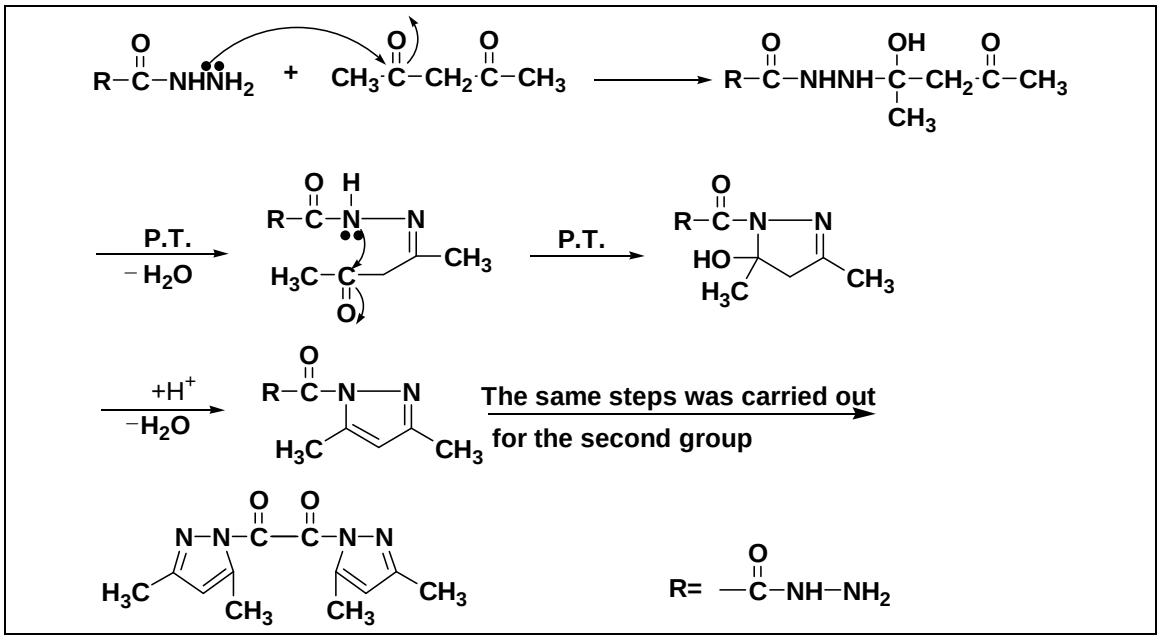
The characteristic bands of compounds [5,6] are shown in table (3-2).

Table (3-2): Characteristic bands of compounds [5, 6]:

Comp. No.	*υ(O-H) cm^{-1}*	*υ(C-H) Aliphatic. cm^{-1}*	*υ(C=O) cm^{-1}*	*υ(C=O) of amide cm^{-1}*	*υ(C=N) cm^{-1}*	*υ(C=C) cm^{-1}*
5	*------*	*2950*	*------*	*1675*	*1650*	*1600*
6	*3440*	*2989.46*	*1735.81*	*1660*	*1620.09*	*1510*

The suggested mechanism for formation of compounds [6,7] as shown below[137]:





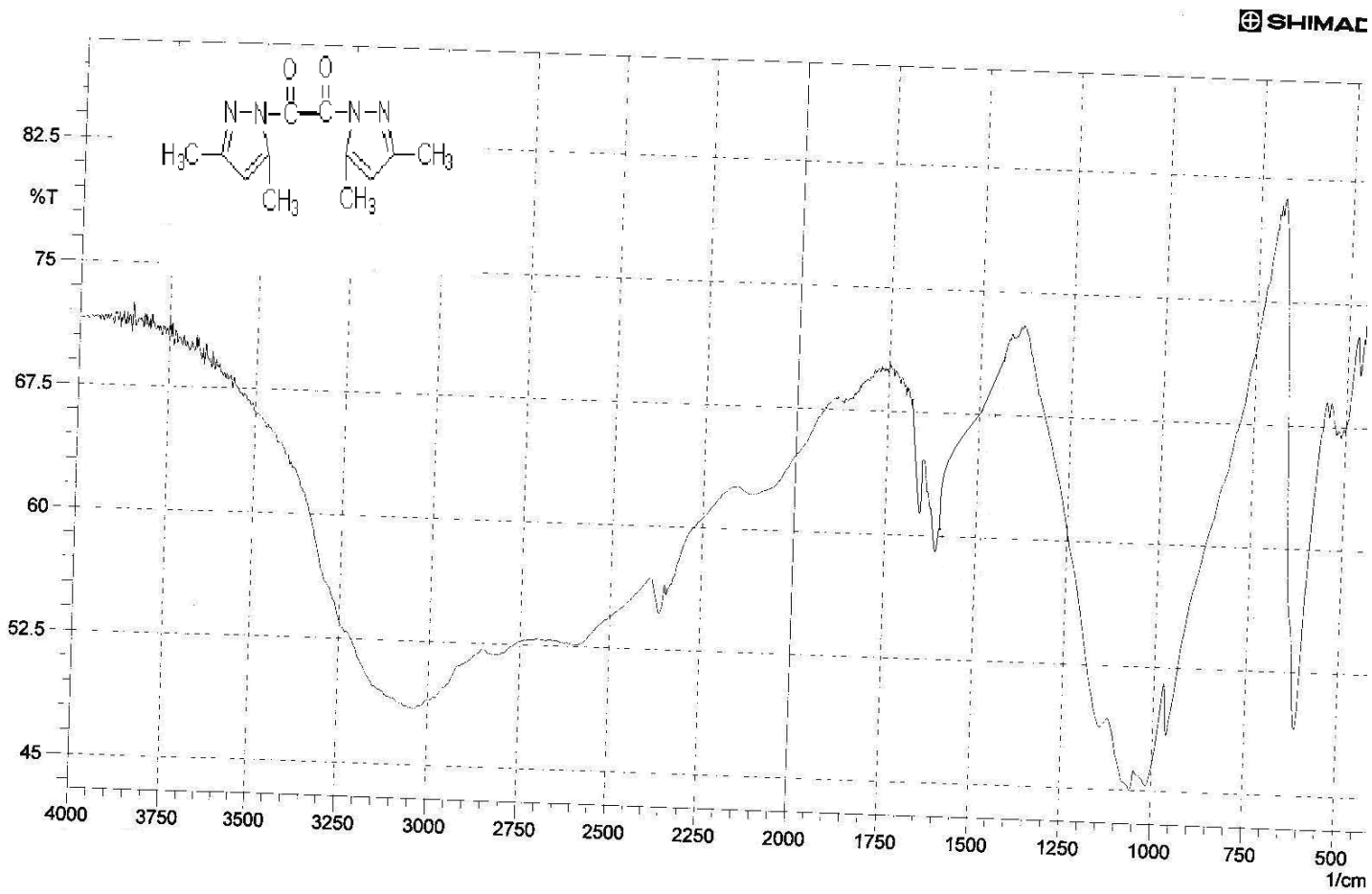


Figure (3-6) FTIR spectrum of compound [bis-(2-formyl-3,5-dimethylpyrazole)] [5]

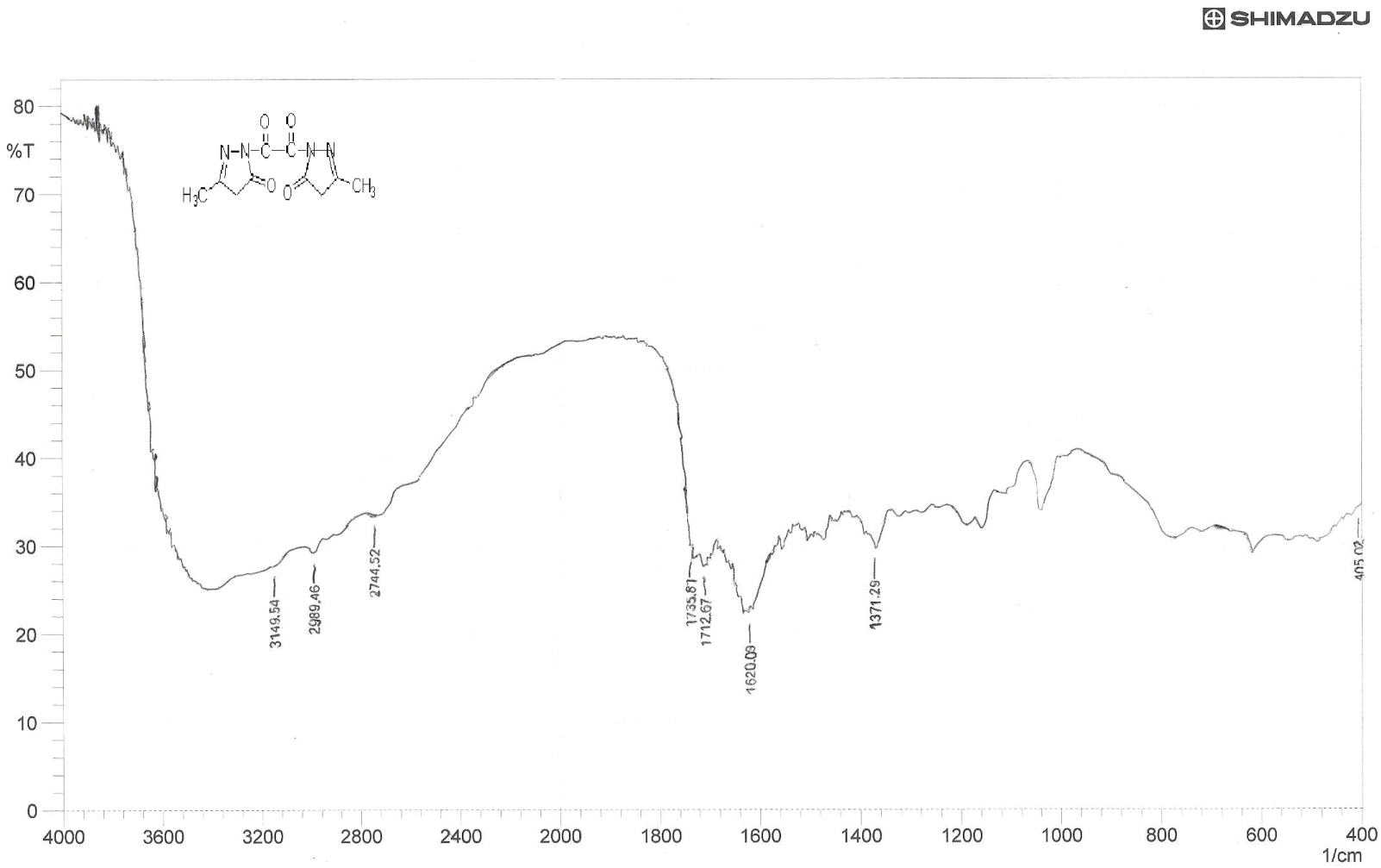
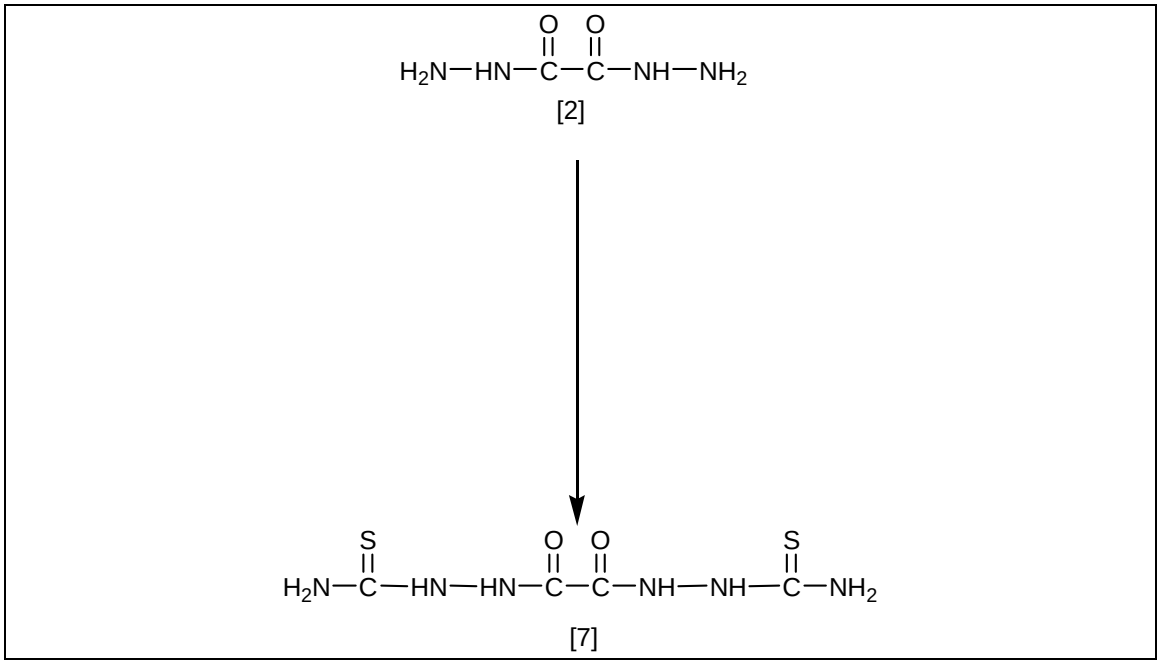


Figure (3-7) FTIR spectrum of compound [bis-(2-formyl-5-methyl-3-pyrazolone)] [6]

3.5 Synthesis of bis-[4-formylthiosemicarbazide] [7] :

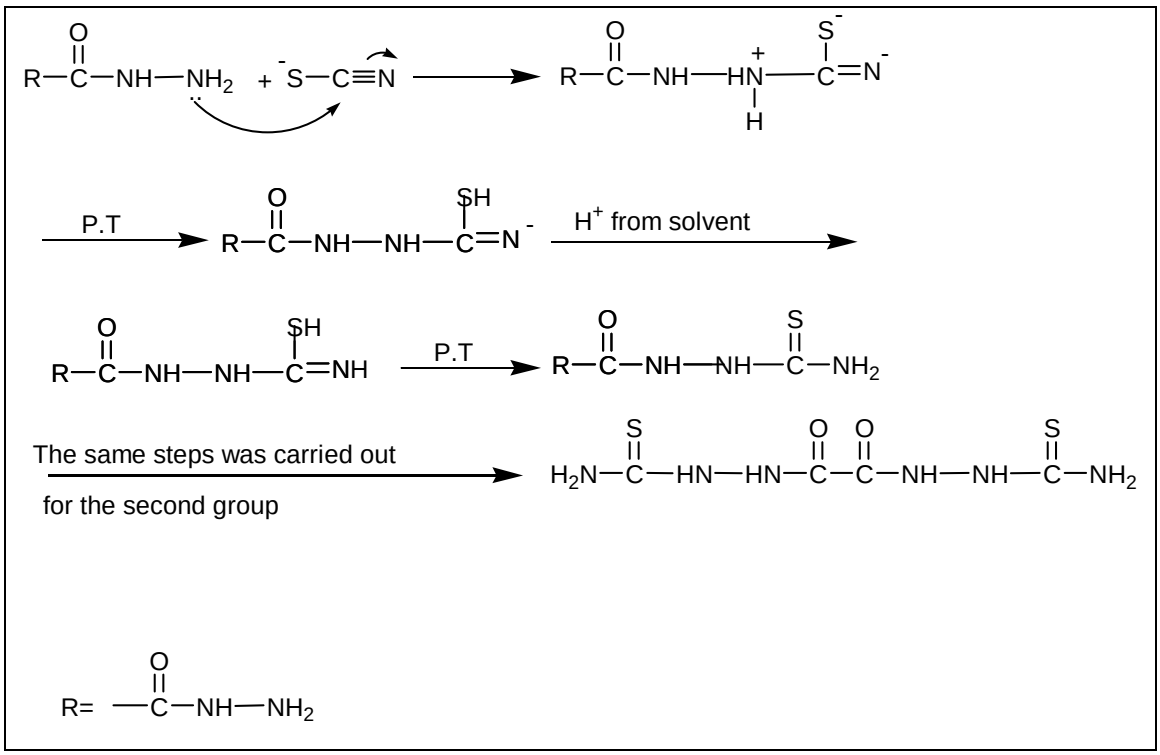


Sceme (3-4) Reagents and Conditions NH_4SCN,abs.EtOH , reflux (4) hrs

The reaction of acid hydrazide with ammonium thiocyanate in absolute ethanol gave the substituted thiosemicarbazide [7].

The FTIR spectrum in figure (3 -8) for bis –[4-formylthiosemicarbazide] show the disappearance of the two absorption bands at (3292.3) cm^{-1} and (3190) cm^{-1}due to asymmetric and symmetric stretching vibration of NH–NH_2 group of acid hydrazide [2] , appearance of the three absorption bands at (3373.27) cm^{-1} , (3284.55-3238.26) cm^{-1} due to the three group of N-H , appearance of band of C=S at (1325.01) cm^{-1} and amide C=O appeared at (1656.74) cm^{-1}.

The mechanism of the reaction is shown below:



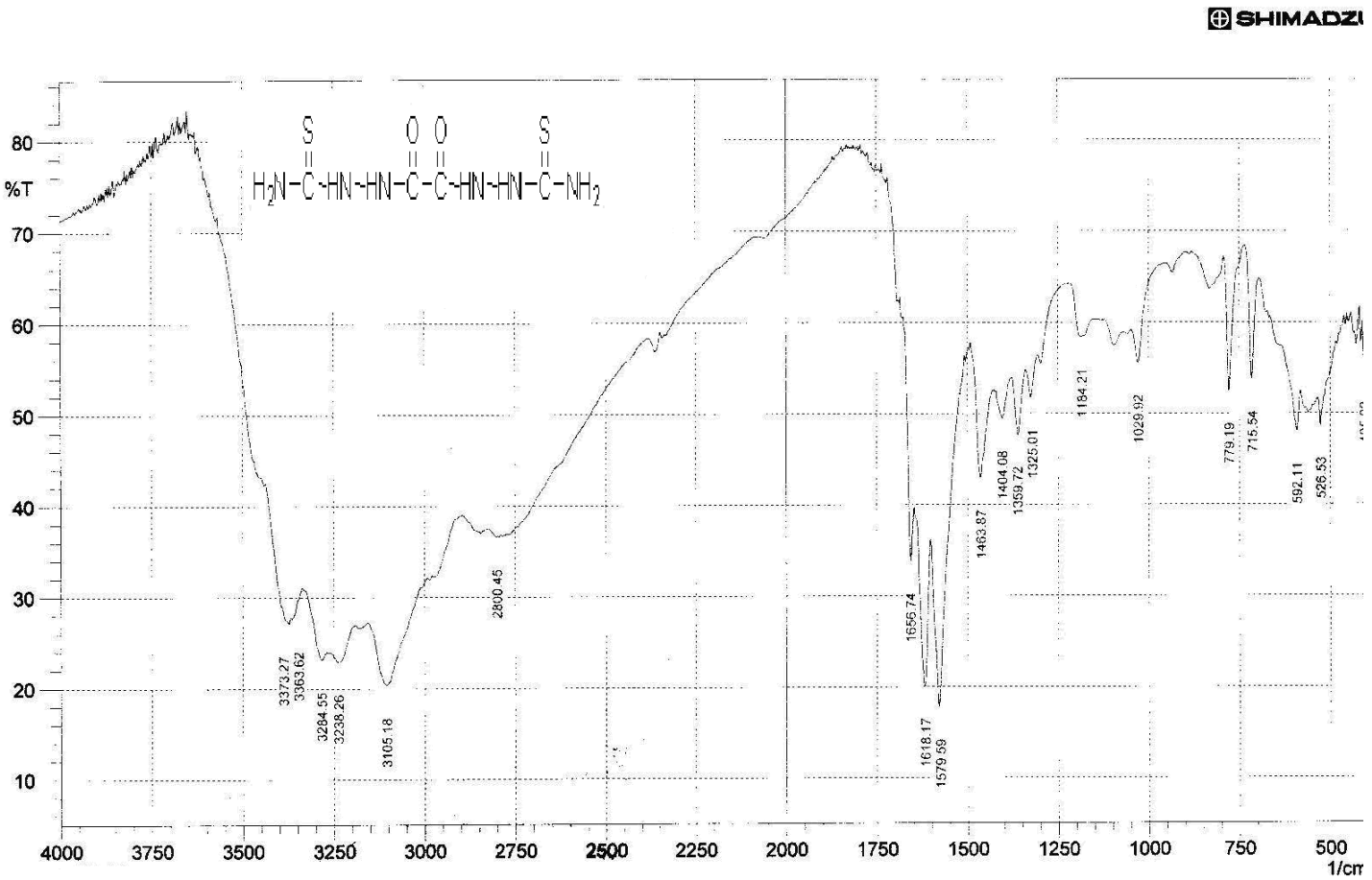
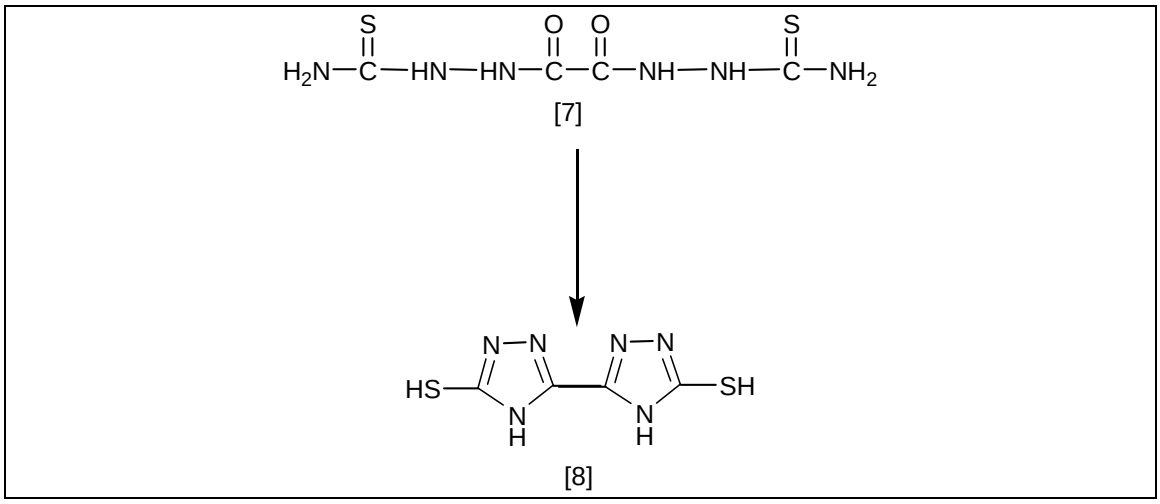


Figure (3-8) FTIR spectrum of compound [bis-(4-formylthiosemicarbazide)] [7]

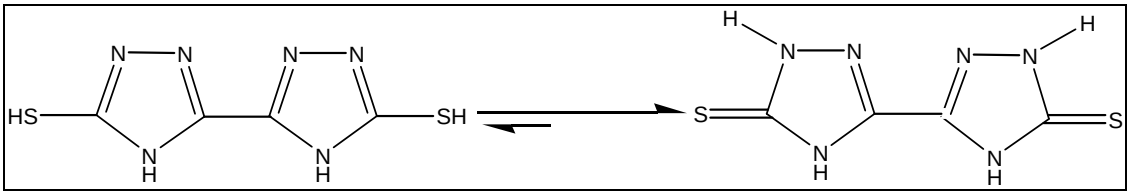
3.6 Synthesis of bis-[5-mercapto-3-yl-1,2,4-triazole] [8]:



Scheme (3-5) Reagents and conditions: 10% NaOH,reflux (4)hrs.

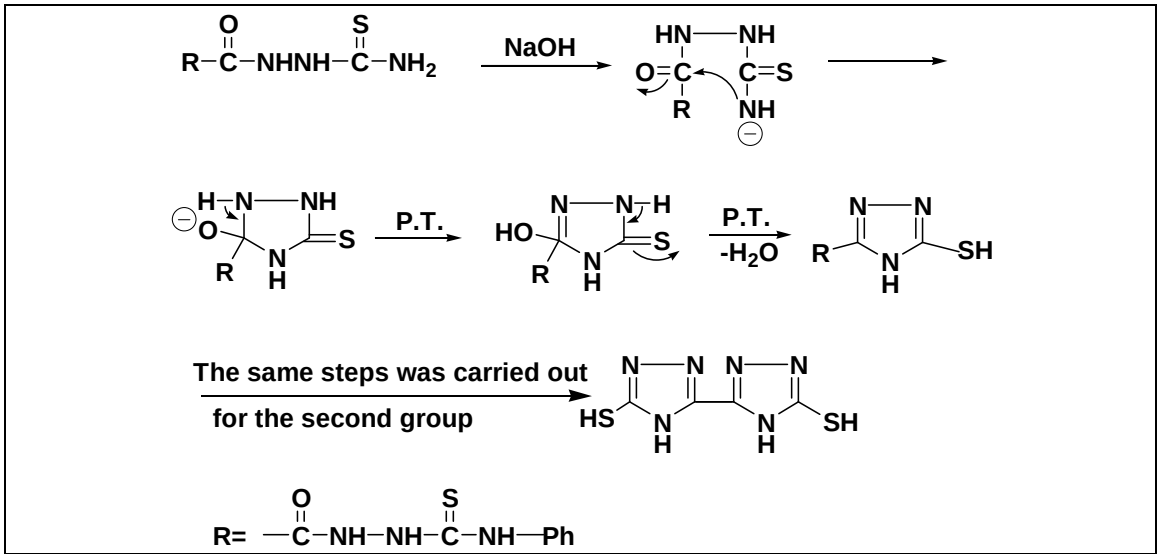
Triazole prepared through the reaction of bis-[4-formylthiosemicarbazide] with NaOH under refluxing condition by intramolecular cyclization through the loss of H_2O.

The FTIR spectrum , figure (3-9) shows the disappearance of the bands at (3373.27) cm^{-1} , (3284.55-3238.26) cm^{-1} due to NH–NH_2 group , appearance of band due to(C=S) group at (1325) cm^{-1} due to toutomeric form.



, also disappearance of the band at (1656.74) cm^{-1} due to C=O of amide , appearance of a band at (1600) cm^{-1} assignable to C=N of triazole ring and (SH) group appeared at (2400) cm^{-1} .

The suggested mechanism for the reaction is shown below :



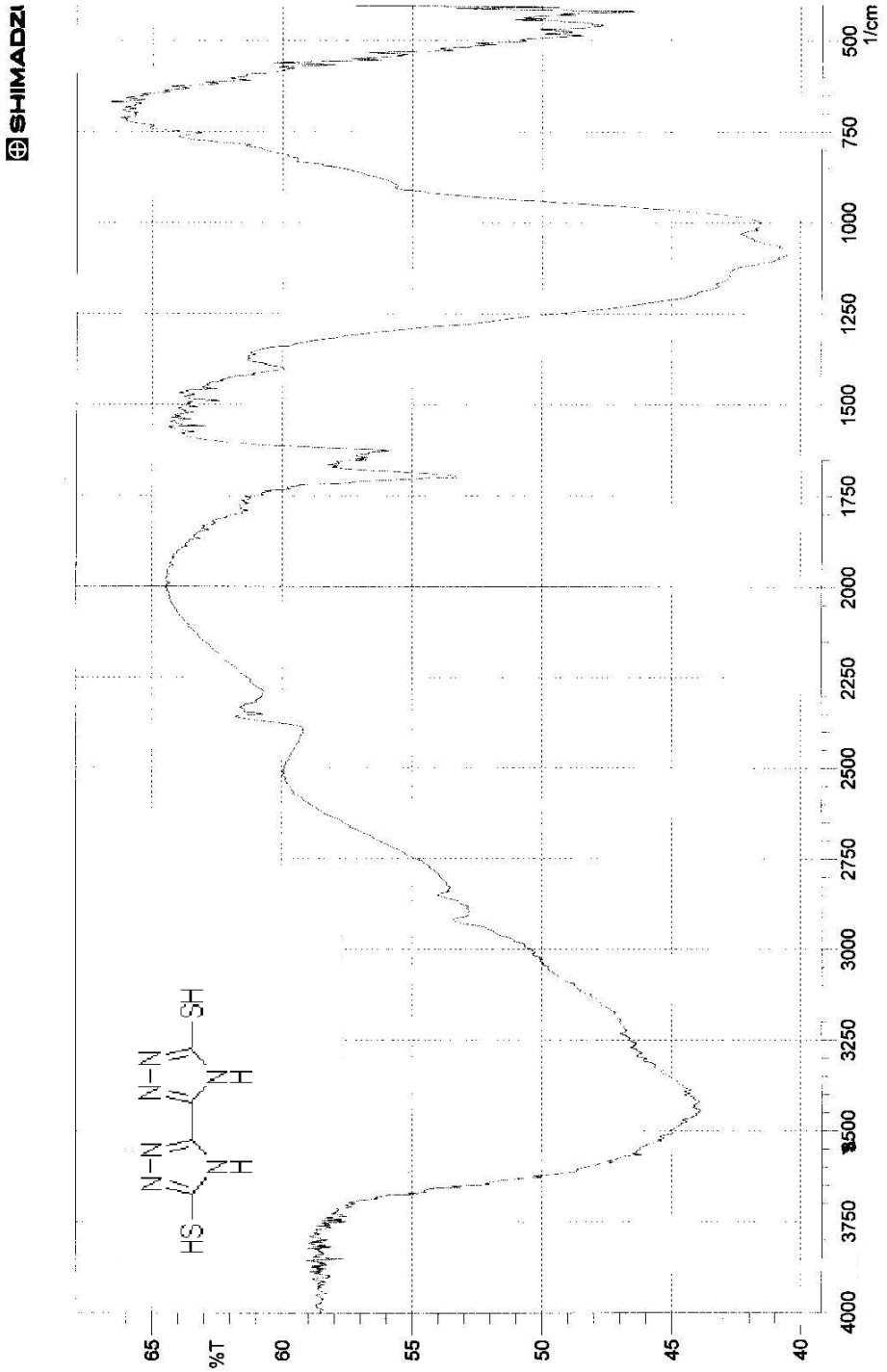
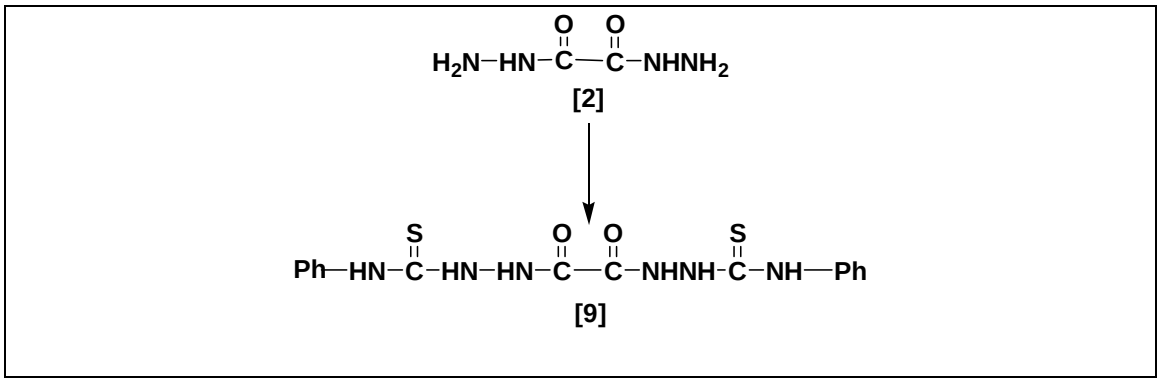


Figure (3-9) FTIR spectrum of compound [bis-(5-mercapto-3-yl-1,2,4-triazole)] [8]

3.7 Synthesis of bis-[1-phenyl-4- (formyl) thiosemicarbazide] [9] :

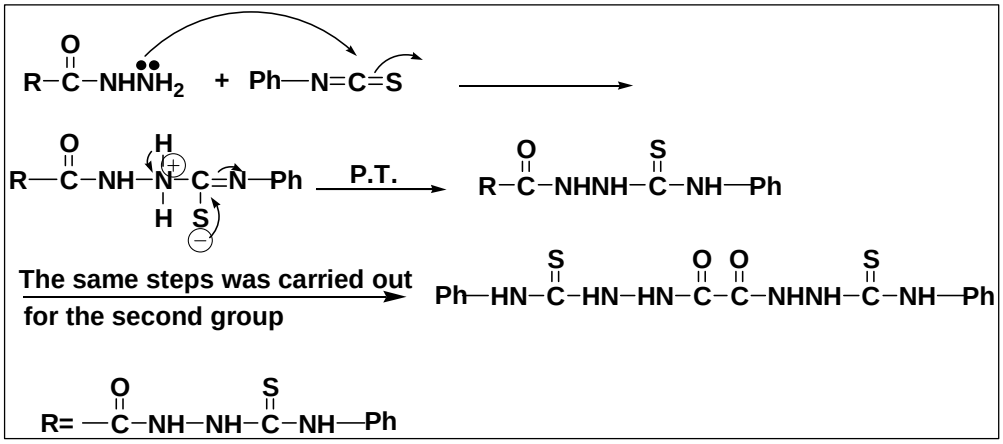


Scheme (3-6): Reagents and conditions: phenyl isothiocyanate, abs. EtOH, reflux (7) hrs.

The reaction of acid hydrazide with phenyl isothiocyanate in absolute ethanol gave the thiosemicarbazide [9].

The FTIR spectrum in figure (3-10) for bis –[1-phenyl-4-formylthiosemicarbazide] show disappearance of the two absorption bands at (3292.3) cm^{-1} , (3190) cm^{-1}due to asymmetric and symmetric stretching vibration of NH–NH_2 group of acid hydrazide [2] , appearance of the two absorption bands at (3213.19) cm^{-1} , (3114.82) cm^{-1} due to the three groups of N-H and appearance band of C=S at (1332.72) cm^{-1} ,aromatic (-CH) appeared at (3000) cm^{-1} ,and amide C=O appeared at (1687.60) cm^{-1}.

The mechanism of the reaction is shown below:



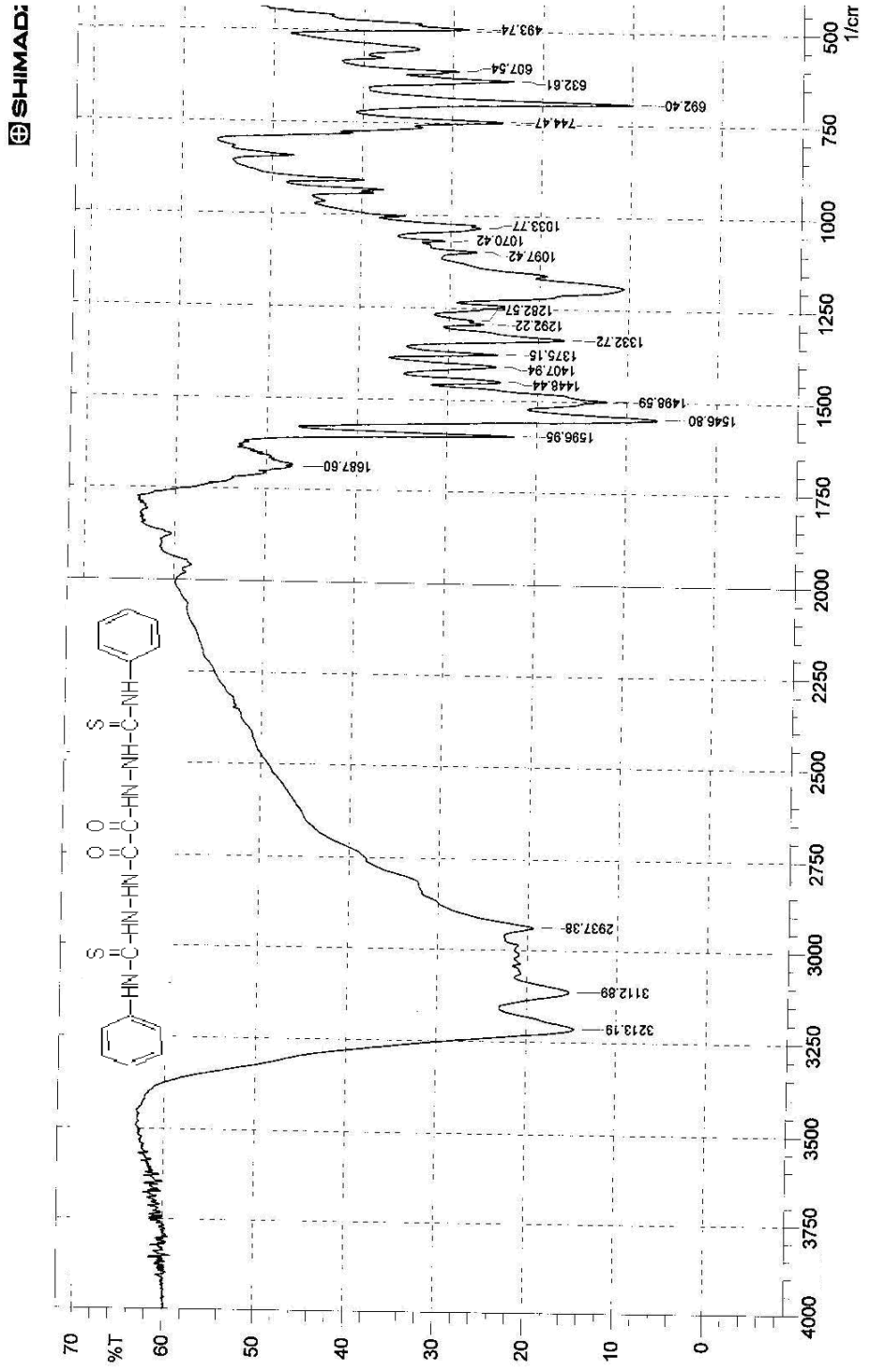
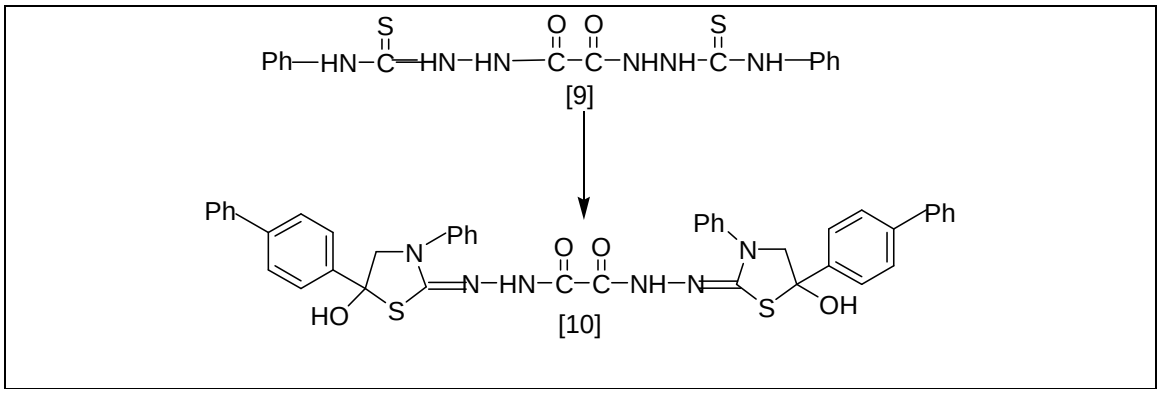


Figure (3-10) FTIR spectrum of compound [bis-(1-phenyl-4-formyl-thiosemicarbazide)] [9]

3.8 Synthesis of bis-[5-biphenyl-2-(acid hydrazide)-3-N-phenyl-5-(hydroxyl)thiazolidine] [10]:

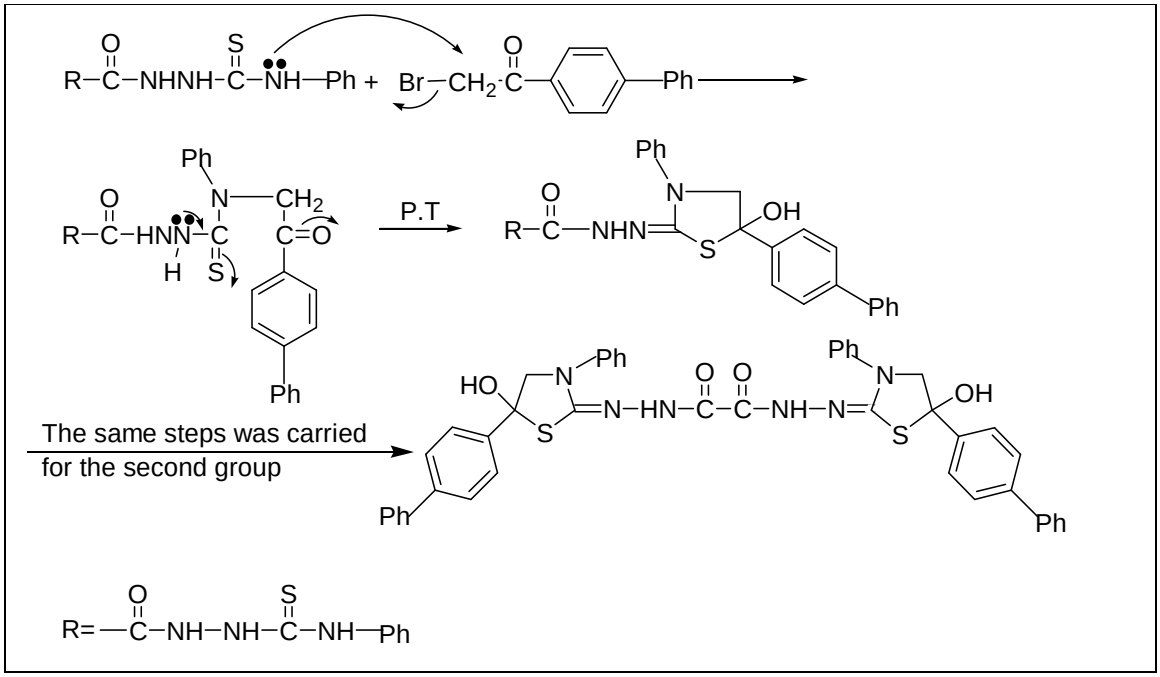


Scheme (3-7): Reagents and Conditions: *p*-phenyl phenacyl bromide, abs. EtOH, reflux (8) hrs.

Thiazolidine derivative [10] was synthesized from the reaction of thiosemicarbazide [9] with *p*-phenyl phenacyl bromide which was used for cyclization of the previous compound.

The FTIR spectrum in figure (3-11) shows the disappearance of thione group of the thiosemicarbazide [9] at (1332.72) cm^{-1} , appearance of band at (3527.56) cm^{-1} assinable to (OH) group, band due to (NH-) group appeared at (3406.05) cm^{-1}, C=N band appears at (1604.66) cm^{-1} and band at (694.33) cm^{-1} belongs to (C-S-C) group.

The mechanism of reaction is shown below:



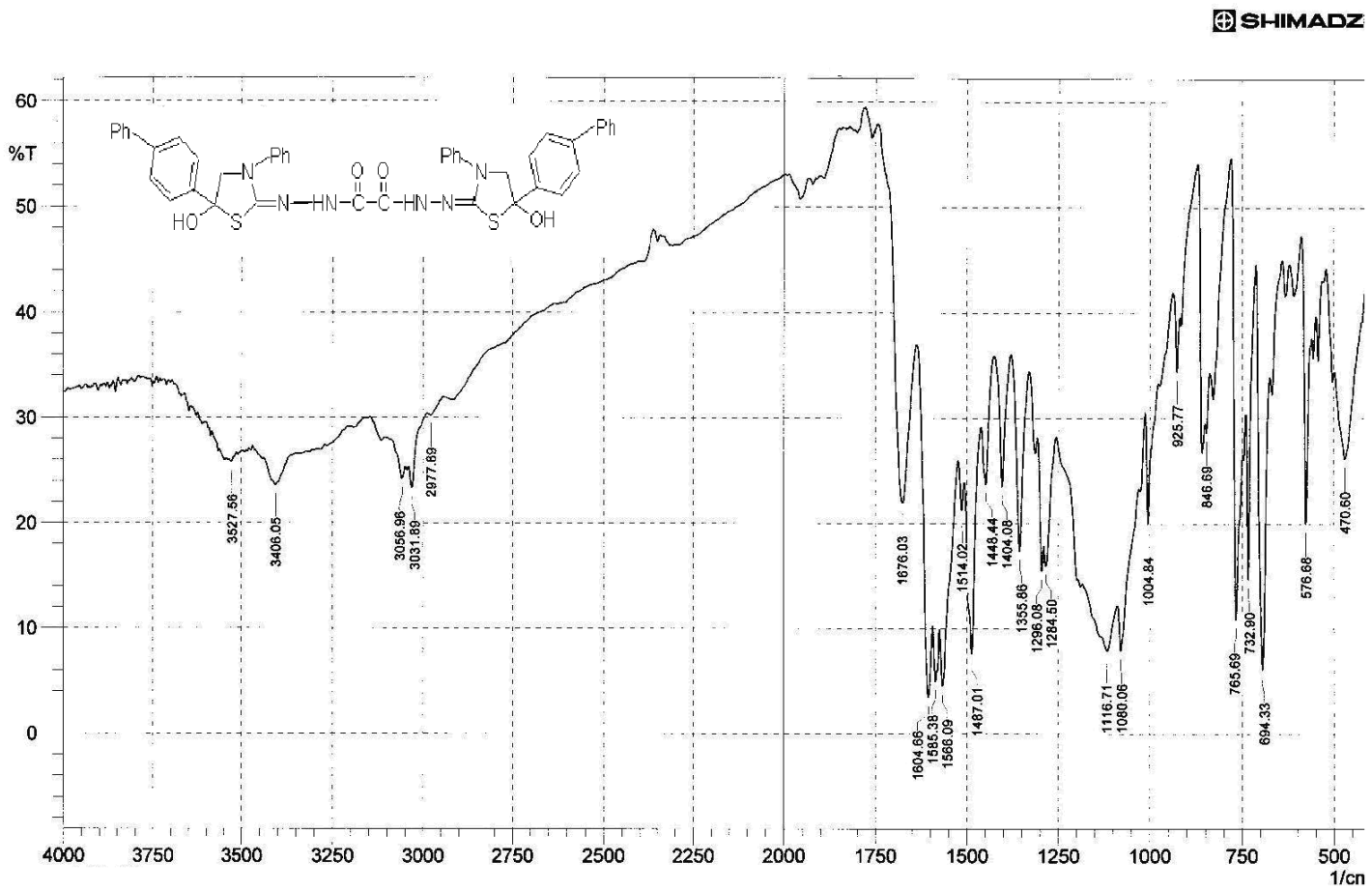
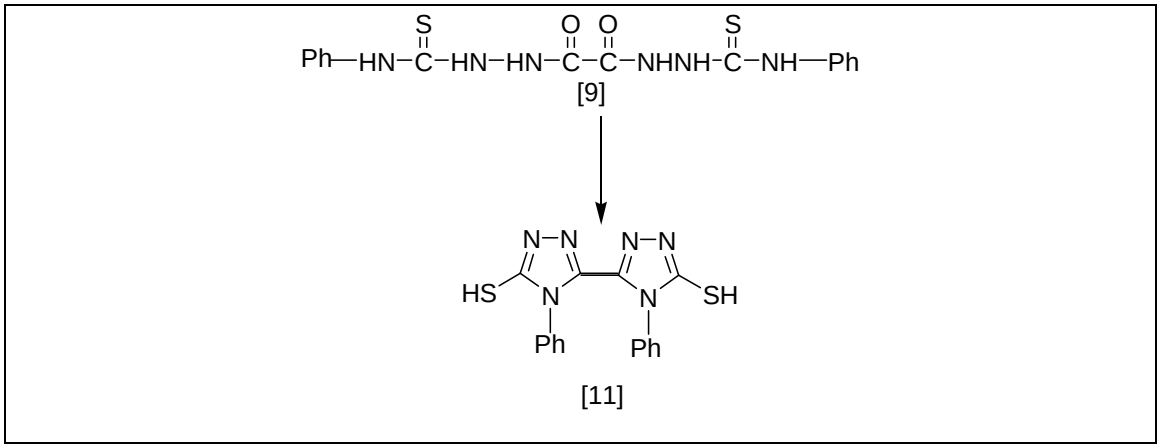


Figure (3-11) FTIR spectrum of compound [bis-(5-biphenyl-2-acidhydrazide-3-N-phenyl-5-(hydroxy) thiazolidine)] [10]

3.9 Synthesis of bis-[5-mercapto-3-yl-4-phenyl-1,2,4-triazole] [11] :

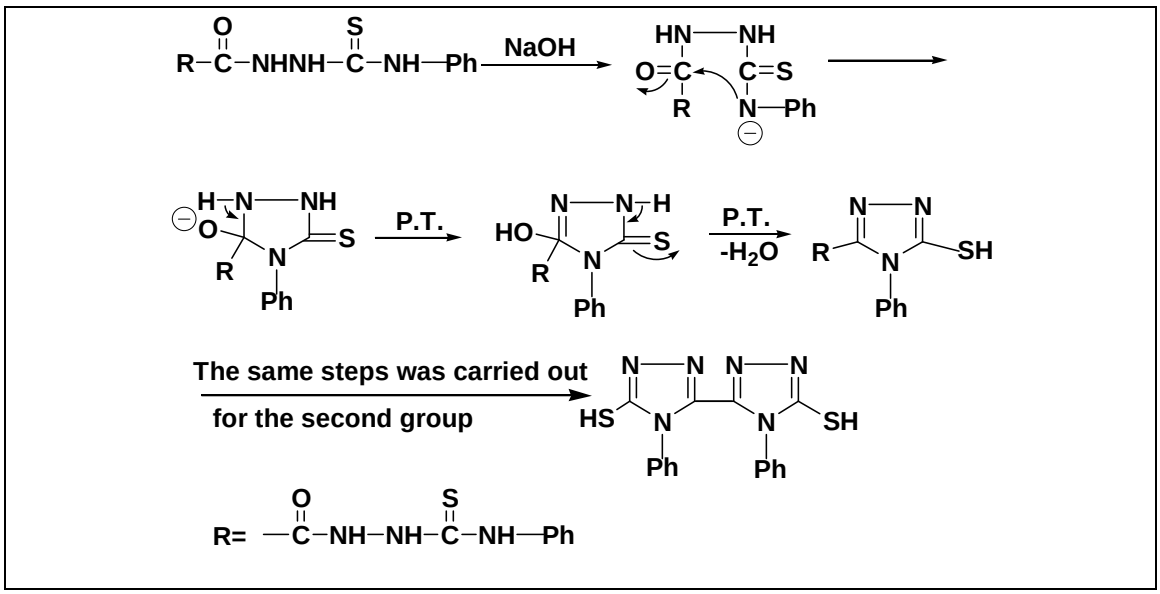


Scheme (3-8): Reagents and conditions: 2N NaOH,reflux (4)hrs.

Thiol-triazole prepared through the reaction of thiosemicarbazide derivative with 2N NaOH under refluxing condition by interamolecular cyclization through the loss of H_2O.

The FTIR spectrum in figure (3-12) shows disappearance of the bands at (3213.19) cm^{-1} ,(3114.82) cm^{-1} due to (NH-NH) group with appearance of a weak band due to (–SH) group at (2400) cm^{-1}, also show the disappearance of the band at (1687.60) cm^{-1} due to C=O of amide I and appearance of a band at (1595) cm^{-1} assignable to C=N of triazole ring.

The suggested mechanism for the reaction is:



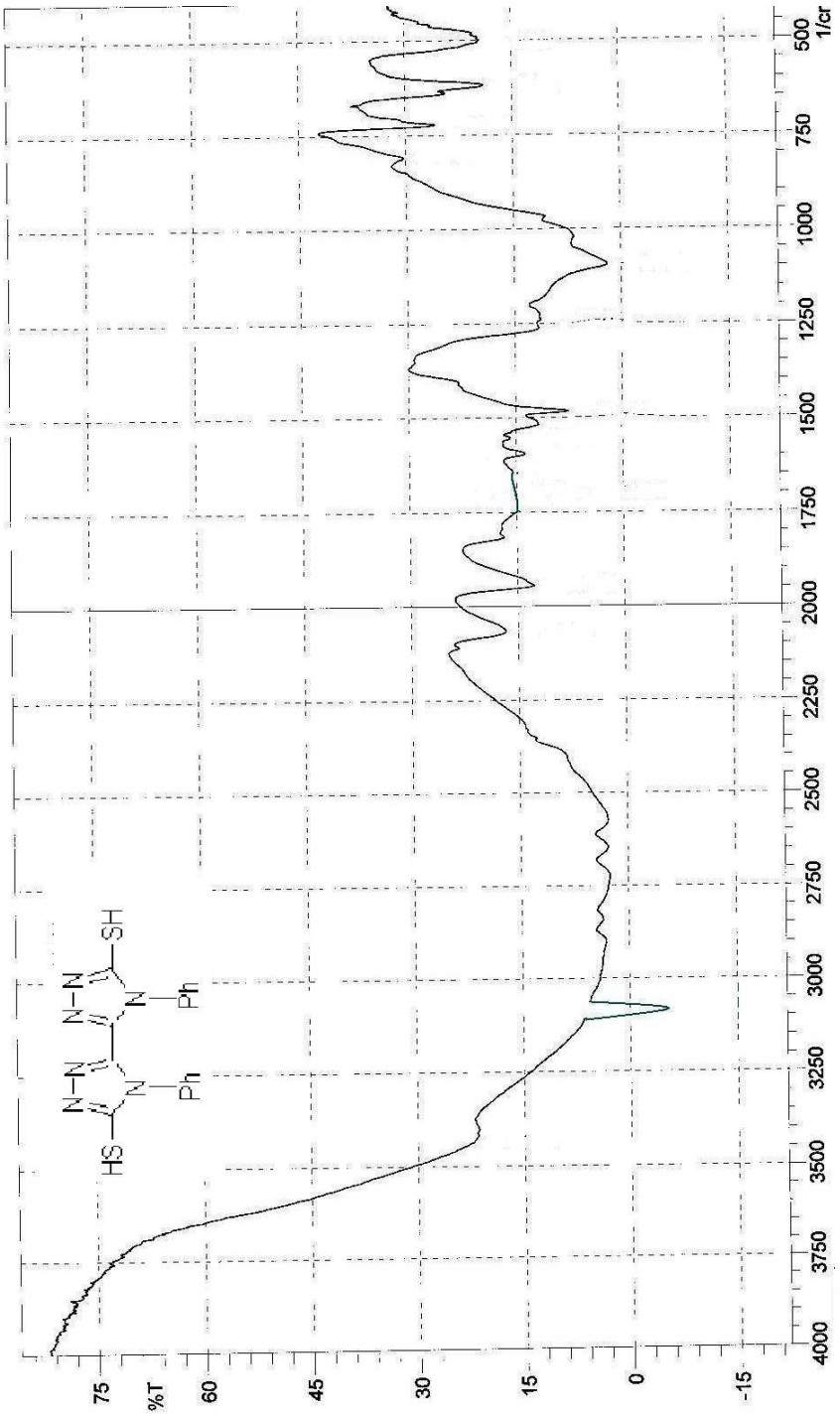
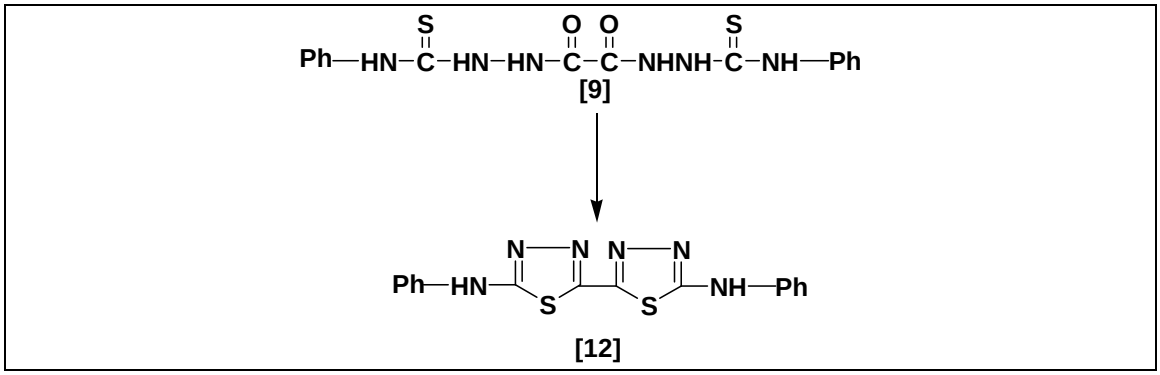


Figure (3-12) FTIR spectrum of compound [bis-(5-mercapto-3-yl-4-phenyl-1,2,4-triazole)] [11]

3.10 Synthesis of bis-[5-(phenylamino)-2-yl-1,3,4-thiadiazole [12] :

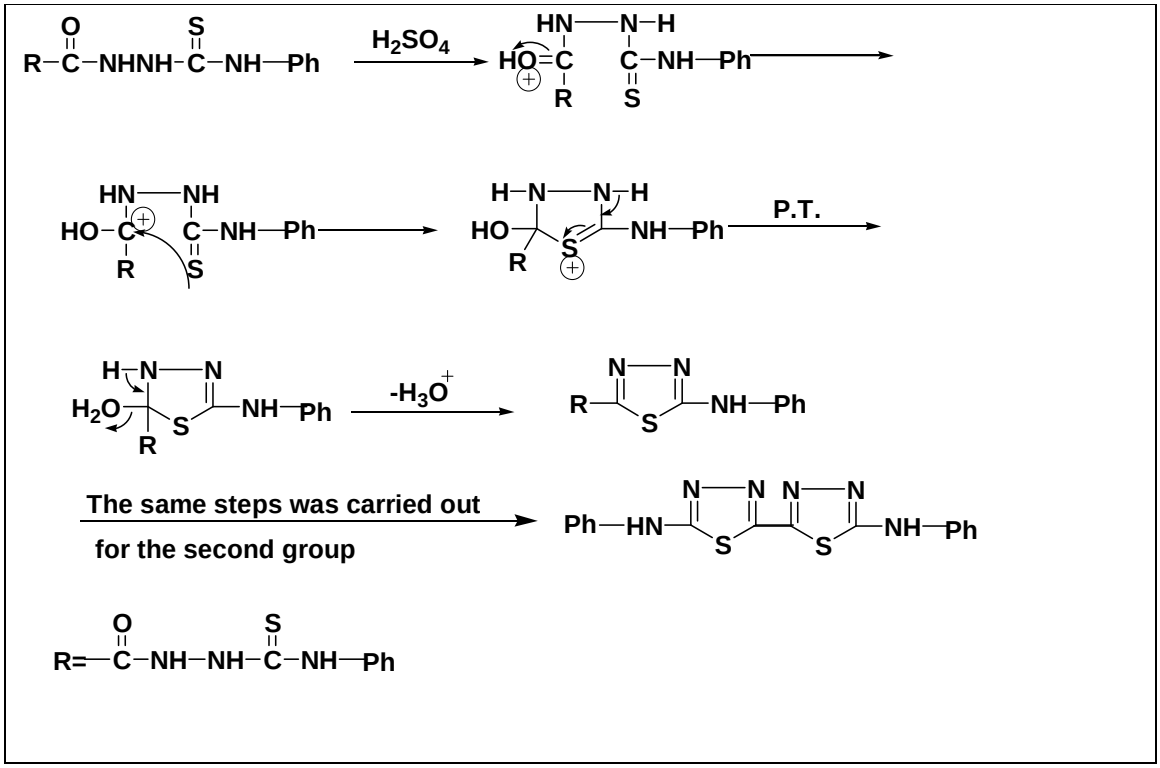


Scheme (3-9): Reagents and Conditions: Conc.H_2SO_4, stirred (3) hrs.

1,3,4-Thiadiazole derivative [12] was synthesized from the reaction of thiosemicarbazide derivative with concentrated sulfuric acid at (0) ^{0}C.

The FTIR spectrum in figure (3-13) shows band at (3300) cm^{-1} due to (N-H) group, band at (1650) cm^{-1} for (C=N) and band at (611.39) cm^{-1} attributed to C-S-C band is a good evidence for thiadiazole formulation.

The mechanism of the reaction was affected by intermolecular cyclization through the lossing of H_2O as shown below [138]:



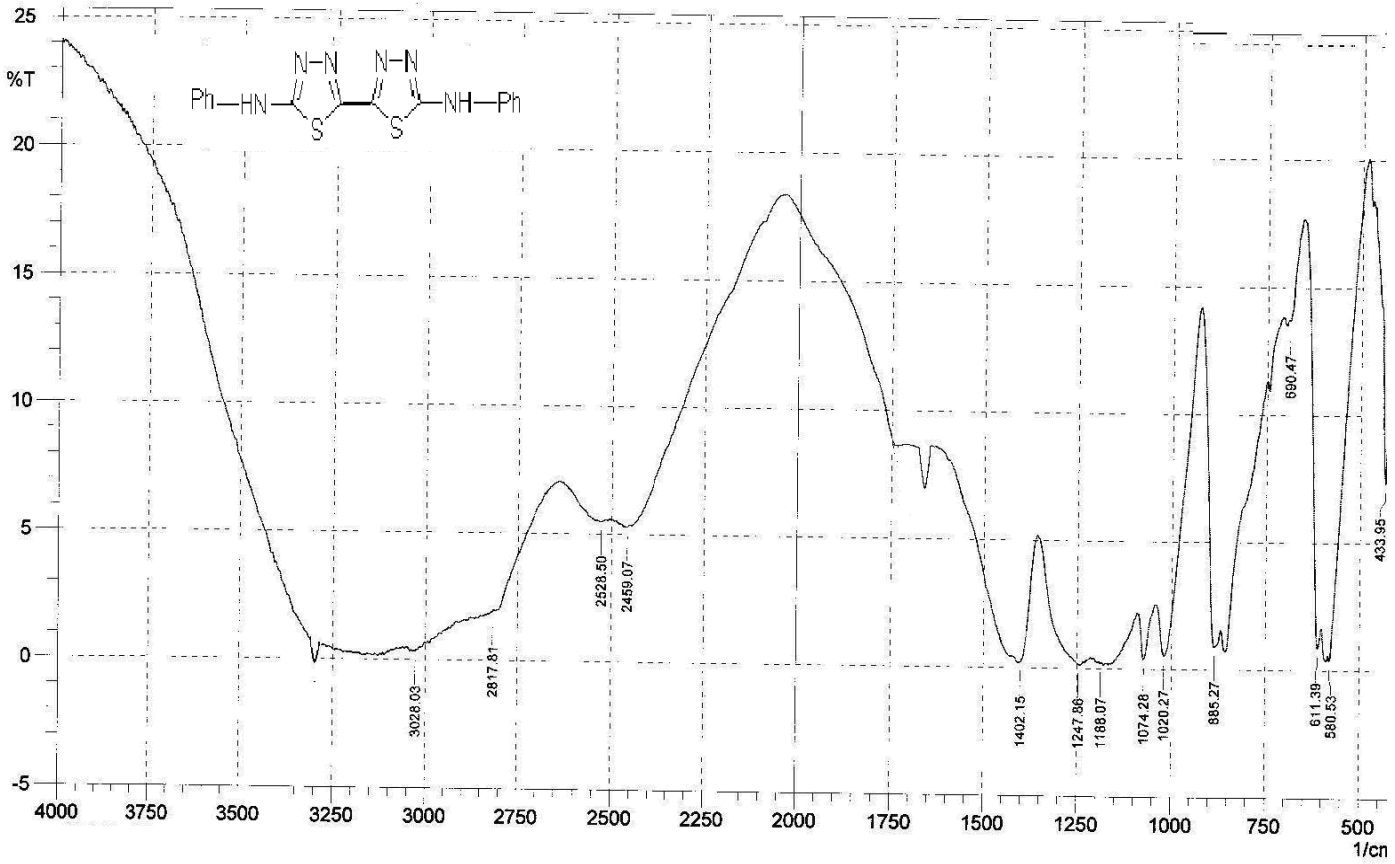
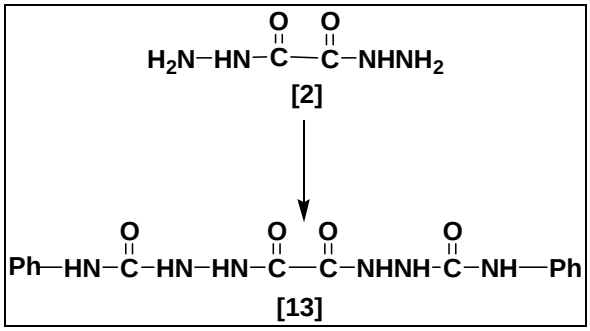


Figure (3-13) FTIR spectrum of compound [bis-(5-phenylamino-2-yl-1,3,4-thiadiazole)] [12]

3.11 Synthesis of bis-[1-phenyl-4-(formyl) semicarbazide] [13] :

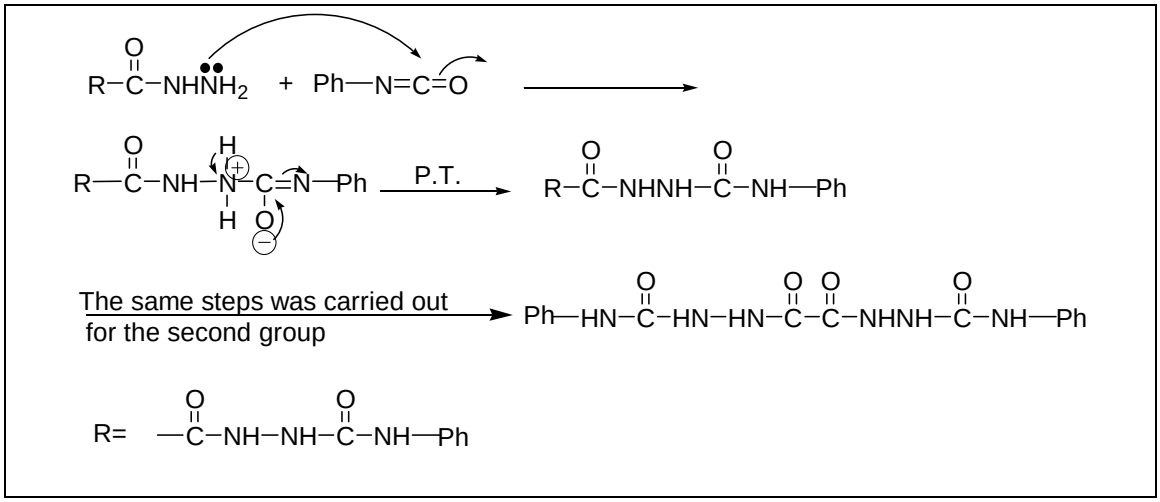


Scheme (3-10): Reagents and conditions: phenyl isocyanate, abs. EtOH, reflux (7) hrs.

The reaction of acid hydrazide with phenyl isocyanate in absolute ethanol gave the substituted semicarbazide [13].

The FTIR spectrum in figure (3-14) for bis–[1-phenyl-4-(formyl)semicarbazide] shows disappearance of the two absorption bands at (3292.3) cm^{-1} , (3190) cm^{-1}due to asymmetric and symmetric stretching vibration of $NH–NH_2$ group of acid hydrazide [2] and the appearance of the two absorption bands at (3396.41) cm^{-1} , (3182.33) cm^{-1} due to the two groups of N-H ,aromatic (-CH) appeared at (3041.53) cm^{-1} , and two (C=O) groups appeared at range (1622.02-1733.09) cm^{-1}.

The mechanism of the reaction is shown below:



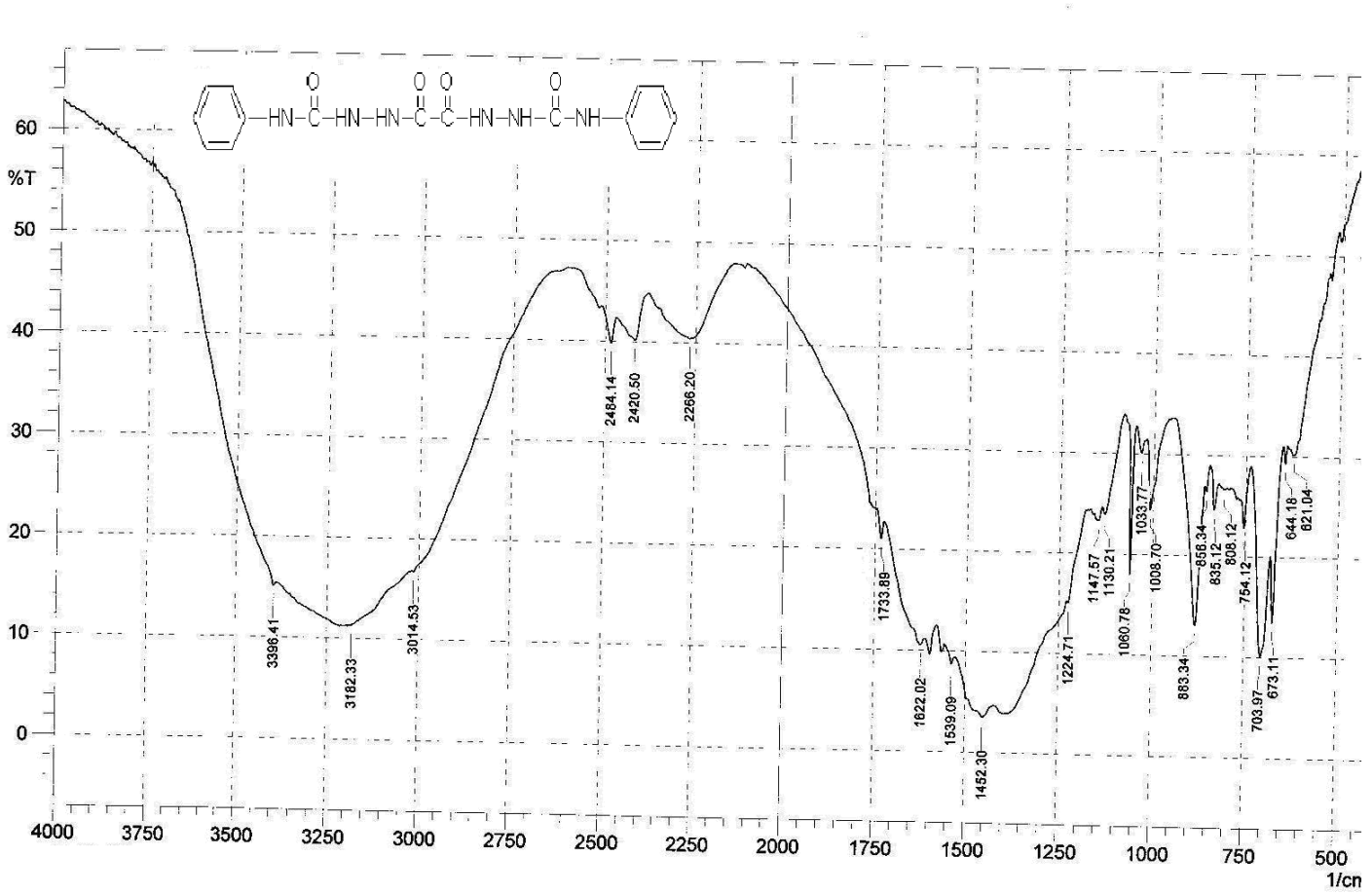
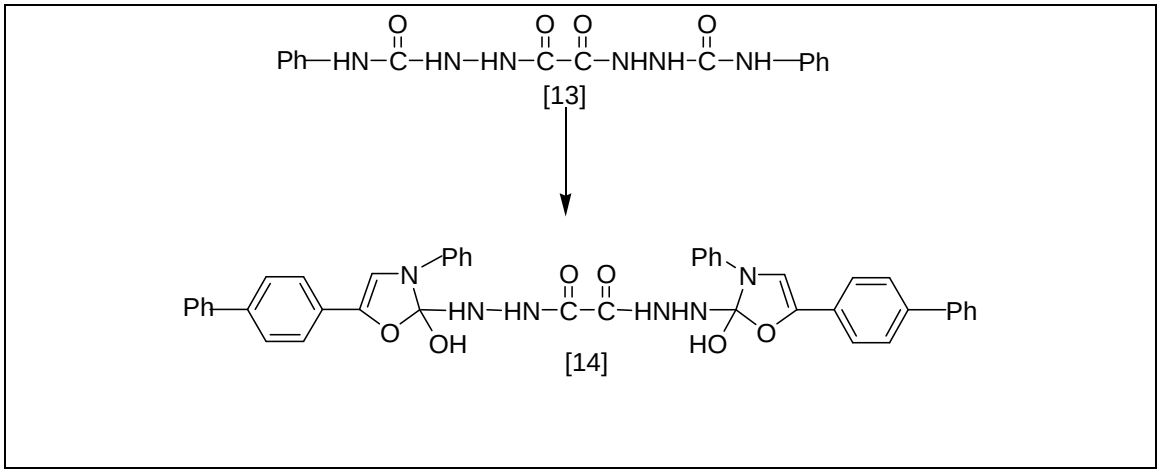


Figure (3-14) FTIR spectrum of compound [bis-(1-phenyl-4-(formyl)semicarbazide)] [13]

3.12 Synthesis of bis-[5-biphenyl-2-acid hydrazide-3-N-phenyl-2-(hydroxyl) oxazoline [14] :

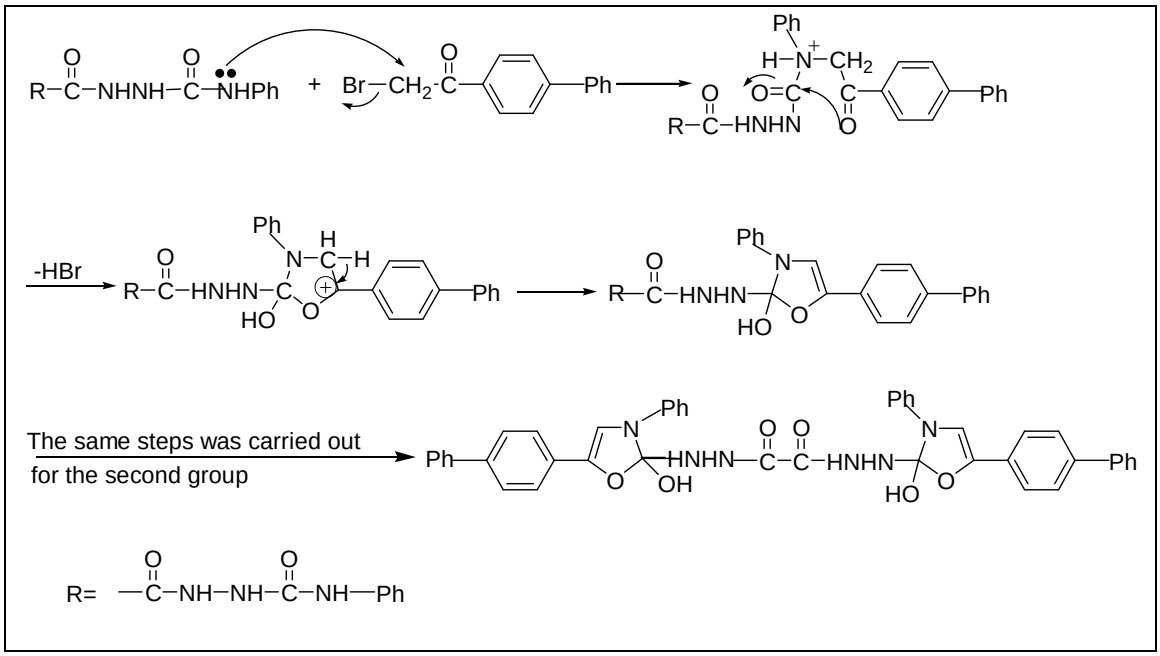


Scheme (3-11) Reagents and Conditions: *p*-phenylphenacyl bromide, abs. EtOH, reflux (8) hrs.

N-subsituted-oxazoline derivative was synthesized through the reaction of semicarbazide [13] with *p*-phenyl phenacyl bromide under refluxing condition affected by intermolecular cyclization through S_N2 mechanism and tetrahedral nuclephilic substitution [(139)].

The FTIR spectrum of compound [14] shows band of O-H group at (3460) cm^{-1}, (C=O) of amide appeared at (1675) cm^{-1},(C=C) band appeared at (1560) cm^{-1},aromatic (C-H) appeared at (3050) cm^{-1} and (C-O-C) asymmetric and symmetric bands appeared at (1125- 1380) cm^{-1} .

The mechanism of this reaction is shown below [140]:



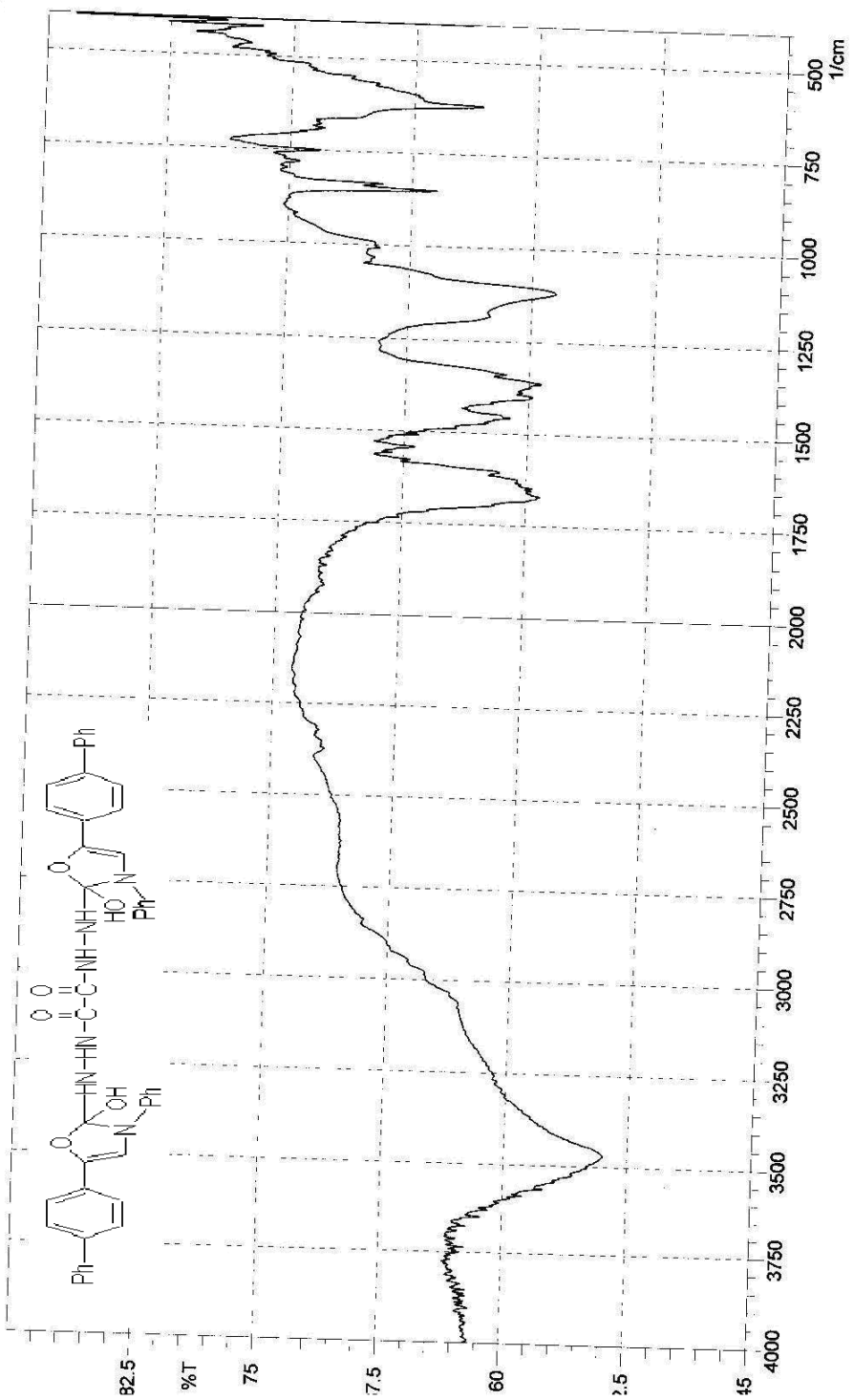
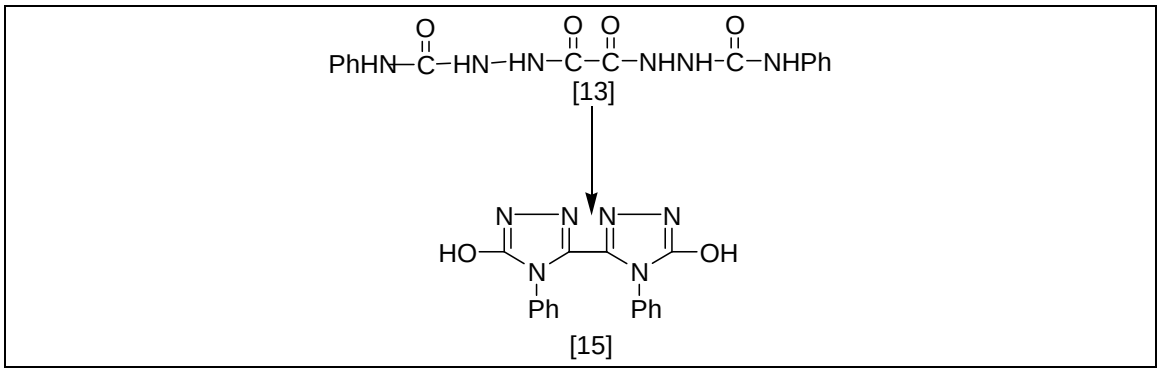


Figure (3-15) FTIR spectrum of compound [bis-(5-biphenyl-2-acid hyrazide-3-N-phenyl-2-(hydroxyl) oxazoline] [14]

3.13 Synthesis of bis-[5-hydroxy-4-phenyl-3-yl-1,2,4-triazole] [15] :

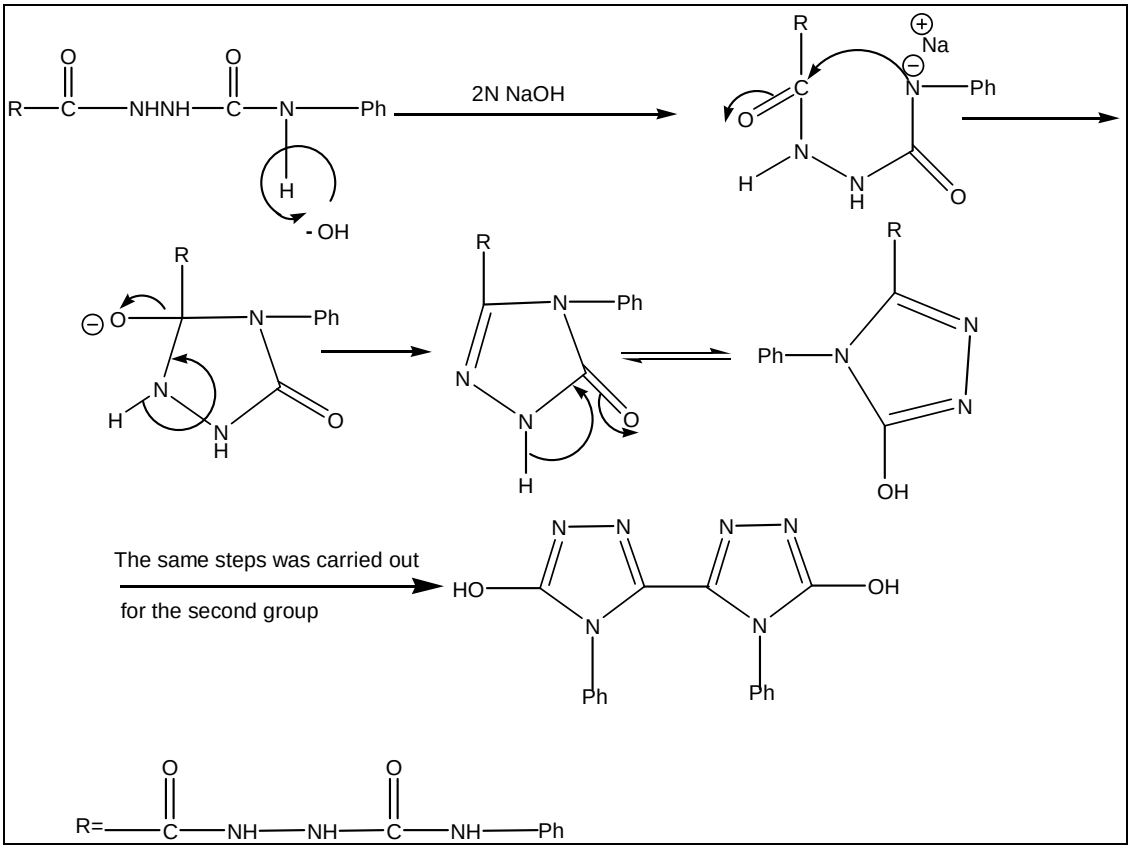


Scheme (3-12) Reagents and Conditions: 2N NaOH, reflux (4) hrs.

1,2,4-Triazole derivative prepared through the reaction of semicarabazide derivatives with NaOH and reflux for (4) hours effected interamolecular cyclization through the loss of H_2O.

The FTIR spectrum of compound [15] shows band at (3425.3) cm^{-1} due to O-H group, the (C=N) band appeared at (1631.7) cm^{-1}, (C=C) band appeared at (1525) cm^{-1} and aromatic (C-H) appeared at (2929.7) cm^{-1}.

The mechanism of the reaction may be posses by the following.



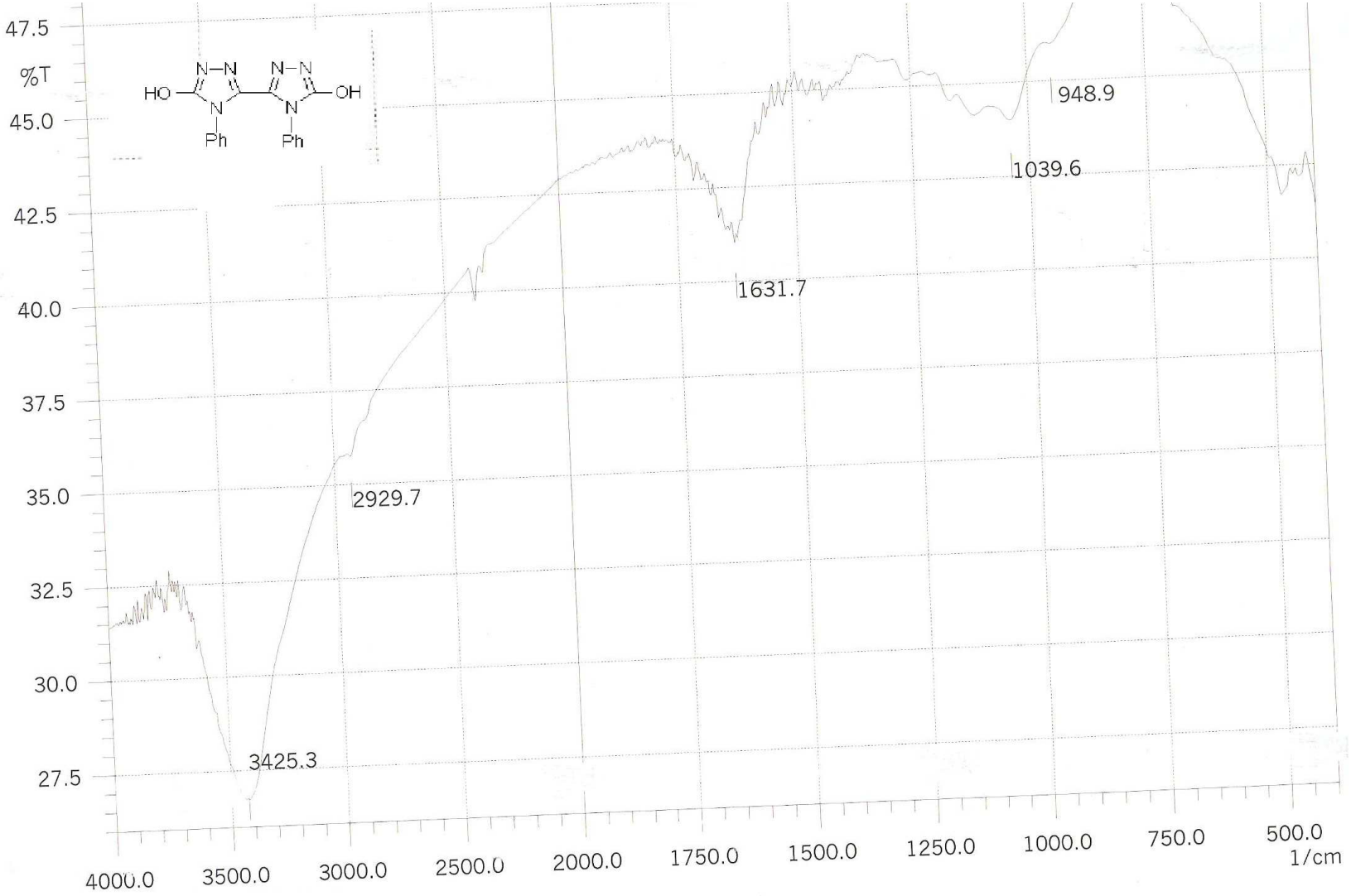
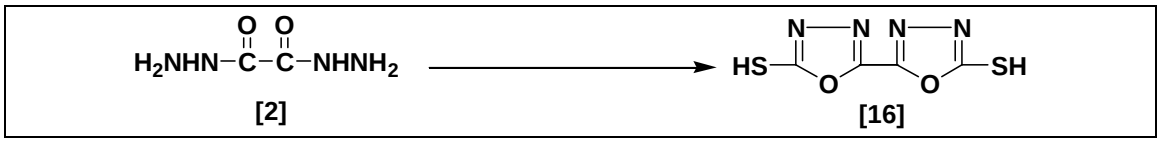


Figure (3-16) FTIR spectrum of compound [bis(-5-hydroxy-4-phenyl-3-yl-1,2,4-triazole)] [15]

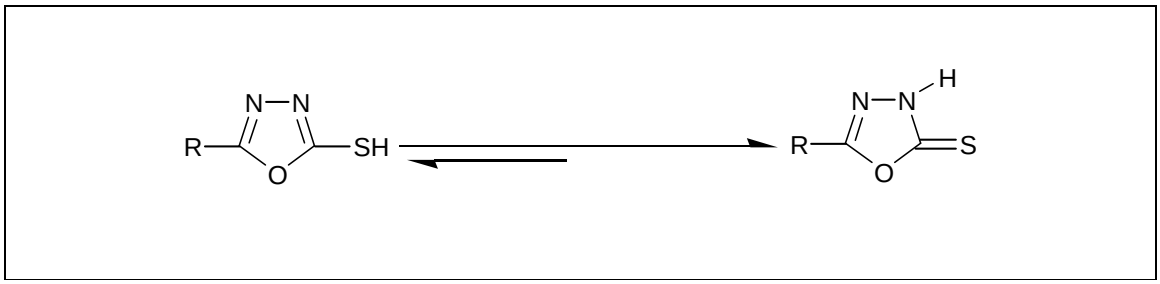
3.14 Synthesis of bis-[5-mercapto-2-yl-1,3,4-oxadiazole] [16]:



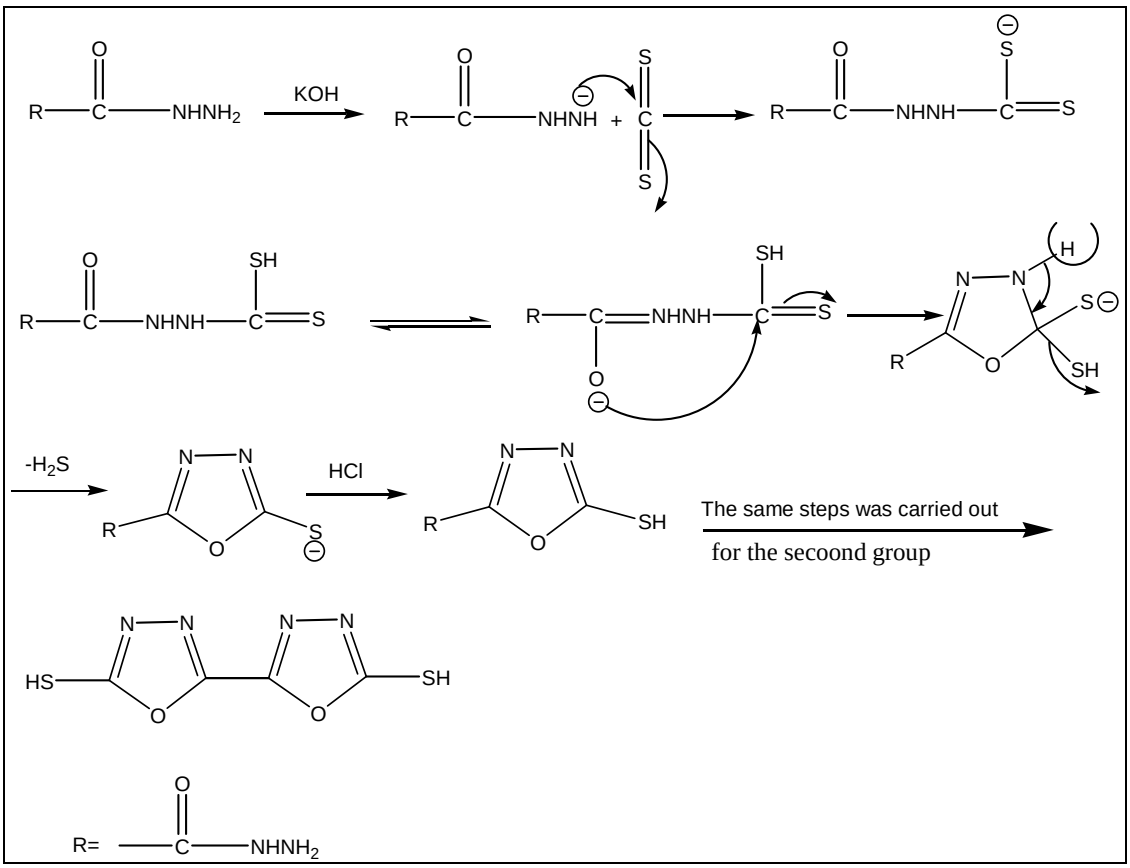
Scheme (3-13): Reagents and Conditions: CS_2, KOH, abs. EtOH, reflux (10) hrs.

Reaction of acid hydrazide [2] with CS_2, KOH in absolute ethanol afforded [16] .

FTIR spectrum of compound [16] in figure (3-17) indicated the disappearance of NH_2 in the range (3292.3-3190) cm^{-1} , disappearance of carbonyl of amide at (1662.5) cm^{-1}, appearance a weak band at (2866.02) cm^{-1} due to S-H group, C-O-C asymmetric and symmetric bands appeared at (1247.86-1116.71) cm^{-1}, appearance of band at range (1600) cm^{-1} assignable to (C=N) of oxadiazole ring, (C=S) appeared at (1247.86) cm^{-1} and appearance of band for (NH) group at (3199.69) cm^{-1} due to the toutomeric form.



The mechanism [141] of the reaction may be outlined as follow:



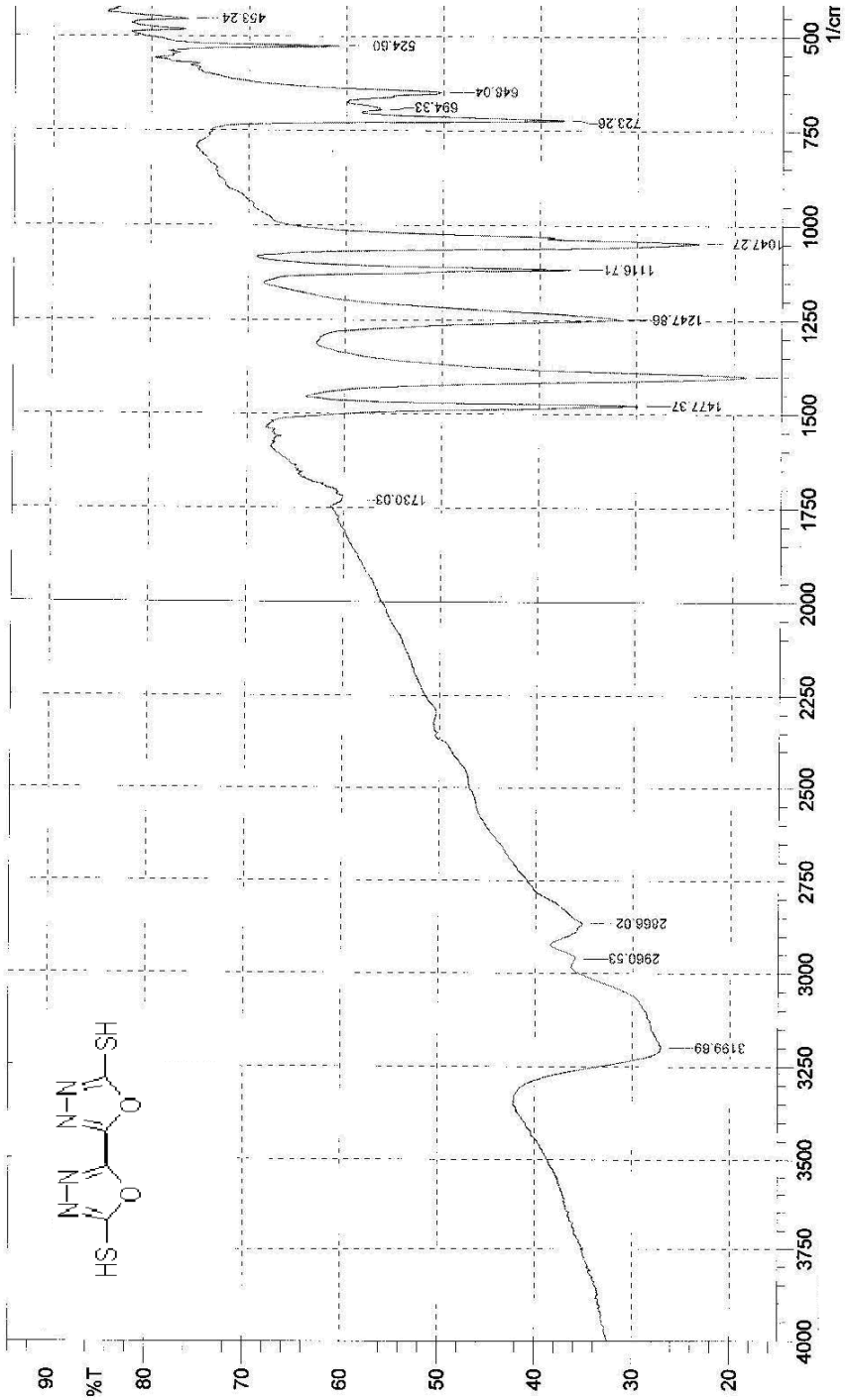
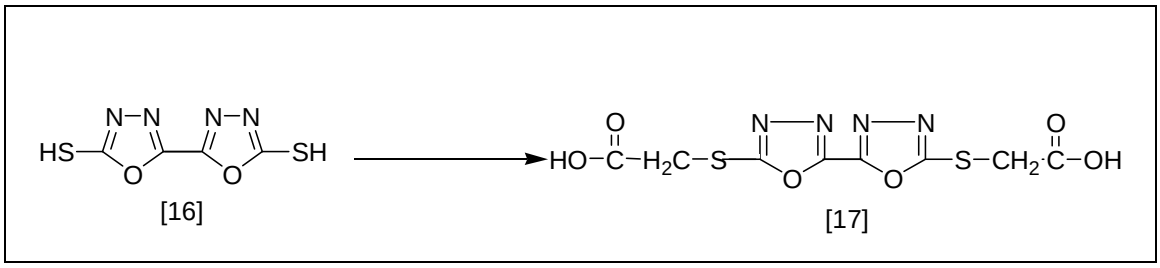


Figure (3-17) FTIR spectrum of compound [bis-(5-mercapto-2-yl-1,3,4-oxadiazole] [16]

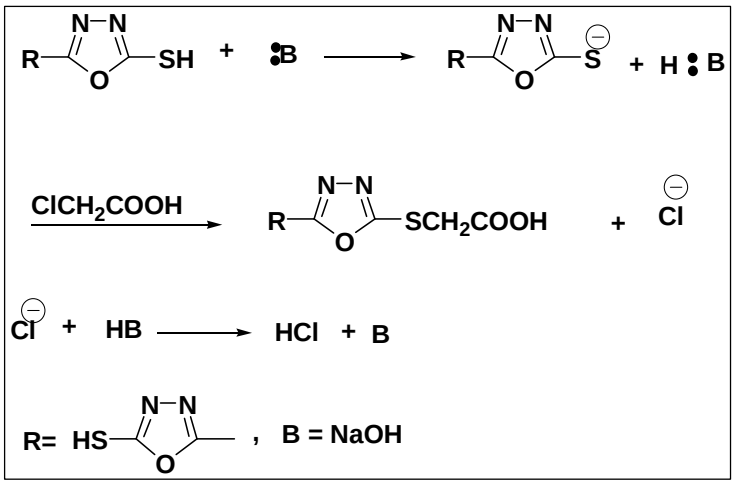
3.15 Synthesis of [2-yl-1,3,4-oxadiazole-5-thioacetic acid] [17]:



Scheme (3-14): Reagents and Conditions: $ClCH_2COOH$, NaOH, abs. EtOH, reflux (3) hours.

The FTIR spectrum in figure (3-18) confirmed the formation of compound [17] from the appearance of (C=O) group of ester at (1725) cm^{-1} , (C-H) aliphatic appeared at (2990) cm^{-1} and (C-O-C) asymmetric and symmetric bands appeared at (1100-1350) cm^{-1}.

The suggested mechanism of the reaction is as shown below:



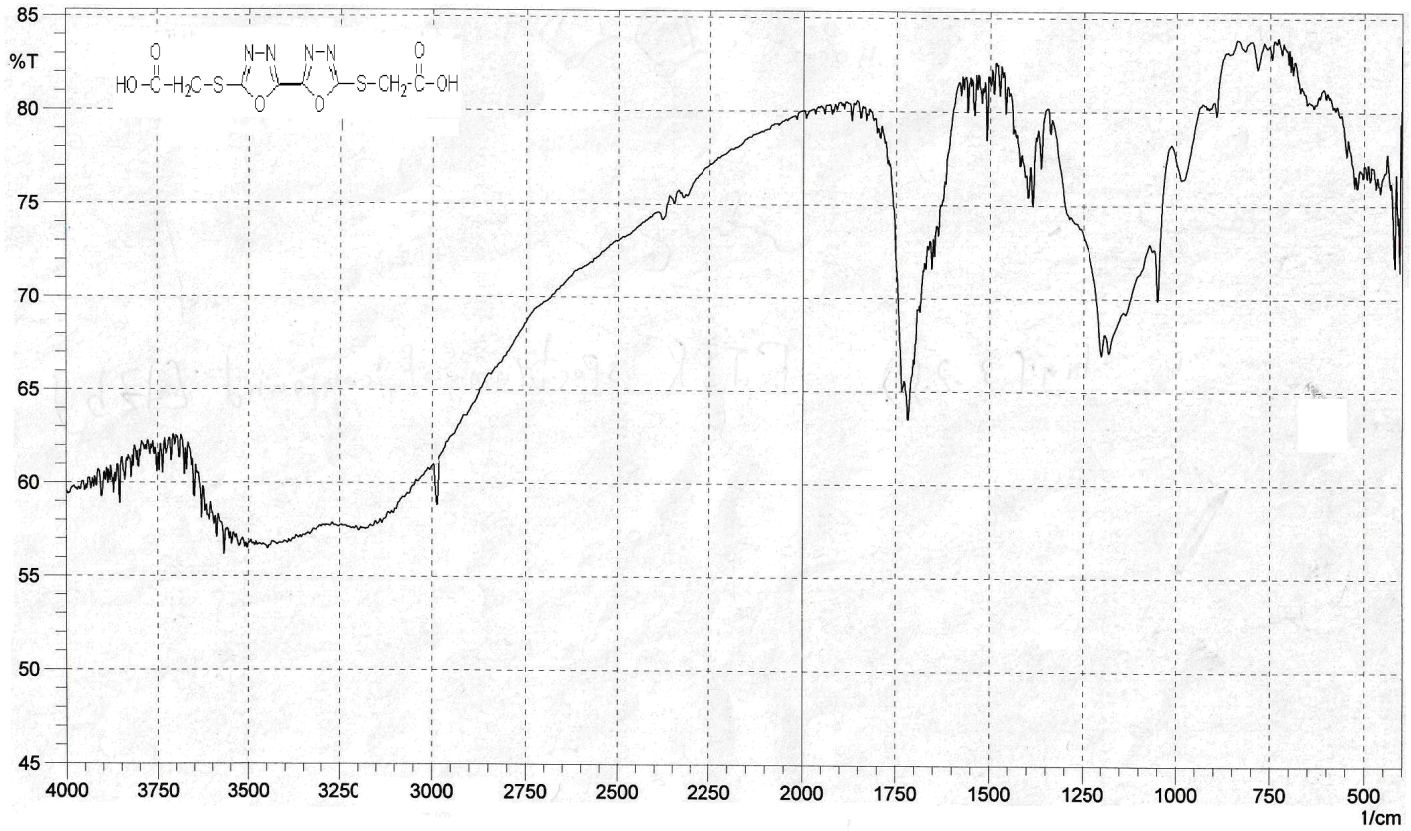
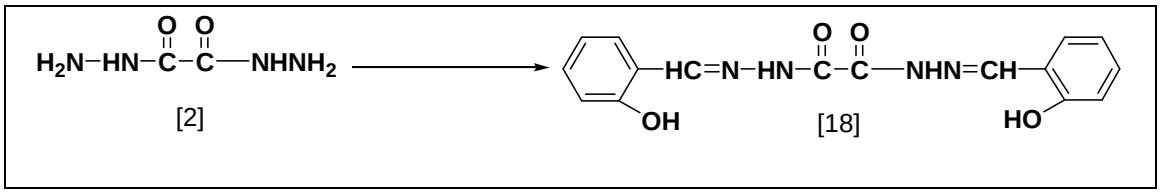


Figure (3-18) FTIR spectrum of compound [bis-(2-yl-1,3,4-oxadiazole-5-thioacetic acid][17]

3.16 Synthesis of bis-[N-(*o*-hydroxybenzylidine)-formyl hydrazide] [18]:

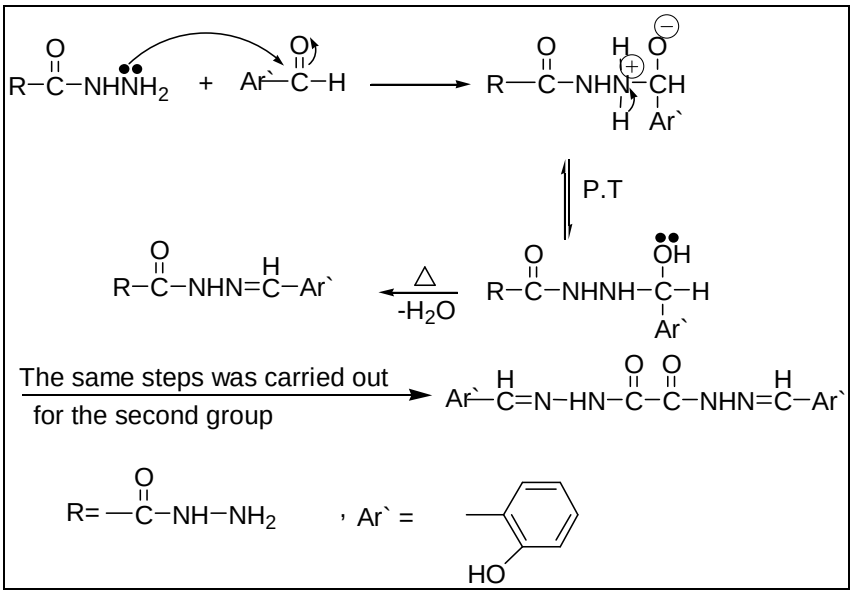


Scheme (3-15): Reagents and Conditions: *o*-hydroxybenzaldehyde, glacial HAc, abs.EtOH, reflux (4) hrs.

Reaction of compound [2] with o-salicylaldyhyde in absolute ethanol gave compound [18].

The FTIR spectrum of compound [18] in figure (3-19) shows the disappearance of ($–NH_2$) stretching bands at (3292.3, 3190) cm^{-1}, carbonyl group appeared at (1690) cm^{-1}, a band of C=C appear at (1568) cm^{-1} ,(C=N) band appeared at (1622) cm^{-1}, aliphatic (C-H) appeared at (2925) cm^{-1} ,aromatic (C-H) appeared at (3050) cm^{-1},and (-OH) groyp appeared at (3400) cm^{-1} .

The mechanism of the reaction is as shown below [(142)]:



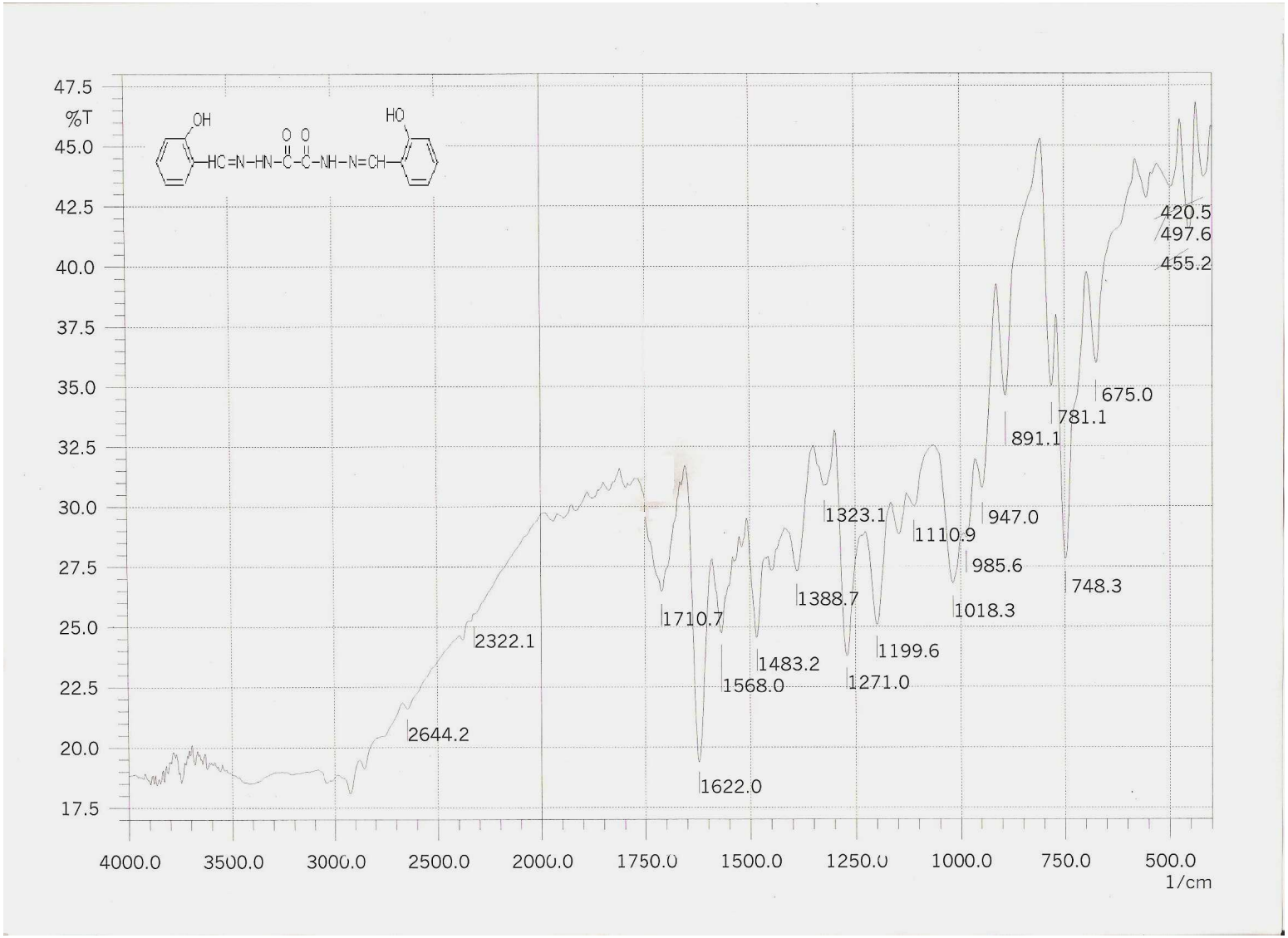
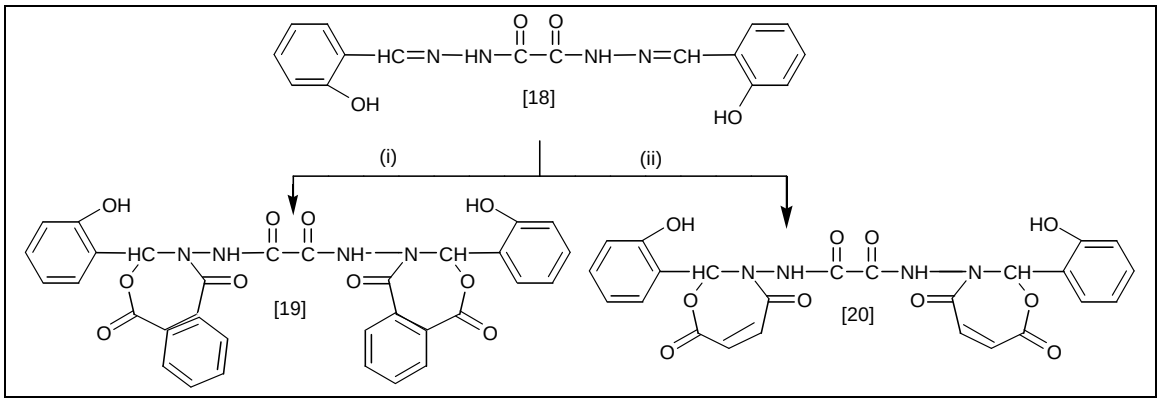


Figure (3-19) FTIR spectrum of compound [bis-(N-o-hydroxybenzylidine)-formyl hydrazide] [18]

3.17 Synthesis of oxazepine derivatives [19,20] :



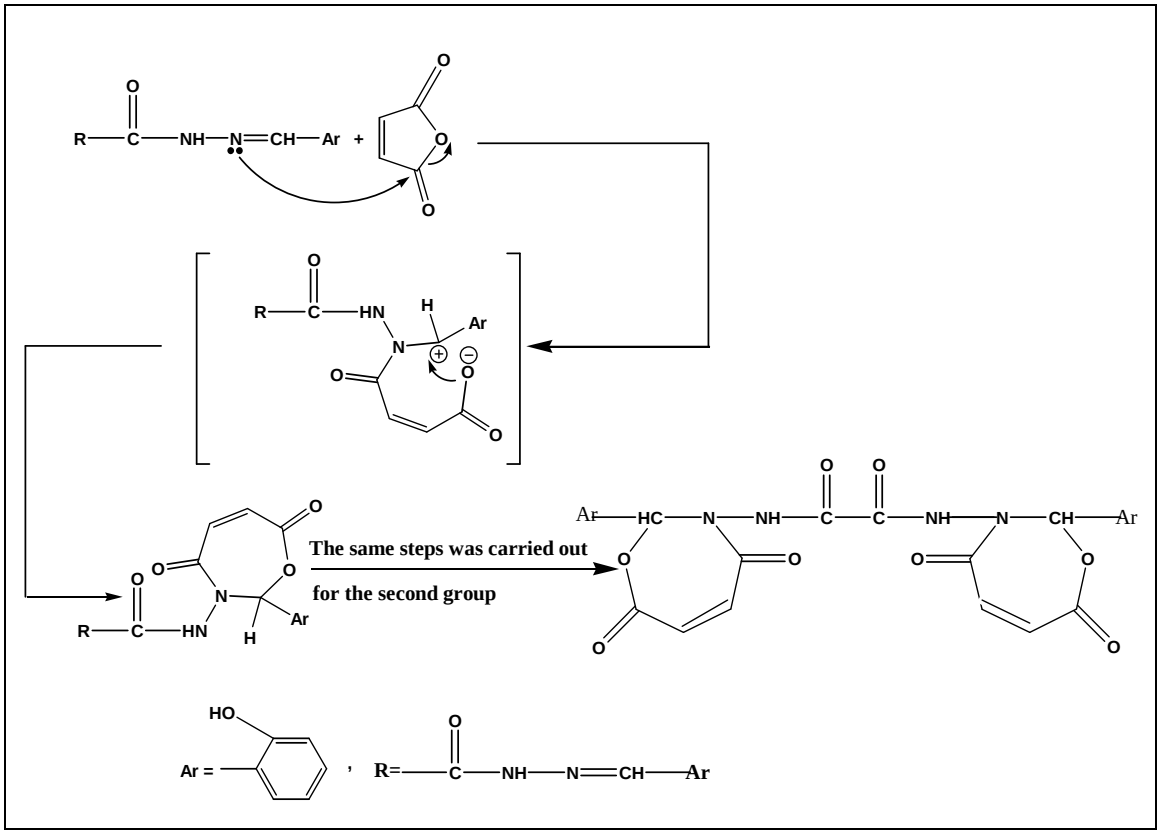
Sceme (3.19) Reagents and conditions: (i) phthalic anhydride, toluene,reflux (7) hrs. (ii) maleic anhydride , toluene, reflux (7)hrs.

The F.T.IR spectrum of compound [19] in Figure (3-20) shows appearance of two carbonyl groups band at (1625.88-1704.96) cm^{-1} , N-H band at (3300) cm^{-1} , C-H aliphatic band appeared at (2844.81 cm^{-1}) ,bands at (1278.72) , 1147.57) cm^{-1} belong to the asymmetric and symmetric (C-O-C) band. .While the F.T.IR spectrum of compound [20] in Figure (3-21) shows appearance of two carbonyl bands at (1668.31-1701.10) cm^{-1} , N-H band at (3278.76) cm^{-1} , C-H aliphatic band at (2850.59 cm^{-1}) and bands at (157.21-1276.79) cm^{-1} belong to the asymmetric and symmetric (C-O-C) band.

Table (3-3): Characteristic bands of compounds [19,20]:

Comp. No.	*ν(C-H) arm. cm^{-1}*	*ν(C-H) aliph. cm^{-1}*	*ν(C=O) cm^{-1}*	*ν(C-O-C)) cm^{-1}*	*ν(-NH) cm^{-1}*	*ν(C=C) cm^{-1}*
19	*3045.39*	*2844.81*	*(1625.88-1704.96)*	*(1278.72-1147.57)*	*3300*	*1487.01*
20	*3045.39*	*2850.59*	*(1668.31-1701.10)*	*(1276.79-1157.21)*	*3278.76*	*1535.23*

The suggested mechanism for the reaction is shown below :



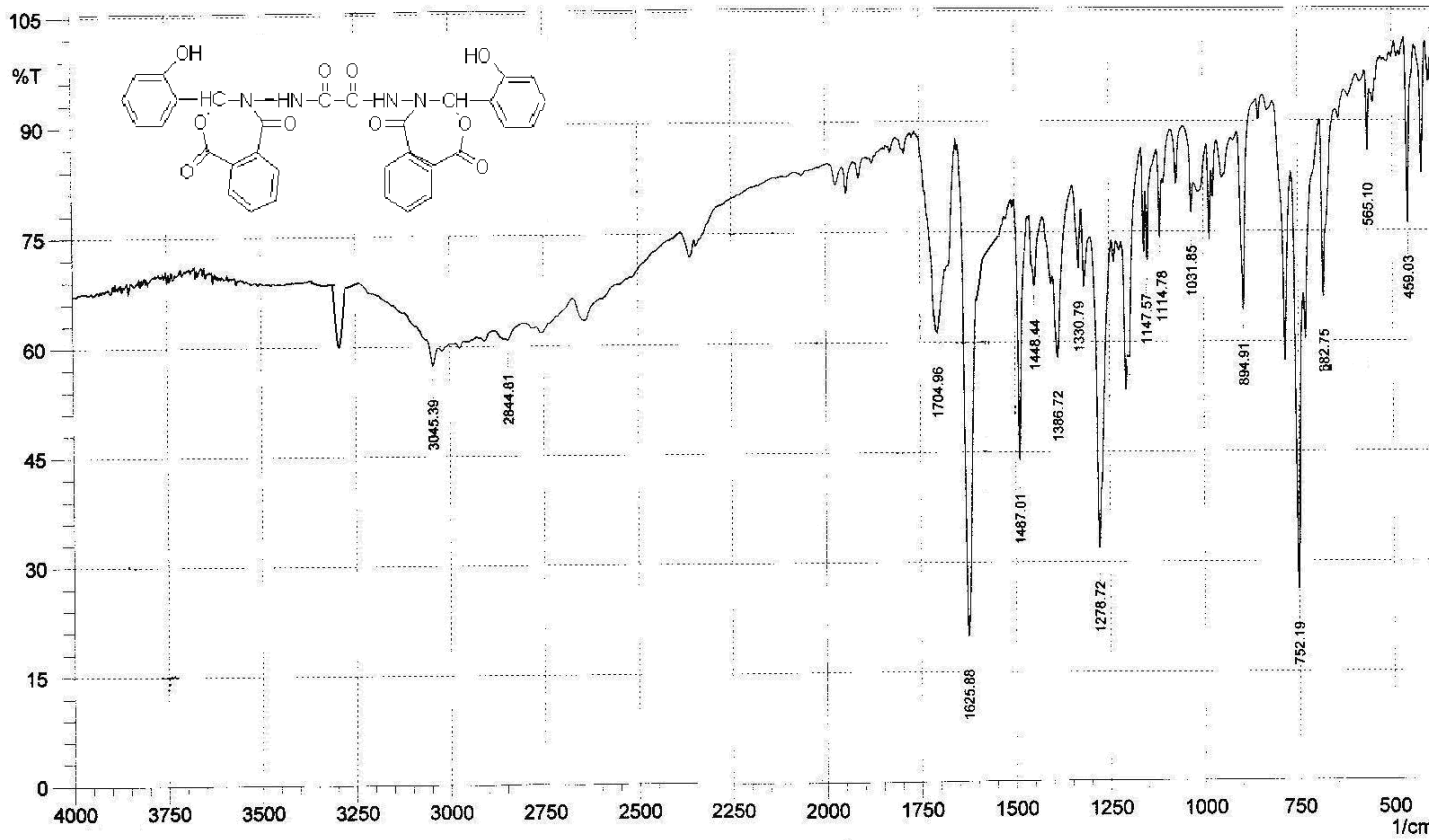


Figure (3-20) FTIR spectrum of compound [bis-N-(2-(o-hydroxyphenyl)-4,7-dione-(5,6-e)phenyl-1,3-oxazepine-3(H)yl) formylhydrazide] [19]

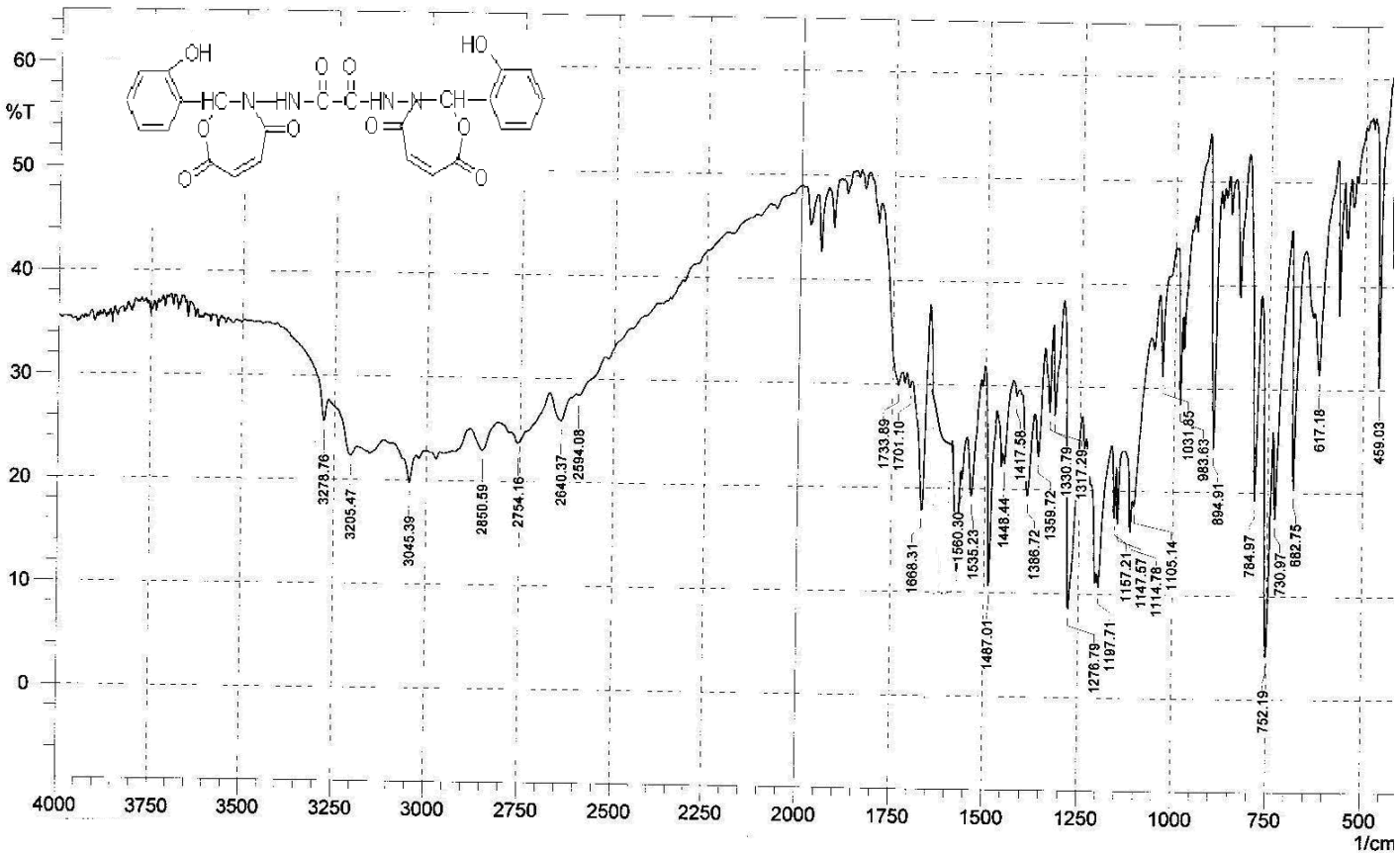


Figure (3-21) FTIR spectrum of compound [bis-(N-(o-hydroxyphenyl)-4,7-dione-2-hydro-1,3-oxazepine-3(H)yl)formylhydrazide] [20]

3.18 Biological activity:

Microorganism causes different kind of diseases to humans and animals. Discovery of chemotherapeutic agents played a very important role in controlling and preventing such diseases.

Chemotherapeutic agents are isolated either from living organism known as antibiotics like penicillin and tetracycline etc., or they are chemical compounds prepared by chemist such as the sulfa drugs etc. [143].

Multiple drug resistant organisms, such as methicillin-resistant Staphyloccus auresus, vancomycin-resistant Enterococci, etc., are becoming common causes of infections in the acute and long term care units in hospitals. The emergence of these resistant bacteria has created a major concern and an urgent need to agents in structural classes distinct from known chemotherapeutic agents.

The most essential feature of good chemotherapeutic agent is that, it must show a high degree of selective toxicity towards a microorganism, so that, it can be given in sufficient doses to inhibit or kill the microorganism through out the body without harming the body cell. Heterocyclic rings constitute an important class of compounds having a wide spectrum of biological activity [144].

3.18.0 Microbiological tests:

In this work, the antibacterial test was performed according to the disc diffusion method. Compounds (3,5,6,8,11,12,14,15 and 20) were assayed for

their antimicrobial activity in vitro against Gram-negative bacteria (*Escherichia coli*) and Gram-positive bacteria (*staphylococcus aurous*). Prepared agar and Petri dishes were sterilized by autoclaving for 15min at 121C°. The agar plates were surface inoculated uniformly from the broth culture of the tested microorganisms. In the solidified medium suitably spaced apart holes were made all 6mm in diameter. These holes were filled with 100µl of the prepared compounds (0.03g of the compound dissolved in 1ml of DMSO solvent), DMSO was used as a solvent. These plates were incubated at 37C° for 24h for both bacteria. The inhibition zones caused by the various compounds were examined. The results of the preliminary screening tests are listed in table (3-4).

The biological activity test showed that compounds with free (-SH) groups and free ($-NH_2$) groups having a biological effect on each of *E.Coli* and *Staph.aureus*, these compounds are also considered biologically active on *bacteria* while when free ($-NH_2$) and (-SH) groups disappeared the existence of Pyridine lead to increase of the biological activity.

Table (3-4):

Antibacterial activities of some of the synthesized compounds

Comp. No.	In figure	Escherichia coli	Staphococcus aureus
3	3	-	++
5	5	-	-
6	6	++	-
8	15	-	+
11	22	++	-
12	24	+	-
14	26	-	++
15	25	-	-
20	19	-	-

Note:

- = No inhibition = inactive
\+ = (5-10) mm = slightly active
++ = (11-20) mm = moderately active

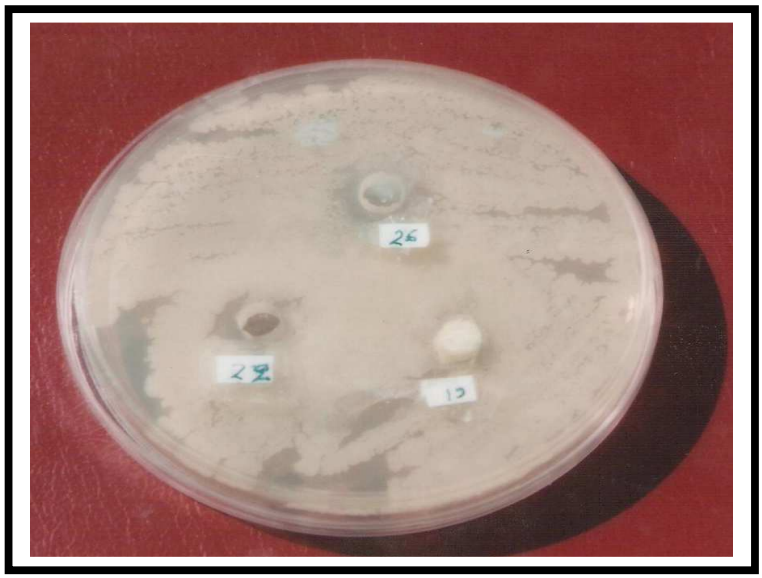


Fig (3-22): Effect of compounds [19], [22] and [26] on Staphylococcus aureus.

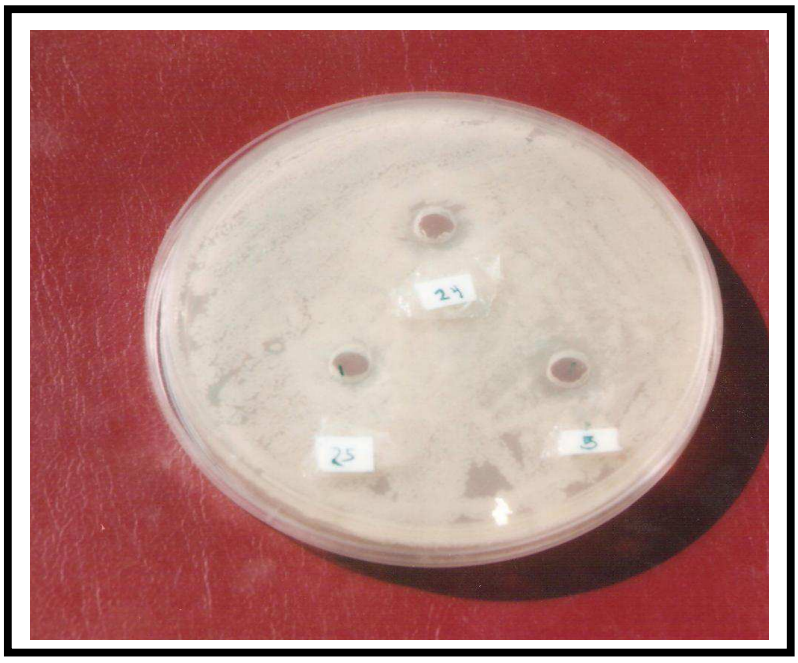


Fig (3-23): Effect of compounds [5], [24] and [25] on Staphylococcus aureus.

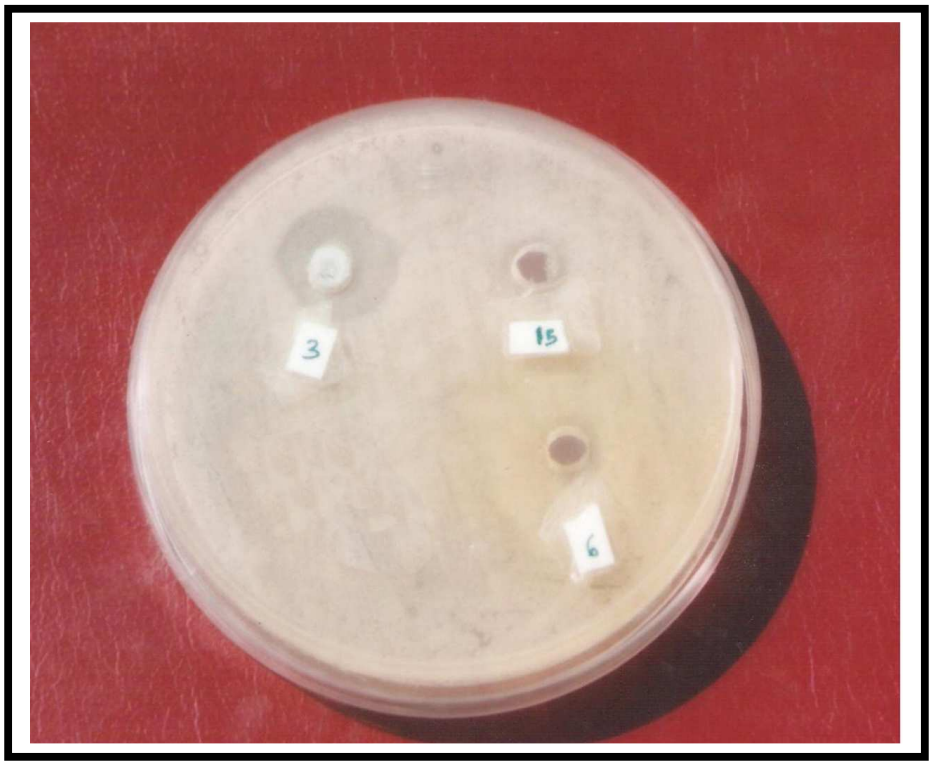


Fig (3-24): Effect of compounds [3], [6] and [15] on *Staphylococcus aureus*.

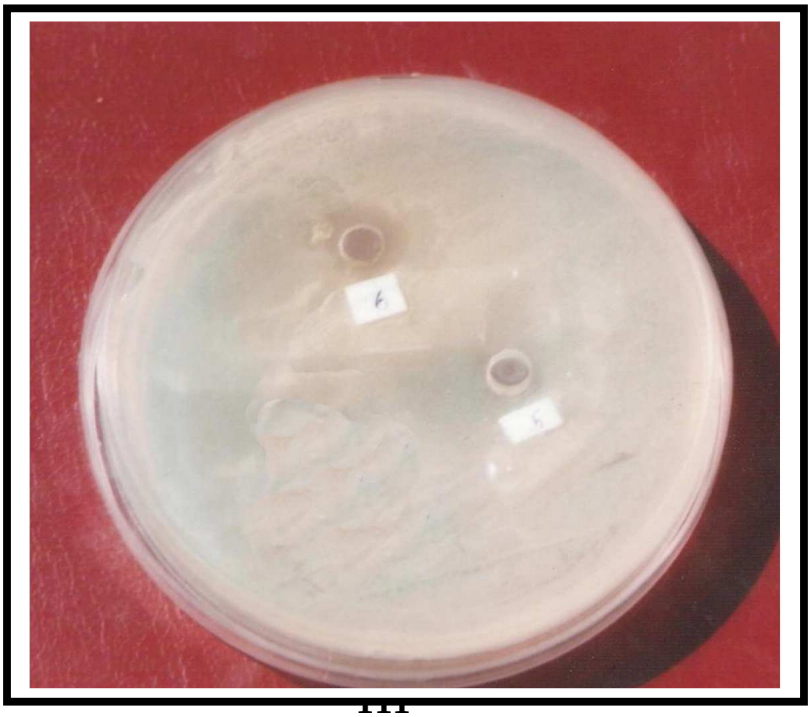


Fig (3-25): Effect of compounds [5] and [6] on *Escherichia coli*.

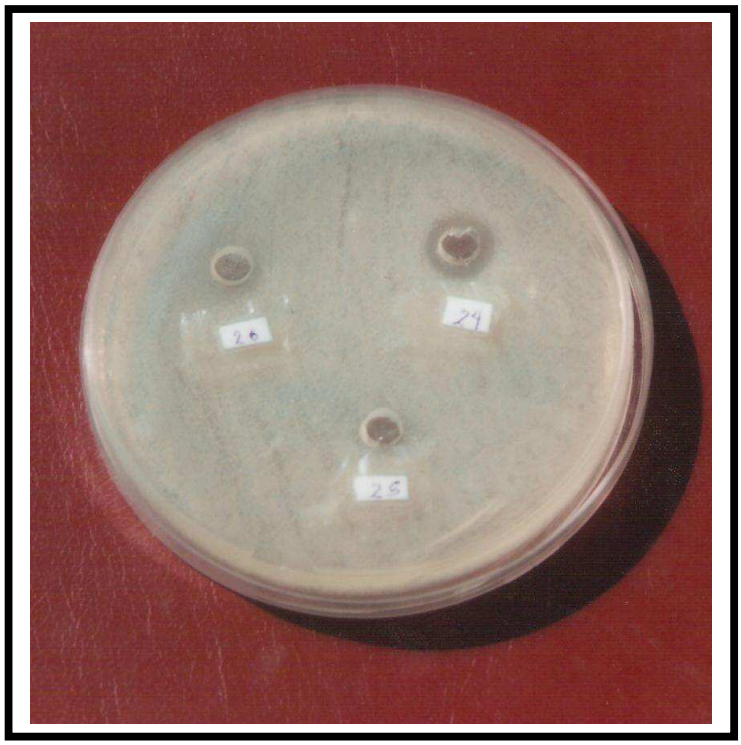


Fig (3-26): Effect of compounds [24], [25] and [26] on Escherichia coli.

Fig (3-27): Effect of compounds [3], [19] and [22] on Escherichia coli.

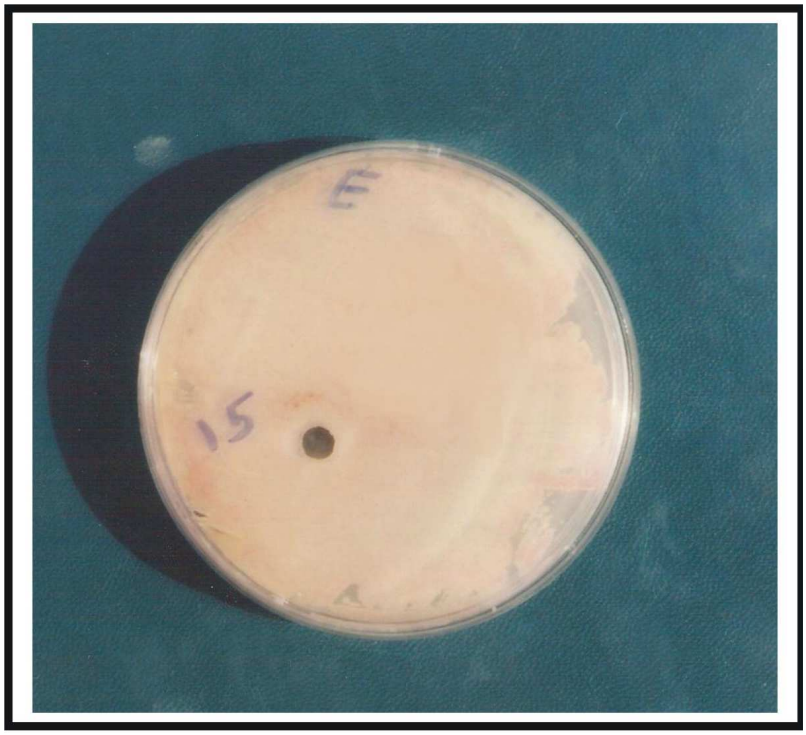


Fig (3-28): Effect of compound [15] on Escherichia coli .

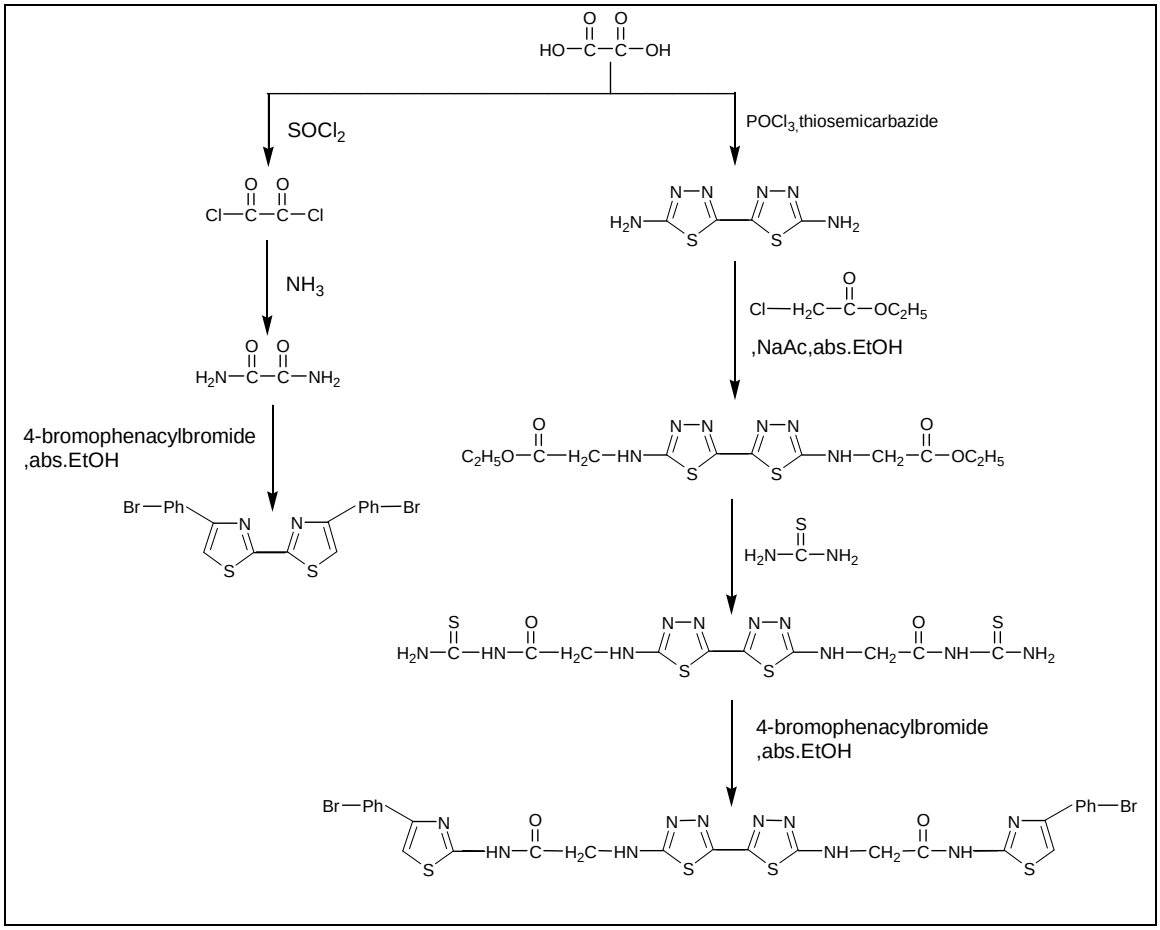
Conclusion

1. Compounds [6 and 11] showed moderate activity on Escherichia coli ,while compound [12] showed slight activity on this bacteria .
2. Compounds [3 and 14] showed moderate activity on *Staphylococcus aureus*, while compound [8] showed slight activity on this bacteria .
3. Compounds [5 ,15 and 20] showed no effect on Escherichia coli and *Staphylococcus aureus* .

Suggestions for further work

On the bases of the experience gained during this work, one can suggest the following as future work:-

1- Synthesis of new oxazole ,thiazole and thiadiazole derivatives from oxalic acid :



2- More detailed investigations are required to reveal the biological activity of the synthesized compounds against other microorganism, their toxicity.

absorption, excretion and the side effects which may produce before they can be used clinically.

Chapter two

Experimental part

2.1 Chemicals:

The chemicals used and the manufacturers are listed in Table (2-1).

Table (2-1) Chemical materials:

Chemicals	Company	Purity %
Acetic acid	Merck	85
Acetyl acetone	Merck	80
Ammonium hydroxide	Merck	90
Ammonium thiocyanate	BDH	85
Carbon disulfide	Fluka	99
Chloroacetic acid	Fluka	55
Di methyl sulphoxide	Fluka	70
Ethanol (absolute)	BDH	99
Ethylacetoacetate	Fluka	90
Ethylchloroacetate	BDH	95
Glacial acetic acid	Merck	90
Hydrazine hydrate	aFluk	80
Hydrochloric acid	BDH	37
Maleic anhydride	BDH	85
Oxalic acid	BDH	70
Phenyl isocyanate	Fluka	98

Chemicals	Company	Purity
Phenyl isothiocyanate	Fluka	98
4-phenylphenacylbromide	Fluka	98
phthalic anhydride	BDH	87
Potassium hydroxide	BDH	85
Salicylaldehyde	Merck	90
Sodium bicarbonate	BDH	70
Sodium hydroxide	Merck	56
Sulfuric acid	Fluka	55
Toluene	BDH	90

2.2 Instruments:

1- Melting points are recorded using hot stage Gallen Kamp melting point apparatus and they were uncorrected.

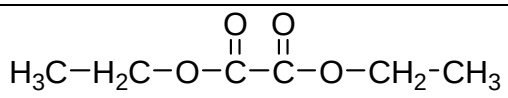
2- Infrared spectra are recorded using Fourier Transform infrared SHIMADZU (8300) (F.T.IR) infrared spectrophotometer, KBr disc or thin film was performed by Chemistry Department, Al-Nahrain University,also Infrared spectra are recorded using Fourier Transform infrared SHIMADZU (8400) (F.T.IR) infrared spectrophotometer, KBr disc or thin film was performed by Central Organization of Standardization and Quality control.

3- Thin layer chromatography (TLC) was carried out, and the plates were developed with iodine vapour.

4- The biological activity was performed by Biotechnology Department, Al-Nahrain University .

2.3.0 Methods:

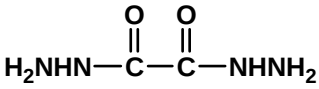
2.3.1 Synthesis of Diethyl oxalate [1][122]:



[1]

Oxalic acid (0.22 mole, 20g) [I] was treated with (20) ml absolute ethanol, (5 ml) of conc. sulfuric acid and refluxed the mixture for 6 hours, yielded the expected esters [1], yield (62.27%).

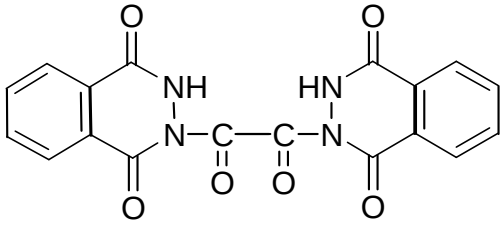
2.3.2 Synthesis of Oxalic acid dihydrazide [2][123]:



[2]

Compound [2] was synthesized by addition of hydrazine hydrate (0.32 mole, 10 ml) to (0.16 mole, 23 ml) [1] in (25) ml of absolute ethanol then the mixture was refluxed for 2 hours. After cooling, the product was filtered off and recrystallized by using ethanol, m.p. for [2](153-155) ^{0}C ,lit [124](151-153),and yield(85%).

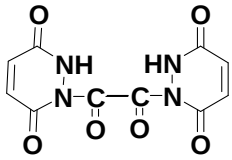
2.3.3 Synthesis of bis-1-(formyl)-1,2-dihydrophthalazin-3,8-dione] [3][125]:



[3]

Compound [2] (0.004 mole, 0.5g) , was mixed with phthalic anhydride (0.008 mole, 1. 254g), in acetic acid (10) ml, the mixture was refluxed for 7 hours then cooled and added to crushed ice. The precipitate was filtered off, washed with water to give the final product, m.p. (291-293) °C, yield (74%).

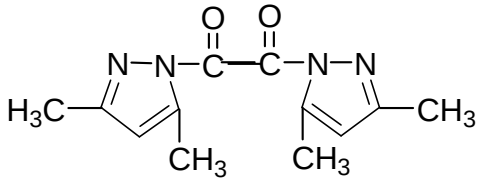
2.3.4 Synthesis of bis-[1-(formyl)-1,2-dihydropyridazin-3,6-dione [4][125]:



[4]

Compound [2] (0.004 mole, 0.5 g) was mixed with maleic anhydride (0. 008 mole, 0.83 g) in acetic acid (10) ml, the mixture was refluxed for 7 hours then cooled and added into crushed ice. The precipitate was filtered off, washed with water to give the final products, m.p (237) °C dec., yield (81%).

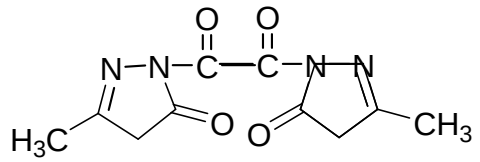
2.3.5 Synthesis of bis-[2-formyl-3,5-dimethyl pyrazole] [5][126]:



[5]

Compound[2] (0.004 mole, 0.5 g)was treated with acetylacetone (0.008 mole, 1ml) and acetic acid(0.5ml) in absolute ethanol (10) ml was heated under reflux for 7 hours. The reaction mixture was cooled and the formed precipitate was filtered off to give the final product [5], m.p. (223-226) °C, yield (77.88%).

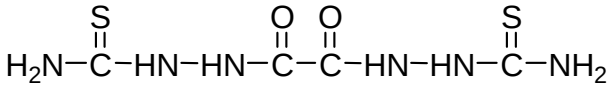
2.3.6 Synthesis of bis-[2-formyl-5-methyl-3-pyrazolone] [6][127]:



[6]

Compound [2b] (0.004 mole, 0.5 g)was treated with ethyl acetoacetate (0.008mole, 1ml) in absolute ethanol (10ml) was heated under reflux for 7 hours.After concentration and cooling ,the oily product was obtained,yield(88.6%).

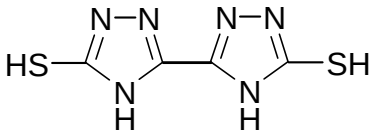
2.3.7 Synthesis of bis-[4-formylthiosemicarbazide] [7][(128)]:



[7]

Compound [2] (1g,0.008 mole) was treated with ammonium thiocyanate (1.288g,0.016 mole) and hydrochloric acid (5ml) was refluxed for 4 hours. The pale yellow solid appeared on cooling was filtered and the excess solvent was removed by vacumm evaporation . The product was recrystallized from ethanol ,m.p.(232-235) °C,yield(70%).

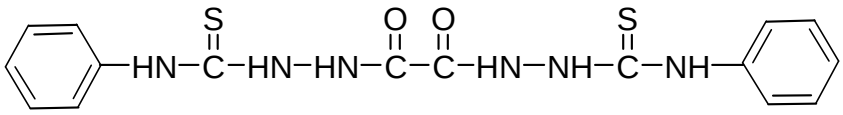
2.3.8 Synthesis of bis-[5-mercapto-3-yl-1,2,4-triazole] [8][(128)]:



[8]

Compound[7](1g,0.004 mole) was refluxed in 10% NaOH solution (10 ml) for 3 hours.The resulting solution was cooled and filtered, the solid compound obtained on cooling was recrystallized from ethanol,m.p.(272-274) °C ,yield (97.15%).

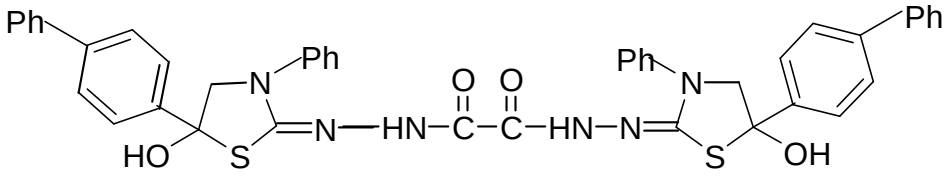
2.3.9 Synthesis of bis-[1-phenyl-4- (formyl) thiosemicarbazide] [9][(129)]:



[9]

Compound [2] (1g,0.008 mole) and phenyl isothiocyanate (2.29ml,0.016 mole) in (15) ml absolute ethanol was refluxed for 7 hours. The solid compound obtained on cooling was filtered off, and then recrystallized from ethanol ,m.p. (215-217) °C, yield (87.92%).

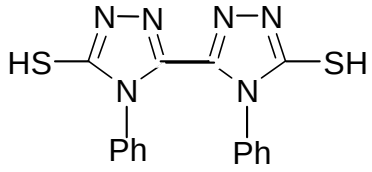
2.3.10 Synthesis of bis[5-(biphenyl)-2-(acid hydrazide)-3-N-phenyl-4-(hydroxyl)thiazolidine [10] [(123)]:



[10]

Compound [9] (0.00036 mole, 0.14 g) and *p*-phenylphenacyl bromide (0.0007 mole, 0.2g) in absolute ethanol (10 ml) was refluxed for 8 hours, cooled and neutralized with ammonium hydroxide solution. The precipitate was filtered off, washed with water , dried and recrystallized from ethanol, m.p. (240) °C dec., yield (93.24%).

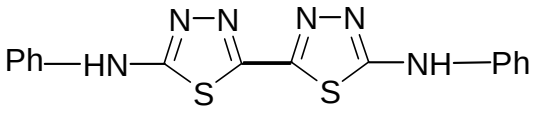
2.3.11 Synthesis of bis-[5-mercapto-3-yl-4-phenyl-1,2,4-triazole] [11] [129]:



[11]

Compound [9] (0.001 mole, 0.5 g) and (15ml) of 2M sodium hydroxide solution was refluxed with stirring for (4) hours. After cooling, the solution was acidified with hydrochloric acid and the precipitate was filtered, m.p. (167-170) °C, yield (73.18%).

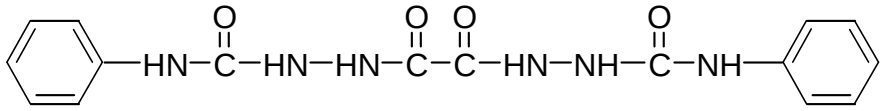
2.3.12 Synthesis of bis-[5-(phenyl amino)-2-yl-1,3,4-thiadiazole][12] [129]:



[12]

Compound [9] (0.0008 mole, 0.3 g) was added portionwise to (5) ml of concentrated sulfuric acid at 0°C with continuous stirring. The reaction mixture was stirred further for 3 hours at room temperature and then allowed to stand overnight. Neutralization with dilute sodium bicarbonate prepcipitated acrude solid, which was filtered and recrystallized from ethanol, m.p. (235-237) °C, yield (77.17%).

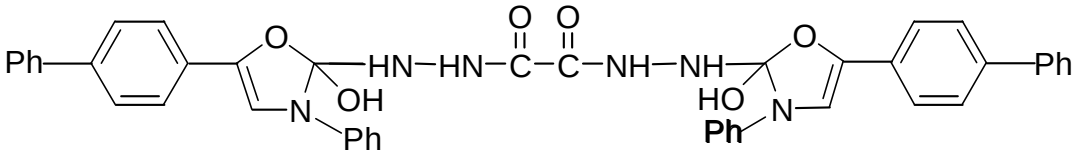
2.3.13 Synthesis of bis[1-phenyl-4-(formyl)semicarbazide] [13] [129]:



[13]

A mixture of compound [2] (0.008 mole, 1 g) and phenyl isocyanate (0,016 mole, 2 ml) in (10) ml absolute ethanol was refluxed for 7 hours. The solid compound obtained on cooling, then filtered off to give final compound, m.p. (250-252) °C, yield (89%).

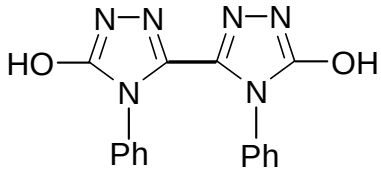
2.3.14 Synthesis of bis-[5-(biphenyl)-2-(acid hydrazide)-3-N-phenyl-2-(hydroxy)oxazoline] [14] [123]:



[14]

A mixture of compound [13] (0.0004 mole, 0.13 g) and *p*-phenylphenacyl bromide (0.0008 mole, 0.2 g) in absolute ethanol (10ml) was refluxed for 8 hours, cooled and neutralized with ammonium hydroxide solution. The precipitate was filtered off, and recrystallized from ethanol to give the final product, (m.p. > 300) °C, yield (69.41%).

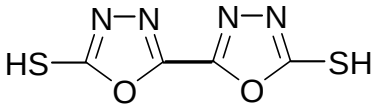
2.3.15 Synthesis of bis-[5-hydroxy-4-phenyl-3-yl-1,2,4-triazole[15] [129]:



[15]

A mixture of compound [13] (0.002 mole, 0.5 g) and 2M sodium hydroxide solution was refluxed with stirring for 4 hours. After cooling, the solution was acidified with hydrochloric acid and the precipitate was filtered to give the final product, (m.p. > 300) °C, yield (74.29%).

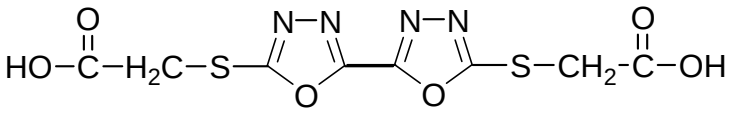
2.3.16 Synthesis of bis-[5-mercapto-2-yl-1,3,4- oxadiazole] [16][130]:



[16]

Compound [2] (1g, 0.008mol) was treated with ethanol (20ml), potassium hydroxide (0.95g, 0.016mole) and carbon disulfide (4ml ,0.016mole) was added respectively. The mixture was heated at reflux for 10 hours or until most of the hydrogen sulfide has been evolved. The solvent was evaporated in vacue, the residue dissolved in ice-water and acidified with conc. hydrochloric acid. The precipitate was filtered and recrystallized from (ethanol-water) (60:40) to give the desired product,m.p (181) °C dec. ,yield (25.18%).

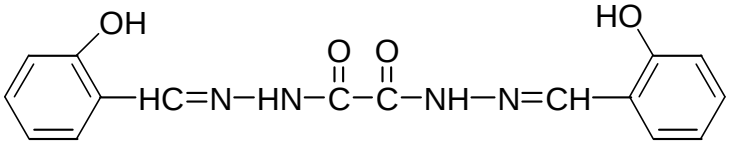
2.3.17 Synthesis of bis-[2-yl-1,3,4-oxadiazole-5 -thioacetic acid] [17][131]:



[17]

To (0.001 mole,0.2g) of [16b] in 10% sodium hydroxide(10ml) was added (0.002 mole,0.123g) of monochloroacetic acid in 10% sodium hydroxide(10ml). The reaction mixture was heated under reflux temperature for 3 hours. The reaction mixture was cooled, acidified with conc. hydrochloric acid and ice – water to precipitate the acid. The obtained compound [17] was filtered, washed with cold distilled water, dried and recrystallized from ethanol, the m.p is (220^0C)dec., yield (53.99%).

2.3.18 Synthesis of bis-[N-(*o*-hydroxy benzylidine) -formyl hydrazide [18][132]:

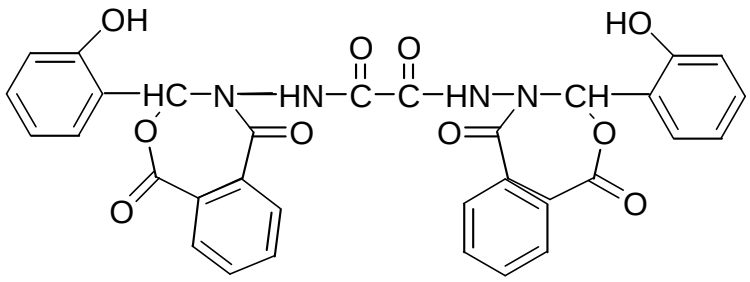


[18]

A mixture of hydrazide [2] (0.003 mole, 0.4 g) with o-salicylaldehyde (0.0068 mole, 1ml) in absolute ethanol (20ml) and two drops of glacial acetic

acid was refluxed for 4 hours. The mixture was cooled to form the precipitate and recrystallized from ethanol, m.p.(185-188) °C, yield (45.25%).

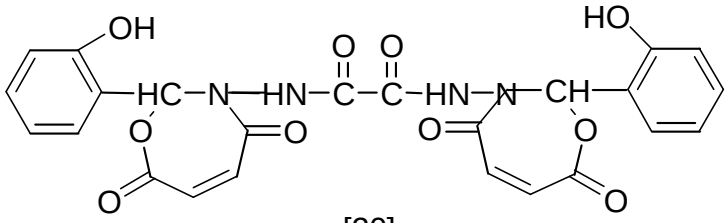
2.3.19 Synthesis of bis-[N-[2-(*o*-hydroxyphenyl)-4,7-dione-[5,6-e]phenyl-2-hydro-1,3-oxazepin-3(H)-yl] formyl hydrazide [19][133]:



[19]

A mixture of Schiff base[18] (0.001mole,0.4g) with phthalic anhydride (0.002 mol,0.36g) dissolved in (10 ml) toluene and then the mixture was refluxed for 7 hours in water bath at (100 ^{o}C). Excess solvent was distilled, filtered off and recrystallized from ethanol, m.p. (196-198) ^{o}C, yield (75.88%).

2.3.20 Synthesis of bis-[N-[2-(*o*-hydroxyphenyl)-4,7-dione-2-hydro-1,3-oxazepin-3 (H)-yl] formyl hydrazide [20][133]:



[20]

A mixture of Schiff base[18] (0.003 mole,0.96g) with maleic anhydride (0.001 mole,0.58g) dissolved in (20 ml) toluene and then the mixture was refluxed for 7hours in water bath at (70 ^{o}C). Excess solvent was distilled, filtered off and recrystallized from ethanol, m.p. (215-217) ^{o}C, yield (83.89%).

Table(2-2) Physical properties of the synthesized compounds:

Comp .No.	Molecular formula	Molecular weight	Reaction time (hr)	Yield (%)	M.P (^{0}C)	Color
1	$C_6H_{10}O_4$	146	6	62.27	-----	colorless
2	$C_2H_6O_2N_4$	118	2	85	153-155	white
3	$C_{18}H_{10}O_6N_4$	378	7	74	291-293	white
4	$C_{10}H_6O_4N_4$	246	7	81	237 dec.	Pale yellow
5	$C_{12}H_{14}O_2N_4$	246	7	77.88	223-226	white
6	$C_{10}H_{10}O_4N_4$	250	7	88.6	-----	Oily yellow
7	$C_4O_2N_6S_2H_8$	236	4	70	232-235	Pale yellow
8	$C_4N_6S_2H_4$	200	3	97.15	272-274	white
9	$C_{16}O_2N_6S_2H_{16}$	388	7	87.92	215-217	white
10	$C_{42}O_4N_6S_2H_{36}$	779	8	93.24	240 dec.	yellow
11	$C_{16}N_6S_2H_{12}$	352	4	73.18	167-170	white
12	$C_{16}N_6S_2H_{12}$	352	3	77.17	235-237	Pale yellow
13	$C_{16}H_{16}O_4N_6$	356	7	89	250-252	green
14	$C_{42}H_{34}O_6N_6$	718	8	69.41	above 300	yellow
15	$C_{16}H_{12}O_2N_6$	320	4	74.29	above 300	white
16	$C_4O_2N_4S_2H_2$	202	10	25.18	181 dec.	yellow
17	$C_8O_6N_4S_2H_6$	318	3	53.99	220 dec.	Pale yellow
18	$C_{16}H_{14}N_4O_4$	326	4	45.25	185-188	yellow
19	$C_{32}H_{22}N_4O_{10}$	622	7	75.88	196-198	white
20	$C_{24}H_{18}N_4O_{10}$	522	7	83.89	215-217	yellow

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List of Abbreviations

Full meaning used in this thesis	Abbreviation
Aryl (substituted phenyl)	**Ar**
Different alkyl groups	**R**
Di methyl sulphoxide	**DMSO**
Proton transfer	**P.T**
Fourier Transform Infrared spectroscopy	**FTIR**
Phenyl	**Ph**
Absolute ethanol	**abs.EtOH**
Acetic acid	**HAc**
Frequincy	***v***
Sodium acetate	**NaAc**
Phenyl isothiocyanate	**PhNCS**
Phenyl isocyanate	**PhNCO**
Figure	**Fig**
Tetrahydrofuran	**THF**

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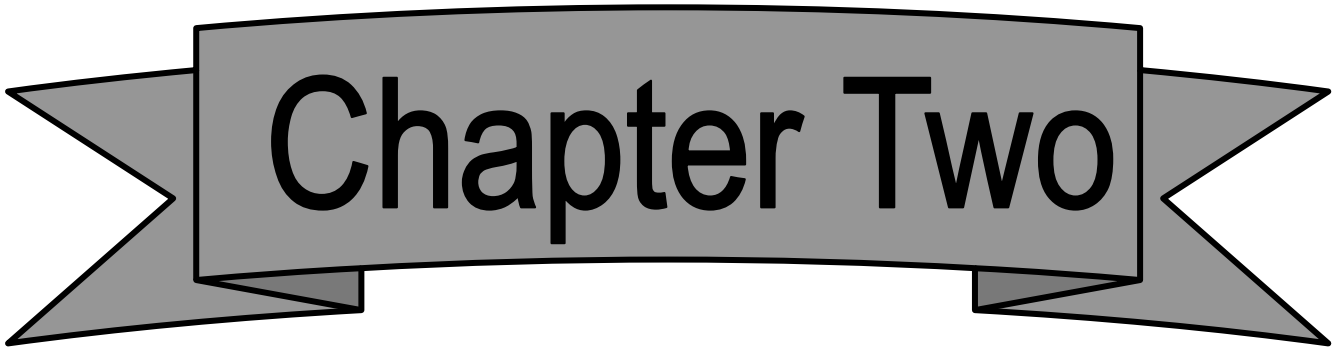
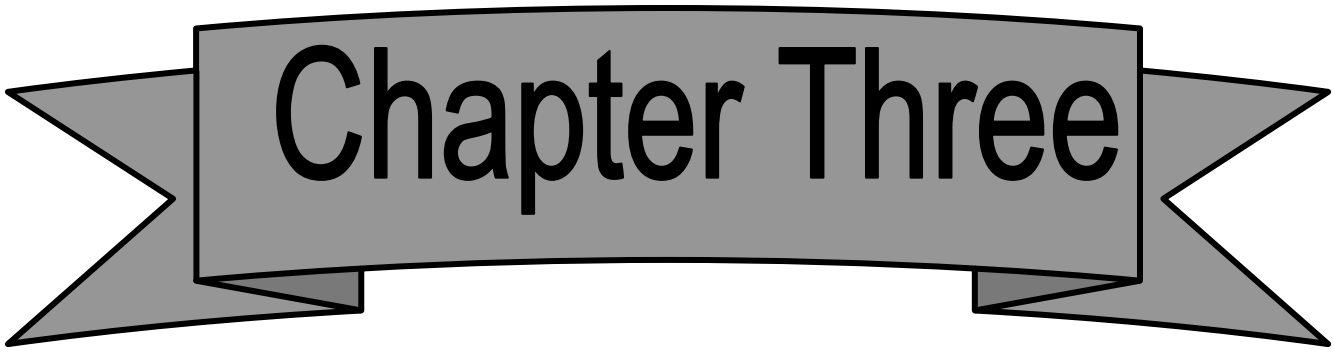
Introduction



Exeperimental part



Results&Discussion

References

Summary

This work involves synthesis of different five and six membered heterocyclic rings starting from oxalic acid and divided into four different parts and the reaction steps for each part are summarized as shown below.

First part:

This part involved the synthesis of pyridazin ,phthalazin, pyrazole ,pyrazolone and triazole derived from oxalic acid hydrazide .Scheme (I).

Second part:

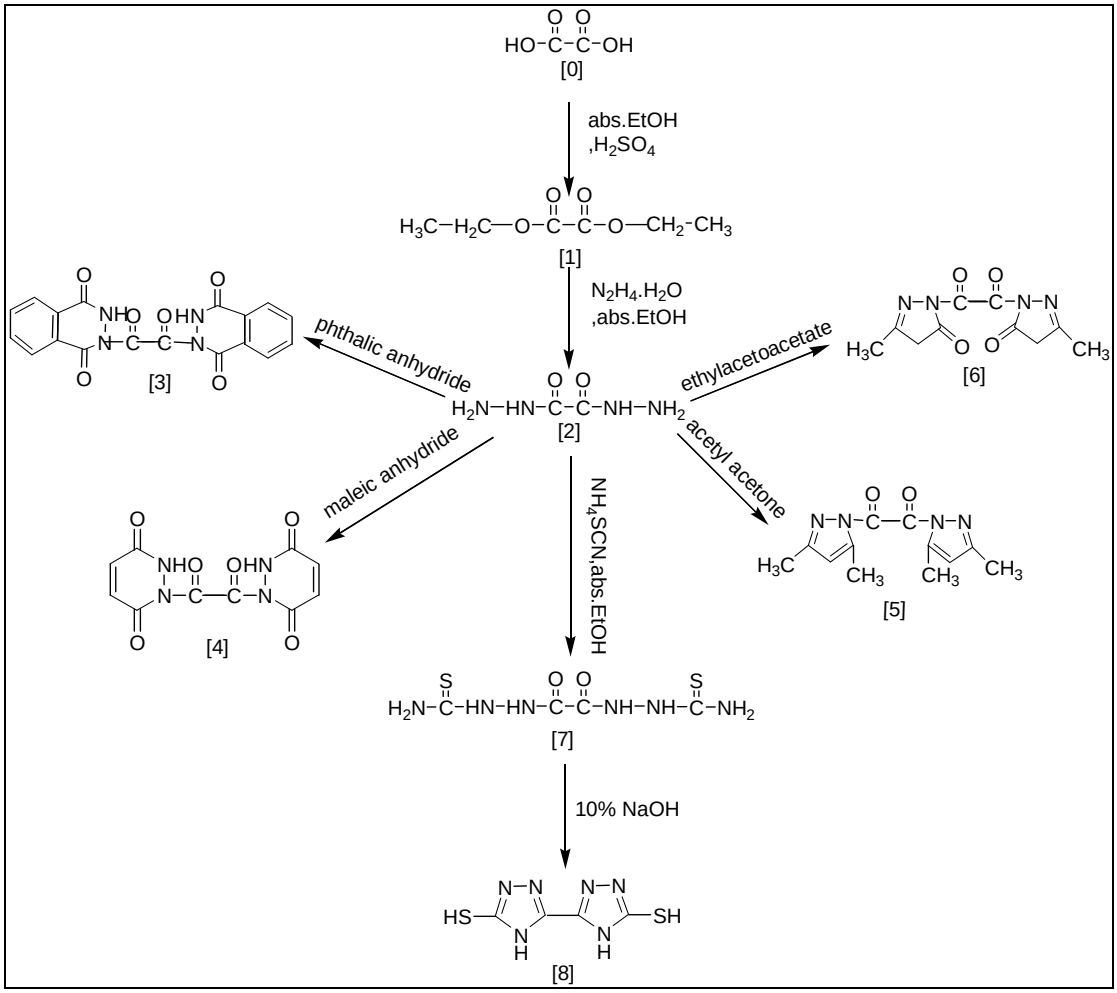
This part involved the synthesis of thiazolidine,triazole,thiadiazole,and Δ^4-oxazoline derivatives via the cyclization of substituted semicarbazide and substituted thiosemicarbazide with *p*-phenylphenacyl bromide ,2N NaOH and sulfuric acid respectively. The substituted semicarbazide and substituted thiosemicarbazide were synthesized through the reaction of oxalic acid hydrazide with phenyl isocyanate and phenyl isothiocyanate .(SchemeII).

Third part:

This part involved the synthesis of 1,3,4-oxadiazole and oxazepine derivatives from oxalic acid hydrazide. (Scheme III).

Fourth part:

This part deals with the evaluation of antibacterial activities of some of the synthesized compounds and comparing these activities with that of the starting materials. These activities were determined in vitro using disc diffusion method against two pathogenic strains of bacteria (Escherichia Coli and Staphylococcus aureus), the results revealed that some of these compounds showed measurable activity.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,H2SO4
[1]
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,abs.EtOH
[2]
phthalic anhydride
ethylacetoacetate
maleic anhydride
acetyl acetone
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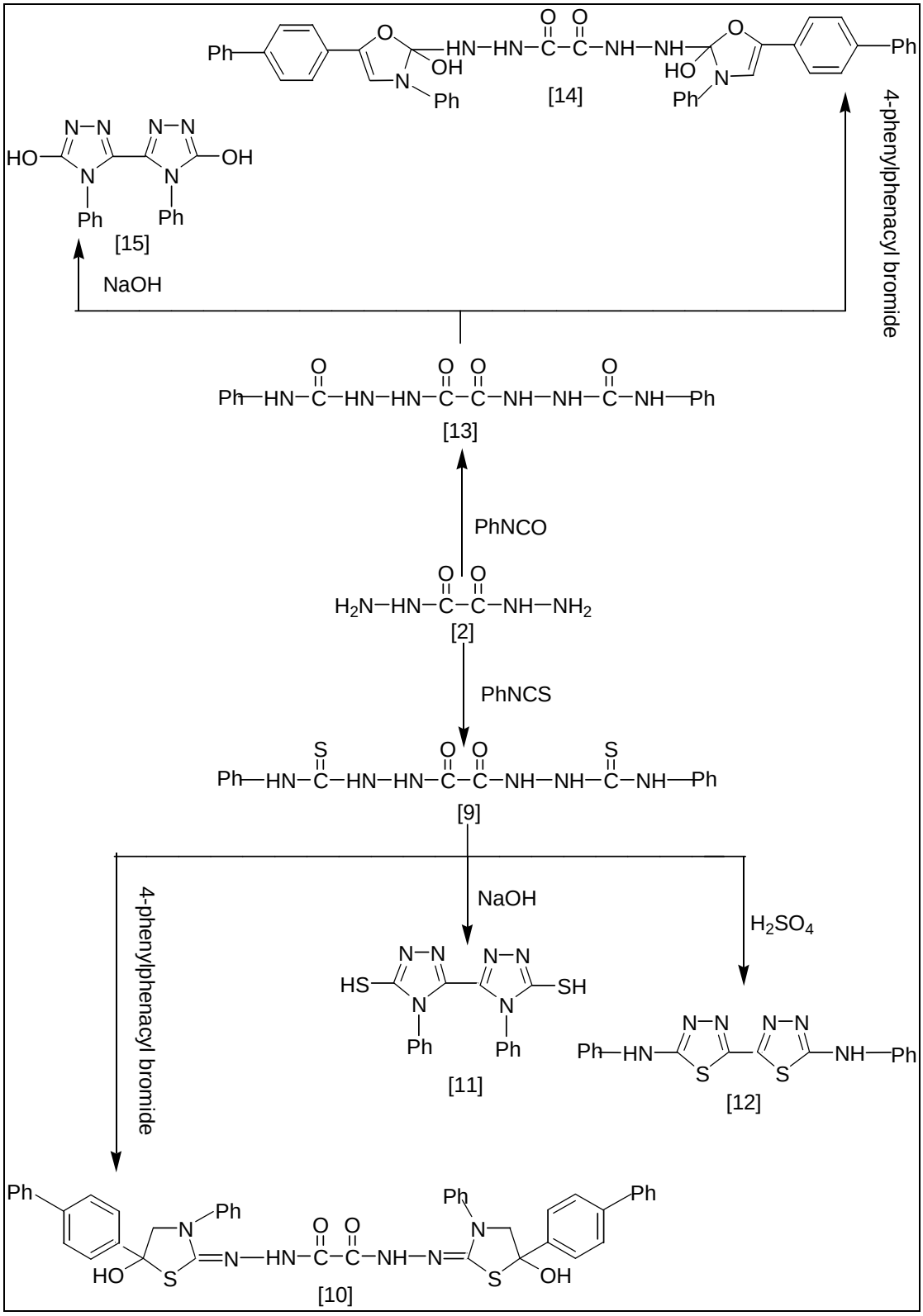
[3]
[4]
[5]
[6]
[7]
10% NaOH
[8]

Scheme (I)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NaOH
[13]
PhNCO
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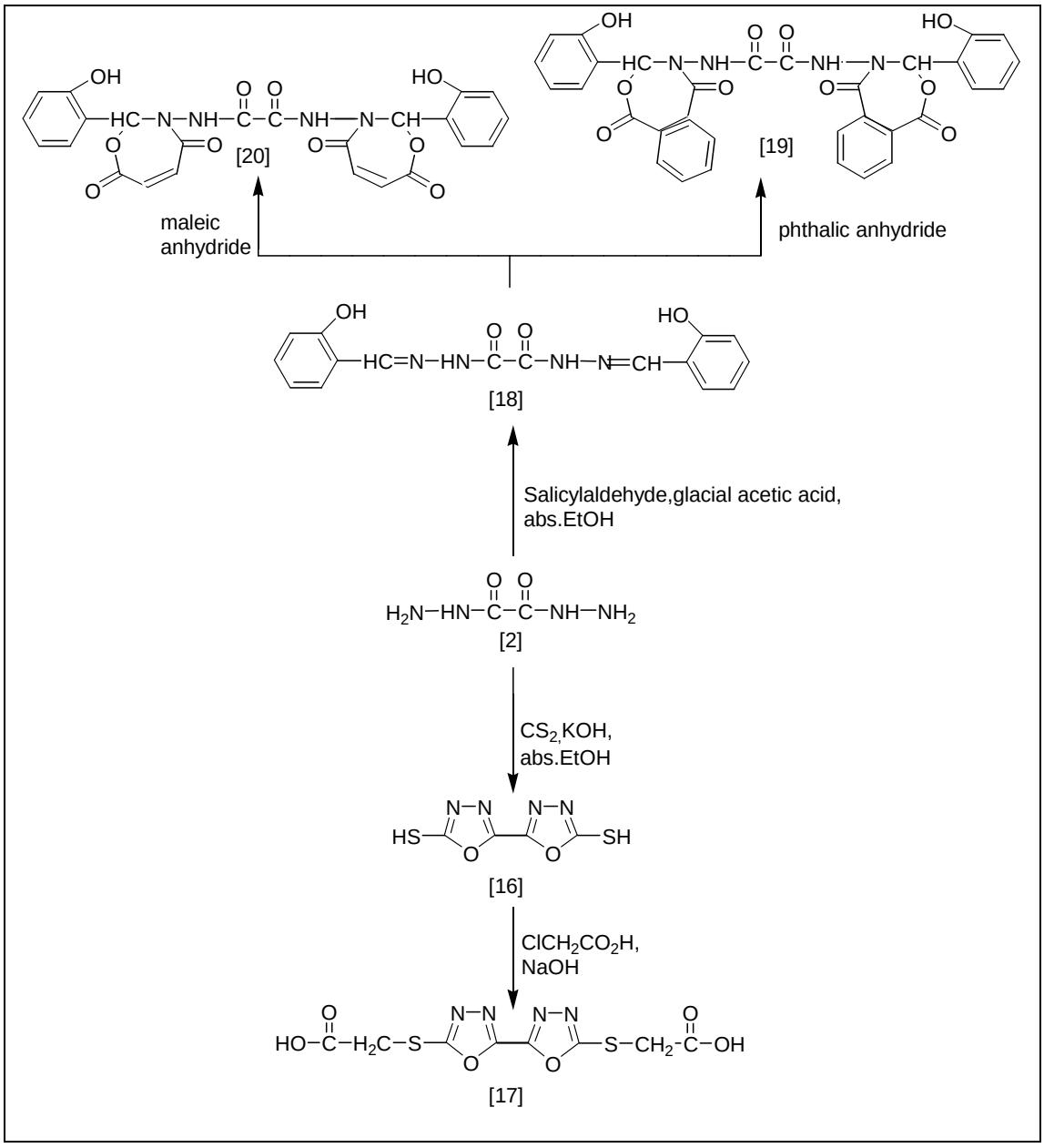
PhNCS
[9]
NaOH
H2SO4
4-phenylphenacyl bromide
[11]
[12]
[10]

Scheme (II)


[20]
[19]
maleic anhydride
phthalic anhydride
[18]
Salicylaldehyde,glacial acetic acid, abs.EtOH
[2]
CS2,KOH, abs.EtOH
[16]
ClCH2CO2H, NaOH
[17]

Scheme (III)

Republic of Iraq
Ministry of Higher Education and Scientific Research
Al-Nahrain University
College of Science
Department of Chemistry

Synthesis of some Heterocyclic Compounds derived from oxalic acid and evaluation The Biological activity for some of them

A Thesis
Submitted to the College of Science Al-Nahrain University as a Partial Fulfillment of the Requirements for the Degree of M. Sc. in Chemistry

By

Abdullah Hatem Mohammad Ahmed

(B.Sc. 2005)

Supervisor

Dr. Ibtisam K. Jassim

January ***Moharram***

2008 ***1429***

Supervisor certification

I certify that this thesis was prepared under my supervision at the Department of Chemistry, College of Science, Al-Nahrain University as a partial requirements for **the Degree of Master of Science in Chemistry.**

Signature:

Name: Dr. Ibtisam K. Jassim

Date: / /

In view of the available recommendation, I forward this thesis for debate by the Examining Committee.

Signature:

Name: Assist. Prof. Dr. Salman A. Ahmed

Head of Chemistry Department

College of Science

Al-Nahrain University

Examining Committee's Certification

We, the Examining Committee, certify that we read this thesis and have examined the student *"**Abdullah Hatem Mohammad**"*, in its contents and that, in our opinion; it is adequate as a thesis for the Degree of Master of Science.

Chairman

Signature:

Name:

Date: / /

Member
Signature:
Name:
Date: / /

Member
Signature:
Name:
Date: / /

Supervisor

Signature:
Name: **Dr. Ibtisam K. Jassim**
Date: / /

Approved for the College of Graduate Studies

Signature:

Name: Assist. Prof. Dr. LAITH ABDUL AZIZ AL-ANI

Address: **Dean of the college of Science Al-Nahrain University**

Date: / /

صدق الله العظيم

الاهداء

الى التي لم تبخل عليّ بسنين عمرها وجادت لي حتى بروحها
الى من سقتني الحنان وكان لي حضنها بر الامان
الى من اضاءت لي الدرب والتي تأنس روحي بقربها ويستنير دربي بدعائها وتعفو أحزاني بأبتسامة عينيها

أمي

حنان الدنيا كلها ورمز التضحيه

الى من توج أسمي بأسمه ولم يبخل عليّ حتى بدمه
الى الذي أفنى عمره ووهب لي عطفه وبره وشد من أزري في ألسعي لطلب العلم

أبي

قدوتي ومصدر فخري

الى من حبهم يجري في عروقي والذين احاطوني برعايتهم وقدموا لي الدعم المعنوي

اخوتي

مصدر عزتي

الى من ملكوني بفضلهم ولم يبخلوا عليّ بجهدهم ووقتهم

أساتذتي وزملائي

واليكم جميعاً أهدي ماوفقني به ربي

عبدالله حاتم

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Abdullah 2008

جمهورية العراق
وزارة التعليم العالي والبحث العلمي
جامعة النهرين
كلية العلوم
قسم الكيمياء

تحضير بعض المركبات الحلقية الغير متجانسة المشتقة من حامض الاوكزاليك وتقييم الفعالية البايولوجية لبعضها

رسالة
مقدمة إلى كلية العلوم جامعة النهرين
وهي جزء من متطلبات نيل درجة الماجستير فلسفة في الكيمياء

من قبل

عبدالله حاتم محمد أحمد

بكالوريوس علوم كيمياء – جامعة النهرين (٢٠٠٥)

اشراف

د. ابتسام خليفه جاسم

كانون الثانى
٢٠٠٨م

محرم
١٤٢٩هـ

خـــلاصـــــــة الرسالة

يتضمن موضوع البحث في هذه الرسالة تحضير مركبات حلقية خماسية وسداسية وسباعية غير متجانسة متنوعة ابتداء من حامض الاوكزاليك. وقد تم تقسيم هذا العمل الى اربعة اقسام :-

القسم الاول

يتضمن هذا القسم تحضير مركبات الفثالازين-٨،٣-دايون، البريدازين-٦،٣- دايون، البايرازول،البايرزولون والترايازول من هايدرازيد حامض الاوكزاليك . وللحصول على هذه المركبات اتبعت الخطوات الموضحة في المخطط رقم واحد.

القسم الثاني

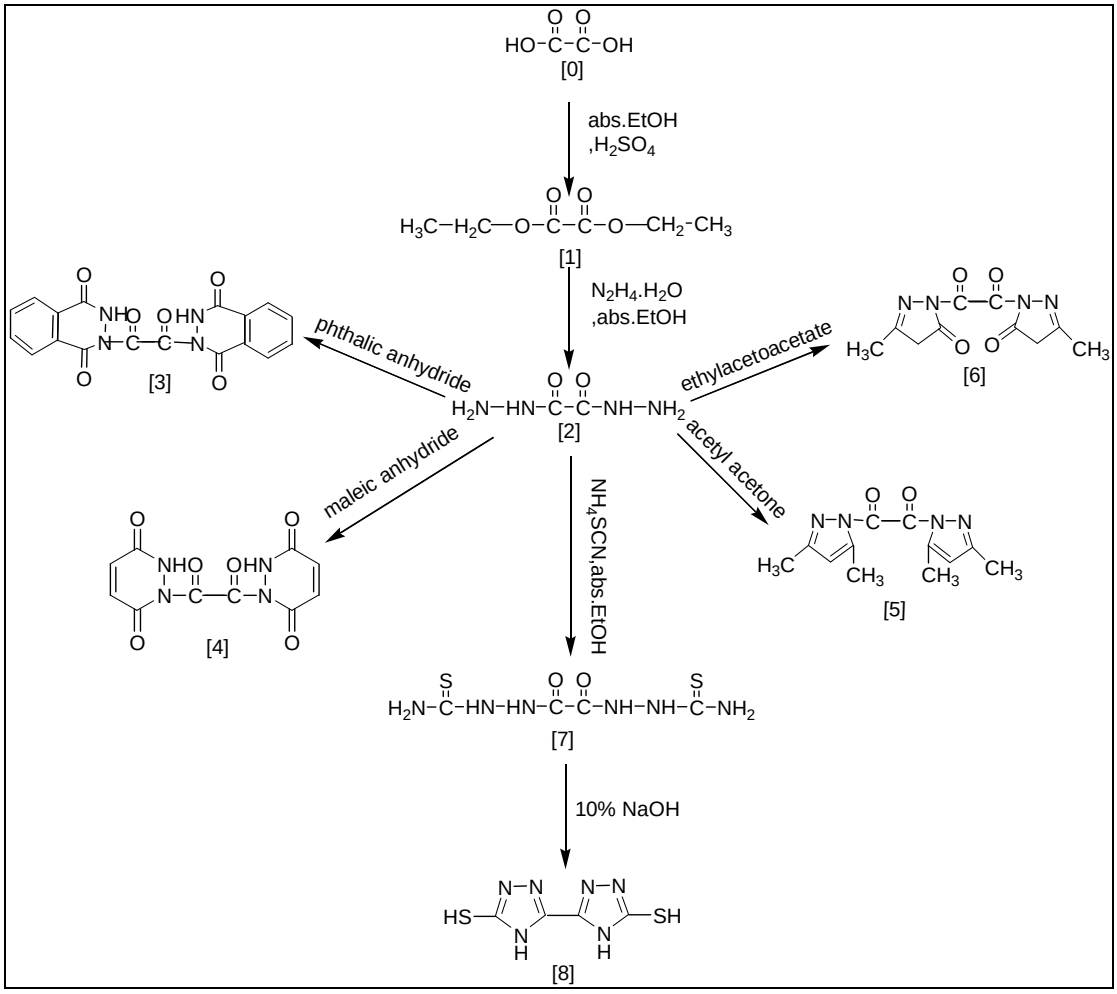
يتضمن هذا القسم تحضير مركبات اوكسازولين و ٤،٢،١-ترايازول معوضة النتروجين والثايدايزول والثايزولدين بوساطة التفاعل بين هايدرازيد حامض الاوكزاليك مع فنيل ايزو سيانيد و فنيل ايزوثايو سيانيد حيث تتم عملية الغلق الحلقي للنواتج الحاصلة باستعمال بارافنيل فيناسيل بروميد و ٢- نورمالي من هيدروكسيد الصوديوم وحامض الكبريتيك. وللحصول على هذه المركبات اتبعت الخطوات الموضحة في المخطط رقم اثنين .

القسم الثالث

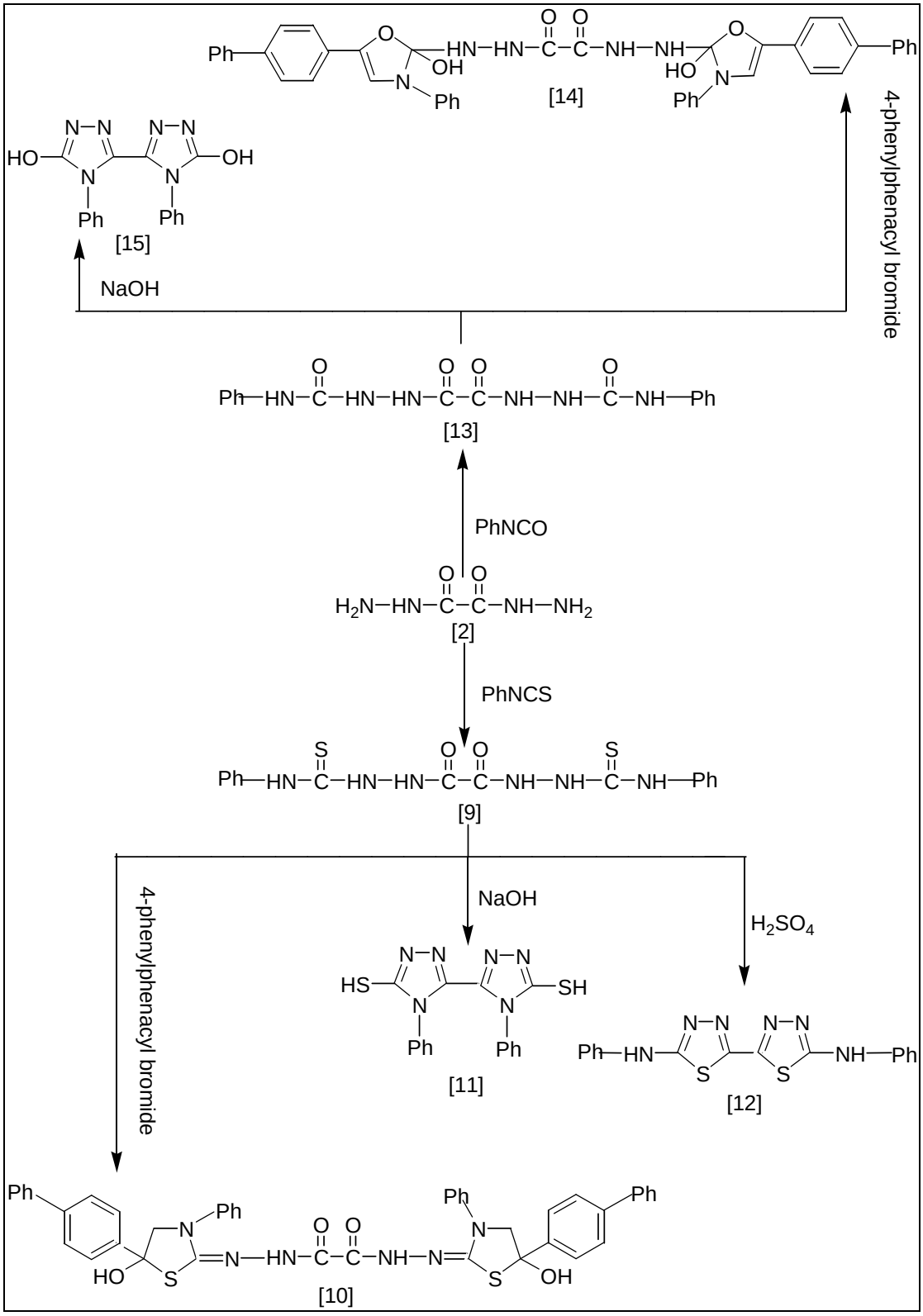
يتضمن هذا القسم تحضير مركبات ٤،٣،١-اوكسادايزول والاوكسازبين من هايدرازيد حامض الاوكزاليك. وللحصول على هذه المركبات اتبعت الخطوات الموضحة في المخطط رقم ثلاثه.

القسم الرابع

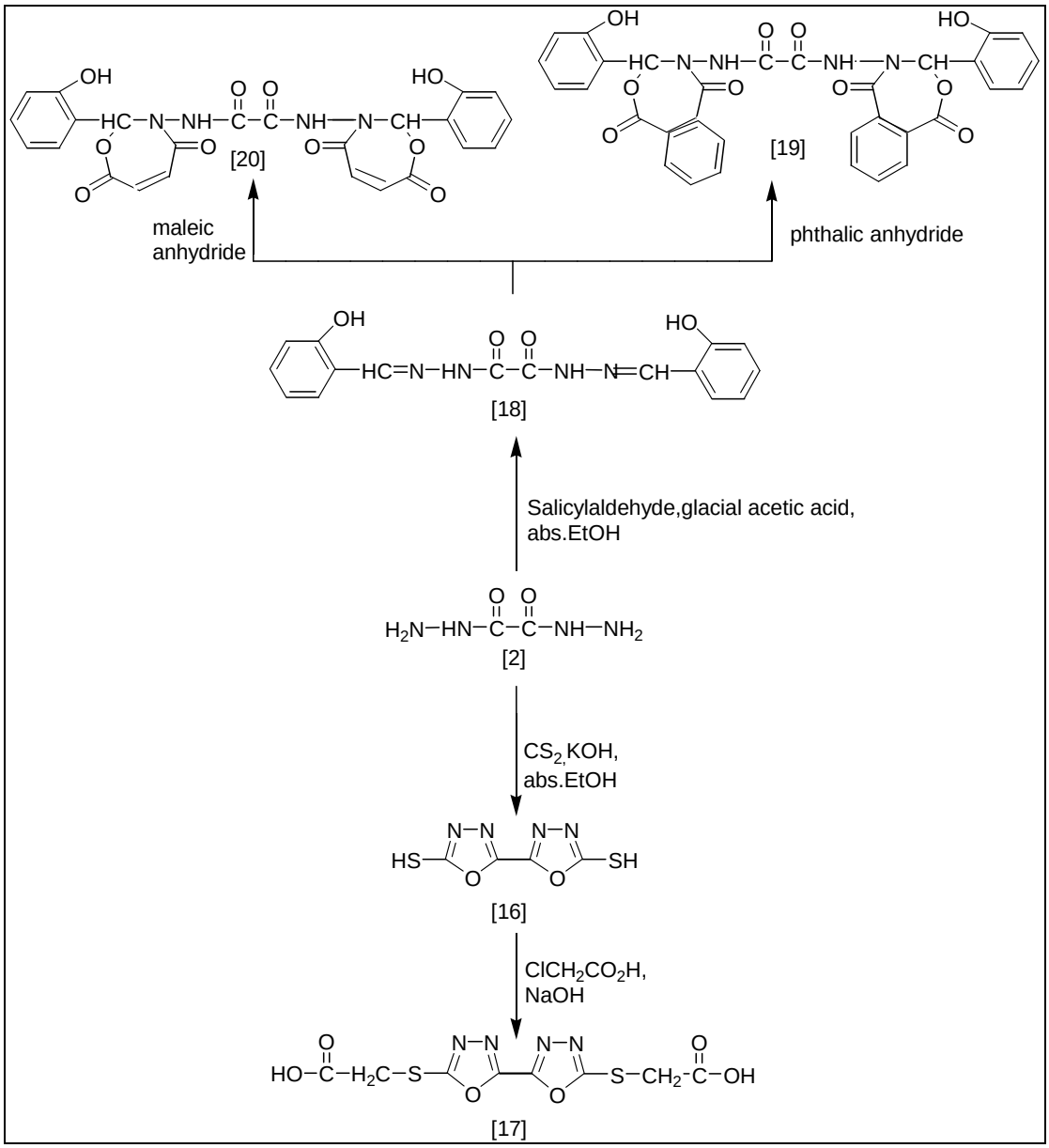
يتضمن هذا القسم اختبار الفعالية البايولوجية لبعض المركبات المحضرة ضد نوعين من البكتيريا وقد دلت النتائج المستحصلة بان بعض المركبات اظهرت فعالية بايولوجية كما هو عليه في الجدول (٣-٤) .


[0]
abs.EtOH
,H2SO4
[1]
N2H4.H2O
,abs.EtOH
[2]
phthalic anhydride
ethylacetoacetate
maleic anhydride
acetyl acetone
NH4SCN,abs.EtOH
[3]
[4]
[5]
[6]
[7]
10% NaOH
[8]

المخطط رقم (١)


[14]
4-phenylphenacyl bromide
[15]
NaOH
[13]
PhNCO
[2]
PhNCS
[9]
NaOH
H_2SO_4
4-phenylphenacyl bromide
[11]
[12]
[10]

المخطط رقم (٢)


[20]
[19]
maleic anhydride
phthalic anhydride
[18]
Salicylaldehyde,glacial acetic acid, abs.EtOH
[2]
CS2,KOH, abs.EtOH
[16]
ClCH2CO2H, NaOH
[17]

المخطط رقم (٣)