Chapter One

Introduction

1.1 Heterocyclic compounds:

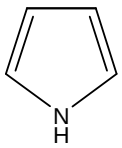
A heterocyclic compound is one which possesses a cyclic structure with at least one different kind of an atom in the ring.

Nitrogen, oxygen and sulfur are considered the most hetero atoms known [1, 2].

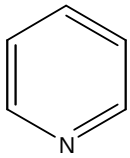
Heterocyclic compounds are found as construction units through several biological molecules [3], mostly are molecules which contain five and six membered rings [4].

Pyridine is the heterocyclic system which most closely resembles benzene in terms of structure and overall stability [5].

For monocyclic rings, the proper nomenclature is derived from combining an appropriate prefix and suffix to a given stem, where the suffix (-ole) and (-ine) are given for unsaturated five and six membered rings containing nitrogen atom [6].



pyrazole



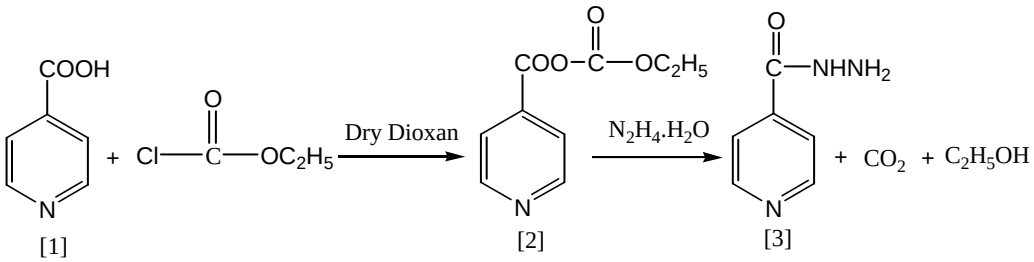
pyridine

1.2 Hydrazide derivatives:

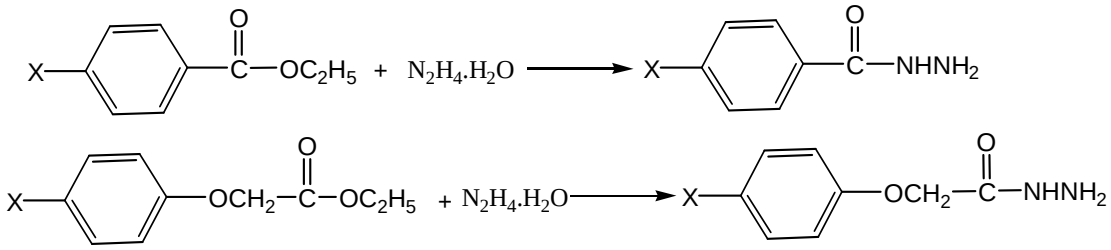
Hydrazide and thiosemicarbazide derivatives attracted a lot of attention because they are considered as intermediates to synthesize several compounds such as ***Schiff*** bases, thiadiazole [7], oxadiazole [8] and triazole[9] derivatives which all were reported to possess biological activities. The structural formula for this type of compounds is (RCONHNH-).

1.2.0 Synthesis of hydrazide derivatives:

Rinder Kenecht [10] found that the isnicotinicacid [1] reacted with ethylchloro format to afford asymmetrical anhydride [2]. Further reaction [2] with hydrazine hydrate led to formation of isonicotinic acid hydrazide:

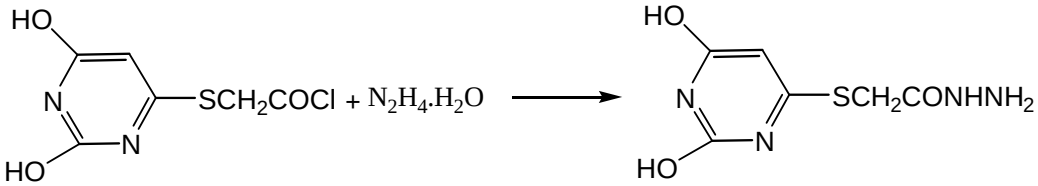


Several methods are available for the synthesis of hydrazide derivatives, the most important of which is based on the reaction of esters with hydrazine hydrate [11] as shown below:



R=CH_3CONH

Acid hydrazide derivatives can also be synthesized from condensation reaction of carboxylic acid chloride with hydrazine hydrate [12].



1.2.1 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 carbohy-

drazides, their derivatives and related compounds are reported to have a plethora of biological activities [13].

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 [14].

Thus, different carbohydrazides were found to be useful as medicaments especially in the treatment of inflammatory and autoimmune disease, osteoarthritis, respiratory diseases, tumors, cachexia, cardiovascular diseases, fever, hemorrhage and sepsis [15].

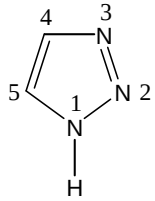
Some heterocyclic carbohydrazides are useful as antifertility agents in rats and pigeons. Other carbohydrazides were reported to be components of deodorant compositions that can be used for removal of offensive odor components [16].

1.3 1, 2, 4-Triazoles: General description

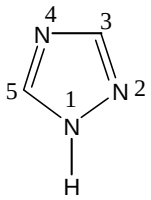
1, 2, 4-Triazole is one of a class of organic heterocyclic compounds containing a five membered di-unsaturated ring structure composed of three nitrogen atoms and two non adjacent carbon atoms. 1, 2, 4-Triazole is a white to pale yellow crystalline solid with a weak odor, soluble in water and alcohol, melts at 120^{o}C [17].

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.

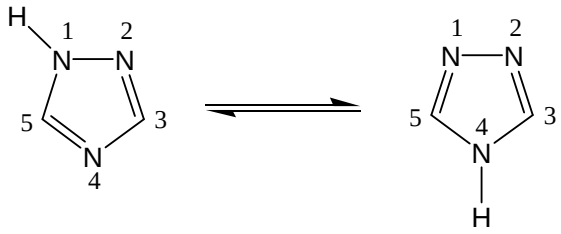


1,2,3-triazole



1,2,4-triazole

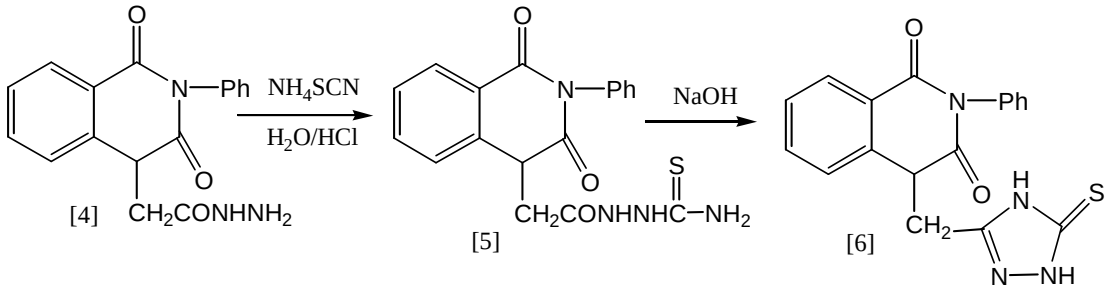
1, 2, 3-Triazole was originally called ʋic-(vicinal) triazoles, and 1, 2, 4-triazole known as sym-(symmetrical) triazoles [18] .



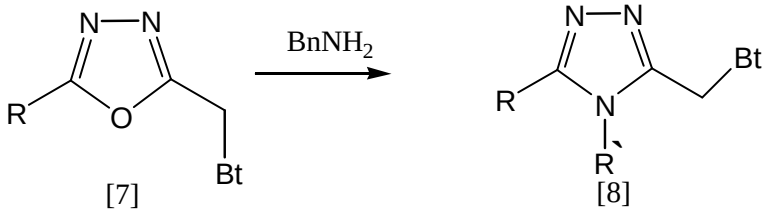
1H-1,2,4-triazole 4H-1,2,4-triazole

1.3.0 Synthesis of 1, 2, 4-triazoles:

El-Tamany et.al., [19] found that the reaction of (3-benzyl-2,4-quinazolin-1-yl)acetylhydrazine [4] with ammonium thiocyante in aqueous acidic medium afforded the thiosemicarbazide derivative [5] which cyclized in alkaline medium to 3'-[(3-benzyl-2,4-quinazolinon-1-yl)-1',2',4'-triazole - 5'thion [6]:

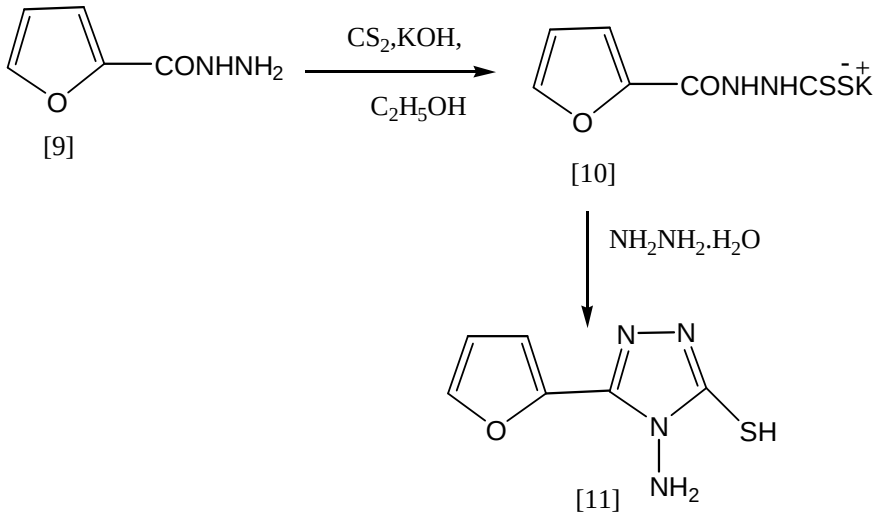


Katritzky et.al., [20] synthesized 1-[(4-Benzyl-5-phenyl-4H-[1, 2, 4] triazol-3-yl) methyl]-1H- benzotriazole [8] from the reaction of 1-[(5-phenyl [1, 3, 4] oxadizol-2-yl) methyl]-1H- benzotriazole [7] with benzyl amine in the presence of n-butanol:

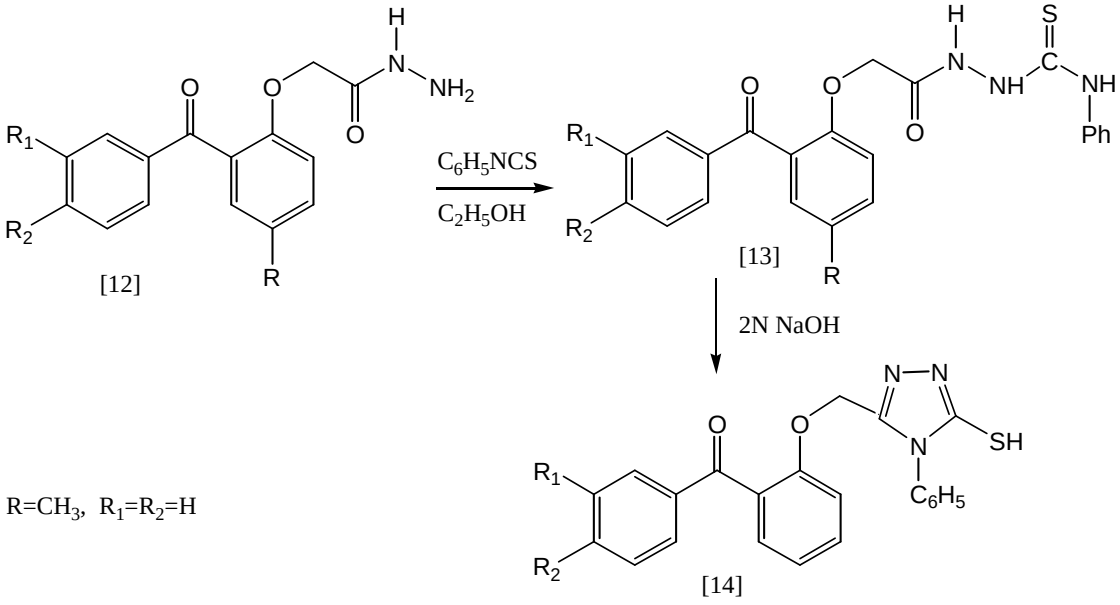


R=Ph, R=$_4$-MeC_6H_4.

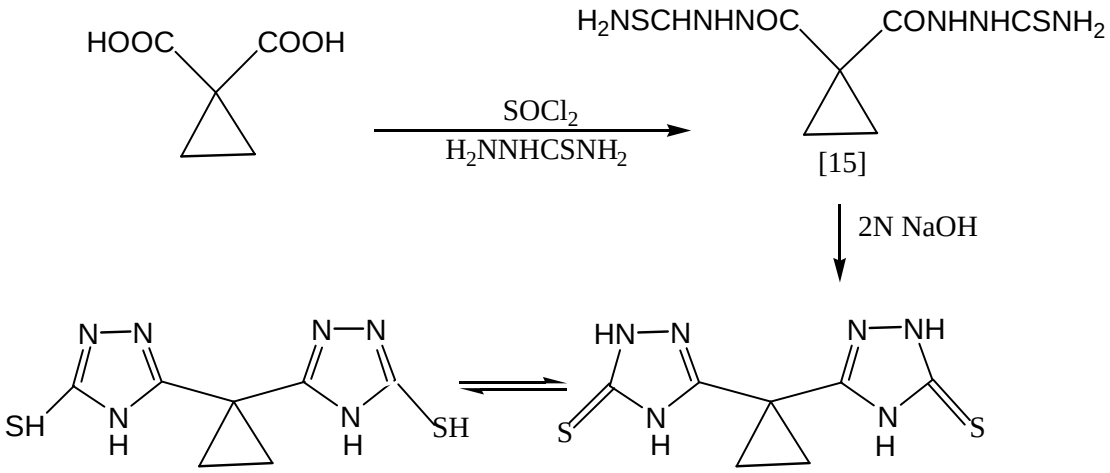
Zhang et.al., [21] found that the the reaction of fourichydrazide [9] with CS_2 and potassium hydroxide in absolute ethanol gave potassium 2-fourichydrazidedithioformate [10]. Further cyclization of [10] with 85% hydrazine hydrate led to formation of 3-(2-furyl)-4-amino-5-mercapto-1, 2, 4-triazole [11]:



Khanum et.al., [22] found that the reaction of 2-(2-aroylaryloxy) acetohydraide [12] with phenylisocyante in the presence of absolute ethanol gave 2-[2-(aroylaryloxy) acetyl]-N-phenylhydrainecarbothio amides [13]. Further cyclization of [13] with 2%NaOH led to formation of 3-(2-aroylaryloxy)methyl-5-mercapto-4-phenyl1,2,4-triazoles [14]:

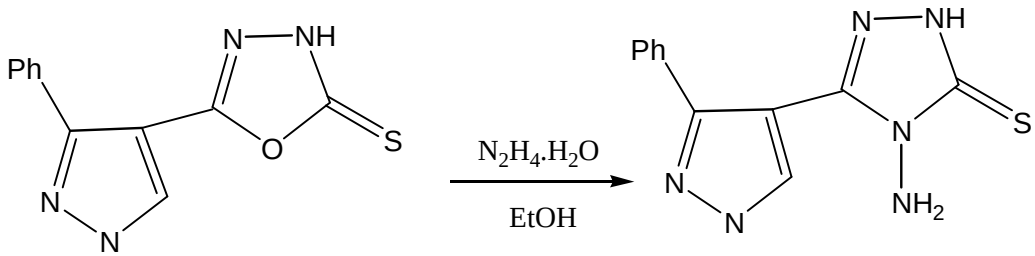


Sharba et.al.,[23]found that the reaction of cyclopropane dicarboxylicacid afforded the respective thiosemicarbazide [15].Further cyclization of [15] in the presence of 2% NaOH leds to the formation of 1,1-bis (3-mercapto-1,2,4-triazol-5-yl)cyclopropane [16]:



[16]

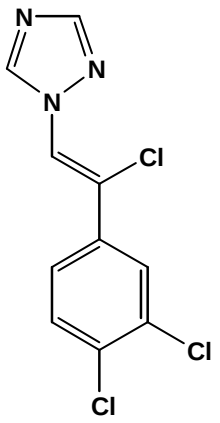
Farghaly et.al., [24] synthesized 4-amino-3-(1, 3-diphenyl-1H-pyrazol-4-yl)-4, 5-dihydro-[1, 2, 4] triazole-5(1H)-thione [18] by reaction oxadiazolethione [17] with hydrazine hydrate in the presence of ethanol:



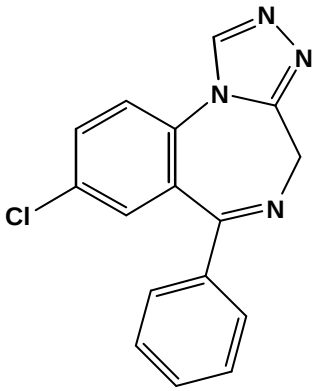
[17] [18]

1.3.1 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[25,26].



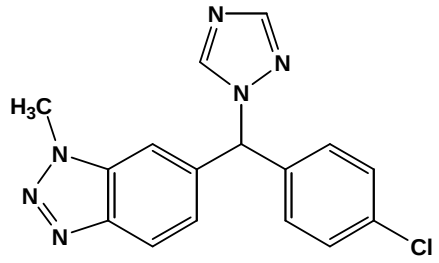
Loreclezole



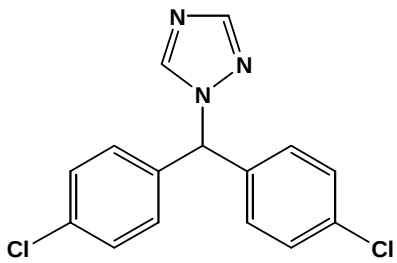
Estazolam

Figure (1-1):

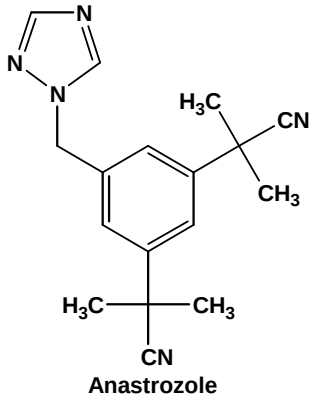
In addition, it was reported that, compounds having triazole moieties, such as vorozole, letrozole and anastrozole, Figure (1-2), appeared to be very useful for preventing breast cancer [27]:



Vorozole



Letrozole



Anastrozole

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 [28].

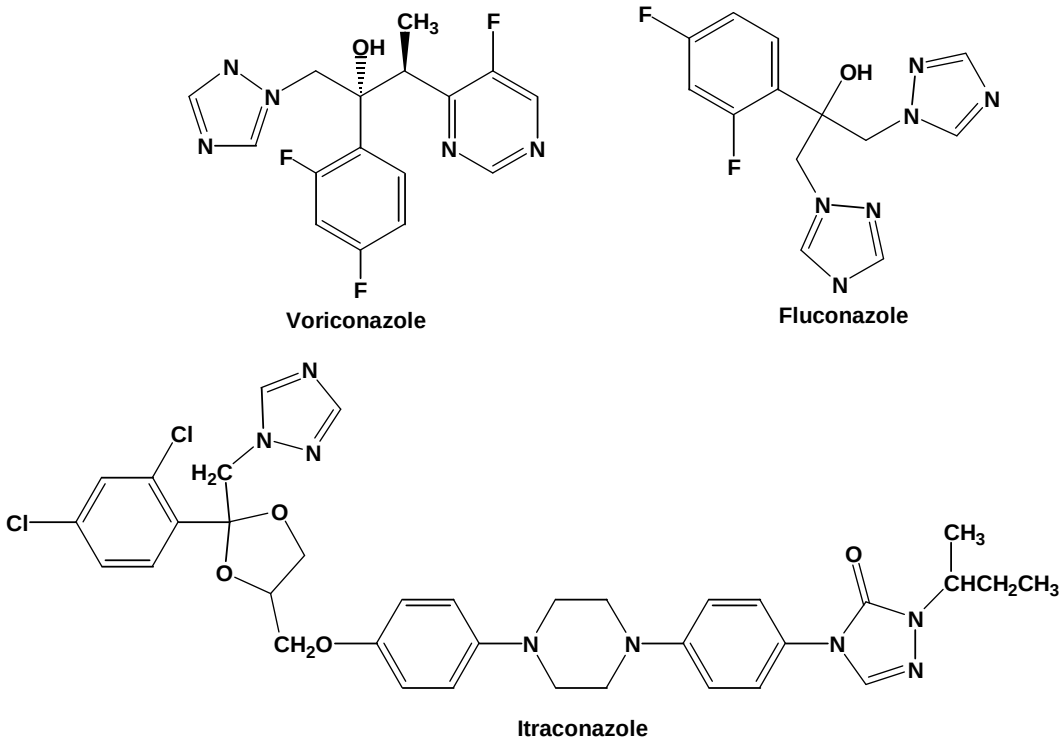
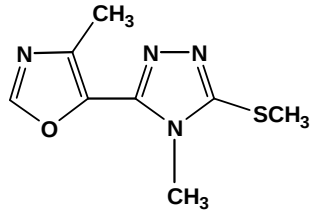
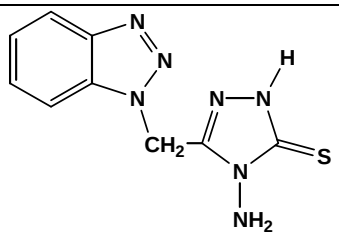
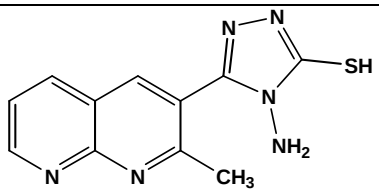
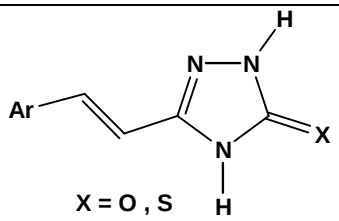
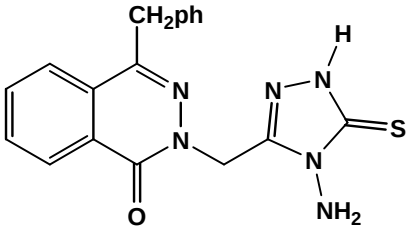


Figure (1-3):

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[29]. Furthermore, some reported mercapto triazole derivatives showed potent activity [30] more than Streptomycin against Candida albicans. Thus, among an important type of fungicides, triazole compounds are highly efficient, low poisonous and inward absorbent [31].

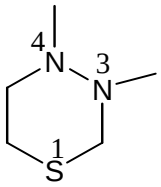
Since the discovery of the biological importance of these compounds, the aim of many research projects was to synthesize many different substituted triazoles, and their biological activity was a subject of many studies. Tables (1-1) include some of these compounds.

Table (1-1): 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	32
2	1-(4-amino-4H-1,2,4-triazol-3-thione-5-yl)methyl-1H-benzotriazole		Potential biological activity	33
3	4-amino-5-mercapto-3-(2'-methyl-1',8'-naphthyridin-3'-yl)-1,2,4-triazole		Anti microbial activity	34
4	Styryl triazoles		Anti inflammatory agent	35
5	4-benzyl-2-(1-amino-2-thioxo-1,3,4-triazol-5-yl-methyl)phthalazin-1-(2H)-one		Anti fungal activity	36

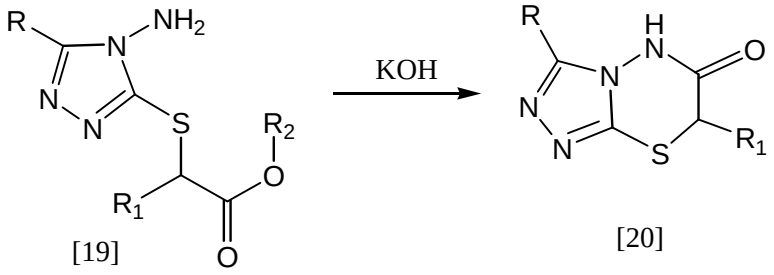
1.4 Thiadiazines: General description

1, 3, 4-thiadiazine is six membered heterocyclic compound contains only one sulfur atom in position 1 and two nitrogen atoms in positions 3 and 4 [37].



1.4.0 Synthesis of 1, 3, 4-thiadiazines:

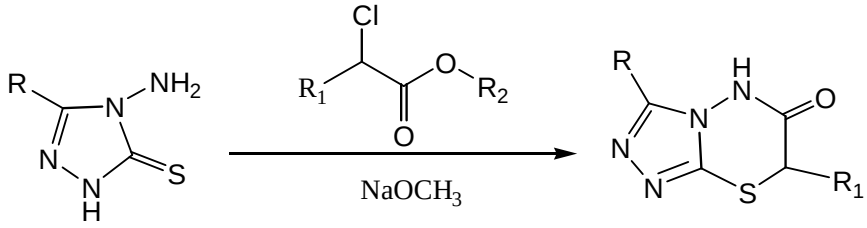
Zircle and Kaiser [38] reported that refluxing of s-alkylated derivatives of [19] with strong base afforded 1, 2, 4 trizaolo [3, 4,-b] [1, 3, 4] thiadiazol-6-one [20]:



[19] [20]

R=alk, CF_3, R_1=H, alk, R_2=alk

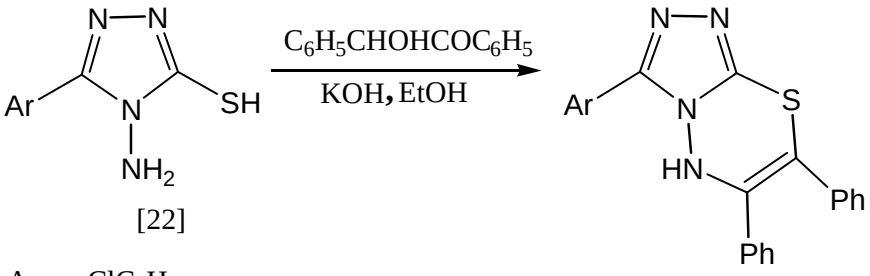
Longer et.al., [39] synthesized compound [20] from the reaction of 5-substituted-4-amino-1, 2, 4-triazole-3-thion [21] with α-chlorosubstituted esters of carbonic acids in the presence of MeONa/MeOH:



[21] [20]

R=alk, CF_3, R_1=H, alk, R_2=alk

Jagmohon et.al.,[40] synthesized 3-m-(chlorophenyl)-6, 7-diphenyl-5H-S-triazolo [3, 4, b] [1, 3, 4] thiadiazine[23] by reaction of 3-m-(cloro phenyl)-4-amino-5-mercapto-s-triazole[22] with benzoin in the presence of ethanol:

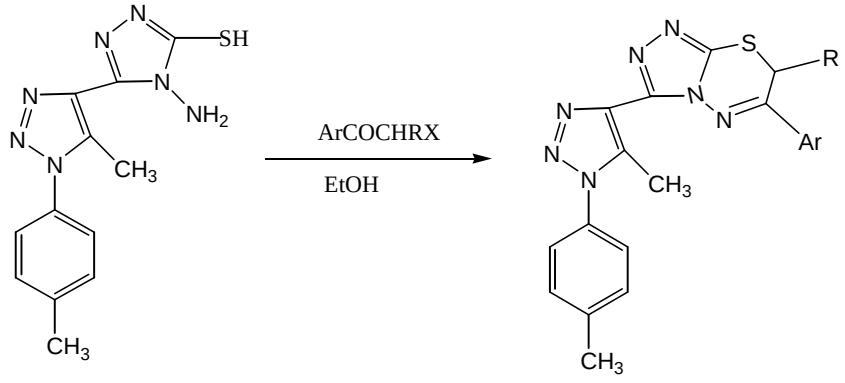


[22]

Ar=m-ClC_6H_5

[23]

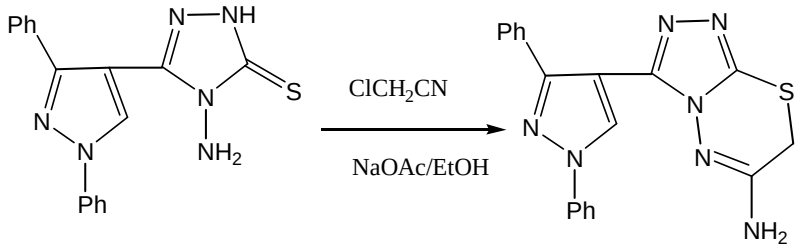
Dong et.al.,[41] synthesized 7H-3-[5-methyl-substituted-S-triazolo [3, 4,-b]-1, 3, 4-thiadiazines[25] from the reaction of 1-amino-2-mercapto-5-[5-methyl-1-(4-methylphenyl)-1, 2, 3-triazol-4-yl]-1,3,4-triazole[24] with α-haloketone such as phenacylbromide or bromoacetone:



[24]

[25]

Fraghaly et.al., [42] found that 4-amino-3-(1,3-diphenyl-1H-pyrazole-4-yl)-4,5-dihydro[1,2,4]triazole-5(1H)-thione [26] reacted with chloroaceto nitrile and sodiumacetate in the presence of ethanol to afford 6-amino-3-(1,3-diphenyl-1H-pyrazol-4-yl)-7H-[1,2,4] triazolo[3,4,-b] [1,3,4] thiadiazine [27]:



[26] [27]

1.4.1 1, 3, 4-Thiadiazine uses:-

In continuation of previous research in the synthesis of pharmacologically active 7H-S-triazolo[3,4-b]-1,3,4-thiadiazine [(43)], it is reported that a 1,3,4-triazole nucleus possesses fungicidal [(44)], insecticidal [(45)], antimicrobial [(46)], bacterial [(47)] properties and a 1,2,3-triazole nucleus possesses antibacterial [(48)], antifungal [(49)], antiviral [(50)], anti inflammatory and analgesic [(51)] properties.

Some new 1,3,4-triazole derivatives have been reported as possible anticonvulsant [(52)], antidepressants, and plant growth regulators [(53)] and 1,2,3-triazole derivatives have been reported to inhibit tumor proliferation, invasion and metastasis [(54)].

Likewise a 1, 3, 4-thiadiazole nucleus which incorporates an N-C-S linkage exhibits a large number of biological activities [(55)].

The fused 1,3,4-triazolo [3,4-b]-1,3,4-thiadiazole derivatives show various biological effects, such as antifungal [(56)], antibacterial[(57)].

A triazolo-thiadiazole system may be viewed as a cyclic analogue of two very important components thiosemicarbazide and biguanide, which often display diverse biological activities [(58)].Therefore, it was planned to investigate a system which combines these three biologic components in a ring and to study their biological activities [(59)].

So, the condensed 7H-3-[5-methyl-1-(4-methylphenyl)-1,2,3-triazol-4-yl]-6-substituted-S-triazolo [3,4-b]-1,3,4-thiadiazine possesses a chemically important nitrogen heterocyclic nucleus with a view to achieve better antimicrobial activity [(60)].

1.5 pyrazoles and pyrazolones: General description

Pyrazole derivatives play a vital role in many biological processes and synthetic drugs. The chemistry of this heterocycle has received much attention in recent years. This is principally due to the unique physical and chemical properties of such compounds, which enable their wide application as an ideal scaffold for the synthesis of anti-inflammatory-antibacterial agent [61].

Pyrazole is a 1,2-diazole, and as its name implies, it may be considered as an azapyrrole. The dimensions (Aº) of the planar molecular are illustrated in Figure (1-4)[62]:

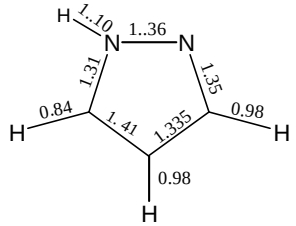


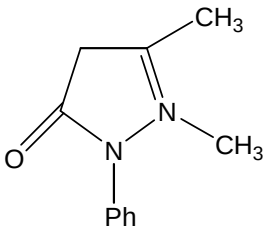
Fig. (1-4) Bond length (Aº) in pyrazole

However, very few pyrazole derivatives occur naturally; this may be due to the difficulty for living organisms to construct the N-N bond. The most important derivatives of pyrazole are in fact pyrazolones [63].

Theoretically, there are three types of oxo-pyrazoline or pyrazolone, but only derivatives of 3-pyrazolone and 5-pyrazolone are known [64].

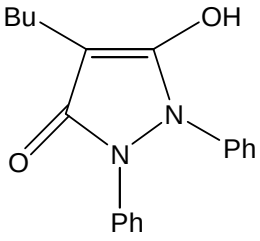
The pyrazol-5-one has been extensively studied, and several useful drugs and dyestuffs containing this ring are known.

Antipyrine (2, 3-dimethyl-1-phenyl-5-pyrazolone)[28], and its derivative exhibit a wide variety of potentially useful applications including biological, clinical and pharmacological[65].



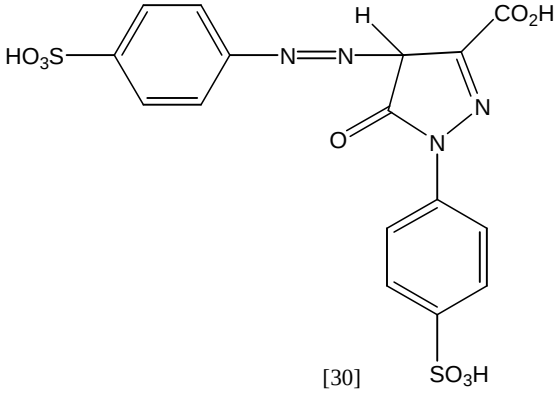
[28]

Butazolidine [29], another pyrazolone, is a powerful anti-inflammatory drug for rheumatic conditions [(66)]:



[29]

Tartrazine [30] is a yellow dye for wool, this dye has been gaining commercial importance [(67)] because they are also used for the artificial coloring of foods:

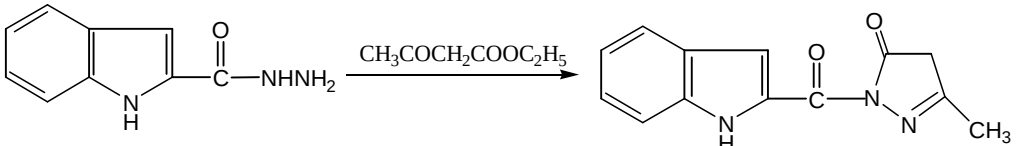


[30]

1.5.0 Synthesis of pyrazoles and pyrazolones:

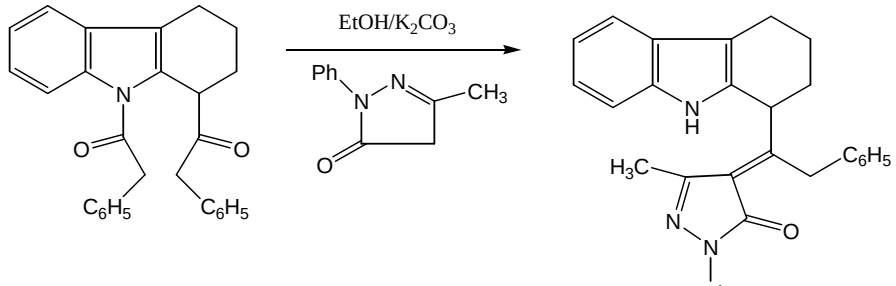
Pyrazolones are biologically interesting compounds and their chemistry has received considerable attention. These variable activities have led to intensive research on their synthesis.

Fahmy et.al., [68] found that the reaction of 2-indol carbohydrazide with ethyl acetoacetate gave 2-[3-methyl-5-oxo-pyrazolin-1-yl]carbonyl indole [31]:



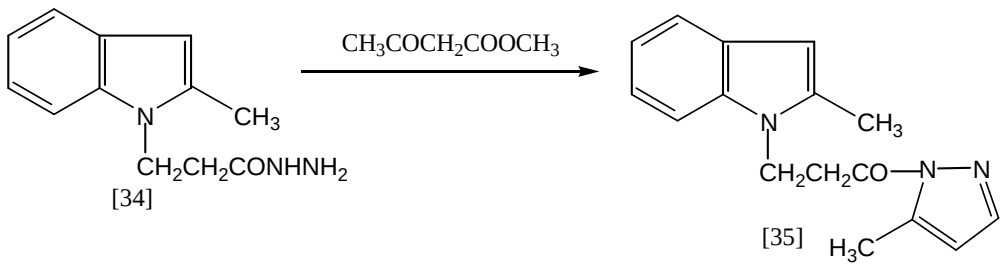
[31]

Skmeiss et.al.,[69] synthesized[1-(2, 3, 4, 9-tetrahydrocarbozol-1-yl)-2-phenyl-1-[(3-methyl-1-phenyl)pyrazol-5-one-1-ylidine]ethane [33] by reaction of 1, 9-diphenylacetyl-1, 2, 3, 4-tetrahydrocarbazole [32] with 3-methyl-1-phenylpyrazol-5-one in the presence of anhydrous potassium carbonate:



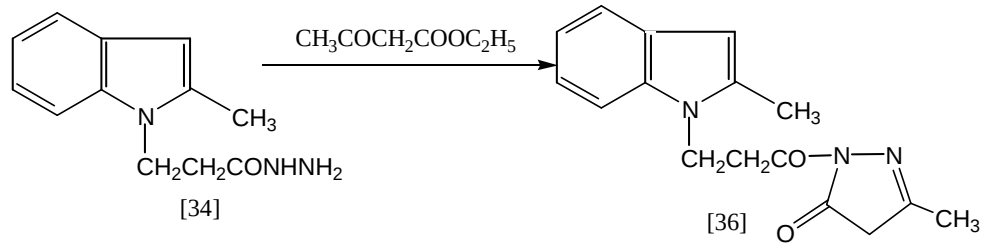
[32] [33]

El-Masry et.al.,[70] found that the reaction of 3-(2-methylbenzi midazol-1-yl) propanoic acidhydrazide [34] with acetylacetone to afford the 1-[3(2-methylbenzimidazol-1-yl]-3, 5-dimthylpyrazole [35]:



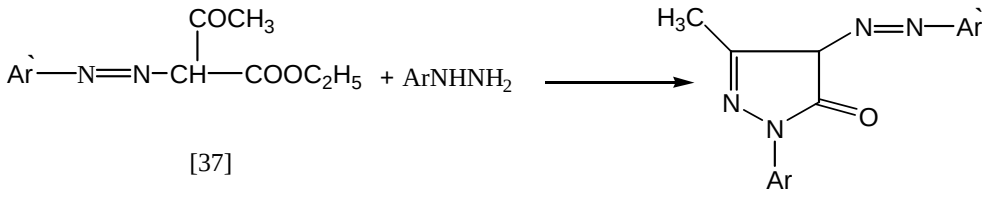
[34] [35]

The reaction of [34] with ethylacetoacetate gave 1-[3-(2-methyl benzimidazole-1-yl) propanyl]-4, 5-dihydro-3-methylpyrazol-5-one [36]:



[34] [36]

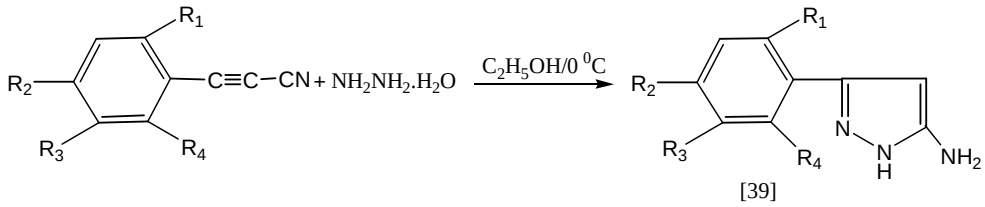
El–Assiery et.al.,[71] synthesized 4-[2-phenyldizenyl]-2-(2, 4-dinitro phenyl)-5-methyl-2, 4-dihyo-3H-pyrazol-3-one[38] by reaction of 2, 4-dinitrophenylhydrazine with ethyl3-oxo-2-[2-phenyldiazenyl] butanoate [37] :



[37] [38]

Ar`=2, 4-$(NO_2)C_6H_3$, Ar=Ph.

Rao et.al., [72] synthesized 3-amino-5-arylpyrazole [39] by reaction of arylalkynenitriles with hydrazine hydrate:

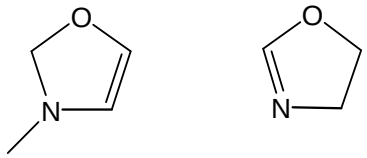


[39]

$R_1=R_3=R_4=H$, $R_2=F$

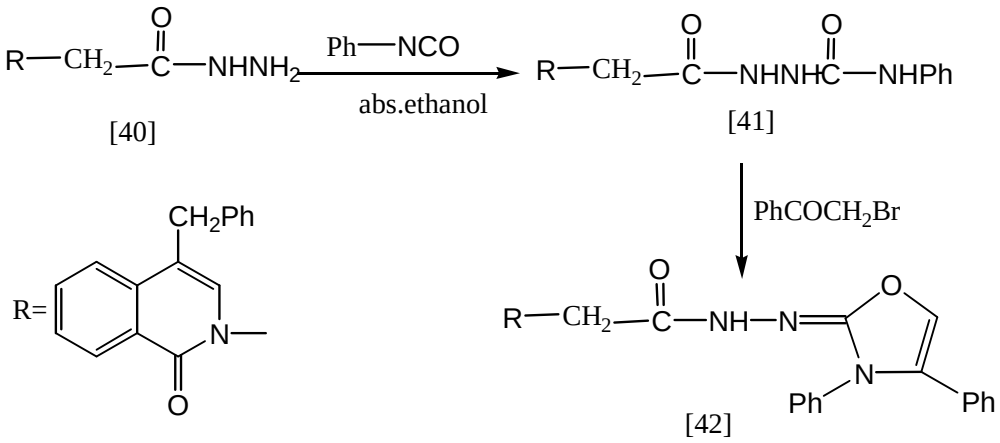
1.6 Oxazolines:

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 [73]:

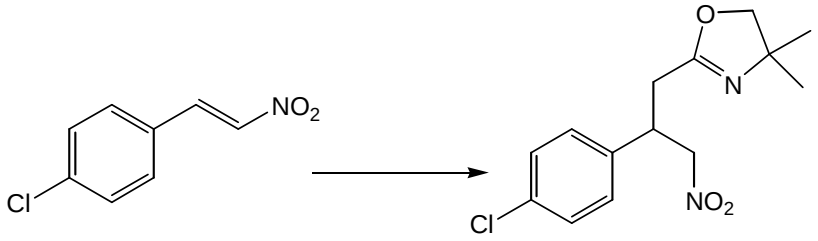


1.6.0 Synthesis of oxazoline[61]:

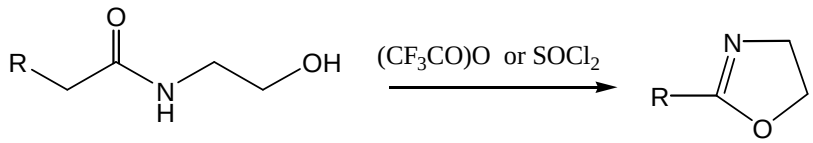
El-Tamaty et.al., [74] found that the reaction of 4-Benzyl-1(2H)-oxa phthalazine-2-ylacetic hydrazide[40] with phenylisocynate afforded the respective semicarbazides[41]. Further cyclization of [41] with phenacyl bromide led to formation 4-Benzyl-2- (3,4-diphenyloxazole-5-yliden hydrazidecarboxymethyl) phthalazine-1 (2H)-one [42]:



Santos et.al., [75] synthesized γ-nitro oxazoline [44] by reaction of p-chloro-β-nitrostyrene [43] with oxazolinecyanocuprate :

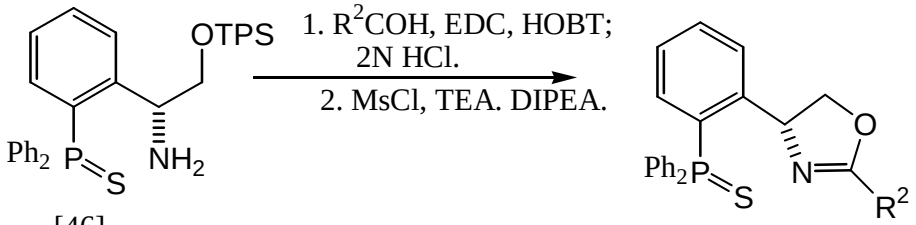


Kuklev and Smith [76] reported that the reaction of dienoic with trienoic fatty acids yielded 2-acyloaolines [45]:



[45]

Liu et.al., [77] found that the reaction of 2-(tert-butyl-dimethyl-silanyloxy)-(1R)-[2-(diphenyl-phoshinoyl)-phenyl]-ethylamine[46] with diphenyl aceticacid afforded 2-benzhydryl-(4R)-[2-(diphenyl-phosphin othionyl)-phenyl]-4,5,dihydro-oxazole [47]:



[46] [47]

R_2=$CHPh_2$;
TBSCI: tert-butyldimethylsilyl chloride;
EDC: 1-[3-(dimethylamino)propyl]-3-ethylcarbodiide hydrochloride;
HOBT: 1-hydroxy-benzotriazole hydrate;
TEA: triethylamine; DIPEA: diisopropylethylamine.

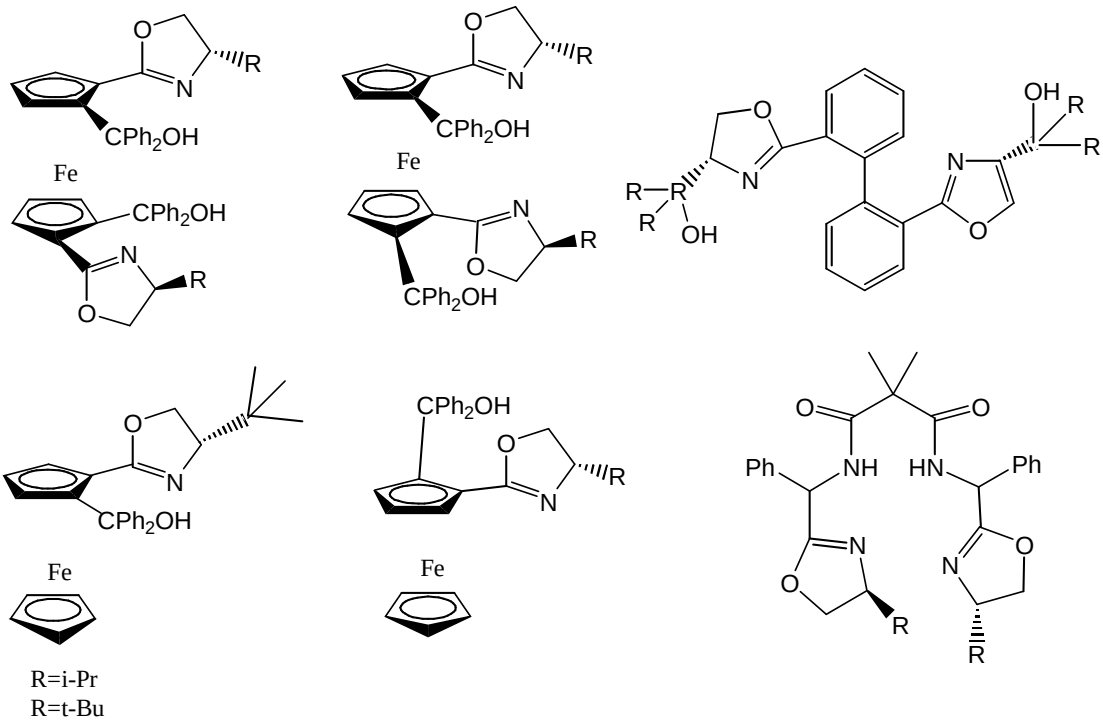
1.6.1 Oxazoline uses:

Chiral oxazolines, especially chiral bis(oxazoline), have been widely applied in many catalytic asymmetric reactions as versatile ligands[78,79].

Oxazoline-base ligands were also found to be effective for the asymmetric addition of diethyl zinc to aldehydes [80,81]. 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[82,83].

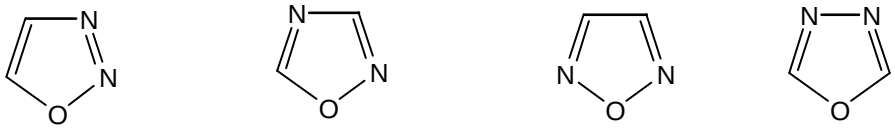
For example, ***Zhang*** et.al., [84] developed the ligands for the asymmetric addition of diethyl zinc to aldehydes and high enantioselectivities were obtained.

Ligands and that explored by ***Bolm*** et.al., [85] and ligands designed by ***Pastor*** and ***Adolfsson***[86], respectively, also showed good catalytic activity. In these ligands, the oxazoline unit and adjacent hydroxy group function together to control the catalytic process.



1.7 1, 3, 4-Oxadiazoles: General description

Each of the four oxadiazole rings contains two carbon atoms, two nitrogen, and one oxygen atom:

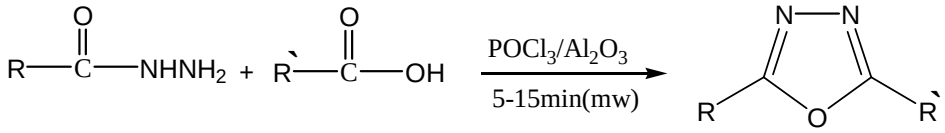


1,2,3-oxadiazole 1,2,4-oxadiazole 1,2,5-oxadiazole 1,3,4-oxadiazole

The parent 1, 3, 4-oxadiazole compound is a liquid, b.p. 150 ºC. There has been a significant increase in the use of 1, 3, 4-oxadiazoles in diverse areas, including drug synthesis, scintillation materials, and dyestuffs, therefore they comprise a large fraction of the literature [87].

1.7.0 Synthesis of 1, 3, 4-oxadiazole:-

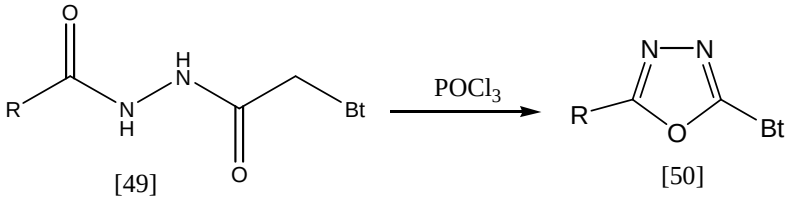
Corlson and Jorgensen [88] synthesized number of 2, 5 disubstituted-1, 3, 4-oxadiazole[48] under microwave irradiation through the reaction of available hydrazides with different carboxylic acids in the presence of phosphorous oxychloride:



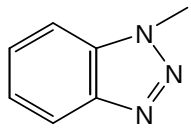
[48]

R=3-pyridinyl
R`=different group

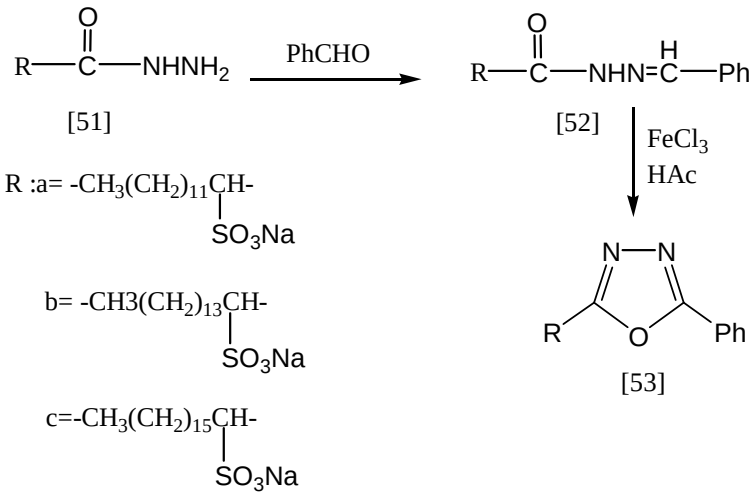
Katritzky et.al.,[89] synthesized1-[(5-phenyl[1, 3, 4]oxadizol-2-yl) methyl]-1H-benzotriazole-1-yl)N-acylacetohydrazides[49]with phosphor--us oxychloride[50]:



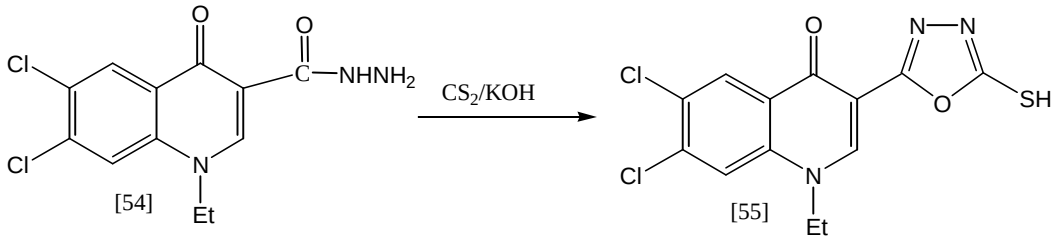
[49] [50]

Bt=  , R=Ph

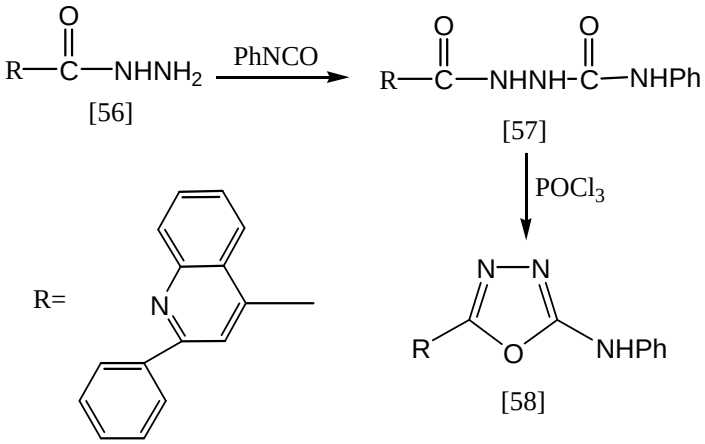
Eissa [90] found that the reaction of fatty acidhydazides [51] with benzaldehyde gives Schif base derivatives [52].Further cyclaztion of [52] with ferric chloride in the presence of acetic acid leds to the formation of oxadiazole derivatives [53]:



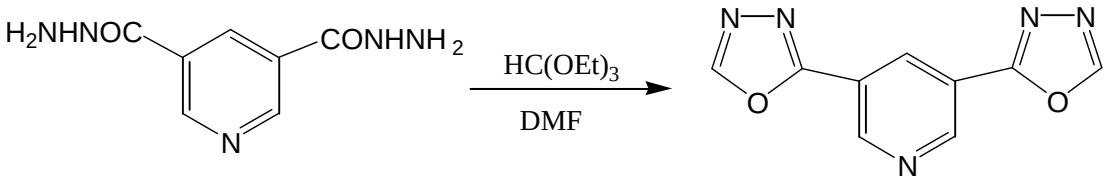
Al-Soud and Al-Masoudi [91] found that the reaction of 6, 7-dichloro-1-ethyl-1, 4-dihydro-4-oxoquinoline-3-carboxylicacid hydrazide [54] with CS_2 / KOH gave the coimpound 3-(1, 3, 4-oxadiazolyl)-quinoline [55]:



Feixu et.al., [92] found that the reaction of cinchophenylhydrazide [56] with phenylisocynate gave 1-cinchophenylamino-5-phenyl carbamide [57]. Further reaction of compound [57] with phosphorous oxychloride gave 2-arylamino-5- cinchophenyl-1, 3, 4-oxadiazoline [58]:



Attia and Abd El-Salam [93]reported that refluxing of 3,5-pyridinedicarbo-hydrazide [59] with ethyl orthoformate in DMF afforded 3,5-bis(1`,3`,4`-oxadiazol-5`-yl)pyridine [60]:



[59] [60]

1.7.1 1, 3, 4-Oxadiazole uses:

It has been reported [94] that heterocycles such as oxadiazoles are themselves important chemotherapeutic agents and exhibit antitubercular, bacteriostatic, hypoglycemic, antiviral, antifungal, antithyroid, carcinostatic and strong herbicidal activities when properly substituted in 2- and 5- positions.

Various 2, 5-diaryl-2, 5-dialkyl-, and 2-alkyl-5-aryl-1, 3, 4-oxadiazoles show herbicidal effect, especially against broad leafed weeds and grasses in crops such as rice and corn [95].

Whereas derivatives of 5-substituted-1, 3, 4-oxadiazole-2-thion are known to possess interesting pharmacodynamic property and some have remarkable activity against Mycobacterium tuberculosis [96, 97].

1.8 Schiff bases:

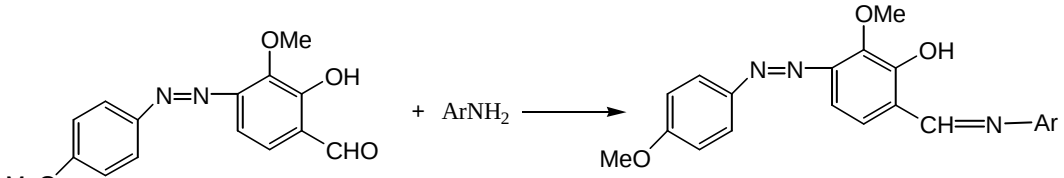
Schiff bases, so called since their synthesis was first reported by German chemist H. Schiff, result from condensation of primary amines with aldehydes or ketones.

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 [98]. Furthermore, Schiff bases are reported to show a variety of interesting biological activities, including antibacterial [99], antifungal [100], anti mouse hepatitis virus (MHV) [101], anticancer [102] and herbicidal activities [103].

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 [104] 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.,[105] prepared eight new azo Schiff bases [61] via condensation of different aromatic amines and new azoaldehydes [62]:



[61] [62]

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-$MeOC_6H_4$

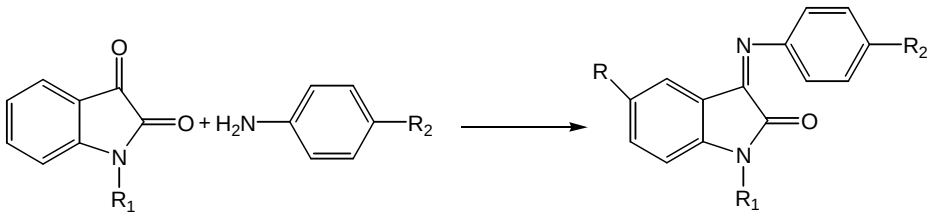
The antifungal and antibacterial activities of these compounds were also determined.

Aldimines have generally used in the formation of a large number of industrial compounds via cycloaddition, ring closure and replacement reactions [106,107].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, [108] synthesized Schiff bases [63] of N-methyl and N-acetyl isatin derivatives, the synthesized compounds have been screened for anticonvulsant activities:



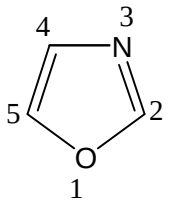
[63]

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 [109].

1.9 Oxazole: General description

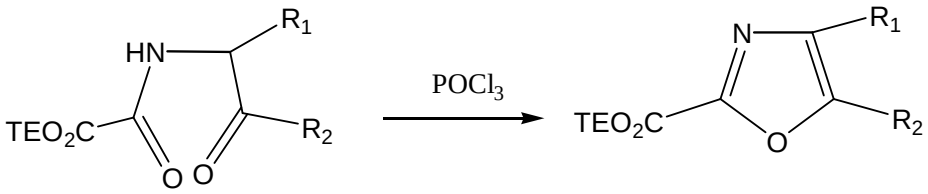
Oxazole is a heterocyclic organic compound, azafuran, with a five – member ring molecular structure, C_3H_3ON, containing three carbon atoms, one oxygen atom, and one nitrogen atom. It is a clear to yellowish liquid with a pyridine like odor [110,111,112].



1.9.0 Synthesize of oxazole:

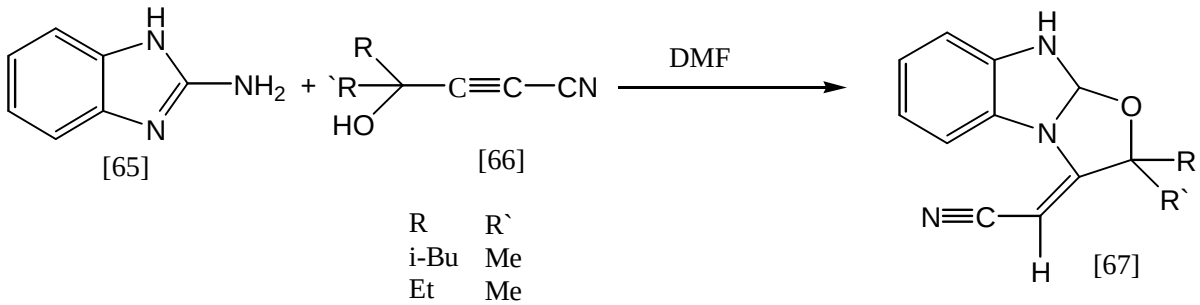
The growing literature demonstrates that the oxazole derivatives are becoming of great interest, this is primarily due to the large number of uses of oxazoles in many diverse areas.

Good and Jones et. al., [113] synthesis ethyl oxazol-2- carboxylates from 2-acylamine ketones with phosphoryl chloride.



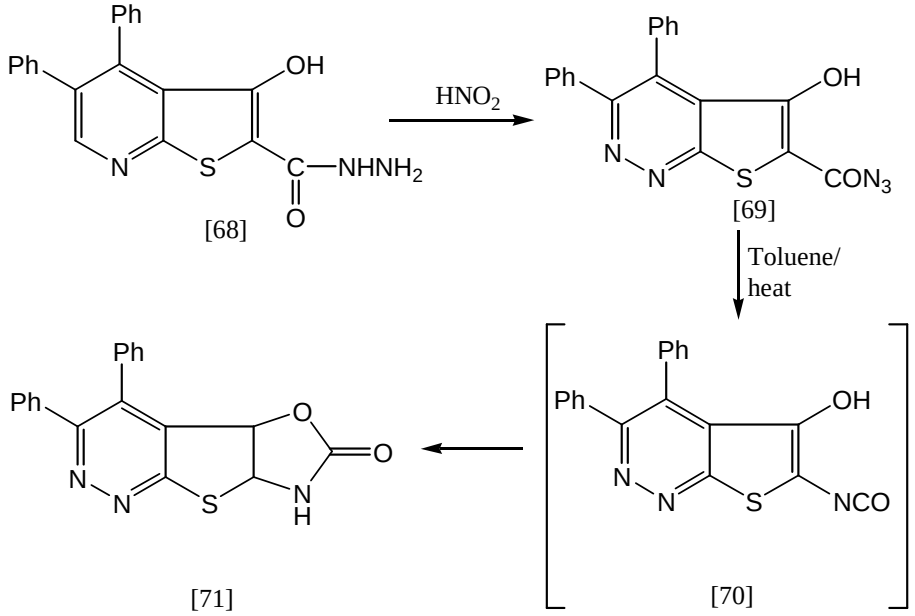
R_1=H, Ph, R_2=XPh, Me.

Wahe et.al.,[114] reported that when 4,4-dialkyl-4-hydroxyacetylenic nitrile [65]was heated under reflux with2-aminobenzimidazole[66]in dimethylforamide (2, 2-dialkyl-2, 3-dihydrooxazolo[3,2-a]benzimidazolyl idene) ethannitrile [67] could be formed:

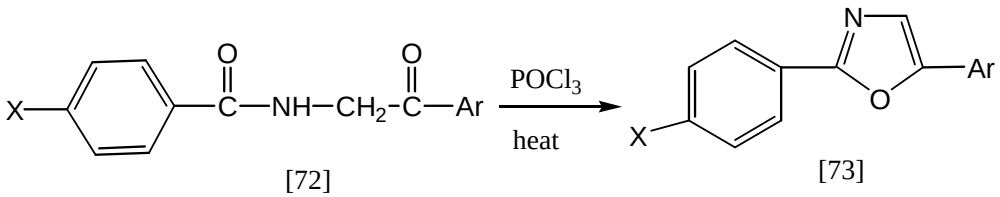


R	R`
i-Bu	Me
Et	Me
Et	Et

Bakhite et.al.,[115] found that the treatment of the carbohydrazide [68] with sodium nitrite in glacial acetic acid produced the carboazide derivative[69]which then refluxed in dry toluene to furnish oxazolo [5`,4`:4,5]thieno[2,3-c]pyridazine[70]via the isocyanate intermediate[71]:



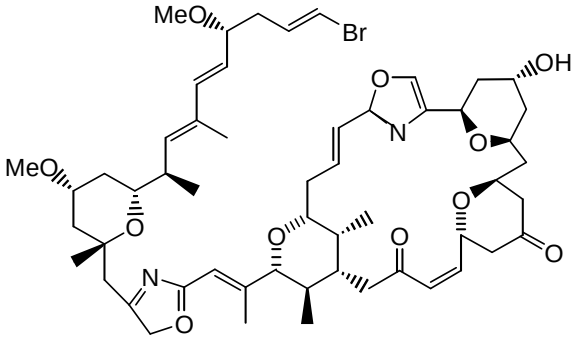
Balaban et.al.,[116] prepared a series of 2[4-(4-halobenzenesulphonyl) phenyl]-5-aryloxazoles [73] through cyclization of 2-aza-1-[4-(4-halo benzensulphonyl)-phenyl]-4-aryl-1,4-butanedione[72] under the action of phosphorus oxychloride:



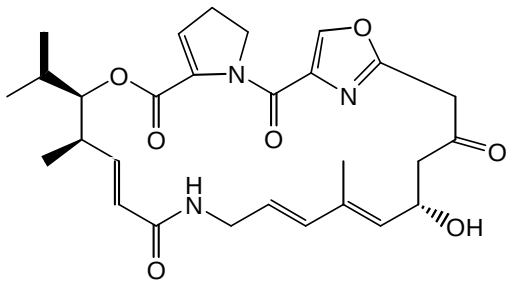
X=p-$BrC_6H_4SO_2$, Ar=Ph
X=p-$ClC_6H_4SO_2$, Ar=Ph
X=p-$BrC_6H_4SO_2$, Ar=p-$CH_3C_6H_4$
X=p-$BrC_6H_4SO_2$, Ar=2,4-$(CH_3)_2C_6H_3$
X=p-$ClC_6H_4SO_2$, Ar=2,4-$(CH_3)_2C_6H_3$

1.9.1 Oxazoles uses:

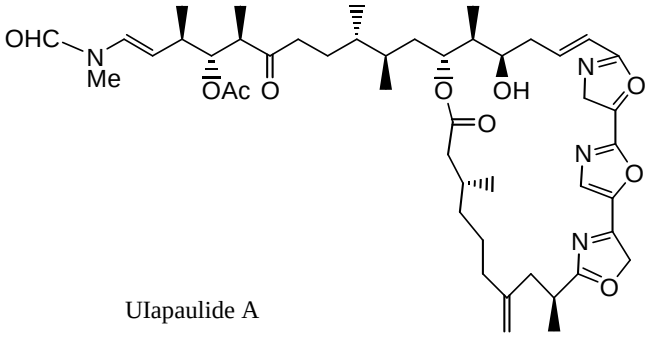
Oxazoles are found in many naturally occurring and biologically active materials as sub-structures within more complicated molecular arrays. In particular oxazole functionalized at both the 2-and 4-position have found important application in the synthesis of the more complex natural products including Phorboxzoles, Virginiamycins, and Ulapualides[115] (Fig.1-5):



Phorboxazole A



Virginiamycine M



UIapaulide A

Fig. (1-5) Marine natural product containing oxazole:

Not surprisingly a number of structures have therefore evolved for the construction and incorporation of disubstituted oxazole into complex synthetic target.

Furthermore, oxazoles are important compounds for the synthesis of anti-inflammatory pharmaceuticals and vitamin for example, 5-ethoxy-4-methoxyoxazole us a precursor for the synthesis of vitamin B_6 [113]. Vitamin B_6 is a related, naturally occurring, highly subsisted pyridine

derivatives with comparable physiologic activity. Vitamin B_6 is water soluble vitamin that is manufactured in bulk as pyridoxine hydrochloride (the predominant from of vitamin B_6, it is an important nutrient and plays an essential role in the body's amino acid biochemical pathways [116].

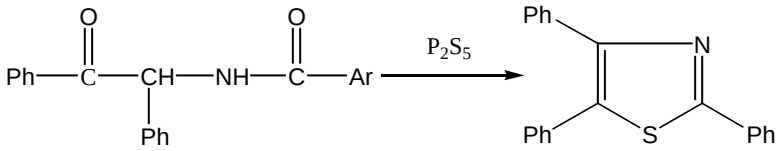
1.10 Thiazole: General description

The history of true thiazole series began in 1879 with the work ***Hoffman*** [117], who prepared derivatives of benzothiazole such as 2-chlorobenzothiazole and 2-phenylbenzothiazole.Simple thiazole nucleus $(C_3H_3)NS$ were first reported by ***Hantzsch and Weber*** [118] ;they proved the existence of both thiazole and isothiazole.

After the pioneer work knowledge of the thiazole system developed and investigation continued by ***Green*** [119], ***Borgert and Chertoff*** [120], ***Mills and Smith*** [121] and till recent days [122].

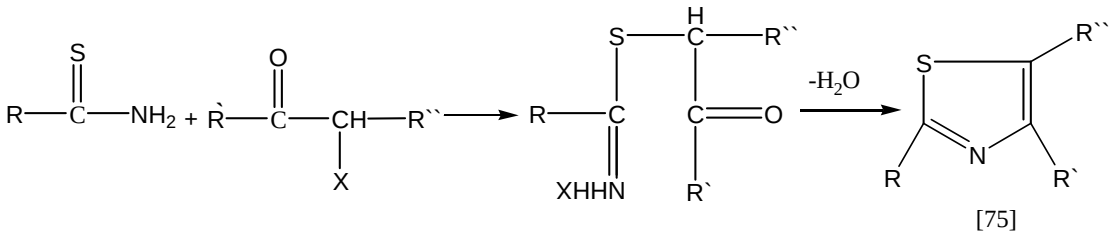
1.10.0 Synthesis of thiazole:

Gabriel[123] found that the reaction of α-acylaminoketone with phosphourous pentaoxide gave thiazole derivatives [74]:



[74]

Belat et.al [124] found that the reaction of an α-haloketone or aldehyde with thioamide gave thiazole derivatives [75]:

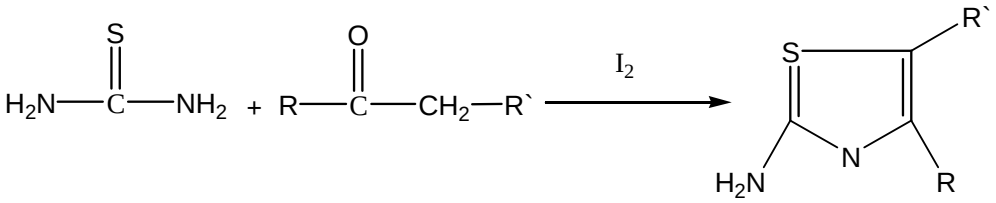


[75]

R'=H , R"=i-Bu, R'"=Et

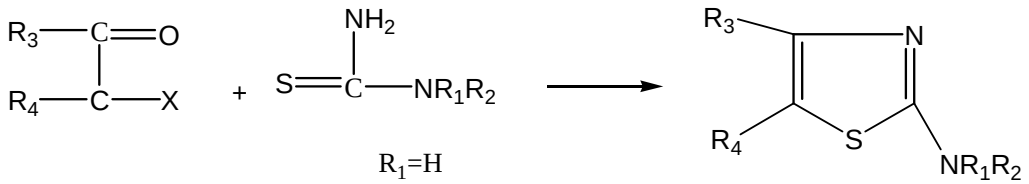
When a stable haloketone is the carbonyl reactant, it is sometime possible to substitute the thioamide by a mixture of oxygen amide $RCONH_2$ and phosphorous pentaoxide [125].

Kurkjy and Brown [126] found that the reaction of α-haloketone, a mixture of a ketone and thiourea was treated with oxidizing agents particularly iodine gave thiazole derivatives [76]:



R=H, R'=Me [76]

Bonzom and Metzger [127] found that the reaction of N, N-disubstituted thiourea with α-halocarbonyl compounds gives 2-disubstituted amino thiazoles [77]:



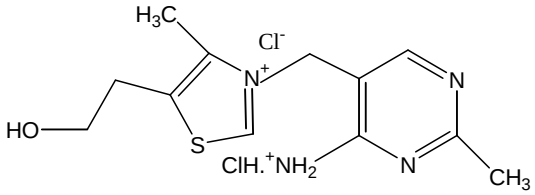
R_1=H
R_2=Me
R_3=ph
R_4=i-Bu

[77]

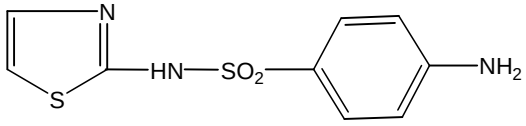
1.10.1 Thiazols uses:

Thiazole compounds are regarded as a class of heterocyclic compounds. It was found that numerous aromas contained thiazole derivatives such as tomato, roasted coffee and roasted peanuts [128].

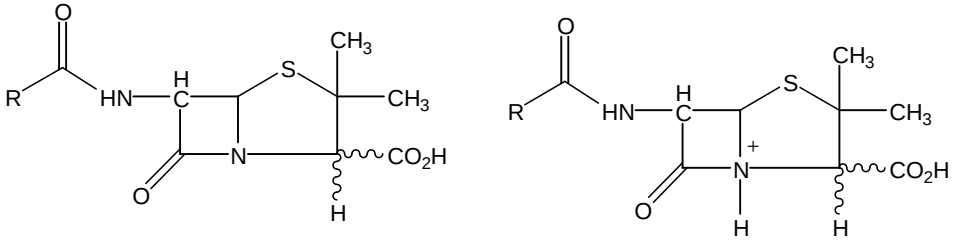
William and Coworkers in 1935 demonstrated existence of simple thiazole ring in vitamin B_1 (thiamine) [129].



Thiazole and its derivatives were used as chemotherapeutic agent for the treatment of bacterial infections [130].



Mills recognized the vale of cyanine days containing the ring as photographic sensitizers. It has also been proved that thiazolidine ring a part of penicillin structure and other compounds which are used as antibacterial agents [131].



Thiazole was also found in the structure of numerous pesticides, fungicides, herbicides and nematocides [132].

Numerous amount of research into potentially pharmacologically active thiazoles and benzothiazoles have been reported and many products which have emerged are antibiotics such as sulfathiazole and a host of related compounds [133]. Diuretics, antihistamines, anthelmintics, mitodepressives, mitostattics, antiparastics, anti-inflammatories, and antivirals have been reported [134].

In addition to these, thiazoles were reported to be of commercial interest. For example, 2-mercapto thiazole was found to have wide use as Accelerators in rubber vulcanization, anti-oxidant, photo-chromics, and dyestuffs [135], so because of these, they have been extensively studied.

Aim of the present work:-

Heterocyclic compounds play an important role in biochemical processes because the side groups of the most typical and essential constituents of living cells are based on aromatic heterocyclic. The presence of heterocyclic ring in biology, pharmacology, optics, electronics, etc. is very well known .Between them, sulfur and nitrogen-containing heterocyclic compounds have maintained the interest of researches through the development of organic synthesis.

This work was designed to reach the following targets:

1-Synthesis of series of triazole derivatives.

2-Synthesis of new Triazolo-Thiadiazine fused rings.

3-Synthesis of series of pyazole and pyrazolone derivatives.

4-Synthesis of Δ^4-oxazoline derivatives.

5- Synthesis of oxadiazole derivatives.

6- Synthesis of Schiff base derivatives.

7- Synthesis of oxazole derivatives.

8- Synthesis of thiazole derivatives.

9-Testing the biological activity for some of the synthesized compounds on different microorganisms.

Chapter Three

Results and Discussion

3.1 Hydrazide derivative [1a,1b]:-

The reaction of hydrazide hydrate with ester is one of the most common reaction to synthesize the acid hydrazide, it is a tetrahedral nucleophilic substitution reaction [148].

The F.T.IR for the hydrazide derivatives [1a, 1b] showed the appearance of the characteristic absorption bands in the region (3294.2-3109) cm^{-1} due to the asymmetric and symmetric stretching vibration of the (-NH-NH_2) group, the F.T.IR for the compound [1a] showed the disappearance of absorption bands at (1679.9) cm^{-1}due to the stretching vibration of carbonyl group of ester, while showed appearance of absorption band at (1616) cm^{-1} [149a] and (1658.7) $cm^{-1}$of the compound [1a,1b] due to stretching vibration of amid I band and appearance of amid II bending vibration band in the region (1585.23-15507) cm^{-1}.Figure (3-2) and (3-3). Table (3-1) shows the characteristic bands of compound [1a, 1b].

Table (3-1): Characteristic bands of compounds 1a and 1b.

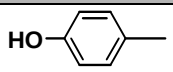
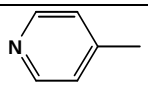
Comp. No.	Ar	υ(O-H) arom. cm^{-1}	υ(-NH-NH_2) cm^{-1}	υ(C-H) arom. cm^{-1}	υ(C=O) cm^{-1}	υ(C=C) cm^{-1}	δ(N-H) cm^{-1}
1a		3317.34	3276.83 3197.76	3004.89	1616	1589.23	1537.16
1b		----------	3294.2 3109.0	3024.2	1658.7	1550.7	1407.9

Figure (3-1) :F.T.IR spectum of compound (0a).

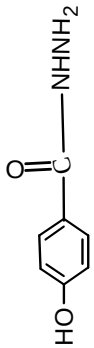
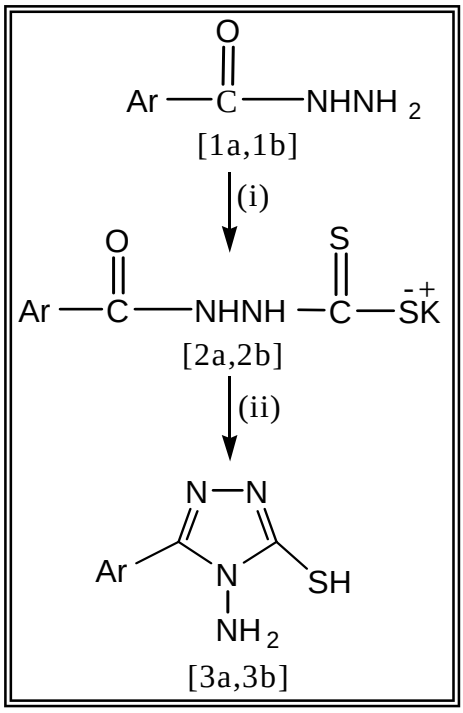


Figure (3-2) :F.T.IR spectum of compound (1a).

Figure (3-3) :F.T.IR spectum of compound (1b).

3.2 Synthesis of 3-mercapto 4-amino-5-aryl-1,2,4-triazole [3a,3b]:-

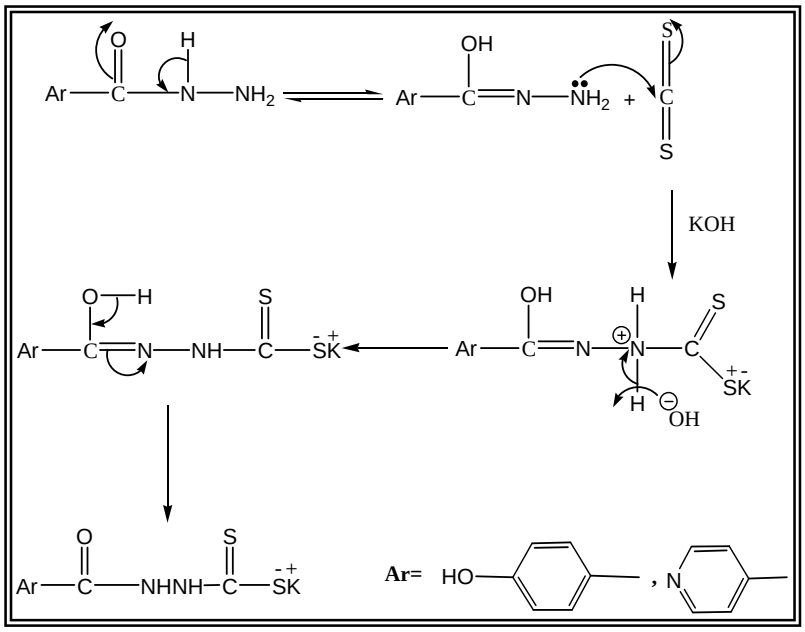
The title compound [3a,3b] was synthesized according to reaction scheme (1).



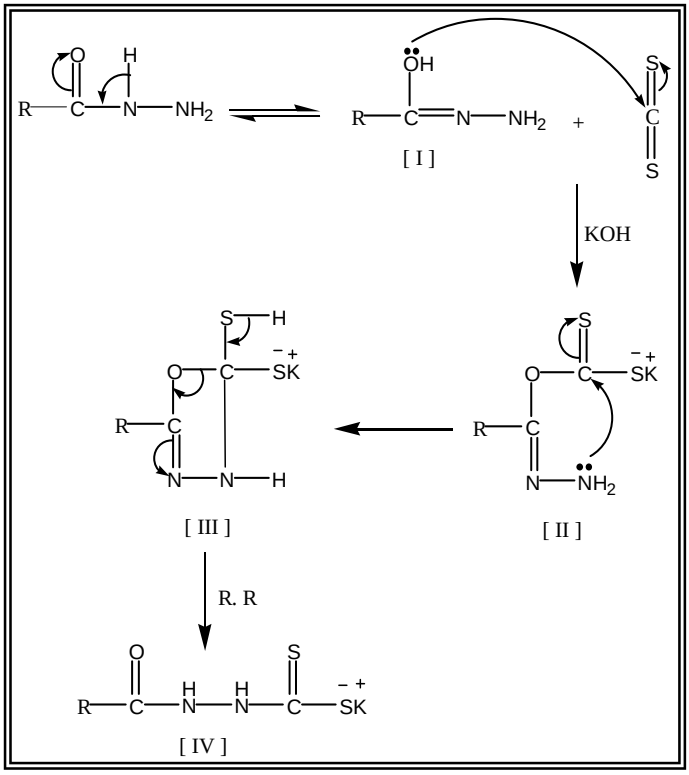
Scheme (1): Reagents and conditions (i) CS_2, KOH, abs. ethanol, reflux 1hr. (ii) $N_2H_4.H_2O$, reflux 4hr.

The 1, 2, 4 –triazole was synthesized according to the sequence in scheme (1).

The acid hydrazides [1a, 1b] were treated with carbon disulfide followed by the addition of hydrazine hydrate. Addition of CS_2 to the acid hydrazide afforded the salt as in the following mechanism [150]:-



Young and wood [151] suggested an alternative mechanism, this involves a nucleophilic attack first by the enol of hydrazide [I] on the thione group of the carbon disulfide forming the xanthate salt [II] which undergoes intramolecular addition to form the intermediate oxadiazoline [III], which might rearrange to produce the salt [IV]by the following mechanicm [157]:-



The salts [2a,2b] were characterized on the basis of there F.T.IR spectra, Fig.(3-4), (3-5); the characteristic IR spectral features showed (N-H) stretching bands at the region (3305.8-3288.40) $cm^{-1}$of compound [2a, 2b]. Beside this, the intense bands in the region (1674.1-1650.95) cm^{-1} and (1595-1550) cm^{-1}were due to the ν(C=O) and δ (N-H), respectively. The spectrum also shows absorption bands at the region (1269.10-1226.65) due to ν(C=S). Fig. (3-4)- (3-5). Table (3-2) shows the characteristics bands of compounds [2a, 2b].

Table (3-2): Characteristic bands of compounds 2a and 2b.

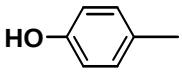
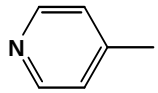
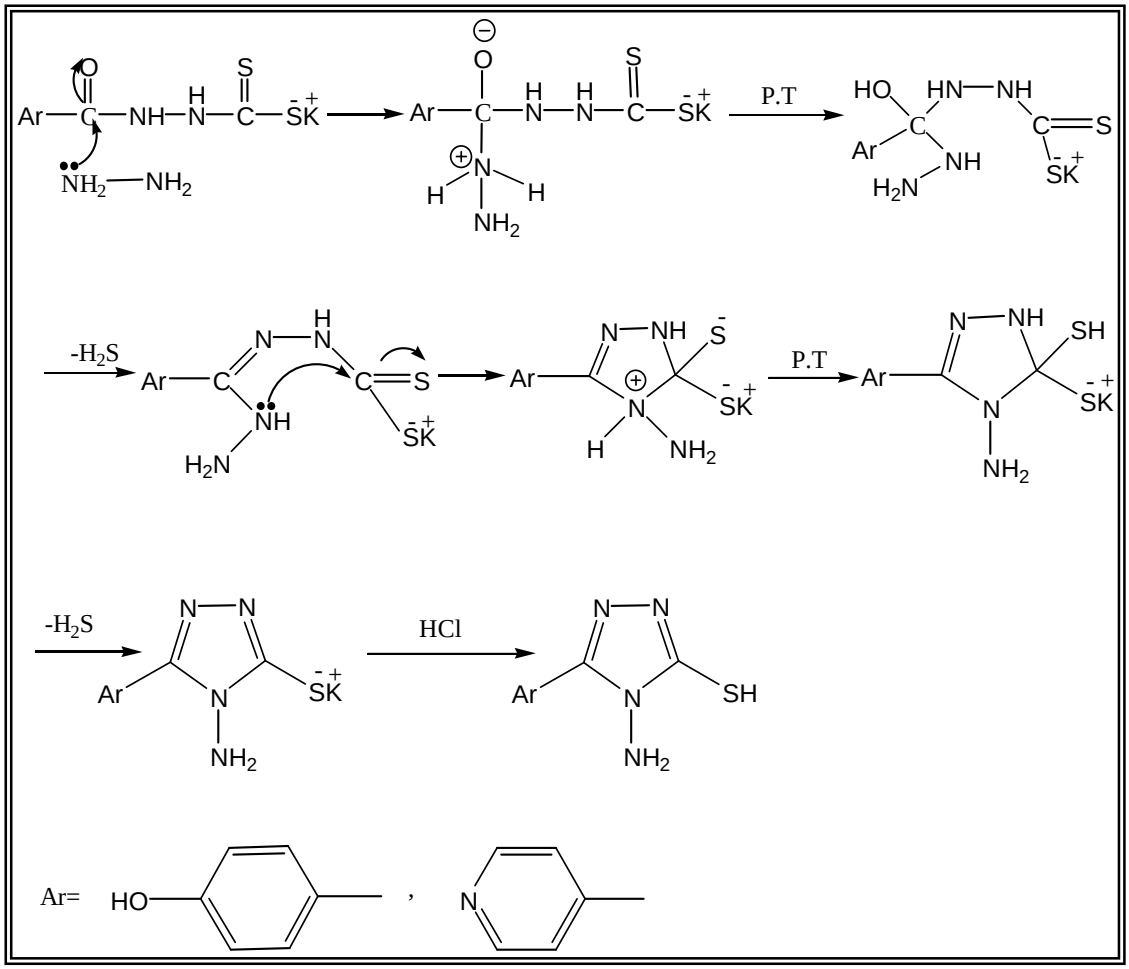
Comp. No.	Ar	υ(O-H) cm^{-1}	υ(N-H) cm^{-1}	υ(C-H) arom. cm^{-1}	υ(C=O) cm^{-1}	υ(C=C) cm^{-1}	υ(C=S) cm^{-1}	δ(N-H) cm^{-1}
2a		**3380.98**	**3288.40**	**2910.38 3000**	**1650.95**	**1606.59**	**1226.65**	**1590**
2b		**------**	**3305.8**	**3085.9**	**1674.1**	**1612.4**	**1269.10**	**1550**

Figure (3-4) :F.T.IR spectum of compound (2a).

Figure (3-5) :F.T.IR spectum of compound (2b).

The suggested mechanism for the cyclization of potassium salt [2a, 2b] by the following mechanism[157]:-



The triazole derivatives were characterized using F.T.IR spectra which showed the disappearance band of carbonyl at the region (1674.10-1650.95) cm^{-1} due to amide I and the appearance of bands in the region (1643.2-1612.24) cm^{-1} due to stretching vibration of (C-N) group, also appeared bands vibration of (C-N) group, appeared bands in the region (1226.64-1328.9) cm^{-1} and (3282.68-3207.4) cm^{-1} were due to ν(C=S) and ν(-NH_2) and ν(-NH) stretching vibrations respectively. Fig (3-6) – (3-7). Table (3-3) shows characteristic bands of compounds 3a and 3b.

Table (3-3): Characteristic bands of compounds 3a and 3b.

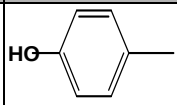
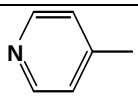
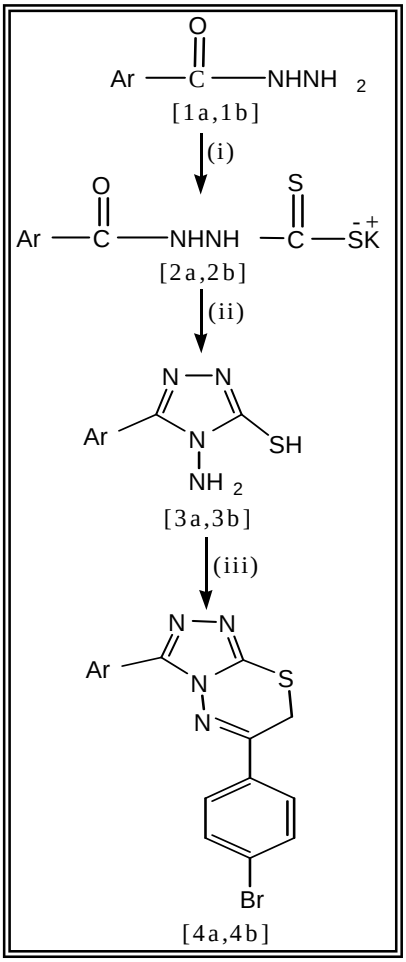
Comp. NO.	Ar	υ(O-H) cm^{-1}	υ(NH) and υ(NH_2). cm^{-1}	υ(C-H) arom. cm^{-1}	υ(C=N) cm^{-1}	υ(C=C) cm^{-1}	δ(NH) cm^{-1}	υ(C=S) cm^{-1}
3a		3305.76	3282.62-3122.54	~30000	1612.24	1550	1498	1226.64
3b		---------	3290-3207	3016.5-3080.1	1643.2	1591.2	1498	1328.9

Figure (3-6) :F.T.IR spectum of compound (3a).

Figure (3-7) :F.T.IR spectum of compound (3b).

3.3 Synthesis of 6-(p-Bromophenyl)-3-aryl-7H-[(1,2,4) - triazolo-(3,4-b) (1,3,4)] thiadiazine [4a,4] :-

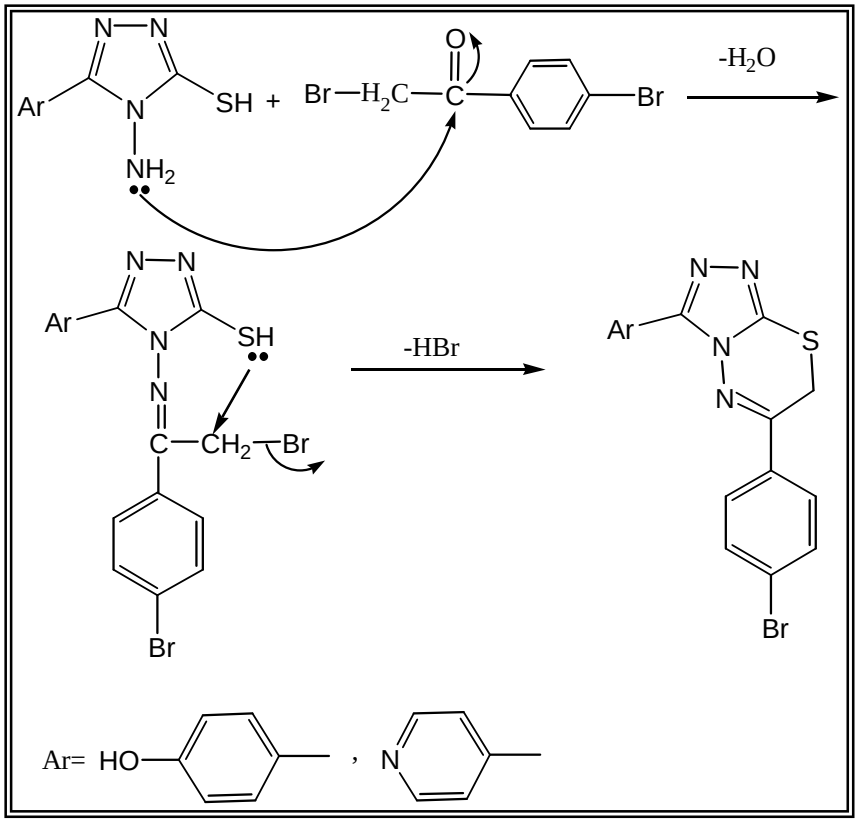
The title compounds [4a,4b] were synthesized according to reaction scheme (2).



Scheme (2): Reagents and conditions(i) CS_2, KOH, abs. ethanol, reflux 1hr; (ii) N_2H_4. H_2O, reflux, 4 hr;(iii) p-bromo phenacylbromide, abs. ethanol, reflux 6 hr.

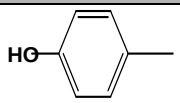
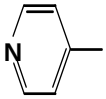
Fused ring thiadiazine derivatives are considered important branch of heterocyclic compounds due to their biological activities [(152)].

Compounds [4a, 4b] were synthesized from the reaction of triazoles[3a, 3b] with bromophenacylbromide according to the below mechanism which consist of $\mathbf{S_N}$2and tetrahedral nucleophilic substitution [(153)]:-



Compounds [4a,4b] were identified by F.T.IR which showed the disappearance of (C=S) & ($-NH_2$) absorption of triazole derivatives at (1328.9 -1226.64) cm^{-1} and (3290-3207) cm^{-1}, respectively. Fig. (3-8)- (3-9). Table (3-4) shows characteristic bands of compounds 4a and 4b.

Table (3-4): Characteristics bands of compounds 4a and 4b.

Comp. No.	Ar	υ(OH) cm^{-1}	υ(C-H) arom. cm^{-1}	υ(C=N-N) cm^{-1}	υ(C=C) cm^{-1}	υ(C-Br) cm^{-1}
4a		**3340.48**	**~30000**	**1585.38**	**1570**	**550**
4b		----------	**~30000**	**1583.4**	**1550**	**568.96**

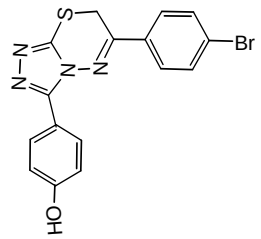


Figure (3-8) :F.T.IR spectum of compound (4a).

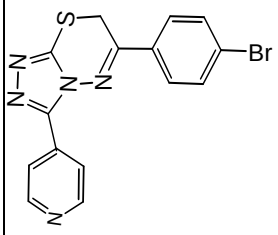
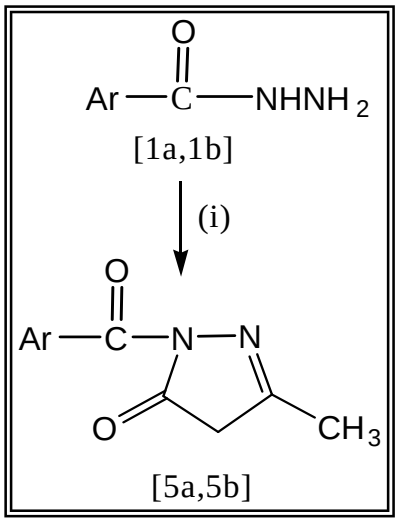


Figure (3-9) :F.T.IR spectum of compound (4b).

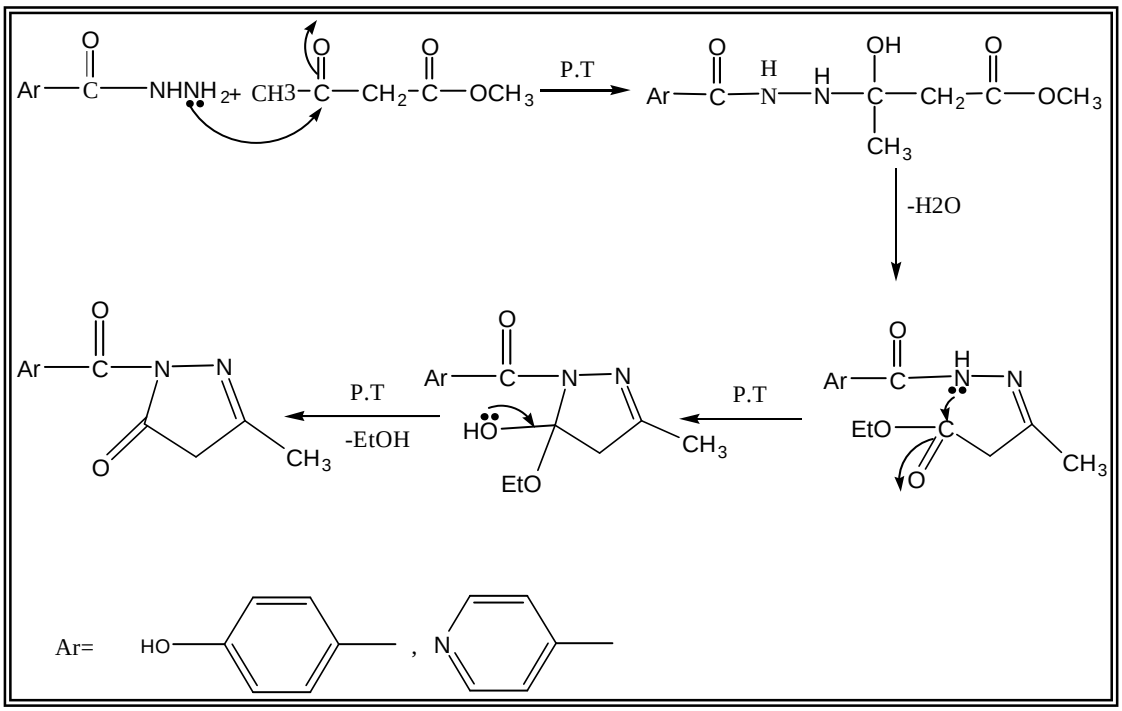
3.4 Synthesis of 2-aroyl-5-methyl-2, 4- dihydro pyrazol -3-one [5a, 5b]:-

The route for the preparation of title compounds (5a, 5b) involves the reaction of acid hydrazide with ethyl acetoacetate, scheme (3).

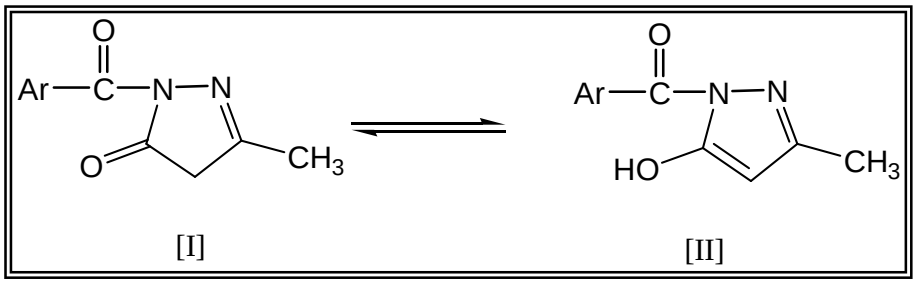


Scheme (3): Reagents and conditions (i) CH_3 CO CH_2COOEt, EtOH, reflux 7 hr.

The suggested mechanism[157] for this reaction involve the nucleophilic attack of nitrogen atom of the hydrazide on the ketonic of ethyl acetoacetate followed by the formation of Schiff base as intermediate compounds, then an other nucleophilic attack occur between the other nitrogen atom of hydrazide and the esteric carbonyl of ethyl acetoacetate as shown:



The derivatives (5a, 5b) were identified by F.T.IR spectra which showed the disappearance of two absorption bands of (-NH_2) group of the starting materials [1a, 1b] at (3294-3109) cm^{-1} and appearance of bands at the regions (1735.8-1730.03) cm^{-1}, and (3379-3300) cm^{-1} were due to the ν(C=O) and ν(O-H) moieties of pyrazole ring, respectively, while the (C=O)stretching of amide occur at rang (1671-1641.31) cm^{-1}. From the above mentioned facts, we can say that compounds [5a, 5b] can exists in equilibrium between keto [I] and enol [II] forms.



The F.T.IR spectra of the above compounds are shown in Figures (3-10)-(3-11). Table (3-5) shows the characteristic bands of compounds [5a-5b].

Table (3-5): Characteristic bands of compounds [5a-5b].

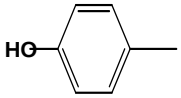
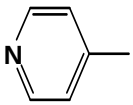
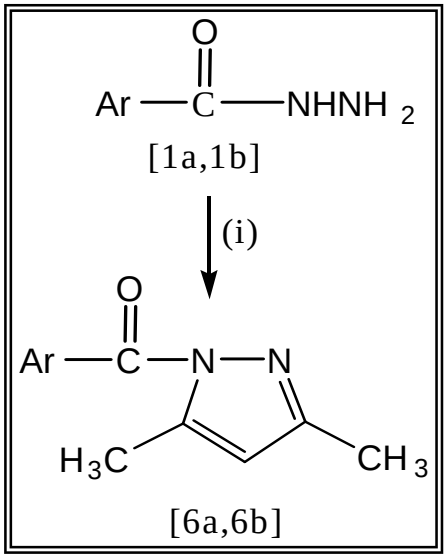
Comp. No.	Ar	υ(O-H) cm^{-1}	υ(C-H) arom. cm^{-1}	υ(C-H) Aliphatic. cm^{-1}	υ(C=O) (cyclic) cm^{-1}	υ(C=O) of amide cm^{-1}	υ(C=N) cm^{-1}	υ(C=C) cm^{-1}
5a		3300	3000	2890	1730.03	1641.31	1610.45	1579.59
5b		3024.2	3024.2	2900 2850.6	1735.8	1671.9	1539.1	1539.1

Figure (3-10) :F.T.IR spectum of compound (5a).

Figure (3-11) :F.T.IR spectum of compound (5b).

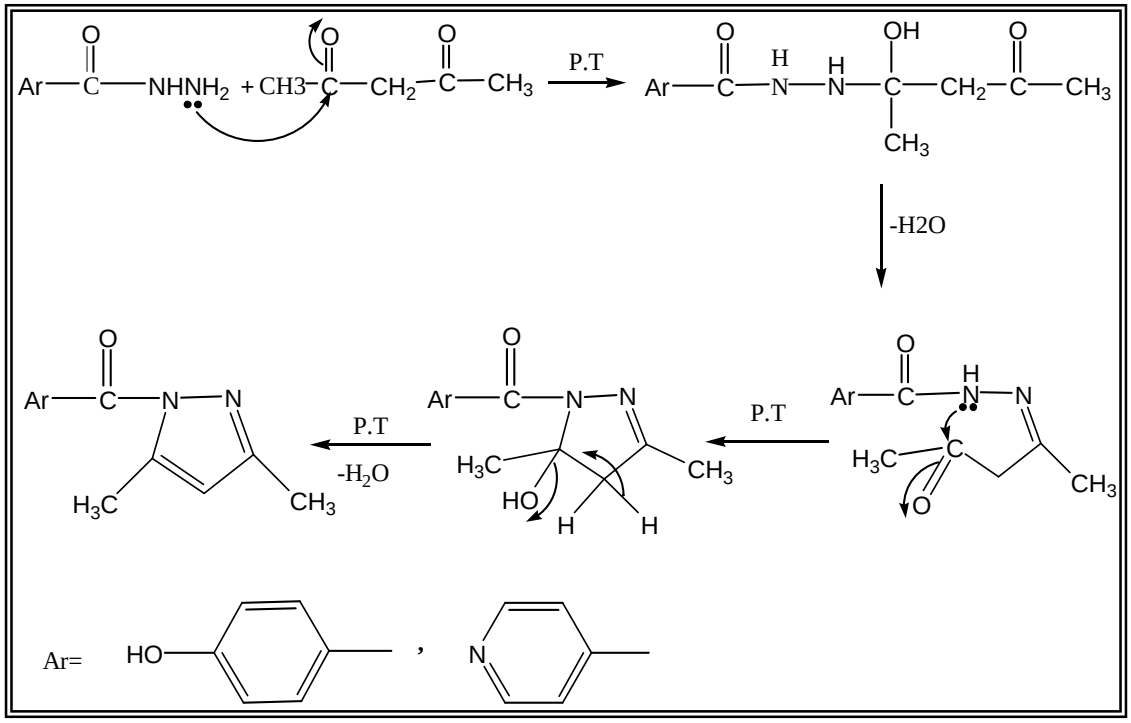
3.5 Synthesis of 2-N-aroyl- 3,5-dimethyl pyrazole[6a, 6b] :-

The route for the preparation of title compounds involves the reaction of acid hydrazide with acetylaceton, scheme (4).



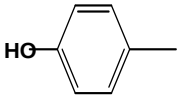
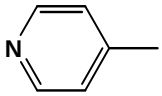
Scheme (4): Reagents and conditions (i) $CH_3COCH_2COCH_3$, abs.EtOH, reflux 7 hr.

The suggested mechanism for this reaction is the nucleophilic attack of nitrogen atom of hydrazide on. The ketonic carbonyl of acetyl acetone followed by the formation of Schiff base as intermediate compounds, then another nucleophilic attack occure between the other nitrogen atom of hydrazide and the esteric carbonyl of acetyl acetone as shown :



The derivatives [6a,6b] were identified by F.T.IR spectra which showed the disappearance of two absorption bands of (-NH_2) group of the starting materials [1a,1b] at (3294-3109) cm^{-1} and appearance of carbonyl group shifted to higher frequency (1680-1670.2) cm^{-1}.The aromatic (C=C) appeared at range (1520-1512) cm^{-1}.Sharp absorption band in the region (1600-1593.1) cm^{-1}. The F.T.IR spectra of above compounds are shown in fig. (3-12),(3-13). Table (3-6) shows the characteristic bands of compounds [6a, 6b].

Table (3-6): Characteristic bands of compounds [6a, 6b].

Comp. No.	Ar	υ(O-H) cm^{-1}	υ(C-H) arom. cm^{-1}	υ(C-H) aliphatic. cm^{-1}	υ(C=O) cm^{-1}	υ(C=N) cm^{-1}	υ(C=C) cm^{-1}
6a		**3392.55**	**3090**	**2827.45**	**1680**	**1600**	**1512.09**
6b		**----------**	**3051.2**	**2927.7**	**1670.2**	**1593.1**	**1512**

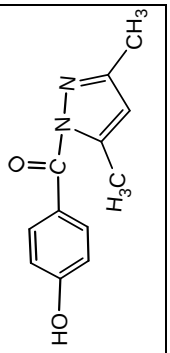
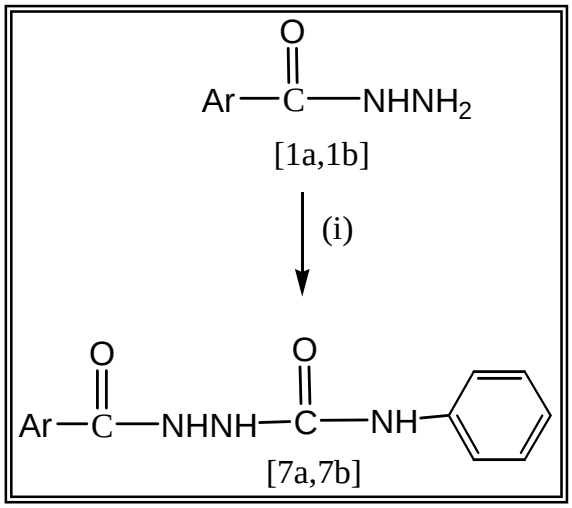


Figure (3-12) :F.T.IR spectum of compound (6a).

Figure (3-13) :F.T.IR spectum of compound (6b).

3.6 Synthesis of 2-N-aroyl-N`-phenylhydrazinecarbox amide [7a,7b]:-

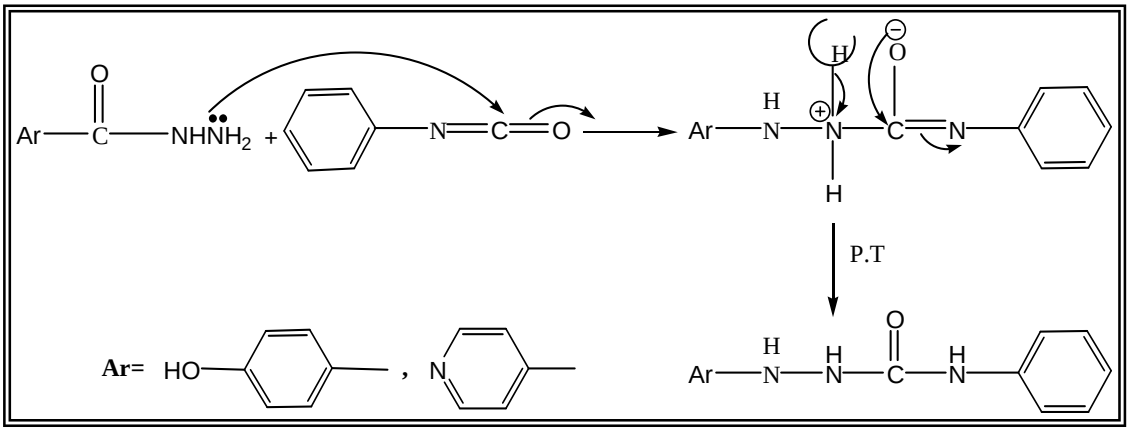
The title compounds [7a, 7b] were synthesized according to reaction (5).



Scheme (5): Reagents and conditions (i) phenyl isocynate, EtOH, reflux 8 hr.

The reaction of phenylisocynate with hydrazide derivatives [1a, 1b] under refluxing condition gave compounds [7a, 7b].

The mechanism [154] of the reaction is shown below.



The derivatives [7a, 7b] were identified by F.T.IR spectra which showed the disappearance of the two absorption bands in the region (3294-3109) cm^{-1} due to the asymmetric and symmetric stretching

vibration of the (-NH_2) group of the acid hydrazide derivatives and appearance of a single band due to (NH-) group at the region (3370-3192) cm^{-1}.

Carbonyl groups appeared as a band and shoulder at the range (1693.4-1631.7) cm^{-1}. The F.T.IR spectra of the above compounds are shown in Figures (3-14) and (3-15). Table (3-7) shows the characteristic bands of compounds [7a, 7b].

Table (3-7): Characteristic bands of compounds [7a, 7b].

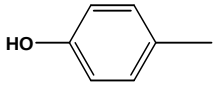
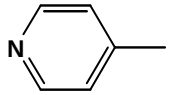
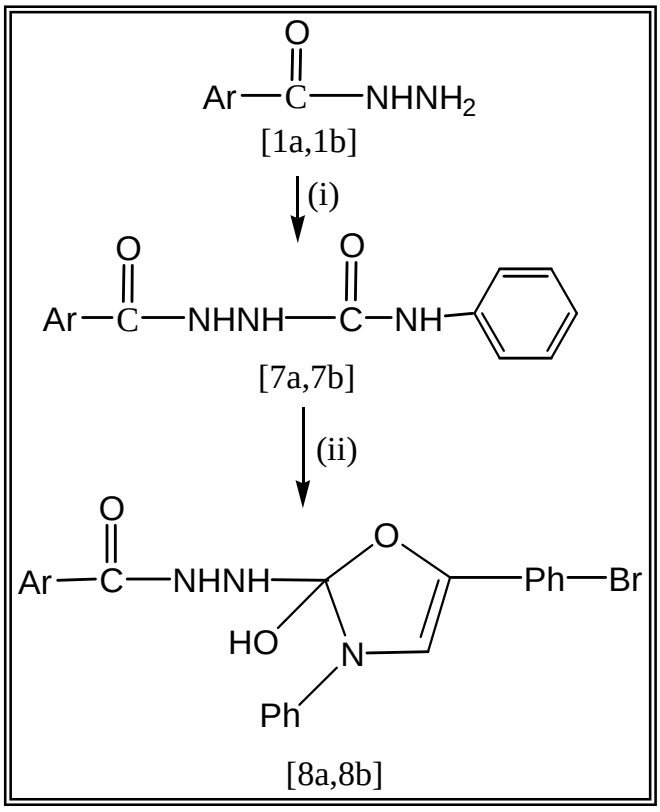
Comp. No.	Ar	υ(OH) cm^{-1}	υ(NH-) cm^{-1}	υ(C-H) arom. cm^{-1}	υ2(C=O) of amid and urea. cm^{-1}	υ(C=C) arom. cm^{-1}
7a		**3390**	**3370-3315.4-3192.0**	**3016.5**	**1679.9-1631.7**	**1556.4**
7b		**----------**	**3325.0-3267.2-3200**	**3001.0**	**1693.4-1647.1**	**1550.7**

Figure (3-14) :F.T.IR spectum of compound (7a).

Figure (3-15) :F.T.IR spectum of compound (7b).

3.7 Synthesis of N-[(2)-5-(p-bromophenyl)-3-phenyl- 1, 3-oxazol-2(3H)-ylidene]- aryl- hydrazide [8a, 8b]:-

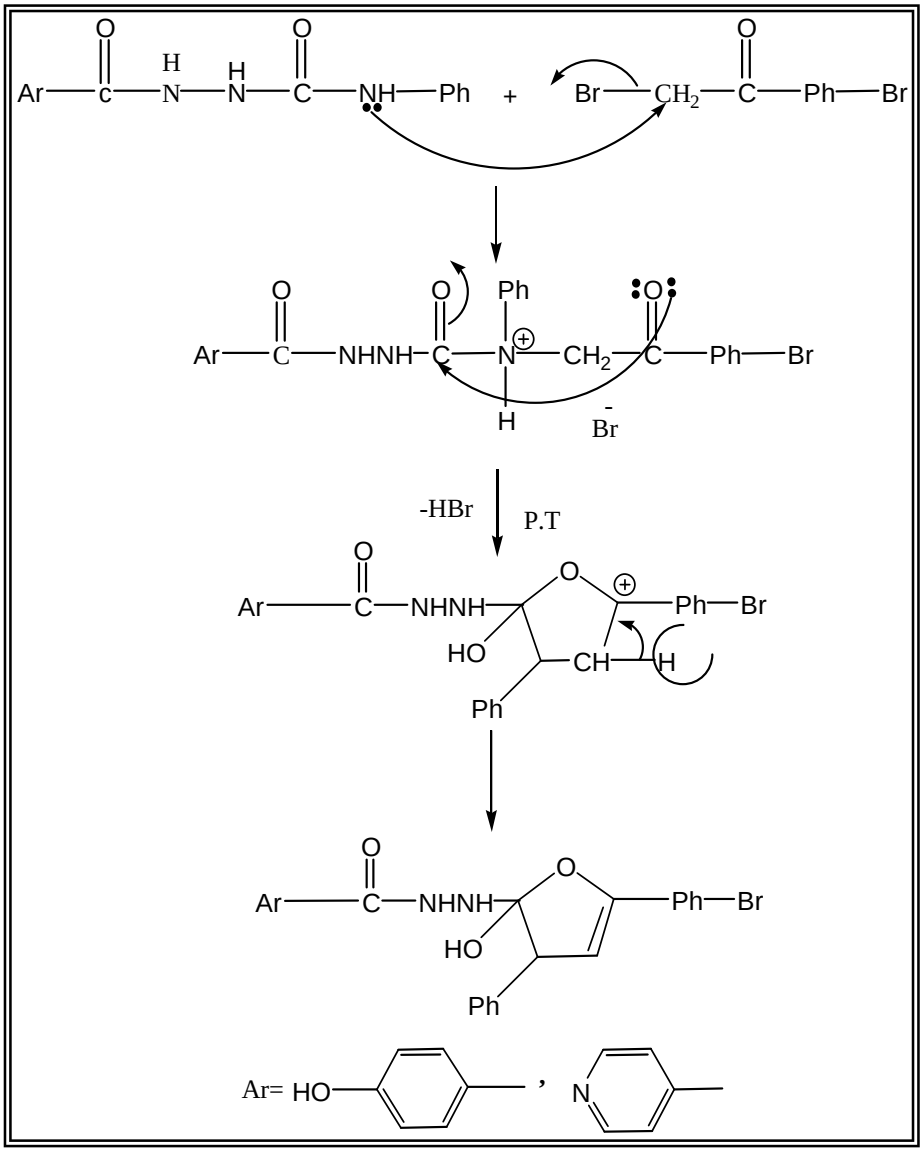
The title compounds [8a,8b] were synthesized according to reaction (6).



Scheme (6): Reagents and conditions(i) Phenyl isocynate, EtOH, Reflux 6h; (ii) p-bromophenacyl bromide, EtOH, reflux 8 hr.

The reaction of compounds [7a, 7b] with p-bromophenacyl bromide under refluxing condition effected on intermolecular cyclization through $\mathbf{S_N}2$ mechanism giving the desired 4- oxazoline derivatives [8a, 8b].

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



Substituted – oxazoline derivatives [6a,8b] were identified by F.T.IR spectra, band due to (-NH) group appeared at range (3350-3201.6) cm^{-1}, carbonyl group shifted to higher frequency (1697.2-1686) cm^{-1} due to disappearance of the possibility of the hydrogen bonding, the aromatic (C=C) of heterocyclic appeared within the range of carbonyl group. Sharp absorption bands appeared at the range (1583.4–1554.5) cm^{-1} due to (C=N) group, band at range (1286.4-1207.4) cm^{-1} due to (C-O-C) band.

The F.T.IR spectra of the above compounds are shown in figures (3-16)-(3-17). Table (3-8) shows the characteristic bands of the compounds (8a, 8b).

Table (3-8): Characteristic bands of the compounds [8a, 8b].

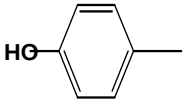
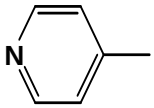
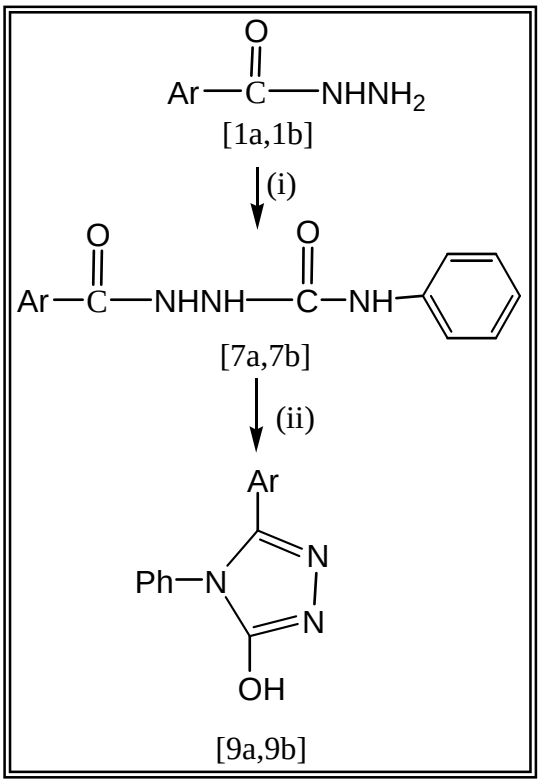
Comp. No.	Ar	υ(O-H) cm^{-1}	υ(N-H) cm^{-1}	υ(C-H) arom. cm^{-1}	υ(C=O) cm^{-1}	υ(C=N) cm^{-1}	υ(C=C) cm^{-1}	υ(C-O-C) cm^{-1}
8a		3400	3350-3311.5	3095.5	1686	1596.9	1554.4	1286.4
8b		3400	3300-3201.6	~30000	1697.2	1583.40	1535.12	1207.4

Figure (3-16) :F.T.IR spectum of compound (8a).

Figure (3-17) :F.T.IR spectum of compound (8b).

3.8 Synthesis of 4-N-phenyl 5-aryl- 1,2,4 -triazol- 3-ol [9a, 9b]:-

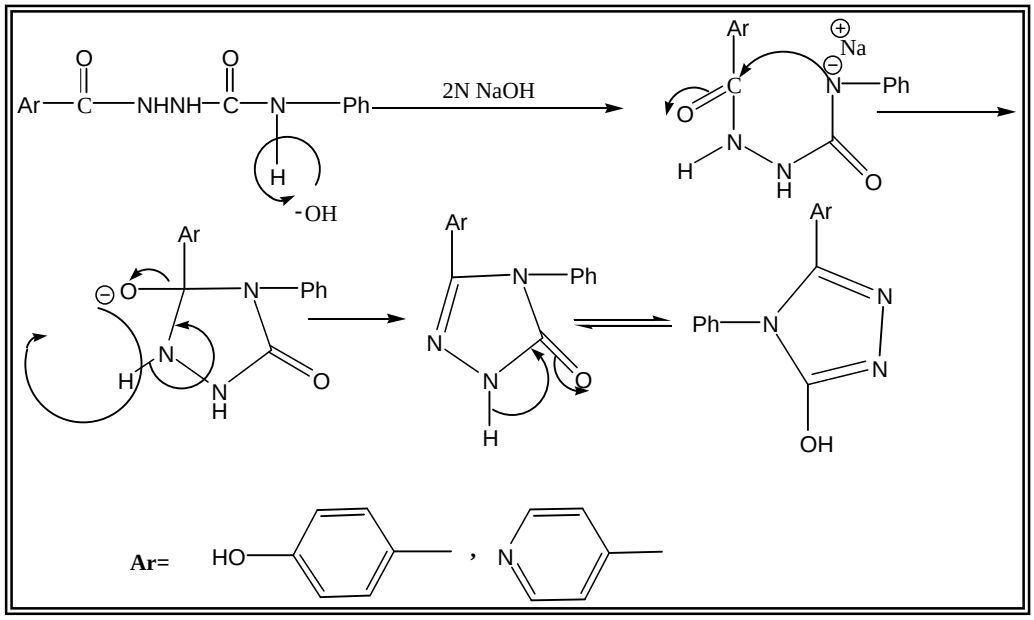
The route for the preparation of title compounds involves the reaction of acid hydrazide with 2N NaOH, scheme (7).



Scheme (7): Reagents and conditions (i) phenyl isosynate, EtOH, reflux 6 hr,(ii) 2N NaOH, reflux 3 hr.

The reaction of compounds [7a, 7b] with 2N NaOH under refluxing condition effected intermolecular cyclization through the loss of H_2O giving the desired hydroxyl triazole derivatives [9a, 9b].

The mechanism of the reaction may be posses by the following mechanism:-



N-substituted triazole derivatives [9a,9b] were identified by F.T.IR spectra, band due to (-NH) group at range (3200-319708) cm^{-1}, carbonyl group shifted to higher frequency (1716.5-1690) cm^{-1} due to disappearance of the possibility of hydrogen bonding, sharp absorption band appeared at the range (1606-1612) cm^{-1} due to (C=N) group, the aromatic (C=C) appeared at range (1596.9-1585) cm^{-1}. Fig (3-18)-(3-19). Table (3-9) shows the characteristic bands of compounds [9a, 9b].

Table (3-9): Characteristic bands of compounds [9a, 9b].

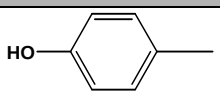
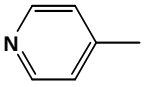
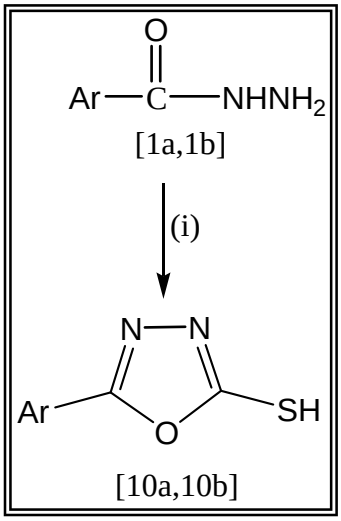
Comp. No.	Ar	υ(OH) cm^{-1}	υ(N-H) cm^{-1}	υ(C-H) arom. cm^{-1}	υ(C=O) cm^{-1}	υ(C=N) cm^{-1}	υ(C=C) cm^{-1}
9a		**3300**	**3200**	**~3000**	**1690**	**1606**	**1585**
9b		**3379**	**31978**	**~3000**	**1716.5**	**1612**	**1596.9**

Figure (3-18) :F.T.IR spectum of compound (9a).

Figure (3-19) :F.T.IR spectum of compound (9b).

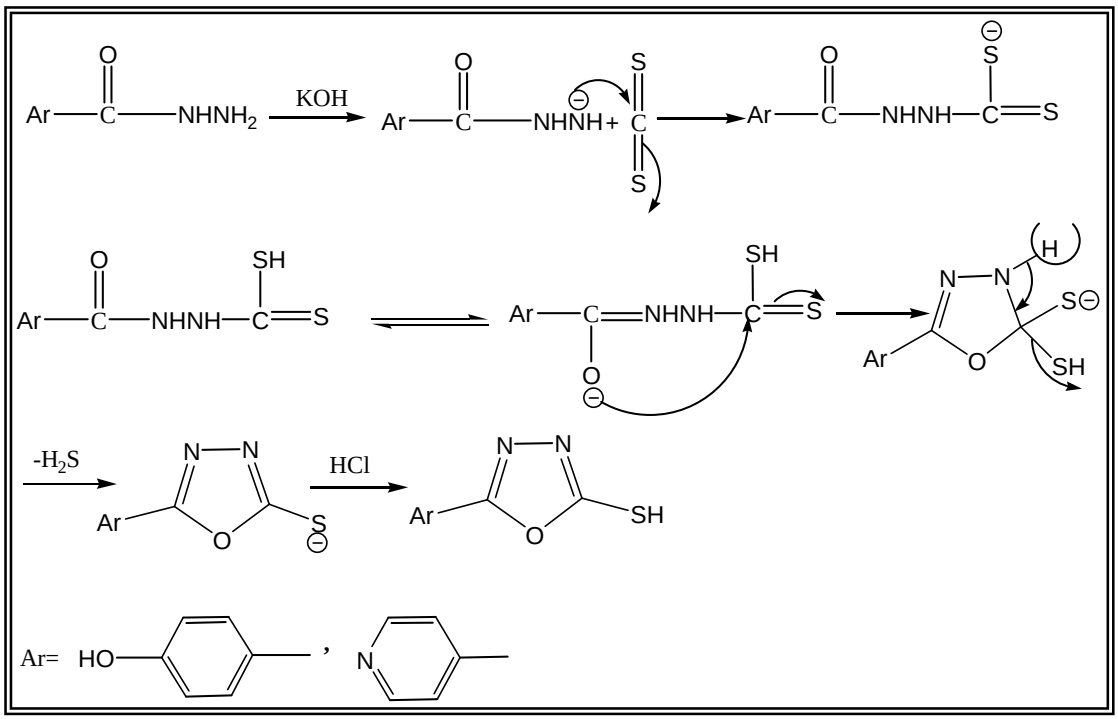
3.9 Synthesis of 2-mercapto -5-aryl -1,3,4-oxadiazole [10a,10b]:-

The 2-substituted -2- thiol -1, 3, 4 – oxadiazole [10a,10b] was obtained by the reaction sequence shown in scheme (8).



Scheme (8): Reagents and conditions (i) KOH, CS_2, EtOH, reflux 7 hr, HCl.

The mechanism [157] of the reaction may be outlined as follow:



The derivatives [10a,10b] were identified by F.T.IR spectra which showed the disappearance of the band at range (1658.7-1616) cm^{-1} due to υ (C=O) with the appearance of a bands at range (1610.5-1596.9) cm^{-1} assignable to υ (C=N) of oxadiazole ring at rang (1269.1-1222.8) cm^{-1} due to υ (C-O-C) (cyclic) group in oxadiazole are good evidences for the structure assigned to this compounds. Strong bands at range (1350-1222.8) cm^{-1} were due to υ (C=S). The aromatic (C=C) appeared at range (1546.8-1521.7) cm^{-1}. Fig. (3-20) - (3-21).Table (3-10) shows the characteristic bands for compounds [10a, 10b].

Table (3-10): characteristic bands of compounds [10a, 10b].

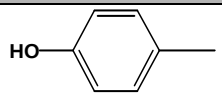
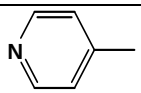
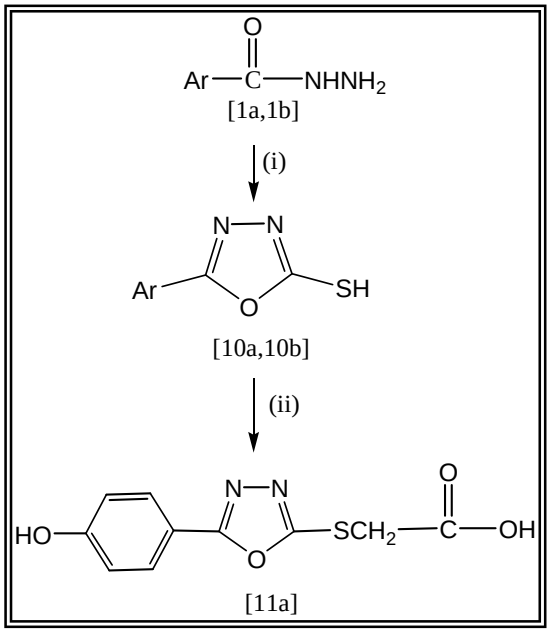
Comp. No.	Ar	υ(O-H) cm^{-1}	υ(N-H) cm^{-1}	υ(C-H) cm^{-1}	υ(C=N) cm^{-1}	υ(C=C) cm^{-1}	υ(C=S) cm^{-1}	υ(C-O-C) cm^{-1}
10a		**3197**	**3197**	**~3000**	**1610.5**	**1521**	**1222.8**	**1269.1**
10b		**--------**	**3197.8**	**3024.2**	**1596.9**	**1546.8**	**1350**	**1222.8**

Figure (3-20) :F.T.IR spectum of compound (10a).

Figure (3-21) :F.T.IR spectum of compound (10b).

3.10 Synthesis of {[5-(p-hydroxy phenyl)-1,3,4-oxadiazol-2-yl]} thioacetic acid [11a]:-

In order to synthesize the title compound, 3-mercapto- 5- (p- hydroxy phenyl)-1,3,4 - oxadiazole [10a] with monochloro acetic acid to produce compound [11a], scheme (9).



Scheme (8): Reagents and conditions (i) KOH, CS_2, reflux 7 hr, HCl;(ii) 10% NaOH, $ClCH_2$ COOH, reflux 3 hr;10%HCl.

The structure of compound [11a] was confirmed by F.T.IR spectrum which shows the disappearance of bands at (3197) cm^{-1} and (1222.8) cm^{-1} attributed to υ (N-H) and υ (C=S) respectively with appearance of bands at (1750) cm^{-1} and (3222.83) cm^{-1} were due to υ (C=O) and υ (O-H). The F.T.IR spectrum also showed the appearance of absorption bands at the region (1608.52) cm^{-1} and (1274.86) cm^{-1} were due to υ (C-O-C) (cyclic) group in oxadiazole ring. The aromatic (C-H) appeared at (3000-2960.53) cm^{-1}.Figure (3-22), displayed other characteristic bands.

Figure (3-22) :F.T.IR spectum of compound (11a).

3.11 Synthesis of N-p-substituted benzylidine – p-hydroxy benzohydrizide [12a-14a]:-

The derivatives[12a, 13a, 14a] were identified by F.T.IR spectra which showed the disappearance of two absorption bands in the region (3276.83-3197.76) cm^{-1} due to asymmetric and symmetric starting vibration of the ($-NH_2$) group of the hydrazid, carbonyl group shifted to higher frequency (1658.67-1640) cm^{-1}. Sharp absorption bands appeared at the region (1606.30-1606) cm^{-1} due to (C=N) group, the appearance of absorption bands at the region (3357.84-3340.48) cm^{-1} and (3200-3172.68) cm^{-1} due to υ (OH) group and υ (N-H) respectively .Fig (3-23)-(3-24)-(3-25). Table (3-11) shows the characteristic bands for compounds [12a, 12b].

Table (3-11): Characteristic bands of compounds [12a- 14a].

Comp. No.	R	υ(O-H) cm^{-1}	υ(N-H) cm^{-1}	υ(C-H) arom. cm^{-1}	υ(C-H) aliphatic. cm^{-1}	υ(C=O) cm^{-1}	υ(C=N) cm^{-1}
12a	**$-NO_2$**	**3340.48**	**3172.68**	**~3000**	**2860**	**1658.67**	**1666.59**
13a	**-OH**	**3340**	**3200**	**~3000**	**2860**	**1640**	**1606.59**
14a	**$-N(CH_3)_2$**	**3357.84**	**3200**	**~3000**	**2815.88**	**1643**	**1606.30**

Figure (3-23) :F.T.IR spectum of compound (12a).

Figure (3-24) :F.T.IR spectum of compound (13a).

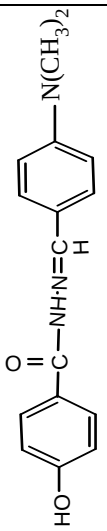
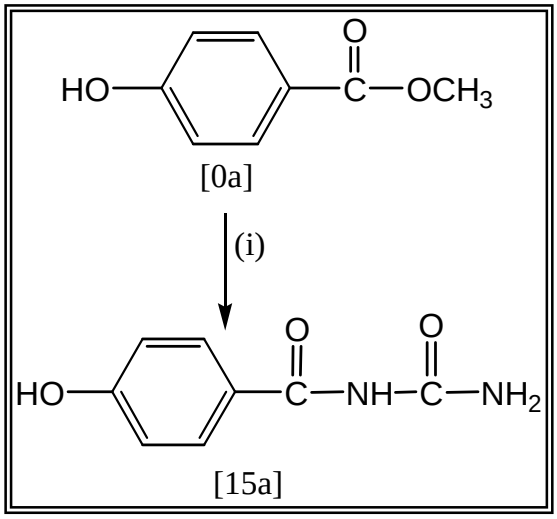


Figure (3-25) :F.T.IR spectum of compound (14a).

3.12 Synthesis of N-(aminocarbonyl)-p-hydroxy benzamide[15a] :-

The refluxing of p-hydroxyl methyl benzoate with urea in absolute ethanol gave compound [15a], scheme (9).



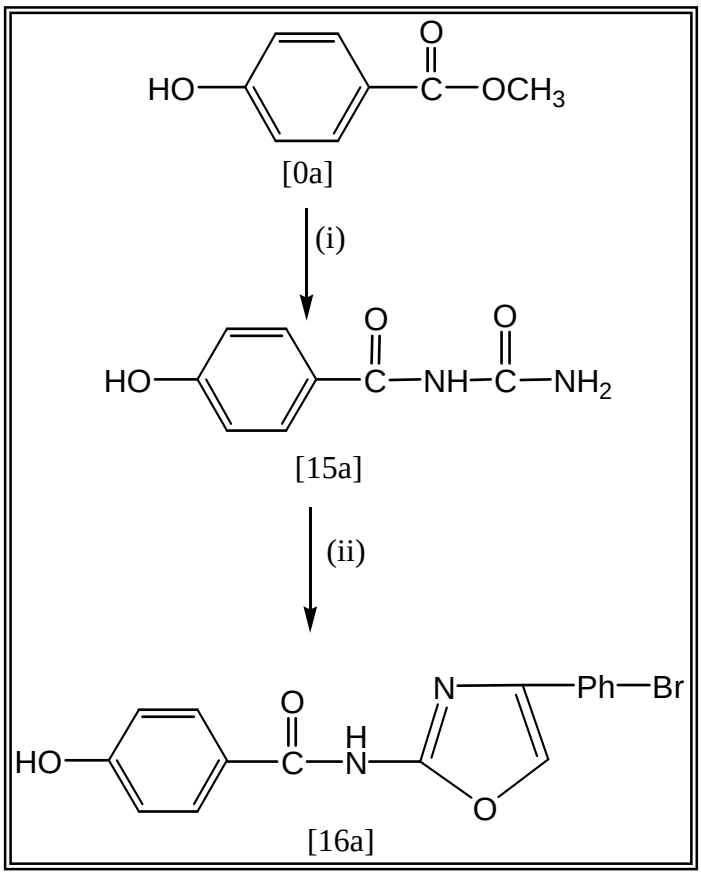
Scheme (9): Reagents and conditions (i) urea, abs. ethanol.

The F.T.IR spectrum showed a split broad bands at (3300-3200) cm^{-1} due to the asymmetric and symmetric bands of (NH_2) and (NH) groups, two other bands at (1650-1639) cm^{-1} for the carbonyl and bands group at (3002.96-1595) cm^{-1} which were due to (C-H) and (C=C) stretching of aromatic system, respectively, and band at (3400) cm^{-1} for (O-H) group. Fig (3-26).

Figure (3-26) :F.T.IR spectum of compound (15a).

3.13 Synthesis of N-[4-(p-bromophenyl)-1, 3-oxazol-2-yl]-p-hydroxy benzamide [16a] :-

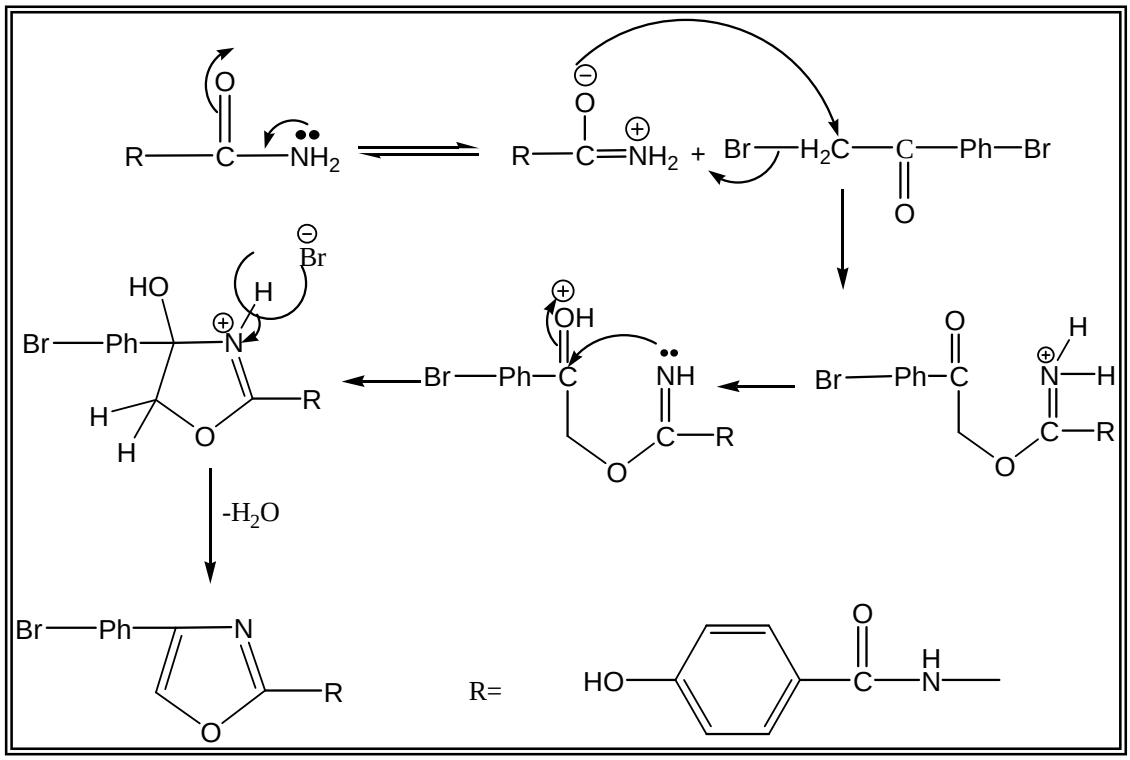
The title compound [16a] was synthesized according to reactions in scheme (10).



Scheme (10): Regents and conditions (i) Urea, abs. ethanol; (ii) p-bromophenacylbromide, abs. ethanol, reflux 8 hr.

The reaction of compound [15a] with p- bromo phenacyl bromide under refluxing condition affected on intermolecular cyclyzation through $\mathbf{S_N}2$ mechanism giving the desired oxazole derivative [16a].

The formation of [16a] may be posses by the following mechanism[157]:-

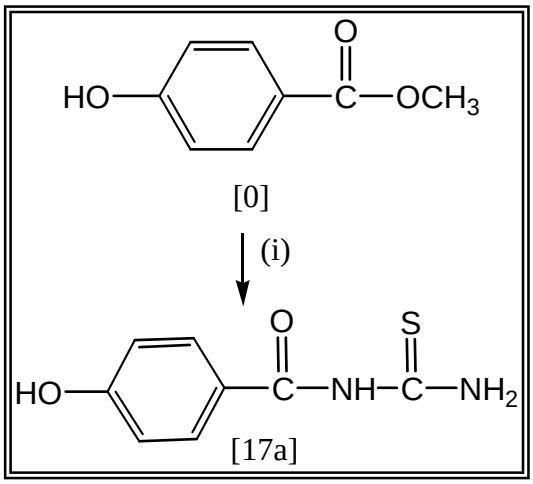


The structure of oxazole derivative was confirmed by F.T.IR spectrum showed a broad band of (O-H) group and (N-H) at (3369.41) cm^{-1}, carbonyl group shifted to higher frequency (1700) cm^{-1} due to disappearance of possibility of hydrogen bonding. Sharp absorption band at (1585.38) cm^{-1} due to υ (C=N) group the aromatic (C=C) at (1566.09) cm^{-1}, stretching band of (C-O-C) at (1284.50) cm^{-1}, band of (C-Br) at (547.75) cm^{-1}, and at (1495) cm^{-1} for δ (-NH). Fig. (3-27).

Figure (3-27) :F.T.IR spectum of compound (16a).

3.14 Synthesis of N-(aminocarbonothioyl)-p- hydroxyl benz amide [17a]:-

The title compound [17a] was synthesized according to reaction scheme (12).



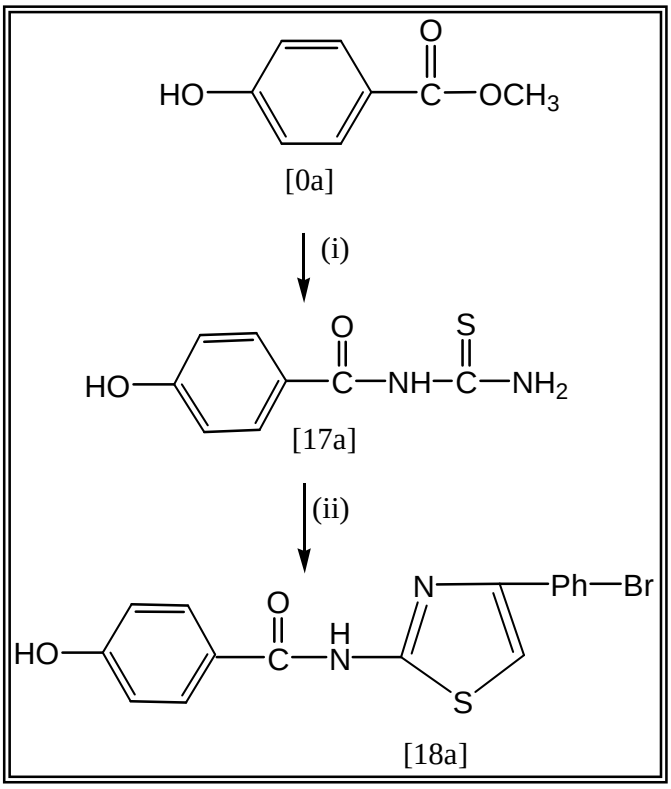
Scheme (11) Reagents and conditions: (i) Thiourea, abs. ethanol.

The F.T.IR spectrum showed a band at (3300-3195) cm^{-1} which was assigned to the asymmetric and symmetric bands of (NH_2) and (NH) groups, at (1650) cm^{-1} for υ (C=O), at (1089.71) cm^{-1} for υ (C=S) [149b] and bands at (3000-1630) cm^{-1} which were due to υ (C-H) and υ (C=C) stretching of aromatic system, respectively, and at (1467.73) cm^{-1} for δ (NH).Fig (3-28).

Figure (3-28) :F.T.IR spectum of compound (17a).

3.15 Synthesis of N-[4-(p-bromophenyl]-1 3-thiazol-2-yl]-p-hydroxy benzamide [18a]:-

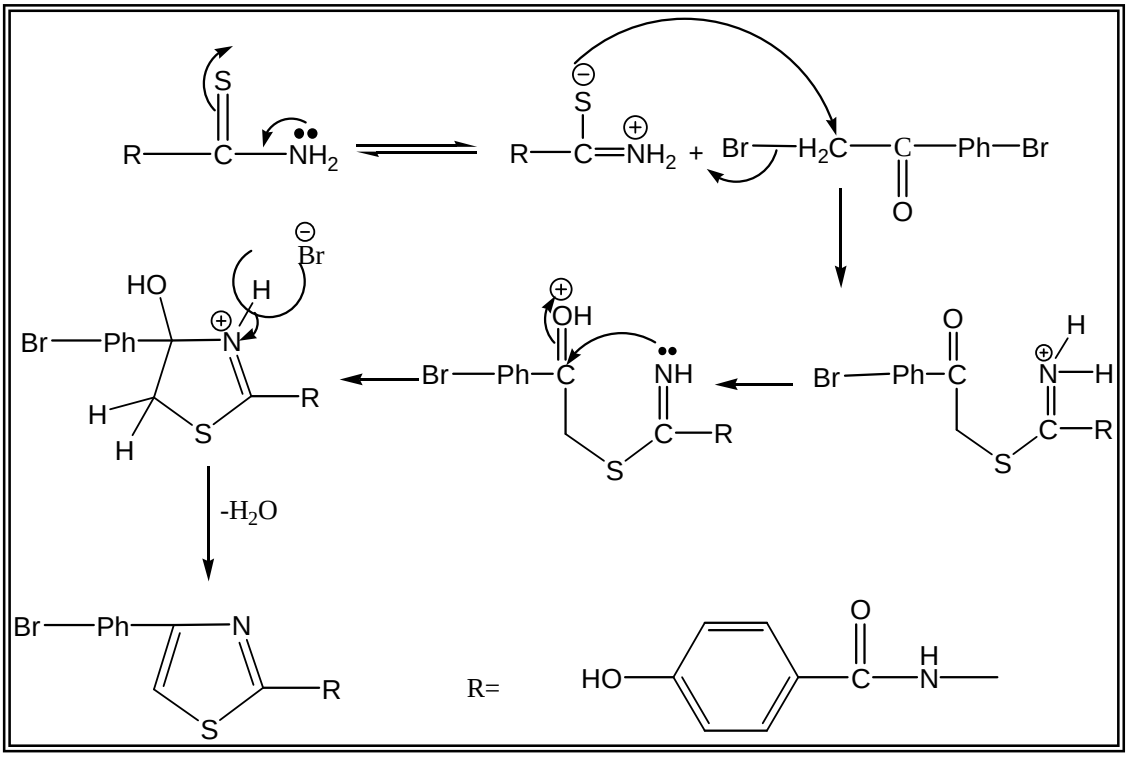
The title compound [18a] was synthesized according to reaction scheme (13).



Scheme(12): Reagents and conditions (i) Thiourea, abs. ethanol; (ii) p-bromophenacylbromide, reflux 8 hr.

The reaction of compound [17a] with p-Bromo phenacyl bromide under refluxing condition affected on intermolecular cyclization through $\mathbf{S_N}2$ mechanism giving the desired thiazole derivative [18a].

The formation of [18a] may be posses by the following mechanism:



The F.T.IR spectrum of compound [18a] showed the disappearance of the (C=S) band of compound (17a) at (1089.71) cm^{-1}, carbonyl group shifted to higher frequency (1701.1) cm^{-1}due to disappearance of possibility of hydrogen bonding. Sharp absorption band at (1631.67) cm^{-1} and (3282.62) cm^{-1} due to υ(C=N) and υ(N-H) cm^{-1}, respectively, the aromatic (C=C) at (1649) cm^{-1}, stretching band of υ (C-S-C) at (725.18) cm^{-1}, and band of (C-Br) at (568.96) cm^{-1}, and band of δ (NH) at (1471.59) cm^{-1}as shown in fig. (3-29).

Figure (3-29) :F.T.IR spectum of compound (18a).

3.16 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. [155].

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 [156].

3.16.0 Microbiological tests:

In this work, the antibacterial test was performed according to the disc diffusion method. Compounds ([1a, 1b], [3a, 3b], [4a, 4b], [8a, 8b], [10a, 10b]) 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 (1mg 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 (3-12).

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 (3-12):

Antibacterial activities of some of the synthesized compounds

Comp. No.	Escherichia coli	Staphococcus aureus
1a	**-**	**-**
1b	**-**	**-**
3a	**+++**	**+++**
3b	**+++**	**+++**
4a	**-**	**-**
4b	**++**	**++**
8a	**++**	**-**
8b	**++**	**-**
10a	**+++**	**+++**
10b	**+++**	**+++**

Note:

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

Fig. (3-30) Effect of compounds [1a], [3a], [4a], [8a], [10a] on *Escherichia coli*

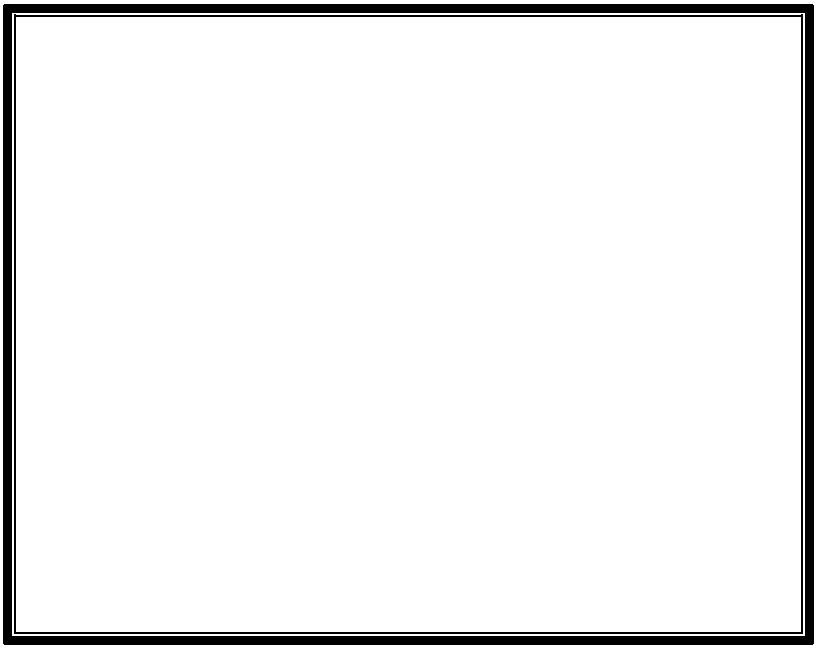


Fig. (3-31) Effect of compounds [1b], [3b], [4b], [8b], [10b] on *Escherichia coli*

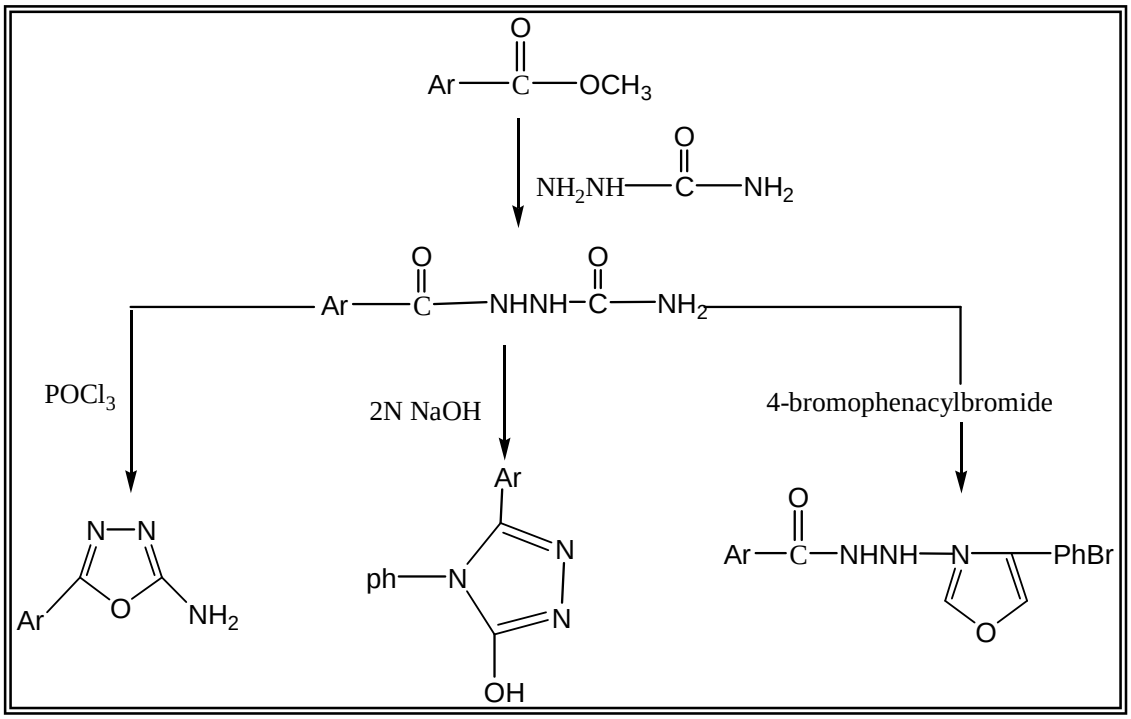
Fig. (3-32) Effect of compounds [1a], [3a], [4a], [8a], [10a] on *Staphylococcus aureus*

Fig. (3-33) Effect of compounds [1b], [3b], [4b], [8b], [10b] on *Staphylococcus aureus*

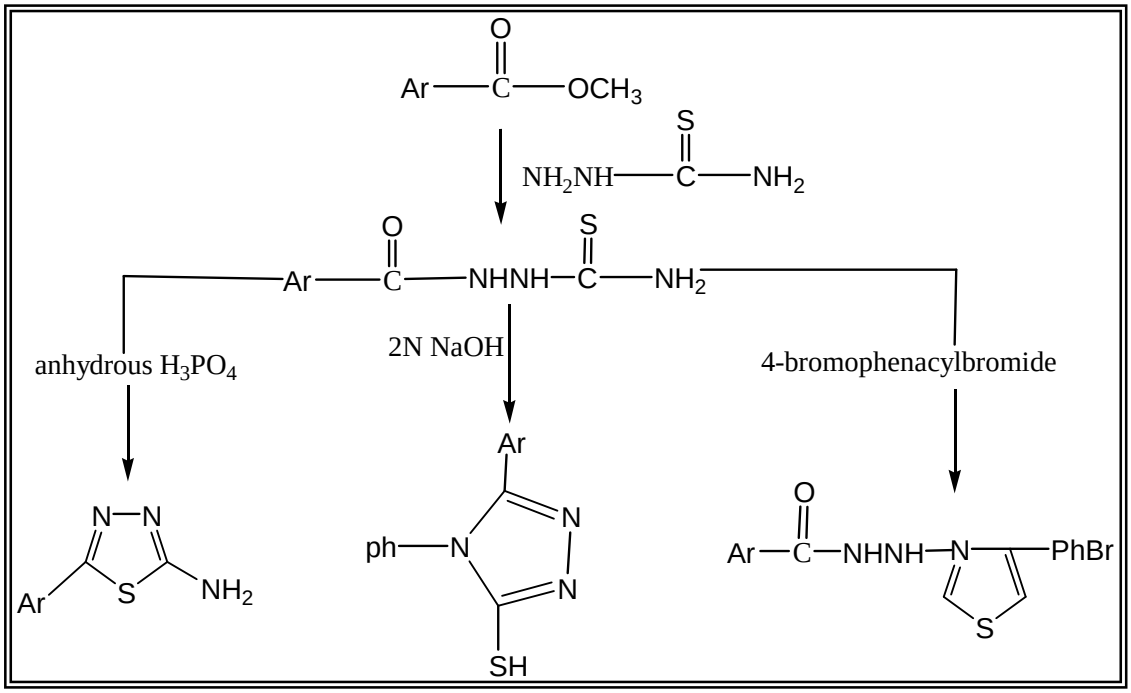
Suggestions for further work:-

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

1-



2-



3-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

2.1 Chemicals:

Chemicals	Company	Purity
p-Hydroxy methylbenzoate	BDH	99%
Isonicotinic acid hydrazide	Fluka	90%
Ethanol (absolute)	BDH	99.9 %
Hydrochloric acid	BDH	37 %
Potassium hydroxide	BDH	85 %
Carbon disulfide	Fluka	99 %
p-Bromophenacylbromide	Fluka	98 %
Phenyl isocyante	Fluka	98 %
Hydrazine Hydrate	Fluka	98 %
Ethylacetoacetate	Fluka	90 %
Acetic acid	Merck	85 %
Chloro acetic acid	Fluka	55 %
Urea	Fluka	99 %
Thiourea	Fluka	80 %
Sodium hydroxide	Merk	56 %
DMSO	Fluka	70%

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.

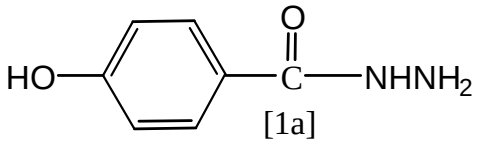
3- Infrared spectra are recorded using Fourier Transform infrared ***SHIMADZU*** (8400) (F.T.IR) infrared spectrophotometer, KBr disc or thin film was performed by Central organization of standardization and quality control.

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

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

2.3.0 Methods:-

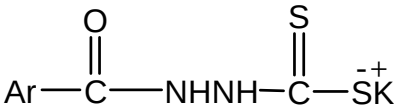
2.3.1 Synthesis of p-hydroxy benzoic hydrazide [1a]:-



[1a]

compound p-hydroxy methylbenzoate [0a] (5g, 0.033mol) was mixed with hydrazine mono hydrate 98% (2.4ml, 0.05mol) was added and refluxed for 2 hours. After cooling the precipitate was filtered and washed with cold water and dried, m.p. (264-266^{0}C), lit [136] (264-266^{0}C), and yield (70%).

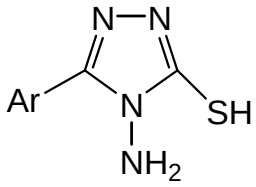
2.3.2 Synthesis of potassium 2-aroyl- di thiocarbazate [2a,2b] [137]:-



[2a,2b]

A mixed of compound [1a] (3g, 0.02mol) or [1b] (2.74g, 0.02mol) was treated respectively with carbon disulfide (3.6ml, 0.06mol) in absolute ethanol (25ml) containing potassium hydroxide (1.68g, 0.03mol) and was then refluxed on a water bath for 1 hour. The solvent was removed and the solid salt which had been formed, cooled, washed by ether, and dried to give pale-yellow crystal of m.p. for [2a] (275-277^{0}C), and for [2b] (275-277^{0}C)while the yield for [2a] is (95.24%) and for [2b] is (90.97%).

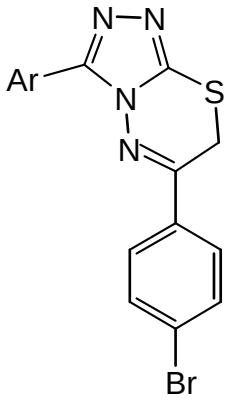
2.3.3 Synthesis of 3-mercapto 4-amino-5-aryl-1,2,4-triazole [3a,3b] [137]:-



[3a,3b]

A suspension of potassium salt [2a] (2.66 g, 0.01mol) or [2b](2.51g, 0.01mol) was treated respectively with excess of hydrazine hydrate 98% (5ml) and refluxed with stirring for 4hours or until the evolution of the hydrogen sulfide was ceased (lead acetate paper);during reflux the color of the reaction mixture changed to green and a homogenous solution resulted . After cooling the reaction mixture was filtered, acidified with 10% HCl to yield a white precipitate which recrystallized from ethanol to give the product, m.p. for [3a] (243-245^{0}C) and for [3b] is (226-228^{0}C), while the yield for [3a] is (96.2%) and for [3b] is (77.72%).

2.3.4 Synthesis of 6-(p-Bromophenyl)-3-aryl-7H-[(1,2,4) - triazolo-(3,4-b) (1,3,4)] thiadiazine [4a,4] [138]:-

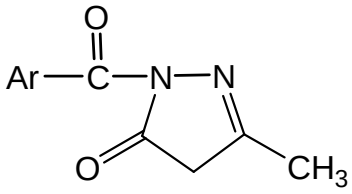


[4a,4b]

A mixture of compound [3a] (0.4g, 0.002mol) or [3b] (0.56, 0.002mol) in absolute ethanol(15ml), p-bromphenacyl bromide (0.65g, 0.002mol)

was added and refluxed for 6hours.Cooling and neutralizing the mixture with aqueous potassium carbonate solution, lead to separate a solid which was filtered , washed with water and recrystallized from ethanol giving pale yellow crystal of m.p. for [4a] (260-262^{0}C) and for[4b] is (248-250^{0}C),while the yield for[4a] is (80.62%) and for [4b] is (60.5%).

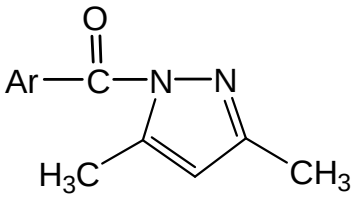
2.3.5 Synthesis of 2-aroyl-5-methyl-2, 4- dihydro pyrazol -3-one [5a, 5b] (139):-



[5a,5b]

A mixture of compound [1a] (0.46g, 0.003mol) or [1b] (0.41, 0.003) was treated respectively with ethylacetoacetate (0.38ml, 0.003mol) in abs. ethanol (15ml) was heated under reflux for 7 hours. After concentration and cooling, the oily product was obtained.

2.3.6 Synthesis of 2-N-aroyl- 3,5-dimethyl pyrazole [6a, 6b] (140):-

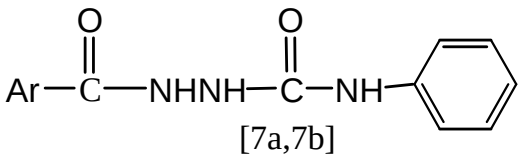


[6a,6b]

A mixture of compound [1a] (0.46g, 0.003mol) or [1b] (0.41g, 0.003mol) was treated respectively with acetyl acetone (0.32ml, 0.003mol) and acetic acid (0.5ml) in abs. ethanol (15ml) was heated under reflux for 7hours.After concentration and cooling, the solid product

that formed was filtered off, and recrystallized from ethanol , the m.p. for [6a] is (158-160^{0}C) and for [6b] is (100-102^{0}C), the yield for[6b] is (99.51%), and for[6b] is(59.26%).

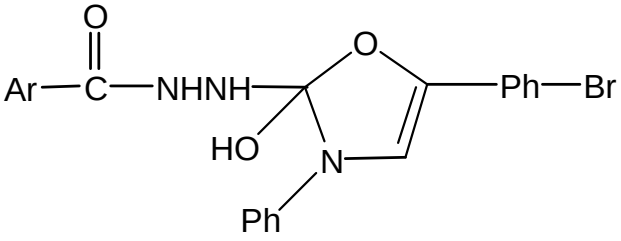
2.3.7 Synthesis of 2-N-aroyl-N`-phenylhydrazinecarbox amide [7a,7b] (141):-



[7a,7b]

A solution of compound [1a] (1.5g, 0.01mol) or [1b] (1.37g, 0.01mol) was treated respectively with absolute ethanol (40ml), phenyl isocynate (1.07ml, 0.01mol) was added with continuous stirring and the mixture was refluxed for 8 hours. The reaction mixture was cooled and formed solid was filtered off, washed with abs. ethanol .The resulting product was recrystallized from ethanol, the m.p. for [7a] (207-209^{0}C) and for [7b] is (218-220^{0}C), the yield for [7a] is (71%) and for [7b] is (58.6%).

2.3.8 Synthesis of N-[(2)-5-(p-bromophenyl)-3-phenyl- 1, 3-oxazol-2(3H)-ylidene]- aryl- hydrazide [8a, 8b] (142):-

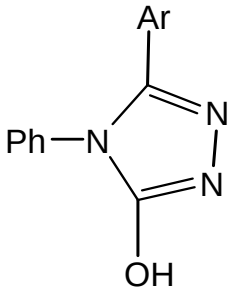


[8a,8b]

A mixture of compound [7a] (0.54g, 0.002mol) and [7b] (0.51g, 0.002mol) was treated respectively with absolute ethanol (15ml),p-bromophenacylbromide (0.56g, 0.002mol) was added. The mixture was refluxed for 8 hours, cooled and neutralized with ammonium hydroxide

solution. The precipitate was filtered off, washed with water, and petroleum ether (80-100) was used for recrystallization, the m.p. for [8a] is (98-100^{0}C) and for [8b] is (113-115^{0}C), the yield for [8a] is (80%) and for [8b] is (88.8%).

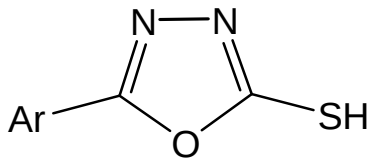
2.3.9 Synthesis of 4-N-phenyl 5-aryl- 1,2,4 -triazol- 3-ol [9a, 9b] (143):-



[9a,9b]

A mixture of compound [7a] (0.54g, 0.002mol) or [7b] (0.51g, 0.002mol) was dissolved in NaOH (18ml, 2N) and refluxed for 4 hours. The reaction mixture was cooled and acidified with 2N hydrochloric acid (pH=4).The precipitate was filtered ,washed with water and recrystallised from ethanol giving the final product, m.p. for [9a] (above 300^{0}C), and for [9b] is (112-114^{0}C), the yield for [9a] is (59.5%),[9b](93.82%).

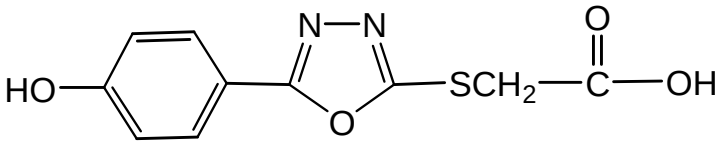
2.3.10 Synthesis of 2-mercapto -5-aryl -1,3,4-oxadiazole [10a,10b] (144):-



[10a,10b]

A mixture of compound [1a] (3g, 0.02mol) or [1b] (2.74g , 0.002 mol) was treated respectively with ethanol (30ml) at ^{0}C, potassium hydroxide (1.12g, 0.02mol) and carbon disulfide (2.4ml ,0.04mol) was added respectively. The mixture was heated at reflux for 7 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) to give the desired product, the m.p. for [10a] is (218-220) and for [10b] is (218-220), the yield for [10a] is (78.43%) and for [10b] is (55.87).

2.3.11 Synthesis of {[5-(p-hydroxy phenyl)-1,3,4-oxadiazol-2-yl]} thioacetic acid [11a](145):-

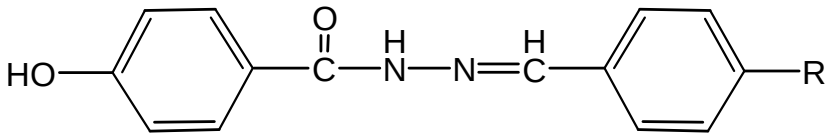


[11a]

To (1.5g, 0.0077mol) of 2-mercapto-5-(p-hydroxy phenyl)-1,3,4-oxadiazole [10a] in 10% sodium hydroxide(8ml) was added (0.73g, 0.007mol) of mono chloroacetic acid in 10% sodium hydroxide(12ml). The reaction mixture was heated under reflux for 3 hours. The reaction mixture was cooled, acidified with conc. hydrochloric acid and ice –water

to precipitate the acid. The obtained compound [11a] was filtered, washed with cold distilled water and, dried, the m.p for [11a] is (140-142^{0}C), yield (29.4%).

2.3.12 Synthesis of N-p-substituted benzylidine – p-hydroxy benzohydrizide [12a-14a] (146):-



[12a,13a,14a]

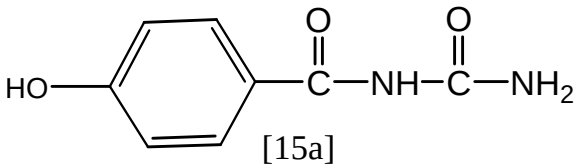
R=p-NO_2,p-HO,p-$(CH_3)_2$N.

A mixture of carbohdrazide [1a] (0.5g, 0.0033mol), absolute ethanol (20ml) and appropriate aldehydes (0.0033mol) were refluxed for (2) hours. After cooling at room temperature the precipitate was filtered and dried. The products were recrystallized from ethanol. The physical properties for the synthesized compound are given in table, (2-2).

Table (2-2): Physical data of compounds [12a-14a]

Comp. No.	R	Molecular formula	Molecular weight g.mol^{-1}	M.P/^{0}C	% Yield
12a	**NO_2**	**$C_{14}H_{11}N_3O_4$**	**185**	**205-207**	**95.4**
13a	**OH**	**$C_{14}H_{12}N_2O_3$**	**256**	**238-240**	**50.5**
14a	**$N(CH_3)_2$**	**$C_{16}H_{17}N_2O_2$**	**283**	**240-242**	**99.10**

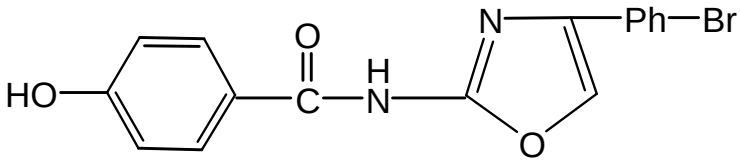
2.3.13 Synthesis of N-(aminocarbonyl)-p-hydroxy benzamide [15a] (147):-



[15a]

A mixture of p-hydroxy methyl benzoate [0a] (0.5g, 0.0033mol) in absolute ethanol (20ml), urea (0.2g, 0.0033mol) was added. The mixture was refluxed for 5hours. After cooling and filtering, the white precipitate was obtained, m.p. for [15a] (99-100^{0}C), yield (99.64%).

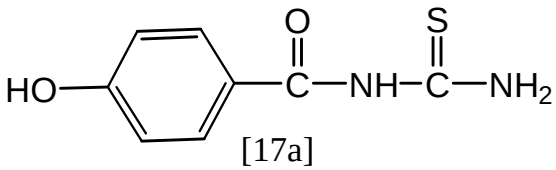
2.3.14 Synthesis of N-[4-(p-bromophenyl)-1, 3-oxazol-2-yl]-p-hydroxy benzamide [16a] (142):-



[16a]

Compound [16a] was prepared by the same method described for the preparation of compound [8a]. Yellow precipitate was obtained, m.p. for [16a] (238-240^{0}C), yield (80.58%).

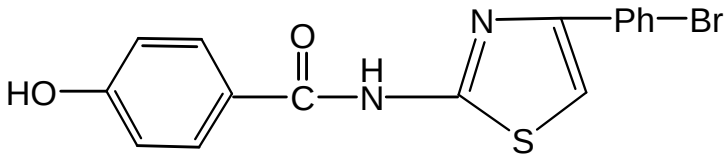
2.3.15 Synthesis of N-(aminocarbonothioyl)-p- hydroxy benz amide [17a] (147):-



[17a]

Compound [17a] was prepared by the same method described for the preparation of [15a], white preparation was obtained, m.p.108-110, yield 97.7%.

2.3.16 Synthesis of N-[4-(p-bromophenyl]-1 3-thiazol-2-yl]-p-hydroxy benzamide [18a] (142):-



[18a]

Compound [18a] was prepared by the same method described for the compound [8a]. Yellow precipitate was obtained, m.p. for [18a] (248-250^{0}C) yield (90.7%).

Table :(2.3) Physical properties of the synthesized compound:

Cod. No.	Molecular formula	Molecular weight (g/mol)	Time reaction (hr)	Yield (%)	M.P (^{0}C)	Color
2a	$C_8O_2N_2S_2KH_7$	266	1	95.24	264-266	Pale yellow
2b	$C_7N_3OS_2KH_6$	251	1	90.97	173	Pale yellow
3a	$C_8H_8N_4OS$	208	4	96.2	243-245	white
3b	$C_7H_7N_5S$	193	4	77.72	226-228	white
4a	$C_{16}HON_4SBr$	387	6	80.62	260-262	Pale yellow
4b	$C_{15}H_{10}N_5SBr$	372	6	60.5	248-250	Pale yellow
5a	$C_{11}H_{10}O_3N_2$	218	7	------	-----	colorless
5b	$C_{10}H_9O_2N_3$	203	7	82.3	86-88	colorless
6a	$C_{12}H_{12}O_2N_2$	216	7	99.51	158-160	colorless
6b	$C_{11}H_{11}ON_3$	201	7	59.26	100-102	colorless
7a	$C_{14}H_{12}O_3N_3$	271	3	71	207-209	white
7b	$C_{13}H_{11}O_2N_4$	256	3	58.6	218-220	white
8a	$C_{21}H_{17}O_3N_3Br$	439	8	80	98-100	brown
8b	$C_{20}H_{16}O_2N_4Br$	424	8	88.8	113-115	brown
9a	$C_{14}H_{11}O_2N_3$	253	3	59.5	above 300	Pale yellow
9b	$C_{11}H_{10}ON_4$	214	3	93.82	112-114	white
10a	$C_8H_6N_2S$	194	7	78.4	218-220	white
10b	$C_7H_5N_3O_3O_5$	179	7	55.87	218-220	yellow
11a	$C_{10}H_8N_2O_4S$	252	3	29.4	240-242	white
12a	$C_{14}H_{11}O_4\ N_3$	285	2	95.4	above 300	yellow
13a	$C_{14}H_{12}O_3N$	256	2	50.5	238-240	Pink
14a	$C_{16}H_{17}N_3O_2$	283	2	99.1	240-242	yellow
15a	$C_8H_8N_2O_3$	180	4	99.64	98-100	white
16a	$C_8H_8N_2O_3$	359	8	80.58	234-240	yellow
17a	$C_8H_8N_2O_2S$	196	4	97.7	108-110	white
18a	$C_8H_8N_2O_2S$	343	8	90.7	248-250	yellow

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Summary

The scheme of this work involves synthesis of different five and six membered heterocyclic rings starting from isonicotinic acid hydrazide and *p*-hydroxy methylbenzoate .

This work is divided into seven different parts and the reaction steps for part are summarized in the comprehensive scheme.

First part:

This part involved the synthesis of fused thiadiazine ring derived from the cyclization of (-NH_2 and –SH) of the 3-mercapto-4-amino-5-aryl-1,2,4-triazole by treatment with *p*-bromophenacyl bromide. The triazole derivatives were synthesized by treating the previous acid hydrazides with carbon disulfide. Scheme.

Second part:

This part involves the synthesis of pyrazole and pyrazolone derivatives from the reaction of (-NH-NH_2) group of the starting materials with acetylaceton, ethylacetoactate. Scheme.

Third part:

This part involves the synthesis of Δ^4-oxazoline and triazole derivatives via the reaction of the acid hydrazides with phenyl isocyanates and cyclization of the resulted products with *p*-bromophenacyl bromide and with 2N NaOH. Scheme.

Fourth part:

This part involves the synthesis of oxadiazole derivatives from the reaction of (-NH-NH_2) group of the starting materials with carbon disulfide. Scheme.

Five part:

This part involved the synthesis of Schiff base derivatives from the reaction of (-NH-NH_2) group of the starting materials with different aldehydes. Scheme.

Six part:

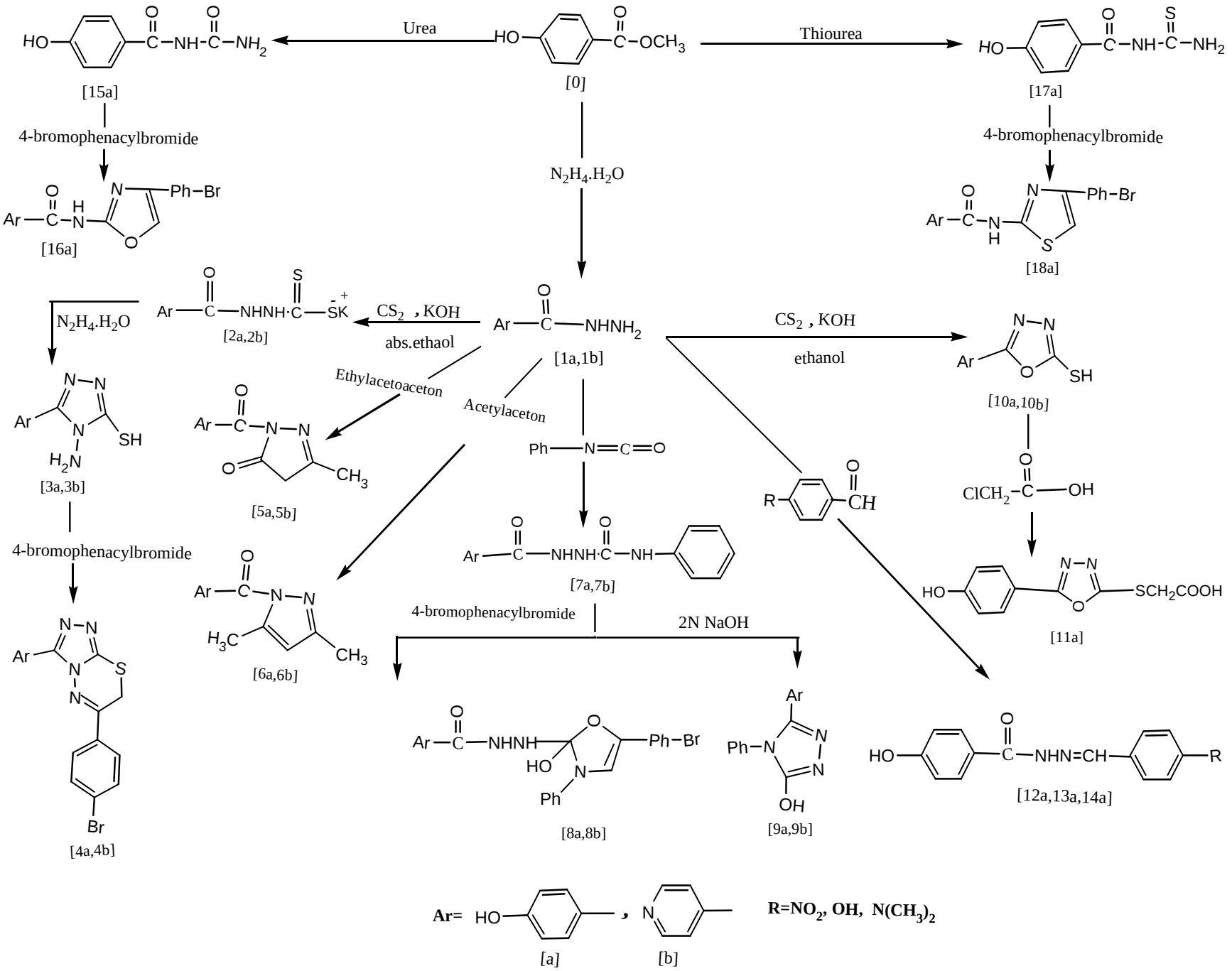
This part involved the synthesis of oxazole and thiazole derivatives via the reaction of *p*-hydroxy methylbenzoate with urea and thiourea and cyclization of the resulted products with p-bromophenacyl bromide. Scheme.

Seven part:

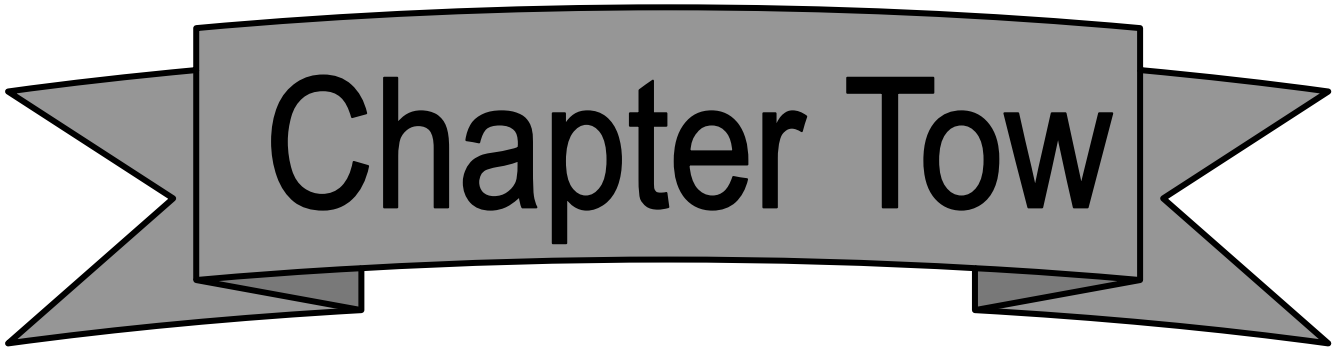
This part deals with the study of antibacterial activities of some of the synthesized compounds and comparing these activities with that of the starting materials. These activities were determined ***in vitro*** using disc diffusion method against three pathogenic strains of bacteria (***Escherichia Coli and staphylococcus aureus***), the results revealed that some of these compounds showed measurable activity.

III

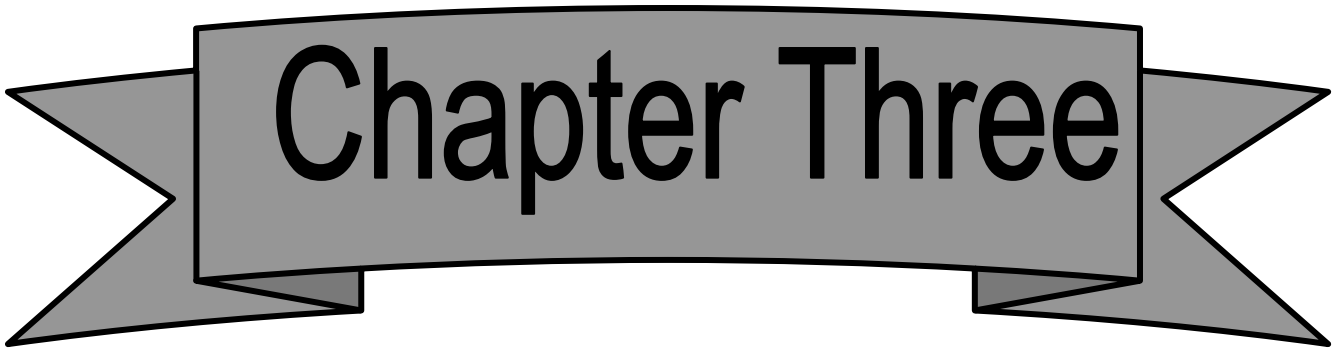
comprehensive scheme



Introduction



Exeperemental



Results&Discussion

Reference

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

Synthesis of Triazole, Thiadiazine, Pyrazole, Oxazoline, Oxadiazole, Oxazole, and Thiazole Derivatives and study 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 Master of Science in Chemistry

By
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B.Sc. Al-Nahrain University (2004)

March *Rabiea El-Awal*

2007 1428

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

تحضير مشتقات
ترايازول، ثاياديازين ، بايرازول، اوكسازولين، اوكسادايازول، اوكسازول، وثايزول ودراسة الفعالية البايولوجية لبعضها

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

من قبل
رشا محمد فوزي عبد الرحمن

بكالوريوس علوم كيمياء – جامعة النهرين (٢٠٠٤)

آذار
٢٠٠٧م

ربيع الأول
١٤٢٨هـ

Supervisor certificate

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: **Signature:**

Assistant Professor **Assistant Professor**

Dr. Sawsan H .Shawkat **Dr. Ibtisam K.Jassim**

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

Signature:

Head of the Chemistry Department

College Science Al-NahrainUniversity

Examining Committee's Certification

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

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Member
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الإهداء

إلى طيب الجنّة وشذاها... خيمة الحُب والحنان

أُمي الغالية

إلى القلب الكبير... ورمز التضحية

والدي الحبيب

إلى من كانوا لي سنداً في كلّ لحظة وثانية ... وكانوا أسوار

المحبة التي تُحيطني بالحُب والوفاء

أخواتي وآخي الأعزاء

إلى رفاقي في كل دروب العلم المتباينة

زميلاتي وزملائي

إلى كلّ من أُحب

أهدي ثمرة جهدي

رشا

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Finally, to all those who helped in one way or another, I would like to express my warmest gratitude.

Rasha 2007

بسم الله الرحمن الرحيم

نَرْفَعُ دَرَجَاتٍ مَنْ نشاء وَفَوْقَ كُلِّ ذي عِلْمٍ

عَلِيمٌ

صدق الله العظيم

سورة يوسف

جزء من أية (٧٦)

خـــلاصـــــــة الرسالة

يتضمن موضوع البحث في هذه الرسالة تحضير مركبات حلقية خماسية وسداسية غير متجانسة متنوعة ابتداء من باراهيدروكسي مثيل بنزوايت و أزونيكوتينك أسيد هيدرازايد. وقد تم تقسيم هذا العمل الى سبعة اقسام :-

القسم الاول

يتضمن هذا القسم تحضير مركبات حلقية غير متجانسة مندمجة الحلقة مشتقة من الغلق الحلقي لمجموعتي($-SH,-NH_2$) لمركبات ٣-ميركابتو-٤-امينو-٥-(اريل)-١،٢،٤-ترايازول باستعمال بارا- بروموفيناسيل بروميد . ان مشتقات الترايازول المستعملة في هذا القسم حضرت من تفاعل هايدرازيدات الحامض المذكورة انفا مع ثنائي كبريتيد الكاربون . وللحصول على هذه المشتقات اتبعت الخطوات الموضحة في المخطط النهائي .

القسم الثاني

يتضمن هذا القسم تحضير مركبات بايرازول و البايرزولون المشتقة من تفاعل مجموعة ($-NH-NH_2$) للمواد الابتدائية المذكورة انفا مع(الاستيل اسيتون ، الاسيتو اثيل اسيتيت) . وللحصول على هذه المشتقات اتبعت الخطوات الموضحة في المخطط النهائي .

القسم الثالث

يتضمن هذا القسم تحضير مركبات اوكسازولين و ١،٢،٤-ترايازول معوضة النتروجين بوساطة التفاعل بين هايدرازيدات الحامض مع فنيل ايزو سيانيد حيث تتم عملية الغلق الحلقي للنواتج الحاصلة باستعمال بارا- بروموفيناسيل بروميد و ٢-

نورمالي من هيدروكسيد الصوديوم. وللحصول على هذه المشتقات اتبعت الخطوات الموضحة في المخطط النهائي .

القسم الرابع

يتضمن هذا القسم تحضير مركبات ٤،٣،١-اوكساديازول المشتقة من تفاعل مجموعة ($-NH-NH_2$) للمواد الابتدائية المذكورة أنفا مع ثنائي كبريتيد الكاربون. وللحصول على هذه المشتقات اتبعت الخطوات الموضحة في المخطط النهائي .

القسم الخامس

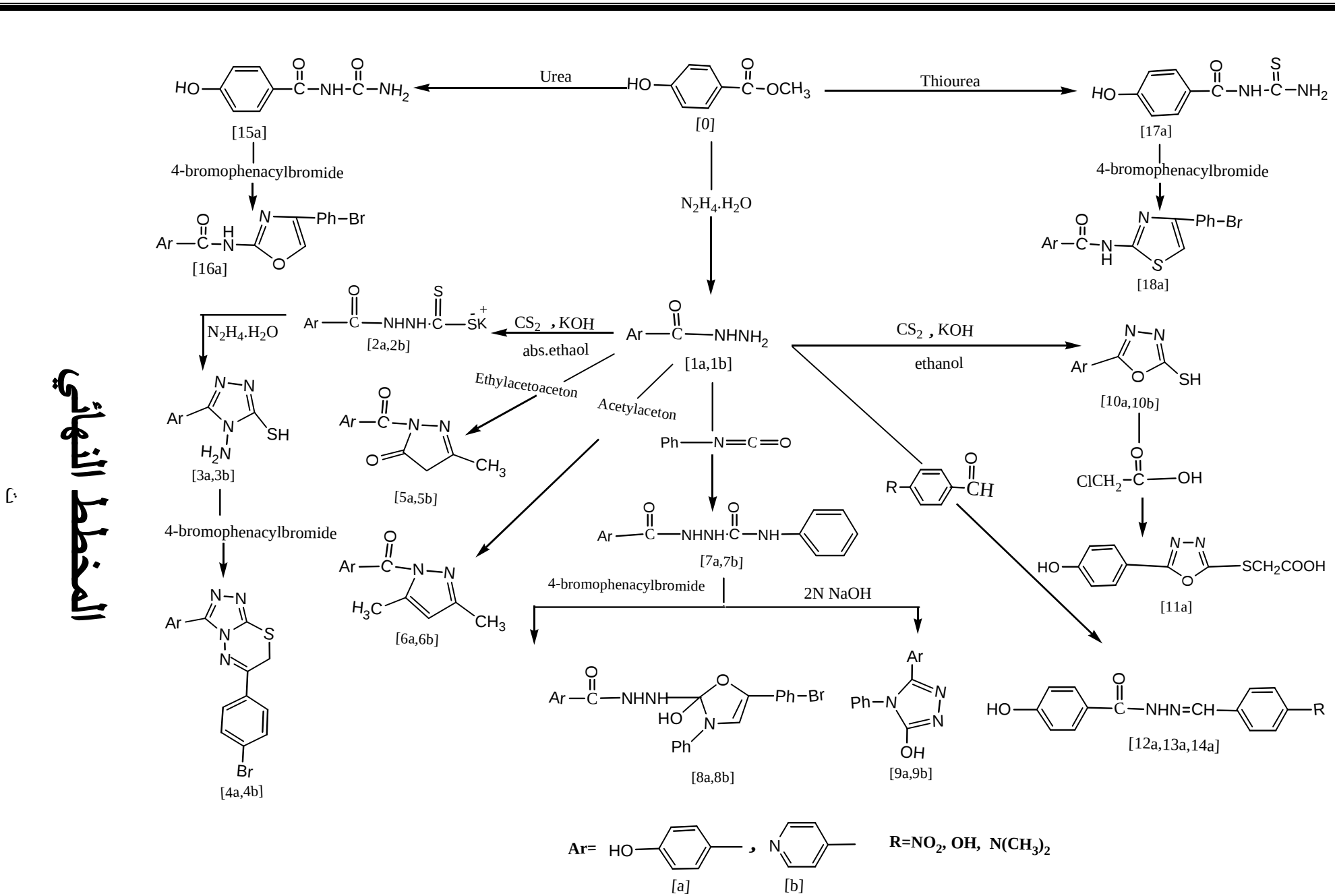
يتضمن هذا القسم تحضير مركبات قواعد شيف المشتقة من تفاعل مجموعة ($-NH-NH_2$) للمواد الابتدائية المذكورة أنفا مع الديهايدات مختلفة. وللحصول على هذه المشتقات اتبعت الخطوات الموضحة في المخطط النهائي .

القسم السادس

يتضمن هذا القسم تحضير مركبات اوكسازول و ثايزول معوضة النتروجين بوساطة التفاعل بين باراهيدروكسي مثيل بنزوايت مع كل من اليوريا و الثايويوريا حيث تتم عملية الغلق الحلقي للنواتج الحاصلة باستعمال بارا- برومو فيناسيل بروميد. وللحصول على هذه المشتقات اتبعت الخطوات الموضحة في المخطط النهائي .

القسم السابع

يتضمن هذا القسم اختبار الفعالية البايولوجية لبعض المركبات المحضرة ضد نوعين من البكتيريا وقد دلت النتائج المستحصلة بان بعض المركبات اظهرت فعالية بايولوجية عالية كما هو عليه في الجدول (٣-١٢) .



المخطط النهائي