Acknowledgement

Above all else, I want to express my great thanks to ALLAH for the uncountable gifts and for helping me to present this thesis.

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Abbass 2007

Chapter One

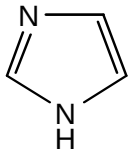
Introduction

1.1 Heterocyclic compounds:

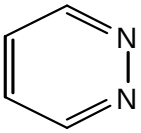
Heterocyclic systems are widespread occurrence in nature, particularly in such natural products as nucleic acids, plant alkaloids, and chlorophyll [(1)].

Heterocyclic compounds are considered one of an important type of organic compounds due to their implication in drugs and industrial studies. A variety of atoms, such as N, O, S, P, Si and As can be incorporated into the ring structures [(2)].

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 [(3)].



1,3-diazole
[1]



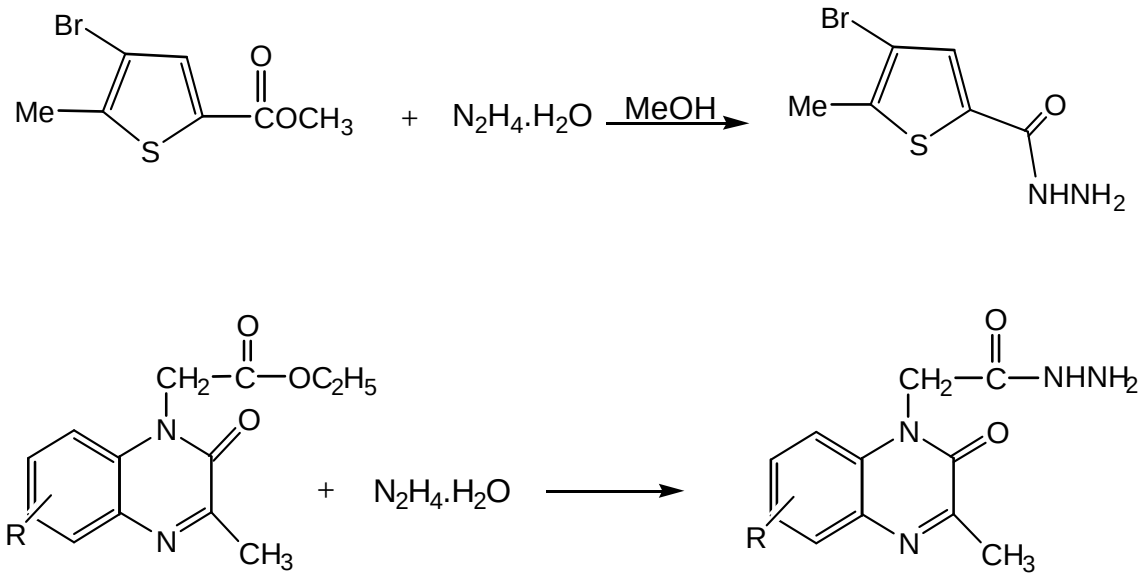
1,2-diazine
[2]

1.2.0 Hydrazide derivatives:

Hydrazides and thiosemicarbazide derivatives attracted a lot of attention because they are considered as intermediates to synthesize several compounds such as ***Schiff*** bases [(4)], oxadiazole [(5)], thiadiazole [(6)], triazole [(7)] and pyridazine [(8)] derivatives which all were reported to possess biological activities. The structural formula for this type of compounds is (RCONHNH-).

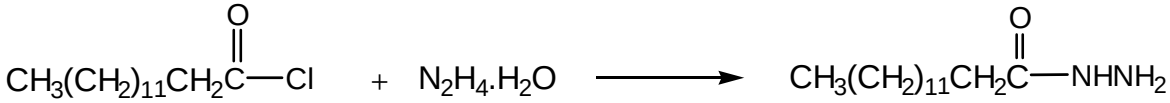
1.2.1 Synthesis of hydrazide derivatives:

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 [9, 10] as shown below:



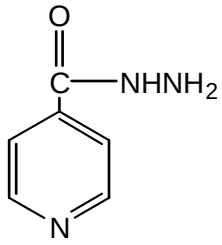
R = 6-Benzoyl, 7-Benzoyl

Acid hydrazide derivatives can also be synthesized from condensation reaction of carboxylic acid chloride with hydrazine hydrate [11].



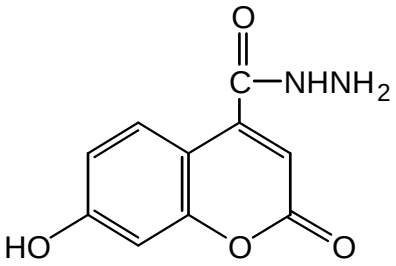
1.2.2 Hydrazide derivatives uses:

Carbohydrazides were found to be useful as medicaments, especially in the treatment of inflammatory, respiratory diseases[12] and tuberculosis[13] such as isoniazide [3].



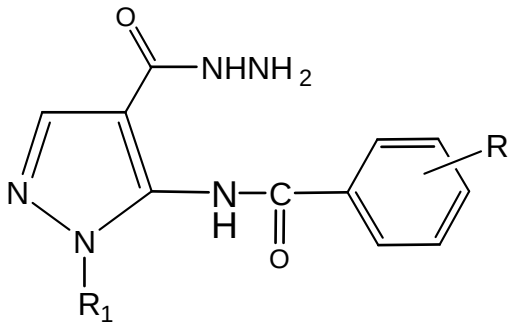
[3]

A number of natural and synthetic coumarin (7-hydroxy-2-oxo-2*H*-chromen-4-yl)-acetic acid hydrazide [4] have been reported to exert notably antimicrobial [(14)].



[4]

Some of carboxylic acid hydrazides were reported to have anti bacterial activities as compound [5] [(15)].



[5]

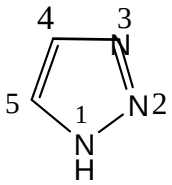
R1	R
Ph	H
Ph	p-Cl
CH_3	o-NO_2
CH_3	p-NO_2

1.3.0 1,2,4-Triazoles:

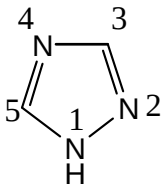
1,2,4-Triazoles is one of a class of organic heterocyclic compounds containing a five membered di-unsaturated ring structure composed of three nitrogen atoms and two non adjacent carbon atoms. 1,2,4-Triazole is a white to a pale yellow crystalline solid with a weak odor, soluble in water and alcohol.

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

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



1,2,3-triazole

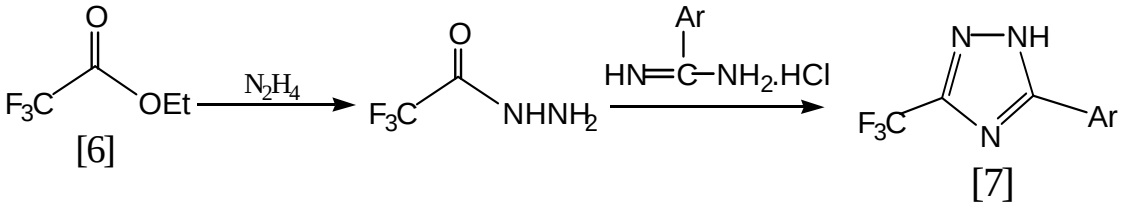


1,2,4-triazole

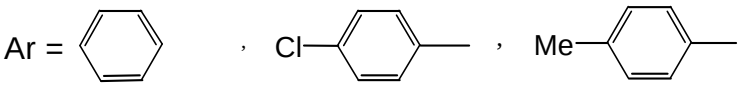
1,2,3-Triazole was originally called υic-(vicinal) triazoles, and 1,2,4-triazole known as sym-(symmetrical) triazoles [16].

1.3.1 Synthesis of 1,2,4-triazoles:

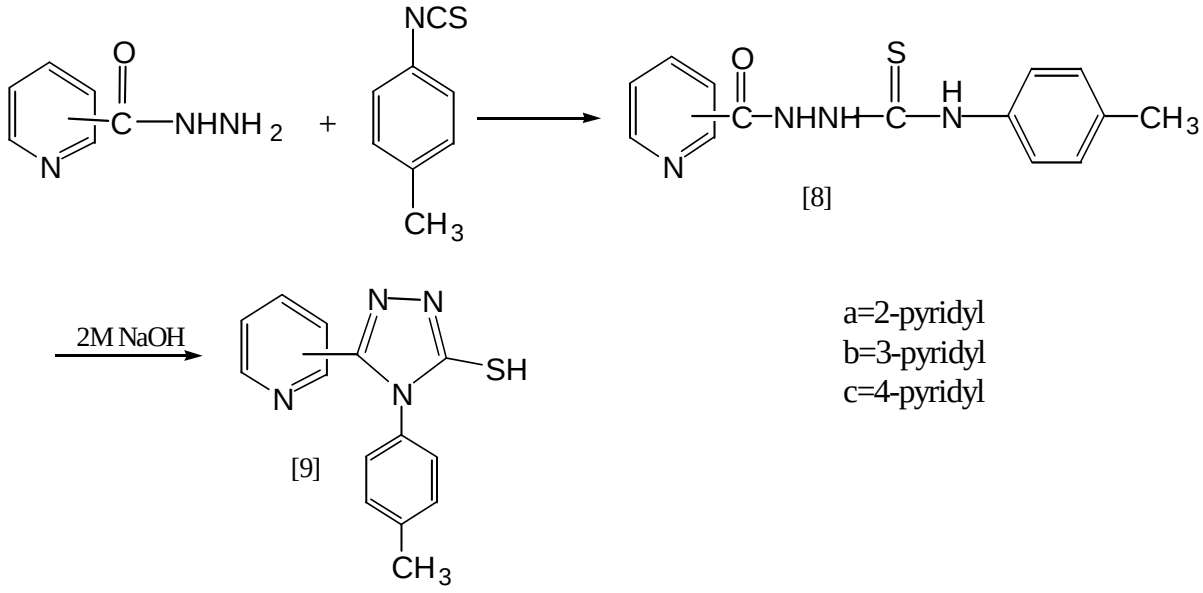
Funabiki et. al.,[17] found that the three component condensation reaction of ethyltrifluoroacetate [6], hydrazine and amidine hydrochloride in the presence of sodium hydroxide in tetrahydrofuran at reflux temperature gave the corresponding 3-trifluoromethyl-5-substituted 1,2,4-triazoles [7]:



[6] [7]



Zamani et. al.,[18] found that the reaction of hydrazide with 4-methyl phenylisothiocyanate afforded the respective thiosemicarbazides [8]. Further cyclization of [8] with 2M sodium hydroxide solution to the formation of 2,4-dihydro-4-(4-methylphenyl)-6-(isomeric pyridine)-3*H*-1,2,4-triazole [9]:

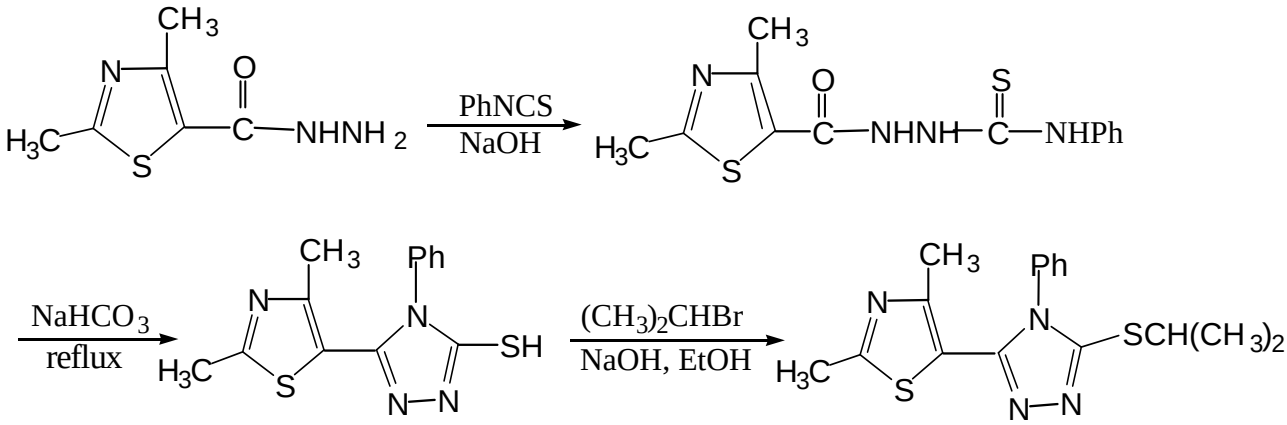


[8]

[9]

a=2-pyridyl
b=3-pyridyl
c=4-pyridyl

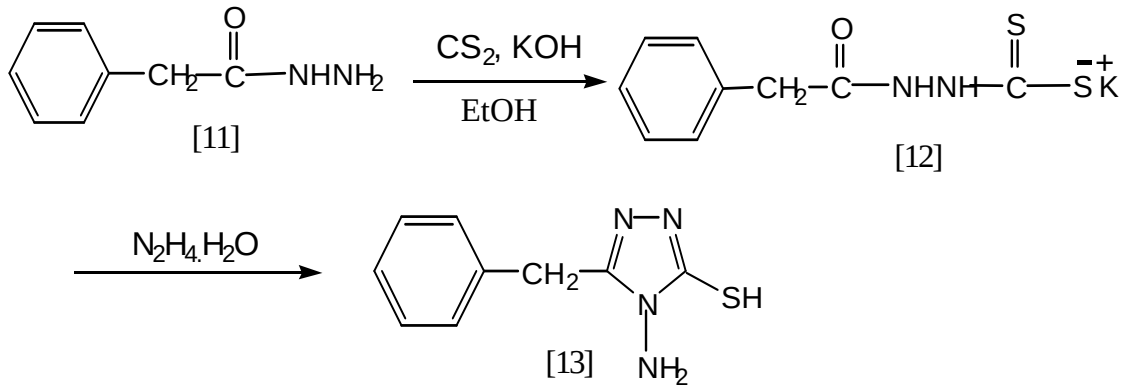
Shafiee et. al.,[19] synthesized 3-(2,4-dimethyl-5-thiazolyl)-4- phenyl -5-isopropyl-thio-4*H*-1,2,4-triazole [10]. The newly synthesized compound was tested for its anticonvulsant activity.



[10]

Caniz et. al.,[20] found that the reaction of phenyl acetic acid hydrazide [11] with carbon disulfide in ethanolic potassium hydroxide afforded the potassium-3-(phenyl acetyl) dithiocarbazate [12].

The compound [12] gave 4-amino-5-benzoyl-4*H*-1,2,4-triazole-3-thiol [13] when reacted with hydrazine hydrate under reflux in solution:



[11] [12] [13]

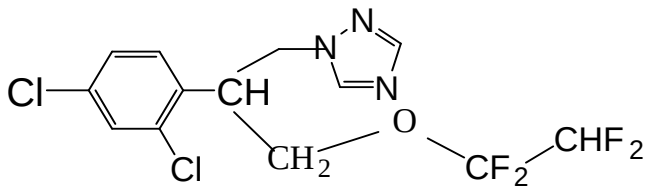
1.3.2 1,2,4-Triazole uses:

The azole moiety is an important and frequent insecticidal, agrochemical structural feature of many biologically active compounds such as tetraconazole [21] [14].

Tetraconazole is broad-spectrum systemic fungicide with protective, curative and eradicant properties.

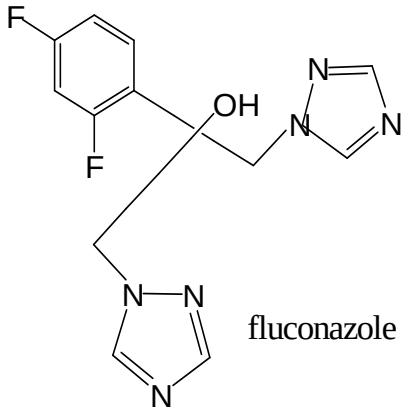
They are important tools against diseases of turfgrasses, vegetables, citrus, field crops and ornamental plants[22].

In addition, they are applied as foliar sprays and seed treatments, but are diverse in use, as they may be applied as protectant or curative treatments [23].

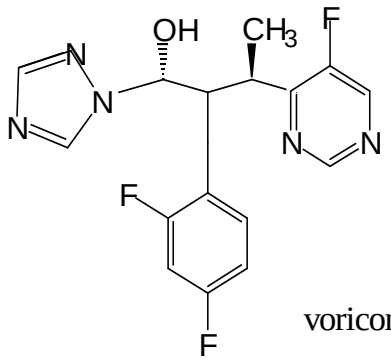


[14]

Several compounds, figure (1-1), containing 1,2,4-triazole rings are well known as drugs. For example fluconazole is used as an antimicrobial drug [24], while voriconazole is a new triazole derivative with broad anti-fungal activity. The approved indications are treatment of invasive aspergillosis, treatment of candidemia in non-neutropenic patients and treatment of fluconazole-resistant serious invasive *Candida* infections (including *C.Krusei*) [25] .



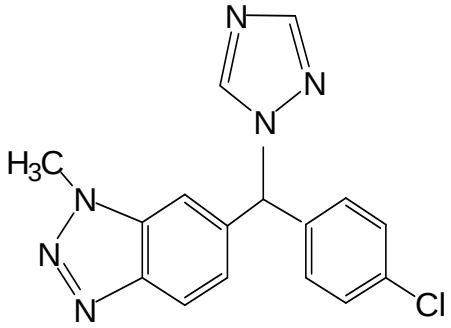
fluconazole



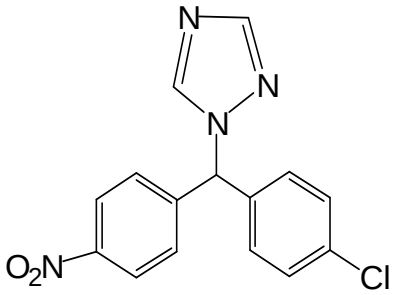
voriconazole

Figure (1-1)

In addition, it was reported that, compounds having triazole moieties, such as vorozole and letrozole, figure (1-2), are non-steroidal drugs used for the treatment of cancer [26].



vorozole

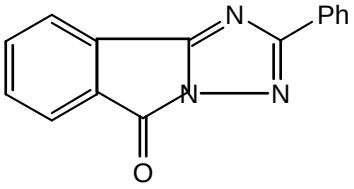
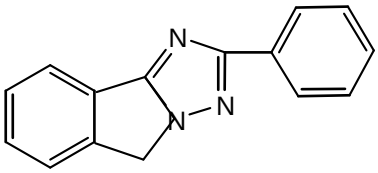
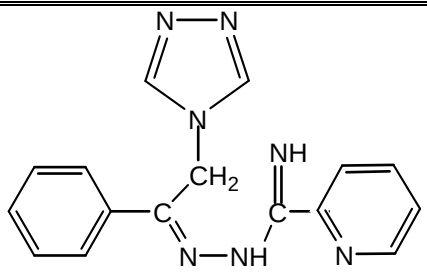
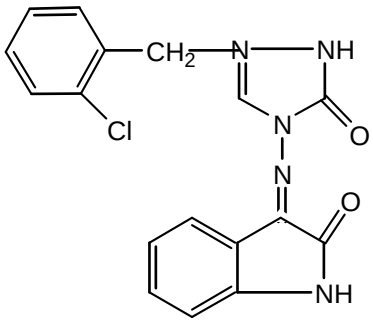
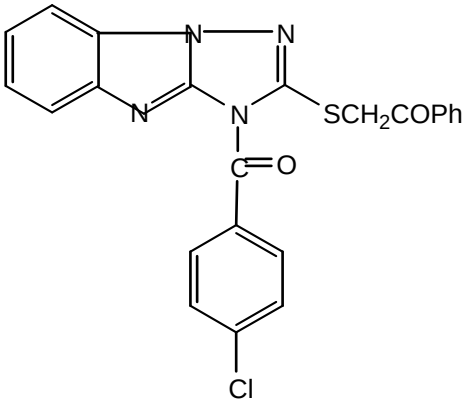


letrozole

Figure (1-2)

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

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

No.	Compound name	Structure	Biological activity	Ref.
1	3-Phenyl-5*H*-1,2,4-triazolo [5,1-a]isoindol-5-one		Anti-inflammatory agent	27
2	3-Phenyl-5*H*-1,2,4-triazolo [5,1-a] isoindole		Anti-gestational agent	28
3	N'-[1-Phenyl-2-(1*H*-1,2,4-triazol-1-yl)-ethylidene]-pyridine-2-carboxamidrazone		Antifungal activity	29
4	3-[3'-(o-Chlorobenzyl)-4',5'-dihydro-1'*H*-1',2',4'-triazol-5'-on-4'-yl]-imino isatin		Antibacterial activity	30
5	1-Acetyl(tosyl)-2-alkylthio-1,2,4-triazolo[2,3-a]bezimidazole		Analgesic activity	31

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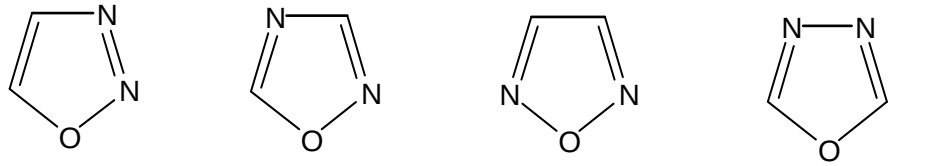
1.4.0 Oxadiazoles:

Oxadiazoles are five membered aromatic ring compounds with three heteroatoms, one oxygen and two nitrogen atoms, four isomeric type are known [32].

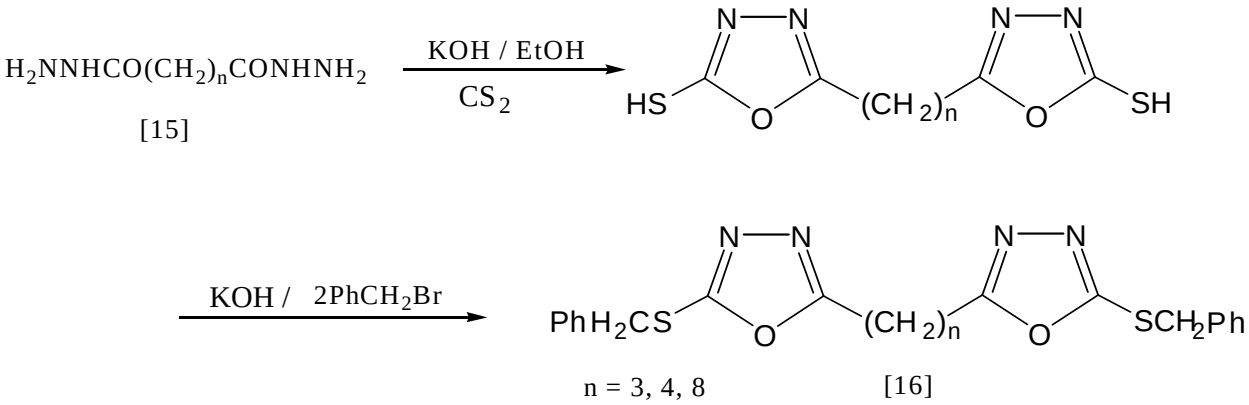


1,2,3-oxadiazole 1,2,4-oxadiazole 1,2,5-oxadiazole 1,3,4 -oxadiazole

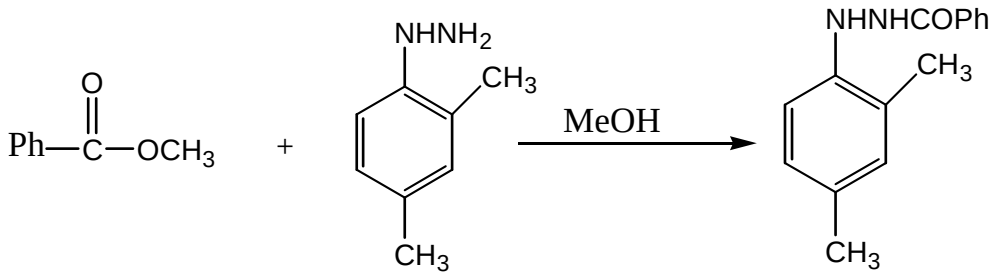
1.4.1 Synthesis of 1,3,4-oxadiazoles:

Several methods have been used for the synthesis of these kinds of compounds.

Maslate et. al.,[33] synthesized a series of new 1,3,4-oxadiazole derivatives from alkanedioc acid dihydrazide [15], as 5,5'-dibenzyl thio-bis-[1,3,4-oxadiazol-2-yl] alkane [16] was prepared by treatment of acid dihydrazide with CS_2 in alcoholic sodium hydroxide solution followed by addition of KOH and benzyl bromide.

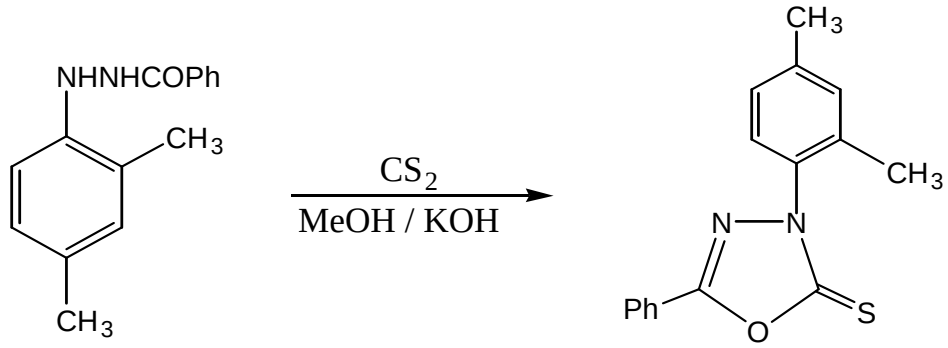


Refluxing of methyl benzoate with 2,4-dimethyl phenyl hydrazine afforded the intermediate acid hydrazine [17]:



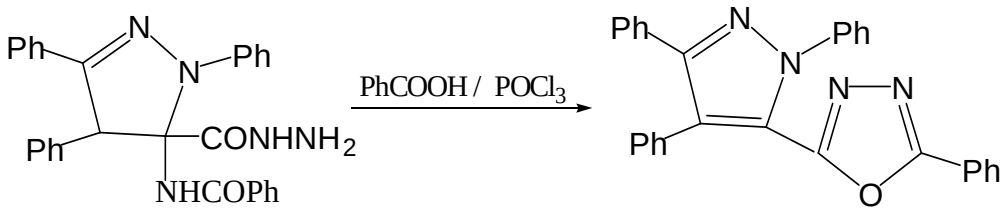
[17]

The compound [17] gave 5-phenyl-3-(2,4-dimethyl phenyl)-1,3,4-oxadiazole-2-thione [18] when reacted with carbon disulfide in methanol with presence of potassium hydroxide [(34)].



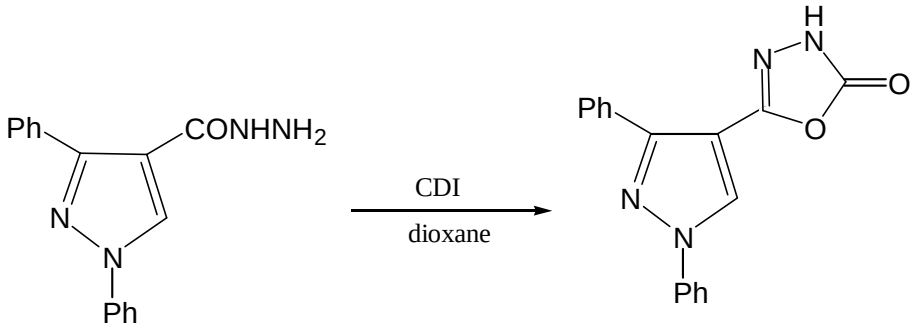
[18]

Mansour et. al.,[(35).] found that the three component condensation reaction of 5-benzolylamino-1,3,4-triphenyl-2-pyrazoline-5-carbohydrazide [19], benzoic acid and phosphorus oxychloride at reflux temperature gave the corresponding 2-(1,3,4-triphenyl pyrazol-5-yl)-5-phenyl-1,3,4-oxadizole [20].



[19] [20]

Farghaly and El-Kashef [36] found that 5-(1,3-diphenyl-1*H*-pyrazol-4-yl) [1,3,4] oxadiazole-2(3*H*)-one [22] was obtained from the reaction of N,N'-carbonyldiimidazole (CDI) with 1,3-diphenyl-1-*H*-pyrazole-4-carboxylic acid hydrazide [21].

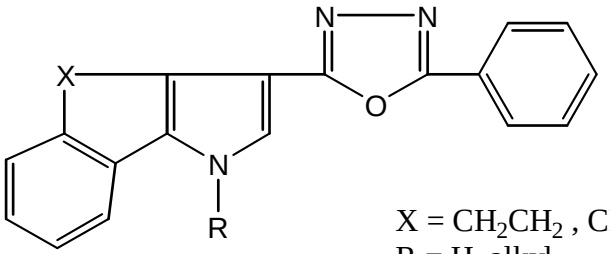


[21] [22]

1.4.2 1,3,4-Oxadiazole uses:

1,3,4-Oxadiazoles exhibit relevant biological properties and a wide varieties of applications, in particular as active compounds in both medicine and agriculture [37].

Cancer is the second leading cause of death in industrialized nations. Cancer chemotherapy commonly involved the use of cytotoxic agents that destroy rapidly dividing cells. A series of compounds have synthesized of general structure [23] was used against 60 tumor cell lines derived from nine cancer cell types. Biological results showed a very interesting anti-tumor activity in particular against leukemia, colon and breast cancer [38].



X = CH_2CH_2 , CH_2 , CH=CH
R = H, alkyl

[23]

Also, some 2,5-disubistituted-1,3,4-oxadiazoles have been reported to show antitubercular agents [39], anti-inflammatory[40], analgesics [41], fungicidal [42] and hypoglycemic [43].

In addition, it was reported that, compounds having oxadiazole moieties, such as symmetrical 2,5-bis (2,4-dichloro phenyl)-1,3,4-oxadiazole and its analogues have been found to be effective insecticide against houseflies, face flies and horn flies.

Also retarding the development of larvae of a number of Lepidoptera [44].

1.5.0 Pyrazole:

Pyrazole is a 1,2-diazole, and as its name implies, it may be considered as an azapyrrole. The dimensions (A^o) of the planar molecular illustrated in figure (1-3) [45].

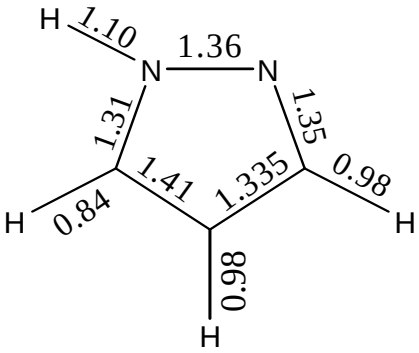
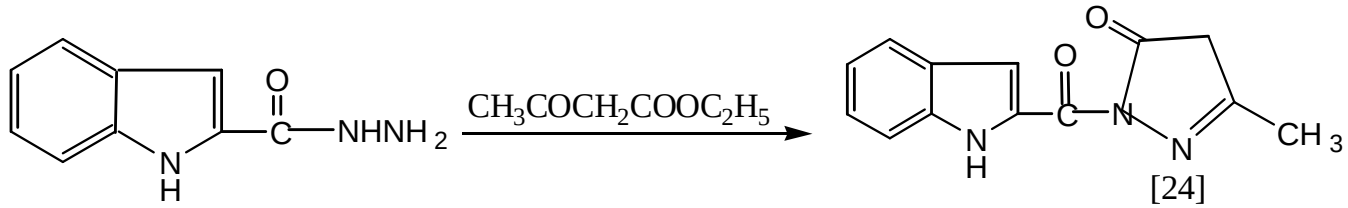


Figure (1-3): Bond length (A^o) in pyrazole

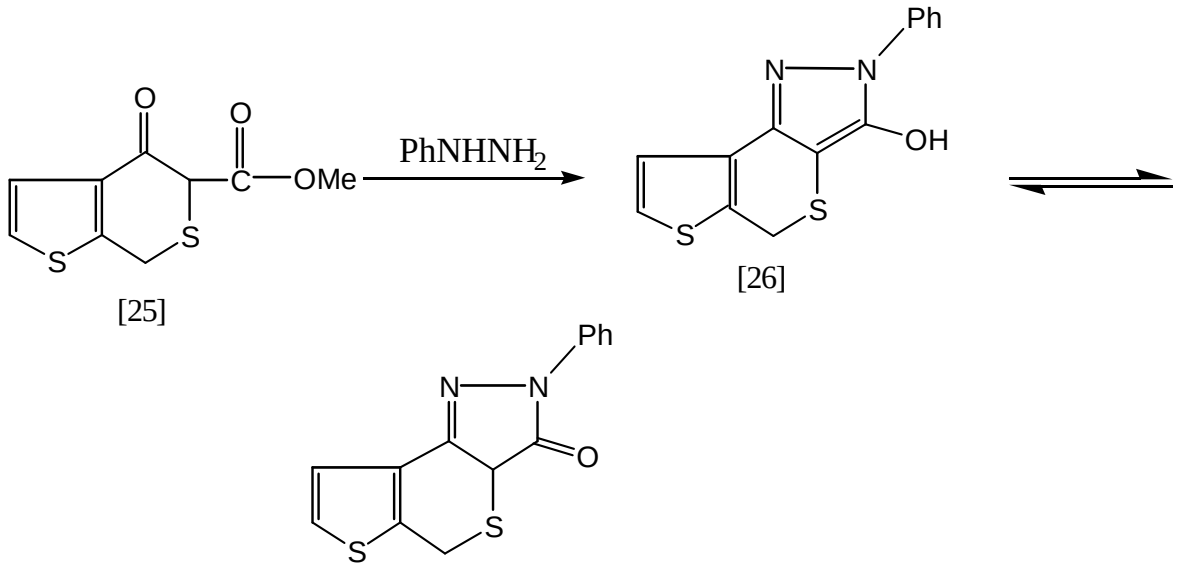
1.5.1 Synthesis of pyrazolones:

Fahmy et. al.,[46] found that the reaction of 2-indol carbohydrazide with ethyl acetoacetate gave 2-[3-methyl-5-oxo -pyrazolin-1-yl] carbonyl indole [24]:



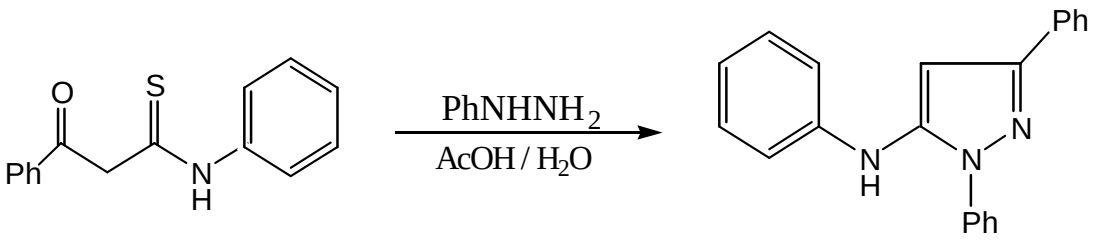
[24]

Sekhar et. al.,[47] found that the β-oxo ester [25] reacted smoothly with phenyl hydrazine in hot methanol to afford the tricyclic compounds 3-hydroxy-2-phenyl-2,5-dihydrothieno[3',4':4,5] thiopyrano [3,2-c] pyrazole [26] in 75% yield:



[25] [26]

Danel et. al.,[48] synthesized pyrazole derivatives [28] by reaction of β-ketothioanilide [27] with phenyl hydrazine:

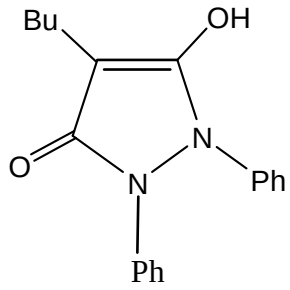


[27] [28]

1.5.2 Pyrazole derivatives uses:

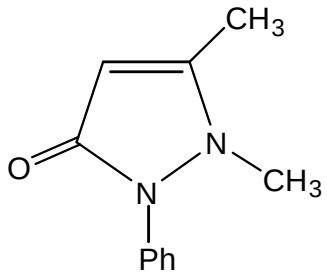
Pyrazole derivatives play a vital role in many biological processes and synthetic drugs. The chemistry of this heterocycle has received much attention in recent years.

Butazolidine [29], another pyrazolone, is a powerful anti-inflammatory drug for rheumatic conditions [(49)].



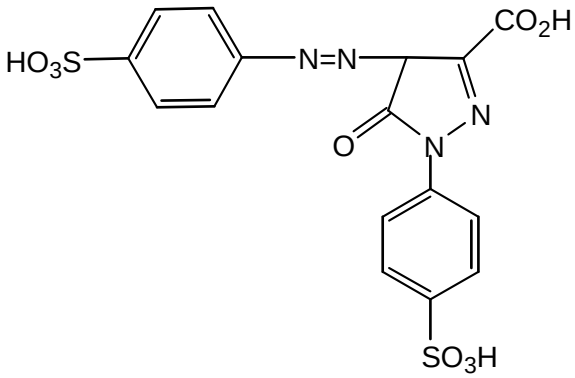
[29]

Antipyrine (2,3-dimethyl-1-phenyl-5-pyrazolone) [30], and its derivative exhibit a wide variety of potentially useful applications including biological , clinical and pharmacological [(50)].



[30]

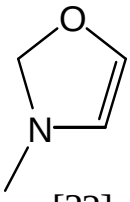
Tartrazine [31] is a yellow dye for wool, this dye has been gaining commercial importance because they are also used for the artificial coloring of foods[51].



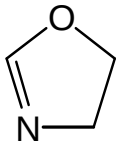
[31]

1.6.0 Oxazoline:

Oxazoline is one of a class of organic heterocyclic compounds containng a five member one unsaturated ring structure composed of one oxygen atom and one nitrogen atom, oxazoline can be represented by two structures [52]:



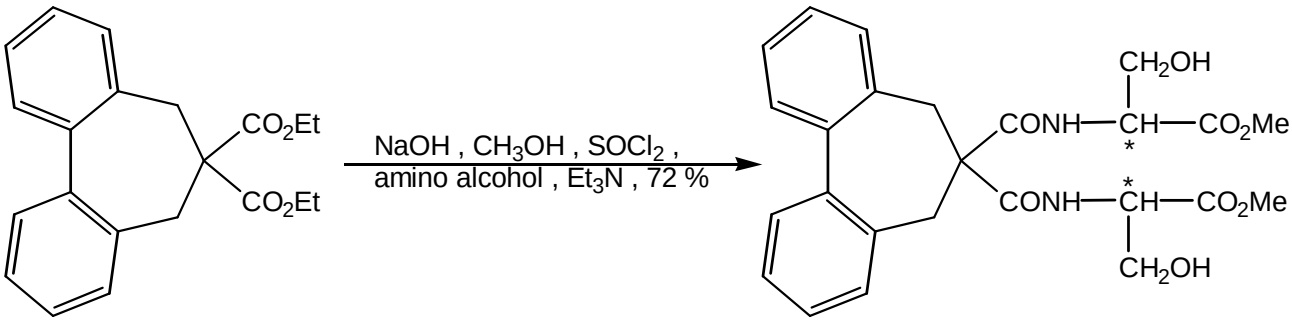
[32]



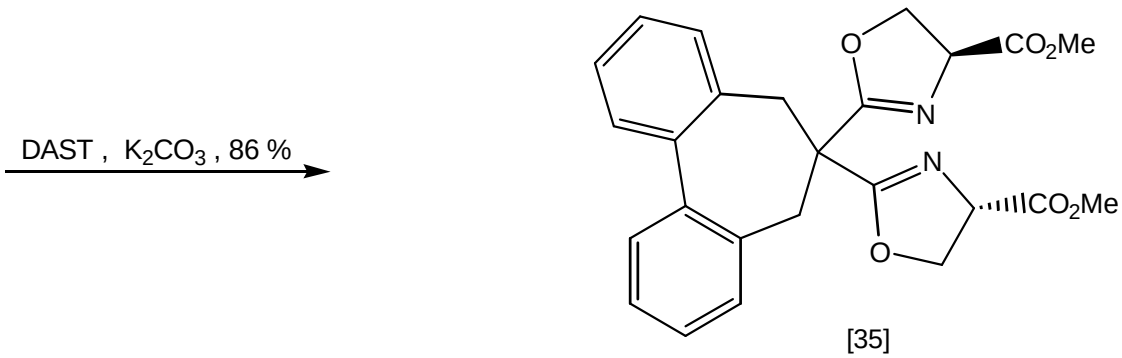
[33]

1.6.1 Synthesis of oxazoline:

Wiliams et. al.,[53] synthesized bis (oxazoline) biscarboxylate [35] in high yield from treatment of dihydroxy diamide [34] with a slight excess of the dehydrating agent, dimethylaminosulfurtrifluoride (DAST) at (-78)ºC in CH_2Cl_2 followed by addition of K_2CO_3 and warming to room temperature.

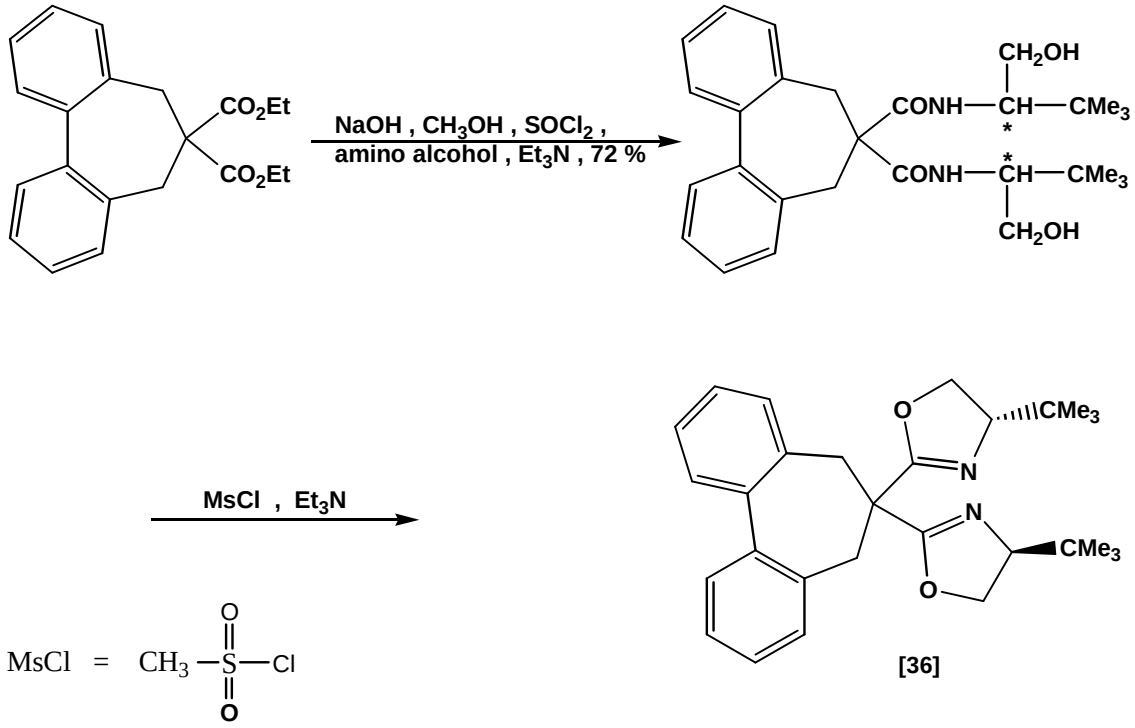


[34]

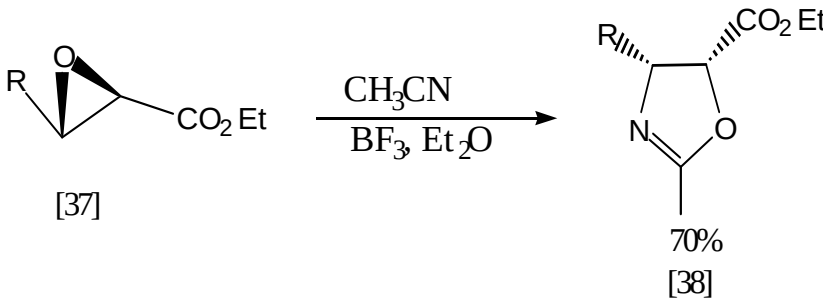


[35]

Compound [36] which bears tert-butyl on the oxazoline ring, was also synthesized following the same procedure using MsCl, Et_3N instead.



The oxirane ester [37] react with acetonitrile to produce oxazolines [38] [(54)].



[37]

[38]

R = C_6H_{13}

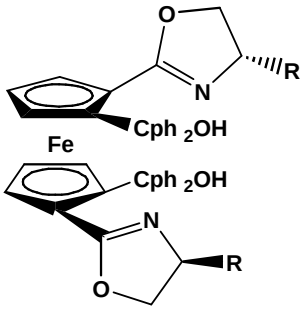
1.6.2 Oxazoline uses:

Chiral oxazolines, especially chiral bis (oxazoline), have been widely applied in many catalytic asymmetric reactions as versatile ligands [(55, 56)]. Oxazoline-base ligands were also found to be effective for the asymmetric addition of diethyl zinc to aldehydes [(57,58)]. In particular, the ligand

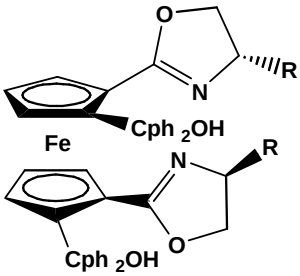
combining the oxazoline ring and hydroxyl group or an amino group have been reported to show excellent catalytic activity in the asymmetric addition of diethyl zinc to aldehydes [59,60].

For example the, ***Ikeda*** et. al.,[61] developed the ligands [40-42] for the asymmetric addition of diethyl zinc to aldehydes and high enantioselectivities were obtained. Ligands [43, and 45] explored by ***Bolm*** et. al., [62] and ligands [46] designed by ***Pastor and Alolfsson*** [63], respectively. Also showed good catalytic activity.

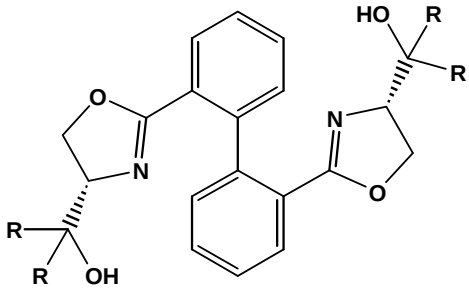
In these ligands, the oxazoline unit and adjacent hydroxyl group function together to control the catalytic process.



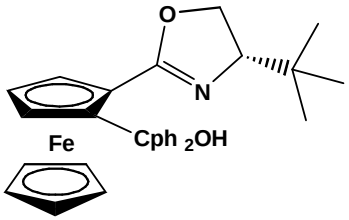
[40a] R = *i*-Pr
[40b] R = *t*-Bu



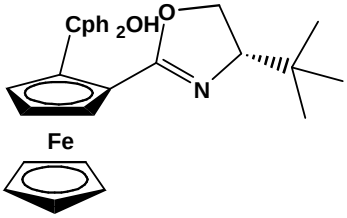
[41a] R = *i*-Pr
[41b] R = *t*-Bu



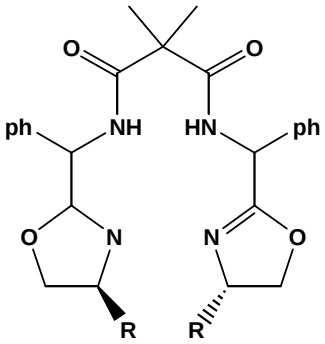
[42a] R = Me
[42b] R = *t*-Bu



[43]



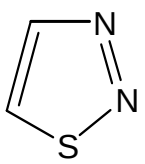
[45]



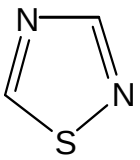
[46a] R = *i*-Pr
[46b] R = ph

1.7.0 Thiadiazoles:

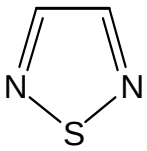
Thiadiazoles are five membered ring compounds with three hetero atoms, one sulfur and two nitrogen atoms. There are four isomeric types [64].



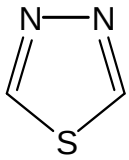
1,2,3-thiadiazole



1,2,4-thiadiazole



1,2,5-thiadiazole

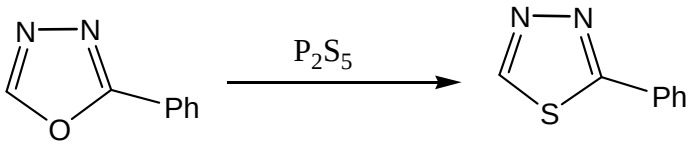


1,3,4-thiadiazole

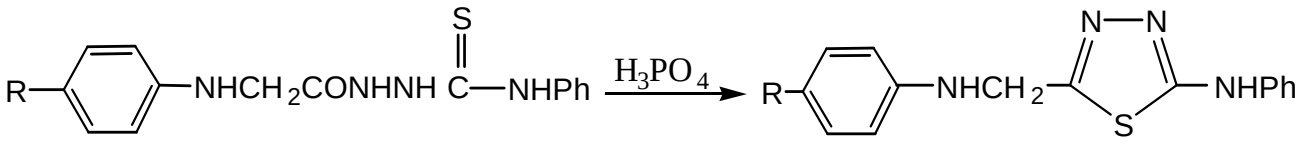
Most of published work on the four thiadiazoles has been on the 1,3,4-thiadiazoles.

1.7.1 Synthesis of 1,3,4-thiadiazoles:

Anisworth [65] prepared in (1958) 2-phenyl-1,3,4-thiadiazole from 2-phenyl-1,3,4-oxadiazole using phosphorus pentathione, as shown below:



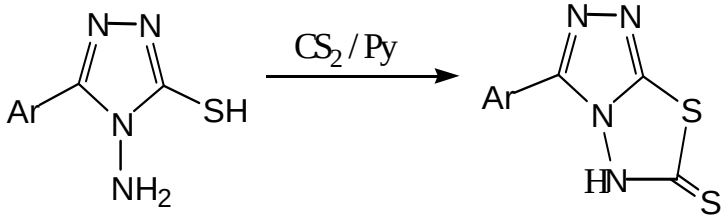
Hiremath et. al.,[66] synthesized a series of 2-amino-5-[4'-(substituted) anilino]-methyl-1,3,4-thiadiazole [48] through cyclo condensation of thiosemicarbazide derivatives [47] with phosphoric acid.



[47] [48]

R = CH_3, OCH_3, Cl

Mohan et. al., [67] prepared 3-aryl-1,2,4-triazole [3,4-b][1,3,4] thiadiazole-6-(5*H*)-thiones [50] by the reaction of 3-aryl-4-amino-5-mercapto-1,2,4-triazoles [49] with CS_2 in the presence of pyridine.



[49] [50]

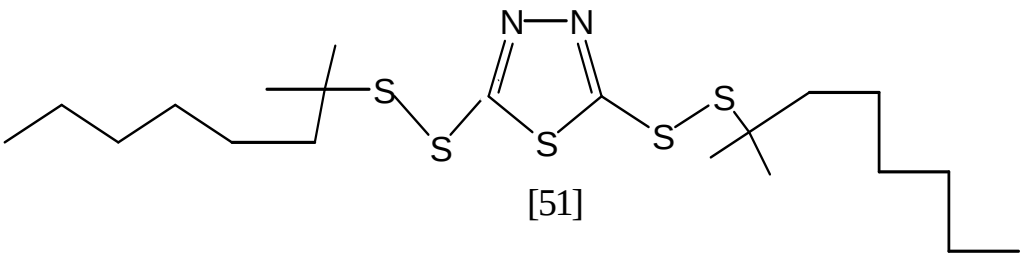
Ar = p-$NO_2C_6H_4$, p-PhC_6H_4

1.7.2 1,3,4-Thiadiazoles uses:

Among azoles, thiadiazole and its derivatives continue to draw the attention of synthetic organic chemists due to the large group of compounds possessing a wide spectrum of uses.

Heterocyclic compounds possessing 1,3,4-thiadiazole ring system show anti-fungal, bacteriostatic as well as anthelmintic effects [68,69] . Compounds containing the above ring, also exhibit anti-inflammatory, antimicrobial properties [70] and the depression effect on the central nervous system[71].

On the other hand, 2,5-bis (tert-nonyldithio) 1,3,4-thiadiazole [51] is used as antioxidant in gasoline and steel corrosion inhibitor [72]. Also used to formulate finished greases and lubricating oils including industrial, gear and some types of automotive and heavy duty diesel [73].

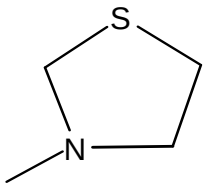


[51]

2,5-bis(tert-nonyldithio)-1,3,4-thiadiazole

1.8.0 Thiazolidine:

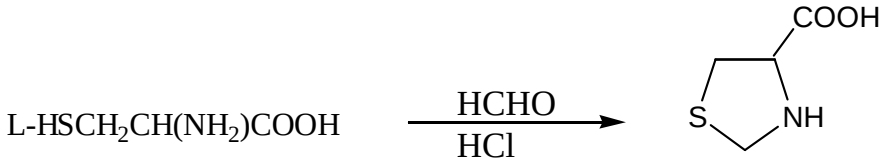
Thiazolidine is one of a class of organic heterocyclic compound containing a five member saturated ring structure composed of one sulfur atom and one nitrogen atom, thiazolidine can be represented by structure:



[52]

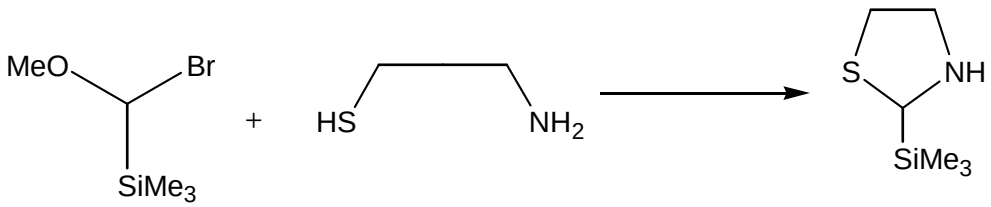
1.8.1 Synthesis of thiazolidine derivatives:

Wang et. al., [74] found that the reaction of L-cysteine with formaldehyde in aqueous acidic medium afforded the L-thiazolidine-4-carboxylic acid [53].



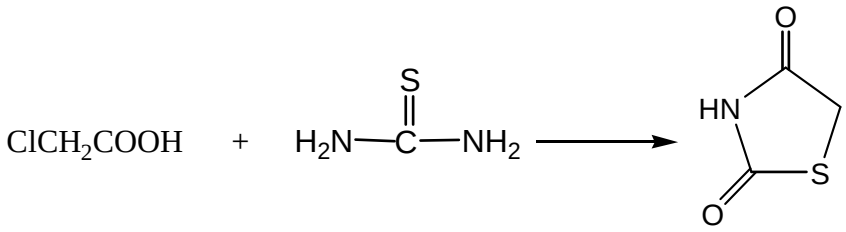
[53]

Capperucci et. al.,[75] found that 2-trimethyl silyl thiazolidine [55] was obtained from the reaction of methoxy bromomethyl trimethyl silane [54] with 2-aminoethanethiol.



[54] [55]

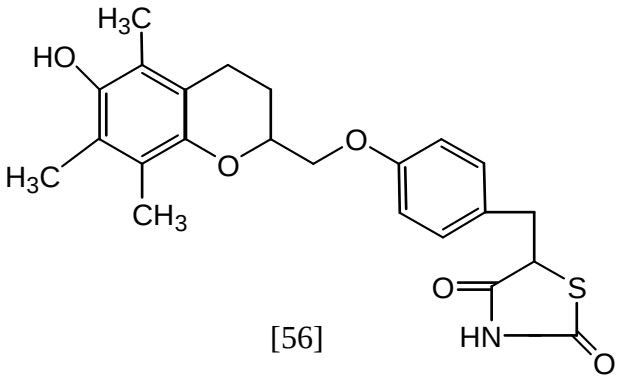
Ünlüsoy et. al.,[76] synthesized 2,4-thiazolidinedione in high yield from treatment of monochloroacetic acid with thiourea in hot water.



1.8.2 Thiazolidine uses:

The presence of thiazolidine ring in pencillins and related derivatives was the first recognition of its occurance in nature.

Troglitazone [56] drug have been further tested in human breast, prostate and colon cancer cells resulting inhibition of cell proliferation [77].

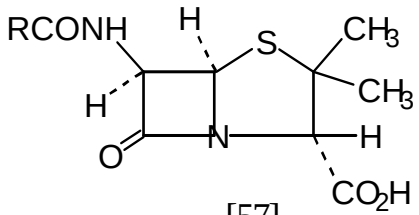


[56]

Some new thiazolidine derivatives have been reported as possible antitussive and antiradiation, and 1-(3-allyl-4-oxothiazolidine-2-ylidine)-4-methyl thiosemicarbazone) exhibits antiarthritic activity [76].

Recently thiazolidine derivatives are reported to show a variety of biological activities. Depending on the substituents, this heterocycle can include different pharmacological properties such as antibacterial, antifungal, antidiebetic, cardiotonic and anticonvulsant [78].

Also, the thiazolidine ring is a part of pencillin stracture [57] owe their importance to their powerful effect on various pathogenic organisms [(79)].

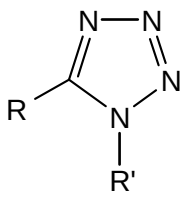


[57]

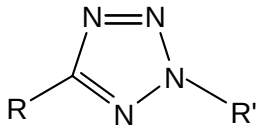
R = -$CH_2CH=CHC_2H_5$, -CH_2Ph

1.9.0 Tetrazoles:

Tetrazoles are aromatic five membered ring containing four nitrogen atoms and having the general structure [58] or [59] with numbering as shown when R'=H the tetrazole exists in two tautomeric forms [58] and [59], the 1*H* from [58] being dominate in solution and the 2*H* from [59] dominant in the gas phase.



[58]



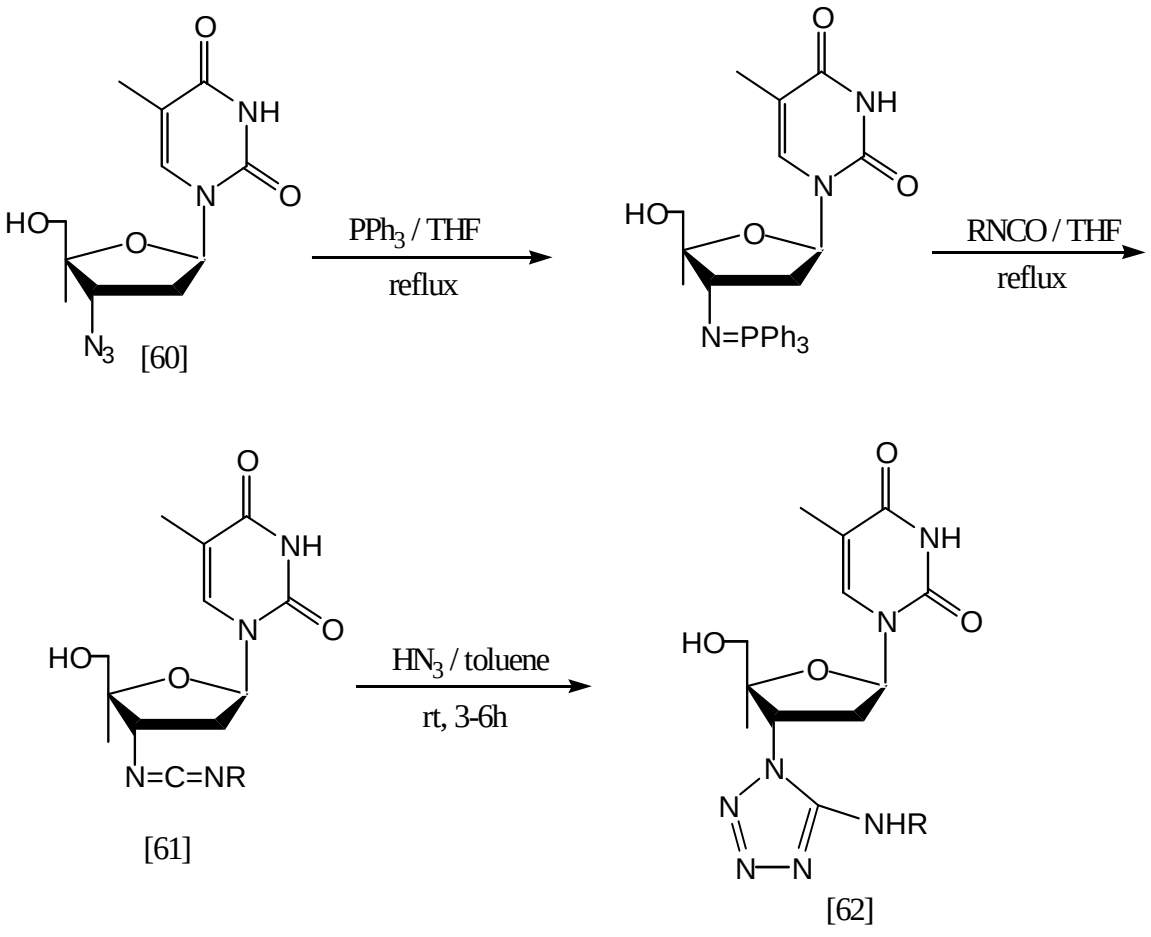
[59]

The first tetrazole was reported over a century ago [(80)] but the chemistry of tetrazole remained relatively obscure until the 1960 when the pharmacological and biological properties of tetrazoles became known.

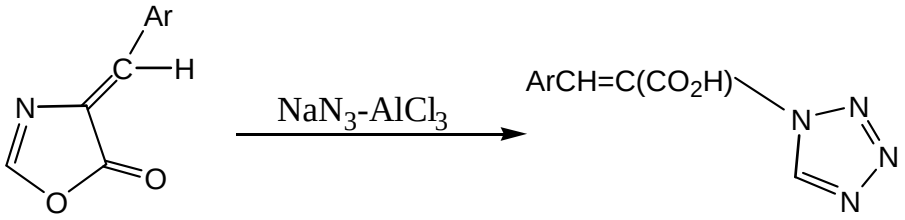
1.9.1 Synthesis of tetrazole:

1,5-Disubstituted 5-aminotetrazoles can be form the reaction of 3'-azido-3'deoxythymidine (AZT) [60] with triphenylphosphine, followed by reaction with an alkyl or aryl isocyanate afforded the intermediate carbodiimide [61].

The carbodiimide [61] was then treated with hydrazoic acid in toluene at room temperature for 6 hours to furnish the 5-aminotetrazole [62] [(81)].

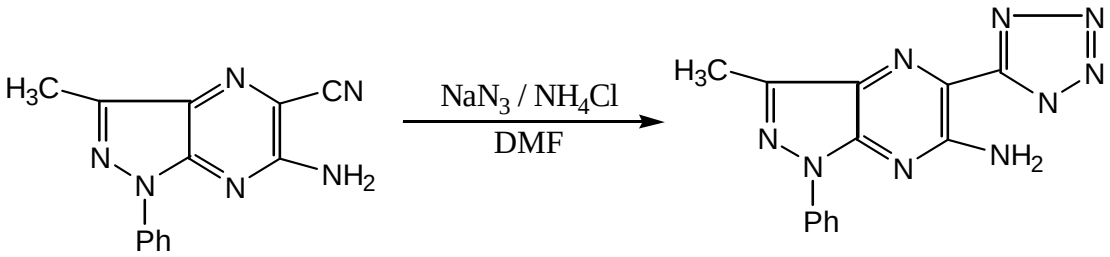


Oxazolones such as [63] reacts with a sodium azide-anhydrous aluminum chloride mixture in tetrahydrofuran to give tetrazolyl acrylic acids [64] [54].



[63] [64]

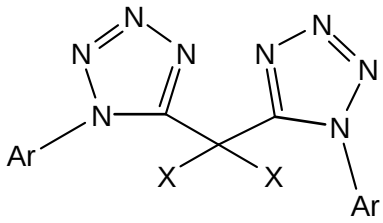
El-Emary et. al.,[82] observed that the 3-methyl-1-phenyl-5-(1-*H*-tetrazol-5-yl)-1*H*-pyrazolo [3,4-b] pyrazin-6-ylamine [66] was produced when 6-amino-3-methyl-1-phenyl-1-*H*-pyrazolo [3,4-b] pyrazin-5-carbonitrile [65] was allowed to interact with sodium azide and ammonium chloride in dimethyl formamide.



[65] [66]

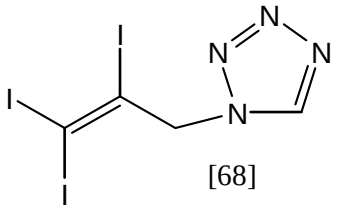
1.9.2 Tetrazole uses:

Although a great deal of the scientific literature concerning tetrazoles is in the area of medicinal chemistry, tetrazoles have also found use in other biological and non-biological applications [83]. In agriculture tetrazoles serve as plant growth regulators, as herbicides and as fungicides. Some examples include the growth inhibitor [67a], stimulant [67b] fungicide [84] [68] and pesticide [69].

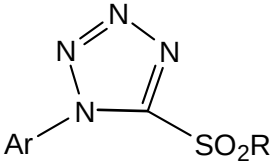


[67a] X =Cl

[67b] X = H



[68]

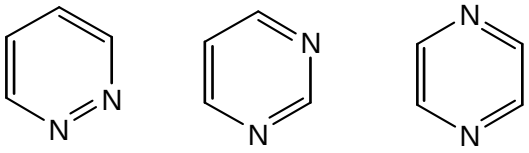


[69]

Tetrazoles have also been incorporated into polymers, used in photography and photoimaging and as fuels and explosives of particular interest is the use of tetrazoles as explosives in air-bags as they give off non-toxic gases composed mainly of nitrogen [85].

1.10.0 Pyridazines:

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

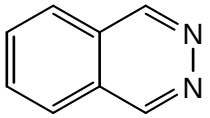


pyridazine pyrimidine pyrazine

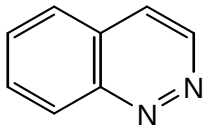
No naturally occurring pyridazines have been reported and indeed this comes as no surprise because of the paucity of chemical compounds containing two nitrogen atoms bonded to one another in nature [86].

Pyridazine is a colorless liquid, its boiling point is equal to (207.4ºC), and its considered as a weak base (pKa=2.331).

Pyridazine ring can be fused onto a benzene ring in two ways, giving phthalazine or cinnoline [86].



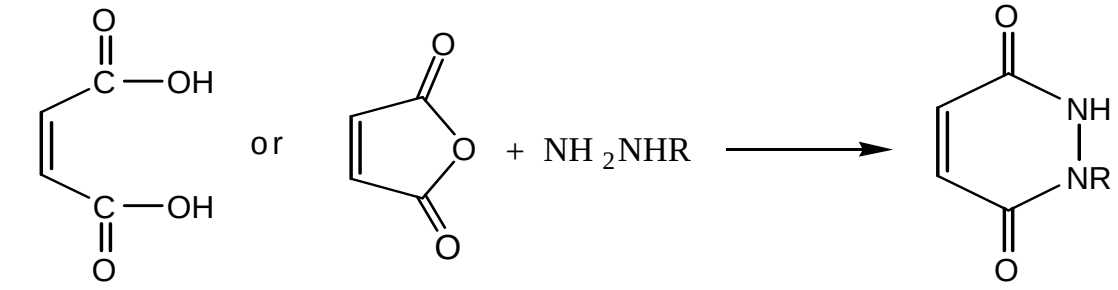
phthalazine



cinnoline

1.10.1 Synthesis of pyridazine derivatives:

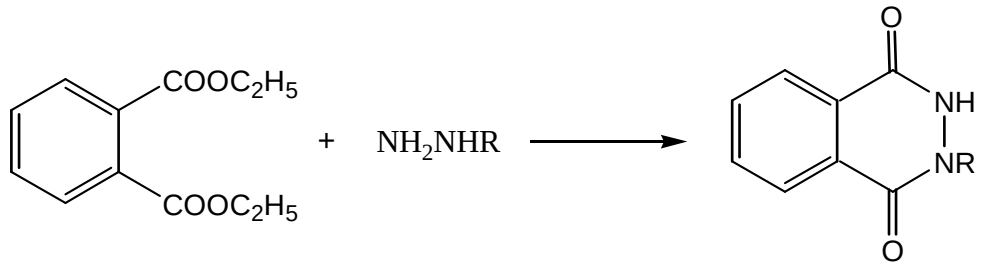
Pyridazine and number of its derivatives were prepared by different methods such as [86,87] from the reaction of maleic acid or malice anhydride with hydrazine or substituted hydrazine.



maleic acid maleic unhydride

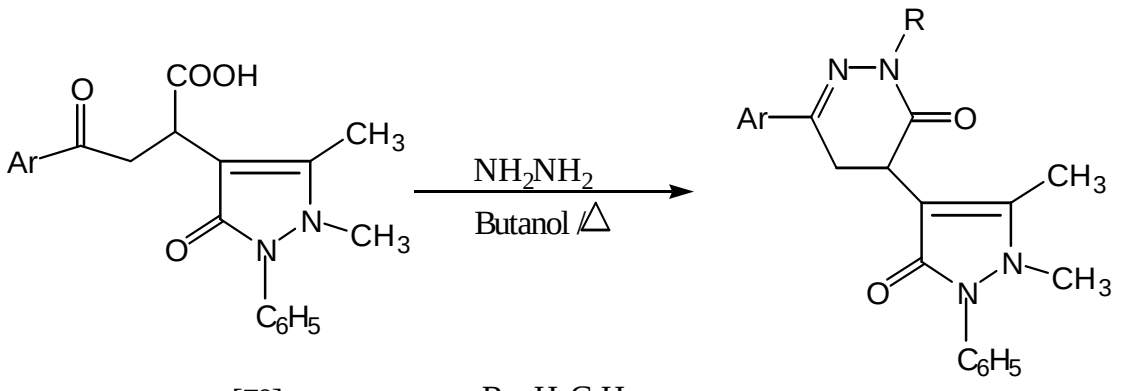
R = H or many different substituents

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



R = many different substituents

Sayed et. al.,[88] found that 6-phenyl-4-(4-antipyrinyl)- 4,5-dihydropyridazin-3(2*H*)-one [71] was obtained from the reaction of hydrazine with 4-phenyl-4-oxo-2-(4-antipyrinyl) butanoic acid [70].

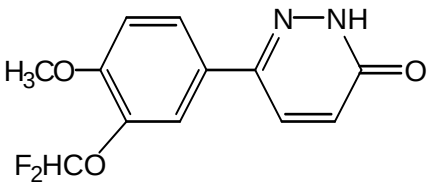


[70] R = H, C_6H_5 [71]

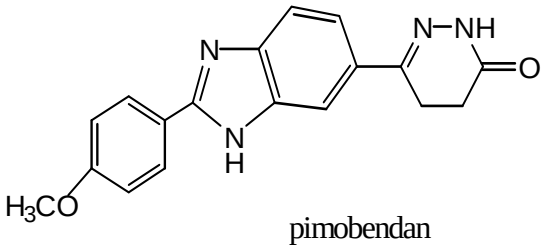
1.10.2 Pyridazine uses:

Pyridazine and condensed pyridazines are reported to have good biological activities. Reported the synthesis of several pyridazino [4,5-b] carbazoles, some of which exhibited significant antitumor activity [(89)].

Also, some 3-(2*H*)-pyridazinone derivatives was the potent in term of analgesic and the highest anti-inflammatory activities and had no ulcerogenic side effects [(90)]. Zardaverine and Pimobendan are drugs used as an antiplatelet activity [(91)].



Zardaverine



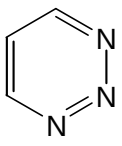
pimobendan

On the other hand, substituted pyridazine have been higher therapeutic index, in particular for treatment of neuropathic pain and anti nociceptive agents [(92)].

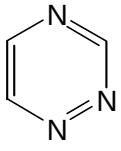
1.11.0 Triazines:

The 1,3,5-triazine, is an aza analogue of pyridine and its derivatives from an important class of heteroaromatic compounds with various interesting biochemical properties.

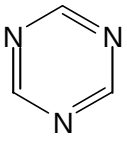
Triazine are six-membered aromatic rings containing three nitrogen atoms, there are three possible arrangements of the nitrogen atoms in the ring[(93)] .



1,2,3-triazine



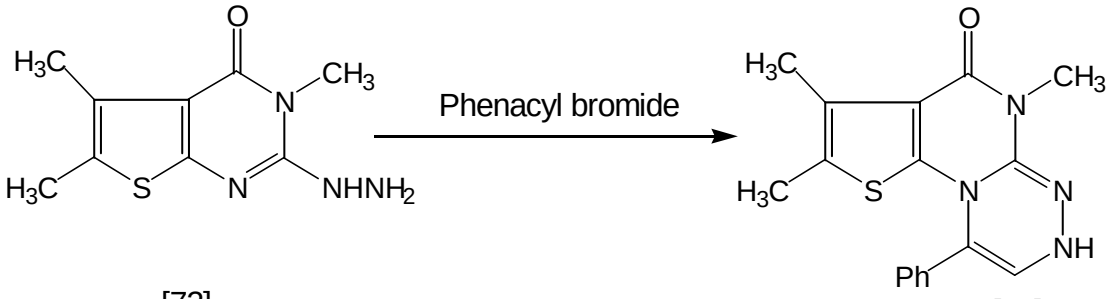
1,2,4-triazine



1,3,5-triazine

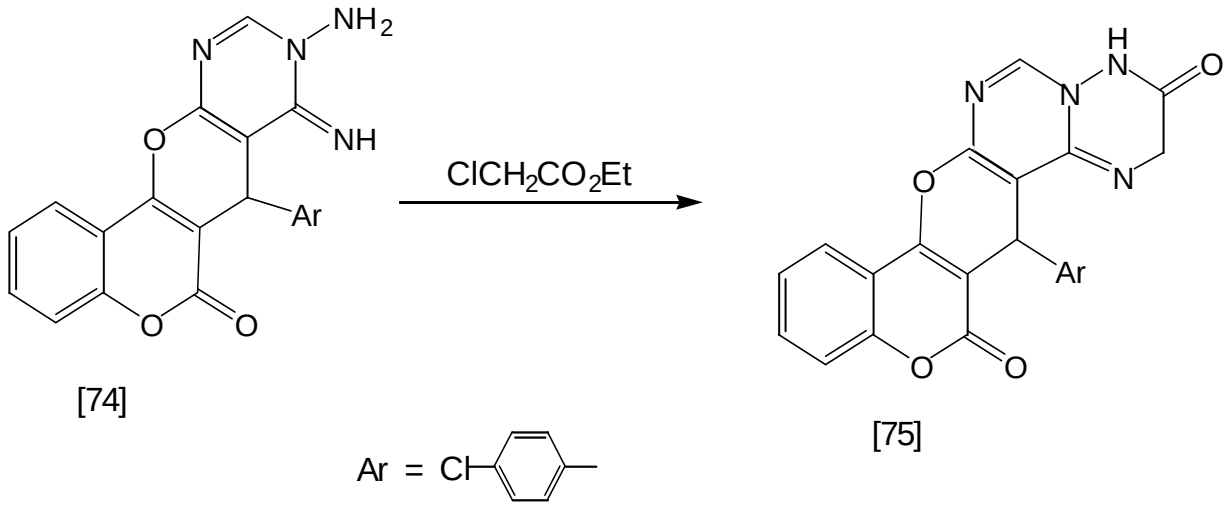
1.11.1 Synthesis of 1,2,4-triazines:

El-Gazzar [(94)] found that the reaction of compound [72] with phenacyl bromide in dry xylene yielded the corresponding 1-phenyl-5,7,8-trimethyl-5,6-dihydrotheno[2',3' : 6,5] pyrimido [2,1-c] [1,2,4]triazin-6-one [73].



[72] [73]

El-Agarody et. al., [(95)] found that the reaction of 9-amino-7-(4'-chlorophenyl)-8,9-dihydro-8-imino-6*H*,7*H*-[1] benzopyrano[3',4' :5,6]-pyrano [2,3-d] pyrimidine-6-one [47] with ethyl chloroacetate in methanolic sodium methoxide afforded the triazin-3,14-dione derivative [75].

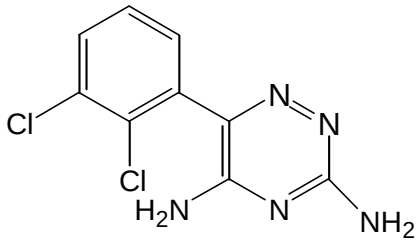


[74] [75]

1.11.2 Triazine uses:

Condensed triazines exhibit a range of pharmacological activities such as anti-inflammatory [(96)] and consequently, dimethyl triazinoimidazole carboxamide is employed principally for the treatment of malignant melanoma [(97)].

Several compounds containing 1,2,4-triazine rings are well known as drugs. For example Lamotrigine is used as a mood stabilizer for patients with bipolar disorder [(98)].



Lamotrigine

The compound 8-(4-fuorophenyl)-2-(2E)-3-phenyl-2-propnoyl)-1,2,3,4-tetrahydropyrazolo[5,1-c] [1,2,4] triazine was identified as a novel, powerful free radical scavenger [(99)].

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 prescence 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:

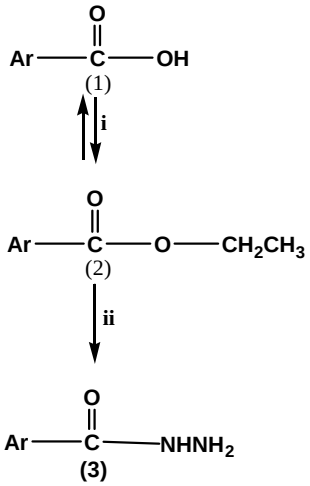
1.Synthesis of new oxadiazole,triazole, tetrazole and triazine fused rings derivatives.

2. Synthesis of oxazoline and thiazolidine derivatives.

3. Synthesis of series of other heterocyclic compounds.

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

3.1.1 Ester and hydrazide derivatives:



Scheme (1): Reagents and conditions:

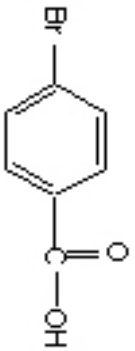
(i) EtOH, H^+, reflux 5 hr. (ii) $N_2H_4.H_2O$, EtOH, reflux 2 hr.

To synthesize 4-bromobenzoic hydrazide derivative, was used (4-bromobenzoic acid).

The carboxylic acid was first converted to ester [2] by the common esterification process, using absolute ethanol and concentrated sulfuric acid[(100)]. The ester was identified by F.T.IR spectrum which showed the disappearance of a wide absorption band in the range (3160-3020) cm^{-1} which belongs to the stretching vibration of the (O-H) group of the carboxylic acid and the disappearance of absorption band at (1681 cm^{-1}**)** which is due to the stretching vibration of the carbonyl group (C=O) of the carboxylic acids.

The F.T.IR spectrum also, showed the appearance of the characteristic absorption band at (1720 cm^{-1}**)** due to the stretching vibration of the (C=O) of the forming ester. The F.T.IR spectrum of above compounds are shown in figs.(3-1) and (3-2).

ρ-Bromo benzoic acid [1].



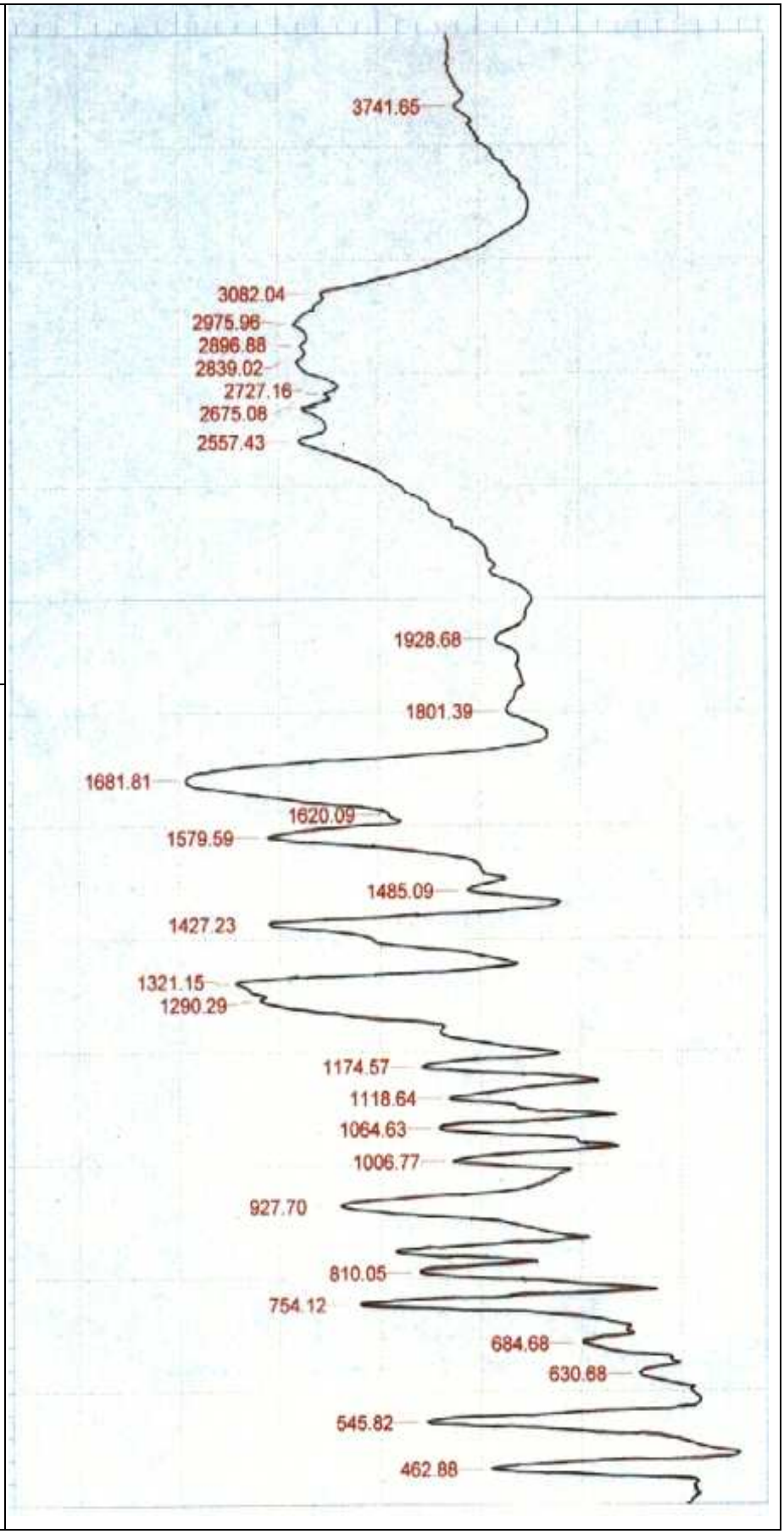
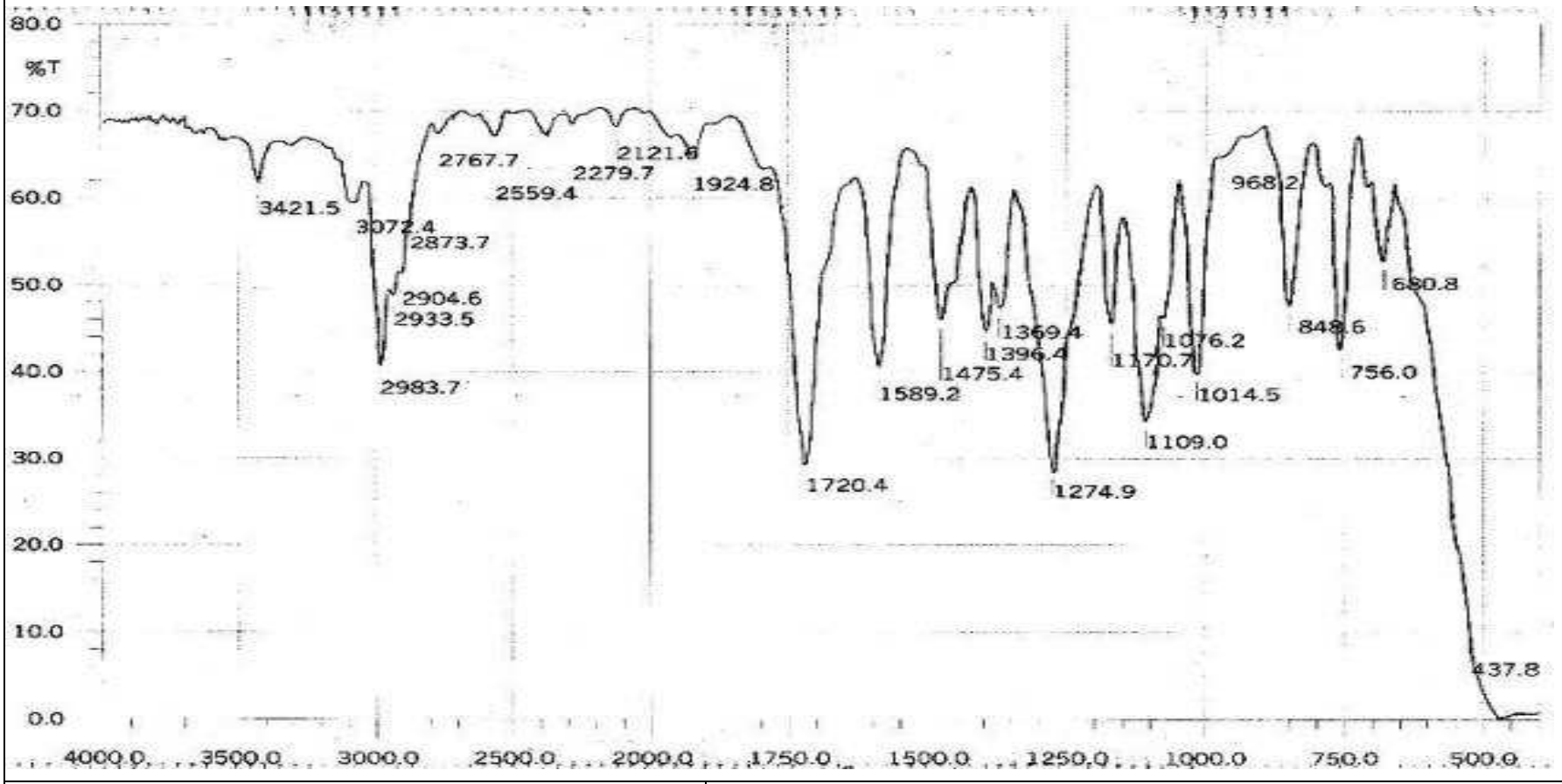


Figure (3-1): F.T.IR spectrum of compound [1].



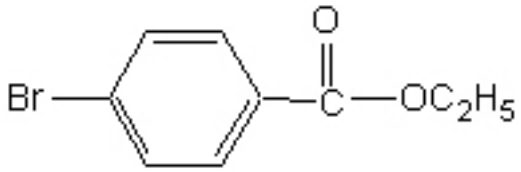
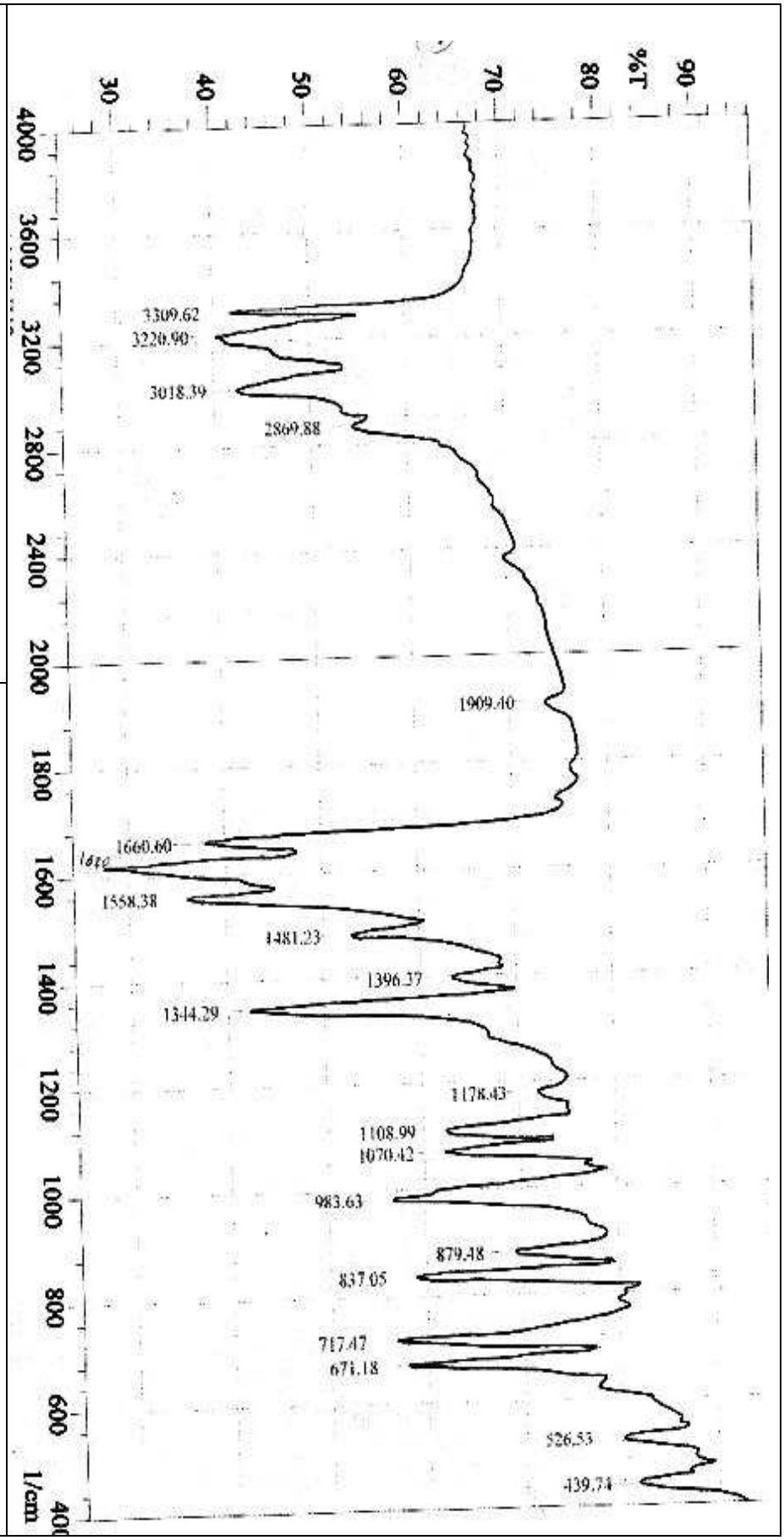
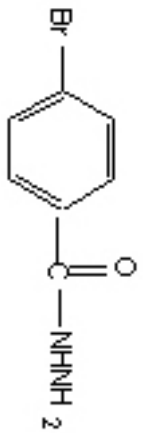
Ethyl-p-bromobenzoate [2].	

Figure (3-2): F.T.IR spectrum of compound [2].

The reaction of hydrazine hydrate with ester is one of the most common reactions to synthesize the acid hydrazide , it is a tetrahedral nucleophilic substitution reaction[109].

The structure of this compound was confirmed by F.T.IR spectral data, the F.T.IR spectrum for the hydrazide showed the appearance of the characteristic absorption bands at (3309 cm^{-1}) and (3221 cm^{-1}) due to the asymmetric and symmetric stretching vibration of the (-NH-NH_2) group. Besides this, the disappearance of absorption band at (1720 cm^{-1}) attributed to carbonyl stretching, fig.(3-2), with the appearance of bands at (1660 cm^{-1}) a amide I and at (1558 cm^{-1}) amide II proved the formation of compound [3]. The F.T.IR spectrum of above compound is shown in fig.(3-3).

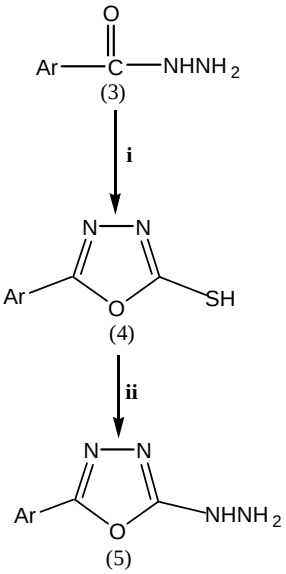




p-Bromobenzoic hydrazide [3].

Figure (3-3): F.T.IR spectrum of compound [3].

3.1.2 2,5-Substituted oxadiazole derivatives:

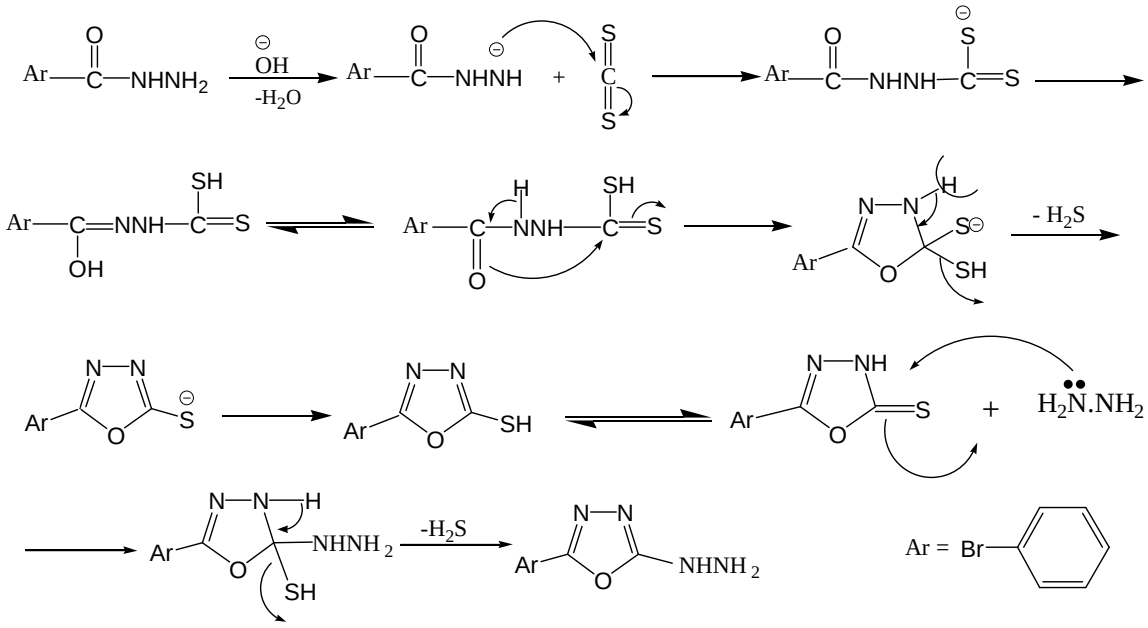


Scheme (2): Reagents and conditions:

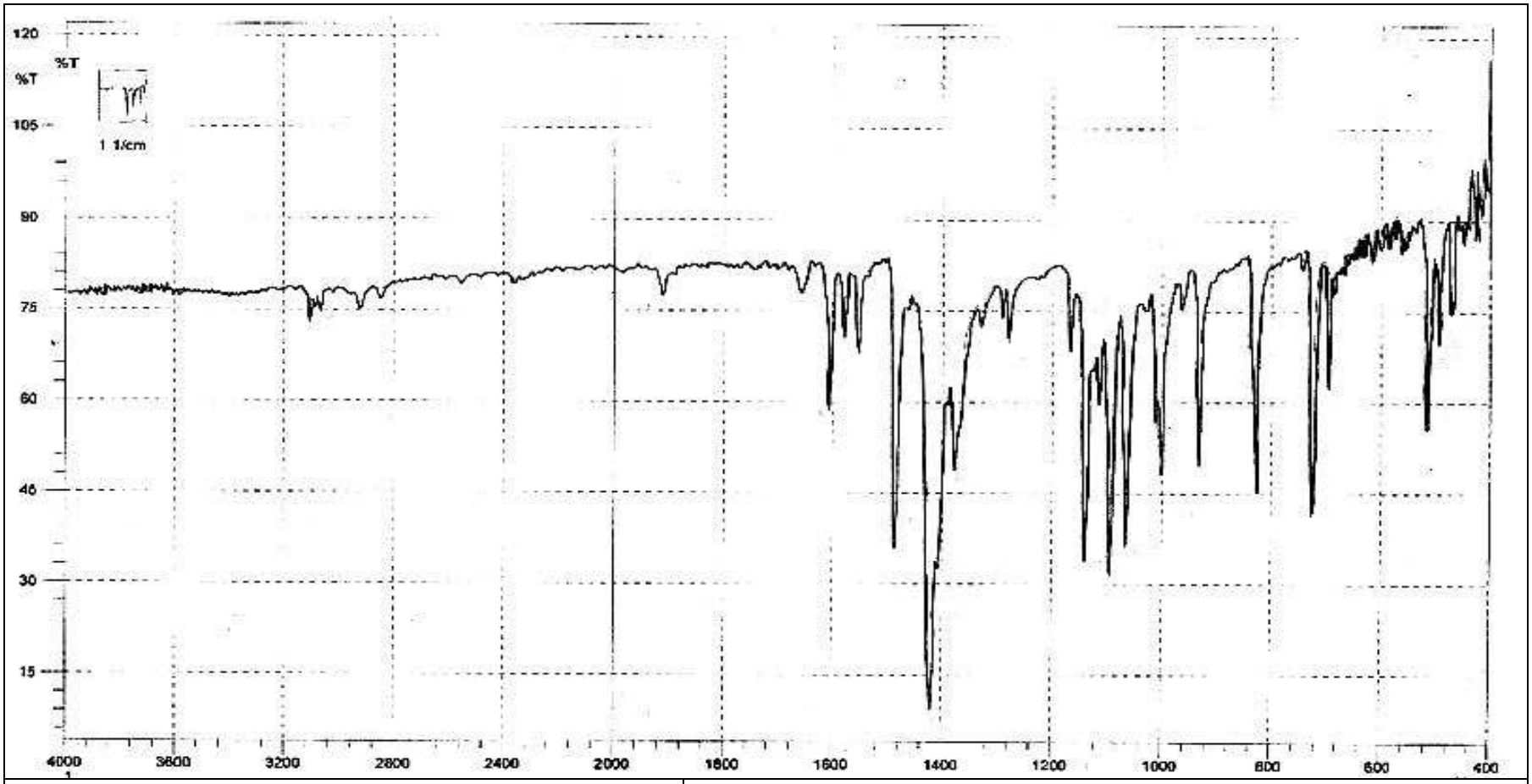
(i) CS_2, KOH, reflux 8 hr.

(ii) $N_2H_4.H_2O$, EtOH, reflux 5 hr.

The hydrazino oxadiazole [5] was synthesized by two steps, first the hydrazide was reacted with carbon disulfide for cyclization of the compound [3] in the presence potassium hydroxide, second step of the reaction the compound [4] gave hydrazino oxadiazole derivative [5] when reacted with hydrazine hydrate in absolute ethanol as a solvent. The mechanism[110] of the reaction is shown below:



The compounds [4] and [5] were identified by F.T.IR spectra which showed the disappearance of the characteristic absorbtion bands at (3309, 3221) cm^{-1} due to the asymmetric and symmetric stretching vibration of the ($NH-NH_2$) group, the F.T.IR spectrum fig. (3-3) also, showed the disappearance of the band at (1660 cm^{-1}) due to ν(C=O) of amide I with the appearance of a bands at (1610 cm^{-1}) assignable to ν(C=N) of oxadiazole ring , ν(C-O-C) asymmetric and symmetric bands appeared at (1130 cm^{-1}) and (1065 cm^{-1}) respectively, the ν(C-O-C) cyclic group in oxadiazole is good evidence for the structure assigned to this compound. Weak band at (2470 cm^{-1}) was due to ν(S-H) group.The F.T.IR spectrum of compound [4], fig.(3-4).



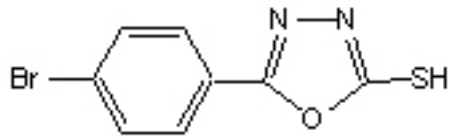
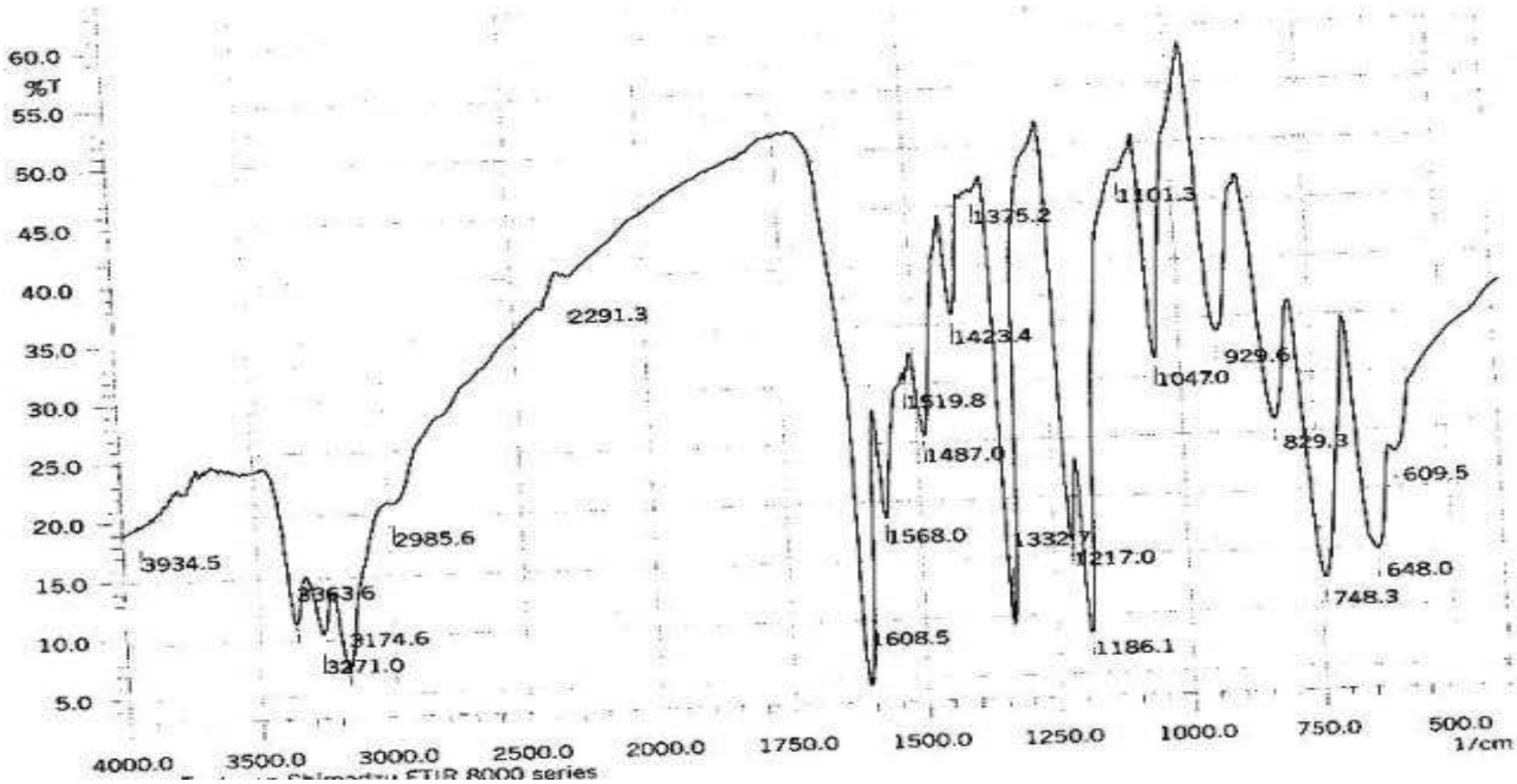
5-(p-Bromophenyl)-3-mercapto-1,3,4-oxadiazole [4].	

Figure (3-4): F.T.IR spectrum of compound [4].

The hydrazino oxadiazole [5] was also identified by F.T.IR spectrum which showed the appearance of the characteristic absorption bands at (3363 cm^{-1}), (3271 cm^{-1}) and (3174 cm^{-1}) due to the asymmetric and symmetric stretching vibration of the ($NH-NH_2$) group with the disappearance of a band at (2470 cm^{-1}) assigned to ν(S-H) group. Sharp absorption bands appeared at (1608 cm^{-1}) and (1568 cm^{-1}) were due to ν(C=N) and ν(C=C) aromatic groups, bands at (1217 cm^{-1}) and (1047 cm^{-1}) belong to the asymmetric and symmetric ν(C-O-C) vibration. Also in this reaction the evolution of hydrogen sulfide, all these are good evidences for the structure assigned to this compound.The F.T.IR spectrum of compound [5], fig.(3-5).



5-(p-bromophenyl)-2-hydrazino-1,3,4-oxadiazole [5].

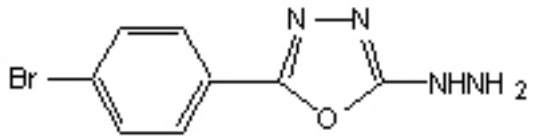
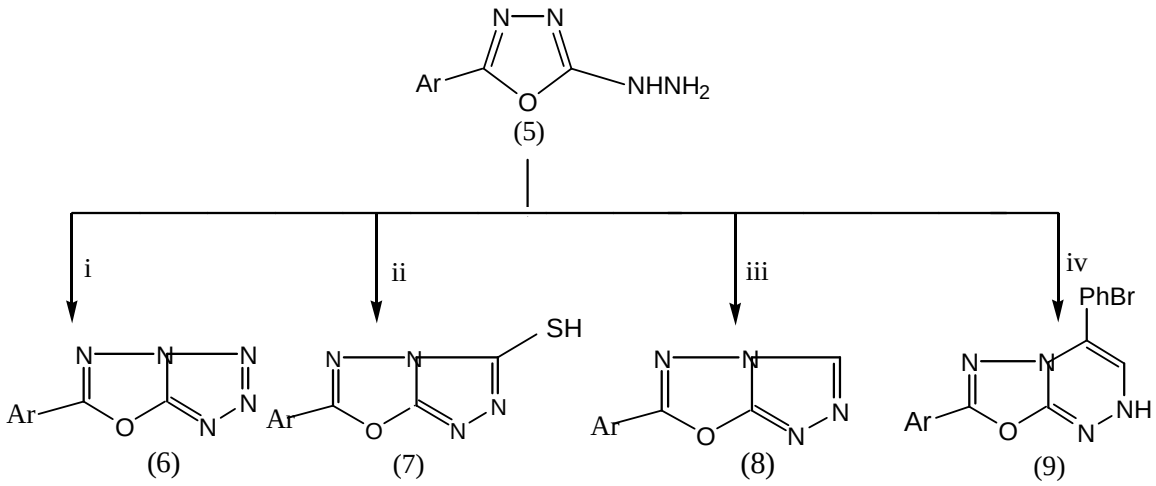


Figure (3-5): F.T.IR spectrum of compound [5] .

3.1.3 Tetrazole, triazole and triazine derivatives:



Scheme (3): Reagents and conditions:

(i) Sodium nitrite, H_2O, acetic acid, stirring 3 hr.

(ii) Carbon disulfide, pyridine, reflux 7 hr.

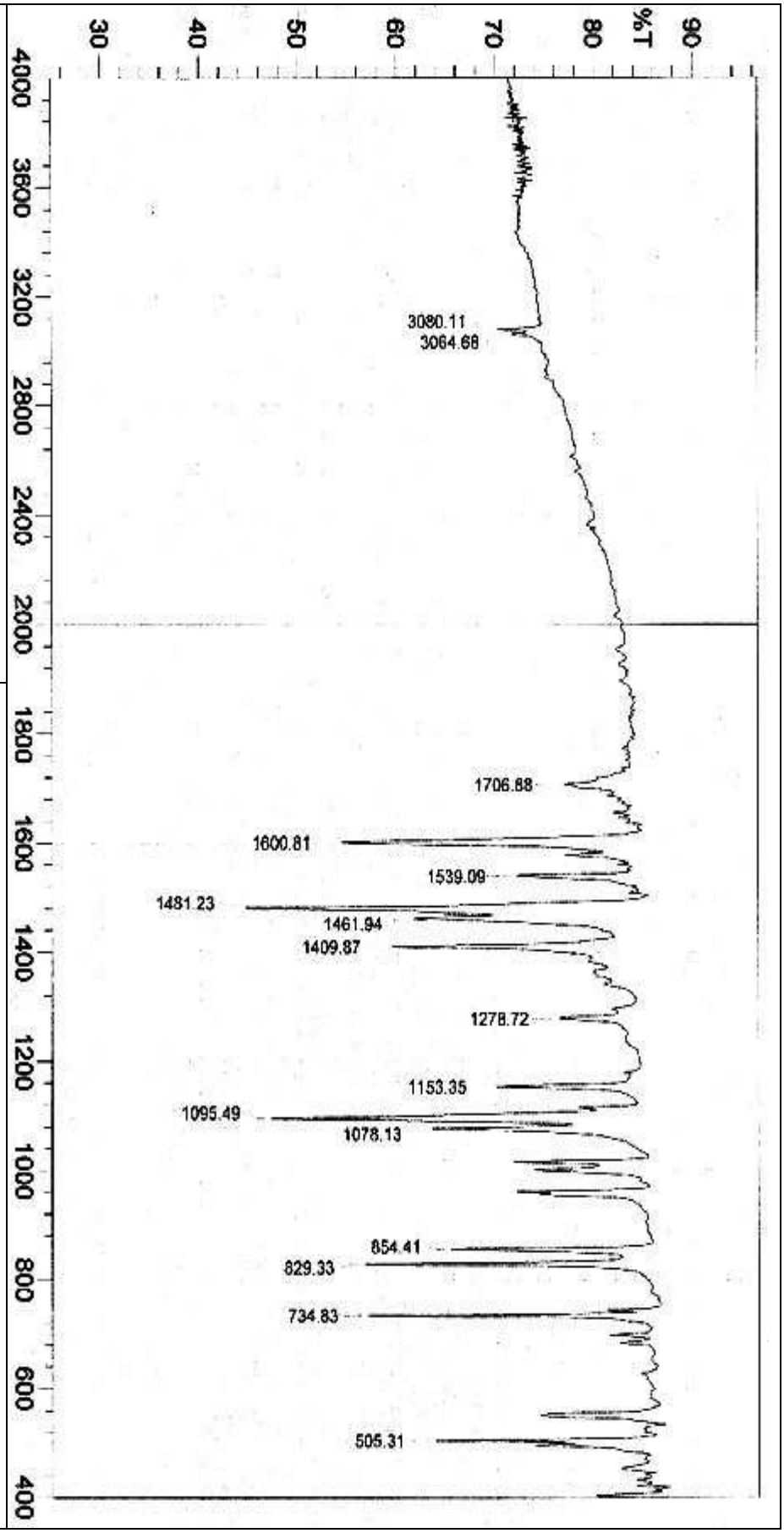
(iii) Formic acid, H^+, reflux 6 hr.

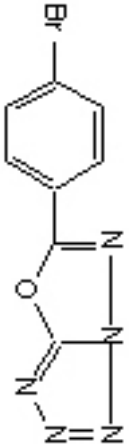
(iv) 4-Bromophenacyl bromide, dry benzene, reflux 5 hr.

The formation of novel fused five and six membered heterocyclic rings are considered important branches of heterocyclic compounds due to their biological activities[(111)], these compounds were characterized by F.T.IR spectra.

Compound [6] was synthesized from the reaction of hydrazino compound [5] with nitrous acid in the presence of acetic acid as solvent and catalyst. The F.T.IR spectrum of tetrazole showed the disappearance of the characteristic absorption band at (3363 cm^{-1}), (3271 cm^{-1}) and (3174 cm^{-1}) attributed to the asymmetric and symmetric stretching vibration of the ($NH-NH_2$) group, disappearance of these stretching bands are good evidences for the success of this step of reaction. A band at (1706 cm^{-1}) was due to the cyclic (C=N) stretching of tetrazole ring[(112)]. Sharp absorption band appeared at (1601 cm^{-1}) attributed to (C=N) group.

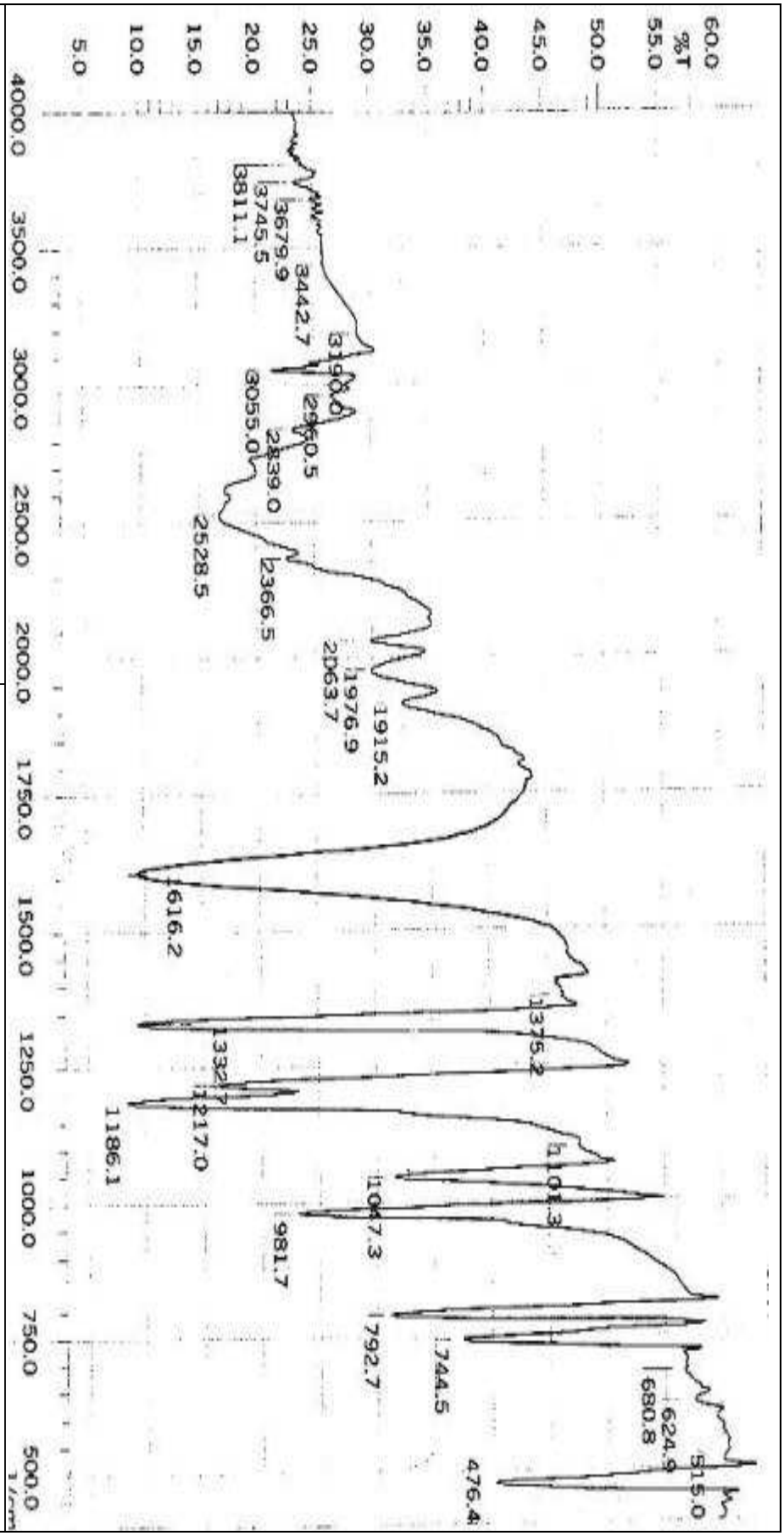
Also the hydrazino derivative [5] was readily cyclized into the corresponding compound [7] upon treatment with carbon disulfide in pyridine. The compounds were identified by F.T.IR spectra, the F.T.IR spectrum of compound [7] indicated the disappearance of ($NH\text{-}NH_2$) bands at (3363 cm^{-1}), (3271 cm^{-1}) and (3174 cm^{-1}) of the starting material compound [5] and appearance of (SH) band at (2528 cm^{-1}). The F.T.IR spectra of the above compounds are shown in figs. (3-6) and (3-7).





6-(p-Bromophenyl)-1,2,3,4-tetrazolo[4,5-b][1,3,4]oxadiazole [6].

Figure (3-6): F.T.IR spectrum of compound [6] .



6-(p-Bromophenyl)-4-mercapto-1,2,4-triazolo[4,5-b][1,3,4]oxadiazole [7].

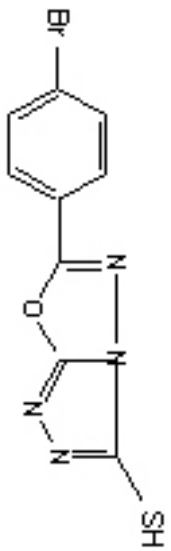
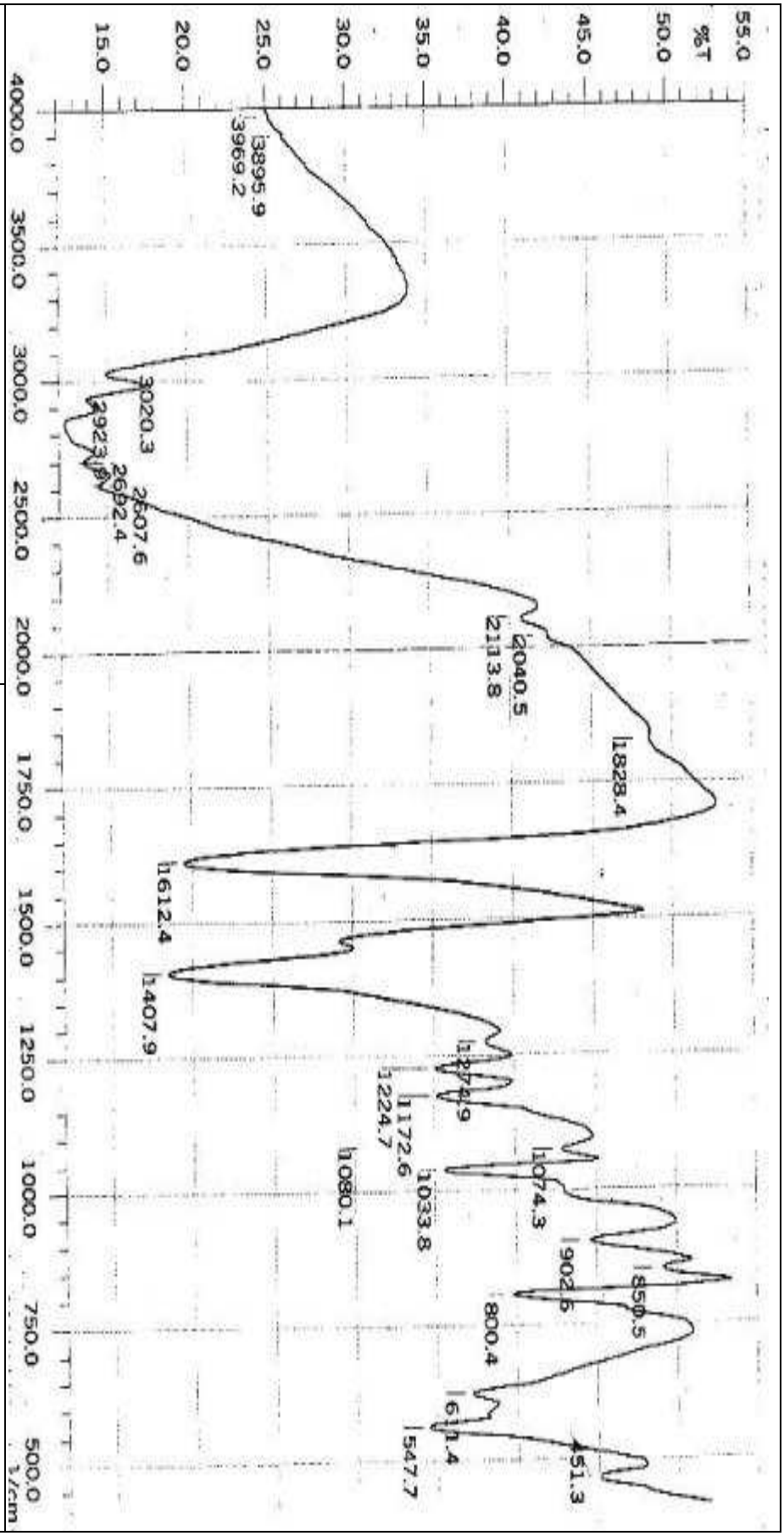


Figure (3-7): F.T.IR spectrum of compound [7] .

Hydrazino compound [5] proved to be versatile synthetic for other new triazoles derivatives, when hydrazino compound was allowed to react with formic acid in the presence of a catalytic amount of hydrochloric acid. The structural formula of newly synthesized compound [8] was elucidated and confirmed by F.T.IR spectrum, the F.T.IR spectrum of compound [8] indicated the disappearance of ($NH-NH_2$) bands at (3363 cm^{-1}), (3271 cm^{-1}) and (3174 cm^{-1}) of the starting material compound [5] and appearance of (C-H) band at (2924 cm^{-1}).

Also hydrazino compound [5] was allowed to react with *p*-bromo phenacylbromide in dry benzene to afford the new triazine derivative [9]. The compound was identified by F.T.IR spectrum, the F.T.IR spectrum of compound [9] indicated the disappearance of (NH_2) bands at (3363 cm^{-1}) and (3271 cm^{-1}) of the starting material compound [5] and appearance of (N-H) band at (3113 cm^{-1}), *ν*(C-H) aromatic appeared as a shoulder at range (3113-3000) cm^{-1}. The F.T.IR spectra of the above compounds are shown in figs. (3-8) and (3-9).



6-(*p*-Bromophenyl)-1,2,4-triazolo[4,5-b] [1,3,4]oxadiazole [8].

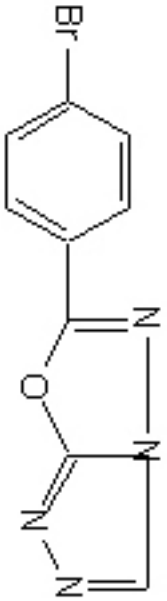
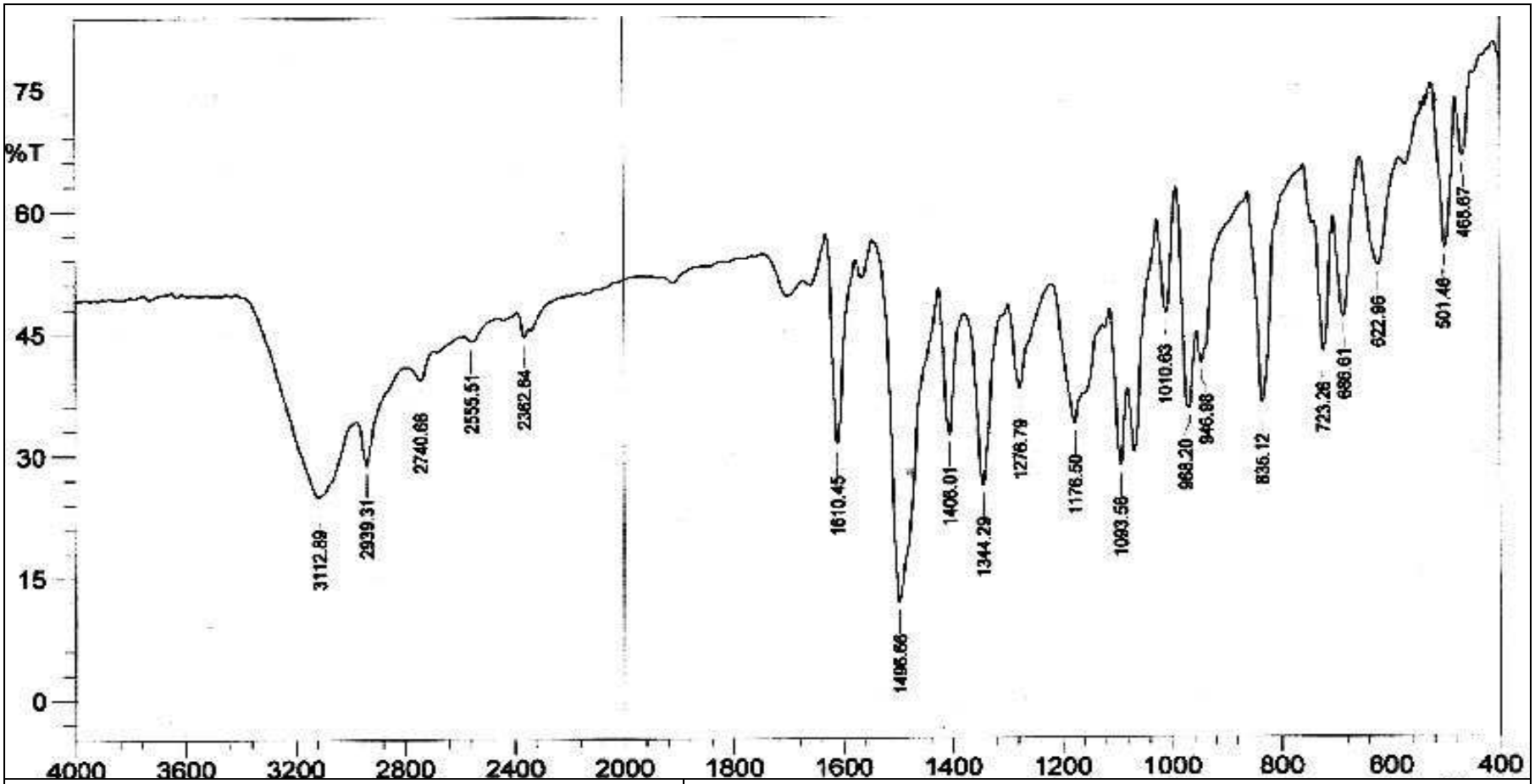


Figure (3-8): F.T.IR spectrum of compound [8] .



7-(p-Bromophenyl)-5-(p-bromophenyl)-1,2,4-triazino[5,6-b][1,3,4]oxadiazole [9].

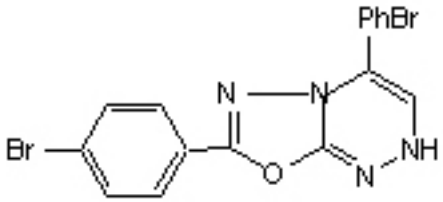
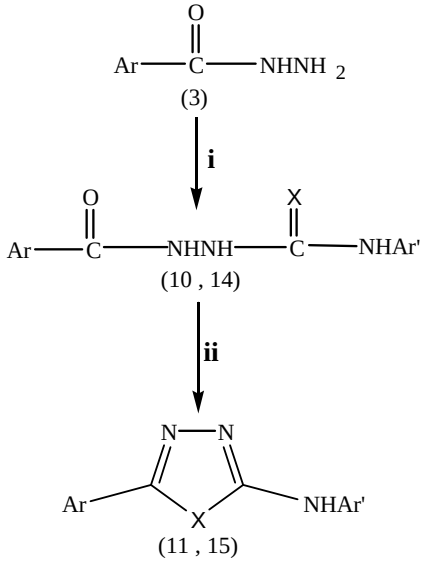


Figure (3-9): F.T.IR spectrum of compound [9] .

3.1.4 Thiosemicarbazide, semicarbazide, thiadiazole and oxadiazole derivatives:

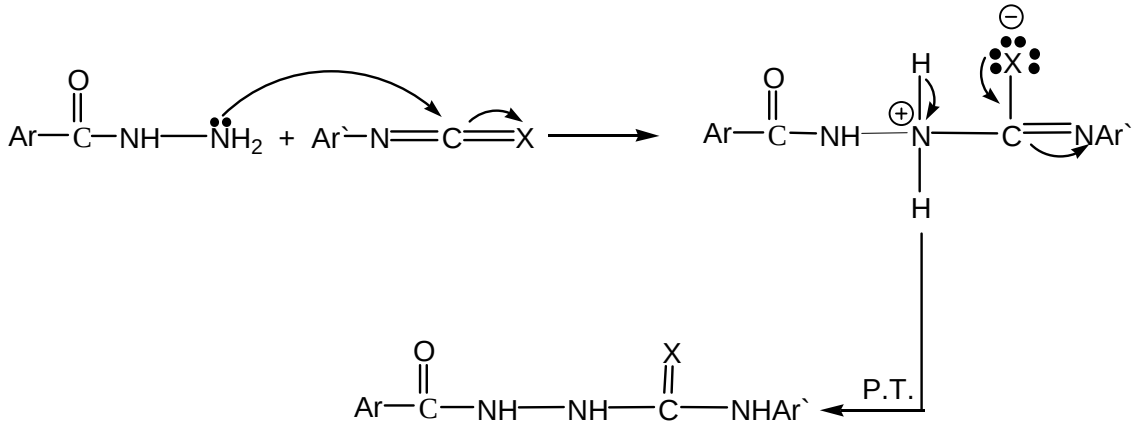


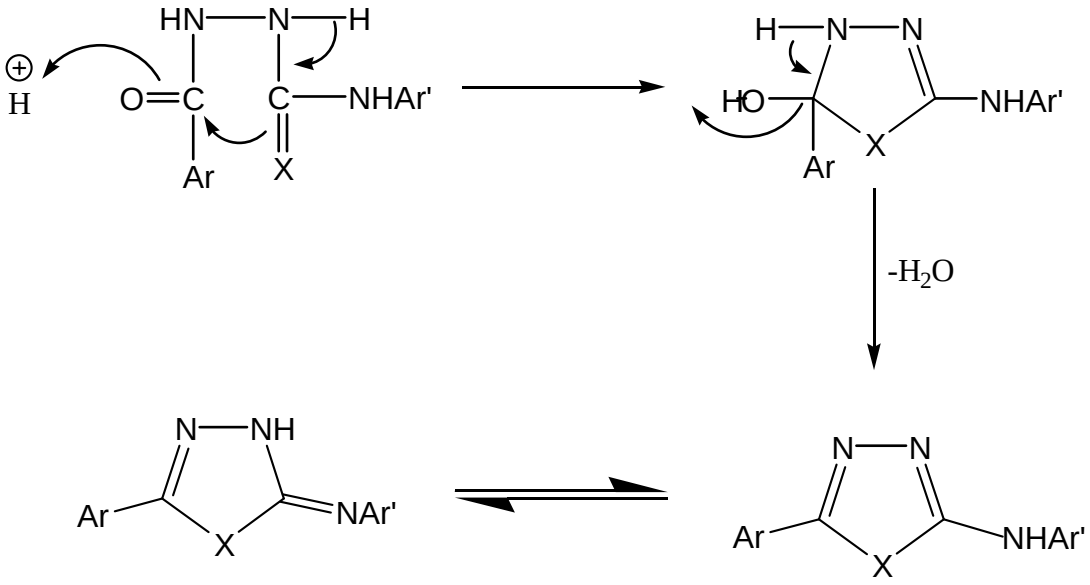
Scheme (4): Reagents and conditions:

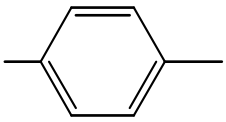
(i) Phenyl isocyanate or isothiocyanate, EtOH, reflux 7 hr.

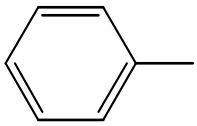
(ii) H^+ , stirred 3 hr and standed overnight.

Oxadiazole and thiadiazole derivatives were synthesized by two steps, first the hydrazide was reacted with phenyl isocyanate or isothiocyanate in the presence of absolute ethanol as a solvent, second step of the reaction conc. sulfuric acid was used for an intramolecular cyclization of the previous compounds with losing a water molecule. The mechanism[113] of the reaction is shown below:





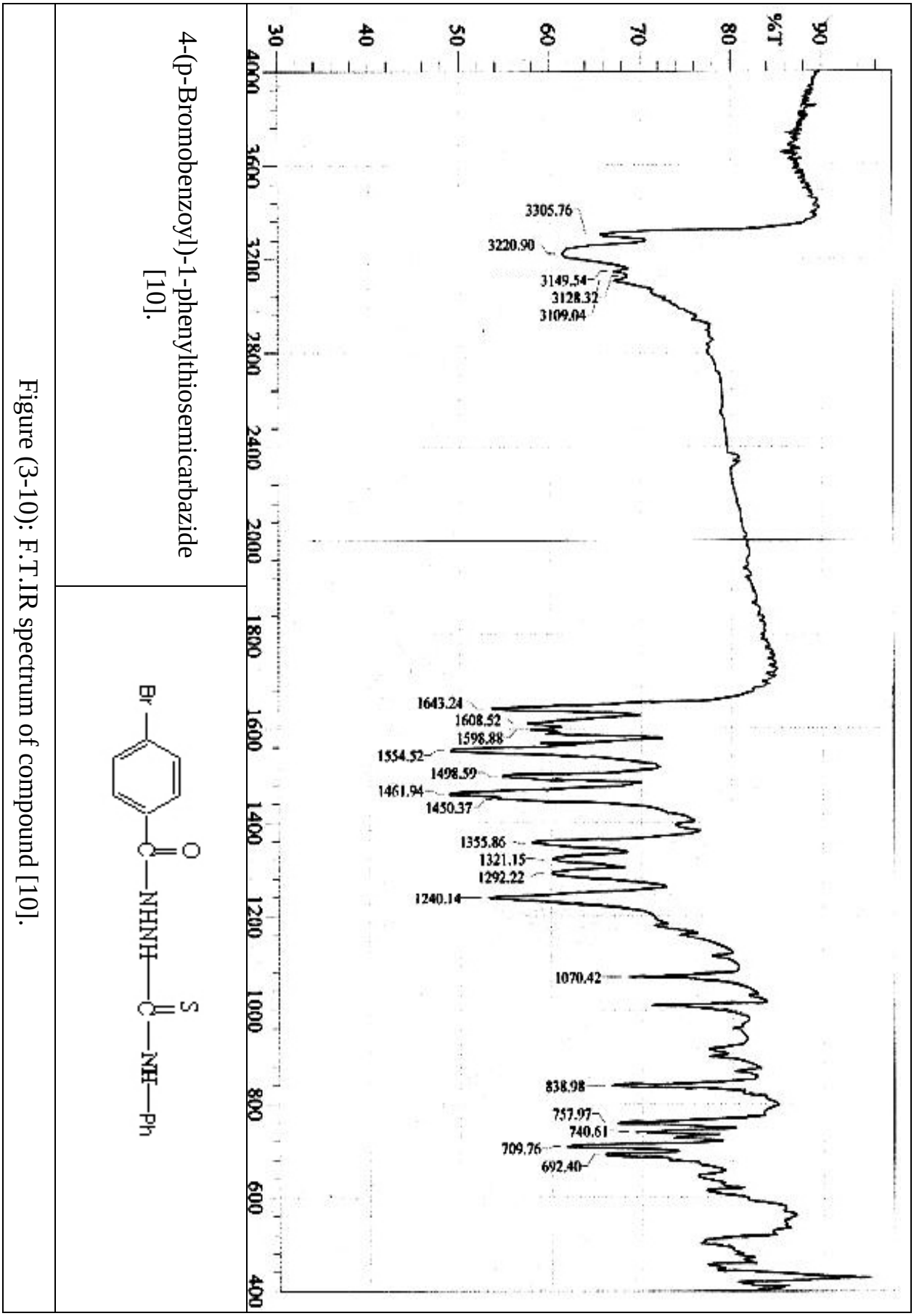
Ar = 

Ar' = 

X = O , S

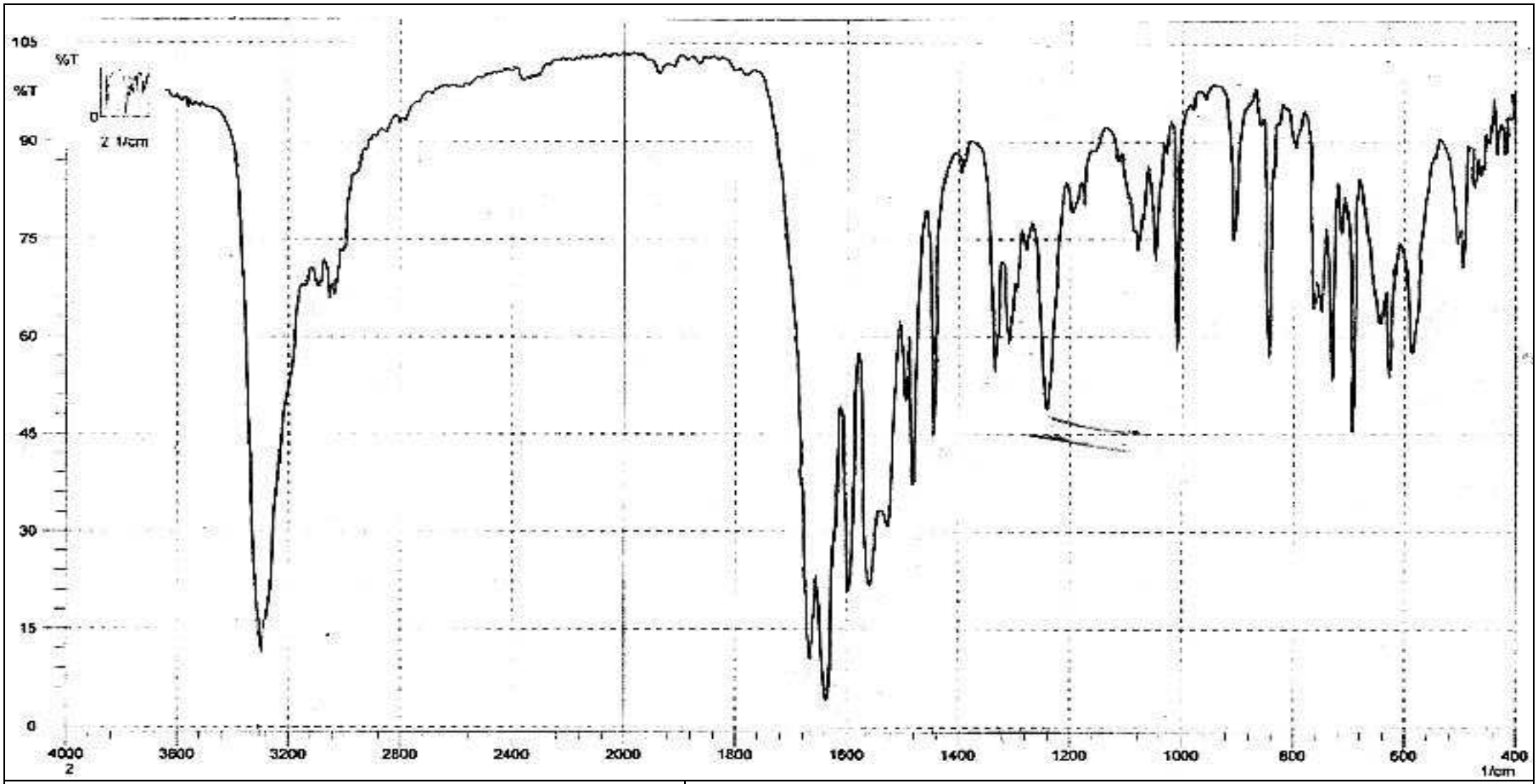
The stractures of thiosemicarbazide [10] and semicarbazide [14] were confirmed by F.T.IR spectral data, the F.T.IR spectrum for the thiosemicarbazide showed the appearance of the three absorption bands at (3305 cm^{-1}), (3221 cm^{-1}) and (3149 cm^{-1}) due to three group of (-NH) and appearance of ν (C=S) band at (1240 cm^{-1}).

Also the F.T.IR spectrum for the semicarbazide showed the disappearance of the two absorption bands at (3309 cm^{-1}) and (3221 cm^{-1}) due to the the asymmetric and symmetric stretching vibration of the (-NH_2) group of the acid hydrazide derivative [3] and appearance of a broad band due to (-NH) group at (3300 cm^{-1}). Two carbonyl groups of compound [14] appeared at (1670 cm^{-1}) and (1643 cm^{-1}) were attributed to urea and amid I respectively. Bands at (3090 cm^{-1}) and (3060 cm^{-1}) were due to the ν(C-H) aromatic group for two aromatic rings. The F.T.IR spectra of the above compounds are shown in figs. (3-10) and (3-11).



4-(p-Bromobenzoyl)-1-phenylthiosemicarbazide [10].

Figure (3-10): F.T.IR spectrum of compound [10].



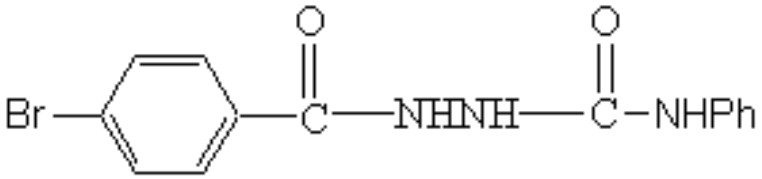
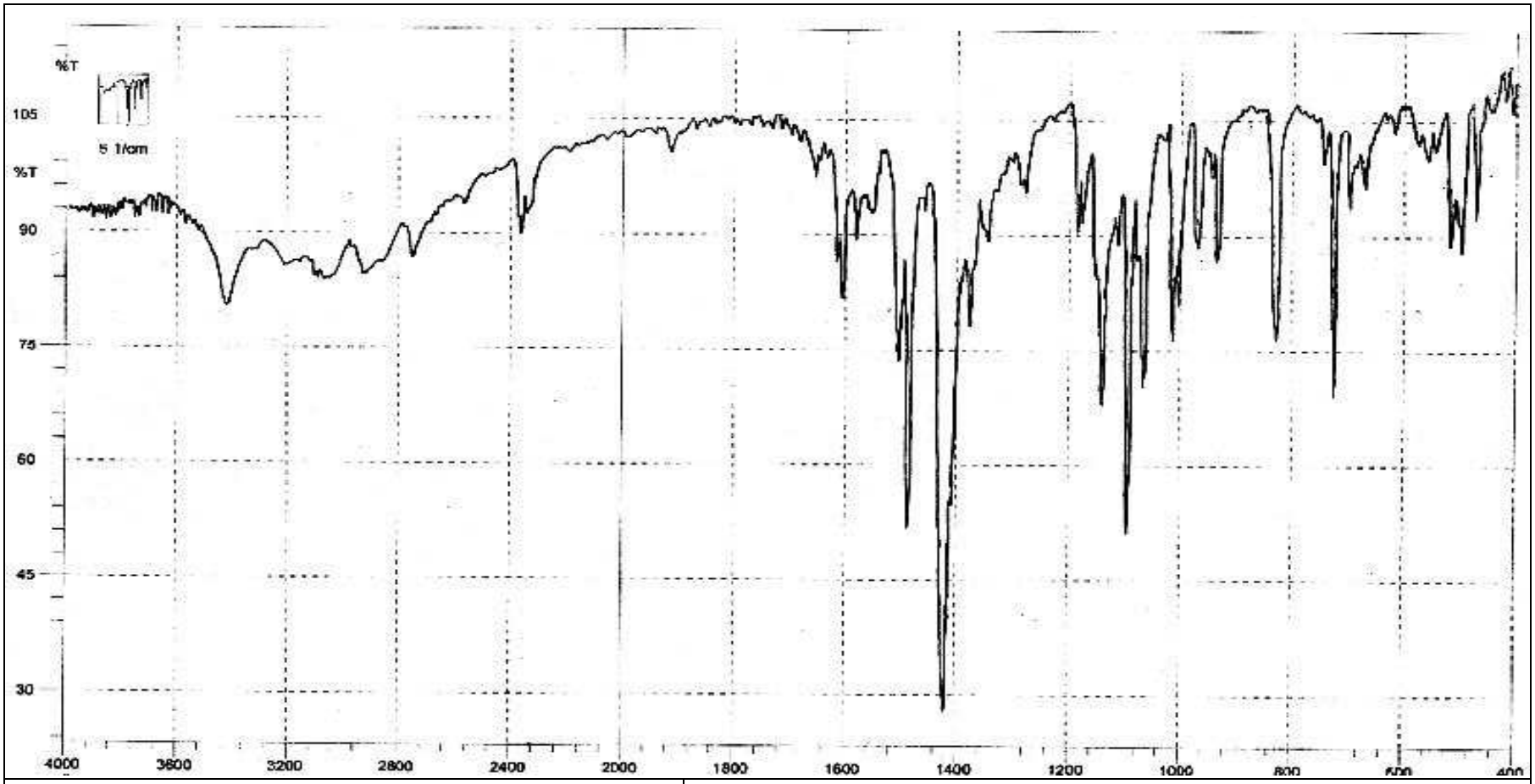
4-(p-Bromobenzoyl)-1-phenylsemicarbazide [14].	

Figure (3-11): F.T.IR spectrum of compound [14] .

The F.T.IR spectrum of 2,5-substituted thiadiazole [11] showed the disappearance of the band at (1643 cm^{-1}) due to ν(C=O) of amide I with the appearance of a band at (1605 cm^{-1}) assignable to ν(C=N) of thiadiazole ring. The F.T.IR spectrum also showed the disappearance of the bands at (3221 cm^{-1}) and (3150 cm^{-1}) due to (NH-NH) groups with appearance of a single band due to (-NH) group at (3395 cm^{-1}) , band at (700 cm^{-1}) belongs to (C-S-C) group.

Also The F.T.IR spectrum of 2,5-substituted oxadiazole [15] showed the disappearance of the two bands of two carbonyl group of the starting material [14] at (1670 cm^{-1}) and (1643 cm^{-1}) and appearance of a band due to ν(C=N) group at (16٠٢ cm^{-1}). The F.T.IR spectrum also showed the disappearance of the band at (3300 cm^{-1}) due to (NH-NH) group with appearance of a band at (3٣٧٥ cm^{-1}) assignable to (-NH) group, ν(C-O-C) asymmetric and symmetric bands appeared at (12٤٠ cm^{-1}) and (10٢٦ cm^{-1}) respectively. The ν(C-O-C) cyclic groups in oxadiazole are good evidences for the structure assigned to these compounds are shown in figs. (3-12) and (3-13).



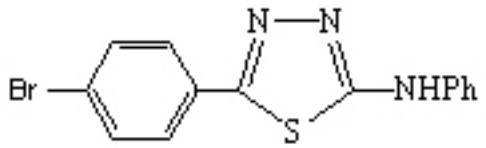
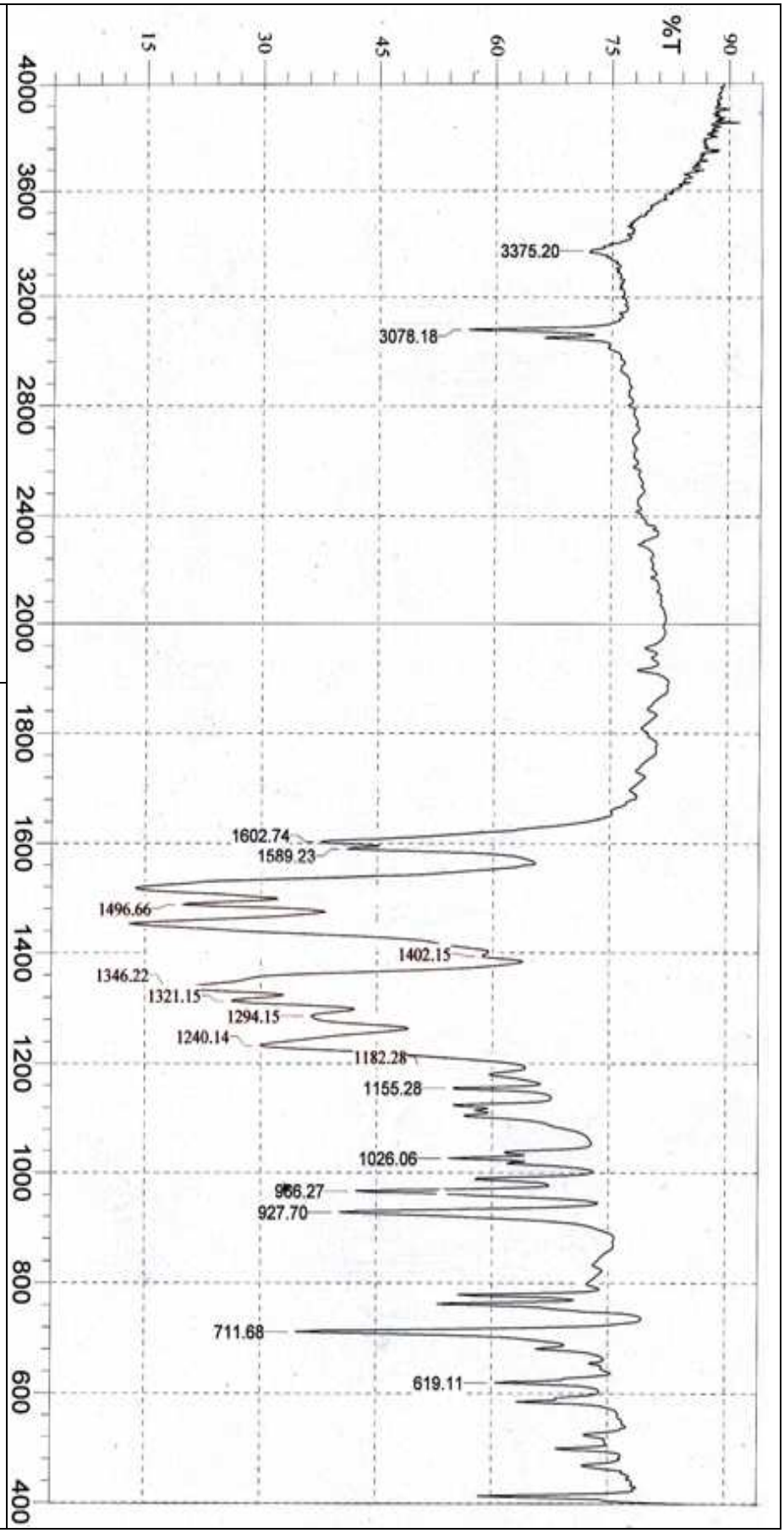
2-(Phenyl amino)-5-(p-bromophenyl)-1,3,4-thiadiazole [11].	

Figure (3-12): F.T.IR spectrum of compound [11] .



2-(Phenyl amino)-5-(p-bromophenyl)-1,3,4-oxadiazole [15].

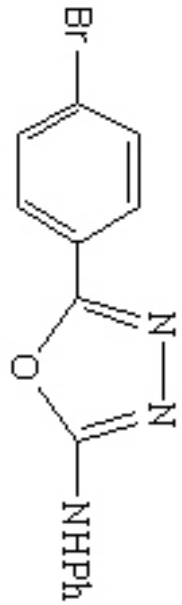
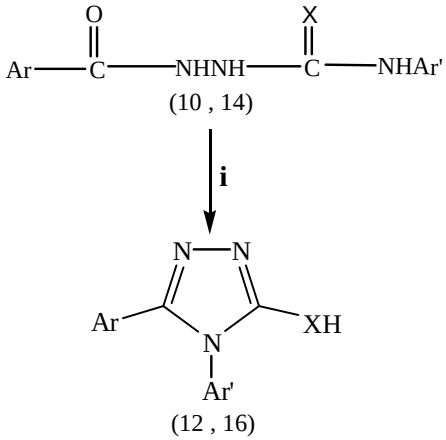


Figure (3-13): F.T.IR spectrum of compound [15].

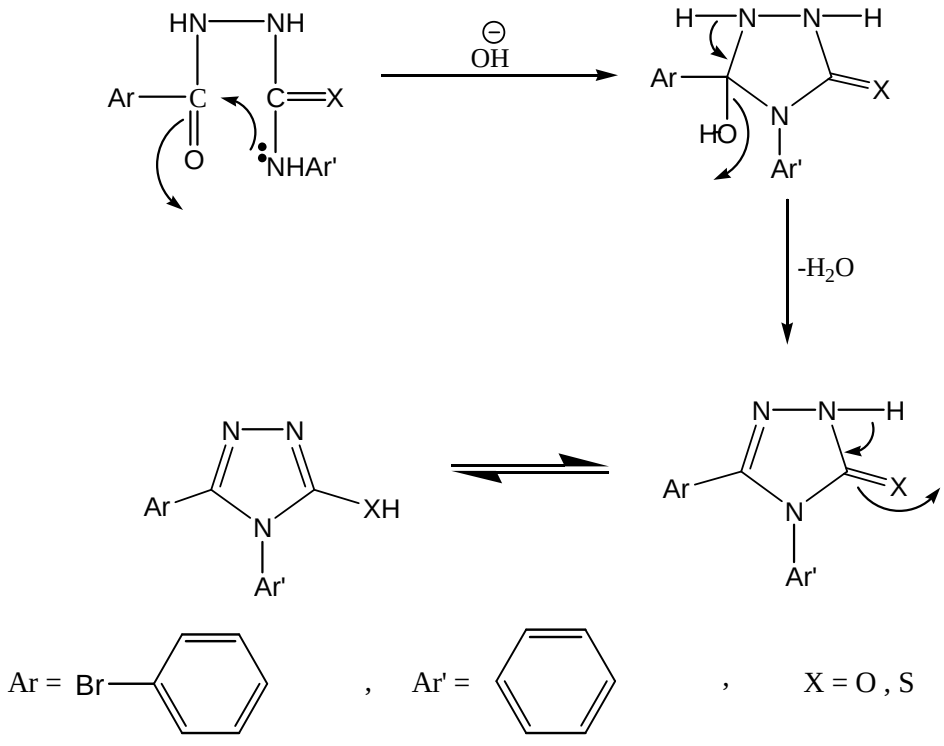
3.1.5 3,4,5-Substituted triazole derivatives:



Scheme (5): Reagents and conditions:

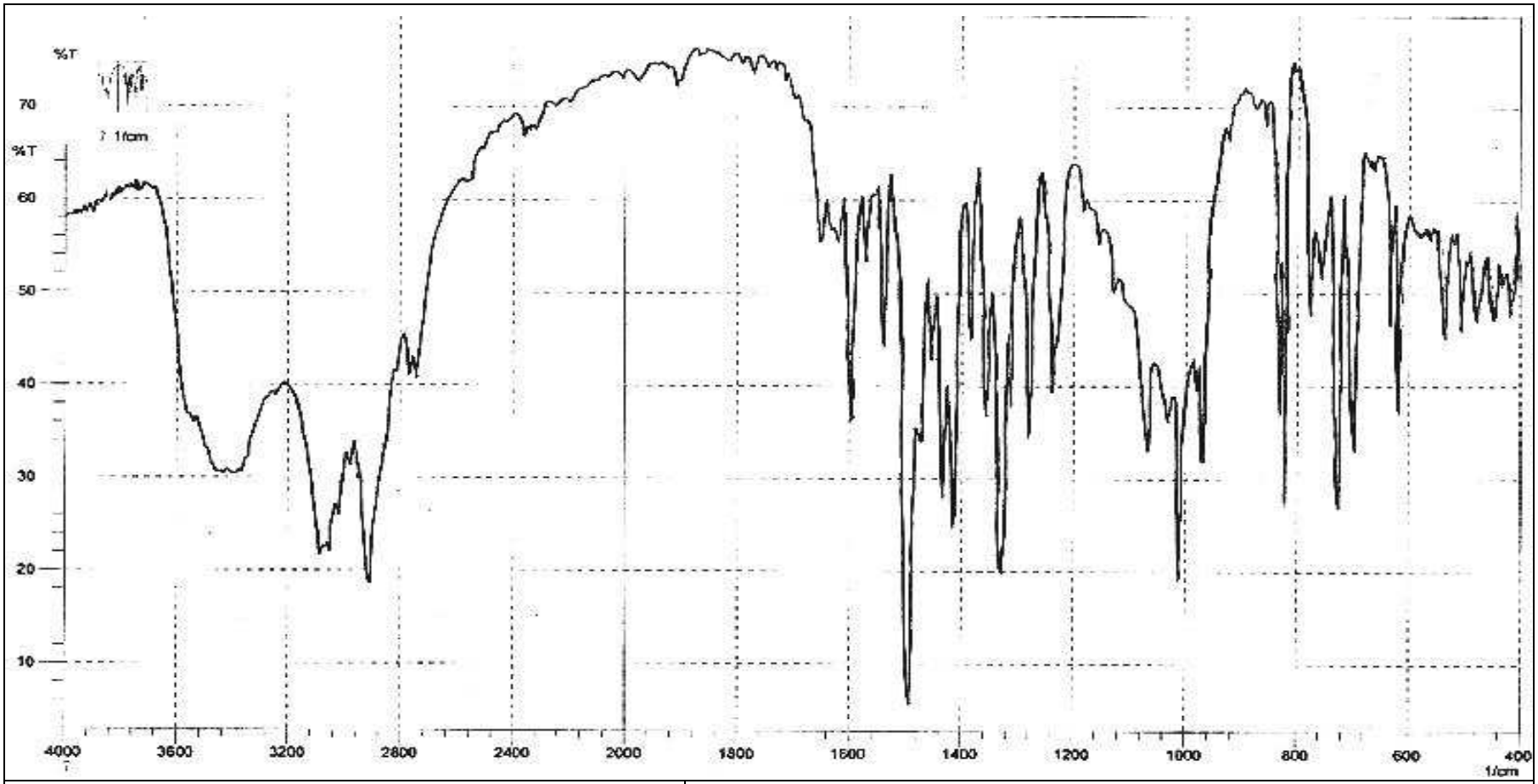
(i) 2N NaOH, reflux 7 hr.

1,2,4-Triazole derivatives [12] and [16] were synthesized from the reaction of thiosemicarbazide [10] or semicarbazide [14] with sodium hydroxide solution under refluxing condition affected intramolecular cyclization through the loss of water molecule giving the desired triazole derivatives [12] and [16], the formation of above compounds may be visualized by the following mechanism(113).



1,2,4-Triazole derivatives [12] and [16] were identified by F.T.IR spectra, the F.T.IR spectrum of 4,5-substituted triazole-3-thion [12] showed the disappearance of the band at (1643 cm^{-1}) due to ν(C=O) of amide I with the appearance of a band at (1600 cm^{-1}) assignable to ν(C=N) of triazole ring, the F.T.IR also showed the disappearance of the bands at (3221 cm^{-1}) and (3150 cm^{-1}) due to (NH-NH) group with appearance of a single band due to (N-H) group at (3400 cm^{-1}), band at (1240 cm^{-1}) belong to ν(C=S) group.

Also , the F.T.IR spectrum of 4,5-substituted triazole-3-one [16] showed the disappearance of the two bands of two carbonyl group of the starting material [14] at (1670 cm^{-1}) and (1643 cm^{-1}) and appearance of a band due to ν(C=N) group at (1608 cm^{-1}), the F.T.IR spectrum also showed the appearance of a band at (3433 cm^{-1}) assignable to (O-H) group. The F.T.IR spectra of the above compounds are shown in figs. (3-14) and (3-15).



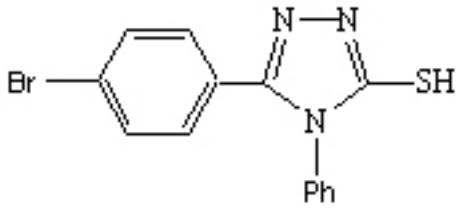
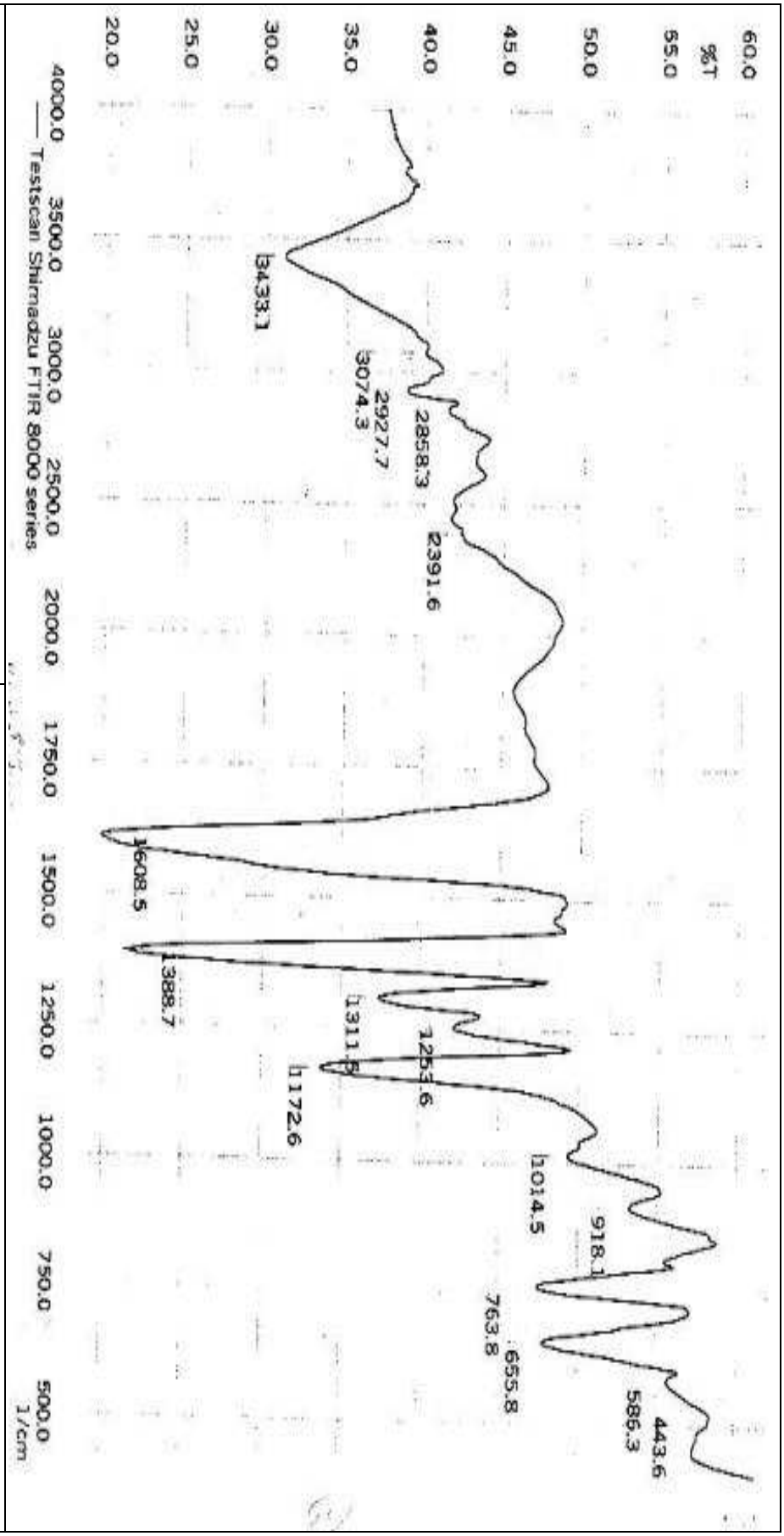
5-(p-Bromophenyl)-4-phenyl-1,2,4-triazole-3-thiol [12].	

Figure (3-13): F.T.IR spectrum of compound [١٢].



5-(p-Bromophenyl)-4-phenyl-1,2,4-triazole-3-ol [16].

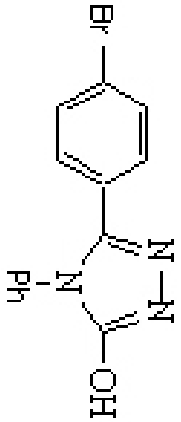
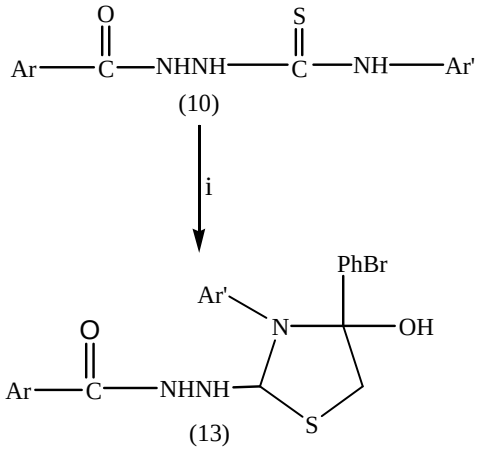


Figure (3-15): F.T.IR spectrum of compound [16] .

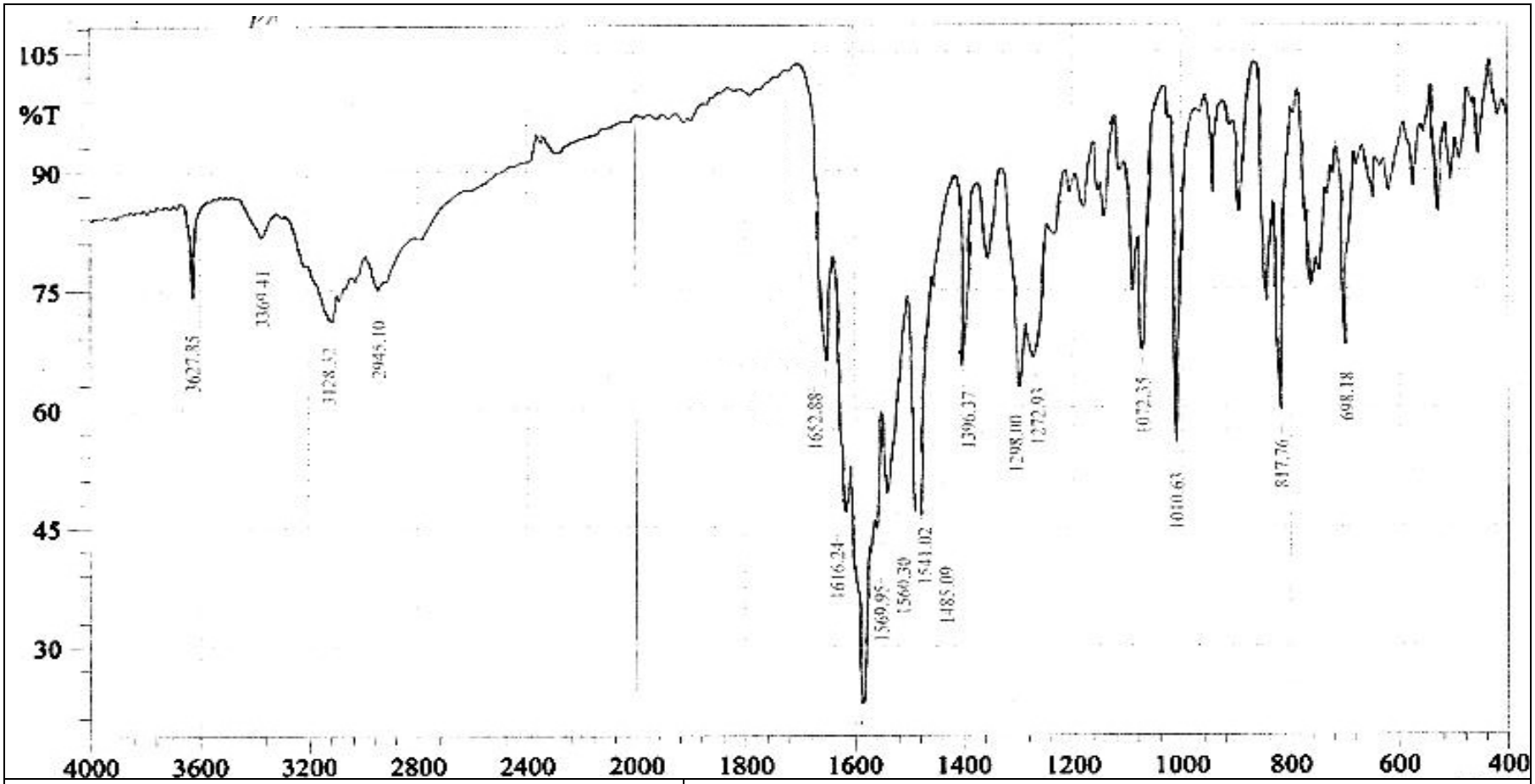
3.1.6 Thiazolidine derivative:



Scheme (6): Reagents and conditions:

(i) p-Bromophenacyl bromide, EtOH , reflux 8 hr.

The thiazolidine derivative was synthesized from the reaction of thiosemicarbazide [10] with *p*-bromophenacyl bromide which was used for cyclization of the previous compound. The stracture of thiazolidine derivative was confirmed by F.T.IR spectrum. The F.T.IR spectrum showed the disappearance of thione group of the thiosemicarbazide [10] at (1240 cm^{-1}) with the appearance of a sharp band at (3627 cm^{-1}) assignable to (O-H) group, two bands due to (NH-NH) group appeared at (3369 cm^{-1}) and (3128 cm^{-1}), strong and sharp band at (698 cm^{-1}) belongs to (C-S-C) group. The F.T.IR spectrum of the above compound is shown in fig. (3-16).



5-(p-Bromophenyl)-2-(p-bromophenyl hydrazide)-1-N-phenyl-5-(hydroxy)thiazolidine [13].

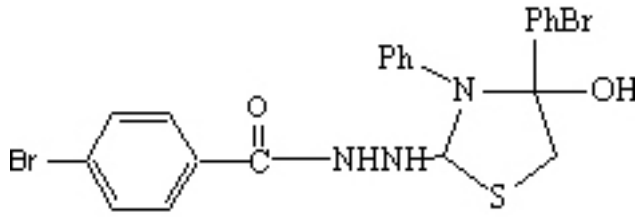
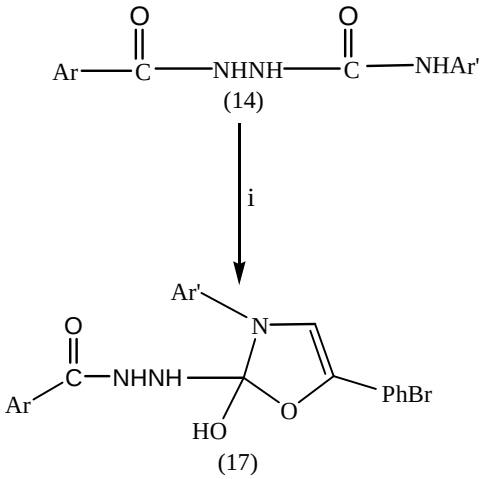


Figure (3-16): F.T.IR spectrum of compound [13] .

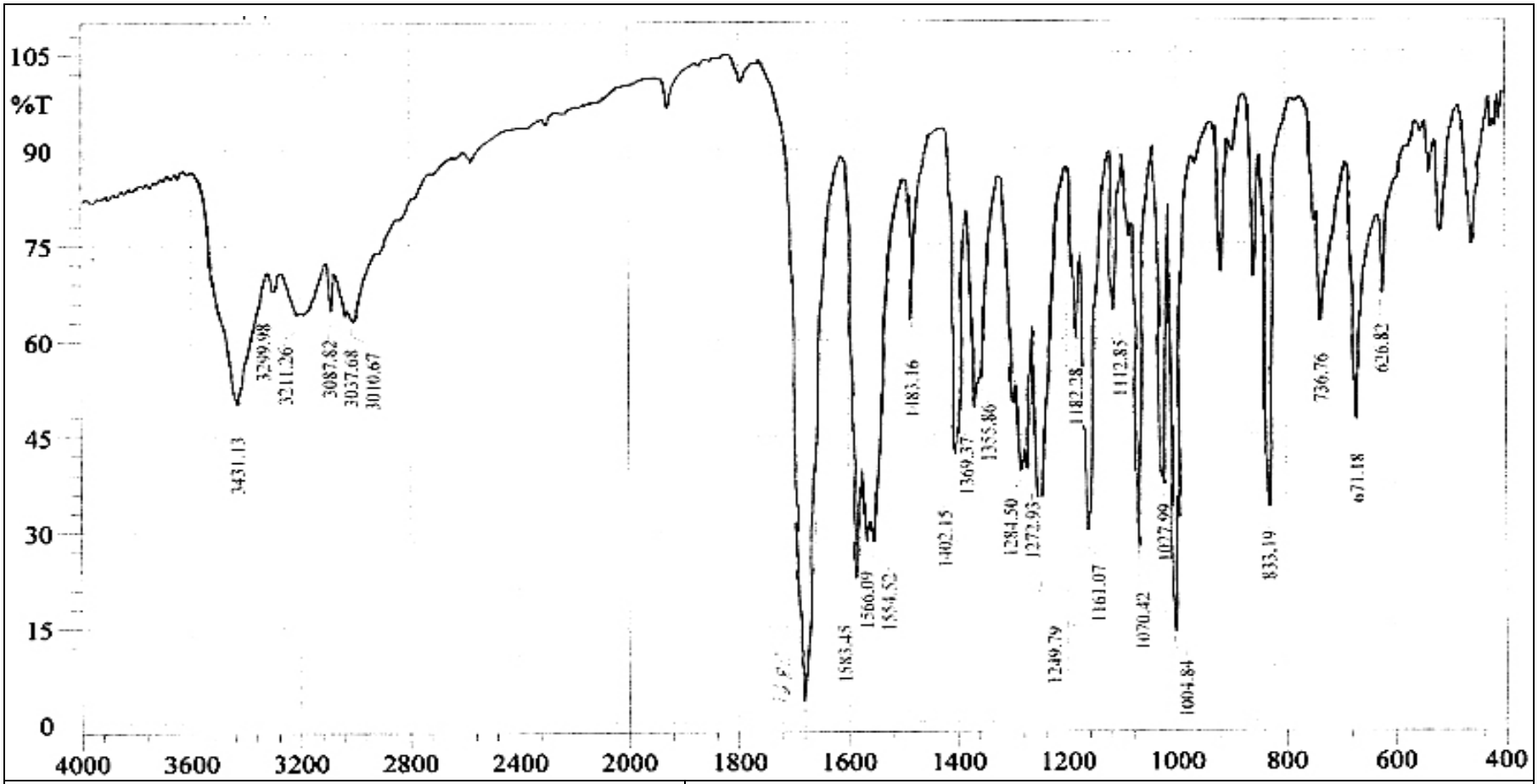
3.1.7 Oxazoline derivative:



Scheme (7): Reagents and conditions:

(i) p-Bromophenacyl bromide, EtOH , reflux 8 hr.

The oxazoline derivative was synthesized from the reaction of semicarbazide [14] with p-bromophenacyl bromide which was used for cyclization of the previous compound. The stracture of oxazoline derivative was confirmed by F.T.IR spectrum, the F.T.IR spectrum showed the disappearance of carbonyl group of the semicarbazide [14] at (1643 cm^{-1}) with the appearance of a band at (3431 cm^{-1}) assignable to (-OH) group, two bands due to (-NH-NH) group appeared at (3300 cm^{-1}) and (3210 cm^{-1}), strong sharp two bands at (1250 cm^{-1}) and (1070 cm^{-1}) belongs to the asymmetric and symmetric (C-O-C) group. The F.T.IR spectrum of the above compound is shown in fig. (3-17).



5-(p-Bromophenyl)-2-(p-bromophenyl hydrazide)-3-N-phenyl-2-(hydroxy)oxazoline [17].

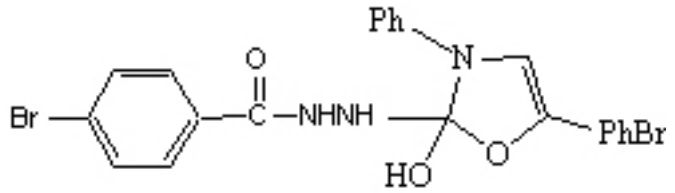
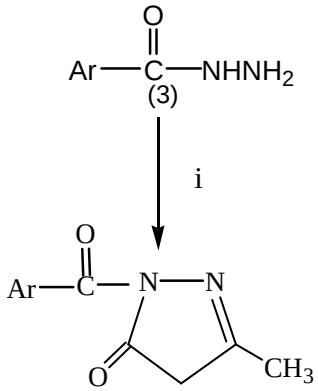


Figure (3-17): F.T.IR spectrum of compound [17].

3.1.8 Pyrazolone derivative:

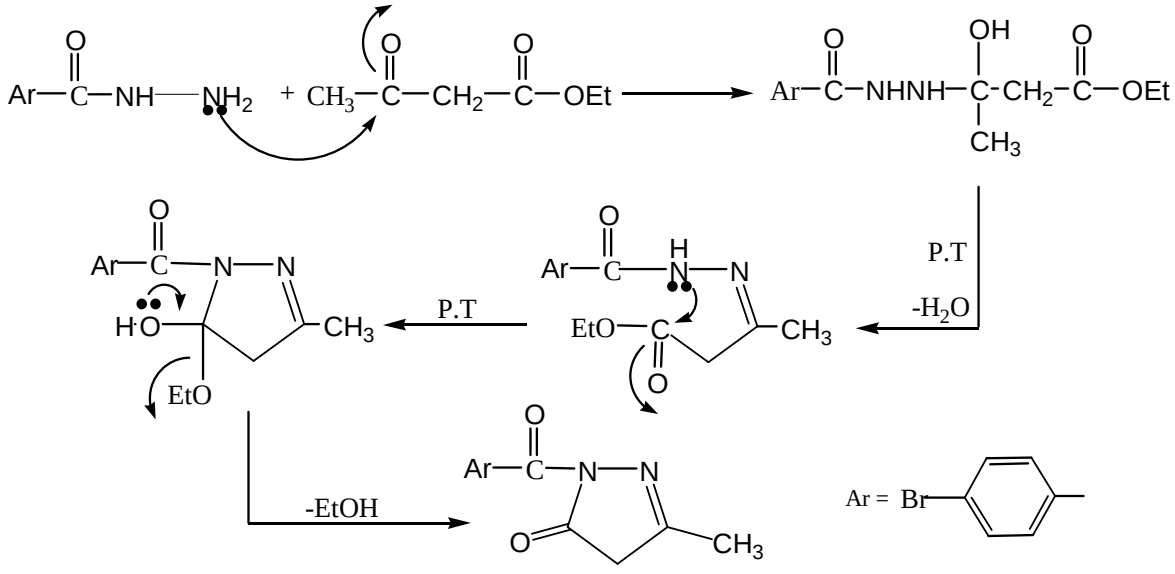


Scheme (8): Reagents and conditions:

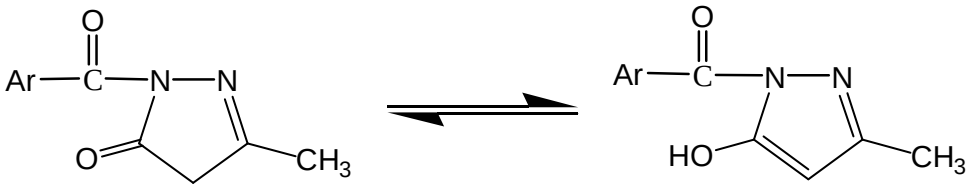
(i) Ethylacetoacetate, EtOH , reflux 5 hr.

Compound [18] was synthesized from reacting hydrazide with ethyl acetoacetate in absolute ethanol. The compound [18] was characterized by F.T.IR spectrum.

The suggested mechanism for this reaction involves the nucleophilic attack of nitrogen atom of the hydrazide on the ketonic carbonyl of ethyl acetoacetate followed by the formation of ***Schiff*** base as intermediate compound, then another intramolecular nucleophilic attack occur between the other nitrogen atom of hydrazide and the esteric carbonyl of ethyl acetoacetate as shown:

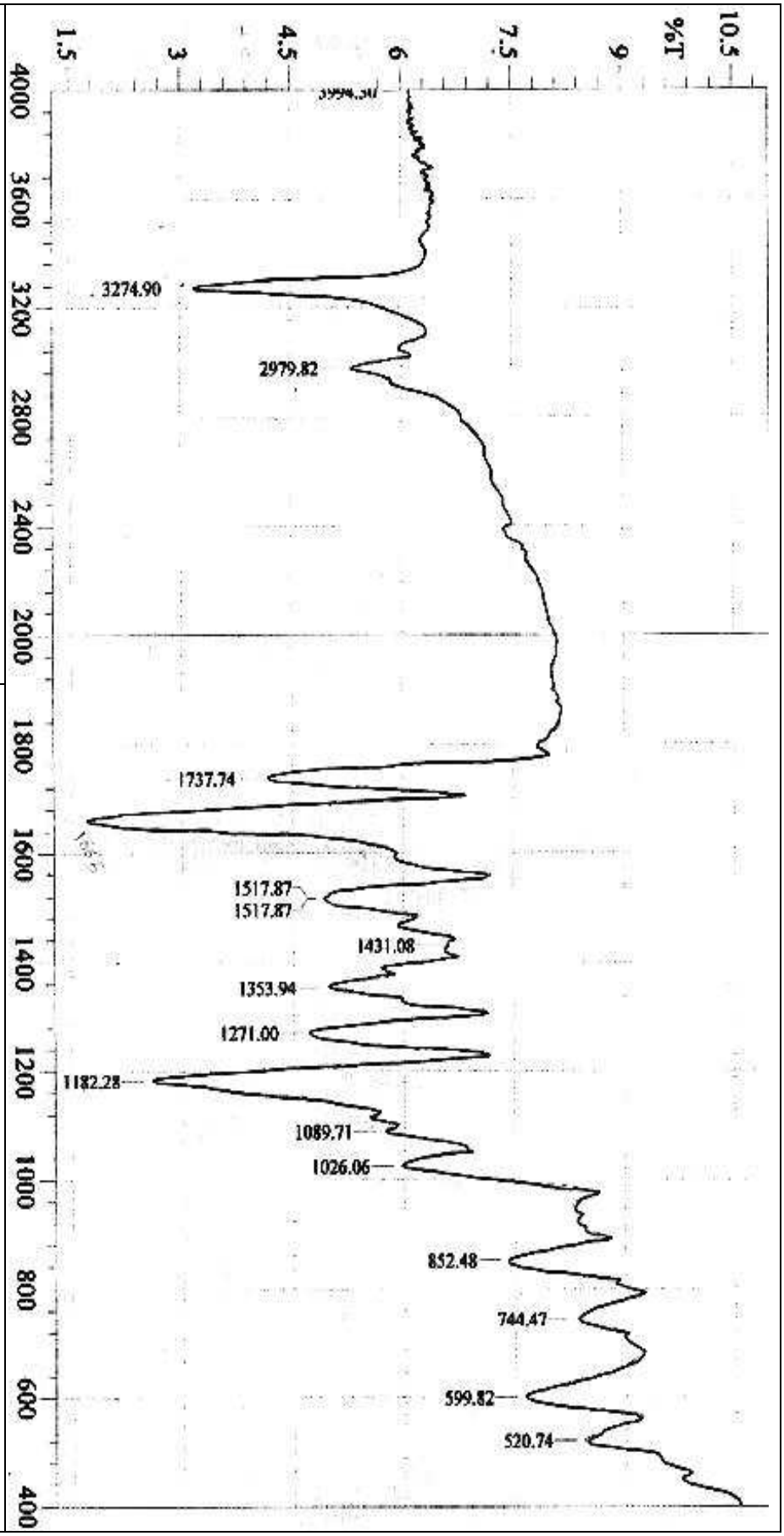


The F.T.IR spectrum of compound [18] showed the presence of bands at (3275 cm^{-1}) and (1737 cm^{-1}) which were due to the ν(-OH) and ν(C=O) moieties of pyrazole ring, respectively, while the (C=O) stretching band of amide I occur at (1661 cm^{-1}). From the above mentioned facts, we can say that compound [18] can exist in equilibrium between keto [I] and enol [II] forms.



[I] [I I]

Also a new band appeared at (2979 cm^{-1}) due to the stretching vibration of the (-C-H) group. The F.T.IR spectrum of the above compound is shown in fig.(3-18).



1-(p-Bromobenzoyl)-3-methyl pyrazol-5-one [18].

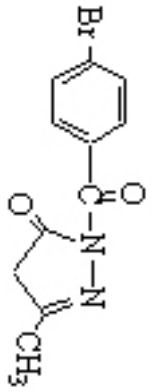
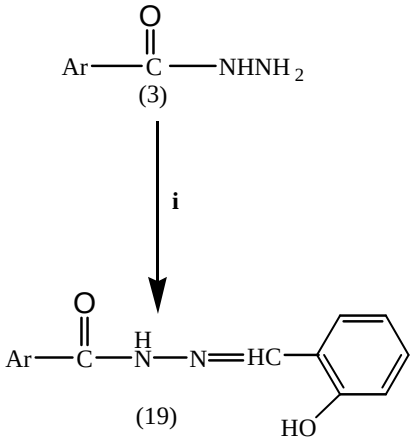


Figure (3-18): F.T.IR spectrum of compound [18].

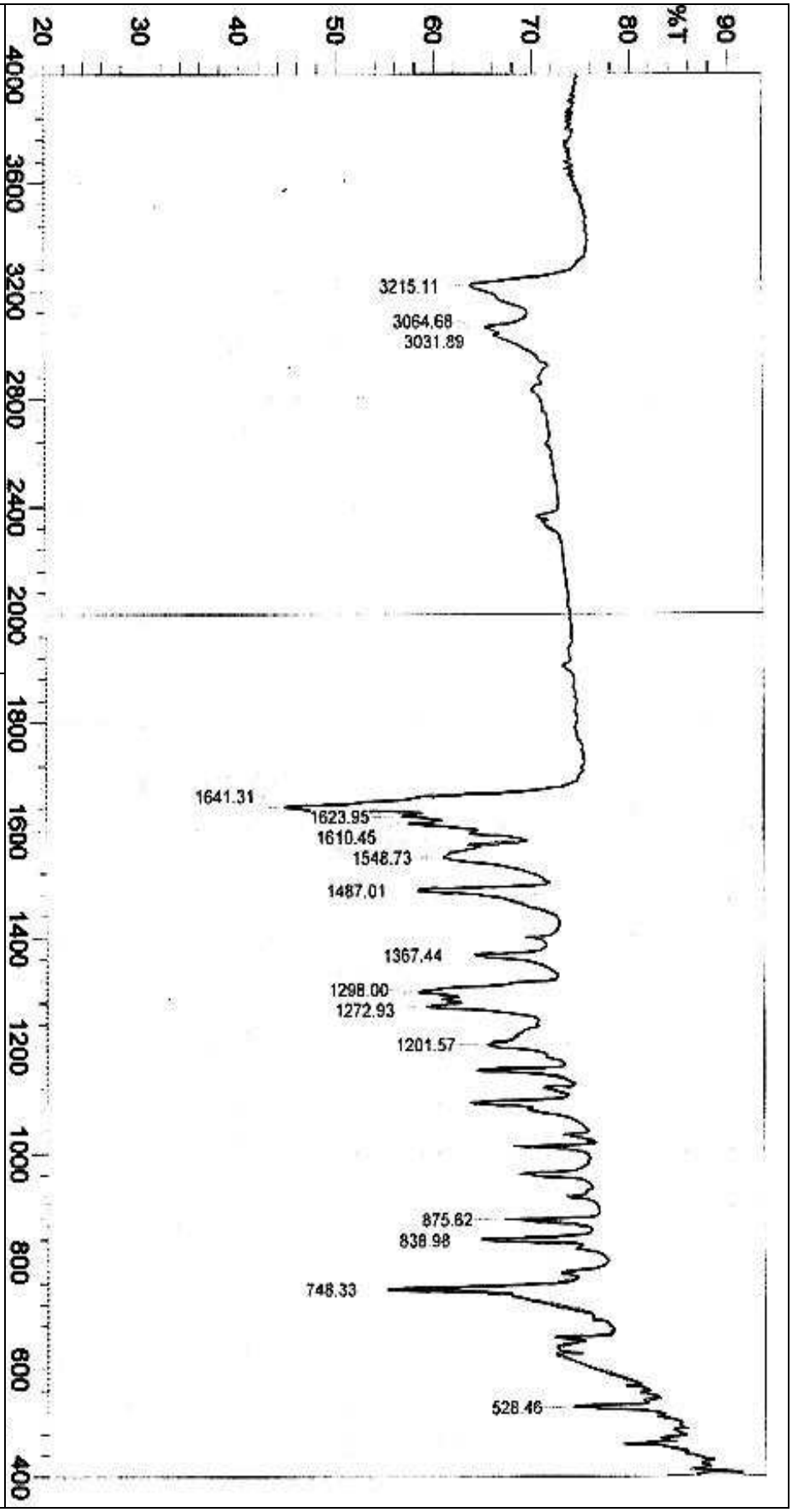
3.1.9 2-hydroxybenzylidine-1- p-Bromophenyl hydrazone:



Scheme (9): Reagents and conditions:

(i) o-Salicylaldehyde, EtOH , reflux 2 hr.

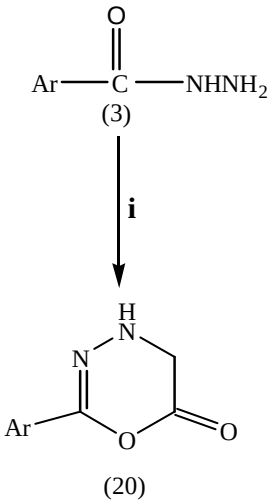
Compound [19] was synthesized from reacting of acid hydrazide with o-salicylaldehyde in absolute ethanol. The compound was characterized by F.T.IR spectrum, a single band due to (-NH) group appeared at (3215 cm^{-1}), the carbonyl group appeared at (1641 cm^{-1}). The disappearance of (O-H) group due to the possibility of hydrogen bonding, the aromatic (C-H) appeared at (3064 cm^{-1}) and (3032 cm^{-1}). The F.T.IR spectrum of the above compound is shown in fig.(3-19).



2-Hydroxybenzylidine -1-p-bromophenyl hydrazone [19].

Figure (3-19): F.T.IR spectrum of compound [19] .

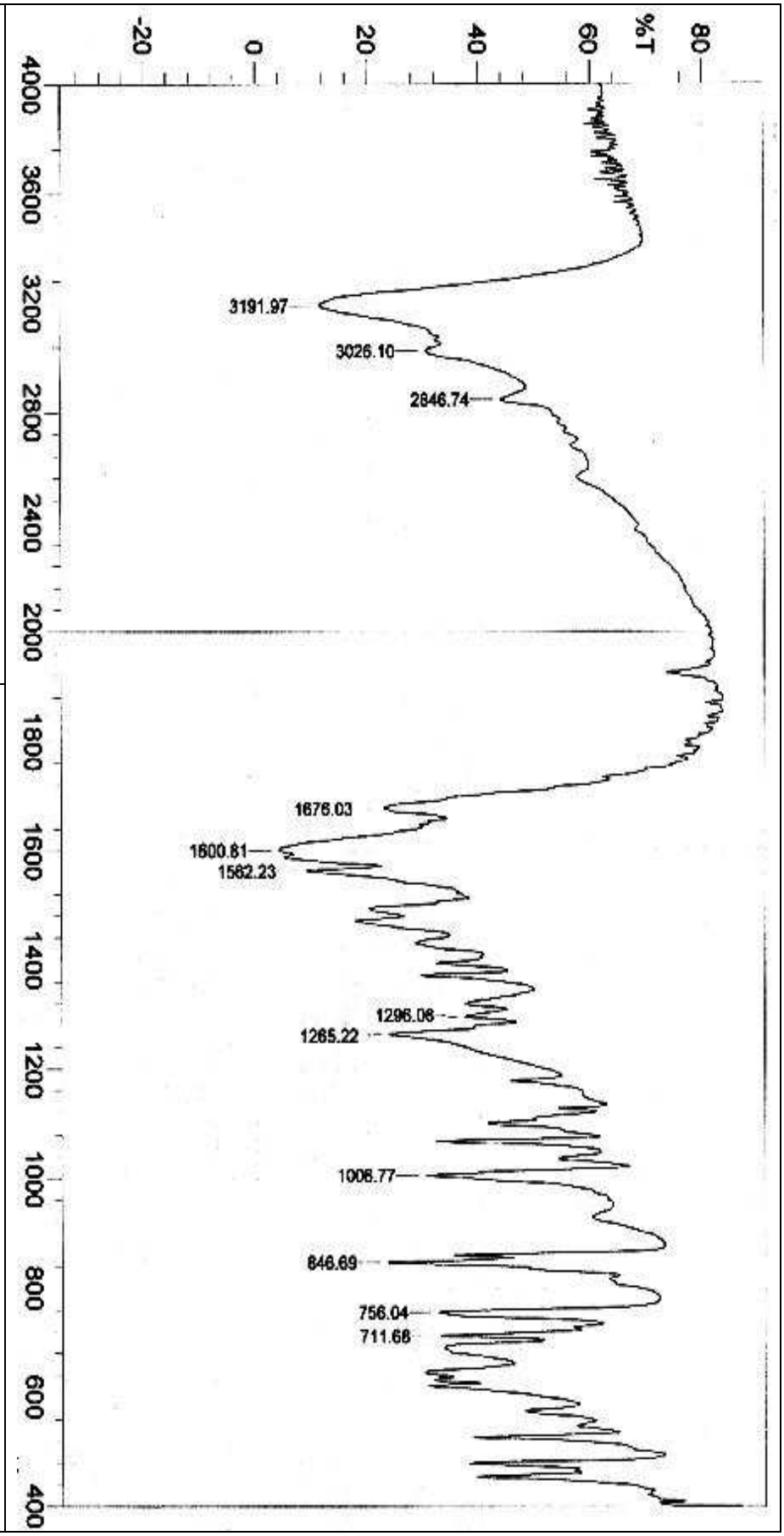
3.1.10 Oxapyridazine derivative:

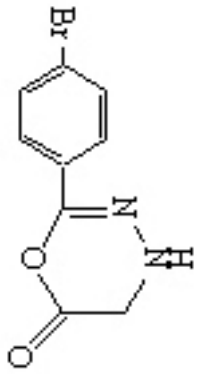


Scheme (10): Reagents and conditions:

(i) Chloroacetic acid, acetic anhydride , reflux 4 hr.

Compound [20] was synthesized from the reacting of acid hydrazide with monochloroacetic acid in acetic anhydride as a solvent. The compound was identified by F.T.IR spectrum, a single band due to (-NH) group appeared at (3192 cm^{-1}), the carbonyl group appeared at (1676 cm^{-1}) [114] . Sharp absorption band appeared at (1600 cm^{-1}) due to (C=N) group, the aromatic (C-H) group appeared at (3026 cm^{-1}), bands at (1265 cm^{-1}) and (1080 cm^{-1}) belongs to the asymmetric and symmetric (C-O-C) band. The F.T.IR spectrum of the above compound is shown in fig.(3-20).

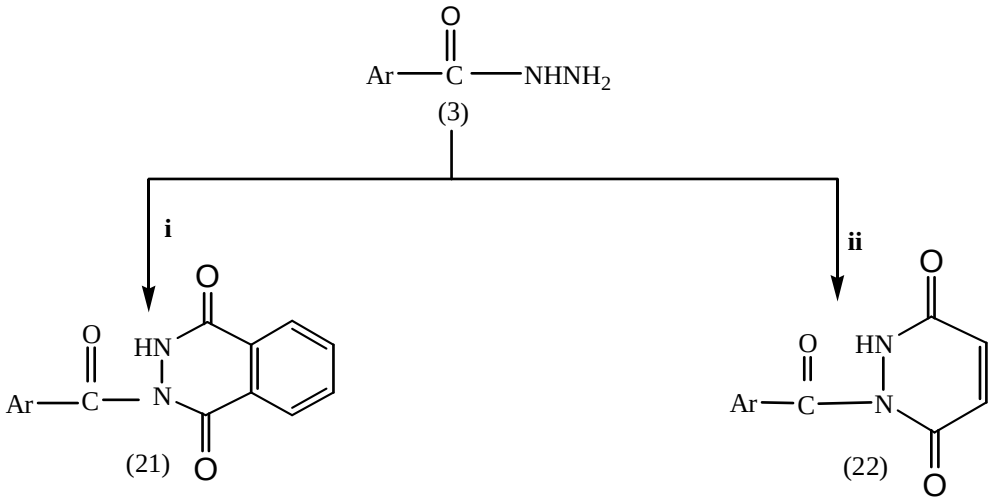




2-(p-Bromophenyl)-4*H*-1,3,4-oxapyridazin-6-one [20].

Figure (3-1): F.T.IR spectrum of compound [٢٠].

3.1.11 Phthalazin and pyridazin-dione derivatives:



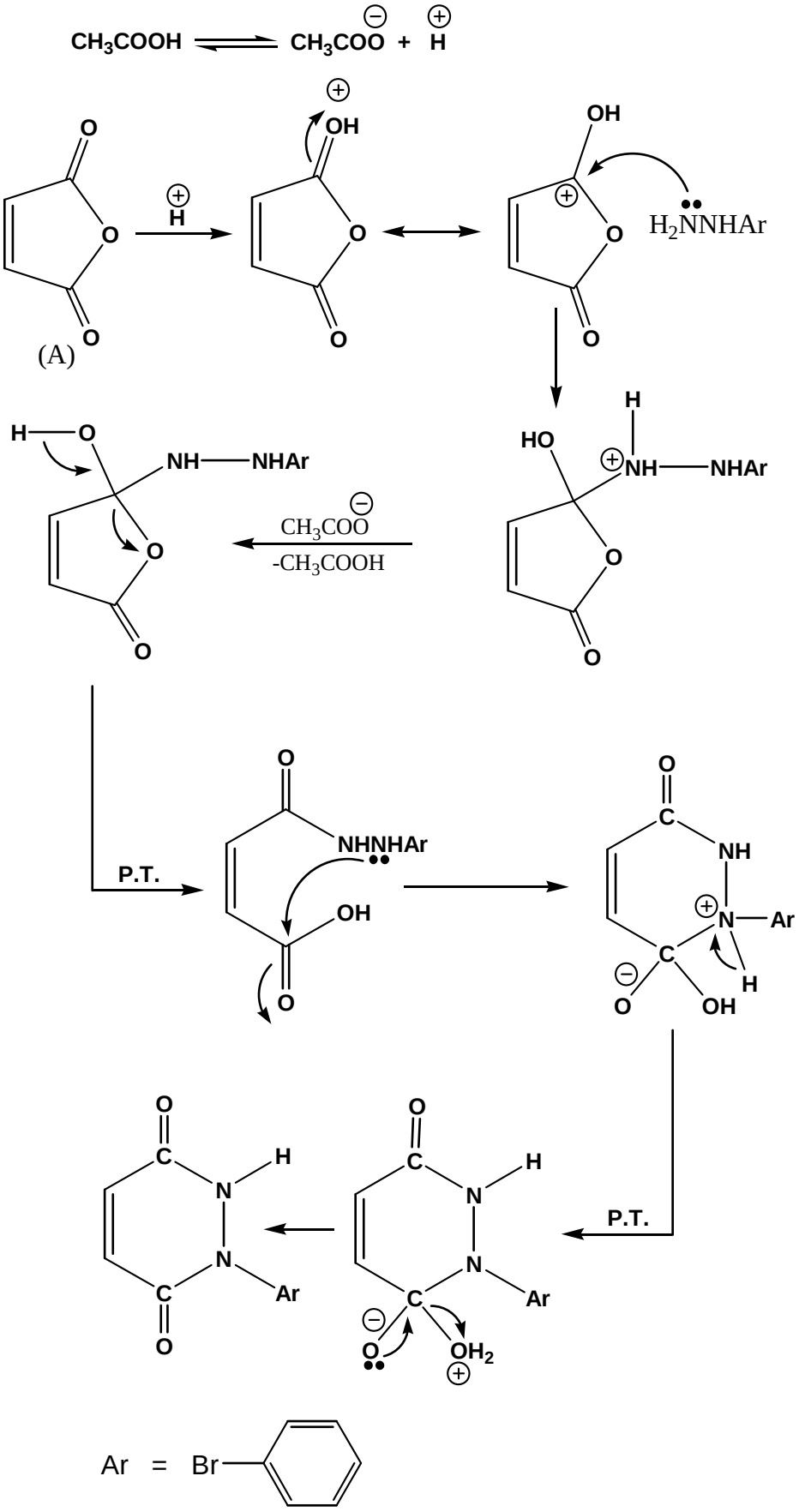
Scheme (11): Reagents and conditions:

(i) Phthalic anhydride, acetic acid, reflux 7 hr.

(ii) Maleic anhydride, acetic acid, reflux 7 hr.

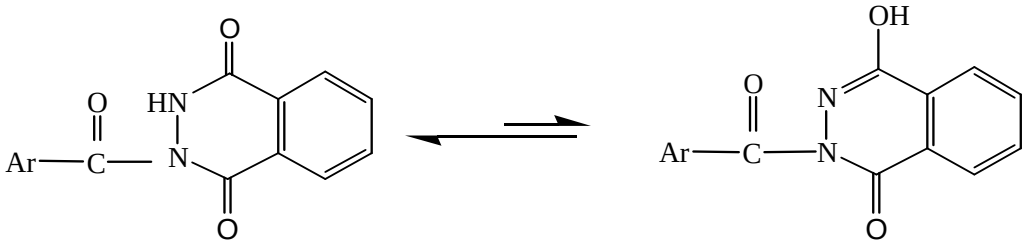
Six membered heterocyclic rings [21] and [22] were synthesized by the reaction of hydrazide [3] with phthalic and maleic anhydride respectively in the presence of acetic acid as a solvent and catalyst. The suggested mechanism for the synthesis of the previous derivatives can be explained as the following general mechanism.

In the first step of the reaction, nucleophilic attack take place by the hydrazide on the carbon atom bearing the positive charge. Lossing a water molecule.



A = maleic anhydride or phthalic anhydride

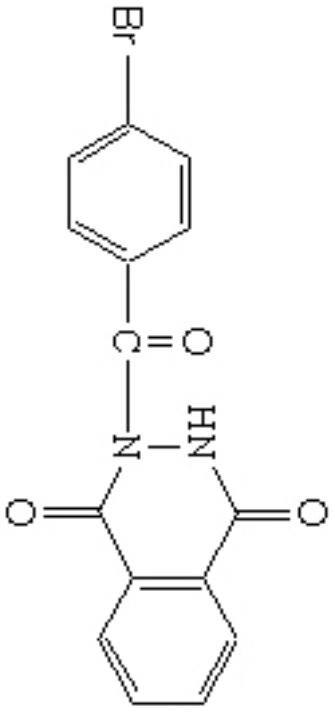
The F.T.IR spectrum of compound [21] shows two bands at (3344 cm^{-1}) and (3199 cm^{-1}) which where assignable to (-O-H) and (-NH) stretching vibration. The band at (1735 cm^{-1}) was due to ν(C=O) moiety of pyridazine ring. Band at (1681 cm^{-1}) was due to the ν(C=O) of amide I. From the above mentioned results we can say that the compound [21] can be exist in two tautomeric forms, keto [I] and enol [II] forms.



[I] [II]

Also, the F.T.IR spectrum of compound [22] showed the disappearance of two bands of (-NH_2) group of starting material [3] at (3309 cm^{-1}) and (3221 cm^{-1}), appearance of a band due to (-NH) group at (3304 cm^{-1}). Two carbonyl group of compound [22] appeared at (1735 cm^{-1}) and (1672 cm^{-1}) for pyridazine ring and at (1643 cm^{-1}) for the amide carbonyl. The F.T.IR spectra of the above compounds are shown in figs.(3-21) and (3-22).

1-N-(p-Bromobenzoyl)-1,2-dihydro-phthalazin-3,8-dione [21].



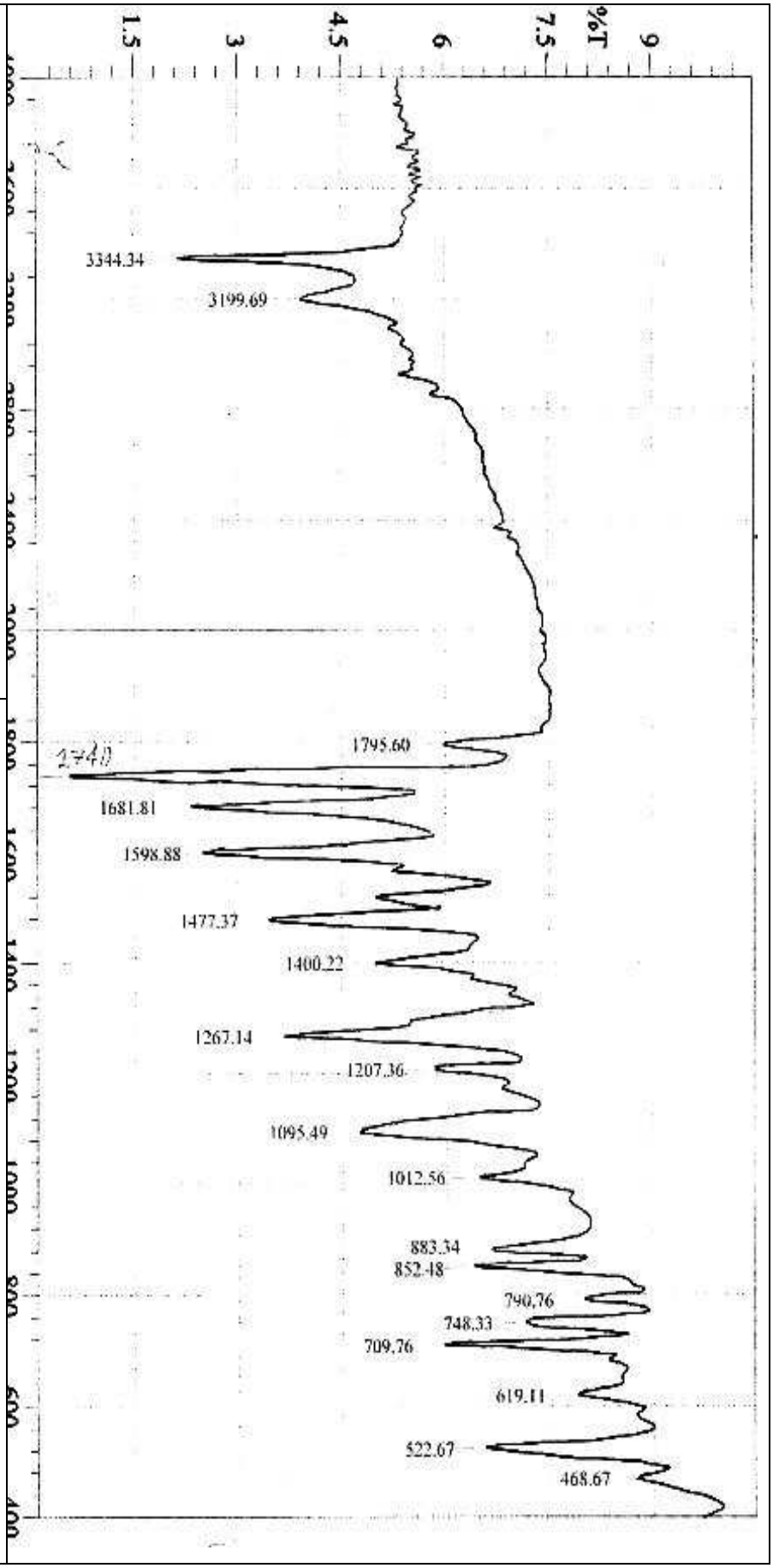
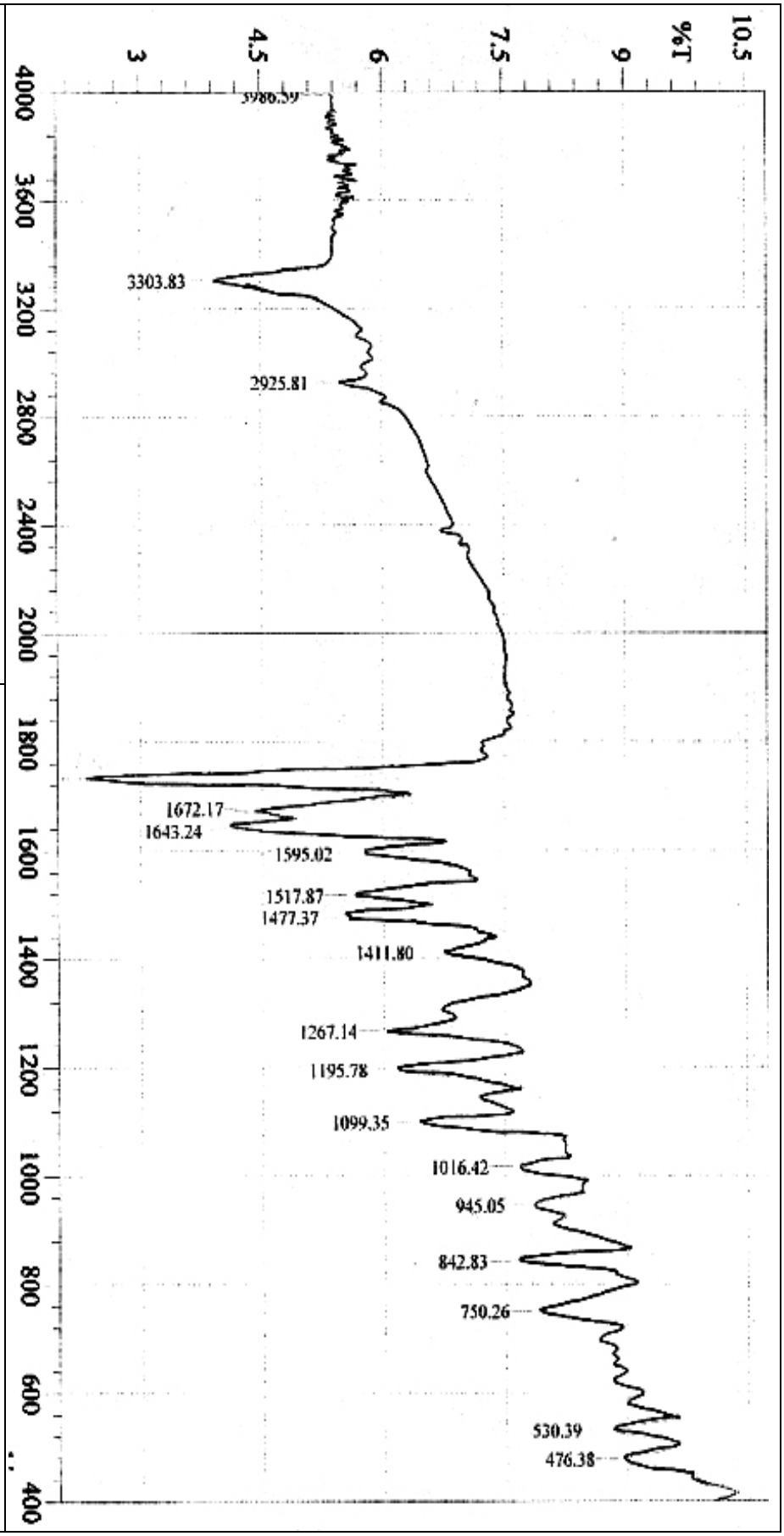
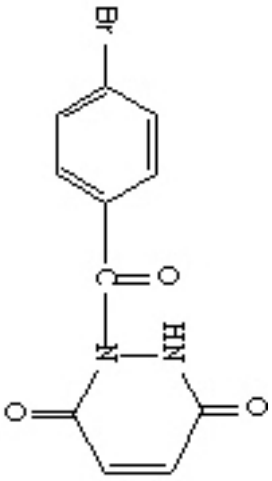


Figure (3-21): F.T.IR spectrum of compound [21] .

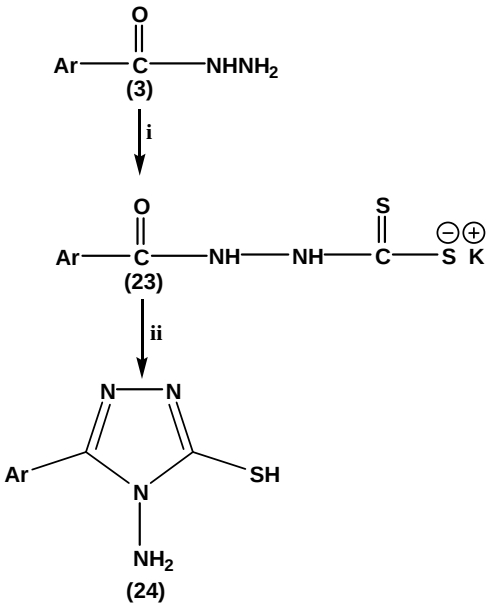




1-N-(p-Bromobenzoyl)-1,2-dihydro-pyridazin-3,6-dione [22].

Figure (3-22): F.T.IR spectrum of compound [22] .

3.1.12 4-Amino-5-aryl-3-mercapto-1,2,4-triazole:



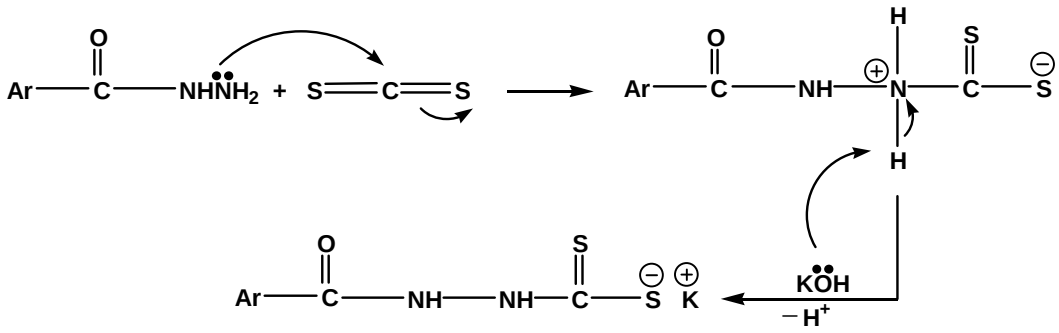
Scheme (12): Reagents and conditions:

(i) CS_2, KOH, reflux 1 hr.

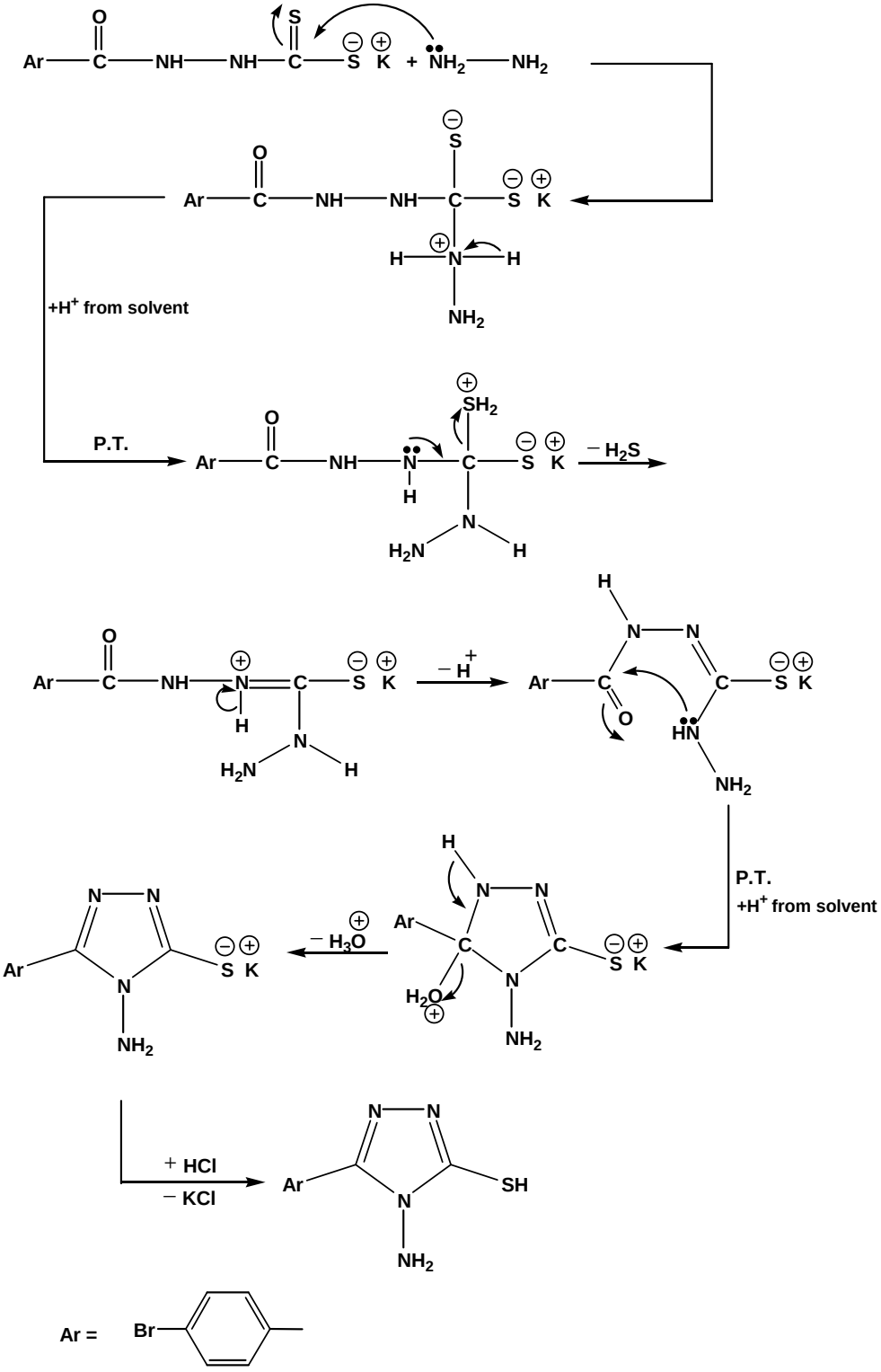
(ii) $N_2H_4.H_2O$, reflux 4 hr.

The 1,2,4-triazole derivative was synthesized according to the sequence in Scheme (12).

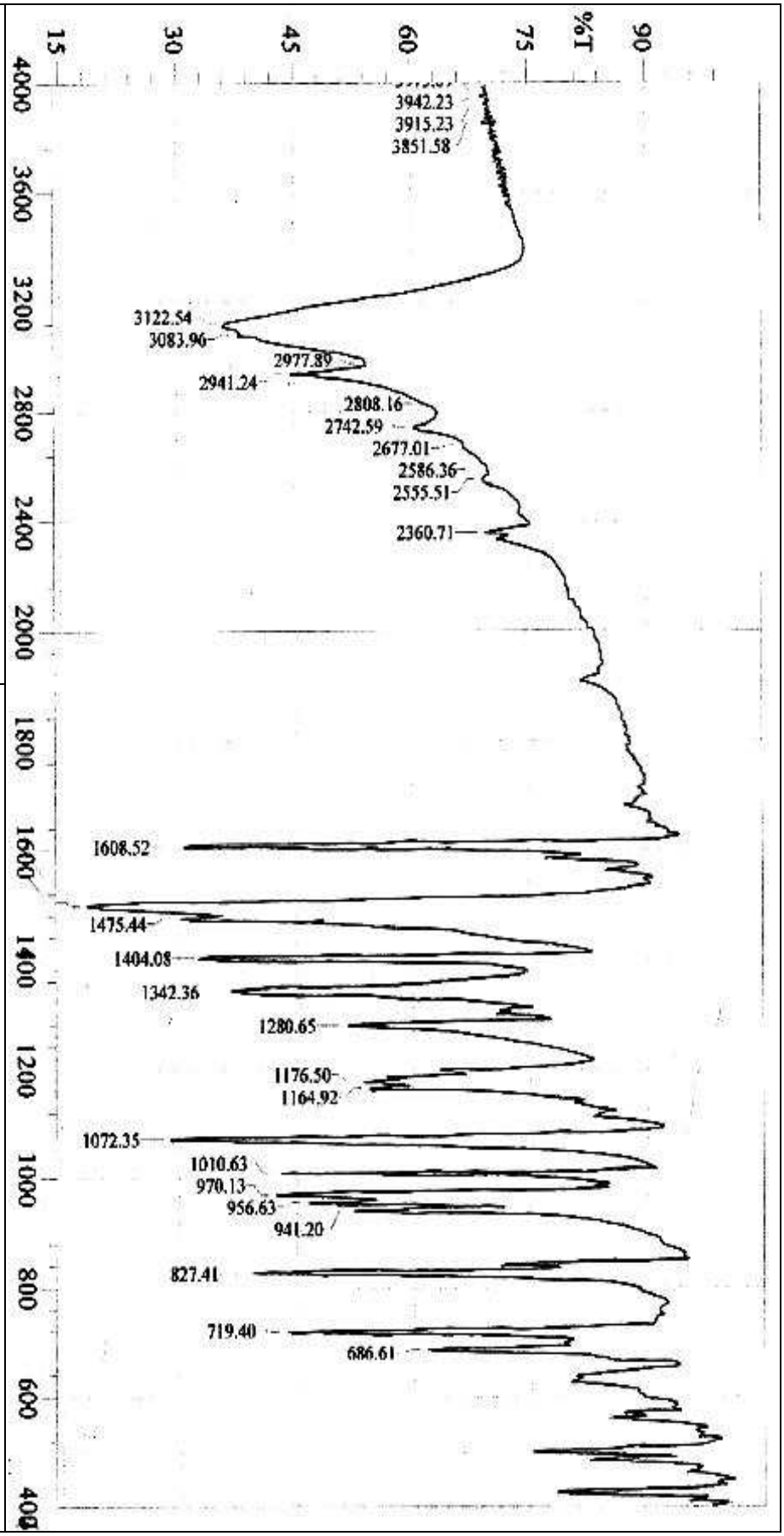
The acid hydrazide [3] was treated with carbon disulfide followed by the addition of hydrazine hydrate. Addition of CS_2 to the acid hydrazide afforded the salt as in the following mechanism[(115)].

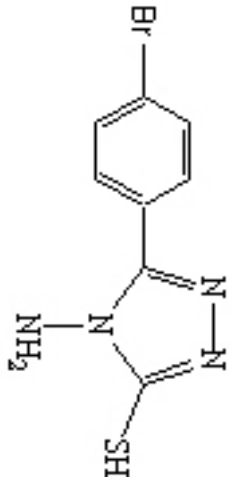


The addition of hydrazine hydrate leads to the cyclization which produces the triazoles (24) as in the following suggested mechanism[110].



The triazole derivative was characterized by using F.T.IR spectrum which showed the disappearance of absorption band at (1660 cm^{-1}) due to amide I and the appearance of a band at (1608 cm^{-1}) due to stretching vibration of (C=N) group, also a weak band appeared at (2555 cm^{-1}) which belongs to ν(S-H) group, asymmetric and symmetric ν(-NH_2) bands appeared at (3122 cm^{-1}). The F.T.IR spectra of the above compound is shown in fig. (3-23).





4-Amino-5-(p-bromophenyl)-3-mercapto-1,2,4-triazole [23].

Figure (3-23): F.T.IR spectrum of compound [23] .

3.2.0 Biological activity:

Microorganism causes different kinds 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 chemists such as the sulfa drugs[116] etc.

Issues of concern regarding Gram-negative bacteria include the extended drug resistance spectrum of ***Escherichia Coli***, ***Klebsiella Pneumonia*** and ***Proteus Vulgaris***[117], 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 synthesize agents of structural classes which resembles the 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 are considered an important class of compounds having a wide spectrum of biological activity[118].

3.2.1 Microbiological tests:

In this work, the antibacterial test was performed according to the disc diffusion method. Compounds ([3], [6], [13], [21] and [24]) were assayed for their antimicrobial activity *in vitro* against three strains of Gram negative bacteria (***Escherichia Coli, Klebsiella Pneumonia*** and

Proteus Vulgaris). Prepared agar and Petri dishes were sterilized by autoclaving for 15min. at 121 ºC. 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 0.1 ml of the prepared compounds (10mg of the compound dissolved in 1ml of DMSO solvent), DMSO was used as a solvent. These plates were incubated at 37 ºC for 24hr for bacteria. The inhibition zones caused by the various compounds were examined. The results of the preliminary screening tests are listed in Table (3-1).

Table (3 - 1)

Antibacterial activities of the synthesized compounds

compound NO.	*Escherichia Coli*	*Klebsiella Pneumonia*	*Proteus Vulgaris*
[3]	+	+	-
[6]	-	-	+
[13]	++	+	-
[21]	-	++	-
[24]	++	++	+

Note:

- = No inhibition = inactive

+ = (5-10) mm = slightly active

++ = (11-20) mm = moderately active

From the obtained data, it is found clearly that compounds [13] and [24] have highest activity against ***E. Coli, Klebsiella*** and ***Proteus*** than others. These compounds that have free ($-NH_2$) and (S-H) groups increase the activity.

Fig .(3 -24) Effect of compounds[3],[6],[13],[21] and [24] on *Escherichia Coli*

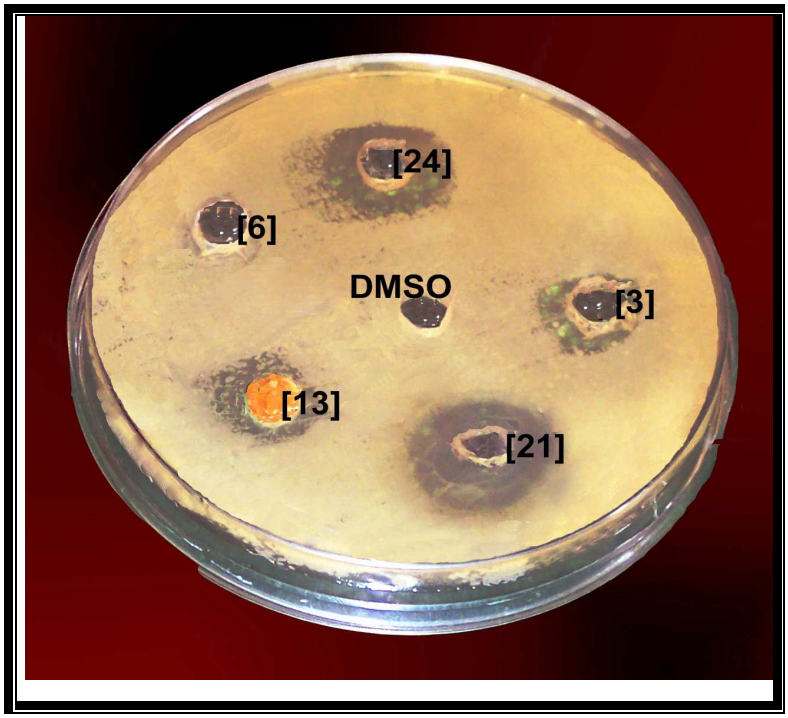


Fig .(3 - 25) Effect of compounds[3],[6],[13],[21] and [24] on *Klebsiella Pneumonia*

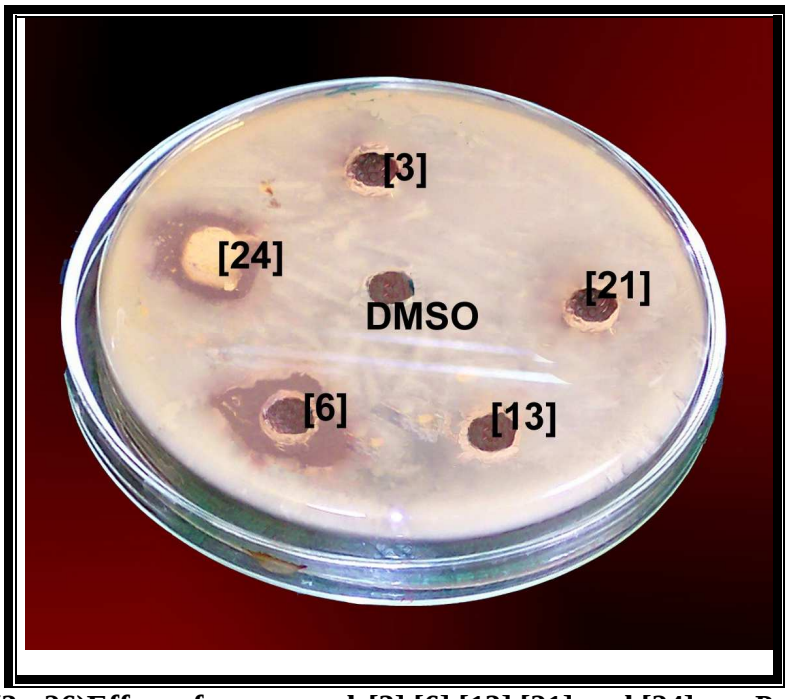
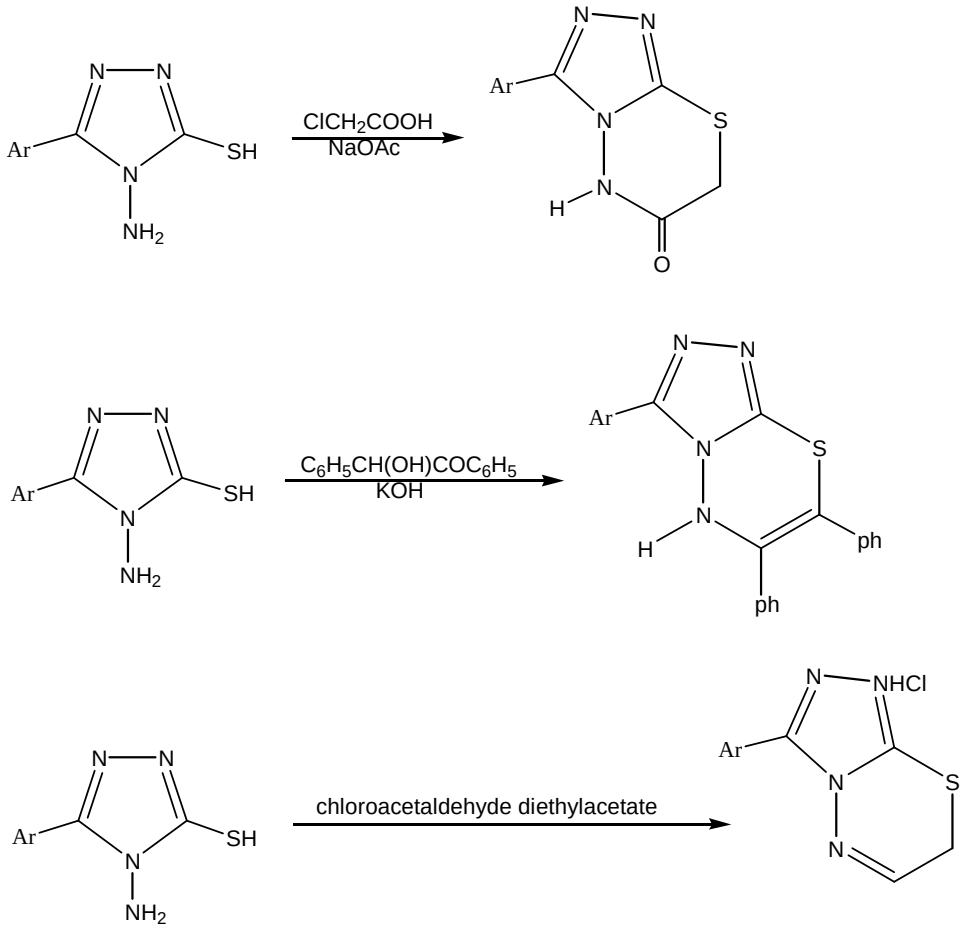


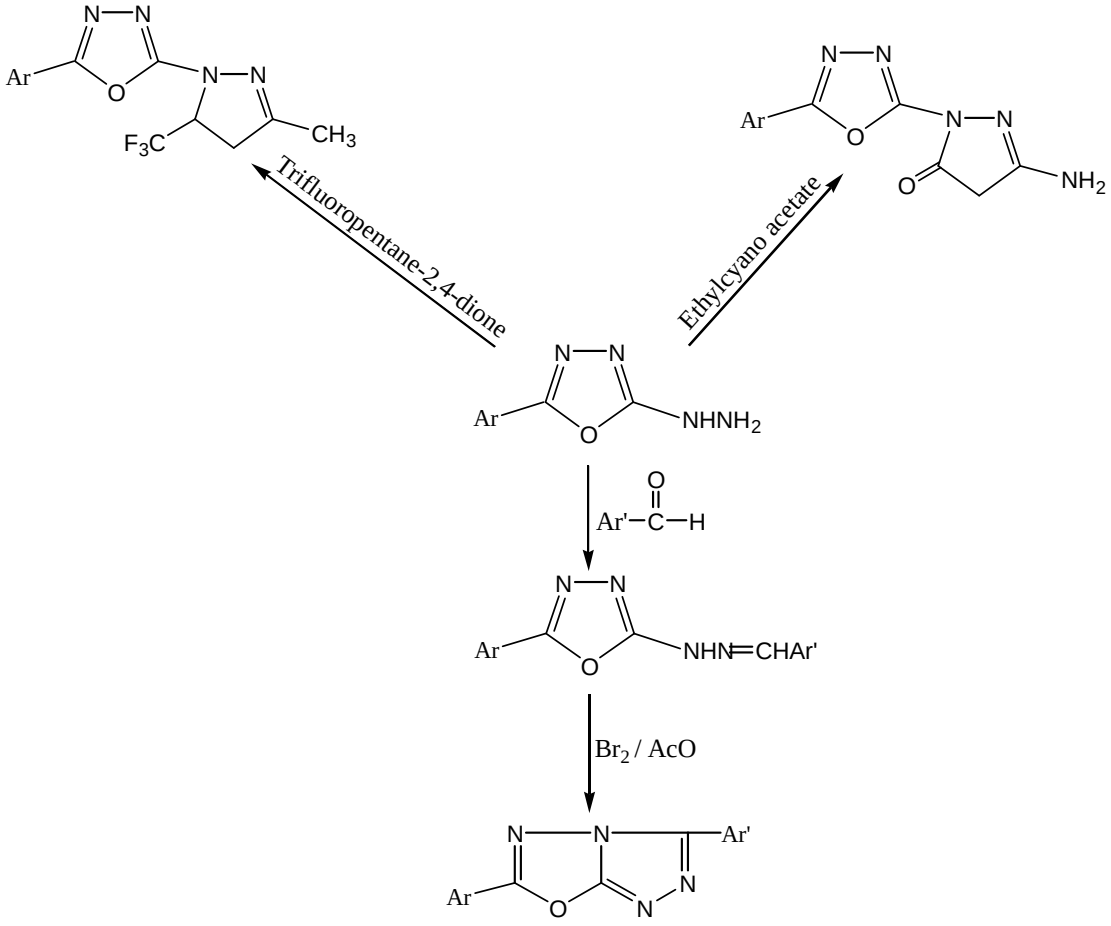
Fig.(3 - 26)Effect of compounds[3],[6],[13],[21] and [24] on *Proteus Vulgaris*

Suggestions for further work:

New fused rings can be synthesized from compound [24] using different organic reagents as shown in the following equations:



Also, new heterocyclic rings can be synthesized from compound [5] using different organic reagents as shown in the following scheme:



Materials and methods

2.1 Materials:

Compounds	Supplied from	Purity
p-Bromobenzoic acid	**BDH**	**98%**
Diethyl ether	**BDH**	**97%**
Chloroform	**BDH**	**95%**
Sodium nitrite	**Merk**	**99%**
Ethanol (absolute)	**BDH**	**99.85%**
Hydrazine hydrate	**KODAK**	**80%**
Hydrochloric acid	**Merk**	**36%**
Methanol	**BDH**	**95%**
Potassium hydroxide	**BDH**	**98%**
Sodium bicarbonate	**BDH**	**98%**
Acetic anhydride	**BDH**	**95%**
Sodium hydroxide	**Fluka**	**98%**
Carbon disulfide	**Fluka**	**98%**
p-Bromophenacyl bromide	**Fluka**	**98.5%**
Phenyl isocyanate	**BDH**	**98%**
Phenyl isothiocyanate	**Fluka**	**98%**
Phthalic anhydride	**Fluka**	**99%**
Maleic anhydride	**Fluka**	**99%**
Formic acid	**BDH**	**60%**
Sodium carbonate	**BDH**	**98%**
Benzene	**Merk**	**96%**

2.2 Instruments:

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

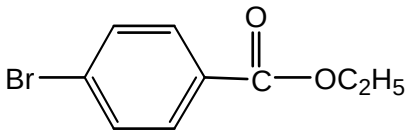
2- Infrared spectra were recorded using Fourier Transform infrared ***SHIMADZU*** (8400) and (8300) (F.T.IR) infrared spectrophotometer, KBr disc or thin film.

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

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

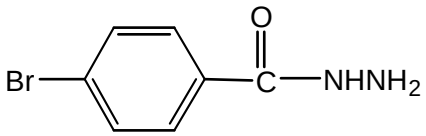
2.3 Procedures:

2.3.0 Preparation o f ethyl-p-bromo benzoate [2] (100)



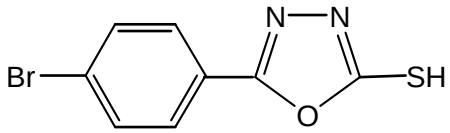
Treating (30g) of p-bromobenzoic acid with (140 mL) absolute ethanol (2.5 mL) conc. sulfuric acid and refluxing the mixture for 5 hours. Neutralization with 10% sodium bicarbonate, after that the ester layer was separated, dried by using unhydrous magnesium sulphate. The product was filtered off. Ester's b.p 249-252 ºC , yield 77%.

2.3.1 Preparation of p-bromobenzoic hydrazide [3] (101).



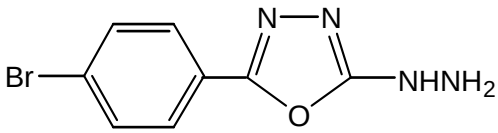
Compound [3] was synthesized by the addition of hydrazine hydrate (72mmole, 3.49g) to (48mmole, 11g) of ester in (5mL) absolute ehanol. The mixture was refluxd for 2 hours. After cooling, the product was filtered off and recrystallized using ethanol, m.p. 153-155 ºC, yield 73%.

2.3.2 Preaparation of 5-(p-bromophenyl)-3-mercapto-1,3,4-oxadiazole [4] (102).



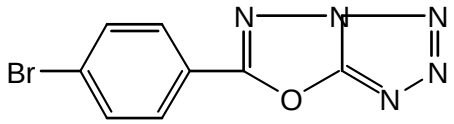
To a mixture of carbohydrazide [3] (10mmole, 2g) in ethanol (20mL) was added a solution of KOH (14mmole, 0.78g) in ethanol (15mL), followed by CS_2 (3mL). The reaction mixture was heated under reflux for 8 hours then it was concentrated, acidified with dilute hydrochloric acid and the resulting solid was collected, washed with water and recrystallized to give compound [4], m.p. 180-182 ºC, yield 71%.

2.3.3 Preparation of 5-(p-bromophenyl)-2-hydrazino-1,3,4-oxadiazole [5] (103).



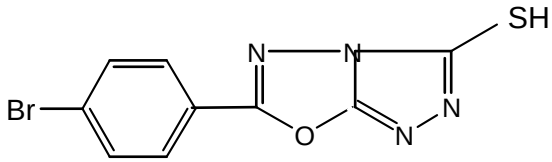
A mixture of compound [4] (3.9 mmole, 1.0g) and hydrazine hydrate (5.86mmole, 0.3g) was refluxed in absolute ethanol (15mL) for 5 hours, or until evolution of H_2S cease. Then allowed to cool, the white precipitate was filtered off and recrystallized from ethanol, m.p. 174-176 ºC, yield 65%.

2.3.4 Preparation of 6-(p-bromophenyl)-1,3,4-tetrazolo[4,5-b][1,3,4] oxadiazole [6] (103).



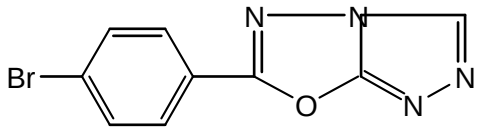
A solution of sodium nitrite (0.78 mmole, 0.06g) in (2mL) of water was added dropwise to an ice-cold solution of compound [5] (0.78 mmole, 0.2g) in acetic acid (10mL) kept an ice bath 0ºC with stirring for 3 hours. The resulting solid was filtered and recrystallized from acetic acid / H_2O as a white crystals, m.p. 159-161 ºC, yield 72%.

2.3.5 Preparation of 6-(p-bromophenyl)-4-mercapto-1,2,4-triazolo [4,5- b] [1,3,4] oxadiazole [7] (103).



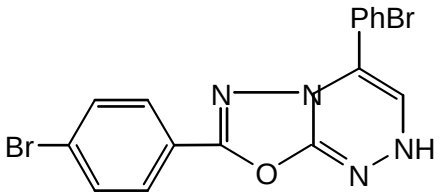
A mixture of compound [5] (0.78 mmole, 0.2g) and carbon disulfide (3mL) in pyridine (10mL) was refluxed on steam bath for 7 hours, then allowed to cool. The solid product thus formed was recrystalized from acetic acid as a brown crystals, m.p. 200-202 ºC , yield 74%.

2.3.6 Preparation of 6-(p-bromophenyl)-1,2,4-triazolo [4,5-b] [1,3,4] oxadiazole [8] (94).



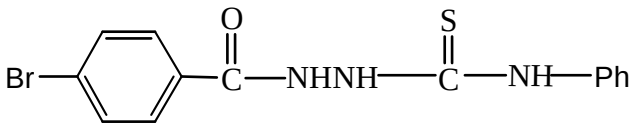
A mixture of compound [5] (1.17mmole, 0.3g), formic acid (10mL) and catalytic amount of concentrated hydrochloric acid was heated under reflux for 6 hours. The reaction mixture was allowed to cool to room temperature and poured into water (50mL). The formed solid was collected by filteration, washed with ethanol, dried and recrystallized from acetic acid as a brown crystal, m.p. 160-162 ºC , yield 73%.

2.3.7 Preparation of 7-(p-bromophenyl)-5-(p-bromophenyl)-1,2,4-triazino [5,6-b] [1,3,4] oxadiazole [9] (94).



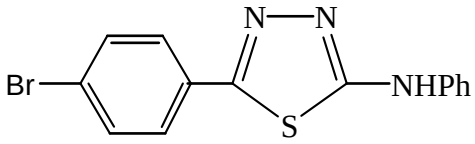
A mixture of compound [5] (1.17mmole, 0.3g) with 4-bromophenacyl bromide (1.17mmole, 0.32g) was heated under reflux 5 hours in dry benzene. The solid precipitate that separated upon cooling was filtered off and recrystallized from benzene as a yellow crystal, m.p. 255-258 ºC, yield 66%.

2.3.8 Preparation of 1-phenyl-4-(p-bromo benzoyl) thiosemicarbazide [10] (104).



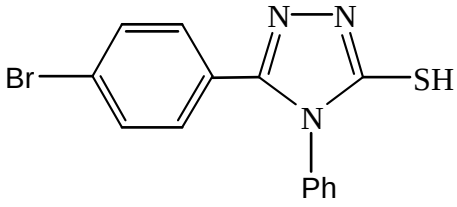
A mixture of compound [3] (3.25 mmole, 0.7g) and phenyl isothiocyanate (3.25mmole, 0.45g) in absolute ethanol (20mL) was refluxed for 7 hours. The solid material obtained on cooling was filtred off and recrystallized from ethanol as a pale yellow crystal, m.p.178-180 ºC, yield 88%.

2.3.9 Preparation of 2-(phenylamino)-5-(p-bromophenyl)-1,3,4-thiadiazole [11] (19).



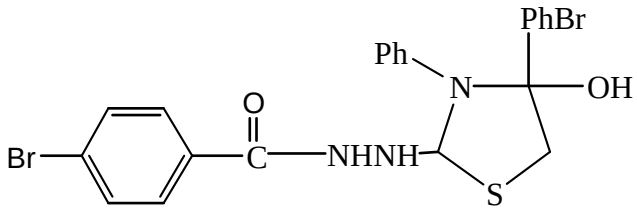
Thiosemicarbazide [10] (0.68mmole, 0.3g) was added portionwise to (5mL) of concentrated sulfuric acid at 0ºC with continuous stirring. The reaction mixture was stirred further for 3 hours at room temperature and then allowed to stand overnight. Neutralization with dilute sodium bicarbonate precipitated a crude solid, which was filtered and washed with water. The crude product was recrystallized from ethanol / water as a yellow crystal, m.p. 259-261 ºC, yield 75%.

5*2.3.10 preparation of 5-(p-bromophenyl)-4-phenyl-1,2,4-triazole-3- thiol [12]* [19].



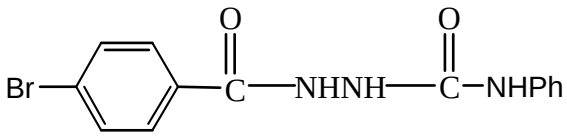
A stirring mixture of compound [10] (0.58mmole, 0.2g) and (15mL) of 2N sodium hydroxide solution was refluxed for 4 hours. After cooling, the solution was acidified with hydrochloric acid and the precipitate was filtered. The precipitate was recrystallized from ethanol as a green-army crystal, m.p.193-195 ºC, yield 79%.

2.3.11 Preparation of 5-(p-bromophenyl)-2-(p-bromophenyl hydrazide)- 1-N-phenyl-5-(hydroxy)thiazolidine [13] [105].



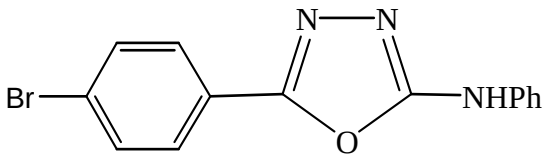
A mixture of compound [10] (0.433mmole, 0.15g) and p-bromophenacyl bromide (0.433mmole, 0.12g) in absolute ethanol (20mL) was refluxed for 8 hours, cooled and neutralized with ammonium hydroxide solution. The precipitate was filtered off, washed with water, dried and recrystallized from ethanol as a white crystal giving the final product, m.p. 165-168 ºC, yield 60%.

2.3.12 Preparation of 1-phenyl-4-(p-bromobenzoyl) semicarbazide [14] (104).



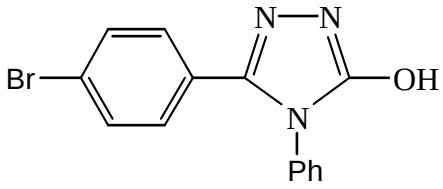
A mixture of compound [3] (3.25mmole, 0.7g) and phenyl isocyanate (3.25mmole, 0.39g) in absolute ethanol (20mL) was refluxed for 7 hours, then cooled and filtered. The formed solid was recrystallized from benzene as a white crystal, m.p. 238-240 ºC, yield 92%.

2.3.13 Preparation of 2-(phenylamino)-5-(p-bromophenyl)-1,3,4-oxadiazole [15] (19).



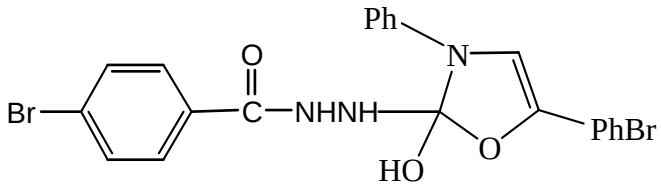
Semicarbazide [14] (0.9mmole, 0.3g) was added portionwise to (5mL) of concentrated sulfuric acid at 0ºC with continuous stirring. The reaction mixture was stirred further for 3 hours at room temperature and then allowed to stand overnight. Neutralization with dilute sodium bicarbonate precipitated a crude solid, which was filtered and washed with water. The crude product was recrystallized from ethanol / water as a white crystal, m.p. 213-216 ºC , yield 70%.

2.3.14 Preparation of 5-(p-bromophenyl)-4-phenyl-1,2,4-triazole-3-ol[16] (19).



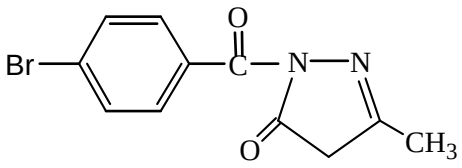
A stirring mixture of compound [14] (2.1mmole, 0.7g) and (15mL) of 2N sodium hydroxide solution was refluxed for 4 hours. After cooling, the solution was acidified with hydrochloric acid and the precipitate was filtered. The precipitate was then recrystallized from ethanol / water, m.p. 185-188 ºC, yield 81%.

2.3.15 Preparation of 5-(p-bromophenyl)-2-(p-bromophenyl hydrazide)- 3-N-phenyl-2- (hydroxy) oxazoline [17] (105).



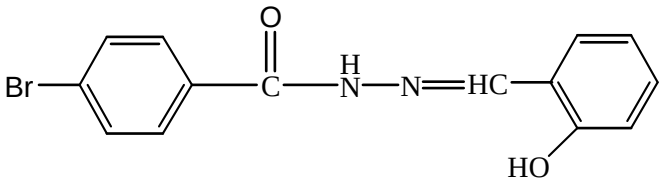
A mixture of compound [14] (3mmole, 1g) and *p*-bromophenacyl bromide (3mmole, 0.83g) in absolute ethanol (20mL) was refluxed for 8 hours, cooled and neutralized with ammonium hydroxide solution. The precipitate was filtered off, washed with water, dried and recrystallized from ethanol giving the final product, m.p. 216-219 ºC, yield 65%.

2.3.16 preparation of 1-(p-bromobenzoyl)-3-methylpyrazol-5-one [18] (4).



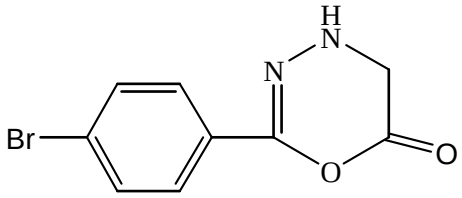
A mixture of carbohydrazide [3] (2.3mmole, 0.5g) and ethylacetoacetate (2.3mmole, 0.3g) in absolute ethanol (20mL) was heated at reflux temperature for 5 hours, the reaction mixture was cooled and the precipitate was filtered off and recrystallized to give the title compound [18], m.p. 85-88 ºC, yield 83%.

2.3.17 Preparation of 2-hydroxybenzylidine-1- p-bromophenyl hydrazone [19](106).



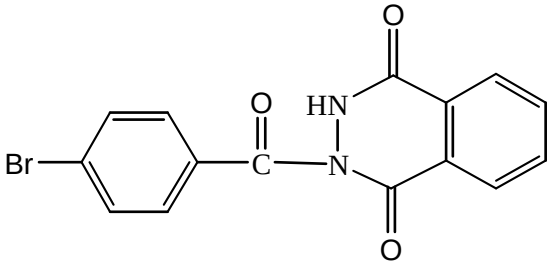
A mixture of compound [3] (2.32mmole, 0.5g), absolute ethanol (15mL) and o-salicyladehyde (2.32mmole, 0.29g) was refluxed for 2 hours. After cooling at room temperature the precipitate was filtered and dried. The product was recrystallized from ethanol, m.p. 211-214 ºC, yield 90%.

2.3.18 Preparation of 2-(p-bromophenyl)-4H-1,3,4-oxapyridazin-6-one [20] (11).



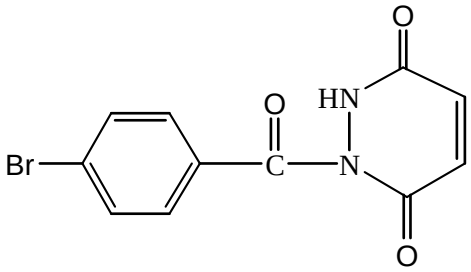
A solution of compound [3] (1.86mmole, 0.4g) and chloroacetic acid (1.86mmole, 0.175g) in presence of sodium acetate and acetic anhydride was refluxed for 4 hours then poured on water, a solid product was obtained. Filtered and recrystallization from suitable solvent, m.p. 179-181 ºC, yield 60%.

2.3.19 Preparation of 1-N-(p-bromobenzoyl)-1,2-dihydro-phthalazin-3,8- dione [21] (107).



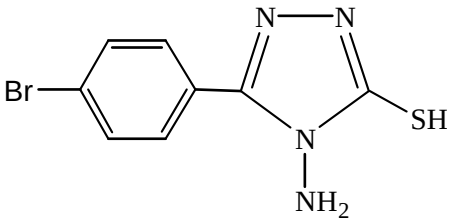
Compound [3] (2.3mmole, 0.5g) was mixed with phthalic anhydride (2.3mmole, 0.34g) in acetic acid (20mL), the mixture was refluxed for 7 hours then cooled and added to crushed ice. The precipitate was filtered off, washed with water and recrystallized to give the final product, m.p. 240-243 ºC, yield 84%.

2.3.20 Preparation of 1-N-(p-bromobenzoyl)-1,2-dihydro-pyridazin-3,6- dione [22] (107).



Compound [3] (2.3mmole, 0.5g) was mixed with maleic anhydride (2.3mmole, 0.22g) in acetic acid (20mL), the mixture was refluxed for 7 hours then cooled and added onto crushed ice, the precipitate was filtered off, washed with water and recrystallized to give the final product, m.p. 225-228 ºC, yield 60%.

2.3.21 Preparation of 4-amino -5-(p-bromophenyl) -3-mercapto -1,2,4- triazole [24] (108).



A mixture of p-bromobenzoic hydrazide [3] (14mmole, 3g), potassium hydroxide (21mmole, 1.18g) and (5mL) carbon disulfide was dissolved in absolute ethanol and refluxed on water bath for 1 hour. The solvent was removed and the residue was dried and then treated with hydrazine hydrate (0.021mole, 1.05g) and refluxed for another 4 hours. The contents were cooled, diluted with water and acidified with HCl. The precipitate was collected by filteration, washed with water, dried and recrystallized from ethanol to give the final product, m.p. 148-151 ºC, yield 70%.

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Summary

The scheme of this work involves synthesis of different five and six membered heterocyclic rings starting from 4-bromobenzoic hydrazide which was synthesized from their carboxylic acid.

This work is divided into four different parts:

First part:

This part involves the synthesis of fused tetrazole, triazole and triazine rings derived from the cyclization of ($NH\text{-}NH_2$) of the 5-(*p*-bromophenyl)-2-hydrazino-1,3,4-oxadiazole by treatment with sodium nitrite, formic acid, carbon disulfide and *p*-bromophenacyl bromide respectively. The oxadiazole derivative was synthesized by treating the previous acid hydrazide with carbon disulfide and potassium hydroxide then with hydrazine hydrate. Scheme I.

Second part:

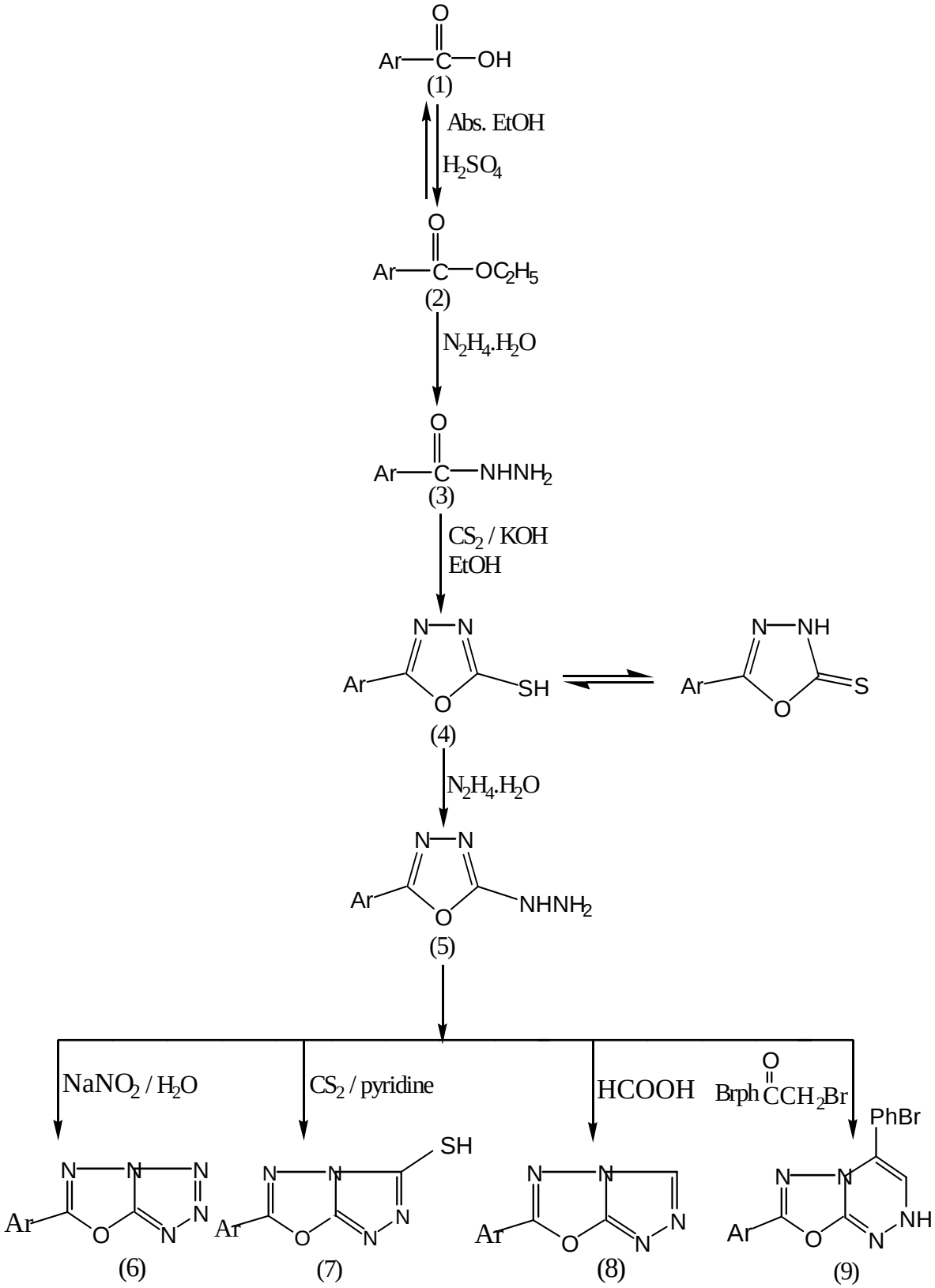
This part involves the synthesis of thiosemicarbazide, semicarbazide, triazole, thiadiazole, oxadiazole, oxazoline and thiazolidine derivatives from the reaction of ($NH\text{-}NH_2$) group of the starting material with different reagents. Scheme II.

Third part:

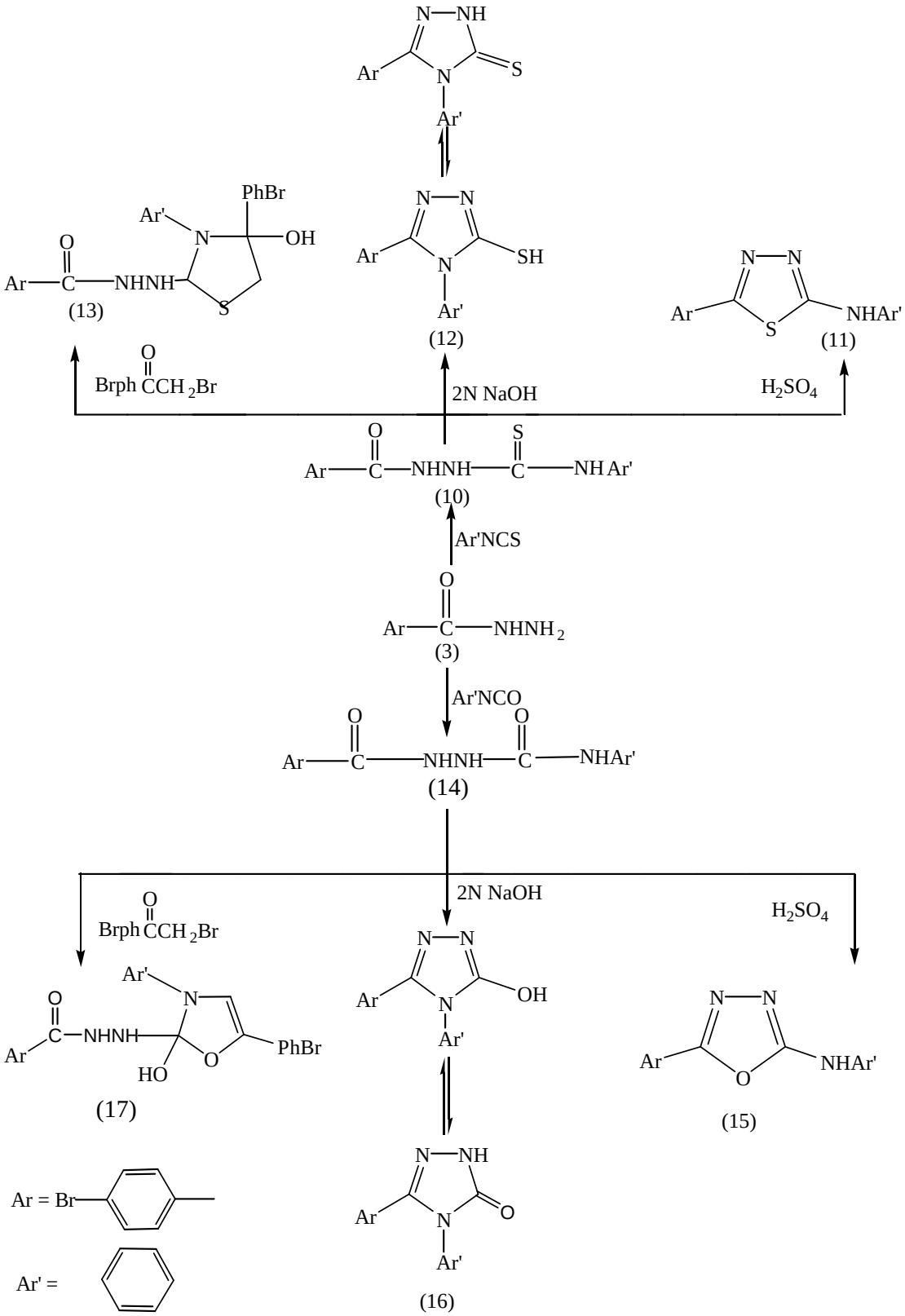
This part involves the synthesis of pyrazole, phthalazine, pyridazine, oxapyridazine and triazole derivatives via the reaction of the acid hydrazide with different reagents. Scheme III.

Fourth part:

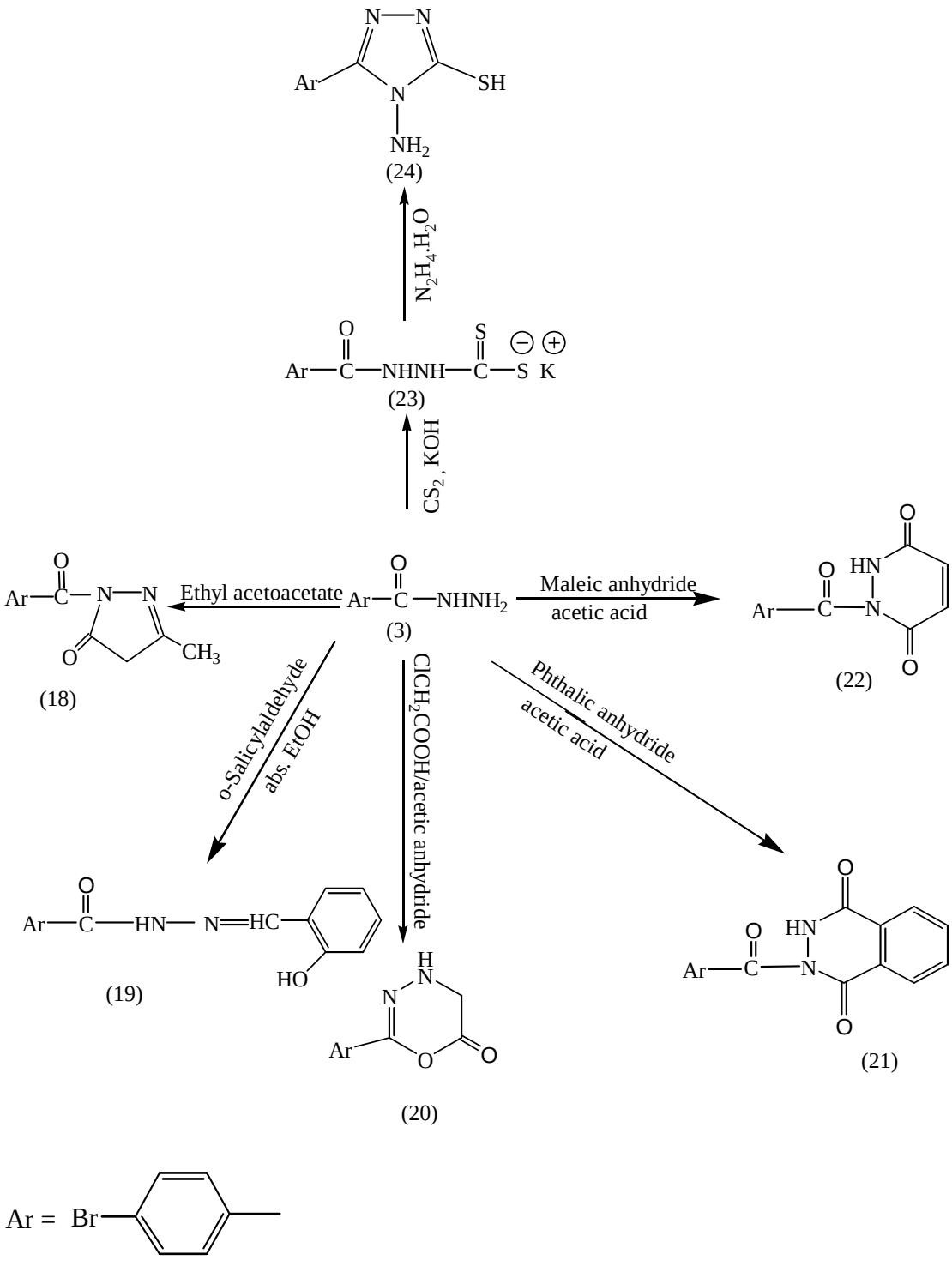
This part deals with the study of antibacterial activities of some of the synthesized compounds and comparing these activities with that of the starting material. These activities were determined ***in vitro*** using disc diffusion method against three pathogenic strains of bacteria (***Escherichia Coli,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


Ar—C—OH
(1)
Abs. EtOH
H2SO4
Ar—C—OC2H5
(2)
N2H4.H2O
Ar—C—NHNH2
(3)
CS2 / KOH
EtOH
Ar
SH
NH
S
(4)
N2H4.H2O
NHNH2
(5)
NaNO2 / H2O
CS2 / pyridine
HCOOH
Brph CCH2Br
PhBr
(6)
(7)
(8)
(9)
Ar = Br

Scheme (I)


Ar
N
NH
S
Ar'
(12)
SH
OH
PhBr
(13)
NHNH
NHAr'
(11)
H_2SO_4
2N NaOH
Brph CCH 2Br
(10)
NH Ar'
Ar'NCS
$NHNH_2$
(3)
Ar'NCO
(14)
(17)
HO
(15)
(16)
Ar = Br
Ar' =

Scheme (II)


(24)
$N_2H_4.H_2O$
(23)
CS_2, KOH
Ethyl acetoacetate
(3)
Maleic anhydride
acetic acid
(22)
(18)
o-Salicylaldehyde
abs. EtOH
$ClCH_2COOH$/acetic anhydride
Phthalic anhydride
acetic acid
(19)
(20)
(21)
Ar = Br

Scheme (III)

Supervisor certification

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

Signature:
Name: Assist.Prof.Dr. Ibtisam K. Jassim
Date:

Signature:
Name: Assist.Prof.Dr. Sawsan H.Shawkat
Date:

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

Signature:
Name:
Head of Chemistry Department
College of Science
Al-Nahrain University

Examining Committee's Certification

We, the Examining Committee, certify that we read this thesis and have examined the student *Abbass Abdul-Ameer Salman* 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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Signature:
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Date:

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Signature:

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

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

Date:

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جامعة النهرين
كلية العلوم
قسم الكيمياء

تحضير ودراسة الفعالية البيولوجية ضد انواع من البكتيريا لمشتقات جديدة لمركبات حلقية غير متجانسة المشتقة من حامض بارا-بروموبنزويك

رسالة
مقدمة الى كلية العلوم- جامعة النهرين
وهي جزء من متطلبات نيل درجة الماجستير في
الكيمياء

من قبل

عباس عبد الأمير سلمان
بكالوريوس ٢٠٠٤ (جامعة النهرين)

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College of Science
Department of Chemistry

Synthesis and antibacterial activity of some new heterocyclic compounds derived from *p*-bromobenzoic acid

A Thesis
submitted to the College of Science Al-Nahrain University in partial fulfillment of the requirements for the Degree of Master of Science in Chemistry

By
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الإهداء

إلى نور الهدى... ومقلة العيون

الحبيب المصطفى

إلى من بذلت النفس لأجل أن أكون

والدتي العزيزة

إلى القلوب التي ماتزال تنبض بالحب

أخواني و اخواتي

إلى كل من دعالي دعوة خالصة

اصدقائي الاعزاء

إلى كل قلب خفق حباً وخوفاً علي

أهدي ثمرة جهدي

عباس

بسم الله الرحمن الرحيم

و علم آدم الأسماء كلها ثم عرضهم

على الملائكة فقال أنبئوني بأسماء

هؤلاء إن كنتم صادقين* قالوا

سبحانك لا علم لنا إلا ما علمتنا

انك أنت العليم الحكيم

صدق الله العلي العظيم

سورة البقرة (الأيات٣٠,٣١)

الخـــلاصـــــــة

يتضمن موضوع البحث في هذه الرسالة تحضير مركبات حلقية خماسية وسداسية غير متجانسة متنوعة ابتداء من بارا- بروموبنزويك هايدرازايد والذي حضر باستعمال الحامض الكاربوكسيلي المقابل . وقد تم تقسيم هذا العمل الى اربعة اقسام :-

القسم الاول

يتضمن هذا القسم تحضير مركبات حلقية غير متجانسة مندمجة الحلقة مشتقة من الغلق الحلقي لمجموعة ($NH-NH_2$) لمركب ٥-بارا بروموفنيل-٢-هيدرازينو-١،٣،٤-اوكسادايازول باستعمال نترات الصوديوم، حامض الفورميك، كاربون ثنائي الكبريت و بارا-بروموفيناسيل برومايد. و مشتق الاوكسادايازول المستعمل في هذا القسم حضر نتيجة تفاعل هايدرازايد الحامض المذكور انفا مع كل من كاربون ثنائي الكبريت وهيدروكسيد البوتاسيوم ثم مع الهيدرازين المائي . مخطط رقم (١) .

القسم الثاني

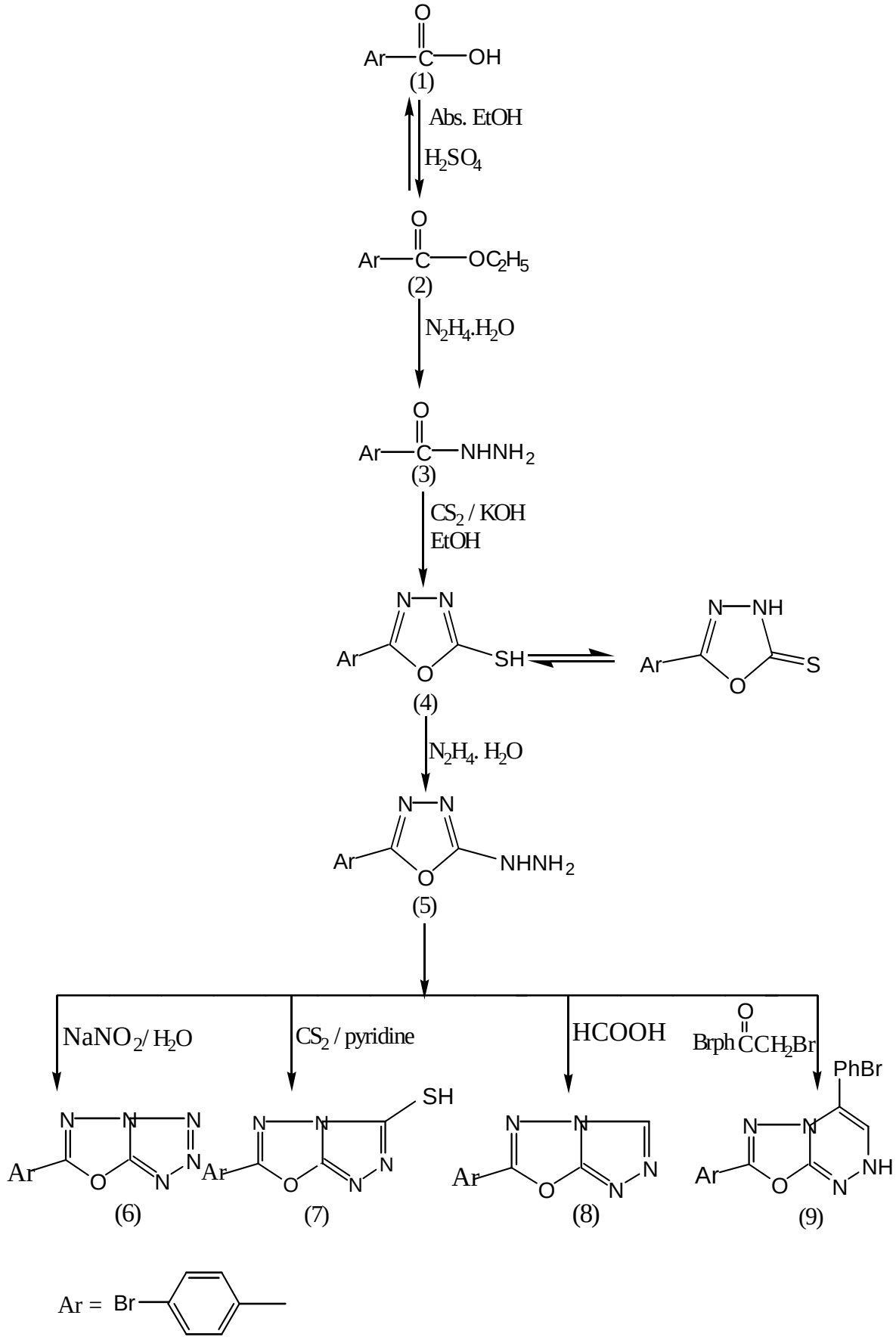
يتضمن هذا القسم تحضير مركبات الثايوسيميكاربزايد، سيميكاربزايد و مشتقات كل من الترايزول، الثايادايازول، الاوكسادايازول، الاوكسازولين و الثيازوليدين و التي اشتقت من تفاعل المادة الاساس انفة الذكر. مخطط رقم (٢).

القسم الثالث

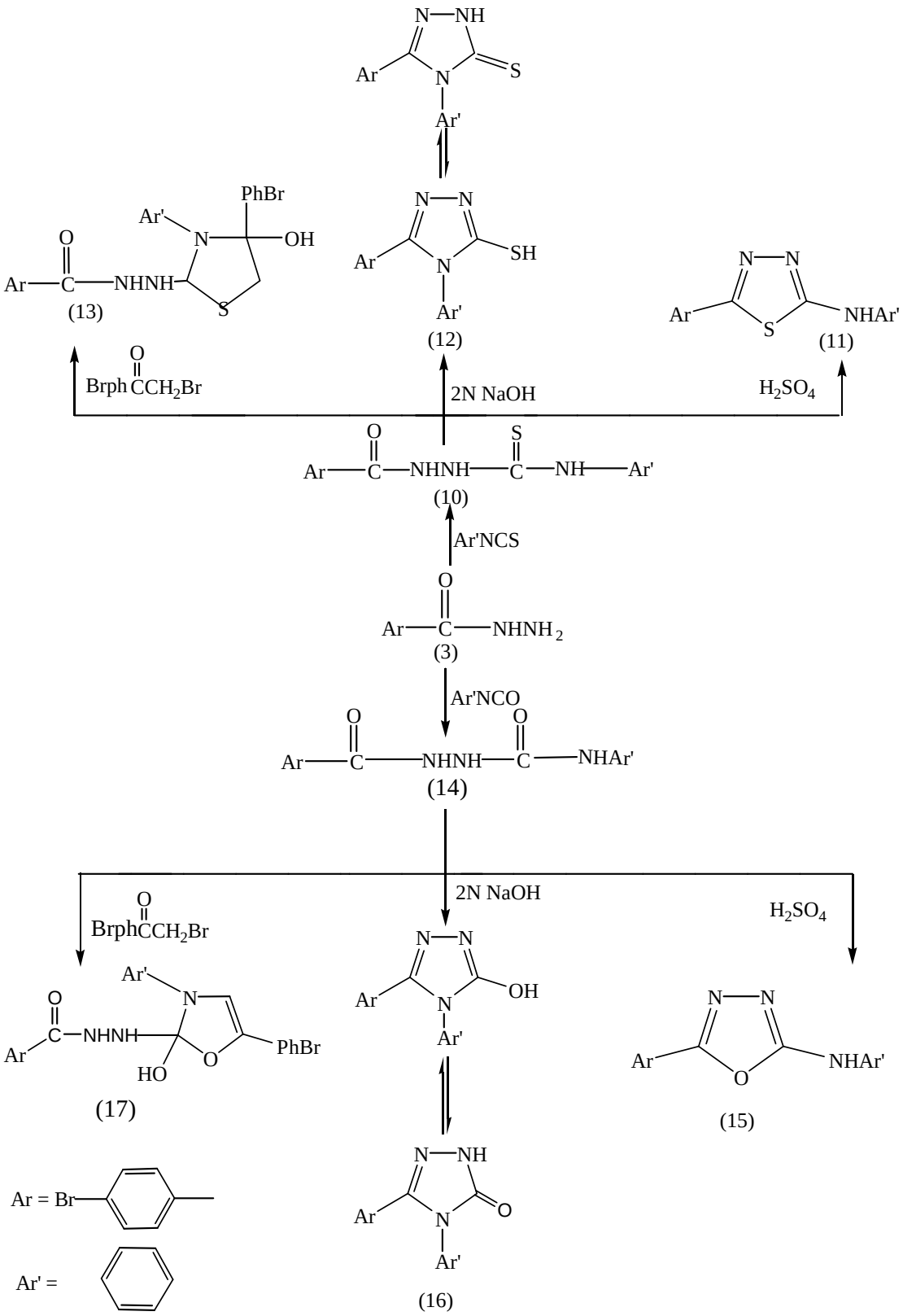
يتضمن هذا القسم تحضير مشتقات البايروزول، الاوكسابريدازين، الفثالازين-دايون، البريدازين-دايون و الترايزول، حيث تتم عملية الغلق الحلقي للنواتج الحاصلة باستعمال مختلف المواد الكيمياوية. و للحصول على هذه المشتقات اتبعت الخطوات الموضحة في مخطط رقم (٣).

القسم الرابع

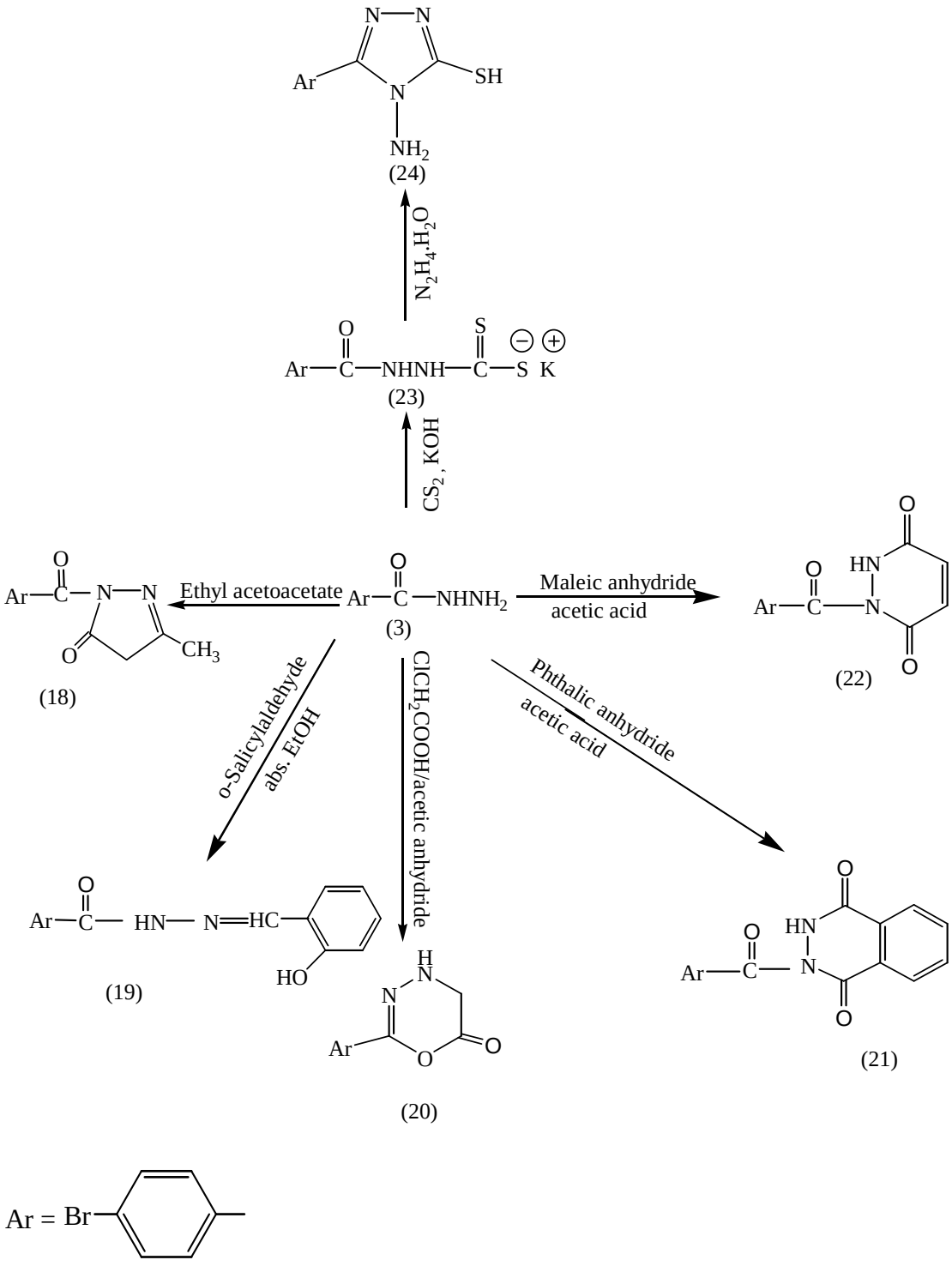
يتضمن هذا القسم اختبار الفعالية البايولوجية لبعض المركبات المحضرة ضد ثلاث انواع من البكتيريا وقد دلت النتائج المستحصلة بان بعض المركبات اظهرت فعالية بايولوجية عالية كما هو عليه في الجدول (١-٣) .


Ar—C(=O)—OH
(1)
Abs. EtOH
H2SO4
Ar—C(=O)—OC2H5
(2)
N2H4.H2O
Ar—C(=O)—NHNH2
(3)
CS2 / KOH
EtOH
(4)
N2H4. H2O
(5)
NaNO2/ H2O
CS2 / pyridine
HCOOH
Brph C(=O) CH2Br
PhBr
(6)
(7)
(8)
(9)
Ar = Br

مخطط رقم (١)


Ar
N
NH
S
Ar'
SH
OH
PhBr
NHNH
(13)
(12)
(11)
NHAr'
H_2SO_4
2N NaOH
$BrphCCH_2Br$
(10)
Ar'NCS
$NHNH_2$
(3)
Ar'NCO
NHAr'
(14)
HO
PhBr
(17)
(15)
(16)
Ar = Br
Ar' =

مخطط رقم (٢)


Ar
SH
NH2
(24)
N2H4.H2O
Ar C NHNH C S K
(23)
CS2, KOH
Ethyl acetoacetate
Ar C NHNH2
(3)
Maleic anhydride
acetic acid
(22)
(18)
o-Salicylaldehyde
abs. EtOH
ClCH2COOH/acetic anhydride
Phthalic anhydride
acetic acid
(19)
(20)
(21)
Ar = Br

مخطط رقم (٣)

الاسم: عباس عبد الأمير سلمان داود الأبيض

الموبايل: ٠٧٨٠١٩٣٠٩٧٧

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تاريخ المناقشة: ٢٠٠٧/٣/٢٧

عنوان الرسالة:

"Synthesis and antibacterial activity of some new heterocyclic compounds derived from *p*-bromobenzoic acid"

أسماء المشرفين: د. سوسن حارث شوكت و د. أبتسام خليفة جاسم.

بكالوريوس جامعة النهرين ٢٠٠٤

الماجستير جامعة النهرين ٢٠٠٧