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.

I wish to express my sincere gratitude and great appreciation to my Supervisor Dr. Ibtisam K. Jassim and Dr. Sawsan H. Shawkat for their guidance and their encouragement throughout this work.

I'm greatly indebted for the assistance given to me by Head and staff of Chemistry Department, College of Science, AL-Nahrain University.

I am especially grateful to my friend Osama Bedran because helps me and stand with me in all times.

I would like to thank my friends Rawya Faiq and Ahmed Abd Al-satar for their help and encouragement.

My special thanks are also extended to Dr. Mohamed Sabry and my sister Lamees for processing the biological part of this work, Microbiology Department, College of Medicine / Babylon University.

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

Nour 2007

Chapter Four

Biological activity

4.1 Introduction:

A few pathogenic species are known to be almost sensitive to certain antimicrobial agents, although in some parts of the world the situation is changing. As strains of pathogenic organism differ from one to another within their species in their antibiotic sensitivities, sensitivity tests are required as a routine [(151)].

Some heterocyclic compounds are considered such 1,2,4-triazole, pyridazine, pyrazole and thiazolidine as chemotherapeutic agents. Chemotherapeutic agents are chemicals which are intended to be toxic for the infectious organism but innocuous for the host. So that, it can be given in sufficient doses to inhibit or kill the microorganism through out the body without harming the body cell [(152)].

Heterocyclic rings are considered an important class of compounds having a wide spectrum of biological activity, the heterocyclic compounds are well known for their antibacterial and antifungal activities [(145)]. There are some types of bacteria:

1. Klebsiella pneumonia*:*

Its gram negative bacilli, non-motile, capsulated, non-spore forming. It is present in the respiratory tract and faces of about 5% of normal individuals. Its causes a small proportion about (1%) of bacterial

pneumonias. It occasionally produces urinary tract infection and bacterium with focal lesions in debilitated patients [153].

Strains of *Klebsiella* that is isolated from patients and strains with multiple antibiotic exposures are almost always resistant because they possess inducible, chromosomally determined, β-lactamases with high affinity for cephalosporin [151].

2. Pseudomonas aeruginosa:-

Its gram negative rod, motile, non-spore forming. *Pseudomonas aeruginosa* is often a major cause of hospital acquired (nonsocial) infections. Infection can occur at many sites and can lead to urinary tract infections, sepsis, pneumonia, pharyngitis and wound infection [154]. These bacteria are clinically important because they are resistance to antibacterial agents and consequently are an important potential contaminant of pharmaceutical and cosmetic preparations. In the preservation of ophthalmic solution, phenylethanol is recommended for use in combination with a suitable broad-spectrum antibacterial such as benzalkonium chloride, or chorocresol, or to a lesser extent chlorhexidine [155].

3. Staphylococcus aureus:

It is gram positive cluster form, non-motile, non-spore forming. It is leading cause of soft tissue infection, as well as toxic shock syndrome and scalded skin syndrome. It has been found to be the causative agent in such illness as pneumonia, meningitis, boils, arthritis and osteomyelitis (chronic bone infection) [156]

It readily killed by phenolic and hypochlorite disinfectants at standard in-use concentrations, and by antiseptic preparation such as hexachlorophene, chlorhexidine and povidone-iodine. There is some

evidence that multiply-antibiotic-resistant strains of *Staphylococcus aureus* are slightly susceptible to some of these agents than ordinary strains [(157)].

Most clinical isolates of Staphylococcus *aureus* resistant to benzylpenicillin, due to the production of a beta-lactamase that bind to the antibiotic and destroys its activity by opining it at beta-lactam ring [(158)]. Methicillin resistance is a complex property and more than one mechanism is involved. Strains of methicillin resistant *Staphylococcus aureus* (MRSA) that are bets-lactamas negative can appear penicillin-sensitive, methicillin-resistant on testing [(159)].

Resistance to other antibiotics is achieved by a number of different mechanisms depending on the class of antibiotic; these include membrane impermeability, alteration of the target site, and enzymic degradation of antibiotic [(158)].

4. Bacillus subtilis*:*

Its gram positive bacilli, motile with lateral flagella, spore forming, non capsulated. Its one of the commonest saprophytes in contaminant in foods, clinical specimens and laboratory cultures. The organism is sometimes found in opportunistic infections or food poisoning [(160)].

4.2 Experimental:

4.2.0 Microbiological tests:

In this work, the antibacterial test was performed according to the disc diffusion method [161]. Compounds (10a, 8a, 6b, 20b, 15b) were assayed for their antimicrobial activity *in vitro* against two strains of Gram negative bacteria (*Pseudomonas aeuroginosa and Klebsiella pneumoniae)* and two strain of Gram positive bacteria *(Staphylococcus aureus and Bacillus subtilus)*

4.2.1 Isolation and Diagnosis:

Klebsiella Pneumoniae, Pseudomonas aeuroginosa and *Staphylococcus aureus were* obtained from Hilla surgical teaching hospital while *Bacillus subtilus* bacteria was obtained from the microbiology lab of the college of medicine/Babylon University.

4.2.2 Activation:

The previous bacteria were activated in a Nutrient Growth medium at 37 ^{o}C for 24 hour.

4.2.3 Sensitivity test:-

The prepared agar and Petri dishes were sterilized by autoclaving for 15min at 121 ^{o}C. The agar was surface inoculated uniformly from the broth culture of the tested microorganisms.

In the solidified medium, suitably spaced apart holes were made (6mm in diameter) these holes were filled with (0.02g) of the prepared

compounds dissolved in (1ml) of DMSO solvent, DMSO was used as a solvent. These plates were incubated at 37^{o}C for 24 hour.

4.3 Results and Discussion:

The biological activity of compounds was determined by measuring the diameter of the empty region around the well (Inhibition zone). The results of preliminary screening tests are listed in table (4-1)

Table (4 - 1)

Antibacterial activities of the synthesized compounds

Comp. No.	In figure	*Klebsiella Pneumoniae*	*Pseudomonas aeuroginosa*	*Staphylococcus aureus*	*Bacillus subtilus*
10a	1	++	-	+	+
8a	2	++	-	+	-
6b	3	-	-	+	+
20b	4	-	-	+	+
15b	5	-	-	+	+

Not:

- = No inhibition = inactive

\+ = (5-10) mm = slightly active

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

The biological activity test showed that compound [10] with free (-NH_2) and (-SH) groups having a biological effect more than other compounds.

4.4 Conclusion:

1. For *Klebsiella Pneumonia*e (G^-), compound [10a, 6b] showed highest activity, while compounds [8a, 20, 15] showed no active on this bacteria.
2. For *Pseudomonas aeuroginosa* (G^-), all compounds have no effect on this bacteria because this bacteria is highly resistant to a wide rang of antibiotic because of the slim poly saccharides in cell wall which blocked antibiotics from bacteria and also there are genetic factor.
3. For *Staphylococcus aureus* (G^+), all compounds have moderate effect on this bacteria.
4. For *Bacillus subtilus* (G^+), all compounds have moderate effect except compound [8a] has no effect on these bacteria.

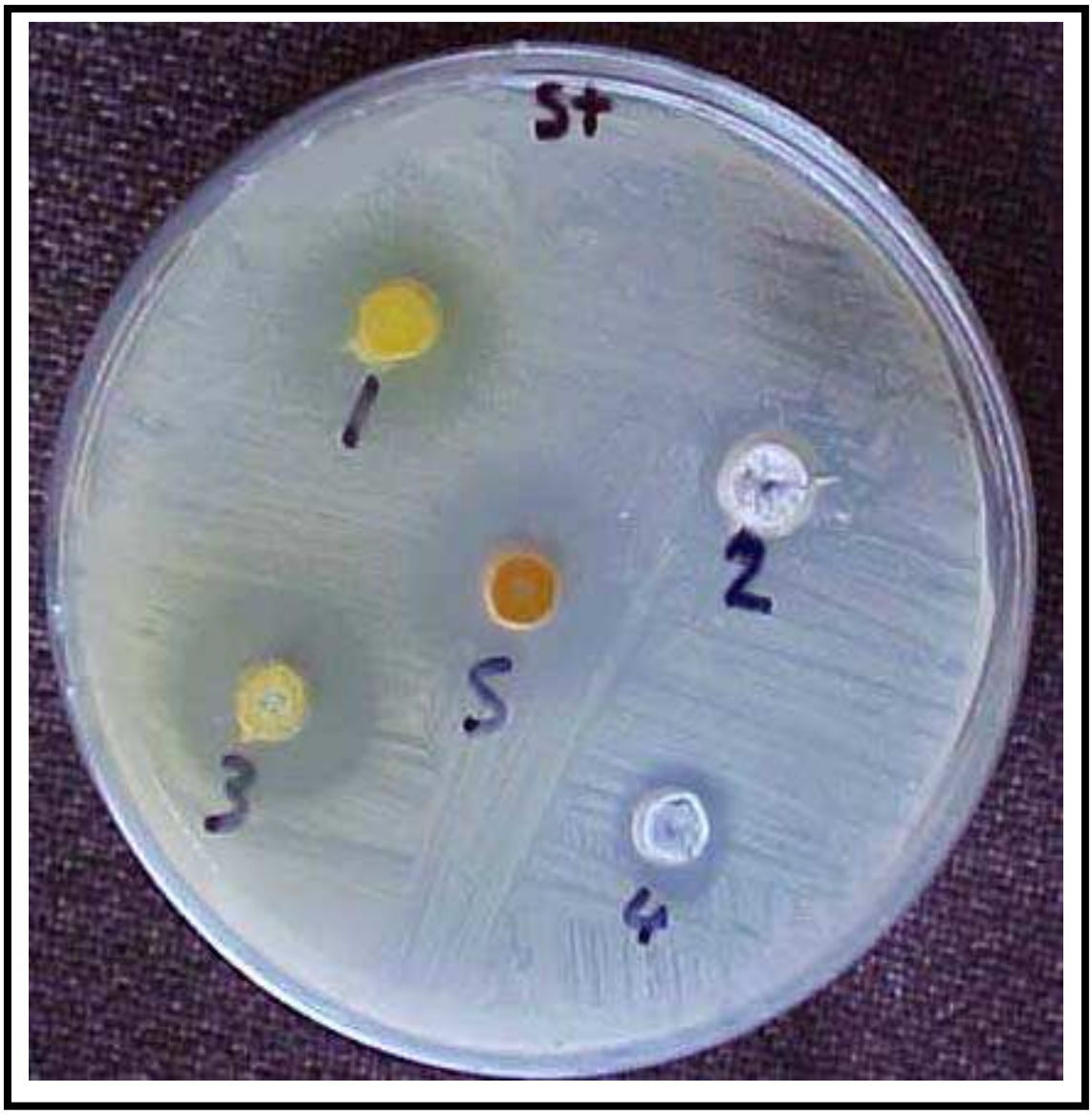


Figure (4-1):- The effect of compounds [1, 2, 3, 4, 5] on *Staphylococcus aureus*

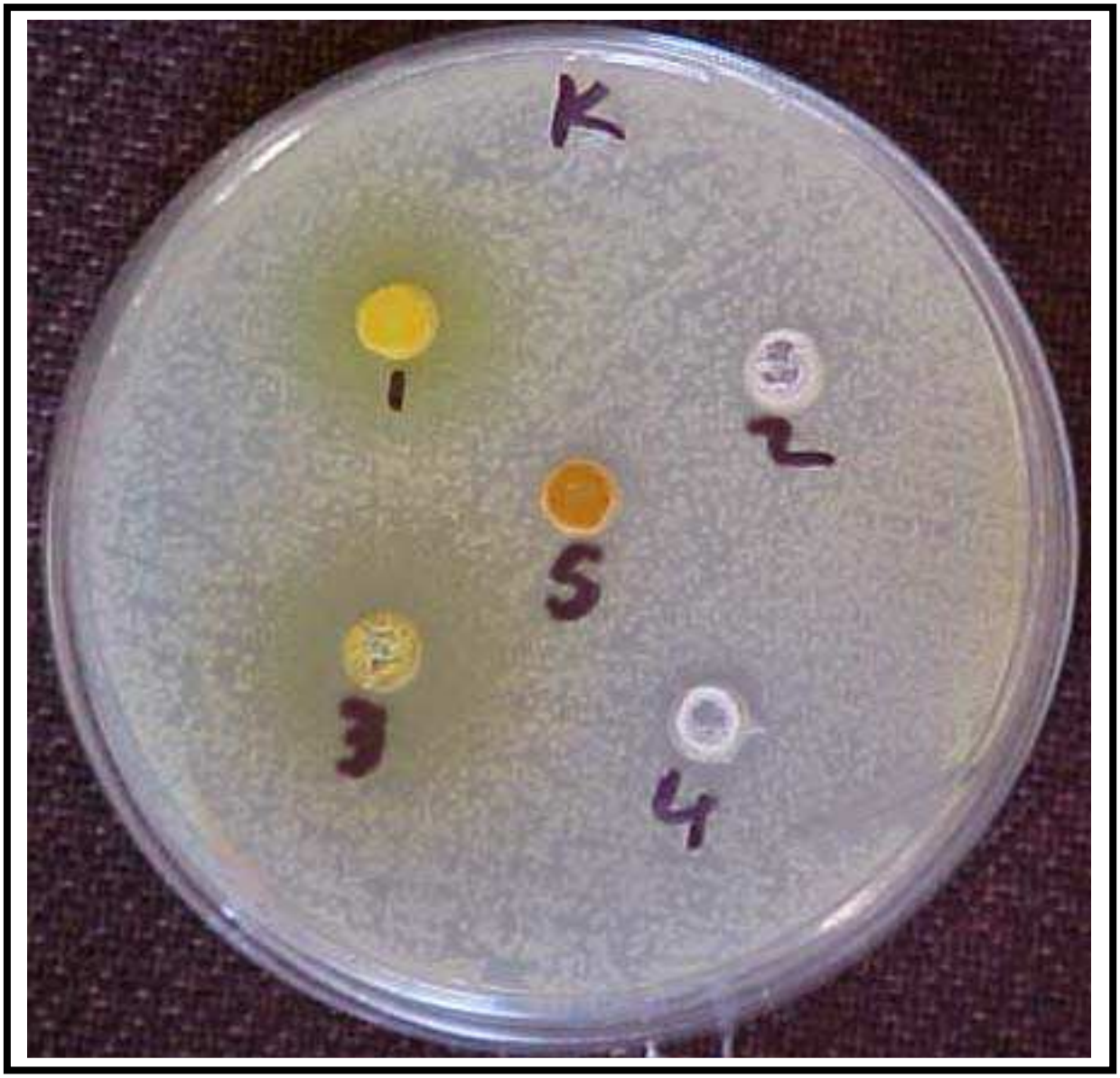


Figure (4-2):- The effect of compounds [1, 2, 3, 4, 5] on *Klebsiella Pneumoniae*

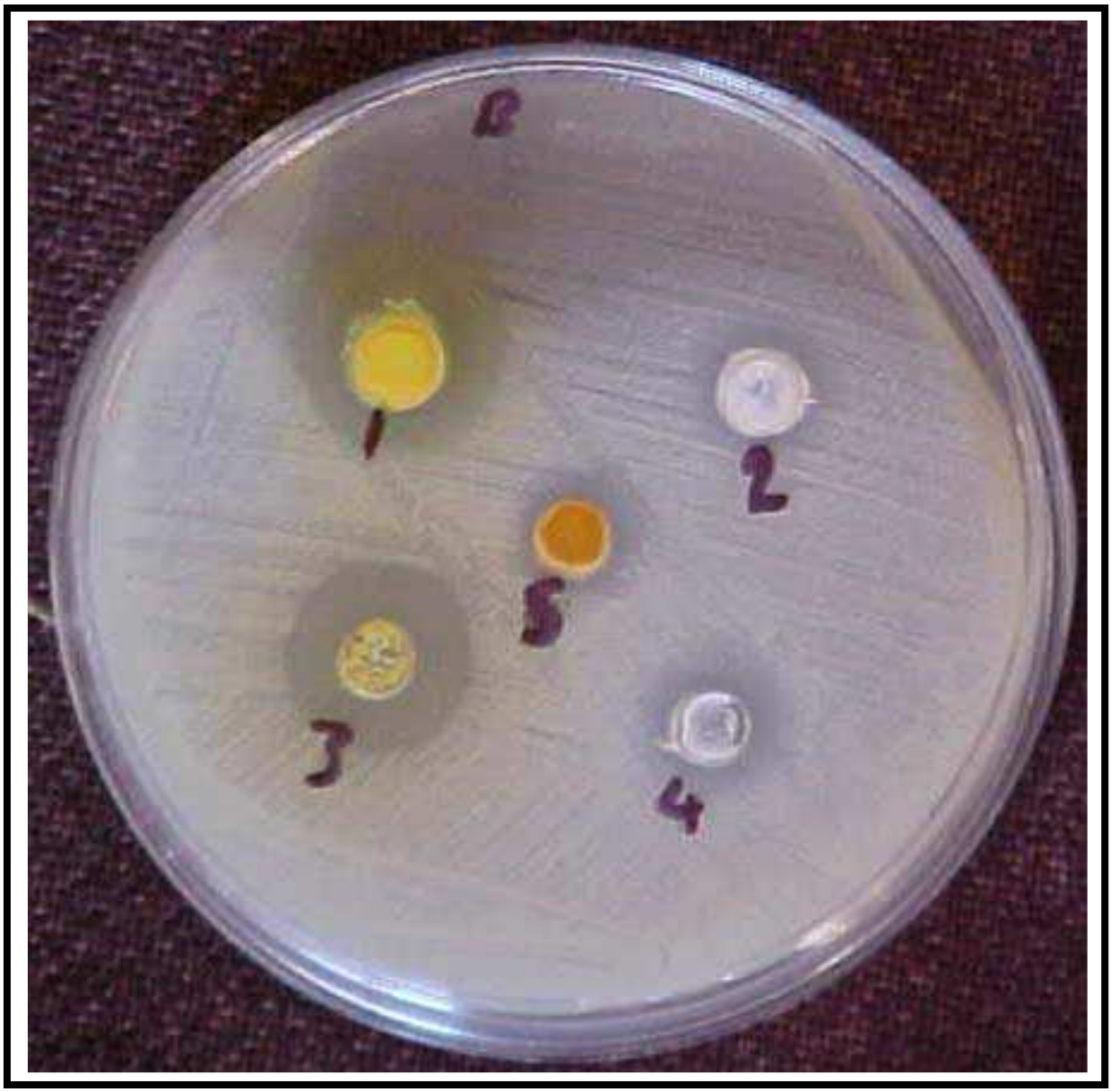
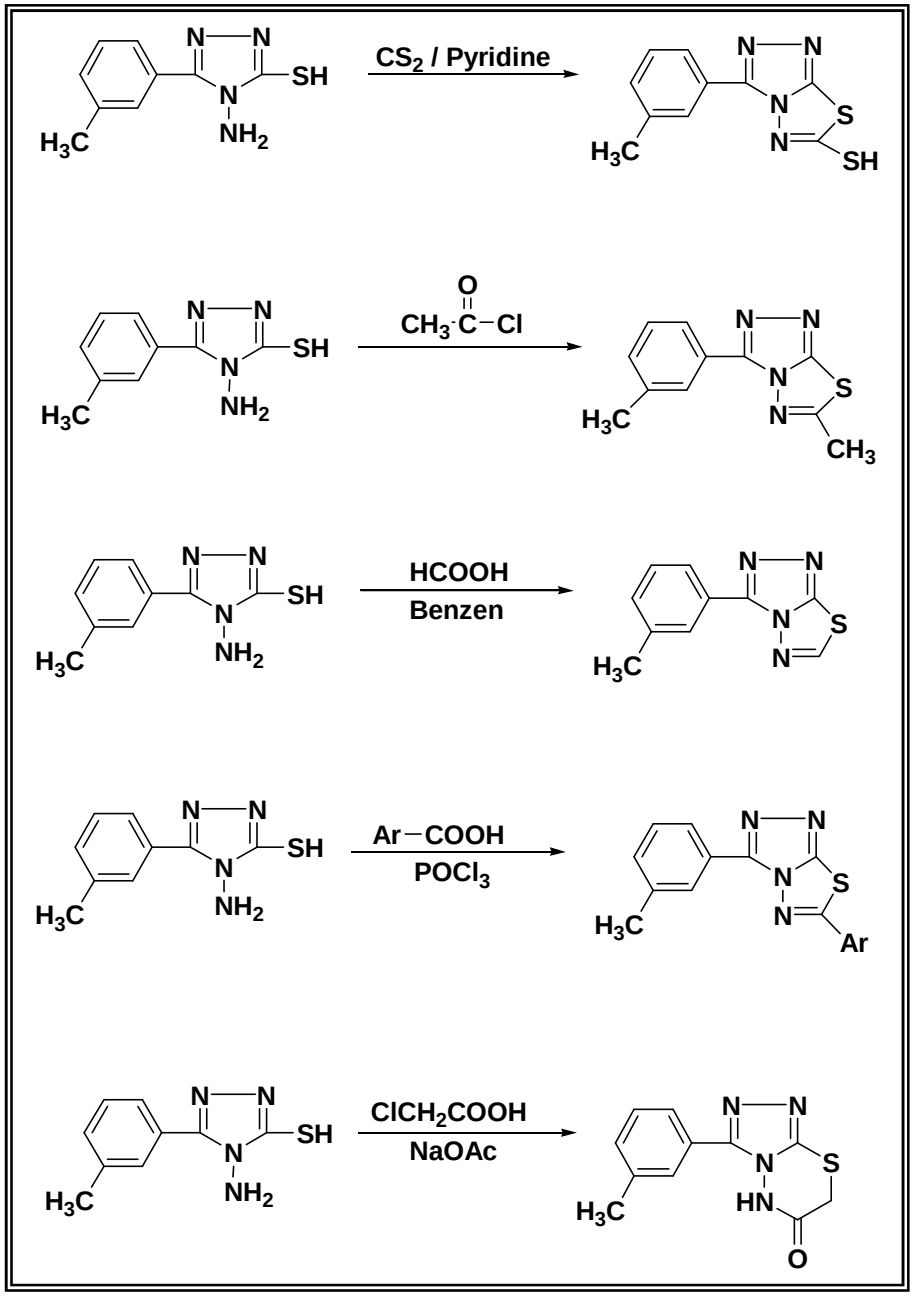
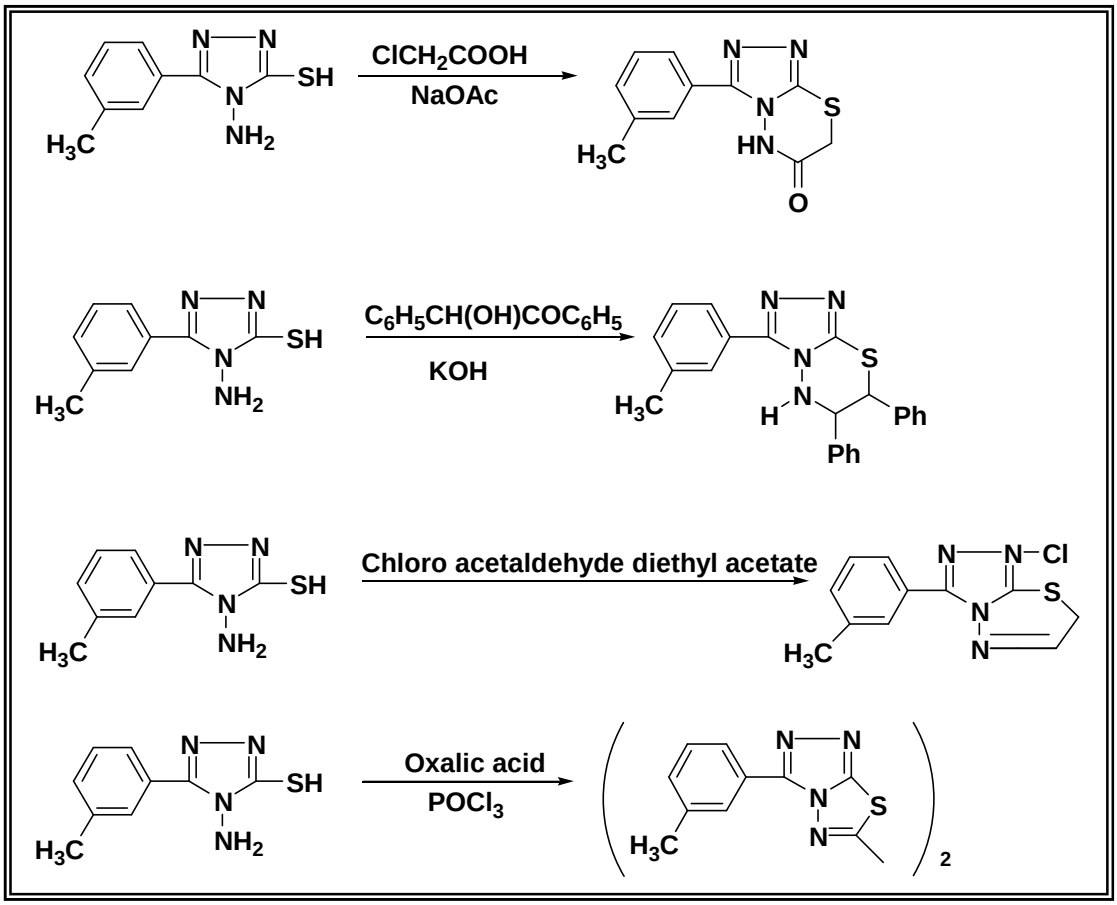


Figure (4-2):- The effect of compounds [1, 2, 3, 4, 5] on *Bacillus subtilus*

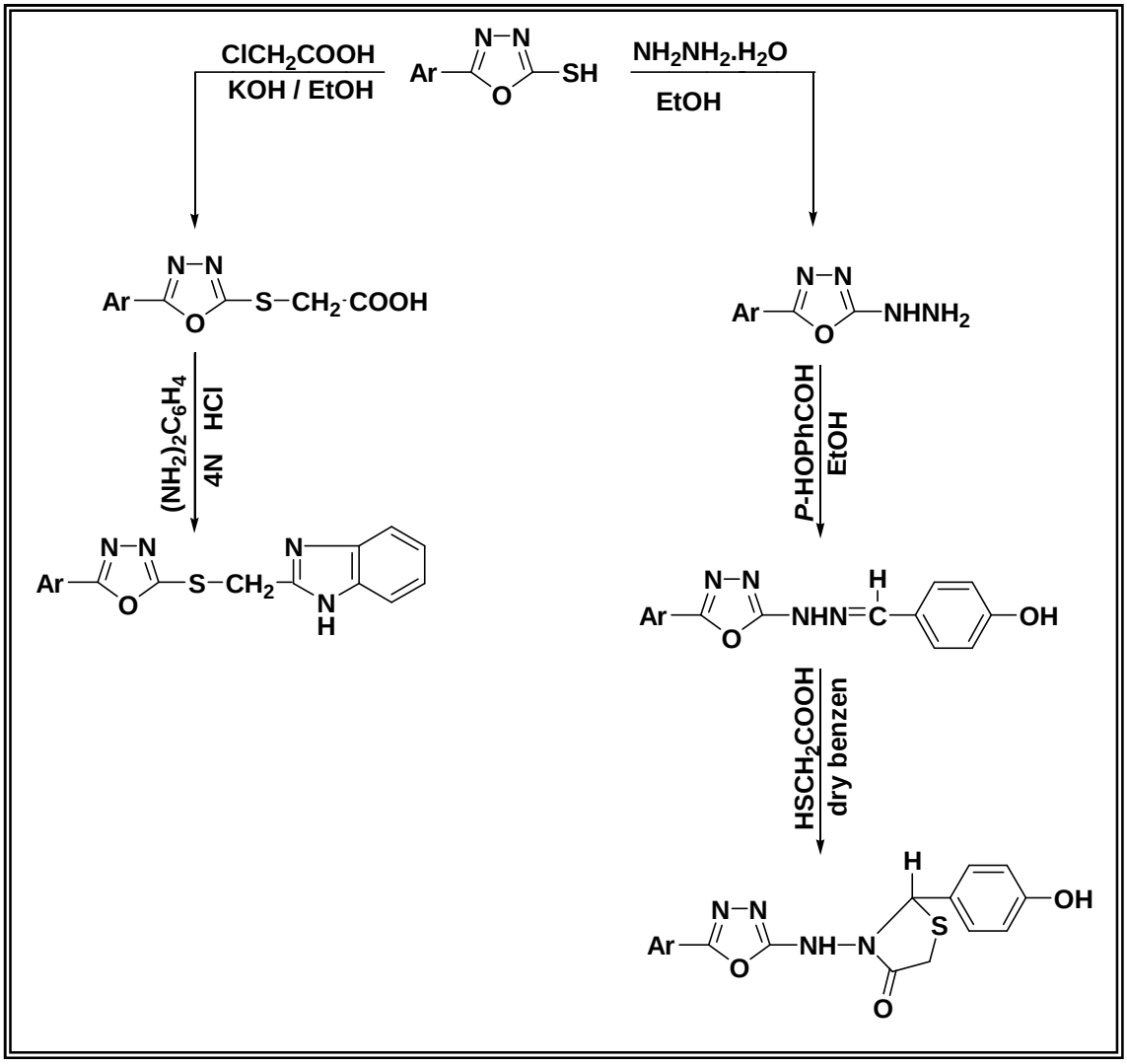
Suggestions for further work

1. Cyclization between the two functional groups (SH and NH_2) of compound [10a] by using different cyclization reagents to form new fuesed rings.




ClCH2COOH
NaOAc
C6H5CH(OH)COC6H5
KOH
Chloro acetaldehyde diethyl acetate
Oxalic acid
POCl3

2. Formation of thiazolidone and fused ring



Chapter One

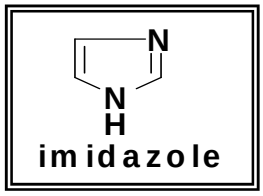
Introduction

1.1 Heterocyclic Compounds:

Heterocyclic compounds are considered an important branch of organic compounds due to their application in drugs and industrial studies [1].

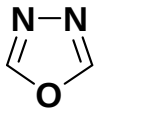
They are major class of organic chemical compounds characterized by the fact that the atoms in their molecules are joined into rings containing at least one hetero atom.

The most common heterocyclic are those with five- or six- membered rings, containing nitrogen (N), oxygen (O), or sulfur (S) [2].



imidazole

Just as with all cyclic compounds, heterocyclic may be aromatic or not aromatic based on the Hückel's rule (4n+2) = π electron [3].



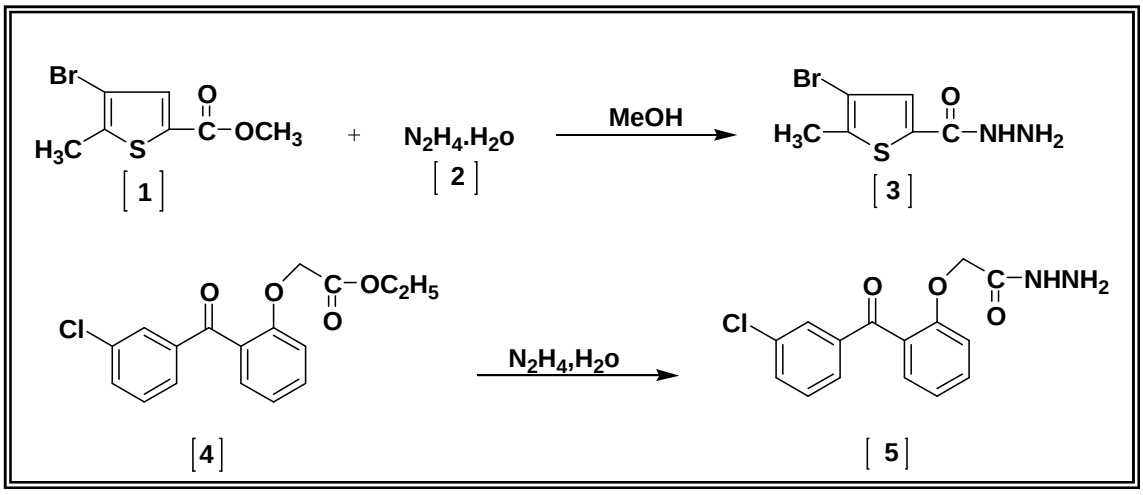
1,3,4-oxadiazole

1.2.0 Hydrazide derivatives:

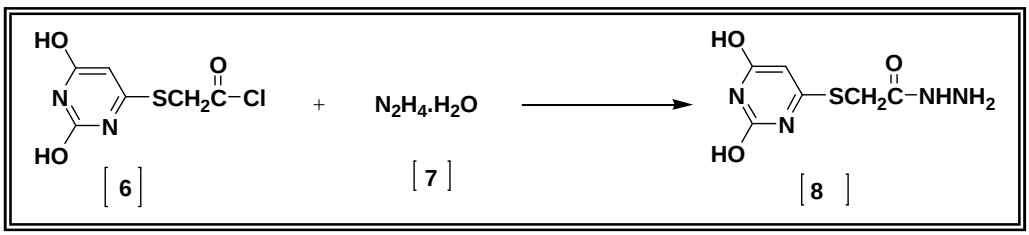
Hydrazide and thiosemicarbazide derivatives attracted a lot of attention because they are considered as intermediates to synthesize several compounds such as Schiff bases, oxadiazole [4], thiadiazole [5],triazole [6], pyridazine [7] and pyrazole [8] derivatives which all were reported to posses biological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

1.2.1 Synthesis of hydrazide derivatives:

Several methods are available for the synthesis of hydrazide derivatives, the most important one is based on the reaction of esters with hydrazine monohydrate [9, 10] as shown below:

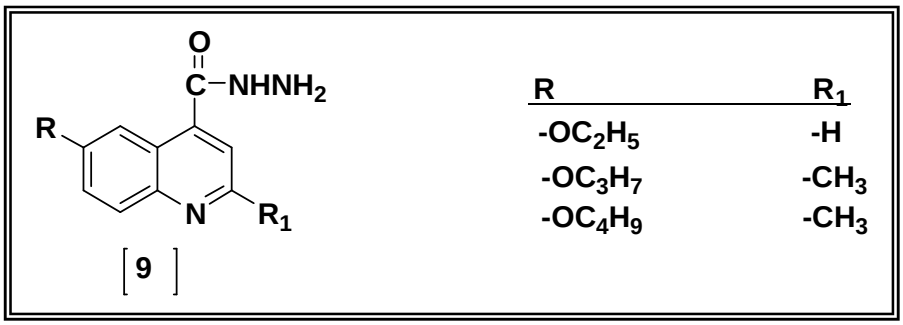


Acid hydrazide derivatives can also be synthesized from condensation reaction of carboxylic acid chloride with hydrazine hydrate [11].

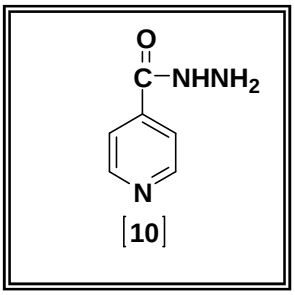


1.2.2 Hydrazide derivatives uses:

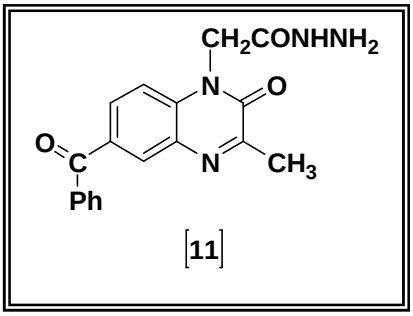
Hydrazide derivatives are considered biologically active; many hydrazide compounds were used in treatment of tuberculosis [(12)] such as compound [9].



Carbohydrazides were found to be useful as medicament especially in the treatment of inflammatory, respiratory diseases and tuberculosis such as isonazide [10] [(10)].

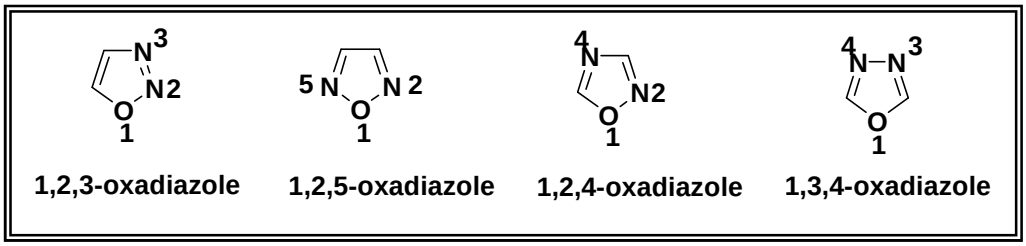


Some of carboxylic acid hydrazides were reported to have antimicrobial activities as compound [11] [(13)]



1.3.0 Oxadiazole:

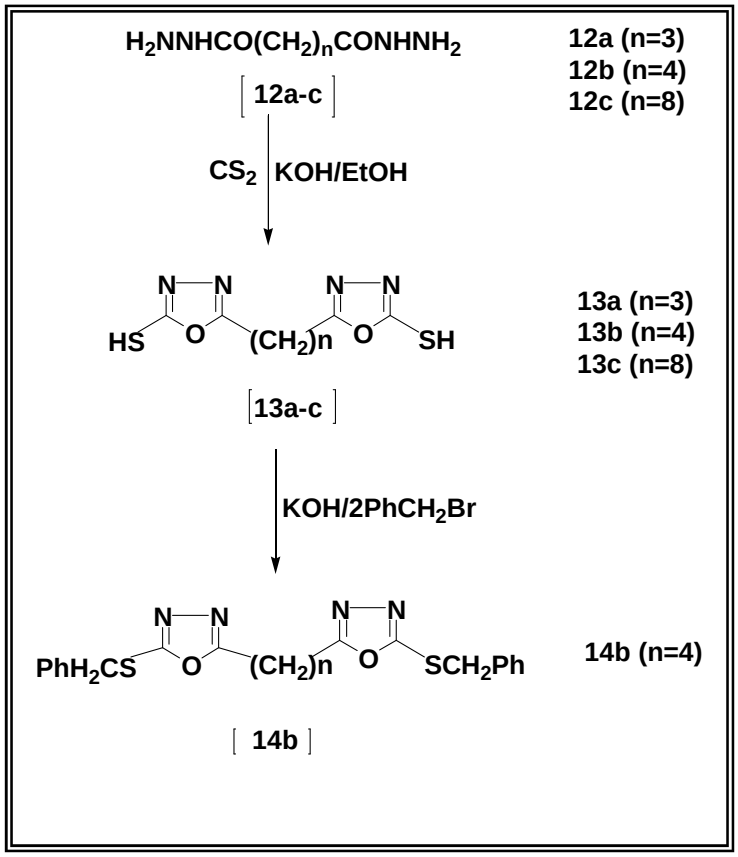
Oxadiazoles are five membered aromatic ring compounds with three heteroatom: one oxygen and two nitrogen atoms exist with different structure formulas [14]:



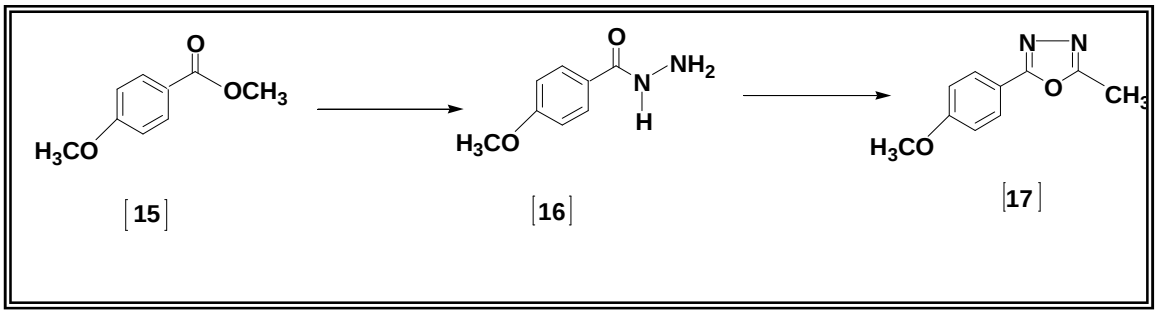
1,3,4-oxadiazole is the most thermally stable isomer and its stability is controlled in general by the electron density at C-2 and C-5 atoms, which is largely dependent on the substitutions, the stability of 1,3,4-oxadiazole is especially enhanced by alkyl and aryl substitution at position 2 and 5 [15].

1.3.1 Synthesis of 1,3,4-Oxadiazole:

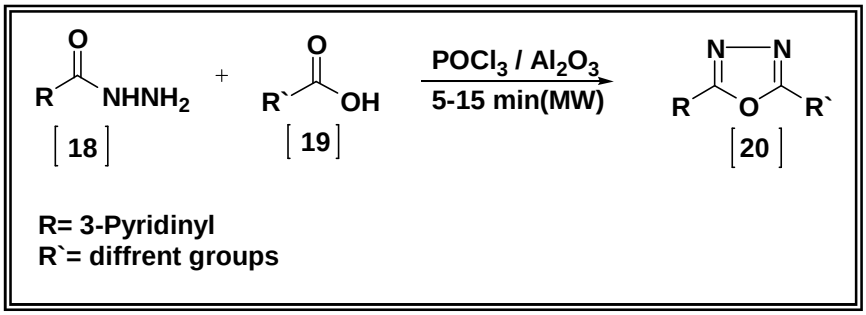
Maslat et. al., [16] have prepared Bis-1,3,4-oxadiazoles [13a-c] by the reactions of alkanedioic acid dihydrazides [12a-c] with carbon disulfide in alcoholic potassium hydroxide solution. Compound [13b] afforded dibenzylmercapto derivative [14b] by reaction of benzyl bromide with KOH in alcohol:



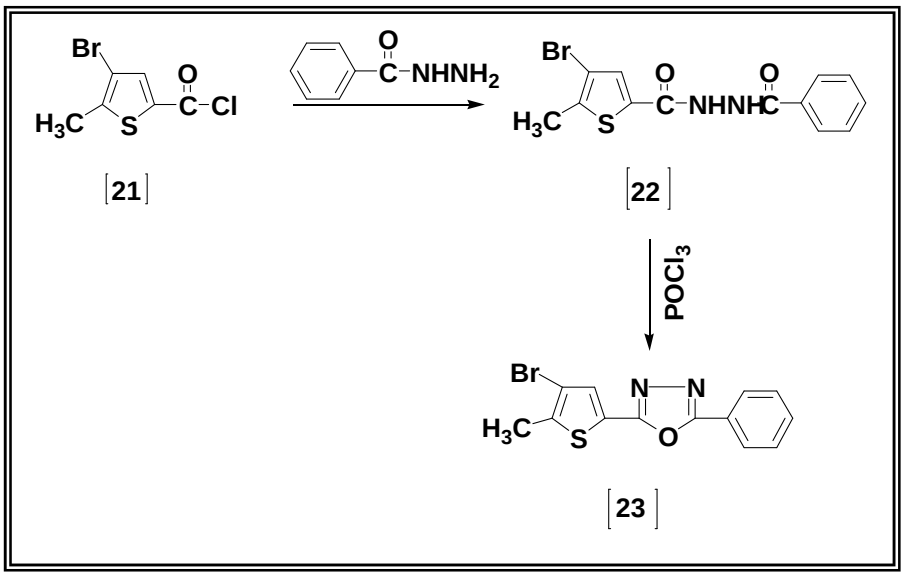
Grabmann et. al., [17] found that when methyl anisate [15] allowed to react with hydrazine monohydrate, the 4-methoxy benzoic acid hydrazide [16] would be formed. Cyclocondensation of the latter compound with triethyl orthoacetate yielded 2-methyl 5-(4-methoxy phenyl)-1,3,4-oxadiazole [17] :



Khan et. al., [18] prepared 2,5-disubstituted 1,3,4-oxadiazoles under microwave irradiation [20] by the reaction of hydrazides [18] with carboxylic acids [19] in the presence of phosphorous oxychloride :



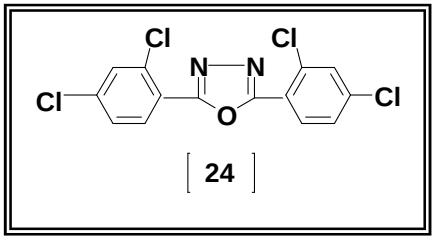
Krayushkin et. al., [19] have synthesized 2-phenyl-5-[2-methyl-3-bromo thiophen]-1,3,4-oxadiazole [23] by reacting acid chloride [21] and benzoic acid hydrazide in pyridine the diacylhydrazide [22] was obtained. Producing diacylhydrazide [22] which was converted after boiling in phosphorous oxychloride to [23]:



1.3.2 Biological activity of 1,3,4-oxadiazoles derivatives:

1,3,4-oxadiazoles are heterocyclic compounds, which serve as biomimtic, reactive pharmacophores and many are potential biological activities [20,21,22] such as, hypotensive [23] analgesic [24], fungicidal activity [25,26], bactericidal [27] and diuretic [28].

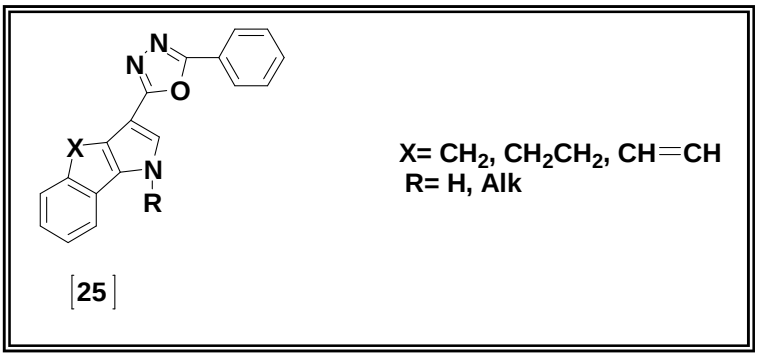
Symmetrical 2,5-bis (2,4-dichlorophenyl)1,3,4oxadiazole (DCPO) [24] and analogues were found to be effective as insecticides towards houseflies, faceflies and hornflies.



[24]

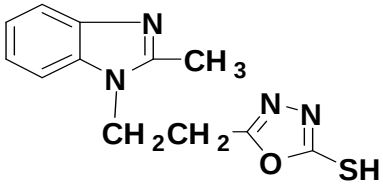
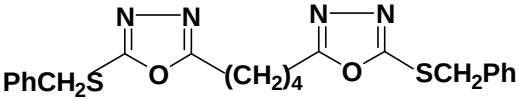
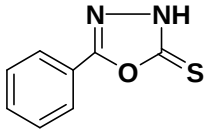
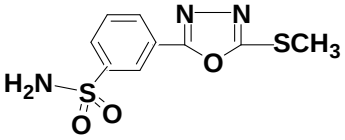
This type of compounds was shown to inhibit chitin synthesis in drosphlia and in musca domestic in vitro and in vivo studies [29].

On the other hand, some of 2,5-disubstituted 1,3,4-oxadiazole used against 60 tumor cell lines derived from nine cancer cell types. Biological results showed a very interesting anti-tumor activity against leukemia, colon and breast cancer, for example 3-(5-phenyl-[1,3,4]oxadiazole-2-yl)1*H*-benzo indole [25] [30].



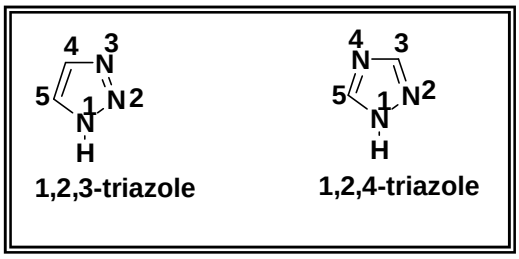
[25]

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

No.	Compound name	structure	Biological activity	Ref.
1.	2-mercapto-5-[2-(2-methyl benzimidazol-1yl)ethyl][1,3,4]oxadiazole		anti-fungal	31
3.	5,5-dibenzylthio-1,4-bis-[1,3,4-oxadiazol-2-yl]butane		anti-bacterial	16
4.	5-phenyl-1,3,4-oxadiazol-2-thione		anti-bacterial	32
5.	5(5-(methylthio)1,3,4-oxadiazol-2-yl)benzensulfonamide		anti-bacterial	33

1.4.0 Triazole:

Triazole is five member heterocyclic compound containing three nitrogen and two carbon atoms, with two structural formulas:

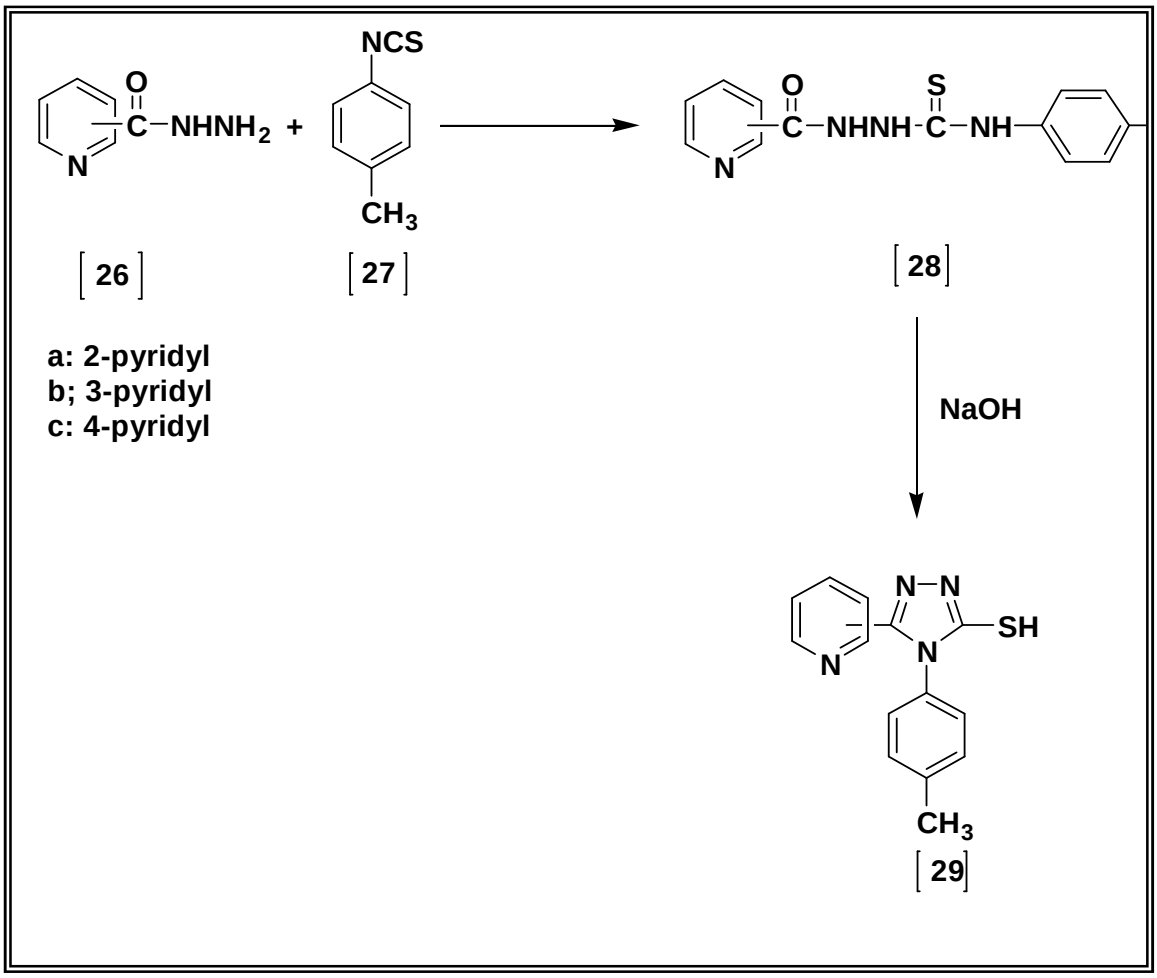


1,2,4-triazoles are The most important, this primarily due to the large number of uses including drug synthesis, herbicide, photographic chemical and dyestuffs.

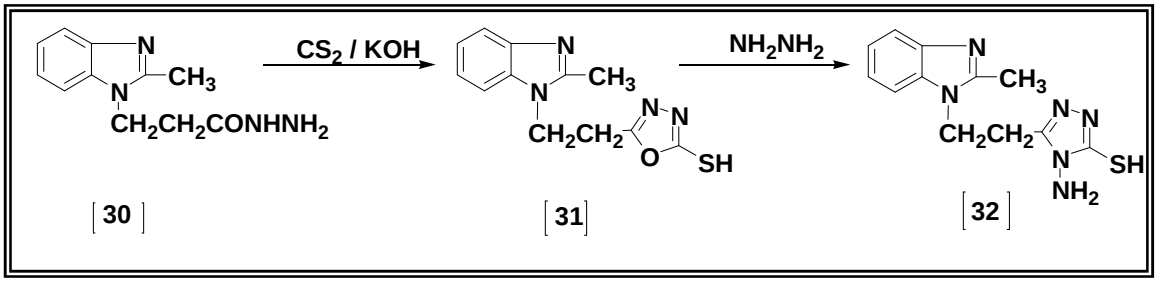
The name triazole was first given to the carbon-nitrogen ring system $C_2N_3H_3$ by ***potts***, who described it's derivatives early at 1885[(34)].

1.4.1 Synthesis of 1,2,4-triazoles:

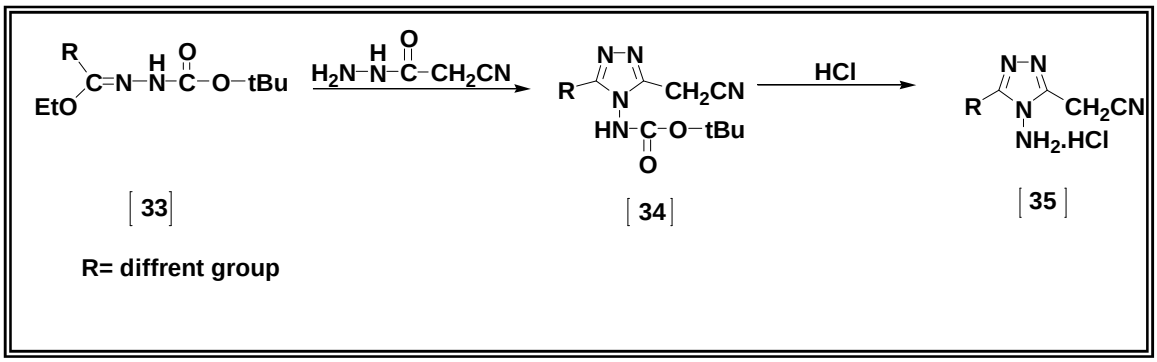
Zamani et. al., [(35)] found that 3-mercapto-2,4-dihydro-4-(4-methyl phenyl)-5-(isomeric pyridyl)- 1,2,4-triazole [29] can be prepared by reaction of substituted pyridine carboxylic acid hydrazides [26] with 4-methyl phenyl isothiocyanate [27] to give 1-(4-methyl phenyl)-4-(isomeric pyridoyl) thiosemicarbazides [28], then adding sodium hydroxide to the latter compound to produce [29] :



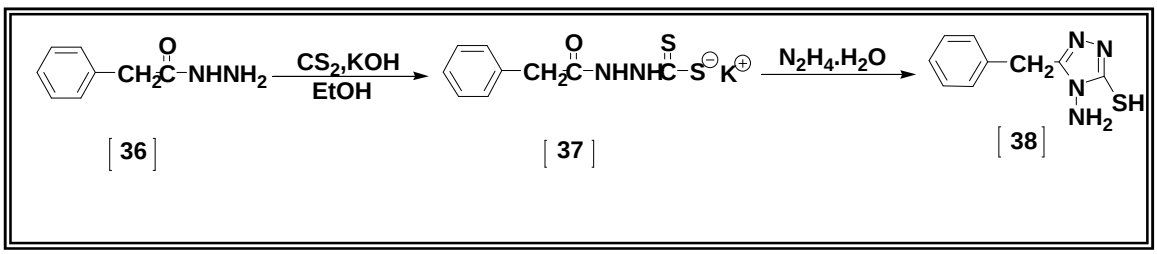
El-masry et. al., [31] found that the reaction of 3(2-methyl benzimidazol-1-yl)propanoic acid hydrazide [30] with carbon disulphide and potassium hydroxide afforded 5-[2-(2-methyl benzimidazol-1-yl) ethyl]-1,3,4-oxadiazole-2(3H)-thione [31]. Compound [31] give 5 [2-(2-methyl benzimidazole-1-yl) ethyl]-4-amino [1,2,4]triazole-3-thiol [32] when reacted with hydrazine hydrate in absolute ethanol :



Demirbas et. al., [36] found that the reaction of N-tert-butyl carboxy-ethoxy hydrazone [33] with cyanoacetic acid hydrazide gave 3-alkyl-4-tert-butoxy carbonyl amino-5-cyanomethyl-4*H*-1,2,4-triazole [34].Compound [34] was converted to 3-alkyl-4-amino-5-cyanomethyl-4*H*-1,2,4-triazole hydrochloride [35] in good yield by treatment with HCl :



Cansiz et. al., [37] found that the reaction of phenyl acetic acid hydrazide [36] with carbon disulfide in ethanolic potassium hydroxid afforded the potassium-3-(phenyl acetyl)dithiocarbazate [37]. Compound [37] gave 3-mercapto-4-amino-5-benzyl-1,2,4-triazole [38] when reacted with hydrazine hydrate under reflux:



1.4.2 Biological activity of 1,2,4-triazoles:

Among the five member heterocyclic compounds triazoles in general and in particular -1,2,4-triazole derivatives have been found to exhibit wide spectrum of biological activities , they attracted attention owing to their pesticidal[38], antianxiety[39], anti-covulsant [40,41], anti-fungal [42-45], anti-cancer[46-49] and anti-bacterial properties [50-53].

Several compounds, Figure (1-1) containing 1,2,4-triazole rings are well known as drugs, for example fluconazole which is a triazole anti-fungal drug, used in the treatment and prevention of superficial and systemic fungal infections, it is commonly marketed under the trade name difucan. Also voriconazole is a new triazole derivative with broad anti-fungal activity [54].

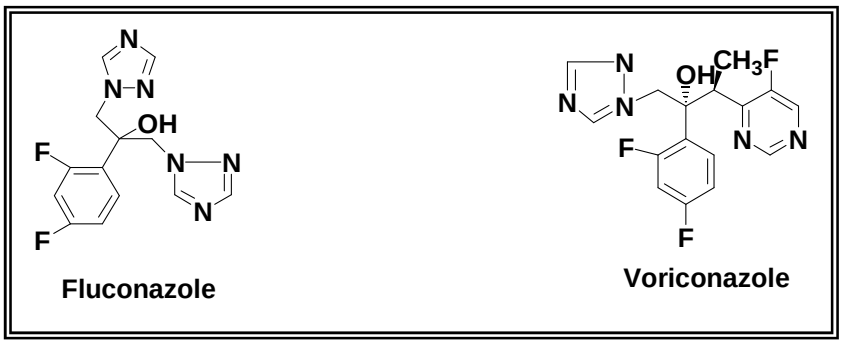


Figure (1-1)

Figure (1.2) containing compounds having triazole moieties Such as vorozole, anastrozole and letrozole which are non-steroidal drugs, used for the treatment of cancer [55].

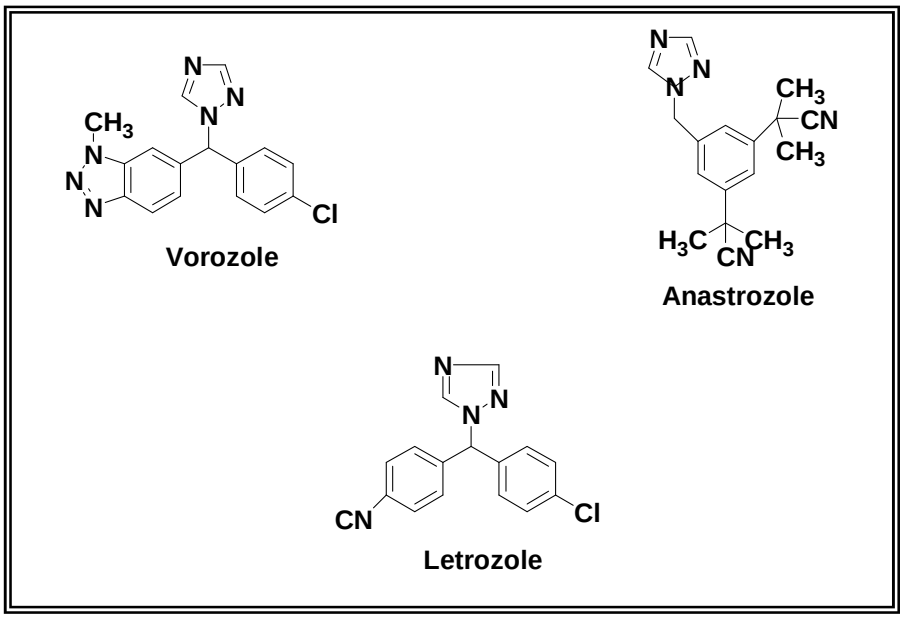
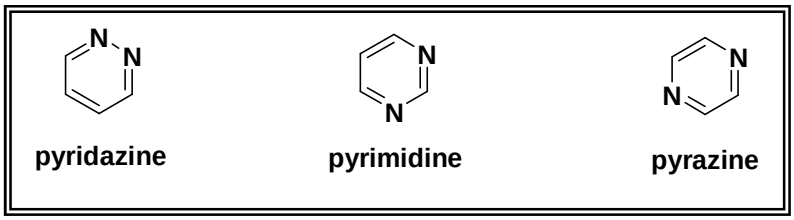


Figure (1-2)

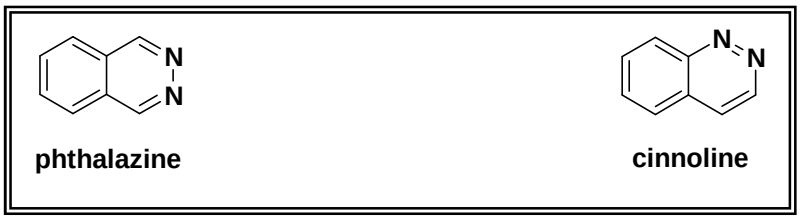
1.5.0 Pyridazines:

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-relation ship:



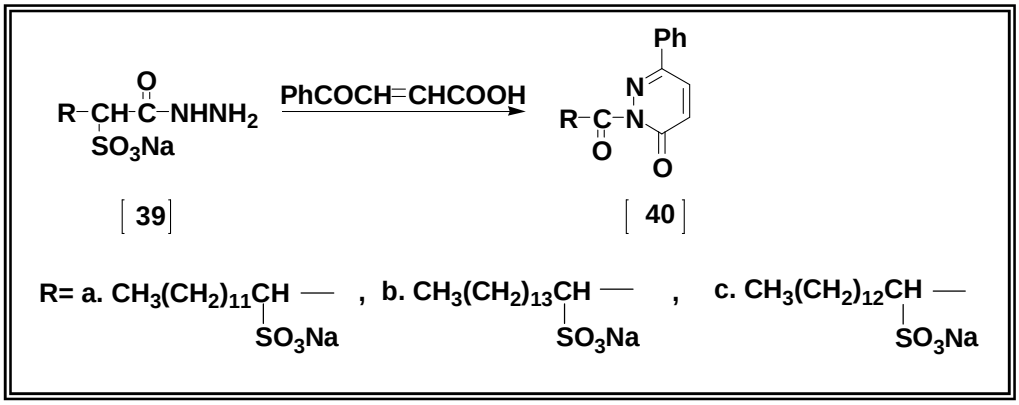
No naturally occurring pyridazines have been reported because of the paucity of chemical compounds containing two nitrogen atoms bonded to one another in nature [56].

Pyridazine ring can be fused with a benzene ring in two ways giving phthalazine or cinnoline [57].

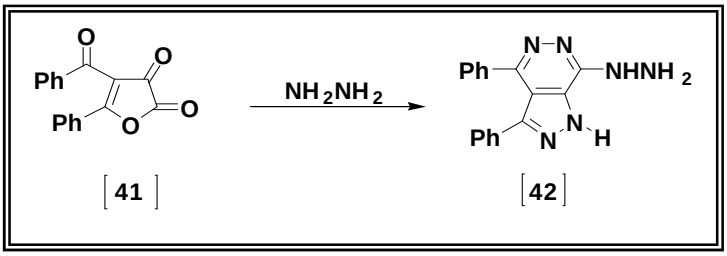


1.5.1 Synthesis of pyridazines:

Eissa [58] found that pyridazine derivatives [40] can be prepared by sodium salt of sulphonated fatty hydrazides [39] with benzoyl acrylic acid in normal ethanol:

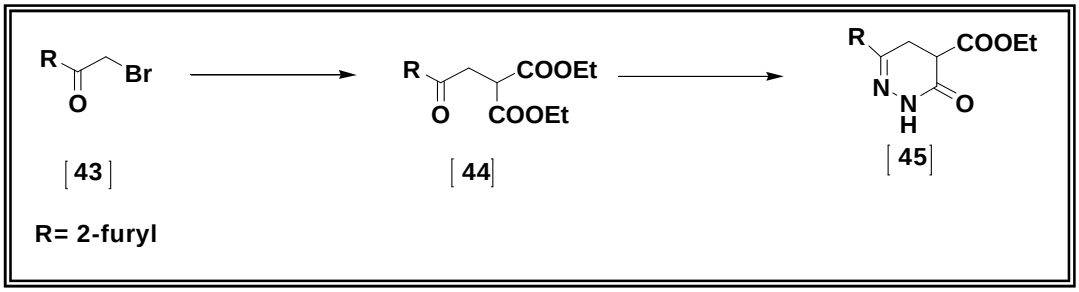


Sener[59] found that the reaction of furandione [41] with anhydrous hydrazine gave 7-hydrazino-3,4-diphenyl-1H-pyrazolo pyridazine [42] :



[41] [42]

Brana et. al., [60] found that when diethyl malonate allowed to react with 2-bromo-1-(2-furyl)ethanone [43], diethyl 2-[2-(2-furyl)-2-oxoethyl] malonate [44] would be formed. Reaction of the later compound [44] with hydrazine hydrate gave ethyl 6-(2-furyl)-3-oxo-2,3,4,5-tetrahydropyri-dazine-4-carboxylate [45] :



[43] [44] [45]

R= 2-furyl

1.5.2 Biological activity of pyridazine:

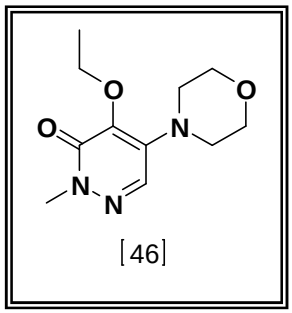
Pyridazine and condensed pyridazine are reported to have good biological activities.

Hydrazine-pyridazines are continue to be an object of interest for improving medicinal drugs for blood pressure control such as hydralazine, which has been used for many years in the treatment of essential hypertension [61-63].

Recently, therapeutic interest in this kind of drug has increase considerably due to their cytotoxic activities, notably decreasing blood flow to tumors [64].

Pyrazolo [3, 4-d] pyridazines have shown good antimicrobial, anti-inflammatory and analgesic activities [(65)].

A number of 3(2H)-pyridazinone derivatives bear analgesic activity as Emorfazone(4-ethoxy-2-methyl-5-morphalino-3(2H)-pyridazinone [46] [(66)].



[46]

1.6.0 Pyrazole:

Pyrazole is a 1, 2-diazole, and as its name implies, it may be considered as an azapyrole. The dimensions (A°) of the planar molecular are illustrated in figure (1 -3) [(67)]

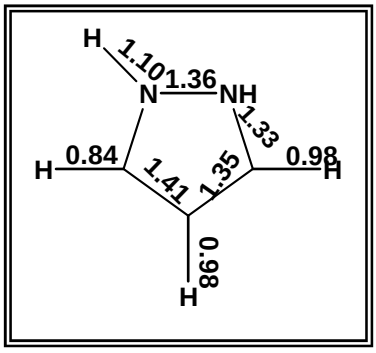
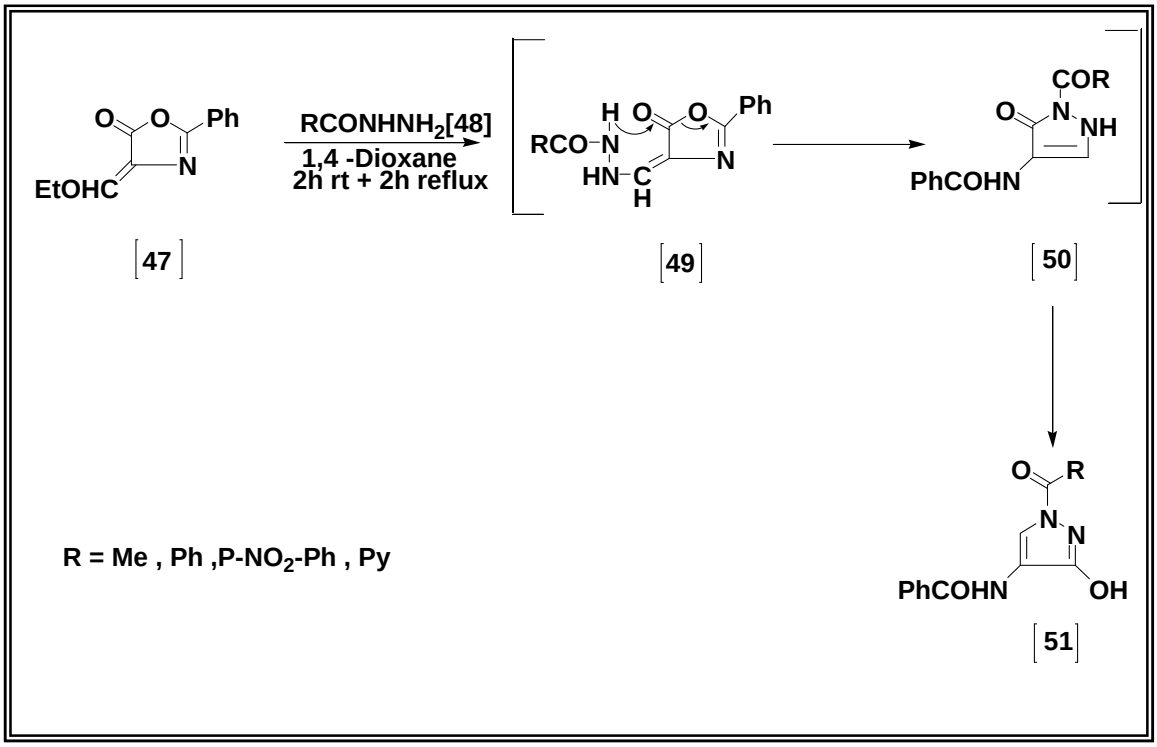


Figure (1-3)

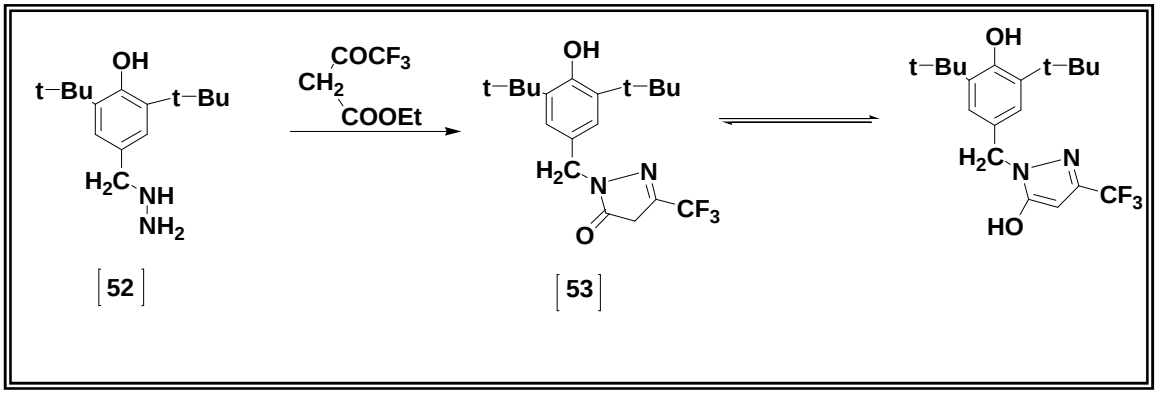
However, very few pyrazole derivatives occur naturally, this may be due to the difficulty for living organisms to construct the N-N bond [(68)].

1.6.1 Synthesis of pyrazole:

Kepe et. al., [69] have synthesized 1-acyl-3-hydroxy-1*H*-pyrazoles [51] and related derivatives from ethoxymethylene oxazolone derivatives [47] and hydrazides or related derivatives [48]. The method includes a migration of an acyl group in the intermediary-formed pyrazolone derivative [50] to yield the rearranged [51] in high yield:

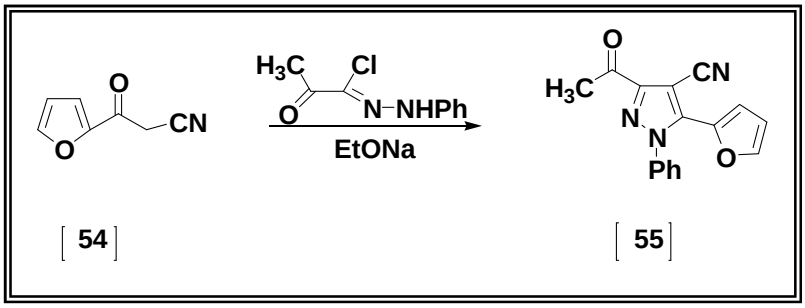


Dinoiu and Lü[2] [70] found that when 3,5-dialkyl-4-hydroxbenzylhydrazine [52] allowed to react with CF_3-contaning 1,3-diketones in ethanol, then refluxed for (10) hours, the 1-(3,5-di-t-butyl-4-hydroxybenzyl)-3-(trifluro-methyl)pyrazole-5-one [53] would be formed :



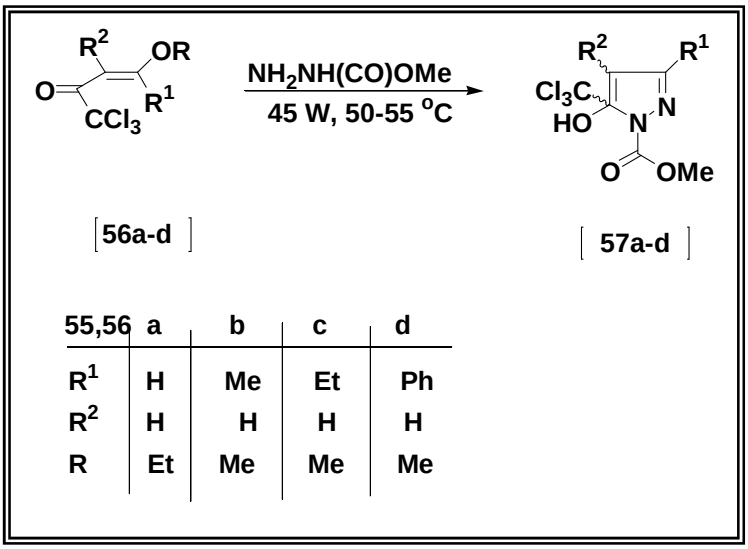
[52] [53]

Dawood et. al., [71] have synthesized [55] through reaction of 3-(2-furyl)-3-oxo-propanitrile [54] with ethanolic sodium ethoxide followed by addition of hydrazonyl halide:



[54] [55]

Martins et. al., [72] prepared a number of 3,4-disubstituted-5-trichloromethyl-5-dihydro-1*H*-1-pyrazole methyl ester [57 a-d] under microwave irradiation through the reaction of 1,1,1-trichloro-4-alkoxy-3-alken-2-one [56 a-d] and methyl hydrazino carboxylate in presence of 10 ٪ HCl :



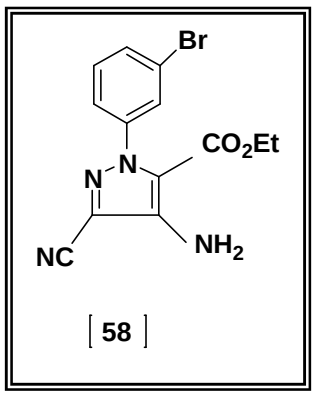
[56a-d] [57a-d]

55,56	a	b	c	d
R^1	H	Me	Et	Ph
R^2	H	H	H	H
R	Et	Me	Me	Me

1.6.2 Biological activity of pyrazole:

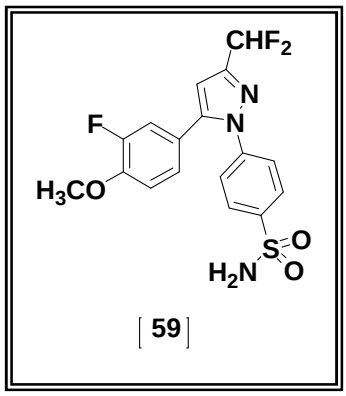
Pyrazole derivatives constitute an important family of compounds due to their applications as pharmaceuticals (analgesics, anti-inflammatory, anti-bacterial, and antidepressant), agrochemicals (insecticides) and dyestuffs [73- 75].

aminopyrazoles such as ethyl-4-amino-1-(3'-bromo-phenyl)-3-cyano-1*H*-pyrazole-5-carboxylate [58] was found potentially useful to prevent protein aggregation which is the first phase of Al-zheirmer or Creutsfeldt-Jakob diseases [76].



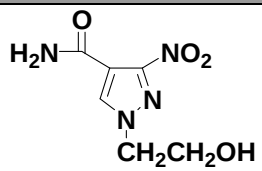
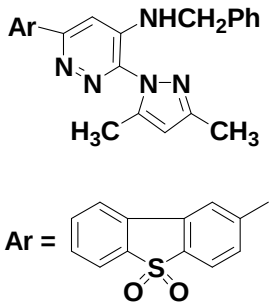
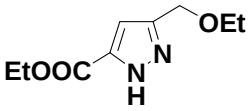
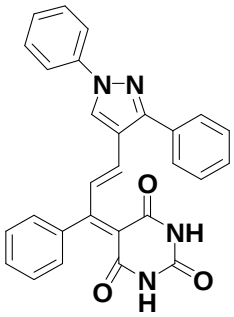
[58]

Deramaxx [59] is apyrazole derivative which is acoxib class of non-narcotic, non-steroidal, cycloxygenase-inhibiting anti-inflammatory drugs for the control of postoperative pain, inflammation associated with orthopedic surgery, for the control of pain and inflammation associated with osteoarthritis in dogs [77].



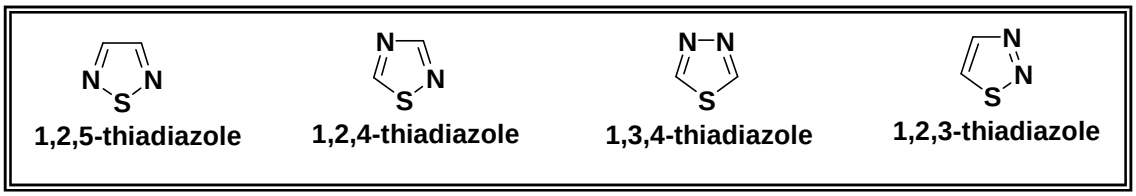
[**59**]

Table (1-2): Biological activity of some pyrazole.

No.	Compound name	structure	Biological activity	Ref.
1.	1-(2-hydroxyethyl)-3-nitro-4-pyrazol-carboxyamide		anti-bacterial	78
2.	4-Benzylamino-3-(3,5-dimethylpyrazol-1-yl)-6-(5,5-dioxodibenzothiophen-2-yl)-4,5-dihydropyridazine		anti-microbial	79
4.	3-ethoxymethyl-5-ethoxycarbonyl-1*H*-pyrazole		anti-nociceptive effect	80
5.	5-[1-Aryl-3-(1,3-diphenyl-4-pyrazoyl)-prop-2-enylidene]barbituraic acid		anti-bacterial	81

1.7.0 Thiadiazole:

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



The development of 1,3,4-thiadiazole chemistry is linked to the discovery of hydrazine and phenyl hydrazine. The first 1,3,4-thiadiazole was prepared by J.Sand in 1882 [82].

Bak et. al., [83] made a careful analysis of the microwave spectrum of 1,3,4-thiadiazole, they could determine the structure of the molecule as shown in figure (1 -4)

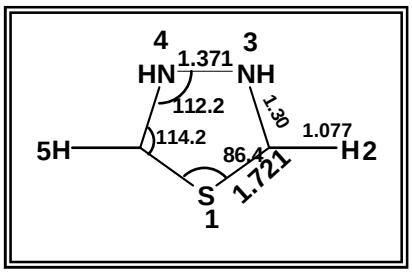
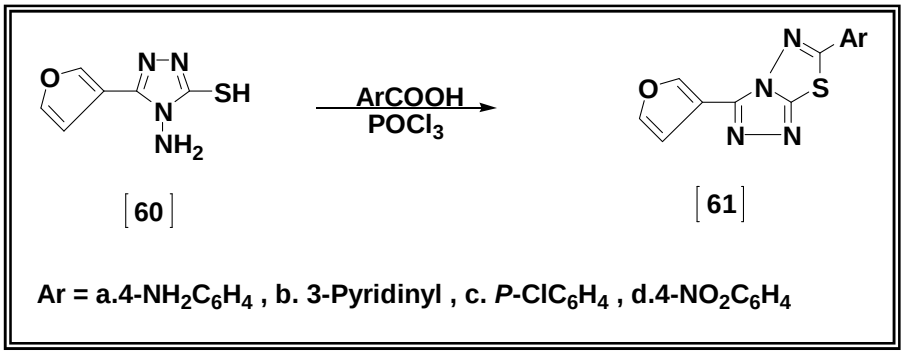


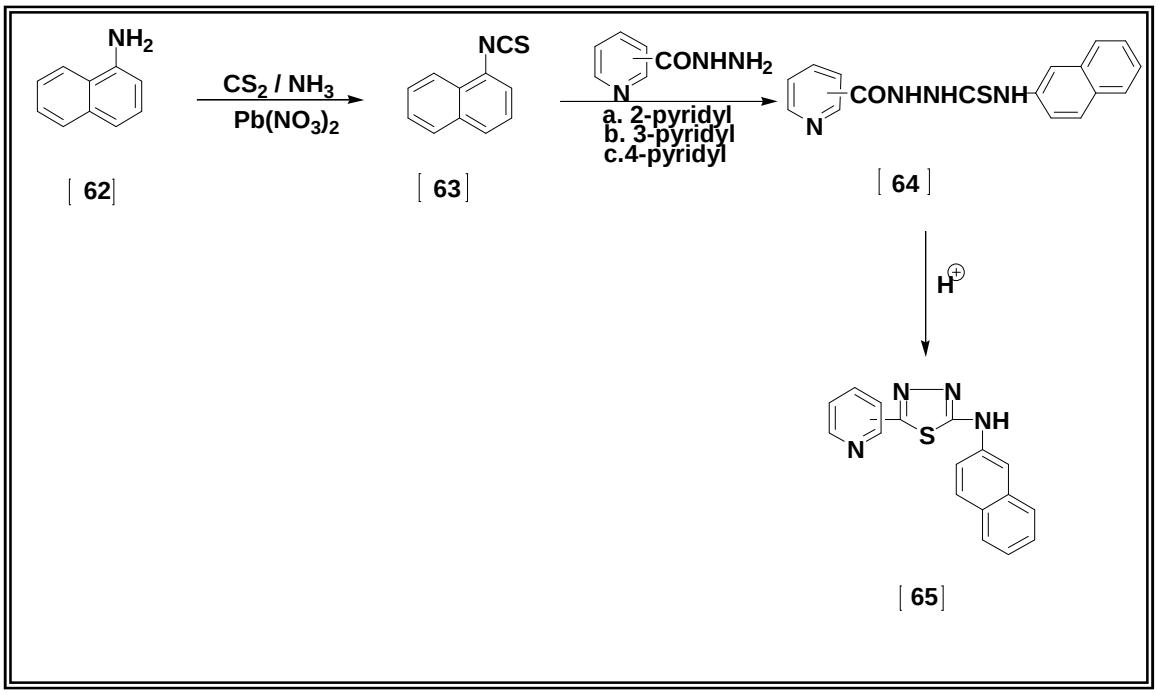
Figure (1-4)

1.7.1 Synthesis of 1,3,4- Thiadiazole:

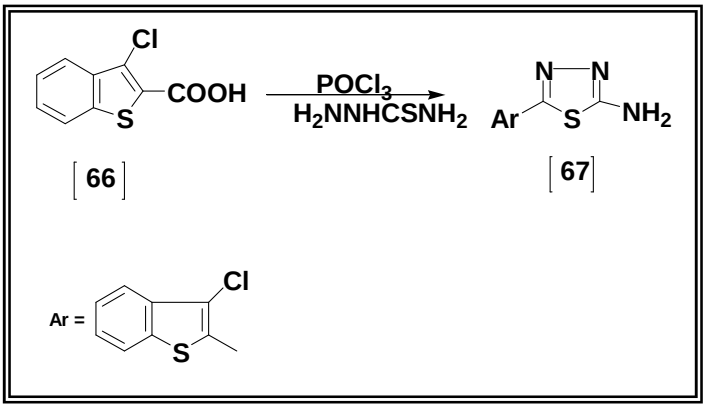
Zhang et. al., [84] have synthesized of 3-(2-furyl)-6-aryl-1,2,4-trizolo[3,4-b]1,3,4-thiadiazoles [61] through the reaction of 3-(2-furyl)-4-amino-5-mercapto-1,2,4-triazole [60] and aromatic acids in phosphorous oxychloride :



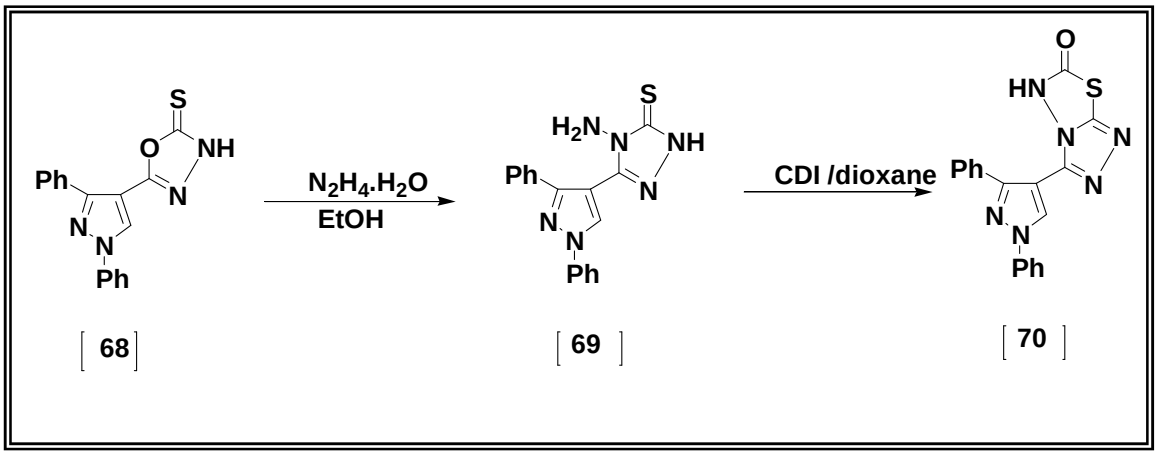
Zamani et. al., [85] found that the reaction of 1-naphthayl amine [62] with carbon disulfide, methanol and ammonia gave 1-naphthyl isothiocyanate [63], followed by adding pyridine carboxylic acid hydrazide afforded 4-(1-naphthyl)-1-(isomeric pyridyl) thiosemicarbazides [64] .The latter compound [64] reacted with sulfuric acid and gave 4-(1-naphthyl amino)-5-(isomeric pyridyl)1,3,4-thiadiazole [65]:



Aly and El-Sayed [86] have synthesized 2-amino-5-(3-chlorobenzo [b]thiophen-2-yl)-1,3,4-thiadiazole [67] through condensation of 3-chlorobenzo[b]thiophene-2-carboxylic acid [66] with thiosemicarbazide by using phosphorous oxychloride as condensing agent:



Farghaly et. al., [87] found that the reaction of oxadiazole thione [68] with hydrazine hydrate afforded 4-amino-3-(1,3-diphenyl-1*H*-pyrazole-4-yl)4,5-dihydro-[1,2,4]triazole-5(1*H*)-thione [69] . Reacted of [69] with 1,1-carbonyldiimidazole (CDI) in dry dioxane gave 3-(1,3-diphenyl-1*H*-pyrazole-4-yl)5,6-dihydro-[1,2,4]trizolo[3,4-b][1,3,4]thiadiazol-6-one [70]:

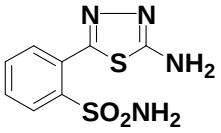
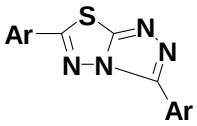
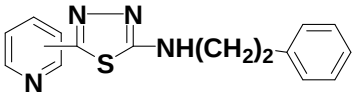
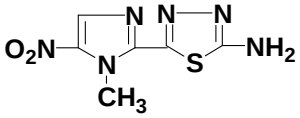
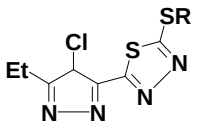


[68] [69] [70]

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

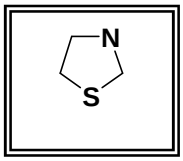
1,3,4-thiadiazoles are known for their broad-spectrum of biological activity such as antifungal [88, 89], antibacterial [90], herbicidal [91], antiviral [92], and analgesic effect [93, 94].

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

No.	Compound name	Structure	Biological activty	Ref
1.	2-amino-5-(2-sulfamoylphenyl)1,3,4-thiadiazole		antiviral activity	92
2.	2,5-disubstituted-s-triazolo[3,4-b][1,3,4]thiadiazole		antibactrial	95
3.	2-benzylamino-5-(2-pyridyl)1,3,4-thiadiazole		antibactrial	96
4.	[2-amino-5(1-methyl-5-nitro-2-imidazolyl)1,3,4-thiadiazole		antibacterial and anti-parastic compound	97
5.	5-(4-chloro-3-ethyl-1-methyl-1-pyrazol-5-yl)-2-alkylthio-1,3,4-thiadiazole	 R = H, CH_3 , CH_3CH_2 , C_3H_7 , C_6H_{11}	fungicidal	98

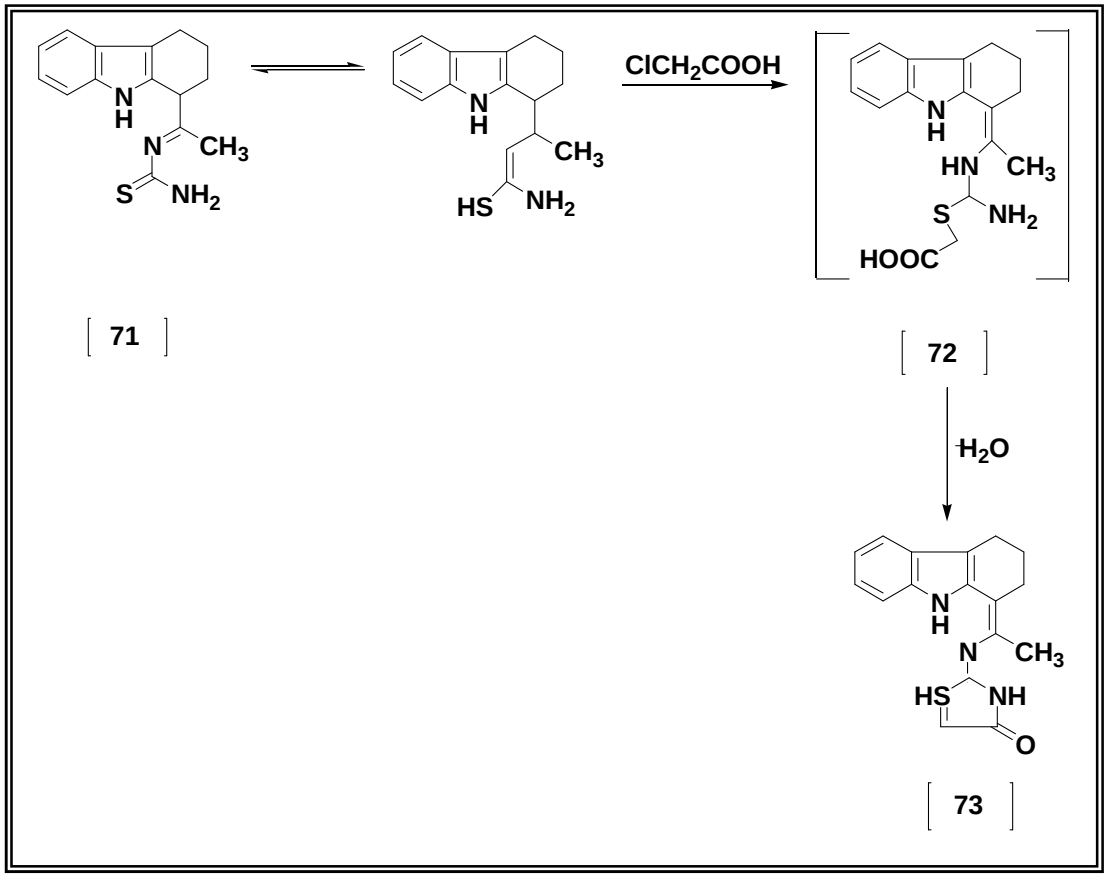
1.8.0 Thiazolidine:

Thiazolidine is one of a class of organic heterocyclic compounds containing a five membered saturated ring with two heteroatoms: one nitrogen and one sulfur atom, thiazolidine can be found in one form.

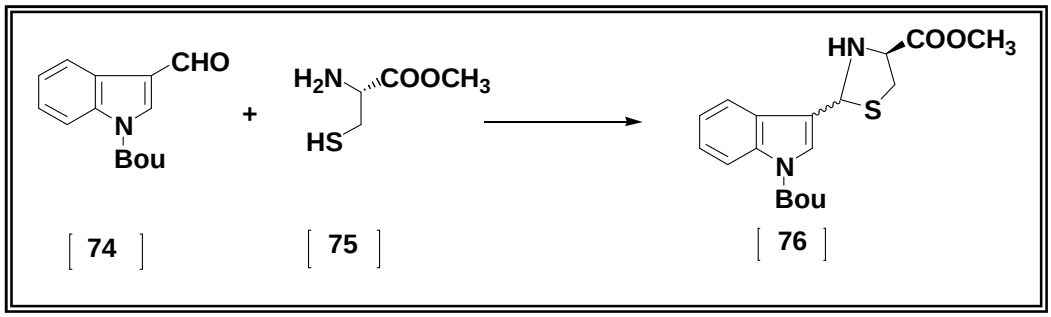


1.8.1 Synthesis of thiazolidine :

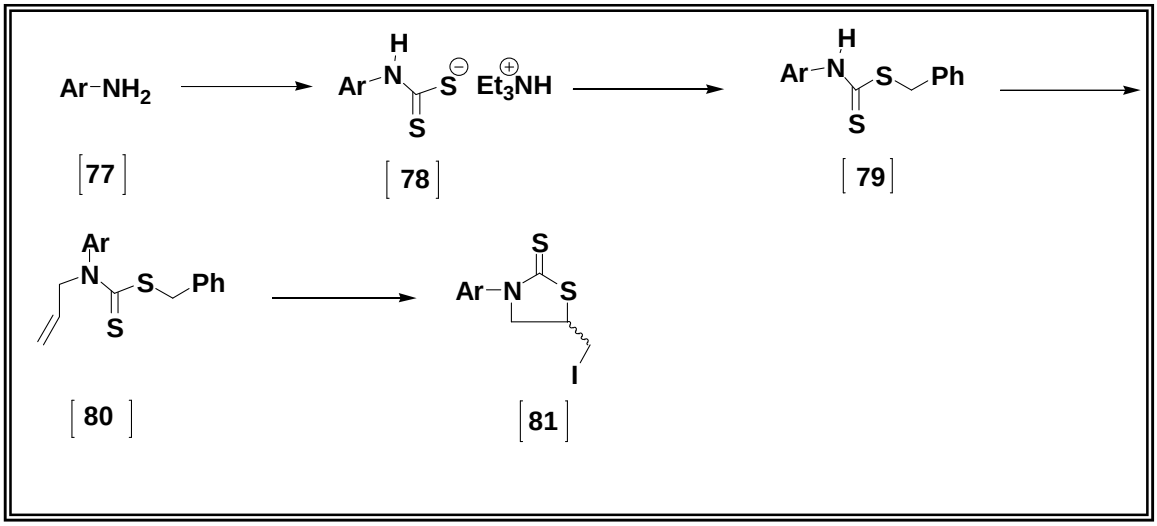
Shmeiss et. al., [99] found that the interaction of 1-(2,3,4,9)-tetrahydro-1H-carbazol-1-yl-)ethylidene thiourea [71] with chloroacetic acid can produce via the formation of an intermediate mercapto acetic acid derivatives [72] which cylizes through elimination of water to give 1-[1-(2,3,4,9-tetrahydrocarbazol-1-ylidene)-N-(thiazolidin-4-one)ethanamine [73]:



Dzurilla et. al., [100] have synthesized 1-(tert-butoxy-carbonyl)-4-methoxycarbonyl-3-(thiazolin-2-yl)indole [76] through the reaction of 1-(tert-butoxycarbonyl)indol-3-carboxaldehyde [74] with methyl L-cystienate [75] in triethylamine :



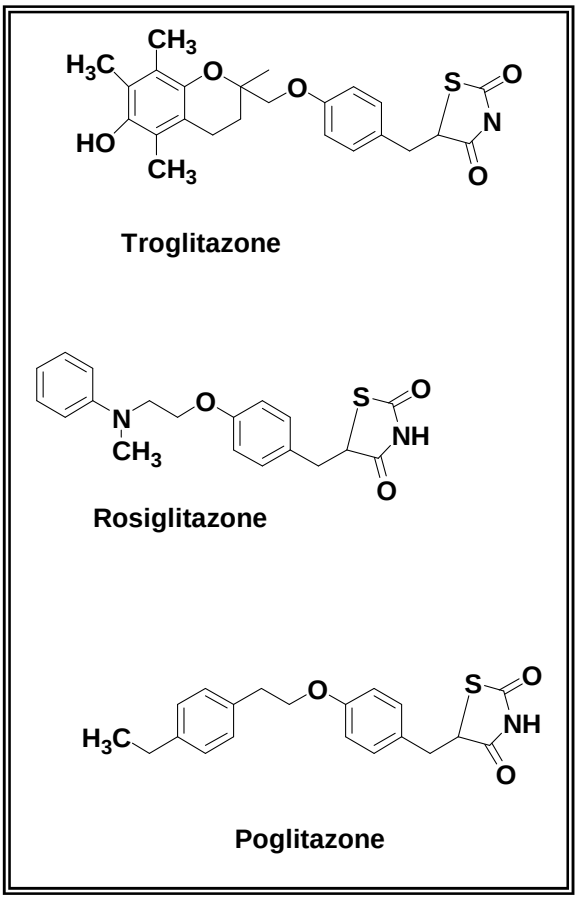
Sattigri et. al., [101] found that the reaction of aniline [77] with carbondisulphide and triethylamine gave thiocarbamino acid salt [78] which react with benzyl bromide to give dithiocarbamate [79], when [79] was allow to react with sodium hydride, allyl bromide and tetra butyl ammonium iodide gave allyl derivatives [80], and when added acetonitrile iodide to [80], (5RS)-5-(iodomethyl)-3-phenyl-1,3-thiazolidine-2-thion [81] was formed :



1.8.2 Biological activity of thiazolidine :

Thiazolidine derivatives are reported to show a variety of biological activities. Depending on the subsitutents, this heterocyclic compounds can induce different pharmacological properties [102] such as antibacterial, antifungal [103], antidiabetic [104,105], cardiotonic [106], anticonvulsant [107], cyclooxygenase and lipoxygenase inhibitory [108].

Thiazolidinones are derivatives of thiazolidine which are important compounds due to their broad range of biological activity [109], such as troglitazone, rosiglitazone and pioglitazone which have antidiabetic effects[110]:



2-Amino-thiazolidin-4-ones have been found to have antifungal activity [111-113] such as 2-amino-3-(arylthiazol-2-yl) -thiazolidine-4-ones [82] [114].

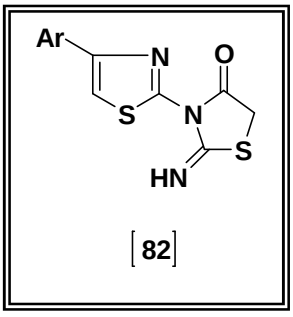
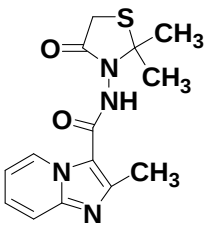
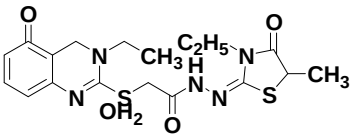
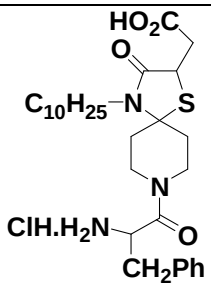


Table (1-4): Biological activity of some thiazolidine.

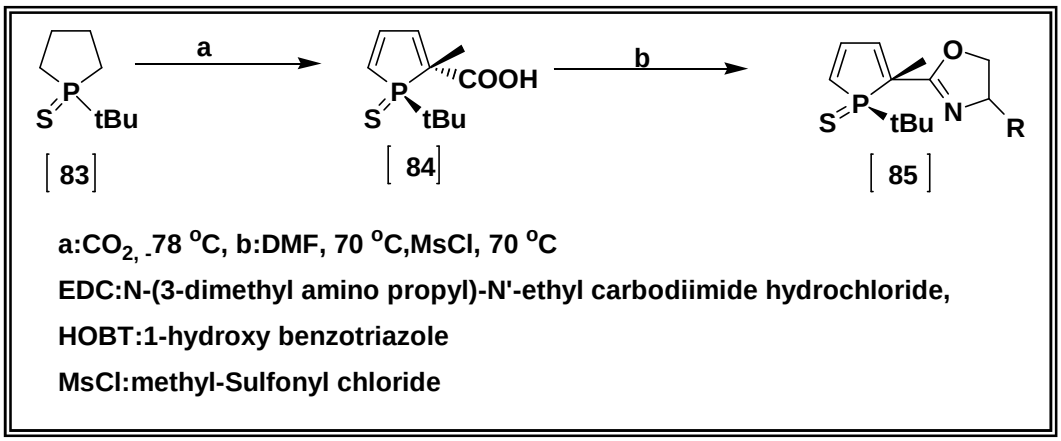
No.	Compound name	structure	Biological activity	Ref.
1	2-methylimidazo[1,2-a]pyridine-3-carboxylic acid (2,2-dimethyl-4-oxo-1,3-thiazolidin-3-yl) amide		anti-mycrobatrial activities	115
2	2(3-ethyl-4(3H)-quinazolinone-2-ylmercaptoacetylhydrazono-3-ethyl/aryl-5-methyl-4-thiazolidine		anticonvulsactivity	116
3	8-substituted(4-dodeyl-3-oxo-1-thia-4,8-diazaspiro[4.5]dec-2-yl) aceticacidhydrochlorides		antimycobactrail	117

1.9.0 Oxazoline:

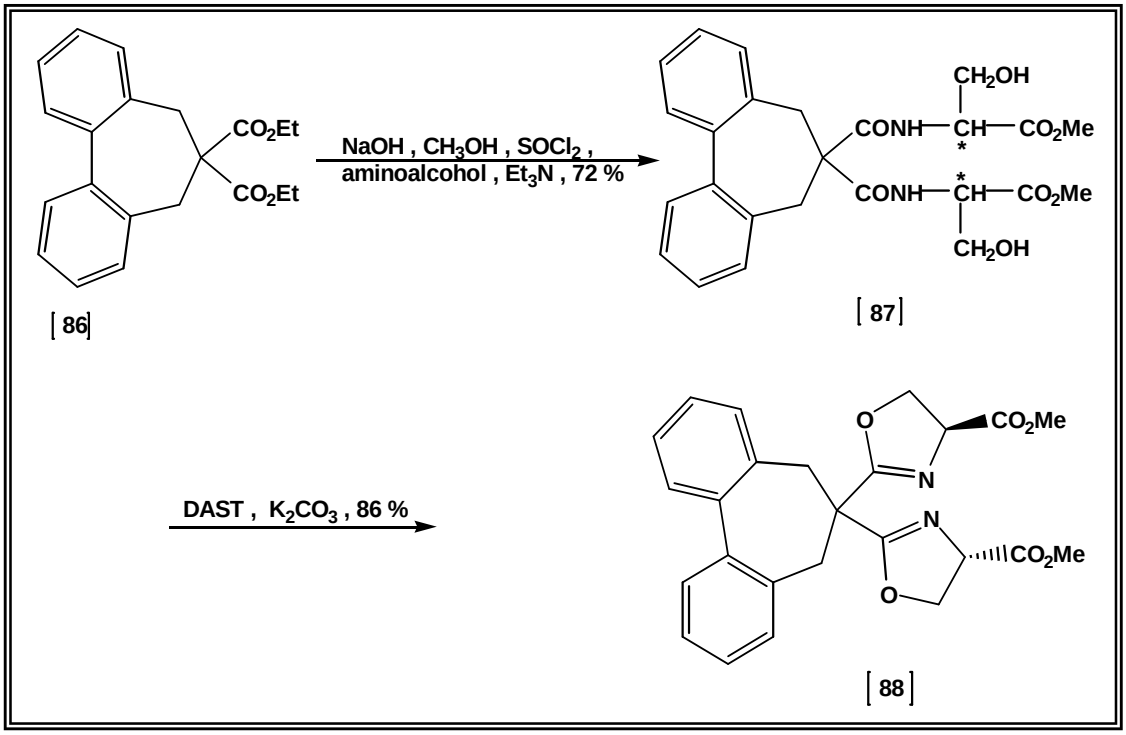
Oxazoline is one of organic heterocyclic compounds which it is a class of five member unsaturated ring containing one oxygen atom and one nitrogen atom, oxazoline can be represented by two forms:

1.9.1 Synthesis of oxazoline:

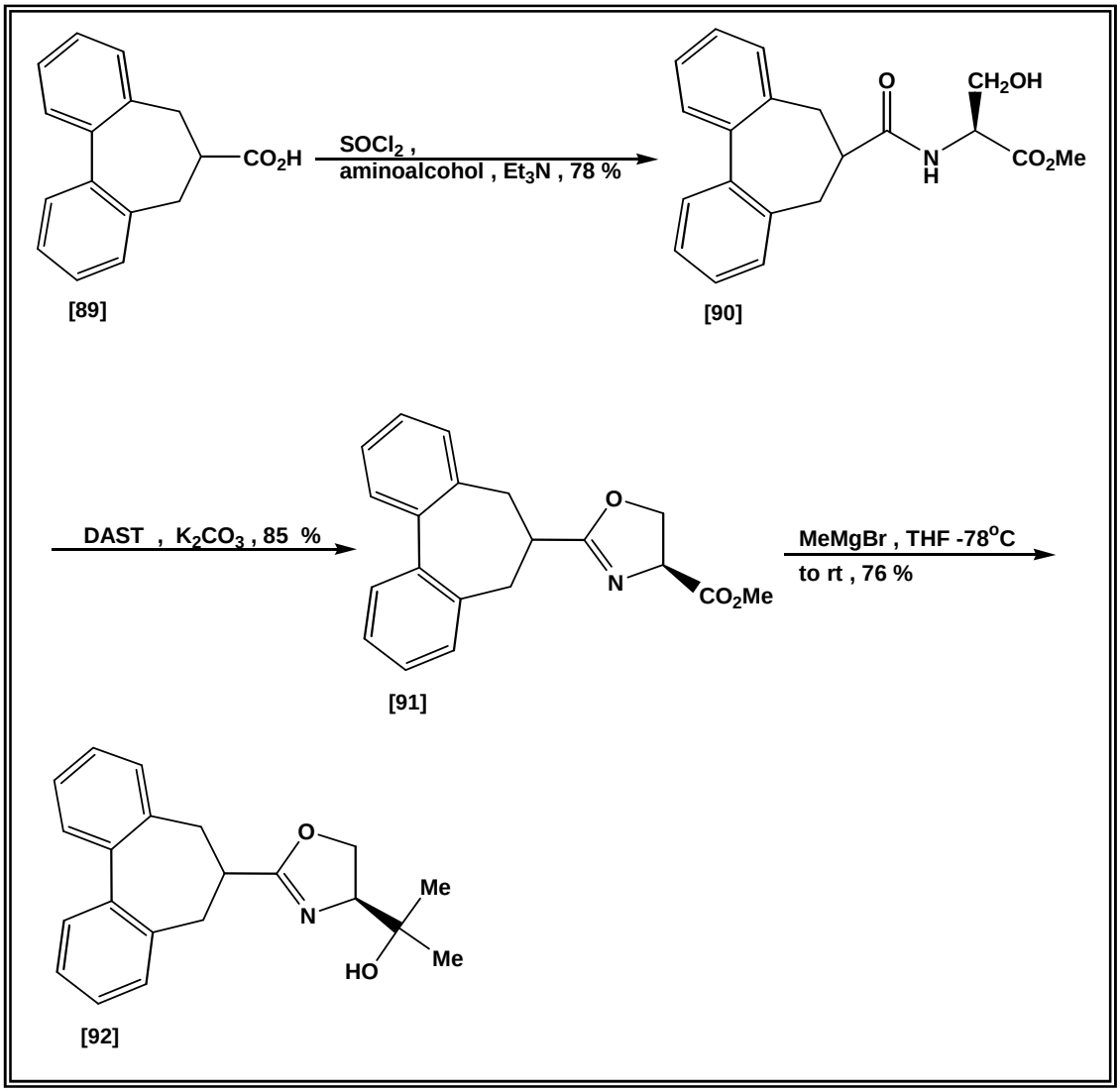
Tang et. al., [118] found that the deprotonation of [83] by n-butyl-lithium in presence of (-)-sparteine gives [84], the condensation of [84] with chiral amino alcohols by using EDC/HOMT afforded [85]:



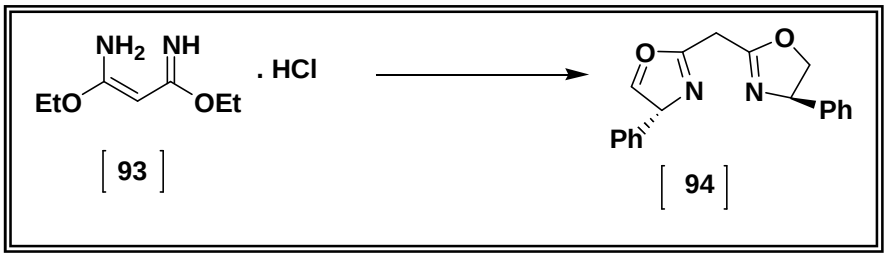
Fu et. al., [119] synthesized bis(oxazoline)biscarboxylate [88] in high yield from treatment of dihydroxy diamide [87] with a slight excess of the dehydrating agent , dimethylaminosulfur tri fluoride (DAST) at (-78) ^{o}C in CH_2Cl_2 followed by addition of K_2CO_3 and leave at room temperature:



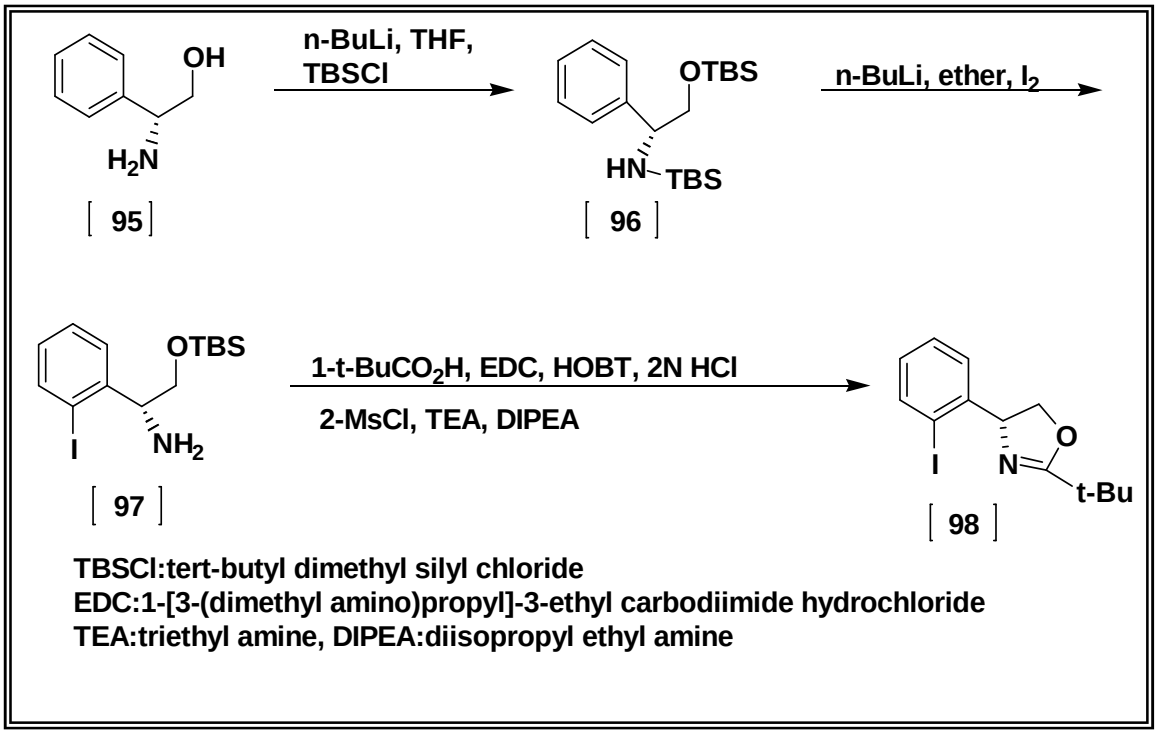
Mono-oxazoline ligand [92] was obtained according to the above similar procedure from a monoacid [89]:



Preparation of bis oxazoline [94] was preformed through the reaction of compound [93] with (R)-phenylglycinol and CH_2Cl_2 for 36 hours [120]:



Oxazoline can be prepared from compound [95] according to the following reaction [(121)]:



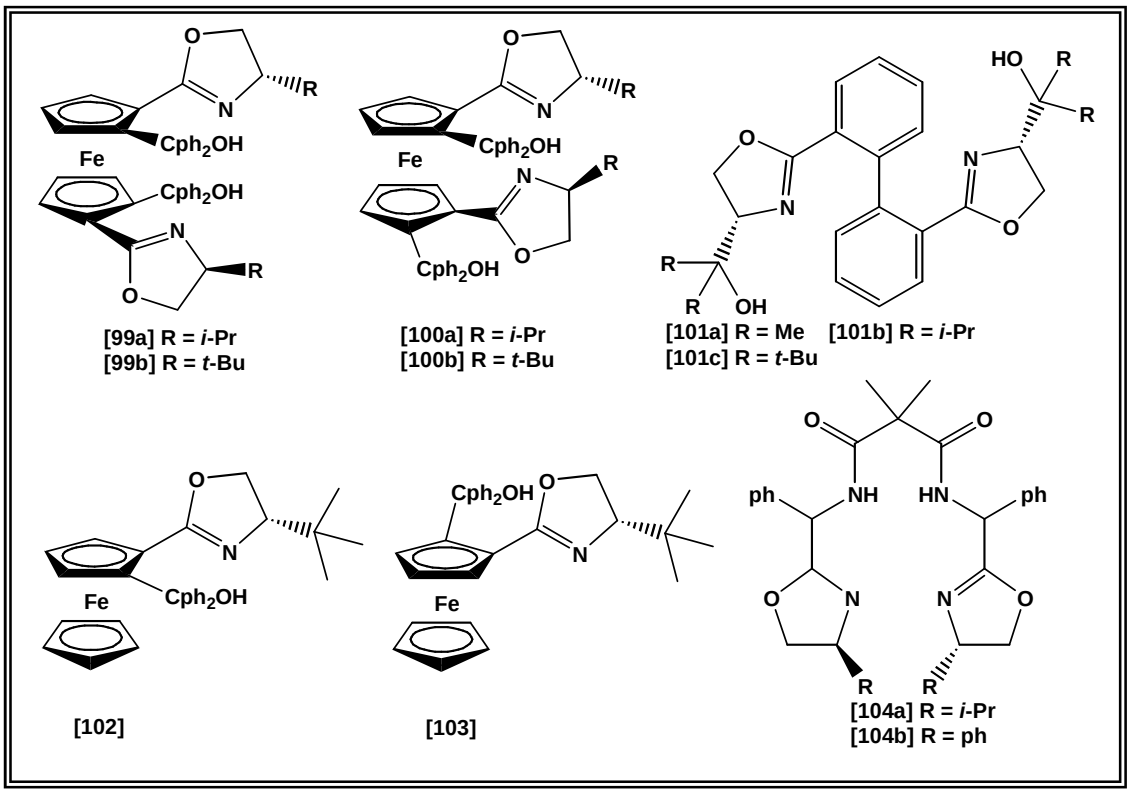
1.9.2 Oxazoline uses:

Chiral oxazolines, especially chiral bis(oxazoline), have been widely applied in many catalytic asymmetric reactions as versatile ligands[(122,123)].

oxazoline-base ligands were also found to be effective for the asymmetric addition of diethyl zinc to aldehydes[(124-126)]. In particular, the ligand combining the oxazoline ring and hydroxy group or an amino group have been reported to show execllent catalytic activity in the asymmetric addition of diethyl zinc to aldehydes[(127-133)].

For example, ***Ikeda*** et. al., [129] developed the ligands [99-101] for the asymmetric addition of diethyl zinc to aldehydes and high enantioselectivities were obtained.

Ligands [102] and [103] explored by ***Bolm*** et al.,[131] and ligands [104] designed by ***Pastor*** and ***Adolfsson*** [133] respectively, also it showed good catalytic activity. In these ligands, the oxazoline unit and adjacent hydroxy group function together control the catalytic process.



Aim of the present work:

Heterocyclic compounds are of great importance because many of the biochemical materials essential to life belong to this class. Nucleic acids, for example, the chemical substances that carry the genetic information controlling inheritance, consist of long chains of heterocyclic units held together by other types of materials.

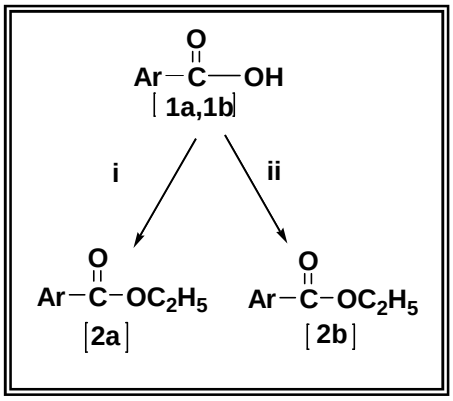
This work was designed to reach the following targets:

1. To synthesize new substituted five and six membered heterocyclic compounds such as 1,3,4-oxadiazole, pyrazole, phthalazine-3,8-dione, pyridazin-3,6-dione, 1,3,4-triazole, thiazolidine, Δ^4-oxazoline and oxapyridazine-6-one.
2. Testing the biological activity for some of the synthesized compounds on different microorganisms.

Chapter Three

Results and discussion

3.1 Synthesis of esters [2a, 2b]:



Scheme (3-1): Reagents and Conditions: i-abs. EtOH, conc. H_2SO_4, reflux (5) hrs. ii-abs. EtOH, conc. H_2SO_4, dry benzene, reflux (16) hrs.

m-methyl ethyl benzoate [2a] prepared by reacting of *m*-toluic acid with conc. H_2SO_4 in absolute ethanol and then refluxed for (5) hrs.

While *p*-nitro ethyl benzoate [2b] prepared by reacting of *p*-nitro benzoic acid with conc. H_2SO_4 in absolute ethanol and dry benzene and then refluxed (16) hrs.

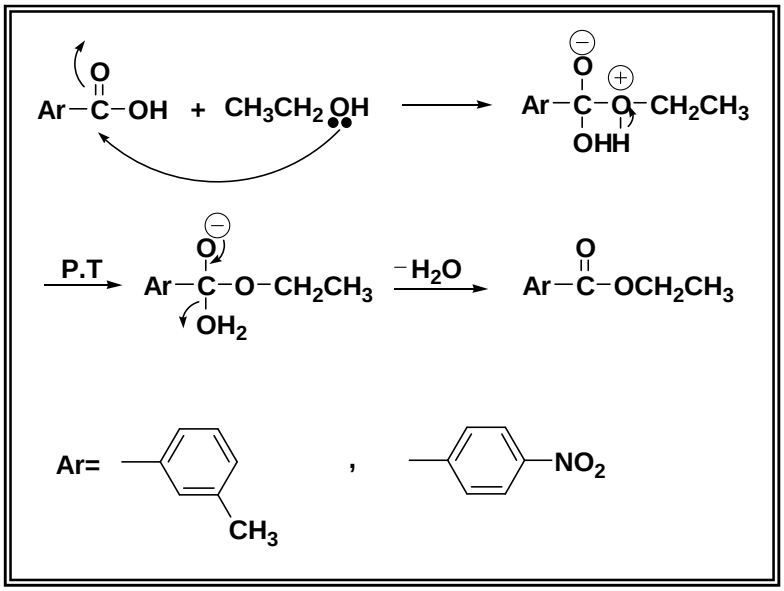
The FTIR spectrum in figures (3-3) and (3-4) show the disappearance of the C=O carbonyl band of *m*-toluic acid and *p*-nitro benzoic acid at (1685) cm^{-1},(1690) cm^{-1} respectively, also disappearance of (OH) of acid at (3150,3180) cm^{-1} and appearance of bands at (1720) cm^{-1} due to the stretching vibration of the C=O of the formed ester, aliphatic C-H appeared in the region (2985-2927) cm^{-1} band of NO_2 asymetric and symmetric

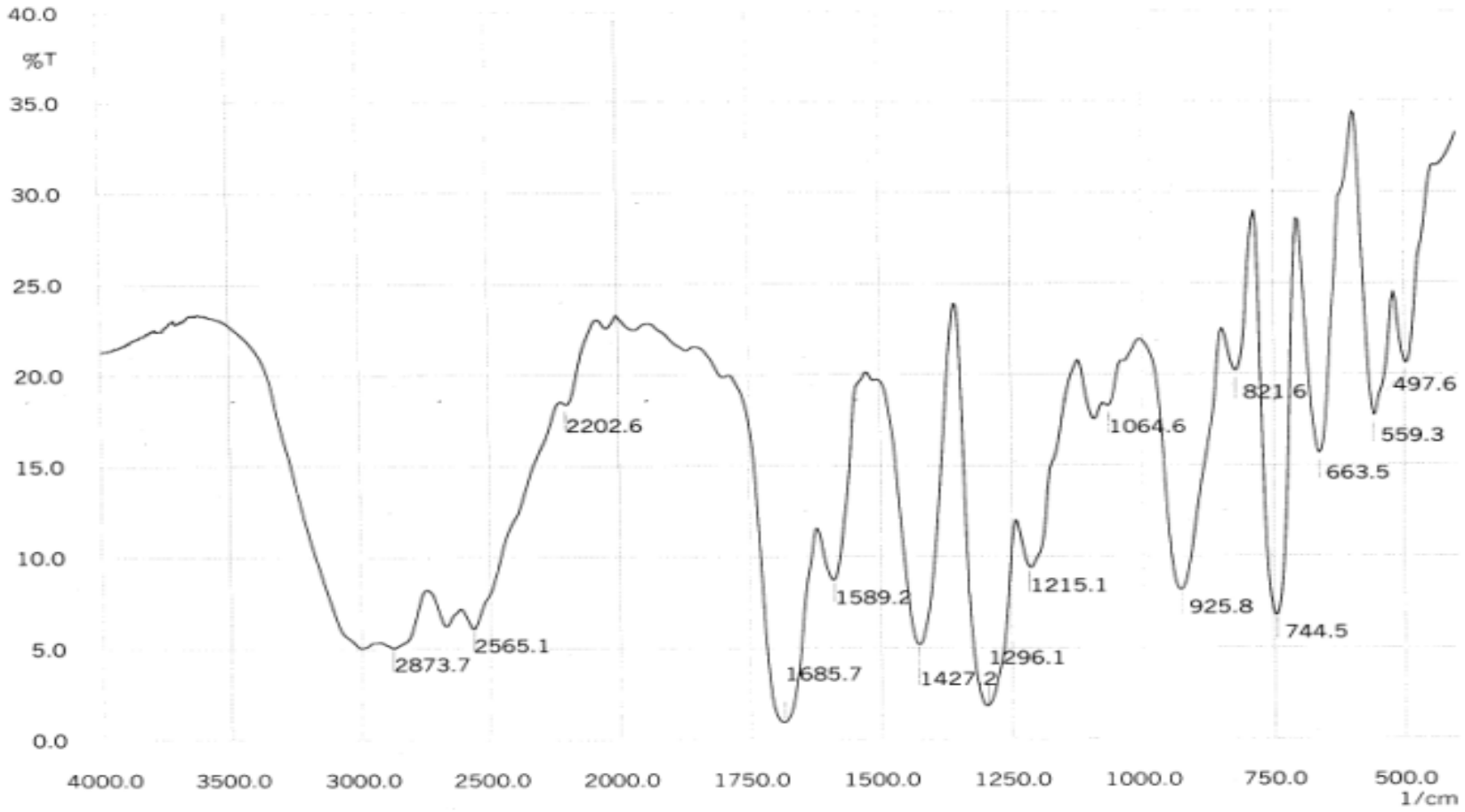
appeared at (1540,1350) cm^{-1} respectively. Table (3-1) shows characteristic bands of compounds [2a, 2b].

Table (3-1): Characteristic bands of compounds [2a, 2b]

Comp. No.	*V(C-H) arom.cm^{-1}*	*V(C-H) aliph.cm^{-1}*	*V(C=O)of ester cm^{-1}*	*V(C=C) cm^{-1}*
2a	*3000*	*2974 2927*	*1720*	*1596*
2b	*3030*	*2985 2975*	*1720*	*1520*

The mechanism of this reaction is shown below:





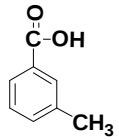
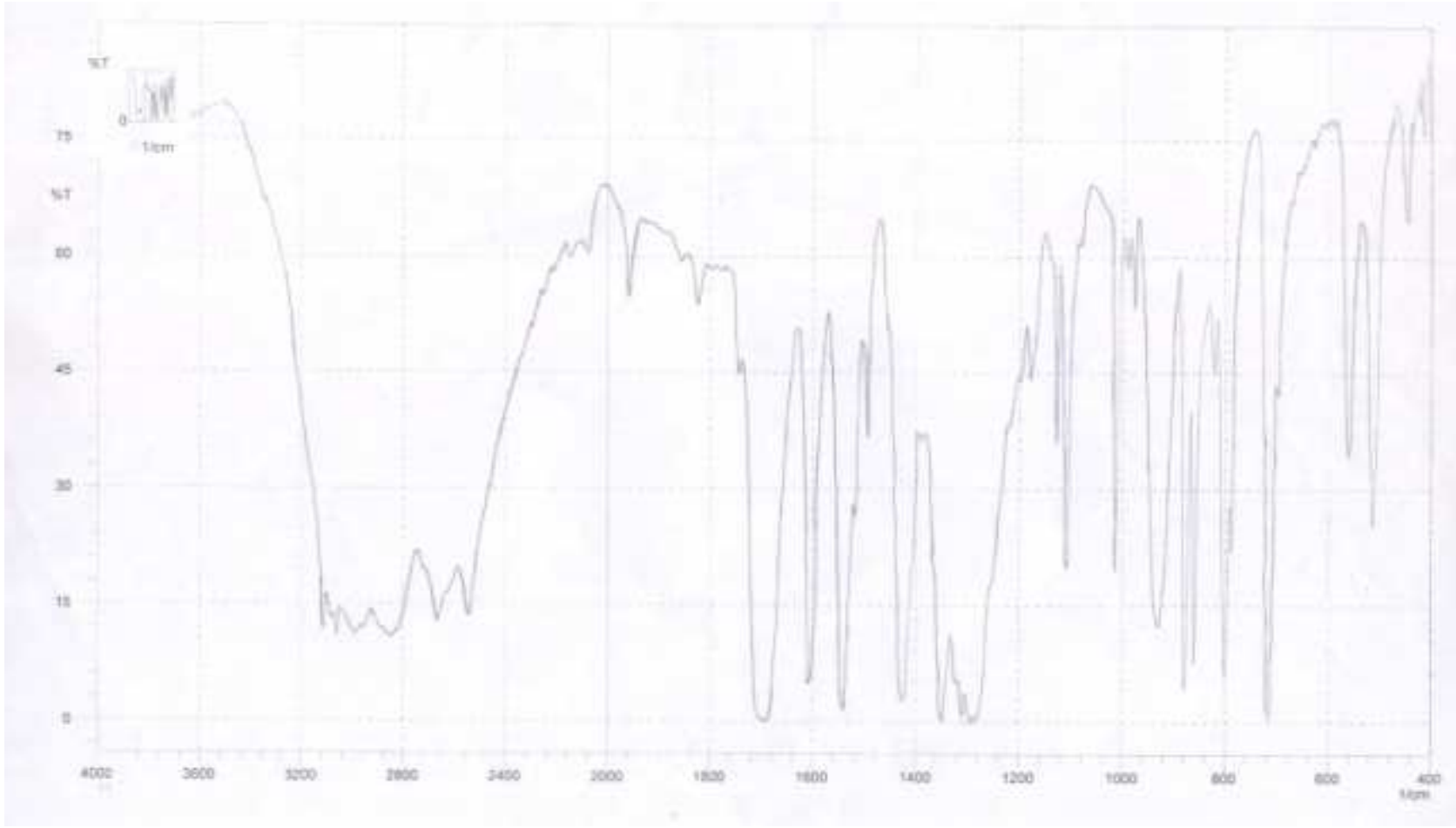
	***M.P* = 107-109 ^{0}C**	**Color: yellow**
		Molecular Weight: 136.15 g/mol
		Molecular Formula: $C_8H_8O_2$

Figure (3-1): Sructure, physical properties and F.T.IR spectrum of *m*-toluic acid [1a].



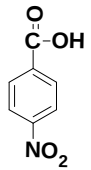
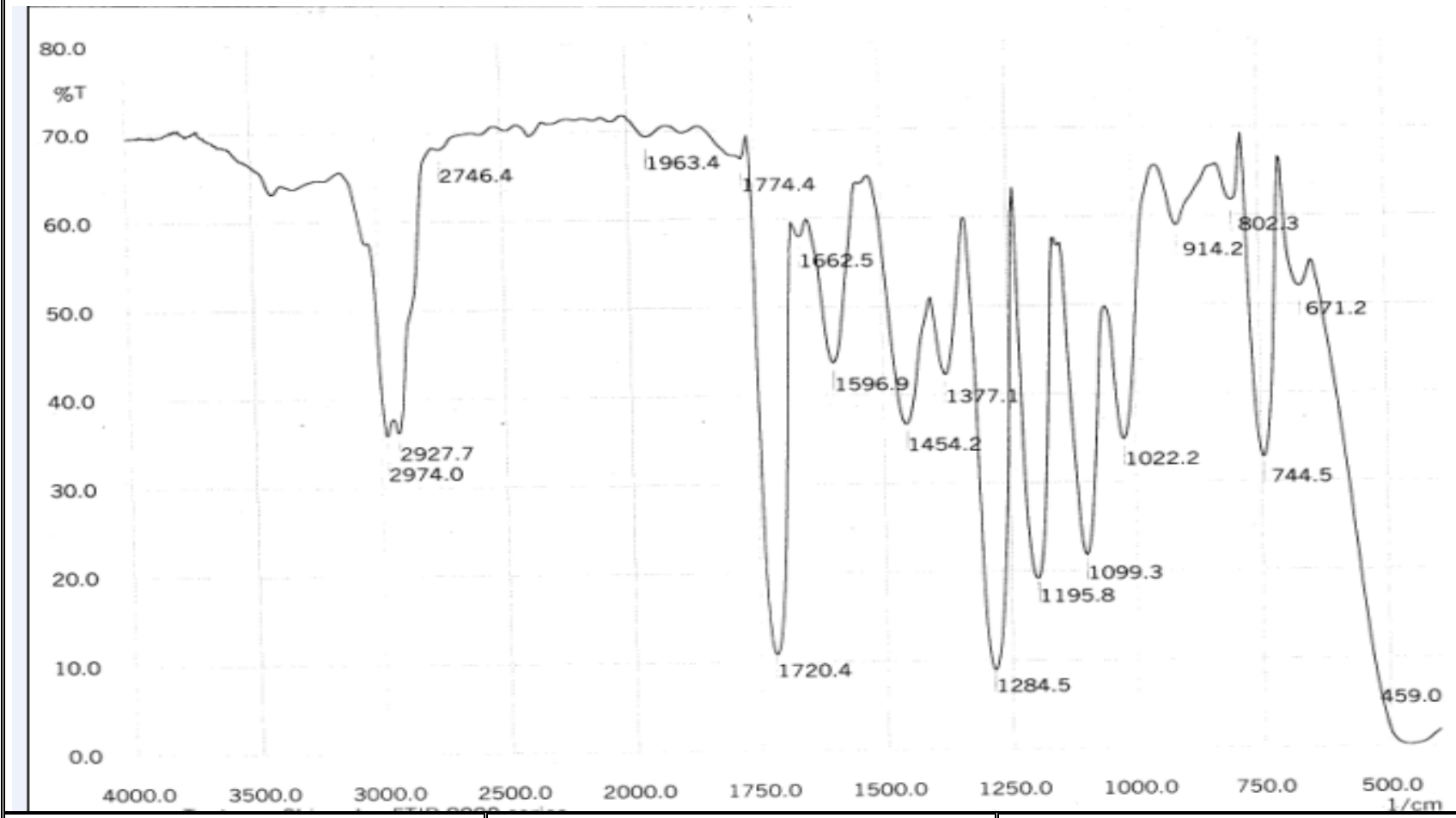
	***M.P* = 238-240**	**Color: Pale yellow**
		Molecular Weight: 167.12g/mol
		Molecular Formula: $C_7H_5NO_4$

Figure (3-2): Structure, physical properties and IR spectrum of *p*-nitro benzoic acid [1b].



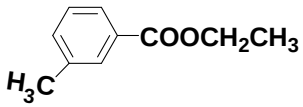
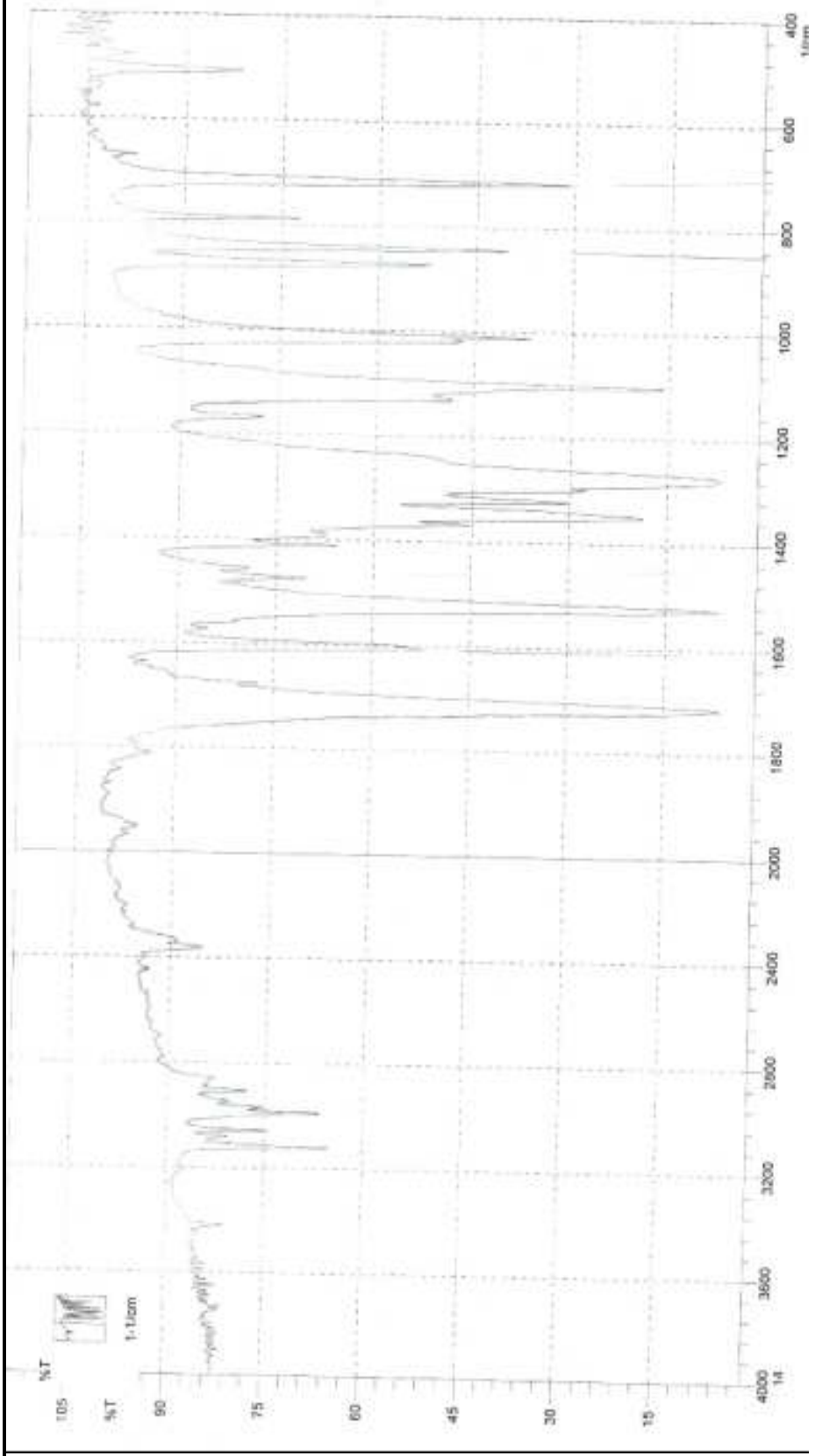
	**Yield percentage : 82.4 %**	**Color: Pale yellow**
		Molecular Weight: 164.20 g/mol
	M.P. : 220-221 ^{o}C	**Molecular Formula: $C_{10}H_{12}O_2$**

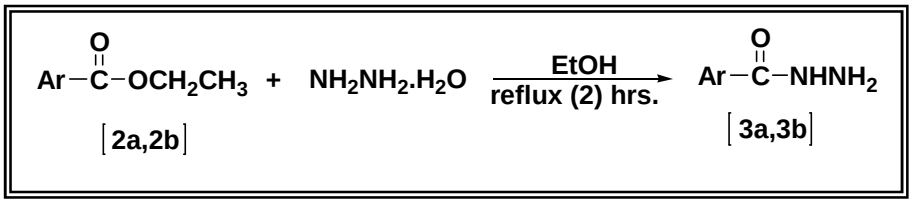
Figure (3-3): structure, physical properties and IR spectrum of *m*-methyl ethyl benzoate [2a].



	Color: Pale Yellow	
	Molecular Weight: 195.17 g/mol	
	Molecular Formula: $C_9H_9NO_4$	
Yield percentage: 71 %	**M.P. : 54-55 ^oC**	$COOC_2H_5$  NO_2

Figure (3-4): structure, physical properties and IR spectrum of *p*-nitro ethyl benzoate [2b].

3.2 Synthesis of acid hydrazide [3a, 3b]:



Scheme (3-2): Reagents and Conditions: $N_2H_4.H_2O$, EtOH, reflux (2) hrs.

The acid hydrazides were synthesized by the reaction of ester [2a,2b] with hydrazine hydrate in absolute ethanol.

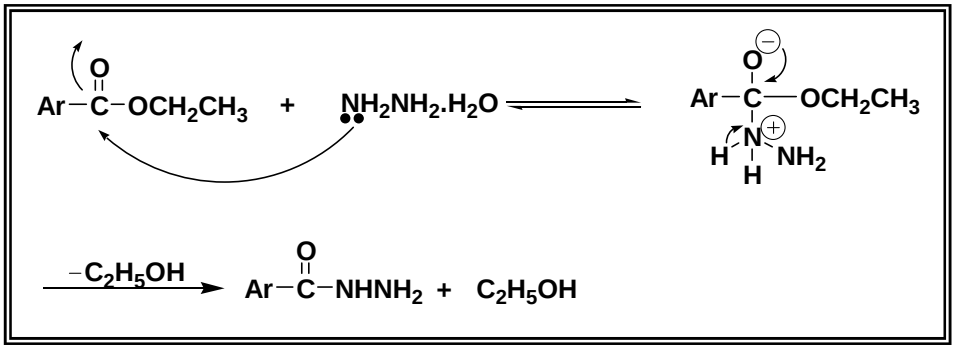
The reaction of hydrazine hydrate with ester is one of the most common reactions to synthesize the acid hydrazide derivatives; it is a tetrahedral nucleophilic substitution reaction [(142)].

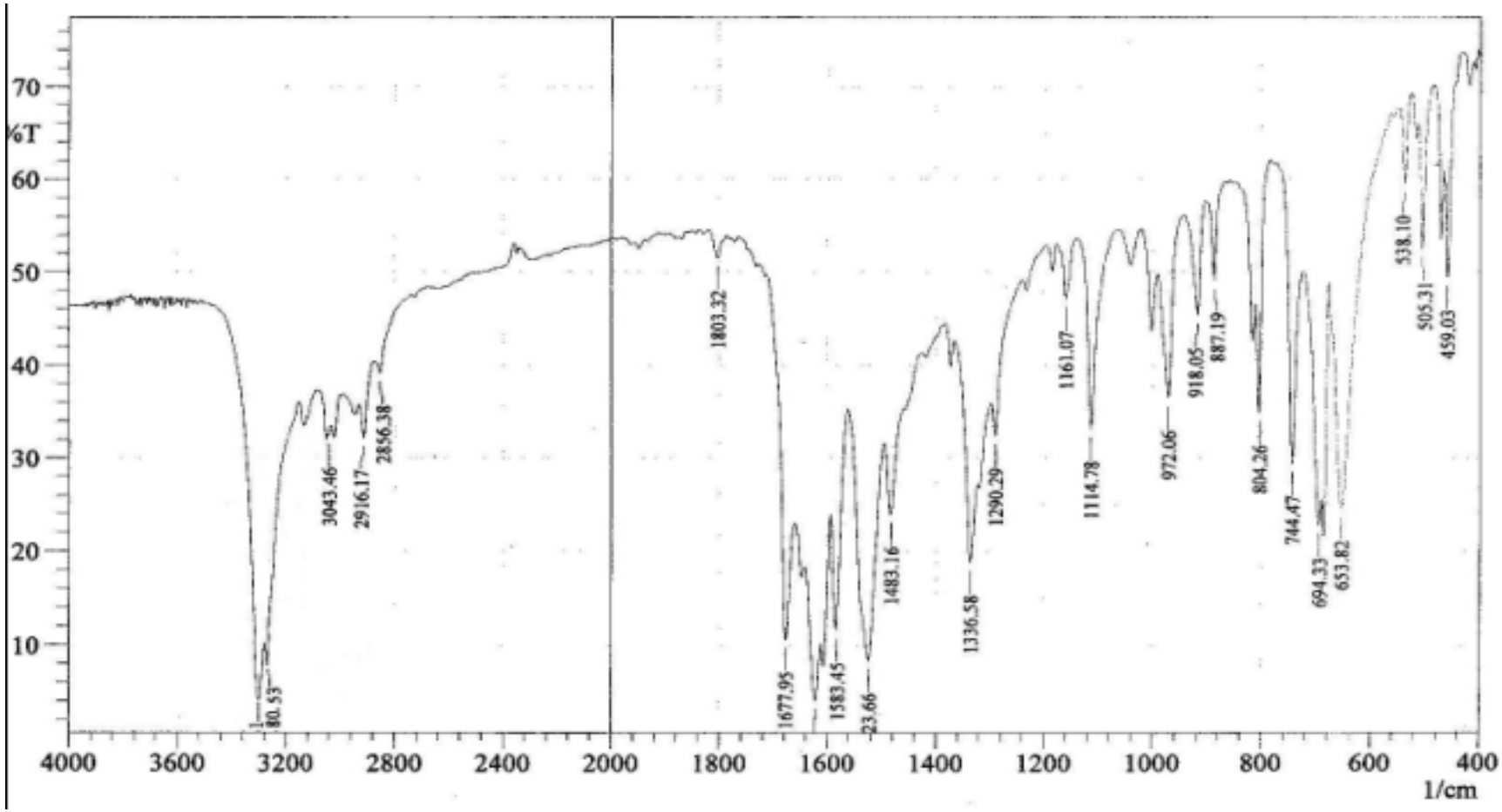
The FTIR spectrum in figures (3-5) and (3-6) for hydrazide derivatives [3a,3b] show the appearance of the characteristic absorption bands in the regions (3332-3276) cm^{-1} due to asymmetric and symmetric stretching vibration of the ($NH-NH_2$) group, the FTIR spectra also show the disappearance of absorption band in the region (1720) cm^{-1} due to the stretching vibration of the carbonyl group of esters, while a new band appeared at (1677) cm^{-1} and (1620) cm^{-1} due to the stretching vibration of amide I and appearance of amide II bending vibration band at (1523) and (1510) cm^{-1} respectively. Table (3-2) shows characteristic bands of compounds [3a, 3b].

Table (3-2): Characteristic bands of compounds [3a, 3b]

Comp. No.	***ν(NHNH$_2$) cm^{-1}***	***ν(C-H) arom. cm^{-1}***	***ν(C-H) aliph. cm^{-1}***	***ν(C=O) cm^{-1}***	***ν(C=C) cm^{-1}***
3a	***3290 3280***	***3043***	***2916***	***1677***	***1583***
3b	***3332 3276***	***3110***	***2990***	***1620***	***1596***

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





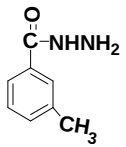
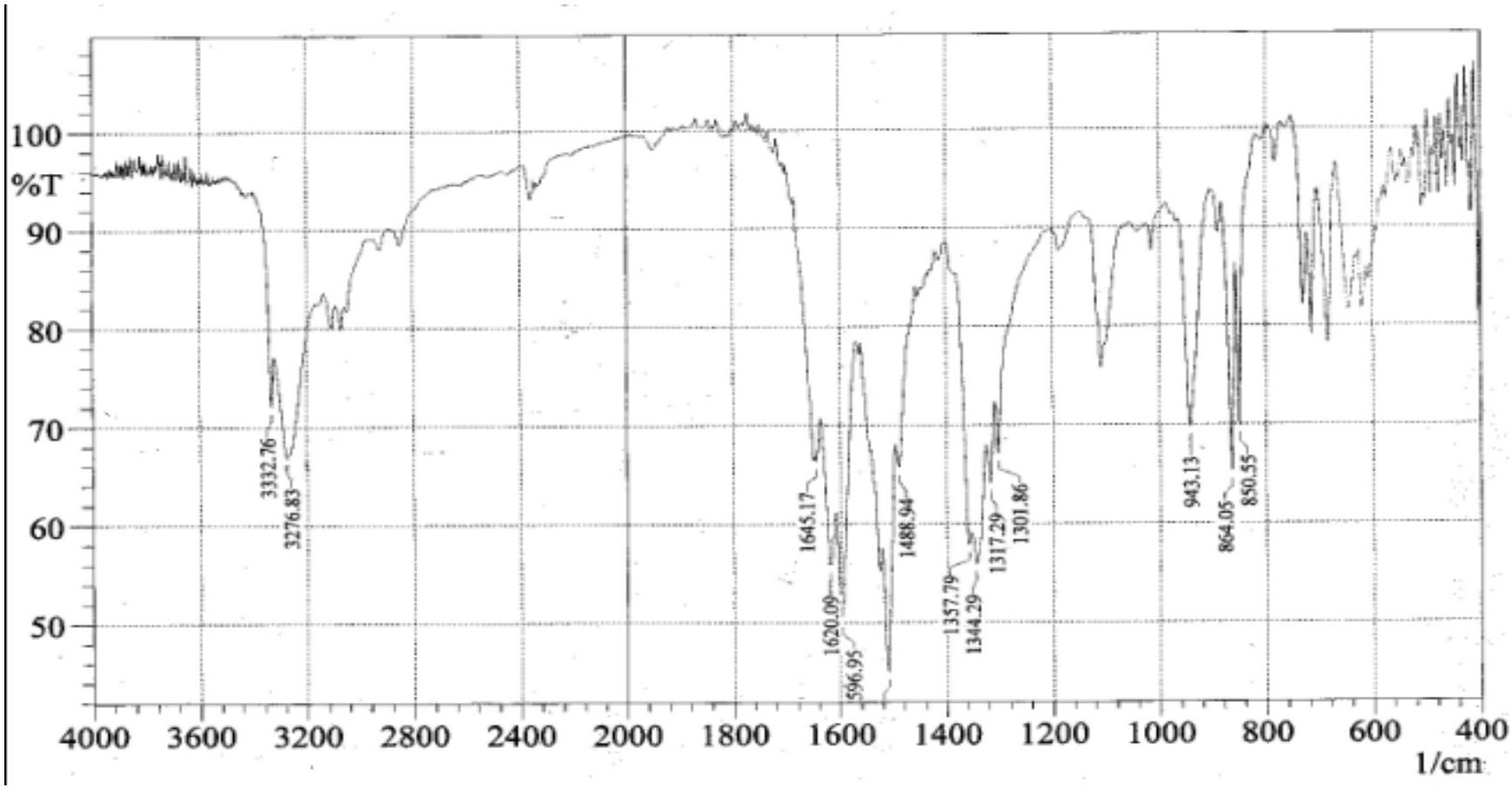
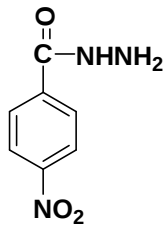
	**Yield percentage: 73 %**	**Color: White**
	M.P. : 84-86 °C	**Molecular Weight: 150.18 g/mol**
		Molecular Formula: $C_6H_{10}N_2O$

Figure (3-5): structure, physical properties and F.T.IR spectrum of *m*-methyl phenyl hydrazide [3a].

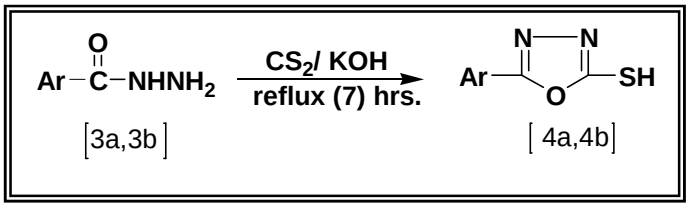




	Yield percentage: *85 %*	**Color: Pale yellow**
	M.P. : 222-224 °C	**Molecular Weight: 181.15 g/mol**
		Molecular Formula: $C_7H_7N_3O_3$

Figure (3-6): Structure, physical properties and F.T.IR spectrum of p-nitro phenyl hydrazide [3b].

3.3 Synthesis of 2-mercapto-5-(substituted phenyl)-1,3,4-oxadiazole [4a,4b] :



Scheme (3-3): Reagents and Conditions: CS_2, KOH, abs. EtOH, reflux (7) hrs.

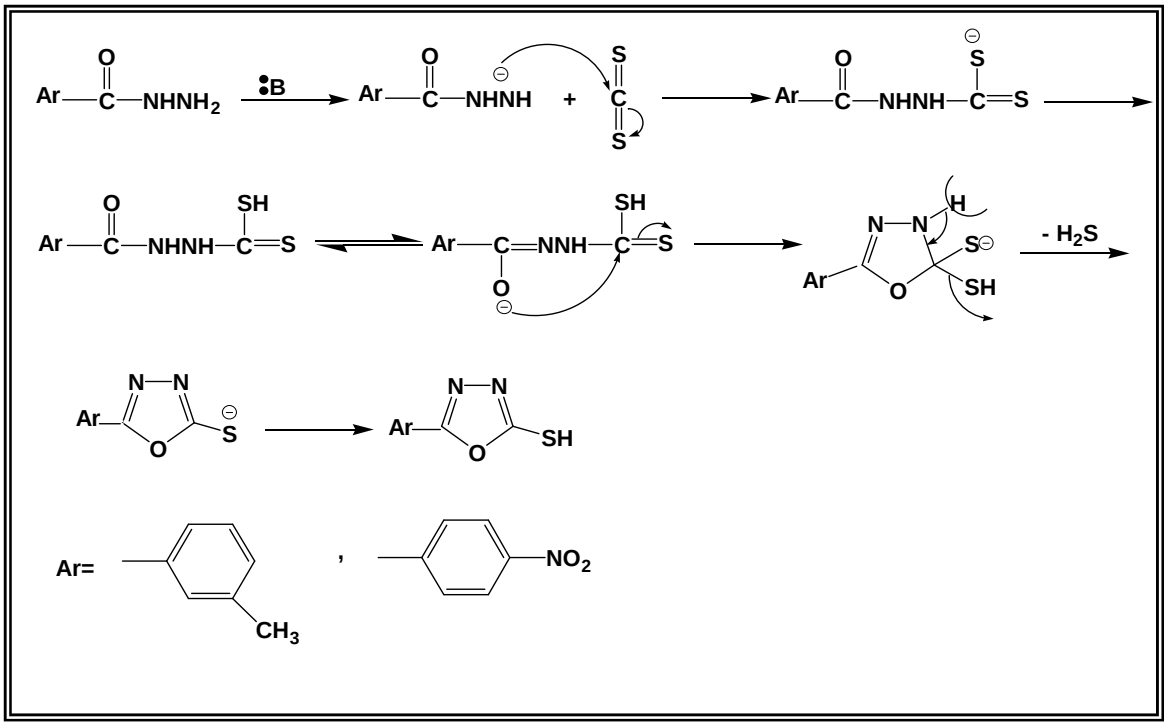
Reaction of hydrazide derivatives [4a, 4b] with CS_2, KOH in absolute ethanol afforded [4a, 4b] respectively.

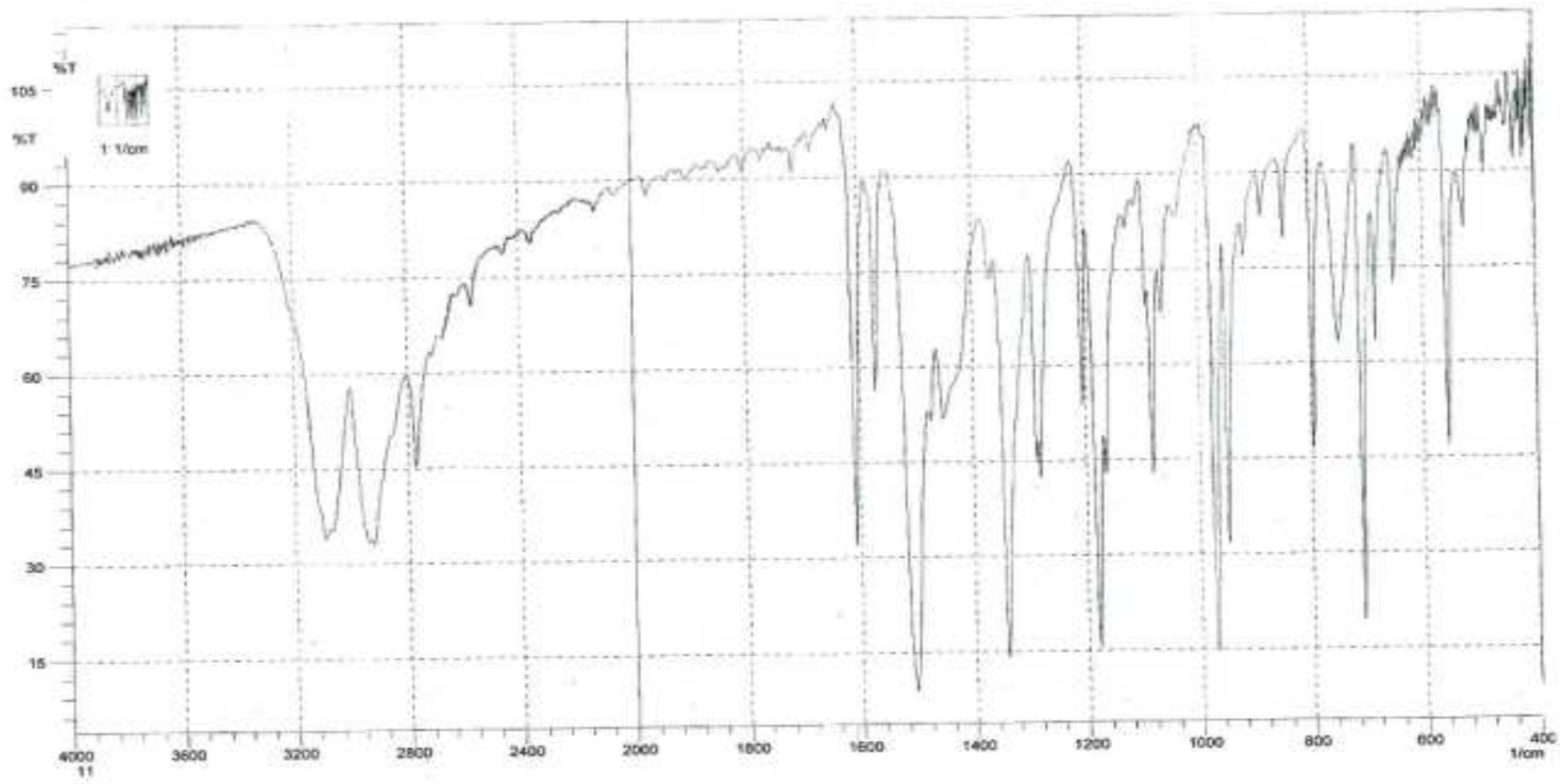
FTIR spectra of compounds [4a, 4b] in figures (3-7) and (3-8) indicated the disappearance of NH_2 in the rang (3332-3276) cm^{-1} and disappearance of carbonyl of amide at (1677, 1620) cm^{-1}, appearance a weak band at (2570, 2542.59) cm^{-1} due to S-H group, C-O-C asymmetric and symmetric bands appeared at (1270, 1276.79) cm^{-1} and (1090, 1064.63) cm^{-1} respectively. Table (3-3) shows characteristic bands of compounds [4a, 4b].

Table (3-3): Characteristic bands of compounds of [4a, 4b]:

Comp. No.	*ν(C-H) arm. cm^{-1}*	*ν(C-H) aliph. cm^{-1}*	*ν(S-H) cm^{-1}*	*ν(C=N) cm^{-1}*	*ν(C=C) cm^{-1}*
4a	*3080*	*2950*	*2570*	*1600*	*1570*
4b	*3087*	*-*	*2542*	*1604*	*1579*

The mechanism of the reaction [143] is as shown below:





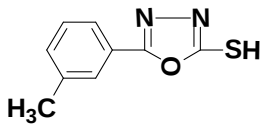
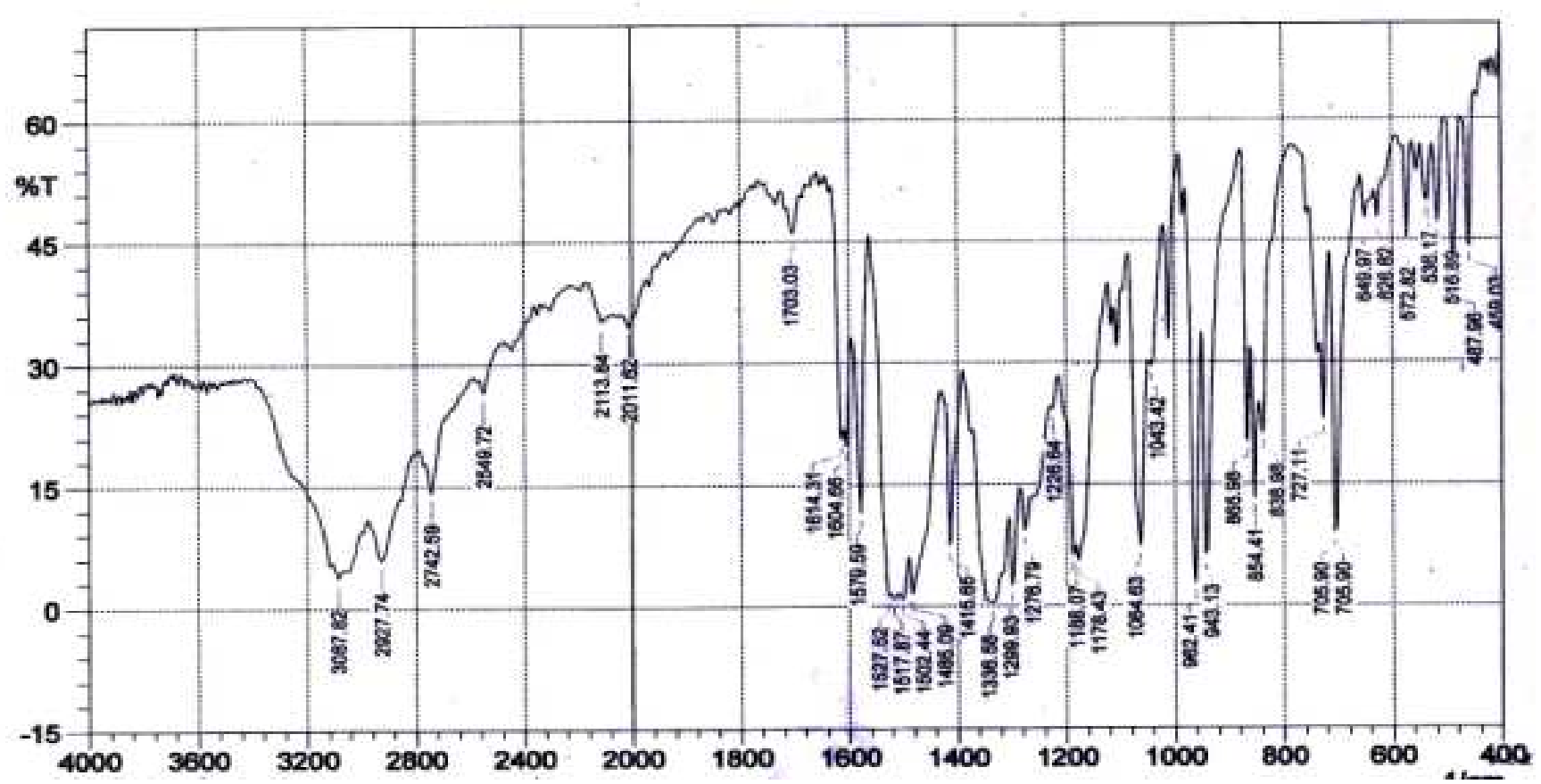
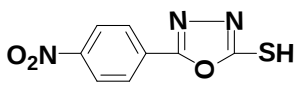
	**Yield percentage: 83 %**	**Color: yellow**
	M.P. : 146- 148 °C	**Molecular Weight: 192.24 g/mol**
		Molecular Formula: $C_9H_8N_2OS$

Figure (3-7): Structure, physical properties and IR spectrum of 2-mercabto-5-(*m*-methyl phenyl)-1,3,4-oxadiazole [4a].

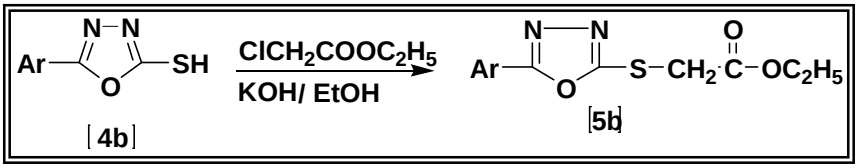




	Yield percentage: 83 %	**Color: yellow**
		Molecular Weight: 223.21g/mol
	M.P. : 230-233 °C	**Molecular Formula: $C_8H_5N_3O_3S$**

Figure (3-8): Structure, physical properties and F.T.IR spectrum of 3-mercabto-5-(*P*-nitro benzoyl)-1,3,4-oxadiazole [4b].

3.4 Synthesis of2-(P-nitro phenyl)-5-thio ethyl acetate-1,3,4-oxadiazole [5b] :



Scheme (3-4): Reagents and Conditions: $ClCH_2COOC_2H_5$, KOH, abs. EtOH. Ref.lux {8}hours.

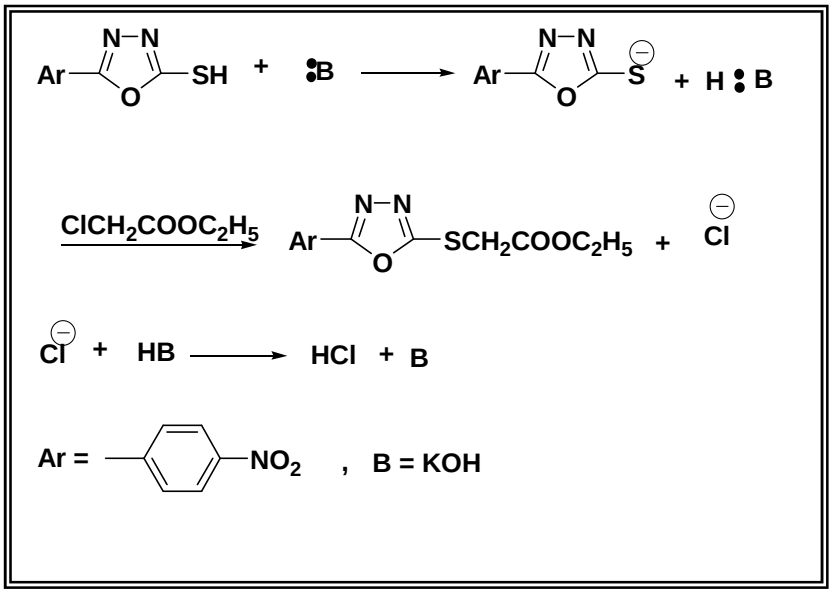
Reaction of compound [4b] with ethyl chloro acetate gave the compound [5b].

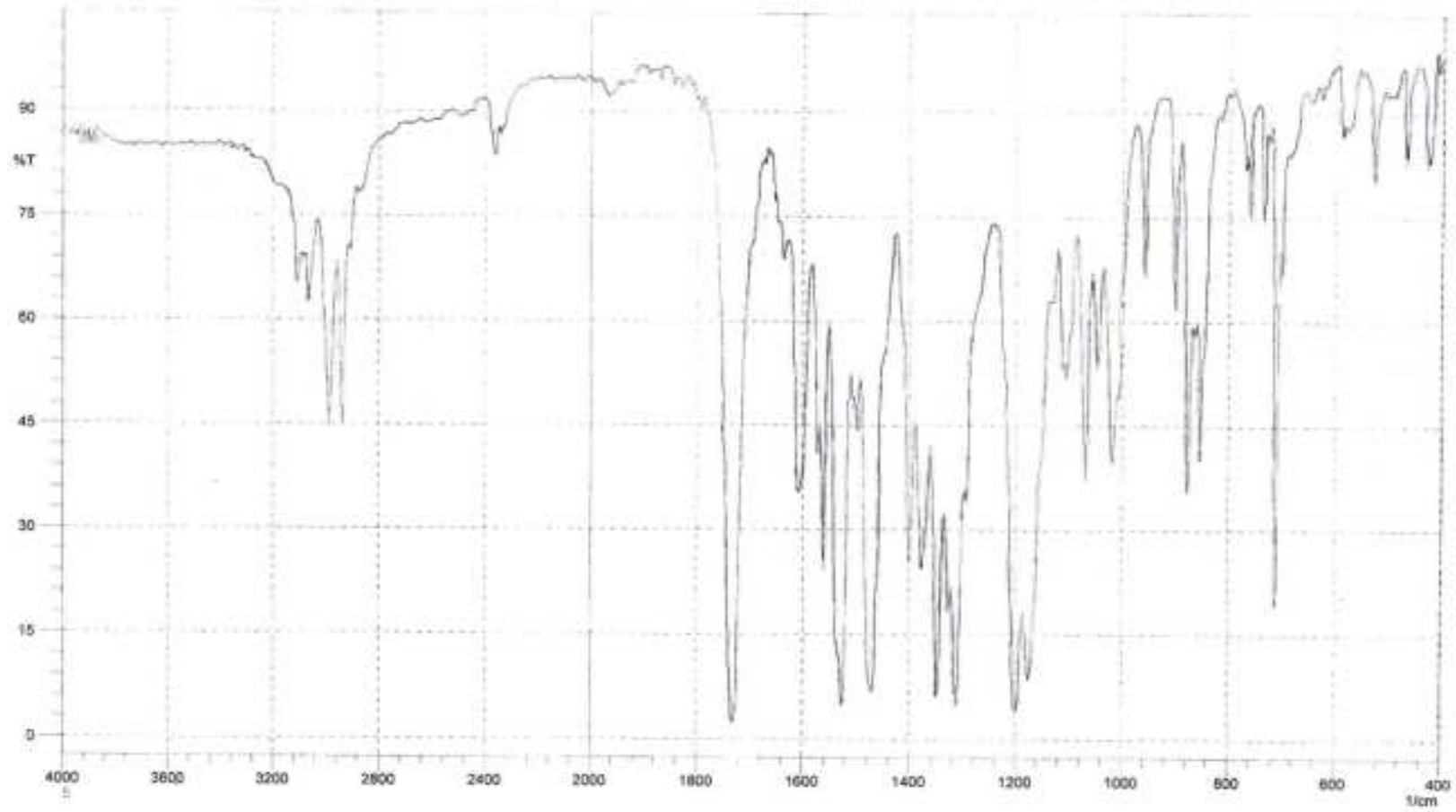
IR spectrum in figure (3-9) confirmed the formation of compound [5b] from the appearance of (C=O) group of ester at (1730) cm^{-1} and C-H aliphatic appears at (2920) cm^{-1}. Table (3-4) shows characteristic bands of compound [5b].

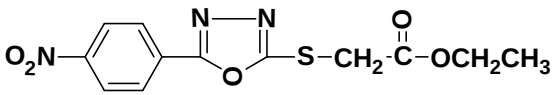
Table (3-4): Characteristic bands of compound [5b]:

Comp. No.	*ν(C-H) arm. cm^{-1}*	*ν(C-H) aliph. cm^{-1}*	*ν(C=O) cm^{-1}*	*ν(C=N) cm^{-1}*
5b	*3000*	*2920*	*1730*	*1600*

The suggested mechanism of the reaction is as shown below:



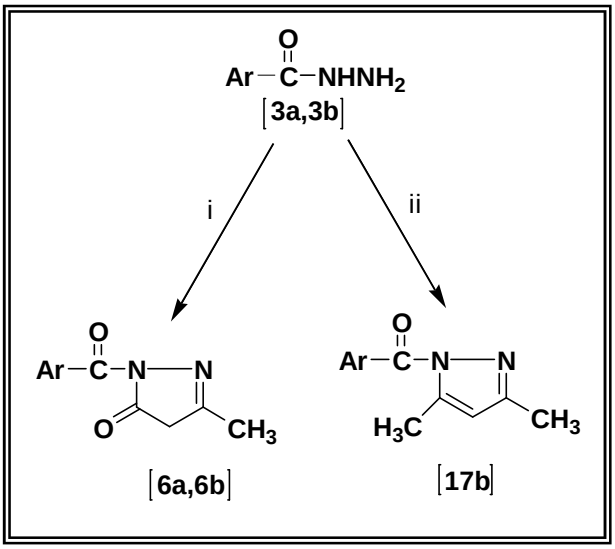




	Yield percentage: 80 %	**Color: yellow**
		Molecular Weight: 309.30 g/mol
	M.P. : 85-87 °C	**Molecular Formula: $C_{12}H_{11}N_3O_5S$**

Figure (3-9): Structure, physical properties and IR spectrum of 2-(*p*-nitro phenyl)-5-thioethylacetate-1,3,4-oxadiazole [5b].

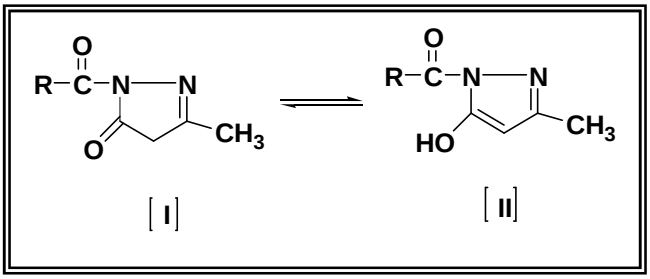
3.5 Synthesis of pyrazol derivatives [6a, 6b,17b] :



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

The pyrazol derivatives were prepared through the reaction of hydrazide derivatives [3a, 3b] with acetyl acetone or ethyl aceto acetate.

IR spectra of compounds [6a,6b] in figure (3-10) and (3-11) show the disappearance of NH_2 and NH bands in the region (3332-3276) cm^{-1} and appearance of OH band at (3200) cm^{-1} of enol form and C=O band at (1740) cm^{-1} and (1720) cm^{-1} respectively of the keto form in addition to the amide C=O at (1660) cm^{-1} and (1650)cm^{-1} respectively. From the above mentioned facts, we can indicate compounds [6a, 6b] can exist in equilibrium between keto [I] and enol [II] forms:

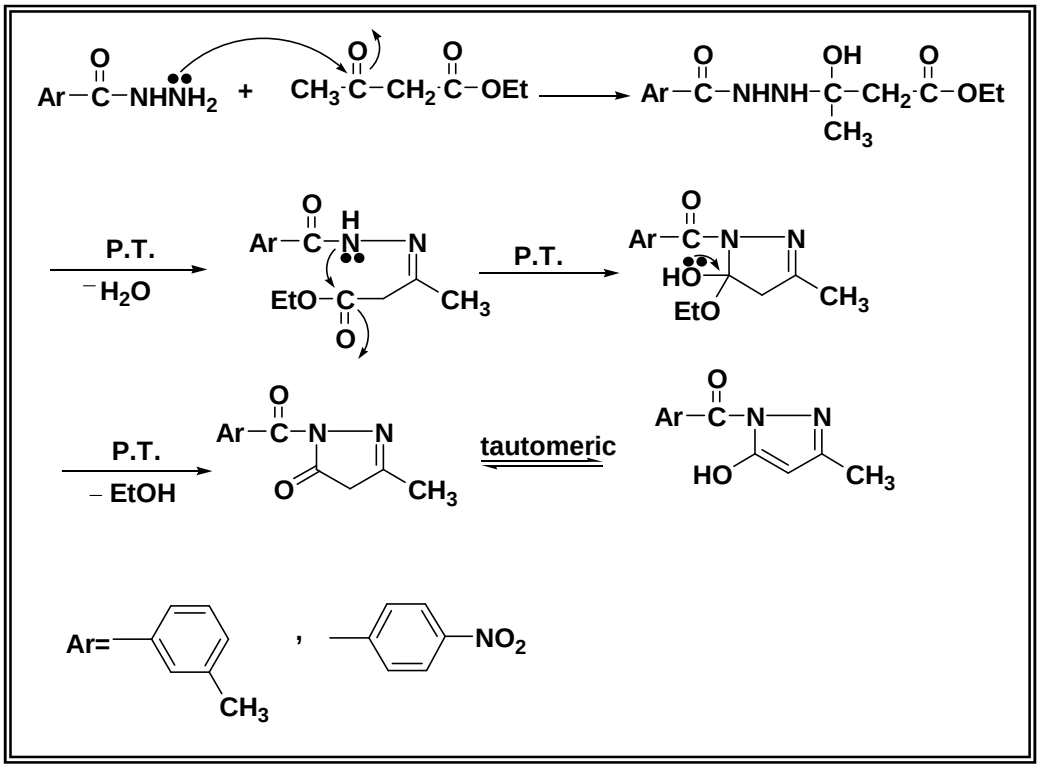


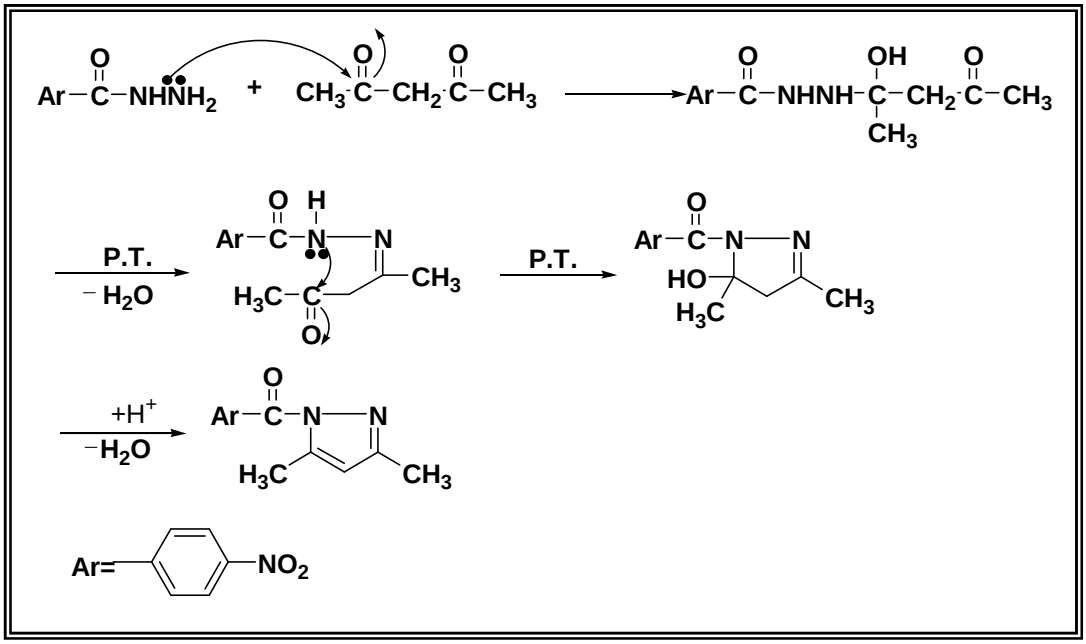
While FTIR of compound [17b] in figure (3-12) shows the disappearance of NH_2 and NH bands in the region (3332, 3276) cm^{-1} and appearance of C-H aliphatic at (2925) cm^{-1}. Amide C=O appeared at (1704) cm^{-1}, C=C aromatic at (1521) cm^{-1}. The characteristic bands of compounds [6a,6b,17b] are shown in table (3-5).

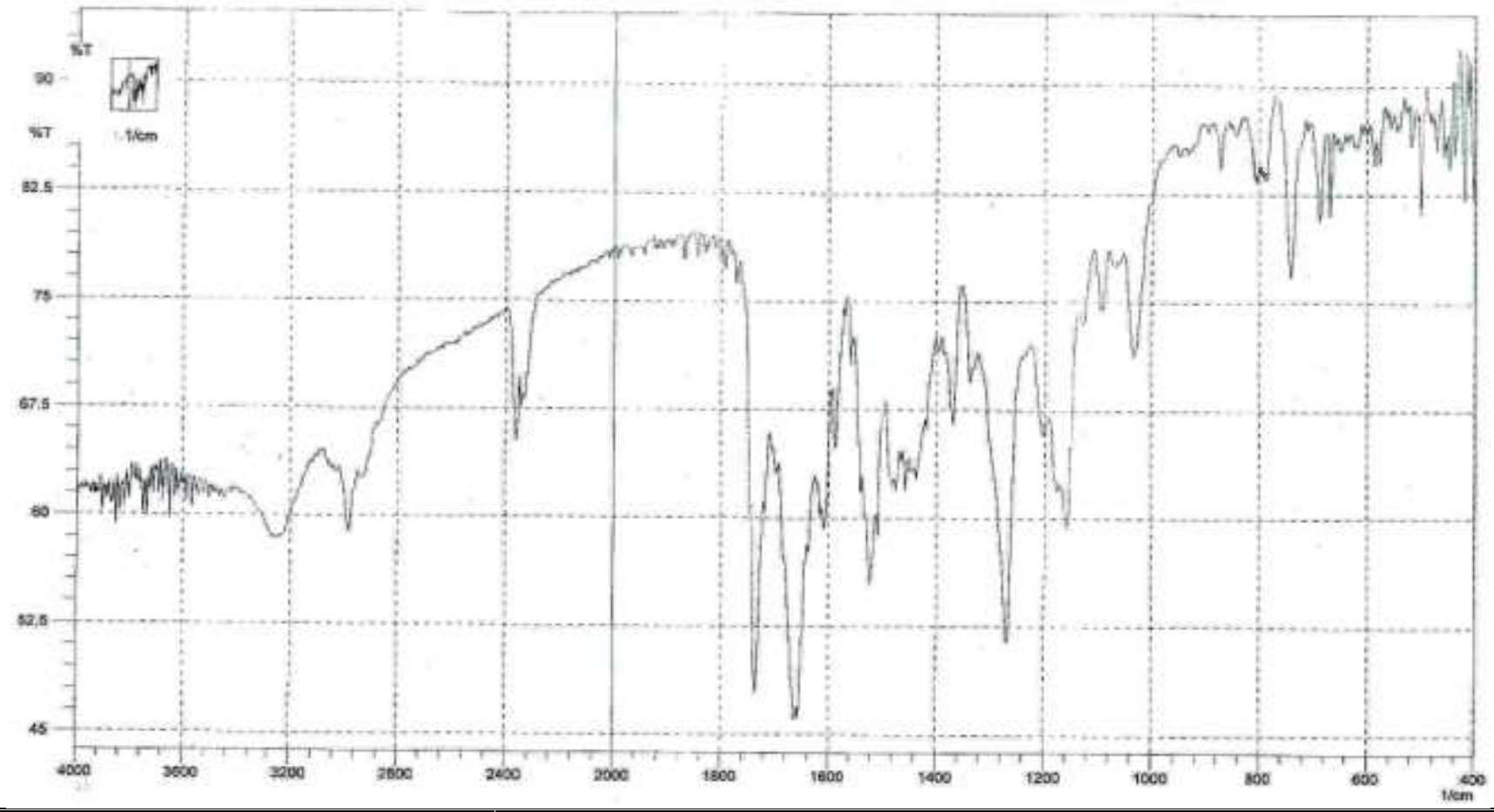
Table (3-5): Characteristic bands of compounds [6a, 6b, 17b]

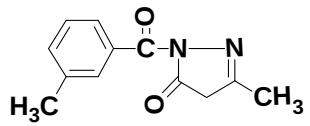
Comp. No.	*ν(-OH) cm^{-1}*	*ν(C-H) arm. cm^{-1}*	*ν(C-H) aliph. cm^{-1}*	*ν(C=O) cm^{-1}*	*ν(C=N) cm^{-1}*	*ν(C=C) cm^{-1}*
6a	*3200*	*3000*	*2970*	*1740 1660*	*1600*	*1520*
6b	*3200*	*3030*	*2980*	*1720 1650*	*1600*	*1520*
17b	*-*	*3078*	*2925*	*1704*	*1602*	*1521*

The suggested mechanism for formation of compounds as shown below[144]:







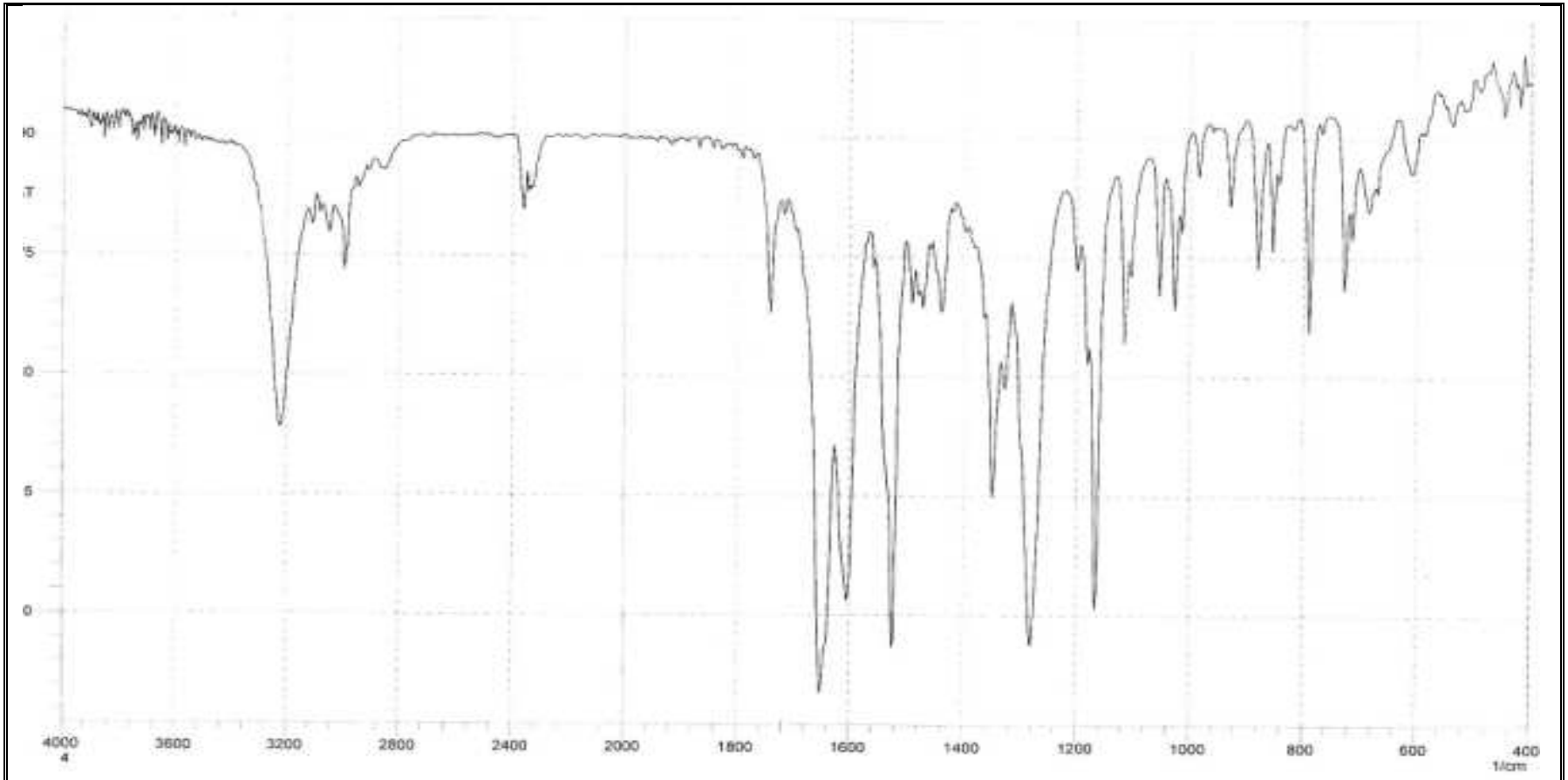


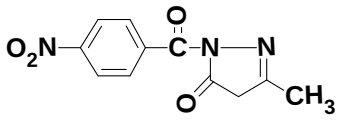
Color: Yellow

Molecular Weight: 216.24 g/mol

Molecular Formula: $C_{12}H_{12}N_2O_2$

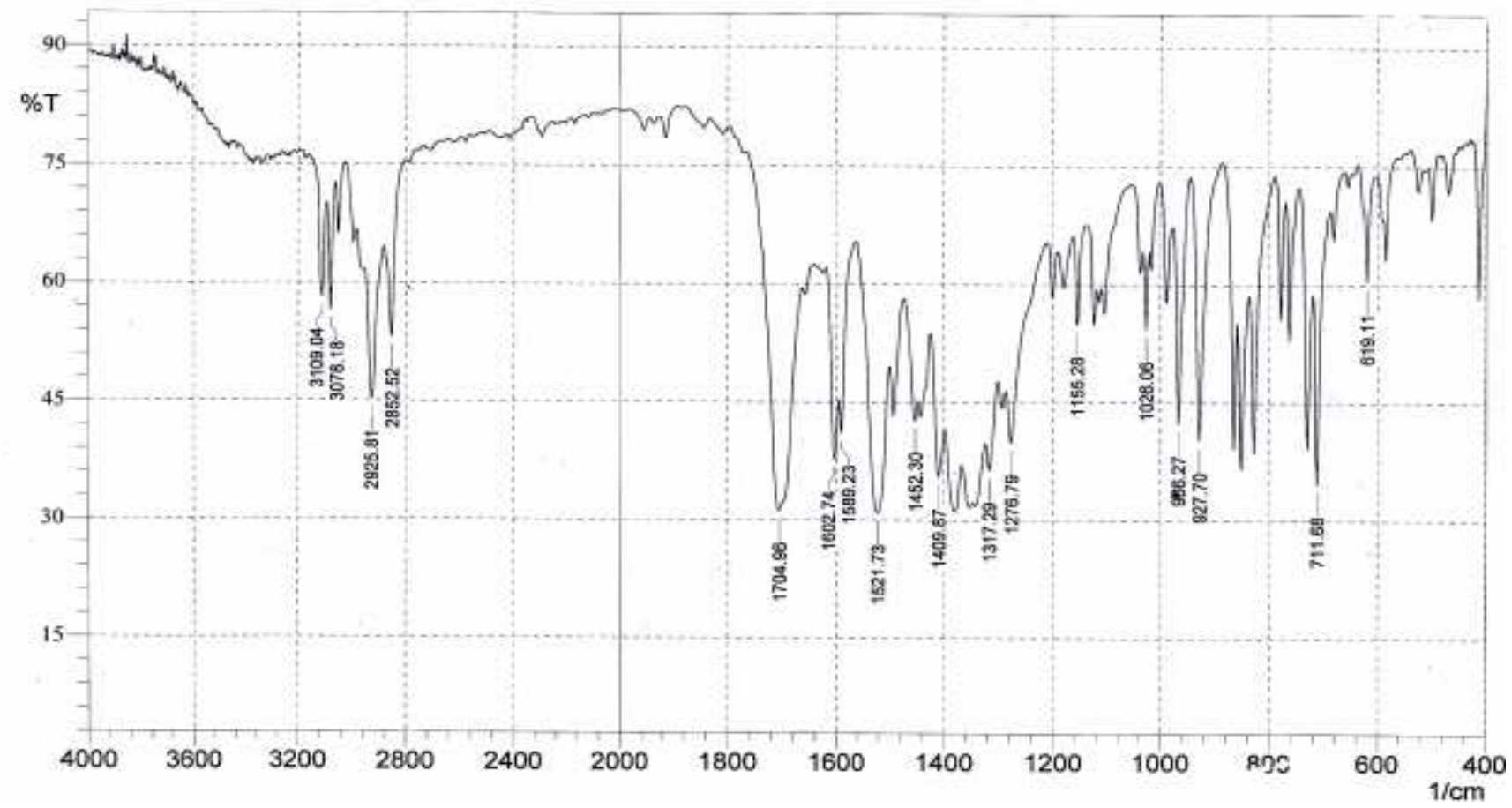
Figure (3-10): Structure, physical properties and IR spectrum of 1-(m-methyl benzoyl)-3-methhyl pyrazol-5-one [6a].





	Yield percentage: 81 %	**Color: Yellow**
		Molecular Weight: 247.21g/mol
	M.P. : 102-104 °C	**Molecular Formula: $C_{11}H_9N_3O_4$**

Figure (3-11): Structure, physical properties and IR spectrum of 1-(*m*-methyl benzoyl)-3-methyl pyrazol-5-one [6b].



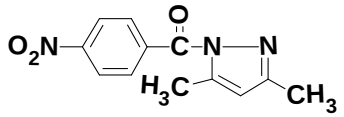
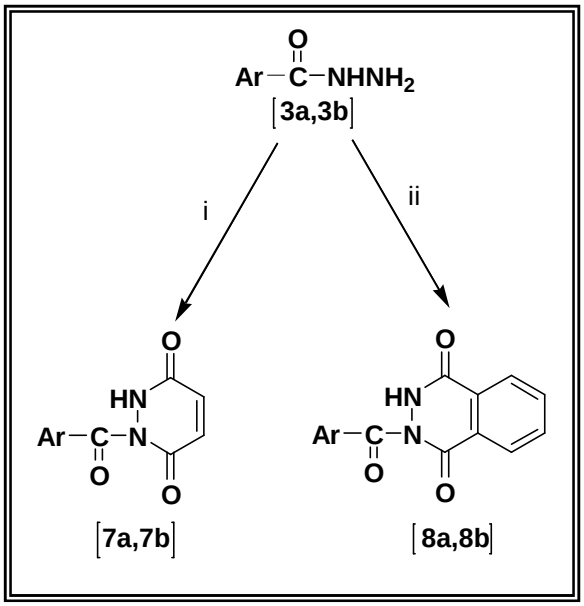
	**Yield percentage: 60 %**	**Color: Yellow**
	***M.P* = 98-100**	**Molecular Weight: 245.08 g/mol**
		Molecular Formula: $C_{12}H_{11}N_3O_3$

Figure (3-12): Structure, physical properties and F.T.IR spectrum of 1-(*p*-nitro benzoyl)-2,4-dimethyl pyrazole [17b].

3.6 Synthesis of pyridazin-dione and phthalazin derivatives [7a,7b,8a,8b] :



Scheme (3-6): Reagents and Conditions: i- maleic anhydride, acetic acid, reflux (7) hrs. ii- phthalic anhydride, acetic acid, reflux (7) hrs.

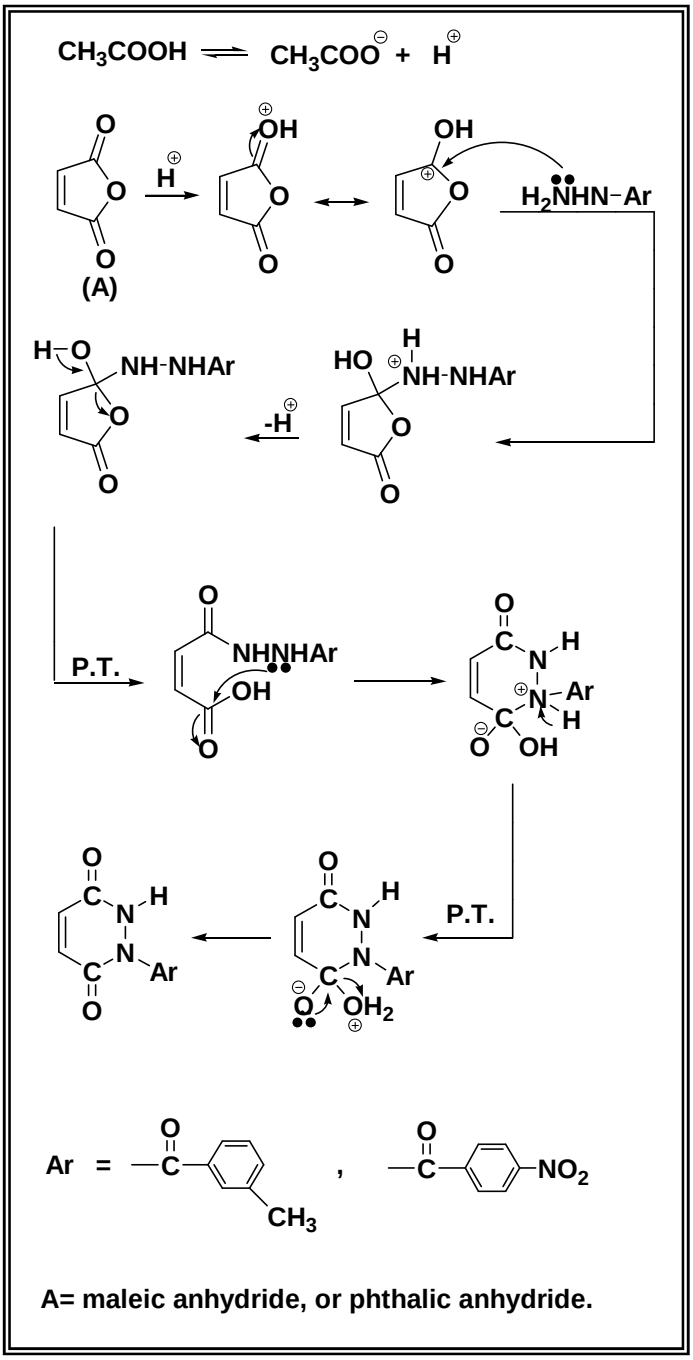
Pyridazin-3,6-dione and phthalazin-3,8-dione derivatives were synthesized by the reaction of hydrazide derivatives [3a, 3b] with maleic anhydride and phthalic anhydride respectively in the presence of acetic acid as asolvent and catalyst.

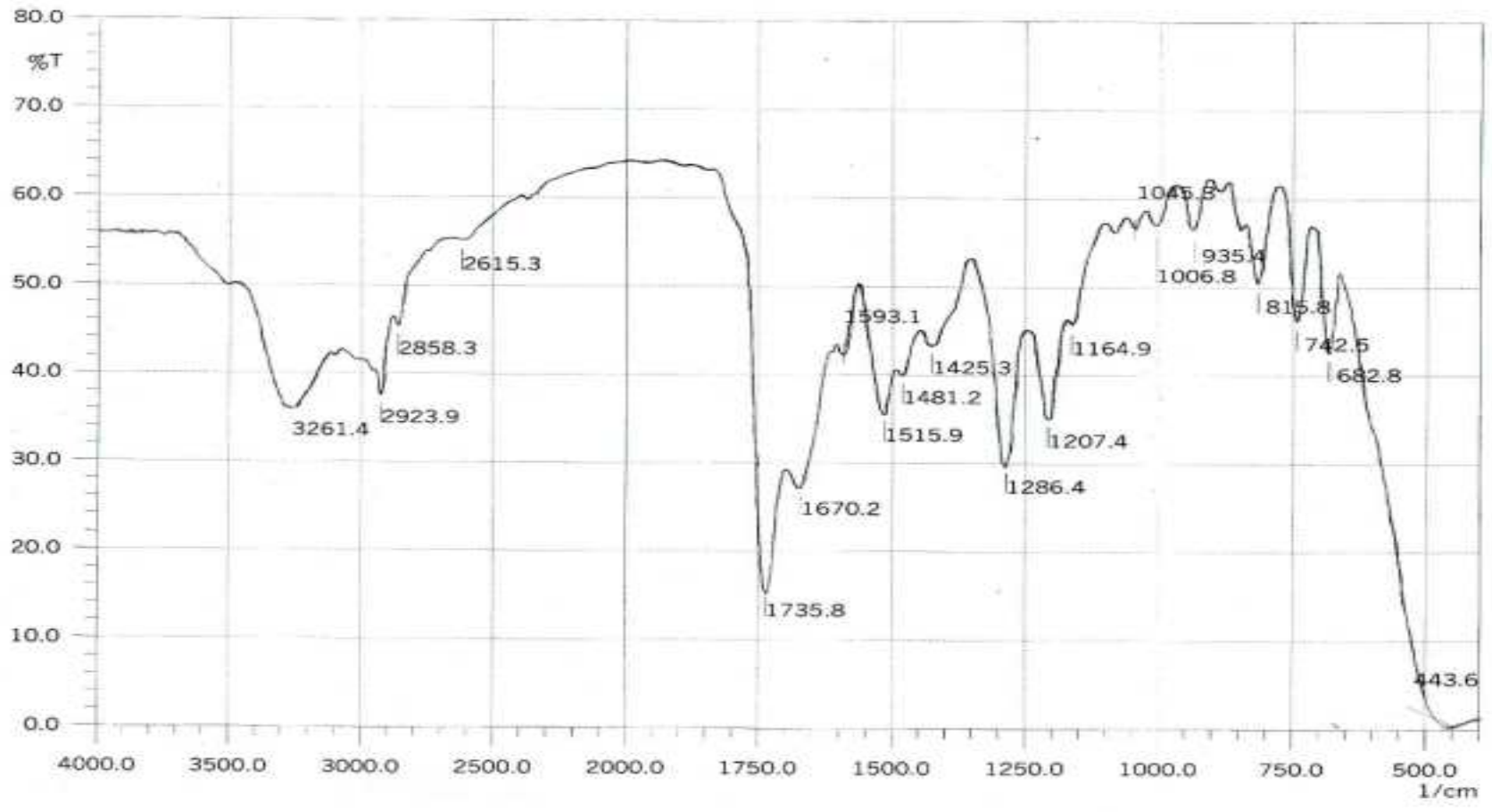
The FTIR spectra of compounds [7a, 7b] [8a, 8b] in figures (3-15) - (3-18) show the disappearance of the two bands of NH–NH_2 group in the region (3332-3276) cm^{-1} and appearance of a band due to (N-H) group at the range (3350-3260) cm^{-1}. Two carbonyl groups of compounds [7a, 7b] [8a, 8b] appeared at (1735-1725) cm^{-1} and at (1691-1670) cm^{-1} for the amide carbonyl. The characteristic bands of compounds [7a, 7b], [8a, 8b] is shown in table (3-6).

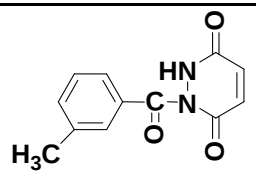
Table (3-6): Characteristic bands of compounds [7a, 7b], [8a, 8b]:

Comp. No.	*ν(-NH) cm^{-1}*	*ν(C-H) arom. cm^{-1}*	*ν(C-H) alph. cm^{-1}*	*ν (C=O) cm^{-1}*	*ν CONH- cm^{-1}*	*ν(C=C) cm^{-1}*
7a	*3261*	*3000*	*2923*	*1735*	*1670*	*1593*
7b	*3282*	*3100*	*-*	*1733*	*1685*	*1523*
8a	*3350*	*3020*	*2990*	*1725*	*1685*	*1580*
8b	*3350*	*3099*	*-*	*1731*	*1691*	*1533*

The mechanism of this reaction is shown below [145]:





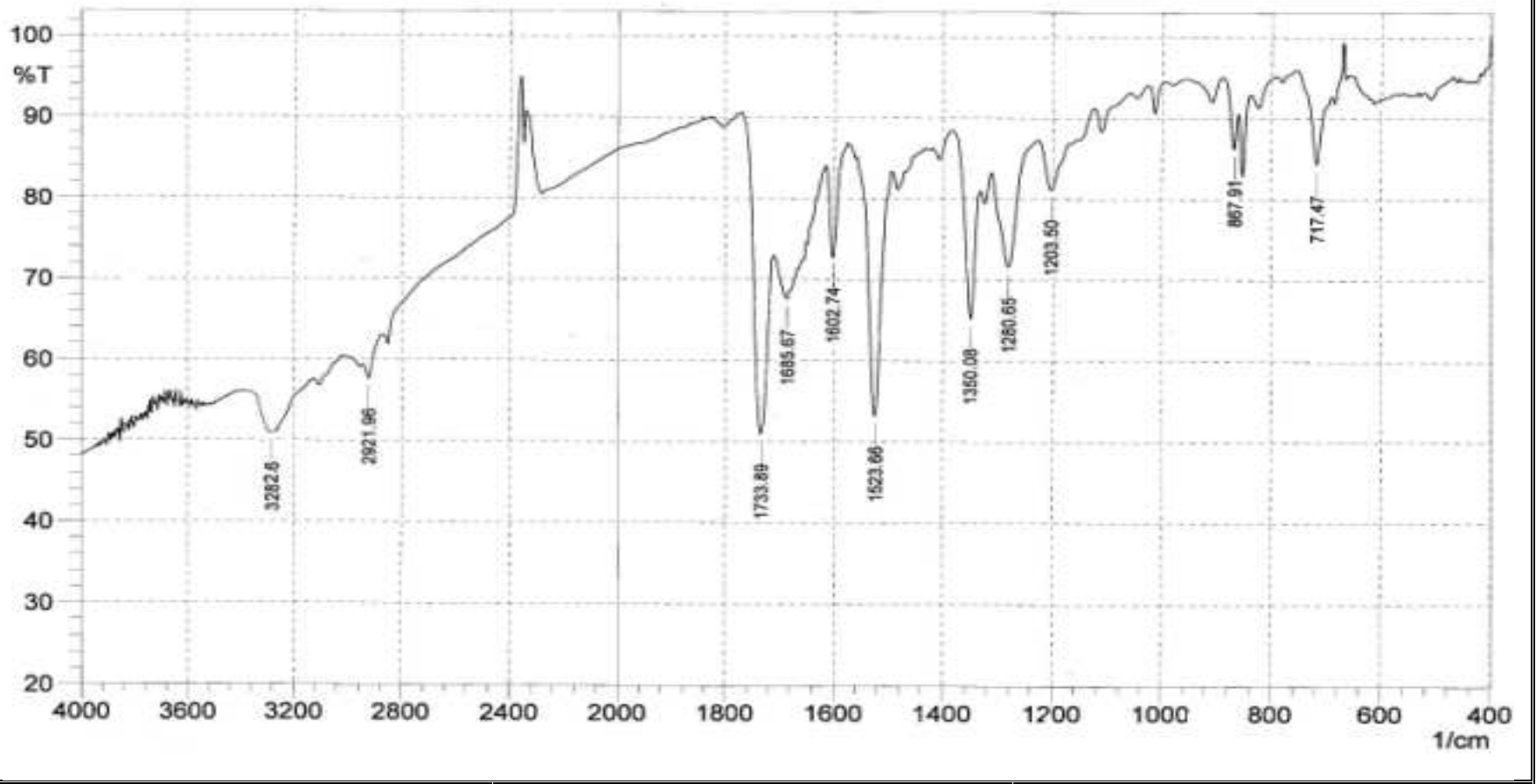


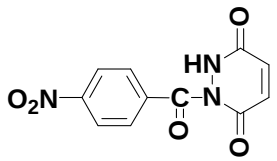
Color: Brown

Molecular Weight: 230.22 g/mol

Molecular Formula: $C_{14}H_{10}N_2O_3$

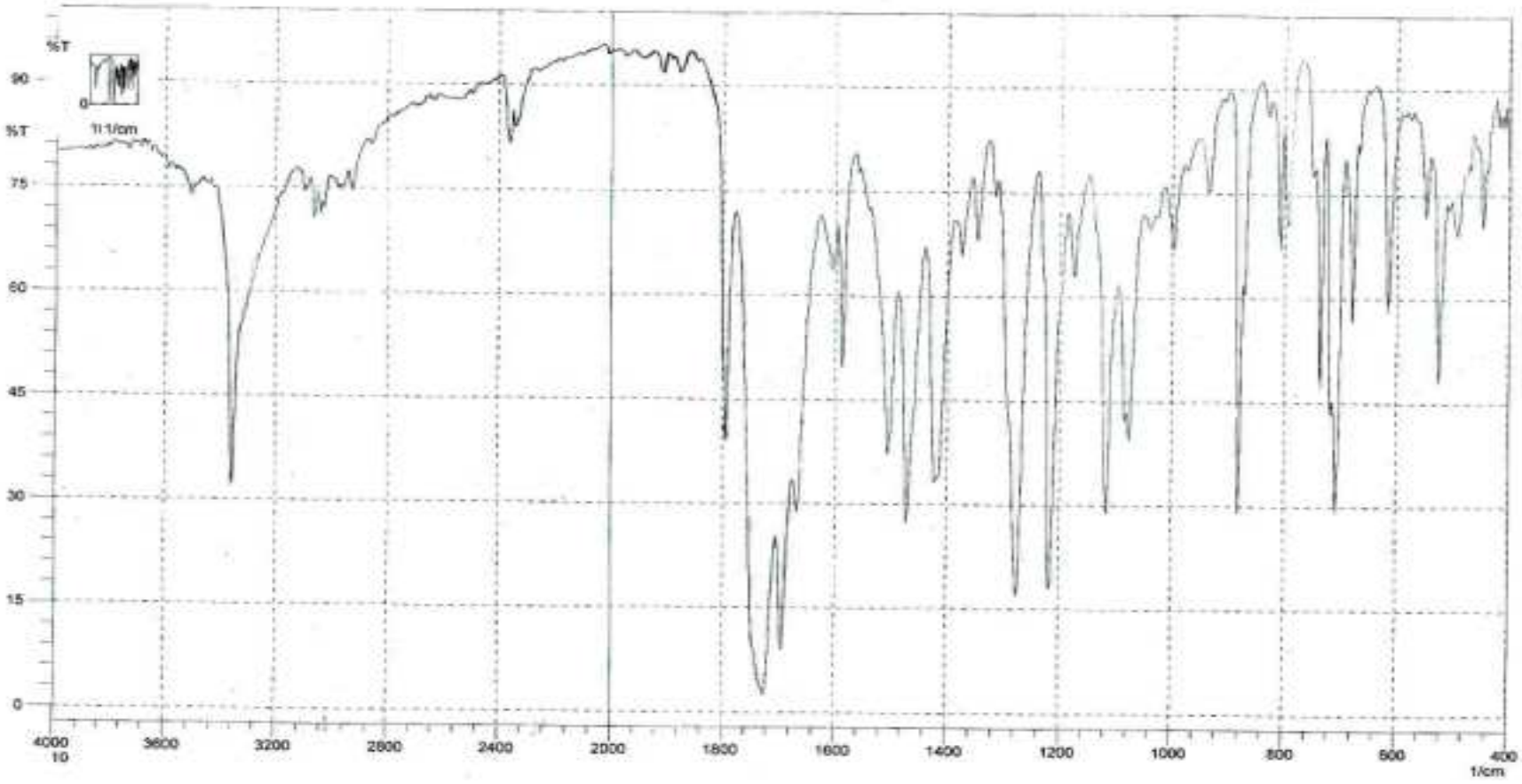
Figure (3-13): Structure, physical properties and F.T.IR spectrum of 1-(*m*-methyl benzoyl)-1,2-dihydropyridazin-3,6-dione [7a].

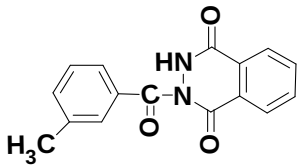




	Yield percentage: 72 %	**Color: yellow**
		Molecular Weight: 261.19 g/mol
	B.P. : 79 °C	**Molecular Formula: $C_{11}H_7N_3O_5$**

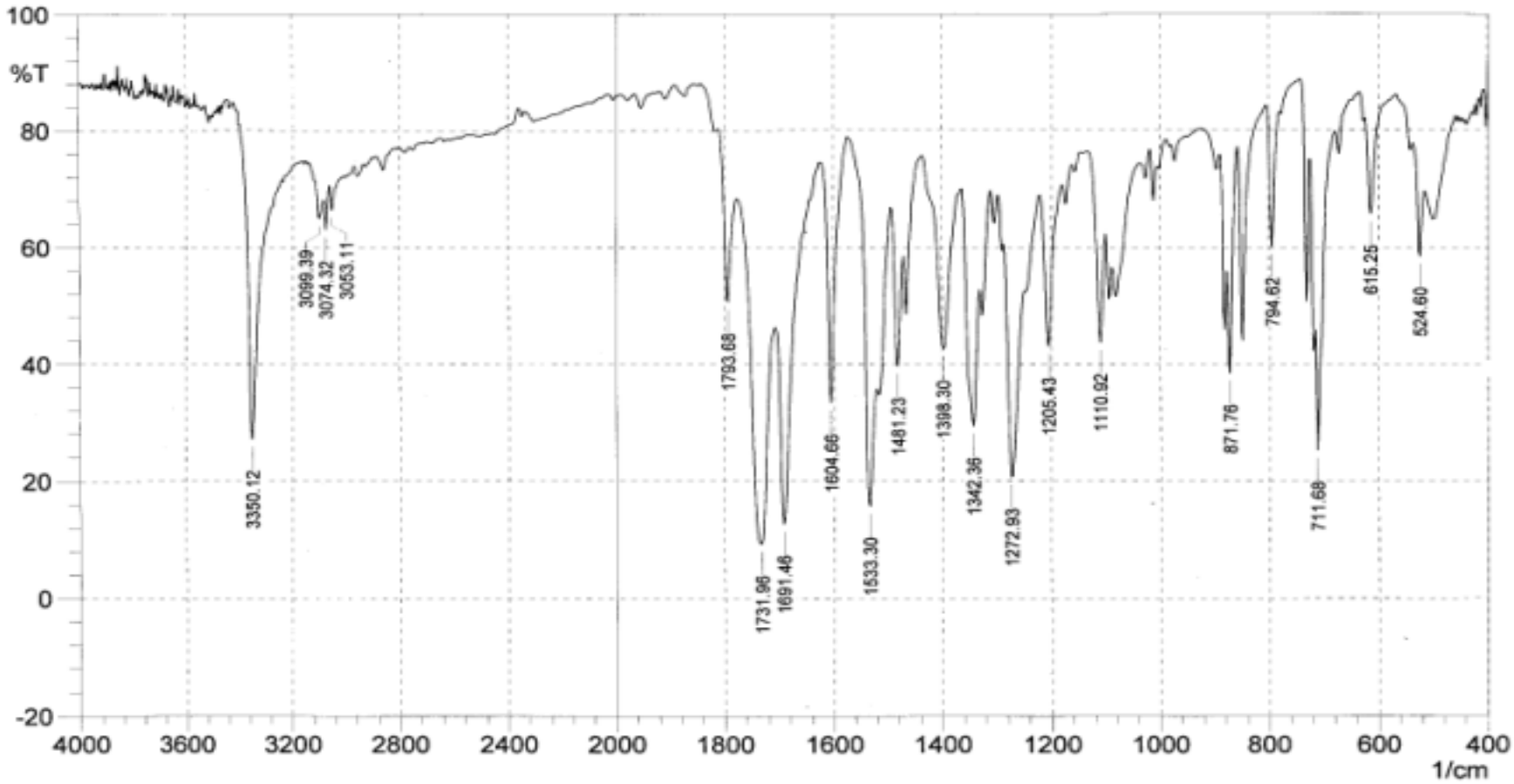
Figure (3-14): Structure, physical properties and F.T.IR spectrum of 1-(*p*-nitro benzoyl)-1,2-dihydropyridazin-3,6-dione [7b].

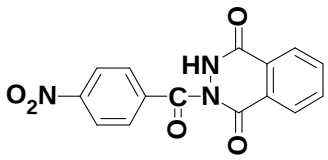




	Yield percentage: 79 %	**Color: White**
	M.P. : 168-170 °C	**Molecular Weight: 280.28 g/mol**
		Molecular Formula: $C_{16}H_{12}N_2O_3$

Figure (3-15): Structure, physical properties and IR spectrum of 1-(*m*-methyl benzoyl)-1,2-dihydro phthalazin-3,8-dione [8a].

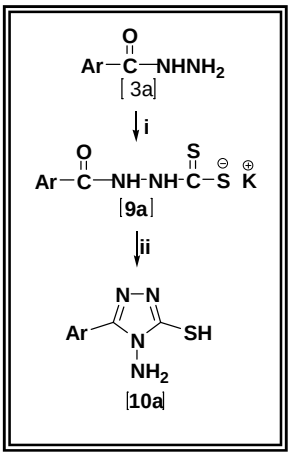




	Yield percentage: 61 %	**Color: White**
	M.P. : 260-263 °C	**Molecular Weight: 311.25 g/mol**
		Molecular Formula: $C_{15}H_9N_3O_5$

Figure (3-16): Structure, physical properties and F.T.IR spectrum of 1-(*p*-nitro benzoyl)-1,2-dihydro phthalazin-3,8-dione [8b].

3.7 Synthesis of 1,2,4-triazole derivative [10a] :

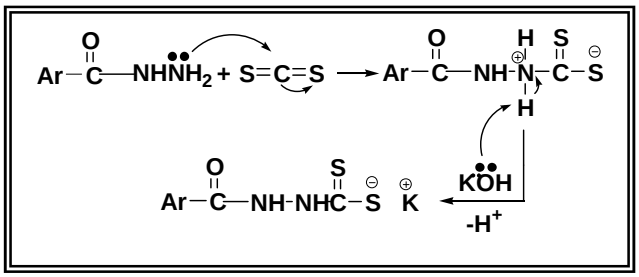


Scheme (3-7): Reagents and Conditions:

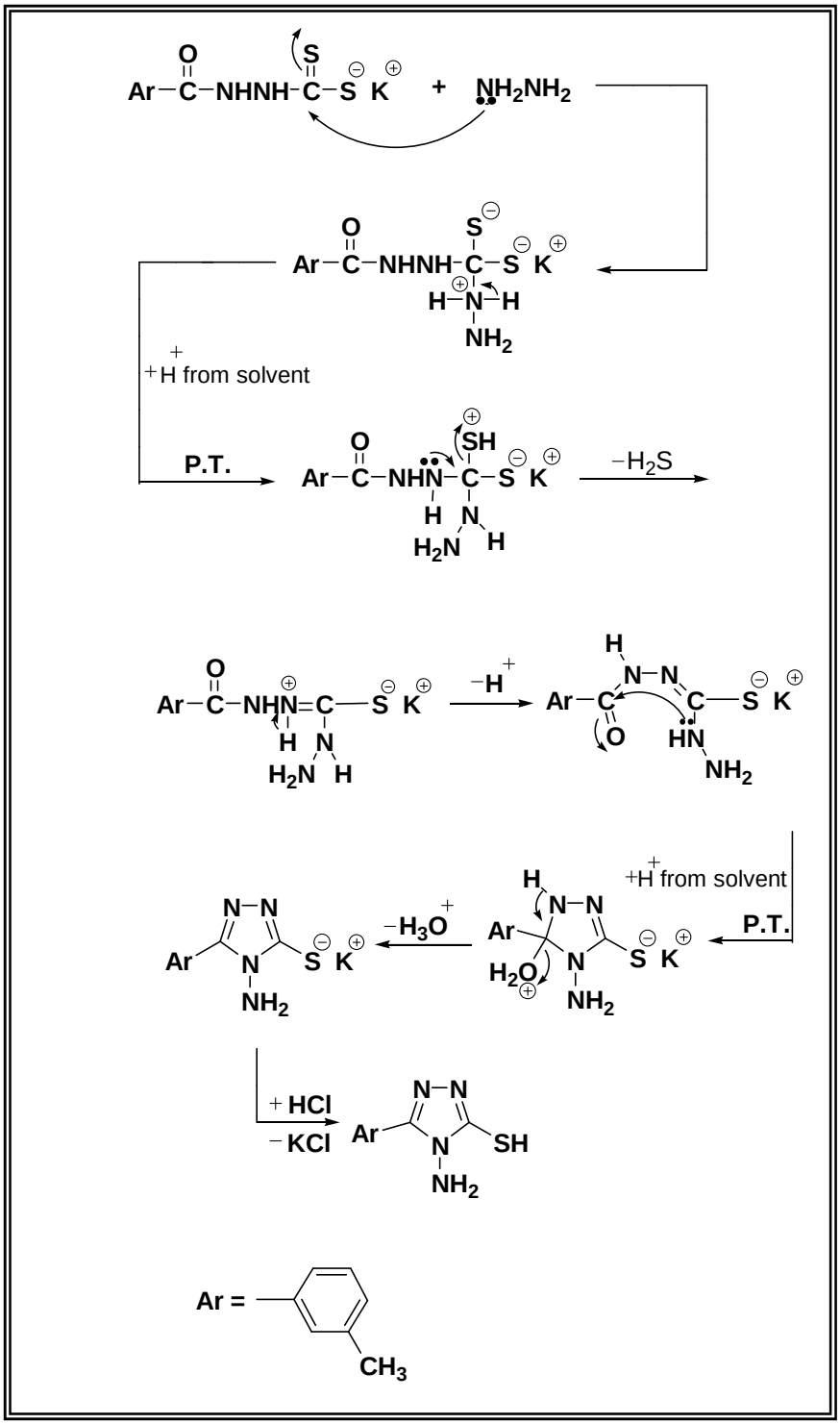
i- CS_2, KOH, reflux (1) hr. ii- $N_2H_4.H_2O$, reflux (4) hr.

The 1,2,4-triazole derivative was synthesized according to the sequence in Scheme (3-7).

The acid hydrazide [3a] was treated with carbon disulfide followed by the addition of hydrazine hydrate. Addition of CS_2 to the acid hydrazide in presence of KOH afforded the salt as in the following mechanism [146, 147].



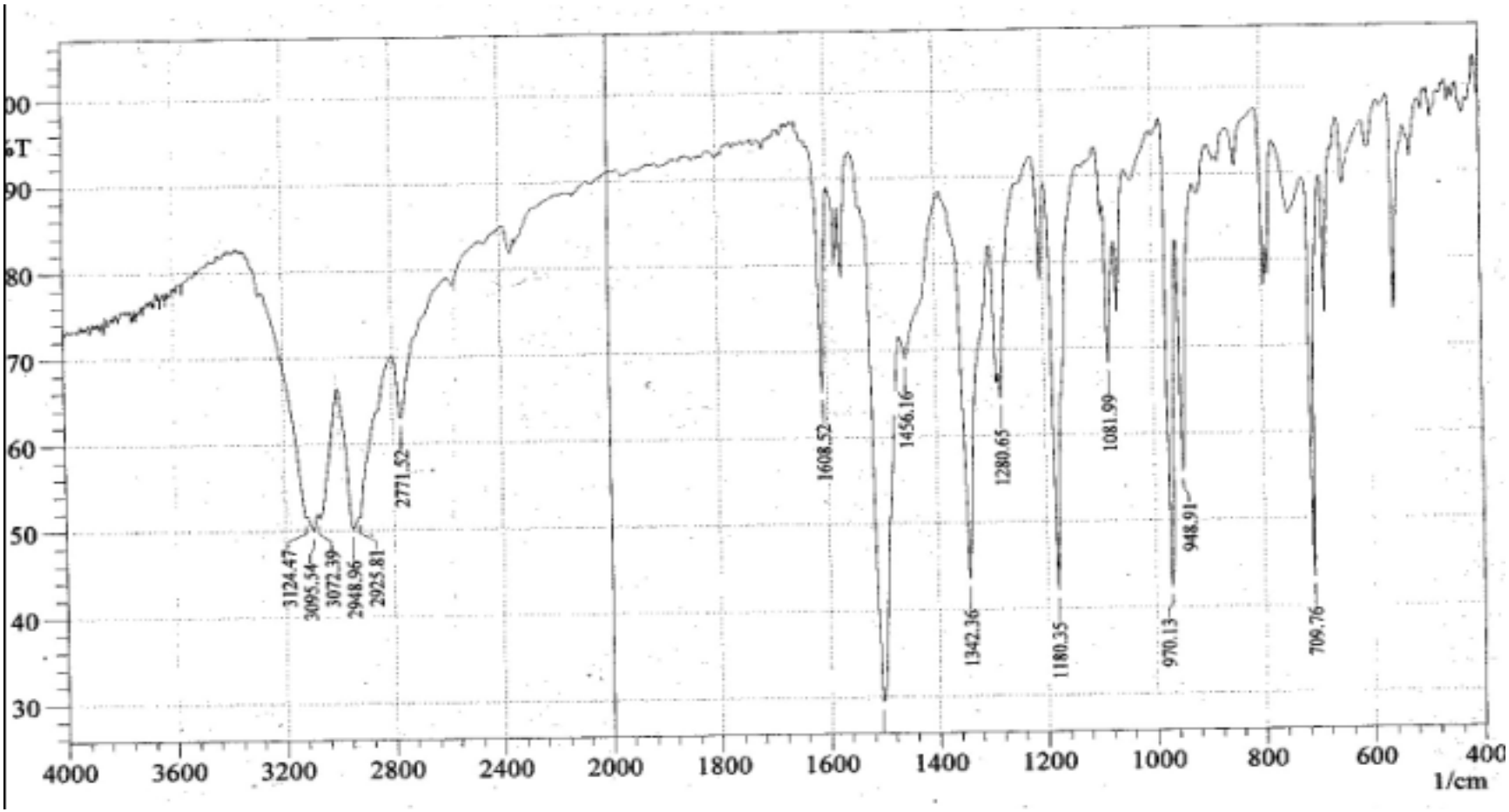
The addition of hydrazine hydrate leads to the cyclization which produces the triazole [10a] as in the following suggested mechanism.



Triazole derivative was characterized by using F.T.IR spectrum which showed the disappearance of absorption band at (1678) 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 (2771) cm^{-1} which belongs to S-H group, Asymmetric and symmetric NH_2 bands appeared at (3124, 3095) cm^{-1}. Table (3-7) shows characteristic bands of compound [10a]. The FTIR spectrum of the above compound is shown in figure (3-17).

Table (3-7): Characteristic bands of compounds [10a]

Comp. No.	***V(-NH_2) cm^{-1}***	***V(C-H) arom.cm^{-1}***	***V (-SH) cm^{-1}***	***V(C=N) cm^{-1}***	***V(C=C) cm^{-1}***
10a	***3124, 3095***	***3072***	***2771***	***1608***	***1500***



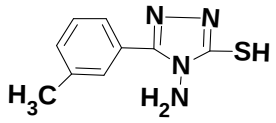
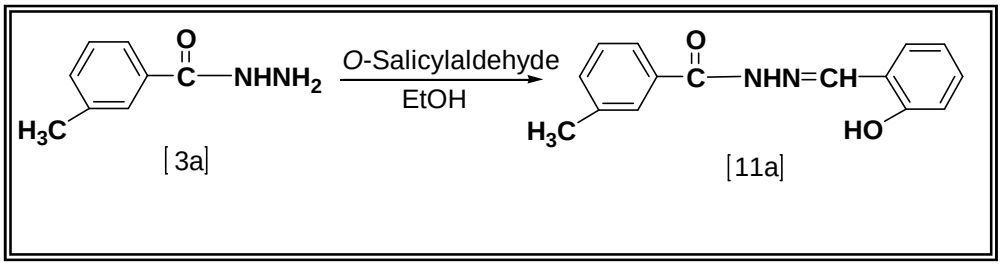
	**Yield percentage: 84 %**	**Color: White**
	M.P. : 130-132 °C	**Molecular Weight:268.12 g/mol**
		Molecular Formula: $C_9H_{10}N_4S$

Figure (3-17): Structure, physical properties and F.T.IR spectrum of 3-mercabto-4-amino-5-(*m*-methyl phenyl)-1,2,4-triazole [10a].

3.8 Synthesis of N[-o-hydroxybenzylidine]-(m-tolyl hydrazide) [11a]:



Scheme (3-8): Reagents and Conditions: o-salicylaldehyde, EtOH, reflux (8)hrs.

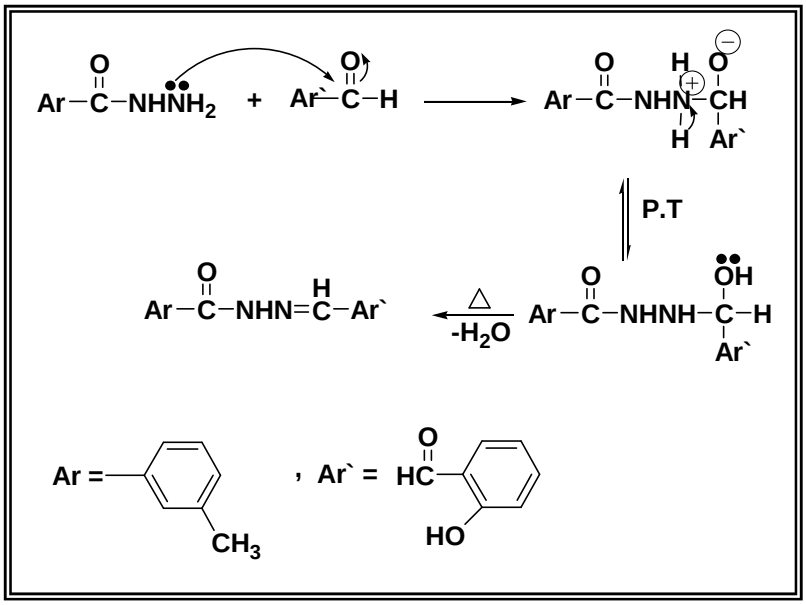
Reaction of compound [3a] with o-salicylaldyhyde in absolute ethanol gave compound [11a].

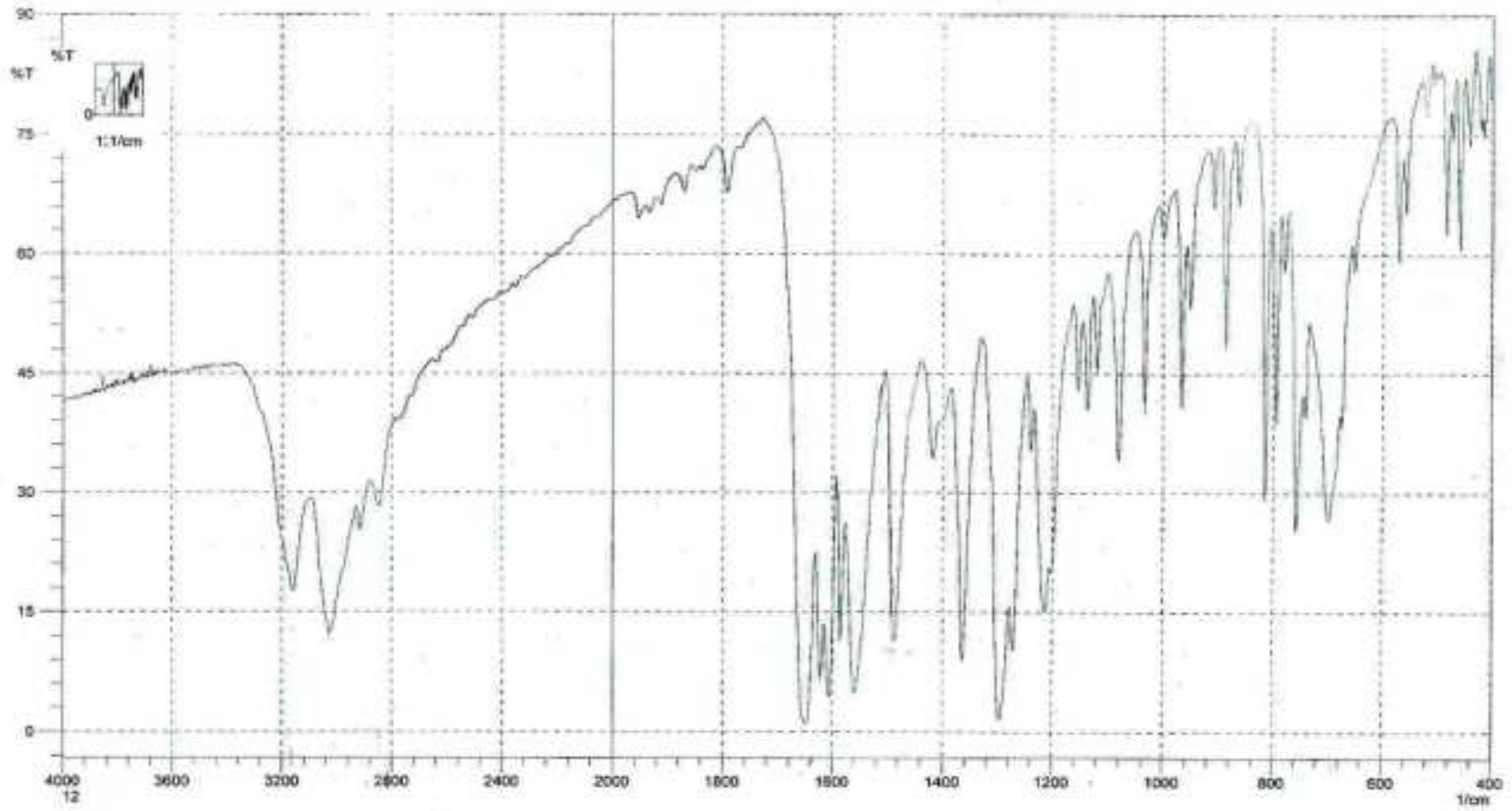
IR spectrum of compound [11a] in figure (3-18) shows the disappearance of $–NH_2$ stretching bands at (3290, 3280.53) cm^{-1} and appearance of –NH band at (3170) cm^{-1}, the carbonyl group appeared at (1650) cm^{-1}, a band of C=C appear at (1600). The disappearance of hydroxyl group confirmed the possibility of the hydrogen bonding. Table (3-8) shows characteristic bands of compound [11a].

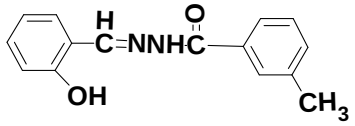
Table (3-8): Characteristic bands of compound [11a]:

Comp. No.	*ν(N-H) cm^{-1}*	*ν(C-H) arm. cm^{-1}*	*ν(C-H) aliph. cm^{-1}*	*ν(C=O) cm^{-1}*	*ν(C=N) cm^{-1}*	*ν(C=C) cm^{-1}*
11a	*3170*	*3010*	*2910*	*1650*	*1600*	*1570*

The mechanism of the reaction is as shown below [148]:



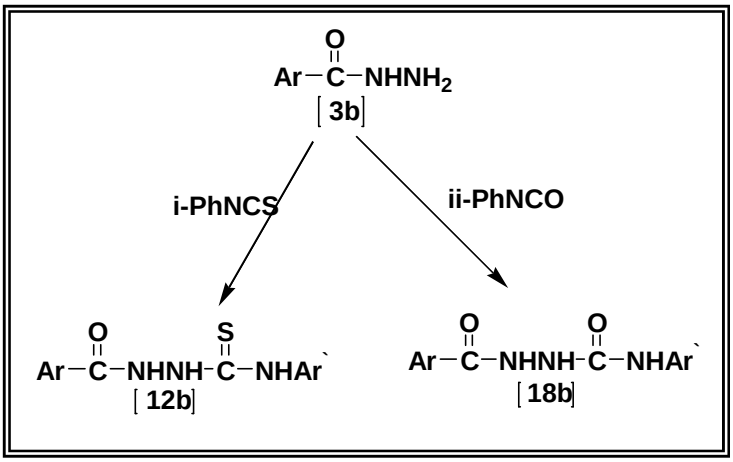




	Yield percentage :75 %	**Color: White**
		Molecular Weight: 254.28 g/mol
	M.P. : 174- 176°C	**Molecular Formula: $C_{15}H_{14}N_2O_2$**

Figure (3-18): Structure, physical properties and IR spectrum of 1-(3-methyl benzoyl hydrazine)-2-(2-hydroxy benzlidine) [11a].

3.9 Synthesis of thiosemicarbazide [12b] and semicarbazide [18b] derivatives:



Scheme (3-9): Reagents and conditions: i- phenyl isothiocyanate, abs. EtOH, reflux (7) hrs. ii- phenyl iso cyanate, abs. EtOH, reflux (7)hrs.

The reaction of acid hydrazide with phenyl isothiocyanate in absolute ethanol gave the thiosemicarbazide [12b] while reaction with phenyl isocyanate gave semicarbazide [18b].

The FTIR spectrum in figure (3 -19) for thiosemicarbazide [12b] show disappearance of the two absorption bands at (3332) cm^{-1} and (3276) cm^{-1}due to asymmetric and symmetric stretching vibration of NH–NH_2 group of acid hydrazide [3b] and the appearance of the two absorption band at (3307) cm^{-1} and (3232) cm^{-1} due to the three group of N-H and appearance band of C=S at (1312) cm^{-1}, amide C=O appeared at (1643) cm^{-1}.

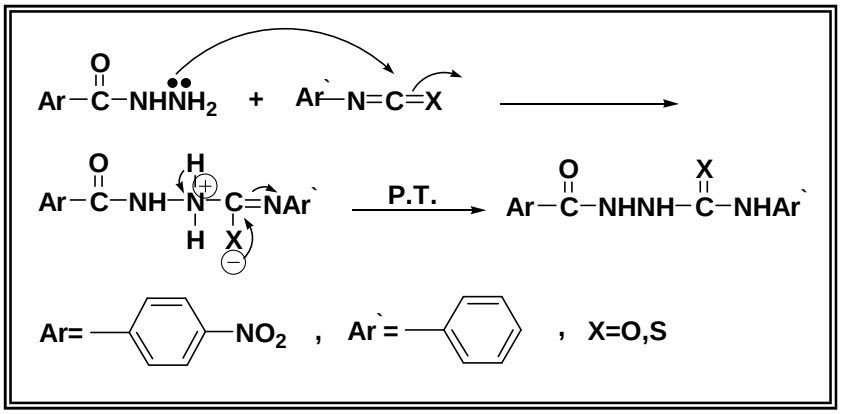
While the FTIR spectrum in figure (3 -20) for the semicarbazide [18b] shows the disappearance of the two absorption bands at (3332) cm^{-1} and (3276) cm^{-1} due to asymmetric and symmetric stretching vibration of NH–NH_2 group of acid hydrazide [3b] and appearance of a broad band due to –

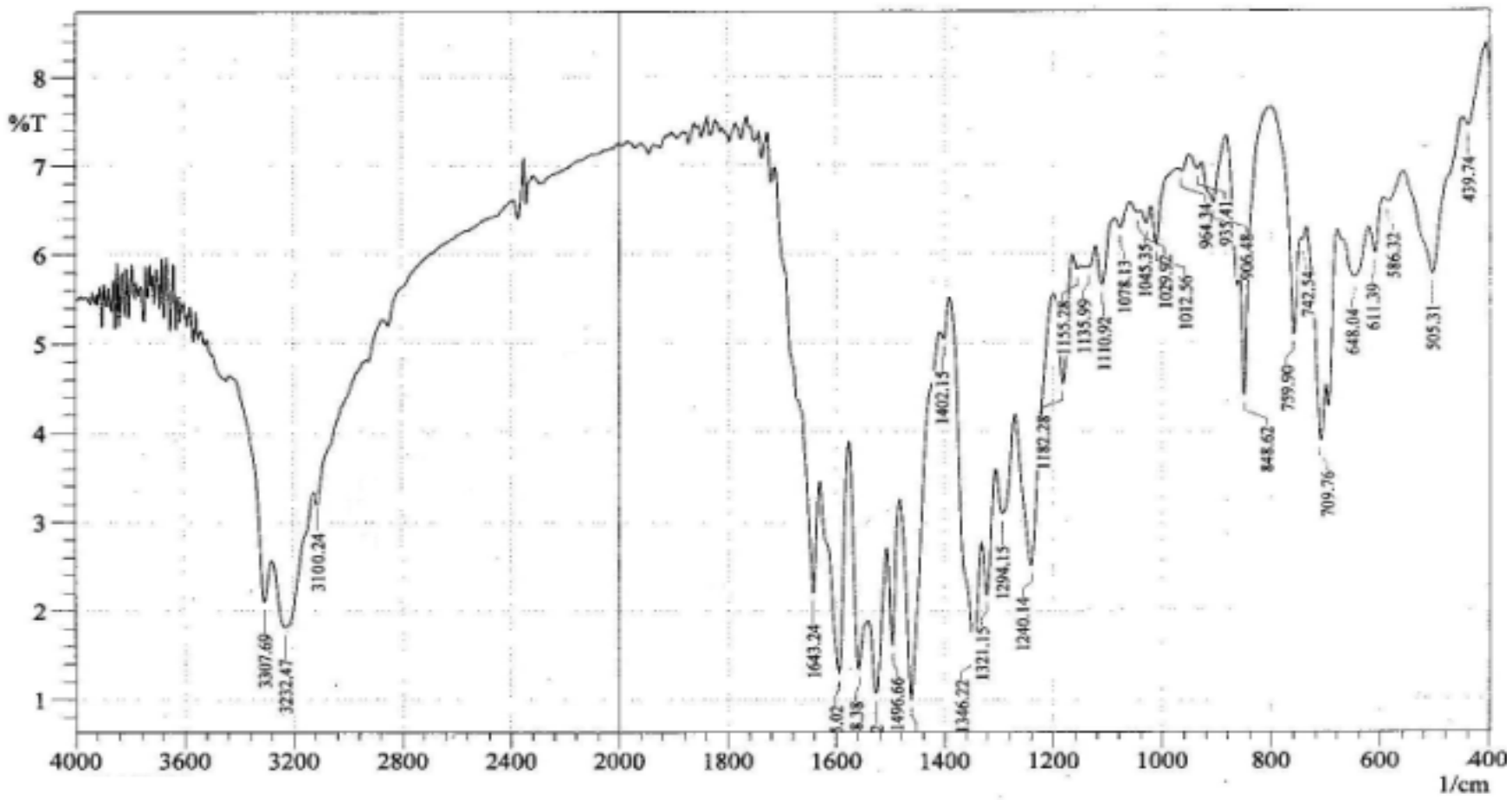
NH group at (3284) cm^{-1} and (3269) cm^{-1}. Two carbonyl groups of compound [18] appeared at (1658) cm^{-1}. Table (3-9) shows characteristic bands of compound [12b, 18b].The FTIR spectra of the above compounds are shown and (3 -20).

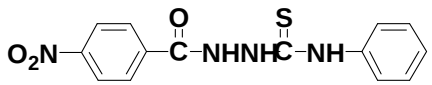
Table (3-9): Characteristic bands of compounds [12b, 18b]:

Comp. No.	*ν(N-H) cm^{-1}*	*ν(C-H) arm.cm^{-1}*	*ν(C=O) cm^{-1}*	*ν(C=C) cm^{-1}*	*ν(C=S) cm^{-1}*
12b	*3307 3232*	*3100*	*1643*	*1600*	*1312*
18b	*3284 3269*	*3049*	*1658*	*1598*	*-*

The mechanism of the reaction is shown below:

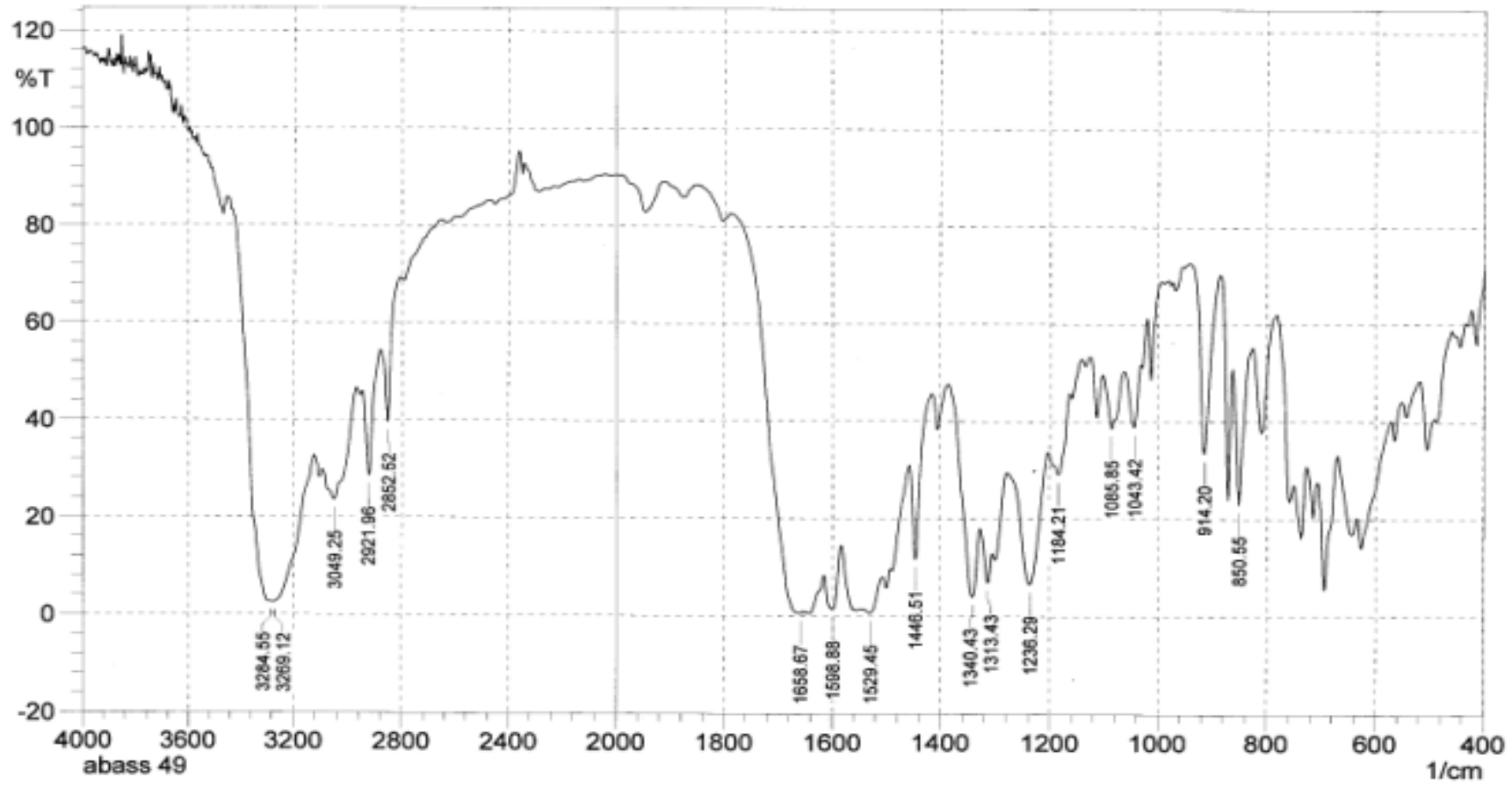






	Yield percentage: 75 %	**Color: Yellow**
		Molecular Weight: 282.25 g/mol
	M.P. : 160- 163 °C	**Molecular Formula: $C_{14}H_{10}N_4O_3$**

Figure (3-19): Structure, physical properties and F.T.IR spectrum of 1-phenyl-4-(*p*-nitro benzoyl)thiosemicarbazide [12b]



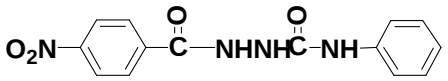
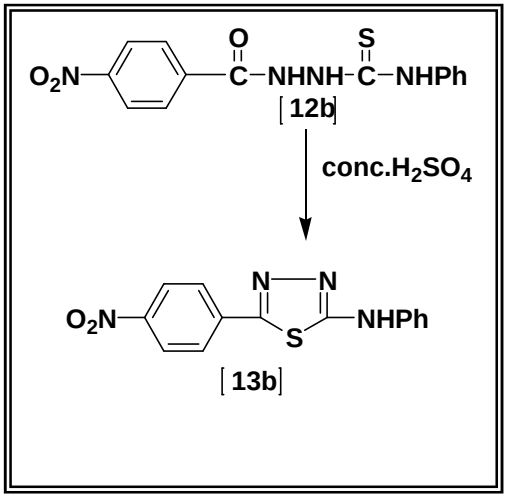
	**Yield percentage: 78 %**	**Color: White**
		Molecular Weight: 300.27 g/mol
	M.P. : 218-220 ^{o}C	**Molecular Formula: $C_{14}H_{12}N_4O_4$**

Figure (3-20): Structure, physical properties and F.T.IR spectrum of 1-phenyl-4-(*p*-nitro benzoyl)semicarbazide [18b].

3.10 Synthesis of 2-(phenyl amino)-5-(p-nitro phenyl)-1,3,4-thiadiazole[13b]:



Scheme (3-10): Reagents and Conditions: Conc.H_2SO_4, stirred (3) hrs.

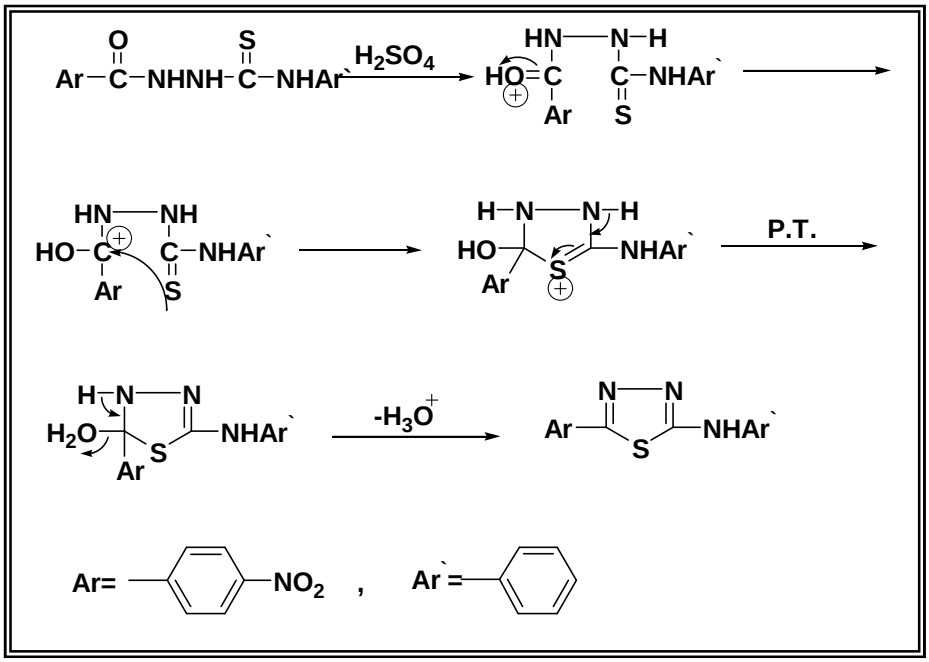
1,3,4-Thiadiazole derivative [13b] was synthesized from the reaction of thiosemicarbazide derivative with concentrated sulfuric acid at (0) ^{0}C.

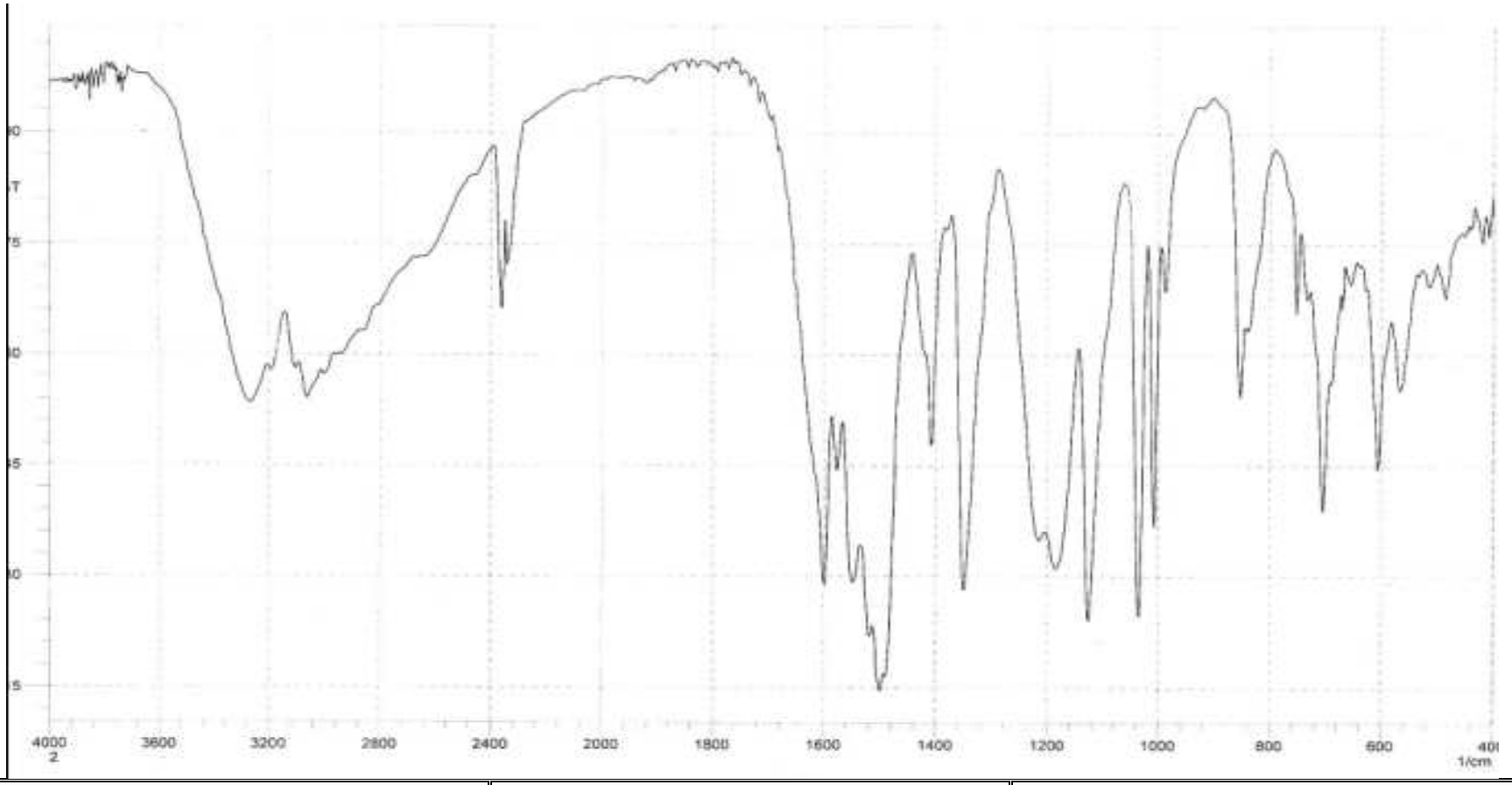
The IR spectrum in figure (3-21) show band at (3290) cm^{-1} due to N-H groups, band at (1600) cm^{-1} for C=N, band at (690) cm^{-1} attributed to C-S-C band is a good evidence for oxadiazole formulation. Table (3-10) shows characteristic bands of compound [13b].

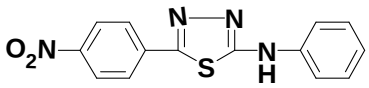
Table (3-10): Characteristic bands of compound [13b]:

Comp. No.	*ν(N-H) cm^{-1}*	*ν(C-H) arm. cm^{-1}*	*ν(C=N) cm^{-1}*	*ν(C-S-C) cm^{-1}*
13b	*3290*	*3080*	*1600*	*700*

The mechanism of the reaction was affected by intermolecular cyclization through the lossing of H_2O as shown below [149]:



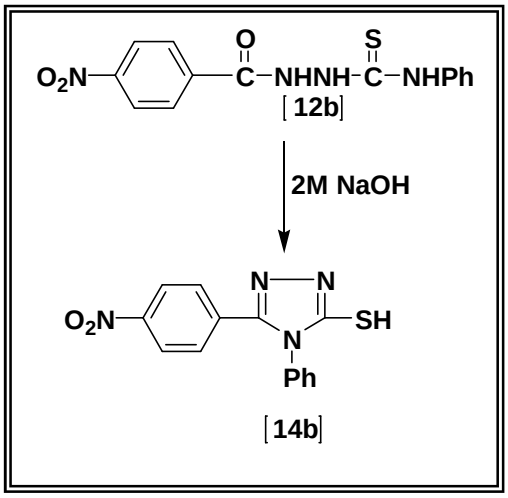




	Yield percentage: 62 %	**Color: Red- Orange**
		Molecular Weight: 298.32 g/mol
	M.P. :195-197 ^{o}C	**Molecular Formula:$C_{14}H_{10}N_4O_2S$**

Figure (3-21): Structure, physical properties and IR spectrum of 2-(phenyl amino)-5-(*p*-nitro phenyl)-1,3,4-thiadiazole [13b].

3.11 Synthesis of 3-mercapto-4-phenyl-5-(P-nitro Phenyl)-1,2,4-triazole[14b]:



Scheme (3-11): Reagents and conditions: 2M NaOH,reflux (4)hrs.

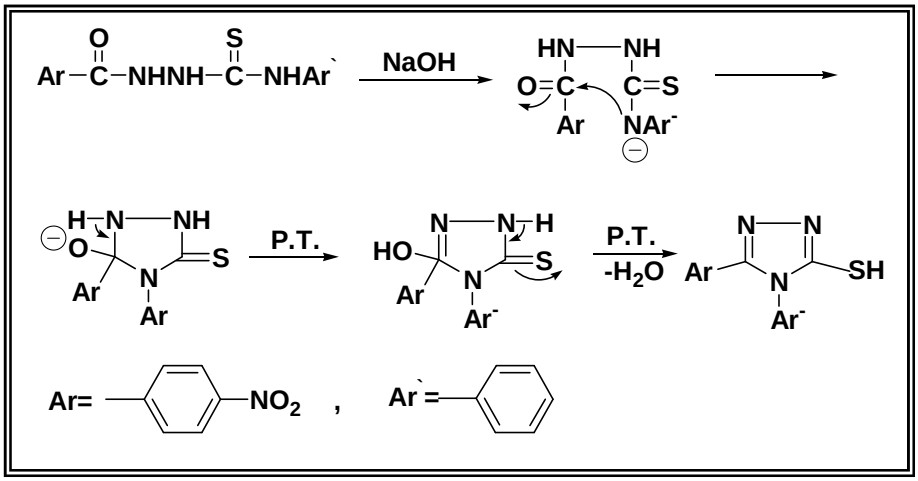
Thiol-triazole prepared through the reaction of thiosemicarbazide derivative with NaOH under refluxing condition affected interamolecular cyclization through the loss of H_2O.

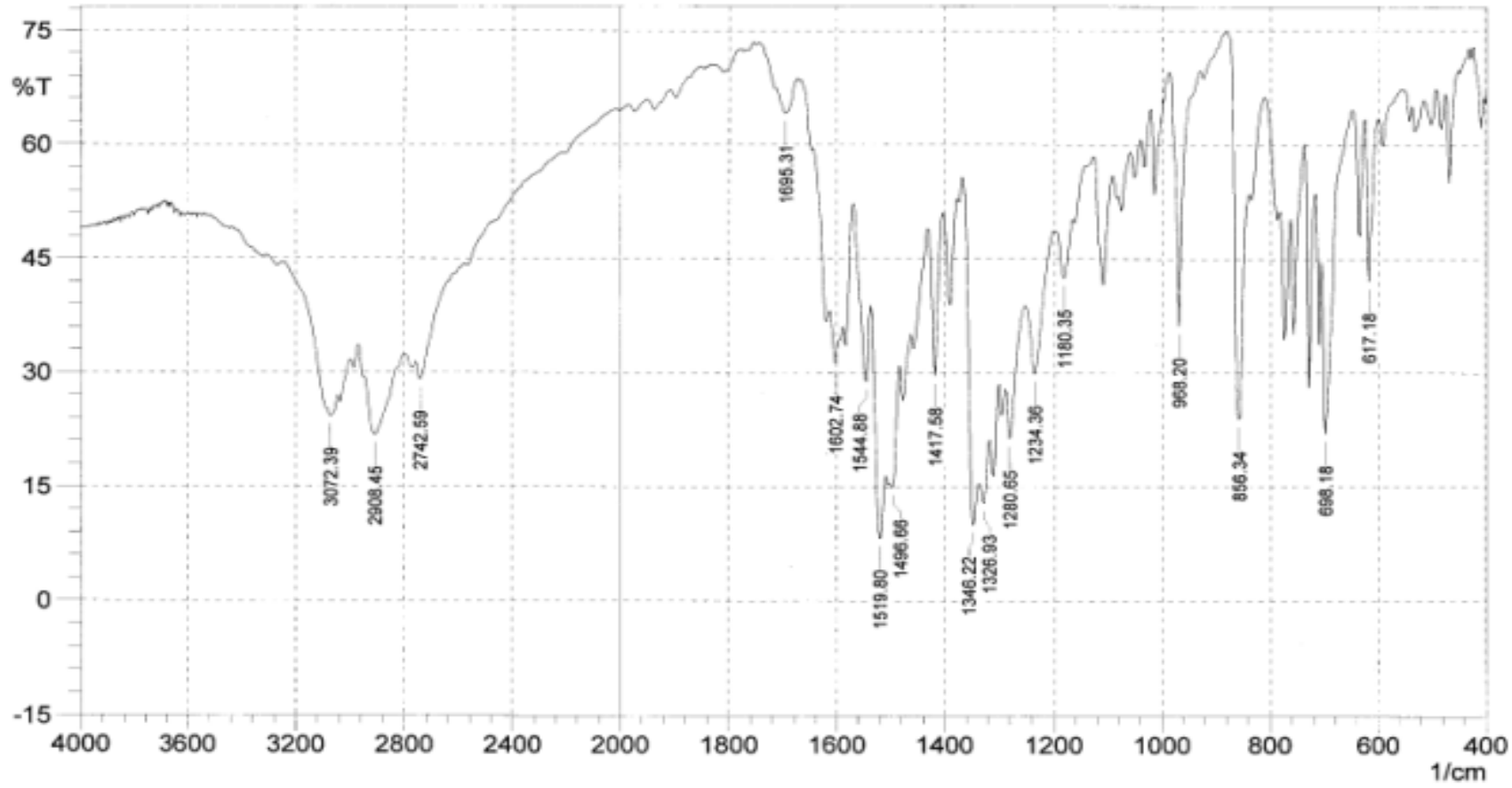
The IR spectrum in figure (3-22) show disappearance of the bands at (3307) cm^{-1} and (3232) cm^{-1} due to NH-NH group with appearance of a weak band due to –SH group at (2742) cm^{-1}, also shows the disappearance of the band at (1643) cm^{-1} due to C=O of amide I with appearance of a band at (1602) cm^{-1} assignable to C=N of triazole ring. Table (3-11) shows characteristic bands of compound [14b].

Table (3-11): Characteristic bands of compound [14b]:

Comp. No.	*ν(C-H) arm. cm^{-1}*	*ν(S-H) cm^{-1}*	*ν(C=N) cm^{-1}*
14b	*3072*	*2724*	*1602*

The suggested mechanism for the reaction is:





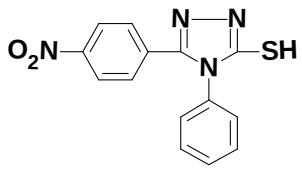
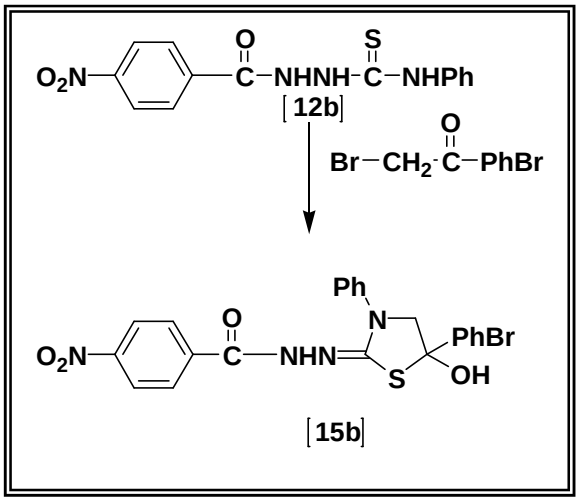
	**Yield percentage: 65 %**	**Color: Orange**
		Molecular Weight: 298.32g/mol
	M.P. : 212-215 ^{o}C	**Molecular Formula: $C_{14}H_{10}N_4O_2S$**

Figure (3-22): Structure, physical properties and F.T.IR spectrum of 5-(*p*-nitro phenyl)-4-phenyl-1,2,4-triazole-3-thiol [14b].

3.12 Synthesis of 4-(p-bromo phenyl)-2-(p-nitrobenzoic acid hydrazide)-3-N-phenyl-4-(hydroxy)thiazolidine [15b]:



Scheme (3-12): Reagents and Conditions: *p*-bromo phenacyl bromide, abs. EtOH, reflux (8) hrs.

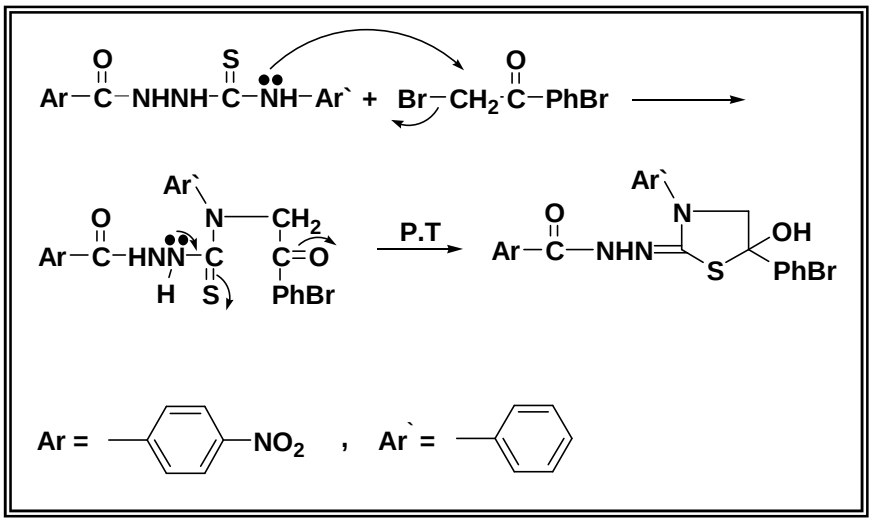
Thiazolidine derivative [15b] was synthesized from the reaction of thiosemicarbazide [12b] with *p*-bromo phenacyl bromide which was used for cyclization of the previous compound.

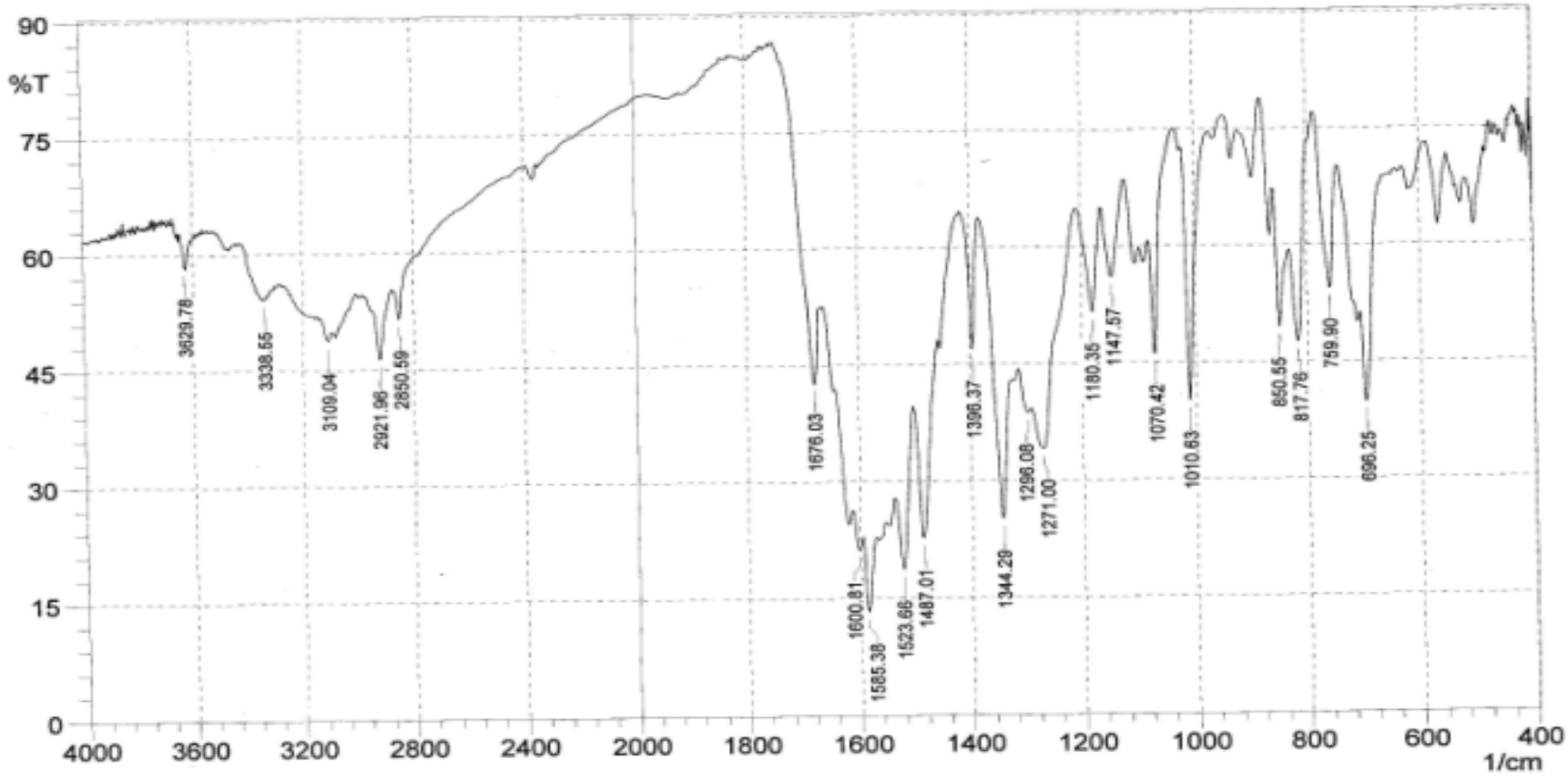
The FTIR spectrum in figure (3-23) shows the disappearance of thione group of the thiosemicarbazide [12b] at (1240) cm^{-1} with the appearance of band at (3629) cm^{-1} assinable to (OH) group, band due to NH-NH group appeared at (3338) cm^{-1}, C=N band appears at (1585) cm^{-1}, band at (696) cm^{-1} belongs to (C-S-C) group. Table (3-12) shows characteristic bands of compound [15b].

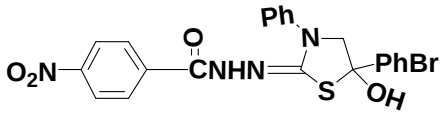
Table (3-12): Characteristic bands of compound [15b]:

Comp. No.	***ν(O-H) cm^{-1}***	***ν(-NH) cm^{-1}***	***ν(C-H) arm.cm^{-1}***	***ν(C=O) cm^{-1}***	***ν(C=N) cm^{-1}***	***ν(C=C) arm. cm^{-1}***	***ν(C-S-C) cm^{-1}***
15b	***3629***	***3338***	***3109***	***1676***	***1585***	***1523***	***696***

The mechanism of reaction is shown below:



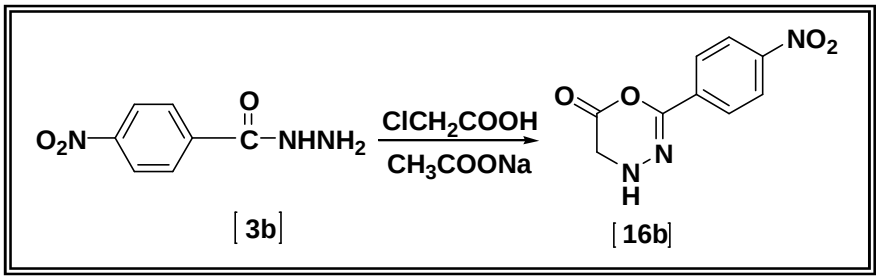




	Yield percentage: 61 %	**Color: Orange**
		Molecular Weight: 298.32g/mol
	M.P. : 212-215 ^{o}C	**Molecular Formula: $C_{14}H_{10}N_4O_2S$**

Figure (3-23): Structure, physical properties and F.T.IR spectrum of 5-(*p*-nitro phenyl)-4-phenyl-1,2,4-triazole-3-thiol [15b].

3.13 Synthesis of 2-(p-nitro phenyl)-4H-oxapyridazin-6-one [16b]:



Scheme (3-13): Reagents and Conditions: $ClCH_2COOH$, CH_3COONa, reflux (4) hrs.

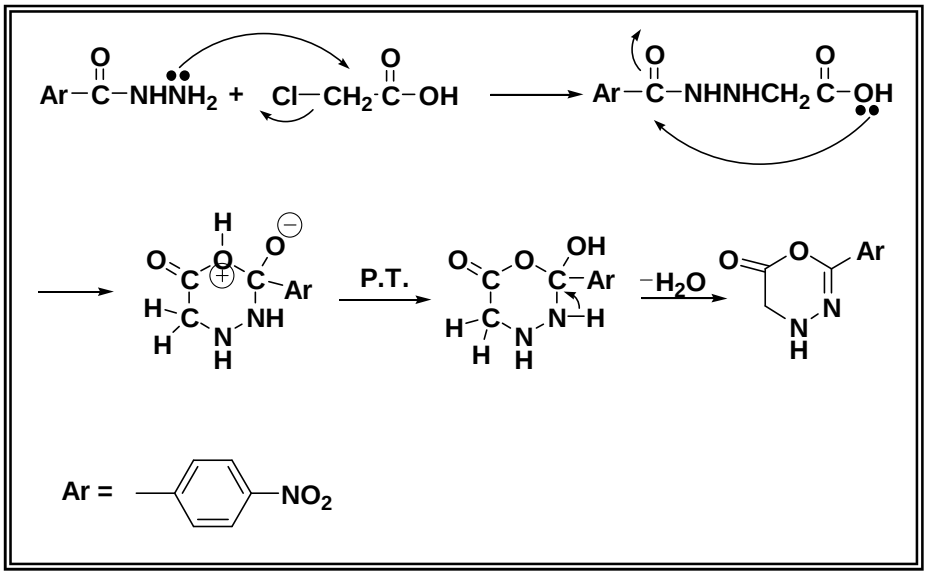
Reacting of acid hydrazide [3b] with chloro acetic acid in presence of sodium acetate and acetic anhydride gave compound [16b].

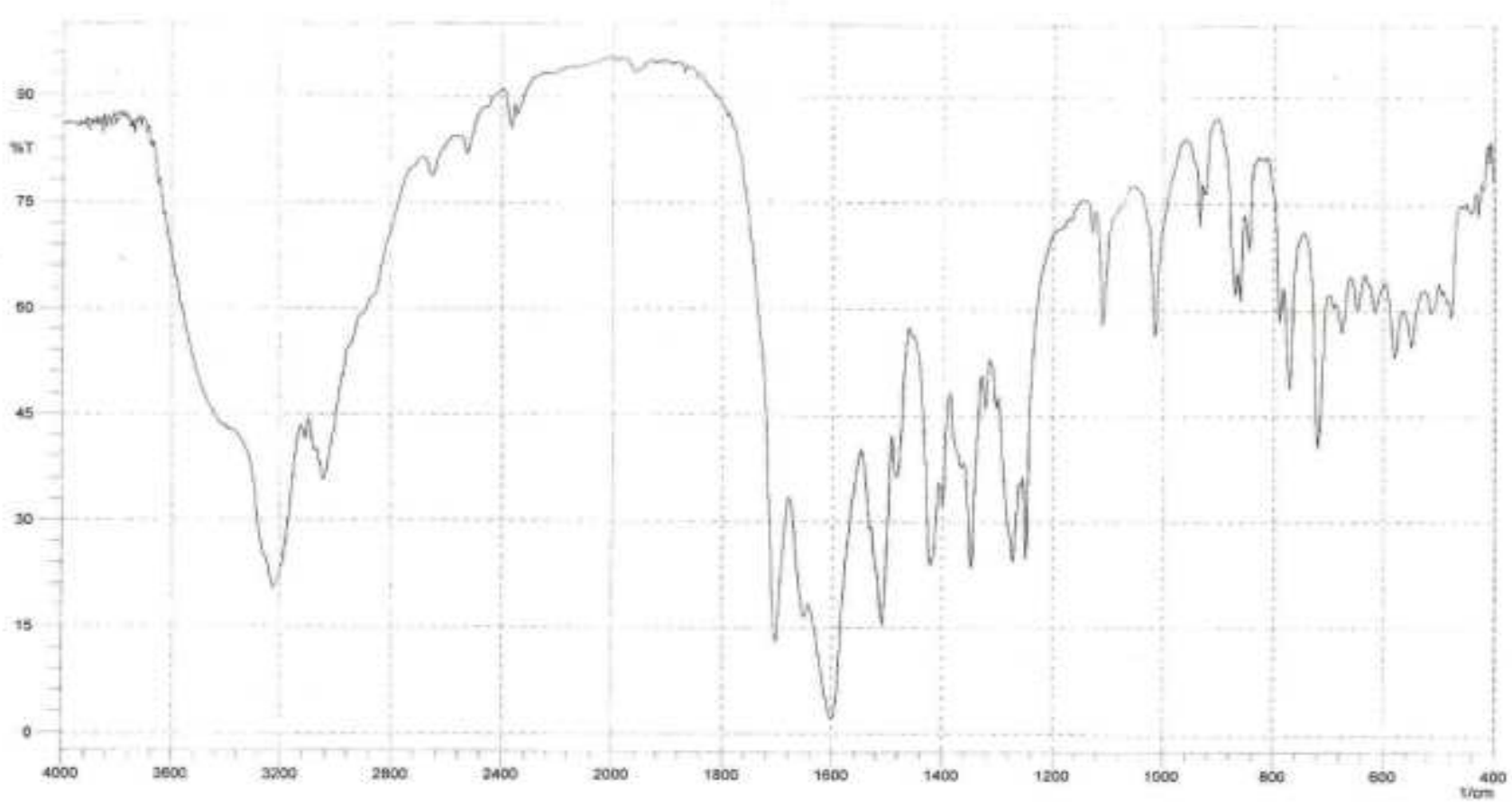
The IR spectrum of the above compound in figure (3-24) show band at (3200) due to N-H group, band at (1700) cm^{-1} due to carbonyl group, C-O-C asymmetric and symmetric bands appear at (1270) cm^{-1} and (1000) cm^{-1} respectively. Table (3-13) shows characteristic bands of compound [16b]. The IR spectrum of compound [16b] is shown in figure (3-24).

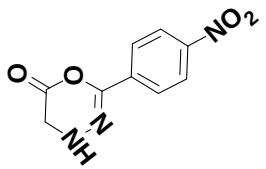
Table (3-13): Characteristic bands of compound [16b]:

Comp. No.	*ν(N-H) cm^{-1}*	*ν(C-H) arom. Cm^{-1}*	*ν(C=O) cm^{-1}*	*ν(C=N) cm^{-1}*	*ν(C-O-C) cm^{-1}*	
16b	*3200*	*3100*	*1700*	*1600*	*Asym.*	*Sym.*
					1270	*1000*

The mechanism of this reaction is shown below:



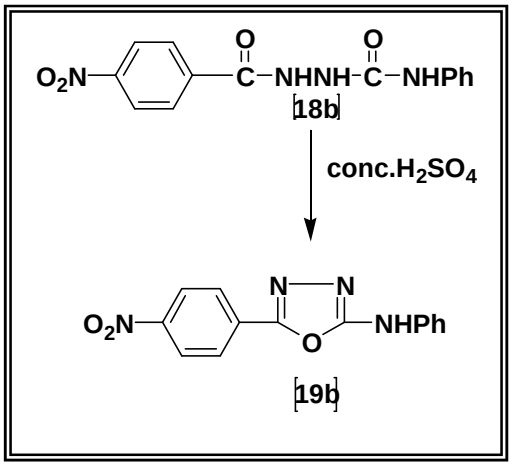




	Yield percentage: 78 %	**Color:White- Gray**
	M.P. : 212-215 ^{o}C	**Molecular Weight: 298.32g/mol**
		Molecular Formula: $C_{14}H_{10}N_4O_2S$

Figure (3-24): Structure, physical properties and IR spectrum of 2-(*p*-nitro phenyl)-4H-oxapyridazin-6-one [16b]

3.14 Synthesis of 2-(phenyl amino)-5-(p-nitro phenyl)-1,3,4-oxadiazole [19b]:



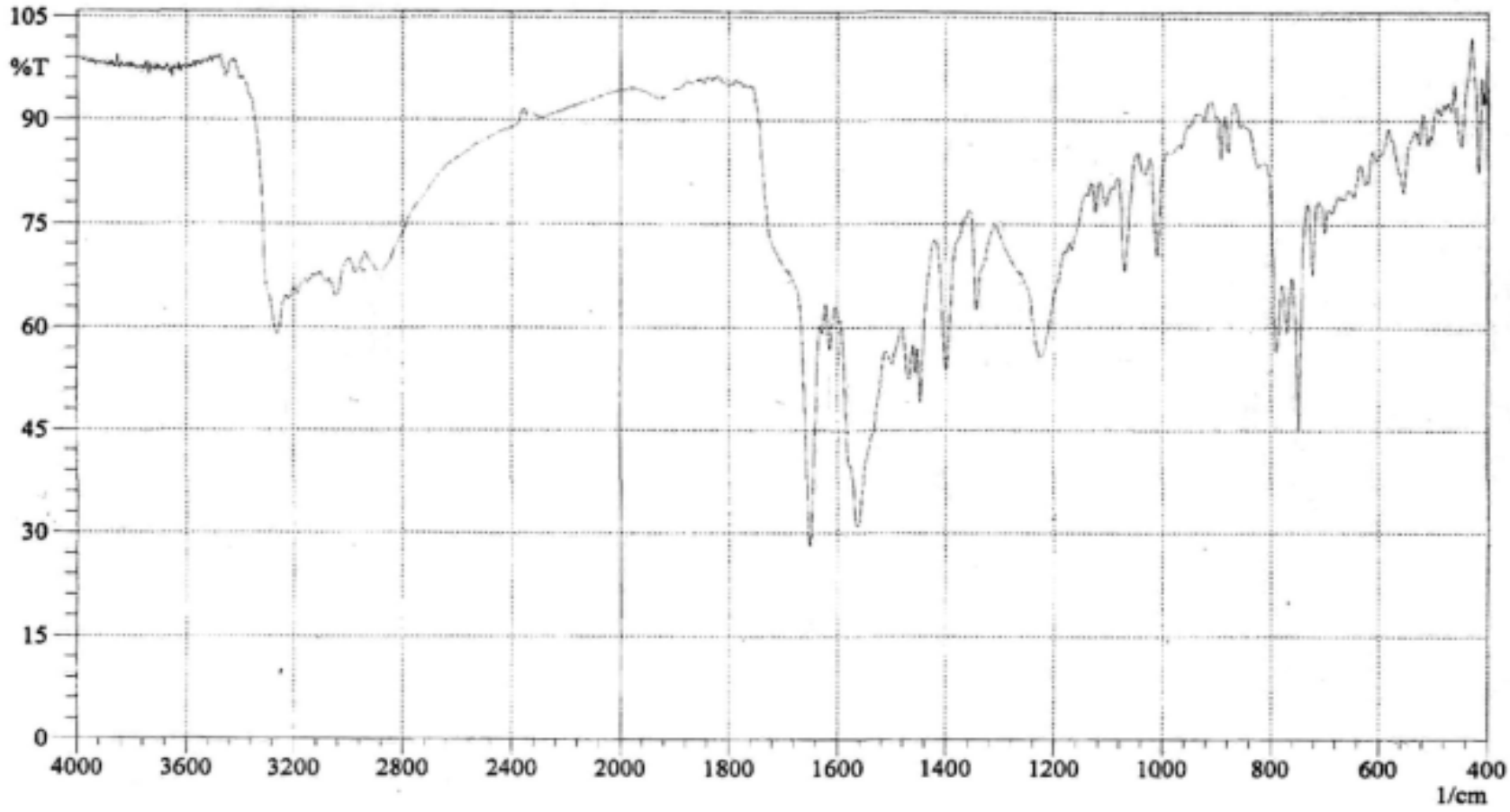
Scheme (3-14): Reagents and Conditions: Conc.H_2SO_4, stirred (3) hrs.

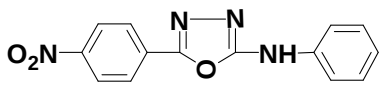
1,3,4-Oxadiazole derivative [19b] was synthesized when semicarbazide derivative was treated with sulfuric acid at (0) ^{0}C It was affected by intermolecular cyclization through the loss of H_2O, which follows the same mechanism of cyclization of thiosemicarbazide with acid which has been described.

The IR spectrum of compound [19b] shows band at (3280) cm^{-1} due to N-H group, appearance of band at (1640) cm^{-1} for C=N, C-O-C asymmetric and symmetric bands appeared at (1210) cm^{-1} and (1000) cm^{-1} respectively. Table (3-14) shows characteristic bands of compound [19b]. The IR spectrum of the above compound is shown in figure (3-25).

Table (3-14): Characteristic bands of compound [19b]:

Comp. No.	*ν(N-H) cm^{-1}*	*ν(C-H) arm. cm^{-1}*	*ν(C=N) cm^{-1}*	*ν(C=C)arm. cm^{-1}*	*ν(C-O-C) cm^{-1}*	
19b	*3280*	*3020*	*1640*	*1570*	*Asym.*	*Sym.*
					1210	*1000*

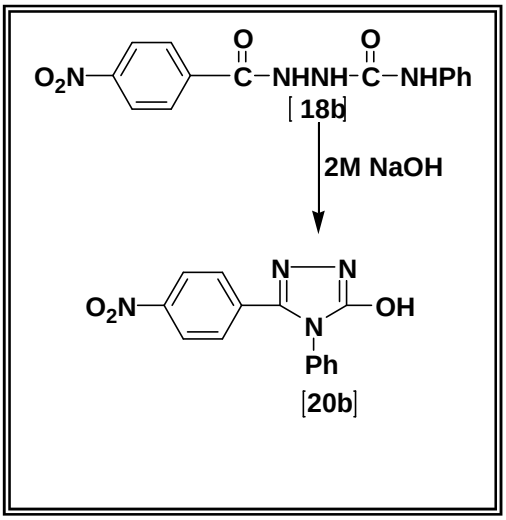




	Yield percentage: 64 %	**Color: yellow**
		Molecular Weight: 282.25 g/mol
	M.P. : 114-116 °C	**Molecular Formula: $C_{14}H_{10}N_4O_3$**

Figure (3-25): Structure, physical properties and IR spectrum of 2-(phenyl amino)-5-(*p*-nitro phenyl)-1,3,4-oxadiazole [19b].

3.15 Synthesis of 3-hydroxy-4-Phenyl-5-(P-nitro Phenyl)-1,2,4-triazole [20b]:



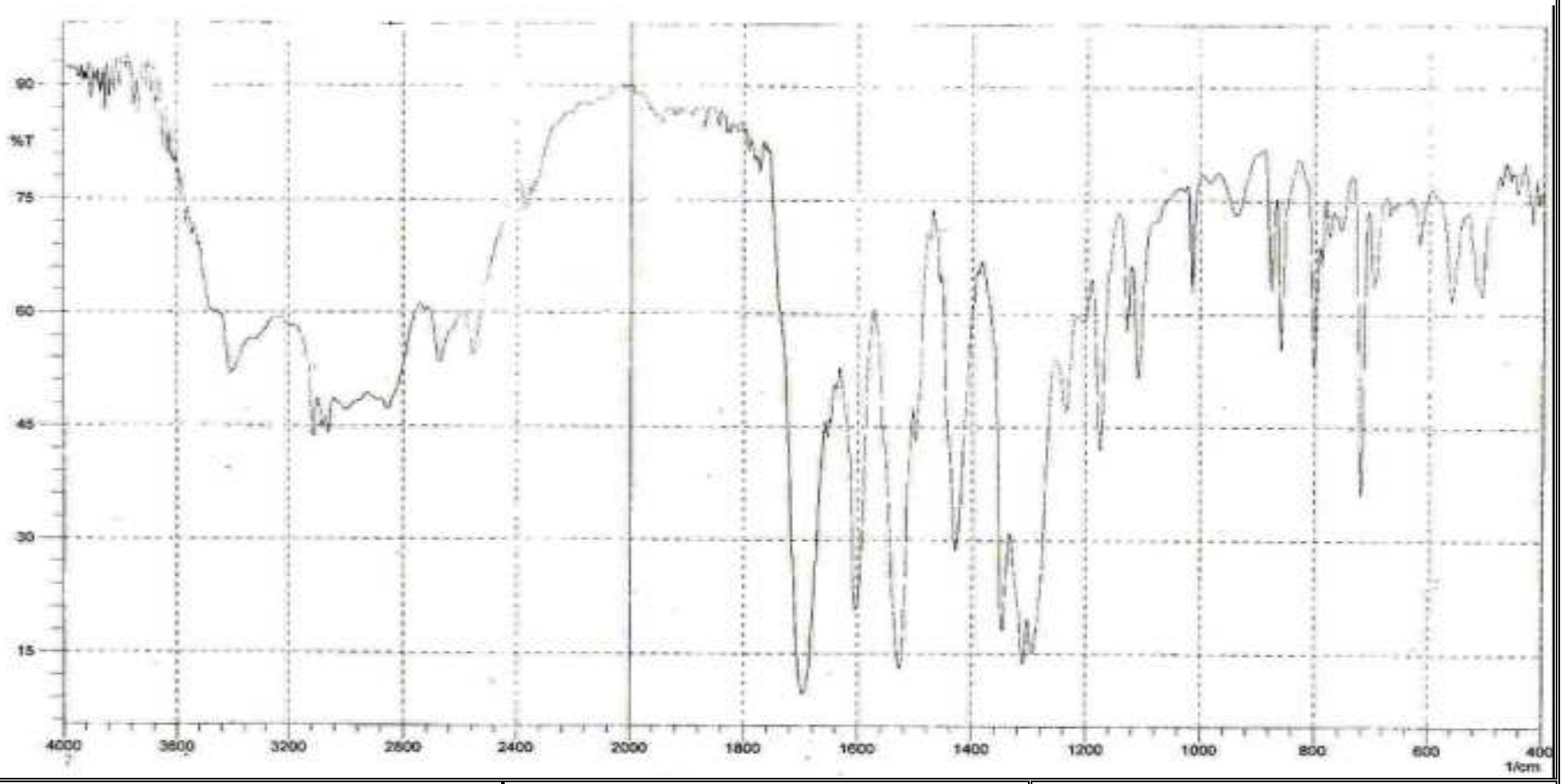
Scheme (3-15): Reagents and Conditions: 2M NaOH, reflux (4) hrs.

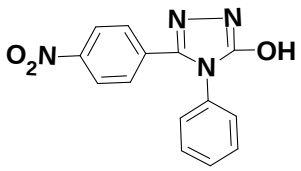
1,2,4-Triazole derivative prepared through the reaction of semicarbazide derivatives with NaOH and reflux for (4) hours effected interamolecular cyclization through the loss of H_2O. Which follow the same mechanism of cyclization of semicarbazide with base which has been described

The IR spectrum show band at (3400) cm^{-1} due to O-H group, N-H band of tautomerism appeared at (3120), band at (1700) cm^{-1} was observed due to C=O group, the C=N band appeared at (1600) cm^{-1}. Table (3-15) shows characteristic bands of compound [20b]. The FTIR spectrum of compound [20b] is shown in figure (3-26).

Table (3-15): Characteristic bands of compound [20b]:

Comp. No.	*ν(O-H) cm^{-1}*	*ν(N-H) cm^{-1}*	*ν(C-H) arm. cm^{-1}*	*ν(C=O) cm^{-1}*	*ν(C=N) cm^{-1}*	*ν(C=C)arm. cm^{-1}*
20b	*3400*	*3120*	*3085, 3070*	*1700*	*1600*	*1530*

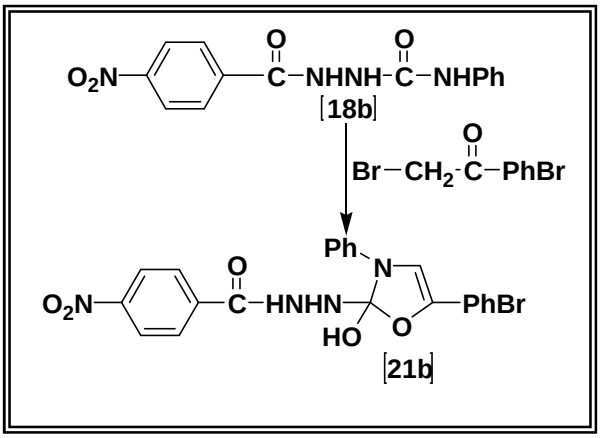




Yield percentage: 75 %	**Color: Orange**
M.P. : 190-193 °C	**Molecular Weight: 282.25 g/mol**
	Molecular Formula: $C_{14}H_{10}N_4O_3$

Figure (3-26): Structure, physical properties and IR spectrum of 2-(phenyl amino)-5-(*p*-nitro phenyl)-1,3,4-oxadiazole [20b].

3.16 Synthesis of 5-(p-bromo phenyl)-2-(p-nitro benzoic hydrazide)-3-N-phenyl-2-(hydroxyl)oxazoline [21b]:



Scheme (3-16): Reagents and Conditions: *p*-bromophenacyl bromide, abs. EtOH, reflux (8) hrs.

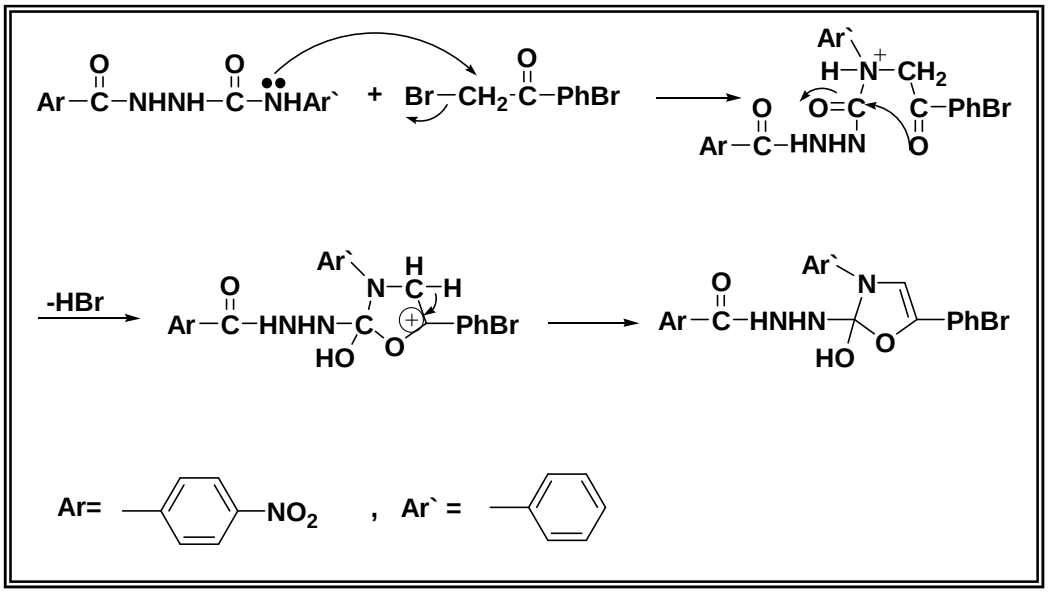
N-subsituted-oxazoline derivative was synthesized through the reaction of semicarbazide [18b] with *p*-bromo phenacyl bromide under refluxing condition affected an intermolecular cyclization through S_N2 mechanism and tetrahedral nuclephilic substitution [(154)].

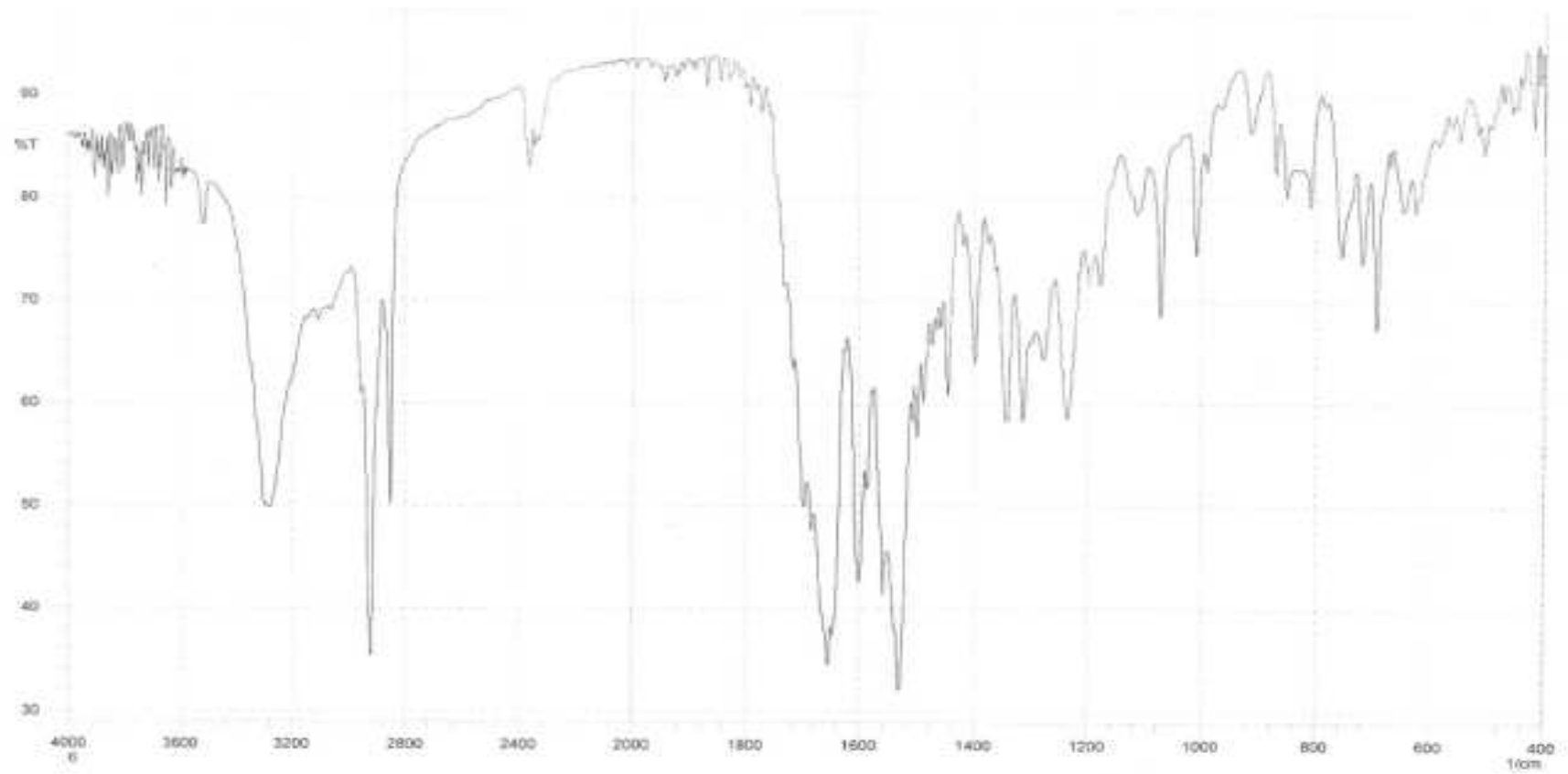
The IR spectrum of show band of O-H group at (3500) cm^{-1}, band of N-H at (3200) cm^{-1}, C=O of amide appeared at (1650) cm^{-1}, C-O-C asymmetric and symmetric bands appeared at (1240) cm^{-1} and (1010) cm^{-1} respectively. Table (3-16) shows characteristic bands of compound [21b]. The IR spectrum of compound [21b] is shown in figure (3-27).

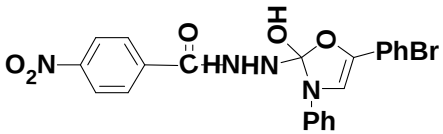
Table (3-16): Characteristic bands of compound [21b]:

Comp. No.	*ν(OH) cm^{-1}*	*ν(-NH) cm^{-1}*	*ν(C-H) arm.cm^{-1}*	*ν(C=O) cm^{-1}*	*ν(C=C)arm. cm^{-1}*
21b	*3500*	*3200*	*3000*	*1650*	*1540*

The mechanism of this reaction is shown below [150]:







	61 %	**Color: Orange**
	M.P. : 145- 147 °C	**Molecular Weight: 497.30 g/mol**
		Molecular Formula: $C_{22}H_{17}BrN_4O_5$

Figure (3-27): Structure, physical properties and IR spectrum of (*p*-bromo phenyl)-2-(p-nitro phenyl hydrazide)-3-N-phenyl-2-(hydroxyl)oxazoline [21b].

Chapter two

Experimental

2.1 Chemicals:

The chemicals used in this work are listed in table (2-1)

Table (2-1)

Chemicals	Supplied from
Absolute ethanol	BDH
Acetic acid	BDH
Ammonium hydroxide	Merck
Acetyl acetone	Merck
Acetic anhydride	Fluka
p-bromo phenacyl bromide	Fluka
Benzene	BDH
Chloro acetic acid	Hopkin and William
Carbon disulfide	Fluka
Ethyl aceto acetate	BDH
Ethyl chloro acetate	BDH
Hydrazine hydrate	Merk
Hydrochloric acid	Merk
Maleic anhydride	Fluka
p-nitro benzoic acid	Merck
Potassium hydroxide	Merk
Phthalic anhydride	Fluka

Chemicals	Supplied from
Phosphorus oxy chloride	Fluka
Phenyl iso thiocyanate	Fluka
Phenyl iso cyanate	Fluka
Sulfuric acid	Fluka
Sodium bicarbonate	BDH
Salicyalaldehyde	Merck
Sodium hydroxide	Fluka
Sodium acetate	Fluka
m-toluic acid	Merck

2.2 Instruments:

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

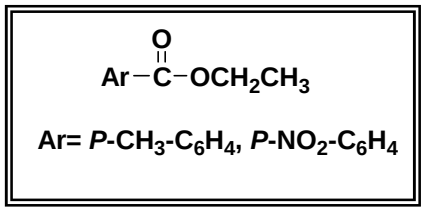
2- Infrared spectra were recorded using Fourier Transform infrared ***SHIMADZU*** (8300) (FTIR) infrared spectrophotometer, Jaban, KBr disc or thin film was performed by Al-Nahrain University.

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

5- The biological activity was performed by Microbiology Department, College of Medicine / Babylon University.

2.3 Methods:

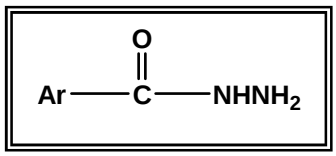
2.3.0 Synthesis of esters [134,135] [2a, 2b]:



For [2a]: treating (0.07 mole, 10g) of *m*-toluic acid [1a] with (60) ml absolute ethanol, (1) ml conc. sulfuric acid and refluxing the mixture for 5 hours, yielded the expected esters [2a] b.p. for 2a (220) lit. (220)^{o}C, yield (82%).

For [2b]: treating (0.126 mole, 21g) of *p*-nitro benzoic acid [1b] with (15) ml absolute ethanol, (2) ml conc. Sulfuric acid and (30) ml of dry benzene, then refluxing the mixture for 16 hours, yields the expected ester [2b], m.p.(54-55) °C lit. (56-58)^{o}C, , yield (71%).

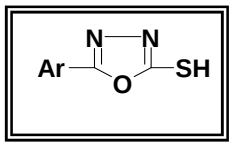
2.3.1 Synthesis of acid hydrazides [136] [3a, 3b]:



Compounds [3a and 3b] were synthesized by the addition of the hydrazine hydrate (0.14 mole, 7 ml), (0.08 mole, 0.4 ml) to (0.009 mole, 15 ml) [2a] and (0.053 mole, 10 g) [2b] in (10, 5) ml of absolute ethanol then the mixture was refluxed for 2 hours. After cooling, the product was

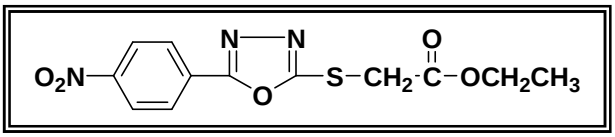
filtered off and recrystallized by using ethanol, m.p. for [3a] (85-87) °C, yield (73%), for [3b] (222-224) °C, yield (76%).

2.3.2 Synthesis of 2-mercapto-5-(subsituted phenyl)-1,3,4-oxadiazole [137] [4a,4b]:



Compounds [4a, 4b] were synthesized from reaction of substituted benzoic hydrazide [3a] (0.001 mole, 0.2g), [3b] (0.003 mole, 0.6 g) with (0.0015 mole, 0.09 ml), (0.0045 mole, 0.27 ml) carbon disulfide and potassium hydroxide (0.001 mole, 0.056 g), (0.003 mole, 0.17 g) respectively which refluxed for 7 hours. Then the solvent was evaporated and the residue was dissolved in water and acidified by diluted hydrochloric acid, the precipitate was filtered, m.p. for [4a] (146-148) °C, yield (83%), for [4b] (230-233) °C, yield (81%).

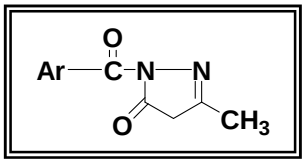
2.3.3 Synthesis of 2-(p-nitro phenyl)-5-thioethylacetate-1,3,4-oxadiazole [135] [5b]:



Ethylchloroacetate (0.0013 mole, 0.137 ml) was added dropwise to a stirred solution of [4b] (0.0013 mole, 0.3 g), KOH (0.0013 mole, 0.073 g) in (7) ml absolute ethanol. The reaction mixture was refluxed for 8 hours,

after that the mixture was filtered and poured on crushed ice. The precipitate was filtered, m.p. (85-87) °C, yield (80%).

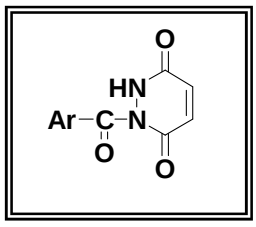
2.3.4 Synthesis of 1-(subsituted benzoyl)-3-methyl pyrazol-5-one [31][6a,6b]:



A mixture of carbohydrazide [3a] (0.003 mole, 0.05 g), [3b] (0.0028 mole, 0.5 g) and ethyl acetoacetate (0.003 mole, 0.42 ml), (0.0028 mole, 0.35 ml) in absolute ethanol was heated under reflux temperature for 5 hours. The reaction mixture was cooled and the formed precipitate was filtered off to give the products, m.p. [6b] (102-104) °C, yield (79%).

.

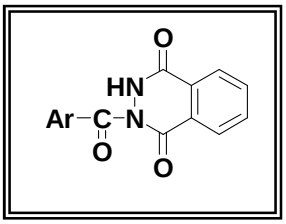
2.3.5 Synthesis of 1-(Aroyl)-1,2-dihydropyridazin-3,6-dione[138] [7a,7b]:



Compounds [3a] (0.003mole, 0.5g) , [3b] (0.0016 mole, 0.3 g) were mixed with maleic anhydride (0.003 mole, 0.33 g), (0.0016 mole, 0.16 g) respectively in acetic acid (30) ml, the mixture was refluxed for 7 hours then cooled and added onto crushed ice. The precipitate was filtered off,

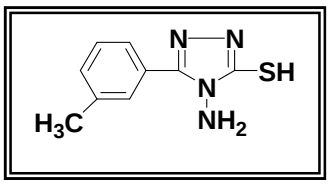
washed with water to give the final products, b.p for [7b] is (79) ^{o}C, yield (72%).

2.3.6 Synthesis of 1-(Aroyl)-1,2-dihydrophthalazin-3,8-dione[138] [8a,8b]:



Compounds 3a (0.003 mole, 0.5g) , 3b (0.0016 mole, 0.3 g) were mixed with phthalic anhydride (0.003 mole, 0.5 g), (0.0016 mole, 0.25g) respectively in acetic acid (30, 35) ml, the mixtures were refluxed for 7 hours then cooled and added to crushed ice. The precipitate was filtered off, washed with water to give the final product, m.p. for [8a] (168-170) °C, yield (75%), for [8b] (260-263) °C, yield (73%).

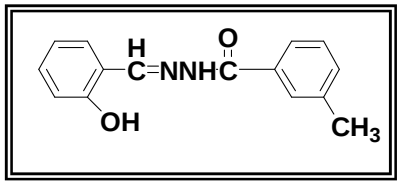
2.3.7 Synthesis of 3-mercapto-4-amino-5-(m-methyl phenyl) -1,2,4-triazole [139] [10a]:



A mixture of *m*-toluic hydrazide [3a] (1g, 0.006 mol), potassium hydroxide (0.0 1mole, 0.56 g) and (0.015 mole, 3 ml) carbon disulfide was dissolved in absolute ethanol and refluxed for 1hour in a water bath. After

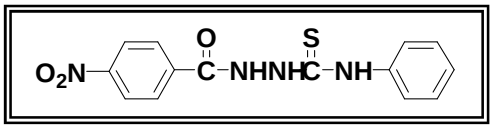
that the excess of ethanol was removed by rotary evaporater. Hydrazine hydrate (0.01mole, 0.5ml) was added to the crude solution and refluxed for 4 hours, cooled and acidification with 20% HCl to produce a white precipitate, m.p. (130-132) °C, yield (84%).

2.3.8 Synthesis of N[-o-hydroxy benzylidine]-(m-tolyl hydrazide)[140] [11a]:



A mixture of hydrazide [3a] (0.005 mole, 1.05 g) with o-salicylaldehyde (0.01 mole, 1.22 g) in absolute ethanol (15) ml and two drops of glacial acetic acid was refluxed for 8 hours. The mixture was cooled to form the precipitate and recrystallized by using ethanol, m.p.(174-176) °C, yield (75%).

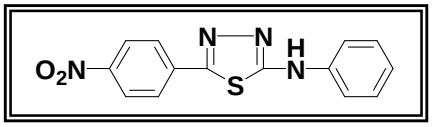
2.3.9 Synthesis of 1-phenyl-4-(p-nitro benzoyl) thiosemicarbazides[141] [12b]:



A mixuter of compound [3b] (0.0028 mole, 0.5 g) and phenyl isothiocyanate (0.003 mole, 0.33 ml) in (15) ml absolute ethanol was refluxed for 7 hours. The solid material obtained on cooling was filtered

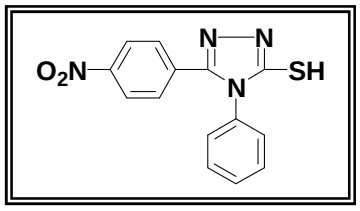
off, and then recrystallized using (ethanol-water), m.p. (160-163) °C, yield (75%).

2.3.10 Synthesis of 2-(phenyl amino)-5-(p-nitro phenyl)1,3,4-thiadiazole [141] [13b]:



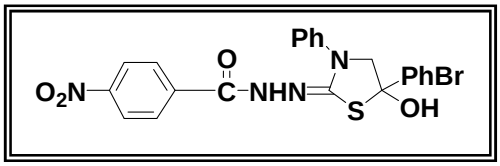
Compound [12b] (0.0006 mole, 0.2 g) was added portionwise to (5) ml of concentrated sulfuric acid at 0°C with continuous stirring. The reaction mixture was stirred further for 3 hours at room temperature and then allowed to stand overnight. Neutralization with dilute sodium bicarbonate prepcipitated acrude solid, which was filtered, and washed with water, m.p. (195-198) °C, yield (63%).

2.3.11 Synthesis of 3-mercapto-4-phenyl-5-(P-Nitro phenyl)-1,2,4-triazole [141] [14b]:



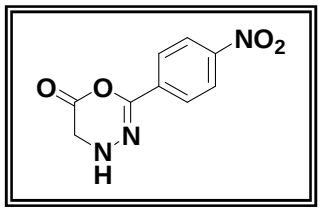
A mixture of compound [12b] (0.0006 mole, 0.2 g) and (15) of 2M sodium hydroxide solution was refluxed with stirring for (4) hours. After cooling, the solution was acidified with hydrochloric acid and the precipitate was filtered, m.p. (212-215) °C, yield (68%).

2.3.12 Synthesis of 4-(p-bromo phenyl)-2-(p-nitro phenyl hydrazide)-1-N-phenyl-4-(hydroxy)thiazolidine [136] [15b]:



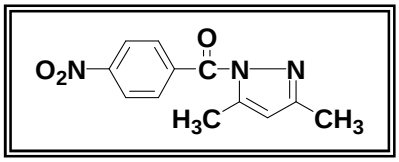
A mixture of compound [12b] (0.0006 mole, 0.2 g) and *P*-bromophenacyl bromide (0.0006 mole, 0.175g) in absolute ethanol (15) ml was refluxed for 8 hours, cooled and neutralized with ammonium hydroxide solution. The precipitate was filtered off, washed with water and dried, m.p. (110-113) °C, yield (65%).

2.3.13 Synthesis of 2-(p-nitrophenyl)-4H-oxapyridazine-6-one [58] [16b]:



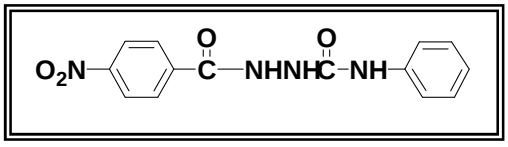
A solution of compound [3b] (0.0027 mole, 0.5 g) and chloroacetic acid (0.0027 mole, 0.26 g) in presence of sodium acetate (0.0027 mole, 0.23 g) and acetic anhydride was refluxed for (4) hours then poured on water, a solid product was obtained, m.p. (120-122) °C, yield (71%).

2.3.14 Synthesis of 1-(p-nitro benzoyl)-3,5-dimethyl pyrazol[31] [17b]:



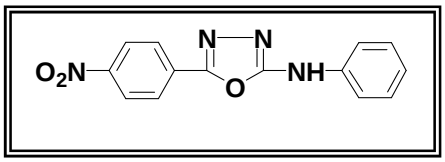
A mixture of carbohydrazide [3b] (0.002 mole, 0.4 g) and acetylaceton (0.002 mole, 0.23 ml) in absolute ethanol (15) ml was heated at reflux temperature for 5 hours. The reaction mixture was cooled and the formed precipitate was filtered off to give the titled compound [17b], m.p. (98-100) °C, yield (65%).

2.3.15 Synthesis of 1-phenyl -4- (p-nitro benzoyl) semicarb-azide[141] [18b]:



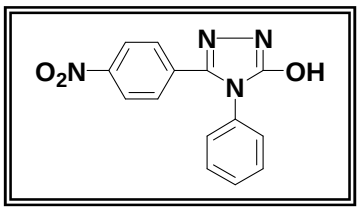
A mixuter of compound [3b] (0.0028 mole, 0.5 g) and phenyl isocyanate (0,003 mole, 0.3 ml) in (15) ml absolute ethanol was refluxed for 7 hours. The solid material obtained on cooling, then filtered off to give final compound, m.p. (218-220) °C, yield (76%).

2.3.16 Synthesis of 2-(phenyl amino)-5-(p-nitro phenyl)1,3,4-oxadiazole[141] [19b]:



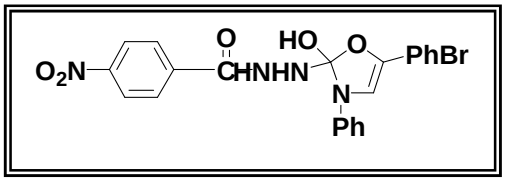
Compound [18b] (0.00067 mole, 0.2 g) was added portionwise to (5) ml of concentrated sulfuric acid at 0°C with continuous stirring. The reaction mixture was stirred for 3 hours at room temperature and then allowed to stand overnight. Neutralization with diluted sodium bicarbonate prepcipitating acrude solide, which was filtered, and washed with water, m.p. (213-215) °C, yield (72%).

2.3.17 Synthesis of 3-hydroxy-4-phenyl-5-P-nitro Phenyl-1,2,4-triazole[141][20b]:



A mixture of compound [18b] (0.0007 mole, 0.2 g) and 2M sodium hydroxide solution was refluxed with stirring for 4 hours. After cooling, the solution was acidified with hydrochloric acid and the precipitate was filtered to give the final product, m.p. (190-193) °C, yield (74%).

2.3.18 Synthesis of 5-(p-bromo phenyl)-2-(p-nitro phenyl hydrazide)-3-N-phenyl-2-(hydroxy)oxazoline [136] [21b]:



A mixture of compound [18b] (0.00067 mole, 0.2 g) and *p*-bromophenacyl bromide (0.00067 mole, 0.19 g) in absolute ethanol (15) ml was refluxed for 8 hours, cooled and neutralized with ammonium hydroxide solution. The precipitate was filtered off, washed with water, and then dried to give the final product, m.p. (145-147) °C, yield (68%).

.

Table (2-1): Physical properties of the synthesized compounds.

Comp. No.	*Molecular formula*	*Molecular Weight (g/mole)*	*Yield (%)*	*M.P (°C)*	*colour*
1a	$C_8H_8O_2$	136.15	-	107-109	White
1b	$C_7H_5N_4O_4$	167,12	-	238-240	Pale yellow
2a	$C_{10}H_{12}O_2$	164.20	82.4	-	Pale yellow
2b	$C_9H_9NO_4$	195.17	71	54-55	Pale yellow
3a	$C_6H_{10}N_2O$	150.18	73	85-87	white
3b	$C_7H_7N_3O_3$	181.15	76	222-224	Pale yellow
4a	$C_9H_8N_2OS$	192.24	83	146-148	Pale yellow
4b	$C_8H_5N_3O_3S$	223.21	81	230-233	Pale yellow
5b	$C_{12}H_{11}N_3O_5S$	309.30	80	85-87	yellow
6a	$C_{12}H_{12}N_2O_2$	216.24	-	-	Oily yellow
6b	$C_{11}H_9N_3O_4$	247.21	79	102-104	yellow
7a	$C_{14}H_{10}N_2O_3$	230.22	-	-	Oily brown
7b	$C_{11}H_7N_3O_5$	261.19	72	-	yellow
8a	$C_{16}H_{12}N_2O_3$	280.28	75	168-170	white
8b	$C_{15}H_9N_3O_5$	311.25	73	260-263	white
10a	$C_9H_{10}N_4S$	268.12	84	130-132	white
11a	$C_{15}H_{14}N_2O_2$	254.28	75	174-176	yellow
12b	$C_{14}H_{12}N_4O_3S$	316.34	75	160-163	yellow
13b	$C_{14}H_{10}N_4O_2S$	298.32	63	195-198	orange-red
14b	$C_{14}H_{10}N_4O_2S$	298.32	68	212-215	orange
15b	$C_{22}H_{19}BrN_4O_4S$	515.38	65	110-113	orange
16b	$C_9H_7N_3O_4$	221.17	71	120-122	White-gray
17b	$C_{12}H_{11}N_3O_3$	245.08	65	98-100	yellow
18b	$C_{14}H_{12}N_4O_4$	300.27	76	218-220	white
19b	$C_{14}H_{10}N_4O_3$	282.25	72	213-215	yellow
20b	$C_{14}H_{10}N_4O_3$	282.25	74	190-193	orange
21b	$C_{22}H_{17}BrN_4O_5$	497.30	68	145-147	orange

Table of Contents

Chapter one: Introduction

Chapter Two: Experimental

Chapter Three: Results and discussion

Chapter Four: Biological activity

List of Tables

List of Figures

الأسم: نور عبد الرزاق عبد اللطيف.

التحصيل الدراسي: ماجستيرعلوم كيمياء.

سنة التخرج: بكالوريوس ٢٠٠٤

الجامعه:جامعة النهرين

المواليد: ١٩٨٣

العنوان : حلة – بابل.

عنوان السكن: محله : ٢١٦ ، الزقاق:١٩، الدار:٥

تاريخ المناقشه : ٢٣-٥-٢٠٠٧

رقم الهاتف: لايوجد

الايميل:no83or@yahoo.com

اسم المشرف:د.ابتسام خلف، د.سوسن حارث

عنوان الاطروحه: تحضير مركبات حلقيه غير متجانسه جديده مشتقه من ميتا-مثيل حامض البنزويك وبارا-نايترو حامض البنزويك، ودراسة الفعاليه البايولوجيه لبعض تلك المركبات.

Examining Committee's Certification

We, the Examining Committee, certify that we read this thesis and have examined the student *Nour abd al-Razzak*, in its contents and that, in our opinion; it is adequate as a thesis for the Degree of Master of Science, in Chemistry.

Chairman

Signature:

Name:

Date:

Member

Signature:
Name:
Date:

Member

Signature:
Name:
Date:

Supervisor

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

Supervisor

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

Approved for the College of Graduate Studies

Signature:

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

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

Date:

References

1. F. A. Carey, "Organic Chemistry", McGraw-hill, Inc. America, **Vol.3,** 453-454 (1996).
2. A. R. Katritzky and J. M. Lagowski, "The Principles of Heterocyclic Chemistry", Beukes, 1967.
3. T. L. Gilchrist, "Heterocyclic Chemistry", Longman, London, 1992.
4. الكيمياء العضويه/ ب-بافالوب وايرنتييف / طبعه ثانيه / مير. موسكو/ ٦٦٥ (١٩٧٥) .
5. K. zamani, K. Faghihi and M. S. Mehranjani, *Pol. J. Pharmacol*, ***55****, 1111-1117 (2003).*
6. G. S. Gadginamath, S. A. Patil, *Ind. J. Chem., **35B**, 1062 (1996).*
7. S. T. Abu-Orabi, *Molecules, **7,** 302 (2002).*
8. V. N. Sonar, S.Parkin and P. A. Crooks, *Acta Cryst. , **C60**, O549 (2004).*
9. N. Verma, B. S.Verma, V. Chawla and O. P. Malilk, *Ind. J. Chem. , **35B**, 688 (1996).*
10. H. V. Ptel, P. S. Fernandes, *Ind. J. Chem. , **29B**, 135 (1990).*
11. G. R. Rania, K.Mogilaiah and Screenivasula, *Ind. J. Chem., **35B**, 339 (1996).*
12. J. Durinda, R. Meedrecky, Ger., **10**, 49 (1965), C. A. 64 (12), 12639 e (1966).
13. G. S. Gadginamath, S. A. Patil, *Ind. J. Chem.*, **35B**, 681 (1996).
14. C. Ainsworth, *J. Am. Chem. Soc., 87, 5800 (1965).*
15. R. C. Elder Field, "Heterocyclic Compounds", C. E. Robert, Editor.7.Wiely, New York (1971).

16. A. O. Maslat, M. Abussaud, H. Tashtoush and M. Al-Talib, *Pol. J. Pharmacol. , **54**, 55-59 (2002).*

17. S. GraBmann, B. Sadek, X. Ligneau, S. Elz, C. R. Ganellin, J. Arrang, J. Schwartz, H. Strak and W. Schunack, *Europran Journal of Pharmaceutical Sciences, **15**, 367-378 (2002).*

18. K. M. Khan, Zia-Ullah, M. Rani, S. Perveen, S. M. Hiader, M. I. Choudhary, Atta-ur-Rahman and W. Voelter, *Letters in Organic Chemistry, **1**, 50-52 (2004).*

19. M. M. Krayushkin, F. M. Stoyannovich, O. Y. Zolotarskaya, E. I. Chernoburova, N. N. Makhova, V. N. Yarovenko, I. V. Zavurzin, A. Y. Martynkin and B. M. Uzhinov, *Chemistry of Heterocyclic Compound, **38**, 2 (2002).*

20. J. P. Joseph and L. Y. Harry, *U. S. Pat. **3**, 141, O22 (1961).*

21. B. Hökfelt, A. Jönsson, *J. Med. Chem. , **5**, 247 (1962).*

22. P. S. Ansel, *U. S. Pat. **2**, 883, 391 (1959*).

23. A. A. Deshmukh, P.B. Sattur and Sheth, *U. K. Indian. J. Exp.Biol., **4**, 166 (1976).*

24. L. Mishra, M. K. Said, H. Itokawa, K. Takeya, *Bio org. Med. Chem., 3 (9), 1241-45 (1995).*

25. H. Singh and Yadav, *L. D. S. Agric. Biol. Chem., **40**, 759 (1976).*

26. T. Misato, K. Ko, Y. Honma, K. Konno and E. Taniyama, *Inst. Phys. Chem. Res., Jap. Pat. 772508 (1977).*

27.I.Chiyomaru, K.Takita, H. Ito and Kumiai, *Chem. Ind. Co. Ltd., Jap*.pat, 7207, 549 (1972).

28. J. Thomas, *Ger. Pat., **2**, 403, 357 (1974).*

29. W. Shi, X. Qian, R. Zhang and G. Song, *J. Agric. Food Chem., **49**, 124-130 (2001).*

30. G. Murineddu, S. Villa, L. Solano, G. Gignarella and G. A. Pinna, *Chem. Pharm. Bull., 50 (6), 754-759 (2002).*

31. A. H. El- masry, *Molecules, **5**, 1429-1438 (2000).*

32. F. Aydogan, Z. Turgut and N. Öcal, *Turk J. Chem, **26**, 159-169 (2002).*

33. R. Iqbal, M. Zareef, S. Ahmed, J. H. Zaidi, M. Arfan, M. Shafique and N. A. Al-Masoudi, *Journal of the Chinese Chemical Society, **53**, 689-696 (2006).*

34. K. Potts, *Chem. Rev., **61**, 87 (1961).*

35. K. Zamani, K. Faghihi, M. R. Sangi and J. Zolgharnein, *Turk. J. Chem, **27**, 300 (1999).*

36. N. Demirbas, A. Demirbas and K. Sancak, *Turk J. Chem., **26**, 801-806 (2002).*

37. M. Caniz, M. Pitucha, M. Dobosz and A. Malm, *Acta Pharma., **54**, 251 (2004).*

38. D. M. Shapiro and M. E. Shils, *Chem. Pharm. Bull., **22**, 2773 (1974).*

39. H. Shailaja. K. Mogilaiah, J. Sudhakar and B. Sreenivasuls, *Indian J. Chem., **3513**, 745 (1996).*

40. J. M. Kane, B. M. Baron, M. W. Dudley, S. M. Sorensen, M. A. Stagear, F. P. Miller, *J. Med. Chem., **33**, 2772-2777 (1990).*

41. İ, Kückgüzel, Ş. G. s. Rollas, G. Ötük-Saiş, O. Özdermir, İ. Bayrak and T. Altuğ, *J. P. I1 Farmaco, **59**, 893-901 (2004).*

42. A. Hazzaa and R. M. Shafik, *J. Pharm. Sci., **19**, 201 (1980).*

43. S. Rollas, N. Kalyoncuglu, D. Sur-Altiner and Y. Yegenoglu, *Pharmazie, **48**, 308-309 (1993).*

44. J. F. Chollet, J. L. Bonnemain, L. Miginiac and O. J. Rohr, *Pestic. Sci. **29**, 427-435 (1990).*

45. A. Murabayashi, M. Masuko, M. Niikawa, Ni Shirane, T. Futura, Y. Hayashi and Y. Makisumi, *J. Pestic. Sci.*, ***16****, 419-427 (1991).*

46. B. E. Gilbert and V. Knight, Antimicrob. Agents Chemother, **30**, 201-205 (1986).

47. B. S. Holla, B. Veerendra, M. K. Shivananda and B. Poojary, *B. Eur. J. Chem.*, ***38****, 759-767 (2003).*

48. G. Turan-Zitouni, M. F. S_1vac_1, S. $K_1l_lç$ and K. Erol, *Eur. J. Med. Chem.*, ***36****, 685-689 (2001).*

49. O. Bekircan, M. Kucuk, B. Kahveci. And S. Kolyl, *Arch. Pharm.*, **338**, *365-372 (2005).*

50. F. Malbec, R. Milcent, P. Vicart and A. M. Bure, *J. Heterocycl. Chem.* ***21****, 1769-1774 (1984).*

51. R. Milcent, P. Vicart and A. M. Bure, *Eur. J. Med. Chim.* ***18****, 215-220 (1983).*

52. N. Gülerman, S. Rollas, M.Kiraz, A. C. Ekinci and A. Vidin, *I1 Farmaco*, ***52****, 691-695 (1997).*

53. A. A. Ikizler, C. B. Johansson, O. Bekircan, and C. Celik, *Acta Polon Pharma-Drug Res.*, ***56****, 283-283 (1999).*

54. Y. Al-Soud, M. A. Al-Dweri, and N. A. Al-Masoudi, *I1, Farmaco*, ***59****, 775 (2004).*

55. M. Clemons, R. E. Coleman, and S. Verma, *Cancer Treat. Rer.*, ***30****, 325-332 (2004).*

56. N. A. Salih, Ph. D. Thesis, College Of science, Al-Nahrain University (2004).

57. E. R. A. Alexander, Principles of Ionic Organic Reactions, U. S. A and U. K., 6 (1960).

58. A. E. F. Eissa, *Olag, Szappan, Kozmetika*, ***4****, 51 (2002).*

59. A. Sener, *Turk J. Chem.*, ***28****, 39-45 (2004).*

60. M. F. Brana, M. Cacho, M. L. Garcia, E. P. Mayoral, B. Lopez, B. D. Pasual-Teresa, A. Ramos, N. Acero, F. llinares, D. Munoz-Mingarro, O-Hozach and L. Meijer, *J. Med. Chem.*, ***48***, *6843-6854 (2005).*

61. M. Campos-Toimil, I. Estevez, E. Ravina, and F. Orallo, *Gen-Pharmac.*, ***30***, *2001 (1998).*

62. M. Khayyal, F. Gross, and V. A. W. Kreye, *J. Pharmac. Exp. Ther.*, *216, 390 (1981).*

63. M. J. Mofna, B. Bardan, M. Campos-Toimil, A. F. Alzueta, *J. Gil-Longo and F.Orallo, Gen. Pharmac.*, ***25***, *156 (1994).*

64. M. R. Horsman, M. Nordsmark, M. Hoyer and J. Overgard, *Br. J. Cancer, 72, 1474 (1995).*

65. A. K. Jewari and A. Mishra, *Bioorganic and Medicinal Chem.*, ***9***, *715 (2001).*

66. O. B. Ostby, L. L.Gundersen, F. Rise and A. Bast, Arch. *Pharma. Med. Chem.*, **334**, 21 (2001).

67. Ehrlic, *Acta. Cryst.*, ***13***, *940 (1960).*

68. V. V. Dabholkar and R. P. Gavande, *J. Serb. Chem. Soc.*, ***68*** *(10), 732 (2003).*

69. V. Kepe, S. Polanc and M. Kocečevar, *Acta Chim. Slov.*, ***45*** *(4), 455-462 (1998).*

70. V. Dinoiu and J. Lü[2], *J. Serb. Chem. Soc.*, ***71*** *(4), 323-330 (2006).*

71. K. M. Dawood, A. M. Farag, and H. A. Abdel-Aziz, *Journal of the Chinese chemical society*, ***53***, *873-880 (2006).*

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

73. V. Kepe, F. Požgan, A. Galobič, S. Polanc, and M. Kočevar, *J. chem.. Soc., Perkin Trans. 1, 2813 (1998).*

74. P. Cankar, I. Wiederm annova an J. Slouka, *Acta Univ. Palacki-Olomuc fac. Rer. Nat. Chemica, **41**, 7 (2002).*

75. J. Elguero, Comprehensive Heterocyclic Chemistry, ed. A. R. Katritzky and C. W. Rees, *Pergamon Press, Oxford, **Vol. 5**, P. 291 (1984).*

76. P. Rzepecki, M Wehner, O. Molt, R. Zadmard, K. Harms, and T. Schrader, *Synthesis, 12, 1815 (2003).*

77. Smith, M. S. T. Gon Glves, and L. M. Rodrigues, "pharmacological Analysis of Cyclo-Oxygenase-1 in Inflammation:, Proc. Natl. Acad. Sci. use A Pharmacology, 95, 13313-13318 (1998).

78. W. E. Wick, D. A. Preston, N. H. Terando, J. S. Welles, and R. S. Gordee, *Antimicrobial Agenat and Chemotherapy, **Vol. 4**, No. 3, P. 343-345 (1973).*

79. A. E. Rashad, A. H. Shamroukh, M. I. Hegab and H. M. Awad, *Acta Chim. Solv., **52**, 429-434 (2005).*

80. Z. Tabarelli, M. A. Rubin, D. M. Berlese, P. D. Sauzem, T. P. Missio, M. V. Teixeira, A. P. Sinhorin, M. A. P. Martins, N. Zanatta, H. G. Bonacorso and C. F. Mello, *Brazillian Journal of Medical and Biological Recearch, **37**, 1531-1540 (2004).*

81. H. G. Sangani, K. B. Bhimani, R. C. Khunt and A. R .Parikh, *J. Sebin. Chem. Soc., **71 (6)**, 587-591 (2006).*

82. J. Sand storm, "Advanced in Heterocyclic Chemistry", C. A. R. Katrizky and A.Bouttan, *Ed J.* **Vol. 9**, Academic Press. Inc. New York, P. 165 (1996).

83. B. Bak, L. Nygaard, E. J. Pederson and J. R. Anderson, *J. Mol. Spectr. **19**, 283 (1966).*

84. L. Zhang, A.Zhang, X. Chen, X. Lei, X. Nan, D. Chen and Z. Zhang, *Molecules, **7**, 681-689 (2002).*

85. K. Zamani, K. Faghihi, T. Tofighi, M. R. Shariatzdeh, *Turk J. Chem.*, ***28****, 95-100 (2004).*

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

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

88. R. K. Mishra and R. K. Tewari, *J. Indian Chem. Soc.* ***68****,110 (1991).*

89. A. Tasaka, N. Tamura, R. Hatashi and K. Itoh, *Chemical and Pharmacentical Bulletin* ***41****, 1035 (1993).*

90. N. A. Abdon and F. M. Amin, *Mansoura J. Pharma. Sci*. **6**, 25 (1990).

91. M. H. Khal and H. Nizamuddin, *Indian J. Chem.*, ***36 B****, 625 (1997).*

92. L. BONINA, G. ORALESI, R. MERENDINO, A. ARENA and P. MASTROENI, Antimicrobial Agents and Chemotherapy, **Vol. 22**, No. 6, P. 1067-1069 Des. (1982).

93. Z. Y. Zhang, M. Li, L. Zhao, Z. M. Li and R. A. Liao, Synthesis of 3-Alkyl / Aryl-6-(3-pyridyl)-s-triazolo [3,4-b]-1,3,4-thiadiazoles. *Chin. J. Org. Chem.*, ***13****, 397-402 (1993).*

94. R. Gupta, S. Sudan, V. Mengi and P. L. Kachroo, *Indian J. Chem.*, *Sect. B,* ***35****, 621-623 (1996).*

95. M.Uher and D. Berkš, *Chem.* ***53 (3)****, 215-217 (1999).*

96. K. Zamani, K. Faghihi and M. S. Mehranjani, *Pol. J. Pharmacol,* ***55****, 111-1117 (2003).*

97. E. Fernanes-Ferreira, C. Mapheu-Nogueira, R. O. A. Soares, D. Gibaldi, C. M. Stutz, E. F. Da Silva, R. C. Fernandes. E. L. S. Lima and M. Bozza, Mem Inst Oswaldo Cruz, Riode Janeiro, **Vol. 94**, Suppl. Il, Nov. 1999.

98. H. Chen. Z. Li and Y. Han, *J. Agric. Food Chem.*, ***48****, 5312 (2000).*

99. N. A. M. M. Shmess, M. M. F. Ismail, A. M. Soliman and H. I. El-Diwani, *Molecules*, ***5****, 1101-1112 (2000).*

100. M. Dzurilla, P. Kutscky, J. Zaletova, M. Ruzinsky and V. Kovacik, *Molecules, **6**, 716-720 (2001).*

101. V. J. Sattigeri, A. Soni, S. Singhal, S. Khan, M. Pandya, P. Bhateja, T. Mathur, A. Rattan, *ARKIVOC, **II**, 46-59 (2005).*

102. M. C. Ünlüsoy, O. B. Dünadar, N. ALTanlar and R. Ertan, *Turk J. Chem, **30**, 355-360 (2006).*

103. M. C. A. Delima, D. L. B. Costa, A. J. S. Goes, S. L. Galdino, I. R. Pitta and C. Luu-Duc, *Pharmazie, **47**, 182-184 (1992).*

104. M. Strumvoll and H. U. Haring, *Ann. Med., **34**, 217-222 (2002).*

105. O. Bozdağ-Dündar, E. J. Verspohl, A. Waheed and R. Ertan, Arzeim-Forsch / Drug Res. / **53**, 831-836 (2003).

106. A. Andreani, M. Rambaldi, A. Locatelli, R. Leoni, M. Bossa, I. Chiericozzi, G. Galatulas and A. Salvatore, *Eur. J. Med. Chem., **28**, 825-829 (1993).*

107. S. A. H. El-Feky, *Pharmazie, **48**, 894-896 (1993).*

108. P. C. Unangst, D. T. Connor, W. A. Cetenko, R. J. Sorenson, J. C. Sircar, C. D. Wright, D. J. Schrier and R. D. Dyer, *Bioorg. Med. Chem Lett. **3**, 193-197 (1983).*

109. W. J. Doran, H. A. Shonle, Dialkyl thiazolidinones, *J. Org. Chem. **3**, 193-197 (1938).*

110. R. Misra, R. Chakrabarti, R. K. Vikramadtthyan, G. Bolusu, S. Juluri, J. Hiryan, C. Gershome, A. Rajjak, P. Kashireddy, S. Yu and S. Surapureddi, *The Journal of Pharmacology and Experimantal Therapeutics, **Vol. 306**, No. 2, 49791 / 1080762 (2003).*

111. R. Lakhan, O. P. Singh, Potential fungiacides part III. Synthesis and evaluation of 5-methyl-thiazolidin-4-ones and 5-methyl-2-thiazolidin-4-ones. *J. Ind. Chem.* Soc. **61**, 784- 787 (1984).

112. P. N. Bhargava, S. Prakash, R. Lakhan, Synthesis of 2-(4`,5`-disubsituted thiazol-2`-ylimino)-3-(m-methyl phenyl)-5-methyl(or H)-thiazolidin-4-ones and their fungicidal activity. *Ind. J. Chem.*, ***20 B****, 927-929.*

113. R. Lakhan, Potenttial fungicides studies of 2-arylimino-3-aryl-thiazolidin-4-ones, their 1,1-dioxides and 5-phenyl azo derivatives. *Agric. Biol. Chem.* ***46****, 557- 560 (1982).*

114. H. Liu, Z. Li and T. Anthonsen, *Molecules*, ***5****, 1055- 1061 (2000).*

115. B. O. Kasimogullari and Z. Cesur, *Molecules* , ***9****, 894- 901 (2004).*

116. A. GÜRSOY, N.TERZIOĞLU, *Turk J. Chem*, ***29****, 247- 254 (2005).*

117. T. Srivastava, A. K. Gaikwad, W. Haq, S. Sinha and S. B. Katti, *ARIVOC*, ***ii****, 120-130 (2005).*

118. W. Tang, W. Wang and X.Zhang, Angew. *Chem. Int. Ed*. **42**, No. 8 (2003).

119. B. Fu, D. Du and J. Wang, *Tetrahedron: Asymmetry*, ***15****, 119- 126 (2004).*

120. A. Lee, W. Kim, J.Lee, T. Hyeon and B. M. kim, *Tetrahedron: Asymmetry*, ***15****, 2595- 2598 (2004).*

121. D. Liu, Q. Dai and X. Zhang, *Tetrahedron*, ***61****, 6460- 6471 (2005).*

122. A. K. Ghosh, P. Mathivanan, Gappiello, *J. Tetrahedron: Asymmetry*, ***9****, 1 (1998).*

123. J. S. Johnson and D. A. Evans, *Acc, Chem. Res.*, ***33****, 325 (2000).*

124. T. H.Chan and G. Z. Zheng, *Can. J. Chem.*, ***75****, 629 (1997).*

125. T.J. Zhu, B. T. Zhao, W. M. Dai, *J*. Zhau and X. J. Hao, *Tetrahedron: Asymmetry* ***9****, 2879 (1998).*

126. R. Shintani and G. C. Fu, *Org. lett.*, ***4****, 3699 (2002).*

127. J. V. Allen, C. G. Frost and J. M. Williams, *J. Tetrahedron*: *Asymmetry*, ***4****, 649 (1993).*

128. W. P. Deng, X. L. Hou and L. X. Dai, ***J. Tetrahedron: Asymmetry, 10****, 4689 (1999).*

129. W. B. Zhang, H. Yoshinga, Y. Imai, Tida and Y. Nakatsuji, I. *Synlett. **10**, 1512 (2000).*

130. Y. Imai, S. Matsuo, W. B. Zhang, Y. Nakatsuji and Ikeda, *I. Synlett., **2**, 239 (2000).*

131. C. Bolm, K. Muniz-Fernandez, A. Seger, G. Raabe and J. Gunther, *J. Org. Chem. **63**, 7860 (1998).*

132. C. Bolm, K. Muniz-Fernandez and J. P. Hildebrand, *Org. Lett., **1**, 491 (1998).*

133. I. M. Pastor and H. Adolfsson, *Tetrahedron Lett., **43**, 1743 (2002).*

134. A. I. Volgel, "Practical Organic Chemistry", **3**, (1945).

135. E. S. El- Tamaty, M. E. Abdel- Fattah and I. M. El- Deen, Indian *J. Chem., **35 B**, 1067 (1996).*

136. F. Axdogan, Z. Turgut and Nüketöcal, *Turk. J. Chem., **26**, 159 (2002).*

137. A. I. Vogel, "Text Book of Practical Organic Chemistry", 3rd Ed., Longman Group Ltd., London (1974).

138. G. E. Wieg and V. J. Bauer, *J. Med. Chem. **12**, 943 (1969).*

139. Z. Shunxue, Z. Anxiong, C. L. Q. Bin and D. Hengshan, *Molecules, **6**, No. 12, P. 92 (2003).*

140. S. A. Nassar and M. A. El- Hashsash, *Egypt J. Chem., **40**, No. 3, 239 (1997).*

141. K. Funabika, N. Noma, G. Kuzuga and K. Shibata, *J. Chem., Recerch, **5**, 300 (1999).*

142. J. Anderson and Dovid, C. A., **Vol. 112**, 178982r (1990).

143. R. W. Young and K. H. Wood, *J. Am. Chem. Soc., **77**, 400 (1973).*

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

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

146. R. W. Young and K. H. Wood, *J. Am. Chem. Soc., **77**, 400 (1955).*

147. F. Hoggarth, *J. Chem. Soc., 4811 (1952).*

148. P. W. Hickomott, *J. Tetrahedron, **38**, 1975 (1982).*

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

150. R. M. Sliverstien and X. Webster, "Spectrometric Identification of Organic Compounds", John-Wiely and Sons, Inc. New Yourk, 6 th Ed., **108** (1998).

151. J. G. Collee, A. G. Fraser, B. P. Marmian and S. A. Simmon, , "Practical Medical Microbiology", Mackin and Mccartney 14th Ed., 151, (1996).

152. H. P. Rang, M. M. Dale and J. M. Ritter, "Pharmacology", 4th Ed., 648, (1999).

153. Eisenstein BI, Azaleznik DF: Enterobacteriaceae. In: Mandell, Douglas, and Bennetts Principles and Practice of infectious Diseases, Meandell GL, Bennett JE, Dolin R (editors). Churchill Livingstone, 5th ed., 369-370, (2000).

154. J. K. G. Dart and D. V. Seal, *Eye **2**, 46-55 (1988).*

155. D. A. B. Dance , *Clinical Microbiology Reviews, **4**,52-60, (1991).*

156. F. D. Lowy, *N Engl J Med, **339**, 520, (1998).*

157. A. R. McLure, *Journal of hospital infection **21**, 291-299 (1992).*

158. B. R. Lyon and R. Skurray, *Microbiological Reviews **51**, 88-134 (1987).*

159. J. F. Richardson and A. H. M. Quoraishi, *Journal of Hospital Infection* ***16****, 109-121 (1990).*

160. F. J. Baker, M. R. Breach, I. Leighton and P. Taylor, "Medical microbiological techniques", Butterworth, London, p 495, (1980).

161. J. F. Macfaddin, "Biochemical test for the identification of medical bacteria", William and Wilkins. Baltimor. USA, 3rd Ed., 175, (2000).

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

Synthesis of New Heterocyclic Compounds derived from m-methyl benzoic acid and P-nitro benzoic acid and study of Biological activity for some of these compounds.

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
Nour Abd Al-Razzak
(B.Sc 2004)AL-Nahrain University

April 2007 Rabye Al-Awal 1428

Summary

This work involves synthesis of different five and six member heterocyclic rings starting from acid hydrazides (*m*-methyl benzoyl hydrazide and *p*-nitro benzoyl hydrazide) which were synthesized from their carboxylic acids.

This work is divided into four different parts:

First part:

This part involved the synthesis of phthalazin-3,8-dione [8a,8b] and pyridazin-3,6-dione [7a,7b], pyrazole [6a,6b] and 1,3,4-oxadiazole [4a,4b,5b] derivatives from acid hydrazides [3a, 3b], as shown in scheme I.

Second part:

This part involved the synthesis of 1,2,4-triazole [10a] and Schiff bases [11a] derivatives derived from *m*-methyl benzoyl hydrazide [3a], as shown in scheme II.

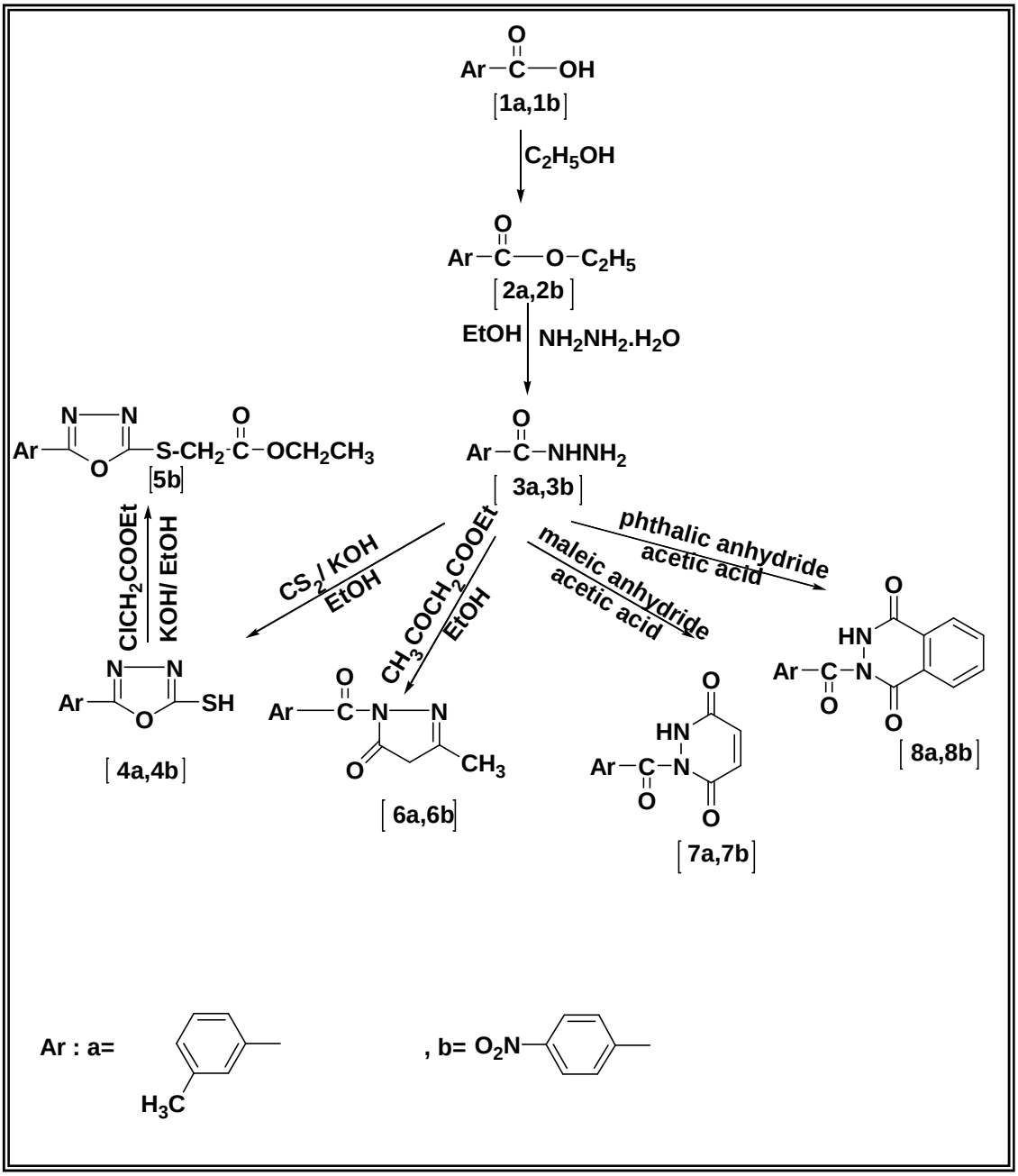
Third part:

This part involved the synthesis of thiosemicarbazide [12b], semicarbazide [18b], 1,2,4-Triazole [14b,20b], 1,3,4-Oxadiazole [19b], 1,3,4-thiadiazole [13b], Thiazolidine [15b], Pyrazole [17b], N-substituted-Δ^4-Oxazoline [21b] and Oxapyridazine-6-one [16b] derivatives from *p*-nitro benzoyl hydrazide [3b], as shown in scheme III.

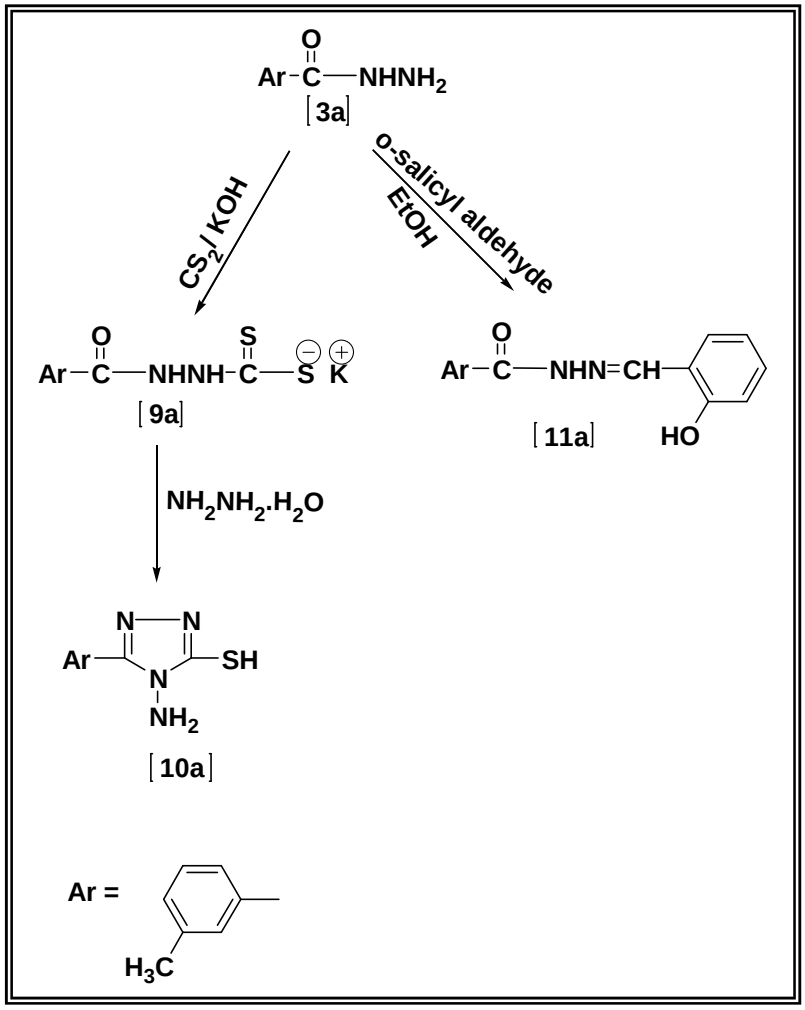
Fourth part:

This part deals with the study of antibacterial activities of some of the synthesized compounds. These activities were determined in vitro using disc diffusion method against four pathogenic strains of bacteria

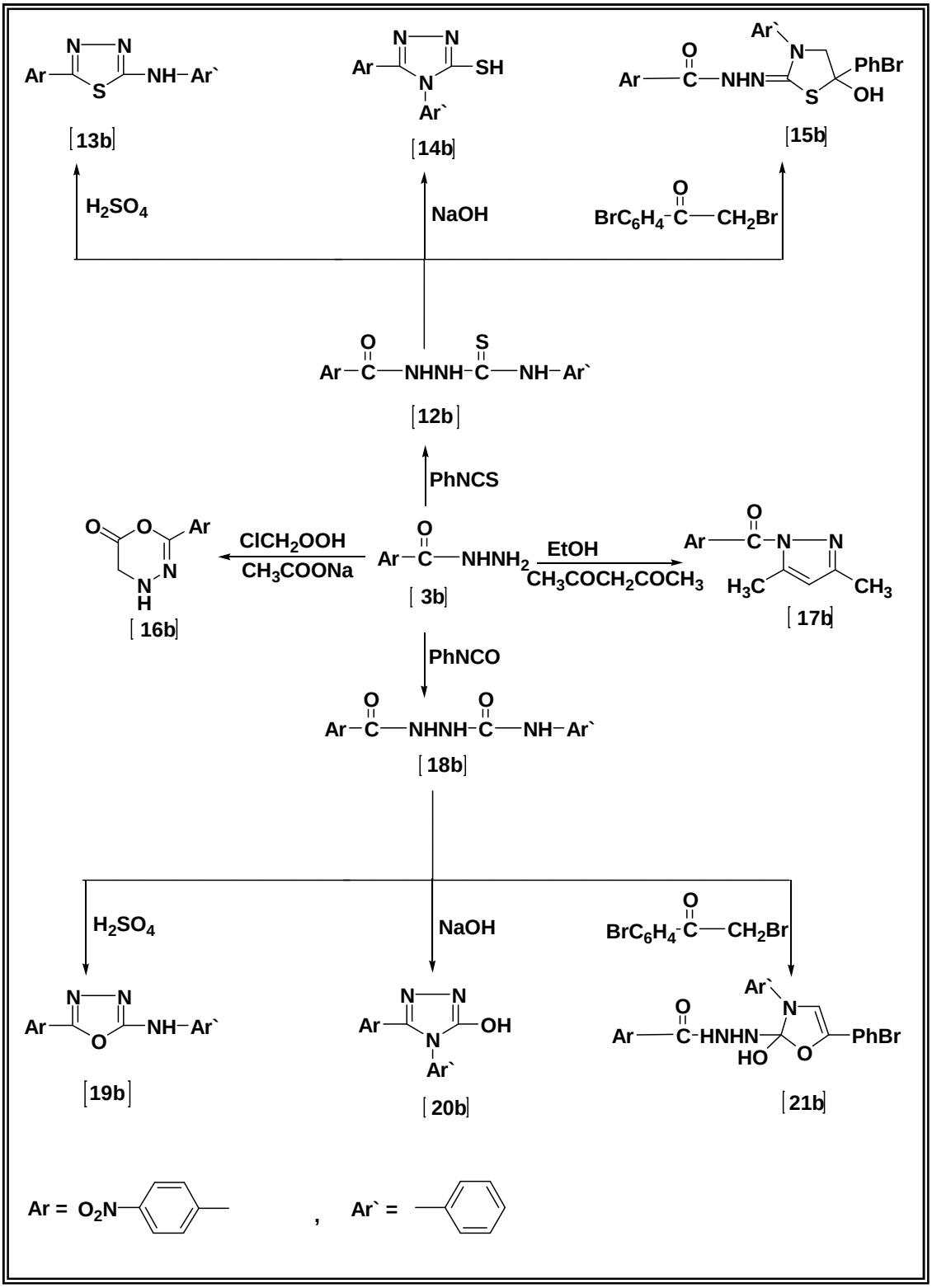
{***Pseudomonas aeuroginosa, Klebsiella pneumoniae, Staphylococcus aureus and Bacillus subtilus***}, as shown in table (4-1).



Scheme (I)


Ar–C(=O)–NHNH2
[3a]
CS2/ KOH
o-salicyl aldehyde
EtOH
Ar–C(=O)–NHNH–C(=S)–S⊖ K⊕
[9a]
Ar–C(=O)–NHN=CH
HO
[11a]
NH2NH2.H2O
Ar
SH
N
NH2
[10a]
Ar =
H3C

Scheme (II)


[13b]
[14b]
[15b]
H2SO4
NaOH
BrC6H4-C(=O)-CH2Br
[12b]
PhNCS
[16b]
ClCH2OOH
CH3COONa
[3b]
EtOH
CH3COCH2COCH3
[17b]
PhNCO
[18b]
[19b]
[20b]
[21b]
Ar = O2N
, Ar` =

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:

Date:

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

Signature:

Name: Assist. Prof. Dr. Afaf Al-Derzi

Head of Chemistry Department

College of Science

Al-Nahrain University

الإهداء

إلى نور الهدى... ومقلة العيون

الحبيب المصطفى (ρ)
إلى الشفاه التي أكثرت لنا
الدعاء كلما نطقت

أمي
إلى معلمي الأول وقدوتي في الحياة

أبي
إلى من أشد بهم أزري في الحياة

أختي وأخوتي
إلى من رفد مسيرتي بالصبر

زوجي
إلى رفاقي في كل دروب العلم
المتباينة

زملائي

الـخلاصة

يتضمن موضوع البحث تحضير مركبات حلقيه خماسيه وسداسيه غير متجانسة متنوعة ابتداء من هايدرازايد الحامض (ميتا- مثيل بنزويل هايدرازايد و بارا-نايترو بنزويل هايدرازايد) والتي حضرت باستعمال حوامضها الكاربوكسيليه المقابله لها.

لقد تم تقسيم هذا العمل على أربعة أجزاء:

الجزء الأول:

يتضمن هذا الجزء تحضير مركبات الفثالازين-٨،٣-دايون، البريدازين-٦،٣- دايون، بايرازول و ٤،٣،١-اوكادايزول المشتقه من هايدرازايد الحامض [3a,3b]، كما موضح بالمخطط I.

الجزء الثاني:

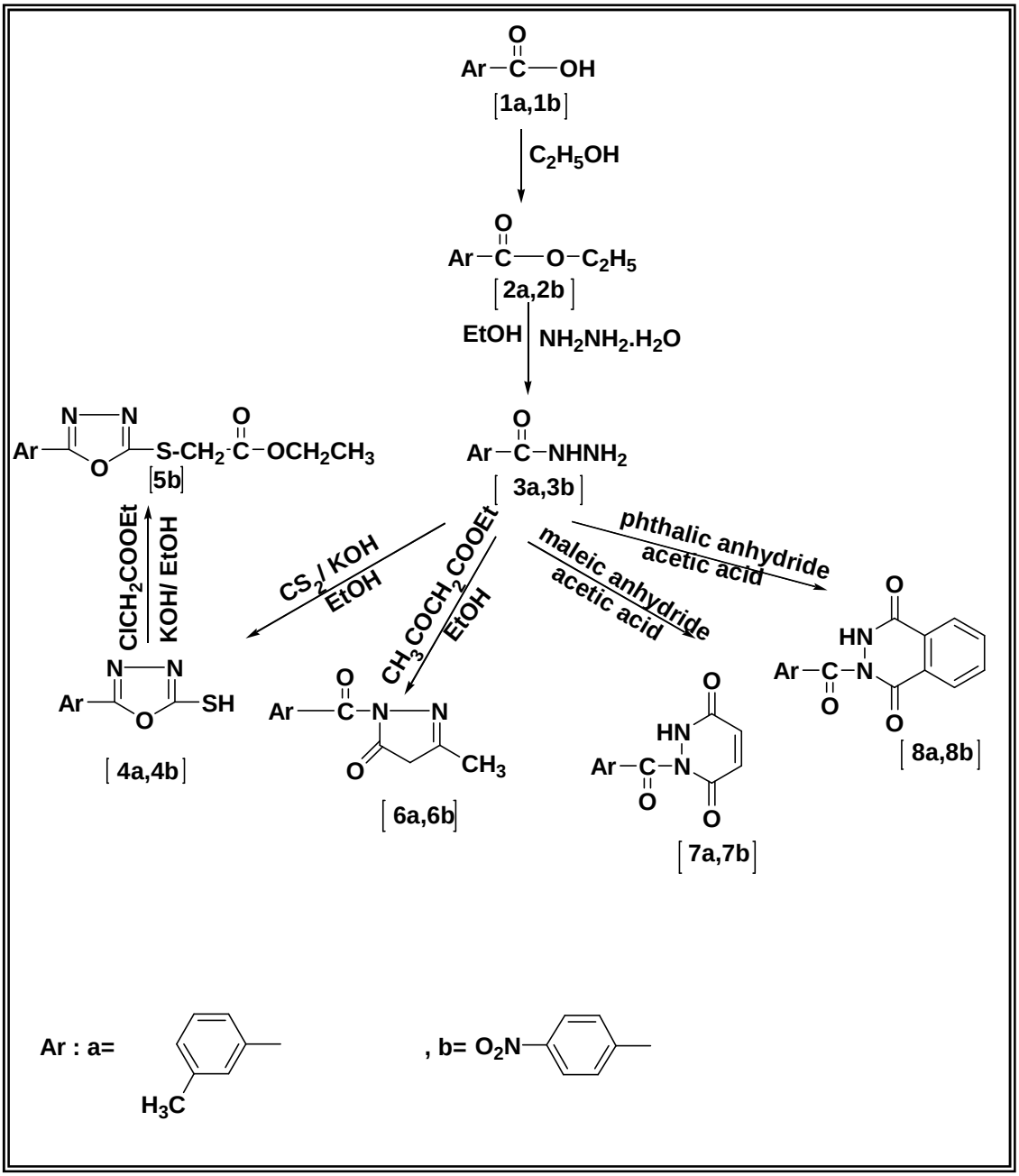
يتضمن هذا الجزء تحضير ٤،٢،١-ترايازول وقواعد شيف المشتقه من ميتا-مثيل بنزويل هايدرازايد [3a]، كما موضح بالمخطط II.

الجزء الثالث:

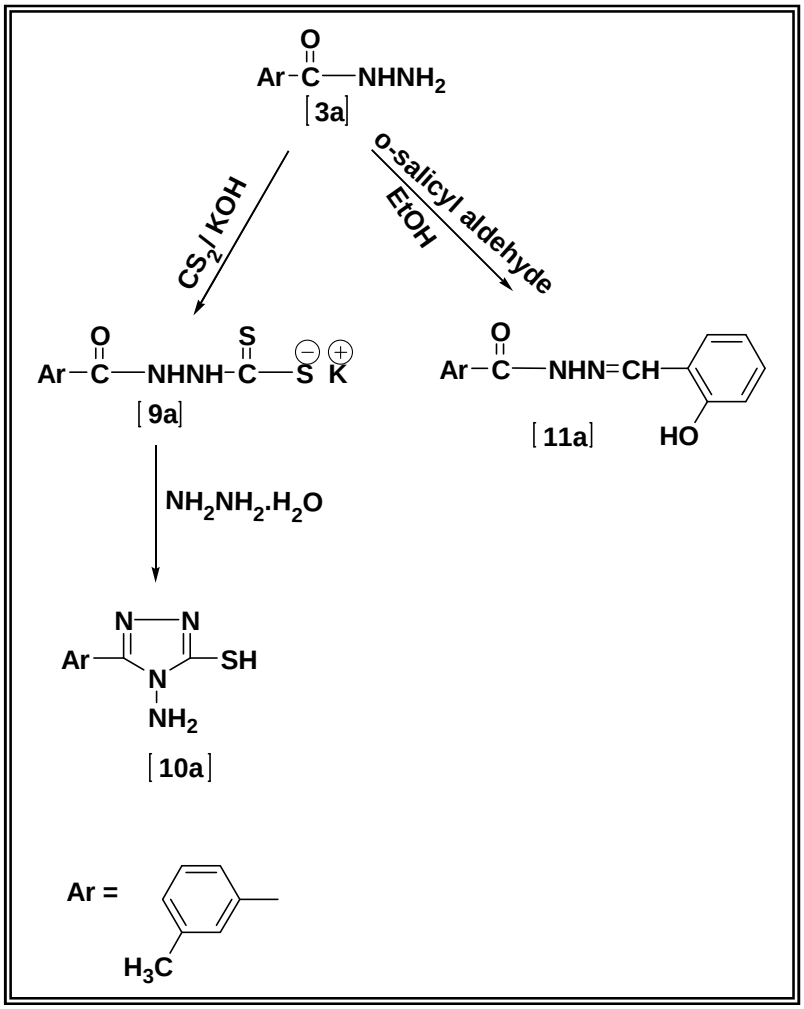
يتضمن هذا الجزء تحضيرثايوسيميكاربزايد، سيميكاربزايد، ٤،٢،١-ترايازول، ٣،٢،١-اوكسادايزول، ثايازولدين، بايرزول، اوكسازولين معوضة النتروجين واوكسابايريدازين-٦-اون المشتقه من بارا-نايترو بنزويل هايدرازايد [3b] ، كما موضح بالمخطط III.

الجزء الرابع:

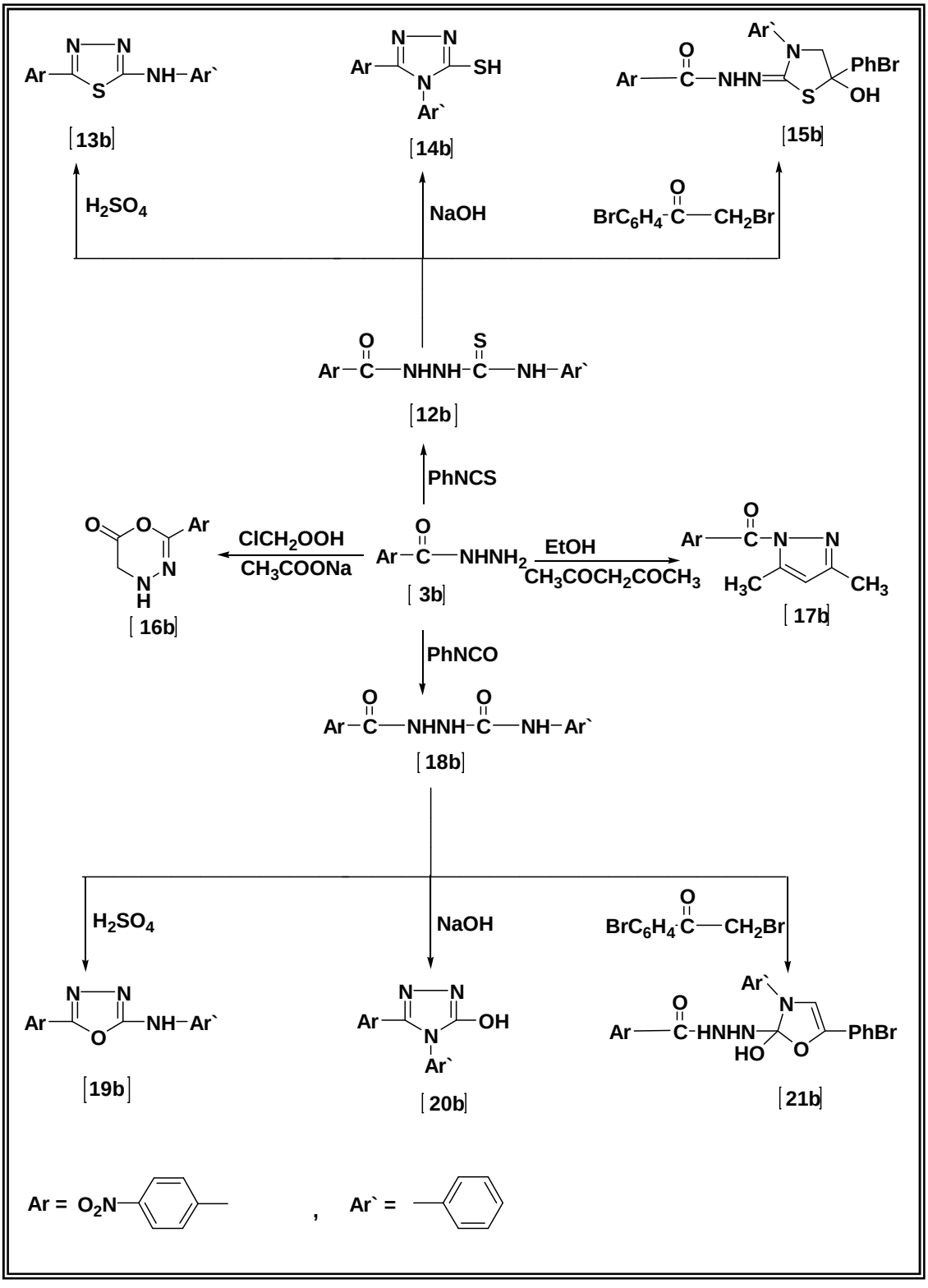
يتضمن اختبار الفعالية البايولوجية لبعض المركبات المحضرة ضد أربع أنواع من البكتيريا، كما موضح في الجدول(1-4).


Ar—C(=O)—OH
[1a,1b]
C2H5OH
Ar—C(=O)—O—C2H5
[2a,2b]
EtOH
NH2NH2.H2O
Ar—C(=O)—NHNH2
[3a,3b]
Ar—C(=O)—S-CH2-C(=O)—OCH2CH3
[5b]
ClCH2COOEt
KOH/ EtOH
CS2 / KOH
EtOH
CH3COCH2COOEt
EtOH
phthalic anhydride
acetic acid
maleic anhydride
acetic acid
[4a,4b]
[6a,6b]
[7a,7b]
[8a,8b]
Ar : a=
, b= O2N
H3C

Scheme (I)


Ar–C(=O)–NHNH2
[3a]
CS2 / KOH
o-salicyl aldehyde
EtOH
Ar–C(=O)–NHNH–C(=S)–S⊖ K⊕
[9a]
Ar–C(=O)–NHN=CH–C6H4–OH
[11a]
NH2NH2.H2O
Ar
SH
NH2
[10a]
Ar =
H3C

Scheme (II)


[13b]
[14b]
[15b]
H2SO4
NaOH
BrC6H4-C(=O)-CH2Br
[12b]
PhNCS
[16b]
ClCH2OOH
CH3COONa
[3b]
EtOH
CH3COCH2COCH3
[17b]
PhNCO
[18b]
H2SO4
NaOH
BrC6H4-C(=O)-CH2Br
[19b]
[20b]
[21b]
Ar = O2N
Ar` =

Scheme (III)

بسم الله الرحمن الرحيم

ويسئلونك عن الروح

قل الروح من امر ربي

وما أوتيتم من العلم

الأ قليلا

صدق الله العظيم

سورة الأسراء (الآية ٨٥)

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

تحضير مركبات حلقية غير متجانسة جديدة مشتقة من ميتا-مثيل حامض البنزويك و بارا-نايترو حامض البنزويك، ودراسة الفعالية البايولوجية لبعض تلك المركبات.

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

من قِبَلْ
نور عبد الرزاق
بكالوريوس٢٠٠٤ (جامعة النهرين)

نيسان ٢٠٠٧ ربيع الأول ١٤٢٨