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

Synthesis, Characterization and Biological Activity study of New Five, Six and Seven Heterocyclic Compounds Derived from 2-Aminopyridine

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

Hasan Fadhil Hussien

(B.Sc in 2006) AL-Nahrain University

November 2008 Shawal 1429

بسم الله الرحمن الرحيم

ويسألونك عن الروح قل
الروح من أمر ربي
وما أوتيتم من العلم
الأ قليلا

صدق الله العظيم

سورة الإسراء الآية (85)

Supervisor certification

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

Signature:
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Date:

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

Signature:
Name: Assist. Prof. Dr. Salman A. Ahmed
Head of Chemistry Department
College of Science
Al-Nahrain University

Examining Committee's Certification

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

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Signature: **lecturer Dr. Nadia Adil Salih**
Name:
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:

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

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HASAN 2008

Summary

This work involves synthesis of different five, six and seven member heterocyclic ring utilizing 2-aminopyridine as a starting material.

This work is divided into four different parts:

Part One :

This part involved the synthesis of 3-biphenyl-4-ylimidazo[1,2-a] pyridine[1], 3-phenylimidazo[1,2-a]pyridine [2], imidazo[1,2-a]pyridine-3(2H)-one [3], 2H-pyrido[1,2-a]pyridine-2,4-(3H)-dione [4], N,N'-1,4-dihydronaphthalene-2,3-diylidenedipyridine-2-amine [5], pyrido[1,2-a] [2,4]benzodiazepine-6,11-dione [6], N-(1,3-benzodioxol-5-ylmethylidene) pyridine-2-amine [7], 3-(pyridine-2-ylimino)-1,3-dihydro-2H-indol-2-one [8], [2-oxo-3-(pyridin-2-ylimino)dihydro-1H-indol-1-yl] acetic acid [9], 1-(1H-benzimidazol-1-ylmetyl)-3-(pyridine-2-ylimino)-1,3-dihydro-2H-indol-2-one [10], directly from the starting material, as shown in scheme (I).

Part Two :

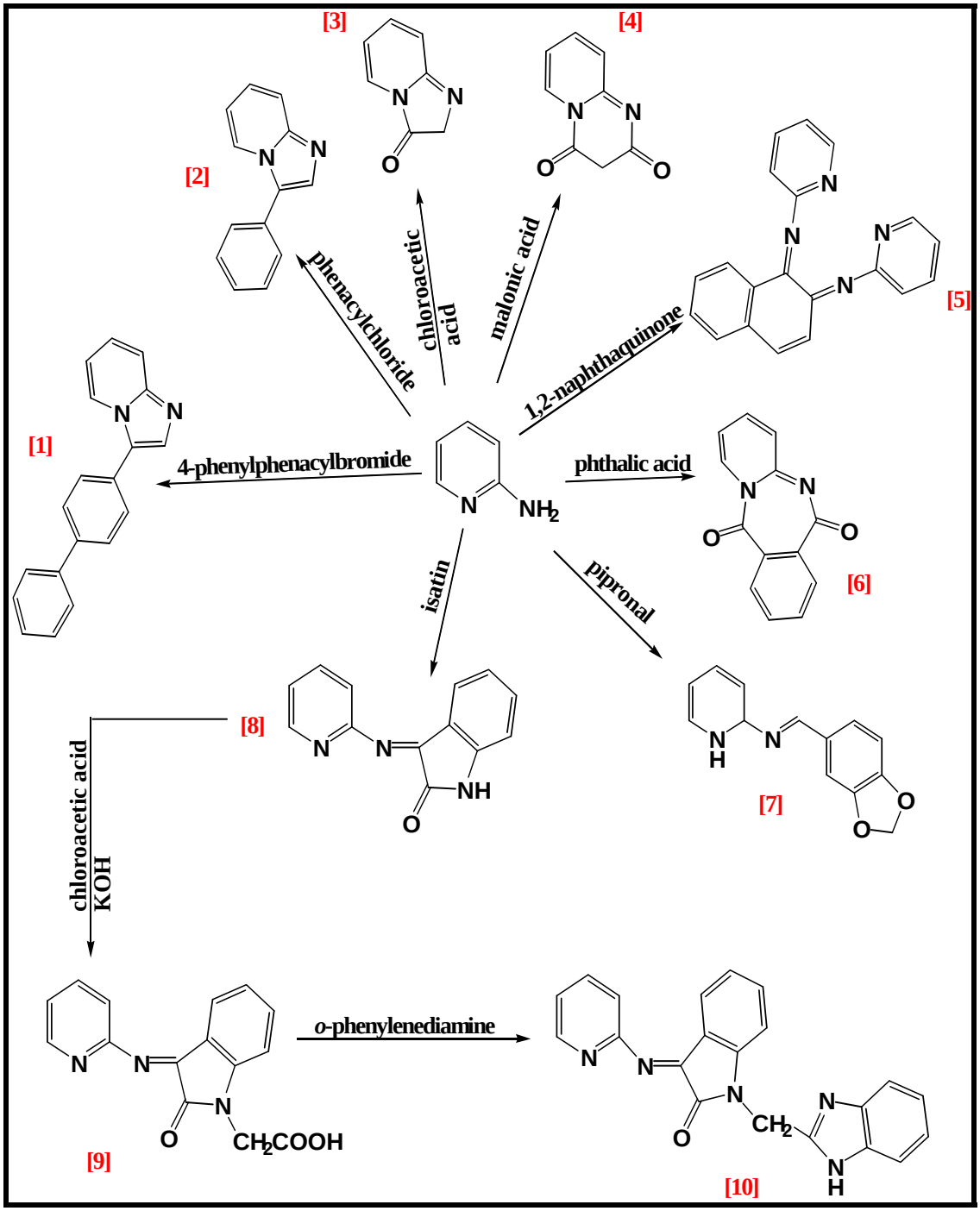
This part involved synthesis of N-carbamoyl-N_2-pyridin-2-ylglycinamid [12], N-(4-biphenyl-4-yl-1,3-oxazol-2-yl)-N_2-pyridine -2-ylglyciamide [13], N-carbothioyl-N_2-pyridin-2-ylglycinamid [14], N-(4-biphenyl-4-yl-1,3-thiazol-2-yl)-N_2-pyridine-2-ylglyciamide [15], from the reaction of 2-aminopyridine with ethylchloroacetate to yield compound [11], this compound was reacted with different organic agents to yield the target molecules, as shown in scheme (II).

Part Three :

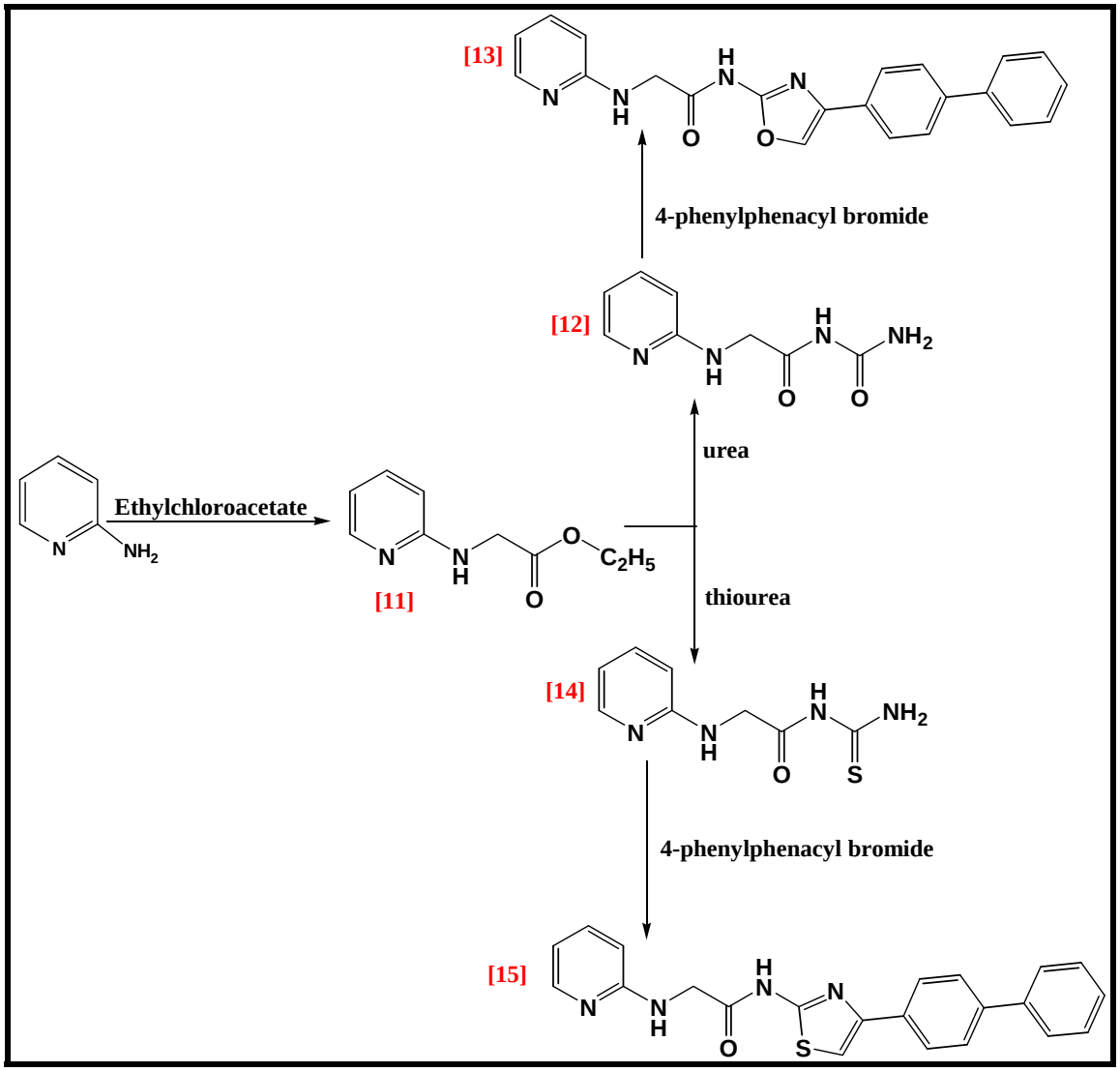
This part involved the synthesis of 2-[(pyridine-2-ylamino)methyl]-4,5-dihydro-6H-1,3,4-oxadiazine-6-one [17], 3-[(pyridine-2-ylamino) methyl]1,6-dihydro-1,2,4-triazin-5(2H)-one [18], 5-[(pyridine-2-ylamino) methyl]-1,3,4-oxadiazole-2-thiol [19], 1-(N-pyridine-2-ylglycyl)-1,2-daizepane-3,7-dione [20], 5-methyl-2-(N-pyridin-2-ylglycyl)-2,4-dihydro-3H-pyrazol-3-one [21], N'-formyl-2-(pyridine-2-ylaminoaceto-hydrazide [22], 2-(pyridine-2-ylamino)-N'-[(1,3-thiazol-2ylamino)methyl] acetohydrazide [23], starting from 2-(pyridine-2-ylamino)acetohydrazide [16]. The latter was prepared from refluxing ethyl-N-pyridin-2-ylglycinate [11] with hydrazine hydrate, as shown in scheme (III).

Part Four :

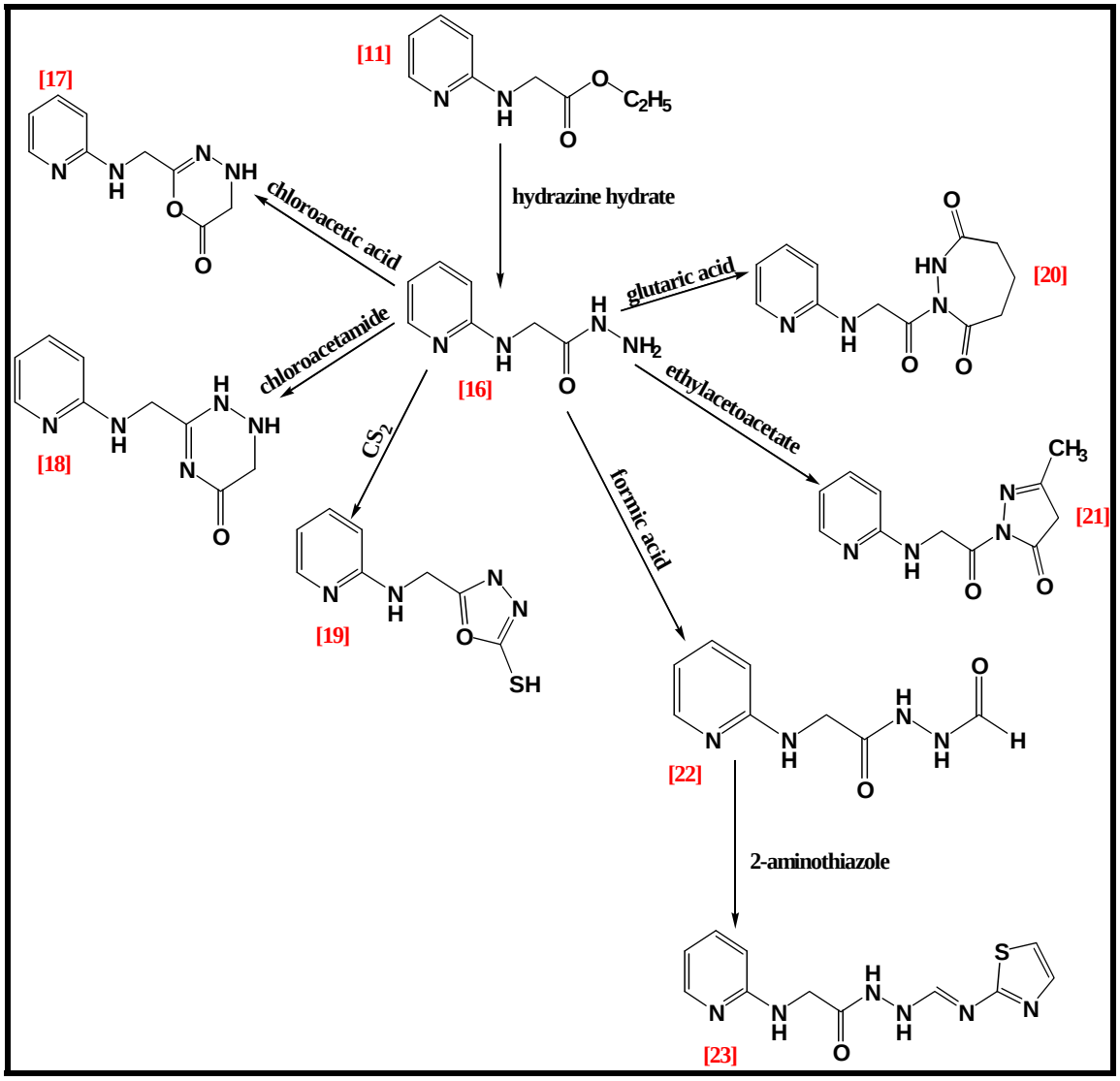
This part deals with the study of anti-bacterial activity of all the synthesized compounds. These activities were determined against two pathogenic stain of bacteria: Staphylococcus aureus and Pseudomonas aeurinosa. The result revealed that some of the synthesized compounds showed measurable activity as shown in Table (4-1).


[1]
[2]
[3]
[4]
[5]
[6]
[7]
[8]
[9]
[10]
4-phenylphenacylbromide
phenacylchloride
chloroacetic acid
malonic acid
1,2-naphthaquinone
phthalic acid
isatin
pipronal
chloroacetic acid
KOH
o-phenylenediamine
NH2
CH2COOH
CH2

Scheme (I)


[13]
4-phenylphenacyl bromide
[12]
urea
Ethylchloroacetate
[11]
thiourea
[14]
4-phenylphenacyl bromide
[15]

Scheme (II)


[11]
[17]
hydrazine hydrate
chloroacetic acid
glutaric acid
[20]
chloroacetamide
[18]
[16]
CS_2
ethylacetoacetate
[21]
[19]
formic acid
[22]
2-aminothiazole
[23]

Scheme (III)

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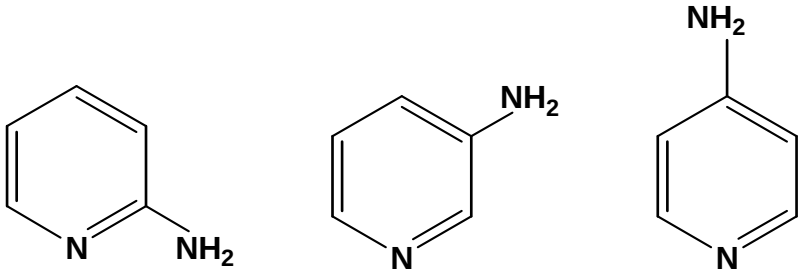
Chapter One

Introduction

1.1.0 Aminopyridine: General description

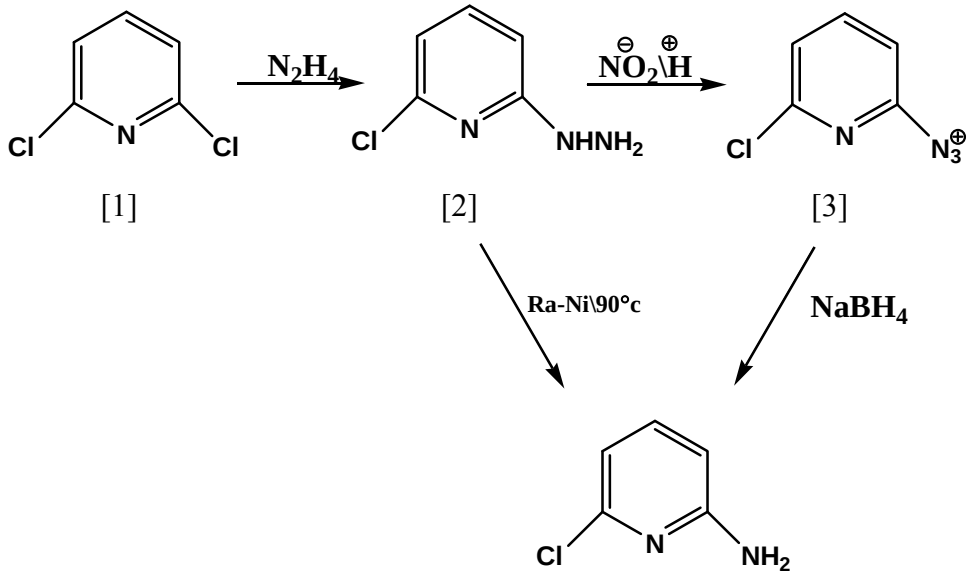
It is an organic compound with the formula of ($H_2N_2C_5H_4$). There are three isomers of amino pyridine: 2-aminopyridine, 3-aminopyridine and 4-aminopyridine.



All three isomers are toxic by ingestion and intravenous routes. Exposure to 2-aminopyridine can cause skin irritation, headache, dizziness, respiratory failure and increasing blood pressure [(1)].

1.1.1 Synthesis of 2-aminopyridine derivatives:

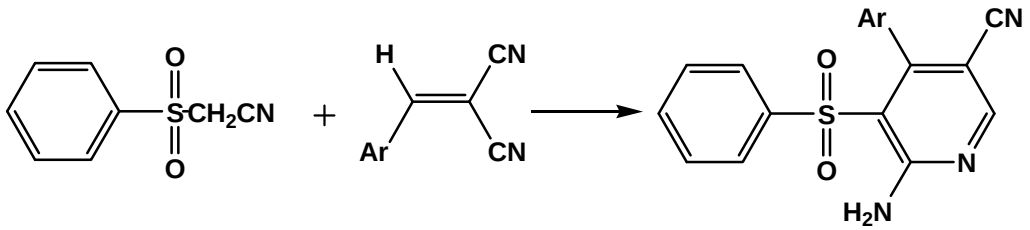
Farmak [(2)] reacted 2,6-dichloropyridine [1] with hydrazine hydrate yielding 2-hydrazino-6-chloropyridine [2] which transformed to 2-azido-6-chloropyridine [3] by the reaction with sodium nitrite in dilute hydrochloric acid. The prepared azide [3] was reduced with sodium borohydride to yield amino pyridine derivatives [4] .On the other hand the reduction of hydrazine derivatives [2] with hydrazine hydrate under the catalysis of Ra-Ni at 90˚C was a good way for the preparation of compound [4]:



[1] [2] [3]

[4]

Fadda et. al. [3] found that reaction of phenylsulfonylacetonitrile [5] and α, β-unsaturated nitriles [6] yields pyridine derivatives [7]:

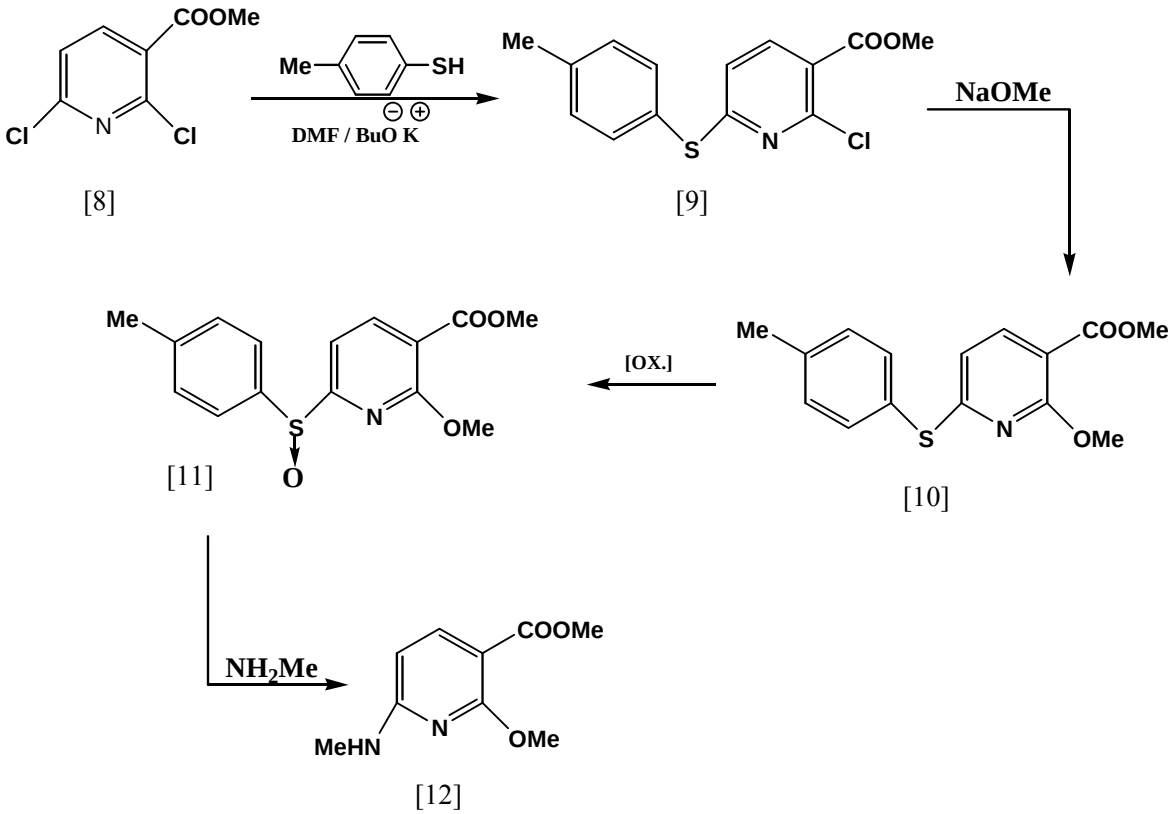


[5] [6a,b] [7a,b]

Ar ⟶ a: $C_6H_4NO_2$
b: C_6H_2-2,3,4-trimethoxy

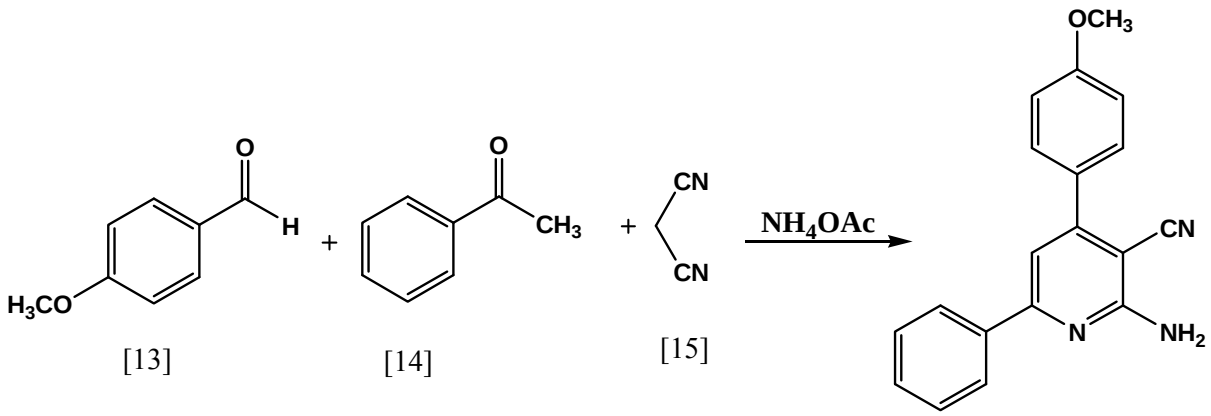
Tamaki et. al. [4] synthesized methyl-2-methoxy-6-methyl-aminopyridine-3-carboxlic acid [12] through the reaction of methyl-2,6-dichloropyridine-3-carboxylate [8] with 4-methylbenzenethiol to yield 2-chloro-6-(4-methylbenzenethio)pyridine-3-carboxylic ester [9] then reaction of [9] with sodium methoxide afforded 2-methoxy-6-(4-methylbenzenethio) pyridine-3-carboxylic ester [10]. Oxidation of [10] by potassium permanganate yielded 2-methoxy-6-(4-methylbenzensulfinyl) pyridine-3-carboxylate [11]. Finally reaction of [11] with methylamine was

carried out to produce methyl-2-methoxy-6-methyl aminopyridine-3-carboxylate [12]:



[8] [9] [10] [11] [12]

Feng et. al. [5] found that when a mixture of anisaldehyde [13], acetophenone [14], malononitrile [15] and ammoniumacetate when irradiated in a microwave oven afforded a 2-amino-4-(4-methoxyphenyl)-6-phenyl-3-cyanopyridine [16] in a good yield (72-86%). This procedure has the advantage of short time, good yield and being environmentally friendly :

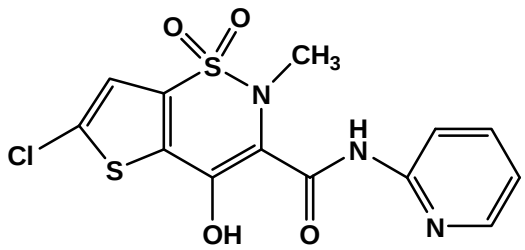


[13] [14] [15] [16]

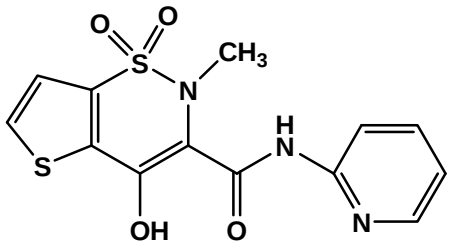
1.1.2 2-Aminopyridine Derivatives Uses:

The primary use of 2-aminopyridine is an intermediate in the manufacture of pharmaceuticals particularly ;anti-histamines and piroxican [(6)].

Lornoxican [17] and Tenoxican [18] are considered as a new non-steroidal, anti-inflammatory drugs of oxicam class, by inhibiting of cyclooxygenase (Cox) the key enzyme of prostaglandin biosynthesis at the site of inflammation [(7)] :

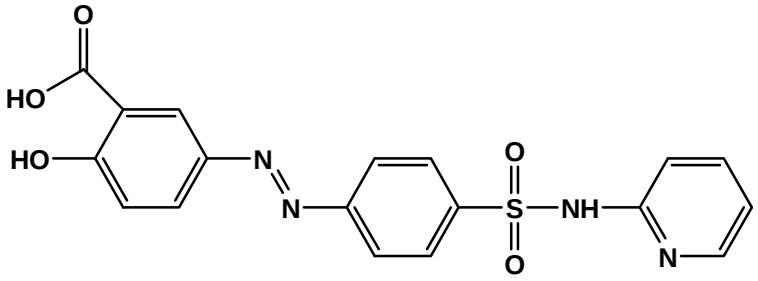


[17]



[18]

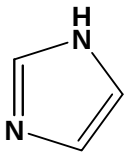
Sulfasazine [19] is an effective compound to reduce the inflammatory response in inflammatory Bowel disease in intestine [(8)] :



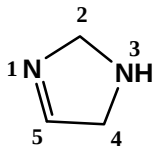
[19]

1.2.0 Imidazole: General description

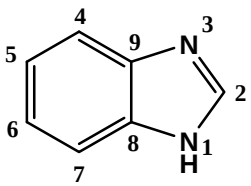
Imidazole is a heterocyclic aromatic compound of five member diunsaturated ring structure, its aromatic compound because it cyclic, planar and associated with the 6π-electron; one from the "pyridine" nitrogen and two from the "pyrrole" nitrogen.



Imidazoline is a nitrogen-containing heterocyclic derived from imidazole. The ring contains an imines' bond, and the carbons at the 2,4-positions are singly bonded, rather than doubly in the case of imidazole.



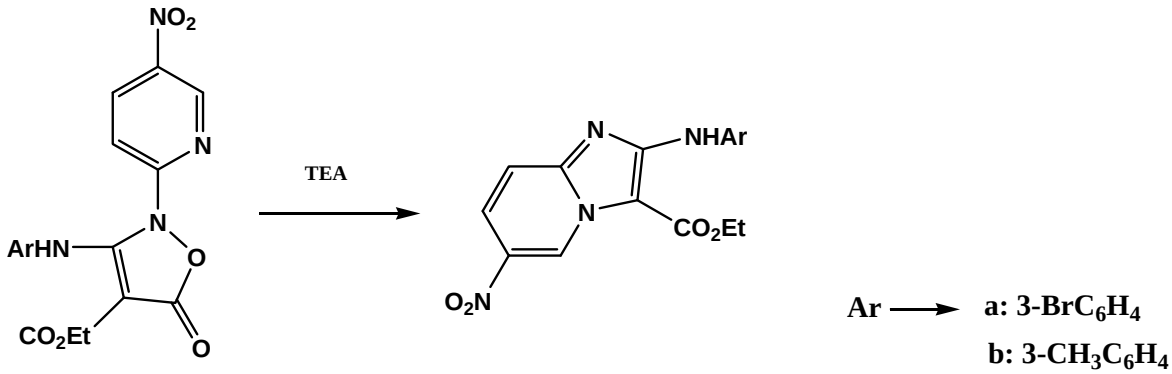
Benzimidazole is a bicyclic compound consists of the fusion of benzene ring and Imidazole ring. The ring is numbered in a way that gives the nitrogen atoms the lowest possible numbers:



Benzimidazoles are aromatic because they are cyclic, planar molecules, have five pairs of decolized π-electrons and its like Imidazole that needs the nitrogen's bonding pair of electron for its aromaticity [9].

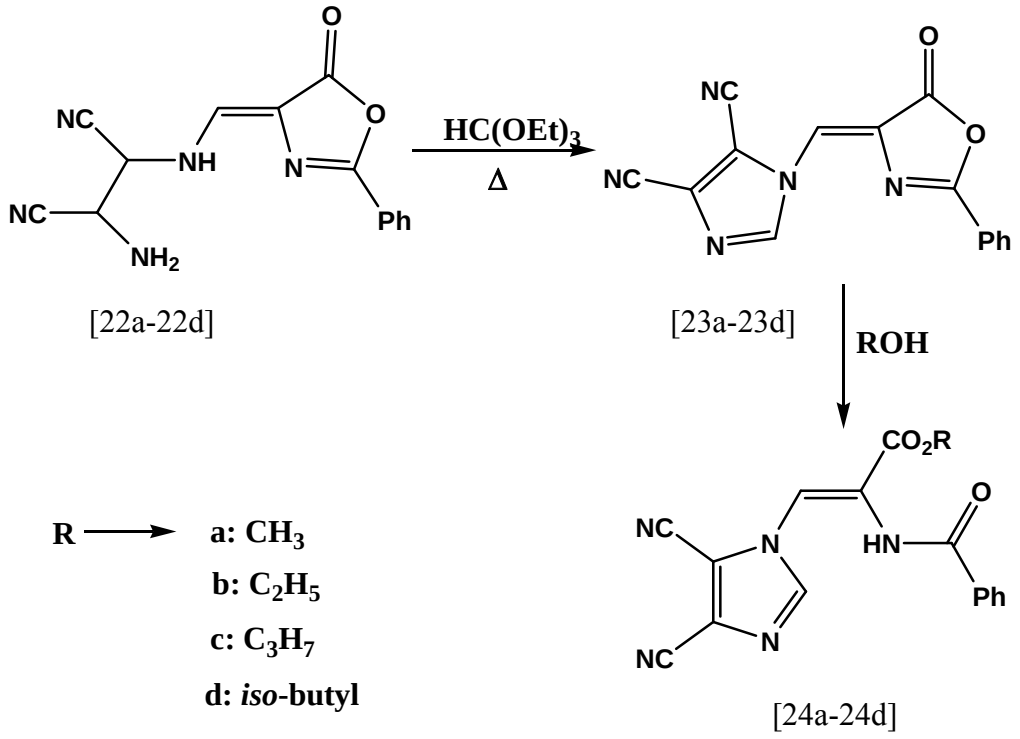
1.2.1 *Synthesis of imidazole derivative:*

Jabbar et. al. [10] synthesized compound [21 a-c] from the rearrangement of ethyl-2-(5-nitropyridine-2-yl)-3phenylamino-5-oxo-pyrrolidine-4-carboxylate [20 a-c] that proceeds during refluxing in ethanol for 24 hours in the presence of triethylamine (TEA):

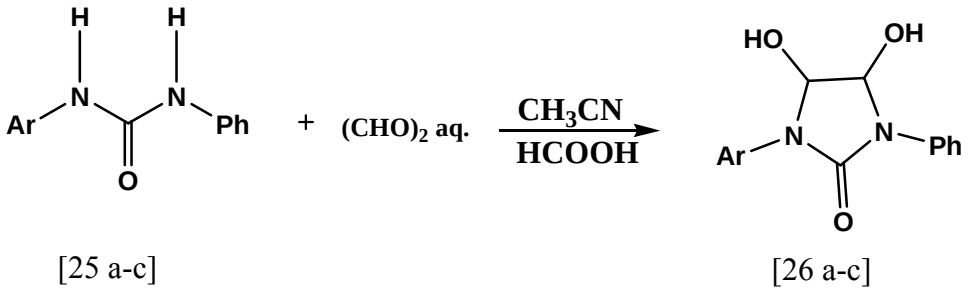


[20 a-c] [21 a-c]

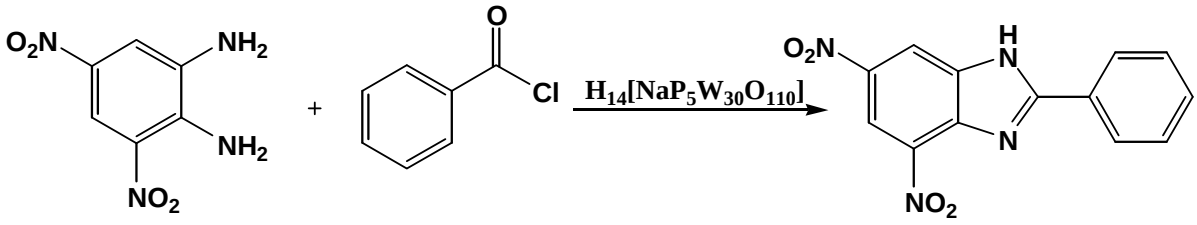
Tomas and Verček [11] founds that the reaction of the N-monosubstituted succinonitrile derivatives [22 a-d] with hot triethylorthoformate afforded 1-(4,5-dihydro-5-oxo-2-phenyl-1,3-oxazole-4-ylidenemethyl)-1*H*-imidazole-4,5-dicarbonitrile [23 a-d] . Subsequent careful treatment of compound [23 a-d] with a series of alcohols (methanol, ethanol, propanol, *iso*-butanol and pentyl alcohol) resulting in the opening of the oxazolone ring affording the corresponding esters [24 a-d]:



Mehdi et.al. [12] found that formic acid catalyzed reaction of N-heteroaryl-Ń-phenyl urea [25 a-c] with aqueous glyoxal to give an unsymmetrical 1,3-disubstituted aryl-4,5-dihydroxy-2-imidazolidinones [26 a-c]:



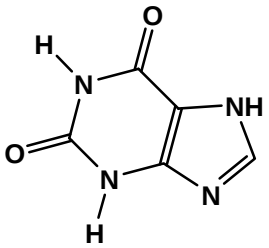
Majid et.al [13] found that refluxing of 3,5-dinitro-*o*-phenylenediamine [27] and benzoylchloride [28] for five hours using heteropolyacids as efficient catalysts{ $H_{14}[NaP_5W_{30}O_{110}]$} produced a 4,6-dinitro-2-phenyl-1*H*-benzimidazole [29]:



[27] [28] [29]

1.2.2 *Imidazole Derivatives Uses:*

Imidazole is incorporated into many important biological molecules; the most obvious is the amino acid histidine which has imidazole side chain. Histidine is present in many proteins and enzymes and play a vital part in the structure and binding function of hemoglobin. Imidazole is present in anti-cancer medication like Mercaptopurine that combats leukemia by interfering with DNA activities. Imidazole also exists in anti-fungal, anti-protozoal and anti-hypertensive medication. Imidazole is apart of the Theophylline molecules [30], found in tea leaves and coffee beans, which stimulates the central nervous system [(14)]:



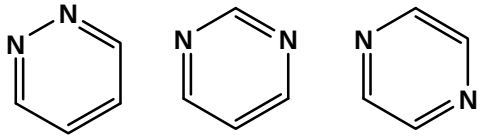
[30]

Many imidazoles have been prepared as potentially pharmacological agents, including 2-nitroimidazole (Azomycine) as a naturally occurring anti-biotic and the synthetic clotrimazole (Canestene) as an anti-imycotic [(15)].

Because of its synthetic utility and broad range of pharmacological activities, the benzimidazole nucleus is an important heterocyclic ring. In order to obtain more effective chemotherapeutic agents, a variety of reports have been presented on the synthesis and biological evaluation of new benzimidazole derivatives [(16)]. Many reports have revealed that the influence of the substitution at the 1,2 and 5-positions of the benzimidazole ring is very important for their pharmacological effects [(17)].

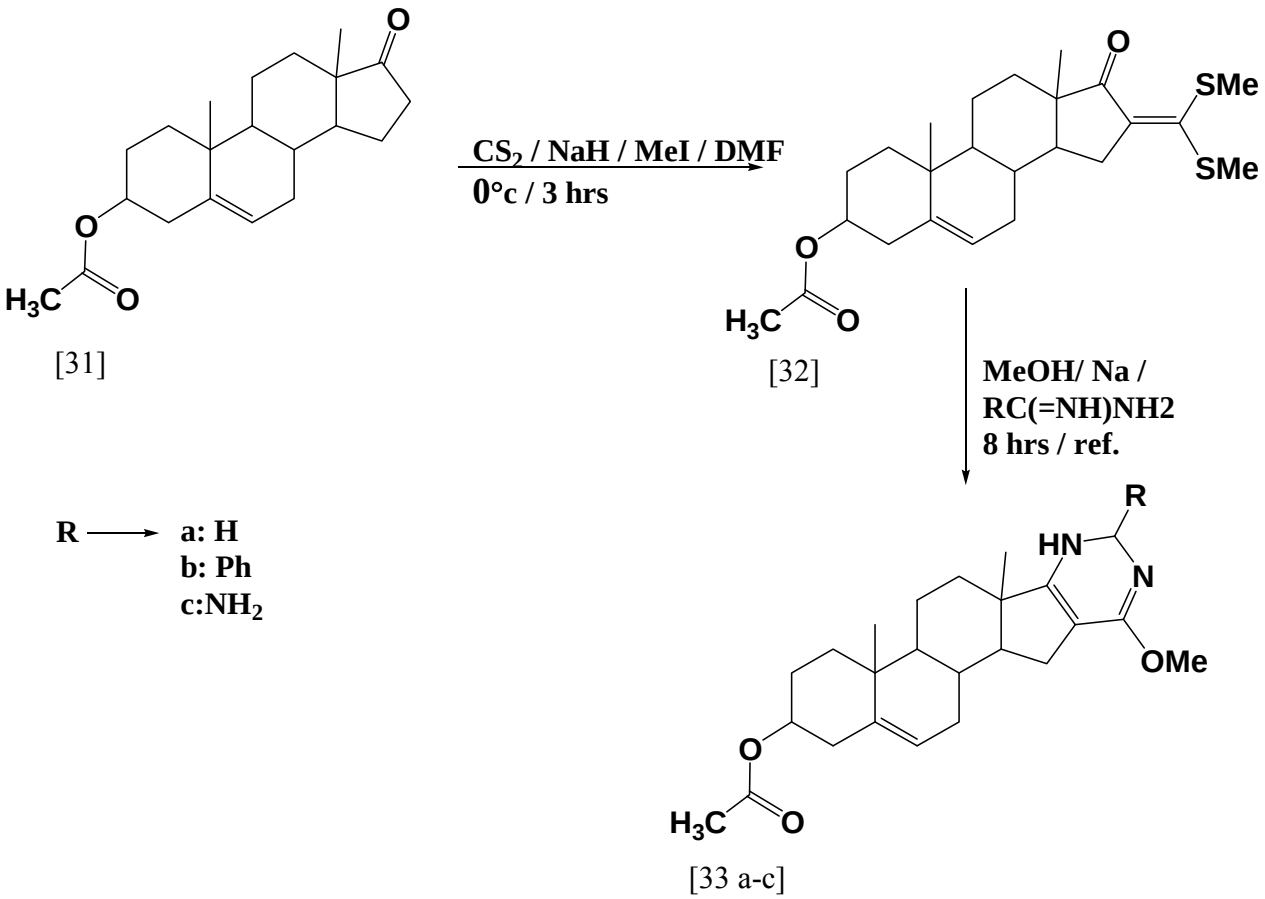
1.3.0 Pyrimidine: General description

Pyrimidine is a heterocyclic ,aromatic, organic compound that analogue to benzene . Pyrimidine, containing two nitrogen atoms at 1,3-positions of the six-member ring [(18)] :



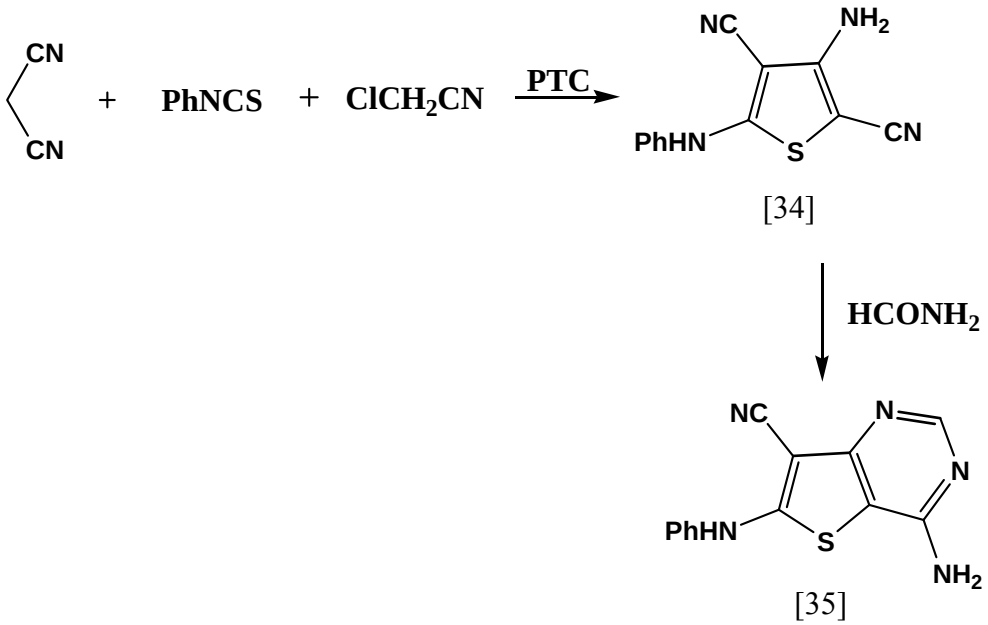
1.3.1 Synthesis of Pyrimidine Derivatives

Daniel et.al. [(19)] found that reaction of andostenolone acetate [31] with carbon disulfide, iodomethane, DMF and sodium hydride ,furnished the formation of compound [32].Treatment of compound [32] with formamidinium acetate, benzamidinium, hydrogen chloride and guanidinium acetate in the presence of sodium yielded the 6'-methoxy-2-substituted pyrimido [5',6':16,17] androst-5-en-3β-ols [33 a-c]:

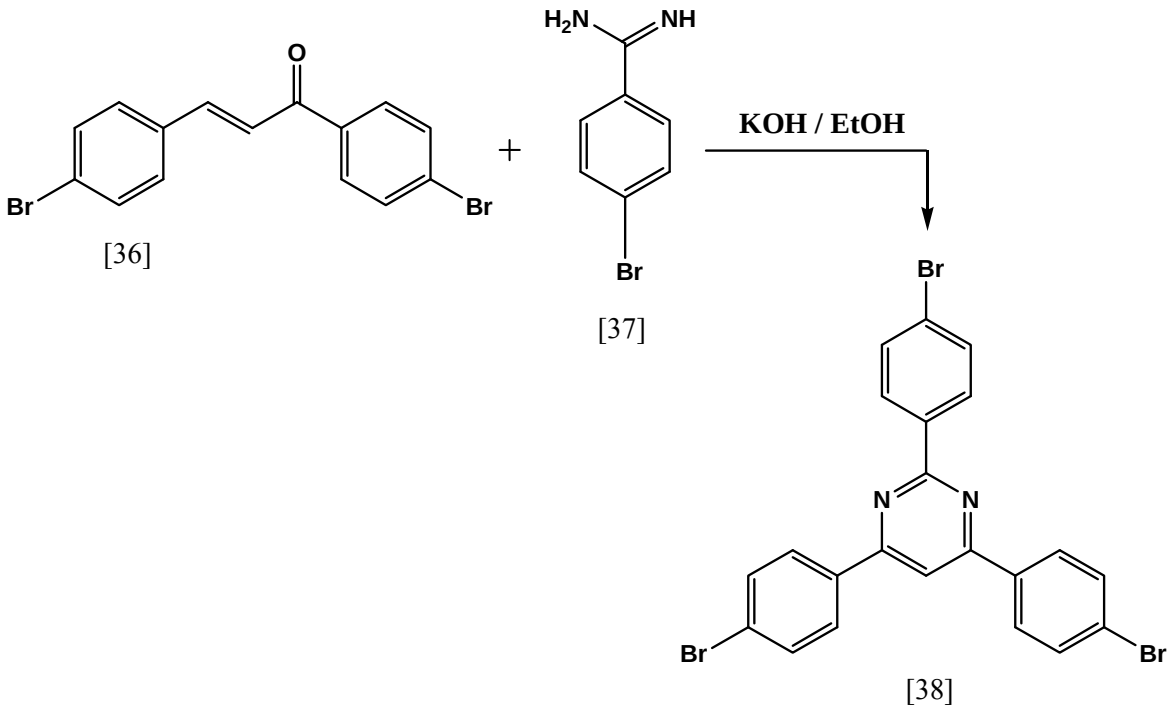


[31] [32] [33 a-c]

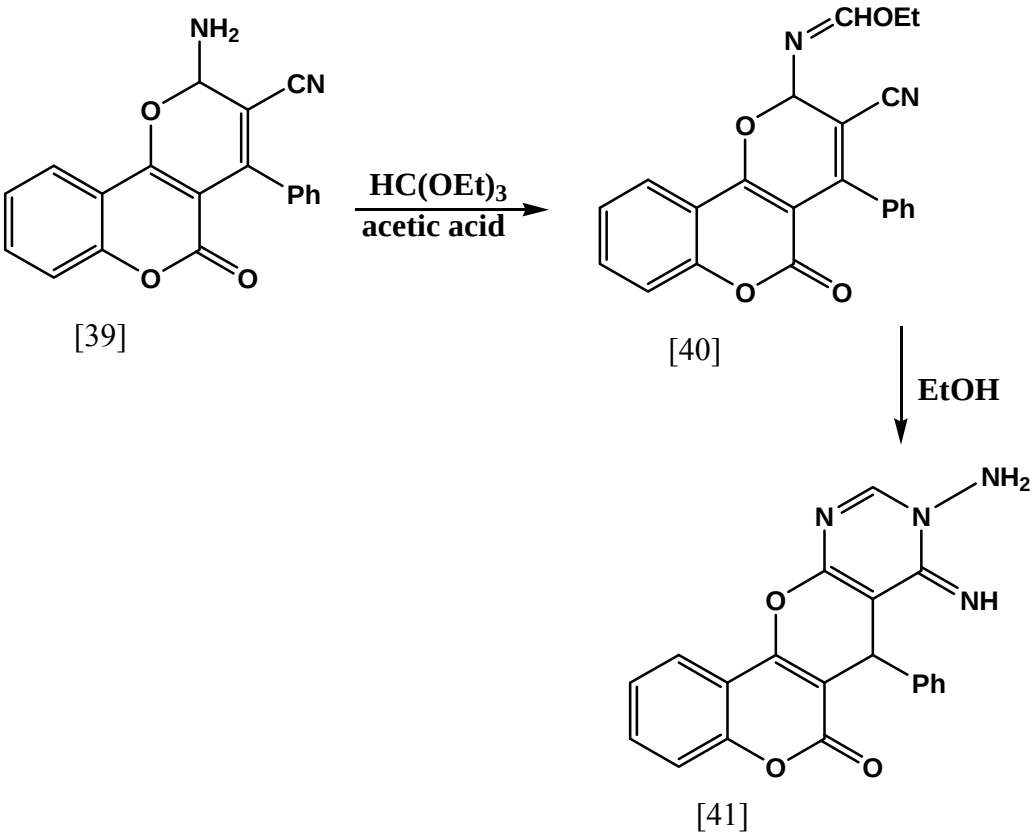
Ahmed [20] prepared 3-amino-5-anilino-2,4-dicyano thiophene [34] in one-pot reaction using phase transfer catalysis (PTC) condition [k_2CO_3 /benzene /tetrabutyl ammonium bromide (TBAB)] from malonitrile, PhNCS and $ClCH_2CN$ compound in a 1:1:1 molar ratio. Reaction of compound [34] with formamide gave the corresponding 4-amino-6-phenylamino-thieno[3,2-d]pyrimidine-7-carbonitrile [35]:



Miroslave and David [(21)] found that the key intermediate 2,4,6-tri (4-bromophenyl)pyrimidine [38] was obtained in good yield by base-promoted condensation between 1,3-di(4-bromophenyl)propen-3-one [36] and 4-bromobenzamidine [37]:



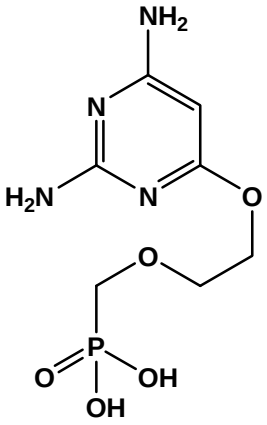
Agroody et.al.[22] found that the refluxing of 2-amino-4-(phenyl)-3-cyano-4*H*,5*H*-pyrano[3,2-c]benzene-5-one [39] with triethylorthoformate in acetic acid, afforded 4-(phenyl)-3-cyano[3,2-c]benzopyran-5-one [40]. Hydrazinolysis of the latter in ethanol at room temperature yielded 9-amino-7-(phenyl)-8,4-dihydro-8-imino-6*H*,7*H*-benzopyrano[3',4':5,6]-pyrano[2,3-d]pyrimidine-6-one [41]:



[39] [40] [41]

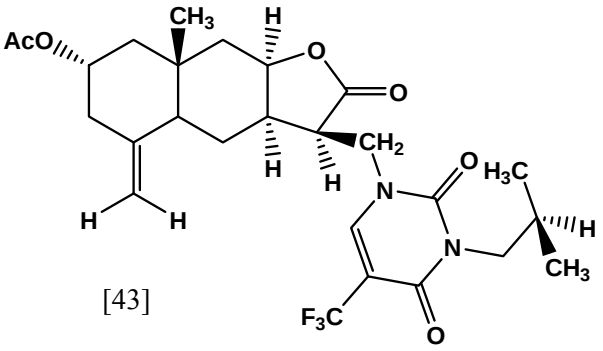
1.3.2 Pyrimidine Derivatives Uses

Pyrimidine ring has received a significant attention owing to their diverse range of biological properties. Acyclic nucleoside phosphate has been discovered in which the base consist of a pyrimidine preferably containing an amino group at C_2 , C_4 and 2-(phosphonomethoxy)ethoxy {PMEO}.The 6-PMEO-2,4-diaminopyrimidine shows potent activity against human immunodeficiency {HIV} [23]:

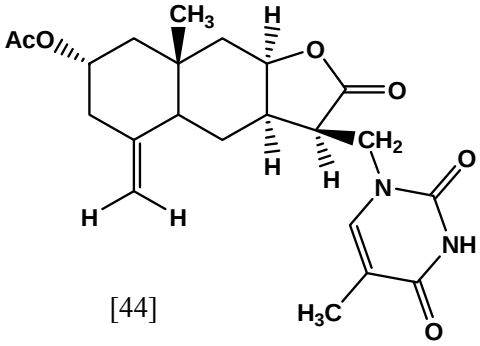


[42]

New pyrimidine derivatives of sesquiterpene lactones ring show an anti-tumor activity ,compounds [43] and [44] ,inhibit the DNA replication in cancer cell line [(24)] :



[43]

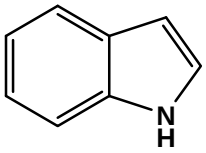


[44]

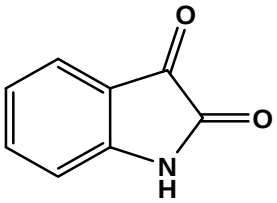
Furthermore, several important sulfa drugs are pyrimidine derivatives namely sulfadiazine ,sulfamerazine and sulfadiamine. A variety of natural products such as alkaloids also contain the pyrimidine ring system, these include Hypoxanthine and Xanthenes which occur in tea, caffeine and Theophylline (the constituents of tea leaves) [(25)].

1.4.0 Indol: General description

1*H*-Indol is an organic aromatic heterocyclic compound. It has a bicyclic structure , consisting of a six-member benzene ring fused to a five –member nitrogen heterocyclic rig; indol need nitrogen's non-bonding pair of electrons for its aromaticity; that's mean that indol is not a base ,and it does not behave like a simple amine [26] :

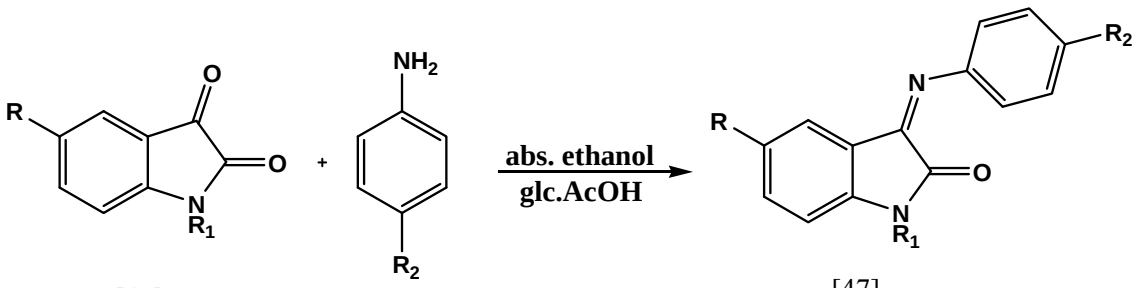


Isatin (1*H*-indole-2,3-dione) are synthetically versatile substrates, where they can be used as a raw material for drug synthesis. Isatin have also been found in mammalian tissue and their function as a modulator of biological processes [27]:



1.4.1 Synthesis of Isatin Derivatives

Manjusha et.al. [28] made a reaction of equi-molar quantities of 5-substituted-N-acetylisatin [45] and aromatic amine [46] in absolute ethanol containing a few drops of glacial acetic acid . The reaction mixture was refluxed for an hour yielding the wanted product [47]:

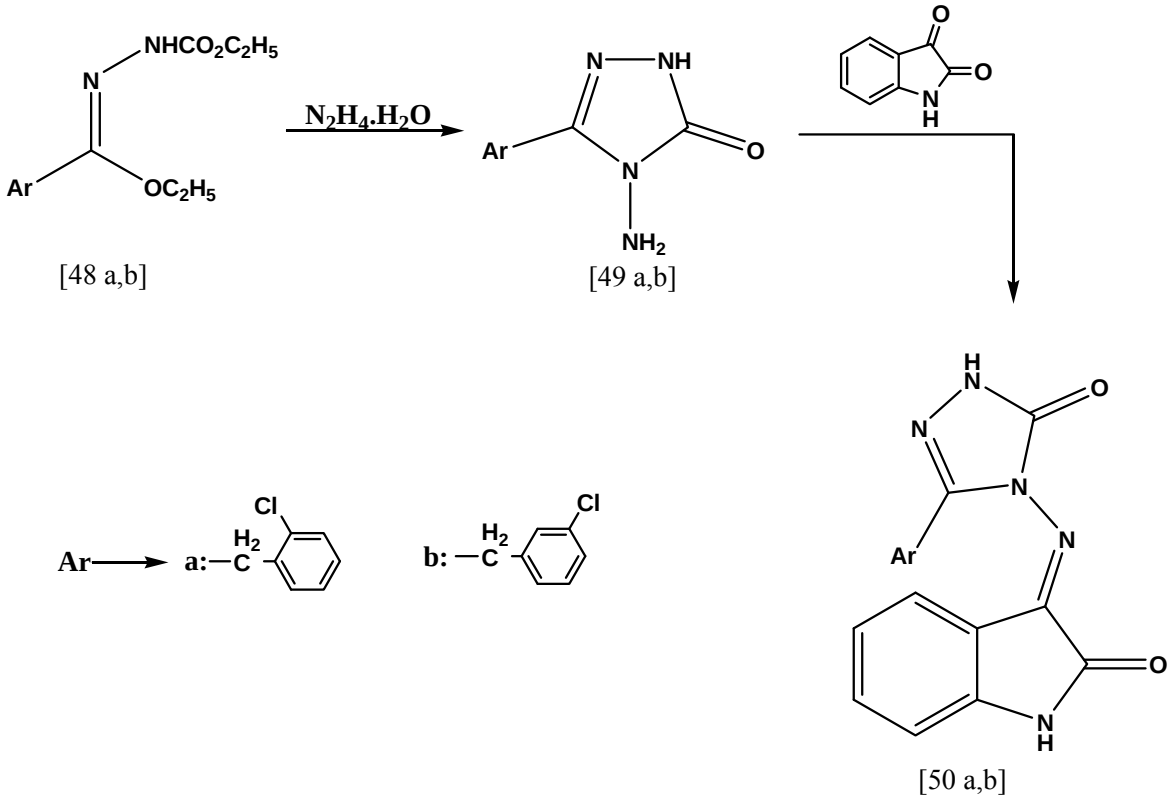


[45] [46] [47]

R ⟶ Br, NO_2 R_1 ⟶ CH_3, $COCH_3$

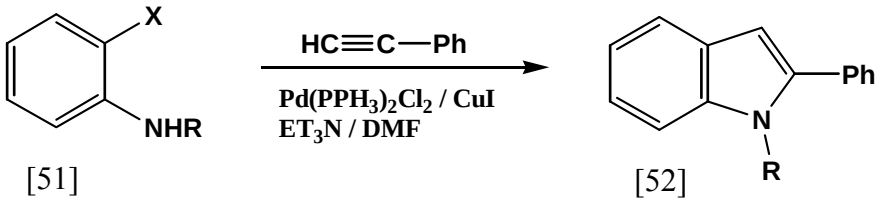
R_2 ⟶ NO_2, COOH, OCH_3, Cl, F

Bahittin [(29)] prepared 3-substituted-4-amino-4,5-dihydro-1*H*-1,2,4-triazole-5-one [49 a,b] from cyclization of ethyl-substituted formate ethoxycarbonyl hydrazones [48 a, b] with hydrazine mono hydrate. A reaction of compound [49 a,b] with isatin afforded the expected isatine-3-imines [50 a, b]:



[48 a,b] [49 a,b] [50 a,b]

Hossien et.al. [30] mixed an aryl halide [51] ; phenyl acetylene, $Pd(PPh_3)_2Cl_2$, CuI and triethylamine in DMF at ambient temperature. The reaction provided 2-phenylindole [52] as a major product:

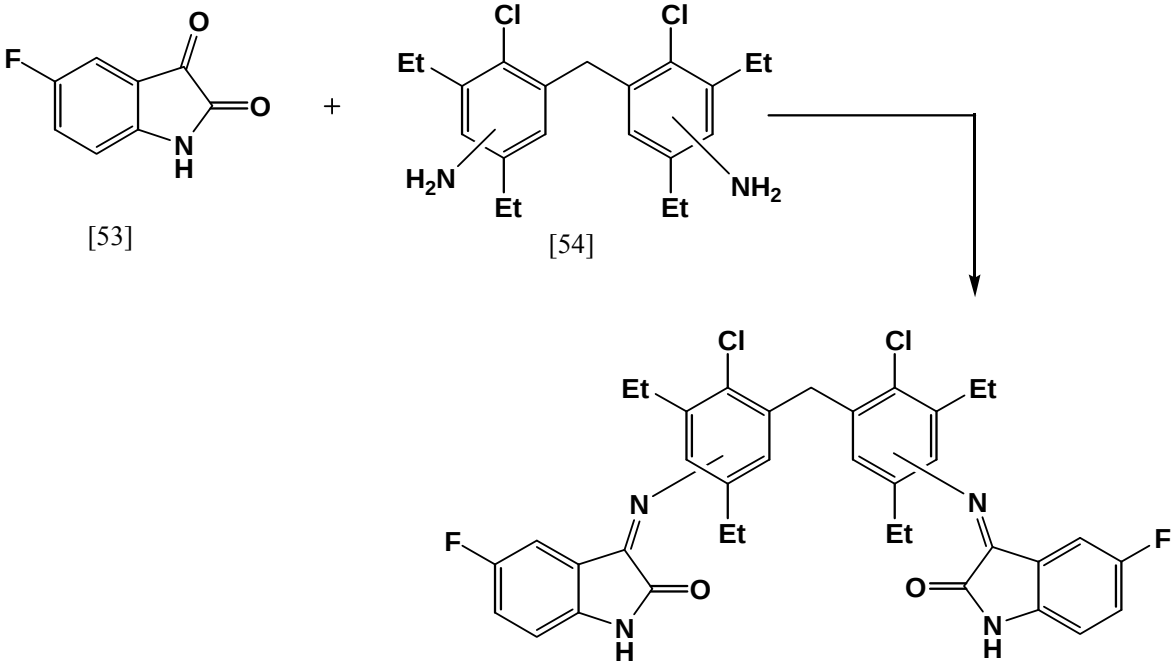


[51] [52]

X ⟶ Br, I

R ⟶ H, CH_3 ,CH_3COO

Jarrahpour et.al. [31] refluxed an 5-flouroisatine derivatives [53] with 3,3-diaminodiphenylmethane [54] at room temperature for 48 hours in absolute ethanol to yield 3,3'[methylenebis(2-chloro-3,5-diethyl-1,4-phenylennitrilo)]bis[1,3-dihydro]-5-fluoro-2*H*-indole-2-one [55]:

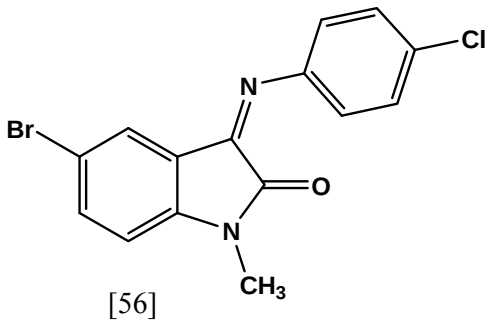


[53] [54] [55]

1.4.2 Isatin Derivatives Uses:

Isatin has been known about 150 years ago and has recently found, like Oxindole and Endogenous polyfunctional heterocyclic compounds, to exhibit biological activity in mammals [(32)]. Isatin also is a synthetically versatile substrate that can be used to prepare a large variety of heterocyclic compounds, such as indol and quinolines, and as a raw material for drug synthesis [(33)]. Some isatin derivatives exhibit anti-plasmodial activity [(34)] . Shiff-bases and Mannich-bases of isatin are known to possess a wide range of pharmacological properties including anti-HIV [(35)] and anti-fungal [(36)]. The shiff-bases of isatin have also been used as ligand for complexation of metals such as copper (II) [(37)] . These complexes catalyzed the oxidation of carbohydrates. Bis-shiff-bases can act as inhibitors of human α-thrombin [(38)] . Recently it has been reported that a bis-imines of isatin has an anti-microbial properties [(39)] and affects the ceel viability [(40)] .

Isatin shiff-base have also been known to possess an anti-bacterial and anti-convulsant activity [(41)] . For example the *N*-methyl-5-bromo-3-(*p*-chlorophenylimino) isatin have been synthesized and screened for anti-convulsant activities [(42)] :



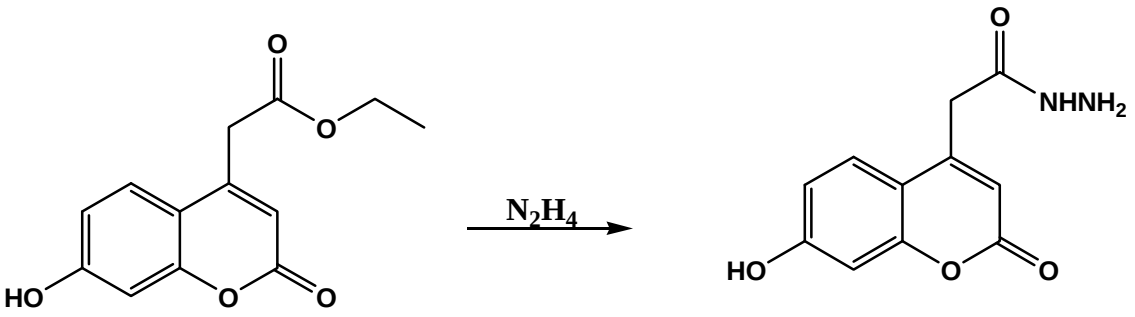
[56]

1.5.0 Hydrazide Derivatives: General description

Hydrazide derivatives attract a lot of attention because it considered as intermediate in synthesis of several compounds such as shiff-base, oxadiazole [43],thiadiazole [44],triazole [45] and pyrazole [46] derivatives which all were reported to possess biological activity.

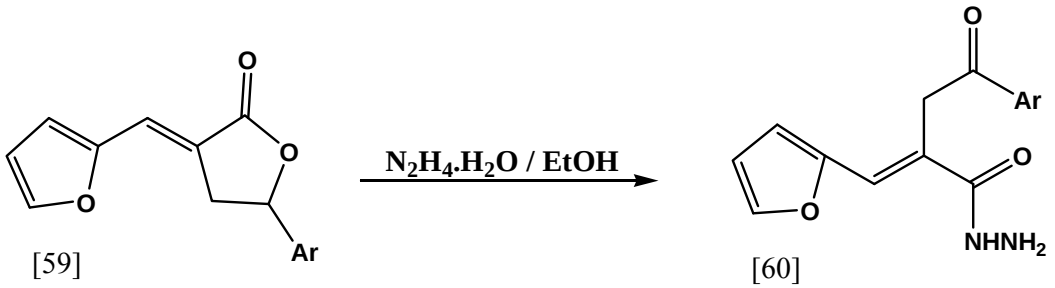
1.5.1 Synthesis of Acid Hydrazide

Milan et.al. [47] applied the hydrazinolysis of (7-hydroxy-2-oxo-2*H*-chromen-4-yl)-ethyl acetate [57] with 100% hydrazine hydrate in methanol at room temperature ;(7-hydroxy-2-oxo-2*H*-chromen-4-yl)acetic acid Hydrazide [58] was prepared:



[57] [58]

Abdel-Sattar et.al. [48] treated 5-aryl-3-furfurylidene-2-(3H)-furanones [59] with hydrazine monohydrate and ethanol, with stirring at room temperature for 2-days and afforded 2-(furan-2-ylmethyl)-4-aryl-4-oxobutanehydrazide [60]:

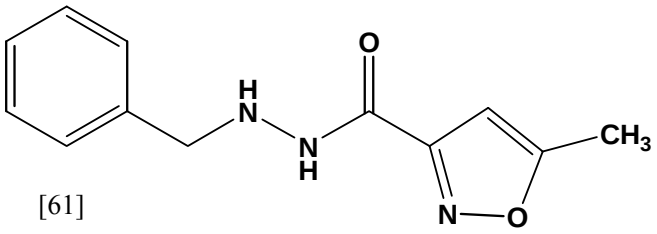


[59] [60]

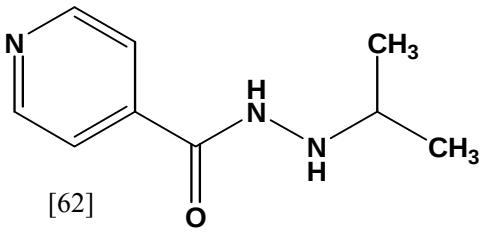
1.5.2 Acid Hydrazide Derivative Uses

Acid hydrazides have a great deal of biological properties ;as a result of their anti-microbial, anti-fungal and anti-bacterial properties. The formation of metal complexes plays an important role in the growth of their biological activity [(49)] .

Iproniazide [61] and Isocarboxazide [62] are used in the treatment of tuberculosis. They have also display an antidepressant effect and patients appear to have a better mood during the treatment [(50)] :

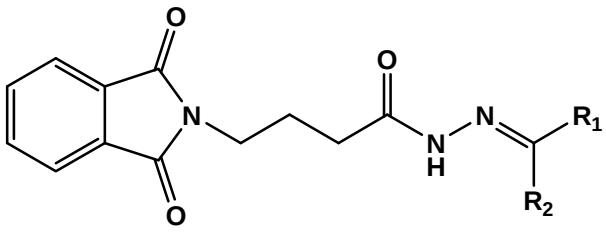


[61]



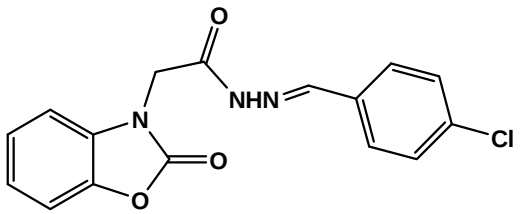
[62]

4-(1,3-dioxo-1,3-dihydro-2*H*-*iso*-indol-2-yl)-N-(propan-2-ylidene) butanehydrazide [63] were designed, synthesized and evaluated for their anticonvulsant properties in different animal models of epilepsy [(51)] :

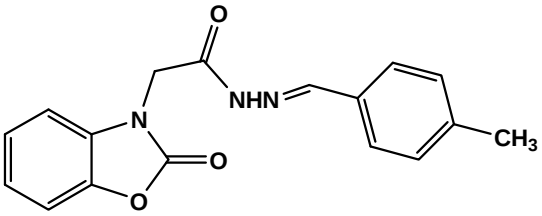


[63]

The analgesic effects of 2-[2(5-methyl-2-benzoxazolin-3-yl)acetyl-N-4-chlorobenzylidene hydrazine [64] and 2-[2(5-methyl-2-benzoxazolin-3-yl) acetyl-N-4-methylbenzylidene hydrazine [65] ,were found to be higher those morphine and aspirin [(52)] :

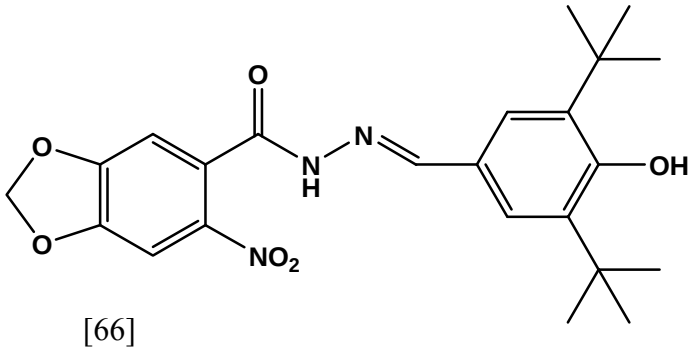


[64]



[65]

Furthermore the N'-(3,5-di-tert-butyl-4-hydroxybenzylidene)-6-nitro-1,3-benzodioxole-5-carbohydrazine [66] was found as a novel anti-inflammatory compound [(53)] :

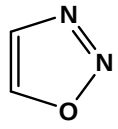


[66]

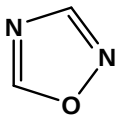
Some carbohydrazide were reported to be components of deodorant composition that used for removal of offensive odor components [(54)] .

1.6.0 Oxadiazole: General description

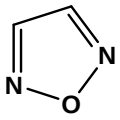
Oxadiazole are 5-member, aromatic ring compound .The Oxadiazole ring has four isomers each one contains two carbon atoms, two nitrogen atoms and one oxygen atom:



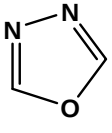
(1,2,3-oxadiazole)



(1,2,4-oxadiazole)



(1,2,5-oxadiazole)

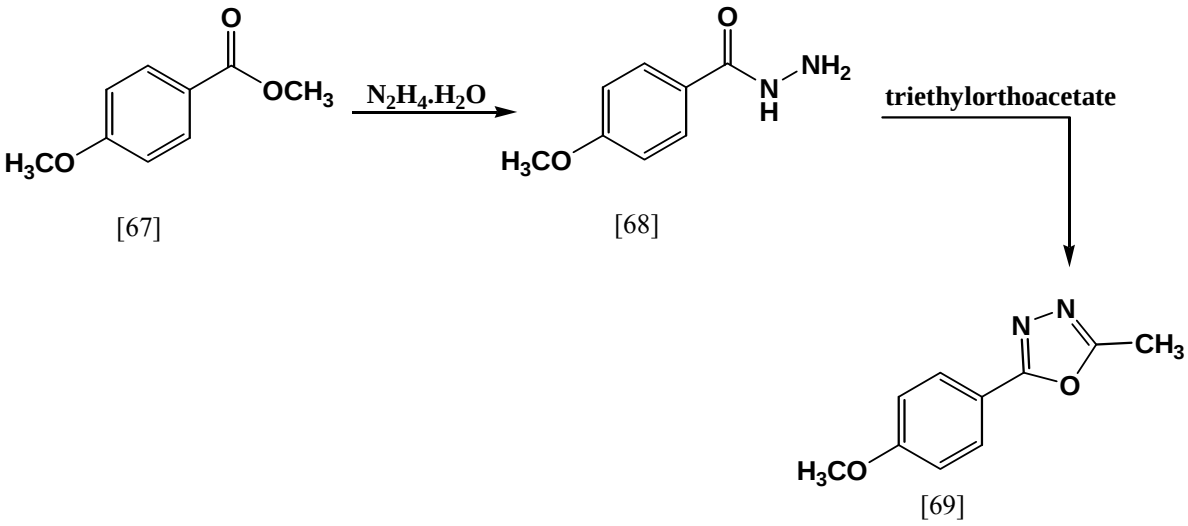


(1,3,4-oxadiazole)

The parent 1,3,4-oxadiazole compound is liquid with boiling point of 150°C. Compounds containing the 1,3,4-oxadiazole ring are well known as a powerful anti-microbial, anti-convulsant, anti-depressant and analgesic agents [(55)] .

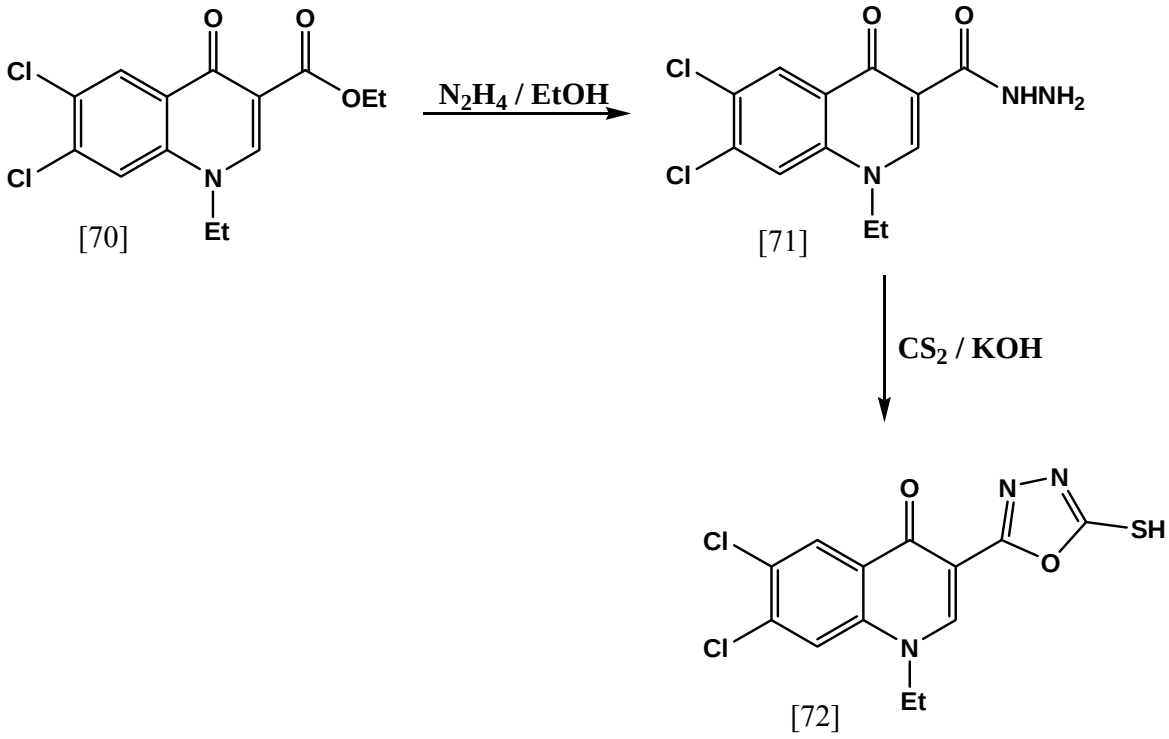
1.6.1 Synthesis of 1,3,4-Oxadiazole Derivatives

Grabmann et.al.[(56)] found that when methyl anisate [67] allowed to react with hydrazine mono hydrate, the anisoyl hydrazide [68] would be form. Cyclocondensation of the latter compound with triethylorthoacetate yielding 2-methyl-5-(4-methoxyphenyl)1,3,4-oxadiazole [69] :

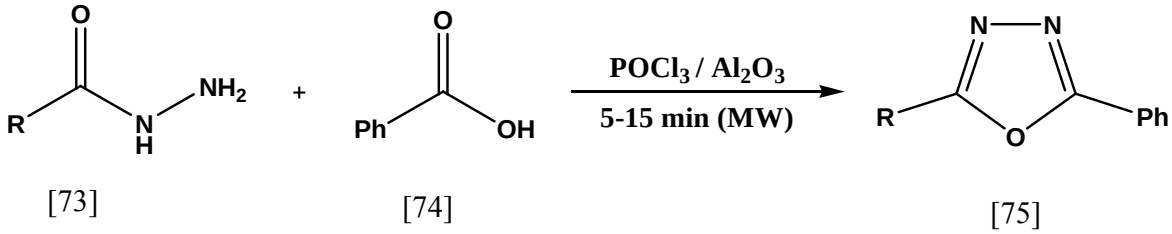


[67] [68] [69]

Al-Soud and Al-Masoudi [(57)] found that the reaction of quinoline derivatives [70] with hydrazine afforded 6,7-dichloro-1-ethyl-1,4-dihydro-4-oxoquinoline-3-hydrazide [71]. Reaction of compound [71] with CS_2 / KOH gave the 3-(5-thiol-1,3,4-oxadiazol-2-yl)quinoline [72] :

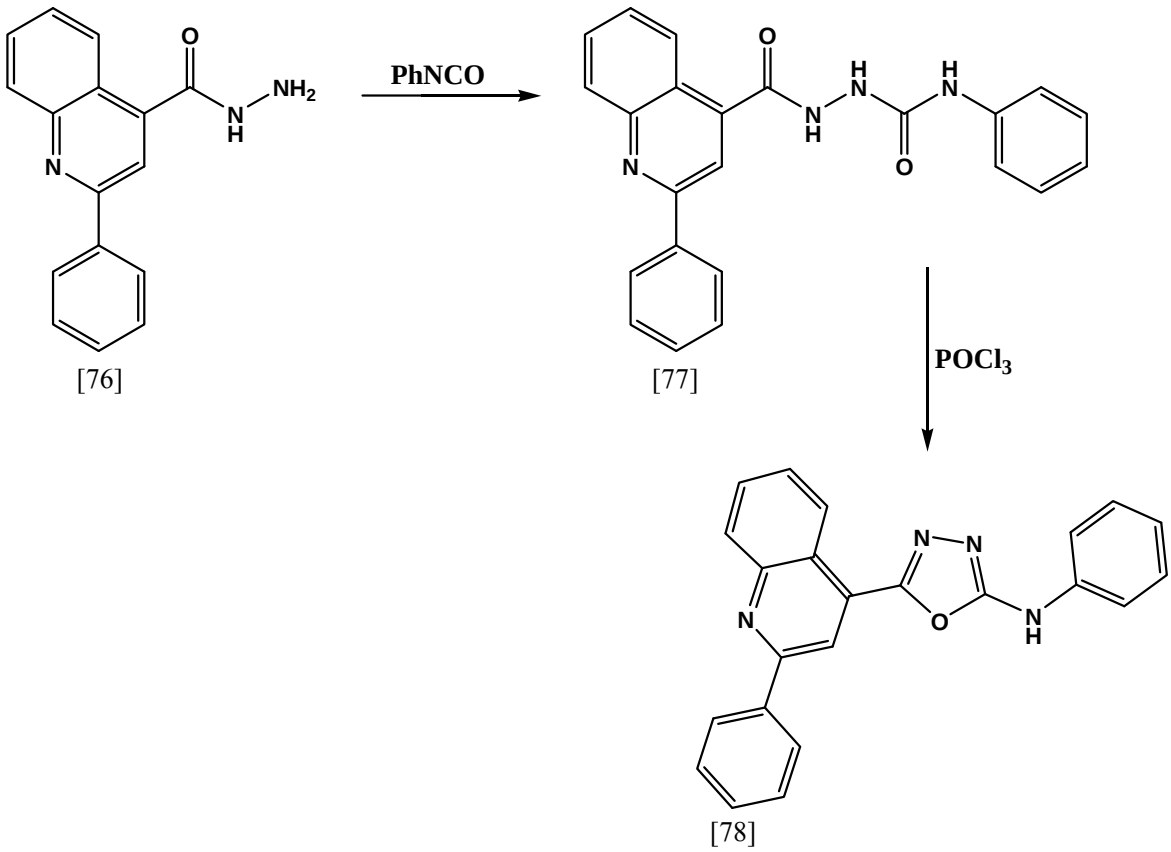


Khan et.al. [58] prepared 2,5-disubstituted-1,3,4-oxadiazole [75] under microwave irradiation by the reaction of hydrazide [73] with benzoic acid [74] in the presence of phosphorous oxychloride :



R ⟶ 3-pyridinyl

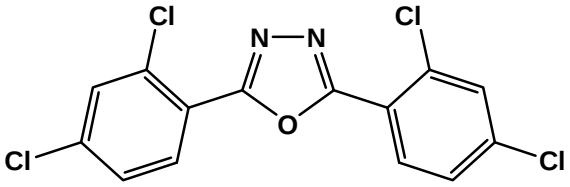
Feixu et.al. [59] found that the reaction of cinchophenyl hydrazide [76] with phenylisocynate gave 1-cinchophenyl amino-5- phenyl carbamide [77]. Further reaction of compound [77] with phosphorous oxychloride afforded 2-arylamino-5-cinchophenyl-1,3,4-oxadiazole [78] :



[76] [77] [78]

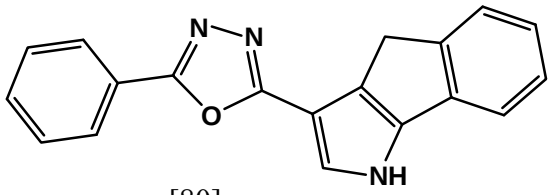
1.6.2 1,3,4-Oxadiazole Derivatives Uses:

It has been reported that heterocycles such as oxadiazoles are important chemotherapeutic agents when properly substituted in 2- and 5-positions [(60)] Symmetrical 2,5-bis(2,4-dichlorophenyl)1,3,4-oxadiazole [79] and its analogue were found to be effective as insecticides towards houseflies, face flies and horn flies. This type of compounds was shown to inhibit chitin synthesis in musca domestic in *vitro* and *vivo* studies [(61)] :



[79]

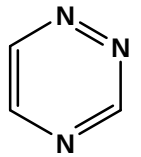
On the other hand, some of 2,5disubstituted 1,3,4-oxadiazole derivatives used against 60 tumor cell lines derived from nine cancer cell types. Biological results showed a very interesting anti-tumor activity against leukemia, colon and breast cancer, for example 3-(5-phenyl-[1,3,4-oxadiazole]-2-yl)-1*H*-bezoindole [80] [(62)] :



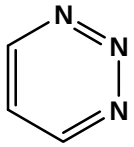
[80]

1.7.0 Triazine: General description

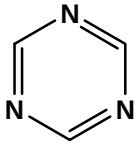
Triazine is a heterocyclic ring analogue to the six-member benzene, but with three carbon atoms replaced by nitrogen atoms .There are three isomers of triazine which is 1,2,3-triazine ; 1,2,4-triazine and 1,3,5-triazine.



(1,2,4-triazine)



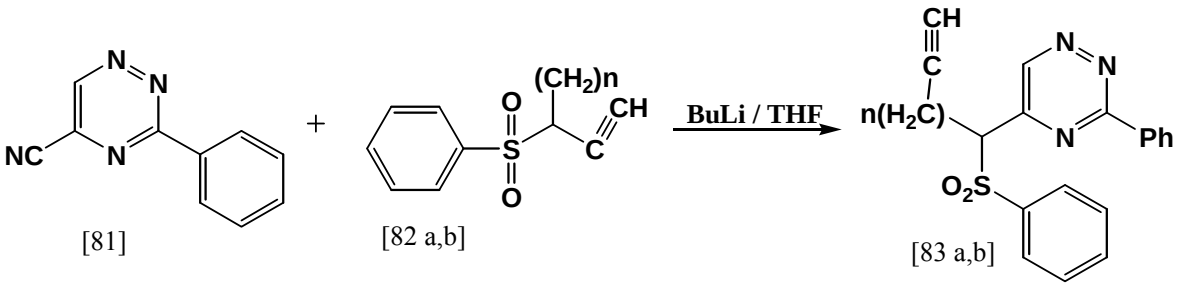
(1,2,3-triazine)



(1,3,5-triazine)

1.7.1 Synthesis of 1,2,4-Triazine Derivatives

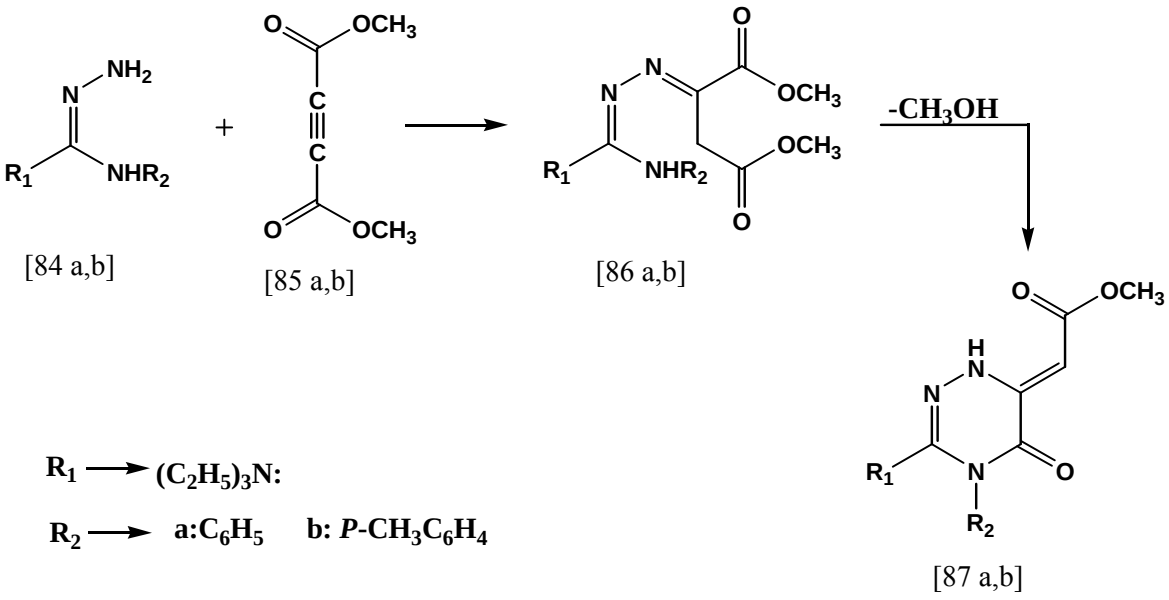
Danuta et.al. [(63)] treated 3-phenyl-1,2,4-triazine-5-carbonitriles [81] with 4-pentyn-3-phenylsulphone or 5-hexyn-4-phenylsulphone [82 a, b] in presence of BuLi and THF as a solvent ; yielding a 3-phenyl-5-[1-(phenylsulphonyl)-pent-4-yn]-1,2,4-triazine [83 a,b] :



[81] [82 a,b] [83 a,b]

n ⟶ a: 2
b: 3

Bozena et.al.[64] found that the reaction of the N^3-substitution amidrazones [84 a,b] with dimethylacetylenedicarboxylate [85 a,b] led to the formation of derivatives of dimethyl-2-[(1-arylamino-1-arylmethylidene) hydrazono]succinate [86 a,b]. The cyclization of compound [86 a,b] was performed in boiling n-butanol led to the formation of derivatives of 5-oxo-1,2,4-triazine-6-carboxylic acid [87 a,b] :

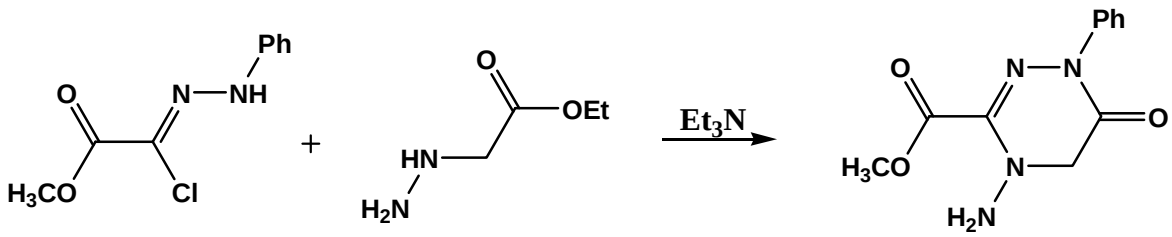


[84 a,b] [85 a,b] [86 a,b] [87 a,b]

R_1 ⟶ $(C_2H_5)_3N$:

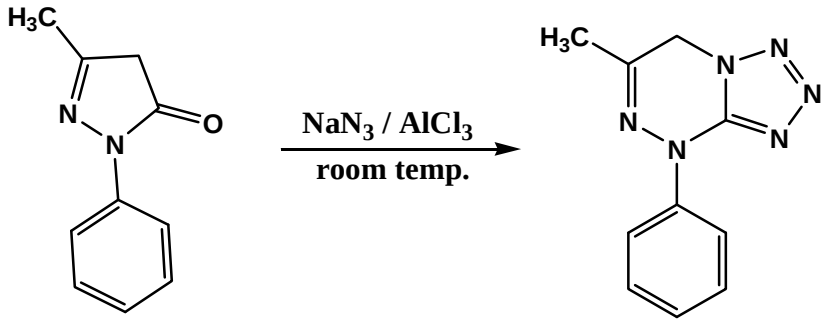
R_2 ⟶ a:C_6H_5 b: *P*-$CH_3C_6H_4$

Abdel-Rahman and Adel Awadallah [65] found that reaction of compound [88] with ethylhydrazino acetate [89] under mild conditions gave 4-amino-1-aryl-3-carboxymethyl-6-oxo-1,4,5,6-tetrahydro-1,2,4-triazines [90] :



[88] [89] [90]

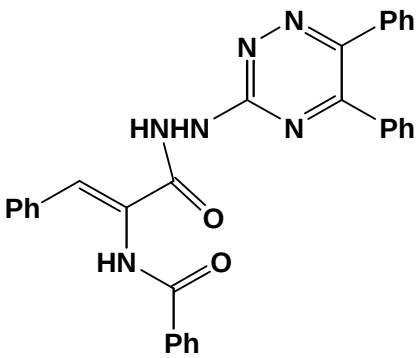
Ragharenda et.al.[66] found that when a mixture of 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazole-3-one [91] and sodium azide was grinded with anhydrous aluminum chloride for 20 minutes , then the mixture was poured into water and filtered ; a 6-methyl-4-phenyl-4,7-dihydrotetrazolo[5,1-c][1,2,4] triazine was formed [92] :



[91] [92]

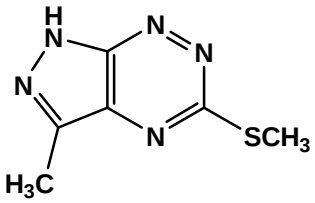
1.7.2 1,2,4-Triazine Derivatives Uses

Compound [93] found to be medically useful in the treatment of tumors [67].



[93]

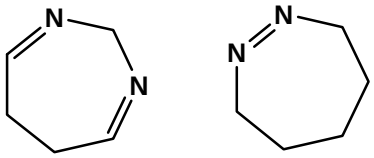
Some pyrazolotriazine derivatives ,such as compound [94] are found to be a moderate inhibitor of bacterial (E-Coli) Purine- Nucleoside Phosphorylase {PNP} , an enzyme employed recently in cancer oriented gene therapy experiments [(68)] :



[94]

1.8.0 Diazepine: General description

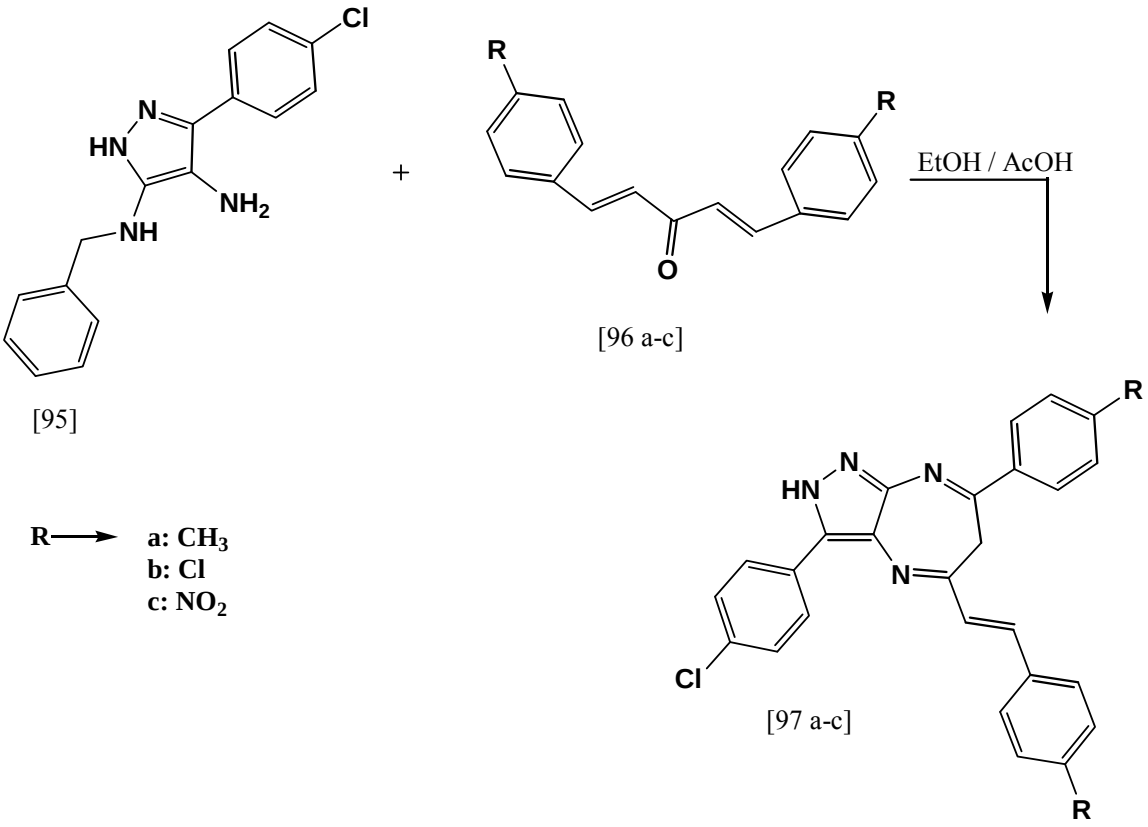
It's a seven-member organic ,heterocylic compound that consist of two nitrogen atoms:



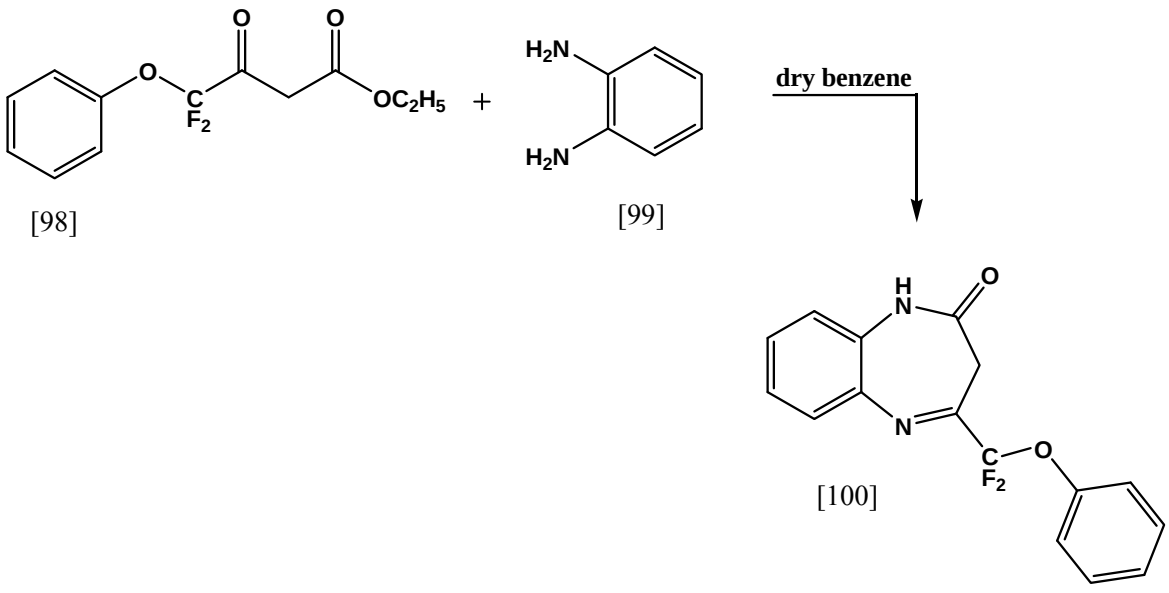
Interest in many of diazepine compounds have been stimulated because of their application in industry, agriculture and because of their biological importance.

1.8.1 Synthesis of Diazepine Derivatives

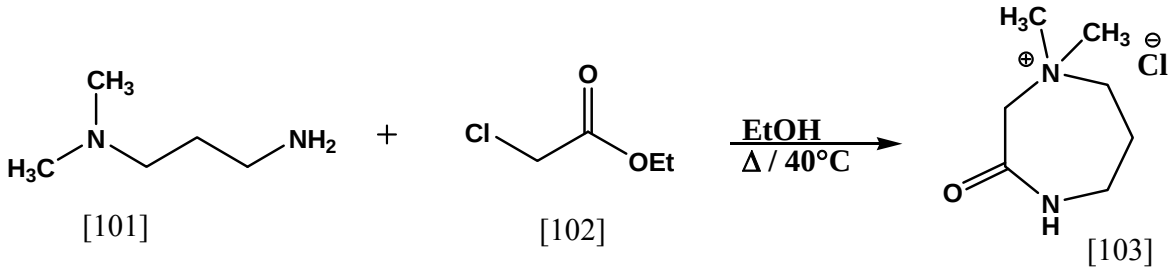
Braulio et.al. [(69)] found that when 3-(4-chlorophenyl)-4-amino-5-benzylamino pyrazole-4,5-diamine [95] was refluxed in ethanol with diarylidene ketones [96 a-c] in the presence of acetic acid , the pyrrazole[3,4-b][1,4]diazepine [97 a-c] was produced :



Solodunkhin et.al. [(70)] found that reaction of ketoester [98] with *o*-phenylenediamine [99] in benzene under neutral condition, furnished 4-(phenoxydifluoro methyl)-1,3-dihydro-1,5-benzodiazepine-2-one [100] :



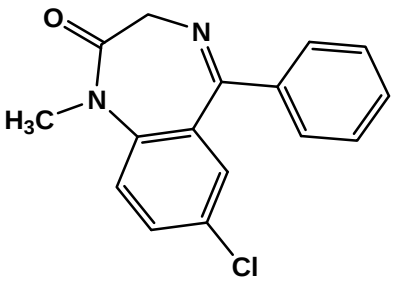
Kowlczk [71] found that quanterization of 1,1-dimethylamino-3-aminopropane[101] with ethylchloroacetate [102] in anhydrous ethanol gave 1,1-dimethyl-3-oxo-1,4-diazipine-1-ium chloride [103] :



[101] [102] [103]

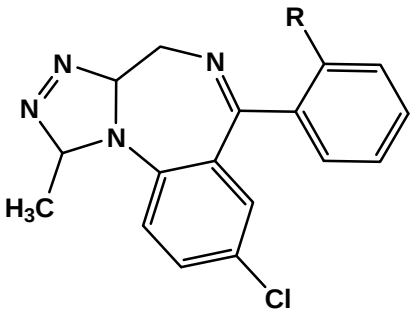
1.8.2 Diazepine Derivatives Uses

Benzodiazepines family of prescription drugs that are used to treat anxiety, sleeplessness, seizures, muscle spasms and alcohol withdrawal. Valium (diazepam) [104] are benzodiazepine sedative drugs, which reduced activities in a certain part of our brain resulting in calming effect [72] :

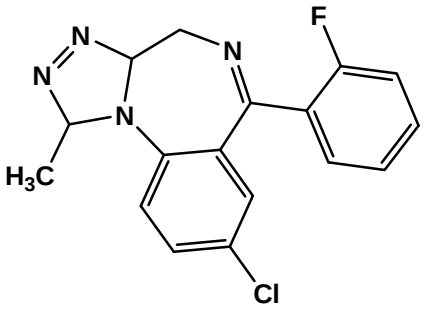


[104]

Alprazolam [105] and Midazolam [106] have an extensive clinical uses as anxiolytic and aesthetics agents respectively [73] :



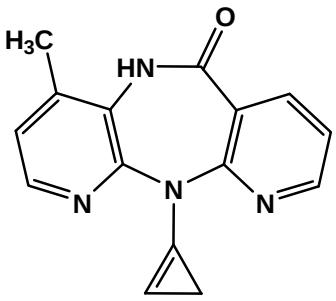
[105]



[106]

R ⟶ H / Cl

Nevirapine [107] shown an activity against HIV-1 Reverse Transcript enzyme [74] :

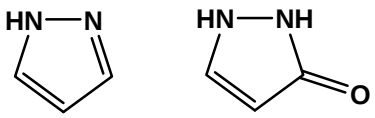


[107]

1.9.0 Pyrazole: General description

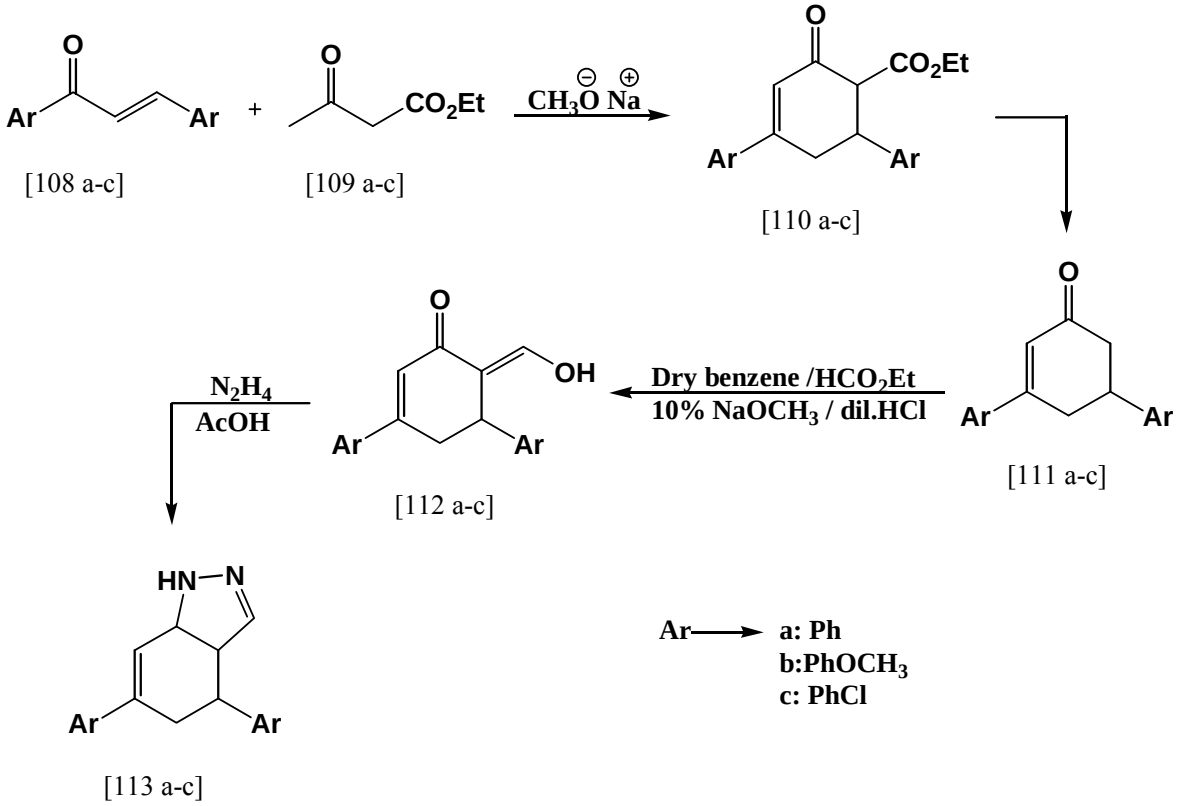
Pyrazole derivatives plays a vital role in many biological process and synthetic drugs. The chemistry of this heterocycles has received much attention in recent years, that is principally due to the unique physical and chemical properties of such compounds which enable their wide application as an ideal scaffold for the synthesis of anti-inflammatory and anti-bacterial agents [75]. The pyrazole ring is a heterocycles compounds containing two contiguous nitrogen atoms and three carbon atoms.

However, very few pyrazole derivatives occurs naturally this may be due to the difficulty for living organism to construct the N-N bond. The most important derivatives of pyrazole are in fact pyrazolones [76]:

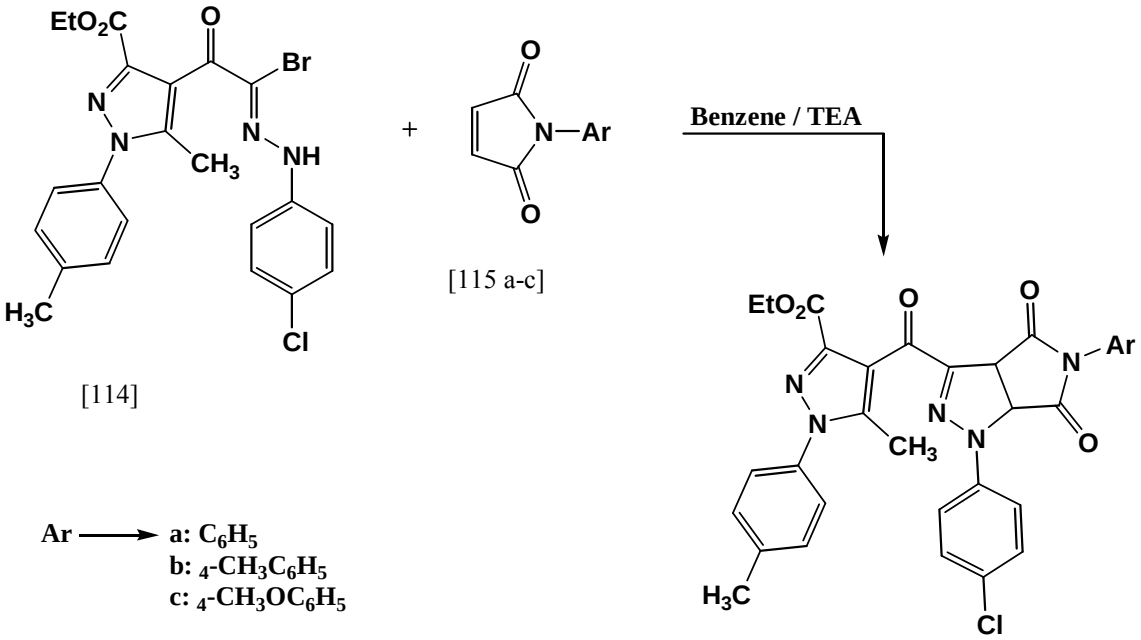


1.9.1 Synthesis of Pyrazole Derivatives

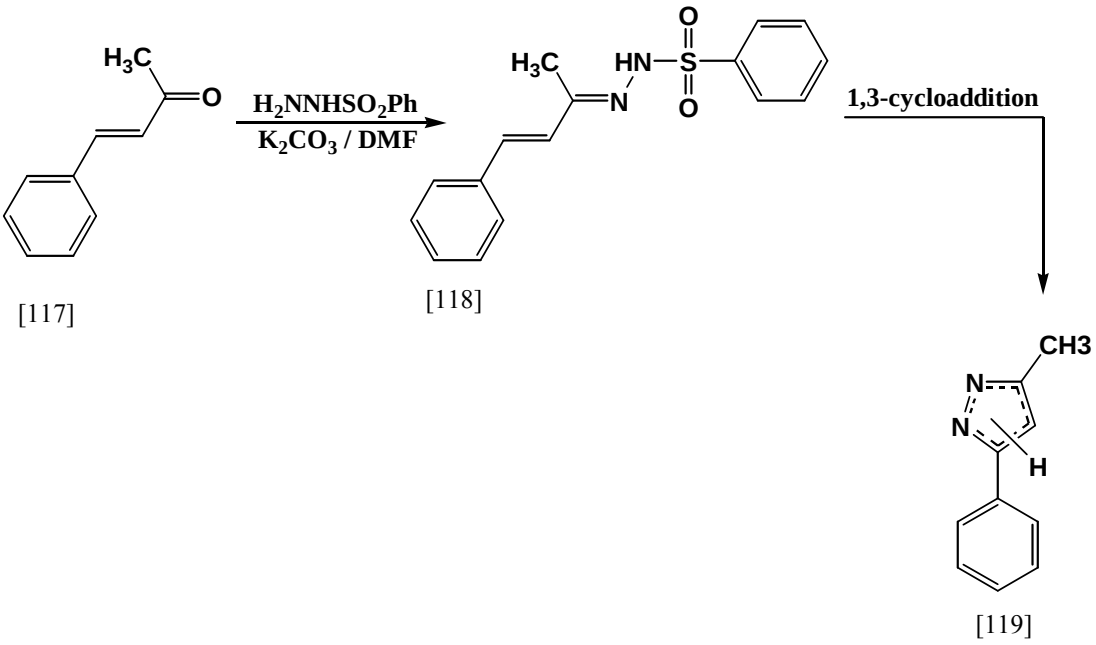
Venkatapuram et.al. [77] prepared 3,5-diaryl-2-cyclohexanones [111 a-c] by decarboxylation of the corresponding 6-carboxyethyl-3,5-diaryl-2-cyclohexene-1-one [110 a-c].The latter were obtained from Konevenagel condensation of ethyl acetoacetate [109 a-c] and 1,3-diaryl-2-propen-1-ones [108 a-c] in presence of sodiumethoxide. Treating of compound [111a-c] with ethyl formate in the presence of sodium ethoxide gave 6-hydroxymethylene -3,5-diaryl-2-cyclohexenones [112 a-c] . Finally the cyclocondensation of [112 a-c] with hydrazine hydrate afforded 1,3-diaryl-4,5-dihydrobenzo[3,4-d]pyrazole [113 a-c] :



Abdel-hamid [78] found that treating of hydrazonoylbromide [114] with the appropriate N-arylmaleimide [115 a-c] in benzene containing few drops of triethylamine, affording pyrrolidino[3,4-d]pyrazoline [116 a-c] :



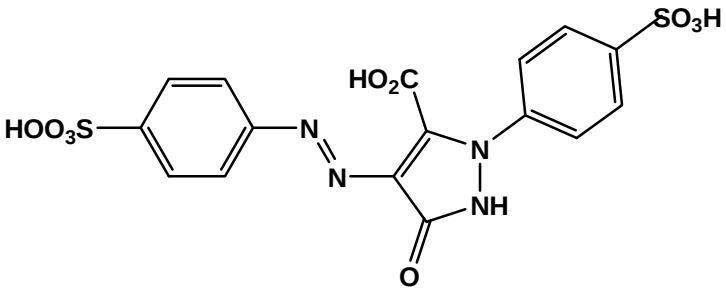
Anna et.al. [79] found that the reaction of compound [117] with benzenesulfonohydrazide afforded the tosylhydrazones [118]. 1,3-cycloaddition of compound [130] yielding pyrazole derivatives [119] :



1.9.2 Pyrazole Derivatives Uses

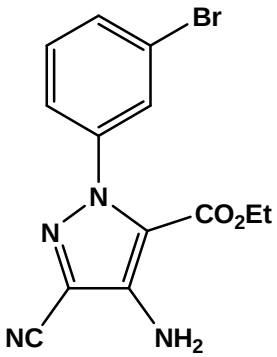
Pyrazole containing compoundshave practcle applications in the medicinal and agrochemical field. The biological activity of pyrazole and its derivates are well documented. Furthermore, the pyrazole ring has shown to be the basic moiety for a number of dyes and drugs [(80)] .

Tartrazine [120] is a yellow dye for wool; this dye has been gaining commercial importance because they are also used as artificial coloring of foods [(81)] :



[120]

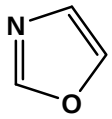
Aminopyrazoles such as ethyl-4-amino-1-(3'-bromophenyl) -3-cyano-1*H*-pyrazole-5-carboxylate [121] was found potentially useful to prevent protein aggregation which is the first phase of Al-Zheimer or Creuts-Jakob disease [(82)]:



[121]

1.10.0 Oxazole: General description

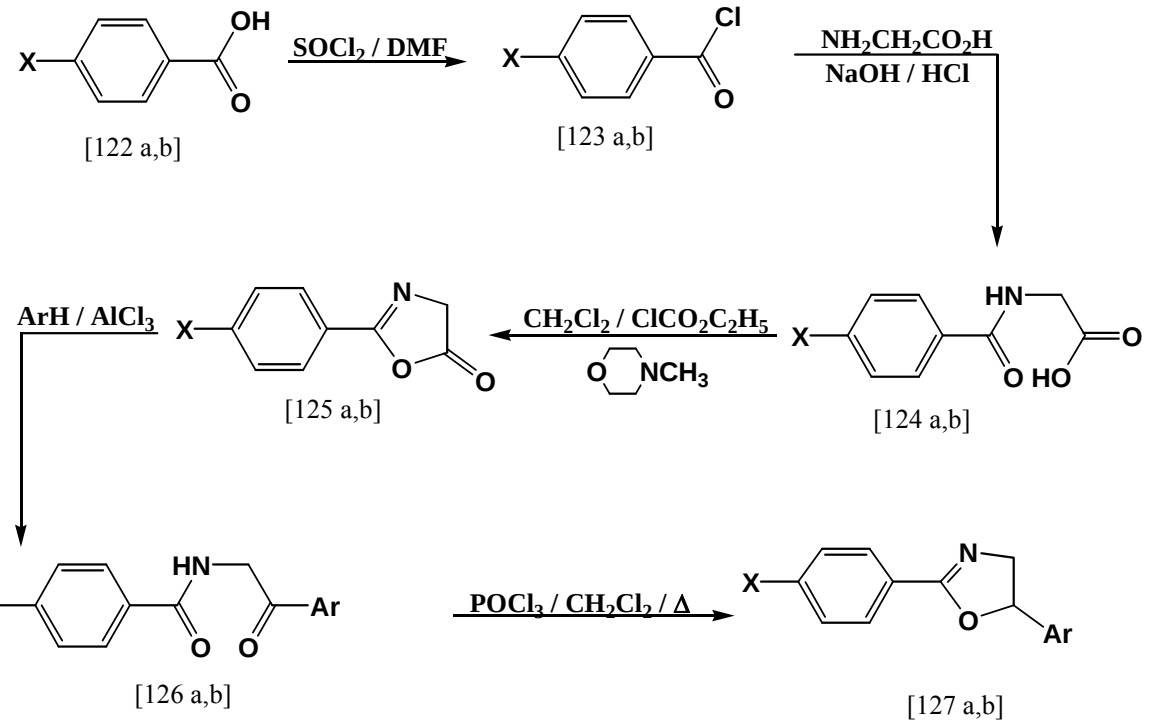
Oxazole is the parent compound for huge class of heterocyclic aromatic organic compound. Oxazole are azoles with an oxygen and nitrogen atoms that are separated by one carbon atom. The oxazole molecule are planar with conjugated π-sextet in cyclic system:



Oxazole and its derivatives are used as building block for biochemical and pharmaceutical as well as in other industrial application such as pesticides, dyes, fluorescent brightening agents, textile auxiliaries and plastics [(83)].

1.10.1 Synthesis of Oxazole Derivatives

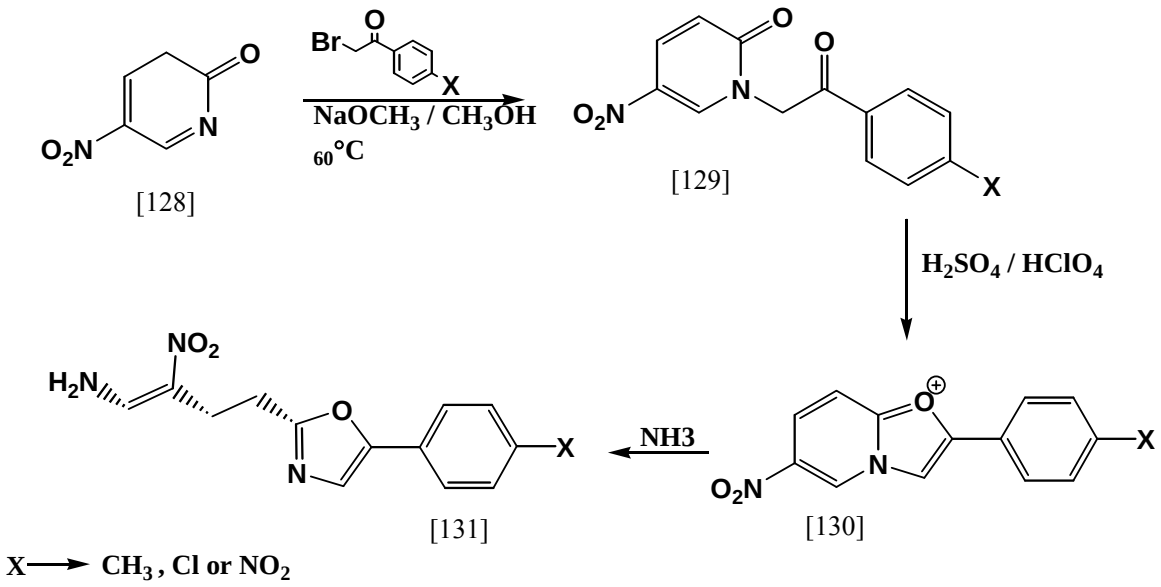
Sehiketanz et.al. [(84)] treated 4-halobenzensulfonyl benzoic acid [122 a,b] with thionylchloride in dimethylformamide yielding acid chloride [123 a,b] which then treated with glycine to afford the corresponding hippuric acid derivatives [124 a,b] which dehydrated to respective azalactones [125 a,b]. The latter were then reacted with benzene, toluene, *m*-xylene and mesitylene under Friedel-Craft reaction conditions using anhydrous aluminum chloride to get the corresponding ketones [126 a,b] which purified and dehydrated in the presence of phosphorus oxychloride to afford the corresponding oxazoles [127 a,b] :



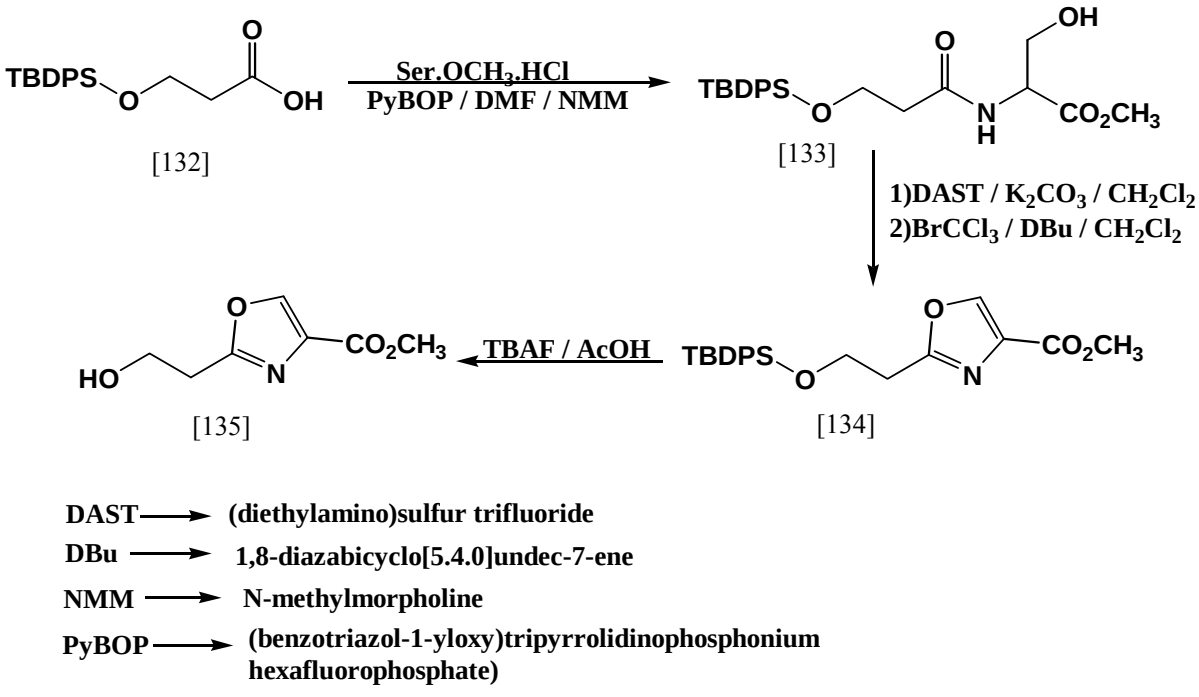
[122 a,b] [123 a,b] [124 a,b] [125 a,b] [126 a,b] [127 a,b]

X ⟶ a: 4-$BrC_6H_4SO_2$- Ar ⟶ a: -C_6H_5
b: 4-$ClC_6H_4SO_2$- b: *p*-$CH_3C_6H_5$

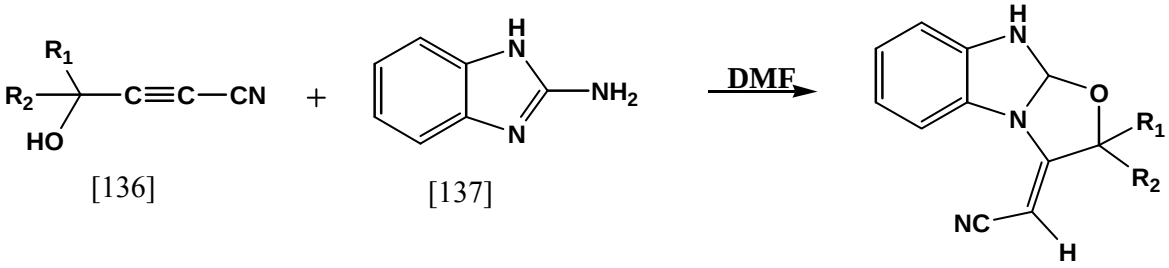
Alexandr et.al.[85] found that 5-nitro-2-pyridone [128] can be selectively N-phenacylated to give N-phenacyl pyridines [129] which then undergo cyclization to 6-nitroxazol[3,2-a]pyridinium salt [130]. These salts are readily react with ammonia leading to the product of 1-amino-2-nitro-4-(5-substituted oxazole-2-yl)-1,3-butadienes [131] :



Parrakari et.al. [(86)] coupled the acid [132] with serine methyl ester hydrochloric acid to afford the hydroxyamide [133] which was cyclized and oxidized to afford the oxazole [134]. The tert-butyldiphenylsilyl (TBDPS) group was removed with tetra-*n*-butyl ammonium fluoride (TBAF) in THF to afford alcohol [135] :



Wahe et.al. [87] reported that ,when 4,4-dialkyl-4-hydroxyacetylenic nitrile [136] was heated under reflux with 2-aminobenzimidazole in [137] in presence of DMF; a 2,2-dialkyl-(2,3-dihydrooxazolo[3,2-a] benzimidazole-ylidene)ethannitrile [138] would be formed :



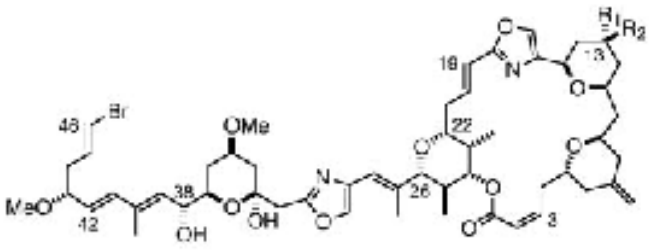
[138]

R_1 ⟶ ***i*-Bu**, C_2H_5, C_2H_5

R_2 ⟶ CH_3, CH_3, C_2H_5

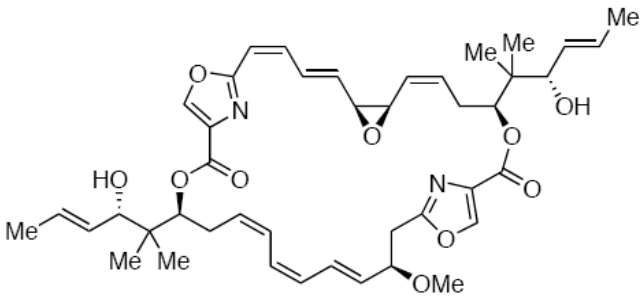
1.10.2 Oxazole Derivatives Uses

Phorboxazole [139] are natural product extracted from the rare Indian ocean sponge (phorbasps) that display unprecedented cytostatic activity against all 60-cell lines of the National Cancer Institution. This compound ranked among the potent cyctostatic agents discovered to date [88] :

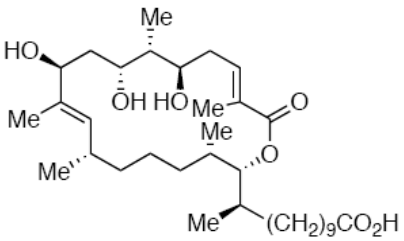


[139]

Oxazole complexes have a biological activity; Disorazole [140] has an anti-proliferative activity and Sorangiolid [141] has biological activities of bactericidal [89] :



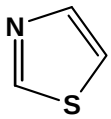
[140]



[141]

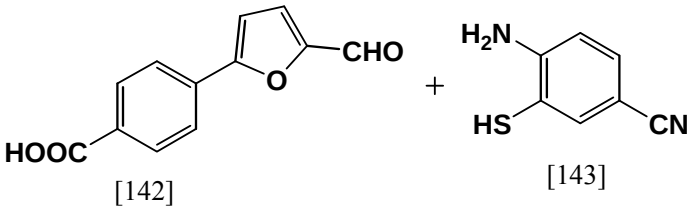
1.11.0 Thiazole: General description

It's a clear to pale yellow flammable liquid with a pyridine-like odor and the molecular formula C_3H_5NS. It's a five-member aromatic ring in which two of the ring atoms are nitrogen and sulfur and the other three are carbon atoms:



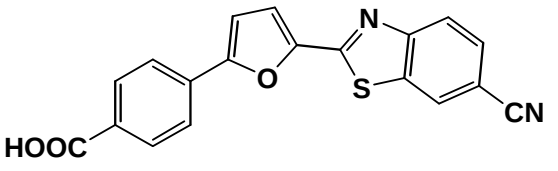
1.11.1 Synthesis of Thiazole Derivatives

Livio et.al. [90] synthesized 4-[5-(6-cyano-1,3-benzthiazole-2-yl)furan-2-yl]benzoic acid [144] from the appropriate aldehyde [142] and 4-amino-3-mercaptobenzonitriles[143]:



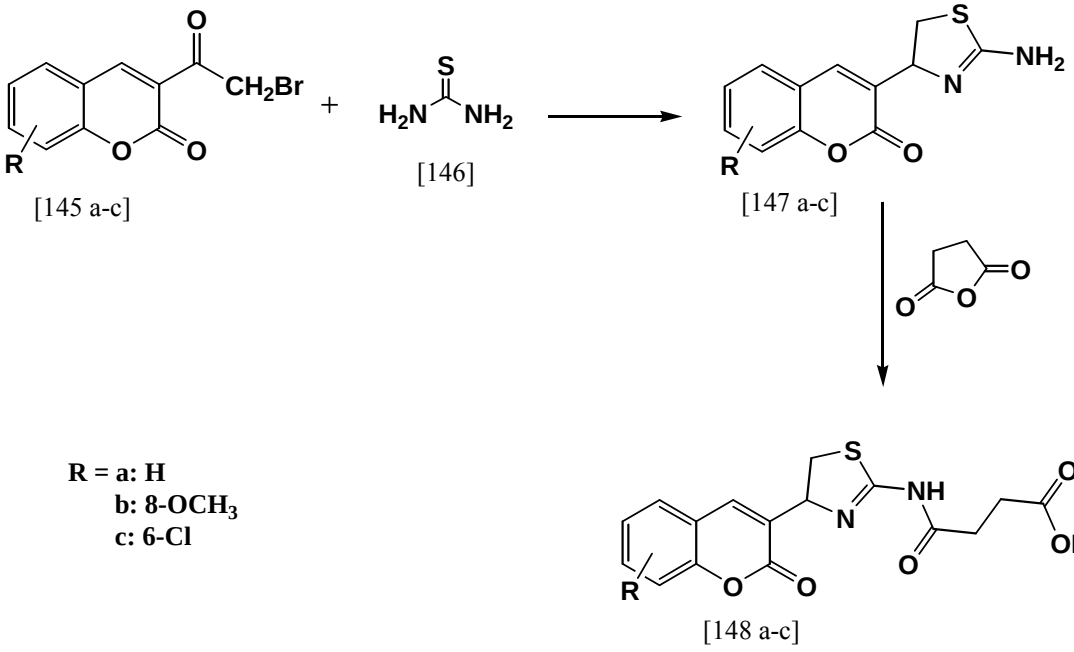
[142]

[143]

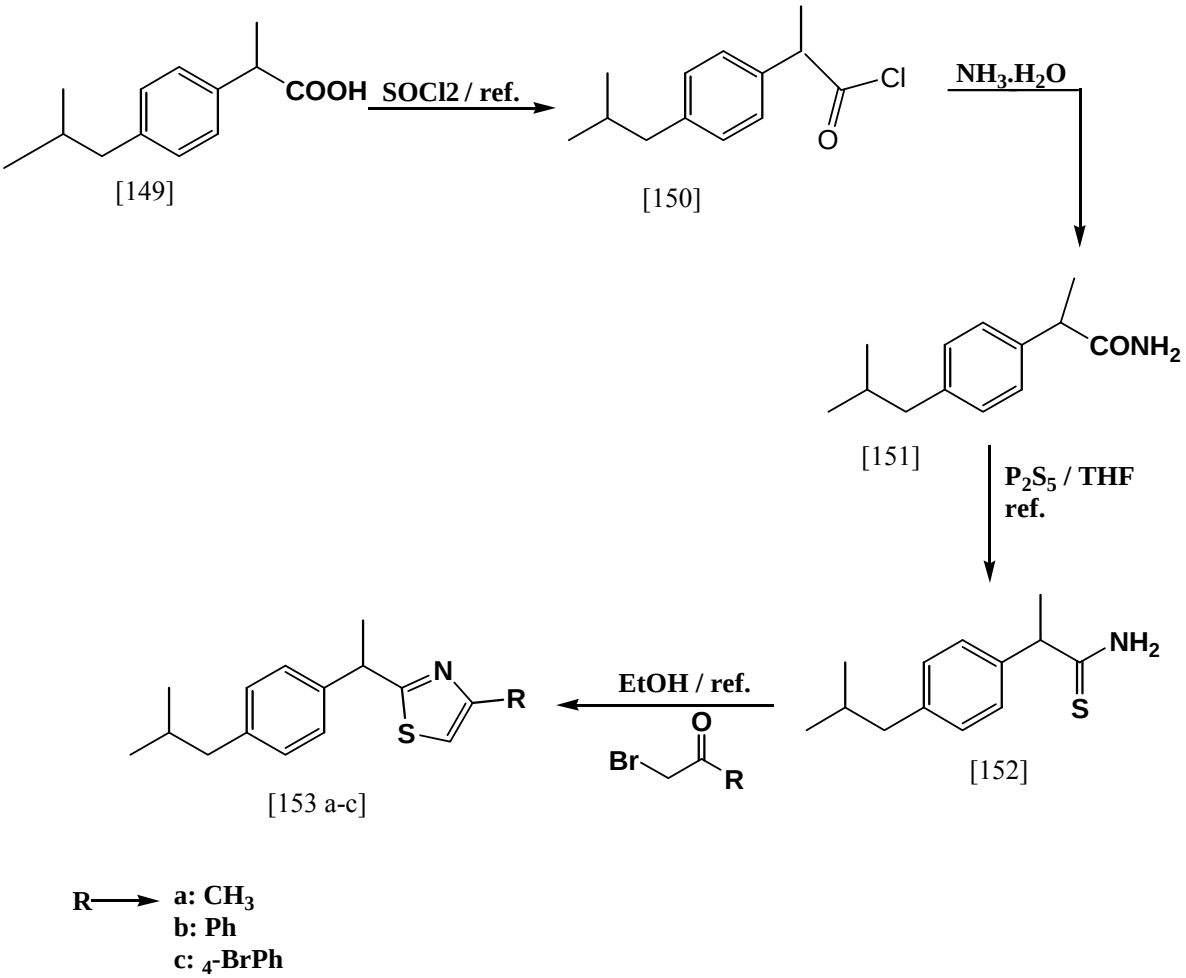


[144] :

Zhuravel et.al. [91] obtained 2-amino-4-(coumarin-3yl)thiazole [147 a-c] by reaction of 3-(ώ-bromoacetyl)substituted coumarine [145 a-c] with thiourea [146]; then it was directly acylated with succinic anhydride to afford 3-[4-(R'-coumarine-3-yl)-1,3-thiazole-2-yl carbomoyl]propanoic acid [148 a-c] :



Chang Bin et.al. [92] treated 2-(4-isobutylphenyl)propanoic acid [149] with thionylchloride to afford acylchloride [150] which react with 28% ammonia to give amide [151] . A suspension of [151] and P_2S_5 in dry THF was heated under reflux to afford thioamide [152]. The latter was cyclized through refluxing with α-bromoketone in absolute ethanol to yield 2-(1-(4-*iso*-butylphenyl)ethyl)-4-substituted thiazole [153 a-c] :

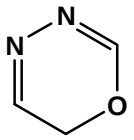


[149] [150] [151] [152] [153 a-c]

R ⟶ **a: CH_3**
b: Ph
c: $_4$-BrPh

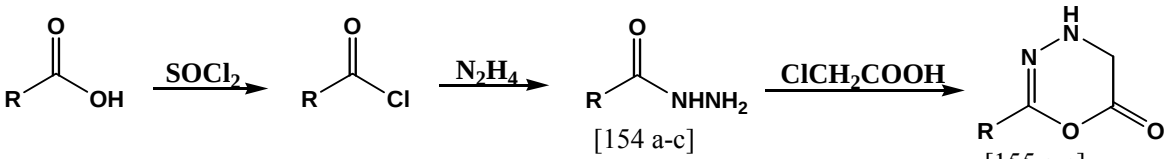
1.12.0 Oxadiazine: General description

Oxadaizine is a heterocyclic ring analogue to the six-membered benzene, but with three carbon atoms replaced by two nitrogen atoms and one oxygen atom:



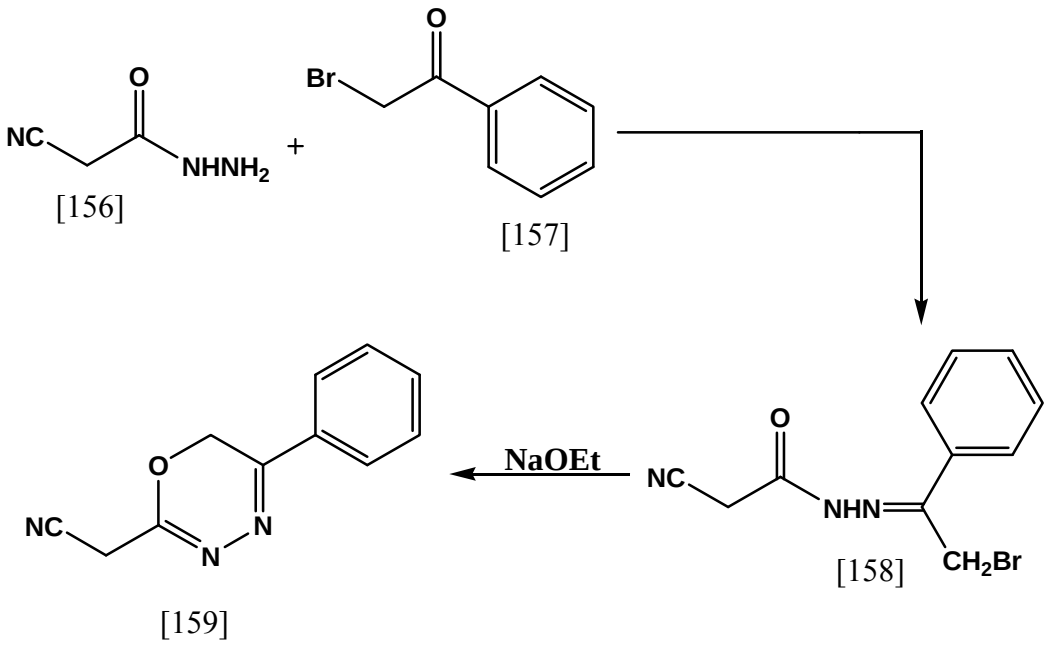
1.12.1 Synthesis of oxadiazine:

Amine et.al. [93] found that when hydrazide [154 a-c] were refluxed with chloroacetic acid in ethylalcohol, 1,3,4-oxadiazine derivatives [155 a-c] were produced :



R → a: $C_{13}H_{27}$
b: $C_{15}H_{31}$
c: $C_{17}H_{35}$

Rafat et.al.[94] found that the reaction of cyanoacetylhydrazine [156] with α-bromoacetophenon [157] gave the condensation product of β-cyano-acetylhydrazone [158]. The latter compound underwent ready cyclization to give the 1,3,4-oxadiazine derivatives [159] :



AIM OF WORK:

Nitrogen containing heterocycles are frequently found in privileged structures (pharmacophores) but their incorporation sometimes possess special problems (multi-step sequence, lack of generality, preparation from cyclic precursors, etc…); thus, only a limited number of strategies have been successfully applied in the synthesis of heterocyclic scaffolds. The development of new, rapid and clean synthesis routes toward focused libraries of such compounds is therefore of great importance to both medicinal and synthetic chemists. Consequently, the design and development of procedure for the generation of new heterocycles receive growing interest.

Five, six and seven membered heterocyclic compounds have been of great interest due to their variety of applications particularly in the field of chemotherapeutic, anti-microbial, pesticidal, agriculture and fungicidal. Therefore this work was directed toward the synthesis of these heterocyclic derivatives and investigation of their anti-bacterial activity.

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Chapter two

Experimental

2.1 Chemicals:

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

Table (2-1): Chemicals and their manufacture

Chemicals	Supplied from
Absolute ethanol	BDH
Acetic acid	BDH
2-aminopyridine	BDH
2-aminothiazole	Merck
Carbon disulfide	Merck
Chloroacetic acid	BDH
Chloroacetamide	Merck
Ethyl acetoacetate	BDH
Formic acid	BDH
Glutaric acid	Merck
Hydrazine hydrate	BDH
Hydrochloric acid	BDH
Isatin	Merck
Malonic acid	Merck
1,2-naphthaquinon	Merck
Phenacyl Chloride	BDH
o-Phenylene diamine	BDH
p-Phenyl phenacyl bromide	BDH
Phthalic acid	Merck
Pipronal	BDH

Chemicals	Supplied from
Potassium hydroxide	BDH
Thioreau	Merck
Urea	Merck

2.2 Techniques:

2.2.1 Melting Point:

Melting points were recorded on a hot stage Gallen Kamp melting point apparatus and were uncorrected.

2.2.2 Thin layer Chromatography:

Thin layer chromatography (TLC) was carried out using Fertigfollen percolated sheets type Polygram SilG, and the spots were developed with iodine vapor.

2.2.3 Infra-Red Spectrophotometer:

FT-IR spectra were recorded using Fourier Transform infrared Shimadzu FTIR-8400 infrared spectrophotometer, Japan, KBr disc or thin film was performed by central organization of standardization and quality control center.

2.2.4 ^{1}H-NMR:

^{1}H-NMR spectra were recorded on a Fourier transform Bruker spectrometer operating at 300.13 MHz with tetramethylsilane as internal standard in DMSO-d_6. Measurements were made at the Drug and Natural Product Synthesis Department, University of Vienna, Austria.

2.2.5 ^{13}C-NMR:

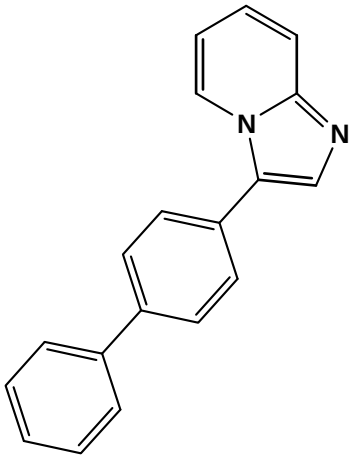
^{13}C-NMR spectra were recorded on a Fourier transform Bruker spectrometer operating at 75.47 MHz in DMSO-d_6**.** Measurements were made at the Drug and Natural Product Synthesis Department, University of Vienna, Austria.

2.2.6 Biological Activity:

The biological activity was performed by Biotechnology department, College of Science / AL-Nahrain University.

2.3 Synthesis of Compounds:

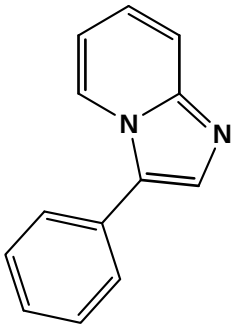
2.3.1 Synthesis of 3-biphenyl-4-ylimidazo[1,2-a]pyridine [1] [95]



[1]

2-Aminopyridine [0] (0.02 mole, 2g) and 4-phenylphenacylbromide (0.02 mole, 5.5g) were heated under reflux for 25 hours in absolute ethanol (25ml). After cooling the formed precipitate was filtered, washed with absolute ethanol, recrystalized and dried to give the final product. Yield 77% ; M.P.= (220-222)°C.

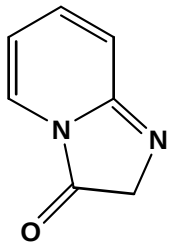
2.3.2 Synthesis of 3-phenylimidazo[1,2-a]pyridine [2] [95]



[2]

A mixture of 2-aminopyridine [0] (0.02 mole, 2g) and phenacylchloride (0.02 mole, 3.08g) in absolute ethanol (20ml) was refluxed for 24 hours. Evaporation in vacoo gave the desired product. Yield 73%; M.P. gummy.

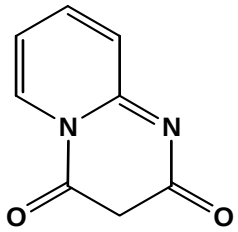
2.3.3 Synthesis of imidazo[1,2-a]pyridine-3(2H)-one [3] (95)



[3]

2-Aminopyridine [0] (0.02 mole, 2g) was added to a mixture of chloroacetic acid (0.02 mole, 1.89g) and (15ml) absolute ethanol. The reaction mixture was refluxed for 12 hours, and then the solvent was distilled off. The precipitate was filtered off and recrystalized from ethanol. Yield 78%; M.P.= (156-158)°C.

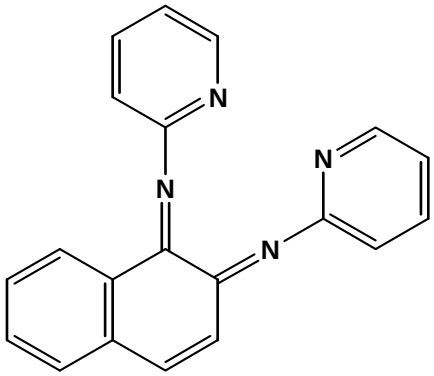
2.3.4Synthesis of 2H-pyrido[1,2-a]pyridine-2,4-(3H)-dione [4] (96)



[4]

A mixture of 2-aminopyridine [0] (0.02 mole, 2g), malonic acid (0.02 mole, 2.08g) and a (20ml) absolute ethanol was refluxed for 14 hours. Cooling the mixture followed by filtration and recrystaliztion from ethanol afforded the target molecule. Yield 96%; M.P. = (158-160) °C.

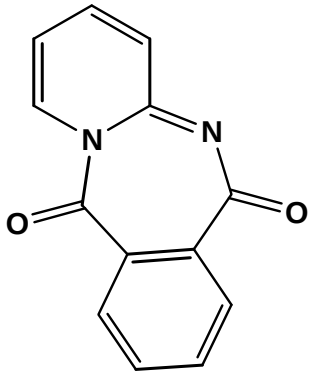
2.3.5 *Synthesis of N,N'-1,4-dihydronaphthalene-2,3-diylidene dipyridine-2-amine* [5]



[5]

2-Aminopyridine [0] (0.04 mole, 4g) was refluxed with 1,2-naphthaquinone (0.02 mole, 6.71g) in (25 ml)absolute ethanol. The mixture was refluxed with absolute ethanol for 10 hours; cooling, filtration and recrystaliztion from ethanol afforded the final product. Yield 83%; M.P. = (196-198) °C.

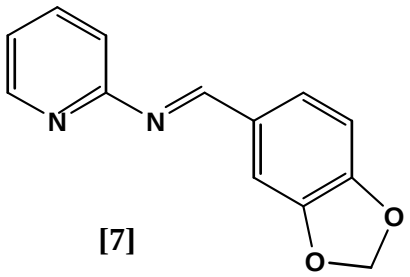
2.3.6 *Synthesis of pyrido[1,2-a][2,4]benzodiazepine-6,11-dione* [6] [97]



[6]

A mixture of 2-aminopyridine [0] (0.02 mole, 2g) and phthalic acid (0.02 mole, 2.32g) was refluxed in (20 ml) absolute ethanol for 12 hours. Then the reacting mixture was recrystalized and washed with ether to give the final product. Yield 84%; M.P. = (80-83) °C.

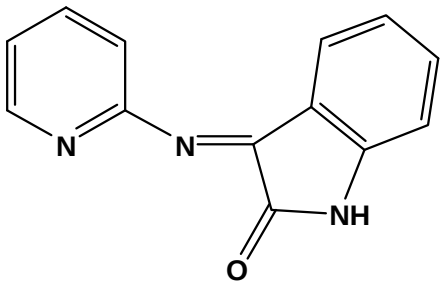
2.3.7 *Synthesis of N-(1,3-benzodioxol-5-ylmethylidene)pyridine-2-amine* [7]



[7]

A mixture of 2-aminopyridine [0] (0.02 mole, 2g) and pipronal (0.02 mole, 3g) was refluxed in (25 ml) absolute ethanol for 16 hours. The reaction mixture was reduced to one-third its volume, recrystalized and a gummy product was obtained as a final product. Place it in a vacuum oven for 5-days afforded the final solid product. Yield 86%; M.P. = (213-215) °C.

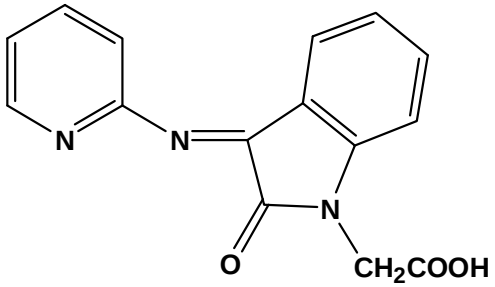
2.3.8 *Synthesis of 3-(pyridine-2-ylimino)-1,3-dihydro-2H-indol-2-one* [8]



[8]

2-Aminopyridine [0] (0.02 mole , 2g) was added to isatin (0.02 mole , 2.94g) in (35 ml) absolute ethanol then the reaction mixture was refluxed for 4 hours, then was filtered. Recrystalization of the product from ethanol then washing with ether afforded fine orange crystals as a final product. Yield 91%; M.P. = (175-177) °C.

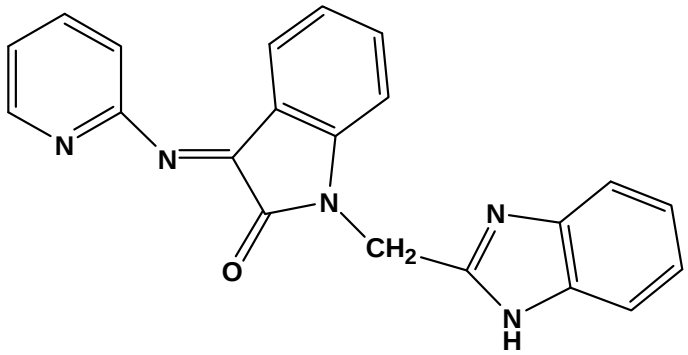
2.3.9 *Synthesis of [2-oxo-3-(pyridin-2-ylimino)dihydro-1H-indol-1-yl] acetic acid* [9]



[9]

A mixture of potassium hydroxide (0.013 mole, 0.56g) and compound [8] (0.013 mole, 3g) was dissolved in (25 ml) absolute ethanol. Then chloroacetic acid (0.013 mole, 1.22g) was added and the reaction mixture was refluxed for 6 hours. The solvent was removed and the formed solid was recrystalized from ethanol. Yield 76%; M.P.= (162-164)°C.

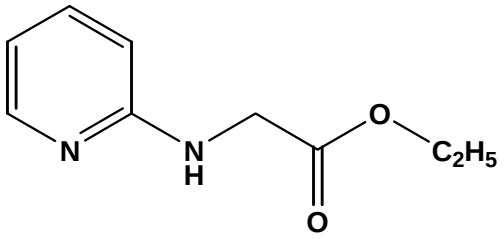
2.3.10 *Synthesis of 1-(1H-benzimidazol-1-ylmetyl)-3-(pyridine-2-ylimino)-1,3-dihydro-2H-indol-2-one* [10] [98]



[10]

Compound [9] (0.007 mole, 2g) was refluxed with *o*-phenylenediamine (0.007 mole, 0.75g) for 5 hours in (20 ml) absolute ethanol. The solvent was reduced to one-third its volume, recrystalized and then acidified with 10% HCl solution to yield the final product. Yield 75%; M.P.=(271-274)°C.

2.3.11 Synthesis of ethyl-N-pyridin-2-ylglycinate [11]

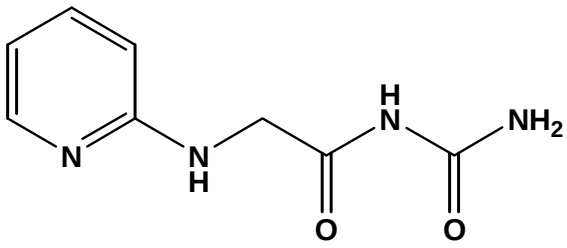


[11]

Ethylchloroacetate (0.27 mole, 29 ml) was added drop wise to a stirred solution of 2-aminopyridine [0] (0.27 mole, 26g), KOH (0.27 mole, 15g) in (60 ml) absolute ethanol. The reaction mixture was refluxed for 5 hours, then it was filtered. The resulting product was dried and recrystallized from ethanol. Yield 97%; M.P. = (242-245)°C.

2.3.12 Synthesis of N-carbamoyl-N_2-pyridin-2-ylglycinamid [12]

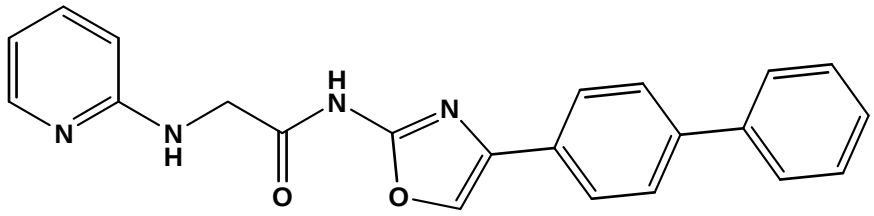
(99)



[12]

Compound [11] (0.02 mole, 4g) was added to urea (0.02 mole, 1.2g) in (25 ml) absolute ethanol. The reaction mixture was refluxed for 6-7 hours, then the solution was filtered and the crude product was recrystalized from ethanol and washed by ether. Yield 70%; M.P. = (195-197)°C.

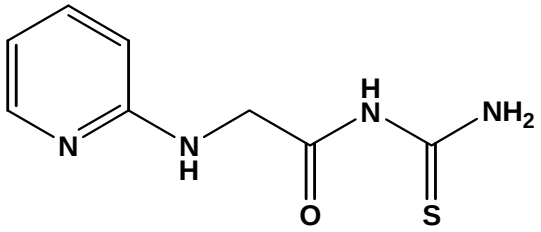
2.3.13 Synthesis of N-(4-biphenyl-4-yl-1,3-oxazol-2-yl)-N_2-pyridine -2-ylglyciamide [13] [100]



[13]

A mixture of compound [12] (0.01 mole, 2g), 4-phenylphenacyl bromide (0.01 mole, 2.75g) and absolute ethanol (20 ml) was refluxed for 10 hours. After distillation off the solvent was removed under reduced pressure and the target product was obtained by filtration and recrystalzation. Yield 83%; M.P. = (161-164)°C.

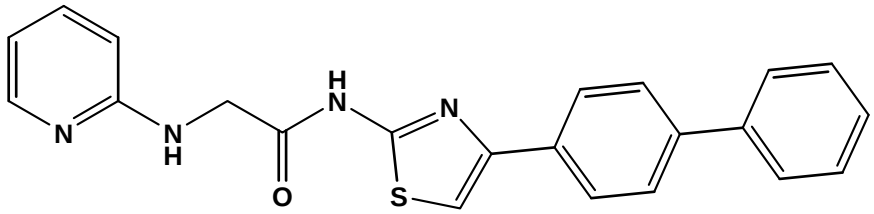
2.3.14 Synthesis of N-carbamothioyl-N_2-pyridin-2-ylglycinamid [14] [99]



[14]

Compound [11] (0.02 mole , 4g) was added to thiourea (0.02 mole , 1.52g) in (20 ml) absolute ethanol. The reaction mixture was refluxed for 6-7 hours. After that , the formed solid product was filtered off and recrystallized from ethanol. Yield 88%; M.P. = (188-190) °C.

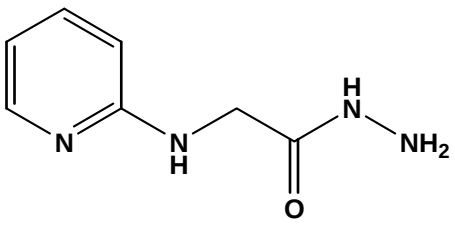
2.3.15 *Synthesis of N-(4-biphenyl-4-yl-1,3-thiazol-2-yl)-N_2-pyridine-2-ylglyciamide* [15] (100)



[15]

A mixture of compound [14] (0.009 mole, 2g) and 4-phenylphenacyl bromide (0.009 mole, 2.47g) in (20 ml) absolute ethanol was heated under refluxe for 10 hours. After concentration and cooling, the formed solid product that forms was filtered off and recrystallized from ethanol. Yield 78%; M.P. = (178-180) C°

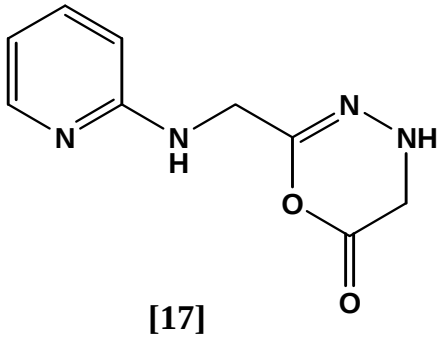
2.3.16 *Synthesis of 2--(pyridine-2-ylamino)acetohydrazide* [16]



[16]

A mixture of ester [11] (0.08 mole, 16g) and hydrazine hydrate (0.08 mole, 2.48 ml) was refluxed for 3 hours, ethanol (40 ml) was added and the reaction mixture was refluxed for another 3 hours. The separated precipitate was collected and recrystalized from ethanol. Yield 85%; M.P. = (220-222) °C.

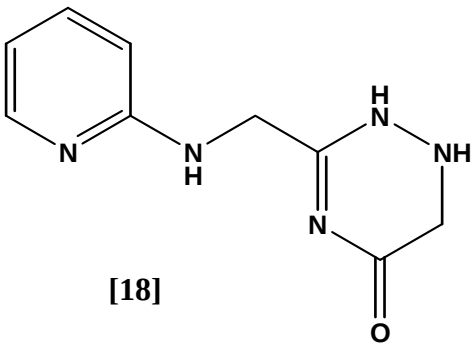
2.3.17 Synthesis of 2-[(pyridine-2-ylamino)methyl]-4,5-dihydro-6H-1,3,4-oxadiazine-6-one [17] [101]



[17]

A mixture of compound [16] (0.012 mole, 2g) and potassium hydroxide (0.012 mole, 0.67g) was stirred with gently heating until the latter was completely dissolved. After cooling to room temperature, chloroacetic acid (0.012 mole, 0.13g) was added and the reaction mixture was refluxed for 14 hours. The separated solid was filtered and recrystalized. Yield 56%; M.P. = (313-315) °C.

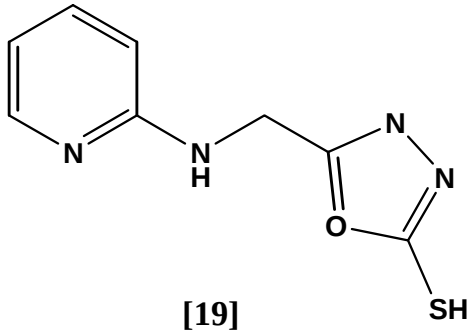
2.3.18 Synthesis of 3-[(pyridine-2-ylamino)methyl]1,6-dihydro-1,2,4-triazin-5(2H)-one [18] (101)



[18]

A mixture of compound [16] (0.012 mole, 2g) and chloroacetamide (0.012 mole, 1.12g) and (20 ml) absolute ethanol was refluxed for 20 hours. The solvent was distilled off and the solid that separated was dried and recrystalized from ethanol. Yield 69%; M.P. = (189-192) °C.

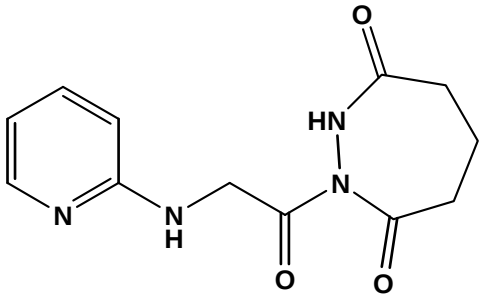
2.3.19 Synthesis of 5-[(pyridine-2-ylamino)methyl]-1,3,4-oxadiazole-2-thiol [19] [102]



[19]

To a solution of carbohydrazide [16] (0.012 mole, 2g) in ethanol (25 ml), potassium hydroxide (0.012 mole, 0.67g) and carbon disulfide (0.012 mole, 0.72 ml) were added respectively. The mixture was refluxed for 17 hours or until most of the hydrogen sulfide has been evolved. The solvent was evaporated in vacuum, the separated solid was filtered and recrystalized from ethanol. Yield 85%; M.P. = (146-149) °C.

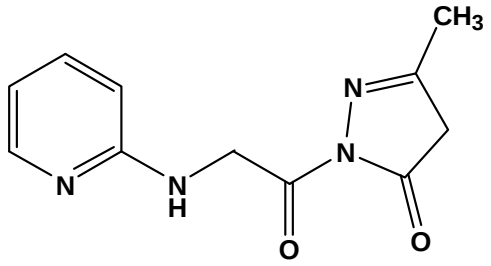
2.3.20 Synthesis of 1-(N-pyridine-2-ylglycyl)-1,2-daizepane-3,7-dione [20] [103]



[20]

Compound [16] (0.012 mole, 2g) and glutaric acid (0.012 mole, 1.58g) was heated under reflux in (20 ml) absolute ethanol for 21 hours. The excess solvent was evaporated and the crude product was collected by filtration. The target compound was obtained through recrystallization from ethanol. Yield 79%; M.P. = (200-203) °C.

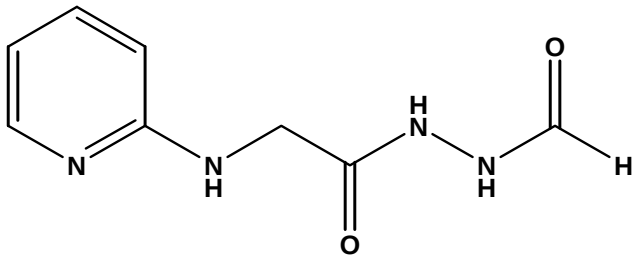
2.3.21 *Synthesis of 5-methyl-2-(N-pyridin-2-ylglycyl)-2,4-dihydro-3H-pyrazol-3-one* [21] [104]



[21]

A mixture of compound [17] (0.012 mole, 2g) and ethylacetoacetate (0.012 mole, 1.56ml) in (20 ml) absolute ethanol was heated under reflux for 21 hours. After concentration, the precipitate was collected by filtration recrystalized and dried to obtain the final product. Yield 81%; M.P.= (213-215)°C.

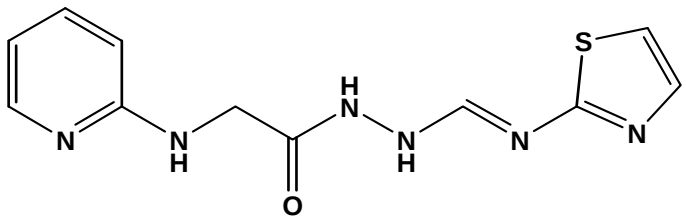
2.3.22 *Synthesis of N'-formyl-2-(pyridine-2-ylaminoaceto-hydrazide* [22] [103]



[22]

Formic acid (0.02 mole, 0.75ml) was added drop wise to compound [16] (0.02 mole, 4g) in (25 ml) absolute ethanol. The reaction mixture was heated under reflux for 14 hours. The excess solvent was evaporated and the formed solid was filtered off. Recrystaliztion from ethanol give the final product. Yield 82%; M.P. = (224-227) °C.

2.3.23 *Synthesis of 2-(pyridine-2-ylamino)-N'-[(1,3-thiazol-2-ylimino)methyl]acetohydrazide* [23] [105]



[23]

Compound [22] (0.01 mole, 2g) was refluxed for 11 hours with 2-aminothiazole (0.01 mole, 1g) in (15 ml) absolute ethanol. The formed precipitate was collected by filtration then recrystalized from ethanol, to obtain the final product. Yield 77%; M.P. = (255-257) °C.

Table (2-2): Physical properties of compounds [1-23]

Comp. No.	Molecular formula	Molecular Weight (g/mole)	Yield (%)	M.P (^{o}C)	color
1	$C_{19}H_{14}N_2$	270	77	220-222	Fine yellow
2	$C_{13}H_{10}N_2$	194	73	gummy	Deep green
3	$C_7H_6N_2O$	134	78	156-158	Pink
4	$C_9H_7NO_2$	151	96	158-160	Pale yellow
5	$C_{20}H_{16}N_4$	312	83	196-198	Black

6	$C_{13}H_{10}N_2O_2$	226	84	80-83	Pale yellow
7	$C_{13}H_{10}N_2O_2$	226	86	213-215	Purple
8	$C_{13}H_9N_3O$	223	91	175 -177	Orange
9	$C_{15}H_{11}N_3O_3$	281	76	162-164	Deep red
10	$C_{21}H_{15}N_5O$	353	75	271 -274	Deep green
11	$C_9H_{12}N_2O_2$	180	97	242-245	Brown
12	$C_8H_{10}N_4O_2$	194	70	195-197	Deep yellow
13	$C_{22}H_{18}N_4O_2$	370	83	161-164	Red
14	$C_8H_{10}N_4OS$	210	88	188-190	Orange
15	$C_{22}H_{18}N_4OS$	386	78	178 -180	Light yellow
16	$C_7H_{10}N_4O$	166	85	220-222	Light brown
17	$C_9H_{10}N_4O_2$	206	56	313-315	Red-brown
18	$C_9H_{11}N_5O$	205	69	189-192	Deep brown
19	$C_8H_8N_4OS$	208	85	146-149	Pale orange
20	$C_{12}H_{12}N_4O_3$	260	79	200-203	pink
21	$C_{11}H_{12}N_4O_2$	232	81	213-215	Brown
22	$C_8H_{10}N_4O_2$	194	82	224-227	Brown
23	$C_{11}H_{12}N_6OS$	276	77	255-257	Dark green

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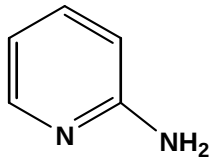
Chapter Three

Result and Discussion

3.0 2-Aminopyridine [0]



Compound bearing pyridine moiety are reported to possess a number of interesting biological activities such as anti-allergic, anti-tubercular, anti-cancer, antihistaminic, etc.[106]. In the light of these findings, we reported here the synthesis of novel heterocyclic compounds derived from 2-aminopyridine.

The F.T.I.R. spectrum of 2-aminopyridine, figure (3-1), shows the following characteristic bands: the two bands in the 3313 cm^{-1} and 3164 cm^{-1} were due to asymmetric and symmetric stretching vibration of (NH_2) group, respectively. Beside this, the bands at 3072 cm^{-1}, 1629 cm^{-1}, 1600 cm^{-1} represented the stretching vibrations of aromatic (C-H), (C=N) and (C=C) groups, respectively [5].

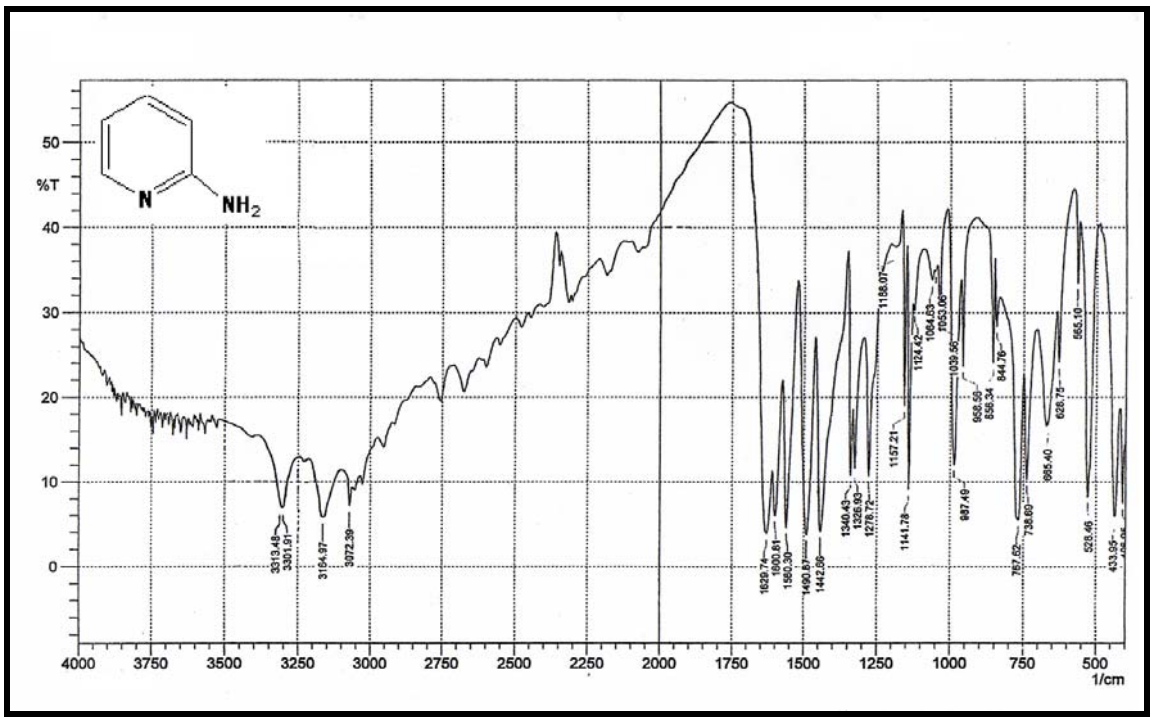
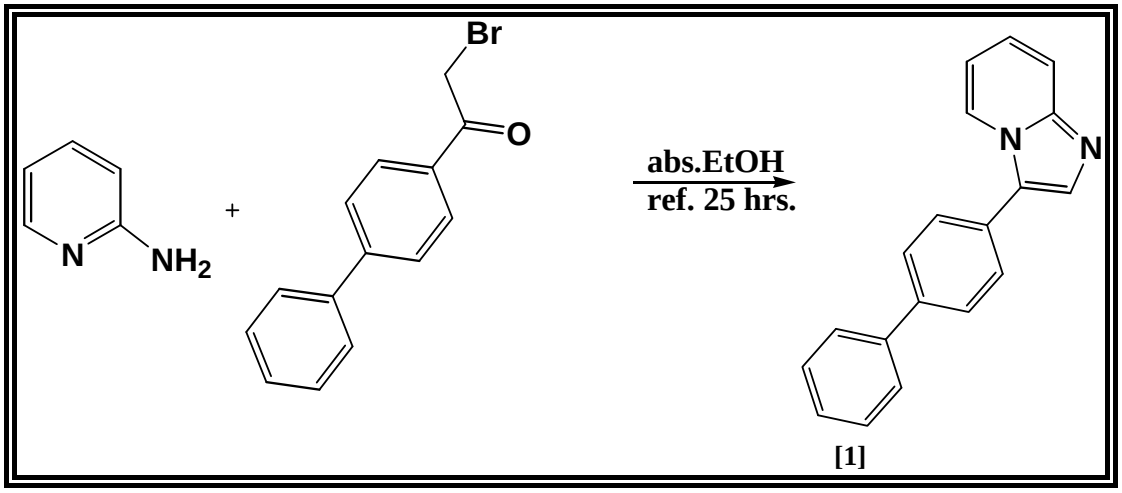


Fig (3-1): FT-IR spectrum of 2-aminopyridine [0]

3.1 Preparation of 3-biphenyl-4-ylimidazo[1,2-a]pyridine [1]

2-Aminopyridine was refluxed with 4-phenylphenacylbromide in absolute ethanol for 25 hours to afford the titled compound.



[1]

The structure of compound [1] was confirmed by its M.P. and FT-IR spectrum.

The disappearance of bands at 3313 cm^{-1} and 3164 cm^{-1}attributed to (NH_2) stretching frequency together with appearances of band at 3058 cm^{-1} assignable to (C-H) aromatic stretching frequency are good evidence for the structure given to the titled compound, figure (3-2). Furthermore, the bands at 1654 cm^{-1} and 840 cm^{-1} attributable to the υ(C=N) of imidazole ring [(13)] and out of plane bending of *p*-disubstituted benzene ring, respectively, agree with the proposed structure assigned to this compound.

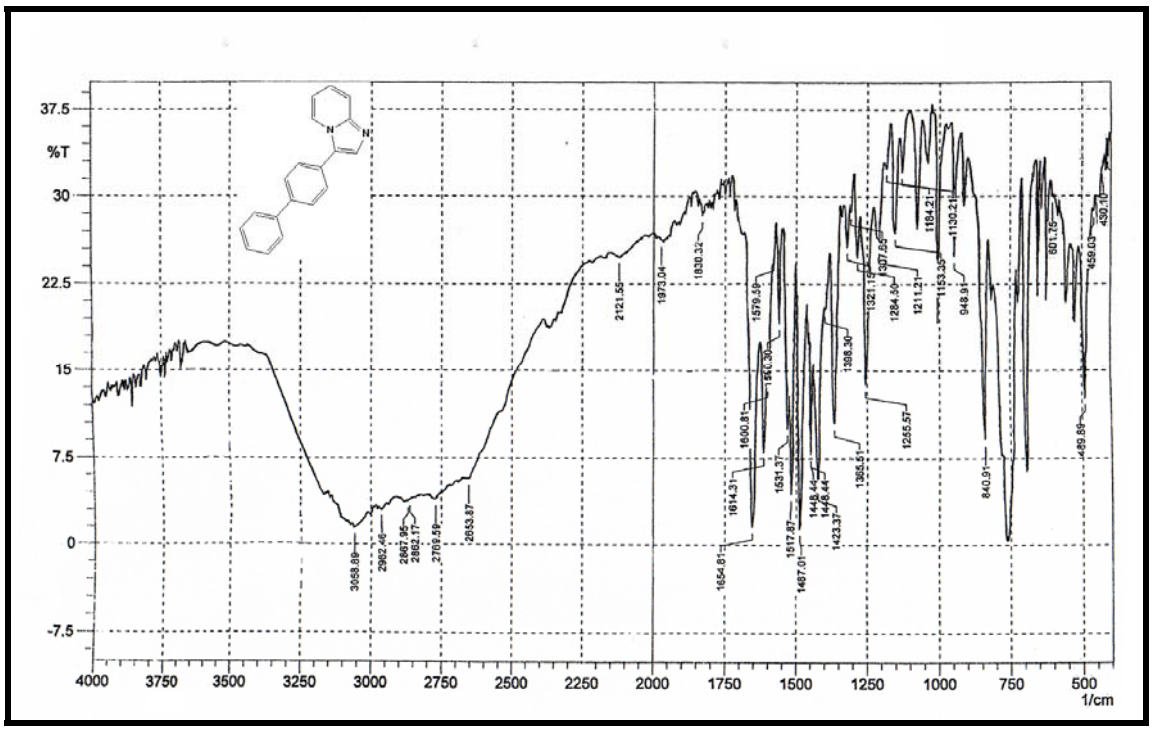
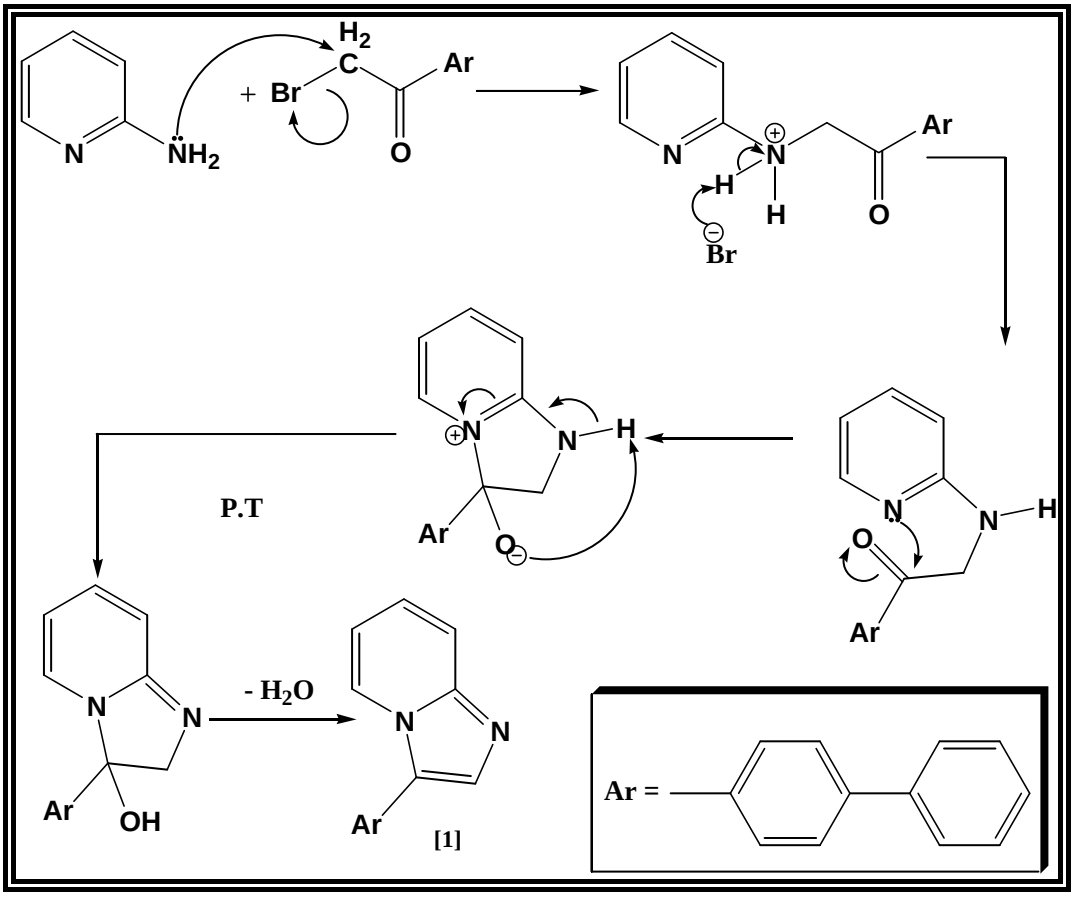


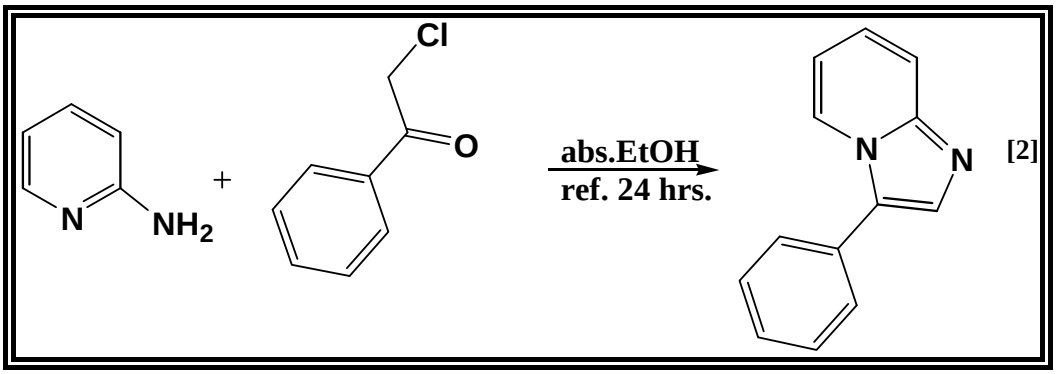
Fig (3-2): FT-IR spectrum of 3-biphenyl-4-ylimidazo[1,2-a]pyridine [1]

For the synthesis of the target titled heterocyclic compound, the following reaction mechanism may be outlined [(95)]:



3.2 *Preparation of 3-phenylimidazo[1,2-a]pyridine* [2]

The 3-phenylimidazo[1,2-a]pyridine [2] was obtained by refluxing equimolar amounts from 2-aminopyridine and phenacylchloride in absolute ethanol. The synthesized compound was characterized by its M.P. and FT-IR spectrum:



In FT-IR spectrum, the disappearance of (NH_2) stretching band of 2-aminopyridine was the most characteristic evidence for the success of cyclization step. Figure (3-3) also shows bands at 3060 cm^{-1} and 1656cm^{-1} assigned to υ(C-H) aromatic and υ(C=N) of imidazole ring [(107)]. Other characteristic band of aromatic system is the appearance of (C-H) at 750 cm^{-1} and 688 cm^{-1} of mono-substituted aromatic ring.

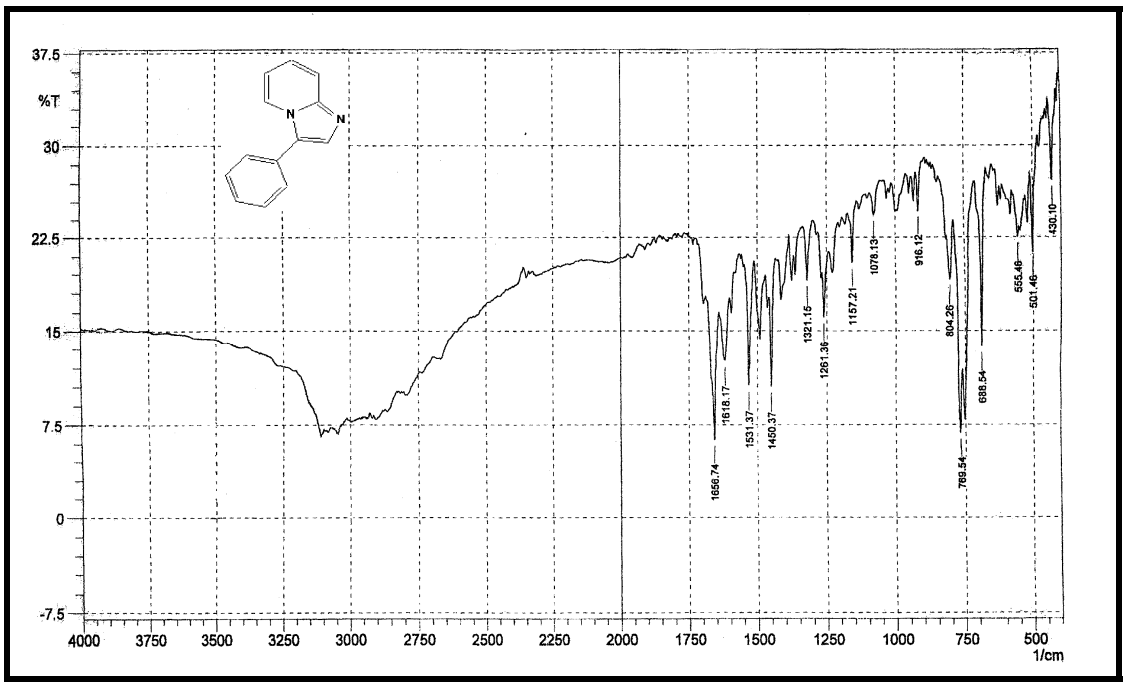
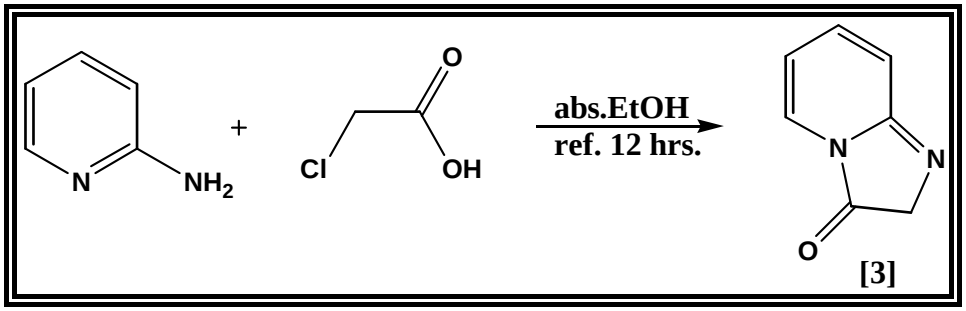


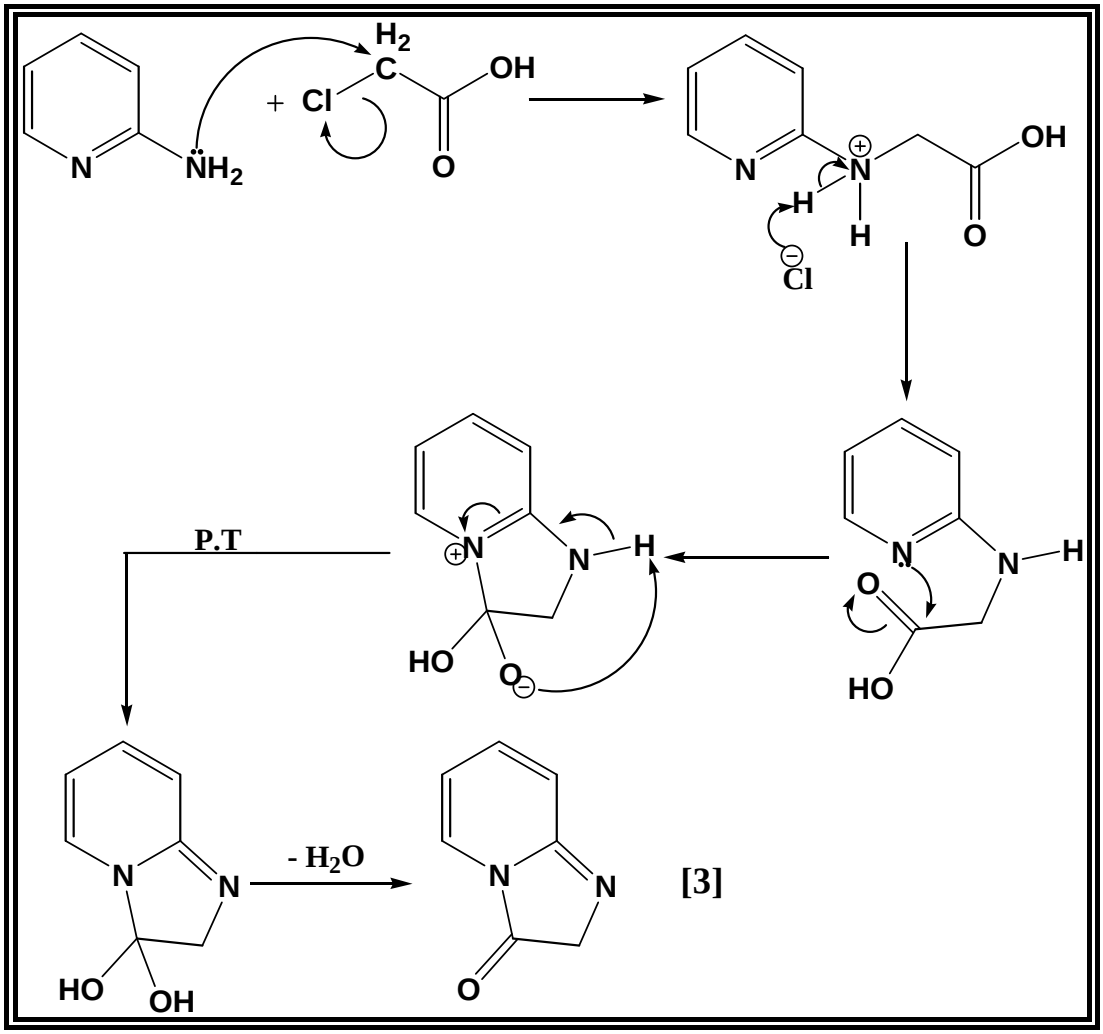
Fig (3-3): FT-IR spectrum of 3-phenylimidazo[1,2-a] pyridine [2]

3.3 Preparation of imidazo[1,2-a]pyridine-3(2H)-one [3]

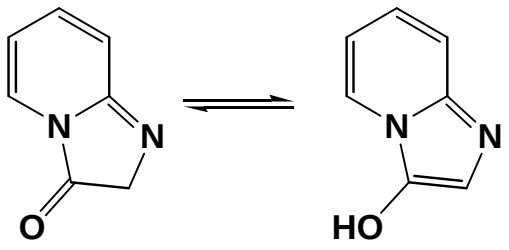
imidazo[1,2-a]pyridine-3(2H)-one was synthesized by refluxing 2-aminopyridine with chloroacetic acid in absolute ethanol for 12 hours:



The suggested mechanism for this reaction can be as follow [95]:



The most characteristic I.R. features, figure (3-4), for the formation of compound [3] are the presence of bands at 3255 cm^{-1} and 1695 cm^{-1} which were due to the υ(O-H) and υ(C=O) [107] moieties of imidazole ring, respectively. From the above mentioned facts, we can say that compound [3] can exist in equilibrium between keto [I] and enol [II] forms:



[I] [II]

Other characteristic bands can be seen in the FT-IR spectrum of the titled compound.

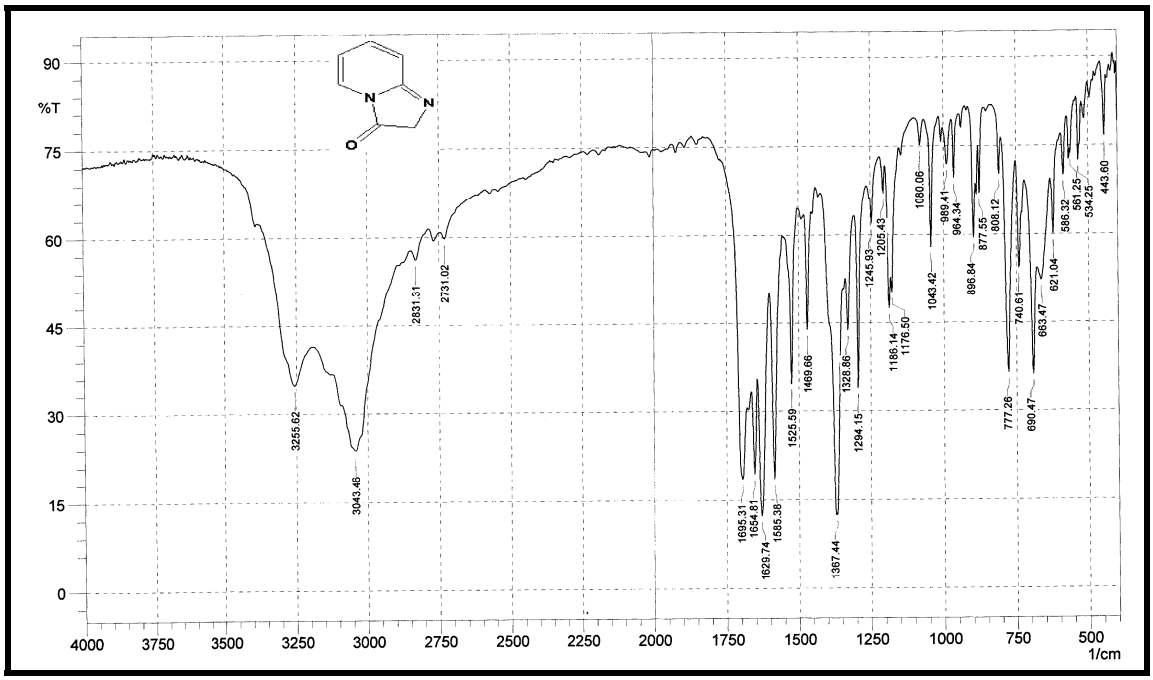
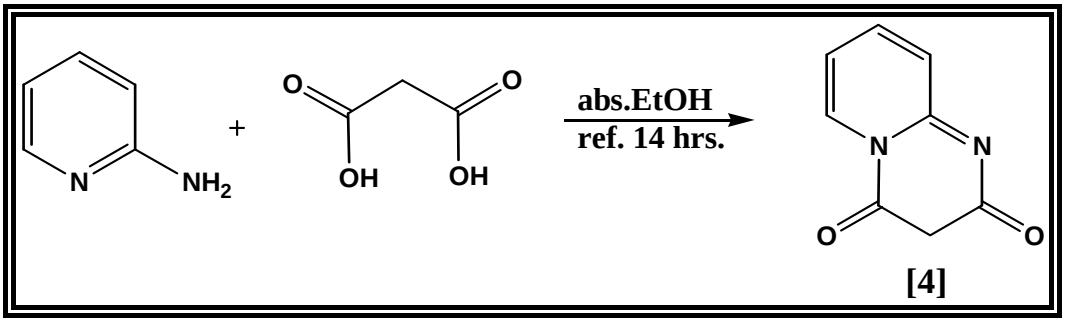


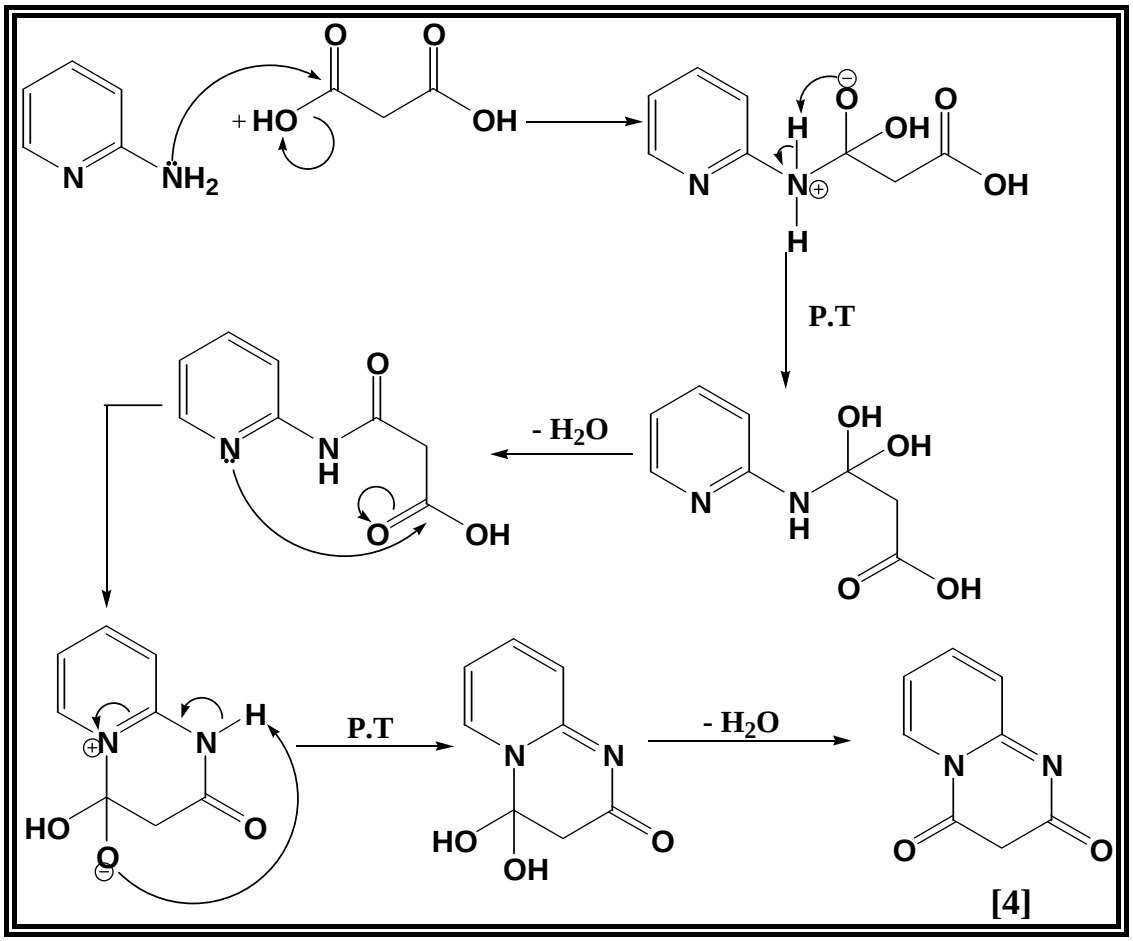
Fig (3-4): FT-IR spectrum of imidazo[1,2-a]pyridine-3(2H)-one [3]

3.4 Preparation of 2H-pyrido[1,2-a]pyridine-2,4-(3H)-dione [4]

Compound [4] was obtained from the reaction of 2-aminopyridine with malonic acid:



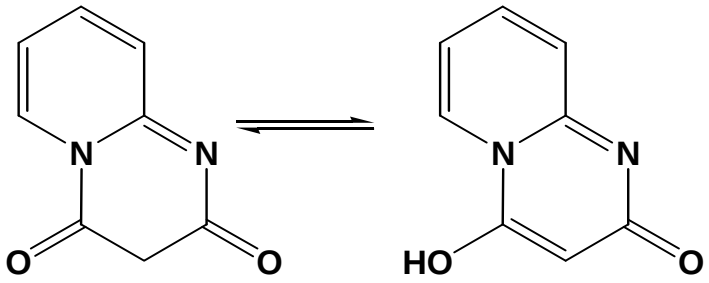
The mechanism of the reaction can be as follows [96]:



The synthesized compound was characterized on the basis of its M.P., FT-IR, ^{1}H- and ^{13}C-NMR.

Infrared spectrum

FT-IR spectrum, figure (3-5), showed bands at 3338 cm^{-1}, 3100 cm^{-1} and 2929 cm^{-1} which were assignable to (O-H), (C-H) aromatic and (C-H) aliphatic stretching vibrations. The band at about 1700 cm^{-1} was due to υ(C=O) moiety of pyrimidine ring. From the above mentioned results we can say that compound [4] can be exist in two tautomeric forms ; keto [I] and enol [II] forms:



[I] [II]

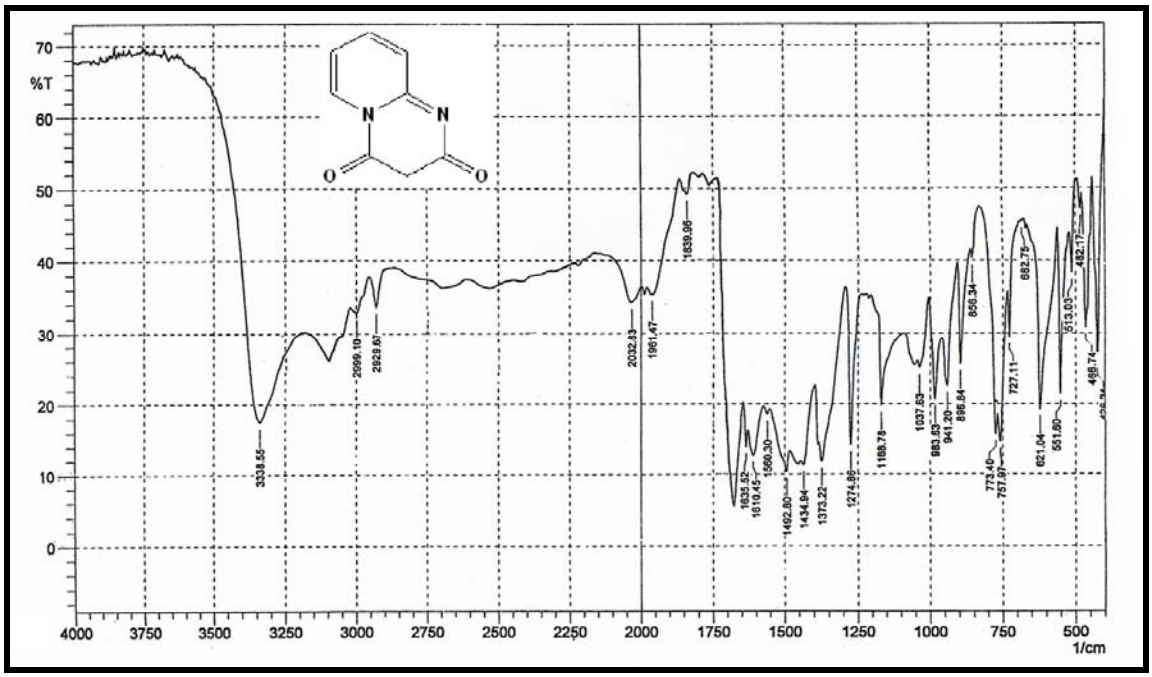


Fig (3-5): FT-IR spectrum of 2H-pyrido[1,2-a]pyridine-2,4-(3H)-dione [4]

^{1}H-NMR spectrum

The ^{1}H-NMR spectrum of compound [4], figure (3-6), shows the following characteristic chemical shift (DMSO-d_6, ppm). The methylene protons of pyrimidine ring resonate at δ 2.07, signal at δ 2.49 was due to DMSO. Four aromatic ring protons appeared in the region of δ(7.2-7.72). furthermore, the signal at δ 3.38 attributable to absorbed water in DMSO.

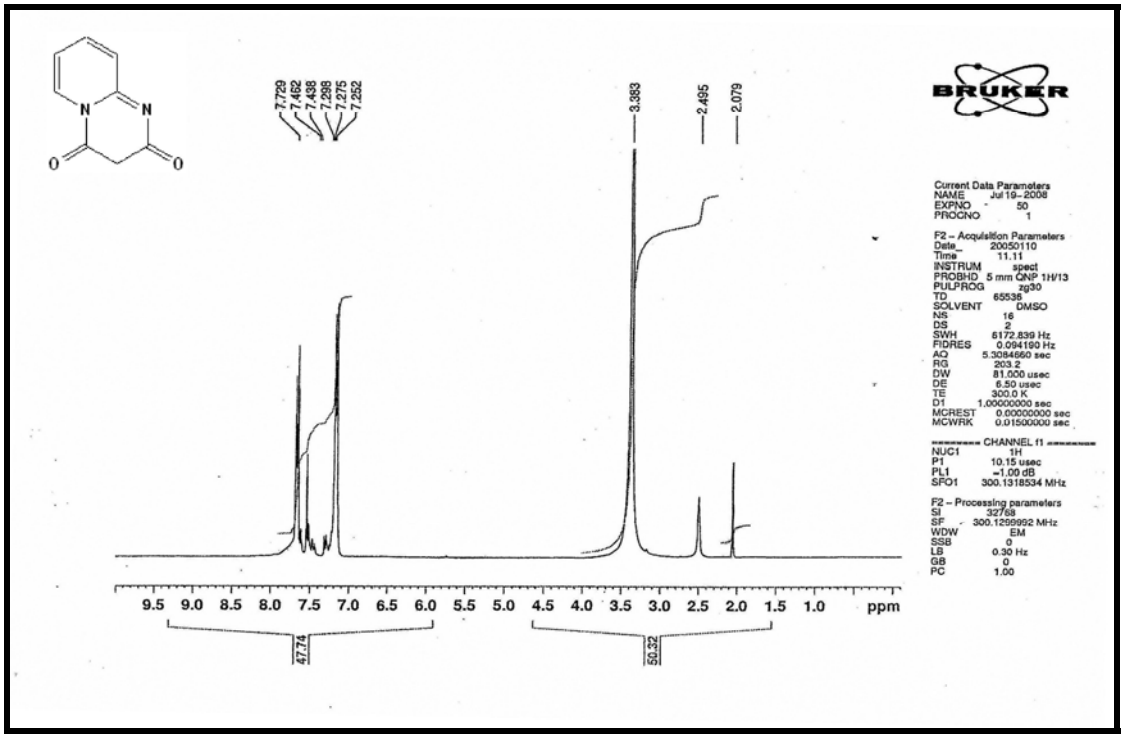


Fig (3-6): ^{1}H-NMR spectrum of 2H-pyrido[1,2-a] pyridine-2,4-(3H)-dione [4]

^{13}C-NMR spectrum

The ^{13}C-NMR spectrum of compound [4], figure (3-7), shows the following characteristic chemical shift (DMSO-d_6, ppm). A signal at δ 21.95 is for methylene group carbon, its shift down field from an ordinary value due to the presence of two carbonyl group adjacent to it. The aromatic carbons signal appear at δ 131.14-145.22. The signals at δ 160.08 and δ 161.09 were due to the two carbonyl carbon atoms.

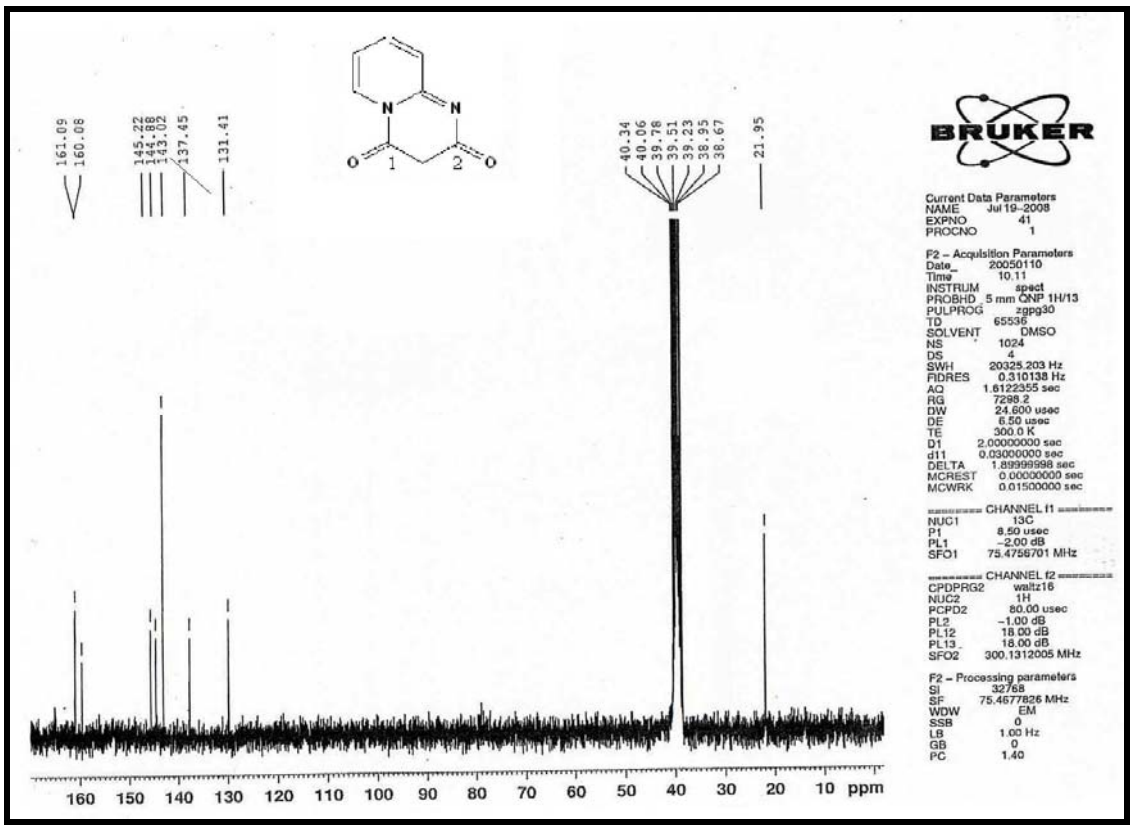
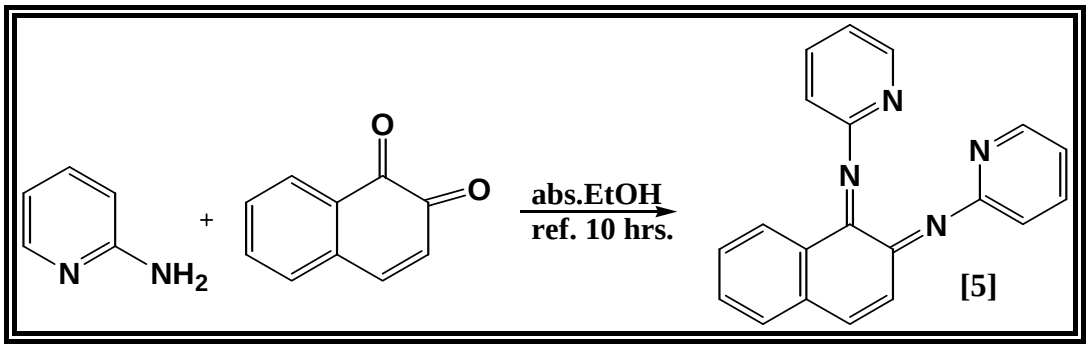


Fig (3-7): ^{13}C-NMR spectrum of 2H-pyrido[1,2-a] pyridine-2,4-(3H)-dione [4]

3.5 Preparation of N,N'-1,4-dihydronaphthalene-2,3-diylidene dipyridine-2-amine [5]

The condensation reaction of equimolar quantity of primary amine with the appropriate aromatic aldehydes is the major method to prepare shiff-base. Compound [5] was produced by refluxing 2-aminopyridine and 1,2-naphthaquinon in absolute ethanol:



The FT-IR spectrum of compound [5], figure (3-8), showed all the expected bands. The more characteristic evidence for the formation of the titled compound are the bands at 3064 cm^{-1}, 1664 cm^{-1} and 1623 cm^{-1} attributable to aromatic (C-H), endocyclic (C=N) and exocyclic imine groups [(108)], respectively, in addition to out of plane bending of substituted benzene ring at 763 cm^{-1} and 663 cm^{-1}.

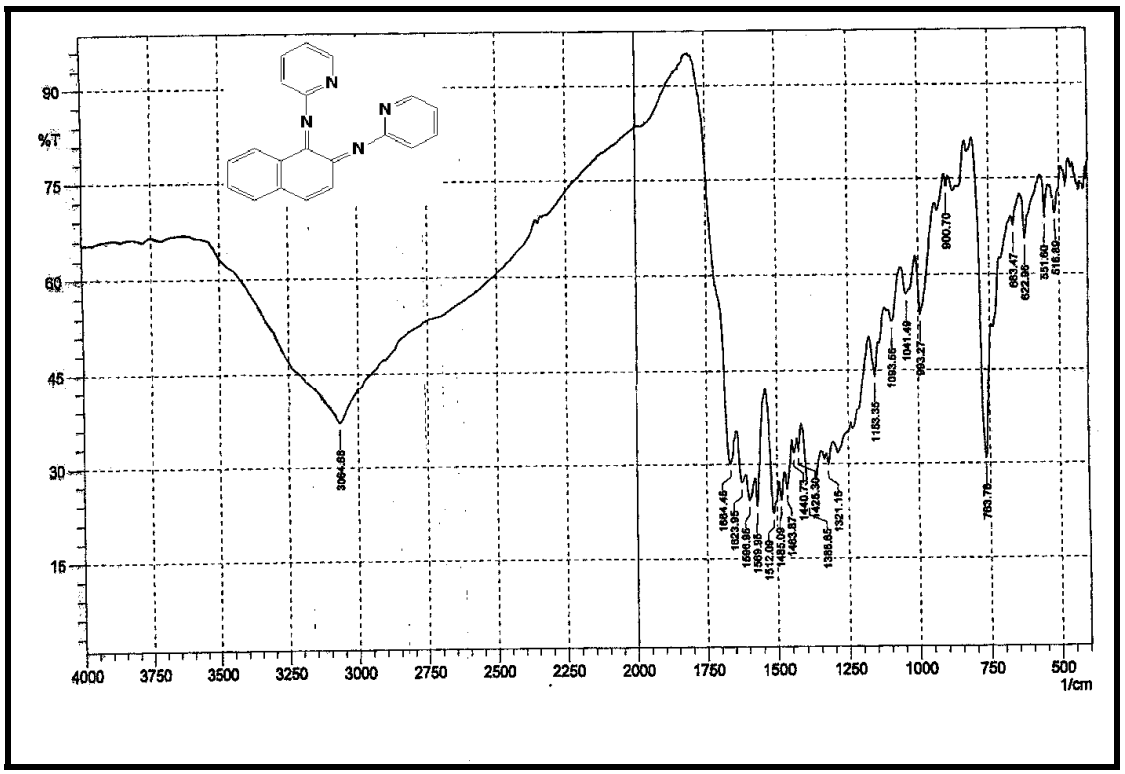
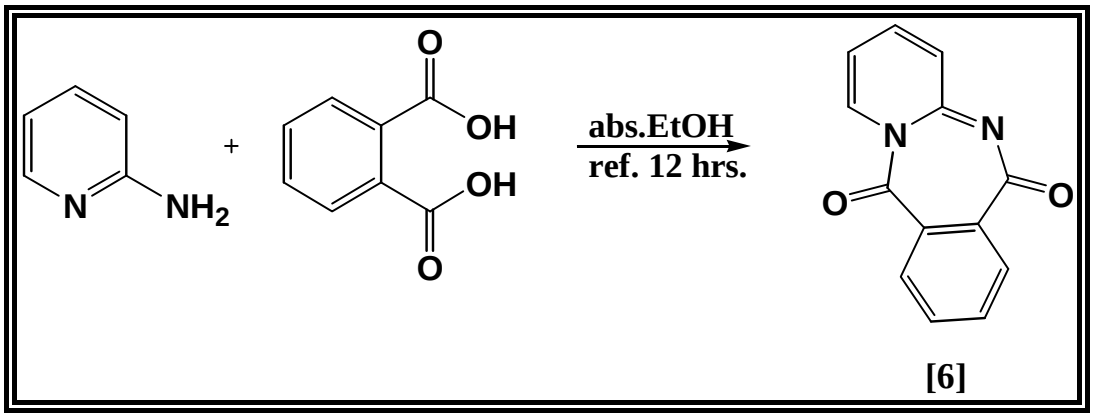


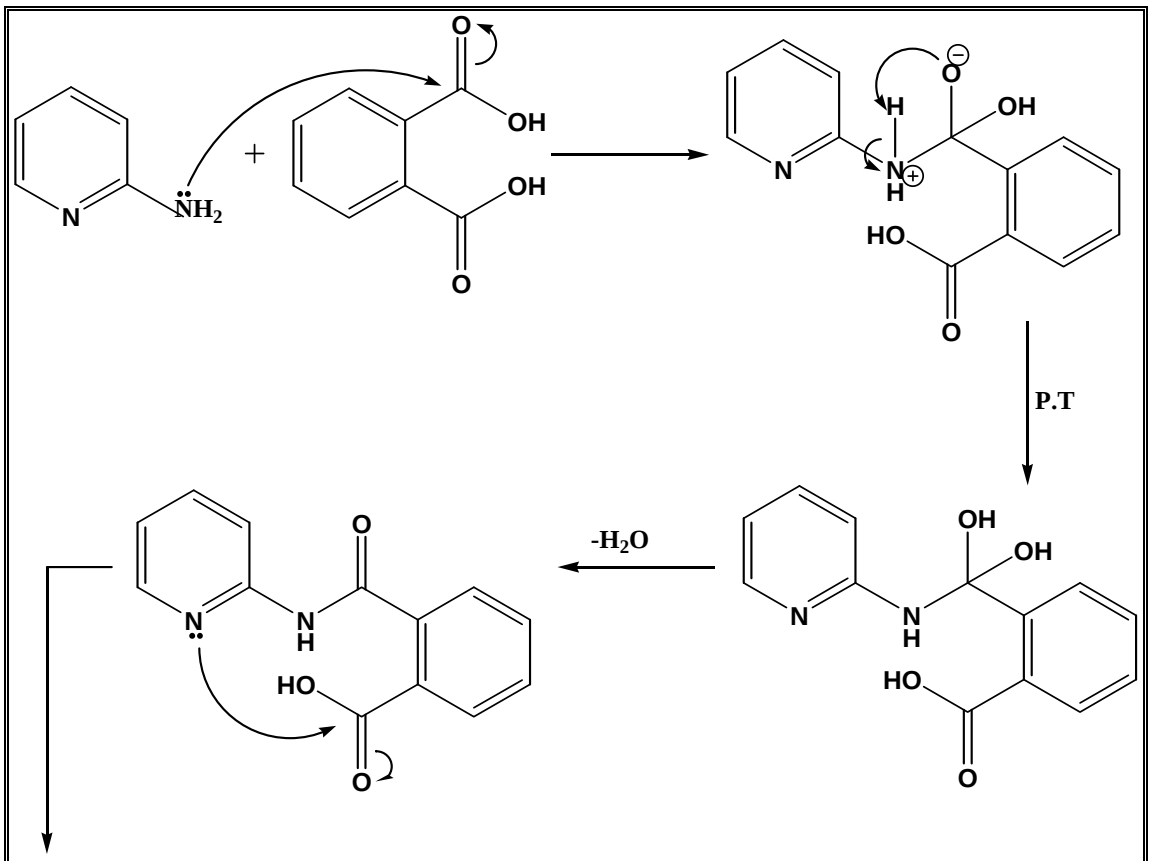
Fig (3-8): FT-IR spectrum of N,N'-1,4-dihydronaphthalene-2,3-diylidene dipyridine-2-amine [5]

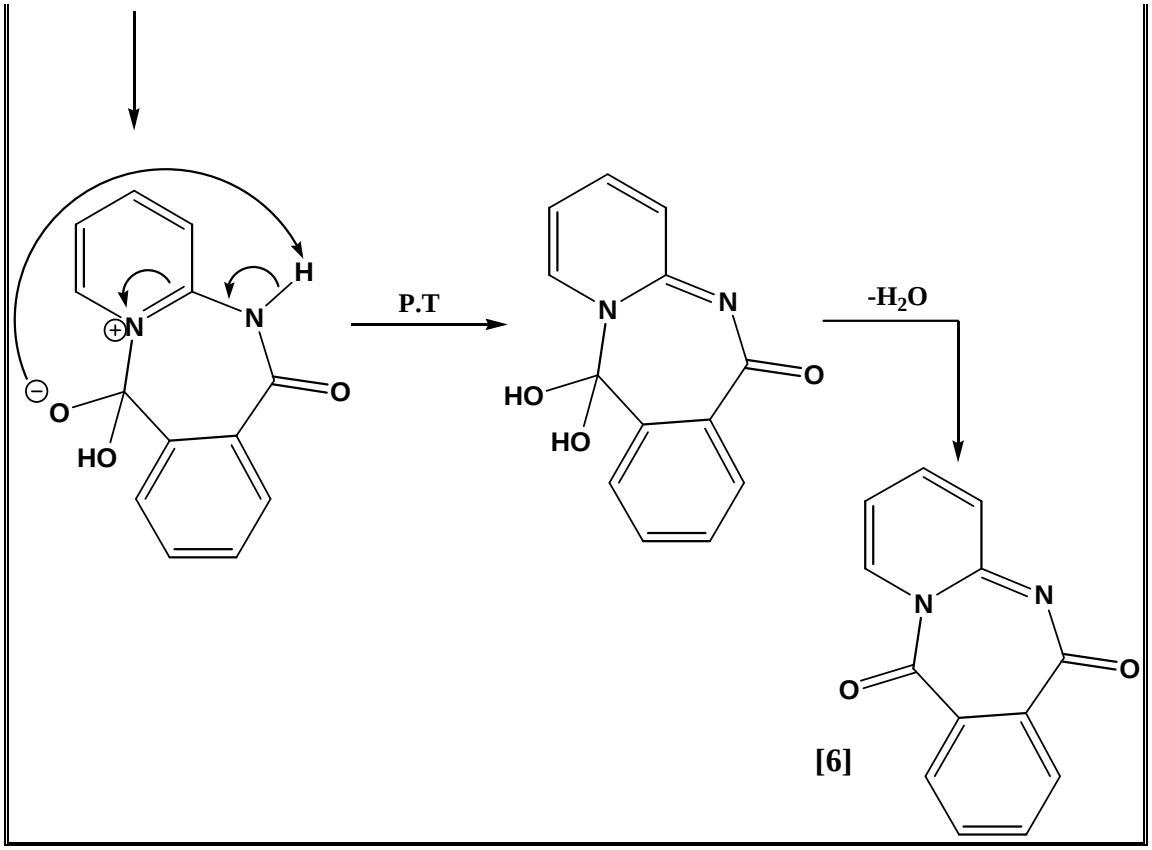
3.6 Preparation of pyrido[1,2-a][2,4]benzodiazepine-6,11-dione [6]

Compound [6] was obtained from the reaction of 2-aminopyridine with phthalic acid in absolute ethanol for 12 hours:



The suggested mechanism to obtain the target product is outlined below [97]:





The structure of the synthesized compound was characterized on the basis of its M.P., FT-IR, ^{1}H-and ^{13}C-NMR spectra:

Infrared spectrum

The FT-IR spectrum, figure (3-9), shows bands at 3100 cm^{-1}, 1676 cm^{-1} and 765 cm^{-1} assignable for υ(C-H) aromatic, υ(C=O) and (C-H) out of plane bending, respectively. These bands represented the most characteristic evidence for the formation of the target compound.

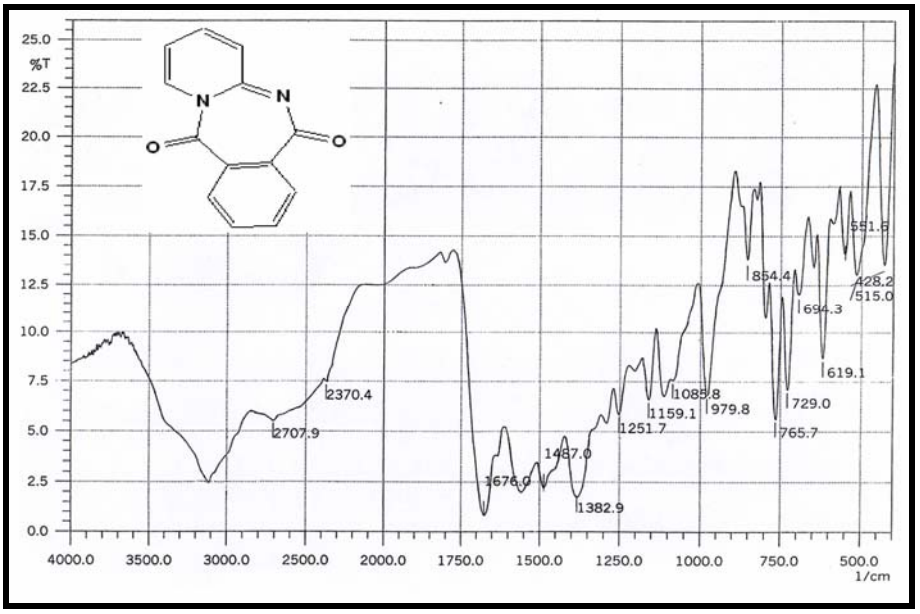


Fig (3-9): FT-IR spectrum of pyrido[1,2-a] [2,4]benzodiazepine-6,11-dione [6]

^{1}H-NMR spectrum

^{1}H-NMR spectrum of compound [6], figure (3-10), shows the following characteristic chemical shifts (DMSO-d_6, ppm). Protons of aromatic ring appeared at the range δ(7.01-7.46)ppm as a multiplet peaks. Signal at δ 3.74was due to absorbed water in DMSO.

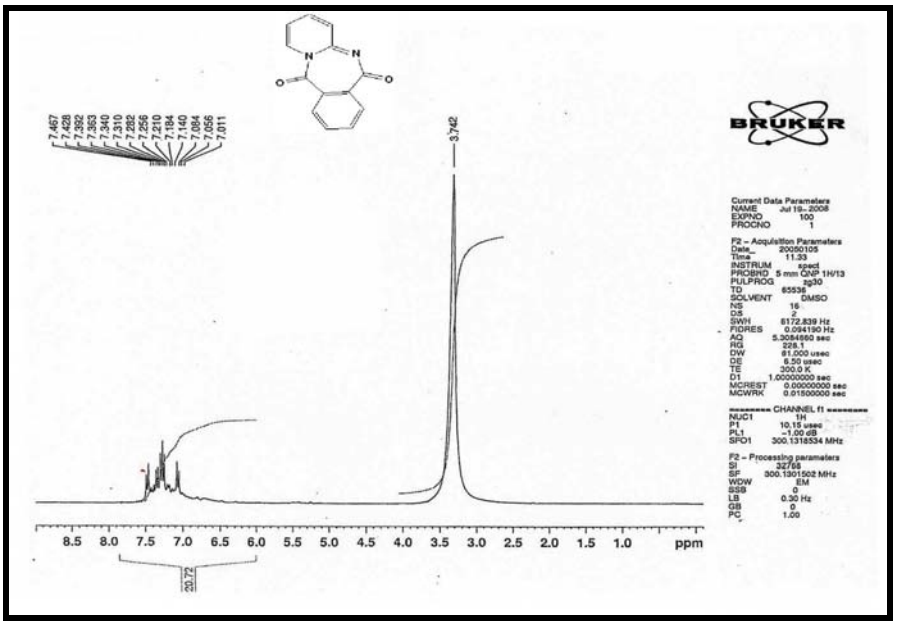


Fig (3-10): ^{1}H-NMR spectrum pyrido[1,2-a] [2,4]benzodiazepine-6,11-dione [6]

^{13}C-NMR spectrum

The ^{13}C-NMR spectrum of compound [6], figure (3-11), shows the following characteristic chemical shifts (DMSO-d_6, ppm). Carbons of aromatic rings appear at δ(125.6-145.39).the signal at δ 174.23 and δ 180.95 were due to the two carbonyl carbon atoms.

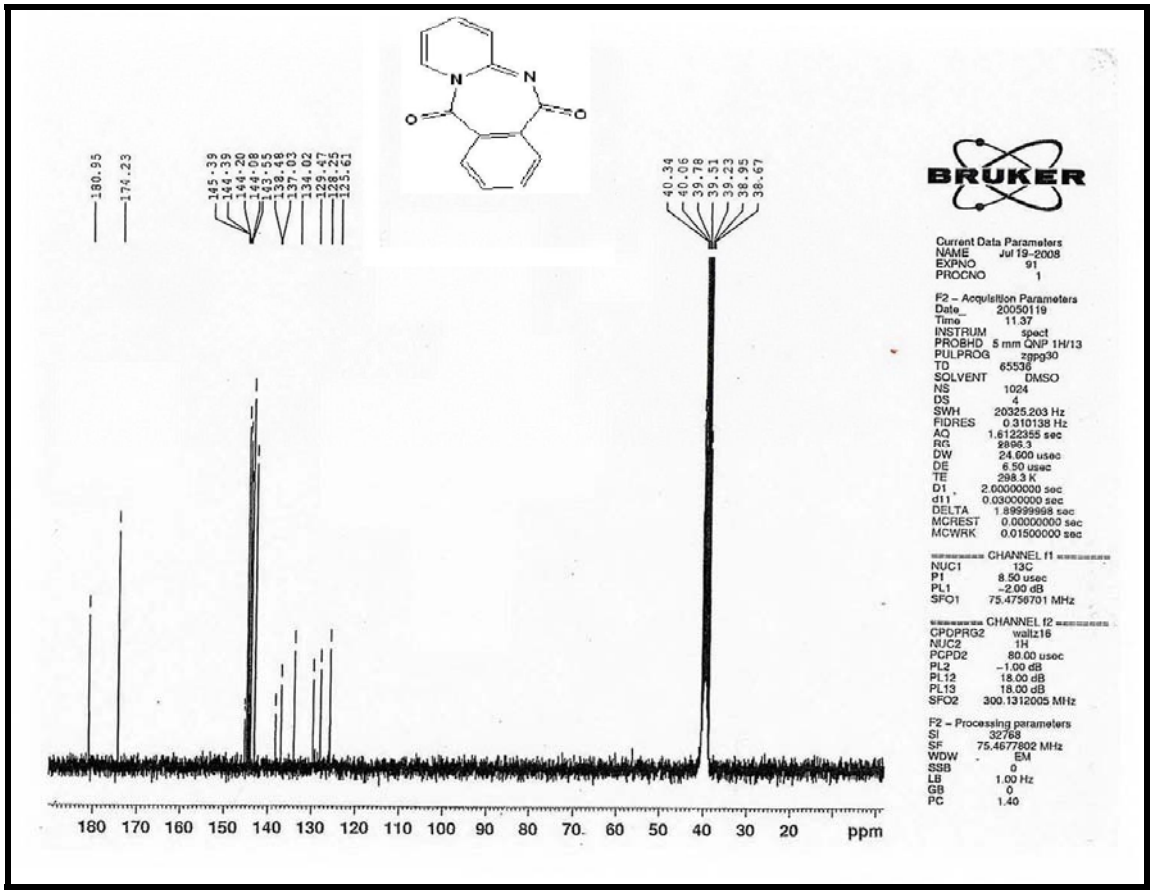
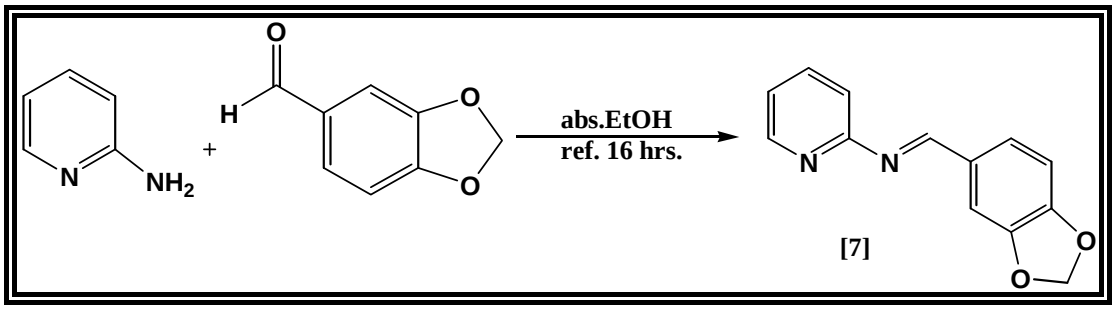


Fig (3-11): ^{13}C-NMR spectrum pyrido[1,2-a] [2,4]benzodiazepine-6,11-dione [6]

3.7 Preparation of N-(1,3-benzodioxol-5-ylmethylidene)pyridine -2-amine [7]

Refluxing 2-aminopyridine with pipronal in absolute ethanol for 16 hours afforded compound [7]:



The structure of compound [7] was characterized on the basis of its M.P., FT-IR spectrum.

FT-IR spectrum, figure (3-12), showed the disappearance of the two absorption bands due to (-NH_2) stretching of 2-aminopyridine [0] with the appearance of υ(C-H) aliphatic at about 2970 cm^{-1}. Bands at about 1635 cm^{-1} was due to the (C=N) stretching vibration of imine group.

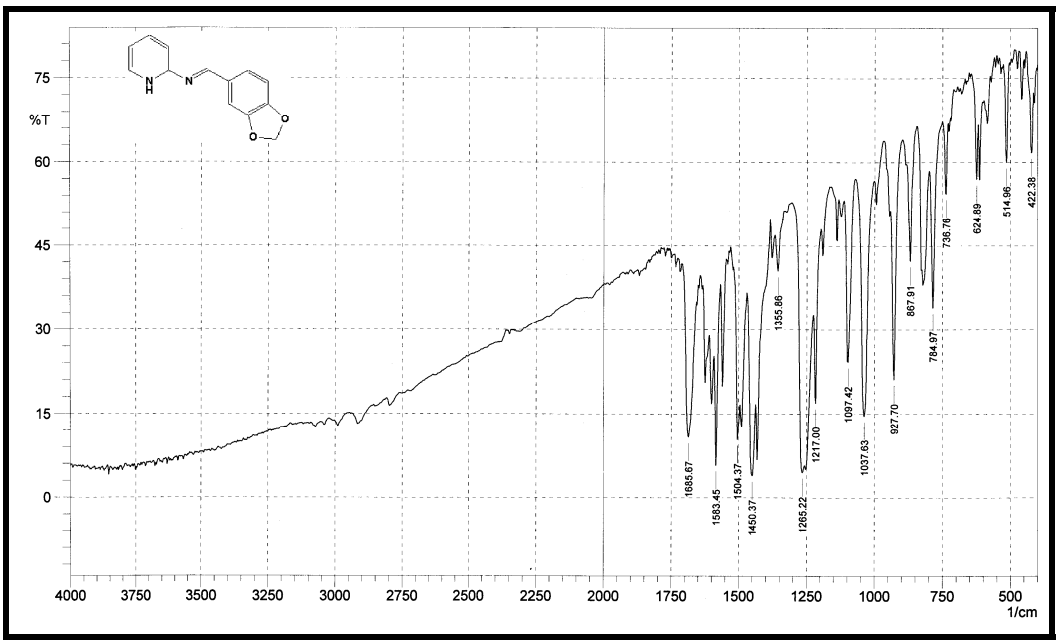
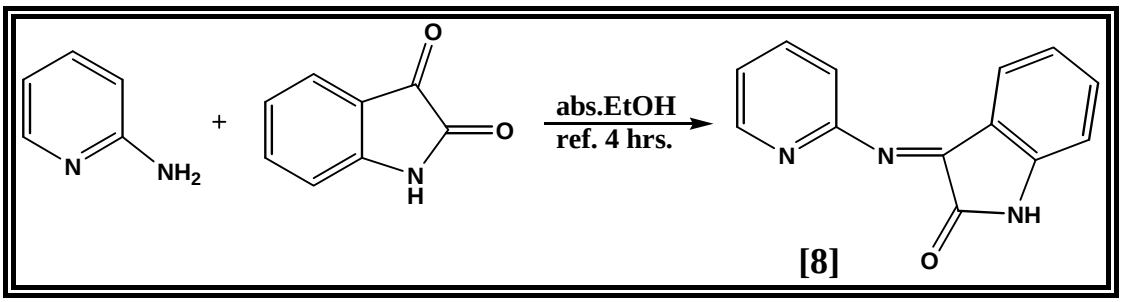


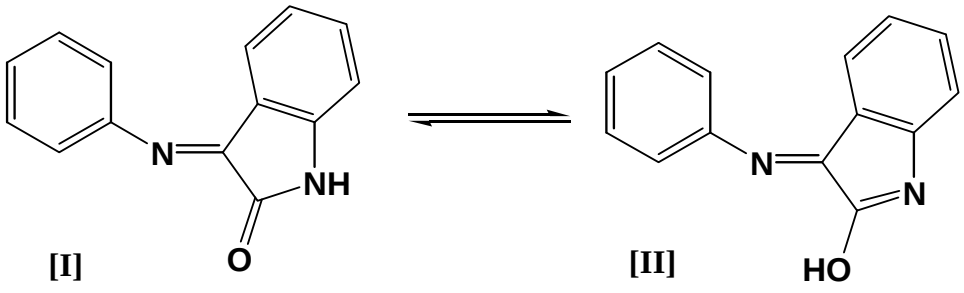
Fig (3-12): FT-IR spectrum of N-(1,3-benzodioxol-5-ylmethylidene)pyridine -2-amine [7]

3.8 Preparation of 3-(pyridine-2-ylimino)-1,3-dihydro-2H-indol-2-one [8]

Due to the diverse structural aspects, a wide range of isatine shiff bases have been synthesized and their complexation behavior studied [(109)]. The titled compound was prepared by refluxing 2-aminopyridine and isatine in absolute ethanol for 4 hours:



FT-IR spectrum of the target compound, figure (3-13), show the following characteristics features: significant bands at 3448 cm^{-1}, 3191 cm^{-1} and 3058 cm^{-1} which were attributed to stretching vibrations of (O-H), (N-H) and (C-H) aromatic. Besides this, (C=O) and imine (C=N) stretching bands appeared at 1728 cm^{-1} and 1616 cm^{-1}, respectively. From the above mentioned facts, we can say that compound [8] can exist in two tautomeric forms; keto [I] and enol [II] forms:



Furthermore, other characteristic bands can be seen in FT-IR spectrum of this compound.

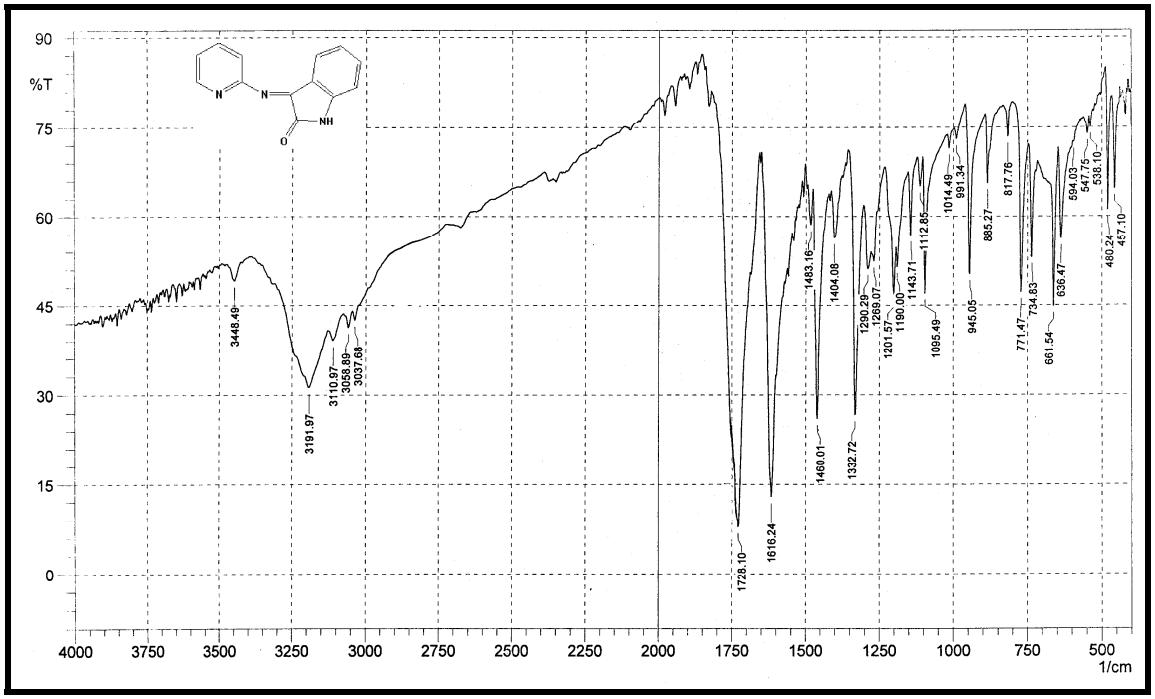
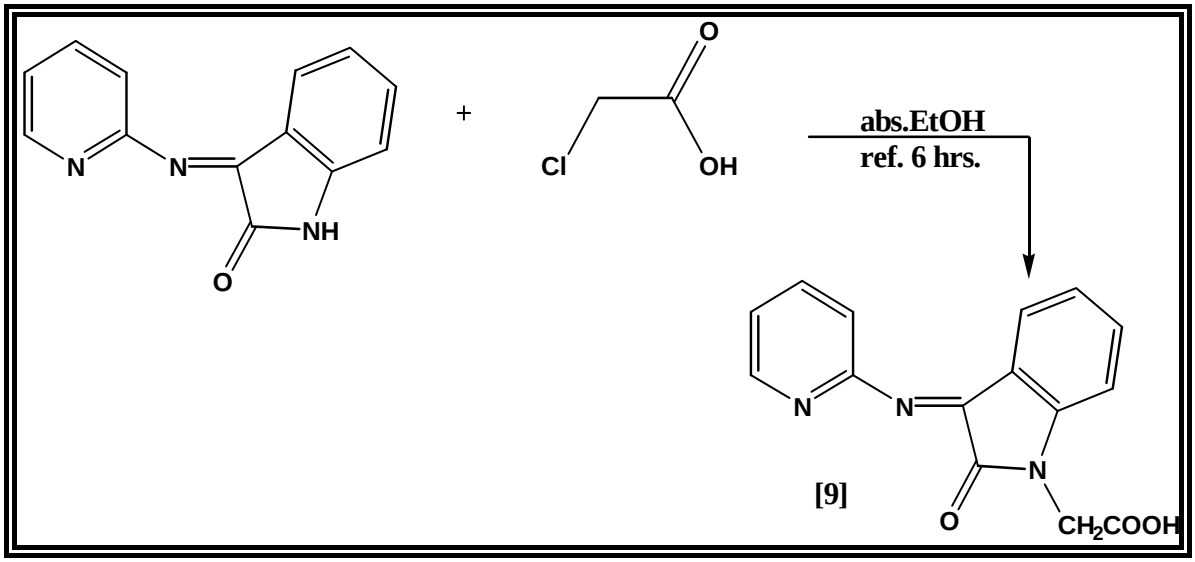


Fig (3-13): FT-IR spectrum of 3-(pyridine-2-ylimino)-1,3-dihydro-2H-indol-2-one [8]

3.9 Preparation of [2-oxo-3-(pyridin-2-ylimino)dihydro-1H-indol-1-yl] acetic acid [9]

A mixture of KOH and compound [8] were dissolved in absolute ethanol and refluxed with chloroacetic acid for 6 hours to afford compound [9]:



The infrared absorption bands, figure (3-14), were utilized to characterized the specific structure of the synthesized compounds. The bands at 3700 cm^{-1} and 1730 cm^{-1} which attributed to υ(O-H) and υ(C=O) of carboxylic acid moiety is good evidence for the success of this step of reaction.

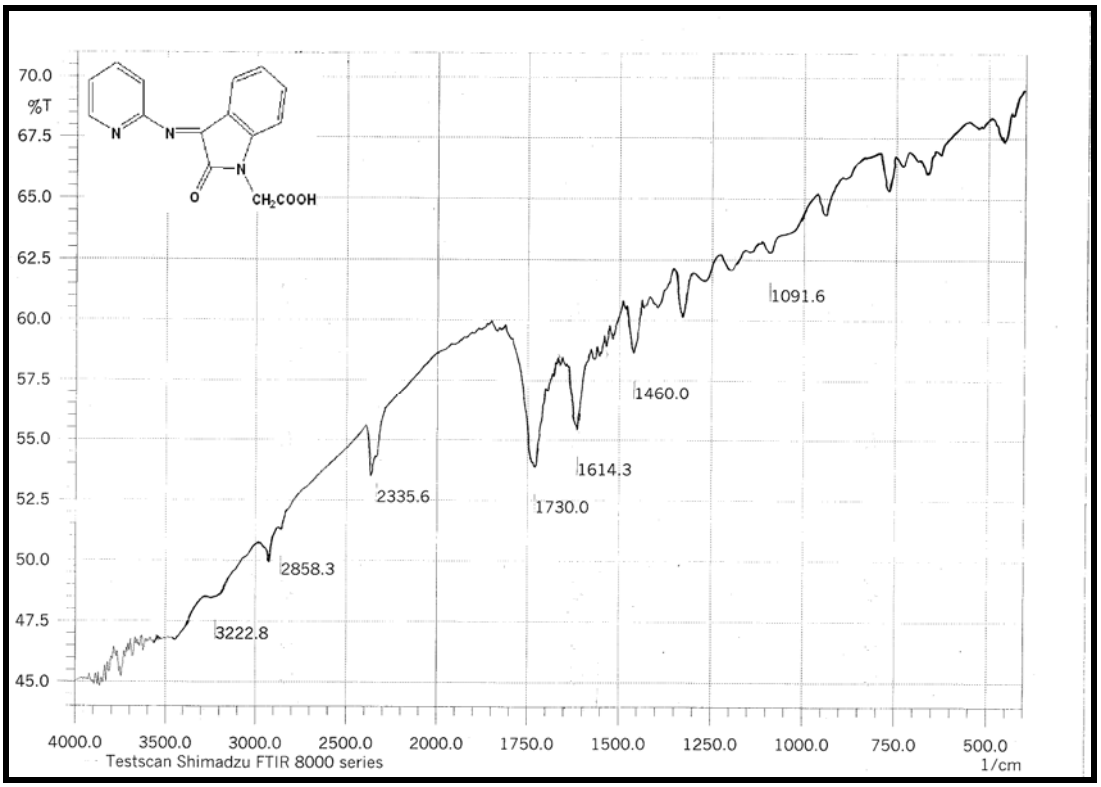
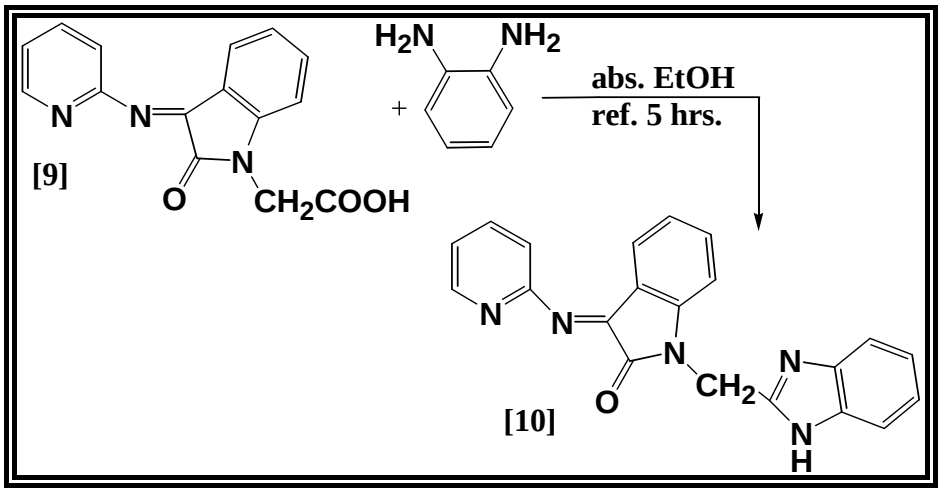


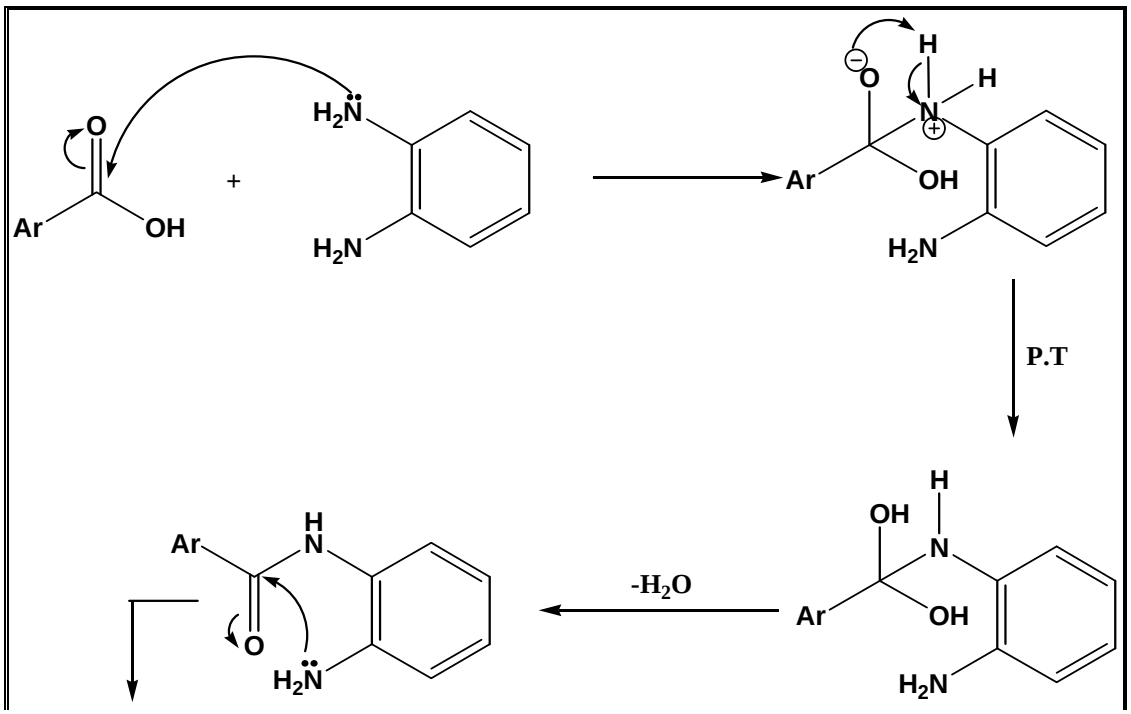
Fig (3-14): FT-IR spectrum of[2-oxo-3-(pyridin-2-ylimino)dihydro-1H-indol-1-yl] acetic acid [9]

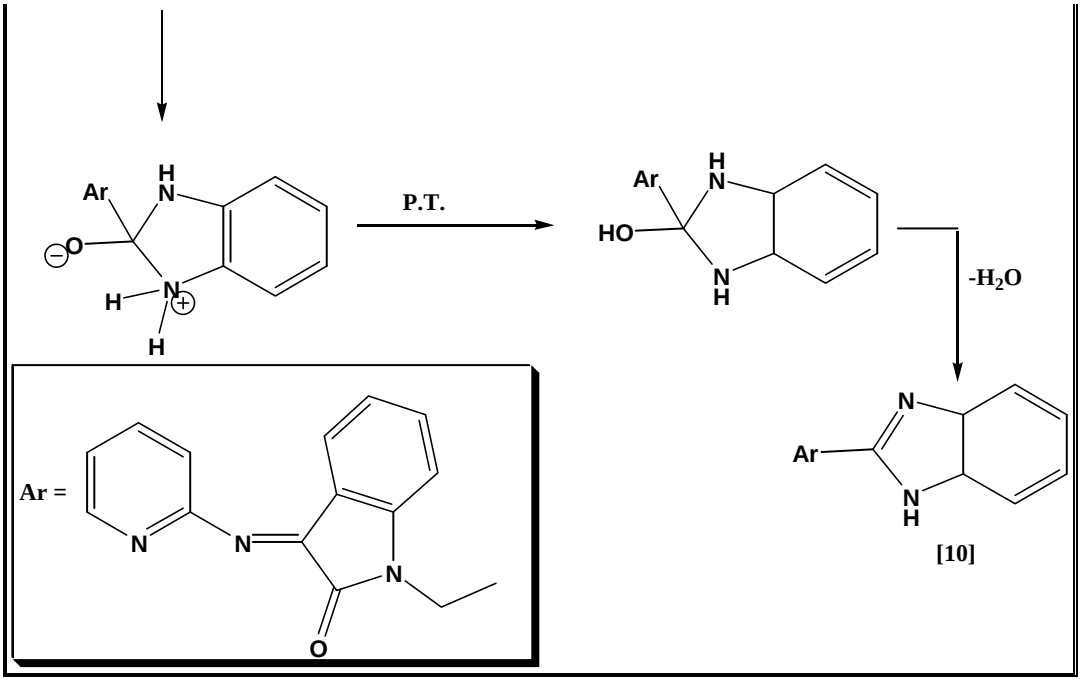
3.10 Preparation of 1-(1H-benzimidazol-1-ylmetyl)-3-(pyridine-2-ylimino)-1,3-dihydro-2H-indol-2-one [10]

Benzimidazole and its derivates have attracted researchers interested in the field of bioorganic and medicinal chemistry. Encouraged by these observations, it was considered worthwhile to synthesize compound [10] through refluxing compound [9] with *o*-phenylenediamine in absolute ethanol for 5 hours:



The mechanism of the reaction may be as follow [98]:





The structure of compound [10] was confirmed by FT-IR spectrum which shows characteristic bands at 3313 cm^{-1}, 2974 cm^{-1} and 1700 cm^{-1} attributed to υ(N-H), υ(C-H) aliphatic and υ(C=O) of isatine ring respectively.

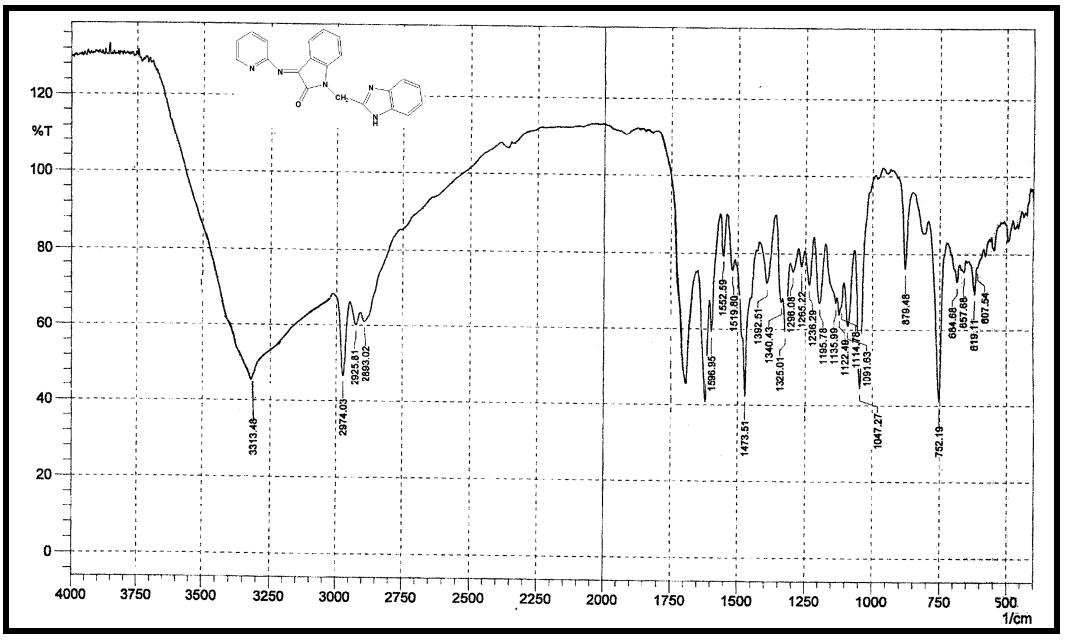
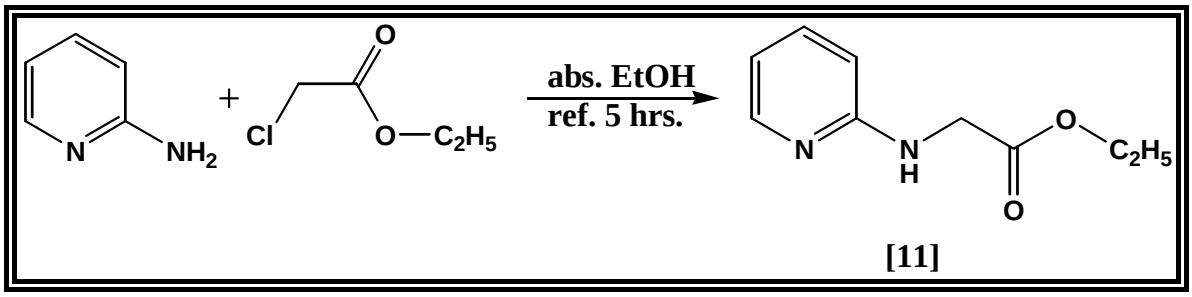


Fig (3-15): FT-IR spectrum of 1-(1H-benzimidazol-1-ylmetyl)-3-(pyridine-2-ylimino)-1,3-dihydro-2H-indol-2-one [10]

3.11 Preparation of ethyl-N-pyridin-2-ylglycinate [11]

Adding ethylchloroacetate to a solution of KOH and 2-aminopyrdine and refluxed in absolute ethanol for 5 hours afforded the target ester:



The FT-IR spectrum of compound [11], figure (3-16), showed stretching bands at 3247 cm^{-1} and 2954 cm^{-1} which were assigned to the (N-H) and (C-H) aliphatic stretching frequencies respectively. Besides this, the appearances of (C=O) stretching band attributable to ester group at 1728 cm^{-1} and two stretching bands at 1176,1186 attributed to C-O-C ester are good evidence for the structure give to this compound.

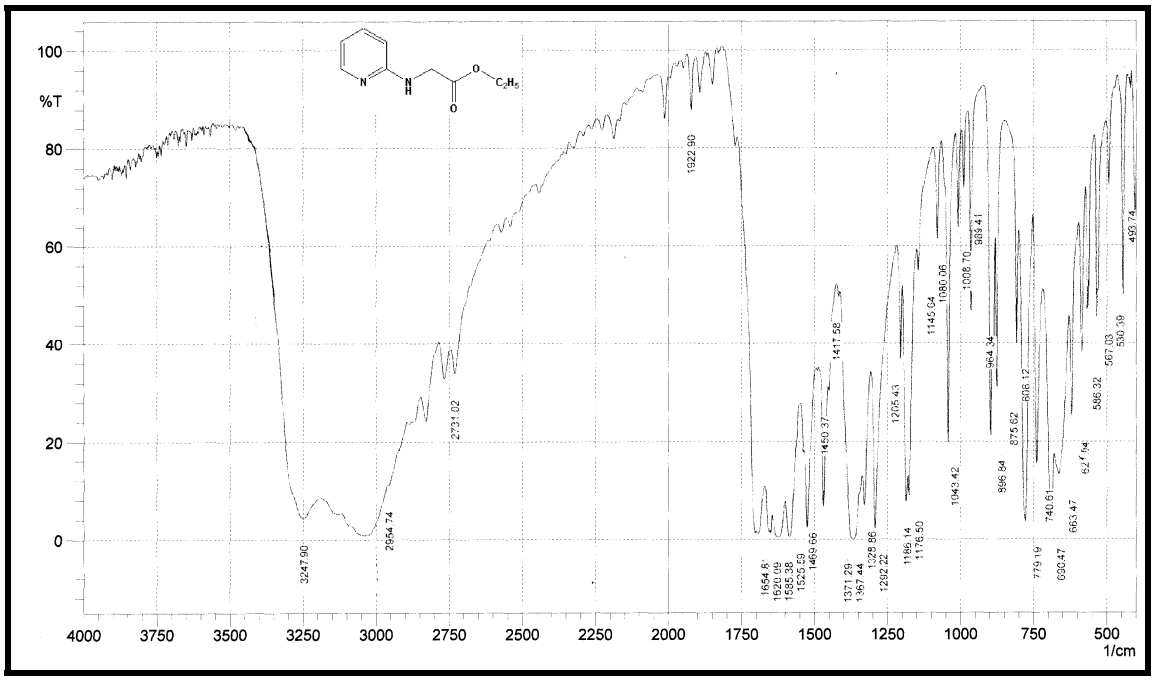
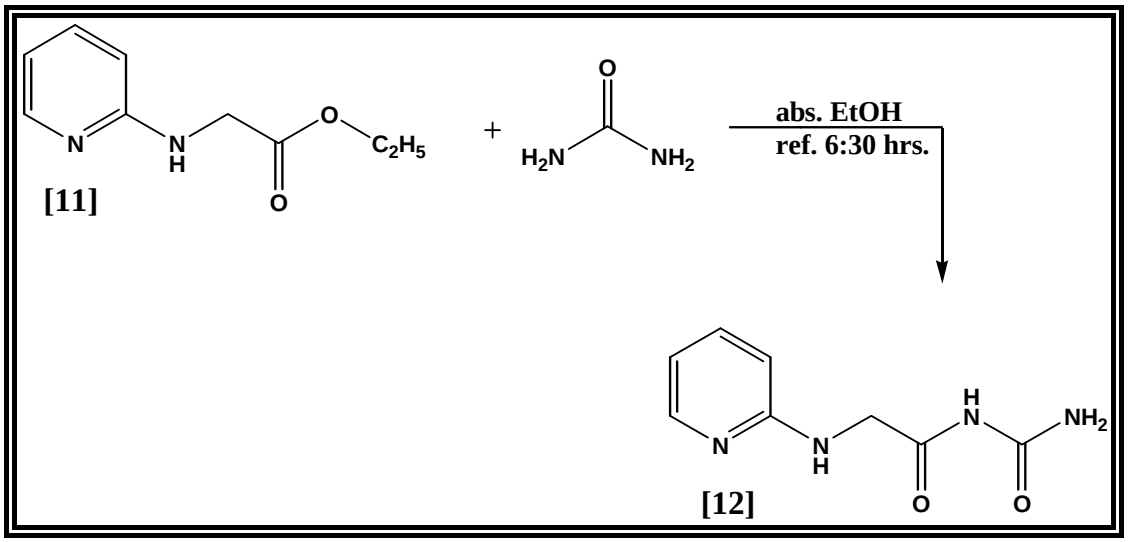


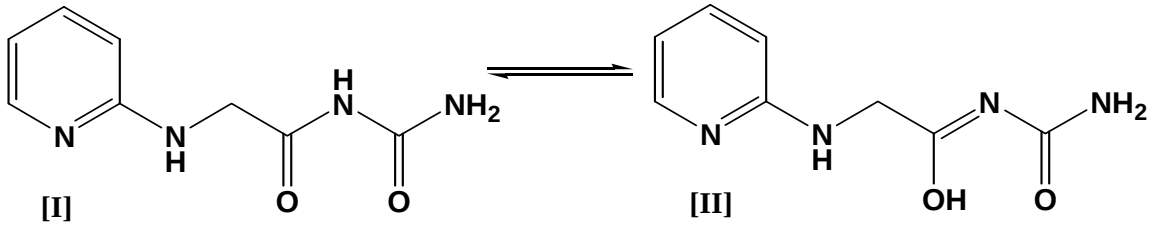
Fig (3-16): F.T.IR spectrum of ethyl-N-pyridin-2-ylglycinate [11]

3.12 Preparation of N-carbamoyl-N_2-pyridin-2-ylglycinamid [12]

Compound [11] was refluxed with urea in absolute ethanol for 6:30 hours to afford the titled compound:



The most characteristic I.R. features, figure (3-17), for the formation of compound [12] are the presence of bands at 3400 cm^{-1}, 3300-3249 cm^{-1}, 3060 cm^{-1} and 1645 cm^{-1} which were due to the stretching vibrations of (O-H), (NH_2), (C-H) aromatic and (C=O) of amide group, respectively. From the above mentioned facts, we can say that compound [12] can exist in equilibrium between keto [I] and enol [II] forms:



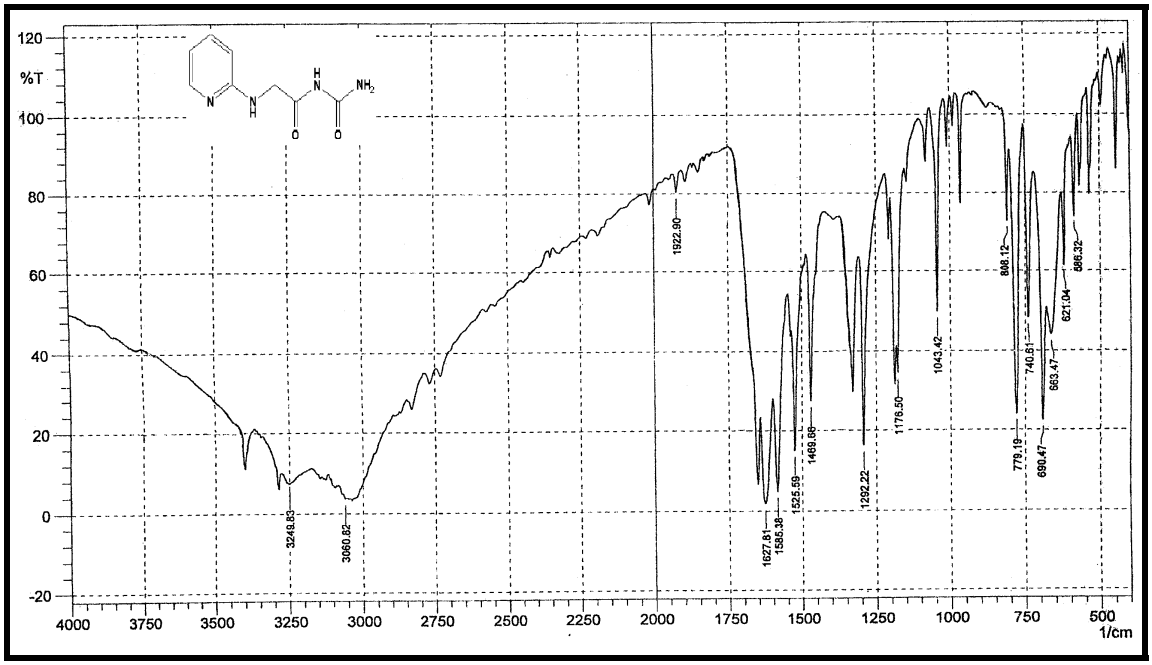
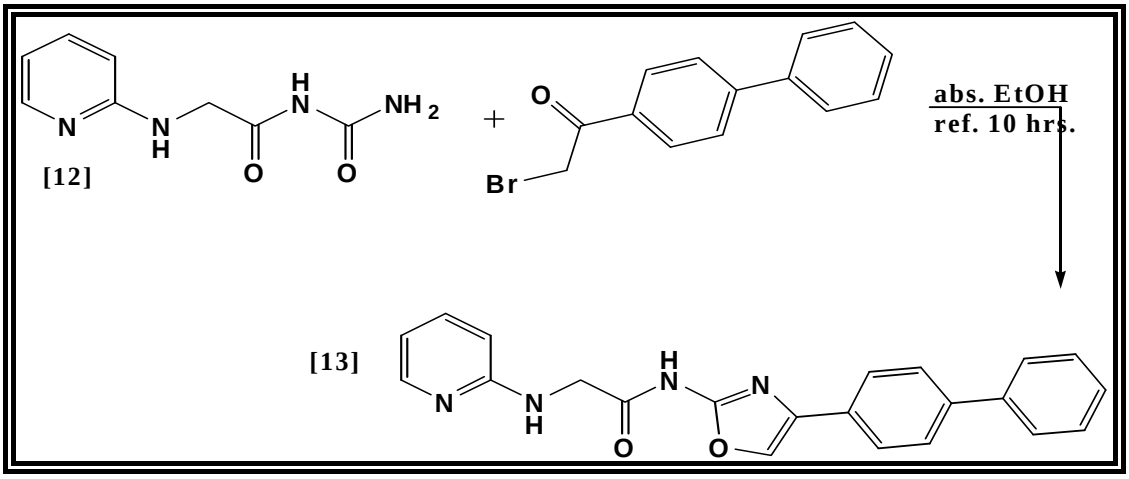


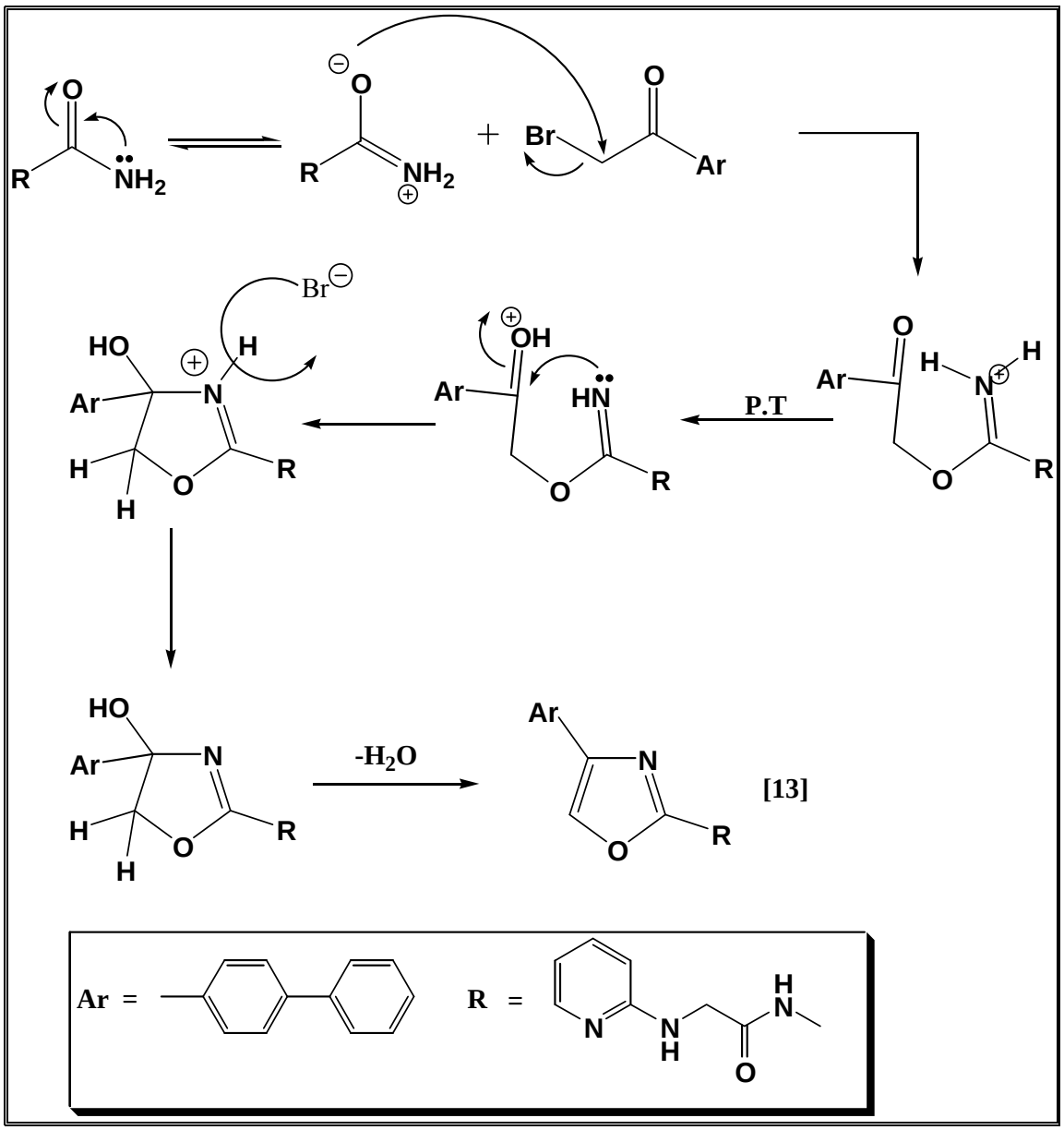
Fig (3-17): FT-IR spectrum of N-carbamoyl-N_2-pyridin-2-ylglycinamid [12]

3.13 Preparation of compound N-(4-biphenyl-4-yl-1,3-oxazol-2-yl)-N_2-pyridine -2-ylglyciamide [13]

Refluxing compound [12] with 4-phenylphenacylbromide in absolute ethanol for 10 hours yielded an oxazole derivatives [13].



For the synthesis of the target titled heterocyclic compound, the following reaction mechanism may be outlined [(100)]:



FT-IR spectrum, figure (3-18), shows the following common features: the disappearance of the bands in the region 3300 cm^{-1} -3249 cm^{-1} attributed to the (-NH2) stretching frequency of amide moiety together with the appearance of band at 1685 cm^{-1} assignable to υ(C=N) of oxazole ring [(110)] are good evidence for the structure given to this compound. Beside

this, a strong band at 1089 cm^{-1} were attributed to υ(=C-O-C=) band (ether linkage) [(111)].

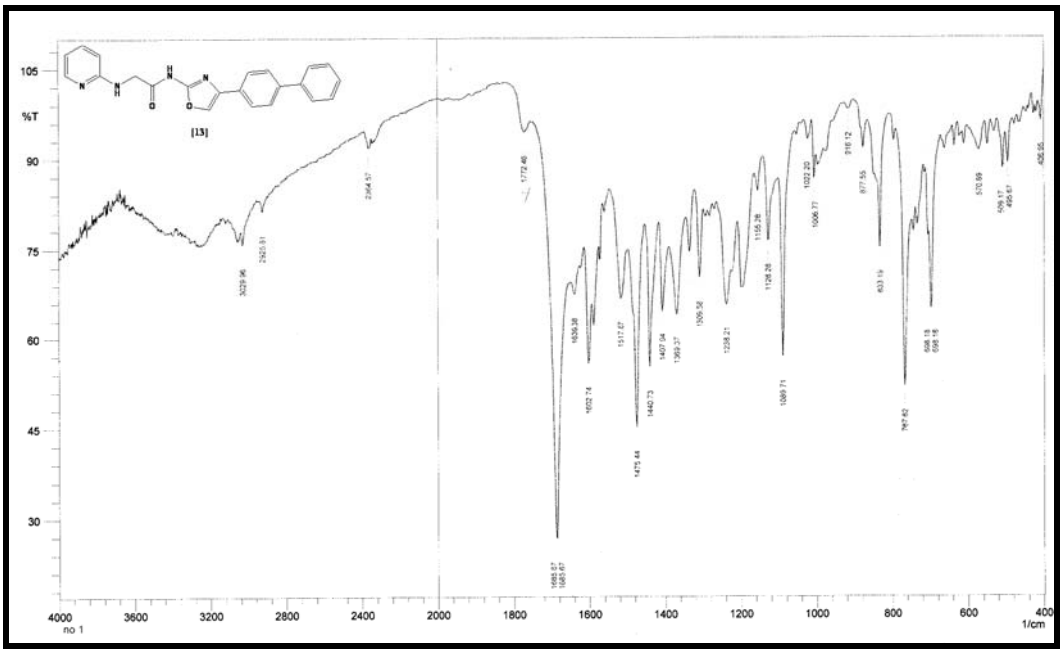
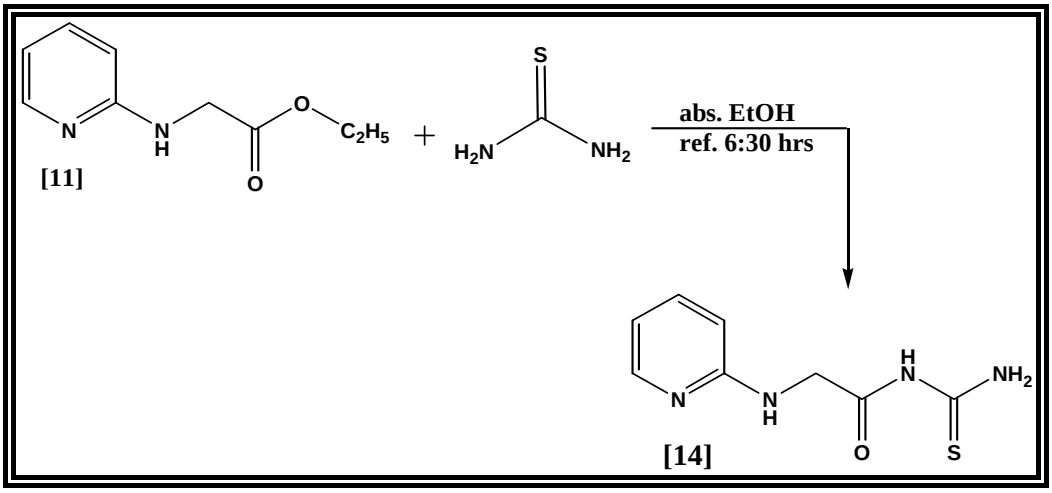


Fig (3-18): FT-IR spectrum of N-(4-biphenyl-4-yl-1,3-oxazol-2-yl)-N_2-pyridine -2-ylglyciamide [13]

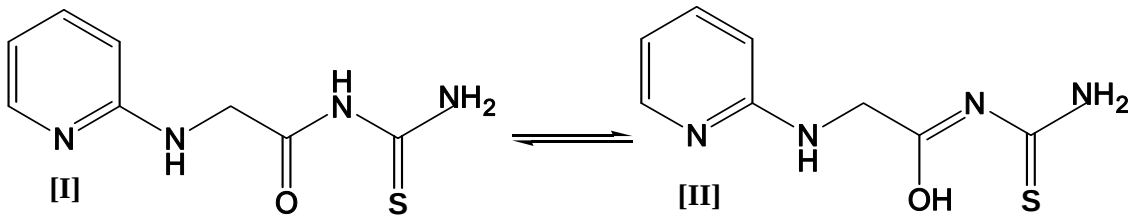
3.14 Preparation of compound N-carbamothioyl-N_2-pyridin-2-ylglycinamid [14]

Compound [11] and thiourea were refluxed in absolute ethanol for 6:30 hours, affording compound [14]:



FT-IR spectrum of compound [14], figure (3-19), showed bands at 3436 cm^{-1}, 3390-3257 cm^{-1},attributed to (O-H) and (N-H) group stretching vibrations. Furthermore, bands at 3080 cm^{-1}, 2829 cm^{-1}, 1625 cm^{-1} and 1367 cm^{-1} were due to the υ(C-H) aromatic, υ(C-H) aliphatic, υ(C=O) and υ(C=S), respectively.

Other characteristic features can be seen in FT-IR spectrum of this compound. From the above mentioned facts, we can say that compound [14] can be in equilibrium between keto [I] and enol [II] forms:



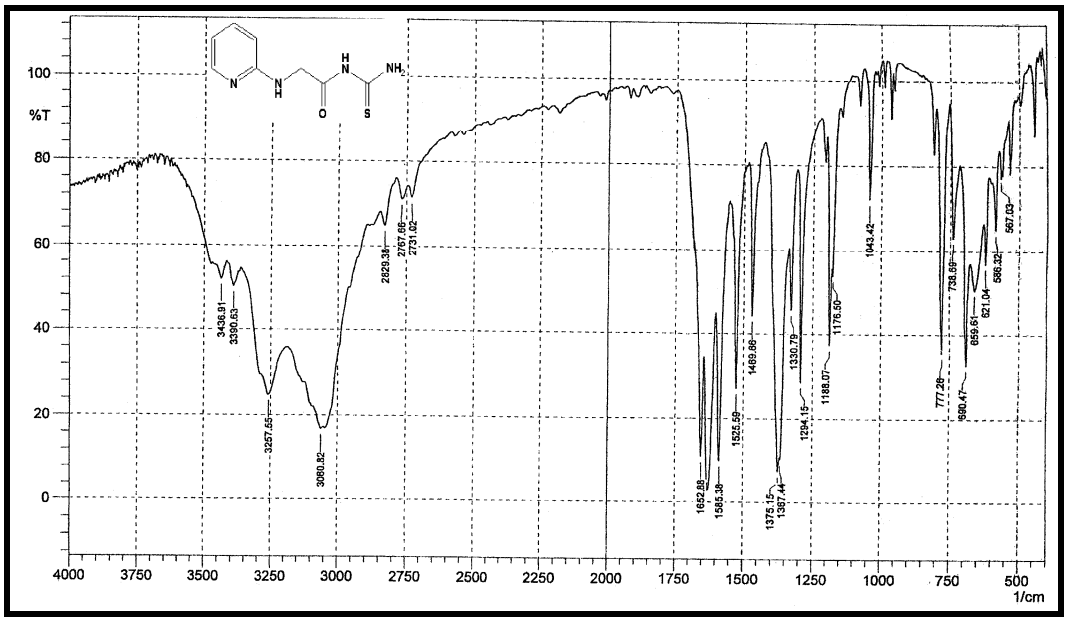
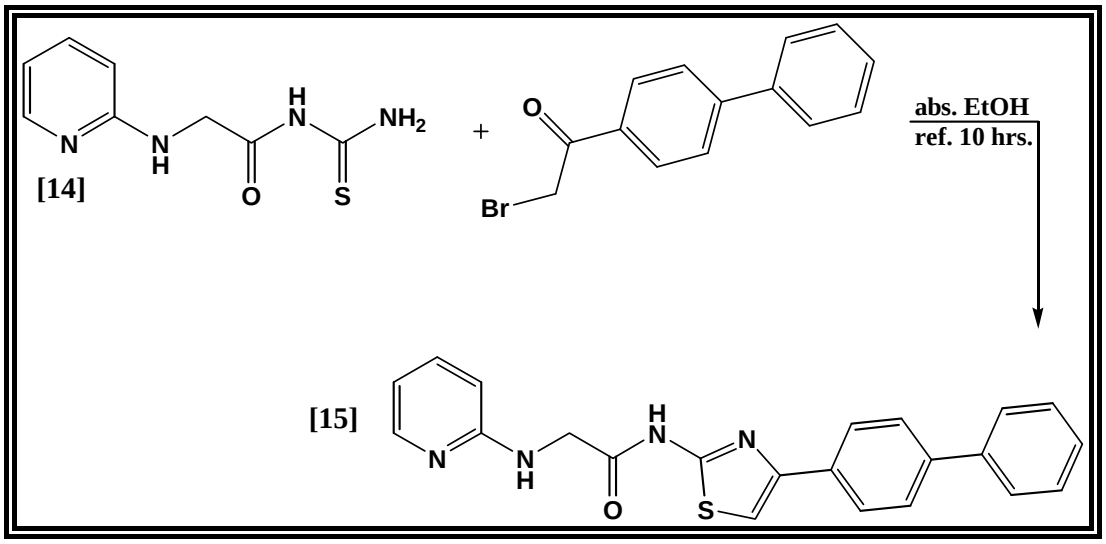


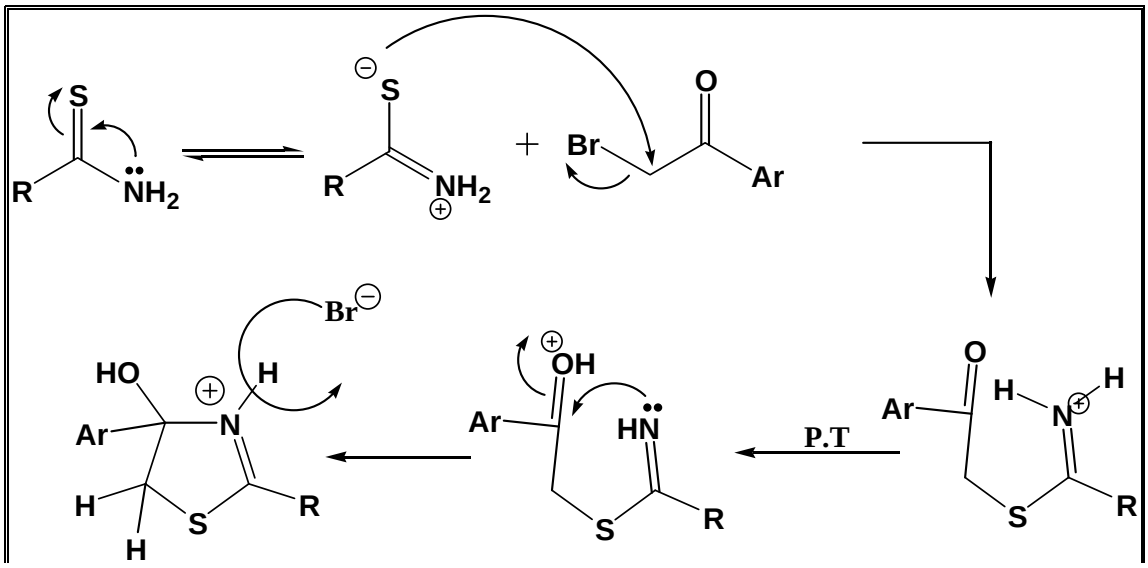
Fig (3-19): F.T.IR spectrum of N-carbothioyl-N_2-pyridin-2-ylglycinamid [14]

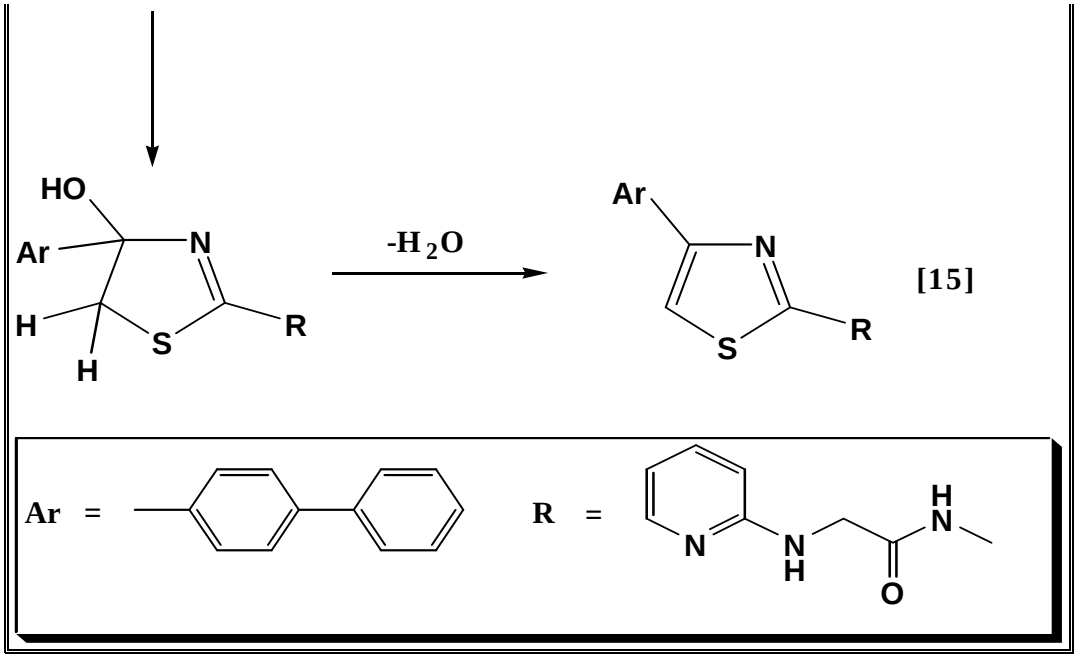
3.15 Preparation of N-(4-biphenyl-4-yl-1,3-thiazol-2-yl)-N_2-pyridine-2-ylglyciamide [15]

The target thiazole were prepared from refluxing compound [14] with 4-phenylphenacylbromide in absolute ethanol for nearly 10 hours:

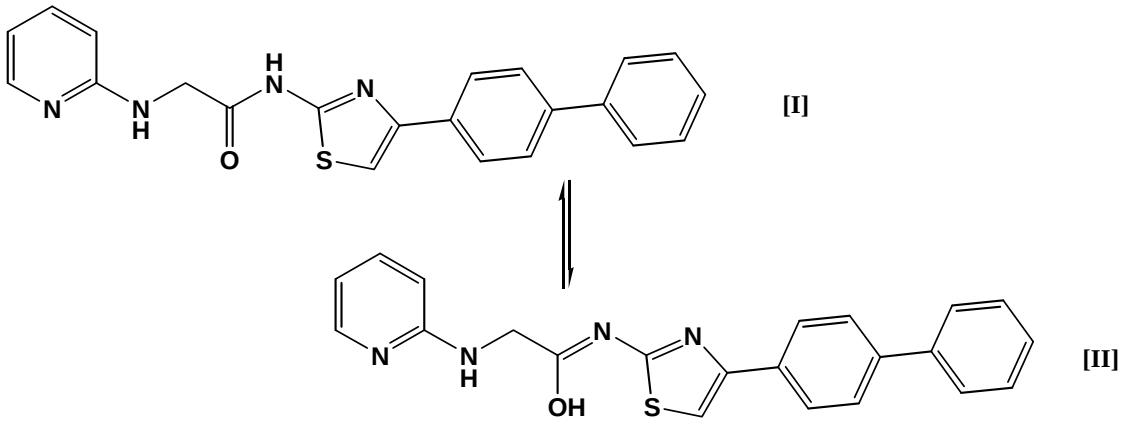


The mechanism of the reaction may be as follow [(100)]:





FT-IR spectrum of the titled compound, figure (3-20), showed disappearance of (NH_2) two stretching band at 3390 $cm^{-1}$and 3257 cm^{-1} with the appearance of broad band at 3400 cm^{-1} -3300 cm^{-1} due to the (O-H) stretching vibration. Band at 1687 cm^{-1} was due to (C=N) stretching vibration of thiazole ring [(91)]. Besides this, the out of plane bending band of *p*-disubstituted aromatic ring were occurred at 833 cm^{-1}. From the above mentioned results, compound [15] can be in equilibrium between keto [I] and enol [II] forms:



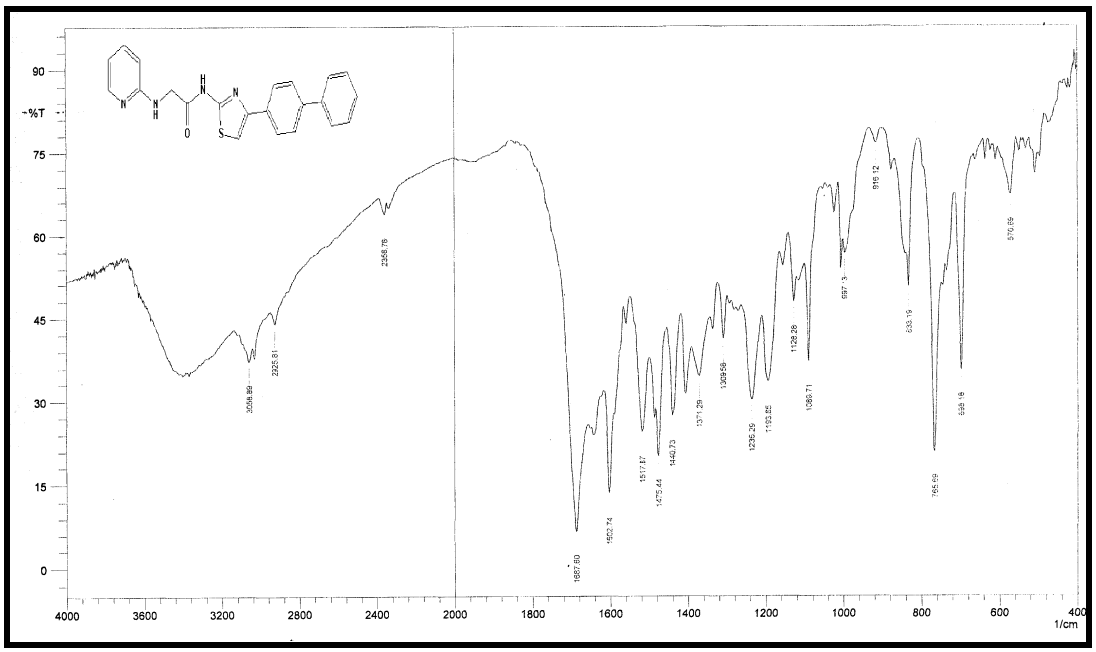
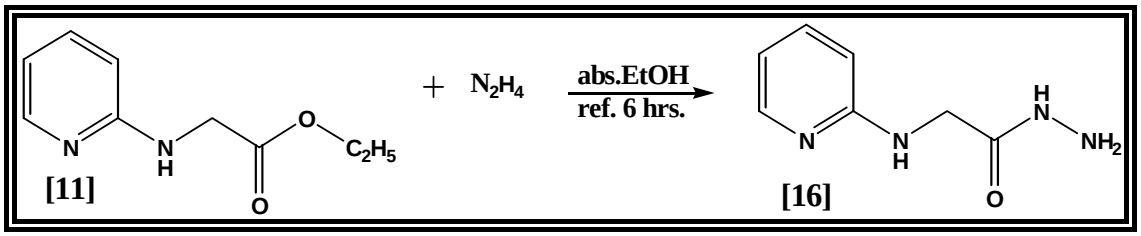


Fig (3-20): FT-IR spectrum of N-(4-biphenyl-4-yl-1,3-thiazol-2-yl)-N_2-pyridine-2-ylglyciamide [15]

3.16 Preparation of 2-(pyridine-2-ylamino)acetohydrazide [16]

Ethyl-N-pyridin-2-ylglycinate [11] was allowed to react with hydrazine hydrate in ethanol to give the desired product. The structure of this compound was confirmed by its M.P. and FT-IR spectral data:



The FT-IR spectrum of aceto hydrazide, figure (3-21), showed stretching bands at 3390 cm^{-1}-3255 cm^{-1} which were assigned to the (-$NHNH_2$) group stretching frequency. Beside this, the disappearance of (C=O) stretching band attributable to ester group at 1728 cm^{-1}, figure (3-16), with the appearance of bands at 1645 cm^{-1} of (AmideI) and at 1585 cm^{-1} of (Amide II) proved the formation of compound [16].

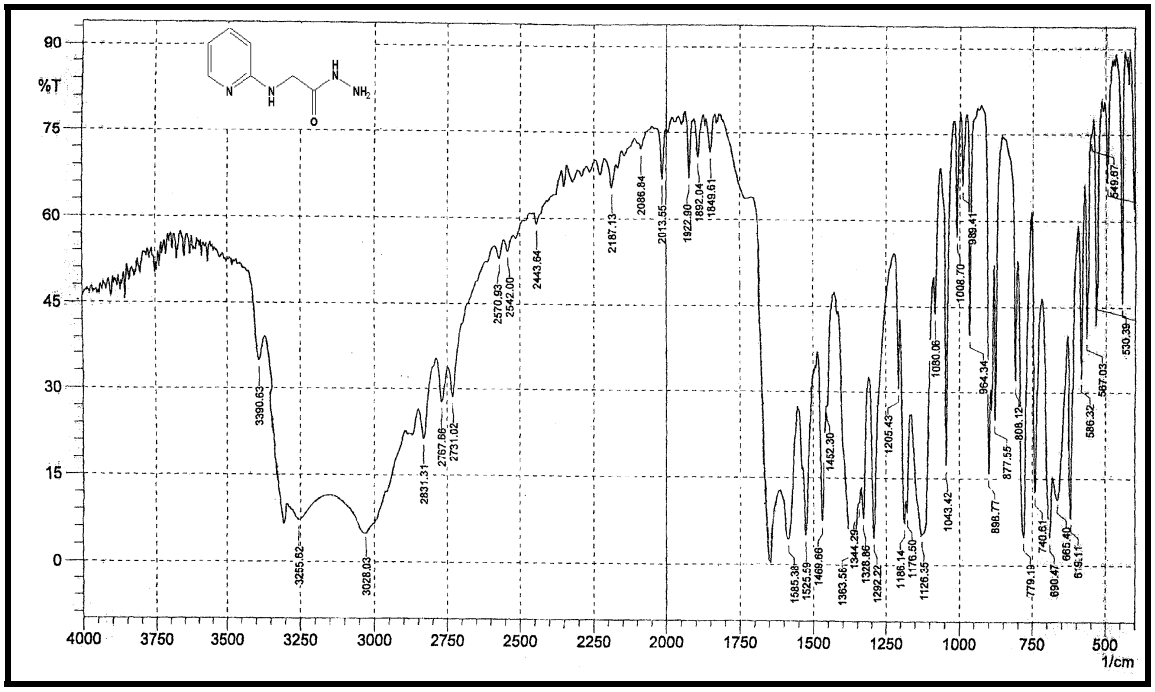
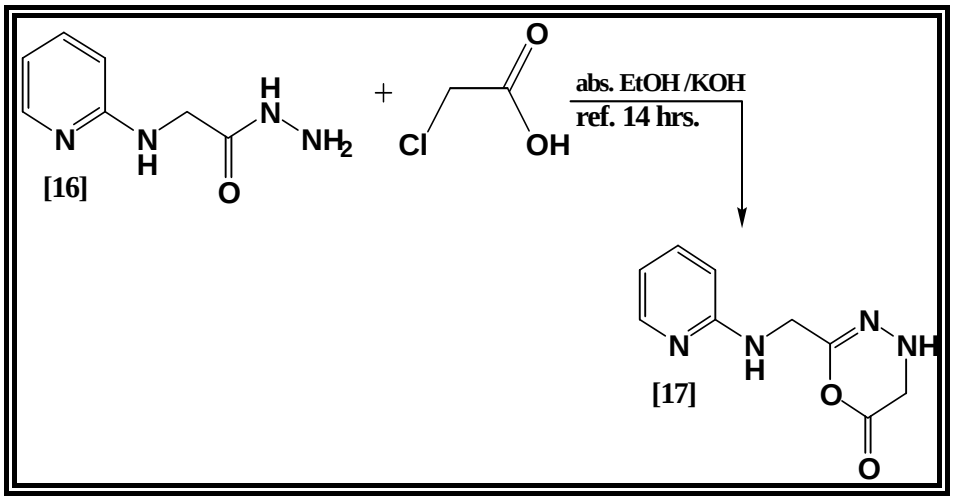


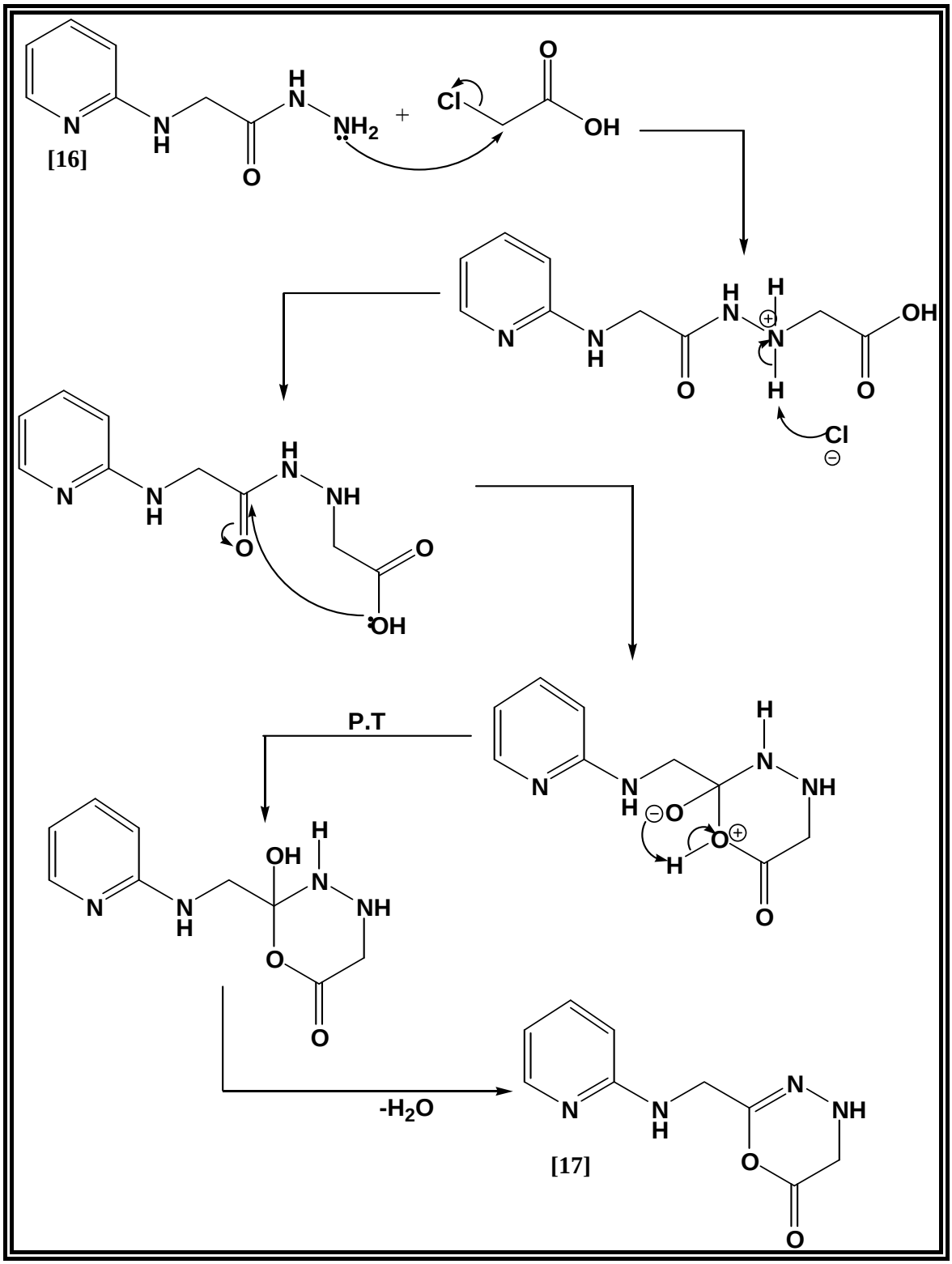
Fig (3-21): FT-IR spectrum of 2--(pyridine-2-ylamino)acetohydrazide [16]

3.17 Preparation of 2-[(pyridine-2-ylamino)methyl]-4,5-dihydro-6H-1,3,4-oxadiazine-6-one [17]

Stirring of compound [16] with potassium hydroxide until it completely dissolved, then chloroacetic acid were added and the reaction mixture were refluxed in absolute ethanol for 14 hours, affording the target oxadiazine:



The suggested mechanism for this reaction can be as follow [101]:



The structure of the titled compound was proved by its M.P. and FT-IR spectrum.

FT-IR spectrum showed the disappearance of the band at 3390-3255 cm^{-1} due to υ(-$NHNH_2$) moiety of compound [16] with the appearance of a band at 3363 cm^{-1} assignable to υ(N-H) of oxadiazine ring [(93)]. Further more, band at 1124 cm^{-1} was due to υ(C-O) of ester group.

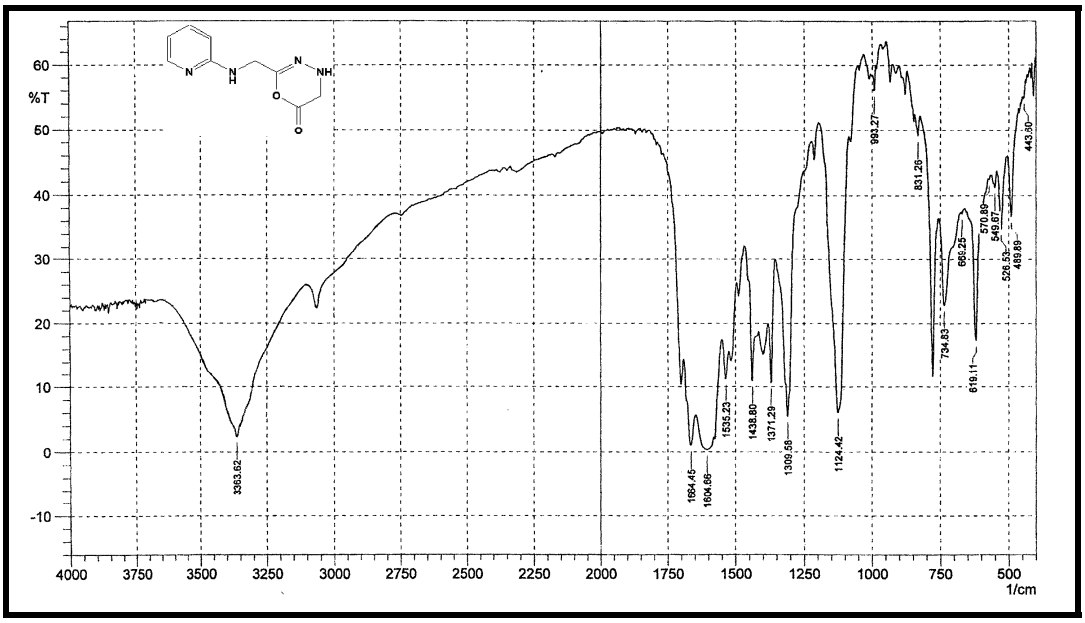
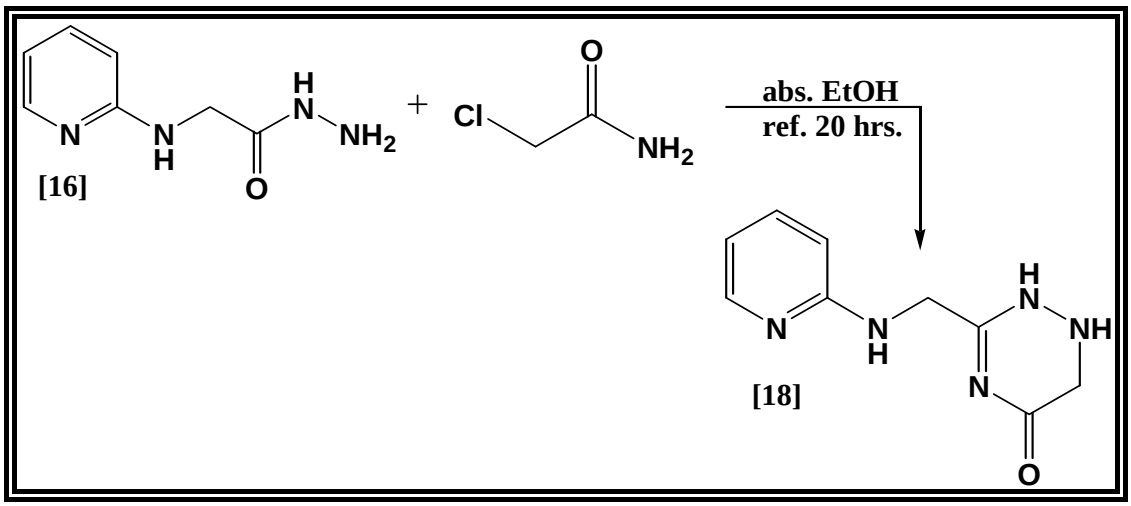


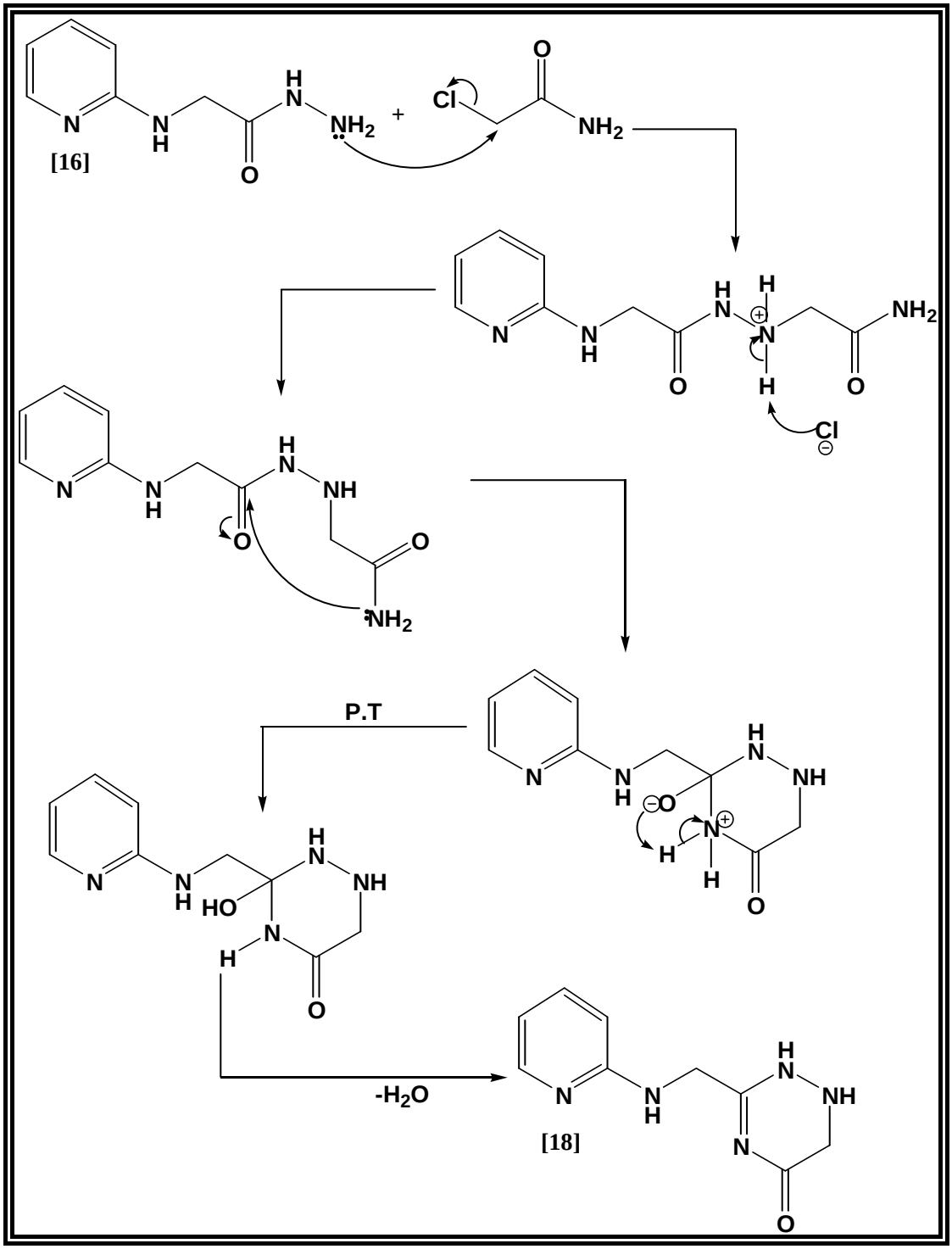
Fig (3-22): FT-IR spectrum of 2-[(pyridine-2-ylamino)methyl]-4,5-dihydro-6H-1,3,4-oxadiazine-6-one [17]

3.18 Preparation of 3-[(pyridine-2-ylamino)methyl]1,6-dihydro-1,2,4-triazin-5(2H)-one [18]

Chloroacetamide was refluxed with compound [16] in absolute ethanol for 17 hours to afford the target triazine:



The mechanism for the formation of the titled compound may be as follow (101).



The synthesized compound was characterized on the basis of its M.P., FT-IR, ^{1}H-and ^{13}C-NMR.

Infrared spectrum

The FT-IR spectrum, figure (3-23), showed bands at 3400-3265 cm^{-1} which were assignable to (O-H) and (N-H) stretching vibrations. The bands at 3093 cm^{-1}, 2827 cm^{-1} and 1650 cm^{-1} were due to υ(C-H) aromatic, υ(C-H) aliphatic and υ(C=O) amide in moiety of triazine ring [(112)], respectively.

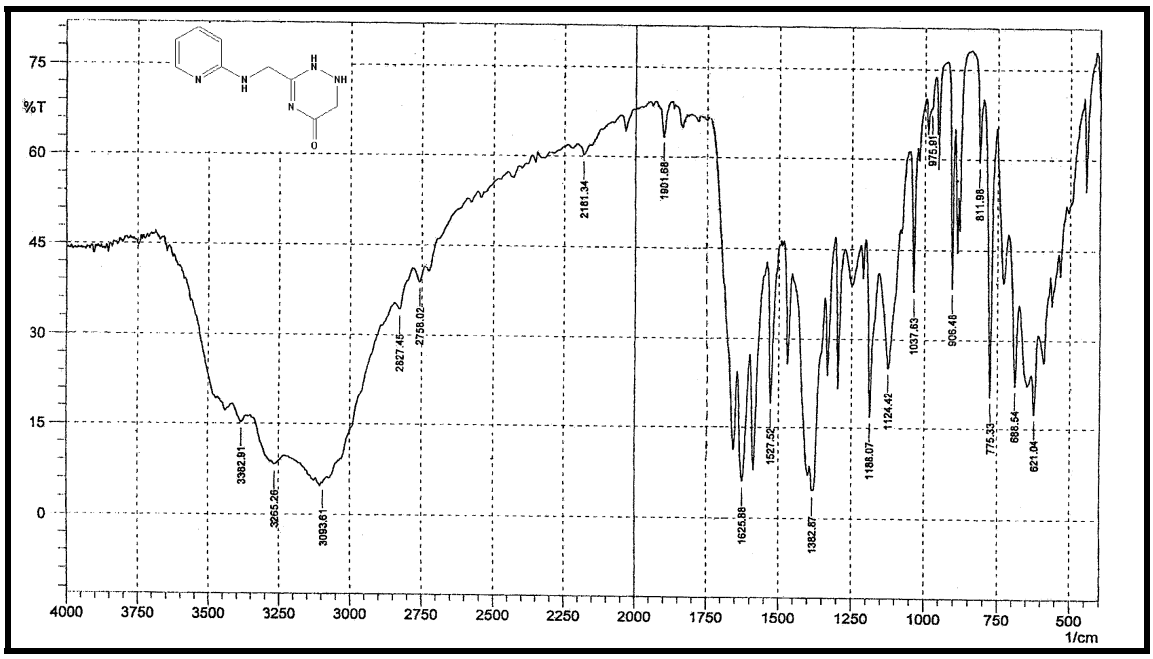


Fig (3-23): F.T.IR spectrum of 3-[(pyridine-2-ylamino)methyl]1,6-dihydro-1,2,4-triazin-5(2H)-one [18]

^{1}H-NMR spectrum

^{1}H-NMR spectrum of compound [18], figure (3-24), shows the following characteristic chemical shifts (DMSO-d_6, ppm). Methylene protons, 2, signal appear at δ 1.67 while methylene protons of triazine ring, 1, appear downfield than expected, at δ 2.21, this is due to the presence of (C=O) adjacent to it [(111)]. The (N-H) singlet absorption occur at δ (4.77-5.88). these signals were further proved by D_2O exchange, figure (3-25).

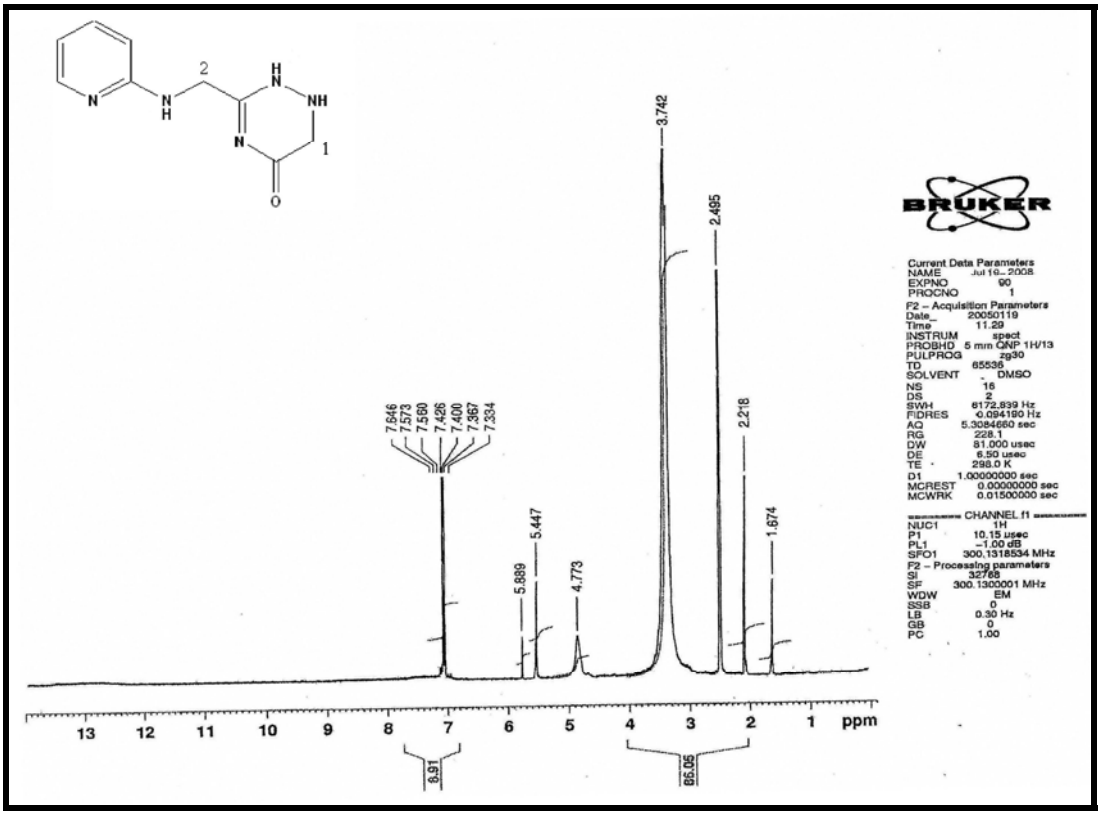


Fig (3-24): ^{1}H-NMR spectrum of 3-[(pyridine-2-ylamino)methyl]1,6-dihydro-1,2,4-triazin-5(2H)-one [18]

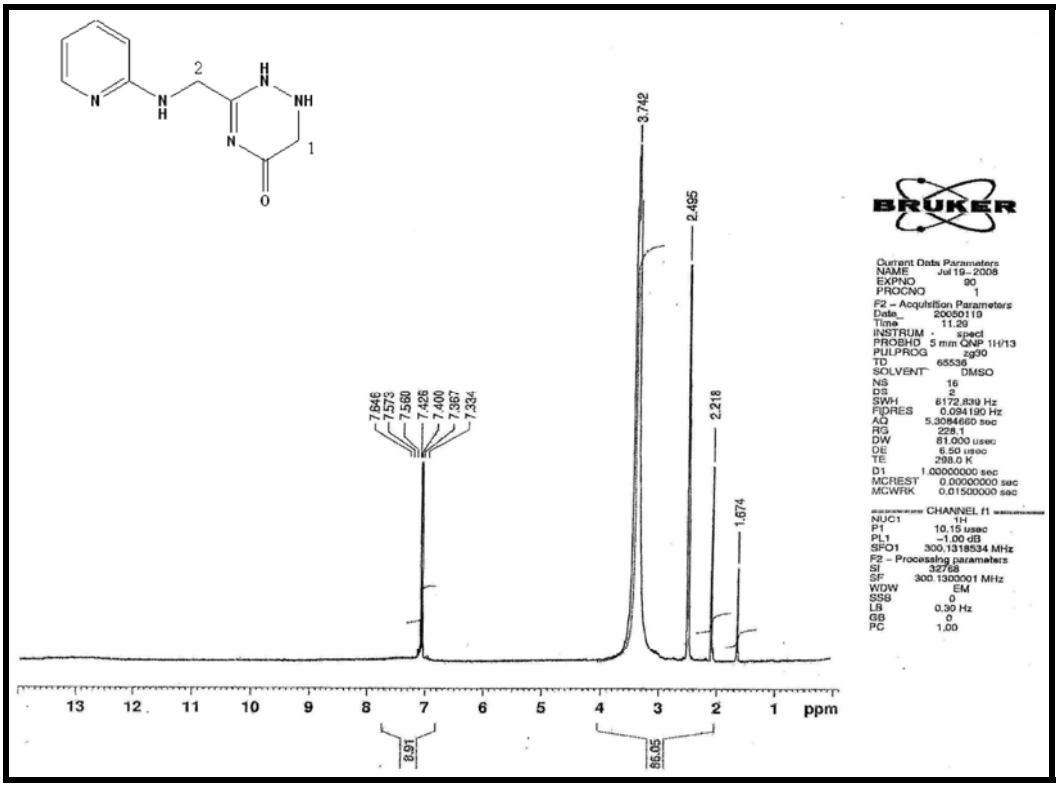


Fig (3-25): D_2O exchange spectrum of 3-[(pyridine-2-ylamino)methyl]1,6-dihydro-1,2,4-triazin-5(2H)-one [18]

^{13}C-NMR spectrum

The ^{13}C-NMR spectrum of compound [18], figure (3-26), shows the following characteristic chemical shift (DMSO-d_6, ppm). The two signals at δ 18.57 and δ 20.48 ppm are characteristic of the two methylene carbons, 1 and 2, respectively. The (=C-), 3, signals occurred at δ 52.48**.** aromatic ring carbon signals appear at δ(127.51-142.32). the signal at δ 173.32 is due to the carbonyl carbon atom.

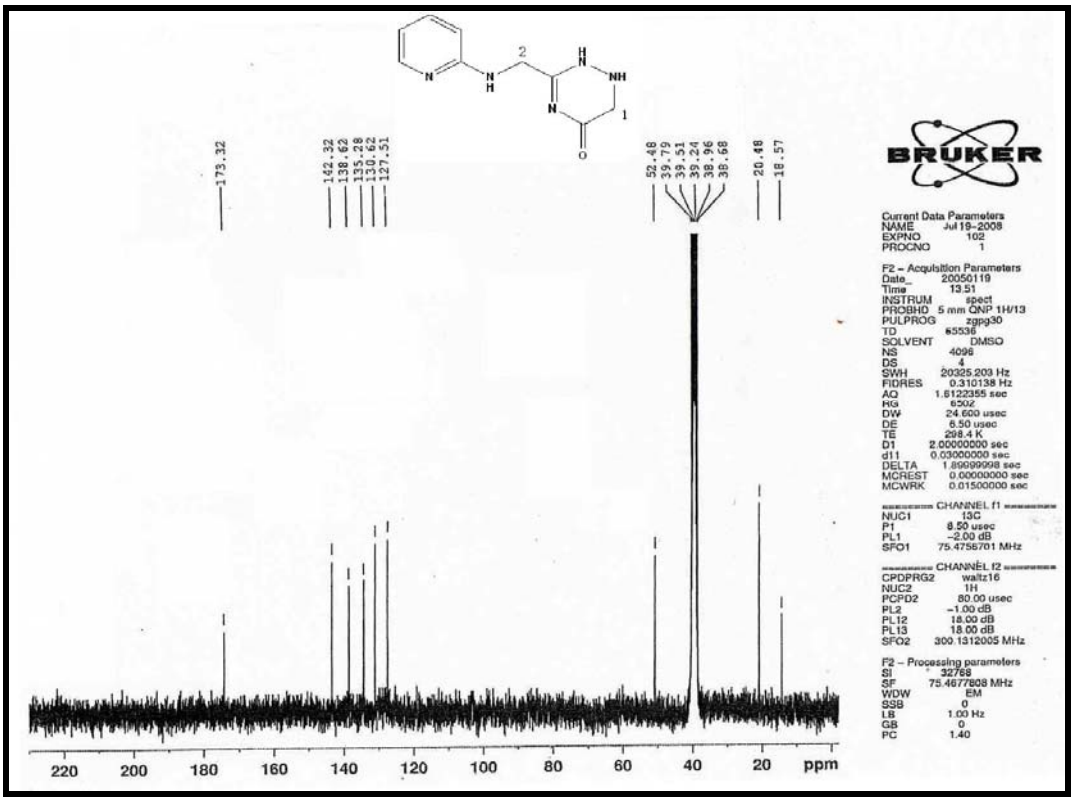
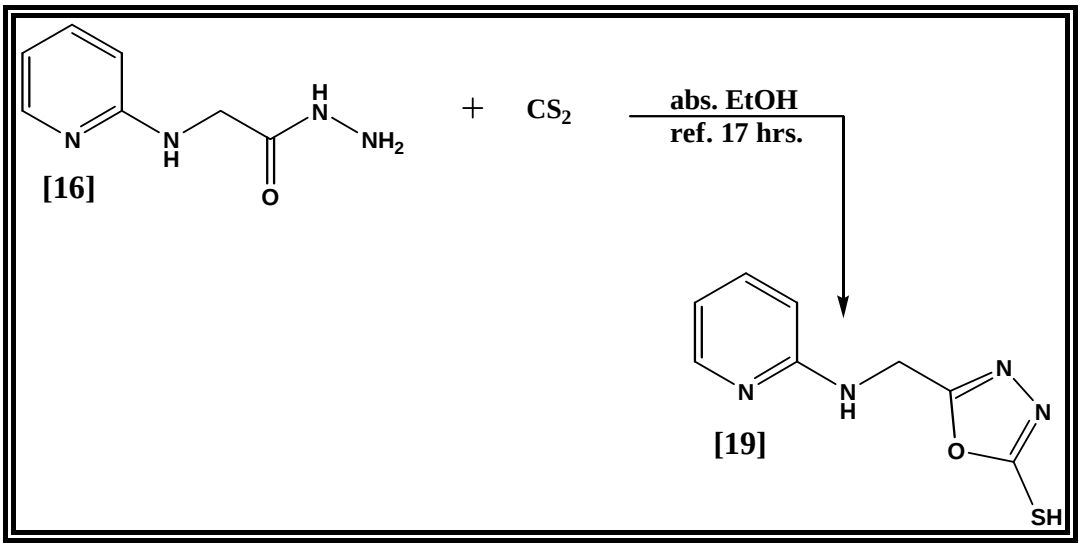


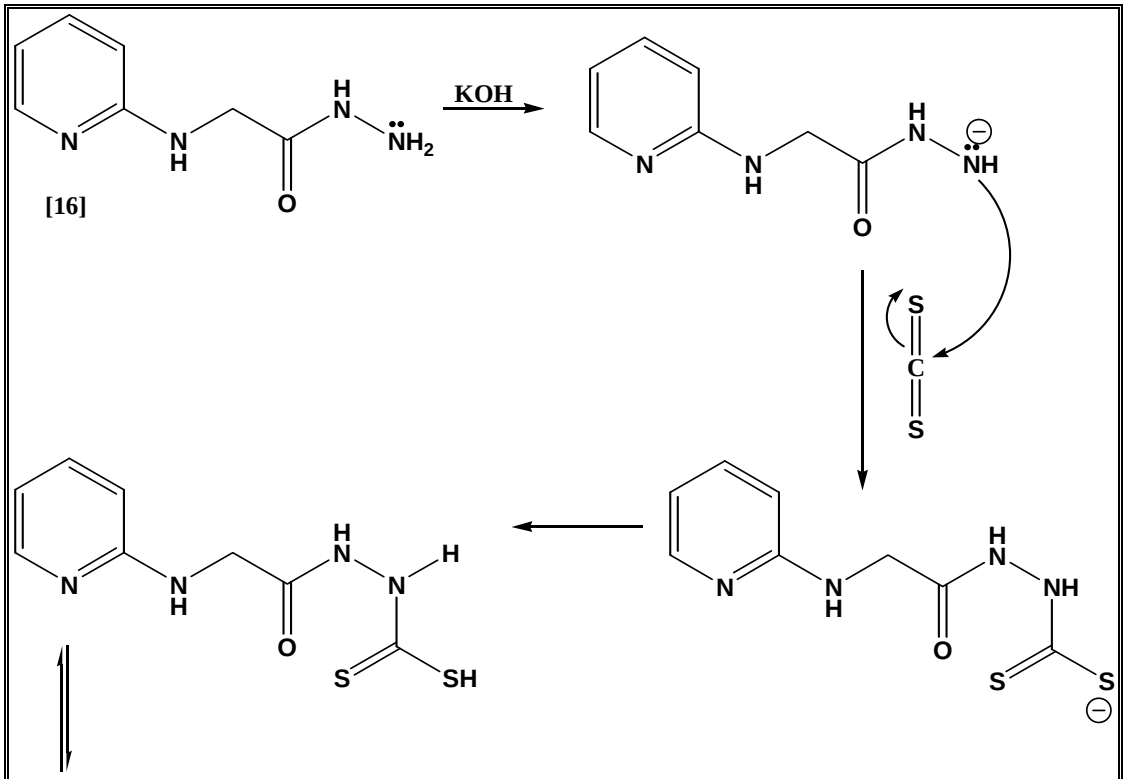
Fig (3-26): ^{13}C-NMR spectrum of 3-[(pyridine-2-ylamino)methyl]1,6-dihydro-1,2,4-triazin-5(2H)-one [18]

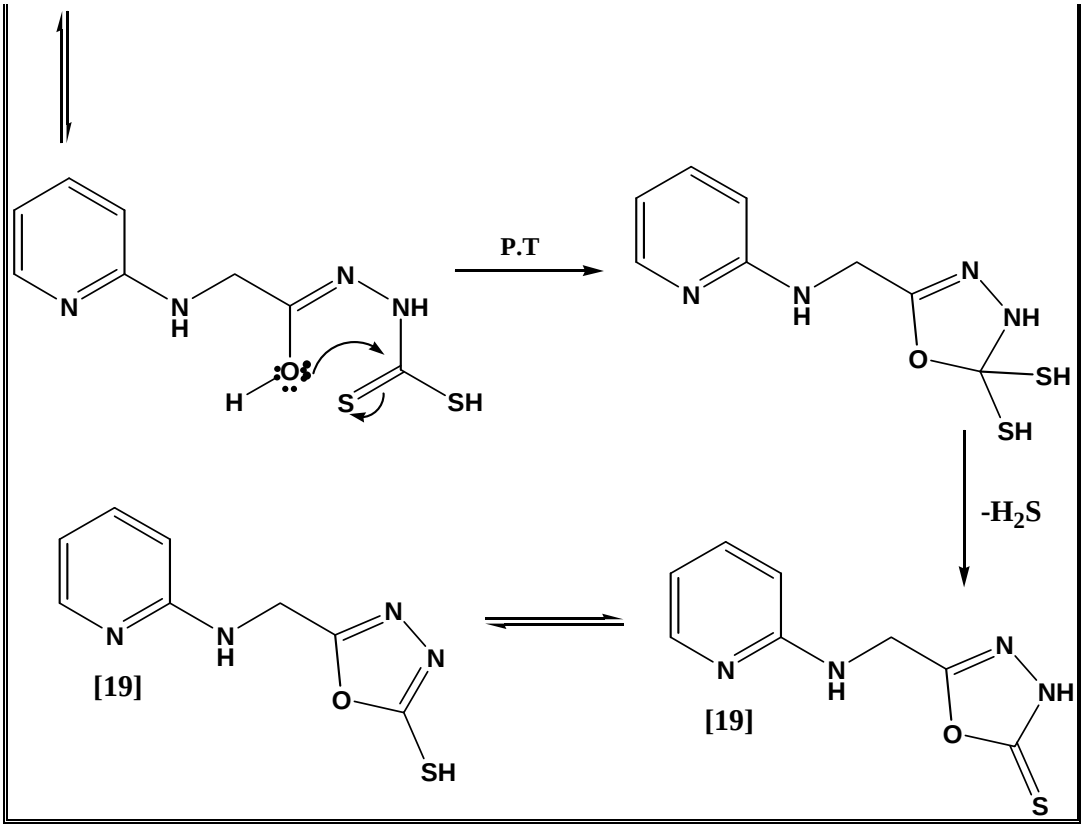
3.19 Preparation of 5-[(pyridine-2-ylamino)methyl]-1,3,4-oxadiazole-2-thiol [19]

The target oxadiazole were synthesized from refluxing the acid hydrazide [16] with carbon disulfide in absolute ethanol for 17 hours:



The mechanism for the formation of the titled compound may be as follow (102):





The structure of the synthesized compound was assigned on the basis of its M.P and FT-IR analysis.

FT-IR spectrum showed disappearance of bands at 3390 cm^{-1} -3255 cm^{-1} due to υ(-$NHNH_2$) moiety of compound [16] with the appearance of bands at 1620 cm^{-1} assignable to γ(C=N) of oxadiazole ring [(93)] and at 1253 cm^{-1} due to υ(C-O-C) cyclic group in oxadiazole which are good evidence for the structure assigned to this compound. Furthermore bands at 1487 cm^{-1} and 1379 cm^{-1} were due to δ (C-N) and υ(C=S), respectively.

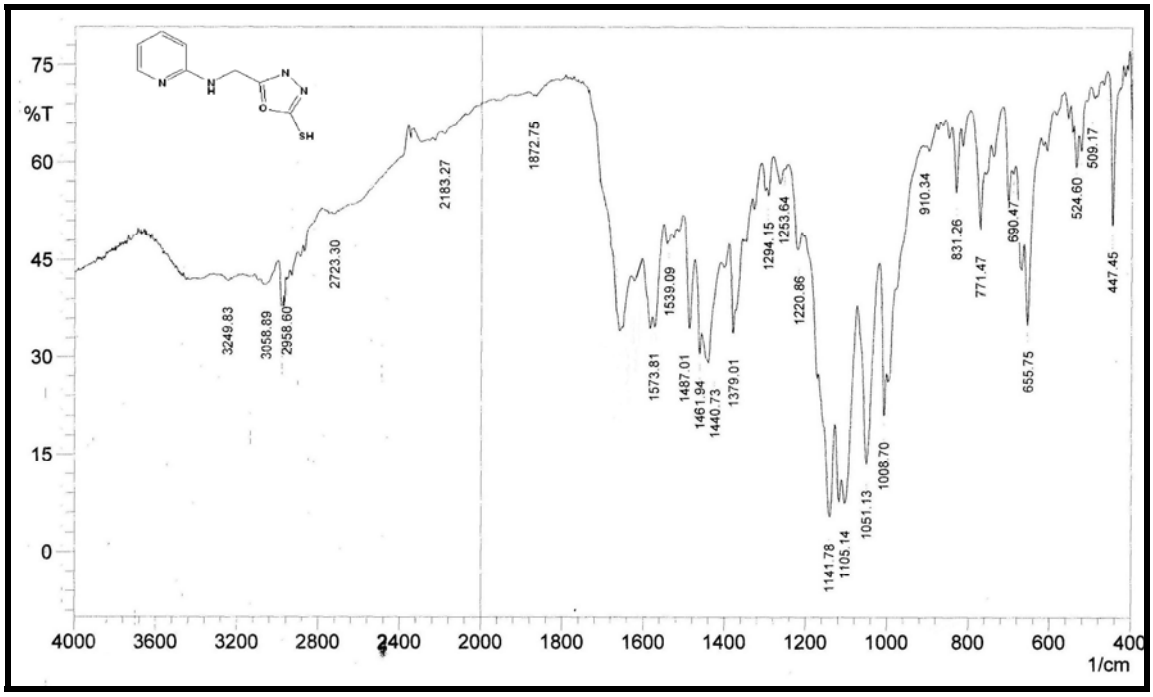
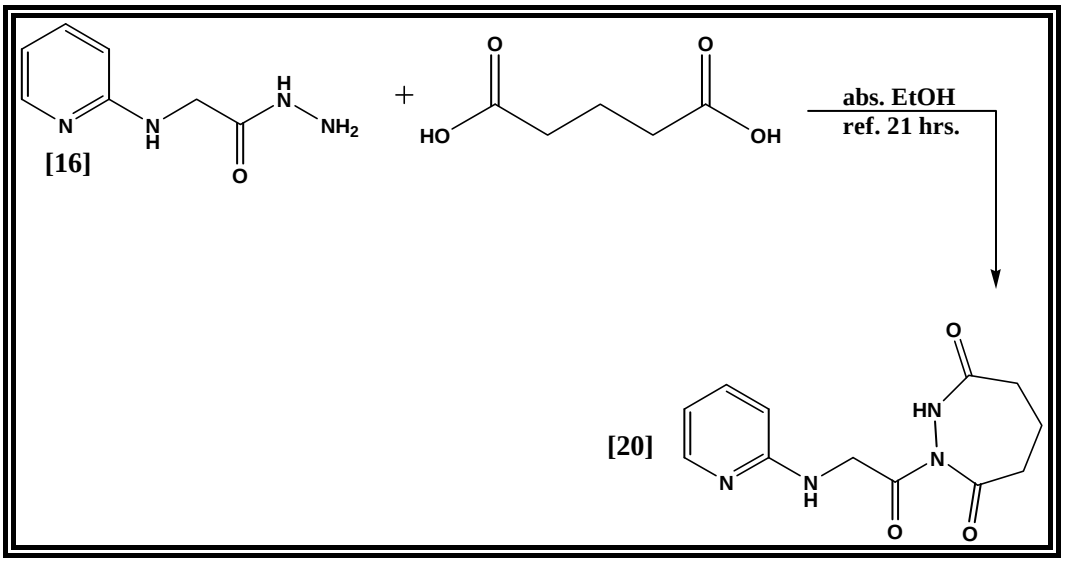


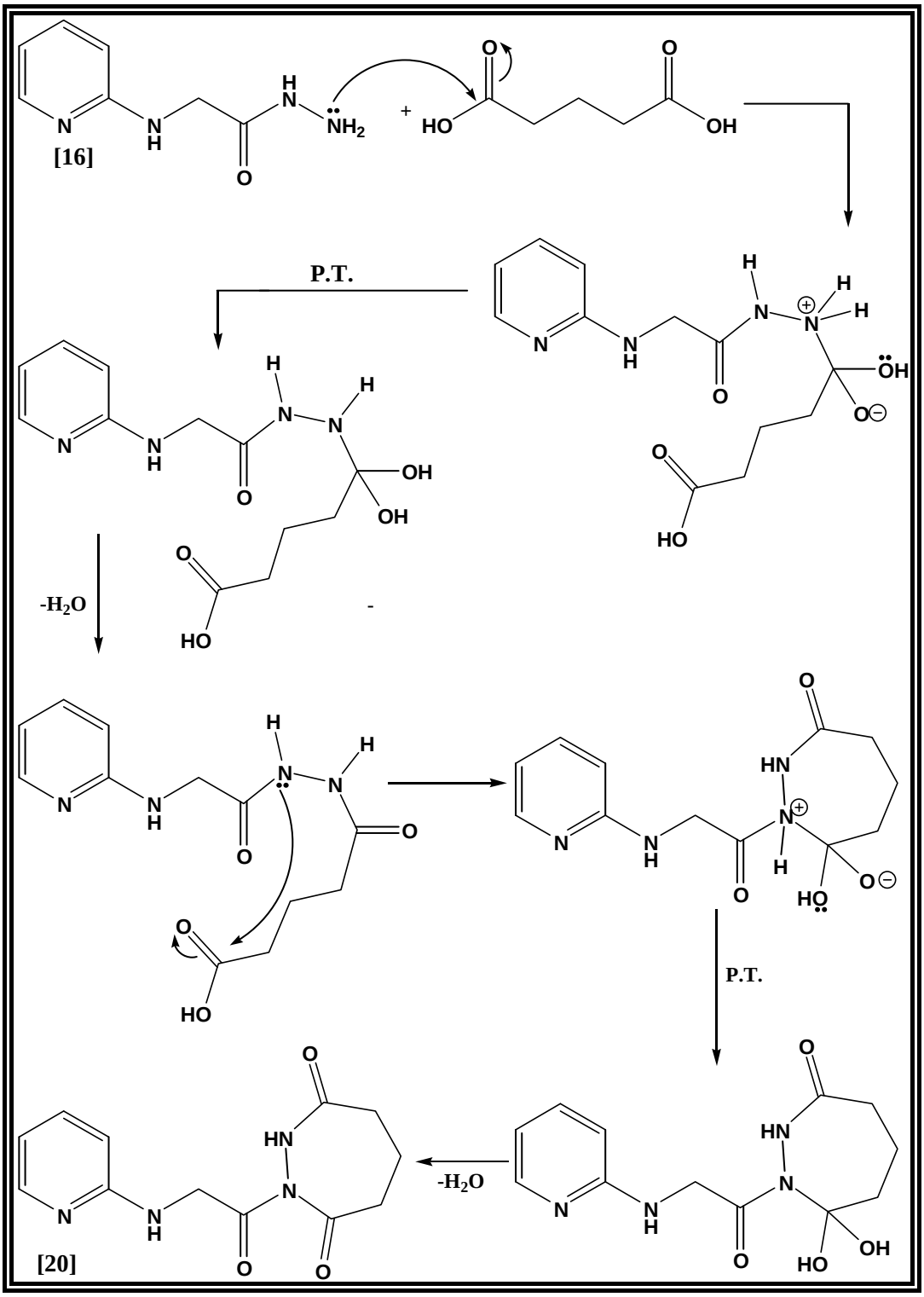
Fig (3-27): F.T.IR spectrum of 5-[(pyridine-2-ylamino)methyl]-1,3,4-oxadiazole-2-thiol [19]

3.20 Preparation of 1-(N-pyridine-2-ylglycyl)-1,2-daizepane-3,7-dione [20]

Compound [16] and glutaric acid were refluxed for 21 hours in absolute ethanol to afford the target diazepine:



The mechanism of this compound can be as follows [(103)]:



The structure of the synthesized compound was assigned by its M.P., FT-IR, ^{1}H-and ^{13}C-NMR.

Infrared spectrum

FT-IR spectrum of compound [20], figure (3-28), shows stretching bands at 3265 cm^{-1}, 3064 cm^{-1}, 2829 cm^{-1} and 1654 cm^{-1} assignable for υ(N-H), υ(C-H) aromatic, υ(C-H) aliphatic and υ(C=O) amide groups, respectively. Other characteristic bands can be seen in FT-IR spectrum of this compound.

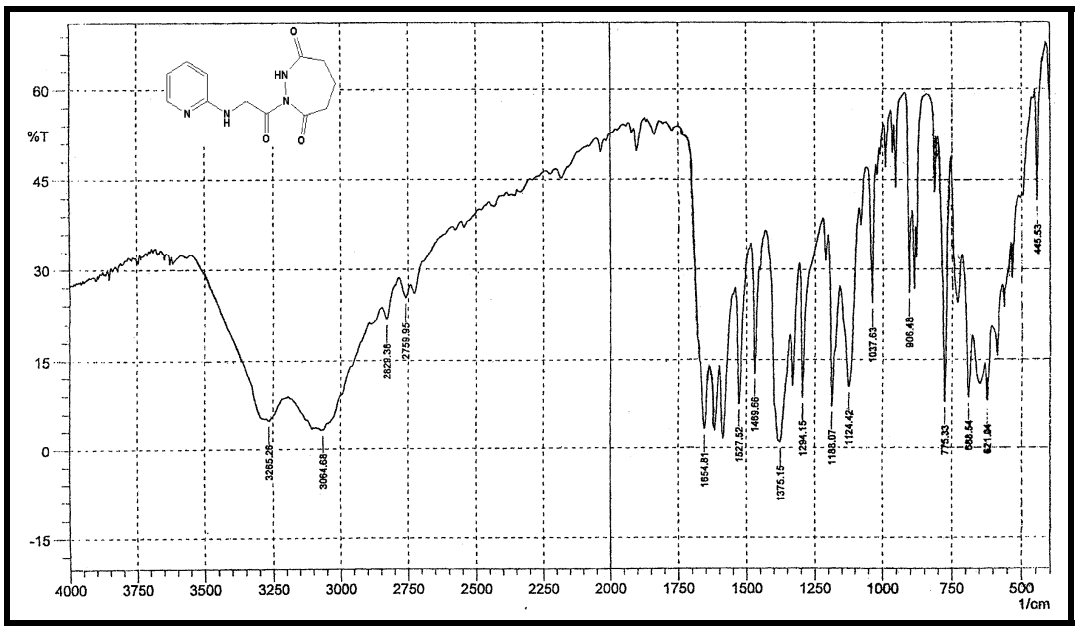


Fig (3-28): FT-IR spectrum of 1-(N-pyridine-2-ylglycyl)-1,2-daizepane-3,7-dione [20]

^{1}H-NMR spectrum

^{1}H-NMR spectrum of compound [20], figure (3-29), shows the following characteristic chemical shifts (DMSO-d_6, ppm). The three methylene groups of diazepine ring appear as multiplet singals in the region δ(1.38-2.26). the other methylene group signal, 1, was appeared at 2.49. The (N-H) absorptions occour at δ(4.77-5.44), which were further characterized by their disappearance due to D_2O exchange, figure (3-30). Aromatic protons appear at δ(7.44-9.50). these results give a good support for the results obtained from IR analysis.

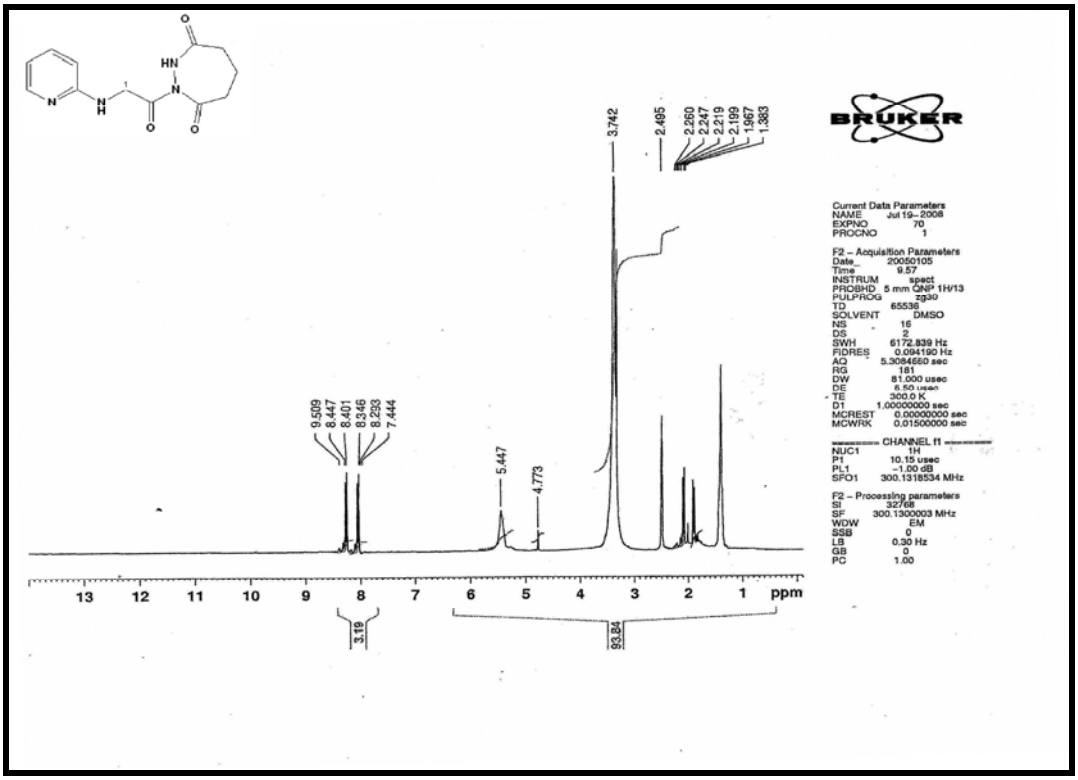


Fig (3-29): Structure and ^{1}H-NMR spectrum of 1-(N-pyridine-2-ylglycyl)-1,2-daizepane-3,7-dione [20]

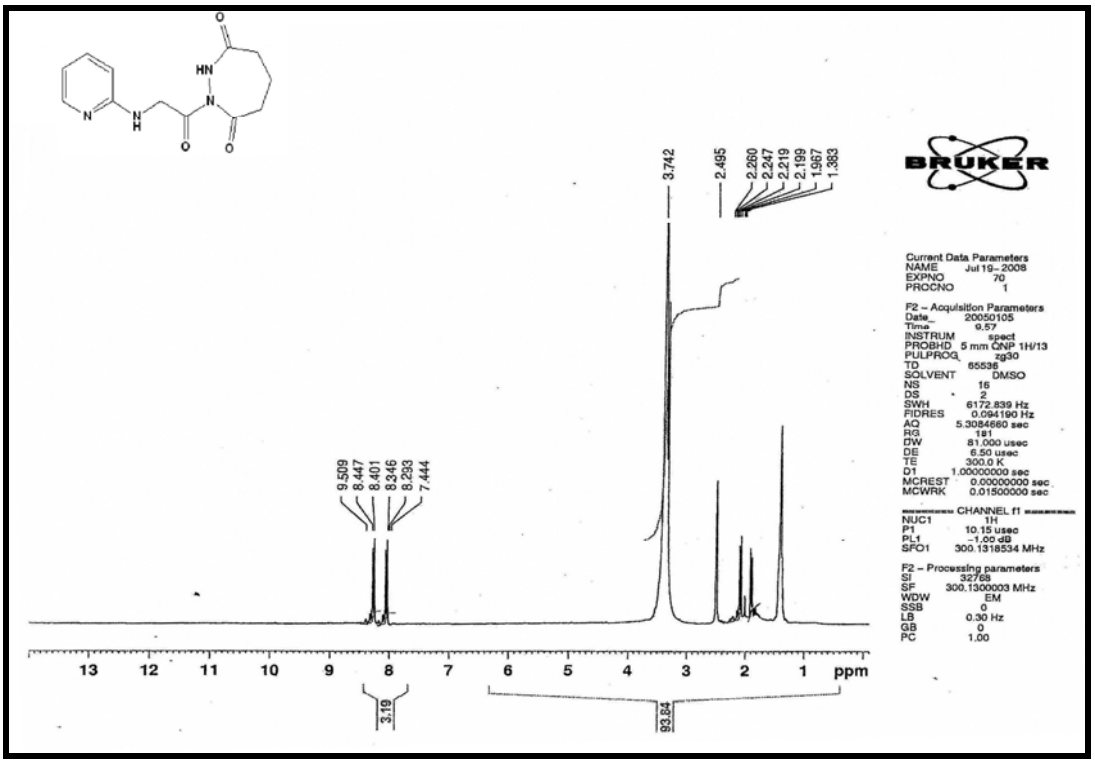


Fig (3-30): D_2O exchange ^{1}H-NMR spectrum of 1-(N-pyridine-2-ylglycyl)-1,2-daizepane-3,7-dione [20]

^{13}C-NMR spectrum of compound [20], figure (3-31), shows the following characteristic chemical shift (DMSO-d_6, ppm). The signals at δ(16.23-20.05) are characteristic of the four methylene group carbons. Aromatic ring carbon atoms appear at δ(127.25-132.02). the signals at δ(167.51-174.88) are due to the absorption of the three carbonyl carbon atoms.

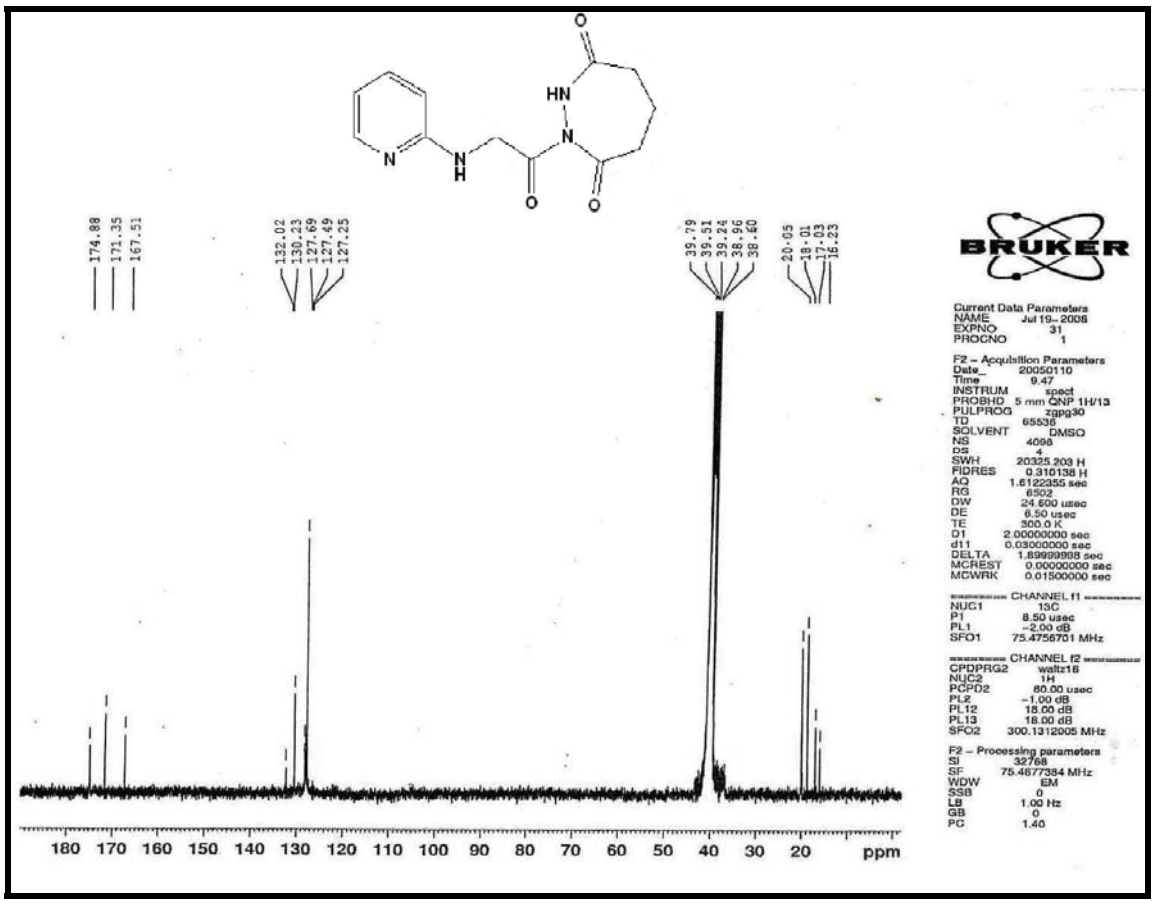
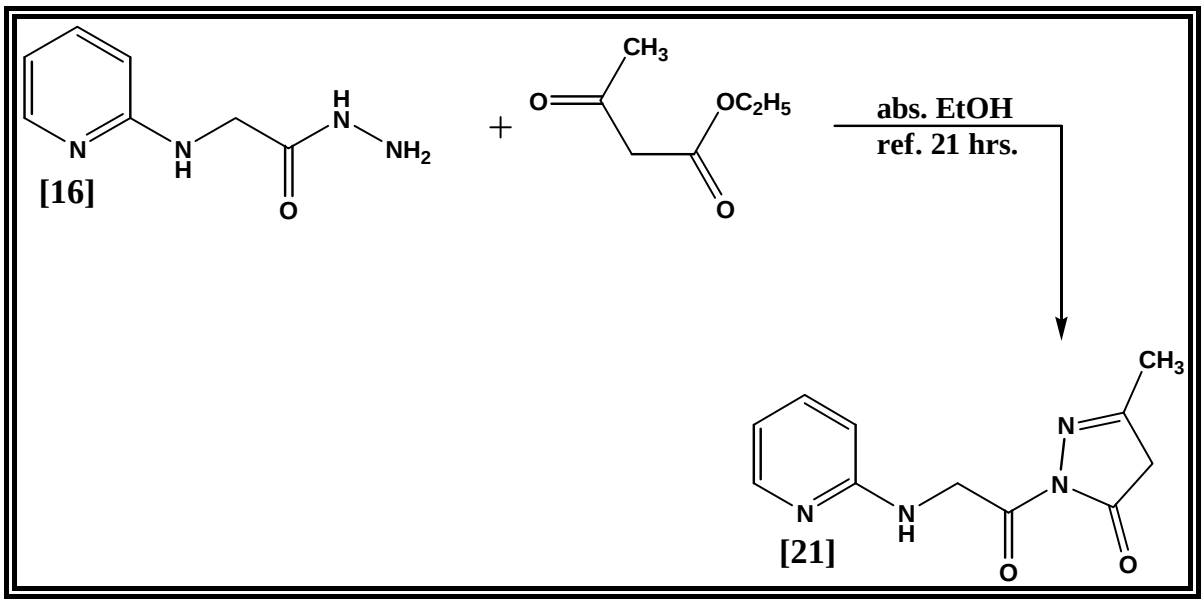


Fig (3-31): ^{13}C-NMR spectrum of1-(N-pyridine-2-ylglycyl)-1,2-daizepane-3,7-dione [20]

3.21 Preparation of 5-methyl-2-(N-pyridin-2-ylglycyl)-2,4-dihydro-3H-pyrazol-3-one [21]

The titled compound was synthesized from refluxing of ethylacetoacetate and acid hydrazide [16] in presence of absolute ethanol for 21 hours:



The structure of the synthesized compound was assigned by its M.P. and FT-IR data.

In the FT-IR spectrum, fig (3-32), the disappearance of carbonyl stretching band attributed to acid hydrazide [16] at 1645 cm^{-1} with the appearance of new band at 1701 cm^{-1}due to υ(C=O) of pyrazolone ring [(113)] of compound [21] was the most characteristic evidence for the formation of the titled compound. Furthermore, bands at 3300 $cm^{-1}$and 3070 cm^{-1} assigned for (N-H) and (C-H) aliphatic stretching vibrations, respectively.

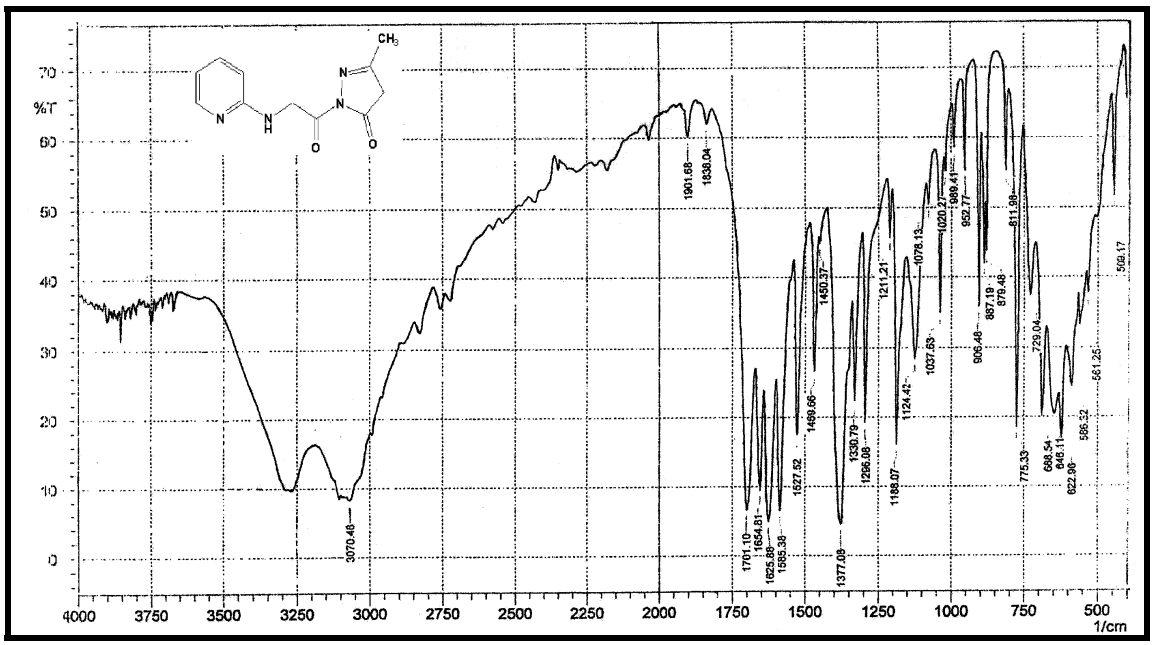
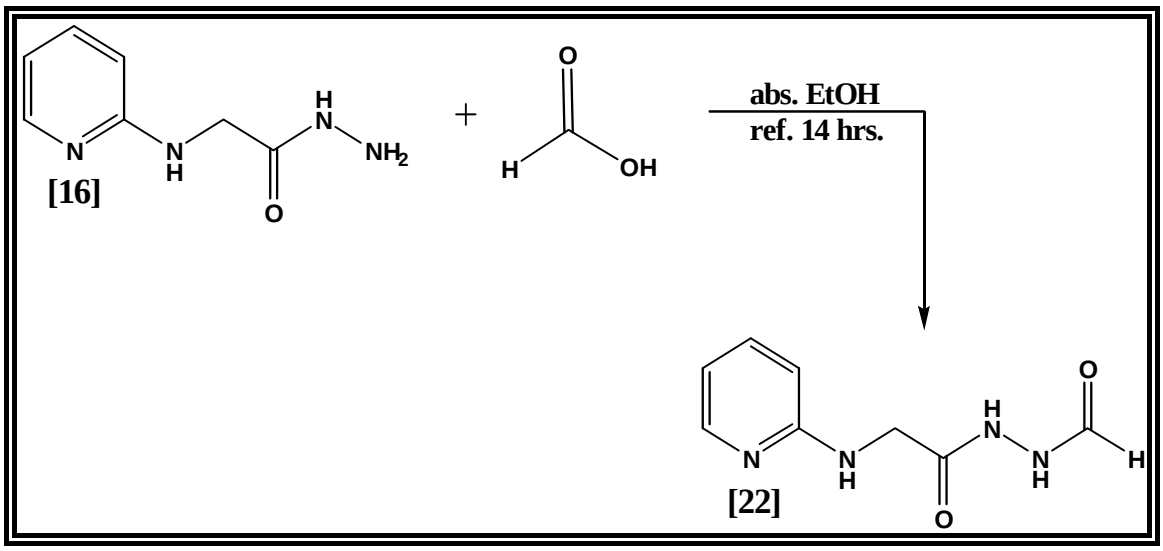


Fig (3-32): FT-IR spectrum of 5-methyl-2-(N-pyridin-2-ylglycyl)-2,4-dihydro-3H-pyrazol-3-one [21]

3.22 Preparation of N'-formyl-2-(pyridine-2-ylaminoaceto-hydrazide [22]

Compound [22] prepared by reaction of formic acid with the acid hydrazide [16] in absolute ethanol and refluxed for 14 hours:



The structure of the synthesized compound was assigned by its M.P. and FT-IR data.

The FT-IR spectrum of compound [22], figure (3-33), shows the following characteristics features : bands at the range 3311 cm^{-1}-3141 cm^{-1} were due to (N-H) stretching vibration. Besides this, υ(C-H) aromatic and υ(C-H) aliphatic appear at 3053 cm^{-1} and 2943 cm^{-1}, respectively. The sharp band at 1737 cm^{-1} was due to (C=O) of aldehyde moiety stretching vibration.

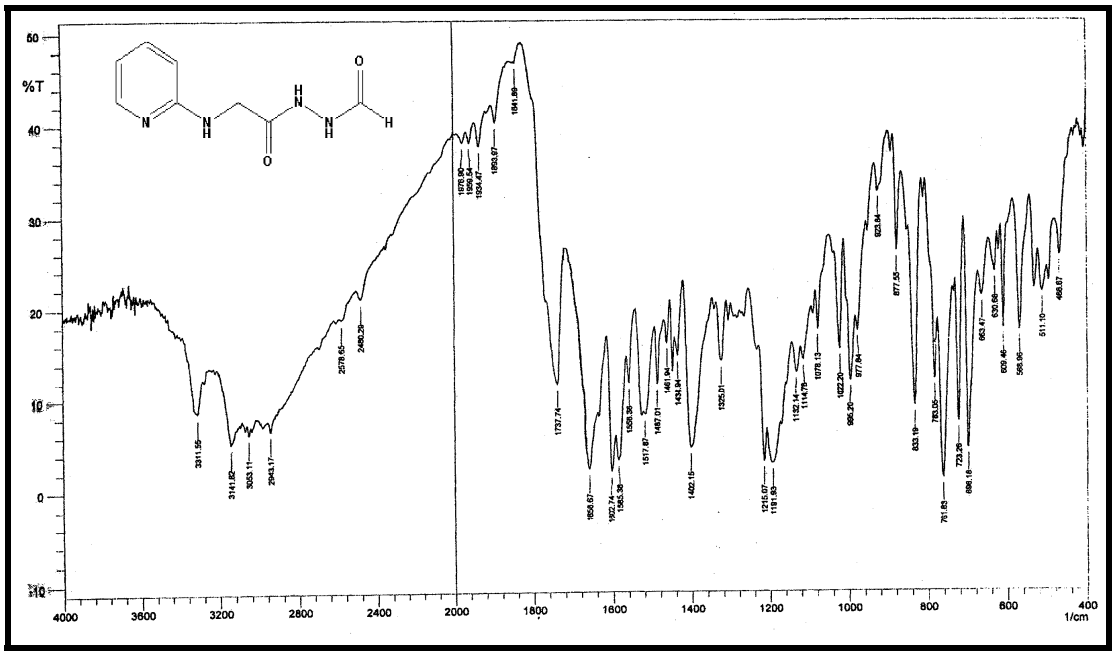
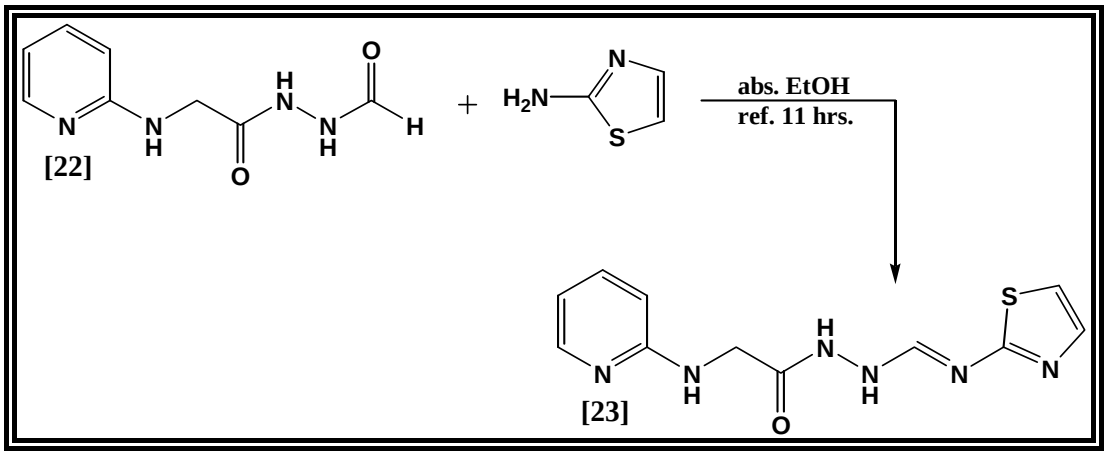


Fig (3-33): FT-IR spectrum of N'-formyl-2-(pyridine-2-ylaminoaceto-hydrazide [22]

3.23 Preparation of 2-(pyridin-2-ylamino)-N'-[(1,3-thiazol-2ylimino)methyl]acetohydrazide [23]

Refluxing of compound [22] with 2-aminothiazole in absolute ethanol for 11 hours yielded the target compound [23]:

The structure of the synthesized compound was assigned by its M.P. and FT-IR data.



In the FT-IR spectrum, figure (3-34) the disappearance of band at 1737 cm^{-1} due to (C=O) of aldehyde moiety with the appearance of bands at 1627 cm^{-1} assignable for υ(C=N) of imine moiety, was the most characteristic for the formation of this compound. Other characteristics bands are that at 3249 cm^{-1} and 3060 cm^{-1} attributable for υ(N-H) and υ(C-H) aromatic, respectively.

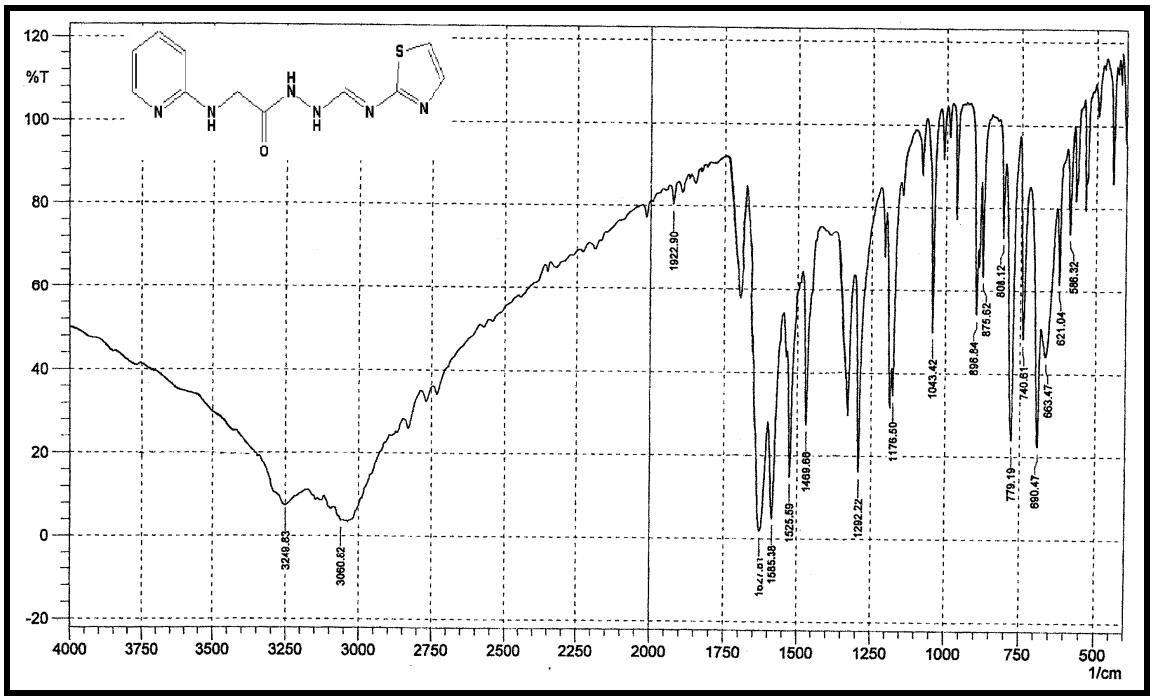


Fig (3-34): FT-IR spectrum of 2-(pyridine-2-ylamino)-N'-[(1,3-thiazol-2ylamino)methyl]acetohydrazide [23]

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4.1 General Description:

Microorganism causes different kinds of diseases to humans and animals. Discovery of chemotherapeutic agents played a very important role in controlling and preventing such diseases. Chemotherapeutic agents are isolated either from living organisms known as anti-biotic like penicillin and tetracycline or they are chemical compounds prepared by chemists such as sulfa drugs [(114)].

Microorganisms have the ability to develop resistance to these chemotherapeutic agents and such strains which are resistance cause major problems in the treatment of microbial infections. For this reason, searching for new anti-microbial agent is continuous process and great efforts have been employed to find new anti-biotic or new chemical compounds with good anti-microbial activity which might be suitable to be used as chemotherapeutic agents.

4.2.1 Staphylococcus aureus:

Staphylococcus (in Greek *staphyle* means *bunch of grapes* and *coccos* means granule) [(115)], figure (4-1).

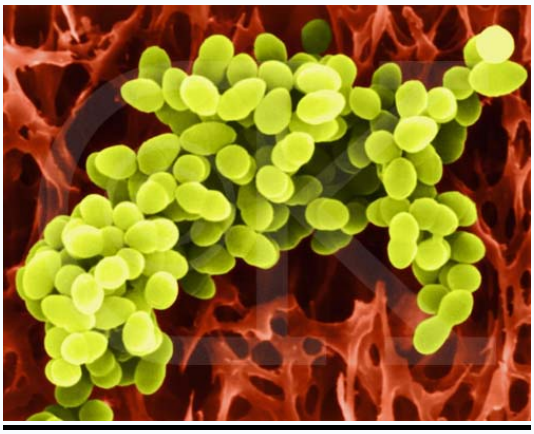


Fig (4-1)

Staphylococcus aureus

Staphylococcus is Gram-positive spherical bacteria; *Staphylococcus aureus* is significant in their interactions with humans. *Staphylococcus aureus* causes a variety of superlative infections and toxinoses in humans. *Staphylococcus aureus* is a major cause of hospital acquired infection of surgical wounds and infections associated with indwelling medical devices. *Staphylococcus aureus* causes food poisoning by releasing enterotoxins into food, and toxic shock syndrome by release of superantigens into the blood stream [(116)].

4.2.2 Pseudomonas aeruginosa:

Pseudomonas (in Greek *pseudo* means *false unit* and *monas* means *a single unit*). The species name *aeruginosa* is derived from the Greek prefix "*ae*" meaning 'old' or 'aged' and the suffix "*ruginosa*" means "wrinkled or bumpy" [(116)], figure (4-2).

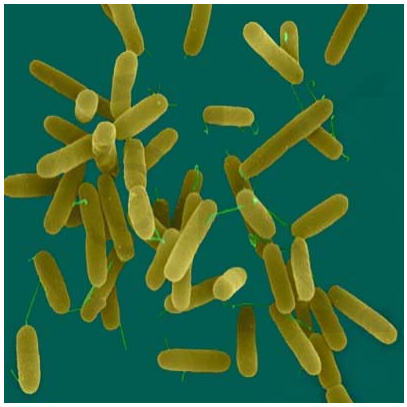


Fig (4-2)

Pseudomonas aeruginosa

Pseudomonas is a Gram-negative rod that belongs to the family Pseudomonadaceae. More than half of all clinical isolates produce the blue-green pigment pyocyanin. *Pseudomonas* often has a characteristic sweet

odor [117]. The pathogenesis of pseudomonal infections is multifactorial and complex. *Pseudomonas* species are both invasive and toxigenic. The 3 stages, according to Pollack, are: (1) bacterial attachment and colonization, (2) local infection, and (3) bloodstream dissemination and systemic disease [118].The importance of colonization and adherence is most evident when studied in the context of respiratory tract infection in patients with cystic fibrosis and in those that complicate mechanical ventilation. Production of extracellular proteases adds to the organism's virulence by assisting in bacterial adherence and invasion. *Pseudomonal* bacteremia occurs in association with malignancy, chemotherapy, AIDS, burn wound sepsis, and diabetes.

4.3 Microbiological Tests:

Preparation of nutrient agar was added to 1L of distilled water in conical flask was stirred with heating until it completely dissolved .The flask was stoppered by cotton and the medium was sterilized by placing it an autoclave for 20min at 121°C under pressure of 15 bound /inch. After that the medium was cooled to (45-55°C) and placed in petridish about (15-20ml)for each one, and was left to cool and solidified. Therefore the medium was ready for bacteria growth. The studied bacteria were placed on the nutrient agar surface using the loop and by streaking processor. After that the disc saturated with the tested compound solution was placed in the dishes which were then incubated for 24hour, at 37°C.

The inhibition zones caused by the various compounds were examined and shown in figures (4-3) – (4-9). The results of the preliminary screening tests are listed in table (4-1).

Table(4-1)
Anti-bacterial activity of the synthesized compounds

figure	Comp. No.	*Staphylococcus aureus* {a}	*Pseudomonas aeuroginosa* {b}
(4-3)	1	+	+
	2	+++	++
	3	-	-
	4	+	+
(4-4)	5	+++	-
	6	+	+
	8	++	+
(4-5)	9	++	+
	10	+	+
	11	-	-
	16	-	-
(4-6)	17	-	-
	19	+++	-
	18	-	-
	20	-	+
(4-7)	21	-	++
	22	+	+
	12	-	-
(4-8)	14	-	-
	13	+	-
	15	-	-
	7	-	-
(4-9)	23	-	-

- = No inhibition = inactive

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

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

+++ = (21 and more) = highly active

4.4 Conclusion:

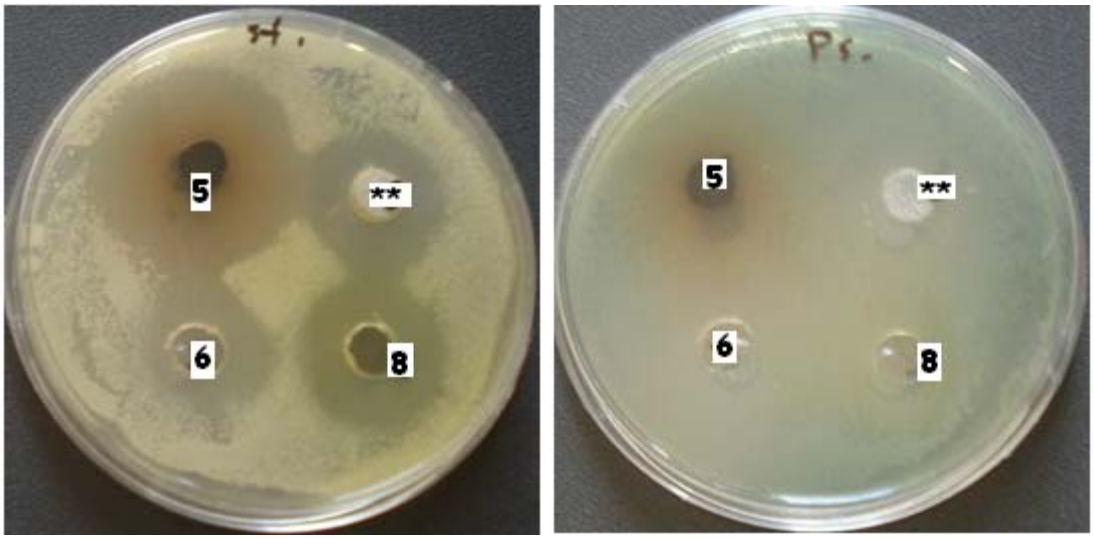
From the data obtained, it is clearly found that:

1) Compounds [2, 5 and 19] have the highest activity against Staphylococcus aureus while compounds [8 and 9] have moderate activity than others.

2) In the case of Pseudomonas aeuroginosa, compound [2 and 21] show the higher activity than others.

{a} *{b}*

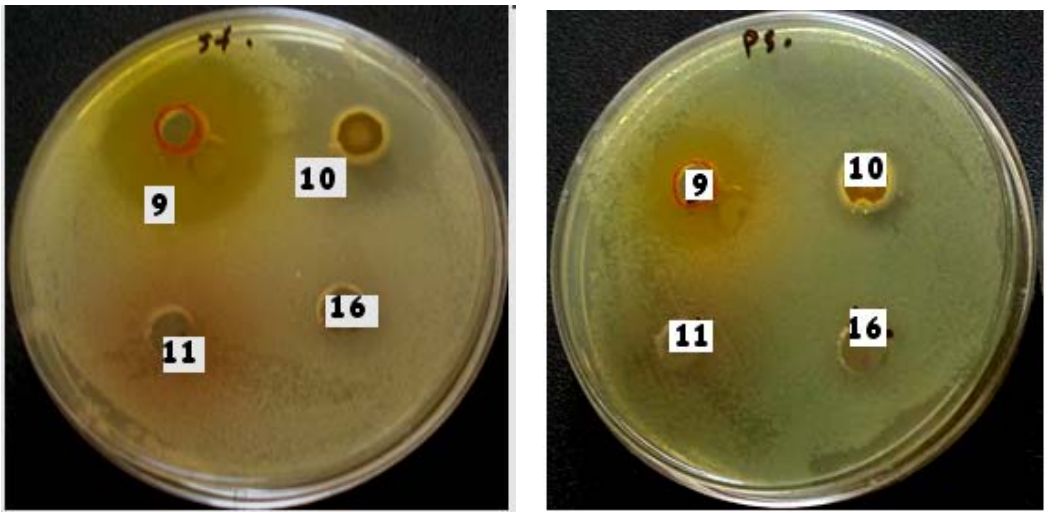
Figure (4-3): the biological activity zone of compound [1, 2, 3 and 4] towards {a}: Staphylococcus aureus, {b}: Pseudomonas aeuroginosa



{a} *{b}*

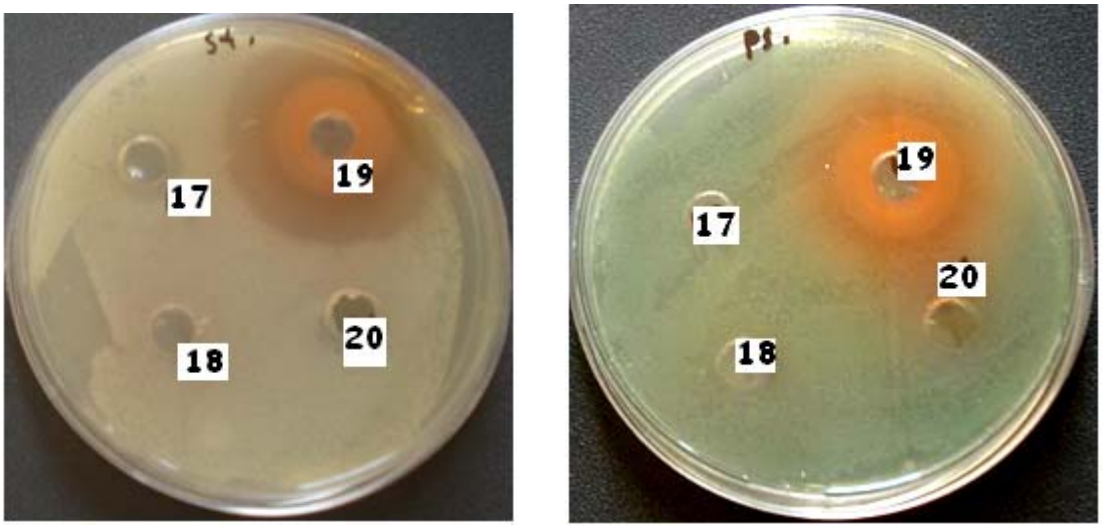
Figure (4-4): the biological activity zone of compound [5, 6 and 8] towards {a}: Staphylococcus aureus, {b}: Pseudomonas aeuroginosa

*** means that this compound has ben cancled*



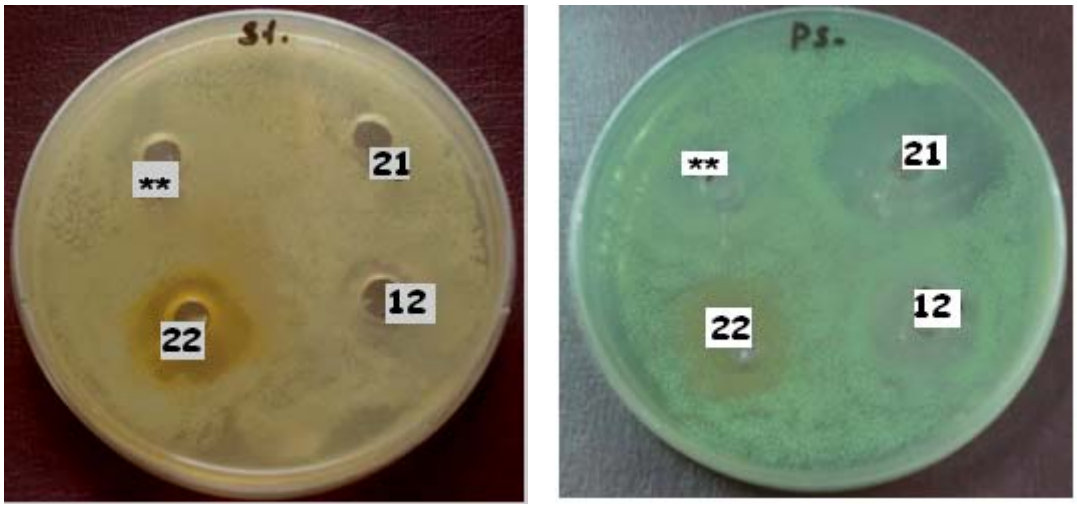
{a} *{b}*

Figure (4-5): the biological activity zone of compound [9, 10, 11 and 16] towards {a}: Staphylococcus aureus, {b}: Pseudomonas aeuroginosa



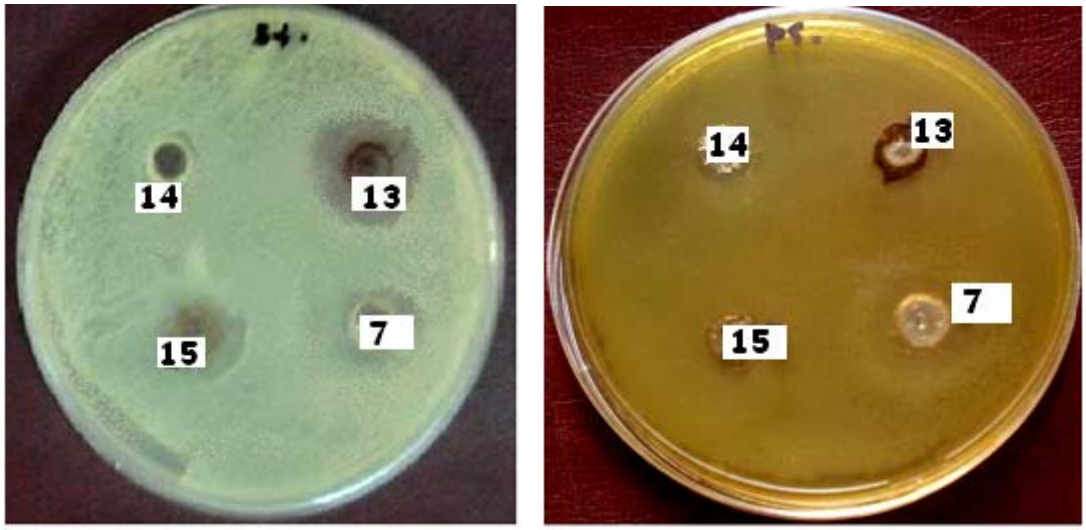
{a} *{b}*

Figure (4-6): the biological activity zone of compound [17, 19, 18 and 20] towards {a}: Staphylococcus aureus, {b}: Pseudomonas aeuroginosa



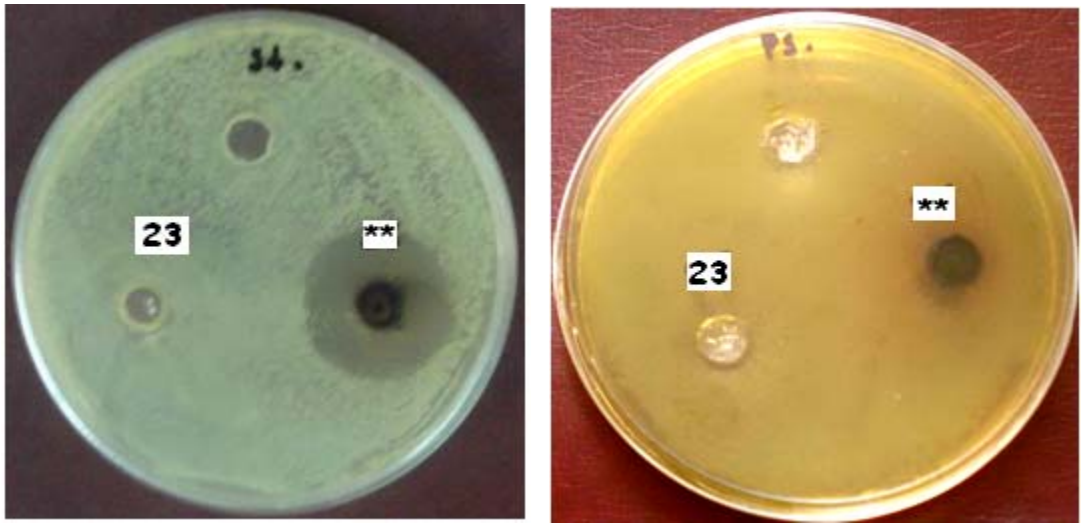
{a} *{b}*

Figure (4-7): the biological activity zone of compound [21, 22 and 12] towards {a}: Staphylococcus aureus, {b}: Pseudomonas aeuroginosa



{a} *{b}*

Figure (4-8): the biological activity zone of compound [14, 13, 15 and 7] towards {a}: Staphylococcus aureus, {b}: Pseudomonas aeuroginosa



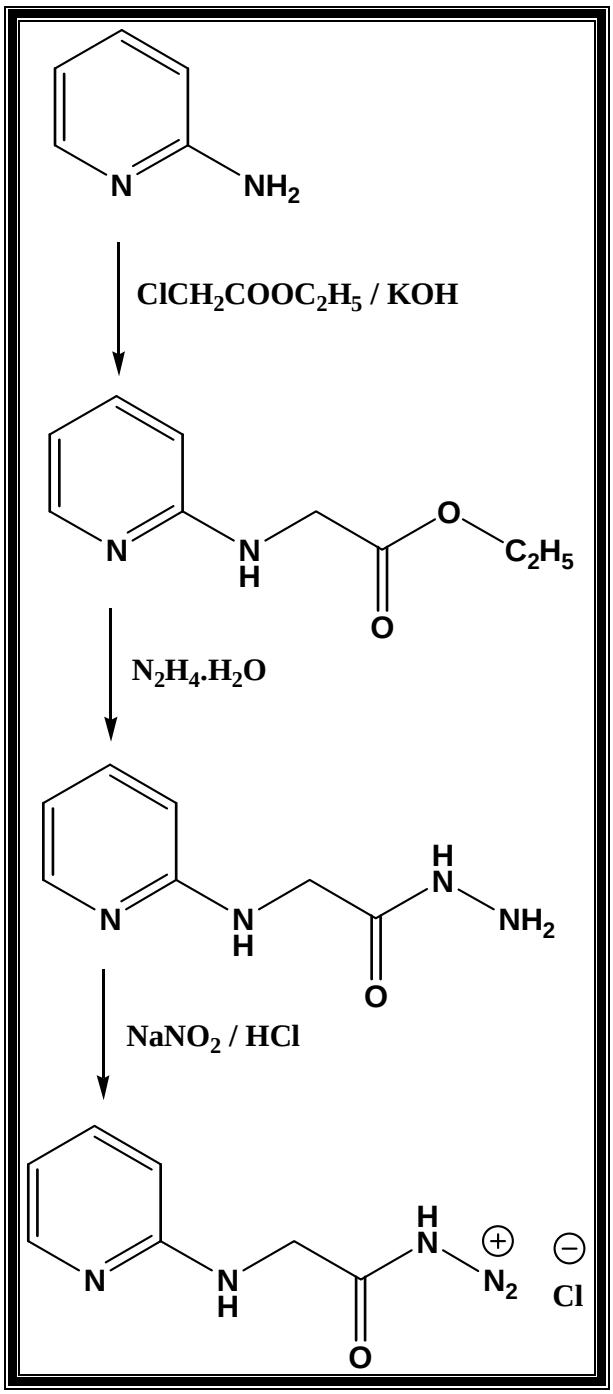
{a} *{b}*

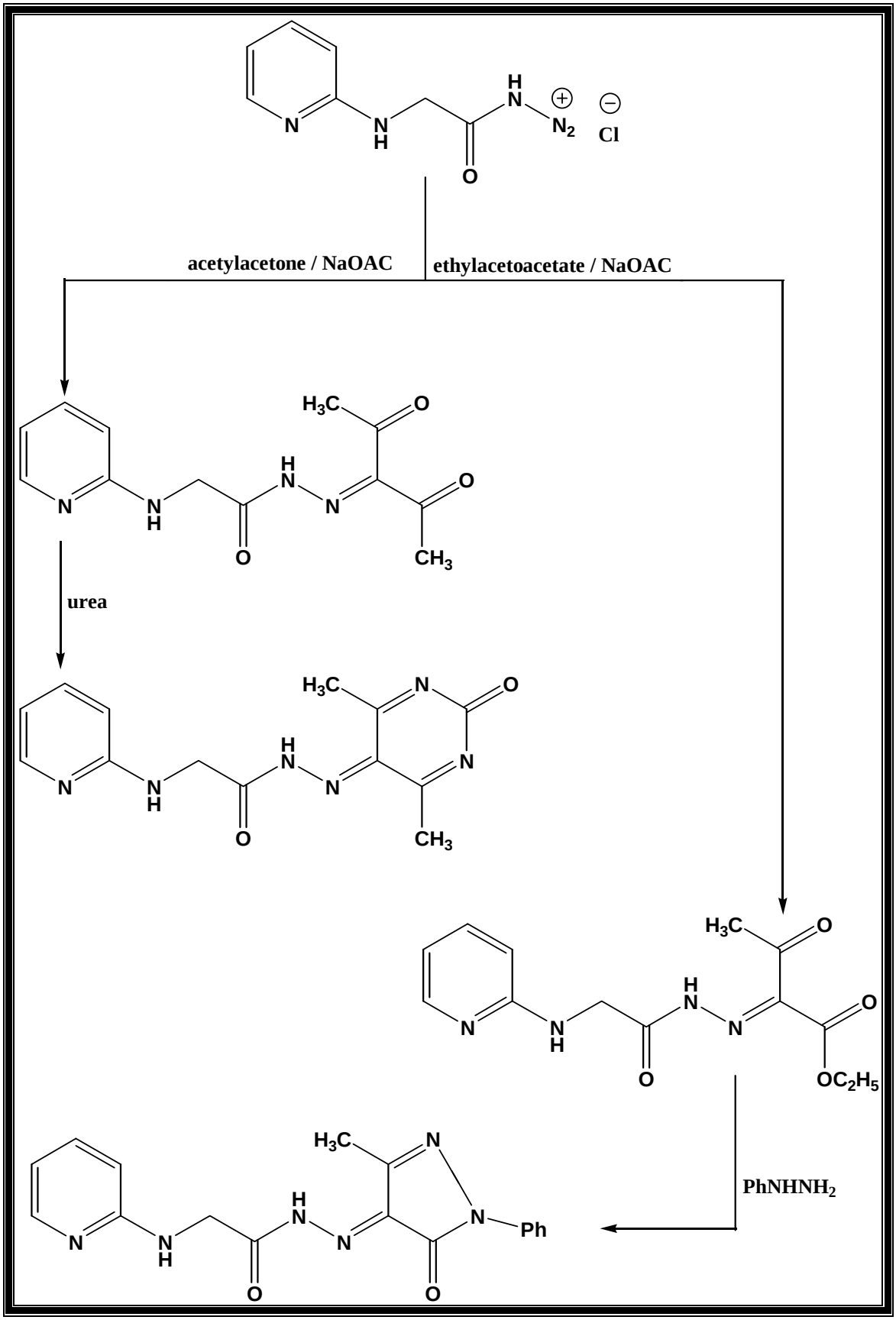
Figure (4-9): the biological activity zone of compound [23] towards {a}: Staphylococcus aureus, {b}: Pseudomonas aeuroginosa

Suggeestions for Further Work:

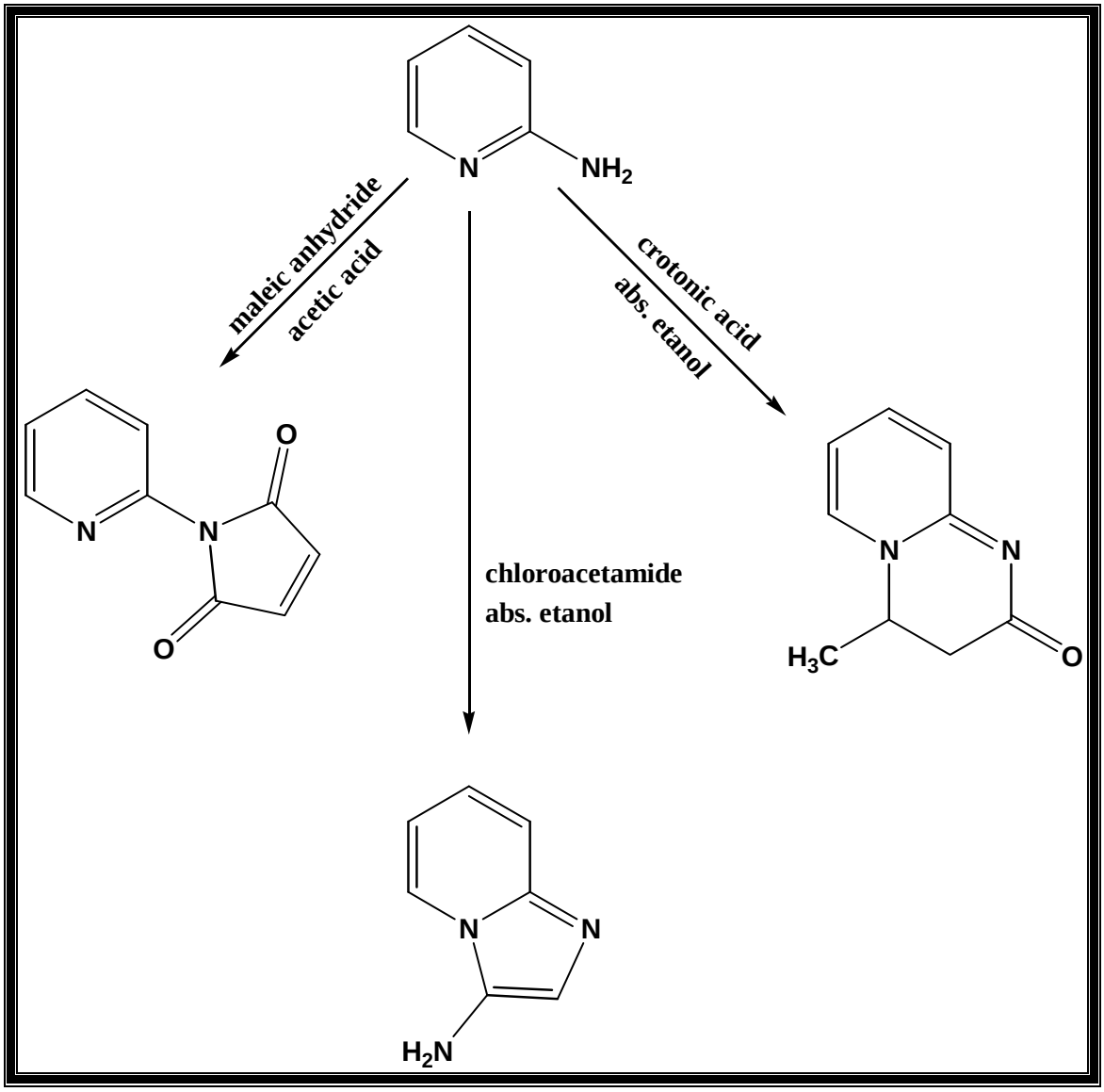
On the bases of the experience gained during this work, one can suggest the following future work:

1)




acetylacetone / NaOAC
ethylacetoacetate / NaOAC
urea
PhNHNH2
Cl
Ph

2)


N
NH2
maleic anhydride
acetic acid
crotonic acid
abs. etanol
chloroacetamide
abs. etanol
O
N
N
O
N
N
H3C
O
N
N
H2N

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الخلاصة

يتضمن موضوع البحث في هذه الرسالة تحضير مركبات حلقية غير متجانسة خماسية, سداسية و سباعية أبتداءً من 2-امينوبريدين كمركب أولي.

لقد تم تقسيم هذا العمل إلى أربع أجزاء:

الجزء الأول:

هذا الجزء يتضمن تحضير عشرة مركبات وهي:

3-biphenyl-4-ylimidazo[1,2-a] pyridine[1], 3-phenylimidazo[1,2-a] pyridine [2], imidazo[1,2-a]pyridine-3(2H)-one [3], 2H-pyrido[1,2-a] pyridine-2,4-(3H)-dione [4], N,N'-1,4-dihydronaphthalene-2,3-diylidenedipyridine-2-amine [5], pyrido[1,2-a] [2,4]benzodiazepine-6,11-dione [6], N-(1,3-benzodioxol-5-ylmethylidene) pyridine-2-amine [7], 3-(pyridine-2-ylimino)-1,3-dihydro-2H-indol-2-one [8], [2-oxo-3-(pyridin-2-ylimino)dihydro-1H-indol-1-yl] acetic acid [9] and 1-(1H-benzimidazol-1-ylmetyl)-3-(pyridine-2-ylimino)-1,3-dihydro-2H-indol-2-one [10].

هذه المركبات حضرت مباشرة من المركب الاولي. كما هو مبين في المخطط (I).

الجزء الثاني:

هذا الجزء يتضمن تحضير :

N-carbamoyl-N_2-pyridin-2-ylglycinamid [12], N-(4-biphenyl-4-yl-1,3-oxazol-2-yl)-N_2-pyridine -2-ylglyciamide [13], N-carbothioyl-N_2-

pyridin-2-ylglycinamid [14] and N-(4-biphenyl-4-yl-1,3-thiazol-2-yl)-N_2-pyridine-2-ylglyciamide [15].

وذلك من تفاعل 2- امينوبريدين مع كلوروخلات الاثيل لينتج المركب [11], الذي تمت مفاعلته مع كواشف عضوية مختلفة لينتج المركب المطلوبة, كما هو موضح في المخطط (II).

الجزء الثالث:

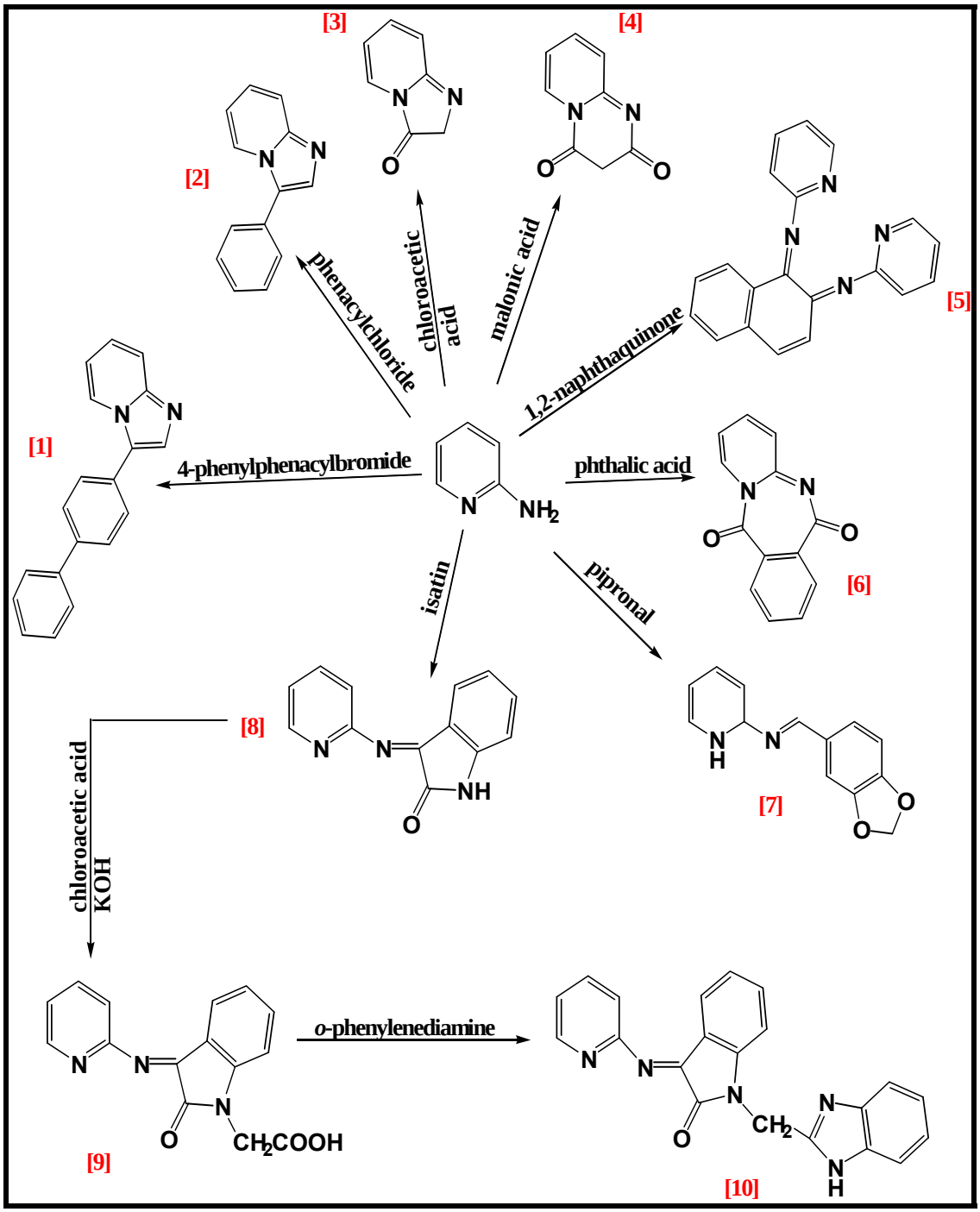
هذا الجزء يتضمن تحضير:

2-[(pyridine-2-ylamino)methyl]-4,5-dihydro-6H-1,3,4-oxadiazine-6-one [17], 3-[(pyridine-2-ylamino) methyl]1,6-dihydro-1,2,4-triazin-5(2H)-one [18], 5-[(pyridine-2-ylamino) methyl]-1,3,4-oxadiazole-2-thiol [19], 1-(N-pyridine-2-ylglycyl)-1,2-daizepane-3,7-dione [20], 5-methyl-2-(N-pyridin-2-ylglycyl)-2,4-dihydro-3H-pyrazol-3-one [21], N'-formyl-2-(pyridine-2-ylaminoaceto-hydrazide [22] and 2-(pyridine-2-ylamino)-N'-[(1,3-thiazol-2ylamino)methyl] acetohydrazide [23].

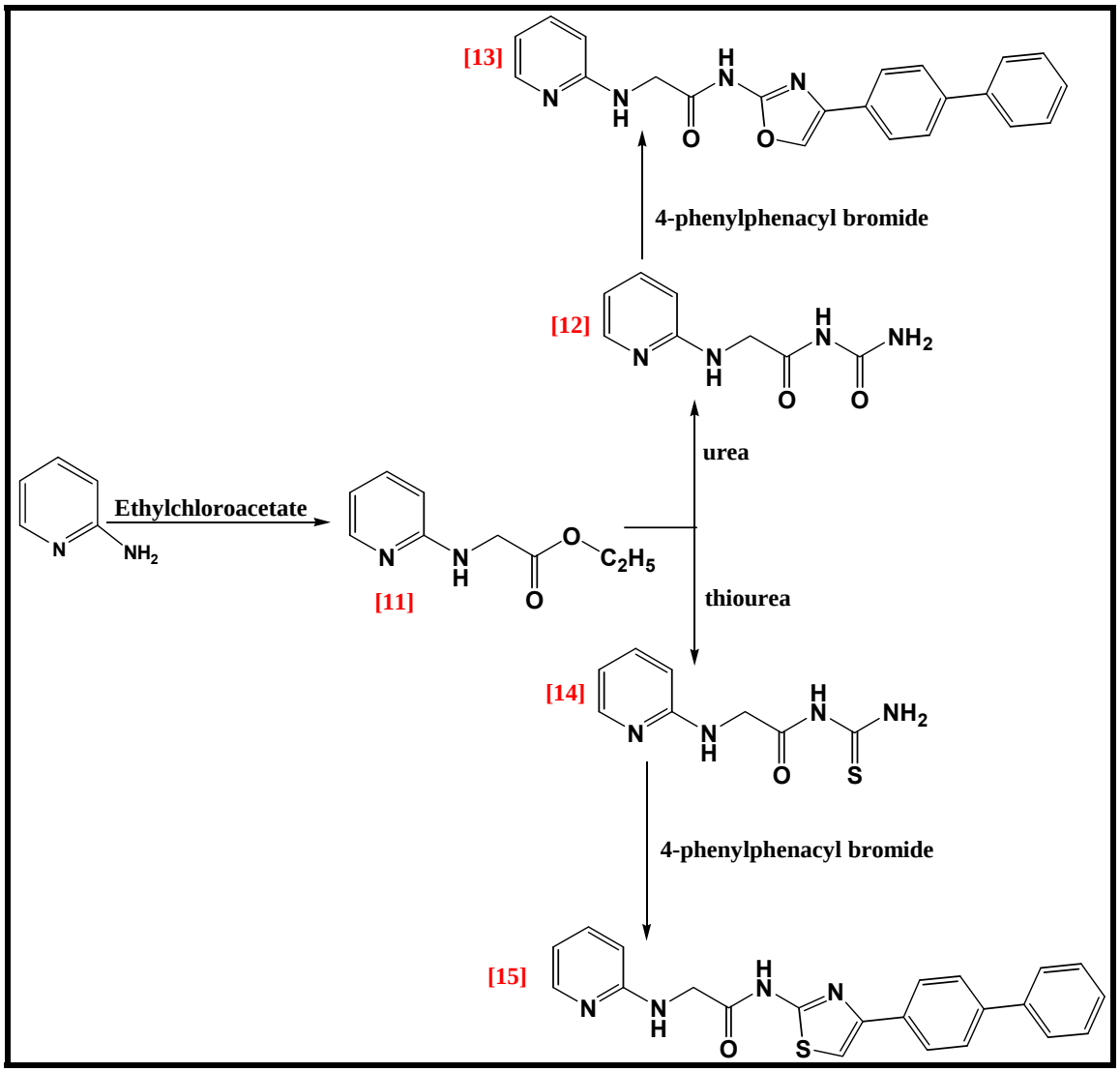
بدأً من المركب رقم [16] الذي حضر عن طريق مفاعله المركب رقم [11] مع هايدرازين هايدريت. كما هو موضح في المخطط (III).

الجزء الرابع:

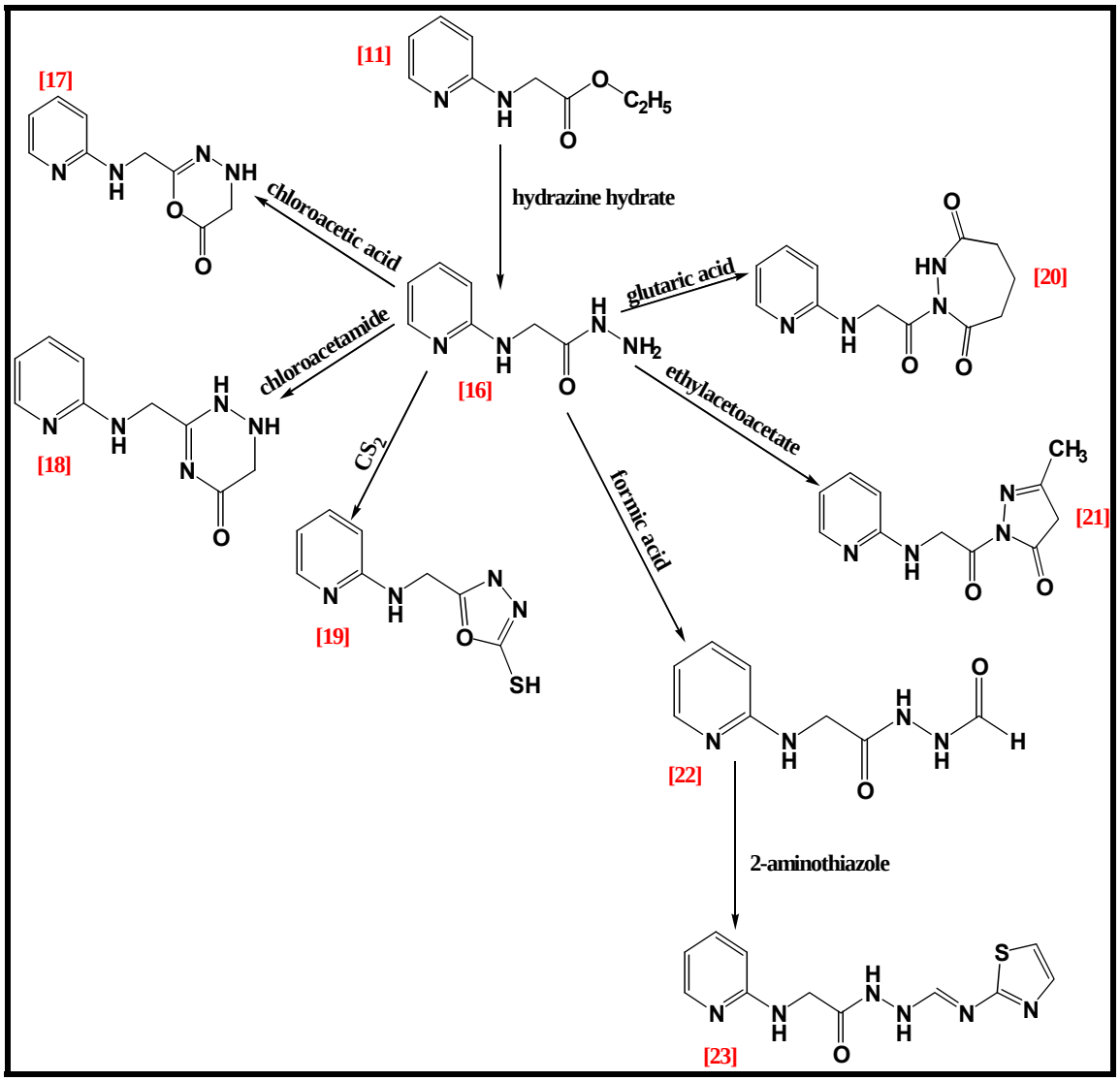
يتعامل هذا الجزء مع دراسة مقاومة نشاطات البكتريا لجميع المركبات المحضرة. هذه الفعاليات حددت ضد نوعين من البكتريا وهما (Staphylococcus aureus) (Pseudomonas aeurinosa). النتائج كشفت إن بعض المركبات ذات فعالية بايولوجية كما هو مبين في جدول (4-1).


[3]
[4]
[2]
chloroacetic acid
malonic acid
phenacylchloride
1,2-naphthaquinone
[5]
[1]
4-phenylphenacylbromide
phthalic acid
[6]
isatin
pipronal
[8]
[7]
chloroacetic acid
KOH
o-phenylenediamine
[9]
[10]

Scheme (I)


[13]
4-phenylphenacyl bromide
[12]
urea
Ethylchloroacetate
[11]
thiourea
[14]
4-phenylphenacyl bromide
[15]

Scheme (II)


[11]
[17]
hydrazine hydrate
chloroacetic acid
glutaric acid
[20]
chloroacetamide
[16]
[18]
ethylacetoacetate
[21]
CS_2
formic acid
[19]
[22]
2-aminothiazole
[23]

Scheme (III)

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

تحضير, تشخيص و دراسة الفعالية البيولوجية لمركبات خماسية, سداسية و سباعية جديدة مشتقة من 2- امينوبريدين

رسالة

مقدمة إلى كلية العلوم- جامعة النهرين

وهي جزء من متطلبات نيل درجة الماجستير في الكيمياء

من قِبَلْ

حسن فاضل حسين

بكالوريوس2006 (جامعة النهرين)

رمضان 1429 أيلول 2008