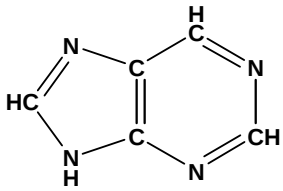
# *Chapter one*

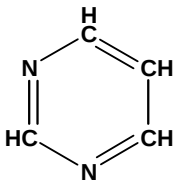
# *Introduction*

## *1.1 Nitrogen Bases:*

There are two kinds of nitrogen containing bases-purines and pyrimidines. Purines consist of a six-member and five-member nitrogen-containing rings, fused together. Adenine and Guanine are purines type found in DNA and RNA. Pyrimidines have only a six-member nitrogen-containing ring; Cytosine, Uracil and Thymine are pyrimidines type. Cytosine is found in both DNA and RNA. Uracil is found in only RNA. While thymine is normally found in DNA. Sometimes, tRNA will contain some thymine as well as Uracil.

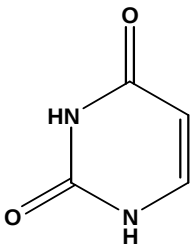



purine ring

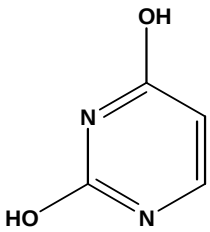



pyrimidine ring

In fact these bases considered as aromatic molecules forming (lactam) or lactim which are tautomers[1].



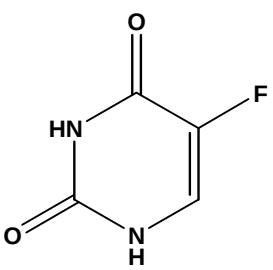

lactam (keto) form



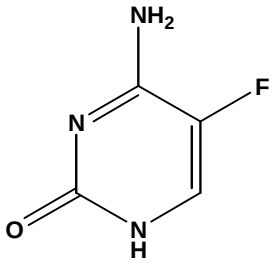

lactim (enol) form

The most iso-derivatives which are used purine and pyrimidines ring with modified group could not form as naturally.

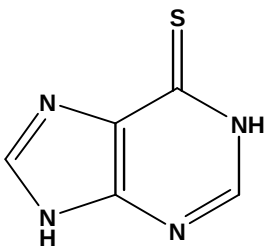
These derivatives and iso-derivatives have activity to change the double bases for example some derivatives[2], 5-fluoro Uracil (Fura)[3] [1], 5-fluoro cytosine[4] [2], 6-mercapto purine [3].




[1]




[2]

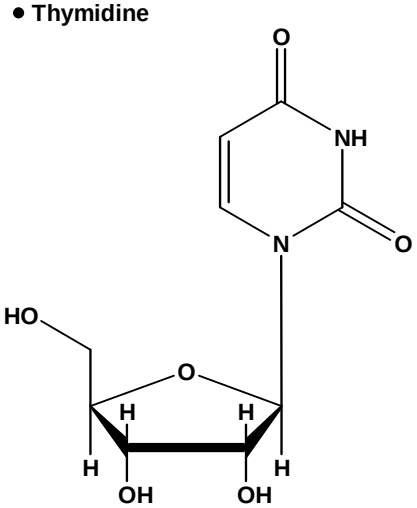



[3]

## *1.2 Nucleosides:*

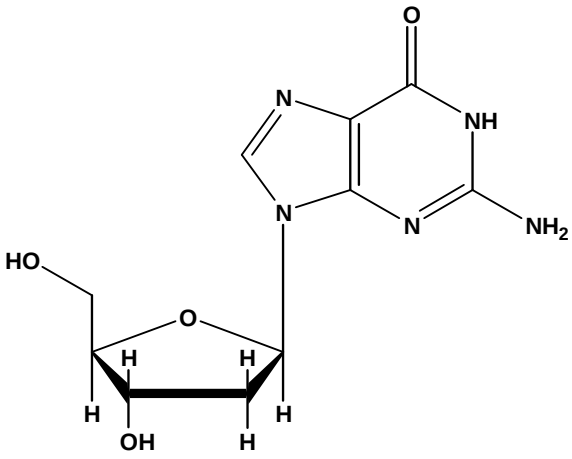
If a sugar, either ribose or 2-deoxyribose, is added to a nitrogen base, the resulting compound is called a nucleoside. Carbon 1 of the sugar is attached to nitrogen 9 of a purine base or to nitrogen 1 of a pyrimidines base. The names of purine nucleosides end in (-osine) and the names of pyrimidine nucleosides end in (-idine). The convention is to number the ring atoms of the base normally end to use 1`, and soon to distinguish the ring atoms of the sugar. Unless otherwise specified the sugar is assumed to be ribose. To indicate that the sugar is 2`-deoxyribose, a deoxy is placed before the name[5].

- **Adenosine**
- **Guanosine**
- **Uridine**
- **Thymidine**




**Uridine**

**[4]**




**Guanosine**

**[5]**

### *1.3 Biological activity of nucleoside analogues:*

The nucleoside is considered as a basic molecule structure of nucleic acid (RNA and DNA) and this today consider which has a very biological activity in processing many of medicine which used in many treatments as antivirus, antibacterial, antifungal, anticancer and AIDS because its activity that stops the growthing the pathogenic cells[6]. Since discoursed nucleoside and studying its activity in this biological veiled for few years ago.

The derivatives of nucleoside which can used in a wide field as biological drugs used as antivirus, antibacterial, anticancer and antifungal[7].

The most nucleoside derivatives dideoxy nucleosides (ddNs) which have been tested as antibiological basically depends on the pyrimidine and purine circle system show in Figure (1-1) and (1-2) which examples to show the relationship between the structure and activity for purine and pyrimidine[8,9].

Nucleoside antibiotics are considered as groups of substances which similar in structure of nucleoside for example to this anti side is 3-amino-3-deoxyadenosine [6] the biological antiside.

This compound has activity for cancer the adenine arabinoside compound [7][10] which used also as medicine for cancer and the substance for anti viruses in human which used for brain viruses that consider as neural disorders which caused by the Herpes virus. Another iso nucleoside for anti virus which is used for treating AIDS caused by human Immunodeficiency virus (HIV) it 3-azido-3-deoxythymidine (AZT)[11,12] [8] and it is the first treatment used for (AIDS) in USA since 1990.

Also 5-fluro deoxyuridine [9] has been used as anticancer, while puromycin [10] considered as antibacterial and it is only anti can used to protein synthesis in bacteria. The iso nucleoside had used as antibiocidal or fungicides (antifungal) which used the compound [11] as antifungal which damages the cell wall[13,14].

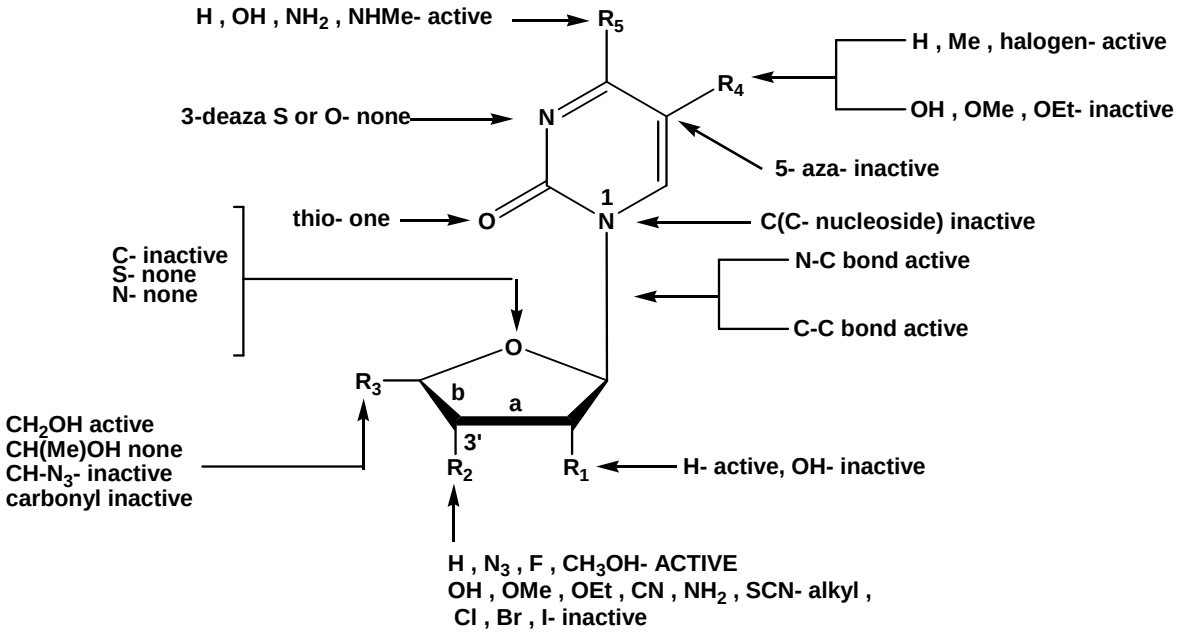



**Figure (1-1): Relationship between structure and activity of isopyrimidines**

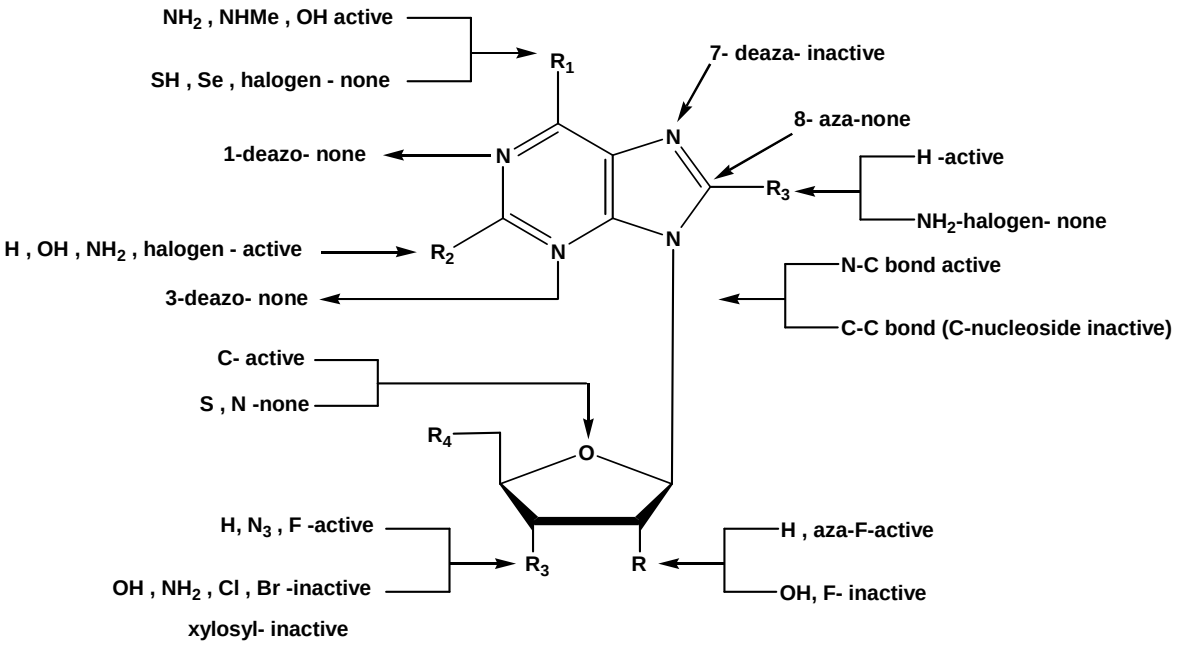
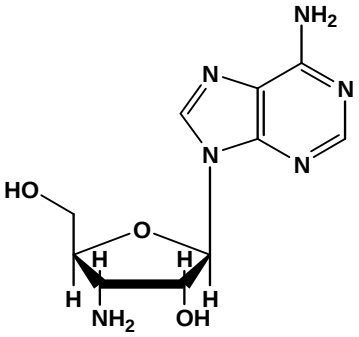
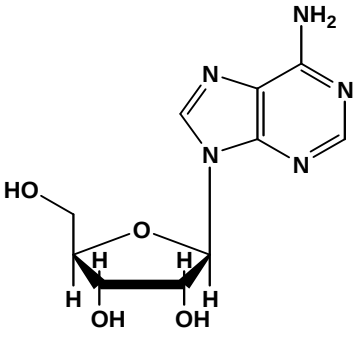



**Figure (1-2): Relationship between structure and activity of isopurines**



[6]



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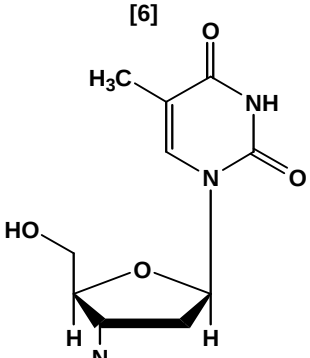

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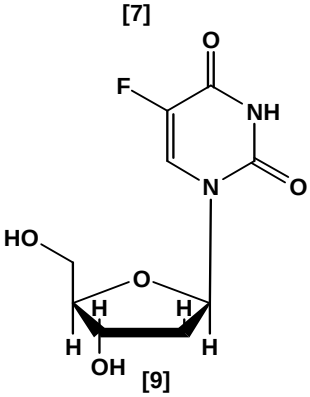
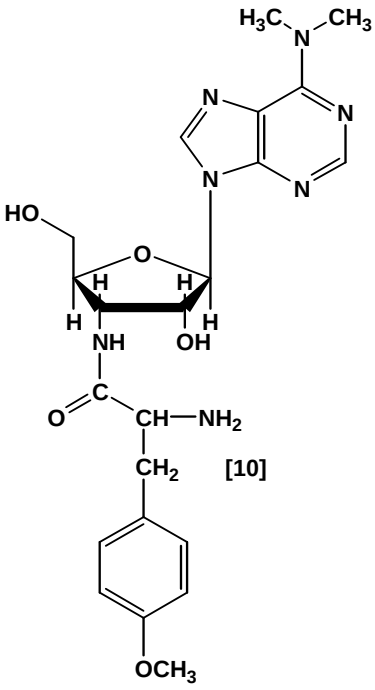
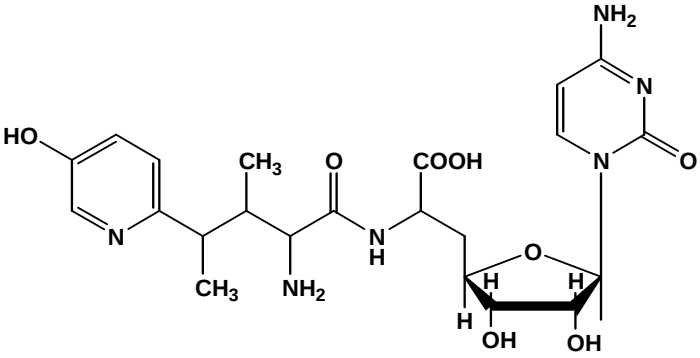


[9]



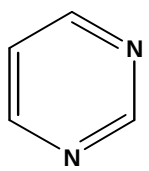
[10]



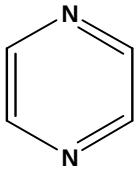
[11]

## *1.4 Pyrimidine and its derivatives:*

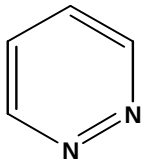
The pyrimidine compounds (a) are one of the diazine derivatives[15], the other of the diazine derivatives are pyrazine (b) and pyridiazine (c).




**1,3-diazine pyrimidine (a)**



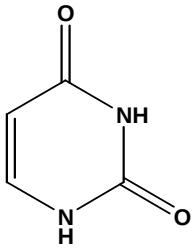

**1,4-diazine pyrzine (b)**



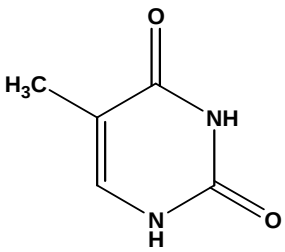

**1,2-diazine pyridazine (c)**

The pyrimidine compounds were stable compounds, colorless some of them dissolved in water, and some of them have high boiling point because being the polarization for nitrogen atom.

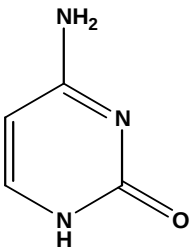
These compounds were important in bio originate for Uracil (d) , thymine (e), cytosine (f) this found in nucleotide.




**Uracil (d)**

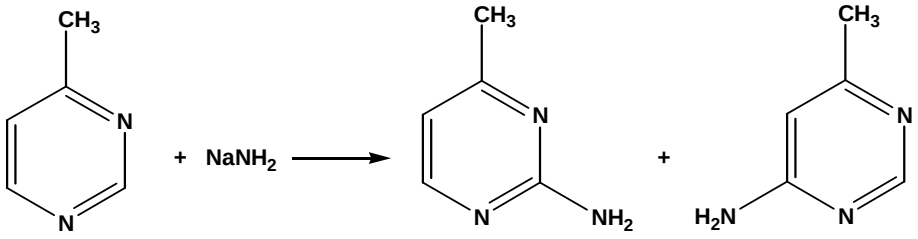



**Thymine (e)**

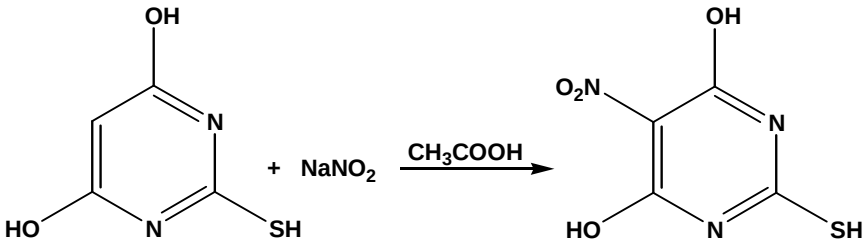



**cytosine (f)**

The pyrimidine ring undergoes nucleophilic substitution reactions by the nucleophilic reagents like in the fellow reaction[16], wherever the 4-methyl pyrimidine reacts with sodium amide, as shown below:



The pyrimidine ring undergoes electrophilic substitution reactions difficulty by electrophilic reagents[17], like in fellow reaction shown below:



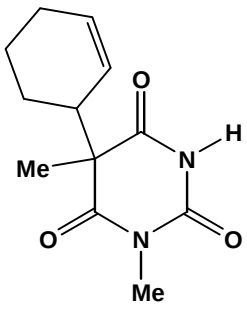

The pyrimidine compounds are important because they used as anticonvulsant[18], anti-inflammatory[19] and analgesic[20]. It is some of drugs contain on the chain from pyrimidine, and it is classified to the four groups:

**First group:** Barbiturates [a] 5-(cyclohex-1-enyl)-1,5-dimethyl barbituric acid[21].

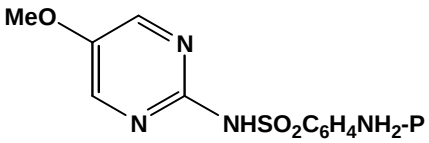
**Second group:** Sulfonamides [b] sulfaprine[22].

**Third group:** Antimicrobial like [c] compound[23,24].

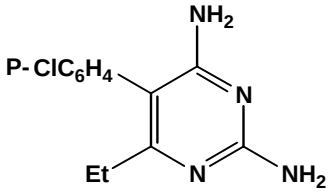
**Fourth group:** Halogeno pyrimidine as antitumer agent[25].




[a]




[b]

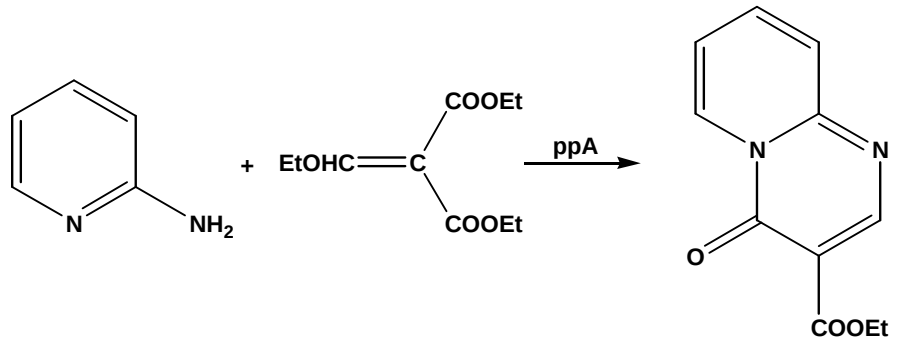



[c]

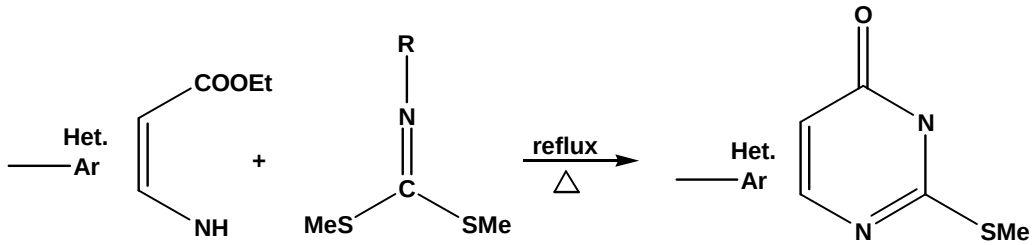
## *1.5 General methods for the preparation of pyrimidine and its derivatives:*

Because of the importance of pyrimidine compounds , there were many attempts have worked to synthesis them . For example 4-H pyrido (1,2-a-pyrimidine-4-one) has biological activity [26,27] and used as drug compound [28,29] .

The researchers work on the preparation more of pyrimidine compounds and diagnosis its by depending on the different methods, wherever prepared the fellow compound from reaction 2-amino pyridinewith β-ketoester by poly phosphoric acid[30, 31].




***Frohlich*** et. al., prepared the compound bellow:

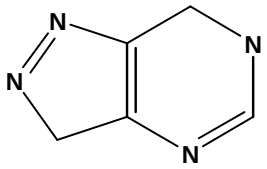



R = -$(CH_2)_{12}$COEt , -NHCOOEt

## *1.6 Biological activity of pyrimidine derivatives:*

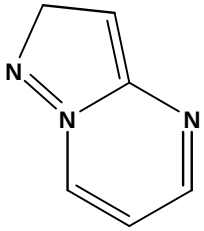
The researchers work on the preparation more from the pyrimidine derivatives because of its biological importance wherever used as antifungal[33] , anticancer[34] and antibacterial[35].

***Shalaby***[36] et. al. proved that the [pyrazolo(3,4-d) pyrimidine] compound [12] describe it one of the purine analogous because it has chemical and pharmacology significance and it used as antileukemic and antitumer.



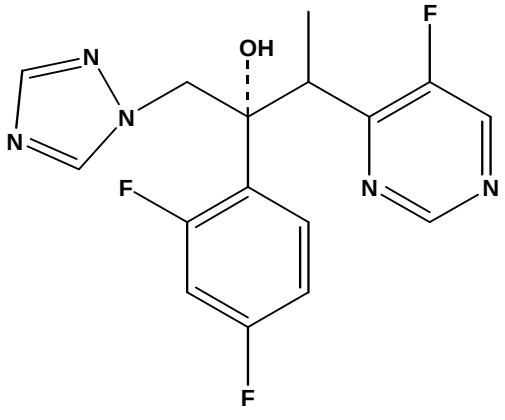
**[12]**

The [pyrazolo(1,5-a) pyrimidine] compound [13] was purine analogous and it has useful property as antimetabolate for purine in biochemistry reactions.



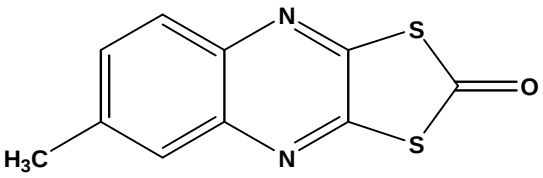
**[13]**

Compound [14] [voriconazole] was found to have biological activity as antifungal[37].



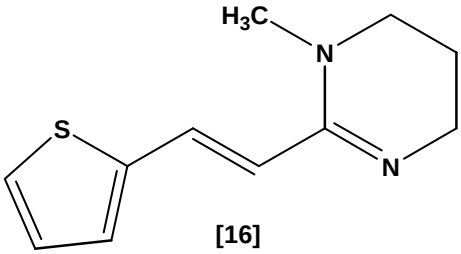
**[14]**

The compound [15] has antifungal activity[38].



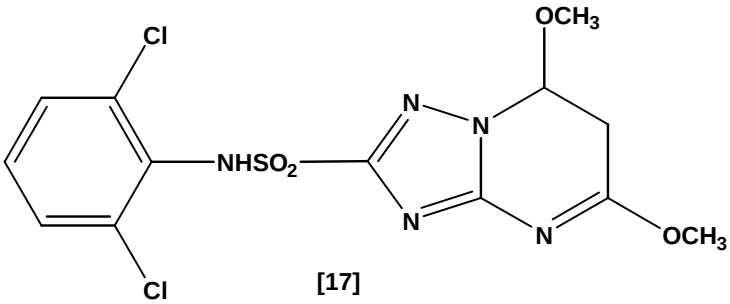
[15]

The compound [16] has medicinal activity as anthlemintic[39].



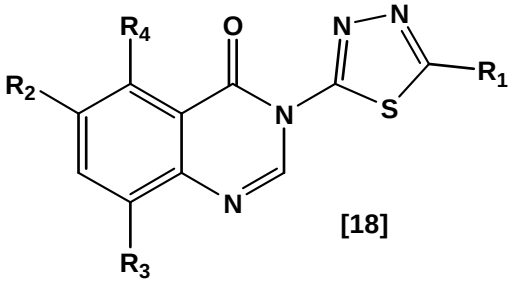
[16]

The compound [17] has activity as herbicidal[40] and as plant growth regulator agent.



[17]

***Cyril***[41] et. al., proved that the compound [18] has activity as antibacterial and anticancer.



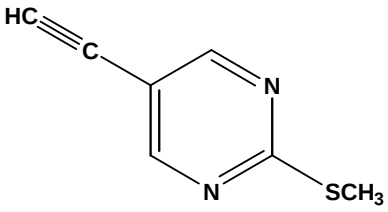
[18]

**R1 = $CF_3$ , t-Bu , Et , cyc - $C_3H_5$**

**$R_2$ = $R_3$ = Br , $R_4$ = Cl**

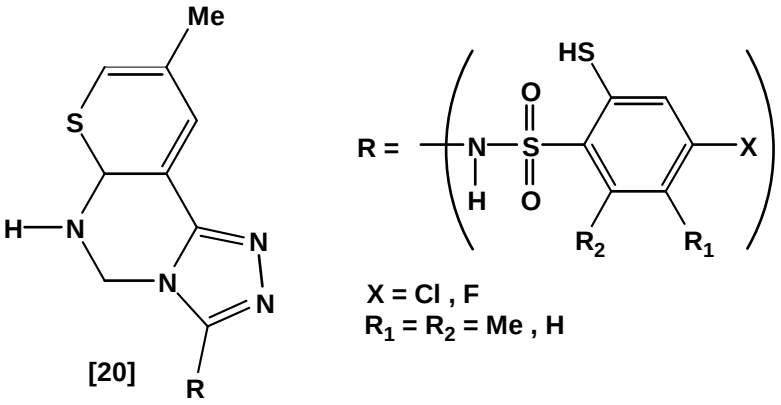
**$R_2$ = $R_3$ = H , $R_4$ =F**

The pyrimidine derivatives used as plant growth regulator[42] dyes[43] and as corrosion inhibitor. Compound [19] has activity as anticancer[44].

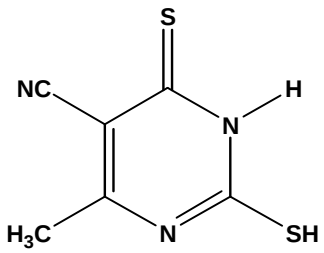



[19]

The compound [20] has activity as (Human Immunodeficiency Virus, HIV)[45].

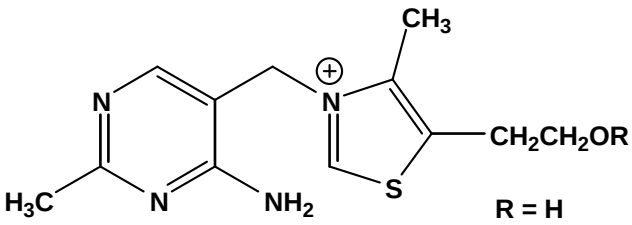



The compound [21] has biological activity wherever used as antifungal and as antisecticidal[46].




[21]

The pyrimidine undergoes in vitamin $B_1$ structure[47] as the compound [22].




[22]

## *1.7 Chemotherapy of Infections:*

Infection is major category of human disease and skilled management of antimicrobial drugs is of the first importance. The term chemotherapy is used for the drug treatment of parasitic infections in which parasites (viruses, bacteria, protozoa, fungi and worms) are destroyed or removed without injuring the host. The use of term to cover all the drug or synthetic drug therapy needlessly removes a distinction which is convenient to the clinician and has the sanction of long usage by convention the term also to include therapy of cancer[48].

### *1.7.1 History of chemotherapy:*

Many substances that we now know to possess therapeutic efficiency were first used in distant past. The ancient Greek used fern, and Aztecs chenopodium, as intestinal antihelminthics. The ancient Hindus treated leprosy with chaulmoogra for hundreds of years would have been applied to wounds, but despite in introduction of mercury as a treatment for syphilis ($16^{th}$ century) and the use of cinchona bark against malaria ($17^{th}$ century) the history of modern rational chemotherapy did not begin until.

***Ehrlich***[49,50] developed the idea from his observation that aniline dyes selectively stained bacteria in tissue microscopic preparations and could selectively kill them.

### *1.7.2 Classification of antimicrobial drugs:*

Antimicrobial agents may be classified according to the type of organism against which they are active as shown below:

1. Antibacterial drugs
2. Antiviral drugs
3. Antifungal drugs

4. Antiprotozoal drugs
5. Antihelminthic drugs

### *1.7.3 How antimicrobial act:*

Is should always be remembered that drugs are seldom the sole instruments of curve but act together with the natural defenses of the body.

In general microorganisms are inhibited or killed by cell wall damage or cell wall synthesis inhibition or impairment of cytoplasmic membranes permeability or altering physical and chemical structures of protein of these microorganisms or through impairment of cellular enzymatic activities or protein and DNA synthesis inhibition[51]. Also the bacterial resistance for chemical compounds may be due to the presence of natural resistance or resistance resulted from genetic mutations or due to plasmid resistance or due to absence of suitable transporter for the compound and thus can not reach the target in the cell[52] or due to thick cell wall as it contains high liquid in the wall. Antimicrobials act at different sites in the target organisms as follows.

#### *1.7.3.1 The cell wall:*

This gives the bacterium its characteristic shape and provides protection against the much lower osmotic pressure of the environment. Bacterial multiplication involves breakdown and extension of the wall; interference with these processes prevents the organism from resisting osmotic pressures, so that it bursts. As these cells of higher, e.g. human, organisms do not possess this type of wall, drugs, which act here may be especially selective, obviously the drugs are effective only against growing cells. They include: penicillins, cephalosporins, vancomycin, bacitracin and cycloserine[53].

#### *1.7.3.2 The cytoplasmic membrane:*

Inside the cell wall is the site of most of the microbial cell's biochemical activity. Drugs that interfere with its function include: polyenes (nystatin, amphotericin), azoles (fluconazole, itraconazole, minconazole) polymixins (colistin, poly-myxin B)[50,53].

### *1.7.3.3 Protein synthesis:*

Drugs that interfere at various points with the liquid up of peptide chains on the ribosomes of the organism include: chloramphenicol, erythromycin, fusidicacid, tetracyclines, aminoglycosides, quinupristindalfoprostin, linezolid.

### *1.7.3.4 Nucleic acid metabolism:*

Drugs may interfere directly with microbial DNA or its replication or repair, e.g. quinolones, metronidazole or with RNA, e.g. fifampicin indirectly on nucleic acid synthesis, e.g. sulphonamides, trimethoprim.

### *1.7.4 Use of antimicrobial drugs:*

### *1) Selection of antimicrobial drugs:*

The general rule is that selection of antimicrobials should be based on identification of the microbe and sensitivity tests. All appropriate specimens (blood, pus, urine, sputum, cerebrospinal fluid) must therefore be taken for examination before administering any antimicrobial. This process inevitably takes time and therapy at least more serious infections must usually started on the basis of the "best guess" with the worldwide rise in prevalence of multiply-resistant bacteria in the last decade knowledge of local antimicrobial resistance rates is an essential prerequisite to guide the choice of local "best guess" or empirical antimicrobial therapy. Knowledge of the likely pathogens (and their current local susceptibility rates to antimicrobials) in the clinical situation thus cephalexin may be a reasonable first choice for lower urinary tract

infection and benzylpenicillin for meningitis in the adult (meningococcal or preumococcal).

***2) Rapid diagnostic test:***

Use of tests in this type is about to undergo revolution with the widespread introduction of affordable, sensitive and specific nucleic acid detection assays (especially those based on the polymerase chain reaction PCR).

***3) Route of administration:***

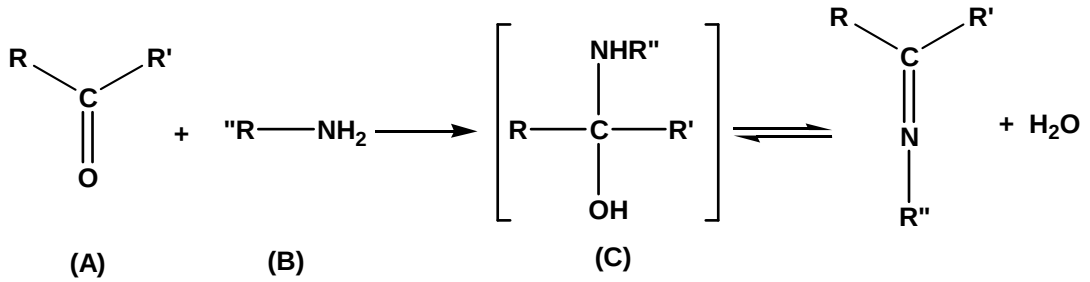
Parentral therapy (which may be IM or IV) is preferred for therapy of serious infections because high therapeutic concentrations are achieved reliably and rapidly. Initial parentral therapy should be switched to the oral route whenever possible.[49,50,54].

***1.8 Schiff bases synthesis of it's:***

The term "Schiff base" used to define those organic compound which contain the functional group (-C=N-) Schiff bases were firstly prepared by Schiff in 1864[55,56] from condensation reaction of aldehydes or ketones with amines. Schiff bases have several nomenclatures such as anils, Imines, azomethines, benzanils and benzylideneaniline[57].

Imines, Schiff bases C=N compound can be reduced with $LiAlH_4$, $NaBH_4$, Na-EtOH, Hydrogen and a catalyst as well as with other reducing agents[58].

Schiff bases rapidly decomposed in aqueous acidic media, but they are very stable in basic solution[59]. Schiff base can be obtained by condensation reaction between carbonyl compound [A] and amine [B] with the formation of amino alcohol as intermediate [C]. the experimental conditions depend on the nature of the amine and especially of the carbonyl compound which determine the position of the equilibrium.




(A) (B) (C)

These bases can also be prepared by the refluxing of equimolar quantities of aldehyde or ketone with amine or by slow melting for 10 minutes and then isolating and purification the product recrystallization or sublimation under reduced pressure[57,60].

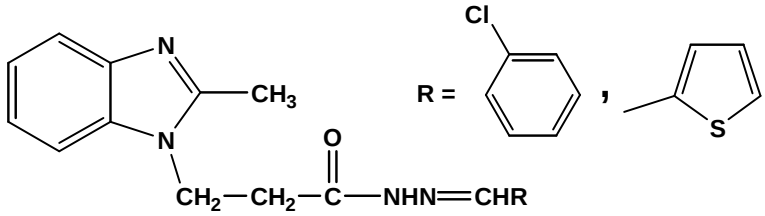
***Staab***[61] prepared Schiff bases by removing water which is formed by condensation of aldehydes with amine by reflux in benzene this is done by mixing the amine and the aldehydes in benzene and then the residual solution is distilled under vacuum.

Bidentate Schiff bases have been among ligands that are extensively used for preparing metal complexes. These ligands are described according their donor set N,N-donor Schiff bases and N,O-donor Schiff bases.

Tridentate Schiff bases may be generally considered as derived from the bidentate analogues by adding another donor group, these have been utilized as an ionic ligands having (N,N,O), (N,N,S), (N,O,O) and (N,S,O) donor sets[62,63].

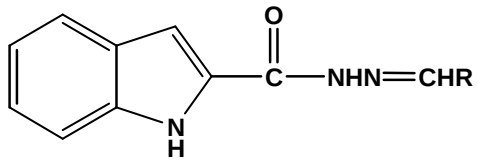
### *1.8.1 Biological activity and uses of Schiff bases:*

***Masry***[64] et. al., show that compound [23] has biological activity as anticancer.

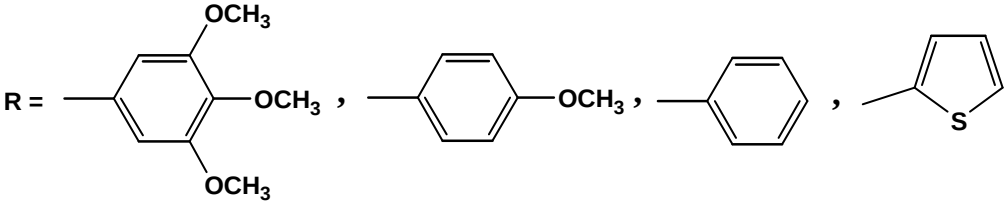



**[23]**

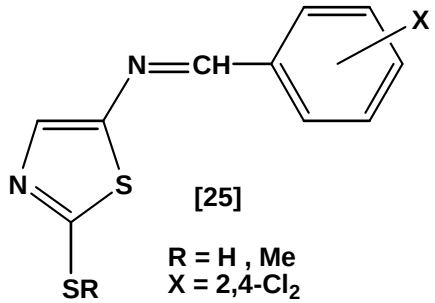
***Fahmy***[65] et. al., show that compound [24] has activity as antimicrobial.




**[24]**



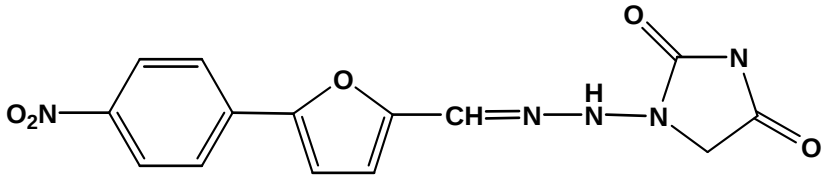

The compound [25] [2-alkylthio-5-benzylidineamine thiazole] has biological activity as antibacterial and as antifungal[66,67].




**[25]**

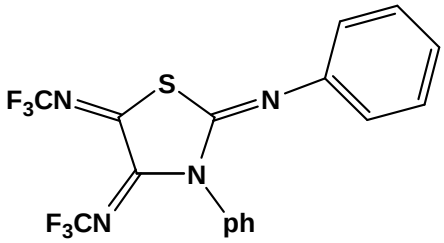
**R = H , Me**
**X = 2,4-$Cl_2$**

The compound [26] used as skeletal muscle relaxant[68,69].



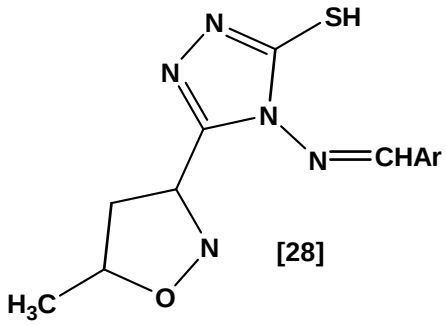

**[26]**

The compound [27] used as antibercular[70].



[27]

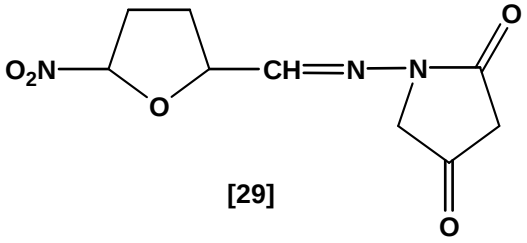
The compound [28] used as antibacterial from type (S. aureus, E. coli and Ps. Aeruginesa)[71],



[28]

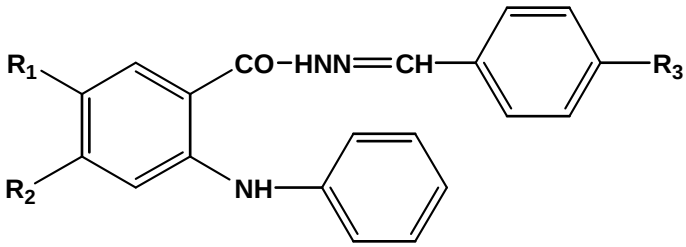
Ar = 4-$(CH_3)_2$-$NC_6H_4$ , 4-Cl-$C_6H_4$

***Hussein***[72] et. al., show that the compound [29] [furadantin] has activity as antibacterial[72].



[29]

The compound [30] has activity as antibercular[73].



[30]

## *1.9 Pathogenic bacteria:*

The pathogenic of bacteria infection includes initiation of the infections process and the mechanisms that lead to development of signs and symptoms of disease. Characteristics of bacteria that are pathogens include transmissibility, adherence to host cell invasion of host cells and tissues. Toxigenicity, and ability to envade the host's immune system. Many infections caused by bacteria that are commonly considered to be pathogens are in apparent or asymptomatic. Disease occurs if the bacteria or immunologic reactions to their presence cause sufficient harm to the person[(74)].

Human and Animals have abundant normal flora that usually do not produce disease but achieve a balance that ensures the survival growth and propagation that are of both the bacteria and the host. Some bacteria that are important causes of disease are cultured commonly with the normal flora (*Streptococcus pneumonia, Staphylococcus aureus*). Sometimes bacteria that are clearly pathogens (*Salmonelly typhi*) are present but infection remains latent or sub clinical and host is a carrier of the bacteria[(74)].

### *1.9.1 Staphylococci:*

They are gram positive spherical cells. Usually arranged in grape like irregular clusters. They grow readily on many types of media and are active metabolically, fermenting carbohydrates and producing pigments that vary from white to deep yellow. Some are members of normal flora of skin and mucous membranes of humans, a variety of pyogenic infections and even fatal septicemia. The pathogenic staphylococci often hemolyze blood. Coagulate plasma and produce a variety of extra cellular en-zymes and toxins. The most common type of food poisoning is caused by a heat-stable staphylococci rapidly develop resistance to many antimicrobial agents and present difficult therapeutic problem.

The genus *Staphylococcus* has at least 30 species. The three main species of clinical important are *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Staphylococcus saprophyticus*.

*Staphylococcus aureus* is coagulase-positive which different it from the other species. S aureus is major pathogens for human. Almost every person will have some type of *S. aureus* infection during a lifetime[(74)].

### *1.9.2 Escherichia coli:*

They are Gram negative cells, part of normal flora and incidentally caused disease, while others the solmonella and shigellae, are regularly pathogenic for humans. *E. coli* cause diarrhea is extremely common worldwide. These *E. coli* are classified by characteristics of their virulence properties and each group caused disease by different mechanism. The small or large bowel epithelial cell adherence properties are encoded by genes or plasmids. Similarly to toxins often are plasmid or phage-mediated. Some clinical aspects of diarrheal diseases.

Enteroputhogenic *E. coli* (EPEC) is an important cause of diarrhea in infants especially in developing countries. EPEC adhere to the mucosal cell small bowel[(74)].

***The aim of the work:***

Preparation of some new pyrimidine derivatives that expected to inhibit antibacterial activity.

There prepared compounds contain structural that may enhance their biological activity various groups: (thiol) SH group, amine groups, hydrazine groups and Schiff bases.

# *Chapter two*

# *Experimental part*

## *2.1 Materials:*

| Substance | Supplier |
|---|---|
| **6-Amino-1,3-dimethyl uracil** | **BDH** |
| **4-Aminodiphrnyl amine** | **BDH** |
| **Diphenyl amine** | **BDH** |
| **2,4-Dinitrophenyl hydrazine** | **BDH** |
| **Ethylaceto acetate** | **Fluka** |
| **Ethanol absolute** | **BDH** |
| **Hydrazine** | **Merck** |
| **Hydrochloric acid** | **Fluka** |
| **4-Hydroxy benzaldehyde** | **Merck** |
| **Glacial acetic acid** | **BDH** |
| **4-N,N-dimethylamino benzaldehyde** | **Merck** |
| **Phenyl hydrazine** | **Merck** |
| **Sodium hydroxide** | **Merck** |
| **Thiourea** | **BDH** |

## *2.2 instruments:*

| Instruments | Supplier |
|---|---|
| Balance | Sertorius (Germany) |
| Oven | Memmert (Germany) |
| Hot plate | Gallenkamp (England) |
| Fourier Transform Infrared spectrophotometer (F.T.IR) | Recorded on *SHIMADZU* 8300 Fourier transform Infrared Spectrophotometer (F.T.IR) by using (KBr) in the wave number range (500-4000) $cm^{-1}$ |
| Melting point | Melting points were measured using hot stage Gallenkamp M.F.B 600.01, melting point was used to measure the m.p. of all prepared compounds |

## *2.3 Experiments:*

### *2.3.1 6-Methyl-4-oxo-1,2,3,4-tetrahydro-2-thiopyrimidine[75]:*

Added the solution of (0.16 mole, 6.5 g) of sodium hydroxide in (4 ml) water with stiring to the mixture of the (0.1 mole, 7.6 g) of thiourea and (0.1 mole, 15.20 g, 14.8 ml) of ethylacetoacetate in (10 ml) of ethanol in round bottomed flask and the mixture was refluxed for (2 hours), then added hot solution from (20 ml) of concentrated hydrochloric acid in (10 ml) of water to the product. The product was filtered and washed with cold distilled water. Table (3-8) shows the m.p. and physical properties for compound (1).

### *2.3.2 2-Hydrazino-6-methyl pyrimidine-4-(3H) one[76]:*

Added (0.03 mole, 4.26 g) of 6-methyl-4-oxo-1,2,3,4-tetrahydro-2-thiopyrimidine and (15 ml) of hydrazine hydrate (99%) in round bottomed flask and mixture was refluxed for (3 hours). The product was filtered and washed with cold distilled water. Table (3-8) shows the m.p. and physical properties of compound (2).

### *2.3.3 6-Methyl-2-(3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl) pyrimidine-4-(3H) one[77]:*

Added (0.046 mole, 5.98 g) of ethylacetoacetate to the (0.64 g) of compound (2) that was dissolved in (30 ml) of ethanol in a round bottomed flask and the mixture was then refluxed for 6 hours at 80 $^{o}$C. The cold solution was then filtered and washed with distilled water. Table (3-8) shows the m.p. and physical properties of compound (3).

### *2.3.4 2-Phenylhydrazino-6-methylpyrimidine-4-(3H) one:*

(0.5 g) of compound (1) was mixed with (3 ml) of phenyl hydrazine in round bottomed flask and the mixture was then refluxed for 3 hours. The mixture was filtered and washed with cold distilled water to

give the orange precipitate. Table (3-8) shows the m.p. and the physical properties of compound (4).

### *2.3.5 2(2,4)-dinitrophenylhydrazino-6-methylpyrimidine-4-(3H) one:*

(1 g) of compound (1) was mixed with 2,4-dinitrophenyl hydrazine (1 g) and the mixture was then dissolved in (10 ml) of absolute ethanol in round bottomed flask, the mixture was refluxed for 3 hours. The product was filtered and washed with cold distilled water to give the brown precipitate. Table (3-8) shows the m.p. and the physical properties if compound (5).

### *2.3.6 2-diphenylamine-6-methylpyrimidine-4-(3H) one:*

(1 g) of compound (1) was mixed with diphenylamine (1.18 g) and the mixture was dissolved in (10 ml) of ethanol in round bottomed, the mixture was then refluxed for 3 hours. The product was filtered with cold distilled water. Table (3-8) shows the m.p. and the physical properties of compound (6).

### *2.3.7 2-(diphenylamine)amino-6-methylpyrimidine-4-(3H) one:*

(1 g) of compound (1) was mixed with 4-aminodiphenyl amine (1.288 g) and the mixture was dissolved in (10 ml) of absolute ethanol in round bottomed flask, the mixture was refluxed for 3 hours. The product was filtered and washed with distilled water. Table (3-8) shows the m.p. and the physical properties of compound (7).

## *2.4 Preparation of Schiff bases:*

### *2.4.1 6(4-N,N-dimethylamine benzylidene)-6-amino-1,3-dimethyl uracil:*

(0.01 mole) of 6-amino-1,3-dimethyl uracil and (0.01 mole) of 4-N,N-dimethyl amino benzaldehyde ware mixed in round bottomed flask, the mixture was then dissolved in (10 ml) of ethanol, 1-2 drops of glacial acetic acid were added, and then was refluxed for 5 hours, ice bath was used to separate the product. Then it was filtered and precipitate was isolated. Table (3-9) shows the m.p. and the physical properties of compound (8).

### *2.4.2 6(4-hydroxybenzylidene)-6-amino-1,3-dimethyl uracil:*

(0.01 mole) of 6-amino-1,3-dimethyl uracil and (0.01 mole) of 4-hydroxybenzaldehyde were mixed in round bottomed flask, the mixture was dissolved in (10 ml) of ethanol, 1-2 drops of glacial acetic acid were added, the mixture was then refluxed for 5 hours, ice bath was used to separate the product. Then it was filtered and precipitate was isolated. Table (3-9) shows the m.p. and the physical properties of compound (9).

### *2.4.3 2(4-N,N-dimethylamino benzylidene) hydrazine-6-methyl pyrimidine-4-(3H) one:*

(0.01 mole) of 2-hydrazino-6-pyrimidine-4-(3H) one and (0.01 mole) of 4-N,N-dimethylamino benzaldehyde were mixed in round bottomed flask, the mixture was dissolved in (10 ml) ethanol, 1-2 drops of glacial acetic acid were added, and the mixture was refluxed for 5 hours, ice bath was used to separate the product, and the mixture was then filtered and precipitate was isolated. Table (3-9) shows the m.p. and physical properties of compound (10).

## *2.5 Biological Study:*

### *2.5.1 Equipments and Apparatus:*

The following equipments and apparatus were used during the study:

| Equipment | Company (Origin) |
|---|---|
| **Oven** | **Gallenkamp Sanyo-(U.K)** |
| **Autoclave** | **Express (west-Germany)** |
| **Incubator** | **Termaks (U.K)** |

### *2.5.2 Chemicals and Media:*

The following chemicals and media were used during the study:

| Media and Material | Company (Origin) |
|---|---|
| **Nutrient broth** | **Difco (Biolife)** |
| **Nutrient agar** | **Difco (Fluka)** |
| **Ethanol (absolute)** | **Difco** |
| **Dimethyl sulfoxide** | **Fluka** |

### *2.5.3 Culture media:*

Some liquid and solid are used and prepared according to method, these media are:

1) Nutrient agar.

2) Nutrient broth prepared by dissolving 38 g for each liter of distilled water and sterilized by autoclaving.

Sterilization by autoclave under pressure of (15 atm) and temperature of (121$^{o}$C) for (15-20) minutes was made.

The medium was cooled to (50$^{o}$C), after that it was poured into the plates and left in room temperature to dry so that the plantation medium will be solid.

### *2.5.4 Microorganisms:*

In this study, two bacterial species were used: one was gram positive bacteria which it was *Staphylococcus aureus* and the other was gram negative bacteria which it was *Escherichia coli* as shown in the following table:

| Microorganism | Source |
|---|---|
| *Escherichia coli*<br>*Staphylococcus aureus* | Al-Nahrain University, College of Science, Department of biotechnology |

### *2.5.5 Activation of bacteria:*

3-5 Colonies of studied bacteria were transported by using a loop to a test tube containing (5 ml) of sterilized nutrient broth. The tube was shaken well and incubated in 37$^{o}$C for two hours. The loop was sterilized by a flame before using in order not to kill the planted bacteria.

Medium inoculated bacteria suspension was diluted by 1/100 by using normal-saline liquid with concentration of (0.85%) to prevent crowded growth. (0.1 ml) Of bacteria diluted suspension was transported

to each plate and spread by using sterilize cotton spreader on test surface. The plates were left for 15-20 minutes in 37$^{o}$C to make observation.

### *2.5.6 Preparation of discs:*

The discs were prepared from filter type (whatman no. 2) using the drill and obtain 6 mm discs. The DMSO solvent was used to prepare four concentrations for each prepared material (10 μg/disc), (100 μg/disc), (250 μg/disc) and (500 μg/disc) for each concentration, 20 discs from filter paper were prepared, then sterilized in autoclave and (0.01 ml) from each solution was applied to discs, then the discs were dried at (40$^{o}$C) for (30 minutes). A control sample was made for the DMSO solvent by adding (0.01 ml) from the solution to each disc from the sterilized filter paper. The above mentioned discs were fixed by a sterilized forceps with a tiny end in addition to light pressure on the disc surface. 25 mm distance was left between each disc and 1 cm between the disc and the edge of plate to prevent interference of inhibition zone.

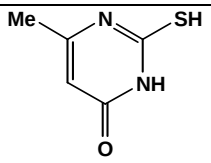
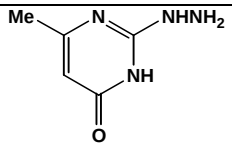
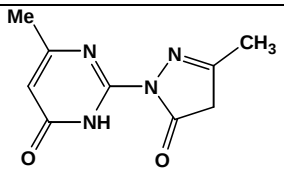
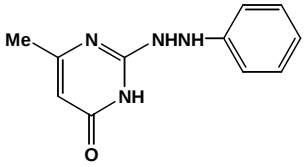
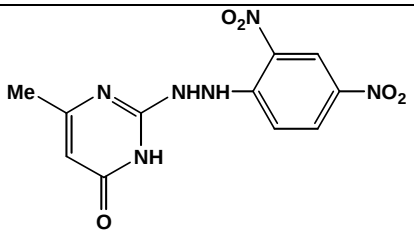
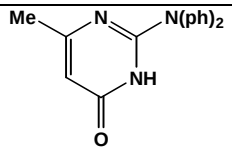
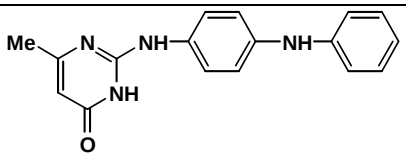
### *2.5.7 Effect of biological activity of the prepared compounds:*

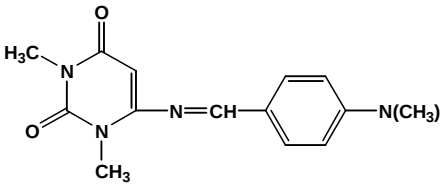
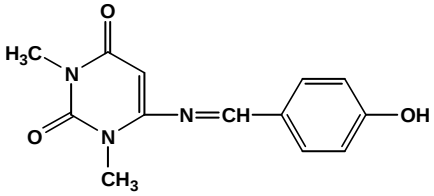
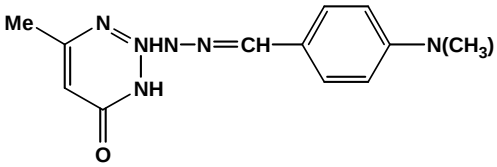
To study effect of the chemical compounds prepared on the species of bacteria Kirby- Baur's[78] method was selected to measure the effect of the prepared compounds on bacteria[79].

Diffusion method depends on the known concentration spread of exposer test measure fatal inhibitor for chemical compounds by taking discs from paper type filter type (whatman no.2) with a (6 mm) diameter in clean glass tubes with spiral plugs sterilized by autoclaving, then sinking it into chemical compounds solution for (5 minutes) and then transporting it into solid agar plate inoculated with (0.1 ml) of a bacterial culture of age 18 hours which was planted on the plate by spreading. The plates were then incubated at (37$^{o}$C) for 24 hours, and the inhibition zones for the area that had no bacteria growth was then measured reflects

the influence of the compounds and depend upon many physical and chemical factors.

**Table (2-1): The Name and Structure of the prepared compounds:**

| No. | Structure | Name |
|---|---|---|
| 1 |  | **6-Methyl-4-oxo-1,2,3,4-tetrahydro-2-thiopyrimidine** |
| 2 |  | **2-Hydrazino-6-methylpyrimidine-4-(3H) one** |
| 3 |  | **6-Methyl-2(3-methyl-5-oxo-4,5-dihydro-1-H-pyrazol-1-yl)pyrimidine-4-(3H) one** |
| 4 |  | **2-Phenylhydrazino-6-methylpyrimidine-4-(3H) one** |
| 5 |  | **2(2,4)-dinitrophenylhydrazino-6-methylpyrimidine-4-(3H) one** |
| 6 |  | **2-Diphenylamine-6-methylpyrimidine-4-(3H) one** |
| 7 |  | **2-(diphenylamine)amino-6-methylpyrimidine-4-(3H) one** |

| | | |
|---|---|---|
| **8** |  | **6(4-N,N-dimethylamine benzylidene)-6-amino-1,3-dimethyl uracil** |
| **9** |  | **6(4-Hydroxybenzylidene)-6-amino-1,3-dimethyl uracil** |
| **10** |  | **2(4-N,N-dimethylamino benzylidene) hydrazine-6-methylpyrimidine-4-(3H)one** |

## *Chapter three*

## *Results and Discussion*

### *3.0 Preparation of pyrimidine derivatives:*

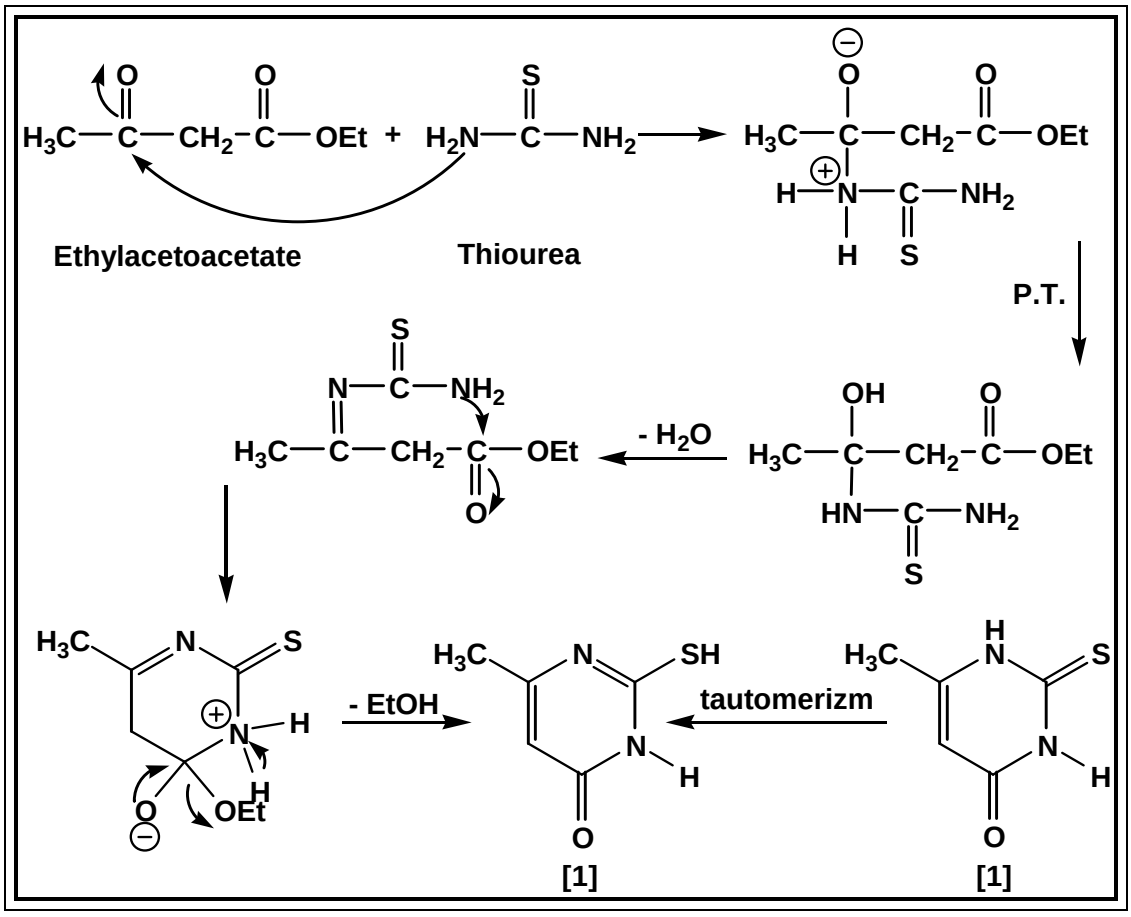
The pyrimidine compounds and its derivatives have a wide range of biological effect. The researchers found the pyrimidine derivatives used as antifungal, anticancer and antibacterial[80].

In this search, work on the preparation of ten new pyrimidine derivatives.

### *3.1 Preparation of 6-methyl-4-oxo-1,2,3,4-tetrahydro-2-thio pyrimidine:*

It was prepared from the reaction of ethylacetoacetate with thiourea in basic medium, and this following suggestive mechanism:

Mechanism:



From the suggested mechanism for this reaction, there are two structural forms (a, b) due to existing equilibrium (-SH) group and nitrogen atom of the ring, the form (a) more stable because it was kept resonance property[81]. The melting point is shown in Table (3-8).

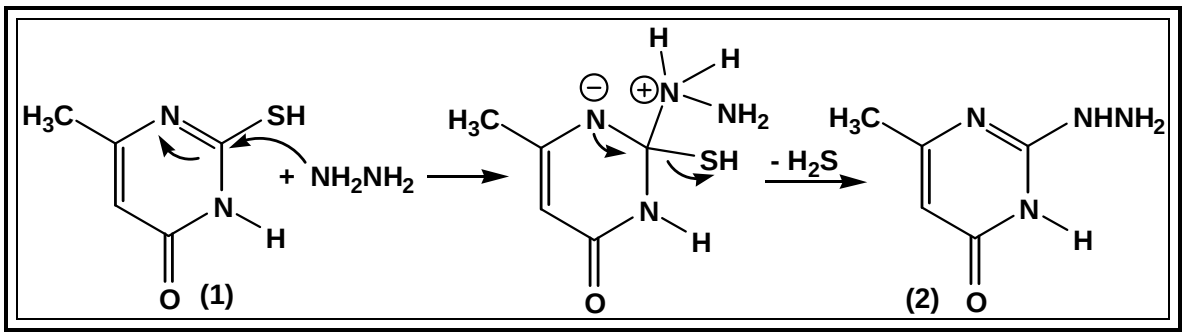
The F.T.IR spectral data for compound (1) are shown in Table (3-1), the absorption band of (S-H) group at 2582.5-2337.6 $cm^{-1}$ could be attributed to stretching vibration[82], the absorption bands at 1240.1-1197.7 $cm^{-1}$ could be attributed to (C=S) stretching vibration and the absorption band at 3112.9 $cm^{-1}$ could be attributed to (N-H) stretching vibration. F.T.IR spectrum is shown in Figure (3-1).

**Table (3-1): F.T.IR spectral data for compound (1).**

| No | ν N-H $cm^{-1}$ | ν C=O $cm^{-1}$ | ν C=N $cm^{-1}$ | ν C-S $cm^{-1}$ | ν C-H $cm^{-1}$ | ν S-H $cm^{-1}$ | ν C=S $cm^{-1}$ |
|---|---|---|---|---|---|---|---|
| 1 | 3112.9 | 1633.6 | 1556.4 | 731.0 | 3020 arm 2889.2 alph | 2582.5-2337.9 | 1240.1-1197.7 |

## *3.2 Preparation of 2-hydrazino-6-methyl pyrimidine-4-(3H) one:*

It was prepared from the reaction of compound (1) with hydrazine hydrate (99%), the reaction takes place by nucleophilic removal of (-SH) group by amino in hydrazine[83], the melting point is shown in Table (3-8) and the suggested mechanism is shown below:




The F.T.IR spectral data for compound (2) is shown in Table (3-2), through the presence of absorption band at 3209.3-3087.8 $cm^{-1}$ could be

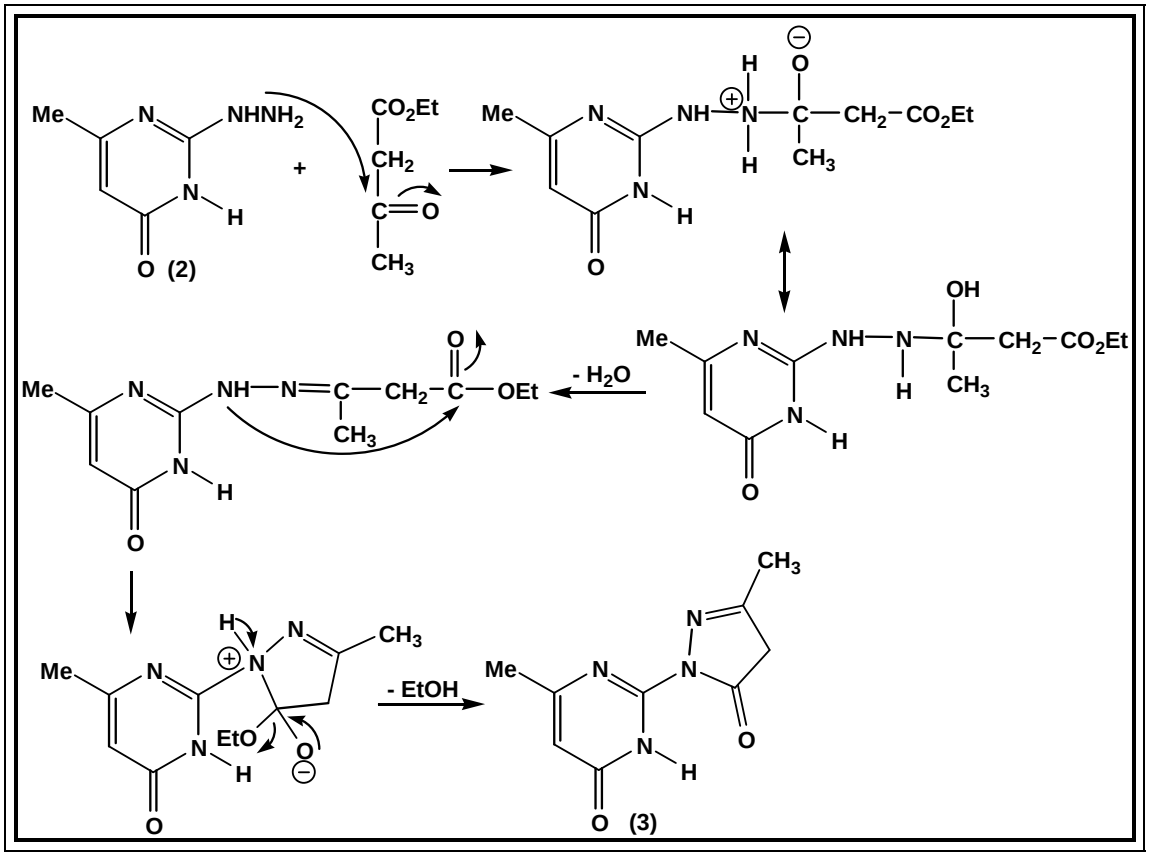
attributed to (NH, $NH_2$) stretching vibration of hydrazine group and thio pyrimidine ring, and absorption band at 1593.1 $cm^{-1}$ could be attributed to (C=N) stretching vibration. F.T.IR spectrum is shown in Figure (3-2). The melting point is shown in Table (3-8).

**Table (3-2): F.T.IR spectral data for compound (2).**

| No | ν N-H $cm^{-1}$ | ν C=O $cm^{-1}$ | ν C=N $cm^{-1}$ | ν C-H alph $cm^{-1}$ | ν C-H arm $cm^{-1}$ |
|---|---|---|---|---|---|
| 2 | 3209.3-3087.8 | 1643.0 | 1593.1 | 2922.0 | 3016.5 |

### *3.3 Preparation of 6-methyl-2-(3-methyl-5-oxo-4,5-dihydro-1-H-pyrazol-1-yl) pyrmidine-4-(3H) one:*

It was prepared from the reaction of compound (2) with ethylaceto acetate in ethanol for 6 hours[84]. The melting point is shown in Table (3-8) and the mechanism of the reaction is shown below.




From suggestive mechanism, a nucleophilic addition from nitrogen atom in hydrazine to the carbon atom of carbonyl compound.

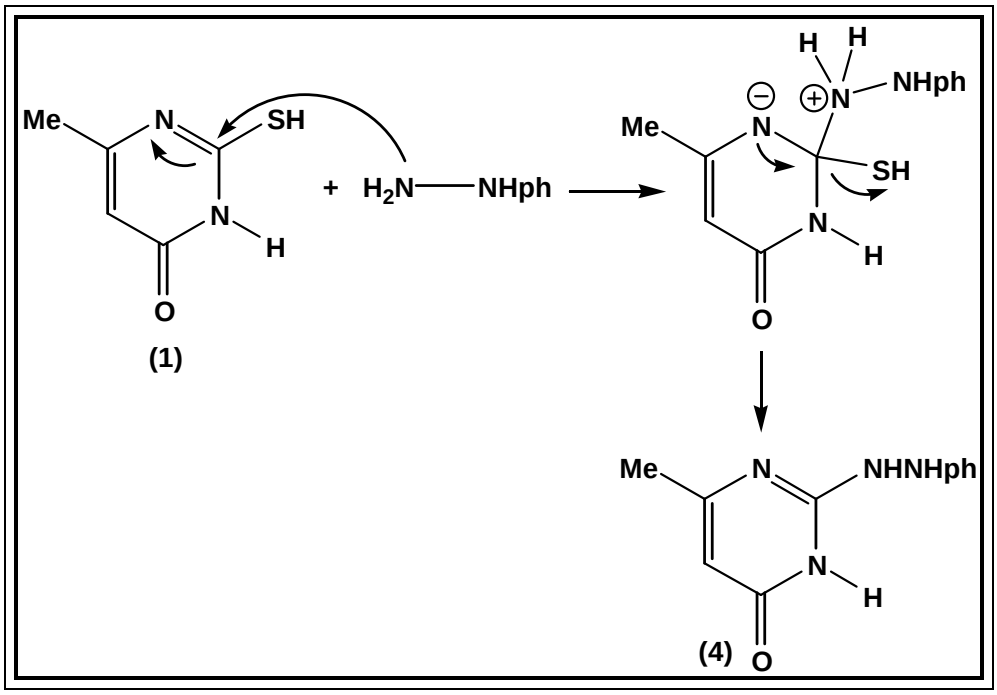
The IR spectral data for compound (3) is shown in Table (3-3), the absorption band at (3340 $cm^{-1}$ could be attributed to (-NH) stretching vibration in pyrimidine ring and absorption band at 1650 $cm^{-1}$ could be attributed to (C=O) stretching vibration. F.T.IR spectrum is shown in Figure (3-3).

**Table (3-3): F.T.IR spectral data for compound (3).**

| No | ν N-H $cm^{-1}$ | ν C=O $cm^{-1}$ | ν C=N $cm^{-1}$ | ν C-H arm $cm^{-1}$ | ν C-H alph $cm^{-1}$ | ν C-N $cm^{-1}$ |
|---|---|---|---|---|---|---|
| 3 | 3340.0 | 1650 | 1580 | 3070 | 2987-2882 | 1250-1230 |

## *3.4 Preparation of 2-phenylhydrazino-6-methyl pyrimidine-4-(3H) one:*

It was prepared from the reaction of compound (1) with phenyl hydrazine. The reaction takes place by nucleophilic removal of (-SH) group by amino group as shown below. The melting point is shown in Table (3-8).



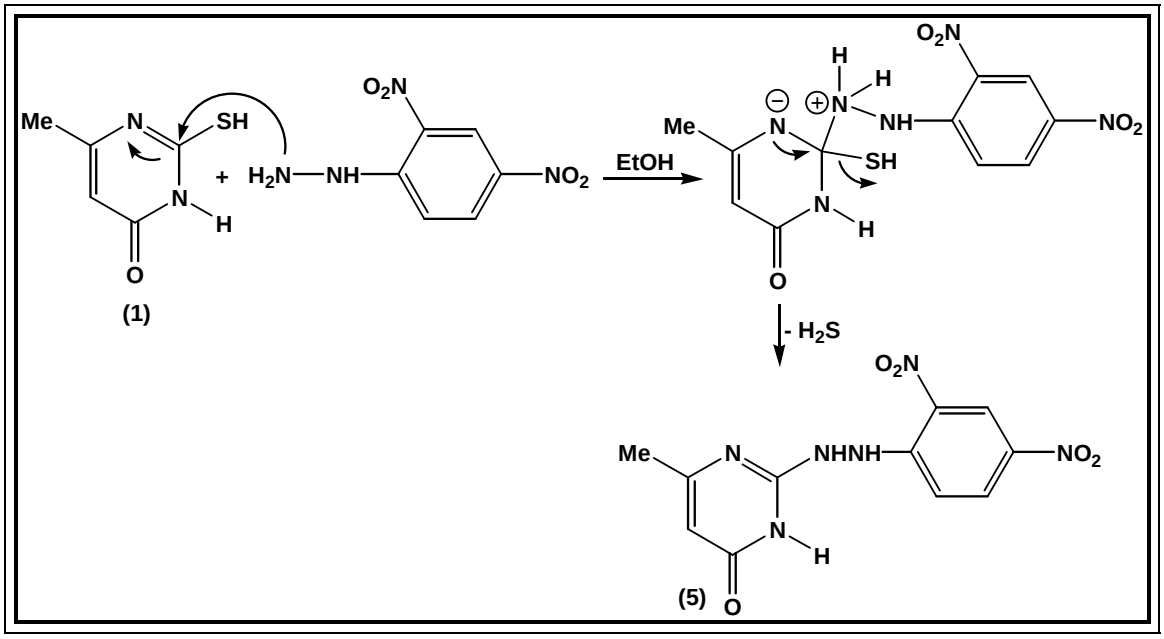
The F.T.IR spectral data for compound (4) is shown in Table (3-4), the absorption band at 3130.25 $cm^{-1}$ could be attributed to (N-H) stretching vibration in phenyl hydrazine group and thio pyrimidine. F.T.IR spectrum is shown in Figure (3-4).

**Table (3-4): F.T.IR spectral data for compound (4).**

| No | ν N-H $cm^{-1}$ | ν C=O $cm^{-1}$ | ν C=N $cm^{-1}$ | ν C-H arm $cm^{-1}$ | ν C-H alph $cm^{-1}$ |
|---|---|---|---|---|---|
| 4 | 3230.25 | 1753.17 | 1676.03 | 2935.46 | 2889.17 |

## *3.5 Preparation of 2-(2,4)-dinitrophenyl hydrazine-6-methyl-pyrimidine-4-(3H) one:*

It was prepared form the reaction of compound (1) with 2,4-dinitrophenyl hydrazine in ethanol, the reaction takes place by the nucleophilic removal of (-SH) group by amino group in 2,4-dinitrophenyl hydrazine, as shown below, the melting point is shown in Table (3-8).



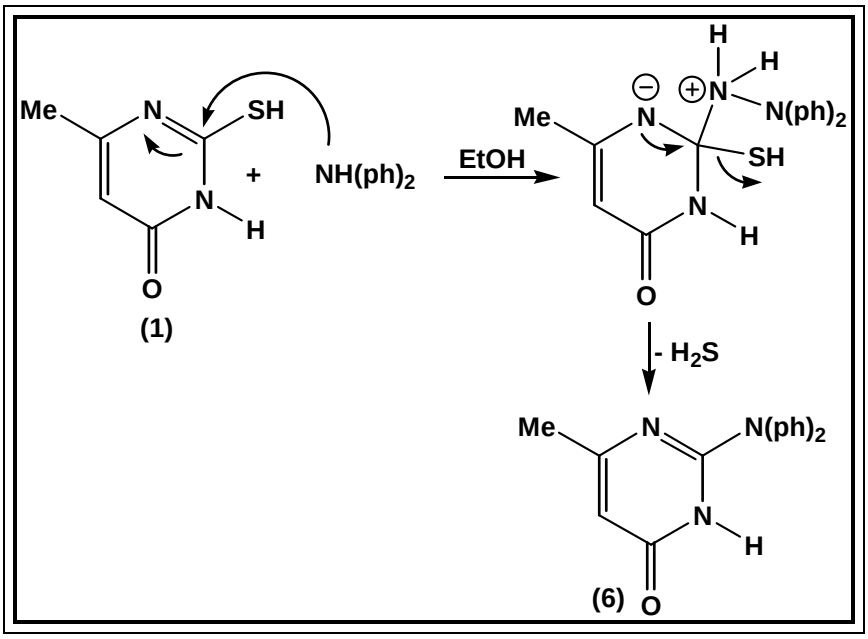

The F.T.IR spectral data for compound (5) is shown in Table (3-5), the absorption band at 3326.98 $cm^{-1}$ could be attributed to (N-H) stretching vibration in 2,4-dinitrophenyl hydrazine group and thio pyrimidine, the other absorption bands are shown in Table (3-5). F.T.IR spectrum is shown in Figure (3-5).

**Table (3-5): F.T.IR spectral data for compound (5).**

| No | ν N-H $cm^{-1}$ | ν C=O $cm^{-1}$ | ν C=N $cm^{-1}$ | ν C-H arm $cm^{-1}$ | ν C-H alph $cm^{-1}$ | ν $NO_2$ $cm^{-1}$ |
|---|---|---|---|---|---|---|
| 5 | 3326.98 | 1680.0 | 1637.45 | 3087.82 | 2929.6-2891.0 | 1560.3-1519.8 |

## *3.6 Preparation of 2-diphenylamine-6-methylpyrimidine-4-(3H) one:*

It was prepared from the reaction of compound (1) with dimethylamine in ethanol for 3 hours, the reaction takes place by nucleophilic removal of (-SH) group by amino group in dimethylamine, as shown below, the melting point is shown in Table (3-8).



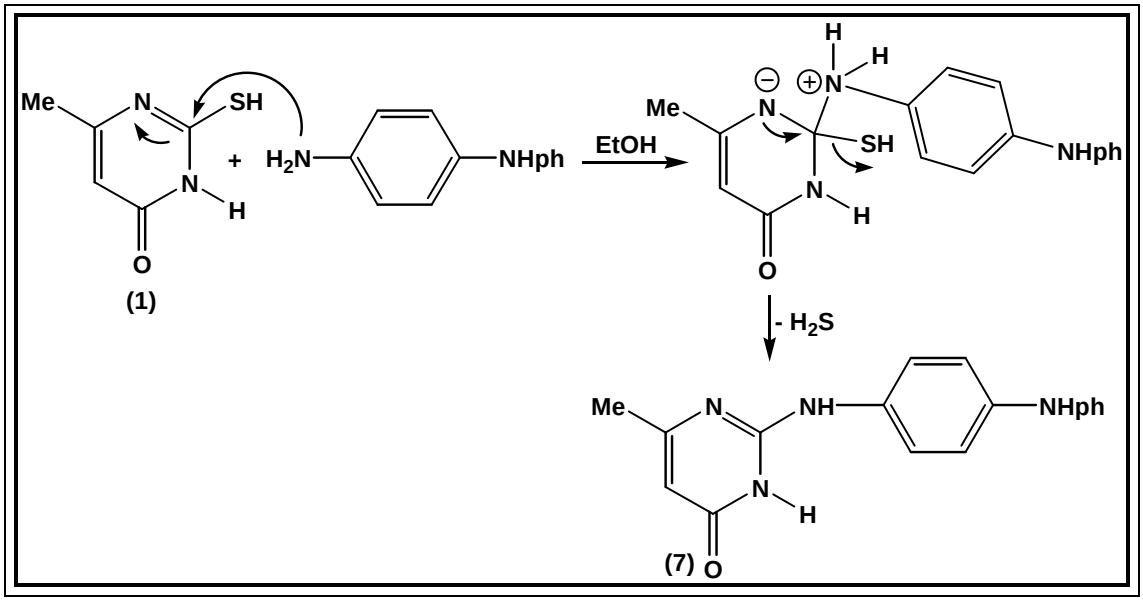

The F.T.IR spectral data for compound (6) is shown in Table (3-6), the absorption band at 3116.75 $cm^{-1}$ could be attributed to (N-H) stretching vibration in thio pyrimidine ring and absorption band at 1676.03 $cm^{-1}$ could be attributed to (C=O) stretching vibration, other groups are shown in Table (3-6). F.T.IR spectrum is shown in Figure (3-6).

**Table (3-6): F.T.IR spectral data for compound (6).**

| No | ν N-H $cm^{-1}$ | ν C=O $cm^{-1}$ | ν C=N $cm^{-1}$ | ν C-H arm $cm^{-1}$ | ν C-H alph $cm^{-1}$ | ν C=C $cm^{-1}$ |
|---|---|---|---|---|---|---|
| 6 | 3116.75 | 1676.03 | 1637.45 | 3014.45 | 2929.6-2889.1 | 1558.38 |

## *3.7 Preparation of 2-(diphenylamine)amino-6-methyl pyrimidine-4-(3H) one:*

It was prepared from the reaction of compound (1) with 4-amino diphenylamine in ethanol for 3 hours, the reaction takes place by nucleophilic removal of (-SH) group by amino group in 4-amino diphenylamine, as shown below, the melting point is shown in Table (3-8).

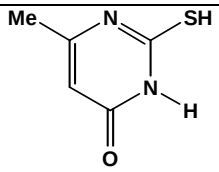
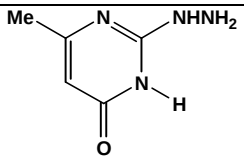
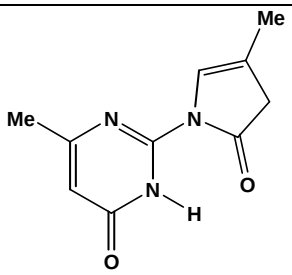
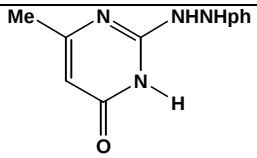
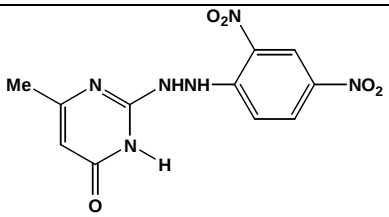
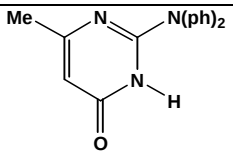
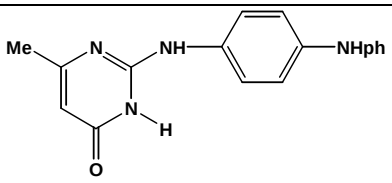


The F.T.IR spectral data for compound (7) is shown in Table (3-7), the absorption band at 3390.63 $cm^{-1}$ could be attributed to (N-H) stretching vibration in thio pyrimidine ring and 4-aminodiphenyl amine, the other bands are shown in Table (3-7). F.T.IR spectrum is shown in Figure (3-7).

**Table (3-7): F.T.IR spectral data for compound (7).**

| No | ν N-H $cm^{-1}$ | ν C=O $cm^{-1}$ | ν C=N $cm^{-1}$ | ν C-H arm $cm^{-1}$ | ν C-H alph $cm^{-1}$ |
|---|---|---|---|---|---|
| 7 | 3390.63 | 1676.03 | 1569.95 | 3107.11 | 2929.67 |

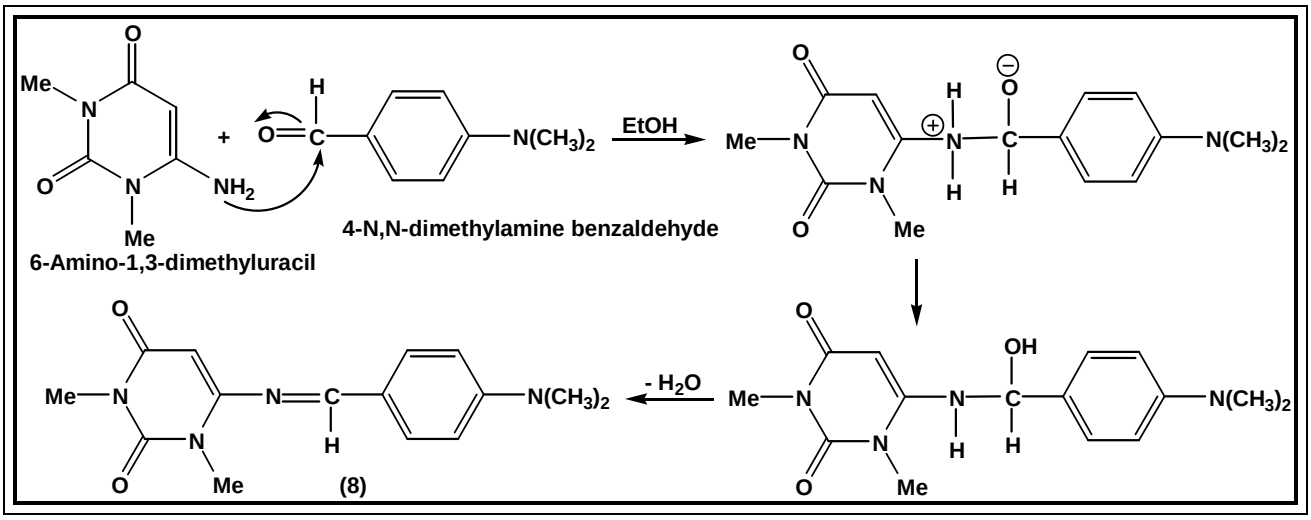
**Table (3-8): The physical properties of the prepared pyrimidine derivatives.**

| No. | Structure | Chemical formula | Molecular weight (g/mol) | Melting point ($^{o}$C) | Color |
|---|---|---|---|---|---|
| 1 |  | $C_5H_6N_2SO$ | 142 | 298-300 | Yellowish-white |
| 2 |  | $C_5H_8N_4O$ | 140 | 212-214 | White |
| 3 |  | $C_8H_9N_4O_2$ | 193 | 285-287 | White |
| 4 |  | $C_{11}H_{12}N_4O$ | 216 | 243-245 | Orange |
| 5 |  | $C_{11}H_{10}N_6O_5$ | 306 | 288-290 | Brown |
| 6 |  | $C_{17}H_{15}N_3O$ | 277 | >310 | White |
| 7 |  | $C_{17}H_{14}N_4O$ | 290 | >320 | Deep brown |

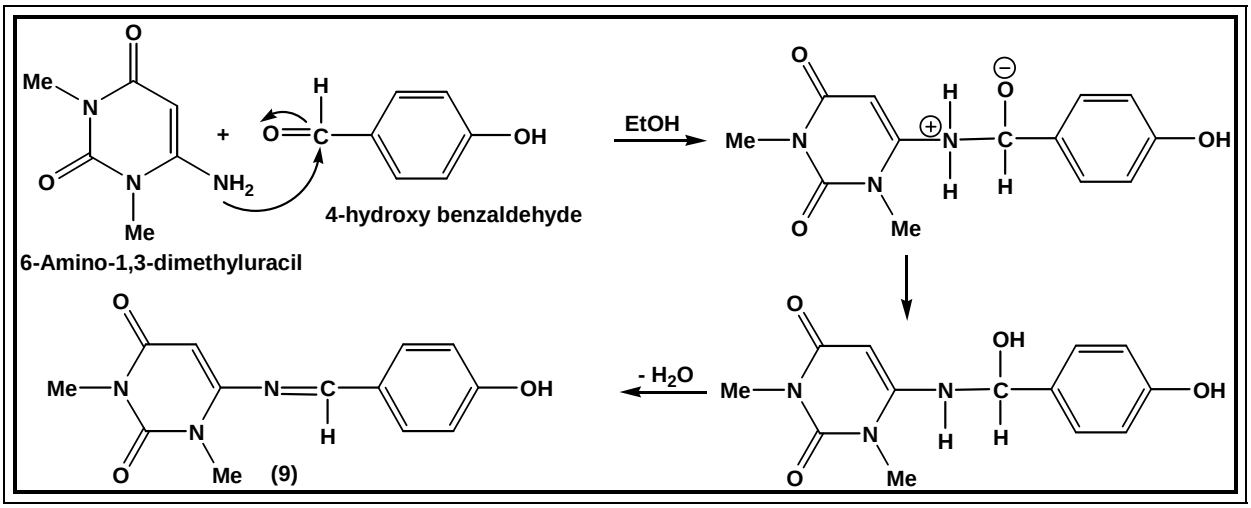
## *3.8 Preparation of Schiff bases compounds:*

Due to the biological activity of the Schiff bases; it is used as antifungal and anticancer, where Schiff bases which contain on the substituted aromatic aldehyde like (X, OH, $OCH_3$, amine) have biological activity as antifungal more than aromatic aldehyde without substituted groups[85].

Three compounds of Schiff bases were prepared, where the reaction was nucleophilic addition by (-NH) group with aldehyde carbonyl group to form N-substituted hemiaminals that losses water molecule to yield stable compounds shown below in following mechanisms[86]. Mechanism for the preparation of 6-(4-N,N-dimethylamino benzylidene)-6-amino-1,3-dimethyl uracil:



Mechanism for the preparation of 4-(4-hydroxybenzylidene)-6-amino-1,3-dimethyl uracil:




Mechanism for the preparation of 2-(4-N,N-dimethylamino benzylidene) hydrazine-6-methyl pyrimidine-4-(3H) one:

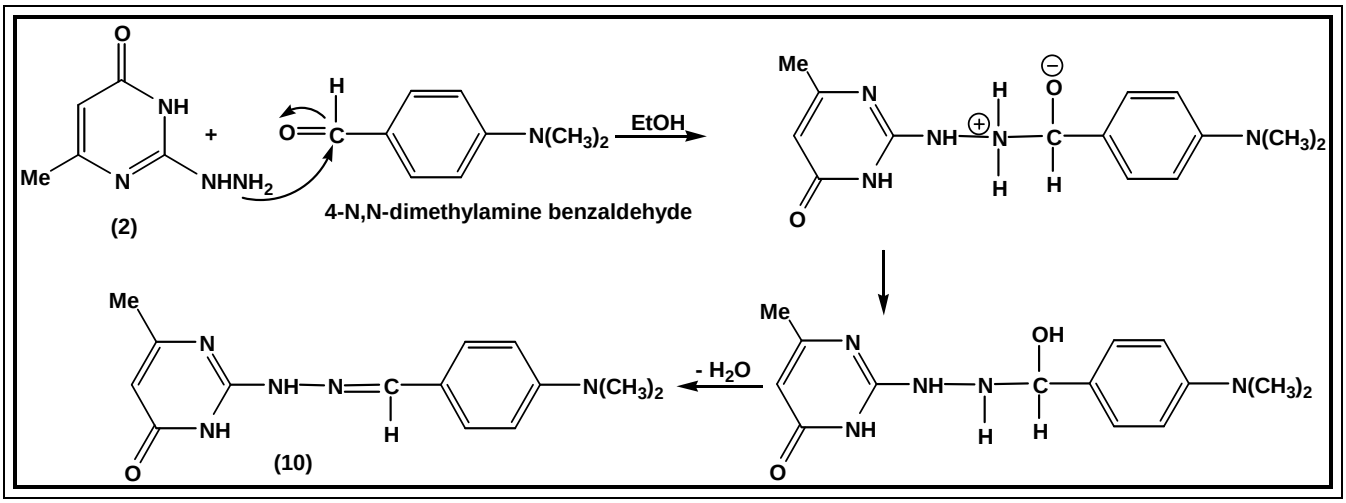
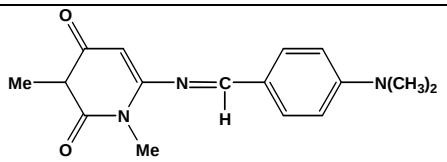
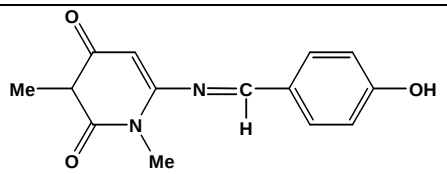
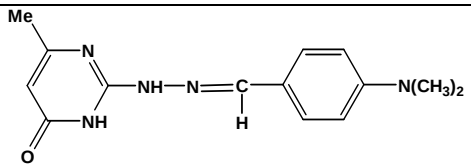


**Table (3-9): The physical properties of Schiff bases.**

| No | Structure | Formula | M. Wt. (g/mol) | M.P. $^{o}$C | Color |
|---|---|---|---|---|---|
| **8** |  | $C_{15}H_{18}N_4O_2$ | 286 | 222-225 | Yellow |
| **9** |  | $C_{13}H_{13}N_3O_3$ | 259 | 212-214 | White |
| **10** |  | $C_{13}H_{17}N_5O$ | 259 | >320 | yellow |

The F.T.IR spectrum of compound (8) showed absorption band at 1658.67 $cm^{-1}$ which could be attributed to (C=N) this bond is characteristic to Schiff bases stretching vibration. Absorption band at 3300.0 $cm^{-1}$ which could be attributed to (C-H) aromatic stretching vibration[87,88].

The F.T.IR spectrum of compound (9) showed absorption band at 3400.0 $cm^{-1}$ which broad band could be attributed to (-OH) stretching vibration. (C=N) group characteristic of Schiff bases showed peak absorption band at 1612.38 $cm^{-1}$ which could be attributed to (C=N) stretching vibration[89].

F.T.IR spectrum of compound (10) (C=N) which is characteristic to Schiff bases showed peak absorption band at ~ 1600 $cm^{-1}$ could be attributed to (C=N) stretching vibration, and showed absorption band at 3267.19-3211.26 $cm^{-1}$ which could be attributed to (N-H) of pyrimidine ring and of hydrazine group[87,88,89]. The F.T.IR spectra of compounds (8), (9) and (10) are shown in Figures (3-8), (3-9) and (3-10) respectively.

**Table (3-10): F.T.IR spectral data of the prepared Schiff bases.**

| No | ν C=N $cm^{-1}$ | ν C=O $cm^{-1}$ | ν C-H arm $cm^{-1}$ | ν C-H alph $cm^{-1}$ | ν others |
|---|---|---|---|---|---|
| 8 | 1658.67 | 1670.24 | 3300.0 | 2950.89 | - |
| 9 | 1612.38 | 1658.67 | 3100.0 | 2950.89 | O-H ~ 3400.0 |
| 10 | ~ 1600 | 1645.17 | 3018.39 | 2921.96 | N-H 3267.19-3211.26 |

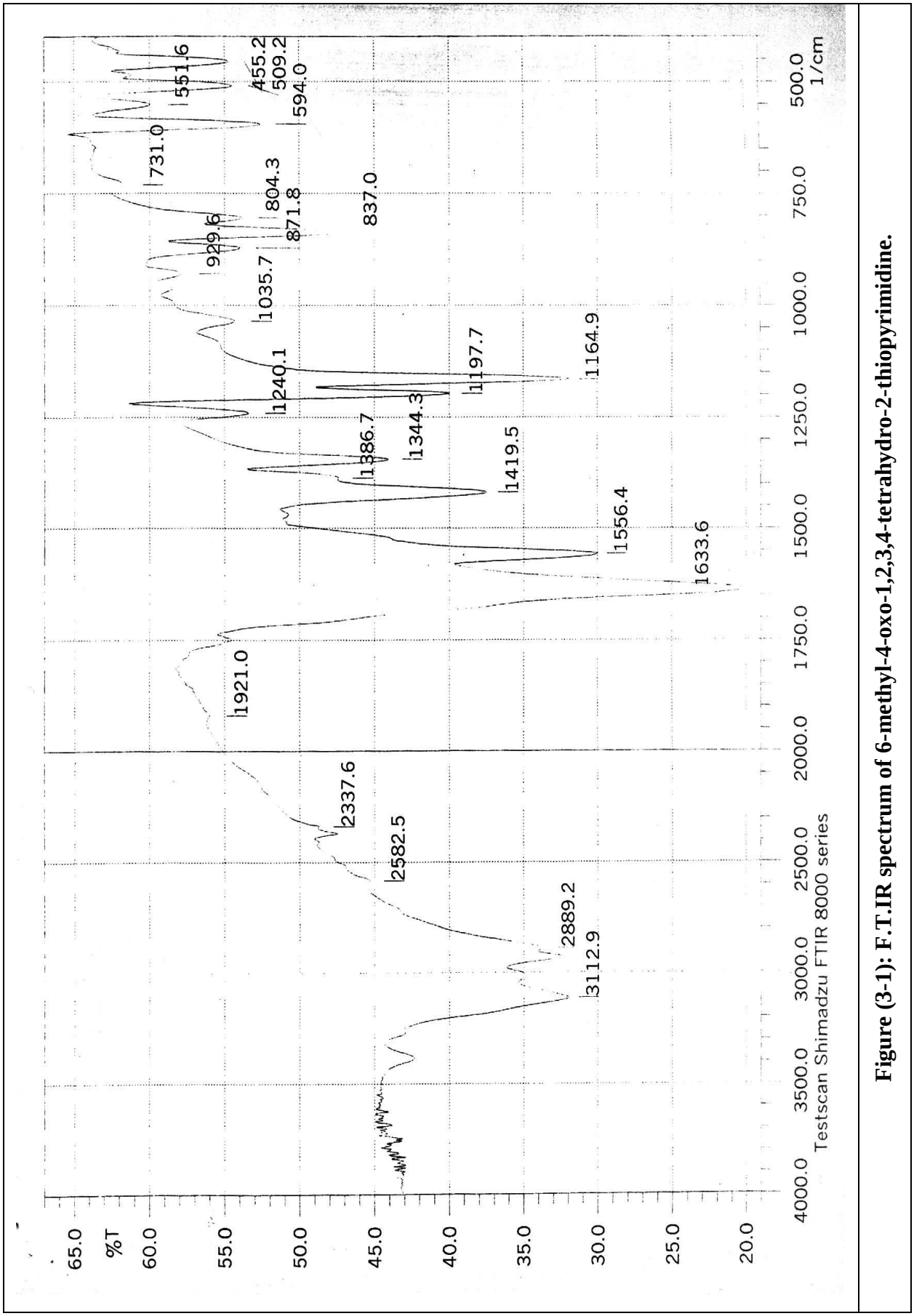



**Figure (3-1): F.T.IR spectrum of 6-methyl-4-oxo-1,2,3,4-tetrahydro-2-thiopyrimidine.**

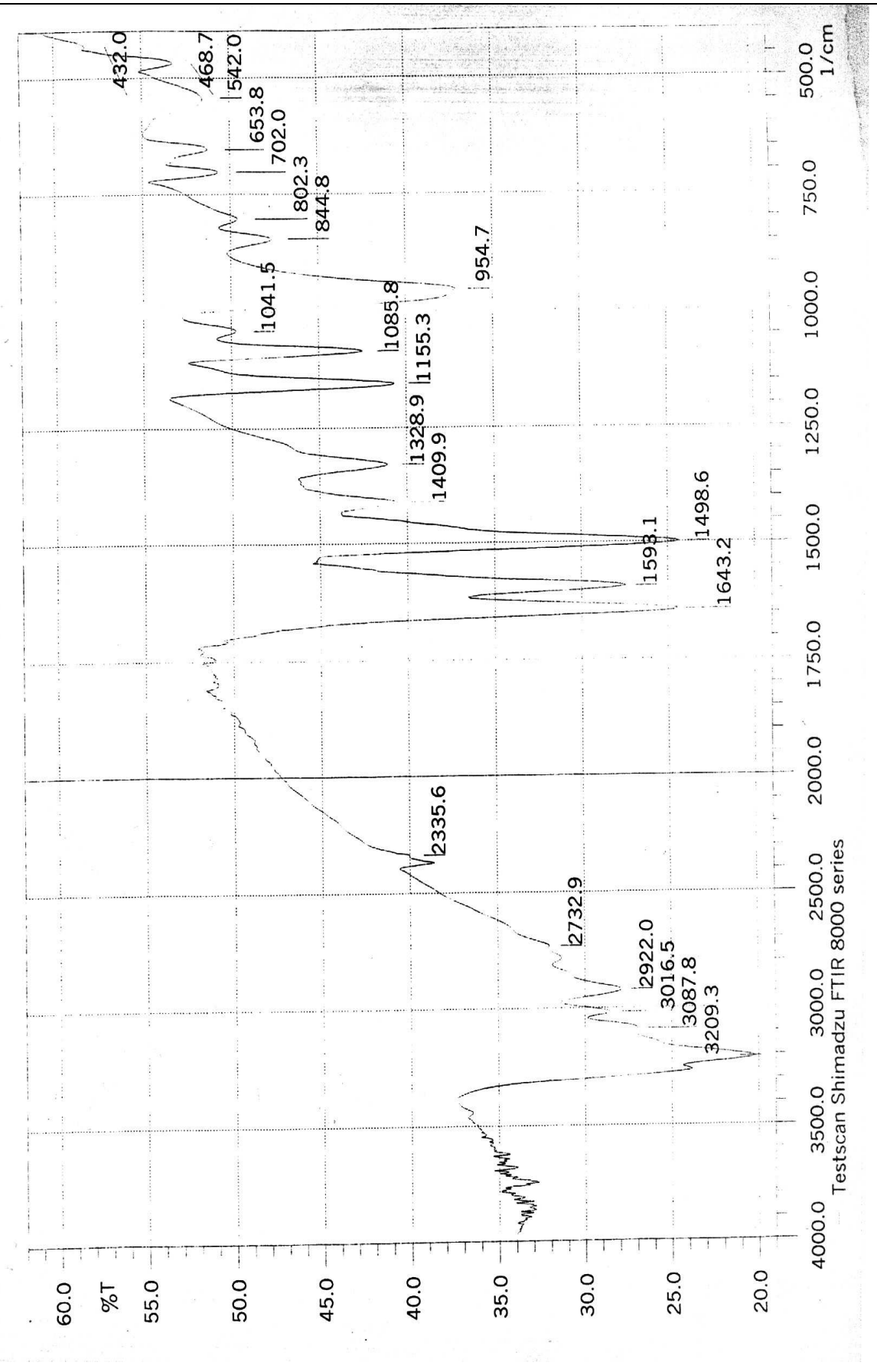



**Figure (3-2): F.T.IR spectrum of 2-hydrazino-6-methyl pyrimidine-4-(3H) one.**

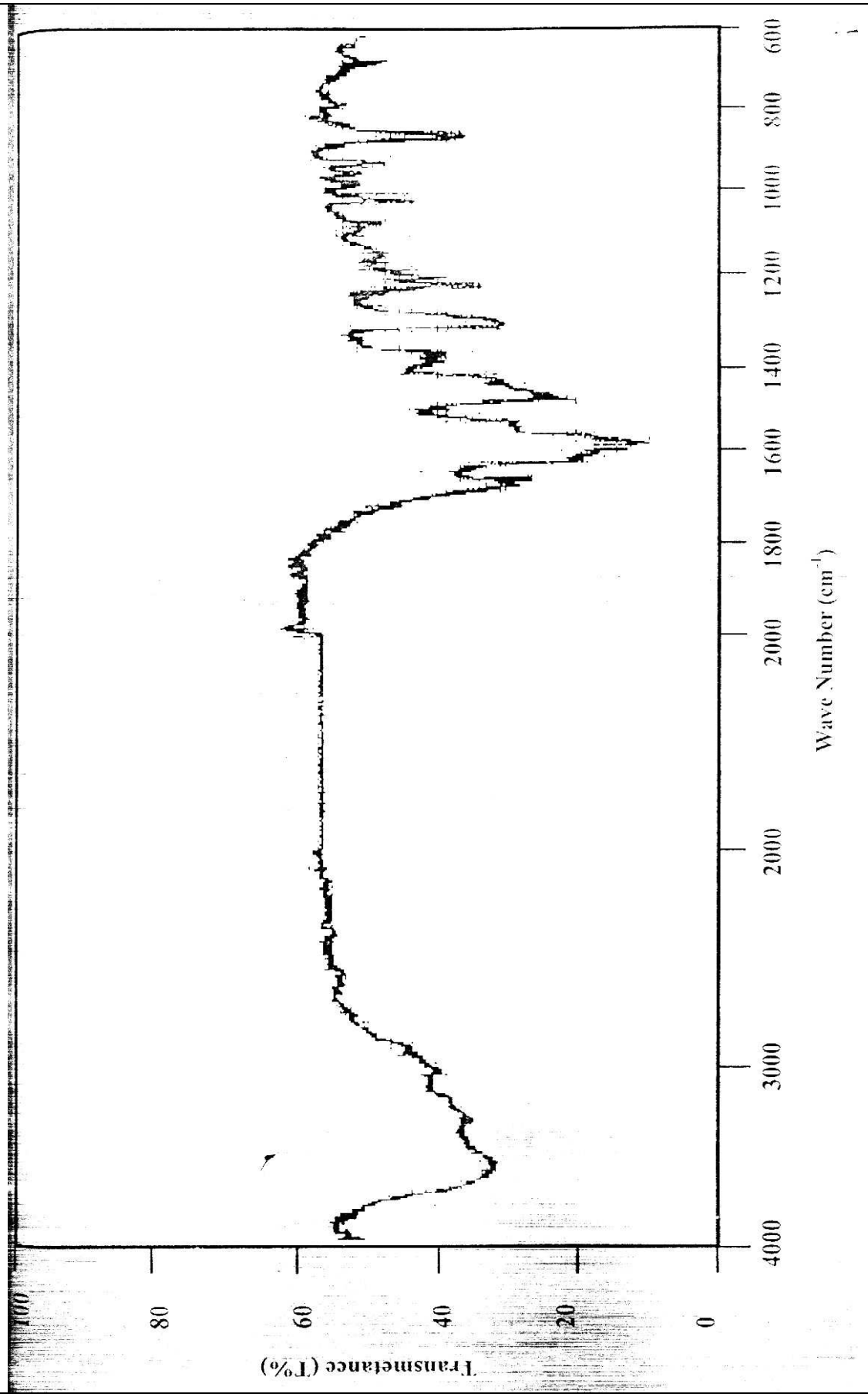



**Figure (3-3): F.T.IR spectrum of 6-methyl-2-(3-methyl-5-oxo-4,5-dihydro-1-H-pyrazol-1-yl) pyrimidine-4-(3H) one.**

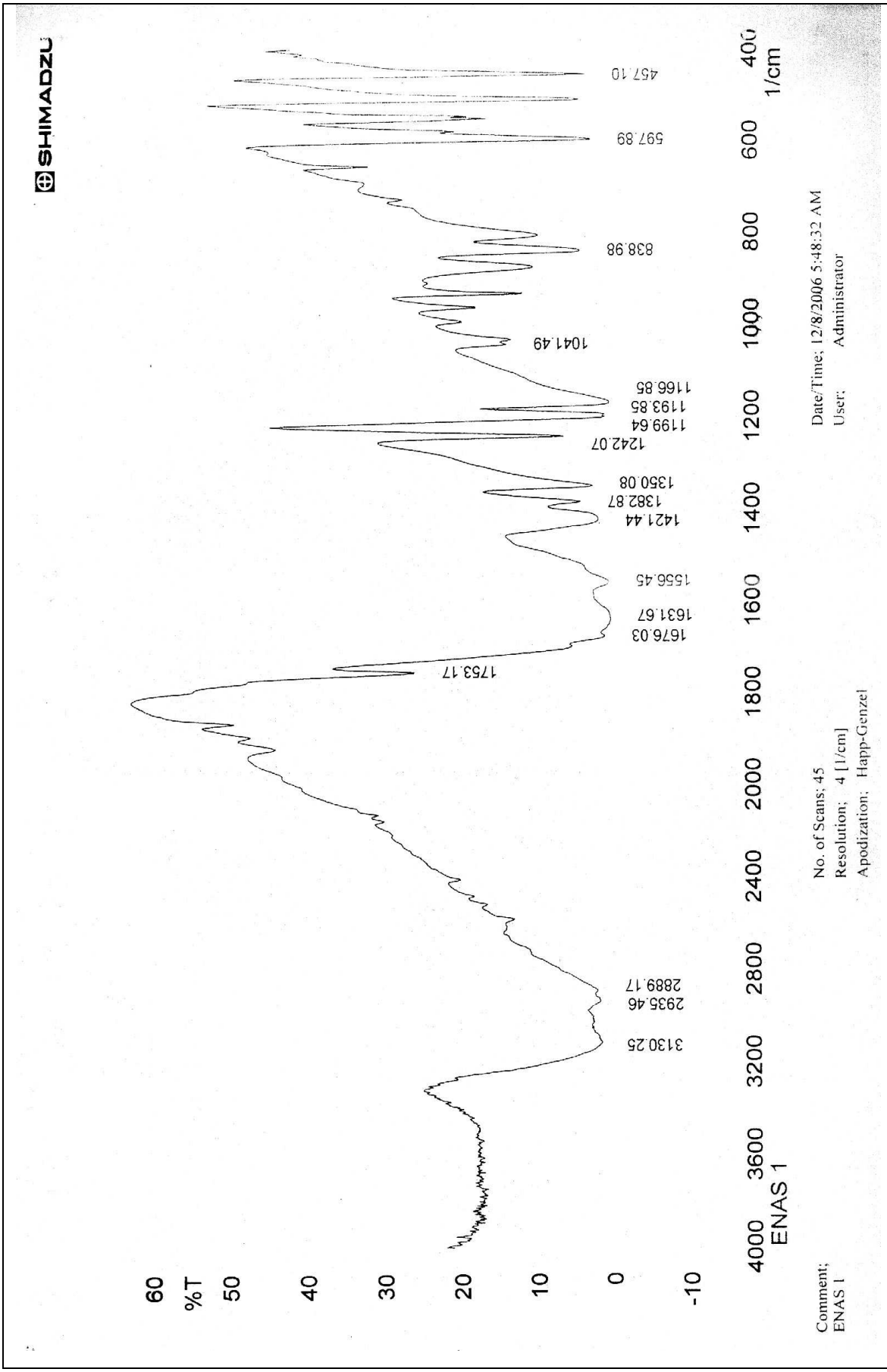



**Figure (3-4): F.T.IR spectrum of 2-phenyl hydrazine-6-methyl pyrimidine-4-(3H) one.**

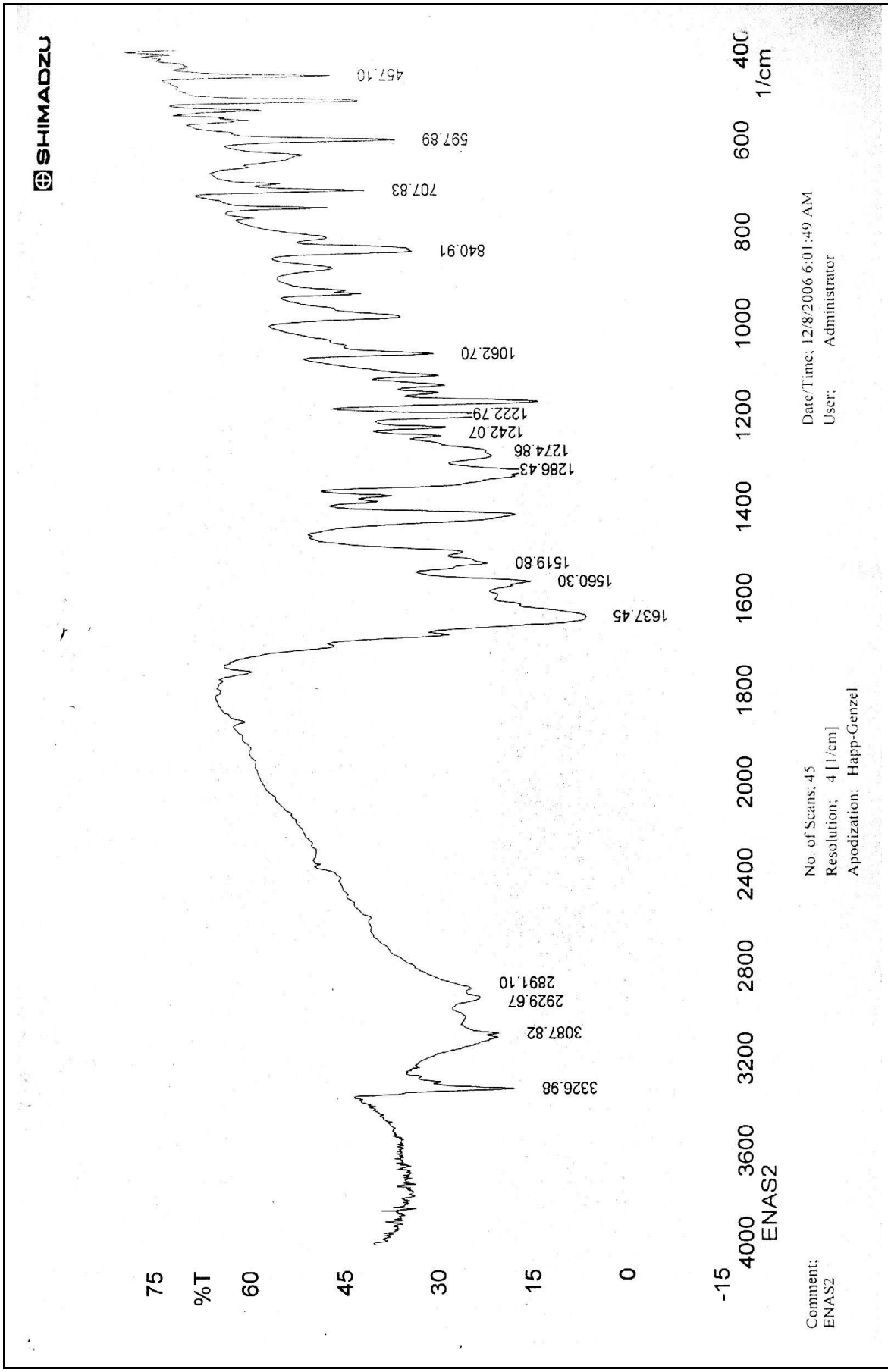



**Figure (3-5): F.T.IR spectrum of 2-(2,4)-dinitro hydrazine-6-methyl pyrimidine-4-(3H) one.**

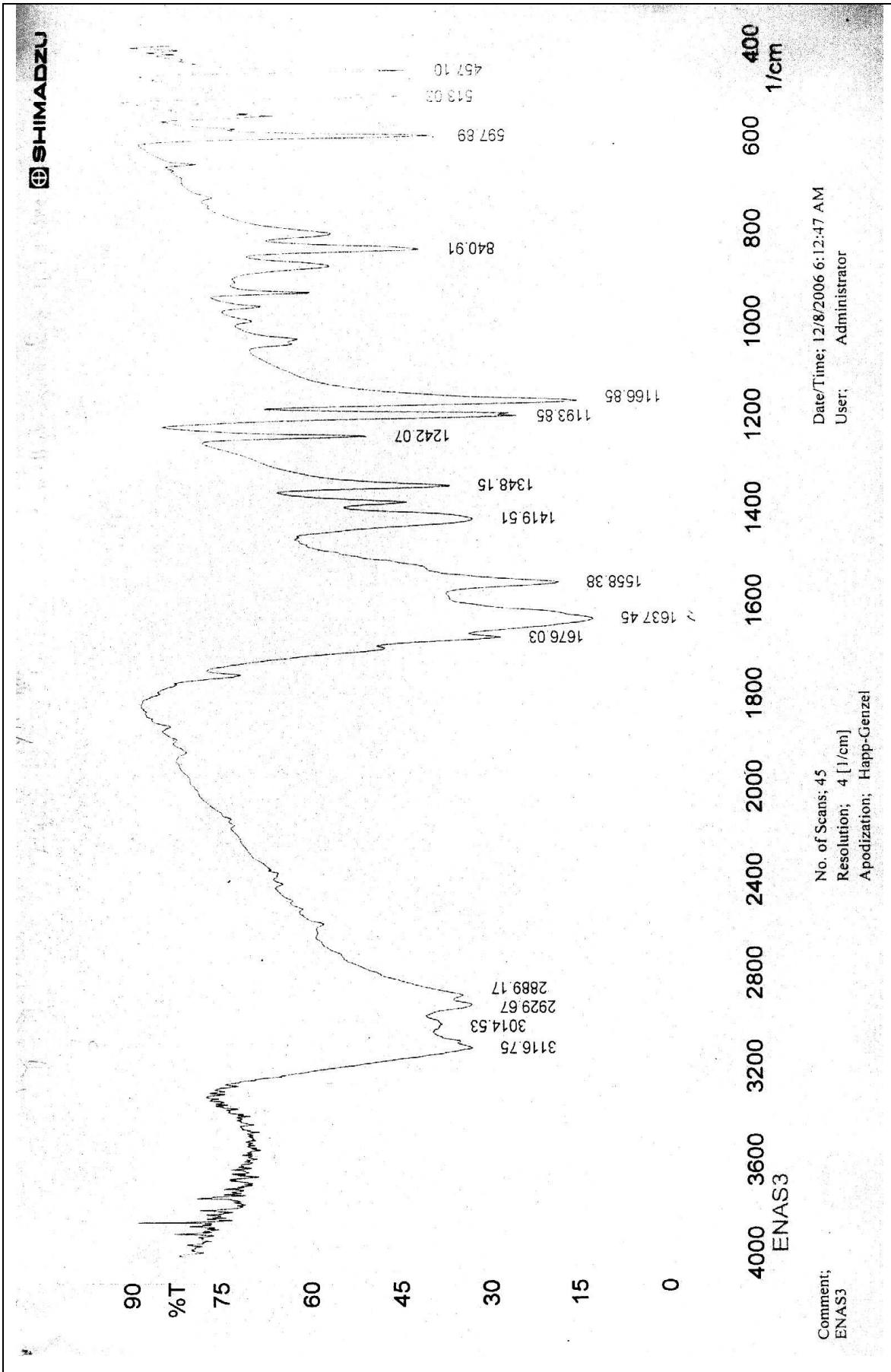



**Figure (3-6): F.T.IR spectrum of 2-diphenylamine-6-methyl pyrimidine-4-(3H) one.**

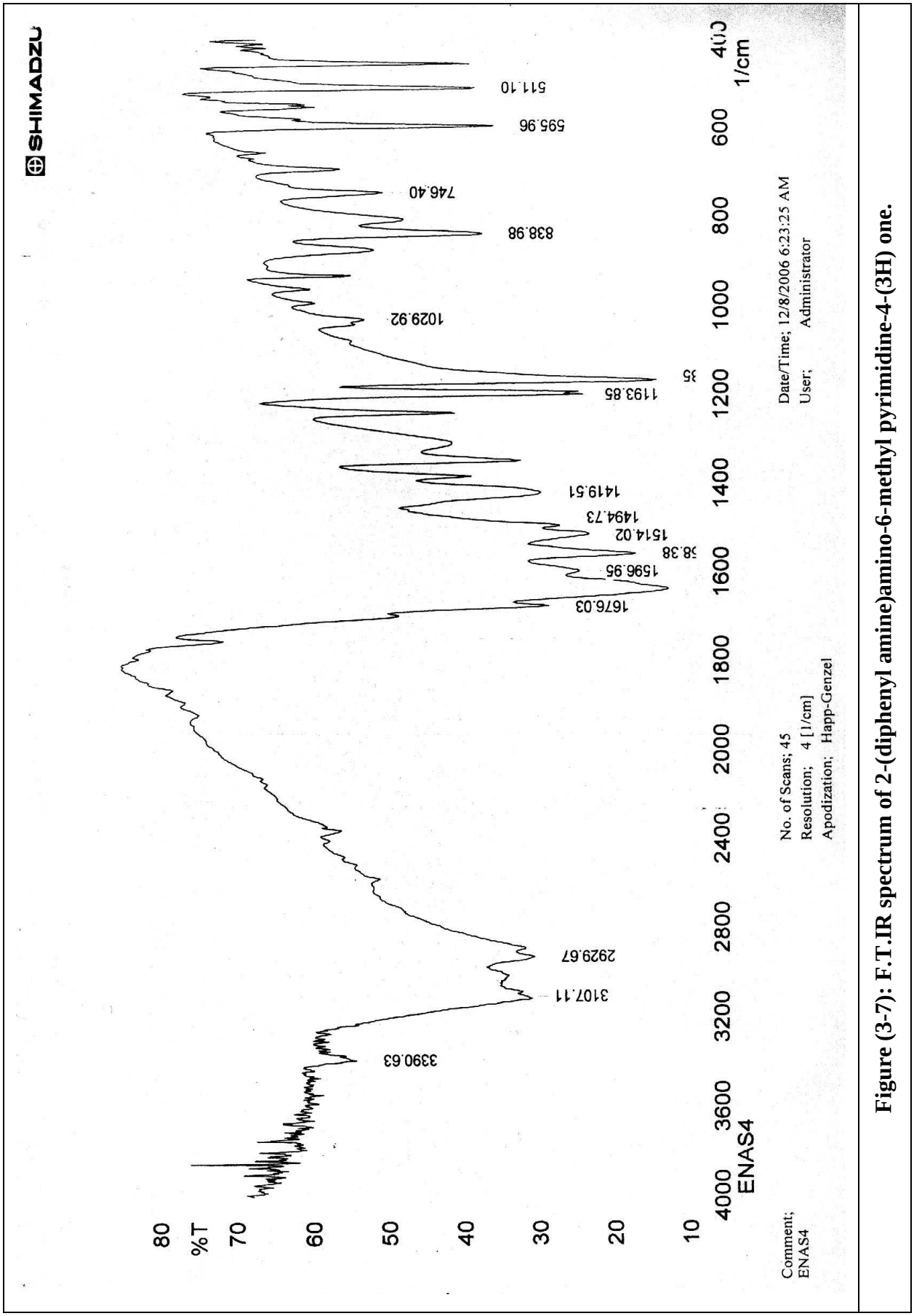



**Figure (3-7): F.T.IR spectrum of 2-(diphenyl amine)amino-6-methyl pyrimidine-4-(3H) one.**

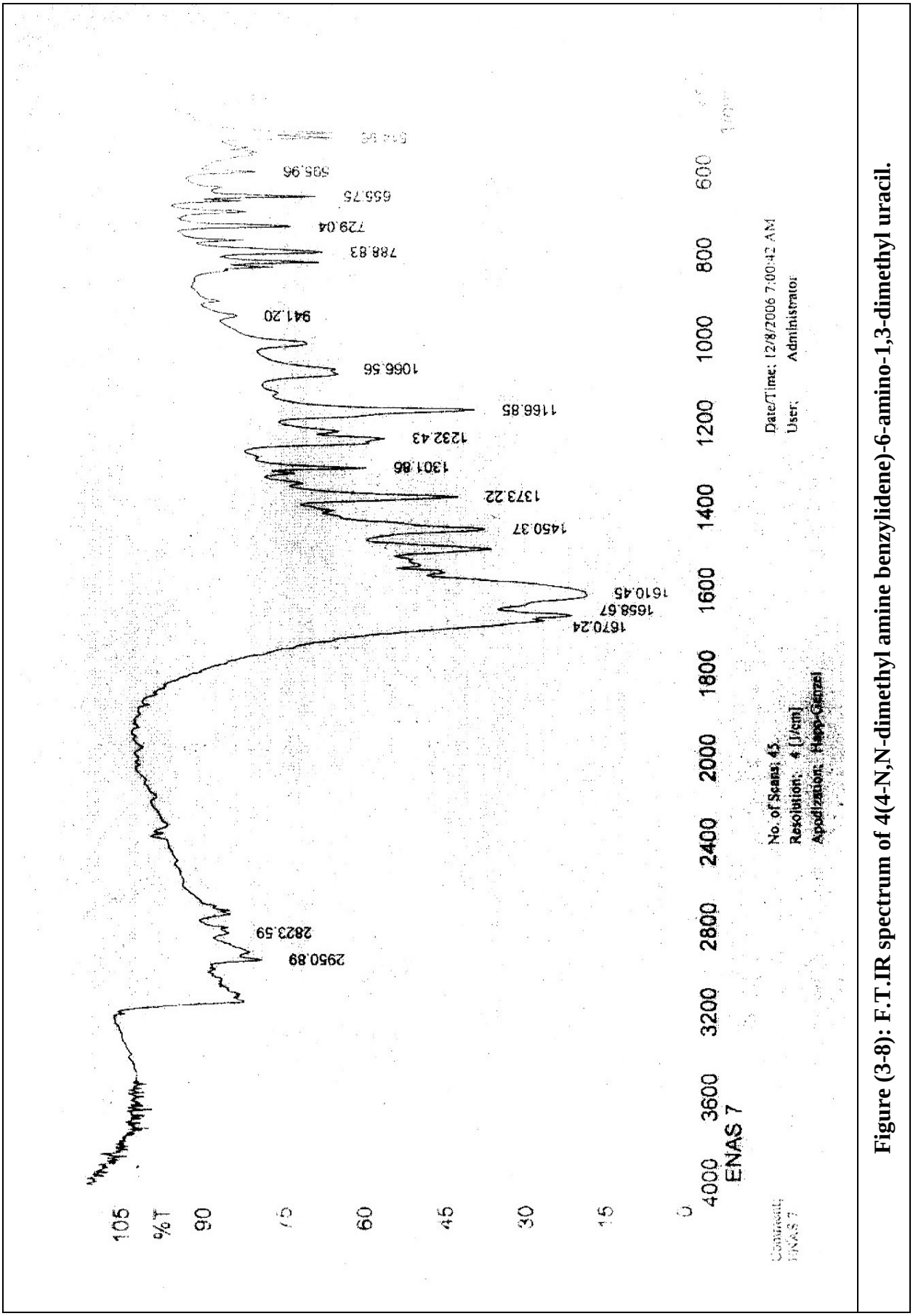



**Figure (3-8): F.T.IR spectrum of 4(4-N,N-dimethyl amine benzylidene)-6-amino-1,3-dimethyl uracil.**

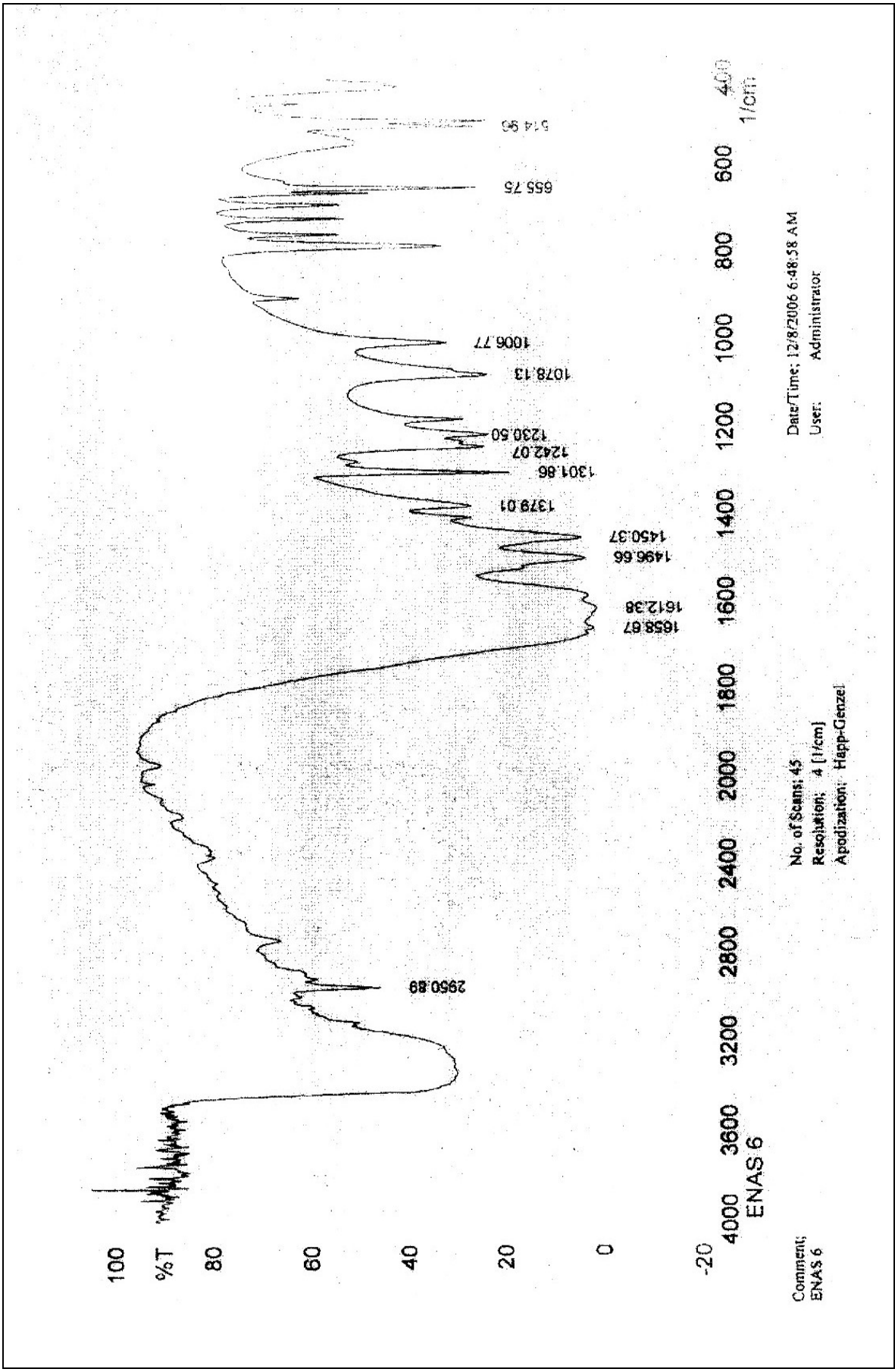



**Figure (3-9): F.T.IR spectrum of 4-(4-hydroxy benzylidene)-6-amino-1,3-dimethyl uracil.**

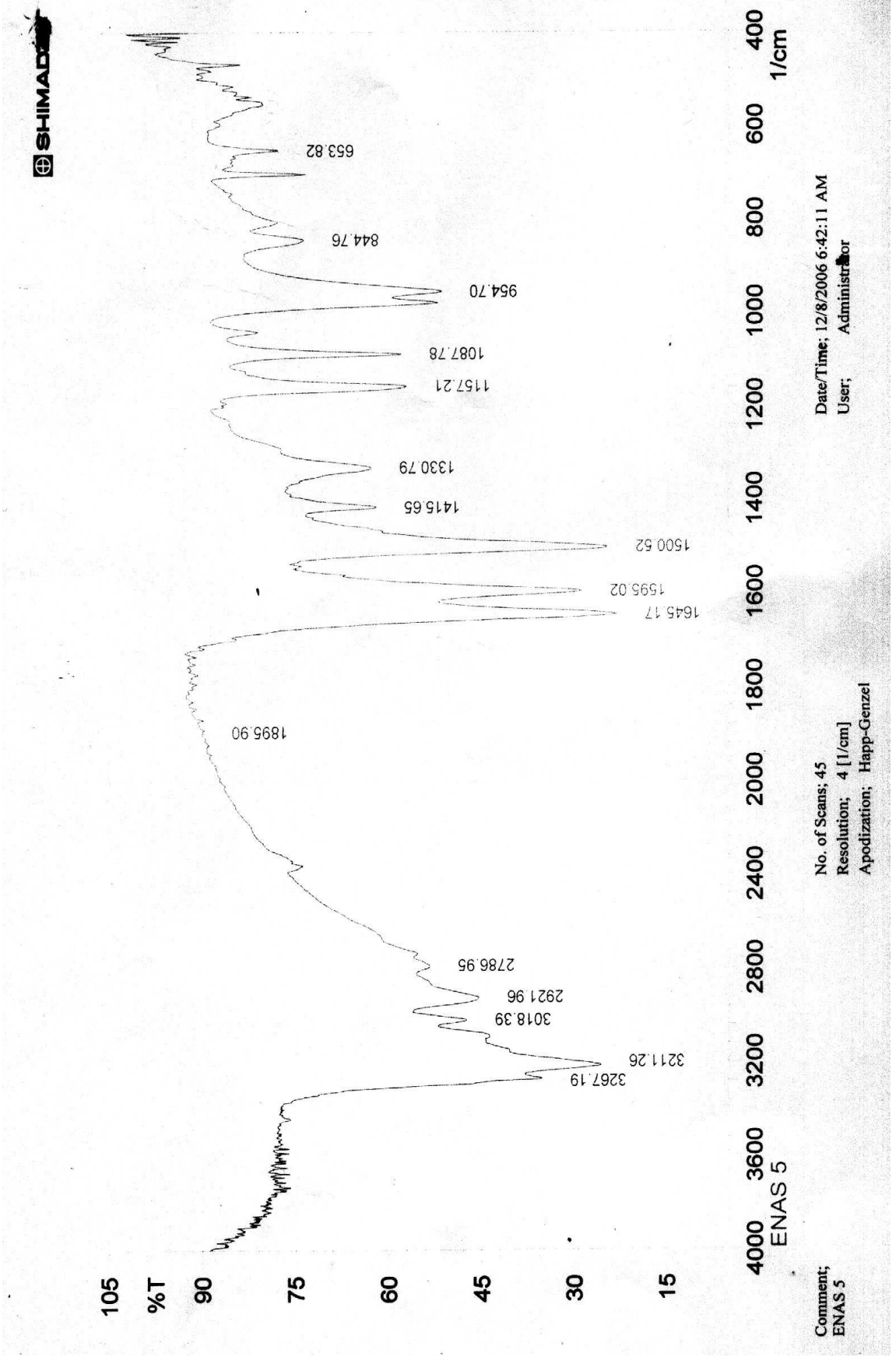



**Figure (3-10): F.T.IR spectrum of 2-(4-N,N-dimethylamino benzylidene) hydrazine-6-methyl pyrimidine-4-(3H) one.**

## *3.9 Results of the biological activity:*

Pathogenic microorganisms cause different kinds of diseases to human and animals .Discovery of chemotherapeutic agents played a very important role in controlling and preventing such diseases. chemotherapeutic agents are isolated either form living organisms known as antibiotics like penicillin and tetracycline……etc, or they are chemical compounds prepared by chemists such the sulpha drugs…..etc[(90)].

From different studies and researchers ,it was found that nitrogen bases derivatives have serious effect on Gram negative and Gram positive bacteria and fungi. pharmalogically, most of active medium are amines[(91)].

In this research, several pyrimidine compounds were prepared as derivatives of nitrogen bases and have various groups:-

Amine group,-SH group, hydrazine derivatives groups and non-homogeneous ring groups.

The studies indicate to great variation to non-homogeneous ring groups as anti- microorganisms. Amino group were used as antibiotics for a long time to eliminate bacterial pollution especially in hospital.

In this study, two bacteria species isolated form different diseases cases in either Gram positive and Gram negative and considering that one of the Gram negative type, It high resistant to many antibiotics. Gram and reproduction process were made, and these bacteria are:

*Escherichia coli* and *Staphylococcus aureus*

DMSO was used as a solvent by using Kirby-Bauer[(78)] method in calculating the inhibition or fatal effect for the compounds by measuring the surrounding area of the discs which had no growth of bacteria. The compounds show positive results as antibacterial for separators used in the test.

## *3.10 Inhibition ability of pyrimidine compounds for Staphylococcus aureus:*

The prepared compounds shows a various abilities of inhibition to Staphylococcus aureus as shown in Table (3-11) Fig(3-11), (3-12), (3-13). Compounds (5,9,10) shows high activities on this bacteria at (500µg/Disc). Inhibition zone for these compounds between (35-48) mm. Compound (5,9,10) shows high activity at (250µg/Disc) and the diameter of inhibition zones was (15-38) mm. compound (9,10) shows highest activity at (100µg/Disc) and the diameter of inhibition zone was (15-30) mm. While the compound (1, 2, 3, 4, 6, 7 and 8) shows various activity at (500µg/Disc) and the inhibition zones for these compounds between (14-22) m. In general, all compounds showed high inhibition ability in higher concentrations than in low concentration.

### *3.10.1 Inhibition ability of pyrimidine compounds for Escherichia coli:*

The examined bacteria was *E. coli*; In *E. coli* compounds (5,9,10) as shown in Table (3-12) Figures (3-14), (3-15), (3-16) shows highest inhibition at(500µg/disc) where inhibition radius rate was (40-20) mm.

The compounds (1, 2, 3, 4, 7 and 8) showed lowest inhibition at highest concentration and the inhibition zone for these compounds was (10-14) mm. Compounds (4,6) did not show any activity towards these bacteria. Generally, all prepared compounds have no inhibition affection on Gram negative bacteria in low concentration (100, 10 µg/disc) except compound number (9) where inhibition zones was (10 mm) in concentration (100 µg/disc).

In comparing the results, it is concluded that the affection of chemical prepared compounds on two Types bacteria, the affection was high on gram positive *S. aureus* and moderate on *E. coli.*

Gram negative bacteria is known by its resistance for many chemical compounds [92]. Those gram negative bacteria, especially *E. coli* have the ability to resist heavy elements and antisepticim. It is concluded that many bacteria resist heavy materials. Also the resistance of any bacterial species to chemical materials is because [93], of resistance resulted form mutation or plasma for in existence of suitable transporter of these compounds and consequently inability to reach their target in the cell or because of cell membrane thickness because it contains high concentration of fats [94], gram negative has three distigtive layer; cytoplasmic membrane, peptidglycon layer and external membrane [95], In general, *E. coli* had multi resistance for chemical compounds and was registered in many studies as it has defensive factors and its resistance reflects the risk of these separators in making infection and leading to difficulty in treatment[96, 97].

Several diseases caused by microorganisms were the cause to prepare chemicals to resist these creatures in many mechanisms[98] such as:

1) Destroying cellular membrane; or prevention to made it.
2) Failure in absorbency of cytoplasmic membrane.
3) Failure in cellular enzyme activity.
4) Stop protein and nucleic acids production, in addition to failure in chemical and physical compositions.

From the above discussion it is explained that prepared pyrimidine compounds have good activity and inhibition towards bacteria species used. This property is due to the following reasons:

1) Catching characteristics of pyrimidine compounds which makes it able to create consistent complexes with mineral ions in bacteria's cell body such as potassium, calcium and iron where tiny creatures are needed, where these elements are deprived from necessary elements and then fail leading to fatality.

2) Ability to inhibit DNA creation in sensitive bacteria cells by its ability to inhibit DNA polymerase.

3) Ability to make hydrogen bond (NH or OH) in prepared compounds and water molecules in bacteria cells, that causes failure of biological activities of the cell and destroy it.

**Table (3-11): The effect of pyrimidine derivatives on (*Staph. aureus*) grown on nutrient agar at (37°C) measured in (mm).**

| Compound no | (500µg/disc) | (250µg/disc) | (100µg/disc) | (10µg/disc) |
|---|---|---|---|---|
| 1 | 14 | 8 | - | - |
| 2 | 18 | 10 | - | - |
| 3 | 16 | 8 | - | - |
| 4 | 14 | 10 | - | - |
| 5 | 45 | 15 | - | - |
| 6 | 15 | 8 | - | - |
| 7 | 16 | 8.5 | - | - |
| 8 | 22 | 10 | - | - |
| 9 | 48 | 38 | 30 | - |
| 10 | 35 | 25 | 15 | - |

**Table (3-12): The effect of pyrimidine derivatives on (*E. Coli.*) grown on nutrient agar at (37$^{o}$C) measured in (mm).**

| Compound no | (500µg/disc) | (250µg/disc) | (100µg/disc) | (10µg/disc) |
|---|---|---|---|---|
| 1 | 12 | 8 | - | - |
| 2 | 14 | 8 | - | - |
| 3 | 13 | - | - | - |
| 4 | - | - | - | - |
| 5 | 20 | 10 | - | - |
| 6 | - | - | - | - |
| 7 | 10 | - | - | - |
| 8 | 14 | 8 | - | - |
| 9 | 40 | 30 | 10 | - |
| 10 | 23 | 13 | - | - |

**Figure (3-11): Inhibited *Staphylococcus aureus* by different concentrations of 2-(2,4)-dinitrophenyl hydrazine-6-methyl pyrimidine-4-(3H) one.**

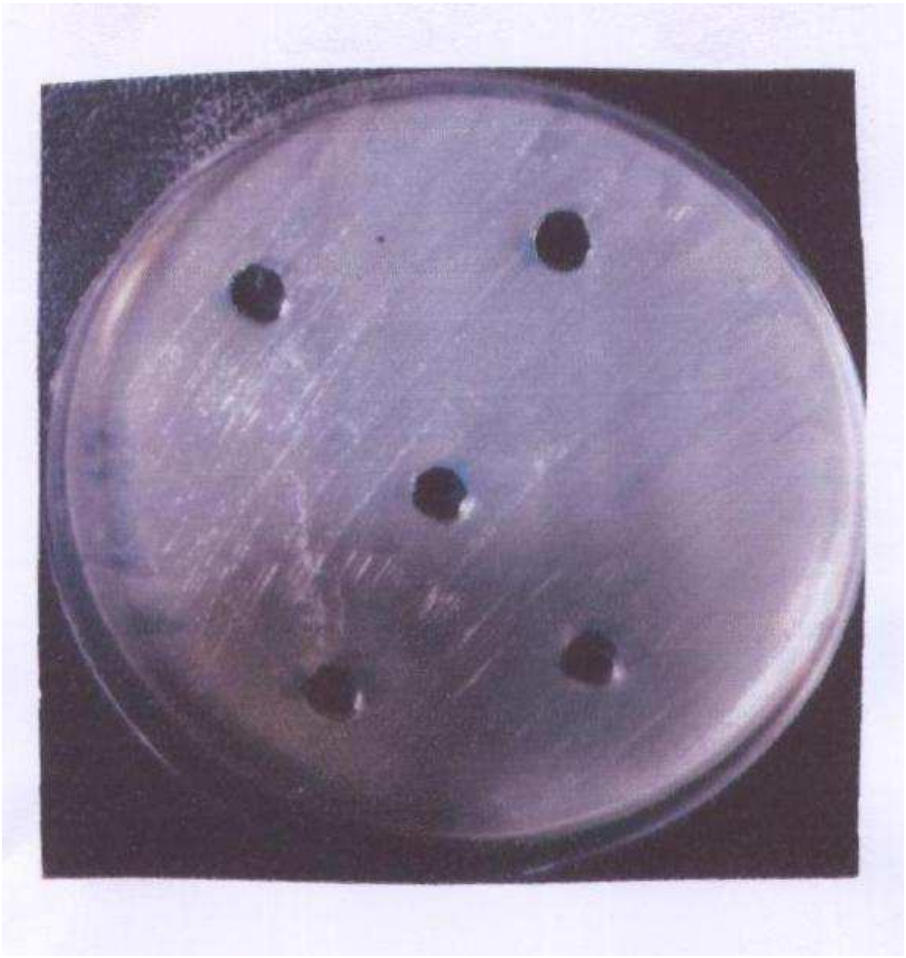


**Figure (3-12): Inhibited *Staphylococcus aureus* by different concentrations of 2-(4-N,N-dimethylamino benzylidene)hydrazine-6-methyl pyrimidine-4-(3H) one.**

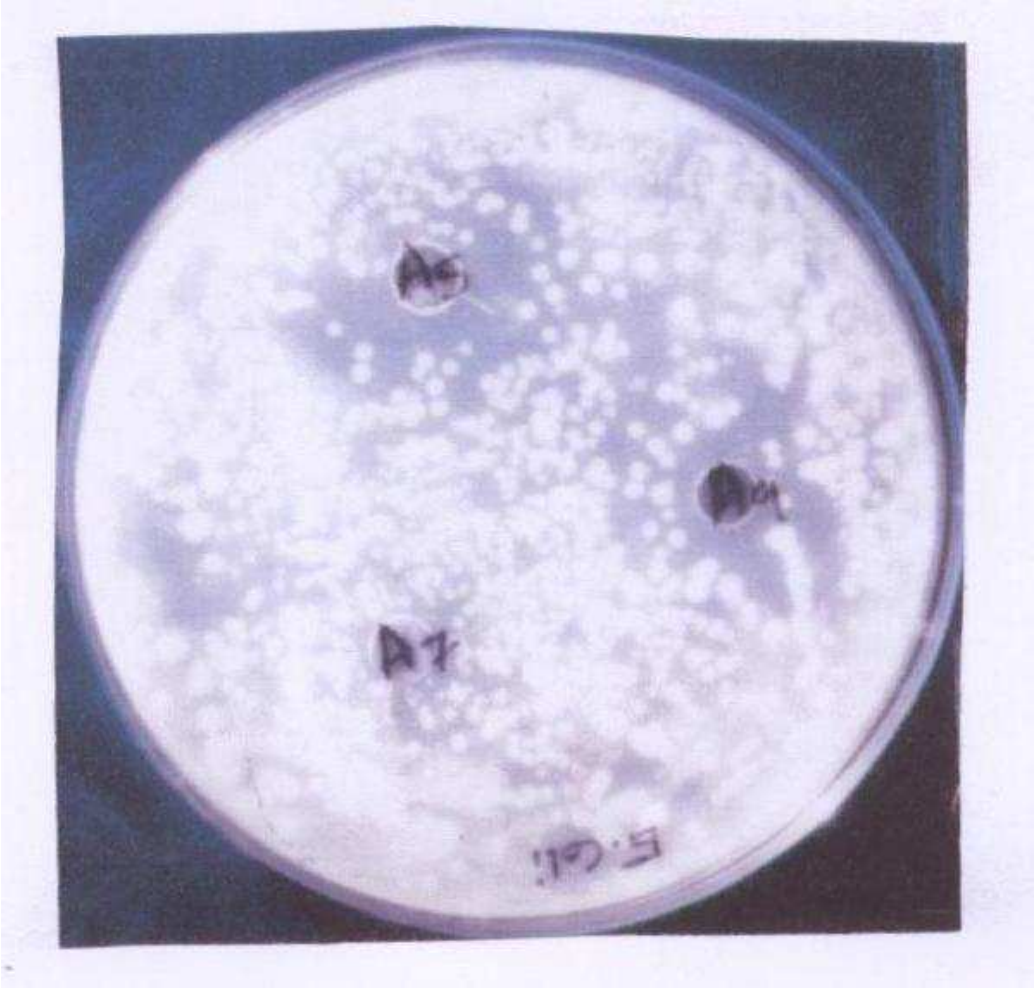



**Figure (3-13): Inhibited *Esherichia coli* by different concentrations of 2-(2,4)-dinitrophenyl hydrazine-6-methyl pyrimidine-4-(3H) one.**

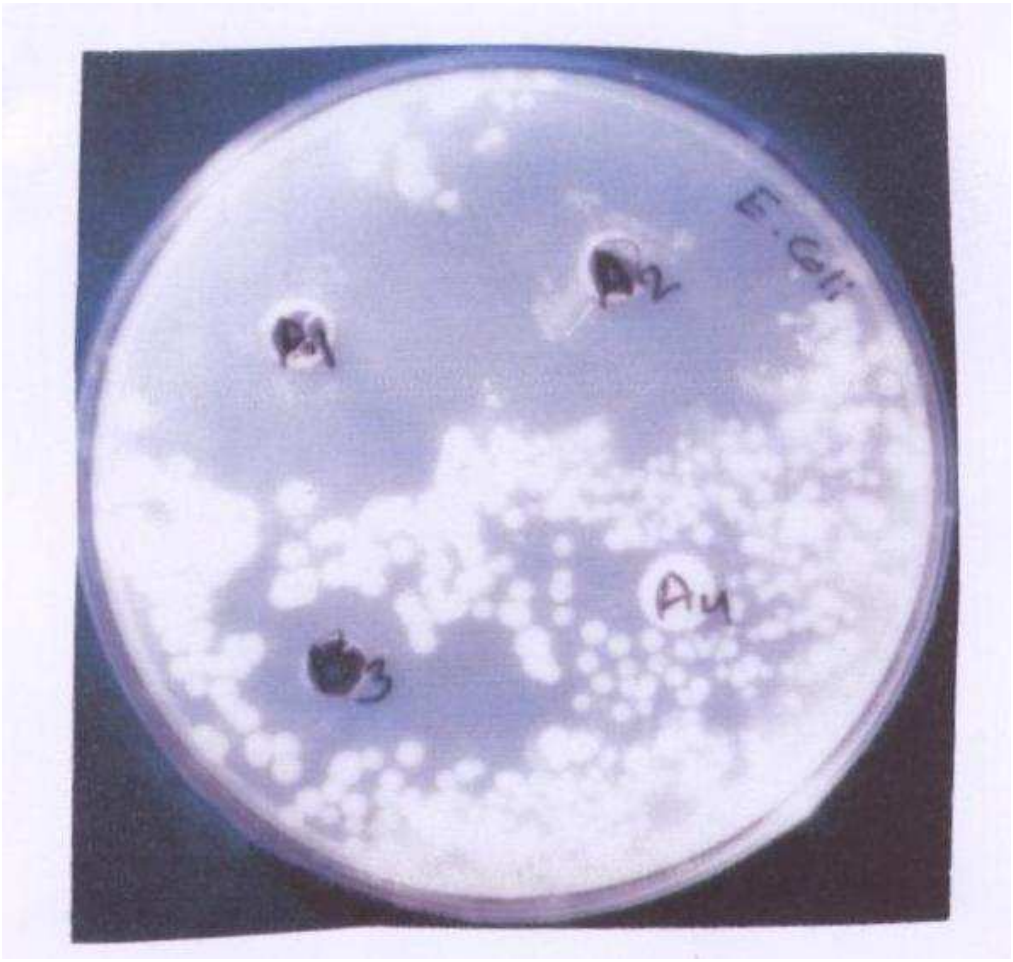



**Figure (3-14): Inhibited *Esherichia coli* by different concentrations of 6-(4-hydroxy benzylidene)-6-amino-1,3-dimethyl uracil.**

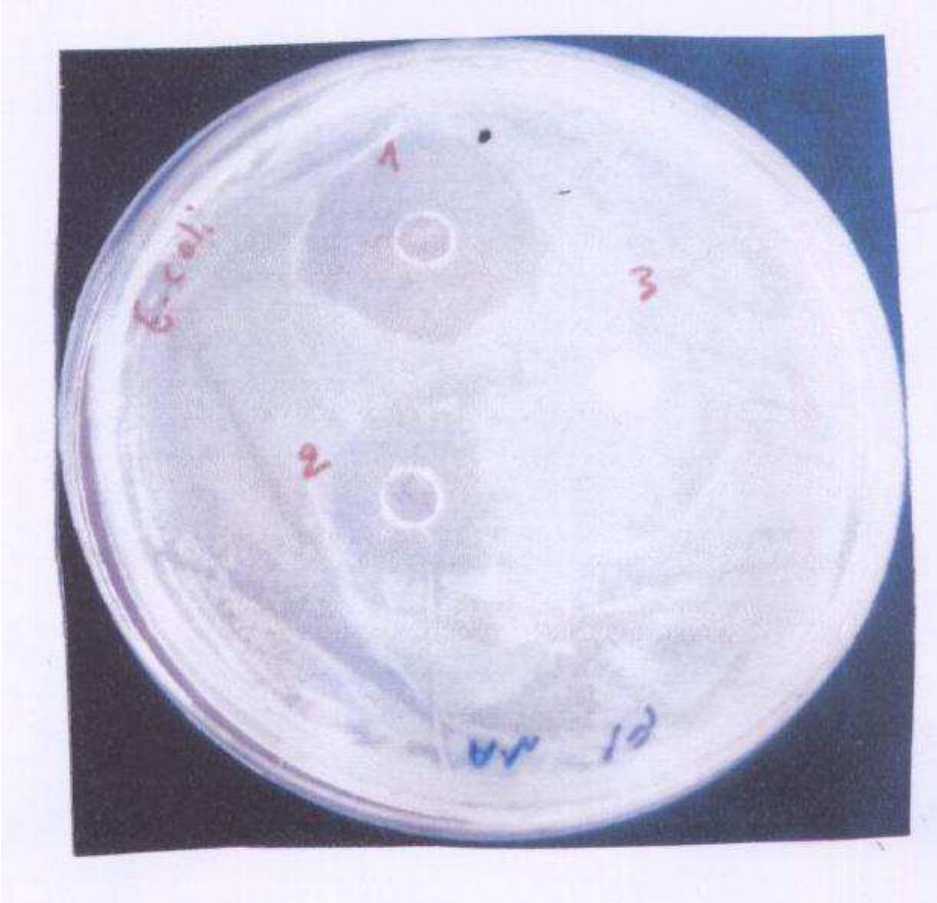



**Figure (3-15): Inhibited *Esherichia coli* by different concentrations of 2-(4-N,N-dimethylamino benzylidene)hydrazine-6-methyl pyrimidine-4-(3H) one.**

## *3.11 Conclusion and Recommendations:*

### *First: Conclusions:*

From the gained results of the current study, we can conclude the following:

1) Most of the pyrimidine compounds have, as derivatives for the nitrogen bases, a biological activity antibacterial, which differ by the difference of their concentrations.

2) The prepared compounds had a large effect on the gram positive bacteria (***Staphylococcus aureus***) by comparison with (***E. coli***) under studied.

Gram negative bacteria (***Esherichia coli***) was the most resistible for the prepared compounds form other species studied.

***Second: Recommendations:***

1) Studying the possibility of using the organic prepared compounds in creating coordinated complexes with several kinds of metallic ions.

2) Continuing studies on these active compounds with different attach group to studying the effect of these groups on the compounds activity.

3) Studying the biological effects of these compounds on different kinds of fungal, or viruses and the ability of improving this study to show its cytotoxicity and mutagenicity carcinogenic and if it succeed it can be used as medical compounds in the future.

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تاريخ المناقشة : ١٠ \ ٦ \ ٢٠٠٧
اسم الأطروحة : تحضير عدد من مشتقات البريميدينات ودراسة فعاليتها البايلوجية
المواليد: ١٩٨٣
رقم الهاتف : ٠٧٩٠٣٧٧٩٠٧٠
الاميل : لا يوجد
العنوان : بغداد \ حي الجهاد \ م ٨٩٥ \ ز ١٧ \ د ٢٨
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التحصيل الدراسي : بكالوريوس ٢٠٠٤ \ ماجستير ٢٠٠٧

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# SYNTHESIS OF SOME PYRIMIDINE DERIVATIVES AND STUDY THEIR ANTIBACTERIAL ACTIVITY

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*
*Enass Abdul Kareem*
*(B.Sc 2004)*

*April 2007*
*Rabee Alawel 1428*


جمهورية العراق

وزارة التعليم العالي والبحث العلمي

جامعة النهرين

كلية العلوم

قسم الكيمياء


# تحضير عدد من مشتقات البريميدينات ودراسة فعاليتها البايلوجية

رسالة

مقدمة إلى كلية العلوم- جامعة النهرين

وهي جزء من متطلبات نيل درجة الماجستير في الكيمياء


من قبل

**إيناس عبد الكريم حازم**

بكالوريوس ٢٠٠٤ (جامعة النهرين)

ربيع الأول١٤٢٨ نيسان٢٠٠٧

## *Supervisor certification*

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

**Signature:**

**Name: Assis. Prof. Dr. Salman Ali Ahmed**

**Date:**

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

**Signature:**

**Assistant Professor**

**Dr. Afaf Al-Durzi**

**Head of the Department of Chemistry 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 ***Enass Abdul Kareem***, in its contents and that, in our opinion; it is adequate as a thesis for the Degree of Master of Science, in Chemistry.

**Signature:**

**Name:**
**(Chairman).**

**Signature:**

**Name:**
**(Member)**

**Signature:**

**Name:**
**(Member)**

**Signature:**

**Name:**
**(Member\advisor)**

**Signature:**

**Name:**
**(Member\advisor)**

Approved for the College of Graduate Studies

**Assistant Professor**

**Dr. Laith Abd Al-Aziz**

**Dean of College of**

**Science Al-Nahrain**
**University**

بِسْمِ اللهِ الرحْمن الرحِيم

﴿وما أُوتِيتمْ مِنْ العِلمِ إلا قَلِيلاً﴾

﴿صَدَقَ اللهُ العَظِيمْ﴾

سورة الإسراء الآية (٨٥)

# الإهداء

إلى روح أبي وأخي ..... اللذين تمنيتهما معي في هذه اللحظة

إلى من يرى الناس جهودها...

أمي

إلى نبع الأخوة ورفقة الطفولة...

أخواني وأخواتي

إلى كل من بذل جهداً لمساعدتي... عرفاناً بالجميل...

عماتي وأعمامي

إلى صديقتي العزيزة ...

أطياف

الى ابن عمتي العزيز أحمد غازي المالكي

إلى كل من ساعدني في إخراج هذا البحث المتواضع...

زملائي وأحبابي

أيناس العبودي

## *Acknowledgement*

*Thank god who granted me love of science and helped me to overcome the obstacles and paved the way for me to acquire more knowledge and peace be upon the prophet Mohammad and His good Family and Companions.*

*As I am finishing this humble work I would like to be honored to thank the kind supervisor Dr. Salman Ali Ahmed because he was generous enough to provide me with his great supportive and scientific advice to accomplish this thesis.*

*Sincere thanks to the Department of Chemistry College of Science Al-Nahrain University and to the staff of the department.*

*Thanks to the Department of Biotechnology College of Science Al-Nahrain University.*

*Special thanks to Mr. Mustafa Katan Al-Maliki for the printing of this thesis.*

*Finally I would like to express my great gratitude for those who are dearest to my hearts my mother, my brothers, my friend Ateaf Sadaa for helping me and encouraging me, my whole life to all people who helped me in this research.*

*2007* *ENASS*

## *Abstract*

The current study involves the preparation of pyrimidine derivatives from reaction of thiopyrimidine with different compounds of hydrazine hydrate derivatives, amines and with ethylaceto acetate as in compounds:

1) 6-methyl-4-oxo-1,2,3,4-tetrahydro-2-thiopyrimidine.

2) 2-hydrazino-6-methylpyrimidine-4-(3H) one.

3)6-methyl-2-(3-methyl-5-oxo-4,5-dihyro-1-H-pyrazol-1-yl)-pyrimidine-4-(H) one.

4) 2-phenylhydrazino-6-methylpyrimidine-4-(3H) one.

5) 2-(2,4)-dinitrophenylhydrazino-6-methylpyrimidine-4-(3H) one.

6) 2-diphenylamine-6-methylpyrimidine-4-(3H) one.

7) 2-(diphenylamine) amino-6-methylpyrimidine-4-(3H) one.

And preparation of three compounds considered as Schiff bases that were prepared from reaction of pyrimidine derivatives with aromatic aldehydes as in the compounds:

8) 6-(4-N,N-dimethylamine benzylidene)-6-amino-1,3-dimethyl uracil.

9) 6-(4-hydroxy benzylidene)-6-amino-1,3-dimethyl uracil.

10)2-(4-N,N-dimethylaminobenzylidene)hydrazine-6-methyl-pyrimidine-4-(3H) one.

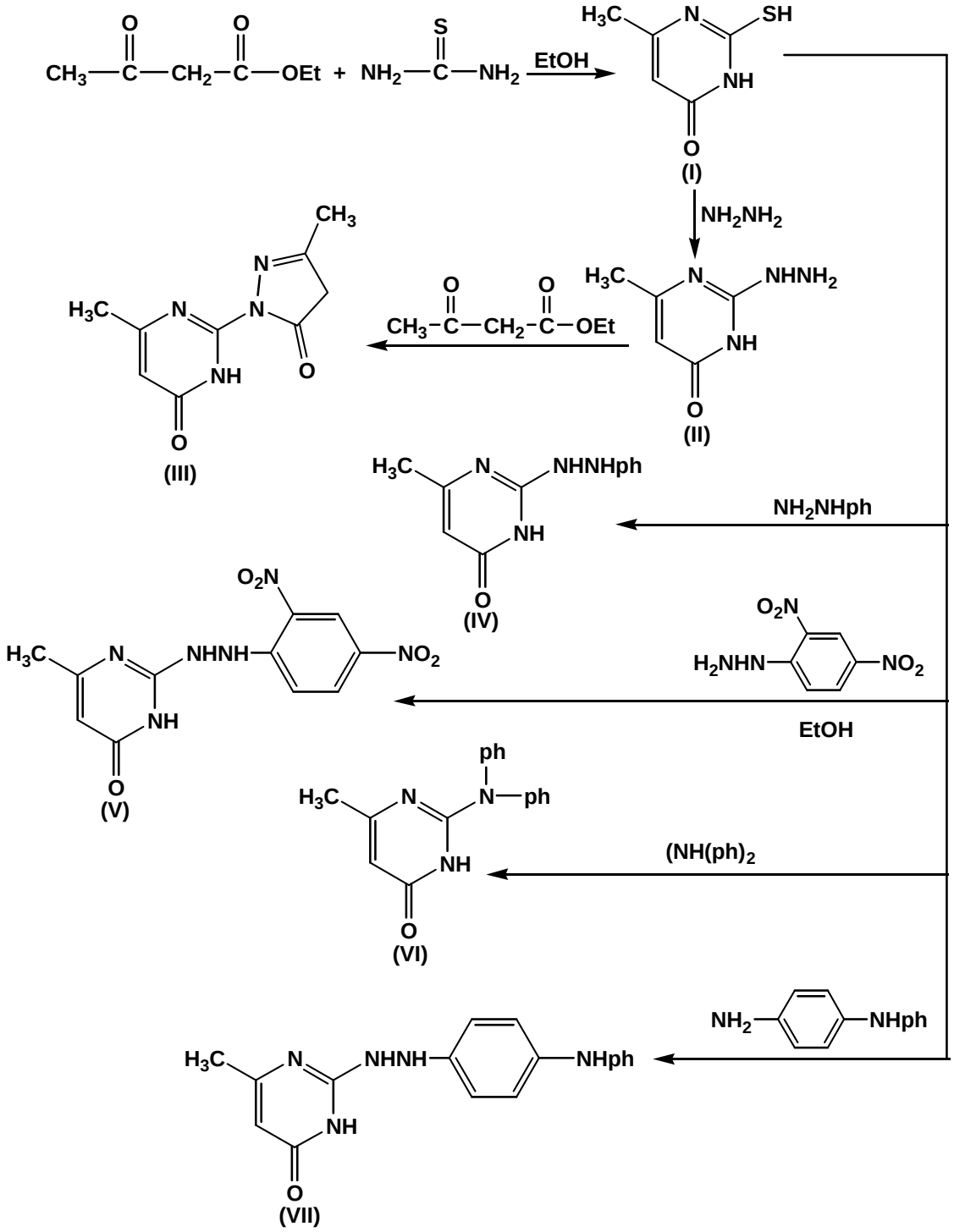
The identification of the prepared compounds was done using spectroscopy (F.T.IR) and melting points for these compounds were determined.

Antibacterial activity of the prepared compounds was done by using disc diffusion method on nutrient agar plate using two types of bacteria strains.

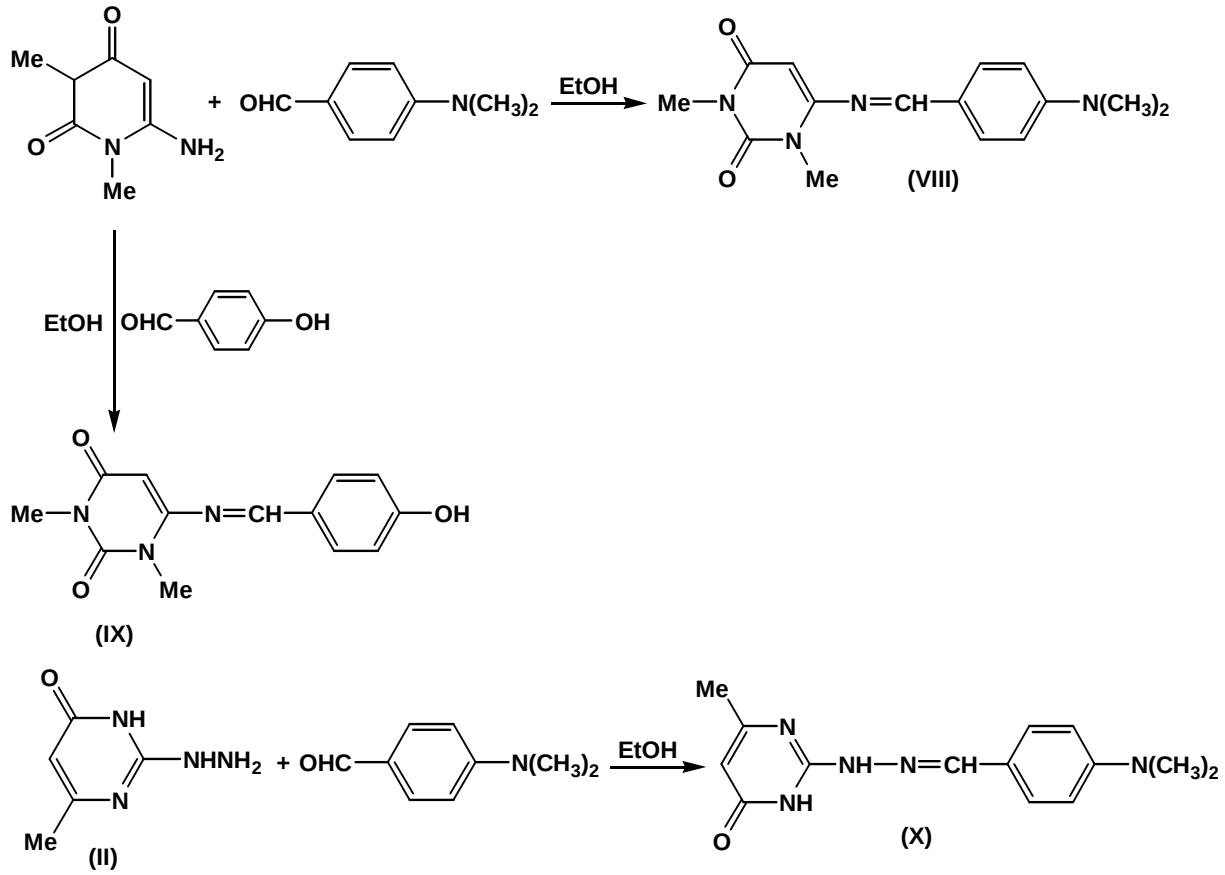
1) *Staphylococcus aureus.*

2) *Escherichia coli.*

Bacterial growth was carried out at ($37^{o}$C), some of the prepared compounds show high ability to inhibit the growth of above mentioned bacteria.




Scheme (1)




Scheme (2)

## الخلاصة

تضمن هذا البحث تحضير عدد من مركبات (مشتقات البريميدينات) من تفاعل ثايوبريميدين مع مركبات مختلفة منها الهيدرازين المائي ومشتقاته، الأمينات، ومع أثيل أسيتو أسيتيت وكانت المركبات المحضرة.

1) 6-methyl-4-oxo-1,2,3,4-tetrahydro-2-thiopyrimidine.

2) 2-hydrazino-6-methylpyrimidine-4-(3H) one.

3)6-methyl-2-(3-methyl-5-oxo-4,5-dihyro-1-H-pyrazol-1-yl-pyrimidine-4-(H) one.

4) 2-phenylhydrazino-6-methylpyrimidine-4-(3H) one.

5) 2-(2,4)-dinitrophenylhydrazino-6-methylpyrimidine-4-(3H) one.

6) 2-diphenylamine-6-methylpyrimidine-4-(3H) one.

7) 2-(diphenylamine)amino-6-methylpyrimidine-4-(3H) one.

بالإضافة إلى تحضير ثلاث مركبات تعتبر من قواعد شف التي حُضِرتْ من تفاعل (pyrimidine derivative) مع الديهايدات حلقية كما في المركبات:

8) 4-(4-N,N-dimethylamine benzylidene)-6-amino-1,3-dimethyl uracil.

9) 4(4-hydroxy benzylidene(-6-amino-1,3-dimethyl uracil.

10)2-(4-N,N-dimethylaminobenzylidene)hydrazine-6-methyl-pyrimidine-4-(3H) one.

تم تشخيص المركبات المحضرة بواسطة الطريقة الطيفية (طيف الأشعة تحت الحمراء F.T.IR) وتم قياس درجة الأنصهار لهذه المركبات المحضرة.

ولبيان الفعالية البايلوجية للمركبات المحضرة أُجريَ أختبار على نوعين من البكتريا وهي

1) *Staphylococcus aureus*.

2) *Escherichia coli*

أستخدمت طريقة الإنتشار حول القرص على الأطباق وسط الأكار، أُجريت.

عمليات تنمية وتكاثر البكتريا في درجة حرارة معينة وأعطت هذه الأختبارات نتائج أولية جيدة ومشجعة للعمل المستقبل.

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## *Abbreviations*

| Number | Symbol | Description |
|---|---|---|
| 1 | DNA | Deoxy ribo nucleic acid |
| 2 | RNA | Ribo nucleic acid |
| 3 | DMSO | Dimethyl sulfoxide |
| 4 | ddNs | Dideoxy nucleosides |
| 5 | AIDS | Acquired Immunedeficiency Syndrome |
| 6 | ppA | Polyphosphoric acid |