

## A REVIEW ON SYNTHESIS AND BIOLOGICAL ACTIVITIES OF PYRIMIDINE DERIVATIVES

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### ABSTRACT

Pyrimidine is a heterocyclic aromatic organic compound containing two nitrogen atoms at positions 1 and 3 of the six-member ring shows wide range of biological activities. Pyrimidine can be synthesized using acetamidine and ethylacetoacetate. Pyrimidine posses wide spectrum of biological activities like including antitubercular, antibacterial, antifungal, antiviral, anti-inflammatory, Antimalarial activity, anticancer and antineoplastic activity, anti-hiv activity. The present reviews attempted to gather the various developments in synthesis and biological activities of Pyrimidine derivatives.

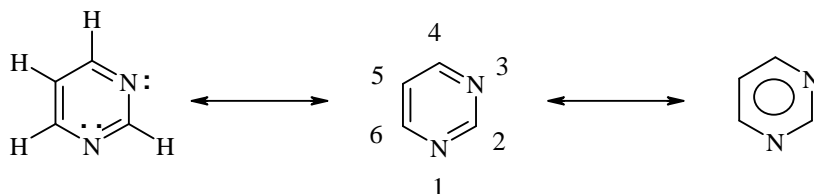
### KEYWORDS

Pyrimidine , Biological activities, Total synthesis.

## INTRODUCTION

### 1.1 Pyrimidine

Pyrimidine is a colourless compound having melting point (225<sup>0</sup>C) and boiling point (124<sup>0</sup>C).

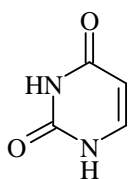


Pyrimidine is a much weaker base than pyridine and soluble in water.

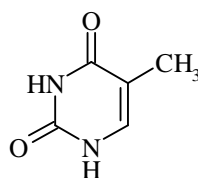
Pyrimidine is a heterocyclic aromatic organic compound containing two nitrogen atoms at positions 1 and 3 of the six-member ring.

### 1.2 Pyrimidine as Biological Importance

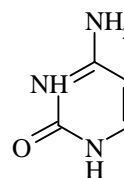
Pyrimidines and its derivatives are integral part of DNA and RNA, it has found to be associated with diverse biological activities.



Uracil



Thymine



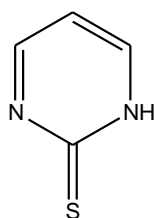
Cytosine

The substituted pyrimidines are complex molecules because of nature substituents. Uracil and Thymine may be considered to contain neutral urea unit or acidic imide moiety. Thymine is also referred as 5-methyluracil.

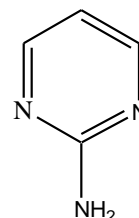
The metabolism of these pyrimidines are unique and important to understand both biochemical utilization of these compounds and drug metabolism of pyrimidine derivatives. Uracil is converted into a useful uridylic acid needed for the synthesis of RNA. Thymine is metabolized by conjugation via salvage pathway with PRPP to the thymine ribosyl-5-phosphate. This form of thymidylic acid can be utilized in

specific RNA molecule. In a similar manner Cytosine is conjugated with PRPP to yield cytosine-5-monophosphate or cytidylic acid. Pyrimidine is the most important member of all the diazines as this ring system occurs widely in living organisms.<sup>1-5</sup>

Pyrimidine and its derivatives have gained prominence because of their potential pharmaceutical values. Many pyrimidine derivatives play vital role in many physiological actions. They are among those molecules that make life possible as being some of the building blocks of DNA and RNA.

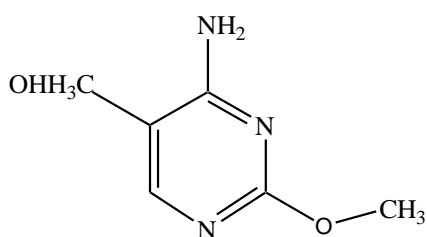


Pyrimidine is considered to be a resonance hybrid of the charged and uncharged canonical structures, its resonance energy has been found to be less than benzene or pyridine. The naturally occurring pyrimidine derivative was first isolated by Gabriel and Colman in



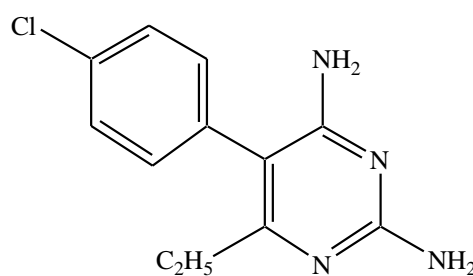
1870, and its structure was confirmed in 1953 as 5-β-D-gluco-pyranoside of divicine.

Some pyrimidines of physiologically as well as pharmacologically importance are as under: e.g., cytosine, bedmethrin (I) and trimethoprim (II).



(I)

Pyrimidine is considered to be a resonance hybrid of the charged and uncharged canonical structures; its resonance energy has been found to be less than benzene or pyridine.<sup>(6-9)</sup>



(II)

### 1.3 Pharmacologically Active Pyrimidines

Pyrimidines and their derivatives are considered to be important for drugs and agricultural chemicals. The use of pyrimidines is critical to successful treatment of various diseases.

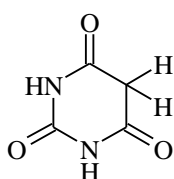
Pyrimidine derivatives possess several interesting biological activities such as antimicrobial, antitumour, and antifungal activities. Many pyrimidine derivatives are used for thyroid drugs and leukaemia. Although there are numerous class of drugs that are routinely used to treat the diseases in humans, there are major four subcategories that contain pyrimidine base structure.

- Barbiturates
- Nitropyrimidines

- Pyrimidinediones
- Pyrimidones

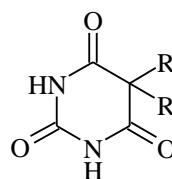
### 1.3.1 Barbiturates

The substituted barbiturates represent a special class of compounds which have been used for sedative hypnotic action. They are depressants of the central nervous system (CNS) that impair or reduce the activity of the brain by acting as Gamma Amino Butyric Acid (GABA) potentiators.



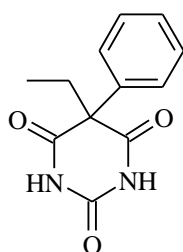
**Barbituric acid**

Phenobarbital (I) is most commonly used as anticonvulsant. It also have sedative and hypnotic action. Methohexital (II) is a short-acting, and has a rapid onset of action Sodium thiopental (III) is a rapid-onset short-acting

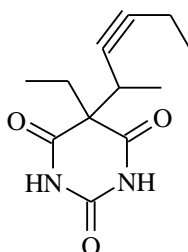


**Barbiturates**

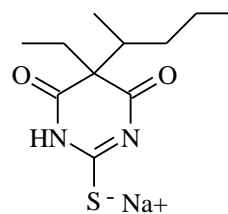
barbiturate general anaesthetic. Further substitution of side chains on the barbituric acid ring produce the pharmacologically active barbiturates.<sup>(1-3)</sup>



**Phenobarbital  
(I)**



**Methohexital  
(II)**

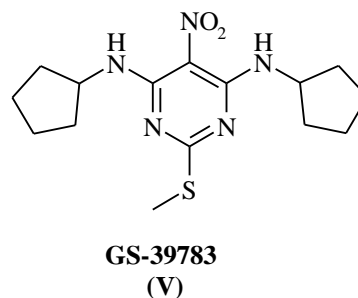
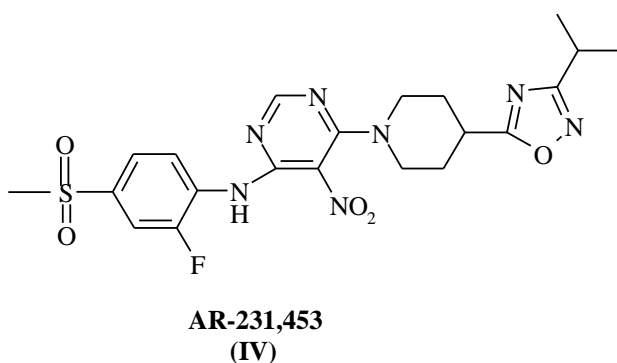


**Sodium thiopental  
(III)**

### 1.3.2 Nitropyrimidine

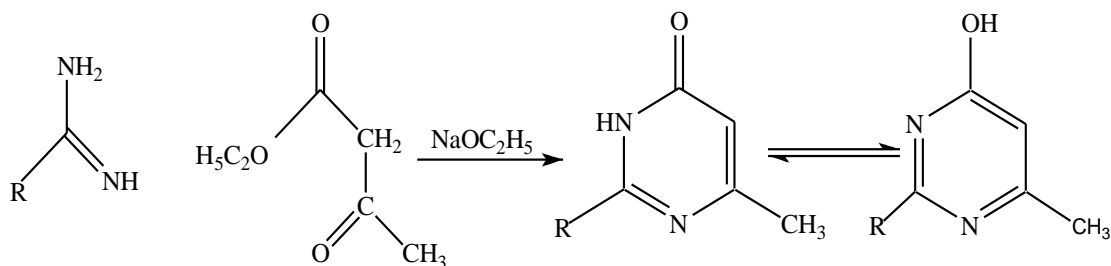
Nitropyrimidine category includes (IV) and (V). (IV) is agonist for the novel cannabinoid receptor. (V) is act as a positive allosteric

modulator at GABA<sub>B</sub> receptor. It has been shown to produce anxiolytic effects and reduce self-administration of ethanol, cocaine and nicotine<sup>(4-5)</sup>



## 2. SYNTHETIC ASPECT

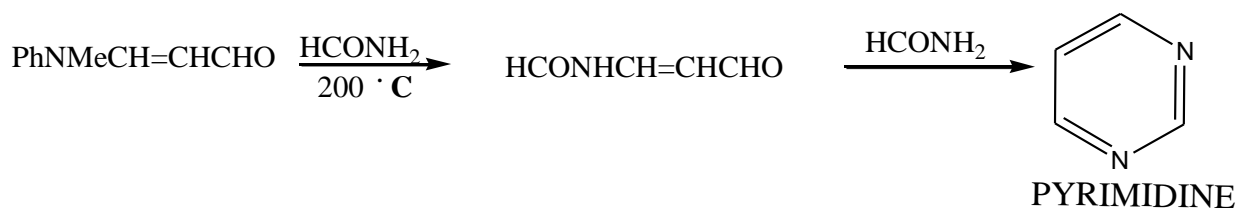
2.1 A very important general method for preparing pyrimidines is the condensation between a three carbon compounds of the type YCH<sub>2</sub>Z, where Y and Z = COR, CO<sub>2</sub>R, CN, and compounds having the amidine structure R(C=NH)NH<sub>2</sub>, where R = OH (urea), SH or SR



(thiourea or its s-derivative). The condensation is carried out in the presence of sodium hydroxide or sodium ethoxide. This general reaction may be illustrate by the condensation of acetamidine with ethylacetoacetate to form 4-hydroxy-2, 6-dimethylpyrimidine.<sup>10</sup>

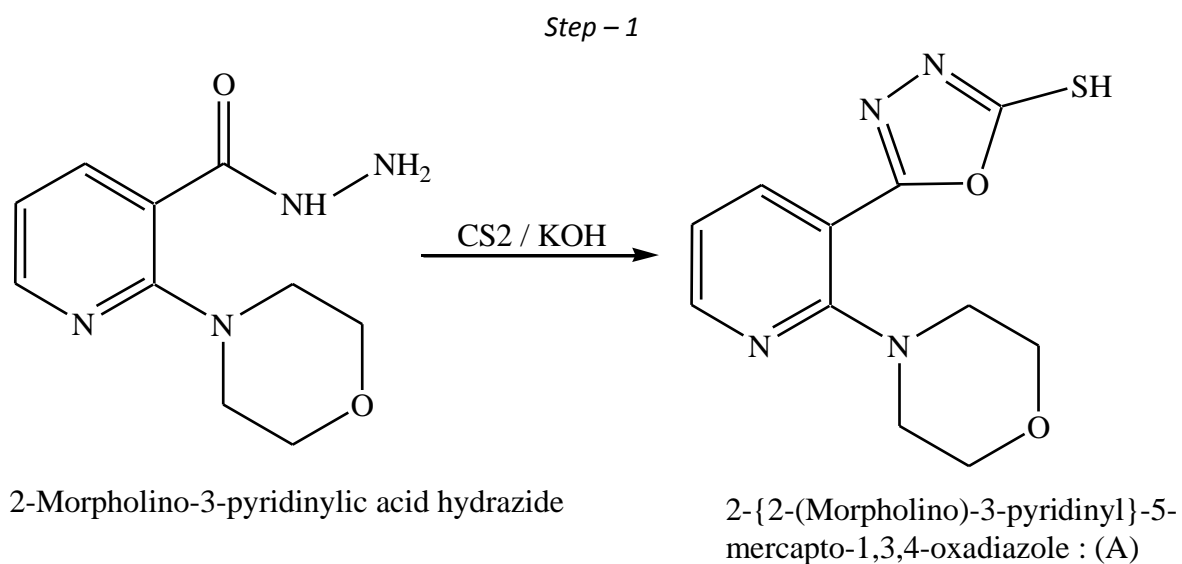
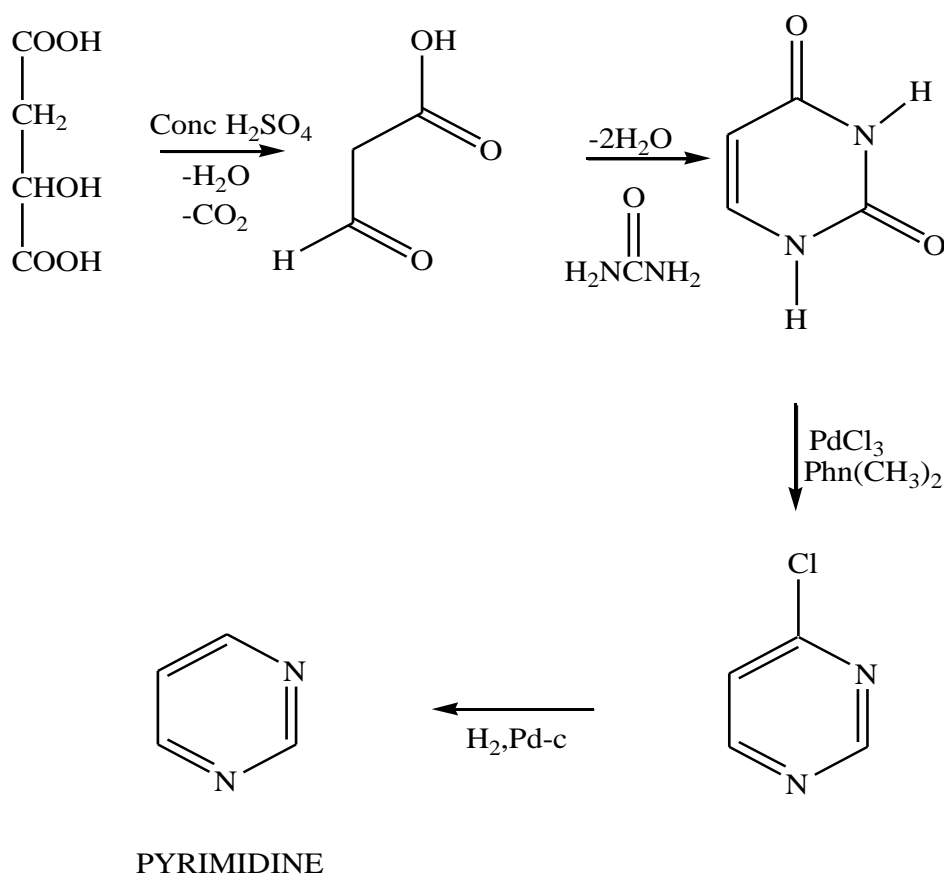
2.2 The reaction of 1,3-dicarbonyl compound or an equivalent reagent with formamide provides

a route of several pyrimidine which are unsubstituted at the 2-position<sup>11</sup>

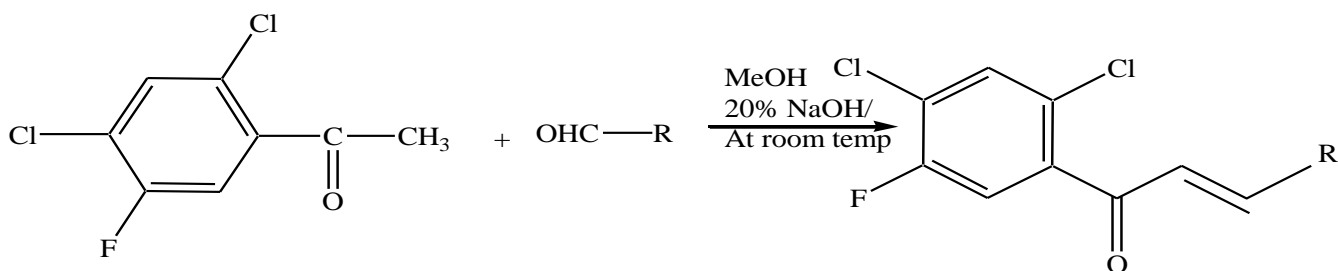


2.3. Decarboxylation of malic acid with conc. sulfuric acid and reaction of the β-ketoacid with urea/uracil can be formed. uracil can be

converted to pyrimidine in the following steps.<sup>(12)</sup>



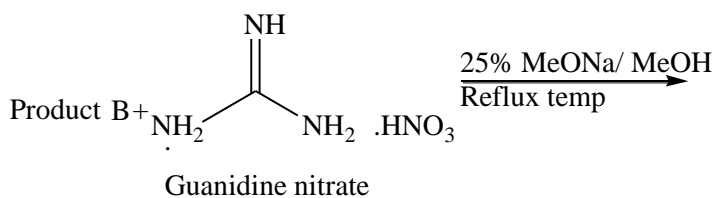
Step – 2



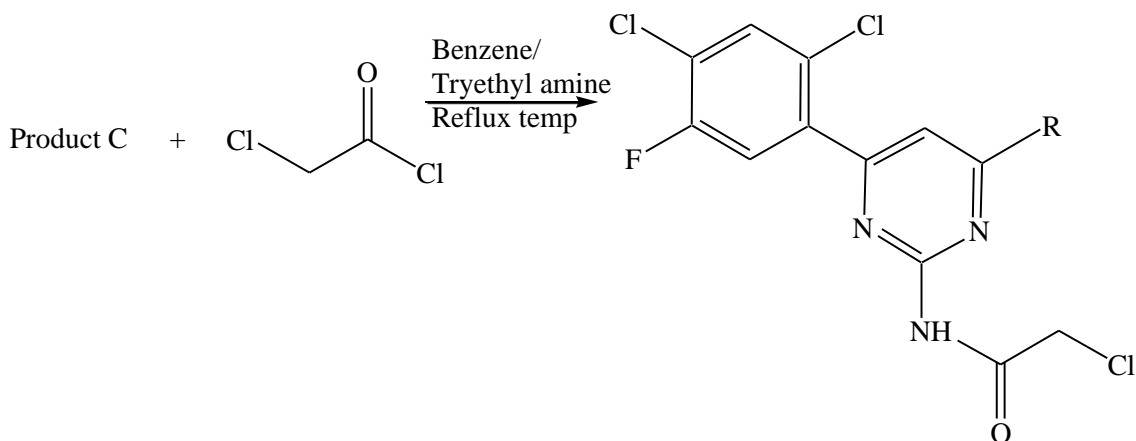
2,4-Dichloro-5-fluoro-  
acetophenone  
Step – 3

Aromatic aldehyde

1-(2,4-Dichloro-5-fluoro phenyl)-3-  
(aryl)-2-propene-1-one : (B)

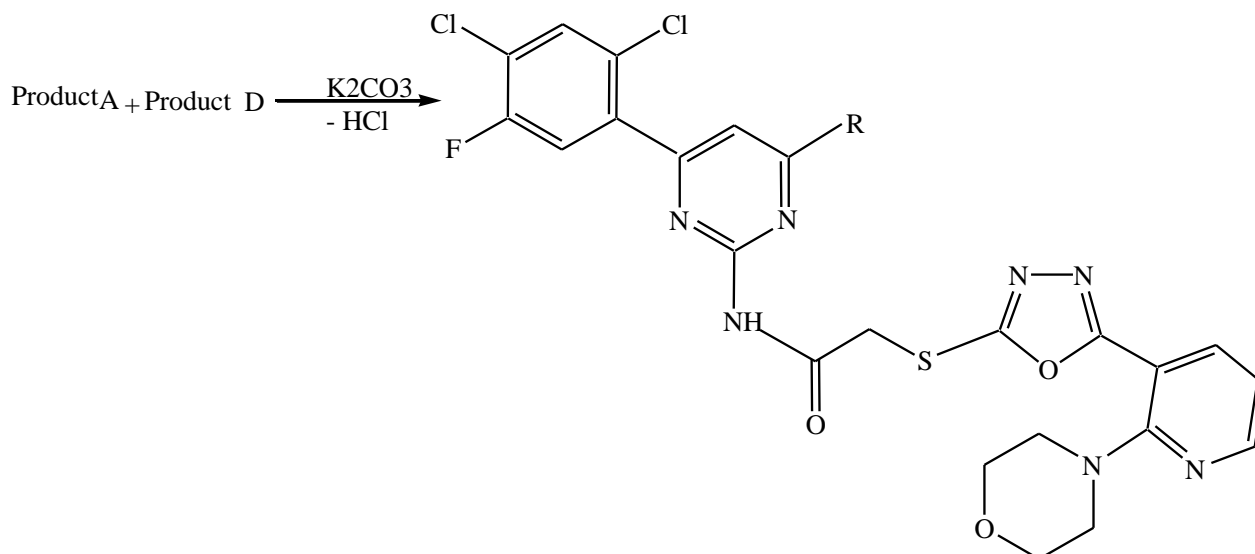


Step – 4



N-Chloro acetyl-2-amino-4-(2,4-dichloro-5-fluoro phenyl)-6-(aryl)-Pyrimidine : (D)

Step – 5



2-[[2-(Morpholino)-3-pyridinyl-5-thio}  
-2-oxoethyl oxadiazolyl]-amino-4-  
(2,4-dichloro-5-fluoro phenyl)-6-(aryl)-pyrimidines

WHERE= R

4-CH<sub>3</sub>-C<sub>6</sub>H<sub>4</sub>

4-N(CH<sub>3</sub>)<sub>2</sub>-C<sub>6</sub>H<sub>4</sub>

2-OH-C<sub>6</sub>H<sub>4</sub>

4-OH-C<sub>6</sub>H<sub>4</sub>

4-Cl-C<sub>6</sub>H<sub>4</sub>

2,4-(Cl)<sub>2</sub>-C<sub>6</sub>H<sub>3</sub>

4-F-C<sub>6</sub>H<sub>4</sub>

2-OCH<sub>3</sub>-C<sub>6</sub>H<sub>4</sub> -

4-OCH<sub>3</sub>-C<sub>6</sub>H<sub>4</sub> -

3,4,5-(OCH<sub>3</sub>)<sub>3</sub>-C<sub>6</sub>H<sub>2</sub>

TN-1

TN-2

TN-3

TN-4

TN-5

TN-6

TN-7

TN-8

TN-9

TN-10<sup>(13)</sup>

### 3. BIOLOGICAL ACTIVITY

#### 3.1. Antimicrobial Activity

The microbiological assay is based upon a comparison of inhibition of growth of microorganisms by measured concentrations of test compounds with that produced by known concentration of a standard antibiotic. Two methods generally employed are turbidometric (tube-dilution) method and cylinder plate (cup-plate) method. In the turbidometric method inhibition of growth of microbial culture in a

uniform ablation of antibiotic in a fluid medium is measured. It is compared with the synthesized compounds. Here the presence or absence of growth is measured. The cylinder plate method depends

upon diffusion of antibiotic from a vertical cylinder through a solidified agar layer in a Petridis or plate to an extent such that growth of added micro-organisms is prevented entirely in a zone around the cylinder containing solution of the antibiotics. The cup-plate method is simple and measurement of inhibition of microorganisms is also easy. Here we have used this method for antimicrobial screening of the test compounds.<sup>(14-15)</sup>

#### 3.1.1 Name of organisms: for antimicrobial activity

##### Gram +Ve microorganisms

- Staphylococcus aureus
- Bacillus subtilis

##### Gram -Ve microorganisms

- Escherichia coli

#### 3.1.2 Working standards

Stock solutions of synthesized compounds and standard drug used were prepared in methanol taken in concentration of 1000µg/ml. The further dilution was made to get concentration of 500µg/ml, 600µg/ml, 700µg/ml, 800µg/ml.

### 3.1.3 Preparation of medium

Nutrient agar : 2%  
Peptone : 1%  
Beef extract : 1%  
Sodium chloride : 0.5%  
Distilled water : up to 100ml.

All the ingredients were weighed and added to water. This solution was heated on water bath for about one and half-hour till it became clear. This nutrient media was sterilized by autoclave at 121°C for 15 minutes at 15 psi.

### 3.1.4 Apparatus

All the apparatus like Petridishes, pipettes, glass rods, test-tubes etc. were properly wrapped with papers and sterilized in hot air oven at 160°C for 3 hours.

### 3.1.5 Culture

S.aureus and B.subtilus were used as gram-positive bacteria and E.coli were used as gram negative bacteria for our study. The master culture was prepared on agar slant of the above nutrient media and kept in refrigerator. The working culture was prepared from it by weekly transferred in nutrient agar medium.

### 3.1.6 Preparation of inoculum

In the aseptic condition from the working culture, small amount of culture was transferred to about 10-15 ml of sterile normal saline (0.9% NaCl solution). This solution was gently mixed and used for the antibacterial

activity. About 0.5 ml of inoculums was added to the sterilized Petridis and melted agar cooled was added, mixed gently and allowed to solidify. Wells were bored in the agar plate by borer and solution of the compounds was filled in the bore at a constant volume. The solution was allowed to diffuse for a period 90 minutes. The Petri dishes were then incubated at 37°C for 24 hours after which zone of inhibition was measured.

### 3.1.7 Preparation of test solution

Specified quantity (100mg) of the compound was accurately weighed and dissolved in 100ml of methanol and further dilution was made to get the concentration of 50 g / ml, 100 g / ml, 500µg/ml, 600µg/ml, 700µg/ml and 800µg/ml.

### 3.1.8 Antimicrobial Screening Method

- All the petri dishes were sterilized in oven at 160°C for 1hr.
- Agar media filter discs and test solutions were sterilized in autoclave at 121°C, 15lbs/sq.inch.
- Pouring molten sterile agar in sterile Petri dishes aseptically.
- Allow to cool the agar at RT and pouring the bacterial suspension on Petri dishes aseptically.
- Placing the sterile paper discs in appropriate four quadrants of Petri dishes aseptically after soaking in the sterile test solutions.
- Incubate the petri dishes at 37°C for 24hrs and observed the zone of inhibition.<sup>(14-15)</sup>



**Table . 1** Antibacterial Activity

S.No		(Zone of inhibition in mm) at 50 g / ml concentration			
	R	<i>E.Coli</i>	<i>S.Aureus</i>	<i>S.Typhi</i>	<i>B.Subtilis</i>
<b>TN-1</b>	4-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	---	---	09	10
<b>TN-2</b>	4-N(CH <sub>3</sub> ) <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	12	11	10	08
<b>TN-3</b>	2-OH-C <sub>6</sub> H <sub>4</sub>	12	09	11	---
<b>TN-4</b>	4-OH-C <sub>6</sub> H <sub>4</sub>	10	09	---	09
<b>TN-5</b>	4-Cl-C <sub>6</sub> H <sub>4</sub>	10	13	09	10
<b>TN-6</b>	2,4-(Cl) <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>	12	13	12	09
<b>TN-7</b>	4-F-C <sub>6</sub> H <sub>4</sub>	11	11	---	---
<b>TN-8</b>	2-OCH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	10	07	09	08
<b>TN-9</b>	4-OCH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	13	12	11	10
<b>TN-10</b>	3,4,5-(OCH <sub>3</sub> ) <sub>3</sub> -C <sub>6</sub> H <sub>2</sub>	14	09	---	---
<b>Standard</b>	Tetracycline	15	19	24	21
<b>Drug</b>	Chloramphenicol	18	25	24	20

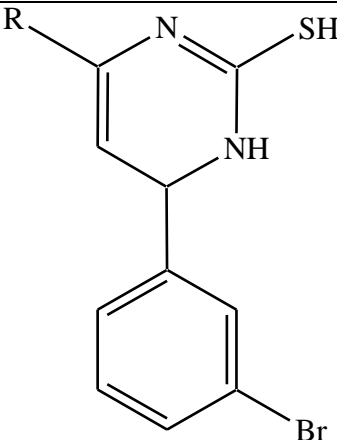
### 3.1.8 CONCLUSIONS

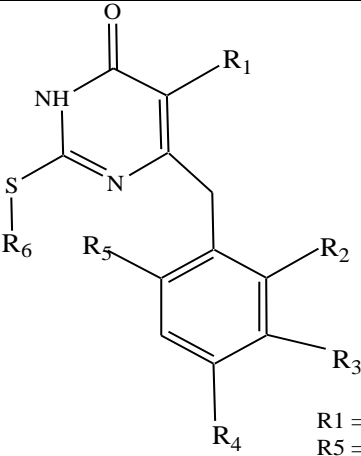
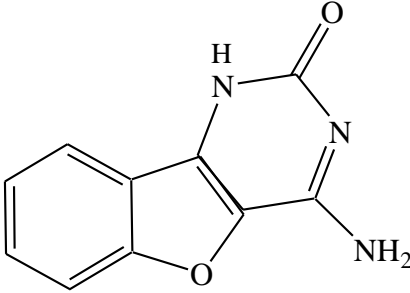
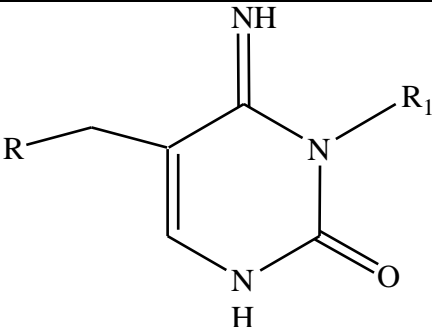
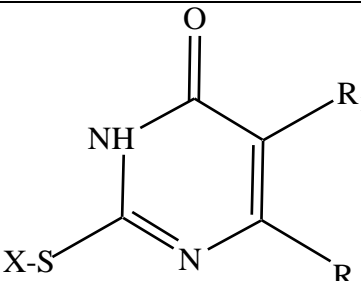
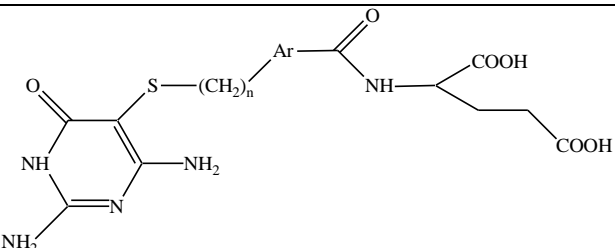
Antimicrobial screening results reveals following points. In the synthesised compounds, some compounds showed moderate to good activity against the entire microorganisms whereas some compounds were found inactive. In comparison with standard drugs compounds TN-1 & TN-10 showed maximum zone of inhibition against E-coli., S.aureus, S.typhi and B.subtilis. In detail

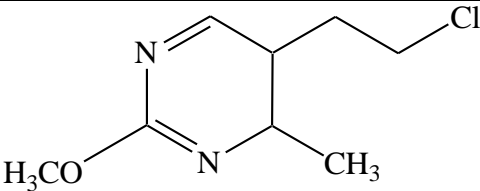
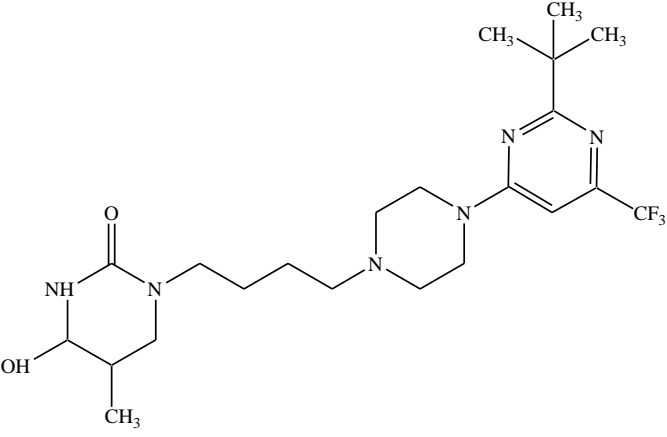
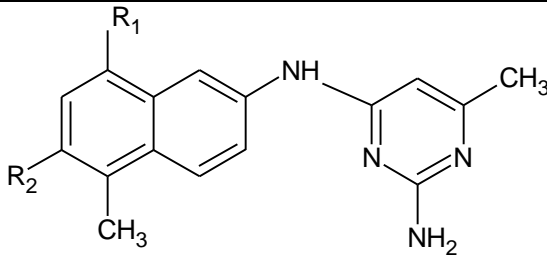
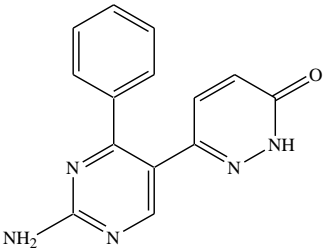
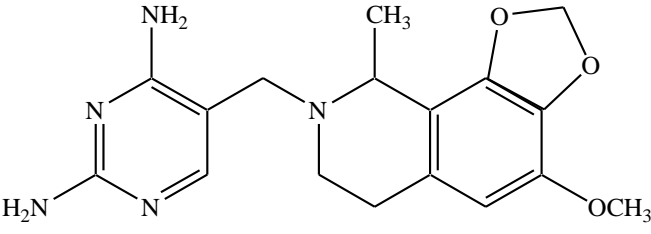
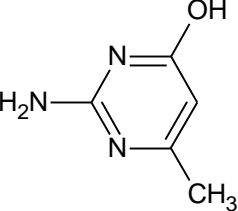
the compound TN-2 have good activity against E. coli. Compound TN-6 & TN-10 have good activity against S.Aureus while compound TN-5 & TN-7 against S.Typhi and TN-7 against B.Subtilis have found modest activity compared to the molecule is essential. Thus from above discussion it may be concluded that it is worthwhile to pursue further investigation by manipulating the above novel mercapto oxadiazole derivate.<sup>(13)</sup>

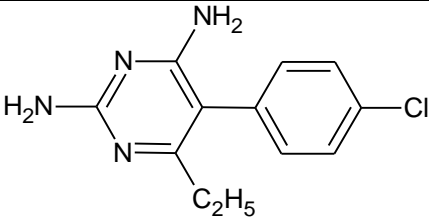
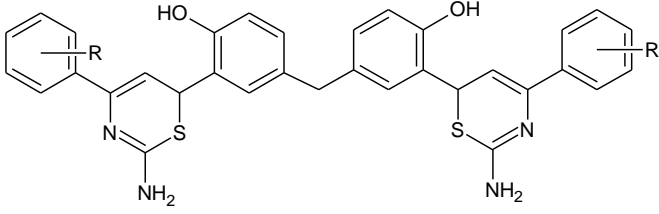
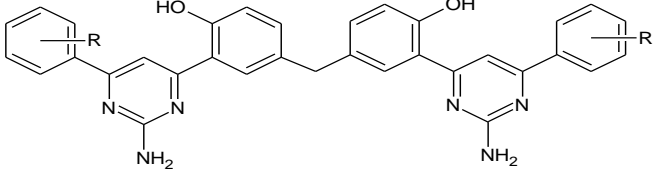
### 4. Various Pharmacological Activities Of Pyrimidines

**Table 1: Various pharmacological activities of pyrimidines**

Sr. No.	Authors	Structure	Pharmacological Activity
1	K.S.Nimavat, K. H. Popat, S. L. Vasoya and H. S. Joshi; 2003 <sup>(16)</sup>		Antitubercular and Antimicrobial agents

2	Antonello Mai, Marino Artico,Gianluca Sbardella and Paolo La Colla:1999 <sup>(17)</sup>	 <p>R1 = H, Me R 2-4 = Cl, F, NO2 R5 = H, Cl, F R6 = alkyl/cycloalkyl</p>	Anti-HIV-1 agents in both cell-based and enzyme
3	S. S. Sangopure and A.M. Mulogi; 2000 <sup>(18)</sup>		Antimicrobial activity
4	Somnath Nag, Richa pathak, Manish kumar, P. K. Shukla and Sanjay Batra;2006 <sup>(19)</sup>		Antimicrobial activity
5	Viney Lather and A. K. Madan;2005 <sup>(20)</sup>		Anti-hiv activity
6	Michael D. Varney, Clindy L. Palmer, Eleanor Howland and Rosanne:1997 <sup>(21)</sup>		Potent inhibitors of glycinamide ribonucleotide transformylase with potent cell growth inhibition

7	B. J. Ghiya and ManojPrabjavat;1992 <sup>(22)</sup>		Anticancer and antineoplastic activity
8	Herve Geneste, Gisela Backfisch, Wilfried Braje.2006 <sup>(23)</sup>		DopamineD3-receptor antagonists activity.
9	Kaplina N. V., Griner A. N., SherdorV.I.,Fomina A.N.1995 <sup>(24)</sup>		Herpes inhibiting activity
10	Tsutsumi,Hideo, Yonishi,Satoshi, 2003 <sup>(25)</sup>		Adenosine receptor antagonists
11	Pierre C. Wyss, Paul Gerber, PeterG.Hartman 2003 <sup>(26)</sup>		Dihydrofolate reductase inhibitors
12	D.T.Tayade,S.P.Dha kite and S.U.Patil 2003 <sup>(27)</sup>		Antimicrobial activity

13	Rastelli,G, Sirawaraporn,W,So mpornpisut, P.2000 <sup>(28)</sup>		Antimalarial activity
14	Nagaraj A.and C.SanjeevaRedd 2008 <sup>(29)</sup>		Antibacterial, Antifungal And Anti- Inflammatory Activities.
15	Nagaraj A. and C.Sanjeeva Reddy 2008 <sup>(29)</sup>		Antibacterial, Antifungal And Anti- Inflammatory Activities.

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