

## A REVIEW ON PYRIMIDINE HETEROCYCLES

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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. Literature indicates that compounds having pyrimidine nucleus have wide range of therapeutic uses. Pyrimidine have been reported to show array of activities like antiinflammatory, antibacterial, anticancer, antiviral, antiHIV, antimalarial, antihypertensive, sedatives and hypnotics, anticonvulsant and antihistaminic. Pyrimidine are among the most frequently encountered scaffolds in drugs and pharmaceutically relevant substances. The nitrogen heterocycles are an attractive source of compounds for the identification of new biological probes. The present reviews attempted to gather the various biological activities of pyrimidine derivatives. This assemblage reveals the emergence of this scaffold in the medicinal chemistry with force on the discovery of nitrogen containing heterocyclic candidates.

**KEYWORDS:** Pyrimidine, Biological activities, Scaffolds, and Nitrogen heterocycles.

### INTRODUCTION

The pyrimidine moiety is a versatile lead molecule in pharmaceutical development because of their diverse chemical reactivity, accessibility and a wide range of biological activities. In the past few years, the therapeutic interest of pyrimidine derivatives in pharmaceutical and medical fields has been given a great attention to the medicinal chemists. Literature survey revealed that pyrimidine derivatives are well-known to have antimicrobial<sup>[1-3]</sup>, anti-malarial<sup>[4]</sup> activities. Pyrimidine derivatives are valuable hetero-aromatic compounds because of their wide spectrum of pharmacological applications such as antimalarial, anthelmintic, anticancer, antimicrobial, anti-convulsion and anti-inflammatory activities.<sup>[5-7]</sup> Pyrimidines are always an attraction point for researchers because of its efficiency towards various pharmacological usages. These compounds are known to possess various biological activities.<sup>[8-16]</sup> Fused pyrimidines have also been attracted considerable interest in medicinal chemistry research due to their versatility and a broad bioactive potential. Inorganic synthetic chemistry have widely popularized in "Pyrimidine" and their derivatives.<sup>[17-19]</sup> Pyrimidine does not exist in nature but in the form of its different derivatives, it is found as a part of more complex system and is widely distributed. Pyrimidine derivatives are of interest because of their

pharmacological properties.<sup>[20-22]</sup> Fused pyrimidines continue to attract considerable attention because of their great practical usefulness, primarily due to very wide spectrum of biological activities. This is evident in particular from publications of regular reviews on the chemistry of systems where the pyrimidine ring is fused to various heterocycles such as purines, quinazolines, pyridopyrimidines, triazolopyrimidines, pyrazolopyrimidines, pyrimidoazepines, furopyrimidines and pyralopyrimidines. Triazolopyrimidines represent an important class of heterocyclic compounds having wide range of pharmaceutical and biological activities.<sup>[23-24]</sup> Amongst all heterocyclic compounds, pyrimidine exhibits broad spectrum of biological activities as of its occurrence in deoxyribonucleic acid (DNA) bases.<sup>[25]</sup> Pyrimidine (C<sub>4</sub>H<sub>4</sub>N<sub>2</sub>),<sup>[26]</sup> an organic aromatic heterocyclic compound, is chemically analogous to pyridine and benzene. Six membered ring having one or two nitrogen atoms are known as azine or pyridine, and diazine respectively.<sup>[27]</sup> Cytosine, thymine, and uracil, are the nitrogenous bases (pyrimidine analogue) found in nucleic acid.<sup>[28]</sup> As pyrimidine is a basic nucleus in DNA & RNA, it has been found to be associated with diverse biological activities.<sup>[29]</sup> The synthesis of substituted pyrimidine and many detailed reviews have appeared.<sup>[30]</sup> Pyrimidine derivatives were also found to possess potential central nervous system-depressant properties<sup>[31-32]</sup> and to act as blocker of calcium channel.<sup>[33]</sup> The five-

membered heterocyclic ring substituted in pyrimidine derivatives have moderate inhibition against the bacterial species.<sup>[34]</sup> Dihydropyrimidines occupy a unique place in medicinal chemistry due to their wide application as drug and drug-intermediates possessing diverse pharmacological activities including antitumor, analgesic, antineoplastic, cardiovascular, and antiallergic activities.<sup>[35-39]</sup> A large number of heterocyclic compounds derived from chalcone group have been reported as active biological entities, where 2-aminopyrimidine play a vital role owing to their wide range of therapeutic activities. Aminopyrimidines exhibit a wide spectrum of pharmacological activities like antimicrobial,<sup>[40]</sup> antitumor,<sup>[41]</sup> cardiovascular,<sup>[42]</sup> inflammatory<sup>[43]</sup> and antiviral.<sup>[44]</sup> Pyrimidines are of great importance in fundamental metabolism, being an integral part of DNA and RNA, found in the three bases uracil, thymine and cytosine of the six present in the nucleotides.<sup>[45]</sup> The most general and widely used route to synthesize pyrimidines involves the combination of a reagent containing the N–C–N skeleton namely (urea, thiourea and guanidine) with C–C–C unit such as 1,3-diketones and diesters.<sup>[46]</sup> Pyrimidines have emerged as an interesting class of five and six membered heterocycles with an astonishingly wide range of applications in pharmaceutical chemistry. Barbituric acid and its derivatives are known as sedatives, hypnotics since a long time. Substituted barbituric and thiobarbituric acids show analgesic, antipyretic and anti-inflammatory activities.<sup>[47-49]</sup> In recent years pyrimidine derivatives have received significant attention owing to their diverse range of biological properties. 2,5-Disubstituted-1,3,4-thiadiazoles represent one of the most active classes of compounds possessing wide spectrum of biological activities.<sup>[50]</sup> Considering the above facts, the goal of the present study was to combine disubstituted pyrimidines with 1,3,4-thiadiazole residues in order to develop hybrid molecules with potential of enhanced activity and to test their antioxidant and antitumor activities.<sup>[51]</sup> The origin of the term pyrimidine dates back to 1884 when Pinner coined the term from a combination of the words pyridine and amidine because of the structural similarity to those compounds.<sup>[52]</sup> Since these initial investigations hundreds of pyrimidine-containing compounds have been found in biochemistry. Azaheterocycles constitute a very important class of compounds. In particular, pyrimidine derivatives include a large number of natural products, pharmaceuticals, and functional materials.<sup>[53]</sup> Several examples of pharmaceutically important compounds include trimethoprim,<sup>[54]</sup> sulfadiazine.<sup>[55]</sup> Pyrimidine nucleotides are essential for a vast number of biological processes, such as the synthesis of RNA, DNA, phospholipids, and glycogen and the sialylation and glycosylation of proteins.<sup>[56]</sup>

Annulated pyrimidine derivatives have received great attention during the past years, because they exhibit a

wide range of biological activities such as antibacterial and antifungal activity.<sup>[57]</sup>

### Heterocyclic Compounds

Heterocycles form by far the leading of the classical divisions of organic chemistry and are of vast importance biologically, industrially, and indeed to the functioning of any developed human society. The majority of pharmaceuticals and biologically active agrochemicals are heterocyclic, as are uncountable additives and modifiers used in industries as varied as cosmetics, reprography, information storage, and plastics. Heterocyclic compounds may be inorganic, most contain within the ring structure at least one atom of carbon, and one or more elements such as sulfur, oxygen, or nitrogen.<sup>[58]</sup> Since non-carbons are frequently considered to have replaced carbon atoms, they are called heteroatoms. The structures may consist of either aromatic or non-aromatic rings. Any of a class of organic compounds whose molecules contain one or more rings of atoms with at least one atom (the heteroatom) being an element other than carbon, most frequently oxygen, nitrogen, or sulphur.<sup>[59]</sup> Heterocyclic derivatives, seen as a group, can be divided into two broad areas: aromatic and non-aromatic. In Figure 1.1, five-membered rings are shown in the first row, and the derivative 1 corresponds to the aromatic derivative, furan, while tetrahydrofuran (2), dihydrofuran-2-one (3), and dihydrofuran-2,5-dione (4) are not aromatic, and their reactivity would be not unlike that expected of an ether, an ester, or a carboxylic anhydride, respectively. The second row shows six-membered rings, initially in an aromatic form as pyridine (5), while piperidine (6), piperidin-2-one (7), and 1,2,3,4-tetrahydropyridine (8) are not aromatic; their reactivity would not be very different from that expected of an amine, amide, or enamine, respectively.

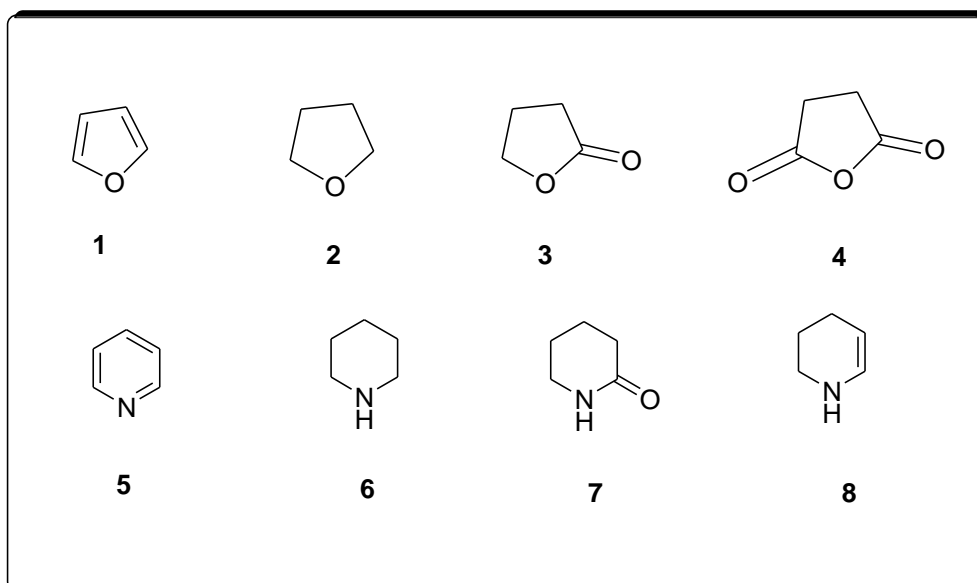


FIGURE 1.1

A molecule of pyridine contains a ring of six atoms-five carbon atoms and one nitrogen atom. Pyrrole, furan, and thiophene molecules each contain five-membered rings, composed of four atoms of carbon and one atom of nitrogen, oxygen, or sulfur, respectively.<sup>[60]</sup> Pyrimidine and pyrrole are both nitrogen heterocycles-their molecules contain nitrogen atoms along with carbon atoms in the rings. Heterocyclic chemistry deals with heterocyclic compounds which organize about sixty-five percent of organic chemistry literature.<sup>[61]</sup> Heterocyclic compounds are widely dispersed in nature and essential to life; they play a vital role in the metabolism of all living cells. Genetic material DNA is also composed of heterocyclic bases-pyrimidines and purines. A large number of heterocyclic compounds, both synthetic and natural, are pharmacologically active and are in clinical use. Heterocyclic compounds have a wide range of application: they are leading among the type of compounds used as pharmaceuticals,<sup>[62]</sup> as agrochemicals and as veterinary products. The popularly pharmaceuticals and biologically active agrochemicals are heterocyclic, as are uncountable additives and modifiers used in industries as varied as cosmetics, reprography, information storage, and plastics. Heterocyclic compounds considered one of the vital classes of organic compounds, which are used in many biological fields, due to its activity in multiple illnesses. Biological molecules such as DNA and RNA, chlorophyll, hemoglobin, vitamins and many more contain the heterocyclic ring in major skeleton. There are a lot of heterocyclic compounds which have application in many common diseases such as; triazine derivatives have been used as antimicrobial herbicides, urinary antiseptics and anti-inflammatory agents.

Benzimidazole derivatives have been reported to possess a wide range of biological activities such as antibacterial, antifungal, antiviral and anthelmintic, etc.<sup>[63]</sup> Heterocycles are abundant in nature and are of great significance to life because their structural subunits exist in many natural products such as vitamins, hormones, antibiotics etc.<sup>[64]</sup> Hence, they have attracted significant attention in the design of biologically active molecules. A practical method for the synthesis of such compounds is of great interest in synthetic organic chemistry. Oxopyrimidines & Thiopyrimidines and its derivatives represent one of the most active classes of compounds possessing a wide spectrum of biological activities. Pyrimidine derivatives which occur in natural products like nucleic acid, vitamin-B and having extraordinary pharmaceutical importance because of their broad spectrum of biological activities. Several analogs of nucleic acids like fluorouracil which has been used in cancer treatment. Pyrimidines 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.<sup>[65]</sup>

## REVIEW OF LITERATURE

ABD EL ALL et al., synthesized novel (1a-1g) series of pyrimidine derivatives among all these compounds, the compound 1c was the most active broad spectrum antimicrobial agent against the chosen microbial strains i.e. *Staphylococcus aureus* and *Staphylococcus epidermidis*.<sup>[66]</sup>

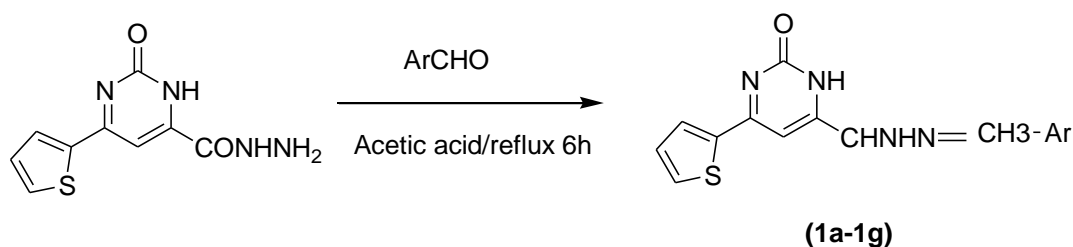
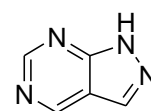
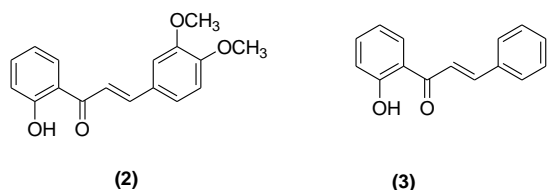


Table 1.1

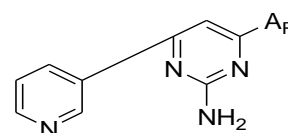
Compound	Ar
1a	C <sub>6</sub> H <sub>5</sub>
1b	4-CH <sub>3</sub> O-C <sub>6</sub> H <sub>4</sub>
1c	4-HO-C <sub>6</sub> H <sub>4</sub>
1d	4-O <sub>2</sub> N-C <sub>6</sub> H <sub>4</sub>
1e	4-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>
1f	4-Cl-C <sub>6</sub> H <sub>4</sub>
1g	3,4,5-(CH <sub>3</sub> O) <sub>3</sub> -C <sub>6</sub> H <sub>2</sub>

R. Ravichandran et al., were studied on Chalcone Derivatives which act as Antioxidant. They synthesized by Claisen- Schmidt Condensation. They synthesized a 2-hydroxy-3,4-dimethoxychalcone, and 2-hydroxychalcone (2 and 3).<sup>[67]</sup>



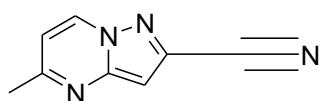
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M. V. Jyoti et al., were assessed Antimicrobial Activity of Some Novel Chalcones of Pyridine and Pyrimidine Derivatives. They synthesized chalcone derivatives by Claisen- Schmidt condensation.<sup>[70]</sup>



(6)

Ming li et al., were synthesized compound 2-cyano-5-methyl pyrazolo [1, 5- a] pyrimidine derivatives which showed various biological activities in the terms of antibacterial, anti-chistosomal and xanthine oxidase inhibitor. The preliminary biological test showed that the compound revealed activity against four fungi G. Zeave, A. Solani, P. Asparangi and C. Aracnicicola hori.<sup>[68]</sup>



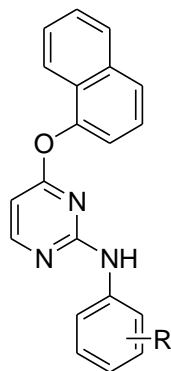
(4)

Amit R. Trivediet et al., were synthesized a series of phenothiazine clubbed pyrazolo [3,4-d]pyrimidines by using the Biginelli multi-component cyclo-condensation reaction and their capacity to forbidden growth of Mycobacterium tuberculosis in vitro have been determined. The results show that revealed superb anti-tubercular activity with percentage inhibition of 93, 91, and 96, respectively, at a minimum inhibitory concentration (MIC) of <6.25 µg/ml.<sup>[69]</sup>

Table 1.2:

Compound	Ar
6a	
6b	
6c	
6d	
6e	
6f	
6g	

Shipra Baluja et al., were prepared 2, 4-disubstituted pyrimidine derivatives (KDB-1 to KDB-9) by using equimolar mixture of 2,4-dichloropyrimidine (DCP), 1-Naphthol (NTL) and 0.015 mole of Potassium carbonate (K<sub>2</sub>CO<sub>3</sub>) in DMF was refluxed for 4 hr and reported antimicrobial activities of synthesized compounds have been screened against some bacterial (both Gram positive and Gram negative) and fungal strains in DMSO.<sup>[71]</sup>

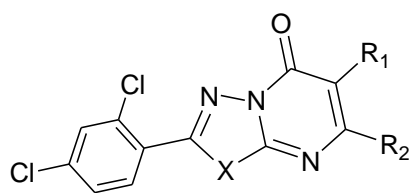


(7)

Table 1.3

Compound	R-Group
KBD-A	4-Cl
KBD-B	4-CH <sub>3</sub>
KBD-C	4-F
KBD-D	3-CF <sub>3</sub>
KBD-E	3-Cl, 4-F
KBD-F	4-OCH <sub>3</sub>
KBD-G	3, 4-dichloro
KBD-H	3-Cl
KBD-I	2-F

Gogia et. al., were synthesized 1,3,4-oxa / thiazolo – (3,2-a)pyrimidin-5-one which exhibited antifungal activity. X = O, S.<sup>[72]</sup>

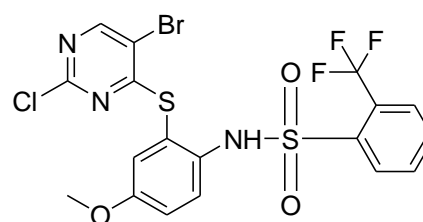


(8)

Nasr MN et al., were synthesized some compound, among all the synthesized compounds few of them showed more antioxidant activity when compared to other compounds in the series by using 2,6-Difluorobenzaldehyde-(5-bromo-2-chloropyrimidin-4-yl)hydrazine and 2,6-difluorobenzaldehyde, 2,4-

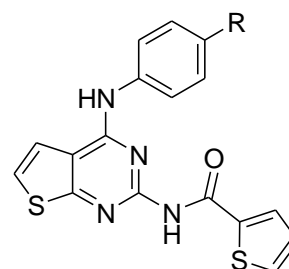
Dimethoxybenzaldehyde-(5-bromo-2-chloropyrimidin-4-yl)hydrazine and 2,4-dimethoxybenzaldehyde.<sup>[73]</sup>

Mallesha L. et al., were synthesized 2-(5-Bromo-2-chloro-pyrimidin-4-ylsulfanyl)-4-methoxy-phenylamine derivatives, among all these derivatives N-[2-(5-bromo-2-chloro-pyrimidin-4-yl sulfanyl)-4-methoxy-phenyl]-2-trifluoromethyl-benzene sulphonamide was more potent against Gram-positive and Gram-negative bacteria. It was synthesized by using the product obtained from 2-(5-bromo-2-chloropyrimidin-4-ylthio)-4-methoxybenzenamine and 2-trifluoromethyl-benzenesulfonyl chloride.<sup>[74]</sup>



(9)

Virupakshi Prabhakar et al., were synthesized series of ten thieno[2,3-d]pyrimidine derivatives, among all these four of them showed potent antimicrobial activity against all tested pathogenic strains by using furan/Thiophene-2-carboxylic Acids (10.2 m.mol) in DMF (5v), HATU (10 m.mol), Hunig's base (N,N-di isopropyl ethyl amine, DIPEA) (20 m.mol), and stir at RT for 10 min under Nitrogen atmosphere.<sup>[75]</sup>



(10)

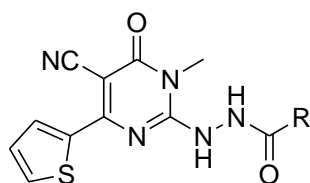
Table 1.4:

Compound	R-Group
10a	OCH <sub>3</sub>
10b	OCF <sub>3</sub>
10c	CF <sub>3</sub>

Nagesh et al., were evaluated the antifungal activity of the test compounds against two different fungal strains namely, *Candida albicans* and *Aspergillus niger* by a filter paper disc technique at 50 and 100 µg/ml concentrations.<sup>[76]</sup>

Ram et al., were synthesized a series of novel 1,6-dihydropyrimidine derivatives by using, A mixture of 2-

hydrazineyl-1-methyl-6-oxo-4-(thiophen-2-yl)-1,6-dihydropyrimidine-5-carbonitrile (2.49 g, 0.01 mol), acetyl chloride (1.40 ml, 0.01 mol) in acetic acid (20 ml) was refluxed for 4 hours.<sup>[77]</sup>

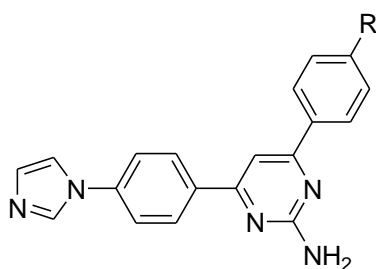


(11)

Table 1.5

Compound	R-Group
11a	CH <sub>3</sub>
11b	C <sub>6</sub> H <sub>5</sub>
11c	furyl
11d	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>

Eswara Rao G. et al., were synthesized pyrimidine derivatives by using, Chalcone (0.001 mol) with guanidine hydrochloride (0.001 mol) in the presence of potassium hydroxide (0.002 mol) in absolute ethanol (5 ml) and reflux for 6 hours. They were also shown that Nitrogenous heterocyclic nucleus containing compounds (pyrimidines) have more potent antibacterial activity.<sup>[78]</sup>

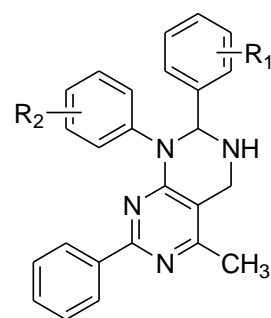


(12)

Table 1.6

Compound	R-Group
12a	OH
12b	Cl

Jerzy cieplik et al., were synthesized 1,2,3,7-tetraaryl-1,2,3,4-tetrahydropyrimido[4,5-d]pyrimidine derivatives and evaluated for their antibacterial activity. The antibacterial activity was tested on 9 selected strains, comparing chemical structure changes with increased microbiological activity.<sup>[79]</sup>

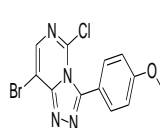


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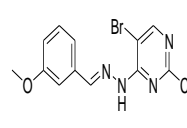
Table 1.7:

Compound	R1	R2
13a	4-OC <sub>2</sub> H <sub>5</sub>	4-NO <sub>2</sub>
13b	4-OCH <sub>3</sub>	3-NO <sub>2</sub>
13c	4-Cl	4-OH
13d	4-F	2-Cl

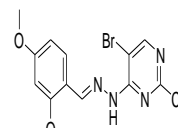
Shih MH et al., were evaluated the antioxidant activity of the synthesized compounds by free radical scavenging (DPPH) assay method. All the compounds showed DPPH radical scavenging activity, where compounds 14, 15 and 16 were the best radical scavengers.<sup>[80]</sup>



(14)

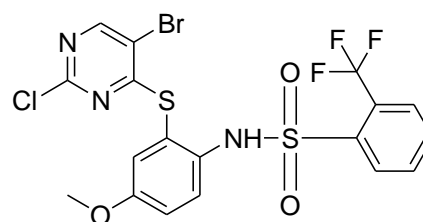


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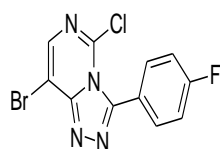
C. Mallikarjunaswamy et al., were synthesized the series of novel 2-(5-bromo-2-chloro-pyrimidin-4-ylsulfanyl)-4-methoxy-phenylamine derivatives by using, 2-(5-bromo-2-chloro-pyrimidin-4-ylsulfanyl)-4-methoxy-phenylamine with various sulfonyl chlorides. Among all these pyrimidine derivatives, the compound 17 showed good antifungal activity against *F.oxysporum*.<sup>[81]</sup>



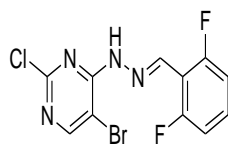
(17)

Castel-Branco MM et al., were synthesized the series of new pyrimidine analogs, using 5-bromo-2,4-dichloropyrimidine and hydrazine hydrate. Among the new synthesized compounds, 18 and 19 are found to be most potent anticonvulsant activity and showed no neurotoxicity.<sup>[82]</sup>



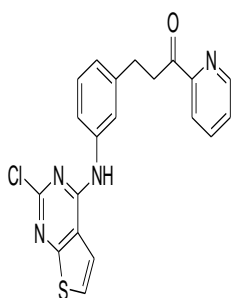


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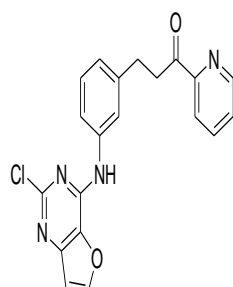


(19)

Bhagchand Jat et al., were synthesized pyrimidine derivatives using Claisen-Schmidt condensation reaction. All the synthesized compounds were evaluated for their antifungal activity. The compounds 20 and 21 exhibited significant antifungal activity against *P. funiculosum*.<sup>[83]</sup>



(20)



(21)

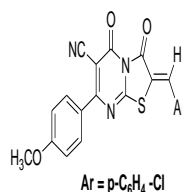
M. Mumtaz MH et al., were synthesized a novel series of 2-hydroxy pyrimidines by using the reaction of thiophene-2-aldehyde with various substituted acetophenones in presence of NaOH in alcohol medium. Among all the synthesized compounds, few of them, showed significant antibacterial activity against various gram positive organisms.<sup>[84]</sup>

B. Andrews et al., were synthesized a series of 10 derivatives of 5-(5-amino-1,3,4-thiadiazole-2-yl)-3,4-dihydro-6-methyl-4-phenylpyrimidin-2(1H)-one and 10 derivatives of 3,4-dihydro-5-(5-mercapto-4H-1,2,4-triazol-3-yl)-6-methyl-4-phenyl pyrimidin-2(1H)-one have been synthesized. They evaluated that triazole substituted compounds have higher inhibition than the thiadiazole substituted compounds, the triazole derivatives showed potent antibacterial activity against three species of pseudomonas aeruginosa, staphylococcus aureus and escherichia coli.<sup>[85]</sup>

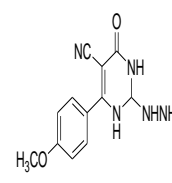
Table 1.8

Compound	R	R1
22a	H	H
22b	Cl	H
22c	N(CH <sub>3</sub> ) <sub>2</sub>	H
22d	H	NO <sub>3</sub>
22e	OH	H
22f	H	H
22g	Cl	H
22h	N(CH <sub>3</sub> ) <sub>2</sub>	H
22i	H	NO <sub>3</sub>
22j	OH	H

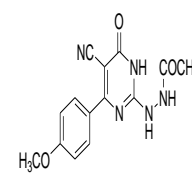
Mohamed M. Mohamed et al., were synthesized a new series of 6-aryl-5-cyano thiouracil derivatives by using, Cyanouracil, monochloroacetic acid and different aldehydes to give thiazolopyrimidine derivatives. All of the new synthesized compounds were evaluated for their antiproliferative activities against HePG-2 and MCF-7 cell lines and antimicrobial activity. Among all of synthesized compounds, the compounds 23, 24, and 25 exhibited potent growth inhibitory effect toward the two cell lines (HePG-2 and MCF-7) and also having a prominent antimicrobial activity against *Staphylococcus aureus*, *Bacillus Subtilis*, *Escherichia coli*, *Candida albicans*, and *Aspergillus flavus*.<sup>[86]</sup>



(23)



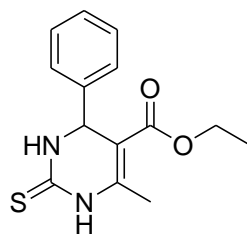
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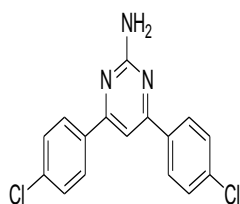
V. M. barot et al., were synthesized 2-aminopyrimidine derivatives by the, condensation of chalcone with guanidine hydrochloride in ethanol, by using 2-aminopyrimidines with acetic anhydride to gives 2-acetamidopyrimidine. All the synthesized compounds have been evaluated for their antibacterial activity and antifungal activity.<sup>[87]</sup>

Padmaja et al., were synthesized a new class of heterocycles, substituted pyrazoles, isoxazoles, pyrimidines, thioxo pyrimidines and were prepared from Michael addition, by using 2-(1,2-diaroyl)malononitrile and 2-(1,2-diarylsulfonyl)malononitrile. The prime compounds were evaluated for their antimicrobial and antioxidant activities.<sup>[88]</sup>

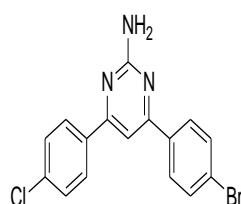


(26)

Kumar et al., were synthesized a novel series of 4, 6-bisaryl-pyrimidin-2-amine derivative. All the synthesized compounds were evaluated for their antioxidant activity by nitric oxide and hydrogen peroxide free radical scavenging method using ascorbic acid as a standard drug. Among these synthesized derivatives, compound 27 and 28 exhibited potent antioxidant activity.<sup>[89]</sup>

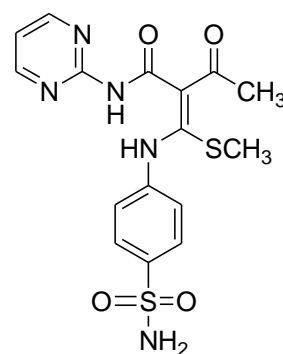


(27)



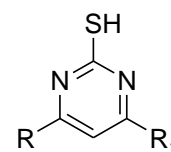
(28)

Abu-Bakr AM El-Adasy et al., were synthesized 2-(methylthio)-((4-sulfamoyl phenyl) amino) methylene-3-oxo-N-(pyrimidin-2-yl)-butanamide by using, dimethylformamide (20 mL), butanamide 1 (0.01 mole), isothiocyanate sulfonamide 2 (0.01 mole) methyl iodide (0.01 mole). They were also evaluated for antioxidant activity and exhibited potent antioxidant activity.<sup>[90]</sup>



(29)

M. A. Azam et al., were synthesized a series of 4, 6-disubstituted pyrimidine-2-thiols by using, a mixture of appropriate chalcones (0.01 mol) and thiourea (0.01 mol) in ethanol (50 ml) and sodium hydroxide (0.01 mol) dissolved in minimum quantity of water was refluxed on a water bath for 12 h. Among all the synthesized compounds, the compounds 30b, and 30c having significant antitumor activity against human breast cancer MCF 7 cell line. However, the compounds 30c, 30d and 30g possesses moderate antioxidant activity.<sup>[91]</sup>



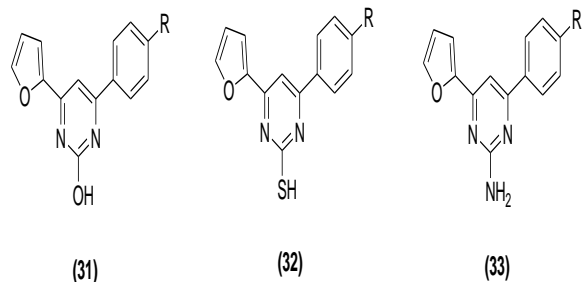
(30)

Table 1.9

Compound	R	R1
30a	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>
30b	C <sub>6</sub> H <sub>5</sub>	4-OCH <sub>3</sub> .C <sub>6</sub> H <sub>4</sub>
30c	C <sub>6</sub> H <sub>5</sub>	2-OH.C <sub>6</sub> H <sub>5</sub>
30d	2-OH.C <sub>6</sub> H <sub>4</sub>	4-OCH <sub>3</sub> .C <sub>6</sub> H <sub>4</sub>
30e	4-NO <sub>2</sub> .C <sub>6</sub> H <sub>4</sub>	4-OCH <sub>3</sub> .C <sub>6</sub> H <sub>4</sub>
30f	4-OH.C <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>
30g	2-OH.C <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub> .CH=CH-
30h	2-OH.C <sub>6</sub> H <sub>4</sub>	3-Furyl
30i	4-NO <sub>2</sub> .C <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub> .CH=CH-

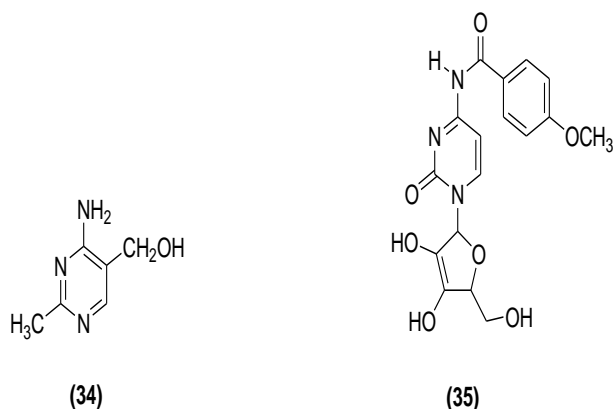
Vishal D. Joshi et al., were synthesized some novel pyrimidine derivatives by using, Furan-2-Carbaldehyde with different acetophenones by Claisen-Schmidt Condensation. Various Pyrimidine derivatives were prepared by reaction of Chalcone with Urea, Thiourea and Guandine HCl in ethanolic sodium hydroxide. The synthesized compounds were evaluated for their anti-inflammatory and analgesic activity. Some of them novel pyrimidine derivatives having Fluoro and Chloro substitution exhibited potent anti-inflammatory and analgesic activity.<sup>[92]</sup>



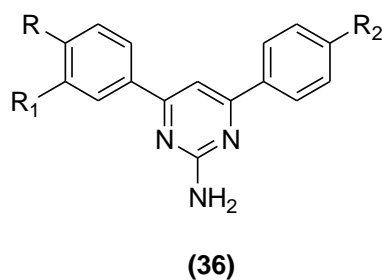
**Table 1.10: R-Group Substitution.**

Compound	31	32	33
a	NH <sub>2</sub>	NH <sub>2</sub>	NH <sub>2</sub>
b	Br	Br	Br
c	NO <sub>2</sub>	NO <sub>2</sub>	NO <sub>2</sub>
d	Cl	Cl	Cl
e	F	F	F
f	CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>

Reddick JJ. et al., were studied bacimethrin (5-hydroxymethyl-2-methoxypyrimidin-4-amine) (compound 34) which is Pyrimidine analogues and acts as antibiotic, which is found to be effective against several staphylococcal infections. Gourgetin (compound 35) a cytosine derivative is active against mycobacteria as well as several Gram-positive and Gram-negative bacteria.<sup>[93]</sup>

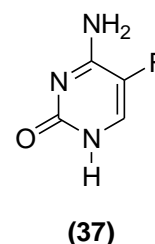


Verma et al., were reported the synthesis and antibacterial activity of 2-amino-4, 6-diaryl pyrimidine derivatives.<sup>[94]</sup>



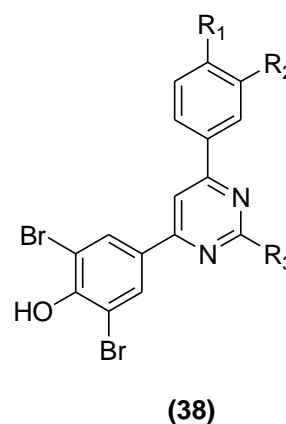
Polak A, Hunter PA et al., were evaluated that Pyrimidines are known to exhibit antifungal properties. Flucytosin (compound 37), which is a pyrimidine

derivative, useful in the case of infection due to candida taalbicans and Cryptococcus neoformans.<sup>[95]</sup>

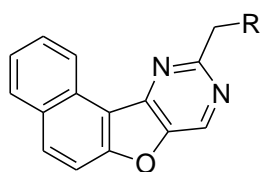


Mathews and Asokan et al., were reported the synthesis of pyrimidine-5-carbaldehydes from  $\alpha$ -formylaroylketene dithioacetals. Amidines were allowed to react with  $\alpha$ -formylaroylketene dithioacetals in DMF or acetonitrile to obtain the pyrimidine-5-carbaldehydes.<sup>[96]</sup>

Verma et al., were synthesized 2-91-piperidinye/1-pyralidinylo- 4-substituted phenyl -6 (3, 5- di bromo-4-hydroxy phenyl)-pyrimidines. The herbicidal activity was carried out by Cyanamid India Ltd. valsad plant valsad in collaboration with Cyana mid U. S. A. compound were tested both pre and post emergence against 18 species in an 80% acetone solution  $\pm$  0.2% in general 1 Kg activity compound at volume of 1600 lit/hect was used for this test. The minimum sample used in this test was 250 mg.<sup>[97]</sup>

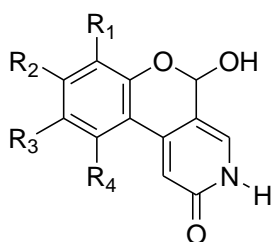


Vaidya et al., were synthesized 2-Alkyl/aryl amino methyl-4-alkyl/aryl naphtha [2, 1- b] furo [3, 2- d] pyrimidines. The activity was evaluated as earth worms pheretima posthuma by reported method. The compounds were tested at a dose of 0.001 mol/ml suspended in tween-80 piperazine citrate suspension was taken as standard.<sup>[98]</sup>



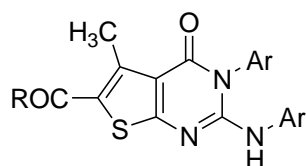
(39)

Karale et al., were reported the synthesis of 2- Thio- 5-hydroxy- 5H- [1, 3- d] pyrimidines derivative. The compound were screened for their antibacterial activity against gram negative bacteria E.Coli and gram positive bacteria S. Albus using filter paper disc method.<sup>[99]</sup>



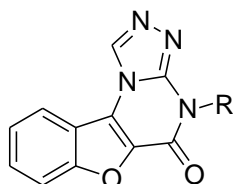
(40)

Rathod et al., were synthesized 2- aryl amino- 3- aryl- 5-methyl- 6- (substituted) thione [2, 3- d] pyrimidin- 4 (3H)- ones. All the synthesized compounds were evaluated for the analgesic activity by tail flick method on albino rats and by writing method on albino mice.<sup>[100]</sup>



(41)

Basavaraja et al., were synthesized 1, 2, 3, 4- tetrahydro- 4- oxo- 2- thiobenzo furo [3, 2- d] pyrimidine. They were evaluated and reported for their activity against S. Aureus and E. Coli.<sup>[101]</sup>

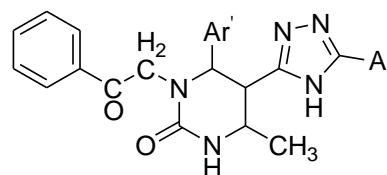


(42)

Table 1.11

Compound	R-Group
42a	CH <sub>3</sub>
42b	C <sub>6</sub> H <sub>5</sub>
42c	C <sub>6</sub> H <sub>4</sub> CH <sub>3</sub>
42d	C <sub>6</sub> H <sub>4</sub> OCH <sub>3</sub>

Mishra et al., were synthesized various derivatives of pyrimidines. The pyrimidine derivatives were evaluated for fungicidal activities against *P. infestans* and *C. falcatum* by the usual agar plate technique at 1000, 100 and 10 ppm concentration.<sup>[102]</sup>

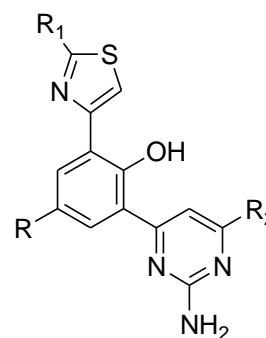


(43)

Table 1.12

Compound	Ar	Ar'
43a	C <sub>6</sub> H <sub>5</sub>	m-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>
43b	p-ClC <sub>6</sub> H <sub>4</sub>	m-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>
43c	m-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	p-OCH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>
43d	p-OCH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	p-OCH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>

Rindhe et al., were prepared 2-Amino-6-substituted thiazolyl pyrimidine compounds with 4-chloro and 4-methoxy substituent at four position showed significant antifungal activity.<sup>[103,104]</sup>

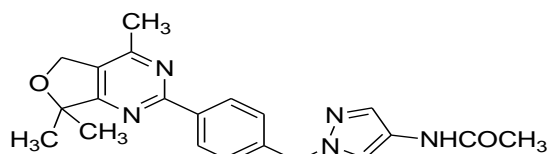


(44)

Table 1.13

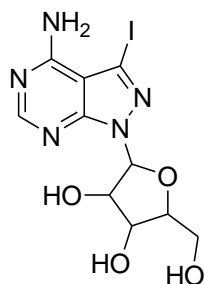
Compound	R	R <sub>1</sub>	R <sub>2</sub>
44a	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	4-OCH <sub>3</sub>
44b	Cl	4-C <sub>6</sub> H <sub>5</sub>	4-Cl

Frederick C et al., were prepared a series of inhibitors of mammalian target of Rapomycin (mTOR) kinase based on a quaternary substituted dihydrofuro-pyrimidine by cyclocondensation of  $\beta$ -keto ester. The compound with 4-acetamido pyrazole moiety was found to be most potent among all the synthesized compounds.<sup>[105]</sup>



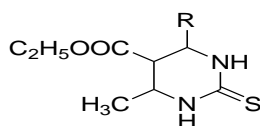
(45)

El-Gaby et al., were prepared some new pyrimidine-2-thiones. Among all the synthesized compounds, some of them, were evaluated for in vitro anticancer activity against Ehrlich Ascites Carcinoma Cells.<sup>[106]</sup>



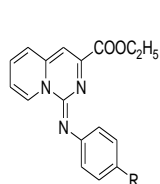
(46)

Cottom et al., were synthesized various pyrazolo[3,4-d]pyrimidine derivatives as potential inhibitor of adenosine kinase. One of the compound was exhibited good anti-inflammatory activity and having potential to inhibit adenosine kinase.<sup>[107]</sup>

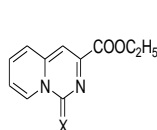


(47)

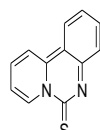
Molina et al., were synthesized a number of pyrido[1,2-C]pyrimidines and confirmed for effects on leukocyte function in vitro and anti-inflammatory activity.<sup>[108]</sup>



(48)



(49)



(50)

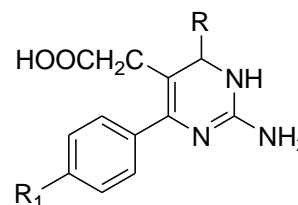
Table 1.14

Compound	R-Group
48a	H
48b	CH <sub>3</sub>
48c	OCH <sub>3</sub>
48d	F
48e	Cl
48f	Br

Table 1.15

Compound	X-Group
49a	O
49b	S

Bahekar et al., were reported the synthesis of some prepared compounds, [2-amino-6-(4-substituted aryl)-4-(4-substituted phenyl)-1,6-dihydropyrimidin-5-yl]acetic acid derivatives and assessed for their anti-inflammatory activity. Among all the prepared derivatives few of them showed significant anti-inflammatory activity.<sup>[109]</sup>

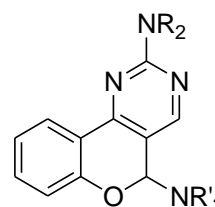


(51)

Table 1.16

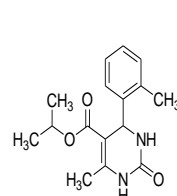
Compound	R <sub>1</sub>
51a	Ph
51b	4-Cl phenyl

Bruno et al., were reported the synthesis of some new 2,5-cycloamino-5H-benzopyrano[4,3-d]pyrimidine derivatives and screened them for anti-inflammatory, analgesic and antipyretic activities and in vitro antiplatelet activity. All the synthesized compounds were failed to showed anti-inflammatory, analgesic and antipyretic activities but they exhibited an remarkable antiplatelet activity.<sup>[110]</sup>

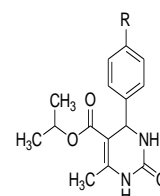


(52)

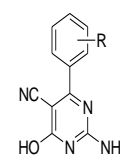
Haleen et al., were evaluated Ester, cyanide and some other substituted Biginelli compounds and are reported to be auspicious anti-bacterial agents.<sup>[111]</sup>



(53)



(54)



(55)

Table 1.17

Compound	R-Group
54a	Cl
54b	NO <sub>2</sub>
54c	F
55a	Cl
55b	NO <sub>2</sub>
55c	F

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