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Research Article

Pharmacological activity and synthesis of Pyrimidine and their Derivatives : A Review

*[1]Vinod Vyas, [1]Pinki Vaishnav, [1]Shanta Jat, [1]Bhawana Kherodiya and [1]Nasir Hussain**
1.R.N.T.P.G College, Kapasan, Dist. Chittorgarh Rajasthan, India. (312202)
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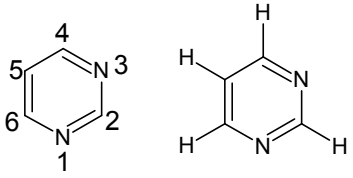
Abstract

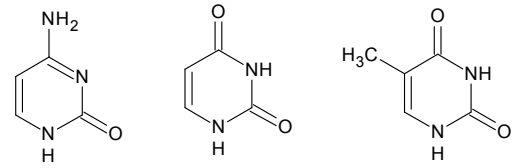
Pyrimidine and its derivatives demonstrate a diverse array of biological and pharmacological activities including anticonvulsant, antibacterial, antifungal, antiviral and anticancer properties. This broad spectrum of biochemical targets has been facilitated by the synthetic versatility of pyrimidine, which has allowed the generation of a large number of structurally diverse derivatives including analogues derived from substitution of the aryl ring, and/or derivatisation of the pyrimidine nitrogen and C2/C4/C5/C6 carbon positions. Pyrimidines are synthetically versatile substrates, where they can be used for the synthesis of a large variety of heterocyclic compounds and as raw material for drug synthesis. It was therefore the objective of this review to systematically evaluate the pharmacological properties of various substituted pyrimidine and collate these findings to be used as a guide for future structure-activity relationship and mode of action studies. This is the first review to comprehensively discuss the pyrimidine and its substituted derivatives.
Keywords Pyrimidine, Marketed drugs.

Introduction and review of literature of Pyrimidine:

Pyrimidine is a heterocyclicaromaticorganic compound similar to benzene and pyridine, containing two nitrogenatoms at positions 1 and 3 of the six-member ring. 1.3-Diazine and m-diazine are other name of pyrimidine.



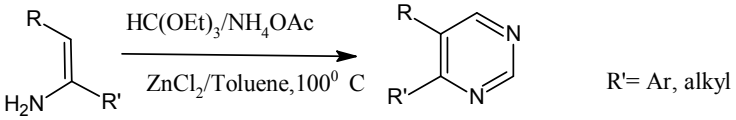
Three nucleobases found in nucleic acids, (DNA and RNA) cytosine (C), thymine (T), and uracil (U), are pyrimidine derivatives.



Cytosine Uracil Thymine

Synthetic aspects

A $ZnCl_2$-catalyzed three-component coupling reaction allows the synthesis of various 4,5-disubstitutedpyrimidine derivatives [1] **(1)** in a single step from functionalized enamines, triethyl orthoformate, and ammonium acetate. The procedure can be successfully applied to the efficient synthesis of mono- and disubstituted pyrimidine derivatives, using methyl ketone derivatives instead of enamines.



R'= Ar, alkyl

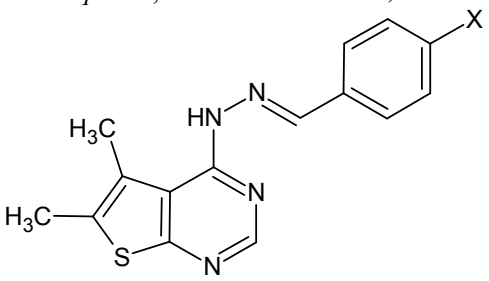
(1)

Pharmacological aspects

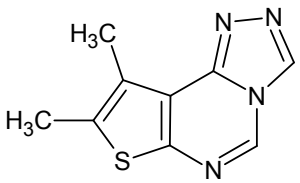
Pyrimidine ring as thienopyrimidine play an important role as potent analgesic [2],anti-inflammatory [3-6], antipyretic [7-9], antimicrobial [10-11], anticonvulsant [12], fungicidal [13], antiplatelet activities [14-16], and central nervous system (CNS) affecting activities[17]. In addition, pyrimidine nucleus can be found in a broad variety of antibacterial, anticancer [18-19]and anti-tumor agents [20] as well as in agrochemicals and veterinary products [21], Pyrimidine derivatives serve both as biomimetic and reactive pharmacophores due to their diverse medicinal properties such as antitumor [22], anticancer [23] (lungs, breast and CNS cancer), immunodilator [24], antiviral [25] etc. Pyrimidine derivatives have activities like tyrosine kinase inhibitors [26], COX-2 inhibitor [27], calcium channel blockers plus antihypertensive [28] and also activity against Y181C HIV-1 mutant strain [29], etc. Diverse biological activities like anticonvulsant [30], diuretic [31], fungicidal[32] and trypanocida [l33]. Pyrimidine derivatives possess several interesting biological activities such as antimicrobial [34], antitumour [35] and antifungal activities[36].

Antibacterial activity

Hossain[37] and co workers were synthesized derivatives of fused pyrimidine **(2)** and **(3)**. All the synthesized compounds were screened for their antibacterial activity against three gram-positive bacteria *Bacillus cereus, Bacillus subtilis* and *Staphylococcus aureus* and three Gram-negative bacteria *Shigella dysenteriae, Salmonela typhi* and *Pseudomonous*. The antifungal activity was tested against the fungi *Macrophomina phaseolina*, *Fusarium equiseti*, *Alternaria alternata, Colletotrichum corchori* and *Curvularia lunata*.

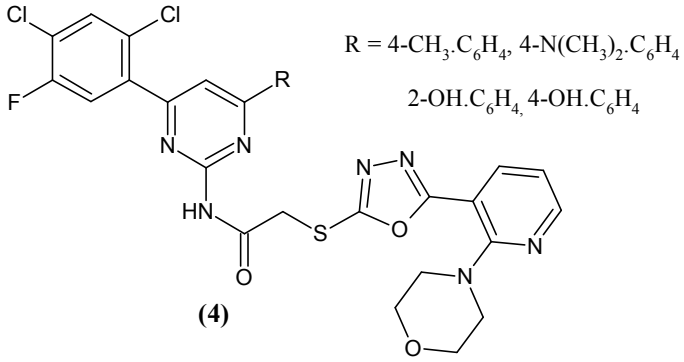


(2) X = OH, CH_3, Cl, NO_2



(3)

Derivatives of 2-[{2-(morpholino)-3-pyridinyl-5-thio}-2-oxoethyl oxadiazolyl]-amino-4-(2,4-dichloro-5-fluoro phenyl)-6-(aryl)-pyrimidines **(4)** have been synthesized by Naik [38] *et al.* All the synthesized compounds were screened for their antibacterial activity against three bacteria *S.aureus, E.coli, S.typhi* and *B.subtilis*.

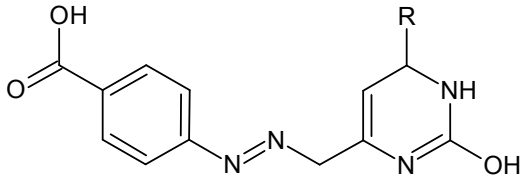


R = 4-CH_3.C_6H_4, 4-$N(CH_3)_2$.C_6H_4

2-OH.C_6H_4, 4-OH.C_6H_4

(4)

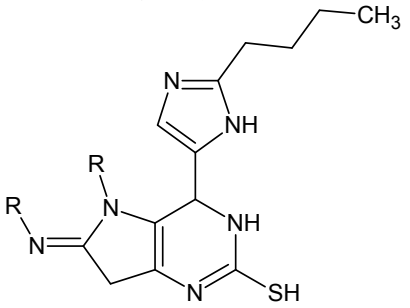
Derivatives of pyrimidines **(5)** were synthesized by Trivedi [39] and co workers by the chalcones. All newly synthesized compounds were evaluated for their antimycobacterial activities against *Mycobacterium tuberculosis* H37Rv.



(5)

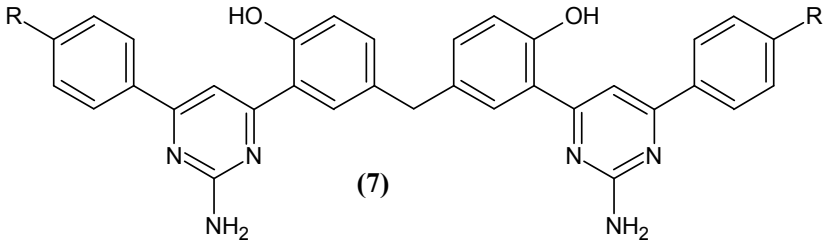
The synthesis of thiazolo-5,4-*d*-pyrimidines [40] **(6)** were achieved from different 5-thiazolidinones, 2-butyl-1*H*-imidazole-5-carbaldehyde and thiourea using microwave irradiation within 5 min. The antimi-

crobial activities of the thiazolo-5,4-*d*-pyrimidines were compared with standard drugs, *viz. ampicillin*, *chloramphenicol*, *ciprofloxacin,norfloxacin* and *griseofulvin*.



(6)

Nagaraj [41] and colleagueswere synthesized of bipyrimidine derivatives **(7)** by the reaction of bis chalcones with guanidine hydrochloride. The compounds **(7)** were screened for their antibacterial activity against human pathogenic bacteria *Escherichia coli, Staphylococcus aureus* and *Bacillus subtilis*.

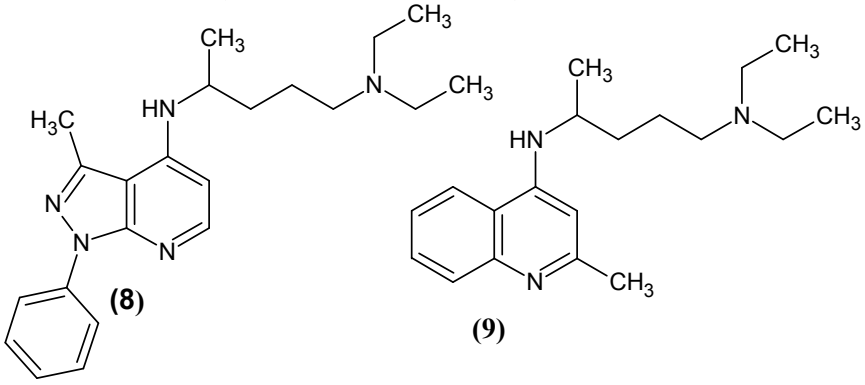


(7)

R, a= H, 4-OCH_3, 4-Cl,-4-NO_2

Antiviral activity

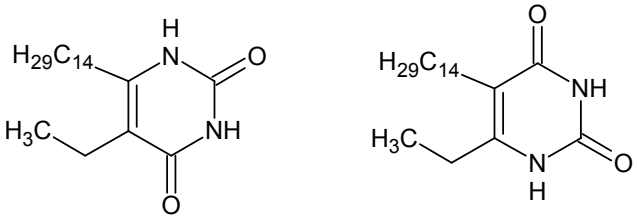
Dias [42] *et al.* were synthesized derivatives of N-4-(3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*] pyridine)-N1,N1-diethyl-1,4-pentanediamine **(8)** and N-4-(quinaldine)-N1,N1-diethyl-1,4-pentanediamine **(9).** Compoundswere evaluated as antiviral agents used as standard drug for the *CoxsackievirusB-3*.



(8) **(9)**

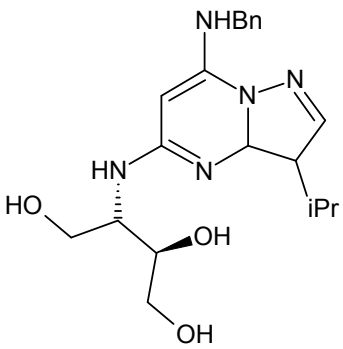
Anti cancer activity

Derivatives of pyrimidine **(10)** and **(11)** were synthesized by Macchia [43] and co-workers. All the synthesized compounds were evaluation of their biologic activity on CCRF-CEM human leukemia cells demonstrated.



(10) **(11)**

Dean [44] *et al*. have reported enantiomer of pyrazolo[1,5-a]pyrimidine derived compound**(12)** and **(13)**, and selective as a potent CDK inhibitor.



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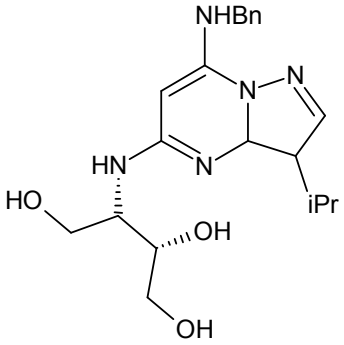
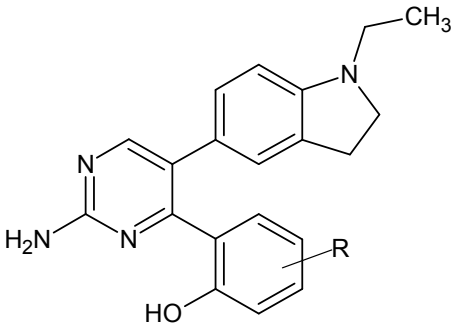


(13)

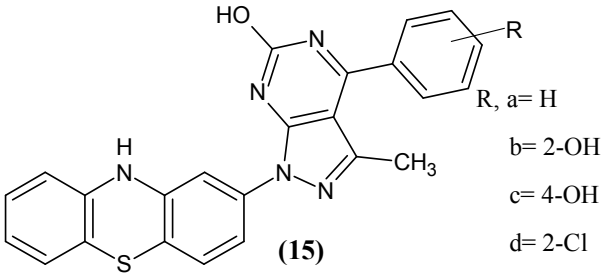
A series of 2,4,5-substituted pyrimidine derivatives **(14)** were synthesized by Fuchun [45] and co workers.The pyrimidine derivatives were initially screened for their antiproliferative activity against the human hepatocellular carcinoma cell line BEL-7402. Cell proliferation was determined by sulforhodamine B cell survival assay after a treatment period of 72 hrs.



(14)

Antitubercular activity

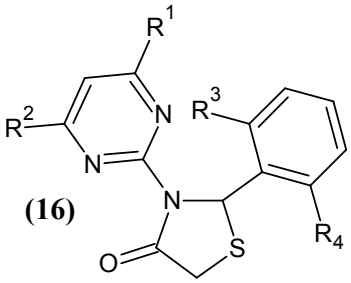
Some novel 2-heterocycle-substituted phenothiazines having a pyrazolo[3,4-d]pyrimidine [46] **(15)**nucleus were achieved by using the Biginelli multi-component cyclocondensation reaction. The products were evaluated for their antitubercular activity against *Mycobacterium tuberculosis* H37 Rv.



(15)

Anti-HIV

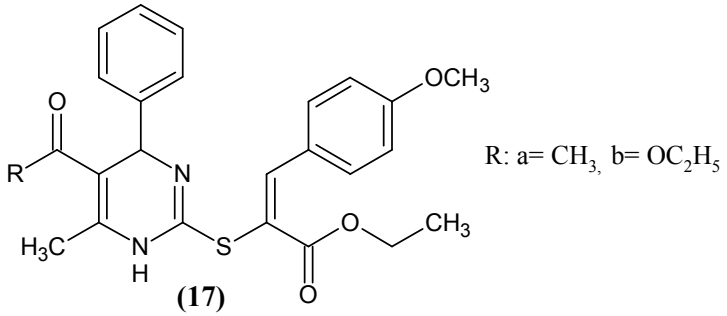
2-(2,6-Dihalophenyl)-3-(pyrimidin-2-yl)-1,3-thiazolidin-4-ones **(16)** were synthesized by the Rao [47] and coworkers. All the synthesized compounds evaluated as anti-HIV agents. The results of the *in vitro* tests showed that some of them were highly effective inhibitors of human immunodeficiency virus type-1 (HIV-1) replication at 10–40nM concentrations with minimal cytotoxicity.



(16)

Antitoxoplasma effects

Saudi [48] and coworkers were synthesized derivatives of pyrimidine **(17)**. Toxoplasmosis is a worldwide infection caused by the obligate intracellular protozoan parasite *Toxoplasma gondii*. Derivatives of pyrimidine were evaluated for antitoxoplasma effects in animal experiments.

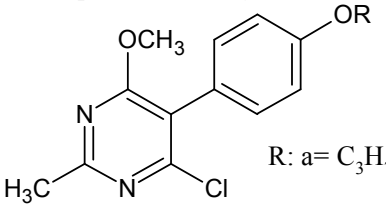


R: a= CH_3, b= OC_2H_5

(17)

Anti tumor activity

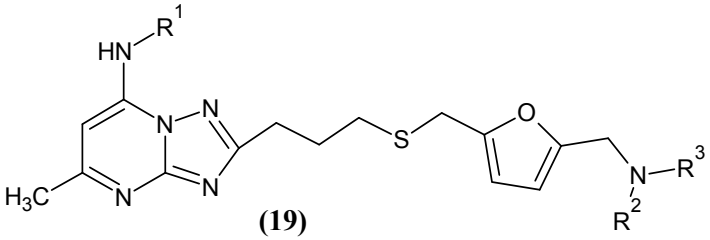
Derivatives of 4-methoxy-6-chloropyrimidines**(18)** were synthesized by Grigoryan [49] and colleagues.Antitumor activity was studied using a sarcoma 45 model as before [50] in 76 white mongrel rats of starting mass 90 – 100 g. Compounds were administered to animals as suspensions in starch paste four days after grafting tumors. They were administered daily for eight days at doses of 50 – 75 mg kg. The criterion for a therapeutic effect was thepercent tumor growth inhibition.



R: a= C_3H_7, b= C_4H_9, c=CH_3

(18)

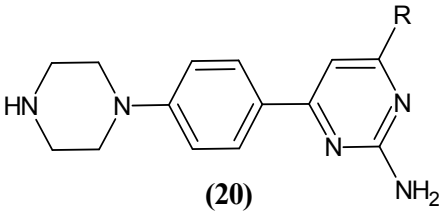
A novel series of [1,2,4]triazolo[1,5-a]pyrimidines **(19)** were synthesized by Zhao [51] *et al.*Anti-tumor activities against cancer cell lines (HT-1080 and Bel-7402) were tested by the MTT method *in vitro*. Among them, many of compounds displayed the best anti-tumor activity with IC50 values of 12.3 μM and 6.1 μM against Bel-7402 and HT-1080 cell lines respectively.



(19)

Antihistaminic activity

Novel Pyrimidines **(20)** were prepared by the condensation of Chalcones of 4′-piperazine acetophenone with guanidine HCl by Rahaman [52] and co-workers. Antihistaminic activity of the synthesized pyrimidine derivatives were estimated on guinea pig of either sex 400g-550g are used. The newly synthesized Pyrimidines showed significant antihistaminic activity. If increases the concentration of Pyrimidine derivatives the % inhibition of histamine also increased.

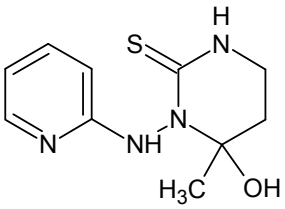


(20)

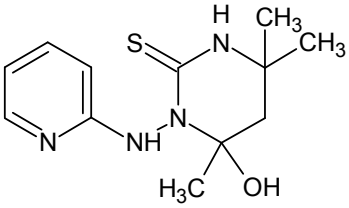
Analgesic activity

A number of pyrimidine derivatives [53] **(21)** and **(22)** were synthesized by condensation reaction. All the synthesized compounds were screened for analgesic as well as antiinflammatory activity Analgesia was

measured by the writhing assay using Swiss mice (15-20 g). Female mice were screened for writhing on day one, by injecting intraperitonially 0.2 cm of aqueous solution of phenylquinone.



(21)



(22)

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