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Review Article

A Review on Pharmacological Aspects of Pyrimidine Derivatives

Vishal Verma^{1*}, Chandra Prakash Joshi¹, Alka Agarwal¹, Sakshi Soni², Udichi Kataria³¹ U S Ostwal Institute of Pharmacy, Mangalwad, Chittorgarh, (Raj.), India² Pacific College of Pharmacy Udaipur, Rajasthan, India³ Geetanjali Institute of Pharmacy Udaipur Rajasthan, India

ABSTRACT

Pyrimidine is an aromatic heterocyclic organic compound similar to pyridine. One of the three diazines (six-membered heterocyclics with two nitrogen atoms in the ring), it has the nitrogens at positions 1 and 3 in the ring. Pyrimidines are typically synthesized by the "Principal Synthesis" involving cyclization of beta-dicarbonyl compounds with N-C-N compounds. Reaction of the former with amidines to give 2-substituted pyrimidines, with urea to give 2-pyrimidiones, and guanidines to give 2-aminopyrimidines are typical. Pyrimidines can be prepared via the biginelli reaction. Many other methods rely on condensation of carbonyls with diamines for instance the synthesis of 2-Thio-6-methyluracil from thiouria and ethyl acetoacetate or the synthesis of 4-methylpyrimidine with 4, 4-dimethoxy-2-butanone and formamide. Pyrimidine derivatives show antimicrobial activity, anticancer activity, anti-inflammatory activity, antidiabetic, and analgesic activity.¹

Keywords: Pyrimidine derivatives, Synthesis, derivatives and pharmacological activities.

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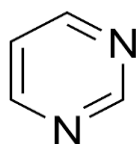
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*Address for Correspondence:

Vishal Verma, U S Ostwal Institute of Pharmacy, Mangalwad, Chittorgarh, (Raj.), India

INTRODUCTION

Pyrimidine is an aromatic heterocyclic organic compound similar to pyridine. One of the three diazines (six-membered heterocyclics with two nitrogen atoms in the ring), it has the nitrogens at positions 1 and 3 in the ring.² The other diazines are pyrazine (nitrogens 1 and 4), pyridazine (nitrogens 1 and 2). Pyrimidine ('m diazine') were known as the breakdown products of uric acid. The first pyrimidine derivative to be isolated was alloxan in 1818 by Brugnatelli. The name pyrimidine (combination of words pyridine and amidine) was first applied by Pinner³.



Pyrimidine

Nucleic acid hydrolysis produces several pyrimidines (uracil, thymine and cytosine) the two types of nucleic acid DNA and RNA, cytosine is found present in both DNA and RNA, while uracil present only in RNA and thymine only in DNA⁴.

PROPERTIES

Physical Properties

Molecular formula	C ₄ H ₄ N ₂
Molar mass	80.088 g mol ⁻¹
Density	1.016 g cm ⁻³
Melting point	20 °C (68 °F; 293 K)
Boiling point	123 °C (253 °F; 396 K)
Acidity (pK _a)	1.10 (protonated pyrimidine)

Like pyridines, in pyrimidines the π-electron density is decreased to an even greater extent.

Therefore electrophilic aromatic substitution is more difficult while nucleophilic aromatic substitution is facilitated. An example of the last reaction type is the displacement of the amino group in 2-aminopyrimidine by chlorine and its reverse.⁵

Electron lone pair availability (basicity) is decreased compared to pyridine. Compared to pyridine, N-

alkylation and N-oxidation are more difficult. The pKa value for protonated pyrimidine is 1.23 compared to 5.30 for pyridine. Protonation and other electrophilic additions will occur at only one nitrogen due to further deactivation by the second nitrogen. The 2-, 4-, and 6- positions on the pyrimidine ring are electron deficient analogous to those in pyridine and nitro- and dinitrobenzene.⁶ The 5-position is less electron deficient and substituents there are quite stable. However, electrophilic substitution is relatively facile at the 5-position, including nitrogen and halogenations.⁷

Reduction in resonance stabilisation of pyrimidines may lead to addition and ring cleavage reactions rather than substitutions. One such manifestation is observed in the Dimer other arrangement.⁸

SYNTHESIS

As is often the case with parent hetero cyclic ring systems, the synthesis of pyrimidine is not that common and is usually performed by removing functional groups from derivatives. Primary syntheses in quantity involving formamide have been reported.⁹

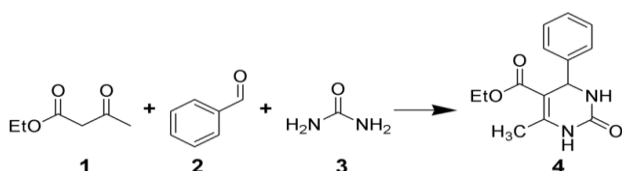
As a class, pyrimidines are typically synthesized by the "Principal Synthesis" involving cyclization of beta-dicarbonyl compounds with N-C-N compounds. Reaction of the former with amidines to give 2-substituted pyrimidines, with urea to give 2-pyrimidiones, and guanidines to give 2-aminopyrimidines are typical.¹⁰

Pyrimidines can be prepared via the biginelli reaction. Many other methods rely on condensation of carbonyls with diamines for instance the synthesis of 2-Thio-6-methyluracil from thiouria and ethyl acetoacetate or the synthesis of 4-methylpyrimidine with 4, 4-dimethoxy-

2-butanone and formamide.¹¹

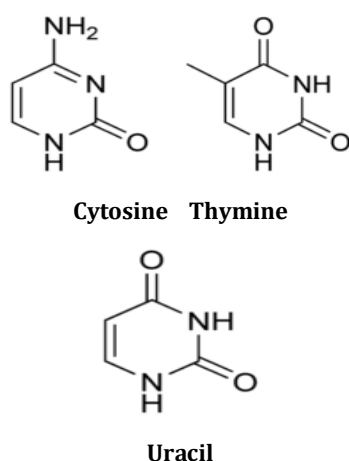
A novel method is by reaction of certain amides with carbonitriles under electrophilic activation of the amide with 2-chloro-pyridine and trifluoromethane sulfonic anhydride.¹²

Biginelli Reaction



Derivatives

Three nucleobases found in nucleic acid, cytosine (C), thymine (T), and uracil (U), are pyrimidine derivatives:^[13]



In DNA and RNA, these bases form hydrogen bond with their complementary purines. Thus, in DNA, the purines adenine (A) and guanine (G) pair up with the pyrimidines thymine (T) and cytosine (C), respectively. In RNA, the complement of adenine (A) is uracil (U) instead of thymine (T), so the pairs that form are adenine: uracil and guanine: cytosine very rarely, thymine can appear in RNA, or uracil in DNA. Other than the three major pyrimidine bases presented, some minor pyrimidine bases can also occur in nucleic acid. These minor pyrimidines are usually methylated versions of major ones and are postulated to have regulatory functions.¹⁴

These hydrogen bonding modes are for classical Watson-Crick base pairing. Other hydrogen bonding modes ("wobble pairings") are available in both DNA and RNA, although the additional 2'-hydroxyl group of RNA expands the configurations, through which RNA can form hydrogen bonds.¹⁵

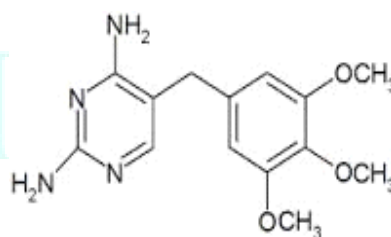
PHARMACOLOGICAL ACTIVITIES

Antimicrobial Activity

Microbes are causative agents for various types of disease like pneumonia, amoebiasis, typhoid, malaria, common cough and cold various infections and some severe diseases like tuberculosis, influenza, syphilis, and AIDS as well. Various approaches were made to check the role of pyrimidine moiety as antimicrobial agent from the discovery of molecule to the present scenario.¹⁶

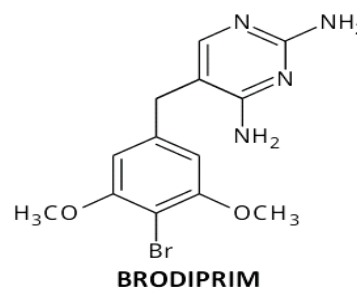
Hitchings, in 1948, made an important observation that a large number of 2, 4-diamino pyrimidines and some 2-amino-4-hydroxy pyrimidines are antagonists of folic acid. These pyrimidines were then eventually proved as inhibitors of the enzyme dihydrofolate reductase (DHFR). Amongst the 2, 4-diaminopyrimidine drugs, pyrimethamine is selective inhibitor of the DHFR of malarial plasmodia.¹⁷

Trimethoprim, antibacterial drug is also a selective inhibitor and selectively inhibits bacterial DHFR.



Trimethoprim

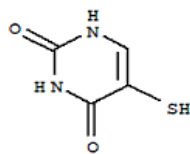
Brodiprim, is also found to be an effective antibacterial compound.



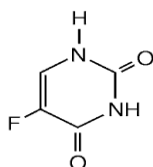
Pyrimidine also shows antifungal properties. Flucytosine is a fluorinated pyrimidine used as nucleosidal anti-fungal agent for the treatment of serious systemic infection caused by susceptible strains of candida and Cryptococcus.¹⁸

Anticancer Activity

The pyrimidine moiety with some substitution shows promising antitumor activity as there are large numbers of pyrimidine based antimetabolites. The structural modification may be on the pyrimidine ring or on the pendant sugar groups. Early metabolite prepared was 5-fluorouracil, a pyrimidine derivative followed by 5-Thiouracil which also exhibits some useful anti-neoplastic activities.¹⁹

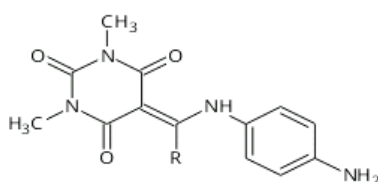


5- Thiouracil



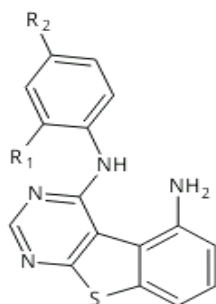
5-Fluorouracil

Reacted 5-benzoyl/ 5-carbaldehyde-/ 5-(3-phenyl acryloyl)-6-hydroxy-1H-pyrimidine-diones with amines provided the corresponding enamines. The investigation for anticancer activity of molecule at 59 human tumor cell lines was done representing leukemia, melanoma and cancer of lung, colon, brain, ovary, breast as well as kidney.



R = H, CH=CH-Ph, Ph

Synthesized 4-(2-Methylanilino) benzo[b] thieno [2, 3-d] pyrimidine (1) and 4-(2-Methoxy anilino) benzo [b] thieno[2, 3-d] pyrimidine (2) which showed a similar cytotoxicity to the standard anti-EGFR gefitinib suggesting a blockade of the EGFR pathway by binding to the tyrosine kinase receptor.²⁰

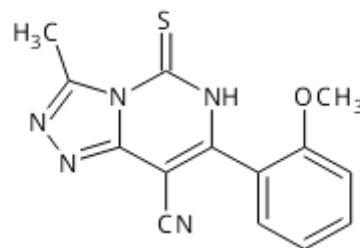


R₁ = CH₃ R₂ = H for (1)

R₁ = OCH₃ R₂ = H for (2)

Synthesized a series of some new pyrimidine derivatives like 7-(2-methoxy phenyl)-3-methyl-5-thioxo-5,6-dihydro[1,2,4]-triazolo[4,3-c]pyrimidine-8-carbonitrile via reaction of

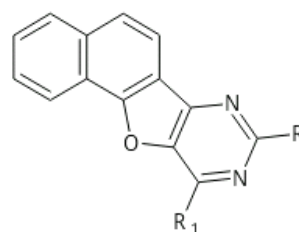
ethylcyanoacetate with thiourea and the appropriate aldehydes namely 2-methyl-benzaldehyde and 2-methoxybenzaldehyde followed via reaction with different reagents. All structures were then screened for bacterial activity and anticancer activity.



Organic compounds and their complex with various ligands have found many applications in biomedicine. Describe the preparation of R₂SnCl₂ complex of some 4H-pyrido [1,2-a] pyrimidin-4-one derivatives as donating ligand having multiple donor sites and examine the cytotoxic activity of some of these complex against fine tumor cell lines.

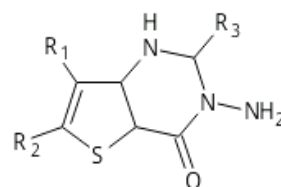
Anti-Inflammatory Activity

Pyrimidine has a remarkable pharmacological efficiency and therefore an intensive research has been focused on anti-inflammatory activity of pyrimidine nucleus. Recently two PCT international applications have been filed for 2-thiopyrimidine derivatives possessing potent activity against inflammation and immune disorders. Pyrimidine was reported by Padama shale *et al.* Carrageenan induced rat paw edema method was employed for evaluating the anti-inflammatory activity. The compounds were given at a dose of 80 mg/kg body weight in albino rats weighing between 150 and 200 g. The edema was produced by injecting carrageenan solution at the left hind paw.



R = CH₃, C₆H₅; R₁ = OCH₃, OC₂H₅, NHC₂H₅, NHC₆H₅

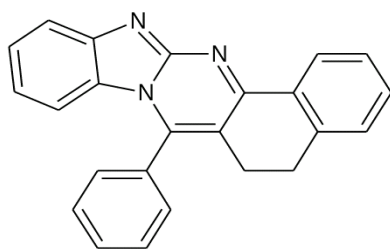
Synthesized some substituted thieno pyrimidines-4-one and screened then for analgesic and anti-inflammatory activity.²¹



R₁, R₂ = -(CH₂)₃, -(CH₂)₅, -(CH₂)₄; R₃ = CH₃

Antidiabetic Activity

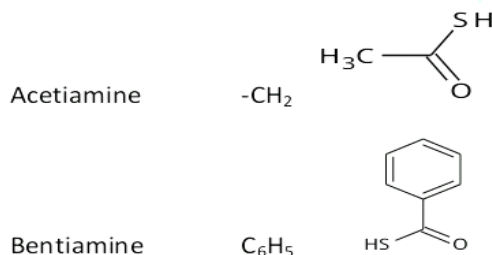
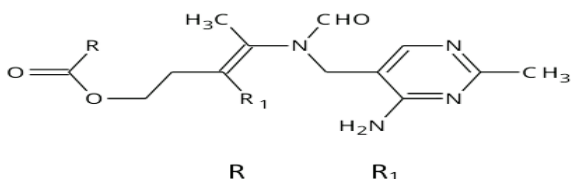
Synthesized some novel pyrimidines derivative having thiazolidine dione. These compounds were evaluated for their glucose and lipid lowering activity using pioglitazone and rosiglitazone as reference compound. Synthesized azolopyrimidine derivatives and compounds were evaluated for hypoglycemic activity.²²



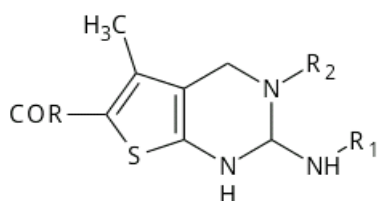
Azolopyrimidine

Analgesic Activity

New forms of thiamine are lipidsoluble like acetiamine, Benti- amine etc., having therapeutic use in beriberi, polyneuritis, encephalopathy, pain, malnutrition and alcoholism and especially in the treatment of long-standing insulin-dependent diabetes mellitus.

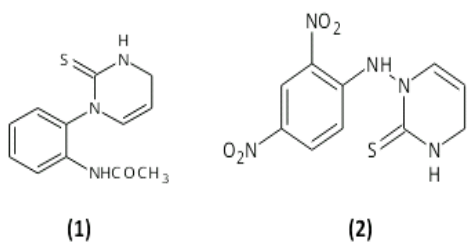


Synthesized substituted thieno [2, 3-d] pyrimidine- 4(3H)- ones and then screened them for analgesic active.



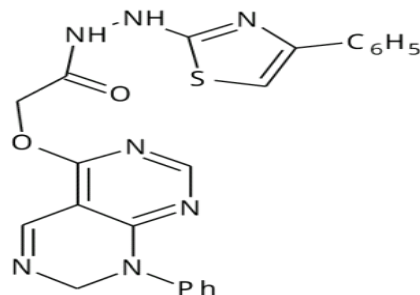
$\text{R} = -\text{CH}_3, -\text{NHPh}; \text{R}_1 = \text{R}_2 = \text{Ph}, o\text{-Anisyl}$

Anti-inflammatory and analgesic activity of synthesized pyrimidine derivatives.



Synthesized some new 2-[c]-phenyl- 1H- pyrazolo [3, 4- d] pyrimidin- 4 yl) Acetohydrazide derivative have been prepared and screened for their analgesic activity by acetic

acid induced writhing test using standard drug diclofenac sodium.²³



Acetohydrazine

CONCLUSION

Pyrimidines occupy a distinct and unique place in our life. This heterocyclic moiety has great biological and medicinal significance. A vast literature has been accumulated over the years and chemistry of pyrimidines continues to be a blossoming field. The biological profiles of this new generation of pyrimidine represent much progress with regard to the older compounds.

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