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AN OVERVIEW ON SYNTHESIS AND BIOLOGICAL ACTIVITY OF PYRIMIDINES

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ABSTRACT

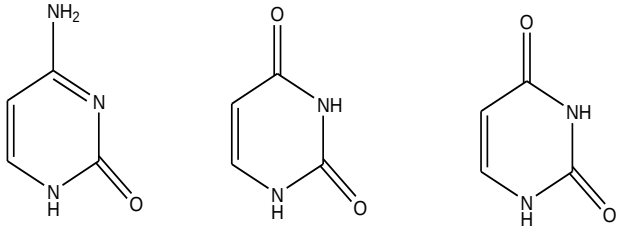
Pyrimidine is a heterocyclic aromatic organic compound containing two nitrogen atoms at positions 1 and 3 of the six-membered ring which shows wide range of biological activities. Numerous methods for the synthesis of pyrimidine and also their diverse reactions offer enormous scope in the field of medicinal chemistry. Pyrimidine possess wide spectrum of biological activities like including antitubercular, antibacterial, antifungal, antiviral, anti-inflammatory, Antimalarial, anticancer, anti-HIV activity. The present review attempts to give brief information about the synthesis and various biological activities of pyimidines and their derivatives.

Key words: Pyrimidine, synthesis, biological activities, anti-cancer, anti malarial.

INTRODUCTION

In medicinal chemistry, the chemist attempts to design and synthesize a medicine or a pharmaceutical agent which will benefit humanity. The practice of medicinal chemistry is devoted to the discovery and development of new agents for treating disease [1].The chemistry of heterocyclic compounds is the most important in the discovery of new drugs. The study or these compounds is of great interest both in theoretical as well as practical aspects[2].Various compounds such as alkaloids, essential amino acids, vitamins, haemoglobin, hormones, large number of synthetic drugs and dyes contain heterocyclic ring systems. There are large number of synthetic heterocyclic compounds, like pyrrole, pyrrolidine, furan, thiophene, piperidine, pyridine and thiazole having important application and many are important intermediates in synthesis [3].

Among all heterocyclic compounds, pyrimidines are one of the most important heterocycles exhibiting remarkable pharmacological activities because it is an essential constituent of all cells and thus of all living matter [4]. Pyrimidine is a six-membered heterocyclic ring containing two nitrogen atoms. It contains two nitrogen atoms at positions 1 and 3 of the six-membered ring. Pyrimidine is a much weaker base than pyridine and soluble in water. Several Pyrimidines have been isolated from the nucleic acid hydrolyses. The metabolism of these pyrimidines is unique and important to understand both biochemical utilization of these compounds and drug metabolism of pyrimidine derivatives [5].



Cytosine Uracil Thymine

Later on Fused pyrimidine chemistry began in 1776, when Scheele isolated uric acid. Pyrimidines are present among the three isomeric diazines. Many simple fused pyrimidines such as purines and pteridines are biologically active by themselves and essential components of very important naturally occurring substances (i.e., nucleic acids). Examples of some biologically active pyrimidine derivatives are prazosin, quinethazone, trimethotrexate, folic acid, riboflavin [6].

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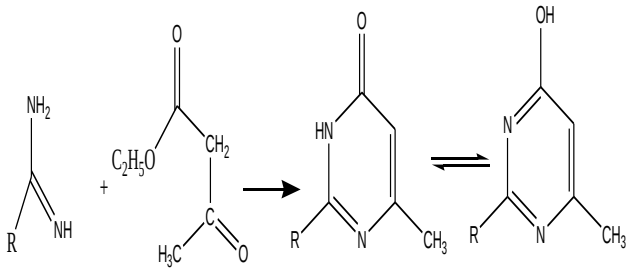
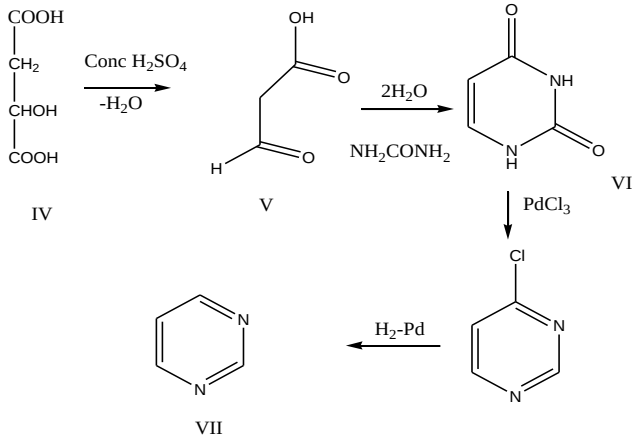
Synthesis Of Pyrimidines

Pyrimidines are generally prepared by the condensation between a three carbon compounds and compounds having the amidine structure (I) where R = OH (urea), SH or SR (thiourea or its s-derivative) in the presence of catalyst sodium hydroxide or sodium ethoxide. This general reaction may be illustrated by the condensation of acetamidine with ethyl acetoacetate (II) to form 4-hydroxy-2, 6-dimethylpyrimidine (III) [7].



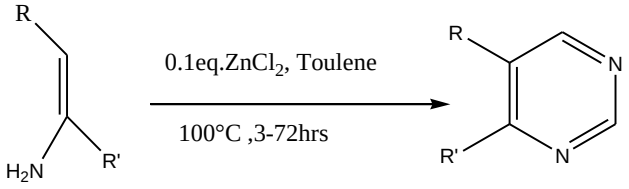
I II III

Decarboxylation of malic acid (IV) with concentrated sulphuric acid forms a β-ketoacid (V) which on reaction with urea produces uracil (VI). Uracil can be converted to pyrimidine (VII) in the following step [8].



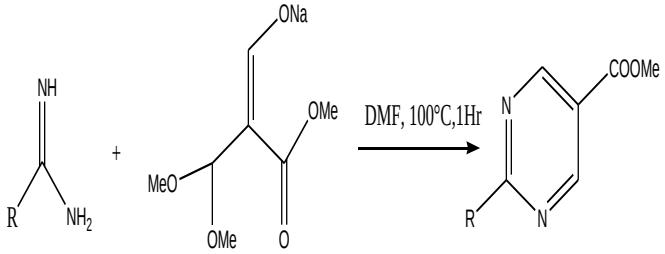
IV V VI VII

Sasada et al reported a $ZnCl_2$-catalyzed three-component coupling reaction for the synthesis of various 4,5-disubstituted pyrimidine derivatives. In this reaction functionalized enamines, triethyl orthoformate, and ammonium acetate are used. Mono- and disubstituted pyrimidine derivatives can be successfully prepared using methyl ketone derivatives instead of enamines.



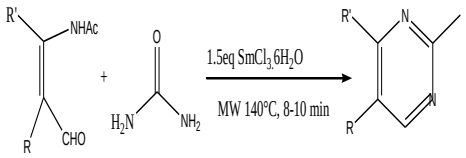
R,R' = Ar

A method for the synthesis of 2-substituted pyrimidine-5-carboxylic esters involves the reaction of sodium salt of 3,3-dimethoxy-2-methoxycarbonylpropen-1-ol (VIII) with a variety of amidinium salts (IX) to afford the corresponding 2-substituted pyrimidine-5-carboxylic esters (X) [9].



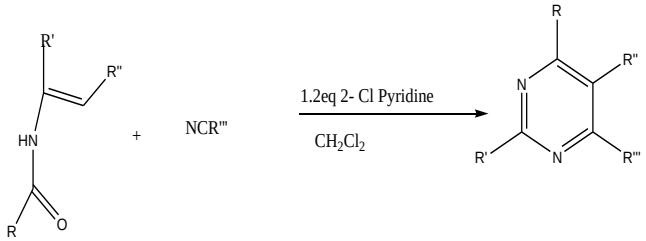
VIII IX X

Barathkur et al., reported a novel and efficient synthesis of pyrimidine from β-formyl enamide which involves samarium chloride catalysed cyclisation of β-formyl enamides (XI) using urea (XII) as a source of ammonia under microwave irradiation [10].

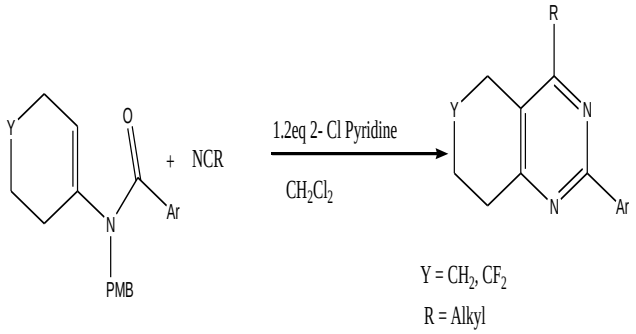


XI XII

A single-step conversion of various N-vinyl and N-aryl amides to the corresponding pyrimidine and quinazoline derivatives involves amide activation with 2-chloropyridine and trifluoro methane sulfonic anhydride followed by nitrile addition into the reactive intermediate and cycloisomerisation[11].



An array of tetra substituted saturated fused pyrimidines has been synthesized through a simple and efficient one-pot operation. The strategic utilization of the N-PMB group enabled the construction of a broad range of N-vinyl tertiary enamide starting materials. This stands as a flexible approach to functionalized pyrimidines with the capability of manipulating either ketone, acid chloride, or nitrile reaction partners. [12]

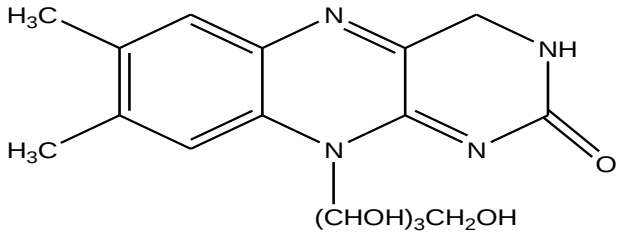


BIOLOGICAL IMPORTANCE

In medicinal chemistry pyrimidine derivatives have been very well known for their therapeutic applications. The presence of a pyrimidine base in thymine, cytosine and uracil, which are the essential building blocks of nucleic acids, DNA and RNA is one of the possible reasons for their activities [13].

Example: Thymine, Cytosine, Uracil.

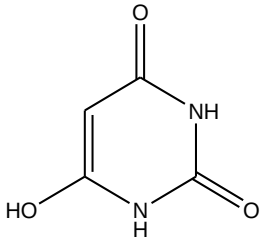
Vitamins are essential for body. Pyrimidine ring is found in vitamins like, Example: riboflavin, thiamine and folic acid [14].



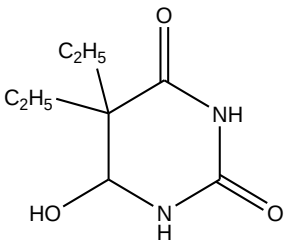
RIBOFLAVIN

Pyrimidine nucleus is also present in barbituric acid and its several derivatives e.g. Veranal which are used as hypnotics [15] .

Example: barbituric acid, veranal.



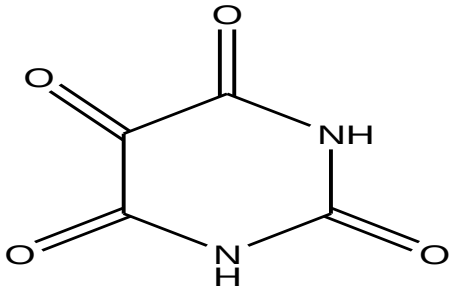
Barbitiric acid



Vernal

In addition to this, pyrimidine nucleus is also found in alloxan, which is known for its diabetogenic action in a number of animals [16].

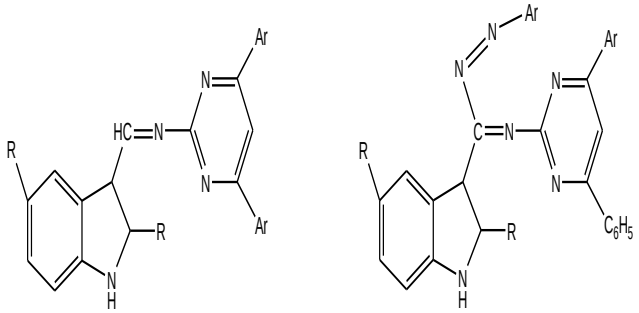
Example: alloxan.



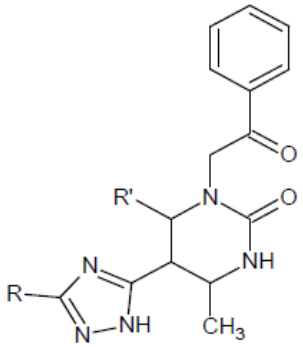
Alloxan

ANTIMICROBIAL ACTIVITY

Padmashri *et al.*, reported the synthesis 2- (2', 5' substituted indolidene amino- 3'- yl) - 4, 6- diaryl pyrimidines (I) and 2 [2', 5'- substituted indole- 3'- yl) (phenyl azo) methylene imino]- 4, 6- Diaryl pyrimidine with a view to screen them for their antimicrobial activity against the gram negative Bacteria E. Coli and Gram-positive bacteria *S. aureous* by cup plate method and show antifungal activity against *A. niger* and A. *flavus* [17].



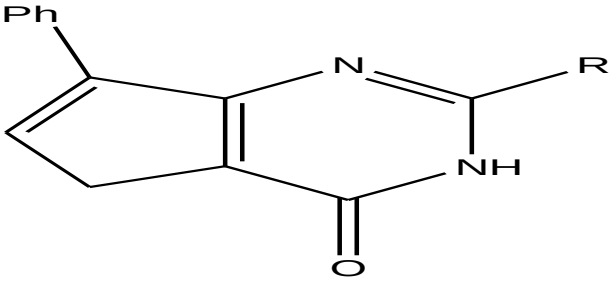
Mishra et al. synthesized various derivatives of pyrimidines and reported their fungicidal activities against *P. infestans* and *C. falcatum* by the usual agar plate method. [18].



R= C_6H_5, p-ClC_6H_4, m-$NO_2C_6H_4$, p-$OCH_3C_6H_4$; R'= m-$NO_2C_6H_4$, p- $OCH_3C_6H_4$

ANTIHYPERLIPIDEMIC ACTIVITY

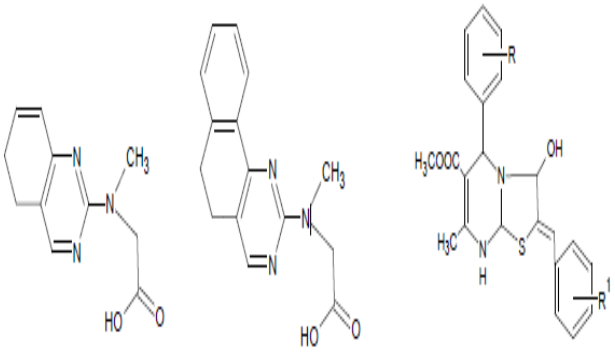
CJ Shishoo *et al.*, have prepared some 2-substituted-6-phenyl and 7-phenyl thieno [3,2-d]pyrimidin-4-ones through cyclo condensation of the corresponding thiopheno amino esters with a variety of nitriles in the presence of dry hydrogen chloride gas and reported anti hyper -lipidemic activity in a few thieno pyrimidines[19].



ANALGESIC AND ANTI-INFLAMMATORY ACTIVITIES

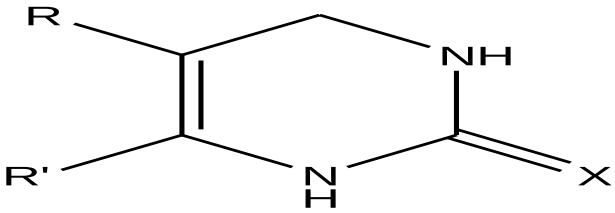
A series of N-methyl-N-pyrimidin-2-yl glycines, having the pyrimidine ring fused with a cyclohexane [N-methyl-N-(5,6,7,8-tetrahydroquinazolin-2 yl) glycine], cyclohexene [N-methyl-N-(5,6-dihydroquinazolin-2-yl) glycine],1,2,3,4-tetrahydronaph –thalene [N-methyl-N-(5,6-dihydrobenzo[e] quinazolin-2-yl) glycine] and benzopyrane [N-methyl-N-(5-phenyl-5H- [1]benzopyrano

[4,3-d] pyrimidin-2-yl) glycine] have been prepared and tested for anti-inflammatory activity [20].



ANTINEOPLASTICS AND ANTICANCER AGENTS

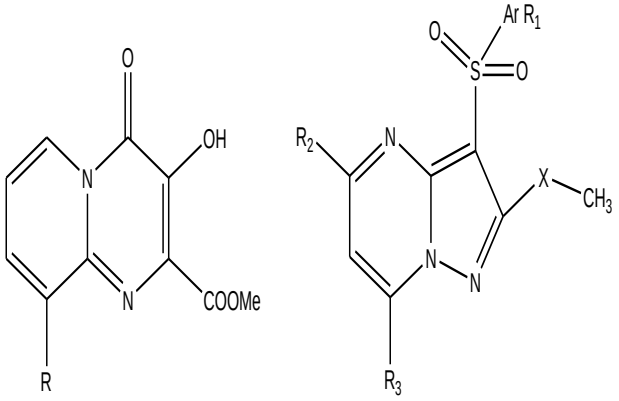
There are a large number of pyrimidine-based antimetabolites. They are usually structurally related to the endogenous substrates that they antagonize. The structural modification may be on the pyrimidine ring or on the dependent sugar groups. One of the early metabolites prepared was 5-fluorouracil3,4 (5-FU), a pyrimidine derivative. 5-Thiouracil also exhibits some useful antineoplastic activities [21].



X = O, R = F, R1 = H, 5-fluorouracil X = O, R = SH, R1 = H, 5-thiouracil

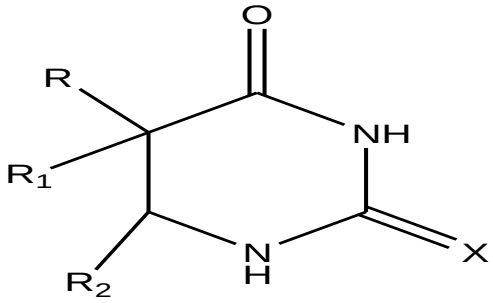
ANTI-HIV AGENTS

An efficient and reliable synthesis of the heterocyclic scaffold methyl-3-hydroxy-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxylate the scope of the synthesis regarding the introduction of substituents on the pyrido fused ring is explored. Thus they devised a new scaffold for HIV-1 integrase inhibitors [22].



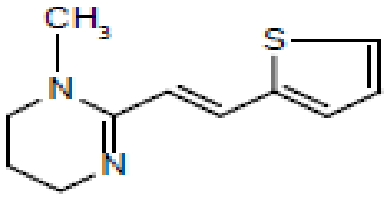
DRUGS FOR HYPERTHYROIDISM

2-Thiouracil and its alkyl analogue, thiobarbital are effective drugs against hyperthyroidism. Propyl thiouracil is used as a drug for hyperthyroidism with minimum side effects [23].



ANTHELMENTICS

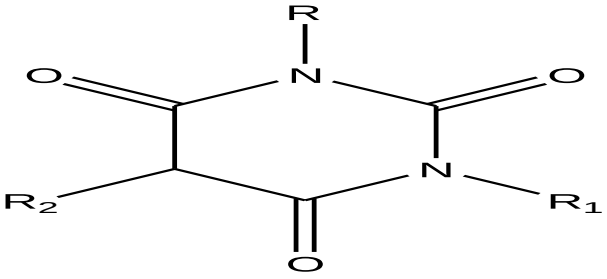
These drugs have the ability of ridding the body of parasitic worms. Pyrantel pamoate is a depolarizing neuromuscular blocking agent that causes spastic paralysis in helminthes and is employed in the treatment of infestations caused by pinworms and roundworms 44. [24].



Pyrantel pamoate

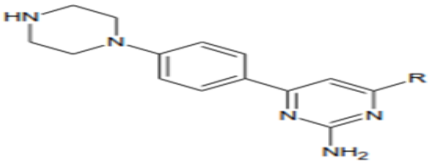
CNS ACTIVITY

Agents involved in this category include sedatives, hypnotic, anticonvulsants, anxiolytic agents, pyrimidine anaesthetics etc. Large variety of barbiturates are used as CNS active agents and are classified as short, intermediate and long acting depending upon duration of action [25].



MISCELLANEOUS ACTIVITY

Novel pyrimidines were synthesized by the condensation of chalcones of 4′-piperazine acetophenone with guanidine HCl. The recorded % of histamine inhibition showed significant antihistaminic activity when compared to the reference antihistaminic drug mepiramine [26].



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 versatile synthetic applicability and biological activity of these heterocycles will help the medicinal chemists to plan, organize and implement new approaches towards discovery of novel drugs.

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