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DihydroPyrimidinones-A Versatile Scaffold with Diverse Biological Activity

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Abstract

Dihydropyrimidinones are important constituents of many important bioactive heterocyclic compounds. They possess diverse biological activities such as anticancer, antimicrobial, antihypertensive, antiulcer, antiinflammatory, antitubercular, antimalarial, antioxidant etc. This developed an interest in reviewing new drug entities based on dihydropyrimidinone ring. This review brings about an overview of novel drug molecules of dihydropyrimidinones and also urges to synthesize more moieties for better enhanced biological activity.

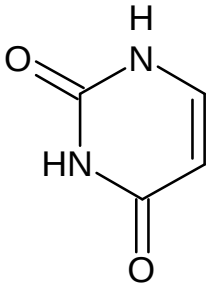
Keywords: Dihydropyrimidinones, Antimalarial, Anticancer, Antimicrobial, Antihypertensive

INTRODUCTION

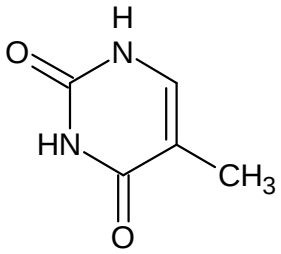
Pyrimidine nucleus is an important pharmacophore in medicinal chemistry. The synthesis of novel pyrimidine derivatives remains a main focus of modern drug discovery. The versatility of new generation pyrimidine would represent a fruitful pharmacophore for development of better medicinal agents. Researchers have been attracted toward designing more potent pyrimidine derivatives having wide range of biological activity.

Pyrimidine is the most important member of all the diazines, as this ring system occurs widely in living organisms. Pyrimidine was first isolated by Gabriel and Colman in 1899. Pyrimidine is a colorless compound with m.p.225^{0}c and b.p. 124^{0}c. It is weakly basic as compared to pyridine or imidazole. Presence of alkyl groups enhances the basicity. Pyrimidine ring is less aromatic compared to pyridine and benzene[1].

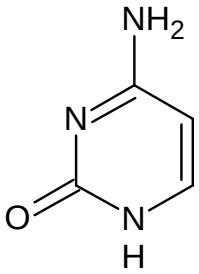
In medicinal chemistry pyrimidine derivatives have been very well known for their therapeutic applications. The essential building blocks of nucleic acids, thymine, cytosine and uracil has pyrimidine nucleus. Pyrimidine ring is found in vitamins such as riboflavin, thiamine and folic acid(Fig.1). Pyrimidine nucleus is also present in barbituric acid and its several derivatives are used as sedatives and hypnotics[2]



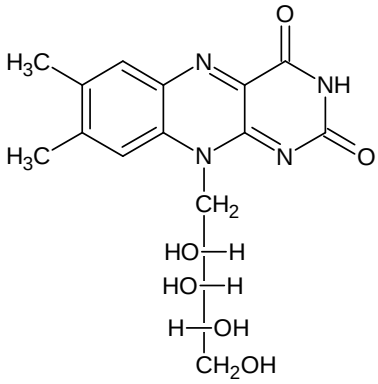
(1) Uracil



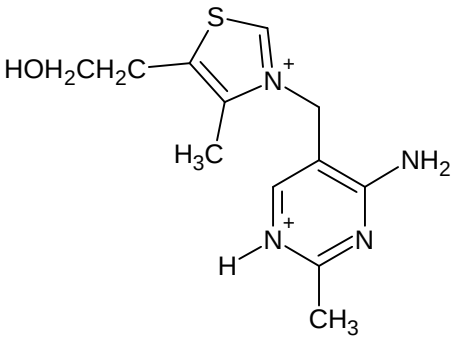
(2) Thymine



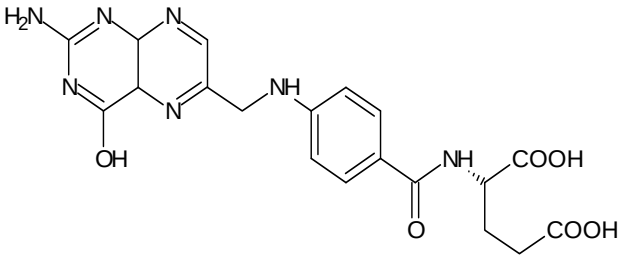
(3) Cytosine



(4) Riboflavin



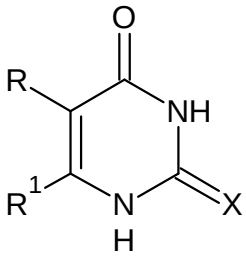
(5) Thiamine



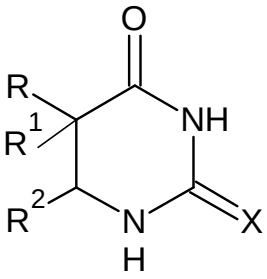
(6) Folic acid

Figure 1: Pyridimine ring system in nucleic acids and vitamins

Pyrimidines are most widely studied drugs as antineoplastics[3]. 5-fluorouracil exhibits antineoplastic activity. Anicancer drugs containing pyrimidine nucleus includes mopidamol, nimustine, raltitrexed, uramustine and trimetrixate.



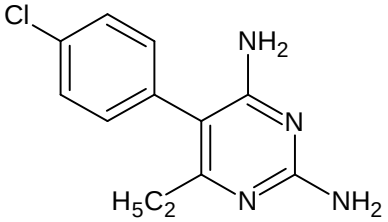
(7a, b)
(7a) X=O, R=F, R_1=H, 5-fluorouracil
(7b) X=O, R=SH, R_1=H, 5-thiouracil



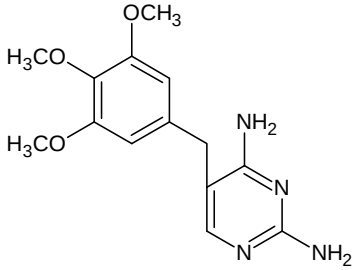
(8a,b)
(8a) R=R_1=C_2H_5, R_2=O, X=S,thiobarbital
(8b)R=R_1=H,R_2=C_3H_7,X=S,propylthiouracil

Figure 2. Pyrimidines as anticancer and antithyroid agents

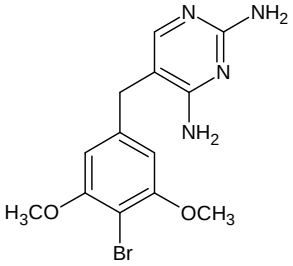
Thiobarbital and propyl thiouracil is used as a drug for hyperthyroidism(Fig.2). Another area of important use of pyrimidine has been used as antibacterial agents. Trimethoprim is an antibacterial drug which selectively inhibits bacterial dihydrofolate reductase. 2,4 diaminopyrimidine are selective inhibitors of malarial parasites. Brodimoprim is an effective antibacterial compound. Flucytosine is a fluorinated pyrimidine used as antifungal agent against candida and Cryptococcus(Fig.3). Pyrantel pamoate is used as an anthelmintic used in the treatment of pinworm and round worm infestations.[4,5,6]



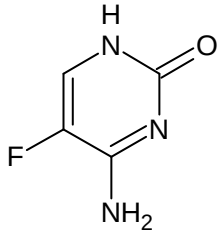
(9) Pyrimethamine



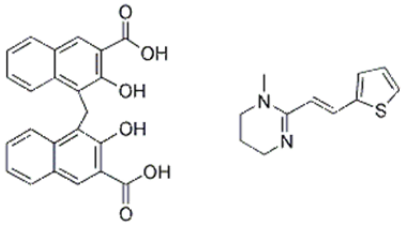
(10) Trimethoprim



(11) Brodimoprim



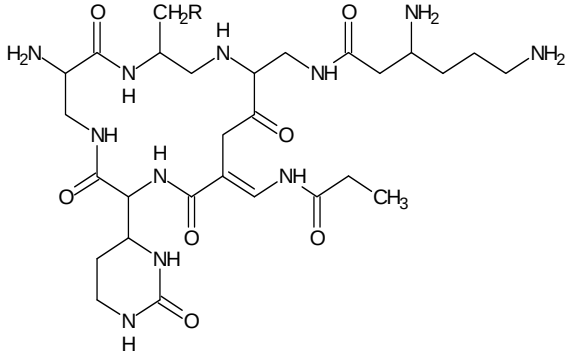
(12) Fluocytosine



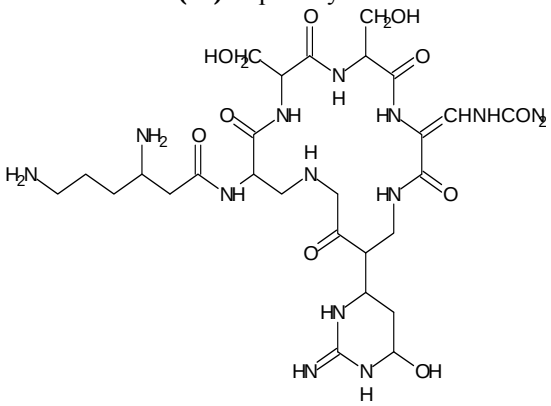
(13) Pyrantel pamoate

Figure 3: Antimicrobial agents with pyrimidine moiety

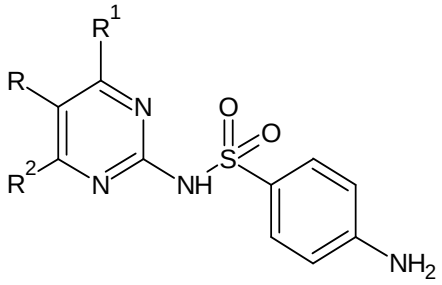
Capreomycin and Viomycin are bacteriostatic antituberculin drugs containing pyrimidine. Other pyrimidines of current medicinal interest are antibacterial sulpha drugs such as sulphadiazine, sulphamerazine and sulphadimidine(Fig.4). Antibiotic, Bacimethrin has also been synthesized.[7]



(14) Capreomycin



(15) Viomycin



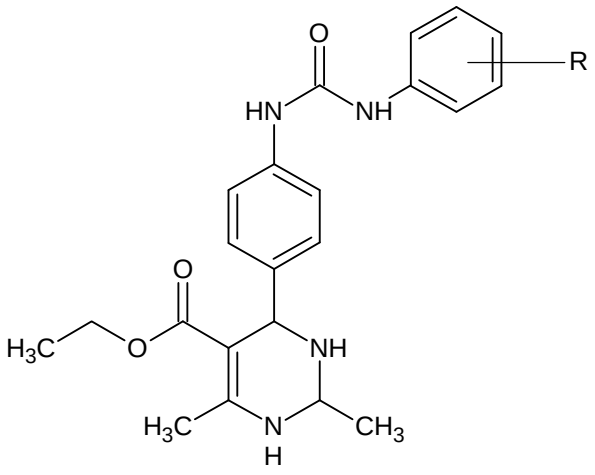
(16a) R=R_1=R_2=H,Sulfadiazine
16(a,b,c) **(16b)**R=H, R_1= CH_3, R_2=H,Sulfamerazine
(16c) R=H,R_1=CH_3,R_2=CH_3,Sulfadimidine

Figure 4. Sulpha drugs of pyrimidines

Urapidil is used in urinary obstruction caused by benign prostate hyperplasia. Pyrimidines have also generated interest as antiviral agents such as 5-Iododeoxyuridine[8].

Dihydropyrimidinones as anti-inflammatory agents

Rajesh H.Tale et al[9] has synthesized a series of novel 3, 4 dihydropyrimidin-2(1H)one urea derivatives by Biginelli reaction, reduction followed by reaction of amines with different arylisocyanates. **(17)** Devanand B.Shinde et al[10] has reported the synthesis of series of [4,6-(4-substituted aryl)-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl]-acetic acid derivatives by base catalysed condensation of β-aroyl propionic acid, thiourea with aldehyde in ethanol. Antiinflammatory activity was evaluated in vivo and compared with standard drug diclofenac sodium **(18)** (Fig.5)



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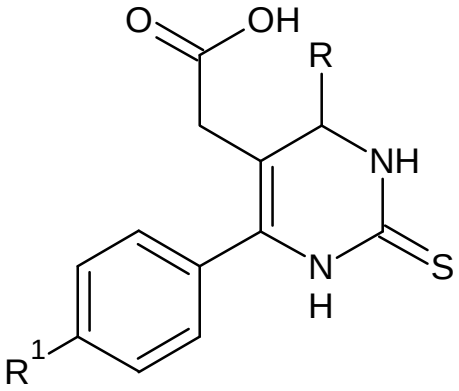
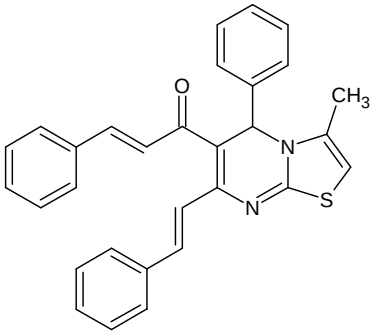


(18)

Figure 5. Dihydropyrimidinones reported as antiinflammatory agents

Dihydropyrimidinones as antimalarial agents

Seerat Fatima et al[11] has synthesized a series of (e)-1-(3-methyl-5-aryl-7-styryl-5H-thiazolo[3,2-a]pyrimidin-6-yl)-3-arylprop-2-en-1-ones and evaluated for antimalarial activity against Plasmodium falciparum and HIV-RT inhibitors **(19)** Jeffery L Brodsky et al[12] has measured whether pyrimidinone-amides, a new class of Hsp70 modulators, could inhibit the replication of the pathogenic P.falciparum stages in human red blood cells **(20,21,22)** (Fig.6)



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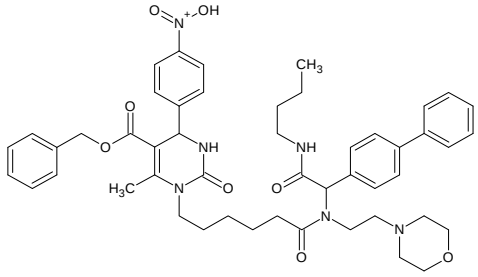

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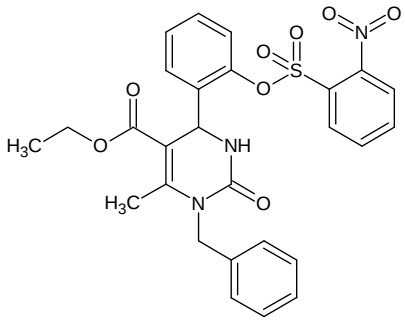

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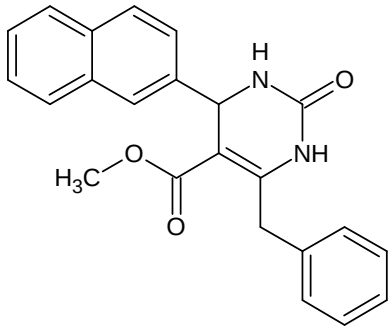

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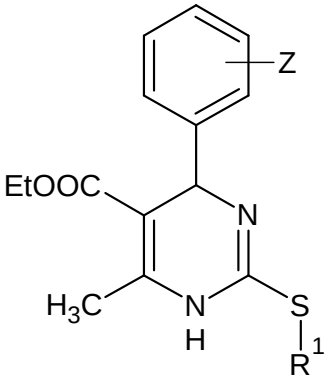
Figure 6. Dihydropyrimidinones reported as antimalarial agents

Dihydropyrimidinones as antiulcer agents

Kulbhudhsn Rana et al[13] has synthesized various 6-methyl-4-substitutedphenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl esters and 6-methyl-4-substitutedphenyl-2-S-alkyl(benzyl)-1,4-dihydropyrimidine-5-carboxylic acid ethyl esters and evaluated their anti-ulcer activity **(23)** (Fig.7)

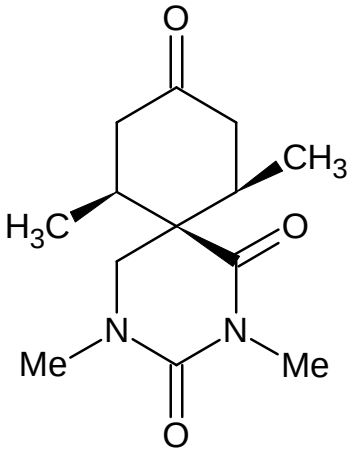


(23)

Figure 7. Dihydropyrimidinones reported as antiulcer agents

Dihydropyrimidinones as antidiabetic agents

Mohammad Shahidul Islam et al[14] has synthesized a series of dihydropyrimidines derivatives and evaluated their α-glucosidase enzyme inhibition activity in comparison to the standard drug acarbose. The compounds were also evaluated for their in vitro Cytotoxic activity against PC-3, HeLa and MCF-3 cancer cells lines and 3T3 mouse fibroblast cell line **(24)** R.P.Tripathi et al[15] has synthesized some dihydropyrimidinones on cyclative amidation of glycosyl ureas and screened for their α-glucosidase inhibitory activity. Some of the compounds exhibited strong inhibition against rat intestinal α-glucosidase **(25)** (Fig.8)



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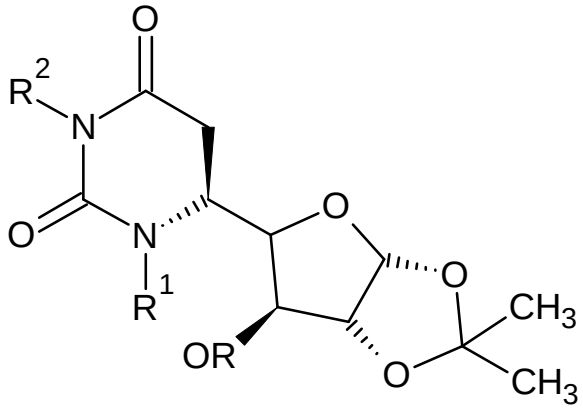

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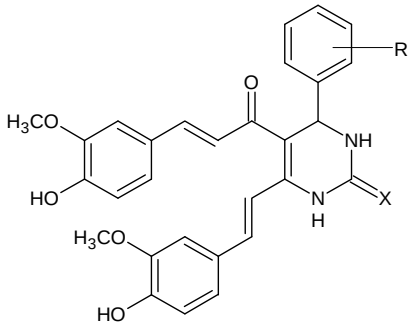
Figure 8. Dihyropyrimidinones reported as antidiabetic agents

Dihydropyrimidinones as anticancer agents

Jaggi Lal et al[16] Has synthesized 3,4 dihydropyrimidinones of curcumiin by multi-component one-pot and tested for in vitro cytotoxicity against three human cancer line Hep-g2, HCT-116 and QG-56 **(26)** Emily.J.Hanan et al[17] has reported the identification of 4-aminoindazolyl-dihydrofuro[3,4-d]pyrimidines as non-covalent inhibitors of EGFR, with excellent activity against the T790M resistance double mutants and initial single activating mutants **(27)** Hanna A.Tawtik et al[18] has synthesized dihydropyrimidine derivatives with multifunctional aromatic substitutions and investigated their tumor anti-initiating activity **(28,29)** (Fig.9)



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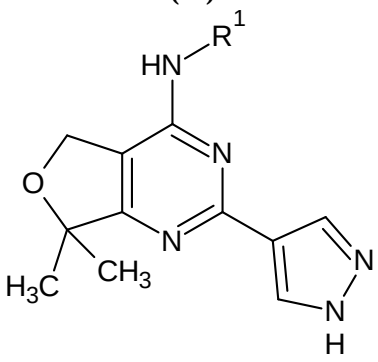

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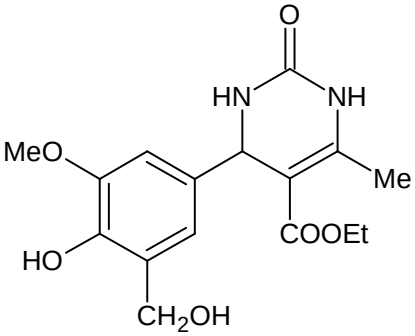

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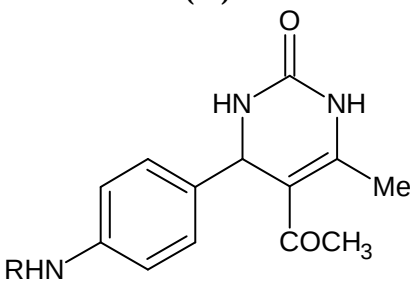
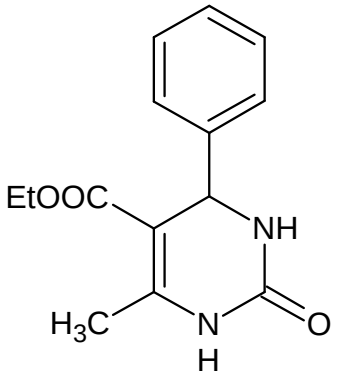


(29)

Figure 9. Dihydropyrimidinones reported as anticancer agents

Dihydropyrimidinones as antimicrobial agents

Okram Mukherjee Singh et al[19] has synthesized a series of dihydropyrimidinones by Biginelli reaction in presence of copper (II) chloride and examined their antifungal activities against the radial growth of three fungal species viz., Trichoderma hammatum, Trichoderma koningii and Aspergillus niger **(30)** Mithun Ashok et al[20] has synthesized a series of 2-(arylidene/5-arylfurfurylidene)-5-(4-methylthiophenyl)-6-carbethoxy-7-methyl-5H-thiazolo[2,3-b]pyrimidin-3(1H)ones by a three component reaction and screened for their antibacterial and antifungal activity **(31)** (Fig.10)



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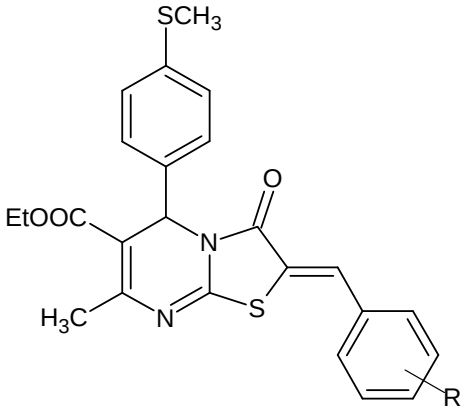

(31)

Figure 10. Dihydropyrimidinones reported as antimicrobial agents

RESULTS AND DISCUSSION

Vast literature survey reveals that dihydropyrimidinones as a heterocyclic moiety occupies a unique place in our life. The review shows that the 5th position of pyrimidine moiety is most prone to substitution and shows prominent biological activity. The review on this nucleus and its chemistry will offer the medicinal chemist to involve in drug development process for newer drugs of pyrimidinones with multiple biological activities.

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