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AN OVERVIEW ON BIOLOGICAL AND MEDICINAL IMPORTANCE OF PYRIMIDINES

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Abstract

Pyrimidine is six member heterocyclic aromatic compounds similar to benzene containing two nitrogen atoms at 1, 3-position in the ring which shows wide range of biological activities. This review article delineates the biological and medicinal importance of one of the highly and most important pyrimidine heterocycles. The present review attempts to give a brief information about the biologically as well as medicinally important compounds containing pyrimidine and its derivatives

Keywords: Biological significance, heterocycles, medicinal significance, pyrimidine.

Subject Classification: Subject Classification 2018

1. Introduction

The compounds containing pyrimidine moiety have a broad occurrence in many natural and synthetic compounds from vitamins to antibiotics such as Thiamine, Riboflavin, Folic acid, Alloxan, Bacimethrin, the barbiturates and the anti- HIV drug Zidovudine [1] (**Fig.1.1** and **Fig.1.2**). Pyrimidine nucleus is the building block of nucleic acids, i.e. RNA and DNA. Uracil, Cytosine and Thymine contain pyrimidine unit which is found universally in living organisms.

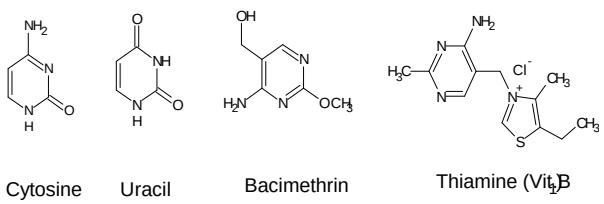

Fig. 1.1: Examples of some natural pyrimidine derivatives

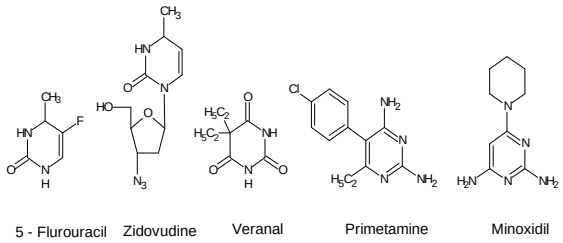

Fig.1.2: Examples of some bioactive synthetic pyrimidine analogous

Pyrimidine is synthesized through the de novo pathway by organisms [2]. The de novo biosynthetic pathway originated with bicarbonate and ammonia, which are derived from glutamine in a multistep process. The first harmonized step in pyrimidine biosynthesis is the formation of carbamoyl phosphate by carbamoyl phosphate synthetase. Carbamoyl phosphate synthetase, aspartate transcarbamoylase, dihydroorotase, dihydroorotate dehydrogenase, UMP synthase, UMP kinase, nucleoside

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diphosphate kinase and CTP synthetase are the enzymes involved in the biosynthesis of pyrimidine. Carbamoyl phosphate and aspartate are the originators of six atoms of the pyrimidine ring (**Fig.1.3)**.

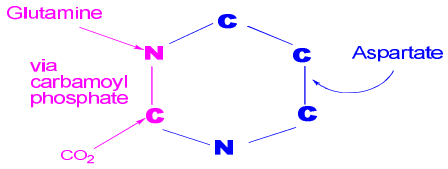


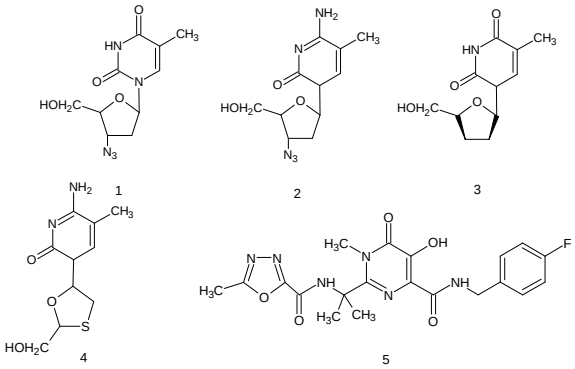
Fig.1.3: Biosynthetic origins of pyrimidine ring atoms

2. Biological and medicinal importance of pyrimidine derivatives

Nitrogen containing heterocycles occupy a unique and distinct position in medicinal chemistry. This heterocyclic compound shows notable biological and pharmaceutical properties. Pyrimidine and their fused analogue are one of the important heterocyclic compounds present in natural products and are building blocks of DNA and RNA. The presence of pyrimidine moiety in thymine, cytosine and Uracil is one possible reason for their significant biological activity.

2.1. Anti-HIV pyrimidine derivatives

HIV is the causative agent of AIDS. Zidovudine or azidothymidine (AZT) is the first US approved antiretroviral drug used for the treatment of AIDS, which inhibit the enzyme reverse transcriptase marketed under the brand name Retrovir (**1**). Zidovudine is an analog of thymidine which contains azido group at 3- position of dideoxyribose moiety. Zalcitabine (**2**), Stavudine (**3**) are pyrimidine nucleosides are effective against HIV when they are given in combination with Zidovudine [3-4]. Lamivudine (**4**) having pyrimidine moiety is also effective against HIV [5-6]. Raltegravir (**5**) is an antiretroviral drug used for the treatment of HIV infection receives approval of FDA in 2007 [7-8].



2.2.Anti-inflammatory pyrimidine derivatives

Epirizole (**6**) is an effective NSAID agent used for the treatment of inflammation and painful condition [9-10]. Dulcerozine (**7**) was also reported to exhibit anti-inflammatory activity. It is also used for the induction of ulcer in experimental animal [11]. The 6-indolylideneamino-2-thiouracile (**8**) showed more potent anti-inflammatory activity than Ibuprofen [12]. The pyrimidine-3-pyrazolin-5-ones and pyrimidine-1, 2, 4, 5, 6, 7-3*H*-hexahydroindazol-3-one derivatives (**9-10**) shows potent anti-inflammatory, analgesic and antipyretic activities than Indomethacin [13]. The derivatives of 4-amino-5-cyano-2, 6-diphenylpyrimidine (**11**) and 4-phthal- imidophenyl derivatives (**12**) were reported to be twofold active as anti-inflammatory agents as acetylsalicylic acid [14].

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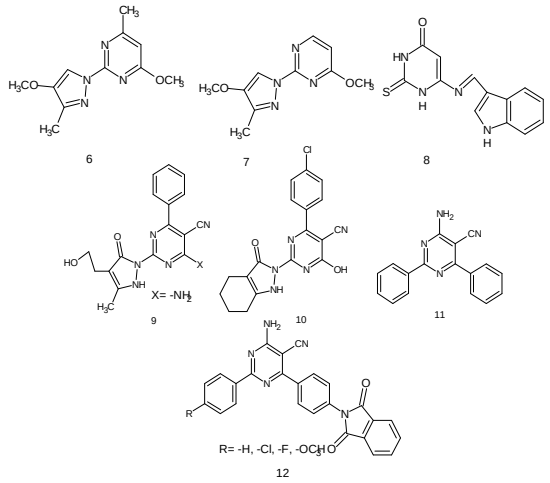
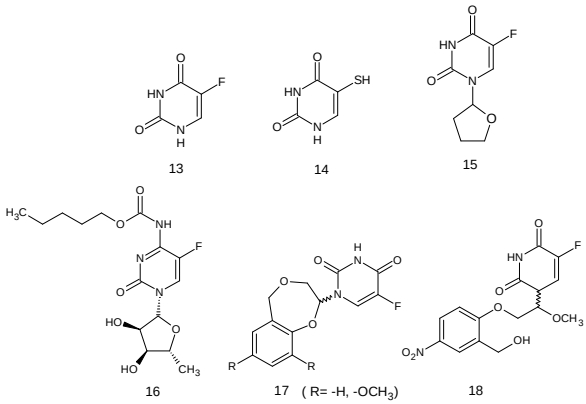
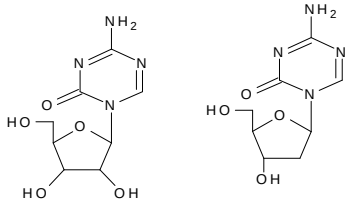




2.3. Anti-cancer pyrimidine

There is a numerous number of pyrimidine based anti-metabolite. 5-flurouracil (5-FA) (**13)** and 5-thio-uracil (**14)** were frequently used for cancer therapy [15-16]. Due to limited selectivity and severe toxicity of 5-flurouracil imposed the development of new potent and selective anticancer agents [17]. 5-fluoro-1-(2-tetrahydrofuryl)-uracil (**15)** has been widely used in the treatment of cancer because of its low toxicity relative to 5-FU [18] and used for the treatment of breast, gastric and colorectal cancers, and also in the treatment of various types of metastatic solid tumors [19]. Capecitabine (**16)** is a prodrug of 5-flurouracil an orally-administered chemotherapeutic agent used in the treatment of metastatic breast and colorectal cancers, gastric cancer and oesophageal cancer which inhibits the growth of tumor tissue [20-21]. The derivatives of 1-(2, 3-dihydro-5*H*-14-benzodioxepin-3-yl)-5-fluorouracils **(17),** and the 1- [o-(hydroxymethyl) phenoxyethyl-1-methoxy]-5-fluorouracil **(18)** act as 5-FU prodrugs were effective against MCF-7 human breast cancer cell line [22].

Azacitidine (**19)** and its deoxy derivative decitabine (**20)** having a pyrimidine ring are currently approved drugs used for the treatment of myelodysplastic syndrome, chronic myelomonocytic leukemia, and acute myeloid leukemia [23].



2.4. Pyrimidine anti-biotics

Many synthetic or natural compounds having pyrimidine moiety were used as antibiotics. Bacimethrin (**21)** is a naturally occurring pyrimidine antibiotic isolated from *Bacillus megatherium* which is used against many bacteria and yeast [24]. Sparsomycin (**22)** is a metabolite of *Streptomyces sparsogenes* or *Streptomyces cuspidosporus* first isolated in 1962 [25]. It displays activity against bacteria and fungi [26]. Sparsomycin and some of their derivatives also shows good activity against various human tumors [27].

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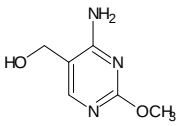

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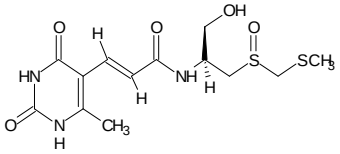

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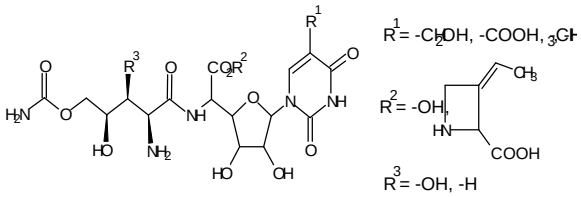
Polyoxins (**23**) and nikkomycins are naturally occurring glycosylated pyrimidine antibiotics, which are isolated from *streptomyces cacoi var. asoenis* and *streptomyces tendae* respectively and effective inhibitors for chitin synthase, which is responsible for the formation of chitin, which is a protective barrier for the cell wall in yeast and fungi [28-29].



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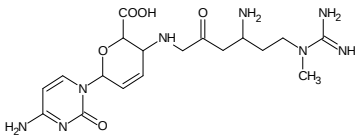
Blasticidin S (**24)** is an antibiotic produced by *streptomyces griseochromogenes* [30-31] is a nucleoside analog consisting of a cytosine, which is widely used as a fungicide to control rice blast disease [32]. Azoxystrobin (**25)** and fluoxastrobine (**26)** are efficient fungicides commonly used in agriculture to control fungal diseases [33-34]. Disubstituted pyrimidine containing amicetin (**27)** antibiotic is active against acid fast and gram-positive bacteria [35].



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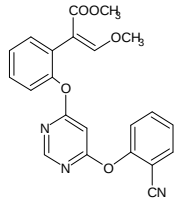

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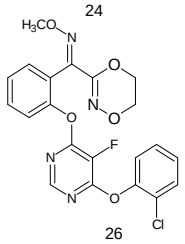

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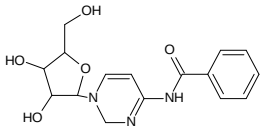

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2.5. Anti-bacterial pyrimidine

Several mono, di and trisubstituted pyrimidine derivatives of sulfa drugs have been recognized as potent bactericidal agents. Sulfa drugs such as sulfadiazine, sulfamerazine, and sulfadimidine are better than other sulfonamides drugs. They are effective against bacterial infections and patients who are allergic to penicillin's [36]. Trimethoprim (**28)** (2, 4-diamino-5-(3, 4, 5-trimethoxybenzyl) pyrimidine) was reported as a potent bacteriostatic drug mainly in the prophylaxis and treatment of urinary tract infections [37].

Trimethoprim which is dihydrofolate reductase inhibitors (DHFRI) was primarily used as monotherapy for the treatment of urinary tract infections. Use of trimethoprim in combination with sulfonamides possesses good antibacterial activity, resulting synergistic effect [38]. The trimethoprim analog epiroprim (**29)** in combination with dapsone possesses potent *in vivo* activity against *mycobacterium ulcerans and mycobacterium leprae* [39].

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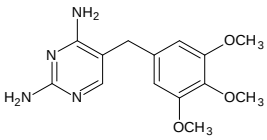

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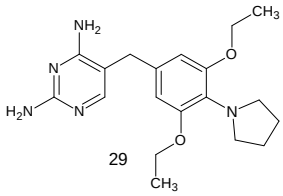

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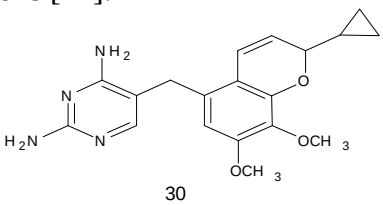
Iclaprim (**30)** is a dihydrofolate reductase inhibitor used for the treatment of complicated skin and soft tissue infections caused by antibiotic resistant pathogens[40].Recently diaminopyrimidine. Iclaprim was approved by the FDA and the European Medicines Agency (EMA) which is effective for the treatment of pneumonia infections [41].



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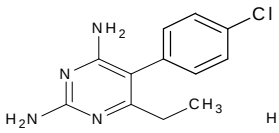
2.6. Antiparasitic pyrimidine derivatives

Many drugs having pyrimidine moiety used to battle several human diseases caused by protozoan organisms. Malaria, leishmaniasis, and trypanosomiasis are the infectious diseases of humans and animals caused by parasitic protozoans. Malaria is mosquito-borne infectious diseases caused by five species of parasites of the genus *Plasmodium* that affect humans and great public health problem worldwide. Malaria is transmitted to humans by the bite of infected female mosquitoes of anopheline species. Malaria due to *Plasmodium falciparum* is the most fatal [42].

Many pyrimidine derivatives are antagonists for folic acid [43] and acts as inhibitors of dihydrofolate reductase [44]. Pyrimethamine (**31)** is one of the notable pyrimidine derivative used in the treatment of malaria. Pyrimethamine in combination with sulfadoxine is useful in case of chloroquine resistant *Plasmodium falciparum strains*. They act by inhibiting dihydrofolate reductase which is the key enzyme in the folate biosynthetic pathway in parasite of malaria. After its clinical use malaria parasite developed resistant to pyrimethamine, many pyrimethamine related 2, 4-diamino-5-(3-and4-trifluoromethylphenyl and 3, 4-methylenedioxyphenyl) pyrimidine derivatives were synthesized and one of them is proved to be most potent anti-malarial (**32**) [45].



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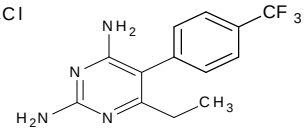

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Chagas disease or American trypansomiasis is a parasitic disease identified by Carlos Chagas in 1909 [46]. The causative organism of Chagas disease is a protozoan, *Trypanosoma cruzi*. [47]. Deoxyuridine5'-triphosphate nucleotidohydrolase (dUTPase) is a valid target against trypanosomatidae [48]. O. K. Mc-Carthy et al. synthesized uracil amino acid conjugates (**33**) and (**34**) were identified as selective inhibitors of *Trypanosoma cruzi* dUTPase [49]

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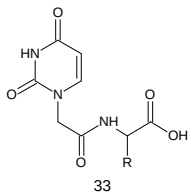

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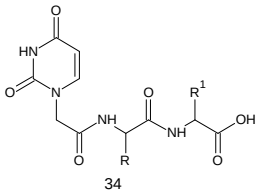
R= -H, -CH_3



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R= -H, -CH_3
R^1 = -H, -CH_2COOH, -$(CH_2)_2$COOH, -$(CH)_2$$CONH_2$, -CHOHC$H_3$, -$(CH)_2$$NH_2$, 4 -$OHC_6H_4CH_2$.

3. Conclusion

During last two decade compounds having pyrimidine entity received considerable attention due to its diverse

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biological and therapeutic properties. Due to a variety of applications of compounds containing pyrimidine ring and valuable importance in nature make it a motivating area to study. The multitalented biological activity of pyrimidines will help the medicinal chemists to put into practice new approaches towards discovery of new drugs.

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