JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

REVIEW ON PHARMACOLOGICAL ACTIVITY OF PYRIMIDINE HETEROCYCLE

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ABSTRACT: The purpose of this review article is to provide a foundation for understanding of Heterocyclic compound. This review emphasizes on the various biological activity of pyrimidine heterocyclic derivatives with a various examples. Pyrimidine is one of the most important heterocycle present in various drug, active pharmaceutical ingredient, starting material for various derivative preparations etc. In this review we discuss on introduction to heterocyclic compound and pyrimidine as a heterocycle. This will give a clear idea about the various pharmacological activities of pyrimidine heterocycle. Various papers reviewed and the derivatives containing pyrimidine heterocycle and their biological activity study is summarized in this paper.

Keywords: Heterocycle, Pyrimidine, Pharmacological activities

I. Introduction to Heterocyclic Compounds

A heterocyclic compound is a cyclic compound which has atoms of at least one different element as members of its ring(s). The counterparts of heterocyclic compounds are homo-cyclic compounds, the rings of which are made of a single element

Heterocyclic compounds may be inorganic, most contain at least one carbon atom and one or more atoms of elements other than carbon within the ring structure, such as sulphur, oxygen or nitrogen. Since in organic chemistry non-carbons usually are considered to replace carbon atoms, they are called heteroatom's meaning different from carbon and hydrogen (rings of heteroatom's of the same element are homocyclic). Heterocyclic chemistry is the branch of chemistry dealing with synthesis, properties, and applications of heterocyclic.

Most biologically active compounds are heterocyclic organic compounds. The number of possible heterocyclic systems is limitless. An enormous number of heterocyclic compounds are known and the number is increasing very rapidly. Over six million compounds are recorded in chemical abstracts and approximately half of these are heterocyclic. Knowledge of heterocyclic chemistry is useful in biosynthesis and in drug metabolism as well. Heterocyclic compounds containing more than one heteroatom have gained more importance because of their versatile role in the biological filed. A heterocyclic ring may comprise of three or more atoms, which may be saturated or unsaturated. Also the ring may contain more than one heteroatom, which may be similar or dissimilar [1].

Introduction to pyrimidine heterocycle

A wide variety of heterocyclic systems exist in Pharmaceuticals. Within this hetrocyclic system, the nitrogen heterocycles are of great importance and pyrimidine is one of the most important nitrogen heterocyclic species because of its synthetic utility and broad spectrum of pharmacological activity. The pyrimidine nucleus is an important heterocyclic ring since several of its derivatives have pharmacological properties and have been marketed as commercial products.

Some Nitrogen containing hetrocycles are as follows –

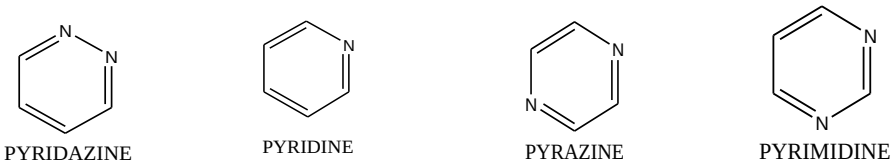


Fig.1:Nitrogen containing heterocycle

Pyrimidine is a heterocyclic aromatic organic compound similar to benzene and pyridine, containing two nitrogen atoms at positions 1 and 3 of the six-member ring. It is isomeric with two other forms of diazine. Pyrimidine has many properties in common with pyridine, as the number of nitrogen atoms in the ring increases the ring π- electrons become less energetic and electrophilic aromatic substitution gets more difficult while nucleophilic aromatic substitution gets easier.

Pyrimidines have been the subject of substantial attention by synthetic and medicinal chemists due to the role of such class of heteroaromatic ring in many biological systems. Pyrimidines, being an integral part of DNA and RNA, impart to diverse pharmacological properties as effective bactericide and fungicides. Certain pyrimidine derivatives are also known to exhibit antimalarial, antifilarial, antileishmanial and anti-HIV activities. Some of the 3,4-dihydropyrimidines (DHPM) have emerged as

integral backbones of several calcium channel blockers, antihypertensive agents, adrenergic and neuropeptide antagonist. Several alkaloids containing 3,4-dihydropyrimidine have been isolated from marine sources and among them are the *batzelladine* alkaloids are found to be potent HIV-gp-120-CD4 inhibitors. Currently, fifteen out of twenty-five drugs approved by US-FDA (United States Food and Drug Administration) for the treatment of viral diseases are purine and pyrimidine derivatives; Idoxuridine, Trifluridine, Acyclovir, Ganiciclovir for herpes; Zidividine and Lamividine for HIV and Ribavarine for RSV infection in children[3].

II. Biological Activities of Pyrimidines

Pyrimidines have been important lead molecules due to their diverse pharmacological activities and have a long and distinguished history extending from the days of their discovery as important constituents of nucleic acids to their current use in the chemotherapy of AIDS. We have emphasized on some of the novel synthetic strategies for the synthesis of biologically active pyrimidines which also includes microwave synthesis and one pot synthetic techniques, with an aim to help medicinal chemist to explore more biologically potent analogs.

- **Antitubercular drugs**

Capreomycin produced by *Streptomyces capreoluse* is a second-line bacteriostatic antituberculin drug containing pyrimidine. Viomycin is more tuberculostatic than p-aminosalicyclic acid. It is effective in the treatment of experimental tuberculosis[2].

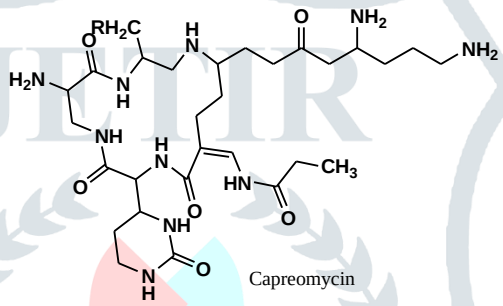


Fig. 1: Example for Antitubercular

- **Antineoplastics and anticancer agents**

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

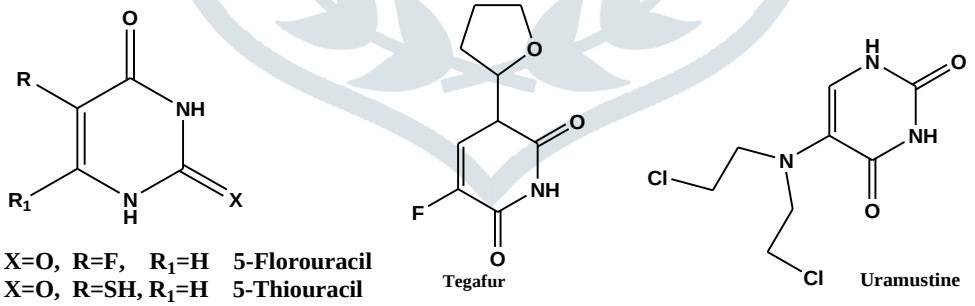
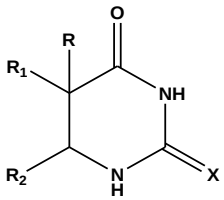


Fig. 2: Example for antineoplastic and anticancer

The antineoplastic compounds possessing the guanine nucleus, in azathioprine, mercaptopurine, thioguanine and tegafur etc. were discovered after formulation of the antimetabolite theory by Woods and Fildes in 1940. These drugs prevent the utilization of normal cellular metabolites. There are many more in recent times, like mopidamol, nimustine, raltitrexed, uramustine and trimetrixate,1-D Arabinosylcytosine (Ara-C,) is also an example of a pyrimidine antimetabolite in which the sugar is arabinose having a beta configuration. It is mainly used as an anticancer agent and also exhibits significant therapeutic effects in patients with herpes virus infections and herpes encephalitis. Gemcitabine, a pyrimidine antimetabolite, shows excellent antitumour activity against marine solid tumours[5].

- **Drugs for hyperthyroidism**

2-Thiouracil and its alkyl analogue, thiobarbital are effective drugs against hyperthyroidism. Propylthiouracil is used as a drug for hyperthyroidism with minimum side effects[6].

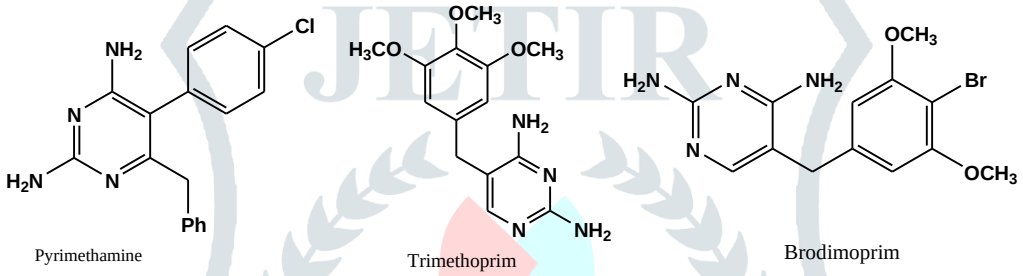


R=R_1=R_2=H, X=S 2-Thiouracil
R=R_1=H, R_2=C_3H_7, X=S Propylthiouracil
R=R_1=C_2H_5, R_2=O, X=S Thiobarbitol

Fig. 3: Example for Hyperthyroidism

• Antibacterials and antiprotozoals

In 1948, Hitchings made an important observation that a large number of 2,4 diaminopyrimidines and some 2-amino-4-hydroxypyrimidines are antagonists of folic acid. Since then, a large number of 2,4-diaminopyrimidines have been synthesized as antifolates. It was eventually proved that these pyrimidines are inhibitors of the enzyme dihydrofolate reductase (DHFR). Notable amongst the 2,4-diaminopyrimidine drugs are pyrimethamine a selective inhibitor of the DHFR of malarial plasmodia; trimethoprim, an antibacterial drug which selectively inhibits bacterial DHFR and most importantly, the very potent but non selective DHFR inhibitors, methotrexate and aminopterin both used in cancer chemotherapy. 3,5 –Dichloromethotrexate which is less toxic and more readily metabolized than methotrexate, has recently been introduced for anticancer therapy. Brodimoprim is also found to be an effective antibacterial compound[7].



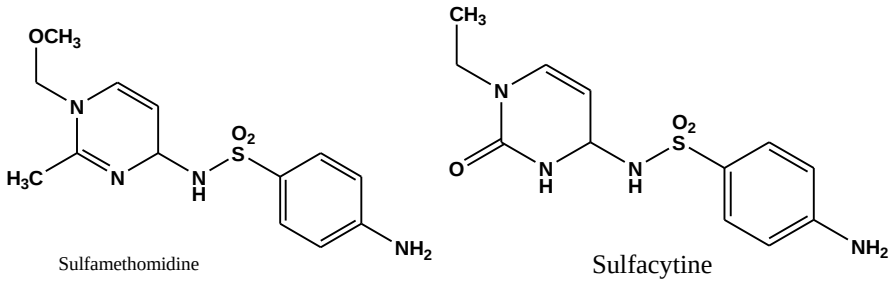
Pyrimethamine Trimethoprim Brodimoprim

Fig. 4: Example for antibacterial and antiprotozoals

• Sulfa drugs

Pyrimidine derivatives of sulfa drugs, namely sulfadiazine, sulfamerazine and sulfadimidine are superior to many other sulfonamides and are used in some acute urinary tract infections, cerebrospinal meningitis and for patients allergic to pencillins. Sulfonamide & trimethoprim combinations are used extensively for opportunistic infections in patients with AIDS. Sulfadoxine, a short and intermediate acting sulfonamide with a half-life of 7-9 days is used for malarial prophylaxis. Sulfisomidine with a half-life of 7 hours is used as a combination sulfa therapy in veterinary medicine. Sulfadiazine, sulfamerazine and sulfadimidine possess good water solubility and therefore carry minimum risk of kidney damage, which makes them safe even for patients with impaired renal functions[8].

In 1959, sulfadimethoxazine was introduced with a half-life of approximately 40 hours. The related 4-sulfanamidopyrimidine, sulfamethoxazine having two methoxy groups in 5 and 6 positions, has by far the longest half-life of about 150 hours. Methyldiazine has a half-life of 65 hours. Also, sulfamethoxydiazine possesses good half-life. A new broad-spectrum sulfonamide, sulfamethomidine is relatively nontoxic and patients do not need extra fluid intake or alkalization. Sulfacytine has been reported to be 3-10 times more potent than sulfaisoxazole and sulfisodimidine[9].



Sulfamethomidine Sulfacytine

Fig. 5: Example for Sulfa drugs

• Antiviral and anti-AIDS drugs

Recently, pyrimidine derivatives have generated widespread interest due to their antiviral properties. 5-Iododeoxyuridine is an antiviral agent of high selectivity. IDU (5-iodo- -deoxyuridine) has been extensively utilized for viral infections. 5-Trifluromethyl-deoxyuridine (F3 TDR) has been found useful against infections resistant to IDU therapy. Ara-A 9-β-D-arabinofuranosyl adenine, a relatively new antiviral drug, is effective against herpes infections of eye, brain and skin. It is especially effective against IDU-resistant herpes virus[10].

Some purine nucleosides are equally noteworthy. Retrovir (AZT-16) is a potent inhibitor of the *in vivo* replication and cytopathic effects of HIV and has been recently approved for use against AIDS and severe ARC. At present Acyclovir is the only remedy for

genital herpes. The oral formulation of Acyclovir is effective against both first and second-degree recurrence-genital herpes with minimal side effects. Ganciclovir (DHPG-2) has shown good in-vivo activity against HCV1 and HCV2.

Several members of a series of acyclic nucleosides, which contain a fused pyrimidine ring (mainly purine), are found to be effective antivirals. Famiciclovir and valacyclovir are drugs used for several DNA viruses, including Hsv types 1 and 2, *Varicella-zoster* virus and *Epstein-Barr* virus. Penciclovir is useful for topical treatment of recurrent herpes, *Libialis*. Cidofovir, an antimetabolite for deoxycytosine triphosphate is used for treatment of cytomegalovirus (CMV) in AIDS patients. amivudine is an effective anti-AIDS drug when used in combination with zidovudine. Zidovudine is an analogue of thymidine in which the azido group is substituted at the 3-position of the dideoxyribose moiety. It is active against RNA tumour viruses retroviruses) that are the causative agents of AIDS and T-cell leukaemia. It is used in AIDS and AIDS-related complex (ARC) to control opportunistic infections by raising absolute CD4+ lymphocyte counts. Also, zalcitabine is another useful alternative drug to zidovudine. It is given in combination with zidovudine, when CD4+ cell counts fall below 300cells/mm^3. Didanosine is a purine dideoxynucleoside, which is an analogue of inosine. Didanosine inhibits HIV RT and exerts a virustatic effect on the retroviruses. Combined with zidovudine, antiretroviral activity of didanosine is increased. Stavudine is a pyrimidine nucleoside analogue that has significant activity against HIV-1 after intracellular conversion of the drug to a D4T-triphosphate. It is more effective than zidovudin or didenosine for treatment in patients for delaying the progression of HIV infection. It is recommended for patients with advanced HIV infection.

Abacavir sulfate was approved in 1998 as a NRTI (Nucleoside Reverse Transcriptase Inhibitor) to be used in combination with other drugs for the treatment of HIV and AIDS. The major use of abacavir appears to be in combination with other NRTIs[11].

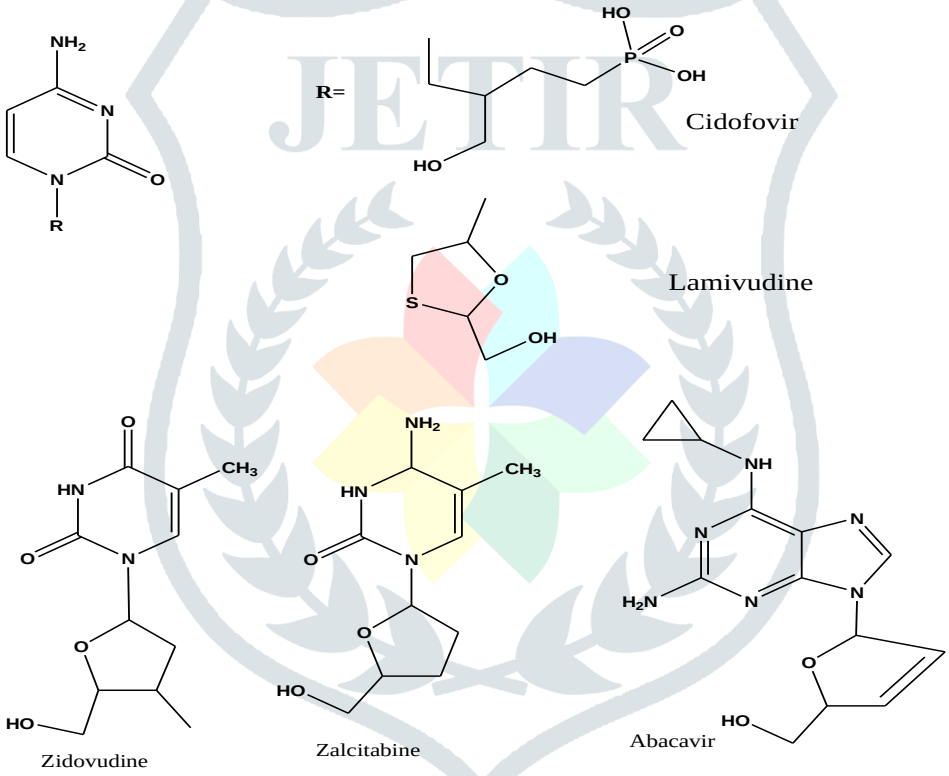


Fig. 6: Example for Antiviral and anti-AIDS drugs

- **Antibiotics**

There are few examples of pyrimidine antibiotics. The simplest of all is bacimethrin (5-hydroxymethyl-2-methoxypyrimidin-4-amine), which is active against several staphylococcal infections. Gourgetin a cytosine derivative is active against mycobacteria as well as several Gram (+) and Gram (-) bacteria. There are more derivatives of cytosine, namely amicetin and plicacetin which exhibit activity against acid fast and Gram-(+) bacteria as well as on some other organisms. Puromycin has a wide spectrum of antitrypanosomal activity. Aminoglycoside antibiotics phleomycin, bleomycin and related families are wide-spectrum antibiotics containing the pyrimidine ring. Another antibiotic tubercidine is reported to exhibit antitumour properties. In addition, they have antineoplastic activity. Bleomycin is already in clinical use against certain tumours like Hodkin's lymphoma and disseminated testicular cancer[12].

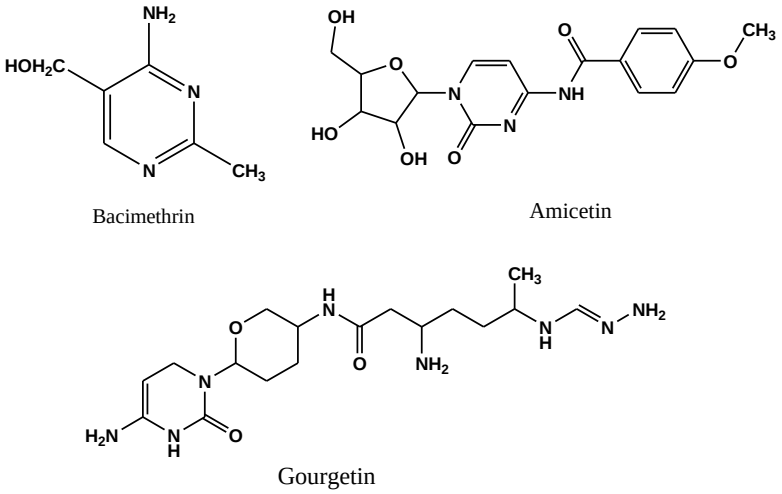


Fig. 7: Example for Antibiotics

• **Antifungals**

Pyrimidines also exhibit antifungal properties. Flucytosine is a fluorinated pyrimidine used as nucleosidal antifungal agent for the treatment of serious systemic infections caused by susceptible strains of candida . Hexitidine is mainly used for the treatment of ulceration[13].

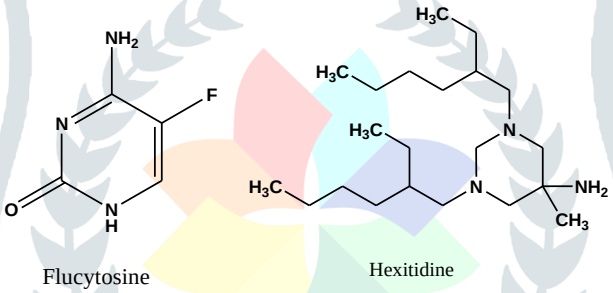


Fig. 8: Example for Antifungals

• **Anxiolytic agents**

Few of the pyrimidine derivatives were also used as anxiolytics. Most important of these is buspirone (azaspirodecanediones), indicated in the management of anxiety disorders accompanied with or without depression. It lacks sedative, anticonvulsant and muscle-relaxant effects and most importantly abuse potential. Buspirone lacks affinity to benzodiazepine receptors, but binds avidly to one subclass of serotonin receptors, the 5-HT1A subtype[14].

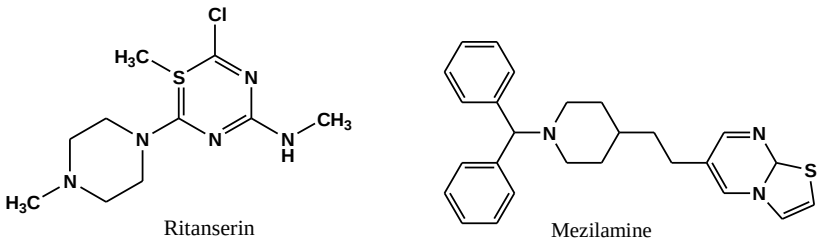
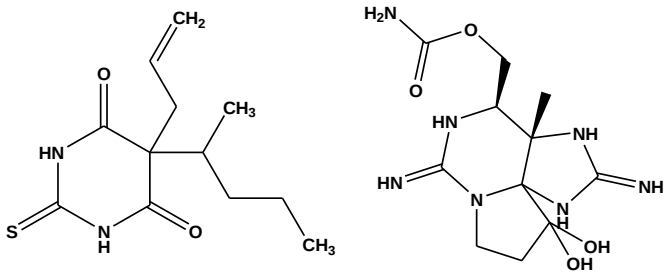


Fig. 9: Example for Anxiolytic agents

• **Pyrimidine anesthetics**

Thimylal is a short acting general anesthetic drug, which is also a pyrimidine analogue. Saxitoxin is a naturally occurring pyrimidine containing anesthetic agent, but is too toxic to be of clinical use. Saxitoxin is isolated from some marine dinoflagellates[20].



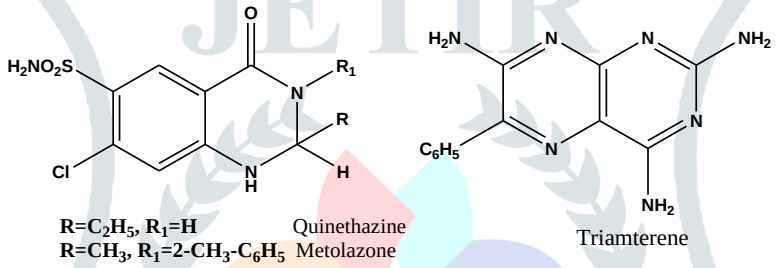
Thimylal Saxitoxin

Fig. 10: Example for anesthetics

• **Diuretics, uricosurics**

Several xanthine derivatives containing fused pyrimidine ring systems like caffeine and analogs of caffeine are, etamiphylline, lomiphylline, etophylline, theophylline and theodrendaline are known to promote a weak diuresis by stimulation of cardiac function and by a direct action on the nephron, acting as adenosine receptor antagonist[21].

There are a few examples of diuretics which contain a pyrimidine ring. Noteworthy are quinethazine , metolazone and triamterene[22] .



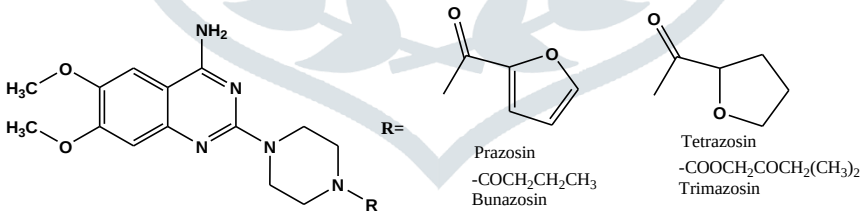
R=C_2H_5, R_1=H Quinethazine
R=CH_3, R_1=2-CH_3-C_6H_5 Metolazone

Triamterene

Fig. 11: Example for Diuretics

• **Cardiac agents: Antihypertensives**

Several pyrimidine ring-containing drugs have exhibited antihypertensive activity. Prazosin, a quinozoline derivative, is a selective α_1-adrenergic antagonist. Its related analogues bunazosin, terazosin and trimazosin are potent anti hypertensive agents[23].

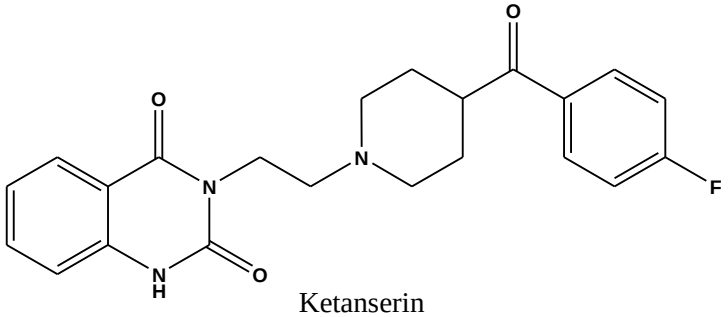


R= Prazosin -$COCH_2CH_2CH_3$ Bunazosin

Tetrazosin -$COOCH_2COCH_2(CH_3)_2$ Trimazosin

Fig. 12: Example for Antihypertensives

Another quinazoline derivative, ketanserin having a similar effect is an antagonist of both α_1-adrenergic and serotonin-S receptors. Its mechanism of action however is still controversial. A triaminopyrimidine derivative, minoxidil, whose mechanism of action and therapeutic action are similar to prazosin, has been introduced in therapy for its side effects, in the treatment of alopecia, male baldness. Besides these, some more pyrimidine derivatives given below were found to be antihypertensives.



Ketanserin

Alfuzocin, a prazocin analogue and an a1-adrenoceptor antagonist as well as urapidil are used especially in urinary obstruction caused by benign prostate hyperplasia[24].

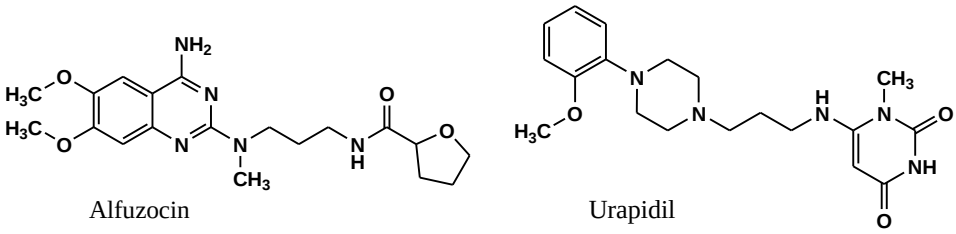


Fig. 13: Example for Antihypertensives

• **Antihistaminic pyrimidines**

Taziphylline is ten times more potent than either astemizole or terfenadine in its affinity for H_1-histamine binding site and appears to be devoid of CNS activity. Another pyrimidine containing antihistaminic drug, temelastine is comparable to mepyramine. Radiolabelled studies have indicated that it does not penetrate the CNS appreciably. Icotidine, a structural analogue of temelastine lacks CNS activity and is a dual antagonist of both H_1 and H_2 receptors[28].

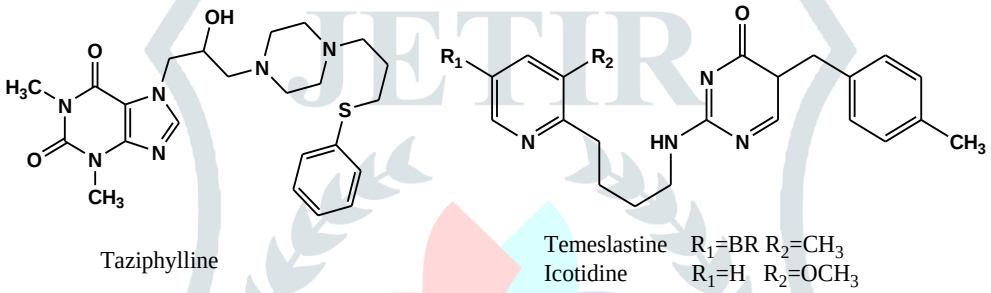


Fig. 14: Example for Antihistaminic

• **Analgesics and NSAID drugs**

Acetiamine, bentiamine and fursultiamine are new lipid-soluble forms of thiamine (vitamin B1) having therapeutic use in beriberi, polyneuritis, encephalopathy, pain, malnutrition and alcoholism and especially in the treatment of long-standing insulin-dependent diabetes mellitus. Fursultamine has been reported to inhibit the arachadonic acid cascade-line activation and reverse the increase in CBF (Coronary Blood Flow)[29].

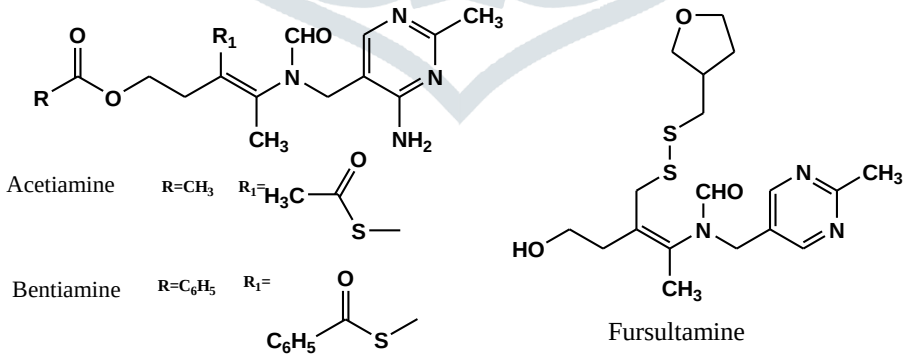
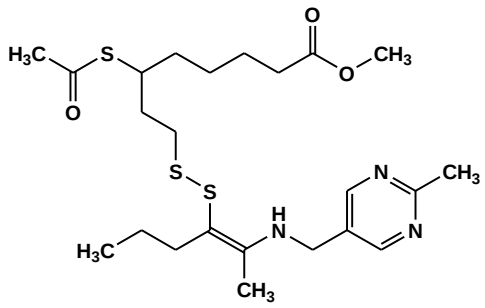
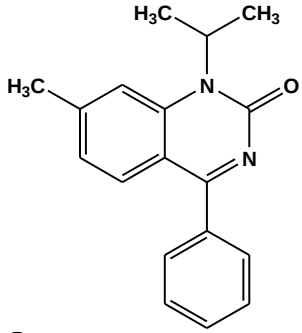


Fig. 15: Example for Analgesics

Ademetionine is primarily used in conjunction to glucosamine and chondroitin therapy. Octotiamine, a vitamin B_1 derivative also exhibits anti-inflammatory activity. Proquazone, a condensed pyrimidin-2-one derivative has been reported to exhibit good NSAID[29].



Octotiamine

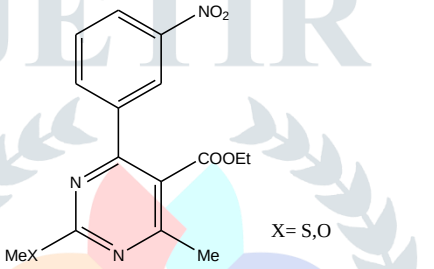


Promaquazone

Fig. 16: Example NSAID

• **Calcium channel blocking activities**

Karnail S. Atwal, George C. Rovnyak *et.al* reported the 3-substituted 1,4-dihydro- pyrimidines shows calcium channel blocking activities[29].



ethyl 2,4-dimethyl-6-(3-nitrophenyl)pyrimidine-5-carboxylate

Fig. 17: Example Calcium channel blockers

DISCUSSION AND CONCLUSION:

Article provide understanding of Heterocyclic compound. This review gives idea about how the pyrimidine heterocycle is important for the various derivative preparation and biological activity of the pyrimidine. Anticancer activity is most probably the important pharmacological activity. The researcher can synthesize various derivative containing pyrimidine heterocycle and can evaluate their derivatives for anti-cancer activity as the cancer is very widely spreading in this world.

ACKNOWLEDGMENT:

One of the most precious things which god created is "The way we express things". Authors are very thankful to the Bharati Vidyapeeth (Deemed to be University), Poona College of Pharmacy, Pune for giving us opportunity to explore PM.

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