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REVIEW ARTICLE

Significance The Biological Activity to Pyrimidine Analogues

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ARTICLE INFORMATIONS

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ABSTRACT

Heterocyclic organic compound make up an extremely important class of compounds." In fact, more than half of all known organic compounds are belong for this class. Many inbred drugs such as morphine, atropine, Vitamin B1 and folic acid are heterocycles compounds and used for treatment of various diseases. Some other synthetic drugs such as barbiturates , capreomycine , flucytosine , pyrantal pamoate, azidothymidine, antipyrine , and the HIV drug are also clasified as very potent heterocycles". pyrimidine is one of the most important Heterocycles compounds, most potent pyrimidines used to treat of various diseases such as cancer, Leukemia . pyrimidine also represents the backbone of RNA and DNA.

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PYRIMIDINES

Pyrimidine is one of the diazine compouned , . Its discovery in 1818 [1] there has been a great interest in this heterocyclic system as a component of many biological active substances, pharmaceutical, agrochemical and veterinary products. Its chemical structure and reactivity have been the subject of many synthetic and theoretical investigations. Results and progress have been summarized periodically in reviews [2-13]. Important aspects of synthesis and transformation have been reviewed in Hoffmann *et al* [14].

The pyrimidine is a weakly basic soluble heterocyclic compound and can be prepared from barbituric acid Formula: $C_4H_4N_2$ is similar to pyridine and essentially flat ring, pyrimidine unlike benzene it forms an irregular hexagon with six different bond lengths and four different bond angles (Fig. 1).

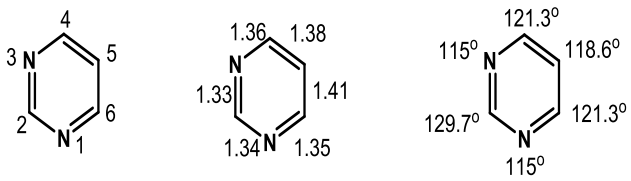


Fig. 1. Structure of Pyrimidine, Its Bond lenths, and Angles

Pyrimidine derivatives such as uric acid and alloxan were known in the early 19th century. The first pyrimidine

analogues to be isolated by oxidation of uric acid with nitric acid [15]. The systematic study of pyrimidine by Pinner [16], where the parent compound was first prepared by Gabriel and Colman by conversion of barbituric acid to 2,4,6-trichloropyrimidine followed by reduction using zinc dust in hot water [17]. Pyrimidin has the nitrogen atoms at positions 1 and 3 in the ring,the other diazines are pyrazine (nitrogen atoms at the 1 and 4 positions) and pyridazine (nitrogen atoms at the 1 and 2 positions). pyrimidine is isomeric with two other forms of nucleic acid hydrolysis produces *several* pyrimidines (uracil, thymine and cytosine) (Fig. 2). Of the two types of nucleic acid DNA and RNA, these bases form hydrogen bonds with their complementary purines. Thus, in DNA, the purines adenine and guanine pair up with the pyrimidines thymine and cytosine respectively. In RNA, the complement of adenine is uracil instead of thymine, so the pairs that form are adenine uracil and guanine, cytosine [18].

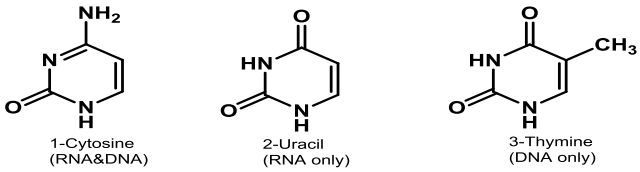


Fig. 2. Pyrimidine nucleobases

The pyrimidine ring is virtually flat, described as π-deficient, and its reactivity exhibited electrophilic and nucleophilic attacks. Electrophilic reagents almost attack pyrimidines at the C-5 positions, it can be easily nitrated, nitrosated, halogenated, sulfonated and coupled with diazonium salt. Although C-2, C-4 and C-6 positions of the pyrimidine ring are the best target for direct nucleophilic attack, only a few examples of reaction are known where direct nucleophilic substitution of hydrogen becauce of electrophilic aromatic substitution is more difficult while nucleophilic aromatic substitution is facilitated [19].

pyrimidine an important role in our life, it has wide occurrence in nature . The nucleobases cytocine 1, uracil 2 and thymine 3 from the main component of the nucleosides cytidine 4, uridine 5 and deoxythymidine 6, respectively. When annulated with imidazole they are also part of the purine nucleobases adenine and guanine, Orotic acid **7** is a key precursore for the pyrimidine nucleotides.

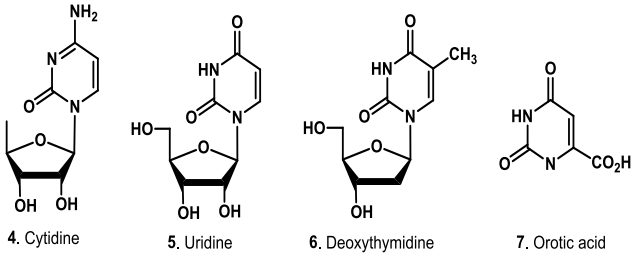


Fig. 3. Pyrimidine-Based Nucleosides and Orotic acid

Lathyrine (tingitanine, 8) containing a pyrimidine ring ,which can be isolated from the seeds of *Lathyrus tingotanus* [20]. Variolin B 9 is an example of pyrimidine-based alkaloid that shows inhibiting cell growth and antiviral activity (Fig. 3) [21]. Natural products with a complex chemical structure and clinically important antitumor agents are the bleomycins A_2 and B_2, uncommon peptides linked to various heterocycle compoundes including a fully substituted pyrimidine ring [22].

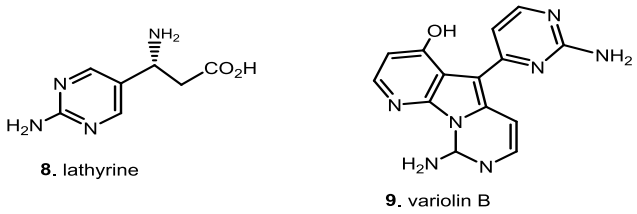


Fig. 4. Naturally Occuring Pyrimidine Lathyrine and Variolin B

Vitamin B_1 (thiamine, 10) was discovered in 1897, was the first vitamin to be isolated in 1926 , it is in the B complex family, thiamine is produced by most microorganisms and plants (Fig. 5). Its biosynthesis has been subject of many investigations [23-25]. Furthermore, there are several antibiotics are contain a pyrimidine ring as a main component. For example, bacimethrine 11 (Fig. 5) is isolated in 1961 from *Bacillus megaterium* and is active against several yeasts and bacteria [26,27].

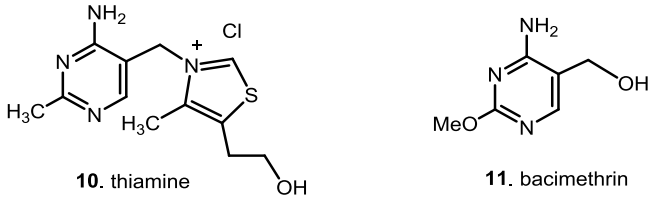


Fig. 5. Thiamine and its Natural Antagonist Bacimethrin

Medicinal Significance of Pyrimidines

Pyrimidine derivatives demonstrated a variety of biological and pharmacological activities including antifolates, antiprotozoal, anti-AIDS and antitumor activity. This broad spectrum of biochemical targets has been facilitated by the synthetic versatility of pyrimidine, which has allowed the generation of a large number of structurally diverse derivatives including analogues derived from substitution of the arylring, and/or derivatisation of the pyrimidine nitrogen and C2/C4/C5/C6 carbon positions. 1n 2006, Jians *et al.* [28] have extensively reviewed the therapeutic properties and the biological activities of pyrimidines with more than 90 references, whereas Arikkat *et al.* [29] and Mishra and Tomar [30] have reported the biological importance of pyrimidines as well.

The biological activities of the pyrimidine indicates the maneuverability and versatility, which offer the medicinal chemist to continued interest in the pyrimidine skeleton in medicinal chemistry and drug development, the development of efficient and reliable methods for the

construction of these molecules will ensure that this is an active and important area of research in heterocyclic chemistry, which has found wide clinical applications. Figure 6 summarizes the medicinal significance of pyrimidines, in general.

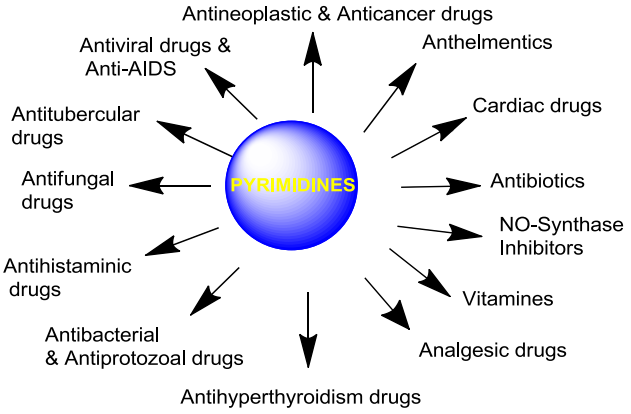


Fig. 6. Medicinal Significance of Pyimidines

Here, we select some interesting medicinal applications of potential pyrimidines as following.

Anticancer agents and antineoplastics

There are a large number of pyrimidine-based antimetabolites. One of these pyrimidine derivative is 5-fluorouracil [22,31,32] (5-FU, 12), which is clinically established anticancer drug for the treatment of tumors of colon, breast , ovary, neck and head [22]. *In vivo*, 5-fluorouracil is activated to 5-fluorodeoxyuridine (floxuridine, 13), which is also used as an anticancer drug [22]. (cytarabin, 14) is a cytosine arabinoside-derived antineoplastic agent with an inverted configuration at C2' [22]. 5-Thiouracil 15 also exhibits some useful antitumer activities [33] (Fig. 7).

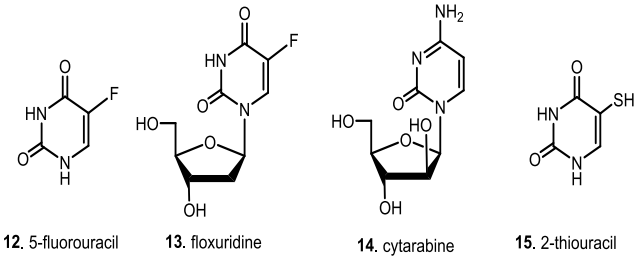


Fig. 7 Structures of Pyrimidine-Based Antimycotic and Antitumor Drugs

In order to increase the effectiveness of some of the pyrimidine derivatives, some modifications are made of pyrimidine nucleobases and nucleosides for the treatment of cancer are shown in Fig. 8, such as gemcitabine 16 [22,34], capecitabine 17 [35,36], tegafur 18 [37] and eniluracil 19 [38] which show excellent antitumour activity against solid tumours.

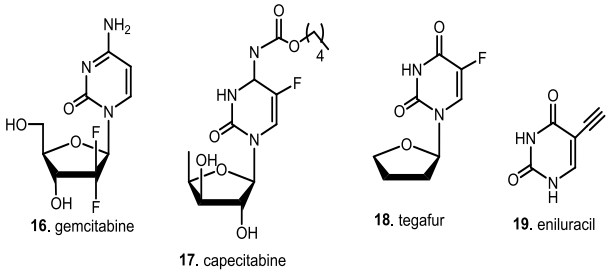


Fig. 8. Novel Pyrimidine-Based Cytostatics

An interesting new agent for the treatment of chronic Leukemia is the tyrosine kinase inhibitor imatinib mesylate (Gleevec, 20), which contains a 4-pyridyl-substituted pyrimidine-2-amine structure as the aromatic heterocyclic element (Fig.9) [39].

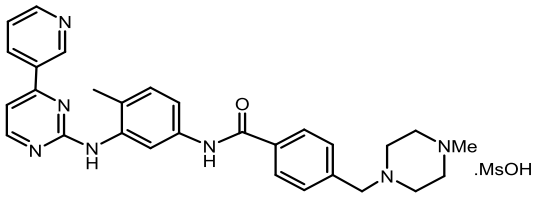


Fig. 9. Chemical Structure of Tyrosine kinase Inhibitor (**Gleevec**, **20**)

The antitumorigenic compounds [40] owning the guanine nucleus 21 *e.g.*: azathioprine 22 [41], mercaptopurine 23 [42], thioguanine 24 [43] were discovered after formulation of the antimetabolite theory by Woods and Fildes in 1940. These drugs inhibit the employment of normal cellular metabolites [40] (Fig. 10).

Fig. 10. Guanine Analogues as Antineoplastic drugs

There are many more in recent times, like mopidamol 25 [44], nimustine 26 [45], raltirexed 27 [46], uramustine 28 [47] and trimetrixate 29 [48] (Fig. 11).

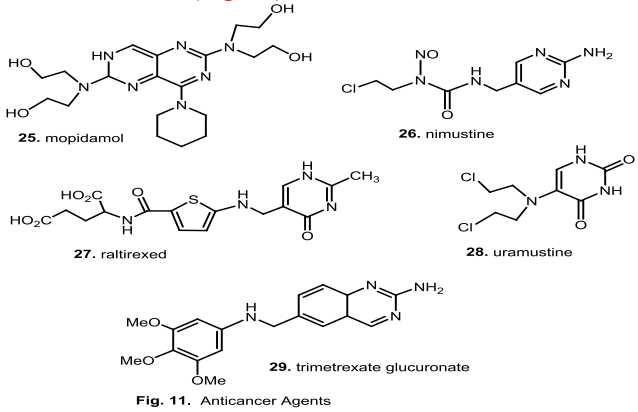
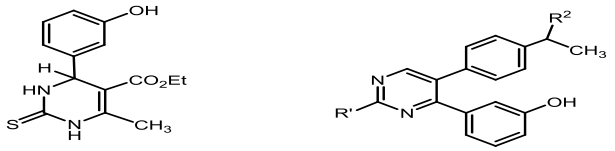


Fig. 11. Anticancer Agents

In 1999, *monastrol*, ethyl 4-(3-hydroxyphenyl)-6-methyl-2-sulfanylidene-3,4-dihydro-1*H*-pyrimidine-5-carboxylate (30) was discovered by Prof. Mayer of Konstanz University, Germany [49], shown to inhibit the Kinesin Eg5, a motor protein important for spindle bipolarity. Drugs that inhibit kinesins are being developed as anti-cancer agents with the hope that they will inhibit proliferation of tumor cells (Fig. 12). In addition, Xie *et al.* [50] have synthesized novel 2,4,5-substituted pyrimidine derivatives 31 and 32 and then estimated *in-vitro* against human hepatocellular carcinoma BEL-74502 cell proliferation. Several compounds presented potent anticancer activity with an IC_{50} less than 0.10 μM (Fig. 12). Using a high-throughput screening campaign, Pease and co-workers [51,52] identified the 4,6-bis-anilino pyrimidines 33 and 34 as inhibitors of the cyclin-dependent kinase (CDK4) for treatment of cancer (Fig. 13).



30. monastrol

31. R' = CH_3, NH_2
32. R^2 = H, CH_3, Et

Fig. 12 pyrimidine derivatives for treatment of cancer

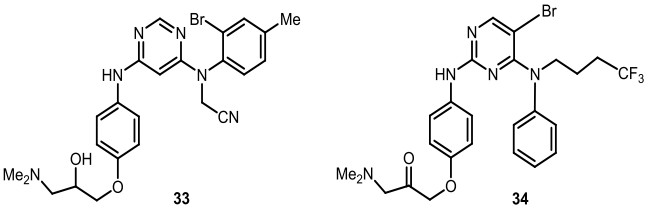


Fig. 13

Several pyrimidine derivatives exhibited significant antitumor activity *e.g.* hydrazine-pyrimidine-5-carbonitrile derivatives 35, with inhibitory effects on the growth of a wide range of cancer cell lines generally at some cases at 10^{-7} M concentrations [53]. Futhermore, 2,4-diamino – 6 - (5 – chloro – 2 – methylphenyl) - N^4 - (4-trifluoromethyl) phenyl) pyrimidnes 36 were identified as blocked proliferation of tumour cell lines *in vivo*, especially duodenum cancer (DU145, IC_{50} = 0.23 μM [54] (Fig. 14).

Azam *et al.* [74] have synthesised pyrimidine bridged thiadiazole derivatives 5 – benzyl – 3 - (((4, 6 – dimethylpyrimidine-2-yl)thio)methyl)-2,3-disubstituted-pyrimidin)1,3,4-thiadiazole 37 (Fig. 16) which exhibited significant antitumor activity against human breast cancer MCF 7 cell line.

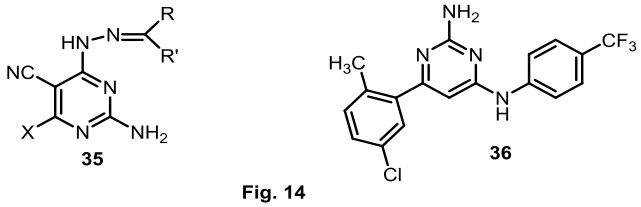
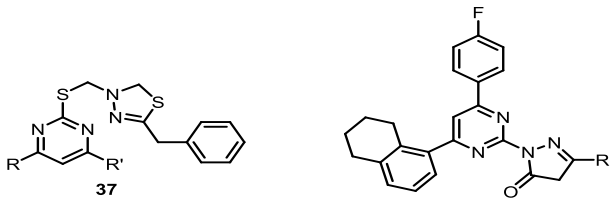


Fig. 14

However, moderate antioxidant activity was observed. Analogously, Amin and *et al.* [56] synthesised three tetralin-6-yl pyrimidines 38 and 39 and found that they were active against liver cancer cell (Hep G2) with IC_{50} = 8.66 and 7.11 μg/mL, respectively (Fig. 15).

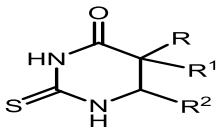


38. R = OEt
39. R = Me

Fig. 15

Drugs for hyperthyroidism

2-Thiouracil compouned 40 and its alkyl derivative, propylthiouracil 41 are effective drugs against hyperthyroidism. Thiobarbital 42 is employeed as a drug for hyperthyroidism with lowermost side effects [57] (Fig. 16).



40. R = R^1 = R^2 = H, X = S; 2-thiouracil
41. R = R^1 = H, R^2 = C_3H_7, X = S; propylthiouracil
42 R = R^1 = C_2H_5, R^2 = O, X = S; thiobarbital

Fig. 16.

Antifolates, antibacterial and antiprotozoal agents

In 1948, Hitchings 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 [58]. Since then, a large number of 2,4-diaminopyrimidines have been synthesized as antifolates [59,60]. Amongst the 2,4-diaminopyrimidine drugs are pyrimethamine 43, an antimalarial drug, trimethoprim 44 [20], an antibacterial drug, methotrexate 45 and aminopterin 46, both used in cancer chemotherapy [57]. Brodimoprim 47 is also found to be an effective antibacterial agent [61] (Fig. 17).

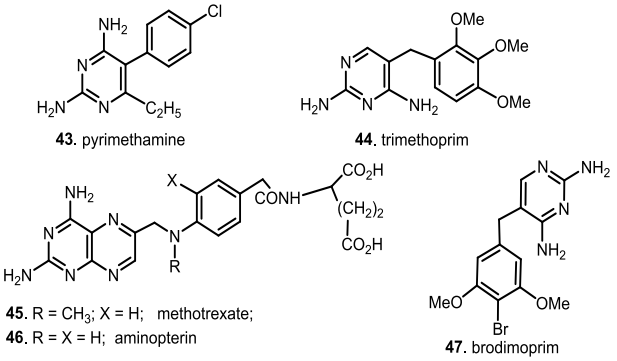


Fig. 17. Antibacterial and Antifolate Drugs

Pyrimidine also showed antifungal properties. Flucytosine 48 is a fluorinated pyrimidine used as nucleosidal antifungal agent and antimycotic drug for the treatment of serious systemic infections caused by susceptible strains of *candida and cryptococcus* [62](Fig. 18).

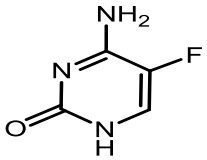


Fig. 18. Antifungal drug 'flucytosine' **48**

Antihelminitic and anti-inflammatory agents

Hunziker [63] had reported pyrantel pamoate 49 as antihelminitic agent in the treatment of infestation caused by pinworms and roundworms, whereas Basararaja *et al.* [64] have synthesized naptho-pyrimidine analogues 50 as anti-inflammatory, antiantihelmintic and antimicrobial agents (Fig. 19).

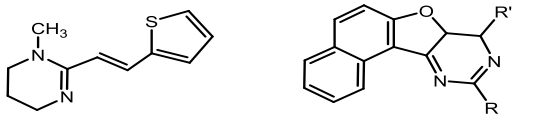


Fig. 19. Antihelminitic and antiinflammatory agents

Antiviral and anti-HIV agents

Recently, pyrimidine derivatives have generated wide-spread interest due to their antiviral properties. Several compouned such as 6-alkylsulfanyl , sulfonyl-5-nitro-uracil family entices significant attention due to their chemotherapeutic importance against HIV. Miyasaki *et al.* [65,66] have synthesized 1-[(2-hydroxy)ethyl]-6-(phenylthio)thymine (51) (HEPT) as a potent anti-HIV agent, meanwhile Balazarini *et al.* [67] reported that the HEPT analogues 52-54 remained active against the majority of viruses containing including the HIV (Fig. 20).

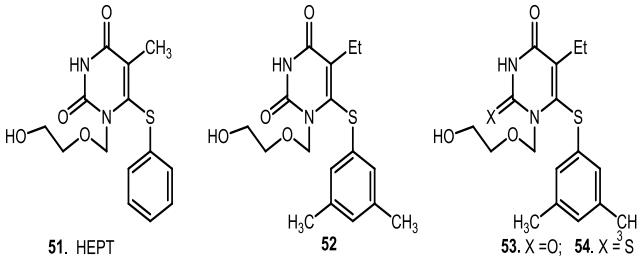


Fig. 20. Anti-HIV agents

Al-Masoudi and co-workers [68] have synthesized a series of 5-nitro and 5-amino-6-arylsulfanyl-1-propyl-pyrimidine-2-4-diones 55 as well as 6-arylsulfanyl-1,3-dimethyl 56, and the 2-amino 57 derivatives with the target to improve new anti-HIV agents (Fig. 21).

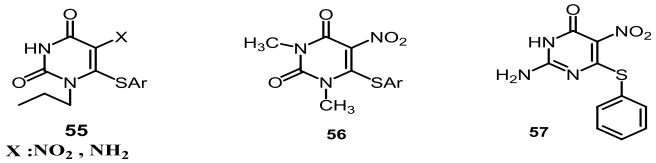


Fig. 21

In searching for new potent and less toxic anti-HIV agents, Al-Masoudi *et al.* [69] have described the synthesis of various substituted 1,2,4-triazolo thymidines **58** with evaluation of their anti-HIV activity (Fig. 22).

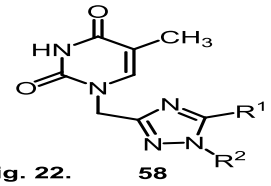


Fig. 22. **58**

Several acyclic nucleosides which containing a pyrimidine ring are found to be effective antivirals, such as famicivlovir 59, valacyclovir 60 are drugs used for several DNA viruses, including herpes simplex (HSV 1 and 2), Varicella-zoster virus and Epstein-Bar virus [70]. Penciclovir 61 is used for treatment of herpes simplex, whereas acyclovir 62 is the drug of choince for treatment of herpes simplex [71]. Cidofovir 64 [72] is used for treatment of cytomegalovirus (CMV) in AIDS patient. Limivudine 63 [73] and abacavir sulfate 65 [74] were approved in 1998 as a nucleoside reverse transcriptase inhibitor to be used for the treatment of AIDS (Fig. 23).

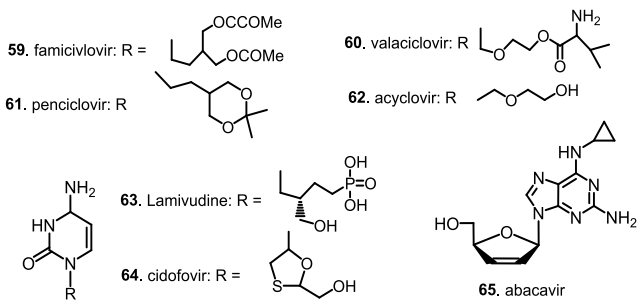


Fig. 23 Antiviral drugs

Antihypertenssive drugs

Several pyrimidine rings containing drugs have exhibited antihypertensive activity. Prazosin **66** is a selective α_1-adrenergic antagonist [75,76] while their analogues bunazosin 67 [77], terazosin 68 [78] and trimazosin 69 [79] are potent antihypertensive agents (Fig. 24).

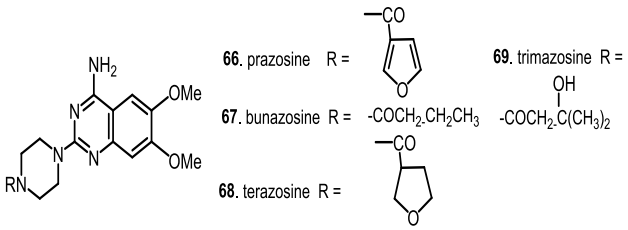


Fig. 24. Antihypertensive drugs

Antituberculosis drugs

Capreomycine 70s produced by *Strepromyces capreolus* is a second-line bacteriostatic antituberculin drug containing pyrimidine backbone [80,81] (Fig. 25).

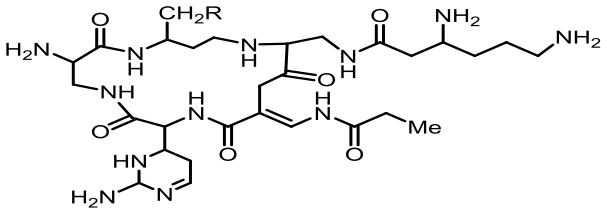


Fig. 25. Capreomycine **70**

Antibiotics

There are few examples of pyrimidine antibiotics. The simplest of all is bacimethrin 11, which is active against several staphylococcal infections [27,82]. Gourgetin 71, a cytosine derivative is active mycobacteria as well several Gram-positive and Gram-negative bacteria [83]. There are more derivatives of cytocine such as amicetin 72 and plicacetin which are active against acid fast and Gram-positive bectria as well some other organism [27] (Fig. 26).

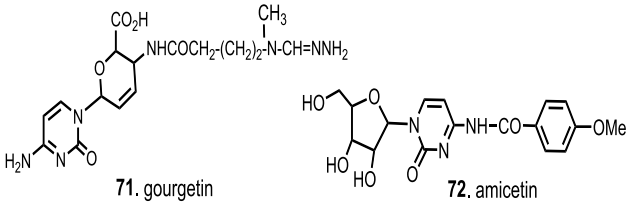


Fig. 26. Some antibiotics containing pyrimidine scaffold

Sulfa drugs

Pyrimidine derivatives of sulfa drugs, namely sulfadiazine, sulfamerazine and sulfadimine are superior to many other sulfonamides and are used in some acute urinary tract infections, meningitis and for patient allergic to pencillins [84]. Sulfadoxine 73 [85], sulfisomidine 74 [86], sulfadiazine 75 [84], sulfamerazine 76 [84], sulfadimidine 77 [84] and sulfamethomidine 78 [87], carrying the pyrimidine backbone are considered the most potent drugs against several diseases (Fig. 27).

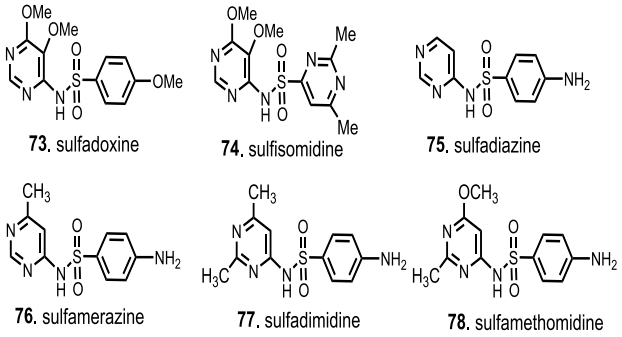


Fig. 27. Some sulfa drugs carrying pyrimidine backbone

Neurotoxines

Terodotoxin (tarichatoxin; 87) [88] is one of the most-powerful-non-protein neurotoxines known. It occurs in the liver and the ovarians of the Japanese puffer fisch or salamander (*Taricha torosa*) (Fig. 28). The structure is based on a 2-iminooctahydro-1*H*-quinazoline skeleton. The total synthesis of 87 has been described in 1972 by Kishi *et al* [89].

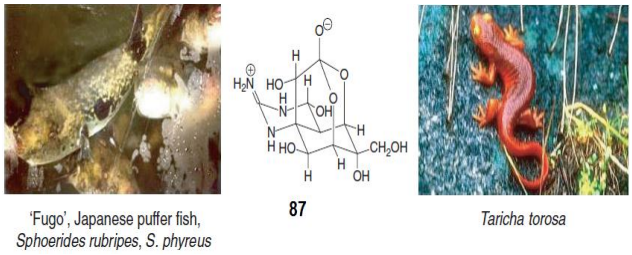


Fig. 28. **Neurotoxine 'Terodotoxin having pyrimidine scaffold' 87**

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