

# Biological and medicinal significance of pyrimidines

K. S. Jain<sup>1,\*</sup>, T. S. Chitre<sup>1</sup>, P. B. Miniyar<sup>1</sup>, M. K. Kathiravan<sup>2</sup>, V. S. Bendre<sup>1</sup>, V. S. Veer<sup>2</sup>, S. R. Shahane<sup>1</sup> and C. J. Shishoo<sup>3</sup>

<sup>1</sup>Sinhgad College of Pharmacy, Pune 411 041, India

<sup>2</sup>Poona College of Pharmacy, Pune 411 038, India

<sup>3</sup>L.M. College of Pharmacy, Ahmedabad 380 009, India

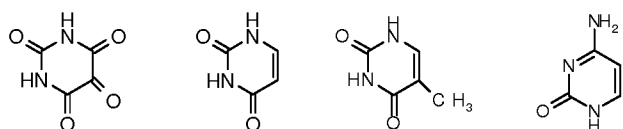
This article outlines the biological significance of one of the most important heterocycles, the pyrimidine. An attempt has been made to cover most of the physiologically as well as medicinally important compounds containing pyrimidine and its derivatives.

**Keywords:** Heterocycles, Pyrimidines: biological significance, Pyrimidines: medicinal significance.

## Biological significance

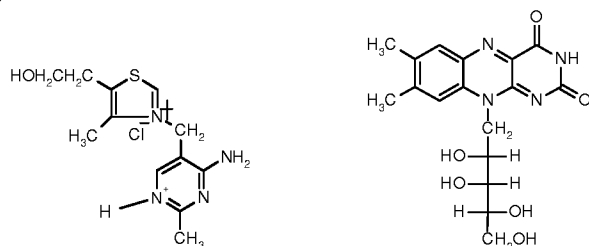
Pyrimidines have a long and distinguished history extending from the days of their discovery as important constituents of nucleic acids to their current use in the chemotherapy of AIDS.

Alloxan (**1**) is known for its diabetogenic action in a number of animals<sup>1</sup>. Uracil (**2**), thymine (**3**) and cytosine (**4**) are the three important constituents of nucleic acids.

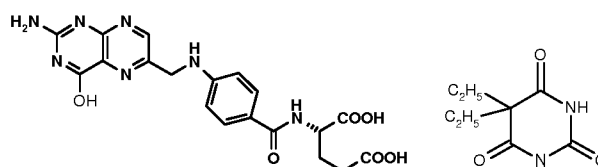


(1) Alloxan (2) Uracil (3) Thymine (4) Cytosine

The pyrimidine ring is found in vitamins like thiamine<sup>2</sup> (**5**), riboflavin<sup>2</sup> (**6**) and folic acid (**7**)<sup>2</sup>. Barbitone<sup>1</sup> (**8**), the first barbiturate hypnotic sedative and anticonvulsant is a pyrimidine derivative<sup>1</sup>.



(5) Thiamine (6) Riboflavin



(7) Folic acid

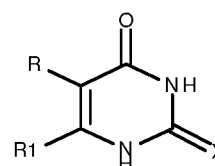
(8) Barbitone

## Medicinal significance

During the last two decades, several pyrimidine derivatives have been developed as chemotherapeutic agents and have found wide clinical applications.

### 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 pendant sugar groups. One of the early metabolites prepared was 5-fluorouracil<sup>3,4</sup> (5-FU, **9a**), a pyrimidine derivative. 5-Thiouracil (**9b**) also exhibits some useful antineoplastic activities<sup>5</sup>.



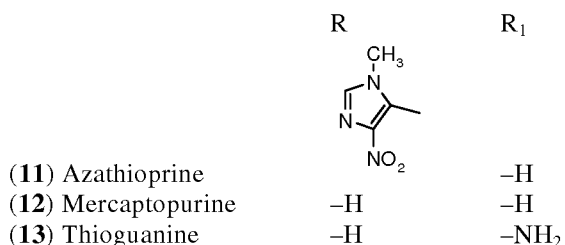
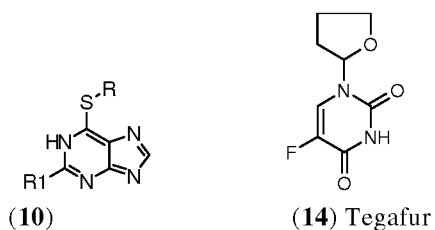
(9a, b)

(9a), X = O, R = F, R<sub>1</sub> = H, 5-fluorouracil

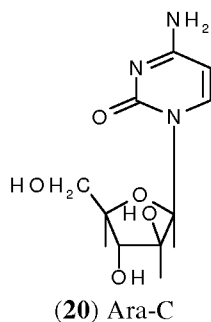
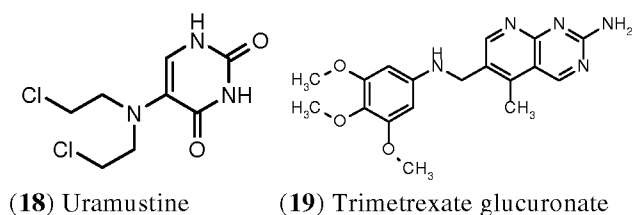
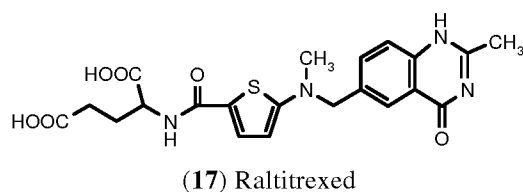
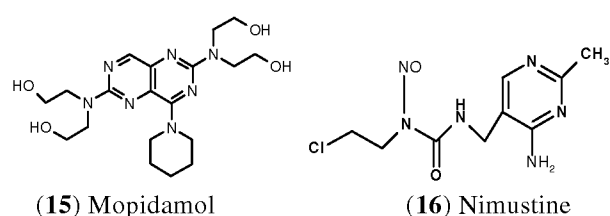
(9b), X = O, R = SH, R<sub>1</sub> = H, 5-thiouracil

The antineoplastic compounds<sup>6</sup> possessing the guanine nucleus (**10**) like azathioprine<sup>7</sup> (**11**), mercaptopurine<sup>8</sup> (**12**), thioguanine<sup>9</sup> (**13**), tegafur<sup>10</sup> (**14**), etc. were discovered after formulation of the antimetabolite theory by Woods and Fildes in 1940. These drugs prevent the utilization of normal cellular metabolites<sup>6</sup>.

\*For correspondence. (e-mail: ks\_jain@vsnl.net)



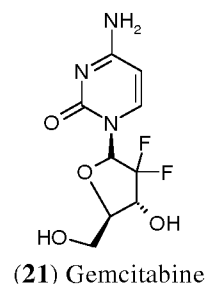
There are many more in recent times, like mopidamol<sup>11</sup> (15), nimustine<sup>12</sup> (16), raltitrexed<sup>13</sup> (17), uramustine<sup>14</sup> (18) and trimetrixate<sup>15</sup> (19).



1-β-D-Arabinosylcytosine<sup>16</sup> (Ara-C, 20) is also an example of a pyrimidine antimetabolite in which the sugar is ara-

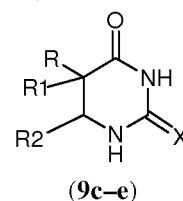
binose having a beta configuration. It is mainly used as an anticancer agent and also exhibits significant therapeutic effects in patients with herpes virus infections and herpes encephalitis.

Gemcitabine (21), a pyrimidine antimetabolite, shows excellent antitumour activity against murine solid tumours<sup>17</sup>.



### Drugs for hyperthyroidism

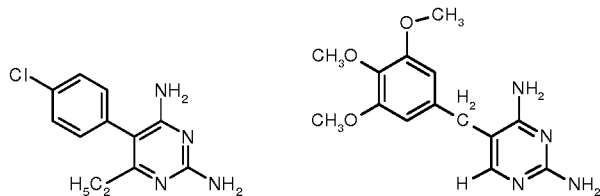
2-Thiouracil (9c) and its alkyl analogue, thiobarbital (9e) are effective drugs against hyperthyroidism. Propylthiouracil (9d) is used as a drug for hyperthyroidism with minimum side effects<sup>18</sup>.



(9c), R = R<sub>1</sub> = R<sub>2</sub> = H, X = S; 2-thiouracil (9d), R = R<sub>1</sub> = H, R<sub>2</sub> = C<sub>3</sub>H<sub>7</sub>, X = S; propylthiouracil (9e), R = R<sub>1</sub> = C<sub>2</sub>H<sub>5</sub>, R<sub>2</sub> = O, X = S; thiobarbital

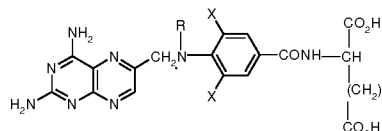
### Antifolates, antibacterials and antiprotozoals

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<sup>19</sup>. 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)<sup>20,21</sup>. Notable amongst the 2,4-diaminopyrimidine drugs are pyrimethamine (22), a selective inhibitor of the DHFR of malarial plasmodia; trimethoprim (23), an antibacterial drug which selectively inhibits bacterial DHFR and most importantly, the very potent but non selective DHFR inhibitors, methotrexate (24a) and aminopterin (24b), both used in cancer chemotherapy<sup>22</sup>. 3',5'-Dichloromethotrexate (24c), which is less toxic and more readily metabolized than methotrexate, has recently been introduced for anticancer therapy<sup>23</sup>. Brodimoprim (25) is also found to be an effective antibacterial compound<sup>24</sup>.



(22) Pyrimethamine

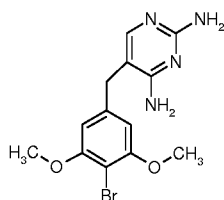
(23) Trimethoprim



(24)

(24a) R = CH<sub>3</sub>, X = H; Methotrexate

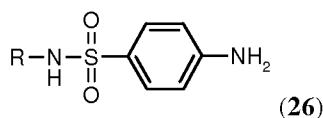
(24b) R = X = H; Aminopterin

(24c) R = CH<sub>3</sub>, X = Cl; 3',5'-dichloromethotrexate

(25) Brodimoprim

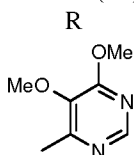
### Sulfa drugs

Pyrimidine derivatives of sulfa drugs, namely sulfadiazine, sulfamerazine and sulfadimidine are superior to many other sulfonamides and are used in some acute UT infections, cerebrospinal meningitis and for patients allergic to penicillins<sup>25</sup>. Sulfonamide-trimethoprim combinations are used extensively for opportunistic infections in patients with AIDS<sup>26</sup>. Sulfadoxine<sup>27</sup> (26a), a short and intermediate acting sulfonamide with a half-life of 7–9 days is used for malarial prophylaxis. Sulfisomidine (26b) with a half-life of 7 h is used as a combination sulfa therapy in veterinary medicine<sup>28</sup>. Sulfadiazine (27a), sulfamerazine (27b) and sulfadimidine (27c) possess good water solubility and therefore carry minimum risk of kidney damage, which makes them safe even for patients with impaired renal functions.

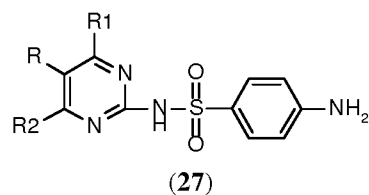
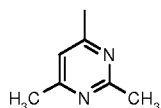


(26)

Sulfadoxine (26a)

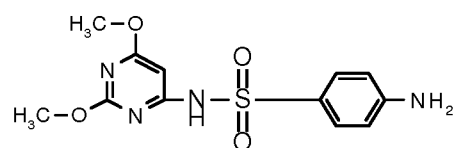


Sulfisomidine (26b)

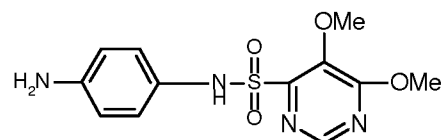


(27)

	R	R <sup>1</sup>	R <sup>2</sup>
Sulfadiazine (27a)	H	H	H
Sulfamerazine (27b)	H	CH <sub>3</sub>	H
Sulfadimidine (27c)	H	CH <sub>3</sub>	CH <sub>3</sub>
Sulfamethoxydiazine (27f)	OCH <sub>3</sub>	H	H
Methyldiazine (27e)	CH <sub>3</sub>	H	H

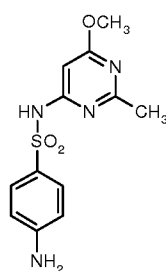


(27d) Sulfadimethoxine

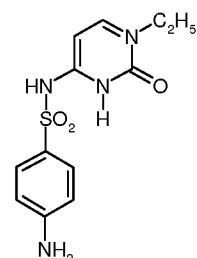


(28) Sulfamethoxine

In 1959, sulfadimethoxine<sup>29</sup> (27d) was introduced with a half-life of approximately 40 h. The related 4-sulfonamido-pyrimidine, sulfamethoxine<sup>29</sup> (28) having two methoxy groups in 5 and 6 positions, has by far the longest half-life of about 150 h. Methyldiazine<sup>29</sup> (27e) has a half-life of 65 h. Also, sulfamethoxydiazine<sup>29</sup> (27f) possesses good half-life. A new broad-spectrum sulfonamide, sulfamethomidine<sup>29</sup> (29) is relatively nontoxic and patients do not need extra fluid intake or alkalization. Sulfacytine<sup>29</sup> (30) has been reported to be 3–10 times more potent than sulfaisoxazole and sulfisodimidine<sup>29</sup>.



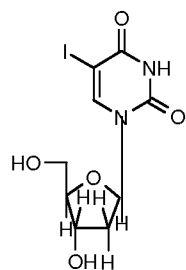
(29) Sulfamethomidine



(30) Sulfacytine

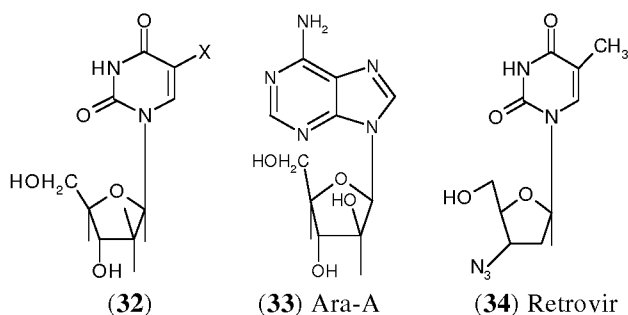
### Antivirals and anti-AIDS

Recently, pyrimidine derivatives have generated widespread interest due to their antiviral properties. 5-Iododeoxyuridine<sup>30</sup> (31) is an antiviral agent of high selectivity.



(31) 5-Iododeoxyuridine

IDU (5-iodo-2'-deoxyuridine) (**32a**) has been extensively utilized for viral infections. 5-Trifluoromethyl-2'-deoxyuridine (F<sub>3</sub> TDR, **32b**) has been found useful against infections resistant to IDU therapy<sup>30</sup>. Ara-A 9-β-D-arabino-furanosyl adenine (**33**), a relatively new antiviral drug, is effective against herpes infections of eye, brain and skin. It is especially effective against IDU-resistant herpes virus<sup>30</sup>.

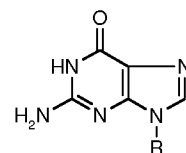


(32a) X = I, 5-iodo-2'-deoxyuridine  
 (32b) X = CF<sub>3</sub>, 5-trifluoromethyl-2'-deoxyuridine

Some purine nucleosides are equally noteworthy. Retrovir (AZT-16, **34**) 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<sup>31</sup>. At present Acyclovir (**35a**) 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<sup>32</sup>. Ganciclovir<sup>33</sup> (DHPG-2, **35b**) has shown good *in vivo* activity against HCV<sub>1</sub> and HCV<sub>2</sub>.

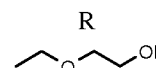
Several members of a series of acyclic nucleosides, which contain a fused pyrimidine ring (mainly purine), are found to be effective antivirals. Famciclovir (**35c**) and valacyclovir (**35d**) are drugs used for several DNA viruses, including Hsv types 1 and 2, Varicella-zoster virus and Epstein-Barr virus<sup>34</sup>. Penciclovir (**35e**)<sup>35</sup> is useful for topical treatment of recurrent herpes, *Libialis*. Cidofovir (**36b**)<sup>35</sup>, an antimetabolite for deoxycytosine triphosphate is used for treatment of cytomegalovirus (CMV) in AIDS patients. Lamivudine (**36a**)<sup>35</sup> is an effective anti-AIDS drug when used in combination with zidovudine (**37**)<sup>35</sup>. Zidovudine<sup>36</sup> 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<sup>+</sup> lymphocyte counts. Also, zalcitabine<sup>36</sup> (**38**) is another useful alternative drug to zidovudine. It is given in combination with zidovudine, when CD4<sup>+</sup> cell counts fall below 300 cells/mm<sup>3</sup>. Didanosine<sup>37</sup> (**39**) 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<sup>37</sup> (**40**) 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<sup>37</sup> (**41**) 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.

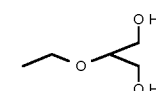


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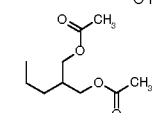
(35a) Acyclovir



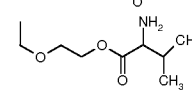
(35b) Ganciclovir



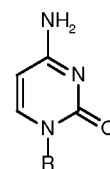
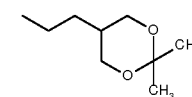
(35c) Famciclovir



(35d) Valacyclovir

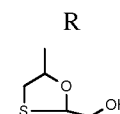


(35e) Penciclovir

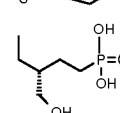


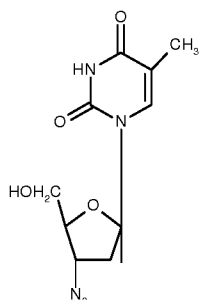
(36)

(36a) Lamivudine

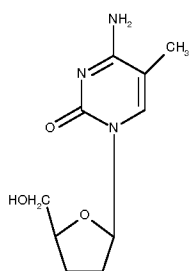


(36b) Cidofovir

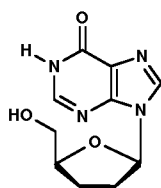




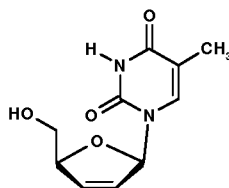
(37) Zidovudine



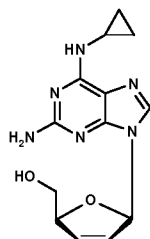
(38) Zalcitabine



(39) Didanosine



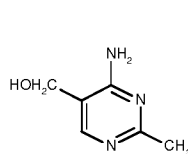
(40) Stavudine



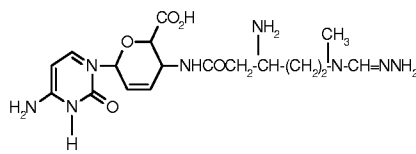
(41) Abacavir

### Antibiotics

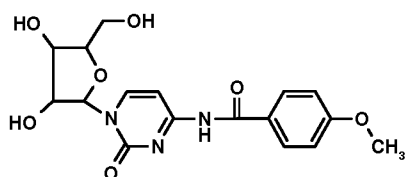
There are few examples of pyrimidine antibiotics. The simplest of all is bacimethrin (5-hydroxymethyl-2-methoxy-pyrimidin-4-amine) (42), which is active against several staphylococcal infections<sup>38</sup>. Gourgetin (43), a cytosine derivative is active against mycobacteria as well as several Gram-positive and Gram-negative bacteria<sup>39</sup>. There are more derivatives of cytosine, namely amicetin (44) and plicacetin (45), which exhibit activity against acid fast and Gram-positive bacteria as well as some other organisms<sup>38</sup>. Puromycin (46) has a wide spectrum of antitrypanosomal activity. Aminoglycoside antibiotics phleomycin (47a), bleomycin (47b) and related families are wide-spectrum antibiotics containing the pyrimidine ring. Another antibiotic tubercidine (48) is reported to exhibit antitumour properties<sup>39</sup>. In addition, they have antineoplastic activity. Bleomycin is already in clinical use against certain tumours like Hodgkin's lymphoma and disseminated testicular cancer<sup>40</sup>.



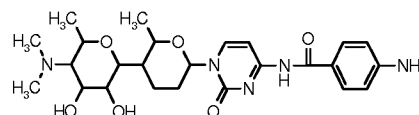
(42) Bacimethrin



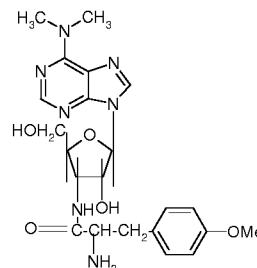
(43) Gourgetin



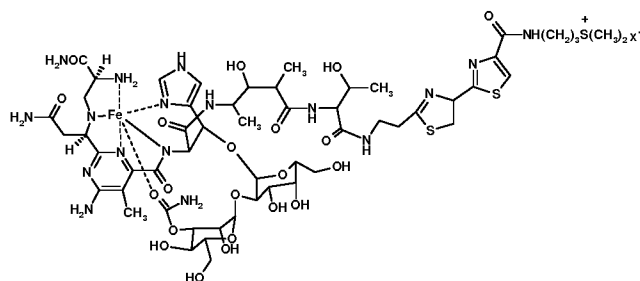
(44) Amicetin



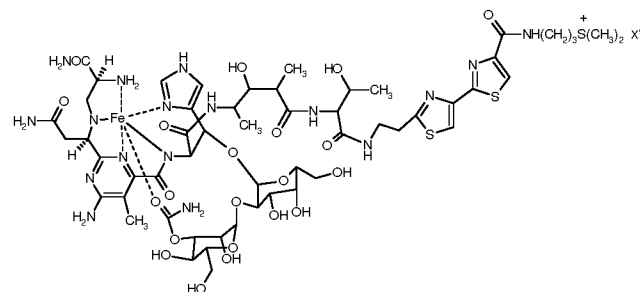
(45) Plicacetin



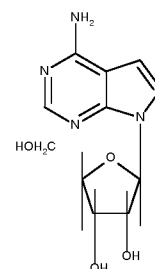
(46) Puromycin



(47a) Phleomycin



(47b) Bleomycin



(48) Tubercidine

### Antifungals

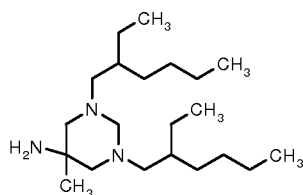
Pyrimidines also exhibit antifungal properties. Flucytosine (49)<sup>41</sup> is a fluorinated pyrimidine used as nucleosidal anti-

fungus agent for the treatment of serious systemic infections caused by susceptible strains of candida and cryptococcus<sup>42</sup>.

Hexitidine<sup>43</sup> (50) is mainly used for the treatment of aphthous ulceration.



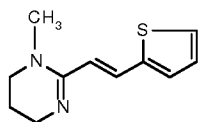
(49) Flucytosine



(50) Hexitidine

### Anthelmintics

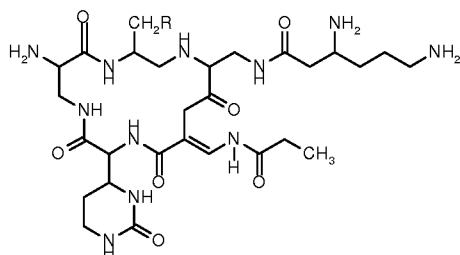
These drugs have the ability of ridding the body of parasitic worms. Pyrantel pamoate (51) is a depolarizing neuromuscular blocking agent that causes spastic paralysis in helminthes and is employed in the treatment of infestations caused by pinworms and roundworms<sup>44</sup>.



(51) Pyrantel pamoate

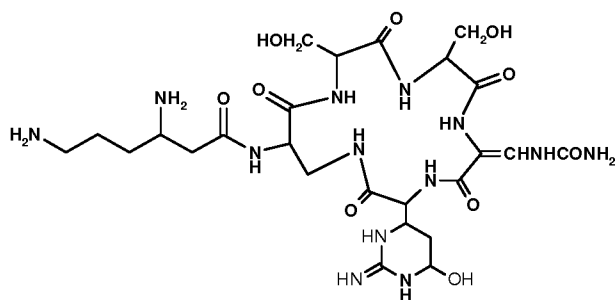
### Antitubercular drugs

Capreomycin (52) produced by *Streptomyces capreolus* is a second-line bacteriostatic antituberculin drug containing pyrimidine<sup>45,46</sup>.



(52) Capreomycin

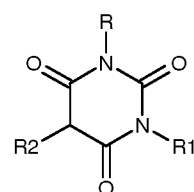
Viomycin (53) is more tuberculostatic than *p*-aminosalicylic acid. It is effective in the treatment of experimental tuberculosis.



(53) Viomycin

### CNS active agents

**Sedative/hypnotic/antiepileptic agents:** Agents of the anxiolytic, sedative and hypnotic group include a wide variety of barbiturates (54a-i) used as sedative and hypnotics and are classified as drugs having short, intermediate and long duration of action<sup>47,48</sup>. Allobarbital (54a), aprobarbital (54b), pentobarbital (54e), phenobarbital (54g) and secobarbital (54i) are frequently used clinically as hypnotic barbiturates<sup>49</sup>. Hexobarbital (54c), cyclobarbital (54d) and propallylonal (54f) are some of the current drugs in the market used as sedative hypnotics<sup>50</sup>. Barbiturates as sedative hypnotics have a long and fascinating history. In fact Eli Lilly<sup>51</sup> patented secbutabarbital (54h) in 1932, while barbitone (8), the first of the barbiturates<sup>1</sup> was introduced in 1903.

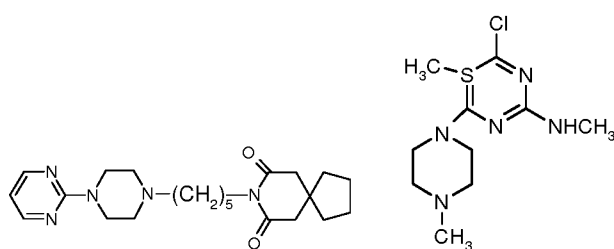


(54)

	R	R <sub>1</sub>	R <sub>2</sub>
(54a) Allobarbital	-H	-H	
(54b) Aprobarbital	-H	-H	
(54c) Hexobarbital	-H	-CH <sub>3</sub>	
(54d) Cyclobarbital	-H	-H	
(54e) Pentobarbital	-H	-H	
(54f) Propallylonal	-H	-H	
(54g) Phenobarbital	-H	-H	
(54h) Secbutabarbital	-H	-H	
(54i) Secobarbital	-H	-H	

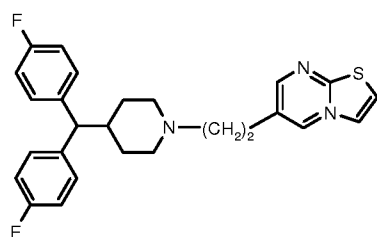
**Anxiolytic agents:** Few of the pyrimidine derivatives are also used as anxiolytics. Most important of these is buspirone (**55**), indicated in the management of anxiety disorders accompanied with or without depression. It lacks sedative, anticonvulsant and muscle-relaxant effects and most importantly abuse potential<sup>52</sup>. Buspirone lacks affinity to benzodiazepine receptors, but binds avidly to one subclass of serotonin receptors, the 5-HT<sub>1A</sub> subtype<sup>53,54</sup>. Ritanserin (**56**), a 5HT<sub>2</sub> antagonist with anxiolytic activity is a pyrimidine derivative<sup>55</sup>.

A simple pyrimidine derivative, mezilamine (**57**) is classified as an antipsychotic agent<sup>56</sup>.



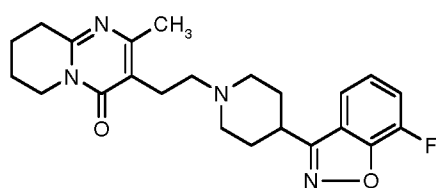
(55) Buspirone

(56) Ritanserin



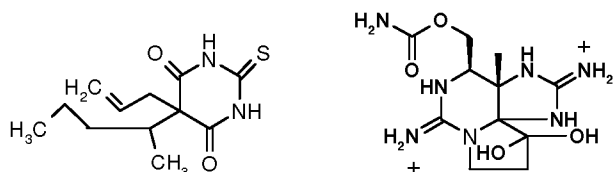
(57) Mezilamine

Risperidone (**58**) is an antipsychotic drug, which is a structural hybrid of butyrophenone and can be used as anxiolytic, antidepressant and antiparkinsonian drug<sup>57</sup>.



(58) Risperidone

**Pyrimidine anaesthetics:** Thimylal (**59**) is a short acting general anaesthetic drug, which is also a pyrimidine analogue<sup>58,59</sup>.

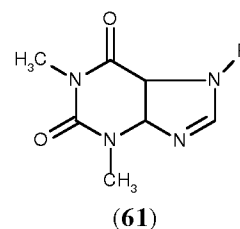


(59) Thimylal

(60) Saxitoxin

Saxitoxin<sup>58</sup> (**60**) is a naturally occurring pyrimidine containing anaesthetic agent, but is too toxic to be of clinical use. Saxitoxin is isolated from some marine dinoflagellates.

**Diuretics, uricosurics:** Several xanthine derivatives (**61**) containing fused pyrimidine ring systems like caffeine<sup>60</sup> (**61a**), etamiphylline<sup>61</sup> (**61b**), lomiphylline<sup>62</sup> (**61c**), etophylline<sup>63</sup> (**61d**), theophylline<sup>60</sup> (**61e**) and theodrenaline<sup>64</sup> (**61f**) are known to promote a weak diuresis by stimulation of cardiac function and by a direct action on the nephron, acting as adenosine receptor antagonists<sup>60</sup>.



(61)

(61a) Caffeine

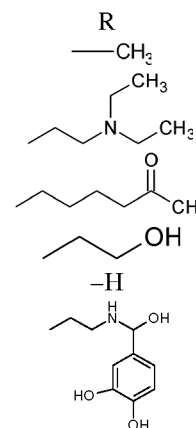
(61b) Etamiphylline

(61c) Lomiphylline

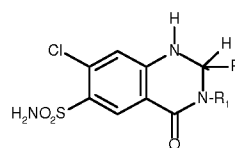
(61d) Etophylline

(61e) Theophylline

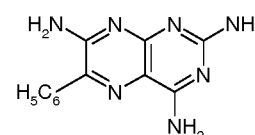
(61f) Theodrenaline



There are a few examples of diuretics which contain a pyrimidine ring. Noteworthy are quinethazine (**62a**), metolazone (**62b**)<sup>65</sup> and triamterene (**63**)<sup>66</sup>.



(62)

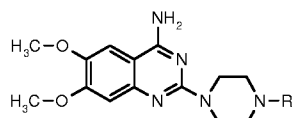
(62a) R = C<sub>2</sub>H<sub>5</sub>, R<sup>1</sup> = H; Quinethazine(62b) R = CH<sub>3</sub>, R<sup>1</sup> = 2-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>; Metolazone

(63) Triamterene

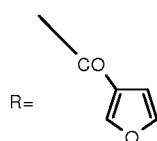
### Cardiac agents

**Antihypertensives:** Several pyrimidine ring-containing drugs have exhibited antihypertensive activity. Prazosin (**64a**), a quinoxaline derivative, is a selective  $\alpha_1$ -adrenergic antagonist<sup>67,68</sup>. Its related analogues bunazosin (**64b**)<sup>69</sup>, terazosin (**64c**)<sup>70</sup> and trimazosin (**64d**)<sup>71</sup> are potent anti-

hypertensive agents. Another quinazoline derivative, ketanserin (**65**)<sup>72</sup> having a similar effect is an antagonist of both  $\alpha_1$ -adrenergic and serotonin- $S_2$  receptors. Its mechanism of action however is still controversial. A triaminopyrimidine derivative, minoxidil (**66**), 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<sup>73</sup>.



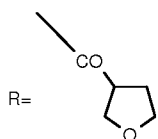
(64)



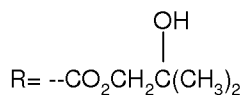
(64a) Prazosin



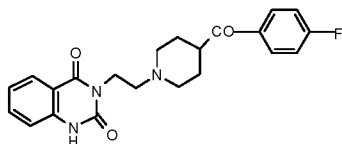
(64b) Bunazosin



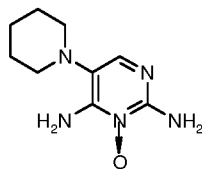
(64c) Terazosin



(64d) Trimazosin

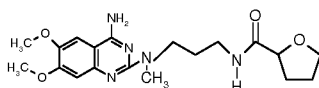


(65) Ketanserin

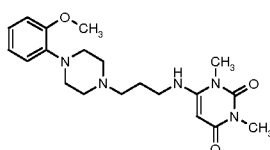


(66) Minoxidil

Besides these, some more pyrimidine derivatives given below were found to be antihypertensives<sup>74,75</sup>.



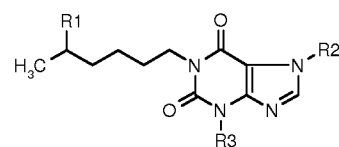
(67) Alfuzocin



(68) Urapidil

Alfuzocin<sup>74</sup> (**67**), a prazosin analogue and an  $\alpha_1$ -adrenoceptor antagonist as well as urapidil<sup>75</sup> (**68**) are used especially in urinary obstruction caused by benign prostate hyperplasia.

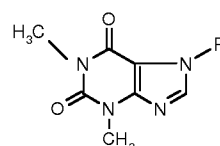
**Vasodilators:** A series of xanthine derivatives are used as peripheral and cerebral vasodilators. Especially, pentifylline (**69a**) and pentoxyphylline (**69b**) are used in cardiovascular disorders<sup>76</sup>.



(69)

	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>
(69a) Pentifylline	-H	—CH <sub>2</sub>	—CH <sub>2</sub>
(69b) Pentoxyphylline	—O	—CH <sub>2</sub>	—CH <sub>2</sub>
(69c) Propentophylline	-H	—CH <sub>2</sub>	—CH <sub>2</sub>

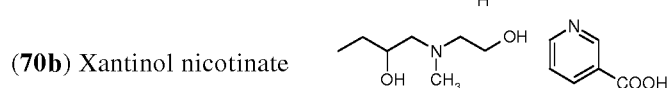
Other derivatives like xantinol nicotinate<sup>77</sup> (**70b**), a vasodilator with general properties like nicotinic acid used in cerebral and peripheral vascular disorders and pimephylline (**70a**) and pyridophylline<sup>78</sup> (**70c**) are noteworthy.



(70)



(70a) Pimephylline

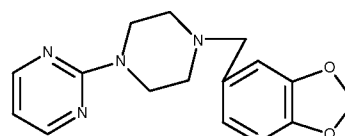


(70b) Xantinol nicotinate



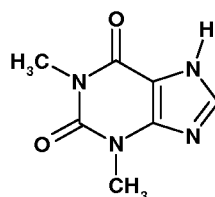
(70c) Pyridophylline

A new dopamine receptor stimulant, pibedil (**71**)<sup>79</sup> is reported to have produced significant improvement in ADL (Activity of Daily Living) in patients suffering from Parkinson's syndrome.

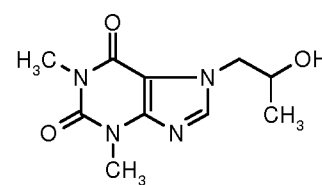


(71) Pibedil

**Cardiotonics/bronchodilators:** Several xanthine derivatives theophylline (**61e**), aminophylline<sup>80</sup> (**72a**) and proxiphylline<sup>80</sup> (**72b**) exhibit good bronchodilator activity.



(72a) Aminophylline

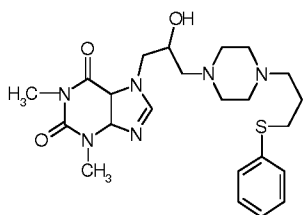


(72b) Proxiphylline

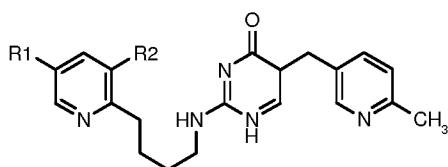


## Antihistaminic pyrimidines

Taziphylline (**73**) is ten times more potent than either astemizole or terfenadine in its affinity for H<sub>1</sub>-histamine-binding site and appears to be devoid of CNS activity<sup>81</sup>. Another pyrimidine containing antihistaminic drug, temelastine (**73a**) is comparable to mepyramine<sup>82</sup>. Radio-labelled studies have indicated that it does not penetrate the CNS appreciably. Icotidine (**73b**), a structural analogue of temelastine lacks CNS activity and is a dual antagonist of both H<sub>1</sub> and H<sub>2</sub> receptors<sup>83</sup>.

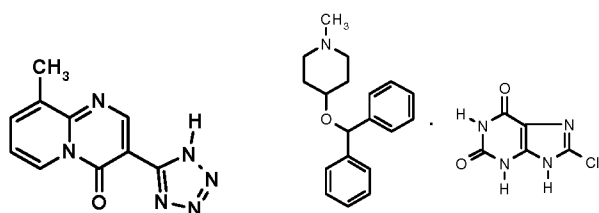


(73) Taziphylline



(73a), R<sup>1</sup> = Br, R<sup>2</sup> = CH<sub>3</sub>; temelastine  
(73b), R<sup>1</sup> = H, R<sup>2</sup> = OCH<sub>3</sub>; icotidine

Pemirolast<sup>84</sup> (**74**), a new oral nonbronchodilator antihistaminic agent is also a pyrimidine derivative. It has demonstrated sufficient antihistaminic activity to warrant its use in severe asthma. Another compound, piprinhydrinate<sup>85</sup> (**75**) is also a pyrimidine derivative.

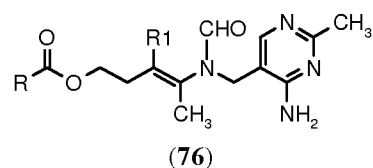


(74) Pemirolast

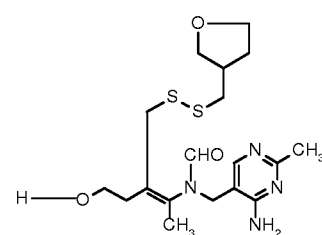
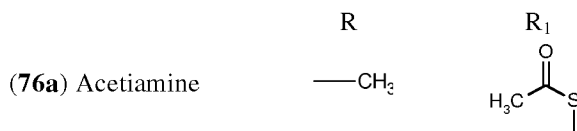
(75) Piprinhydrinate

## Analgesics and NSAID drugs

Acetiamine<sup>86</sup> (**76a**), bentiamine<sup>86</sup> (**76b**) and fursultiamine<sup>87</sup> (**76c**) are new lipid-soluble forms of thiamine (vitamin B<sub>1</sub>) having therapeutic use in beriberi, polyneuritis, encephalopathy, pain, malnutrition and alcoholism and especially in the treatment of long-standing insulin-dependent diabetes mellitus. Fursultiamine has been reported to inhibit the arachadonic acid cascade-line activation and reverse the increase in CBF (Coronary Blood Flow).

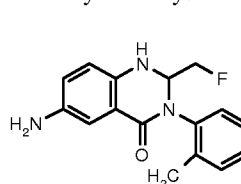


(76)

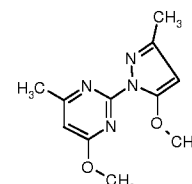


(76c) Fursultiamine

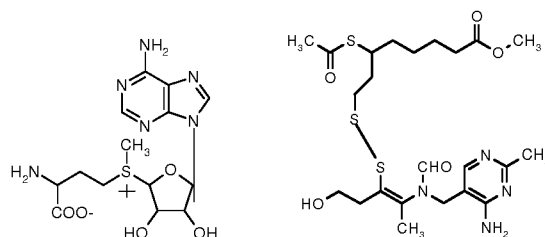
Afloqualone<sup>88</sup> (**77**) has been evaluated as a successful anti-inflammatory agent with lower back pain patients. Epirazole<sup>89</sup> (**78**), another NSAID, is suggested to be a COX-2 inhibitor. Ademetionine<sup>90</sup> (**79**) is primarily used in conjunction to glucosamine and chondroitin therapy. Octotiamine<sup>91</sup> (**80**), a vitamin B<sub>1</sub> derivative also exhibits anti-inflammatory activity.



(77) Afloqualone

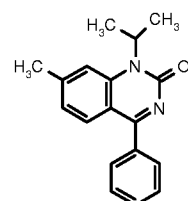


(78) Epirazole



(79) Ademetionine

(80) Octotiamine

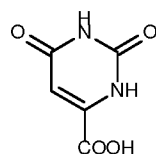


(81) Proquazone

Proquazone<sup>92</sup> (**81**), a condensed pyrimidin-2-one derivative has been reported to exhibit good NSAID potential.

### Metabolic electrolytes

Orotic acid<sup>93</sup> (**82**), a simple pyrimidine derivative and its mineral forms are used in metabolic therapy, especially for cardiovascular patients to prevent heart failure in cardiomyopathy. Oroate is needed as a key intermediate in biosynthesis of pyrimidine nucleotides, which are building blocks for DNA and RNA required for the final protein synthesis.



(**82**) Orotic acid

### Conclusion

Pyrimidines occupy a distinct and unique place in our life. This heterocyclic moiety has great biological and medicinal significance. A large array of pyrimidine drugs possess a variety of medicinal properties. These properties include anticancer, antibacterial, antiprotozoal, antimicrobial, antiviral, antihypertensive, antihistaminic, anti-inflammatory, analgesic, CNS-active to metabolic adjuvants.

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