

THE PHYSIOLOGICAL AND MEDICINAL POTENTIAL PYRIMIDINES & DIFFERENT SCHEME TO SYNTHESIZE PYRIMIDINE HETEROCYCLES: AN UPDATE

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ABSTRACT

Pyrimidine is a heterocyclic aromatic organic compound. This article outlines the different scheme to synthesize different derivatives of pyrimidine heterocycle & 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, Biological significance, Medicinal significance.

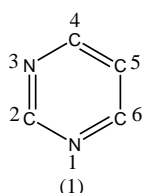
INTRODUCTION

The present review attempts to give a brief account of the Chemistry of Pyrimidine Ring including its Structure, Geometry and Electronic Structure, pKa, Reactivity and general Method of Synthesis of Pyrimidine Ring.

1 The chemistry of Pyrimidine Ring

1.1 The structure of pyrimidine ¹

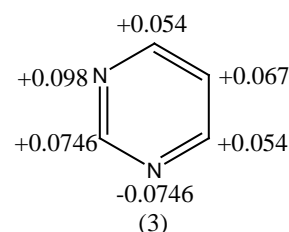
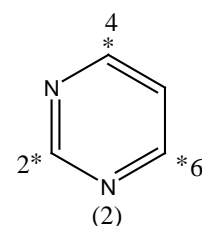
Pyrimidine is the most important six membered aromatic heterocyclic ring containing two nitrogen atoms. The replacement of 'C-H' units Meta to each other in a benzene ring by two nitrogen atoms gives pyrimidine (1), generally results in a reduced symmetry with bonds of unequal length. However, it retains its symmetry about 2, 5-axis so that three differing pairs of equal bond density centers for the p-electrons which are otherwise equally distributed about the ring system in benzene. Therefore, the reactivities of 2, 4, 5 and 6 carbon atoms of pyrimidines, as well as, the substituent attached to them vary individually.



1.2 The geometry and electronic structure of the pyrimidine ring ¹

The pyrimidine ring is virtually flat. The depletion of electron density at the position *ortho* and *para* to the electronegative nitrogen atoms is more marked in the pyrimidine than the other two diazines: pyrazine and pyridazine. This is because the two 'N' atoms of this 1, 3-diazine is so positioned that their individual effects reinforce each other, and thus act in unison. That is why the resultant effect is greater in the pyrimidine than its isometric diazines, in which the electronic effects of the two 'N' atoms instead of adding up, in fact partly antagonize each other. Thus, the marked positions (*) C-2, C-4 and C-6 in the pyrimidine ring (2) become strong electropositive centers, while the position C-5 retains some electronegativity, though only to a lesser extent. At the same time, the localization of p-electrons at the two 'N' atoms results in decreased aromaticity of the pyrimidine ring. Thus pyrimidine is not truly aromatic; whatever little appearance of aromaticity is left in the system is at C-5 position. This leads to a sharp fall in its stability reflected by low resonance energy of only 26 kcal/mole.

The following electron density diagram shows the distribution of electrical charges. i.e. the gain or loss of the p-electrons at each atom of the molecule has been calculated for the pyrimidine (3).



1.3 The pKa of pyrimidine ¹

Pyrimidine is a weaker base (pKa 1.31) than pyridine (pKa 5.2) because the second ring nitrogen shares the available p-electrons with the first and the system therefore approximates to 3-nitropyridine (pKa 0.8). Its basicity is intermediate to that of the other two isometric diazine namely, pyridazine (pKa 2.33) and pyrazine (pKa 0.6) respectively. The basic strength of pyrimidine no longer has the capacity of a ring 'N' to attract p-electrons.

1.4 Reactivity of pyrimidine ¹

1.5 The electrophilic attack

Electrophilic reagents almost invariably attack pyrimidine at the C-5 positions, the least electron-depleted site of all. It can be easily nitrated, nitrosated, halogenated, sulfonated and coupled with diazonium salt.

1.6 The nucleophilic attack

Although, the C-2, C-4 and C-6 position of the pyrimidine ring are the best target for direct nucleophilic attack, only a few examples of the reaction are known where direct nucleophilic substitution of hydrogen takes place.

1.7 General methods for the synthesis of pyrimidine

Synthesis of pyrimidines has been of great interest to organic chemists because of their varied biological and pharmacological activities. In 1818, Gaspare B. isolated the first pyrimidine derivative, alloxan, by the oxidation of uric acid with nitric acid. The first example of principal pyrimidine synthesis was the synthesis of barbituric acid, in 1878, from malonic acid and urea.

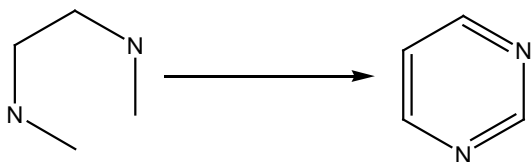
Since then synthesis and chemistry of pyrimidine have been discussed by Kenner in 1957³, Ramage and Landquist in 1959⁴. The most common route to such pyrimidine derivatives is through the principal synthesis involving the condensation of 1, 3-dicarbonyl compounds with bisnucleophiles like amidines. A number of such fruitful condensations have been effected with a host of 1, 3-dicarbonyl analogues to obtain appropriately substituted pyrimidines.

The methods of synthesis of pyrimidines are classified on the basis of components employed in the pyrimidine cyclization. The classes are as follows:

1.8 One component synthesis⁵⁻⁷

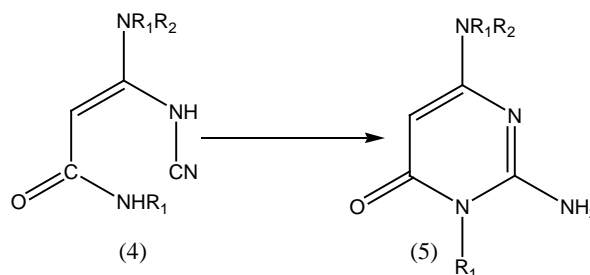
This involves the intramolecular cyclization of certain open chain intermediates to yield the pyrimidine nucleus. This method can be further subclassified according to the position of the bond formed during the cyclization.

[A] 1, 2(2, 3)-bond formation

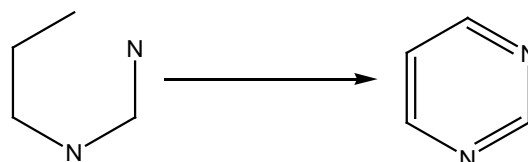


One of the examples of this type is the base catalyzed cyclization of the N-cyanoamine

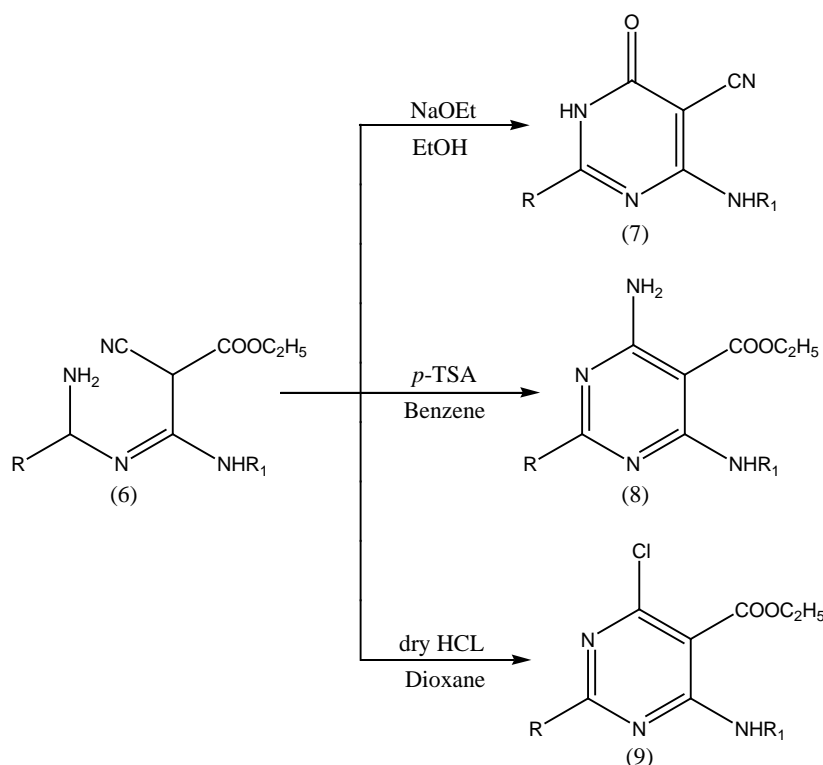
Derivative (4) to 2-aminopyrimidine (5).



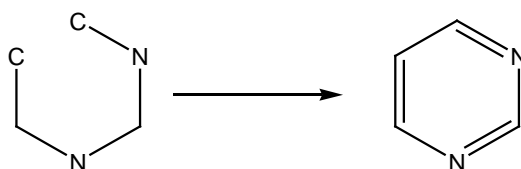
[B] 3, 4(1, 6)-bond formation



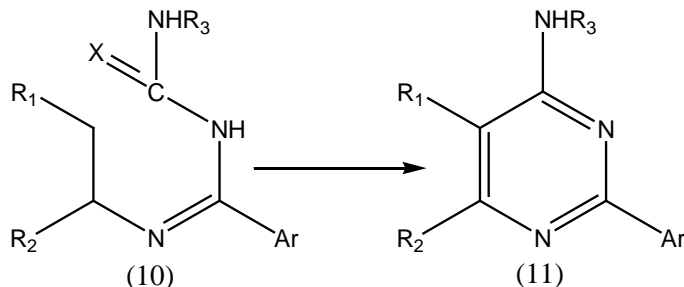
The pyrimidine synthesis through the condensation of 1, 3-dicarbonyl compounds with amidines presumably proceeds via the vinylamidine intermediate (6). Intramolecular cyclization of the vinylamidine leads to the 3, 4(1, 6)-bond formation. Vinylamidine intermediate (6) has been cyclized under acidic and basic conditions to give different functionalized pyrimidines (7-9).



[C] 4, 5(6, 5)-bond formation



N-vinyl-N-acylbenzamidines (10) on heating with pyridine in the presence of *p*-toluene sulfonylchloride cyclizes to give 4-aminopyrimidines (11).



1.9 Two component synthesis⁸

This is the most versatile and widely used method of pyrimidine synthesis. It involves the condensation of two reactants. One of the

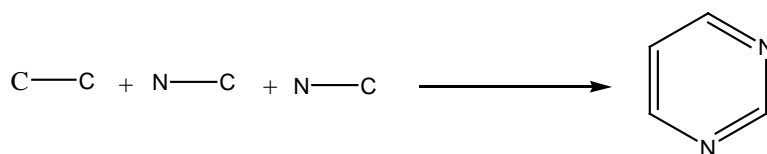
components used may contribute three, four or five atoms of the pyrimidine ring system, while the other contributes three, two or one atom, respectively. Different types of this synthesis are described as follows:

1.	C-C-C	+	N-C-N
2.	C-C-N	+	C-N-C
3.	C-C-C-N	+	C-N
4.	C-N-C-N	+	C-C
5.	C-C-N-C	+	N-C
6.	N-C-C-C-N	+	C
7.	C-C-C-N-C	+	N
8.	C-C-N-C-N	+	C

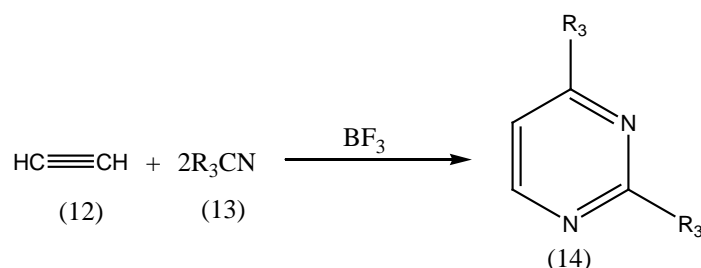
Most widely used method is method (1), which is also known as principal synthesis of pyrimidine.

1.10 Three component synthesis

Very few reports are available on this type of synthesis. Generally, each of the three components, contributes two atoms each, for the pyrimidine cyclization.



The reaction of acetylene (12) with two molecules of a nitrile (13) in the presence of borontrifluoride to yield the substituted pyrimidine (14) represents the above type.⁹

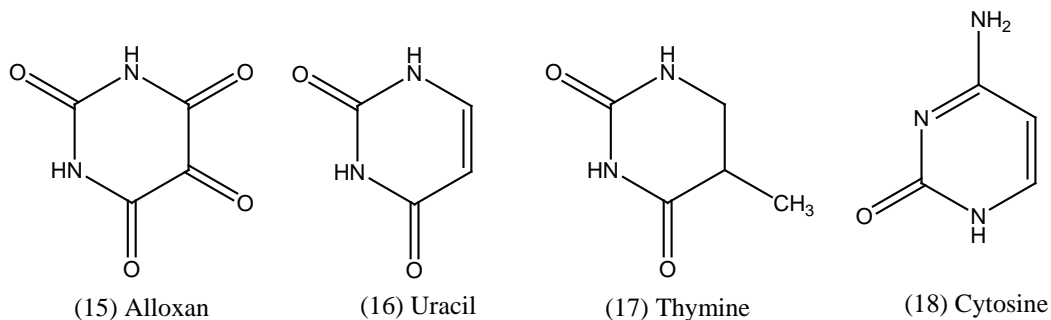


2. Physiological Significance of Pyrimidine

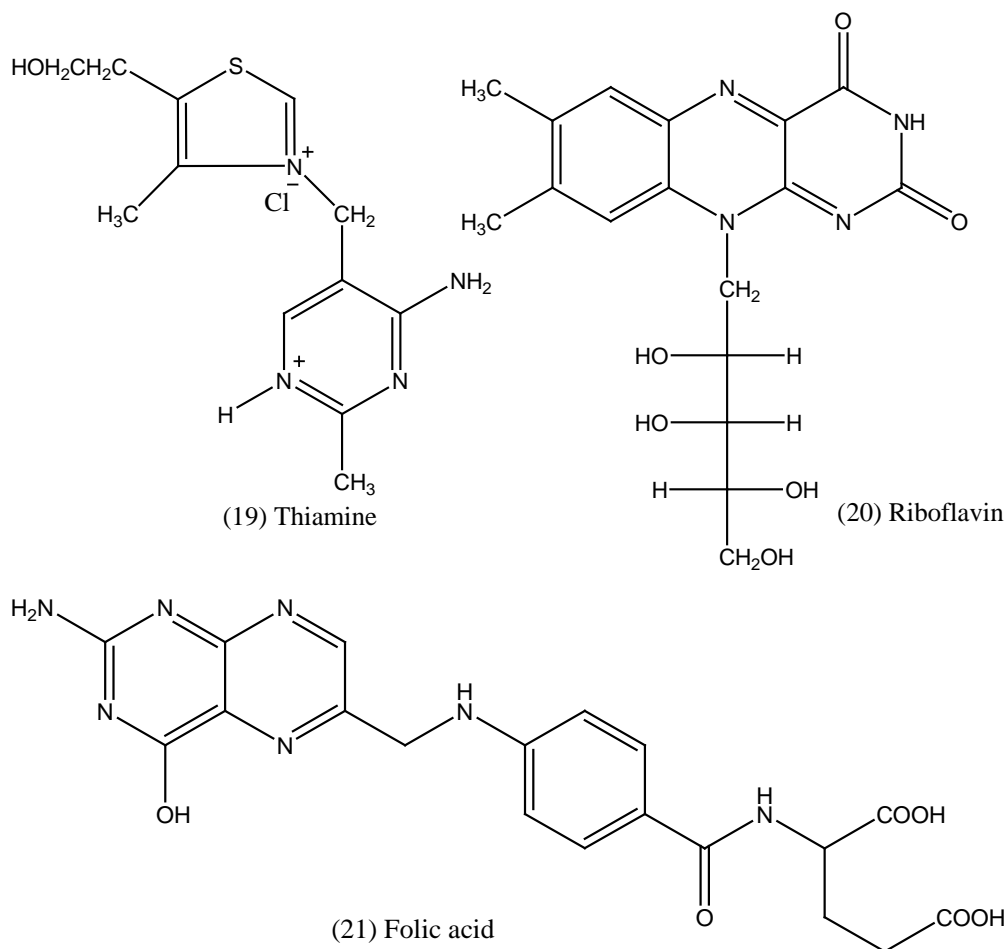
Pyrimidine, one of the bases of hydrolyzed product of nucleosides continues to be an interesting subject to the medicinal chemist by virtue of their diverse biological activities. They do not block nucleotide biosynthesis but are also used in the therapy of AIDS, cancer, hypertension and diabetes. Uric acid and its oxidation product, alloxan (15) are among the oldest of pyrimidine derivatives

of biological interest. Alloxan is known for its diabetogenic action in number of animal¹⁰. Uracil (16), thymine (17), and cytosine (18) are the three important constituents of nucleic acids. The role of uracil and thiamine in controlling the metabolism, reproduction, and growth of living

Organism, especially in the transcription of genetic information and biosynthesis of proteins, has been extensively reviewed.



The pyrimidine ring is found in vitamins like thiamine¹¹ (19), riboflavin¹¹ (20) and folic acid¹¹ (21).

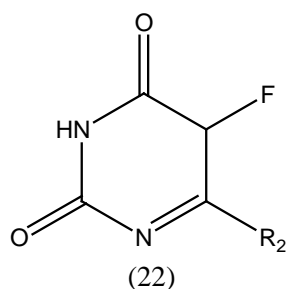


3. Medicinal Significance of Pyrimidine

3.1 Pyrimidines as anticancer agents

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

clinical application. 5-Fluorouracil (5-FU, 22)¹² and its deoxyriboside (5-FUDR)¹³ are reported as potent anticancer agents, and valuable drugs for the treatment of tumors of breast, colon or rectum and to a lesser extent gastric, hepatic, pancreatic, uterine, ovarian and bladder carcinomas.

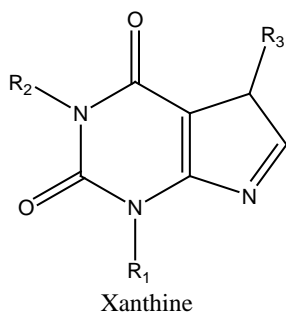


3.2 Pyrimidine in xanthine derivatives¹⁴

Caffeine (23), theophylline (24) and theobromine (25) are the important widely used naturally occurring xanthine derivatives. Caffeine is CNS stimulant. Theophylline exhibits a potent

bronchodilatory action and theobromine is used as a diuretic agent. Aminophylline (theophyllineethylenediamine) has proved to be the most effective drug when given

Intravenously for bronchospasm resistant to epinephrine.



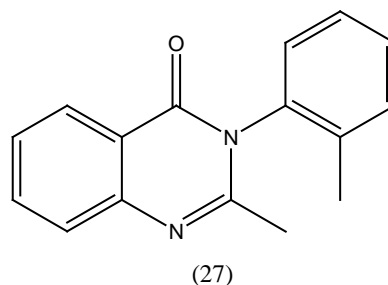
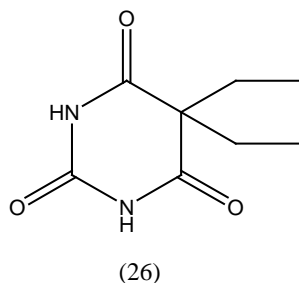
Compounds	R ₁	R ₂	R ₃
23	-CH ₃	-CH ₃	-CH ₃
24	-CH ₃	-CH ₃	-H
25	-H	-CH ₃	-CH ₃

3.3 Pyrimidines as CNS drugs^{15,16}

Notable amongst the drugs having a pyrimidine nucleus are the barbiturates, used in the therapy for a long time for their hypnotic, sedative and anticonvulsant properties. Barbitone (26) was the first

hypnotic to be introduced in medicine in year 1903. Another pyrimidine containing drug,

methaqualone (27) was introduced in 1965, as a potent hypnotic and sedative.

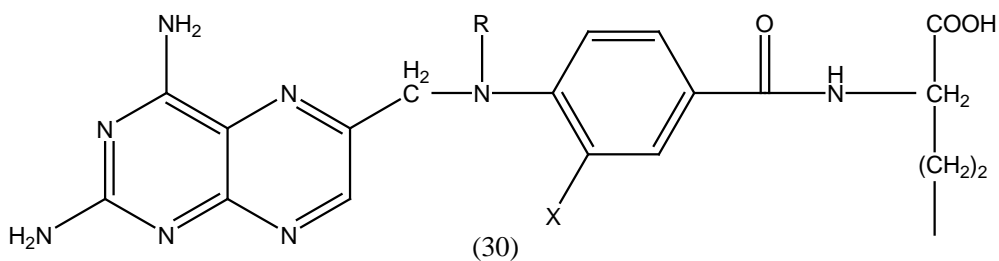
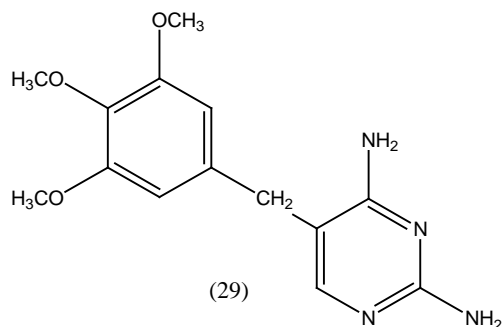
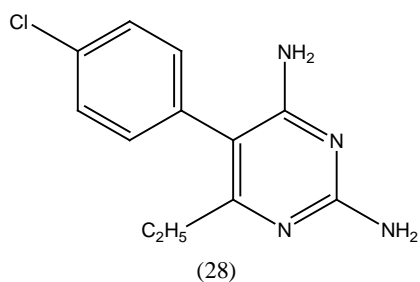


3.4 Pyrimidines as Antifolates, antibacterials and antiprotozoals

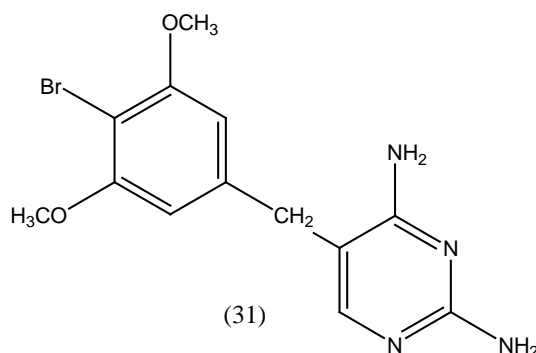
In 1948, Hitchings made an important observation that a large number of 2, 4-diaminopyrimidines and some 2-amino-4-hydroxypyrimidines are antagonists of folic acid¹⁷.

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)^{18,19}. Notable amongst the 2, 4-diaminopyrimidine drugs are

pyrimethamine (28), a selective inhibitor of the DHFR of malarial plasmodia; trimethoprim (29), an antibacterial drug which selectively inhibits bacterial DHFR and most importantly, the very potent but non selective DHFR inhibitors, methotrexate (30a), and aminopterin (30b), both used in cancer chemotherapy²⁰. 3 ϵ , 5 ϵ -Dichloromethotrexate (30c), which is less toxic and more readily metabolized than methotrexate, has recently been introduced for anticancer therapy²¹. Brodimoprim (31) is also found to be an effective antibacterial compound²².

(30a) R= CH₃, X= H

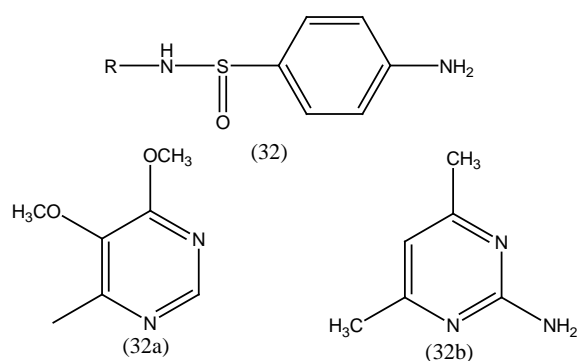
(30b) R= X= H;

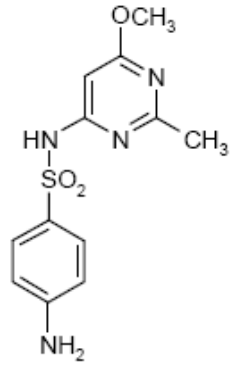
(30c) R= CH₃, X= Cl

3.4.1 Sulfa drugs

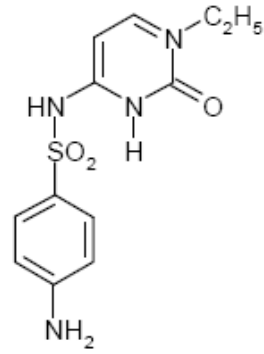
Pyrimidine derivatives of sulfa drugs, namely sulfadiazine, sulfamerazine and sulfadimidine are superior to many other sulfonamides and are used in some acute UT infections, cerebrospinal meningitis and for patients allergic to penicillins²³. Sulfonamide-trimethoprim combinations are used extensively for opportunistic infections in patients with AIDS²⁴. Sulfadoxine²⁵ (32a),

a short and intermediate acting sulfonamide with a half-life of 7–9 days is used for malarial prophylaxis. Sulfisomidine (32b), with a half life of 7 h is used as a combination sulfa therapy in veterinary medicine²⁶. Sulfadiazine (33a), sulfamerazine (33b), and sulfadimidine (33c), possess good water solubility and therefore carry minimum risk of kidney damage, which makes them safe even for patients with impaired renal functions.

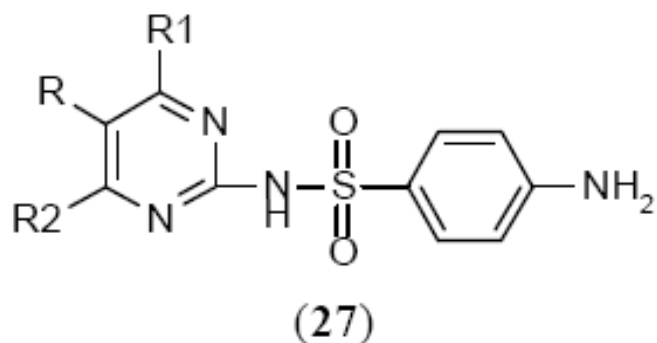




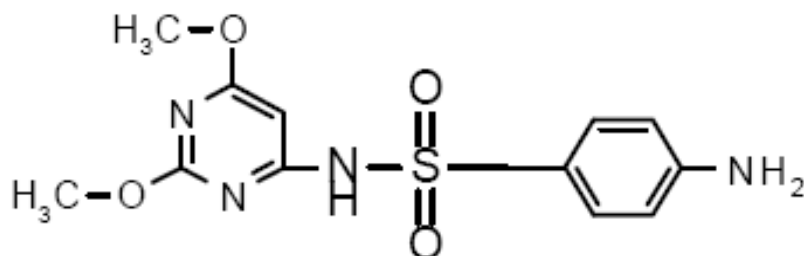
(29) Sulfamethomidine



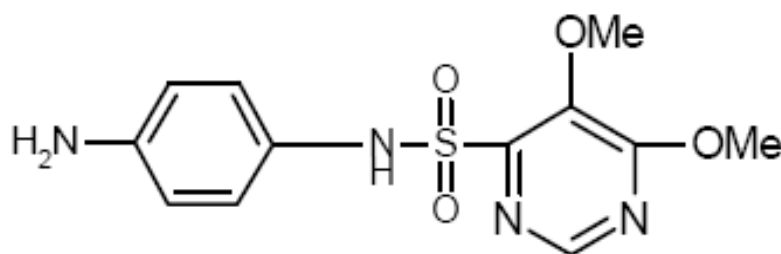
(30) Sulfacytine



	R	R ¹	R ²
Sulfadiazine (27a)	H	H	H
Sulfamerazin (27b)	H	CH ₃	H
Sulfadimidine (27c)	H	CH ₃	CH ₃
Sulfametoxydiazine (27f)	OCH ₃	H	H
Methyldiazine (27e)	CH ₃	H	H



(27d) Sulfadimethoxine



(28) Sulfamethoxine

In 1959, sulfadimethoxine²⁷ (27d) was introduced with a half-life of approximately 40 h. The related 4-sulfonamidopyrimidine, sulfamethoxine²⁷ (28) having two methoxy groups in 5 and 6 positions, has by far the longest half life of about 150 h.

Methyldiazine²⁷ (27e) has a half-life of 65 h. Also, sulfamethoxydiazine²⁷ (27f) possesses good half-life. A new broad-spectrum sulfonamide, sulfamethomidine²⁷ (29) is relatively

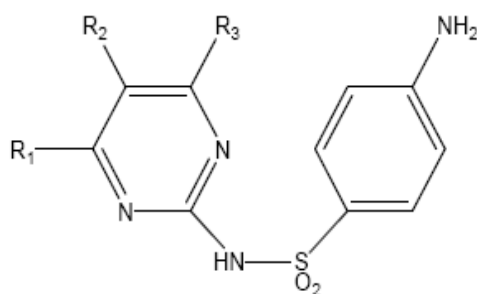
nontoxic and patients do not need extra fluid intake or alkalinization. Sulfacytine²⁷ (30) has been reported to be 3-10 times more potent than Sulfisoxazole and sulfisomidine²⁷.

3.5 Pyrimidines as diuretics

There are few examples of sulfonamide diuretics, which contain a pyrimidine ring. Noteworthy is quinethazine, metolazone and triamterene. Other sulfonamides like sulfadiazine (80a), sulfamerazine (80b) and sulfadimidine (80c), all pyrimidine

analogues possess good diuretic activity with acceptable water

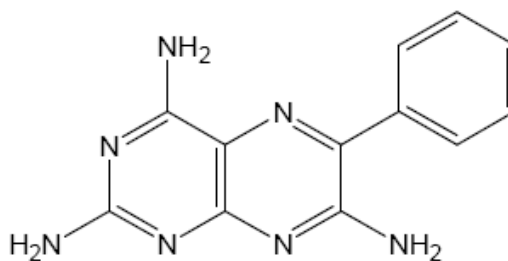
solubility to avoid kidney damage.²⁸



(80)

Compounds	R ₁	R ₂	R ₃
80a	H	H	H
80b	-CH ₃	-CH ₃	H
80c	-CH ₃	H	-CH ₃

Triamterene (**82**) is another pyrimidine analog that is widely used as diuretic.²⁹

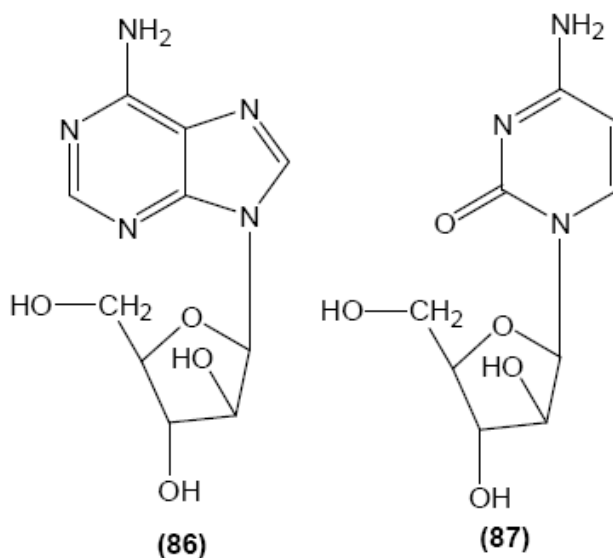


(82)

3.6 Pyrimidines as antiviral and anti HIV drugs

Pyrimidine derivatives have generated a wide spread interest due to their antiviral properties. Notables amongst are some purine and

pyrimidine nucleosides. Ara-a (9-b-D-arabinofuranosyladenine) Vidarabine (**86**)³⁰ is effective against herpes infection of eye, brain and skin. Cytarabine (**87**)³¹ exhibited significant effects in patients with herpes virus infections and herpes encephalitis.

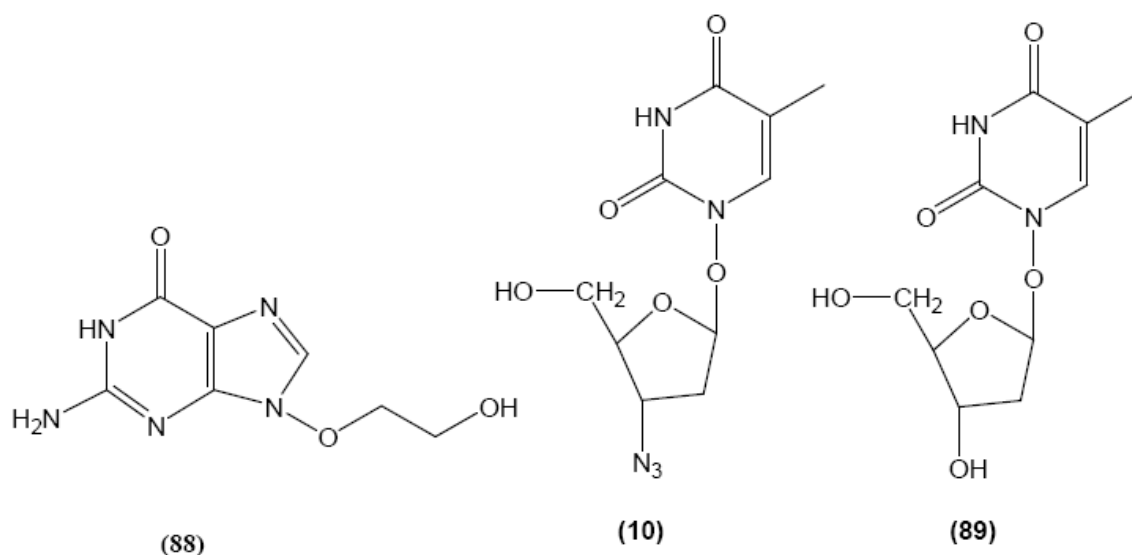


(86)

(87)

Acyclovir (**88**)³² at present is the only effective treatment for genital herpes with minimal side effects. Azidothymidine (AZT-16; **10**)³³ is a potent inhibitor of the replication and cytopathic

effects of HIV *in vivo* and has been used against AIDS. 5-Iododeoxyuridine (**89**)³⁴ is a selective antiviral agent currently used in practice.



Cidofovir (**36b**)³⁵, an antimetabolite for deoxycytosine triphosphate is used for treatment of cytomegalovirus (CMV) in AIDS patients. Lamivudine (**36a**)³⁵ is an effective anti-AIDS drug when used in combination with zidovudine (**37**)³⁵. Zidovudine³⁶ 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, zalcitabine³⁶ (**38**) is another useful alternative drug to zidovudine. It is given in combination with zidovudine, when CD4+ cell counts fall below 300 cells/mm³. Didanosine³⁷ (**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.

Stavudine³⁷ (**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 zidovudine or didanosine for treatment in patients for delaying the progression of HIV infection. It is recommended for patients with advanced HIV infection. Abacavir sulfate³⁷ (**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.

3.7 Antibiotics

There are few examples of pyrimidine antibiotics. The simplest of all is bacimethrin (5-hydroxymethyl-2-methoxypyrimidin-4-amine) (**42**), which is active against several staphylococcal infections³⁸. Gourgetin (**43**), a cytosine derivative is active against mycobacteria

as well as several Gram-positive and Gram-negative bacteria³⁹. There are more derivatives of cytosine, namely amicitin (**44**) and plicacitin (**45**), which exhibit activity against acid fast and Gram-positive bacteria as well as some other organisms³⁸.

3.8 Antifungals

Pyrimidines also exhibit antifungal properties. Flucytosine (**49**)⁴⁰ is a fluorinated pyrimidine used as nucleosidal antifungal agent for the treatment of serious systemic infections caused by susceptible strains of candida and cryptococcus⁴¹. Hexitidine⁴² (**50**) is mainly used for the treatment of aphthous ulceration.

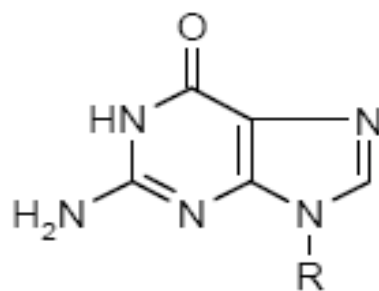
3.9 Anthelmintics

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 roundworms⁴³.

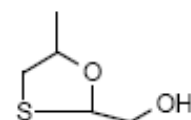
3.10 Analgesics and NSAID drugs

Acetiamine⁴⁴ (**76a**), bentiamine⁴⁴ (**76b**) and fursultiamine⁴⁵ (**76c**) are new lipid-soluble forms of thiamine (vitaminB1) having therapeutic use in beriberi, polyneuritis, encephalopathy, pain, malnutrition and alcoholism and especially in the treatment of long-standing insulin-dependent

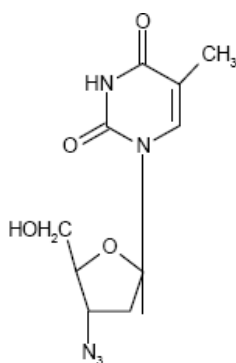
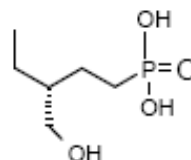
Diabetes mellitus. Fursultamine has been reported to inhibit the arachadonic acid cascade-line activation and reverse the increase in CBF (Coronary Blood Flow).



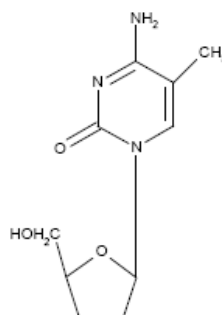
(36a) Lamivudine



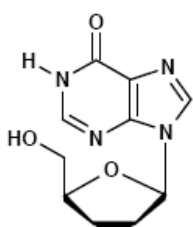
(36b) Cidofovir



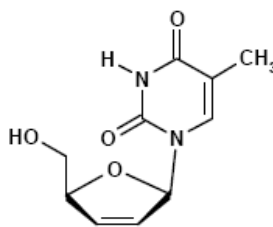
(37) Zidovudine



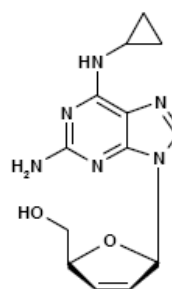
(38) Zalcitabine



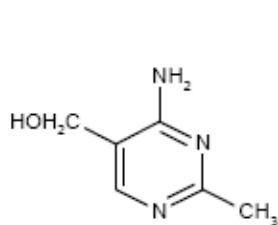
(39) Didanosine



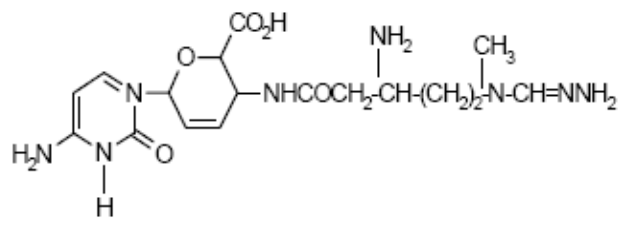
(40) Stavudine



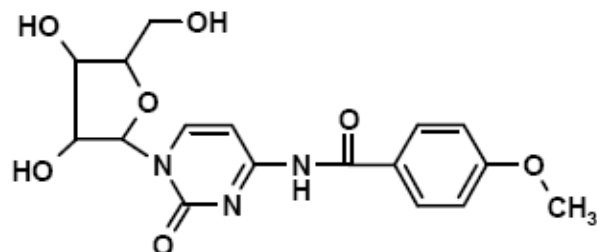
(41) Abacavir



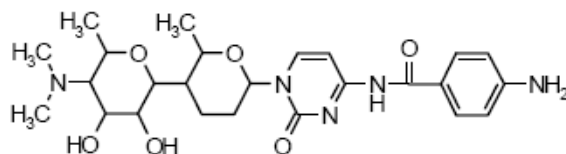
(42) Bacimethrin



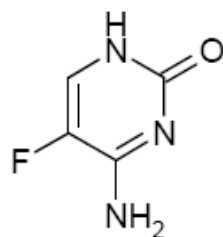
(43) Gourgetin



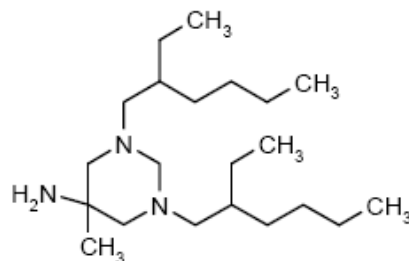
(44) Amicetin



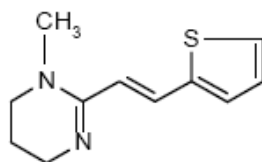
(45) Plicacetin



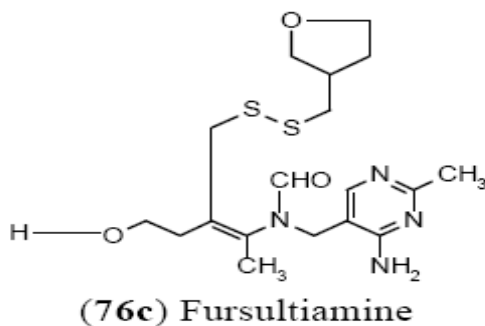
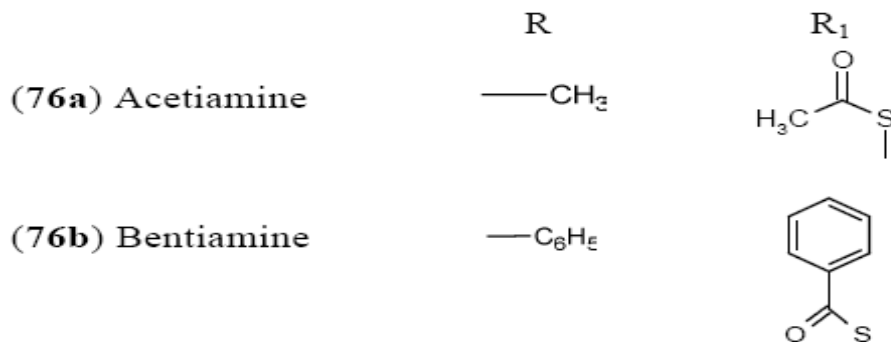
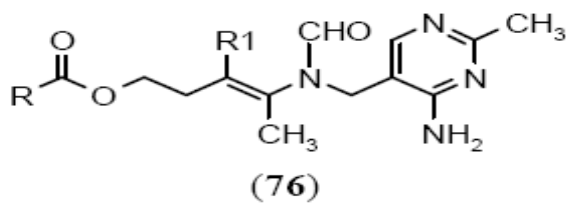
(49) Flucytosine



(50) Hexitidine

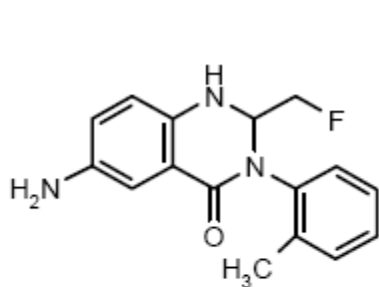


(51) Pyrantel pamoate

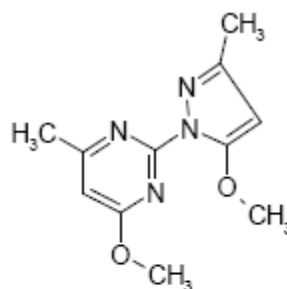


Afloqualone⁴⁶ (77) has been evaluated as a successful anti-inflammatory agent with lower back pain patients. Epirazole⁴⁷ (78), another NSAID, is suggested to be a COX-2 inhibitor. Ademetionine⁴⁸

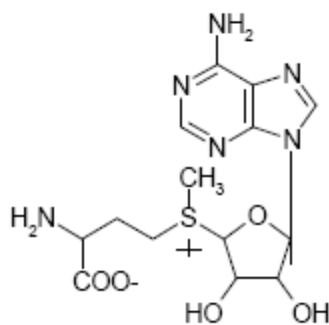
(79) is primarily used in conjunction to glucosamine and chondroitin therapy. Octotiamine⁴⁹ (80), a vitamin B1 derivative also exhibits anti-inflammatory activity.



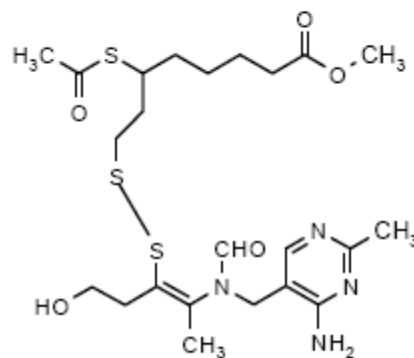
(77) Afloqualone



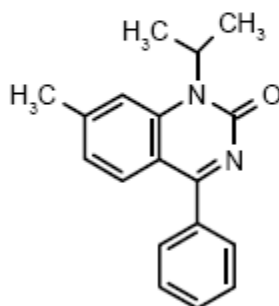
(78) Epirizole



(79) Ademetionine



(80) Octotiamine



(81) Proquazone

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 possesses a variety of medicinal properties. These properties include anticancer, antibacterial, antiprotozoal, antimicrobial, antiviral, antihypertensive, antihistaminic, anti-inflammatory, analgesic, and CNS-active to metabolic adjuvants.

REFERENCE

1. Kenner, G. W. "Heterocyclic Compounds", 9, John Wiley & sons, New York, 1957, 234.
2. Ramage, G. R.; Landquist, L. "Rodd's The Chemistry of Carbon Compounds", 4, Elsevier Publishing Co., 1959, 1257.
3. U.S. Department of Health and Human Services. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*. October 10,2006.
4. Hoetelmans, R. M. W. Novel compound in preclinical/early clinical development of the NNRTIs (Tipranavir), *Current Opin. Anti infect. Invest. Drugs*. 1999 ,1, 241-45.
5. Marlinez, A. G.; Fernandez, A. H.; Vilchez, D. M.; Hanack, M.; Subramaniam, L. R., An improved synthesis of 5-Halopyrimidines: Reaction of a-halo ketones with Nitriles. *Synthesis*, 1992, 1053.
6. Ellis, G. P.; Smalley, R. K. "Heterocyclic Chemistry", 1, The Chemical Soc. London, 1980, 257.
7. Stoss, P.; Kaes, E. J. Novel pyrimidines and pyrimido[1,2-a]pyrimidine derivatives. By-products of a Guanidine based thymine synthesis. *J Het. Chem*, 1991, 28, 231.
8. Butter, M. Large scale synthesis of 4-Ethylpyrimidine. *J Het Chem*, 1992, 29, 1369.
9. Garvey, D.; Schroeder, J. Preparation and formulation of nitrosated and nitrosylated nitrogen containing heterocyclic a-adrenergic receptor antagonist compounds for treatment of impotence or erectile disfunction. US 5,994,294, (1996), through *Chem Abstr*, 2000, 132(2), 12305k.
10. Eussell, J. A., *Annu. Rev. Biochem.*, 1945, 14, 309.
11. Cox, R. A., *Quart. Rev.*, 1968, 22, 499.
12. Skold, O. Enzymic ribosidation and ribotidation of 5-fluorouracil by extracts of the Ehrlich-ascites tumor. *Biochim. Biophys. Acta.*, 1958, 29, 651.
13. Heidelberger, C. Fluorinated pyrimidines and their nucleosides. In Sartorelli, A. C.; Johns, D. J. *Handbook of Experimental Pharmacology*, New York, Springer-Verlag.1975, 38 part-2, 193.

14. Isaacson, E. I. Central Nervous System Stimulants. Wilson and Gisvold's Text Book of Organic Medicinal And Pharmaceutical Chemistry, Lipincott Williams & Wilkins, 11th ed, 2004, pp. 511
15. Vida, J. A., Central Nervous System Depressants: Sedative-Hypnotic, Foye, W. O.; Lemke, T. L.; Williams, D. A. Text Book of Principles of Medicinal Chemistry, Williams & Wilkins, 4th ed. 1995, pp. 154.
16. Hitchings, G. H.; Eilon, B.; Wanderwerf, H.; Falco, B. F. Pyrimidine derivative as antagonists of Pteroylglutamic acid. *J Biol Chem*, 1948, 174, 765.
17. Hitchings, G. H., Elion, G. B., Wanderers, H. and Falco, E. A., *J. Biol. Chem.*, 1948, 174, 765.
18. Futterman, S., *J. Biol. Chem.*, 1957, 228, 1031.
19. Werkheiser, W. C., *J. Biol. Chem.*, 1961, 236, 888
20. Cheng, C. C. and Roth, B., In *Progress in Medicinal Chemistry* (eds Ellis, G. P. and West, G.B.), Butterworths, London, 1982, vol. 19, p. 267.
21. Montgomery, J. A., Johnston, T. P. and Shealy, Y. F., In *Burgers Medicinal Chemistry, Part II* (ed. Wolf, M. E.), Wiley-Interscience, New York, 1979, p. 595.
22. Kompis, I. and Wick, A., *Helv. Chim. Acta*, 1977, 60, 3025.
23. Shinogi, US Patent, 2 888 455, 1959.
24. MacDonald, L. and Kazanijan, P., *Formulary*, 1996, 31, 470.
25. White, N. J., *N. Engl. J. Med.*, 1996, 335, 800.
26. Von Zabern, I., Nolte, R., Przyklenk, H. and Vogt, W., *Int. Arch. Allergy Appl. Immunol.*, 1985, 76, 205-213.
27. Huges, J., Roberts, L. C. and Coppridge, A. J., *J. Urol.*, 1975, 114, 912-914.
28. Fink, C. A.; Werner, L. H. Diuretic and Uricosuric Agents, Manfred, E. W., Burger's Text Book of Medicinal Chemistry Drug Discovery, A John Wiley and Sons, Inc., 5th ed., 1996, 2, 379.
29. Fink, C. A.; Werner, L. H. Diuretic and Uricosuric Agents, Manfred, E. W. Burger's Text Book of Medicinal Chemistry Drug Discovery, A John Wiley and Sons, Inc., 5th ed., 1996, 2, 381.
30. Puvin-Langston, D. Adenosine Arbinoside, An Antiviral agent. Newyork, Raven Press, 1975.
31. Walwick, E. R. *Proc. Chem. Soc.* London, 1959, 84
32. Schaeffer, H. J. 9-(2-hydroxyethoxymethyl) guanine activity against viruses of the herpes group. *Nature*.1978, 272, 583.
33. Lin, T. S.; Prusoff, W. H. Synthesis and biological activity of several amino analogs of thymidine. *J. Med. Chem.* 1978, 21, 109.
34. Prusoff, W. H. Clinical Use of Antiviral Drugs, 1988, 15-24.
35. Van Leeuwen, R., *J. Infect. Dis.*, 1995, 171, 1161.
36. Mitsuya, H. (ed.), *Anti-HIV Nucleosides: Past, Present and Future*, Chapman and Hall, New York, 1997.
37. Gorbach, S. L., Barlett, J. G. and Blacklow, N. R., *Infectious Diseases*, Saunders and Company, Philadelphia, 1998, pp. 330-350; 1154-1168.
38. Reddick, J. J., Saha, S., Lee, J., Melnick, J. S., Perkins, J. and Begley, T. P., *Bioorg. Med. Chem. Lett.*, 2001, 11, 2245-2248.
39. Singh, P., Kumar, R. and Sharma, B. K., *J. Enzyme Inhib. Med. Chem.*, 2003, 18, 395-402.
40. Polak, A. and Scholer, H. J., *Chemotherapy*, 1975, 21, 113
41. Hunter, P. A., Darby, K. G. and Russel, N. J., Fifty years of antimicrobials: Past perspectives and future trends. In *Symposia of the society for General Microbiology* (ed. Collins, M.), Cambridge University Press, Cambridge, 1995.
42. Chadwick, B., Addy, M. and Walker, D. M., *Br. Dent. J.*, 1991, 71, 83-86.
43. Hunziker, F., *Helv. Chim. Acta*, 1967, 50, 1588.
44. Gauthier, B., *Ann. Pharm. Fr.*, 1963, 21, 655.
45. Takeda, US Patent, 3 016 380, 1962.
46. Tani, J., *J. Med. Chem.*, 1979, 22, 95.
47. Vanderhaeghe, H. and Claesen, M., *Bull. Chim. Belg.*, 1959, 68,
48. Schlenk, *Enzymologia*, 1965, 29, 283.
49. Fujisawa, US Patent, 3 098 856, 1963.