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PHARMACOLOGICAL SIGNIFICANCE OF NITROGEN CONTAINING HETEROCYCLIC COMPOUNDS – A LITERATURE BASED REVIEW

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Abstract:
Heterocyclic compounds have a role in most fields of sciences such as medicinal chemistry, biochemistry also another area of sciences. More than 90% of new drugs contain heterocycles and the interface between chemistry and biology, at which so much new scientific insight, discovery and application is taking place is crossed by heterocyclic compounds. Compounds derived from heterocyclic rings in pharmacy, medicine, agriculture, plastic, polymer and other fields. Most active heterocycles that have shown considerable biological actions as anti-fungal, anti-inflammatory, anti-bacterial, anti-convulsant, anti-protozoal, anti-allergic, herbicidal, anti-cancer activity. Heterocyclic compounds are a highly valuable and unique class of compounds. Different heterocyclic analogues have been evaluated for their diverse biological activities. Heterocyclic compounds are present in abundance in our surroundings. They owe their importance in the biological system due to uniqueness in their structural skeleton parts. They are naturally found in nucleic acid, vitamins, anti-biotics, hormones etc. Nitrogen containing heterocyclic compounds are an important class of heterocyclic compounds that has paid significant contribution towards medicinal chemistry. This review highlights the trends in the use of nitrogen-based moieties in drug design and the development of different potent and competent candidates against various diseases. This review shall give researchers access and detailed understanding on various application of a novel heterocyclic subsidiary into diverse areas for new process or application. In this study, we will understand the biologically active heterocyclic compounds, biological importance of nitrogen-containing heterocyclic compounds and pyridine containing medicinal agents. The number of novel N-heterocyclic moieties with significant physiological properties and promising applications in medicinal chemistry is ever-growing. 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.

Key words: *Heterocyclic compounds, heteroatom, nitrogen-based heterocycles, biological activities, pyrimidine, nucleosides.*

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INTRODUCTION:

In organic chemistry, largest families of organic compounds belong to heterocyclic compounds. In place of a carbon atom incorporation of an oxygen, a nitrogen, a sulfur, or an atom of a related element gives rise to a heterocyclic compound. Heterocyclic compounds are of very essential for our day-to-day life. It has a broad range of applications in medicinal chemistry as well as in agrochemical products. Heterocyclic chemistry is the branch of chemistry dealing with the synthesis, properties, and applications of heterocycles.

Medicinal chemistry had its beginning when chemists, pharmacist and physicians isolated and purified active principles of plants and animal tissues and taken from micro-organism and their fermentation products. These compounds have been associated with therapeutic properties. Medicinal chemistry which has leaned on the classical fields of chemistry, especially organic chemistry and biology. Various natural and synthetic compounds are serving directly as therapeutic agents and some other uses in agriculture. Most of the drugs belong to the class of heterocyclic compounds.

These heterocyclic compounds played a vital role in the metabolism of all living cells; large numbers of them are five and six membered heterocyclic compounds having one, two and three hetero atoms in their nucleus. The compounds may be pyrimidine and purine basis of genetic material DNA, and these heterocyclic compounds may be isolated or fused heterocyclic systems. Some of the common heterocyclic compounds used in the medicines are as amino acids like proline, histidine and tryptophan, the vitamins and coenzymes precursors such as thiamine, riboflavin, pyridoxine, folic acid, biotin, vitamin B_{12} and vitamin E. There are various pharmacologically active heterocyclic compounds, many of which are in regular clinical use.

Heterocyclic compounds are frequently abundant in plants and animal products; and they are one of the important constituents of almost one half of the natural organic compounds known. Alkaloids, natural dyes, drugs, proteins, enzymes etc. are some important classes of natural heterocyclic compounds. Heterocyclic compounds can be easily classified based on their electronic structure. Heterocyclic compounds are primarily classified as saturated and unsaturated. The saturated heterocyclic compounds behave like the acyclic derivatives with modified steric properties. Piperidine and tetrahydrofuran are the conventional amines and ethers of this category.

However, unsaturated heterocyclic compounds of 5- and 6- member rings have been studied extensively because of their unstrained nature. The unstrained unsaturated heterocyclic compounds include pyridine, thiophene, pyrrole, furan and their benzo fused derivatives. Quinoline, isoquinoline, indole, benzothiophene, and benzofuran are some important examples of benzo fused heterocycles. Heterocyclic compounds have a wide application in pharmaceuticals, agrochemicals and veterinary products. Many heterocyclic compounds are very useful and essential for human life. Various compounds such as hormones, alkaloids antibiotics, essential amino acids, hemoglobin, vitamins, dyestuffs and pigments have heterocyclic structure.

A large number of heterocyclic compounds, both synthetic and natural, are pharmacologically active and are in clinical use. Several heterocyclic compounds have applications in agriculture as insecticides, fungicides, herbicides, pesticides etc. They also find applications as sensitizers, developers, anti-oxidants, co-polymers etc. They are used as vehicles in the synthesis of other organic compounds. Chlorophyll-photosynthesizing and haemoglobin-oxygen transporting pigments are also heterocyclic compounds. Heterocyclic is the largest and most varied family of organic compounds, heterocyclic system can be 3, 4, 5, 6, 7, 8 membered rings.

Synthetic heterocycles have widely used therapeutic uses such as anti-bacterial, anti-fungal, anti-mycobacterial, trypanocidal, anti-HIV, anti-leishmanial, genotoxic, anti-tumoral, anti-inflammatory, muscular relaxants, anti-convulsant, anti-cancer, and lipid peroxidants, hypnotic agents, non-depressants and anti-transplants. There are more synthetic heterocyclic compounds with other essential uses, such as fungicides, herbicides, anti-bodies, photo stabilizers, agrochemicals, dyestuffs, copolymers, development photographers, fluorescent whiteners, sensitizers, boosters, rubber anti-oxidants, and flavourers. The compounds of pyrimidine (cytoses, uracils, and thymines) and purine (adenine and guanines) are monocyclic and bicyclic heterocycles, each of which consists of two and four nitrogen atoms. The deoxyribonucleic acid (DNA) molecules are essential components that engage directly in the decoding of genetic material.

Classification of heterocyclic compounds

Based on the structural and electronic arrangement the heterocyclic compounds may be classified into two categories.

i. Aliphatic heterocyclic compounds,
ii. Aromatic heterocyclic compounds.

The aliphatic heterocyclic compounds are the cyclic amines, cyclic amides, cyclic ethers and cyclic thioethers. Aliphatic heterocycles those do not contain double bonds are called saturated heterocycles. The properties of aliphatic heterocycles are mainly affected by the ring strain. Examples of aliphatic heterocyclic compounds are shown in Figure 1.

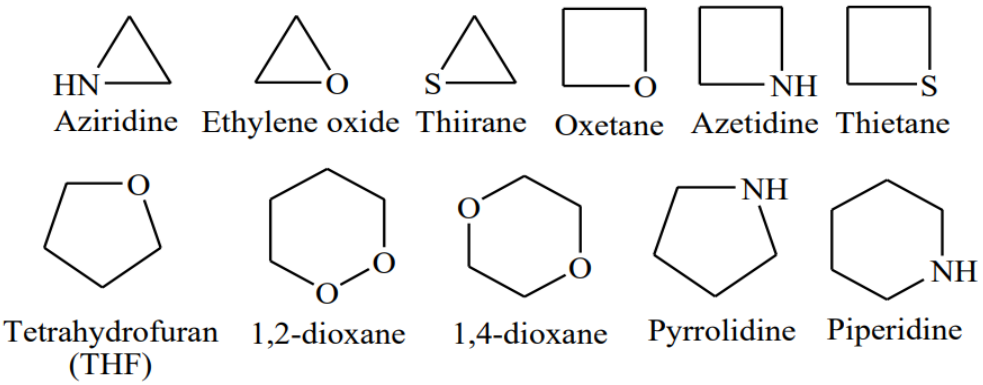


Figure 1: Aliphatic heterocyclic compounds

However, aromatic heterocyclic compounds are analogous of benzene. The aromatic heterocyclic compounds also follow the Huckel's rule. According to Huckel's rule an aromatic compounds must be cyclic in nature with planar geometry due to conjugate double bonds and must have $(4n+2)\pi$ electrons. Examples of aromatic heterocyclic compounds are shown in Figure 2.

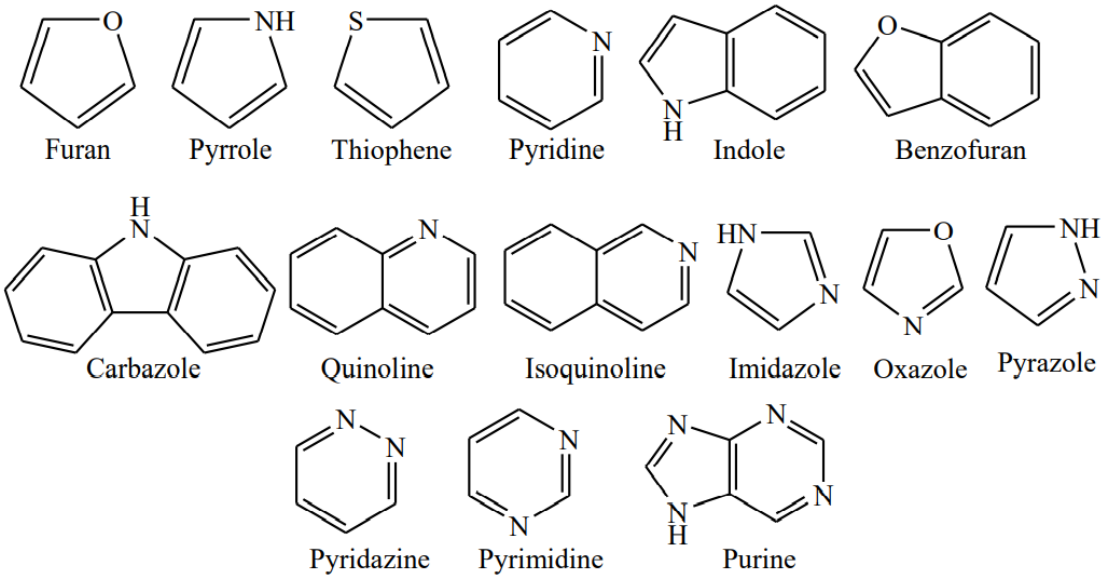


Figure 2: Examples of aromatic heterocyclic compounds

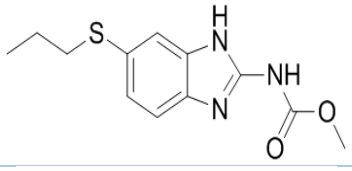
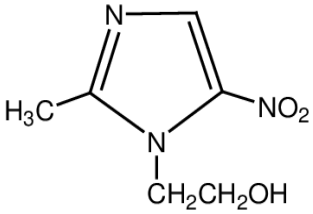
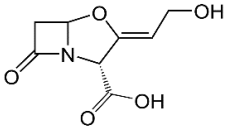
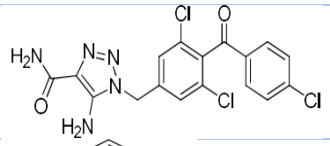
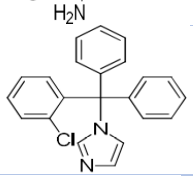
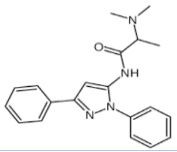
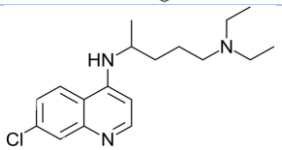
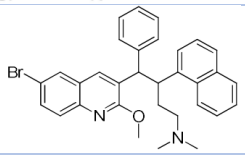
A heterocyclic ring may comprise of three or more than three atoms, which may be saturated or unsaturated. Also, heterocyclic ring may contain more than one heteroatom which may be either similar or different.

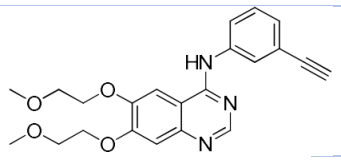
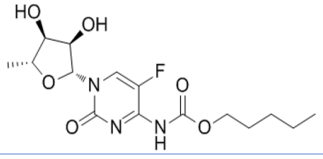
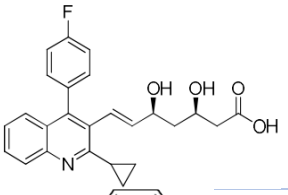
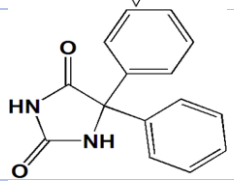
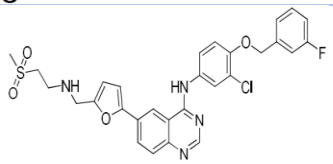
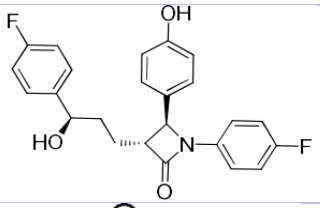
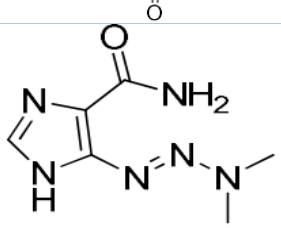
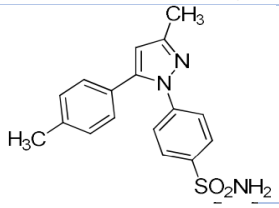
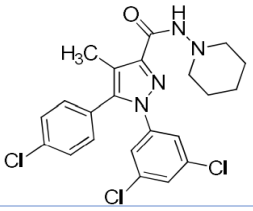
Nitrogen-based heterocyclic chemistry is an important and unique class among the applied branches of organic chemistry, with a significant amount of research dedicated to the development of novel molecules and composites. These molecules have received increasing attention over the past two decades. They contributed to the development of numerous organic synthesis protocols and found abundant applications in the chemical sciences. Many N-heterocyclic compounds that are broadly distributed in Nature, possess physiological and pharmacological properties and are constituents of many biologically important molecules, including many vitamins, nucleic acids, pharmaceuticals, antibiotics, dyes and agrochemicals, amongst many others. Moreover, they form an integral part of many pharmacologically

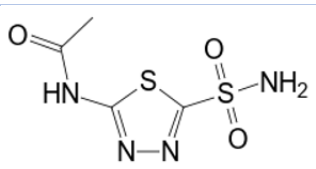
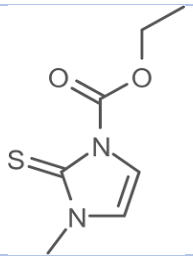
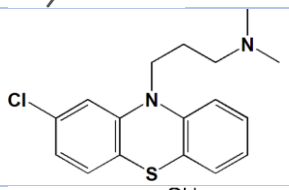
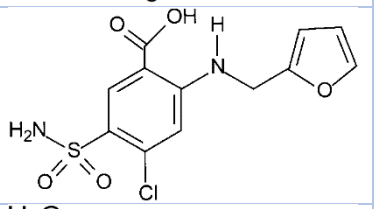
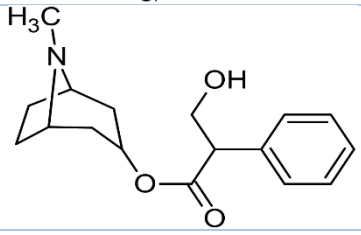
active molecules. The base pairs of DNA and RNA (guanine, cytosine, adenine, and thymine) are also made up of N-heterocyclic compounds, namely purines, pyrimidines, etc.

These nitrogen-containing heterocyclic molecules with distinct characteristics and applications have gained prominence in the rapidly expanding fields of organic and medicinal chemistry and the pharmaceutical industry. A glance at the FDA databases reveals the structural significance of nitrogen-based heterocycles in drug design and engineering of pharmaceuticals. Nearly 75% unique small-molecule drugs contain a nitrogen heterocycle. The N-heterocyclic skeletons feature significantly various classes of therapeutic applications and are used as the building blocks of a number of new drug candidates, due to the ability of the nitrogen atom to easily form hydrogen bonding with biological targets.

Table 1: Nitrogen containing pharmaceutical drugs

S. No.	Drug Name	Pharmacological activity	Structure
1	Albendazole	Anthelmintic	
2	Metronidazole	Anti-amoebic drug	
3	Clavulanic acid	β-Lactamase inhibitor	
4	Carboxyamidotriazole	Calcium channel blocker and anti-cancer	
5	Clotrimazole	Anti-fungal	
6	Difenamizole	Analgesic	
7	Chloroquine	Anti-malarial	
8	Bedaquiline	Anti-TB drug	

9	Erlotinib	Treating metastatic non-small cell lung cancer	
10	Capecitabine	Anti-breast cancer	
11	Pitavastatin	Cholesterol lowering agent	
12	Phenytoin	Anti-convulsant	
13	Lapatinib	Anti-breast cancer	
14	Ezetimibe	Cholesterol absorption inhibitor	
15	Dacarbazine	Treatment of metastatic melanoma	
16	Celecoxib	Anti-inflammatory	
17	Rimonabant	Anti-obesity	

18	Acetazolamide	Diuretic	
19	Carbimazole	Anti-thyroid drug	
20	Chlorpromazine	Anti-psychotic	
21	Furosemide	Diuretic	
22	Atropine	Anti-cholinergic	

Pyrimidine - general introduction

Pyrimidines are the heterocyclic aromatic compounds similar to benzene and pyridine containing two nitrogen atoms at positions 1 and 3 of the six membered rings. Heterocycles containing pyrimidine moiety are of great interest because they constitute an important class of natural and non-natural products, many of which exhibit useful biological activities and clinical applications. Substituted purines and pyrimidines occur very widely in living organisms and were some of the first compounds studied by the organic chemists (Figure 3). Pyrimidines are biologically very important heterocycles and represent by far the most ubiquitous members of the diazine family with uracil and thymine being constituents of ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) and with cytosine both being present in Figure 3. In addition to this, pyrimidines skeleton is also present in many natural products such as vitamin B_1 (thiamine-Figure 4) and many synthetic compounds, such as barbituric acid and veranal which are used as hypnotics.

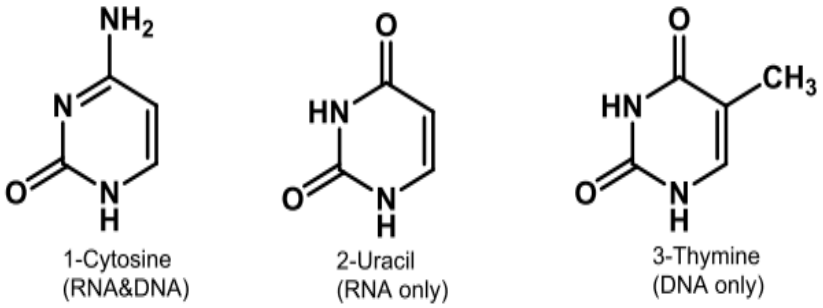


Figure 3: Pyrimidine nucleobases

Pharmacological applications of pyrimidine ring containing drugs

The presence of pyrimidine base in thymine, cytosine, and uracil, which are the essential building blocks of nucleic acids DNA and RNA, is one possible reason for their widespread therapeutic applications. The pyrimidines represent one of the most active classes of compounds possessing wide spectrum of biological activities like significant *in-vitro* activity against unrelated DNA and RNA, viruses including polio herpes viruses, diuretic, anti-tumour, anti-HIV, and cardiovascular. The literature survey indicated that a wide range of pharmacological activities are exhibited by the compounds encompassing pyrimidines nucleus. In addition to this, various analogues of pyrimidines have been found to possess anti-bacterial, anti-fungal, anti-leishmanial, anti-inflammatory, analgesic, anti-hypertensive, anti-pyretic, anti-viral, anti-diabetic, anti-allergic, anti-convulsant, anti-oxidant, anti-histaminic, herbicidal, and anti-cancer activities and many of pyrimidine derivatives are reported to possess potential central nervous system (CNS) depressant properties and also act as calcium channel blockers.

Clinical and ethnopharmacological applications of pyrimidine in the world: marketed drugs

The top selling active pharmaceutical ingredients comprise of pyrimidine nucleus are, flucytosine (5-FC), floxuridine, lopinavir, lamivudine, zidovudine, pyrimethamine and minoxidil. Recently, the US-FDA approved some pyrimidine and pyrimidinone derivatives (ibrutinib, capecitabine, folinic acid and monastrol) as anti-cancer agents (Figure 5). These pyrimidines and their scaffolds exhibit a broad spectrum of bioactivity; hence they occupy privileged positions in drug discovery studies. Lathyrine (tingitanine) containing a pyrimidine ring, which can be isolated from the seeds of *Lathyrus tingotanus*. Variolin B is an example of pyrimidine-based alkaloid that shows inhibiting cell growth and anti-viral activity (Figure 6).

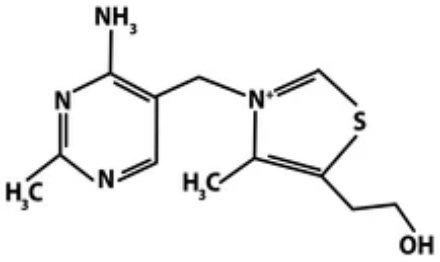


Figure 4: Chemical structure of thiamine

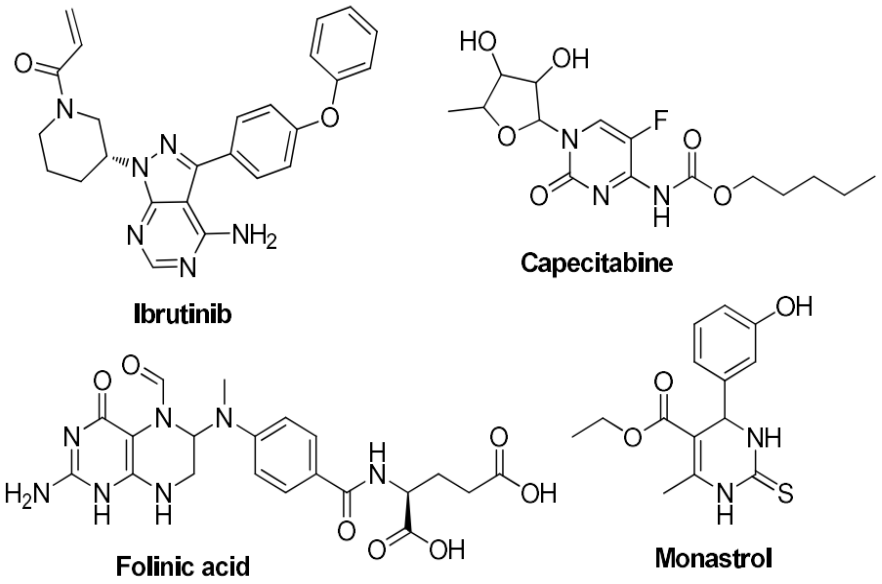


Figure 5: Pyrimidine clinical drugs

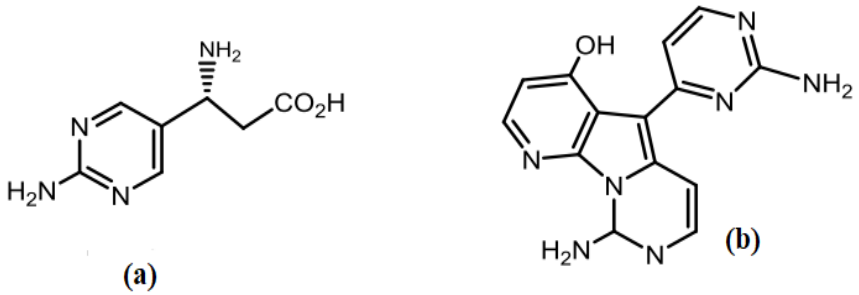


Figure 6: Naturally occurring pyrimidine compounds, structures of Lathyrine (a) and Variolin B (b)

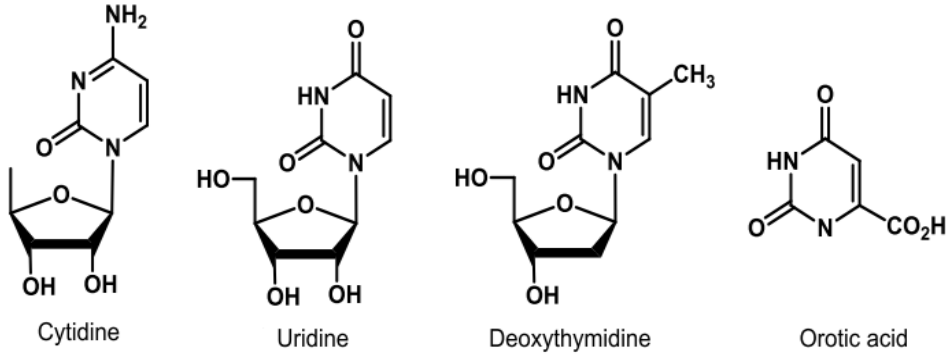


Figure 7: Pyrimidine based nucleosides

Combining thienopyridine and pyrimidine cores in the same molecular architecture, forming a pyridothienopyrimidine nucleus, serves as an attractive strategy for designing a novel scaffold with more favourable pharmacological effects. Recently, various pyridothienopyrimidine derivatives were reported to produce significant anti-microbial and anti-cancer activities, as well as to suppress protein kinases such as serine/threonine kinase and vascular endothelial growth factor receptor (VEGFR-2).

Brodiprim (1) is found to be an effective anti-bacterial compound. Iclaprim (2) which is a new selective dihydrofolate inhibitor was synthesized based on rational drug design and this drug is found to be active against methicillin-, TMP-, and vancomycin-resistant strains. Trimethoprim (3) is an anti-bacterial drug which selectively inhibits bacterial dihydrofolate reductase (DHFR). Pyrimethamine (4) is a selective inhibitor of the dihydrofolate reductase (DHFR) of malarial plasmodia (Figure 8).

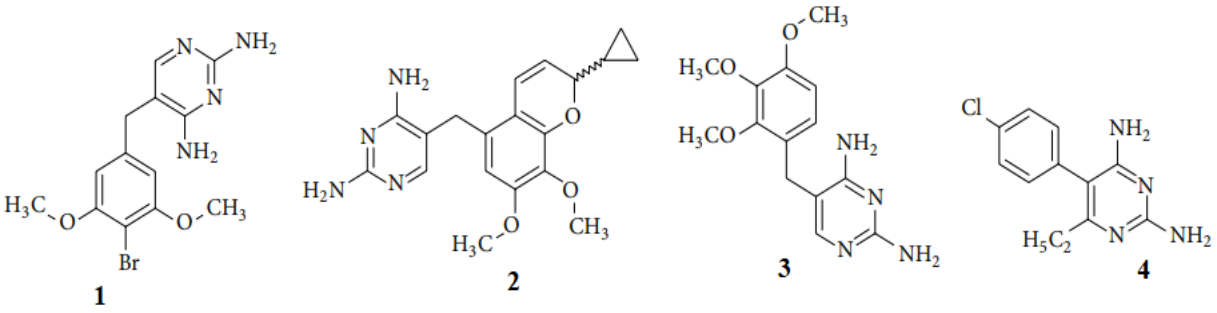


Figure 8: Anti-bacterial drugs containing substituted pyrimidines

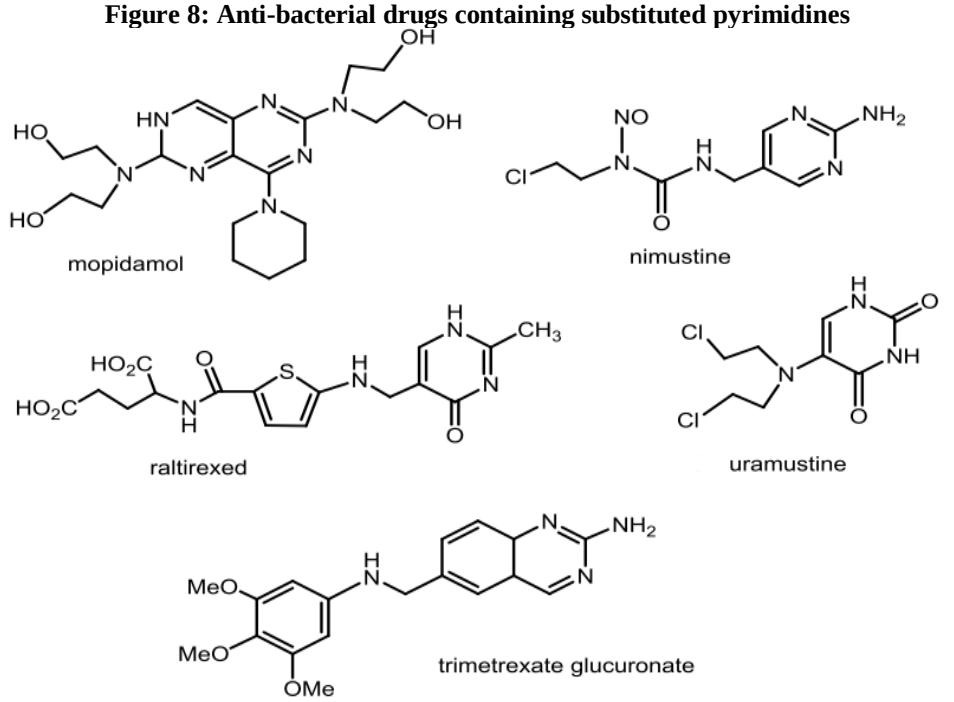


Figure 9: Anti-cancer drugs

Capreomycin produced by *Streptomyces capreolus* is a second-line bacteriostatic anti-tuberculin drug containing pyrimidine backbone (Figure 10).

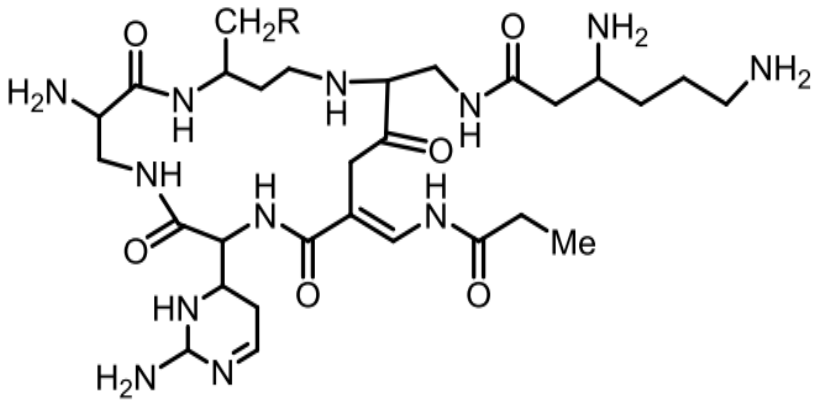


Figure 10: Molecular structure of capreomycin

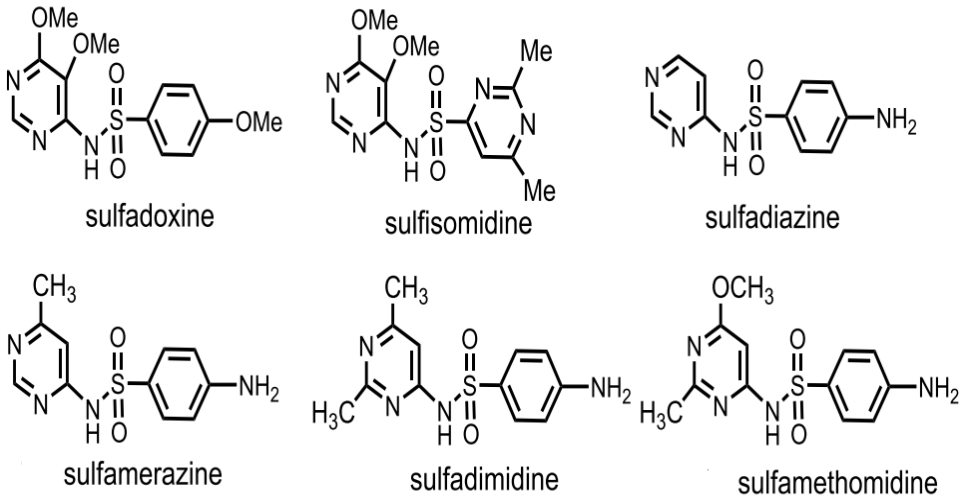
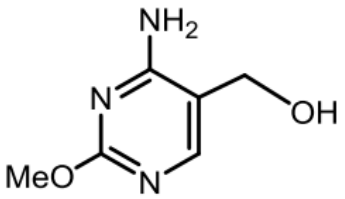
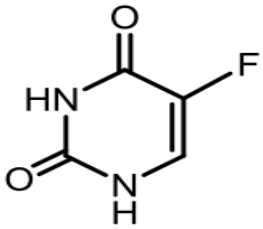
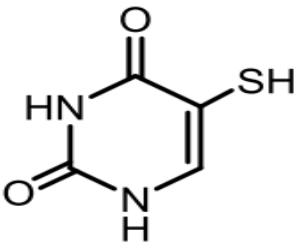
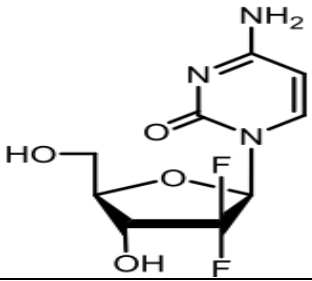
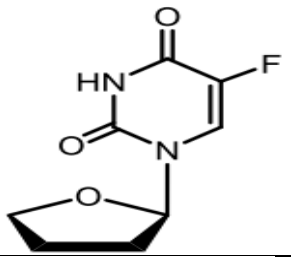
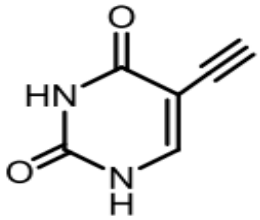
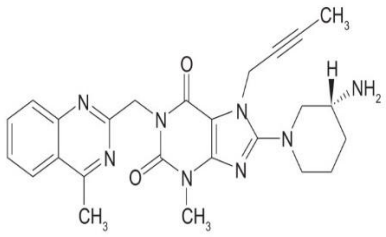
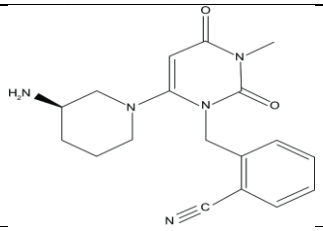
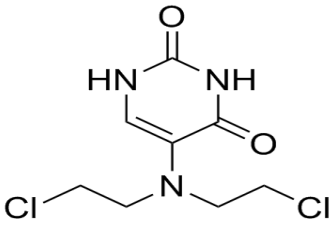
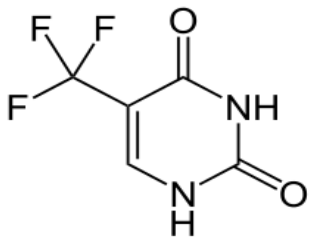
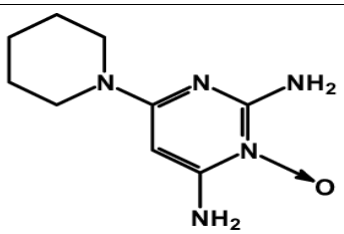
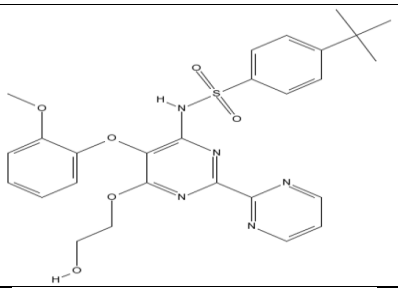
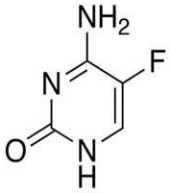
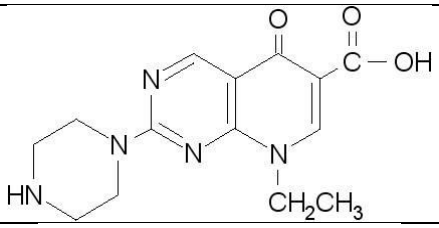
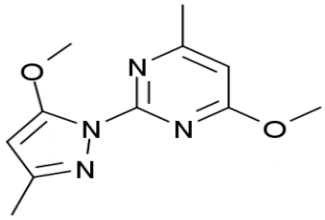
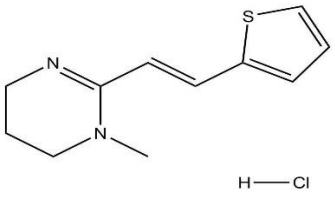
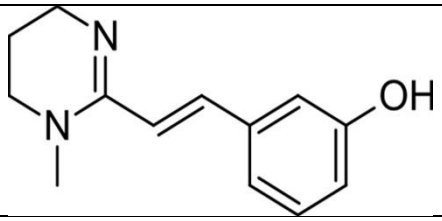


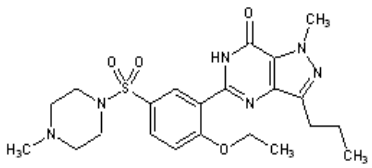
Figure 11: Sulfadrugs (sulphonamides) carrying pyrimidine skeleton

Table 2: Examples of pyrimidine containing medicinally active drugs

S. No.	Structure	Drug Name	Activity
1		Bacimethrine	Anti-biotic
2		5- fluorouracil	Anti-cancer
3		5-Thiouracil	Anti-cancer
4		Gemcitabine	Anti-tumour

5		Tegafur	Anti-tumour
6		Eniluracil	Anti-tumour
7		Linagliptin	Anti-diabetic
8		Aglogliptin	Anti-diabetic
9		Uramustine	Anti-cancer
10		Triflurdine	Anti-viral

11		Minoxidil	Anti-hypertensive
12		Bosentan	Endothelin receptor antagonist used in the treatment of pulmonary artery hypertension
13		Flucytosine	Anti-fungal
14		Pipemidic acid	Treatment of UTI
15		Epirizole	Anti-inflammatory
16		Pyrantel	Anthelmintic
17		Oxantel	Anthelmintic

18		Sildenafil	Treatment for erectile disfunction

An interesting new agent for the treatment of chronic leukemia is the tyrosine kinase inhibitor imatinib mesylate (Gleevec), which contains a 4-pyridyl-substituted pyrimidine-2-amine structure as the aromatic heterocyclic element (Figure 12).

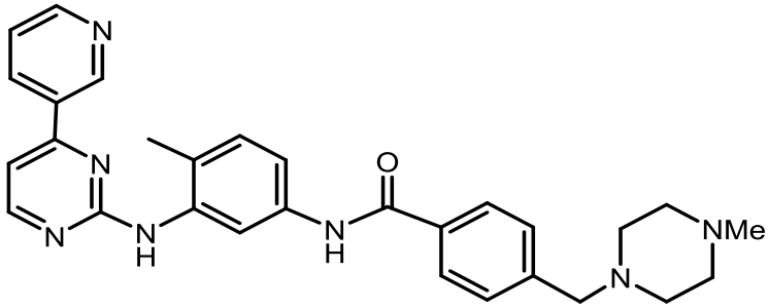


Figure 12: Chemical structure of gleevec

2-Thiouracil compound and its alkyl derivatives, methylthiouracil, propylthiouracil are effective drugs against hyperthyroidism (Figure 13).

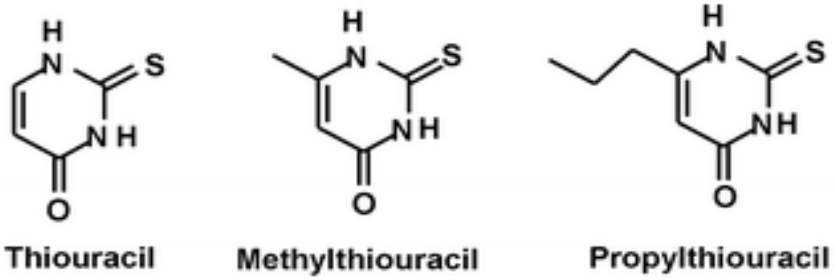


Figure 13: Anti-thyroid drugs

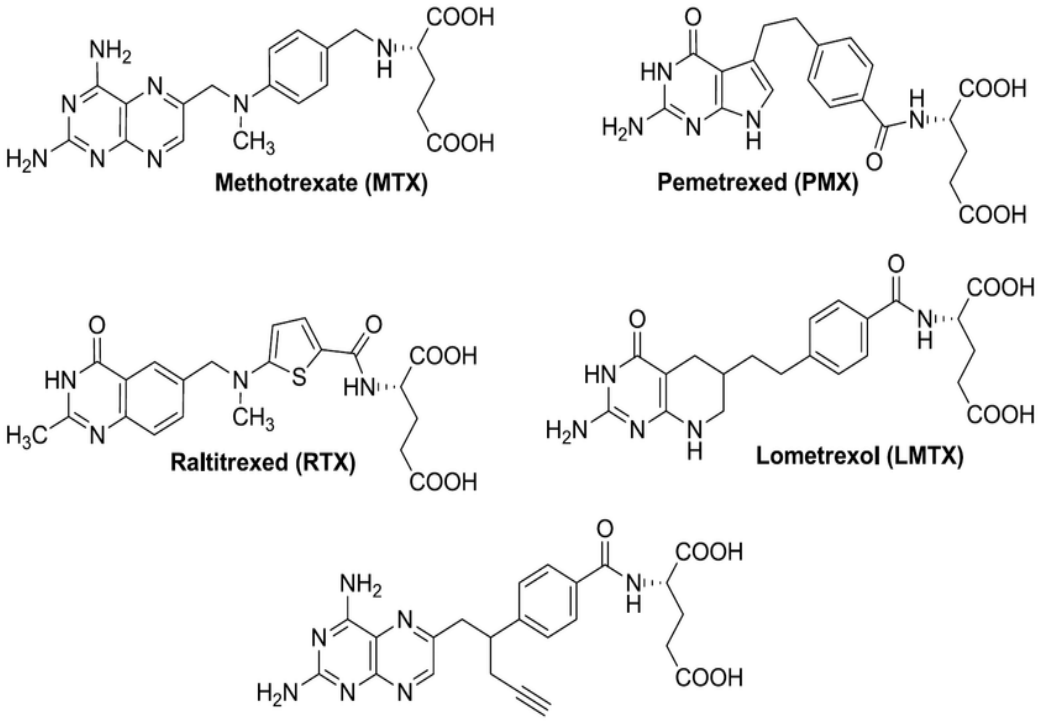
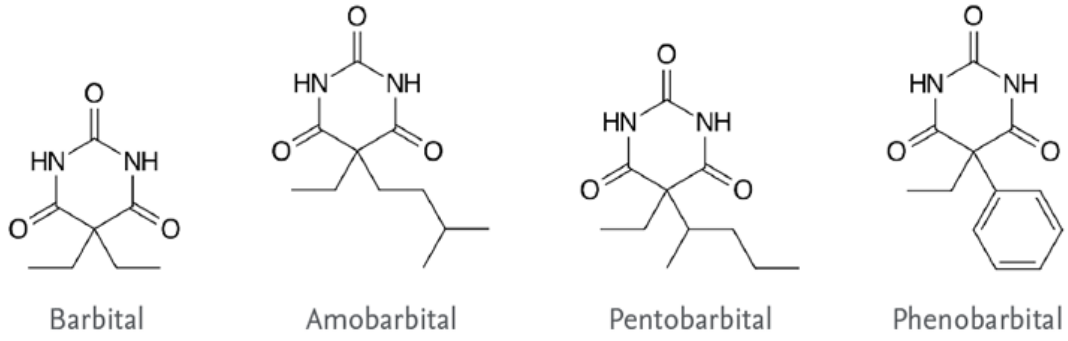


Figure 14: Anti-cancer agents

Figure 15: Hypnotics, sedatives and anti-convulsants



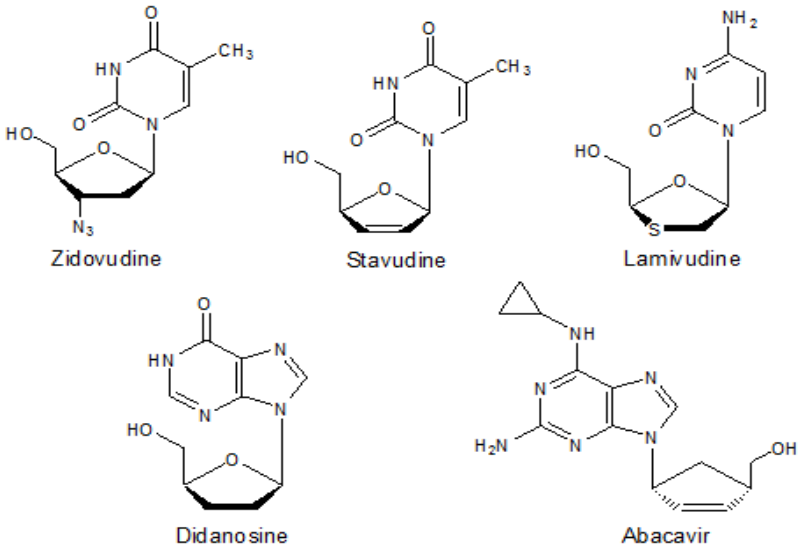


Figure 16: Anti-viral agents

Importance to life and industry

Many heterocyclic compounds are biosynthesized by plants and animals and are biologically active. Over millions of years these organisms have been under intense evolutionary pressure, and their metabolites may be used to advantage; for example, as toxins to ward off predators, or as colouring agents to attract mates or pollinating insects. Some heterocycles are fundamental to life, such as haem derivatives in blood and the chlorophylls essential for photosynthesis. Similarly, the paired bases found in RNA and DNA are heterocycles, as are the sugars that in combination with phosphates provide the backbones and determine the topology of these nucleic acids. The biological properties of heterocycles in general make them one of the prime interests of the pharmaceutical and biotechnology industries.

Nitrogen heterocycles are important structural subunits that occur widely in bioactive natural products, pharmaceuticals, agrochemicals, dyes, cosmetics, and functional materials. Considering the importance of these useful compounds in modern science, the synthesis of N-heterocycles and their derivatives has always been a hot topic in organic synthesis.

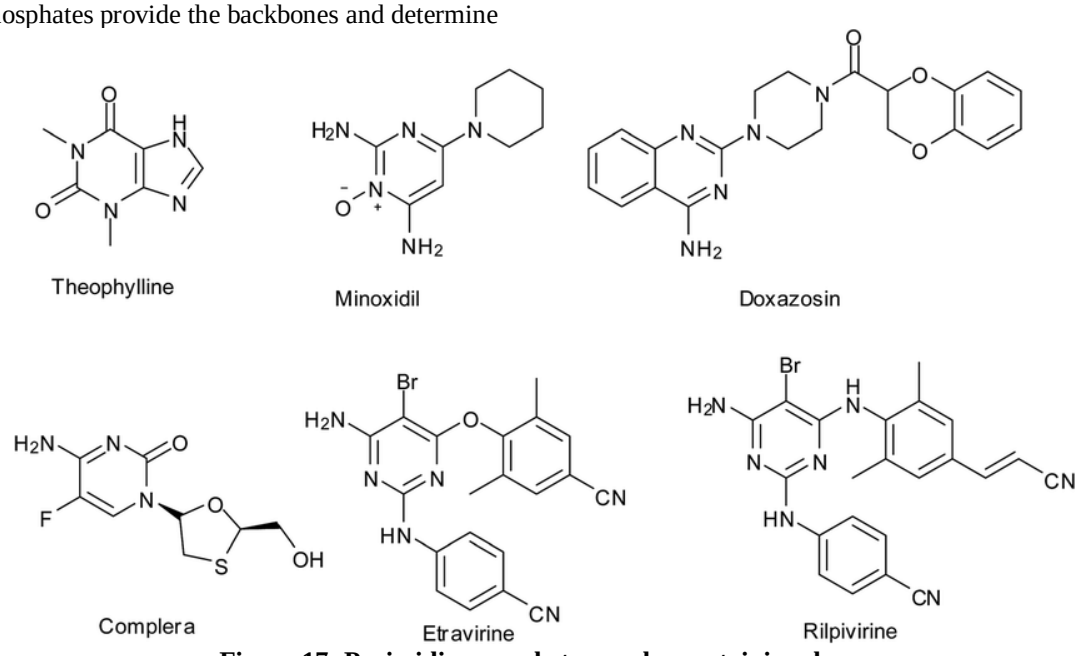


Figure 17: Pyrimidine core heterocycles containing drugs

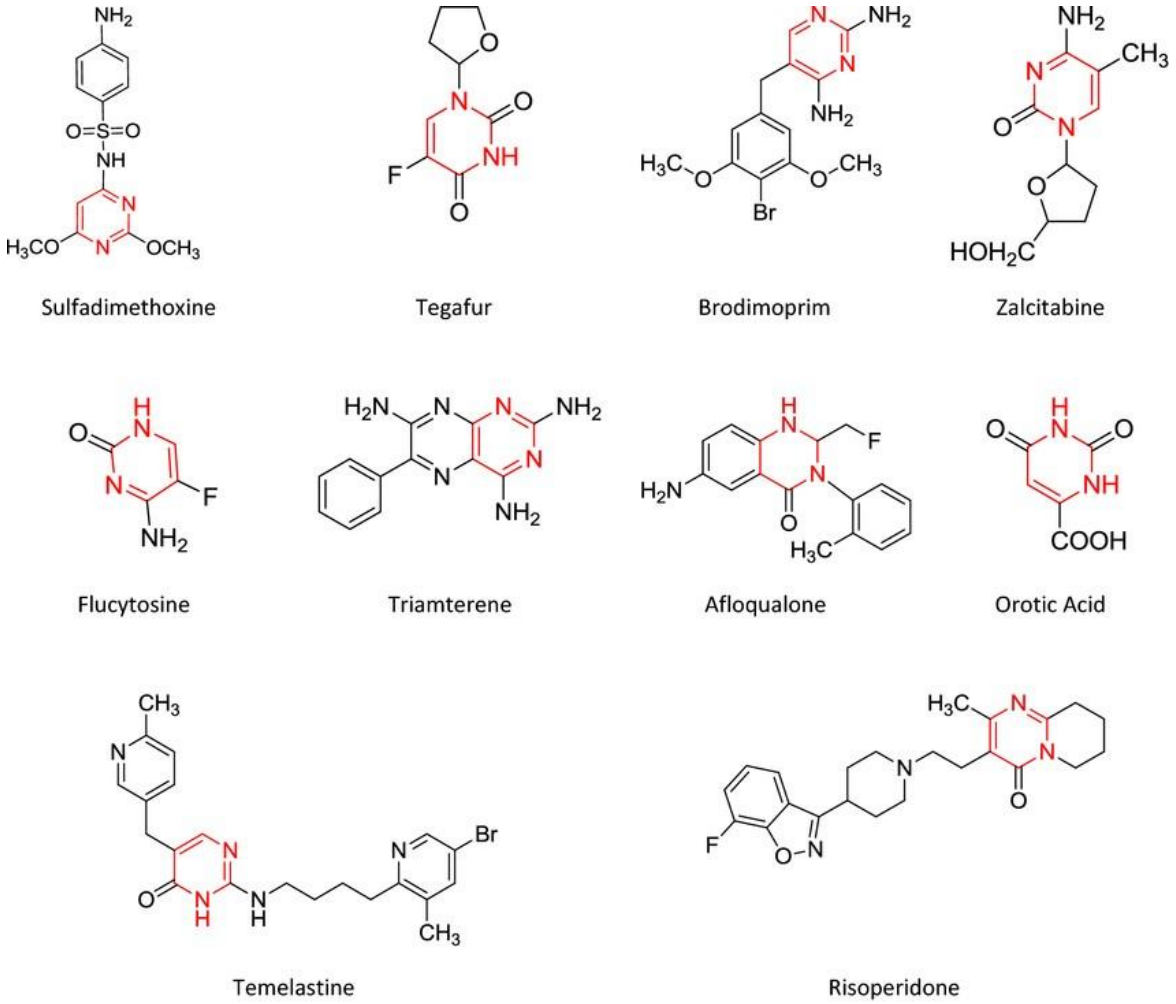


Figure 18: Marketed drugs containing pyrimidine ring

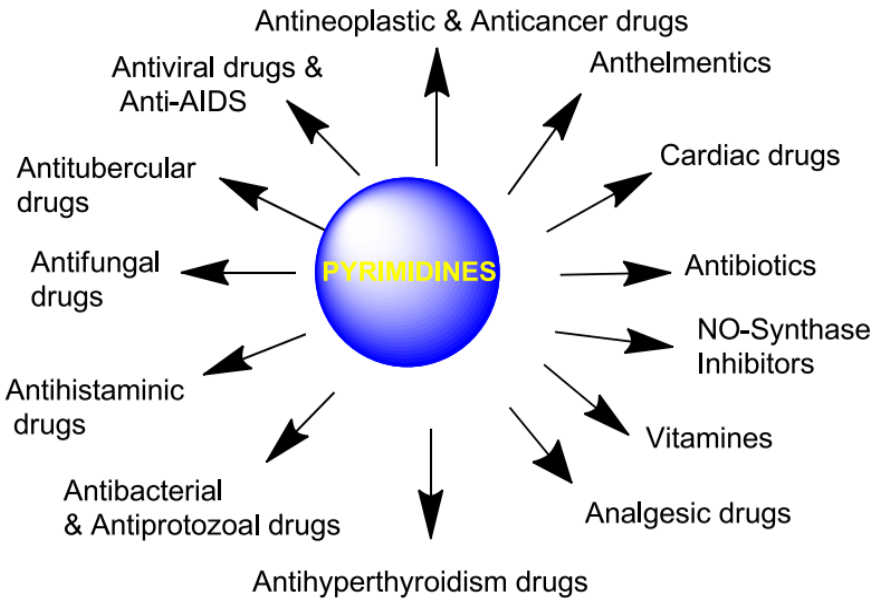


Figure 19: Ethnomedicinal significance of pyrimidines

CONCLUSION:

The scope of nitrogen-based compounds in medicine is growing daily and their diverse analogues provide a viable and important path for the discover of drugs with various biological applications. The N-heterocyclic frameworks offer a high degree of structural diversity that has proven useful for the search of new therapeutic agents in improving the pharmacokinetics and other physicochemical features. Numerous drugs that are currently in clinical practice have fatal side-effects and have developed multidrug resistance, and have been extensively used in practice to treat various types of diseases with high therapeutic potency. Research and development of nitrogen-based compounds in medicinal chemistry has become a rapidly developing and increasingly active topic. A large amount of work has been made towards N-heterocyclic skeleton medicinal chemistry. The overwhelming advantages of nitrogen-containing drugs in the medicinal field, including easy preparation, low toxicity, less adverse effects, high bioavailability, lower drug resistance, good biocompatibility, etc., encourage efforts towards further research and development. Hence, the properties of these scaffolds are vital to the synthetic strategy in the current drug discovery and design system. These significant points confirm the enormous potential of various N-heterocyclic cores in pharmaceutical applications suggesting a massive scope for these promising moieties because of their diverse molecular targets. We believe that this review will be valuable for encouraging the structural design and development of sustainable and effective nitrogen-based drugs against various diseases, with minimal side-effects.

Nitrogen containing six membered heterocyclic compounds have numerous applications in the pharmaceutical field which are pharmacologically and physiologically active and it is used in the treatment of various diseases. On the basis of various literature surveys these derivatives show various activities like anti-microbial, anti-inflammatory, analgesic, anti-cancer, anti-depressant, anti-viral, anti-tubercular and anti-fungal. This paper reviewed some of the biological activities of these compounds. The possible improvements in the activity can be further achieved by slight modifications in the substituents on the basic nucleus of these compounds. Thus, has been long focused for research interest in the field of medicine, due to excellent activities exhibited by its derivatives.

This review is endeavouring to find potential future directions in the development of more potent and specific analogues of nitrogen containing compounds for the biological target. The information illustrated in this review also encourage organic chemist for the design of novel molecules to identify many more biologically active heterocycles for the benefit of humanity.

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antimicrobial and antiviral evaluation of substituted imidazole derivatives. European Journal of Medicinal Chemistry. 2009; 44(6):2347–2353.
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