BIOLOGICAL SIGNIFICANCE OF HETEROCYCLIC COMPOUNDS: A REVIEW

Goyal Anjali[1,3*], Noolvi M.N[2], Mittal Sanjiv[3]

Article History: Received:12/10/22 Revised:10/11/22 Accepted: 11/11/22

Abstract:
One of the most important areas of research in organic chemistry is heterocyclic chemistry. Heterocyclic compounds form a major class of organic compounds. Heterocyclic compounds have one or more hetero atoms in their structure. The simplest of five membered heterocyclic compounds are pyrrole, furan, thiazole, thiadiazole, and imidazole. Heterocyclic compounds are widely distributed in nature and are essential in our daily life processes. It has extensive range of applications in medicinal chemistry. Presently lots of heterocyclic compounds are known and day by day the number is increasing rapidly due to enormous synthetic research and their synthetic utility. They also have a vast number of applications in the field of agriculture, biochemistry, and electronics and as dyestuff. Some naturally occurring antibiotics like penicillin, cephalosporins have heterocyclic portion. The review article covers the most active heterocycles that have shown considerable biological actions as antifungal, antimalarial, anti-inflammatory, antineoplastic, anthelmintic, antiviral, anticonvulsant, diuretic activity, antiulcer, antidepressant and antibacterial activity and their sundry applications in electronics as organic conductors, biology, optics, pharmacology, as a dye, as a lubricating agent, as a corrosive agent, waterproofing agent etc.

Keywords: Heterocyclic compounds, features, antimalarial, antidepressant, diverse applications, organic conductors.

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DOI: 10.53555/ecb/2022.11.12.266

Introduction

Heterocyclic compounds are cyclic compounds with the ring containing carbon and other elements such as oxygen, nitrogen and sulphur. The simplest of the five-membered heterocyclic compound are pyrrole, furan and thiophene, each of which contains a single heteroatom.[1] The five membered rings also containing more than one or two hetero atoms such as azole, thiazole, thiadiazole, oxadiazole, triazene, imidazole, purines etc.

Heterocyclic compounds may be classified into **aliphatic and aromatic**.

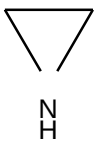
The aliphatic heterocyclics are the cyclic analogues of amines, ethers, thio ethers, amides, etc. Their properties are particularly influenced by the presence of strain in the ring. These compounds generally consist of small (3- and 4-membered) and common (5 to 7 membered) ring systems.

The aromatic heterocyclic compounds, in contrast, are those which have a heteroatom in the ring and behave in a manner similar to benzene in some of their properties.[2]

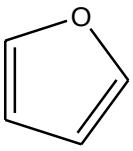
Heterocyclic compounds are widely distributed in nature and are essential to life. They play a essential role in the metabolism of all living cells. There are a vast number of pharmacologically active heterocyclic compounds, many of which are in regular clinical use. Some of these are natural products act as antibiotics such as penicillin and cephalosporins, alkaloids such as vinblastine, morphine, reserpine, and cardiac glycosides such as those of digitalis. Synthetic heterocyclic chemistry has not only played an important role in every place of human life but also found their wide range of applications in many fields such as in pharmaceuticals, agriculture, polymer and various industries.[3] Most of the synthetic heterocyclic compounds act as drug is used as anticonvulsants, antiviral, anti-inflammatory, anti-fungal, antiulcer, anthelmintic and antineoplastic, antibacterial, diuretic activity, antibacterial activity and antidepressant etc. [4]

Importance of heterocyclic compound

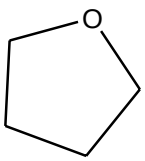
1. Used as solvent



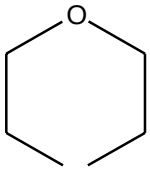
Ethylenediamine



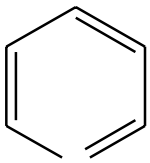
Furan



Tetrahydrofuran

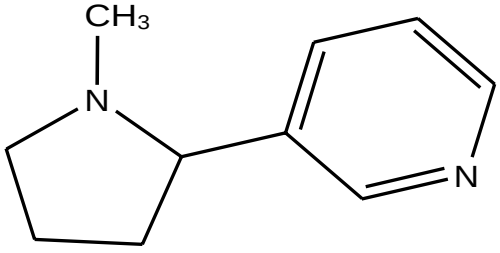


Dioxane



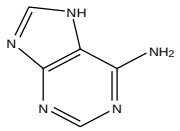
Pyridine

2. Found as natural product

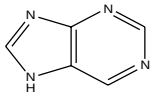


Nicotine in tobacco

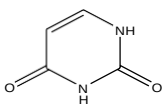
3. Heterocyclic compounds found in biomolecules



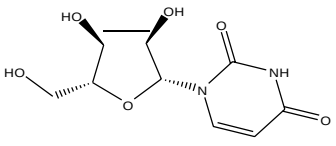
Adenine



Purine



Uracil



Uridine

FEATURES OF HETEROCYCLIC COMPOUNDS

- Most common heterocycles are those having five or six membered rings and containing heteroatoms of nitrogen (N), oxygen (O) or Sulfur (S). Simple known heterocyclic compounds are pyridine, pyrrole, furan and thiophene. A molecule of pyridine contains a ring of six atoms -five carbon atoms and one nitrogen.
- Pyrrole, furan, and thiophene molecules each contain five-membered rings, composed of four of carbon and one atom of nitrogen, oxygen or sulfur.
- Furan is an oxygen-containing heterocycle. Pyridine and pyrrole are both nitrogen heterocycles their molecules contain nitrogen atom along with carbon atom in the rings.
- In general, the physical and chemical properties of heterocyclic compounds are best understood by comparing them with ordinary organic compounds that do not contain heteroatoms

- Heterocyclic chemistry deals with heterocyclic compounds which constitute 65% of organic chemistry.
- Some of the natural products e.g. antibiotic such as penicillin, cephalosporin; alkaloids such as morphine, reserpine etc. [5]

HISTORY OF HETEROCYCLIC CHEMISTRY:

The history of the heterocyclic chemistry began in 1800s, in step with the improvement of organic chemistry. Some noteworthy developments in heterocycles are -

The physical and chemical properties of heterocyclic compounds are best understood by comparing them with ordinary organic compounds that do not contain hetero atoms.

1818: From uric acid, Brugantell isolates alloxan.

1832: Dobereiner produces furfural (a furan) by treating starch with sulfuric acid.

1834: Runge obtains pyrrole ("fiery oil') by dry distillation of bones.

1906: Friedlander synthesizes Indigo dye.

1936: From crude oil, Treibs isolates chlorophyll derivatives.

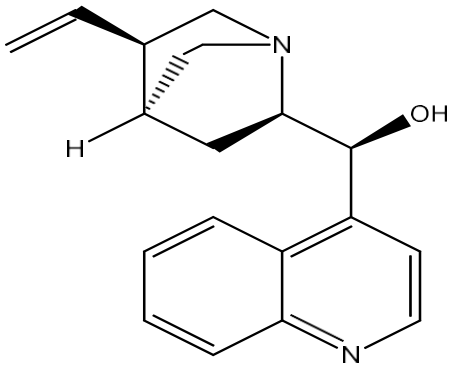
1951: The role of heterocyclic compounds (purines and pyrimidines) in the genetic codeexplained by Chargaff's rules. [5,6]

Biological importance of Heterocyclic Compounds

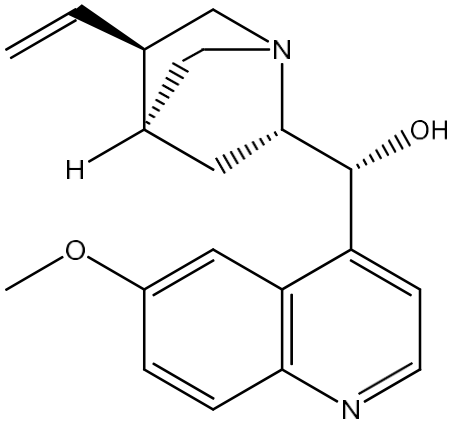
Heterocycles are an important class of compounds, making up more than half of all known organic compounds. Heterocycles are present in a wide variety of drugs, most vitamins, many natural products, biomolecules, and biologically active compounds, including antitumor, anthelmintic, anti-inflammatory, antidepressant, antimalarial, anti-HIV, antimicrobial, antibacterial, antifungal, antiviral, antidiabetic, herbicidal, fungicidal, and insecticidal agents.The alkaloids form a major group of naturally occurring heterocyclic compounds having varied biological activity. Most alkaloids contain basic nitrogen atoms. Ergotamine, the indole based alkaloid exhibits antimigraine activity. Cinchonine, a quinolone class of alkaloid shows antimalarial activity. Many heterocyclic compounds are found as key components in biological processes. Essential diet ingredients such as Thiamin (Vitamin B1), Riboflavin (Vitamin B2), Nicotinamide (Vitamin B3), Pyridoxal (Vitamin B6) and Ascorbic acid (Vitamin C) are heterocyclic compounds. Two of the essential amino acids tryptophan and histidine are also heterocycles. Also, they have been frequently found as a key structural unit in synthetic pharmaceuticals and agrochemicals.[7]

Antimalarial Activity:

Malaria is a life- threatening disease caused by parasites that are transmitted to people through bites of infected Anopheles mosquitoes. A large population of world is infected by malaria.Malaria still continues to be widespread infection disease. About 300 to 500 million clinical cases of malaria per year. Antimalarial drugs are used to treat malaria.There are antimalarial drugs of heterocyclic category which shows higher activity towards the treatment of malaria.Cinchonine, Quinine, Chloroquine and primaquine are class of alkaloid shows antibacterial activity. Quinine, Chloroquine areknown for higher activity to treat malaria and have lower toxicity.[8]

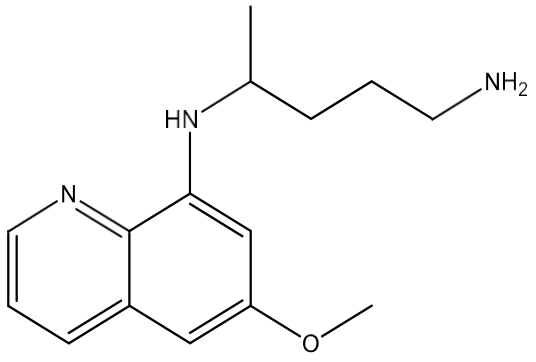


Cinchonine



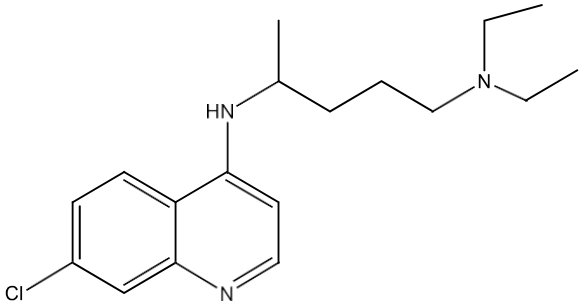
Quinine

Primaquine is the drug of 8-aminoquinoline class, which is connected to amino acids by forming peptide bond to the amino group. These amino acid derivatives are known for higher activity and lower toxicity. It is used for malaria due to Plasmodium vivax and Plasmodium ovale along with other medications and for prevention if other options cannot be used.

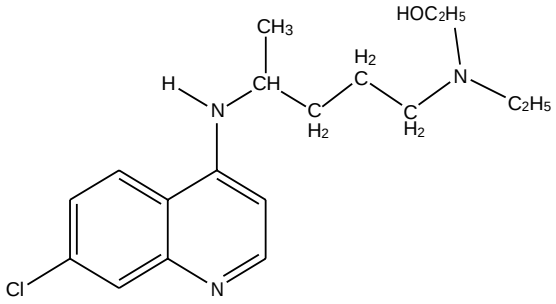


Primaquine

Chloroquine, the main drug among the 4-aminoquinoline class, is one of the most successful antimalarial agents ever produced.[8]



Chloroquine



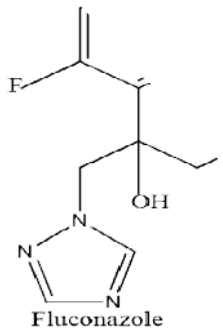
Hydroxychloroquine

Antifungal Activity:

There are several fungal species which are pathogenic for humans. Fungal infections are superficial and systematic. The fungi causing infections of hair, mucous membranes, nails or skin include Candida. The systemic infection includes those due to Aspergillus, Blastomyces.

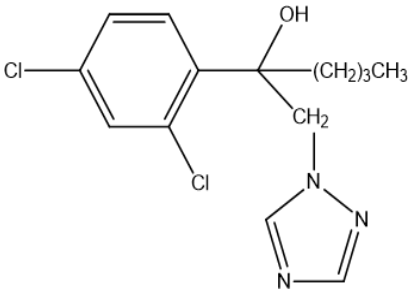
Most of the antifungal agent used clinically are either natural antibiotics or synthetic related to imidazole and triazole heterocycles. Fungi are heterotropic microorganisms that lack photosynthetic ability.[9]

Fluconazole is a triazole agent. It is antifungal used to treat cryptococcal meningitis and local or systematic candida infection.



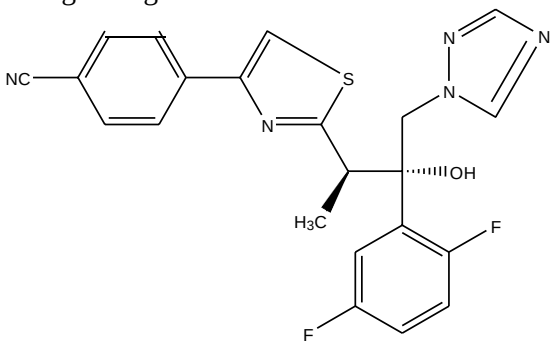
Fluconazole

Hexaconazole is a broad-spectrum systemic triazole fungicide used for the control of many fungi particularly Ascomycetes and Basidiomycetes.[9]



Hexaconazole

Isavuconazole is a water-soluble triazole prodrug with broad-spectrum antifungal activity. Isavuconazole is absorbed easily, given either orally or intravenously. Isavuconazole is a 1,3-thiazole that is butan-2-ol which is substituted at positions 1, 2, and 3 by 1,2,4-triazol-1-yl, 2,5-difluorophenyl, and 4-(p-cyanophenyl)-1,3-thiazol-2-yl groups, respectively. It has a role as an ergosterol biosynthesis inhibitor, an EC 1.14.13.70 (sterol 14alpha-demethylase) inhibitor and an orphan drug. It is a member of 1,3-thiazoles, a nitrile, a difluorobenzene, a tertiary alcohol, a triazole antifungal drug and a conazole antifungal drug.

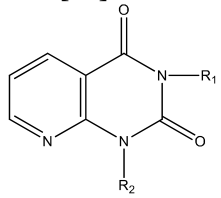


Isavuconazole

Posaconazole is a triazole antifungal drug. It is active against the microorganism candida, asperigillus, zygomycetes.[10]

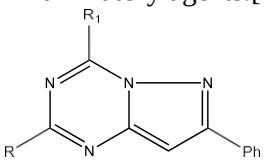
Anti-inflammatory Activity:

Inflammation is the body's first response to infection or injury and is critical for both innateandadaptiveimmunity. It often results in musculoskeletal disorders such as rheumatical arthritis, osteoarthritis and ankylosing spondylitis. Anti-inflammation is the property of a substance that reduces inflammation or swelling. Anti-inflammatory drugs make up of half of analgesics, remedying pain by reducing inflammation which affect the central nervous system to block pain J.A. Beres and Coworkers have reported the compound Pyrido[2,3-d] pyrimidine derivatives have been found to possess anti-inflammatory activities.[11]



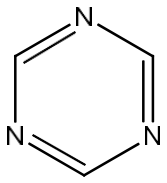
R_1= H, halo, alkyl
R_2= Ph, Cyclohexyl, alkyl, OH

Kim et al have synthesized 7-Phenyl pyrazolo-[1,5-a]-1,3,5-triazine derivatives as anti-inflammatory agents.[11] [12]



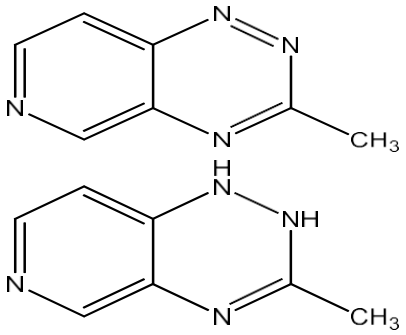
R= Thia alkyl
R1= substituted amino, N-heterocycloalkyl

Triazine derivatives have also shown anti-inflammatory activity.

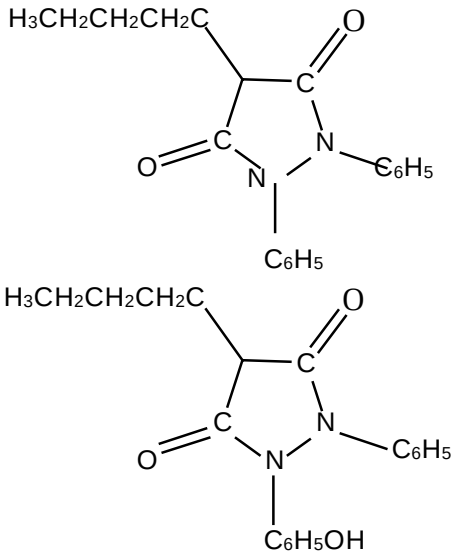


Triazine

Lewis have synthesized 3-substituted-Pyrido-[3,4-e]- as triazines. These compounds showed anti-inflammatory activity [13].



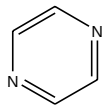
Anti-inflammatory refers to the property of a substance that reduces inflammation. An anti-inflammatory drug make up about half of analgesics, relieving pain by reducing inflammation and does not affect the central nervous system. Triazine derivatives also show anti-inflammatory activity. For example phenylbutazone, oxyphenbutazone

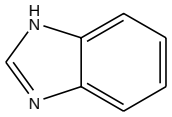


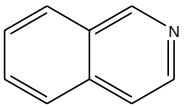
Anthelmintic Activity:

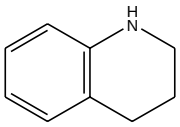
Anthelmintics are drugs that have the capability of ridding the body of parasitic worms or helminths. Helminths are parasitic worms which infects most of the world population and the infection caused by parasitic worms is known as Helminthiasis. Helminthic infections contribute to malnutrition, Anemia, stunted growth cognitive impairment and increased suspectibility to other diseases. In the world, over 2 billion people are affected by Helminthiasis. The diseases are more wide spread in less developed countries. [14]

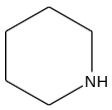
Benzimidazole, pyrazine, isoquinoline, tetrahydropyramidine, tetrahydro quinolone, piperidine, piperazine, triazoles, indoleisoxazole derivatives are the different types of heterocyclic used as anthelmintics.

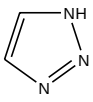

pyrazine


benzimidazole

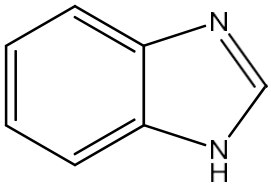

isoquinoline

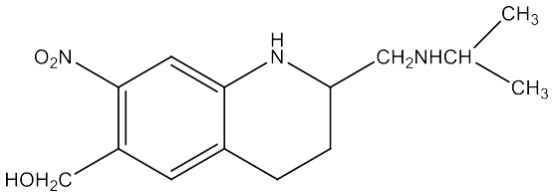

tetrahydroquinoline


piperidine

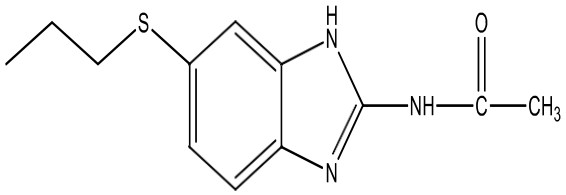

triazole

Oxamniquine is an antischistosomal agent that is indicated for the treatment of *S.mansoni* infection.[15]


Benzmidazole


Oxamniquine

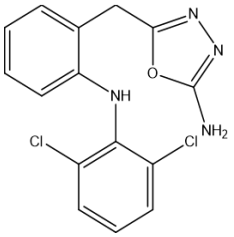
Albendazole is the most active benzimidazole anthelmintic drug.


Albendazole

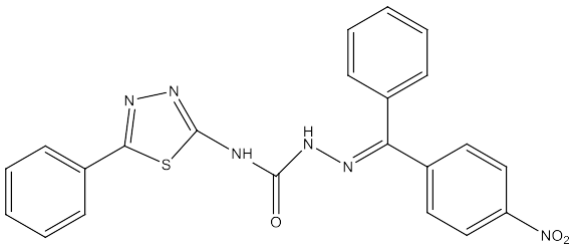
Anticonvulsant Activity:

Anticonvulsants also known as antiepileptic drugs are a diverse group of pharmacological agents used in the treatment of epileptic seizers. Epilepsy is a brain disorder and is characterized by more or less frequent recurrence of seizures, associated with loss or disturbance of consciousness and usually accompanied with convulsions or other body movements. The seizures are correlated with abnormal and excessive discharge in the electroencephalogram. Epilepsy afflicts about 20 to 40 million people worldwide.

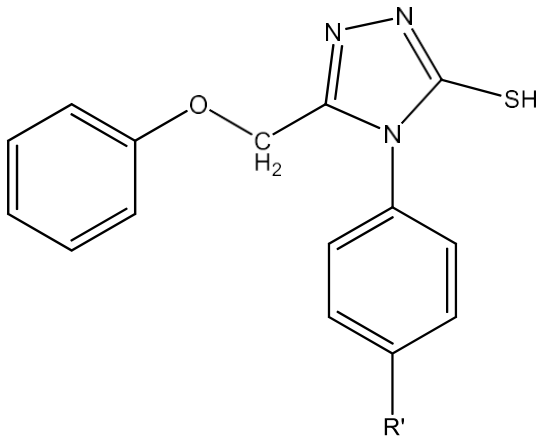
Heterocyclic compounds containing 2,5-disubstituted 1,3,4-oxadiazoles such as 2-amino-5-{2-[(2,6-dichlorophenyl) amino] benzyl}-1,3,4-oxadiazole has shown anticonvulsant activity.[16]


2-amino-5-{2-[(2,6-dichlorophenyl) amino] benzyl}-1,3,4-oxadiazole

Rajak et.al carried out the synthesis of some 2,5-Disubstituted 1,3,4- Thiadiazoles and evaluated their potential activity. 4-nitrophenyl-substituted semi-carbazone were most active.[17]


4-nitrophenyl-substituted semicarbazone

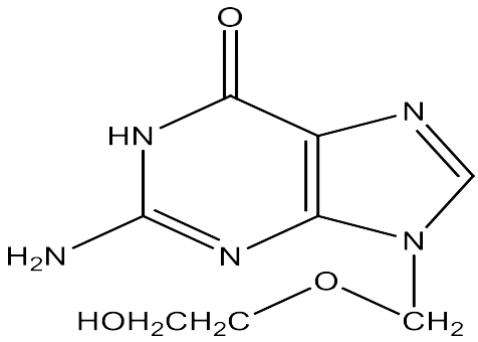
Series of new-substituted Mercapto-triazoles and Thiazolidines derivatives synthesized and evaluated their MAO Inhibitory & anticonvulsant activity.[18]



Antiviral Activity:

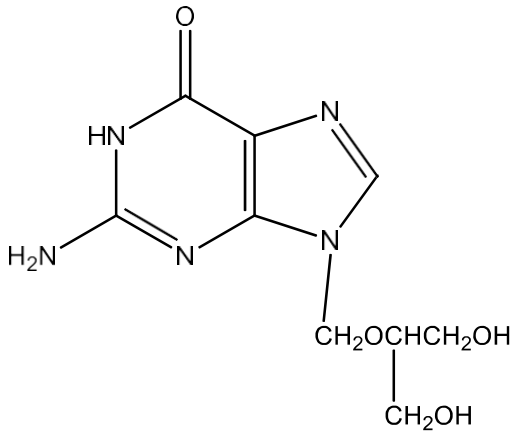
Antiviral drugs are the agents used in the treatment of viral infections.The diseases due to viral infections are more frequent. The viral infections are possibly responsible for over 60% of the human illnesses, whereas only 15% may be due to bacterial infections.Viruses are obligate cellular parasites composed of nucleic acid core surrounded by a protein aceous outer shell.[19]

Acyclovir is the most effective member of a series of acyclic nucleosides with anti-viral activity. It is having a potent activity against several DNA viruses.



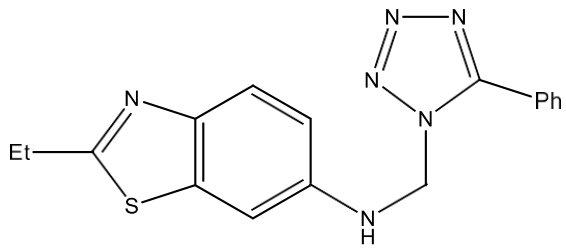
Acyclovir

Ganciclovir is an antiherpetic agent and is more active Cytomegalovirus infections. [20]



Ganciclovir

Heterocyclic compounds containing tetrazole derivative has shown some antiviral activity. 6-aminomethyl(5-tetrazolyl) benzothiazoles has antiviral activity.[21]



6-aminomethyl 5- tetrazolyl) benzothiazole

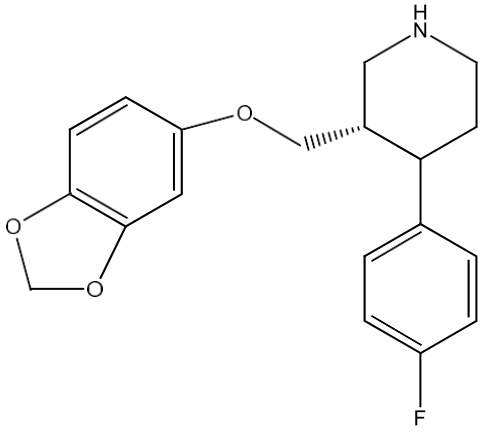
Anti-Depressant:

Depression is an extremely common and terrible disease that decreases a person's mood and quality of life. Research over the past two decades has shown that people with heart disease are more likely to suffer from depression than people without heart disease. Depression in adolescence frequently co-occurs with other disorders such as anxiety, disruptive behaviour, and eating disorders. Sometimes it leads to an increase risk of suicide.[22]

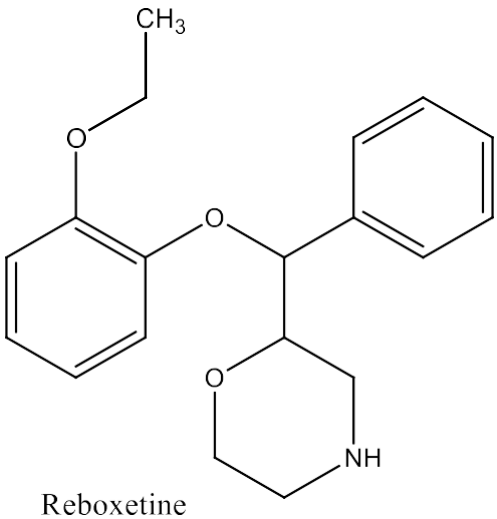
There are three types of chemicals that can affect person's mood:

(a) Serotonin (b) Norepinephrine (c) Dopamine

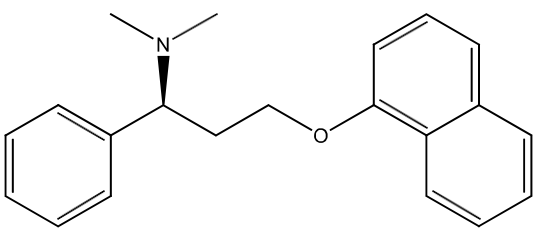
Anti-depressant is amedication used to treat major depressive disorders, some anxiety disorder, chronic pain conditions and dysthymia. Paroxetine, Reboxetine, Dapoxetine, Fluoxetine are some most useful anti-depressants containing heterocyclic moiety in their structure [23]. Some piperidine, pyrimidine and pyrazolines and Indole derivatives also possess anti-depressant activity.



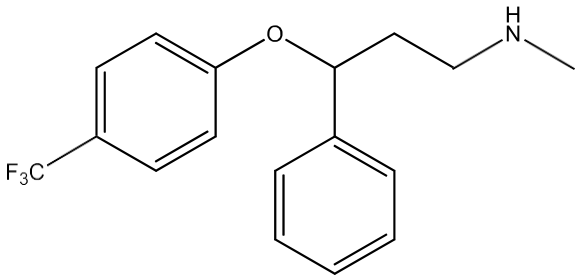
Paroxetine



Reboxetine



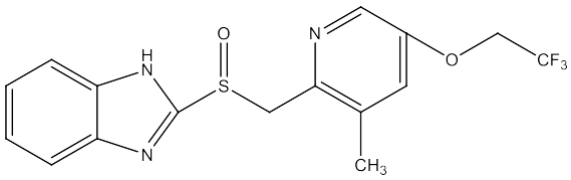
Dapoxetin



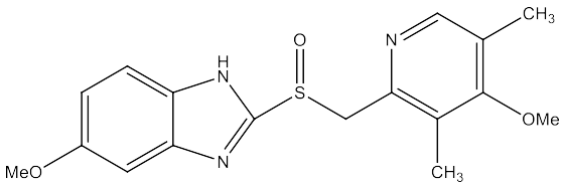
Fluoxetine

Antiulcer Activity:

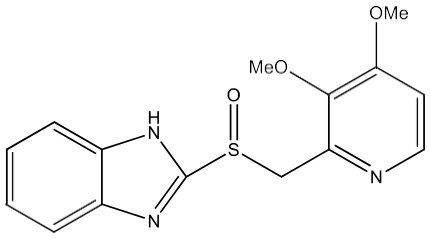
Anti-ulcer agents reduce the excess acidity in the stomach that results in the formation of ulcers. Pyridine ring plays an important role in human metabolism due to its interaction with amino acids. Many of the active drugs in the market contain pyridine moiety. Benzimidazoles also are well known for their pharmacological properties [24].A series of pyridyl sulfinyl benzimidazole molecules like Omeprazole possess gastric antisecretory and consequently anti-ulcerative activity. Later Omeprazole analogues like Lansoprazole, Pantoprazole have been introduced. [25]



Omeprazole



Lansoprazole

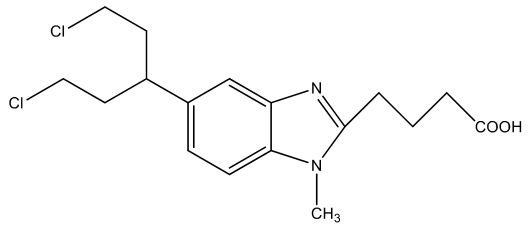


Pantoprazole

Antineoplastic Activity:

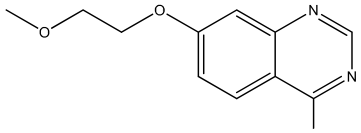
Cancer is a class of diseases in which a group of cells displays uncontrolled growth, invading adjacent tissues and sometimes metastasis or spreading to other locations in the body via lymph or blood. Cancer presents an intellectually complex set of problems because of multiple sites and causation, inadequately understood biology and myriad intervention strategies. Cancer is considered to be primarily an environmental disease, though genetics influence the risk of some cancers. A malignant tumour grows rapidly and continuously, and even when it has impoverished its host and source of nutrition, it still retains the potentiality for further proliferation. Besides, malignant tumours invade and destroy neighbouring tissues and possess no effective capsule, a malignant tumour readily ulcerate and tend sooner or later to disseminate and form metastases. Resistance to chemotherapeutic agents remains a key challenge in the fight against cancer.[26]

Compounds that alkylated DNA have long been of interest as anticancer drugs. Different types of antineoplastic agents are developed, which include nitrogen mustards (Bendamustine), tyrosine kinase inhibitors, 26S proteasome inhibitors etc.[27]

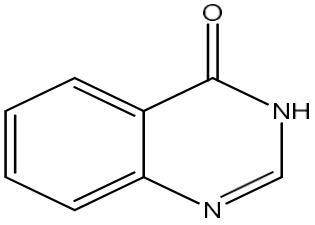


Bendamustine

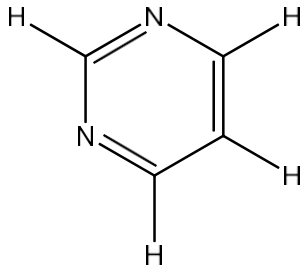
The quinazoline derivative drugs like erlotinib, and lapatinib are also important tyrosine kinase inhibitors.[28]



Different types of quinozoline and pyrimidine derivatives possess anticancerous activity.



Quinozoline



pyrimidine

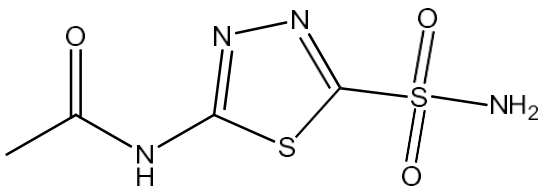
Diuretic Activity:

Diuretics are the agents which increase the rate of urine formation. They eliminate excess of liquid and toxic products from the tissues and circulation. Diuretics are used in the treatment of heart failure or in hepatic, renal or pulmonary disease. The primary action of diuretics is the direct inhibition of Na+ transport at one or more of the four major anatomical sites along the nephron where Na+ reabsorption takes place.

Acetazolamide is the first heterocyclic compound that has showed diuretic activity. Acetazolamide is a potent carbonic anhydrase inhibitor, effect in the control of fluid secretion in the treatment of certain Convulsive disorders and in the promotion of diuresis in instances of abnormal fluid retention.[29]

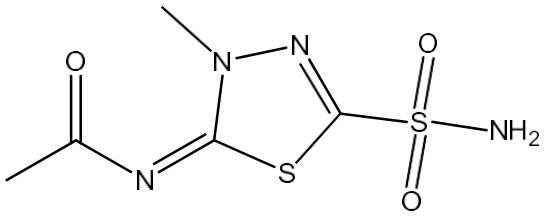
Acetazolamide is not a mercurial diuretic. Rather, it is non-bacteriostatic sulphonamide possessing a chemical structure and pharmacological activity distinctly different from the bacteriostatic sulphonamides. The anticonvulsant activity of acetazolamide may depend on a direct inhibition of carbonic anhydrase in the CNS, which decreases carbon dioxide tension in the pulmonary alveoli, thus increasing arterial oxygen tension.

The diuretic effect depends on the inhibition of carbonic anhydrase, causing a reduction in the availability of hydrogen ions for active transport in the renal tubule lumen. This leads to alkaline urine and increase in the excretion of bicarbonate, sodium, potassium, and water.[30]



acetazolamide

Further, a more potent carbonic anhydrase inhibitor Methazolamide was found. It is seldom used as a diuretic for the same reasons stated for acetazolamide.



Methazolamide

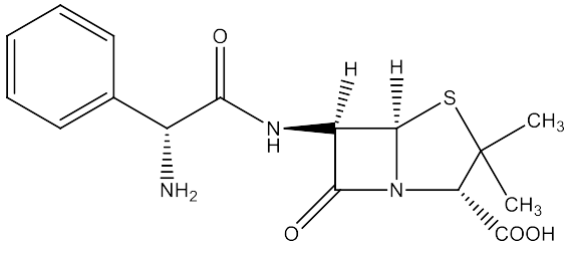
Anti-bacterial Activity:

Antibacterial or antibiotics is a term that used to describe the drugs which are used for treatment of bacterial infections. They may either by killing or inhibit the growth of bacteria. Some antibiotics also show Antiprotozoal Activity. Antibiotics belong to a class of antimicrobials, a large group which also includes antivirals, antifungals and antiparasitic drugs. Some antibiotics can be used to treat a wide range of infections and are known as broad-spectrum antibiotics.

Antibiotics are not effective against viral infections such as the common cold or influenza. The emergence of resistant organisms may happen if the using of antibiotics was inappropriate. The classification of antibiotics is according to the mechanisms of actions or chemical structural. Aromatic heterocyclic derivatives represent an important part of antibiotics, chemical structure such as β-lactam derivatives.[31]

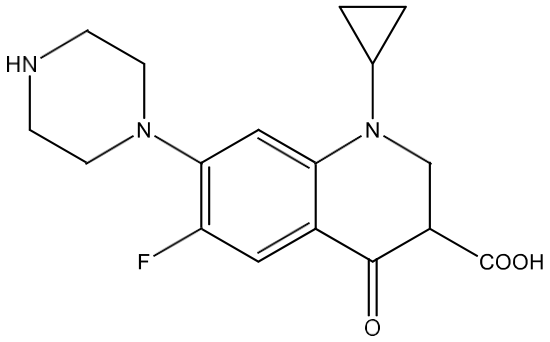
Some purely synthetic antibacterial are: the sulphonamides, the quinolines and the oxazolidinones. Among the antibiotics and anti-bacterial category are beta lactams and quinoline derivatives.[32]

Beta lactams have two different hetero atoms in their structure, e.g. ampicillin. Ampicillin has an antibacterial spectrum broader than that of penicillin G. It is active against the same Gram-positive organisms which are susceptible to other penicillin. Besides, it is also found to be more active against certain Gram-negative organisms and enterococci than are other penicillin.



Ampicillin

Among the quinoline derivatives Ciprofloxacin is an effective drug. It comes under the family of Fluoroquinolone's.



Ciprofloxacin

Other applications of heterocyclic compounds:

Heterocyclic compounds have widespread applications in medical chemistry as well as in photochemistry, biological formulation, polymer science, electronics, biology, optics, material science and pharmacology etc. Some heterocyclic compounds exhibit a noteworthy solvatochromic, photochromic, and biochemi-luminescence properties.

In materials science as dyestuff, fluorescent sensor, brightening agents, information storage, plastics, and analytical reagents and especially in conjugated polymer.

In electronics act as organic conductors, optical data carriers, organic light-emitting diodes (OLEDs), semiconductors, molecular wires, photovoltaic cells, light harvesting systems, liquid crystalline compounds and chemically controllable switches.[33]

Heterocycles are also of considerable interest because of their synthetic utility as synthetic intermediates, protecting groups, chiral auxiliaries, organ catalysts, and metal ligands in asymmetric catalysts inorganic synthesis and as lubricants [34]. Therefore, substantial attention has been paid to develop efficient new methods to synthesize heterocycles.

Nitrogen containing compound pyridine is used also as a solvent, a waterproofing agent, a rubber additive, an alcohol denaturant, and a dyeing adjunct.

Some of the heterocyclic compounds such as, 2-Phenyl-3-phenylimino-5-p-methoxyphenylim ino-1,2,4-thiadiazolidine has been found to be relatively effectual in the lubrication of bearing balls of different compositions [34].

6. Conclusion

Heterocyclic compounds are one of the most important classes of organic compounds. They are widely distributed in nature and play a vital role in medicinal agents. Heterocyclic compounds and their derivatives known to exhibit biological activities such as antimalarial, anti-convulsant, anti-inflammatory, antineoplastic activity, anti-depressants and anti-fungal, diuretics activity.

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