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IMPORTANCE OF HETEROCYCLIC CHEMISTRY: A REVIEW

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ABSTRACT

Heterocyclic compounds are of very much interest in our daily life. Heterocyclic compounds have one or more hetero atoms in their structure. They may be cyclic or non cyclic in nature. Heterocyclic compunds have a wide range of application. They are predominantly used as pharmaceuticals, as agrochemicals and as veterinary products. They also find applications as sanitizers, developers, antioxidants, as corrosion inhibitors, as copolymers, dye stuff. They are used as vehicles in the synthesis of other organic compunds. Some of the natural products e.g. antibiotics such as penicillin's, cephalosporin; alkaloids such as vinblastine, morphine, reserpine etc. have heterocyclic moiety.

INTRODUCTION: Any of a major class of organic chemical compounds characterized by the fact that some or all of the atoms in their molecules are joined in rings containing at least one atom of an element other than carbon. The cyclic part of heterocyclic indicates that at least one ring structure is present in such a compound, while the prefix hetero refers to the noncarbon atoms, or heteroatoms, in the ring. In their general structure, heterocyclic compounds resemble cyclic organic compounds that incorporate only carbon atoms in the rings but the presence of the heteroatoms gives heterocyclic compounds physical and chemical properties that are often quite distinct from those of their all-carbon-ring analogs.

General features of Heterocyclic Compounds: The most common heterocycles are those having five- or six-membered rings and containing heteroatoms of nitrogen (N), oxygen (O), or sulfur (S). The best known of the simple heterocyclic compounds are pyridine, pyrrole, furan, and thiophene. A molecule of pyridine contains a ring of six atoms-five carbon atoms and one nitrogen atom. Pyrrole, furan, and thiophene molecules each contain five-membered rings, composed of four atoms of carbon and one atom of nitrogen, oxygen, or sulfur, respectively [1].

Pyridine and pyrrole are both nitrogen heterocycles-their molecules contain nitrogen atoms along with carbon atoms in the rings. The molecules of many biological materials consist in part of pyridine and pyrrole rings, and such materials yield small amounts of pyridine and pyrrole upon strong heating. In fact, both of these substances were discovered in the 1850s in an oily mixture formed by strong heating of bones. Today, pyridine and pyrrole are prepared by synthetic reactions.

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Their chief commercial interest lies in their conversion to other substances, chiefly dyestuffs and drugs. Pyridine is used also as a solvent, a waterproofing agent, a rubber additive, an alcohol denaturant, and a dyeing adjunct [2].

Furan is an oxygen-containing heterocycle employed primarily for conversion to other substances (including pyrrole). Furfural, a close chemical relative of furan, is obtained from oat hulls and corncobs and is used in the production of intermediates for nylon. thiophene, a sulfur heterocycle, resembles benzene in its chemical and physical properties. It is a frequent contaminant of the benzene obtained from natural sources and was first discovered during the purification of benzene. Like the other compounds, it is used primarily for conversion to other substances. Furan and thiophene were both discovered in the latter part of the 19th century [3].

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 about sixty-five percent of organic chemistry literature [4]. Heterocyclic compunds are widely distributed in nature and exxential to life; they play a vital role in the metabolism of all living cells.Genetic material DNA ia also composed of heterocyclic bases-pyrimidines and purines. A large number of heterocyclic compunds, both synthetic and natural, are pharmacologically active and are in clinical use.

Heterocyclic compunds have a wide range of application: they are predominant among the type of compounds used as pharmaceuticals[5] , as agrochemicals and as veterinary products. They also find applications as sentizers, developers, antioxidants, as corrosion inhibitors, as copolymers, dyestuff [6].They are used as vehicles in the synthesis of other organic compunds.

Some of the natural products e.g. antibiotics such as penicillin's, cephalosporin; alkaloids such as vinblastine, morphine, reserpine etc. have heterocyclic moiety.

One of the resons for the widespread use heterocyclic compounds is that their structures can be subtly manipulated to achieve a required modification in function. Many heterocycles cab ve fitted into one of a few broad groups of structures that have overall similarities in their properties but siginificant variations within the group. Such variations can include differences in acidity or bascity, different polarity [7]. The possible structural variations include the change of one heteroatom for another ring and different positioning of the same heteroatoms within the ring.

History of Heterocyclic Chemistry: The history of heterocyclic chemistry began in the 1800s, in step with the development of organic chemistry. Some noteworthy developments

1818: Brugnatelli isolates alloxan from uric acid.

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

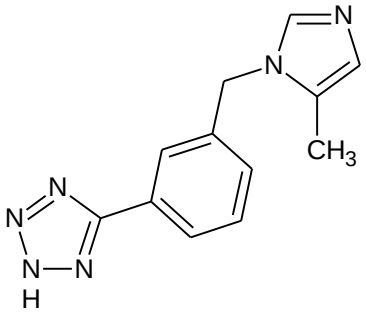
1834: Runge obtains pyrrole ("fiery oil") by dry distillation of bones

1906: Friedlander synthesizes indigo dye, allowing synthetic chemistry to displace a large agricultural industry

1936: Treibs isolates chlorophyl derivatives from crude oil, explaining the biological origin of petroleum.

1951: Chargaff's rules are described, highlighting the role of heterocyclic compounds (purines and pyrimidines) in the genetic code.

An important feature of the structure of many heterocyclic compunds is that it is possible to incorporate functional groups either as subsituents or as part of the ring itself. For example, basic nitrogen atoms can be incorporated both as amino substituents and as part of a ring. This means that the structures are particularly versatile as a means of providing, or of mimicking a functional group. For example the uses of tetrazole ring system[1] as a mimic [8] of a carboxylic and functional group because of its similarity in acidity and in steric requirement. Tetrazole group is superior in terms of metabolic stability, bioavailibilty and four nitrogen atoms present in the tetrazole ring can create a greater charge distribution.



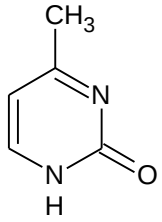
(1)

Another example , ocatanol [9] can be used to mimic the amphiphilic nature of lipid, because it has a polar head group (primary alcohal) and a long hydrocarbon chain as tail, such as that oh fatty acids which make up part of a lipid membrane. Armed with this understanding, the organic chemist can 'tailor' a structure to meet a particular need by modifying the heterocyclic component.

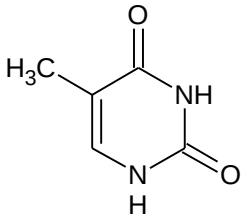
Heterocyclic compunds are also finding an increasing use as intermediate in organic synthesis[10-12]. Very often this is because a relatively stable ring system can be carried through a number of synthetic steps and then cleaved at the required stage in a synthesis to reveal other functional groups. For e.g. 4-chloro-5(4*H*)-oxazolones are useful intermediates [13] in organic synthesis. In particular hydrolytic cleavage affords α-chloro-αacylaminoketones. More ever they are the logical intermediate to prepare 4-(phospho-ranylidene)-5(4*H*)-oxazolones, that are very important and useful ligands.

Some sterically congested 'roofed' 2-thiazolines as new chiral ligands for Cu(II)-catalyzed asymmetric Diels-Alder reactions, leading to excellent endo/exo ratio and endo-enantioselectivity compared to the corresponding chiral 'roofed' 2-oxazoline ligand.

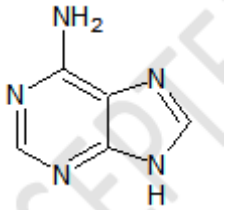
Heterocyclic compunds are widely distributed in nature. Many are of fundamental importance to living systems: it is striking how often a heterocyclic compund is found as a key component in biological processes. For example the nucleic acid bases, which are derivatives of the purine, namely adenine, guanine and pyrimidine, namely thymine, cystosine as being crucial to the mechanism of replication. Some purine and pyrimidines can act as antibiotics, by interference with DNA synthesis. Puromycin is an example of such an antibiotic.



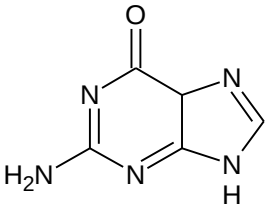
Cytosine



Thymine

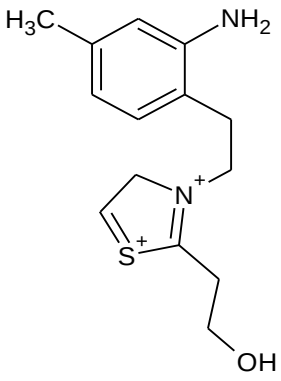


Adenine

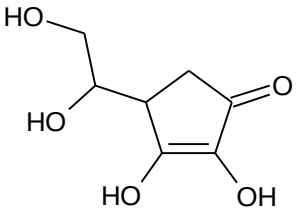


Guanine

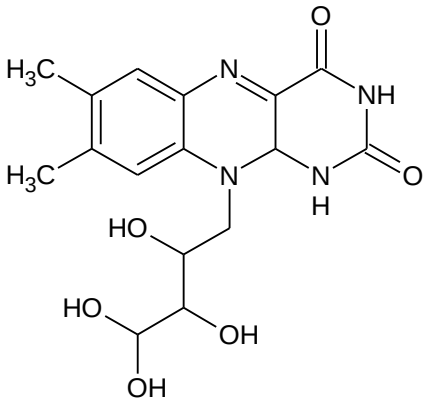
Chlorophyll and heme, which are derivatives pf porphyrin ring system are the components required for the photosynthesis and for oxygen transport in higher plants and in animal. Essential diet ingredients such as thiamin (vitamin B_1), riboflavin (vitamin B_2), pyridoxol (vitamin B_6), nicotinamide (vitamin B_3) and ascorbic acid (vitamin C) are heterocyclic compounds.



Thiamine

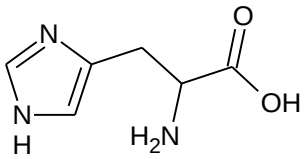


Vitamin C

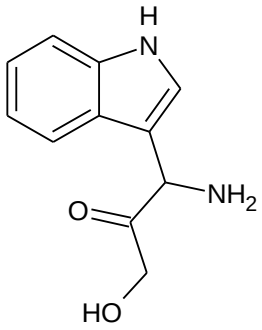


Riboflavin

Of the twenty amino acids commonly found in different proteins, three, namely histidine, proline and tryptophan, are heterocyclic. It is not surprising, therefore that a great deal of current research work is concerned with methods of synthesis and properties of heterocyclic compunds.



Histidine

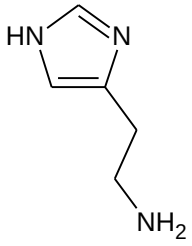


Tryptophan

Many of the pharmaceuticals and most of the other heterocyclic compunds with practical applications are nor extracted from natural sources but are synthesized. The origins of organic chemistry do, however lie in the study of natural products. These have formed the basis for the design of many of the useful compunds developed subsequently: examples are the early development of vat dyes based on the structure of indigo and the continuing invention of new antibacterial agents based on the β-lactam structure of pencillin. Some examples of drugs having β-lactam moiety are cephalosporin C**,** amoxicillin, clavuanic acid, peninicillin etc.

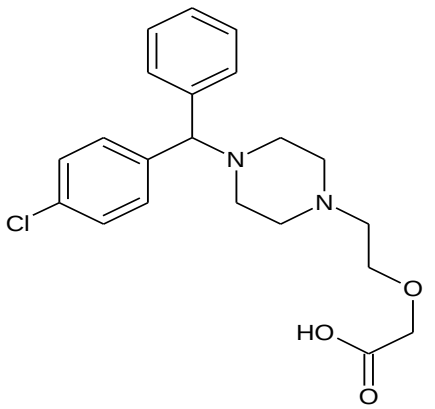
Three different group pf pharmaceutical with structures related to natural products are described briefly below as illustrations of the ways in which natural products chemistry interacts with synthetic heterocyclic chemistry.

Pharmaceuticals related to Histamine. Histamine, a monosubstituted imidazole, is derived *in vivo* from the amino acid histidine by decarboxylation by enzyme histidine decarboxylase. Hisatmine, [2] a biogenic amine involved in local immune responses and also acts as neurotransmitter [14]. It is involved in allergic reactions and is liberated from skin cells on injury and also participates in the regulation of gastric acid secretion.



(2)

From the 1940s onwards several synthetic drugs became available that can act as histamine antagonists. Two different types of histamine receptor were distinguished in the body; these were labeled as H_1 and H_2 receptors. Cetrizine [3], chlorpheniramine [4] etc act as blockers of H_1 receptors.



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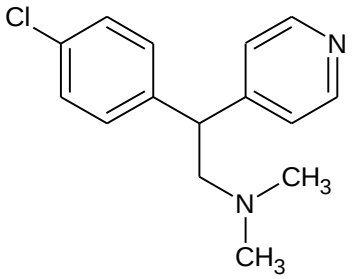
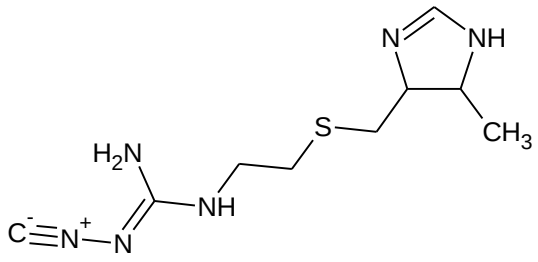


(4)

The search for a specific histamine H_2 receptor antagonist that could potentially control gastric acid secretion, thus provide the basis for treatment for peptic ulcers, started in 1964. Having little information to guide their intial choice, the chemists used the structure of histamine for the synthesis of new compunds. Although it took a long period to discover active compounds, the work eventually resulted in 1976 was the introduction of a drug, cimetidine an imidazole derivative for the treatment of peptic ulcers [15-16].

The success of cimetidine [5] has prompted the introduction of other drugs having structures that are closely related but with the replacement of imidazole ring by other heterocycles. Rantidine [6] containing a furan ring, is also an important and successful drug for the treatment of peptic ulcer[17-18]. Another drug, Famotidine having thiazole moiety, inhibits stomach acid production and gastroesophageal reflux disease [19] (GERD).



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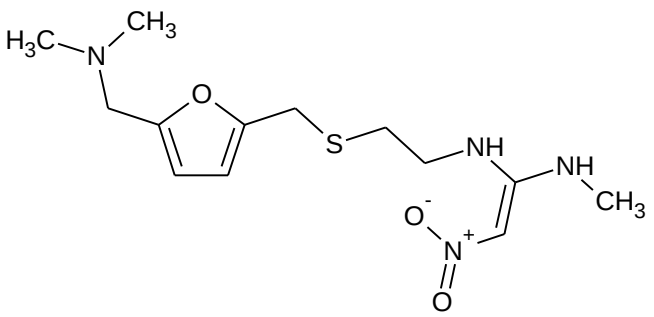

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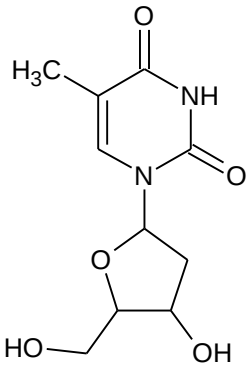
Nucleoside Analogues: A logical starting point in the search for drugs to combat cancer and viruses is the structure of DNA. One of the approaches that have been intensively explored is to investigate the use of analogues [20-21] of the nucleosides. These nucleic acid fragments consist of a heterocyclic nitrogenous base (a purine or a pyrimidine) linked to a sugar; for example 2′deoxythymidine [7].

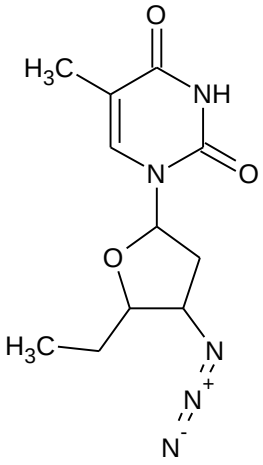


(7)

Analogues can be made in which the structure of the heterocyclic nitrogenous base is modified, or that of the sugar is modified, or boht. Such a compuund might interfere in the replicative cycle of a virus, for example by incorporating in place of natural nucleoside. The main problem is of selectivity, because majority of such compunds are also likely to prove toxic to normal cells.

Nevertheless, some important drugs of this type have been produced. Zidovudine/azidothymidine (AZT) [8] (also called ZDV) is a nucleoside analog reverse transcriptase inhibitor [23-25] (NRTI), atype of antiretroviral [26-27] drug used in the treatment of AIDS, is an analogue of 2′-deoxythymidine. Acyclovir (ACV) [9] is an analogue of 2′-deoxyguanosine, in which the acyclic side chain part mimics the sugar in the natural nucleoside.

It is a useful drug for the treatment of herpes simplex [28] and herpes zoster viral infections due to high selectivity [29] and low cyptotoxicity. Ganciclovir [10] is a structurally related antiviral agent that has been used for the treatment of cytomegalovirus infections [30-31] in AIDS patient and in recipients of organ transplants.



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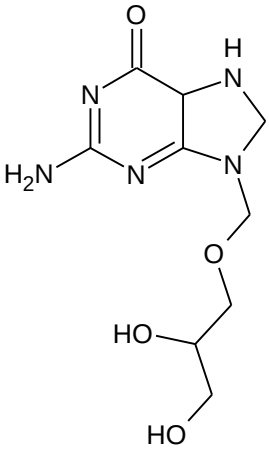

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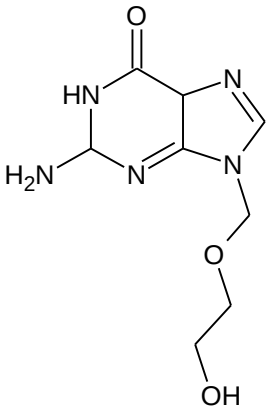
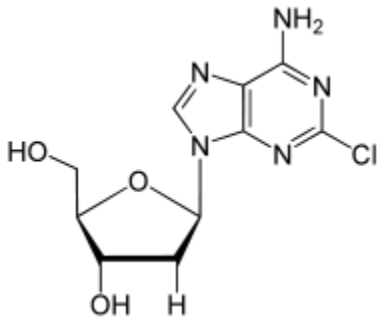


(10)

Cladribine (Leustatin) [32] [11] and Pentostatin [33] [12] are drugs, used to treat hairy cel leukaemia (leukemic reticuloendotheliosis) and multiple sclerosis.

Chemically, it mimics the nucleoside adenosine and thus inhibits the enzyme adenosine deaminase, which interfaces with the cell's ability to process DNA.



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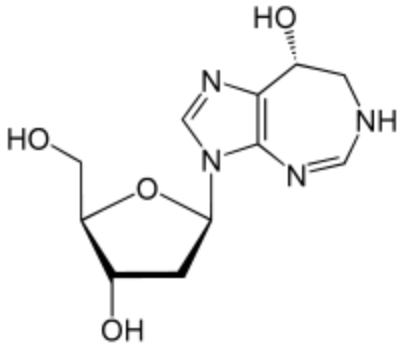
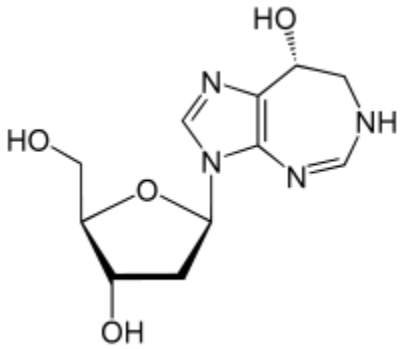


(12)

Compounds related to Serotonin: Natural products often occur in small quantities and therefore difficult to investigate if the compunds have to be extracted from the natural source. Organic chemists can provide a solution to the problem by devising practicable laboratory synthesis. An example is provided by serotonin [13] (commonly called 5-hydroxy tyrpamine, or 5-HT). This compund is widely distributed in nature but occurs only in low concentration . It is derived in nature from the amino acid tryptophan, by the short pathway including two enzymes, tryptophan hydroxylase and amino acid decarboxylase.



(13)

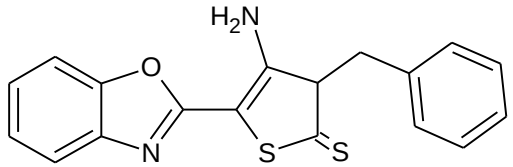
Setotnin is known to have a wide and complex range of pharmacological actions. These include the contraction of smooth and blood platelet aggregation.

It acts as a constrictor of arteries in the brain and is implicated in migraine [34]. Changes in serotnin concentration in the brain also alter mood [35-36] and appetite. However, it is too rapidly metabolized to have any potential as a pharmaceutical agent.

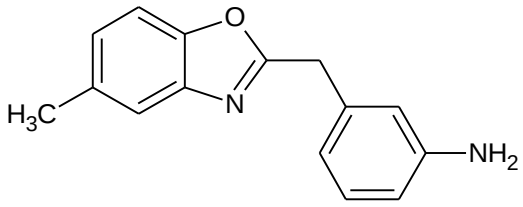
There is a group of alkaloids with hallucinogenic properties (i.e they alter perception and mood) which are closely related in structure to serotnin, but which are mood stable *in vivo* [37]. Psilocin is one of the active constituents of Mexican mushrooms which are used since at least 1500 BC. In Aztec and mayan culture as hallucinogens. Bufotenine is another hallucinogen that occurs in toadstools. These hallucinogenic compounds act as agonists (i.e. as promoter activity) at serotnin receptors in the brain. The indole derivative, sumatriptan also acts as agonist to serotnin receptor sites in the brain and introduced in medicine as a drug for the treatment of migrane.

The ergot alkaloids have more complex structures but they are all based on indole with a β-aminoethyl side chain at the 3-position. An example, ergotamine in small doses has been shown to be useful in treating migraine but is also highly toxic and its mechanism of action is complex [38]. The structurally related compund is lysergic acid diethylamide (LSD) now notorious as a hallucinogen, is a product of laboratory syntheis; its properties were first discovered accidental inhalation of the compund.

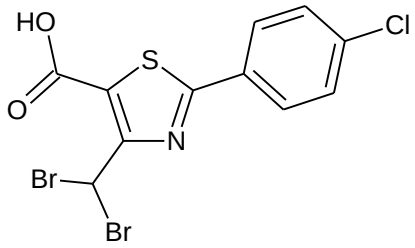
Some of the biological properties of some heterocyclic compunds, known in literature are summarized as;



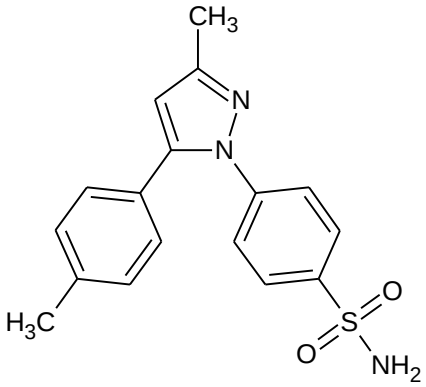
Anticancer, anti-HIV and antimicrobial [39]



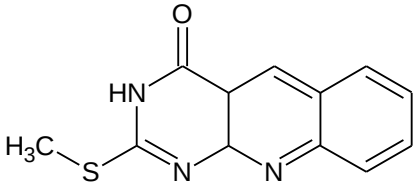
Genotoxic active agent [40]



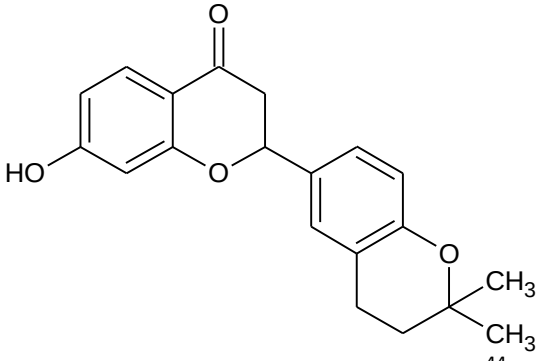
Antiviral agents targeting virus proteins [41]



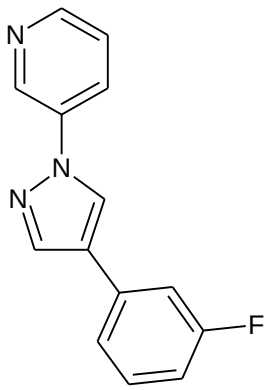
COX-2 inhibitors and anti-inflammatory [42]



Antitumor activity [43]



Anti-oxidant and cytotoxic activity [44]



Anticancer agents [45]

Heterocyclics From Marine Source: Marine invertebrates are the source of many novel, natural products [46-47], some without terrestrial counterparts or analogy. More than 18 000 compounds appear in the 2006 Marinlit database [48]. While in the 1960s and 1970s, because of the applied extraction techniques, the majority of the isolated compounds were isoprenoids and polyketides, N-atom-containing compounds ("alkaloids"), isolated mainlyfrom sponges and ascidians, only became more common in later years.

The latter group includes many novel bioactive heterocycles with no terrestrial counterparts. Representative new heterocycles, isolated by us from Red Sea and Indo-Pacific sponges, tunicates, and a few soft corals, are shown in. All depicted new compounds exhibit unique structures, some of which display interesting bioactivity, for example, the antiviral activity of ptilomycalin A [49], the actin-binding activity of the latrunculins [50] and the cytotoxicity of the pyridoacridines, eilatin and norsegoline [51].

The interesting activity of the latter group has triggered the synthesis of several of these compounds and their analogues.

CONCLUSION: The rate at which heterocyclic compunds continue to be invented testifies to the strength and vitality of this area of organic chemistry. The challenges of discovering new heterocyclic systems and of understanding their properties also continue to stimulate research in the area.

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