Chapter 1 Introduction

Jie Jack Li

1.1 Nomenclature of Heterocycles

What's in a name? That which we call rose by any other name would smell as sweet. [William Shakespeare, *Romeo and Juliet* (II, ii, 1–2)].

Contrary to Shakespeare's exclamation, *naming heterocycles* is an integral part of our learning of heterocyclic chemistry. They are the professional jargon that we routinely use to communicate with our peers.

Heterocycles, as the name suggests, are cyclic compounds containing one or more heteroatoms such as N, O, S, P, Si, B, Se, and Se. They may be further divided into aromatic heterocycles and saturated heterocycles. This book will focus largely on aromatic heterocycles. Saturated heterocycles represent a smaller portion of drugs. Another way of naming heterocycles is using the size of the heterocyclic rings. Therefore, they may be classified as three-, four-, five-, six-, and seven-membered heterocycles, and so on.

Three-membered heterocycles are important reaction intermediates in organic chemistry and in preparing medicines. But they usually do not exist in final drugs because they are reactive in physiological environments. Exceptions are found in cancer drugs such as epothilone A and mitomycin C (see Section 1.4, page 9), where their reactivities are taken advantage of for therapeutic purposes.

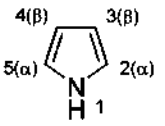
The most frequently encountered three-membered heterocycles are oxirane, thiirane, aziridine, and azirine.

oxirane thiirane aziridine azirine

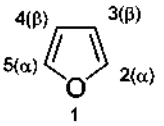
Four-membered heterocycles include oxetane, 2*H*-oxete, thietane, 2*H*-thiete, azetidine, and azete. In the field of drug discovery, oxetanes and azetidines are more and more incorporated into drugs for modulating biological and physical properties as well as for expanding intellectual properties space.

oxetane 2*H*-oxete thietane 2*H*-thiete azetidine azete

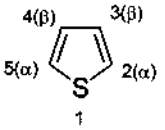
Five- and six-membered heterocycles are of utmost importance to both life and drug discovery. The most common five-membered heterocycles with one heteroatom are pyrrole, furan, and thiophene.



pyrrole

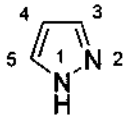


furan

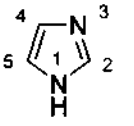


thiophene

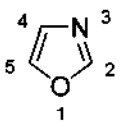
Popular five-membered heterocycles with two heteroatoms include pyrazole, imidazole, oxazole, isoxazole, thiazole, and isothiazole.



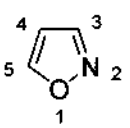
pyrazole



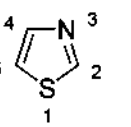
imidazole



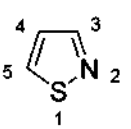
oxazole



isoxazole



thiazole



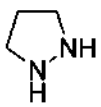
isothiazole

All these aromatic heterocycles have their counterparts in the corresponding saturated heterocycles. Among those, pyrrolidines, tetrahydrofurans, and oxazolidines are more frequently encountered in drug discovery.

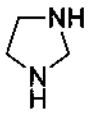
pyrrolidine

tetrahydrofuran

tetrahydrothiophene

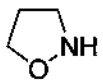


pyrazolidine



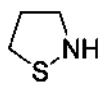
imidazolidine

oxazolidine

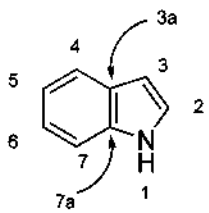


isoxazolidine

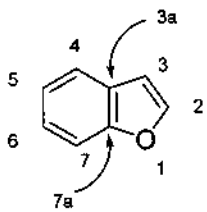
thiazolidine



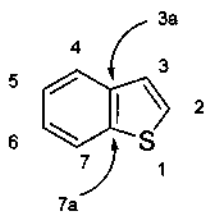
isothiazolidine



indole

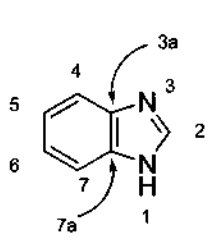


benzofuran

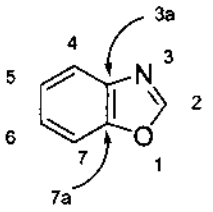


benzothiophene

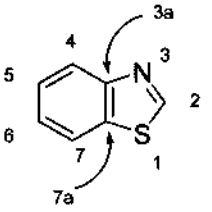
Some of the important benzene-fused five-membered heterocycles are indole, benzofuran, benzothiophene, benzimidazole, benzoxazole, and benzothiazole. The numbering of these heterocycles is shown below:



benzoimidazole

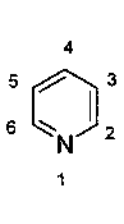


benzooxazole

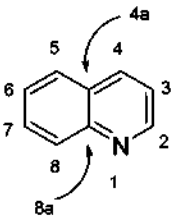


benzothiozole

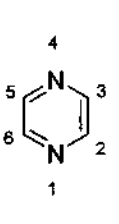
Chief among the six-membered heterocycles, pyridine and its benzene-fused derivative quinoline are most ubiquitous. Pyrazine and its benzene-fused analogue, quinoxaline, also play an important role in heterocyclic chemistry.



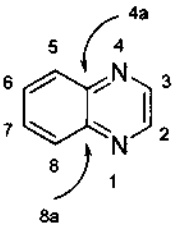
pyridine



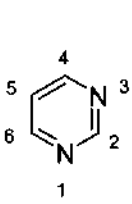
quinoline



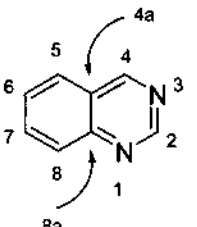
pyrazine



quinoxaline

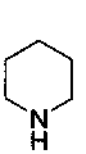


pyrimidine

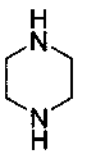


quinazoline

Their corresponding saturated derivatives often encountered in drug discovery are piperidine and piperazine.

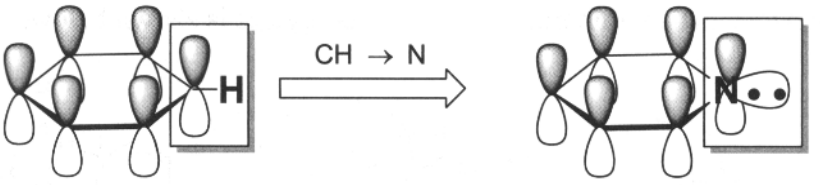


piperidine



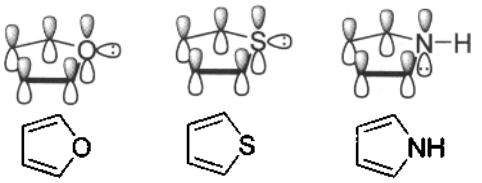
piperazine

1.2 Aromaticity of Heterocycles



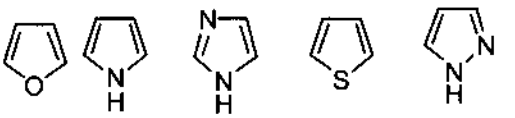
benzene pyridine

The major thrust of this book is aromatic heterocycles. According to Hückel's rule of aromaticity, a cyclic ring molecule is aromatic when the number of its π-electrons equals 4n + 2, where n is zero or any positive integer. The most common aromatic compound is benzene, which has 4 + 2 = 6 π-electrons. Pyridine, an electron-deficient aromatic heterocycle, also has 6 π-electrons. In comparison with benzene, pyridine has an additional lone pair of electrons at the nitrogen atom after it contributes a pair of two electrons to make up the 6 π-electrons for aromaticity. These lone pair electrons are responsible for much of pyridine's unique physical and chemical properties. On the other hand, furan, an electron-excessive aromatic heterocycle also with 6 π-electrons, is different from both benzene and pyridine. The oxygen atom has two lone pairs of electrons, one of which contributes to the 6 π-electrons to achieve the aromaticity. The second pair of electrons is located in an sp^2 hybrid orbital in the plane of the furan ring. Thiophene is similar to furan in its aromaticity although thiophene is more "aromatic" because the S atom is larger than the O atom.

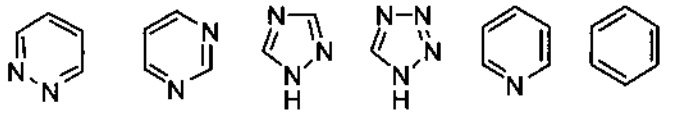


furan thiophene pyrrole

The relative aromaticity of common heterocycles is shown below:



furan	pyrrole	imidazole	thiophene	pyrazole
12	31	43	45	61

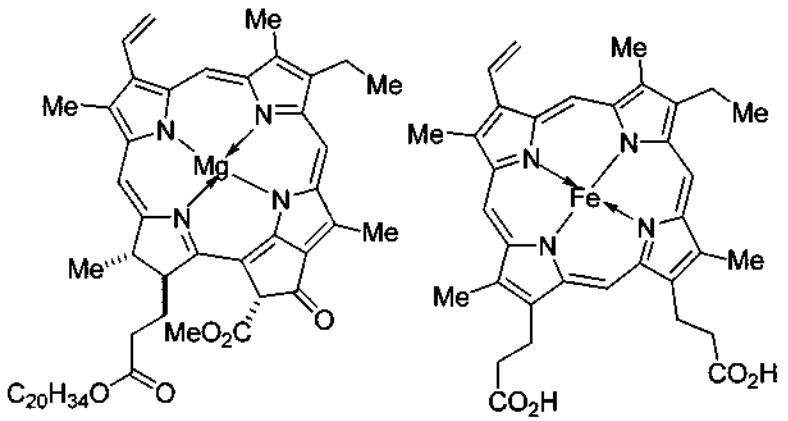


pyridazine 65 | pyrimidine 67 | triazole 71 | tetrazole 80 | pyridine 82 | benzene 100

Pyrrole, also an aromatic heterocycle with 6 π-electrons, is probably the most unique of all among the aromatic heterocycles. Different from furan and thiophene, the nitrogen atom on the pyrrole ring only has one lone pair of electrons, which both contributed to the 6 π-electrons to achieve the aromaticity. As a consequence, although pyrrole is also an electron-excessive aromatic heterocycle, just like furan and thiophene, pyrrole has many of its own characteristics. For instance, it is probably the most reactive as a nucleophile among all aromatic heterocycles (see Chapter 2). In addition, pyrrole's conjugation effect outweighs the nitrogen's inductuve effect in the contributing dipole moment, with the partial positive charge resting at the nitrogen atom.

1.3 Importance of Heterocycles in Life

The importance of heterocycles in life was recognized as the nascent stage of organic chemistry two centuries ago with isolation of alkaloids such as morphine from poppy seeds, quinine from cinchona barks, and camptothecin from the Chinese joy tree. Today, heterocycles are found in numerous fields of biochemical and physiological such as photosynthesis, amino acids, DNA bases, vitamins, endogenous neurotransmitters, and so on.



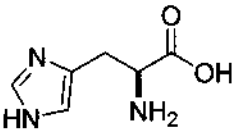
chlorophyll-a heme

To begin with, chlorophyll is porphyrin (a tetramer of pyrrole) surrounding a magnesium atom. It is the molecule that absorbs sunlight and

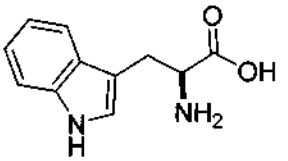
uses its energy to synthesize carbohydrates from CO_2 and water. This process, known as photosynthesis, is the basis for sustaining the life processes of all plants.

On the other hand, the heme consists of a porphyrin ring surrounding an *iron* atom. The ring contains a large number of conjugated double bonds, which allows the molecule to absorb light in the visible part of the spectrum. The iron atom and the attached protein chain modify the wavelength of the absorption and give hemoglobin its characteristic color.

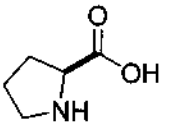
Several amino acids, the building block of life, are made of heterocycles. Histidine has an imidazole; tryptophan has an indole; yet proline has a pyrrolidine.



histidine

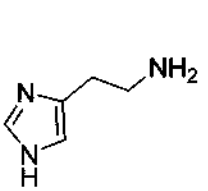


tryptophan

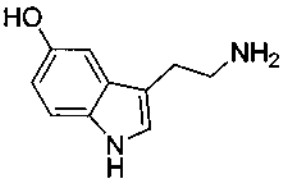


proline

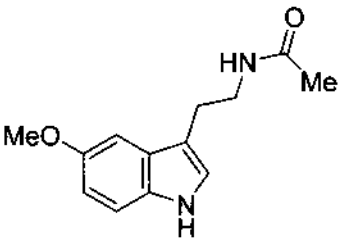
Heterocycles also play an important role as endogenous neurotransmitters. Chief among them are serotonin and histamine, which are of paramount importance in modulating the body's physiological and biochemical processes.



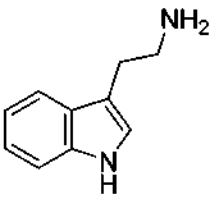
histamine



serotonin



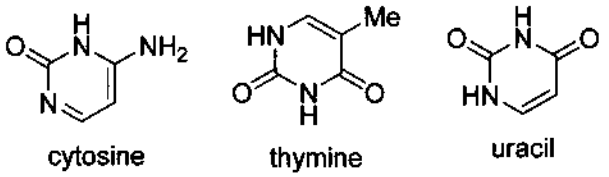
melatonin

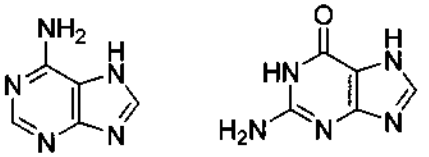


tryptamine

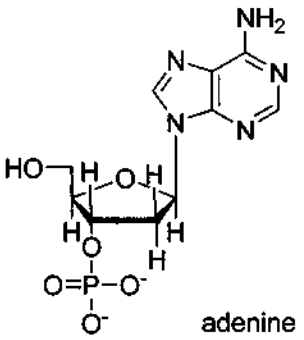
Melatonin regulates circadian rhythms, most noticeably sleep, whereas tryptamine is closely related to melatonin and the amino acid tryptophan.

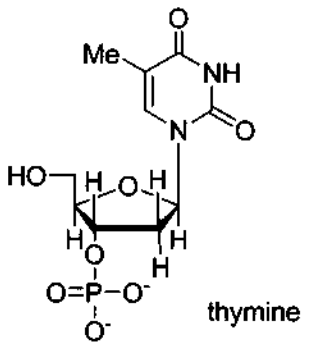
The double helix of DNA, the code of life, comprises two base pairs: adenine/thymine (A/T) and cytosine/guanine (C/G).

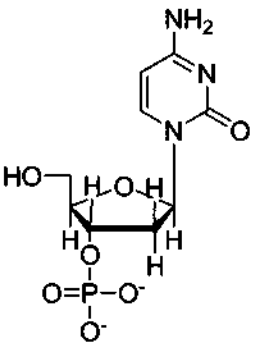


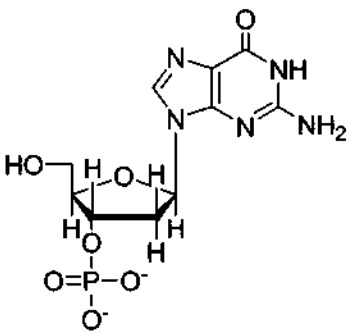


By adding the ubiquitous sugar fragments, we are left with nucleic acids contaning pyrimidine bases, including cytosine, thymine, and uracil and purine bases such as adenine and guanine.

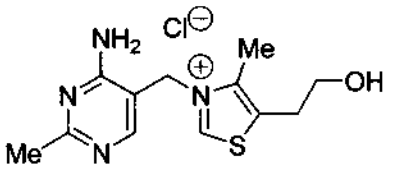






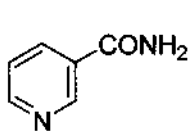


Thiazoles also play a prominent role in nature. For example, the thiazolium ring present in vitamin B_1 serves as an electron sink and its coenzyme form is important for the decarboxylation of α-keto-acids. The left-hand fragment of vitamin B_1 is an aminopyrimidine.

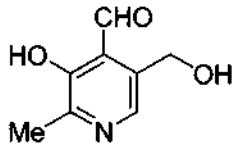


Vitamin B_1

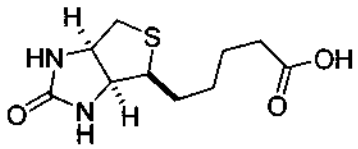
Vitamin B_5 (nicotinic acid amide) and vitamin B_6 (pyridoxal) are pyridine-based molecules, whereas vitamin B_7 (biotin) is a bi-heterocycle fusing reduced imidazole and thiophene.



vitamin B_5 (nicotinic acid amide)



vitamin B_6 (pyridoxal)



vitamin B_7 (biotin)

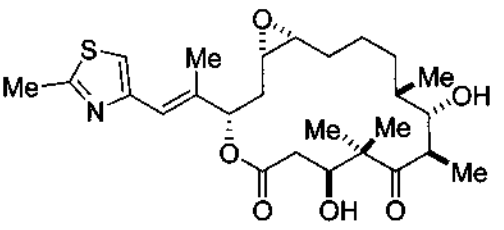
1.4 Importance of Heterocycles in Drug Discovery

It will be evident from the ensuing chapters that heterocycles play an extremely important role in drug discovery, in general, and in medicinal chemistry, in particular. Heterocycle-containing drugs are found in all therapeutic areas including cardiovascular and metabolic diseases, central nervous system (CNS), anti-cancer, anti-inflammatory, anti-ulcer, anti-infective drugs, and so on.

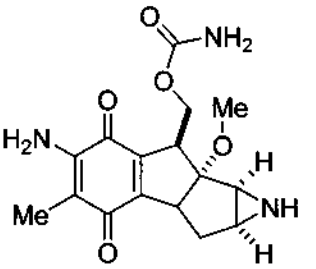
1.4.1 Five-Membered Heterocycles with One Heteroatom

Three-membered heterocycles are usually not fragments of drugs because they are reactive toward nucleophiles in physiological environments. Cancer

drugs such as epothilone and mitomycin are exceptions rather than the rules. The epothilones have shown their eminent cytotoxic activity against tumor cells, taxol-like mitose inhibition and toxicity against multiple drug-resistant tumor cell lines. On the other hand, mitomycin C is isolated from a strain of bacteria called *Streptomyces lavendulae*. It is a chemotherapy agent because of its anti-tumor properties. It is indicated as a useful therapeutic agent in combination with other anticancer drugs for the treatment of disseminated adenocarcinoma of the pancreas and the stomach.

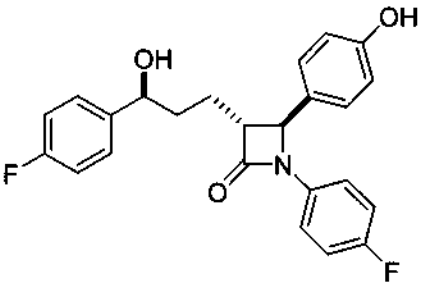


epothilone A



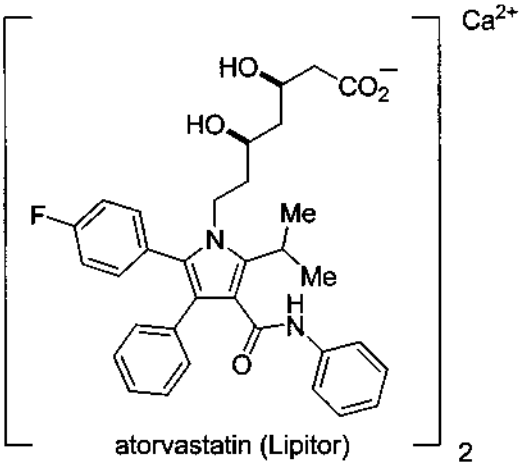
mitomycin C

Not many drugs contain four-membered heterocycles either. The best-known drug containing an azetidine-ring is Schering-Plough's ezetimibe (Zetia). Launched in 2002 as a cholesterol absorption inhibitor, its mechanism of action is the inhibition of the Nieman–Pick C1-like 1 (NPC1L1) protein.

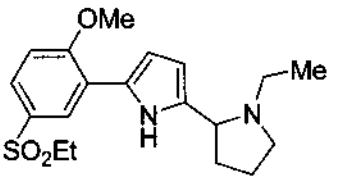


ezetimibe (Zetia), NPC1L1 inhibitor

Just as in life, five-membered heterocycles are of utmost importance to drug discovery. The most conspicuous of all is probably atorvastatin (Lipitor), an HMG-CoA inhibitor. Another bioactive pyrrole shown below is an antipsychotic agent.

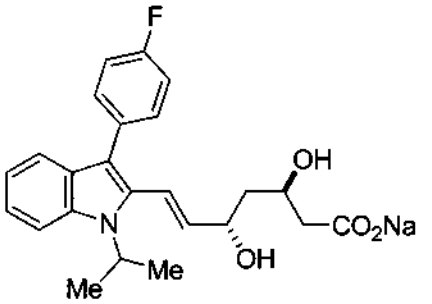


atorvastatin (Lipitor)



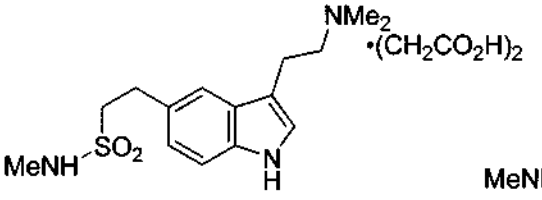
antipsychotic

Many drugs contain the indole-ring as their core structures. Fluvastatin sodium (Lescol) is an HMG-CoA reductase inhibitor.

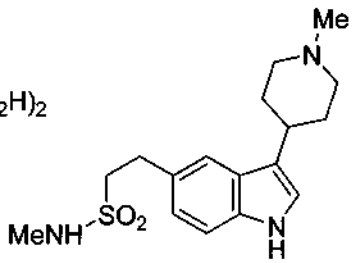


fluvastatin sodium (Lescol)

In addition, sumatriptan succinate (Imitrex), a serotonin receptor (5-HT_{1B1D}) agonist, is used to treat migraines. And naratriptan (Naramig) is a "me-too," indole-containing anti-migraine drug on the market.

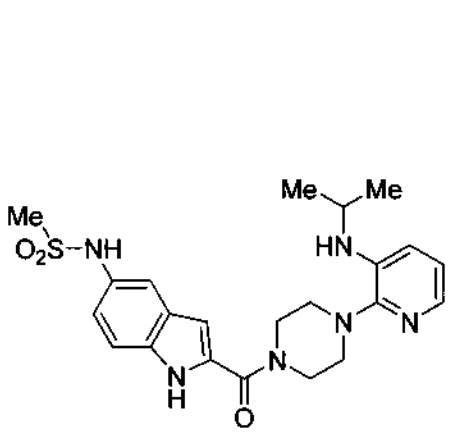


sumastriptan (Imitrex)

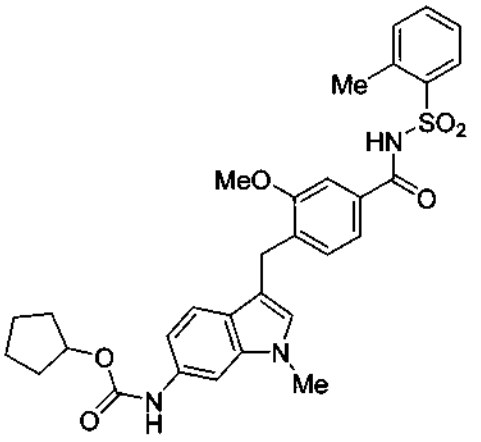


naratriptan (Naramig)

Furthermore, delavirdine (Rescriptor) is a novel HIV-1 reverse transcriptase inhibitor for HIV-positive individuals and zafirlukast (Accolate) is an antiasthma drug.

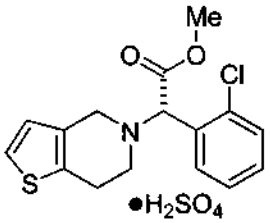


delavirdine (Rescriptor)



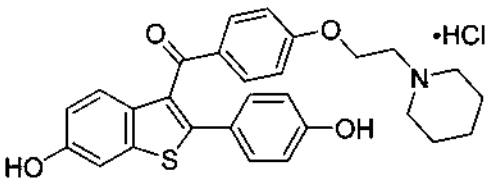
zafirlukast (Accolate)

Bristol-Myers Squibb's thiophene-containing clopidogrel (Plavix) inhibits platelet aggregation induced by adenosine diphosphate (ADP), a platelet activator that is released from red blood cells, activated platelets, and damaged endothelial cells. Clopidogrel, launched in 1993, achieved great commercial success. But its mechanism of action (MOA) was not elucidated until 1999: through the antagonism of the P2Y12 purinergic receptor and prevention of binding of ADP to the P2Y12 receptor by its active metabolite. Therefore, clopidogrel is a *bona fide* pro-drug.



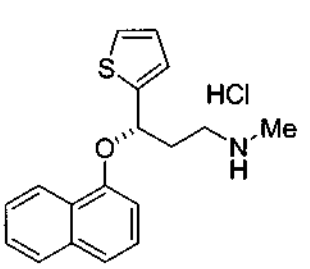
clopidogrel (Plavix)

Eli Lilly's raloxifene (Evista) is a selective estrogen receptor modulator (SERM) indicated for osteoporosis and breast cancer. Its core structure is a benzothiophene.

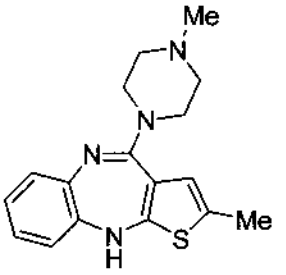


raloxifene (Evista)

Thiophene seems to be very popular in Li Lilly drugs. Its dual selective serotonin and norepinephrine reuptake inhibitor (SSNRI) for depression, duloxetine (Cymbalta), contains a thiophene. And its atypical antipsychotic drug olanzapine (Zyprexa) has a fused thiophene as its core structure.



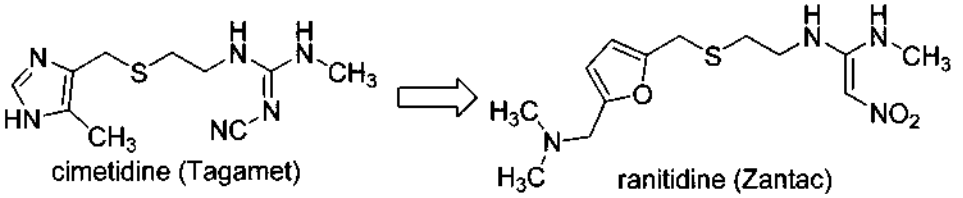
duloxetine (Cymbalta)



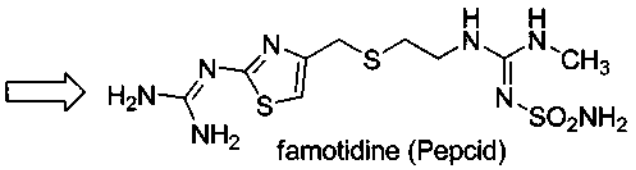
olanzapine (Zyprexa)

1.4.2 Five-Membered Heterocycles with Two Heteroatoms

Histamine-2 (H_2) receptor antagonists as anti-ulcer drugs best showcased the versatility of heterocycles in drug discovery. Marketed in the United States in 1977, SmithKline & French's cimetidine (Tagamet) became the first blockbuster drug ever in medical history in 1985. Transforming the imidazole ring into the dimethylamino-furan in combination with replacing cyanoguanidine with nitrovinyl guanidine gave rise to ranitidine (Zantac). Later on, Yamanouchi arrived at famotidine (Pepcid) using guanidinothiazople as its core structure and sulfamoyl-amidine as its side chain. All of these drugs went on to become blockbuster drugs.

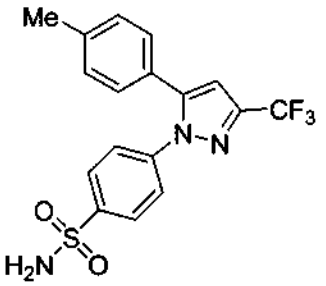


cimetidine (Tagamet) ranitidine (Zantac)



famotidine (Pepcid)

Anti-inflammatory cyclooxygenase-2 (COX-2) selective inhibitor celecoxib (Celebrex) has the tri-substituted pyrazole as its core structure.

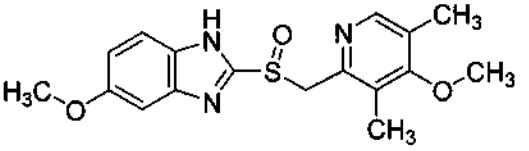


celecoxib (Celebrex)

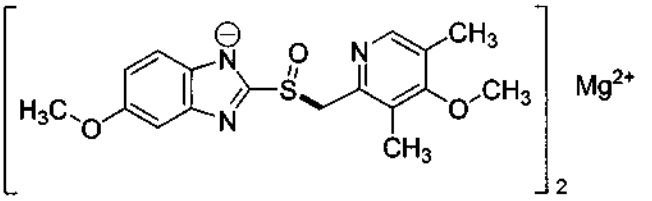
1.4.3 Six-Membered Heterocycles with One Heteroatom

As we mentioned in Section 1.2, pyridine has an additional lone pair of electrons at the nitrogen atom after it contributes a pair of two electrons to make up the 6 π-electrons for aromaticity. These lone pair electrons are responsible for much of pyridine's unique physical and chemical properties.

One prominent example is AstraZeneca's H^+/K^+-ATPase inhibitor, pyridine-containing omeprazole (Prilosec) and its enantiomerically pure follow-up esomeprazole (Nexium).

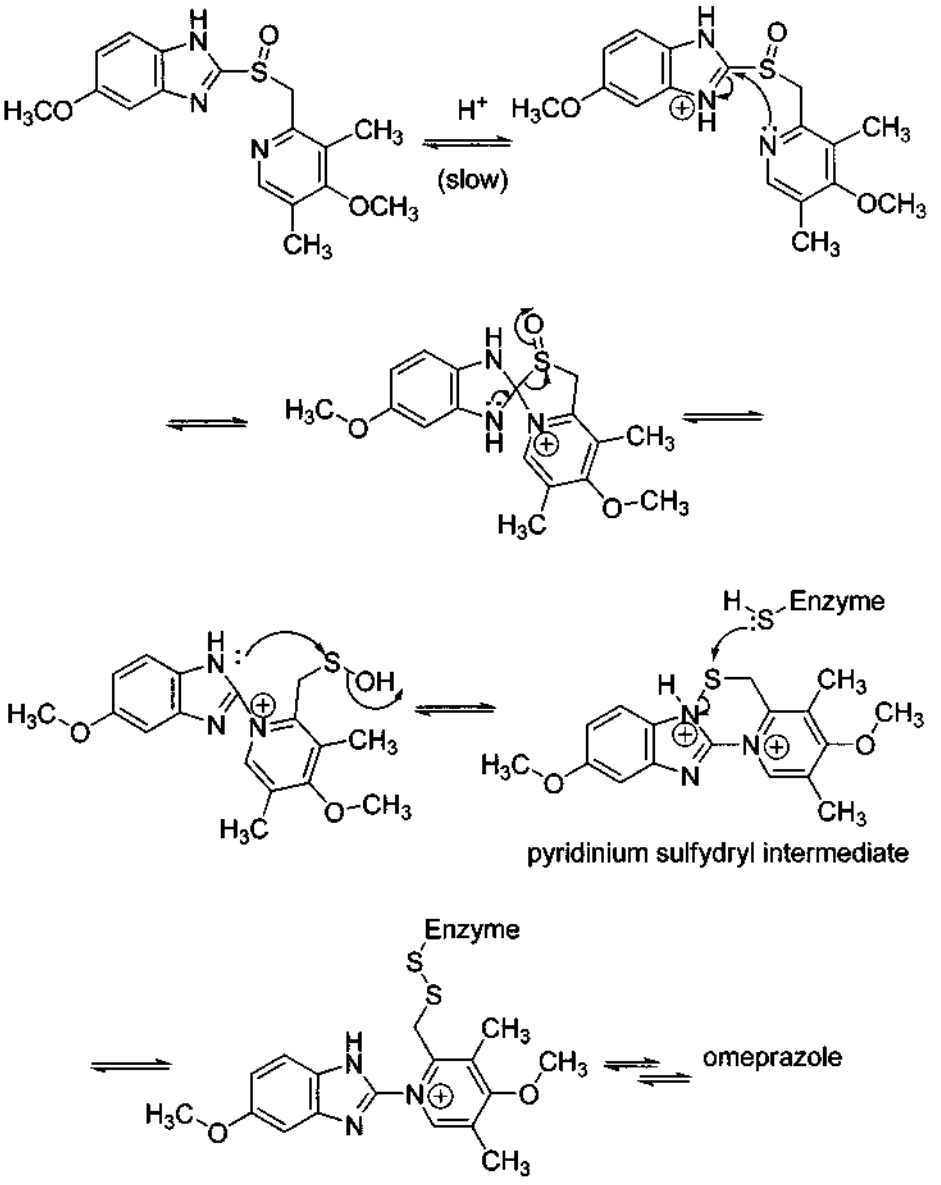


omeprazole (Prilosec)



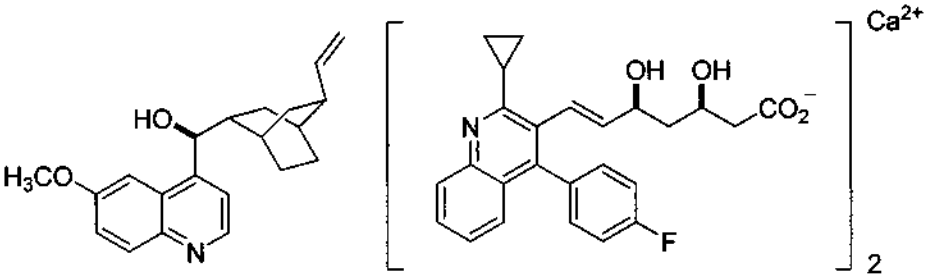
esomeprazole (Nexium)

They are both pro-drugs and their MOA is through the "omeprazole cycle," initiated by pyridine's lone pair of electrons. In fact, pyridine's lone pair of electrons could be viewed as the engine that propels the "omeprazole cycle." The pyridinium sulfydryl intermediate is the actual inhibitory species.



There are quinoline-containing drugs from both nature and synthesis. Natural product drugs may be exemplified by quinine, an anti-malarial drug used for three centuries. Synthetic quinoline-containing drugs are

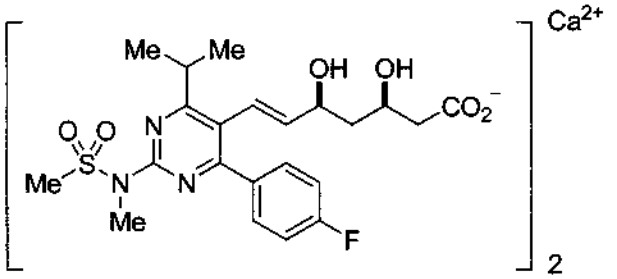
represented by pitavastatin calcium (Livalo), Sankyo's HMG-CoA inhibitor for lowering cholesterol.



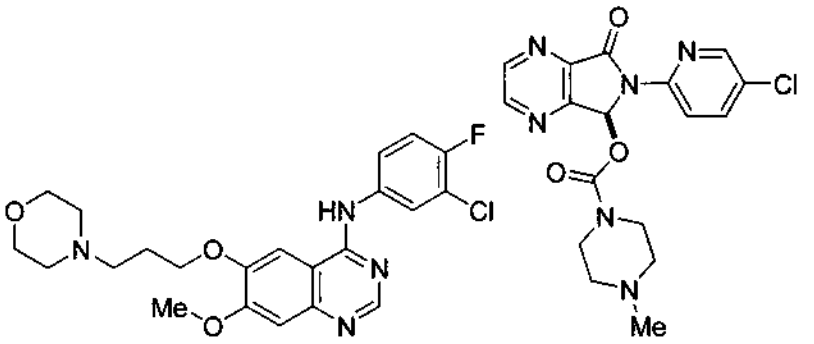
quinine pitavastatin calcium (Livalo)

1.4.4 Six-Membered Heterocycles with Two Heteroatoms

The best-known pyrimidine-containing drug of today is probably AstraZeneca's rosuvastatin (Crestor) as an HMG-CoA redutase inhibitor for lowering cholesterol. By choosing a sulfonamide substituent, a unique intellectual property position was achieved.



rosuvastatin calcium (Crestor)

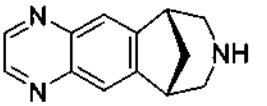


gefitinib (Iressa) eszopiclone (Lunesta)

AstraZeneca's gefitinib (Iressa)'s core structure is a quinazoline. It is an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) indicated for the treatment of cancers. Several other protein kinase inhibitors also used the quinazoline ring as their core structure. They include OSI's erlotinib (Tarceva) and GSK's lapatinib (Tykerb).

Sepracor's eszopiclone (Lunesta) contains a pyrazine ring. It is a $GABA_A$ receptor agonist for the treatment of insomia.

Finally, Pfizer's varenicline (Chantix) used a fused quinoxaline ring. It is an $\alpha 4\beta 2$ nicotinic receptor partial agonist for smoking cessation.



varenicline (Chantix)

In this section, only a small portion of marketed drugs are shown to illustrate the importance of hetereocyclic chemistry in drug discovery. Many drugs containing saturated heterocycles, heterocycles with more than two heteroatoms, and non-heterocycles. In the ensuing chapters, the most popular types of heterocycles in drug discovery are reviewed for their physical and chemical properties, their constructions in the context of medicinal chemistry, and their potential liabilities as drugs when applicable.