

Edited by **Jie Jack Li**

Heterocyclic Chemistry in Drug Discovery



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Jie Jack Li

Bristol-Myers Squibb Company

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Dedicated To

Li Jing Ya, Li (Zhen) Cheng-Cheng, Li Chun, and Li Lei

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Preface

There is a disconnection in our education of organic chemists whose inspiration is to work on drug discovery in either industry or academia. The traditional textbooks are no longer adequate in preparing our undergraduate and graduate students in entering the pharmaceutical industry. The original philosophy was that one could learn medicinal chemistry “on the job” after a strong synthetic chemistry background.

In this book, attempts have been made to fuse the two fields: heterocyclic chemistry and drug discovery. I hope it will give our undergraduate and graduate students a “jump-start” in this competitive employment market. As a matter of fact, there is no sacrificing of a solid education in “authentic” heterocyclic chemistry here. All aspects of reactions, reactivity, and mechanisms are still intact, except they are discussed in the context of medicinal chemistry and drug discovery.

I welcome your critique! Please send your comments to me directly: lijiejackli@hotmail.com.



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Chapter 1 Introduction

Jie Jack Li

1.1 Nomenclature of Heterocycles

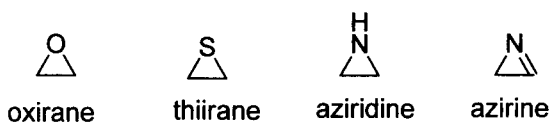
What's in a name? That which we call rose by any other name would smell as sweet. [William Shakespeare, *Romeo and Juliet* (II, ii, 1–2)].

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.

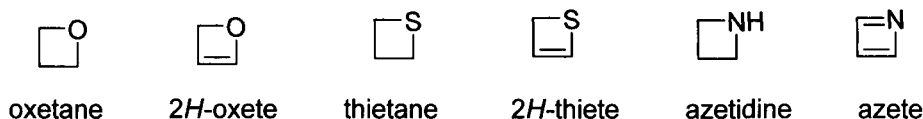
Heterocycles, as the name suggests, are cyclic compounds containing one or more heteroatoms such as N, O, S, P, Si, B, Se, and Se. They may be further divided into aromatic heterocycles and saturated heterocycles. This book will focus largely on aromatic heterocycles. Saturated heterocycles represent 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.

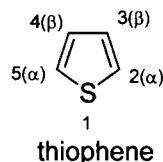
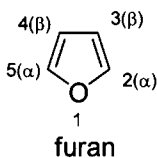
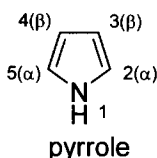
The most frequently encountered three-membered heterocycles are oxirane, thiirane, aziridine, and azirine.



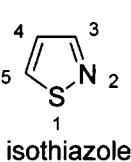
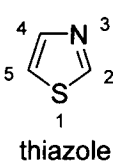
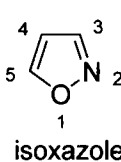
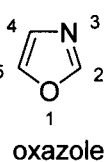
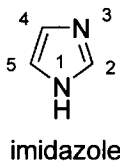
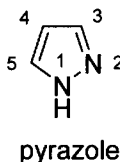
Four-membered heterocycles include oxetane, 2*H*-oxete, thietane, 2*H*-thiete, azetidines, and azete. In the field of drug discovery, oxetanes and azetidines are more and more incorporated into drugs for modulating biological and physical properties as well as for expanding intellectual properties space.



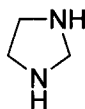
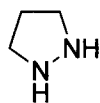
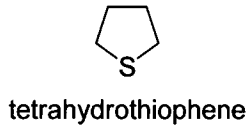
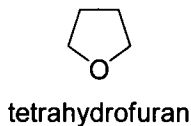
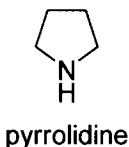
Five- and six-membered heterocycles are of utmost importance to both life and drug discovery. The most common five-membered heterocycles with one heteroatom are pyrrole, furan, and thiophene.



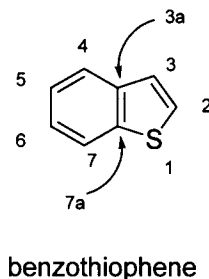
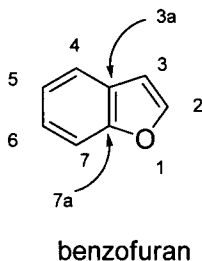
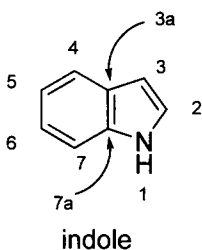
Popular five-membered heterocycles with two heteroatoms include pyrazole, imidazole, oxazole, isoxazole, thiazole, and isothiazole.



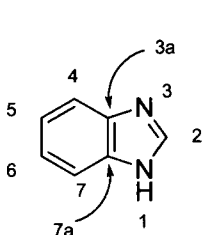
All these aromatic heterocycles have their counterparts in the corresponding saturated heterocycles. Among those, pyrrolidines, tetrahydrofurans, and oxazolidines are more frequently encountered in drug discovery.



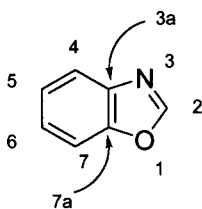
pyrazolidine imidazolidine oxazolidine isoxazolidine thiazolidine isothiazolidine



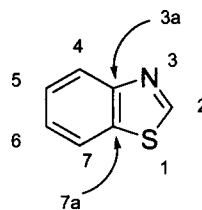
Some of the important benzene-fused five-membered heterocycles are indole, benzofuran, benzothiophene, benzimidazole, benzoxazole, and benzothiazole. The numbering of these heterocycles is shown below:



benzoimidazole

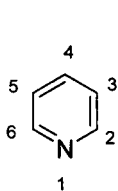


benzoxazole

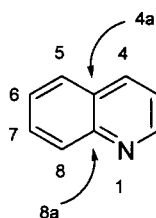


benzothiazole

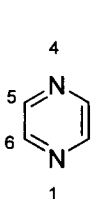
Chief among the six-membered heterocycles, pyridine and its benzene-fused derivative quinoline are most ubiquitous. Pyrazine and its benzene-fused analogue, quinoxaline, also play an important role in heterocyclic chemistry.



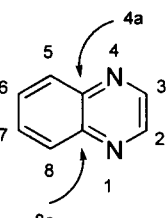
pyridine



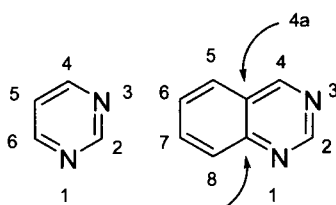
quinoline



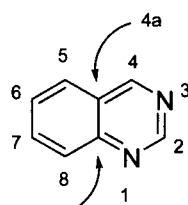
pyrazine



quinoxaline

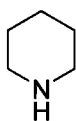


pyrimidine

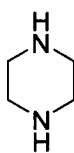


quinazoline

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

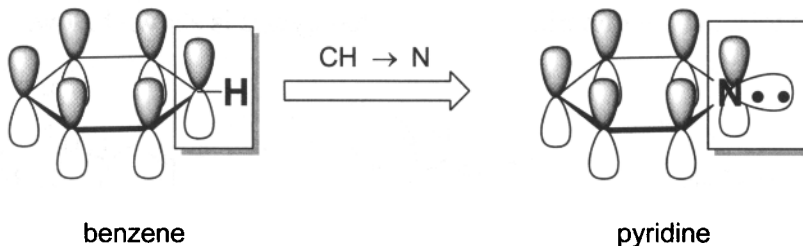


piperidine

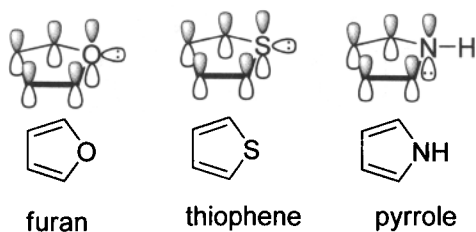


piperazine

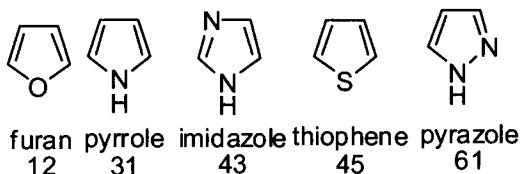
1.2 Aromaticity of Heterocycles

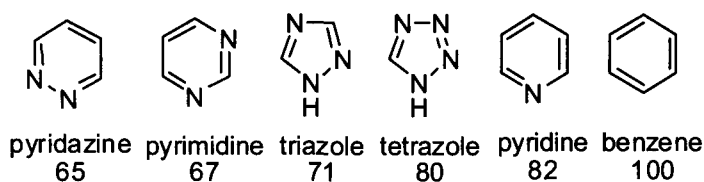


The major thrust of this book is aromatic heterocycles. According to Hückel's rule of aromaticity, a cyclic ring molecule is aromatic when the number of its π -electrons equals $4n + 2$, where n is zero or any positive integer. The most common aromatic compound is benzene, which has $4 + 2 = 6$ π -electrons. 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.



The relative aromaticity of common heterocycles is shown below:

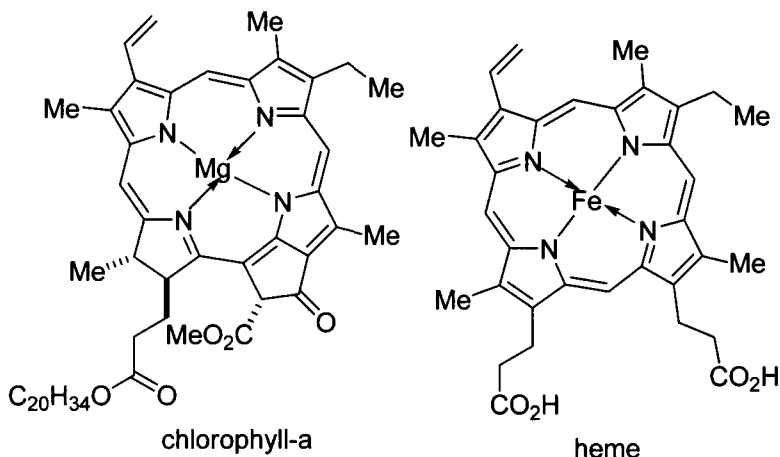




Pyrrole, also an aromatic heterocycle with 6 π -electrons, is probably the most unique of all among the aromatic heterocycles. Different from furan and thiophene, the nitrogen atom on the pyrrole ring only has one lone pair of electrons, which both contributed to the 6 π -electrons to achieve the aromaticity. 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 inductive 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.

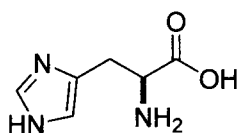


To begin with, chlorophyll is porphyrin (a tetramer of pyrrole) surrounding a magnesium atom. It is the molecule that absorbs sunlight and

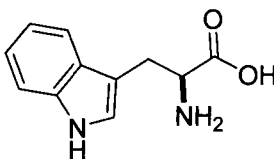
uses its energy to synthesize carbohydrates from CO_2 and water. This process, known as photosynthesis, is the basis for sustaining the life processes of all plants.

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.

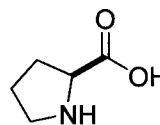
Several amino acids, the building block of life, are made of heterocycles. Histidine has an imidazole; tryptophan has an indole; yet proline has a pyrrolidine.



histidine

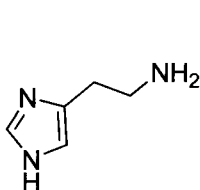


tryptophan

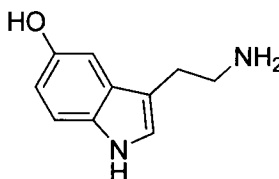


proline

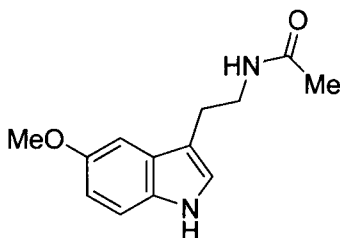
Heterocycles also play an important role as endogenous neurotransmitters. Chief among them are serotonin and histamine, which are of paramount importance in modulating the body's physiological and biochemical processes.



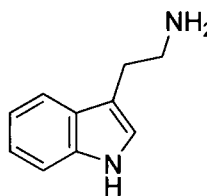
histamine



serotonin



melatonin



tryptamine