



Introduction to Heterocyclic Chemistry

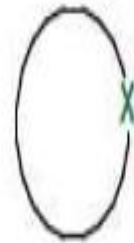
Assist. Prof. Dr. Ayad MR Raauf

Introduction

- Heterocycles contain one or more heteroatoms in a ring



carbocycle



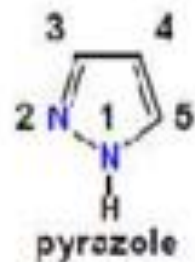
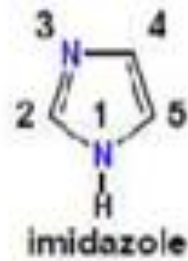
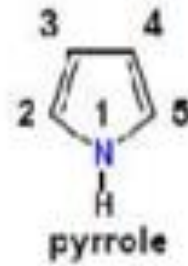
heterocycles - X, Y, Z are usually O, N or S

- Heterocycles are important and a large proportion of natural products contain them
- Many pharmaceuticals and agrochemicals contain at least one heterocyclic unit

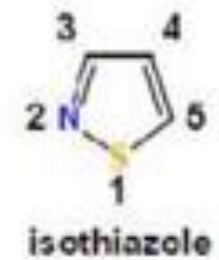
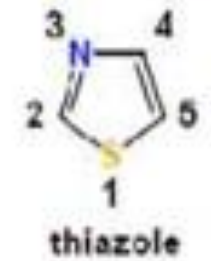
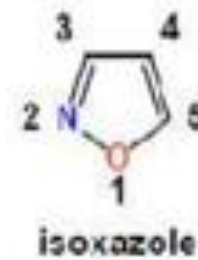
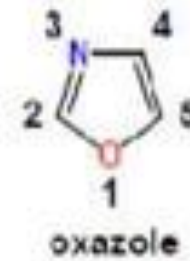
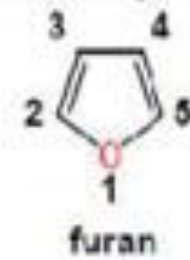
Classification – Unsaturated / Saturated

Classification – Aromatic Five-Membered

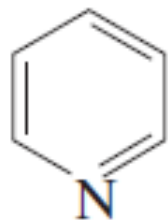
Isoelectronic carbocycle



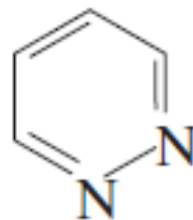
Heterocycles



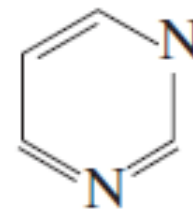
Classification – Aromatic Six-Membered



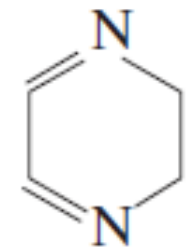
Pyridine



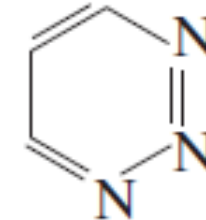
Pyridazine



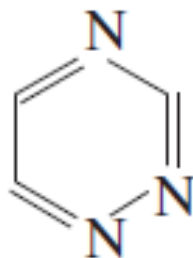
Pyrimidine



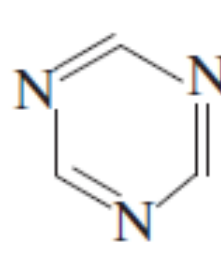
Pyrazine



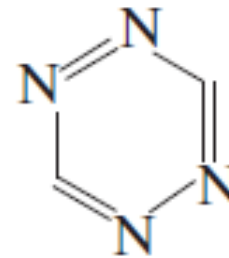
1,2,3-Triazine



1,2,4-Triazine

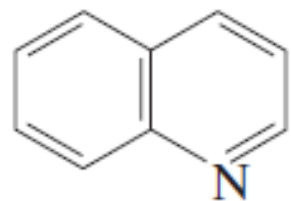


1,3,5-Triazine

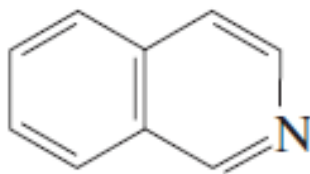


1,2,4,5-Tetrazine

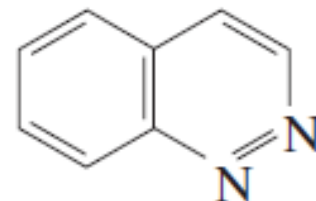
There are fused-ring system aromatic heterocycles.



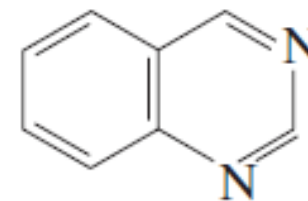
Quinoline



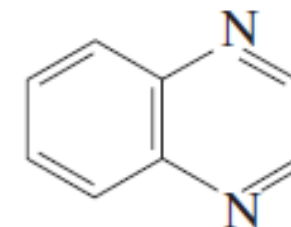
Isoquinoline



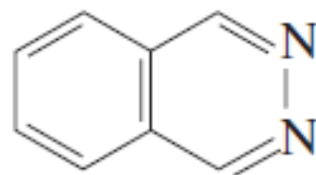
Cinnoline



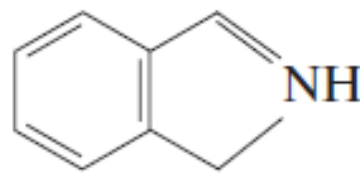
Quinazoline



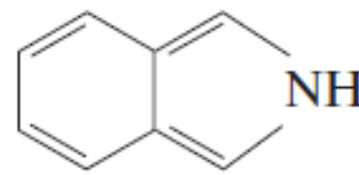
Quinoxaline



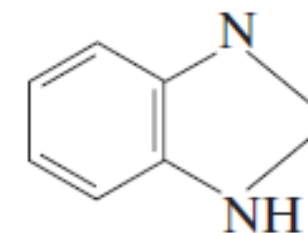
Phthalazine



Indole

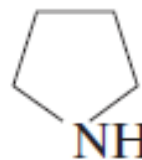


Isoindole

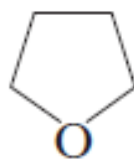


Benzimidazole

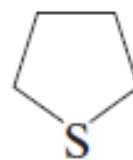
Besides the above fully unsaturated aromatic heterocycles, there are other nonaromatic small-ring heterocyclic compounds that may be either partially or fully saturated.



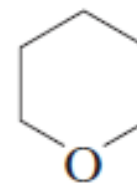
Pyrrolidine



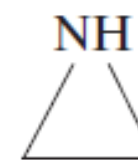
Tetrahydrofuran



Thiolan



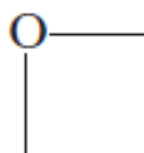
Pyran



Aziridine

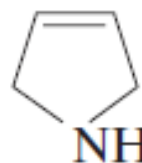


Oxiran

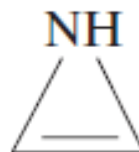


Oxetan

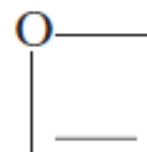
Fully saturated nonaromatic heterocycles



Dihydropyrrole



Azirine



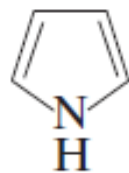
Oxetene

Partially saturated nonaromatic heterocycles

AROMATIC HETEROCYCLIC COMPOUNDS (5-atom, six- π -electron aromatic heterocycles)

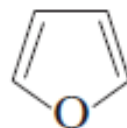
Structure of pyrrole, furan, and thiophene

The simplest of the five-membered heterocyclic compounds are **pyrrole**, **furan**, and **thiophene**, each of which contains a single heteroatom.



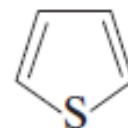
I

Pyrrole



II

Furan



III

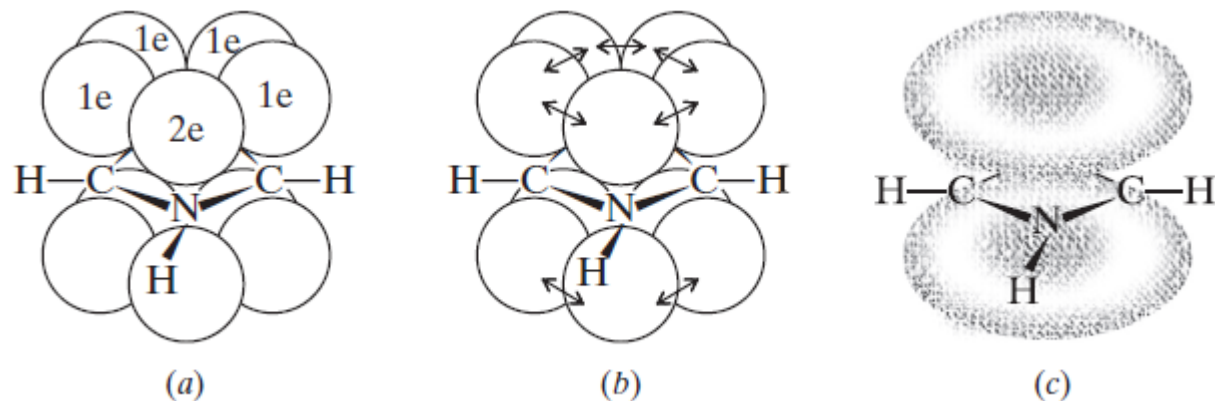
Thiophene

Heats of combustion indicate resonance stabilization to the extent of 22–28 kcal/mol; somewhat less than the resonance energy of benzene (36 kcal/mol)

On the basis of these properties, pyrrole, furan, and thiophene must be considered *aromatic*.

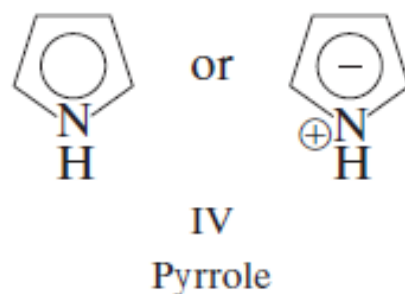
Structure of pyrrole, furan, and thiophene

Let us look at the orbital picture of one of these molecules, pyrrole. Each atom of the ring, whether carbon or nitrogen, is held by a σ bond to three other atoms. In forming these bonds, the atom uses three sp^2 orbitals, which lie in a plane and are 120° apart. After contributing one electron to each σ bond, each carbon atom of the ring has left *one* electron and the nitrogen atom has left *two* electrons; these electrons occupy p orbitals. Overlap of the p orbitals gives rise to π clouds, one above and one below the plane of the ring; the π clouds contain a total of six electrons, the *aromatic sextet*.



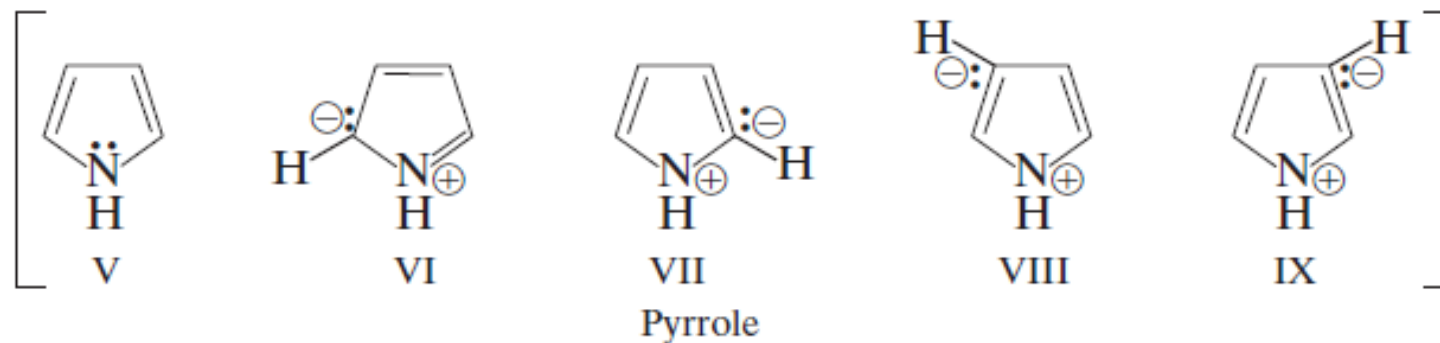
Pyrrole molecule. (a) Two electrons in the p orbital of nitrogen; one electron in the p orbital of each carbon. (b) Overlap of the p orbitals to form π bonds. (c) Clouds above and below the plane of the ring; a total of six π electrons, the aromatic sextet.

It thus appears that pyrrole is better represented by IV,



in which the circle represents the aromatic sextet.

What does IV mean in terms of conventional valence-bond structures? Pyrrole can be considered a hybrid of structures V-IX. Donation of electrons to the ring by



nitrogen is indicated by the ionic structures in which nitrogen bears a positive charge and the carbon atoms of the ring bear a negative charge.

Furan and thiophene have structures that are analogous to the structure of pyrrole. Where nitrogen in pyrrole carries a hydrogen atom, the oxygen or sulfur carries an unshared pair of electrons in an sp^2 orbital. Like nitrogen, the oxygen or



sulfur atom provides two electrons for the π cloud; as a result these compounds, too, behave like extremely reactive benzene derivatives.

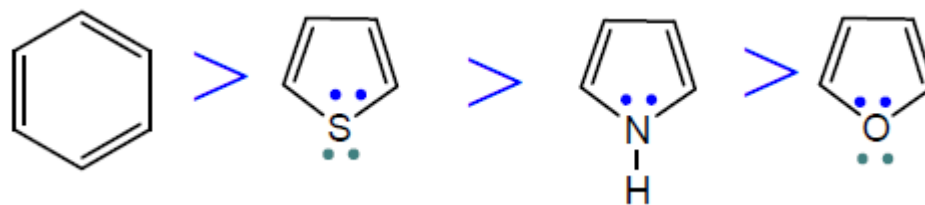


Structure and Aromaticity

Pyrrole, furan, and thiophene are aromatic because:

1) they fulfill the criteria for aromaticity, the extent of delocalization of the nonbonding electron pair is decisive for the aromaticity, thus the grading of aromaticity is in the order of: **furan < pyrrole < thiophene < benzene**. This order is consistent with the order of electronegativity values for oxygen (3.44), nitrogen (3.04) and thiophene (2.56).

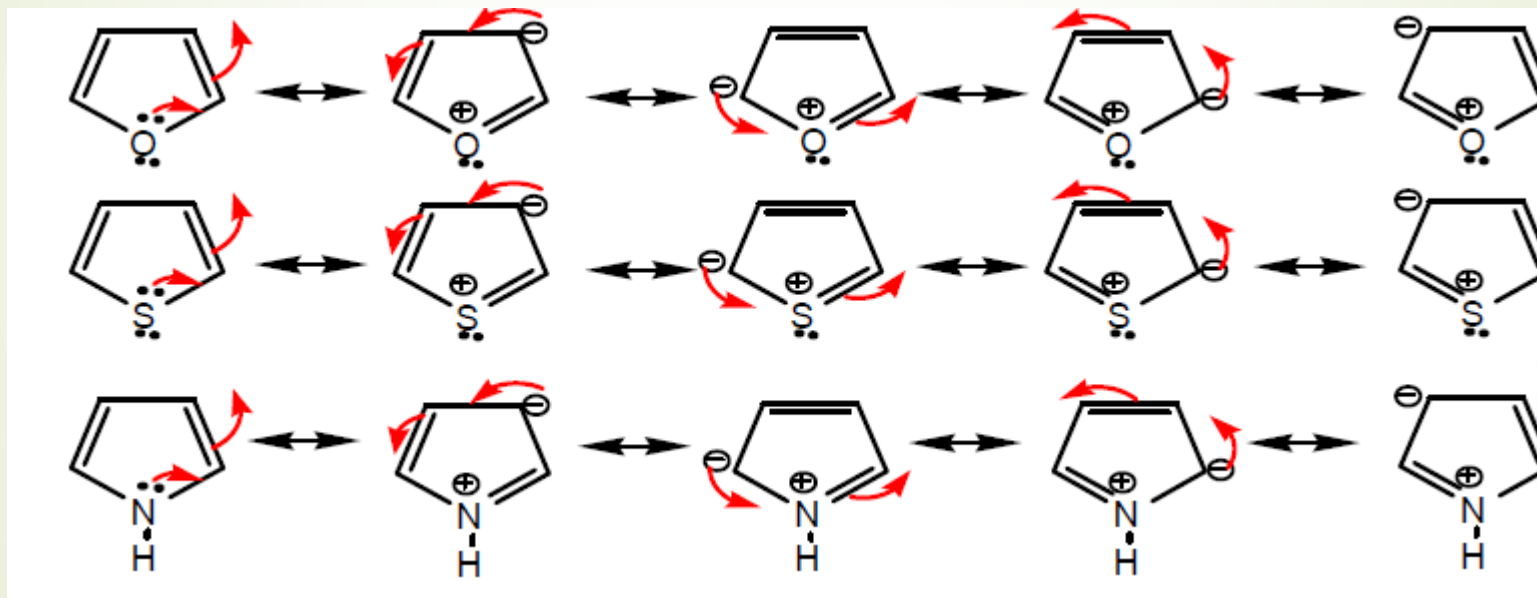
Order of aromaticity





Structure and Aromaticity

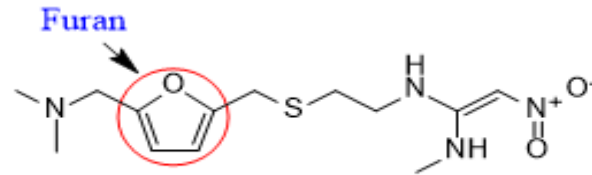
2) They tend to **react by electrophilic substitution** due appearance of **-ve charge** on carbon atoms (2 & 3) due to delocalization as shown in the following **resonance structures**



In comparison to benzene the order of reactivity in electrophilic substitution is as follows:

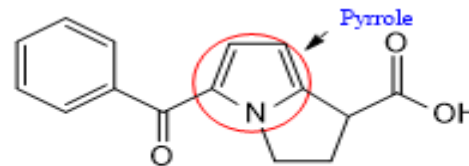


Bioactive Furans, Pyrroles and Thiophenes



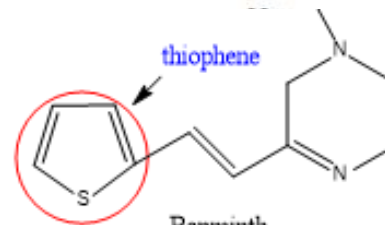
Ranitidine

- Ranitidine (Zantac®, GSK) is one of the biggest selling drugs in history. It is an H₂-receptor antagonist and lowers stomach acid levels – used to treat stomach ulcers



Ketorolac

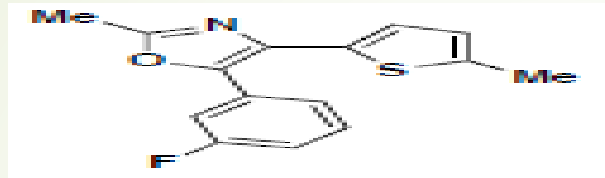
- Ketorolac (Toradol®, Roche) is an analgesic and anti-inflammatory drug



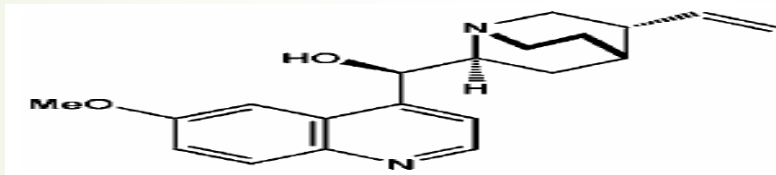
Banminth

- Pyrantel (Banminth®, Phibro) is an anthelmintic agent and is used to treat worms in livestock

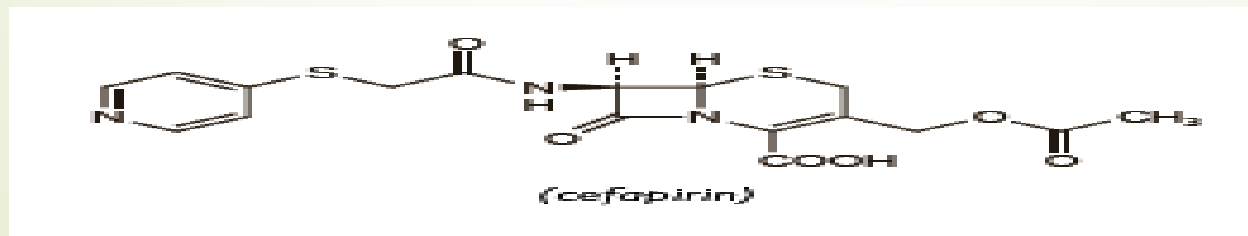
Give the systematic name for the following heterocyclic ring of drugs.



- a. oxazole b. thiazole c. pyrazole d. imidazole

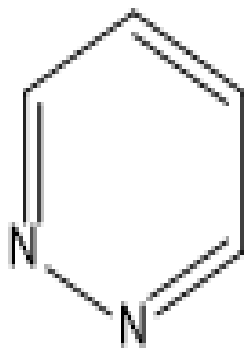


- a. cinnoline b. isoquinoline c. quinoline d. isoindole

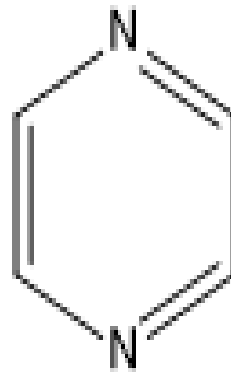


- a. pyridine b. furane c. thiophine d. pyrrole

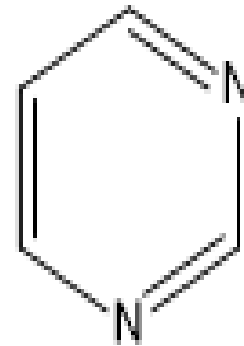
Which of the following compounds has correct name (pyridazine)?



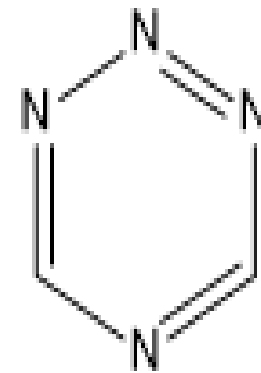
a.



b.



c.



d.

_____ is not a heterocyclic aromatic compound.

- a) Furan b) Pyrrole c) Thiophene **d) Naphthalene**

_____ is a 6 membered heterocyclic compound.

- a) Furan b) Pyrrole c) Thiophene **d) Pyridine**

. Molecular formula of pyrrole is _____

- a) C₄H₅N** b) C₄H₄N c) C₅H₅N d) C₆H₆N

Which of the following is a not a five membered ring?

- a) Pyridine
b) Pyrrole
c) Furan
d) Thiophene