**Syllabus for Heterocyclic compounds second course for pharmacy colleage**

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| **Subject** | **Hours** |
| Heterocyclic system: Classes of heterocyclic systems; general structures; properties; Occurrence in nature and in medicinal products. | **5** |
| Five-membered ring heterocyclic compounds: pyrrole; furan and thiophen. | **3** |
| Source of pyrrole, furan and thiophen. | **2** |
| Electrophilic substitution in pyrrole, furan and thiophen: Reactivity and orientation. | **5** |
| Six-membered ring heterocyclic compounds: Structure & reactions of pyridine. | **4** |
| Saturated five-membered heterocyclic compounds. | **6** |
| Heterocyclic of five & six member rings with two & three heteroatoms. | **5** |

**Recommended Reading :**

**Text Book**

*Heterocyclic Chemistry, Morrison &Boyd 7th edition*

**Other Books and References**

\* Heterocyclic Chemistry, R. Gupta, M. Kumar, V. Gupta

\* Heterocyclic Chemistry, J. A. Joule, G. F. Smith

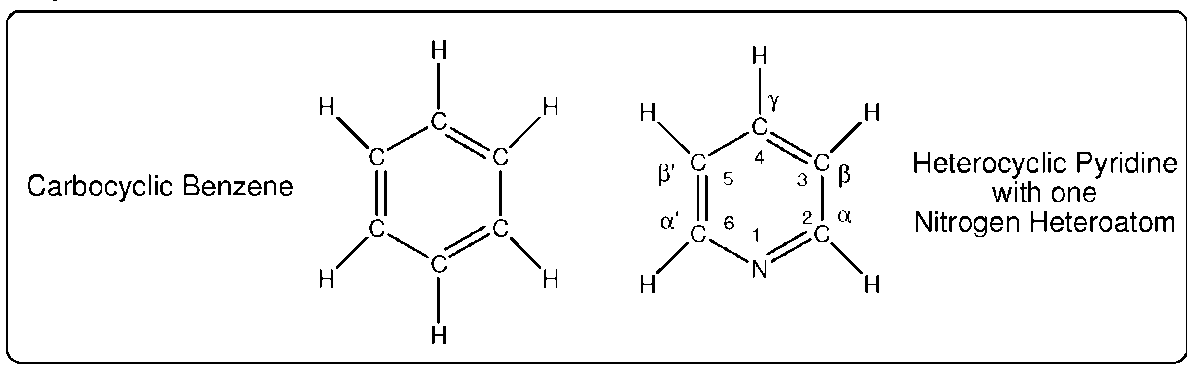
**Heterocyclic Compounds**

**Learning Objective :**

1. Heterocyclic System and correlation with Homocyclic system
2. Types of heterocyclic Molecules with Aromaticity .
3. Application in our life .

**Introduction :**

Cyclic compound having only carbons as the ring members, such as benzene are called carbocyclic compounds. As only carbon forms the backbone of the ring, it is also a homocyclic compound.



**Figure 1: Structure of Homocyclic Benzene and Heterocyclic Pyridine**

In contrast, cyclic compounds having at least one atom other than carbon as ring members, (e.g**. Pyridine** with nitrogen replacing one of the carbon atom) may be termed as heterocyclic compounds. These atoms are termed as heteroatoms. The structure of benzene and pyridine are provided in ( **figure 1)**

**Heterocyclic Compounds By definition :**

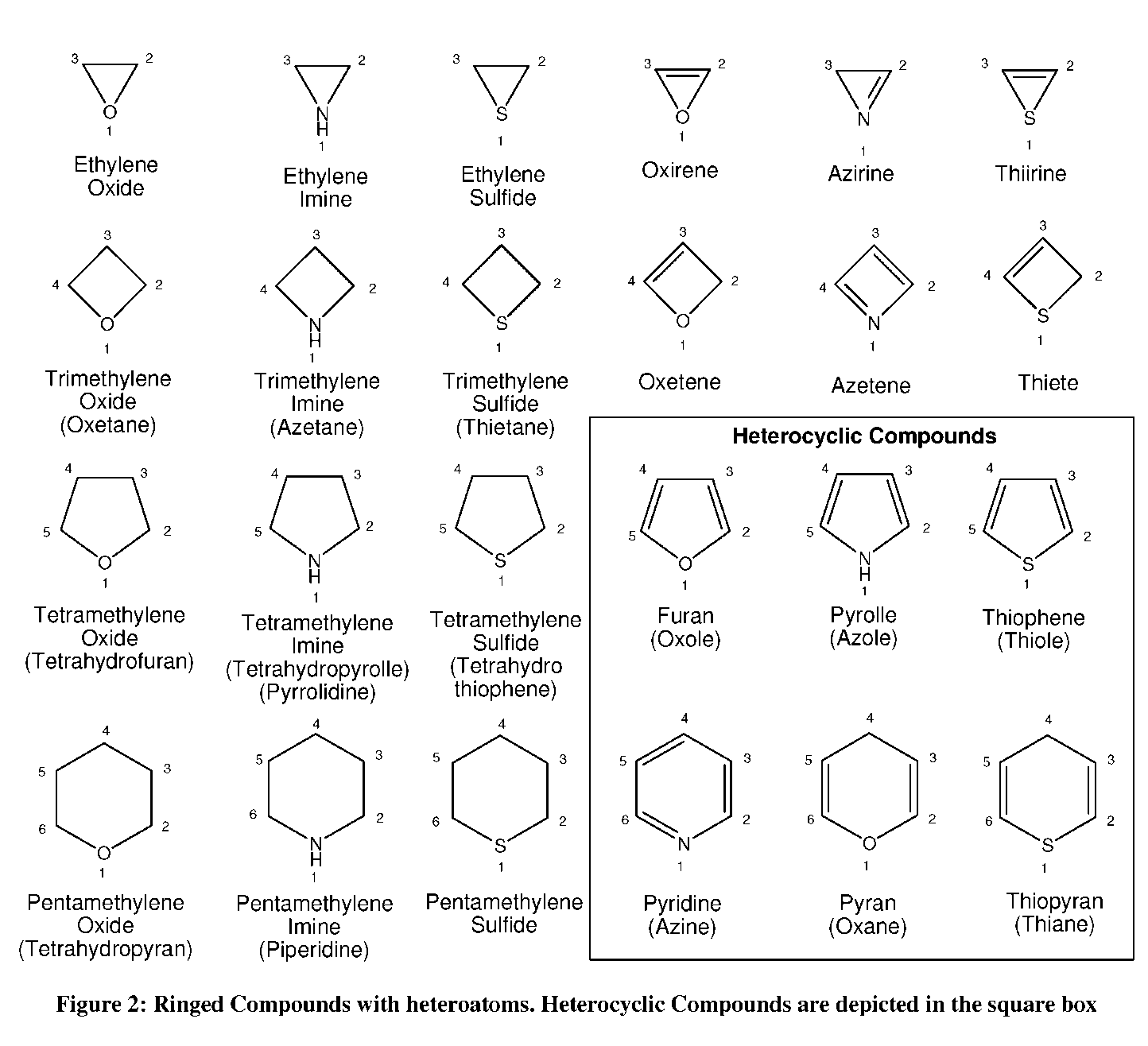
heterocyclic compounds are five and six membered ringed compounds, that contain at least one hetero-atom, relatively stable and show aromaticity. (However, other sources claim that aromaticity is not a prerequisite for defining heterocyclic compounds. But, we will stick to the textbook definition ).

So, let us check below the significance of the terms defined above:

1. **At least one heteroatom,**
2. **Five and Six Membered Rings,**
3. **Relatively Stable and**
4. **Show Aromaticity.**

1. **Heteroatom** Although any atom (other than carbon) can form the heterocyclic ring, **usually N, O, and S** are the heteroatoms found in nature, especially in biological macromolecules.
2. **Five and Six Membered Ringed** Structures Containing a Heteroatom . A ring system can be theoretically made up of 3, 4, 5, 6 or more ring members. Examples of such compounds containing one heteroatom is depicted in the **figure 2**. All compounds in the first 3 columns have **saturated carbon atoms and do not possess a conjugated bond system are not aromatic compounds**. The last 3 columns contain compounds that contain unsaturation, however not all of them are aromatic (as defined below).
3. **Stability** The 3 and 4 membered ring compounds however are not stable due to **the strain in the ring system.** Hence, by definition of heterocyclic compounds these compounds are not heterocyclic compounds.
4. **Aromaticity** Aromatic compounds should satisfy the following **4 conditions:**
5. A system of conjugated and delocalized pi bonds.
6. A planar molecule.
7. A ring system following Huckle’s rule, which requires( 4n+2 ) pi electrons in the ring system (where n=0,1,2,3…). So, aromaticity normally exists when n=2, 6, 10… pi electrons exist in the ring system. In special cases, a pair of pi electrons may be substituted by non-bonding, “n” electrons. Hence a conjugated bond system with 2, 6, or 10 pi or n electrons is a prerequisite for aromaticity.
8. A relatively stable structure

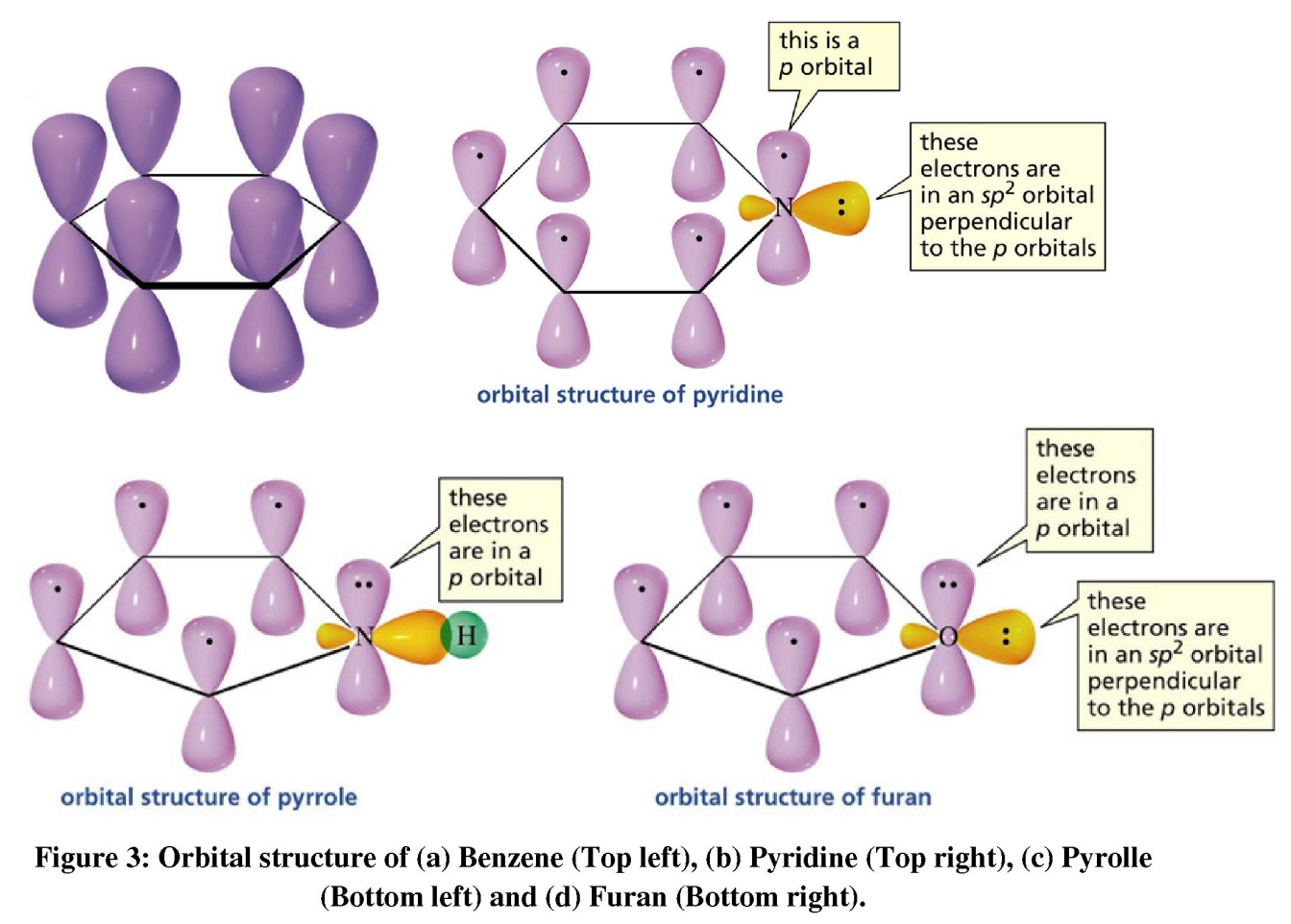
Hence, by definition, only compounds present in the box **in figure 2**, Furan, Thiophene, Pyrolle, Pyridine, Pyran and Thiopyran are heterocyclic compounds because they are 5 or 6 membered ring structures with at least one atom, relatively stable and show aromaticity.



Benzene is a typical aromatic compound which is planar, having a system of conjugated and delocalized pi bonds. It has a ring structure with 6 pi electrons forming 3 pi bonds and obeying the huckle rule (n=1, so 4n+2 = 6) as shown in the **figure 3**

By definition, all heterocyclic compounds have aromaticity.

Ex. in Pyridine as shown in **figure 3,** there are only 5 pi electrons of carbon, but endocyclic nitrogen contributes one electron to have 6 pi electrons needed for aromaticity. The lone-pair electrons in pyridine are held in a sp2 hybrid orbital perpendicular to the orbitals in the pi system, so they are not part of the pi system.



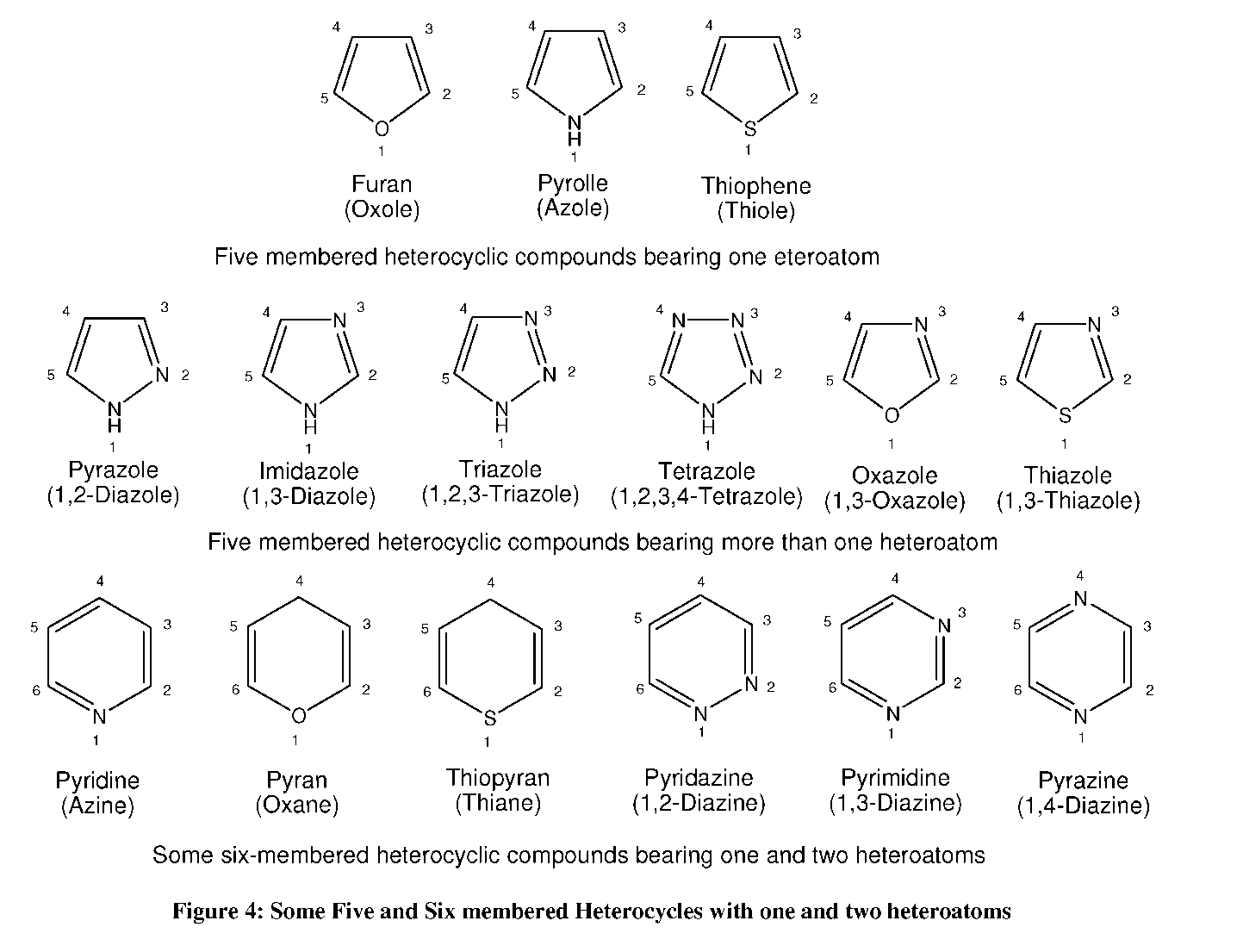
Heterocyclic Compounds with more than one heteroatom Some 5 and 6 membered ringed structures with one or two heteroatoms, that are relatively stable and possess aromaticity are depicted in the **figures 4.** By definition, these are heterocyclic compounds.

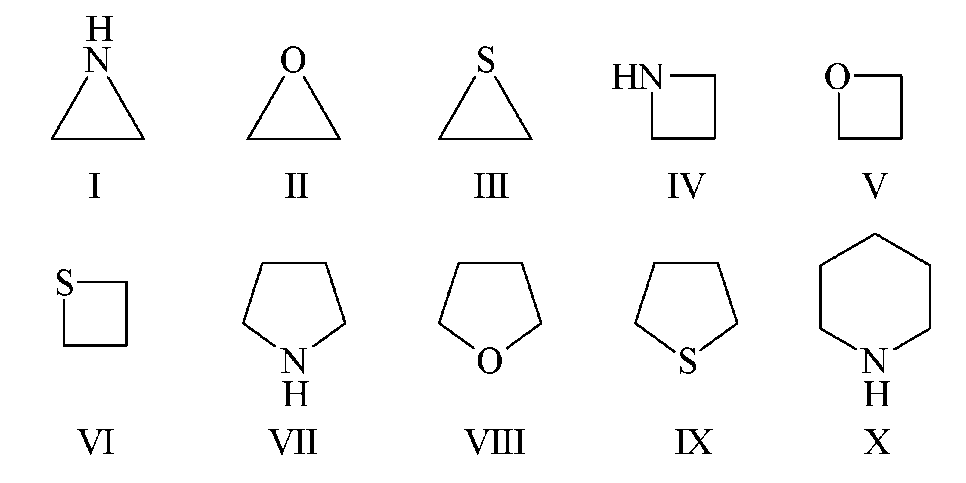
**Classification of Heterocyclic Compounds** :

Heterocyclic compounds may be classified into three types:

1. **Five Membered,**
2. **Six Membered and**
3. **Fused or Condensed Heterocyclic compounds**.

Five-membered heterocyclic compounds bearing one more heteroatom The five membered heterocyclic compounds containing one heteroatom is shown in the **figure 4**. In these cases, **oxygen, nitrogen and sulfur** with non-bonding lone pair of electrons contribute to conjugated pi bond system in 5 membered ring system and are therefore have stable aromatic structures, “**furan, pyrolle and thiophene**” respectively.

**Another way to classification of Heterocyclic Compounds :**

Heterocyclic compounds may be classified as aliphatic and aromatic heterocycles. The aliphatic heterocycles are the cyclic analogues of amines, ethers and thioethers and their properties are influenced by the ring strain. The three and four membered aliphatic heterocyclic rings are more strained and reactive compared to five and six membered rings. The common aliphatic heterocyclic compounds are **aziridine (I), oxirane (II), thiirane (III), azetidine (IV), oxetane (V), thietane (VI), pyrrolidine (VII), tetrahydrofuran (VIII), tetrahydrothiophene (IX) and piperidine (X)**

**Occurrence in Nature :**

Many heterocyclic compounds occur naturally and are actively involved in biology e.g., nucleic acids (purine and pyrimidine bases), vitamins (Thiamine B1, Riboflavin B2, Nicotinamide B3, Pyridoxol B6 and Ascorbic acid C), heme and chlorophyll, penicillins, cephalosporins, macrolides etc. The study of heterocyclic chemistry is a vast and expanding area of chemistry because of their applications in medicine, agriculture, photodiodes and other fields.

**Examples about Aromaticty ( Huckel Rule)**



**Pyrrole, Furan and Thiophene :**

The simplest of five membered heterocyclic compounds are Pyrrole (1) , furan(2) and thiophene (3) .each of which contain a single hetero atom.