**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 :**

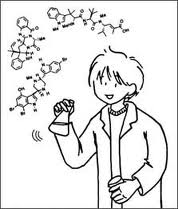
**Text Book**

*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

[](http://www.google.com.sa/url?sa=i&rct=j&q=&esrc=s&frm=1&source=images&cd=&cad=rja&docid=mYk7VOFFauQofM&tbnid=0Sg2JXevnu0PTM:&ved=0CAUQjRw&url=http://chemistryondemand.com/medicinal-chemistry&ei=v1IjUrzVE4qVswb0vYDQAw&psig=AFQjCNFivzSPgKH5Oaob_xOzm9fz-3PS7Q&ust=1378133039973918)**Five-membered Heterocycles L.3**

**Pyrrole, Furan and Thiophene**

**Objectives:**

1-To identify types of five membered heterocyclic compounds

2- To know their sources .

3-To know syntheses methods of five membered heterocyclic compounds

4-To understand their chemical reactions .

**A. Five-membered Rings with one Heteroatom**

1. The main reason for the study of pyrrole came from the work on the structure of heme; the blood respiratory pigment, and the chlorophyll; the green photosynthetic pigment of plants.
2. Thiophene and its derivatives occurs in [petroleum](https://en.wikipedia.org/wiki/Petroleum).
3. Furan occurs widely in secondary plant metabolites, especially in terpenoids.

Unsubstituted pyrrole, furan, and thiophene are usually obtained from petroleum.



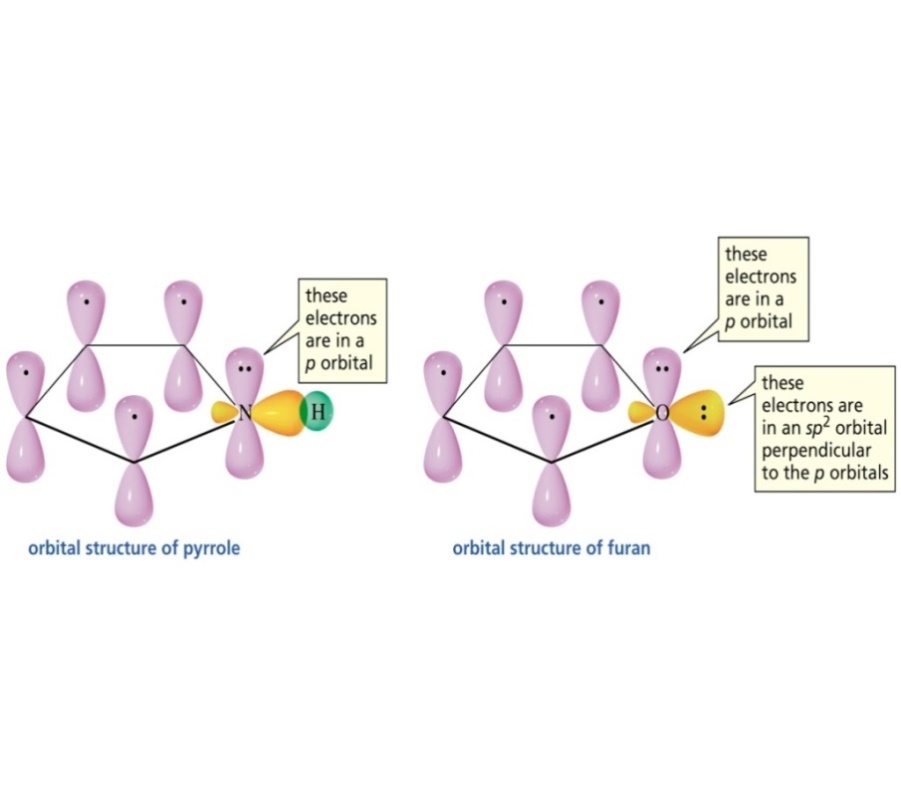
1. Pyrrole, furan and thiophene are colorless liquids of boiling points 126o, 32o, and 84oC respectively.
2. Pyrrole has a relatively high boiling point as compared to furan and thiophene, this is due to the presence of **intermolecular hydrogen bonding** in pyrrole.



**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).

1. They tend to react by electrophilic substitution due appearance of –ve charge on carbon atoms due to delocalization as shown in the following resonance structures



**3-** Electrons not available for protonation—hence not basic

**4-** 6 π electrons over 5 ring atoms ….. Electron rich… so more reactive than benzene towards **electrophilic substitution.**



**The order of reactivity is:**

**Pyrrole > Furan > Thiophene > Benzene**

**5- The pattern of reactivity with Electrophilic reagents.**

Aromatic compounds : By substitution addition followed by proton loss

**[ onium intermediate ]**

**Order of reactivity : Pyrrole > Furan > Thiophene > Benzene**



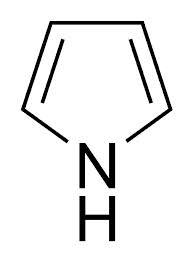
**6-**The order of aromaticity

**Benzene > Thiophene > Pyrrole > Furan**



In case of Thiophene [S] donate & accept electrons ., so delocalization

as complete as benzene.

In case of **Pyrrole [N]** -Diene-like character CH2=CH-CH=CH2

In case of **Furan [O]** electronegativity more …. Diene-like character CH2=CH-CH=CH2



Question : prove pyrrole have aromatic characters ?

The Evidences of aromatic character in pyrrole are :

It tends to react by electrophilic substitution



* Its exceptional lack of basicity and strong acidity as a secondary amine compared to the aliphatic analog (pyrrolidine). This can be explained on the basis of participation of **N** lone pair in aromatic sextet (**see the resonance structures)**



So Its weak acid not basic as the secondary amines .

Lone pair of N is involved in π cloud and not available for sharing with acids



thus the dipole moment of pyrrole compared with pyrolidine is reverted and thus protonation occurs at **carbons not at N**



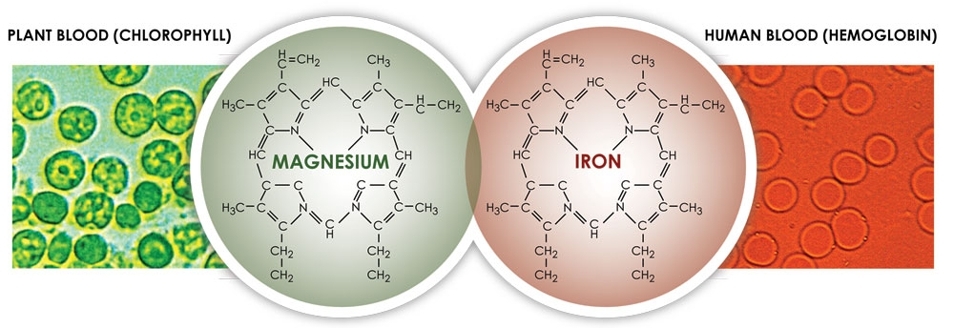


**Sources & Synthesis:**

**A) Sources**

Pyrrole & Thiophene …. **Coal Tar**

**Pyrrole ring …. Porphyrin system….. Chlorophyll & Hemoglobin**

[](http://www.nadyapeche.com/wp-content/uploads/chlorophyll-hemoglobin.jpg)

**Furan ….. Decarboxylation of Furfuraldehyde …….**  **Oat hulls, corn cobs or rice hulls**



**rice hulls**

**corn cobs**

**Oat hulls**

**B) Synthesis**





**Pyrrole**

**Thiophene**

**Furan**

**Reactions of pyrrole**

