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PHARMACEUTICAL ORGANIC CHEMISTRY – III

UNIT 3

TOPIC :

- **Heterocyclic compounds :**

  Nomenclature and classification

  Synthesis, reactions and medicinal uses of following compounds/derivatives

  Pyrrole, Furan, and Thiophene

  Relative aromaticity and reactivity of Pyrrole, Furan and Thiophene

Heterocyclic Compounds

- Heterocyclic compounds are organic compounds that contain a ring (cyclic) structure composed of at least one atom other than carbon within the ring.
- The non-carbon atoms present in the ring are called heteroatoms.
- Common heteroatoms include nitrogen (N), oxygen (O), and sulfur (S).
- These compounds are widely present in natural products, pharmaceuticals, agrochemicals, dyes, and biomolecules (like nucleic acids, hemoglobin, and vitamins).

Importance

- Found in biological molecules (DNA, RNA, porphyrins, vitamins, alkaloids).
- Many drugs (e.g., pyridine derivatives, furan, thiophene, imidazole, quinoline) are heterocyclic in nature.
- Play a key role in medicinal chemistry due to their chemical reactivity and biological activity.

Classification of Heterocyclic Compounds

Heterocyclic compounds can be classified on different bases:

1. Based on Ring Size
2. Based on Aromaticity
3. Based on Number of Rings
4. Based on Type of Heteroatom

(Based on Ring Size)

- Heterocyclic compounds are classified according to the number of atoms forming the ring and the type of heteroatoms present.

1. Three-Membered Heterocyclic Compounds

These are **three-membered ring compounds** containing **one or two heteroatoms**.

(a) With One Heteroatom

- **Aziridine (NH)** → contains nitrogen atom.
- **Oxirane (Ethylene oxide)** → contains oxygen atom.
- **Thiirane** → contains sulfur atom.

(b) With Two Heteroatoms

- **Diaziridine (N–N)** → contains two nitrogen atoms.
- **Dioxirane (O–O)** → contains two oxygen atoms.
- **Azirine** → unsaturated 3-membered ring with N.

Example Structures:

- Aziridine (C_2H_4NH)
- Oxirane (C_2H_4O)
- Diaziridine ($C_2H_4N_2$)

2. Four-Membered Heterocyclic Compounds

These are four-membered ring compounds with one or more heteroatoms.

(a) With One Heteroatom

- **Azetidine (NH)** → 4-membered ring with nitrogen.
- **Oxetane (O)** → 4-membered ring with oxygen.
- **Thietane (S)** → 4-membered ring with sulfur.

(b) With More Than One Heteroatom

- **Diazetidine (N–N)**
- **Oxazetidine (O + N)**
- **Thiazetidine (S + N)**

Examples are less stable due to ring strain.

3. Five-Membered Heterocyclic Compounds

These are five-membered rings with one or more heteroatoms.

(a) With One Heteroatom (Aromatic)

- **Pyrrole (NH)**
- **Furan (O)**
- **Thiophene (S)**

(b) With Two Heteroatoms (Aromatic)

- **Imidazole (2N)**
- **Oxazole (O + N)**
- **Thiazole (S + N)**

Importance: Many of these are aromatic and widely used in medicinal chemistry.

4. Six-Membered Heterocyclic Compounds

(a) With One Heteroatom

- **Pyridine (N)**
- **Pyran (O)**
- **Thiopyran (S)**

(b) With More Than One Heteroatom

- **Diazines (two N atoms):**
  - **Pyridazine**
  - **Pyrimidine**
  - **Pyrazine**
- **Other examples:** Triazines, Dioxanes.

Examples in biology: Pyrimidines are found in nucleic acids (Cytosine, Thymine, Uracil).

5. Seven-Membered Heterocyclic Compounds

These are seven-membered rings with one or more heteroatoms.

(a) With One Heteroatom

- **Azepane (N)**
- **Oxepane (O)**
- **Thiepane (S)**

(b) With More Than One Heteroatom

- **Diazepane (2N atoms)**
- **Thiazepane (S + N)**
- **Oxazepane (O + N)**

Some are used as **drug scaffolds** (e.g., benzodiazepines).

(Based on Aromaticity)

- Heterocyclic compounds can be divided into aromatic and non-aromatic based on the presence or absence of aromatic character.

1. Aromatic Heterocyclic Compounds

- These are heterocyclic compounds that obey Huckel's Rule (4n + 2 π-electrons) for aromaticity.
- They contain a planar cyclic conjugated π-electron system that provides stability.
- Aromatic heterocycles are often highly stable and widely present in natural products, drugs, and biomolecules.

Examples

- **Pyridine (C_5H_5N)** → six-membered aromatic heterocycle with one nitrogen.
- **Pyrrole (C_4H_5N)** → five-membered aromatic heterocycle with nitrogen.
- **Furan (C_4H_4O)** → five-membered aromatic heterocycle with oxygen.
- **Thiophene (C_4H_4S)** → five-membered aromatic heterocycle with sulfur.
- **Imidazole, Oxazole, Thiazole** → five-membered with two heteroatoms.

2. Non-Aromatic Heterocyclic Compounds

- These heterocycles do not obey Huckel's Rule (4n + 2 rule).
- They lack complete delocalization of π-electrons.
- They are generally saturated or partially saturated rings.

Examples

- **Tetrahydrofuran (THF, C_4H_8O)** → saturated five-membered ring with oxygen.
- **Piperidine ($C_5H_{11}N$)** → saturated six-membered ring with nitrogen.
- **Morpholine (O + N in a six-membered ring)**.
- **Tetrahydropyran ($C_5H_{10}O$)**.

(Based on Number of Rings)

Heterocyclic compounds can also be classified depending on the **number of rings** in their structure. They may have a single heteroatom-containing ring or multiple fused heteroatom-containing rings.

1. Monocyclic Heterocyclic Compounds

- Compounds that contain only one heteroatom-containing ring in their structure.
- They may have one or more heteroatoms in that single ring.

Examples

- Pyridine (C_5H_5N) → six-membered ring with one nitrogen atom.
- Furan (C_4H_4O) → five-membered ring with oxygen atom.
- Pyrrole (C_4H_5N) → five-membered ring with nitrogen atom.
- Thiophene (C_4H_4S) → five-membered ring with sulfur atom.

Monocyclic heterocycles are common in drugs and biomolecules.

2. Bicyclic or Polycyclic Heterocyclic Compounds

- Compounds that contain two or more fused rings, where at least one of the rings contains a heteroatom.
- Fusion may occur between heterocyclic–heterocyclic or heterocyclic–carbocyclic rings.

Examples

- Quinoline (C_9H_7N) → fused benzene + pyridine ring.
- Isoquinoline (C_9H_7N) → fused benzene + pyridine (different fusion).
- Indole (C_8H_7N) → fused benzene + pyrrole ring.
- Purine ($C_5H_4N_4$) → fused pyrimidine + imidazole rings.
- Acridine ($C_{13}H_9N$) → three fused rings with nitrogen.

These heterocycles are very important in medicinal chemistry:

- Purines & Pyrimidines → form nucleic acids (DNA & RNA).
- Quinoline derivatives → used as antimalarials (e.g., chloroquine).
- Indole derivatives → found in serotonin and tryptophan.

Based on Type of Heteroatom

- **Nitrogen heterocycles**: Pyridine, Pyrrole, Imidazole, Quinoline.
- **Oxygen heterocycles**: Furan, Pyran, Dioxane.
- **Sulfur heterocycles**: Thiophene, Thiazole, Benzothiazole.
- **Mixed heteroatom heterocycles**: Oxazole (O + N), Thiazole (S + N).

Nomenclature of Heterocyclic Compounds

- Heterocyclic compounds are named using different systems, but the Hantzsch–Widman system is the most widely accepted and is also recommended by IUPAC. It provides a systematic way of naming both simple and complex monocyclic heterocycles.

Hantzsch–Widman Nomenclature

This system names heterocyclic compounds based on:

1. Type of heteroatom(s) present.
2. Size of the ring.
3. Saturation or unsaturation of the ring.

The general formula is:

Prefix (heteroatom) + Stem (ring size) + Suffix (saturation/unsaturation)

1. Prefix

- The prefix denotes the type of heteroatom present in the ring.
- Common prefixes:

Heteroatom	Prefix
Oxygen (O)	**Oxa-**
Sulfur (S)	**Thia-**
Nitrogen (N)	**Aza-**
Selenium (Se)	**Sela-**
Tellurium (Te)	**Tellura-**

2. Stem (Ring Size)

- The stem indicates the **number of atoms in the ring** (ring size).
- Common stems:

Ring Size	Stem (Unsaturated)	Stem (Saturated)
3	-ir-	-irane
4	-et-	-etane
5	-ol-	-olane
6	-in-	-inane
7	-ep-	-epane
8	-oc-	-ocane

3. Suffix (Saturation/Unsaturation)

- The suffix specifies whether the ring is saturated or unsaturated:
  - **-ane** → saturated ring.
  - **-ine / -ole** → unsaturated ring (aromatic or conjugated).

Examples

1. **Oxirane (C_2H_4O)**

- Three-membered ring with oxygen (oxa-) + 3-membered ring (-ir-) + saturated (-ane).
- Name: Oxirane.

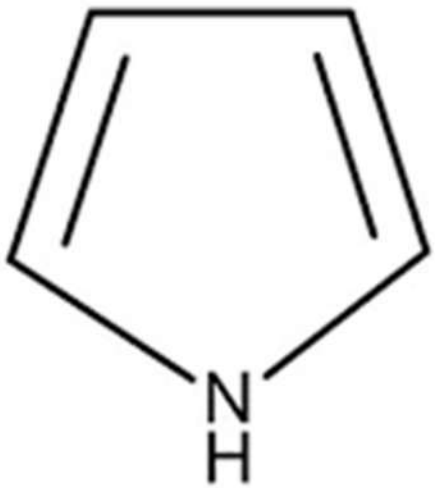
2. **Aziridine (C_2H_5N)**

- Three-membered ring with nitrogen (aza-) + 3-membered ring (-ir-) + saturated (-ane).
- Name: Aziridine.

Pyrrole

- Pyrrole is a five-membered aromatic heterocyclic compound with molecular formula C_4H_5N.
- It is a colorless, volatile liquid that darkens upon exposure to air.
- Pyrrole is considered one of the most important five-membered heterocycles.
- It naturally occurs in many biomolecules such as:
  - Hemoglobin (heme group contains pyrrole rings)
  - Chlorophyll
  - Alkaloids
  - Vitamin B_{12}

Structure and Resonance



- Pyrrole consists of a five-membered ring with one nitrogen atom.
- The nitrogen atom contributes its lone pair of electrons to the aromatic π-system.
- Thus, pyrrole has a total of 6 π-electrons (4 from double bonds + 2 from nitrogen lone pair) → satisfies Hückel's rule.
- Resonance leads to delocalization of electrons, which gives pyrrole its aromatic character.

Synthesis of Pyrrole (Methods of Preparation)

1. Industrial Method

- Furan when treated with ammonia at 400 °C under pressure forms pyrrole.

$$C_4H_4O + NH_3 \xrightarrow{400^\circ C} C_4H_5N + H_2O$$

2. From Acetylene

- A mixture of acetylene and ammonia is passed through a red hot tube to yield pyrrole.

$$2CH \equiv CH + NH_3 \longrightarrow C_4H_5N$$

3. Paal–Knorr Synthesis

- 1,4-diketone reacts with ammonia or primary amine to yield pyrrole derivatives.

$$CH_3CO\ CH_2\ CH_2\ COCH_3 + NH_3 \longrightarrow 2,5-dimethylpyrrole + 2H_2O$$

4. Hantzsch Pyrrole Synthesis

- β-ketoester (ethyl acetoacetate) reacts with α-chloro ketone in presence of ammonia to give substituted pyrrole.

5. From Succinimide

- Dry distillation of succinimide with zinc dust gives pyrrole.

$$C_4H_5NO_2 + Zn \longrightarrow C_4H_5N + ZnO$$

Chemical Reactions of Pyrrole

Due to electron-rich nature, pyrrole undergoes reactions mainly at the C-2 position.

1. Electrophilic Substitution Reactions
   - Pyrrole is much more reactive than benzene towards electrophiles.
   - Halogenation:
     Pyrrole + Br_2 → 2-Bromopyrrole.
   - Nitration:
     Pyrrole + HNO_3 (acetic anhydride) → 2-Nitropyrrole.
   - Sulfonation:
     Pyrrole + fuming H_2SO_4 → 2-Pyrrole sulfonic acid.
2. Reduction
   - Pyrrole is reduced by H_2/Ni at high temperature to form pyrrolidine (saturated heterocycle).
3. Reimer–Tiemann Reaction
   - Pyrrole reacts with chloroform ($CHCl_3$) + KOH to give 2-formylpyrrole.
4. Oxidation
   - Pyrrole is oxidized with chromium trioxide (CrO_3) in H_2SO_4 to form maleimide derivatives such as pyrrole-2,5-dione.

Medicinal Uses of Pyrrole

1. **Building Block in Drugs**
   - Atorvastatin (Lipitor) – cholesterol-lowering drug.
   - Tolmetin – NSAID (anti-inflammatory drug).
   - Sunitinib – anticancer drug.
2. **Antimicrobial Agents**
   - Pyrrole derivatives show **antibacterial, antifungal, and antiviral activities**.
3. **Anti-inflammatory and Analgesic**
   - Pyrrole-based compounds reduce inflammation and pain.
4. **Biological Significance**
   - **Heme (hemoglobin, cytochromes)** → contains pyrrole units in the porphyrin ring.
   - **Chlorophyll** → pyrrole ring system in plants.
   - **Vitamin B_{12}** → corrin ring contains pyrrole subunits.

Furan

- Furan is a five-membered aromatic heterocyclic compound consisting of four carbon atoms and one oxygen atom.
- Molecular formula: C_4H_4O
- It is a colorless, volatile, flammable liquid with a boiling point around 31°C.
- It has a characteristic chloroform-like odor.
- Furan is considered important because it forms the basis of many natural products, pharmaceuticals, and synthetic intermediates.
- Its oxygen heteroatom provides lone pair electrons that contribute to resonance and aromatic stabilization.

Resonance in Furan

- Furan shows resonance due to delocalization of ***π*-electrons** across the five-membered ring.
- Out of two lone pairs of oxygen, **one lone pair participates in resonance**, contributing **two electrons** to the aromatic sextet (Hückel's rule: $4n+2 = 6$).
- This makes furan **aromatic and planar**.
- Resonance structures explain its relative stability and reactivity.

Synthesis of Furan (Methods of Preparation)

1. **Industrial Method (from Xylose / Pentose sugars)**
    - When pentose sugars (like xylose) are heated in the presence of mineral acids, they undergo dehydration to form furfural.
    - Furfural upon decarbonylation gives furan.

$$C_5H_{10}O_5 \xrightarrow[H^+,\ heat]{} C_5H_4O_2\ (\text{Furfural}) \xrightarrow[ZnO]{} C_4H_4O\ (\text{Furan})$$

2. **From 1,4-Diketones (Paal–Knorr Furan Synthesis)**

- 1,4-diketone on dehydration in acidic medium yields furan.

$$OHC - CH_2 - CH_2 - CHO \xrightarrow[H^+]{} C_4H_4O$$

3. **From Furfural**
   - Furfural is decarbonylated with palladium catalyst to produce furan.

4. **Laboratory Method (from Alcohols)**
   - Butane-1,4-diol on dehydration with strong acids yields furan.

Chemical Reactions of Furan

Like pyrrole, furan undergoes electrophilic substitution reactions, mainly at C-2 position due to greater electron density.

1. **Halogenation**

$$C_4H_4O + Br_2 \longrightarrow \text{2-Bromofuran}$$

1. **Nitration**
   - With acetyl nitrate, gives **2**-nitrofuran.
2. **Sulfonation**
   - With fuming H_2SO_4 → furan-2-sulfonic acid.
3. **Friedel–Crafts Acylation**
   - With acyl chlorides in the presence of $AlCl_3$ → **2**-acylfuran.
4. **Reduction**
   - Furan + H_2 (Ni catalyst) → tetrahydrofuran (THF).
   - THF is an important solvent in organic chemistry.
5. **Oxidation**
   - Furan gets oxidized to maleic anhydride using chromium trioxide.

Medicinal Uses of Furan and its Derivatives

1. **Antibacterial and Antifungal Agents**
    - Nitrofurans (like nitrofurantoin, furazolidone) are widely used as urinary tract antiseptics.
2. **Anticancer Agents**
    - Some furan derivatives show cytotoxic activity and are used in anticancer therapy.
3. **Anti-inflammatory Agents**
    - Furan derivatives are components in NSAIDs.
4. **Solvent Use (THF)**
    - Tetrahydrofuran is used as a polar aprotic solvent in drug formulations.
5. **Building Block in Natural Products**
    - Furan units are present in many alkaloids, vitamins (Vit. B_1 = thiamine), and antibiotics.

Thiophene

- Thiophene is a five-membered aromatic heterocyclic compound containing four carbon atoms and one sulfur atom.
- Molecular formula: C_4H_4S
- It is a colorless liquid with a benzene-like odor and a boiling point of about 84°C.
- Thiophene resembles benzene in its properties and is often found as an impurity in coal tar and crude oil.
- Its aromatic character is due to delocalization of π-electrons with sulfur contributing a lone pair.

Resonance in Thiophene

- The sulfur atom has two lone pairs of electrons; one lone pair participates in resonance with the π-electron cloud of the ring.
- Thus, thiophene has 6 π-electrons (following Hückel's rule: 4n+2).
- This gives thiophene aromatic stability.
- Resonance structures show delocalization of electrons across the ring, similar to benzene.

Synthesis of Thiophene (Methods of Preparation)

1. **From Butane**
   - When butane is passed with sulfur at high temperature (500°C), thiophene is formed.

$$C_4H_{10} + S \xrightarrow{500^\circ C} C_4H_4S + H_2$$

2. **Paal–Knorr Synthesis**

- 1,4-diketone reacts with phosphorus pentasulfide (P_2S_5) to yield thiophene.

$$OHC - CH_2 - CH_2 - CHO \xrightarrow{P_2S_5} C_4H_4S$$

3. **From Sodium Succinate and P_2S_5**
    - Sodium succinate when heated with P_2S_5 undergoes cyclization to give thiophene.

4. **Laboratory Method**
    - From furan by replacement of oxygen atom with sulfur (using Lawesson's reagent).

Chemical Reactions of Thiophene

Since thiophene is aromatic, it undergoes electrophilic substitution reactions, mostly at C-2 position due to greater resonance stabilization.

1. **Halogenation**

$$C_4H_4S + Br_2 \longrightarrow \text{2-Bromothiophene}$$

1. **Nitration**
    - With acetyl nitrate → 2-nitrothiophene.
2. **Sulfonation**
    - With fuming H_2SO_4 → thiophene-2-sulfonic acid.
3. **Friedel–Crafts Acylation/Alkylation**
    - With acyl/alkyl halides in presence of $AlCl_3$ → substituted thiophenes.
4. **Reduction**
    - With H_2/Ni → tetrahydrothiophene, a useful solvent.
5. **Oxidation**
    - Thiophene oxidizes to give sulfur dioxide + maleic acid.

Medicinal Uses of Thiophene and its Derivatives

1. **Anti-inflammatory Drugs**
    - Tiaprofenic acid (NSAID) is a thiophene derivative used to reduce inflammation and pain.
2. **Antihypertensive Agents**
    - Ticlopidine (platelet aggregation inhibitor) contains a thiophene ring.
3. **Anticonvulsants**
    - Some thiophene derivatives are used in treatment of epilepsy.
4. **Antimicrobial Agents**
    - Substituted thiophenes exhibit antibacterial and antifungal activity.
5. **Building Block in Drug Design**
    - The thiophene ring acts as a bioisostere of benzene, used in designing more potent and soluble drugs.