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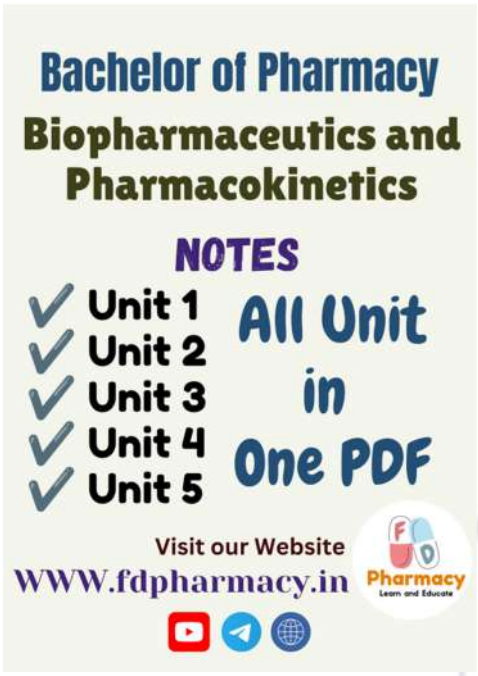
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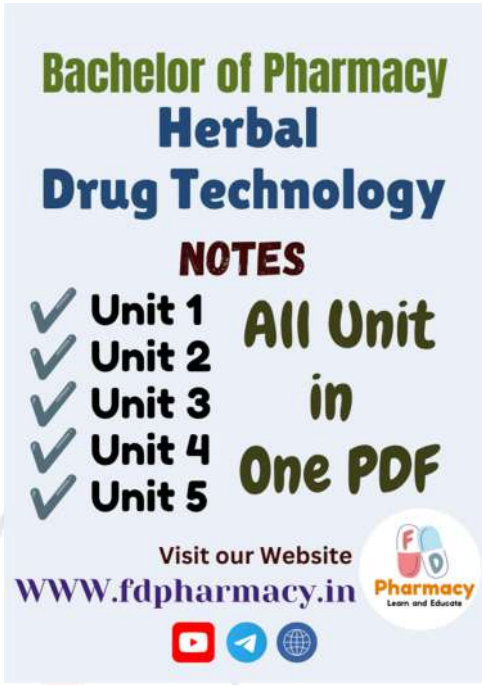
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MEDICINAL CHEMISTRY - III

UNIT 5

TOPIC :

- **Combinatorial Chemistry** : Concept and applications chemistry : solid phase and solution phase synthesis

Combinatorial Chemistry

→ Combinatorial chemistry is a modern technique used in drug discovery to rapidly synthesize a large number of related compounds (chemical libraries) by combining sets of building blocks in different ways.
It plays a major role in lead discovery and optimization.

Concept of Combinatorial Chemistry

➢ Combinatorial chemistry is a method by which multiple chemical compounds are synthesized simultaneously using a systematic and repetitive approach.

Basic Concept

◈ Uses building blocks (A, B, C…)
◈ Combines them in all possible combinations
◈ Produces a chemical library
◈ Library is screened for biological activity

Example

- If:
  - 5 amines
  - 5 acids
- Total compounds formed = **5 × 5 = 25 compounds**

Key Terms

⅄ Building blocks: Small reactive molecules
⅄ Library: Collection of compounds
⅄ High Throughput Screening (HTS): Rapid biological testing

Objectives of Combinatorial Chemistry

❖ Rapid identification of lead compounds
❖ Study of Structure–Activity Relationship (SAR)
❖ Reduction of time and cost in drug discovery
❖ Generation of molecular diversity

Types of Combinatorial Chemistry

A. Solid-Phase Combinatorial Chemistry

B. Solution-Phase Combinatorial Chemistry

A. SOLID-PHASE COMBINATORIAL CHEMISTRY

→ Solid-phase combinatorial chemistry is a technique in which chemical synthesis is carried out on a solid support (resin or polymer beads).

Solid Support (Resin)

- Commonly used resins:
  - Polystyrene resin
  - Merrifield resin
  - PEG-based resins

Principle

- ◈ First molecule is anchored to resin
- ◈ Reactions occur stepwise
- ◈ Excess reagents are washed away
- ◈ Final product is cleaved from resin

Steps in Solid-Phase Synthesis

- ⇨ Attachment
  - First building block attached to resin
- ⇨ Deprotection
  - Removal of protecting group
- ⇨ Coupling
  - Addition of next building block
- ⇨ Repetition
  - Cycle repeated to generate library
- ⇨ Cleavage
  - Final compound removed from resin

Split-and-Mix Method

- ⅄ Resin beads are split into portions
- ⅄ Each portion reacts with different reagents
- ⅄ Beads are mixed again
- ⅄ Produces large libraries

Advantages

- Easy purification (washing)
- Automation possible
- High yield
- Suitable for large libraries

Limitations

- Reaction monitoring is difficult
- Resin cost is high
- Limited reaction types

Applications

- Peptide synthesis
- Drug lead generation
- Enzyme inhibitor discovery

B. SOLUTION-PHASE COMBINATORIAL CHEMISTRY

➢ Solution-phase combinatorial chemistry is a method where all reactions occur in solution without any solid support.

Principle

- Reactions carried out in solution
- Products isolated using chromatography or precipitation
- Similar to conventional organic synthesis

Steps

- ◈ Selection of building blocks
- ◈ Chemical reactions in solution
- ◈ Separation and purification
- ◈ Screening for biological activity

Techniques Used

- ✪ Parallel synthesis
- ✪ Fluorous tagging
- ✪ Polymer-assisted solution synthesis

Advantages

- ⅄ Better reaction control
- ⅄ Easy reaction monitoring
- ⅄ Suitable for complex reactions

Limitations

- ❖ Difficult purification
- ❖ Time-consuming
- ❖ Less suitable for very large libraries

Applications

- Small-molecule drug synthesis
- SAR studies
- Optimization of lead compounds