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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 = $5 \times 5 = 25$ 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

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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