Peptidomimetics

Peptidomimetics: Introduction and Classification

Introduction to Peptidomimetics

- **Peptidomimetics** are compounds designed to mimic the structure and function of natural peptides but with improved properties.
- **Peptides are short chains of amino acids involved in important biological processes such as:**
  - Cell signaling
  - Enzyme activity
  - Immune response

Limitations of Natural Peptides

- **Natural peptides have several disadvantages:**
  - Easily degraded by enzymes (proteases)
  - Poor stability in the body
  - Low oral bioavailability
  - Short half-life
  - Difficulty in crossing cell membranes

First Hope

Need for Peptidomimetics

- To overcome the limitations of natural peptides
- To improve drug-like properties
- To enhance stability, absorption, and biological activity
- To maintain interaction with biological targets like receptors and enzymes

Key Features of Peptidomimetics

- Mimic the 3D structure of peptides
- Bind to the same biological targets (receptors, enzymes)
- More stable than natural peptides
- Resistant to enzymatic degradation
- Improved pharmacokinetic properties (absorption, distribution, metabolism)
- Better selectivity and reduced side effects

Importance in Pharmaceutical Science

- Widely used in drug design and development

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- Help target specific biological pathways
- Provide better therapeutic effectiveness compared to natural peptides

Advantages of Peptidomimetics

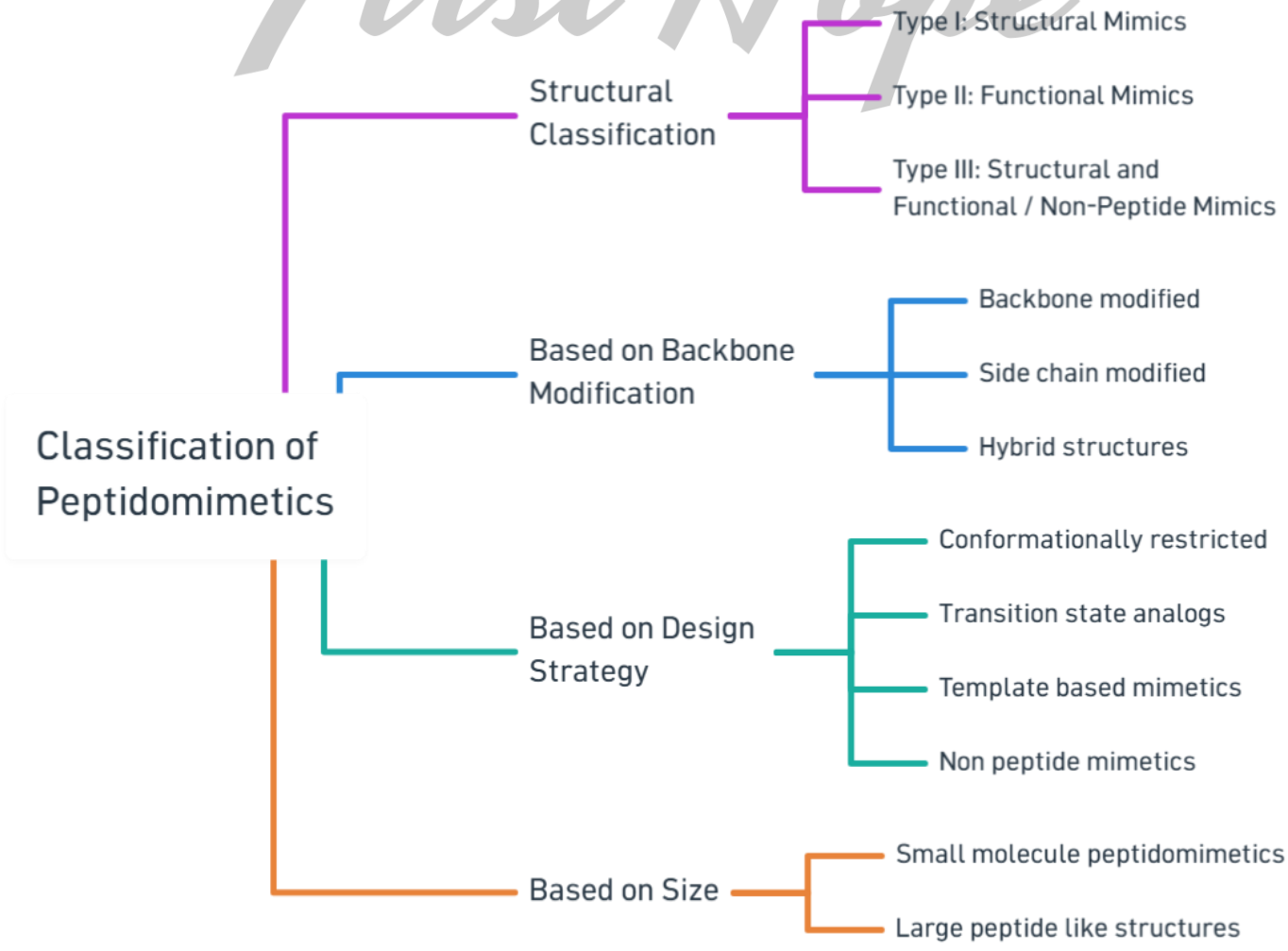
- Increased resistance to enzymatic degradation
- Improved stability and longer half-life
- Better pharmacokinetic properties
- Enhanced receptor selectivity
- Reduced side effects

Applications

- Drug development (antiviral, anticancer, antibacterial drugs)
- Enzyme inhibitors
- Receptor modulators
- Therapeutic agents targeting specific pathways

Classification of Peptidomimetics

Peptidomimetics can be classified based on structure, modification, and design strategy.



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1. Structural Classification

A. Type I: Structural Mimics

- Very similar to natural peptides
- Only minor modifications in backbone or side chains
- Example: replacement of peptide bonds with similar chemical groups

B. Type II: Functional Mimics

- Do not closely resemble peptide structure
- Mimic only the biological function
- Still interact with the same target

C. Type III: Structural and Functional / Non-Peptide Mimics

- May have different structures from peptides
- Retain essential features required for binding and activity

2. Based on Backbone Modification

A. Backbone-modified peptidomimetics

- Changes in peptide bonds (e.g., amide bond replacement)

B. Side-chain modified peptidomimetics

- Alteration of amino acid side chains

C. Hybrid structures

- Combination of peptide and non-peptide components

3. Based on Design Strategy

A. Conformationally restricted peptidomimetics

- Designed to lock the molecule in a specific shape

B. Transition state analogs

- Mimic the transition state of enzyme reactions

C. Template-based mimetics

- Use a structural framework to arrange functional groups

D. Non-peptide mimetics

- Completely different structure but same function

4. Based on Size

- Small molecule peptidomimetics
- Large peptide-like structures

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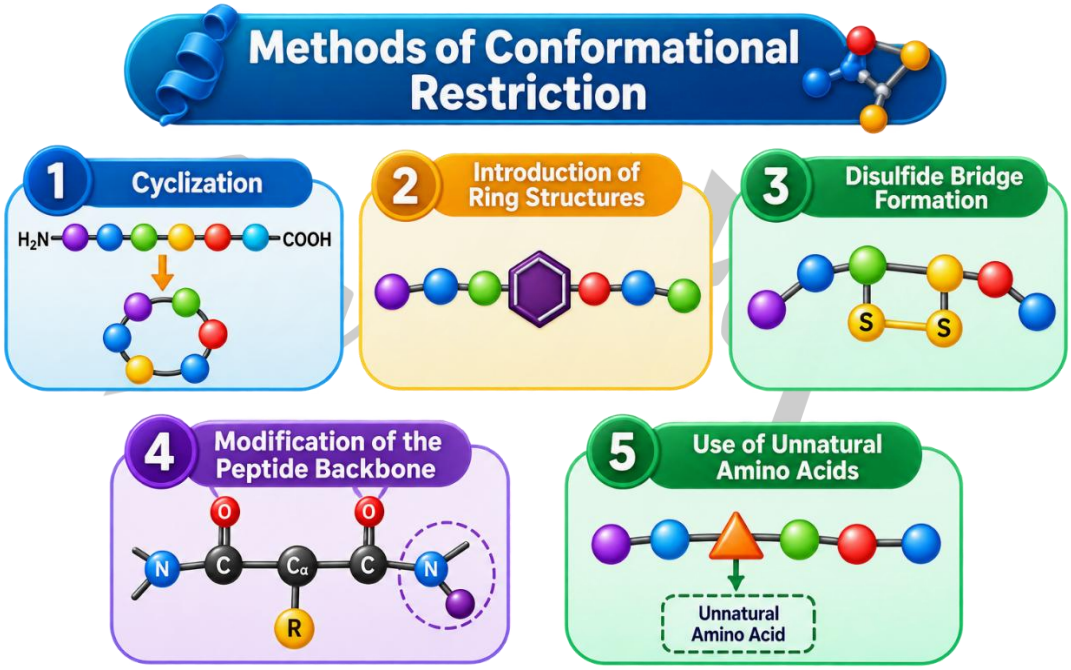
Conformationally Restricted Peptides

- **Conformationally** restricted peptides are peptides designed to have **limited flexibility**.
- Natural peptides are flexible and can adopt many shapes, which may reduce binding efficiency.

Why Restrict Conformation

- Improves binding specificity to target molecules
- Enhances binding affinity by reducing entropy loss
- Increases stability
- Reduces enzymatic degradation
- Improves overall biological activity

Methods of Conformational Restriction



1. Cyclization

- The peptide chain can be converted from a linear structure into a cyclic structure.
- Cyclization reduces the freedom of movement of the peptide chain.
- Cyclic peptides are often more resistant to enzymatic degradation than corresponding linear peptides.

2. Introduction of Ring Structures

- Ring-containing amino acids or other cyclic groups can be introduced into the peptide.
- These rings restrict rotation around particular bonds.

3. Disulfide Bridge Formation

- A disulfide bond can form between two cysteine residues.

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- This bond holds different parts of the peptide together and limits flexibility.

4. Modification of the Peptide Backbone

- The normal peptide backbone can be chemically modified.
- Such modifications can force the molecule to adopt a preferred conformation.

5. Use of Unnatural Amino Acids

- Unnatural amino acids can introduce steric or structural restrictions.
- They can help maintain the orientation required for biological activity.

Advantages

- Conformational restriction can increase binding affinity.
- It can improve selectivity for the desired biological target.
- It can increase resistance to enzymatic degradation.
- It can increase the duration of biological activity.

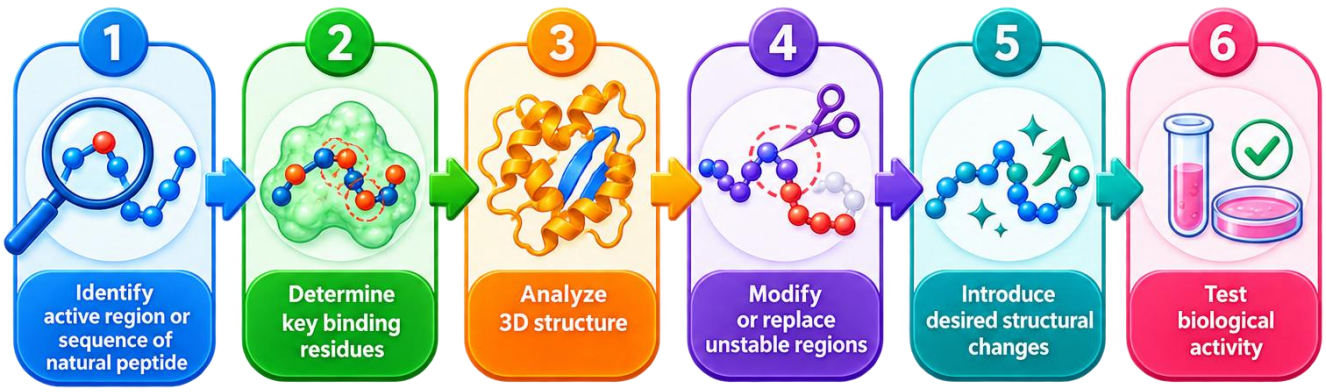
Design of Peptides

- Designing peptides involves selecting and modifying amino acids to achieve the desired structure and function.
- In peptidomimetics, unstable parts are replaced with more stable alternatives.

Key Considerations in Design

- Target protein or receptor
- Structure of binding site
- Stability requirements
- Bioavailability
- Solubility and delivery
- Toxicity and safety

Steps in Design



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