Peptidomimetics and Eicosanoid Chemistry

Introduction to Peptides and Peptidomimetics

- A **peptide** contains amino-acid residues linked mainly through amide bonds called peptide bonds.
- A **peptidomimetic** is a molecule designed to reproduce the arrangement of groups responsible for a peptide's biological activity while changing part or all of the peptide framework.
- It may remain recognisably peptide-like or use a smaller nonpeptide scaffold; the defining aim is to reproduce the important recognition features, called the **pharmacophore**.
    - A peptide recognition pattern depends on the arrangement of side chains, backbone hydrogen-bonding groups and three-dimensional conformation.
    - A mimetic aims to preserve the useful arrangement while changing properties such as susceptibility to proteolysis, flexibility or membrane passage.

Why Peptides Are Useful Leads

- Peptides can recognise receptors, enzymes and other proteins through a precise arrangement of side chains and backbone groups.
    - The same recognition features can guide the design of a more stable or more readily delivered analogue.

Limitations of an Unmodified Peptide

- Proteases can cleave susceptible peptide bonds.
- A flexible chain can adopt many conformations, only some of which may fit the target.
- Multiple polar groups often reduce passive membrane permeability.
- Rapid clearance and limited oral absorption can make delivery difficult.

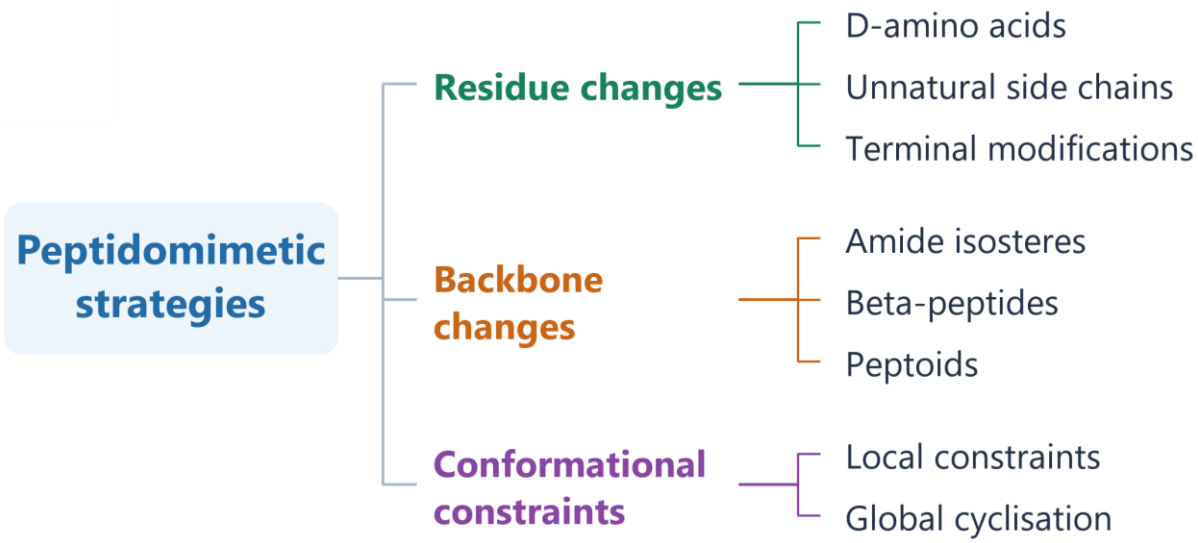
What a Mimetic Tries to Preserve

- Retain the groups that provide essential charge, hydrogen bonding, hydrophobic contact and spatial arrangement.
    - Other peptide features can be changed if they are not required for recognition.

Main Design Approaches

- The approaches below change different structural levels: **individual residues**, the **backbone linkage** or the accessible **three-dimensional conformations**.
- They can be combined, but each modification must be checked against the original binding and property requirements.

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- Modify amino-acid side chains or stereochemistry.
- Change a peptide bond or another part of the backbone.
- Restrict a local segment or constrain the overall molecule through cyclisation.
- More extensive designs can replace much of the peptide framework with a nonpeptide scaffold.

Therapeutic Values of Peptidomimetics

- Peptidomimetics aim to preserve useful peptide-like recognition while improving properties needed for treatment.

Potential Therapeutic Advantages

1. **Improved Metabolic Stability**
   - A **D-amino acid**, an **N-methylated** bond or another carefully selected modification can make a susceptible site less easily recognised by a protease.
     - Stability must be measured because changing one cleavage site can expose another.
2. **Improved Selectivity**
   - A restricted conformation can favour one receptor or enzyme over related targets.
   - Removing unnecessary interactions can also reduce activity at an unwanted target.
3. **Useful Exposure and Delivery**
   - Changes in charge, hydrogen bonding and conformation may improve permeability or reduce rapid clearance.
     - These changes do not automatically make a peptide orally active, because dissolution and metabolism still matter.
4. **Longer Duration of Action**
   - Greater resistance to degradation or altered distribution can prolong useful exposure.

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- A longer effect must remain controllable and compatible with the therapeutic aim.

Examples of the Design Principle

1. Desmopressin

- **Desmopressin** is **1-deamino-8-D-arginine vasopressin**: the N-terminal amino group is removed and L-arginine at position 8 is replaced by D-arginine.
- These changes give a **longer duration** and a more favourable **antidiuretic-to-vasopressor activity profile** than vasopressin.
- This example shows that a small number of well-placed residue changes can improve a peptide hormone without replacing its complete scaffold.

2. Enzyme-Inhibitor Design

- Peptide-like substrate recognition has guided development of several enzyme-inhibitor classes, including ACE inhibitors.
  - The final inhibitor may retain selected substrate-recognition features while replacing a readily cleaved peptide arrangement.
- **Example: Captopril** retains a proline-containing recognition scaffold and uses a thiol group to coordinate the catalytic zinc of ACE.
- The inhibitor blocks peptide hydrolysis without being a normal peptide substrate, illustrating recognition mimicry rather than simple sequence copying.

Limitations

- A stable analogue can lose activity if the modification removes an essential interaction.
  - New stereochemistry, difficult synthesis and unwanted distribution can offset the expected advantage.

Benefits and Trade-offs of Common Modifications

Modification	Intended benefit	Possible trade-off
D-residue or selected backbone change	Reduce cleavage by a protease.	Target recognition may also be reduced.
Local or global constraint	Favour a useful conformation.	The molecule may be locked in the wrong shape.
N-Methylation	Alter hydrogen bonding and conformational behaviour.	An essential donor can be lost.
Side-chain modification	Improve fit, selectivity or metabolic properties.	Solubility or exposure may worsen.

Design of Peptidomimetics by Manipulation of Amino Acids

- Amino-acid manipulation changes side-chain identity, stereochemistry or substitution while retaining selected elements of the peptide framework.

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Major Approaches

1. D-Amino-Acid Substitution

A. Stereochemical Change

- Replacing an **L-residue** by its **D-form** reverses the local stereochemical arrangement.

B. Possible Consequences

- This can reduce recognition by some proteases and alter the accessible conformations.
- The substitution may also weaken target binding if the original side chain must point in a specific direction.

2. Nonproteinogenic Amino Acids

- A residue not commonly used in natural protein synthesis can introduce a different size, polarity or conformational preference.
- Examples include residues with modified aromatic groups or additional substitution near the backbone.
- **Example:** Replacing an oxidation-prone side chain with a suitably chosen nonproteinogenic analogue can improve stability, provided that its size and orientation remain compatible with the target.

3. α-Carbon Substitution

- Additional substitution at the α-carbon restricts local backbone geometry and can affect protease recognition.
  - **α-Aminoisobutyric acid**, often abbreviated **Aib**, is an example used to influence peptide conformation.

4. Side-Chain Replacement

A. Mapping a Recognition Contact

- A **side chain** may be made larger, smaller, more polar or less oxidisable while retaining the overall peptide sequence.
- Such a series helps identify the contacts responsible for activity.

B. Example: Alanine Scanning

- An **alanine scan** replaces selected side chains with the small methyl side chain of alanine; a large loss of activity suggests that the removed side-chain features or the resulting conformational change matter.

5. N-Methylation

A. Chemical Change

- Adding a **methyl group** to a backbone amide nitrogen removes that nitrogen's **hydrogen-bond-donor** function.

First Hope

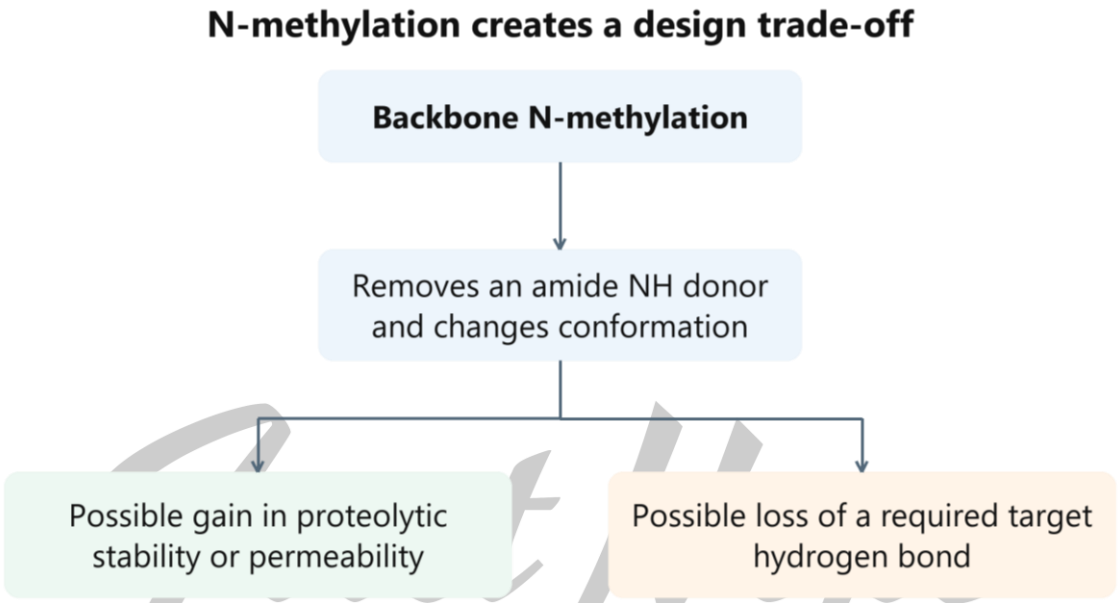
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B. Conformational and Property Consequences

- It also changes steric interactions and the balance of accessible conformations.
- **N-methylation** may alter the **cis–trans amide balance** and shield polar backbone groups, but improved permeability depends on the site and the complete peptide conformation.

C. Interpreting the Trade-Off Diagram

- Follow the two branches in the diagram: losing an **NH donor** can reduce an unwanted interaction with solvent, yet it can also remove an essential interaction with the biological target.



The same backbone change can improve a limiting property and weaken recognition; its value depends on the position modified and the full peptide scaffold

6. Terminal-Group Modification

A. N-Terminal Capping

- Blocking a free **N-terminal amino group** changes its ionisation and can reduce recognition by aminopeptidases, if that group is not essential for target binding.

B. C-Terminal Amidation

- Converting a **C-terminal carboxyl group** to a carboxamide removes the usual terminal negative charge and can change recognition by carboxypeptidases.
- Neither change protects every internal peptide bond, so overall degradation must still be examined.

How to Select the Modification

- Identify the residue's role in recognition and determine whether it is also a site of degradation.
- Change the feature that causes the limitation while testing whether the essential interaction remains.
  - Several properties should be measured together because stability, binding and permeability may move in different directions.

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