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REVIEW ARTICLE

Peptidomimetics : A New Era in Drug Discovery

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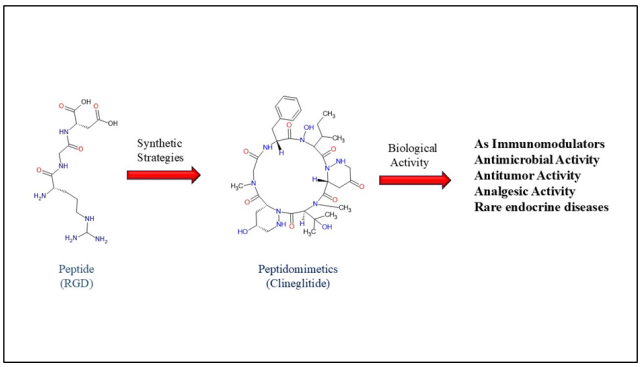
ABSTRACT

Peptides are made up from amino acid sequences which possess importance in various biological processes, making them attractive candidates for therapeutic development. But due to the limitations, such as susceptibility to proteolysis, Blood–brain barrier, poor bioavailability, short half-life, and rapid clearance, suppress their applications in drug development. Peptidomimetics, designed by modification in side chain or the backbone of peptide to mimic the structural and functional properties of peptides to overcome these limitations. After the modification they emerged as a promising class of therapeutic agents in drug discovery and development. Various synthetic strategies such as replacement of natural amino acids with unnatural amino acid, cyclization, implemented to develop peptidomimetics from peptide. Peptidomimetics shows antimicrobial and anticancer properties, also work as immunomodulator. This comprehensive review will help the reader to understand concept of peptidomimetics, their design strategies, diverse applications in various therapeutic areas, limitation and future directions.

Graphical Abstract



Keywords: Peptidomimetics; Bioavailability; Antimicrobial Activity; Stability

INTRODUCTION

Peptides consist of polyamide main chains bearing substituents.[1] There are around 7000 known naturally occurring peptides, and these peptides have a wide range of biological functions, including those of hormones, immunomodulators, substrates, enzyme inhibitors, and neurotransmitters.[2] After binding to their corresponding receptors or enzymes, they can influence cell-cell communication and control a series of vital functions such as metabolism, immune defense, digestion, respiration, sensitivity to pain, reproduction, behavior, and electrolyte levels. In order to build new peptide-based medicinal medicines, a great deal of research has been done to try to understand the physiological consequences of these peptidic molecules.[3]

The use of peptides as therapeutic agent is significantly limited by several factors: a) due to the high molecular weight

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and pronounced polarity peptides are poorly absorbed after oral administration.B) peptides are metabolically unstable because they easily degraded by proteases in the gastrointestinal tract and in serum. c] peptide quickly excrete via the liver and kidneys. d] their side-effects caused by interaction between conformationally flexible peptides with distinct receptors.[4,5]

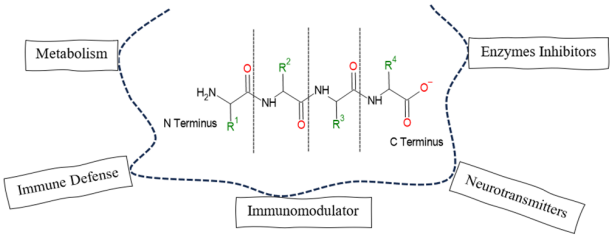


Fig. 1: Peptide

Peptidomimetic drug design has become a crucial technique for medicinal chemists and peptide chemists alike in an attempt to address these issues.[6] This approach has evolved as an interdisciplinary scientific endeavor combining organic chemistry, biochemistry and pharmacology.[7] The term "peptidomimetics"[8] can encompass compounds designed to resemble peptide main chains, side chains, or both.[9,10] Peptidomimetics that can present side chains on main-chain scaffolds containing amide bonds are ubiquitous because medicinal chemists frequently design analogues of bioactive peptides using this approach.[11] For instance, peptidomimetics involving substitution of amide bonds with surrogate or transition-state analogues are common. compounds that mimic secondary structures by peptide modifications.[12] Since the term originated in the late 1970s, peptididomimetics are synthetically modified peptides with modified molecular properties for particular biological or therapeutic applications have been a significant class of drug molecules because of their potential features, high potency, and low toxicity.[13]

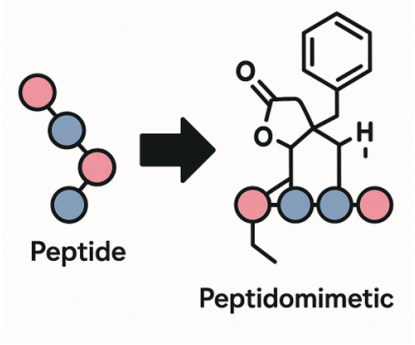


Fig. 2: Concept of Peptidomimetics

A number of compounds have been created to imitate the secondary structures of peptides, including helices, P-turns, and P-sheets, as part of one of the main initiatives in organic chemistry.[14] In order to explore the structure-activity relationships (SAR) of bioactive peptides, a number of strategies have been developed by incorporation of conformationally constrained amino acids, modification of the peptide backbone by amide bond isosteres, cyclization's, attachment of pharmacophores to a template or scaffold, and the synthesis of nonpeptide analogs. Due to these efforts, it has been shown that peptidomimetics are superior to native peptides in terms of potency and selectivity, adverse effect reduction, oral bioavailability, and half-life of activity due to reduced enzymatic degradation.[15,16] Using peptidomimetics is one approach to get overcome these drawbacks of natural short polypeptides. These tiny molecules mimic proteins and are made by mimicking natural peptides or proteins.[17] These mimetics should have the ability to bind to their natural targets in the same way as the natural peptide sequences do from which their structure was derived and hence should produce the same biological effects.[18] These compounds can be synthesized to exhibit the same biological effects as their peptide analogs, but with improved characteristics such as increased bioavailability, increased proteolytic stability, and frequently increased potency or selectivity. They are therefore desirable targets for the development of novel therapeutic candidates.[19] Overall, the development of peptidomimetics is primarily based on understanding the electronic, conformational, and topochemical properties of the native peptide to its target. Two structural factors are particularly important for the synthesis of peptidomimetics with high biological activity: first, the mimetic must fit the binding site conveniently, and second, the functional groups, polar, and hydrophobic regions of the mimetic must be positioned in specific ways to enable the beneficial interactions to occur.

This article reviews the current development of peptidomimetics, the new classification is categories on the basis of their degree of similarity to the natural peptide precursor which is recently proposed by Grossmann and coworkers, discovery and development of peptidomimetics, strategies for the synthesis of peptidomimetic, pharmacological activity of modified peptide, challenges, limitation and future prospective of peptidomimetics.

CLASSIFICATION OF PEPTIDOMIMETICS

Historically peptidomimetics categories on the basis of their similarity with the native substrate, but this classification of peptidomimetics does not comply with recent advancement in the field of chemistry and biotechnology.[20–22]

i. **Type I (Backbone Modifications) :** These peptidomimetics focus on modifying the peptide backbone to mimic the local topography of the amide bond, often to enhance stability or prevent proteolysis.

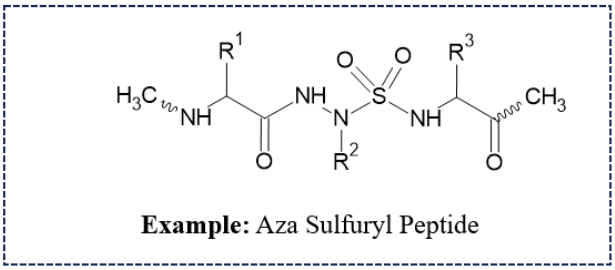
ii. **Type II (Functional Mimetics) :** These compounds mimic the biological activity of a peptide without necessarily mimicking its structure, focusing on binding to the same target site.

iii. **Type III (Topographical Mimics) :** These peptidomimetics utilize novel scaffolds to position the relevant amino acid side chains, mimicking the overall shape and function of the parent peptide.

iv. **Type IV (Non-peptide mimetics) :** These are structurally similar to type I peptidomimetics but bind an enzyme form that cannot be accessed by type I.

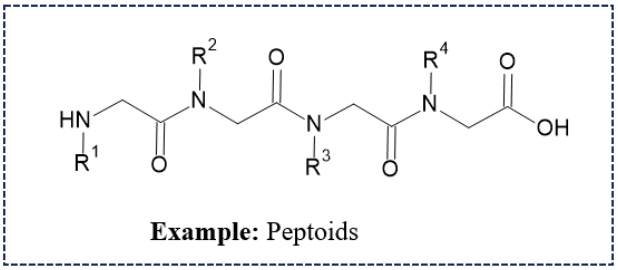
The new classification is categories on the basis of their degree of similarity to the natural peptide precursor which is recently proposed by Grossmann and coworkers.[23–27]

i. **Class A (modified peptides):** These primarily comprise the amino acid sequence of the parent peptide. To stabilize the bioactive conformation and lower the rate of proteolysis breakdown, just a small amount of modified amino acids is added. A class A mimetic's side chains and backbone closely match the precursor peptide's bioactive conformation.



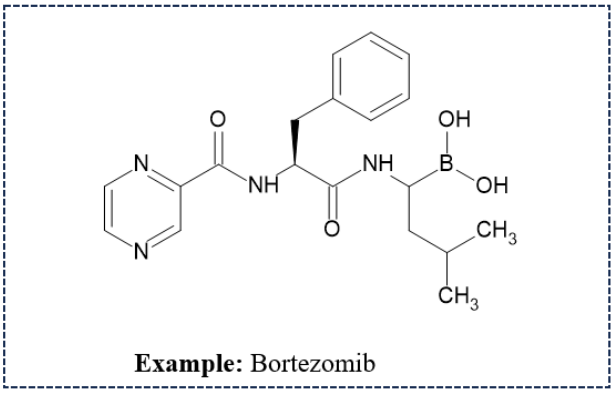
Example: Aza Sulfuryl Peptide

ii. **Class B (Foldamers):** It contain additional modifications to class A mimetics that include significant backbone changes, isolated small-molecule building blocks, and/or different non-natural amino acids. Foldamers, such β- and α/β-peptides, and peptides that arrange their side chains topologically similarly to the precursor peptide are also included in this family.



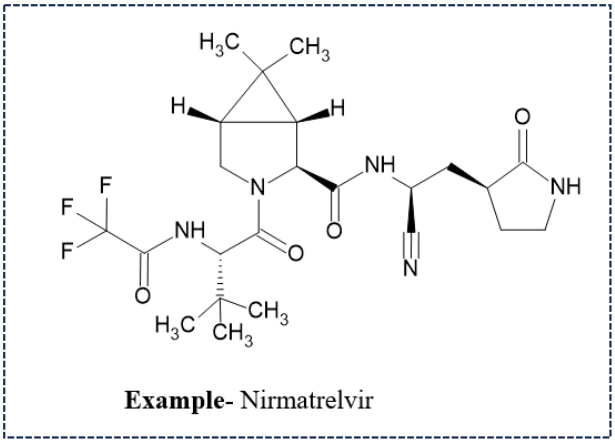
Example: Peptoids

iii. **Class C (Structural mimetics):** The peptide backbone is entirely replaced by significantly modified structures with small-molecule characteristics. Similar to how important residues (like hot spots) are oriented in the parent peptide's bioactive conformation, the central scaffold projects substituents.



Example: Bortezomib

iv. **Class D (Mechanistic mimetics):** These are compounds that, without having a direct connection to the side chain functions of a bioactive peptide, replicate its mode of action. These compounds can be produced by optimizing the affinity of a class C molecule, or they can be found through screening of compound libraries or virtual libraries in silico.



Example- Nirmatrelvir

DISCOVERY AND DEVELOPMENT OF PEPTIDOMIMETICS

The history of mimicking peptides, or peptidomimetics, spans from the early 20th-century synthesis of peptides to their current use in drug discovery and biomaterials, with key milestones including the isolation of insulin and the development of strategies to stabilize and enhance peptide activity.[28]

German chemist Emil Fischer, a Nobel laureate, discovered the chemical reaction to join amino acids into a chain, creating peptides.[29,30] The isolation of insulin

from livestock pancreata in the 1920s and its use to treat diabetes marked a significant early application of peptides as therapeutics.[31] The development of peptide synthesis techniques, including solid-phase peptide synthesis, allowed for the creation of a wider range of peptides with diverse structures and functions.[32] Peptide hormones, their analogs, and mimetics became important in the pharmaceutical industry for hormonal replacement therapy and other applications.[33] Peptidomimetic approaches have been used to design small molecules that selectively target cancer cells, an approach known as targeted chemotherapy. Peptides are also used in biomaterial engineering due to their biocompatibility, biodegradability, and functional selectivity. Researchers have focused on designing peptides that mimic specific protein-protein interactions, including those involved in disease processes.[34,35]

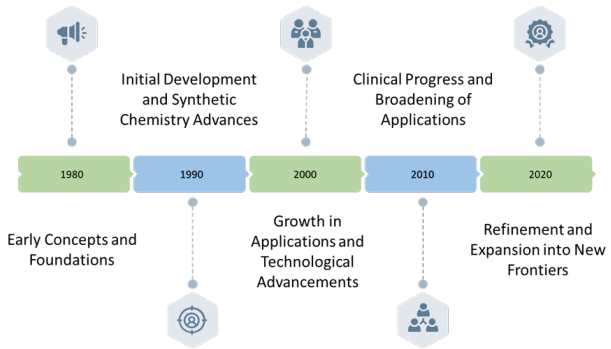


Fig. 3: Historic Overview of Peptidomimetics

STRATEGIES FOR THE SYNTHESIS OF PEPTIDOMIMETIC

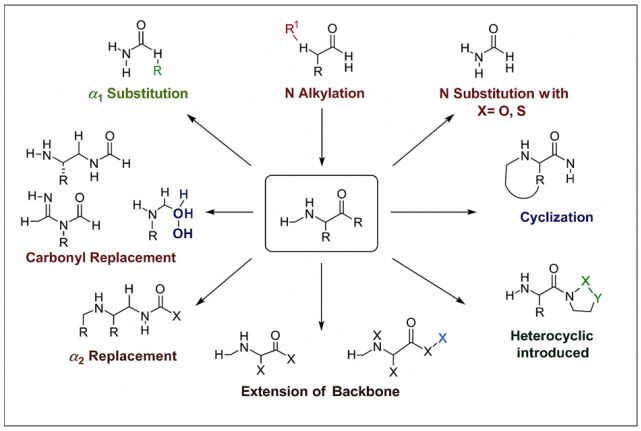


Fig. 4: Strategies For the Synthesis of Peptidomimetic

The design and synthesis of these peptide-mimicking molecules require innovative strategies that often involve modifications to the peptide backbone, alteration of amino acid side chains, or the construction of entirely non-peptidic scaffolds.

Backbone Modifications

Backbone modifications are one of the most commonly used strategies to improve the stability and pharmacological properties of peptidomimetics. By altering the peptide backbone, typically through the substitution of peptide bonds with more stable, non-peptide linkages, peptidomimetics can resist enzymatic degradation while maintaining their ability to bind to target proteins.[36]

- **Amide Bond Replacement:** The amide bond, which links amino acids in a peptide chain, is highly susceptible to proteolysis. Replacing the amide bond with more stable linkages, such as β-amino acids, N-methylated peptides, or urea-based linkers, can improve resistance to enzymatic cleavage and increase stability.[37]
- **Backbone Cyclization:** The introduction of a cyclic structure to the peptide backbone can enhance the stability and rigidity of the molecule. Cyclization also improves the bioactivity by increasing the conformational constraint of the peptide, leading to stronger and more specific interactions with the target.[38]

Incorporation of Non-Natural Amino Acids

Incorporating non-natural amino acids into peptidomimetics is a powerful strategy for enhancing their stability, specificity, and bioactivity. These non-natural amino acids can be designed to mimic natural amino acids or introduce unique functional groups that are not present in natural peptides.

- **D-Amino Acids:** The use of D-amino acids (the mirror image of the natural L-amino acids) can increase resistance to proteolysis and enhance the stability of the peptidomimetic without affecting its bioactivity.[39]
- **Non-Natural Side Chains:** Modifying the side chains of amino acids, such as incorporating aromatic or aliphatic groups, can improve the binding affinity and specificity for the target receptor or protein. This also provides more flexibility in optimizing the pharmacokinetic properties of the compound.[40]

Peptide Bond Surrogates

One of the central strategies in peptidomimetic design is replacing the traditional peptide bond with synthetic surrogates that maintain the desired biological activity. These surrogates can enhance the metabolic stability and bioavailability of the compound.[41–43]

- **Hydrazone Bonds:** Hydrazones are stable, non-peptidic replacements for amide bonds, allowing

for better stability and resistance to enzymatic degradation.

- **Thioesters or Thioureas:** Replacing the oxygen in the peptide bond with sulfur (thioester) or nitrogen (thiourea) can also increase resistance to enzymatic cleavage while still allowing for effective receptor binding.
- **Isosteric Replacements:** Isosteric replacements involve substituting atoms or groups in the peptide structure with those of similar size and shape, which helps preserve the bioactivity while enhancing stability. Examples include replacing oxygen atoms with sulfur or using azapeptides (where the carbonyl group is replaced by a nitrogen atom).

Side Chain Modifications

The side chains of amino acids play a critical role in peptide-receptor interactions. Modifying these side chains can improve the affinity, selectivity, and overall pharmacological properties of the peptidomimetic.

- **Aromatic Modifications:** Aromatic groups can be introduced to enhance π-π stacking interactions, leading to stronger binding to target proteins. These modifications can also improve the lipophilicity of the peptidomimetic, enhancing membrane permeability.[44]
- **PEGylation:** The attachment of polyethylene glycol (PEG) groups to the peptidomimetic can increase its solubility, stability, and half-life in circulation, which is particularly useful for therapeutic applications.[45]

Conformational Constraint

To mimic the specific three-dimensional structure of peptides, it is often important to induce a constrained conformation in peptidomimetics. This can be achieved through:

- **Ring Formation:** The creation of cyclic structures (e.g., lactams or disulfide bridges) can stabilize the desired conformation, mimicking the bioactive conformation of natural peptides.[46]
- **Intramolecular Interactions:** Strategies such as the use of hydrogen bonding, hydrophobic interactions, and electrostatic interactions within the molecule can stabilize a specific conformation that is optimal for binding to the target protein or receptor.[47]

PHARMACOLOGICAL ACTIVITY OF PEPTIDOMIMETICS

Peptidomimetics as immunomodulators:

In past decades, treatments for autoimmune disorders have often involved immune system suppression in addition to symptom reduction. The majority of autoimmune illnesses are inflammatory in origin, involving the generation of cytokines and a T-cell response.[48] In past decades, treatments for autoimmune disorders have often involved immune system suppression in addition to symptom reduction. The majority of autoimmune illnesses are inflammatory in origin, involving the generation of cytokines and a T-cell response.[49,50] Mikyung Kim and co-workers[51] developed peptides and peptidomimetics for immunomodulation by targeting CD2-CD58/CD48 costimulatory molecules. In order to modify CD2-CD58/CD48 interactions, they created a peptide based on structural and mutagenesis research. With an IC50 value of 6 nM, the proposed peptide has been demonstrated to block the cell adhesion interaction using in vitro experiments. A dibenzofuran moiety was used to change the peptide into a peptidomimetic.[52,53]

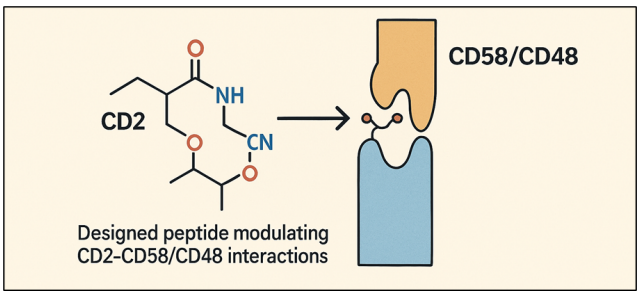


Fig. 5: Peptidomimetics for immunomodulation by targeting CD2-CD58/CD48 costimulatory molecules

Antimicrobial Activity:

Dahui Liu and co-workers[54] designed a series of amphiphilic L+2 helical β-peptides, was to replicate the general physicochemical characteristics of a class of membrane-active antimicrobial peptides, such as cecropin and magainin. These peptides demonstrated strong antibacterial action[55], but they also shown notable activity against human erythrocytes.

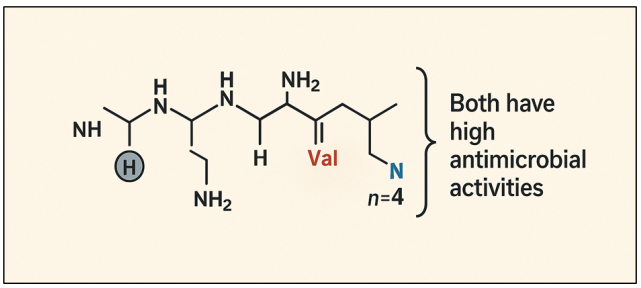


Fig. 6: β-peptides H-(β3-HAla-β3-HLys-β3-Hval)n-NH2

Assuming that their high hydrophobicity was the cause of their lack of specificity, two more β-peptides, H-(β3-HAla-β3-HLys-β3-Hval)n-NH2 (n = 4, 5), were created

and produced. Despite having very low hemolytic potencies, both have strong antibacterial properties. Phospholipid vesicles are bound by the peptides in a L+2 shape, which causes trapped small molecules to seep out. The peptides attach firmly to vesicles that contain 10 mol% acidic phosphatidylserine lipids, but they have little affinity for membranes made of neutral phosphatidylcholine lipids. [56–58]

Antitumor activity:

Preliminary data suggests that this radioligand may be useful for non-invasive tumor metastasis monitoring and early tumor detection in a variety of conditions. In the first-in-human trial, this radiolabeled peptidomimetic was shown to be effective in patients with breast cancer and non-small cell lung cancer. [59,60] Bhaskar C. Das and co-workers [61] generated a chemical library of peptidomimetic derivatives of 4-HPR in an attempt to create a more biologically active compound for use as a therapeutic agent against RTs and other tumors. By replacing the alkene backbone with a ring structure, they synthesized a novel peptidomimetic chemical substances that maintains its biological activity in rhabdoid tumor cell culture models. Using a survival assay against rhabdoid tumor cells, they also discovered a peptidomimetic chemical derivative (11d, IC50 $\sim$ 3 μM) that was almost five times more potent than 4-HPR (1, IC50 $\sim$ 15 μM). According to these research, novel chemotherapeutic drugs that are promising against RTs and other malignancies are peptidomimetic compounds that maintain their cytotoxic efficacy. [62,63]

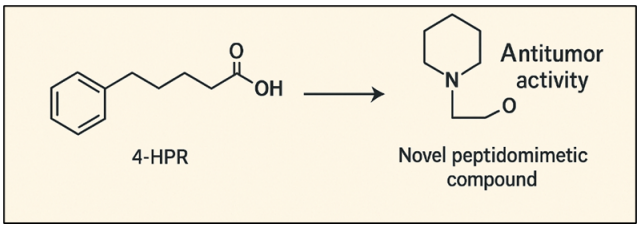


Fig. 7: Peptidomimetic derivatives of 4-HPR

Antimalarial Activity:

Synthetic analogs known as peptidomimetics, which mimic peptides both structurally and functionally while avoiding proteolytic breakdown, have become effective antimalarial drugs. [64] In the past, peptide-based inhibitors that targeted Plasmodium proteases, like plasmepsins and falcipains, showed promise but were constrained by low bioavailability and stability. The development of peptidomimetic scaffolds with limited conformations, backbone alterations, and non-natural amino acids represented a major breakthrough in avoiding these pharmacokinetic risks. [65] Shuren Zhu and co-workers [66] A modified 5-aminopyrimidone ring and a Michael acceptor side chain, methyl 2-hydroxymethyl-but-2-enoate, make up the novel agents' fundamental structure. The synthesis of 1—6 included an SN2 Mitsunobu reaction with diethyl azadicarboxylate (DEAD), triphenylphosphine (Ph3P), and different acids, as well as a Baylis—Hillman reaction of different aldehydes with methyl acrylate catalyzed by 1,4-diazabicyclo(2.2.2)octane (DABCO). The novel compounds demonstrated strong in vitro growth inhibitory activity (IC 50 = 10—30 ng/mL) against Plasmodium falciparum [67] clones. Compound 6 (IC50 = 6—8 ng/mL) is the most active compound of the class, the antimalarial efficacy of which is comparable to that of chloroquine.

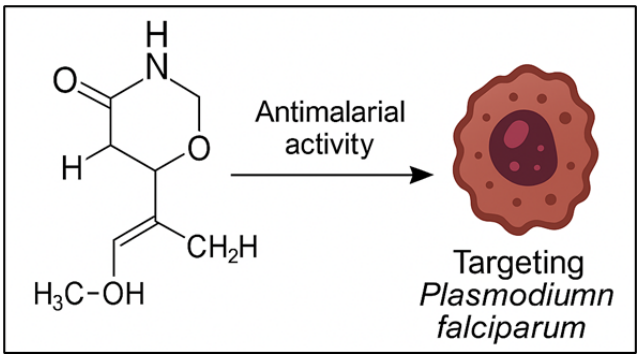


Fig. 8: Pyrimidinyl peptidomimetic agents possess antimalarial activities against *Plasmodium falciparum*

CHALLENGES AND LIMITATIONS

The new period of peptide medicines comes with some bright news but also accompanied with being and implicit challenges. Some of the challenges have been addressed in the history as bandied in the below section, but other obstacles still need farther examinations. In this section, many of these challenges have been assessed completely. [68–70]

- **Complexity of Design and Synthesis:** Mimicking the complex 3D structure and intricate interactions of peptides is a significant challenge. The synthesis of peptidomimetics can be complex and time-consuming, often requiring multi-step processes and specialized reagents. This can increase the cost of drug development.
- **Pharmacokinetic Properties:** Peptidomimetics, like peptides, can be susceptible to rapid degradation by enzymes in the body, leading to short half-lives and reduced bioavailability. Many peptidomimetics have limited oral bioavailability due to poor absorption across the gastrointestinal tract. It may have difficulty crossing cell membranes, hindering their ability to reach their targets within cells.
- **Toxicity and Immunogenicity:** Peptidomimetics, like any drug, can have unintended side effects due to interactions with off-target proteins or biological pathways.

It is especially those containing non-natural amino acids or modifications, can elicit an immune response, leading to allergic reactions or the development of antibodies that neutralize the drug.

- **Predicting Biological Activity:** Understanding the relationship between the structure of a peptidomimetic and its biological activity can be challenging, requiring extensive experimental and computational studies.
- **High Development Costs:** The development of peptidomimetic drugs is a lengthy and expensive process, requiring significant investment in research, development, and clinical trials.

FUTURE PROSPECTIVE OF PEPTIDOMIMETICS

Peptidomimetics offer a promising future in drug discovery and development. Here are some key prospective areas:[71–73]

- **Improved Drug-likeness:** Peptidomimetics can be designed to resist proteolytic degradation, increasing their bioavailability and half-life in vivo. This is crucial for oral delivery and sustained therapeutic effects. Many peptides have poor cell permeability, limiting their efficacy. It can be modified to improve their ability to cross cell membranes, increasing their target engagement also, can be optimized to minimize off-target effects and improve their safety profile.
- **Expanded Therapeutic Applications:** Peptidomimetics offer a potential solution to the growing problem of antimicrobial resistance by targeting novel bacterial pathways or mechanisms. It can be designed to modulate protein-protein interactions involved in neurodegenerative diseases, such as Alzheimer's and Parkinson's. It can be used to inhibit tumor growth, induce apoptosis, and modulate the immune response against cancer. Peptidomimetics can be developed to target viral proteins and inhibit viral replication, offering potential treatments for emerging viral diseases.
- **Advanced Technologies:** The use of computational methods, such as molecular docking and dynamics simulations, can accelerate the design and optimization of peptidomimetics. Combinatorial chemistry techniques can be used to generate large libraries of peptidomimetics, increasing the chances of identifying potent and selective compounds. Conjugating peptidomimetics to drugs or other molecules can enhance their therapeutic efficacy and selectivity.

CONCLUSION

Peptidomimetics represent a promising frontier in modern drug discovery, offering significant advantages over native peptides, including enhanced metabolic stability, improved bioavailability, and increased target specificity. Through strategic modifications of the peptide backbone, incorporation of non-natural amino acids, and innovative structural scaffolding, peptidomimetics have demonstrated broad therapeutic potential across diverse areas such as oncology, infectious diseases, and immunomodulation. Although several challenges persist such as synthetic complexity, limited oral bioavailability, and potential immunogenicity ongoing advancements in molecular modeling, combinatorial chemistry, and high-throughput screening are facilitating the rational design of next-generation peptidomimetics. With continued interdisciplinary research, peptidomimetics are poised to play a pivotal role in the development of novel, efficacious, and safer therapeutic agents.

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