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PEPTIDOMIMETICS-THE NEXT GENERATION OF THERAPEUTICS

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ABSTRACT

In the last twenty years, peptide drug discovery has seen a big revival, thanks to the growing use of organic chemistry and biotechnology. These fields have been key in creating peptidomimetics that are more stable, specific, and easier for the body to absorb than traditional peptides. Peptides have been used as treatments, but they often come with problems like not being well absorbed, breaking down quickly in the body, and being removed from the system too fast. To overcome these issues, scientists create peptidomimetics, which are modified versions of natural peptides. These modified molecules are better suited for use in medicine, which is why they are commonly used in drug development programs. There's a lot of ongoing work to find new and better peptidomimetic therapies, as shown by the new compounds currently being tested in clinical trials. Over time, new methods have been developed to make these peptidomimetics. This overview looks at recent advances in designing and making peptidomimetic drugs, as well as how they work against different targets. The development of peptidomimetics represents a dynamic frontier in medicinal chemistry. By addressing the inherent limitations of native peptides, peptidomimetics provide drug candidates with improved stability, receptor affinity, and

selectivity. Synthetic strategies—including β-turn mimetics, constrained scaffolds, and hybrid peptide–small molecule constructs—have expanded the chemical space available for drug discovery. These approaches allow fine-tuning of conformational flexibility and pharmacological profiles, making peptidomimetics a versatile toolbox for targeting protein–protein interactions and enzyme inhibition. Their adaptability positions them as promising leads in therapeutic areas ranging from metabolic disorders to neurodegenerative diseases.

KEYWORDS: Peptidomimetics, Traditional peptide, biotechnology, neurodegenerative disease, constrained scaffolds, conformational flexibility

1. INTRODUCTION

Peptidomimetics are chemical compounds that copy the important parts of a natural peptide or protein in three-dimensional space. They are made to work with the same biological targets and create the same effects as the original peptides. These compounds are designed to solve some of the problems that natural peptides face, like breaking down too quickly in the body and not being well absorbed. Peptidomimetics can also improve other features, such as how well they bind to receptors or how strong their effects are. This makes them very useful in finding new drugs. The process of creating these compounds starts by studying how the structure of a molecule affects its activity, which helps identify the smallest active part or the most important features that lead to the desired biological effect.[1] Peptides and proteins are essential parts of cells, playing key roles in many important biological processes. They help build and support cells and tissues, send signals between cells, control body functions, and support the immune system. These molecules come in different shapes and sizes, from small peptides that have simple or random structures to larger proteins with complex shapes made up of coils, flat sheets, and bends. This variety in structure shows how flexible and useful peptides and proteins are in carrying out their important jobs inside living cells.[2] Peptidomimetics refer to the alteration of peptide sequences to enhance their biological functions, along with replacing the natural peptide structure with a different molecular framework (Kuppusamy et al. 2019). These molecules are created to remain stable in the body, easily absorbed, and very specific in their action.[7]

2. HISTORY OF PEPTIDOMIMETICS

The history of peptide therapeutics includes important events, progress, and drug approvals. The first peptide drug was insulin, which was taken from the pancreas of cows and pigs. In 1954, Vincent du Vigneaud's team successfully made oxytocin and vasopressin in the lab, a

major achievement that earned them the Nobel Prize in Chemistry in 1955. Another big step came when Bruce Merrifield came up with the idea of using a solid phase to build peptides automatically, leading to the development of solid-phase peptide synthesis in 1963, which was later honored with the Nobel Prize in Chemistry in 1984. In the 1980s, recombinant technology allowed for the production of longer peptides in a cleaner way. To extend the time peptides stay in the bloodstream, scientists started linking them to lipids, bigger proteins, and polyethylene glycol. New methods like phage display help find peptides with better drug-like qualities from large collections. Flexizyme technology lets researchers include non-standard amino acids into these collections. Also, finding peptides from natural sources like venoms and using new chemistry methods are pushing the field forward. The lower part of the figure shows some approved peptide drugs and when they first got regulatory approval based on these developments.[3]

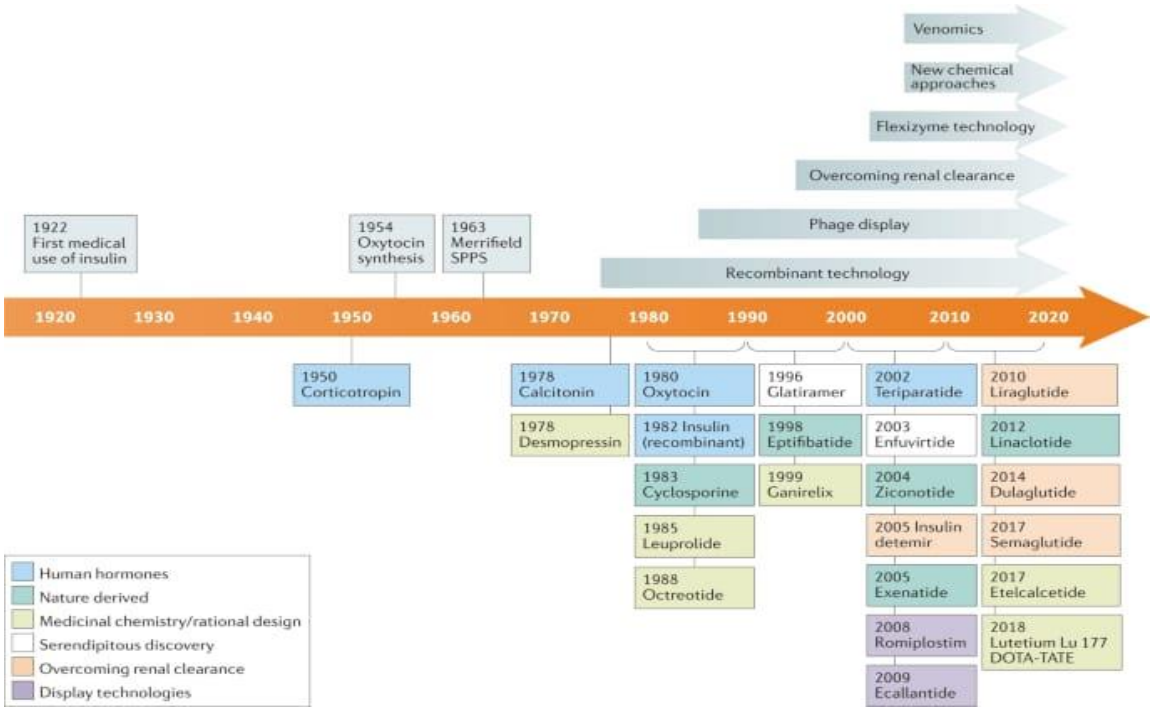


IMAGE 01. HISTORY OF PEPTIDOMIMETICS OR LIST PEPTIDE DRUG.

3.TYPES OF PEPTIDOMIMETICS

This type of classification is totally depends on their structure and functions.this traditional type of classification is mainly categorize the mimetics based on how closely they resembles the original peptides structure and topography.

3.1 STRUCTURAL MIMETICS/PSEUDOPEPTIDE

Pseudopeptides are special man-made molecules made by combining parts that look like peptides with other non-biological building blocks. Because of this, they get the best features from both peptide-like and non-biological structures. They can be easily built in different ways, have a wide variety of chemical and functional properties, can be shaped into specific 3D forms, are usually very stable in the body, and don't cause much harm to healthy cells. In recent years, these kinds of molecules have been used in many areas of biomedical research, such as sensing biological signals, moving ions across cell membranes, recognizing important biological molecules, delivering drugs, and helping genes get into cells. This review covers some of the most important and recent developments in this area.[4]

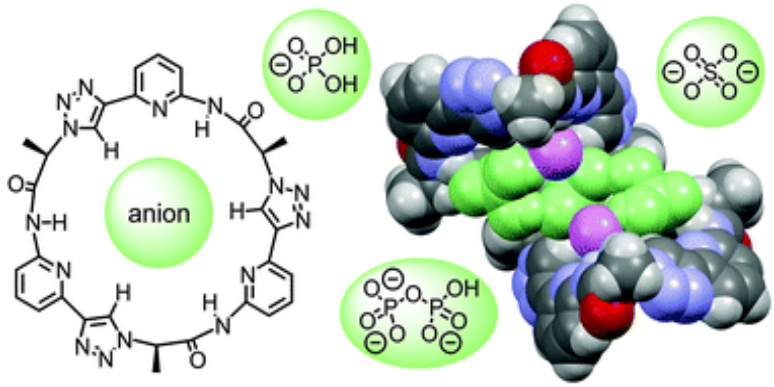
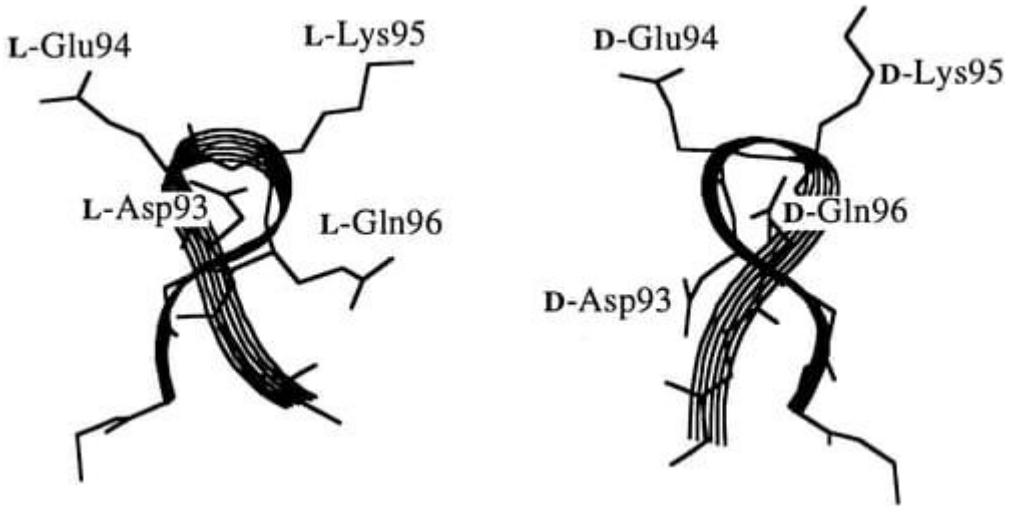


Fig.no-02 pseudomimetics /structural mimetics.

3.2 FUNCTIONAL MIMETICS

These peptidomimetics are made using methods like molecular modeling and high throughput screening. They are small molecules that aren't peptides but can attach to peptide receptors. Morphine was the first clear example of this kind of peptidomimetic. At first, type I1 mimetics were thought to be similar in structure to the natural peptides. However, studies using site-directed mutagenesis showed that antagonists for many receptors bind to different parts of the receptor than the original peptide does. This means that functional mimetics might not look like the parent peptide. Even with this uncertainty, this method has been very effective and has led to several possible drug candidates. For example, G-protein coupled receptor (GPCR) antagonists.[5]



3.3 TYPE-III OR STRUCTURAL-FUNCTIONAL MIMETICS

Type III mimetics, also known as functional-structural mimetics, are components that interact in the same spatial arrangement as the original molecule but have a very different structural framework.[6] A structural or functional mimic is a non-peptide molecule that has a similar shape or arrangement to the original peptide but doesn't match it exactly at the atomic level (Pelay-Gimeno et al. 2015; Floris and Moro 2012). The fourth type, or non-peptide mimics, looks similar to type I peptidomimetics but can bind to a different form of an enzyme that type I mimetics cannot reach (Kharb et al. 2011).[7]

3.4 TYPE IV OR NON-PEPTIDE MIMETICS

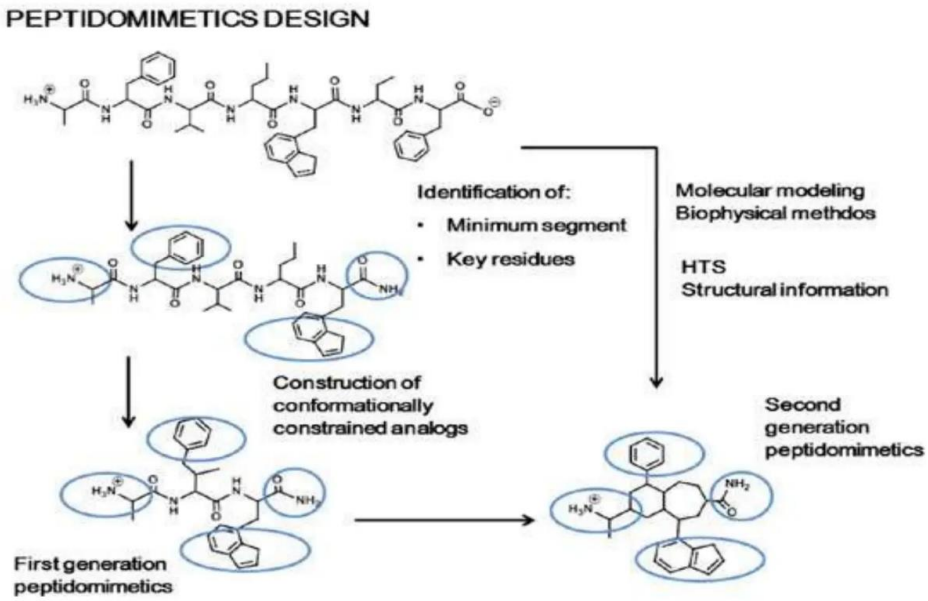
These are synthesized by Group Replacement Assisted Binding (GRAB) technique of drug design. These structures might share structural functional features of type I peptidomimetics, but they bind to an enzyme form not accessible with type I peptidomimetics for example piperidine inhibitors [8] This class of peptidomimetics was recently discovered. They are known as GRABpeptidomimetics, which stands for group replacement-assisted. They have some functional features that are similar to Type-I peptidomimetics and can take part in certain unique interactions with enzymes. An example of this type is Piperidine inhibitors. These are used to create non-peptidic rennin inhibitors that are more conformationally stable compared to natural protein inhibitors.[16]

4. DESIGN APPROACH OF PEPTIDOMIMETICS

There are two different approaches to design peptidomimetics: a medicinal chemistry approach, where parts of the peptide are successively replaced by non-peptide moieties until getting a non-peptide molecule and a biophysical approach, where a hypothesis of the

bioactive form of the peptide is sketched and peptidomimetics are designed based on hanging the appropriate chemical moieties on diverse scaffolds. Although both approaches have been used in the past, the former has been more widely used to design peptidomimetics of secretory peptides, whereas the latter is nowadays getting momentum with the recent interest in designing protein-protein interaction inhibitors. The present report summarizes the relevance of the information gathered from structure-activity studies, together with a short review of the strategies used to design new peptide analogs and surrogates. In the following section, there is a short discussion on the characterization of the bioactive conformation of a peptide, to continue describing the process of designing conformationally constrained analogs producing first and second generation peptidomimetics. Finally, there is a section devoted to reviewing the use of organic scaffolds to design peptidomimetics based on the information available on the bioactive conformation of the peptide. [9] Peptidomimetics designed to mimic peptide biological activity with multiple drug-like habitats are increasingly crucial in medicinal chemistry. They offer enhanced systemic delivery, mobile penetration, target specificity, and safety against peptidases when compared to their native peptide counterparts. Already used to treat a variety of diseases such as neurodegenerative disorders, cancer, and infectious diseases, their future in medicine seems vibrant, with many peptidomimetics in scientific trials or improvement stages. Peptidomimetics are nit-perfect for addressing disrupted protein-protein interactions (PPIs) that regularly underlie various diseases. Structural biology and computational methods such as molecular dynamics simulations facilitate rationalizing the configuration, while gadget learning algorithms accelerate protein structure prediction, enabling the improvement of green drugs.[10] Conformational constraints Peptidomimetics include features like cyclic structures, beta-turn mimetics, and peptide pulleys to keep the molecule in a specific shape that is active and improves how well it binds to its target. Backbone variations Peptidomimetics use changes in the main chain, such as N-methylation, alpha-amino acid replacements, and peptide objectification, to make the molecule more resistant to being broken down by enzymes and improve its ability to be taken up orally. Side chain variations Peptidomimetics also change the side chains, often by replacing natural amino acids with non-standard ones or adding different functional groups, to make the molecule interact better with target proteins and boost its binding strength. Scaffold hopping Peptidomimetics use scaffold hopping methods to look for new chemical structures and find better molecular frameworks that have improved drug properties and more specific targeting. Computational design Peptidomimetics use computer-based techniques like molecular docking, molecular dynamics simulations, and structure-based design to

predict and refine how molecules interact with target proteins, supporting more efficient and targeted drug development and optimization.[20]



PEPTIDOMIMETICS DESIGNING

5. DIFFERENCE BETWEEN PEPTIDE BOND AND PEPTIDOMIMETICS

Peptide bond (amide linkages) connect natural amino acids to form biodegradable, flexible proteins, but they are highly susceptible to enzymatic degradation and have poor bioavailability.Peptidomimetics are synthetic, peptide-like molecules designed to mimic these structures while incorporating modifications to enhance stability, protease resistance, and bioavailability. [11]

5.1 Key Differences

- **Structure:** Peptides are made of natural amino acids; peptidomimetics use non-natural amino acids, altered backbones (e.g., urea, thioamide), or non-peptide scaffolds.[12]
- **Stability:** Peptide bonds are easily broken by enzymes (proteases); peptidomimetics are designed to resist this, increasing their metabolic half-life.[13]

- **Flexibility:** Peptides are typically highly flexible; peptidomimetics often incorporate constraints (like cyclization or unnatural amino acids) to lock them into the bioactive conformation.
- **Function:** Peptides are mostly natural signaling molecules; peptidomimetics are developed as therapeutic drugs to overcome the pharmacokinetic limitations of peptides. [14]

6.SIGNIFICANCE OF PEPTIDOMIMETICS

6.1 Expanding the Drug Target Space

Peptidomimetics overcome the limitations of natural peptides by targeting difficult protein-protein interactions and intracellular targets that were previously considered undruggable [15].

6.2 Enhanced Pharmacokinetic Properties

Peptidomimetics offer better pharmacokinetic properties, such as increased stability, higher bioavailability, and longer half-life compared to natural peptides, which allows for more effective delivery and sustained therapeutic effects [23].

6.3 Target Specificity and Selectivity

Peptidomimetics can be designed with high target specificity and selectivity, reducing off target effects and improving the safety of therapeutic interventions [24].

6.4 Structural Diversity and Versatility

Peptidomimetics exhibit a wide range of structural diversity, from small molecules to macrocycles, offering versatility in drug design and development for targeting various molecular pathways and disease mechanis.[25]

6.5 Facilitating Rational Drug Design

Peptidomimetics provide a rational approach to drug design, allowing precise manipulation of structural and functional properties to optimize interactions with target proteins and improve therapeutic efficacy [26].

5.6 Overcoming Peptide Limitations

Peptidomimetics address limitations of natural peptides, such as susceptibility to enzymatic d egradation and poor membrane permeability, making them viable therapeutic agents [27].

6.7 Modulating Protein Function

Peptidomimetics modulate protein function by mimicking the binding interfaces of natural pe ptides, disrupting protein-
protein interactions or enzyme activity involved in disease progression [28].

6.8 Expanding Therapeutic Targets

Peptidomimetics expand the range of drug targets by targeting unique binding pockets or stru ctural motifs on proteins, enabling the development of therapies for previously untapped dise ase pathways [29].

6.9 Advancing Precision Medicine

Peptidomimetics play a key role in advancing personalized medicine by enabling the design o f tailored therapies that target specific molecular markers or genetic mutations associated wit h individual patients [30].

6.10 Combating Drug Resistance

Peptidomimetics offer strategies to overcome drug resistance mechanisms by targeting essent ial pathways or developing multi-targeted therapies that inhibit multiple disease-
related proteins simultaneously [31].

6.11 Enhancing Drug Delivery

Peptidomimetics serve as versatile platforms for drug delivery, enabling targeted delivery of t herapeutics to specific tissues or cell types, thus improving drug efficacy and reducing system ic toxicity [32].

6.12 Facilitating Biomolecular Imaging

Peptidomimetics have applications in biomolecular imaging, serving as molecular probes or contrast agents for imaging specific biomarkers or disease-related processes in vivo [33]. Polymerases, Pivotal for Pathogen Survival and Replication [34]. Antiviral Agents Peptidomimetics developed as antiviral agents target viral proteins or processes essential for viral replication, such as enzyme inhibitors and protease inhibitors [35]. Antimicrobial Agents Peptidomimetics mimic natural antimicrobial peptides, disrupting bacterial membranes or inhibiting bacterial cell wall synthesis, offering new treatments for antibiotic-resistant infections [36].

7. Application of peptidomimetics

7.1 Improving drug-like characteristics including metabolic activity,BBB permeability, Stability,and oral bioavailabilty

The use of opioid peptides in clinical settings has been limited because they don't stay stable in the body for long and have a hard time getting past the blood-brain barrier . Being able to cross the blood-brain barrier and reach the central nervous system to bind to opioid receptors and provide pain relief depends on their physical and chemical characteristics such as size, how well they dissolve in fats, how they hold onto water, how resistant they are to enzymes, and other structural traits. These properties of opioid peptides have not been ideal, which has made it difficult for them to be taken orally and have enough effect in the body. Peptidomimetics, which are not made of peptides, might help fix these problems by making the drugs more effective and longer lasting at their target area . Because of this, many different peptidomimetic methods have been developed to create better molecules that work well in the central nervous system. However, there are still no clear replacements for traditional pain medicines.[15]

7.2 PEPTIDOMIMETICS AS ANTIDIABETIC

There is a lot of obesity happening around the world, but not many new medicines have been approved to treat it. Because of this, there is a big need for new ways to treat obesity. Bioactive peptides have been used to help with metabolic issues like type-2 diabetes and obesity.[17] In people with diabetes, keeping blood sugar levels under control is very important to stop more damage to the body and to avoid serious problems like strokes, heart attacks, or kidney failure (Snell-Bergeon and Wadwa, 2012). Right now, treatments that mimic incretins, especially GLP-1R agonists and DPP4 inhibitors, are the main medicines used for type 2 diabetes (Drucker and Nauck, 2006). As peptidomimetics, GLP-1R agonists work like the body's own hormone GLP-1. They help the body release more insulin when blood sugar is high, stop the release of glucagon, reduce the liver's production of glucose, and slow down how fast food leaves the stomach. Also, GLP-1 helps the body use glucose more effectively, which is very important for diabetes, and it can also help the pancreas grow and develop more beta cells (Drucker and Nauck, 2006; Meier, 2012). Additionally, GLP-1R agonists can work both quickly and over a long time, which means doctors can create treatment plans that are tailored to each patient (Neumiller, 2015).DPP-4 is an enzyme that breaks down GLP-1, so stopping DPP-4 can help keep more GLP-1 in the blood, which in turn increases the levels of incretins in the body (Deacon et al., 1998, Deacon,

2011).Treatments that mimic incretins have other good effects, such as a lower chance of causing low blood sugar, helping to control blood sugar spiks after meals (with DPP4 inhibitors and short-acting GLP-1R agonists), and possibly helping with weight loss (with GLP-1R agonists; Neumiller, 2015).[18]

7.3 PEPTIDOMIMETICS IN CANCER THERAPY

Peptidomimetics focus on cell surface receptors that are overactive in cancer cells, helping with better diagnosis, determining the stage of cancer, and treatment. Integrin receptors, especially the αvβ3 type, are main targets. Peptidomimetics that imitate the RGD (Arg-Gly-Asp) sequence work as integrin blockers and tools for imaging. Radioactive tracers such as 18F-Galacto-RGD, 99mTc-NC100692, and 18F-fluciclatide, along with nanoparticles like Gd^{3+} liposomes, quantum dots, and gold nanoparticles, are used in imaging techniques such as PET and SPECT. Bifunctional diketopiperazine (DKP) RGD peptidomimetics bind with low nanomolar strength to αvβ3 and αvβ5 integrins. Clinical examples such as Cilengitide help stop the growth of new blood vessels in tumors and are being tested for use in several types of cancer. Radiolabeled cyclic peptidomimetics have been effective in early detection of tumors and watching for cancer spread in breast and non-small cell lung cancer. Research is also looking into targeting other integrin subtypes, such as α5β1, for more targeted treatments and imaging because they play roles in tumor spread, metastasis, and resistance to treatment. Peptidomimetics are being used more often for imaging cancer. LLP2A is a strong binder for the α4β1 integrin; its 18F- and 64Cu-labeled forms are used in PET imaging to detect and monitor multiple myeloma early. FAP-2286, which targets fibroblast activation protein (FAP), shows potential in finding metastatic areas in various solid tumors. Peptidomimetics can also target other biomolecules like CRIP1, which is overexpressed in breast and cervical cancers. Cyclic peptides such as A1M (CLDGGGKGC), developed through phage display and computer modeling, bind CRIP1 at micromolar levels, allowing for imaging of cancer tissues. Overall, molecular imaging and targeting protein interactions using peptidomimetics show great promise in cancer diagnosis.[19]

7.4 PEPTIDOMIMETICS AS ANTIVIRAL AGENT AGAINST SARS-COV2

Nirmatrelvir was created to specifically attack the SARS-CoV-2 main protease, also called 3 chymotrypsin-like protease (3CLpro). This enzyme is very important for the coronavirus because it helps break down a long protein chain into smaller parts that the virus needs to grow and spread. The enzyme cuts this chain in at least 11 spots to make the necessary

proteins and enzymes. Nirmatrelvir is a peptidomimetic, which means it's designed to look like a part of the natural 3CLpro substrate that recognizes the enzyme. The molecule has a special part at the end called an electrophilic nitrile. When the drug binds to the active site of the 3CLpro enzyme, this nitrile reacts with a sulfur group on the enzyme's Cys145 residue, forming a lasting bond. This bond stops the enzyme from working, which stops the virus from replicating. The patent application talks about 98 new inhibitors that are similar to Nirmatrelvir. These inhibitors are meant to stop the virus from multiplying and could be used to treat people with COVID-19. It also covers ways to give these inhibitors to patients as part of a medicine.[21]

8. LIMITATIONS OF PEPTIDOMIMETICS

Peptidomimetics, which are designed to be better than natural peptides, still have some major challenges. These include difficult and costly multi-step synthesis processes, and possible toxicity because of poor selectivity. Even though they are more stable than natural peptides, they might have weaker binding ability, not-so-good absorption in the body, and trouble dissolving in water. Primary Limitations of Peptidomimetics are as follow.

8.1 Complex Synthesis:

Creating peptidomimetics with modified backbones or unusual amino acids is often difficult and expensive, which can result in low production amounts[37].

8.2 Reduced Affinity and Specificity:

Changing the backbone can sometimes make the mimic less effective at attaching to its intended receptor compared to the original peptide.[38]

8.3 Pharmacokinetic Issues:

While better than natural peptides, some peptidomimetics still have poor oral absorption, low water solubility, and issues with how long they stay active in the body.[39]

8.4 Toxicity:

Altering the structure can lead to harmful effects on body tissues, especially when the mimic isn't very selective.[40]

8.5 Design Challenges:

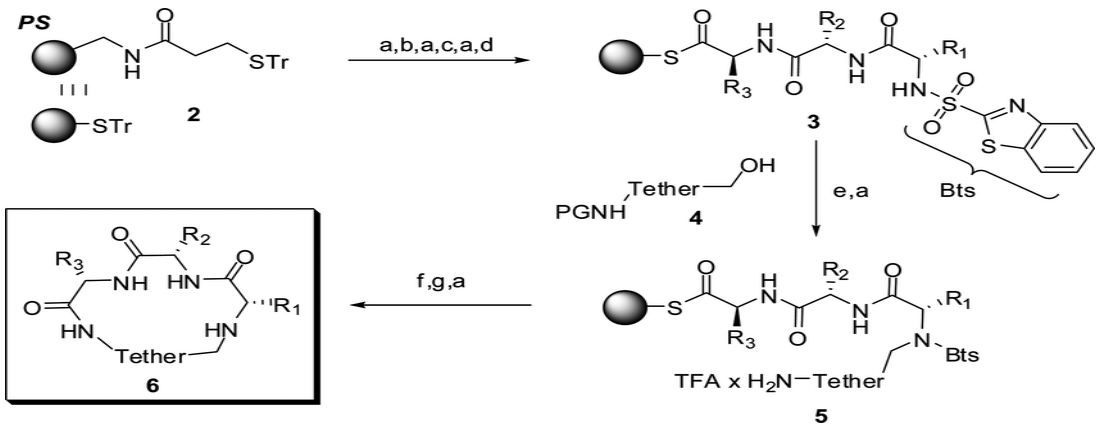
It's tough to exactly copy the complex shape and flexibility of natural peptides, especiall y when parts of the molecule aren't next to each other.[41]

8.6 Serum Binding:

Like natural peptides, some peptidomimetics stick too tightly to proteins in the blood, which lowers their concentration at the right location in the body.[42]

METHOD OF SYNTHESIS OF PEPTIDOMIMETICS

Peptidomimetics are synthesized by modifying peptide backbones or side chains to improve stability, typically using Solid-Phase Peptide Synthesis (SPPS) with Fmoc or Boc strategies. Key methods include introducing-amino acids, non-peptide backbone components, and cyclization techniques like lactamization, disulfide bridges, or click chemistry.



MARKETED PREPARATION OF PEPTIDOMIMETICS

Table no 01- Marketed Preparation of Peptidomimetcs.

Drug Name	Class / Target	Therapeutic Use	Peptidomimetic Feature	Explanation
Saquinavir, Ritonavir, Indinavir	HIV protease inhibitors	Antiretroviral therapy for HIV/AIDS	Transition-state mimetics of peptide Substrates	These drugs mimic the peptide bond cleavage site of HIV protease, blocking viral replication. Their design stabilizes against enzymatic degradation.
Valsartan, Losartan	Angiotensin II receptor blockers	Hypertension, heart failure	Mimic peptide hormone angiotensin II	They act as peptidomimetics of angiotensin II,

Drug Name	Class / Target	Therapeutic Use	Peptidomimetic Feature	Explanation
	(ARBs)			competitively blocking AT1 receptors, reducing vasoconstriction and blood pressure.
Bortezomib	Proteasome inhibitor	Multiple myeloma, mantle cell lymphoma	Boronic acid–based dipeptidomimetic	Bortezomib mimics peptide substrates of the proteasome, binding reversibly to its catalytic site, leading to apoptosis in cancer cells.
Eptifibatide, Tirofiban	Integrin (GP IIb/IIIa) antagonists	Antiplatelet therapy in Acute coronary syndrome	Cyclic peptide mimetics of fibrinogen	These drugs mimic the RGD (Arg-Gly-Asp) motif of fibrinogen, preventing platelet aggregation and thrombosis.
Enfuvirtide	Fusion inhibitor	HIV/AIDS	Synthetic peptide mimetic	Though peptide-based, it is engineered to mimic viral fusion domains, blocking HIV entry into host cells.
Maraviroc	CCR5 antagonist	HIV/AIDS	Chemokine receptor peptidomimetic	Mimics peptide ligands of CCR5, preventing HIV from binding and entering immune cells.

9. FUTURE PERSPECTIVE OF PEPTIDOMIMETICS

In this section, different ways to deal with the challenges faced in developing peptide drugs have been discussed. These methods mainly aim to solve problems related to how these drugs are made, how they are delivered to the body, and how they work against diseases. Many of the difficulties with using injections have been explained, and there's a clear need to find better ways to deliver these drugs. Different forms like sprays, ointments, creams, eye drops, films, aerosols, powders, gels, tablets, and patches can be used for various routes like nasal, topical, ocular, buccal, pulmonary, sublingual, transdermal, vaginal, and rectal (Erak et al., 2018; Mitragotri et al., 2014). Inhaling drugs has been suggested as a good way to deliver antimicrobial peptides (AMPs) for treating respiratory infections (Wang et al., 2022). Microneedles are also being used as a better way to deliver hydrophilic (Zhang et al., 2014) and hydrophobic (Zhao et al., 2017) peptides, proteins (Kirkby et al., 2020), vaccines (Pires et al., 2020), and so on. Recent studies have even created swallowable microneedle devices to

help deliver insulin and other large molecules through the mouth (Abramson et al., 2019a, 2019b). Another promising method for better oral delivery of AMP drugs is using nanotechnology. For instance, using nanoparticles to deliver insulin in mice showed a high bioavailability of 85% (Artursson and Lundquist, 2020). Zhang et al. developed a multi-layered nano-liposome coating that helps insulin get absorbed quickly and protects it from the stomach (Zhang et al., 2021b). Panigrahi et al. created a self-assembled peptide nanosphere to deliver a gene therapy tool for treating cancer (Panigrahi et al., 2022).

Combining peptides with other drugs can help in improving their effectiveness, fighting drug resistance, and making them more efficient. This approach is especially useful during pandemics such as the one caused by the coronavirus. Combining AMPs with antibiotics has shown a strong effect against drug-resistant (MDR) and dangerous pathogens (Duan et al., 2021; Cote et al., 2020). Similarly, combining peptides with other drugs for cancer treatment has been reviewed (Liu et al., 2021). Another area of interest is the use of peptide-drug conjugates (PDCs), which are made by linking the peptide to a drug with a special chemical bond (Wang et al., 2017). Peptides can be joined with SMDs to improve effectiveness and safety (He et al., 2019), with antibiotics to fight MDR (David et al., 2018; Liu et al., 2020b), or with other drugs to target cancer cells specifically (Hoppenz et al., 2020). The goal of PDCs is to make the drug more effective while reducing the issues with peptides. This could help bring back drugs that were taken off the market due to resistance and other problems. It might also cut down the time and money needed to develop new medicines. Synergy between drugs is expected to help prevent resistance (Lazzaro et al., 2020; Yu et al., 2016). Peptides can be combined with other peptides, antibiotics, SMDs, or biologics to work together better, reducing the minimum inhibitory concentration (MIC) while enhancing effectiveness and other desirable properties. Also, we need to learn from past mistakes with antibiotic use that led to resistance. In terms of making peptides, there's a need for faster, cheaper, and more eco-friendly methods. Some techniques have been discussed in previous reviews (Behrendt et al., 2016; Isidro-Llobet et al., 2019; Martin et al., 2020). More attention should also be paid to using recombinant DNA (rDNA) technology to make the pharmaceutical industry more sustainable. Recently, the full sequence of the human genome has been completed (Nurk et al., 2022), which will greatly help in developing new peptide drugs. Overall, the availability of tools, software, resources, databases, omics techniques, and gene editing tools like CRISPR-Cas9, along with advancements in artificial intelligence, machine learning, and rDNA, will create a bright future for developing peptide-based drugs. Peptides can be

modified in the ways discussed above to avoid issues related to how the body uses and processes them, but care must be taken to avoid changing their function or causing harmful effects on cells.[43]

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10.CONCLUSION

Peptidomimetics, compared to natural peptides, offer better stability, selectivity, and adaptability, making them a big change in drug development and treatment. These compounds fall between peptides and small molecules, helping to expand the range of possible drugs and enabling new ways to treat diseases. They show promise in personalized medicine and meeting specific treatment needs for various conditions, especially when designed with smart methods and structural changes. However, to use peptidomimetics effectively in real-world medical applications, future research must focus on improving their absorption in the body and reducing unwanted side effects. With the use of different scientific approaches and exploring new research areas, peptidomimetics have the potential to change drug development and play a key role in precision medicine.

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