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# Peptidomimetics Based Therapy Across Cancer, Diabetes, Infection, Neurological and Cardiovascular Disease

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**Keywords**

Stability, bioavailability, synthetic strategies, protein-protein interaction, amide bond surrogates, peptidomimetics.

**Abstract**

Peptidomimetics are synthetic compounds designed to mimic the structural and functional features of natural peptides while overcoming limitations such as poor stability, low bioavailability, and rapid degradation. These compounds maintain the ability to interact with biological targets, offering enhanced receptor selectivity, potency, and pharmacokinetic properties. Traditional classification divides peptidomimetics into structural, functional, and functional-structural types, while modern approaches categorize them into Classes A-D based on similarity to the native peptide. Advanced synthesis methods-including solid-phase peptide synthesis (SPPS), liquid-phase peptide synthesis (LPPS), and hybrid approaches-enable production of complex molecules with improved yields and purity. Local modifications, such as amide bond surrogates, N-methylation, or incorporation of non-natural amino acids, and global restrictions, like cyclization, further optimize stability and bioactivity. Peptidomimetics play a critical role in treating diverse conditions including cancer, type 2 diabetes mellitus, and cardiovascular diseases by modulating key biological pathways. Mechanistically, they influence protein-protein interactions, receptor signaling, and enzymatic activity, with clinical applications expanding rapidly. Market potential continues to grow, driven by technological advancements and demand for targeted therapeutics. This review highlights classification frameworks, design strategies, and synthetic approaches, emphasizing their impact on modern drug discovery and therapeutic development.

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## 1. Introduction

Peptidomimetics are structurally engineered molecules that reproduce the essential pharmacophoric features of natural peptides or proteins while maintaining their three-dimensional arrangement and biological activity. These compounds are designed to interact with the same molecular targets as their native peptide counterparts but possess enhanced physicochemical and pharmacokinetic properties [1]. Unlike natural peptides, peptidomimetics exhibit improved resistance to enzymatic degradation, prolonged biological activity, greater receptor selectivity, enhanced potency, and better bioavailability. Their design is guided by structure–activity relationship (SAR) studies, which identify the minimal active sequence and key pharmacophoric residues responsible for biological function. Structural modifications are subsequently introduced to preserve the optimal three-dimensional orientation required for effective target recognition while improving therapeutic performance. Consequently, peptidomimetics have become an important class of molecules in modern drug discovery, offering solutions to many of the limitations associated with conventional peptide therapeutics [2].

The therapeutic potential of peptides was first demonstrated in the early twentieth century with the successful use of insulin purified from bovine pancreas to treat diabetes, establishing that

endogenous peptide molecules could effectively manage human diseases. However, the early development of peptide-based medicines was hindered by significant challenges, including inefficient peptide synthesis, poor product purity, limited stability, rapid enzymatic degradation, and complex methods of drug administration [3]. Major technological advances, particularly the development of solid-phase peptide synthesis and high-performance liquid chromatography (HPLC), revolutionized peptide chemistry by enabling efficient synthesis, improved purification, and cost-effective large-scale production. These innovations also facilitated the rational optimization of endogenous peptide sequences, accelerating the development of synthetic peptide therapeutics with enhanced pharmacological properties [4].

Peptide therapeutics have since emerged as a rapidly expanding class of pharmaceuticals, with numerous peptide-based drugs approved for clinical use and many additional candidates progressing through various stages of clinical development. Several peptide drugs have achieved remarkable commercial success, reflecting the growing importance of peptide-based therapies in modern medicine [5]. Despite these advances, naturally occurring peptides continue to face several inherent limitations that restrict their broader therapeutic application. Most linear peptides are metabolically unstable, exhibit poor membrane permeability and oral bioavailability, and possess short plasma half-lives due to rapid degradation by proteolytic enzymes in the blood, liver, kidneys, and gastrointestinal tract, as well as rapid renal clearance. Consequently, many peptide drugs require parenteral administration, such as intravenous or subcutaneous injection, which can reduce patient compliance and increase treatment costs [6].

To overcome these challenges, researchers have developed peptidomimetics through the strategic modification of natural peptide sequences. These modifications include the incorporation of non-proteinogenic amino acids, backbone alterations, cyclization, side-chain modifications, and other chemical transformations that enhance molecular stability while preserving biological activity. Such structural optimization improves resistance to proteolytic degradation, extends circulation time, enhances receptor specificity, increases membrane permeability, and minimizes undesirable side effects [7]. A classic example is desmopressin, a modified analogue of vasopressin in which a single amino acid substitution significantly reduces vasopressor activity while retaining its desired antidiuretic effect. Similar optimization strategies have led to the successful development of numerous clinically important peptidomimetic therapeutics, demonstrating how rational peptide engineering can transform naturally occurring bioactive peptides into safer, more effective, and clinically valuable medicines [8].

## 2. Classification of Peptidomimetics

### 2.1 Traditional Classification

Peptidomimetics are traditionally classified according to the extent to which they structurally and functionally resemble their parent peptide. This classification categorizes peptidomimetics into three major types based on their mechanism of target recognition and structural similarity [9].

#### 2.1.1 Type I Peptidomimetics

Type I peptidomimetics closely resemble the three-dimensional structure of the native peptide and preserve the spatial orientation of the key pharmacophoric groups responsible for binding to receptors or enzymes. By maintaining the essential topographical features of the parent peptide, these mimetics effectively reproduce the biological activity while offering improved stability and pharmacokinetic properties [10].

#### 2.1.2 Type II Peptidomimetics

Type II peptidomimetics retain the biological function of the parent peptide without necessarily exhibiting significant structural similarity. Instead of replicating the peptide backbone, these molecules interact with the same biological target through alternative chemical frameworks that generate comparable pharmacological responses [11].

#### 2.1.3 Type III Peptidomimetics

Type III peptidomimetics incorporate entirely different molecular scaffolds that replace the native peptide backbone while maintaining the correct spatial arrangement of the functional groups required for biological activity [12]. These scaffold-based mimetics use non-peptidic frameworks to present pharmacophoric residues in orientations that mimic those of the original peptide, thereby preserving target recognition while significantly improving metabolic stability, oral bioavailability, and synthetic flexibility [13].

### 2.2 Modern Classification

With advances in peptide chemistry, structural biology, and rational drug design, a more comprehensive classification system has been introduced to better describe the diverse spectrum of peptidomimetic molecules. This modern classification groups peptidomimetics into four classes (A-D) according to their degree of structural similarity to the parent peptide, with Class A

representing the highest similarity and Class D the lowest [14].

#### 2.2.1 Class A Peptidomimetics

Class A peptidomimetics consist primarily of the original peptide sequence with only limited structural modifications introduced to stabilize the biologically active conformation. These modifications often involve incorporation of a small number of non-natural amino acids or peptide stapling techniques that preserve the native backbone while enhancing conformational rigidity, metabolic stability, and receptor affinity. Because these molecules closely resemble the parent peptide, they largely correspond to the traditional Type I peptidomimetics [15].

#### 2.2.2 Class B Peptidomimetics

Class B peptidomimetics contain more extensive modifications, including non-natural amino acids, backbone replacements, and small-molecule building blocks. Although the peptide backbone is substantially altered, the side-chain topology remains similar to that of the parent peptide, allowing preservation of the essential pharmacophoric arrangement [16]. Foldamers, β-peptides, α/β-peptides, and other backbone-modified analogues belong to this category and provide improved stability against proteolytic degradation while maintaining biological activity [17].

#### 2.2.3 Class C Peptidomimetics

Class C peptidomimetics are highly modified small molecules in which the peptide backbone is completely replaced by a non-peptidic scaffold. These scaffolds are specifically designed to orient critical substituents in positions analogous to the key binding residues of the native peptide [18]. Common scaffold architectures include cyclohexane, aromatic rings, heterocycles, carbohydrates, and other rigid molecular frameworks that effectively reproduce the spatial arrangement of pharmacophoric groups. Class C compounds correspond closely to the traditional Type III or scaffold-based peptidomimetics [19].

#### 2.2.4 Class D Peptidomimetics

Class D peptidomimetics exhibit the least structural resemblance to the original peptide but successfully reproduce its biological function. Rather than mimicking the peptide's side-chain arrangement directly, these molecules are identified through hit-to-lead optimization or high-throughput screening and are designed to achieve the same therapeutic outcome by interacting with the target through alternative molecular mechanisms [20]. Their simplified chemical structures often provide superior pharmacokinetic properties, increased oral bioavailability, and enhanced suitability for medicinal chemistry optimization [21].

#### 2.2.5 Representative Examples of Modern Peptidomimetics

Representative examples of modern peptidomimetic design include thyrotropin-releasing hormone (TRH) analogues based on cyclohexane scaffolds, where the peptide backbone is replaced while preserving the spatial orientation of the pharmacophoric groups essential for receptor binding [22]. Another well-established example is the replacement of peptide fragments in somatostatin analogues with a D-glucose scaffold, which effectively mimics the β-turn conformation of the parent peptide. The carbohydrate scaffold offers defined stereochemistry, synthetic accessibility, and improved stability, demonstrating how non-peptidic frameworks can successfully reproduce peptide architecture while enhancing drug-like properties [23].

## 3. Current Peptide Manufacturing Processes

Peptide therapeutics are predominantly manufactured using chemical synthesis, although recombinant and enzymatic approaches have gained increasing importance for large and structurally complex molecules [24]. More than 100 peptide active pharmaceutical ingredients (APIs) have been approved for pharmaceutical use, with sequence lengths ranging from short pentapeptides to proteins containing approximately 60 amino acids. Depending on peptide length, structural complexity, production scale, and regulatory requirements, different manufacturing strategies are selected to balance efficiency, cost, purity, and scalability [25].

### 3.1 Chemical Peptide Synthesis

Chemical synthesis remains the most widely employed approach for peptide production and is primarily performed using solid-phase peptide synthesis (SPPS) or liquid-phase peptide synthesis (LPPS). While SPPS is generally used for linear peptide assembly, LPPS supports both linear and convergent synthesis strategies. Recent innovations such as soluble tag-assisted LPPS and hybrid synthesis approaches have further expanded the versatility of chemical peptide manufacturing. These technologies enable the efficient production of peptides with improved purity while facilitating the synthesis of increasingly complex therapeutic molecules [26].

#### 3.1.1 Solid-Phase Peptide Synthesis (SPSS)

Solid-phase peptide synthesis is the dominant platform for manufacturing pharmaceutical peptides due to its robustness, automation capability, and well-established chemistry. In SPPS, peptide elongation occurs on an insoluble resin, allowing

repeated coupling and deprotection cycles with availability of automated synthesizers, standardized amino acid derivatives, and reliable supply chains has made SPPS the preferred method for early drug development as well as commercial-scale manufacturing [27]. Production-scale reactors ranging from laboratory instruments to several thousand liters have enabled the successful synthesis of peptides containing approximately 70 amino acid residues. Nevertheless, cumulative losses during repeated coupling reactions reduce overall yield as peptide length increases, and practical synthesis generally becomes challenging beyond approximately 100 amino acids. Long peptide synthesis may also suffer from incomplete coupling, resin aggregation, secondary structure formation, and impurity generation [28].

#### 3.1.2 Liquid-Phase Peptide Synthesis (LPPS)

Liquid-phase peptide synthesis is particularly suitable for short peptides, generally containing 5–10 amino acid residues. Unlike SPPS, LPPS permits direct analytical monitoring of reaction progress using techniques such as HPLC and TLC, facilitating process optimization and impurity control [29]. The use of different protecting group strategies, including Boc and Cbz chemistry, provides flexibility for synthesizing structurally complex targets. Careful optimization of each synthetic step can reduce reagent consumption and improve product purity. However, LPPS generally requires more extensive process development, involves greater manual intervention, and is associated with longer production times, increased risk of racemization, and more challenging scale-up compared with SPPS [30].

#### 3.1.3 Hybrid SPPS–LPPS Strategies

To overcome the limitations associated with long linear peptide synthesis, hybrid manufacturing strategies combine the advantages of SPPS and LPPS. In this approach, shorter peptide fragments are synthesized independently using SPPS and subsequently coupled in solution using LPPS. Fragment condensation reduces cumulative synthetic losses, minimizes difficult coupling reactions, improves impurity profiles, and often enhances overall yield. Furthermore, simultaneous production of peptide fragments enables convergent synthesis, significantly shortening manufacturing time. Several commercially important peptide therapeutics, including enfuvirtide and tirzepatide, have been successfully manufactured using hybrid synthetic strategies [31].

#### 3.1.4 Soluble Tag-Assisted Liquid-Phase Synthesis

Soluble tag-assisted LPPS represents an important simplified purification between synthetic steps. The advancement that replaces insoluble solid supports with soluble molecular tags or anchors. During synthesis, the growing peptide remains dissolved in the organic phase while excess reagents and by-products are removed by aqueous extraction or selective precipitation [32]. This approach substantially reduces organic solvent consumption and allows direct monitoring of coupling and deprotection reactions by TLC, HPLC, NMR, and mass spectrometry. The technology has demonstrated successful multikilogram-scale production of short peptide sequences and offers significant environmental and analytical advantages compared with conventional SPPS [33].

### 3.2 Recombinant and Enzymatic Peptide Production

Recombinant biotechnology provides an alternative manufacturing strategy for producing peptides, particularly those composed exclusively of natural L-amino acids. Compared with chemical synthesis, recombinant production can significantly reduce manufacturing costs for long peptide sequences while offering excellent scalability for industrial production. However, current recombinant expression systems remain limited in their ability to incorporate non-natural amino acids and chemically modified residues that are frequently required in modern peptide therapeutics [34]. Consequently, recombinant approaches are primarily employed for long natural peptides, whereas chemically synthesized peptides remain the preferred choice during drug discovery and clinical development. Enzymatic ligation and semirecombinant production methods further complement recombinant technology by enabling the assembly of complex peptide structures through site-specific fragment coupling [35].

### 3.3 Selection Criteria for Manufacturing Strategy

Selection of an appropriate peptide manufacturing process depends on multiple technical and economic considerations. Important factors include peptide length, structural complexity, production scale, manufacturing capacity, automation requirements, raw material availability, process robustness, development timeline, production cost, regulatory strategy, and overall product lifecycle management [36]. Short peptides are often economically synthesized using LPPS, whereas SPPS is generally preferred for medium-length therapeutic peptides due to its automation and reproducibility. Hybrid synthesis becomes advantageous for long or structurally demanding peptides, while recombinant production is most suitable for very large peptides

and proteins composed of natural amino acids [37].

### 3.4 Manufacturing Equipment

#### 3.4.1 Jacketed Glass Stirred-Tank Reactor

Figure 1 illustrates the architecture and operating principle of a laboratory-scale jacketed glass stirred-tank reactor widely employed in pharmaceutical synthesis and nanotechnology research. The integrated agitation system, temperature-controlled jacket, pressure monitoring, and controlled inlet–outlet configuration enable precise control of reaction parameters, ensuring reproducible synthesis, crystallization, nanoparticle fabrication, and scalable process development [38].

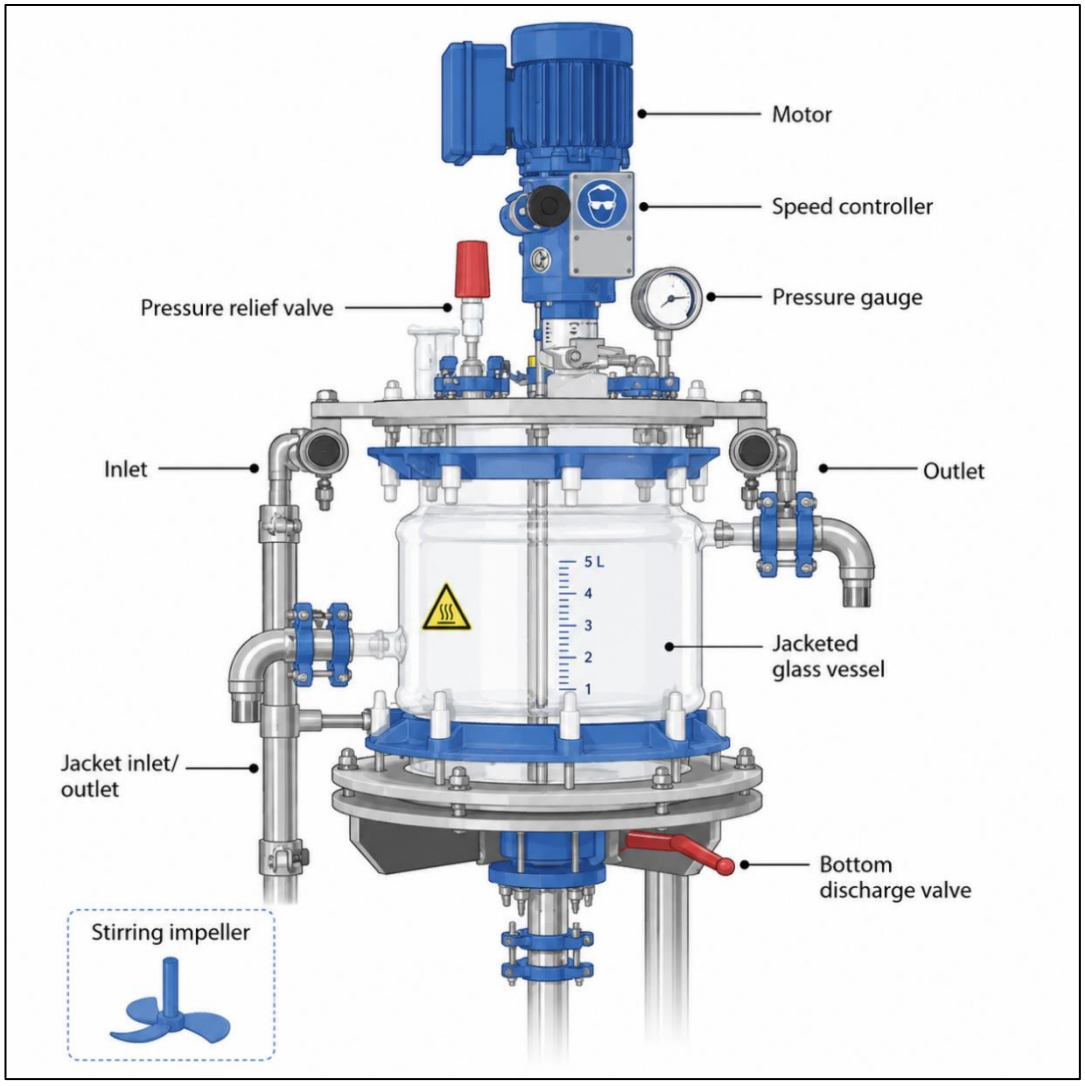


**Figure 1:** Schematic representation of a laboratory-scale jacketed glass stirred-tank reactor used for controlled pharmaceutical synthesis and nanoparticle fabrication.

#### 3.4.2 Orbital Flask Shaker

Figure 2 presents the structural design and operational components of an orbital flask shaker widely used in microbiology, biotechnology, and pharmaceutical laboratories. Controlled orbital motion enhances mixing efficiency, oxygen transfer, and nutrient distribution, thereby providing reproducible cultivation conditions for microbial fermentation, cell culture, recombinant protein expression, and bioprocess optimization [39].


**Figure 2:** Schematic of an orbital flask shaker used for microbial culture and bioprocess incubation.

### 3.5 Regulatory Considerations

Regulatory classification of peptide therapeutics depends primarily on manufacturing methodology and molecular size. Recombinantly produced peptides are generally regulated as Biologics License Applications (BLA), whereas chemically synthesized peptides containing up to approximately 40 amino acids are typically submitted as New Drug Applications (NDA). Synthetic peptides exceeding this threshold are generally regulated as biologics and require submission through the BLA pathway, reflecting the increasing complexity of their manufacturing, characterization, and quality control requirements [40].

## 4. Strategic Approaches to Peptidomimetic Design

Peptidomimetic design is a systematic process that transforms biologically active peptides into drug-like molecules with improved pharmacokinetic and pharmacodynamic properties while retaining their therapeutic efficacy. The primary objective is to preserve the essential pharmacophoric elements responsible for biological activity while overcoming the inherent limitations of natural peptides, including poor metabolic stability, limited oral bioavailability, rapid enzymatic degradation, and short plasma half-life [41]. Modern peptidomimetic design integrates medicinal chemistry, structural biology, computational modeling, and structure–activity relationship (SAR) studies to generate molecules with enhanced receptor selectivity, potency, and clinical applicability. The overall design strategy involves progressive structural modifications ranging from minor amino acid substitutions to complete replacement of the peptide backbone with non-peptidic scaffolds [42].

### 4.1 Basic Principles of Peptidomimetic Design

The development of peptidomimetics generally begins after the identification of a biologically active peptide capable of interacting with a specific receptor or enzyme. Peptide hits are commonly discovered through techniques such as phage display, combinatorial peptide libraries, and high-throughput screening[43,44]. Structural characterization of the target protein using molecular biology techniques, including sequencing, cloning, site-directed mutagenesis, and molecular modeling, provides critical information regarding peptide–target interactions. Based on these data, several fundamental principles guide the rational design of peptidomimetics [45].

#### 4.1.1 Replacement of the Peptide Backbone

One of the principal strategies in peptidomimetic

design is the replacement of the peptide backbone with non-peptidic frameworks. Since peptide bonds are highly susceptible to enzymatic hydrolysis, replacing amide linkages with chemically stable isosteres substantially improves metabolic stability and oral bioavailability without compromising biological activity [46].

#### 4.1.2 Preservation of Pharmacophoric Side Chains

The side chains of key amino acid residues constitute the pharmacophore responsible for molecular recognition. Therefore, preserving their spatial orientation is essential for maintaining biological activity. Modifications such as chain extension, isosteric replacement, and conformational restriction are introduced while retaining the critical interactions with the biological target [47].

#### 4.1.3 Conformational Flexibility and Rigidity

Early generations of peptidomimetics generally retain considerable conformational flexibility. Once biological activity is confirmed, rigidifying structural elements are introduced to stabilize the bioactive conformation, thereby improving receptor affinity, selectivity, and metabolic stability while reducing entropic penalties during target binding [48].

#### 4.1.4 Pharmacophore-Guided Target Selection

Successful peptidomimetic development depends on accurate identification of the pharmacophore through structure–activity relationship studies and three-dimensional structural analysis. Knowledge of the bioactive conformation enables rational lead optimization while minimizing the synthesis of biologically inactive analogues [49].

#### 4.1.5 Identification of Enzymatic Cleavage Sites

Potential proteolytic cleavage sites within peptide sequences are identified experimentally using plasma, serum, tissue homogenates, and purified proteases, followed by HPLC or LC–MS analysis of degradation products. Identification of metabolically vulnerable regions provides valuable guidance for introducing stabilizing structural modifications [50].

### 4.2 Hierarchical Strategy for Lead Optimization

Lead optimization follows a hierarchical approach in which structural modifications are introduced progressively to transform an active peptide into a therapeutically useful peptidomimetic. Each modification provides valuable information regarding the contribution of individual amino acid residues to biological activity and helps establish detailed structure–activity relationships [51].

#### 4.2.1 Peptide Size Reduction

The initial optimization step involves systematic shortening of the peptide sequence by sequential removal of amino acids from the N- or C-terminus. This approach identifies the minimal peptide sequence required for biological activity and serves as the foundation for subsequent peptidomimetic design [52].

#### 4.2.2 Alanine Scanning

Alanine scanning involves systematic replacement of each amino acid residue with alanine to identify residues essential for receptor binding. Loss of biological activity following substitution indicates that the replaced residue contributes directly to molecular recognition and constitutes part of the pharmacophore [53].

#### 4.2.3 D-Amino Acid Scanning

Replacement of L-amino acids with their D-enantiomers provides insight into stereochemical requirements for biological activity while simultaneously improving resistance to enzymatic degradation. This approach also assists in defining the three-dimensional organization of the bioactive peptide conformation [54].

#### 4.2.4 N-Methylation Strategy

Systematic N-methylation of peptide amide bonds reduces hydrogen-bonding capability, alters conformational preferences, and improves metabolic stability. In addition, N-methylation promotes cis/trans amide isomerization, providing valuable information regarding the conformational requirements for receptor binding [55].

#### 4.2.5 Conformational Optimization and Lead Refinement

After identification of the minimal bioactive sequence and essential pharmacophoric residues, progressively more extensive structural modifications are introduced to reduce peptide character while improving receptor affinity, selectivity, pharmacokinetics, and pharmacodynamics. These first-generation peptidomimetics subsequently undergo additional structural refinement toward non-peptidic lead compounds [56].

### 4.3 Local Structural Modifications

Local structural modifications represent the most conservative approach to peptidomimetic optimization because they preserve the overall peptide architecture while introducing controlled conformational bias. These modifications are generally limited to individual amino acid residues

and include both backbone and side-chain alterations designed to enhance stability, receptor affinity, and metabolic resistance [57].

### 4.3.1 Backbone Modifications

Backbone modifications involve replacement of the amino, α-carbon, or carbonyl components of individual amino acids with chemically related isosteres. Common substitutions include oxygen, keto-methylene, N-hydroxyl, sulfur, phosphonate, boronate, and methylene groups, all of which influence hydrogen bonding, conformational flexibility, and resistance to proteolytic degradation [58].

### 4.3.2 Side-Chain Modifications

Modification of amino acid side chains provides opportunities to optimize steric interactions, hydrophobicity, hydrogen bonding, and electronic properties without disrupting the overall peptide framework. Unnatural amino acids, homologated residues, and rigid cyclic amino acids are frequently incorporated to improve biological activity and conformational stability [59].

## 5. Mechanism of Peptidomimetics in Cancer

Peptidomimetics exert potent anticancer activity by selectively modulating key molecular pathways involved in tumor initiation, progression, angiogenesis, and metastasis. Unlike conventional chemotherapeutic agents, these molecules are designed to mimic the structural and functional properties of bioactive peptides while exhibiting enhanced metabolic stability and target specificity [60]. A major mechanism involves disruption of protein–protein interactions, including inhibition of the BCL-2 family to induce mitochondrial apoptosis and blockade of the MDM2–p53 interaction, thereby restoring p53-mediated tumor suppressor activity. Integrin-targeting peptidomimetics inhibit tumor cell adhesion, migration, invasion, and angiogenesis by interfering with αvβ3 and αvβ5 integrin signaling. Additional peptidomimetics target receptor tyrosine kinases, growth factor signaling, and intracellular oncogenic pathways such as PI3K/AKT and MAPK, suppressing cancer cell proliferation and survival [61]. Their high receptor selectivity minimizes off-target toxicity while improving therapeutic efficacy. Consequently, peptidomimetics have emerged as promising precision therapeutics for a broad range of solid tumors and hematological malignancies, with several candidates already approved or undergoing clinical evaluation [62].

Table 1 summarizes the diverse therapeutic applications of peptidomimetics across major human diseases, highlighting their representative compounds, molecular targets, mechanisms of action, and current clinical status. The table demonstrates how peptidomimetics are engineered to selectively modulate protein–protein interactions, receptors, enzymes, and signaling pathways implicated in cancer, metabolic disorders, infectious diseases, neurological disorders, and cardiovascular diseases. It also illustrates the translational progress of these molecules from preclinical investigations to approved therapeutics. Overall, the table provides a concise overview of the expanding clinical relevance of peptidomimetics and emphasizes their potential as highly selective, stable, and effective next-generation therapeutic agents [63].

**Table 1:** Therapeutic applications of peptidomimetics across human diseases.

| S. No. | Disease | Representative Peptidomimetic/Drug | Primary Molecular Target | Mechanism of Action | Clinical Status | References |
|---|---|---|---|---|---|---|
| 1. | Breast cancer | Venetoclax | BCL-2 | Induces apoptosis by inhibiting anti-apoptotic proteins | Approved | [64] |
| 2. | Colorectal cancer | Cilengitide | Integrin αvβ3/αvβ5 | Inhibits tumor angiogenesis and metastasis | Clinical | [65] |
| 3. | Lung cancer | MDM2 inhibitors | MDM2–p53 interaction | Reactivates p53-mediated apoptosis | Clinical | [66] |
| 4. | Prostate cancer | RGD peptidomimetics | Integrins | Blocks tumor cell adhesion and invasion | Preclinical | [67] |
| 5. | Pancreatic cancer | BH3 mimetics | BCL-XL/BCL-2 | Promotes mitochondrial | Clinical | [68] |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | apoptosis | | |
| 6. | Melanoma | Cyclic RGD peptides | Integrins | Suppresses angiogenesis | Clinical | [69] |
| 7. | Type 2 Diabetes Mellitus | Sitagliptin | DPP-4 | Prevents GLP-1 degradation, increases insulin secretion | Approved | [70] |
| 8. | Type 2 Diabetes Mellitus | Saxagliptin | DPP-4 | Enhances incretin signaling | Approved | [71] |
| 9. | Type 2 Diabetes Mellitus | Linagliptin | DPP-4 | Improves glucose homeostasis | Approved | [72] |
| 10. | Obesity/Diabetes | Tirzepatide | GIP/GLP-1 receptors | Dual incretin receptor agonism | Approved | [73] |
| 11. | HIV infection | Enfuvirtide | gp41 | Prevents viral membrane fusion | Approved | [74] |
| 12. | Bacterial infection | Omiganan | Bacterial membrane | Disrupts membrane integrity | Clinical | [75] |
| 13. | Fungal infection | Histatin-derived mimetics | Fungal membrane | Induces membrane permeabilization | Preclinical | [76] |
| 14. | Antimicrobial therapy | Host-defense peptide mimetics | Microbial membrane | Broad-spectrum antimicrobial action | Clinical | [77] |
| 15. | Alzheimer's disease | β-sheet peptidomimetics | Amyloid-β | Inhibits amyloid aggregation | Preclinical | [78] |
| 16. | Parkinson's disease | α-Synuclein inhibitors | α-Synuclein | Prevents protein aggregation | Preclinical | [79] |
| 17. | Stroke | Neuroprotective peptidomimetics | NMDA receptor | Reduces excitotoxic neuronal injury | Preclinical | [80] |
| 18. | Hypertension | Angiotensin receptor peptidomimetics | AT1 receptor | Inhibits vasoconstriction | Approved | [81] |
| 19. | Heart failure | Natriuretic peptide mimetics | NPR receptors | Promotes vasodilation and natriuresis | Approved | [82] |
| 20. | Thrombosis/Cardiovascular disease | Integrin antagonists | GPIIb/IIIa receptor | Inhibits platelet aggregation | Approved | [83] |

Figure 2 illustrates the structural design and operating components of an orbital flask shaker widely used in microbiology, biotechnology, and pharmaceutical laboratories. Controlled orbital motion enhances mixing efficiency, oxygen transfer, and nutrient distribution, ensuring reproducible cultivation conditions for microbial fermentation, cell culture, recombinant protein expression, and bioprocess development [84].

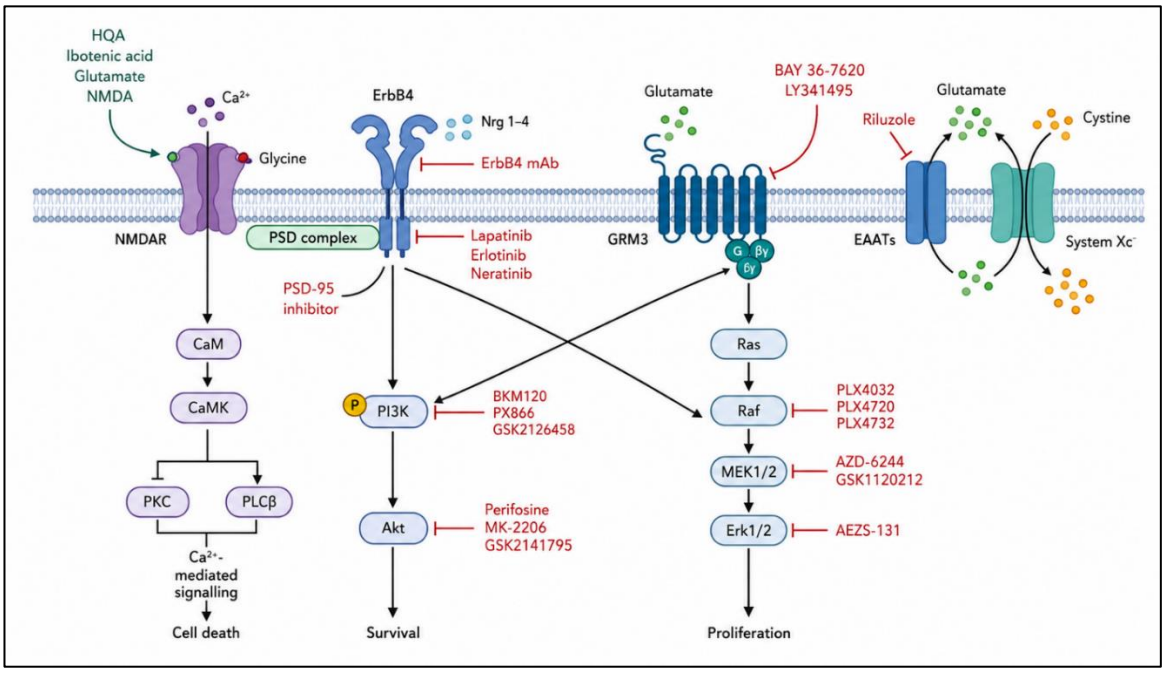


**Figure 2:** Schematic of an orbital flask shaker used for microbial culture and bioprocess incubation.

## 6. Mechanism of Peptidomimetics in Type 2 Diabetes Mellitus

Peptidomimetics play a crucial role in the management of type 2 diabetes mellitus (T2DM) by mimicking endogenous peptide hormones that regulate glucose homeostasis, particularly glucagon-like peptide-1 (GLP-1). These molecules activate GLP-1 receptors on pancreatic β-cells, enhancing glucose-dependent insulin secretion while suppressing glucagon release from α-cells [85]. Additionally, they delay gastric emptying, reduce appetite, and promote weight loss, thereby improving insulin sensitivity and glycemic control. Structural modifications increase resistance to dipeptidyl peptidase-4 (DPP-4)-mediated degradation, resulting in prolonged biological activity and improved pharmacokinetics. Consequently, peptidomimetics provide sustained glucose regulation, reduce cardiovascular risk, and improve long-term metabolic outcomes in patients with T2DM [86].

Figure 4 illustrates the pathogenesis of type 2 diabetes mellitus and the therapeutic role of DPP-4 inhibitors. By preventing incretin degradation and enhancing GLP-1 receptor signaling, DPP-4 inhibition improves glycemic control, preserves β-cell function, attenuates oxidative stress, and reduces the risk of long-term microvascular and macrovascular diabetic complications [87].

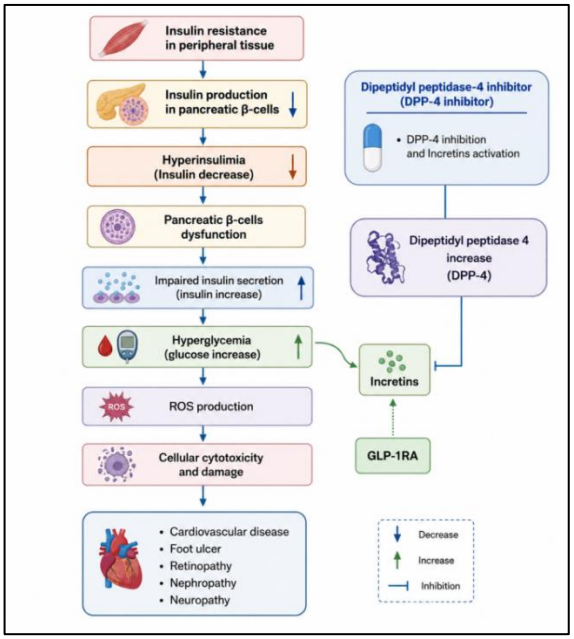


**Figure 4.** Schematic illustrating the pathophysiological progression of type 2 diabetes mellitus and the therapeutic mechanism of dipeptidyl peptidase-4 (DPP-4) inhibitors.

## 7. Mechanism of Peptidomimetics in Cardiovascular Disease

Peptidomimetics have emerged as promising therapeutic agents for cardiovascular diseases by selectively targeting molecular pathways involved in hypertension, heart failure, thrombosis, myocardial ischemia, and vascular remodeling. These compounds mimic endogenous cardiovascular peptides while exhibiting improved metabolic stability, receptor selectivity, and prolonged biological activity [88]. Angiotensin receptor-targeting peptidomimetics inhibit the renin–angiotensin–aldosterone system (RAAS), thereby reducing vasoconstriction, oxidative stress, inflammation, and cardiac remodeling. Natriuretic peptide mimetics enhance cyclic guanosine monophosphate (cGMP) signaling, promoting vasodilation, natriuresis, and improved cardiac function. In thrombotic disorders, integrin (GPIIb/IIIa) peptidomimetics prevent platelet aggregation and thrombus formation, reducing the risk of myocardial infarction and stroke. Additionally, peptide-based inhibitors targeting inflammatory mediators and oxidative stress pathways protect endothelial cells, improve vascular integrity, and limit ischemia–reperfusion injury. Through their high target specificity and reduced off-target toxicity, peptidomimetics offer a precision medicine approach for managing cardiovascular disorders and continue to advance as next-generation therapeutics in both preclinical and clinical development [89].

Figure 5 illustrates the BNP signaling cascade activated during heart failure. Myocardial stress induces pro-BNP production, which is cleaved into inactive NT-proBNP and biologically active C-terminal BNP. Active BNP stimulates natriuretic peptide receptors, increasing cGMP production and promoting vasodilation, natriuresis, and cardioprotection. Sacubitril inhibits neprilysin, preventing BNP degradation and enhancing its beneficial cardiovascular effects [90].

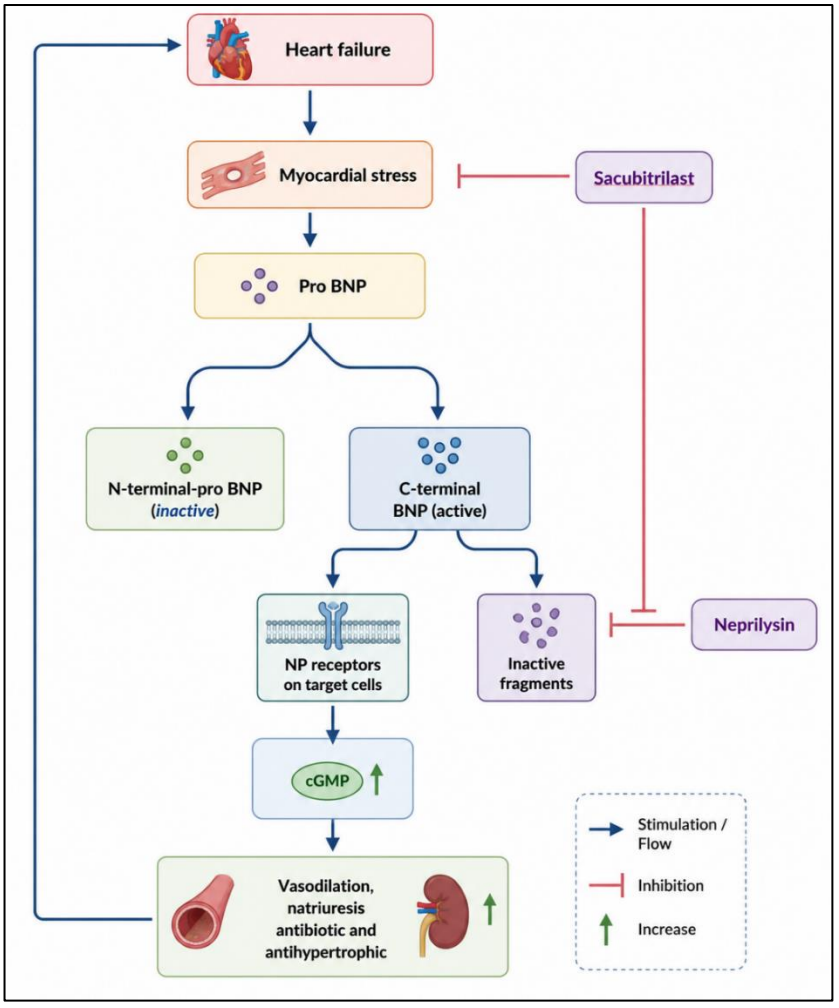


**Figure 5:** Mechanism of B-type natriuretic peptide (BNP) signaling in heart failure and the therapeutic action of sacubitril through neprilysin inhibition.

## 8. Current Challenges

Despite their significant therapeutic potential, peptidomimetics face several challenges that limit their widespread clinical translation. Although they exhibit improved stability compared with native peptides, many peptidomimetics still undergo

enzymatic degradation and exhibit suboptimal oral bioavailability, necessitating parenteral administration. Their complex chemical synthesis, purification, and large-scale manufacturing increase production costs and limit commercial accessibility [91]. Achieving high target specificity while minimizing off-target interactions and toxicity remains a critical challenge during drug design. In addition, limited membrane permeability and inefficient intracellular delivery reduce therapeutic efficacy, particularly for intracellular protein–protein interaction targets. Pharmacokinetic variability, immunogenicity, and rapid systemic clearance also affect clinical performance. Furthermore, translating promising preclinical findings into successful clinical outcomes is hindered by insufficient long-term safety data, limited clinical trials, and regulatory complexities. Future advances in computational drug design, artificial intelligence, peptide engineering, targeted drug delivery systems, and sustainable manufacturing technologies are expected to overcome these limitations and accelerate the development of next-generation peptidomimetic therapeutics [92].

## 9. Future Prospects

The future of peptidomimetics is highly promising, driven by advances in computational drug design, artificial intelligence, structural biology, and precision medicine. Emerging technologies such as machine learning-assisted peptide optimization, high-throughput screening, and molecular modeling are accelerating the discovery of highly selective and stable peptidomimetic candidates. Integration with nanotechnology, targeted drug delivery systems, and stimuli-responsive formulations is expected to improve bioavailability, tissue-specific delivery, and therapeutic efficacy. Furthermore, innovations in green peptide synthesis and scalable manufacturing will reduce production costs. Continued clinical evaluation and interdisciplinary research are likely to expand the application of peptidomimetics in oncology, metabolic, infectious, neurological, and cardiovascular diseases [93].

## Conclusion

Peptidomimetics are synthetic compounds designed to mimic the structural and functional features of natural peptides while overcoming limitations such as poor stability, low bioavailability, and rapid degradation. These compounds maintain the ability to interact with biological targets, offering enhanced receptor selectivity, potency, and pharmacokinetic properties. Traditional classification divides peptidomimetics into structural, functional, and functional-structural types, while modern approaches categorize them into Classes A-D based on similarity to the native peptide. Advanced synthesis methods-including solid-phase peptide synthesis (SPPS), liquid-phase peptide synthesis (LPPS), and hybrid approaches-enable production of complex molecules with improved yields and purity. Local modifications, such as amide bond surrogates, N-methylation, or incorporation of non-natural amino acids, and global restrictions, like cyclization, further optimize stability and bioactivity. Peptidomimetics play a critical role in treating diverse conditions including cancer, type 2 diabetes mellitus, and cardiovascular diseases by modulating key biological pathways. Mechanistically, they influence protein-protein interactions, receptor signaling, and enzymatic activity, with clinical applications expanding rapidly. Market potential continues to grow, driven by technological advancements and demand for targeted therapeutics. This review highlights classification frameworks, design strategies, and synthetic approaches, emphasizing their impact on modern drug discovery and therapeutic development.

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## Author Contributions

**AS:** Conceptualization; **SB:** Data curation and Visualization; **H:** Validation and Writing—review & editing; **KKV:** Supervision and Project administration.

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The authors declare no conflict of interest regarding the publication of this manuscript.

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## AI Declaration

The authors declare that they did not use artificial intelligence (AI) tools to generate or draft the scientific content of this manuscript. ChatGPT and Grammarly AI were used solely to improve the language, grammar, readability, and clarity of the manuscript. All AI-assisted suggestions were carefully reviewed, verified, and edited by the authors, who take full responsibility for the accuracy, originality, and integrity of the final content.

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