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Peptidomimetics as next – generation therapeutic applications

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Abstract

Peptidomimetic agents are synthetic compounds engineered to mimic the structure and biological functions of natural peptides, but with improved pharmacokinetic properties such as enhanced stability, activity, and bioavailability. Despite the therapeutic success of natural peptides, limitations including low metabolic stability, poor solubility, and challenging delivery have hampered their widespread clinical utility. Peptidomimetics overcome these drawbacks through chemical modifications, including backbone alterations and the incorporation of non-natural amino acids, thereby offering superior resistance to enzymatic degradation and tailored biological activities. This review explores the classification of peptidomimetics, advances in their design strategies, and methodologies for backbone and side-chain modification, as well as their major pharmacological applications. An emphasis is placed on their promise in anticancer, antiviral, and antibacterial therapies, with examples of compounds in preclinical and clinical development. The evolution of peptidomimetics marks a transformative direction for modern drug discovery and therapeutic intervention.

Keywords: Lead structure, Rational design, Peptidomimetics, Anti-angiogenesis, Apoptosis induction, Peptide backbone, Drug design, protease in inhibitors

Introduction

The first successful insulin treatment of a diabetic child in the 1920s demonstrated that human diseases could be managed using endogenous peptides. However, peptide-based therapeutics face challenges such as low yield, limited solubility, and complex delivery methods. To date, around 60 peptide drugs have been approved globally, with over 140 others in various clinical stages.

Peptidomimetic agents are synthetic compounds designed to mimic the structure and function of natural peptides while improving their stability, activity, and bioavailability through backbone or side-chain modifications. These molecules replicate the three-dimensional pharmacophore of natural peptides, enabling interaction with similar biological targets. Their enhanced resistance to enzymatic degradation and superior pharmacokinetic properties make them promising candidates for therapeutic and research applications.

Structural Modifications and Classification

Structural modifications in peptidomimetics include backbone alterations, incorporation of non-natural amino acids (e.g., D- or aza-amino acids), and cyclization, which enhance stability and may modify biological activity.

From peptide to peptidomimetics

Peptidomimetic development focuses on targeted backbone modifications while retaining the stereochemical and biological features of the parent peptide. Side-chain conformations and functional requirements for target recognition are optimized through selective amino acid substitutions or replacements.

Classification of Peptidomimetics

The classification of peptidomimetics, first defined by Grossmann, includes four classes (A–D) based on structural similarity to native peptides.

- **Class A:** Closely resembles the parent peptide in backbone and side chain structure, retaining native conformation and slowing proteolysis. Example: *Pentagastrin*, used diagnostically to assess gastric acid secretion.
- **Class B:** Features significant backbone modifications or incorporation of unnatural amino acids, such as in helical mimetics (foldamers), maintaining the topological arrangement of side chains.
- **Class C:** Consists of small-molecule scaffolds that mimic the spatial orientation of key residues in the native peptide's bioactive form.
- **Class D:** Shows minimal similarity to the parent peptide, often developed from Class C structures during hit-to-lead optimization.

Replacement of Amide Bonds and Variations

Peptide properties depend on amino acid side chains and the polyamide backbone. Amino acids are classified as hydrophobic (aliphatic: Ala, Val, Leu, Ile, Met; aromatic: Phe, Tyr, Trp) or hydrophilic (polar: Ser, Thr, Asn, Gln; acidic: Asp, Glu; basic: Lys, Arg, His). Special residues include Cys, forming disulfide bonds for structural stability or catalytic functions, and Pro, which induces conformational constraints within peptide chains.

β-Turn and β-Sheet Mimetics (Concise Version)

Designing small-molecule inhibitors for protein–protein interactions (PPIs) is challenging due to complex polar and hydrophobic interactions at target sites. One effective approach involves mimicking peptide secondary structures while preserving side-chain functionalities.

β-Sheets and β-Turns are key secondary structures in proteins, formed by hydrogen bonding between β-strands. These motifs play vital roles in molecular recognition, such as antibody binding and protein–protein or protein–DNA interactions. β-Sheet mimetics are particularly important in developing therapeutics for central nervous system (CNS) diseases.

Methodologies for Designing Peptides

(i). Bioactive Conformation (Concise Version)

Understanding the three-dimensional structure of peptide–receptor complexes, signal transduction pathways, and molecular interactions is essential for rational peptidomimetic design. Although the structural analysis of large, hydrophobic G-protein-coupled receptors remains challenging, advances in molecular modeling, site-directed mutagenesis, and structure–activity relationship studies have greatly improved insight into peptide–receptor interactions.

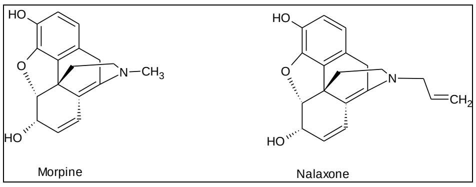
Endogenous ligands often serve as lead structures for peptidomimetic development. Small to medium peptides (under 30–50 amino acids) exist in multiple conformations in solution, but the biologically active (receptor-bound) conformation typically has higher receptor affinity due to reduced entropy loss upon binding. However, this active conformation may be sparsely populated in solution and differ from structures observed via X-ray crystallography or NMR.

Conformational Restriction: Designing conformationally restricted or structurally constrained peptide analogues that closely mimic the receptor-bound form of endogenous ligands is an effective strategy in peptidomimetic development. Such analogues exhibit enhanced selectivity and metabolic stability, as typically only a few (3–8) amino acid side chains are crucial for biological activity.

Metabolic Stability and Ligand Optimization

Peptidase cleavage sites influence a peptide's metabolic stability, which can be enhanced by structural simplification, C-terminal amidation, or N-terminal acylation. Identifying key amino acids for receptor recognition and activation enables the design of shorter, conformationally restricted analogues. Systematic modification of residues helps evaluate factors like stereochemistry, charge, and lipophilicity. Although this empirical process is costly and time-consuming, it guides the development of low-molecular-weight non-peptide ligands. Notably, peptide analogues designed as antagonists may unexpectedly show agonist-like effects in vivo, often detected only during advanced testing.

Lead Structure: Identifying a lead structure through large-scale screening of natural products or compound libraries is crucial for developing nonpeptide peptidomimetics. Lead compounds often show partial pharmacological activity but may lack selectivity, stability, or bioavailability. Optimization requires synthesizing and testing multiple variants to refine desirable properties. Examples include opioid alkaloids—nonpeptide ligands like morphine, which mimics endogenous opioids (β-endorphin, Met-enkephalin), and naloxone, a morphine derivative acting as a universal opioid receptor antagonist. These illustrate how small nonpeptide molecules can effectively mimic peptide receptor agonists or antagonists.



Rational Design

Rational design of low-molecular-weight nonpeptide ligands is an emerging field aimed at transforming peptides into more stable and bioavailable compounds. Studies show that amino acid side chains are key for receptor recognition, while the peptide backbone affects enzyme binding. Peptide conformation studies reveal folded bioactive structures (10–15 Å). Using site-directed mutagenesis, molecular modeling, spectroscopy, and peptide synthesis, researchers can identify critical receptor residues and develop pharmacophore models. These guide scaffold selection and structural optimization to produce compounds with improved pharmacodynamics and bioavailability for therapeutic use.

Strategies for the Development of Peptidomimetics

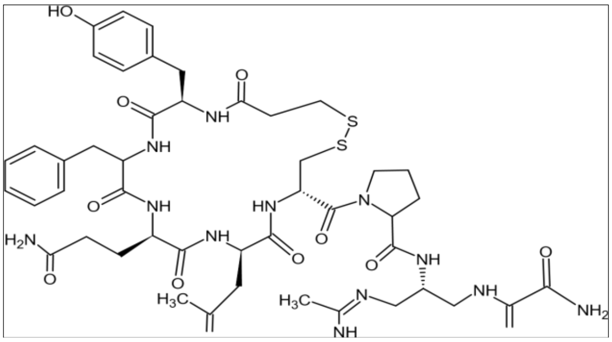
Modifications of amino acids

Conformationally restricted nonproteinogenic (uncoded) amino acids help clarify the bioactive conformation of peptides. However, few analogs provide limited structural flexibility without disrupting peptide stereoelectronic properties. To maintain biological activity, structural constraints must modify the backbone while preserving essential side-chain interactions. For this purpose, chimeric and non-natural amino acids are developed through α-/βalkylation, cyclization, or introducing olefinic bonds between α- and β-carbons. Amino acids with specific stereochemistry or bulky side chains are also employed to enhance structural rigidity.

L- to D-Amino Acid Substitution

Most natural amino acids are Lisomers, while D-amino acids are rare in humans but found in other organisms. Incorporating D-amino acids into peptides enhances metabolic stability, as human enzymes poorly hydrolyze D-peptide bonds.

A key example is desmopressin (1-desamino-8-D-arginine vasopressin), a synthetic vasopressin analogue where the first residue is deaminated and the eighth L-Arg replaced with D-Arg. These modifications improve receptor selectivity, slow metabolism, and enhance activity—desmopressin has tenfold higher antidiuretic activity but much lower vasoconstrictor effects than vasopressin. It is used to treat diabetes insipidus, nocturnal enuresis, and abnormal bleeding, and can be administered orally, sublingually, or intravenously.



Desmopressin

Dipeptide and Oligopeptide Analogues

Dipeptide mimetics, created by bridging two successive amino acids, reduce flexibility and can mimic secondary structure elements like β-turns. Lactams, formed by cyclizing the peptide bond nitrogen with an amino acid side chain, were first used as turn-inducing moieties. Examples include GnRH analogues, renin inhibitors (Phe-His replacement), chymotrypsin inhibitors, somatostatin analogues, and Cyclosporin A derivatives, where mono-, bi-, and tricyclic lactams enhanced activity and selectivity. Piperazinones, formed by linking two dipeptide nitrogens with a two-carbon spacer, are used in Leu-enkephalin analogues and cholecystokinin receptor antagonists. Advances in chiral synthesis now allow access to all diastereomers of 3,6-substituted piperazinones, expanding their utility in peptidomimetic design.

Peptide Bond Surrogates: Replacing peptide bonds with surrogates can enhance metabolic stability, modify lipophilicity, and probe backbone roles in receptor binding and activity. Such modifications may alter hydrogen bonding, secondary structure, and interactions with receptors or membranes, and can influence metal ion (e.g., Ca^{2+}) complexation. Common amide bond surrogates include methylene amino ($-CH_2NH-$), E-alkene (-CH=CH-), and retro-inverso (HN-CO) groups. Methylene amino substitutions have yielded cholecystokinin and somatostatin receptor agonists and bombesin antagonists, though electrical properties may differ from native peptides. E-alkene and fluoro-olefin surrogates have been used in enkephalin analogues, preserving steric/electronic features and enhancing receptor affinity, such as improved binding in Phe-Gly hexapeptide derivatives for substance P receptors. Other surrogates include heterocycles like thiazoles, imidazolines, and chiral tetrahydropyrimidines, which have generated potent NK-1 antagonists, opioid receptor ligands, and cysteine protease inhibitors. These approaches demonstrate the versatility of amide bond mimetics in developing biologically active peptide analogues.

Pharmacological activities of the Peptidomimetics

The various types of pharmacological activities displayed by peptidomimetics have been discussed as below:

Anti-Cancer Activity

Novel peptidomimetics, such as hydroxyethylurea derivatives, have been designed to inhibit secretase, neuroblastoma differentiation, tumorigenesis, and malignancy, serving as potential leads for anticancer drugs.

i. Peptidomimetics facilitated cancer diagnosis

Peptidomimetics target overexpressed cell surface receptors on cancer cells, enabling molecular imaging for improved diagnosis, staging, and therapy. Integrin receptors, particularly αvβ3, are key targets. Peptidomimetics mimicking the RGD (Arg-Gly-Asp) motif act as integrin antagonists and imaging agents. Radionuclide-based tracers (e.g., 18F-Galacto-RGD, 99mTc-NC100692, 18F-fluciclatide) and nanoparticles (e.g., Gd^{3+} liposomes, quantum dots, gold nanoparticles) facilitate PET, SPECT, and other imaging modalities.

Bifunctional diketopiperazine (DKP) RGD peptidomimetics show low nanomolar affinity for αvβ3 and αvβ5 integrins. Clinical examples like Cilengitide suppress tumor angiogenesis and are in trials for various cancers. Radiolabeled cyclic peptidomimetics have demonstrated efficacy in early tumor detection and monitoring metastasis in breast and non-small cell lung cancer. Targeting other integrin subtypes (e.g., α5β1) is under investigation for selective therapeutics and imaging due to their roles in tumor invasion, metastasis, and therapy resistance.

Peptidomimetics are increasingly used for targeted cancer imaging. LLP2A is a high-affinity ligand for α4β1 integrin; its 18F- and 64Cu-labeled derivatives enable PET imaging for early detection and monitoring of multiple myeloma. FAP-2286, targeting fibroblast activation protein (FAP), shows promise for detecting metastatic lesions in various solid tumors. Beyond integrins, peptidomimetics can target other biomolecules, such as CRIP1, overexpressed in breast and cervical cancers. Cyclic peptides like A1M (CLDGGGKGC), developed via phage display and computational design, bind CRIP1 at micromolar concentrations, enabling molecular imaging of cancer tissues. Overall, molecular imaging and peptide–protein interaction (PPI) targeting highlight the potential of peptidomimetics in cancer diagnostics.

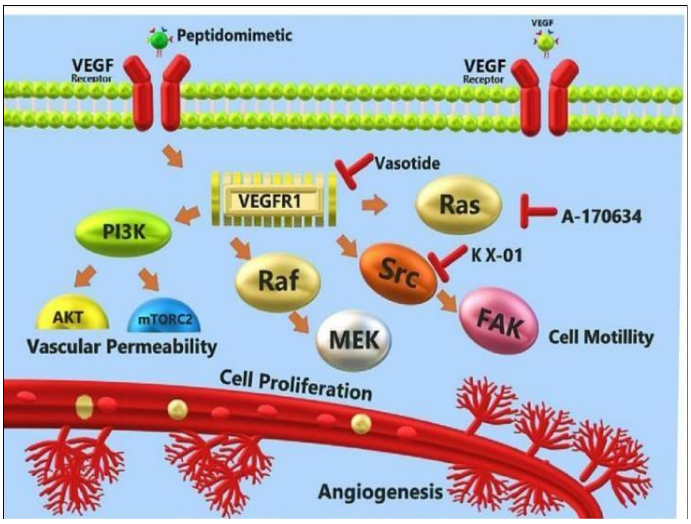


Fig 1: Implantation of peptidomimetics against tumor angiogenisis

ii. Peptidomimetics' capacity to suppress angiogenesis

Angiogenesis is critical for tumor growth and metastasis, making it a key target for anticancer therapy. Peptidomimetics have been developed to suppress angiogenesis via multiple pathways:

- IFNγ-derived mimetics: *Mimγ* and *Fibroferon* target PDGFβR, reducing lymphatic and blood vessel formation in preclinical models.
- Src kinase inhibition: *KX-01* binds the Src substrate pocket, inhibiting kinase activity and downstream signaling, reducing microvessel density in breast cancer xenografts.
- Targeted proapoptotic peptides: RGD-4C-peptide fused to apoptotic sequences induces endothelial cell apoptosis, reducing neovascularization.
- VEGF pathway inhibition: *Vasotide* targets NRP-1 and VEGFR-1, decreasing pathological angiogenesis in murine and primate models.
- Integrin-targeted cyclic RGD peptidomimetics: Cyclo[DKP-RGD] 1 binds αVβ3/αVβ5 integrins and inhibits VEGF-, EGF-, IGF-I-, FGF2-, and IL-8-mediated angiogenesis.

Peptidomimetics-induced apoptosis

Apoptosis, or programmed cell death, occurs via intrinsic mitochondrial pathways (cytochrome c release) or extrinsic death receptor signaling and is crucial in disease regulation. Peptidomimetics enhance the stability and activity of peptide-based inhibitors, improving their therapeutic potential. Targeting the p53/MDM2 interaction, a key regulator of intrinsic apoptosis, has led to peptidomimetics such as DPMI-α, M06, sMTide-02/02A, ATSP-7041, p53p-Ant, Peptide, and ReACp53**,** which disrupt the complex and promote tumor cell apoptosis. PACE4, a proprotein convertase, is a therapeutic target in several tumors. The ML-peptide (Ac-LLLLRVKR-NH_2) is a potent PACE4 inhibitor but suffers from rapid clearance. Peptidomimetic modifications improved its stability: substituting the C-terminal Arg with a decarboxylated aminobenzylamide (Amba) and replacing the N-terminal Leu with D-Leu protected against proteolysis. The resulting analog, Ac-[DLeu]LLLRVK-Amba, demonstrated low nanomolar PACE4 inhibition and was four times more potent than the parent ML-peptide in prostate cancer cell lines (DU145, LNCaP), enhancing its therapeutic potential.

Cell Cycle Arrest: ML-peptide analogs cause dose-dependent G_0/G_1 arrest and increased apoptosis in cancer cells.

Bcl-XL Targeting: *072RB*, a Bim-derived BH3 mimetic with natural and non-natural amino acid substitutions, downregulates Bcl-XL and Mcl-1, inducing apoptosis in B-CLL cells.

Src Kinase Inhibition: *KX-01* triggers apoptosis in MDA-MB-468 breast cancer cells at low nanomolar concentrations, unlike higher doses of dasatinib.

Mitochondrial Disruption: Peptidomimetics like $D(KLAKLAK)_2$ depolarize mitochondria, induce membrane expansion, and enhance caspase-like activity.

BCL2 Suppression: *MYBMIM* accumulates in AML nuclei, disrupts the MYB: CBP/P300 complex, and downregulates BCL2, leading to apoptosis.

MLL1/WDR5 Inhibition: *MM-102* binds WDR5, blocks MLL1/WDR5 interaction, and induces apoptosis in leukemia cells with MLL1 fusion proteins.

Hormone Receptor Modulation: SRC2-SP3, PERM1, and ER-1b target ER-α, while peptoid-based multivalent constructs inhibit androgen receptor (AR) activity, suppressing resistant prostate cancer cell proliferation.

Growth Factor Inhibition: P29, a high-affinity FGF2 inhibitor, blocks FGF2-induced signaling (FRS2, ERK1/2, AKT) and G_1/G_0 to S-phase transition in gastric cancer cells.

HER2/EGFR Targeting: DOX- or stearic acid-conjugated peptidomimetics (e.g., HERP5, Stearic acid-Arg-(S) Anapa-Phe-OH, Cyclo (1,10) PpR®Anapa-FDDF-®-Anapa) bind HER2 or inhibit EGFR heterodimerization, reducing proliferation in breast and lung cancer cells.

Enzyme Inhibition: Sulfonamide peptidomimetics inhibit μ-calpain, while pentyloxy-3-phenylpropionyl methionine-sulfone targets farnesyltransferase, disrupting Ras signaling and tumor growth in prostate cancer models.

Integrin and RGD-Based Peptidomimetics: S137 and cyclic RGD/isoDGR conjugates block integrin-mediated signaling, endothelial proliferation, and enhance tumor targeting (MDA-MB-468, A549, U87).

Other Targets: Peptidomimetics inhibit c-KIT1 (HepG2 cells), ERG in prostate cancer, PACE4 in prostate tumor cells, and DNA topoisomerase II (XK469 analogs in hepatoma). RGD–Paclitaxel conjugates show selective antiproliferative activity in leukemic cells.

Antiviral peptidomimetic

Peptidomimetics Potentially Active Against Coronaviruses

In recent years, peptidomimetics have emerged as promising agents against SARS-CoV-2 by targeting its main protease (Mpro or 3CLpro), a cysteine protease essential for viral replication. Mpro contains a catalytic dyad (Cys45 and His41) located in the S1/S2 pockets and cleaves polypeptides between P1 glutamine and P1′ amino acids such as alanine or glycine. Peptidomimetic inhibitors mimic natural peptide substrates, featuring modified P1–P3 residues and a C-terminal electrophilic "warhead" (P1′) that covalently inactivates the protease. Inhibition occurs in two steps: (i) reversible binding of the peptide backbone to the active site, followed by (ii) nucleophilic attack by the Cys45 thiol (activated by His41) on the electrophilic warhead, forming a covalent bond. The stability of this bond determines reversibility—peptidyl aldehydes typically cause reversible inhibition, whereas Michael acceptor–based peptidomimetics act irreversibly.

Current developments in peptididomimetics as a novel class of antibacterial agents:

Antibacterial Peptidomimetics: Mechanism of Action

The antibacterial activity of peptidomimetics depends on their structure–activity relationship, particularly the balance between cationic and hydrophobic groups that governs membrane interaction. By tuning this ratio, amphiphilic peptide-based molecules with strong and broad-spectrum activity can be developed.

Modern antibacterial peptidomimetics, such as AApeptides (α-AApeptides and γ-AApeptides), are synthetic analogs of natural antimicrobial peptides (AMPs). These molecules form amphipathic conformations upon contact with bacterial membranes, mimicking natural AMPs. Studies have shown α-AApeptides (e.g., α1, α2) display potent, low-hemolytic activity against pathogens including MRSA and VRE, while certain γ-AApeptides (e.g., γ-4) exhibit strong bactericidal action against Gram-positive bacteria. However, increased hydrophobicity, while enhancing efficacy, can raise cytotoxicity—an effect mitigated by adding cationic residues. Lipo-AApeptides (e.g., α3, α4) with lipid tails further enhance bacterial membrane interactions, yielding broad-spectrum activity. Cyclic γ-AApeptides show superior antibacterial potency due to their semirigid, amphipathic structures that improve stability and selectivity. Synthesis methods include the building block approach (using Fmoc-protected amino acids) and the submonomeric method, which allows diverse functionalization without pre-made blocks. Interestingly, antibacterial activity often does not depend on rigid secondary structures; flexible backbones can still confer strong, broad-spectrum effects. Peptidomimetics incorporating D- or β-amino acids enhance enzyme resistance and reduce toxicity. For example, D(KLAKLAK)$_2$ demonstrates potent activity against Gram-negative bacteria like *E. coli* and *K. pneumoniae* and even exhibits antifungal properties.

Antimicrobial Peptidomimetics: Therapeutic Potential

Peptidomimetics offer major advantages over natural antimicrobial peptides (AMPs), including high stability, resistance to enzymatic degradation, and tunable selectivity, making them strong candidates for therapeutic use. Several antibacterial peptidomimetics have advanced into clinical development.

- Arylamide foldamers, mimicking AMPs, show strong efficacy against *S. aureus* and *E. coli* and are in Phase II trials.
- Lytixar™ (LTX-109) by Lytix Biopharma has shown potent activity against MRSA and staphylococcal biofilms (Phase I/IIa).
- Brilacidin (PMX30063), a broad-spectrum bactericidal peptidomimetic active against Gram-positive and Gram-negative bacteria, demonstrated up to 87% clinical success in Phase II skin infection trials.
- POL7080, developed by Polyphor Ltd., selectively targets *Pseudomonas aeruginosa* via protein epitope mimetic technology and has completed Phase I trials with confirmed safety.

Antiviral and Anti-HIV Potential

Certain γ-AApeptides inhibit both Gram-positive and Gram-negative bacteria and mimic the HIV Tat peptide, binding HIV-1 RNA effectively. Peptidomimetic CXCR4 ligands, such as POL3026 and RCP222, act as potent anti-HIV agents by blocking viral entry through CXCR4. ALX40-4C similarly prevents HIV infection by interfering with Tat–TAR and gp120–CXCR4 interactions. Nanoparticle formulations of antiviral peptides (e.g., p41) further enhance stability and delivery.

Anticancer Potential

Peptidomimetics can selectively target negatively charged tumor cell membranes, inducing membrane disruption and apoptosis. Examples include radiolabeled γ-AApeptides used in imaging and the CXCR4 antagonist FC092, which inhibits tumor growth in vivo. Other notable agents include isoDGR and KLAKLAK-based peptides, which prevent angiogenesis, and AGAP, a scorpion-derived peptide that induces cancer cell cycle arrest.

Mechanistic Insights and Challenges

Antitumor activity often involves electrostatic binding to cancer membranes or inhibition of oncogenic pathways such as STAT3 signaling. Nano-formulations—liposomes, dendrimers, and polymeric carriers—enhance stability, bioavailability, and targeted delivery. Despite promising potency and specificity, challenges include poor pharmacokinetics, limited solubility, and potential toxicity.

Applications of Peptidomimetics

- Endocrine and Metabolic Disorders: Synthetic analogues like desmopressin mimic vasopressin to treat diabetes insipidus and bleeding disorders, offering improved stability and receptor selectivity.
- Protein–Protein Interaction Inhibition: Peptidomimetics disrupt key disease-related interactions, such as the MDM2/p53 axis in cancer and targets in neurodegenerative diseases.
- Molecular Imaging: Used as PET/SPECT tracers, peptidomimetics enable precise tumor and metastasis localization by targeting receptors like integrins and CRIP1.
- Diagnostics: Peptidomimetic markers, e.g., pentagastrin analogues, help assess organ functions such as gastric acid secretion.

- Drug Delivery: Conjugation with nanocarriers, liposomes, or nanoparticles allows targeted delivery, enhancing efficacy and reducing off-target toxicity.
- Immune Modulation: Certain peptidomimetics, like fibroferon, modulate immune and angiogenic pathways to reduce fibrosis and pathological angiogenesis.

Conclusion

Peptidomimetics are an emerging class of therapeutics bridging chemistry, biology, and pharmacology to overcome the limitations of natural peptides. Through structural optimization and advanced synthesis, they offer enhanced stability, selectivity, and bioavailability, enabling applications in cancer, infectious, and metabolic diseases. Their ability to target protein–protein interactions and combat drug resistance underscores their clinical potential. Despite challenges in large-scale production and delivery, ongoing advances in molecular design and nanotechnology are driving their evolution as next-generation, precision-based therapeutics combining the strengths of small molecules and biologics.

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