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INSIGHTS INTO PEPTIDOMIMETICS AND THEIR ANTICANCER ACTIVITIES

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ABSTRACT

Peptidomimetics are synthetic compounds designed to mimic the biological properties of peptides, including their ability to bind to specific receptors and enzymes. These compounds are used as tools for studying the structure and function of peptides, as well as for developing therapeutic agents with improved pharmacological properties. Peptidomimetics are a diverse class of molecules that can be designed to exhibit a range of biological activities, including enzyme inhibition, receptor agonism or antagonism, and protein-protein interaction modulation. They have been used in the development of drugs for a variety of diseases, including cancer, infectious diseases, and metabolic disorders. This study provides an overview on the field of peptidomimetics, including their design principles, synthesis strategies, and biological applications.

KEYWORDS: Peptidomimetics, anticancer, Solid-phase peptide synthesis, Solution-phase peptide synthesis.

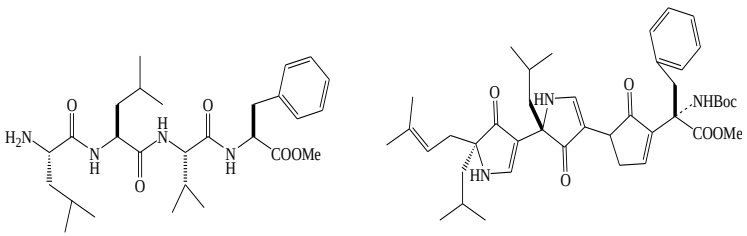
INTRODUCTION

A peptidomimetic is a small protein-like chain designed to mimic a peptide. Peptidomimetics are developed by modifications of native peptides with the aim of obtaining molecules that are more suitable for clinical development.[1] They typically arise either from modification of an existing peptide, or by designing similar systems that mimic peptides, such as peptoids and β-peptides.[2] Irrespective of the approach, the altered chemical structure is designed to advantageously adjust the molecular properties such as stability or biological activity.[3] Peptidomimetics can respond to peptide limitations by displaying higher metabolic stability,

good bioavailability and enhanced receptor affinity and selectivity.[4] These are designed to mimic the structural and functional properties of natural peptides, with the aim of achieving higher stability, specificity, and efficacy than their natural counterparts. Peptides are involved in a variety of physiological processes, including hormone signaling, enzymatic reactions, immune responses, and cell communication, making them promising targets for drug development.[5] Peptides show great pharmaceutical potential as active drugs and diagnostics in several clinical areas such as endocrinology, urology, obstetrics, oncology, etc. and as functional excipients in drug delivery systems to overcome tissue and cellular membrane barriers.[6]

Peptidomimetics can be categorized based on their structural and functional properties, which determine their mode of action and therapeutic potential. The major types of classification of peptidomimetics are as follows:

Structural Peptidomimetics (Type I mimetics): Structural peptidomimetics are designed to mimic the secondary and tertiary structures of peptides, such as α-helices, β-sheets, and turn motifs, which are critical for their binding to target proteins. These show an analogy of a local topography with the native substrate, and they carry all the functionalities responsible for the interaction with an enzyme or a receptor in a well-defined spatial orientation. This approach aims to enhance the stability and specificity of peptidomimetics by reducing susceptibility to proteolysis and increasing their affinity for the target protein. Examples of structural peptidomimetics are β-Peptides and Peptide nucleic acids.[7,8]



PEPTIDE PYRROLINONE ANALOG

PEPTIDE AND PYRROLINONE ANALOGS HAVE TOPOLOGICAL SIMILARITIES

a. β-Peptides: These are composed of β-amino acids, which have a side chain attached to the β-carbon rather than the α-carbon, as in natural amino acids. β-Peptides can adopt stable β-sheet structures and exhibit enhanced resistance to proteolysis and higher affinity for protein targets. These have been used as antimicrobial agents and inhibitors of protein-protein interactions.[9]

b. Peptide nucleic acids (PNAs): PNAs are synthetic oligonucleotides that mimic the structure of DNA and RNA, but with a peptide backbone instead of a sugar-phosphate backbone. PNAs can bind to complementary DNA and RNA strands with high specificity and stability, making them useful for gene therapy and diagnostic applications.[10,11]

2. Functional Peptidomimetics (Type II mimetics**):** Functional peptidomimetics are designed to mimic the biological function of peptides, such as enzymatic activity, receptor binding, and ion channel modulation, without necessarily mimicking their structure. Here the analogy with the native compound is based on the interaction with the target receptor or enzyme, without apparent structural analogies. This approach aims to enhance the specificity and potency of peptidomimetics by optimizing their functional properties. Examples of functional peptidomimetics are peptoids and Stapled peptides.

a. Peptoids: Peptoids are synthetic polymers composed of N-substituted glycines, which can adopt a wide range of conformations and exhibit high resistance to proteolysis. Peptoids can be designed to mimic the structure and function of natural peptides, such as antimicrobial peptides and neuropeptides, with improved stability and activity. Peptoids have been used as antibacterial agents, modulators of ion channels, and inhibitors of protein-protein interactions.[12,13]

b. Stapled peptides: Stapled peptides are designed to stabilize α-helical structures by introducing a covalent bond between two side chains, typically through an olefin metathesis reaction. Stapled peptides can exhibit enhanced cell permeability, stability, and affinity for protein targets, making them useful for targeting intracellular proteins and oncogenic signaling pathways.[14]

3. **Type III mimetics, or functional-structural mimetics**: These are synthetic compounds designed to mimic the structure and function of naturally occurring peptides. Type III mimetics are also known as functional-structural mimetics (FSMs). These are a specific class of peptidomimetics that mimic the 3D structure of a peptide rather than its sequence. This allows them to interact with the same binding sites as the original peptide, even though the actual amino acid sequence may be different. This is a useful approach because the 3D structure of a peptide is often more important for its biological activity than its exact amino acid sequence. One example of a type III mimetic is a compound called peptoid-peptide hybrid. This is a synthetic molecule that combines a peptide backbone with side chains made

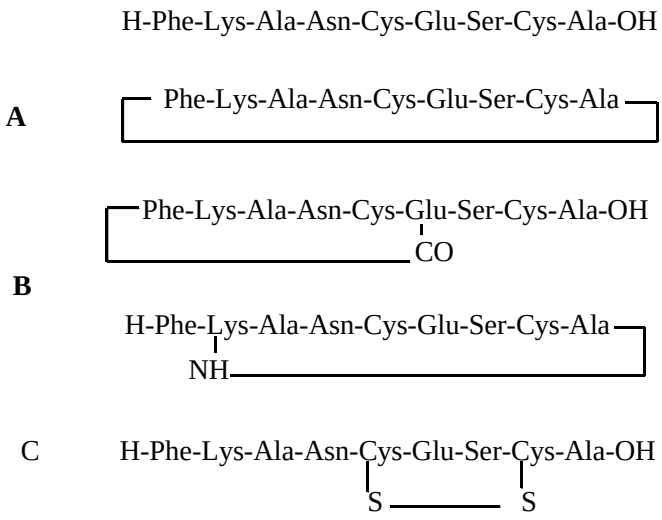
from peptoids, which are synthetic mimics of amino acids. The peptoid side chains can be designed to mimic the spatial orientation of the side chains of a natural peptide, allowing the hybrid molecule to interact with the same binding sites. The example of a type III mimetic is the HIV-1 protease inhibitor darunavir, which is used to treat HIV/AIDS. Darunavir is designed to mimic the substrate of the HIV-1 protease, which cleaves viral polyproteins into functional proteins required for viral replication. By binding to the active site of the protease, darunavir inhibits its activity and prevents the production of infectious virions. Another example of a type III mimetic is the GLP-1 receptor agonist exenatide, which is used to treat type 2 diabetes. Exenatide is designed to mimic the biological activity of glucagon-like peptide-1 (GLP-1), which stimulates insulin secretion and glucose uptake in response to food intake. By binding to the GLP-1 receptor, exenatide activates downstream signaling pathways and enhances insulin secretion and glucose uptake, thereby improving glycemic control.[15]

4. **Type-IV peptidomimetics:** These are compounds that mimic the structural and functional features of peptides but do not contain peptide bonds. These compounds are typically designed to target enzymes or receptors that are not accessible with Type-I peptidomimetics, which are small molecules that mimic the structure of peptide bonds. The example of a Type-IV peptidomimetic is the piperidine inhibitor. Piperidine inhibitors are designed to target enzymes that have a binding pocket that is too small to accommodate a peptide-based ligand. By mimicking the key functional groups of the peptide, such as the amino and carboxyl groups, the piperidine inhibitor can interact with the target enzyme in a similar way to a peptide-based ligand.

Methodologies for design peptides

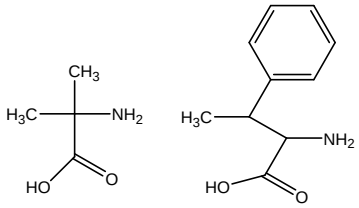
One of the greatest challenges in designing biologically active peptides is considering their conformational properties during synthesis. Peptides typically exist as a collection of conformational states in solution, which can dilute the biologically active species if the activity is only associated with a single conformer. This problem is especially pronounced for peptides designed to mimic a portion of a protein structure, where the intramolecular interactions characteristic of the protein structure are lost. To increase the selectivity of synthetic peptides beyond that provided by the sequence alone, a strategy is to reduce the number of accessible conformations by introducing local or global constraints into the peptide sequence.

Global Restriction: Cyclization is a simple way to introduce conformational constraints in a peptide sequence, resulting in increased in vivo stability compared to linear peptides. Cyclization can occur by connecting the N- and C-termini of the peptide sequence (head-to-tail) or by linking the N- or C-terminus to one of the side chains (backbone-to-side chain) or two side chains (side chain-to-side chain) that are not involved in specific interactions with other residues. The most common side chain-to-side chain cyclization involves the oxidation of two cysteine residues to form a disulfide bond. Alternatively, amide bonds can form between the side chains of lysine and aspartic/glutamic acid residues. However, side chain-to-side chain cyclization can only constrain a limited section of the polypeptide. To address this limitation, several covalent bridges can be incorporated into one sequence.[16,17]



Local restrictions: The introduction of local constraints on amino acid residues can involve substituting a methyl group for a hydrogen adjacent to a rotable bond. This has been extensively studied in the case of the α-hydrogen yielding Cα-tetrasubstituted α-amino acids, such as α-aminoisobutyric acid (Aib), which can be obtained by replacing the α-hydrogen on alanine with a methyl group [18]. Aib was found in peptide sequences from a fungal source and its steric bulk reduces the rotational freedom of the two peptide backbone angles Ψ and Φ. The allowable Ψ and Φ backbone angles in peptides containing Aib are restricted to values near –57°, -47° and +57°, +47°.[19] In addition to α-substitution, introducing alkyl groups at the β-position or on the aromatic ring of naturally occurring amino acids can also rigidify the conformational flexibility of the side chain. Three natural amino acids have β-disubstitutions: Val (two methyl groups), Ile (a methyl and an ethyl) and Thr (a methyl and a hydroxyl). These modifications do not greatly perturb the backbone, allowing the peptide backbone and the side chains some degree of flexibility, which is often crucial for the activity

of peptide mimetics. Moreover, these modifications can enhance the lipophilicity of peptides, helping them to overcome the membrane barrier [20]. Finally, the introduction of a covalent bond between the aromatic ring of an α-amino acid residue and the peptide backbone can provide an additional conformational restriction, leading to peptides with improved biological activity.



Aib MePhe

Backbone modification

Peptide backbone modifications can be achieved through isosteric or isoelectronic substitutions.[21] Peptidomimetics that include pseudopeptides or peptide bond surrogates are synthesized and designed to enhance the pharmacological properties of peptide analogs. When the peptide bond is substituted with other chemical groups, an amide bond surrogate is created that has a well-defined three-dimensional structure, different polarity, hydrogen bonding capacity, and acid-base properties. However, the adjacent α-carbon atoms' structural and stereochemical integrities remain unchanged, which can significantly enhance the peptide's metabolic stability and prevent protease cleavage of the amide bond. Despite this, the conformation, flexibility, and hydrophobicity of the peptide may be negatively impacted. Therefore, the selection of an amide bond surrogate necessitates a compromise between the benefits on pharmacokinetics and bioavailability and the potential drawbacks on activity and specificity. The surrogate's ability to replicate the steric, electronic, and solvation features of the amide bond is crucial in determining the effectiveness of pseudopeptide analogs. A. Spatola introduced the psi-bracket ([ ]) nomenclature to denote this type of modification. Various types of amide bond surrogates, such as peptidosulfonamides, phosphonopeptides, oligoureas, depsides, depsipeptides, peptoids, and azapeptides, can be synthesized using techniques similar to standard solid-phase peptide synthesis, but different reagents, coupling approaches, and protecting groups are necessary.[8,16]

Methods of Preparation of Peptidomimetics

There are several synthetic methods for the preparations of peptidomimetics among them important are discussed here:

Solid-phase peptide synthesis (SPPS)

Solid-phase peptide synthesis (SPPS) is a widely used method for the chemical synthesis of peptides. It was first developed by R. Bruce Merrifield in the 1960s and has since become an essential tool for the production of synthetic peptides. SPPS is a stepwise approach that allows the efficient and automated synthesis of peptides of up to hundreds of amino acids in length. In this process, the peptide is synthesized from the C-terminus to the N-terminus using an insoluble solid support.

The basic principle of SPPS involves the use of a solid support, typically a resin, to which the first amino acid residue is attached. This initial amino acid is usually protected by a temporary functional group that prevents unwanted reactions during the synthesis. The amino acid attached to the resin is then coupled with the next amino acid in the sequence, which is also protected. This process is repeated until the desired peptide sequence is achieved. The synthesis of peptides using SPPS involves four main steps. These are resin functionalization, coupling, deprotection, and cleavage.

1. **Resin functionalization**: The first step in SPPS is to functionalize the solid support with a linker that will allow the attachment of the first protected amino acid. This is typically done using a chloromethylated resin, which reacts with the amino group of the first amino acid.
2. **Coupling**: The next step involves the coupling of the protected amino acid to the resin-bound linker. This is typically accomplished by activating the carboxyl group of the amino acid with a coupling agent such as dicyclohexylcarbodiimide (DCC) and adding it to the resin-bound linker. This forms an amide bond between the amino acid and the linker.
3. **Deprotection**: After each coupling step, the temporary protecting group on the amino acid is removed using a suitable reagent, such as trifluoroacetic acid (TFA). This exposes the reactive functional group on the amino acid for the next coupling step.
4. **Cleavage**: Once the desired peptide sequence has been achieved, the peptide is cleaved from the resin using a suitable cleavage reagent, such as TFA. The resulting crude peptide can then be purified using a variety of techniques, such as high-performance liquid chromatography (HPLC).

SPPS offers several advantages over other methods of peptide synthesis. One of the main advantages is the ability to automate the synthesis, which makes it possible to produce large

quantities of peptides rapidly and efficiently. SPPS is also highly flexible, allowing the incorporation of a wide range of amino acids and modifications. Additionally, SPPS produces peptides with a high degree of purity, which is important for many applications. A well-known peptidomimetic synthesized using SPPS is RGD peptide mimetic, which is used as an integrin antagonist in cancer treatment.[22]

Solution-phase peptide synthesis

Solution-phase peptide synthesis is a method of synthesizing peptides that involves the sequential addition of amino acids to a growing peptide chain in solution. This method of peptide synthesis is widely used in research laboratories, pharmaceutical industries, and biotechnology companies.

The process of solution-phase peptide synthesis involves the use of protected amino acids that are activated by coupling reagents, such as carbodiimides or phosphonium salts. The protected amino acids have a temporary protective group attached to the amino and carboxyl ends of the molecule to prevent unwanted reactions from occurring during the coupling process.

The first step in solution-phase peptide synthesis is the activation of the protected amino acid. This is achieved by treating the amino acid with a coupling reagent, which generates an activated intermediate that is ready to react with the next amino acid in the sequence. The activated amino acid is then added to the growing peptide chain in a stepwise fashion. The peptide chain is elongated by repeating this process until the desired length is achieved. After each addition, the excess reagents and byproducts are removed by washing and filtration. Once the peptide chain is complete, the protective groups are removed to reveal the amino and carboxyl groups of the peptide. This deprotection step is typically carried out using a strong acid, such as trifluoroacetic acid (TFA) or hydrochloric acid (HCl).

The final product of solution-phase peptide synthesis is a crude peptide that may require further purification to remove any impurities or side products. Common purification methods include reverse-phase high-performance liquid chromatography (RP-HPLC) and gel filtration chromatography.

Solution-phase peptide synthesis is a flexible and versatile method of synthesizing peptides, as it allows for the incorporation of a wide range of amino acids and modifications, such as

fluorophores, biotin, or other chemical groups. Additionally, it can be used to synthesize peptides of varying lengths and complexities, from simple linear peptides to more complex cyclic or branched peptides. Example of a peptidomimetic synthesized using solution-phase peptide synthesis is the β-turn mimetic, which is used to stabilize protein structures.[23,24]

FDA Approved peptidomimetics

Some peptidomimetics used as FDA-approved drugs, are as Romidepsin (Istodax), Atazanavir (Reyataz), Saquinavir (Invirase), Oktreotid (Sandostatin), Lanreotide (Somatuline), Plecanatide (Trulance), Ximelagatran (Exanta), Etelcalcetide (Parsabiv), and Bortezomib (Velcade).[25,26]

Romidepsin is a natural product obtained from the bacterium *Chromobacterium violaceum*. It is an anticancer agent used in cutaneous T-cell lymphoma (CTCL) and other peripheral T-cell lymphomas (PTCLs). Romidepsin works by blocking enzymes known as histone deacetylases, thus inducing apoptosis. It is sometimes referred to as depsipeptide, after the class of molecules to which it belongs.

Atazanavir is an antiretroviral medication used to treat HIV/AIDS. It is generally recommended for use with other antiretrovirals. It may be used for post exposure prophylaxis (PEP) after a needlestick injury or other potential exposure. Saquinavir (Invirase) is also an antiretroviral medication used to treat or prevent HIV/AIDS. Typically, it is used with ritonavir or lopinavir/ritonavir to increase its effect.

Octreotideis is an octapeptide that mimics natural somatostatin pharmacologically, though it is a more potent inhibitor of growth hormone, glucagon, and insulin than the natural hormone. It binds predominantly to the somatostatin receptors SSTR2 and SSTR5. Octreotide (Mycapssa) is the first and only oral somatostatin analog (SSA) approved by the FDA.

Lanreotide is used in the treatment of acromegaly, due to both pituitary and non-pituitary growth hormone-secreting tumors, and the management of symptoms caused by neuroendocrine tumors, particularly carcinoid tumors and VIPomas. It is a long-acting analogue of somatostatin,

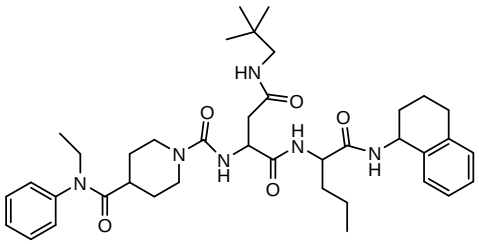
Plecanatide is a medication for the treatment of chronic idiopathic constipation and irritable bowel syndrome with constipation. Plecanatide is an agonist of guanylate cyclase-C. Plecanatide increases intestinal transit and fluid through a build up of cGMP.

Etelcalcetide is used for the treatment of secondary hyperparathyroidism in people with chronic kidney disease (CKD) on hemodialysis. Hyperparathyroidism is the condition of elevated parathyroid hormone (PTH) levels and is often observed in people with CKD.

Bortezomib is an anti-cancer medication used to treat multiple myeloma and mantle cell lymphoma. This includes multiple myeloma in those who have and have not previously received treatment. It is generally used together with other medications.

Anticancer peptidomimetics

Yu Cao et al designed a series of novel non-covalent peptidomimetic proteasome inhibitors with N-alkylation at the N-terminus and a bulky group at the C-terminus to increase their metabolic stability in vivo. These target compounds were screened for inhibitory activities against human 20S proteasome, with most analogs displaying significant potency, as evidenced by IC50 values lower than 10 nM, compared to the positive control bortezomib. These compounds also exhibited strong cytotoxic activities against multiple myeloma (MM) cell lines and human acute myeloid leukemia (AML) cells. Selected compounds underwent whole blood stability and in vivo proteasome inhibitory activity experiments, with the representative compound 1 (IC50 = 8.39 ± 2.32 nM, RPMI-8226: IC50 = 15.290 ± 2.281 nM, MM-1S: IC50 = 9.067 ± 3.103 nM, MV-4-11: IC50 = 2.464 ± 0.713 nM) revealing a half-life extension of greater than 9-fold (329.21 min VS 36.79 min) and potent proteasome inhibitory activity in vivo.27.



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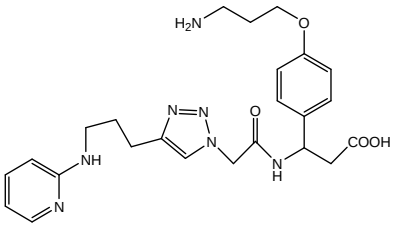
Innocenti et al reported the synthesis of a novel functionalized triazole-based RGD (**Arginine-glycine-aspartic)** peptidomimetic and its covalent conjugation on pegylated gold nanostars. These highly stable nanoconstructs showed a multivalent effect in binding αvβ3 integrin receptors and proved to inhibit M21 cell adhesion at 25 pM concentration. Targeted gold nanostars, thanks to their peculiar surface plasmon resonance in the "NIR transparent window", may represent a promising agent for anticancer multi-modality treatments.[28]



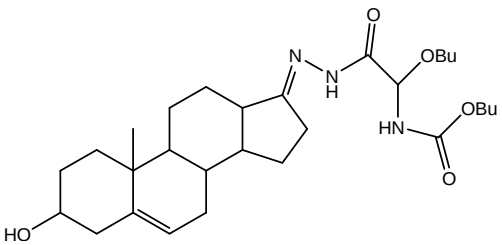
2

In the current study, Ahmadi et al have investigated a series of non-naturally modified RGD peptide mimic (MOH) nanoconjugates with low molecular weight branched polyethylenimine (bPEI 1.8 kDa). The projected peptide mimic, Fmoc-FFARKA (MOH), has already been demonstrated to have high binding efficiency for αVβ3 integrins and enhanced cell adhesive ability with high stability compared to the natural RGD counterpart. Nanoconjugate vectors, PEI-MOH (PMOH), have been designed to enhance the tumor targeting ability, therapeutic proficiency, transfection efficiency, and proteolytic stability. The synthesized nanoconjugates displayed the ability to protect the bound DNA with low cytotoxicity, and their pDNA complexes showed enhanced transfection efficiency. Furthermore, a competitive study confirmed their selective behavior towards liver cancer cells, HepG2. Lastly, PMOH nanoconjugates also exerted significant antimicrobial effects against drug-resistant pathogens. Altogether, the data suggest that nanosized non-naturally modified RGD peptide mimic-based gene vectors hold great potential as efficient biomaterials for targeted gene delivery and antimicrobial applications.[29]

Five new complexes of the type [(AuBr2)-Br-III (dtc-AA(1)-AA(2)-OR] with different amino acid sequences and chiral configurations were designed to enhance tumor selectivity and bioavailability. The peptidomimetic ligand targets two peptide transporters, PEPT1 and PEPT2, which are upregulated in several tumor cells. The compounds were synthesized and fully characterized using elemental analysis, one- and two-dimensional NMR spectroscopy, FT-IR, and UV/Vis spectrophotometry. The crystal structures of three compounds were solved by X-ray diffraction. *In vitro* cytotoxicity studies using a panel of human tumor cell lines showed that the dtc-Pro-Aib-OtBu derivative was highly effective with GI (50) values much lower than those of cisplatin. This complex was chosen for further evaluation of stability under physiological conditions, possible interactions with serum albumin, PARP-1 enzyme inhibition assays, and preliminary ex vivo toxicity experiments on healthy rat tissues.[30]

Recently, there has been a growing interest in peptidomimetics, which are structural or functional mimetics of natural active peptides. They can preserve the bioactivity of lead peptides while improving bioavailability and specificity towards the targets. Peptidomimetics with high bioactivity can be designed through various methods such as conformation restriction, modification, and non-peptide design. The development of cancer chemotherapeutic drugs has shifted from cytotoxic drugs to target-based drugs. Many proteases and peptidases that play key roles in the process of tumor genesis and development have been discovered. Therefore, peptidomimetics have the potential to be developed as cancer chemotherapeutic drugs and should be given close attention. Su et al has focused on the development of small-molecule peptidomimetic inhibitors of APN, MMPs, and HDACs as target-based anticancer agents. These three zinc-dependent metalloproteinases play crucial roles in the process of tumor genesis, invasion, metastasis, angiogenesis, and matrix degradation. Small-molecule peptidomimetic inhibitors based on them would have high selectivity and be promising in the development of chemotherapeutic drugs.[31]

A series of novel peptidomimetics bearing dehydroepiandrosterone moiety were designed, synthesized, and evaluated for their inhibition activities against cell proliferation. According to the preliminary studies on inhibitory activities, some of the newly prepared compounds indicated significantly inhibition activities against human hepatoma cancer (HepG2), human lung cancer (A549), human melanoma (A875) cell lines compared with the control 5-fluorouracil. Especially, compound 3 (IC50) showed the most potent activity against all three cancer cell lines.[32]



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CONCLUSION

In conclusion, the development of peptidomimetics as a novel class of anticancer agents has been the focus of extensive research in recent years. Peptidomimetics have emerged as a promising alternative to traditional chemotherapy due to their ability to mimic the structural and functional features of peptides while overcoming their inherent limitations, such as poor

stability and bioavailability. This review has provided insights into the design, synthesis, and anticancer activities of peptidomimetics, highlighting their potential as effective anticancer agents. The application of peptidomimetics in cancer treatment represents a significant advancement in the field of medicinal chemistry, and further research is warranted to optimize their therapeutic efficacy and minimize their toxicity. Overall, the development of peptidomimetics holds promise for improving cancer treatment and patient outcomes in the future.

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