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REVIEW

Design, Synthesis and Pharmacological Properties of Peptidomimetics

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Peptidomimetics represent a unique class of future therapeutics with many potential applications in modern medicine. By structurally and functionally mimicking the key characteristics of endogenous peptides, various structural variants of peptidomimetics are designed, synthesized and evaluated for numerous biological activities. Advances in the area of drug design through peptidomimetics have resulted in many therapeutically potential candidates in preclinical as well as clinical trials. This review covers the strategies for the design, syntheses and applications of peptidomimetics.

Keywords: Peptidomimetics, Natural peptides.

INTRODUCTION

The existence of living system is built upon physiological processes that are dependent on protein-protein interactions. Proteins and peptides play important roles in converting genomic information into the appropriate biological responses and thus many physiological processes are regulated by them. Some proteins and peptides directly involve in endocrine signals, neurotransmitters and neuromodulators through a mechanism similar to the binding of dietary proteins to proteases and the binding of hormones to their receptors[1]. For over a century, peptides such as insulin, luteinizing hormone-releasing factor (LHRF), growth factors and cyclosporins are being used as endocrinological therapeutic drugs[2].

Although natural peptides serve as an important source for lead compound discovery and development, their intrinsic hydrophilic nature and high molecular weight limit their use as therapeutic drugs[3]. High molecular weight peptides decrease their ability to penetrate through the biological barriers such as the gastrointestinal lumen. Proteolysis by proteases and peptidases in the intestinal lumen hydrolyzes the peptide bond and converts it into smaller amino acid units that can easily pass through the gut wall. As a result, its actual pharmacological activity is reduced or lost. Similarly, increased first pass effects also limit the oral bioavailability of peptide-based drugs[1]. Moreover, peptides have short half-lives due to rapid excretion by the kidneys and/or liver[3]. Other shortcoming includes its inclination to multiple interactions with various receptors, due to peptide chain flexibility.

As a consequence, various strategies to improve peptide delivery by modern pharmaceutical methods have been undertaken. Several studies have described the improvement of insulin delivery by inhalation or by sublingual delivery[4]. Although these administration routes are not convenient for every patients, they surpass the first pass effects but, unfortunately, the bioavailability remains unsatisfactory. Nonetheless, a paradigm shift in the drug design, development and delivery has resulted in the birth of peptidomimetics as an essential drug design tool. Peptidomimetics are molecules that resemble and are easily identifiable to peptides, *i.e.*, they have ligands that can bind to biological receptors to produce a desired response as would natural peptides[5]. In general, peptidomimetics are chemically modified molecules which possess pharmacodynamic properties with improved pharmacokinetic properties as compared to those of natural peptides. For example, peptide proteolysis can be circumvented by modification of its backbone structure[6].

The vital part of peptidomimetics, called pharmacophores, mimics the natural peptides and produce similar biological effects by binding to specific receptor targets. Their non-peptide moiety can be modified by incorporating cyclic peptides or non-natural amino acids, or by altering the backbone

structure to increase the bioavailability and half-life[5]. Properties that are usually lacking in the natural peptides are thus improved such as enhanced receptor selectivity and reduced metabolic liabilities resulting in increased potency[7]. The discovery of peptidomimetics has since opened a new area for drug design and development. Several types of peptidomimetics have been developed and evaluated so far. This review covers the strategies for the design, syntheses and applications of peptidomimetics.

Classification of peptidomimetics: On the basis of structural changes in natural peptides, peptidomimetics are classified into four types which are type I-peptide backbone mimetics, type II-functional mimetics, type III-topographic mimetics and type IV-non-peptide mimetics[8].

Type-I peptide backbone mimetics: They are also known as pseudo-peptides and these peptidomimetics have different peptide backbone from those of the parent peptide compounds but they retain the necessary bioactive part responsible for interaction with a receptor's binding site[9]. This class of peptidomimetics is characterized by changes in the backbones such as stabilized-turn mimetics in which aromatic[10,11], bicyclic[12,13], cyclic compounds[12,14] and amide bond isosteres[12] are the common structural features. The latest studies are concerned with transition-state isosteres or collected substrate/product mimetics prepared to mimic reaction pathways intermediate to the enzyme-catalyzed reactions[9]. They are synthesized using structure-based drug design techniques and one example of this class of mimetic is the pyrrolinones[15].

Type-II functional mimetics: These types of peptidomimetics are small non-peptide molecules that bind to the peptide receptor and are direct structural analogue of the original peptides. Their ligands have capability to assert the same biological activity as native peptide ligands. Therefore, these functional mimetics do not mimic the structure of the parent compound essentially[11]. Their syntheses are aided by molecular modeling and high-throughput screening techniques. One example is OCP-21268 which is the first non-peptide orally active vasopressin receptor inhibitor (Fig. 1)[15].

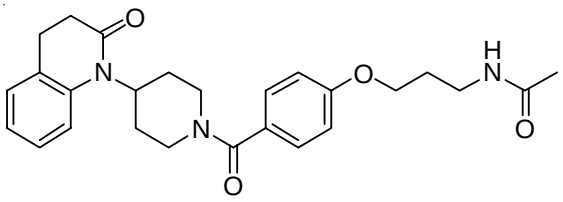

Fig. 1. Chemical structure of OCP-21268

Type-III topographic mimetics: These types of peptidomimetics have the original peptide models but lack the peptide core structures. However, they still retain crucial groups whose positions are the key function for interaction with the receptors, as they resemble the original peptide structure[16]. They are considered to be the ideal peptidomimetics as they possess novel templates which lack any structural similarity to the original peptides but contain the necessary groups located on a novel non-peptide scaffold to serve as topographical mimetics[17,18]. These types of peptidomimetics are synthesized by structure-based drug design techniques and one example is non-peptide protease inhibitors (Fig. 2)[15].

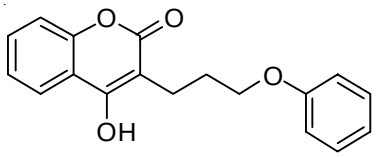

Fig. 2. Chemical structure of non-peptide HIV-1 protease inhibitor

Type-IV non-peptide mimetics: These peptidomimetics possess some common properties as those of pseudopeptides, but in terms of their binding capabilities, they bind to enzymes differently from those bound by type I peptidomimetics[5]. These types of peptidomimetics are synthesized by the group replacement assisted binding drug design technique and one example of this class of peptidomimetics is piperidine inhibitors (Fig. 3)[15].

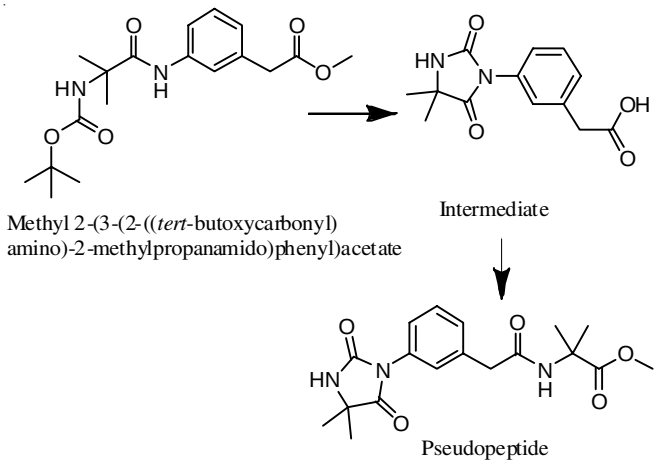

Fig. 3. Synthesis of pseudopeptide

Strategy for peptidomimetic design: A major problem of natural peptides is their conformational flexibility that are associated with many unwanted side effects. While designing peptides that mimic the protein structure, the intermolecular forces are often lost, so this conformational flexibility issue becomes more severe. There are several approaches for overcoming this problem.

Introduction of cyclization: Cyclization is used to reduce peptide conformational flexibility and thus increase peptidomimetic stability *in vivo*. Cyclization can be accomplished in three ways: 1) to connect the C- and N-terminus of the peptide sequence, also called head-to-tail cyclization or end-to-end cyclization; 2) to connect the C-terminus of the peptide sequence to the N-terminus of the side chain or *vice versa*, also called backbone-to-side chain cyclization; and 3) to connect the C-terminus and N-terminus of the side chains by using disulfide bonds, also called side-chain-to-side-chain cyclization (Fig. 4). In the third method, a limited portion of the peptides are constrained. Further covalent bonds can be introduced to increase conformational rigidity[19].

Introduction of methyl group: Methyl groups are introduced adjacent to rotatable peptide bond as a way to introduce conformational constraint in peptidomimetics by virtue of diminished bond rotation. For example, α-amino isobutyric acid is obtained by replacing the α-hydrogen on alanine with a methyl group (Fig. 5). Substitution at the β-position will cause formation of a second asymmetric

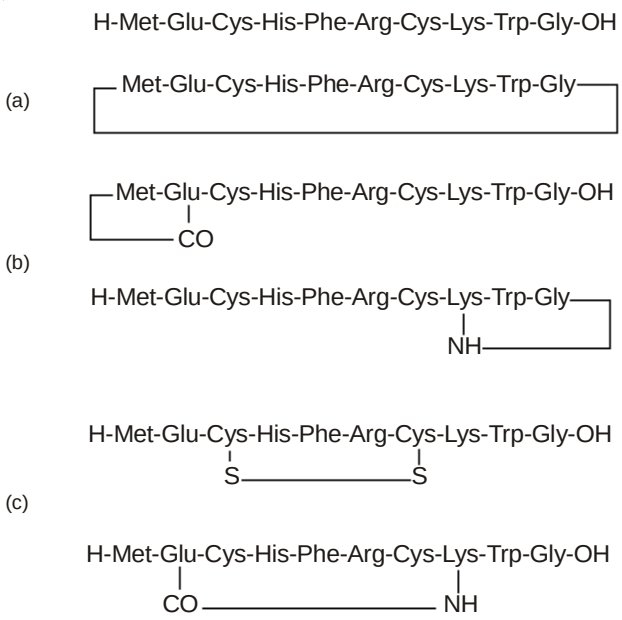

Fig. 4. Types of cyclization of peptides: (a) end-to-end cyclization, (b) backbone-to-side chain cyclization and (c) side chain-to-side chain cyclization

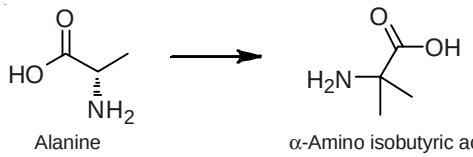

Fig. 5. Introduction of methyl group into alanine to form α-amino isobutyric acid

centre, which allows some conformational degree of freedom to the peptide backbone, but it is necessary for peptidomimetic activity[20]. Methyl group also increases the lipophilicity of the peptides, which helps to enhance its pharmacokinetic properties[21]. On the other hand, N-methylation reduces the conformational flexibility of the neighbouring amino acids.

Change in backbone: Chemical groups such as sulfones, ether and amine, which have the same three-dimensional structures as those of amide bond, are introduced to reduce the flexibility as well as to increase the pharmacological activity of many peptidomimetics. Several changes in the backbone structure using amide bond substitutes are shown in Fig. 6[22].

Although the amide substitute introduction reduces the hydrophobicity and improves the bioavailability of the peptide by virtue of reduced proteolytic degradation but it results in negative effect on the activity of the peptide. One consequence is that the specificity is compromised.

Synthesis of peptidomimetics: Liquid phase synthesis and solid phase synthesis are two widely used methods for the

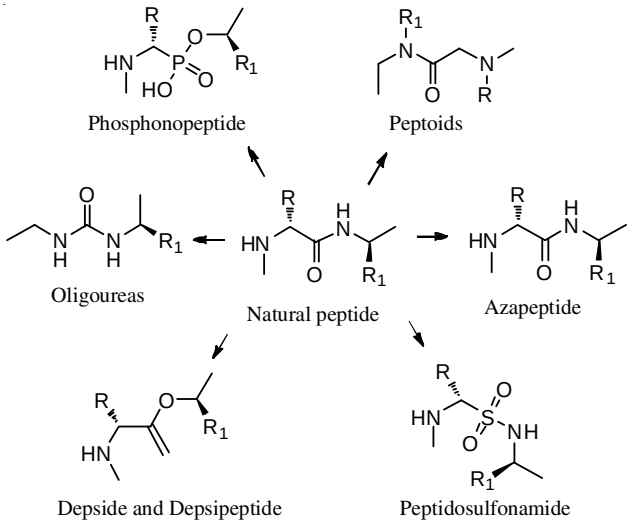

Fig. 6. Some important peptide bond substitutes

synthesis of peptidomimetics. The classical liquid phase method is commonly used in large scale manufacturing, but it is time consuming and expensive due to the need of optimized conditions and many purification steps[23]. On the other hand, solid phase synthesis is comparably low-cost and fast. This method uses a liable linker to attach the amino acid C-terminus to an insoluble polymeric support and the attached peptide is extended by a series of coupling cycles. This process has high yields and uses excess soluble reagents, which can be recycled by simple filtration without much loss. After the peptide is prepared, it is easily removed from the solid support[24].

Solid phase peptide synthesis involves repeated amino acid protection and de-protection processes, whereby acid labile α-amino protecting group *tert*-butyloxycarboxyl (Boc) or base labile α-amino protecting group fluorenylmethyloxycarbonyl (Fmoc) are commonly used. De-protection process is then accomplished with trifluoroacetic acid and piperidine, respectively. Both these methods are summarized in Table-1. After synthesis of peptides, the purification and quality evaluation is usually done by high performance liquid chromatography (HPLC) or reverse phase (RP)-HPLC. Mass spectra (MALDI/ESI-TOF) and NMR (mono- and bi-dimensional) techniques are used for the peptide identification.

Fransson[25] discovered two new methods with the intension to prepare bioactive neuropeptide substance P 1-7 analogue H-Phen-Phen-NH_2. In the first method, for the direct arylation of N-terminal imidazole, microwave assisted protocol was used while in the second method, imidazole moiety was assimilated to the peptide sequence at N-terminal by using aminocarbonylation reaction with carbon monoxide source[25]. By these methods, six different H-Phen-Phen-NH_2 mimetics were successfully synthesized.

TABLE-1
COMPARISON OF Fmoc AND Boc-BASED SOLID PHASE PEPTIDE SYNTHESIS PROCEDURES

Aspects	Fmoc chemistry	Boc chemistry
Side chain protection	Acid sensitive	Strong acid sensitive (hydrogen fluoride)
N^{α}-deprotection	20 % piperidine in DMF	50 % Trifluoro aniline in dichloromethane
Final cleavage	Trifluoro aniline in SPSS vessel	HF (special equipment)
Automation	Yes	Yes
Synthetic steps	Deblock, wash, couple, wash	Deblock, neutralization, wash, couple, wash
Resin	Acid or super-acid sensitive	Merrifield type

Applications of peptidomimetics

Antimicrobial field: The use of synthetic combinatorial libraries for peptidomimetics has generated new methods of research, understanding and deeper insights into antimicrobial possibilities[26]. The following are few peptidomimetic antimicrobial studies that have been done. For example Aberg *et al.*[27] synthesized and studied the *in vivo* use of 24 substituted bicyclic 2-pyridones to target *P. pili* virulence in uropathogenic *Escherichia coli*, but found them to be less potent than 2-pyridone parent compounds, suggesting the need for more research in antibacterial peptidomimetics.

For *Staphylococcus spp*, Eichler and Houghten[26] reported good antimicrobial activity of N-methylated peptidomimetics against *S. aureus* and *S. sanguis*, which can be developed as alternative drugs. Gorske and Blackwell[28] studied the *Staphylococcal spp* agar surface proteins and their structure-activity relationships and discussed the possibility of peptidomimetic peptoid design to specifically target any of its virulence factors. Hein-Kristensen *et al.*[29] reported good antimicrobial activity of 6 alternate N-alkylated α-amino acids and β-alanine in α-peptide/β-peptoid chimeras against *S. aureus,* which happened *via* disrupting cell membranes and it was found that chain length is an important factor in antimicrobial activity.

Srivinas *et al.*[30] developed a novel peptidomimetic class of antibiotics against the drug resistant strains of *Pseudomonas spp*. This antibiotic had a non-membrane lytic mechanism of action and showed potent activity against a mouse septicemia infection model. Recently, in 2012, a new antimicrobial peptide, SB056 (Fig. 7)[31] was discovered. This promising AMP has shown activity against resistant gram negative bacteria but had little activity against the gram positive bacteria. Rotem and Mor[32] reviewed a wide variety of peptoids, β-peptides, arylamide and phenylene-ethynylene oligomers of their antimicrobial activity against many microbes. McGrath *et al.*[33] tested an all-D-enantiomer peptidomimetic against many Gram-negative bacteria and successfully disrupted the bacteria's surface lipid bilayer function and integrity, which further adds to the list of drugs to treat problematic bacteria.

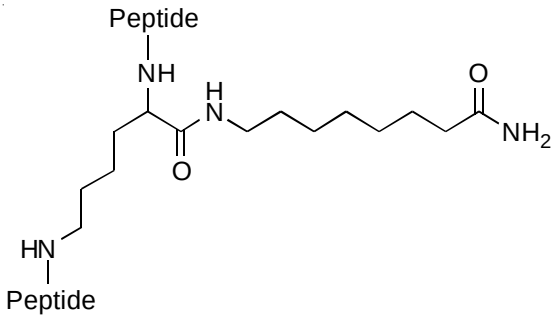

Fig. 7. Chemical structure of dendrimeric peptide SB056

The antifungal studies performed include those of Muñoz *et al.*[34] who used the antimicrobial PAF26 successfully against *Saccharomyces cerevisiae*, *Neurospora crassa*, *Candida albicans* and *Aspergillus fumigatus*, although Eichler and Houghten[26] noted that N-methylated peptidomimetics was ineffective against *Candida albicans*. Overall, peptidomimetics has shown great potential in treating bacteria and fungi and more research in these fields are strongly recommended.

Peptidomimetics as antiviral agents: The ubiquitous virus in any environment poses danger to one's health and since it is not uncommon for its constant DNA mutations, research must pick up the pace to prepare for emergency situations to combat it. In the study of hepatitis C virus (HCV), Barbotte *et al.*[35] synthesized a novel amino acid-substituted peptide capable of granting hepatitis C virus stronger resistance to the drug telaprevir in an attempt to understand the complexity of hepatitis C virus protease inhibitor resistance. Welsch *et al.*[36] working on sequence and structural analysis, has determined that natural hepatitis C virus protease NS3/4A amino acid sequence variation influences HCV's resistance to first generation of direct-acting antivirals like ketoamide and telaprevir respectively. Based on the scientific findings in this area, it might lead to better drug design that could catch up with the pace of mutation and incapacitate the hepatitis C virus eventually.

Severe acute respiratory syndrome (SARS) is one of the most lethal airborne diseases to hit mankind in recent years, alongside influenza A. Shie *et al.*[37] synthesized α,β-unsaturated peptide esters as a potential effective non-toxic anti-SARS drug and demonstrated modest SARS virus 3CL protease inhibition *in vitro*, backed by *in silico* molecular docking studies. Konno *et al.*[38] similarly did synthesis, *in vitro* studies and molecular docking studies of tripeptide-type 3CL protease inhibitors with electrophilic arylketone moiety and found potency at nanomolar scales. The study has also determined structural factors essential for any peptidomimetic to possess anti-SARS activity.

Human immunodeficiency virus-1 (HIV-1) is the most well-known of all viral species and peptidomimetic research is being carried out to target on this virus. Allemann *et al.*[39] reviewed studies of peptidomimetic HIV-1 protease inhibitors *in vivo* by oral administration in beagle dogs and mice with nanospheres and the results showed encouraging pharmacokinetic and pharmacodynamic results. Lebon and Ledecq[40] reviewed approaches of effective inhibitor design, for instance inhibitors that are site-active, substrate-based and substrate-backbone modified. Randolph and DeGoey[41] reviewed the clinical studies and discovery process of approved protease inhibitors and methods for enhancing pharmacokinetic and resistance. Qiu and Liu[42] reported syntheses of newer peptides, which aims to circumvent drug and cross resistance.

Peptidomimetics as anticancer agents: The field of cancer studies for peptidomimetics has been a vast one. There are many studies focusing on opioid receptor ligands[26] from which peptidomimetics have contributed to physiological functions like analgesia, anti-depression, euphoria and diuresis of the individual and further understanding of biology and physiology. Ruzza *et al.*[22] has reviewed a wide range of peptide receptor ligands developed such as somatostatin-14 and -28, neuro peptide Y and MSH (melanoma), which correspond to various tumour receptors like those of melanoma, pancreatic, lung, neuroendocrine and neuroblastoma cancers, to name a few, which assisted in cancer imaging and anticancer drug development.

The p53 tumour suppressor gene is an important cause of tumorigenesis which is being heavily researched on. Fasan *et al.*[43] designed a β-hairpin structure with ability to mimic α-helix backbone which is essential for inhibiting the interaction of p53 proteins to the original binding site of HDM2, reducing likelihood of cell stress and cancer formation. This effort is paving way to more peptide-based drug development. Zhong and Carlson[44] investigated the affinity of p53 peptides *in silico* to HDM2 domains, identifying amino acid sites responsible for original p53 binding and also speculated the possibility of reducing cancer cell growth. More synthesis studies are needed to substantiate *in silico* analyses above so that the p53-HDM2 complex may be inhibited clinically. Besides that, it was found that, some drugs have been developed to target p53 through different actions. They are small molecules that restore the mutated p53 to its wild type function. One drug called Phikan 083, a carbazole derivative, was found to bind to p53 and revert it to its original function. CP-31398, another small molecule, was found to intercalate with DNA and alter its conformation by destabilising the DNA-p53 complex and restore the destabilized p53 mutants[45,46]. Shangary *et al.*[47] have shown MI-219 to be a selectively toxic to tumours by activating p53. MI-219 was found to interfere with the MDM2-p53 in cancerous cells, resulting in selective apoptosis naturally in cancerous cells and with complete tumour inhibition.

Another promising area for cancer treatment with peptidomimetics involved caspase-based drug therapy. A malignant cell can acquire resistance to apoptosis by reduced caspase function. Caspases are considered important in the initiation and execution of apoptosis and they can be classified into two broad groups. The first group is called caspases I, which is involved in cytokine and inflammatory processes. The second group consists of initiators caspases and effector caspases. This second group of caspases are considered more relevant because caspases bound drug therapy is using small molecules of peptidomimetics. Apoptin is an example of a caspase-inducing drug which selectively induces apoptosis in cancer cells leaving normal cells intact, in a study based on the chicken anaemia virus[48].

The signal transducer and activator of transcription 3 (STAT3) protein enable tumour cells to grow and survive *via* aberrant signalling pathways. Turkson *et al.*[49] generated new peptidomimetic substituted derivatives of previously-identified STAT3 PY*L peptides that inhibit STAT3 dimerization and thus may prevent or treat cancer. Gunning *et al.*[50] went further by designing peptides that selectively inhibit STAT1 or STAT3 homo-dimerization, with STAT1 homo-dimerization inhibited more potently than STAT3. Shahani *et al.*[51] similarly synthesized STAT3-selective inhibitors that however only lasted for 24 h before aberrant activity recovered, suggesting the need for further refinement *via* prodrug synthesis. Finally, Shaaban *et al.*[52] designed quinone peptide multifunctional redox modulators to target tumours formed from oxidative stress, causing tumour apoptosis and inhibiting tumour proliferation. Similar to the antimicrobial applications, peptidomimetics have demonstrated good promise in the ongoing anticancer drug development and studies and greater advancement would be expected in not too distant future.

Peptidomimetics as antihypertensive agents: Medications to control hypertension have been the subject of various studies and national guidelines. The main goal of the therapy is to prevent complications that may arise from high blood pressure such as heart attack, stroke and heart failure. Several antihypertensive agents that lower blood pressure based on various mechanisms have been available such as β-blockers, calcium channel blockers, angiotensin-converting-enzyme (ACE) inhibitors, angiotensin II receptor blockers and diuretics[53]. Angiotensin-converting-enzyme inhibitors, one of the most effective antihypertensive drugs were considered as synthetic peptidomimetics. Captopril (Fig. 8) for example, was used as the first drug to inhibit angiotensin-converting-enzyme, by catalyzing the hydrolysis of angiotensin I to angiotensin II (a potent vasoconstrictor), thus reducing blood pressure by lowering peripheral vascular resistance[54].

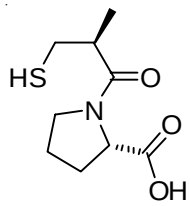

Fig. 8. Chemical structure of captopril

Peptidomimetics as antimalarial agents: Malaria is widespread around different areas of the world, including sub-Saharan Africa, Asia and the Americas[55]. Older antimalarial drugs are becoming less effective due to increasing parasite resistance, toxicity, low efficacy and high cost. Thus, new drugs had emerged to supersede the older ones[56]. For example, new synthesized peptidomimetics containing acylal $R_2C(OCOR')_2$ derivatives had shown higher anti-plasmodial effects compared to parent peptides and they might expect to exhibit antitrypanocidal effects[57]. Furthermore, Carrico *et al.*[58] did *in vitro* and *in vivo* studies of peptide farnesyltransferase inhibitors with significant potency against malaria and it is expected to advance clinically in the near future.

Miscellaneous: Peptidomimetics were also utilized in fields other than those mentioned earlier, having potential for advanced applications as well. Bloom *et al.*[59] designed a potent selective peptidomimetic FISLE-412 with a previously-reported DWEYS pentapeptide to neutralize anti-double-stranded DNA/*N*-methyl-D-aspartate lupus autoantibodies as a strategy to treat systemic lupus erythematous. Ponte-Sucre *et al.*[60] synthesized aziridine-2,3-dicarboxylates as nontoxic cysteine protease inhibitors with potency at mid-micromolar range against leishmaniasis. This might be a potential alternative to the toxic antimonials currently in use. Loiarro *et al.*[61] designed a peptide after the adaptor protein MyD88 translation initiation region domain BB-loop heptapeptide, which showed inhibition of MyD88 dimerization, suppressing inflammation and white cell proliferation, in a dose-dependent manner. Statz *et al.*[62] reviewed a class of peptides that has shown potential application for antifouling of post-surgery implanted devices in the human body in long term. Walensky *et al.*[63] devised a method called hydrocarbon stapling that generates cell-permeable and protease-resistant BCL-2 homology-3 peptides.

It is capable of activating cell apoptosis *via* the BCL-2 protein pathway, killing leukemia cells and inhibiting human leukemia xenografts growth *in vivo*. This has a tremendous potential to assist further understanding of protein-protein interactions and other biological pathways directed toward more effective drug design.

Conclusion

Peptidomimetics have become the focus of research target in drug discovery and development, in which effort is directed towards the *in silico* design in order to engineer better pharmacokinetics and pharmacodynamics properties than those of any parent peptides. Various developments in design, synthesis and applications of peptidomimetics have been covered in this review. The field of peptidomimetics merits more research as it has the potential to surpass the performance of older synthetic drugs.

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