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Current Development in Peptide Surrogates Synthesis and Their Biological Applications

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Abstract

Many new peptide therapeutics are increasingly making their way to rapid and successful clinical application. In fact, some naturally derived peptide chains have been very successful drugs for many years. With the emergence of very large libraries of peptides with high biological properties, it is expected that many promising candidates can soon be added to the list of peptides under development. Already recently, these advances have introduced novel strategies for the administration of drugs derived from polypeptide chains and improvements in the purification half-life in vivo. Despite remaining potential hurdles, peptide therapies are poised to play an important role in treating diseases ranging from Alzheimer's disease to cancer.

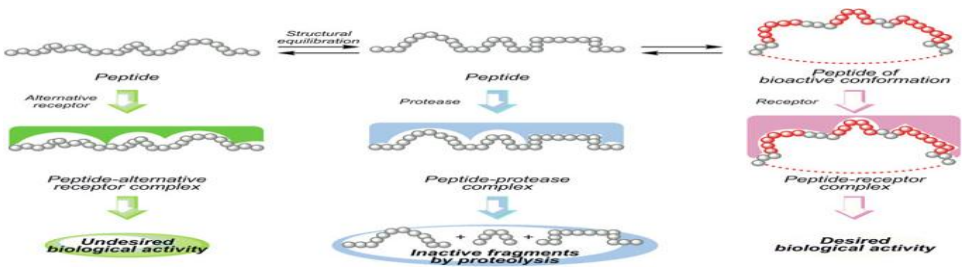
Keywoeds: Amino Acid and Peptides; Biological Applications; Anticancers; Antimicrobials; Alzheimer's disease; Malaria.

1. Peptide as drugs and their drawbacks

The first treatment of a child with diabetes with insulin purified from bovine pancreas during the early 1920s discovers the concept that human diseases can be treated by endogenously occurring peptides [1].

Peptides are important biological molecules having various physiological processes peptides are crucial for many physiological functions through their interaction with the various receptors. There are a great number of natural and modified peptides which are used in therapy and they are increases every moment. Novel therapies of bioactive peptides are discovered and developed daily as biologically active peptides during the last quarter-century. They control and affect the living cell physiological functions via the interaction with their various receptors. There is still proportional increase in the developments that have led to the discovery of novel therapies and in the use of natural and modified peptides as therapeutics.

Peptide-based drug discovery may help bring about the development of useful medicines that are highly safe and show **potent** pharmacological effects in small doses



(Fig. 1). The different conformations of peptides and their interactions.

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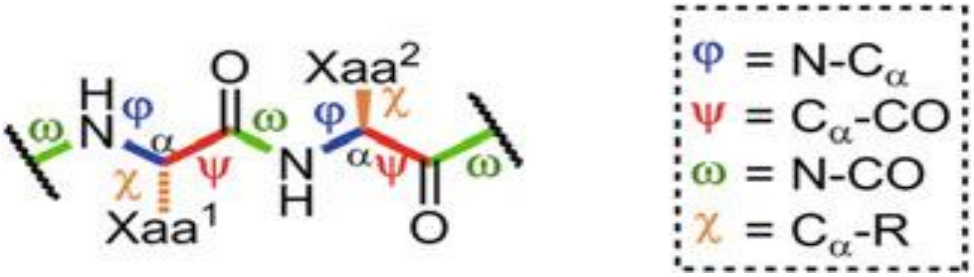
peptides as therapeutics had several drawbacks, such as low metabolic stability toward proteases and unfavorable activity, which resulting from interactions of flexible peptide structures with several receptors simultaneously (fig .1) [2, 3].

1.1. Why the peptides have different conformations?

The inherent polypeptides flexibility caused by each residue in the peptide chain, promotes variable and multiple conformations. It is resulted from freedom of conformational on two level of by N–Cα, Cα–CO, N–CO and Cα–R rotational bonds, which are described by φ, ψ, x, and ω dihedral angles, respectively in the following (fig.2).



(Fig. 2). Dihedral angles that are correlated to conformational flexibility in peptides.

2. Drawbacks of the peptides as therapeutics or as drugs:

1- Low stability in both gastrointestinal trac as well as in serum against proteolysis decreases the half life time in the order of minutes.

2- Low transport and absorption properties.

Since the fairly high molecular weight of peptide oftencause a rapid excretion by both liver and kidneys.

3 - Certain peptide molecules interact with many targets, producing low selectivity and bad side actions. This is because of the intrinsic flexibility of the amide bonds of each residue.

4- Unpredictable interaction of the peptide chains with binding sites of antibodies in the competent host induces antigenicity and an immune response [4]. So there is a great need for peptide modification through peptide surrogates or peptidomimetic formation.

3. Peptide surrogates or Peptidomimetics:

They are a small peptide chains act like protein and usually have built to replace native analogs to obtain targeted pharmacological effects [5-7].

Peptide surrogates are ‘molecules possessed a pharmacophore or mimic a native peptide or protein effects. They should give the same activity [8].

It involves the surrogating of the amide nitrogen (Nα- atom substitution, Nα-atom derivatization), Cα substitution, α-carbonyl group, amino group, amide bond extension, changing side chain of amino acid residues, changing the amino acid residue itself, pepide chain or backbone modification, cyclization ....etc., to obtain peptide surrogates or peptidomimetics (both expressions are equivalent in meaning).

3.1. *Approches for Peptidomimetics or peptide surrogates synthesis:* [9-11]

Generally, they have been obtained from coupling of suitable non-natural amino acids and/or cyclization of linear peptide chains (site of surrogates in the peptide chain) [5-7, 12].

The unnatural amino acids can be obtained from the modifications of [1] native analogs by variable chemical synthetic steps such as amine alkylation [2, 13-17], structural bond extension [3, 18-23] cyclization [4, 24, 25] side chain substitution [5, 26-29] and isosteric substitution [7, 30, 31] within the residue or within a peptide chain, the isosteric replacements produce the surrogate molecule possess a variable electrostatic properties with concomitant new secondary conformations that improve its final pharmaco-kinetic properties.

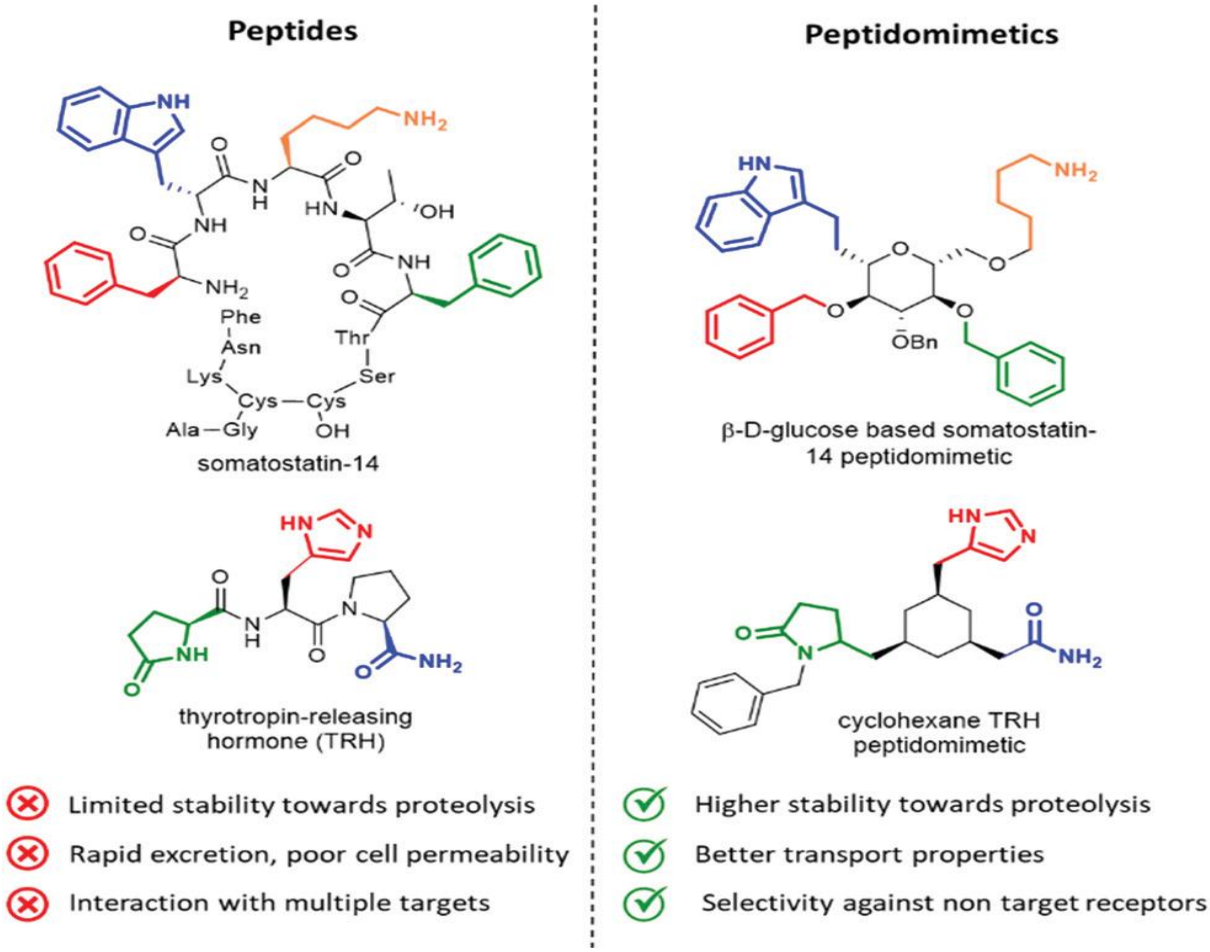
3.2. Biological importance of peptide surrogates (The biological mean)

Peptide surrogating: is a process of overcoming the previous mentioned limitations, as they modify the peptide chain to give new molecule acquiring good bioavailability, metabolic stability, selectivity and high receptor affinity. The lead peptide structure is potentiated by carrying out or doing functional modifications which capable of treating the bad

receipting of that peptides, but keeping their structural features needed for activity (fig. 3, right) [32]. Over the last three decades, the field of peptide surrogates has changed largely. It developed from backbone local modifications of bioactive peptides, to the usage of ad hoc rational design.

Somatostatin analogue is an example of a peptide surrogating compound, where the beta-D-glucose shows the four sites of side branches of the binding interactions exist intact as in the parent peptide chain (fig. 3) [33].

Also, thyrotropin-releasing hormone (TRH) mimetic as in (fig. 3, down) follow the same way of somatostatin. [34].



(Fig. 3). Advantages of peptidesurrogates over peptides

3.2. Peptide surrogates classification

Over the years both the progress and the classification of Peptide surrogates has evolved. Historically, Peptide surrogates were arranged into three categories according to the structure and their function properties [35, 36] while recently, a wider new one consider the high molecular weight is suggested [37]

Table 1; Comparison between ancient and recent peptide surrogates categorization [38-42]

Ancient Peptide surrogates categorization	**Recent Peptide surrogates categorization**
These three types according to structure and function features and Categorizes the Peptide surrogates their	This recent approaches based categorizes the Peptide surrogates according to their degree of peptide

similarity relative to the native peptide: their classes are:	nature:, their classes are:
Class I surrogates, They are structural surrogates that possess The functional groups that lead to the exact spatial arrangements	**Class A surrogates**: They are the most closer to the main peptide, with a small local substitutions that stabilize the conformation and minimize the proteolysis.
Class II surrogates, They have not enough structural similarity with the native peptide, but have the ability to do its activity by the interaction in a similar way with the target enzyme or receptor.	**Class B surrogates**: This class are, still possess great number of peptide-like character. The modifications comprise the using of variable unnatural aminoacidsl residues.
Class III surrogates, They are functional as well as structural surrogates, that markedly different from the native substrate but, assembling the active positions and the interacting elements towards the same conformation.	**Class C surrogates** They have a non-peptide unnatural framework and characterized by increase in small molecule character, which completely substitute the peptide chain. The active sites are directed toward the same conformation existed in the bioactive parent peptide conformation.
	Class D mimics They are hardly resemble to the main peptide. But similar only in the way of effect of a biologically active peptide and there in no direct bonding to their side chain functions.

Any compound that is able to imitate or acquire the structural properties and/or biological activities of a peptide is referred to as a peptidomimetic or Peptide surrogates.

3.3. The rational design approaches for synthetic strategy of peptide surrogates

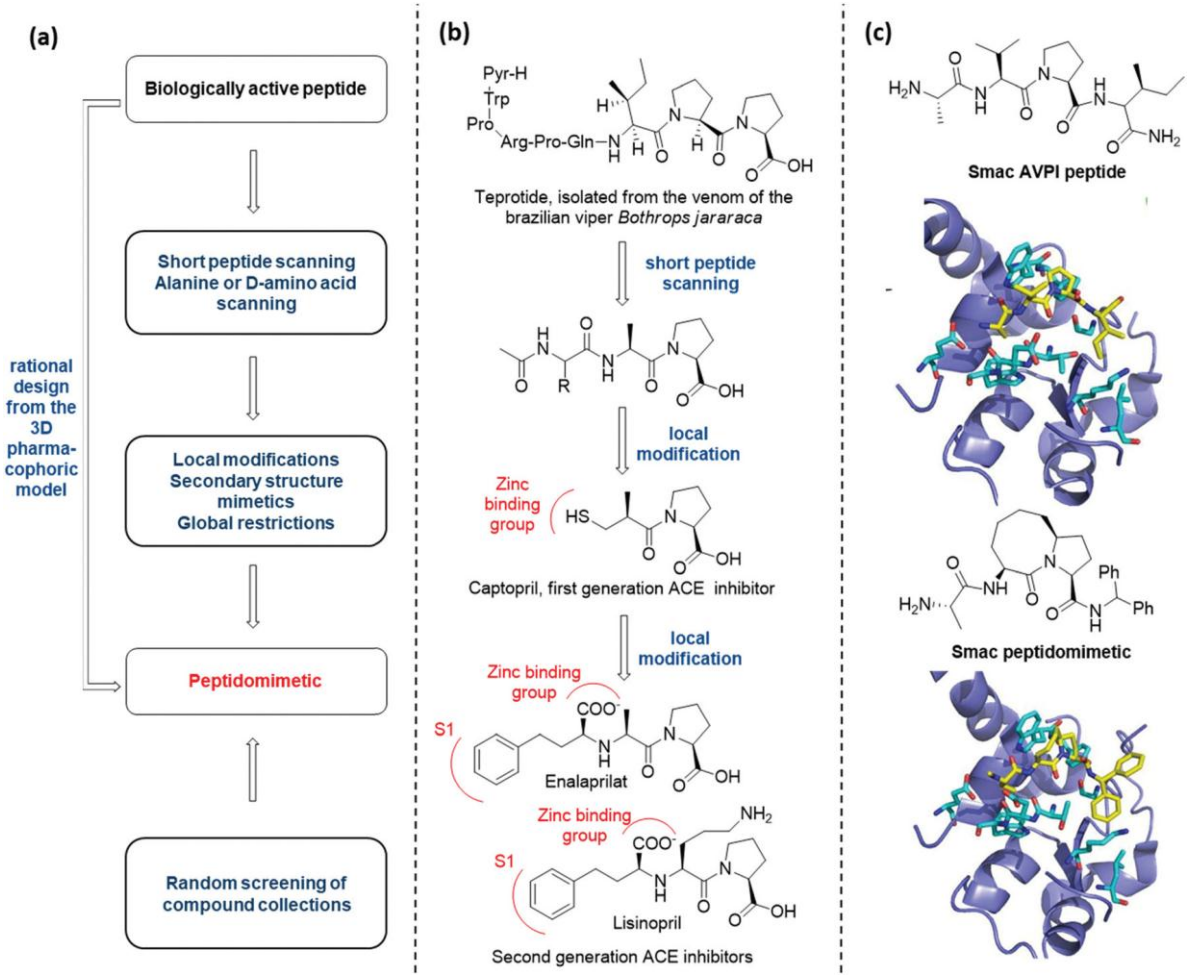
Some important features we need to rationally design a peptidomimetic compounds. We must know all the characteristics of the targeted protein such as their structure, sequence, function, as well as their sites of binding.

From the primary structure of active peptide, a hierarchical approach used to develop the surrogates (fig. 4a).Different approaches of synthesis (mentioned above both old and recent ones) enable to optimize of hit peptide surrogates, thus leading to orally available drug candidates. An example is ACE inhibitors as in (fig 4b).

In the early Eighties using these steps, the drug Captopril was developed as to be the highly effective ACE inhibitors. Advanced developments of ACE inhibitors were performed by substituting the thiol instead of carboxylate group to reduce side effects of Captopril and incerting hydrophobic part organizing the S1 part of the catalytic site, to obtain Lisinopril and Enalaprilat [43-45].

Knowing the three-dimensional pharmacophoric model may help in skipping the above mentioned steps, using rationally designing peptidomimetic compounds according to the interacting elements responsible for the molecular recognition

If there is no information about the bioactive peptide or about the pharmacophoric model structure, the random screening peptide surrogates libraries is the only possible way that can be solve such problem as shown by (fig. 4a).



(Fig. 4). (a) Hierarchical approach to peptide surrogates design; (b) history of the development of peptide surrogates ACE inhibitors; (c) Smac peptidomimetic inhibitor of the X-linked inhibitor of apoptosis protein (XIAP) developed by rational design.

4. Novel uses of peptides

It has been observed during recent references that synthetic organic chemistry has a distinct biological activity in all different applied directions [46-87].

4.1. Cancer: vaccination and drug targeting

Cancer along with cardiovascular disease are the main causes of death in the industrialised countries around the World. Conventional cancer treatments are losing their therapeutic uses due to drug resistance, lack of tumour selectivity and solubility and as such there is a need to develop new therapeutic agents. Therapeutic peptides are a promising and a novel approach to treat many diseases including cancer. They have several advantages over proteins or antibodies: as they are (a) easy to synthesise, (b) have a high target specificity and selectivity and (c) have low toxicity. Therapeutic peptides do have some significant drawbacks related to their stability and short half-life. In this review, strategies used to overcome peptide limitations and to enhance their therapeutic effect will be compared. The use of short cell permeable peptides that interfere and inhibit protein-protein interactions will also be evaluated [88, 89].

An exciting potential use of peptides is in the treatment of cancer. Most of the anticancer treatments used currently lack specificity and cause significant side-effects. Peptides are being used to generate

therapeutics for enhancing cellular uptake [90], drug targeting [91-95] and vaccination [96, 97].

Vaccination is an attractive potential mechanism for peptide therapeutics because patients should develop an active immunity to the cognate cancer, thereby preventing further recurrence. Synthetic peptide vaccines are based on the idea that cancerous cells display epitopes on their surface that are not present on normal cells [98]. Several clinical trials have already been performed using synthetic peptide vaccines to various tumor antigens, with no major toxicity observed [99, 100]. Unfortunately, significant efficacy has also not yet been observed in these clinical trials.

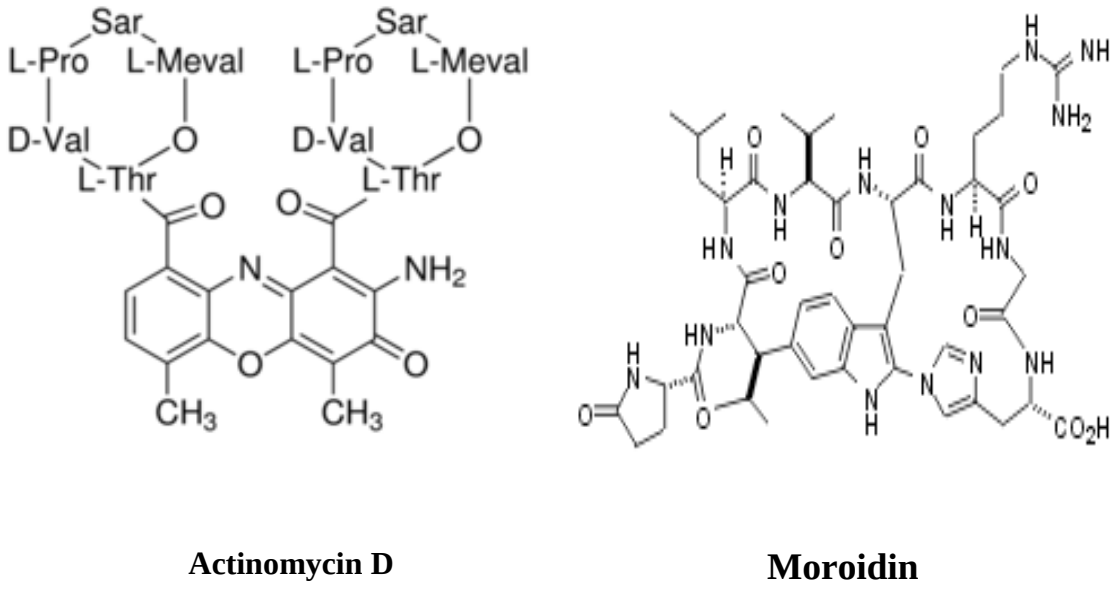
Although contributing to the lack of toxicity, the low immunogenicity of peptides unfortunately translates to inefficient priming of the immune system. One strategy for overcoming this problem is to include several peptide epitopes in the vaccine, either as discrete peptides or in the context of a larger peptide that will be processed *in vivo*. In the larger peptide approach, one complication is the potential generation of cryptic epitopes that lead to an immune response but do not represent epitopes expressed on the surface of target proteins (or cells). In one recent study, although natural epitopes to the tumor antigen NY-ESO-1 were used, proteolytic processing *in vivo* resulted in the generation of a cryptic epitope with improved binding to the MHC molecule compared with the natural epitope [97]. Owing to preferential binding of the cryptic epitope, the cytotoxic T cell (Tc) response to the cryptic epitope – rather than a surface epitope – dominated the immune response.

By contrast, studies in mice showed, in some cases, complete eradication of established tumors expressing human papilloma viral epitopes when the mice were treated with a long peptide containing both helper T cell (Th) and Tc epitopes, but not when the Tc epitope was administered alone [88]. Lack of reproducibility in humans of results from animal studies could originate from several causes. Several studies have shown that the immune response of humans and mice is affected not only by the host physiology but also by the method of vaccine delivery and type of adjuvant used [101]. Thus, a better understanding of the adaptive immune response is needed for peptide vaccines to become viable.

Another role for peptides in cancer therapy is in drug targeting. For example, the angiogenic vasculature displays molecular markers at either higher levels or different to those found in quiescent endothelial cells. Proliferating endothelial cells can be targeted by peptides isolated by *in vivo* panning of combinatorial phage libraries in mice [92, 94, 95, 102]. Some of these peptides serve the dual purposes of targeting angiogenic (tumor) tissue while blocking α_V integrins from binding to their ligands, or inhibiting matrix metalloproteases [94]. The result of either of these actions is apoptosis of the endothelial cells in the newly formed blood vessels, thereby halting or reversing tumor progression in mouse models. In other studies, tumor-targeting peptides were conjugated to cytotoxic reagents such as doxorubicin [92] or tumor necrosis factor α [90]. In these studies, peptide-mediated targeting of the drug to the tumor resulted in increased drug efficacy and lower systemic toxicity.

For successful tumor targeting, peptides must home specifically to human tumor epitopes rather than to normal human tissue. As the expression patterns of some genes have been shown to be different in humans and mice [103-105], *in vivo* panning of a phage library was recently undertaken in a human cancer patient [106]. Sequences specific for certain organs were detected; some appeared within known human proteins, suggesting that the peptides isolated might mimic known ligands. Further work is needed to substantiate this hypothesis and to determine the extent to which variability between individuals influenced the result of this initial experiment.

4.1.1. Some examples of peptide anti-cancer derivatives [107-108]



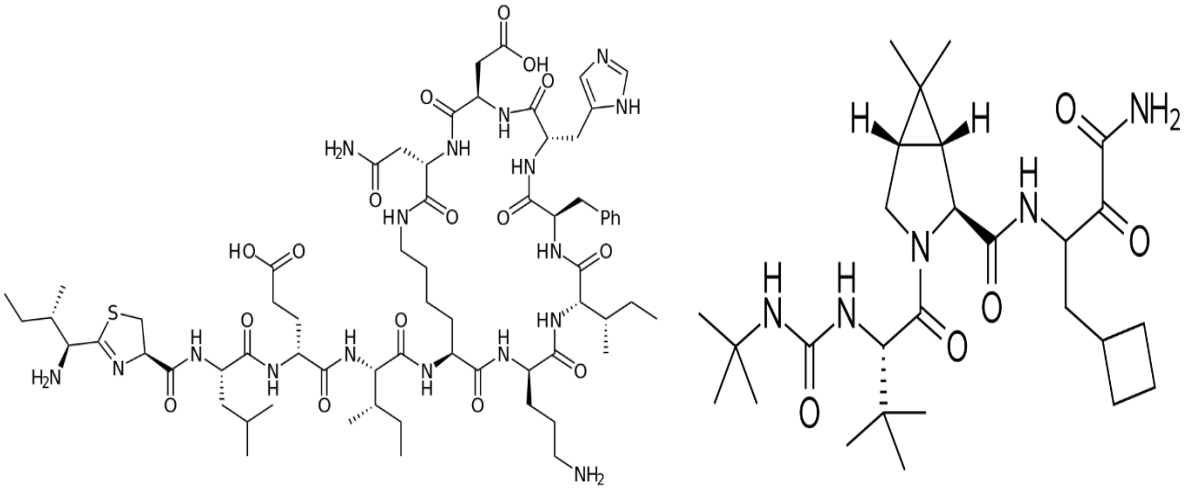
(Fig. 5). Structure of Actinomycin D and Moroidin

4.2. Antimicrobials

The evolutionary success of the innate immune system suggests that peptides could potentially be used as antimicrobial therapeutics because all higher organisms naturally produce a large number of antimicrobial peptides (e.g. defensins and cathelicidins [109]). Although there is little sequence conservation between them, many of these peptides are short, cationically charged, and able to form amphipathic structures in non-polar solvents. They are thought to act by disrupting negatively charged bacterial cell membranes to which they are electrostatically attracted, rather than mammalian cell membranes, which are usually neutral. Upon binding, the hydrophobic face of the amphipathic structure disrupts the lipid bilayer by unknown mechanisms.

Antimicrobial peptides have been produced from *de novo* designs [110] or based on naturally occurring products [111]. For example, in a Phase I clinical trial for oral mucositis, the synthetic protegrin analog IB-367 showed a rapid and broad-spectrum activity, lack of systemic toxicity, and a relative lack of resistance development [111]. Antimicrobial peptides have also been used for the induction of apoptosis in cancer cells. Linking of these peptides to sequences isolated from *in vivo* phage panning enabled targeting of the peptides to angiogenic vasculature in mice with breast [102] and prostate carcinomas [92]. These peptides are internalized by the proliferating endothelium, resulting in the disruption of the mitochondrial membrane (resembling that of bacteria) and, hence, cell death. The selectivity of antimicrobial peptides and the lack of resistance to them make these peptides highly attractive as potential therapeutics.

4.3. Some examples of peptide antimicrobials derivatives [112-114]



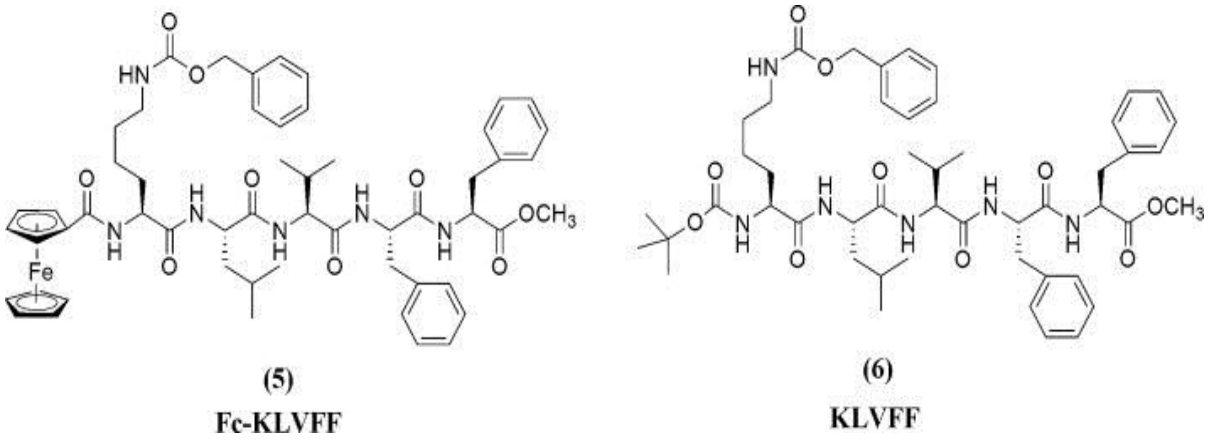
Bacitracin **Boceprevir**

***(*Fig. 6)**. Structure of Bacitracin and Boceprevir

4.4. Alzheimer's disease and prion-associated disease

Peptides sometimes occur naturally as by-products of a disease condition or even as the cause of disease. Several neural disorders are associated with distinct alterations in protein conformation. Alzheimer's disease and Creutzfeld-Jakob disease are associated with the proteins β-amyloid and prion protein, respectively, proteins that are mainly α-helical. A change in β-sheet conformation promotes the formation of fibrils that are correlated with disease progression. Interestingly, mice suffering from amyloid deposition and cerebral damage showed reduced deposition compared with controls when treated with a five-residue β-sheet-breaking peptide, iAβ5p [115]. This peptide was able to cross the blood–brain barrier (a difficult task for larger molecules) and disrupt amyloid fibrils through binding to the β-amyloid protein and inhibiting β-sheet formation [116, 117]. Encouragingly for this therapeutic approach (compared with the approach described earlier), the mice did not develop antibodies to the peptides during a two-month treatment, even though relatively high doses were used [115]. A similar approach has been taken with the prion protein [118, 119]. Treatment of protease-resistant forms of the protein with a 13-residue peptide, iPrP13, resulted in conversion of some of the protein back to a protease-sensitive conformation. Co-injection of this peptide and infectious prion protein into mice resulted in delayed onset of symptoms compared with prion injection alone [118]. Although these results are promising, further *in vivo* investigations are needed. There is evidence to suggest that soluble oligomers of β-amyloid are neurotoxic [120]; inhibition of fibrillogenesis might therefore be insufficient to guarantee therapeutic results. Furthermore, as the effects of these peptides are species-dependent [118, 119], promising results in mice cannot be directly extrapolated to humans.

4.4.1. Some examples of peptide Alzheimer derivatives [121, 122]



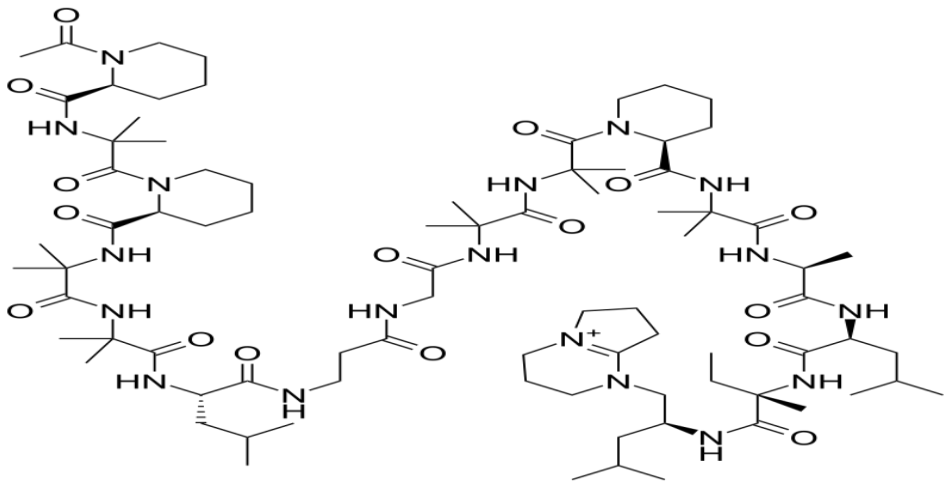
(Fig. 7). Structure of ferrocenoyl pentapeptide Fc-KLVFF and pentapeptide KLVFF

4.5. Malaria

Malaria is one of the most prevalent infections in tropical areas throughout the world. In humans, induction of immunity by vaccination with appropriate parasitic epitopes has not yet been particularly successful [91]. However, preventing transmission of the pathogen by mosquitoes can also control the incidence of malaria. *In vivo* panning of phage libraries was used to isolate a 12-residue peptide (termed SM1) that specifically bound to the salivary gland and midgut epithelia of *Anopheles gambiae* [123]. These sites are crossed by the parasite at different stages in its life cycle. Upon feeding, transgenic *Anopheles stephensi* mosquitoes expressing an SM1 tetramer in the midgut showed reduced maturation of *Plasmodium* (oocyst formation was inhibited 68.7–94.9% compared with control mosquitoes). Furthermore, transgenic mosquitoes were unable to transmit the parasite to naïve mice in two of three experiments, and transmission was more than halved in the third experiment [124].

lThese results show promise as one component of a multi-tiered strategy to control malaria. To achieve the greatest chance of success, preventative treatments need to be developed for other stages of the parasite life-cycle, for example, invasion of host erythrocytes [125, 126]. Significant hurdles that remain are reproduction of these results in humans, the difficulty of displacing native mosquito populations with transgenic versions, and the possibility of resistance development.

4.5.1 Some examples of peptide Malaria derivatives [127, 128]



(Fig. 8). Structures of Efrapeptin F is a type of Efrapeptin

5. Conclusion:

It is clear that, despite the remaining obstacles, peptides will comprise a large part of future therapeutics, owing to the ease with which combinatorial peptide libraries can be produced and screened, their (potentially) low immunogenicity, their potential for delivery by less-invasive methods than intravenous injection, and their chemical manipulability. Already, promising lead candidates are being discovered by modification of natural products, phage display and combinatorial chemistry, and several of these are in clinical trials. To optimize the efficacy of these new drugs, new strategies for administration are also being developed. In this case, the progress is slower, and the optimal delivery method for each peptide will probably be influenced by its physicochemical characteristics. Furthermore, it takes time to assess the long-term immunogenicity or other effects of administration of the peptide via various routes. However, with the extensive peptide discovery, characterization and clinical investigation that is underway, the future of new peptide therapeutics seems very promising.

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