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Recent Advances in the Synthesis of Peptide Surrogates and Their Biological Applications

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Abstract

More and more novel peptide therapies are finding their way to quick and effective clinical use. In reality, several peptide chains that are naturally produced have long been highly effective medicines. It is anticipated that several promising candidates can soon be added to the list of peptides being developed since extremely big libraries of peptides with high biological characteristics have emerged. These developments have lately brought up novel methods for administering medications made from polypeptide chains as well as enhancements to the purifying half-life in vivo. Peptide therapeutics are set to play a significant role in the treatment of illnesses ranging from cancer to Alzheimer's disease, notwithstanding any potential future obstacles.

Keywoeds: Amino Acid; Peptides; Biological Applications.

The design approaches for the synthetic strategy of peptide surrogates.

The modifications of peptide backbone to achieve excellent biological activity andovercome all the peptides drawbacks as drugs can be achieved with the use of isosteres to surrogate an atom of the amino acid residue, atom of peptide bond (s) or surrogating peptide bond with a moiety giving the same physical and biological properties of the whole molecule. In this article we will spot on the peptide surrogates produced from isosteres in amino acid residue and that of amid or peptide bond ones. First of all we must know what is meant by isosteres and bioisostrism?

The term "isosterism" is defined as investigating the similarities of different physical properties of atoms in molecules [1]. Subsequently, widespread application of isosteres for biological activity led to the term "bioisosterism" [2]. Bioisosteres are bioactive compounds or groups that possess very similar molecular shapes and volumes, and approximately the same distribution of electrons.

Bioisosteres: are molecules exhibit similar physical properties of bioactive molecules. [2] Practically, the concept of isosterism has been applied to the development of peptidomimetics in medicinal chemistry [3, 4].

1. Isosteric surrgates within amino acid backbone (Local Modification):

It deals with substitution of one atom or more of these constitute the amino acid residue in the peptide backbone by another isostreic atom. Such changes are restricted to amino acid backbone and will be exemplified as follow:

1-Isosteric changes in the amino group:

In which the amino group was subjected to one of the following to give different peptide surrogates:

Amine alkylation- amine substitution- nitrogen atom exchanges with other such oxygen, sulfur, carbon, phosphorus).

2- Ther modification or replacement of CH group of the amino acid backbone.

3- Expanding the amino acid backbone by one or more atoms.

4- Crbonyl function modification at the amino acid backbone (thioamide peptides).

The obtained peptide surrogates for such local substitution acquire the minimal alteration at such specific sites and nearly possess the same electronic distribution and similar physical properties [5-7].

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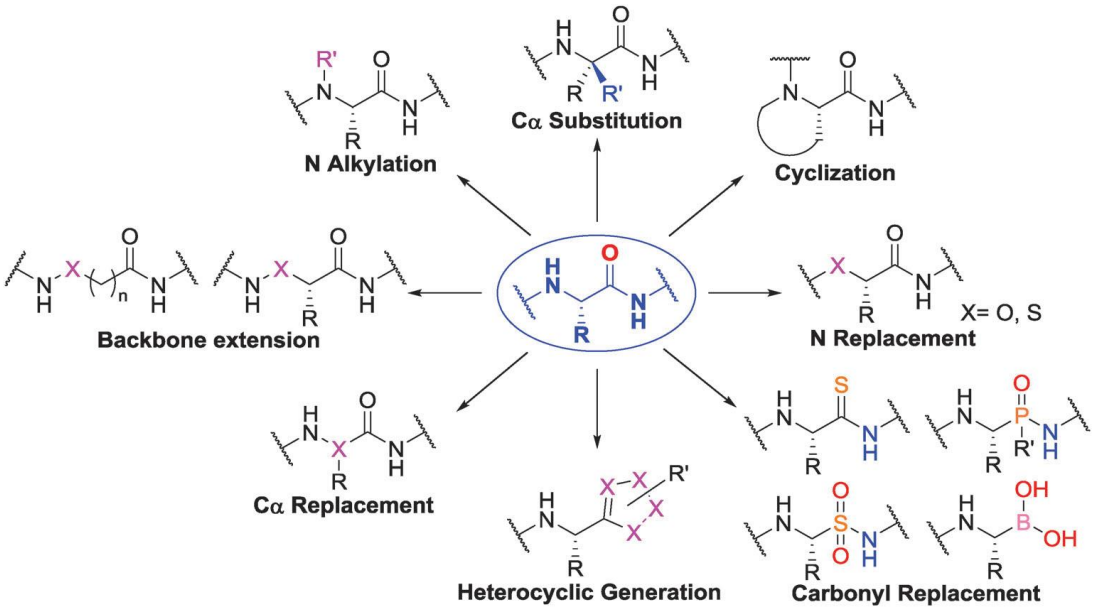
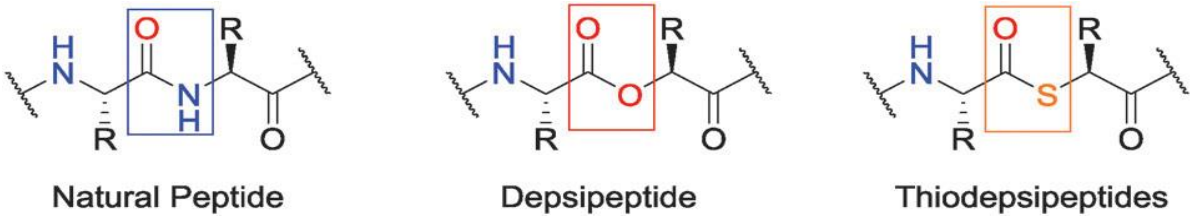


(Fig. 1) Peptidomimetic manipulations of native amino acids

1.1 Changing the amino functionality

A subset of Peptide surrogates obtained from substitution of the amino group of the amino acid residue in a peptide chain with an isosteric atom (oxygen, sulfur, phosphorus) forming subset of peptide surrogates such as depsipeptides (O), thiodepsipeptides (S) Fig. 2). Such alteration creates a significant change in the peptides secondary structure as well as their folding behavior of the molecule through modulating the hydrogen bonding pattern [8, 9].



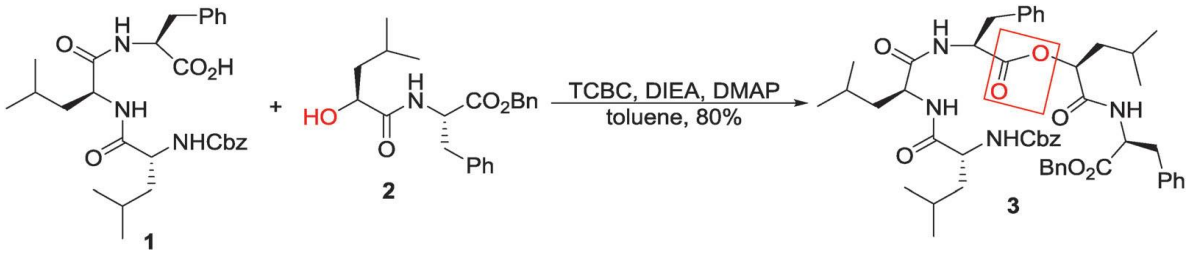
(Fig. 2)Isosteric atom replacement of the amino functionality

1.1.1. Depsipeptides:

They areobtained from exchanging one NH2 group or more in the peptidic molecule by atom of oxygen. So, the isosteric atom here is oxygen which creates the N-H bonding which is the driving force for secondary and folding structure s of peptide chains. The disappeared N-H group causes a hydrogen bonding ability in the molecule. This motivates structural distortion in β-sheet [10, 11] and helix structures. [12-14] Depsipeptides have more flexible structures than their amide analogs. Since, in ester group there is a decrease in resonance delocalization compared to that in amide and this lowers the rotational barriers for cis–trans isomerization [15, 16].

Many researches have been meansioned for the synthesis of depsipeptide family.

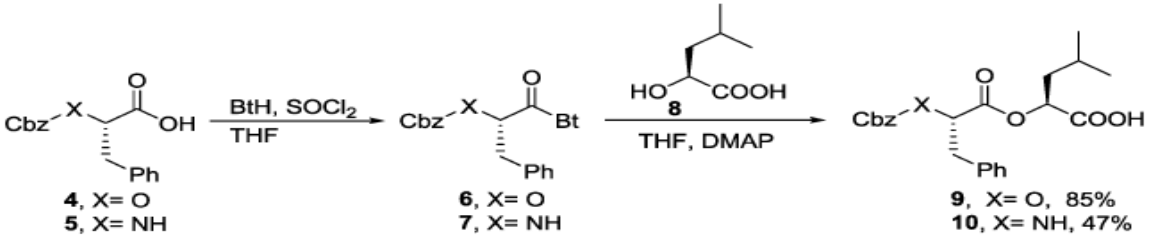
The introduction of oxygen leads to ester bond formation, which is the key step for the activation of a carboxylic acid group followed by coupling with α-hydroxy acids to produce depsipeptides. Variable coupling reagents, individually or combined, such as CDI [17], DIC / DMAP [18], DCC / DMAP [19, 20], EDCI / DMAP [21], PyBroP /DIEA [22] have been used to form unstable intermediates in situ. Moreover, asymmetric mixed anhydrides were produced using benzenesulfonyl chloride with pyridine or under Yamaguchi conditions (TCBC, DIEA, DMAP) [23] for coupling with a-hydroxy acids (Scheme 1) the two previous sysnthetic approaches gave yields near 50% yields [24].



[Scheme 1] the depsipeptide under Yamaguchi conditions.

Good results were obtained by employing acid chlorides to give (61%) yield.urethane N- carboxy anhydrides yields (80%) and by PyBroP coupling agent gives (82%). Kuisle et al. [18] optimize coupling reagents and times to produce (2–92%) yields with coupling times of 2–20 h. Optimum results (92%, 2 h) were obtained employing DIC in the presence of DMAP.

Recently, O-Protecting group (a hydroxyacyl) benzotriazo-les 6 and N-Pg(a-aminoacyl) benzotriazoles 7 were obtained as stable intermediates that were coupled with unprotected α-hydroxyl acids 8 and amino acids to synthsize depsipeptides 10 through O-acylation (47–76%), N-acylation (74–94%) and chiral oligoesters 9 (75–86%) (Scheme 2) [25, 26].



[Scheme 2]Benzotriazole-mediated preparations of 9 and depsipeptides 10 via O-acylation of unprotected a-hydroxyl acids 8.

Solid phase synthesis of depsipeptides has been used where, ester bond fragment already have coupled through N-acylation on solid support to assemble longer depsipeptides [17].

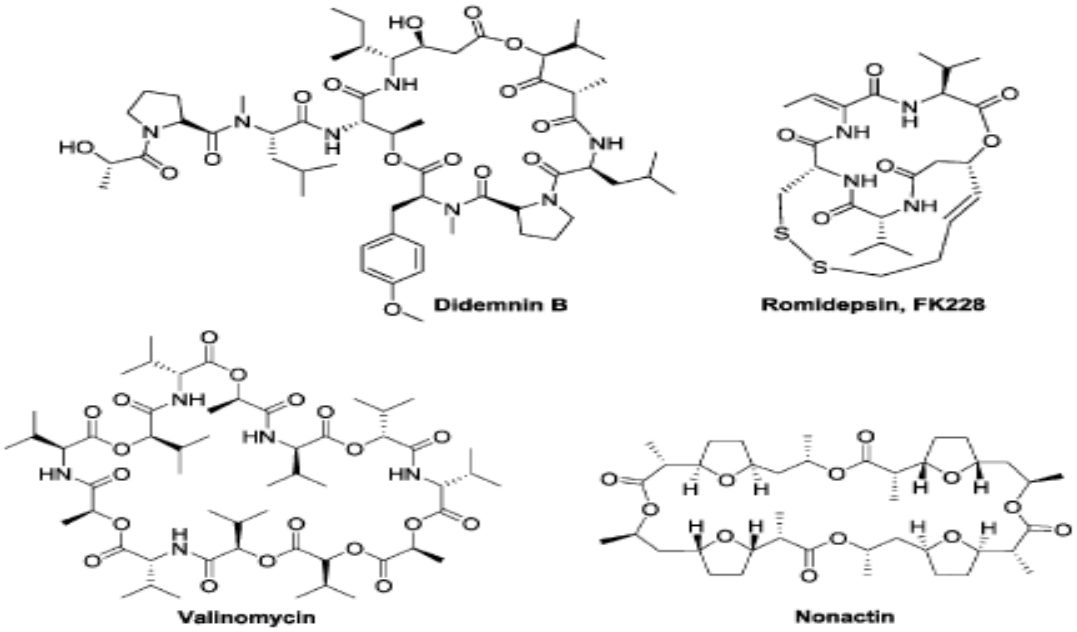
The first solid phase strategy for synthesizing a linear tetra-depsipeptide possessing three alpha hydroxy acids was carried out using mixed anhydride coupling method, where the ester bond was formed in pyridine through the activation by benzenesulfonyl chloride [27].

Recently, two protocols for solid phase depsipeptides synthesis have been used and demonstrated. On Wang resin, a method uses HATU and Py / BroP as coupling reagent foralpha hydroxy acids and t-Butyldimethylsilyl groups were employed for temporary hydroxyl protection, and t-butyl ammonium fluoride were used as de-protecting agent of alpha-hydroxy.[56]Kuisle et al. [18] devised another protocol, wherethe was esterification was done by DIC / DMAP coupling of alpha-hydroxy acids. Linear depsipeptides can be cyclized via esterification under Mitsunobu conditions [18, 28] and via amidation by HATU coupling or acid chlorides [18].

Micro-organisms such as bacteria, marine organisms and fungi are considered the source of natural depsipeptides, especially cyclic ones. They show a wide spectrum of biological activity including antifungal, antiinflammatory, antimicrobial, antitumor, and immune-suppressive activity.

A cyclic depsipeptide, romidepsin (FR228) (Fig. 3). It is bacterium Chromobacterium violaceum extract approved by FDA as anticancer drug with common name Istodaxt. It is used for treating the cutaneous T-cell lymphoma [29-31].

Also, didemnin B and extensively studied phase II of the drug dolastine-10 showed their anti-tumor efficacy [32-34].

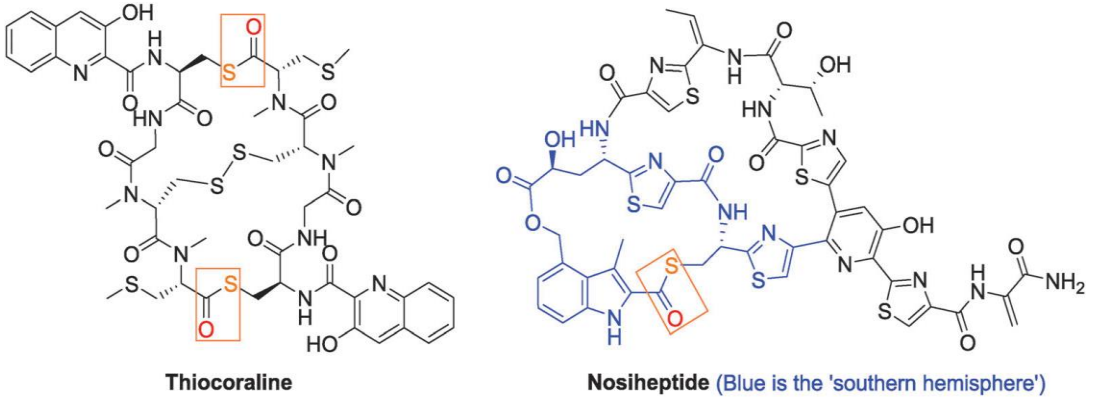


[Fig. 3] Didemnin B and romidepsin (FK228)

1.1.2. Thiodepsipeptides

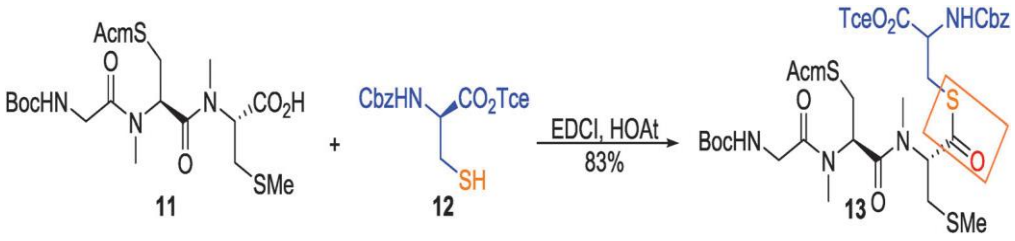
Thiodepsipeptides are class of peptides in which the peptide bond nitrogen atom was replaced by a sulphur. It can be obtained by thio- esterification of a thiol group from cysteine with the carboxy of amino acids, hydroxy acids or N-alkyl amino acids. Macrocyclic thiodepsipeptides, Thiocoraline (Fig.4), it was isolated from Micromonosporasp and Verrucosisporasp. Both had valuable applications in medicine as a potentmacro cyclic antitumor antibiotic [35].

Thiocoraline was synthesized and the two pendant 3-hydroxyquinoline had stereo chemically studied [36].



[Fig -4] Thiocoraline and nosiheptide

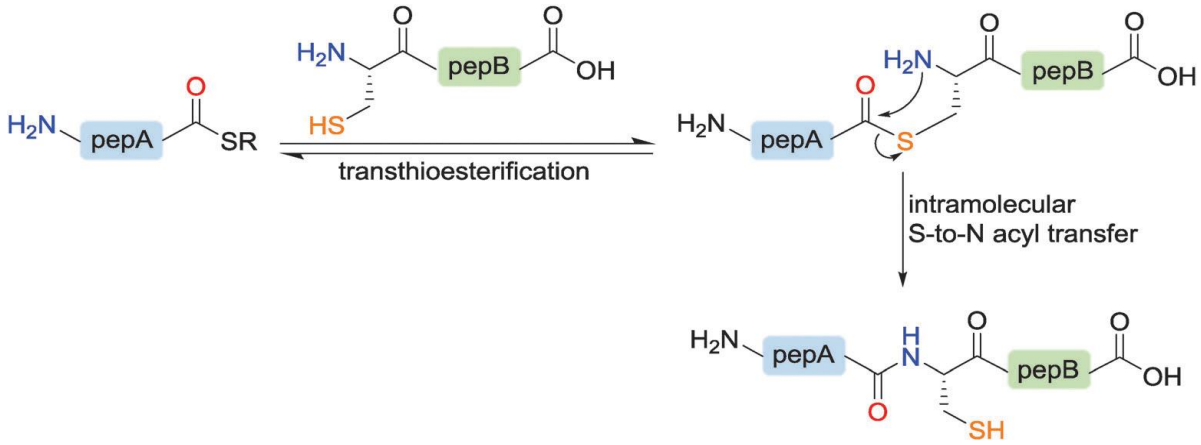
The thiol esterification formation of tripeptide 11 and protected D-cys derivative 12 was carried out under near racemization-free conditions, using EDCI - HOAt to afford the thio-derivative 13 (83%, de 95 : 5) as in (Scheme 3) [36].



[Scheme 3-]Thiol esterification between tripeptide 11 and the D-cysteine derivative 12.

BE-22179, Thiocoraline analog, possesses high availability for binding to DNA and represent markedly toxic activity towards the L1210 cell line inpico molar concentration [36].

Native chemical ligation (NCL), is an efficient method for constructing peptides and proteins much longer. NCL connects an activated thioester peptide C-terminal with an N-terminal component containing the cysteine residue forming a single amide bond (Fig. 5) [37, 38]. Transthioesterification reaction of N-terminal cysteine free thiol of (peptide B) and an active thioester (peptide A) produce an S-acyl peptidic intermediate. The intermediate undergoes S-to-N acylation transfer and finally native new amide bond formation.



[Fig.5] Native chemical ligation.

Backbone Thioester Exchange (BTE) is conceptual methodology concerns with S- and O-acyl ligation in isopeptides to investigate the conformational-structural stability of peptides as well as their preferences [38-40].

1.2. Replacement of α-CH of amino acid residue

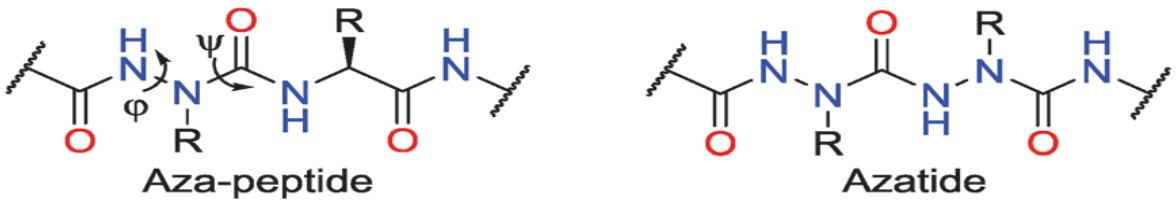
The modifications of the alpha-carbon in peptide bonds produce new peptide surrogates and pseudo peptides. The modifications comprise, surrogating the alpha-hydrogen (by the aryl, alkyl or other group), invert the configuration at alpha-carbon. The isoelectronic substitution of the alpha-carbon by heteroatom (such as nitrogen) gives azapeptides. Such mimicking at the alpha-carbon chain produce new molecules have peptidic character with new secondary structures possess new pharmacological activity.

1.2.1. Azapeptides

Substituting the alpha-carbon of any amino acid in peptide chain by nitrogen atom produces novel category named ‘‘azapeptides’’as in (fig.6).

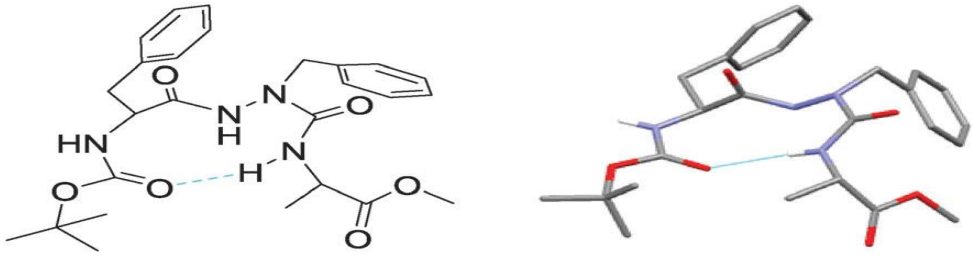
Azapeptides are considered as semi-carbazide derivatives of natural peptides in which the alpha carbon has been surrogated by amino group, giving the –NHNHC(=O)NH– moiety. So, aza-peptides are synthesized by the condensation of hydrazines or hydrazides derivativesand carbonyl-giving an intermediate followed by direct linking with isocyanates or linking with amino acid [41].

In azapeptides the flixibly Cα –C(O) bond was converted to a rigid Nα –C(O) urea bond leading to remarkable alterations in the chemical and biological characteristics [41].



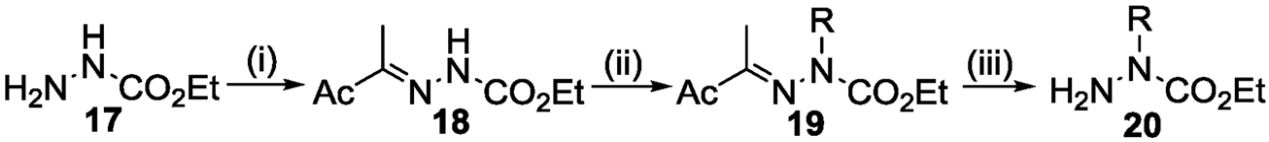
[Fig.6] Aza-peptide and azatide.

This substitution excludes chirality of the alpha-site and reduces the carbonyl carbon electrophilicity. Since, by changing the group orientation at the alpha-site from tetrahedral conformation to trigonal one, with the dihedral angles value (φ= 90o± 30 o or – 90 o± 30 o, and ψ = 0 o – 30 o or 180 o±30 o) leading to new conformations of β-turn type [42] β-Turn conformations in azapeptide, have been studied by spectroscopy [43], X-ray crystallography [44] and by computational models (Fig. 7) 42].



(Fig.7) H-bonding pattern and b-turn of the X-ray crystal structure of Boc-Phe-azaPhe-Ala-OMe.

Early, azapeptides were synthesized from ethyl carbazate through three stepsas illustrated by [Scheme 4)] [45].

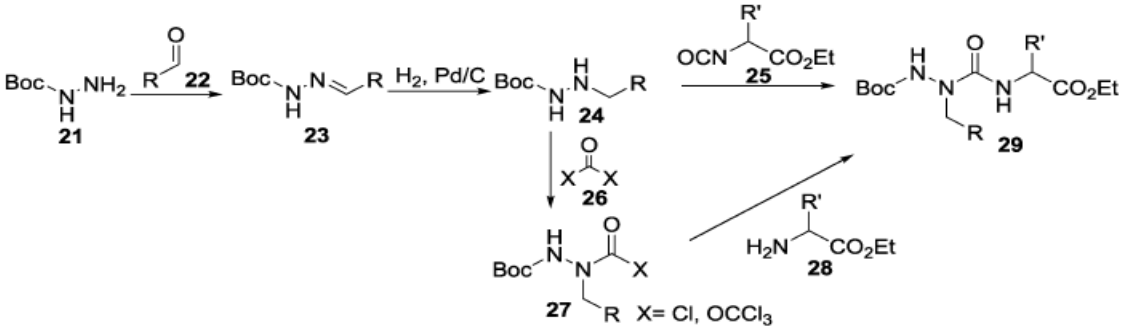


[Scheme 4] Synthesis of N[a]-substituted ethyl carbazates 20.

The aza-amino acid synthesis considered basis for azapeptide synthesis in both solid and liquid phases [46].

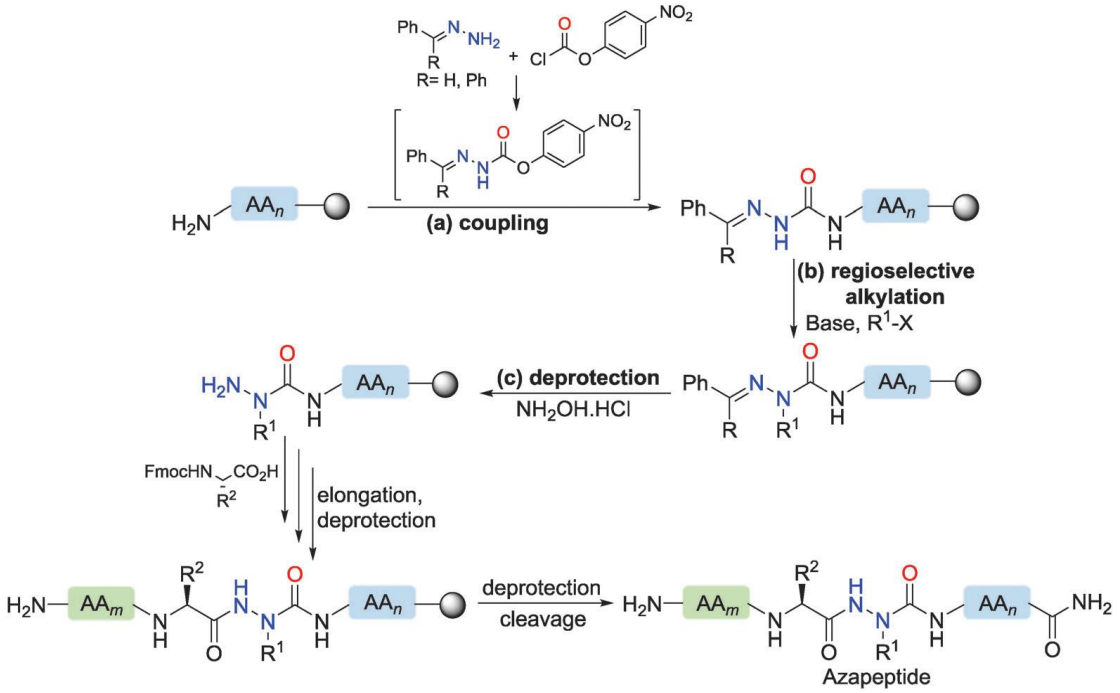
The reaction of Boc-hydrazide 21 with the targeted adehyde 22 givethe corrosponding hydrazones 23, which was subjected to hydrogenation over palidium –charcoal catalyst to produce thecompound24 (N-Boc -N'-alkylhydrazines). Two pathways for synthesizing azapeptides family:

(a). The first is condensation of isocyanates and compound 24. The second is by condensation ofcompound 24directly and carbonyl compounds 26 to give the intermediates 27 followed by attaching with amino acid esters 28 (or aminated polymeric support derivatives) to give aza-peptides 29as in (Scheme 5) [46. The protection of hydrazine with groups such as Boc, Fmoc, Cbz and Ddz wre used in solid as well as liquid phase synthetic strategies of azapeptides. [47, 48].



[Scheme 5]Azapeptide synthesis.

Recently, the peptide-bound aza-Gly residues were alkylated regioselectivelyand employed for the Nα-substituted azapeptides on a solid support [47, 48], it comprises three step as in: [(Fig. 8].



(Fig. 8) Preparation of Nα-substituted azapeptides via regioselective alkylation of peptide-bound aza-Gly[81a]

Biological applicationof azapeptides

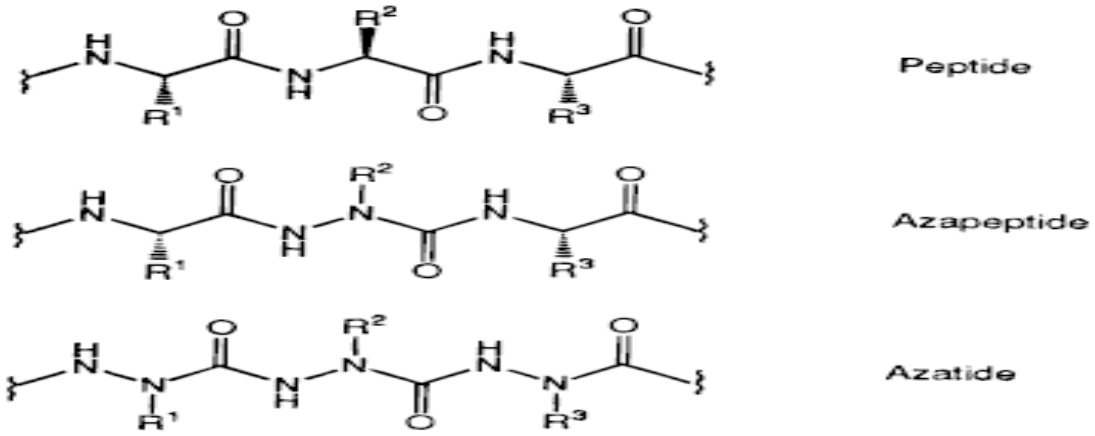
Since azapeptides are more enzymatically stable, they are promising targets in drug design as Inhibitors. Serine and cysteine protease [49], hepatitis C virus NS3 serine protease, hepatitis A virus (HAV) 3C protease, human neutrophil protease 3, and HIVprotease are all azapeptide inhibitors [50] Also, Atazanavir (Reyatazt) which is approved by FDA as antiretroviral drug which used as HIV highly active, is azapeptide protease inhibitor [51].

The ‘‘aza-amino acid scan’’ approach, in which an amino acid residues in native peptides was systematicallysubstituted by their aza counter parts and also, structure-activity relationships (SARs) of aza-peptides are very commonly studied nowadays for obtaining novel drug candidates that possess improved pharmacokinetic and pharmacological properties. It has been observed during recent references that synthetic peptides has a distinct biological activity in all different applied directions

[52-92]. Biologically active peptides including hormone analogues, and enzyme inhibitors, azapeptides act as [93] potent agonist of melanocortin receptors [94] growth hormone releasing peptide-6 (GHRP-6) [47] and cyclic integrin receptor antagonists have been synthesized in order to investigate their secondary structure and biological activity.

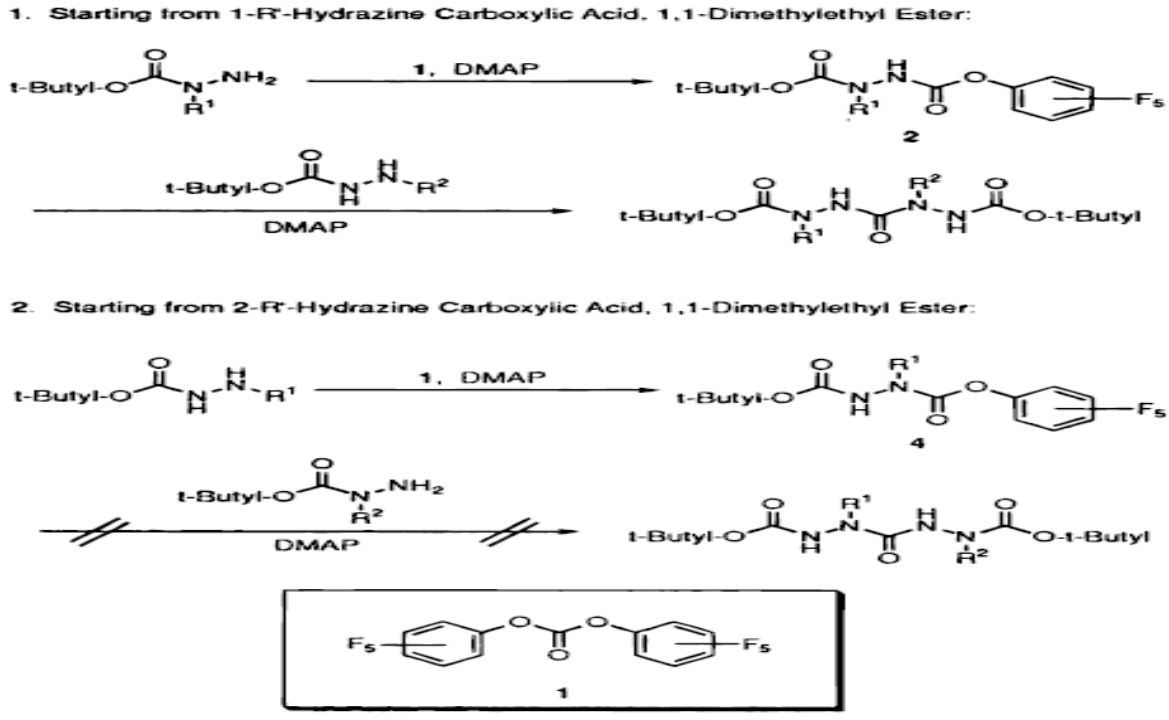
1.2.2 Azatides

Azatides are peptide surrogates biopolymers ‘‘pure azapeptides, in whichalpha aza- amino acids residues were coupled repetitively [95].



[Fig. 9]

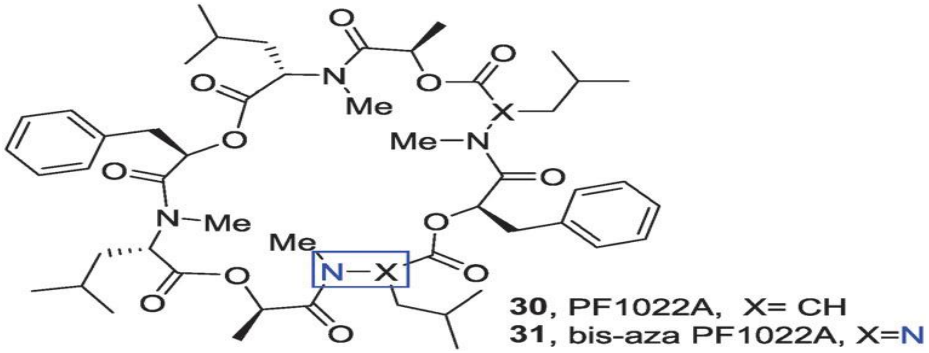
A wide variation of α-aza Boc-amino acids were synthesized as unit monomers and condensed step wisely giving the azatides molecules (leu-enkephalin surrogates) as linear chains. This can be done either by solution or liquid-phase strategies [95]. Bis (pentafluorophenyl) carbonate was employed for activation of carbonyl reagent as in (fig. 10).



[Fig. 10]. Routes for Solution Phase Diazatide Synthesis

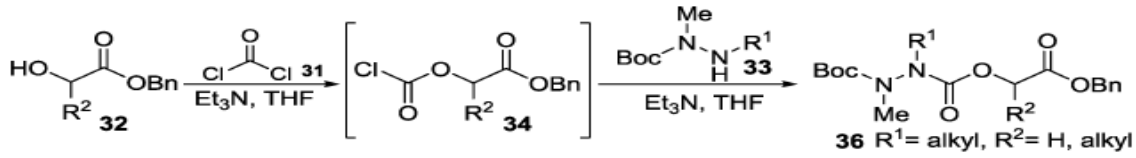
1.2.3 Azadepsipeptides

Azadepsipeptides are kind of peptide surrogates obtained by hybridization of azapeptides molecules and depsipeptides. The azadepsipeptides represent characteristic features of parental pseudo peptides, they acquire chirality lack of Azapeptides and the decrease or destroying the hydrogen-bonding character of NH in depsipeptides.

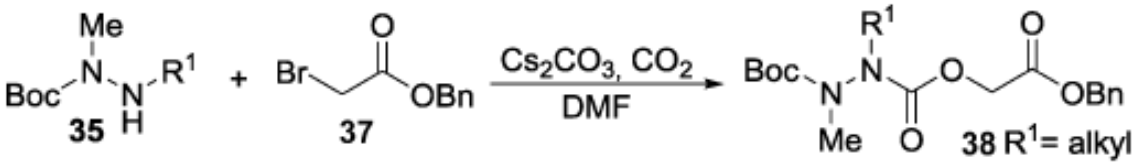


(Fig.11)PF1022A 30 and bis-aza PF1022A 31.

Azadepsipeptide starting compound36, were used in the synthesis of a bis-aza derivatives of the anti-parasitic cyclo-octa-depsipeptide PF1022A 31(Fig.12) [96]. PF1022A 30 and bis-aza PF1022A 31 were obtained through two step reactions. The first step was coupling of N-protected hydrazine compound35 with compound 34, which prepared from alpha -hydroxy carboxylic esters 32 as in [Scheme 6]. The carbazate derivatives 38 in next step, were synthesizes from CO_2 gas and alpha -bromo acetate 37 with hydrazines 35 [Scheme 6].



[Scheme 6] Preparation of azadepsipeptides through activated formats



[Fig. 12] Preparation of azadepsipeptides by forming carbamic acids generated in situ.

The X-ray and NMR analysis of compound 31 bis-aza PF1022A revealed that no great differences from natural one PF1022A 30, (Fig. 13) [96].

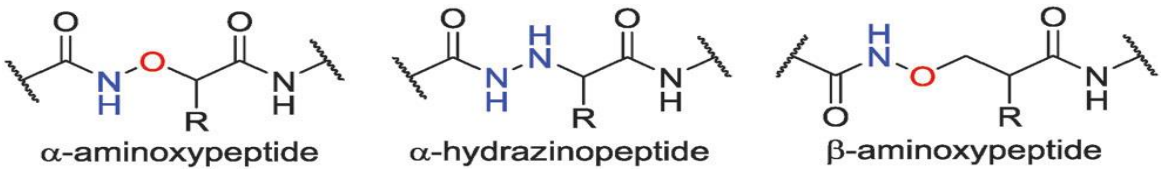
3-(iii) Backbone extension of the peptide bond (by one or more atoms).

Backbone extended peptides means adding extra carbon atom or other kind than carbon atoms flanked between COOH and the NH of an amino acid residue. Novel oligomers of peptidic nature had been synthesized producing a large number of configurationally as well as constitutional enantiomers [97, 98].

The sheets, helices and turns conformers are ‘‘protein-like’’ secondary structures that can be obtained the extension of the peptide chains original

built from β or γ-amino acids and their cyclic derivatives [97-99]. Since the lone pair electrons on an atom next to nitrogen atom secure an alpha effect. The alpha effec stimulate the negative charge nitrogen atom and alters the torsional properties of bonds as well as H-bonding and give consequently, the folding properties and bioactivity [98-100].

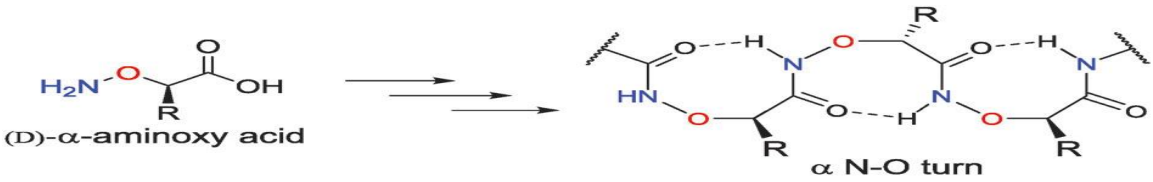
This change in the extended peptide backbone causes excellent stability toward proteolytic enzymes and enlarged pharmacokinetic properties growing the interest towards their therapeutic potential. [97, 98]. Peptide surrogate scaffolds, namely aminoxy and hydrazino acids were produced from exchanging a carbon atom in amino acids extended - backbone with another atom (Fig. 13).



[Fig. 13] Heteroatom backbone extended peptidomimetics.

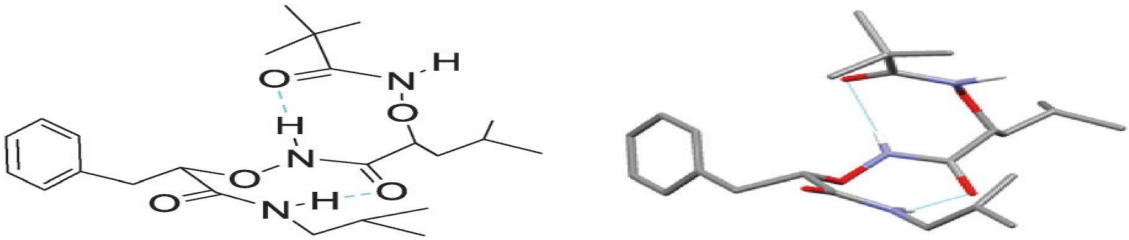
1.2.4α-Aminoxypeptides

Alpha -Aminoxy acids belongs the beta-amino acid class where the beta-carbon was substituted by anoxygen. Peptides of alpha-aminoxy acids produce novel foldamers [99, 100], with unusual conformations and interesting bioactivity [93-96].



[Fig. 14] D-a-Aminoxy acid and an a-aminoxy oligomer with an a N–O turn

They have a great tendency for producing more rigid peptides than their natural ones, (Fig. 15) [100-104].



(Fig. 15)Reverse turn of a heterochiral a-aminoxy peptide in the X-ray crystal structure.

The alpha effect of neighboring oxygen establishes astrong hydrogen bonds in the aminoxy peptide chain, and potentiate the negative charge on nitrogen. Many approaches for the synthesizing the peptides and hybrid analogs of α-aminoxy acids form their components are as follow:

(i) References herein discuss the application of some peptide coupling combinations [104-111].

(ii) N-hydroxysuccinimide active ester of [110] and

(iii) N-protected (alpha-aminoxyacyl) benzotriazoles [111].

The over acylation of aminoxy NH group during coupling reaction increases due to the increase of the negative charge on nitrogen atom [109].

A new method under Mitsunobu conditions was used for the synthesis of chiral N-(Phth)- α-aminoxyacids [100, 104, 106] t-Butyl esters of D-N-(Phth)- α-aminoxyacids were prepared in 36–56% overall yield and in 95–99% ee starting from L-amino acids [100].

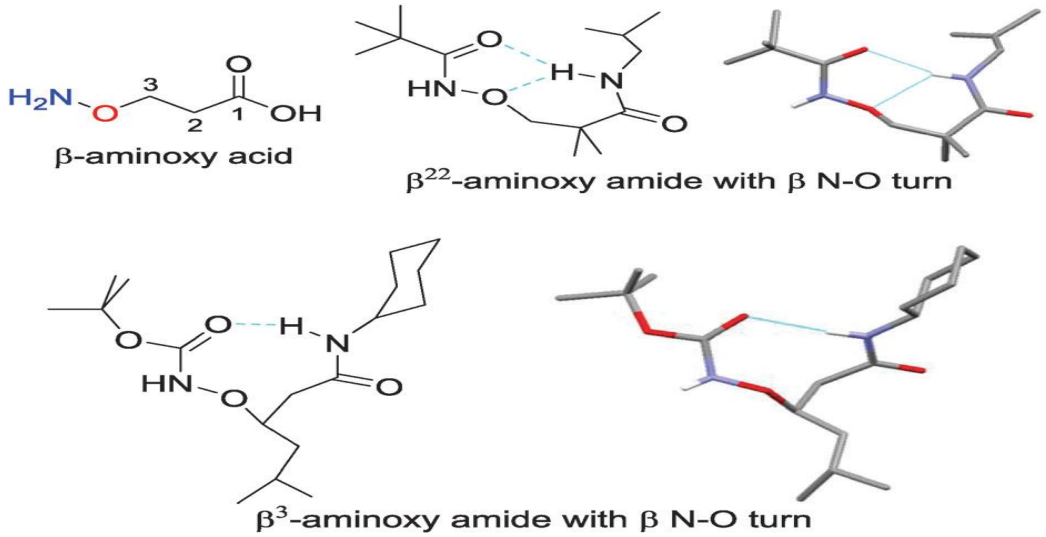
The first solid phase synthesis of α-aminoxy

oligomers was done by Shin et al. in a stepwise coupling of D-N-phthaloyl protected α-aminoxy acids [106]. The synthesized Oligomers of aminoxy acids were assembled on a PS-PEG solid support by sequential coupling using (BOP/HOBt/NEM for 6 h in DMF) and deprotection (5% hydrazine in MeOH for 15 min) steps until the target surrogate obtained and, finally were cleaved TFA–TES (98 : 2) mixture for 1.5 h. [106].

Alpha-aminoxy acids peptides had better metabolic, gastro intestinal and hepatic stabilities than natural analoges [103, 106]. Guanidinium ion -rich peptides of both D and L alpha-aminoxy acids were tested as (CPP) which increases their cytosolic distribution and diffusion within living cells [102]. They represented high resistance as well as low toxicity toward serum [102].

1.2.5β- and γ-aminoxypeptides

Backbone extension of alpha-aminoxy acid with one extra carbon atom more, gives the beta- and gama-aminoxy-peptides so, both were considered as analogs of the parent alpha-aminoxy acid. The beta isomers are more flexible due to their backbone extension and substitution (Fig. 16).

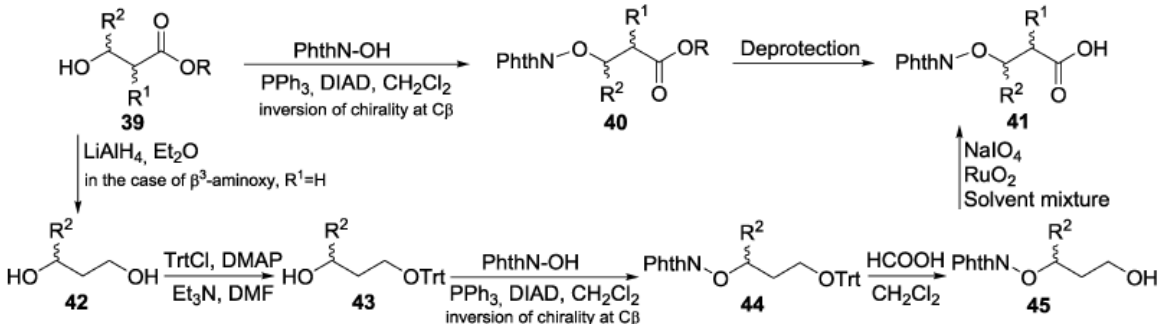


[Fig.16] β-aminoxy acid and β-N–O turn of a β-aminoxy acid amide in the X-ray crystal structure [101].

β-aminoxy acids peptides are typified according to the substitution at alpha-carbon and beta-carbon atoms in the aminooxy acids to β2, β3, β2,2, β3,3 and β2,3. Such peptides acquire N-O turn as wellas helical secondary structure forming nine member ring structure (Fig.17).

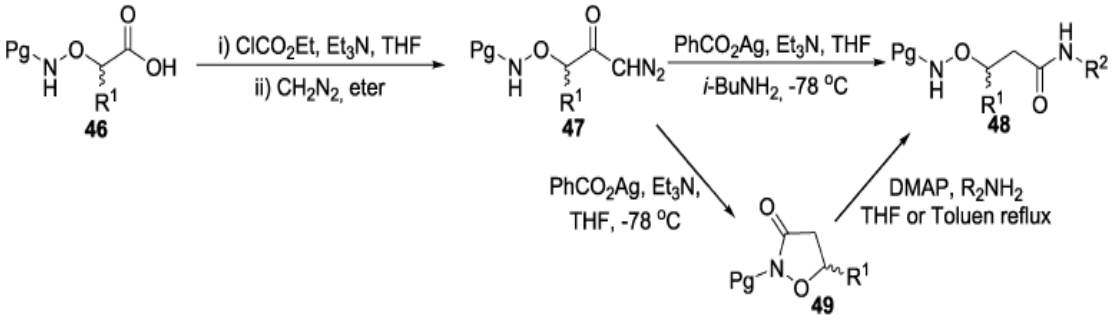
The synthesis of beta- aminoxy acids 41 based on the introduction of N-O bond in beta-hydroxy carboxylic acid esters 39 using Mitsunobu conditions as in (Scheme 7) [102].

In a similar way scheme 7 showed the synthesis of areγ-Aminoxy acids



[Scheme. 7] Synthesis of β-aminoxy acids 41 via Mitsunobu reactions of a-aminoxy acids

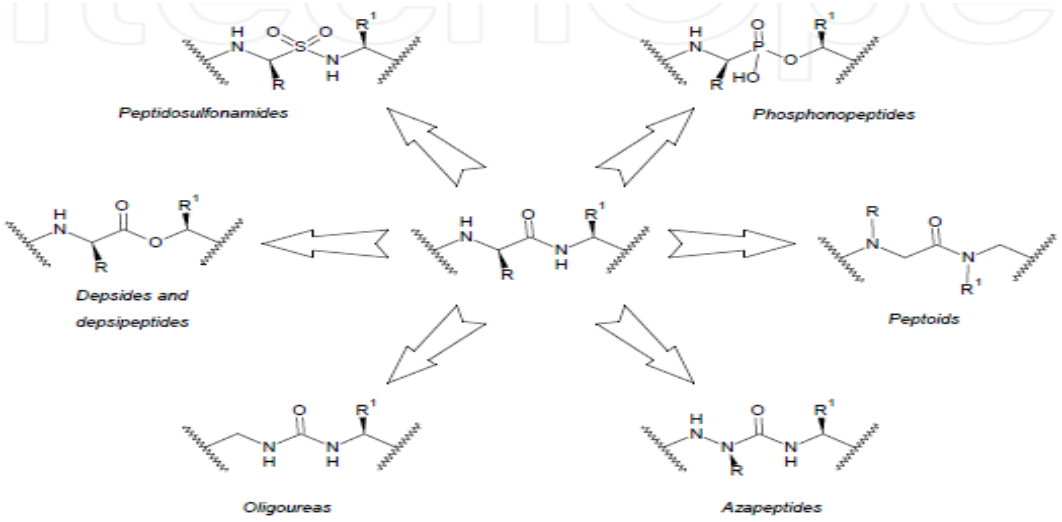
In a similar way scheme 8 showed the synthesis of are γ-Aminoxy acids



[Scheme 8]

2. Peptide bond isosteres.

The peptide chemists investigate work hardly to use the synthetic strategies for synthesizing peptides or their surrogates to improve their stability against in vivoproteolysis. However, these improvements can modulate both chemical and physical properties of the amide bond, especially their conformational pattern and accordingly their binding activity with the target protein. [(Fig18) [113, 114].



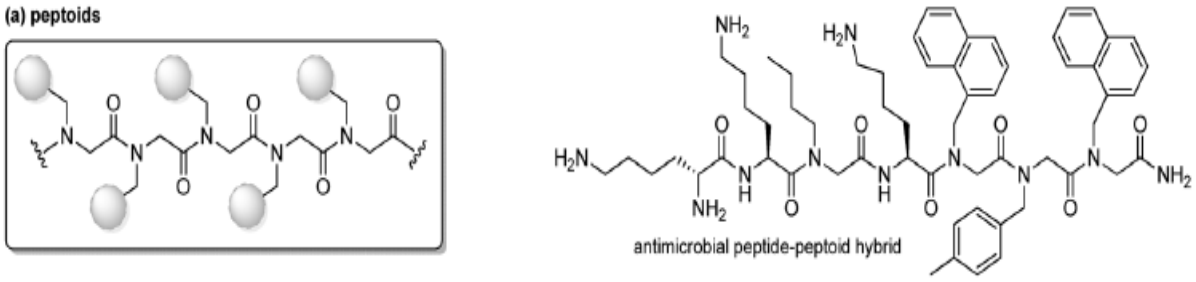
(Fig. 18)Examples of peptide bond isosteres.

Backbone modification approaches invent an amide bond surrogate with targeted three dimensional structures and with significant differences in polarity, acid-base character and hydrogen bonding capability. Also, the stereo chemical and structural integrities of the adjacent pair of α -carbon atoms in these pseudo peptides are unchanged. So, the choice of an amide bond modification is a compromise between positive effects on bioavailability and pharmacokinetics and potential negative effects on specificity and activity [115]. The ability of the modifications to mimic the electronic, steric and solvation properties of the amide bond is actually the most important characteristic in defining the potency of pseudo peptide analogs. Synthetically the methods for assembly of peptide analogs of phosphono, sulfonamides, oligoureas, azapeptides depsides, depsipeptides, and that ofpeptoids are parallel for standard SPPS, employing different reagents and different coupling and protecting strategies need to be employed.

The backbone of a peptide can be modified in various ways by isosteric or isoeletronic substitution [115] (Figure 19), summarizes the most important ways to modify the peptide backbone.

2.1. Peptoids.

Peptoids defined as alpha peptide surrogates, where the amino acid side chains are coupled to nitrogen atom of the amide not to the alpha-carbon atom. This results in changing the side chain positioning and characters leading to a great stability proteolysis and cell pentration (Fig. 19). It was also known as poly N-substituted glycine polymer in which the side chains of the amino acids residues were employed in the N-substitution.



(Fig. 19)

The first reported peptoids was in 1992 [116], where N-substituted glycines, N (methyl imidazole) Gly as Homo-His or including N-(1-phenylethyl) Gly as β-Methyl –Phe are the monomers of surrogate. Actually, the peptoide molecules can furnish distorted Cis and Trans amide isomers, and also solid turns.

The biological importance of Peptoids is their applications as antimicrobial peptides (AMPs). Such amphiphilic small peptides surrogates has a cationic region which is critical forpentrating the bacterial cytoplasm membrane, and specific for mammalian cell membrane [117, 118].

Recently, novel hybrid of peptide–peptoid used for fighting bacterial pathogens through engaging in canine skin infections (Fig.20). This case comprises Pseudomonas aeruginosa and Staphylococcus pseud intermedius, which are resistant to other antimicrobial compounds [119].

2.2. Amino acid residues Side chain isosteres.

The importance of side chain isosteres based on using either D-, β- and γ-amino acids or unnetural amino acids with accessory that added to increase the binding ability of the interacting groups with the active sites on the targeted surface.

The classes of side chain isosteres are:

1- The substituted aromatic side chains by larger aromatic groups or heterocycles, this magnifies hydrophobicity and the size for van der Waals as well as π-adhering interactions (Fig.20) [120].

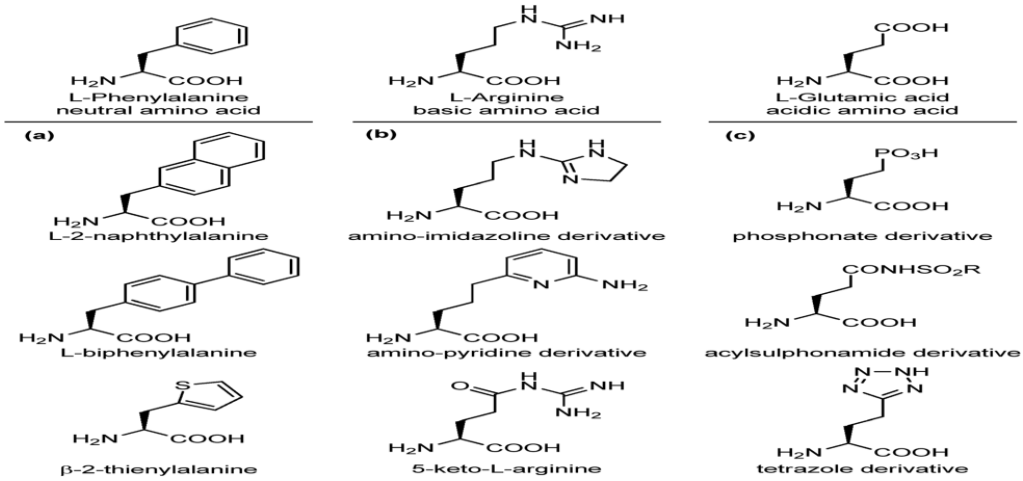
2- Also, many peptide surrogate of acidic and basic character of side chains, which was modified to decrease or increase their acidity, their basicity ratio and optimize the ionic interactions. Some examples are listed below:

a- The guanidino of arginine which highly basic group exists in many natural and synthesized trypsine-like serine proteases inhibitors of and the integrin receptors, and it is often responsible of poor oral availability and low selectivity. So, many isosteres of guanidine have been employed to modulate the basicity of that group through the use of amino-pyridine or imidazoline heterocycles, as well as replacing of the anext by CH_2 group with a carbonylmoiety (Fig.20).

b- Many isosteres of the acidic carboxyl of aspartic and that of glutamic have been suggested to modify both the acidity and the charcters of lipophilicity. The case of angiotensin II and integrin receptor agonists [92]. The replacement of carboxy group with hydroxamic acid (useful to chelate metals), phosphonate (more acidic), acylsulphonamides (less acidic), or the tetrazole ring, which presents similar electrostatic potential of that molecules and planar structure and hydrogen-bonding pattern (Fig. 20).

3- 3- Tethering strategies, of the local surrogates near side chains bonds, adjust the flexibility of bonds that can rotate and optimize the conformational profile of the overall peptide and assembling the dihedral torsion angles of the amino acids residue in the peptide surrogates (ψ, ϕ, χ, Fig. 20). Many synthetic methods are included in this strategies for example:

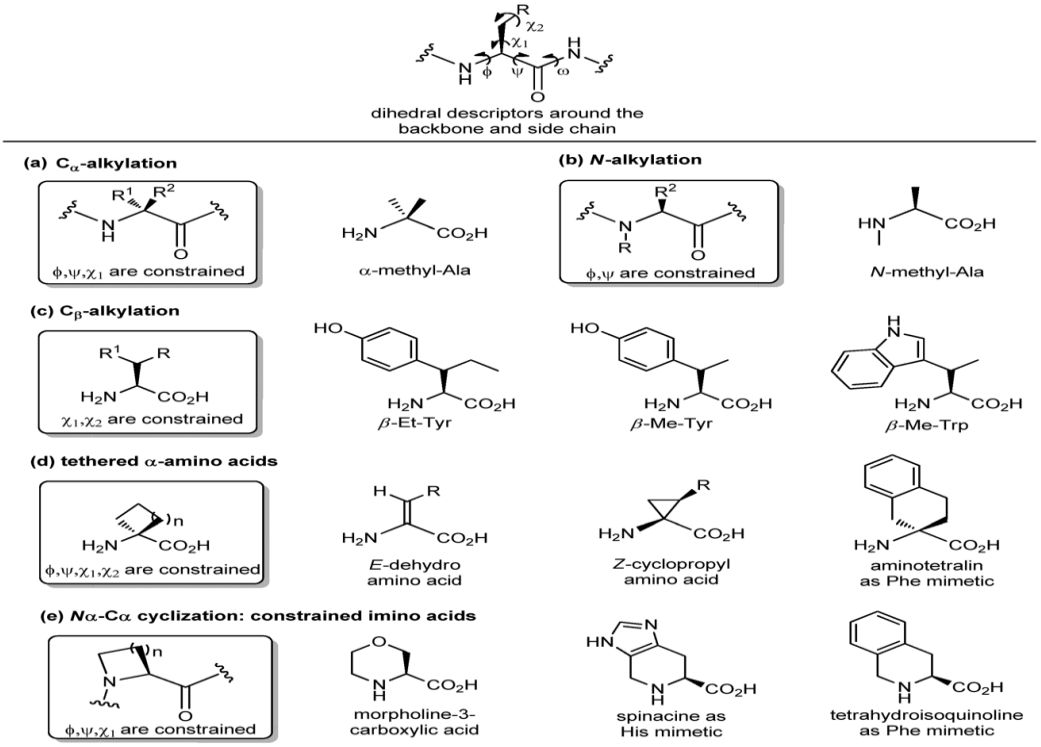
a- The alkylation of the alpha carbon atoms produce quaternary carbon atoms see (Fig. 20) .the alpha-Substituted residue have a decreased rotation around N–Cα bond as well as Cα–CO bonds, which reduces the free rotational around backbone bonds of to nearly about 90%. The famous example for the α-alkylated amino acid, is α-Me-alanine.



[Fig.20] Side chain isosteres of (a) neutral, (b) basic or (c) acidic amino acids.

b- The constraining of backbone dihedral angles in peptides, largely reduce the conformational freedom and decrease the side chain free rotation. The both are necessary for thebiological activity and interactions of peptide surrogates [121, 122].

Both restriction around the dihedral angles bonds(around Cα–Cβbond as well as around the Cβ–Cγbond), could be attained by employing the cyclopropyl-amino acids residue or the so- called dehydro-amino acids (α, β-unsaturated α-amino acids)where the double bond choose the suitable E or Z isomer to block the definite position. Also, the cyclization of Nα –Cα - amino acids leads toboth ϕ and Xdihedral angles constraining (Fig. 21).



[Fig. 21] Panel of different synthetic approaches for constraining the backbone and side chain dihedral angles: (a) Ca-alkylation, (b) N-alkylation, (c) Cβ-alkylation, (d) formation of tethered a-amino acids and (e) Na–Ca cyclization.

2.3. Sulfonamide and Cyclic sulfonamide peptide surrogates

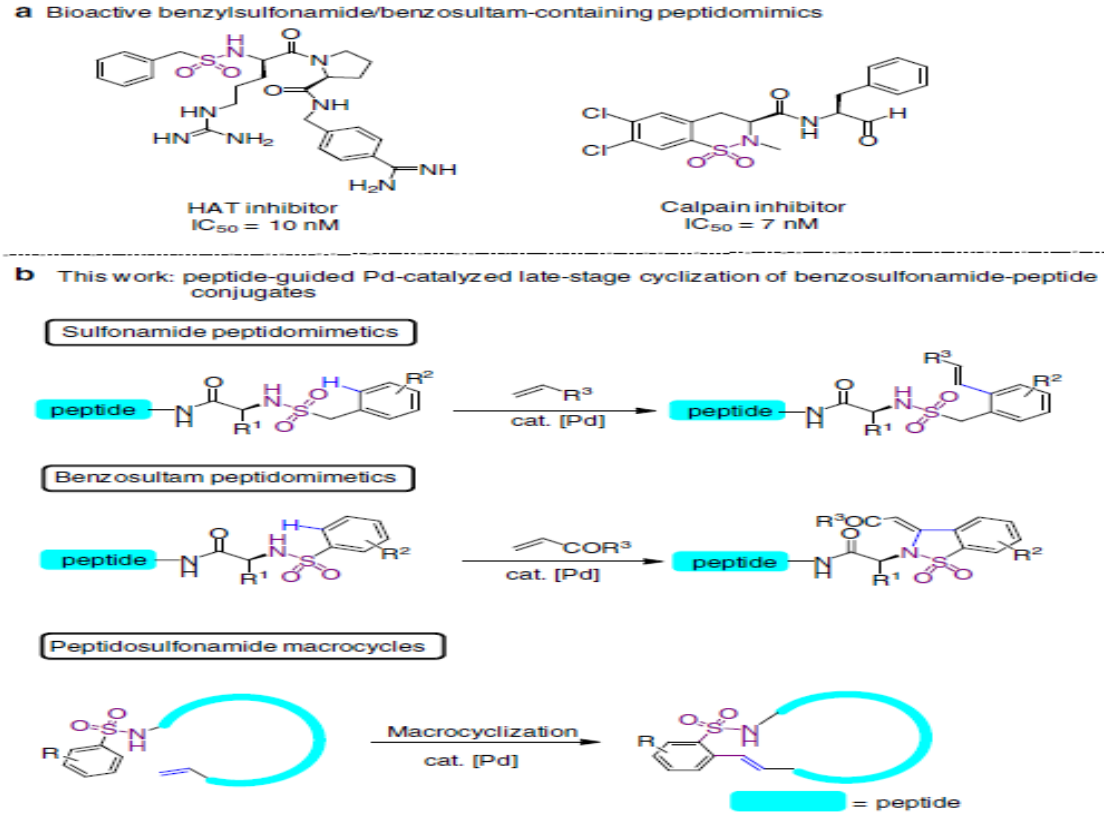
In medicinal chemistry, arylsulfonamides and sultams (cyclic sulfonamide) are important pharmacophores [123], and introduction of sulfonamide functionality into peptides usually provides improved proteolytic stability, hydrogen-bonding possibilities and improved biological activities [124]. Peptide surrogates containing benzofused sulfonamides or sultams are among the most potent inhibitors of disease-related proteases, and benzosultam derivatives often exhibit improved pharmaceutical properties (Fig. 22) [125]. Despite their promising bioactivities, the development of this class of compounds is hindered by the lack of facile synthetic methodologies, especially for the construction of benzosultam motifs. As an example, the 6, 7-dichlorobenzothiazine unit of a calpain inhibitor (Fig. 22) requires six steps of synthesis before conjugation to 2-amino-3-phenyl-propanal [126]. Asdirect construction of benzosultams by intermolecular cyclization is uncommon [127], synthesis of benzosultams often relies on intramolecular cyclization of elaborated precursors, whose preparation is often challenging [128-131]. Despite recent advances, facile and efficient methods for the diversification and cyclization of peptide - sulfonamides are still in demand ass seen from (fig. 22):

Finally, the simultaneous modification of two contiguous amino acids with the use of dipeptide isosteres, including D-amino acids, to give D-peptides is another well-established approach for the development of peptide surrogates with improved peptide stability and enhanced biological activity.

3. D-peptidesurrogates

A D-peptide peptidomimetics are defined as a small sequence of D-amino acids that designed to mimic natural L-peptides which commonly posesses therapeutic properties. D-peptides rarely occur naturally in organisms and are not easily degraded in the stomach

or inside cells by proteolysis or digested by the normal enzymes or metabolized normally, since the ribosomes are specific to deal with L-amino acids only. So, D-peptide drugs can be administrated orally, have long lived time period and. In some cases, have a low immunogenic response [123 -129].

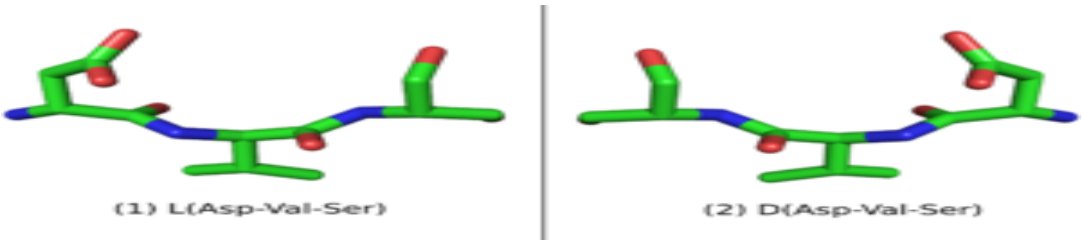


[Fig. 22]Synthesis of peptide surrogate containing aryl sulfonamide motif.

(a) Bioactive benzylsulfonamide and benzosultam-containing peptide surrogate.

(b) Peptide-guided functionalization and macrocyclization of sulfonamide-containing peptide surrogate by Pd(II)-catalyzed late-stage C–H activation. HAT human airway trypsin-like protease.

3.1. Properties of D-peptides



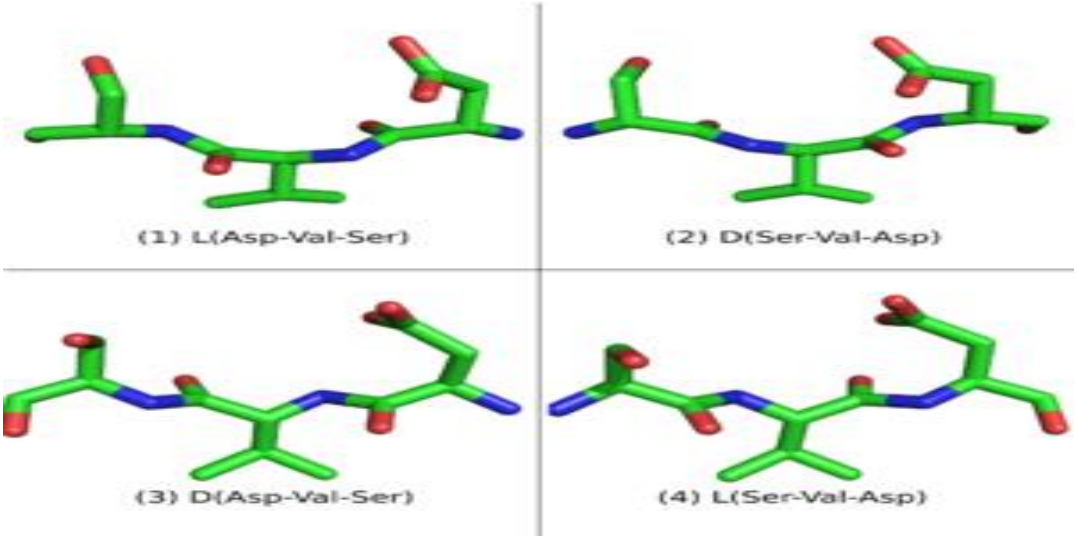
(Fig 23) An L-peptide (1) sequence has three analogues: the D-enantiomer (3) with the same sequence, the retro L-peptide (4) with the inverted sequence, and the retro-inverso D-peptide (2), with all D-amino acids and the inverted sequence.

3.1.2. Methods for designing D-peptides

To understand the retro, inverso and the retro inverso peptides let us consider a peptide chains built of three amino acid residues L and D enantiomers (Figure 24). For example peptide chain composed of Asp-Val-Ser

- The retro-peptide, composed of the same sequence of L amino acids but in reverse order.
- The inverso-peptide with the same sequence, but of D-amino acids and a mirror conformation of each residue.
- The D-retro-enantiomer peptide or retro-invero, consisting of D-amino acids in the reversed sequence [124- 131].
- The L-retro-peptide consists of the mirror image of the D-retro-inverso-peptide. Both, the L-peptide and the D-retro-inverso-peptide have a similar orientation of side-chains, despite their carboxyl and amino groups were oriented in opposing directions.

The structures of L-peptide and its D- enantiomer are mirror of each other, Also the structure of L-retro-peptide and its D-retro-inverso-peptide are the mirror image of each other as well. The D-retro-inverso-peptide and L-peptide possess a similar configuration of side-chains, apart from their amino and carboxyl groups direct towards opposing directions (fig. 24). For the small peptides, their L-retro-peptide and its D-retro-inverso-peptide are likely possess a similar binding affinity with a target L-protein.



[Figure 24]An L-peptide and its analogues.

An L-peptide (1) sequence has three analogues: the D-enantiomer (3) with the same sequence, the retro L-peptide (4) with the inverted sequence, and the retro-inverso D-peptide (2), with all D-amino acids and the inverted sequence.

In this image (1) and (3) are shown from C-terminus on the left to N-terminus on the right, while (2) and (4) are shown from N-terminus to C-terminus. Note that (1) and (2) have similar side chain positions; one is the retro-inverso sequence of the other. The same applies to (3) and (4).

Conclusion:

Despite the remaining challenges, it is evident that peptides will play a significant role in the development of future therapeutics due to their low immunogenicity, their chemical manipulability, the ease with which combinatorial peptide libraries can be created and screened, and the possibility of their delivery via less invasive means than intravenous injection. By modifying natural compounds, using phage display, and using combinatorial chemistry, potential lead candidates are being found; some of these are currently undergoing clinical trials. New administration techniques are also being developed to maximize the efficacy of these new medications. In this case, the development is more gradual, and each peptide's ideal delivery route is likely to depend on its physicochemical properties. Additionally, evaluating the long-term immunogenicity or other consequences of administering the peptide via several routes takes time. Given the substantial peptide characterization, discovery, and clinical research that is being conducted, the future of novel peptide therapies seems to be very promising.

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