Asian Journal of Chemistry; Vol. 29, No. 9 (2017), 1879-1887

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2017.20802

REVIEW

A Review on Azapeptides: The Promising Peptidomimetics

ARIFA BEGUM*, D. SUJATHA, K.V.S.R.G. PRASAD and K. BHARATHI

Department of Pharmaceutical Chemistry, Institute of Pharmaceutical Technology, Sri Padmavati Mahila Visvavidyalayam (Women's University), Tirupati-517 502, India

*Corresponding author: E-mail: arifa.medchem@gmail.com

Received: 25 May 2017; *Accepted*: 15 June 2017; *Published online*: 15 July 2017; AJC-18458

Peptidomimetics, the mimics of natural peptides are considered as promising therapeutics with potential applications in modern medicine. Among the various structural variants of peptidomimetics that have been designed and synthesized, the azapeptides serve as the interesting peptide backbone modifications owing to their diversified biological and pharmacokinetic properties. The aim of this review is to highlight the significance of azapeptide in enhancement of stability and bioavailability, represent the various scaffolds of azapeptides as peptidomimetics, notify their significance as cysteine and serine protease inhibitors, provide an insight on the various biologically significant azapeptides and emphasize the main features on the conventional to modified synthetic strategies of azapeptides.

Keywords: Azapeptides, Cysteine protease, Serine protease, Peptidomimetics.

INTRODUCTION

Peptides and proteins are the important molecules in the development of potential therapeutic agents as they play a crucial role in virtually all biological processes. To overcome the limitations of degradation by proteases, low membrane permeability and to improve metabolic stability and biological absorption, a number of backbone modified peptides have been the focus of research over past several years. Among these modifications, azapeptides formed by the replacement of the α-carbon (c^{α}) of amino acid residues with a nitrogen (N) atom are promising peptidomimetic compounds as depicted in Fig. 1 [1].

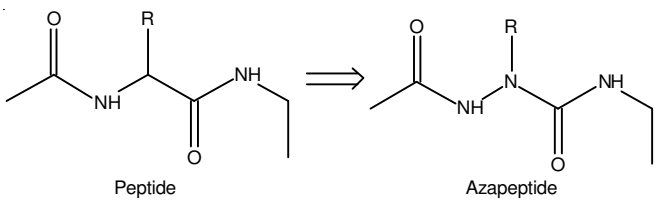

Fig. 1. Formation of azapeptides

Azaamino acids: Azaamino acids serve as an attractive tool for drug design leading to the development of azapeptides as the most useful peptidomimetic drug candidates. Aza analogues of many natural amino acids *e.g.*, glycine, alanine, tyrosine, tryptophan, asparagine, ornithine, proline, pyroglutamic acid, aspartic acid and glutamine have been reported [2-7].

Incorporation of azaamino acids in a peptide chain confer interesting properties such as (i) imparts unique conformational property to peptide structure because of loss of asymmetry associated with C^{α}–C bond in amino acid (ii) may increase the biological activity or improve the pharmacokinetic properties of the parent peptide (iii) impart enzymatic stability and thus have been investigated as novel protease inhibitors (iv) may exhibit better interaction with protein receptors and enhanced stability to enzymatic and chemical degradation [8-11].

Aza scan which involve systematic replacement of amino acid residues in a peptide with their aza counter parts has proved to be promising for the development of desirable bioactive agents. In addition, an amino acid scan of biologically active peptides was introduced as a method for identifying biologically active conformations of different proteins [12].

Peptides containing the amino acid analogue aza-proline (azPro) were shown to stabilize the *cis*-amide conformer and prefer the type VI β-turn of the native peptide without incorporation of additional steric bulk. Complete substitution of all asymmetric substituted α-carbons is represented by pure azapeptides termed azatides [13]. The aza scan of a potent peptide based PKB/AKt inhibitor was reported using aza-arginine and aza-proline precursors [14].

Therapeutic potential of azapeptides: In recent years azapeptides have attracted much interest because of their biological and pharmaceutical applications as hormone analogs, receptor ligands, enzyme inhibitors *viz*. protease inhibitors (cysteine proteases, serine proteases and aspartic proteases) active site titrants, design of drug candidates, pro-drugs and imaging agents. The combination of peptide bond and conformational stabilization imparted by azapeptides provided a promising antiviral agent Atazanavir (Fig. 2) as the first protease inhibitor approved for patients with HIV infection [15]. Since then extensive work in research of azapeptides became populous and few analogues are in the preclinical phase as drug candidates.

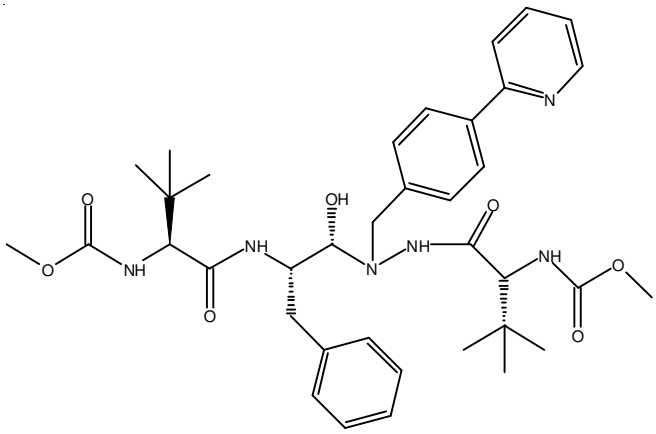

Fig. 2. Atazanavir

Significance of aza scaffold in enhancement of stability and bioavailability: Azapeptides are preferably more stable in biological medium compared to native peptides. For this reason, they have been used to improve the stability and bioavailability of the peptide drugs. The synthesis and spectroscopic investigations of β^2 peptide analogs consisting of (S)-3-aza-β-amino acids carrying the side chains of valine, alanine and leucine and enzymatic stability studies were performed, among which the N-Boc- of β^2-tri and N-Boc of β^2-hexapeptide esters were shown to be more stable against proteinases K, chymotrypsin, trypsin, carboxypeptidase A and 20 S proteosome [16]. Depending on the position of aza amino acid residue in the sequence, azapeptides can adapt different kinds of secondary structures especially β-turns [17,18]. Few examples of azapeptides which led to improved pharmacokinetics are given in Table-1.

Various azapeptide scaffolds as peptidomimetics: In order to improve biological stability and potency of the parent lead peptides, much effort has been devoted towards the development of various azapeptide scaffolds for peptidomimetic chemistry.

Aza peptoids: Peptoids are oligo-N-alkyl glycines and serve as important class of peptide like compounds. The side chains are connected to nitrogen atom of peptide backbone rather than to α-carbon as in amino acids [23]. The advantages of peptoids include their ease of construction, serum stability and cell permeability, but the utility of peptoids is limited because of lack of conformational constraints. Hence many strategies were introduced to incorporate structural constraints and azapeptoids gained attention [24]. A change in peptoids structure yields biologically active peptoids, hydrazino-azapeptoids, retro hydrazino-azapeptoids and peptoid-azapeptoid hybrids (Fig. 3). The boronic acid derivatives of hydrazine-azapeptoids (which contain NHNRCO bonds instead of CONRNH bonds) showed less inhibitory effect than Ac-Leucyl-Leucyl-Norleucinal (ALLN) and PS-341 the reference boronic acid inhibitor but the active boronic acid derivatives were more selective than ALLN [25,26]. Since then a number of aza peptoids, hydrazine aza peptoids, retro hydrazine aza peptoids and N-azapeptoid oligomers have been reported [27].

A series of hydrazine-aza and N-aza peptoids, analogues of Ac-Leucyl-Leucyl-norleucinal, a non-specific peptidyl aldehyde was synthesized and investigated for *in vitro* antiproliferative activity. The potency of the synthesized analogues was less in comparison to Bortezomib, a potent proteosome inhibitor which entered clinical trials [28]. A library of prodrugs of peptide-peptoid hybrid termed peptomers were synthesized and reported to be selectively activated by prostate cancer cells [29].

Aza-β^3-peptides: β-Peptides are peptides which have the amino group bound to the β-carbon instead of α-carbon. These are characterized by special features like improved membrane permeability and greater protease resistance. The replacement β-carbons (C^{β}) atoms of β-amino acid residues with nitrogen (N) leads to hydrazine peptide also known β-3-azapeptides or Aza-β^3-peptides the general structure of which is depicted in Fig. 4. Exploring their valuable significance the solid phase synthesis of "mixed "peptidomimetics was reported using Fmoc-protected Aza-β^3-amino acids and α-amino acids [30].

TABLE-1
SIGNIFICANCE OF AZA SCAFFOLD IN ENHANCEMENT OF STABILITY AND BIOAVAILABILITY

S. No.	Peptide hormone/receptor	Modification	Effect of modification
1	Angiotensin-II	Asp-Arg-AzaVal-Tyr-Val-His-Pro-Phe [aza-val3]-angiotensin-II analog	Longer duration of action but less active than parent peptide [19]
2	Oxytocin	[Aza Asn^5]-Oxytocin [Aza Gly^9]-Oxytocin	Inactive to induce labor contractions 1.5 folds greater activity than parent peptide [7]
3	Eledoisin	[Aza-Asn^5]-eledoisin	Prolongation of action and more potent than parent peptide [20]
4	Luteinizing hormone releasing hormone [LH-RH]	[D-Ser(t-Bu)^6,aza Gly^{10}] LH-RH (Goserelin acetate)	Clinically approved and Used for prostate and breast cancer [8]
5	Calcitonin gene related peptide (CGRP)	[Aza Gly^{33}]-CGRP	10 fold increased inhibitory activity [21]
6	Growth hormone releasing peptide (GHRP-6)	[Aza Phe^4]-GHRP-6	Improved binding, selectivity and affinity to cluster of differentiation (CD36) scavenger receptor which is implicated in atherosclerosis, angiogenesis and age related macular degeneration [22]

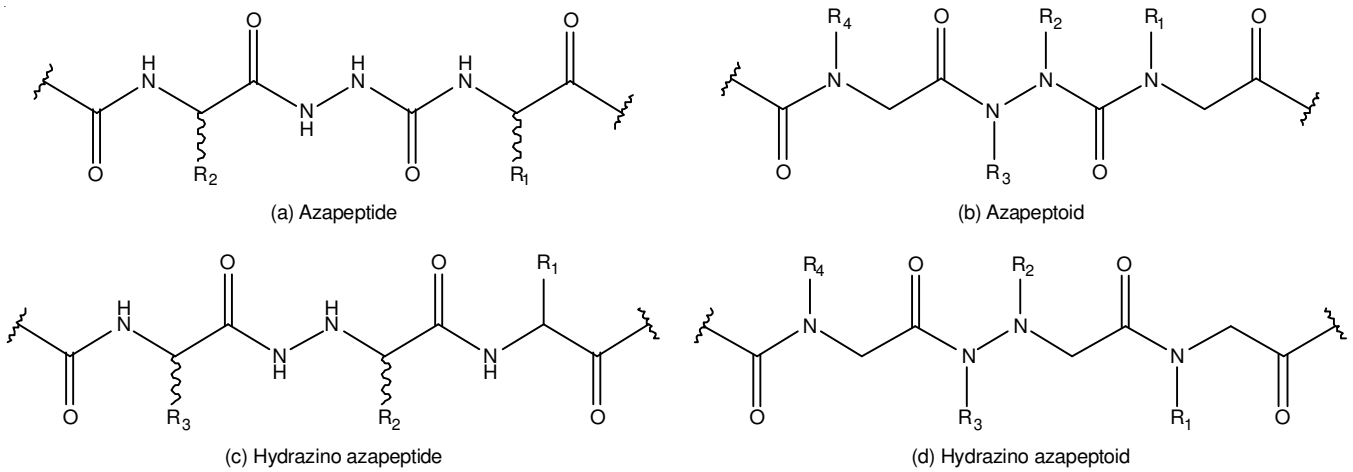

Fig. 3. Structural features of (a) Azapeptide, (b) Azapeptoid, (c) Hydrazino azapeptide, (d) Hydrazino azapeptoid

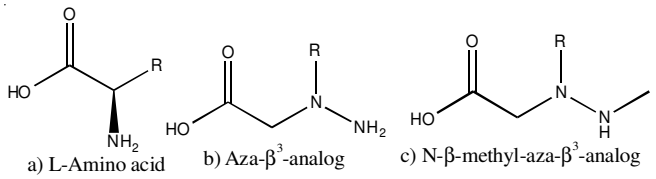

Fig. 4. General structure of (a) L-amino acid, (b) aza-β^3-analog and (c) N^{β}-mehtyl-aza-β^3-analog

Crystals of aza-β^3-peptides, a new class of foldamers relying on a framework of hydrazine turns have been obtained and the structures make it clear that the H-bond network developed by aza-β^3-peptides differs from those of β^3-peptides [31].

Peptide nucleic acid (PNA) a class of non hydrolyzable peptides is composed of a backbone built from amino ethylglycine units. Several attempts have been made to overcome the major limitations *viz*. poor solubility in aqueous medium, insufficient cellular uptake due to uncharged backbone [32]. One such attempt was made to synthesize new building blocks, the hydrazino ethylglycine units or the reduced diaza-β^3-peptides that could be integrated in a peptide in construction to give aza analogues of peptide nucleic acid [33].

Owing to the great enzymatic stability of azapeptides, the β-peptide concept was utilized in the development of a new class of RGD (Arg-Gly-Asp) peptidomimetics containing β^3-aza amino acid residues with enhanced proteolytic resistance [34].

Peptidomimetic analogs of peptide substrate for protein kinase A with conserved sequence of amino acids and phosphorylatable serine residue (Arg-Arg-Ala-Ser-Val-Ala) (RRASVA) were synthesized by consecutive replacement of natural amino acids by their aza-β^3-analogs and tested as cAMP- dependent Protein Kinase substrates (PKA). N^{β}-Fmoc-N^{β}-Me-aza-β^3 amino acids were synthesized and comparative studies were carried out to study the effect of N^{β}-methylation on kinetics of PKA-catalyzed phosphorylation of peptide substrate RRASVA analogs and results revealed that N^{β}-methylation changed the pattern of substrate recognition by the enzyme [35,36].

Oxyazapeptides: The new family of peptidomimetics obtained by substituting the typical native N-C^{α} with an O-N^{α} bond is known as oxyazapeptides. These scaffolds are hydrolytically stable and display very interesting conformational behaviour. The conformational analysis suggests that the oxyaza moiety can effectively induce β-turns. These features make oxyazapeptides as useful tools for drug discovery and design of biologics (Fig. 5) [37].

Cyclic analogues of azapeptides: The cyclic peptides are proven to enhance the binding potency, selectivity and protease stability. The cyclic aza scaffolds are known to enhance conformational rigidity and reactivity. The 3-aza-6,8-dioxa-bicyclo-[3.2.1]octane containing bicyclic molecular scaffolds were proven as mimetic of β-turns [38]. The aza-β3-cyclohexapeptides (24 membered macro cycles) showed interesting conformational and configurational properties [31]. The aza-pipecolyl peptidomimetics were reported to display antibacterial and antidiabetic activities, based on their conformational significance, the synthesis of new modular sulphur containing dipeptide

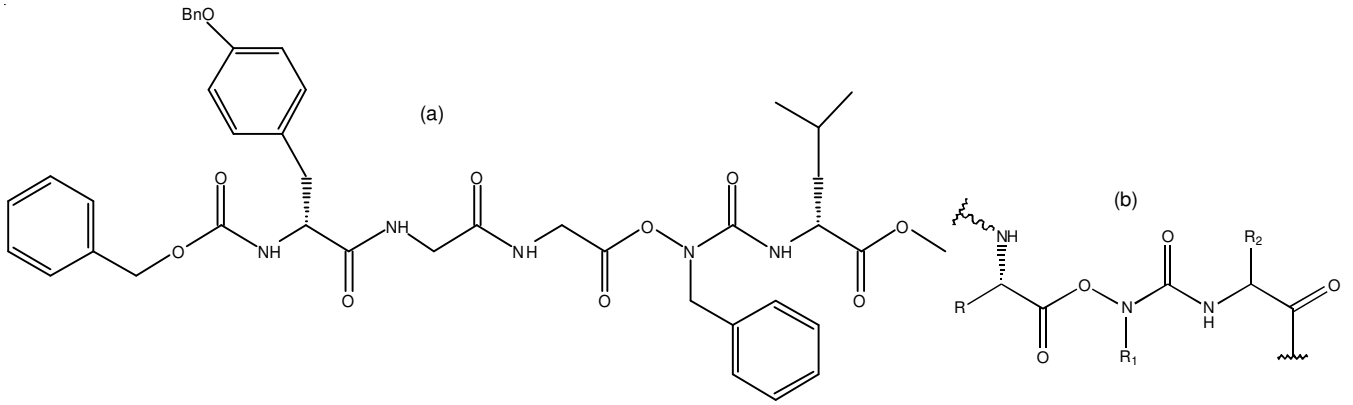

Fig. 5. (a) Oxyazapeptides analogue of active Leu-enkephalin (b) General structure of oxyazapeptide

mimetics (diazabicycloalkanes) and azapolycyclic compounds was performed [39]. Few cyclic aza-GHRP-6 analogs exhibited unprecedented affinity for the CD36 receptor and also reduced the pro-inflammatory cytokines [40].

Importance of azapeptides as cysteine and serine protease inhibitors: A number of human diseases are associated with aberrant activity of mammalian, viral, bacterial or parasitic proteases. The four classes of proteases include: Cysteine proteases, serine proteases, aspartic proteases and metallo proteases [41].

Azapeptides are ideal protease inhibitors because they are more resistant to cleavage by the proteases *in vivo* and can incorporate a reactive warhead. A number of azapeptides have been investigated as novel specific inhibitors of chymotrypsin [42], subtilisin [43], elastase [44], angiotensin converting enzymes (ACE) [45], cysteine and serine proteases [46].

Azapeptides as cysteine protease inhibitors: The cysteine proteases categorized as one among the four major classes of proteases, are proteins with molecular weight about 21-30 KDa [47]. These are involved in numerous important physiological processes including protein turnover, tumor progression, mitosis and apoptosis [48]. Since azapeptides are effective covalent inhibitors of cysteine proteases, the synthesis of a series of O-acyl hydroxamates, their azapeptide analogues and a new class of azaglycine-containing O-acyl hydroxamates have been explored [49]. The key strategy that azapeptides impart distinct conformational properties to the peptide chain has been applied to an important chemo type of cysteine protease inhibitors, *i.e.* the C-terminal portion of dipeptide nitriles, affording aza dipeptide nitriles with higher inhibitory potency [50,51].

Azapeptides as legumain inhibitors: Legumains (asparaginyl endopeptidases) an important member of clan CD, were originally identified in leguminous plant and the parasitic blood fluke schist soma mansoni [52]. Parasitic diseases are one area in which irreversible Legumain inhibitors could have great potential for short term therapeutic administration. In an effort to design and synthesize more specific and selective legumain inhibitors the synthesis of a novel class of cysteine protease inhibitors known as azapeptide epoxides was elaborated [53]. Further studies reported the design, synthesis and evaluation of azapeptide epoxides as selective and potent inhibitors of caspases-1,-3,-6 and -8 with second order inhibition rates up to $1910000M^{-1}S^{-1}$ [54].

Azapeptides as caspases inhibitors: Caspases also known as cysteinyl aspartate-specific proteases are important mediators of inflammations and apoptosis (programmed cell death). Hence these are recognized as novel therapeutic targets for CNS diseases in which cell death occurs mainly by an apoptosis mechanism [55]. The presence of near absolute specificity for residue at P_1 is a distinctive feature of this family of enzymes and so in an effort to obtain greater potency and selectivity a variety of azapeptide Michael acceptors with P_1 Asp residue were synthesized as potential inhibitors for caspases [56,57].

A series of constrained azapeptides from the second mitochondrial-derived activator of caspases (Smac) protein and tested for their ability to induce apoptosis in MCF-7 breast cancer cell. The results indicated that the aza-cyclohexanylglycine analog was found to induce cell death more efficiently than the parent tetra peptide likely by a caspases-9 mediated apoptotic pathway [58].

Azapeptides as cathepsin inhibitors: The over expressions of cysteine cathepsins (proteolytic enzymes) belonging to pain like cysteine peptidase has been implicated in pathological conditions *viz.* tumor progression, metastasis. Inhibitors of cathepsin L an endosomal cysteine protease provide potential starting points for drug discovery efforts as cathepsin L is known to play a key role in disease states such as cancer, rheumatoid arthritis and osteo-arthritis. Efforts to identify inhibitors of cysteine (cathepsins B, L, S) resulted in identification of azapeptide analogs as inhibitor of cathepsin L [59,60].

Cathepsin K inhibition has emerged as a promising target on the basis of inhibition of osteoclastic bone resorption. The front runner cathepsin K inhibitors odanacatib is a non basic and non-lysosomotropic peptidomimetic nitrile and is widely used once weekly treatment for osteoporosis [61,62]. Based on the significance of nitrile type inhibitors aza dipeptide nitriles have been introduced as a new class of inhibitors [63]. Further, the chemo type of 3-cyano-3-aza-β-amino acid derivatives was designed in which the N-cyano group is centrally arranged to allow for interaction with the unprimed and primed binding regions of cathepsin K [64].

Azapeptides as calpain inhibitors: Calpains, a class of intracellular cysteine proteases possess several important physiological functions like cell adhesion, motility, gene expression and cell cycle progression. The over expression of these could be associated with disorders like Alzheimer's, Huntington's and Parkinson's diseases**.** Based on the significance of these Calpains in research field the synthesis and characterization of azapeptides possessing various levels of Calpain inhibitions has been reported [65].

Azapeptides as serine protease inhibitors: Serine proteases are enzymes that cleave peptide bonds in proteins. In humans these serine proteases coordinate various physiological functions including digestion, immune response, blood coagulation and reproduction. The serine protease inhibitors abbreviated as serpins inhibit platelet functions and coagulations and have been used to reduce deposition of micro emboli in cases of sepsis [66].

In seeking different classes of inhibitors for serpins a series of azapeptide *p*-nitrophenyl esters have been synthesized and N-acetyl-L-alanyl-L-alanyl-α-azanorleucine *p*-nitrophenyl ester and N-acetyl-L-alanyl-α-azaphenylalanine *p*-nitrophenyl-ester were found to be useful as active site titrants and inhibitors of serine proteases with chymotrypsin –like activity [44].

Non-structural protein 3 (NS3) is a serine protease which is required for viral replication and infectivity. It is required for processing of Hepatitis C virus (HCV) polyprotein. Incorporation of noncleavable aza aminoacyl residues provided azapeptide inhibitors of hepatitis C virus (Fig. 6) [67-69].

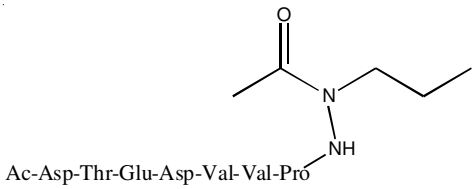

Fig. 6. HCV NS3 serine protease inhibitor

Insights on biological activities of azapeptides: Azapeptides, the most promising peptidomimetics, contain a semicarbazide residue within the peptide backbone. This imparts the pre-organized β-turn secondary structure, which is responsible for high affinity and selective binding to a target receptor or enzyme and modulates its therapeutic activity. Insertion of azaglycine instead of glycine in cell adhesion motif Arg-Gly-Asp (RGD) led to enhanced activity and selectivity than the parent peptide (Fig. 7) [70]. Aza-Gly analog of goserelin, a synthetic analogue of a naturally occurring luteinizing-hormone releasing hormone (LHRH) received FDA approval in 1989 for the treatment of prostate and breast cancer (Fig. 8) [71].

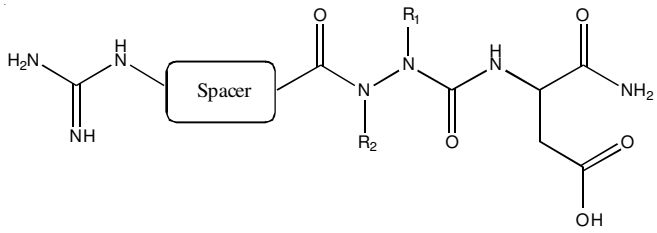

Fig. 7. Aza glycine incorporation in the cell adhesion Arg-Gly-Asp (RGD) motif

Synthesis and biological evaluation of aza analogues of potent growth hormone secretagogues, involved in treatment of burns, Turner's syndrome, sleep enhancement and reduction of some age related effects was performed (Fig. 9) [72].

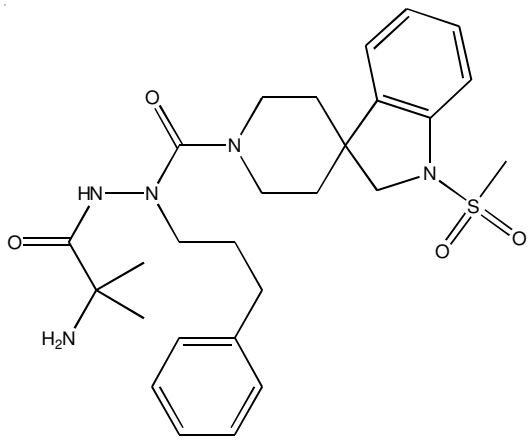

Fig. 9. Aza analog of potent growth hormone secretagoues

Azapeptides are extensively studied for a wide variety of biological actions like anticonvulsant, antimicrobial (Fig. 10) and various other activities (Table-2).

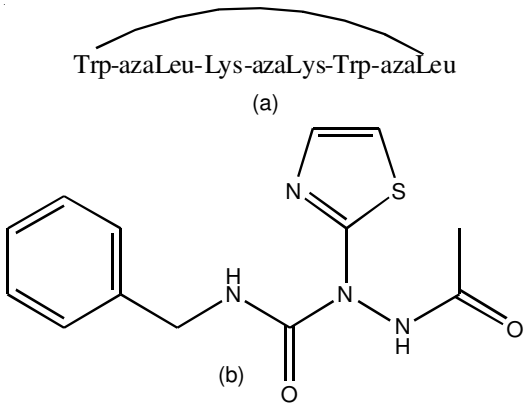

Fig. 10. (a) *De novo* cyclic pseudo peptides composed of a-amino and azaamino acids with antimicrobial activity. (b) Functionalized azaamino acid derivative with anti convulsant activity

Important methods of synthesis of azapeptides: Azapeptides can be synthesized by incorporation of the azaamino acids into the parent peptide by various possible routes like coupling i) protected hydrazine with isocyanate ii) activated aryl ester (C-activated and N-activated esters with carbono-chloridic esters and carbonic diesters iii) acid chloride with phosgene iv) 1,3,4-oxadiazol-2(3H)-ones with various N-un-protected azapeptides v) azolides with hydrazides [87].

The liquid and solid phase synthesis is the widely used methods for the synthesis of peptides. The liquid phase is time consuming and requires purification steps. The solid phase method is considerably fast and preferable method [88]. The most usual method of synthesis of azapeptides is performed on solid phase by coupling protected azaamino acids precursors to the peptidyl resin. This could be achieved by any of the possible routes as given in Table-3.

A solid-phase synthesis of three aza-, iminoaza- and reduced azapeptides using the Boc-strategy was reported [92]. By performing an aza-amino acid scan of antagonist peptides, a set of aza-hCGRP analogues was synthesized to examine the relationship between turn secondary structure and biological activity [12].

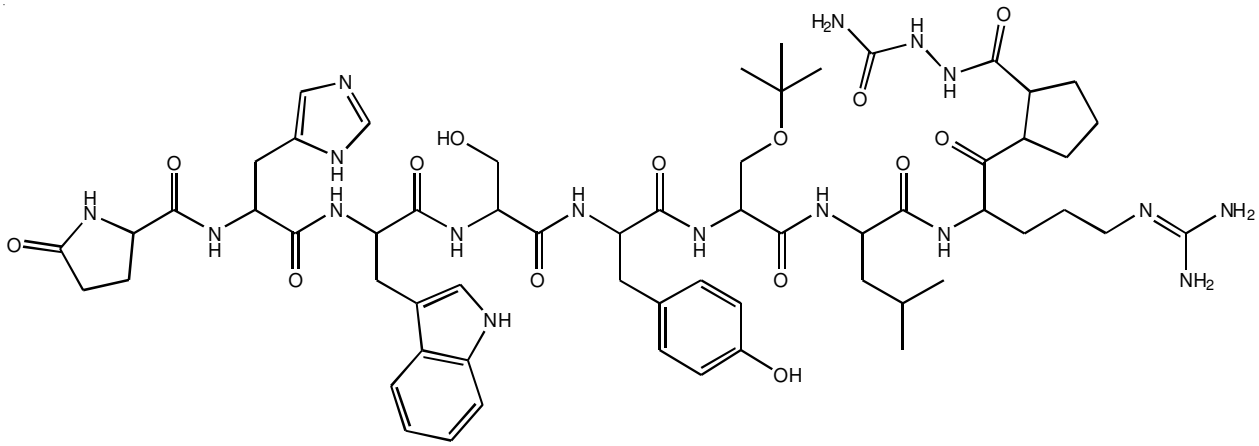

Fig. 8. Aza analog of luteinizing-hormone releasing hormone (LHRH), goserelin

TABLE-2
VARIOUS BIOLOGICAL ACTIVITIES OF AZAPEPTIDES

S. No.	Azapeptide analogs	Activity reported
1	Aza analogues of functionalized amino acids	Anticonvulsant activity [73]
2	Azapeptide-based inhibitors of the Hepatitis C virus (HCV) NS3 serine protease.	Antiviral activity [67]
3	The DNA methylation inhibitor 5-Aza-2'-deoxycytidine (5-Aza-CdR)	For acute and chronic myeloid leukemia [74]
4	ABPs (Activity based probes) based on aza-aspartate inhibitory scaffold.	Selective targeting of caspases [75]
5	The potent undecapeptide antagonist [D31, P34, F35] CGRP27-37 obtained by performing aza scan at positions 31-32, 32-33, 33-34, 34-35 of the backbone of a Calcitonin gene-related peptide antagonists	Pain, migraine headache and inflammation [76]
6	Series. of novel 1-aza-9-oxafluo-renes.	GSK-3beta inhibitors, Alzheimer's disease (AD) [77]
7	Azapeptide derivatives targeting the cluster of differentiation 36 (CD36) class B scavenger receptor.	Cardio protective effect [78]
8	Cyclic aza-peptides containing the RGD (Arg-Gly-Asp) sequence.	Human tumor metastasis and tumor-induced angiogenesis [39]
9	*De novo* cyclic pseudo peptides of alpha and aza amino acids.	Antibacterial activity [79]
10	The 3-aminoquinazolin-4-one scaffold, 2-(2-Methyl-4-oxoquinazolin-3(4H)-ylamino)-N'-(benzylidene) acetohydrazides.	Antibacterial activity (*E. coli, S, aureus, P. mirabilis*) [80]
11	Azapeptides based on the Ala-Val-Pro-Ileu peptide.	Activators of apoptosis mediated by caspase-9 in cancer cells [81]
12	Azabicycloalkanone amino acid and azapeptide mimics.	Modulators of the prostaglandin F2α receptor for delaying preterm birth [82]
13	Oxyazapeptides and cyclic peptides was reported.	Anticancer and antibacterial activity [83]
14	Aza-peptide analogue AzaAla-Val-Pro-Phe-Tyr-NH2.	A lead for anti-cancer [84]
15	Novel azapseudopeptide derivatives.	Antimicrobial activity [85]
16	Aza-peptide aldehyde and ketone compounds with Z-Leu-Leu-ALeu-COH.	Proteosome inhibitor [86]

TABLE-3
SOLID PHASE METHODS FOR INCORPORATION OF AZA RESIDUES INTO PEPTIDE CHAIN

S. No.	Method	Drawback
1	Coupling of an aza-tripeptide synthon to the N-terminus of a Resin bounded peptide	Partial epimerization [89]
2	Conversion of resin bound N-terminal amino group into isocyanate by a base catalyzed reaction using *bis*(2,4-dinitrophenyl) carbonate	Hydantoin formation [90]
3	Transformation of N-terminal protected hydrazine into activated carbazic acid using nitrophenylchloro formats or *bis*(2,4-dinitrophenyl) carbonate	Long coupling time, High temperature, Poor yields, Numerous side chains [91]

Modified solid phase methods: With an aim to eliminate the hydantoin side product an efficient method utilizing N-2-hydroxy-4-methoxy benzyl (Hmb) reversible amide bond protecting group was adapted to obtain the desired azapeptides in excellent purity and good yields [93]. Coupling the N-Boc aza dipeptide and tripeptide segments to the amine terminus of a growing peptide chain could also circumvent formation of hydantoin byproduct [94]. In an effort to synthesize the azapeptides more efficiently novel strategies (methods) have been introduced which include:

- Fmoc/Ddz-strategy: Azaamino acid scanning method
- Submonomer solid phase method
- Ugi four component method
- Chemical ligation method

Fmoc/Ddz-strategy: Azaamino acid scanning method: The most common aza-amino acid building blocks prepared for the solid phase synthesis of azapeptides are Fmoc protected N'-alkyl hydrazine and N-Boc-aza-dipeptide fragments as well as N-Fmoc and N-2-(3,5-dimethoxy phenyl)propan-2-yloxy-carbonyl (Ddz) protected aza amino acid chlorides [12]. Among these, Fmoc/Ddz-strategies are useful in producing libraries of azapeptides for exploring structural activity relationships with target receptors. The N-2-(3,5-dimethoxy phenyl)propan-2-yloxy-carbonyl (Ddz) is an attractive protecting group which can be removed under extremely mild conditions. Nevertheless, the solid phase synthesis of C-terminal azapeptides has remained a challenge and so the synthesis of few C-terminal azapeptides using N-(Fmoc)-aza-amino acid and (Ddz)-aza-amino acid chlorides have been reported [95].

To explore the relationship between the melanocortin agonist putative sequences His-Phe-Arg-Trp designated as "message" sequence for melanocortin, seven aza analogs of Ac-His-D-Phe-Arg-Trp-NH_2were synthesized and evaluated. The aza analogues in which the C-terminal amino acid tryptophan (Trp^4) was replaced with aza-2-napthylalanine, aza-1-napthylalanine and aza-biphenylalanine showed potential for improving metabolic stability [9].

Based on the scientific and industrial value of hydrazine derivatives the synthesis of N'-substituted 2-(3,5-dimethoxy phenyl)propan-2-yloxy-carbonyl (Ddz) protected hydrazines have been described [96,97]. The synthesis of new *m*-Calpain substrate based azapeptide inhibitors was performed by solid phase methodology on MBHA resin using Boc/Bzl strategy [65].

The limitations of Fmoc/Ddz strategies: i) Difficult to synthesize aza amino acid monomers ii) Necessitate the preparation of aza amino acid monomer in solution prior to incorporation within azapeptide sequences by conventional solid phase peptide synthesis. iii) Requires efficient introduction of a suitably protected aza glycine residue, its chemo selective alkylation, deprotection and chain extension reaction.

Submonomer solid phase strategy: The submonomer azapeptide synthesis strategy is highly advantageous because

it circumvents the need for monomer preparation and does not require stereo chemical control for building aza residue in solid phase. The submonomer solid phase synthesis provides regioselective modification of semicarbazone peptide on solid phase to generate novel N-alkylated and N-arylated aza residues useful for structural activity relationship studies.

The synthesis of aza-arylglycine Growth-Hormone-Releasing-Peptide-6 (GHRP-6) analogs by copper catalyzed N-arylation of semicarbazone peptide bound support and new GHRP-6 azapeptides containing aza-1,2,3-triazole-3-alanine residues prepared on aza-propargly glycine residues by a copper catalyzed 1,3-dipolar cycloaddition reaction with azides has been reported [98]. Ten aza analogs of GHRP-6 were synthesized, among which the [aza-phe^4]-GHRP-6, showed stable β-turn and favoured selective binding to cluster of differentiation 36 (CD36) receptor thereby presenting a lead for angiogenic disorders [99].

The azapeptide analogues of growth hormone releasing peptide GHRP-6 His-D-Trp-Ala-Trp-D-Phe-Lys-NH_2 were synthesized targeting the CD36 receptor. Substituted N-amino imidazoline-2-one prepared by a base catalyzed cyclization of aza-properglyl glycine residues and N-amino-imidazoline-2-one peptidomimetics have been developed [100,101]. Solid phase submonomer synthesis of azapeptide ligands of insulin receptor tyrosine kinase domain was reported [71]. The synthesis of C-terminal GHRP-6 was communicated by application of benzhydrylidene-aza-glycinamide rink resin [102]. In addition, the utility of this method has been demonstrated by the synthesis of [aza-Lys^6] GHRP-6 derivatives by a protocol featuring regioselective alkylation of benzhydrylidene aza-glycinamide [103].

Ugi four component method: Though the submonomer solid phase method is highly feasible and advantageous it suffers from the disadvantage of long or difficult sequences to be followed. So alternative methods for fast and easy synthesis of peptides and various azapeptide scaffolds has been designed which resulted in U-4CR method (Ugi-four component reaction), considered as the most versatile and robust method. The strategy is based on the formation of an acylhydrazino-peptomer *via* an initial hydrazino-Ugi reaction followed by hydrazinolysis reaction [104].

Chemical ligation method: The chemical ligation method would allow the incorporation of aza amino acid in large structures in a convergent way. Replacement of Gly by azagly (Agly) has been used for improving the stability [18]. Apart from the usual solid phase peptide synthesis (SPPS) method the Agly incorporation can be carried out in solution using chemo selective ligation method. A novel site specific chemo selective approach following two strategies, one based on reaction between C-terminal peptide thioester and an N-terminal azagly peptides and other based on reaction of a C-terminal peptide hydrazide with a N-terminal phenyl thio carbonyl (PTC) peptide has been reported suggesting that silver catalyzed reactions allow convergent and chemo selective synthesis of peptide [105,106].

Conclusion

The review mainly emphasizes the key role of azapeptides in the modifications of pharmacokinetic properties of the parent peptide and accordingly modifying the pharmacological significance. This paves the path for the development of different scaffolds of azapeptides with various biological activities. Various developments in the synthesis and applications of azapeptides have been covered and the submonomer method is considered to be the potential method to surpass the drawbacks of the conventional solution and solid phase methods.

REFERENCES

1. J. Gante, M. Krug, G. Lauterbach, R. Weitzel and W. Hiller, *J. Pept. Sci.*, **1**, 201 (1995); https://doi.org/10.1002/psc.310010307.
2. A.S. Dutta and J.S. Morley, *J. Chem. Soc., Perkin Trans. I*, 1712 (1975); https://doi.org/10.1039/P19750001712.
3. A.S. Dutta, B.J.A. Furr, M.B. Giles and B. Valcaccia, *J. Med. Chem.*, **21**, 1018 (1978); https://doi.org/10.1021/jm00208a004.
4. A.S. Dutta, B.J.A. Furr and M.B. Giles, *J. Chem. Soc., Perkin Trans. I*, 379 (1979); https://doi.org/10.1039/P19790000379.
5. J. Gray, J.C. Ireson and R.C. Parker, *Tetrahedron*, **33**, 739 (1977); https://doi.org/10.1016/0040-4020(77)80185-3.
6. M.D. Gray, S.A. Jesch and G.H. Stein, *J. Cell. Physiol.*, **149**, 477 (1991); https://doi.org/10.1002/jcp.1041490317.
7. H. Niedrich and C. Oehme, *Adv. Synth. Catal.*, **314**, 759 (1972); https://doi.org/10.1002/prac.19723140508.
8. A. Zega, *Curr. Med. Chem.*, **12**, 589 (2005); https://doi.org/10.2174/0929867053362802.
9. S. Eustache, J. Leprince and P. Tufféry, *Expert Opin. Drug Disc.*, **11**, 771 (2016); https://doi.org/10.1080/17460441.2016.1201058.
10. Y.F. Cai, L. Li, M.-X. Luo, K.-F. Yang, G.-Q. Lai, J.-X. Jiang and L.-W. Xu, *Chirality*, **23**, 397 (2011); https://doi.org/10.1002/chir.20940.
11. C. Proulx, D. Sabatino, R. Hopewell, J. Spiegel, Y.G. Ramos and W.D. Lubell, *Future Med. Chem.*, **3**, 1139 (2011); https://doi.org/10.4155/fmc.11.74.
12. R.E. Melendez and W.D. Lubell, *J. Am. Chem. Soc.*, **126**, 6759 (2004); https://doi.org/10.1021/ja039643f.
13. Che and G.R. Marshall, *J. Org. Chem.*, **69**, 9030 (2004); https://doi.org/10.1021/jo0487303.
14. N.S. Freeman, Y. Tal-Gan, S. Klein, A. Levitzki and C. Gilon, *J. Org. Chem.*, **76**, 3078 (2011); https://doi.org/10.1021/jo102422x.
15. Z. Lv, Y. Chu and Y. Wang, *HIV/AIDS–Res. Palliat. Care*, **7**, 95 (2015); https://doi.org/10.2147/HIV.S79956.
16. G. Lelais and D. Seebach, *Helv. Chim. Acta*, **86**, 4152 (2003); https://doi.org/10.1002/hlca.200390342.
17. E. Wieczerzak, S. Jankowska, A. Rodziewicz-Motowidlo, J. Gieldon, Z. Lagiewka, M. Grzonka, A. Abrahamson, A. Grubb and D. Brömme, *J. Pept. Res.*, **66**, 1 (2005); https://doi.org/10.1111/j.1747-0285.2006.00329.x.
18. E. Wieczerzak, R. Hamel Jr., V. Chabot, V. Aimez, M. Grandbois, P.G. Charette and E. Escher, *Peptide Sci.*, **90**, 415 (2008); https://doi.org/10.1002/bip.20945.
19. H.J. Hess, W.T. Moreland and G.D. Laubach, *J. Am. Chem. Soc.*, **85**, 4040 (1963); https://doi.org/10.1021/ja00907a036.
20. J. Bergmann, P. Oehme, M. Bienert and H. Niedrich, *Experientia*, **30**, 1315 (1974); https://doi.org/10.1007/BF01945205.
21. D. Boeglin, F.F. Hamdan, R.E. Melendez, J. Cluzeau, A. Laperriere, M. Héroux, M. Bouvier and W.D. Lubell, *J. Med. Chem.*, **50**, 1401 (2007); https://doi.org/10.1021/jm061343w.
22. C. Proulx, É. Picard, D. Boeglin, P. Pohankova, S. Chemtob, H. Ong and W.D. Lubell, *J. Med. Chem.*, **55**, 6502 (2012); https://doi.org/10.1021/jm300557t.
23. R.J. Simon, R.S. Kania, R.N. Zuckermann, V.D. Huebner, D.A. Jewell, S. Banville, S. Ng, L. Wang, S. Rosenberg and C.K. Marlowe, *Proc. Natl. Acad. Sci. USA*, **89**, 9367 (1992); https://doi.org/10.1073/pnas.89.20.9367.

24. S.M. Miller, R.J. Simon, S. Ng, R.N. Zuckermann, J.M. Kerr and W.H. Moos, *Drug Dev. Res.*, **35**, 20 (1995); https://doi.org/10.1002/ddr.430350105.
25. S. Aubin, B. Martin, J.-G. Delcros, Y. Arlot-Bonnemains and M. Baudy-Floc'h, *J. Med. Chem.*, **48**, 330 (2005); https://doi.org/10.1021/jm049455f.
26. F. Liu, A.G. Stephen, C. Adamson, K. Gousset, M.J. Aman, E.O. Freed, R.J. Fisher and T.R. Burke, *Org. Lett.*, **22**, 5165 (2008); https://doi.org/10.1021/ol0622211.
27. B.K. Sarma, M.Yousufuddin and T. Kodadek, *Chem. Commun*., **47**, 10590 (2011); https://doi.org/10.1039/C1CC12750K.
28. K. Bouget, S. Aubin, J.-G. Delcros, Y. Arlot-Bonnemains and M. Baudy-Floc'h, *Bioorg. Med. Chem.*, **11**, 4881 (2003); https://doi.org/10.1016/j.bmc.2003.09.018.
29. J. Lee, W. Huang, J.M. Broering, A.E. Barron and J. Seo, *J. Bioorg. Med. Chem. Lett.*, **25**, 2849 (2015); https://doi.org/10.1016/j.bmcl.2015.04.092.
30. O. Busnel, L. Bi, H. Dali, A. Cheguillaume, S. Chevance, A. Bondon, S. Muller and M. Baudy-Floc'h, *J. Org. Chem.*, **70**, 10701 (2005); https://doi.org/10.1021/jo051585o.
31. A. Salaün, A. Favre, B. Le Grel, M. Potel and P. Le Grel, *J. Org. Chem.*, **71**, 150 (2006); https://doi.org/10.1021/jo051887q.
32. P. Wittung, M. Eriksson, R. Lyng, P.E. Nielsen and B. Norden, *J. Am. Chem. Soc.*, **117**, 10167 (1995); https://doi.org/10.1021/ja00146a001.
33. O. Busnel and M. Baudy-Floc'h, *Synthesis*, 2591 (2005); https://doi.org/10.1055/s-2005-917100.
34. W. Bi, J. Cai, S. Liu, M. Baudy-Floc'h and L. Bi, *Bioorg. Med. Chem.*, **15**, 6909 (2007); https://doi.org/10.1016/j.bmc.2007.08.022.
35. K. Kisseljova, A. Kuznetsov, M. Baudy-Floc'h and J. Jarv, *Bioorg. Chem.*, **38**, 229 (2010); https://doi.org/10.1016/j.bioorg.2010.05.004.
36. K. Kisseljova, M. Baudy-Floc'h, A. Kuznetsov and J. Järv, *Org. Med. Chem. Lett*., **1**, 16 (2011); https://doi.org/10.1186/2191-2858-1-16.
37. S. Biswas, N.E. Abo-Dya, A. Oliferenko, A. Khiabani, P.J. Steel, K.A. Alamry and A.R. Katritzky, *J. Org. Chem.*, **78**, 8502 (2013); https://doi.org/10.1021/jo401234g.
38. D. Scarpi, D. Stranges, A. Trabocchi and A. Guarna, *Tetrahedron*, **62**, 1575 (2006); https://doi.org/10.1016/j.tet.2005.11.008.
39. J. Spiegel, C. Mas-Moruno, H. Kessler and W.D. Lubell, *J. Org. Chem.*, **77**, 5271 (2012); https://doi.org/10.1021/jo300311q.
40. J. Zhang, M. Mulumba, H. Ong and W.D. Lubell, *Angew. Chem. Int. Ed*., **56**, 6284 (2017); https://doi.org/10.1002/anie.201611685.
41. S. Lustigman, J. Zhang, J. Liu, Y. Oksov and S. Hashmi, *Mol. Biochem. Parasitol.*, **138**, 165 (2004); https://doi.org/10.1016/j.molbiopara.2004.08.003.
42. J.E. Semple, D.C. Rowley, T.K. Brunck and W.C. Ripka, *Bioorg. Med. Chem. Lett.*, **7**, 315 (1997); https://doi.org/10.1016/S0960-894X(97)00005-X.
43. B.F. Gupton, D.L. Carroll, P.M. Tuhy, C.M. Kam and J.C. Powers, *J. Biol. Chem.*, **259**, 4279 (1984);
44. J.C. Powers, R. Boone, D.L. Carroll, B.F. Gupton, C.M. Kam, N. Nishino, M. Sakamoto and P.M. Tuhy, *J. Biol. Chem.*, **259**, 4288 (1984).
45. W.J. Greenlee, E.D. Thorsett, J.P. Springer, A.A. Patchett, E.H. Ulm and T.C. Vassil, *Biochem. Biophys. Res. Commun.*, **122**, 791 (1984); https://doi.org/10.1016/S0006-291X(84)80103-5.
46. J.L. Asgian, K.E. James, Z.Z. Li, W. Carter, A.J. Barrett, J. Mikolajczyk, G.S. Salvesen and J.C. Powers, *J. Med. Chem.*, **45**, 4958 (2002); https://doi.org/10.1021/jm025581c.
47. E. Wieczerzak, P. Drabik, L. Lankiewicz, S. Oldziej, Z. Grzonka, M. Abrahamson, A. Grubb and D. Brömme, *J. Med. Chem.*, **45**, 4202 (2002); https://doi.org/10.1021/jm020850k.
48. M. Sajid and J.H. Mckerrow, *Mol. Biochem. Parasitol.*, **120**, 1 (2002); https://doi.org/10.1016/S0166-6851(01)00438-8.
49. S.H. Verhelst, M.D.Witte, S. Arastu-Kapur, M. Fonovic, M. Bogyo, *ChemBioChem.*, **7**, 943 (2006); https://doi.org/10.1002/cbic.200600001.
50. R. Loser, M. Frizler, K. Schilling and M. Gutschow, *Chem. Int. Ed.*, **47**, 4331 (2008); https://doi.org/10.1002/anie.200705858.
51. M. Frizler, M. Stirnberg, M.T. Sisay and M. Gutschow, *Curr. Top. Med. Chem.*, **10**, 294 (2010); https://doi.org/10.2174/156802610790725452.
52. K. Müntz and A.D. Shutov, *Trends Plant Sci.*, **7**, 340 (2002); https://doi.org/10.1016/S1360-1385(02)02298-7.
53. K.E. James, M.G. Götz, C.R. Caffrey, E. Hansell, W. Carter, A.J. Barrett J.H. McKerrow and J.C. Powers, *Biol. Chem.*, **384**, 1613 (2003); https://doi.org/10.1515/BC.2003.179.
54. K.E. James, J.L. Asgian, Z.Z. Li, Ö.D. Ekici, J.R. Rubin, J. Mikolajczyk, G.S. Salvesen and J.C. Powers, *J. Med. Chem.*, **47**, 1553 (2004); https://doi.org/10.1021/jm0305016.
55. J.C. Friedland, J.N. Lakins, M.G. Kazanietz, J. Chernoff, D. Boettiger and V.M. Weaver, *J. Cell Sci.*, **120**, 3700 (2007); https://doi.org/10.1242/jcs.03484.
56. O.D. Ekici, M.G. Götz, K.E. James, Z.Z. Li, B.J. Rukamp, J.L. Asgian, C.R. Caffrey, E. Hansell, J. Dvorák, J.H. McKerrow, J. Potempa, J. Travis, J. Mikolajczyk, G.S. Salvesen and J.C. Powers, *J. Med. Chem.*, **47**, 1889 (2004); https://doi.org/10.1021/jm049938j.
57. O.D. Ekici, Z.Z. Li, A.J. Campbell, K.E. James, J.L. Asgian, J. Mikolajczyk, G.S. Salvesen, R. Ganesan, S. Jelakovic, M.G. Grütter and J.C. Powers, *J. Med. Chem.*, **49**, 5728 (2006); https://doi.org/10.1021/jm0601405.
58. R. Chingle, S. Ratni, A. Claing and W.D. Lubell, *Biopolym. Pept. Sci.*, **106**, 235 (2016); https://doi.org/10.1002/bip.22851.
59. A.G. Jamieson, N. Boutard, K. Beauregard, M.S. Bodas, H. Ong, C. Quiniou, S. Chemtob and W.D. Lubell, *J. Am. Chem. Soc.*, **131**, 7917 (2009); https://doi.org/10.1021/ja9010628.
60. J. Schedel, C.A. Seemayer, T. Pap, M. Neidhart, S. Kuchen, B.A. Michel, R.E. Gay, U. Müller-Ladner, S. Gay and W. Zacharias, *Gene Ther.*, **11**, 1040 (2004); https://doi.org/10.1038/sj.gt.3302265.
61. J.Y. Reginster, A. Neuprez, C. Beaudart, M.P. Lecart, N. Sarlet, D. Bernard, S. Disteche and O. Bruyere, *Drugs Aging*, **31**, 413 (2014); https://doi.org/10.1007/s40266-014-0179-z.
62. K.W. Ng and T.J. Martin, *Curr. Opin. Pharmacol.*, **16**, 58 (2014); https://doi.org/10.1016/j.coph.2014.03.004.
63. R. Loser, M. Nieger and M. Gutschow, *Crystals*, **2**, 1201 (2012); https://doi.org/10.3390/cryst2031201.
64. J. Schmitz, A.-M. Beckmann, A. Dudic, T. Li, R. Sellier, U. Bartz and M. Gütschow, *ACS Med. Chem. Lett.*, **5**, 1076 (2014); https://doi.org/10.1021/ml500238q.
65. Z. Bánóczi, A. Tantos, A. Farkas, Z. Majer, L.E. Dókus, P. Tompa and F. Hudecz, *J. Pept. Sci.*, **19**, 370 (2013); https://doi.org/10.1002/psc.2511.
66. L. Hedstrom, *Chem. Rev.*, **102**, 4501 (2002); https://doi.org/10.1021/cr000033x.
67. R. Zhang, J.P. Durkin and W.T. Windsor, *Bioorg. Med. Chem. Lett.*, **12**, 1005 (2002); https://doi.org/10.1016/S0960-894X(02)00102-6.
68. A.-M. Faucher, M.D. Bailey, P.L. Beaulieu, C. Brochu, J.-S. Duceppe, J.-M. Ferland, E. Ghiro, V. Gorys, T. Halmos, S.H. Kawai, M. Poirier, B. Simoneau, Y.S. Tsantrizos and M. Llinàs-Brunet, *Org. Lett.*, **6**, 2901 (2004); https://doi.org/10.1021/ol0489907.
69. J.T. Randolph, X. Zhang, P.P. Huang, L.L. Klein, K.A. Kurtz, W. He, A.K. Konstantinidis, W.M. Kati and D.J. Kempf, *Bioorg. Med. Chem. Lett.*, **18**, 2745 (2008); https://doi.org/10.1016/j.bmcl.2008.02.053.
70. C. Gibson, S.L. Goodman, D. Hahn, G. Hölzemann and H. Kessler, *J. Org. Chem.*, **64**, 7388 (1999); https://doi.org/10.1021/jo9906173.
71. L.A. Kurian, T.A. Silva and D. Sabatino, *Bioorg. Med. Chem. Lett.*, **24**, 4176 (2014); https://doi.org/10.1016/j.bmcl.2014.07.046.
72. B. Peschke, M. Ankersen, B.S. Hansen, T.K. Hansen, N.L. Johansen, J. Lau, K. Madsen, H. Petersen, H. Thøgersen and B. Watson, *Eur. J. Med. Chem.*, **34**, 363 (1999); https://doi.org/10.1016/S0223-5234(99)80086-5.

73. S.V. Andurkar, C. Béguin, J.P. Stables and H. Kohn, *J. Med. Chem.*, **44**, 1475 (2001); https://doi.org/10.1021/jm000517l.
74. F.A. Steiner, J.A. Hong, M.R. Fischette, D.G. Beer, Z.S. Guo, G.A. Chen, T.S. Weiser, E.S. Kassis, D.M. Nguyen, S. Lee, J.B. Trepel and D.S. Schrump, *Oncogene*, **24**, 2386 (2005); https://doi.org/10.1038/sj.onc.1208376.
75. K.B. Sexton, D. Kato, A.B. Berger, M. Fonovic, S.H.L. Verhelst and M. Bogyo, *Cell Death Differ.*, **14**, 727 (2007); https://doi.org/10.1038/sj.cdd.4402074.
76. P.L. Durham and C.V. Vause, *CNS Drugs*, **24**, 539 (2010); https://doi.org/10.2165/11534920-000000000-00000.
77. B. Voigt, M. Krug, C. Schächtele, F. Totzke and A. Hilgeroth, *ChemMed Chem*, **3**, 120 (2008); https://doi.org/10.1002/cmdc.200700175.
78. V.L. Bessi, S.M. Labbe, D.N. Huynh, L. Menar, C. Jossart, M. Febbraio, B. Guerin, M. Bentourkia, R. Lecomte, A.C. Carpentier, H. Ong and S. Marleau, *Cardiovasc. Res.*, **96**, 99 (2010); https://doi.org/10.1093/cvr/cvs225.
79. M. Laurencin, M. Amor, Y. Fleury and M. Baudy-Floc'h, *J. Med. Chem.*, **55**, 10885 (2012); https://doi.org/10.1021/jm3009037.
80. A.J. Kh. Atia and S.S. Al-Mufrgeiy, *Am. J. Chem.*, **2**, 150 (2012); https://doi.org/10.5923/j.chemistry.20120203.09.
81. C.B. Bourguet, P.L. Boulay, A. Claing and W.D. Lubell, *Bioorg. Med. Chem. Lett.*, **24**, 3361 (2014); https://doi.org/10.1016/j.bmcl.2014.05.095.
82. C.B. Bourguet, A. Claing, A.S. Laporte, T.E. Hébert, S. Chemtob and W.D. Lubell, *Can. J. Chem.*, **92**, 1031 (2014); https://doi.org/10.1139/cjc-2014-0289.
83. T. Albers, D.L. Watkins, A.F. Gameiro, V. Povstyanoy, M.V. Povstyanoy and I.O. Lebedyeva, *Top. Heterocycl. Chem*., **43**, 95 (2016); https://doi.org/10.1007.7081_2015_182.
84. M.A. Elsawy, I.G. Tikhonova, L. Martin and B. Walker, *Protein Pept. Lett.*, **22**, 836 (2015); https://doi.org/10.2174/0929866522666150622101626.
85. C. Redouane, M. Bouhaous, A. Naser and J.K. Muleng *Asian J. Org. Med. Chem.*, **1**, 33 (2016); https://doi.org/10.14233/ajomc.2016.AJOMC-P14.
86. K. Kasper, Arts and Sciences Undergraduate Research Theses and Honors Research Theses (2017); http://hdl.handle.net/1811/80636.
87. A. Zega and U. Urleb, *Acta Chim. Sol.*, **49**, 649 (2002).
88. P.K. Deb, I.H. Ooi, D. El-Rabie, F.O. Shuaib and R. Rajasingam, *Asian J. Chem.*, **27**, 3137 (2015); https://doi.org/10.14233/ajchem.2015.18962.
89. C.J. Gray, M. Quibell, N. Bagget and T. Hamerie, *Chem. Biol. Drug Des.*, **40**, 351 (1992).
90. M. Quibell, W.G. Turnell and T. Johnson, *J. Chem. Soc.*, *Perkin Trans. 1*, 2843 (1993); https://doi.org/10.1039/p19930002843.
91. F. Andre, G. Boussard, D. Bayeul, C. Didierjean, A. Aubry and M. Marraud, *J. Pept. Res.*, **49**, 556 (1997); https://doi.org/10.1111/j.1399-3011.1997.tb01163.x.
92. C. Frochot, R. Vanderesse, A. Driou, G. Linden, M. Marraud and M.T. Cung, *Lett. Pept. Sci.*, **4**, 219 (1997); https://doi.org/10.1007/BF02442879.
93. M. Liley and T. Johnson, *Tetrahedron Lett.*, **41**, 3983 (2000); https://doi.org/10.1016/S0040-4039(00)00534-7.
94. W.D. Lubell, J.W. Blankenship, G. Fridkin and R. Kaul, Science of Synthesis, Chap. 21.11, Chemistry of Amides, Thieme, Stuttgart, pp. 713-809 (2005).
95. D. Boeglin and W.D. Lubell, *J. Comb. Chem.*, **7**, 864 (2005); https://doi.org/10.1021/cc050043h.
96. N.S. Freeman, M. Hurevich and C. Gilon, *Tetrahedron*, **65**, 1737 (2009); https://doi.org/10.1016/j.tet.2008.11.038.
97. Y. Garcia-Ramos, C. Proulx and W.D. Lubell, *Can. J. Chem.*, **90**, 985 (2012); https://doi.org/10.1139/v2012-070.
98. C. Proulx and W.D. Lubell, *J. Org. Chem.*, **75**, 5385 (2010); https://doi.org/10.1021/jo100957z.
99. D. Sabatino, D.C. Proulx, P. Pohankova, H. Ong and W.D. Lubell, *J. Am. Chem. Soc.*, **133**, 12493 (2011); https://doi.org/10.1021/ja203007u.
100. Y.-S. Ho, D. Chun-Hei Poon, T.-F. Chan and R. Chuen-Chung Chang, *Curr. Pharm. Des.*, **18**, 15 (2012); https://doi.org/10.2174/138161212798919039.
101. Y.G. Ramos and W.D. Lubell, *J. Pept. Sci.*, **19**, 725 (2013); https://doi.org/10.1002/psc.2572.
102. M. Traore, N.D. Doan and W.D. Lubell, *Org. Lett.*, **16**, 3588 (2014); https://doi.org/10.1021/ol501586y.
103. N.-D. Doan, J. Zhang, M. Traoré, W. Kamdem and W.D. Lubell, *J. Pept. Sci.*, **21**, 387 (2015); https://doi.org/10.1002/psc.2711.
104. A.F.S. Barreto, V.A. Santos and C.K.Z. Andrade, *Beilstein J. Org. Chem.*, **12**, 2865 (2016); https://doi.org/10.3762/bjoc.12.285.
105. S. Besret, N. Ollivier, A. Blanpain and O. Melnyk, *J. Pept. Sci.*, **14**, 1244 (2008); https://doi.org/10.1002/psc.1063.
106. N. Ollivier, S. Besret, A. Blanpain and O. Melnyk, 30th Edition of European Peptide Symposium, Helsinki, pp. 1-05-179, 174-175 (2008).