AZAPEPTIDES

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Abstract

This review gives an overview on recently published methods for the synthesis, conformational properties and biological action of the promising peptidomimetic compounds, azapeptides.

Introduction

Peptidomimetics have gained enormous popularity and relevance in recent years because they can mimic a natural peptide, retaining the main biological effect of the latter, while, at the same time, improving any undesirable therapeutic characteristics such as poor bioavailability, poor metabolic stability and receptor selectivity. In recent years numerous structural modifications, involving both the peptide backbone and the amino acid side chains, have been considered and proved to be promising for future development.[1-3]

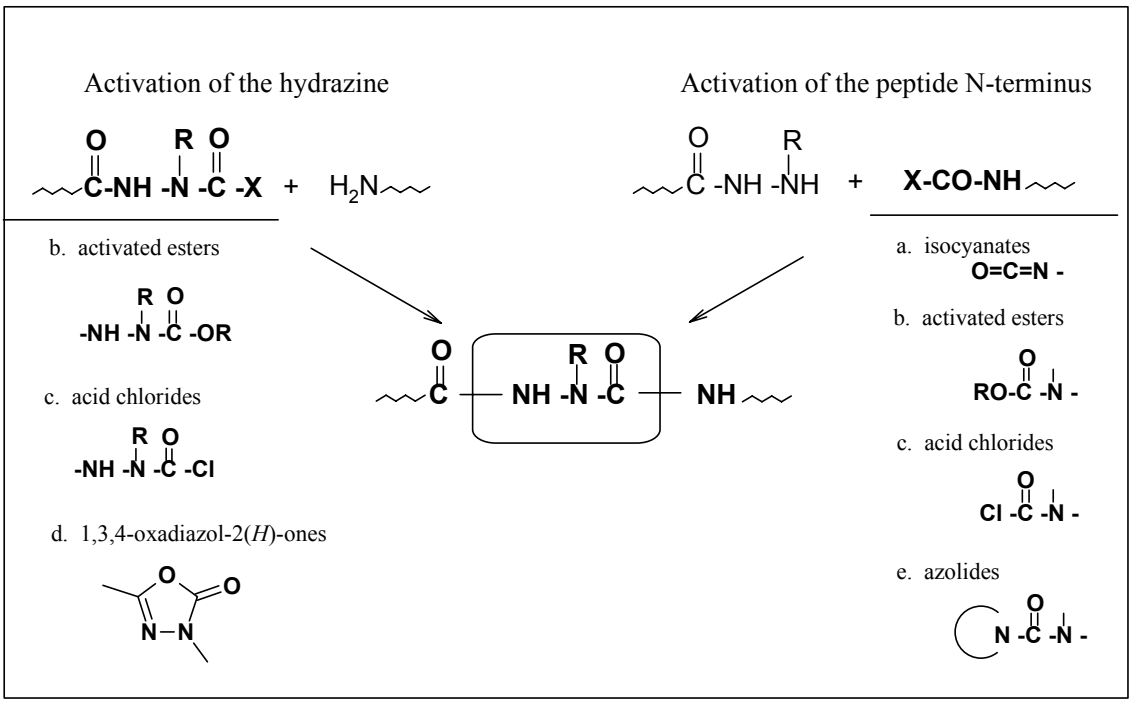
Among these modifications, azapeptides, formed by the replacement of the C^{α} of amino acid residues with a nitrogen atom, are promising peptidomimetic compounds. Azaamino acids impart a unique conformational property to peptide structure because of the loss of chirality and reduction of the flexibility of the parent linear peptide.[4] The peculiar conformational properties make azaamino acids an attractive tool for drug design based on specific secondary structure in peptides and proteines. Hess et al. were the first to replace an amino acid residue in a natural peptide by an azaamino acid.[5] Since then, azapeptides have been actively developed by several groups for the design of hormone analogues, protease inhibitors and active site titrants.

One of the advantages of azapeptides is their unproblematic synthesis allowing retention of the side chain in the proteinogenic amino acid.

Synthesis

Since N–N(R)CO units are generally components of substituted semicarbazides (C–terminal azaamino acid esters are exceptions), the construction of azapeptides from substituted hydrazines or hydrazides by the formal introduction of carbonyl group between two nitrogen atoms can be carried out very simply. Incorporation of an aza–residue in a peptide chain is a combination of hydrazine and peptide chemistry.[4]

The various possibilities for the synthesis of azaamino acid residues are shown in Scheme 1.

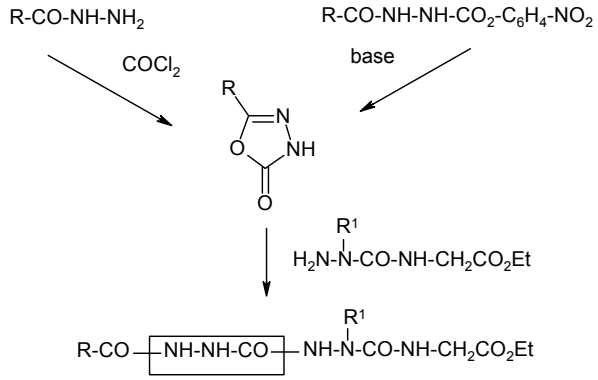


Scheme 1. Possible routes for the synthesis of azaamino acid residues and pathways for their incorporation into a peptide chain

a. The most frequently used method involves adding adequately protected hydrazines to an isocyanate obtained by the action of phosgene, or activated aryl chloroformates or carbonates, on the peptide N–terminus.[4,6,7]

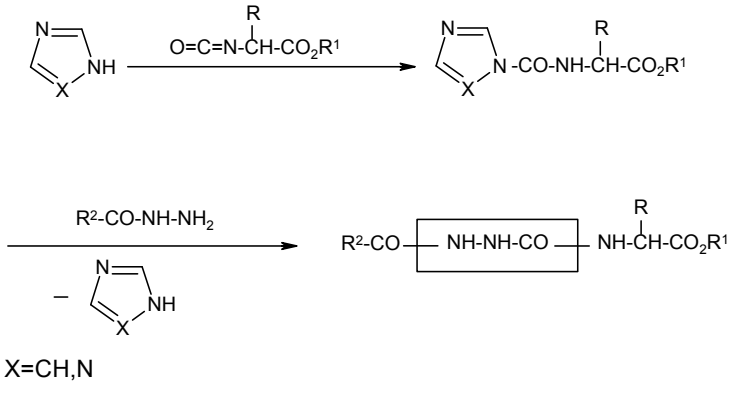
b. Another method is based on activated aryl esters.[6,7] C–Activated esters are prepared by reacting hydrazides with carbonochloridic esters, and N–activated esters by reaction of the free amino group of the N–terminal amino acid or azaamino acid residues with the corresponding carbonochloridic esters and carbonic diesters.[4]

c. In the acid chloride method, *Z*–hydrazine is reacted with phosgene to form *Z*–azaglycine chloride. Coupling requires a high temperature and yields a product as polyazaglycine mixture. *Z*–Azaleucine, for example is more stable and gives corresponding azapeptide derivative.[4,9]



Scheme 2.

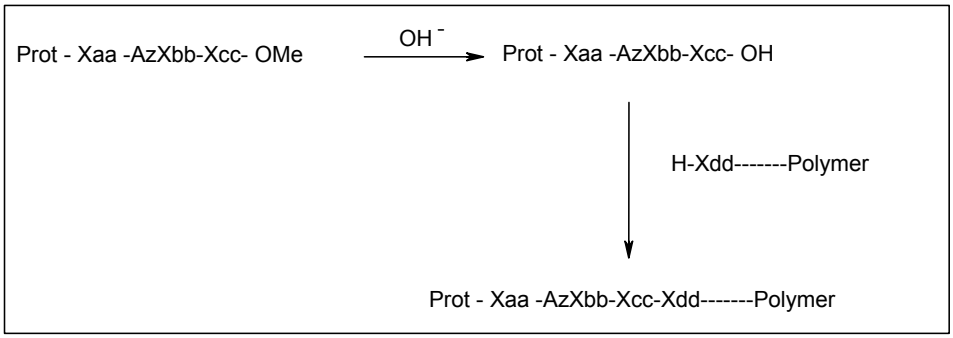
d. The next method is to react 1,3,4-oxadiazol-2(3*H*)-ones, which are alkyl–, aryl–, and *Z*–amino–alkyl–substituted in the 5–position, with various N–unprotected azadipeptides, with ring opening and addition to aza tri– and tetrapeptides with directly linked azaamino acid residues. Heterocycles can be derived by the reaction of the corresponding hydrazide with phosgene, or from azaamino acid 4-nitrophenylesters with bases.[4,8,10,11] (Scheme 2)



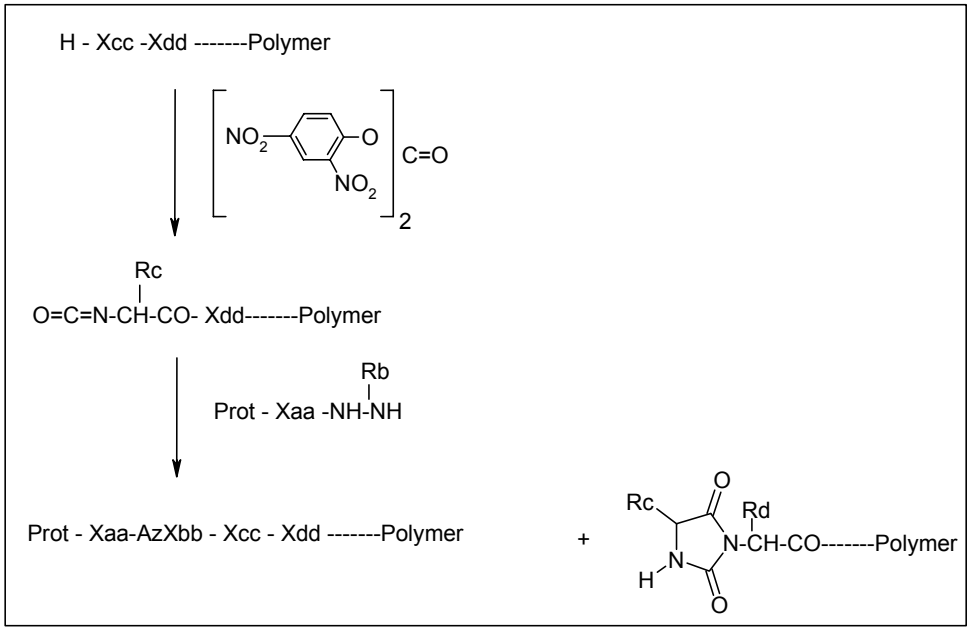
Scheme 3.

e. A further way of synthesizing azapeptides is to react azolides (imidazolides and 1,2,4-triazolides) with hydrazides, yielding imidazole or 1,2,4-triazole.[4,12,13] (Scheme 3)

Azapeptides have recently been obtained by solid–[14-18] and liquid–[16] phase synthesis. The synthesis of longer azapeptides of biological interest is best carried out using solid–phase procedures. One strategy consists of coupling an aza–tripeptide synthon to the N–terminus of a resin–bonded peptide. In this method the problem is partial epimerization of the Xaa residue during saponification of the C–terminal ester in the synthon, and of the Xcc residue (except for glycine or proline) during coupling of the synthon to the resin. (Scheme 4)



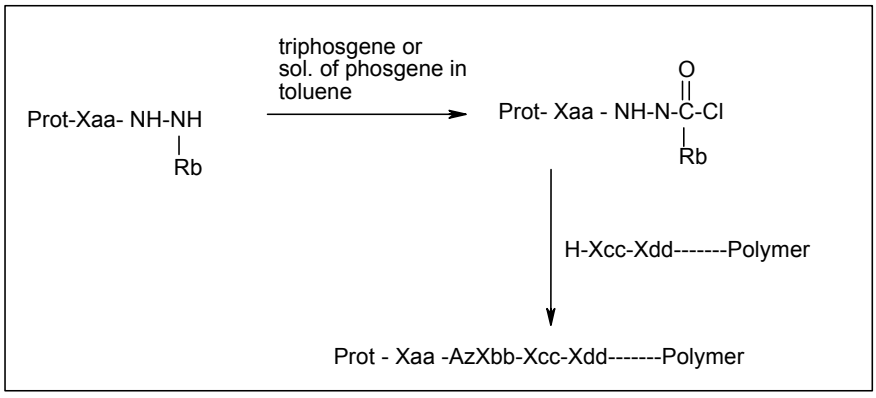
Scheme 4. Solid phase procedure for introduction of an aza–residue in azapeptide chain



Scheme 5. Solid phase procedure for introducing an aza–residue into an azapeptide chain

The preferred strategy is the conversion of the resin–bound N–terminal amino group into isocyanate by using bis(2,4-dinitrophenyl) carbonate in the presence of base.

(Scheme 5) Reaction with a protected amino acid hydrazide, bearing the appropriate side–chain group Rb on the β–nitrogen, then completes the aza structure.[14,15,18] Unfortunately, the N–terminal isocyanate is more or less partially converted into hydantoin moiety regardless of the Boc[14,15] or Fmoc[15,18] strategy used. Hydantoin formation arises as a result of intramolecular nucleophilic attack on the activated intermediate by a secondary nitrogen from the preceding C–terminal peptide backbone chain.[14,18] (Scheme 5) To eliminate this side reaction, a reversible amide bond protecting group, *N*-2-hydroxy-4-methoxybenzyl (Hbm), was used.[18] The transformation of the N–protected hydrazines into activated carbazic acids seems promising, since resin–bound peptides can be treated with an excess of activated agent to force complete reaction. The reagents usually used for the carbonylation–activation step are either nitrophenylchloroformates or bis(2,4-dinitrophenyl) carbonate. The resulting nitrophenylcarbazates are not very reactive and require long coupling times and, mostly, high temperature, thus giving rise to poor yields and numerous side products. Triphosgene (bis(trichlorophenyl) carbonate)[16] or solutions of phosgene in toluene[17] have been used as mild and efficient carbonylating agents for azapeptide synthesis in both solid– and liquid– phase procedures.(Scheme 6)



Scheme 6. Solid phase procedure for introducing an aza–residue into an azapeptide chain

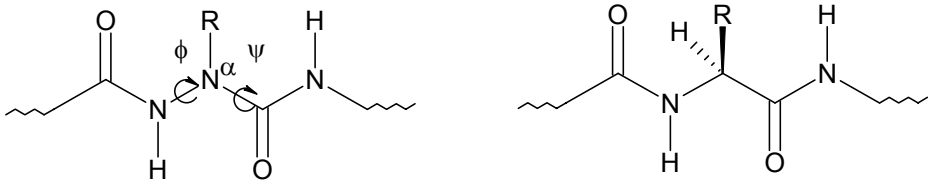
In solution phase synthesis for this step, bis(pentafluorophenyl) carbonate was also used because pentafluorophenol is a powerful electron–withdrawing group, while the fluoro substituents minimize steric problems.

Conformational properties

The biological activity of peptides is strongly dependent on their 3D molecular structure. Because bioactive peptides must adopt a specific conformation in order to bind to an acceptor molecule, the exploration of a binding conformation is one of the most important processes involved in the effort to obtain potent and selective therapeutic agents. Stabilization of particular conformational features by the introduction of geometrical constraints may be of major interest for the establishment of structure–activity relationship.

Substitution of nitrogen for the C^{α} leads to significant changes in the structure and dynamics of the peptide backbone. Azaamino acids were expected to provide a unique conformational property to the protein or peptide backbone because of loss of asimmetry associated with the C^{α} and free rotation of the C^{α}–C bond in the amino acid. This might lead to removal of the flexibility of the parent linear peptide.

Introduction of an N^{α} atom generates two structural elements: hydrazine, whose conformation is described by the peptide torsion angle φ, and urea constituent, where the peptide rotation angle ψ indicates the various conformation possibilities. (Fig. 1)[19]



a b

Figure 1. Azamino acid (a) and *L*-amino acid (b) constituents

In order to understand the conformation of azapeptides, several model systems were examined. The most interesting structure variation in azapeptide sequences when compared with peptides is the hydrazine moiety. The conformations of hydrazine and its 1,2-diformyl derivative, which resemble hydrazine moiety in the azapeptides, were

systematically investigated in different quantum chemical studies.[19-23] Calculations which have been used to determine the minimum energy structures of 1,2-diformyl hydrazine and its N–substituted derivatives show that the global minimum is the nonplanar structure in which the nitrogen lone pairs are perpendicular to one another. However the energy barrier required for (*Z,Z*)-diformylhydrazine to adopt a planar structure is very low (due to attractive intramolecular hydrogen bonds between the N–hydrogens and the carbonyl oxygens). When the nitrogens are substituted, these hydrogen bonds are lost and the planar structure becomes less stable relative to the twisted rotamer.[24] The most important conclusions which could be drawn from the well–known planar structure for urea and from hydrazine and 1,2-diformylhydrazine results, concern the peptide torsion angles which should be in azapeptides expected around 90° for φ and about 180° or , alternatively, 0° for ψ.[19] It was found out that these values of the steric permited torsion angles correspond to some of the torsion angles for the major types of β–turns.

On the many peptide secondary structures, β–turns are at the centre of interest in drug design since they have been identified as bioactive conformations in many peptides. β–Turns are formed by four amino acids. They are classified into several types according to the torsion angles of the second and third residues (*i*+1 and *i*+2). Additionally, they contain a hydrogen bond between the carbonyl oxygen of residue *i* and the amide hydrogen of residue *i*+3.[25] (Fig.2)

Turn	Φ_{i+1} (°)	Ψ_{i+1} (°)	Φ_{i+2} (°)	Ψ_{i+2} (°)
βI	-60	-30	-90	0
βI'	60	30	90	0
βII	-60	120	80	0
βII'	60	-120	-80	0
βIII	-60	-30	-60	-30
βIII'	60	30	60	30

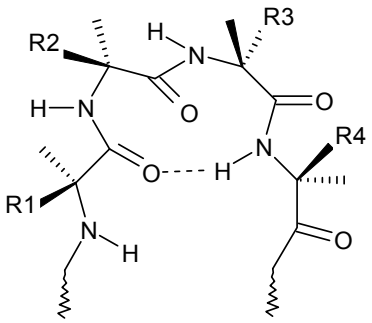


Figure 2. Structure of β–turn and standard torsion angles for the major types of β–turns.

In order to better understand typical elements of secondary structure in peptides, such as β–turns and helices, various model azapeptide analogues have been examined.

The conformational characterization of azaamino acids in peptides has been limited to the several models for azapeptides associated with the proline residue.[26-32] These azaamino acid–containing peptides associated with proline residue appeared to be strong β–turn–inducing motifs. However, it is important to note that the role of azaamino acids as β–turn motifs is somewhat ambiguous because the proline residue itself is known to be strong β–turn–inducing motif.

Theoretical studies on azapeptide models, For-azaXaa-NH_2 (Xaa = Gly, Ala, Leu) showed that the preferred conformations for these residues are limited to the range of stereochemically allowed dihedral angle ($\varphi = \pm 90 \pm 30°$, $\psi = 0 \pm 30°$ or $\pm 180 \pm 30°$) unlike the amino acid residues. Among these characteristic dihedral angles of amino acids in peptides the dihedral angle ($\varphi = \pm 90 \pm 30°$, $\psi = 0 \pm 30°$) appeared to be the β–turn motif for the *i*+2 residue.[33] Recent studies of model peptides containing various azaamino acids using ab initio calculations and NMR spectroscopy, also indicate that the preferred backbone conformations of azaamino acids in peptides are similar regardless of the side–chain functional groups.[33] Therefore, the specific conformational properties of azaamino acid residues, make them a very useful tool for secondary structure design in peptides and proteins.

The replacement of an C^{α} by N in a biologically active peptide will doubtless affect its absorption, transport, distribution, enzyme or receptor binding, and metabolic stability in the organism.[4] Azapeptides are unable to adopt the extended peptide conformation characteristic of β–sheet structures. For example, chymotrypsin–like proteases, which bind the peptide substrate in the extended conformation forming an antiparallel β–sheet structure, are unable to cleave azapeptides, making them stable to this type of protease.[19]

This replacement results in an additional possibility for the formation of hydrogen bonds.[4] The acidity of the NH group attached to the N^{α} has been shown to be higher than in non-aza peptides, thus favouring stronger H–bonding. On the other hand, it has been found to prevent protonation from occurring at physiological pH.[4]

These findings suggest that azapeptides could be useful for the design of drug candidates and molecular devices.

Biological action

The presence of an azaamino acid residue may increase the biological activity and/or improve the pharmacokinetic properties of the parent peptide.[4]

Hess et al. synthesized modified angiotensin II derivative with reduced activity but longer duration of action.[5] It was not until 1995 that Gante et al. synthesized the first all–aza analogue of a natural peptide.[35]

In analogues of the peptide hormone oxytocin, both losses and increases of efficacy were observed depending on the position of the incorporated azaamino acid residue.[36,37]

Some aza–analogs of eledoisin are more potent than the original and a prolongation of action was observed.[36-39]

Aza–analogues of the ACE inhibitors enalaprilate and lisinopril have been made with strong enzyme inhibiting effects comparable with the original inhibitors.

Particularly good results were found with aza analogues of the ovulation–inducing hormone luliberin.[40-49] The most active compounds were about 100 times as potent as luliberin and one product from this series was introduced into the pharmaceutical market as a drug for treating carcinoma of the prostate (Zoladex®). In addition effective antagonistic analogues with ovulation–inhibiting activity have been prepared.

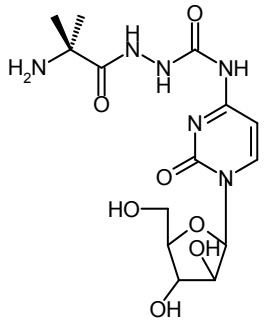
A great problem of the enkephaline series is their rapid degradation *in vivo* and the existence of multiple receptor subunits. With exchange of amino acids for the corresponding aza–analogs in various positions activity and selectivity was increased using a molecular combination of opioid alkaloids linked to fragments of Leu–enkephalin via azaglycine residue.[50-52]

Introduction of an aza residue near the scissile peptide bond could give a compound with competitive or mechanism based inhibitory activity. Inhibition of serine proteases by the activated azapeptide esters and simpler azaamino acid derivatives is believed to be due to acylation of the active site serine residue. The nitrogen atom of the aza–substrate adjacent to the acyl carbonyl group gives a special stability to the acyl–enzymes, which are less reactive towards deacylation than normal acyl enzymes. As a result, enzyme accumulates in a catalytically inactive form.[53-60] Azaamino acid derivatives without reactive leaving groups do not acylate serine proteases, but simply

act as reversible inhibitors.[61] Enzyme inhibitors and/or active site titrants with azapeptide structures have been developed for serine proteases[55] such as trypsin, thrombin and elastase[61-63] and also for cysteine proteases.[64,65] A series of azaproline dipeptides were synthesized as possible active site directed inhibitors of two proline–specific serine proteases, dipeptidyl peptidase IV and prolyl oligopeptidase. Some compounds show moderate activity.[66] Azapeptide analogs containing a (hydroxyethyl)hydrazine isostere led to potent HIV–1 protease inhibitors with high antiviral activity.[67] Peptidyl carbazate esters, such as Boc-VLFazaG-Oph, inhibit serine and cysteine proteases by carbamoylating the active site nucleophile. A serie of azapeptides of this type indicated inhibitory activity on human rhinovirus 3C protease.[68] Haloacetyl azaglutamine tetrapeptides and a sulfenamide derivative react irreversibly with the hepatitis A virus (HAV) 3C proteinase active site thiol.[69]

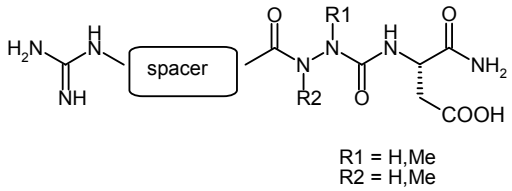
Renin inhibitors with statine structure, together with an azaamino acid residue, have been prepared [70] and azaamino acid residues were used in the design of ACE inhibitors and β–lactamase inhibitors.[71]

Ara–C (cytosin arabinose) is a pyrimidine nucleotide analogue and one of the most effective anticancer drugs for the treatment of acute myelogenous leukemia. The major impediment to its more general use is the rapid metabolism of the drug in plasma. An azapeptide prodrug of *ara*–C (**1**) produced weak growth inhibition in cultured murine leukemia cells reflecting the slow release of active drug.[72]



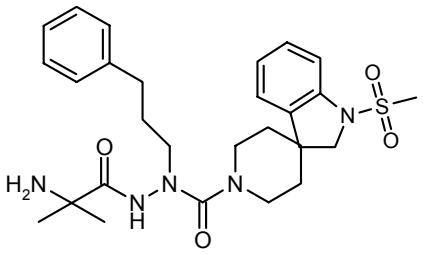
1

Insertion of azaglycine instead of glycine in the cell adhesion motif Arg-Gly-Asp (RGD) (**2**) demonstrated that both activity and selectivity can be influenced through the substitution pattern of the azabuilding block.[17]



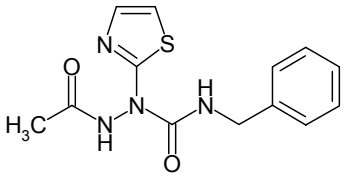
2

Aza analogues of known potent growth hormone secretagogues (**3**) with possible applications including treatment of burns, Turners syndrome, sleep enhancement and reduction of some age–related effects, were synthesized and their biological potencies were measured; some compounds showed good results. [73]



3

Certain aza analogues (**4**) of functionalized amino acids exhibited significant anticonvulsant activity in the maximal electroshock seizure test, but most are less potent than their amino acid counterparts.[74]

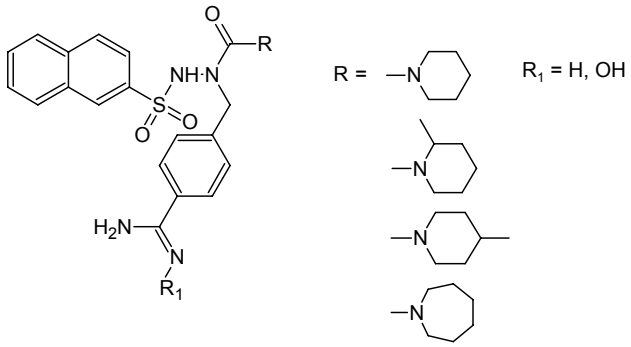


4

T cells play a pivotal role in the initiation, amplification and memory function of the mammalian acquired–immune response. It has been shown that substitution of one or more of the amino acids in an antigenic peptide bound to an MHC II (major histocompatibility complex class II) protein with azaamino acids can elicit a T–cell activation state different from that stimulated by the native peptide. AzaAla residues were singly substituted at each position of the hen–egg ovalbumin 325–339 (OVA) peptide that encompassed the sequence binding to MHC II. All aza–substituted peptides

showed detectable MHC binding, some were found to show T–cell activation potency equal to the native peptide and several were found to be weak or partial agonists.[75]

Thrombin plays a major role in thrombosis, which is one of the leading causes of cardiovascular disease and mortality in developed societies. An azaphenylalanine scaffold was incorporated into the central part of the argatroban–like low molecular weight thrombin inhibitor structure (**5**). Thrombin inhibitory activities and the anticoagulant potency of aza inhibitors are higher than those of the C–analogues. Some of these new compounds exhibit higher, or at least the same thrombin inhibitory activities as argatroban.[76,77]



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Povzetek

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