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Peptidomimetics – A Versatile Route to Biologically Active Compounds

Andreas Grauer[a] and Burkhard König*[a]

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Proteins are vital for basically every known organism. Therefore the investigation of their structure, the development of a deeper understanding of protein–protein interactions and the design of novel peptides, which selectively interact with proteins are fields of active research. Small peptides consisting of the 20 natural amino acids typically show high conformational flexibility and a low in-vivo stability which hampers their application as tools in medicinal diagnostics or molecular biology. One very versatile strategy to overcome such drawbacks is the use of peptidomimetics. These are small molecules which mimic natural peptides or proteins and thus produce the same biological effects as their natural role models. As the field of peptidomimetics is developing fast this review can only provide selected approaches together with examples and is not intended to be comprehensive. We focus on the discussion of amino acid modifications, backbone modifications, global restrictions by cyclisation and on synthetic backbone scaffolds.

1. Introduction

Proteins are omnipresent in the living world. The structure, function and metabolism of all cells and tissues rely on the presence of specific proteins. They are in some way the carrier of the live functions and can be found likewise in animal, plants and microorganism, for example in muscles (actin, myoglobin), in the blood (hemoglobin), in connective tissues, sinews and ligaments (collagen, elastin) to mention only a very few. But not only is their occurrence manifold, their functions are also very diverse for example in the immune response, as hormone- or neurotransmitter-receptors b so as enzymes and regulators.[1]

One way how nature controls these protein functions within living cells is by regulating protein–protein interactions. These interactions exist on nearly every level of cellular function which means they are of key importance for virtually every process in a living organism. They regulate for example the signal transduction pathway important for the transportation of information through the organism and from the exterior of cells to the inside, the transport machinery across the biological membranes, the regulation

[a] Institute für Organische Chemie, Universität Regensburg, 93040 Regensburg, Germany
Fax: +49-941-943-1717
E-mail: Burkhard.Koenig@chemie.uni-regensburg.de

Burkhard König received his doctorate in 1991 from the University of Hamburg under the direction of Professor A. de Meijere. He continued his scientific education as a postdoctoral fellow with Professor M. A. Bennett, Canberra, and Professor B. M. Trost, Stanford. In 1996 he obtained his "Habilitation" at the University of Braunschweig. Since 1999 he is full professor of organic chemistry at the University of Regensburg. His current research interests include the development of synthetic receptors for peptide and protein recognition.

Andreas Grauer was born in Neu-Ulm, Bavaria, Germany, in 1979. He studied chemistry at the University of Regensburg and received his PhD at this university in the group of Professor B. König in 2009.

of gene expression or the muscle contraction. Protein–protein interactions also play a decisive role in biological processes and their disregulation leads to diseases like Creutzfeld-Jacob, Alzheimer, cancer or AIDS.[2]

In the same way that the structure analysis and the development of a deeper understanding of protein–protein interactions are fields of active research, the de novo design of natural occurring or novel peptides able to interact with proteins is also being investigated.[3] Synthesis methods like the solid-phase peptide synthesis (SPPS) developed by B. Merrifield made it possible to synthesize polypeptides with fifty or more amino acids in length in quantities making them available for pharmacological and clinical testing as well as for use as drugs or in diagnostics.[4] As a result, different new peptide-based drugs are nowadays available for the treatment of prostate and breast cancer, as HIV protease inhibitors or as ACE inhibitors to treat hypertension and congestive heart failures, to mention only a few.[5]

Despite the fact that such polypeptides based on natural amino acids are widely used as therapeutic agents, there are also problems connected with the use of natural peptides as drugs. The problems arise mainly from the low stability against proteolysis resulting in a short duration of activity in vivo and a low bioavailability, thus limiting the use of peptides as drugs. They also often show a decreased activity in comparison to the protein from which they are derived. A major difficulty in these studies is the conformational flexibility of most peptides and the high dependence of their conformations on the surrounding environment which often leads to a conformational equilibrium.[6]

The high flexibility of natural polypeptides is due to the multiple conformations that are energetically possible for each residue of the incorporated amino acids. Every amino acid has two degrees of conformational freedom, N–C^{α} (Φ) and C^{α}–CO (Ψ) resulting in approximately 9 (3^2) stable local conformations. For a small peptide with only 40 amino acids in length the number of possible conformations which need to be considered escalates to nearly 10^{40}.[7] Pioneering work by Ramachandran et al. resulted in the so-called Ramachandran plots which restrict the allowed values for the torsion angles Φ and Ψ and with that the conformational space accessible to the amino acids to about one-third of the total structural space. Nevertheless the remaining degrees of freedom still make a prediction of the structure extremely difficult. This extraordinary high flexibility of natural amino acids leads to the fact that short polypeptides consisting of the 20 proteinogenic amino acids rarely form any stable 3D structures in solution[8] (Figure 1).

There are only few examples reported in the literature where short to medium-sized peptides (< 30–50 amino acids) were able to form stable structures. In most cases they exist in aqueous solution in numerous dynamically interconverting conformations. Additionally, the number of stable short peptide structures, which are accessible is very limited because of the need to use amino acids having a strong structure inducing effect like for example helix-inducing amino acids as leucine, glutamic acid or lysine. In addition, it is questionable whether the solid state conformations determined by X-ray analysis are identical to those occurring in solution or during the interactions of proteins with each other.[10]

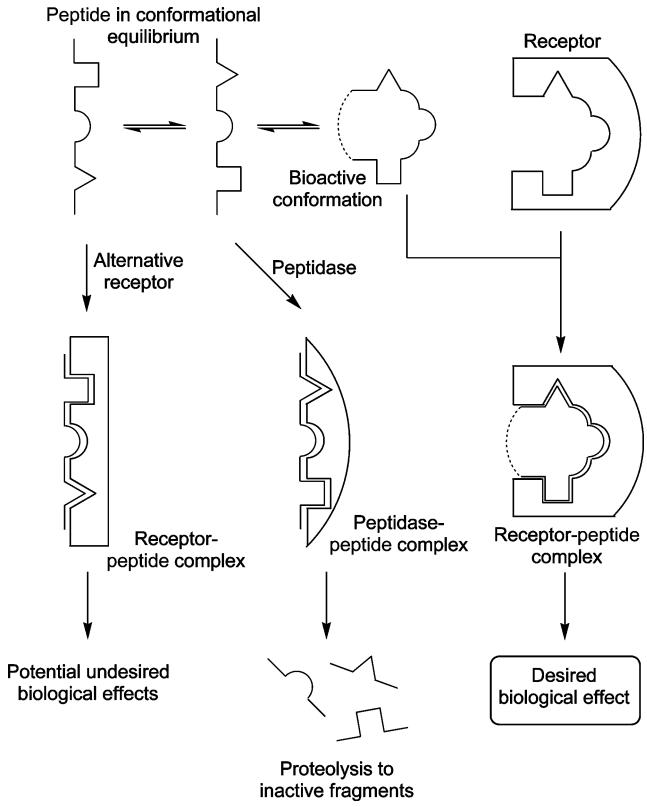


Figure 1. Peptides can exist in different conformations. By introducing conformational constraints into the peptide backbone (dashed line) the equilibrium can be shifted towards the conformation which leads to the desired biological effect. In addition, it might be possible to suppress undesired side effects or proteolysis (adapted from literature[9]).

2. Peptidomimetics

One way to overcome these disadvantages of natural short polypeptides is the use of peptidomimetics. These are small protein-like molecules designed to mimic natural peptides or proteins. These mimetics should have the ability to bind to their natural targets in the same way as the natural peptide sequences do from which their structure was derived and hence should produce the same biological effects. It is possible to design these molecules in such a way that they show the same biological effects as their peptide role models but with enhanced properties like a higher proteolytic stability, higher bioavailability and also often with improved selectivity or potency. This makes them interesting targets for the discovery of new drug candidates.[11–14]

For the development of potent peptidomimetics it is necessary to understand the forces that lead to protein–protein interactions with nanomolar or often even higher affinities. These strong interactions between peptides and their corresponding proteins are mainly based on side chain interactions indicating that the peptide backbone itself is not an

absolute requirement for high affinities. This allows chemists to design peptidomimetics basically from any scaffold known in chemistry by replacing the amide backbone partially or completely by other structures. Most important is that the backbone is able to place the amino acid side chains in a defined 3D-position to allow interactions with the target protein. Therefore it is necessary to develop an idea of the required structure of the peptidomimetic to show a high activity against its biological target. This can be achieved by conducting structure-activity relationship (SAR) investigations. By this method, the shortest active sequence in the natural protein–protein interaction can be identified. To do so, shorter analogues of the natural sequence are synthesized and tested against the target protein to identify the minimum sequence necessary for biological activity. The most significant parameters such as stereochemistry, charge and hydrophobicity can be examined by systematic exchange of single amino acids. As a result, the key residues which are essential for the biological activity can be identified. As next step the 3D arrangement of these key residues needs to be analyzed by the use of compounds with rigid conformations to identify the most active structure.[10,15] When a clear model of the moieties necessary for the interaction and their location in 3D space has been gathered, these elements can then be reassembled by the use of peptidic or non-peptidic structures to form a peptidomimetic with the same biological activity as the natural role model which it should replace.[16] This is a rather expensive and time-consuming method but the use of new techniques that allow the fast synthesis and analysis of receptor binding of a great variety of peptides allows the whole process to become more efficient.[17,18]

All in all, the development of peptidomimetics is based mainly on the knowledge of the electronic, conformational and topochemical properties of the native peptide to its target. Two structural factors are especially important for the synthesis of peptidomimetics with high biological activity. Firstly the mimetic has to have a convenient fit to the binding site and secondly the functional groups, polar and hydrophobic regions of the mimetic need to be placed in defined positions to allow the useful interactions to take place.[19]

As previously mentioned the major problem in this area of research is the conformational flexibility of most natural peptides and the high dependence of their conformation on the environment. One very successful approach to overcome these drawbacks is the introduction of conformational constraints into the peptide sequence. This can be done for example by the incorporation of amino acids which can only adopt a very limited number of different conformations or by cyclisation (main chain to main chain; side chain to main chain or side chain to side chain).[20]

In the following, a summary of approaches leading to peptidomimetics is given. Different approaches to the design of peptidomimetics will be presented together with a few select examples. However, due to the large number of different unnatural amino acids and peptidomimetics the overview can not be comprehensive. Therefore the following selection should be seen as an overview illustrating the importance and diversity in the design and the synthesis of peptidomimetics.

3. Amino Acid Modifications

Conformationally restricted and metabolically more stable peptidomimetics are obtained using unnatural amino acids. In principal, two different starting points exist for the modification of peptides at the amino acid level. One is the amino acid side chain which can be rigidified for example by the use of sterically demanding groups; the other is the backbone of the peptide.

3.1 Side Chain Modification

Side chains of natural amino acids are of great importance for the activity of proteins due to their various functional groups which allow them to interact with other peptides or proteins. The problem hereby is their quite high conformational flexibility with energy barriers of rotation around their torsion angles χ^1 (C^α–Cβ bond), χ^2 (C^β–C^γ bond), etc. of normally less than 8 kcal/mol. Therefore they can rotate freely at physiological temperatures, with the exception the proline which is restricted due to the five-membered ring system.[21] In order to derive more information about the interactions of peptides with proteins, nucleic acids, other peptides, lipids and sugars in biological systems, side chain conformational restriction can be a useful tool in the design of peptidomimetics.[22]

3.1.1 β-Substitution

β-Substituted analogues of the naturally occurring amino acids are one example for rigidification in the side chain. Three of the natural 20 amino acids also show β-disubstitutions. These are valine **1** bearing two β-methyl substituents, isoleucine **2** which has a β-methyl and a β-ethyl substitution and threonine **3** which has a β-methyl and a β-hydroxy substitution (Figure 2). Both the isoleucine **2** and the threonine **3** have a β-chiral center. Various analogues of natural amino acids alkylated at the β-carbon can be found in literature. For example, the introduction of three methylgroups at the 2′-, 6′- and β-position of natural tyrosine hinders the free rotation around the C^β–C^γ bond and by that might result in the formation of biologically active conformations of type **4**.[23] Introduction of a methyl group into the side chains of phenylalanine or tryptophan leads to β-MePhe **5** and β-MeTrp **6**. Replacement of the natural amino acids Phe or Trp by their rigidified analogues **5** in the former and **6** in the latter case often results in a comparably higher activity and an increased biological stability of the modified peptides.[24] For example, the activity of short peptides which are active at the δ-opioid receptor was successfully altered by exchanging phenylalanine by its β-methylated analogue **5**.[25]

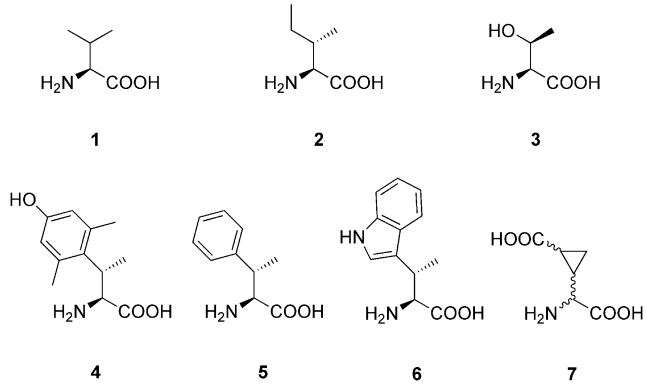


Figure 2. The three β-methylated natural amino acids valine **1**, isoleucine **2** and threonine **3** and some selected examples of unnatural β-methylated amino acids **4**–**7**.

Another interesting example is 2-(carboxycyclopropyl)-glycine (CCG) **7**. A library containing all possible diastereomers of compound **7** was used to investigate neuroreceptors activated by L-glutamic acid. Several types of such receptors are known until now and it has been suggested that L-glutamic acid interacts with different receptors adopting different conformations. This hypothesis was strongly supported by the findings resulting from the use of the CCG diastereomers.[26]

Besides β-disubstituted amino acids numerous other side-chain-modified amino acids were synthesized, for example the 2-naphthylalanine (**8**).[27] This compound in combination with other unnatural amino acids can be used for the synthesis of Gonadotropin-releasing hormone (GnRH) antagonists which show a high affinity to the receptor[28] (Figure 3).

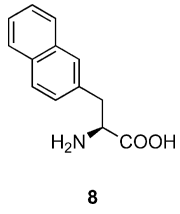


Figure 3. 2-Naphthylalanine (**8**), a building block for novel GnRH antagonists.

3.1.2 Proline Analogues

A further, thoroughly investigated group of side-chain-modified amino acids are analogues of the natural proline. Proline has a special place among the proteinogenic amino acids because of its secondary structure inducing and stabilizing properties and hence its influence on the biological behavior of peptides.[29] This is due to the cyclic structure of proline which restricts the conformational space of the peptide chain drastically[30] (Figure 4).

Besides proline itself, numerous derivatives were found in proteins as results of posttranslational modifications. *cis*-4-Methyl-L-proline (**10**) was discovered in hydrolysates of different leucinostatine.[31] These are peptide antibiotics which were isolated from several *Paecilomyces* strains and

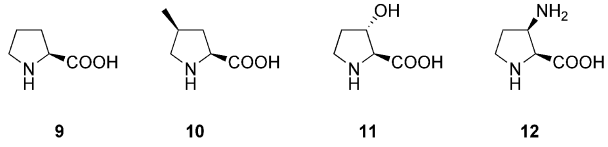


Figure 4. L-Proline (**9**) and some natural derivatives **10**–**12**.

which show antitumor activity as well as a wide antimicrobial spectrum against yeast, fungi and Gram-positive bacteria.[32] The proline derivative **11** (*trans*-4-hydroxy-L-proline) was first found in hydrolysates of Mediterranean sponge and later also in several other organisms.[33] The free amino acid **11** can also be found in human urine as a result of collagen metabolism. Also amino side chain modified proline derivatives like the *cis*-3-amino-L-proline (**12**) can be found in nature.[34] Additionally to the naturally occurring proline analogues countless proline derivatives were synthesized by the introduction of alkyl chains or aromatic groups in the 3-, 4- and 5-position of the ring.[35] Derivatives with additional heteroatoms and halogenated prolines were also synthesized and extensively studied.[35]

3.2 Backbone Modification

Apart from the side chains, the backbone of a peptide can also be modified in various ways by isosteric or isoelectronic exchange of units in the peptide or by the introduction of additional fragments.[36] Figure 5 summarizes the most important ways to modify the backbone of peptides at different positions.

Three main groups of modifications are known, with the first being the exchange of individual groups like, the replacement of the α-CH group by nitrogen to form azapeptides, the change from amide to ester bond to get depsipeptides and exchange of the carbonyl function by a CH_2 group. The second possibility is the extension of the backbone for example by one or two CH_2 groups resulting in polypeptides built from β-amino acids in the former and γ-amino acids in the latter case. A third widely used technique is the amide bond inversion, yielding a retro-inverso peptidomimetic. Carba, alkene or hydroxyethylene groups are also used in exchange for the amide bond. Most of these modifications do not lead to a higher restriction of the global conformations, but they have influence on the secondary structure due to the altered intramolecular interactions like different hydrogen bonding. Additionally, the length of the backbone can be different and a higher proteolytic stability occurs in most cases.

3.2.1 Azapeptides

Interesting and synthetically easy to approach are the so called azapeptides in which the α-CH group of the backbone was replaced isoelectronically by a nitrogen atom while the side chains remain untouched. The synthesis of azapeptides from substituted hydrazines or hydrazides can be carried out very easily.[38] When incorporating azaamino acid esters like compound **13** into a peptide chain azapep-

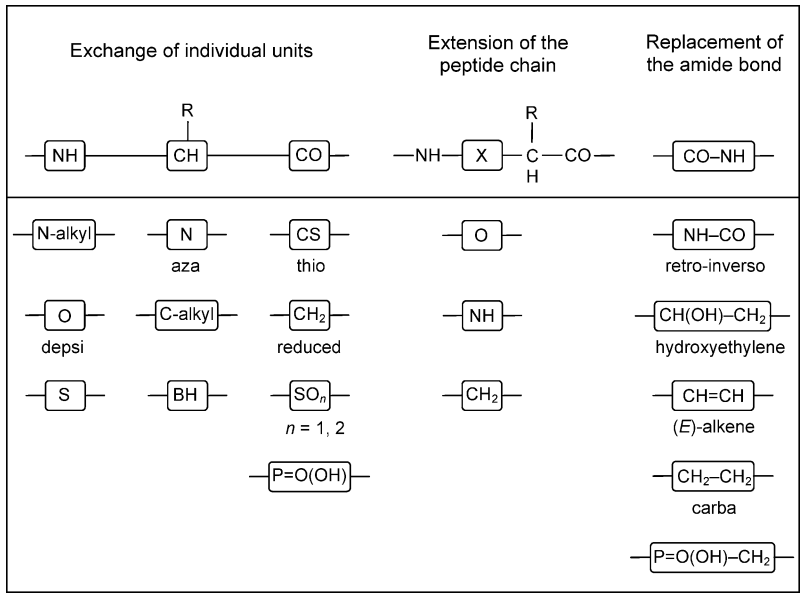
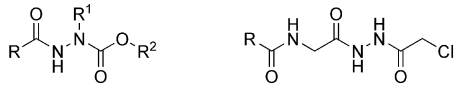


Figure 5. Some of the more common modifications to the peptide backbone (adapted from literature[37]).

tides are formed which can be therapeutically relevant inhibitors of serine and cystein proteases.[39] The same is true for the aza analogue **14** including an amino acid chloromethyl ketone. Both compounds **13** and **14** can be easily prepared by the acylation of hydrazines[40] (Figure 6).

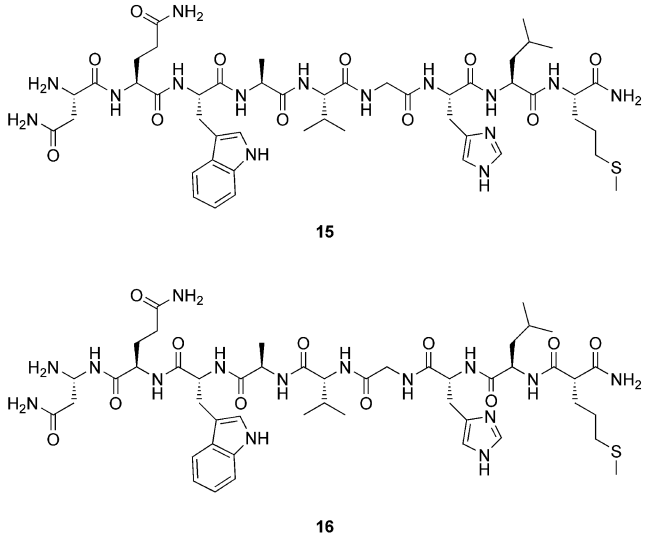


13 **14**

Figure 6. Peptides containing aza amino acids (R = peptide chain; R^1 = H, alkyl, benzyl; R^2 = alkyl, aryl).

3.2.2 Retro-Inverso Peptides

Another approach to peptidomimetics makes use of retro-inverso modifications.[41] These peptidemimetics can be synthesized in the same way as normal peptides just by exchanging the natural L-amino acids by D-amino acids and simultaneously reversing the sequence from *N*- to *C*-terminus. As shown in Figure 7 the side chain topologies of the natural peptide and the peptidomimetic are the same. Of course, the retro-inverso modification does not lead to a more highly constrained polypeptide. The major advantage over their natural models lies in the higher in vivo stability as they are no substrates for proteases any more. One disadvantage of these peptidomimetics is that with the inversion of their sequence the termini are also exchanged. This means that the positive charge located at the *N*-terminus of the natural sequence is replaced by a negative one in the peptidomimetic. The same is true for the *C*-terminus where the negative charge is replaced by a positive one. To avoid this, one can introduce modified termini or the retro-inverso structures can be incorporated into larger peptides.



15

16

Figure 7. A natural peptide sequence **15** (top) and the retro-inverso analogue **16** (bottom).

The nonapeptide **15** is an active agonist for bombesin while in contrast the retro-inverso analogue **16** shows no activity at all.[42] Unfortunately only a limited number of retro-inverso derivatives show a comparable activity to their native sequences which strongly indicates that the backbone although not always directly involved often has a large impact on the protein–protein binding.[43]

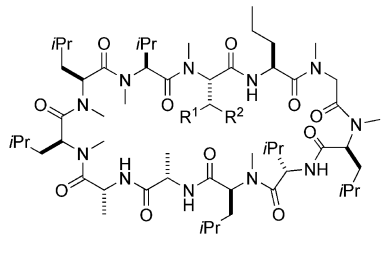
3.2.3 N-Alkylated Peptides

One very important modification of the peptide bond is the *N*-alkylation. The *N*-methylation for example is widely used by scientists but also occurs in the sequences of natural

peptides from different sources. Some of these compounds show high biological activity as antibiotics (e.g. monamycins,[44] echinomycin[45]), insecticides,[46] antitumor agents (e.g. bouvardin[47]) and antiinflammatory peptides (e.g. cyclomarins[48]).[49] Numerous peptides which show biological activity were modified by the use of *N*-methyl amino acids (NMAs), resulting in analogues with improved pharmacological properties such as metabolic stability, selectivity, enhanced potency and bioavailability.[50,51]

N-Methylated analogues of biologically relevant peptides have been intensively examined to derive more information about the structural effects of *N*-alkylation. They normally show increased proteolytic stability, increased membrane permeability (lipophilicity) and altered conformational preferences of the amide bond properties.[52] These effects result from the different property changes in the peptide going along with the introduction of *N*-methylation. Firstly, there are steric constraints introduced by the *N*-alkyl group,[53] which have an effect not only on the conformational freedom of the peptide backbone but also on the side chain of the neighbouring amino acid.[54] Secondly, the number of inter- and intramolecular hydrogen bonds decreases due to the removal of the backbone NH groups. And thirdly, the attached carbonyl group shows an increased basicity and decreased polarity.

In natural proteins only the *N*-methylation and *N*-benzylation were observed until now. One of the most outstanding examples of an *N*-methylated peptide is the cyclic undecapeptide cyclosporine A (Figure 8) with seven *N*-methylated amino acids. It was first isolated from *Trichoderma polysporum* and is a member of the cyclic peptide immunosuppressants which in addition shows good pharmacological properties and low toxicity. These properties make it one of the most successful drugs (Sandimmun, Neoral) used after organ transplantations.[55] Although the total synthesis of cyclosporine A was already accomplished by Wenger et al. in 1984,[56] the interest in this group of immunosuppressants has not decreased as the example of cyclosporine O shows which was synthesized on solid support by Thern et al. in 2002.[57]



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cyclosporin A (CsA): R^1 = OH; R^2 = $CH(CH_3)CH_2CH{=}CHCH_3$

cyclosporin O (CsO): R^1 = R^2 = CH_3

Figure 8. Structures of Cyclosporin A and O.

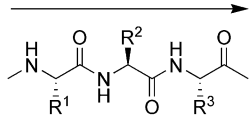
N-Alkylation is also a powerful and often used tool for the study of structure-activity relationships. Biologically active peptides often have insufficient pharmacological properties due to the low in vivo stability and their high flexibility. These properties disfavor their use as pharmacophores and in clinical studies. *N*-Alkylated amino acids which are introduced into peptide chains can help to overcome the shortfalls of their natural models due to the above mentioned effects.

Another important advantage of NMAs is that many of them are commercially available in protected form allowing the direct use of these building blocks in solid-phase peptide synthesis while several others can be easily synthesized.[58] By this method, libraries of natural product analogues can be produced in a short time. By successively alkylating each backbone NH and evaluating the biological activity of the produced compounds, the most active peptide can be found and with that the residues important for the interaction can be identified. The method is known as *N*-alkyl scan. This concept was invented by Sugano et al. who synthesized a series of analogues of the peptide H-Lys-Phe-Ile-Gly-Leu-Met-NH_2 in which each peptide bond was *N*-methylated one after the other. Screening of this series of five peptides on the depressor activity of rabbit blood revealed that the modification of Ile and Met lead to inactive compounds while the modification of Phe and Leu showed no effect. Using this information the peptidomimetic H-Lys-(Me)-Phe-Ile-Gly-(Me)Leu-Met-NH_2 was prepared. This compound showed full depressor activity while having a higher resistance against degradation.[59]

3.2.4 Peptoids

An interesting subgroup of the *N*-alkylated amino acids are peptoids that contain *N*-alkylated glycines linked in a peptide-like manner. The α-CH groups have been replaced by nitrogen atoms (like in aza peptides) and conversely, the NH groups by CH_2 groups (similar to carba peptides). As a result, the side chains and the carbonyl groups remain at their places, while the backbone CH and NH groups change their places.

Figure 9 illustrates that the sequence of peptoids are opposite to the ones of native peptides, which is similar to the retro-inverso peptidomimetics. Another difference to natural sequences is the loss of stereoinformation as the chiral α-carbon of natural amino acids is replaced by a CH_2 group and the side chains are now attached to nitrogen atoms. Peptoid analogues of most natural amino acids have been prepared and they can also be used in solid phase synthesis.[60] Analysis of peptoids has shown that they are stable to proteolytic enzymes and that they have an even higher conformational flexibility compared to natural peptides. Further studies revealed that peptoids like Ac-Nhtrp-Nharg-Nhtyr-NH_2[61] can be as active as their natural models (Ac-Trp-Arg-Tyr-OMe), in this case as an α-amylase inhibitor. An interesting aspect of this system is that the inverse peptoid sequence Ac-Nhtyr-Nharg-Nhtrp-NH_2 shows an even higher activity than the nature-like forward sequence.[37]



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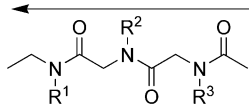

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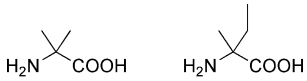
Figure 9. Comparison of a natural peptide sequence **18** with a topologically similar peptoid sequence **19**.

3.2.5 C^{α}-Tetrasubstituted α-Amino Acids

Other backbone modifications which have been extensively investigated in the last years are C^{α}-tetrasubstituted α-amino acids (or $C^{\alpha,\alpha}$-disubstituted glycines).[62] This kind of amino acids also occurs in natural sequences, for example in proteins in fungi. 50 years ago the first α-aminobutyric acid (Aib, **20**) was found in peptide sequences from a fungal source.[63] Because of their unique bioactivities and conformations, a fast growing group of peptide antibiotics, the so-called peptaibiotics, has regained particular interest.[64] As the majority of Aib- or isovaline- (Iva, **21**) containing peptides carry a *C*-terminal residue representing a 2-amino alcohol, they are referred to as peptaibols[65] (Figure 10).

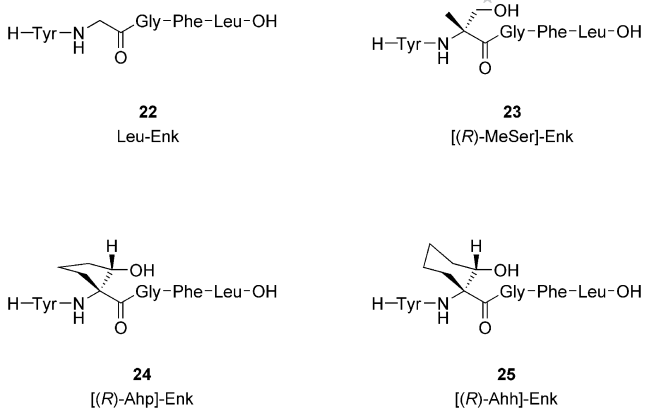


20 **21**

Figure 10. C^{α}-tetrasubstituted α-amino acids: α-aminobutyric acid (Aib, **20**) and isovaline (Iva, **21**) are found in natural products.

One interesting peptaibol example is the Alamethicin. It is an antimicrobial membrane-active peptide which is proposed as an alternative for the treatment of infections since the resistance to normal antibiotics becomes an increasing medical problem.[66]

Besides the natural occurring peptidomimetics based on C^{α}-tetrasubstituted α-amino acids, a rapidly increasing number of unnatural amino acids are developed by scientists and used for the synthesis of peptidomimetics.[67] Exchange of one glycine in the Leu-Enk sequence of **22**, which is an enkephalin (enkephalin is a pentapeptide involved in regulating pain and nociception in the body) by C^{α}-tetrasubstituted α-amino acids leads to the peptides **23**–**25** (Figure 11). All of these analogues possess a β-turn like structure in solution induced by the unnatural amino acid and show high activity with IC_{50} values between 0.01 nM and 0.4 nM.[68]



22 Leu-Enk

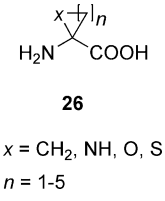
23 [(*R*)-MeSer]-Enk

24 [(*R*)-Ahp]-Enk

25 [(*R*)-Ahh]-Enk

Figure 11. Structures of the enkephalin **22** and three potent analogues **23**–**25**.

As mentioned C^{α}-tetrasubstituted α-amino acids are commonly used to introduce constrains into a peptide backbone through the stable quaternary α-carbon and the attached substituents.[69] One way to add even larger constraints is to covalently link the substituents at the α-carbon with each other leading to cyclic C^{α}-tetrasubstituted α-amino acids. This leads to a change in the chemical reactivity of the surrounding functional groups, like a reduced hydrolysis rate of an amide bond or ester group[70,71] (Figure 12).



26

x = CH_2, NH, O, S

n = 1-5

Figure 12. General representation of cyclic C^{α}-tetrasubstituted α-amino acids.

One representative of the group of cyclic unnatural amino acids are the C^{α}-tetrasubstituted tetrahydrofuran amino acids (TAAs) which were developed by König et al.[72] Attractive features of these amino acids are the easy accessibility in a four-step synthesis starting from commercially available starting materials. In addition the amino acids do not only possess a stable quaternary stereocenter at the α-carbon of the amino acid but also a second one at the β-carbon. An additional benefit is the variety of aromatic and aliphatic aldehydes which can be used in the ring-forming reaction leading to numerous different amino acids with functional groups in the amino acid side chain[73] (Figure 13).

The unnatural amino acid **27** was used by the same group for the synthesis of short peptides with an alternating sequence of *S*- or *R*-valine and a length of up to eight residues. The structure analysis of these peptides revealed a 3_{10}-helical structure for all peptides in solid state and in solution with the all-*S*-configured peptides **30** and **31** showing right-handed helices while the all-*R*-configured peptides **32**–**34** have the opposite handedness[74] (Figures 14 and 15).

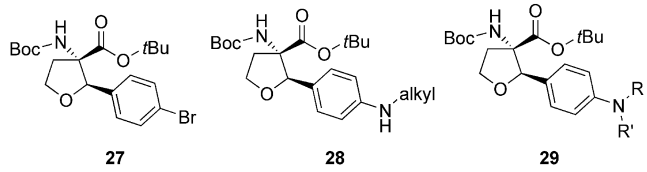


Figure 13. Selected examples **27**–**29** of C^{α}-tetrasubstituted tetrahydrofuran amino acids (TAAs).

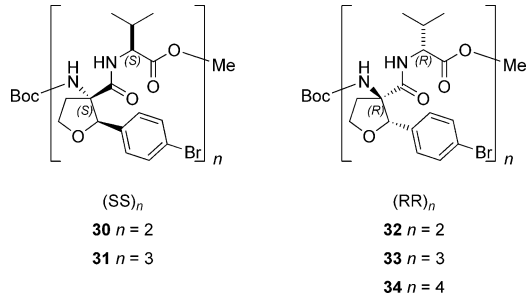


Figure 14. Helix-forming tetra-, hexa- and octapeptides prepared by König et al.

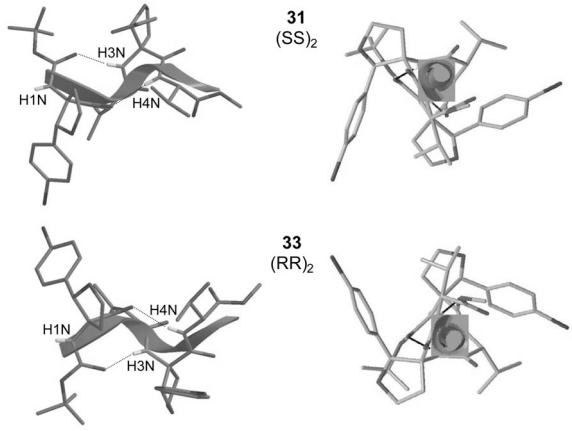


Figure 15. Crystal structures of the right-handed (top) and left-handed (bottom) helix-forming peptides **31** and **33** (view from the side on the left; view perpendicular to the helical axis on the right). Hydrogen atoms except NH-protons were omitted for clarity.

4. Introduction of Global Restrictions

Besides amino acid modifications several other methods for the preparation of highly active peptidomimetics exist. One example is the introduction of global restrictions into the peptide via cyclisation of the peptide strand. This typically results in a higher in vivo stability of the cyclic peptidomimetics compared to their linear analogues. Because of their reduced conformational flexibility they can be used to present divers functionalities in a defined and predictable manner. A variety of different techniques were developed for the synthesis of cyclic peptidomimetics. In principal three ways exist for the formation of cyclic analogues of natural peptides. The first is the connection of the *N*- with the *C*-terminus (head-to-tail), the second is to couple either the *C*- or the *N*-terminus with one of the side chains (backbone/side chain) and the third is to connect two side chains that are not involved in the interaction with other proteins with each other (side chain/side chain).[75]

4.1 Head-to-Tail Cyclisation

Although new ways were developed for the head-to-tail cyclisation of peptides, most of them are still formed by the cyclisation of activated precursors in solution phase, which means in most cases the use of standard peptide coupling conditions using HOBt/HBTU or HOAt/HATU as activating reagents. One example for the head-to-tail cyclisation of natural products is the previously shown cyclosporine O (**17**, see Figure 8).[76] This methodology was further applied to the preparation of numerous cyclic RGD peptidomimetics, in which the RGD (Arg-Gly-Asp) is flanked by other amino acids to form a ring system. These compounds offer the possibility to present the side chains of the RGD sequence in a specific conformation. Amongst others these cyclopeptides have been developed as fibrinogen receptor antagonists or as selective $\alpha_V\beta_3$ integrin antagonists for treatment of human tumor metastasis and tumor induced angiogenesis, bone remodelling and osteoporosis.[77]

4.2 Side Chain-to-Side Chain Cyclisation

The most common methods to lock peptide chains into defined structures like α-helices by the formation of cyclic analogues are the disulfide linkage via the oxidation of two Cys residues and the formation of amide bonds between the side chain residues of the amino acids Lys and Asp/Glu. Disulfide bridging was used for example in the development and synthesis of the cyclic enkephalin analogue **40** which is active at the δ-opiate receptor. In this example the ring system was formed by linking two penicillamine residues via a disulfide bridge with each other (Figure 16).

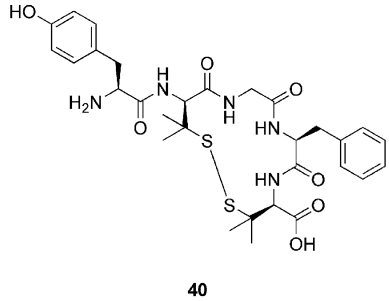
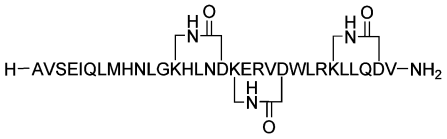


Figure 16. The enkephalin analogue **40** is active at the δ-opiate receptor.

One limiting factor of these methods is that one single covalent bridge is only able to constrain a limited section in the polypeptide. To overcome this problem several covalent bridges need to be incorporated into one sequence. One example showing the effectiveness of this method is the modification of the 31 *N*-terminal residues of the human parathyroid hormone (hPTH) to deliver the therapeutic osteogenic agent **41** (Figure 17). The introduction of three lactam

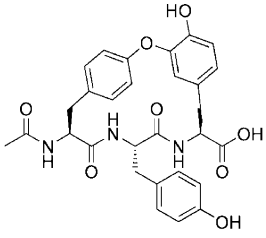
bridges between the *i* and *i*+4 amino acids results in a highly constrained peptide in which the amino acids 13–30 are forced into a helical structure. This makes the analogue a much more active compound than the natural sequence.[78]



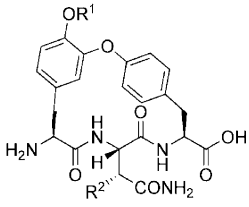
41

Figure 17. The peptidomimetic **41** consisting of **31** residues of the human parathyroid hormone is stabilized by three lactam bridges.

Besides standard methods employed in peptide coupling reactions, other strategies have been developed. One example is the ruthenium-catalyzed intramolecular nucleophilic aromatic substitution (S_NAr) to form cyclic biphenyl ethers. In Figure 18, two natural products together with some analogues are shown. K-13 (**35**) is a natural non-competitive inhibitor of angiotensin converting enzyme (ACE),[79] while OF4949-III (**38**) is a competitive inhibitor for aminopeptidase B. The compound family **36**–**39** exhibits immunopotentiating activity and were confirmed to have antitumor activity, without showing toxicity.[80]



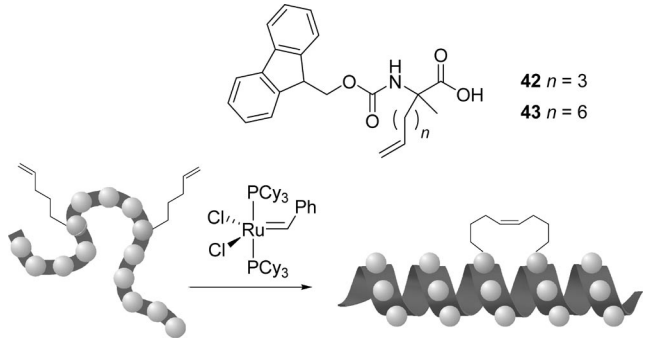
35



36 R^1 = Me, R^2 = OH
37 R^1 = H, R^2 = OH
38 R^1 = Me, R^2 = H
39 R^1 = H, R^2 = H

Figure 18. Structures of the naturally occurring protease inhibitor K13 (**35**) and OF4949-III (**38**) together with some analogues **36**, **37** and **39**.

While disulfide and also lactam bridges effectively stabilize 3D structures, such structural elements are not always stable in vivo as they also occur in natural sequences and are susceptible to degradation. To overcome this limitation, cross-links consisting only of hydrocarbons were investigated as replacement for the above shown linking methods. The ring-closing step for example can be performed by a metathesis reaction using a Grubbs catalyst.[81] An interesting approach was the synthesis of Fmoc-protected C^{α}-tetrasubstituted α-amino acids which are α-methylated and in addition bear a second alkene side chain. They can be used in solid-phase peptide synthesis and if two of them are incorporated into one chain they can be cyclized by the use of metal catalysts.[82] One example of this hydrocarbon cyclisation methodology is shown in Figure 19. The mimic of the minimal death domain BH3 of the pro-apoptotic sub-family of proteins can be forced into a helical conformation through a metathesis reaction. This results in a significantly enhanced stability and an altered in-vitro and in-vivo activity.[83,84]

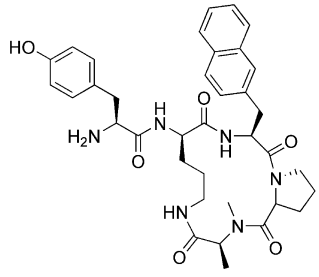


42 *n* = 3
43 *n* = 6

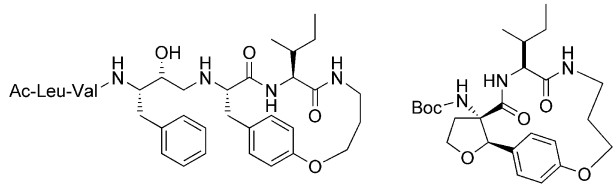
Figure 19. α-Methyl Fmoc-protected unnatural amino acids **42** and **43** (top); scheme of a helix introduction into a peptide sequence via a ring-closing metathesis reaction with Grubbs' catalyst (bottom) (adapted from the literature[83]).

4.3 Backbone-to-Side Chain Cyclisation

A further way to introduce global constraints into peptides is the formation of backbone to side chain cyclisations. One example for such a molecule is the cyclic derivative **44** (Tyr-c[-D-Orn-2-Nal-D-Pro-NMe-Ala]) of the natural occurring β-casomorphin-5. β-Casomorphins are short acyclic peptides derived from the milk protein β-casein and show a high selectivity for the μ-opioid receptor.[85] The derivative **44** proved to be a selective and potent μ-opioid receptor agonist with an IC_{50} of 35 nM[86] (Figure 20).



44



45 **46**

Figure 20. The cyclic β-casomorphin-5 derivative Tyr-c[-D-Orn-2-Nal-D-Pro-NMe-Ala] **44** (left), macrocyclic HIV protease inhibitor **45** (middle) and the macrocyclic peptidomimetic **46**.

Another example for a backbone-side chain cyclisation is the cyclic peptidomimetic inhibitor of HIV-1 protease **45** (Figure 20). In the mimetic **45** the tripeptide sequence Phe-Ile-Val from the peptide Ac-Leu-Val-Phe-$CHOHCH_2$-{Phe-Ile-Val}-NH_2 was replaced by a cyclic motif consisting of a tyrosine, a leucine and an alkylamine. In an inhibition assay such peptides showed IC_{50}-values of up to 2 nM.[87] Inhibitors for HIV 1 protease are of great interest as this enzyme is essential for the assembly of the viral proteins. A successful inhibition would thus lead to non-infective virions.[88,89]

The combined use of C^{α}-tetrasubstituted α-amino acids with the introduction of global constraints via a backbone-to-side chain cyclisation leading to a cyclic tripeptide mimetic **46** was recently reported.[90] The aromatic ether was obtained by an *O*-arylation reaction using palladium catalysis.[73]

5. Synthetic Backbone Scaffolds

All of the previously presented peptidomimetics show a still peptide-like scaffold. However, more or less nonpeptidic mimetics have also been developed. A huge variety of compounds were synthesized as potential β-turn inducing building blocks (see Figure 21).

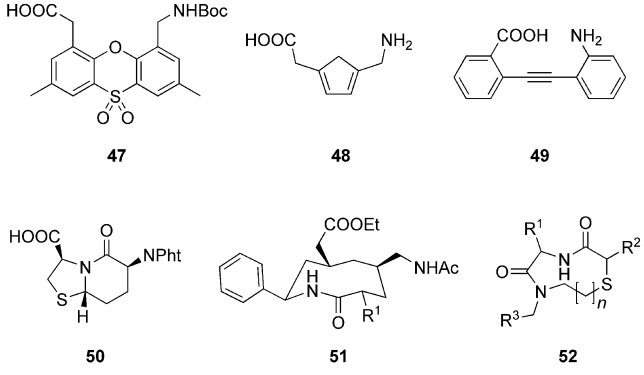


Figure 21. A selection of different β-turn mimetics: **47**,[91] **48**,[92] **49**,[93] **50**,[94] **51**[95] and **52**.

One successful approach towards the use of β-turn mimetics in the synthesis of biologically active peptidomimetics was developed by Ellman et al.: They were able to produce a library of 1152 analogues of compound **52** on solid support and screen them in a competitive radioligand binding assay against the fMLF receptor to discover two active substances.[96] A second generation of these molecules developed by the same group was found to comprise potent ligands for the somatostatin receptors.[97,98]

Besides β-turns also β-sheets play an important role in the structure of proteins. Therefore it is not surprising that a variety of β-sheet mimetics was designed in recent years.[99] Two examples of artificial β-sheet mimetics based on cyclic compounds are shown in Figure 22. Compound **53** developed by Nowick et al. contains 2-methoxybenzoic acid amide and hydrazide derivatives and has the ability to mimic the hydrogen pattern of an anitparallel β-sheet.[100] Other building blocks used in the synthesis of β-sheet peptidomimetics are the so-called MOPAS (methoxypyrrole amino acids). König et al. were able to introduce this compound into a peptide sequence to form **54** and to proof its ability to form β-sheet like structures in solid state and solution.[101]

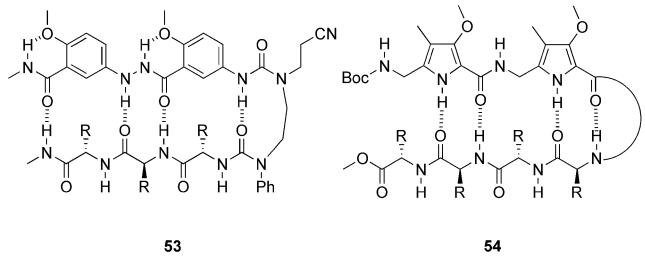


Figure 22. Two examples **53** and **54** of artificial β-sheet mimetics.

The first example of an entirely non-peptidic mimetic allowing a modular synthesis was reported by Hamilton et al. in 2002.[102] These compounds present their residues with similar distances and angular relationships to those found in the side chains of α-helices. Subsequently, modifications to the initial terphenyl scaffold design were made to improve synthetic accessibility, solubility and flexibility.[103] Inhibitors based on the terphenyl scaffold **56** were developed for example to inhibit the interaction of Calmodulin (CaM) with smooth muscle myosin light chain kinase (smMLCK). CaM has a variety of functions in the cell cycle and interacts with a number of proteins including smMLCK which is supposed to play a significant role in the signalling cascade leading to muscle contraction, but it is also supposed to play a role in cancer.[104] The designed derivative showed an IC_{50} of 800 nM and with that is one of the most potent CaM antagonists known until now[105] (Figure 23).

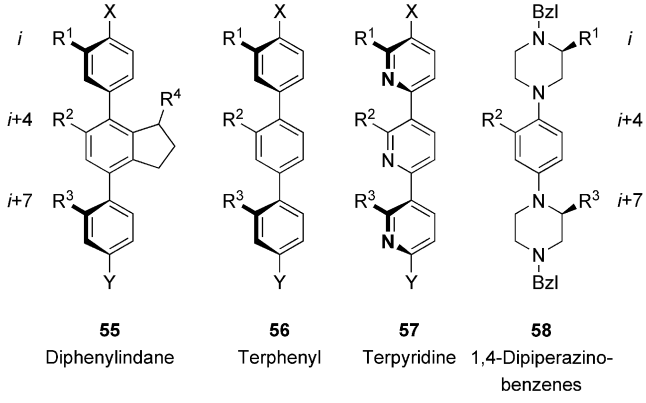


Figure 23. α-Helix mimics developed by Hamilton et al. **55**–**57** and by König et al. **58**. The residues R^1–R^3 are mimics of *i*, *i*+3, *i*+4 and *i*+7 residues of the helix.

Another interesting approach was the synthesis of 1,4-dipiperazinobenzene **58**, using a stepwise transition metal-catalyzed *N*-arylation of chiral piperazines to a benzene core. The structure determined by X-ray crystallography revealed a geometric arrangement of the side chains resembling the orientation of α-helical *i*, *i*+3 and *i*+7 residues.[106]

Conclusions

The different examples discussed illustrate that there are many ways for designing peptide mimetics. They can be synthesized using modified amino acids, through changes in the backbone, by cyclisation reactions or through a combination of several such strategies. All of these strategies have been successfully applied to obtain active substitutes for natural peptides. However, synthetic availability of peptidomimetics and the predictability of resulting structures still limit the use and call for further development. Peptidomimetics will continue to find many applications in medicinal chemistry, molecular biology and in drug discovery and design.

Acknowledgments

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