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Constrained Cyclic Peptides

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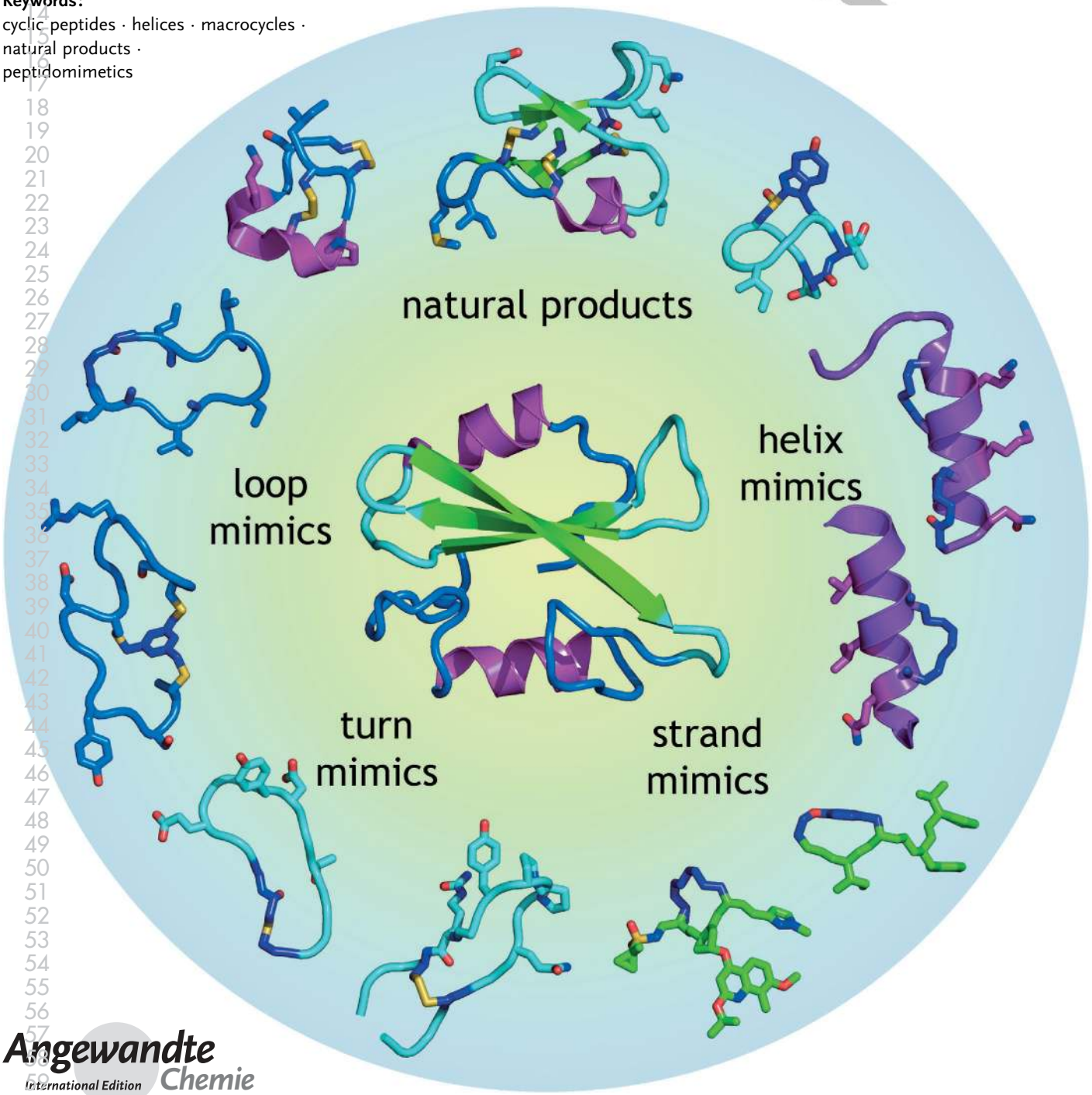

Many proteins exert their biological activities through small exposed surface regions called epitopes that are folded peptides of well-defined three-dimensional structures. Short synthetic peptide sequences corresponding to these bioactive protein surfaces do not form thermodynamically stable protein-like structures in water. However, short peptides can be induced to fold into protein-like bioactive conformations (strands, helices, turns) by cyclization, in conjunction with the use of other molecular constraints, that helps to fine-tune three-dimensional structure. Such constrained cyclic peptides can have protein-like biological activities and potencies, enabling their uses as biological probes and leads to therapeutics, diagnostics and vaccines. This Review highlights examples of cyclic peptides that mimic three-dimensional structures of strand, turn or helical segments of peptides and proteins, and identifies some additional restraints incorporated into natural product cyclic peptides and synthetic macrocyclic peptidomimetics that refine peptide structure and confer biological properties.

From the Contents

1. Introduction

Interactions of proteins with other proteins, DNA, RNA and small molecules mediate most biological processes that define life, growth, reproduction, ageing, disease and death.[1,2] The functions of proteins are determined by specific three-dimensional protein structures, which arise through highly ordered folding of their polypeptide backbones.[1] Frequently, the action of proteins is localized to small structurally defined regions created by backbone folding, stabilized by the protein environment, and often endowed with entropy advantage through preorganization to a specific, though pliable, shape recognized by a binding partner.[2,3] There has been great interest in recreating these functional polypeptide regions within small molecules, based on the premise that structural mimicry can confer functional mimicry and lead to biologically active small molecules.[3–8] The early targets for this interest have been extensively reviewed for β- and γ-turns,[3–5] and more recently β-strands,[6] β-sheets[7] and α-helices[8] (Figure 1), which feature polar amide NH and CO groups within the peptide backbone hydrogen bonded to induce and stabilize protein secondary structure. Short synthetic peptide sequences corresponding to small folded protein epitopes do not however tend to form thermodynamically stable structures in water,[9] due to competing hydrogen bonding from water for peptide backbone polar atoms which disfavors peptide structure.

There is enormous potential for mimicking protein surfaces using small molecules, however most research has instead focused on the easier objective of modifying biologically active peptides, inserting constraints to enhance their properties. Peptides do exhibit a wide range of biological properties, but their uses as drugs have been significantly handicapped by degradation by proteases, negligible membrane permeability or oral bioavailability, high clearance and metabolic instability.[10] Short peptide sequences normally have negligible or random structure in water, whereas their binding targets usually recognize a specific conformation. To overcome some of these deficiencies, cyclization has frequently been used as a device to restrict peptide conformational flexibility, and to increase peptide resistance to degradation by proteases by virtue of removing free N- and C-termini that are respectively truncated by amino- and

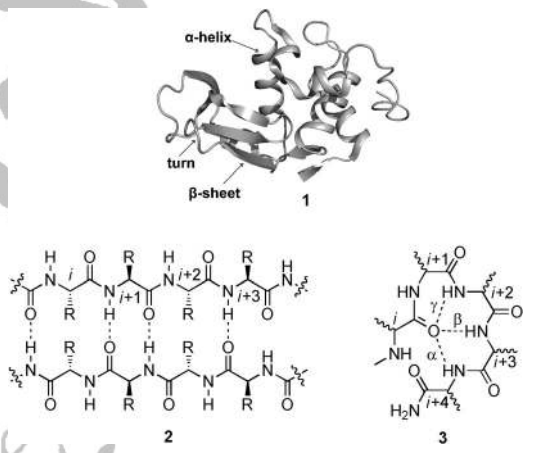

Figure 1. Protein (**1**), 2 strands in a β-sheet (**2**), α, β or γ turn (**3**).

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carboxy-peptidases. On the strength of reports to that time, we commented twenty years ago on the emerging field of "macrocyclic peptidomimetics—forcing peptides into bioactive conformations", highlighting reviews and examples of natural and synthetic bioactive macrocyclic peptides that contained different molecular constraints, fewer rotatable bonds and more stable peptide conformations than acyclic analogues.[3a] The nature of the constraints was correlated with their effects on three-dimensional structures and on available biological activities.[3a] It was noted that designing macrocyclic peptidomimetics held great promise for structural and functional mimicry of protein surfaces.[3–8] The development of small synthetic cyclic peptides, structurally fine-tuned with additional molecular constraints, to mimic elements of protein secondary structure and thereby downsize protein surfaces to smaller molecules has since become much more of a reality. Cyclic peptides are now known to reproduce peptide backbones constrained to strand, sheet, helix, turn or loop conformations and this Review highlights some examples of constrained cyclic peptides that demonstrate the potential for mimicry of protein structure.

Finally, there has been a resurgence of interest in peptides and cyclic peptides during recent years, in part because of the recognition by pharmaceutical companies and academic researchers that these molecules enable quick access to relatively underexploited higher molecular weight chemical matter that is beyond rule-of-five[11] chemical space and smaller than antibodies. There is growing realization that the valuable guidelines,[11] previously developed and successfully used to acquire orally bioavailable small molecules, have become medicinal chemistry rules that have heavily restricted the chemical diversity[11f] now needed to address larger and less hydrophobic surface areas involved in many protein–protein interactions. Cyclic peptides are candidates for exploring the next level of higher molecular weight space beyond traditional small organic molecules, and they can also more closely reproduce specific interactions involved in PPIs. The present Review covers mainly new reports over the last twenty years of cyclic peptides that mimic peptide strands, turns or helices and finishes by pointing to underexploited avenues to constrain peptide structure as inspired by nature's use of peptide cyclization.

2. Cyclic Peptide β-Strands

The β-strand/sheet accounts for ca. 30% of protein secondary structure. Peptide β-strands[6] are extended "linear" peptides, usually paired in proteins as antiparallel, parallel or barrel β-sheets,[7] the strands joined together by an array of hydrogen bonds that stabilize structure. Distinctive phi (ϕ, C′-N-C$^{\alpha}$-C′) and psi (ψ, N-C$^{\alpha}$-C′-N) dihedral torsion angles (**4**, Figure 2) distinguish strands and sheets (e.g. antiparallel, $\phi = -139°$, $\psi = 135°$; parallel, $\phi = -119°$, $\psi = 113°$) from α-helix (−58°, −47°) and β-turn (e.g. type I −60°, −30°) structures. Amino acids that favor strands in proteins are branched residues Val, Ile, Thr as well as Tyr, Cys, Trp, Phe. A key feature of the β-strand is that alternating side chains (e.g. i, $i+1$) point in opposite directions and thus first and third residues (e.g. i, $i+2$) in a peptide sequence have sidechains on the same face of a strand/sheet, bringing them into proximity for potential ring closure to cyclic peptides (e.g. **5**, **6**; Figure 2).

Strands are now recognized in their own rite as important recognition motifs in protein–protein interactions (PPIs) by proteases,[12] amyloids,[13] major histocompatibility complex (MHC) proteins,[14] transferases,[15] SH2 domains,[16] PDZ domain proteins[17] and other PPIs involving recognition of an

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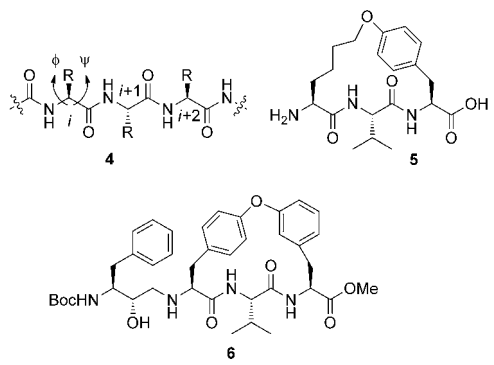


Figure 2. Peptide β-strand showing ψ/ϕ angles (**4**); tri-peptide macrocycles showing cyclization via *i* and *i*+2 sidechains (**5**, **6**). Boc = *tert*-butoxycarbonyl.

isolated strand[17] or strand within a sheet.[7] The most studied targets for β-strand mimicry[6] have been polypeptide interactions with proteases,[12] enzymes important in the synthesis and turnover of all proteins and in development of many diseased states. Inhibitors of proteases are used to treat high blood pressure, human immunodeficiency and hepatitis C viral infections, type 2 diabetes, cancers, multiple myeloma, parasitic infections, stroke and inflammatory conditions.[18] A feature of hundreds of proteases is their recognition of a peptide β-strand in their substrates and inhibitors, evidenced in over 1500 crystal structures for >100 aspartic, serine, cysteine, metallo, threonine and asparagine proteases bound to substrates and inhibitors.[12] We and others have used sidechain-to-sidechain (e.g. **5**, **6**) or sidechain-to-mainchain linkages to create cyclic derivatives (e.g. **7**–**15**) of peptide substrates and inhibitors, as short as 2–3 amino acids.[19] Importantly, these cycles lock constituent peptide residues into a β-strand backbone conformation that is maintained (**7**) within active sites of protease enzymes (Figure 3).[20–22] Such cyclic β-strands were potent (K_i 0.1–50 nM) and selective inhibitors (e.g. **8**, **9**) of the enzyme HIV-1 protease and were cell permeable with potent antiviral activity (IC_{50} 1–50 nM) in infected cells.[21] We showed for HIV-1 protease that such "pre-organization" of β-strands enhanced affinity of substrates/inhibitors for enzymes by 10^1–10^4-fold, and that cyclic peptide strands could be linked to peptides, non-peptides (**8**, **9**) or each other (**10**), all retaining the β-strand backbone conformation in solution and when protease-bound.[20–22]

The distinctive ϕ angles for consecutive peptide residues of a strand translate into proton NMR coupling constants ($^3J_{NHC\alpha}$ 8–10 Hz)[18–22] that are readily distinguishable from those of consecutive α-helical turns ($^3J_{NHC\alpha} < 6$ Hz) and from isolated turns.

Similarly, cyclic peptide β-strands have been developed to inhibit many other proteases (Figure 4), including other *aspartic proteases*[23] (e.g. renin (e.g. **12**–**14**), β-secretase (e.g. **15**, **16**),[25] plasmepsins (e.g. **17**),[26] penicillopepsin (e.g. **18**, **19**)),[27] *serine proteases*[23] (e.g. HCV protease (**20**–**22**),[28] plasmin,[29] thrombin/trypsin (e.g. **23**, **24**),[30] tryptase, prolyl endopeptidase), *metalloproteases*[23] (e.g. angiotensin converting enzyme (ACE), neutral endopeptidase NEP (e.g. **25**),

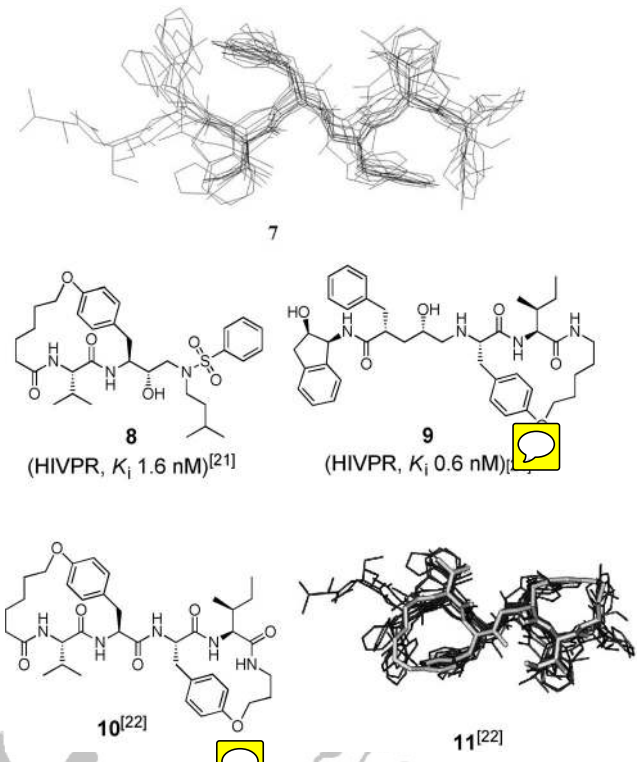


Figure 3. HIV-1 protease and its substrates (**7**), inhibitors (**8**, **9**) and bicycles (**10**) in a common β-strand conformation (**11**) (enzyme not shown), tripeptide segments being mimicked by cycles.[12,19–22] HIVPR = ■■.

thermolysin, aminopeptidase, MMP 1, 3, 8, 9 (e.g. **26**), TNFα-converting enzyme TACE), and *cysteine proteases* like calpains (e.g. **27**).[31] Such macrocycles feature functionalized side chains of Tyr (e.g. **8**, **9**, **20**, **26**, **27**), His (**12**), Glu (**13**), Ser (**14**), Phe (**15**, **16**), Lys (**17**), Cys (**19**), as well as Thr, Trp, Arg, Orn, Asp, Pro, Asn and derivatives. These facilitate cyclization and can introduce additional conformational constraints that enable cyclic peptides to adopt shapes that mimic β-strand peptide backbones. Many of these and other macrocycles have been co-crystallized with a protease and crystal structures show the macrocycles fitting neatly into the protease active site, while projecting sidechains into indentations that line the substrate-binding grooves of proteases. The macrocycles are potent and selective inhibitors of specific proteases (e.g. Figure 4),[23] some with potent activity in cells and animals. HIV-1 protease inhibitors **8**, **9** and analogues had potent anti-HIV activity. Hepatitis C NS3/4A protease inhibitors[28b] **21** (simeprevir, TMC435350)[28c,d] and **22** (vaniprevir, MK-7009),[28e] derived from earlier macrocycles[28b] including ciluprevir (BILN-2061), had anti-HCV activity in cells and humans. Simeprevir was FDA approved in 2013 for treating HCV infection. BACE1 inhibitors (e.g. **15**) lowered brain and plasma amyloid in mice.[25c] Inhibitors of calpain-2 (**26**) prevented ovine lens opacification and cortical cataracts in animals.[32]

There is enormous untapped potential for designing β-strand/sheet mimetics to interfere in protein–protein interactions (PPIs) or mimic one of the binding partners.[6,7] PPI

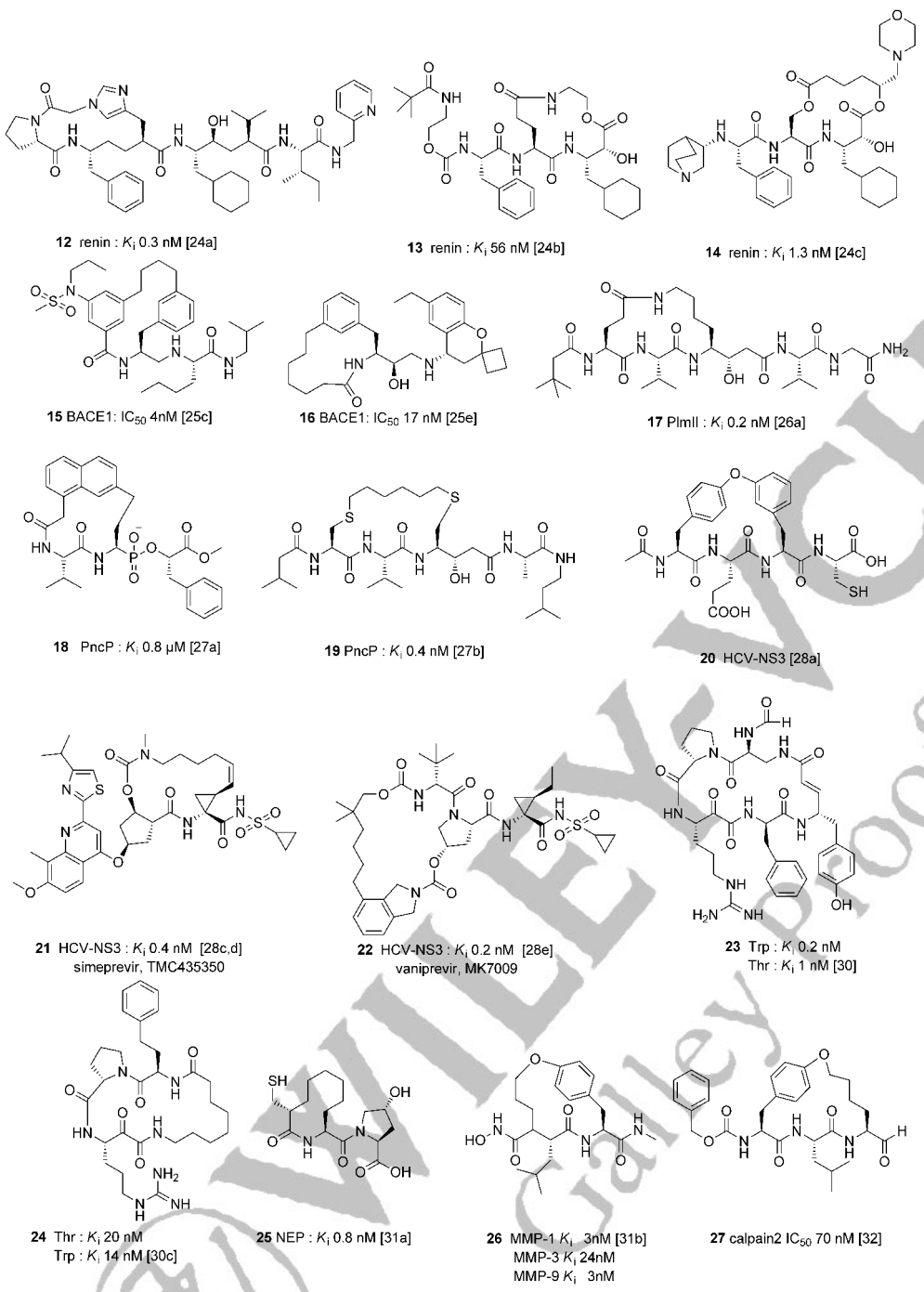


Figure 4. Structures and activities of other macrocyclic inhibitors of aspartic-, serine-, metallo- and cysteine-proteases.[24–32]

interactions often occur over large polar surface areas with only shallow indentations that cannot be effectively targeted by small hydrophobic molecules. Because one face of a β-strand is often exposed to solvent, every second sidechain can potentially be linked to form a β-strand mimicking macrocycle, which might be linked to another β-strand macrocycle β_n (e.g. ββ in **10**), or α-helical macrocycles (e.g. βα, αβα, etc), or acyclic peptide chains, or nonpeptide appendages (e.g. **8**, **9**). Use of macrocycles as templates to produce strand mimetics can be a valuable new approach to engineering tool compounds for investigating the importance of β-strand surfaces of difficult and less "druggable" protein targets. Even from the few examples of macrocycles described above, it is clear that constraints within the macrocycle (e.g. aromatic rings, heterocycles, amides, esters, cycloalkanes, disulfides, N-methylation, D-residues) can impose further restrictions on macrocycle conformation that can influence receptor selectivity, cell permeability and bioavailability, as described elsewhere.[3–8,12,19–32] Understanding how individual molecular constraints influence macrocycle structure, receptor binding and membrane permeability is key to rationally producing bioactive macrocycles as novel biological probes and drug leads.

3. Cyclic Peptide Turns

Turns are motifs that reverse the direction of peptide strands and helices. Turns of increasing size are defined as gamma, beta or alpha (and other) subtypes by adjacent phi (ϕ) and psi (ψ) angles of 3, 4 or 5 consecutive amino acids in a peptide sequence (Figure 5); by 7-, 10- and 13-membered H-bonded rings; and by distances

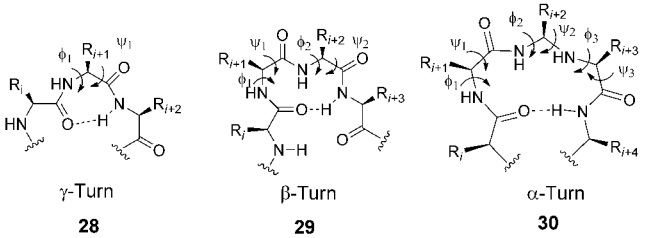


Figure 5. γ-, β- and α-turns defined by torsional angles.

between $C\alpha_i \ldots C\alpha_{i+2}$, $C\alpha_i \ldots C\alpha_{i+3}$ (< 5.5 Å) and $C\alpha_i \ldots C\alpha_{i+4}$ (< 6.5 Å) residues (Figure 5). There is a vast chemical literature for β- and γ-turn subtypes[3–5,33] classified by variable phi/psi angles. Many small molecule turn mimics are known with potent biological activities, and some have been developed to drugs.[5,33]

Cyclization of peptides has been the most common method used to stabilize turns. Cyclization can be accomplished in a variety of ways (head to tail, head to side chain, side chain to tail, side chain to side chain). Many chemical approaches have been used to achieve cyclization, ranging from disulfide or lactam formation to RCM and click chemistry. The chemistry of peptide cyclization has been reviewed in detail.[34] However, cyclization alone is often not enough to stabilize a turn structure.[34b] Other turn-inducing structural features are often needed to help constrain a cyclic peptide into a turn (Figure 6). One method is to introduce

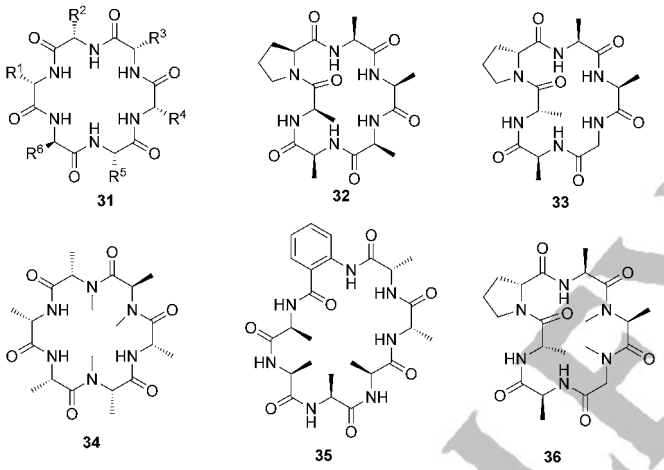


Figure 6. Cyclic peptides with turn-inducing components, such as a D-amino acid (**31**), L-proline (**32**), D-proline (**33**), N-methylation (**34**), aromatic linker (**35**), or combinations of some of these (**36**).

a *cis*-amide bond into a peptide chain, forming a motif analogous to a β-turn.[35] This is often achieved by incorporating a proline ring, glycine, D-amino acid or N-methyl into peptide structures. Proline has the highest tendency of all amino acids to occur in reverse turns in nature, while glycine has the smallest side chain (just a proton) and has the most conformational freedom due to the lack of side chains, enabling it to mimic both D- or L-amino acids without steric hindrance. Incorporating D-amino acids into peptides has a turn-inducing effect, which can be enhanced or locked in place by subsequent cyclization.[36] N-methylation can have a similar effect as proline in favoring some proportion of *cis*-amide conformation that enables reverse turn formation in cyclic peptides.[37] N-methylation can also be substituted with an *N*-(4-Azido butyl) group to induce *cis*-amide bond formation.[38] The triazole group formed by click chemistry has also been utilized as a turn-inducing *cis*-proline mimetic.[39] Pseudo-prolines[40] and heterocycles[41] have been used to introduce turn structures into cyclic peptides. 4*S*-Azidoprolines have also been used to generate all *cis* cyclic peptides.[42]

Constrained cyclic peptides mimicking β-turns have been widely used to target G-protein coupled receptors (GPCRs) due to their preference in recognizing turn conformations.[5f,43] Examples are outlined below.

A series of β-turn cyclic peptides, designed to mimic the C-terminus of a 74 residue proinflammatory human protein (complement C5a), are related to cyclo-(2,6)-Phe-[Orn-Pro-(D-Cha)-Trp-Arg] (**37**, Figure 1).[44–47] They feature a pentapeptide macrocycle formed through a 2→6 sidechain to C-terminus lactam bridge. Between 1980–1995, many companies sought antagonists to block the C-terminus of C5a from binding to its GPCR on immune cells, but orally active full antagonists as prospective anti-inflammatory drugs proved elusive. Knowing that GPCRs tend to bind turns of proteins[3,43] and that cyclization can force peptides into bioactive conformations,[3a] cyclic analogues (e.g. **37**) of the C-terminus of C5a (**38**, Figure 7) were developed to stablize a γ- and β-

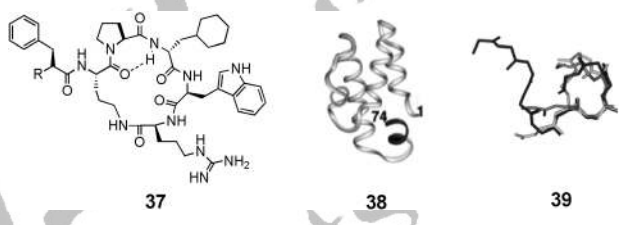


Figure 7. a) Cyclic C5aR antagonists (**37**); R = AcNH (3D53 or PMX53),[44] R = H (3D624 or PMX205);[45] b) helix bundle of human C5a (**38**) showing activating C-terminus (bold); c) NMR structures (**39**) of peptides en route to **37**.[44]

turn in short acyclic peptides (**39**, Figure 7).[44–47] Cycles featured a Pro-(D-Cha) turn-inducing constraint, effecting 10^6-fold higher affinity for the C5a receptor than the hexapeptide C-terminus of C5a, potent full antagonism ($IC_{50} \approx 30$ nM) with high selectivity, long residence time and oral activity at 0.3–5.0 mg kg^{-1} doses in rodent models of inflammatory and other diseases. This was the first mimic of a protein "helical" (but not α-helical) turn to enter phase II clinical trials.[47]

Somatostatin is a 14 amino acid cyclic peptide AG[CKNFFWKTFTSC] expressed in the central nervous system, gastrointestinal tract, and endocrine tissues.[48] The octapeptide sandostatin (octreotide) is a potent analogue of somatostatin with a longer half life, and it is currently used in the clinic to treat cancer and acromegaly. NMR[49] and X-ray[50] studies show that sandostatin adopts a type II β-turn or a type II′ β-turn around D-Trp8-Lys9 which has been stabilized in the hexapeptide **40** (constrained via proline and the D-Trp8) and bicyclic compound **41**.[48] More recent examples have used a dicarba linker **42**, biphenyl scaffolds **43** or cyclic α-amino acid [1*S*,2*S*,5*R*]-2-amino-3,5-dimethyl-2-cyclohex-3-enecarboxylic acid substitution **44** for proline (Figure 8).[51] Other turn mimetics for GPCR targets include agonists (**45**–**52**) of melanocortin, bradykinin, casmorphin, endothelin, enkephalin, GHRP-2, gonadotrophin RH, oxytocin and vasopressin (Figure 9).[52–57] Aside from GPCRs, constrained cyclic peptides have been developed to mimic turns from many other protein and peptides. This includes the integrins,

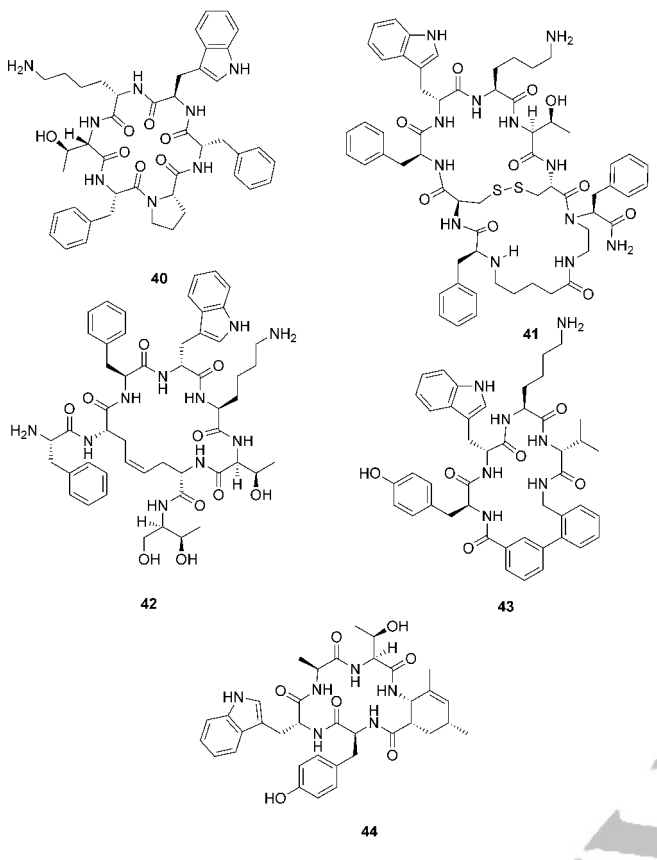


Figure 8. Somatostatin analogues utilizing different turn constraints.

which are an important class of surface receptors involved in cell–cell and cell–matrix interactions. Highly potent and selective inhibitors have been developed through constraining the pharmacophore sequence RGD into small cyclic peptides presenting this motif in a turn conformation. This has lead to the development of cilengitide (**53**) (Figure 10) which has been in clinical trials for glioblastoma.[58] Constrained turn structures have also been used in developing antibacterial analogues of gramicidin S (**54**) and antivirals targeting HIV and Hepatitis.[59,60]

In contrast to β-turn mimics, only a couple of α-turn mimics are reported.[61] Cyclic tetrapeptides have been constrained through (i, $i+3$) sidechain to C-terminus (**55**) or ($i+3$, i) side chain to N-terminus (**56**) (Figure 11), giving CD spectra in 10 mM phosphate buffer very similar to peptide α-helices. NMR analysis and MD simulations showed **55** to be an α-turn type Iα-RS, while **56** was an α-turn type IIα. These cyclic peptides were pseudo-planar with no helical pitch and mimicked α-turns in a number of protein structures.[61]

The γ-turn has also been constrained in a number of small cyclic peptides.[3–5] Due to the highly constrained nature of the γ-turn cyclic scaffolds have generally been employed in the peptide backbone. Recently, γ-turn mimetics have been used to develop analogues of angiotensin (**57**), melanocyte stimulating hormone, desmopressin (**58**) and oxytocin (**59**) (Figure 12).[62]

The β-hairpin, with two consecutive hydrogen bonded antiparallel β-strands connected by a turn or loop, occurs

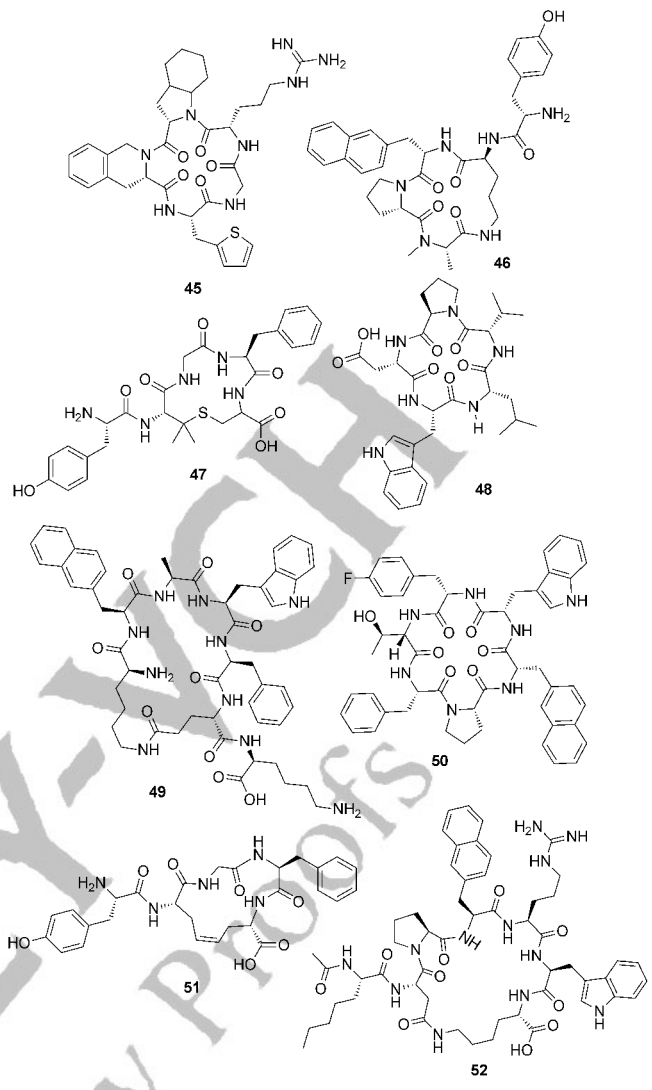


Figure 9. Other macrocyclic agonists and antagonists of GPCRs.

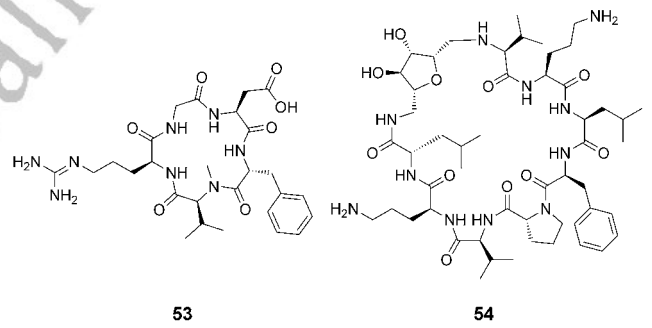
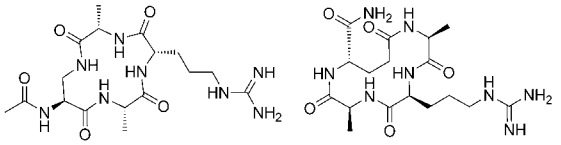


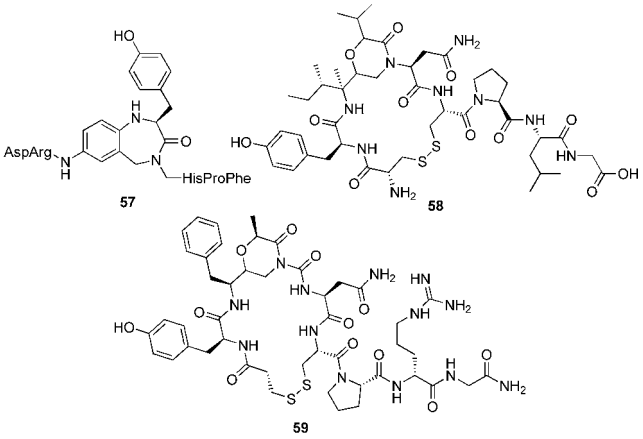
Figure 10. RGD integrin antagonist clengitide (**53**) and gramicidin analogue (**54**).

widely in nature in various forms distinguished by chain length, hydrogen bonding pattern and turn or loop motifs. Mimetics were most commonly created by transplanting a hairpin sequence onto a semi-rigid hairpin-stabilizing template, such as a D-Pro-L-Pro heterochiral diproline like **60** (Figure 13).[63] This compound disrupts interaction



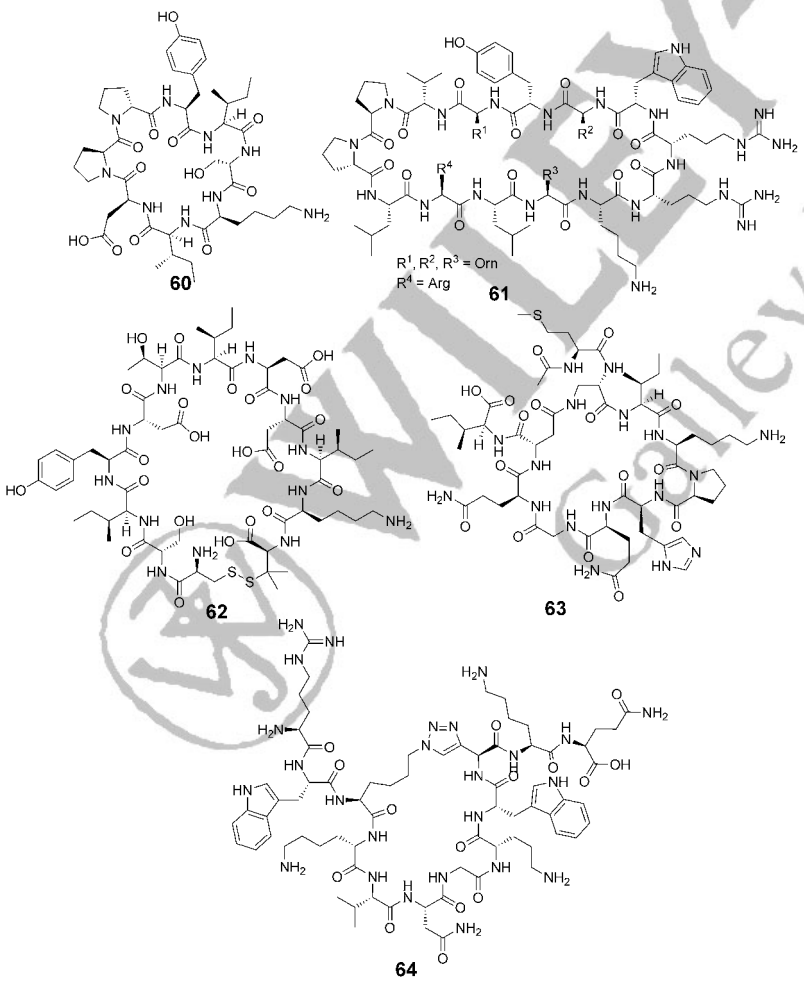
55 56

Figure 11. Mimics of non-classical α-turns



57 58 59

Figure 12. Examples of γ-turn promoting scaffolds



60 61 62 63 64

Figure 13. Constrained macrocycles with β-hairpins.

between cell adhesion molecule CD2 and its ligand CD58, NMR solution structures and molecular dynamics simulations indicating a β-hairpin structure in **61**. The D-Pro-L-Pro motif has also been used to develop antimicrobial **62** and antiviral peptides, protease inhibitors and PPI inhibitors. Other scaffolds have used turn-mimicking motifs (**63**) and click chemistry to constrain the hairpin structure **64**.[63–69]

4. Cyclic Peptide Helices

Helices are defined by consecutive turns linked together by hydrogen bonds that bridge across turns. Among helical structures observed in proteins are the α-helix, 3_{10}-helix and π-helix. Multiple consecutive β-turns form a 3_{10}-helix and display $i+3\rightarrow i$ backbone amide hydrogen bonds between amide proton and carbonyl oxygen. Multiple consecutive α-turns of a specific type ($\phi=-58°$, $\psi=-47°$) define α-helices and display $i+4\rightarrow i$ hydrogen bonds. The π-helix displays $i+5\rightarrow i$ hydrogen bonding and is generally not observed in shorter than seven residue sequences.

The α-helix represents 40% of secondary structural motifs in proteins. In the PDB, >60% of all complexed proteins involve an α-helix at their interface.[70] Developing methods to mimic helical regions at protein-protein interfaces has attracted great attention,[71] but short peptides display little propensity to form a helical structure in water under physiological conditions and have limited biological stability. Constraining a peptide to its bioactive helical conformation can overcome the entropy penalty of folding and can prevent degradation by proteases that recognise the extended (β-strand) conformation.[72] The α-helix diameter is too large to fit into most protease active sites, some yeast proteases being exceptions.

4.1. Side-Chain ~~linkages~~

Historically, the most common method of inducing or stabilizing helical peptide structure was insertion of covalent sidechain-to-sidechain amide linkages between lysine/ornithine and glutamic/aspartic acid residues separated by 2 or 3 residues. The synthesis of lactam-bridged peptides for stabilizing α-helical peptides has been reviewed.[8b] Early research[73] focused on characterizing helical peptides for application to biological targets. In particular $i\rightarrow i+4$ and $i\rightarrow i+3$ side chain linkages were applied in 15–30 residue peptides to improve bioactivity. This was demonstrated in peptide hormones, such as neuropeptide Y,[74] dynorphin A[75] parathyroid hormone (PTH),[76] CRF,[77] galanin,[78] calcitonin,[79] GCN4,[80] secretin[81] and GLP-1.[82] However, there was no real consensus as to

the best lactam bridge for stabilizing an α-helix. A range of lactam bridges were used to stabilize the LXXLL motif in GRIP1 co-activator peptides.[83a,b] The Glu(*i*)→Lys(*i*+4) bridge (**65**, Figure 14) conferred 10-fold more potent inhibition of the thyroid receptor (IC_{50} 0.62 μM) (**66**, Table 1) than the Lys(*i*)→Asp(*i*+4) bridge (IC_{50} 5.8 μM). Subsequent studies using cyclo-(7,11)-EKHKIX_1-[**E**R$X_2$$X_3$**K**]DS as scaffold, with X_1–X_3 substituted by hydrophobic residues, gave selectivity for oestrogen receptor isoforms.[83c,d]

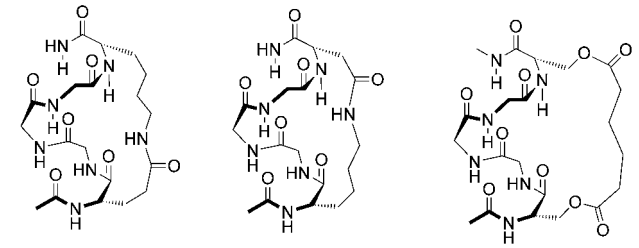


Figure 14. Lactam and ester *i*→*i*+4 bridges to stabilize α-helicity.

A systematic study in 2005 examined combinations of side chains to form the macrocyclic lactam in a model pentapeptide, and Lys(*i*)→Asp(*i*+4) (**67**, Figure 14) was found to be superior to other lactam bridging combinations for stabilizing α-helicity.[84] The cyclic pentapeptides, for example, Ac-cyclo-(1,5)-[**K**ARA**D**]-NH_2, were the smallest α-helices reported in water, displaying ca. 100% α-helicity in phosphate-buffered saline (PBS)[84] They were unaffected by helix-inducing (TFE = ■■) or helix-denaturing (8 M guanidine) reagents, resistant to proteases, and could be linked together.[8d] These exceptional properties were dependent on the peptide having α-helix favoring residues (Ala, Leu, Met, Arg, Gln, Glu, Lys)[72,84] and being amide-capped at N- and C-termini to form three α-helix defining hydrogen bonds. Uncyclized sequences had negligible α-helicity in water.[8d,72,84–88]

Multiple cyclo-(1,5)-[**K**XXX**D**] lactam bridged modules have been inserted into biologically active peptide sequences from protein α-helices to downsize proteins to smaller synthetic molecules that maintain potency and stability to biological fluids and proteases.[72] This technique was applied (Table 1) to inhibiting viral fusion (RSV) (**68, 69**),[85] (HIV-Rev) (**70**),[72] anti-bacterials (CSP-1) (**71**),[86] ORL-1 receptor agonists (**72**) and antagonists (**73**),[87] and transcription factor antagonists (cFos) (**74**).[88] Agonist **72** caused prolonged antinociceptive effects in mice, and these effects could be reversed by co-administering **73**.[87] A lactam bridge was used to downsize a μ-conotoxin KIIIA protein recently, but analogues had reduced biological activity.[89]

An alternative approach to lactam bridges involves diester-bridged peptide fragments, for example from parathyroid hormone (PTH_{1-11}).[90] Compounds obtained by sidechain acylation of Ser6 and Ser10 with adipic acid resulted in a 23-membered ring (**75**, Figure 14). The diester **76** (Table 1) was more potent than the corresponding Glu(*i*)→Lys(*i*+4) lactam-bridged peptide, even though the cyclic peptide component is two atoms larger and less compact by NMR. Cross-linking two serine side chains with dicarboxylic acids produced bridges of variable lengths, with the two ester groups being potential hydrogen bond acceptors.

Hydrocarbon bridges have been increasingly used in recent years for stabilizing helical structures in peptides.[8f,g,91] Constraining peptides using sidechain–sidechain hydrocarbon linkers was first demonstrated using O-allyl protected serine or homoserine located at the *i* and *i*+4 positions in a model peptide, Boc-V[**X**LAibV**X**]L-OMe[91a] Cross linking via a metathesis reaction gave peptides with improved helicity as measured by CD spectra. An X-ray crystal structure of a bis-homoserine cyclic peptide, after ring-closing metathesis and hydrogenation of the double bond, indicated that cyclization stabilized an α-helix.[91b]

The next generation of hydrocarbon-linked peptides involved unnatural α,α-di-substituted amino acids with α-methyl groups and side chains of different lengths with terminal alkene units. These amino acids can be at *i*→*i*+3 (**77**), *i*→*i*+4 (**78**), *i*→*i*+7 (**79**) positions in a peptide (Figure 15). Subsequent cross-linking by ring-closing metathesis gave cyclic peptides that stabilized one or two turns of an α-helix. This technique was coined hydrocarbon "stapling". The *i*→*i*+3 and *i*→*i*+4 hydrocarbon linkers could be combined in tandem to give more stable bicyclic peptides.[92–94] A recent study[95] showed that a stapled BID peptide with no α-methyl groups in the bridging amino acids had equivalent helicity, affinity and proteolytic stability as α-methyl amino acids. Hydrocarbon linkers have been applied to the development of inhibitors of numerous protein–protein interactions (Table 1). The commercial availability of the requisite amino acids needed to prepare such peptides will see their applications expanded further.

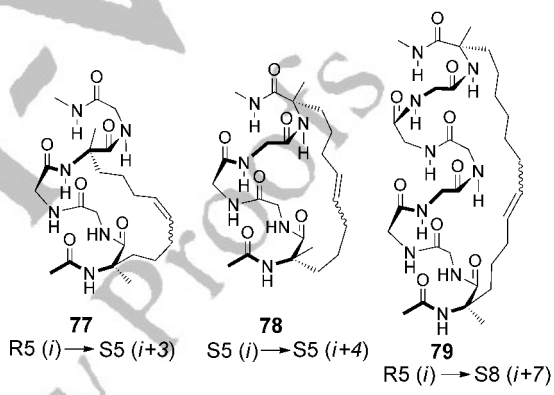


Figure 15. Different hydrocarbon *i*→*i*+3, *i*→*i*+4, *i*→*i*+7 linkers. The stereochemistry of the α,α-disubstituted amino acid is indicated (*S* or *R*) along with the number of carbons (5 or 8).

Application of these *i*→*i*+4 linkers to bioactive peptides (Table 1) was first demonstrated on the BID BH3 peptide (**80**),[96] improving its affinity and stability. One of the linked peptides caused tumour regression in mice with human leukaemia xenographs. These peptides bound directly to Bax, initiating mitochondrial apoptosis. Photo-reactive analogues of BH3 members BIM (**81**) and BAD (**82**) were also

developed using a benzophenone-containing peptide to study Bcl-2 interactions.[97] An inhibitor of Mcl-1[98] was also reported (**83**). An antagonist (**84**) of the oncogenic NOTCH 1 transcription factor ternary complex was developed. The 15-residue peptide from $MAML1_{21-36}$ blocked full length MAML1 binding to the ternary complex, suppressed NOTCH-1 signalling and had anti-leukemic activity in vivo.[99] Inhibitors of the p53-hDM2/hDMX interaction have been developed utilizing $i \rightarrow i+7$ staples (**85**–**87**). The initially reported **85** showed high helicity and affinity for HDM2 and efficacy in mice.[100] Similar linked peptides (**86**) from another group[101] inhibited MDM2 and reactivated p53 more potently than **85** and the small molecule nutlins. Aileron therapeutics recently reported **87**[102] with impressive affinity and good anti-MDM2 activity in cancer cell lines and a mouse xenograft cancer model.

Hydrocarbon linkers continue to be applied to diverse targets (Table 1) including EZH2-EED (**88**),[103] ER/co-activator (**89**),[104] HIV (**90**),[105] a cardiovascular transporter,[106] and diabetes.[106] However, recent results have shown that introducing such a linker is no guarantee of bioactivity[107] or cell permeability, which seems highly sequence-dependent due to endocytic uptake.[108] Stabilizing helicity in a peptide does not always improve bioactivity, and improved in vitro affinities do not necessarily translate to cell activity. Crystal structures of stapled peptides bound to MDM2, the oestrogen receptor and MCL-1 show that interactions of the linker with a protein are sometimes key to improving potency. Hydrocarbon linkers may endow a peptide with cell permeability versus its corresponding linear analogue.[109] Cell permeability is critical for targeting intracellular proteins like transcription factors.

Huisgen azide–alkyne 1,3-dipolar cyclization chemistry has been successfully applied to develop helix-constrained peptides. This uses specialized amino acids with azide and alkyne functional groups, notably an azide functionalized norleucine and L- (**91**, Figure 16) or D-propargylalanine (**92**, Figure 16), at i and $i+4$ positions in the peptide. Peptides derived from parathyroid hormone (PTH),[110] cyclized using L-azidonorleucine and L-propargylalanine, showed helical structures. Mono- and bis-click cyclized peptides from BCL9 used L-azidonorleucine and L- or D-propargylalanine to yield

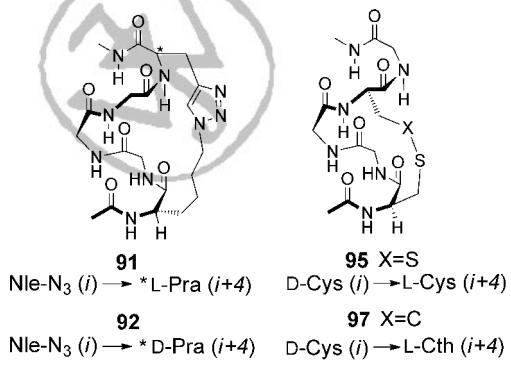


Figure 16. Helix stabilization peptides using $i \rightarrow i+4$ triazole linkages (**91**–**92**) or $i \rightarrow i+3$ disulfide (**95**) and thioether (**97**) cyclization. Nle-N3 = azidonorleucine, Pra = propargylalanine, Cth = cystathionine.

peptide inhibitors of β-catenin (**93**, **94**; Table 1).[111] Interestingly, L-azidolysine to D-propargylalanine was more optimal for both stabilizing α-helicity and improving affinity for β-catenin.

Macrocyclic disulfides have been used to stabilize helical conformations using D- and L-cysteine at i and $i+3$ positions, respectively (**95**, Figure 16). When incorporated into NR box peptides they potently inhibited ERα and ERβ (**93**, Table 1). Interestingly, the disulfide cyclized peptides were more potent than lactam-bridged peptides previously reported.[112] A later study using L-cystathionine at the $i+3$ position to produce a redox stable cyclic peptide (**97**, Figure 16) that was slightly more potent (**98**, Table 1).

Crosslinking bis-cysteine containing peptides with aryl moieties has stabilized α-helicity (**99**–**102**, Figure 17). Bis-arylmethylene dibromides were used to crosslink i and $i+7$ cysteine residues. Mcl-1 peptides[113] prepared using this

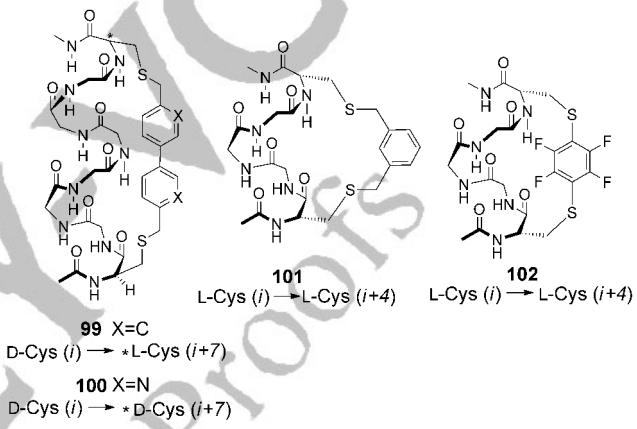


Figure 17. Helix stabilization of bis-cysteine peptides by $i \rightarrow i+7$ and $i \rightarrow i+4$ crosslinking with arylmoieties (**99**–**102**).

strategy had D-cysteine and L-cysteine at i and $i+7$ positions (**99**, Figure 17) resulting in 20–30-fold improved affinity and more helicity than the acyclic precursor. N-methylation, N-terminal carbamoylation, and mutagenesis, made the net peptide charge zero and led to greater cell permeability (**103**, Table 1). MDM2/MDMX inhibitors using a slightly modified aryl moiety (**100**, Figure 17) had D-cysteine at both positions (**104**)[114] allowing the biaryl bridge to make favorable interactions with the protein. Activity-based probes based on calpastatin that inhibited calpain incorporated a short specificity-determining sequence crosslinked with dibromoxylene to stabilize helicity (**101**, Figure 17; **105**, Table 1).[115] A perfluorobenzene linker (**102**, Figure 17) was shown to chemoselectively crosslink two cysteine side chains occupying the i and $i+4$ positions in an unprotected HIV capsid assembly peptide to improve binding and cellular uptake (**106**).[116]

Azobenzene crosslinks have been attached to cysteines located at i and $i+4$, $i+7$ and $i+11$ positions (**107**–**109**, Figure 18). The azobenzene moiety underwent *cis*/*trans* isomerization upon UV irradiation, leading to large conformational changes from random coil to α-helical. When the azobenzene moiety was linked at i and $i+4$ (**107**) or $i+7$

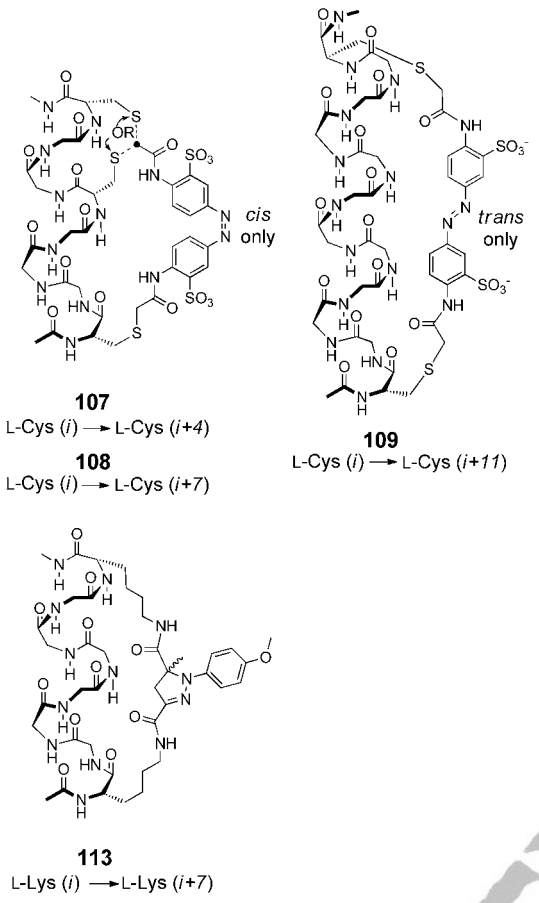


Figure 18. Helix stabilization of bis-cysteine peptides by $i \rightarrow i+4$ and $i \rightarrow i+7$ crosslinking with diazobenzene moieties (**107**–**109**) and bis-lysine peptides with a diacylpyrazoline unit (**113**).

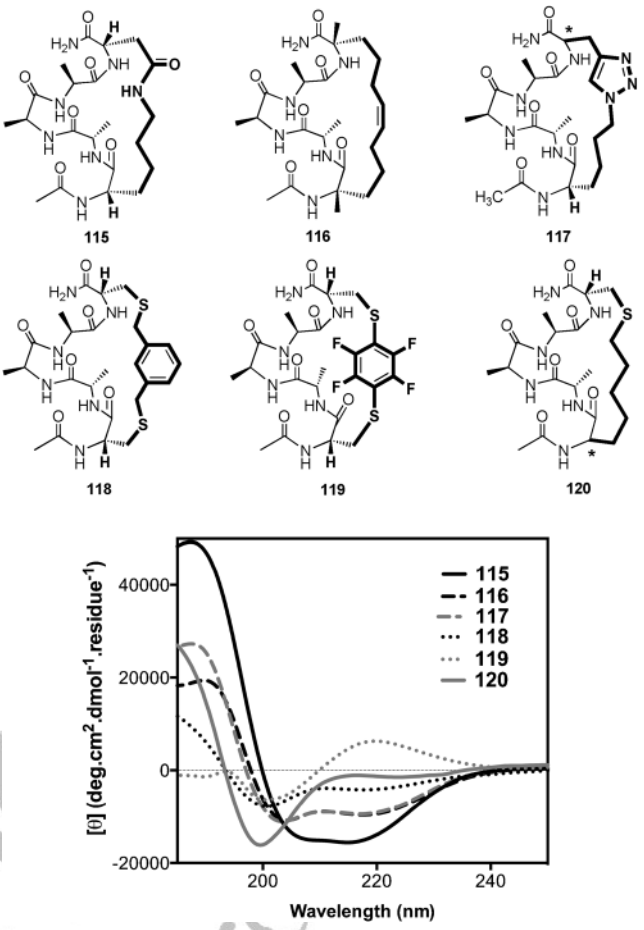


Figure 19. Cyclic pentapeptides **115**–**120** with different linkers compared for α-helicity in 10 mM phosphate buffer (pH 7.2, 298 K) by circular dichroism spectra.[119]

(**108**) positions, only the *cis* conformation stabilized helicity. However, when i and $i+11$ positions (**109**) were crosslinked, only the *trans* conformation stabilized helicity. This technique was applied successfully to develop potent BID (**110**, Table 1) and Bak (**111**, **112**; Table 1) peptide mimetics targeting the anti-apoptotic Bcl-X_L.[117]

Incorporating lysines at i and $i+4$ positions, acylating them with methacrylate and carboxytetrazole respectively, and exposure to UV light, facilitated a 1,3-dipolar cycloaddition reaction to generate a fluorescent pyrazoline crosslink that improved helicity (**113**, Figure 18). This approach was applied to disruption of the p53-MDM2/MDMX interaction (Table 1; **114**). Although the crosslinked peptides showed modest in vivo activity, the fluorescent crosslink facilitated cellular uptake relative to the acyclic peptides.[118]

4.2. Comparison of Helix-Inducing Linkers

Effects of different linkers on α-helicity of cyclic pentapeptides **115**–**120** have been compared in water by NMR and CD spectroscopy (Figure 19).[119] The Lys-Asp lactam linker (**115**) was about twice as α-helical as the hydrocarbon (**116**) and triazole (**117**) linkers, which may have some 3_{10}-helicity, whereas the thioether cycles (**118**–**120**) had little helicity in PBS. Addition of the helix-stabilizing solvent TFE increased α-helicity by CD analysis for all except **115**, which was unaffected and already optimally α-helical in water.

4.3. Hydrogen Bond Surrogates

An alternative approach to using sidechain crosslinks to constrain helical structures is to introduce a crosslink to replace an $i \rightarrow i+4$ hydrogen bond, a hydrogen bond surrogate (HBS). This creates a covalent macrocycle between the N-terminus of the peptide and the amide nitrogen of the $i+4$ residue, closely mimicking the 13-membered hydrogen-bonded α-turn in canonical α-helices (**121**, Figure 20). The ring size is critical for forming and nucleating stable artificial α-helices.[120,121] The HBS approach was initially developed using a covalent hydrazone $i \rightarrow i+4$ link (**122**, Figure 20). While successful, hydrazone instability has limited applications.[122] The hydrazone has been replaced by an alkenyl hydrocarbon linker synthesized by incorporating alkenes into the peptide and using ring-closing metathesis (RCM)[123] for cyclization (**123**, Figure 2[illegible]). The chemistry for synthesizing these molecules by solid phase has been refined[124] and modified to replace the alkene link with a disulfide or

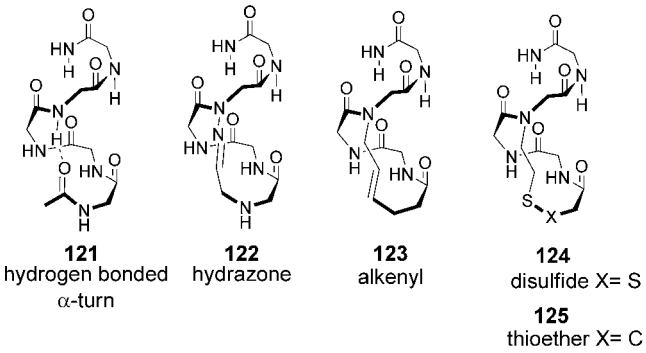


Figure 20. Hydrogen bond α-helical turn (**121**) and hydrogen bond surrogate approaches (**122**–**125**).

a thioether (**124**, **125**; Figure 20).[125] A 1.15 Å X-ray crystal structure of a short HBS stabilized peptide has been determined and the structure matched that of a canonical α-helix.[126] HBS peptides utilizing the RCM-derived alkenyl linker have been been applied to targets (Table 1) including p53 (**126**),[127] Bcl-xL (**127**),[128] HIV gp41 (**128**),[129] HIF-1α (**129**)[130] and Ras (**130**).[131]

4.4. Unusual Helix Mimicry

An unusual approach to mimic bioactive helices utilized cyclic β-hairpin peptides (Figure 21). Backbone cyclic deca- or tetradeca-peptides incorporating an D-Pro-L-Pro template formed a well-defined β-hairpin template. The cyclic peptides positioned their side chains in positions that roughly mimicked those in an α-helix. The strategy has been used to mimic $i, i+4$ and $i+7$ positions in the p53 helix (**131**),[132] the $i, i+1$, $i+4$, $i+5$, $i+8$ and $i+9$ positions in the HIV Rev helix (**132**),[133] and sulfated tyrosine residues at $i, i+4$ positions in the CCR4 helix (**133**).[134]

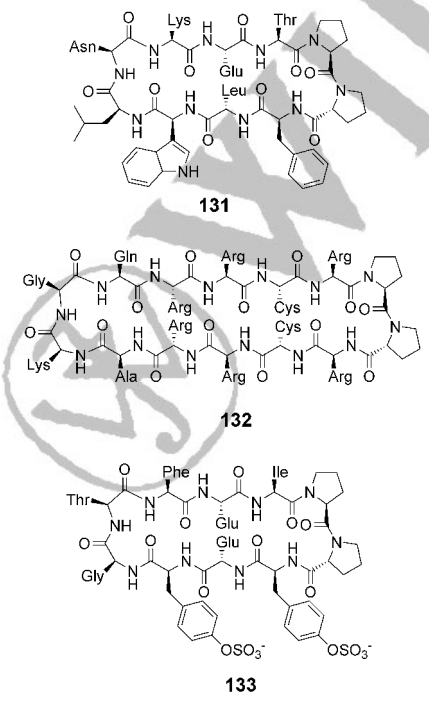


Figure 21. α-Helix mimicry using cyclic β-hairpin peptides with turn inducing D-Pro-L-Pro unit.

5. From Nature to the Laboratory

Clues to engineering specific shapes of cyclic peptides also come from nature's use of a diverse array of molecular constraints to regulate three-dimensional structure, confer high functional potency, produce high stability and enable membrane permeability of cyclic peptides.[135] Nature produces most cyclic peptides through ribosomal synthesis, involving mRNA translation to peptide chains of L-amino acids, often post-translationally modified and cyclized by enzymes.[136] However, nature also extensively uses non-ribosomal synthesis, involving enzymes to catalyse assembly of non-proteinogenic amino acids and derivatives followed by cyclization.[137] Every point of an amino acid has been used as a linker to cyclize peptides. A few examples are shown here to highlight constraint diversity and to inspire synthesis and application of new cyclic peptides.

5.1. Monocyclic ~~peptides~~

The simplest natural cyclic peptides are monocyclic, with ring closing connectivity rigidifying the peptide. The simplest and most common cyclization is a conventional head to tail macro-cyclization that removes charged N- and C-termini. Such cyclization often encourages intramolecular hydrogen bonds that help to bury polar surface area. For example, the fungal metabolite cyclosporin A (**134**; Figure 22) is a registered immunosuppressant drug used to prevent organ rejection in transplantation surgery.[138] This 11-residue peptide has seven N-methylated amino acids, the remaining four being tied up in hydrogen bonds, that confer good membrane permeability and make it one of the few known orally bioavailable cyclic peptides. The mushroom metabolite antamanide (**135**) is another immunosuppressant that achieves lipophilicity differently, with four prolines that reduce both amide NH donors and rotatable bonds in the decapeptide.[139] The heptapeptide sanguinamide A (**136**) is a thiazole cyclic peptide from the sea slug *H. sanguineus*. It is constrained by three heterocyclic rings, a *cis* Phe2–Pro3 amide bond, and an Ile-thiazole dipeptide mimetic that together induce two transannular antiparallel hydrogen bonds, and **136** shows some oral absorption by rats.[140] In these cases cyclization, coupled with molecular constraints, hydrogen bonds and hydrophobic sidechains, shields polar atoms from water solvation, enabling passive transport from the gut and into cells.

Condensation of adjacent amino acids (as in **136**) occurs in many different ways in a large group of azotides[141] (thiazole/thiazoline/thiazolidine and/or oxazole/oxazoline peptides) that are incorporated into cyclic peptides. These heterocycles (Figure 23) constrain the macrocycle conformation to facili-

Table 1: Some biologically active helices stabilized by different methods.

Formula number	Linker structure type[a]	Sequence[b]	α-Helix	Activity	Reference
Lactam bridges					
66	65	Ac-EKHKIL[**X**RLL**X**]DS	GRIP1	$K_i = 0.62$ μM	[83]
68	67	Ac-FP[**X**DEF**X**][**X**SIS**X**]N-NH_2	RSV-F protein	$IC_{50} = 36$ nM	[85]
69	67	Ac-1Nal-[**X**DEF**X**][**X**SIS**X**]N-NH_2		$IC_{50} = 0.18$ nM	[72]
70	67	Ac-TRQA[**X**RNR**X**]RR[**X**RER**X**]-NH_2	HIV_{34-50} Rev	$IC_{50} = 50$ nM	[72]
71	67	E-Nle-RL[**X**KFF**X**][**X**FIL**X**]RKK-NH_2	Sp CSP-1	$IC_{50} = 0.5$ μM	[72, 86]
72	67	FGG-(4F)F-[**X**ARS**X**][**X**ANQ**X**]-NH_2	nociceptin	$EC_{50} = 0.04$ nM	[72, 87]
73	67	Bn-GGG-(4F)F-[**X**ARS**X**][**X**ANQ**X**]-NH_2		$IC_{50} = 7.5$ nM	[87]
74	67	Ac-Cha-R[**X**EIY**X**]LR[**X**KAN**X**]LR[**X**HIA**X**]-Cha-NH_2	cFos	$K_i = 7.25$ μM	[88]
Diester linker					
75	75	Aib-V-Aib[**XL**-Nle-H**X**]-Har	PTH	$EC_{50} = 0.2$ nM	[90]
Hydrocarbon bridges					
80	78	EDIIRNIARHLA[**X**VGD**X**]-Nle-DRSIW	BID BH3	$IC_{50} = 40$ nM	[96, 97]
81	78	IWIAQELR[**X**IGD**X**]FNAYYARR	BIM BH3	$IC_{50} = 16$ nM	[97]
82	78	NLWAAQRYGRELR[**X**-Nle-SD**X**]FVDSFKK	BAD BH3	$IC_{50} = 60$ nM	[97]
83	78	KALETLRRVGDGV[**X**RNH**X**]TAF	Mcl1 BH3	$K_i = 0.84$ μM	[98]
84	78	βA-ERLRRRI[**X**LCR**X**]HHST	MAML1	$IC_{50} = 16$ nM	[99]
85	78	Ac-QSQQTF[**X**NLWRLL**X**]QN-NH_2	p53	$K_D = 50$ nM	[100]
86	78	Ac-TSF[**X**EY-(6Cl)W-ALL**X**]QN-NH_2	p53	$K_D = 6$ nM	[101]
87	78	Ac-LTF[**X**EYWAQ-Cba-**X**]SAA-NH_2	p53	$K_D = 0.9$ nM	[102]
88	78	FSSNR[**X**KIL**X**]RTQILNQQWKQRRIPQPV	EZH2	$K_D = 468$ nM	[103]
89	78	YT[**X**LIH**X**]LIEESQNQQEKNEQELLEL[**X**KWA**X**]LWNWF	HIV GP41	$IC_{50} = 2.5$ nM	[104]
90	78	EKHKIL[**X**RLL**X**]DS	GRIP1	$K_D = 75$ nM (ERα) $K_D = 155$ nM (ERβ)	[105]
Triazole linkers					
93	91	Ac-LSQEQLEHR[**X**RSL**X**]TLRDIQRMLF-NH_2	Bcl9	$K_i = 330$ nM	[111]
94	92	Ac-LSQEQLEHR[**X**RSL**X**]TLRDIQRMLF-NH_2	Bcl9	$K_i = 130$ nM	[111]
Disulfide/thioether linkers					
96	95	R[**X**IL**X**]GRLLQ-NH_2	NR Box	$K_i = 11$ nM	[112a]
98	97	R[**X**IL**X**]GRLLQ-NH_2	RB Box	$K_i = 6.9$ nM	[112b]
Cystine linkers					
103	99	Moc-MeA-MeA[**X**GRAIGD**X**]VNLAQALLN-NH_2	Mcl1	$IC_{50} = 22$ nM	[114]
104	100	LTF[**X**LRAIGD**X**]S-COOH	p53	$IC_{50} = 5.4$ nM $IC_{50} = 14$ nM	[115]
105	100	EtO-Epoxysuccinate-βAAIPPKY[**X**ELL**X**]K-NH_2	Calpain-ABP	$K_i = 10.2$ μM	[116]
106	102	ITF[**X**DLL**X**]YYGKKK-NH_2	HIV CAP	$K_D = 1$ μM	[117]
110	107	DIIRNIARHLA[**X**DVG**X**]IDRSI	BID	$K_D = 55$ nM	[118]
111	108	GQVGR[**X**LAIIGD**X**]INR	BAK	$K_D = 42$ nM	[118]
112	109	G[**X**VGRALAIIGD**X**]INR	BAK	$K_D = 21$ nM	[118]
Pyrazoline linker					
114	113	LTF[**X**HYWAQL**X**]S	p53	$IC_{50} = 6.2$ nM	[117]
Hydrogen bond surrogates[c]					
126	117	[-QE-]-GASDLWKLLS-NH_2	p53	$K_D = 160$ nM	[127]
127	117	[-QV-]-GRQLAIIGD-K(Ac)-INR-NH_2	Bak BH3	$K_D = 69$ nM	[128]
128	117	[-MT-]-WEEWDKKIEEYTKKI-NH_2	HIV GP41	$K_D = 42.7$ μM	[129]
129	117	[-FE-]-GIYRLELLKAEEAN-NH_2	Ras	$K_D = 28$ μM	[130]
130	117	[-EL-]-ARALDQ-NH_2	HIF1α	$K_D = 690$ nM	[131]

[a] These numbers refer to type of linker as shown by structures in the text. [b] [**X...X**] indicates macrocycle-forming linkers involving connections between sidechains of these residues. [c] [**-....-**]- indicates hydrogen bond surrogate. 1Nal = 1-naphthylalanine; (4F)F = 4-fluorophenylalanine; Cha = cyclohexylalanine; Aib = α-aminoisobutyric acid; Har = homoarginine; Nle = norleucine; (6Cl)W = L-6-Chlorotryptophan; Cba = cyclobutylalanine; βA = β-alanine; Moc = methoxycarbonyl; MeA = N-methylalanine; K(Ac) = acetyllysine.

tate protein binding, for example in the potent enzyme inhibitors GE2270A (**137**)[142] and largazole (**138**),[143] which use an acyclic "arm" to bind a protein.

Another type of cyclization is through linking a sidechain peptide terminus. For example, sidechain to C-terminus urs in cationic cyclic heptapeptides called polymyxins, like

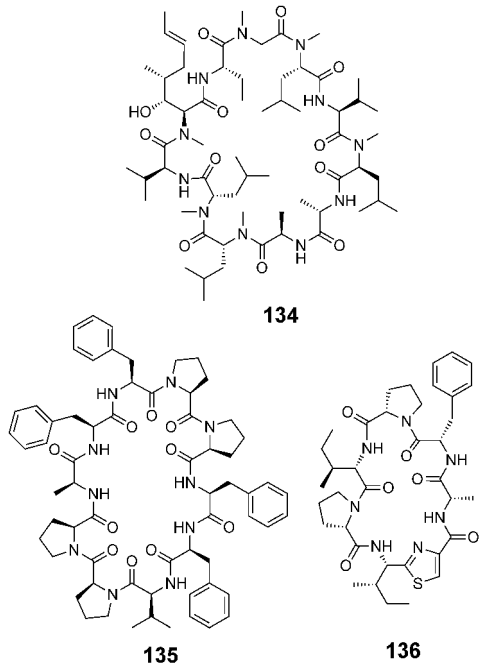


Figure 22. Orally bioavailable monocyclic peptides.

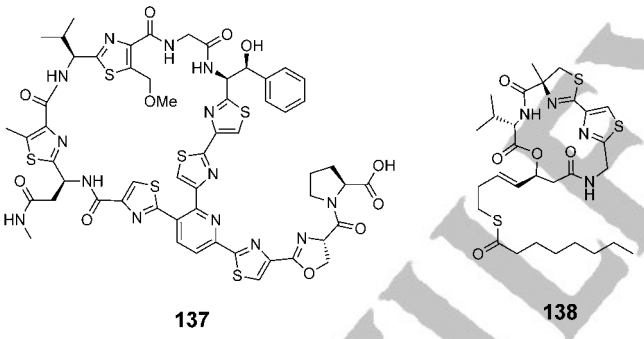


Figure 23. Constrained monocyclic azotides.

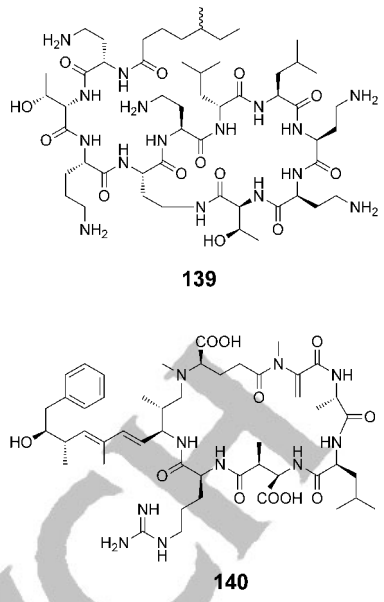


Figure 24. Sidechain-to-terminus linked monocyclic peptides

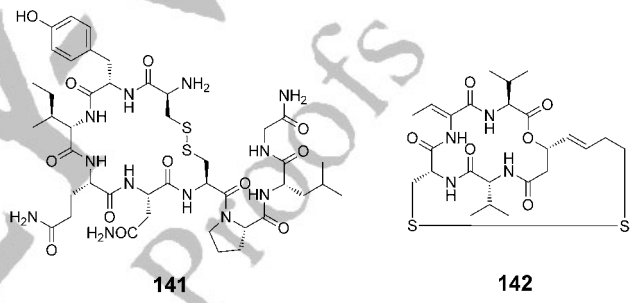


Figure 25. Sidechain-to-sidechain linked cyclic peptides

colistin (**139**, Figure 24), which have antimicrobial activity against mainly Gram-negative bacteria. Hydrophobic (N^{α}-fatty acyl chain and a D-Leu-L-Leu type II′ β-turn) and hydrophilic (3 or 4 cationic amino acids) components in such cyclic peptides create amphiphilic surfaces that enable detergent-like interactions with bacterial membranes and bactericidal action.[144] Microcystin LR (**140**) is representative of many cyclic heptapeptides formed through an alternative sidechain to N-terminus linkage, and features D-Glu, N-methyl dehydroalanine, D-Ala, D-methyl-Asp, and β-amino acid Adda. These macrocyclic cyanotoxins are produced in toxic blue-green algal blooms by cyanobacteria, inhibit protein phosphatases 1 (IC_{50} 1.7 nM) and 2A (IC_{50} 0.04 nM), cause liver toxicity after oral ingestion, and are tumour promoters.[145]

Sidechain to sidechain crosslinks are also common. Representative is the pituitary hormone oxytocin (**141**; Figure 25), a nonapeptide with a Cys-Cys disulfide bond that creates a cyclic hexapeptide component which projects into the cleft of its carrier protein neurophysin.[146] Oxytocin adopts a β-turn at residues Tyr2-Asn5 to activate its cell surface GPCR and promote uterine contractions during labor, milk ejection during lactation, and multiple behavioral functions. Sometimes the cyclization crosslink confers pro-drug status, enabling membrane permeation, after which the bioactive agent is released from the protected form. This is most often accomplished by ester protection of an alcohol or carboxylic acid, but may also be effected by reductive cleavage of a disulfide bond to thiols, as for the bicyclic drug romidepsin **142**,[147] a potent inhibitor of histone deacetylase enzymes.

5.2. Other Disulfide Cross-Linked Cyclic Peptides

Disulfide bonds are also frequently used by nature to effect multiple sidechain to sidechain crosslinks,[148] creating highly compressed globular structures through complex folding patterns. These folded structures access specific conformations that bind selectively to recesses or hinge regions of target proteins, often resulting in exquisitely

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selective biological actions. Many of these are ribosomally expressed cysteine-rich toxins found in spiders,[149] scorpions,[150] snakes,[151] venomous sea creatures, lizards, plants, and some mammals.[152] Selective combination of cysteines is favored by the reversibility of disulfide bond formation, producing the most stable peptide conformations. Some spider toxins contain up to seven distinct disulfide bonds. The sunflower trypsin inhibitor-1[153] and the α-conotoxins from cone snail venoms are some of the smallest compounds in this class.[154] An example of the latter is Vc1.1 (**143**; Figure 26) a potent nAChR antagonist.[155] The α-conotoxins contain two disulfide bonds that facilitate folding into an α-helical motif (**144**).[154]

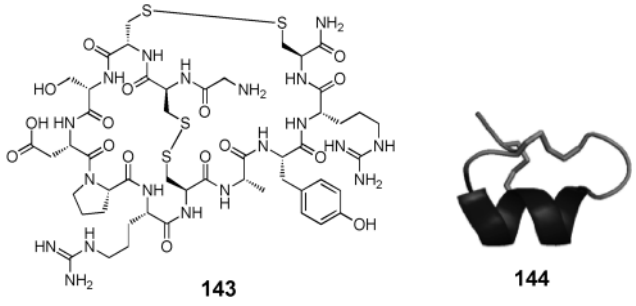

Figure 26. Chemical structure and shape of α-conotoxin Vc1.1.

Cysteine rich peptides are also expressed in the immune system,[156] exemplified by human β-defensin 2 (**145**; Figure 27),[157] which is an antimicrobial peptide mainly produced and excreted in response to skin lesions. It contains three disulfide bonds that stabilize a β-sheet structure consisting of three β-strands and an α-helix motif. A related class of lactam macro-cyclized peptides containing sidechain to sidechain crosslinks have been isolated from fungi, plants and animals.[158] Among these are the cyclotides, which have a cystine knot motif of three disulfide bonds.[158] The knot is also found in many peptides without lactam cyclization.[159] One of the most studied cyclotides is kalata B1 (**146**), which is hemolytic, has potent insecticidal activity as well as HIV inhibiting properties.[160] These effects primarily arise from selective binding to phospholipids in membranes, inducing leakage.[161b] Linaclotide (**147**) is another highly constrained peptide of 14 residues, featuring three intramolecular disulfide bonds between C1–C6, C2–C10 an C5–C13.[161] It has been approved as Linzess by the US FDA for treating irritable bowel syndrome. Linaclotide is a homolog of the enterotoxin STa, produced by *E. coli* causing diarrhoea, and targets guanylate cyclase C type C receptor in the intestine to increase intestinal motility and transit.

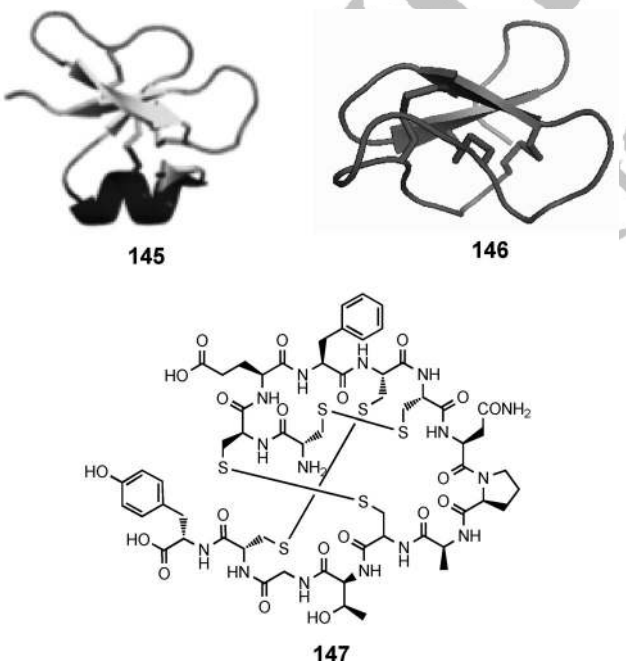

Figure 27. Beta-defensin 2 (**145**), kalata-B1 (**146**), linaclotide (**147**)

5.3. Bicyclic Peptides

Synthetic bicyclic peptides are an emerging class of compounds attracting interest for biological activities. They are inspired by naturally occurring bicyclic peptides such as α -amanitin,[162] phalloidin,[163] bouvardin[164] and moroidin.[165] For example, α-amanitin (**148**; Figure 28) is a cyclic octapeptide in which a sidechain to sidechain transannular Trp–Cys crosslink creates two conjoined macrocycles with an oxidized thio-group.[162] It is a potent toxin (LD_{50} 0.1 mg kg^{-1}) from mushrooms.[162] It acts by inhibiting RNA polymerase II,[162b] leading to liver failure and death.[162c]

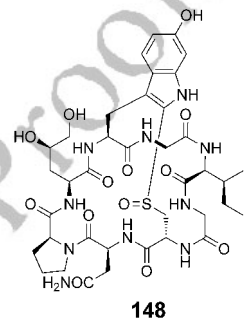

Figure 28. Chemical structure of α-amanitin **148**.

Nature has inspired the development of a number of synthetic bicyclic peptides (Figure 29). Phage-derived peptides containing three cysteines were converted to bicycles (**149**) using 1,3,5-trisbromomethylbenzene (TBMB).[166] Several rounds of phage panning identified potent inhibitors of urokinase-type plasminogen activator and more recently kallikrein. Rings of different sizes have been explored, as have alternatives to the TBMB bicyclic constraint. Bis-disulfide bicyclic peptide inhibitors of uPa have also been investigated by phage display, the peptides were selective, but less potent than TBMB-cyclized peptides. A solid-phase strategy for preparing bicyclic inhibitors of TNF-α (**150**) has also been reported.[167] The peptides utilize a C-terminal

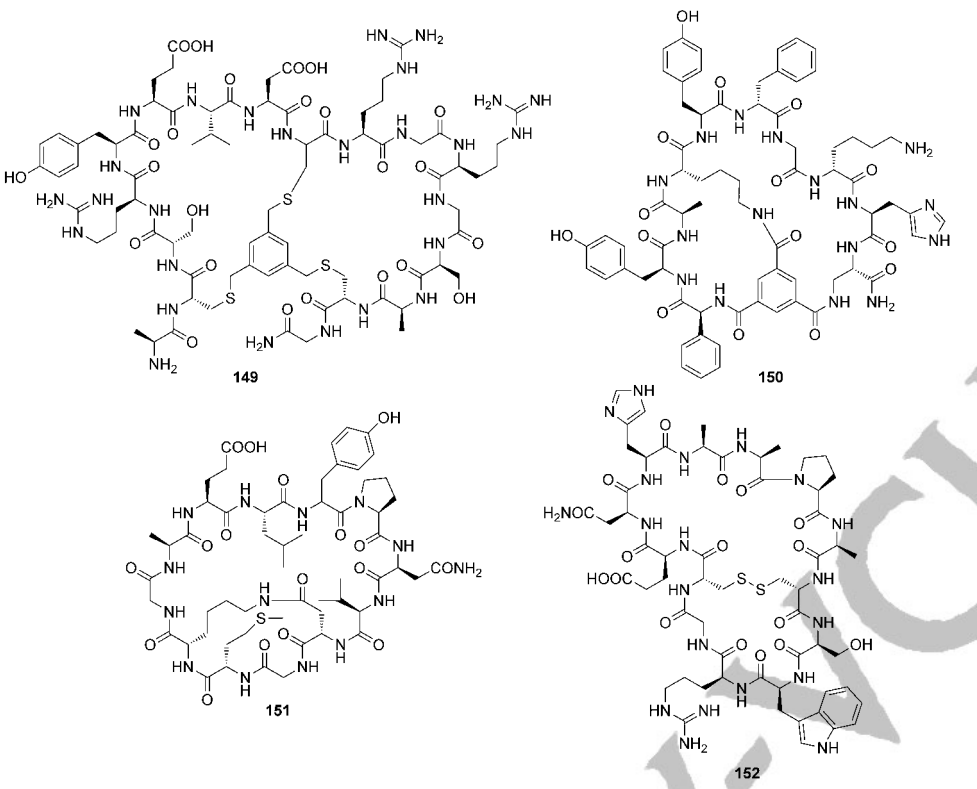

Figure 29. Designed bicyclic peptide inhibitors (**149**–**152**).

diaminopropanoic (Dap) residue, and internal lysine and Orn cyclized using a planar trimesic acid moiety that simultaneously acylates the N-terminal amine and side chain amino groups of Dap and Lys residues. The bicyclic decamer had K_D 450 nM for inhibiting TNF-α. Bicyclic peptide inhibitors of the Grb2-SH2 domain have been developed (**151**).[168] A micromolar cyclic disulfide undecapeptide inhibitor, incorporating a key Glu–Tyr–Asn motif, was cyclized head to tail to slightly improve activity. Further constraining the macrocycle using a Lys–Asp lactam bridge produced a sub-micromolar inhibitor that was 60-fold more potent, 200 times more selective and stable for 24 h in serum. Using a similar approach, a novel bicyclic inhibitor of uPa (**152**) was also created. A disulfide cyclized peptide was head to tail cyclized and optimized by incorporating an internal disulfide. The bicyclic peptide showed improved, but modest, inhibition (26 μM).[169]

5.4. Multicyclic Peptides

Nature creates many peptides with multicyclic motifs. Examples are the lantibiotics such as nisin (**153**) and the more compact mersacidin (**154**) (Figure 30).[170] The most dominant crosslink within the lantibiotics is a thioether, formed by attack of the cysteinyl thiol on 2,3-didehydroalanine or 2,3-didehydrobutyrine. This leads to structures that bind to phospholipid II which leads to pore formation and/or blocks membrane biosynthesis.[170] Both compounds have potent antibacterial properties and nisin has been used in food preservation for more than 40 years.[170]

A group of very ridgid peptides are the glycopeptide antibiotics like vancomycin (**155**),[171] an injectable antibiotic used as the last resort in hospitals to treat drug resistant gram positive bacterial infections, such as methicillin resistant staphylococcus aureus. Its rigidity originates from two rings formed through condensation of two β-hydroxychlorotyrosine (β-hTyr) residues with a trihydroxyphenylglycine, and a third ring from condensation of 4-hydroxyphenylglycine (HPG) and a 3,5 dihydroxyphenylglycine (3,5-DPG). Vancomycin binds the D-Ala-D-Ala motif of the pentapeptide precursor of the bacterial membrane polymer, thereby inhibiting the enzymatic cross-linkages which destabilize the bacterial cell walls.[172]

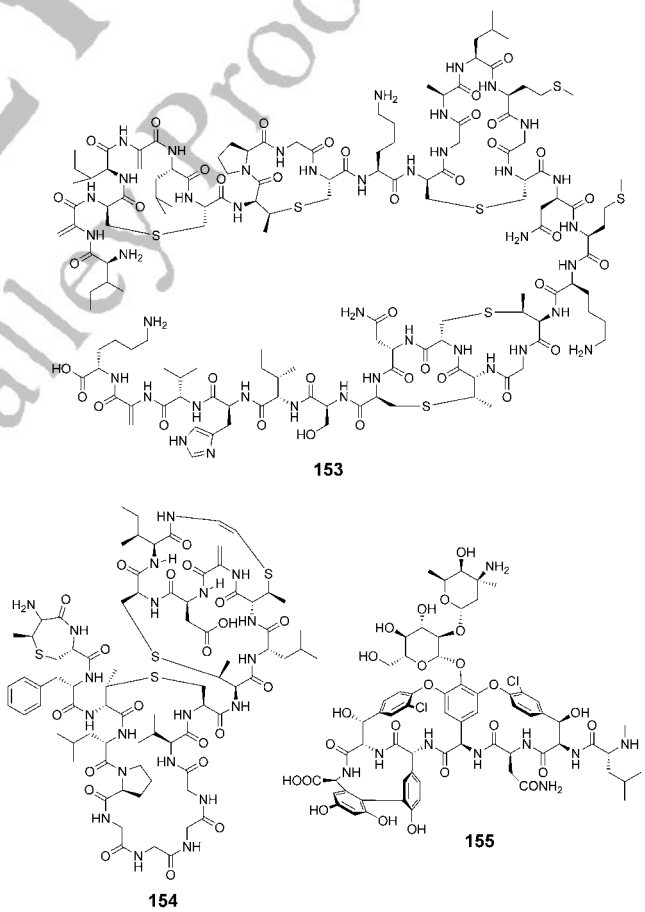

Figure 30. Nisin (**153**), mersacidin (**154**), vancomycin (**155**).

6. Summary and Outlook

Sections 2–4 of this Review have highlighted how different kinds of cyclization can be used to constrain backbones of short peptide sequences into strand, turn or helix structures akin to secondary structural motifs in proteins. Some examples highlighted how researchers optimized specific structures to mimic a specific bioactive protein peptide surface. Often this structural mimicry translated into potent and exquisitely selective biological activity that mirrored the potency and specificity of a protein. In some cases, constrained macrocycles have progressed to human clinical trials and to registered drugs.

The final Section 5 very briefly introduced how nature uses peptide macrocyclization, in conjunction with a myriad of different kinds of molecular constraints, to shape and protect peptide fragments to form compounds with potent biological properties. Nature's combination of cyclization linkers and molecular constraints is a powerful mix for fine-tuning shape in short peptide segments to enhance receptor affinity, selectivity, function and membrane permeability. How this is achieved and how it translates, for example, into potent enzyme inhibitors, protein agonists and antagonists, anti-infectives, tumour regulators and other medicinal compounds, can provide important clues to chemists seeking to mirror protein function in smaller, more bioavailable molecules. In the majority of cases naturally occurring cyclic peptides still have unknown three dimensional structures, and greater efforts to determine their structures promise many important new lessons for chemists.

The focus herein has been on minimalist approaches to recreating the smallest structural elements (α, β, γ) of proteins in small cyclic peptides. Of course there are many more examples where much larger motifs make up discontinuous protein surfaces that might need to be mimicked (α_n, β_n, αβα, βαβ, etc). There have been advances in these areas too using cyclic peptides, but this field is still very much in its infancy due in part to the difficulty in rationally controlling and predicting larger structures. Significant gains in this area can be expected in the next decade.

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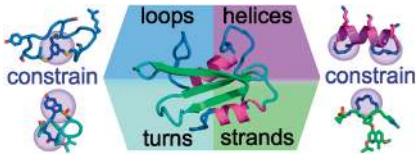
Reviews

Constrained Cyclic Peptides

T. A. Hill, N. E. Shepherd, F. Diness, D. P. Fairlie* ———— ■■■■–■■■■

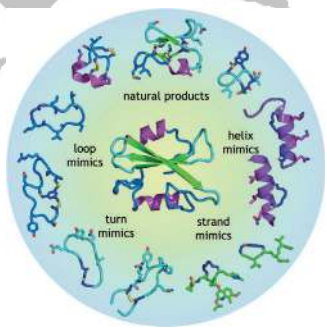
Constraining Cyclic Peptides To Mimic Protein Structure Motifs



Short peptides can be constrained by cyclization to recreate key folded elements of protein structure, like β-strands and β-sheets, α-helices, and turn motifs. Coupled with internal molecular constraints, cyclization has led to many protease-resistant, potent and target-selective, biologically active compounds for use in biology and medicine.

Cover Picture:

Picture 1:



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Pfad: L:/daten/Verlage/VCH/ACH/hefte/pool/
Status Neusatz
Datum: 37 KW., 11. September 2014 (Donnerstag)
Pagina: 25
Seite: 24 te von 24
Umfang (Seiten): 24
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