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# Brief Summary on Cyclic peptides

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**ABSTRACT**

We briefly summarize the cyclotides, its types, importance, artificially laboratory synthesis method, and natural sources. Cyclopeptides are peptides in which the terminal amino and carboxyl groups form a peptide bond, thus making compound a cyclic molecule. They are also formed by the intrapeptide linkage between two cystine residues in a peptide chain. These cyclic peptides have several applications in medicine and biology. Cyclic peptides combine several favorable properties such as good binding affinity, target selectivity and low toxicity that make them an attractive modality for the development of therapeutics. We can find several cyclic peptides from natural peptide hormones such as calcitonin, oxytocin, somatostatin, vaso¬pressin, and so on. The synthetic method can provide more versatile cyclic peptide compounds as the repertoire of amino acids and the way of forming cyclic peptides is diverse. Solid-phase peptide synthesis combined with split-and-pool synthesis can prepare fairly large libraries. Cyclopeptides are ubiquitously present in Nature. Their high physiological activity is often a result of the stabilization of certain bio-active conformations upon cyclization while the cyclic structure simultaneously protects against degradation by proteases.

## 1. Introduction

Cyclopeptides are ubiquitously present in Nature. Their high physiological activity is often a result of the stabilization of certain bio-active conformations upon cyclization while the cyclic structure simultaneously protects against degradation by proteases. Cyclopeptides cannot only act as (small) substrates for (larger) receptors; the macrocyclic structure also allows them to serve as receptors for (smaller) guest molecules that can be bound inside the cavity. The natural cyclodepsipeptide *valinomycin* is a prominent example of such a receptor whose antibiotic activity is due to the ability to complex and transport potassium ions along bacterial cell membranes. Although pioneering work on the development of cyclopeptide derived macrocyclic ligands was carried out in the group of E. Blout already between 1970 and 1990, the concept of using cyclopeptides as synthetic receptors in molecular recognition was not widely accepted in spite of the fact that cyclopeptide-based receptors possess various advantages with respect to macrocyclic receptors derived from, for example, crown ethers, calixarenes, or cyclodextrins. These considerations motivated us to systematically study the host-guest chemistry of cyclopeptides. In this context, we concentrated on compounds containing natural and non-natural aromatic amino acid subunits in an alternating sequence along the ring with the rigid aromatic subunits mainly serving to reduce conformational flexibility.

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**Cyclic peptides** are polypeptide chains in which the amino termini and carboxyl termini; amino termini and side chain; carboxyl termini and side chain; or side chain and side chain are linked with a covalent bond that generates the ring. A number of cyclic peptides have been discovered in nature and a plethora has been synthesized in the laboratory. Their length ranges from just two amino acid residues to hundreds. These cyclic peptides have several applications in medicine and biology.[1]

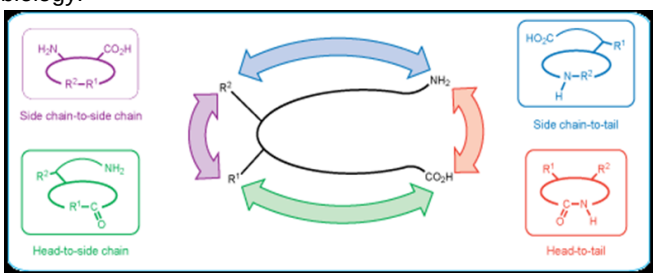


Fig.1 Depending on its functional groups, a peptide can be cyclized in four different ways: head-to-tail (C-terminus to N-terminus), head-to-side chain, side chain-to-tail, or side-chain-to-side-chain.[2]

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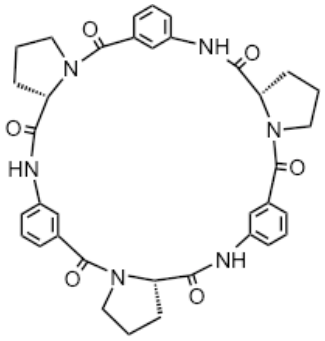
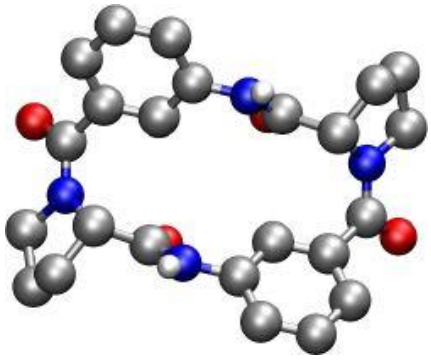


Our work thus clearly demonstrates the potential of such cyclopeptides as synthetic receptors and we expect a number of interesting applications for these compounds.

So far, cyclic tetra-, hexa-, and octapeptides containing 3-aminobenzoic acid derived subunits have been synthesized in the group. Since hexapeptides were used in the majority of binding studies, these peptides were structurally varied the most. A cyclic natural α-amino acid must be used for the preparation of cyclic octapeptides. If the natural amino acid is proline, cyclic tetrapeptides are accessible. The crystal structure of one of these tetrapeptides reveals that the amide groups at the proline residues adopt the *cis* conformation.[4]



The crystal structure also shows that such tetrapeptides lack a well-defined cavity. Cation affinity is therefore lower than that of corresponding hexapeptides.[5-9] Tetrapeptides are, however, promising candidates for the development of pincer-type receptors.[1] In this context, we have developed a bisboronic acid based on a cyclic tetrapeptide that binds glucose in aqueous solution enantioselectively.[10-13]

Cyclic peptides combine several favorable properties such as good binding affinity, target selectivity and low toxicity that make them an attractive modality for the development of therapeutics.[14] Over 40 cyclic peptide drugs are currently in clinical use and around one new cyclic peptide drug enters the market every year on average. The vast majority of clinically approved cyclic peptides are derived from natural products, such as antimicrobials or human peptide hormones.[4-5] Cyclic peptides show great success as therapeutics. Examples of widely applied cyclic peptide drugs are the hormones or hormone analogues oxytocin, octreotide and vasopressin, the antibiotics vancomycin, daptomycin and polymyxin B or the immunosuppressant cyclosporine.[15-19] The success of this restrained peptide format as a therapeutic can be attributed to several favourable properties. First, cyclic peptides display a large surface area that provides a high affinity and selectivity for protein targets.[20-23] The limited conformational flexibility of the macrocyclic structure improves their favourable binding properties as well by reducing the entropic penalty upon binding. Second, cyclic peptides often have little to no toxicity due to their benign amino acid make-up.[24] Third, cyclic peptides are easily produced by automated chemical synthesis, and they are simple to modify, handle, and characterize, which are all important properties for therapeutics. In this review, the first section provides a look into the past by discussing the cyclic peptide therapeutics that have reached the market in the last ten years and details the techniques that were used to develop them. This section will highlight that nearly all of these drugs are based on natural products or derivatives thereof. In a second section, we look at the present by discussing cyclic peptides that are currently undergoing clinical studies. This overview will show that there are several original cyclic peptide drug candidates developed de novo by rational design or in vitro evolution instead of through the modification of natural products. In a third section, we will look to the future by discussing the most promising new cyclic peptide formats and predict the technologies that will comprise the next generation of cyclic peptide therapeutics. Peptide macrocycle drugs approved in the last ten years In the last ten years, 2006–2015, the FDA and EMA have approved nine cyclic peptide drugs, which account for 3% of the new drugs that entered the market in this time period. Four of these cyclic peptides, telavancin, dalbavancin, oritavancin and anidulafungin, are employed in bacterial and fungal infections. Three peptides, lanreotide, romidepsin, and pasireotide are oncology drugs, and one, linaclotide, is specific for gastrointestinal disorders. The last drug, peginesatide, was developed for the treatment of anemia during dialysis but was withdrawn soon after approval due to safety concerns.[25-30]

Several important challenges remain in the development of cyclic peptide therapeutics, the two most important ones being oral availability and cell permeability. Innovative approaches applied in recent years address one or both of these challenges, including the use of cell penetrating peptide, the stabilization of peptides in a-helical conformations with hydrocarbon linkers, or the in vitro evolution of N-methylated peptides. In order to develop cyclic peptides that have a good oral availability and that efficiently enter cells by passive diffusion, it might be necessary to consider molecules with smaller molecular weights and fewer peptide bonds. One could imagine that future macrocycles will contain only one or a few amino acids with an additional polyketide type component in the backbone.[31] A good role model is the orally available and cell permeable drug tacrolimus 28 Next generation therapeutics Current Opinion in Chemical Biology 2017, 38:24–29 www.sciencedirect.com which contains a backbone based on one amino acid and a polyketide chain wherein the amino acid forms key interactions with the target. To develop such chimeric peptide/polyketide macrocycle ligands, it will be crucial to create efficient chemistries and strategies that allow the synthesis and screening of large combinatorial libraries.

Cyclopeptides or cyclic peptides represent a family of fantastic compounds with complex structures and various bioactivities, such as antibiotic gramicidin S, antitumor RA-VII, uterotonic polypeptide kalata B1, antibacterial albonoursin , and cytotoxic patellamide D. The head-to-tail cyclized backbone protects cyclopeptides against proteolytic cleavage. Most cyclopeptides are products of non-ribosomal peptide synthetases (NRPSs). These peptides are cyclized by thioesterase (TE) domains located in C-terminal of NRPSs. The cyclization occurs by nucleophilic attacking of nucleophile (e.g.amine group, hydroxyl group, or thiol group) against carbonyl group of ester bond linking to the TE domain. More and more cyclopeptides have been confirmed to be ribosomal products or at least independent of NRPSs, including some cyclopeptides that were previously considered as non-ribosomal peptides (NRPs), such as microviridin.[32]

Till date, pathways both of NRPS and ribosomal have been discussed including the cyclization mechanisms in the NRPS pathway. Some genetic information of these ribosomally

synthesized cyclopeptides has been discussed, such as gene clusters of cyanobactins and cDNA sequences of cyclotides. However, no review has specifically discussed the cyclization mechanisms of peptides synthesized independently of NRPSs, although several intriguing mechanisms have been reported for the cyclization of these cyclopeptides, e.g. endopeptidase-catalyzed cyclization of cyclotides and cyanobactins, artificial cyclization with a permuted intein in cyanobacterium and peptide synthetase-catalyzed cyclization of albonoursin. These mechanisms of enzymatic cyclization in the ribosomal biosynthetic pathway have extended the knowledge of enzymatic reactions and brought the ribosomal and non-ribosomal pathways together. To modify the ribosomal system is easier than modifying the non-ribosomal system, because the NRPSs are too large to be processed by gene operation. This knowledge will help to develop new technologies in combinatorial biosynthesis and bioengineering to produce novel bioactive compounds.[33-38]

Endopeptidases present a family of enzymes, which catalyze the hydrolysis of the peptide bond (or breaking the peptide bond in other words). Now some evidences show that the enzymes of this family also catalyze the transpeptidation by forming a peptide bond, which includes cyclization. Cyclotides and cyanobactins are good examples of endopeptidase-catalyzed cyclization.[39]

Cyclotides belong to plant cyclopeptides type VIII, which is a family of mini disulfide-rich peptides derived by plants with ~30 amino acids and contains a unique protein motif cyclic-cystine-knot. This motif, which includes three disulfide bonds, together with cyclic backbone makes cyclotides exceptionally stable. The first cyclotide kalata B1 was discovered in the African traditional herb *Oldenlandia affinis* that had been used as uterotonic medicine, which showed that cyclotides could be used in clinic safely.[40] Till 2009, various cyclotides with activities of hemolysis, anti-HIV, antimicrobe, cytotoxin, and insecticide have been reported. A study confirmed that the linear analogues lacked bioactivity even if the N-terminals were blocked by the acetyl group. So, the cyclic backbone is very important to cyclotides' bioactivities.[41]

Cyclotides were confirmed as gene-coded products and spliced from larger propeptides. The cyclization of backbone occurs after the forming of a cyclic cystine knot *in vivo*, although chemical synthetic research shows that the cyclic backbone is preferred for the generation of cyclic cystine knot *in vitro*.[42-43] The cyclization of the backbone is catalyzed by asparaginyl endopeptidase (AEP). There are six conserved residues (XXNGLP), which are recognized by AEPs. The reaction is initiated by the electron transferring from histidine to cysteine. Then the thio group will attack the carbonyl group of the asparagine, break the peptide bond, and link the N-terminal of propeptide to the enzyme. The amino group of glycine accepts the proton from histidine and the C-terminal germin-like protein (GLP) tripeptide leaves. Then the N-terminal propeptide folds and the first three residues, which are conserved GLPs, fit into recognizing site S1', S2', and S3'. The amino group of glycine residue initiates a nucleophilic attack to form the peptide bond and completes the cyclization. This research gives a novel mechanism of peptidase, in which a pair of reversing activities occurs in a single catalytic site. Peptidases were considered to catalyze the reaction of either breaking or forming a peptide bond. Although the activities both of hydrolysis and transpeptidation share a similar catalytic center (catalytic triad Asp-Ser-His), the nucleophilic attacking groups are different in these two reactions, which are $H_2O$ in hydrolysis but $NH_2$ in transpeptidation. If we may define the cyclization of cyclotides as intramolecular transpeptidation, this research is the first example to catalyze both of two reactions in order.[44]

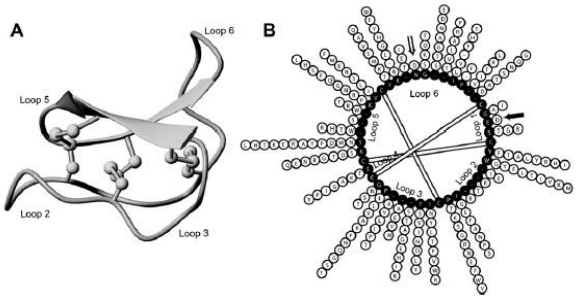



**Fig:** Cyclotide structures and sequences. Panel A shows the prototypic cyclotide kalata B1 (PDB ID:1NB1), illustrating the cyclic backbone and cystine knot motif, along with a small b-sheet and loops between successive Cys residues. Panel B shows a diversity wheel representation of sequence variation seen in cyclotides. The inner circle shows the consensus sequence of all cyclotides, with the radiating arms showing residues that are substituted at corresponding positions in currently known cyclotides. At each position amino acids are sorted according to their frequency, the closer to the wheel being the more conserved. There are only a few positions, apart from the completely conserved cystine residues, that are almost invariant.

## 2. Conclusion

Cyclic peptides are naturally occurring mini protein bioactive molecules with interesting pharmacological and biochemical properties. They are present in several species of plant families such as Annonaceae, Araliaceae, Asteraceae, Caryophyllaceae, Euphorbiaceae, Fabaceae, Labiatae, Linaceae, Olacaceae, Rhamnaceae, Rubiaceae, Rutaceae, Schizandraceae, Solanaceae, and Violaceae, Basidiomycetes is the group of higher fungi and these cyclopeptides display various biological properties such as protease inhibitory, antimicrobial, insecticidal, cytotoxic, anti-human immunodeficiency virus, cytotoxic, antimalarial, estrogenic, sedative, nematicidal, immunosuppressive, and enzyme-inhibitory activities.[1] Gramicidin S is an example of naturally occurring cyclic decapeptide extracted from the soil bacterium Aneurinibacillus.[2,3] The biological characteristic features of cyclic peptides are different from linear peptides. There are different ways to cyclize peptides. The linear peptide strand can be cyclized not only from head to tail, connecting the C and N-termini, but also by linking to amine and carboxylic functions in amino acid side chains, giving side-chain-to-head or side-chain-to-tail connections. Side-chain-to-side-chain bridges have also been observed.

***Acknowledgement***

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