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Cyclic Peptides: Prominent Next Generation Targeted Therapies

Manjula Reddy Pallerla[1,*], Bhairaiah Mara[1], Ramesh babu Konda[1], Ataharoddin Khaja[1]

[1]Peptide R&D, Matrix Pharmacorp Pvt. Ltd. Plot No. 1-60/35/A, 6th to 9th Floor, HITEC City, Phase II, Gachibowli Serilingampally Mandal, Ranga Reddy District, Hyderabad, Telangana, India, Pin code - 500 081

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Corresponding author:

Manjula Reddy Pallerla, Peptide R&D, Matrix Pharmacorp Pvt. Ltd. Plot No. 1-60/35/A, 6th to 9th Floor, HITEC City, Phase II, Gachibowli Serilingampally Mandal, Ranga Reddy District, Hyderabad, Telangana, India, Pin code - 500 081.

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Abstract

Cyclic peptides are expected to play a significant role in the future of drug discovery and development. Their unique properties, such as enhanced target affinity, metabolic stability, and favorable pharmokinetic profiles, make them promising candidates for addressing complex therapeutic targets. Innovations in design and synthetic techniques, including phage display and genetic code expansion with noncanonical amino acids, are enabling the development of diverse cyclic peptide libraries. These advancements are expected to bridge the gap between traditional small molecules and biologics, offering significant promise in the treatment of complex diseases.

The therapeutic potential of cyclic peptides is broad, with applications in various pharmacological activities, including antibiotics, antifungals, anticancer, and immunosuppressants. The number of cyclic peptide drugs under research has reached hundreds, some have entered the late clinical stage. With ongoing research, more cyclic peptide drugs are expected to be approved and enter the market in the future.

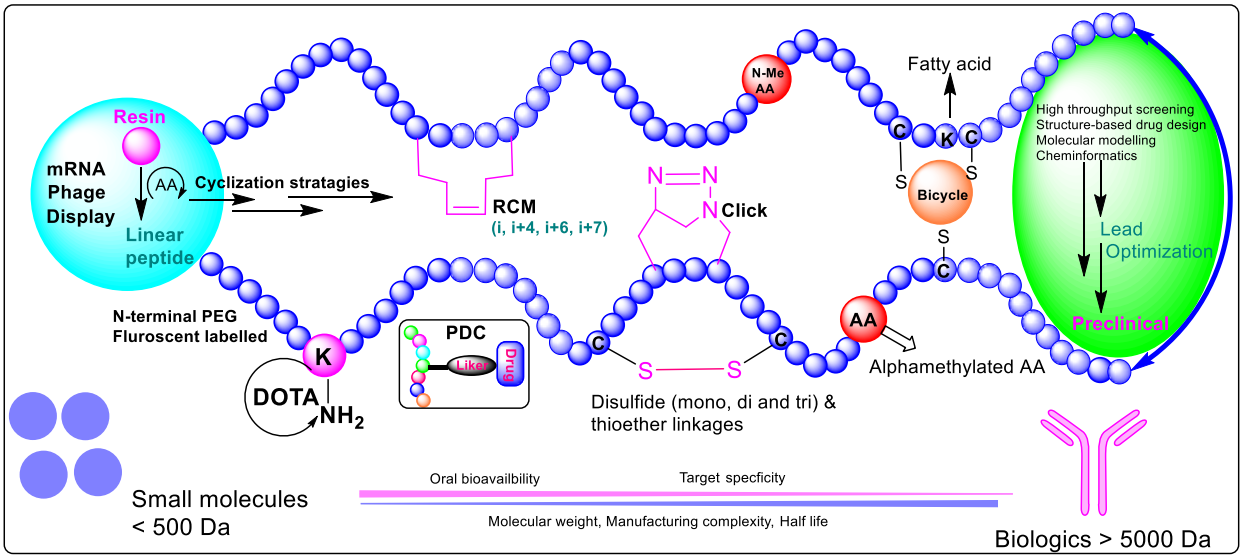
Cyclic peptides are also valuable research tools, suitable for probes that selectively modulate target proteins or high affinity ligands for biomolecular imaging. The development of selection strategies and various cyclization strategies, non-natural amino acids, and functional building blocks further enhance their functionality and utility in drug development.

In summary, Cyclic peptides are poised to be a valuable class of molecules in the future, with ongoing research and development efforts aimed at optimizing their properties and expanding their therapeutic applications.

Introduction

Cyclic peptide drugs represent a unique category of therapeutics that offer improved stability, specificity for targets, and the potential for oral bioavailability, effectively bridging the characteristics of small molecules and biologics [1-12] [Table 1]. These peptides are created by connecting the N and C-termini or side chains of linear peptides, resulting in a ring-like structure that enhances conformational rigidity and binding affinity to targets. This cyclization not only increases metabolic stability and resistance to proteolytic degradation but also

Graphical Abstract



diminishes polarity by removing free terminal groups, which can enhance membrane permeability and facilitate the targeting of intracellular proteins, an advantage not typically seen with linear peptides or larger biologics such as antibodies [13-15]. Furthermore, cyclic peptides can effectively bind to complex protein surfaces, including those involved in protein-protein interactions that are often deemed "undruggable" by traditional drugs, thus merging the selectivity of biologics with the cell permeability of small molecules, making them highly valuable in drug discovery [16-18]. As of June 2024, a total of sixty-six cyclic peptide drugs has received global approval [Table 2], with 39 of these approved since 2000. Notable examples include Rezafungin, an antifungal for candidemia, Motixafortide, a CXCR4 antagonist for multiple myeloma, and Zilucoplan [19], a self-administered C5 inhibitor for generalized myasthenia gravis [Figure 1]. While cyclic peptides primarily target extracellular proteins, like cyclosporine, demonstrate oral bioavailability [20] and the ability to traverse cell membranes despite their high molecular weight, attributed to favorable intramolecular hydrogen bonding and reduced polarity. To address challenges such as poor metabolic stability and limited membrane permeability, various strategies are employed, including backbone modifications that incorporate D-amino acids, N-Me & alpha methylated AA and fatty acid linkages [21,22].

Table 1. Properties of Cyclic peptides Vs Linear Peptides

Property	**Cyclic peptides**	**Linear peptides**
Confirmation	Restricted	Flexible
Terminal Residues	Absent or less	Present
Polarity	Lower	Higher
Affinity	Higher	Lower
Hydrogen Bonds	Intramolecular	Intermolecular
Permeability	Higher	Lower
Oral Administration	Feasible	Less likely
Stability	Higher	Lower
Intracellular targets	Feasible	Less likely

Table 2. FDA approved cyclic peptides drugs from 2001-2022 (Reference: J. Med. Chem. 2022, 65, 11913-11926).

Trade name	Generic Name	Target	Indication	Approval
Istodax	Romidepsin	Histone deacetylases	Anticancer	2009
Lupkynis	Voclosporin	Calcineurin	Lupus nephritis	2021
Prialt	Ziconotide	Calcium channel	Severe and Chronic pain	2004
Lizness	Linaclotide	Guanylate cyclase	Irritable bowel syndrome	2012
Trulance	plecanatide	Guanylate cyclase	Chronic idiopathic constipation	2017
Signifor	Pasireotide	Somatostatin receptor	Cushing's disease	2012
Somatuline	Lanreotide	Somatostatin receptor	Neuroendocrine tumors	2007
Vasostrict	Vasopressin	Vasopressin receptor	Antidiuretic hormone deficiency	2014
Teripressin	Terlipressin	Vasopressin receptor	Low blood pressure	2009
Vylessi	Bremelanotide	Melanocortin receptors	Hypoactive sexual desire disorder	2019
Imcivree	Setmelanotide	Melanocortin 4 receptor	obesity	2020
Cubicin	Daptomycin	Membrane pore formation	Antibiotic	2005
Vibative	Telavancin	Cell wall synthesis	Antibiotic	2009
Dalvance	Dalbavancin	Cell wall synthesis	Antibiotic	2014
Orbactiv	Oritavancin	Cell wall synthesis	Antibiotic	2014
Cancidas	Caspofungin	1,3-β-glucan synthase	antifungal	2001
Mycamine	Micafungin	1,3-β-glucan synthase	antifungal	2005
Eraxis	Anidulafungin	1,3-β-glucan synthase	antifungal	2006
Lutathera	177Lu-DOTA-TATE	Somatostatin receptor	Neuroendocrine tumors	2018

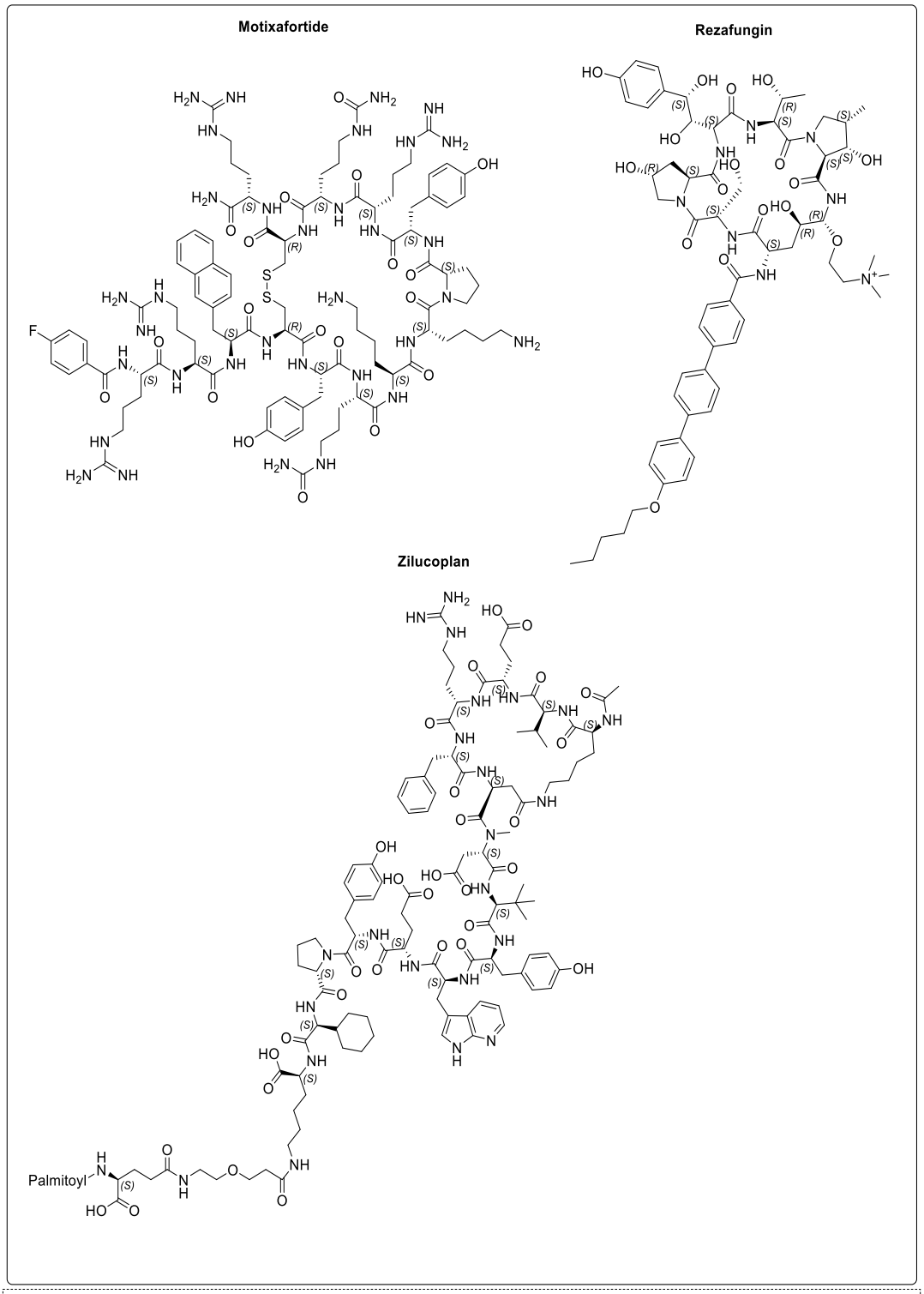


Figure 1. FDA approved peptides in 2023

Screening technologies such as phage and mRNA display have broadened the scope of macrocyclic peptide pharmaceuticals leading to the development of new drugs against diverse targets. The combination of such techniques with genetic code reprogramming has further broadened the utility of macrocyclic peptides by allowing the discovery of orally available molecules capable of intracellular targeting. The coming decade is highly likely to see the approval of numerous entirely novel macrocyclic peptide

Table 3. Macrocyclic peptides in Clinical trials

Drug Name	Highest Clinical Phase	Source Type	Clinical Trial ID	Route of Administration
AP301	Phase III	Natural product derivative	NCT07030595	Oral
BMS-986229	Phase III	mRNA display	NCT04161781	Injectable
JNJ-2113	FDA approved/Mar 2026	Phage display	NCT05364554	Oral
MK-0616	FDA approved/June 2026	mRNA display	NCT07216482	Oral
ORMD-0801	Phase III	Natural product derivative	NCT06731075	Oral
PL9643	Phase III	Natural product derivative	NCT05201170	Ophthalmic
Plitidepsin	Phase III	Natural product source	NCT01102426	Injectable
Balixafortide	Phase III	Natural product derivative	NCT03786094	Injectable
Rusfertide	Phase III	Natural product derivative	NCT05210790	Injectable
BT8009	Phase II/III	Phage display	NCT04561362	Injectable
VT1021	Phase II/III	Natural product derivative	NCT03364400	Injectable
ALRN-6924	Phase II	Stapled peptide design	NCT02264613	Injectable
AMY-101	Phase II	Phage display	NCT04395456	Injectable
AZP-3813	Phase II	mRNA display	NCT05239221	Injectable
Certepediol	Phase II	Phage display	NCT03517116	Injectable
Dolcamatide	Phase II	Natural product derivative	NCT03300570	Oral
PL8177	Phase II	Natural product derivative	NCT05466890	Oral
THR-149	Phase II	Phage display	NCT04527107	Injectable
TE-232	Phase II	Natural product derivative	NCT06801236	Injectable
BHV-1100	Phase I/II	mRNA display	NCT04634435	Injectable
BT1718	Phase I/II	Phage display	NCT03486730	Injectable
FOG-001	Phase I/II	Phage display	NCT05919264	Injectable
Lonodelestat	Phase I/II		NCT03748199	Inhalation
BT5528	Phase I/II	Phage display	NCT04180371	Injectable
BT7480	Phase I/II	Phage display	NCT05163041	Injectable
LUNA18	Phase I	mRNA display	NCT05012618	Oral

-based drugs [23-30] [Table 3].

These recent approvals underscore the increasing significance of cyclic peptides within the pharmaceutical sector, as they provide enhanced drug-like characteristics and improved stability.

Cyclic peptides exhibit improved pharmacokinetic properties compared to linear peptides due to their cyclized structure, which enhances conformational rigidity, proteolytic stability, and binding affinity [31-34]. They are less susceptible to enzymatic degradation and have a longer half-life, making them more stable in the bloodstream. However, they still face challenges such as low oral bioavailability and rapid clearance, which can be mitigated through various strategies, including backbone engineering, side chain modification, and attachment to other carrier moieties. These adaptations help improve the pharmacokinetic profiles of cyclic peptides, making them suitable for various therapeutic applications.

Emerging Technology

Emerging technologies in peptide synthesis and purification are significantly transforming the field, driven by innovations such as green chemistry, artificial intelligence, continuous-flow techniques, and advanced downstream processing. While Solid-Phase Peptide Synthesis (SPPS) remains the leading method, it is increasingly challenged by its environmental impact and high solvent consumption, prompting the adoption of green chemistry principles to enhance sustainability in large-scale production. The future of green chemistry in peptide synthesis appears highly promising, driven by ongoing research aimed at developing sustainable and efficient methodologies [35]. Innovations in synthesis processes, such as liquid-phase and enzymatic peptide synthesis, are being investigated to minimize waste and enhance efficiency. Additionally, advancements in purification technologies, including continuous-flow synthesis and improved chromatographic techniques, are being designed to streamline purification while reducing chemical waste. The application of the 12 principles of green chemistry is also pivotal, as it guides the design of processes that limit the use of hazardous substances without sacrificing product quality. Furthermore, the integration of artificial intelligence and automation is optimizing reaction conditions, thereby reducing trial-and-error waste and expediting sustainable peptide manufacturing. Circular economy models are being explored to establish a sustainable peptide production framework that minimizes chemical waste and encourages recycling. Collectively, these advancements not only address environmental challenges but also enhance the efficiency and sustainability of peptide production, positioning green chemistry as a vital component in the future of the peptide industry.

Furthermore, advancements in purification technologies are crucial for therapeutic peptides, particularly for complex molecules like GLP-1 receptor agonists, as they now incorporate digital solutions and data analytics to optimize processes, improve yields, and allow for real-time troubleshooting.

Cyclic peptides are a transformative class of therapeutics, uniquely positioned between traditional small molecules and large biologics in modern drug discovery. They offer enhanced conformational rigidity, proteolytic stability, and exceptional target affinity, enabling them to engage challenging molecular surfaces, especially protein-protein interactions (PPIs) long considered "undruggable" by conventional modalities.

Advancements in peptide engineering, computational design, and high-throughput screening accelerate the development of cyclic peptides, which now offer a powerful strategy for overcoming historical limitations in specificity, selectivity, and delivery.

The biopharmaceutical industry increasingly views cyclic peptides as a versatile and scalable platform

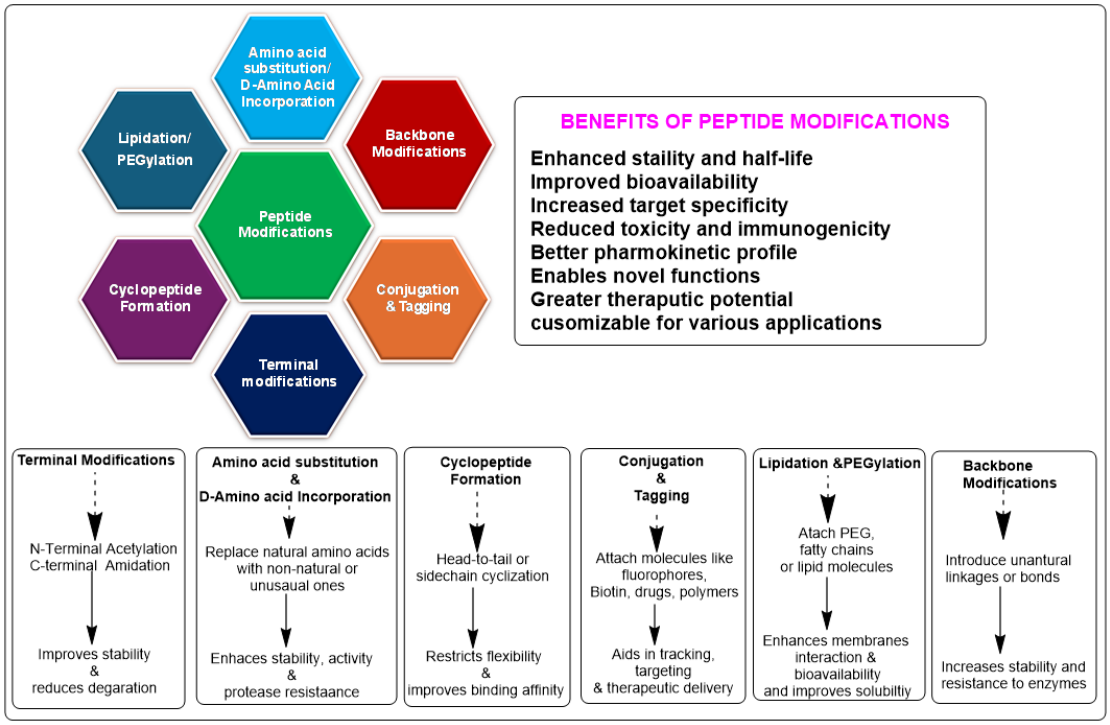
for next-generation drug design, offering several key advantages that significantly enhance their therapeutic potential compared with their linear counterparts.

Types of cyclic peptides

Cyclic peptides are polypeptide chains characterized by a circular structure formed through various chemical linkages. They can be categorized based on the types of bonds that create the ring, including homodetic cyclic peptides, which consist of standard peptide bonds, as seen in cyclosporin A; cyclic isopeptides, which feature at least one non-alpha amide linkage, exemplified by bacitracin; cyclic depsipeptides [36], which incorporate at least one lactone linkage, such as aureobasidin A; and bicyclic peptides, which contain structures with bridging groups, like amanitins. These cyclic peptides possess distinctive properties, including enhanced stability and conformational rigidity, rendering them highly valuable in drug development and various biological applications.

Peptide modifications

The landscape of peptide drug design is undergoing significant transformation, propelled by technological advancements and novel therapeutic applications. Solid-phase peptide synthesis has emerged as a fundamental technique, enhancing the efficiency and specificity of peptide production, thereby solidifying its role in peptide therapeutics. Additionally, recombinant technologies have improved the production of peptides with optimized characteristics, such as enhanced stability and bioavailability. The advent of macrocyclization chemistry facilitates the creation of intricate peptide structures tailored for specific therapeutic outcomes. Furthermore, rational design strategies have played a crucial role in addressing historical challenges in peptide development, including issues related to poor oral bioavailability and rapid degradation by proteolytic enzymes. Innovations in delivery systems, including cell-penetrating peptides, nanocarriers, and peptide-drug conjugates, have broadened the clinical applicability of peptides, extending their use beyond traditional injectable forms. Collectively, these advancements have transitioned peptides from theoretical constructs to clinically approved entities, with nearly 100 drugs currently available and many more in advanced stages of development, marking a significant renaissance in peptide therapeutics that is vital for the future of drug design and development.



Strategies to enhance stability include

- **Backbone Modifications**: Incorporating D-amino acids, non-canonical amino acids (e.g., β-/γ-amino acids), and N-methylation. Bioisosteric modifications could preserve pharmacophore geometry while enhancing metabolic stability.
- **Cyclization Optimization**: Selecting optimal ring size and introducing double cyclization to reduce conformational flexibility and proteolytic degradation [38-40].

Secondary Structure Stabilization: Using α-helices, β-sheets, stapled peptides, or α/β-hybrid peptides [37].

Various strategies and their Key advantages/Key Limitations

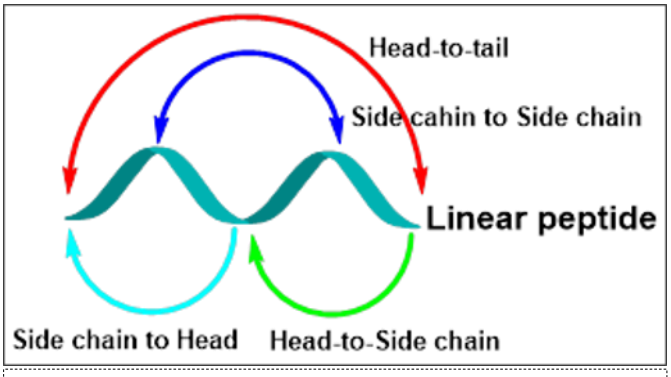


Figure 2. Types of cyclic peptides

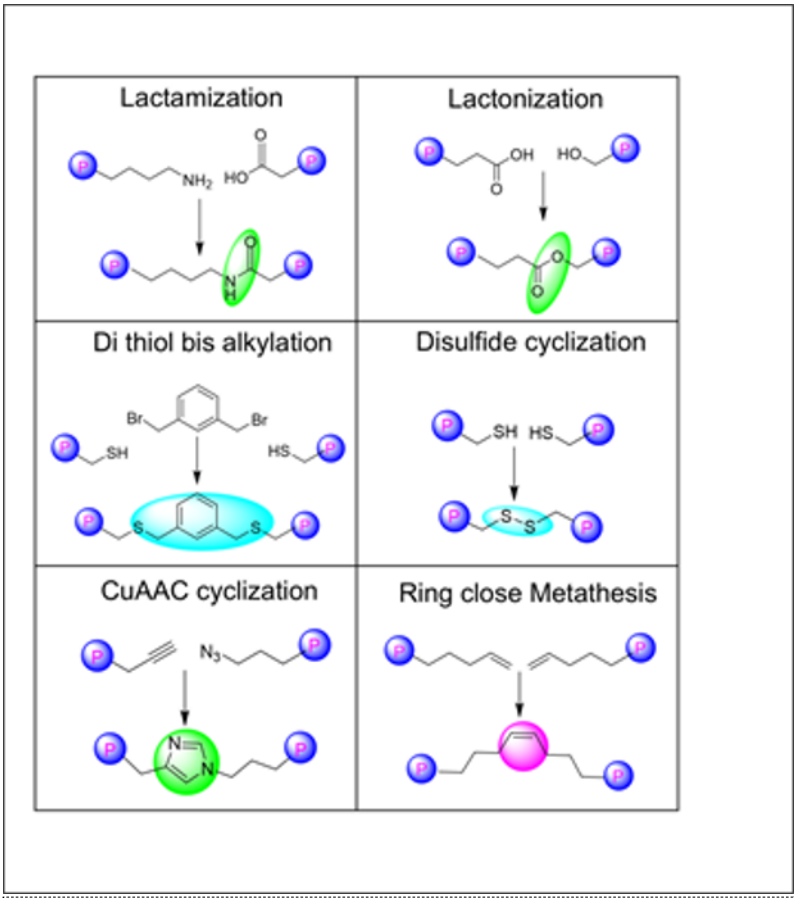


Figure 3. Types of different side chain to side chain cyclization strategy

Head-to-Tail

This method involves forming an amide bond between the N-terminus and C- terminus of a linear peptide. It is the most intuitive approach and is commonly used to generate cyclic peptide libraries [Figure 2].

Side-Chain-to-Sidechain

This approach forms covalent bonds between reactive side chains of amino acids within the same pepti de, such as cysteine-cysteine disulfide bridges, Lactamization, lactonization, dithiol-bis alkylation, Click chemistry and Ring close Metathesis (RCM, i, i+3, i+4, i+6 and i+7) [41-43] [Figure 3].

Head-to-Sidechain and Side-Chain-to-Tail

These less common methods involve linking the N- or C-terminus to a side chain, providing additional structural diversity and conformational control. They are useful for designing peptides with specific spatial arrangements or functional motifs.

Cyclic peptide applications

Their applications are numerous, ranging from therapeutic drugs and food preservatives to pesticides in agriculture and valuable research tools. Below are some examples of applications in life sciences and drug discovery:

Cyclic peptide therapeutics (e.g., antibiotics, antiviral, cancer therapy) – Their interesting properties make them valuable candidates for therapeutic applications in drug discovery.

- Protein-protein interaction inhibitors/activators
- Cell-penetrating peptides

S. No	Cyclization Strategy	Key advantages	Key Limitations
01	N-Methylation	Enhance a peptide's resistance to enzymatic degradation	Reduced binding affinity or selectivity
02	D-Amino acids	Proteolytic stability and antimicrobial activity	Complicate the synthetic process
03	Lipidation	Improves stability and half-life of peptides	Formulation Challenges
04	Disulfide formation	Reduces flexibility and improves binding affinity	Combinatorial Challenge
05	Noncanonical amino acids	Enhanced stability and improved functionality	Poor solubility and low bioavailability
06	Lactamization (Head-to-Tail)	Mimics natural peptide backbone; well established chemistry	Risk of epimerization and dimerization, especially for small rings
07	Thioether Formation	Chemically stable; can be formed with various linkers	Requires specific amino acid functionalization
08	Click Chemistry (CuAAC)	High efficiency and orthogonality; bio compatible	Requires incorporation of azide and alkyne functionalities; residual copper concerns
09	Ring-Closing Metathesis (RCM)	Creates stable, all hydrocarbon staples; tunable linker length	Requires specialized, non-natural amino acids and a ruthenium catalyst

- Nanotechnology and drug delivery systems
- Mimics of protein structural motifs
- Biosensors

Imaging and diagnostics: For instance, radiolabeled cyclic RGD (Arg-Gly-Asp), a peptide known to target overexpressed integrin αvβ3 in cancer cells, shows promising results as imaging probes for early cancer detection and non-invasive tumor monitoring

Peptide Library Technologies

Peptide library technologies, which encompass methods for generating and screening extensive collections of peptide variants, serve as the driving force behind peptide drug discovery. The progression from *phage display*, offering 10^9 diversity, to *mRNA display* with 10^{13} diversity, and finally to fully synthetic *DNA-encoded libraries* featuring 10^{12} diversity with non-canonical amino acids, has significantly reduced the timeline from target identification to hit discovery from years to mere weeks. It is crucial for any organization involved in peptide drug discovery to comprehend the trade-offs associated with these platforms.

The Technology Spectrum RaPID (flexizyme) | 10^{12}–10^{13} | 400+ ncAAs | Broadest chemical diversity | IP controlled by PeptiDream. One-bead-one-compound, commonly referred to as OBOC | 10^5–10^7 | Wide | No biological constraint | Smallest libraries; bead handling. The *RaPID platform*, which stands for Random non-standard Peptides Integrated Discovery, was developed by *Hiroaki Suga* at the University of Tokyo and is exclusively licensed to PeptiDream. This platform represents the most significant advancement in peptide library technology over the past decade. RaPID integrates mRNA display with flexizyme, a ribozyme that acylates tRNAs with non-canonical amino acids, allowing for the incorporation of more than 400 building blocks beyond the standard 20 amino acids. This dramatically increases the chemical space available to peptide libraries, facilitating the discovery of macrocyclic peptides with drug-like characteristics that would be unattainable in traditional libraries.

Ribosome display maintains a direct genotype-phenotype link throughout the selection process. The physical connection between the protein (phenotype) and its encoding mRNA (genotype) ensures that when a desired protein is selected, its corresponding genetic information is immediately available. This direct linkage streamlines the identification and amplification of the genes responsible for the desired binding or catalytic activity.

SICLOPPS: One method for the intracellular generation of libraries is split-intein circular ligation of peptides and proteins (SICLOPPS).

Conclusions

Recent progress in peptide synthesis has been marked by notable advancements in solid-phase peptide synthesis (SPPS), green chemistry, and catalytic methods. These developments have facilitated the creation of peptides that were once deemed too complex for conventional techniques, including those with sequences longer than 50 amino acids. Nonetheless, issues such as aggregation during synthesis and the necessity for predictive models for peptide delivery systems persist. Future efforts in peptide therapeutics will focus on tackling these challenges through a combination of computational and experimental methodologies, alongside the innovation of nano formulation strategies to navigate biological obstacles.

Significant advancements have been made in peptide-based therapeutics; however, substantial

challenges remain in achieving their full clinical efficacy, especially concerning oral administration. The gastrointestinal (GI) tract poses a significant obstacle, as the bioavailability of most oral peptides is typically below 1% due to factors such as enzymatic degradation, instability related to pH, and restricted epithelial permeability. Although the use of permeation enhancers and enzyme inhibitors can alleviate some of these challenges, their long-term safety, potential to disrupt intestinal barrier integrity, and variable efficacy based on dosage require further investigation through preclinical and clinical studies. Future innovations should embrace interdisciplinary approaches to overcome these limitations. For instance, structural engineering techniques like D-amino acid substitution, backbone cyclization, and hydrophobic stapling may improve resistance to proteolytic enzymes while maintaining target interaction. Additionally, novel delivery systems such as mucus-penetrating nanoparticles, pH-responsive enteric coatings, and FcRn-targeted carriers show promise in enhancing intestinal absorption and systemic bioavailability. Furthermore, computational methods, including AI-driven molecular dynamics simulations and machine learning, could expedite the assessment of peptide stability, membrane permeability, and pharmacokinetic characteristics. By integrating these advancements, the next generation of oral peptides could significantly impact precision medicine, facilitating targeted treatments for conditions such as cancer, antibiotic-resistant infections, and metabolic disorders, thereby narrowing the gap between preclinical potential and practical therapeutic application.

Methodology and Scope

Databases: E-Journals, Communications, books, reviews, Patents, SciFinder

The date range covered: **1980-2026**

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