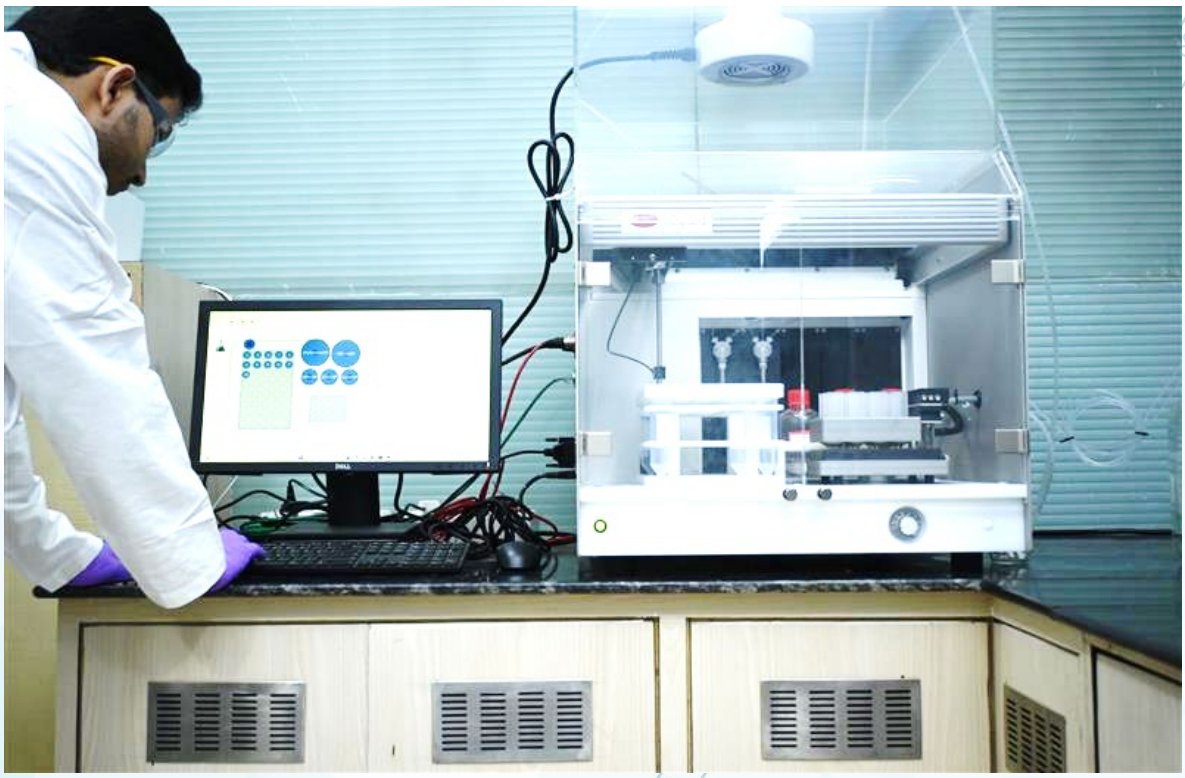


Peptide Chemistry: Approaches, Capabilities and Applications in Drug Discovery

Peptides are at the forefront of modern drug discovery and development, offering structural diversity, specificity, and therapeutic potential across a broad range of indications. Over the last decade, peptide chemistry has evolved significantly, supported by advances in synthesis technologies and analytical methods.

Peptides hold significant potential in drug discovery research, and numerous peptides have been approved by the FDA, with a notable increase in approvals in recent years. Examples include semaglutide (for diabetes), ziconotide (for chronic pain), rezafungin (for candidemia), and motixafortide (for multiple myeloma). Peptide drugs are highly regarded for their high potency, specificity, low side effects, and lower production costs compared to antibody-based therapies. The estimated value of the global peptide drugs market is around USD 46 billion in 2024 and is projected to reach approximately USD 260 billion by 2030, growing at a compound annual growth rate (CAGR) of ~10.77%.

Approaches to Peptide Synthesis

Modern peptide synthesis primarily uses solid-phase peptide synthesis (SPPS) and liquid-phase peptide synthesis (LPPS). LPPS can be limited by complex purification requirements, low scalability, and high solvent consumption, while SPPS offers

automatable, high-yield, scalable synthesis with simplified purification, lower environmental impact, high-throughput parallelisation, and consistent quality control. Hybrid SPPS–LPPS workflows are frequently employed to optimise routes for complex, multifunctional, or cyclic peptides.

Automated synthesis platforms such as Biotage® Initiator+ Alstra™, CSBio, and Syro I have transformed laboratory practice. These systems enable parallel synthesis and scalable production in the 0.5 to 5 mmol range, while microwave-assisted methods improve coupling efficiency, particularly for difficult or sterically hindered sequences.

< Peptides-Peptidomimetics-Synthesis >

Expanding Structural Diversity

Peptide drugs are categorised into linear peptides and cyclic peptides. Compared to linear peptides, their cyclic counterparts, owing to their enhanced conformational rigidity, intramolecular hydrogen bonding, lower polarity, and higher target binding affinity, exhibit superior drug-like properties such as enhanced metabolic stability, improved permeability, enabling oral administration or targeting intracellular sites.

Peptide design today extends far beyond linear chains. Chemists routinely generate cyclic, branched, and multifunctional structures to improve stability and biological activity. Macrocyclisation strategies include disulfide, thioether, lactam, stapled, and click-based ring closures.

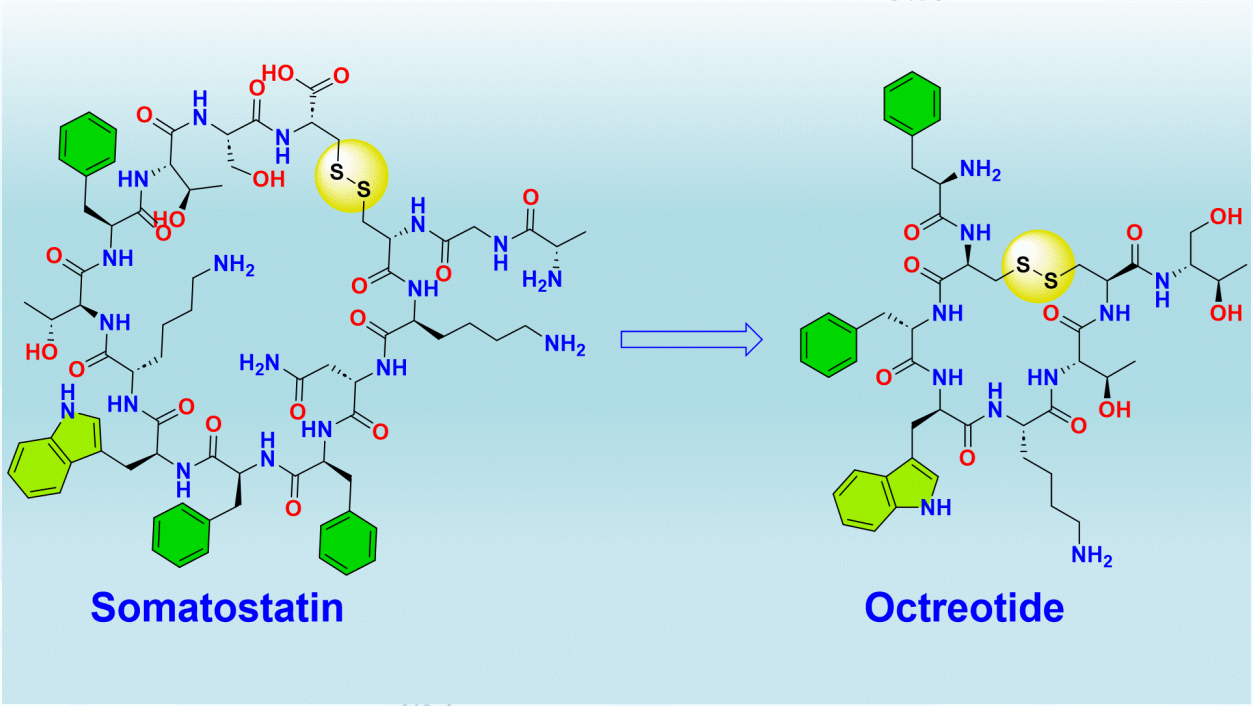
Chemical modifications further expand structural diversity. PEGylation, lipidation, biotinylation, and fluorophore conjugation allow tuning of pharmacokinetic behaviour, while the incorporation of unnatural amino acids, N-alkylated residues, and custom linkers enhances chemical and biological versatility.

- ***Case Study: From Somatostatin to Octreotide***

A well-known example of structural optimisation comes from somatostatin, a natural cyclic peptide of 14 amino acids with a plasma half-life of less than 3 minutes. Through structural modifications — replacing L-phenylalanine and L-tryptophan with their D-

amino acid counterparts and converting the C-terminal carboxyl to an alcohol group — an 8-mer analogue, octreotide, was developed.

Octreotide exhibits a significantly improved half-life of 100 minutes and is clinically used for treating growth hormone–producing tumours. This example illustrates how peptide chemistry can transform natural scaffolds into drug candidates with enhanced pharmacokinetic properties.



Analytical and Purification Considerations

With structural complexity comes the need for robust purification and analytical control. High-quality peptides are typically purified by reverse-phase preparative HPLC and recovered through lyophilisation or salt-exchange methods.

Analytical tools such as LC-MS, UPLC, NMR, and chiral SFC play a crucial role in confirming identity, purity, and stereochemical integrity. To ensure reproducibility, detailed Certificates of Analysis (CoA) are generated, covering parameters such as identity, purity, TFA content, and impurity profiles.

< Analytical-Chemistry >

Beyond Synthesis: Challenges of Peptides as Drugs

Despite their promise, peptides face key challenges as drug candidates, including poor cell penetration, short plasma half-life, and low oral bioavailability. Addressing these barriers requires both design strategies and integrated support from downstream services.

- Medicinal chemistry approaches such as backbone modifications (e.g., D-amino acid incorporation, N-methylation, bioisosteric replacements, ring size selection for cyclic peptides, modulation of polar surface area, and control of hydrogen bond donors) can significantly improve metabolic stability and permeability.

- DMPK services provide solutions through high-throughput experimental platforms and cutting-edge equipment to rapidly generate high-quality data, helping advance projects efficiently.

  < DMPK >

- Formulation strategies, including nanoformulation of lipopeptides under sterile conditions, are increasingly used to overcome metabolic instability and delivery challenges. Analytical methods are employed to evaluate encapsulation efficiency and reproducibility, ensuring consistent quality for downstream studies.

Looking Ahead

The growing importance of peptides in therapeutic development is matched by advances in synthetic chemistry, medicinal chemistry, analytical sciences, and DMPK support. From linear peptides to multifunctional architectures and nanoformulations, the field continues to expand its scope. These developments highlight both the opportunities and the technical challenges involved in translating peptide chemistry into drug discovery applications.