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PBP-like Cyclases as Biocatalysts for Generation of Cyclic Peptides

Novel compounds that potently inhibit viral replication with strong drug-like properties.

Researchers at Purdue University have discovered enzymes that cyclize peptide natural products. The method harnesses penicillin-binding proteins (PBP) as biocatalysts for efficient cyclization of small rings. Cyclic peptides are great sources of medicine, but current methods are challenging and often not applicable to many compounds of interest. This is especially relevant to small cyclic peptides such as tetrapeptides, which are notoriously difficult to synthesize. Conventional cyclic peptide synthesis provides fast reaction rates but results in scalability issues and competing side reactions.

Unlike traditional chemical methods like on-resin cyclization and pseudoproline residues, this innovation does not require acidic residue or pseudoproline. This innovation greatly improves cyclic peptide yields and allows easy access to derivatives. The enzymes are adaptable to work with peptides still on resin and more traditional thioester linked peptides. They fulfill an unmet need for cyclizing small peptides that can be scaled for production.

Technology Validation:

Bioinformatic analysis, X-ray crystal structure, and docking studies were conducted to explain the structural basis behind substrate promiscuity and increased catalytic activity of the PBP enzymes. Findings showed approximately 10-fold better activity and 15-fold greater total turnover when cyclizing both pentapeptides and tetrapeptides.

Advantages:

- Easy access to cyclic peptides, especially tetrapeptides

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Category

Biotechnology & Life Sciences/Biomarker Discovery & Diagnostics
Biotechnology & Life Sciences/Analytical & Diagnostic Instrumentation
Chemicals & Advanced Materials/Materials Processing & Manufacturing Technologies

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- Capable of cyclizing a wide variety of peptides

- Scalable to production processes

Applications:

- Medicines such as antibiotics, cholesterol-lowering drugs, and immune suppressants

- Agricultural companies

- Pharmaceutical companies

TRL: Pharmaceuticals

Intellectual Property:

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