ORGANIC SEMINAR

Biocatalytic Peptide Macrocyclization

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Macrocyclic peptides are promising scaffolds for chemical tools and potential therapeutics. However, synthetic methods for peptide macrocyclization often face challenges such as C-terminal epimerization and oligomerization, which hinder scalability.

In this talk, I will present the characterization of Ulm16 and PBP-TE_1, peptide cyclase enzymes from the penicillin-binding protein-type class of thioesterases (PBP-TE), which catalyze the head-to-tail macrolactamization of nonribosomal peptides. Both Ulm16 and PBP-TE_1 exhibit unprecedented substrate promiscuity, with Ulm16 efficiently catalyzing the cyclization of various nonnative peptides ranging from 4 to 6 amino acids, achieving catalytic efficiencies of up to 3×10^6 M^{-1} s^{-1}. PBP-TE_1, identified through bioinformatics, demonstrates the unique ability to cyclize tetrapeptides that no other reported PBP-TE can and a substrate scope well beyond that of Ulm16. Additionally, I will discuss the discovery and validation of a thioesterase domain capable of forming an indolamide bond during macrocyclization.

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