ORGANIC SEMINAR

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Mild Macrocyclization: New Chemoselective Strategies to Access Conformationally Constrained Peptides

Although peptides are ideal candidates to modulate protein function and disrupt protein-protein interactions, their biological applications have been limited by low intracellular stability, poor cell permeability, and rapid in vivo clearance. Peptide macrocyclization has been shown to be an effective strategy for mitigating these unfavorable pharmacokinetic characteristics. The chemical diversity of macrocyclic peptides, however, is limited by the scarcity of orthogonal synthetic methods for chemoselective cyclization of peptides.

I will discuss my lab's efforts to develop new orthogonal methods for peptide macrocyclization at tyrosine or lysine. These methods expand current capabilities by being (1) chemoselective, (2) operationally simple, and (3) progressing under mild and sustainable conditions. We exploit the chemoselective control of these methods for the synthesis of cyclic and stapled peptide analogs and demonstrate enhanced serum stability and bioactivity against a wide array of biological targets.