Expanding the Chemical Space of Lasso Peptides: Enzymatic Maturation of Synthetic Peptide Precursors

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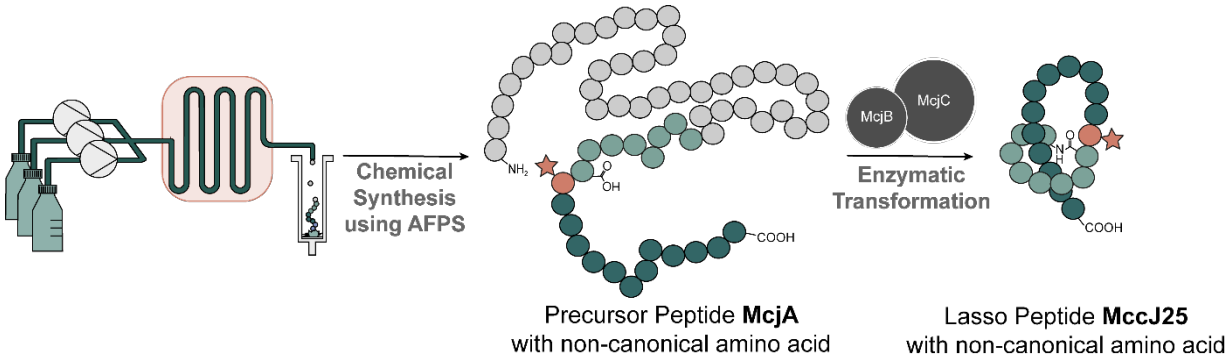
Lasso peptides are a class of ribosomally synthesized and post-translationally modified peptides (RiPPs), and many display antimicrobial, antiviral, and antitumor activity.[1] Their biological activities and their excellent stability against heat treatment and enzymatic digestion make them potential therapeutic agents, and chemical modifications would be desirable to explore this potential.[2] However, chemical synthesis is challenging because of the unique knot-like structure. Therefore, the most prominent member of their class – Microcin J25 (MccJ25), which shows activity against Gram-negative bacteria[3] – has not been chemically synthesized to date. Here, we **use flow-based peptide synthesis in combination with in vitro enzymatic maturation to investigate the promiscuity of the processing enzymes and give access to several chemically modified MccJ25 derivatives including non-canonical amino acids.** We confirm lasso-formation by ion-mobility mass spectrometry and perform antimicrobial assays to obtain additional information about the influence of these chemical modifications on activity. Lasso peptides are promising targets for drug design due to their enhanced stability and incorporating non-canonical amino acids will expand the chemical space. This allows for library synthesis and enables grafting onto this scaffold.



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