From Peptides to Drugs: Expanding the Frontiers of Medicinal Chemistry

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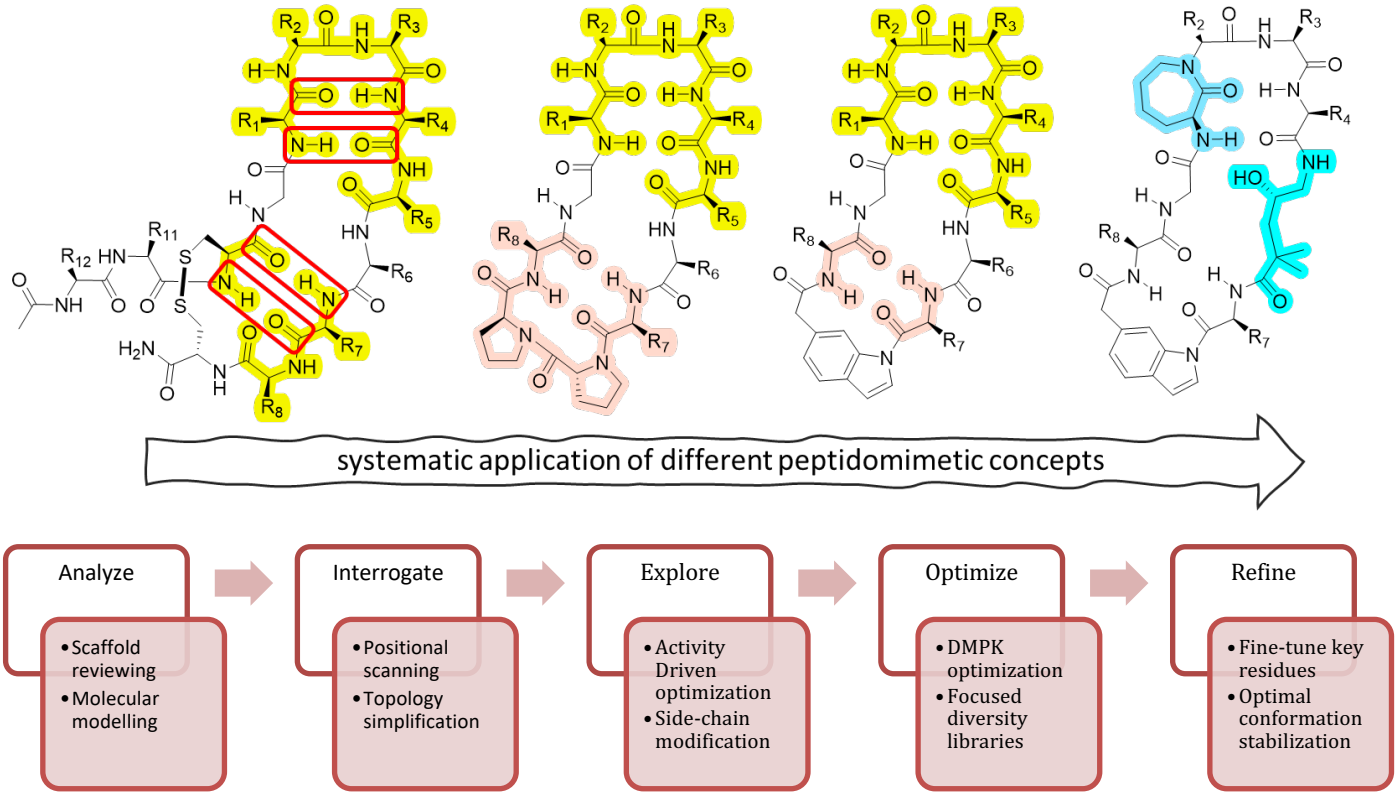
The field of medicinal chemistry is witnessing growing interest in peptides, peptidic, and semi-peptidic macrocycles as promising beyond rule-of-5 (bRo5) therapeutic modalities.[1,2] These complex structures are proving effective in modulating targets that were previously considered "undruggable".[3] However, both linear and cyclic peptides present several limitations that hinder their broader therapeutic development. These challenges include rapid metabolic degradation, fast clearance from the body, high conformational flexibility—resulting in reduced target specificity—and the potential for immunogenicity. To effectively evolve peptides into drug-like candidates, medicinal chemists need robust tools that support the systematic de-peptidization of lead compounds.



In this talk, we will showcase a typical workflow from e.g., an mRNA-display derived hit, over tractable leads to potential candidates, highlighting our toolbox based peptidomimetic approach that comprises multiple coupling chemistries on solid phase, tailor-made non-canonical amino acid residues, traditional dipeptide isosteres with replaced amide bonds, reverse turn- and extended strand-stabilizing mimetics, as well as non-peptide linkers for macrocyclization.

[1] D. G. Jimenez, V. Poongavanam, J. Kihlberg, *J. Med. Chem*. **66**, 5377 (2023)
[2] A. A. Rzepiela, L. A. Viarengo-Baker, V. Tatarskii, R. Kombarov, A. Whitty, *J. Med Chem.* **65**, 10300 (2022)
[3] T. Kim, E. Baek, J. Kim, *Pharmaceuticals*, **18**, 617 (2025)