DEVELOPMENT OF HIGHLY FUNCTIONALIZED PEPTIDOMIMETICS AND THE APPLICATION TO BIOACTIVE CYCLIC PEPTIDES

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With advances in genome science, development of efficient methodologies for the rational design of therapeutically relevant agents from natural ligands including peptides and proteins is an area of increasing importance. Natural and artificial modifications of bioactive peptides and proteins provide opportunities to achieve a better understanding of the mechanisms underlying the bioactivities of parent structures as well as identifying novel functionalities that may be applied to new purposes. Application of unnatural amino acids and peptidomimetics constitutes one of the most powerful methodologies in such chemical approaches to understanding ligand-protein interactions.

We have developed several types of peptide bond mimetics and functionalized amino acids that provide global and/or local conformational constraints of bioactive peptides. One is multi-substituted alkene dipeptide isosteres, which was designed based on the ω-dihedral angle planarity of peptide bonds. The other example is phosphotyrosine (pTyr) mimetics having cyclic and/or acyclic structural motifs, that can stabilize β-bend conformations. These mimetics were introduced into several cyclic peptides possessing inhibitory activity against cancer progression. A summary of our design, synthesis and application of these peptidomimetics will be presented.

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