A New Synthetic Chemistry of Cyclic Peptides for the Development of Mid-sized Peptide Drugs

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Biography

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Abstract

Development of the new chemistry in the synthesis of cyclic peptide is highly important for the mid-sized drug development. In the presentation, to efficiently construct cyclic peptides, I would like to introduce two topics based on the chemistry of 3-nitro-2-pyridinesulfenyl (Npys) group[1], i.e., new solid- or none-solid-supported 3-nitro-2-pyridinesulfenates (Npys-OR) as disulfide bond-forming agents[2] and solid-phase-assisted disulfide ligation method using an Npys-Cl resin[3,4], as well as another topic on the synthesis of microorganism derived cyclic depsipeptide MA026[5] which has a epithelial tight junction (TJ) opening activity.

In the first topic, our developed Npys-OMe realizes "on-resin" disulfide bond formation[6] for preparing cyclic peptides in combination with the treatment of 2-mercaptoethanol for the deprotection of tBu-thiol groups from two Cys residues in SPPS, which can be applied to the automated solid-phase protocol. Moreover, by the combination with iodine oxidation, more complicated disulfide peptides like "α-conotoxin" with four Cys residues can be successfully synthesized on resin.

In the second topic, by using Npys-Cl resin, we synthesized a disulfide peptide from two kinds of Cys-containing peptide fragments in a simple solid-phase assisted procedure, which can lead to the syntheses of 1) cyclic peptides via the subsequent intra-molecular amide bond formation and[3,7], 2) multi-connecting disulfide peptides via the repetitive disulfide ligation. Moreover, this chemistry is useful to construct a variety of disulfide conjugates. One of the typical examples is a conjugation between peptide and drug with a different solubility to the reaction solvent[4]. In the presentation, we will also discuss the development of a stable Npys-Cl surrogate, Npys-OPh(*p*F), to increase the efficiency of this technology[8,10].

In the final topic, we would like introduce structure correction of MA026[11], an N-terminal acylated cyclic depsipeptide with 14 amino acid residues from *Pseudomonas*, through the synthesis of MA026 derivatives and their HPLC, NMR and MS analyses. The synthesized cyclic depsipeptide with the corrected structure showed the same physicochemical property and TJ opening activity as natural MA026. The N-terminal modification and alanine scanning of the peptide revealed the important structural factors for the activity.

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