Recent Advances in Orally Bioavailable Cyclic Peptides

Reported by Nathaniel Gehrke 3 December 2024

Introduction

The field of peptide-based therapeutics began with the first medical use of insulin in 1922, now regarded as a monumental scientific achievement. Since then, therapeutic peptides have maintained a significant portion of the global pharmaceutical market, accounting for over $70 billion in global sales in 2023. When compared to traditional small molecule drugs, peptides offer unique intrinsic advantages including improved target specificity or the ability to inhibit protein-protein interactions. On the other hand, peptides display low membrane permeability and *in vivo* stability, leading to their poor oral bioavailability and thus intravenous delivery. Cyclic peptides are unique as they possess similar molecular characteristics to linear peptides, such as those described by Lipinski's "Rule of 5", but can display improved oral bioavailability. This phenomenon is prominently showcased in Cyclosporin A (**Fig. 1**), which, despite its high molecular weight and polar surface area, can be administered orally. While cyclization improves the oral bioavailability of peptide therapeutics, it is still too low for most cyclic peptides for practical oral administration. Thus, the development of novel methods to improve their oral bioavailability is of great interest. This seminar will cover three strategies to improve the membrane permeability and *in vivo* stability of a cyclic peptide allowing for its oral administration.

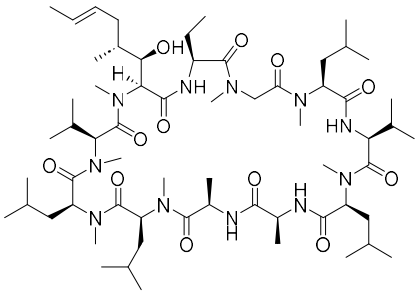

Figure 1: Cyclosporin A

Side Chain-to-Backbone Hydrogen Bonding

A major restriction to the passive membrane permeability of cyclic peptides is the high desolvation energy from the NH groups on the amide scaffold, lowering the molecules ability to enter the lipophilic environment of the membrane. Previous methods, such as *N*-methylation of the amide backbone, have masked these hydrogen-bond donors (HBDs) but are limited as they often decrease drug potency. The Lokey group has developed a method to sequester the exposed HBDs of a cyclic peptide by introducing side chains bearing hydrogen-bond acceptors (HBAs) (**Fig. 2**). By adding an *N,N*-pyrrolidinylglutamine side chain, impressive membrane permeability is displayed in a series of cyclic peptide diastereomers while also dramatically improving their aqueous solubility.

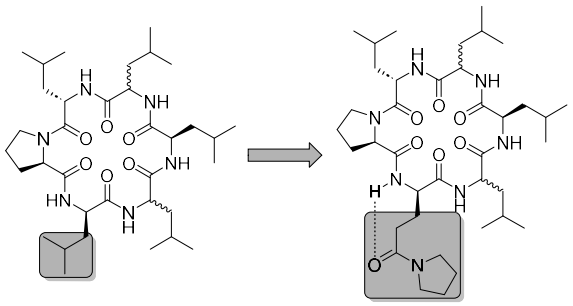

Figure 2: Side Chain-to-Backbone Hydrogen Bonding

Amide-to-Ester Substitution

While many naturally occurring cyclic peptides with promising membrane permeability have some esters, rather than amides, in their backbones, this direct substitution has not been evaluated. The Sando group, in collaboration with the Lokey group, demonstrate that systematically changing amide linkages to ester bonds on a variety of cyclic peptide molecules improves their membrane permeability (**Fig. 3**). In a direct comparison to the previously known method of *N*-methylation, these so-called depsipeptides display comparable and often superior membrane permeability. Despite ester bonds being considered vulnerable to enzymatic degradation, the depsipeptides displayed sufficient stability under a variety of proteolytic conditions, suggesting the potential for oral administration.

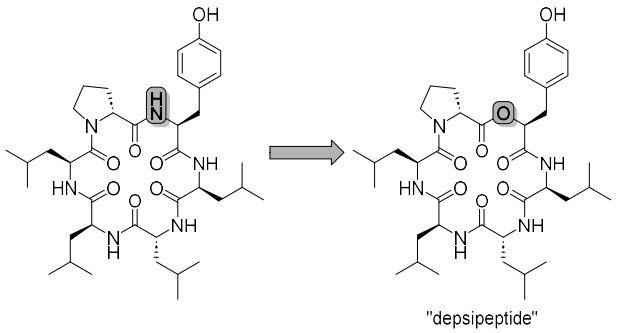

Figure 3: Amide-to-Ester Substitution

Amide-to-Thioamide Substitution

Previous efforts to increase oral bioavailability of cyclic peptides have aimed to shield or remove the HBDs of the amide scaffold. The Chatterjee group demonstrate that the HBAs of the peptide backbone can be masked via thioamide substitution (**Fig. 4**). Upon thioamidation, the membrane permeability and proteolytic stability of a cyclic peptide is increased significantly. Compared to an analogous *N*-methylated compound, the thioamidated derivatives displayed comparable permeability and stability. When applied to a bioactive compound, thioamidation did not disrupt the *in vivo* efficacy while maintaining an improvement in oral bioavailability.

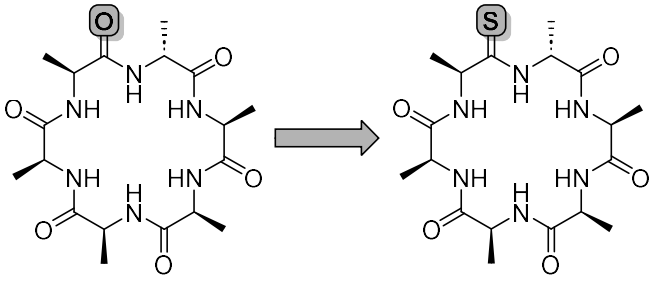

Figure 4: Amide-to-Thioamide Substitution

References

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