Design and Synthesis of DNA-Encoded Libraries of Peptidic and Peptidomimetic Macrocycles

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Macrocycles of peptides/peptidomimetics have been received a significant interest as a promising class of compounds that offers a great opportunity to discover potent therapeutic candidates. Macrocyclization increases the conformational rigidity of the molecules and minimizes the entropy penalty upon target engagement, thereby enhancing the binding affinity. Macrocyclic peptides/peptidomimetics can even engage therapeutic targets that are involved in protein-protein interactions (PPIs), which have rarely been targeted by small molecule drugs, as their relatively large size is able to fit the flat and wide interfaces. Moreover, peptide macrocycles exhibit higher proteolytic stability compared to their linear counterparts. Despite their promising properties as therapeutic candidates, technologies for screening of macrocycles of unnatural peptidomimetics have been rarely reported, while technologies for the discovery of cyclic peptide ligands, such as phage display and mRNA display, are well established.

In this study, we describe the design and synthesis of DNA-encoded libraries of macrocyclic peptides/peptidomimetics, including cyclic peptides and bicyclic peptoids.[1] We developed a robust, DNA-compatible synthetic method that afforded DNA-encoded libraries containing 100 million unique macrocycles with various side chains. We performed screening of the synthesized DNA-encoded libraries against target proteins, and identified cyclic peptides and bicyclic peptoids that strongly bind to the targets. We believe that the DNA-encoded libraries of macrocycles will serve as versatile tools for the discovery of potent ligands of challenging targets, including ones engaged in PPIs.

References

[1] Lee, K. J.; Bang, G.; Kim, Y. W.; Shin, M. H.; Lim, H.-S. *Bioorg. Med. Chem.* **2021**, *48*, 116423.