A general strategy for synthesis of cyclophane-braced peptide macrocycles via palladium-catalyzed intramolecular sp^3 C—H arylation

With the support by the National Natural Science Foundation of China, the research team directed by Prof. Chen Gong (陈弓) at the State Key Laboratory of Elemento-Organic Chemistry, Nankai University, recently reported a powerful method for chemical synthesis of peptide macrocycles, which was published in *Nature Chemistry* (2018, DOI:10.1038/s41557-018-0006-y).

Peptide macrocycles with large size and extended surface have been receiving significant attention in recent drug discovery research due to their unique ability to engage challenging biological targets, such as protein-protein interactions, that are difficult to mediate by the conventional Lipinski-type drugs with small molecular size. However, the methods for constructing large peptide macrocycles with well-defined structural features and favorable drug properties are currently limited compared with the synthetic methods for small molecule drugs. Inspired by the biosynthesis of complex cyclic peptide natural products, Chen's lab developed an unusual macrocyclization method based on palladium-catalyzed auxiliary-directed intramolecular arylation of inert alkyl C-H bonds. Linear peptide precursors can be selectively cyclized at the side chains of either aromatic or modified non-aromatic amino acid units with unactivated C-H bond on appended alkyl tail capped with an aminoquinoline (AQ) group to form "cyclophane-braced" peptide macrocycles of varied size and shape (Figure).

This C-H macrocyclization chemistry is highly efficient, operationally simple, and remarkably tolerant toward the size and composition of peptide chains. This study also made a surprising discovery that cyclophane compounds with extreme ring strain can also be efficiently prepared by the new macrocyclization method. X-ray analysis showed that the benzene planes of some para-cyclophanes are notably bent within the cyclic framework. Preliminary biological activity assay of the pilot library prepared by this C-H cyclization method revealed a potent lead compound with selective cytotoxicity toward proliferative Myc-dependent cancer cell lines, demonstrating the unique potential of these cyclophane-braced peptide macrocycles in drug discovery. Chen hopes that further exploration of this strategy will enable the discovery of more novel peptide macrocycles to tackle various challenging biological targets.

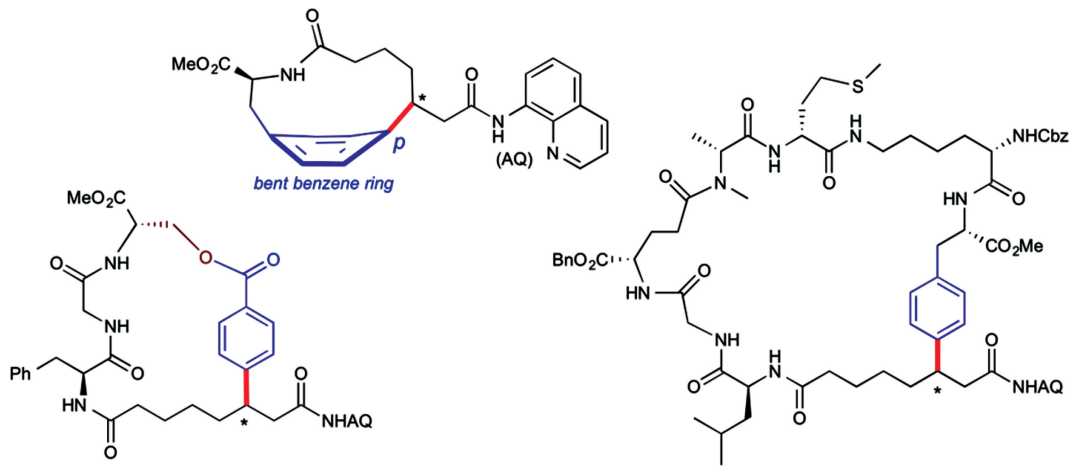

Figure Representative structures of cyclophane-braced peptide macrocycles.