Peptidomimetic inhibitors of Wnt signaling that directly target β-catenin

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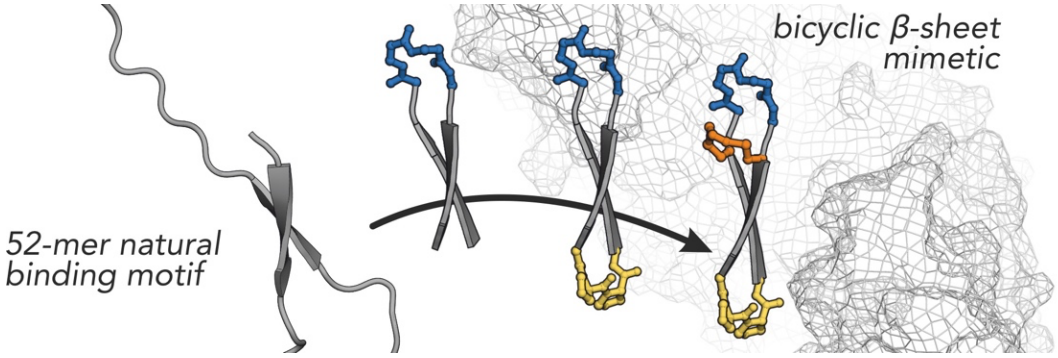
The inhibition of disease-relevant protein-protein interactions (PPI) represents an appealing strategy towards the development of novel therapeutics. Due to the extended nature of involved interaction areas, conventional ligand-discovery approaches that rely on small molecular scaffolds often fail to provide potent PPI inhibitors. A prime example for a therapeutically interesting protein which participates in numerous PPIs is the transcriptional coactivator β-catenin serving as the central intracellular interaction hub of the Wnt signaling pathway.[1] Importantly, complex formation between β-catenin and transcription factor proteins of the T-cell factor (TCF) family activates the expression of Wnt target genes thereby stimulating cell growth and proliferation. Hyperactivation of the Wnt pathway is associated with various forms of cancer rendering the inhibition of the β-catenin/TCF interaction an attractive strategy for therapeutic intervention. Due to the challenges associated with the use of small molecules, the development of peptide-derived PPI inhibitors represents an appealing strategy.[2]



Our group developed different strategies towards peptidomimetic Wnt inhibitors.[3,4] Recently, we described the structure-based design of β-sheet mimicking bicycles that target β-catenin and inhibit its interaction with a TCF transcription factor. Based on the known structure of β-catenin in complex with the protein E-cadherin, a macrocyclic binder of β-catenin was developed which comprises a short antiparallel β-sheet. A crystal structure of the macrocycle bound to β-catenin was obtained supporting the design of a library of bicyclic peptidomimetics. Among those mimetics, we identified a bicyclic structure that inhibits Wnt signaling in a cell-based assay and shows cellular uptake comparable to the cell penetrating Tat peptide.

[1] H Clevers, R Nusse, *Cell* **2012**, *149*, 1192–1205.
[2] M Pelay-Gimeno, A Glas, O Koch, TN Grossmann, *Angew. Chem. Int. Ed.* **2015**, *54*, 8896–8927.
[3] L Dietrich, B Rathmer, K Ewan, T Bange, S Heinrichs, TC Dale, D Schade, TN Grossmann, *Cell Chem. Biol.* **2017**, *24*, 958–968.
[4] M Wendt, R Bellavita, A Gerber, NL Efrém, T van Ramshorst, NM Pearce, PRJ Davey, I Everard, M Vazquez-Chantada, E Chiarparin, P Grieco, S Hennig, TN Grossmann, *Angew. Chem. Int. Ed.* **2021**, *60*, 13937–13944.