Design and Synthesis of Bicyclic Helical Peptides as β-Catenin Binders

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Small molecule inhibitors for intracellular protein-protein interactions have been a key focus point for research in the past decades.[1-3] Many attempts have been carried out, but especially when the proteins of interest lack a defined cavity for binding, this has been shown to be extremely challenging.

As a prime example of challenging target, we have the β-catenin protein, a transcriptional co-activator and oncogene. This protein, involved in the Wnt signaling pathway through interactions with several different modulators, lacks defined binding pockets for therapeutical small molecule compounds. Wnt signaling is one of the oldest and most conserved signaling pathway in cells and it is mainly involved in cell proliferation and differentiation. A dysregulation of this pathway, therefore, has been linked to the onset and progression of a variety of cancer types.[4,5] Numerous approaches have been tested so far to target and modulate the activity of β-catenin, but so far there is only a limited pool of candidates, comprised of either small molecules with low affinity, or binders with higher affinity but large molecular weight. These then require either binding with cell penetrating peptides or conversion into PROTACs to facilitate bioactivity.[6,7]

Herein, we present the rational design and synthesis of small peptidomimetics based on the structure of the α-helical β-catenin-binding motif of Axin.[8] By sequence maturation and bicyclization, we obtained a class of stitched peptides which binding mode and site were confirmed by crystal structure. A lead peptide (**StC-b**) with unprecedented crosslink structure showed single-digit micromolar activity in a cell-based assay. Further optimization on the structure was carried out to prevent possible oxidation of the compound in the cellular environment. For this, removal of a thioether moiety on the *C*-terminus by substitution of the sulphur atom with a CH_2 unit generated a more stable compound (**StX**).

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