

Conquest of a PPI Everest: Disrupting the YAP/TEAD PPI with Small Molecules

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The YAP-TEAD protein-protein interaction is a therapeutic target of current interest in oncology to treat cancers associated with a dysregulation of the Hippo pathway. The very extended surface of interaction of the two proteins presents a formidable challenge for a small molecule inhibitor approach. Virtual screening allowed us to identify a weakly active hit binding to one the two main sites of interaction of YAP at the surface of TEAD. By structure-based and compound property-based design it was possible to improve the potency of this hit by several orders of magnitude. The main features of this work that had led to the identification of the first representatives of a new class of cellularly active YAP-TEAD interaction inhibitors will be presented.