New approaches towards small molecular protein-protein interaction modulators.

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Protein-protein interactions (PPIs) are ubiquitous in nature and essential to almost all biological processes including signal transduction, gene-expression and pathogenicity. Therefore, modulation offers attractive therapeutic opportunities. [1] One major challenge of targeting PPIs arises from the chemical space of appropriate molecules which differs from the chemical space of conventional small molecule drugs in a way that is not yet completely understood. Thus, the hit rate of commercial compound collections is typically rather low since these are designed around the traditional drug´s chemical space. [2] A reason for this observation is the intrinsic planarity of these interfaces and their lack of well-defined binding-pockets.

Our approach for the design of PPI inhibitors is to elucidate and mimic the important, limited-sized elements that actually act as protein recognition motifs. [3] Up to now, only strand and helix mimetics were successfully used as interaction inhibitors, although irregular turn structures prevail as regions of high affinity binding in weak and transient heterodimer interfaces of greater pharmacological interest. [4] The turn backbones provide valuable information for the design of new drugs since they act as scaffolds for positioning the relevant side chains in the correct specific orientation. [5]

As a first example, our analysis of a bacterial GTPase-activating PPI [6] (responsible for the correct formation of flagella) leads us to a crucial interaction turn entity of type n(4)I. This type of β-turns is already known to be well-replaced by the benzodiazepine scaffold. The synthesis of the basic scaffold has been successfully established and now our focus is on identifying the required functionalization pattern using structure-based design and docking. Subsequently, the synthesis of these rationally designed benzodiazepine-based turn mimetics will lead to a small library to be tested for its capability to modulate the bacterial GTPase-activating PPI.

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