Identification of protein-protein complexes that are potentially suited for inhibition by alpha-helix mimetics

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Protein-protein interactions play a key role in biological processes, such as signal transduction, programmed cell death, cell proliferation, and differentiation. The modulation of protein-protein interactions with small molecules offers valuable therapeutic possibilities but is considered to be challenging. Therefore, it is important to develop strategies to selectively disrupt these interactions. Rational design of structural mimetics represents a promising approach. The most common protein secondary structure element, the alpha-helix, is an important motif in numerous protein-protein interfaces and, thus, an interesting target region in protein interfaces. Consequently, we aimed at identifying protein-protein complexes that are potentially suited for inhibition by alpha-helix mimetics [1] in this study.

To identify such protein-protein complexes, we screened protein-protein interaction databases for complexes with an alpha-helix in the interface. In the following steps we analyzed structural properties to identify druggable protein-protein interfaces: (I) computational alanine scanning with FoldX [2] was applied to search for hot spot residues in the helical regions; (II) potential binding pockets were calculated using the grid-based Pocket Analyzer algorithm [3]; (III) relative binding free energies ($\Delta\Delta G$) for helices in the interface were calculated and put in relation to the complex interaction energy. With this strategy, we intended to identify complexes with a large energetic contribution of the alpha-helix.

The result of this study is a dataset of protein-protein complexes that can be potentially inhibited or modulated by alpha-helix mimetics. We finally examined the proteins' biological functions and their relevance for human diseases.

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