Title: Comprehensive Analysis of Hot Loops at Protein-Protein Interfaces as Targets for Macrocyclic Inhibitors

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Abstract:

Inhibiting protein-protein interactions (PPIs) with synthetic molecules remains a frontier of drug discovery. Most PPIs that have been successfully targeted are mediated by regular secondary structures such as alpha-helices and beta-strands, but most PPIs are mediated by non-helical, non-strand “loops”. Despite their prominence, the universe of known PPIs mediated by loop structures has not been previously identified or characterized. To this end, we wrote LoopFinder, a customizable program that identifies loop-mediated PPIs, and applied it to all protein-protein complexes in the Protein Data Bank. We identified 25,005 PPI interface loops, and scored them using computational alanine scanning to identify those that contribute significantly to binding interactions. In analogy to protein-binding hot spots, we chose to call these “hot loops.” Hot loops encompass a surprising variety of structural motifs, and analysis of amino acid compositions revealed unique features of loop-mediated PPIs for the first time. Validating this method as a tool for designing macrocylic inhibitors of PPIs, LoopFinder identified hot loops for several therapeutically relevant PPIs, some of which have been targeted with macrocyclic compounds and others for which no inhibitors are yet known. Taken together, this overall methodology, the set of interface loops, and the set of hot loops provide an original analysis of molecular recognition involving short peptide loops, and provide starting points for the rational design of macrocycles as PPI inhibitors.