Molecular Recognition Principles in Protein-Ligand Interactions as a Prerequisite for the Design of Specific and Selective Leads

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In order to bind to a protein, a ligand has to exhibit correct shape and interaction properties complementary to the residues exposed towards the binding pocket of a target protein. Since protein-ligand binding is a process of mutual molecular recognition, rational drug design is greatly concerned with understanding the principles of molecular recognition. The statistical analysis of geometries of protein-ligand complexes provides a powerful tool to retrieve and correlate information about recognition patterns with respect to protein binding. To efficiently access such data, we have developed Relibase [1,2] as a database system particularly tailored to handle protein-ligand related problems, e.g. the induced adaptation of proteins upon ligand binding, the role of water in the binding process, the mapping of hot-spots of ligand binding or analyzing the versatile molecular recognition properties of functional groups.

The function of proteins is almost invariably linked with the specific recognition of substrates and ligands in well-defined binding pockets. In consequence, proteins of related function should share comparable recognition properties exposed to these pockets. Cavbase has been developed as new module for Relibase that stores protein cavities in terms of simple surface-exposed physicochemical properties [3]. These descriptors allow for fast retrieval of proteins with functional relationships independent of a particular sequence or fold homology. The approach also allows to detect unexpected cross-reactivity of ligands among unrelated proteins. Via the alignment of binding pockets across protein family members, the consensus pattern representative for individual protein families can be extracted and mutually compared. By decomposing binding pockets into elementary sub-pocket motifs the analysis of preferred ligand occupants can be achieved.

Mapping preferred interaction sites in binding pockets in terms of knowledge-based approaches such as SuperStar [4] or DrugScore [5,6] "hot spots" of ligand binding can be elucidated. Such information can be translated in a protein-based pharmacophore hypothesis and serves as guideline for ligand docking and virtual screening [7].

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