Targeting Fundamental Aspects of Protein-Ligand Interactions to Improve Computer-Aided Molecular Design

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Molecular recognition, based on non-covalent interactions between protein and ligands, plays a key role in biological processes. Currently we lack detailed knowledge and understanding of the factors influencing protein-ligand binding, which substantially retards rational drug design. Our approach is to design and synthesize sets of organic molecules that are used as chemical probes to target fundamental aspects of protein-ligand interactions, including the electronic properties, enthalpy/entropy components, dynamics, and solvent effects. The experimental data is scrutinized and used for model building using chemometrics, quantum mechanics and molecular modelling. The presentation will, for example, include studies of aromatic interactions and non-classical hydrogen bonds between protein and ligands, using acetylcholinesterase as the model system. The research is conducted with the objective to contribute to increased mechanistic knowledge, and to the discovery of antidotes for nerve agent/pesticide intoxication and new insecticides to combat mosquito-borne vector diseases.