Abstract

Computational approaches have become an established and valuable component of pharmaceutical research. Computer-aided drug design aims to reduce the time and cost of the drug development and also to bring deeper insight into the inhibitor binding to its target. The complexity of biological systems together with a need of proper description of non-covalent interactions involved in molecular recognition challenges the accuracy of commonly used molecular mechanical methods (MM). There is on the other side a growing interest of utilizing quantum mechanical (QM) methods in several stages of drug design thanks to increased computational resources.

This doctoral thesis's topic is the QM-based methodology for the reliable treatement of intermolecular interactions. It consists of eight original publications devided into three topics and an accompanying text that aims to emphasize selected outcomes of the work. Firstly, the nature of nonclassical non-covalent interactions - so called σ-hole bonding - is studied by high-level QM methods. The strength and origin of halogen-, chalcogen- and pnicogen bonded model systems in extended datasets are accurately explored by coupled cluster QM method (CCSD(T)/CBS) and symmetry adapted perturbation theory (SAPT). The second part is devoted to three pharmaceutically important protein targets, *i.e.* HIV-1 protease, secreted aspartic protease and carbonic anhydrase, and shows benefits of corrected DFT and semiempirical quantum mechanical (SQM) methods used in protein-ligand complexes involving proton-transfer phenomena, metal ions and unusual compounds such as boranes. A hybrid QM/MM approach unveils here the features of the structure that are not accessible to the crystallographic experiment and explains fundamental differences in the binding modes of inhibitors. Finally, SQM-based scoring function that describes quantitatively all types of non-covalent protein–ligand interactions is simplified for virtual screening of compound libraries. The reliability of this physics-based SQM/COSMO filter is tested on four unrelated difficult-to-handle protein-ligand systems. In this last part of the thesis it is shown how the SQM/COSMO filter outperforms eight standardly used scoring functions and thus may become an effective tool for accurate medium-throughput refinement in later stages of virtual screening.