Quantum Chemistry-based Docking and Scoring for Design of Protein Kinase Inhibitors

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In silico drug design relies on i) correct prediction of the structure of the protein-ligand complex and ii) accurate ranking of alternative structures. For the first task we used molecular docking enhanced by QM calculations in order to correctly describe halogen bonding [1,2]. The second problem was tackled using a quantum-chemistry based scoring function [3]. This scoring function uses semi-empirical quantum chemical method, PM6, augmented with advanced dispersion, hydrogen-bonding and halogen bonding corrections (PM6-D3H4X) [4]. This method reliably describes different types of non-covalent interactions and is thus generally applicable. The scoring function is constructed as a sum of physical terms, i.e. interaction free energy including solvation effects, the interaction entropy, and the change of the conformation free energy of the ligand and protein upon binding. The scoring function has already been successfully applied to series of HIV protease, CDK2 and CK2 inhibitors [3,5,6,7].

Here, we present a project aiming at discovery of new halogenated inhibitors of CK2 kinase which is implicated in various cancer types. A series of brominated compounds has been designed using the above methodologies, synthesized and tested *in vitro* for inhibition activity. In summary, we propose a general computational strategy to guide rational drug design.

References

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