Conformational and tautomer sampling of small molecules in solution with quantum-chemical accuracy

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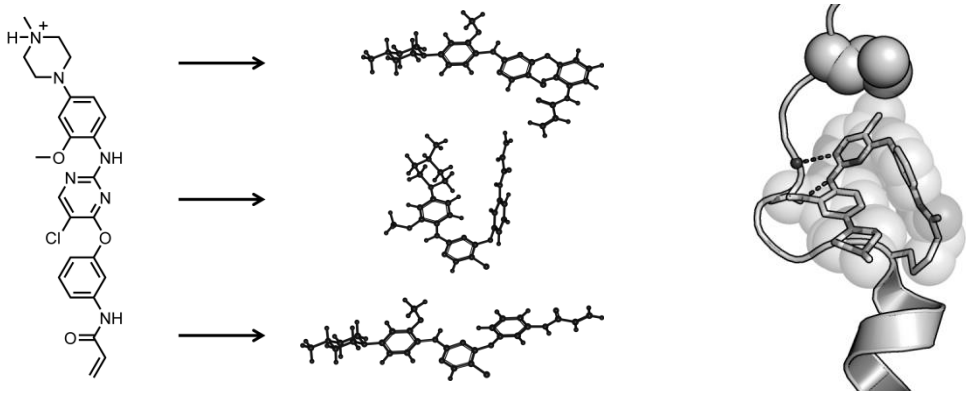
High-throughput screening of the tautomer and conformational space of small drug-like molecules in solution provides important information for molecular design. In particular, predicting and controlling free ligand conformations is essential for minimizing the entropic penalty to reorganize a ligand's geometry upon binding to a protein. Overcoming the deficiencies of common small molecule force fields represents a particular challenge due to the considerable computational cost of high-level quantum-chemical calculations for predicting tautomer prevalence and the conformational manifold.

Here we demonstrate the performance of a hierarchical filtering scheme that allows for the identification of dominant tautomers and conformations together with their proper statistical weight measured by their free energies in solution with quantum-chemical accuracy. The automated workflow implies a sequence of force field-based high-temperature molecular dynamics simulations using implicit solvent models, clustering and filtering steps, and high-level geometry optimizations in solution employing the polarizable continuum model (PCM) as well as the embedded cluster reference interaction site model (EC-RISM) [1] for final scoring.



As proof of concept, we apply the workflow to protein kinase inhibitors where a conformational pre-arrangement has a dramatic influence on the inhibitory efficacy. In particular, we focus on WZ4002 that is known as a highly active kinase inhibitor for the drug-resistant mutant of the epidermal growth factor receptor (EGFR T790M) [2]. EGFR and its mutant variants play an important role in non-small cell lung cancer (NSCLC). WZ4002 is a suitable candidate for this approach since its binding mode in the active site of the protein and with it the ligand's geometry is known from the X-ray complex structure. We discuss implications for gaining valuable insights into the significance of the substitution pattern at pivotal ligand regions with the intention to adapt this approach to further kinase inhibitor scaffolds.

[1] T. Kloss, J. Heil, S. M. Kast, *J. Phys. Chem. B*, **2008**, *112*, 4337–4343.
[2] W. Zhou et al., *Nature*, **2009**, *462*, 1070-1074.