Conformational sampling of drug-like molecules in solution with quantum-chemical accuracy

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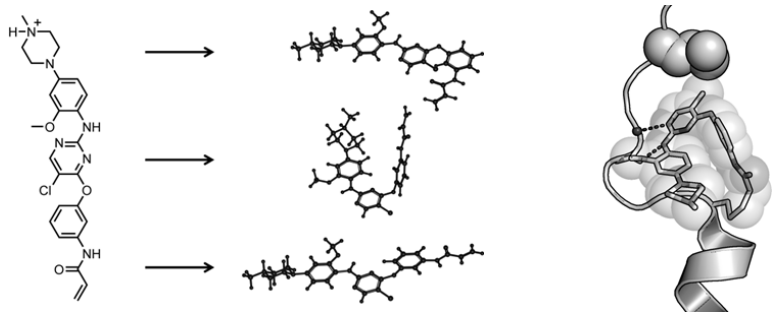
Accurate assessment of the conformational space of drug-like molecules in free solution is a frequently underestimated, yet relevant ingredient of molecular design. In particular, predicting and controlling free ligand conformations is essential for minimizing the entropic penalty to reorganize a ligand's 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 the conformational manifold.



Here we demonstrate the performance of a hierarchical filtering scheme that allows for the identification of dominant conformations together with their proper statistical weights 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 scoring and calculation of theoretical NMR spectra [2] to be compared with experiments. We apply the workflow to variants of the protein kinase inhibitor WZ4002 that is highly active against a drug-resistant mutant of the epidermal growth factor receptor (EGFR-T790M). [3,4] The relative significance of conformational pre-arrangement in comparison with modulation of direct protein-ligand interactions upon chemical substitution is discussed.

[1] T. Kloss, J. Heil, S. M. Kast, *J. Phys. Chem. B*, **2008**, *112*, 4337-4343.
[2] R. Frach, S. M. Kast, *J. Phys. Chem. A*, **2014**, *118*, 11620-11628.
[3] W. Zhou et al., *Nature*, **2010**, *462*, 1070-1074.
[4] W. Zhou et al., *Bioorg. Med. Chem. Lett.*, **2011**, *21*, 638-643.