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Ligand-side tautomer enumeration and scoring for structure-based drug-design

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Tautomeric rearrangements of a molecule lead to distinct equilibrated structural states of the same chemical compound that may differ significantly in molecular shape, surface, nature of functional groups, hydrogen-bonding pattern and other derived molecular properties [1]. Especially for the structure-based pharmacophore modeling of ligand-protein complexes [2], knowledge of the most favorable tautomeric ligand states may be crucial for the quality and correctness of the generated pharmacophore models and derived putative binding modes. We will present a ligand-side tautomer enumeration and ranking algorithm that considers both geometrical constraints imposed by the conformation of the bound ligand as well as intra- and inter-molecular energetic contributions to find the preferred tautomeric states of the ligand in the macromolecular environment of the binding-site. The presented tautomer ranking algorithm is based on scores that are derived solely from MMFF94 [3-9] energies (thus the method works for a wide range of organic molecules) and has proven to be able to top-rank known preferred tautomeric states of ligands in a series of investigated protein complexes.

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