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Multi-parameter scoring functions for ligand- and structure-based *de novo* design

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Successful drug discovery often requires optimization against a set of biological and physical properties. We describe de novo design studies that demonstrate successful scaffold hops between known classes of ligands for p38 MAP kinases using ligand-based and structure-based multi-parameter scoring functions coupled to the molecular invention engine Muse.

The ligand-based scoring function includes pharmacophoric and steric tuplets and structural (fingerprint based) similarity. In addition various selectivity or ADME related properties (e.g. Lipinski properties, polar surface area, activity at off-targets, etc.). can be taken into account to guide the evolution of structures meeting multiple design criteria.

The structure-based scoring function uses Surflex-Dock to pose and score invented structures inside the target's active site. In addition, a number of simple molecular properties (e.g. clogP, Lipinski properties, etc.) are used as score components to focus the design on medicinally relevant chemistries. With the ability of Surflex-Dock to start the docking process with a single or multiple placed fragments, this scoring function can be applied in fragment based drug discovery to optimize attachments onto a pre-placed substructure.

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