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SQUIRRELnovo: *de novo* design of a PPARα agonist by bioisosteric replacement

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Shape complementarity is a compulsory condition for molecular recognition [1]. In our 3D ligand-based virtual screening approach called SQUIRREL, we combine shape-based rigid body alignment [2] with fuzzy pharmacophore scoring [3]. Retrospective validation studies demonstrate the superiority of methods which combine both shape and pharmacophore information on the family of peroxisome proliferator-activated receptors (PPARs). We demonstrate the real-life applicability of SQUIRREL by a prospective virtual screening study, where a potent PPARα agonist with an EC50 of 44 nM and 100-fold selectivity against PPARγ has been identified.

SQUIRREL molecular superposition is based on a graph-matching routine [4] and allows partial matching. We used this advantage for searching for bioisosteric replacement suggestions in a database of molecular fragments derived from a collection of drug-like compounds [5]. The bioisosteric groups suggested by our tool SQUIRRELnovo, can be used for ligand-based de novo design by a human expert. Using the fibrate derivative GW590735 [6] as query, we designed a novel lead structure by substitution of the acidic head group and hydrophobic tail. The synthesis and following testing in a cell-based reporter gene assay [7,8] revealed that the designed structure activates PPARα with an EC50 of 510 nM.

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