

Oral presentation

Open Access

SQUIRREL_{novo}: *de novo* design of a PPAR α agonist by bioisosteric replacement

E Proschak*, K Sander, H Zettl, Y Tanrikulu, P Schneider, O Rau, H Stark, M Schubert-Zsilavec and G Schneider

Address: Goethe-University Frankfurt am Main, Siesmayerstr. 70, D-60323 Frankfurt am Main, Germany

* Corresponding author

from 4th German Conference on Chemoinformatics
Goslar, Germany. 9–11 November 2008

Published: 5 June 2009

Chemistry Central Journal 2009, **3**(Suppl 1):O4 doi:10.1186/1752-153X-3-S1-O4

This abstract is available from: <http://www.journal.chemistrycentral.com/content/3/S1/O4>

© 2009 Proschak et al; licensee BioMed Central Ltd.

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 PPAR α agonist with an EC₅₀ of 44 nM and 100-fold selectivity against PPAR γ 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 SQUIRREL_{novo}, 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 PPAR α with an EC₅₀ of 510 nM.

References

- Schneider G, Baringhaus K-H: **Molecular Design – Concepts and Applications**. Wiley-VCH: Weinheim, New York; 2008.
- Proschak , et al.: *J Comput Chem* 2008, **29**:108.

- Tanrikulu , et al.: *Chem Bio Chem* 2007, **8**:1932.
- Bron C, Kerbosch J: *Communications of the ACM* 1973, **16**:575-577.
- Schneider P, Schneider G: *QSAR Comb Sci* 2003, **22**:713-718.
- Sierra , et al.: *J Med Chem* 2007, **50**:685.
- Rau , et al.: *Planta Med* 2006, **72**:881.
- Derksen , et al.: *Chem Med Chem* 2006, **1**:1346.