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Ligand Based Screening Tools for Insulin Receptor Activating Compounds

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Current treatments of type 2 diabetes mellitus have sometimes severe side effects. Therefore, the identification of new treatments is still an urgent need. The binding of insulin to the extracellular part of the insulin receptor is a key step in the insulin signalling pathway. As type 2 diabetes is characterized among others by a resistance of cells against insulin, activating the insulin receptor might be an interesting approach. In 1999, Zhang et al. discovered a small molecule from a fungal extract which activates the human insulin receptor by binding directly to its intracellular domain [1]. This compound (L-783,281 or demethylasterriquinone B-1, DMAQ-B1) was shown to lower blood glucose levels in mouse models of type 2 diabetes mellitus.

During the last years, approximately 100 derivatives of this compound have been synthesized (e.g. [2–4]), all of them containing similar scaffolds. The aim of the current study was to search for new compounds with different types of scaffolds using various ligand based computational methods. Tools used were self-organizing maps with 2 types of descriptors (VSA and 2D autocorrelation vectors), Tanimoto similarity of 8 different fingerprint types (including MACCS and pharmacophore based fingerprints) and shape similarity search.

The *in silico* screening of more than 600.000 compounds of the ChemDiv database led to the identification of 367 structures with approx. 100 new scaffolds. Biological evaluation of selected compounds will show the usability of the different approaches to identify new insulin receptor activating compounds.

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