3D-QSAR AND VIRTUAL SCREENING OF PROTEIN-TYROSINE-PHOSPHATASE 1B INHIBITORS

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Insulin resistance in type 2 diabetes is due to a defect in the insulin receptor signalling pathway. The inhibition of protein tyrosine phosphatase (PTP) 1B, the key enzyme that disrupts this signal transduction system and abrogates the antihyperglycaemic effect of insulin, represents an effective target for the treatment of type 2 diabetes.
Beside the detailed investigation available X-ray crystal structures of PTP1B, we examined in our study a set of about 130 known inhibitors of PTP 1B [1]. Starting with the generation of traditional ligand based pharmacophore models with the use of the programs FlexS and GRID/GOLPE we obtained a 3D-QSAR model with significant correlation to the biological activities ($q^2_{L\text{-}20\%\text{-}O} = 0.71$). Subsequently a receptor based model was generated by an automatic docking procedure with an optimised version of the program Autodock. Although the ligand alignment obtained by means of this procedure shows marginal differences compared to the ligand based model, the 3D-QSAR analysis resulted in comparable statistical results ($q^2_{L\text{-}20\%\text{-}O} = 0.76$).
In order to identify new lead structures for the synthesis of novel ligands a virtual screening run of a database of 30,000 compounds that were already screened by *in vitro* methods for inhibitory activity on PTP1B was performed with the aim to compare the results of different *in silico* and in vitro screening methods. The first approach was a three step filtering with FeatureTrees, Autodock and GRID/GOLPE, a combination of ligand based and receptor based methods. Due to the differences in chemical space of the studied inhibitors and the compound database, the hits were filtered out with FeatureTrees, and a prediction with GOLPE was not expected to be successful. In a second, purely target based approach, a diverse subset of 1000 compounds from the original database was analysed by different docking and scoring combinations, using various methods (Autodock, FlexX, GOLD, C-Score and X-Score). Most of the results showed a significant enrichment of active compounds achieving the highest enrichment with the combination of Autodock and X-Score.

[1] M. S. Malamas et al., J. Med. Chem. 2000, 1293