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Case study: Pharmaceutical

Novel PTP1B inhibitors design using SCOPE method

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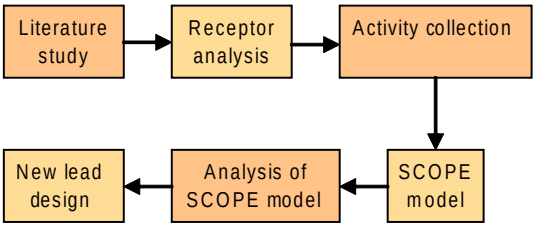
Customer type

A leading pharmaceutical company

Software modules

BioPredicta

VLife Engine



Application

Lead optimization

Techniques

SCOPE

Background:

Protein tyrosine phosphatase 1b(PTP1B) is involved in negative regulation of insulin signaling. Mice lacking PTP1B show increased insulin sensitivity and resistance to diet induced obesity. PTP1B inhibitors are known to have their beneficial effect in type 2 diabetes. PTP1B has emerged as the key target for treating type 2 diabetes and obesity in the recent time.

Design challenge:

The active site cavity of PTP1B consists of many charged residues. Owing to this, most of the potent inhibitors of PTP1B developed to date are charged. But charged ligands will have problem in bio-availability as charged molecules cannot readily cross lipid membrane. The aim of the project was to develop neutral and potent PTP1B inhibitors.

Project work:

The crystal structures of PTP1B co-complexed with its inhibitors were collected from Protein Data Bank. The ligands were extracted from complexes and saved without disturbing their position. Hydrogen were added to protein structures and ligands were cleaned with respect to their bond orders. The activity values for these inhibitors were collected from literature sources.

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VLifeMDS

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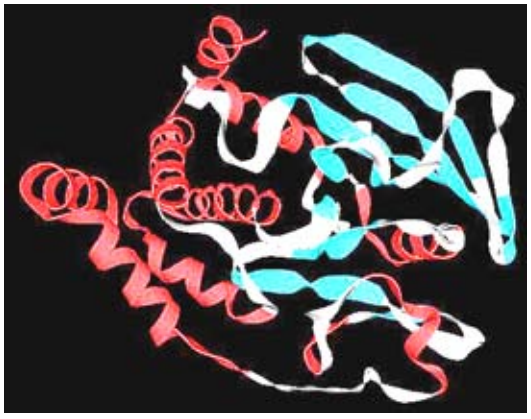
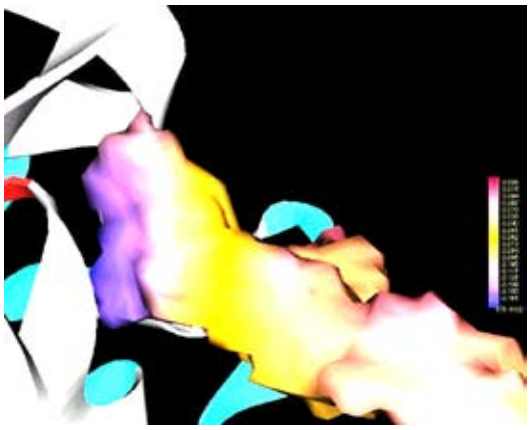


PTP1B Crystal Structure



PTP1B active site cavity with complementary electro static potential mapped

SCOPE module of VLifeMDS was used to calculate steric and hydrogen bond energy terms for each of the residues near the active site. These steric and hydrogen bond energy terms were calculated based on PLP scoring function. Then a QSAR model was built for activity of selected ligands as a function of these energy terms.

Result analysis:

SCOPE model obtained has a r2 value of 0.83, cross validated r2(q2) value of 0.72 and predicted r2 value of 0.84.

The model has given insights into the importance of each residue and its interaction type with the ligand in modulating the activity of the ligand. This model has further helped customer in designing neutral inhibitors for PTP1B with nano molar activity. Using this model, VLife screened customer's in-house databases of ligands to select potential inhibitors.

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