INTRODUCTION

Drug metabolizing enzymes and transporters are often involved in clinically relevant drug-drug interactions. These functional proteins can be induced by a wide range of xenobiotics. A group of receptors known as orphan nuclear receptors mediates this effect.

The pregnane X receptor (PXR) – as a member of this receptor family – regulates the expression of multiple Cytochrome P450 families (e.g. CYP 3A and 2B), phase II enzymes (e.g. UDP glucuronosyl transferases), and transporters (e.g. multidrug resistance protein 1). [1]

Recently, the crystal structure of PXR co-crystallized with the co-activator peptide SRC-1 and the ligand SR12813 was published [2]. Therefore we used the 3D coordinates of the PDB [3] entry 1NRL as a template to develop a pharmacophore model for PXR ligands.

AIM OF THE STUDY

Starting from the 3D coordinates of 1NRL [2], a chemical feature-based pharmacophore model was constructed and used as a prediction tool for potential PXR activation.

METHODS

We used the software package CATALYST [4] for:
- generation of structure models for the test set
- conformational analysis (Monte Carlo)
- manual generation and validation of the pharmacophore models
- 3D-database search (Derwent WDI [5])

RESULTS: PHARMACOPHORE MODELS

The examination of the binding pocket revealed potential sites of interactions which were then transformed into a pharmacophore model. Amino acid residues within the binding pocket were included into the model as excluded volume spheres.

Conversion of binding information from the crystal structure into a pharmacophore hypothesis consisting of one hydrogen bond acceptor (green), six hydrophobic features (turquoise), and 15 excluded volume spheres (grey). Based on this pharmacophore model, a two step filter for potential PXR ligands was created.

Hypothesis A consisting of four features and 15 excluded volume spheres was able to identify all PXR ligands of our test set.

Hypothesis B consisting of seven features – three of them defined as “leave-one-out”, 15 excluded volume spheres, and a combined shape (SR12813 or rifampicin) is able to identify SR12813, hyperforin, and rifampicin as highly potent PXR ligands.

THE PXR FILTER

CASE STUDY: WDI

We achieved a filter consisting of two hypotheses to predict PXR activity of compounds present in a 3D database. Hypothesis A was able to identify 100% of a test set consisting of 31 PXR ligands as active. However, it can only serve as a first indicator for PXR activity because of many false positive results.

Hypothesis B was shown to be able to identify highly active PXR ligands, e.g. hyperforin and rifampicin. It could be used to highlight probably highly active PXR ligands out of a hitlist derived from a database search with Hypothesis A.

Our model could serve as a useful tool in the early drug discovery process to identify the potential of a new compound to activate PXR.

LITERATURE

[4] CATALYST Version 4.9, MSI, San Diego, CA, USA

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