KP226 Pharmacophore Estimation and 3D-QSAR of Ligands for Organic Anion Transporting Polypeptide 1B1 (OATP1B1)

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1. Introduction

The liver is one of the most important organs responsible for the elimination of xenobiotics including many kinds of drugs used clinically. It has been shown that transporters are involved in the hepatic uptake of xenobiotics. Among these transporters, we focused on organic anion transporting polypeptide 1B1 (OATP1B1) in this study. OATP1B1 is predominantly expressed in the sinusoidal membrane of liver parenchymal cells (hepatocytes), and mediates cellular uptake of a variety of xenobiotic compounds, particularly amphipathic organic anions. Substrates of OATP1B1 include clinically important anionic drugs, such as HMG-CoA reductase inhibitors (including pravastatin and pitavastatin) and angiotensin II receptor antagonists (including valsartan and olmesartan). In vitro transport studies using cryopreserved human hepatocytes have shown that it makes a significant contribution to the hepatic uptake of such clinically important drugs. For most OATP1B1 substrates, hepatic uptake mediated by OATP1B1 is one of the determining factors of the systemic exposure. Inhibition of OATP1B1 by its inhibitors and genetic polymorphisms/mutations of *OATP1B1* resulting in a reduced transport activity produce a significant increase in the systemic exposure of OATP1B1 substrate drugs [1-3]. Therefore, a logical molecular design based on substrate recognition mechanisms of OATP1B1 will facilitate optimization of the pharmacokinetic properties of anionic drugs.

In the present study, we investigated the binding conformation of ligands to human OATP1B1and the spatial arrangement of the key functional groups for binding to OATP1B1 (pharmacophore) using *in silico* ligand-based drug design methods followed by the three dimensional quantitative activity relationship (3D-QSAR) study between ligands and OATP1B1.

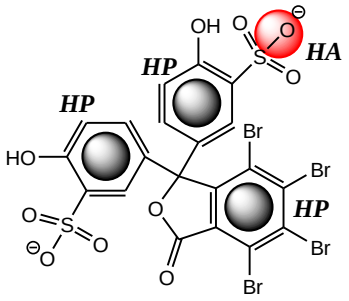
2. Method

To generate a set of energetically stable conformers of 13 OATP1B1 ligands (bromosulfophthalein, KP-496, pitavastatin, valsartan, rosuvastatin, estradiol

17β-glucuronide, glycoursodeoxycholate, taurocholate, atorvastatin, olmesartan, dehydroepiandrosterone sulfate, bosentan and pravastatin), we used the automated program CAMDAS (Conformation Analyzer with Molecular Dynamics and Sampling) [4]. The conformers generated by CAMDAS were represented by 6 types of physicochemical property spheres (hydrogen bond donor, hydrogen bond acceptor, hydrogen bond donor/acceptor, hydrophobic, aromatic and halogen) and were superposed on each other using the SUPERPOSE program [5]. Each type was represented as a sphere with a predefined radius and was assigned to a functional group in a molecule. The superposition was scored and conformers with high scores were selected in each ligand. The pharmacophore of OATP1B1 was obtained by the arrangement of physicochemical property spheres shared in all the OATP1B1 ligands. 3D-QSAR analysis using Comparative Molecular Similarity Indices Analysis (CoMSIA) correlated three-dimensional steric, electrostatic and hydrophobic properties of molecules with the activity (K_m value) of each ligand [6], and a regression equation to predict activity was investigated.

3. Results and Discussion

The CAMDAS calculation generated many conformers of the 13 OATP1B1 ligands. Superposition of these conformers revealed a candidate binding conformation of ligands to OATP1B1. In this conformation, four physicochemical property spheres (1 hydrogen bond acceptor group and 3 hydrophobic groups) common in all the ligands were identified, which constituted the pharmacophore of OATP1B1 ligands.



HA : hydrogen bond acceptor
HP : hydrophobic

Fig1. pharmacophore of OATP1B1 ligand

CoMSIA generated a good 3D-QSAR model with a moderate q^2 value (0.389) and a high conventional r^2 value (0.997) based on the molecular alignment obtained from the superposition of the conformers. To obtain a better 3D-QSAR model with higher q^2 value, we are attempting to select another molecular alignment for CoMSIA and add more ligands to the training set compounds.

References

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