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Title: Ligand-based and Structure-based Studies to Understand the Molecular Basis of Inhibition of ABC Transporters Expressed in the Liver

Abstract in English

ABC-transporters such as the bile salt export pump (BSEP), the breast cancer resistance protein (BCRP) and P-glycoprotein (P-gp) play an important role in the pharmacokinetics of several drugs and small molecules. Predicting inhibition of these transporters by small molecules facilitates identification of potential drug-drug interactions and adverse effects such as drug-induced liver injuries. Thus far, *in silico* identification of inhibitors is dominated by ligand-based approaches that most often employed Quantitative structure–activity relationship (QSAR) and machine learning methods. Although the models based on these methods are reported to be efficient, they do not consider the properties of the protein and thus fail to provide insights into the mechanism of inhibition. While structure-based studies could investigate these details, the lack of high-resolution structural information and the polyspecific binding behaviour of these transporters pose a serious obstacle.

This thesis outlines three independent studies that explore structure-based methods to investigate the molecular basis of inhibition of transporter proteins relevant to liver toxicity and another study that employs ligand-based methods to deal with the imbalanced datasets. The structure-based studies presented here describe the use of homology modeling and molecular docking to uncover the protein-ligand interactions involved in the mechanism of inhibition.

In our first study, a homology model was constructed for BSEP, followed by the development of structure-assisted, docking-based classification models for prediction of BSEP inhibitors. Further, we analyzed the protein-ligand interaction fingerprints which revealed specific functional group-amino acid residue interactions that could play a key role in ligand binding. In the BCRP study, a structure-based modeling approach facilitated elucidation of binding hypothesis for arylmethyloxyphenyl derivatives, which after experimental validations could guide rational optimization of this compound class to improve potency. In the third study, we compared the binding site interaction profiles of human, rat and mouse P-gp structures to reveal a significant overlap between the binding site interacting residues which suggests the transferability of *in vitro* human P-gp activity data in the development of *in silico* models to predict *in vitro* and *in vivo*

effects in rodents. In our ligand based study, we dealt with the problem of learning on imbalanced datasets relevant to toxicity by evaluating the performance of seven distinct meta-classifiers and provided recommendations in choosing an appropriate classifier depending on the dataset in hand.

The results of this thesis work further improve our understanding of protein-ligand interactions at the molecular level, stimulating scientists to conduct new experiments and thus also aid in the extrapolation of molecular hypotheses from rodents to humans and *vice-versa*. Furthermore, combining ligand-based and structure-based approaches would significantly enhance the performance of virtual screening experiments in drug discovery and provide detailed insights on the molecular features involved in crucial interactions, thereby assisting lead optimization.