Computational approaches for preclinical ADMET optimization

Thesis Summary

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The most desired objective of drug discovery is delivering efficient and safe drugs to exert significant contribution to human welfare. Due to the immense complexity of the underlying biochemical processes of the human body, medicinal chemistry faces a multidimensional optimization task. In silico methodologies can support the optimization of chemical series in terms of ADMET related modifications and therefore have crucial importance and contributed significantly to the success in clinical development.

During the preparation of the thesis I was employed in the Computer Assisted Drug Design team of Discovery Chemistry Laboratory at Gedeon Richter Plc. Due to my involvement in the drug discovery projects I met the requirements of medicinal chemists on several ADMET optimization issues. Three major areas were found to demand in silico support that inspired my research: (i) relationships between metabolic stability and ligand structure and the site of metabolism, (ii) active efflux mechanism mainly mediated by P-glycoprotein (P-gp), and (iii) assessment of compound quality from multidimensional optimization aspects. Finally, these three fields were selected as bases for my research activity.

First, I developed a novel methodology for computational prediction of the site of metabolism. The theoretical background of the method is based on the crystal structural information of the catalytic cycle of the cytochrome P450 enzyme catalyzed biotransformations. As a proof of concept I evaluated the knowledge-based docking method by using MetabolExpert for metabolite generation and Glide for docking into the binding site of the CYP2C9 crystal structure.

Second, I developed and validated the human P-gp protein model and used for induced-fit docking of experimentally characterized P-gp substrates. I have tested the applicability of the developed homology model for virtual screening purposes using enrichment studies aimed at discriminating inhibitors and substrates from decoys. Since the enrichment studies resulted in only limited enrichments, I concluded that in the case of P-gp protein incorporation of flexibility is crucial.

Third, I investigated the correlation between lipophilic efficiency metrics namely LLE and LELP measures and ADME as well as safety risks. I concluded that monitoring LLE and LELP both have clear benefits on ADME and safety assay results that can deconvoluted to ADMET assay endpoints.