

Targeting Drug Efflux Pumps – A Pharmacoinformatic Approach

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Within the drug development process, more than 40% of compounds fail due to improper ADMET (Absorption – Distribution – Metabolism – Elimination- Toxicity) properties. Thus, there is currently a strong focus on the development of methods to predict the bioavailability of drug candidates at a very early stage of the pipeline. Within the past decade, the importance of drug efflux pumps such as P-glycoprotein (P-gp) in the field of ADMET-profiling was increasingly recognized. These ATP-driven, trans-membrane proteins export a wide variety of structurally and functionally diverse drugs out of cells. They are responsible for e.g. multiple drug resistance in tumours, poor absorption properties of drugs in the gastrointestinal tract as well as permeation of the blood-brain barrier. Inhibition of these pumps thus represents a versatile tool for overcoming multidrug resistance in tumours and microbial diseases and for improvement of ADMET-properties.

In line of our studies on propafenone-type inhibitors of P-gp, we applied several methods to approach virtual screening tools for identification of new P-gp inhibitors on one hand and the molecular basis of ligand-protein interaction on the other hand. For virtual screening, a combination of autocorrelation vectors and selforganizing artificial neural networks proved extremely valuable in identifying P-gp inhibitors with structurally new scaffolds. For a closer view on the binding region for propafenone-type ligands we applied a combination of pharmacophore driven photoaffinity labeling and protein homology modeling. On LmrA, a bacterial homologue of P-gp, we were able to identify distinct regions on transmembrane helices 3, 5 and 6 which show significant changes in the labeling pattern during different steps of the catalytic cycle. These results were used for preliminary docking studies of our in house compound library, which yielded in the identification of a binding site close to the membrane interface.