The human ATP-binding cassette transporter ABCB1 (P-glycoprotein, P-gp, MDR1), which is strongly related to multidrug resistance, is known for its high polyspecificity, thus binding a large number of structurally diverse molecules. The molecular basis of this polyspecificity in terms of binding site(s) is still not resolved and proposals range from a huge binding zone to up to seven distinct drug binding sites that are partly overlapping. Nevertheless, mutagenesis studies and photoaffinity labeling showed that transmembrane (TM) helices 1, 3, 11 and 12, as well as 5, 6, 7 and 8 are involved in ligand binding [1, 2].

To shed more light on the molecular basis of drug binding we started to expand our ligand-based studies based on propafenone analogues [3] towards structure-based approaches, such as docking. Unfortunately there is still no high resolution structure available. Therefore, a homology model of ABCB1 based on the bacterial ABC transporter SAV1866 (PDB code: 2HYD) was used for docking [4]. Although the template resembles the energized open-outward state of the catalytic cycle it was chosen due to its high homology to ABCB1 (52 % homology) and its proper resolution of 3.0 Å. The docking was performed using FlexX implemented in MOE as placement methodology. As scoring function London dG Scoring was selected. Similar poses of different propafenone analogs were compared using protein ligand interaction fingerprints. The results did not show any interaction with the putatively important amino acid residues of the TM helix 5. Since propafenones rather bind to the apo-form of P-gp, the missing contact might be a first hint for the changes in the interaction pattern responsible for the affinity decrease upon ATP-binding.

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