APPLICATION OF MiPhaK ROUTINE TO GENERATE QSAR MODELS FOR PROPAFENONE TYPE P-GYLCOPROTEIN INHIBITORS

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The ATP-driven multidrug efflux pump P-glycoprotein (P-gp) is increasingly recognised as major limiting factor for bioavability and brain uptake. Additionally, its overexpression in tumour cells leads to resistance to a broad variety of divers natural product toxins. Vice versa, inhibitors of P-gp are proposed to resensitise multidrug resistant tumour cells. Due to a sort of promiscuity in the binding interaction of P-gp with ligands, the use of rational drug design approaches results rather difficult. Therefore, we used a novel computational routine, MiPhaK [1], that calculates a set of new descriptors by molecular surface estimation. These descriptors are determined from the calculated energy of interaction between the molecule and a probe atom around molecular or solvent accessible surface. They relate to pharmacophoric features such as molecular electrostatic potential, H-bond donor/acceptor capability and hydrophobicity of the whole molecule.

Our *in house* dataset of 131 propafenone type P-gp inhibitors served as training set for QSAR model generation. In total 70 descriptors were used, including ten co called classical molecular descriptors such as molecular weight, volume, polar/apolar surface area etc. We performed partial least squares analysis (PLS) – implemented in MOE - to correlate the biological activity, expressed as log(1/EC50), with the calculated properties. Validation was carried out by Leave-one-out cross-validation procedure (LOO) and by external prediction of 50 P-gp inhibitors of the propafenone type, that did not contribute to the establishment of the model. Both methods led to excellent results with a squared correlation coefficient of R^2=0.73 (LOO) and 0.71 (external) and a cross-validated correlation coefficient of Q^2=0.77 (LOO) and 0.73 (external). Hence, the use of MiPhaK descriptors for ADME profiling is suposed to be a valuable tool for multispecific targets.

[1] Meniconi, M.; Costantino, G.; Macchiarulo, A.; Pellicciari, R.. QSAR and Comb. Sci 2004. Submitted.