# Three-Dimensional Quantitative Structure-Activity Relationship Analyses of Substrates of the Human $H^+$/Amino Acid Transporter PAT1

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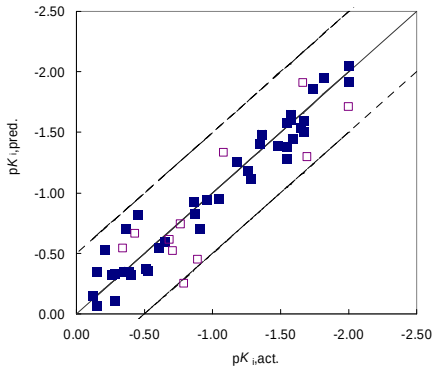
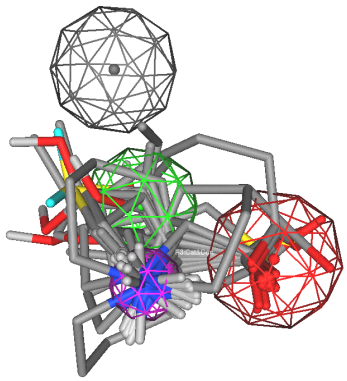
The proton coupled amino acid transporter PAT1 has recently gained much interest due to its ability to transport small drugs thereby allowing their oral administration.[123] A three-dimensional quantitative structure-activity relationship (3D QSAR) study has been performed on its natural and synthetic substrates employing comparative molecular similarity indices analysis (CoMSIA) to investigate the structural requirements for substrates and to derive a predictive model that may be used for the design of new prodrugs. The cross-validated CoMSIA models were derived from a training set of 40 compounds and the predictive ability of the resulting models was evaluated against a test set of 11 compounds. Despite the relatively narrow range of binding affinities ($K_i$ values) reliable statistical models with good predictive power were obtained. The best CoMSIA model in terms of a proper balance of all statistical terms and the overall contribution of individual properties was obtained by considering steric, hydrophobic, hydrogen bond donor and acceptor descriptors ($q^2_{cv}$ = 0.670, $r^2$ = 0.958 and $r^2_{pred}$ = 0.666). The 3D QSAR model provides insight in the interactions between substrates and PAT1 on the molecular level and allows the prediction of affinity constants of new compounds.



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