Modeling of ligand interactions for the human 5-HT_{1A} receptor: Docking, pharmacophores and virtual screening of databases containing drug-like compounds

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A database of known 5-HT_{1A} receptor ligands (113 binders, 68 strong binders) has been built by using the Instant Jchem database manager system from the ChemAxon program package. The ligands have been classified into groups according to chemical similarities (scaffolding groups, e.g. arylpiperazines) and according to their pharmacological activity (full agonists, partial agonists and antagonists). Information for 6369 5-HT_{1A} receptor ligands (true actives and decoys) were retrieved from the ChEMBL database [1] and clustering approaches were utilized for selection of training and test sets of structurally diverse ligands for use in pharmacophore and receptor modeling. Separate pharmacophore hypothesis were developed and tested for each clustered groups of ligands using the SCHRÖDINGER PHASE program. Homology models of the 5-HT_{1A} receptor were built based on crystal structures of the β_2 adrenergic [2] and dopamine D_3 receptors [3] using the ICM-PRO program. Since the binding pockets inside these initial homology models were too narrow to allow docking of all 5-HT_{1A} ligands, modified receptor models were built by utilizing induced fit docking techniques in ICM-PRO. Ligand-guided receptor model optimization was based on the ALiBERO protocol that includes ICM docking and scoring, NMA (normal mode analysis) backbone changes and ICM flexible side chain sampling [4]. ALiBERO calculations generate ensembles (consisting of 100 conformations representing backbone and side chain pocket flexibility) and perform VLS docking on every conformer using ligand training sets with 1:1 ratio actives:decoys. The best performing conformer according to VLS is refined with top-scoring actives (using distance restraints for amine-Asp116(3.32) and sometimes also OH-Ser199(5.42) interactions) and the procedure is repeated iteratively until VLS threshold is reached. Databases containing ~4.1 million drug-like compounds (Enamine, ChemBridge, ChemDiv, Life Chemicals, Asinex and Princeton BioMolecules databases) were screened for 5-HT_{1A} receptor actives that fulfill our pharmacophore hypotheses and that have high predicted scores in docking studies. A set of SERT (presynaptic serotonin transporter) ligands from databases that have been predicted to have strong SERT binding affinity were also tested in the best 5-HT_{1A} receptor and pharmacophore models. The best scored ligands identified in the databases containing drug-like compounds according to our pharmacophore and receptor models will be tested in radioligand binding studies and the best of these again will be further tested in functional 5-HT_{1A} receptor assays in Poland.

[1] https://www.abi.ac.uk/chembl/
[2] Cherezov et al., 2007, Science 318: 1258-65
[3] Chien et al., 2010, Science 330: 1091-1995
[4] Katritch et al. 2009, Proteins 78: 197-211.

Gastrin regulates the urokinase plasminogen activator system