THE SEARCH FOR NEW LIGANDS WITH DUAL ACTIVITY FOR SERT AND SEROTONIN RECEPTORS

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A strategy that has attracted considerable attention in current medicinal chemistry is based on the conjugation of two biologically active molecules into one hybrid compound. The aim of our study is development of new hybrid compounds both SERT inhibitors and agonist of 5-HT_{1A} receptors (preferentially at postsynaptic) and/ or antagonists at 5-HT6 and 5-HT7 receptors.

A series of compounds with dual activity to SERT/5-HT_{1A}, SERT/5-HT6 SERT/5-HT7 available from ChEMBL database were docked to 13 conformations of serotonin transporter model. The SERT models were based on the crystal structures of leucine transporter from Aquifex aeolicus in complex with a panel of SSRIs, SNRIs and TCA ligands. In addition one of SERT models was based on the crystal structure of the Drosophila melanogaster dopamine transporter bound to the tricyclic antidepressant nortriptyline. Virtual Ligand Screening (VLS) in ICM was performed by docking ligands to a protein structure followed by an evaluation of the docked conformation with a binding-score function.

For each of the ligand–protein complexes, which were obtained in the docking procedure structural interaction fingerprints (SIFts) are calculated and analyzed. The analysis of the docking results will leads to selection of SERT models in searching for dual-acting compounds.

This study was supported by a grant Pol-Nor/198887/73/2013.