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Docking of Multiple Ligands into a New Homology Model of the Serotonin Transporter

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The serotonin transporter (SERT) is a presynaptic membrane protein that terminates neuronal transmission of serotonin (5HT) by transporting its substrate into the emitting neuron. Recently new crystal structures of the Leucine Transporter (LeuT) with multiple bound ligands have been published [1]. LeuT is a bacterial sodium dependent amino acid transporter, which is a homologue of the mammalian neurotransmitter sodium symporter (NSS) family (tcdb-code 2.A.22, www.tcdb.org), such as SERT. In light of our studies on the molecular basis of inhibitor binding we constructed a new homology model of SERT and used this for docking studies of a series of pharmacologically active ligands.

As template for the new homology model of SERT we used the LeuT structure with the bound inhibitor tryptophane (Trp) (pdb-code: 3F3A). Basis setting of the docking parameters was achieved by redocking experiments of Trp into LeuT by using the software package MOE (Chemical Computing Group, www.chemcomp.com). Subsequently we docked a variety of substrates (e.g. amphetamines) and inhibitors (e.g. cocaine and derivatives) to elucidate main differences in binding modes and interacting residues, with a special focus on tricyclic antidepressants (TCA). The evaluation and selection of the final docking poses was performed using the geometrical and statistical approach previously described [2].

Our results indicate that substrates are predominantly placed into the central binding site, orientated in a similar modality as we found in previous docking studies [2]. Concerning the TCAs, we found placements preferring interactions with residues located in the external vestibule. Final validation of these hypotheses will be achieved via in-vitro experiments such as site directed mutagenesis.

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