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Comparison of Ligand Docking to Different SERT Conformations.

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The serotonin transporter (SERT) plays a key role in the regulation of synaptic serotonin (5-hydroxtryptamine, 5-HT) levels and therefore is the major target for antidepressants including both the tricyclic antidepressants and selective serotonin reuptake inhibitors. The antidepressants affect the concentration of the serotonin by inhibiting the reuptake of the 5-HT into pre-synaptic nerve cells.
To examine the molecular mechanism of SERT, the interactions between SERT and ligands with different binding affinities were studied. Two different models representing different conformational states of SERT were used. One model represented the substrate-occluded conformation closed at both sides, while the other model represents an outward-facing conformation. X-ray crystallographic structures of corresponding conformational states of the bacterial homologue of the Na^+/Cl^- dependent neurotransmitter transporters from *Aquifex aeolicus* ($LeuT_{Aa}$) [1, 2] were used as templates for the homology modelling. The ligands were docked into the binding site of both models using the automatic docking module of the ICM molecular modelling software. Asp98 in TMH1 was the anchoring point for ligand docking into SERT models. In both models the docking studies indicated that the ligands interacted strongly with amino acids in transmembrane helix 1, 3, 6 and 8 of SERT. In the model of the outward-facing conformation the ligand also interacted with aminoacids in the extracellular loop 4 (EL4).

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[1] Yamashita A., Singh S.K., Kawate T., Jin Y., Gouaux E.: *Nature* 437 (2005), 21.
[2] Singh S. K., Piscitelli C. L., Yamashita A., Gouaux E.: *Science* 322 (2008), 1655.