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Differences in binding site conformations between substrate-bound and inhibitor-bound dopamine (DAT), serotontin (SERT) and noradrenalin (NET) transporters

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The dopamine (DAT), serotontin (SERT) and noradrenalin (NET) transporters are molecular targets for different classes of psychotropic drugs. The crystal structures of Aquifex aeolicus LeuTAa, complexed with a substrate (Leucine) in an occluded conformation, and with an inhibitor (Tryptophane) in an open-to-out conformation, have been used as templates for molecular modeling of DAT, SERT and NET. ICMPocketFinder has been used to investigate differences in binding site conformations between substrate-bound and inhibitor-bound transporters. Several putative ligand binding pockets where detected in the occluded conformation, while in the open-to-out conformation the binding sites where "fused" and overlapping, yielding one putative ligand binding pocket. Amino acid side chains formed gates of ionic- and hydrogen bonds between the putative binding pockets in the occluded conformation, and these bonds were broken in the open to out conformation. Psychostimulants and antidepressants have been docked into both conformations of the DAT, SERT, and NET models to reveal molecular explanations for the various selectivities of these drugs.

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