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An analysis of molecular interactions between the 5-HT_6 receptor and non-basic ligands

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The newest version of the ChEMBL database, the largest collection of information about the biological activity of chemical compounds, contains 1626 compounds acting on the 5-HT_6 receptor (K_i or equivalent equal or less than 100 nM) [1]. Despite the fact that typical 5-HT_6R ligands possess positively polarizable nitrogen which forms a crucial, charge-assisted interaction with the D3.32 residue, nearly 15% of actives have low basicity (basic pK_a less than 6) [2,3]. To examine binding modes of non-basic 5-HT_6R ligands, class-specific homology models based on seven different templates were generated utilizing previously applied methodology [4]. Models characterized by the highest values of the AUROC parameter in virtual screening experiments were selected for binding mode evaluation. This analysis indicated that the non-basic ligands bind to the receptor through hydrogen bonding with the D3.32 although the charge assisted contribution is missing; hydrogen bonds with T5.46 and T7.39 are also widespread. The most common way of non-basic ligands binding are hydrophobic interactions, among which stackings with aromatic cluster (W6.48, F6,51 and F6.52) are crucial.

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