P.5-16

Halogen bonding enhances affinity at 5-HT$_7$R in a series of N-[2-(dimethylamine)ethyl]-N-(2-phenylehtyl)anilines

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Background: Halogen bonds (XB) are specialized non-covalent interactions known since XIX century, but only recently they were recognized as important in binding of a biologically active molecules. They can be described by general structure DX···A, where DX is a halogen bond donor (X = Cl, Br, I), and A is a Lewis base.
Materials and Methods: All of the obtained compounds were obtained in a two step synthesis involving firstly nucleophilic substitution of 2-chloroalkyldimethylamine with aniline and secondly reductive amination of phenylacetaldehyde. Molecular modeling of halogen bonds was performed using combined quantum-polarized ligand docking (QPLD) and Molecular-Mechanics-Generalized-Born/Surface Area (MM/GBSA) free-energy calculation. Affinity values at 5-HT$_7$R were obtained through a radioligand binding assay.
Results: Here we present a series of N-[2-(dimethylamine)ethyl]-N-(2-phenylehtyl)aniline derivatives that were found in a bioisosteric query designed for creating a dual D$_2$R/5-HT$_6$R ligands. One of the obtained chlorine substituted compounds revealed to possess also a high affinity for 5-HT$_7$R (K_i = 4 nM). A QM/MM docking experiments suggest that halogen bonding with Ser5.42 may be responsible for its high 5-HT$_7$R affinity.
Conclusions: The chlorine substituted compound, possessing selective activity at both 5-HT$_6$R and 5-HT$_7$R, might provide an interesting candidate for an antipsychotic/antidepressant drug with procognitive properties. Analysis of Structure-Activity Relationship enforced with molecular modeling revealed, in the case of obtained series, important role of halogen bonding in receptor binding affinity and selectivity.
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