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Binding mode analysis of a series of novel 5-HT_{1A} ligands

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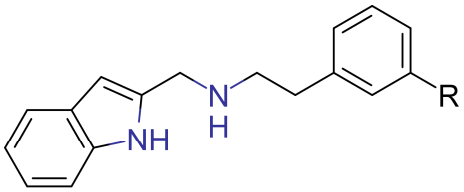
Halogens, especially the lighter fluorine and chlorine, are widely used substituents in medicinal chemistry. Until recently, they were merely perceived as hydrophobic moieties and Lewis bases in accordance with their electronegativities. It has to be stressed however, that compounds containing chlorine, bromine, or iodine can also form directed close contacts of the type R−X···Y−R', where the halogen X acts as a Lewis acid and Y can be any electron donor moiety. This interaction, referred to as “halogen bonding” since 1978, is driven by the σ-hole, a positively charged region on the hind side of X along the R−X bond axis that is caused by an anisotropy of electron density on the halogen.[1,2,3]
Within the arylmethyl-(2-phenylethyl)amines developed in our lab as serotonin receptor ligands, [(1*H*-indol-2-yl)methyl](2-phenylethyl)amines emerged as potent and selective 5-HT_{1A} receptor ligands. Introduction of halogen atoms to the benzene ring resulted in a significant increase in affinity. Notably, the -chloro (K_i = 19 nM) and -bromo (K_i = 34 nM) derivatives outperform both unsubstituted (K_i = 216 nM) and -fluoro (K_i = 160 nM), -methyl (K_i = 52 nM) and -trifluoromethyl (K_i = 81 nM) substituted compounds indicating the hydrophobicity of the substituent to be of secondary importance. The -methoxy substituted derivative exhibited K_i = 47 nM. The compounds structures were docked to 5-HT_{1A} receptor homology models using QM/MM protocol to investigate the possibility and nature of halogen bonding.



R = H, Cl, Br, F, Me, MeO, CF_3

[1] Clark, T.; Hennemann, M.; Murray, J. S.; Politzer, P. *J. Mol. Model.* 2007, *13*, 291−296,
[2] Clark, T. σ-Holes. Wiley Interdiscip. Rev. *Comput. Mol. Sci.* 2012, *3*, 1−8,
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