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The potential of halogen bonding in class A of GPCRs: application of XB hot spots for rational design of 5-HT$_7$R ligands

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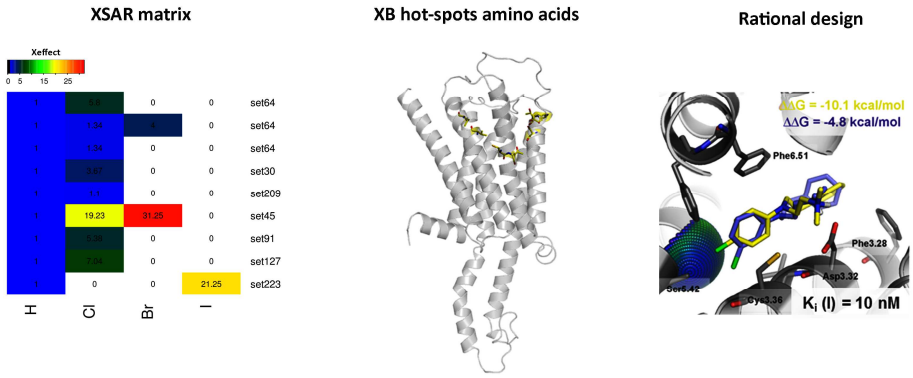
Since many years, halogen atoms have been regularly used in drug optimization processes, only recently their role in protein–ligand complexes has been attributed to the formation of a specific, direct interactions called halogen bonds. Incorporation of halogen atoms into molecule structure changes its steric (volumetric), electrostatic and conformational properties, lipophilicity (influencing membrane permeability and the oral absorption), and may lead to even 300-fold increase in the affinity for a given biological target [1, 2].



Herein we report on a systematic molecular modeling approach used to study the role of halogen atoms in the interaction of ligands with all crystallized receptors of family A GPCRs. The performed calculations distinguished several hot-spot amino acids, which were used to rational design/optimization of potent 5-HT$_7$R ligands.

[1] Iltzsch MH, et al., *Biochem. Pharmacol*. 49 (1995) 1501–1512,
[2] Benjahad A, et al., *Bioorg. Med. Chem. Lett.*, 13 (2003) 4309–4312,

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