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The potential role of halogen bonding in interactions of ligands with class A GPCRs – the β2 adrenergic receptor case study

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Halogen atoms are one of common features in biologically active compounds and drugs. 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]. Although, 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 formation of specific, direct interactions called halogen bonds.

To date, systematic and comprehensive studies on the role and significance of halogen bonds in family A GPCRs have not been published. There are also no studies showing the use of the concept of halogen bonds in the rational design of potential ligands of these receptors.

Herein we report on a systematic molecular modeling approach, i.e. generation of X-SAR sets fetched from ChEMBL database, molecular docking and hybrid QM/MM calculations, used to study the different role of halogen atoms in ligand-receptor interaction (i.e. steric hindrances, interaction of positive σ-hole with negatively charged atoms of the protein and interaction of the negative electrostatic potential of fluorine with positively charged atoms of the protein). The results obtained by application of developed computational workflow are discussed on the example of β2 adrenergic receptor.

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