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DIFFERENT ROLES OF HALOGEN SUBSTITUENTS IN LIGAND-RECEPTOR INTERACTIONS – A CLASS A GPCRS CASE STUDY

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Substitution of halogen atoms is a common and frequently used strategy in hit and/or lead optimization since many years.[1,2] Moreover, the incorporation of halogen atoms is usually used to increase membrane permeability and hence, improve the oral absorption,[3] to enhance the blood-brain barrier permeability, what is a requirement for the CNS drugs.[4] However, the applicability of halogen atoms in drug design is still far from been completely explored, e.g. the most SAR discussions of halogenated compounds have only considered the classical steric parameters, ignoring other contributions and effects of such atoms. In recent years the role of halogen atoms in protein–ligand complexes has been attributed to the formation of specific and direct interactions called halogen bonding.[6,7]
Herein, the different roles of halogen atoms were studied regarding the influence of: the type of halogen atom used (Cl, Br and I), the position of substitution in aromatic ring and the number of halogen atoms used, on the biological activity. The all crystalized GPCRs A were used as a testing set. For a given target, sets containing halogenated and unsubstituted derivatives were extracted from ChEMBL database using in-house scripts. The sets were next docked and analyzed by using previously tested QM/MM-GBSA procedure.[5]
The results showed that, in majority of cases, increasing the size of halogen atom (Cl < Br < I) substituted in the same position of aromatic ring increased the compound's activity, however, a sort of *plateau* effect was observed, where the most active derivative contained chlorine, whereas activity decreased for the bromine and iodine derivatives. A significant correlation between the position of substitution of halogen atom in aromatic ring was found. For instance, switching Br position in phenyl ring can decrease 11-fold, as well as, increase 27-fold (compared to unsubstituted compounds) an activity of the compound. Also very interesting dependencies between the number of halogen substituents in one aromatic ring and biological activity were noted.
It is suggested, that the reported effects can be a result of interplay between hydrophobic, halogen bonding and entropic contributions to the ligand binding energy.

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