OP-9

EVALUATION OF HALOGEN BONDING HOT SPOTS BY VIRTUAL SCREENING OF COMMERCIAL DATABASES – A CASE STUDY OF 5-HT$_7$R

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A halogen bond (XB) is a non-covalent interaction defined as a directional bond between a covalently bound halogen atom (acting as a donor) and a Lewis base as an acceptor.[1-3] The XB strength is comparable to weak or moderate hydrogen bonds and increases in the order of Cl < Br < I. XB has been indicated to play an essential role in supramolecular systems, liquid crystal engineering, nanomaterials, nanowire formation, catalysis, and also recently, in drug design and lead optimization processes.[4,5]
The main aim of early stages of rational drug design is to rank drug candidates to select the ones with a significant probability of becoming a drug. Virtual screening is generally used with large databases of compounds which are purchasable or easy to synthesize.
Herein, the recently developed and used systematic molecular modeling approach to search of XB amino acids hot spots among all crystallized GPCRs A was applied to one of the not yet crystallized family member, i.e. 5-HT$_7$R. The sets containing the halogenated and unsubstituted derivatives were extracted from purchasable collection of Mcule database (https://mcule.com/), which contains more than 35M compounds (access: 14.12.2016). Next, the resultant sets were filtered by CNS MPO (>4), 3D pharmacophore models, and finally docked to a set of 5-HT$_7$R homology models using previously tested QM/MM-GBSA procedure.[7] The sets in which halogenated derivative showed increase of the free binding energy upon formation of halogen bonding with any of the predicted hot spots were purchased and tested in 5-HT$_7$R radioligand binding assay. The results revealed that for the majority of sets the halogenated derivatives exhibited higher affinity for 5-HT$_7$R than their unsubstituted analogue. The studies provide evidence that only specific amino acids (XB hot spots) are able to create halogen bonding in the binding site and, hence, can be used in rational optimization and design of new drug candidates.

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