Targeting acetylcholinesterase with halogenated ligands: finding halogen bonding hotspots

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Acetylcholinesterase (AChE) is one of the most relevant therapeutic targets for the symptomatic treatment of Alzheimer's disease. Hence, the development of new molecules capable of inhibiting AChE activity is an effective therapeutic strategy. The incorporation of halogens (X) in drug molecules is a common way to enhance drug ADME (absorption, distribution, metabolism, and excretion) properties, often leading to increased potency. However, halogenation can also improve drug-target binding affinity due to the existence of halogen bonds (HaBs) established with the receptor. Halogen bonds (R-X...B) are noncovalent interactions between a positive region on the electrostatic potential of X, called sigma-hole, and a nucleophile, such as a lone pair of a Lewis base (B).
Since there were virtually no reports on the use of HaBs to target AChE, in this work, we searched for amino acids frequently targeted by halogen bonding (called hotspots) in the AChE binding site. For that purpose, all the compounds containing a moiety capable of halogen bonding (Ph-X, Ph = phenyl, and X=Cl, Br, I) were retrieved from the ChEMBL database and docked into the AChE binding site using AutoDock Vina XB whose scoring function takes into account the sigma-hole. Multiple X-ray structures and molecular dynamics snapshots from the target were used to account for conformational variability. By applying a geometrical criteria, we selected all halogens atoms engaged in HaBs, thus being able to identify halogen bonding hotspots on the binding pocket. These preliminary results will be the starting point for obtaining new halogenated scaffolds to target AChE, hopefully helping in the design of new and more effective AChE inhibitors.

Acknowledgements: FCT/MCTES (IF/00069/2014, IF/00069/2014/CP1216/CT0006, SFRH/BD/116614/2016, UID/MULTI/00612/2019 and UID/MULTI/04046/2019). FCT/MCTES, Lisboa 2020, Portugal 2020, FEDER/FN, and European Union (LISBOA-01-0145-FEDER-028455, PTDC/QUI-QFI/28455/2017).