Targeting acetylcholinesterase with halogenated ligands: finding halogen bonding hotspots

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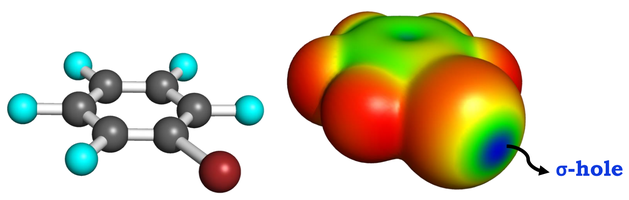
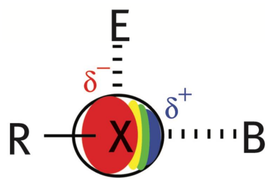
Introduction

Halogen Bonds (HaBs)

Halogen bonds (R–X···B) are noncovalent interactions between a positive region on the electrostatic potential of halogen (X = Cl, Br, I), called **σ–hole**, and a nucleophile, such as a lone pair of a Lewis base (B).

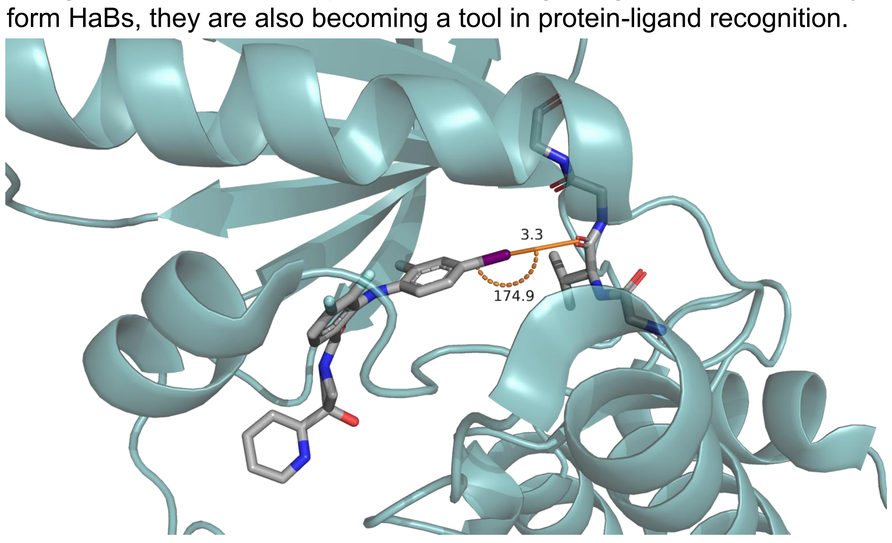


HaBs are linear interactions, orthogonal to interactions of the type R–X···E (E = electrophile). [1]



Halogen Bonding in biomolecular systems

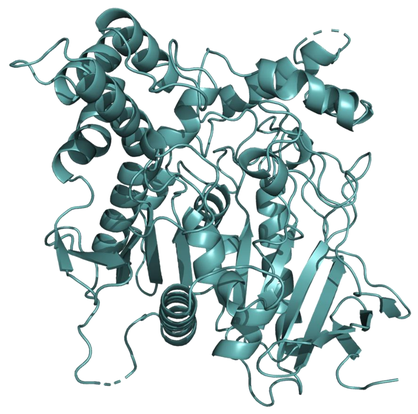
Halogen atoms have an important role in drug design. Given their ability to form HaBs, they are also becoming a tool in protein-ligand recognition.



A good example of this phenomena is the X–ray crystal structure of cobimetinib in complex with MEK1 kinase (PDB ID: 4LMN). Cobimetinib is a kinase inhibitor approved for the treatment of BRAF-mutant melanoma. [2]

Objective

There are virtually no reports on the use of HaBs to target acetylcholinesterase (AChE).

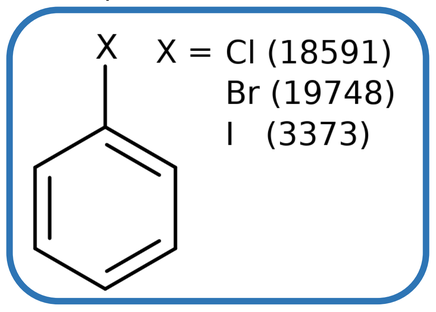


Can we find HaBs hotspots in AChE?

Methods

New method to find AChE HaBs hotspots

Retrieve halogenated compounds from ChEMBL



AutoDock Vina XB [3]

10 independent runs per compound

Multiple X-ray structures for AChE [4]

PDB ID: 4EY4

PDB ID: 4EY6

PDB ID: 4EY7

Select lowest energy pose

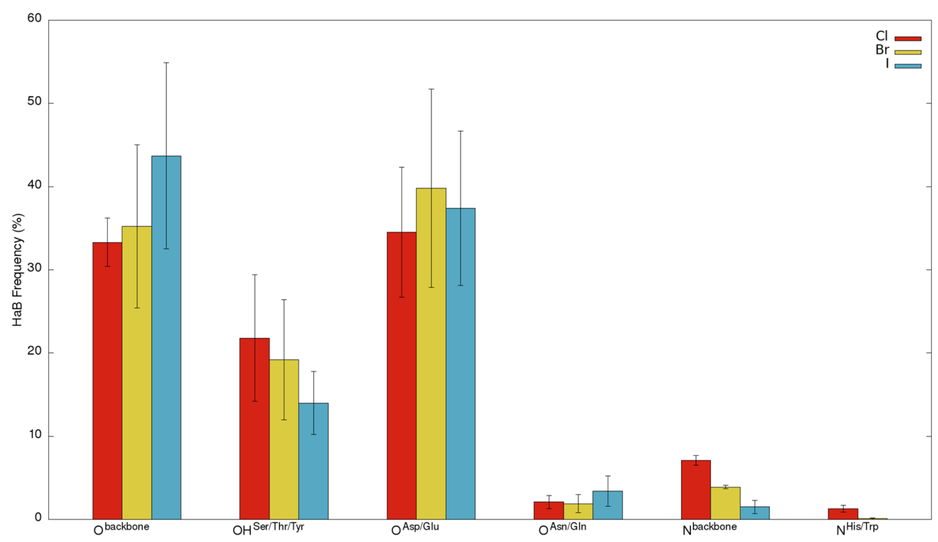
Filter HaBs using geometrical criteria [5]

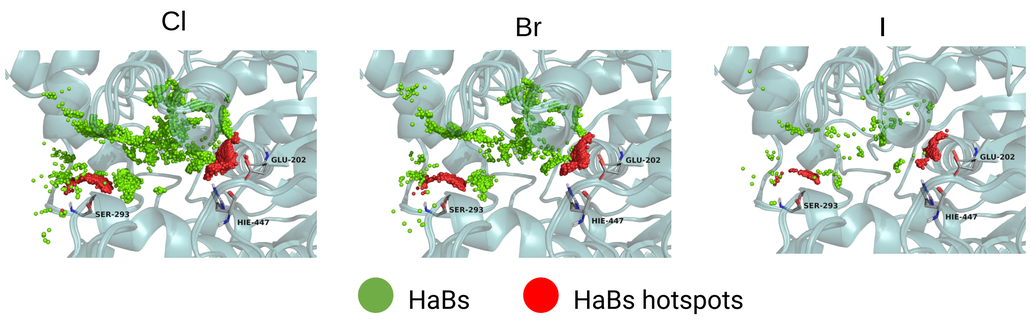
Hotspots

Results

HaBs frequency

Each acceptor type shows distinct propensity for halogen bonding. With backbone C=O and sidechain COO^- being the most favored acceptor types, followed by sidechain OH.

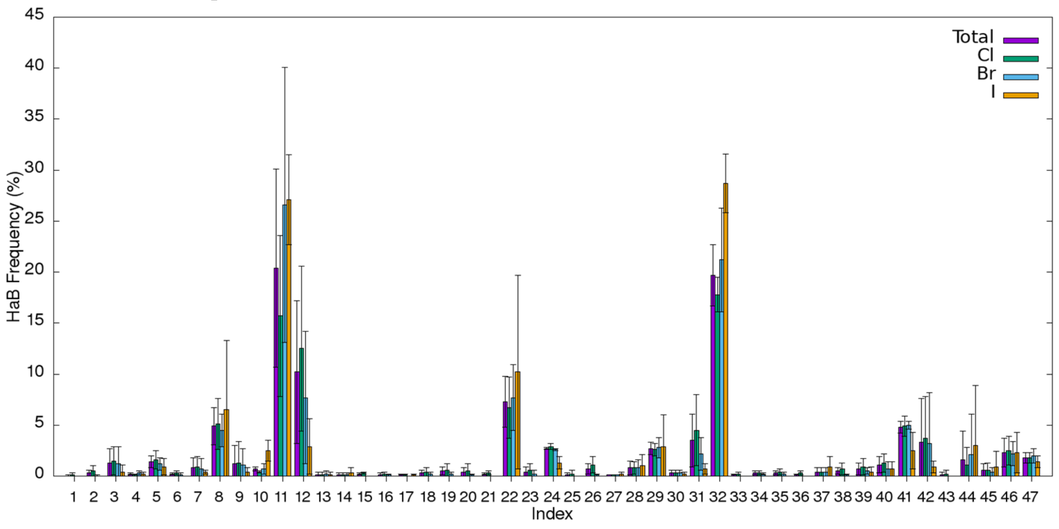




HaBs

HaBs hotspots

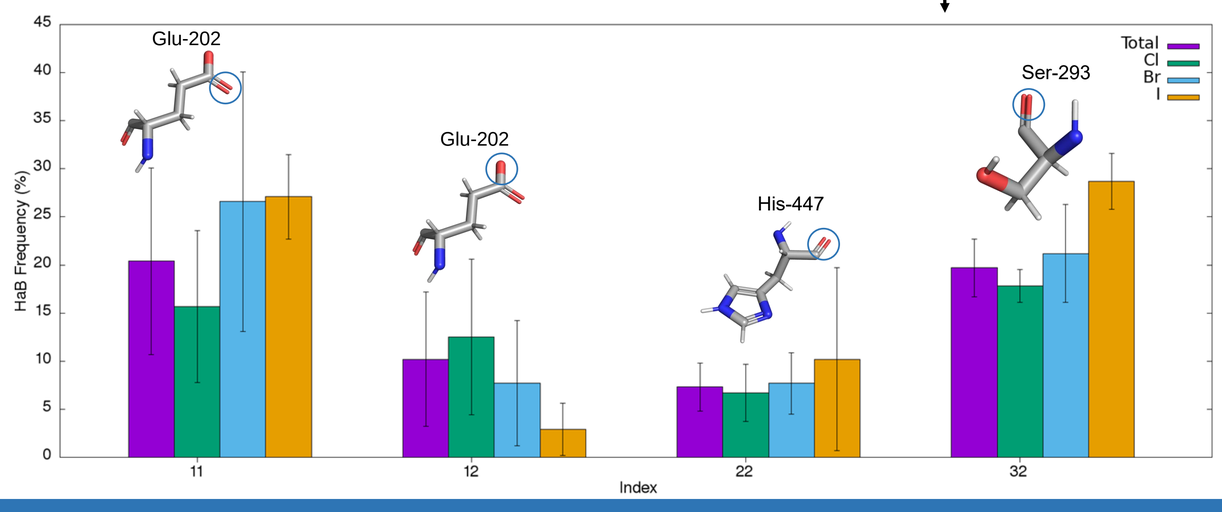
HaBs hotspots



All residues/atoms involved in halogen bonds

Applying a 7.5% cut off, we get the AChE HaBs hotspots

HaBs hotspot representation per halogen



References

[1] P. J. Costa, *Phys. Sci. Rev.* **2017**, 2, 20170136. | [2] P. J. Costa, R. Nunes, D. Vila-Viçosa, *Expert Opin. Drug Discov*. **2019**, *14*, 805–820. | [3] M. R. Koebel, G. Schmadeke, R. G. Posner, S. Sirimulla, *J. Cheminformatics*. **2016**, 8, 1–8. | [4] J. Cheung, J. J. Height, *et al., J. Med. Chem*. **2012**, 55, 10282–10286. | [5] Z. Xu, W. Zhu, *et al., J. Chem. Inf. Model*. **2014**, 54, 69–78

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