The significance of halogen bonding in ligand-receptor interactions - the lesson learned from Molecular Dynamic simulations of D_4 receptor

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Introduction

Halogen bond (XB, Figure 1) 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].

Recently, a computational approach combining a structure-activity relationship library containing pairs of halogenated and the corresponding unsubstituted ligands (called XSAR) with QM-based molecular docking and binding free energy calculations was developed and used to search for amino acids frequently targeted by halogen bonding (hot spots) and tested for 5-HT_7R [6].

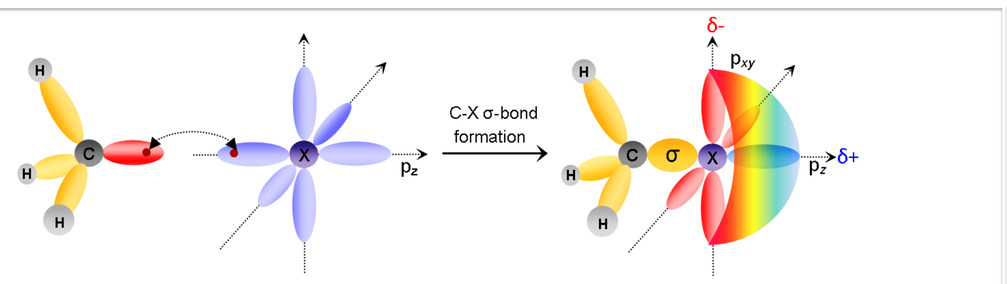
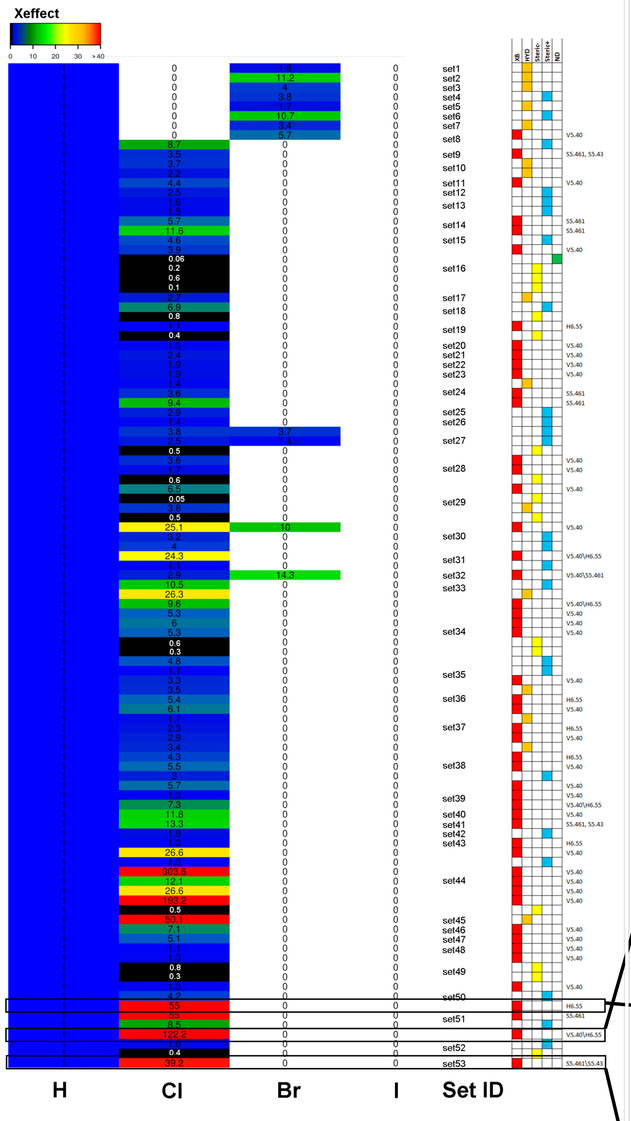


Figure 1. The illustration of the σ-hole concept. The formation of a covalent carbon−halogen bond (a C–X σ-bond) by pairing of the electrons from the valence orbitals of the two atoms. As a result, the portion of the p_z orbital of the halogen opposite the σ-bond becomes depopulated, resulting in an electropositive crown (in blue), whereas the p_x and p_y orbitals retain their complement of electrons to account for the overall negative charge of the halogen (in red).

Methodology

A structure-activity relationship library containing pairs of halogenated and the corresponding unsubstituted ligands (called XSAR) was generated for D_4 receptor.



Workflow of computational algorithm to identify amino acids (hot spots) that are common anchoring points for halogen bond

Optimization of the D_4R binding site using the induced-fit docking procedure and XSAR sets.

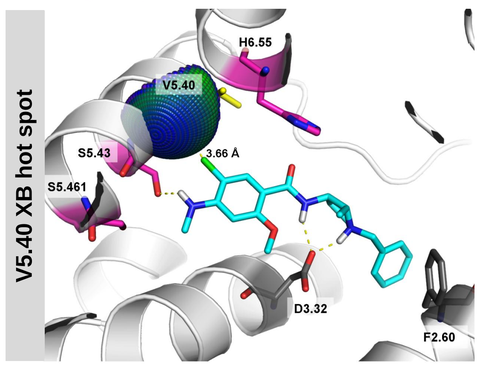
A 60 ns MD simulations were performed using Schrödinger Desmond software. Each ligand–receptor complex was immersed into a POPC (300 K) membrane bilayer, and system was solvated by water molecules described by the TIP4P potential. All calculations were performed on GPU (CUDA) processors. OPLS3 force field was used to describe the modeled systems.

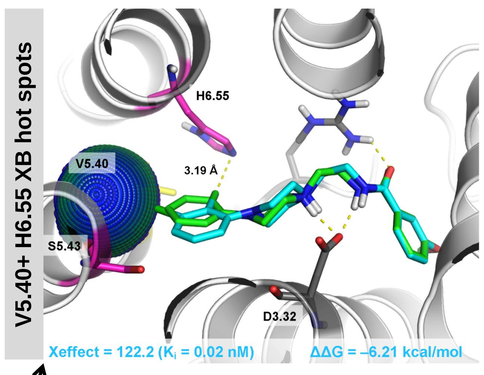
Results

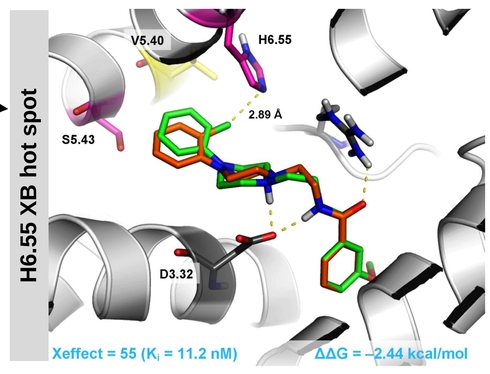
secondary XB hot spot

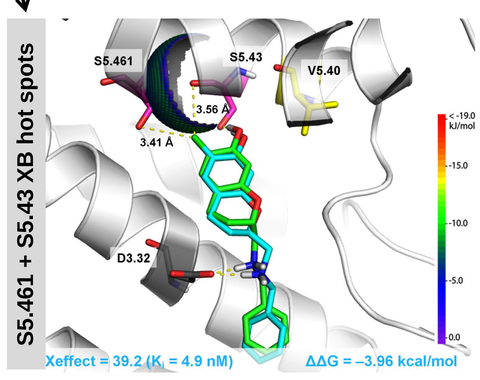
primary XB hot spot

5WIU: D_4 receptor in complex with Nemonapride









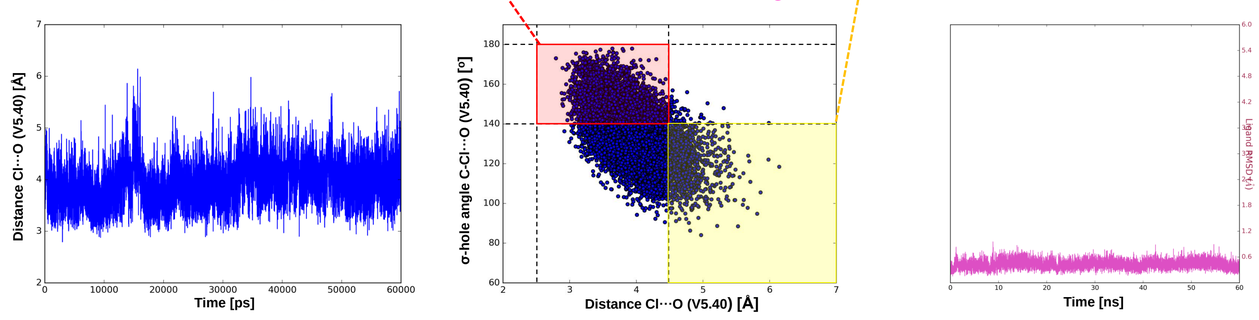
Area indicating halogen bonds formation

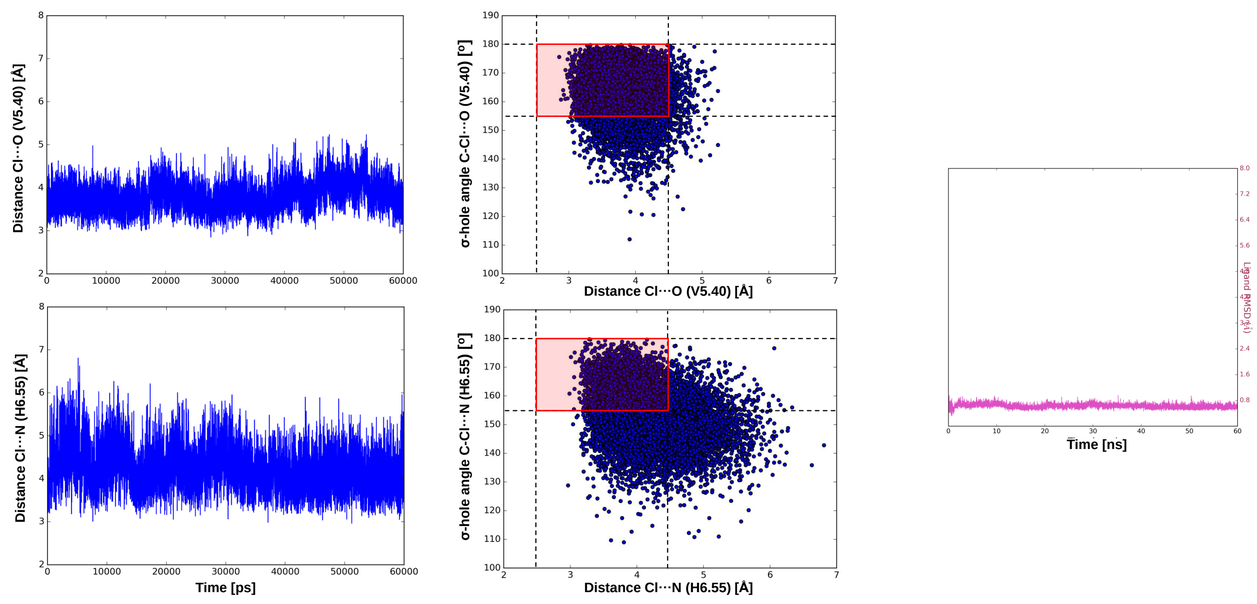
No ability to formation of halogen bonds

XB distance change during the 60 ns MD simulations

Multivariate plot: XB distance vs. σ-hole angle

Ligand RMSD





Conclusions

The results of MD simulations supported by the experimental data showed that steric restrictions and the topology of the molecular core have a key impact on the stabilization of the ligand-receptor complex by halogen bonding. The amount of enhancement in the activity of the halogen derivative compared to its unsubstituted analog depends on the stability of the halogen bond. The proposed methodology combining the MD simulations and XSAR confirmed the hypothesis of secondary and primary halogen bonding hot spots. The carbonyl oxygen of V5.40 and nitrogen of H6.55 can be used to as XB anchoring points for new D_4 ligands.

References

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Acknowledgments

The study was supported by the National Science Center, Poland, Grant No 2014/15/D/NZ7/01782.

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