P66

The significance of halogen bonding in ligand-receptor interactions - the lesson learned from Molecular Dynamic simulations of D4 receptor

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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].

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) [6]. However, the analysis of ligand–receptor complexes with halogen bonds obtained by molecular docking provides only a limited ability to study the role and significance of halogen bonding in biological systems. Thus, we performed a set of molecular dynamic simulations (MD) using OPLS3 force field, which have a well-documented parametrization for XB. The dopamine 4 receptor, recently crystalized with antipsychotic drug nemonapride (5WIU) and XSAR library (containing 52 sets), were used to define staring geometries. A 100 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.
The results of MD simulations supported by the experimental data showed that steric restrictions, and the topology of 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.

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