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PERSPECTIVES OF DIRECT MODELING OF HALOGEN BONDING IN EARLY DRUG DISCOVERY

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Halogen bonding (XB), defined as attractive interaction between a heavy halogen atom in a molecule and an electron rich donor, has received considerable attention recently [1] as a new promising interaction pattern (such as e.g. hydrogen bonding, hydrophobic interactions, pi-pi stacking, etc.) that could be used rationally in early stages of drug discovery [2]. XB uniquely combines hydrophobic properties and directional electrostatic interactions. Moreover, halogen atoms are abundant in drugs and drug candidates [3], therefore the route to additional optimization of a molecule is open.

Despite its potential usefulness, XB description in computer-aided tools used in the early drug discovery has not reached the level ensuring their comprehensive utilization. As of today only a few molecular mechanics descriptions of XB were reported, as well as a few attempts to incorporate XB explicitly in scoring functions used for molecular docking and virtual screening. Thus, XB interactions are not properly represented in the current tools for early stages of computer aided drug discovery.

We observe the perspectives and means for incorporation of XB description at different levels of approximation consistent with the approaches proved to be fruitful in drug discovery and, hence, incorporated in a series of tools used in drug discovery practice. The spectrum of levels of XB description should span from the force field to empirical scoring functions.

Starting from the nature of the XB interactions – high molecular electrostatic potential anisotropy – we have compared and optimized earlier two approaches to incorporate XB in a force field modeling [4,5]. Our current focus is on the explicit incorporation of the XB description in the current scoring functions used for molecular docking and virtual screening studies. The main challenge is to quickly (avoiding quantum chemical calculation) assign proper values of anisotropic electrostatic parameters to a molecule belonging to a broad and diverse space of pharmaceutically relevant compounds. On the route to build an empirical scheme to assign the electrostatic XB parameters for diverse organic molecules we investigated the extent and the nature of dependence of those parameters on the substitution pattern on an archetypal set of mono- and di-substituted phenyl halides. Since the relative importance of resonance and inductive effects were estimated, our current aim is to check the findings within the molecular docking environment.

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