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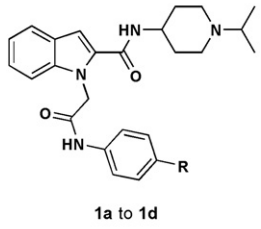
The importance of aryl C–Cl···π interaction in ligand–protein binding

In recent years, aryl C–Cl···π interaction has been increasingly recognized as a key contribution to the binding of ligand to protein. In a series of serine protease factor Xa inhibitors, the conventional interaction of a P1 amidine moiety with Asp189 in the S1 pocket, which has a negative impact on oral bioavailability, could be traded for an interaction between Tyr228 located in the same pocket with a P1-arylchloride. This modification provided up to −10 kJ/mol change in free energy of binding, leading to potent and orally bioavailable inhibitors. A related SAR study also demonstrated that aryl bromide analogs conferred a similar gain in binding energy, whereas interactions with aryl fluoride analogs were weaker with $\Delta\Delta G$ of −3.5 kJ/mol (Fig. 1) [1]. A survey of RCSB Protein Data Bank (www.rcsb.org) revealed that the aryl C–Cl···π interaction is not uncommon in nature. In addition to serine proteases, this interaction has also been observed in the binding of ligands to other protein families, including farnesyltransferase, the *N*-methyl-*D*-aspartase receptor as well as HIV reverse transcriptase. Together with a search in the Cambridge Structural Database, a preferred aryl C–Cl···π interaction geometry was identified. The chlorine atom resides on top of the neighboring aryl ring at an angle of 60–90° with a Cl to centroid(1) distance of about 3.4–4.2 Å and a centroid(1) to centroid(2) distance of 5–7 Å (Fig. 2). Results from *ab initio* calculations of benzene/halobenzene interactions at the MP2 level were also consistent with these preferred parameters and estimated $\Delta\Delta G$, and indicated that an electron rich aryl partner, for example phenol and indole, will further stabilize the interaction. The understanding of this general nonbonding interaction should be useful for compound design [2].



1a to 1d

1	R	Ki (nM)	ΔΔG (kJ/mol)
a	H	204	0
b	Cl	3	-10.46
c	Br	3	-10.46
d	F	63	-3.46

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FIGURE 1

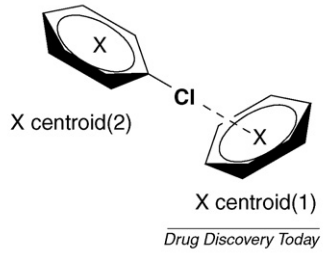

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FIGURE 2

1 Matter, H. *et al.* (2009) Evidence for C–Cl/C–Br···π interactions as an important contribution to protein–ligand binding affinity. *Angew. Chem. Int. Ed.* 48, 2911–2916

2 Lam, P.Y.S. *et al.* Structure-based drug design utilizing halogen bonding: Factor Xa inhibitors. *Abstract ORGN 58*, 238th National Meeting of the American Chemical Society, Washington, DC, Aug 16–20, 2009.

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