Interactions of Halogen Atoms to Protein Binding Sites and Contributions to Binding Affinity

Hans Matter*, Stefan Güssregen, Marc Nazaré

* Hans.Matter@sanofi.com
Sanofi-Aventis Deutschland GmbH
R&D LGCR/Structure, Design & Informatics FF
Industriepark Hoechst
Bldg. G878, Room 408
D-65926 Frankfurt am Main

Experimental evidence suggests that organic chlorine and bromine atoms are involved in non-bonded protein-ligand interactions, thus contributing to binding affinities. These interactions include halogen-bonding and contacts to aryl rings. Introducing halogen atoms at distinct positions of factor Xa inhibitors consistently improves free energy of binding by interaction to a tyrosine ring in the active site. The nature of these interactions was studied to understand the contribution to affinity. Geometric preferences for this contact were revealed by investigations in protein and small-molecule databases. It will be discussed how these atypical interactions can be introduced into field-based molecular descriptions. As classical force-fields can not adequately account for halogen-mediated interactions due to missing treatment of the “sigma”-hole, we have extracted local properties from quantum-mechanical techniques that do not suffer from these limitations. Regression models from those fields provide a significant advantage to understand SAR features.