The potential role of halogen bonding in interactions of ligands with class A GPCRs – the β2 adrenergic receptor case study

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The σ–hole concept

The unique nature of halogens can be explained by the fundamental properties of a covalent σ-bond between atoms in C–X group. The halogen atoms have five electrons occupying the p atomic orbitals of the valence shell and the single valence electron of the p_z orbital is involved in creation of a covalent σ-bond with a carbon atom. As a result, the depopulation of this orbital opposite to the C–X σ-bond leaves a hole that partially exposes the positive nuclear charge. This so-called σ-hole accounts for the electropositive crown and polar flattening associated with the polarization effects (anisotropy in charge distribution), whereas the four remaining electrons in the p_x, p_y orbitals account for the electronegative ring lying perpendicular to the σ-bond. This may lead to the attractive, non-covalent interactions between C–X moiety and classical hydrogen bond acceptors (O, N, S – see right).
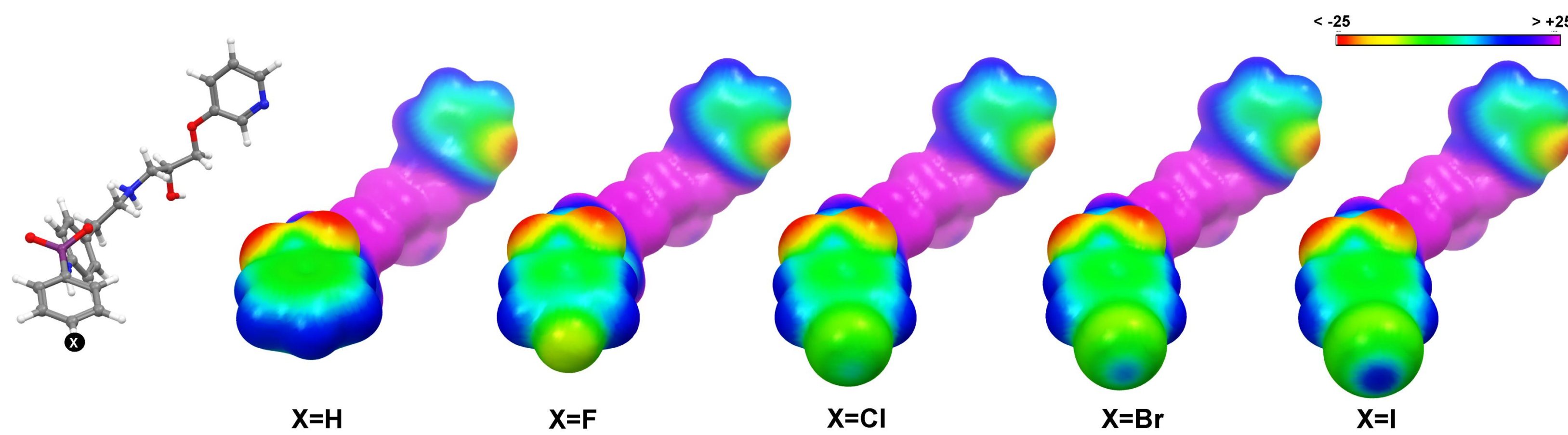

Fig. 1. Molecular surface electrostatic potential of compounds from X-SAR set_102 (not used in the study due to a lack of affinity data), computed on the 0.001 au. contour of the electronic density. Computational level: B3PW91/cc-pVTZ.

Halogen bonding

A halogen bond (X-bond) can be defined as a directional bond between a covalently bound halogen atom (acting as a donor) and a Lewis base as an acceptor (Fig. 2). This type of bond is attributed to the anisotropic distribution of the charge density on the halogen atom, resulting in the formation of a positive cap (σ-hole – see left) centered on the C–X axis (Fig. 1) [1,2]. Its strength is comparable to the weak or moderate hydrogen bonds (5–180 kJ/mol) [3]; and increases in the order Cl < Br < I. Notably, F atom does not form halogen bond, because of lack of a σ-hole [3].

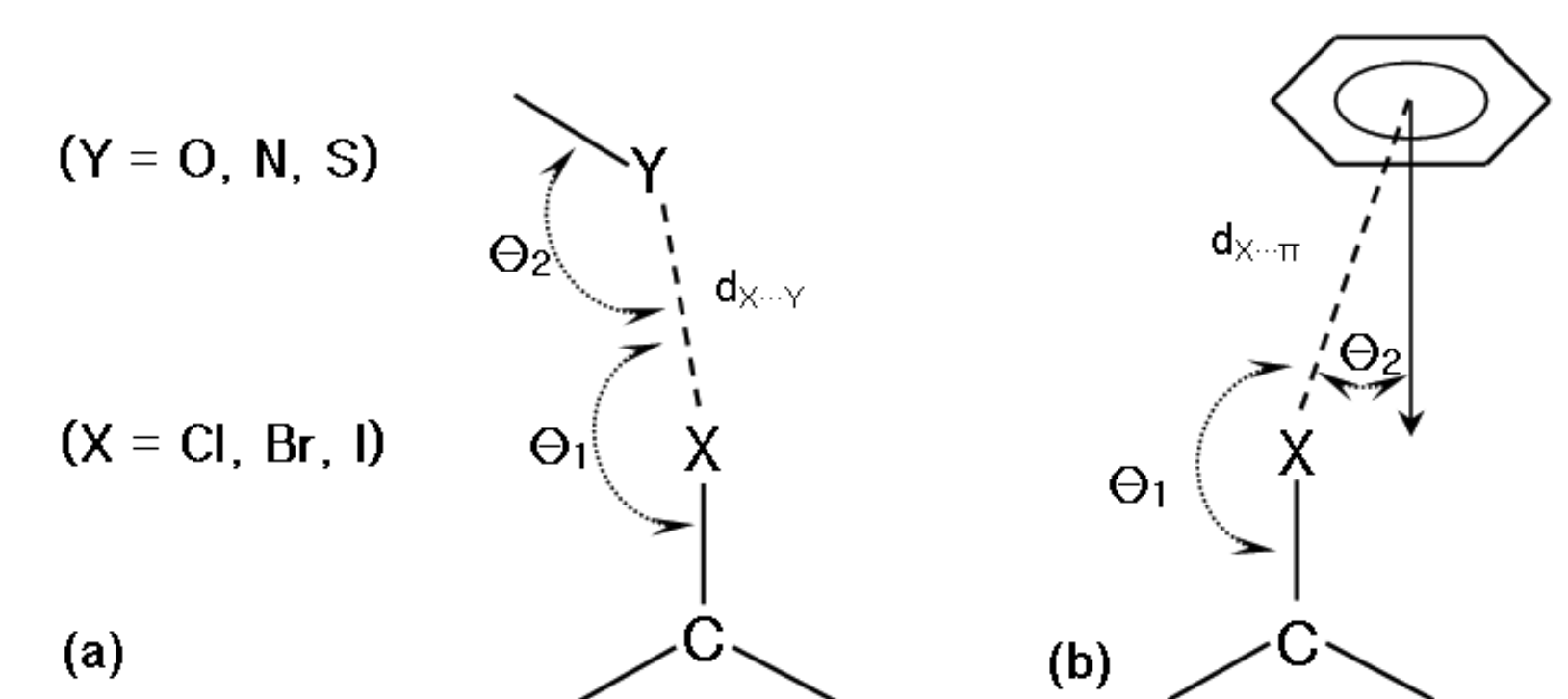Fig. 2. The two models of halogen bonding observed in biological systems: (a) C-X···Y and (b) C-X···π.

Methodology

Workflow for generation of Structure-Activity Relationships datasets of halogenated analogues

- fetch data (structures and affinities) from ChEMBL database,
- define molecular query (find all halogenated structures and remove halogen atoms),
- do substructure search for all queries (scaffolds),
- select only halogenated derivatives for a given scaffold,
- calculate X-Effect parameter,

$$X-Effect = \frac{Affinity(parent)}{Affinity(halogenated)}$$

Set_101
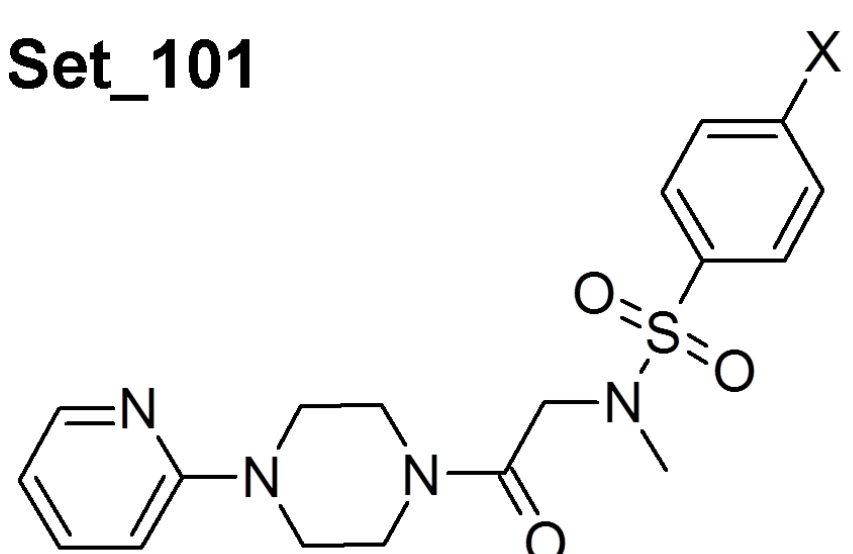
| X	EC50 [nM]	X-Effect
H	274	1
Cl	40	6.92
Br	36	7.7

QM-Polarized Ligand Docking

- Glide docking,
- single-point energy calculation on each complex (QM/MM using QM:B3LYP/6-31G* and MM:OPLS-2005),
- deriving partial atomic charges using electrostatic potential fitting,
- re-docking with new QM/MM-derived charges,
- return the most energetically favorable poses.

Free Binding Energy Calculations

- OPLS-2005 force field and Generalized-Born/Surface Area continuum solvent model,
- partial charges calculated in QPLD,
- estimated ΔG values to select right poses between possible binding modes.

-123.6 kcal/mol   -97.7 kcal/mol
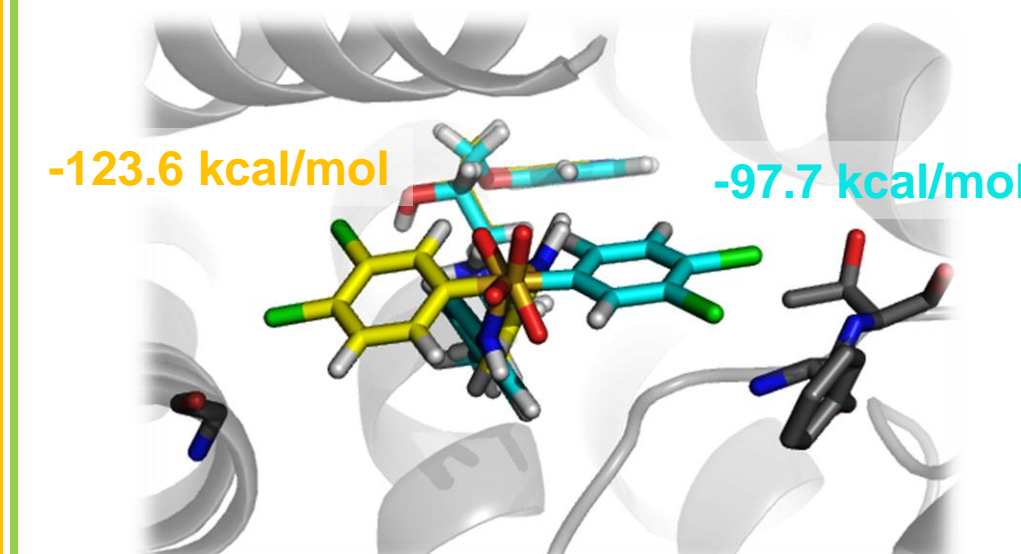
Interaction Analysis

- interaction spheres for halogen interactions [4],
- measurment of distance and valence angles,
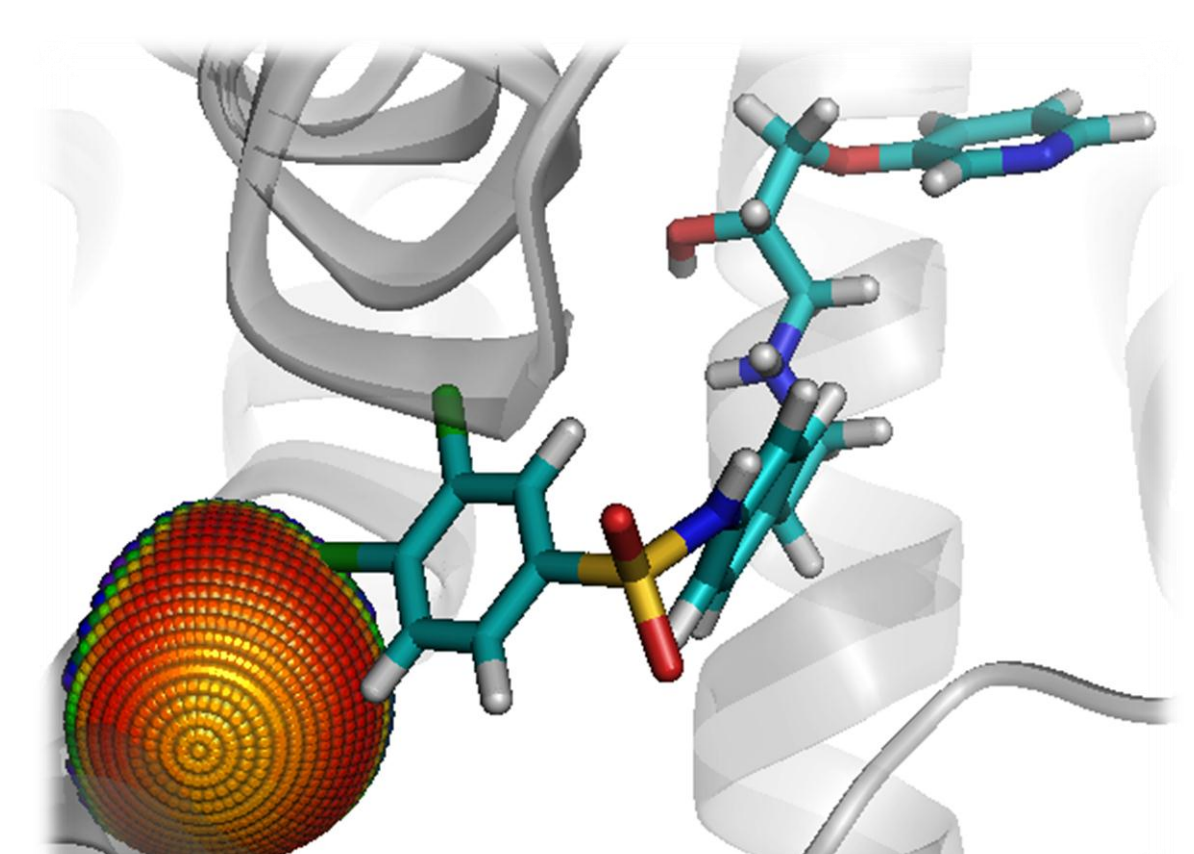
X-SAR → **Docking** → **Scoring** → **L-R Complex Analysis**

Results and Conclusions

Tab. 1. The X-SAR datasets used to study the impact of halogenation of the β2 ligands.

No	X-SAR	Substitution	F	Cl	Br	I
29	F_Cl_Br	orto	2.29	0.92	3.31	
		meta	9.12	1.29	2.57	
		para	2.19	2.14	1.91	
30	F_Cl_Br	para	0.71	1.85	0.22	
80	F_Cl_Br	para	0.83	1.74	3.26	
174	F_Cl_Br	para	0.63	0.64	1.66	
56	F_Cl	para	7.31	32.65		
		meta		3.26		
		orto+meta		5.17		
33	Cl_Br	para		0.69	1.06	
101	Cl_Br	para		6.92	7.7	NA
66	Cl	para		3.96		
89	Cl	para		4.55		
310	Cl	orto		6.84		
		meta		15		
		para		3.25		
193	Br				5.02	
188	F	orto	0.36			
		meta	0.3			
		para	0.16			
693	F	para	0.05			

Gly90

ΔG = –59.4 kcal/mol

Gly90

ΔG = –73.5 kcal/mol

Gly90

ΔG = –81.6 kcal/mol

Fig. 3. Statistics of halogen bonding interaction generated based on X-SAR analysis. X-SAR set_101 complexes are marked in circles in upper graphs.

- Overall, using in-house script, 93 X-SAR sets were identified, but due to affinity data inconsistency only 13 were finally studied.

- No sets containing iodine analogues were found.

- Almost in all sets, substitution of H to Cl or Br led to significant increase of compound's affinity (X-Effect parameter ranged from 1.29–32.65 and 1.06–7.7 for Cl and Br, respectively).

- The fluorination showed dual impact on affinity, (from 9-fold increase to 20-fold decrease).
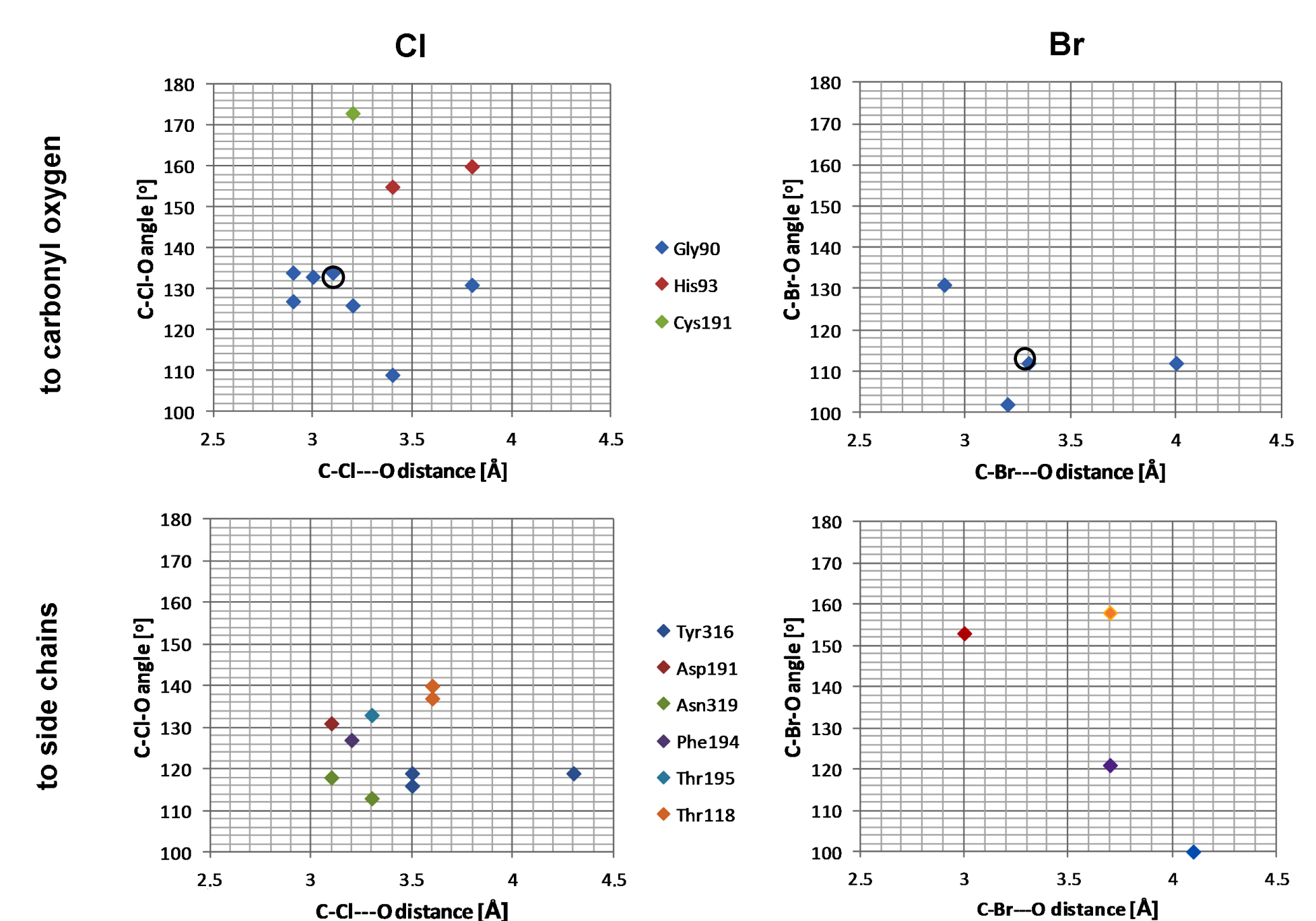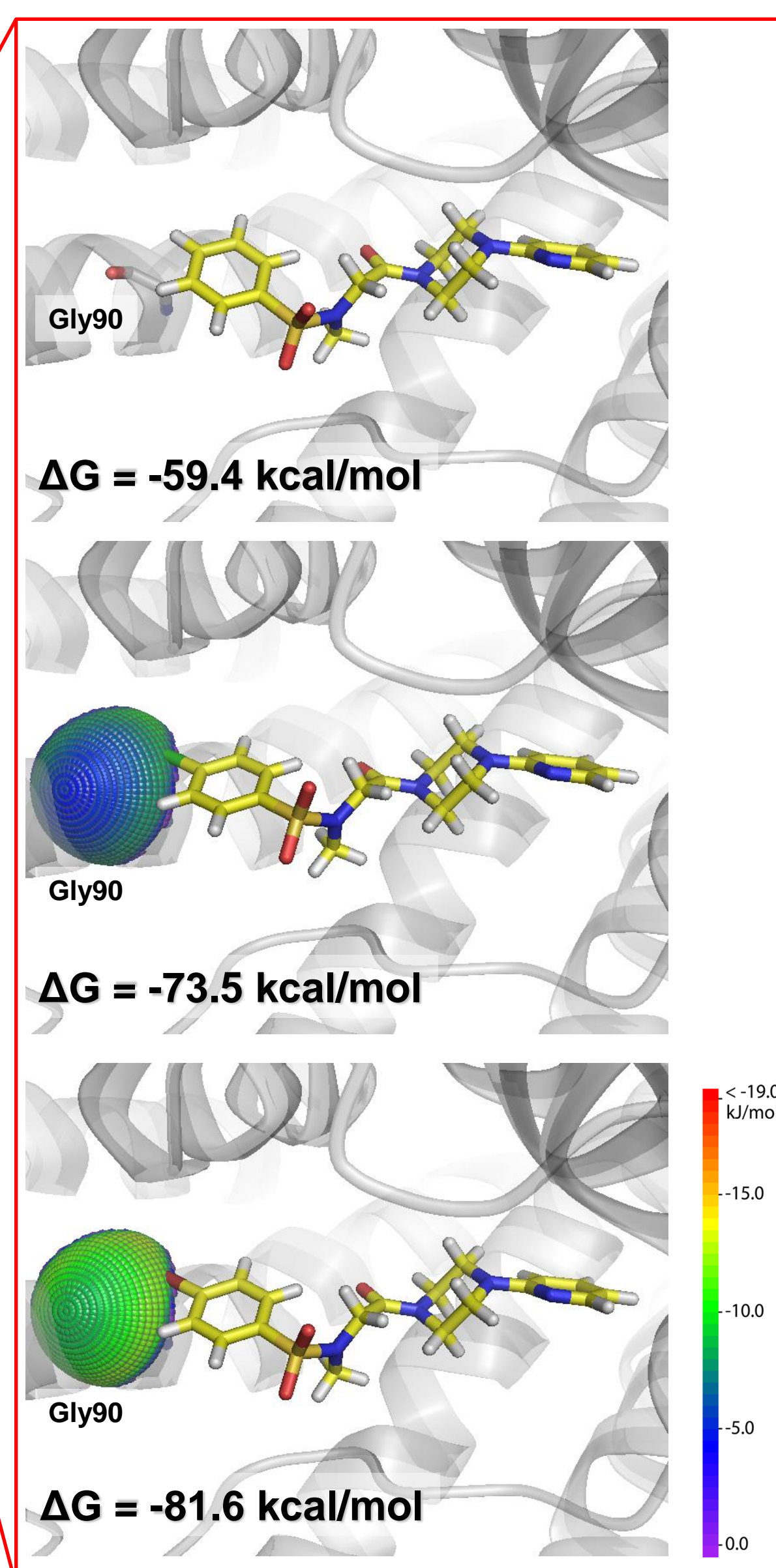
- Interaction analysis of L-R complexes indicated that carbonyl oxygen of Gly90 (Fig. 3) is the most often targeted amino acid to forming halogen bonds,

- MM-GBSA results showed good correlation with affinity and X-Effect values,

- the orthogonal dipolar interactions (Fig. 4) between C–F fragment of a ligand and backbone C=O or N-H bond of Gly90 and Asp192 respectively, can be responsible for ambigues effect of fluorination.
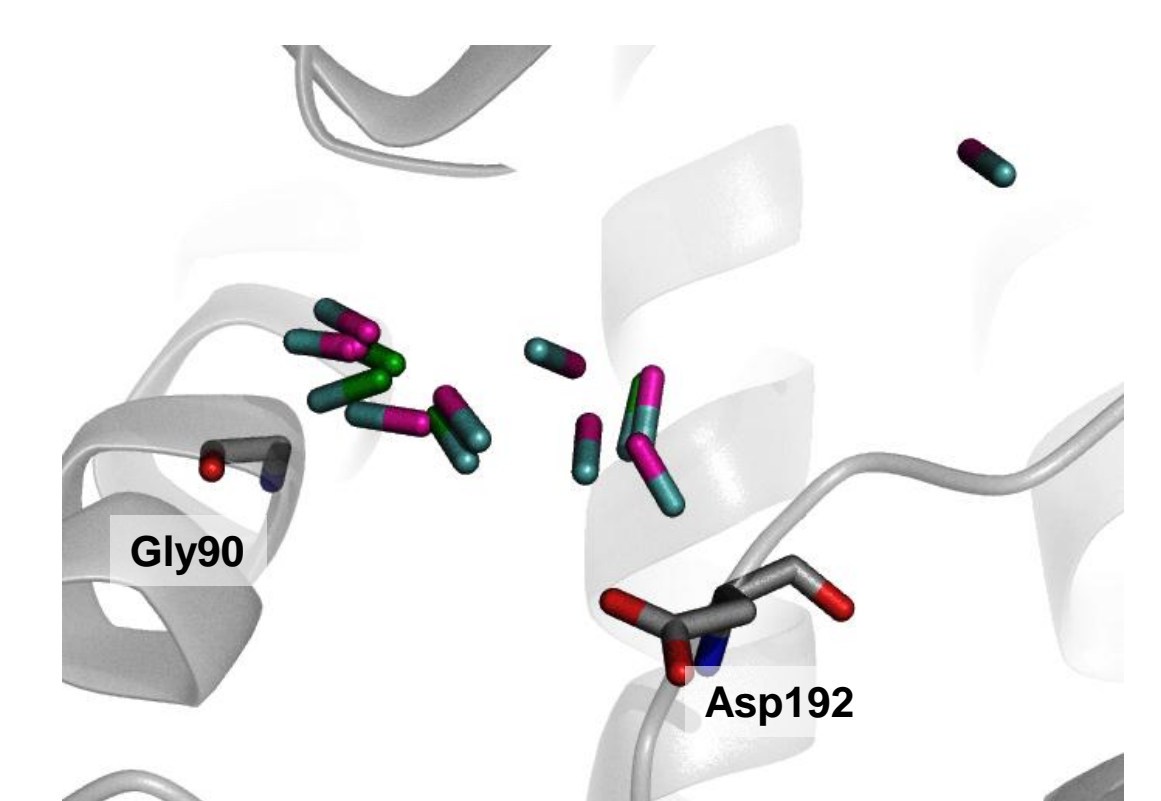

Fig. 4. The distribution of C-F residues of ligands in β2 binding site (red sticks for X-Effect < 1 and green for X-Effect > 1).

References

[1] Politzer P, Lane P, Concha M, Ma Y, Murray J, *J. Mol. Model.*, **2007**, *13*, 305–311,
[2] Clark T, Hennemann M, Murray JS, Politzer P, *J. Mol. Model.*, **2007**, *13*, 291–296,
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[4] Wilcken R, Zimmermann MO, Lange A, Zahn S, Boeckler FM, *J. Comput. Aided. Mol. Des.*, **2012**, *26 (8)*, 935–945.

Acknowledgments