Halogen bonding enhances affinity for 5-HT$_7$R in a series of N-[2-(dimethylamine)ethyl]-N-(2-phenylethyl)anilines

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Background

Halogen bonds (XB) are specialized non-covalent interactions known to chemists since XIX century, but only recently they were recognized as important in biological molecules.[1] According to IUPAC definition, halogen bond is "a net attractive interaction between an electrophilic region associated with a halogen atom in a molecular entity and a nucleophilic region in another, or the same, molecular entity".[2] In biological targets the XB can involve carbonyl oxygen, hydroxyl groups of serine, threonine and tyrosine, carboxylate groups of aspartic and glutamic acid, sulphur of cysteine and methionine and the π-surfaces of phenylalanine, tyrosine, histidine and tryptophane.

Within the serotonergic system, 5-HT$_7$, the last identified serotonin receptor, is one of the most valuable drug targets.[3] Experiments using animal models have shown that the receptor is involved in many physiological processes, i.e. regulation of body temperature, smooth muscle relaxation of cerebral arteries, circadian rhythm, learning and memory, as well as patophysiological processes such as mood disorders, anxiety, inflammatory processes in the CNS, schizophrenia and pain.[4] 5-HT$_7$R antagonists have been proposed as potential drugs targeting depression.[5] It was established that 5-HT$_7$ blockade can induce promnesic effects implicating the possibility to develop atypical procognitive antidepressants.[6]

Molecular modelling

The QM-Polarized Ligand Docking (QPLD)6 in the Schrödinger Suit was used to dock all synthetized compounds 5-HT$_7$ homology models. Next, QSite was used to perform a single-point energy calculation for each obtained L-R complex, treating the ligand with ab initio (B3LYP/6-31G*) and the receptor with the MM (OPLS-2005) level of theory. Partial atomic charges were calculated using the electrostatic potential fitting method. Glide was subsequently applied to re-dock the ligand using each of the ligand charge sets calculated by QSite, and the QPLD algorithm was used to return the most energetically favourable poses. For a particular ligand, the Generalized-Born/Surface Area continuum solvent model was used to estimate ΔG values to select the correct poses between possible binding conformations. To visualize (plotting interaction spheres) the possible contribution of halogen bonding to the resulting ligand-receptor complexes, the Halogen Bonding Webserver was used (access 1.12.2015, http://www.halogenbonding.com/).
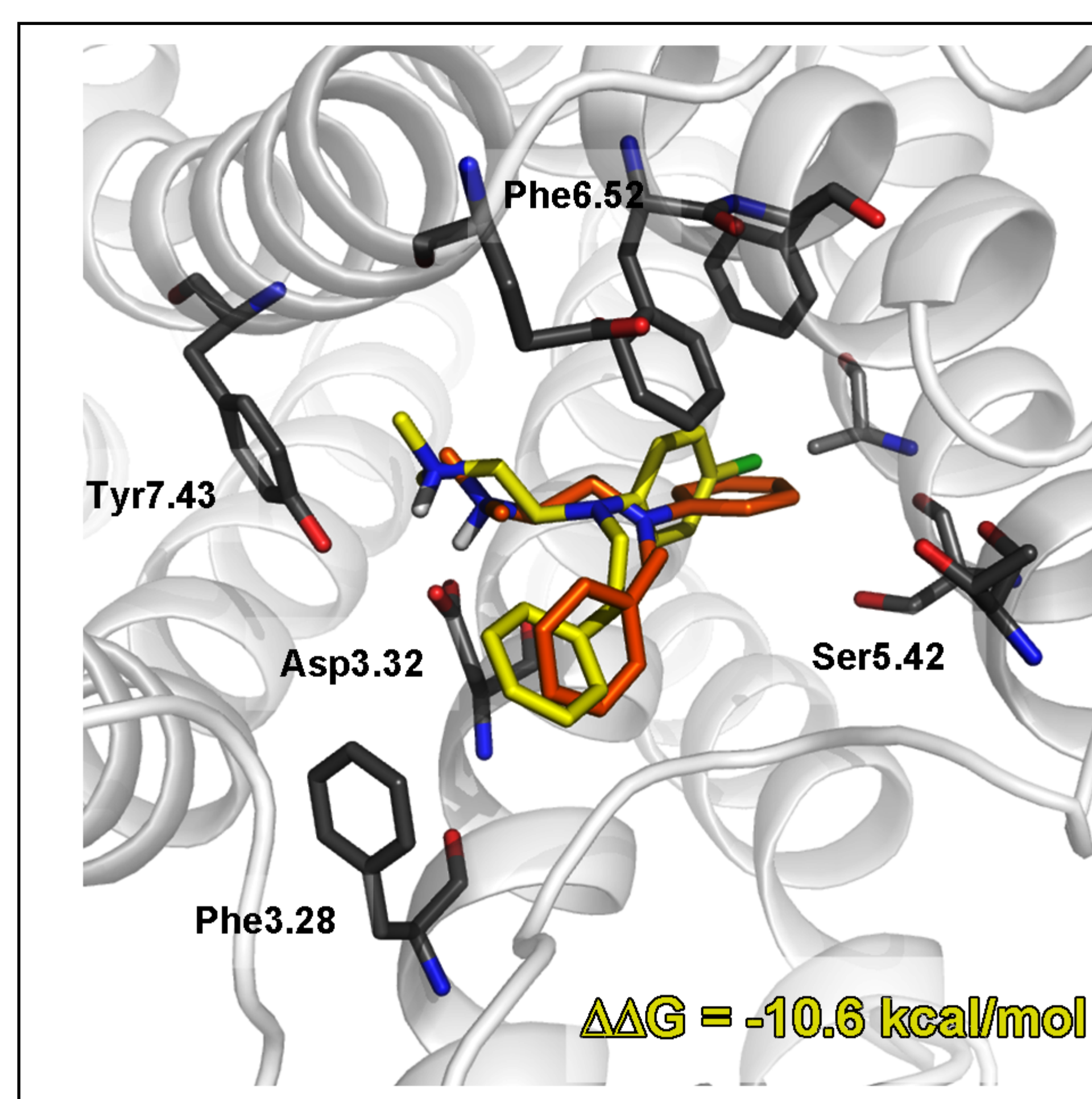
Synthesis

R2, R3, R4 = H, Me, OMe, F, Cl, Br, I.

R1 = Me, Et
n = 1,2

1 — 21

Binding affinity

Radioligand binding assays were used to determine the affinity and selectivity profiles of the synthesized compounds for human serotonin 5-HT$_{1A}$R, 5-HT$_{2A}$, 5-HT$_6$R, 5-HT$_{7b}$R and D$_{2L}$R, which were stably expressed in HEK293 cells.

Table 1. Binding affinities of the synthesized compounds

Cmpd.	n	R1	Substitution			K_i [nM]				
			R2	R3	R4	5-HT$_{1A}$	5-HT$_{2A}$	5-HT$_6$	5-HT$_7$	D$_2$
1	1	Me	H	H	H	1682	233	63	121	476
2	1	Et	H	H	H	7614	128	51	205	266
3	2	Me	H	H	H	4486	228	67	623	55
4	1	Me	H	H	F	5707	58	23	31	37
5	1	Me	H	H	Me	482	70	25	10	33
6	1	Me	H	H	CF$_3$	5341	809	61	30	274
7	1	Me	H	H	OMe	>10000	863	234	141	1147
8	1	Me	H	Me	H	605	777	264	2253	n.d.
9	2	Me	H	H	F	8969	27	38	38	80
10	1	Me	H	F	H	>10000	312	64	748	594
11	1	Me	Cl	H	Cl	>10000	472	597	387	1176
12	1	Me	H	OMe	H	>10000	721	355	4512	1738
13	2	Me	H	H	Me	2140	204	83	24	108
14	1	Me	H	H	Cl	5960	212	24	4	153
15	1	Me	Me	H	H	>10000	348	380	1040	n.d.
16	1	Me	naphthyl		H	137	4749	137	4749	2037
17	1	Me	H	F	F	>10000	79	21	114	n.d.
18	1	Me	H	H	Br	n.d.	295	90	19	505
19	1	Me	H	H	I	n.d.	372	79	10	691
20	1	Me	Me	H	Me	n.d.	518	347	597	1751
21	1	Me	H	Cl	H	n.d.	311	150	353	675

n.d. − not determined

Figure 1. Representative L-R complexes (top scores based on ΔG) of unsubstituted compound 1 (orange) and 4-chloro substituted 14 (yellow). Amino acids that were selected as crucial for the binding of the presented compounds are shown as sticks. A basic nitrogen atom forms a charge-assisted hydrogen bond with aspartic acid Asp3.32, an aniline aromatic ring interacts with Phe6.52. The ΔΔG [kcal/mol] value shows the difference between ΔG of complexes of a particular compound (14) and an unsubstituted analogue 1.
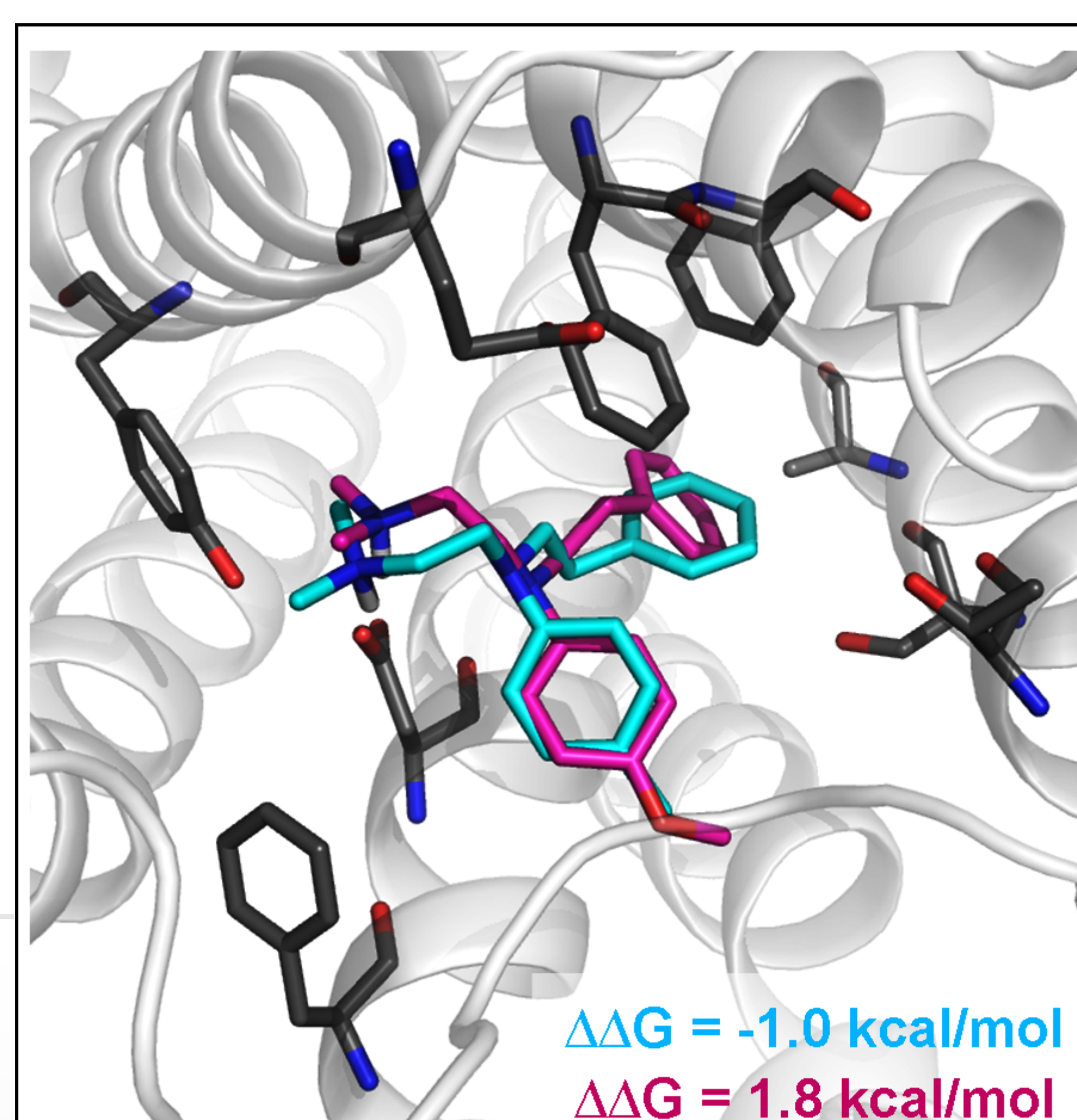
Figure 2. Representative L-R complexes (top scores based on ΔG) of a 4-methyl substituted compound 5 (cyan) and 4-methoxy substituted 7 (magenta).
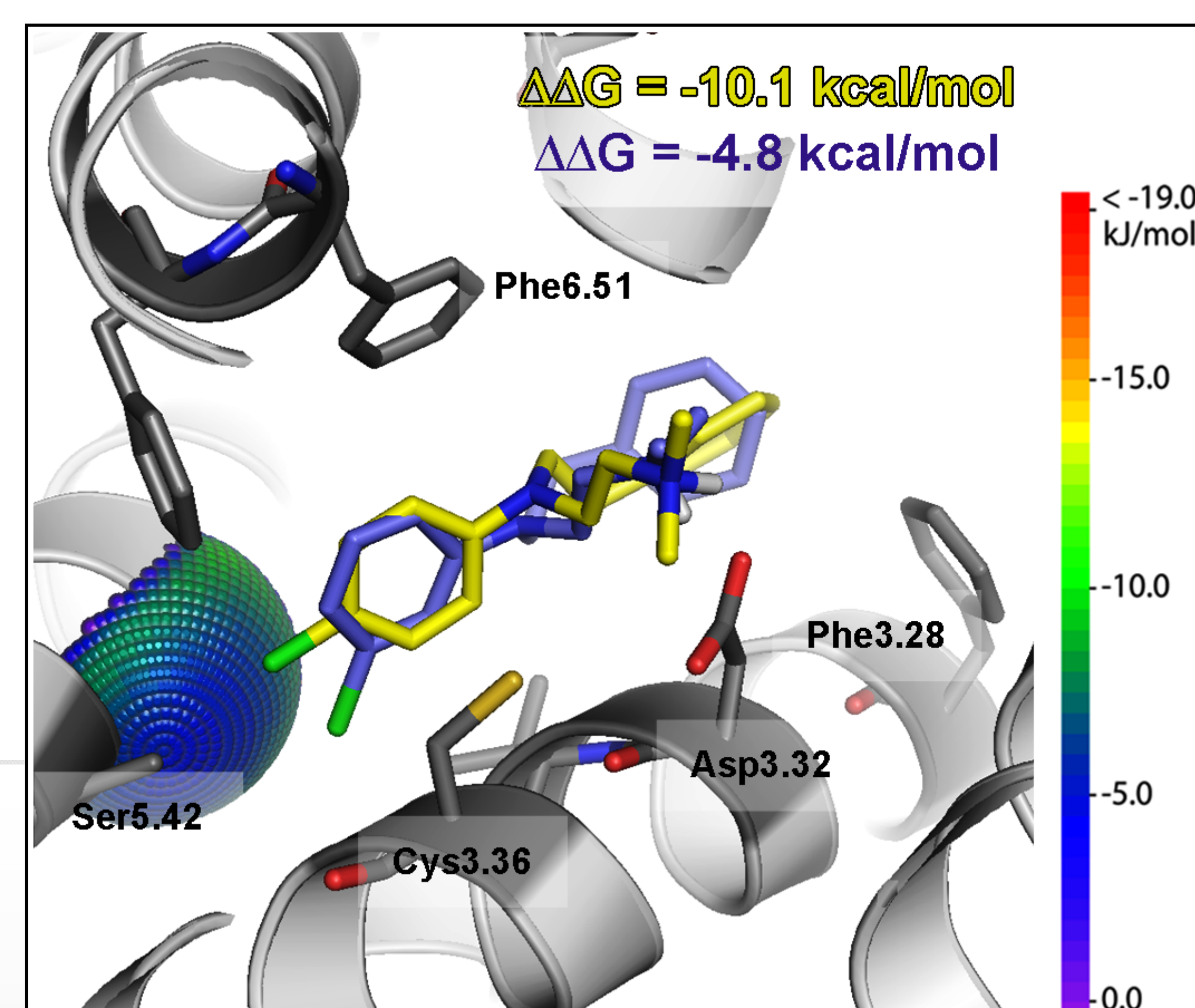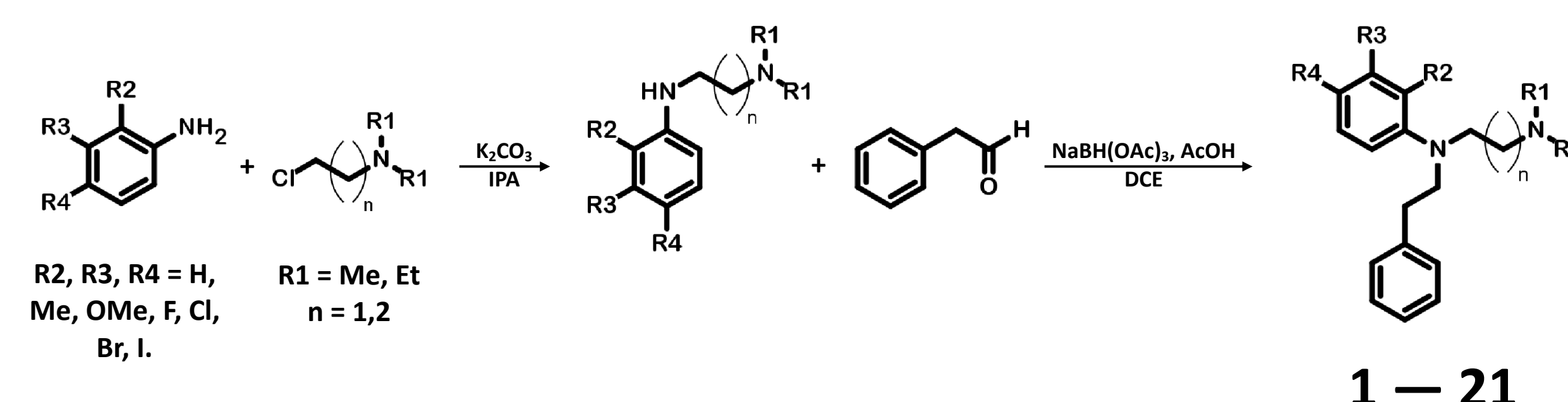
Figure 3. A superposition of the top scored poses of 4-Cl (4m, yellow) and 3-Cl (4t, blue) derivatives against putative halogen binding pocket interaction spheres. The higher binding energy value for 3-Cl than for 4-Cl derivatives illustrates the highly directional nature of the identified halogen bond interaction. The methodology applied has been described by Wilcken et al..[7]

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