Supporting Information for

Evolution of Angiotensin Peptides and Peptidomimetics as AT2 Receptor Agonists

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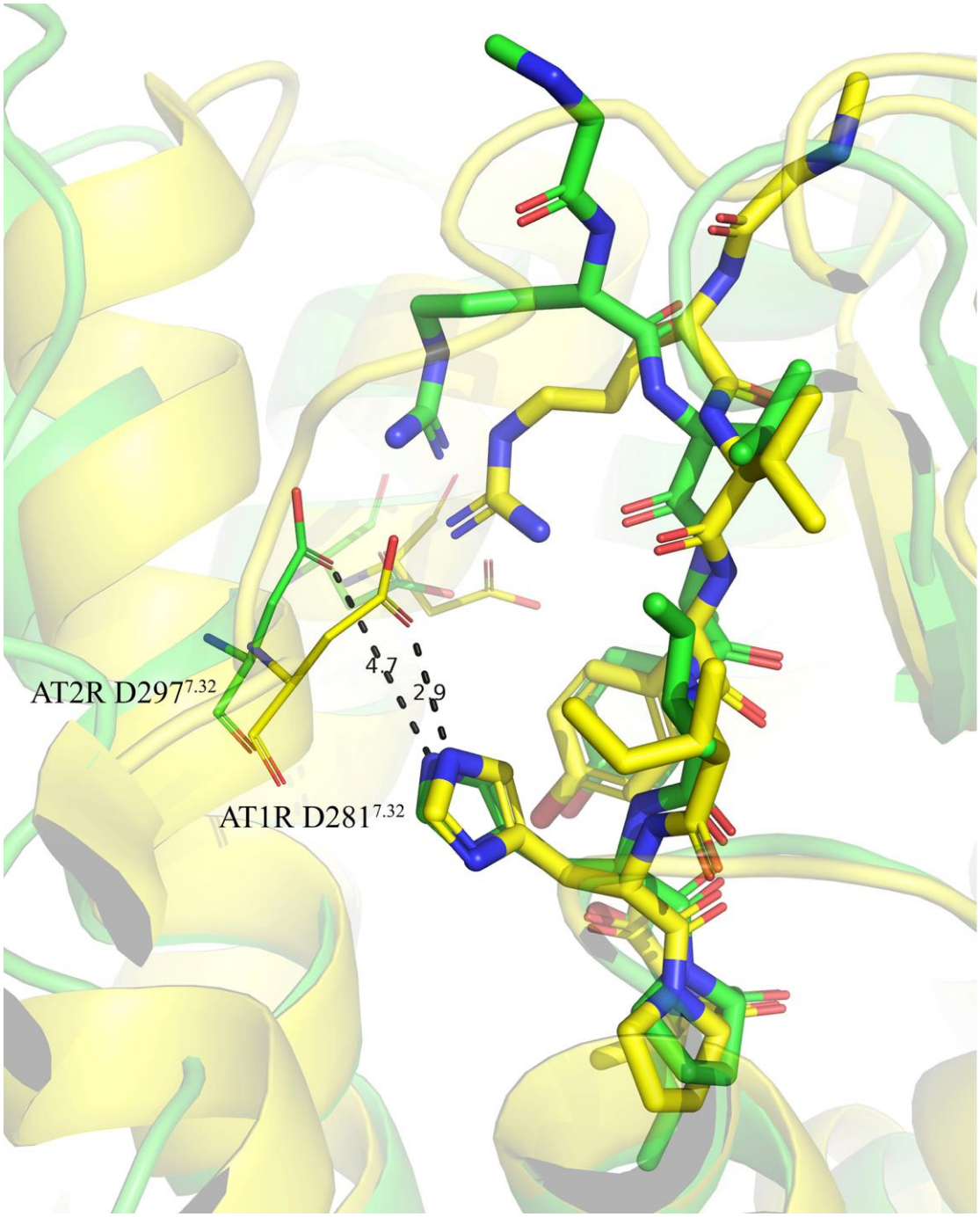

Figure S1 Comparison of the relative position of His^6 in AT1R (yellow) and AT2R (green)

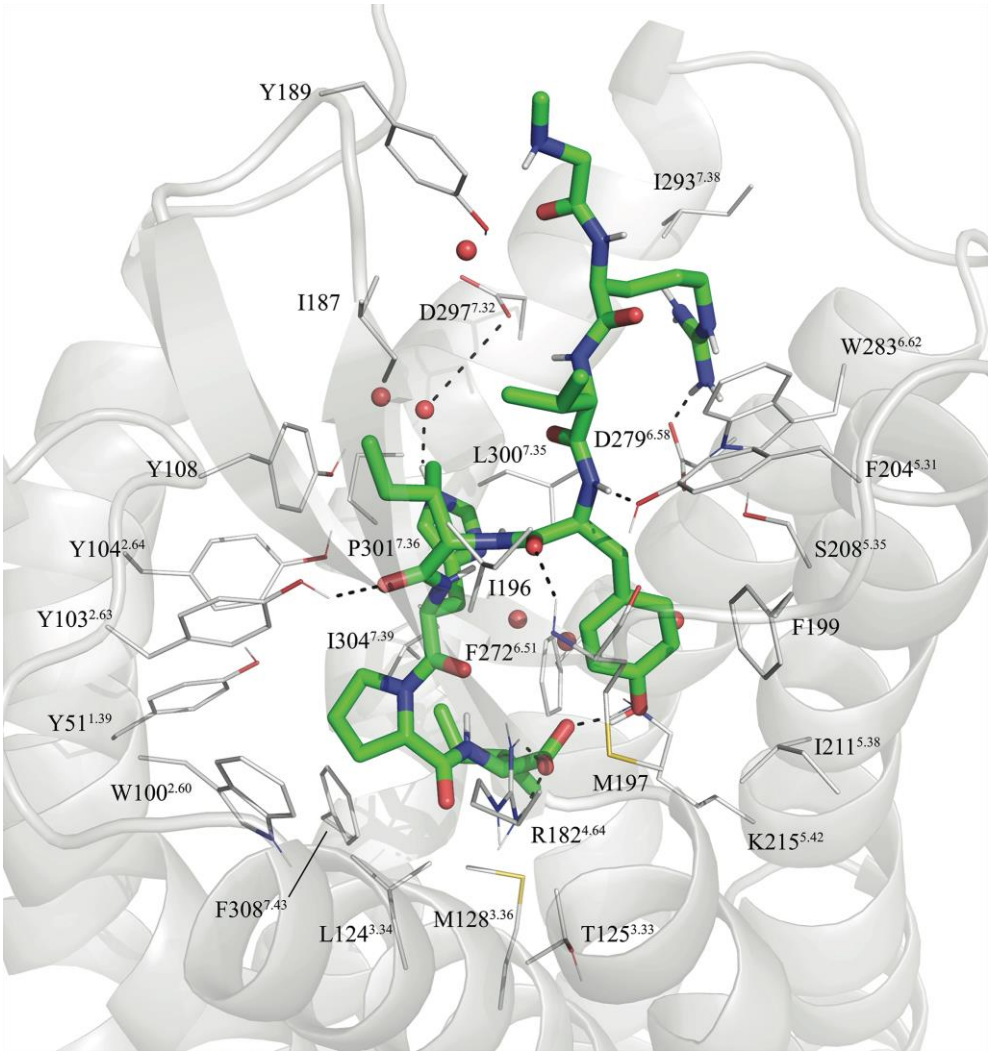

Figure S2: Binding pocket of sarile (**1**) in AT2R

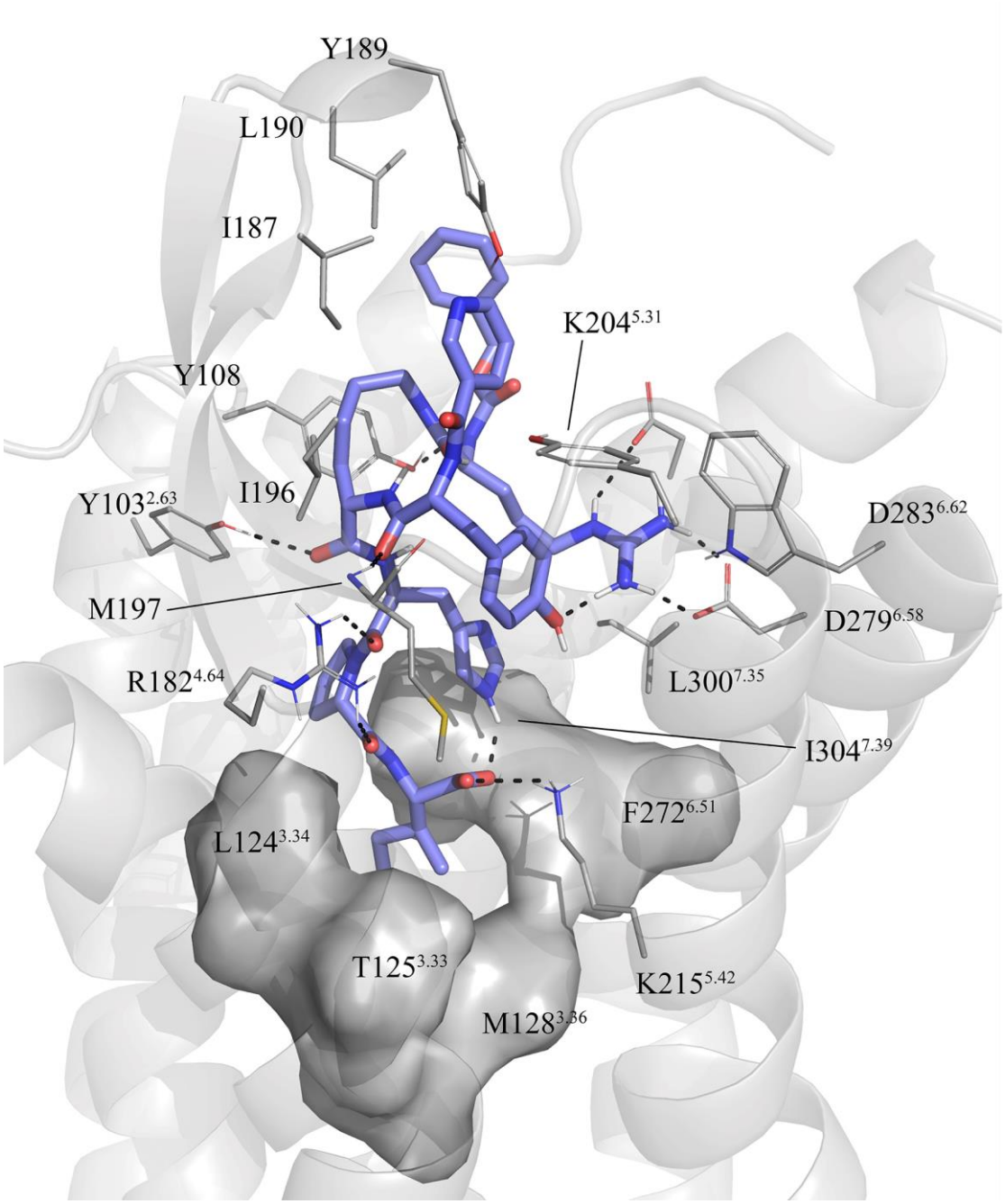

Figure S3: Binding mode of compound **2**

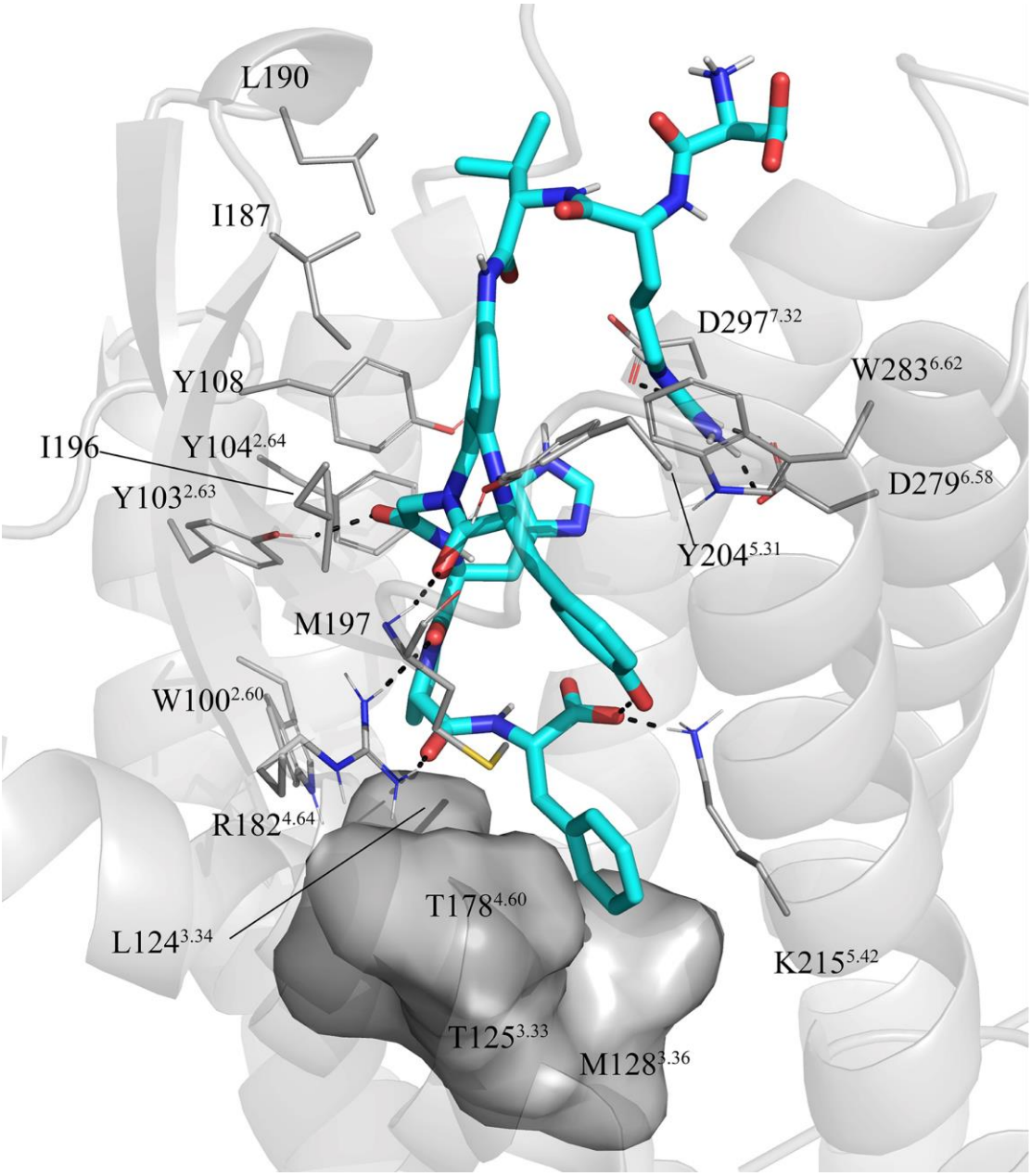

Figure S4: Binding mode of compound **3**

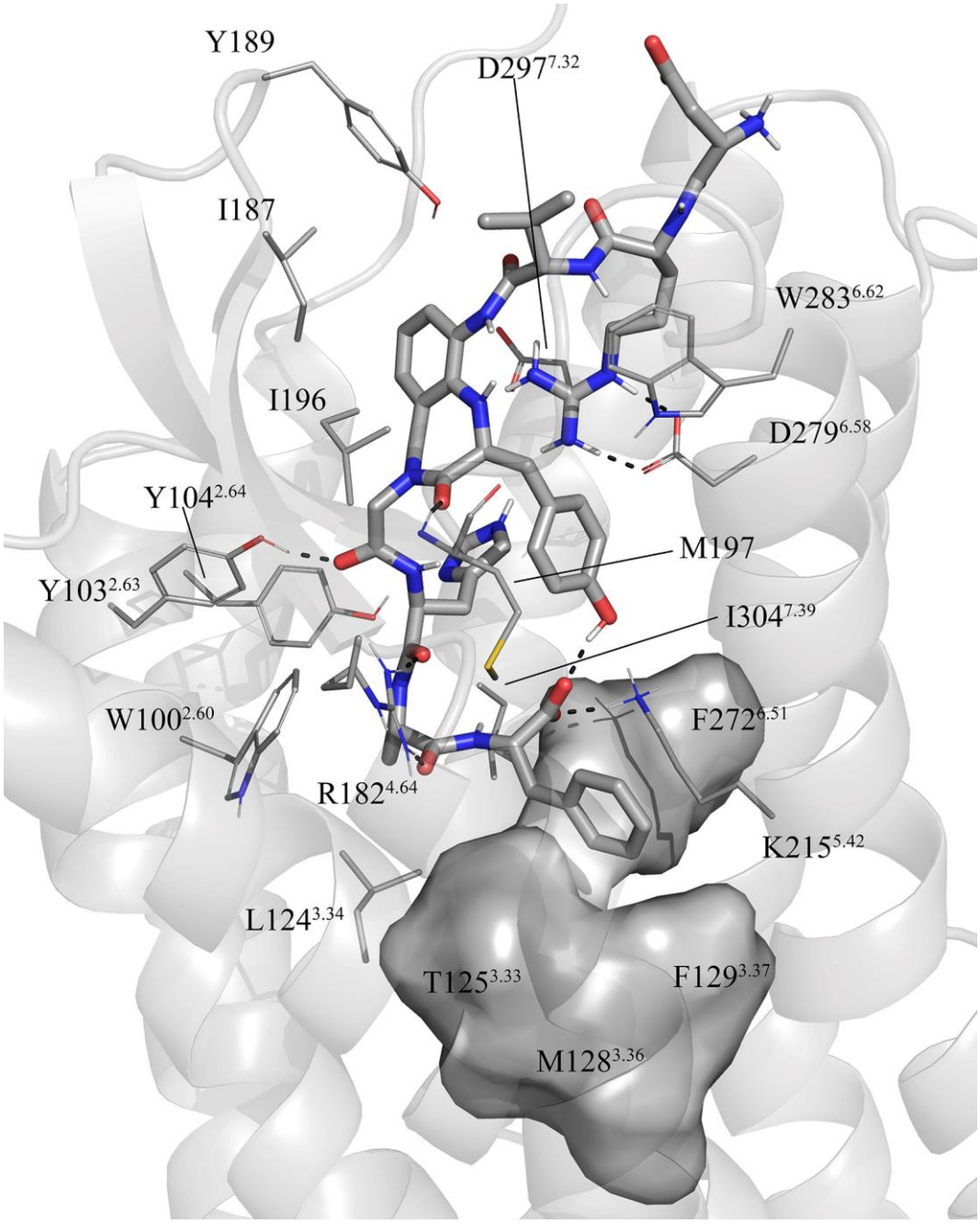

Figure S5: Binding mode of compound **4**

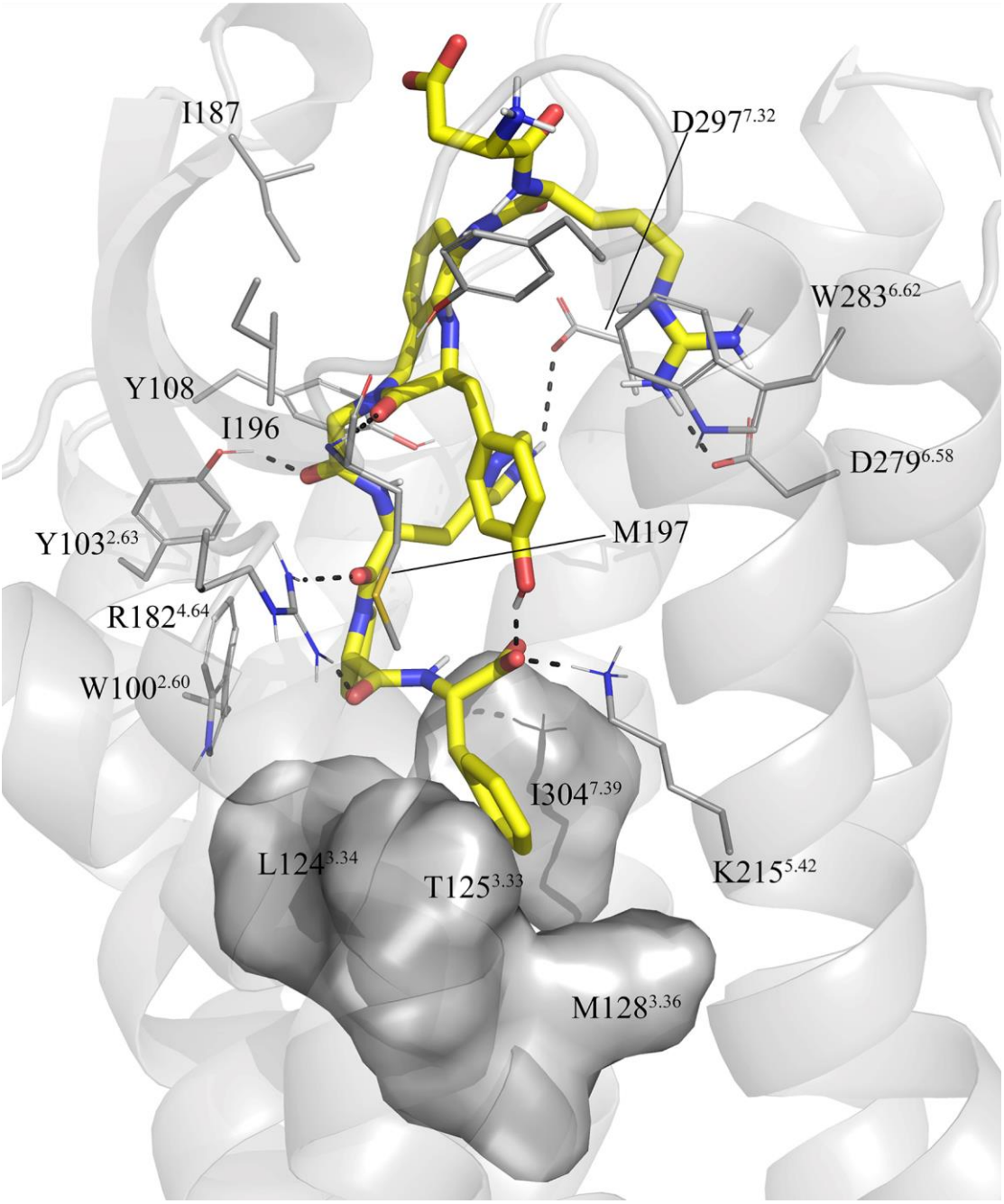

Figure S6: Binding mode of compound **5**

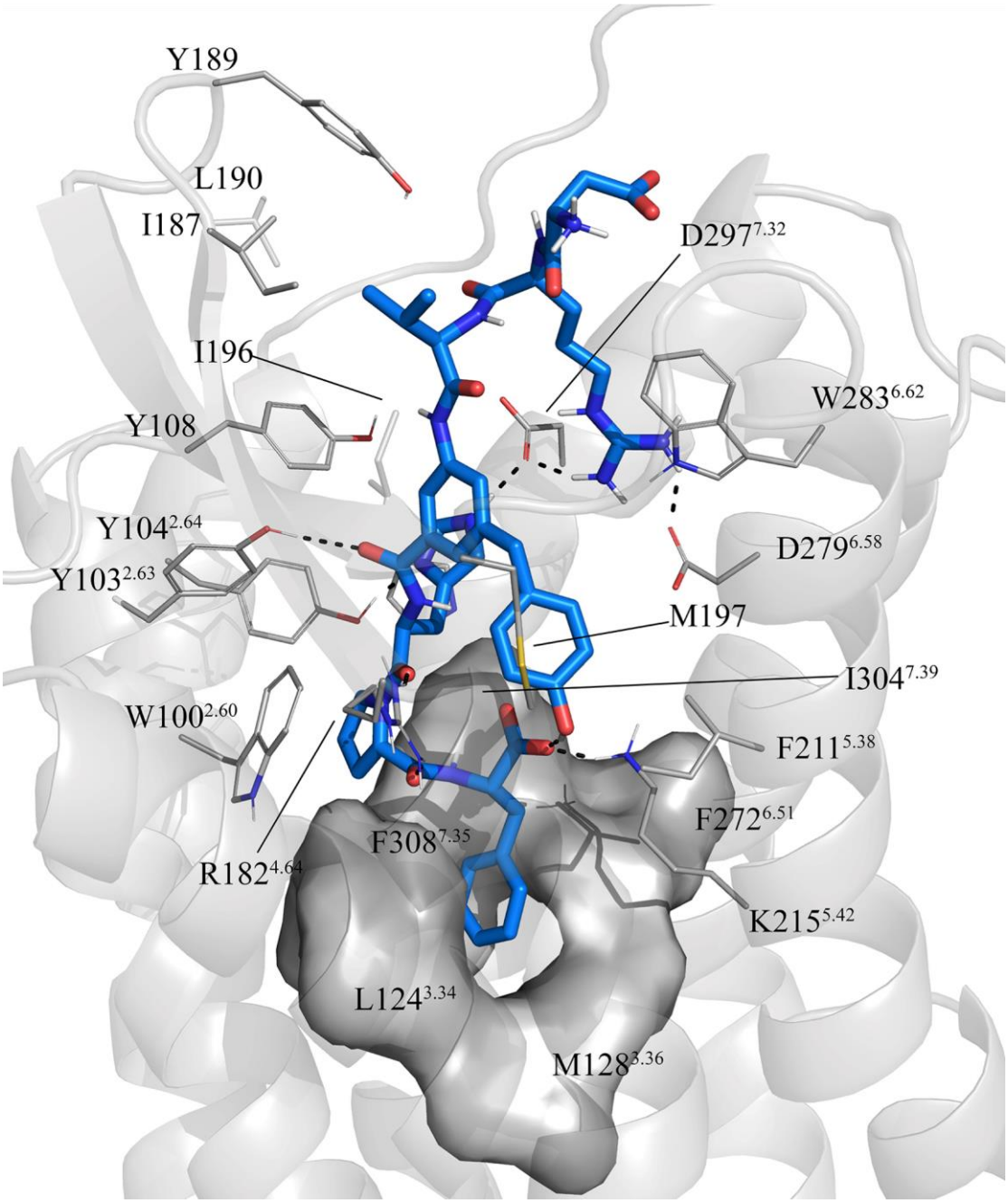

Figure S7: Binding mode of compound **6**

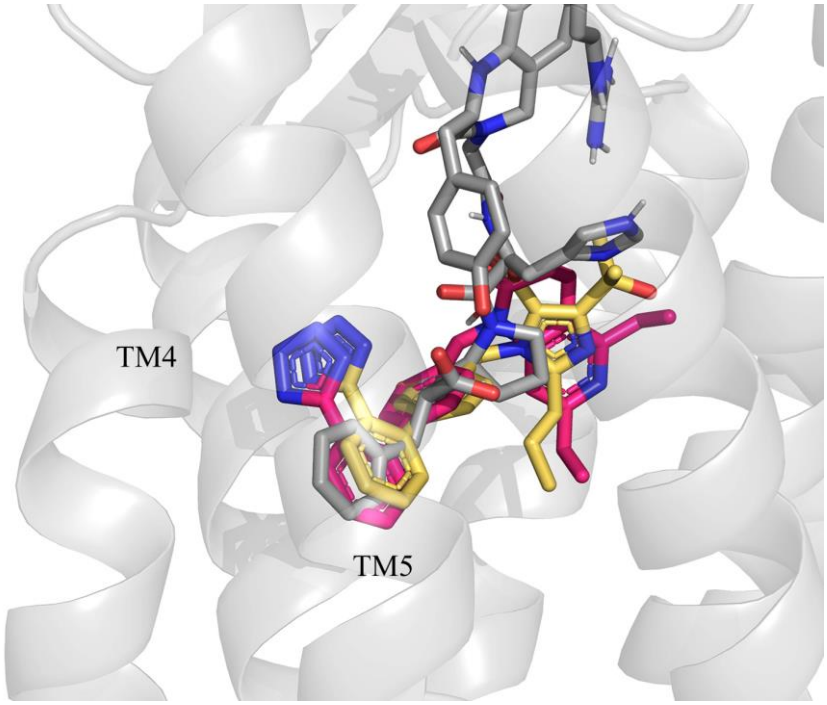

Figure S8: Comparison of the C-terminus orientation of **4** with co-crystallised AT2 antagonist

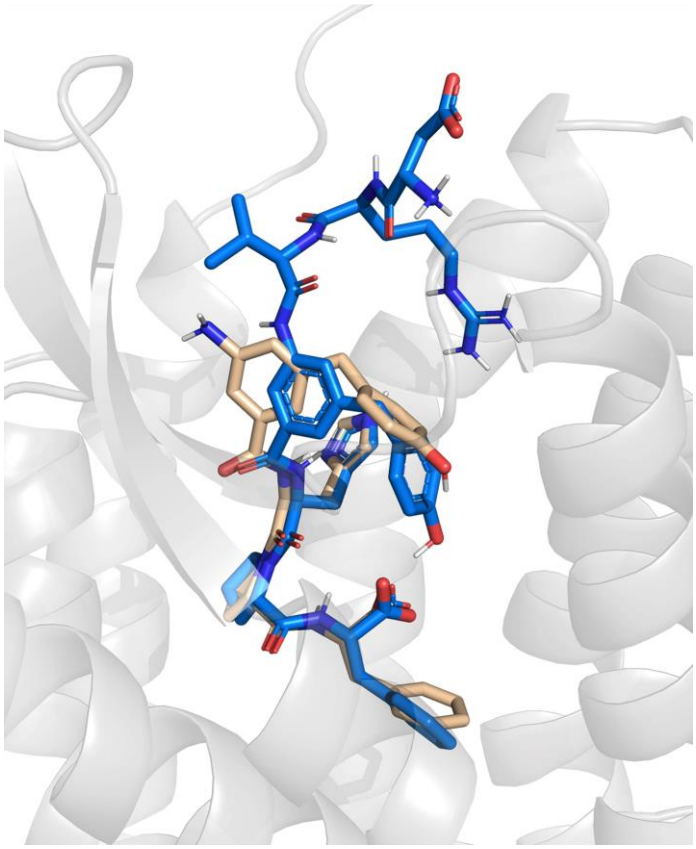

Figure S9: Comparison of the binding modes of **6** and **11**. The NH_2 of **11** is an extension of the gamma-turn mimic of **6**

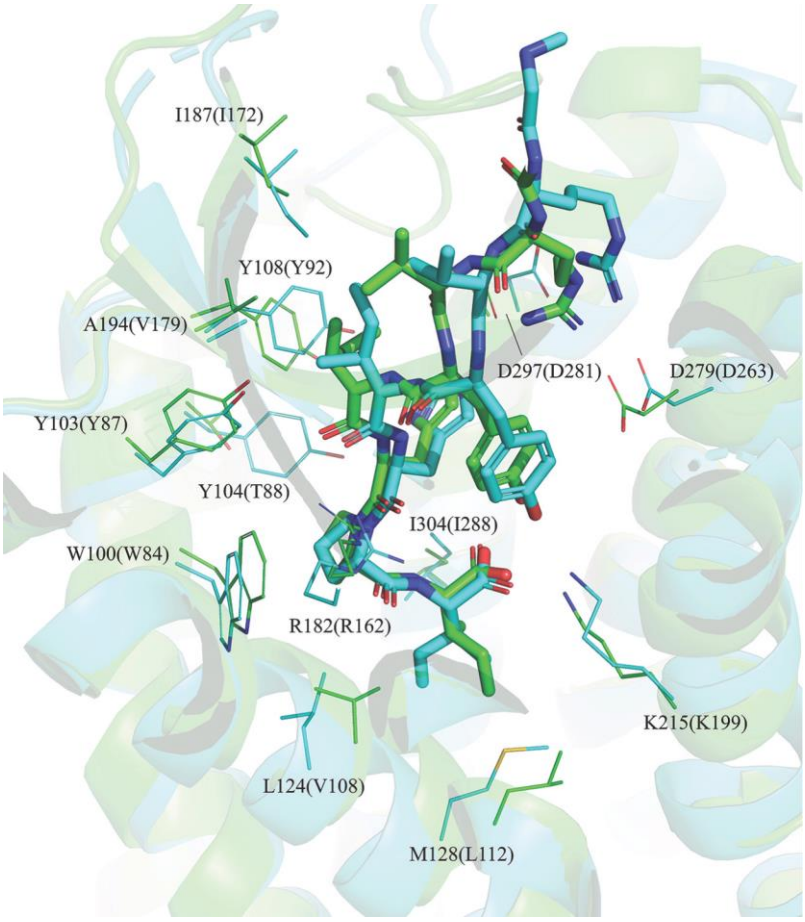

Figure S10: Comparison of the binding modes of sarile in AT1R (green) and AT2R (cyan).

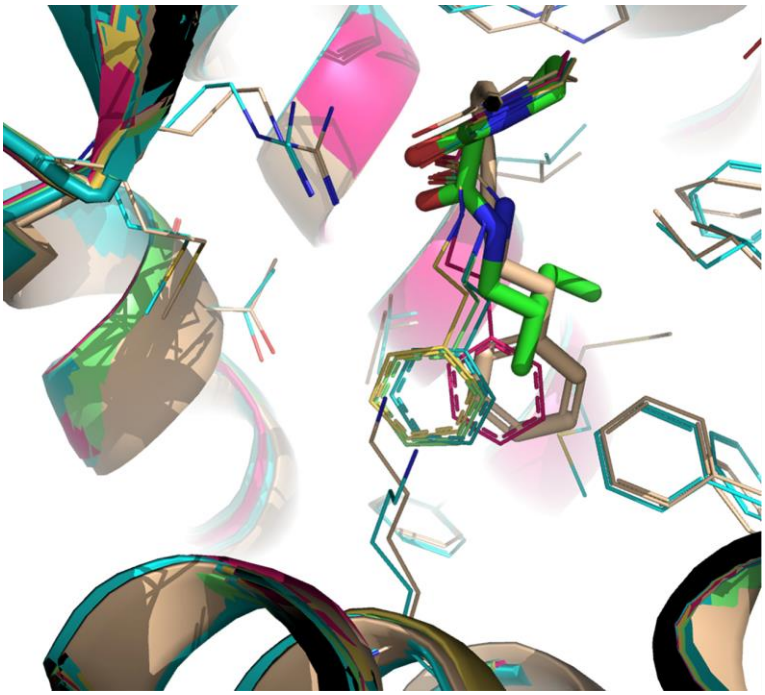

Figure S11: Sarile (green) and AngII (brown) C-terminal residues, overlaid with our docked compounds (green=3, cyan=4, yellow=5, magenta=6). The predicted rotamer of the Phe is actually the same as in AngII

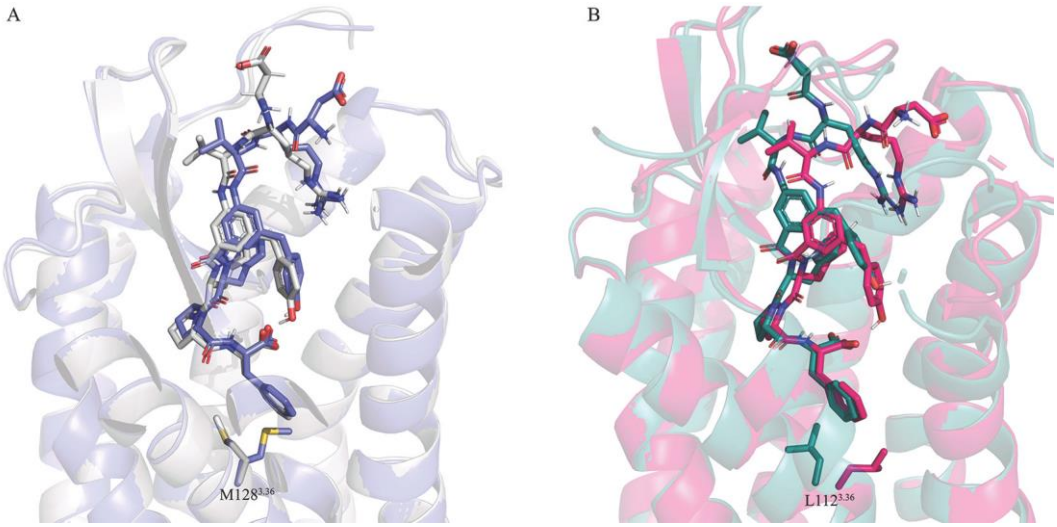

Figure S12: Comparison between the docking poses of compound 6 based on sarile or ATII-bound ATR structures. A) AT2R with sarile-based modelling in violet, AngII-based model in gray. B) AT1 structure, with sarile-based model in magenta, AngII-model in green.

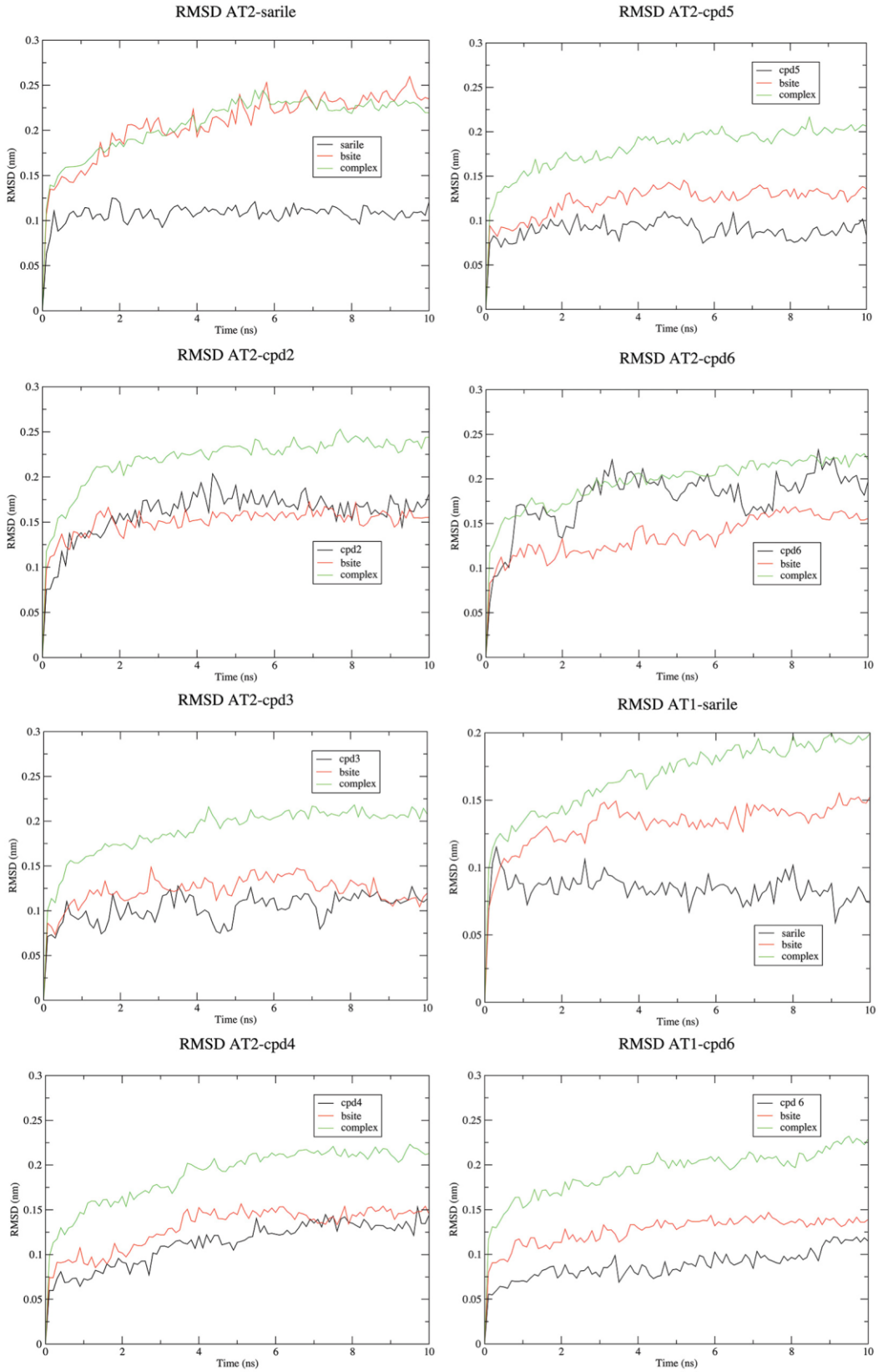

Figure S13: Average RMSD of each system subjected to 3 x 10 ns of MD simulations. Black lines represent the average RMSD of the ligands, red lines represent the average RMSD of the binding sites and green lines represent the average RMSD of the complexes (receptor-ligand).

Table S1: Relative binding affinity (in terms of experimental and calculated shifts in the free energy of binding) between two pairs of AT2 agonists, assuming the same binding pocket for the Phe/Ile sidechain on the C-terminus (related to Table 1).

Mutation	Chemical modification	$\Delta\Delta G_{exp}$ ± s.e.m. (kcal/mol)	$\Delta\Delta G_{calc}$ ± s.e.m. (kcal/mol)
8 → **7**$_{alternative}$	Ile → Phe	1.54 ± 0.06	-0.41 ± 0.58
10 → **9**$_{alternative}$	Ile → Phe	2.38 ± 0.07	-0.96 ± 0.76