Supporting Information of

Theoretical Study of the Binding Profile of the Allosteric Modulator NS-1738 with a Chimera Structure of the α7 Nicotinic Acetylcholine Receptor

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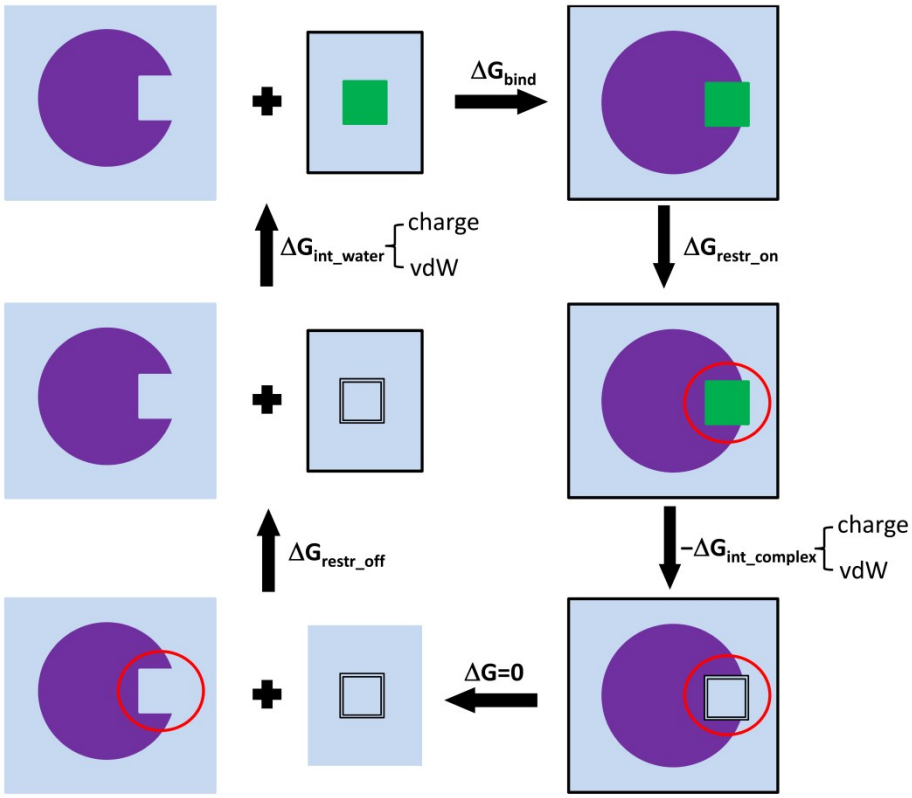
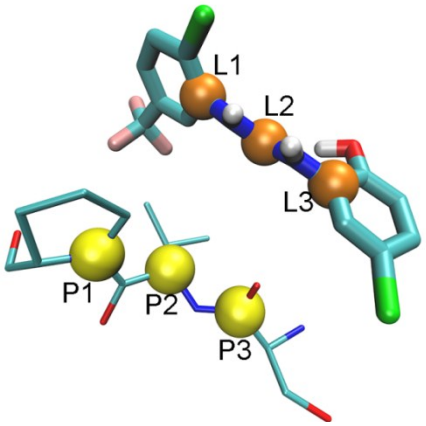


Supplementary Fig. S1. The thermodynamic cycle used to calculate the absolute binding free energy. In this diagram, the protein is shown in a circular shape with a breach, which represents the binding pocket. The ligand is shown as a green square when full interactions are present and as a transparent square when the electrostatic and van der Waals interactions are decoupled. The light blue background represents the water. The red circle means restraints are applied. The black surrounding box means simulation is implemented for that system. In the left column only the ligand was simulated, whereas in the right column both the protein and the ligand were simulated.

Supplementary Table S1. The reference atoms and reference values for the restraints used to keep the ligand in the binding pocket of the protein. For the ligand the reference atoms (L1, L2 and L3) are the same in each system, whereas for the protein the reference atoms (P1, P2 and P3), which are the heavy atoms close to the ligand, are dependent on the binding mode. The details of the calculation of the contribution of the restraints to the binding free energy are given in the Method section of the manuscript.



Binding Site	Binding Mode	Protein Reference Atoms	d^* (nm)	θ_1 (degree)	θ_2 (degree)	ϕ_1 (degree)	ϕ_2 (degree)	ϕ_3 (degree)
Top pocket	T1	P1: L6 CA P2: Y7 N P3: Y7 CB	0.62	122.44	67.98	-151.22	-44.12	-96.54
	T2	P1: L6 CA P2: Y7 N P3: Y7 CB	0.6	108.47	64.65	41.26	-85.07	-126.12
	T3	P1: S77 C P2: V78 CA P3: P79 N	0.49	91.2	84.53	92.05	-177.35	97.11
	T4	P1: L10 CA P2: V11 N P3: V11 C	0.5	66.62	89.51	9.77	-146.5	138.4
Vestibule pocket	V1	P1: L88 N P2: L88 C P3: A89 CA	0.47	60.12	95.51	-64.28	-81.77	-143.64
	V2	P1: L88 CB P2: L88 C P3: A89 CA	0.46	91.42	94.23	3.77	-174.73	109.78
Agonist sub-pocket	A1	P1: Y91 N P2: N91 C P3: N92 CA	0.52	61.83	145.6	73.6	170.94	-172.15

* The distance (d), angles (θ_1 and θ_2), dihedrals (ϕ_1, ϕ_2 and ϕ_3) are defined as:

d: L2—P2;

θ_1: L1—L2—P2;

θ_2: P1—P2—L2;

ϕ_1: L1—L2—L3—P2;

ϕ_2: L1—L2—P2—P1;

ϕ_3: P1—P2—P3—L2.