Supporting information for the paper:

Another brick in the wall. Validation of the σ_1 receptor 3D model by computer-assisted design, synthesis, and activity of new σ_1 ligands

*Erik Laurini, Domenico Marson, Valentina Dal Col, Maurizio Fermeglia, Maria Grazia Mamolo, Daniele Zampieri, Luciano Vio, Sabrina Pricl**

[a]Molecular Simulation Engineering (MOSE) Laboratory, Department of Industrial Engineering and Information Technology (DI3), University of Trieste, Via Valerio 10, 34127 Trieste, Italy
[b]Department of Chemical and Pharmaceutical Sciences, University of Trieste, 34127 Trieste, Italy

The features of the 3D pharmacophore model employed in this work (see references 17 and 19 in the main text) and the relevant geometrical relationships among them are shown in Figure SI1.

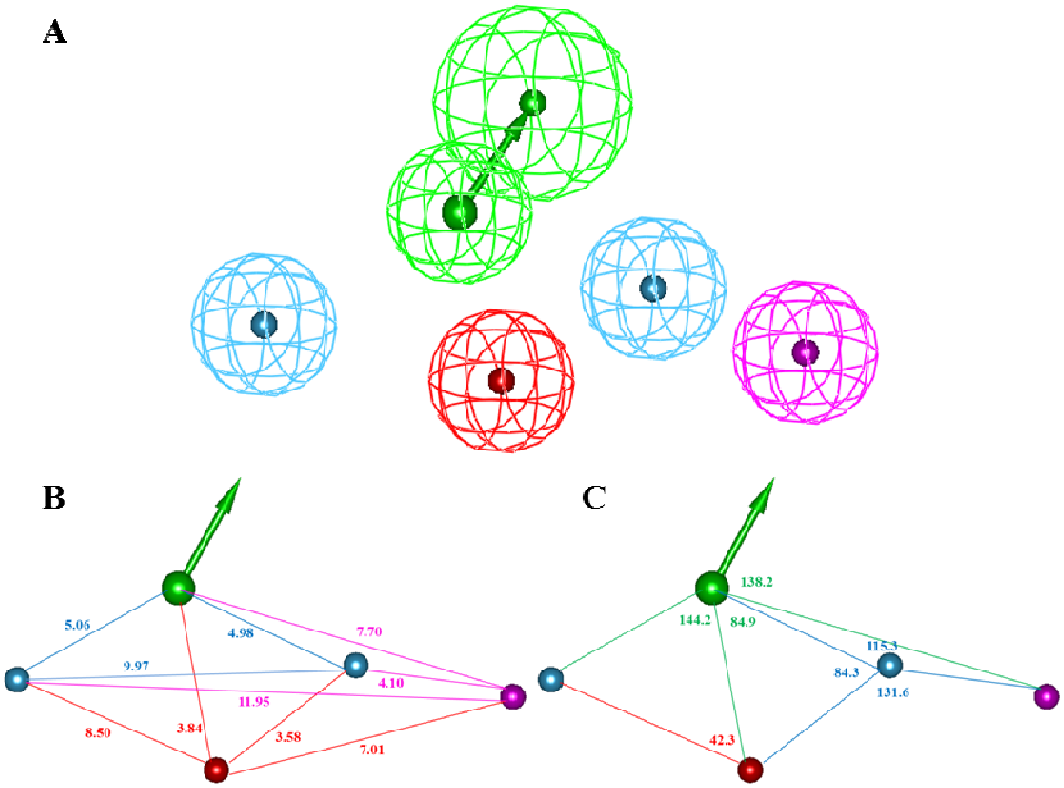
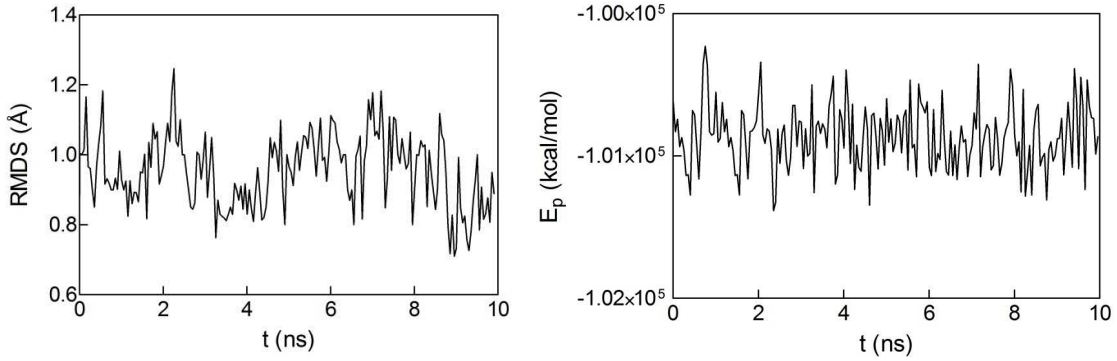


Figure SI1. (A) Features of 3D pharmacophore model employed in this work and geometrical relationships (B) and (C) among these features. The hypothesis features are portrayed as mashed spheres, color-coded as follows: red, positive ionizable (PI); light blue, hydrophobic aromatic (HYAr); pink, hydrophobic (HY), light green, hydrogen bond acceptor (HBA). HBA is actually represented as a pair of spheres (the smaller sphere represents the location of the HBA atom on the ligand and the larger one the location of an HB donor on the receptor). Selected distances (Å) and angles (º) are labeled.

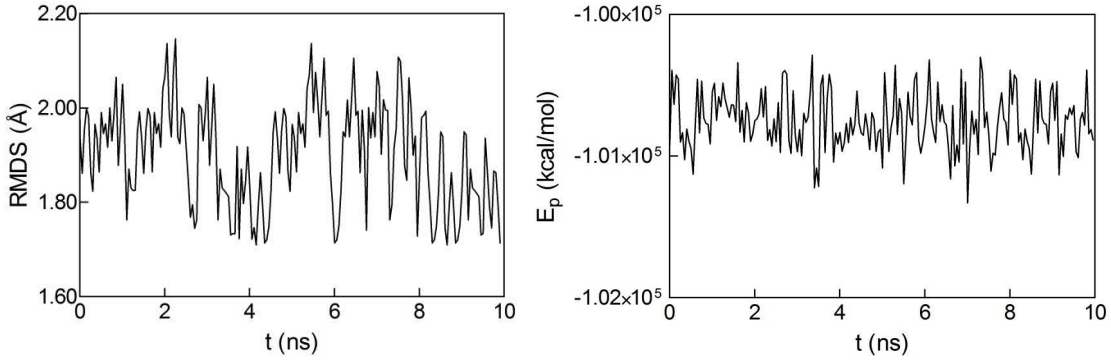
The σ_1 model structure remained stable for all 10 ns of the MD trajectory, as indicated by the small fluctuations of the root-mean-square deviation (RMSD) of the simulated position of the backbone atoms with respect to those of the initial structure and the corresponding total potential energy of the system E_p shown in Figure SI2.



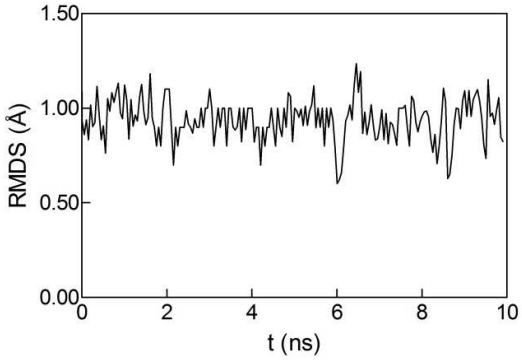
(A) (B)

Figure SI2. (A) RMSD of the coordinates of the backbone atoms of the 3D model of the σ_1 receptor along the 10 ns MD simulation compared with those of the initial structure. (B) time behavior of the total potential energy of the σ_1 receptor 3D model in water during the same MD simulation.

The same parameters showed very low fluctuations during both MD equilibration and data harvesting steps also in the cases of all receptor/ligand complexes, indicating that the presence of a bound ligand does not result in large protein structural deviations. Figure SI3 shows the same data of Figure SI1 for the σ_1/**2e** complex as an example. The same Figure also reports the difference in the RMSDs between the σ_1 in its uncomplexed form and in complex with **2e** (see text for discussion).



(A) (B)



(C)

Figure SI3. (A) RMSD of the coordinates of the backbone atoms of the σ_1 receptor/**2e** complex in water along the 10 ns MD simulation compared with those of the initial structure. (B) time behavior of the total potential energy of the σ_1 receptor/**2e** complex in water during the same MD simulation. (C) RMSD difference between the protein in the uncomplexed form (Figure SI1(A)) and in complex with **2e** (this Figure, panel (A)).

Table SI1. Elemental analysis for compound **1a-r** and **2a-l**.

	Calculated (%)			Found (%)		
Compound	**C**	**H**	**N**	**C**	**H**	**N**
1a	78.40	7.24	9.14	78.18	7.42	9.31
1b	70.06	6.76	8.17	69.83	6.91	8.30
1c	78.22	8.13	8.69	78.46	7.97	8.45
1d	78.22	8.13	8.69	78.41	7.97	8.57
1e	70.67	7.06	7.85	70.53	7.16	7.78
1f	78.53	8.39	8.33	78.47	8.20	8.19
1g	81.37	7.59	7.03	81.46	7.72	6.85
1h	74.90	6.75	6.47	75.09	6.90	6.31
1i	81.51	7.82	6.79	81.33	8.02	7.01
1j	73.76	7.49	13.58	73.63	7.60	13.41
1k	73.76	7.49	13.58	73.85	7.69	13.32
1l	73.76	7.49	13.58	73.59	7.38	13.77
1m	74.27	7.79	12.99	74.51	7.56	13.12
1n	74.27	7.79	12.99	74.16	7.93	12.87
1o	74.27	7.79	12.99	74.47	7.68	13.21
1p	78.16	7.32	10.52	78.33	7.54	10.29
1q	78.16	7.32	10.52	78.28	7.24	10.61
1r	78.16	7.32	10.52	78.01	7.49	10.70
2a	78.53	8.39	8.33	78.37	8.20	8.54
2b	81.37	7.59	7.03	81.50	7.33	7.21
2c	71.24	7.34	7.55	71.39	7.15	7.68
2d	74.90	6.75	6.47	74.74	6.59	6.65
2e	71.24	7.34	7.55	71.43	7.51	7.33
2f	74.90	6.75	6.47	74.80	6.96	6.53
2g	65.19	6.46	6.91	64.97	6.62	7.12
2h	69.38	6.04	5.99	69.11	6.27	6.17
2i	78.82	8.63	7.99	78.67	8.71	8.13
2j	81.51	7.82	6.79	81.32	7.73	6.98
2k	71.76	7.69	7.28	71.93	7.75	7.39
2l	75.23	6.99	6.27	75.42	7.14	6.03