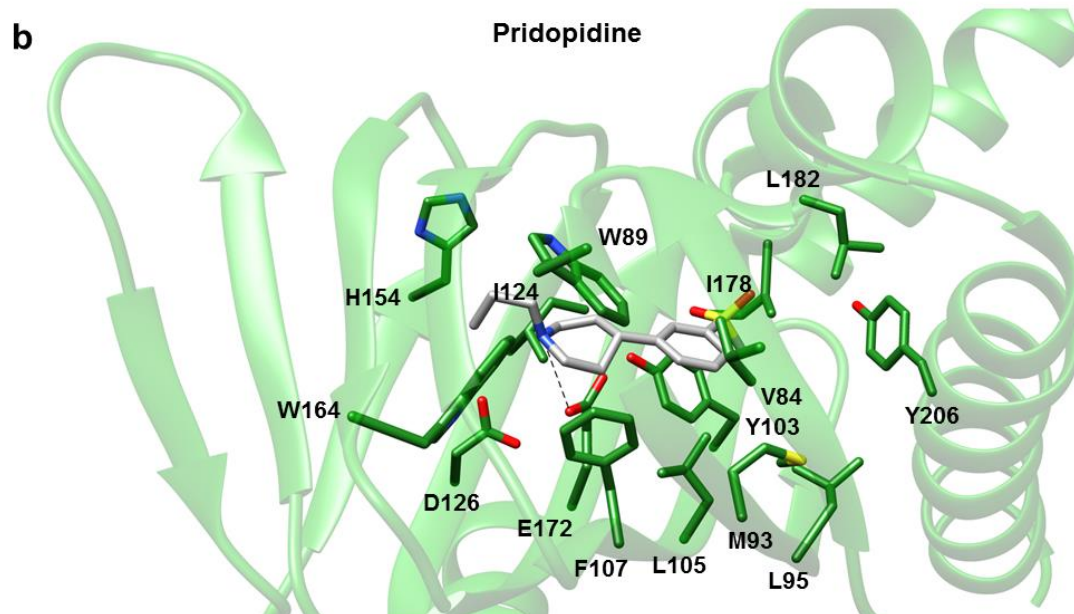
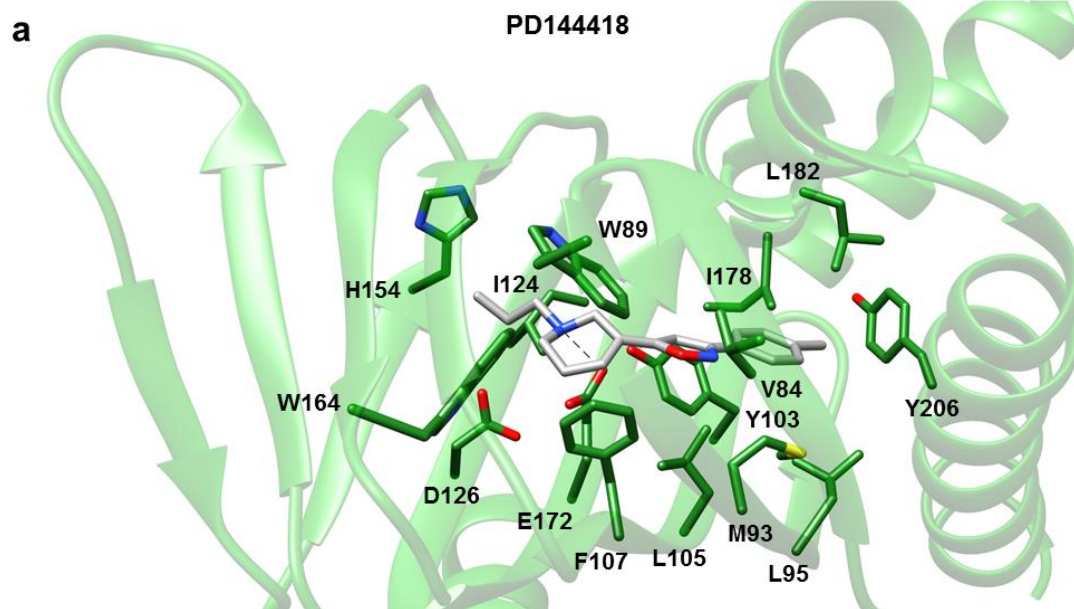


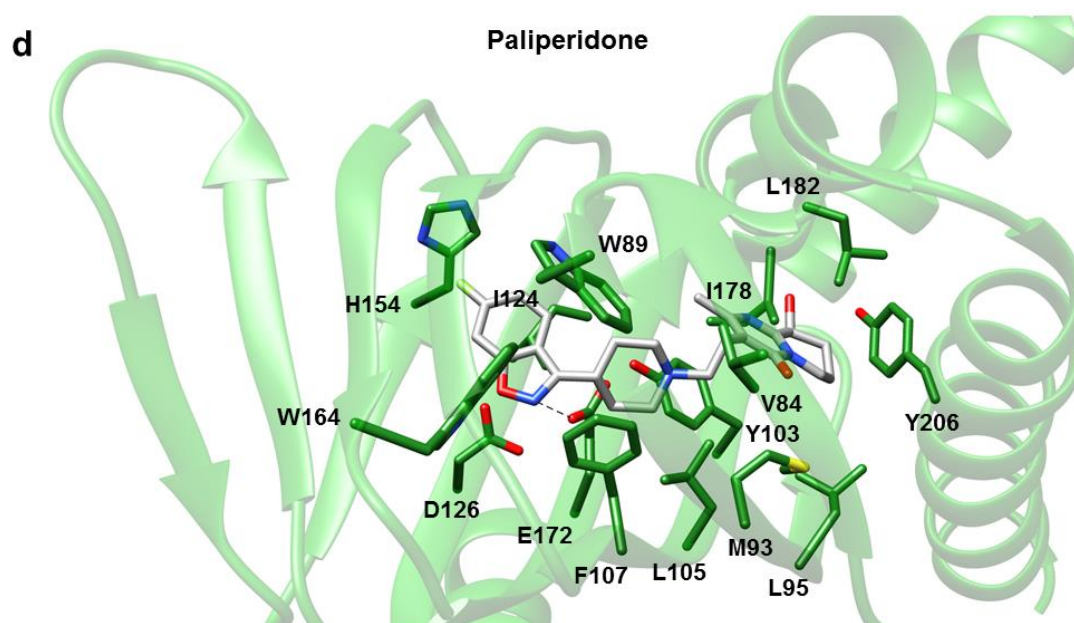
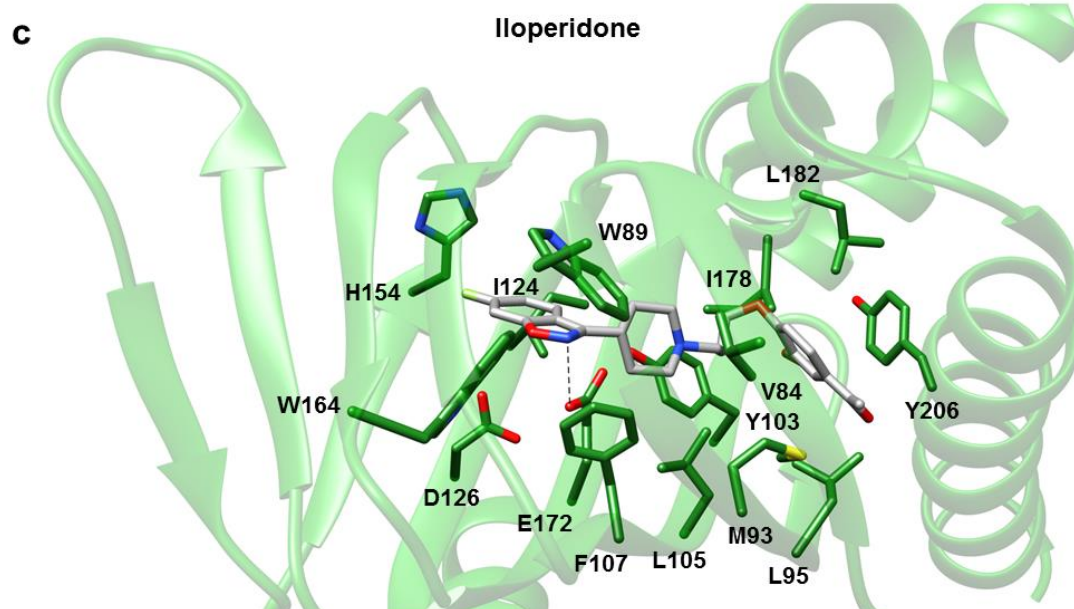
Supplementary Information

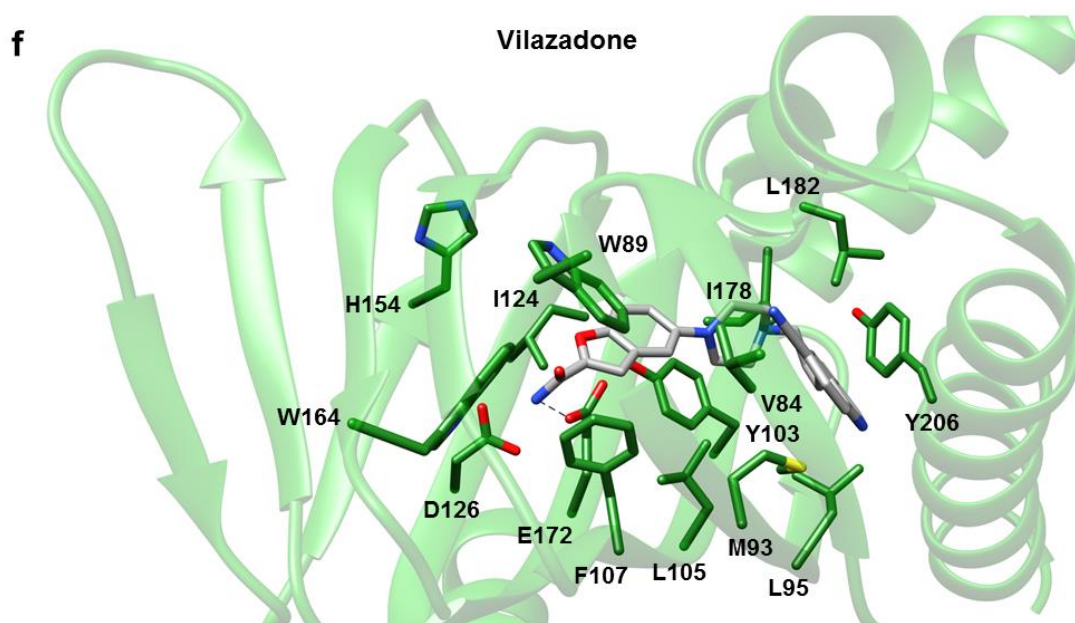
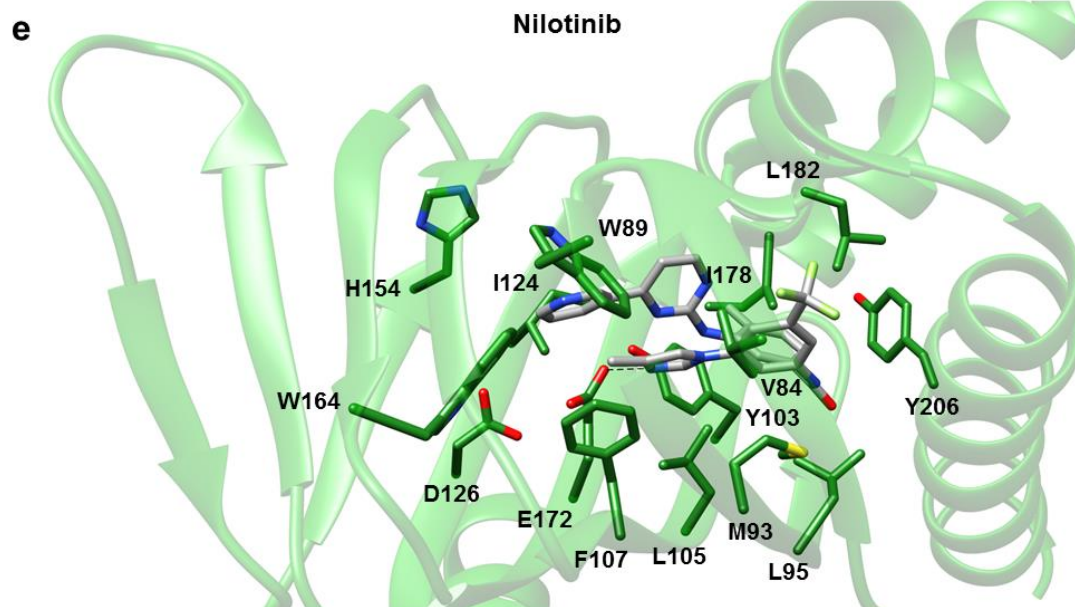
Table S1. All-against-all structure comparison of σ 1R ligand binding domain in the available 3D structures determined by X-ray crystallography. The ligand binding domain comprises residues 29-212 in 5HK2 chain B and 35-218 in all other chains. RMSD values calculated after optimal all-against-all pairwise superposition of either C α or all atoms are reported in the lower and upper part of the matrix, respectively.

		5HK1			5HK2			6DJZ			6DK0			6DK1		
		A	B	C	A	B	C	A	B	C	A	B	C	A	B	C
5HK1	A	-	0.34	0.45	0.37	0.44	0.28	0.14	0.36	0.46	0.17	0.37	0.47	0.38	0.58	0.53
	B	0.66	-	0.31	0.31	0.33	0.36	0.35	0.14	0.34	0.37	0.18	0.35	0.49	0.44	0.44
	C	0.77	0.60	-	0.48	0.19	0.49	0.46	0.34	0.14	0.49	0.37	0.19	0.60	0.51	0.42
5HK2	A	0.73	1.23	0.79	-	0.46	0.33	0.37	0.33	0.51	0.39	0.34	0.52	0.50	0.55	0.54
	B	0.76	0.61	0.49	0.79	-	0.47	0.44	0.35	0.20	0.47	0.37	0.20	0.55	0.50	0.40
	C	0.59	0.69	0.66	0.70	0.81	-	0.28	0.37	0.51	0.28	0.38	0.52	0.44	0.58	0.56
6DJZ	A	0.18	0.67	0.78	0.70	0.77	0.60	-	0.35	0.46	0.11	0.36	0.46	0.35	0.57	0.52
	B	0.66	0.18	0.62	0.65	0.62	0.68	0.66	-	0.34	0.37	0.11	0.35	0.48	0.41	0.43
	C	0.72	0.62	0.19	0.60	0.50	0.78	0.72	0.62	-	0.49	0.36	0.14	0.58	0.50	0.39
6DK0	A	0.26	0.69	0.26	0.75	0.80	0.61	0.22	0.67	0.75	-	0.37	0.49	0.33	0.56	0.52
	B	0.66	0.22	0.64	0.66	0.65	0.70	0.67	0.16	0.64	0.68	-	0.37	0.48	0.40	0.43
	C	0.73	0.62	0.24	0.83	0.50	0.80	0.73	0.63	0.17	0.75	0.64	-	0.56	0.46	0.36
6DK1	A	0.55	0.82	0.92	0.83	0.88	0.75	0.53	0.80	0.87	0.52	0.80	0.86	-	0.53	0.47
	B	0.93	0.67	0.83	0.84	0.80	0.98	0.92	0.61	0.79	0.93	0.63	0.77	0.83	-	0.40
	C	0.89	0.79	0.61	0.90	0.71	0.91	0.89	0.78	0.57	0.89	0.78	0.55	0.81	0.79	-

Supplementary Figure 1. Ligand binding to σ 1R. The protein backbone in co-ordinate file 5HK1 is shown as transparent green ribbon. σ 1R residues involved in ligand binding in the 3D structures listed in Table 1 are labelled, shown as sticks and colored by atom type: C, green; N, blue; O, red. Ligands are shown as sticks and colored by atom-type: C, white; N, blue; O, red; S, yellow F, light green. Glu172 side-chain oxygen and the closest ligand atom able to establish a polar interaction with it are connected by a dashed line. The co-ordinates of the complex with PD144418 **(a)** have been experimentally determined by X-ray crystallography (PDB ID: 5HK1). The conformation of Pridopidine **(b)** was predicted by virtual screening. The conformation of all the other ligands corresponds to the best energy pose of the most populated cluster predicted by docking simulations (see Materials and Methods): **(c)** Iloperidone; **(d)** Paliperidone; **(e)** Nilotinib; **(f)** Vilazodone; **(g)** Linagliptin; **(h)** Flibanserin.







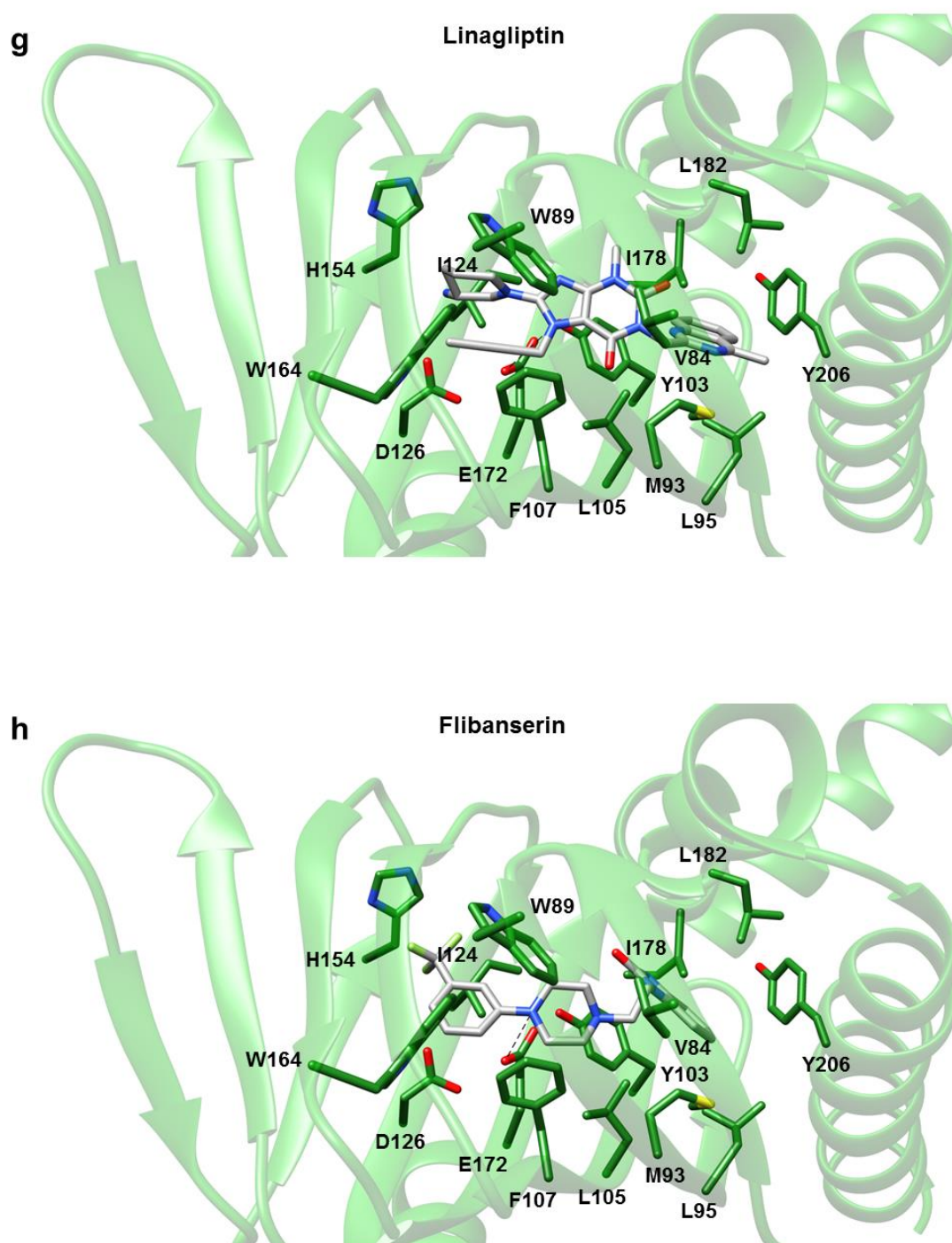


Figure S1. Ligand binding to σ 1R title