Supplementary Materials for:

The Binding Mode of Vilazodone to Human Serotonin Transporter Elucidated by Ligand Docking and Molecular Dynamics Simulation

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Table S1. The rules of detecting protein-ligand interactions[1].

Interaction type	Protein atoms	Ligand atoms	Rule 1[a]	Rule 1[b]
Hydrophobic	Hydrophobic	Hydrophobic	$\|\vec{Y_1Y_2}\| \leq 4.5$ Å	
Aromatic (face to face)	Aromatic	Aromatic	$\|\vec{\alpha_1\alpha_2}\| \leq 4$ Å & $\|\vec{\alpha_i\alpha_j}\| \leq 12$ Å	$\langle \vec{n_1},\vec{n_2} \rangle \in \left[\frac{-\pi}{6},\frac{\pi}{6}\right]$
Aromatic (edge to face)	Aromatic cycle	Aromatic cycle	$\|\vec{\alpha_1\alpha_2}\| \leq 4.0$ Å[c]	$\langle \vec{n_1},\vec{n_2} \rangle \in \left[\frac{\pi}{6},\frac{5\pi}{6}\right]$
H-bond (Protein: acceptor)	H-bond acceptor	H-bond donor	$\|\vec{DA}\| \leq 3.5$ Å	$\langle \vec{DH},\vec{HA} \rangle \in \left[\frac{-\pi}{4},\frac{\pi}{4}\right]$
H-bond (Protein: donor)	H-bond donor	H-bond acceptor	$\|\vec{DA}\| \leq 3.5$ Å	$\langle \vec{DH},\vec{HA} \rangle \in \left[\frac{-\pi}{4},\frac{\pi}{4}\right]$
Ionic (Protein: anionic)	Negative ionizable	Positive ionizable	$\| \vec{+-} \| \leq 4.0$ Å	
Ionic (Protein: cationic)	Positive ionizable	Negative ionizable	$\| \vec{+-} \| \leq 4.0$ Å	

[a]Y, hydrophobe; a_1, protein interacting atom; a_2, ligand interacting atom; a_i, any atom of the protein aromatic ring; a_j, any atom of ligand aromatic ring; D, H-bond donor; A, H-bond acceptor; +, cation; -, anion; [b]n, normal to the aromatic ring; H, hydrogen. [c] for 5 pairs of protein-ligand interacting aromatic atoms.

Table S2. The energy contributions (kcal/mol) of the residues located on TM1 as well as the proportion of their contributions to that of the 24 residues.

TMs	Residues	Lig.29	Lig.39	Lig.47	Lig.15	Lig.22	Lig.20	Esc.
TM1	Y95	-1.34	-1.88	-2.14	-1.34	-2.92	-3.76	-4.97
	A96	-0.05	-0.88	-0.54	-0.11	-0.63	-1.25	-0.70
	D98	-3.45	-4.50	-1.04	-1.89	-2.86	-1.	-5.54
	R104	-2.10	-0.06	-0.17	-2.09	0.06	0.11	0.21
	Sum	-6.94	-7.32	-3.89	-5.43	-6.35	-6.84	-11.00
	Proportion	23.41%	25.14%	13.28%	21.56%	25.05%	26.30%	38.76%

Table S3. The energy contributions (kcal/mol) of the residues located on TM3 as well as the proportion of their contributions to that of the 24 residues.

TMs	Residues	Lig.29	Lig.39	Lig.47	Lig.15	Lig.22	Lig.20	Esc.
TM3	A169	-0.63	-0.61	-0.82	-1.00	-0.17	-0.71	-0.37
	I172	-2.42	-3.48	-3.59	-2.49	-2.32	-3.09	-3.21
	A173	-1.28	-0.85	-0.76	-0.63	-0.	-0.71	-0.56
	Y175	-0.47	-1.01	-1.26	-0.63	-0.35	-0.36	-0.44
	Y176	-2.84	-1.75	-2.66	-3.17	-2.78	-2.21	-2.33
	N177	-0.	-0.05	-0.47	-0.03	-0.86	-0.13	-0.17
	Sum	-8.58	-7.75	-9.56	-7.95	-7.42	-7.21	-7.08
	Proportion	28.94%	26.67%	32.83%	34.43%	29.21%	27.60%	24.76%

Table S4. The energy contributions (kcal/mol) of the residues located on TM6 as well as the proportion of their contributions to that of the 24 residues.

TMs	Residues	Lig.29	Lig.39	Lig.47	Lig.15	Lig.22	Lig.20	Esc.
TM6	A331	-1.00	-0.05	-0.07	-0.44	-0.04	-0.04	-0.04
	Q332	-0.95	-0.08	-0.06	-0.71	-0.08	-0.05	-0.04
	F334	-0.19	-1.00	-0.25	-0.16	-1.03	-0.53	-0.25
	F335	-3.44	-2.28	-4.13	-2.32	-2.46	-1.62	-0.77
	S336	-0.42	-0.33	-0.99	-0.65	-0.26	-0.61	-1.18
	G338	-0.38	-0.70	-1.08	-0.14	-0.58	-0.72	-0.85
	F341	-0.44	-0.68	-1.53	-1.00	-0.62	-1.27	-1.24
	V343	-0.58	-0.48	-0.55	-0.41	-0.14	-0.16	-0.19
	Sum	-7.40	-5.60	-8.66	-5.83	-5.21	-5.00	-4.56
	Proportion	24.96%	19.27%	29.74%	25.25%	20.51%	19.14%	15.95%

Table S5. The energy contributions (kcal/mol) of the residues located on TM8 as well as the proportion of their contributions to that of the 24 residues.

TMs	Residues	Lig.29	Lig.39	Lig.47	Lig.15	Lig.22	Lig.20	Esc.
TM8	S438	-3.03	-1.43	-0.88	-1.48	-2.17	-1.59	-0.85
	T439	-1.72	-1.08	-0.92	-1.38	-0.63	-1.70	-1.19
	G442	-0.87	-0.92	-1.55	-0.96	-0.39	-0.84	-1.33
	L443	-1.00	-1.03	-1.26	-0.94	-0.92	-1.01	-0.82
	Sum	-6.62	-4.46	-4.61	-4.76	-4.11	-5.14	-4.19
	Proportion	22.33%	15.35%	15.83%	20.61%	16.18%	19.68%	14.66%

Table S6. The energy contributions (kcal/mol) of the residues located on TM10 as well as the proportion of their contributions to that of the 24 residues.

TMs	Residues	Lig.29	Lig.39	Lig.47	Lig.15	Lig.22	Lig.20	Esc.
	E493	-1.54	-1.09	-1.01	-0.87	-0.52	-0.29	-0.24
TM10	T497	-0.38	-1.77	-1.19	-0.20	-0.82	-0.99	-0.54
	V501	-0.29	-1.13	-0.37	-0.14	-0.91	-0.54	-0.77
	Sum	-2.21	-3.99	-2.57	-1.21	-2.25	-1.82	-1.55
	Proportion	7.45%	13.73%	8.83%	5.24%	8.86%	6.97%	5.42%

SI Figures

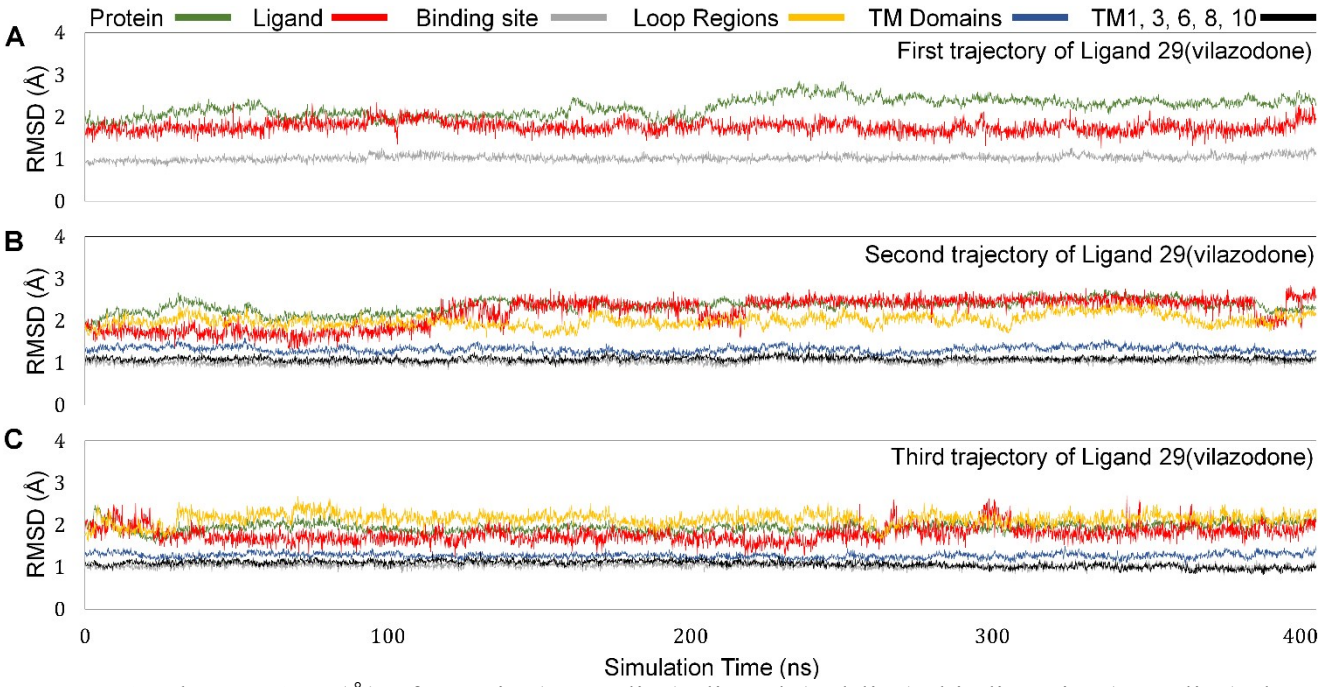

Figure S1. The RMSDs (Å) of protein (green line), ligand (red line), binding site (gray line), loop regions (yellow line), TM1-12 domains (blue line), and TM1, 3, 6, 8, 10 (dark line) surrounding S1 binding pocket as a function of the simulation time (ns) calculated from the three trajectories of ligand 29 (vilazodone) system in three different independent simulations.

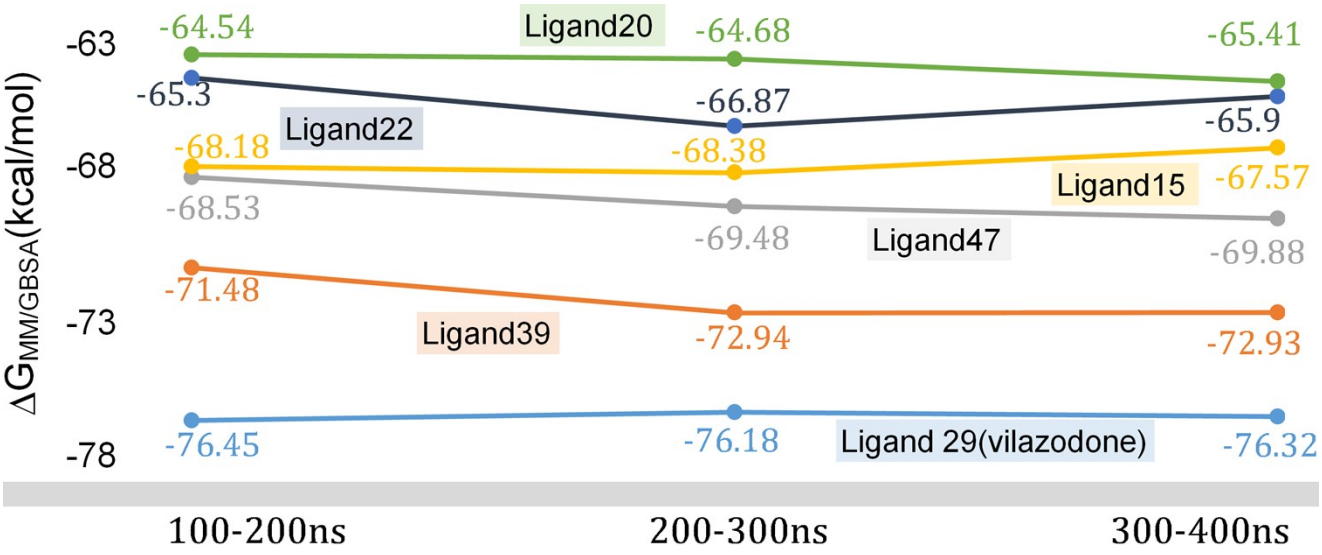

Figure S2. The binding free energies of 3 different simulation periods for 6 studied systems via MM/GBSA based on 1000 snapshots

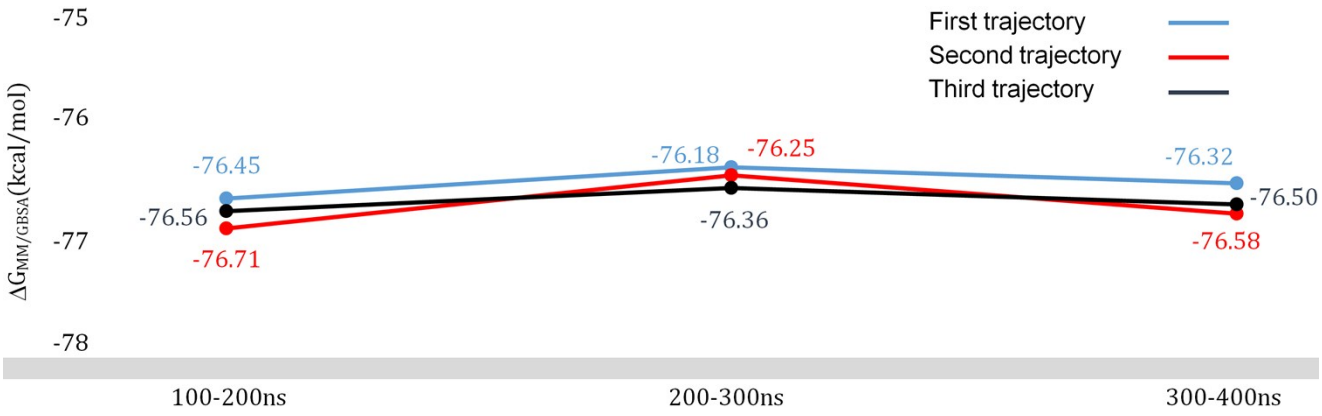

Figure S3. The binding free energies ($\Delta G_{MM/GBSA}$) of 3 different simulation periods for ligand 29 (vilazodone) system via MM/GBSA based on 1000 snapshots in three independent simulations.

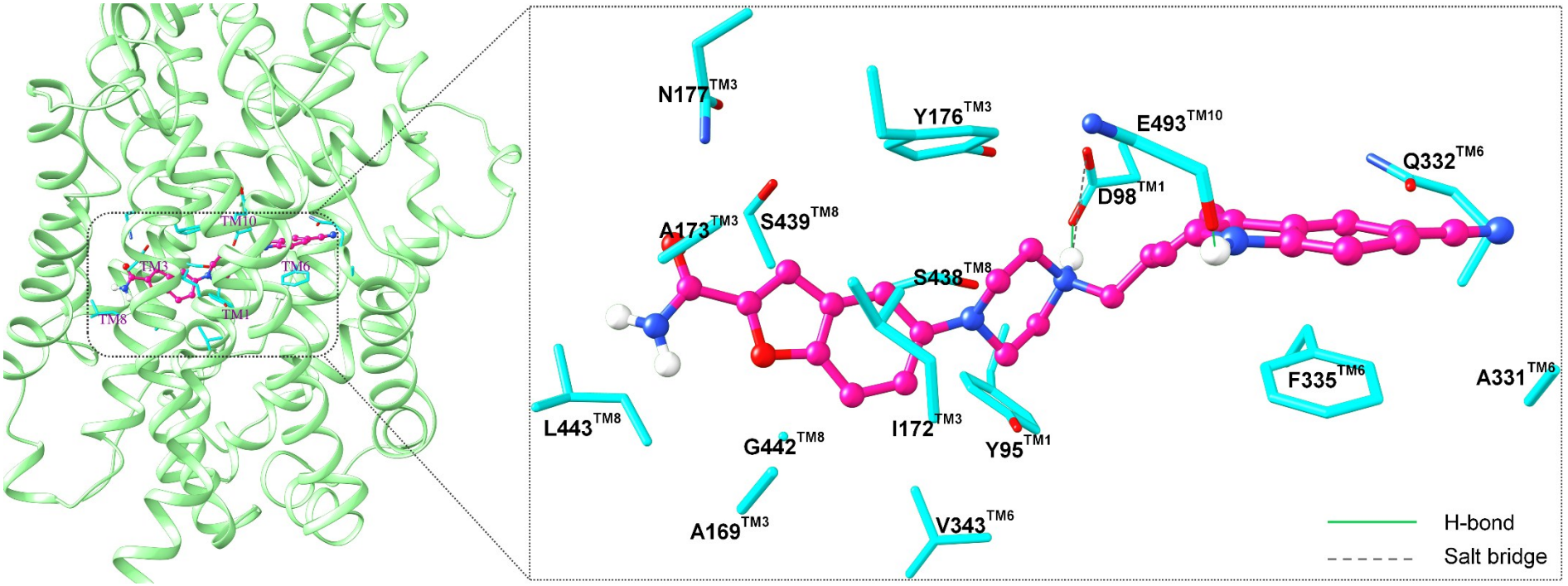

Figure S4. Global distribution of the key residues contributing to vilazodone's binding in hSERT.

Reference

1. J. Desaphy, E. Raimbaud, P. Ducrot and D. Rognan, *J. Chem. Inf. Model.*, 2013, **53**, 623-637.