Supplementary Materials

1. Supplementary Figures

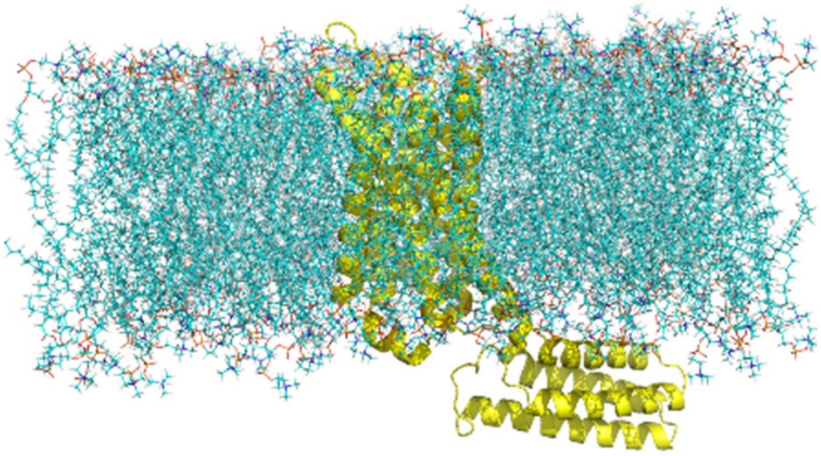

Figure S1. α_{2A}-AR receptor and lipid bilayer membrane model used in the molecular dynamic simulations.

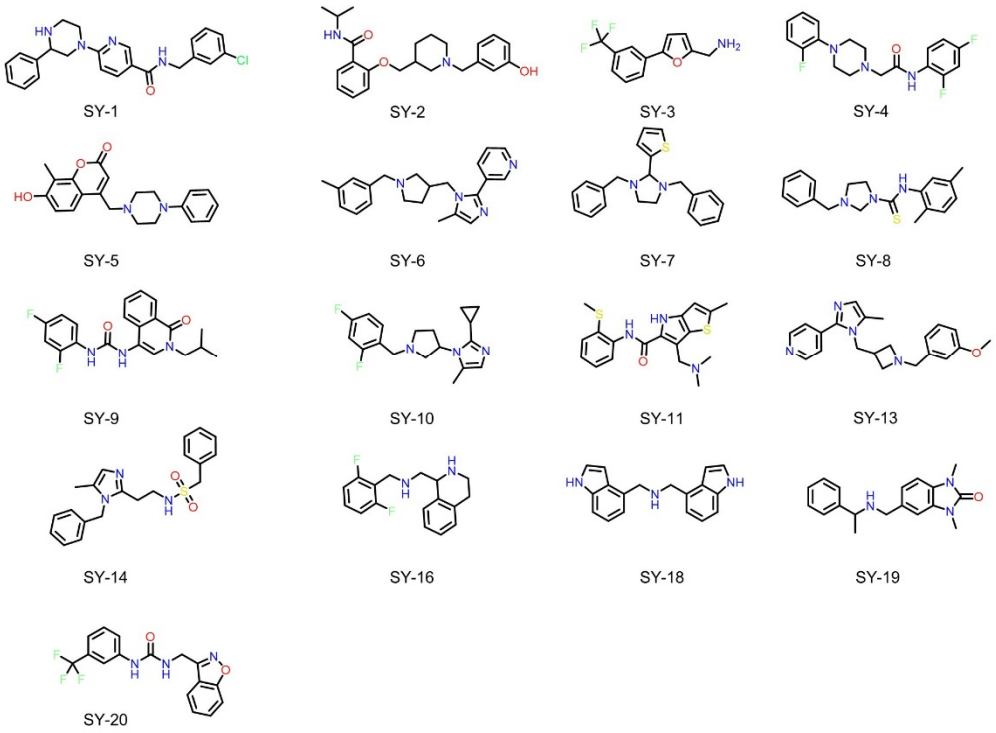

Figure S2. The chemical structure of candidate molecules.

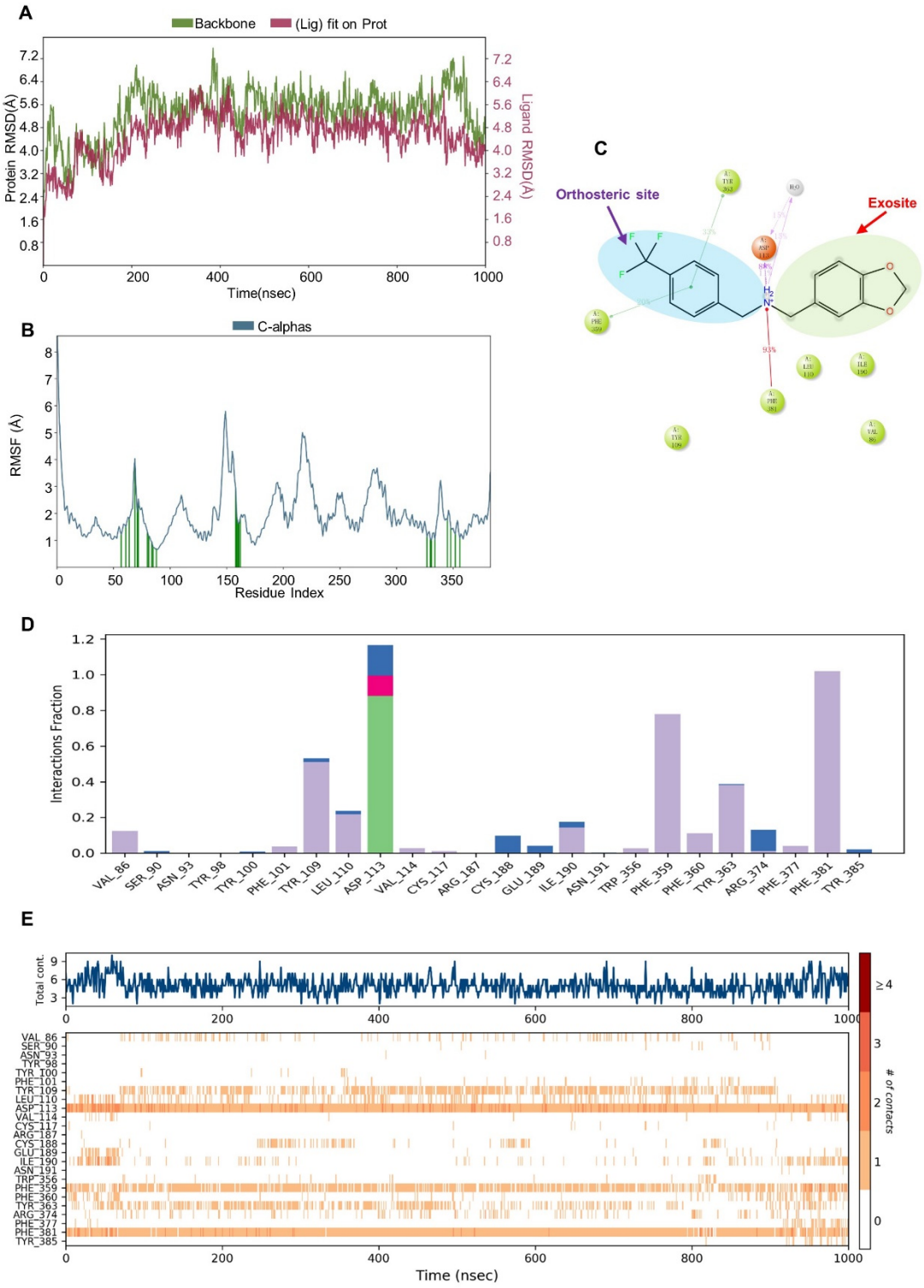

Figure S3. MD simulation of **SY-15** and α_{2A}-AR complex. (**A**) The RMSD plot of α_{2A}-AR with ligand **SY-15**; (**B**) The RMSF plot of α_{2A}-AR; (**C**) The percentage of simulation time of residue interactions during 1000 ns simulation shown with L-P plot; (**D**) The interaction fractions α_{2A}-AR active residues with ligand **SY-15**; (**E**) The plots of protein-ligand contacts and interactions during 1000 ns simulation;

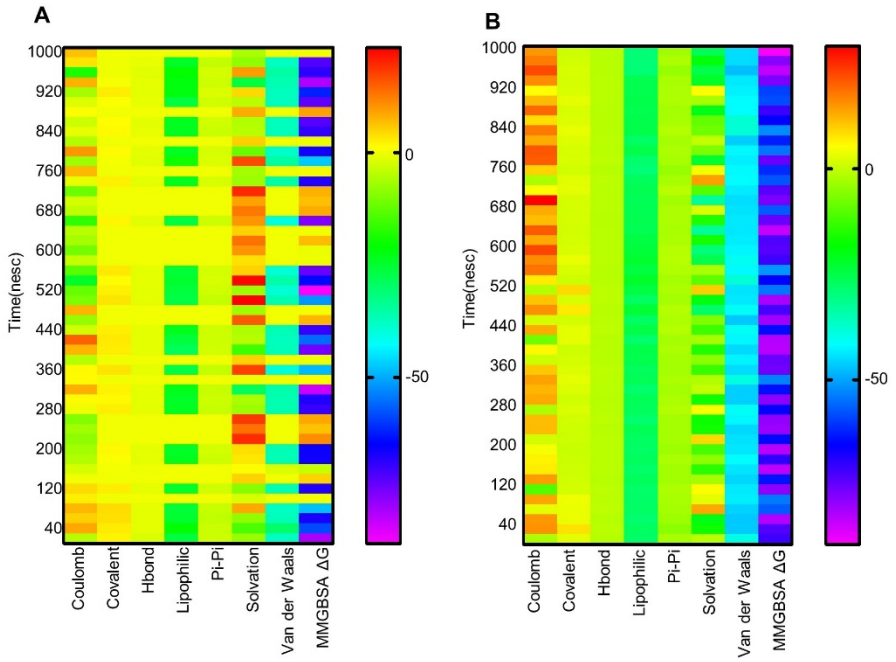

Figure S4. (**A**) Constituent parts of bind free energy for **SY-15** during the MD simulation; (**B**) Constituent parts of bind free energy for **SY-17**.

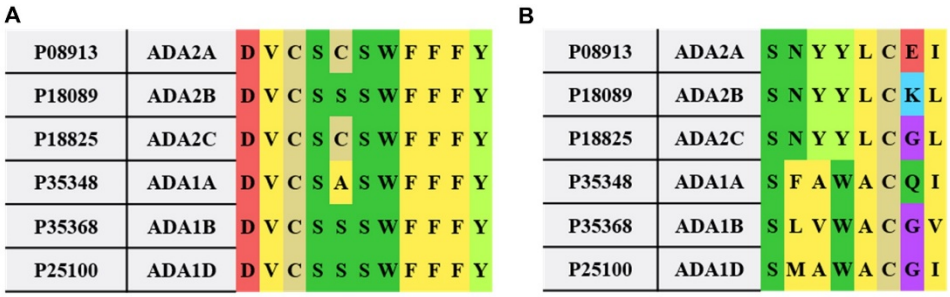

Figure S5. (**A**) Multiple sequences alignment of orthosteric sites for α-AR receptor family; (**B**) Multiple sequences alignment of exosite for α-AR receptor family.

2. Supplementary Tables

Table S1. The ADME/T properties of the candidate compounds for in vitro assay

Compound Name	IDNUMBER	PSA	SASA	logP	WPSA	FOSA	QPlogHERG	rotatable bonds	FISA	HumanOral Absorption	CNS	QPlogBB	RuleOfFive	donorHB	accptHB	mol MW
SY-1	P801-0655	63.73	750.87	4.20	71.57	162.45	−8.04	6	79.72	1	1	0.07	0	2	5.5	406.91
SY-2	M735-1116	65.00	716.06	2.49	0.00	342.89	−6.76	9	87.75	3	1	−0.42	0	2	6	382.50
SY-3	8019-8601	34.04	465.04	3.29	117.63	58.53	−5.61	3	61.10	3	2	0.58	0	2	1.5	241.21
SY-4	K940-1464	43.63	623.47	3.20	105.25	163.18	−6.72	5	45.18	3	2	0.59	0	1	5.5	349.36
SY-5	Y041-4036	67.45	652.16	3.08	0.00	245.44	−6.71	4	117.07	3	1	−0.41	0	1	6.25	350.42
SY-6	S779-1061	34.93	656.05	3.05	0.00	275.67	−6.58	5	58.10	3	1	0.16	0	0	5	346.47
SY-7	8007-8950	10.99	615.44	3.39	26.06	119.64	−7.77	5	8.06	3	2	1.11	0	0	4	334.48
SY-8	K788-3789	26.30	639.59	5.27	48.50	289.08	−6.60	5	16.65	3	2	0.73	0	1	4.5	325.47
SY-9	E942-0016	68.95	710.18	2.93	89.10	187.20	−5.53	6	89.43	3	0	−0.47	0	2	5	371.39
SY-10	S694-0761	21.01	594.29	3.59	70.81	318.20	−5.75	4	20.85	3	2	0.82	0	0	3.5	317.38
SY-11	M372-1199	51.43	642.78	3.82	63.61	328.19	−6.09	6	38.04	3	1	0.45	0	2	5	359.50
SY-12	P801-0725	61.30	737.95	3.51	0.00	251.75	−7.77	6	62.80	3	1	0.10	0	2	5.5	386.50
SY-13	S696-1461	42.75	712.25	1.86	0.00	292.19	−6.70	6	57.44	1	0	−0.36	1	0	3.75	348.45
SY-14	T161-0947	66.47	681.71	1.78	0.00	174.72	−6.45	8	101.54	3	-1	−0.94	0	1	6	369.48
SY-15	4964-4916	32.40	507.64	3.99	117.34	154.68	−5.22	5	16.75	3	2	0.87	0	1	3	309.29
SY-16	8013-2958	23.82	537.49	2.87	63.58	164.58	−6.63	4	21.51	3	2	1.08	0	2	3	288.34
SY-17	4964-4708	17.98	572.37	4.53	117.11	204.32	−5.99	7	11.55	3	2	0.78	0	1	2.25	309.33
SY-18	8019-9725	40.95	537.20	3.17	0.00	48.26	−6.53	4	74.70	3	1	0.04	0	3	1.5	275.35
SY-19	D215-0599	46.07	596.22	2.93	0.00	266.21	−6.28	4	66.44	3	1	0.08	0	1	3.5	295.38
SY-20	E567-0008	74.01	574.01	3.34	114.04	42.82	−4.40	6	104.58	3	0	−0.35	0	2	3.5	335.29