Electronic Supplementary Material (ESI) for Physical Chemistry Chemical Physics.

Identification of active ligands for metabotropic glutamate receptor 4 (mGluR4) using a hierarchical virtual screening method

[Supporting Information]

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Table S1. The mGluR proteins resolved crystal structure information from Protein Data Bank and respective data count of ligand experimental activity from ChEMBL database by the time this paper was writing.

Group	Protein	Ligand experimental KI data count	Structure information (human) -- PDBID
Group 1	mGluR1	106	3KS9, 4OR2, 3LMK
	mGluR5	498	3LMK, 6FFI, 6FFH, 4OO9, 6N4X, 6N50, 6N52, 6N51, 5CGD, 6N4Y, 5CGC
Group 2	mGluR2	203	4XAQ, 4XAS, 6DUP, 5KZN, 5KZQ, 5CNJ, 4XAR, 5CNI
	mGluR3	85	4XAR, 6B7H, 5CNK, 5CNM, 3SM9, 4XAQ
Group 3	mGluR4	76	NA
	mGluR6	24	NA
	mGluR7	19	3MQ4, 5C5C
	mGluR8	20	6BSZ, 6BT5

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mGluR4    111   HMNSIRIDGDITLGGLFPVHGRGSEGKPCGELKKEKGIHRLEAMLFALDRINNDPDLLPNITLGARILDTCSR
mGluR8    108   -AHSIRVDGDIILGGLFPVHAKGERGVPCGELKKEKGIHRLEAMLYAIDQINKDPDLLSNITLGVRILDTCSR

mGluR4    207   DTHALEQSLTFVQARVVGVIGASGSSVSIMVANILRLFKIPQISYASTAPDLSDNSRYDFFSRVVPSDTYQAQ
mGluR8    204   DTYALEQSLTFVQ-KISGVIGAAASSVSIMVANILRLFKIPQISYASTAPELSDNTRYDFFSRVVPPDSYQAQ

mGluR4    280   AMVDIVRALKWNYVSTVASEGSYGESGVEAFIQKSREDGGVCIAQSVKIPREPKAGEFDKIIRRLLETSNARA
mGluR8    277   AMVDIVTALGWNYVSTLASEGNYGESGVEAFTQISREIGGVSIAQSQKIPREPRPGEFEKIIKRLLETPNARA

mGluR4    353   VIIFANEDDIRRVLEAARRANQTGHFFWMGSDSWGSKIAPVLHLEEVAEGAVTILPKRMSVRGFDRYFSSRTL
mGluR8    350   VIMFANEDDIRRILEAAKKLNQSGHFLWIGSDSWGSKIAPVYQQEEIAEGAVTILPKRASIDGFDRYFRSRTL

mGluR4    438   DNNRRNIWFAEFWEDNFHCKLKCTNRERIGQDSAYEQEGKVQFVIDAVYAMGHALHAMHRDLCPGRVGLCPRM
mGluR8    434   ANNRRNVWFAEFWEENFGCKLKCTGLERIARDSSYEQEGKVQFVIDAVYSMAYALHNMHKDLCPGYIGLCPRM

mGluR4    508   DPVDGTQLLKYIRNVNFSGIAGNPVTFNENGDAPGRYDIYQYQLRNDSAEYKVIGSWTDHLHLRIERMHW*
mGluR8    504   STIDGKELLGYIRAVNFNGSAGTPVTFNENGDAPGRYDIFQYQITNKSTEYKVIGHWTNQLHLKVEDMQW*
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■ α-helix ■ β-sheet □ Target sequence ■ Template sequence

Fig. S1 Sequence comparison and alignment of mGluR4 with its template mGluR8. The PDB code of resolved crystal structure of mGluR8 is 6BT5.

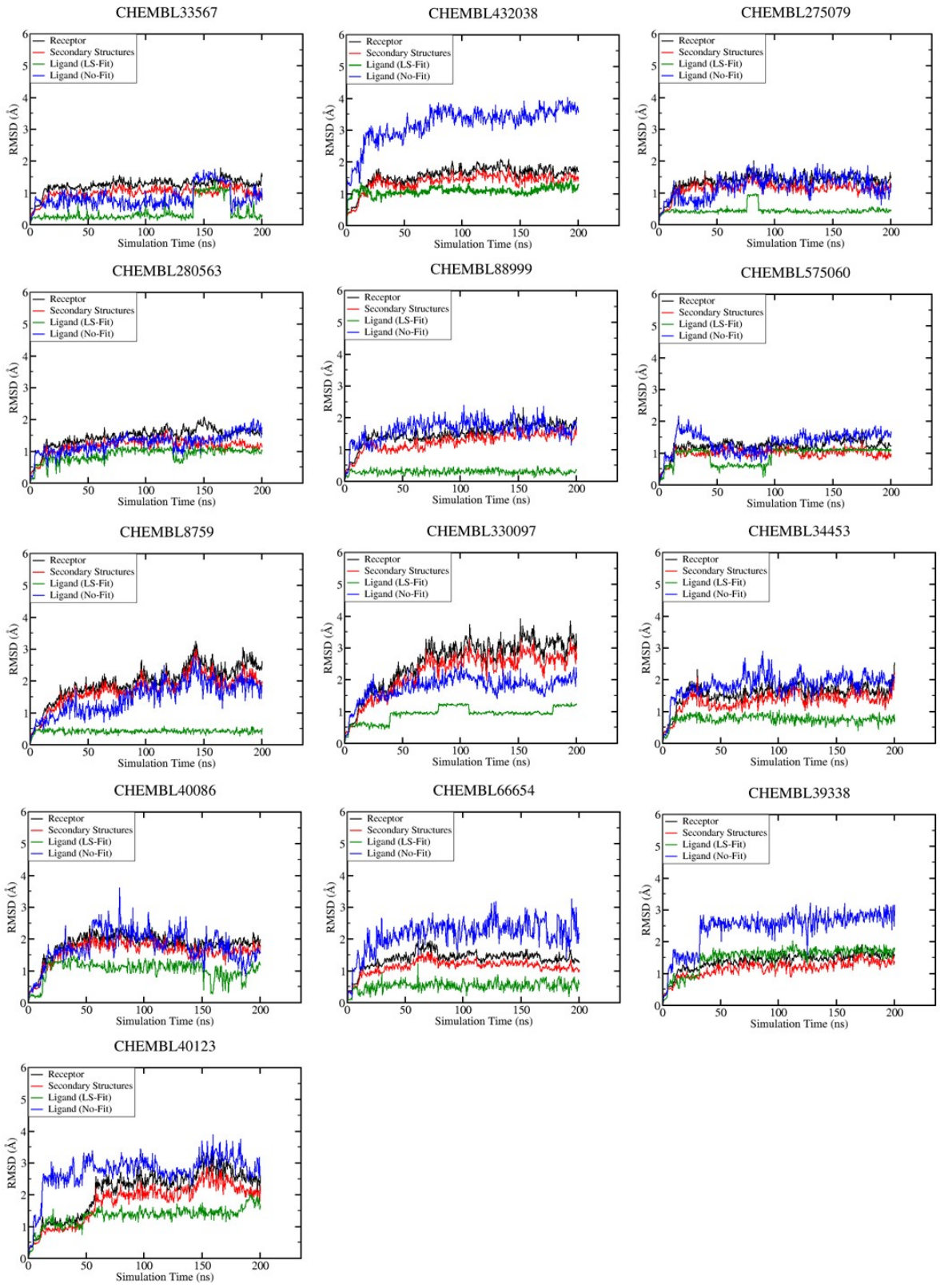


Fig. S2 Fluctuations of Root-Mean-Square Deviations (RMSDs) along the time course of MD simulations for twelve mGluR8-ligand systems, of which the fluctuations are within 6 Å.

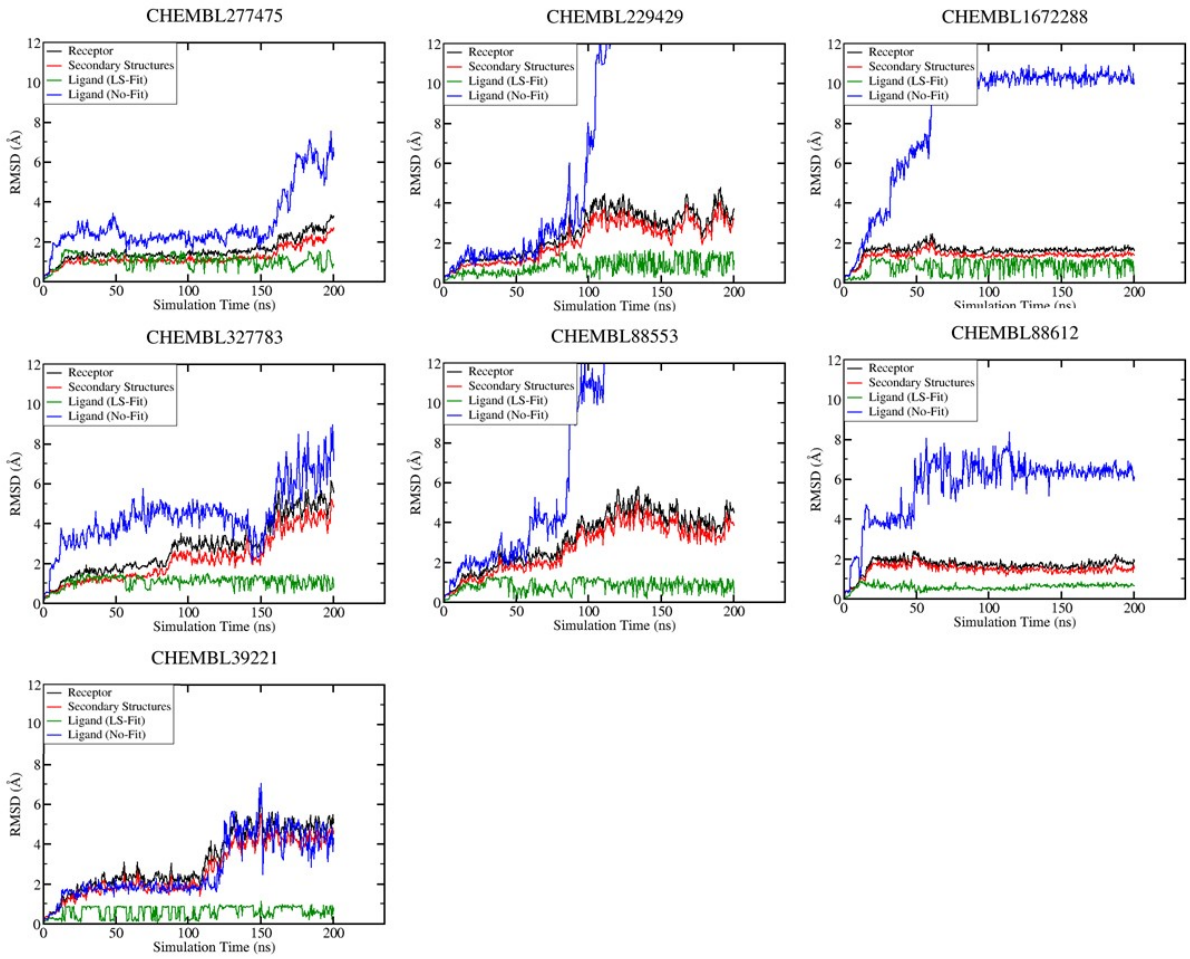


Fig. S3 Fluctuations of Root-Mean-Square Deviations (RMSDs) along the time course of MD simulations for eight mGluR8-ligand systems, of which the fluctuation is larger than 6 Å.

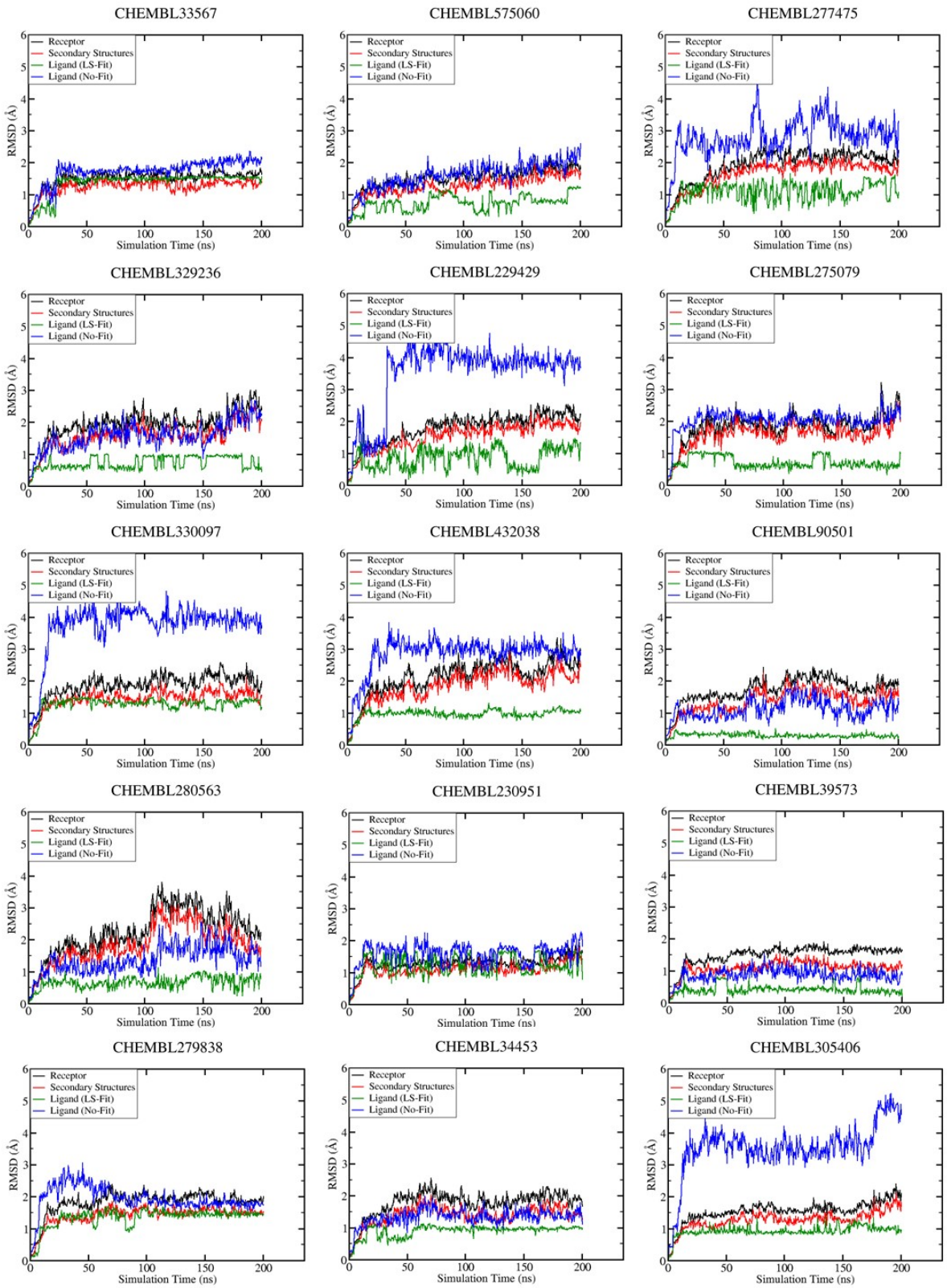
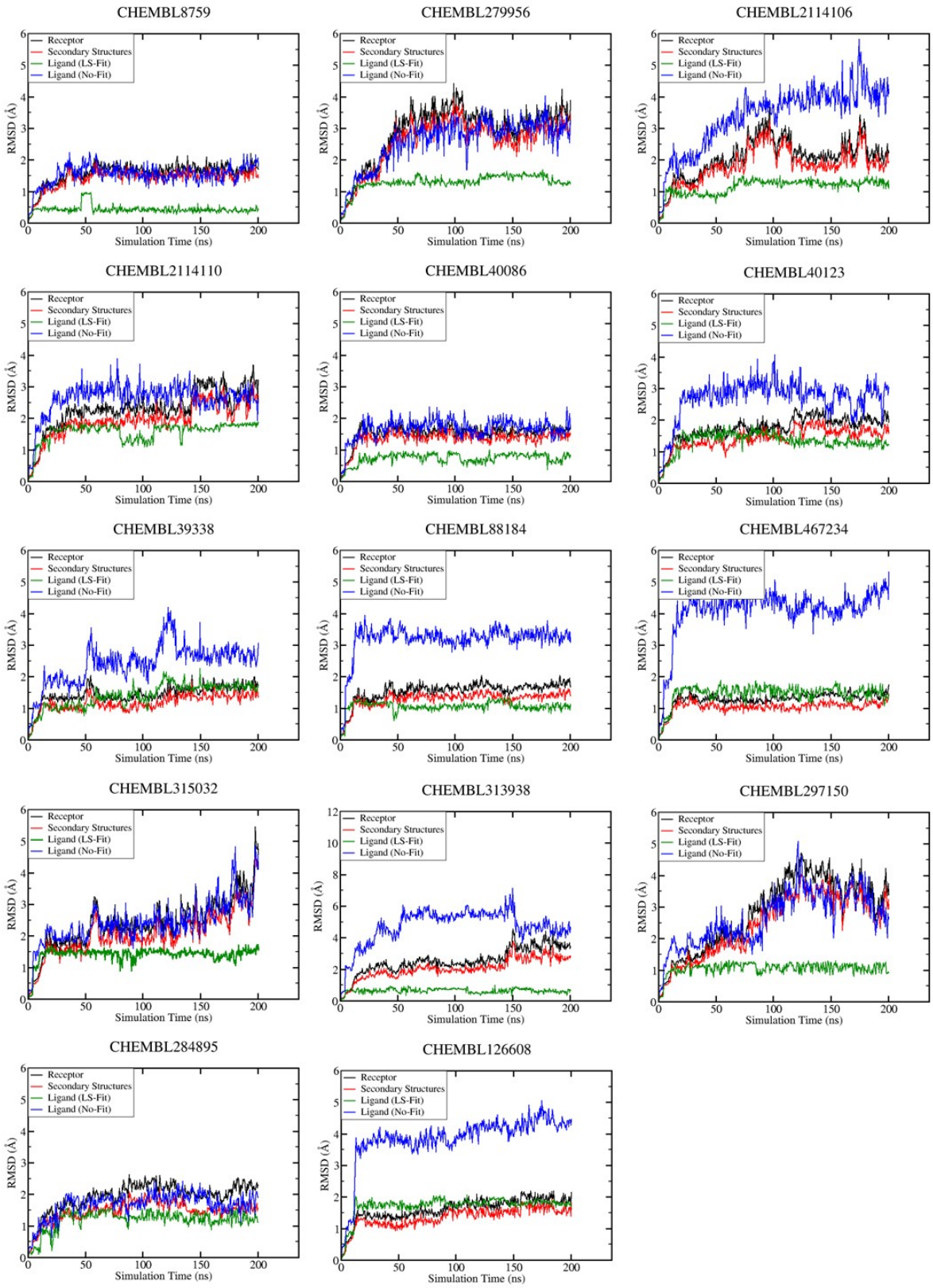


Fig. S4 Fluctuations of Root-Mean-Square Deviations (RMSDs) along the time course of MD simulations for 16 mGluR4-ligand systems, of which the fluctuation is within 6 Å.



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ig. S4 (continue) Fluctuations of Root-Mean-Square Deviations (RMSDs) along the time course of MD

simulations for 16 mGluR4-ligand systems, of which the fluctuation is within 6 Å.

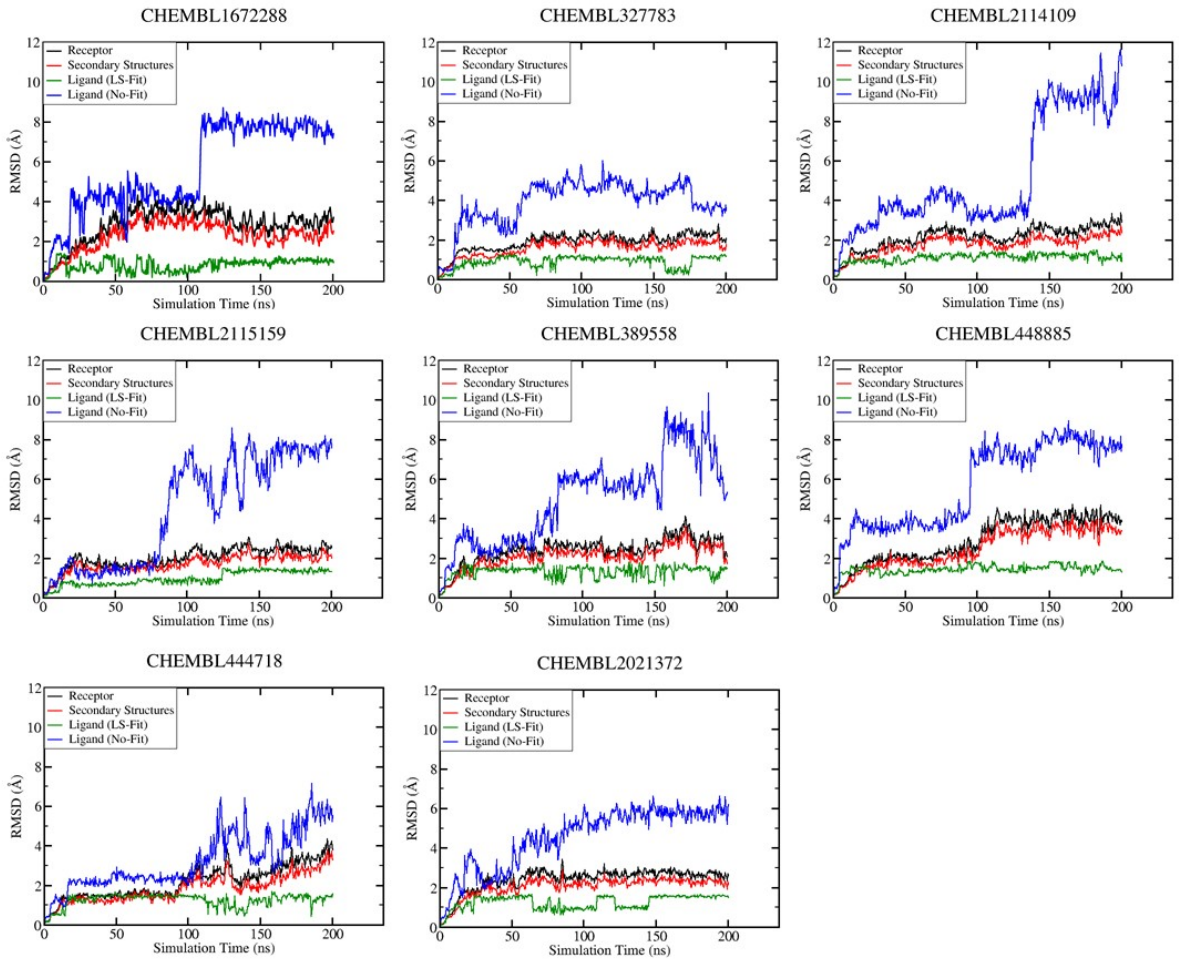

Fig. S5 Fluctuations of Root-Mean-Square Deviations (RMSDs) along the time course of MD simulations for 9 mGluR4-ligand systems, of which the fluctuation is larger than 6 Å.

Table S2. Calculated individual energy terms of mGluR8 ligands using MM-PBSA (PB model) method in kcal/mol.

Ligands	ΔE_{vdw}	ΔE_{ele}	ΔG_{p}^{sol}	ΔG_{np}^{sol}	$T\Delta S$	$\Delta G_{MM/PBSA}$
CHEMBL575060	-14.22±0.45	-196.08±2.21	158.93±0.55	-1.19±0.00	-18.20±0.05	-34.36±1.32
CHEMBL33567	-15.58±1.41	-193.72±3.21	158.63±2.12	-1.42±0.02	-18.74±0.08	-33.35±0.42
CHEMBL275079	-17.37±0.82	-167.31±3.44	136.81±1.76	-1.39±0.02	-18.42±0.04	-30.84±1.29
CHEMBL88999	-19.59±0.68	-151.13±3.37	126.42±1.52	-1.56±0.00	-18.71±0.08	-27.16±1.45
CHEMBL280563	-15.06±0.49	-167.10±0.52	138.40±2.29	-1.36±0.01	-18.10±0.02	-27.01±1.52
CHEMBL8759	-16.48±0.85	-183.68±3.03	156.75±1.47	-1.48±0.01	-18.31±0.09	-26.59±0.89
CHEMBL330097	-14.30±0.62	-185.25±2.00	166.90±1.78	-1.56±0.01	-18.00±0.03	-16.20±1.90
CHEMBL432038	-43.87±0.78	-132.23±0.86	139.80±1.18	-3.14±0.00	-23.41±0.02	-16.02±0.27
CHEMBL34453	-18.50±0.75	-152.12±1.75	140.59±2.28	-1.52±0.02	-18.13±0.08	-13.41±0.82
CHEMBL39338	-43.79±1.08	-124.77±1.29	137.29±1.06	-3.99±0.03	-23.28±0.10	-11.98±0.90
CHEMBL327783	-24.25±0.41	-16.68±0.89	29.41±1.15	-1.87±0.06	-16.01±0.12	2.62±0.31
CHEMBL229429	-17.57±0.86	-2.73±0.39	9.99±0.55	-1.35±0.07	-15.07±0.20	3.41±0.90
CHEMBL66654	-36.56±0.54	-8.44±0.24	36.17±0.87	-2.51±0.01	-18.29±0.13	6.96±0.58
CHEMBL40123	-31.82±0.61	-97.29±2.15	120.72±1.32	-2.99±0.03	-19.97±0.20	8.59±0.68
CHEMBL88553	-5.95±0.11	-3.28±0.91	6.86±1.14	0.12±0.02	-11.66±0.03	9.40±0.36
CHEMBL88612	-30.25±0.41	-7.01±0.13	32.59±0.76	-2.40±0.01	-17.70±0.03	10.63±0.62
CHEMBL277475	-14.06±0.68	-213.18±8.47	223.62±7.60	-2.13±0.02	-17.31±0.08	11.55±0.92
CHEMBL1672288	-28.80±0.07	-14.61±0.21	42.59±0.41	-2.16±0.02	-17.71±0.09	14.73±0.59
CHEMBL40086	-19.04±0.35	-88.77±2.17	111.40±2.23	-1.68±0.01	-16.58±0.05	18.49±0.32
CHEMBL39221	23.90±4.51	-43.25±2.62	108.31±0.21	-1.34±0.01	-15.24±0.06	102.86±2.05

Table S3. Calculated individual energy terms of mGluR8 ligands using MM-GBSA (GB1 model) method in kcal/mol.

Ligands	ΔE_{vdw}	ΔE_{ele}	ΔG_{p}^{sol}	ΔG_{np}^{sol}	$T\Delta S$	$\Delta G_{MM/GBSA}$
CHEMBL33567	-15.58±1.41	-193.72±3.21	112.24±1.75	-3.62±0.00	-18.74±0.08	-81.95±1.09
CHEMBL575060	-14.22±0.45	-196.08±2.21	121.62±0.84	-3.45±0.01	-18.20±0.05	-73.93±1.72
CHEMBL432038	-43.87±0.78	-132.23±0.86	90.51±1.65	-5.63±0.03	-23.41±0.02	-67.80±0.20
CHEMBL275079	-17.37±0.82	-167.31±3.44	102.42±2.05	-3.26±0.01	-18.42±0.04	-67.10±0.95
CHEMBL39338	-43.79±1.08	-124.77±1.29	87.86±0.50	-6.51±0.02	-23.28±0.10	-63.94±0.61
CHEMBL88999	-19.59±0.68	-151.13±3.37	93.50±1.83	-3.28±0.02	-18.71±0.08	-61.79±1.54
CHEMBL280563	-15.06±0.49	-167.10±0.52	106.32±0.90	-3.18±0.02	-18.10±0.02	-60.91±0.25
CHEMBL8759	-16.48±0.85	-183.68±3.03	124.59±1.29	-3.40±0.03	-18.31±0.09	-60.66±1.27
CHEMBL330097	-14.30±0.62	-185.25±2.00	133.29±1.26	-3.26±0.03	-18.00±0.03	-51.52±0.89
CHEMBL34453	-18.50±0.75	-152.12±1.75	110.56±2.06	-3.40±0.00	-18.13±0.08	-45.33±0.59
CHEMBL40123	-31.82±0.61	-97.29±2.15	86.54±1.17	-4.92±0.07	-19.97±0.20	-27.52±0.66
CHEMBL277475	-14.06±0.68	-213.18±8.47	188.84±7.24	-3.78±0.04	-17.31±0.08	-24.88±1.33
CHEMBL40086	-19.04±0.35	-88.77±2.17	76.19±1.79	-3.30±0.02	-16.58±0.05	-18.33±0.50
CHEMBL66654	-36.56±0.54	-8.44±0.24	16.36±0.11	-4.41±0.05	-18.29±0.13	-14.76±0.37
CHEMBL1672288	-28.80±0.07	-14.61±0.21	20.61±0.18	-4.12±0.04	-17.71±0.09	-9.21±0.21
CHEMBL88612	-30.25±0.41	-7.01±0.13	14.61±0.09	-4.25±0.02	-17.70±0.03	-9.21±0.39
CHEMBL327783	-24.25±0.41	-16.68±0.89	22.22±1.20	-2.97±0.07	-16.01±0.12	-5.67±0.21
CHEMBL229429	-17.57±0.86	-2.73±0.39	7.80±0.43	-2.55±0.10	-15.07±0.20	0.02±0.74
CHEMBL88553	-5.95±0.11	-3.28±0.91	5.42±1.00	-0.81±0.01	-11.66±0.03	7.04±0.21
CHEMBL39221	23.90±4.51	-43.25±2.62	59.72±1.23	-2.45±0.02	-15.24±0.06	53.16±2.08

Table S4. Calculated individual energy terms of mGluR8 ligands using MM-GBSA (GB2 model) method in kcal/mol.

Ligands	ΔE_{vdw}	ΔE_{ele}	ΔG_{p}^{sol}	ΔG_{np}^{sol}	$T\Delta S$	$\Delta G_{MM/GBSA}$
CHEMBL33567	-15.58±1.41	-193.72±3.21	111.18±1.42	-3.62±0.00	-18.74±0.08	-83.01±1.70
CHEMBL575060	-14.22±0.45	-196.08±2.21	126.15±2.04	-3.45±0.01	-18.20±0.05	-69.41±3.87
CHEMBL275079	-17.37±0.82	-167.31±3.44	103.09±3.13	-3.26±0.01	-18.42±0.04	-66.43±3.36
CHEMBL280563	-15.06±0.49	-167.10±0.52	106.11±1.23	-3.18±0.02	-18.10±0.02	-61.12±1.43
CHEMBL432038	-43.87±0.78	-132.23±0.86	97.81±2.74	-5.63±0.03	-23.41±0.02	-60.50±1.27
CHEMBL88999	-19.59±0.68	-151.13±3.37	102.01±1.21	-3.28±0.02	-18.71±0.08	-53.28±2.44
CHEMBL8759	-16.48±0.85	-183.68±3.03	137.84±3.47	-3.40±0.03	-18.31±0.09	-47.40±1.93
CHEMBL39338	-43.79±1.08	-124.77±1.29	106.13±1.34	-6.51±0.02	-23.28±0.10	-45.67±1.52
CHEMBL330097	-14.30±0.62	-185.25±2.00	153.02±2.52	-3.26±0.03	-18.00±0.03	-31.79±1.45
CHEMBL34453	-18.50±0.75	-152.12±1.75	137.36±2.70	-3.40±0.00	-18.13±0.08	-18.53±0.60
CHEMBL40123	-31.82±0.61	-97.29±2.15	103.04±2.26	-4.92±0.07	-19.97±0.20	-11.02±0.50
CHEMBL277475	-14.06±0.68	-213.18±8.47	203.60±7.53	-3.78±0.04	-17.31±0.08	-10.12±1.00
CHEMBL66654	-36.56±0.54	-8.44±0.24	23.28±0.65	-4.41±0.05	-18.29±0.13	-7.84±0.96
CHEMBL88612	-30.25±0.41	-7.01±0.13	19.29±0.44	-4.25±0.02	-17.70±0.03	-4.52±0.56
CHEMBL327783	-24.25±0.41	-16.68±0.89	27.79±1.08	-2.97±0.07	-16.01±0.12	-0.10±0.61
CHEMBL1672288	-28.80±0.07	-14.61±0.21	29.88±0.20	-4.12±0.04	-17.71±0.09	0.05±0.13
CHEMBL229429	-17.57±0.86	-2.73±0.39	11.88±0.15	-2.55±0.10	-15.07±0.20	4.10±0.52
CHEMBL40086	-19.04±0.35	-88.77±2.17	101.13±2.50	-3.30±0.02	-16.58±0.05	6.61±0.44
CHEMBL88553	-5.95±0.11	-3.28±0.91	6.88±0.88	-0.81±0.01	-11.66±0.03	8.49±0.18
CHEMBL39221	23.90±4.51	-43.25±2.62	75.51±2.46	-2.45±0.02	-15.24±0.06	68.96±3.66

Table S5. Calculated individual energy terms of mGluR8 ligands using MM-GBSA (GB5 model) method in kcal/mol.

Ligands	ΔE_{vdw}	ΔE_{ele}	ΔG_{p}^{sol}	ΔG_{np}^{sol}	$T\Delta S$	$\Delta G_{MM/GBSA}$
CHEMBL33567	-15.58±1.41	-193.72±3.21	93.29±2.88	-3.62±0.00	-18.74±0.08	-100.89±3.07
CHEMBL280563	-15.06±0.49	-167.10±0.52	81.61±1.89	-3.18±0.02	-18.10±0.02	-85.62±2.62
CHEMBL575060	-14.22±0.45	-196.08±2.21	111.73±5.79	-3.45±0.01	-18.20±0.05	-83.83±7.57
CHEMBL275079	-17.37±0.82	-167.31±3.44	87.51±8.50	-3.26±0.01	-18.42±0.04	-82.01±8.83
CHEMBL88999	-19.59±0.68	-151.13±3.37	101.08±4.99	-3.28±0.02	-18.71±0.08	-54.21±5.78
CHEMBL432038	-43.87±0.78	-132.23±0.86	104.67±5.07	-5.63±0.03	-23.41±0.02	-53.64±3.73
CHEMBL39338	-43.79±1.08	-124.77±1.29	108.92±3.69	-6.51±0.02	-23.28±0.10	-42.88±3.86
CHEMBL8759	-16.48±0.85	-183.68±3.03	149.62±5.79	-3.40±0.03	-18.31±0.09	-35.63±3.99
CHEMBL277475	-14.06±0.68	-213.18±8.47	211.55±7.01	-3.78±0.04	-17.31±0.08	-2.17±1.78
CHEMBL34453	-18.50±0.75	-152.12±1.75	161.47±3.39	-3.40±0.00	-18.13±0.08	5.58±2.36
CHEMBL330097	-14.30±0.62	-185.25±2.00	190.55±4.28	-3.26±0.03	-18.00±0.03	5.74±3.40
CHEMBL66654	-36.56±0.54	-8.44±0.24	37.47±1.90	-4.41±0.05	-18.29±0.13	6.35±2.22
CHEMBL88612	-30.25±0.41	-7.01±0.13	32.83±1.23	-4.25±0.02	-17.70±0.03	9.02±1.21
CHEMBL88553	-5.95±0.11	-3.28±0.91	8.52±1.10	-0.81±0.01	-11.66±0.03	10.14±0.33
CHEMBL229429	-17.57±0.86	-2.73±0.39	20.12±1.17	-2.55±0.10	-15.07±0.20	12.33±1.11
CHEMBL327783	-24.25±0.41	-16.68±0.89	41.27±1.58	-2.97±0.07	-16.01±0.12	13.38±1.53
CHEMBL40123	-31.82±0.61	-97.29±2.15	130.30±3.76	-4.92±0.07	-19.97±0.20	16.24±2.43
CHEMBL1672288	-28.80±0.07	-14.61±0.21	46.54±0.23	-4.12±0.04	-17.71±0.09	16.72±0.10
CHEMBL40086	-19.04±0.35	-88.77±2.17	149.35±3.53	-3.30±0.02	-16.58±0.05	54.82±1.51
CHEMBL39221	23.90±4.51	-43.25±2.62	102.98±7.04	-2.45±0.02	-15.24±0.06	96.42±8.58

Table S6. Calculated individual energy terms of mGluR4 ligands using MM-PBSA (PB model) method in kcal/mol.

Ligands	ΔE_{vdw}	ΔE_{ele}	ΔG_{p}^{sol}	ΔG_{np}^{sol}	$T\Delta S$	$\Delta G_{MM/PBSA}$
CHEMBL33567	-21.93±1.06	-232.70±2.95	199.11±1.69	-1.36±0.00	-19.02±0.01	-37.85±1.50
CHEMBL39573	-25.26±0.27	-199.86±1.36	178.55±1.88	-2.08±0.01	-19.51±0.06	-29.14±0.28
CHEMBL8759	-17.78±0.56	-228.11±1.43	200.12±1.14	-1.50±0.01	-18.55±0.03	-28.72±0.66
CHEMBL230951	-20.71±0.99	-213.19±0.86	188.30±1.85	-1.30±0.01	-18.72±0.08	-28.18±0.30
CHEMBL275079	-17.09±0.84	-237.98±2.30	212.15±0.70	-1.40±0.01	-18.22±0.04	-26.09±0.95
CHEMBL90501	-19.31±0.37	-215.64±3.31	193.31±2.45	-1.38±0.01	-18.49±0.05	-24.53±0.82
CHEMBL40086	-20.07±0.35	-236.90±2.25	215.86±2.02	-1.26±0.01	-18.30±0.08	-24.07±2.27
CHEMBL329236	-19.01±0.83	-356.81±4.84	334.49±4.16	-1.68±0.01	-19.45±0.07	-23.57±0.48
CHEMBL34453	-21.29±0.28	-206.49±2.98	187.32±2.47	-1.38±0.01	-18.45±0.06	-23.39±1.24
CHEMBL575060	-14.36±1.03	-223.63±2.17	199.61±1.96	-1.22±0.01	-18.17±0.06	-21.43±0.92
CHEMBL432038	-33.74±1.91	-230.74±4.65	227.35±3.65	-3.10±0.01	-22.32±0.09	-17.90±1.46
CHEMBL40123	-35.84±1.92	-195.14±1.60	198.24±1.02	-3.31±0.01	-22.57±0.10	-13.48±0.77
CHEMBL39338	-44.27±0.89	-190.38±3.58	206.29±1.70	-4.06±0.02	-23.37±0.10	-9.04±1.25
CHEMBL315032	-18.81±0.33	-191.83±2.72	186.17±1.87	-1.66±0.03	-17.31±0.16	-8.84±0.65
CHEMBL297150	-18.47±0.48	-183.22±4.26	178.12±3.53	-1.45±0.02	-17.05±0.04	-7.97±0.89
CHEMBL313938	-17.03±0.24	-175.06±3.54	169.43±2.93	-1.95±0.01	-16.80±0.11	-7.80±0.45
CHEMBL279838	-18.67±0.95	-194.44±1.17	188.98±1.31	-1.58±0.02	-18.69±0.09	-7.02±0.92
CHEMBL2021372	-14.45±0.40	-220.56±0.91	215.45±2.14	-2.12±0.01	-16.97±0.04	-4.71±1.17
CHEMBL277475	-15.43±0.45	-331.32±5.32	330.65±4.39	-2.12±0.00	-17.10±0.04	-1.12±1.32
CHEMBL280563	-14.45±0.99	-167.57±0.96	165.98±1.35	-1.38±0.00	-16.39±0.02	-1.02±0.53
CHEMBL444718	-10.02±1.27	-184.31±0.94	181.13±1.53	-1.52±0.08	-14.79±0.22	0.08±0.70
CHEMBL279956	-19.12±0.93	-76.75±1.57	81.81±1.49	-1.49±0.02	-17.00±0.11	1.45±0.64
CHEMBL448885	-11.20±1.13	-232.27±1.57	231.74±2.68	-2.00±0.04	-16.70±0.10	2.96±0.38
CHEMBL2114109	-17.44±0.62	-186.44±1.36	192.73±3.76	-2.16±0.02	-17.17±0.19	3.86±2.04
CHEMBL2115159	-19.42±1.13	-159.87±6.09	168.24±4.32	-2.25±0.05	-17.64±0.17	4.34±1.32
CHEMBL2114110	-22.20±0.57	-128.25±2.94	140.13±2.60	-2.06±0.03	-16.78±0.29	4.40±1.33
CHEMBL88184	-23.89±1.07	-108.59±2.74	119.98±2.15	-1.46±0.02	-18.59±0.04	4.64±0.50
CHEMBL284895	-16.89±0.29	-109.56±1.11	116.03±0.63	-1.36±0.00	-17.19±0.06	5.41±1.03
CHEMBL389558	-13.26±0.57	-208.25±3.20	212.96±4.38	-1.37±0.05	-15.48±0.11	5.56±1.96
CHEMBL330097	-16.57±0.67	-140.19±4.01	148.15±3.09	-1.78±0.03	-16.05±0.07	5.68±0.61
CHEMBL2114106	-21.05±0.26	-170.15±3.95	182.61±2.16	-2.19±0.03	-17.36±0.09	6.59±1.75
CHEMBL1672288	-34.56±0.72	-18.41±0.31	42.85±0.70	-2.41±0.01	-20±0.15	7.47±0.51
CHEMBL467234	-26.10±0.32	-191.63±2.05	208.71±1.83	-2.14±0.03	-19.51±0.14	8.34±1.75
CHEMBL126608	-26.80±0.55	-94.66±2.71	112.63±1.99	-1.75±0.00	-18.94±0.06	8.36±0.27
CHEMBL229429	-36.06±0.27	-4.98±0.67	33.51±1.02	-2.87±0.00	-18.88±0.07	8.47±0.32
CHEMBL327783	-29.38±0.42	-9.35±1.66	32.94±1.46	-2.49±0.02	-17.1±0.17	8.82±0.20
CHEMBL305406	-46.77±0.67	-6.21±0.36	44.57±0.61	-3.39±0.02	-22.43±0.13	10.62±0.99

Table S7. Calculated individual energy terms of mGluR4 ligands using MM-GBSA (GB1 model) method in kcal/mol.

Ligands	ΔE_{vdw}	ΔE_{ele}	ΔG_{p}^{sol}	ΔG_{np}^{sol}	$T\Delta S$	$\Delta G_{MM/GBSA}$
CHEMBL33567	-21.93±1.06	-232.70±2.95	160.29±1.17	-3.85±0.02	-19.02±0.01	-79.18±1.58
CHEMBL39573	-25.26±0.27	-199.86±1.36	137.94±2.32	-4.10±0.01	-19.51±0.06	-71.77±0.95
CHEMBL432038	-33.74±1.91	-230.74±4.65	176.14±1.86	-5.50±0.00	-22.32±0.09	-71.52±1.74
CHEMBL39338	-44.27±0.89	-190.38±3.58	146.85±2.00	-6.67±0.06	-23.37±0.10	-71.09±0.99
CHEMBL279838	-18.67±0.95	-194.44±1.17	128.65±1.26	-3.92±0.02	-18.69±0.09	-69.69±1.33
CHEMBL230951	-20.71±0.99	-213.19±0.86	149.98±2.04	-3.94±0.03	-18.72±0.08	-69.14±0.62
CHEMBL40123	-35.84±1.92	-195.14±1.60	146.24±1.15	-5.92±0.06	-22.57±0.10	-68.10±0.67
CHEMBL329236	-19.01±0.83	-356.81±4.84	293.73±3.23	-4.08±0.05	-19.45±0.07	-66.73±1.01
CHEMBL8759	-17.78±0.56	-228.11±1.43	165.28±2.12	-3.49±0.02	-18.55±0.03	-65.55±1.02
CHEMBL90501	-19.31±0.37	-215.64±3.31	154.51±2.89	-3.33±0.02	-18.49±0.05	-65.29±0.83
CHEMBL40086	-20.07±0.35	-236.90±2.25	177.70±1.73	-3.32±0.02	-18.30±0.08	-64.29±1.85
CHEMBL275079	-17.09±0.84	-237.98±2.30	177.29±1.15	-3.39±0.03	-18.22±0.04	-62.95±0.60
CHEMBL34453	-21.29±0.28	-206.49±2.98	152.66±2.81	-3.39±0.01	-18.45±0.06	-60.06±1.28
CHEMBL575060	-14.36±1.03	-223.63±2.17	164.04±2.35	-3.65±0.01	-18.17±0.06	-59.43±0.69
CHEMBL467234	-26.10±0.32	-191.63±2.05	159.21±1.10	-4.36±0.03	-19.51±0.14	-43.37±0.66
CHEMBL88184	-23.89±1.07	-108.59±2.74	79.30±1.83	-3.76±0.01	-18.59±0.04	-38.34±0.26
CHEMBL2021372	-14.45±0.40	-220.56±0.91	183.82±1.29	-3.32±0.02	-16.97±0.04	-37.54±0.67
CHEMBL277475	-15.43±0.45	-331.32±5.32	295.90±3.36	-3.72±0.03	-17.10±0.04	-37.47±1.66
CHEMBL315032	-18.81±0.33	-191.83±2.72	160.50±1.86	-3.28±0.07	-17.31±0.16	-36.12±0.87
CHEMBL297150	-18.47±0.48	-183.22±4.26	151.98±3.08	-3.21±0.03	-17.05±0.04	-35.88±1.22
CHEMBL126608	-26.80±0.55	-94.66±2.71	70.72±1.30	-3.83±0.04	-18.94±0.06	-35.63±0.86
CHEMBL2115159	-19.42±1.13	-159.87±6.09	134.79±4.67	-3.77±0.06	-17.64±0.17	-30.64±0.67
CHEMBL284895	-16.89±0.29	-109.56±1.11	82.07±0.20	-3.16±0.02	-17.19±0.06	-30.35±1.01
CHEMBL448885	-11.20±1.13	-232.27±1.57	200.01±2.90	-3.14±0.05	-16.70±0.10	-29.90±1.04
CHEMBL280563	-14.45±0.99	-167.57±0.96	138.88±0.71	-2.98±0.03	-16.39±0.02	-29.72±0.24
CHEMBL313938	-17.03±0.24	-175.06±3.54	151.40±2.71	-3.37±0.03	-16.80±0.11	-27.25±1.69
CHEMBL2114109	-17.44±0.62	-186.44±1.36	165.99±2.79	-3.77±0.06	-17.17±0.19	-24.48±1.02
CHEMBL2114106	-21.05±0.26	-170.15±3.95	153.59±3.17	-3.84±0.04	-17.36±0.09	-24.08±0.80
CHEMBL279956	-19.12±0.93	-76.75±1.57	58.65±1.14	-3.20±0.04	-17.00±0.11	-23.43±0.70
CHEMBL389558	-13.26±0.57	-208.25±3.20	185.87±2.28	-2.97±0.06	-15.48±0.11	-23.13±1.56
CHEMBL444718	-10.02±1.27	-184.31±0.94	161.89±0.55	-2.46±0.08	-14.79±0.22	-20.11±0.47
CHEMBL305406	-46.77±0.67	-6.21±0.36	16.80±0.20	-5.63±0.05	-22.43±0.13	-19.39±0.69
CHEMBL2114110	-22.20±0.57	-128.25±2.94	121.53±2.47	-3.42±0.05	-16.78±0.29	-15.57±1.07
CHEMBL1672288	-34.56±0.72	-18.41±0.31	25.24±0.11	-5.10±0.05	-20.00±0.15	-12.83±0.43
CHEMBL229429	-36.06±0.27	-4.98±0.67	14.21±0.42	-4.80±0.02	-18.88±0.07	-12.75±0.37
CHEMBL330097	-16.57±0.67	-140.19±4.01	135.00±2.98	-2.86±0.03	-16.05±0.07	-8.55±0.76
CHEMBL327783	-29.38±0.42	-9.35±1.66	16.89±0.95	-3.72±0.05	-17.10±0.17	-8.45±0.80

Table S8. Calculated individual energy terms of mGluR4 ligands using MM-GBSA (GB2 model) method in kcal/mol.

Ligands	ΔE_{vdw}	ΔE_{ele}	ΔG_{p}^{sol}	ΔG_{np}^{sol}	$T\Delta S$	$\Delta G_{MM/GBSA}$
CHEMBL33567	-21.93±1.06	-232.70±2.95	146.29±2.65	-3.85±0.02	-19.02±0.01	-93.17±2.07
CHEMBL230951	-20.71±0.99	-213.19±0.86	141.13±2.33	-3.94±0.03	-18.72±0.08	-77.99±0.68
CHEMBL39573	-25.26±0.27	-199.86±1.36	138.58±2.49	-4.10±0.01	-19.51±0.06	-71.12±0.89
CHEMBL39338	-44.27±0.89	-190.38±3.58	151.90±2.78	-6.67±0.06	-23.37±0.10	-66.05±0.47
CHEMBL432038	-33.74±1.91	-230.74±4.65	186.11±2.97	-5.50±0.00	-22.32±0.09	-61.55±1.33
CHEMBL329236	-19.01±0.83	-356.81±4.84	302.15±4.07	-4.08±0.05	-19.45±0.07	-58.31±0.26
CHEMBL8759	-17.78±0.56	-228.11±1.43	172.99±2.20	-3.49±0.02	-18.55±0.03	-57.85±1.25
CHEMBL275079	-17.09±0.84	-237.98±2.30	187.42±1.16	-3.39±0.03	-18.22±0.04	-52.81±2.14
CHEMBL575060	-14.36±1.03	-223.63±2.17	175.05±2.95	-3.65±0.01	-18.17±0.06	-48.42±1.62
CHEMBL90501	-19.31±0.37	-215.64±3.31	172.76±4.19	-3.33±0.02	-18.49±0.05	-47.04±2.80
CHEMBL40123	-35.84±1.92	-195.14±1.60	168.96±1.43	-5.92±0.06	-22.57±0.10	-45.38±0.38
CHEMBL279838	-18.67±0.95	-194.44±1.17	158.26±0.43	-3.92±0.02	-18.69±0.09	-40.08±1.98
CHEMBL34453	-21.29±0.28	-206.49±2.98	174.41±4.74	-3.39±0.01	-18.45±0.06	-38.31±3.72
CHEMBL389558	-13.26±0.57	-208.25±3.20	180.14±2.14	-2.97±0.06	-15.48±0.11	-28.86±3.52
CHEMBL40086	-20.07±0.35	-236.90±2.25	214.95±1.34	-3.32±0.02	-18.30±0.08	-27.04±1.44
CHEMBL280563	-14.45±0.99	-167.57±0.96	144.20±1.08	-2.98±0.03	-16.39±0.02	-24.40±0.58
CHEMBL277475	-15.43±0.45	-331.32±5.32	310.05±2.68	-3.72±0.03	-17.10±0.04	-23.32±2.40
CHEMBL2115159	-19.42±1.13	-159.87±6.09	144.68±5.83	-3.77±0.06	-17.64±0.17	-20.75±0.73
CHEMBL313938	-17.03±0.24	-175.06±3.54	159.58±3.56	-3.37±0.03	-16.80±0.11	-19.07±3.31
CHEMBL2114106	-21.05±0.26	-170.15±3.95	159.87±2.88	-3.84±0.04	-17.36±0.09	-17.80±1.55
CHEMBL2114109	-17.44±0.62	-186.44±1.36	174.33±2.74	-3.77±0.06	-17.17±0.19	-16.13±1.10
CHEMBL467234	-26.10±0.32	-191.63±2.05	187.25±1.78	-4.36±0.03	-19.51±0.14	-15.33±0.53
CHEMBL2021372	-14.45±0.40	-220.56±0.91	206.45±2.14	-3.32±0.02	-16.97±0.04	-14.91±1.25
CHEMBL88184	-23.89±1.07	-108.59±2.74	105.11±2.38	-3.76±0.01	-18.59±0.04	-12.53±1.24
CHEMBL2114110	-22.20±0.57	-128.25±2.94	124.75±1.86	-3.42±0.05	-16.78±0.29	-12.35±1.28
CHEMBL315032	-18.81±0.33	-191.83±2.72	186.82±1.51	-3.28±0.07	-17.31±0.16	-9.80±1.21
CHEMBL297150	-18.47±0.48	-183.22±4.26	181.69±3.95	-3.21±0.03	-17.05±0.04	-6.17±1.03
CHEMBL284895	-16.89±0.29	-109.56±1.11	106.63±0.96	-3.16±0.02	-17.19±0.06	-5.79±0.89
CHEMBL1672288	-34.56±0.72	-18.41±0.31	34.32±0.44	-5.10±0.05	-20.00±0.15	-3.74±0.27
CHEMBL229429	-36.06±0.27	-4.98±0.67	25.03±0.91	-4.80±0.02	-18.88±0.07	-1.94±0.26
CHEMBL448885	-11.20±1.13	-232.27±1.57	229.62±3.85	-3.14±0.05	-16.70±0.10	-0.29±1.80
CHEMBL444718	-10.02±1.27	-184.31±0.94	181.99±0.46	-2.46±0.08	-14.79±0.22	0.00±0.70
CHEMBL279956	-19.12±0.93	-76.75±1.57	82.68±1.78	-3.20±0.04	-17.00±0.11	0.61±0.64
CHEMBL126608	-26.80±0.55	-94.66±2.71	107.54±4.03	-3.83±0.04	-18.94±0.06	1.19±2.02
CHEMBL305406	-46.77±0.67	-6.21±0.36	38.03±1.04	-5.63±0.05	-22.43±0.13	1.84±0.75
CHEMBL330097	-16.57±0.67	-140.19±4.01	146.84±3.05	-2.86±0.03	-16.05±0.07	3.29±1.51
CHEMBL327783	-29.38±0.42	-9.35±1.66	36.45±1.03	-3.72±0.05	-17.10±0.17	11.11±1.55

Table S9. Calculated individual energy terms of mGluR4 ligands using MM-GBSA (GB5 model) method in kcal/mol.

Ligands	ΔE_{vdw}	ΔE_{ele}	ΔG_{p}^{sol}	ΔG_{np}^{sol}	$T\Delta S$	$\Delta G_{MM/GBSA}$
CHEMBL33567	-21.93±1.06	-232.70±2.95	115.87±4.90	-3.85±0.02	-19.02±0.01	-123.59±5.41
CHEMBL230951	-20.71±0.99	-213.19±0.86	114.61±2.55	-3.94±0.03	-18.72±0.08	-104.51±1.12
CHEMBL39573	-25.26±0.27	-199.86±1.36	124.84±6.70	-4.10±0.01	-19.51±0.06	-84.86±5.18
CHEMBL39338	-44.27±0.89	-190.38±3.58	151.47±3.08	-6.67±0.06	-23.37±0.10	-66.47±1.10
CHEMBL8759	-17.78±0.56	-228.11±1.43	165.85±3.20	-3.49±0.02	-18.55±0.03	-64.99±2.66
CHEMBL329236	-19.01±0.83	-356.81±4.84	307.27±5.57	-4.08±0.05	-19.45±0.07	-53.19±2.27
CHEMBL432038	-33.74±1.91	-230.74±4.65	196.76±3.12	-5.50±0.00	-22.32±0.09	-50.90±1.49
CHEMBL275079	-17.09±0.84	-237.98±2.30	192.62±3.44	-3.39±0.03	-18.22±0.04	-47.62±4.74
CHEMBL389558	-13.26±0.57	-208.25±3.20	165.30±5.42	-2.97±0.06	-15.48±0.11	-43.70±7.57
CHEMBL90501	-19.31±0.37	-215.64±3.31	180.30±7.65	-3.33±0.02	-18.49±0.05	-39.49±6.73
CHEMBL575060	-14.36±1.03	-223.63±2.17	186.37±5.85	-3.65±0.01	-18.17±0.06	-37.11±4.96
CHEMBL34453	-21.29±0.28	-206.49±2.98	186.44±9.46	-3.39±0.01	-18.45±0.06	-26.28±8.55
CHEMBL40123	-35.84±1.92	-195.14±1.60	197.99±2.40	-5.92±0.06	-22.57±0.10	-16.34±0.69
CHEMBL277475	-15.43±0.45	-331.32±5.32	319.34±2.05	-3.72±0.03	-17.10±0.04	-14.03±4.31
CHEMBL280563	-14.45±0.99	-167.57±0.96	160.20±1.37	-2.98±0.03	-16.39±0.02	-8.40±1.39
CHEMBL2114110	-22.20±0.57	-128.25±2.94	133.54±1.31	-3.42±0.05	-16.78±0.29	-3.56±1.78
CHEMBL2114106	-21.05±0.26	-170.15±3.95	174.73±2.38	-3.84±0.04	-17.36±0.09	-2.94±4.01
CHEMBL2115159	-19.42±1.13	-159.87±6.09	164.16±9.06	-3.77±0.06	-17.64±0.17	-1.27±4.03
CHEMBL279838	-18.67±0.95	-194.44±1.17	200.11±0.71	-3.92±0.02	-18.69±0.09	1.77±1.80
CHEMBL2114109	-17.44±0.62	-186.44±1.36	193.82±2.41	-3.77±0.06	-17.17±0.19	3.35±1.31
CHEMBL313938	-17.03±0.24	-175.06±3.54	183.98±6.68	-3.37±0.03	-16.80±0.11	5.32±6.41
CHEMBL40086	-20.07±0.35	-236.90±2.25	248.59±1.58	-3.32±0.02	-18.30±0.08	6.60±3.30
CHEMBL1672288	-34.56±0.72	-18.41±0.31	52.55±1.28	-5.10±0.05	-20.00±0.15	14.48±1.05
CHEMBL467234	-26.10±0.32	-191.63±2.05	218.49±2.47	-4.36±0.03	-19.51±0.14	15.91±0.78
CHEMBL229429	-36.06±0.27	-4.98±0.67	47.41±1.92	-4.80±0.02	-18.88±0.07	20.44±1.24
CHEMBL88184	-23.89±1.07	-108.59±2.74	140.98±3.94	-3.76±0.01	-18.59±0.04	23.34±3.83
CHEMBL315032	-18.81±0.33	-191.83±2.72	229.51±1.16	-3.28±0.07	-17.31±0.16	32.89±2.39
CHEMBL297150	-18.47±0.48	-183.22±4.26	222.63±5.02	-3.21±0.03	-17.05±0.04	34.77±4.56
CHEMBL284895	-16.89±0.29	-109.56±1.11	147.24±2.06	-3.16±0.02	-17.19±0.06	34.82±1.51
CHEMBL330097	-16.57±0.67	-140.19±4.01	178.49±3.68	-2.86±0.03	-16.05±0.07	34.94±2.13
CHEMBL279956	-19.12±0.93	-76.75±1.57	122.21±2.56	-3.20±0.04	-17.00±0.11	40.14±1.04
CHEMBL2021372	-14.45±0.40	-220.56±0.91	262.66±3.37	-3.32±0.02	-16.97±0.04	41.30±2.26
CHEMBL444718	-10.02±1.27	-184.31±0.94	224.90±0.79	-2.46±0.08	-14.79±0.22	42.91±0.77
CHEMBL305406	-46.77±0.67	-6.21±0.36	82.51±2.69	-5.63±0.05	-22.43±0.13	46.32±2.13
CHEMBL327783	-29.38±0.42	-9.35±1.66	77.08±2.63	-3.72±0.05	-17.10±0.17	51.74±3.59
CHEMBL126608	-26.80±0.55	-94.66±2.71	161.36±8.29	-3.83±0.04	-18.94±0.06	55.01±6.23
CHEMBL448885	-11.20±1.13	-232.27±1.57	288.72±5.20	-3.14±0.05	-16.70±0.10	58.81±3.11