Supporting Information

Estimation of ligand efficacies of metabotropic glutamate receptors from conformational forces obtained from molecular dynamics simulations

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Validation of Ligand Parameters

All ligands were initially constructed based on the internal coordinates in CGenFF [1] and assigned physiologically pertinent protonation states consistent with neutral pH. CGenFF parameters are assigned based on analogy between the atoms of the ligands and previously optimized parameters of similar atom types.[2, 3] The accuracy of the prediction is scored with a penalty number. These penalty scores for all the parameters of all the ligands used in the study were low (less than 10) indicating the analogy is satisfactory, requiring little or no further optimization as recommended by the CGenFF protocol. This was expected as the functionalities in the studied ligands are common to amino acids as well as drug-like molecules and therefore well represented in CGenFF. However, the MM parameters for DHPG, and ACPT-II were validated targeting QM vibrational spectra, geometries and potential energy surfaces. [4]

VIBRATIONAL SPECTRA

The quantum mechanical (QM) target vibrational frequency spectra for the ligands were calculated after an MP2/6-31G* level geometry optimization of the ligands with tight tolerances. This MP2/6-31G* vibrational spectrum was sufficiently well reproduced by the molecular mechanical (MM) model using the CGenFF bond, valence angle, Urey-Bradley, improper and torsion force constant parameters. The QM F-matrix is scaled by a factor of 0.89, which corresponds to scaling all frequencies by a factor 0.943 [5] and a symbolic potential energy distribution (PED) analysis was performed in the local internal valence coordinate space proposed by Pulay et al [6]. The PED analysis in MM was performed using the MOLVIB [7] module in CHARMM. [8] Equilibrium geometry and vibrational spectra for DHPG and ACPT-II are shown in Table S1. MM and MP2/6-31G* level equilibrium geometry of DHPG.Table S1, Table S2, Table S3 and Table S4, respectively.

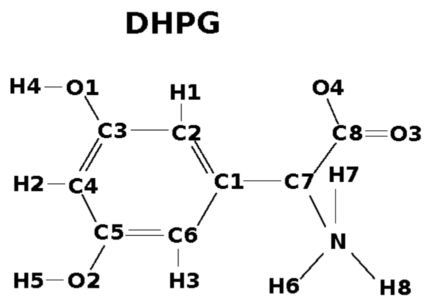

Figure S1. Atom Numbering for DHPG

Table S1. MM and MP2/6-31G* level equilibrium geometry of DHPG.

Coordinate	QM	MM	Difference
Bonds			
C1-C2	1.401	1.413	0.012
C1-C6	1.397	1.412	0.015
C1-C7	1.500	1.501	0.001
C2-C3	1.397	1.396	-0.001
C2-H1	1.090	1.081	-0.008
C3-C4	1.395	1.396	0.001
C3-O1	1.370	1.395	0.025
C4-C5	1.394	1.396	0.003
C4-H2	1.085	1.080	-0.005
C5-C6	1.399	1.399	0.000
C5-O2	1.372	1.407	0.034
C6-H3	1.090	1.079	-0.010
H1-O3	2.506	2.507	0.001
O1-H4	0.974	0.960	-0.014
O2-H5	0.974	0.958	-0.015
C7-N	1.516	1.474	-0.042
C7-H9	1.092	1.112	0.020
C7-C8	1.582	1.537	-0.044
C8-O3	1.285	1.264	-0.021
C8-O4	1.233	1.249	0.016
Angles			
C2-C1-C6	120.6	118.5	-2.0
C2-C1-C7	118.5	121.7	3.2
C6-C1-C7	120.8	119.7	-1.1
C1-C2-C3	119.1	120.6	1.5
C1-C2-H1	119.5	119.6	0.1
C3-C2-H1	121.3	119.8	-1.4
C2-C3-C4	121.0	120.2	-0.8
C2-C3-O1	122.5	119.8	-2.7
C4-C3-O1	116.5	120.0	3.4
C3-C4-C5	119.2	119.9	0.8

C3-C4-H2	120.4	119.9	-0.5
C5-C4-H2	120.4	120.1	-0.3
C4-C5-C6	120.8	120.2	-0.6
C4-C5-O2	116.6	119.5	2.9
C6-C5-O2	122.6	120.3	-2.3
C1-C6-C5	119.3	120.4	1.2
C1-C6-H3	120.2	119.9	-0.3
C5-C6-H3	120.5	119.6	-0.9
C3-O1-H4	108.4	107.6	-0.8
C5-O2-H5	108.6	108.4	-0.2
C1-C7-N	108.6	108.3	-0.3
C1-C7-H9	112.3	111.8	-0.4
C1-C7-C8	111.5	111.8	0.3
N-C7-H9	109.7	108.6	-1.1
N-C7-C8	102.9	104.4	1.5
H9-C7-C8	111.5	110.7	-0.8
C7-N-H6	96.7	99.6	2.9
C7-N-H7	113.4	113.4	0.0
C7-N-H8	113.1	112.0	-1.2
H6-N-H7	113.9	111.1	-2.8
H6-N-H8	109.4	108.8	-0.7
H7-N-H8	109.7	110.1	0.3
C7-C8-O3	111.0	112.2	1.2
C7-C8-O4	116.3	117.4	1.1
O3-C8-O4	132.7	131.4	-1.3
Dihedrals			
C6-C1-C2-C3	1.5	-0.6	-2.1
C6-C1-C2-H1	177.3	177.6	0.3
C7-C1-C2-C3	178.5	176.4	-2.1
C7-C1-C2-H1	-5.7	-5.3	0.3
C2-C1-C6-C5	-1.8	1.1	2.9
C2-C1-C6-H3	-179.3	-179.0	0.3
C7-C1-C6-C5	-178.7	-176.0	2.7
C7-C1-C6-H3	3.8	3.9	0.1
C2-C1-C7-N	-67.9	-64.2	3.7
C2-C1-C7-H9	170.7	169.3	-1.4
C2-C1-C7-C8	44.8	46.5	1.7
C6-C1-C7-N	109.1	107.8	-1.3
C6-C1-C7-H9	-12.3	-13.7	-1.4
C6-C1-C7-C8	-138.3	-136.5	1.8
C1-C2-C3-C4	-1.5	-0.8	0.7
C1-C2-C3-O1	179.1	179.1	0.0
H1-C2-C3-C4	-177.3	-179.0	-1.7
H1-C2-C3-O1	3.3	0.8	-2.5
C2-C3-C4-C5	1.9	1.8	-0.1
C2-C3-C4-H2	179.2	-180.0	0.8
O1-C3-C4-C5	-178.7	-178.0	0.7
O1-C3-C4-H2	-1.4	0.2	1.6
C2-C3-O1-H4	-6.7	-8.9	-2.1
C4-C3-O1-H4	173.8	173.0	-0.9

C3-C4-C5-C6	-2.2	-1.4	0.8
C3-C4-C5-O2	179.1	178.9	-0.2
H2-C4-C5-C6	-179.5	-179.6	-0.1
H2-C4-C5-O2	1.8	0.7	-1.1
C4-C5-C6-C1	2.2	-0.1	-2.2
C4-C5-C6-H3	179.7	-180.0	0.3
O2-C5-C6-C1	-179.2	179.7	0.5
O2-C5-C6-H3	-1.7	-0.2	1.4
C4-C5-O2-H5	-175.1	-174.5	0.6
C6-C5-O2-H5	6.2	8.8	2.6
C1-C7-N-H6	101.3	104.6	3.4
C1-C7-N-H7	-18.4	-17.2	1.2
C1-C7-N-H8	-144.2	-140.5	3.7
H9-C7-N-H6	-135.7	-136.5	-0.8
H9-C7-N-H7	104.6	101.6	-3.0
H9-C7-N-H8	-21.2	-22.3	-1.1
C8-C7-N-H6	-17.0	-18.4	-1.4
C8-C7-N-H7	-136.7	136.5	-0.1
C8-C7-N-H8	97.5	-95.7	-1.8
C1-C7-C8-O3	-97.0	-95.7	-1.2
C1-C7-C8-O4	80.5	80.8	0.3
N-C7-C8-O3	19.2	17.3	-1.9
N-C7-C8-O4	-163.3	164.3	0.9
H9-C7-C8-O3	136.7	134.4	-2.2
H9-C7-C8-O4	-45.9	-46.0	-0.1

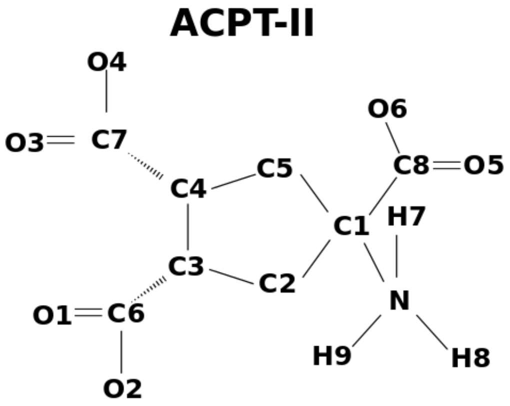

Figure S2. Atom numbering for ACPT-II.

Table S2. MM and MP2/6-31G* level equilibrium geometry of ACPT-II.

Coordinate	QM	MM	Difference
Bonds			

C1-C2	1.524	1.526	0.002
C1-C5	1.518	1.530	0.012
C1-N	1.528	1.480	-0.048
C1-C8	1.558	1.519	-0.039
C2-C3	1.545	1.562	0.017
C2-H1	1.101	1.096	-0.005
C2-H2	1.094	1.105	0.011
C3-C4	1.574	1.602	0.028
C3-H3	1.104	1.101	-0.003
C3-C6	1.571	1.514	-0.056
C4-C5	1.538	1.552	0.014
C4-C7	1.571	1.509	-0.062
C4-H4	1.105	1.101	-0.004
C5-H5	1.101	1.095	-0.006
C5-H6	1.092	1.104	0.012
C6-O1	1.265	1.266	0.001
C6-O2	1.263	1.258	-0.004
C7-O3	1.261	1.264	0.002
C7-O4	1.266	1.260	-0.006
C8-O5	1.294	1.266	-0.027
C8-O6	1.244	1.257	0.013
Angles			
C2-C1-C5	101.1	102.1	1.0
C2-C1-N	106.3	105.6	-0.7
C2-C1-C8	117.2	120.0	2.8
C5-C1-N	107.7	107.9	0.2
C5-C1-C8	120.7	120.5	-0.1
N-C1-C8	103.0	100.4	-2.5
C1-C2-C3	104.8	105.3	0.5
C1-C2-H1	113.0	115.1	2.1
C1-C2-H2	107.9	108.3	0.3
C3-C2-H1	114.3	113.0	-1.4
C3-C2-H2	108.0	109.6	1.6
H1-C2-H2	108.5	105.5	-3.0
C2-C3-C4	103.9	104.3	0.5
C2-C3-H3	110.3	107.1	-3.2
C2-C3-C6	108.3	111.5	3.2
C4-C3-H3	109.4	108.4	-1.0
C4-C3-C6	120.0	120.6	0.6
H3-C3-C6	104.9	104.9	-0.1
C3-C4-C5	105.2	104.2	-1.0
C3-C4-C7	120.5	122.8	2.3
C3-C4-H4	106.3	104.2	-2.0
C5-C4-C7	113.4	114.1	0.8
C5-C4-H4	108.5	105.8	-2.7
C7-C4-H4	102.3	101.7	-0.5
C1-C5-C4	103.7	103.9	0.2
C1-C5-H5	113.1	114.7	1.7
C1-C5-H6	109.7	109.3	-0.4

C4-C5-H5	113.9	113.2	-0.7
C4-C5-H6	109.3	109.6	0.4
H5-C5-H6	107.2	106.1	-1.1
C3-C6-O1	115.1	115.3	0.3
C3-C6-O2	114.7	117.6	2.9
O1-C6-O2	130.0	128.8	-1.1
C4-C7-O3	114.4	115.6	1.3
C4-C7-O4	115.5	117.2	1.7
O3-C7-O4	129.8	126.9	-2.9
C1-N-H7	110.6	106.8	-3.8
C1-N-H8	98.6	99.8	1.2
C1-N-H9	110.7	108.9	-1.7
H7-N-H8	116.7	115.1	-1.6
H7-N-H9	108.3	109.1	0.8
H8-N-H9	111.7	111.8	0.2
C1-C8-O5	113.6	115.7	2.0
C1-C8-O6	117.4	117.2	-0.2
O5-C8-O6	128.9	126.7	-2.2
Dihedrals			
C5-C1-C2-C3	-43.5	-40.7	2.8
C5-C1-C2-H1	-168.6	-165.8	2.8
C5-C1-C2-H2	71.4	73.5	2.0
N-C1-C2-C3	68.9	72.0	3.1
N-C1-C2-H1	-56.3	-53.1	3.1
N-C1-C2-H2	-176.2	-175.9	0.4
C8-C1-C2-C3	-176.7	-177.1	-0.4
C8-C1-C2-H1	58.2	57.8	-0.3
C8-C1-C2-H2	-61.8	-59.9	1.9
C2-C1-C5-C4	44.8	44.9	0.0
C2-C1-C5-H5	168.6	168.9	0.3
C2-C1-C5-H6	-71.8	-72.1	-0.3
N-C1-C5-C4	-66.5	-66.1	0.3
N-C1-C5-H5	57.3	58.0	0.6
N-C1-C5-H6	176.9	176.9	0.0
C8-C1-C5-C4	175.9	-179.1	3.2
C8-C1-C5-H5	-60.3	-60.0	0.2
C8-C1-C5-H6	59.3	61.9	2.6
C2-C1-N-H7	-10.6	-12.9	-2.3
C2-C1-N-H8	112.2	112.1	-0.2
C2-C1-N-H9	-130.6	-130.5	0.1
C5-C1-N-H7	97.1	92.7	-4.4
C5-C1-N-H8	-140.1	-141.4	-1.3
C5-C1-N-H9	-22.9	-21.9	1.0
C8-C1-N-H7	-134.3	-132.8	1.6
C8-C1-N-H8	-11.5	-12.9	-1.3
C8-C1-N-H9	105.6	104.6	-1.0
C2-C1-C8-O5	-107.8	-107.2	0.6
C2-C1-C8-O6	71.0	69.2	-1.9
C5-C1-C8-O5	128.4	-130.6	2.2
C5-C1-C8-O6	-52.7	-50.8	-2.0

N-C1-C8-O5	8.5	7.0	-1.4
N-C1-C8-O6	-172.7	-174.6	-1.9
C1-C2-C3-C4	25.0	22.9	-2.1
C1-C2-C3-H3	-92.1	-89.4	2.7
C1-C2-C3-C6	153.6	156.5	2.9
H1-C2-C3-C4	149.3	147.3	-2.0
H1-C2-C3-H3	32.2	33.1	0.9
H1-C2-C3-C6	-82.1	-81.1	1.0
H2-C2-C3-C4	-89.9	-91.4	-1.5
H2-C2-C3-H3	153.0	154.3	1.4
H2-C2-C3-C6	38.7	40.2	1.5
C2-C3-C4-C5	2.7	6.5	3.8
C2-C3-C4-C7	132.4	130.2	-2.2
C2-C3-C4-H4	-112.2	-114.3	-2.0
H3-C3-C4-C5	120.5	118.7	-1.8
H3-C3-C4-C7	-109.9	-107.6	2.3
H3-C3-C4-H4	5.5	7.9	2.4
C6-C3-C4-C5	-118.3	-120.1	-1.8
C6-C3-C4-C7	11.4	11.6	0.2
C6-C3-C4-H4	126.8	127.2	0.4
C2-C3-C6-O1	119.0	120.5	1.5
C2-C3-C6-O2	-56.0	-54.0	2.0
C4-C3-C6-O1	-122.2	-121.0	1.2
C4-C3-C6-O2	62.8	63.5	0.7
H3-C3-C6-O1	1.2	1.0	-0.2
H3-C3-C6-O2	-173.8	-171.5	2.3
C3-C4-C5-C1	-29.5	-31.5	-2.0
C3-C4-C5-H5	-152.8	-156.5	-3.8
C3-C4-C5-H6	87.4	85.3	-2.1
C7-C4-C5-C1	-163.2	-165.9	-2.7
C7-C4-C5-H5	73.5	74.1	0.5
C7-C4-C5-H6	-46.3	-45.1	1.2
H4-C4-C5-C1	83.9	84.1	0.2
H4-C4-C5-H5	-39.4	-38.0	1.4
H4-C4-C5-H6	-159.2	-155.1	4.0
C3-C4-C7-O3	64.5	67.0	2.5
C3-C4-C7-O4	-121.1	-122.4	-1.3
C5-C4-C7-O3	-169.6	-167.2	2.4
C5-C4-C7-O4	4.9	4.4	-0.4
H4-C4-C7-O3	-53.0	-52.8	0.2
H4-C4-C7-O4	121.5	121.9	0.4

Table S3. Scaled MP2/6-31G* and MM level vibrational spectra of DHPG[1]

QM(scaled by a factor 0.943)							MM						
Freq	Mode	%	Mode	%	Mode	%	Freq	Mode	%	Mode	%	Mode	%
26	torC7-C1	92					40.4	torC7-C1	92				
64.5	torC7-C8	70					72.8	torC7-C8	77				
95.9	dC1C7C8	36	wC1H	25			99.2	wC1H	48	dC1C7C8	15		
150.6	dC1H	32	wC1H	17			165.5	dC1H	38				
203.8	tp6RNG1	38	ta6RNG1a	21			192.2	wC5H	25	wC3H	23	ta6RNG1a	20
216.3	ta6RNG1a	24					204.6	ta6RNG1	34	wC3H	27	wC5H	27
226.4	ta6RNG1	70	ta6RNG1a	24			238.2	ta6RNG1	30	wC3H	17	wC5H	15
291	dNC7C1	23	dC5H	20	ta6RNG1a	16	273.1	dNC7C1	31	ta6RNG1a	16		
311.7	torO2-C5	97					326.5	torO2-C5	47				
325.9	dC3H	31	dC5H	18	dNC7C1	16	334.6	dC5H	22	dC3H	19		
335	dC8C7	53	dC8C7N	26			341.8	dC8C7	50				
349.4	torO1-C3	94					350.7	torO1-C3	81				
363.4	torC7-N	85					361.2	torC7-N	85				
457	sC7-C8	23	da6RNG1a	19			421.2	sC5-C6	15				
483	da6RNG1	24					466.7	da6RNG1	56	wC2H	17		
495.2	da6RNG1	51					492.2	tp6RNG1	23				
513.5	da6RNG1a	34	dC5H	15			502	da6RNG1a	24	sC3-O1	17	sC5-O2	15
526.6	tp6RNG1	45	wC5H	40	wC3H	26	526	da6RNG1	50				
553.5	dt6RNG1	16					549.6	dNC7C1	25	wC1H	20	ta6RNG1a	18

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[1] Only vibrational modes with 15% or more contributions are shown here, but if no vibrational mode for a frequency higher than 15% contribution can be found, then the one with the highest contribution is shown. Notations for the PED are: daRNG1, dt6RNG1, t6RNG1, taRNG1,tpRNG1, asymmetric deformation, trigonal deformation, torsion, asymmetric torsion, and pucker; s stands for bond stretching, ss and sa stand for group symmetric and asymmetric stretching; r for rocking, i for twisting; w for wagging; c for scissoring; tor for torsions; same notation applied for the ACPT-II table below.

562.4	wC3H	52	wC5H	37			574.6	da6RNG1a	20				
631.3	dNC7C1	27	wC1H	17			662.6	tp6RNG1	90				
683.8	dC8O3	36					711.5	dC8O3	48				
702.3	wC6H	96					837.5	dC8O3	20	sC8-O3	16		
754.6	wC8C7	36	dC8O3	19	dC1C7C8	16	878.7	wC6H	52	wC4H	30	wC2H	29
756.3	wC4H	80					889	rNH	26				
795.2	wC2H	82					902.1	dC8C7N	63				
825	sC7-C8	35					925.7	wC6H	49	wC4H	43		
877.9	sC7-N	50					927.1	wC8C7	60	rNH'	23		
965.8	dt6RNG1	22					932.1	wC2H	58	wC4H	29		
971.7	dt6RNG1	31					947.3	sC7-N	35				
977	sC3-O1	16					971.8	dt6RNG1	50				
1048.3	rNH	45	rC7H'	26			1005.4	rNH	29	rNH'	17		
1084.4	rNH'	59					1038.9	rNH'	49				
1118.3	dC4H	51					1151.1	dC5H	19				
1138.2	dC6H	31	rC7H	23			1169.3	dC6H	33	dC4H	23	dC2H	17
1171.3	iO2	38	iO1	35			1253.3	iO2	21	iO1	20		
1187.7	dC2H	24					1286.6	rC7H'	27				
1201	rC7H'	28					1289.9	dC4H	22				
1202.7	sC8-O3	48	dsNH	23			1308.4	sC8-O3	20	rC7H	19		
1277.6	dC2H	17					1348.2	dC4H	26				
1292.4	rC7H	17	dC6H	15			1361.9	dC2H	21	rC7H	18		
1327.4	dsNH	38	sC8-O3	15			1382.7	dsNH	60				
1336.9	sC3-O1	18	sC1-C7	16			1416.2	sC8-O3	15				
1410.7	sC2-C3	20	sC5-C6	18			1459.7	sC1-C2	24				
1439	sC1-C2	16					1481.1	iO2	30				
1493.2	iO2						1485	iO1	34				
1565.4	daNH	42	daNH'	36	dsNH	17	1548.2	daNH'	71				
1589.9	sC2-C3	24	sC5-C6	21			1556.4	sC1-C7	19	rC7H	19	sC6-C1	15
1601.9	daNH'	45	daNH	24			1624.9	daNH	90	daNH'	17		
1606.4	sC4-C5	16	sC3-C4	16			1633.3	sC4-C5	18	sC3-C4	15		

Freq	Mode	%	Mode	%	Mode	%	Freq	Mode	%	Mode	%	Mode	%
1748.7	sC8-O3	90					1662.8	sC8-O3	81	daNH	16		
2714	sN-H	93					2811.4	sN-H	99				
2999.5	sC7-H	99					3053.4	sC7-H	99				
3026.1	sC6-H3	99					3055.5	sC6-H3	71	sC2-H1	29		
3029.4	sC2-H1	99					3061.4	sC2-H1	66	sC6-H3	25		
3081.2	sC4-H2	99					3146.3	sC4-H2	91				
3172	sN-H	99					3253.9	sN-H	99				
3268.3	sN-H	99					3263.2	sN-H	99				
3536.2	sO1-H	99					3681.4	sO1-H	51	sO2-H	49		
3543.2	sO2-H	99					3682.8	sO2-H	51	sO1-H	49		

Table S4 Scaled MP2/6-31G* and MM level vibrational spectra of ACPT-II.

QM (scaled by a factor of 0.943)							MM						
Freq	Mode	%	Mode	%	Mode	%	Freq	Mode	%	Mode	%	Mode	%
27.9	torC8-C1	33	t5RNG1	21			25.4	torC8-C1	29	ssC1H2	27	torC7-C4	20
45.7	torC7-C4	61	torC6-C3	19			38.2	torC7-C4	28	torC6-C3	22		
56.5	torC8-C1	46	t5RNG1	24			58.4	t5RNG1a	30	t5RNG1	29		
64	torC6-C3	69	torC7-C4	25			67	torC6-C3	56	torC7-C4	42		
93.7	rC4H2	20	dC6C3	18			126.5	t5RNG1a	17	rC1H2	17		
101.5	rC1H2	18	t5RNG1a	17			137.2	iC4H2	23	wC4H2	16		
129.5	iC1H2	25	wC1H2	21	dC6C3	15	145.9	wC1H2	22	iC1H2	18		
214.1	iC1H2	30	saC4H2	20	dC6C3	18	197.7	iC1H2	35	dC6C3	28	dC6O1	19
237.8	rC3H2	17					236.1	rC1H2	24	d5RNG1	18	t5RNG1	15
246	saC4H2	43	dC6C3	21	cC1H2	17	254.9	dC6C3	72	saC4H2	15	dC6O1	12
293.2	dC6O1	67	dC6C3	15			272.9	saC4H2	50	dC6C3	17	torC8-C1	30
326.1	torN-C1	54	torC8-C1	14	saC1H2	14	330.6	torN-C1	91				
338.9	dC6C3	42					340.3	saC4H2	30	dC6C3	29	dC6O1	10
388.7	dC8C1	25	saC4H2	16			375.2	dC6C3	67	saC4H2	51	dC6O1	23
397.1	torC8-C1	58	cC1H2	36	ssC1H2	4	377.8	saC4H2	20	dC6C3	40	iC1H2	21
421.7	saC4H2	75	dC6C3	20	wC1H2	9	401.4	torC8-C1	53	cC1H2	16	ssC1H2	10

485.2	saC4H2	24	dC6C3	14	dC6O1	65	508.9	saC4H2	11	dC6C3	53	dC7C4	18
517.5	dC6C3	44	dC7C4	31	saC4H2	24	534.7	dC6C3	57	saC4H2	25	dC8C1	30
537.8	dC8C1	31	saC4H2	22	cC1H2	19	557.7	saC4H2	11	dC6O1	66	dC6C3	28
615.5	dC6C3	21	saC4H2	13	dC6O1	45	632.7	dC6C3	68	saC4H2	27	dC6O1	18
682.8	dC6O1	81	saC4H2	14	wC7C4	23	700.3	dC8O5	22				
704.7	wC8C1	32	saC4H2	28	dC6O1	27	759.6	dC6O1	14	saC4H2	68	dC7O3	15
712	dC8O5	15					781.5	dC6O1	39	saC4H2	37	dC7O3	28
722.9	wC8C1	34	dC7O3	16			791.2	dC8O5	26	dC6O1	19	sC1-C2	16
748.6	dC8O5	40	ssC1H2	25			867.8	wC8C1	46	ssC1H2	20		
767.4	wC6C3	30	dC6O1	29	saC4H2	20	882.4	saC4H2	45	rC2H2	24	dC6O1	21
779.7	saC4H2	53	dC6O1	13	dC6C3	14	891	saC4H2	63	dC6C3	29	wC6C3	11
863.2	dC6O1	67	saC4H2	11	dC6C3	20	900.7	wC7C4	48	rC5H2	16		
885.1	saC1H2	36					922.2	iC2H2	20				
925.6	saC4H2	18	rC2H2	16			934.3	saC4H2	34	dC6C3	31	rC2H2	29
943.2	saC4H2	46	dC6C3	8			946.5	rC5H2	25	saC4H2	19		
975.7	dC6C3	20	sC2-C3	19	iC5H2	17	980.4	saC4H2	40	dC6C3	31	rC5H2	24
998.5	saC4H2	48	dC6C3	43	rNH	18	1057.5	saC4H2	16				
1002.1	rNH'	33	sC5-C1	22			1111.9	saC4H2	49	dC6C3	38	dC6O1	21
1047.9	sC3-C4	28	sC4-C5	21			1165	iC5H2	25	dsNH	18		
1093.6	dC6C3	28	saC4H2	26	iC5H2	23	1205.4	dC6C3	66	saC4H2	15	sC2-C3	27
1140.5	rNH	24	rNH'	16			1210.1	rNH	49	torC8-C1	20		
1179.1	wC5H2	27	wC2H2	23			1249.7	wC4H2	36				
1191.8	cC3H2	34	cC4H2	15			1268.5	iC2H2	21				
1232.6	dsNH	27	sC8-O5	17			1317.6	dsNH	62				
1243.7	cC4H2	19					1334.4	wC5H2	57				
1259.6	wC3H2	19	iC3H2	16			1352.9	wC2H2	54	sC6-O1	15		
1270.3	wC4H2	36	iC4H2	21	sC6-O1	17	1367.2	ssC1H2	20	iC2H2	17	saC1H2	16
1273.3	wC5H2	16					1385.6	dC6O1	19	saC4H2	76	dC6C3	34
1291.1	sC7-O3	36	saC4H2	35	dC6O1	29	1402.6	dC6O1	40	saC4H2	10	dC6C3	28
1309.2	sC8-O5	38	dsNH	32			1466.3	saC1H2	37	sC8-O5	17	torC8-C1	17
1315.1	dC6O1	38	saC4H2	35	sC7-O3	28	1521.4	saC4H2	44	sC6-O1			

1442.9	cC5H2	66	cC2H2	33			1531.9	cC2H2	91				
1466.3	cC2H2	64	cC5H2	32			1558.9	cC5H2	90				
1555.7	daNH'	56	daNH	31			1577.8	daNH'	85				
1601	daNH	63	daNH'	24			1624.1	daNH	88				
1662.4	sC7-O3	59	sC6-O1	34			1652.7	sC7-O3	44	dC6C3	24	cC4H2	22
1675.5	sC6-O1	58	sC7-O3	35			1666.2	sC8-O5	91				
1690.1	sC8-O5	87					1681.3	dC6C3	45	sC7-O3	38	saC4H2	16
2812.6	saC4H2	74	dC6C3	40	ssC4H2	33	2873.7	saC4H2	84	dC6C3	50	ssC4H2	30
2842.6	dC6C3	38	saC3H2	34	ssC3H2		2887.5	dC6C3	49	saC4H2	32	saC3H2	31
2886.7	sN-H	92					2904.4	sN-H	100				
2892.4	ssC2H2	63	saC2H2	18			2905.8	ssC5H2	77	ssC2H2	17		
2897.8	ssC5H2	57	saC5H2	22			2929	saC2H2	71	saC5H2	25		
2998.9	saC2H2	77	ssC2H2	22			2931.2	saC5H2	72	saC2H2	24		
3022.5	saC5H2	70	ssC5H2	28			3138.6	ssC2H2	76	ssC5H2	18		
3168	sN-H	100					3261.2	sN-H	99				
3243	sN-H	100					3264.5	sN-H	100				

POTENTIAL ENERGY SURFACES

Torsion parameters were further validated by comparing relaxed QM and MM potential energy surfaces (PES). QM PES calculations were performed at the MP2/G-31G(d) level using the relaxed potential energy scan facility of the default redundant internal coordinate optimizer (keyword “Opt= ModRedundant”) in Gaussian03.[9] This facility constrains the internal coordinates being scanned and minimizes all other coordinates at every scan point. MM PES were calculated by reading the QM geometries of all the scan points into CHARMM, harmonically restraining the target dihedral angles with a force constant of 10,000 kcal/mol rad, and minimizing all the other degrees of freedom. This makes it more likely that the portions of the molecule that are not being scanned have the same local minimum conformation in the QM and in the MM scan.

The QM and MM PES scans around a dihedral connecting the phenyl ring, C_α and the amino terminal in DHPG (C2-C1-C7-N) are shown in Figure S3. This phenyl-C_α linkage exists in the other ligands. Hence, together with the equilibrium geometries and the vibrational spectra analysis, these PES scans across the MM and QM validate the MM parameters for the other ligands as well.

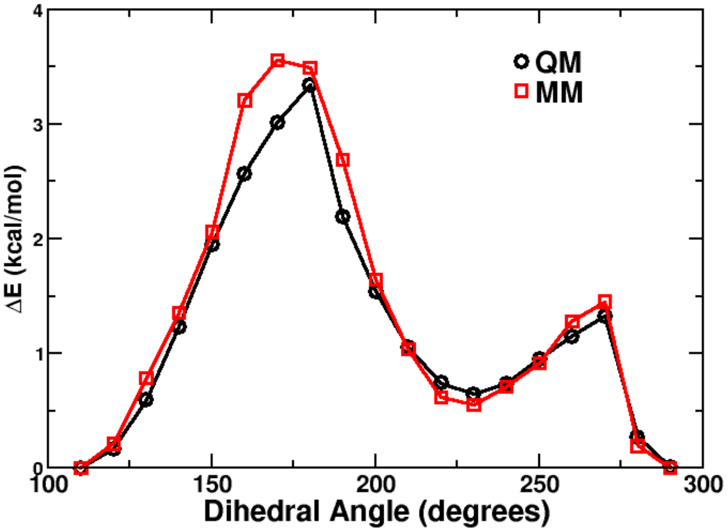

Figure S3. Potential energy scan in QM and MM for the C2-C1-C7-N dihedral.

Conformational Sampling of LBR-ligand complexes

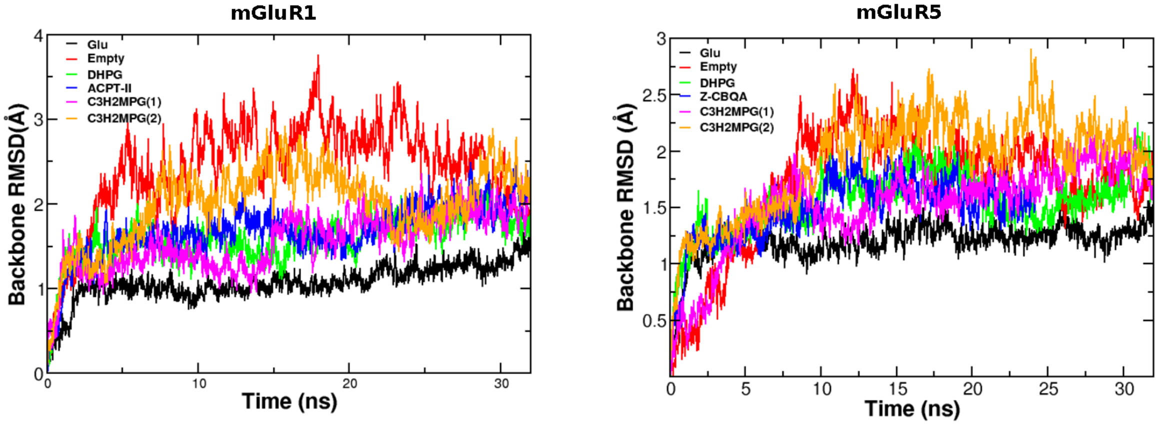

Figure S4. Root Mean Squared Deviation (RMSD) of the backbone atoms of the dimeric LBR-ligand complexes (excluding the loops: 33-38, 125-153, 378-410 and 513-22 for mGluR1 and 14-24, 116-140, 360-390, 496-505 for mGluR5) through unconstrained 32 ns explicit water MD simulations. Distances between the pocket α-carbon atoms pairs from these runs are used to plot the conformationally sampled free energy surfaces in Fig. 5 and 6.

Table S5. Fraction of the simulation time spent by the mGluR1+ligand complexes in the closed and maximally open conformations. The maximally opened state is defined as a conformation (defined by the inter-lobe distances, d^i and d^o) when the sampled free energy is the lowest. When the minima conformation (d^i, d^o) is less than 1 Å from the closed conformation (defined by d^i and d^o of mGluR1+Glu), then it is treated as a closed conformation. Same definition is applicable for Table S6.

Ligand	Fraction of Time	
	closed	$d^{max/open}$
Glu	0.99	0
Empty	0.20	0.55
DHPG	0.65	0
ACPT-II	0.29	0.45
C3H2MPG(1)	0.63	0
C3H2MPG(2)	0.14	0.55
HOMQ	0.29	0
C3HPG(1)	0.97	0
C3HPG(2)	0.39	0.4

Table S6. Fraction of the simulation time spent by the mGluR5+ligand complexes in the closed and maximally open conformations.

Ligand	Fraction of Time	
	closed	$d^{max/open}$
Glu	0.96	0
Empty	0.30	0.4
DHPG	0.75	0
Z-CBQA	0.37	0
C3H2MPG(1)	0.57	0
C3H2MPG(2)	0.12	0.43
HOMQ	0.23	0.31
C3HPG(1)	0.88	0
C3HPG(2)	0.12	0.23

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