Table SI. Four conformations in $E2_{dithiol}$ (conformers A1, A2, A3, and B1) and four conformations in $E2_{disulfide}$ (conformers B2, B3, B4, and B5)

Conf.	Loop extent	Salt bridge[c,d]	Aromatic stacking[c,e]	E2 contact number[f,g]	$F268^{E2}$	$H270^{E2}$ stacked to $F268^{E2}$	Simulation time
A1	E1: $F177^{E1}$-$S185^{E1}$ E2: $G254^{E2}$-$H270^{E2}$ ($C257^{E2}$-$V263^{E2}$)[a] E3: $G369^{E3}$-$I375^{E3}$	$D176^{2.63}$/$R182^{E1}$ $D176^{2.63}$/$K192^{3.28}$ $D184^{E1}$/$K192^{3.28}$ $R186^{3.22}$/$E258^{E2}$ $D266^{E2}$/$K370^{E3}$	$F170^{2.57}$/$W356^{6.48}$ $F174^{2.61}$/$H178^{2.65}$ $F177^{2.64}$/ $F268^{E2}$ $F177^{2.64}$/$F379^{7.35}$ $F189^{3.25}$/ $F268^{E2}$ $F200^{3.36}$/$F278^{5.42}$ $F200^{3.36}$/$W356^{6.48}$ $F268^{E2}$/$Y275^{5.39}$ $F268^{E2}$/$F379^{7.35}$ $Y275^{5.39}$/$F278^{5.42}$ $Y275^{5.39}$/$W356^{6.48}$ $W279^{5.43}$/$F368^{6.60}$ $Y365^{6.57}$/$F368^{6.60}$	E1: 2 E3: 24 TMH: 250	*in*	*no*	20 ns
A2	E1: $V179^{E1}$-$S185^{E1}$ E2: $W255^{E2}$-$I271^{E2}$ ($C257^{E2}$-$S265^{E2}$)[a] E3: $G369^{E3}$-$I375^{E3}$	$D176^{2.63}$/$R182^{E1}$ $D176^{2.63}$/$K192^{3.28}$ $D184^{E1}$/$K192^{3.28}$ $D272^{5.36}$/$K370^{E3}$ $D366^{6.58}$/$K373^{E3}$	$F170^{2.57}$/$W356^{6.48}$ $F177^{2.64}$/$F189^{3.25}$ $F177^{2.64}$/$F379^{7.35}$ $F200^{3.36}$/ $Y275^{5.39}$ $F200^{3.36}$/$F278^{5.42}$ $F268^{E2}$/$F379^{7.35}$ $F278^{5.42}$/$W356^{6.48}$ $W279^{5.43}$/$F368^{6.60}$	E1: 0 E3: 29 TMH: 256	*out*	*no*	13 ns
B1	E1: $F180^{E1}$-$S185^{E1}$ E2: $W255^{E2}$-$S262^{E2}$ ($W255^{E2}$-$S262^{E2}$)[a,b] E3: $G369^{E3}$-$I375^{E3}$	$D176^{2.63}$/$R182^{E1}$ $D184^{E1}$/$K192^{3.28}$ $D366^{6.58}$/$K370^{E3}$	$F170^{2.57}$/ $F200^{3.36}$ $F170^{2.57}$/$W356^{6.48}$ $F177^{2.64}$/$F379^{7.35}$ $F200^{3.36}$/$W356^{6.48}$ $Y275^{5.39}$/$F278^{5.42}$ $Y365^{6.57}$/$F368^{6.60}$	E1: 0 E3: 0 TMH: 141	*out*	*yes*	15 ns
A3	E1: $V179^{E1}$-$R186^{E1}$ E2: $G254^{E2}$-$I271^{E2}$ ($C257^{E2}$-$S262^{E2}$)[a] E3: $V367^{E3}$-$L374^{E3}$	$R186^{3.22}$/$E258^{E2}$ $D366^{6.58}$/$K370^{E3}$	$F170^{2.57}$/ $F200^{3.36}$ $F170^{2.57}$/$W356^{6.48}$ $F177^{2.64}$/$F379^{7.35}$ $F200^{3.36}$/$W356^{6.48}$ $Y275^{5.39}$/$F278^{5.42}$ $Y365^{6.57}$/$F368^{6.60}$	E1: 20 E3: 1 TMH: 238	*in*	*no*	13 ns
B2	E1: $H181^{E1}$-$S185^{E1}$ E2: $L253^{E2}$-$I271^{E2}$ ($G254^{E2}$-$L260^{E2}$)[a] E3: $G369^{E3}$-$I375^{E3}$	$D176^{2.63}$/$R182^{E1}$ $D184^{E1}$/$K192^{3.28}$ $R186^{3.22}$/$E258^{E2}$ $D366^{6.58}$/$K370^{E3}$	$F170^{2.57}$/$W356^{6.48}$ $Y172^{2.59}$/$F191^{3.27}$ $F174^{2.61}$/$F177^{2.64}$ $F177^{2.64}$/$F379^{7.35}$ $F189^{3.25}$/ $F268^{E2}$ $F200^{3.36}$/ $Y275^{5.39}$ $F200^{3.36}$/$W356^{6.48}$ $Y275^{5.39}$/$F278^{5.42}$ $Y275^{5.39}$/$W279^{5.43}$ $Y365^{6.57}$/$F368^{6.60}$	E1: 1 E3: 0 TMH: 312	*out*	*no*	25 ns
B3	E1: $H179^{E1}$-$S185^{E1}$ E2: $W255^{E2}$-$I271^{E2}$ ($C257^{E2}$-$L260^{E2}$)[a] E3: $D366^{E3}$-$I375^{E3}$	$D176^{2.63}$/$R182^{E1}$ $K183^{E1}$/$D266^{E2}$ $D184^{E1}$/$K192^{3.28}$ $R186^{3.22}$/$E258^{E2}$ $D366^{6.58}$/$K370^{E3}$	$F170^{2.57}$/ $F200^{3.36}$ $F170^{2.57}$/$W356^{6.48}$ $F174^{2.61}$/$F381^{7.37}$ $F177^{2.64}$/$F189^{3.25}$ $F177^{2.64}$/$F379^{7.35}$	E1: 30 E3: 11 TMH: 231	*in*	*yes*	53 ns

			F189$^{3.25}$/F268^{E2} F189$^{3.25}$/F379$^{7.35}$ F200$^{3.36}$/W356$^{6.48}$ F268^{E2}/Y275$^{5.39}$ F268^{E2}/F379$^{7.35}$ H270^{E2}/Y275$^{5.39}$ Y275$^{5.39}$/F278$^{5.42}$ Y275$^{5.39}$/W279$^{5.43}$ Y365$^{6.57}$/F368$^{6.60}$			
B4	E1: F180^{E1}-S185^{E1} E2:L253^{E2}-I271^{E2} (C257^{E2}-L260^{E2})[a] E3: G369^{E3}-I375^{E3}	D184^{E1}/K192$^{3.28}$ K183^{E1}/E258^{E2} K192$^{3.28}$/D266^{E2} D272$^{5.36}$/K370^{E3} D366$^{6.58}$/K370^{E3}	F170$^{2.57}$/W356$^{6.48}$ F174$^{2.61}$/F177$^{2.64}$ F177$^{2.64}$/F379$^{7.35}$ F189$^{3.25}$/ F268^{E2} F200$^{3.36}$/ Y275$^{5.39}$ F200$^{3.36}$/W356$^{6.48}$ F268^{E2}/F379$^{7.35}$ Y275$^{5.39}$/F278$^{5.42}$ Y275$^{5.39}$/W279$^{5.43}$ Y365$^{6.57}$/F368$^{6.60}$	E1: 14 E3: 18 TMH: 359	*out*	*no*	36 ns
B5	E1: F180^{E1}-S185^{E1} E2: L253^{E2}-D272^{E2} (L253^{E2}-L260^{E2})[a,b] E3: G369^{E3}-I375^{E3}	D176$^{2.63}$/R182^{E1} D176$^{2.63}$/K192$^{3.28}$ D184^{E1}/K192$^{3.28}$ D266^{E2}/ K370^{E3}	F170$^{2.57}$/W356$^{6.48}$ F177$^{2.64}$/F189$^{3.25}$ F177$^{2.64}$/F379$^{7.35}$ F200$^{3.36}$/W356$^{6.48}$ Y275$^{5.39}$/F278$^{5.42}$ Y365$^{6.57}$/F368$^{6.60}$	E1: 0 E3: 8 TMH: 214	*out*	*yes*	10 ns

[a]The residues forming the helical segment within E2 at the end of the simulation. It should be noted that residues C257^{E2}-L260^{E2} for E2$_{disulfide}$ were constrained to be helical during the SA simulation (see MATERIALS AND METHODS).

[b]H4 extends to include the E2 helical segment as part of H4.

[c]Only the extracellular half of the receptor is considered.

[d]Estimated by measuring the distance between the side chain O atom of a negatively charged residue and the side chain N atom of a positively charged residue with the cut-off distance of 3.20 Å.

[e]Estimated by measuring the distance between one atom from E2 and the other atom from either E1, E3, or the TM helices with the cut-off distance of 3.50 Å. His residue was not considered for simplicity.

[f]Estimated by measuring the distance between the aromatic rings of two aromatic residues with the cut-off distance of 8.00 Å.

[g]The value calculated by averaging over the last 1 ns of the MD simulation.

Table SII. Molecular interaction energy and contact number analysis of $CB_1(E2_{dithiol})$ and $CB_1(E2_{dithiol})$

(i) Interaction energies between E2 and E1, E3, and TM helices

	$CB_1(E2_{dithiol})$	$CB_1(E2_{disulfide})$
$E_{inter,E2}$ (total)	-147.0(50.1)[a]	-252.9(32.1)
E2/E1	-13.5(10.5)	-22.5(15.6)
E2/E3	-28.9(28.2)	-4.1(4.2)
E2/TMH	-104.6(26.0)	-226.0(33.2)

[a]The energy value with its standard deviation in parenthesis was averaged over the last 10 ns of the simulation.

(ii) Contact numbers between E2 and E1, E3, and the TM helices

	$CB_1(E2_{dithiol})$	$CB_1(E2_{disulfide})$
total	257(24)[a]	248(28)
E2/E1	8(5)	7(7)
E2/E3	44(13)	26(10)
E2/TMH	205(19)	214(24)

[a]The energy value with its standard deviation in parenthesis was averaged over the last 10 ns of the simulation.

(iii) Contact number analysis of the extracellular half of the TM helices in $CB_1(E2_{dithiol})$ and $CB_1(E2_{dithiol})$

	$CB_1(E2_{dithiol})$	$CB_1(E2_{disulfide})$	CB_1[†]
H1/H2	21(6)[a]	28(8)	16(4)
H1/H7	35(11)	51(15)	60(14)
H2/H3	50(12)	36(14)	48(12)
H2/H4	1(2)	0	0
H2/H6	12(4)	10(5)	13(4)
H2/H7	77(13)	80(13)	75(12)
H3/H4	57(14)	62(12)	47(14)
H3/H5	31(9)	16(6)	20(9)
H3/H6	40(10)	51(13)	46(11)
H3/H7	0	0	0
H4/H5	19(8)	21(7)	22(10)
H5/H6	20(9)	21(8)	17(8)
H6/H7	77(14)	73(15)	91(13)

[a]Estimated by counting the number of inter-atomic contacts with the cut-off distance of 3.50 Å. The value with its standard deviation in parenthesis was averaged over the last 10 ns of the simulation.

[b]The CB_1 receptor model[32] whose TM helical bundle structure was same both in $CB_1(E2_{dithiol})$ and in $CB_1(E2_{disulfide})$ at the beginning of the respective simulations.

(iv) Contact number analysis of the intracellular half of the TM helices in $CB_1(E2_{dithiol})$ and $CB_1(E2_{dithiol})$

	$CB_1(E2_{dithiol})$	$CB_1(E2_{disulfide})$	CB_1[b]
H1/H2	70(12)[a]	73(13)	67(14)
H1/H7	28(6)	29(7)	25(7)
H2/H3	54(12)	56(10)	57(11)
H2/H4	32(6)	25(6)	30(11)
H2/H6	8(6)	6(4)	3(2)
H2/H7	10(7)	32(7)	33(6)
H3/H4	40(9)	36(11)	29(9)
H3/H5	118(17)	96(17)	115(16)
H3/H6	50(11)	74(16)	51(14)
H3/H7	0	1(1)	2(4)
H4/H5	0	0	0
H5/H6	58(13)	71(15)	54(12)
H6/H7	69(13)	81(18)	77(15)

[a]Estimated by counting the number of inter-atomic contacts with the cut-off distance of 3.50 Å. The value with its standard deviation in parenthesis was averaged over the last 10 ns of the simulation.

[b]The CB_1 receptor model[32] whose TM helical bundle structure was same both in $CB_1(E2_{dithiol})$ and in $CB_1(E2_{disulfide})$ at the beginning of the respective simulations.

Table SIII. Output from deconvolution of $E2_{dithiol}$ and $E2_{disulfide}$ CD spectra using CONTIN L analysis program[a]

Peptide	Helix 1	Helix 2	Strand1	Strand2	Turns	Unordered	Total	NRMSD
$E2_{dithiol}$	0.57	0.204	0	0.142	0.084	0	1	0.332
$E2_{disulfide}$	0.458	0.114	0	0	0.428	0	1	0.318

[a]Ref. 53.

Figure S1. The RMSD plots for E2 (in red) as well as TMH (in black) of four conformations in $E2_{dithiol}$ (conformers **A1**, **A2**, **A3**, and **B1**) and our conformations in $E2_{disulfide}$ (conformers **B2**, **B3**, **B4**, and **B5**)