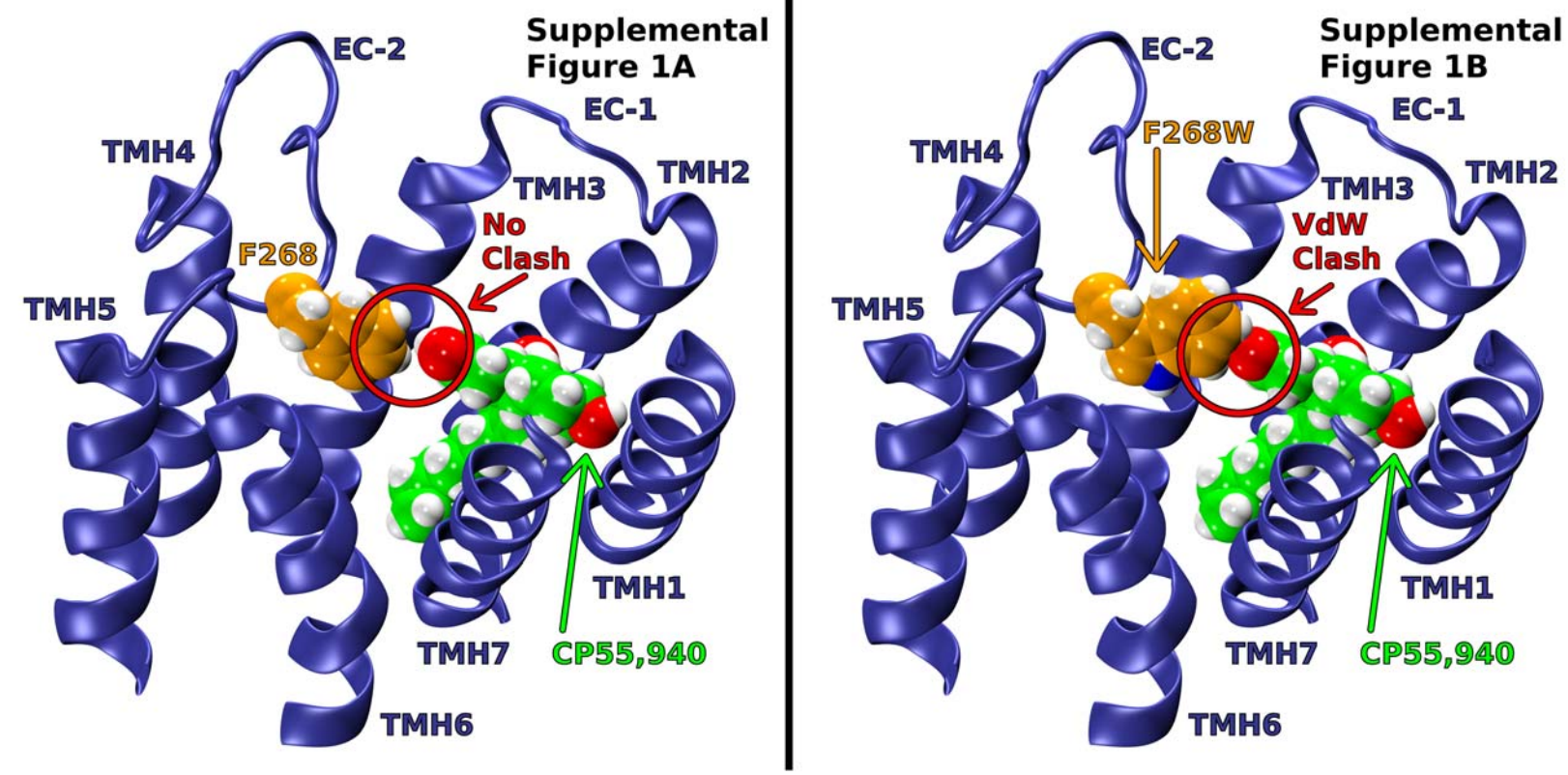

Supplemental Figure 1. EC-2 loop conformation of WT and F268W mutant CB1 receptors in the active (R*) state. CP55,940 is shown in green; F268 and F268W are shown in orange. A) Red circle indicates that there is not a Van der Waals (VdW) clash between F268 and CP55,940. B) Red circle highlights VdW clash between F268W and CP55,940. This modeling was based on mutation studies from the Kendall lab (see Methods and reference 16).

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Supplemental Table 1: Pairwise interaction energies of CP55,940 at the CB_1 wild-type R* model.

		kcal/mol:			
B/W #:	**Absolute #:**	**Coulombic:**	**VdW:**	**Total:**	**% total:**
K3.28	**LYS-192**	-13.79	0.64	-13.15	**21.58**
Q1.32	**GLN-116**	-6.68	-0.69	-7.37	**12.08**
L7.43	**LEU-387**	0.12	-4.48	-4.36	**7.15**
S7.39	**SER-383**	-1.46	-2.50	-3.96	**6.50**
F2.57	**PHE-170**	0.09	-3.38	-3.29	**5.39**
S1.39	SER-123	-1.18	-1.70	-2.88	4.73
F2.64	PHE-177	0.44	-3.09	-2.65	4.35
V3.32	VAL-196	0.03	-2.63	-2.60	4.27
A7.36	ALA-380	-0.38	-2.01	-2.39	3.92
I1.35	ILE-119	-0.53	-1.80	-2.33	3.83
S2.60	SER-173	-0.38	-1.66	-2.04	3.35
F3.25	PHE-189	-0.22	-1.73	-1.95	3.20
I2.56	ILE-169	0.11	-1.64	-1.52	2.50
F3.36	PHE-200	0.06	-1.55	-1.49	2.45
EC-3	ILE-375	0.05	-1.34	-1.29	2.12
S7.46	SER-390	0.10	-1.07	-0.97	1.59
C7.42	CYS-386	0.00	-0.87	-0.86	1.42
M7.40	MET-384	-0.07	-0.60	-0.67	1.10
S3.35	SER-199	-0.21	-0.44	-0.65	1.07
N7.45	ASN-389	0.12	-0.75	-0.63	1.03
D2.50	ASP-163	-0.25	-0.35	-0.60	0.98
F7.35	PHE-379	-0.08	-0.50	-0.58	0.96
L1.33	LEU-117	-0.33	-0.25	-0.58	0.95
EC-3	MET-371	-0.30	-0.20	-0.50	0.82
A1.36	ALA-120	1.56	-1.98	-0.42	0.69
L1.40	LEU-124	-0.01	-0.26	-0.27	0.45
L7.44	LEU-388	-0.01	-0.17	-0.18	0.30
N/A	WAT-344	-0.04	-0.14	-0.18	0.29
F2.67	PHE-180	0.06	-0.21	-0.15	0.25
G1.43	GLY-127	0.03	-0.18	-0.15	0.25
EC-2	PHE-268	0.48	-0.61	-0.13	0.21
EC-3	LYS-373	0.41	-0.49	-0.09	0.14
Q1.31	GLN-115	0.07	-0.14	-0.08	0.13
EC-2	ILE-267	0.06	-0.05	0.01	-0.02

Totals:	**-22.12**	**-38.84**	**-60.95**	**100.00**

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Supplemental Table 2: Pairwise interaction energies of CP55,940 at the CB_1 $D2.63^{176}A$ mutant R* model.

		kcal/mol:			
B/W #:	**Absolute #:**	**Coulomb:**	**VdW:**	**Total:**	**% total:**
K3.28	**LYS-192**	-14.28	1.09	-13.19	**21.88**
Q1.32	**GLN-116**	-6.34	-0.72	-7.07	**11.72**
S7.39	**SER-383**	-1.55	-3.02	-4.56	**7.57**
L7.43	**LEU-387**	0.11	-4.60	-4.49	**7.45**
F2.57	**PHE-170**	0.09	-3.43	-3.34	**5.54**
F2.64	PHE-177	0.23	-3.23	-2.99	4.97
S1.39	SER-123	-1.19	-1.60	-2.79	4.62
V3.32	VAL-196	0.04	-2.77	-2.72	4.52
I1.35	ILE-119	-0.55	-1.92	-2.47	4.10
A7.36	ALA-380	-0.32	-1.97	-2.29	3.80
S2.60	SER-173	-0.27	-1.83	-2.10	3.48
I2.56	ILE-169	0.11	-1.63	-1.52	2.52
F3.36	PHE-200	0.07	-1.46	-1.39	2.30
S7.46	SER-390	0.08	-1.27	-1.19	1.97
C7.42	CYS-386	0.00	-0.97	-0.97	1.61
F7.35	PHE-379	-0.12	-0.79	-0.91	1.51
EC-2	PHE-268	-0.21	-0.51	-0.72	1.20
M7.40	MET-384	-0.08	-0.62	-0.70	1.15
S3.35	SER-199	-0.22	-0.47	-0.69	1.15
D2.50	ASP-163	-0.28	-0.40	-0.67	1.12
N7.45	ASN-389	0.12	-0.79	-0.67	1.11
L1.33	LEU-117	-0.31	-0.25	-0.56	0.93
A1.36	ALA-120	1.55	-2.07	-0.52	0.86
F3.25	PHE-189	-0.03	-0.36	-0.38	0.63
EC-3	MET-371	-0.04	-0.32	-0.37	0.61
L1.40	LEU-124	-0.01	-0.27	-0.28	0.47
L7.44	LEU-388	-0.01	-0.18	-0.19	0.32
N/A	WAT-344	-0.04	-0.15	-0.18	0.30
G1.43	GLY-127	0.03	-0.19	-0.16	0.26
I6.54	ILE-362	-0.01	-0.12	-0.14	0.23
Q1.31	GLN-115	0.08	-0.14	-0.06	0.11

Totals:	**-23.34**	**-36.94**	**-60.28**	**100.00**

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Supplemental Table 3: Pairwise interaction energies of CP55,940 at the CB_1 K373A mutant R* model.

		kcal/mol:			
B/W #:	**Absolute #:**	**Coulomb:**	**VdW:**	**Total:**	**% total:**
K3.28	**LYS-192**	-16.47	-2.40	-18.87	**30.13**
Q1.32	**GLN-116**	-5.94	-1.08	-7.02	**11.21**
S7.39	**SER-383**	-2.10	-2.25	-4.34	**6.94**
L7.43	**LEU-387**	-0.41	-3.36	-3.77	**6.02**
F2.57	**PHE-170**	0.00	-3.44	-3.44	**5.49**
S1.39	SER-123	-0.99	-1.66	-2.66	4.24
F2.64	PHE-177	-0.08	-2.40	-2.48	3.96
S2.60	SER-173	-0.32	-1.80	-2.11	3.37
C7.42	CYS-386	-0.04	-1.90	-1.94	3.10
A1.36	ALA-120	0.14	-2.05	-1.91	3.05
F7.35	PHE-379	-0.48	-1.39	-1.87	2.98
F3.36	PHE-200	-0.64	-1.22	-1.86	2.97
V3.32	VAL-196	0.11	-1.80	-1.68	2.69
I2.56	ILE-169	0.17	-1.65	-1.48	2.36
S7.46	SER-390	-0.27	-0.79	-1.06	1.70
I1.35	ILE-119	0.97	-1.86	-0.89	1.42
A7.36	ALA-380	0.36	-1.16	-0.81	1.29
L1.33	LEU-117	-0.49	-0.23	-0.72	1.15
EC-2	PHE-268	-0.40	-0.31	-0.71	1.14
D2.50	ASP-163	-0.29	-0.39	-0.68	1.08
F3.25	PHE-189	0.25	-0.92	-0.67	1.07
N7.45	ASN-389	0.13	-0.72	-0.59	0.94
L1.40	LEU-124	0.02	-0.27	-0.25	0.40
M7.40	MET-384	0.07	-0.31	-0.23	0.38
G1.43	GLY-127	0.00	-0.18	-0.19	0.30
S3.35	SER-199	0.45	-0.59	-0.14	0.22
I6.54	ILE-362	-0.08	-0.04	-0.12	0.19
L7.44	LEU-388	0.45	-0.56	-0.11	0.18
Q1.31	GLN-115	0.11	-0.14	-0.03	0.04
EC-3	MET-371	0.00	0.00	0.00	0.00
N/A	WAT-344	0.00	0.00	0.00	0.00
	Totals:	**-25.74**	**-36.87**	**-62.62**	**100.00**

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Supplemental Table 4: Pairwise interaction energies of CP55,940 at the CB_1 D2.63[176]A-K373A mutant R* model.

kcal/mol:					
B/W #:	**Absolute #:**	**Coulomb:**	**VdW:**	**Total:**	**% total:**
K3.28	**LYS-192**	-14.07	0.88	-13.18	**21.19**
Q1.32	**GLN-116**	-6.37	-0.94	-7.31	**11.75**
L7.43	**LEU-387**	0.12	-4.60	-4.48	**7.21**
S7.39	**SER-383**	-1.51	-2.92	-4.43	**7.13**
F2.57	**PHE-170**	0.09	-3.43	-3.34	**5.38**
F2.64	PHE-177	0.40	-3.22	-2.82	4.54
S1.39	SER-123	-1.15	-1.61	-2.76	4.43
V3.32	VAL-196	0.05	-2.75	-2.71	4.35
I1.35	ILE-119	-0.49	-1.91	-2.39	3.85
A7.36	ALA-380	-0.38	-2.00	-2.38	3.82
S2.60	SER-173	-0.30	-1.82	-2.12	3.41
EC-1	HID-181	-0.79	-1.06	-1.85	2.97
I2.56	ILE-169	0.11	-1.63	-1.52	2.45
F3.36	PHE-200	0.07	-1.45	-1.38	2.22
S7.46	SER-390	0.08	-1.26	-1.17	1.88
C7.42	CYS-386	0.00	-0.98	-0.97	1.56
F3.25	PHE-189	0.16	-1.03	-0.87	1.40
F7.35	PHE-379	-0.11	-0.67	-0.78	1.26
EC-2	PHE-268	-0.25	-0.48	-0.74	1.18
S3.35	SER-199	-0.22	-0.50	-0.72	1.15
M7.40	MET-384	-0.08	-0.61	-0.68	1.10
D2.50	ASP-163	-0.28	-0.39	-0.68	1.09
N7.45	ASN-389	0.12	-0.78	-0.65	1.05
A1.36	ALA-120	1.46	-2.09	-0.63	1.01
L1.33	LEU-117	-0.31	-0.24	-0.56	0.90
L1.40	LEU-124	-0.01	-0.27	-0.28	0.45
L7.44	LEU-388	-0.01	-0.18	-0.19	0.30
N/A	WAT-344	-0.04	-0.14	-0.18	0.29
K7.32	LYS-376	0.06	-0.23	-0.17	0.27
G1.43	GLY-127	0.04	-0.19	-0.15	0.25
I6.54	ILE-362	-0.01	-0.09	-0.10	0.16
Q1.31	GLN-115	0.07	-0.14	-0.07	0.11
	Totals:	**-23.61**	**-38.60**	**-62.22**	**100.00**

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Supplemental Table 5: Pairwise interaction energies of CP55,940 at the CB_1 $D2.63^{176}K$-K373D mutant R* model.

		kcal/mol:			
B/W #:	**Absolute #:**	**Coulomb:**	**VdW:**	**Total:**	**% total:**
K3.28	**LYS-192**	-14.58	1.33	-13.26	**20.89**
Q1.32	**GLN-116**	-7.09	-0.22	-7.31	**11.51**
S7.39	**SER-383**	-1.60	-2.97	-4.57	**7.20**
L7.43	**LEU-387**	0.11	-4.61	-4.50	**7.09**
F2.57	**PHE-170**	0.10	-3.38	-3.29	**5.18**
F2.64	PHE-177	0.14	-3.30	-3.16	4.97
S1.39	SER-123	-1.17	-1.69	-2.87	4.51
V3.32	VAL-196	0.03	-2.78	-2.75	4.33
I1.35	ILE-119	-0.65	-1.92	-2.57	4.05
A7.36	ALA-380	-0.21	-2.03	-2.24	3.52
S2.60	SER-173	-0.23	-1.83	-2.05	3.24
I2.56	ILE-169	0.11	-1.61	-1.50	2.36
EC-3	ASP-373	-1.09	-0.41	-1.50	2.36
F3.36	PHE-200	0.07	-1.46	-1.39	2.19
S7.46	SER-390	0.08	-1.27	-1.19	1.87
EC-3	ILE-375	-0.03	-1.14	-1.17	1.84
F7.35	PHE-379	-0.14	-1.00	-1.14	1.80
C7.42	CYS-386	-0.03	-0.97	-0.99	1.57
EC-3	MET-371	-0.38	-0.59	-0.97	1.52
S3.35	SER-199	-0.22	-0.48	-0.71	1.11
M7.40	MET-384	-0.07	-0.62	-0.69	1.09
N7.45	ASN-389	0.11	-0.79	-0.68	1.07
D2.50	ASP-163	-0.26	-0.40	-0.65	1.03
L1.33	LEU-117	-0.32	-0.26	-0.58	0.92
F3.25	PHE-189	0.10	-0.66	-0.56	0.88
A1.36	ALA-120	1.66	-1.98	-0.32	0.51
L1.40	LEU-124	-0.02	-0.26	-0.28	0.44
I6.54	ILE-362	-0.03	-0.17	-0.20	0.32
L7.44	LEU-388	-0.01	-0.18	-0.19	0.30
N/A	WAT-344	-0.04	-0.15	-0.18	0.29
F2.67	PHE-180	0.07	-0.25	-0.18	0.29
G1.43	GLY-127	0.03	-0.18	-0.15	0.24
EC-2	PHE-268	0.16	-0.26	-0.10	0.16
Q1.31	GLN-115	0.09	-0.14	-0.06	0.09
K2.63	LYS-176	0.59	-0.12	0.47	**-0.75**
	Totals:	**-24.72**	**-38.74**	**-63.46**	**100.00**