

Supplementary information Table S2. Summary of cAMP inhibition assay of S1PR1

Receptor	cAMP inhibition assay								Expression level (%WT)
	EC ₅₀ (nM)	Fold	EC ₅₀ (nM)	fold	EC ₅₀ (nM)	fold	EC ₅₀ (nM)	fold	
S1PR1	siponimod		ozanimod		SEW2871		cenerimod		
WT	3.58±0.85	1.0	6.18±2.48	1.0	0.62±0.32	1.0	4.95±1.73	1.0	100
Y29A	82.54±20.52	23.1	20.43±5.78	3.3	15.04±10.31	24.2	-	-	94.68±18.9
K34A	ND	ND	1.02±0.40	0.2	4.45±3.14	7.2	-	-	93.39±17.5
N101 ^{2.60} A	4.61±1.70	1.28	5.34±2.84	0.8	6.17±3.94	9.9	411.4±162.0	83.1	123±21.4
R120 ^{3.28} A	680±482	189.9	7.77±2.83	1.2	14.78±7.73	23.8	-	-	85.60±17.5
E121 ^{3.29} A	10.9±3.88	3.0	28.34±12.69	4.6	86.66±5.36	139	8.18±2.74	1.6	107.7±18.9
F210 ^{5.47} A	10.44±5.53	1.9	8.3±2.88	1.3	-	-	13.74±2.78	2.7	89.94±21.4
F273 ^{6.52} A	10.7±6.37	2.9	9.16±5.11	1.5	-	-	18.59±8.31	3.7	71.6±27.6
C206 ^{5.43} A	24.58±14.44	6.8	28.7±11.5	4.6	-	-	17.98±8.36	3.6	72.76±17.5
T207 ^{5.44} A	32.23±3.27	9.0	2.4±3.7	0.4	-	-	203.6±150.2	41.1	119.6±17.5
L128 ^{3.36} A	17.69±4.92	4.9	-	-	-	-	-	-	139.8±18.9
W269 ^{6.48} F	24.46±11.4	6.8	-	-	-	-	-	-	82.68±17.5
W269 ^{6.48} A	ND	ND	-	-	-	-	-	-	76.26±21.4
K250 ^{6.29} A	ND	ND	-	-	-	-	-	-	101.7±18.9
R78 ^{2.37} A	23.64±10.44	6.6	-	-	-	-	-	-	83.46±17.5
R142 ^{3.50} A	ND	ND	-	-	-	-	-	-	88.46±18.9
R238 ^{ICL3} A	19.21±1.78	5.3	-	-	-	-	-	-	132.9±17.5
ICL3 ^{R238A/K239A/K243A}	25.5±1.71	7.1	-	-	-	-	-	-	126.3±18.7
L151 ^{ICL2} A	2.22±0.59	0.6	-	-	-	-	-	-	77.63±17.5
L151 ^{ICL2} F	3.87±1.39	1.1	-	-	-	-	-	-	69.84±16.8
L151 ^{ICL2} P	3.05±1.45	0.8	-	-	-	-	-	-	103.5±18.4
M149 ^{ICL2} A	ND	ND	-	-	-	-	-	-	76.85±17.5
N30D	4.44±3.05	1.2	-	-	-	-	-	-	113.4±18.9
N30Q	6.64±2.28	1.8	-	-	-	-	-	-	85.02±17.5
N30A	19.6±1.30	5.5	-	-	-	-	-	-	70.56±18.9
R292 ^{7.34} Q	3.24±0.70	0.9	-	-	5.4±3.56	8.7	-	-	86.9±18.9
R292 ^{7.34} A	5.77±4.35	1.6	-	-	14.6±5.52	23.5	-	-	64.1±17.5
S1PR1-N-T 4L-DC338	3.69±0.95	1.0	-	-	-	-	-	-	135±16.5

ND means not detected. “-” means no measurement.