Supplementary Information Table S1. Cryo-EM data collection, refinement and validation statistics.

Data collection and processing	S1PR1-Gi-Siponimod	S1PR1-Gi-Cenerimod	S1PR1-Gi-Ozanimod	S1PR1-Gi-SEW2871	S1PR5-Gi-Siponimod
Magnification	105,000	105,000	165,000	165,000	165,000
Voltage (kV)	300	300	300	300	300
Electron exposure (e⁻/Å)	63	63	50	53	56
Defocus range (μm)	-2.5 ~ -0.3	-2.9 ~ -0.5	-2.3 ~ -0.8	-2.6 ~ -0.4	-3.4 ~ -0.6
Pixel size (Å)	0.855	0.855	0.85	0.85	0.85
Symmetry imposed	C1	C1	C1	C1	C1
Initial particle images (no.)	4,099,015	2,149,555	2,919,708	5,964,002	2,946,284
Final particle images (no.)	591,794	367,642	271,592	438,020	366,479
Map resolution (Å)	2.98	3.07	3.42	3.27	3.4
FSC threshold	0.143	0.143	0.143	0.143	0.143
Map resolution range (Å)	3.0~4.6	3.1~4.2	3.4~4.5	3.2~4.7	3.3~6.8
Refinement					
Initial model used (PDB code)					
Model resolution (Å)	3.7	3.7	3.9	3.8	3.4
FSC threshold	0.5	0.5	0.5	0.5	0.5
Map sharpening B factor (Å)	-129.8	-133.2	-132.9	-128.2	-145.1
Model composition					
Non-hydrogen atoms	9,024	9,078	8,987	9,004	8,728
Protein residues	1,144	1,144	1,142	1,144	1,128
Ligands	1	1	1	1	1
Lipid	0	4	0	0	0
B factor (Å)					
Protein	87.14	95.65	82.68	89.93	81.63
Ligand	98.45	115.10	97.60	140.33	141.02
R.m.s. deviations					
Bond lengths (Å)	0.003	0.002	0.003	0.002	0.002
Bond angles (°)	0.578	0.535	0.601	0.550	0.613
Validation					
MolProbity score	1.66	1.57	1.53	1.61	1.72
Clash score	8.78	6.83	6.64	6.68	12.24
Ramachandran plot					
Favored (%)	96.89	96.80	97.06	96.36	97.38
Allowed (%)	3.11	3.20	2.94	3.64	2.62
Outliers (%)	0	0	0	0	0