

Supplementary Materials:

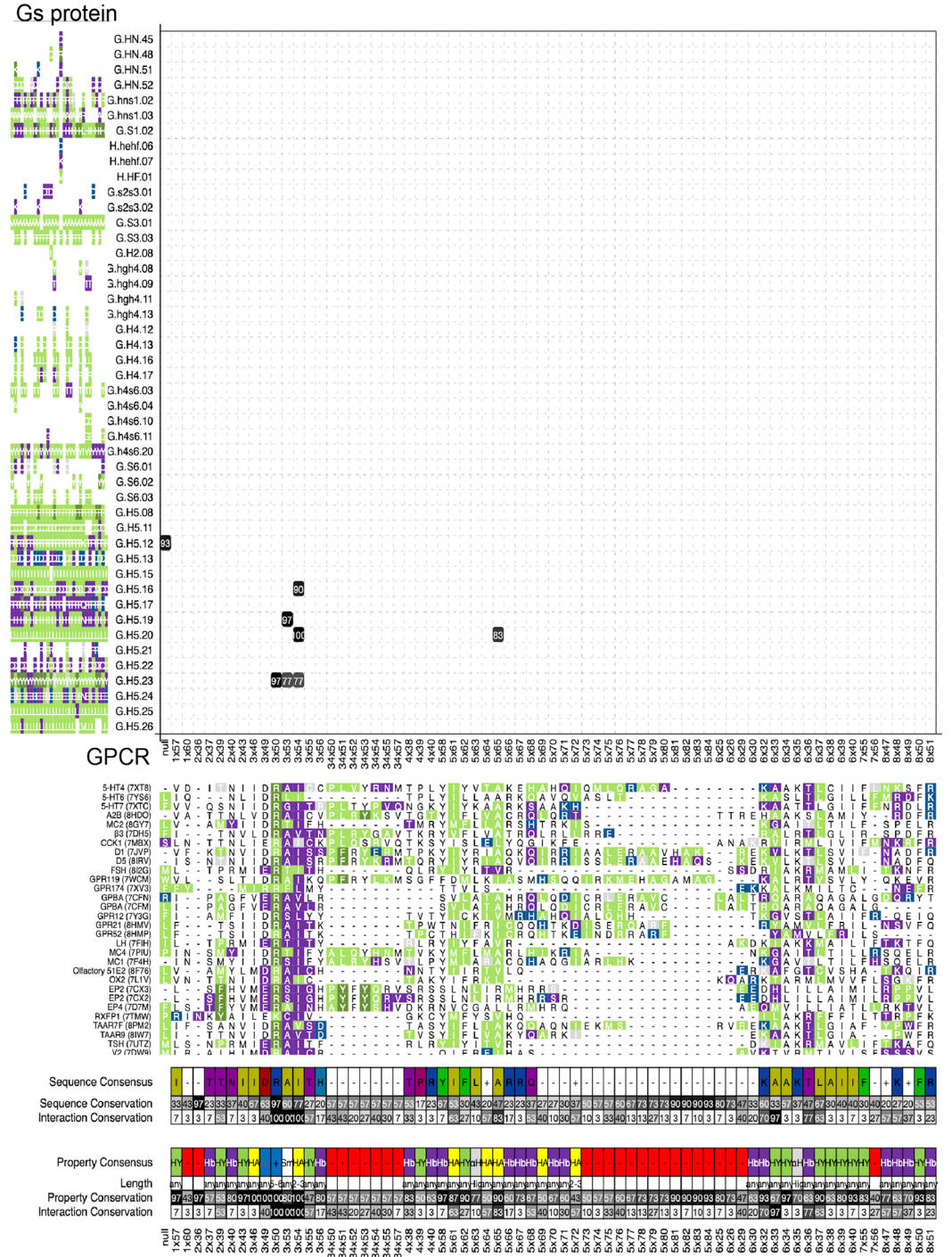


Figure S1. High-Resolution Human Class A GPCR-Gs Contact Interface Matrix: Gs-CB1 contact interface matrix derived from 30 experimentally resolved GPCR/Gs complexes representing 28 different receptors. The data were extracted from the GPCRdb database, considering only high-resolution structures of human class A GPCRs in complex with Gs. For clarity, the matrix displays only contact pairs with at least 75% conservation.

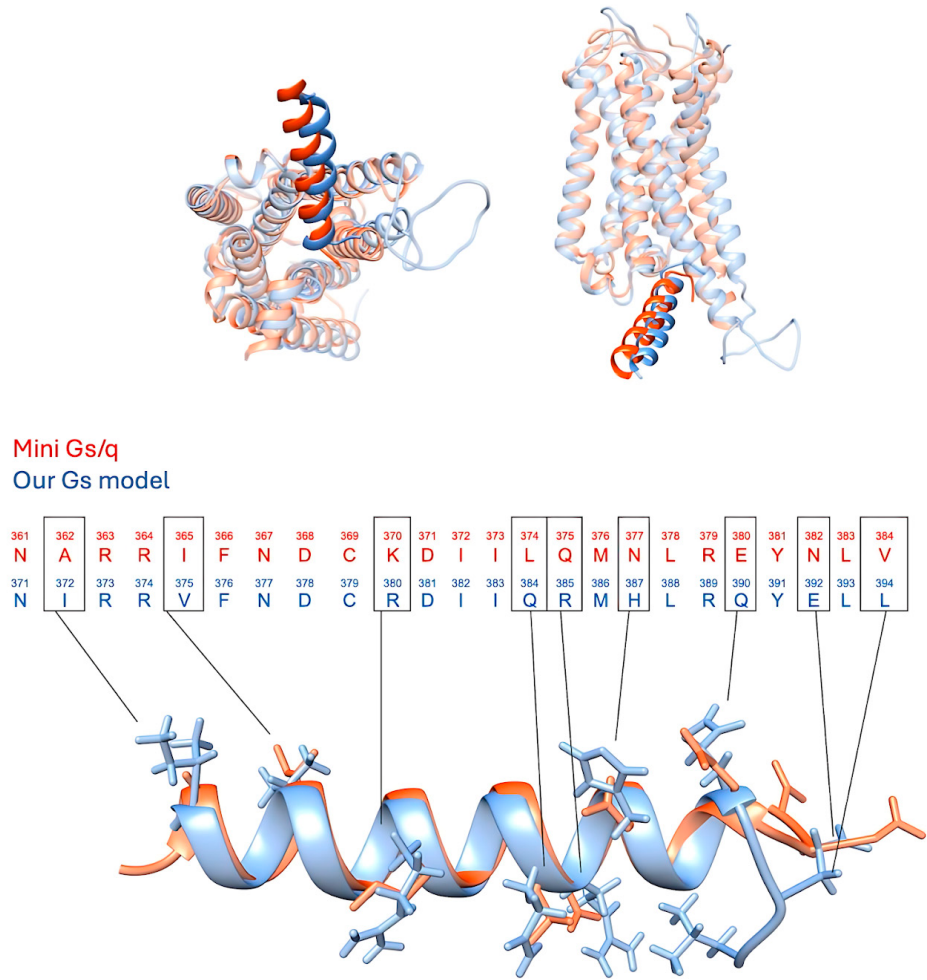


Figure S2: Mini Gq/s- Gs comparison. on the top Orientation of the $\langle 5$ helix of the crystal structure of Gq protein (red) and Gs predicted model (blue). On the bottom $\langle 5$ helix not conserved residues between Gq protein (red) and Gs predicted model (blue)

Cluster	Members	Representative	Weighted_Score
0	146	Center	-888.88
		Lowest_Energy	-926.16
1	129	Center	-657.79
		Lowest_Energy	-825.49
2	76	Center	-668.89
		Lowest_Energy	-826.62
3	66	Center	-735.47
		Lowest_Energy	-913.09
4 - selected cluster	61	Center	-654.84
		Lowest_Energy	-752.53
5	50	Center	-668.58
		Lowest_Energy	-722.86
6	43	Center	-680.50
		Lowest_Energy	-721.28
7	42	Center	-666.06
		Lowest_Energy	-727.98
8	41	Center	-666.58
		Lowest_Energy	-731.62
9	38	Center	-715.34
		Lowest_Energy	-746.95
10	35	Center	-679.60
		Lowest_Energy	-726.17
11	33	Center	-751.42
		Lowest_Energy	-895.49
12	30	Center	-675.42
		Lowest_Energy	-726.93
13	27	Center	-718.75
		Lowest_Energy	-794.14
14	24	Center	-654.39
		Lowest_Energy	-735.18
15	19	Center	-650.17
		Lowest_Energy	-698.98
16	19	Center	-671.07
		Lowest_Energy	-792.60
17	16	Center	-703.28
		Lowest_Energy	-742.48
18	14	Center	-664.48
		Center	-715.84
19	12	Lowest_Energy	-646.81
		Center	-680.43
20	10	Lowest_Energy	-670.92
		Center	-672.30
21	10	Lowest_Energy	-666.47
		Center	-880.11
22	10	Lowest_Energy	-646.08
		Center	-759.06
23	7	Lowest_Energy	-648.63
		Center	-678.92

Table S1: Docking scores obtained from the ClusPro protein-protein docking analysis online server. We excluded any complexes in which the Gs protein was positioned within the lipid bilayer