

Supplementary information, Figure S1

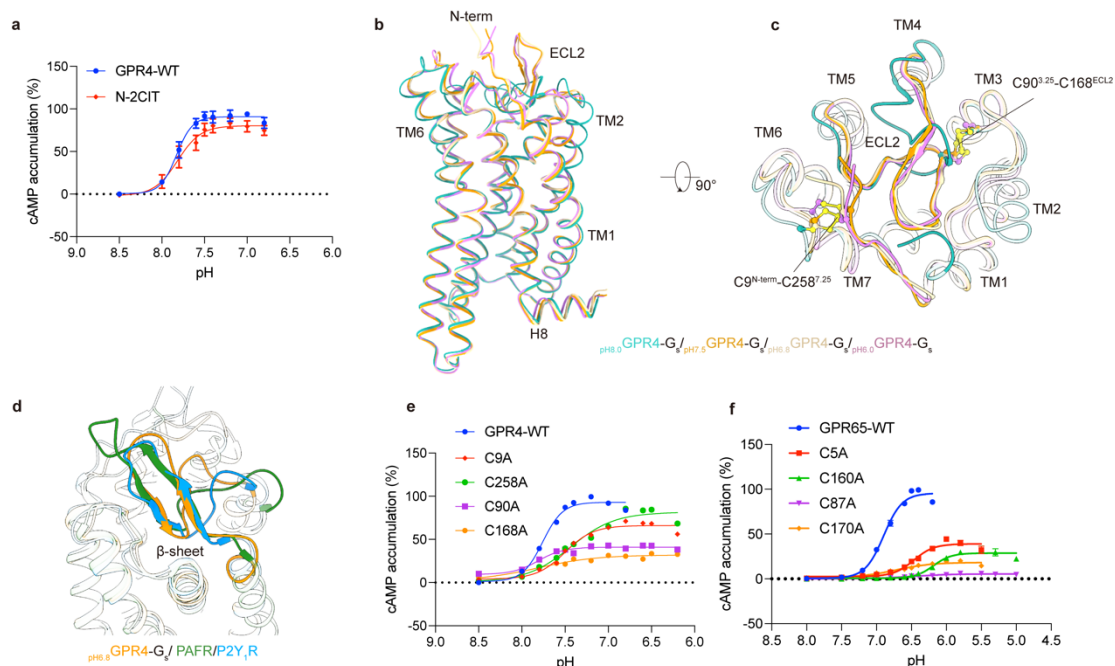


Fig. S1 Structures of different pH activated GPR4-Gs complexes. **a**, Concentration–response curves of protons with Fusion-GPR4 by measuring the cellular cAMP accumulation through the GloSensor assay. Data are means $\pm$ SEM of three biological replicates. **b-c**, Structural alignment of GPR4-G_s at pH7.5, pH6.8, pH6.0, and pH8.0 in side view (**b**) and extracellular view (**c**). **d**, ECL2 adopts the β -sheet hairpin structure in the $\text{pH}_{6.8}$ GPR4-G_s complex, which is similar to the δ -branch GPCRs, PAFR (PDB: 5ZKP) and P2Y₁R (PDB: 7XXH). **e-f**, Concentration–response curves of protons with alanine mutations of residues forming disulfide bonds in GPR4 (**e**) and GPR65 (**f**) by measuring the cellular cAMP accumulation through the GloSensor assay. Data are means $\pm$ SEM of three biological replicates.