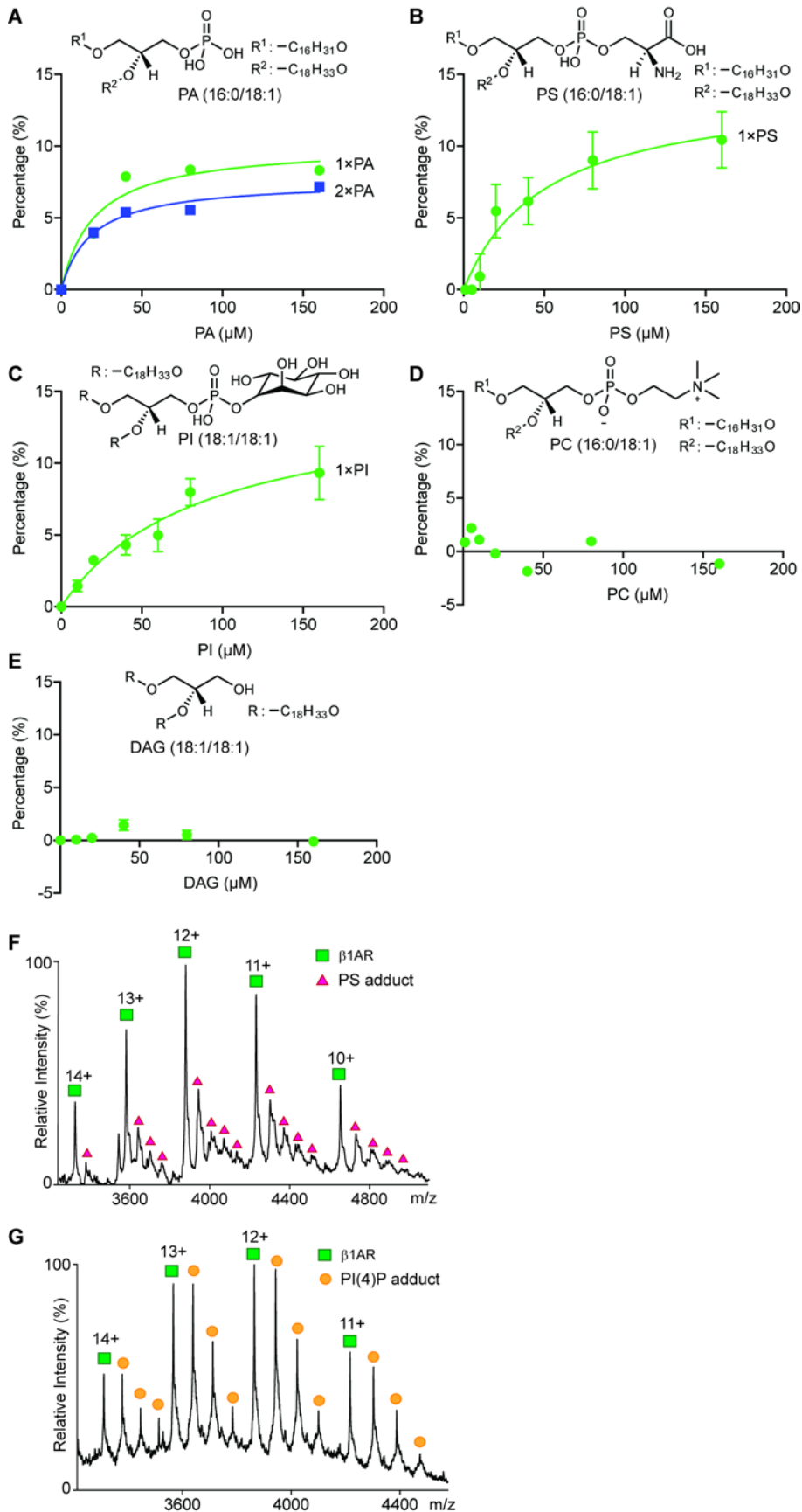
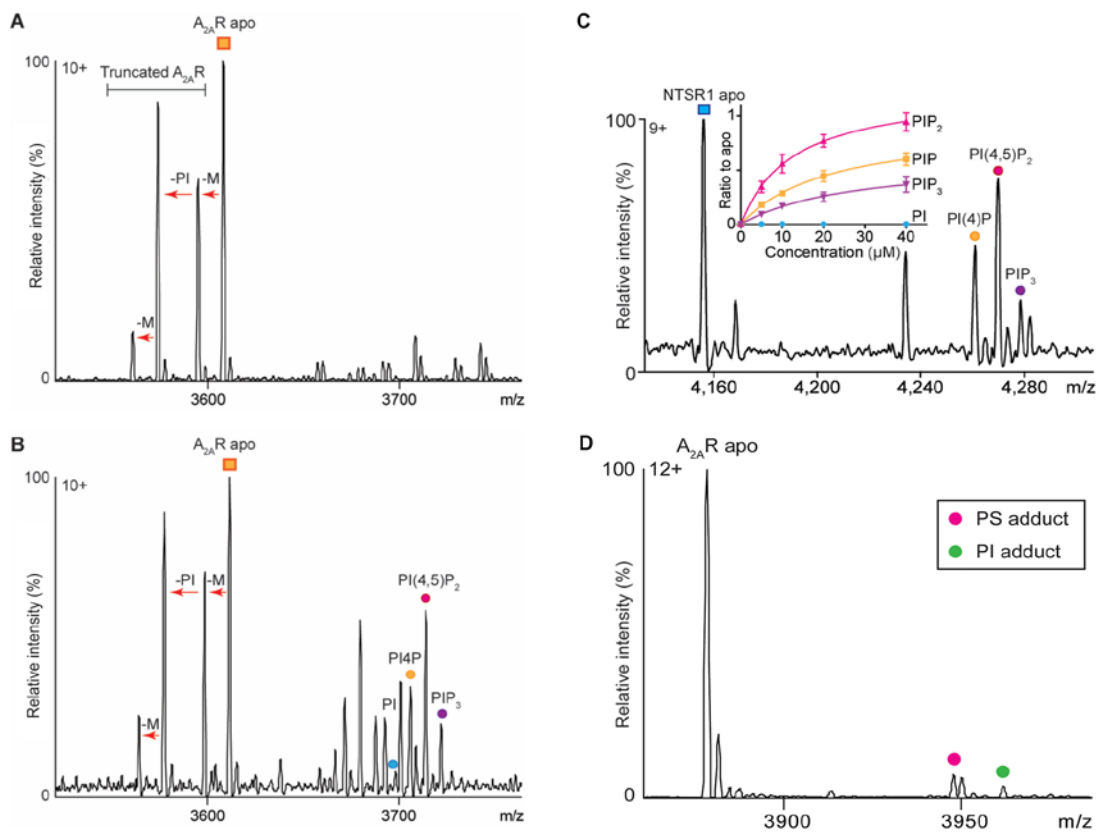


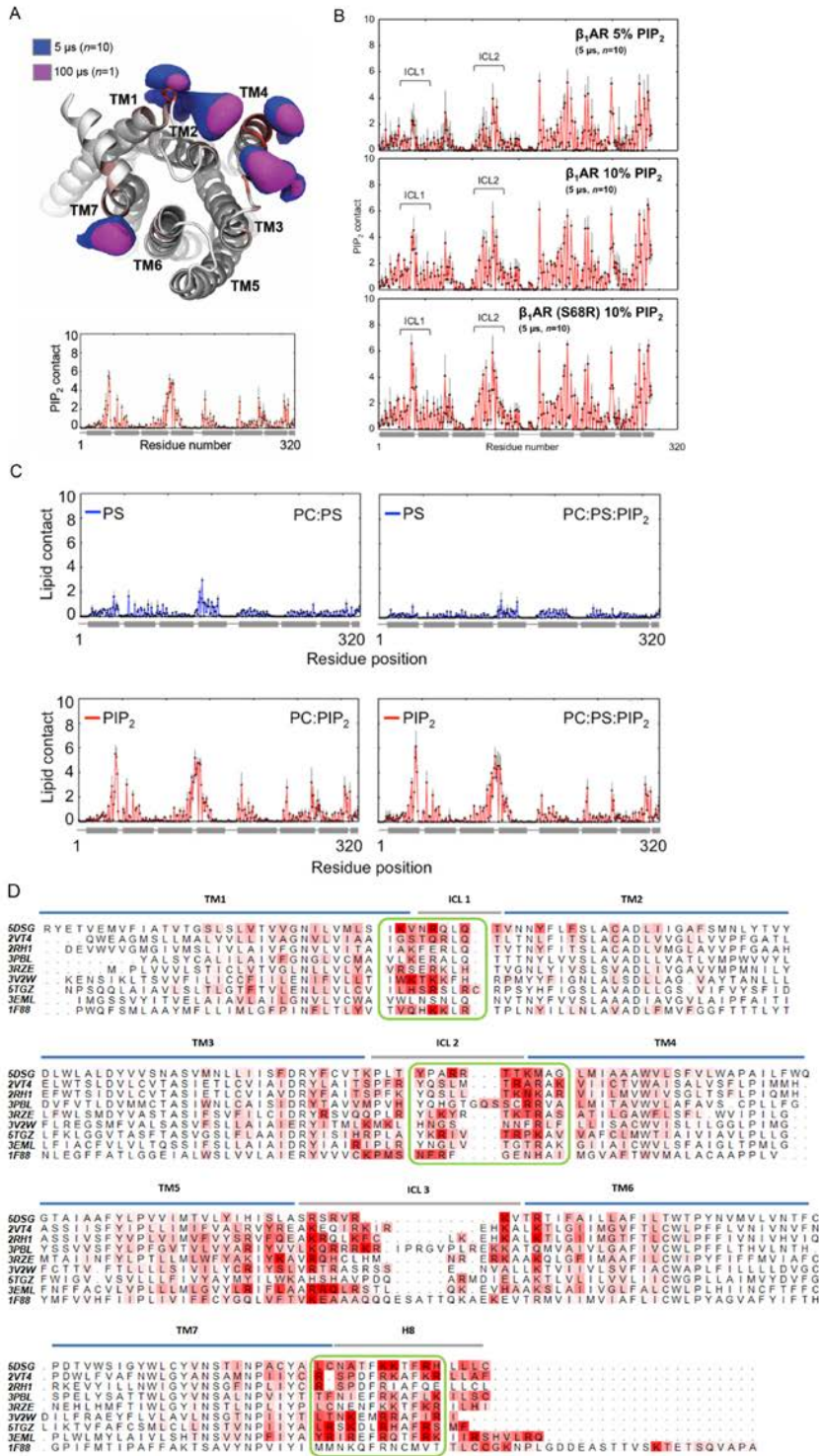
Extended Data Figure 1. Identification of lipids bound to NTSR1 HTGH4-ΔIC3B.



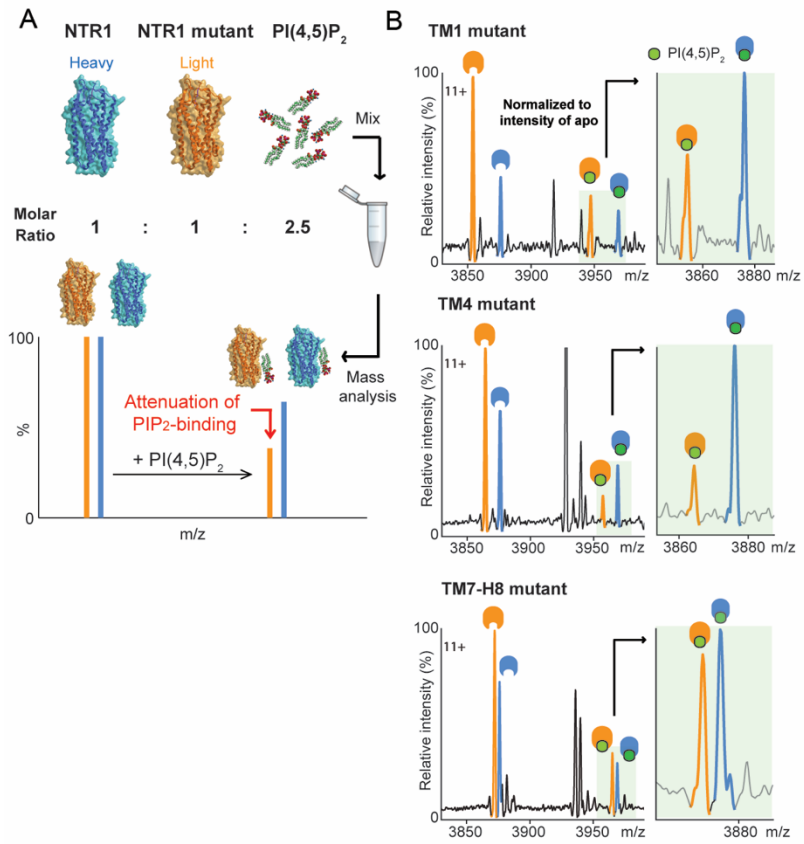
Extended Data Figure 2. Lipid binding preference of NTSR1 and β_1 AR.



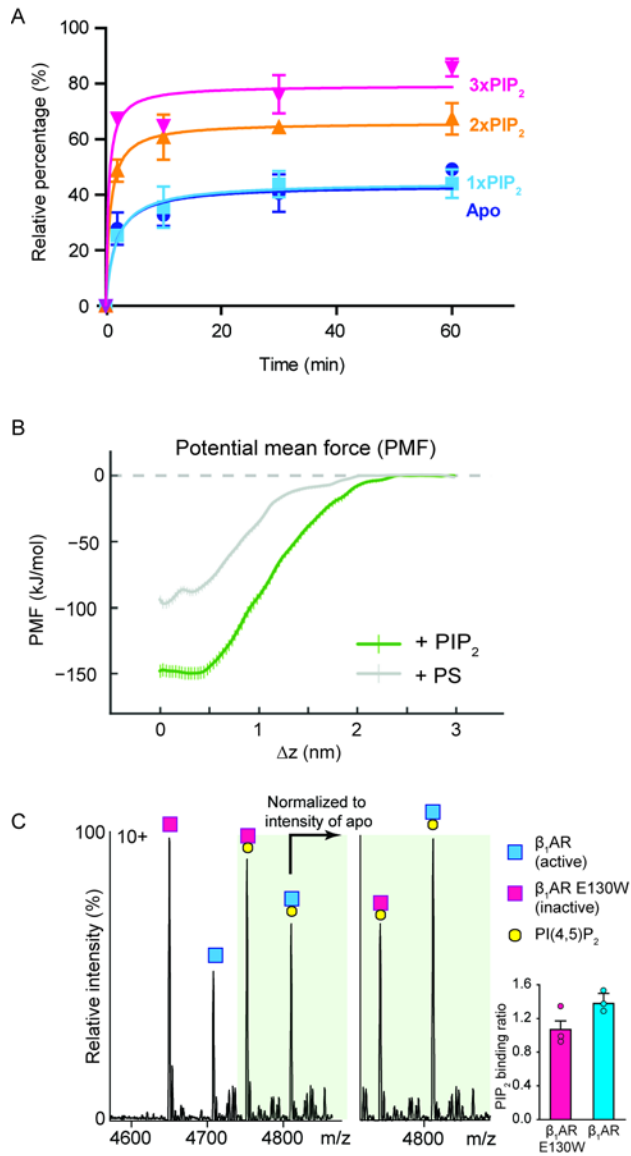
Extended Data Figure 3. Investigation of the phospholipid preferences of $A_{2A}R$ and NTSR1.



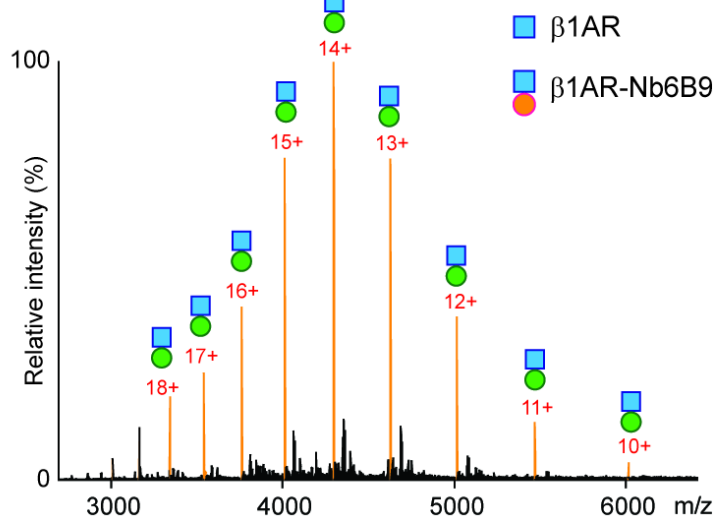
Extended Data Figure 4. NTSR1- and β_1 AR-PIP₂ interactions within CGMD simulations and comparison of PIP₂ contacts over different GPCRs.



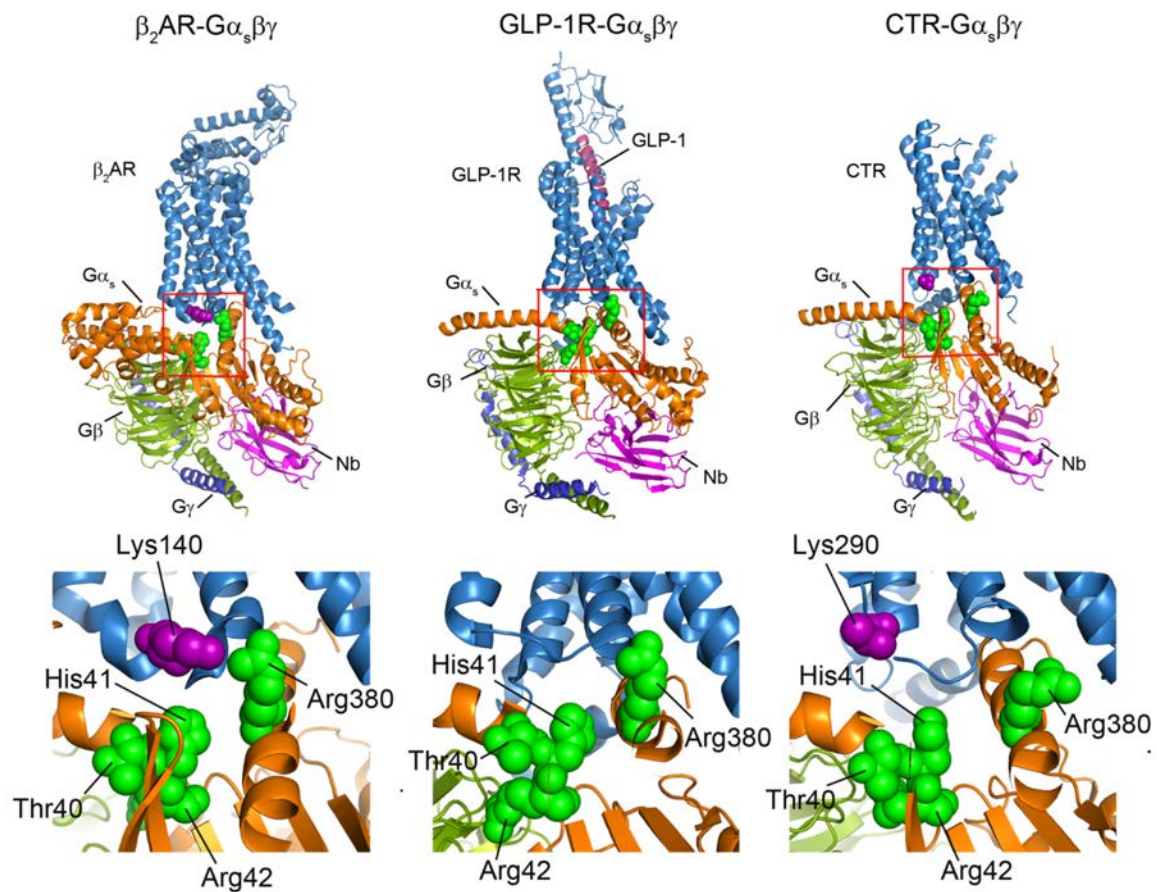
Extended Data Figure 5. Site-directed mutagenesis attenuates PIP₂ binding to NSTR1.



Extended Data Figure 6. PIP₂ binds preferentially to β_1 AR in an active state and stabilises β_1 AR coupled to mini-G_s and A_{2A}R-mini-G_s complex.



Extended Data Figure 7. Detection of nanobody coupling to β_1 AR.



Extended Data Figure 8. Structural comparison of class A and class B GPCRs in complex with trimeric $G\alpha\beta\gamma$ complexes.

Table 1. Lipidomics analysis of purified β_1 AR

Mass (Da)	Lipid ID
824.61	PC (36:0)
716.52	PE (34:1)
742.54	PE (36:2)
714.51	PE (34:2)
772.59	PE (38:1)
752.57	PE (37:4)
793.57	PG (38:6)
807.50	PI (32:1)
833.52	PI (34:2)
865.58	PI (36:0)
835.53	PI (34:1)
863.57	PI (36:1)
861.55	PI (36:2)
891.60	PI (38:1)
758.50	PS (34:2)
760.51	PS (34:1)
786.53	PS (36:2)
1019.60	PIP (42:5)
1343.90	CL (64:4)
1371.93	CL (66:4)
1399.96	CL (68:4)

Table 2. Simulations run. Lipids were symmetrically distributed between leaflets.

Name	Length	Bilayer Composition
NTSR1	10 x 5 μ s	POPC(95%):PIP ₂ (5%)
NTSR1	3 x 5 μ s	POPC(95%):PS(5%)
NTSR1	10 x 5 μ s	POPC(95%):PS(5%):PIP ₂ (5%)
NTSR1 extended	1 x 100 μ s	POPC(95%):PIP ₂ (5%)
β_1 AR (5%)	10 x 5 μ s	POPC(95%):PIP ₂ (5%)
β_1 AR (10%)	10 x 5 μ s	POPC(90%):PIP ₂ (10%)
β_1 AR (S68R, 10%)	10 x 5 μ s	POPC(90%):PIP ₂ (10%)
A _{2A} R-mini-G _s	10 x 8 μ s	POPC(95%):PIP ₂ (5%)

