

**Supplemental Figure 1. GPRC6A Homology Modelling.** (A) MSA between 16 sequences shown using clustalx color code. Alignment is shown for helix-4, extracellular loop-2 and helix-5 regions. (B) Sequence similarity scores between 16 sequences after MSA. Sequence 1: GPRC6A, Sequences 2-9: class-C GPCR's, Sequences 10-16: class-A GPCR's. mGluR-1 (sequence-2) and mGluR-5 (sequence-3) taken as main templates for transmembrane domain modelling (C, D) GPRC6A transmembrane homology models based on the mGlu-1 and mGlu-5 receptor structures.

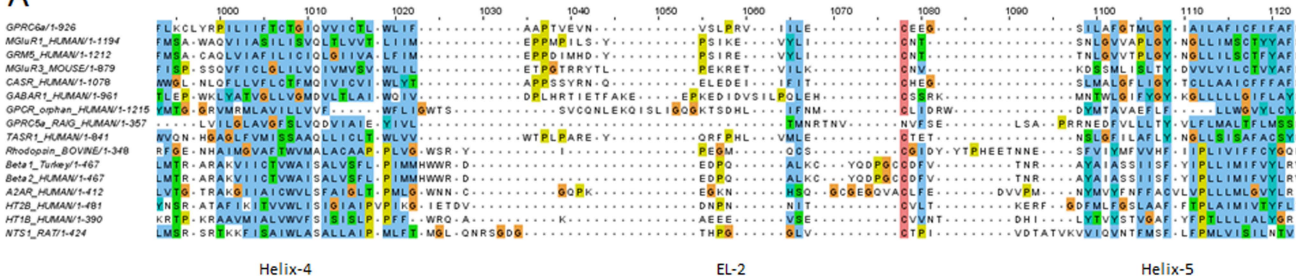
**Supplemental Figure 2. Generation of GPRC6A knockdown PC-3 cells using CRISPR-Cas9 system.**

(A) The lentiCRISPR vector from Addgene. Location and sequences of GPRC6A sgRNA-3 (B) , and sequence mutagenesis of GPRC6A in PC-3 cells with CRISPR-Cas9 system (C). GPRC6A messenger RNA (D) and protein expression (E) in GPRC6A knockdown PC-3 cells using CRISPR-Cas9 system.

**Supplemental Figure 3. Docking of DJ-I-267R to GPRC6A.** Residues surrounding DJ-I-267R in the binding pocket.

**Supplemental Figure 4. Docking of DJ-I-267S to GPRC6A.** Residues surrounding DJ-I-267S in the binding pocket.

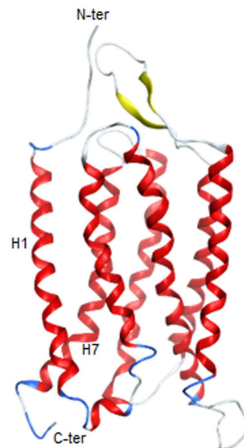
A



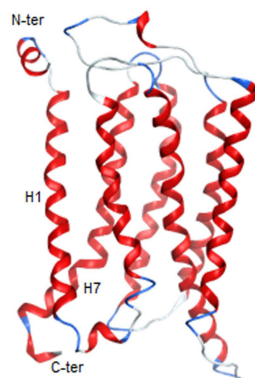
B

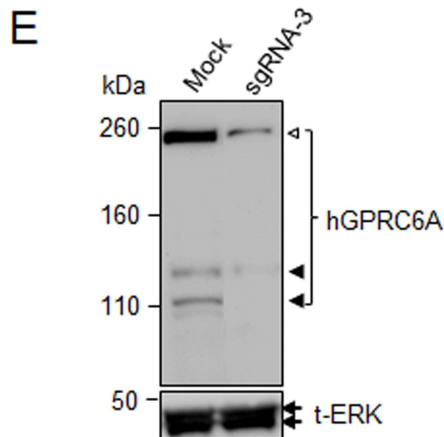
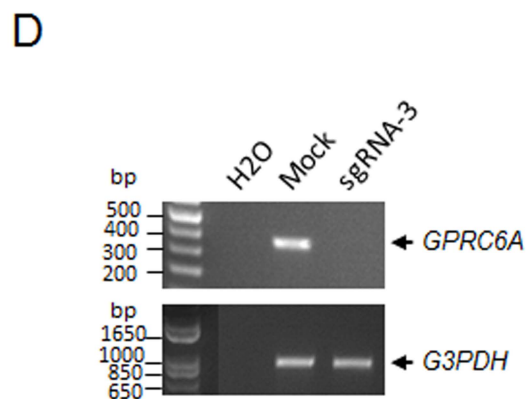
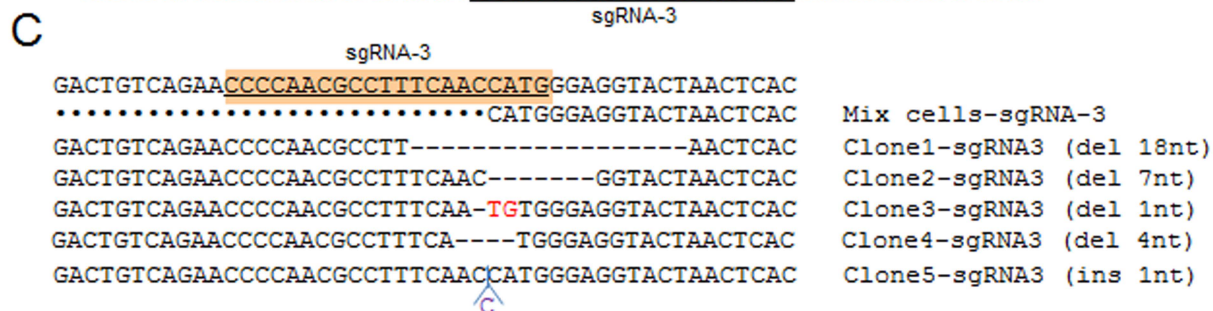
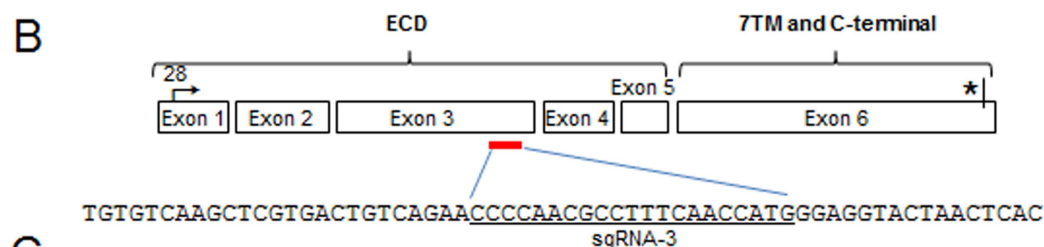
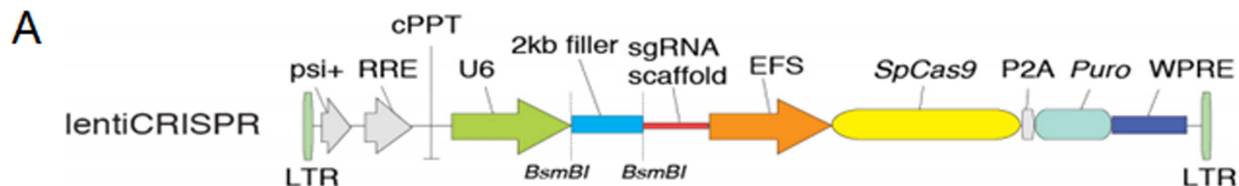
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1:GPRC6a	33.5	34.2	44.7	45.0	27.5	37.9	29.1	49.2	27.6	22.5	22.5	21.4	22.9	22.1	25.9	
2:MGIuR1_HUM...	43.2	73.8	62.3	44.0	29.9	25.2	35.3	43.5	24.7	24.2	24.2	23.5	23.7	19.7	23.1	
3:GRMS_HUMAN...	44.7	75.0	60.9	42.7	30.1	23.9	32.8	43.6	25.9	22.3	22.3	22.3	22.5	20.0	22.9	
4:MGIuR3_MOUSE...	42.4	45.1	44.1	38.9	30.2	36.9	31.9	40.1	25.6	20.1	20.1	19.2	18.3	21.0	22.4	
5:CASR_HUMAN...	52.4	39.7	38.0	47.7	27.4	20.7	31.9	49.3	26.4	20.3	20.3	19.2	22.5	20.0	23.3	
6:GABAR1_HUM...	28.5	24.0	23.8	33.0	24.4	19.8	26.3	30.6	26.1	22.3	22.3	19.7	20.4	23.6	26.9	
7:GPCR_orpha...	23.4	25.6	23.9	23.3	23.4	25.0	26.9	24.3	24.7	21.0	21.0	23.5	18.7	19.2	22.9	
8:GPRC5a_RAI...	31.2	10.6	9.7	33.0	10.6	9.8	7.3	31.1	19.8	16.1	16.1	16.3	16.4	16.7	18.2	
9:TASR1_HUMA...	44.7	30.7	30.3	38.3	38.5	26.7	36.8	26.1	26.1	19.5	19.5	18.0	19.8	19.2	23.6	
10:Rhodopsin...	30.4	7.2	7.4	10.1	8.5	9.5	7.1	19.3	10.8	26.6	26.6	29.6	27.2	33.3	29.7	
11:Beta1_Turk...	31.3	9.5	8.6	10.7	8.8	10.8	8.1	21.0	10.8	35.6	99.8	40.8	37.2	46.9	34.2	
12:Beta2_HUMA...	31.3	9.5	8.6	10.7	8.8	10.8	8.1	21.0	10.8	35.6	99.8	40.8	37.2	46.9	34.2	
13:A2AR_HUMAN...	9.5	8.1	7.9	9.0	7.3	8.4	8.0	18.8	8.8	35.1	36.0	36.0	33.1	35.1	29.0	
14:HT2B_HUMAN...	31.9	9.5	8.9	10.0	10.2	7.4	22.1	11.3	37.6	38.3	38.3	38.6	44.4	34.2		
15:HT1B_HUMAN...	9.3	6.4	6.4	9.1	7.2	9.6	6.7	18.2	8.9	37.4	39.2	39.2	33.3	36.0	31.8	
16:NTS1_RAT/1...	31.9	8.2	8.0	10.8	9.2	11.9	8.0	21.4	11.9	36.2	31.0	31.0	29.9	30.1	34.4	

C

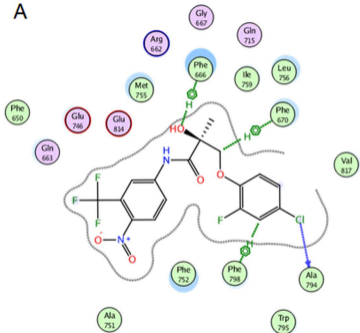


D

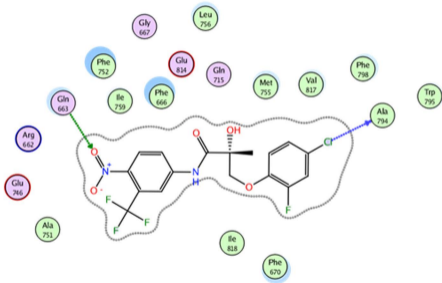




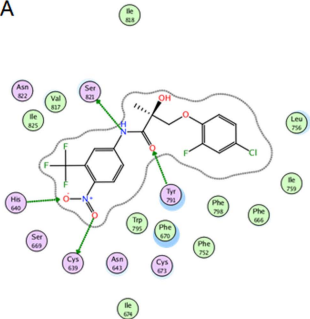
A



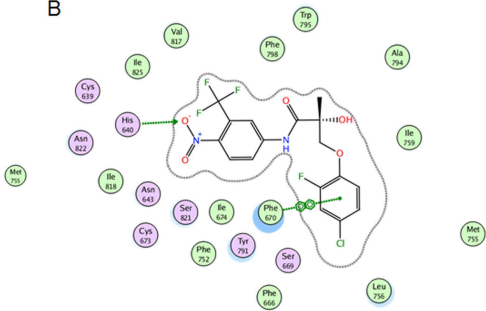
B



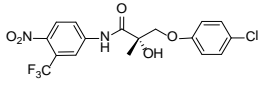
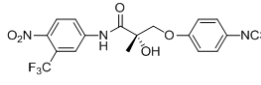
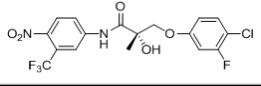
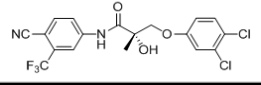
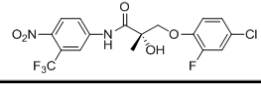
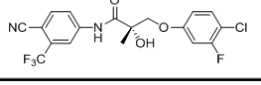
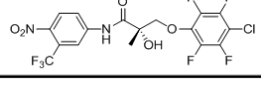
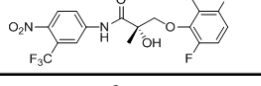
A



B



**Supplemental Table 1. The list of SARMs.**

NAME	ACTIVITY	STRUCTURE
DJ-I-17	++	
DJ-I-47	-	
DJ-I-157	+	
DJ-I-225S	++	
DJ-I-267S	++	
DJ-III-127	++	
DJ-III-129	+	
DJ-III-159	++	
DJ-IV-5S	-	