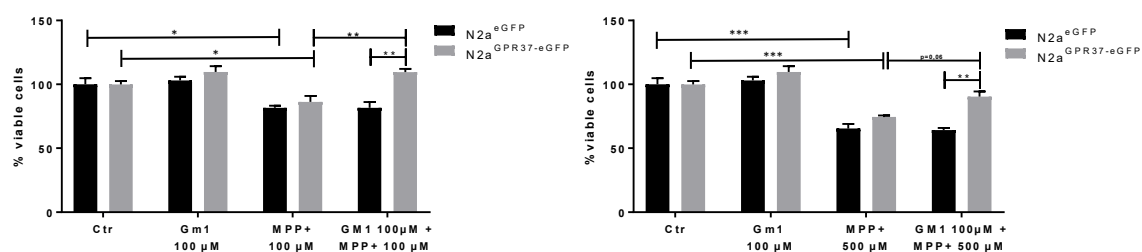
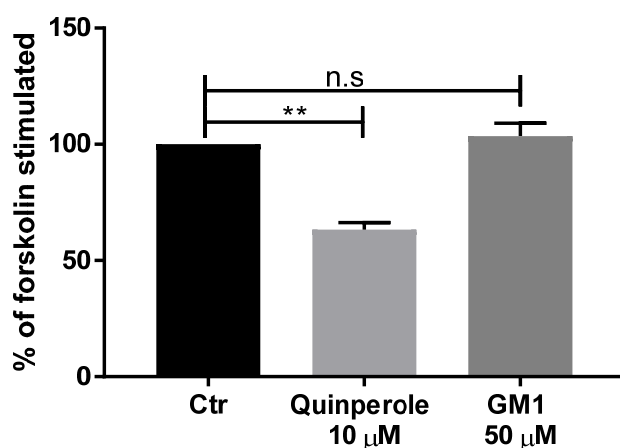


## Supplementary Information and Figures



**Supplementary Figure S1.** GPR37-specific rescue with GM1 treatment (100 μM) against MPP+ treatments of different concentrations. GPR37-specific rescue of GM1 pretreatment (100 μM) against MPP+ treatments of different concentrations in stable N2a<sup>GPR37-eGFP</sup> compared to N2a<sup>eGFP</sup> after 24 h measured by rezasurin assay. n=3 \* p<0.05 \*\* p<0.01, \*\*\* p<0.001 (2-way ANOVA, Tukey posthoc test).



**Supplementary Figure S2.** Positive control in signaling experiments. Signaling from transiently transfected HEK293T with D2R-tdTomato show expected decrease in cAMP when stimulated with 10 μM quinpirole. GM1 does not change cAMP level. n=3, \*\* p<0.01, (Kruskal-Wallis test followed by Dunn's test for multiple comparisons).

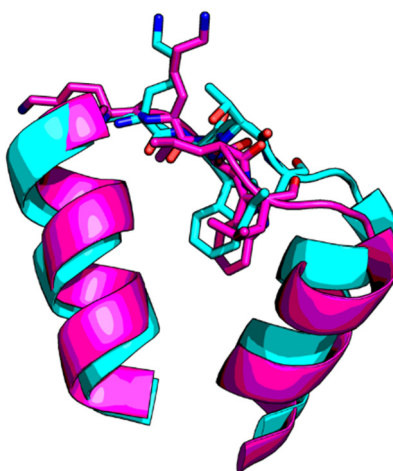
## Homology modeling

GPR37 structure was predicted using MODELLER<sup>1</sup> with the crystal structure of the Endothelin B receptor (PDB ID: 5GLH) used as a template. Briefly, the sequences were aligned manually using Jalview<sup>2</sup> followed by the generation of 100 models using MODELLER, which were ranked based on the DOPE score<sup>3</sup>. The top models were then evaluated manually and refined. The predicted active structure of 5HT1A was obtained from GPCRdb and aligned to the top GPR37 model using Pymol. Similarly, inactive and active predicted structures of GPR37 were obtained from GPCRdb<sup>4</sup>, aligned and compared with the active or inactive predicted model of the 5HT1A receptor.

A)

		ECL1			
Residue number		23	23	23	23
Sequence-based ()		.49	.50	.51	.52
Structure-based (GPCRdb)		x49	x50	x51	x52
[Human] 5-HT <sub>1A</sub> receptor		-	K	W	T
[Human] GPR37		K	K	W	L
Seq consensus		+	K	W	+
Prop consensus		K	K	W	L
Length		5	5	6	

B)



**Supplementary Figure S3.** Homology modeling method and figure. Sequence alignment from GPCRdb<sup>4, 5</sup> showing conserved lysine and tryptophan residues, claimed to be important for GM1 binding to 5HT1A (A). Model of inactive states with GPR37 in magenta and 5HT1A in turquoise (B).

## References

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4. Pándy-Szekeres G, Munk C, Tsonkov TM, et al. GPCRdb in 2018: adding GPCR structure models and ligands. *Nucleic Acids Res* 2018;46(D1):D440-D446.
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