COMPUTATIONAL TARGET PROFILE

GPR85

An Orphan Class A GPCR, Characterised Without An Experimental Structure

The conserved CNS orphan, assessed conservatively. The most conserved vertebrate GPCR, still an orphan — a *medium*-confidence, lipid-adjacent pocket (not forced into a high-confidence claim), with topology, PTM and validation guidance.

UniProt P60893 · 370 aa · Class A (rhodopsin-like) · IDG tier: T_{bio} · PDB: none · July 2026

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At A Glance

Fold	Seven transmembrane helices; multi-pass plasma-membrane receptor; non-enzyme; likely monomeric.
Orthosteric Pocket	**Testable hypothesis — medium confidence.** A residue-level pocket at the **canonical class A orthosteric site** (TM3, ECL2, TM5, TM6, TM7); its nearest structural match is a cholesterol/lipid-type site. No confirmed endogenous ligand — only weak (∼1 µM) synthetic tool compounds reported.
Structural Anchors	**Conserved TM3–ECL2 disulfide (C93–C171).** Strongly predicted; plus a C-terminal S-palmitoylation site (C356) and N-terminal N-glycosylation (N2).
Flexible Regions	A large disordered ICL3 (193–273), a short disordered N-terminus (1–10) and C-tail (356–370) — ∼30% disordered overall.
Clean Signal	No amyloidogenic segments predicted.

PREDICTION CONFIDENCE

Figure 1. Model-reported confidence for the headline calls. The pocket (amber) is the load-bearing prediction that the rest of this profile builds on.

1 The Gap

GPR85 (SREB2) is a paradox. It is the **most evolutionarily conserved GPCR in vertebrates** — 100% identical in amino-acid sequence across human, rat and mouse [3] — yet it remains a class A orphan with **no confirmed endogenous ligand**, **no experimental structure in the PDB**, and only a thin literature (understudied; IDG T_{bio}) [2]. Its biology is CNS-focused: mild over-expression reduces brain size and produces schizophrenia-endophenotype behaviours in mice [4], and the receptor negatively regulates adult hippocampal neurogenesis [5]. The only ligands reported to date are weak (∼1 µM) synthetic tool compounds [6].

That combination — **high interest, near-zero structural information** — is exactly where prediction earns its keep: everything below is computed from the canonical 370-residue sequence and derived structural predictions, with no experimental GPR85 structure or validated ligand used as input. For a genuine orphan, there is nothing to look up.

2 Receptor Architecture And Topology

The receptor is a canonical class A seven-helix bundle. Helix boundaries and the intervening loops are resolved cleanly, with three flexible regions that matter for anyone planning to express, truncate, or crystallise the protein.

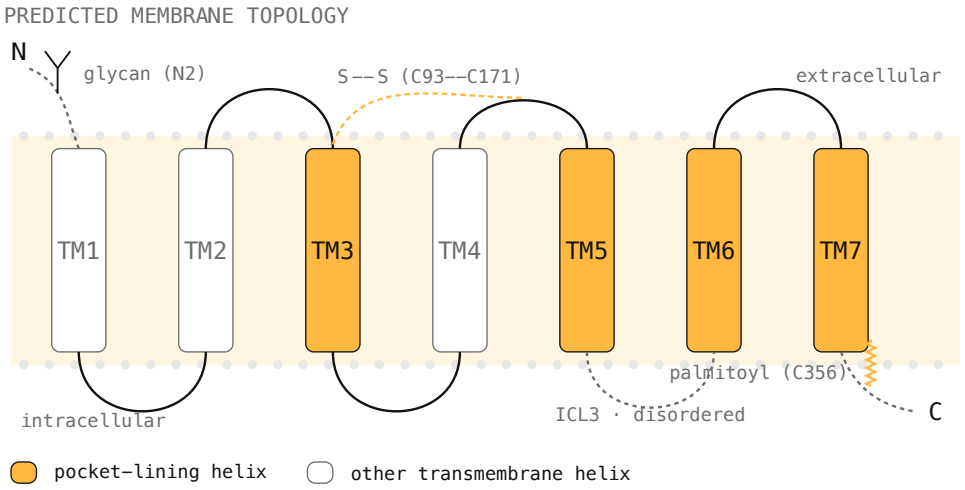

Figure 2. Predicted membrane topology. Seven transmembrane helices with an extracellular N-terminus and intracellular C-terminus; amber marks the four pocket-lining helices. The conserved C93–C171 disulfide, N2 glycosylation, C356 palmitoylation and the disordered ICL3 are drawn in place.

Element	Residues	Note
N-terminus	1–20	Short, extracellular; disordered 1–10; glycosylated at N2.
TM1–TM7	see figure	21–43, 59–79, 93–116, 139–161, 181–200, 288–310, 320–339.
ECL2	162–180	Carries C171 of the conserved disulfide; contributes to the pocket.
ICL3	201–287	Large disordered core (193–273); clustered phospho-sites (putative GRK/PKC).
C-terminus	340–370	Disordered 356–370; palmitoylation anchor at C356.

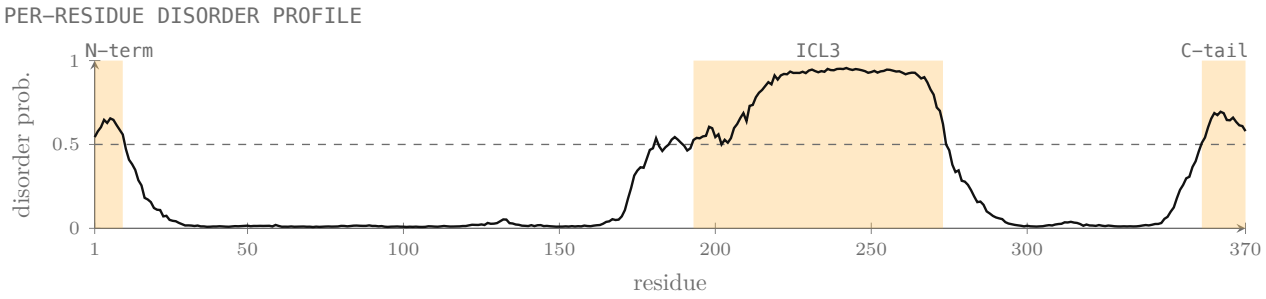

Figure 3. Predicted disorder across the sequence. Amber bands mark the three disordered regions (dashed line = 0.5 call threshold). The ordered seven-helix core between them is the region most amenable to structural work once the usual thermostabilisation and fusion strategies are applied.

3 The Predicted Orthosteric Pocket

Every class A GPCR has an orthosteric pocket, so its existence is not the finding. The useful question is *which residues line it* — the input a docking run or a selectivity argument actually needs, and the one thing you cannot read straight off the sequence. Astra resolves that residue set and places it at the **canonical class A orthosteric site** (TM3, ECL2, TM5, TM6, TM7): a **testable, residue-level hypothesis (medium confidence)**. The nearest structural match is a cholesterol/lipid-type site, so treat this as a lipid-facing cavity to probe rather than a proven druggable pocket. GPR85 has *no confirmed endogenous ligand*; only weak (∼1 µM) synthetic

tool compounds have been reported [6].

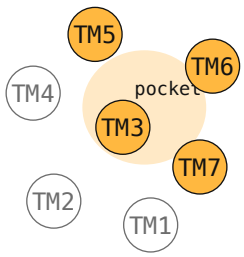

Figure 4. Schematic extracellular (top-down) view. Amber helices line the pocket; ECL2 caps it.

POCKET-LINING RESIDUES

TM3	94, 100–106
ECL2 / TM5	152, 172–174, 191
TM6	294, 298, 300–303, 305–306
TM7	321, 327–328, 331, 335

AlphaFold gives a fold; Astra adds the annotation. An AlphaFold model of GPR85 exists, and it is a useful input — but a fold alone does not tell you which cavity is the orthosteric pocket, where the modification and disordered boundaries fall, or how far to prioritise each for experiment. This profile is that annotation layer. As a control, the same pocket detection recovers the known orthosteric site on class A GPCRs whose structures *are* solved (e.g. the fatty-acid receptor GPR84), so the GPR85 pocket is a like-for-like prediction rather than an extrapolation into empty space. The net effect: GPR85 goes from an orphan sequence to a **ranked experimental hypothesis map**.

4 Post-Translational And Structural Features

The predicted modification map is coherent with a working class A receptor and points to specific, testable residues:

- **Conserved disulfide C93–C171 (strongly predicted).** Links the extracellular tip of TM3 to ECL2 — the canonical class A bridge that caps the orthosteric pocket. A high-confidence structural sanity check and mutagenesis handle.
- **S-palmitoylation at C356.** In the C-terminal tail, consistent with a membrane-anchored helix 8 that forms a fourth intracellular loop — relevant to trafficking and G-protein coupling.
- **N-glycosylation at N2.** On the short extracellular N-terminus.
- **Phosphorylation clusters** in the disordered ICL3 (224–265) and the C-tail (341–366) — the expected footprint of GRK/PKC regulation and a starting point for signalling studies.

5 Recommended Experimental Follow-Up

This turns an orphan sequence into a ranked, executable plan: each prediction is paired with the experiment that would test it and the readout to watch for.

Prediction	Experiment	Readout
Orthosteric-pocket residues (TM3, TM6, TM7)	Alanine scan + docking / fragment screen at the predicted site	Ligand binding or SAR at the predicted pocket
Conserved disulfide C93–C171	Cys→Ala mutagenesis (C93A, C171A)	Expression / fold loss — fold-integrity check
S-palmitoylation at C356	C356A point mutant	Trafficking / signalling shift
Large disordered ICL3 (193–273)	Fusion-partner insertion or loop deletion	Expression / stability improvement
Weak synthetic tool compounds [6]	Structure-guided SAR at the predicted pocket	Improved potency / selectivity

The receptor's CNS expression and schizophrenia / neurogenesis links [4, 5] indicate where a resulting tool compound would first be worth evaluating.

6 Where This Fits In A Discovery Workflow

Team	What they get from this profile
Target biology	Testable residue-level hypotheses and a validation plan
Structural biology	Construct boundaries, disordered regions, fusion / deletion ideas
Medicinal chemistry	Pocket / active-site residues for docking and SAR
BD / platform evaluation	Evidence Orbion can prioritise dark targets quickly

7 Methods

All predictions were generated with Orbion's Astra suite from the canonical GPR85 sequence (UniProt P60893 [1]). Modules used, with method publications cited where available: **AstraSUIT2** and **AstraROLE2** [7] (membrane and functional class, oligomeric state), **AstraUNFOLD** (topology, disorder, aggregation), **AstraPTM2** [8] (modification sites) and **AstraBIND** [9] (binding pocket). Reported values are model outputs; model internals are out of scope. Confidence scores are model-estimated probabilities (0–1) that rank and gate each call — not calibrated rates of experimental success.

PREDICTION PROVENANCE

Target & input	GPR85 · UniProt P60893, canonical isoform (370 aa)
Structure source	AlphaFold2 predicted model (no experimental PDB entry)
Feature inputs	ESM-2 embeddings + AlphaFold2-derived structural features [7–9]
Models	AstraSUIT2 · AstraROLE2 · AstraUNFOLD · AstraPTM2 · AstraBIND
Binding-site model	GATv2 detector trained on >250k protein–ligand complexes [9]
Confidence & calibration	Per-call model probability; per-model calibration, thresholds and benchmarks reported in [7]–[9]

Scope And Limitations

- **Prediction, not experiment.** These are computational hypotheses to prioritise experiments — not a substitute for a structure or an assay. No result here has been validated in the wet lab.
- **The pocket is predicted; the ligand is not named.** For a genuine orphan the honest output is a residue-level pocket hypothesis, not a drug. We make no claim about ligandability or which chemotype binds.
- **Biology caveats.** GPR85's phenotypes come from mouse over-expression / knockout models [4, 5]; the endogenous ligand is unknown and reported synthetic ligands are weak [6]. And the pocket here is a *medium-confidence, lipid-adjacent* call — treat the therapeutic case as a hypothesis.

8 References

[1] UniProt Consortium. UniProtKB entry P60893 (GPR85, human). uniprot.org.

[2] Pharos / Illuminating the Druggable Genome. GPR85 target record — T_{bio}. pharos.nih.gov/targets/P60893.

[3] Matsumoto M., Saito T., Takasaki J., et al. An evolutionarily conserved G-protein coupled receptor family, SREB, expressed in the central nervous system. *Biochem. Biophys. Res. Commun.* **272**(2), 576–582 (2000). doi:10.1006/bbrc.2000.2829.

[4] Matsumoto M., Straub R.E., Marenco S., et al. The evolutionarily conserved G protein-coupled receptor SREB2/GPR85 influences brain size, behavior, and vulnerability to schizophrenia. *Proc. Natl. Acad. Sci. USA* **105**(16), 6133–6138 (2008). doi:10.1073/pnas.0710717105.

[5] Chen Q., Kogan J.H., Gross A.K., et al. SREB2/GPR85, a schizophrenia risk factor, negatively regulates hippocampal adult neurogenesis and neurogenesis-dependent learning and memory. *Eur. J. Neurosci.* **36**(5), 2597–2608 (2012). doi:10.1111/j.1460-9568.2012.08180.x.

[6] Sakai A., Yasui T., Watanave M., et al. Development of novel potent ligands for GPR85, an orphan G protein-coupled receptor expressed in the brain. *Genes Cells* **27**(5), 345–355 (2022). doi:10.1111/gtc.12931.

[7] Bozkurt Ç., Vasilyeva A., Goteti A. AstraROLE2 & AstraSUIT2: Multi-Task Annotation Models for Functional Profiling of Proteins. *bioRxiv* 2025.06.21.660734 (2025). doi:10.1101/2025.06.21.660734.

[8] Bozkurt Ç., Vasilyeva A., Goteti A. AstraPTM2: A Context-Aware Transformer for Broad-Spectrum PTM Prediction. *bioRxiv* 2025.10.03.680341 (2025). doi:10.1101/2025.10.03.680341.

[9] Goteti A., Vasilyeva A., Bozkurt Ç. AstraBIND: Graph Attention Network for Predicting Ligand Binding Sites. *bioRxiv* 2025.11.10.687555 (2025). doi:10.1101/2025.11.10.687555.