COMPUTATIONAL TARGET PROFILE

GPR27

A super-conserved brain orphan GPCR, characterised without an experimental structure

A brain-enriched SREB orphan, highly conserved across vertebrates yet still without a confirmed ligand or a defined function. No solved structure, no confirmed endogenous ligand, only β-cell and metabolic hints — resolved into a topology, a residue-level orthosteric-pocket hypothesis, and a validation plan.

UniProt Q9NS67 · 375 aa · Class A (Rhodopsin-Like) Orphan GPCR · SREB1 · IDG tier: Tbio · PDB: none · July 2026

Have your own under-characterised target? Send a UniProt ID to contact@orbion.life for a preview like this one.

At A Glance

Fold	Seven transmembrane helices; multi-pass plasma-membrane receptor; non-enzyme.
Orthosteric Pocket	High-priority hypothesis (AstraBIND confidence 0.718). A residue-level pocket in the class A helical bundle (TM5, TM6, TM7) — a concrete starting point for docking and mutagenesis, not a claim of proven ligandability. No validated ligand.
Structural Anchors	Conserved TM3–ECL2 disulfide C95–C171; N-glycosylation at N3 (UniProt).
Flexible Regions	Elevated predicted disorder — disordered N-terminus (1–13), long intracellular loop (209–281) and C-tail (353–373) — the natural truncation boundaries for construct design.
Clean Signal	No amyloidogenic segments predicted.

PREDICTION CONFIDENCE

Figure 1. Model-reported confidence for the headline calls (amber = load-bearing / soft prediction).

1 The Gap

Most tractable receptor families have been structurally explored. GPR27 remains dark: an IDG Tbio class A GPCR with no experimental structure in the PDB, no confirmed endogenous ligand, and a thin primary literature. It is one of the three SREB receptors — super-conserved receptors expressed in brain — highly conserved across vertebrates, a conservation that usually marks a function under selection, yet the receptor stays orphan; UniProt can place it only tentatively, as a possible amine-like receptor. Interest is nonetheless real: a pancreatic β-cell siRNA screen implicated GPR27 in insulin production, and later work tied it to glucose homeostasis.

That combination — genuine interest, near-zero structural information — is exactly where prediction earns its keep: everything below is computed from the canonical 375-residue sequence with Orbion's Astra suite, with no experimental GPR27 structure or validated ligand used as input. For a genuine orphan, there is nothing to look up.

2 Architecture And Topology

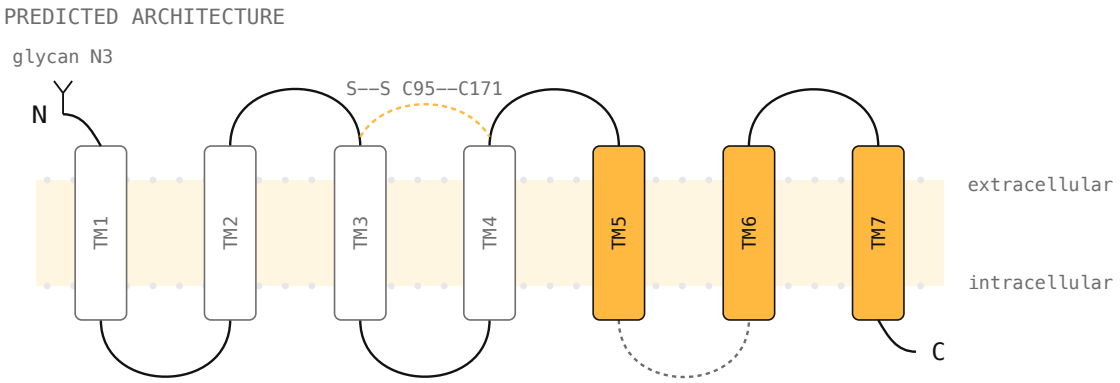

Figure 2. Predicted membrane topology from the sequence: transmembrane helices drawn in the bilayer, amber marks the pocket-lining helices, dashed loops are disordered, and the N/C termini and key modifications are placed in situ.

Element	Residues	Note
Transmembrane Helices	7 predicted	Boundaries: 24–44; 56–76; 98–118; 140–160; 182–202; 286–306; 321–341.

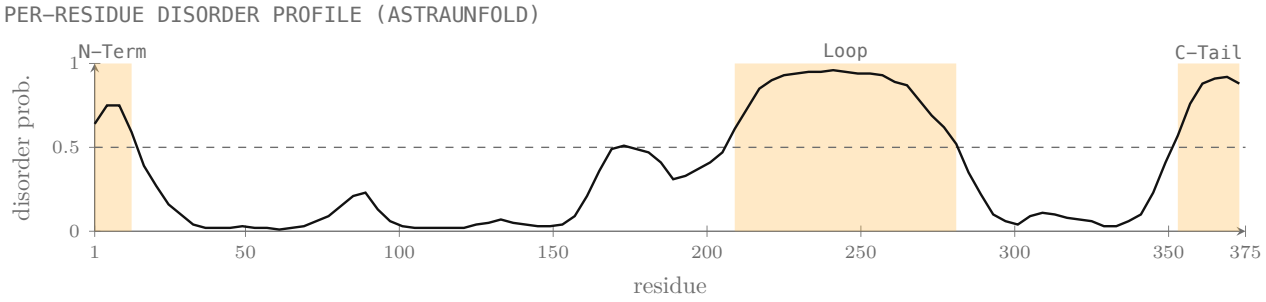

Figure 3. Predicted per-residue disorder (dashed = 0.5 call threshold); amber bands mark flexible regions — natural construct / truncation boundaries.

3 The Predicted Orthosteric Pocket

Astra resolves a residue-level site — the input a docking run or a mutagenesis plan actually needs. Predicted location: **Class A helical bundle (extracellular-facing cavity)**.

PREDICTED POCKET / FUNCTIONAL RESIDUES

TM5	184, 186–187
TM6	293, 295–305, 307
TM7	320, 323, 326–327, 329–330

A residue-level orthosteric hypothesis from AstraBIND (confidence 0.718). As a positive control, AstraBIND places it at the canonical class A orthosteric site — a Ballesteros–Weinstein 3.32 anchor hit, the same pocket the detector recovers on class A GPCRs with solved structures — so this is a like-for-like prediction, not an extrapolation into empty space. Still a computational hypothesis: no validated ligand, and not a proven druggable site.

4 Post-Translational And Structural Features

- **Disulfide bond C95–C171.** Annotated in UniProt (rule-based); the conserved class A TM3–ECL2 bridge that caps the orthosteric pocket — a fold sanity-check and a Cys→Ala mutagenesis handle.

- **N-glycosylation** at position 3 — on the short extracellular N-terminus (UniProt).
- **No amyloidogenic segments predicted.** A clean aggregation profile across the sequence — one fewer liability for construct design.

5 Recommended Experimental Follow-Up

Prediction	Experiment	Readout
Orthosteric-Pocket Residues (TM5, TM6, TM7)	Alanine scan + docking / fragment screen at the predicted site	Ligand binding or SAR at the predicted pocket
Disulfide C95–C171	Cys→Ala mutagenesis (C95A, C171A)	Expression / fold loss — fold-integrity check
Disordered ICL3 (209–281) and C-Tail (353–373)	Fusion-partner insertion or terminal truncation	Expression / thermostability for structural work
Predicted Amine-Like Receptor Class	Surrogate-agonist / β-arrestin recruitment assay	Confirm coupling and functional annotation

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 GPR27 sequence (UniProt Q9NS67): **AstraSUIT** and **AstraROLE** (membrane / functional class), **AstraUNFOLD** (topology, disorder, aggregation), **AstraPTM** (modification sites) and **AstraBIND** (binding pocket). Reported values are model outputs; model internals are out of scope. No experimental GPR27 structure or ligand was used as input. Predictions are computational hypotheses to prioritise experiments, not validated results.

8 References

1. UniProt Consortium. UniProtKB entry Q9NS67 (GPR27, human). uniprot.org.
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5. Nath AK et al. Genetic deletion of gpr27 alters acylcarnitine metabolism, insulin sensitivity, and glucose homeostasis in zebrafish. (2020). https://doi.org/10.1096/fj.201901466r