COMPUTATIONAL TARGET PROFILE

GPR176

A Gz-coupled orphan receptor tied to the circadian clock, characterised without an experimental structure

An orphan that helps set the pace of the circadian clock — Gz-coupled, repressing cAMP with agonist-independent basal activity, and lately tied to cancer progression too. No solved structure, no confirmed ligand — resolved into a topology, a residue-level binding-pocket hypothesis, and a validation plan.

UniProt Q14439 · 515 aa · Class A (Rhodopsin-Like) Orphan GPCR · 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.
Binding Pocket	Predicted binding pocket (AstraBIND confidence 0.767, high). A residue-level cavity in the class A helical bundle (TM6, TM7) — a starting point for docking and mutagenesis; unclassified, with no validated ligand.
Structural Anchors	N-glycosylation on the extracellular N-terminus — predicted sequons at N4, N11, N17 and N27, experimentally confirmed (Wang 2020).
Flexible Regions	Elevated predicted disorder — disordered N-terminus (1–31) and an unusually long cytoplasmic C-tail (346–511) — 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. GPR176 remains dark: an IDG Tbio class A GPCR with no experimental structure in the PDB and no confirmed ligand. Its defining feature is constitutive: it couples to the G(z) subclass and, without any agonist, holds cAMP production repressed — a basal tone reported to help set the pace of circadian behaviour in the brain's master clock. More recent work links it to cancer progression, giving a second, independent reason to characterise it.

That combination — genuine interest, near-zero structural information — is exactly where prediction earns its keep: everything below is computed from the canonical 515-residue sequence with Orbion's Astra suite, with no experimental GPR176 structure or validated ligand used as input. For a genuine orphan, there is nothing to look up.

2 Architecture And Topology

PREDICTED ARCHITECTURE

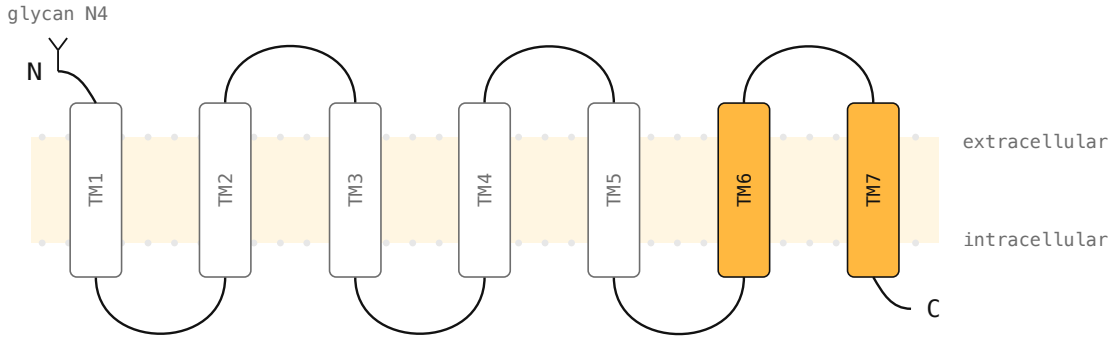

Figure 2. Predicted membrane topology from the sequence: transmembrane helices drawn in the bilayer, amber marks the pocket-lining helices, dashed loops are disordered, and the N/C termini and key modifications are placed in situ.

Element	Residues	Note
Transmembrane Helices	7 predicted	Boundaries: 43–63; 83–103; 119–139; 161–181; 208–228; 268–288; 300–320.

PER-RESIDUE DISORDER PROFILE (ASTRAUNFOLD)

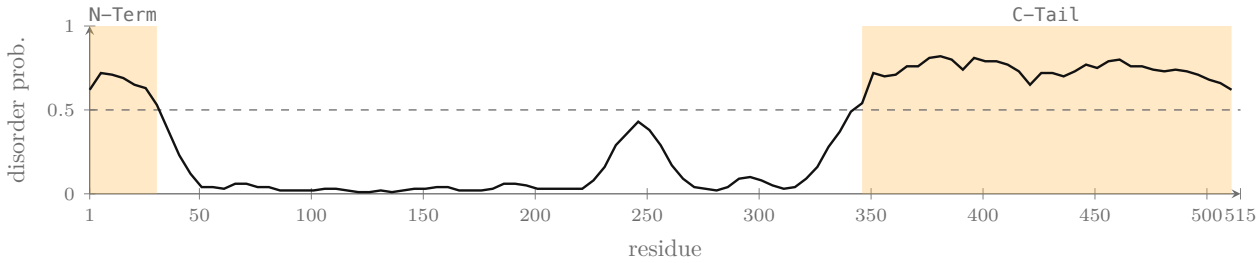

Figure 3. Predicted per-residue disorder (dashed = 0.5 call threshold); amber bands mark flexible regions — natural construct / truncation boundaries.

3 A Predicted Binding 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

TM6	275, 279, 282
TM7	304–310, 312, 316

For this genuine orphan, AstraBIND has no ligand-bound relative to retrieve from — so these residues are a structure-based cavity prediction, not a retrieval-grounded pocket, and the score reflects cavity geometry rather than a known binding site. Treat them as an exploratory starting point for mutagenesis only; the topology, disorder and modification maps above are the higher-confidence outputs for this target. No validated ligand; not a proven druggable site.

4 Post-Translational And Structural Features

- **N-glycosylation** at position 4, 11, 17, 27 — a cluster on the extracellular N-terminus whose N-linked glycosylation has been functionally characterised for GPR176 (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
Binding-Pocket Residues (TM6, TM7)	Alanine scan + docking / fragment screen at the predicted pocket	Binding or SAR at the predicted site
N-Glycosylation Cluster (N4, N11, N17, N27)	N→Q mutagenesis of the N-terminal sites	Trafficking / surface-expression shift
Disordered N-Term (1–31) and Long C-Tail (346–511)	Terminal truncation or fusion-partner insertion	Expression / thermostability for structural work
Constitutive G(z) Signalling	cAMP assay for agonist-independent basal activity	Confirm G(z) coupling and basal cAMP repression

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 GPR176 sequence (UniProt Q14439): **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 GPR176 structure or ligand was used as input. Predictions are computational hypotheses to prioritise experiments, not validated results.

8 References

1. UniProt Consortium. UniProtKB entry Q14439 (GPR176, human). uniprot.org.
2. Pharos (Illuminating the Druggable Genome). GPR176 target record — Tbio. pharos.nih.gov.
3. Doi M et al. Gpr176 is a Gz-linked orphan G-protein-coupled receptor that sets the pace of circadian behaviour. (2016). https://doi.org/10.1038/ncomms10583
4. Tang J et al. GPR176 Promotes Cancer Progression by Interacting with G Protein GNAS to Restrain Cell Mitophagy in Colorectal Cancer. (2023). https://doi.org/10.1002/advs.202205627
5. Wang T et al. Identification and functional characterisation of N-linked glycosylation of the orphan G protein-coupled receptor Gpr176. (2020). https://doi.org/10.1038/s41598-020-61370-y