COMPUTATIONAL TARGET PROFILE

GPR173

A candidate phoenixin receptor in reproductive signalling, characterised without an experimental structure

A reproductive-axis orphan with a named peptide but no solved structure. Phoenixin is reported to signal through GPR173 to activate GnRH and kisspeptin neurons, yet there is no experimental structure and no confirmed small-molecule ligand — resolved into a topology, a residue-level lipid-facing-surface hypothesis, and a validation plan.

UniProt Q9NS66 · 373 aa · Class A (Rhodopsin-Like) Orphan GPCR · SREB3 · 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.
Lipid-Facing Surface	Predicted lipid-facing surface (AstraBIND confidence 0.679, medium). A residue-level membrane-interface hypothesis — a starting point for docking and mutagenesis, not a claim of an orthosteric drug pocket. No validated ligand.
Structural Anchors	Conserved TM3–ECL2 disulfide C96–C174; N-glycosylation at N3 and N184 (UniProt).
Flexible Regions	Elevated predicted disorder — disordered N-terminus (1–17), long intracellular loop (209–277) and C-tail (353–373) — the natural truncation boundaries for construct design.
Clean Signal	One aggregation-prone segment flagged (AstraUNFOLD max 0.536) — worth screening in construct design.

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. GPR173 remains dark: an IDG Tbio class A GPCR with no experimental structure in the PDB and a thin primary literature. It is SREB3 — one of three super-conserved receptors expressed in brain — and is reported to be the receptor for the neuropeptide phoenixin, through which it augments gonadotropin-releasing-hormone signalling in the hypothalamus and pituitary and promotes granulosa-cell proliferation in the ovary. That pairing is largely inferred by similarity and from rodent and cell models, so even the receptor's pharmacology is unsettled.

That combination — genuine interest, near-zero structural information — is exactly where prediction earns its keep: everything below is computed from the canonical 373-residue sequence with Orbion's Astra suite, with no experimental GPR173 structure or validated ligand used as input. For a genuine orphan, there is nothing to look up.

2 Architecture And Topology

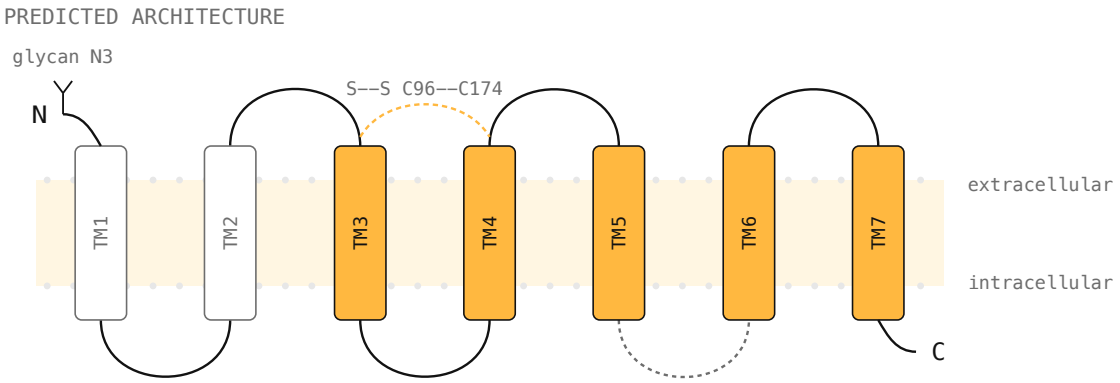

Figure 2. Predicted membrane topology from the sequence: transmembrane helices drawn in the bilayer, amber marks the pocket-lining helices, dashed loops are disordered, and the N/C termini and key modifications are placed in situ.

Element	Residues	Note
Transmembrane Helices	7 predicted	Boundaries: 27–47; 60–80; 98–118; 140–160; 189–209; 288–308; 323–343.

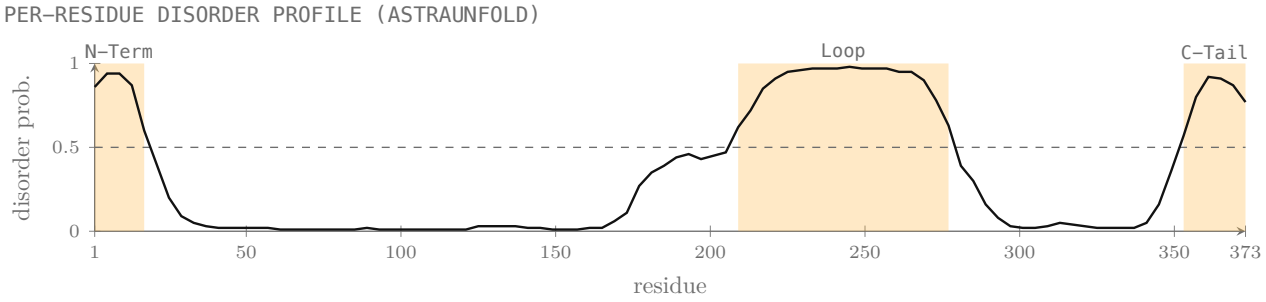

Figure 3. Predicted per-residue disorder (dashed = 0.5 call threshold); amber bands mark flexible regions — natural construct / truncation boundaries.

3 A Predicted Lipid-Facing Surface

Astra resolves a residue-level site — the input a docking run or a mutagenesis plan actually needs. Predicted location: **Membrane-facing / lipid interface (transmembrane surface)**.

PREDICTED POCKET / FUNCTIONAL RESIDUES

TM3	96, 102–108
TM4	154
TM5	190
TM6	295, 297–307, 309
TM7	322, 328–329, 332
Loop / Surface	174–176

AstraBIND classifies this as a membrane-mimetic / lipid-facing surface, not an orthosteric pocket — so we present it as a membrane-interface hypothesis only, and a low-confidence one (no ligand-bound relative to retrieve from). It is an exploratory surface for mutagenesis, not a validated ligand site or a druggable pocket.

4 Post-Translational And Structural Features

- **Disulfide bond C96–C174.** Annotated in UniProt (rule-based); the conserved class A TM3–ECL2 bridge that caps the pocket — a fold sanity-check and a Cys→Ala mutagenesis handle.
- **N-glycosylation** at position 3, 184 — on the extracellular N-terminus and ECL2 (UniProt).
- **Aggregation-prone segment flagged** (AstraUNFOLD amyloid max 0.536) — a modest aggregation liability worth screening during construct design.

5 Recommended Experimental Follow-Up

Prediction	Experiment	Readout
Lipid-Facing Surface Residues (TM3, TM6, TM7)	Alanine scan + docking at the predicted membrane-facing site	Binding or SAR at the predicted surface
Disulfide C96–C174	Cys→Ala mutagenesis (C96A, C174A)	Expression / fold loss — fold-integrity check
Disordered ICL3 (209–277) and C-Tail (353–373)	Fusion-partner insertion or terminal truncation	Expression / thermostability for structural work
Reported Phoenixin Receptor Activity	Phoenixin-14 / -20 challenge in a GnRH / kisspeptin neuron model	Confirm receptor–peptide coupling

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 GPR173 sequence (UniProt Q9NS66): **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 GPR173 structure or ligand was used as input. Predictions are computational hypotheses to prioritise experiments, not validated results.

8 References

1. UniProt Consortium. UniProtKB entry Q9NS66 (GPR173, human). uniprot.org.
2. Pharos (Illuminating the Druggable Genome). GPR173 target record — Tbio. pharos.nih.gov.
3. Treen AK et al. Phoenixin Activates Immortalized GnRH and Kisspeptin Neurons Through the Novel Receptor GPR173. (2016). https://doi.org/10.1210/me.2016-1039
4. Stein LM et al. Hypothalamic action of phoenixin to control reproductive hormone secretion in females: importance of the orphan G protein-coupled receptor Gpr173. (2016). https://doi.org/10.1152/ajpregu.00191.2016
5. Nguyen XP et al. Effect of the neuropeptide phoenixin and its receptor GPR173 during folliculogenesis. (2019). https://doi.org/10.1530/rep-19-0025