DISTILLATION №48 · ALEMBIC LABS

IPAMORELIN — CONJUGATE A PALMITOYL (C16) FATTY ACID TO THE LYS-4 E-AMINE VIA A ΓGLU SPACER, YIELDING AIB-HIS-DBNAL-DPHE-LYS(ΓGLU-PALM)-NH2

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REFINED | PERFORMANCE

CONJUGATE A PALMITOYL (C16) FATTY ACID TO THE LYS-4 E-AMINE VIA A ΓGLU SPACER, YIELDING AIB-HIS-DBNAL-DPHE-LYS(ΓGLU-PALM)-NH2

GROWTH HORMONE SECRETAGOGUE RECEPTOR TYPE 1

AVERAGE CONFIDENCE	PTM / IPTM	VERDICT
77.8%	0.858 / 0.820	REFINED

TARGET	UNIPROT	BINDING PROBABILITY
Growth hormone secretagogue receptor type 1	Q92847	—

TLDR

Fold №48 applies a γGlu-C16 palmitoyl lipidation to the Lys-5 ε-amine of Ipamorelin, yielding Aib-His-D2Nal-DPhe-Lys(γGlu-Palm)-NH2, with the goal of extending plasma half-life via reversible albumin binding. Structure prediction returned strong confidence metrics (pLDDT 0.78, ipTM 0.82), with the pharmacophore retaining its compact β-turn and the lipid tail projecting freely away from the receptor-engaging face. This is the first Ipamorelin fold to address pharmacokinetics through albumin-binding lipidation — an orthogonal strategy relative to the N-terminal methylation explored in Fold #4 and the C-terminal cyclization of Fold #33. All results are in silico predictions only and require wet lab validation.

EXECUTIVE SUMMARY

Ipamorelin Lys-5(γGlu-Palm): pLDDT 0.778, ipTM 0.820. Pharmacophore β-turn intact; lipid tail projects freely from receptor face. First albumin-binding PK extension fold for this peptide — structurally promising, empirically untested.

DETAILED ANALYSIS

Ipamorelin (Aib-His-D-2-Nal-D-Phe-Lys-NH2) is a selective, potent pentapeptide agonist of the growth hormone secretagogue receptor GHSR-1a, distinguished from earlier ghrelin mimetics by its narrow secretory profile — releasing GH without co-stimulating cortisol, prolactin, or gonadotropins at therapeutic doses. Its compact N-terminal tetrapeptide pharmacophore (Aib-His-D-2-Nal-D-Phe) is the receptor-engaging motif, confirmed by SAR studies from the Novo Nordisk group, while the C-terminal Lys-5-NH2 serves primarily as a solubility and charge handle. The compound's central clinical liability is its short plasma half-life (~2 hours in humans; Gobburu et al., 1999), which in practice demands multiple daily subcutaneous injections to sustain anabolic signaling.

Fold №48 addresses this liability directly by conjugating a palmitoyl (C16) fatty acid to the Lys-5 ε-amine via a γGlu spacer — the same linker chemistry validated in liraglutide — to enable reversible albumin binding. Reversible noncovalent association with serum albumin's fatty acid binding sites (principally FA7 for long-chain fatty acids) is the pharmacological mechanism that converted native GLP-1 (t½ ~2 min) into liraglutide (t½ ~13 hours, once-daily) and semaglutide (t½ ~165 hours, once-weekly). The hypothesis is that an analogous depot effect could convert ipamorelin from a thrice-daily injection to a once-daily or twice-daily regimen without sacrificing GHSR-1a agonism.

Structure prediction (AlphaFold2-derived, with Boltz-2 scoring) returned a pLDDT of 0.778 — solidly in the high-confidence range for a modified pentapeptide — with pTM 0.858 and ipTM 0.820 for the ligand–receptor complex. The predicted structure shows the Aib-His-D-2-Nal-D-Phe core retaining its canonical compact conformation consistent with the bioactive β-turn, while the γGlu-palmitoyl chain extends as a flexible appendage from the Lys-5 ε-amine without folding back onto the pharmacophore or occluding the receptor interface. The ipTM of 0.82 is particularly noteworthy: it suggests the lipidated analog can dock into GHSR-1a in a pose geometrically compatible with native ipamorelin engagement, implying that the ~50% MW increase from the lipid addition does not fundamentally disrupt binding geometry.

This fold sits in meaningful dialogue with the lab's prior Ipamorelin work. Fold #4 explored N-terminal N-Me-Aib substitution as a proteolytic stability strategy — a metabolic protection approach. Fold #33 closed a Lys-5 ε-amine to Asp-6 β-carboxylate lactam, exploiting the same Lys-5 ε-amine nucleophile for

conformational constraint rather than PK extension. Fold №48 is the first to leave Lys-5 open for pharmacokinetic modification, leveraging it as an acylation handle rather than a cyclization anchor — a conceptually orthogonal and arguably more translationally relevant strategy. Notably, Fold #33's lactam REFINED verdict (pLDDT 0.73) confirms that modifications at Lys-5 are structurally well-tolerated, and the higher pLDDT here (0.78) suggests the open-chain lipid appendage is even less structurally disruptive than the lactam bridge.

The heuristic property profile provides useful but speculative signal. Aggregation propensity is estimated at 0.177 — relatively low, suggesting the C16 chain does not drive strong self-assembly under the modeled conditions, though micelle formation at physiological concentrations is a legitimate concern for pentapeptide lipid conjugates not captured by this estimator. The half-life estimate of 'moderate-to-long (~1–6 hours)' is conservative relative to what albumin-binding lipidation achieves for larger peptides; for a pentapeptide, albumin binding may be partially offset by rapid dissociation kinetics. The stability score of 0.447 is modest, which may reflect the heuristic's difficulty modeling the metabolic protection that albumin binding confers — a key limitation of sequence-based estimates for lipopeptides.

The literature context adds important nuance. Fowkes et al. (2018) demonstrated that bulky acyl groups on the Lys-5 ε-amine of ipamorelin-related scaffolds are tolerated by GHSR-1a (IC50 = 69 nM, EC50 = 1.1 nM for a 4-fluorobenzoyl conjugate), providing the strongest published precedent for the lipidation site. However, a C16 aliphatic chain differs from an aromatic acyl group in hydrophobicity, flexibility, and aggregation behavior, and no published data exists for any albumin-binding lipidated GHSR-1a agonist. The risk that the pentapeptide's short backbone provides insufficient spatial separation between the albumin-binding fatty acid and the receptor pharmacophore — a steric concern that is less acute for 30-residue GLP-1 — cannot be dismissed without empirical data.

Overall, the structural prediction supports the REFINED verdict: the predicted complex interface, high pLDDT, and pharmacophore geometry are all consistent with a viable lipidated analog. The modification rationale is mechanistically sound, the lipidation site is literature-supported, and the albumin-binding strategy is clinically validated in adjacent peptide classes. The critical unknowns — actual albumin Kd, in vivo half-life, receptor potency retention with the full palmitoyl chain, and self-assembly behavior — cannot be resolved computationally and represent the primary experimental agenda for this compound.

RESEARCH BRIEF

FOLD №48 — IPAMORELIN LYS-5(ΓGLU-PALM) LIPIDATION

Verdict: REFINED | pLDDT 0.778 | ipTM 0.820 | pTM 0.858

> All results are in silico predictions only. This is research, not medical advice. No wet lab validation has been performed.

MECHANISM OF ACTION

Ipamorelin acts as a selective, high-affinity agonist at the growth hormone secretagogue receptor GHSR-1a (UniProt Q92847), the same receptor activated by the endogenous hunger hormone ghrelin. Receptor activation triggers Gαq/11-coupled phospholipase C signaling in somatotrophs, mobilizing intracellular calcium and driving pulsatile growth hormone (GH) secretion from the anterior pituitary. Ipamorelin's selectivity — GH release without significant co-stimulation of cortisol, prolactin, or gonadotropins — distinguishes it from first-generation GHRPs (GHRP-6, GHRP-2) and underlies its favorable safety profile in research settings.

The binding pharmacophore is the N-terminal tetrad Aib-His-D-2-Nal-D-Phe, which adopts a compact β-turn conformation that mimics the bioactive conformation of ghrelin's N-terminal Aib-Ser-Ser-Phe-Leu pentapeptide. The C-terminal Lys-5-NH2 does not contribute meaningfully to receptor contacts and functions primarily as a structural and solubility element — making it the ideal site for pharmacokinetic modification without pharmacophore disruption.

PERFORMANCE APPLICATIONS

Ipamorelin is used in the performance and longevity research context for its capacity to amplify endogenous GH pulsatility, supporting:

- **Anabolism and body composition**: GH-driven IGF-1 release promotes lean mass accretion and adipose mobilization
- **Recovery acceleration**: GH facilitates collagen synthesis and tissue repair
- **Sleep quality**: GH secretion is coupled to slow-wave sleep; GHSR-1a agonism may enhance the sleep-linked GH pulse
- **Longevity/anti-aging contexts**: Restoration of blunted GH pulsatility in aging populations

The native compound's ~2-hour half-life and requirement for multiple daily injections are the primary barriers to practical use and clinical development. A once-daily lipidated analog would represent a meaningful advance in usability and pharmacokinetic predictability — paralleling what liraglutide and semaglutide achieved for GLP-1.

MODIFICATION RATIONALE

The γGlu-C16 palmitoyl modification conjugated to the Lys-5 ε-amine was selected based on four converging lines of reasoning:

1. **Site permissibility**: Fowkes et al. (2018) demonstrated that bulky acyl groups at the Lys-5 ε-amine in ipamorelin-family scaffolds retain GHSR-1a engagement (IC50 = 69 nM, EC50 = 1.1 nM), establishing the position as tolerant of substantial steric additions. This complements Fold #33's finding that a lactam bridge closing at Lys-5 ε-amine yielded a REFINED structure (pLDDT 0.73), confirming the position's modification tolerance from a structural prediction standpoint.
2. **Albumin-binding mechanism**: C16 (palmitoyl) fatty acids bind reversibly to albumin's FA7 site (Kd ~μM range), creating a plasma depot that protects the conjugated peptide from renal filtration and proteolytic degradation. Albumin (t½ ~19 days) becomes a slow-release carrier, extending effective peptide exposure without covalent modification of endogenous proteins.
3. **Validated linker chemistry**: The γGlu spacer is the clinically validated linker used in liraglutide (C16 via γGlu) and is known to optimize the geometry between fatty acid and peptide backbone for albumin engagement while maintaining conformational freedom at the receptor binding interface. It is a pharmaceutical-grade solution to the albumin-binding geometry problem.
4. **Orthogonality to prior folds**: Fold #4 explored N-terminal metabolic stabilization (N-Me-Aib at position 1), and Fold #33 exploited Lys-5 for conformational constraint via lactam cyclization. Fold №48 is the first Ipamorelin fold to use Lys-5 as a pharmacokinetic extension handle, representing a genuinely new chemical space for this peptide in the lab.

PREDICTED PROPERTIES (FAVOURABLE CHANGES FROM NATIVE IPAMORELIN)

Property	Native Ipamorelin	Lys-5(γGlu-Palm) Prediction	Confidence
		0.778	High

Property	Native Ipamorelin	Lys-5(γGlu-Palm) Prediction	Confidence
pLDDT (pharmacophore core)	Ref (~0.75–0.80)		
ipTM (GHSR-1a complex)	Ref	**0.820**	High
Plasma half-life (heuristic)	~2 hours (clinical)	moderate-to-long (~1–6 h estimated; albumin effect not fully captured)	Low-moderate
Aggregation propensity (heuristic)	Low	**0.177** (low)	Moderate
Stability score (heuristic)	Ref	0.447 (modest)	Low
BBB penetration (heuristic)	Low	**0.159** (low; expected for lipopeptide)	Moderate
Pharmacophore conformation	β-turn	β-turn retained	High
Lipid tail orientation	N/A	Projects away from pharmacophore	High

Key predicted structural finding: The γGlu-palmitoyl chain extends as a flexible appendage from Lys-5 without folding back onto the Aib-His-D-2-Nal-D-Phe receptor-engaging face. The ipTM of 0.82 is consistent with a productive receptor docking pose geometrically compatible with native ipamorelin binding.

Heuristic caveat: The half-life estimate of 'moderate-to-long' is a sequence-based estimate that does not model albumin-binding kinetics. Real-world lipidated peptide half-life extensions can far exceed this range (liraglutide achieves 13 hours; semaglutide 165 hours) — or may be attenuated for very short pentapeptide scaffolds. These numbers are illustrative, not predictive.

SUGGESTED NEXT STEPS

COMPUTATIONAL (IN SILICO)

1. **Ensemble structure prediction**: Run 5+ AlphaFold2/Boltz-2 independent seeds to assess pharmacophore conformation reproducibility and lipid tail conformational sampling. Single-run pLDDT of 0.778 is promising but should be ensembled to confirm stability.

2. **Albumin docking**: Model the palmitoyl-γGlu-ipamorelin conjugate docked at human serum albumin FA7 site (PDB: 1E7I or 1BJ5) to evaluate binding geometry and estimate whether the ipamorelin pharmacophore would clash with albumin surface when bound.
3. **Linker length comparison**: Predict structures for γGlu-γGlu-C16 (di-γGlu, as in semaglutide-like linkers) and miniPEG-γGlu-C16 variants to assess whether additional spacer length improves predicted pharmacophore accessibility.
4. **Comparative fold with Fold #33**: Model a combined lactam-bridge + lipidation variant (if Asp-6 extension is retained while Lys-5 bears the palmitoyl — requiring a different cyclization anchor) to explore whether conformational pre-organization could synergize with half-life extension.

WET LAB (VALIDATION PRIORITY ORDER)

1. **Synthesis and HPLC/MS characterization**: Solid-phase peptide synthesis of Aib-His-D-2-Nal-D-Phe-Lys(γGlu-Palm)-NH2 with on-resin Fmoc-Lys(ivDde) orthogonal protection strategy; confirm MW and purity.
2. **GHSR-1a binding assay**: Competitive radioligand binding (^{3}H-ghrelin or ^{125}I-His-D-Trp-Ala-Trp-D-Phe-Lys-NH2) against native ipamorelin to directly measure whether palmitoylation at Lys-5 retains potency (benchmark: IC50 ≤ 100 nM, tolerating up to ~10× loss vs. ipamorelin's ~1–2 nM).
3. **Albumin binding (HSA-HPLC or ITC)**: Measure Kd for human serum albumin FA7 site using isothermal titration calorimetry or immobilized HSA chromatography. Optimal range for half-life extension without sequestration is Kd ~1–100 μM.
4. **In vivo PK in rodent**: Single-dose SC administration in Sprague-Dawley rats with serial blood sampling; compare terminal half-life against native ipamorelin's ~2 hours. This is the definitive pharmacokinetic endpoint.
5. **GH pulse amplitude and duration**: Conscious rat GH assay (cannulated jugular, 15-min sampling) to confirm that albumin-bound conjugate releases sufficient free peptide for GHSR-1a activation and that GH pulses are sustained rather than merely delayed.

VARIANTS WORTH TESTING (ADJACENT FOLDS)

- **C18 diacid via di-γGlu** (semaglutide-like): Stronger albumin binding, potentially once-weekly dosing range
- **C12 lauryl chain**: Weaker albumin binding, may improve receptor access for a short scaffold
- **Combined N-Me-Aib(1) + Lys-5(γGlu-Palm)**: Stack the proteolytic N-terminal protection from Fold #4 with the PK extension here — potentially additive half-life gains
- **PEGylated analog (2 kDa PEG at Lys-5)**: Alternative PK extension strategy without self-assembly risk, for comparison

SEQUENCES

NATIVE

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AibHisDBNalDPheLysNH2
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MODIFIED

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Aib-His-D2Nal-DPhe-Lys(γGlu-Palm)-NH2
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CAVEATS

- in silico prediction only — requires wet lab validation
- single-run prediction (not ensembled); pharmacophore conformation and ipTM should be confirmed across multiple independent seeds
- predicted properties may not reflect real-world biological behavior
- this is research, not medical advice
- heuristic half-life estimate (moderate-to-long, ~1–6 hours) is sequence-based and does not model albumin-binding kinetics; actual half-life extension from C16 lipidation is unknown for pentapeptide scaffolds and could be substantially higher or lower
- heuristic aggregation propensity (0.177) does not capture concentration-dependent micelle or nanostructure formation, which is a documented risk for lipidated short peptides
- no published data exists for any albumin-binding lipidated GHSR-1a agonist; translation from GLP-1 lipidation precedents to a pentapeptide scaffold is extrapolation, not validated chemistry
- the Boltz-2 affinity module and Chai-1 agreement metrics were unavailable for this fold; binding change prediction is absent
- heuristic stability score (0.447) does not account for albumin-mediated protection against proteolysis, likely underestimating metabolic stability of the lipidated conjugate

CITATIONS

1. **PMID —** (1998) — — Ipamorelin, the first selective growth hormone secretagogue.
2. **PMID —** (1999) — — Pharmacokinetic-pharmacodynamic modeling of ipamorelin, a growth hormone releasing peptide, in human volunteers.

3. **PMID —** (2018) — — Peptidomimetic growth hormone secretagogue derivatives for positron emission tomography imaging of the ghrelin receptor.
4. **PMID —** (2001) — — Highly potent growth hormone secretagogues: hybrids of NN703 and ipamorelin.
5. **PMID —** (1999) — — Ipamorelin, a new growth-hormone-releasing peptide, induces longitudinal bone growth in rats.
6. **PMID —** (2001) — — The growth hormone secretagogue ipamorelin counteracts glucocorticoid-induced decrease in bone formation of adult rats.
7. **PMID —** (2009) — — Efficacy of ipamorelin, a novel ghrelin mimetic, in a rodent model of postoperative ileus.
8. **PMID —** (2026) — — Safety and Efficacy of Approved and Unapproved Peptide Therapies for Musculoskeletal Injuries and Athletic Performance
9. **PMID —** (2026) — — Evaluation of Research Grade Peptides Marketed Directly to Consumers Reveals Extensive Variability in Purity and Measured Abundance
10. **PMID —** (2024) — — The growth hormone secretagogue receptor 1a agonists, anamorelin and ipamorelin, inhibit cisplatin-induced weight loss in ferrets.

SOLANA SIGNATURE 3WuMPWH7vwZgVPUg2C6nTuAW9MqcAUAoA37yqrVmpQiKiVTk5oqKNES4CHSy2hh5HehqUmU4Ao1AN6BEwNtvdoBy
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