

RESEARCH MONOGRAPH . COMPOUND PROFILE

Pregabalin

A GABA structural analog binding the alpha-2-delta subunit of voltage-gated calcium channels; approved for neuropathic pain, fibromyalgia, and partial seizures.

DOCUMENT	KDC-MN-251
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COMPOUND CLASS	Alpha-2-delta calcium channel ligand (GABA analog)

ABSTRACT

Pregabalin ((S)-3-(aminomethyl)-5-methylhexanoic acid; CAS 148553-50-8; molecular formula C₈H₁₇NO₂; molecular weight 159.23) is a GABA structural analog developed at Pfizer (Northwestern University origin, Lipton/Silverman) and approved by the FDA in 2004 under the trade name Lyrica. Despite the structural resemblance to GABA, the compound does not act on GABA-A, GABA-B, or GABA reuptake mechanisms; the molecular target is the alpha-2-delta-1 subunit of voltage-gated calcium channels, where high-affinity binding (K_i approximately 22 nM) reduces presynaptic calcium influx and consequent release of glutamate, norepinephrine, substance P, and CGRP. Plasma half-life is 6.3 hours; renal excretion is the principal clearance pathway with linear pharmacokinetics. Approved indications include neuropathic pain (diabetic peripheral neuropathy, postherpetic neuralgia), fibromyalgia, partial-onset seizures (adjunctive), and generalized anxiety disorder (in EU). The compound has scheduled status (Schedule V in the US) reflecting modest abuse potential at supratherapeutic doses, where users report euphoria and benzodiazepine-like effects. Used as the canonical alpha-2-delta calcium channel ligand reference.

1. Compound Identification

Pregabalin is described as alpha-2-delta calcium channel ligand (gaba analog). A GABA structural analog binding the alpha-2-delta subunit of voltage-gated calcium channels; approved for neuropathic pain, fibromyalgia, and partial seizures.

1.1 Class summary

Alpha-2-delta calcium channel ligand (GABA analog)

1.2 Subtitle

A GABA structural analog binding the alpha-2-delta subunit of voltage-gated calcium channels; approved for neuropathic pain, fibromyalgia, and partial seizures.

2. Abstract

Pregabalin ((S)-3-(aminomethyl)-5-methylhexanoic acid; CAS 148553-50-8; molecular formula C₈H₁₇NO₂; molecular weight 159.23) is a GABA structural analog developed at Pfizer (Northwestern University origin, Lipton/Silverman) and approved by the FDA in 2004 under the trade name Lyrica. Despite the structural resemblance to GABA, the compound does not act on GABA-A, GABA-B, or GABA reuptake mechanisms; the molecular target is the alpha-2-delta-1 subunit of voltage-gated calcium channels, where high-affinity binding (K_i approximately 22 nM) reduces presynaptic calcium influx and consequent release of glutamate, norepinephrine, substance P, and CGRP. Plasma half-life is 6.3 hours; renal excretion is the principal clearance pathway with linear pharmacokinetics. Approved indications include neuropathic pain (diabetic peripheral neuropathy, postherpetic neuralgia), fibromyalgia, partial-onset seizures (adjunctive), and generalized anxiety disorder (in EU). The compound has scheduled status (Schedule V in the US) reflecting modest abuse potential at supratherapeutic doses, where users report euphoria and benzodiazepine-like effects. Used as the canonical alpha-2-delta calcium channel ligand reference.

3. Mechanism of Action

Alpha-2-delta-1 subunit binding on voltage-gated calcium channels; reduces presynaptic neurotransmitter release. No direct GABA receptor activity despite structural resemblance.

The mechanistic profile described above represents the consensus position from peer-reviewed literature where available; for compounds with sparse formal characterization, this section reflects vendor-grade reports and structurally-related class pharmacology and should be interpreted with appropriate caution.

4. Pharmacokinetics and Routes of Administration

Pharmacokinetic data are summarized within the abstract for compounds with formal Phase 1 records. Compounds without published human pharmacokinetic studies are noted as such; investigators should treat the absence of data as a research limitation.

5. Reported Research Dose Ranges

Clinical 75 to 600 mg per oral administration daily, in divided doses. Rodent studies 5 to 100 mg/kg/day.

Doses are scaled from clinical use where the compound is approved as a medicine, from Phase 2/3 trials where development advanced, or from rodent dose-response data scaled by allometric assumptions where the compound has no human clinical record. Investigators should treat dose ranges from research-chemical-grade vendors as starting points for their own pharmacokinetic and tolerability characterization rather than validated dosing recommendations.

6. Sourcing and Quality Verification

Investigators should obtain analytical confirmation of identity (mass spectrometry; for peptides, additionally amino acid analysis or N-terminal sequencing) and purity (HPLC area-percent, ideally greater than 95 percent) on every lot. Vendor certificates of analysis vary in quality; third-party analytical confirmation through independent laboratories (e.g., Janoshik Analytical, Anabolic Lab) is the gold standard for research-grade peptides and small molecules.

For compounds with established pharmaceutical-grade marketing in any jurisdiction, sourcing from the marketed product (where legal and accessible) provides the highest quality assurance.

7. Reconstitution and Handling

Peptides should be reconstituted in bacteriostatic water or sterile water for injection in the volume appropriate to the desired concentration; lyophilized peptides should be allowed to come to room temperature before reconstitution to minimize precipitation. Reconstituted peptides should be stored refrigerated and used within the timeframe specified by the manufacturer (typically 14 to 30 days for bacteriostatic water reconstitutions, shorter for sterile water).

Small molecules: storage conditions vary by compound; consult the certificate of analysis for the specific product. Most are stable at room temperature in dry, dark conditions; oxidation-sensitive compounds (e.g., catecholamine precursors) require cool storage and protection from light.

8. Stack Interaction Considerations

Investigators combining this compound with other research substances should consider receptor-level interactions (additive effects at shared targets), enzyme-level interactions (CYP-mediated drug-drug interactions where applicable), and pharmacodynamic interactions (additive sedation, additive serotonergic activity, additive hemodynamic effects).

The stack interaction section in published monographs of well-characterized compounds is necessarily incomplete for any specific combination; investigators should treat novel combinations with elevated caution and titrate gradually.

9. References

1. Field MJ, et al. Identification of the alpha2-delta-1 subunit of voltage-dependent calcium channels as a molecular target for pain mediating the analgesic actions of pregabalin. Proc Natl Acad Sci 2006.
2. Tassone DM, et al. Pregabalin: a novel gamma-aminobutyric acid analogue. Clin Ther 2007.
3. Hauser P, Devinsky O. The pharmacokinetics of pregabalin and its therapeutic applications. Curr Neurol Neurosci Rep 2007.

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