

RESEARCH MONOGRAPH . COMPOUND PROFILE

Gabapentin

A GABA analog binding the alpha-2-delta subunit of voltage-gated calcium channels; the structural and clinical predecessor to pregabalin.

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ABSTRACT

Gabapentin (1-(aminomethyl)cyclohexaneacetic acid; CAS 60142-96-3; molecular formula C₉H₁₇NO₂; molecular weight 171.24) is a GABA analog developed at Parke-Davis (Pfizer) in the 1980s and approved by the FDA in 1993 under the trade name Neurontin. Mechanism mirrors pregabalin: binding to the alpha-2-delta-1 subunit of voltage-gated calcium channels (K_i approximately 80 nM, weaker than pregabalin), reducing presynaptic neurotransmitter release. No direct GABA receptor activity. Plasma half-life is 5 to 7 hours. Distinguished from pregabalin by saturable absorption: oral bioavailability ranges from 80 percent at 100 mg to 27 percent at 1600 mg, producing nonlinear dose-response and unpredictable individual responses at higher doses. Approved for postherpetic neuralgia and partial-onset seizures (adjunctive); off-label use is extensive (anxiety, alcohol withdrawal, restless legs syndrome, hot flashes, hiccups, neuropathic pain of all causes, migraine prophylaxis). The compound has been the subject of extensive off-label promotion litigation and is now scheduled in some US states reflecting abuse potential. Used as the canonical alpha-2-delta-1 calcium channel ligand and a reference compound in seizure pharmacology.

1. Compound Identification

Gabapentin is described as gaba analog calcium channel ligand. A GABA analog binding the alpha-2-delta subunit of voltage-gated calcium channels; the structural and clinical predecessor to pregabalin.

1.1 Class summary

GABA analog calcium channel ligand

1.2 Subtitle

A GABA analog binding the alpha-2-delta subunit of voltage-gated calcium channels; the structural and clinical predecessor to pregabalin.

2. Abstract

Gabapentin (1-(aminomethyl)cyclohexaneacetic acid; CAS 60142-96-3; molecular formula $C_9H_{17}NO_2$; molecular weight 171.24) is a GABA analog developed at Parke-Davis (Pfizer) in the 1980s and approved by the FDA in 1993 under the trade name Neurontin. Mechanism mirrors pregabalin: binding to the α -2- δ -1 subunit of voltage-gated calcium channels (K_i approximately 80 nM, weaker than pregabalin), reducing presynaptic neurotransmitter release. No direct GABA receptor activity. Plasma half-life is 5 to 7 hours. Distinguished from pregabalin by saturable absorption: oral bioavailability ranges from 80 percent at 100 mg to 27 percent at 1600 mg, producing nonlinear dose-response and unpredictable individual responses at higher doses. Approved for postherpetic neuralgia and partial-onset seizures (adjunctive); off-label use is extensive (anxiety, alcohol withdrawal, restless legs syndrome, hot flashes, hiccups, neuropathic pain of all causes, migraine prophylaxis). The compound has been the subject of extensive off-label promotion litigation and is now scheduled in some US states reflecting abuse potential. Used as the canonical α -2- δ -1 calcium channel ligand and a reference compound in seizure pharmacology.

3. Mechanism of Action

Alpha-2-delta-1 subunit binding (weaker than pregabalin); saturable absorption produces nonlinear dose-response.

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 300 to 3600 mg per oral administration daily, in divided doses. Rodent studies 30 to 300 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. Sills GJ. The mechanisms of action of gabapentin and pregabalin. Curr Opin Pharmacol 2006.
2. Maneuf YP, et al. Gabapentin and the alpha-2-delta auxiliary subunit. Pharmacol Ther 2003.
3. Mack A. Examination of the evidence for off-label use of gabapentin. J Manag Care Pharm 2003.

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