

RESEARCH MONOGRAPH . COMPOUND PROFILE

Tiagabine

A nipecotic acid derivative selective GABA reuptake inhibitor; the prototype GAT-1 transporter blocker.

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COMPOUND CLASS	GAT-1 selective GABA reuptake inhibitor

ABSTRACT

Tiagabine ((R)-1-[4,4-bis(3-methyl-2-thienyl)-3-butenyl]-3-piperidinecarboxylic acid; CAS 115103-54-3; molecular formula C₂₀H₂₅NO₂S₂; molecular weight 375.55) is a nipecotic acid derivative selective inhibitor of the GABA transporter GAT-1, developed at Novo Nordisk and approved by the FDA in 1997 under the trade name Gabitril. Mechanism: high-affinity inhibition of GAT-1 (the principal neuronal GABA reuptake transporter) prolongs synaptic GABA availability after release, enhancing GABA-A and GABA-B receptor activation. Selectivity for GAT-1 over GAT-2 and GAT-3 is greater than 100-fold. Plasma half-life is 7 to 9 hours; metabolism is via CYP3A4. Approved as adjunctive therapy in partial-onset seizures in patients aged 12 and older. Off-label use in generalized anxiety disorder has been complicated by FDA warnings of new-onset seizures in patients without epilepsy (incidence approximately 1 percent at off-label doses). Used as the canonical GAT-1 selective inhibitor in mechanism studies.

1. 1. Compound Identification

Tiagabine is described as gat-1 selective gaba reuptake inhibitor. A nipecotic acid derivative selective GABA reuptake inhibitor; the prototype GAT-1 transporter blocker.

1.1. 1.1 Class summary

GAT-1 selective GABA reuptake inhibitor

1.2. 1.2 Subtitle

A nipecotic acid derivative selective GABA reuptake inhibitor; the prototype GAT-1 transporter blocker.

2. Abstract

Tiagabine ((R)-1-[4,4-bis(3-methyl-2-thienyl)-3-butenyl]-3-piperidinecarboxylic acid; CAS 115103-54-3; molecular formula C₂₀H₂₅NO₂S₂; molecular weight 375.55) is a nipecotic acid derivative selective inhibitor of the GABA transporter GAT-1, developed at Novo Nordisk and approved by the FDA in 1997 under the trade name Gabitril. Mechanism: high-affinity inhibition of GAT-1 (the principal neuronal GABA reuptake transporter) prolongs synaptic GABA availability after release, enhancing GABA-A and GABA-B receptor activation. Selectivity for GAT-1 over GAT-2 and GAT-3 is greater than 100-fold. Plasma half-life is 7 to 9 hours; metabolism is via CYP3A4. Approved as adjunctive therapy in partial-onset seizures in patients aged 12 and older. Off-label use in generalized anxiety disorder has been complicated by FDA warnings of new-onset seizures in patients without epilepsy (incidence approximately 1 percent at off-label doses). Used as the canonical GAT-1 selective inhibitor in mechanism studies.

3. Mechanism of Action

Selective inhibition of the GAT-1 GABA transporter (greater than 100-fold over GAT-2/GAT-3). Prolongs synaptic GABA after release.

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. 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. 5. Reported Research Dose Ranges

Clinical 32 to 56 mg per oral administration daily, in divided doses. Rodent studies 5 to 30 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. 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. 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. 9. References

1. Borden LA, et al. Tiagabine, SK&F 89976-A, CI-966, and NNC-711 are selective for the cloned GABA transporter GAT-1. Eur J Pharmacol 1994.
2. Suzdak PD, Jansen JA. A review of the preclinical pharmacology of tiagabine. Epilepsia 1995.
3. Krogsgaard-Larsen P, et al. GABA uptake inhibitors. Design, molecular pharmacology and therapeutic aspects. Curr Pharm Des 2000.

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