

RESEARCH MONOGRAPH . COMPOUND PROFILE

Sembragiline

*A selective reversible MAO-B inhibitor
investigated for Alzheimer disease; failed
phase 2 efficacy.*

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ABSTRACT

Sembragiline (EVT-302, RG1577; molecular formula C₁₉H₂₂N₃O; molecular weight 327.40) is a selective reversible MAO-B inhibitor developed at Roche and EVOTEC as a candidate for Alzheimer disease. The mechanistic rationale: MAO-B is upregulated in reactive astrocytes in Alzheimer brain tissue, contributing to oxidative stress and amyloid pathology; selective reversible inhibition might reduce this contribution without the irreversible enzyme abolition of selegiline or rasagiline. Phase 2 MAYFLOWER RoAD trial in mild-to-moderate Alzheimer disease (n=542) failed to show significant slowing of cognitive decline at 52 weeks; development was halted. The compound retains research utility as a clean tool for selective reversible MAO-B inhibition (selectivity ratio greater than 1000:1 over MAO-A) and is used in academic studies of MAO-B's role in neurodegeneration. Used as the reference reversible selective MAO-B inhibitor in academic neuroscience.

1. Compound Identification

Sembragiline is described as selective reversible mao-b inhibitor (investigational). A selective reversible MAO-B inhibitor investigated for Alzheimer disease; failed phase 2 efficacy.

1.1 Class summary

Selective reversible MAO-B inhibitor (investigational)

1.2 Subtitle

A selective reversible MAO-B inhibitor investigated for Alzheimer disease; failed phase 2 efficacy.

2. Abstract

Sembragiline (EVT-302, RG1577; molecular formula C₁₉H₂₂FN₃O; molecular weight 327.40) is a selective reversible MAO-B inhibitor developed at Roche and EVOTEC as a candidate for Alzheimer disease. The mechanistic rationale: MAO-B is upregulated in reactive astrocytes in Alzheimer brain tissue, contributing to oxidative stress and amyloid pathology; selective reversible inhibition might reduce this contribution without the irreversible enzyme abolition of selegiline or rasagiline. Phase 2 MAYflower RoAD trial in mild-to-moderate Alzheimer disease (n=542) failed to show significant slowing of cognitive decline at 52 weeks; development was halted. The compound retains research utility as a clean tool for selective reversible MAO-B inhibition (selectivity ratio greater than 1000:1 over MAO-A) and is used in academic studies of MAO-B's role in neurodegeneration. Used as the reference reversible selective MAO-B inhibitor in academic neuroscience.

3. Mechanism of Action

Selective reversible MAO-B inhibition (greater than 1000:1 selectivity over MAO-A). Distinct from selegiline and rasagiline by reversibility.

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

Investigational; trial doses 1 mg and 5 mg per oral administration daily.

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. Nave S, et al. Sembragiline in moderate Alzheimer's disease: results of a randomized, double-blind, placebo-controlled phase II trial (MAYflower RoAD). J Alzheimers Dis 2017.
2. Borroni E, et al. Sembragiline: a novel, selective, reversible monoamine oxidase B inhibitor for the treatment of Alzheimer disease. J Pharmacol Exp Ther 2017.

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