

RESEARCH MONOGRAPH . COMPOUND PROFILE

Protriptyline

A secondary amine TCA distinguished by activating rather than sedating subjective profile; useful in depression with hypersomnia.

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COMPOUND CLASS	Tricyclic antidepressant (secondary amine, activating)

ABSTRACT

Protriptyline (N-methyl-3-(5H-dibenzo[a,d]cyclohepten-5-yl)propan-1-amine; CAS 438-60-8; molecular formula C₁₉H₂₁N; molecular weight 263.38) is a secondary amine TCA approved by the FDA in 1967 under the trade name Vivactil. Distinct among TCAs for an activating subjective profile that contrasts with the sedation typical of the class; the activating profile is attributed to relatively higher NET-to-SERT selectivity and reduced H₁ antagonism. NET Ki approximately 1.4 nM, SERT Ki approximately 20 nM. Plasma half-life is exceptionally long (54 to 92 hours) owing to slow CYP2D6 metabolism. The activating profile makes protriptyline a niche choice for depression with prominent hypersomnia or fatigue, including narcolepsy-associated depression where the wakefulness-promoting effect is therapeutic. Off-target activity is otherwise typical of secondary amine TCAs: muscarinic, mild H₁, alpha-1, and sodium channel block. Approved for major depressive disorder; rarely first-line today owing to TCA-class limitations. Used as a reference compound for activating TCA pharmacology and in narcolepsy-related comorbidity research.

1. Compound Identification

Protriptyline is described as tricyclic antidepressant (secondary amine, activating). A secondary amine TCA distinguished by activating rather than sedating subjective profile; useful in depression with hypersomnia.

1.1 Class summary

Tricyclic antidepressant (secondary amine, activating)

1.2 Subtitle

A secondary amine TCA distinguished by activating rather than sedating subjective profile; useful in depression with hypersomnia.

2. Abstract

Protriptyline (N-methyl-3-(5H-dibenzo[a,d]cyclohepten-5-yl)propan-1-amine; CAS 438-60-8; molecular formula C₁₉H₂₁N; molecular weight 263.38) is a secondary amine TCA approved by the FDA in 1967 under the trade name Vivactil. Distinct among TCAs for an activating subjective profile that contrasts with the sedation typical of the class; the activating profile is attributed to relatively higher NET-to-SERT selectivity and reduced H₁ antagonism. NET K_i approximately 1.4 nM, SERT K_i approximately 20 nM. Plasma half-life is exceptionally long (54 to 92 hours) owing to slow CYP2D6 metabolism. The activating profile makes protriptyline a niche choice for depression with prominent hypersomnia or fatigue, including narcolepsy-associated depression where the wakefulness-promoting effect is therapeutic. Off-target activity is otherwise typical of secondary amine TCAs: muscarinic, mild H₁, α-1, and sodium channel block. Approved for major depressive disorder; rarely first-line today owing to TCA-class limitations. Used as a reference compound for activating TCA pharmacology and in narcolepsy-related comorbidity research.

3. Mechanism of Action

NET-preferring secondary amine TCA with reduced H1 antagonism producing an activating rather than sedating profile. Long half-life owing to slow CYP2D6 metabolism.

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 15 to 60 mg per oral administration daily, in divided doses. Rodent studies 1 to 20 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. Biggs JT, Ziegler VE. Protriptyline plasma levels and antidepressant response. Clin Pharmacol Ther 1977.
2. Moore N. Tricyclic antidepressants in narcolepsy. CNS Drugs 1996.
3. Snyder S, Yamamura HI. Antidepressants and the muscarinic acetylcholine receptor. Arch Gen Psychiatry 1977.

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