

RESEARCH MONOGRAPH . COMPOUND PROFILE

Nortriptyline

The N-desmethyl active metabolite of amitriptyline; a NET-preferring TCA with a more favorable side effect profile.

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COMPOUND CLASS	Tricyclic antidepressant (secondary amine)

ABSTRACT

Nortriptyline (3-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-N-methylpropan-1-amine; CAS 72-69-5; molecular formula C₁₉H₂₁N; molecular weight 263.38) is the N-desmethyl active metabolite of amitriptyline, marketed independently as Pamelor and Aventyl after FDA approval in 1964. As a secondary amine TCA, the compound exhibits substantially greater NET selectivity than amitriptyline (NET K_i approximately 4 nM, SERT K_i approximately 18 nM) and reduced muscarinic antagonism (M₁ K_i approximately 150 nM versus 18 nM for amitriptyline), producing a cleaner side effect profile. H₁ antagonism remains significant (K_i approximately 10 nM) and contributes to residual sedation, but the anticholinergic burden is meaningfully lower. Plasma half-life is 18 to 35 hours; metabolism is via CYP2D6 (primary). Approved for major depressive disorder; widely used at low dose (10 to 75 mg) for chronic pain, neuropathy, and as a smoking cessation aid (off-label). Therapeutic plasma concentrations are well-defined (50 to 150 ng/mL) and routinely monitored, distinguishing nortriptyline from most modern antidepressants. Used as the canonical secondary amine TCA in mechanism studies.

1. Compound Identification

Nortriptyline is described as tricyclic antidepressant (secondary amine). The N-desmethyl active metabolite of amitriptyline; a NET-preferring TCA with a more favorable side effect profile.

1.1 Class summary

Tricyclic antidepressant (secondary amine)

1.2 Subtitle

The N-desmethyl active metabolite of amitriptyline; a NET-preferring TCA with a more favorable side effect profile.

2. Abstract

Nortriptyline (3-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-N-methylpropan-1-amine; CAS 72-69-5; molecular formula C₁₉H₂₁N; molecular weight 263.38) is the N-desmethyl active metabolite of amitriptyline, marketed independently as Pamelor and Aventyl after FDA approval in 1964. As a secondary amine TCA, the compound exhibits substantially greater NET selectivity than amitriptyline (NET K_i approximately 4 nM, SERT K_i approximately 18 nM) and reduced muscarinic antagonism (M₁ K_i approximately 150 nM versus 18 nM for amitriptyline), producing a cleaner side effect profile. H₁ antagonism remains significant (K_i approximately 10 nM) and contributes to residual sedation, but the anticholinergic burden is meaningfully lower. Plasma half-life is 18 to 35 hours; metabolism is via CYP2D6 (primary). Approved for major depressive disorder; widely used at low dose (10 to 75 mg) for chronic pain, neuropathy, and as a smoking cessation aid (off-label). Therapeutic plasma concentrations are well-defined (50 to 150 ng/mL) and routinely monitored, distinguishing nortriptyline from most modern antidepressants. Used as the canonical secondary amine TCA in mechanism studies.

3. Mechanism of Action

NET-preferring TCA with reduced muscarinic burden compared to amitriptyline. Active metabolite of amitriptyline; defined therapeutic plasma window.

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 25 to 150 mg per oral administration daily, with plasma level monitoring.
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. Roose SP, et al. Comparison of nortriptyline and SSRIs in elderly depressed patients. Am J Geriatr Psychiatry 1998.
2. Watson CP, et al. Nortriptyline versus amitriptyline in postherpetic neuralgia: a randomized trial. Neurology 1998.
3. Mavissakalian MR, Perel JM. Long-term maintenance and discontinuation of imipramine therapy. Arch Gen Psychiatry 1999.

This monograph is provided for research use only. Not for medical, diagnostic, or therapeutic purposes. Not for human consumption. Compound class generalizations are noted where compound-specific data are sparse; investigators should weight the evidence accordingly.