

RESEARCH MONOGRAPH . COMPOUND PROFILE

Amitriptyline

A foundational tertiary amine TCA with potent serotonergic, noradrenergic, anticholinergic, and antihistaminergic activity; widely repurposed for chronic pain.

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RESEARCH USE ONLY

ABSTRACT

Amitriptyline (3-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-N,N-dimethylpropan-1-amine; CAS 50-48-6; molecular formula C₂₀H₂₃N; molecular weight 277.40) is a dibenzocycloheptene tertiary amine TCA developed at Merck and approved in the US in 1961 under the trade name Elavil. The parent compound exhibits balanced SERT and NET inhibition (SERT K_i approximately 4 nM, NET K_i approximately 35 nM); the active metabolite nortriptyline (formed by CYP-mediated demethylation) is a more selective NET inhibitor and contributes substantially to steady-state activity. Off-target activity is extensive: muscarinic M₁-M₅ antagonism (K_i approximately 18 nM at M₁) produces strong anticholinergic effects, H₁ antagonism (K_i approximately 1 nM) drives sedation and weight gain, alpha-1 adrenergic antagonism causes orthostatic hypotension, and sodium channel block contributes to cardiotoxicity in overdose. Plasma half-life is 10 to 28 hours; metabolism is via CYP2D6, CYP2C19, CYP3A4. Approved for major depressive disorder; widely used at lower doses (10 to 75 mg) for migraine prophylaxis, postherpetic neuralgia, diabetic neuropathy, fibromyalgia, and tension-type headache. Used as the canonical TCA reference compound in mechanism studies.

1. Compound Identification

Amitriptyline is described as tricyclic antidepressant (tertiary amine). A foundational tertiary amine TCA with potent serotonergic, noradrenergic, anticholinergic, and antihistaminergic activity; widely repurposed for chronic pain.

1.1 Class summary

Tricyclic antidepressant (tertiary amine)

1.2 Subtitle

A foundational tertiary amine TCA with potent serotonergic, noradrenergic, anticholinergic, and antihistaminergic activity; widely repurposed for chronic pain.

2. Abstract

Amitriptyline (3-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-N,N-dimethylpropan-1-amine; CAS 50-48-6; molecular formula C₂₀H₂₃N; molecular weight 277.40) is a dibenzocycloheptene tertiary amine TCA developed at Merck and approved in the US in 1961 under the trade name Elavil. The parent compound exhibits balanced SERT and NET inhibition (SERT K_i approximately 4 nM, NET K_i approximately 35 nM); the active metabolite nortriptyline (formed by CYP-mediated demethylation) is a more selective NET inhibitor and contributes substantially to steady-state activity. Off-target activity is extensive: muscarinic M1-M5 antagonism (K_i approximately 18 nM at M1) produces strong anticholinergic effects, H₁ antagonism (K_i approximately 1 nM) drives sedation and weight gain, alpha-1 adrenergic antagonism causes orthostatic hypotension, and sodium channel block contributes to cardiotoxicity in overdose. Plasma half-life is 10 to 28 hours; metabolism is via CYP2D6, CYP2C19, CYP3A4. Approved for major depressive disorder; widely used at lower doses (10 to 75 mg) for migraine prophylaxis, postherpetic neuralgia, diabetic neuropathy, fibromyalgia, and tension-type headache. Used as the canonical TCA reference compound in mechanism studies.

3. Mechanism of Action

Balanced SERT/NET inhibition; potent anticholinergic, antihistaminergic, alpha-1 adrenergic, and sodium channel block. Active metabolite nortriptyline shifts selectivity toward NET.

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 10 to 300 mg per oral administration daily (low for pain, high for depression). Rodent studies 1 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. 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. Bryson HM, Wilde MI. Amitriptyline. A review of its pharmacological properties and therapeutic use in chronic pain states. *Drugs Aging* 1996.
2. Coupland N, et al. The biochemistry of melancholia: TCA-class pharmacology. *Br J Psychiatry* 1992.
3. Lawson K. Tricyclic antidepressants and fibromyalgia: what is the mechanism of action? *Expert Opin Investig Drugs* 2002.

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