

RESEARCH MONOGRAPH . COMPOUND PROFILE

Desipramine

The N-desmethyl active metabolite of imipramine; the most NET-selective TCA in clinical use.

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COMPOUND CLASS	Tricyclic antidepressant (secondary amine)

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ABSTRACT

Desipramine (3-(10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)-N-methylpropan-1-amine; CAS 50-47-5; molecular formula C₁₈H₂₂N₂; molecular weight 266.38) is the N-desmethyl active metabolite of imipramine, approved by the FDA in 1964 under the trade name Norpramin. The compound is the most NET-selective TCA in clinical use (NET K_i approximately 0.83 nM, SERT K_i approximately 17 nM, ratio approximately 20). Off-target activity is reduced compared to imipramine: muscarinic (M₁ K_i approximately 200 nM), H₁ (K_i approximately 60 nM), and alpha-1 (K_i approximately 100 nM) antagonism are all weaker than the parent compound, producing a cleaner profile though still TCA-like. Plasma half-life is 15 to 24 hours; metabolism is via CYP2D6 and CYP2E1. Approved for major depressive disorder; used at higher doses (150 to 300 mg) for moderate-severe depression, at lower doses for ADHD (off-label) and neuropathic pain. Sodium channel block and consequent cardiotoxicity in overdose remain limitations. Used as the canonical NET-selective TCA in mechanism studies and as a reference compound for noradrenergic pharmacology.

1. Compound Identification

Desipramine is described as tricyclic antidepressant (secondary amine). The N-desmethyl active metabolite of imipramine; the most NET-selective TCA in clinical use.

1.1 Class summary

Tricyclic antidepressant (secondary amine)

1.2 Subtitle

The N-desmethyl active metabolite of imipramine; the most NET-selective TCA in clinical use.

2. Abstract

Desipramine (3-(10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)-N-methylpropan-1-amine; CAS 50-47-5; molecular formula C₁₈H₂₂N₂; molecular weight 266.38) is the N-desmethyl active metabolite of imipramine, approved by the FDA in 1964 under the trade name Norpramin. The compound is the most NET-selective TCA in clinical use (NET Ki approximately 0.83 nM, SERT Ki approximately 17 nM, ratio approximately 20). Off-target activity is reduced compared to imipramine: muscarinic (M1 Ki approximately 200 nM), H1 (Ki approximately 60 nM), and alpha-1 (Ki approximately 100 nM) antagonism are all weaker than the parent compound, producing a cleaner profile though still TCA-like. Plasma half-life is 15 to 24 hours; metabolism is via CYP2D6 and CYP2E1. Approved for major depressive disorder; used at higher doses (150 to 300 mg) for moderate-severe depression, at lower doses for ADHD (off-label) and neuropathic pain. Sodium channel block and consequent cardiotoxicity in overdose remain limitations. Used as the canonical NET-selective TCA in mechanism studies and as a reference compound for noradrenergic pharmacology.

3. Mechanism of Action

Most NET-selective TCA; reduced anticholinergic and antihistaminergic burden compared to imipramine. Active metabolite of imipramine.

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 50 to 300 mg per oral administration daily. 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. 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. Tatsumi M, et al. Pharmacological profile of antidepressants and related compounds at human monoamine transporters. Eur J Pharmacol 1997.
2. Reimherr FW, et al. Desipramine for adult attention deficit disorder. Am J Psychiatry 1995.
3. Goldstein DJ. Long-term treatment of depression with desipramine and imipramine. Br J Clin Pharmacol 1991.

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