

## RESEARCH MONOGRAPH . COMPOUND PROFILE

# Phenelzine

*A first-generation hydrazine MAOI; a non-selective irreversible inhibitor still used for atypical and treatment-resistant depression.*

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| COMPOUND CLASS | Irreversible non-selective MAO inhibitor (hydrazine) |

## ABSTRACT

Phenelzine (2-phenylethylhydrazine; CAS 51-71-8; molecular formula  $C_8H_{12}N_2$ ; molecular weight 136.19) is a hydrazine class non-selective irreversible monoamine oxidase inhibitor approved by the FDA in 1961 under the trade name Nardil. The compound covalently inactivates both MAO-A and MAO-B by hydrazine-mediated cofactor adduction at the FAD prosthetic group; recovery requires de novo enzyme synthesis (approximately 14 to 21 days). The non-selective inhibition increases brain serotonin, norepinephrine, and dopamine concurrently, producing classical MAOI antidepressant pharmacology along with the well-known tyramine cheese-effect risk: dietary tyramine, normally degraded by intestinal MAO-A, accumulates and triggers hypertensive crisis through indirect sympathomimetic action. Plasma half-life is 11.6 hours, but the irreversible binding produces effective enzyme inhibition for 2 to 3 weeks. Hydrazine metabolism may produce hepatotoxic byproducts; chronic dosing requires hepatic monitoring. Approved for major depressive disorder; remains a benchmark for atypical depression with reverse vegetative features and for treatment-resistant cases where SSRIs and TCAs have failed.

# 1. Compound Identification

**Phenelzine** is described as irreversible non-selective mao inhibitor (hydrazine). A first-generation hydrazine MAOI; a non-selective irreversible inhibitor still used for atypical and treatment-resistant depression.

## 1.1 Class summary

Irreversible non-selective MAO inhibitor (hydrazine)

## 1.2 Subtitle

A first-generation hydrazine MAOI; a non-selective irreversible inhibitor still used for atypical and treatment-resistant depression.

## 2. Abstract

Phenelzine (2-phenylethylhydrazine; CAS 51-71-8; molecular formula C<sub>8</sub>H<sub>12</sub>N<sub>2</sub>; molecular weight 136.19) is a hydrazine class non-selective irreversible monoamine oxidase inhibitor approved by the FDA in 1961 under the trade name Nardil. The compound covalently inactivates both MAO-A and MAO-B by hydrazine-mediated cofactor adduction at the FAD prosthetic group; recovery requires de novo enzyme synthesis (approximately 14 to 21 days). The non-selective inhibition increases brain serotonin, norepinephrine, and dopamine concurrently, producing classical MAOI antidepressant pharmacology along with the well-known tyramine cheese-effect risk: dietary tyramine, normally degraded by intestinal MAO-A, accumulates and triggers hypertensive crisis through indirect sympathomimetic action. Plasma half-life is 11.6 hours, but the irreversible binding produces effective enzyme inhibition for 2 to 3 weeks. Hydrazine metabolism may produce hepatotoxic byproducts; chronic dosing requires hepatic monitoring. Approved for major depressive disorder; remains a benchmark for atypical depression with reverse vegetative features and for treatment-resistant cases where SSRIs and TCAs have failed.

### 3. Mechanism of Action

Irreversible non-selective MAO-A and MAO-B inhibition via hydrazine adduction. Increases brain serotonin, norepinephrine, and dopamine.

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 45 to 90 mg per oral administration daily, in divided doses. 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. Robinson DS, et al. A controlled study of phenelzine in atypical depression. Psychopharmacol Bull 1973.
2. Krishnan KR. Revisiting monoamine oxidase inhibitors. J Clin Psychiatry 2007.
3. Stewart JW, et al. Phenelzine in atypical depression. J Clin Psychiatry 1989.

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