

RESEARCH MONOGRAPH . COMPOUND PROFILE

Diphenhydramine

An ethanolamine first-generation H1 antihistamine; the canonical sedating antihistamine and OTC sleep aid.

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ABSTRACT

Diphenhydramine (2-(diphenylmethoxy)-N,N-dimethylethanamine; CAS 58-73-1; molecular formula C₁₇H₂₁NO; molecular weight 255.36) is an ethanolamine first-generation H₁ antihistamine developed at Parke-Davis and approved in 1946. The compound is the canonical sedating H₁ blocker (K_i approximately 16 nM) with significant anticholinergic activity (M₁-M₅ antagonism, K_i approximately 70 nM). The combined activity produces sedation, dry mouth, blurred vision, and confusion (especially in elderly). Plasma half-life is approximately 4 to 8 hours. Approved indications: allergic conditions, motion sickness, parkinsonism, anaphylaxis. OTC sleep aid use in branded products (Tylenol PM, ZzzQuil) is widespread despite limited efficacy and concerning anticholinergic burden in elderly (associated with dementia risk in long-term use per BEERS criteria). The compound has dose-dependent abuse potential at high doses (deliriant effect from anticholinergic activity). Used as the canonical first-generation H₁ antihistamine in research.

1. Compound Identification

Diphenhydramine is described as first-generation h1 antihistamine + anticholinergic. An ethanolamine first-generation H1 antihistamine; the canonical sedating antihistamine and OTC sleep aid.

1.1 Class summary

First-generation H1 antihistamine + anticholinergic

1.2 Subtitle

An ethanolamine first-generation H1 antihistamine; the canonical sedating antihistamine and OTC sleep aid.

2. Abstract

Diphenhydramine (2-(diphenylmethoxy)-N,N-dimethylethanamine; CAS 58-73-1; molecular formula C₁₇H₂₁NO; molecular weight 255.36) is an ethanolamine first-generation H₁ antihistamine developed at Parke-Davis and approved in 1946. The compound is the canonical sedating H₁ blocker (K_i approximately 16 nM) with significant anticholinergic activity (M₁-M₅ antagonism, K_i approximately 70 nM). The combined activity produces sedation, dry mouth, blurred vision, and confusion (especially in elderly). Plasma half-life is approximately 4 to 8 hours. Approved indications: allergic conditions, motion sickness, parkinsonism, anaphylaxis. OTC sleep aid use in branded products (Tylenol PM, ZzzQuil) is widespread despite limited efficacy and concerning anticholinergic burden in elderly (associated with dementia risk in long-term use per BEERS criteria). The compound has dose-dependent abuse potential at high doses (deliriant effect from anticholinergic activity). Used as the canonical first-generation H₁ antihistamine in research.

3. Mechanism of Action

First-generation H1 antagonism with significant muscarinic antagonism. Sedation, dry mouth, anticholinergic effects.

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 50 mg per oral administration every 4 to 6 hours (max 300 mg/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. Simons FE. Advances in H1-antihistamines. N Engl J Med 2004.
2. Glass JR, et al. Acute pharmacological effects of temazepam, diphenhydramine, and valerian in healthy elderly subjects. J Clin Psychopharmacol 2003.
3. Gray SL, et al. Cumulative use of strong anticholinergics and incident dementia. JAMA Intern Med 2015.

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.