

RESEARCH MONOGRAPH . COMPOUND PROFILE

Hydroxyzine

A first-generation piperazine H1 antihistamine with anxiolytic activity; the first non-controlled anxiolytic widely used in psychiatry.

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AUTHOR	Kodiac bioLabs Research
COMPOUND CLASS	First-generation H1 antihistamine anxiolytic

ABSTRACT

Hydroxyzine (2-(2-{4-[(4-chlorophenyl)(phenyl)methyl]piperazin-1-yl}ethoxy)ethanol; CAS 68-88-2; molecular formula C₂₁H₂₇ClN₂O₂; molecular weight 374.91) is a first-generation piperazine H₁ antihistamine developed at UCB and approved by the FDA in 1956 under the trade names Atarax and Vistaril. Distinct from later antihistamines by clinically significant CNS penetration, producing the sedation and anxiolytic effects characteristic of first-generation H₁ blockers. H₁ affinity approximately 2 nM; secondary 5-HT_{2A} antagonism (K_i approximately 10 nM) and weak D₂ antagonism contribute to the anxiolytic profile. The principal active metabolite cetirizine retains H₁ antagonism but loses CNS penetration owing to addition of a carboxylic acid group, and is marketed separately as a non-sedating antihistamine (Zyrtec). Plasma half-life is 14 to 25 hours; metabolism is hepatic. Approved for anxiety, pruritus, and as a preoperative sedative; off-label use in insomnia and as a benzodiazepine-sparing anxiolytic. Used as the canonical first-generation H₁ antihistamine in mechanism studies.

1. Compound Identification

Hydroxyzine is described as first-generation h1 antihistamine anxiolytic. A first-generation piperazine H1 antihistamine with anxiolytic activity; the first non-controlled anxiolytic widely used in psychiatry.

1.1 Class summary

First-generation H1 antihistamine anxiolytic

1.2 Subtitle

A first-generation piperazine H1 antihistamine with anxiolytic activity; the first non-controlled anxiolytic widely used in psychiatry.

2. Abstract

Hydroxyzine (2-(2-{4-[(4-chlorophenyl)(phenyl)methyl]piperazin-1-yl}ethoxy)ethanol; CAS 68-88-2; molecular formula C₂₁H₂₇ClN₂O₂; molecular weight 374.91) is a first-generation piperazine H₁ antihistamine developed at UCB and approved by the FDA in 1956 under the trade names Atarax and Vistaril. Distinct from later antihistamines by clinically significant CNS penetration, producing the sedation and anxiolytic effects characteristic of first-generation H₁ blockers. H₁ affinity approximately 2 nM; secondary 5-HT_{2A} antagonism (K_i approximately 10 nM) and weak D₂ antagonism contribute to the anxiolytic profile. The principal active metabolite cetirizine retains H₁ antagonism but loses CNS penetration owing to addition of a carboxylic acid group, and is marketed separately as a non-sedating antihistamine (Zyrtec). Plasma half-life is 14 to 25 hours; metabolism is hepatic. Approved for anxiety, pruritus, and as a preoperative sedative; off-label use in insomnia and as a benzodiazepine-sparing anxiolytic. Used as the canonical first-generation H₁ antihistamine in mechanism studies.

3. Mechanism of Action

First-generation H1 antagonism with CNS penetration; secondary 5-HT_{2A} antagonism. Active metabolite cetirizine is non-CNS-penetrant.

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 100 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. Schweizer E, et al. Hydroxyzine versus buspirone for anxiety. J Clin Psychiatry 1986.
2. Rickels K. Use of antianxiety agents in anxious outpatients. Psychopharmacology 1978.
3. Simons FE, et al. Cetirizine, the major metabolite of hydroxyzine. J Allergy Clin Immunol 1986.

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