

RESEARCH MONOGRAPH . COMPOUND PROFILE

Cyproheptadine

A piperidine first-generation antihistamine with 5-HT_{2A} and 5-HT_{2C} antagonist activity; used for appetite stimulation, serotonin syndrome reversal, and migraine prophylaxis.

DOCUMENT	KDC-MN-353
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AUTHOR	Kodiac bioLabs Research
COMPOUND CLASS	First-generation antihistamine + 5-HT ₂ antagonist

ABSTRACT

Cyproheptadine (4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-methylpiperidine; CAS 129-03-3; molecular formula C₂₁H₂₁N; molecular weight 287.40) is a piperidine first-generation antihistamine with potent 5-HT_{2A} and 5-HT_{2C} antagonist activity, approved by the FDA in 1961 (Periactin). The compound combines H₁ antihistamine activity (K_i approximately 1 nM, comparable to diphenhydramine) with strong 5-HT₂ antagonism (K_i approximately 1 nM at 5-HT_{2A}); the combined activity drives appetite stimulation (5-HT_{2C} antagonism, the same mechanism as the appetite gain seen with olanzapine and clozapine), serotonin syndrome reversal, and migraine prophylaxis. Plasma half-life is approximately 8 hours. Approved for allergic conditions; off-label use in failure-to-thrive (pediatric appetite stimulation), serotonin syndrome (the only specific antidote besides supportive care), and post-SSRI sexual dysfunction (5-HT_{2A} antagonism). Used as the canonical 5-HT₂ antagonist antihistamine in research.

1. Compound Identification

Cyproheptadine is described as first-generation antihistamine + 5-HT₂ antagonist. A piperidine first-generation antihistamine with 5-HT_{2A} and 5-HT_{2C} antagonist activity; used for appetite stimulation, serotonin syndrome reversal, and migraine prophylaxis.

1.1 Class summary

First-generation antihistamine + 5-HT₂ antagonist

1.2 Subtitle

A piperidine first-generation antihistamine with 5-HT_{2A} and 5-HT_{2C} antagonist activity; used for appetite stimulation, serotonin syndrome reversal, and migraine prophylaxis.

2. Abstract

Cyproheptadine (4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-methylpiperidine; CAS 129-03-3; molecular formula C₂₁H₂₁N; molecular weight 287.40) is a piperidine first-generation antihistamine with potent 5-HT_{2A} and 5-HT_{2C} antagonist activity, approved by the FDA in 1961 (Periactin). The compound combines H₁ antihistamine activity (K_i approximately 1 nM, comparable to diphenhydramine) with strong 5-HT₂ antagonism (K_i approximately 1 nM at 5-HT_{2A}); the combined activity drives appetite stimulation (5-HT_{2C} antagonism, the same mechanism as the appetite gain seen with olanzapine and clozapine), serotonin syndrome reversal, and migraine prophylaxis. Plasma half-life is approximately 8 hours. Approved for allergic conditions; off-label use in failure-to-thrive (pediatric appetite stimulation), serotonin syndrome (the only specific antidote besides supportive care), and post-SSRI sexual dysfunction (5-HT_{2A} antagonism). Used as the canonical 5-HT₂ antagonist antihistamine in research.

3. Mechanism of Action

First-generation H1 antihistamine combined with potent 5-HT_{2A} and 5-HT_{2C} antagonism. 5-HT_{2C} blockade drives appetite stimulation; 5-HT_{2A} blockade reverses serotonin syndrome.

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 4 to 16 mg per oral administration daily, in divided doses.

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. Goldman MJ. Cyproheptadine: a brief review of its multiple therapeutic uses. J Tenn Med Assoc 1976.
2. Boyer EW, Shannon M. The serotonin syndrome. N Engl J Med 2005.
3. Couch JR. Cyproheptadine in the prophylaxis of migraine in adults. Headache 2011.

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