

RESEARCH MONOGRAPH . COMPOUND PROFILE

Tacrine

The first FDA-approved Alzheimer disease therapy (1993), withdrawn for hepatotoxicity but historically important and retained as a research probe.

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COMPOUND CLASS	Aminoacridine acetylcholinesterase inhibitor

ABSTRACT

Tacrine (Cognex, 1,2,3,4-tetrahydroacridin-9-amine; CAS 321-64-2; molecular formula C₁₃H₁₄N₂; molecular weight 198.27) is the first FDA-approved cholinesterase inhibitor for Alzheimer disease, granted approval in 1993 and subsequently withdrawn from the US market in 2013 due to hepatotoxicity (approximately 50 percent of patients developed clinically significant ALT elevation requiring monitoring or discontinuation). The compound is a non-selective reversible AChE and BChE inhibitor based on an aminoacridine scaffold. Mechanism includes additional weak NMDA receptor antagonism and modest sodium channel blockade, distinguishing the pharmacology from the more selective subsequent AChE inhibitors. The historical significance of tacrine is substantial; the compound established cholinesterase inhibition as a viable therapeutic strategy for Alzheimer disease and led to development of the more tolerable second-generation agents. The compound retains research utility as a pharmacological probe and AChE reference compound. Pharmacokinetics: short half-life (3 to 4 hours), four-times-daily dosing required in the marketed formulation. Hepatotoxicity is dose-related and reversible on discontinuation in most cases.

1. Compound Identification

Tacrine is described as aminoacridine acetylcholinesterase inhibitor. The first FDA-approved Alzheimer disease therapy (1993), withdrawn for hepatotoxicity but historically important and retained as a research probe.

1.1 Class summary

Aminoacridine acetylcholinesterase inhibitor

1.2 Subtitle

The first FDA-approved Alzheimer disease therapy (1993), withdrawn for hepatotoxicity but historically important and retained as a research probe.

2. Abstract

Tacrine (Cognex, 1,2,3,4-tetrahydroacridin-9-amine; CAS 321-64-2; molecular formula C₁₃H₁₄N₂; molecular weight 198.27) is the first FDA-approved cholinesterase inhibitor for Alzheimer disease, granted approval in 1993 and subsequently withdrawn from the US market in 2013 due to hepatotoxicity (approximately 50 percent of patients developed clinically significant ALT elevation requiring monitoring or discontinuation). The compound is a non-selective reversible AChE and BChE inhibitor based on an aminoacridine scaffold. Mechanism includes additional weak NMDA receptor antagonism and modest sodium channel blockade, distinguishing the pharmacology from the more selective subsequent AChE inhibitors. The historical significance of tacrine is substantial; the compound established cholinesterase inhibition as a viable therapeutic strategy for Alzheimer disease and led to development of the more tolerable second-generation agents. The compound retains research utility as a pharmacological probe and AChE reference compound. Pharmacokinetics: short half-life (3 to 4 hours), four-times-daily dosing required in the marketed formulation. Hepatotoxicity is dose-related and reversible on discontinuation in most cases.

3. Mechanism of Action

Non-selective AChE and BChE inhibitor; secondary NMDA antagonism and sodium channel blockade.

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

40 to 160 mg per day in four divided doses (when marketed).

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. Davis KL, et al. A double-blind, placebo-controlled multicenter study of tacrine for Alzheimer's disease. N Engl J Med 1992.
2. Watkins PB, et al. Hepatotoxic effects of tacrine administration in patients with Alzheimer's disease. JAMA 1994.

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