

RESEARCH MONOGRAPH . COMPOUND PROFILE

Amoxapine

A 2-chloro-loxapine derivative TCA with substantial D2 antagonism; an antidepressant with antipsychotic-class side effects including extrapyramidal symptoms.

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COMPOUND CLASS	Tricyclic antidepressant with antipsychotic-like activity

ABSTRACT

Amoxapine (2-chloro-11-(piperazin-1-yl)dibenzo[b,f][1,4]oxazepine; CAS 14028-44-5; molecular formula $C_{17}H_{16}ClN_3O$; molecular weight 313.78) is a dibenzoxazepine TCA developed at Lederle as a derivative of the antipsychotic loxapine, approved by the FDA in 1980 under the trade name Asendin. NET K_i approximately 16 nM, SERT K_i approximately 58 nM; the compound retains the dibenzoxazepine scaffold of loxapine which confers D2 antagonism (K_i approximately 100 nM) atypical for an antidepressant. Active metabolite 7-hydroxyamoxapine has even more potent D2 antagonism. The dopaminergic activity produces extrapyramidal side effects (akathisia, tardive dyskinesia, parkinsonism) and rare neuroleptic malignant syndrome at clinical doses, distinguishing amoxapine from other TCAs and complicating its safety profile. Plasma half-life is 8 to 30 hours. Approved for major depressive disorder; effective in psychotic depression where D2 antagonism is therapeutic, but the antipsychotic-class adverse events have limited mainstream use. Used as a reference compound for combined monoaminergic and dopaminergic antagonist pharmacology.

1. Compound Identification

Amoxapine is described as tricyclic antidepressant with antipsychotic-like activity. A 2-chloro-loxapine derivative TCA with substantial D2 antagonism; an antidepressant with antipsychotic-class side effects including extrapyramidal symptoms.

1.1 Class summary

Tricyclic antidepressant with antipsychotic-like activity

1.2 Subtitle

A 2-chloro-loxapine derivative TCA with substantial D2 antagonism; an antidepressant with antipsychotic-class side effects including extrapyramidal symptoms.

2. Abstract

Amoxapine (2-chloro-11-(piperazin-1-yl)dibenzo[b,f][1,4]oxazepine; CAS 14028-44-5; molecular formula C₁₇H₁₆ClN₃O; molecular weight 313.78) is a dibenzoxazepine TCA developed at Lederle as a derivative of the antipsychotic loxapine, approved by the FDA in 1980 under the trade name Asendin. NET Ki approximately 16 nM, SERT Ki approximately 58 nM; the compound retains the dibenzoxazepine scaffold of loxapine which confers D2 antagonism (Ki approximately 100 nM) atypical for an antidepressant. Active metabolite 7-hydroxyamoxapine has even more potent D2 antagonism. The dopaminergic activity produces extrapyramidal side effects (akathisia, tardive dyskinesia, parkinsonism) and rare neuroleptic malignant syndrome at clinical doses, distinguishing amoxapine from other TCAs and complicating its safety profile. Plasma half-life is 8 to 30 hours. Approved for major depressive disorder; effective in psychotic depression where D2 antagonism is therapeutic, but the antipsychotic-class adverse events have limited mainstream use. Used as a reference compound for combined monoaminergic and dopaminergic antagonist pharmacology.

3. Mechanism of Action

NET inhibition combined with D2 antagonism; active metabolite is a more potent D2 antagonist. Pharmacology resembles a hybrid TCA-antipsychotic.

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 50 to 600 mg per oral administration daily. 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. Greenblatt DJ, et al. Amoxapine: clinical pharmacology and therapeutic application. J Clin Psychopharmacol 1981.
2. Kapur S, et al. Antidepressant amoxapine occupies dopamine D2 receptors. Neuropsychopharmacology 1999.
3. Kuhn KU, et al. Amoxapine in psychotic depression. Pharmacopsychiatry 1991.

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