

RESEARCH MONOGRAPH . COMPOUND PROFILE

Doxepin (Low-Dose)

A tricyclic antidepressant FDA-approved at low doses (3 to 6 mg) as Silenor for sleep maintenance insomnia, exploiting selective H1 antihistamine activity at the low end of the dose range.

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COMPOUND CLASS	Tricyclic antidepressant / H1 antagonist

ABSTRACT

Doxepin (Silenor at low doses; CAS 1668-19-5) is a tricyclic antidepressant approved at antidepressant doses (75 to 300 mg) since 1969 and reformulated at low doses (3 to 6 mg) by Somaxon and approved as Silenor in 2010 for sleep maintenance insomnia. At low doses, the compound shows selective H1 antihistamine activity; muscarinic, alpha-1 adrenergic, and serotonergic activities relevant at higher antidepressant doses are minimal. The H1-mediated sleep maintenance effect targets sleep continuity rather than sleep onset. Pharmacokinetics: plasma half-life 15 hours; CYP2D6 and CYP1A2 metabolism. Schedule status: prescription-only; not federally scheduled.

1. Compound Identification

Doxepin (Low-Dose) is described as tricyclic antidepressant / h1 antagonist. A tricyclic antidepressant FDA-approved at low doses (3 to 6 mg) as Silenor for sleep maintenance insomnia, exploiting selective H1 antihistamine activity at the low end of the dose range.

1.1 Class summary

Tricyclic antidepressant / H1 antagonist

1.2 Subtitle

A tricyclic antidepressant FDA-approved at low doses (3 to 6 mg) as Silenor for sleep maintenance insomnia, exploiting selective H1 antihistamine activity at the low end of the dose range.

2. Abstract

Doxepin (Silenor at low doses; CAS 1668-19-5) is a tricyclic antidepressant approved at antidepressant doses (75 to 300 mg) since 1969 and reformulated at low doses (3 to 6 mg) by Somaxon and approved as Silenor in 2010 for sleep maintenance insomnia. At low doses, the compound shows selective H1 antihistamine activity; muscarinic, alpha-1 adrenergic, and serotonergic activities relevant at higher antidepressant doses are minimal. The H1-mediated sleep maintenance effect targets sleep continuity rather than sleep onset. Pharmacokinetics: plasma half-life 15 hours; CYP2D6 and CYP1A2 metabolism. Schedule status: prescription-only; not federally scheduled.

3. Mechanism of Action

At low dose: selective H1 antihistamine. At antidepressant doses: tricyclic with serotonergic and adrenergic activity.

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

3 to 6 mg at bedtime for sleep maintenance.

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. Krystal AD, et al. Efficacy and safety of doxepin 1 mg, 3 mg, and 6 mg in adults with primary insomnia. Sleep 2011.

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