

RESEARCH MONOGRAPH . COMPOUND PROFILE

Levomilnacipran

The (1S,2R)-enantiomer of milnacipran; a pure SNRI with strong NET selectivity over SERT and minimal off-target activity.

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COMPOUND CLASS	Pure SNRI ((1S,2R)-enantiomer)

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ABSTRACT

Levomilnacipran ((1S,2R)-2-(aminomethyl)-N,N-diethyl-1-phenylcyclopropanecarboxamide; CAS 96847-55-1 (HCl salt); molecular formula C₁₅H₂₂N₂O; molecular weight 246.35) is the (1S,2R)-enantiomer of milnacipran, marketed as Fetzima by Forest Pharmaceuticals after FDA approval in 2013. Distinct among SNRIs for inverse selectivity: NET affinity (K_i approximately 11 nM) exceeds SERT affinity (K_i approximately 19 nM) by approximately 2-fold, the opposite of duloxetine and venlafaxine. The compound has minimal off-target activity at adrenergic, dopaminergic, muscarinic, or histaminergic sites. Plasma half-life is approximately 12 hours; metabolism is primarily renal (excreted unchanged) with minor CYP3A4 contribution, producing minimal drug-drug interaction potential. Approved for major depressive disorder; off-label investigation in attention deficit and chronic pain conditions. The dosing form is extended-release; 40 to 120 mg once daily. Used as the reference NET-selective SNRI in mechanism studies.

1. Compound Identification

Levomilnacipran is described as pure snri ((1s,2r)-enantiomer). The (1S,2R)-enantiomer of milnacipran; a pure SNRI with strong NET selectivity over SERT and minimal off-target activity.

1.1 Class summary

Pure SNRI ((1S,2R)-enantiomer)

1.2 Subtitle

The (1S,2R)-enantiomer of milnacipran; a pure SNRI with strong NET selectivity over SERT and minimal off-target activity.

2. Abstract

Levomilnacipran ((1S,2R)-2-(aminomethyl)-N,N-diethyl-1-phenylcyclopropanecarboxamide; CAS 96847-55-1 (HCl salt); molecular formula C₁₅H₂₂N₂O; molecular weight 246.35) is the (1S,2R)-enantiomer of milnacipran, marketed as Fetzima by Forest Pharmaceuticals after FDA approval in 2013. Distinct among SNRIs for inverse selectivity: NET affinity (K_i approximately 11 nM) exceeds SERT affinity (K_i approximately 19 nM) by approximately 2-fold, the opposite of duloxetine and venlafaxine. The compound has minimal off-target activity at adrenergic, dopaminergic, muscarinic, or histaminergic sites. Plasma half-life is approximately 12 hours; metabolism is primarily renal (excreted unchanged) with minor CYP3A4 contribution, producing minimal drug-drug interaction potential. Approved for major depressive disorder; off-label investigation in attention deficit and chronic pain conditions. The dosing form is extended-release; 40 to 120 mg once daily. Used as the reference NET-selective SNRI in mechanism studies.

3. Mechanism of Action

NET-selective SNRI (NET preferred over SERT, opposite of typical SNRIs). Minimal off-target receptor 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

Clinical 40 to 120 mg per oral administration once daily (ER). Rodent studies 3 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. Auclair AL, et al. Levomilnacipran (F2695), a norepinephrine-preferring SNRI: profile in vitro and in models of depression and anxiety. *Neuropharmacology* 2013.
2. Asnis GM, Henderson MA. Levomilnacipran for the treatment of major depressive disorder. *Drug Des Devel Ther* 2015.
3. Sansone RA, Sansone LA. Serotonin norepinephrine reuptake inhibitors: a pharmacological comparison. *Innov Clin Neurosci* 2014.

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