

RESEARCH MONOGRAPH . COMPOUND PROFILE

Duloxetine

A balanced-affinity SNRI distinguished by approval for chronic pain and diabetic peripheral neuropathy in addition to depression.

DOCUMENT	KDC-MN-209
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COMPOUND CLASS	Serotonin-norepinephrine reuptake inhibitor

ABSTRACT

Duloxetine ((S)-N-methyl-3-(naphthalen-1-yloxy)-3-(thiophen-2-yl)propan-1-amine; CAS 116539-59-4; molecular formula C₁₈H₁₉NOS; molecular weight 297.41) is a balanced-affinity SNRI developed at Eli Lilly and approved by the FDA in 2004 under the trade name Cymbalta. SERT (K_i approximately 0.8 nM) and NET (K_i approximately 7.5 nM) affinities are both nanomolar, with a SERT/NET ratio of roughly 10, more balanced than venlafaxine (ratio approximately 30). The compound exhibits weak DAT inhibition (K_i approximately 240 nM) of marginal clinical relevance. Plasma half-life is approximately 12 hours; metabolism is via CYP1A2 (primary) and CYP2D6 (secondary). The compound is itself a moderate CYP2D6 inhibitor, producing relevant interactions with TCAs, antipsychotics, and tamoxifen. Approved indications include major depressive disorder, generalized anxiety disorder, fibromyalgia, diabetic peripheral neuropathic pain, and chronic musculoskeletal pain. The pain indications reflect the noradrenergic component's role in descending pain modulation. Used as the canonical balanced SNRI in mechanism studies and as a reference compound for descending pain modulation research.

1. Compound Identification

Duloxetine is described as serotonin-norepinephrine reuptake inhibitor. A balanced-affinity SNRI distinguished by approval for chronic pain and diabetic peripheral neuropathy in addition to depression.

1.1 Class summary

Serotonin-norepinephrine reuptake inhibitor

1.2 Subtitle

A balanced-affinity SNRI distinguished by approval for chronic pain and diabetic peripheral neuropathy in addition to depression.

2. Abstract

Duloxetine ((S)-N-methyl-3-(naphthalen-1-yloxy)-3-(thiophen-2-yl)propan-1-amine; CAS 116539-59-4; molecular formula C₁₈H₁₉NOS; molecular weight 297.41) is a balanced-affinity SNRI developed at Eli Lilly and approved by the FDA in 2004 under the trade name Cymbalta. SERT (K_i approximately 0.8 nM) and NET (K_i approximately 7.5 nM) affinities are both nanomolar, with a SERT/NET ratio of roughly 10, more balanced than venlafaxine (ratio approximately 30). The compound exhibits weak DAT inhibition (K_i approximately 240 nM) of marginal clinical relevance. Plasma half-life is approximately 12 hours; metabolism is via CYP1A2 (primary) and CYP2D6 (secondary). The compound is itself a moderate CYP2D6 inhibitor, producing relevant interactions with TCAs, antipsychotics, and tamoxifen. Approved indications include major depressive disorder, generalized anxiety disorder, fibromyalgia, diabetic peripheral neuropathic pain, and chronic musculoskeletal pain. The pain indications reflect the noradrenergic component's role in descending pain modulation. Used as the canonical balanced SNRI in mechanism studies and as a reference compound for descending pain modulation research.

3. Mechanism of Action

Balanced SERT/NET inhibition with weak DAT inhibition. Noradrenergic component mediates analgesic effects via descending pain modulation.

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 30 to 120 mg per oral administration daily. 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. Bymaster FP, et al. Comparative affinity of duloxetine and venlafaxine for serotonin and norepinephrine transporters. Neuropsychopharmacology 2001.
2. Wernicke JF, et al. The clinical pharmacokinetic profile of duloxetine. Hum Psychopharmacol 2008.
3. Smith HS, et al. Duloxetine in the management of chronic musculoskeletal pain. Ther Clin Risk Manag 2012.

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