

RESEARCH MONOGRAPH . COMPOUND PROFILE

Tapentadol

A mu-opioid agonist with norepinephrine reuptake inhibition; an analgesic with reduced opioid side effects through the dual mechanism.

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COMPOUND CLASS	Mu-opioid agonist + norepinephrine reuptake inhibitor

ABSTRACT

Tapentadol (3-[(2R,3R)-1-(dimethylamino)-2-methylpentan-3-yl]phenol; CAS 175591-23-8; molecular formula C₁₄H₂₃NO; molecular weight 221.34) is a mu-opioid agonist with norepinephrine reuptake inhibition developed at Grunenthal and approved by the FDA in 2008 (Nucynta). The compound is a moderate-affinity mu-opioid agonist (K_i approximately 0.16 microM, intermediate between morphine and tramadol) with concurrent NET inhibition (K_i approximately 0.5 microM); distinct from tramadol by absence of meaningful SERT activity, eliminating the serotonin syndrome risk. The dual MOR/NRI mechanism produces strong analgesia with reduced opioid-mediated side effects (constipation, nausea, respiratory depression) at equianalgesic doses, an opioid-sparing effect supported by clinical trials. Plasma half-life is approximately 4 hours; metabolism is via glucuronidation (no active metabolites). Schedule II in the US (higher than tramadol). Used as a reference dual MOR/NRI analgesic in research.

1. Compound Identification

Tapentadol is described as mu-opioid agonist + norepinephrine reuptake inhibitor. A mu-opioid agonist with norepinephrine reuptake inhibition; an analgesic with reduced opioid side effects through the dual mechanism.

1.1 Class summary

Mu-opioid agonist + norepinephrine reuptake inhibitor

1.2 Subtitle

A mu-opioid agonist with norepinephrine reuptake inhibition; an analgesic with reduced opioid side effects through the dual mechanism.

2. Abstract

Tapentadol (3-[(2R,3R)-1-(dimethylamino)-2-methylpentan-3-yl]phenol; CAS 175591-23-8; molecular formula C₁₄H₂₃NO; molecular weight 221.34) is a mu-opioid agonist with norepinephrine reuptake inhibition developed at Grunenthal and approved by the FDA in 2008 (Nucynta). The compound is a moderate-affinity mu-opioid agonist (K_i approximately 0.16 microM, intermediate between morphine and tramadol) with concurrent NET inhibition (K_i approximately 0.5 microM); distinct from tramadol by absence of meaningful SERT activity, eliminating the serotonin syndrome risk. The dual MOR/NRI mechanism produces strong analgesia with reduced opioid-mediated side effects (constipation, nausea, respiratory depression) at equianalgesic doses, an opioid-sparing effect supported by clinical trials. Plasma half-life is approximately 4 hours; metabolism is via glucuronidation (no active metabolites). Schedule II in the US (higher than tramadol). Used as a reference dual MOR/NRI analgesic in research.

3. Mechanism of Action

Direct mu-opioid agonism ($K_i \sim 0.16 \text{ } \mu\text{M}$) with NET inhibition ($K_i \sim 0.5 \text{ } \mu\text{M}$). No SERT activity; no active metabolites. Opioid-sparing analgesia.

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 250 mg per oral administration every 4 to 6 hours.

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. Tzschentke TM, et al. (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol hydrochloride (tapentadol HCl): a novel mu-opioid receptor agonist/norepinephrine reuptake inhibitor with broad-spectrum analgesic properties. J Pharmacol Exp Ther 2007.
2. Hartrick CT, Rozek RJ. Tapentadol in pain management: a pharmacological review. CNS Drugs 2011.
3. Riemsma R, et al. Systematic review of tapentadol in chronic severe pain. Curr Med Res Opin 2011.

This monograph is provided for research use only. Not for medical, diagnostic, or therapeutic purposes. Not for human consumption. Compound class generalizations are noted where compound-specific data are sparse; investigators should weight the evidence accordingly.