

RESEARCH MONOGRAPH . COMPOUND PROFILE

Tramadol

A weak mu-opioid agonist with serotonin-norepinephrine reuptake inhibition; an atypical analgesic with abuse and serotonin syndrome risk.

DOCUMENT	KDC-MN-348
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COMPOUND CLASS	Atypical opioid (mu-opioid + SNRI)

ABSTRACT

Tramadol ((1R,2R)-rel-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexan-1-ol; CAS 27203-92-5; molecular formula C₁₆H₂₅NO₂; molecular weight 263.38) is an atypical opioid analgesic developed at Grunenthal in the 1970s and approved by the FDA in 1995 (Ultram). The compound is a weak mu-opioid receptor agonist (K_i approximately 2 microM, low affinity); the active metabolite O-desmethyltramadol (M1, formed via CYP2D6) has approximately 200-fold higher mu-opioid affinity. Distinct from pure opioids by additional serotonin and norepinephrine reuptake inhibition (SERT K_i approximately 1 microM, NET K_i approximately 0.4 microM), contributing to the analgesic profile and to serotonin syndrome risk when combined with other serotonergic drugs. Plasma half-life is approximately 6 hours; metabolism is via CYP2D6 (M1 production) and CYP3A4. Schedule IV in the US since 2014. The combined opioid and SNRI activity produces seizures (rare at therapeutic doses, more common in overdose), serotonin syndrome (with concurrent serotonergic drugs), and abuse potential intermediate between non-opioid analgesics and full opioids. Used as the canonical atypical opioid in research.

1. 1. Compound Identification

Tramadol is described as atypical opioid (mu-opioid + snri). A weak mu-opioid agonist with serotonin-norepinephrine reuptake inhibition; an atypical analgesic with abuse and serotonin syndrome risk.

1.1. 1.1 Class summary

Atypical opioid (mu-opioid + SNRI)

1.2. 1.2 Subtitle

A weak mu-opioid agonist with serotonin-norepinephrine reuptake inhibition; an atypical analgesic with abuse and serotonin syndrome risk.

2. Abstract

Tramadol ((1R,2R)-rel-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexan-1-ol; CAS 27203-92-5; molecular formula C₁₆H₂₅NO₂; molecular weight 263.38) is an atypical opioid analgesic developed at Grunenthal in the 1970s and approved by the FDA in 1995 (Ultram). The compound is a weak mu-opioid receptor agonist (K_i approximately 2 microM, low affinity); the active metabolite O-desmethyltramadol (M1, formed via CYP2D6) has approximately 200-fold higher mu-opioid affinity. Distinct from pure opioids by additional serotonin and norepinephrine reuptake inhibition (SERT K_i approximately 1 microM, NET K_i approximately 0.4 microM), contributing to the analgesic profile and to serotonin syndrome risk when combined with other serotonergic drugs. Plasma half-life is approximately 6 hours; metabolism is via CYP2D6 (M1 production) and CYP3A4. Schedule IV in the US since 2014. The combined opioid and SNRI activity produces seizures (rare at therapeutic doses, more common in overdose), serotonin syndrome (with concurrent serotonergic drugs), and abuse potential intermediate between non-opioid analgesics and full opioids. Used as the canonical atypical opioid in research.

3. Mechanism of Action

Weak mu-opioid agonism with active metabolite M1 driving most opioid effect (CYP2D6-dependent); concurrent SERT and NET inhibition. Atypical opioid pharmacology.

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. 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. 5. Reported Research Dose Ranges

Clinical 50 to 400 mg per oral administration daily, in divided doses.

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. 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. 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. 9. References

1. Grond S, Sablotzki A. Clinical pharmacology of tramadol. Clin Pharmacokinet 2004.
2. Lassen D, et al. The pharmacogenetics of tramadol. Clin Pharmacokinet 2015.
3. Beakley BD, et al. Tramadol, pharmacology, side effects, and serotonin syndrome: a review. Pain Physician 2015.

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.