

RESEARCH MONOGRAPH . COMPOUND PROFILE

# Trazodone

*A triazolopyridine antidepressant repurposed at low dose as a hypnotic via potent H1 and 5-HT2A antagonism.*

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| AUTHOR         | Kodiac bioLabs Research                            |
| COMPOUND CLASS | Serotonin antagonist and reuptake inhibitor (SARI) |

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## ABSTRACT

Trazodone (2-{3-[4-(3-chlorophenyl)piperazin-1-yl]propyl}-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one; CAS 19794-93-5; molecular formula C<sub>19</sub>H<sub>22</sub>ClN<sub>5</sub>O; molecular weight 371.86) is a triazolopyridine SARI developed at Angelini and approved by the FDA in 1981. The compound is a weak SERT inhibitor (K<sub>i</sub> approximately 160 nM) but a potent 5-HT<sub>2A</sub> and H<sub>1</sub> antagonist (5-HT<sub>2A</sub> K<sub>i</sub> approximately 36 nM, H<sub>1</sub> K<sub>i</sub> approximately 220 nM). The active metabolite mCPP (m-chlorophenylpiperazine) is a 5-HT<sub>2C</sub> agonist contributing to anxiogenic side effects in some patients. Pharmacological profile distinguishes trazodone from SSRIs: at antidepressant doses (150 to 600 mg daily) the SERT inhibition contributes meaningfully, but at the more common hypnotic doses (25 to 100 mg) the H<sub>1</sub> and 5-HT<sub>2A</sub> antagonism dominates, producing pronounced sedation without the GABAergic dependency profile of benzodiazepine hypnotics. Plasma half-life is bimodal: 3 to 6 hours alpha phase, 5 to 9 hours beta phase. Adverse events include orthostatic hypotension and the rare but serious priapism (1 in 1000 to 1 in 10000 incidence). Used as a low-dose hypnotic and as a reference compound for 5-HT<sub>2A</sub> receptor pharmacology.

# 1. 1. Compound Identification

**Trazodone** is described as serotonin antagonist and reuptake inhibitor (sari). A triazolopyridine antidepressant repurposed at low dose as a hypnotic via potent H1 and 5-HT2A antagonism.

## 1.1. 1.1 Class summary

Serotonin antagonist and reuptake inhibitor (SARI)

## 1.2. 1.2 Subtitle

A triazolopyridine antidepressant repurposed at low dose as a hypnotic via potent H1 and 5-HT2A antagonism.

## 2. Abstract

Trazodone (2-{3-[4-(3-chlorophenyl)piperazin-1-yl]propyl}-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one; CAS 19794-93-5; molecular formula C<sub>19</sub>H<sub>22</sub>ClN<sub>5</sub>O; molecular weight 371.86) is a triazolopyridine SARI developed at Angelini and approved by the FDA in 1981. The compound is a weak SERT inhibitor (K<sub>i</sub> approximately 160 nM) but a potent 5-HT<sub>2A</sub> and H<sub>1</sub> antagonist (5-HT<sub>2A</sub> K<sub>i</sub> approximately 36 nM, H<sub>1</sub> K<sub>i</sub> approximately 220 nM). The active metabolite mCPP (m-chlorophenylpiperazine) is a 5-HT<sub>2C</sub> agonist contributing to anxiogenic side effects in some patients. Pharmacological profile distinguishes trazodone from SSRIs: at antidepressant doses (150 to 600 mg daily) the SERT inhibition contributes meaningfully, but at the more common hypnotic doses (25 to 100 mg) the H<sub>1</sub> and 5-HT<sub>2A</sub> antagonism dominates, producing pronounced sedation without the GABAergic dependency profile of benzodiazepine hypnotics. Plasma half-life is bimodal: 3 to 6 hours alpha phase, 5 to 9 hours beta phase. Adverse events include orthostatic hypotension and the rare but serious priapism (1 in 1000 to 1 in 10000 incidence). Used as a low-dose hypnotic and as a reference compound for 5-HT<sub>2A</sub> receptor pharmacology.

### 3. Mechanism of Action

Weak SERT inhibition; potent 5-HT<sub>2A</sub> and H<sub>1</sub> antagonism. Active metabolite mCPP is a 5-HT<sub>2C</sub> agonist.

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. 5. Reported Research Dose Ranges

Clinical 25 to 600 mg per oral administration daily (lower for hypnotic, higher for antidepressant use). Rodent studies 1 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. 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. Stahl SM. Mechanism of action of trazodone: a multifunctional drug. CNS Spectr 2009.
2. Mendelson WB. A review of the evidence for the efficacy and safety of trazodone in insomnia. J Clin Psychiatry 2005.
3. Haria M, et al. Trazodone. A review of its pharmacology, therapeutic use in depression and therapeutic potential. Drugs Aging 1994.

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