

RESEARCH MONOGRAPH . COMPOUND PROFILE

D-Serine

D-stereoisomer of serine; an endogenous obligatory co-agonist at the NMDA receptor glycine site.

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COMPOUND CLASS	Endogenous NMDA receptor co-agonist

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ABSTRACT

D-serine ((R)-2-amino-3-hydroxypropanoic acid; CAS 312-84-5; molecular formula $C_3H_7NO_3$; molecular weight 105.09) is the D-stereoisomer of serine, an endogenous obligatory co-agonist at the glycine site of NMDA receptors. The compound is biosynthesized in the brain by serine racemase (the enzyme that converts L-serine to D-serine) and is metabolized by D-amino acid oxidase (DAAO). D-serine is the principal endogenous co-agonist for synaptic NMDA receptors in the cortex and hippocampus, while glycine itself co-agonizes extrasynaptic NMDA receptors. Pharmacologically, exogenous D-serine elevates NMDA receptor function, with research interest in schizophrenia (where reduced NMDA function is hypothesized as a contributor to negative symptoms and cognitive deficits) and depression (NMDA modulation as antidepressant target). Phase 2 trials in schizophrenia have shown small effects. Plasma half-life is approximately 4 hours; oral bioavailability is moderate. The DAAO inhibitor approach is an alternative to direct D-serine administration. Used as the canonical NMDA glycine-site co-agonist in research.

1. Compound Identification

D-Serine is described as endogenous nmda receptor co-agonist. D-stereoisomer of serine; an endogenous obligatory co-agonist at the NMDA receptor glycine site.

1.1 Class summary

Endogenous NMDA receptor co-agonist

1.2 Subtitle

D-stereoisomer of serine; an endogenous obligatory co-agonist at the NMDA receptor glycine site.

2. Abstract

D-serine ((R)-2-amino-3-hydroxypropanoic acid; CAS 312-84-5; molecular formula $C_3H_7NO_3$; molecular weight 105.09) is the D-stereoisomer of serine, an endogenous obligatory co-agonist at the glycine site of NMDA receptors. The compound is biosynthesized in the brain by serine racemase (the enzyme that converts L-serine to D-serine) and is metabolized by D-amino acid oxidase (DAAO). D-serine is the principal endogenous co-agonist for synaptic NMDA receptors in the cortex and hippocampus, while glycine itself co-agonizes extrasynaptic NMDA receptors. Pharmacologically, exogenous D-serine elevates NMDA receptor function, with research interest in schizophrenia (where reduced NMDA function is hypothesized as a contributor to negative symptoms and cognitive deficits) and depression (NMDA modulation as antidepressant target). Phase 2 trials in schizophrenia have shown small effects. Plasma half-life is approximately 4 hours; oral bioavailability is moderate. The DAAO inhibitor approach is an alternative to direct D-serine administration. Used as the canonical NMDA glycine-site co-agonist in research.

3. Mechanism of Action

Endogenous NMDA receptor glycine-site co-agonist; obligatory for synaptic NMDA receptor activation. Biosynthesized by serine racemase; degraded by DAAO.

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 trials 30 to 120 mg/kg per oral administration daily; supplement 1 to 4 g/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. Mothet JP, et al. D-serine is an endogenous ligand for the glycine site of the N-methyl-D-aspartate receptor. Proc Natl Acad Sci 2000.
2. Tsai G, et al. D-serine added to antipsychotics for the treatment of schizophrenia. Biol Psychiatry 1998.
3. Wolosker H. D-serine regulation of NMDA receptor activity. Sci Signal 2006.

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