

RESEARCH MONOGRAPH . COMPOUND PROFILE

NACET

The ethyl ester of N-acetylcysteine, a lipophilic NAC analog with substantially higher cellular and central nervous system bioavailability than the parent acid.

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ABSTRACT

NACET (N-acetyl-L-cysteine ethyl ester; CAS 59587-09-6; molecular formula $C_7H_{13}NO_3S$; molecular weight 191.25) is the ethyl ester prodrug of N-acetylcysteine (NAC), developed at the University of Southern California and at Italian academic groups during the 2000s as a lipophilic alternative to NAC with markedly improved cellular and central nervous system bioavailability. The parent NAC is a polar carboxylic acid with low oral bioavailability (approximately 6 to 10 percent), poor blood-brain barrier penetration, and limited intracellular accumulation; NACET is a neutral ester at physiological pH, crosses cell membranes by passive diffusion, and is hydrolyzed intracellularly by ubiquitous esterases to release NAC inside the cell. Published in vitro studies report cellular glutathione (GSH) elevation 30 to 50 percent above baseline after NACET exposure compared to less than 10 percent for equimolar NAC, owing to the difference in cellular delivery. Published rodent in vivo work reports brain GSH elevation after oral NACET that is not detectable after equimolar oral NAC, consistent with the BBB-penetration argument. The pharmacological consequence is that NACET delivers the antioxidant and glutathione-precursor activity of NAC at lower oral doses with central nervous system exposure. Reported applications in research include neuroprotection, oxidative stress modulation, and as a research tool for cysteine delivery in cell culture. Human pharmacokinetic data are limited and no large clinical trials have been published. The compound is not approved by FDA or EMA for any indication. NAC itself is approved as an antidote for acetaminophen overdose and as a mucolytic; the ester form is sold only as a research-grade compound or supplement.

Stability is moderate at room temperature; refrigerated storage is preferred for solid material.

1. Compound Identification

NACET is described as lipophilic ester of n-acetylcysteine and glutathione precursor. The ethyl ester of N-acetylcysteine, a lipophilic NAC analog with substantially higher cellular and central nervous system bioavailability than the parent acid.

1.1 Class summary

Lipophilic ester of N-acetylcysteine and glutathione precursor

1.2 Subtitle

The ethyl ester of N-acetylcysteine, a lipophilic NAC analog with substantially higher cellular and central nervous system bioavailability than the parent acid.

2. Abstract

NACET (N-acetyl-L-cysteine ethyl ester; CAS 59587-09-6; molecular formula C₇H₁₃NO₃S; molecular weight 191.25) is the ethyl ester prodrug of N-acetylcysteine (NAC), developed at the University of Southern California and at Italian academic groups during the 2000s as a lipophilic alternative to NAC with markedly improved cellular and central nervous system bioavailability. The parent NAC is a polar carboxylic acid with low oral bioavailability (approximately 6 to 10 percent), poor blood-brain barrier penetration, and limited intracellular accumulation; NACET is a neutral ester at physiological pH, crosses cell membranes by passive diffusion, and is hydrolyzed intracellularly by ubiquitous esterases to release NAC inside the cell. Published in vitro studies report cellular glutathione (GSH) elevation 30 to 50 percent above baseline after NACET exposure compared to less than 10 percent for equimolar NAC, owing to the difference in cellular delivery. Published rodent in vivo work reports brain GSH elevation after oral NACET that is not detectable after equimolar oral NAC, consistent with the BBB-penetration argument. The pharmacological consequence is that NACET delivers the antioxidant and glutathione-precursor activity of NAC at lower oral doses with central nervous system exposure. Reported applications in research include neuroprotection, oxidative stress modulation, and as a research tool for cysteine delivery in cell culture. Human pharmacokinetic data are limited and no large clinical trials have been published. The compound is not approved by FDA or EMA for any indication. NAC itself is approved as an antidote for acetaminophen overdose and as a mucolytic; the ester form is sold only as a research-grade compound or supplement. Stability is moderate at room temperature; refrigerated storage is preferred for solid material.

3. Mechanism of Action

Ethyl ester of NAC; hydrolyzed by intracellular esterases to release NAC inside the cell. Glutathione precursor with markedly improved CNS and cellular delivery relative to parent acid.

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

Rodent and in vitro doses 1 to 50 mg/kg. Research-grade human doses reported in the supplement literature 100 to 600 mg per oral administration once or twice daily.

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. Giustarini D, et al. N-Acetylcysteine ethyl ester (NACET): a novel lipophilic cell-permeable cysteine derivative. Free Radic Biol Med 2012.
2. Tosi G, et al. Penetration of the blood-brain barrier by N-acetylcysteine ethyl ester. Eur J Pharm Sci 2014.
3. Atkuri KR, et al. N-Acetylcysteine: a safe antidote for cysteine/glutathione deficiency. Curr Opin Pharmacol 2007.

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