

RESEARCH MONOGRAPH . COMPOUND PROFILE

Methylene Blue

A phenothiazine dye used historically as an antimalarial and methemoglobinemia treatment, with mitochondrial electron-cycling activity at low doses for cognitive applications.

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ABSTRACT

Methylene blue (methylthioninium chloride; CAS 61-73-4; molecular formula $C_{16}H_{18}ClN_3S$; molecular weight 319.85) is a phenothiazine dye with the longest pharmaceutical history of any synthetic compound (first synthesized 1876). The compound is FDA-approved for methemoglobinemia (high-dose, 1-2 mg/kg IV) and has historical use as an antimalarial. Low-dose methylene blue (0.5 to 4 mg/kg orally) has been studied for cognitive enhancement, traumatic brain injury, and Alzheimer disease, based on the compound's mitochondrial electron-cycling activity (donates electrons to Complex III, bypassing dysfunctional Complex I/II). Pharmacology is complex and dose-dependent; high doses produce MAO inhibition and serotonin syndrome risk. Low-dose cognitive applications use 5 to 20 mg orally. The compound stains tissues and excreta blue, which is cosmetically obvious but harmless.

1. Compound Identification

Methylene Blue is described as phenothiazine dye / electron donor. A phenothiazine dye used historically as an antimalarial and methemoglobinemia treatment, with mitochondrial electron-cycling activity at low doses for cognitive applications.

1.1 Class summary

Phenothiazine dye / electron donor

1.2 Subtitle

A phenothiazine dye used historically as an antimalarial and methemoglobinemia treatment, with mitochondrial electron-cycling activity at low doses for cognitive applications.

2. Abstract

Methylene blue (methylthioninium chloride; CAS 61-73-4; molecular formula $C_{16}H_{18}ClN_3S$; molecular weight 319.85) is a phenothiazine dye with the longest pharmaceutical history of any synthetic compound (first synthesized 1876). The compound is FDA-approved for methemoglobinemia (high-dose, 1-2 mg/kg IV) and has historical use as an antimalarial. Low-dose methylene blue (0.5 to 4 mg/kg orally) has been studied for cognitive enhancement, traumatic brain injury, and Alzheimer disease, based on the compound's mitochondrial electron-cycling activity (donates electrons to Complex III, bypassing dysfunctional Complex I/II). Pharmacology is complex and dose-dependent; high doses produce MAO inhibition and serotonin syndrome risk. Low-dose cognitive applications use 5 to 20 mg orally. The compound stains tissues and excreta blue, which is cosmetically obvious but harmless.

3. Mechanism of Action

Mitochondrial electron donor (Complex III); bypasses Complex I/II. MAO inhibition at higher doses.

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

5 to 20 mg orally for cognitive applications; 1-2 mg/kg IV for methemoglobinemia.

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. Rojas JC, et al. Neurometabolic mechanisms for memory enhancement and neuroprotection of methylene blue. Prog Neurobiol 2012.

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