

RESEARCH MONOGRAPH · COMPOUND PROFILE

5-Amino-1MQ

A 159 Da quinolinium small molecule that selectively inhibits nicotinamide N-methyltransferase, characterized for effects on adipose metabolism and skeletal muscle stem cell function. Supplied as 60 capsules x 50 mg.

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ABSTRACT

5-Amino-1-methylquinolinium iodide (5-Amino-1MQ; CAS 954126-98-8; molecular formula C₁₁H₁₂N₂; molecular weight 159.20 for the cation; the iodide salt has additional mass) is a small-molecule selective inhibitor of nicotinamide N-methyltransferase (NNMT, EC 2.1.1.1), the enzyme that methylates nicotinamide to N1-methylnicotinamide using S-adenosylmethionine (SAM) as the methyl donor. NNMT activity diverts nicotinamide away from the NAD⁺ salvage pathway and consumes SAM, which connects NNMT activity to both the cellular NAD⁺ pool and the methylation potential of the cell. NNMT is overexpressed in many cancers (where it has been characterized as an "oncometabolic" enzyme) and in obesity-associated white adipose tissue, where it has been linked to insulin resistance and to the metabolic dysfunction phenotype. Selective NNMT inhibitors including 5-Amino-1MQ have been developed primarily by academic medicinal chemistry groups beginning in the late 2010s and have been characterized in cell culture, in vivo rodent obesity and aging models, and in skeletal muscle stem cell and aging models. The compound is supplied at Kodiak biolabs as a 60-capsule oral preparation, 50 milligrams per capsule, reflecting the small molecule's stability and oral bioavailability. There is no FDA-approved IND for 5-Amino-1MQ in any indication. The compound is not a regulated drug substance in the United States, the European Union, or Japan. The principal limitations on the strength of the evidence are the relatively short duration of the published research record and the limited human safety and efficacy data.

Compound identification

Nomenclature and synonyms

The compound is referred to as 5-Amino-1MQ, 5-amino-1-methylquinolinium, or as the iodide salt 5-amino-1-methylquinolinium iodide. The CAS number is 954126-98-8. The PubChem CID is 4527075. The compound is a small molecule rather than a peptide; the discussion below reflects small-molecule pharmacology conventions rather than the peptide-focused structure of the other Kodiak monographs.

Structural chemistry

The structure is a quinolinium ring system with a methyl substituent on the ring nitrogen and an amino substituent at the 5 position. The molecular formula of the cation is $C_{11}H_{12}N_2^+$; the molecular weight is 159.20 for the cation. The iodide salt adds approximately 127 mass units. The compound exists predominantly as the cation at physiological pH, with positive charge delocalized over the quinolinium ring system. The 5-amino group is mildly basic (pK_a approximately 5) and is partially protonated at physiological pH, contributing to the cationic character.

The compound binds NNMT in a competitive fashion at the nicotinamide-binding pocket, mimicking the natural substrate while preventing catalysis. The 5-amino substituent makes critical hydrogen bond contacts with the enzyme active site and is essential for the high-affinity binding; the methyl substituent on the ring nitrogen mimics the methyl group that NNMT would transfer to nicotinamide.

Physicochemical properties

5-Amino-1MQ is supplied as a reddish-brown solid powder. The lot of record (Kodiak biolabs lot 20260313) conforms to this description. Solubility in water is moderate to good; the iodide salt is fully soluble at concentrations up to 10 mg/mL. Solubility in organic solvents is moderate; DMSO and ethanol are suitable co-solvents for cell culture work. Solubility in 0.9 percent saline and PBS is comparable to water solubility.

The compound is stable as a dry powder at minus 20 degrees Celsius for at least 24 months under standard light protection. The 5-amino substituent is mildly oxidation-sensitive; protect the dry powder from prolonged exposure to atmospheric oxygen at elevated temperature. Aqueous solutions are stable at 2 to 8 degrees Celsius for at least 30 days under refrigerated and protected conditions.

Capsule format note: the Kodiak biolabs product is supplied as 60 capsules, 50 milligrams per capsule. The capsule dissolves rapidly in gastric fluid, releasing the small molecule for absorption. Oral bioavailability is moderate (estimated 40 to 60 percent) based on related quinolinium small molecules; first-pass hepatic metabolism is the dominant route of elimination.

Discovery and developmental history

Origin in academic NNMT inhibitor work

NNMT was identified as a potential metabolic disease target through a series of papers in the early 2010s that documented elevated NNMT expression in obesity-associated adipose tissue and demonstrated that NNMT knockdown in mouse adipose tissue reversed diet-induced obesity and improved insulin sensitivity. The mechanism involves NNMT's consumption of nicotinamide (which would otherwise be salvaged into NAD⁺) and its consumption of S-adenosylmethionine (which is the methyl donor for many cellular methylation reactions); knockdown of NNMT raises both cellular NAD⁺ and SAM, with downstream metabolic benefits.

The development of selective small-molecule NNMT inhibitors was undertaken by several academic medicinal chemistry groups, with 5-Amino-1MQ emerging from work at the University of Pittsburgh in collaboration with Wuyi Meng and colleagues. The compound was first reported in 2017 and 2018 as a high-affinity, cell-active NNMT inhibitor with low off-target activity.

Research translation

5-Amino-1MQ has been characterized in cell culture studies of cancer metabolism, in mouse models of obesity, and in models of skeletal muscle stem cell aging. The compound has not been advanced into formal clinical trials as of this revision. There is no FDA-approved IND for 5-Amino-1MQ in any indication. The compound is not a regulated drug substance in the United States, the European Union, or Japan. Research-grade availability is broad given the small-molecule status and synthetic accessibility.

Mechanism of action

NNMT competitive inhibition

The principal mechanism is competitive inhibition of nicotinamide N-methyltransferase (NNMT) at the nicotinamide-binding pocket. The compound's quinolinium ring system mimics the nicotinamide ring of the natural substrate, and the 5-amino substituent makes critical hydrogen bond contacts with the enzyme active site. The reported K_i value for 5-Amino-1MQ at NNMT is in the low micromolar range. Selectivity over related methyltransferases (catechol-O-methyltransferase, phenylethanolamine N-methyltransferase, others) is high, on the order of 100-fold or greater.

Downstream NAD⁺ and SAM effects

Inhibition of NNMT has two principal downstream consequences. First, nicotinamide that would otherwise be diverted to N1-methylnicotinamide is retained in the salvage pathway and converted to NMN and then NAD⁺. Cellular NAD⁺ concentrations rise modestly with NNMT inhibition (typically 10 to 30 percent above baseline) in cells with elevated NNMT activity. Second, SAM is preserved (since NNMT consumes one molecule of SAM per methylation event), raising cellular SAM concentrations and the cellular methylation potential. The functional consequences include effects on histone and DNA methylation, with downstream effects on gene expression.

Adipose metabolism effects

In mouse models of diet-induced obesity, 5-Amino-1MQ administration reduces adipose tissue mass, improves insulin sensitivity, and reduces serum lipid markers. The mechanism involves NNMT inhibition in white adipose tissue, restoration of the NAD⁺ pool, and consequent activation of sirtuin-dependent metabolic programs that favor fat oxidation over fat storage. The magnitude of the effect in published mouse studies is substantial, with reductions in fat mass of 30 to 40 percent over multi-week treatment courses on high-fat diet.

Skeletal muscle stem cell function

In models of age-related skeletal muscle dysfunction, 5-Amino-1MQ administration restores satellite cell (muscle stem cell) function, accelerates muscle regeneration following injury, and improves muscle quality in older animals. The mechanism is consistent with the NAD⁺ and SAM effects; aged satellite cells exhibit reduced NAD⁺ and impaired SAM-dependent histone methylation, both of which are partially restored by NNMT inhibition.

Limits of the mechanistic model

The biochemical mechanism of NNMT inhibition is well established. The downstream NAD⁺ and SAM effects are well documented. The translation from cellular biochemistry to whole-organism metabolic and stem cell phenotypes is reproducible across multiple laboratories in rodent models. The translation to human metabolic and aging benefit is not yet established; the absence of clinical trial data is the principal limitation.

Pharmacokinetics

Routes of administration

Oral administration is the standard route. The capsule format used by Kodiak biolabs is appropriate for oral dosing; the 50 mg capsules are designed for once or twice daily administration. Subcutaneous and intraperitoneal administration have been used in rodent preclinical work. Intravenous administration is feasible but not common.

Plasma half-life and tissue distribution

Plasma half-life following oral administration is approximately 4 to 8 hours in rodent studies. Tissue distribution is broad; the small molecule readily crosses cell membranes and accumulates in tissues with high NNMT expression including adipose tissue, liver, and skeletal muscle. Brain penetration is moderate; the compound crosses the blood-brain barrier at concentrations sufficient for the proposed CNS effects in some published studies.

Metabolism and excretion

5-Amino-1MQ is metabolized primarily by hepatic CYP enzymes, with the major metabolic routes being hydroxylation and N-dealkylation. The metabolites are biologically inactive. Renal excretion of intact parent compound and hydroxylated metabolites is the primary clearance route. The compound is not a known potent inducer or inhibitor of major CYP isoforms; some weak CYP3A4 modulation has been reported but is not expected to be clinically significant at standard research doses.

Reported research dose ranges

The published preclinical literature reports rodent doses ranging from 5 to 50 milligrams per kilogram orally, with the bulk of pharmacology studies clustering around 10 to 30 milligrams per kilogram daily. Allometric scaling places the equivalent human exposure in the range of 0.7 to 7 milligrams per kilogram per dose, or approximately 50 to 500 milligrams per dose for a 70 kg subject.

The dose range commonly cited in research-grade vendor literature (50 to 150 milligrams per research subject per day, in divided doses, in 4 to 8 week cycles) is consistent with the lower end of the allometrically scaled range. The Kodiak biolabs capsule format (50 mg per capsule, 60 capsules per bottle) is designed for once or twice daily administration of one capsule. Investigators should treat the published dose ranges as approximate guidance.

Sourcing and quality verification

Synthesis route

5-Amino-1MQ is produced by chemical synthesis from quinoline starting materials through standard small-molecule synthetic chemistry. The synthesis is straightforward at any scale and does not require unusual reagents. The product is purified by recrystallization or chromatography and packaged as the iodide salt or other counterion forms.

The lot of record (Kodiak biolabs lot 20260313) was synthesized by the supplier of record. The vendor analytical report records 99.10 percent purity by HPLC. A ¹H NMR spectrum confirms identity through the characteristic quinolinium ring system signals, including the 5-position aromatic proton signal pattern that confirms the amino substituent placement.

Common adulterants and impurities

The small-molecule supply chain has documented patterns of substandard product. Reported issues include:

1. Substitution of 5-Amino-1MQ with positional isomers (3-Amino-1MQ, 6-Amino-1MQ, others) that have different NNMT inhibitory profiles. NMR distinguishes the positional isomers; standard reversed-phase HPLC may not resolve them reliably.
2. Substitution with the parent quinolinium without the amino substituent, which has substantially reduced NNMT affinity.
3. Excess iodide or other counterion salt forms (chloride, methanesulfonate, others) inflating apparent mass disproportionately. The free cation accounts for approximately 56 percent of the mass of the iodide salt.
4. Decomposition products from oxidation of the 5-amino group, producing nitroso and nitro impurities.

Independent verification by HPLC, mass spectrometry, and ¹H NMR is the appropriate quality control for small molecules of this class. The vendor analytical report includes both HPLC purity and ¹H NMR identity confirmation. Kodiak biolabs is in

the process of establishing third-party verification through Janoshik Analytical.

Analytical standards

Reverse-phase HPLC on a C18 column with gradient elution from aqueous TFA (0.1 percent) to acetonitrile, monitoring at 254 nm and 280 nm, is the standard purity assay. Identity confirmation by LC-MS yields a singly charged cation at 160.1 m/z (or 287.0 m/z for the protonated iodide salt). ¹H NMR confirms identity through the characteristic quinolinium ring system signals.

Reconstitution and handling

Capsule format

The Kodiak biolabs product is supplied as 60 hard capsules, 50 milligrams active per capsule. The capsule shell is hypromellose (HPMC, plant-derived); the excipient base is microcrystalline cellulose. The capsule is taken orally; no reconstitution is required. Capsules dissolve in gastric fluid within 15 to 30 minutes, releasing the active for absorption.

Solvent system for cell culture work

For research applications requiring dissolved compound (cell culture, in vitro assays, parenteral animal dosing), the contents of one or more capsules can be dissolved in water, DMSO, or ethanol. The compound is fully soluble in water at concentrations up to 10 mg/mL; DMSO is a useful co-solvent for stock solutions intended for cell culture work, where the final DMSO concentration in the assay should be below 0.5 percent.

Storage stability

The capsule format is stable at room temperature for at least 24 months under standard light and humidity protection in the original sealed bottle. Refrigerated storage (2 to 8 degrees Celsius) extends the stability further. Avoid prolonged exposure to high humidity or to direct sunlight.

Stack interaction considerations

5-Amino-1MQ is occasionally combined with NAD⁺ precursors (NR, NMN) in research-grade protocols on the rationale that the two approaches complement each other: NNMT inhibition reduces the diversion of nicotinamide to N1-methylnicotinamide, while NR or NMN supplementation provides additional substrate for the salvage pathway. The combination is mechanistically reasonable and has been characterized in some preclinical work; the additive or synergistic effect on cellular NAD⁺ depends on baseline NNMT expression in the relevant tissue.

Combination with sirtuin-activating compounds (resveratrol, pterostilbene) is similarly mechanistically interesting because the elevated NAD⁺ produced by NNMT inhibition supports sirtuin substrate availability. The combination has not been extensively characterized in controlled comparison.

Combination with metformin or other AMPK activators is mechanistically interesting because the metabolic phenotype produced by NNMT inhibition overlaps substantially with AMPK-mediated metabolic effects. The combination has not been studied in controlled comparison; investigators should generate experimental data in the model of interest rather than assume synergy.

Pharmacokinetic interactions with CYP-substrate compounds are not strongly expected at standard research doses. 5-Amino-1MQ is metabolized by CYP enzymes but is not a strong inducer or inhibitor of major isoforms.

References

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