5-amino-1mq

5-Amino-1MQ is a small-molecule NNMT inhibitor (not a peptide) based on a methylquinolinium scaffold, developed as a tool compound to modulate NAD^+ metabolism, adipocyte bioenergetics, and lipogenesis in preclinical models. There are currently no human clinical trials, no approved indications, and its use in humans is strictly experimental. [1] [2] [3]

Identity and chemistry

- Chemical name: 5-amino-1-methylquinolinium iodide (often marketed simply as "5-Amino-1MQ"). [2]
- Class: Small-molecule nicotinamide N-methyltransferase (NNMT) inhibitor; cationic quinolinium salt. [1] [2]
- CAS: 42464-96-0. [2]
- Not a peptide: despite how clinics and vendors market it, it is a synthetic quinolinium compound, no amino acid sequence. [4] [2]

Preclinical work from Neelakantan et al. showed 5-amino-1MQ as a selective NNMT inhibitor with low micromolar IC_{50} (~1 μM) and high membrane permeability in Caco-2 assays. [1]

Mechanism of action (preclinical)

- NNMT function: NNMT methylates nicotinamide using SAM, forming 1-methylnicotinamide (1-MNA), effectively acting as a "drain" on the NAD^+ salvage pool and SAM. [3] [1]
- 5-amino-1MQ: competitive inhibitor that occupies the NNMT active site, reducing formation of 1-MNA. [3] [1]
- Downstream effects seen in vitro/in vivo:
  - Increased intracellular NAD^+ and SAM availability. [2] [1]
  - Upregulation of polyamine flux enzymes and altered histone methylation patterns in adipocytes. [2]
  - Reduced lipogenesis and adipocyte size, with shifts toward fat oxidation in preclinical adipocyte models. [5] [1]

In obese rodent models, NNMT inhibition with 5-amino-1MQ reduced fat mass and adipocyte size without lowering food intake, suggesting a metabolism-centric rather than appetite-centric mechanism. [3] [1]

Pharmacokinetics and bioavailability (animal data)

Current PK information is extrapolated from rodent data and expert commentary, not formal human studies:

- Oral bioavailability: ~38% reported in rodent PK work and discussed by Jackson.[3]
- Half-life: ~7 hours orally; ~4 hours IV, in rodent models.[3]
- Good passive and active transport across membranes, with minimal efflux in Caco-2 cells, consistent with "high permeability".[1]

These properties are why it is being explored as an orally active NNMT inhibitor, but translation to human PK/PD is unvalidated.

Preclinical effects relevant to longevity/metabolism

From rodent and cell studies plus mechanistic extrapolation:

- Adipose tissue:
  - Decreased adipocyte size and reduced lipogenesis.[1]
  - Reported ~5% body weight reduction in obese mice over ~2 weeks without caloric restriction.[3]
- NAD^+ / SAM / polyamine axis:
  - Preservation/increase of NAD^+ pool by limiting nicotinamide "drain".[1] [3]
  - Increased SAM with effects on polyamine pathway and acetyl-CoA utilization, reducing substrate for de novo lipogenesis.[2] [3]
- Potential metabolic outcomes (preclinical/marketing narrative):
  - Improved insulin sensitivity and muscle preservation signals in rodent models.[5] [3]
  - Shifts in mitochondrial energetics via NAD^+/SAM modulation, though direct mitochondrial data are still limited.[5] [2]

No human efficacy data exist; all claims about fat loss, mitochondrial function, or "anti-aging" are extrapolations from these rodent/cell findings and speculative marketing.[6] [5] [3]

Human use, dosing, and safety context

- Regulatory status:
  - Research chemical, not an approved drug; sold under "for research use only / not for human consumption" disclaimers.[7] [8] [2]
  - No FDA/EMA-approved NNMT inhibitors; no registered human trials on 5-amino-1MQ as of 2026.[3]
- Clinical data:
  - No controlled human safety, PK, or efficacy data published.[3]
- "Real-world" protocols:

- Online forums and some clinics report oral ranges of ~25–100 mg/day, split BID–TID, based on mechanistic extrapolation from half-life and rodent data. [4] [3]
- These are explicitly anecdotal, uncontrolled, and high-risk; Jackson and others emphasize unknown safety and long-term effects. [3]

Given the NNMT–NAD^+–SAM–polyamine–histone axis, off-target or long-term epigenetic/metabolic consequences in humans are completely under-characterized.

Key caveats for your context

Given your profile and interest in rigorous, mechanism-driven interventions:

- It is a reasonably well-characterized tool compound for NNMT inhibition in vitro/in vivo (rodent) with clear NAD^+/SAM/adipocyte biology. [2] [1]
- Human translation is speculative; there is no high-quality clinical, safety, or longevity data. Any body-composition or "anti-aging" protocol is essentially self-experimentation.
- The compound sits at a mechanistically important junction (NAD^+ salvage and methylation economy), so the risk of unintended systemic or epigenetic effects is non-trivial, especially under chronic exposure.

If you tell me what you're considering (e.g., combination with GLP-1s, NAD^+ boosters, exercise, or specific metabolic phenotypes), I can map out mechanistic interaction hypotheses, risk domains, and a preclinical literature grid you might want to interrogate before any experimental protocol design.

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stability in aqueous solution

For 5-amino-1MQ in aqueous solution, practical guidance from research-chemical vendors and handling guides suggests that reconstituted solutions are reasonably stable for *weeks* at refrigerator temperatures but should be treated as short-term preparations, not long-term stocks. Long-term stability is assigned only to the dry lyophilized/crystalline form at −20 °C; aqueous solutions are generally recommended to be used within 2–4 weeks when stored at 2–8 °C and protected from light. [10] [11] [12]

Solid vs solution stability

- **Lyophilized/crystalline solid:**
  - Stored dry at −20 °C in the dark, stability estimates up to 24–36 months depending on source. [12] [10]
  - Highly sensitive to moisture uptake; guidance uniformly stresses minimizing condensation and keeping vials sealed until use. [11] [12]
- **Aqueous/organic solutions:**
  - Handling guides recommend reconstitution in sterile saline or DMSO/water mixtures, with solubility ≈ 33 mg/mL in DMSO–water. [10]

- Once in solution, “optimal activity” is associated with storage at −80 °C (for lab stocks) and using freshly thawed aliquots. [10]
- Clinical-style peptide vendors (10 mg vials with BAC water) typically advise refrigeration at 2–8 °C and using within 2–4 weeks, avoiding freeze–thaw cycles. [11] [12]

Practical implications for aqueous storage

From the above:

- For **research-grade lab use**:
  - Prepare concentrated stock in DMSO or mixed solvent, aliquot, and store at −80 °C; treat as stable up to ~12 months, but discard at first sign of precipitation or discoloration. [10]
- For **BAC water / saline reconstitution for short-term use**:
  - Store at 2–8 °C, protected from light, and plan to exhaust the vial within 2–4 weeks. [12] [11]
  - Avoid repeated warming/cooling cycles and agitation that might accelerate degradation.

There is, so far, no publicly available formal ICH-style stability data (forced degradation, LC–MS purity follow-up) in aqueous media; all timelines above are empiric/vendor-derived rather than rigorously validated. If you are considering constructing your own stability profile (e.g., multi-timepoint HPLC/LC–MS under various pH/temperature/light conditions), I can outline a protocol grid for that in detail.

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“Increased SAM” what is this

“Increased SAM” refers to increased levels of **S-adenosylmethionine (SAM)** inside cells or tissues — i.e., a higher SAM pool and usually a higher SAM/SAH ratio, which directly affects methylation, polyamine synthesis, and sulfur amino acid metabolism. [19] [20] [21]

What SAM is

- SAM (S-adenosylmethionine, AdoMet) is a sulfonium-containing metabolite formed from methionine and ATP. [20] [22]
- It is the primary **methyl donor** for DNA, RNA, protein, phospholipid, and small-molecule methyltransferase reactions, and also a precursor for polyamines and glutathione via transsulfuration. [23] [24] [20]
- After donating its methyl group, SAM becomes S-adenosylhomocysteine (SAH), which then feeds back to regulate methylation. [21] [20]

What “increased SAM” implies biologically

When SAM levels rise (or SAM/SAH ratio increases), several things happen:

- **Methylation capacity changes**
  - Higher SAM/SAH ratio is often interpreted as greater “methylation potential,” meaning more methyl groups are available for DNA, histone, and protein methylation. [25] [19] [21]
  - This can lead to **hyper-methylation** of methyltransferase substrates if sustained, altering gene expression, chromatin state, and signaling. [26] [19]
- **Growth and biosynthetic signaling**
  - Elevated SAM can activate growth pathways (e.g., via SAMTOR–mTORC1) and drive flux into polyamine synthesis, using SAM as an aminopropyl donor. [24] [19] [20]
  - Cells often interpret high SAM as a cue to grow/divide and synthesize “building blocks” (polyamines, etc.), thereby consuming SAM. [19]
- **Methionine / sulfur amino acid metabolism**
  - SAM sits at the hub of transmethylation, transsulfuration (toward cysteine and glutathione), and polyamine synthesis. [22] [20] [24]
  - Changing SAM levels can therefore shift redox balance, homocysteine handling, and glutathione production.

Why “more SAM” is not always “better”

Exogenous SAM or excessive intracellular SAM can have **non-linear and sometimes adverse** effects:

- Excess SAM may be catabolized into methylthioadenosine and adenine, which can inhibit methylation and disrupt circadian rhythms despite the high SAM load. [26]
- The methyl cycle is sensitive; perturbing SAM far above its homeostatic range can dysregulate methyltransferases, gene expression, and cellular stress responses. [24] [19] [26]

In the 5-amino-1MQ context: inhibition of NNMT is hypothesized to conserve both NAD^+ and SAM, increasing the SAM pool and shifting flux into polyamine synthesis and altered histone methylation in adipocytes — i.e., “increased SAM” as a mechanistic lever on methylation and metabolic programming, rather than just a benign “more cofactor” state. If you want, I can sketch a pathway diagram specifically for NNMT inhibition → SAM/NAD^+ → polyamine/histone methylation in adipocytes. [20] [19] [24]

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Yes, please sketch that pathway diagram for me

Here’s a text “sketch” of the NNMT–SAM–NAD^+–polyamine–histone axis in adipocytes, based on Kraus et al. 2014 and subsequent NNMT reviews. [33] [34] [35] [36]

Core reaction (NNMT)

1. **NNMT enzymatic step**
    - Substrates:
        - Nicotinamide (NAM)
        - S-adenosylmethionine (SAM)
    - Products:
        - 1-methylnicotinamide (1-MNAM)
        - S-adenosylhomocysteine (SAH) [35] [36] [33]
2. **Immediate consequences**
    - **Consumes NAM** → less NAM available for the NAD^+ salvage pathway.
    - **Consumes SAM, produces SAH** → depletes methyl donors and increases a methyltransferase inhibitor. [34] [36] [33] [35]

So, **high NNMT activity** drives:

> ↓ NAM → ↓ NAD^+
> ↓ SAM & ↑ SAH → ↓ methylation potential

When you inhibit NNMT (e.g., 5-amino-1MQ context)

NNMT inhibition or knockdown in white adipose tissue (WAT): [36] [37] [34] [35]

1. **Metabolite shifts**
    - NAM is no longer methylated → **NAM accumulates**.
    - More NAM feeds **NAD^+ salvage** → ↑ **NAD^+ levels** in adipocytes. [34] [35]
    - SAM is no longer drained into MNAM → ↑ **SAM pool**, ↓ **SAH**, thus ↑ **SAM/SAH ratio** (higher methylation potential). [35] [34]
2. **Epigenetic / transcriptional effects**
    - Higher SAM/SAH ratio + less SAM consumption by NNMT → more SAM available to **histone methyltransferases**.
    - In adipose tissue specifically, NNMT inhibition has been shown to **increase histone H3K4 methylation (H3K4me)** on promoters of polyamine-flux genes (Odc, Sat1, etc.). [37] [33] [34]
    - H3K4me enrichment → **transcriptional activation** of these genes.
3. **Polyamine flux activation**
    - Upregulated enzymes:
        - Ornithine decarboxylase (ODC) – polyamine synthesis.
        - Spermidine–spermine N^1-acetyltransferase (SSAT, Sat1) – polyamine catabolism/acetylation.
        - Polyamine oxidase (PAO). [37] [34] [35]

- Net effect: **increased polyamine flux** (synthesis, acetylation, oxidation, excretion).
- Evidence: elevated diacetylspermine in urine/adipocyte secretome; increased oxygen consumption dependent on ODC/SSAT/PAO. [34] [37]

4. **Energy expenditure and adipocyte phenotype**
   - Polyamine acetylation consumes **acetyl-CoA** and drives energy use; enhanced flux increases **O_2 consumption and energy expenditure** in adipocytes. [35] [34]
   - Result: reduced adipocyte size, decreased adiposity, improved insulin sensitivity in diet-induced obesity models. [34] [35]

So, the **diagram in words**:

> NNMT active
> NAM + SAM → 1-MNAM + SAH
> ↓ NAM → ↓ NAD^+
> ↓ SAM, ↑ SAH → ↓ SAM/SAH → ↓ histone methylation (H3K4me) on polyamine-flux genes → ↓ ODC/SSAT/PAO → ↓ polyamine flux → ↓ energy expenditure → ↑ adiposity, insulin resistance. [33] [36] [35] [34]

> NNMT inhibited (e.g., by 5-amino-1MQ, or NNMT knockdown)
> NAM preserved → ↑ NAD^+ → ↑ SIRT1 signaling, improved redox/energy metabolism in adipocytes. [35] [34]
> SAM preserved, SAH reduced → ↑ SAM/SAH → ↑ histone H3K4 methylation → ↑ transcription of Odc, Sat1, etc. → ↑ polyamine flux → ↑ oxygen consumption and energy expenditure → ↓ adipocyte size, ↓ fat mass, improved insulin sensitivity in obese mice. [36] [37] [34] [35]

If you'd like, I can convert this into a compact, stepwise "pathway block" you can drop directly into a figure or schematic (e.g., for a slide or manuscript), or tailor it specifically to how 5-amino-1MQ might interact with other interventions you're considering (NAD^+ boosters, GLP-1s, etc.).

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NNMT expression levels in different adipose tissue depots

NNMT is highly expressed in adipose tissue overall, but its levels differ markedly by depot, species, metabolic state, and browning status. In general, **visceral/white depots show higher NNMT and stronger obesity-linked upregulation than classical brown or beige depots**, and NNMT tends to be *anti-browning* in subcutaneous fat. [41] [42] [43] [44]

Broad tissue and depot overview

- **Species differences**
  - In **humans**, NNMT expression is highest in liver, then adipose tissue, with lower levels in skeletal muscle and other organs. [43]
  - In **mice**, adipose NNMT expression exceeds hepatic levels by at least an order of magnitude (~10-fold higher in WAT vs liver). [45] [43]
- **Within adipose tissue**
  - NNMT is robustly expressed in **white adipose tissue (WAT)** and **visceral depots**, and is lower in classical brown fat and some beige depots under basal conditions. [42] [41] [43]
  - Adipose NNMT is dynamic and context-dependent (obesity, cold, β-adrenergic agonists, weight loss). [44] [41] [42] [43]

Mouse depot-specific patterns (preclinical)

Key depots studied: interscapular brown adipose tissue (iBAT), inguinal subcutaneous WAT (sWAT), and epididymal WAT (eWAT; visceral). [41] [45]

- **Baseline and obesity/insulin-resistance states**
  - Nnmt is one of the strongest genes reciprocally regulated in WAT when comparing adipose-specific GLUT4 knockout vs overexpressors; expression increases in insulin-resistant WAT and decreases in insulin-sensitive WAT. [45]
  - NNMT protein is increased 1.5–2-fold in WAT of ob/ob, db/db, and high-fat diet (HFD) mice compared with lean controls; liver NNMT also increases, whereas BAT changes are much smaller. [45]
  - Adipose Nnmt expression is high in obesity-prone mouse strains and low in obesity-resistant strains. [43] [45]
- **Cold exposure / beige remodeling** (Jia et al. 2022):
  - Interscapular BAT (iBAT), inguinal sWAT, and eWAT were examined under cold and β3-agonist (CL316,243) treatment. [41]
  - NNMT is **induced in WAT (especially sWAT and eWAT) during the "cold remodeling" phase**, but its expression correlates **negatively** with browning markers UCP1 and PGC-1α at the protein level. [41]
  - β3-agonist (CL316,243) decreases Nnmt expression in WAT (white adipocytes) but not significantly in BAT. [41]

Interpretation:

- White/visceral depots (eWAT, sWAT) show strong, dynamic NNMT regulation and a **negative association with browning**.
- BAT generally maintains lower Nnmt and is less responsive to obesogenic upregulation compared with WAT. [45] [41]

Human depot-specific patterns and obesity

- **Visceral vs subcutaneous**
  - NNMT is upregulated in WAT in obesity/diabetes models and specifically in the **visceral adipose tissue of morbidly obese patients.** [42]
  - Human adipose NNMT expression is positively correlated with **obesity and insulin resistance**, and antisense or genetic suppression reduces body weight, fat mass, and improves insulin sensitivity in models. [44]
- **Variability and depot methylome**
  - There is high inter-subject variability in human adipose NNMT expression, comparable to the ~20-fold inter-strain variation seen in mouse WAT. [43]
  - An epigenetic study in human adipose tissue found **577 differentially methylated CpG sites** associated with NNMT expression; lower methylation globally paralleled higher NNMT, linking adipose NNMT levels to a distinct depot-specific methylation signature. [46]
- **Weight loss / metabolic interventions**
  - During weight reduction, human adipose NNMT expression tends to increase, but plasma MNAM can paradoxically decrease, indicating that circulating 1-MNAM is not a simple linear readout of adipose NNMT activity and that other tissues/clearance mechanisms contribute. [43]

Functional interpretation by depot

Putting this together for your purposes:

- **Visceral WAT (e.g., omental/mesenteric in humans, eWAT in mice)**
  - High basal NNMT in obesity/metabolic syndrome, with further upregulation in insulin-resistant states. [42] [44] [45]
  - Functionally associated with **enhanced fat storage, reduced energy expenditure, and insulin resistance**; NNMT knockdown in WAT improves these parameters. [42] [45]
- **Subcutaneous WAT (sWAT, gluteofemoral/abdominal)**
  - Moderate NNMT at baseline, inducible by cold remodeling but **negatively correlated with browning markers.** [41]
  - Suggests NNMT acts as a **brake on beige adipogenesis** and thermogenic programming in subcutaneous depots; lowering NNMT promotes a more oxidative/beige phenotype. [42] [41]
- **Brown adipose tissue (BAT)**
  - Generally lower Nnmt expression than WAT and less responsive to obesogenic upregulation. [45] [41]
  - Cold or β3-agonist responses in BAT involve NAD^+ pathway remodeling with relatively less dependence on NNMT compared with WAT. [41]

Implications for targeting with NNMT inhibitors (e.g., 5-amino-1MQ)

Mechanistically, targeting NNMT is likely to:

- Have **strongest metabolic impact in visceral and insulin-resistant WAT**, where NNMT is highest and most obesity-linked.
- Favor **browning / beiging** in subcutaneous depots by removing an NNMT-linked brake on UCP1/PGC-1α expression.[41]
- Have comparatively **less direct effect on classical BAT**, though systemic NAD^+/SAM shifts and endocrine/adipokine changes will still feed back.

If you want to go one level deeper, I can sketch a depot-specific table mapping NNMT level → NAD^+/SAM changes → histone marks → polyamine flux → expected phenotype for: visceral WAT, subQ WAT, and BAT under (a) obesity, (b) cold/β3-agonist, and (c) NNMT inhibition.

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