

RESEARCH MONOGRAPH . COMPOUND PROFILE

78c

A potent, specific, reversible, and uncompetitive small-molecule inhibitor of the NAD⁺ glycohydrolase CD38, developed from a thiazoloquinolin(on)e medicinal chemistry series and distinguished by low-nanomolar potency, oral bioavailability, and demonstrated reversal of age-related tissue NAD⁺ decline with extension of lifespan and healthspan in murine aging models.

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ABSTRACT

Compound 78c (CD38-IN-78c; CAS 1700637-55-3) is a thiazoloquinolin(on)e small molecule identified as the lead compound from a structure-activity exploration of CD38 inhibitors reported by Haffner, Bhatt, and colleagues in 2015. It is a potent, specific, reversible, and uncompetitive inhibitor of the ectoenzyme CD38 (cluster of differentiation 38), a type II transmembrane glycoprotein with NAD⁺ glycohydrolase, ADP-ribosyl cyclase, and cyclic ADP-ribose hydrolase activities, with half-maximal inhibitory concentration (IC₅₀) values of 7.3 nM against human CD38 and 1.9 nM against murine CD38, and an inhibition constant (K_i) of 8.4 nM. The compound is cell-permeable, orally bioavailable in rodent species, and non-toxic at pharmacologically active doses in chronic administration studies extending to 20 months. CD38 has been identified as the principal enzyme responsible for age-related tissue NAD⁺ decline, a process that contributes to mitochondrial dysfunction, impaired sirtuin signaling, metabolic derangement, and the progressive physiological deterioration characteristic of aging. By inhibiting CD38-mediated degradation of NAD⁺ and its biosynthetic precursors nicotinamide mononucleotide (NMN) and nicotinamide riboside (NR), compound 78c elevates tissue NAD⁺ levels (greater than 5-fold in liver and greater than 1.2-fold in skeletal muscle in diet-induced obese mice at a 2-hour time point) and thereby restores the activity of NAD⁺-dependent enzymes including sirtuins 1, 3, and 6 and poly(ADP-ribose) polymerases.

The landmark 2018 publication by Tarrago, Chini, and colleagues in *Cell Metabolism* demonstrated that chronic oral administration

of 78c to naturally aged mice and to Cockayne syndrome progeroid mice reverses age-related NAD⁺ decline and improves glucose tolerance, exercise capacity, muscle function, and cardiac function. A follow-up 2022 study by Peclat and colleagues in *Aging Cell* extended these findings to chronological aging, reporting that 78c increases median lifespan by approximately 10 percent, extends maximal lifespan, and improves multiple healthspan parameters including treadmill endurance, grip strength, body composition, and metabolic markers in naturally aged C57BL/6 mice, with sex-dependent differences in the magnitude of benefit. Additional preclinical studies have demonstrated cardioprotection against ischemia-reperfusion injury through preservation of tetrahydrobiopterin (BH₄) and endothelial nitric oxide synthase coupling; anti-inflammatory activity through suppression of NF-kappaB-dependent cytokine expression (IL-1beta, IL-6, TNF-alpha) in macrophages and microglia; therapeutic efficacy in collagen-induced arthritis through restoration of regulatory T cell populations and immune balance; and attenuation of osteoclastogenesis and inflammatory bone resorption. The compound does not cross the blood-brain barrier at appreciable concentrations but exerts systemic anti-inflammatory and metabolic effects relevant to age-related neurodegeneration through peripheral NAD⁺ homeostasis.

Compound 78c has not entered human clinical trials. It is supplied by multiple research chemical vendors at greater than 98 percent purity as a research tool compound. The current research state is one of strong and replicable preclinical efficacy across aging, cardiovascular, inflammatory, and metabolic disease models, with absent clinical pharmacokinetic and safety data in humans. This monograph reviews the chemistry, synthesis, and structure-activity relationships of 78c; the molecular pharmacology of CD38

inhibition and NAD⁺ metabolism; the preclinical pharmacokinetic profile; the preclinical efficacy data across aging, cardiovascular, inflammatory, and metabolic disease models; sourcing and quality considerations; reconstitution and handling; stack-interaction considerations with NAD⁺ precursors and other metabolic agents; adverse-event and safety signal from chronic animal dosing; and a comparative assessment of five alternative CD38-targeting or NAD⁺-elevating compounds (MK-0159, apigenin, luteolin, quercetin, and daratumumab) against 78c on five competency standards (novelty, effect size, promising potential, side-effect profile, and overall validation).

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

Common name: Compound 78c; CD38 inhibitor 78c.

Alternative designations: CD38-IN-78c, CD38 inhibitor 1, MDK-7553, Axon 3570, Tocris 6391.

Chemical Abstracts Service registry number: 1700637-55-3.

International Union of Pure and Applied Chemistry name: 4-[[trans-4-(2-methoxyethoxy)cyclohexyl]amino]-1-methyl-6-(1,3-thiazol-5-yl)quinolin-2(1H)-one.

Development origin: Compound 78c was identified as the lead compound from a series of thiazoloquin(az)olin(on)es synthesized and evaluated as CD38 inhibitors by Haffner, Bhatt, Gribble, and colleagues at the Reagent Research Group, published in the Journal of Medicinal Chemistry in 2015 [1]. The compound number "78c" derives from its position in the synthetic series described in that publication.

1.2 Structural class and chemistry

Compound 78c is a substituted 2-quinolinone bearing a thiazol-5-yl group at the 6-position, a methylamino group at the 1-position, and a trans-4-(2-methoxyethoxy)cyclohexyl amino substituent at the 4-position. The structural class is thiazoloquin(az)olin(on)e, a designation reflecting the thiazole-quinolinone pharmacophore that constitutes the core binding element for the CD38 active site.

Molecular formula: C₂₂H₂₇N₃O₃S.

Molecular weight: 413.53 g/mol.

Physical properties: The compound is supplied as a white to off-white solid. It is soluble in dimethyl sulfoxide (DMSO) at concentrations up to 100 mM, sparingly soluble in ethanol and methanol, and poorly soluble in water at neutral pH. LogP is approximately 2.8 to 3.2 (calculated), consistent with moderate lipophilicity and oral bioavailability in rodent species.

Stereochemistry: The cyclohexyl ring substituent is present as the trans isomer. No additional chiral centers are present in the molecule.

1.3 Synthesis

The published synthesis of 78c proceeds through a convergent route involving construction of the 2-quinolinone core, introduction of the thiazole at the 6-position via palladium-catalyzed cross-coupling (Suzuki or Stille coupling with a thiazol-5-yl-boronic acid or stannane), N-methylation at the 1-position, and installation of the trans-4-(2-methoxyethoxy)cyclohexylamino group at the 4-position by nucleophilic aromatic substitution or Buchwald-Hartwig amination [1]. The trans-4-(2-methoxyethoxy)cyclohexylamine side chain is prepared separately from trans-4-aminocyclohexanol by O-alkylation with 2-bromoethyl methyl ether or by reductive amination approaches. The final compound is purified by column chromatography or preparative high-performance liquid chromatography and characterized by nuclear magnetic resonance spectroscopy, high-resolution mass spectrometry, and analytical HPLC. Yields for the final coupling step are typically 50 to 70 percent. The compound is manufactured at gram scale by multiple research chemical suppliers (Tocris, Sigma-Aldrich, Cayman Chemical, MedChemExpress, Selleckchem, Axon Medchem) at greater than 98 percent purity.

2. Abstract

Compound 78c is the most potent and best-characterized small-molecule inhibitor of the NAD⁺ glycohydrolase CD38 reported in the literature. CD38, a type II transmembrane glycoprotein expressed on the surface of immune cells, hepatocytes, endothelial cells, and multiple other cell types, catalyzes the hydrolysis of NAD⁺ to nicotinamide and ADP-ribose, the cyclization of NAD⁺ to cyclic ADP-ribose (cADPR), and the hydrolysis of cADPR to ADP-ribose. These enzymatic activities, collectively designated as NADase activity, position CD38 as the principal consumer of cellular and extracellular NAD⁺ in mammalian tissues. CD38 expression and activity increase with age, driven by the accumulation of CD38-positive inflammatory cells (macrophages, T cells, and other immune populations) in metabolic tissues including white adipose tissue, liver, and skeletal muscle [2, 3]. This age-related increase in CD38 activity is the dominant driver of the well-documented decline in tissue NAD⁺ levels during aging, a decline that impairs sirtuin-dependent deacetylation, poly(ADP-ribose) polymerase-dependent DNA repair, and mitochondrial electron transport chain function [4, 5].

Compound 78c inhibits CD38 with IC₅₀ values of 7.3 nM (human) and 1.9 nM (murine) and a K_i of 8.4 nM, making it approximately 1000-fold more potent than the best-characterized natural flavonoid CD38 inhibitors (apigenin, luteolin, quercetin, IC₅₀ values in the low micromolar range) and the most potent CD38 inhibitor reported prior to the development of MK-0159 by Merck [1, 6]. The inhibition is reversible and uncompetitive, decreasing both the apparent V_{max} and K_m of CD38 for NAD⁺, a kinetic mechanism that confers target specificity and avoids competition with the physiological substrate [7].

The compound was validated in vivo by the Chini laboratory at Mayo Clinic in the landmark 2018 Cell Metabolism publication, which demonstrated that chronic oral administration of 78c to naturally aged mice (beginning at 16 months of age, continuing to approximately 24 months) reversed tissue NAD⁺ decline, improved glucose tolerance, increased exercise capacity, improved cardiac function, and enhanced muscle strength [7]. A subsequent 2022 Aging Cell publication from the same laboratory extended these findings to chronological lifespan, reporting that 78c increases median survival by approximately 10 percent and maximal lifespan by a comparable margin in naturally aged C57BL/6 mice, with concurrent improve-

ments in treadmill endurance, grip strength, and metabolic biomarkers [8]. Additional preclinical applications have been demonstrated in cardiac ischemia-reperfusion injury [9], rheumatoid arthritis [10], inflammatory bone loss [11], and neuroinflammation [12].

Compound 78c has not entered human clinical trials. It is a research tool compound with no established human pharmacokinetic, tolerability, or efficacy data. The current research positioning is as the benchmark small-molecule CD38 inhibitor for preclinical aging, metabolic, and inflammatory disease research, and as a pharmacological probe for the role of CD38 in NAD⁺ metabolism.

3. Discovery and Development History

3.1 Origin

The development of 78c originated from a medicinal chemistry program aimed at identifying potent and specific small-molecule inhibitors of the ectoenzyme CD38. Prior to 2015, the available CD38 inhibitors were limited to natural flavonoids (apigenin, quercetin, luteolin, kuromanin) with low micromolar potency and poor selectivity, and to the non-specific nicotinamide analogue nicotinamide itself, which inhibits CD38 at millimolar concentrations but also inhibits sirtuins and other NAD⁺-dependent enzymes. The absence of a potent, selective, and orally bioavailable CD38 inhibitor limited the ability to test the hypothesis that CD38 inhibition could reverse age-related NAD⁺ decline in vivo.

Haffner, Bhatt, Gribble, and colleagues addressed this gap by synthesizing and evaluating a series of thiazoloquin(az)olin(on)es as CD38 inhibitors [1]. The series was designed on the basis of a high-throughput screen hit and iterative medicinal chemistry optimization of potency, selectivity, oral bioavailability, and metabolic stability. Compound 78c emerged as the lead compound from this series on the basis of its combination of low-nanomolar potency (IC₅₀ 1.9 nM against murine CD38, 7.3 nM against human CD38), favorable oral pharmacokinetic properties in mice, and demonstration of in vivo NAD⁺ elevation in diet-induced obese (DIO) C57BL/6 mice (greater than 5-fold NAD⁺ elevation in liver and greater than 1.2-fold in skeletal muscle at 2 hours post-dose) [1].

3.2 Validation as an aging intervention

The critical validation of 78c as a pharmacological aging intervention was published in 2018 by Tarrago, Chini, and colleagues from the Chini laboratory at Mayo Clinic, in collaboration with multiple institutions [7]. This study, published in *Cell Metabolism*, represents the most comprehensive in vivo characterization of a CD38 inhibitor in aging models. The investigators administered 78c chronically via diet (compounded into standard mouse chow) to naturally aged C57BL/6 mice beginning at 16 to 18 months of age and to Cockayne syndrome group B (CSB) progeroid mice. The study demonstrated that 78c reversed age-related tissue NAD⁺ decline;

improved glucose tolerance; increased exercise capacity (treadmill endurance testing); improved cardiac function (echocardiographic parameters); and enhanced skeletal muscle function. The physiological effects were dependent on tissue NAD⁺ levels, as co-administration of FK866 (an inhibitor of nicotinamide phosphoribosyl-transferase, the rate-limiting enzyme in the NAD⁺ salvage pathway) abolished the benefits of 78c, confirming that the mechanism of action is NAD⁺ elevation through CD38 inhibition rather than an off-target effect.

3.3 Extension to lifespan and healthspan

The Peclat et al. (2022) study in *Aging Cell* extended the Tarrago et al. (2018) findings to the gold-standard aging endpoint of chronological lifespan [8]. Naturally aged C57BL/6 mice were administered 78c via diet beginning at 18 months of age and followed to natural death. The compound increased median lifespan by approximately 10 percent and extended maximal lifespan. Healthspan improvements included enhanced treadmill endurance, improved grip strength, favorable body composition changes (reduction in fat mass, preservation of lean mass), and improved metabolic markers. The effects were sex-dependent, with male mice showing more pronounced lifespan extension and female mice showing more pronounced metabolic improvements.

3.4 Expansion to disease models

Following the aging validation, multiple independent laboratories have characterized 78c in disease-specific models. Boslett et al. (2019) demonstrated cardioprotection against ischemia-reperfusion injury in isolated mouse hearts [9]. Zhang et al. (2023) demonstrated therapeutic efficacy in collagen-induced arthritis and in fibroblast-like synoviocytes from rheumatoid arthritis patients [10]. Kim et al. (2024) characterized anti-inflammatory and anti-osteoclastogenic activity in murine bone marrow-derived macrophages [11]. Roboon et al. (2021) demonstrated suppression of lipopolysaccharide-induced neuroinflammation in primary astrocytes and microglia [12]. These studies collectively position 78c as a multi-indication preclinical tool compound with consistent efficacy across aging, cardiovascular, autoimmune, and neuroinflammatory disease models.

3.5 Current development status

Compound 78c has not entered human clinical development. It remains a research tool compound without an Investigational New Drug (IND) application or equivalent regulatory filing. The Chini laboratory at Mayo Clinic continues to use 78c as the reference CD38 inhibitor in aging and metabolic disease research. The pharmaceutical development of CD38 inhibitors for aging-related indications has been advanced by Merck with MK-0159, an orally bioavailable CD38 inhibitor with improved pharmacokinetic properties that has been characterized in ischemia-reperfusion models [6]. The transition from 78c to clinical-grade CD38 inhibitors represents an active area of translational research.

4. Mechanism of Action

Compound 78c exerts its pharmacological effects through potent and specific inhibition of the ectoenzyme CD38. The mechanism of action is understood at the molecular, cellular, tissue, and organismal levels.

4.1 CD38 enzymology and NAD⁺ metabolism

CD38 (cluster of differentiation 38) is a 45-kDa type II transmembrane glycoprotein with dual orientation on the cell surface (the catalytic domain can face the extracellular space or the cytoplasm depending on the cellular context). CD38 possesses three enzymatic activities: (1) NAD⁺ glycohydrolase activity, cleaving NAD⁺ to nicotinamide and ADP-ribose; (2) ADP-ribosyl cyclase activity, converting NAD⁺ to cyclic ADP-ribose (cADPR), a calcium-mobilizing second messenger; and (3) cADPR hydrolase activity, converting cADPR to ADP-ribose [13, 14]. Of these, the NAD⁺ glycohydrolase activity is quantitatively dominant, consuming approximately 100 molecules of NAD⁺ for every 1 molecule of cADPR produced.

Because CD38 is predominantly an ectoenzyme (active site facing the extracellular space), it degrades not only extracellular NAD⁺ but also the NAD⁺ biosynthetic precursors nicotinamide mononucleotide (NMN) and nicotinamide riboside (NR) before they can be transported into cells and converted to intracellular NAD⁺ [3, 15]. This ecto-enzymatic activity positions CD38 as a gatekeeper of organismal NAD⁺ homeostasis: by degrading both NAD⁺ and its precursors in the extracellular space, CD38 limits the substrate available for intracellular NAD⁺ biosynthesis.

4.2 CD38 in aging

CD38 expression and enzymatic activity increase progressively with age in multiple tissues, including white adipose tissue, liver, skeletal muscle, and spleen [2, 3]. The increase is driven by the accumulation of CD38-positive inflammatory cells (resident and infiltrating macrophages, T cells, and other immune populations) in metabolic tissues, a process linked to the chronic low-grade inflammation characteristic of aging (often termed "inflammaging") [3, 16]. Senescent cells, which accumulate with age, secrete pro-inflammatory cytokines and chemokines (the senescence-as-

sociated secretory phenotype, or SASP) that upregulate CD38 expression on neighboring immune and parenchymal cells, creating a feedforward loop between senescence, inflammation, and NAD⁺ decline [17].

The Chini laboratory has established through genetic and pharmacological studies that CD38 is the dominant NADase responsible for age-related tissue NAD⁺ decline. CD38 knockout mice are protected from age-related NAD⁺ decline and from many features of metabolic aging [4, 5]. The pharmacological recapitulation of this genetic protection by 78c in wild-type aged mice is the core translational finding of the Tarrago et al. (2018) study [7].

4.3 Inhibition kinetics of 78c

Compound 78c inhibits CD38 NADase activity with an uncompetitive mechanism. Uncompetitive inhibition is characterized by binding of the inhibitor exclusively to the enzyme-substrate complex (rather than to the free enzyme), reducing both the apparent V_{max} and the apparent K_m. This kinetic mechanism confers favorable pharmacological properties: uncompetitive inhibitors become more potent as substrate concentration increases (in contrast to competitive inhibitors, which become less effective at high substrate concentrations), and the mechanism is inherently specific because binding requires the formation of the enzyme-substrate complex [1, 7].

The IC₅₀ values (1.9 nM murine, 7.3 nM human) and the K_i of 8.4 nM place 78c among the most potent small-molecule inhibitors of any NAD⁺-metabolizing enzyme described in the literature. The inhibition is fully reversible, as demonstrated by dialysis experiments in which CD38 enzymatic activity returns to baseline following removal of 78c [1].

4.4 Downstream consequences of CD38 inhibition

Elevation of tissue NAD⁺ by CD38 inhibition restores the activity of multiple NAD⁺-dependent enzyme families:

Sirtuins. The sirtuins (SIRT1 through SIRT7) are NAD⁺-dependent protein deacetylases and ADP-ribosyltransferases that regulate metabolism, stress resistance, inflammation, and gene expression. SIRT1 deacetylates PGC-1α, FOXO transcription factors, p53, and NF-κB; SIRT3 deacetylates mitochondrial enzymes involved in fatty acid oxidation and the electron transport chain; SIRT6 deacetylates

histone H3 lysine 9 and lysine 56 and regulates DNA repair and glucose metabolism [18]. All sirtuins require NAD⁺ as a co-substrate, and their activity declines in parallel with tissue NAD⁺ during aging. Restoration of NAD⁺ by 78c restores sirtuin activity, improving mitochondrial function, reducing inflammation, and enhancing metabolic homeostasis.

Poly(ADP-ribose) polymerases (PARPs). PARP1 and PARP2 consume NAD⁺ during DNA repair. NAD⁺ depletion impairs PARP-dependent DNA damage repair, contributing to genomic instability during aging. Restoration of NAD⁺ by 78c supports PARP activity and genomic maintenance.

CD38 itself. CD38 uses NAD⁺ as substrate; NAD⁺ elevation paradoxically provides more substrate for CD38, but the pharmacological inhibition by 78c prevents this substrate from being consumed, creating a net positive NAD⁺ balance.

4.5 Tissue-specific effects

The tissue-specific effects of 78c reflect the tissue distribution of CD38 and the local NAD⁺ metabolic demand. Liver shows the most dramatic NAD⁺ elevation (greater than 5-fold in DIO mice), consistent with high hepatic CD38 expression and high hepatic NAD⁺ turnover. Skeletal muscle shows more modest NAD⁺ elevation (greater than 1.2-fold), consistent with lower CD38 expression in muscle relative to liver but with high metabolic demand for NAD⁺ in mitochondrial oxidative phosphorylation [1, 7]. Cardiac tissue shows intermediate NAD⁺ elevation and functional improvement, particularly under ischemia-reperfusion stress where CD38-mediated NAD⁺ consumption is acutely upregulated [9].

5. Pharmacokinetics and Routes of Administration

5.1 Absorption and oral bioavailability

Compound 78c is orally bioavailable in mice. The compound has been administered chronically via admixture in standard rodent chow, a route that provides continuous oral exposure and avoids the stress of daily gavage [7, 8]. When administered at a dietary concentration calculated to deliver approximately 30 mg/kg/day in mice, 78c produces sustained elevation of tissue NAD⁺ levels, indicating adequate oral absorption and systemic exposure [8].

Formal oral bioavailability (as a percentage of intravenous exposure) has not been reported in published pharmacokinetic studies. The consistent *in vivo* efficacy following dietary administration and the tissue NAD⁺ elevation data support adequate, though incompletely characterized, oral bioavailability.

5.2 Distribution

Compound 78c distributes to metabolically active tissues including liver, skeletal muscle, white adipose tissue, and heart, as inferred from tissue NAD⁺ elevation studies and from the tissue-specific pharmacological effects. The compound does not cross the blood-brain barrier at appreciable concentrations, as indicated by the absence of central nervous system NAD⁺ elevation in published studies and by the report that 78c does not achieve brain concentrations sufficient for direct neuroprotection [12]. The moderate lipophilicity (calculated LogP 2.8 to 3.2) is consistent with the observed tissue distribution to peripheral organs.

5.3 Metabolism

The metabolic disposition of 78c has not been fully characterized in published studies. The thiazoloquinolinone scaffold is expected to undergo hepatic cytochrome P450-mediated oxidation, with potential metabolic liabilities at the thiazole ring (oxidative ring opening), the methyl group on the quinolinone nitrogen (N-demethylation), and the methoxyethoxy side chain (O-demethylation). Specific CYP

isoform contributions have not been reported. The sustained pharmacological activity following chronic dietary administration suggests adequate metabolic stability for chronic dosing in mice [7, 8].

5.4 Elimination

Elimination pathways for 78c have not been formally characterized. Given the molecular weight (413.53) and the moderate lipophilicity, a combination of hepatic metabolism and biliary excretion is expected, with renal elimination of polar metabolites.

5.5 Routes of administration

Dietary admixture (chronic oral). The principal route for aging and metabolic disease studies. Compound 78c is compounded into standard mouse chow at a concentration calculated to deliver the target dose based on estimated daily food consumption (typically 3 to 5 g/day for an adult mouse). This route provides continuous exposure and is the method used in the Tarrago et al. (2018) and Peclat et al. (2022) chronic studies [7, 8].

Intraperitoneal injection. Used in acute pharmacokinetic studies and in some disease-model studies (arthritis, inflammation) at doses of 10 to 30 mg/kg [10, 11].

Ex vivo perfusion. Used in isolated heart ischemia-reperfusion studies at micromolar concentrations in perfusion buffer [9].

In vitro. Cell culture studies typically use 78c at concentrations of 1 to 50 micromolar in complete cell culture medium with DMSO as vehicle (final DMSO concentration 0.1 percent or less) [11, 12].

5.6 Special populations

No human pharmacokinetic data are available. No pediatric, geriatric, renal impairment, or hepatic impairment pharmacokinetic data exist. The compound is a preclinical research tool and has not been characterized for human pharmacokinetic optimization.

6. Preclinical Pharmacology

6.1 Aging and metabolic dysfunction

The Tarrago et al. (2018) Cell Metabolism study is the seminal preclinical pharmacology demonstration for 78c [7]. The study enrolled three cohorts: (1) naturally aged C57BL/6 mice (16 to 18 months at enrollment, approximately equivalent to 55 to 60 human years), treated with 78c via dietary admixture for approximately 6 to 8 months; (2) young adult C57BL/6 mice as age controls; and (3) Cockayne syndrome group B (CSB) progeroid mice, which exhibit accelerated aging with tissue NAD⁺ decline, treated with 78c from young adulthood.

In naturally aged mice, 78c reversed the age-related decline in tissue NAD⁺ levels, restoring NAD⁺ to levels approaching those of young animals. This NAD⁺ restoration was accompanied by improvements in glucose tolerance (oral glucose tolerance test), exercise capacity (treadmill endurance), cardiac function (echocardiographic fractional shortening and ejection fraction), and skeletal muscle function. The physiological effects were abolished by co-administration of FK866, an inhibitor of nicotinamide phosphoribosyltransferase (NAMPT, the rate-limiting enzyme of the NAD⁺ salvage pathway), demonstrating that the mechanism of benefit is through NAD⁺ elevation rather than through direct target modulation by 78c [7].

In CSB progeroid mice, 78c improved survival and reversed several features of the accelerated aging phenotype, providing evidence that the compound addresses a fundamental aging mechanism rather than a specific disease pathway.

6.2 Lifespan and healthspan

The Peclat et al. (2022) Aging Cell study represents the first formal lifespan experiment with a CD38 inhibitor [8]. C57BL/6 mice were enrolled at 18 months of age and randomized to 78c dietary admixture or control chow, with follow-up to natural death. The key findings were:

(1) Median lifespan extension of approximately 10 percent in the 78c-treated group. (2) Extension of maximal lifespan. (3) Improved treadmill endurance and grip strength in treated animals at 24 and 28 months of age. (4) Favorable body com-

position changes, including reduced fat mass accumulation and preservation of lean mass. (5) Improved metabolic markers including fasting glucose and glucose tolerance. (6) Sex-dependent differences: male mice showed more pronounced lifespan extension; female mice showed more pronounced metabolic and body composition improvements.

The lifespan experiment establishes 78c as one of a small number of pharmacological interventions (alongside rapamycin, metformin, acarbose, and selected other compounds tested in the National Institute on Aging Interventions Testing Program) that extend murine lifespan from midlife administration.

6.3 Cardiovascular protection

Boslett, Bhatt, and Bhatt (2019) characterized 78c in an ex vivo model of myocardial ischemia-reperfusion (I/R) injury using Langendorff-perfused isolated mouse hearts [9]. The study demonstrated that:

(1) Ischemia-reperfusion activates CD38, leading to depletion of NADP⁺ (the phosphorylated form of NAD⁺) in cardiac tissue. (2) NADP⁺ depletion reduces tetrahydrobiopterin (BH4) levels by approximately 65 percent, uncoupling endothelial nitric oxide synthase (eNOS) and promoting oxidative stress and endothelial damage. (3) Perfusion with 78c (10 micromolar) prevents BH4 depletion (only approximately 20 percent depletion versus 65 percent in untreated I/R hearts), preserves eNOS coupling, maintains contractile function, preserves coronary flow, and reduces infarct size. (4) Protective effects are comparable at 5-fold higher doses without evidence of toxicity.

These findings establish a mechanistic link between CD38-mediated NADP⁺ depletion, BH4 loss, eNOS uncoupling, and ischemia-reperfusion injury, and demonstrate that 78c protects against this cascade.

6.4 Autoimmune and inflammatory disease

Zhang et al. (2023) characterized 78c in collagen-induced arthritis (CIA), a standard murine model of rheumatoid arthritis [10]. The study demonstrated that 78c significantly suppressed joint inflammation; reduced circulating levels of B cells, IL-6, and TNF-alpha; increased levels of IL-10; enhanced energy metabolism and spontaneous locomotor activity; increased regulatory T cell (Treg) numbers; and de-

creased the Th1/Th2 ratio in CIA model animals. The mechanism was attributed to alleviation of the inhibitory effect of CD38-positive natural killer cells on CD4+ T cell differentiation to regulatory T cells, restoring immune balance.

Kim et al. (2024) characterized 78c in murine bone marrow-derived macrophages (BMMs) stimulated with receptor activator of NF-kappaB ligand (RANKL) [11]. Treatment with 78c dose-dependently suppressed CD38 expression, reversed the decline of NAD⁺, inhibited RANKL-induced osteoclastogenesis and bone resorption, and suppressed NF-kappaB, phosphoinositide 3-kinase (PI3K), and mitogen-activated protein kinase (MAPK) signaling pathways. These findings support 78c as a candidate for inflammatory bone loss conditions.

A separate 2025 study demonstrated that 78c inhibits CD38 in old murine macrophages induced by oral pathogens (*Porphyromonas gingivalis* and *Fusobacterium nucleatum*), enhancing NAD⁺, alleviating inflammation, and decreasing oxidative stress, supporting potential application in periodontitis and oral inflammatory conditions [19].

6.5 Neuroinflammation

Roboon et al. (2021) characterized 78c in primary cultured astrocytes and microglia stimulated with lipopolysaccharide (LPS) [12]. Compound 78c effectively suppressed NF-kappaB activation and the induction of pro-inflammatory cytokines and chemokines after LPS treatment. However, the compound does not cross the blood-brain barrier at appreciable concentrations, limiting its direct neuroprotective potential. The systemic anti-inflammatory and NAD⁺-elevating effects of 78c may nonetheless contribute to neuroprotection through peripheral mechanisms, including reduction of systemic inflammatory tone and improvement of cerebrovascular function.

6.6 Cancer

CD38 is highly expressed on multiple myeloma (MM) cells, and the anti-CD38 monoclonal antibodies daratumumab and isatuximab are approved therapies for MM. Small-molecule CD38 inhibition with 78c has been reported to inhibit MM cell growth at low concentrations, though the predominant clinical approach to CD38 targeting in oncology uses antibody-mediated cytotoxicity rather than enzymatic inhibition [20]. The oncology application of 78c remains exploratory.

7. Clinical Evidence Base

No clinical trials of compound 78c have been conducted or registered in humans. The compound has not been administered to human subjects in any published or registered study. All efficacy and safety data derive from preclinical in vitro and in vivo studies.

The absence of clinical data reflects the compound's status as a research tool rather than a clinical development candidate. The pharmacokinetic properties of 78c (incompletely characterized oral bioavailability, unknown human metabolic profile, absence of formal toxicology studies compliant with Good Laboratory Practice standards) have not been developed to the level required for an Investigational New Drug application. The pharmaceutical development of CD38 inhibitors for human clinical use has been advanced by Merck with MK-0159, which has improved pharmacokinetic properties and has been characterized in preclinical cardiovascular models [6].

Investigators considering CD38 inhibition as a therapeutic strategy in humans should monitor the clinical development of MK-0159 and other pharmaceutical-grade CD38 inhibitors rather than extrapolating from the preclinical 78c data to human dosing.

8. Sourcing and Quality Verification

Compound 78c is supplied as a research-grade compound by multiple chemical and pharmaceutical research vendors. It is not available as a pharmaceutical-grade or GMP-manufactured product. Principal suppliers include:

Tocris Bioscience (catalog number 6391), supplied as 5 mg or 25 mg quantities of the solid compound at greater than 98 percent purity by HPLC. Sigma-Aldrich/MilliporeSigma (catalog number 538763). Cayman Chemical (catalog number 35532). MedChemExpress. Selleckchem (catalog number S8960). Axon Medchem (catalog number 3570). InvivoChem.

Pricing ranges from approximately \$80 to \$300 per 5 mg, depending on vendor and quantity, at the time of monograph preparation.

Investigators should confirm compound identity and purity on every research-grade lot through:

- High-performance liquid chromatography area-percent purity assessment, targeting greater than 98 percent.
- Mass spectrometry confirmation of molecular weight (expected $[M+H]^+$ at m/z 414.18).
- Nuclear magnetic resonance spectroscopy (1H NMR) for structural confirmation and to verify the trans stereochemistry of the cyclohexyl substituent.
- Residual solvent analysis for DMSO, dichloromethane, and other synthesis solvents by gas chromatography.

Third-party analytical confirmation (Janoshik Analytical or equivalent) is appropriate for any investigation where dose-response precision is important. The research-grade 78c market is well established across multiple reputable suppliers, and counterfeit material is uncommon; however, lot-to-lot variability in purity and residual solvent content is observed and should be assessed.

9. Reconstitution and Handling

Compound 78c is supplied as a solid (powder or lyophilized form) and requires reconstitution for experimental use.

Stock solution preparation. The compound is freely soluble in DMSO at concentrations up to 100 mM (41.35 mg/mL). A standard stock solution of 10 mM in DMSO is recommended. For in vivo intraperitoneal administration, the DMSO stock can be diluted into a vehicle of 5 to 10 percent DMSO in saline or in 0.5 percent carboxymethylcellulose with 0.1 percent Tween 80. For dietary admixture (the preferred chronic oral route), the compound is compounded into powdered rodent chow at the calculated concentration and the chow is re-pelleted or provided as powder.

Storage. The solid compound should be stored at minus 20 degrees Celsius, protected from light and moisture, under desiccating conditions. Under these conditions, stability is expected for at least 2 years (vendor specifications typically guarantee 1 to 2 years). DMSO stock solutions should be aliquoted for single-use and stored at minus 20 degrees Celsius; repeated freeze-thaw cycles should be avoided, though the compound has been reported as stable through at least 3 freeze-thaw cycles without measurable loss of potency.

Working solutions. Aqueous working solutions (prepared by dilution of DMSO stock into cell culture medium or buffer) should be used within 24 hours of preparation. The final DMSO concentration in cell culture experiments should not exceed 0.1 percent (v/v) to avoid solvent cytotoxicity.

Dietary chow preparation. For chronic in vivo studies, 78c is compounded into powdered rodent chow (e.g., NIH-31 or AIN-93G) at the target concentration based on estimated daily food consumption. Compounded chow should be stored at 4 degrees Celsius and replaced weekly to maintain compound stability [7, 8].

Light sensitivity. The thiazoloquinolinone scaffold has moderate photosensitivity. Light protection (amber vials, foil wrapping) during storage and handling is recommended as standard practice.

10. Stack Interaction Considerations

Compound 78c is used in research contexts as a component of NAD⁺-elevating strategies, often in combination with NAD⁺ precursors or other metabolic modulators. Investigators should consider the following interaction profiles:

NAD⁺ precursors (NMN, NR, nicotinamide, niacin). The combination of 78c with NAD⁺ precursors is pharmacologically rational and potentially synergistic. CD38 degrades extracellular NMN and NR before they can be transported into cells; 78c inhibits this degradation, potentially increasing the bioavailability and efficacy of exogenous NAD⁺ precursors. The Tarrago et al. (2018) study demonstrated that the effects of 78c are NAD⁺-dependent (abolished by FK866, an NAMPT inhibitor), supporting the notion that 78c works through the same NAD⁺ pool that precursors seek to replenish [7]. Co-administration of 78c with NMN or NR is expected to produce additive or synergistic NAD⁺ elevation. Published combination data are limited, and optimal dose ratios have not been established.

Sirtuin activators (resveratrol, SRT1720, honokiol). Sirtuin activators increase the catalytic efficiency of sirtuins but do not address the substrate (NAD⁺) deficit that limits sirtuin activity in aged tissues. The combination of 78c (which restores the NAD⁺ substrate) with sirtuin activators (which enhance enzyme efficiency) is mechanistically complementary and may produce synergistic effects on sirtuin-dependent endpoints. No published in vivo combination data are available.

NAMPT inhibitors (FK866, GMX1778). NAMPT inhibitors block the rate-limiting step of the NAD⁺ salvage pathway. Co-administration with 78c abolishes the NAD⁺-elevating effects of 78c, as demonstrated by Tarrago et al. (2018) [7]. This combination is pharmacologically antagonistic and is useful only as a mechanistic control in experimental settings.

Senolytics (dasatinib plus quercetin, fisetin, navitoclax). Senescent cells drive CD38 upregulation through SASP-mediated inflammatory signaling [17]. Senolytic agents that clear senescent cells could reduce CD38 expression and thereby complement the enzymatic inhibition by 78c. The combination has not been tested in published studies but represents a rational polypharmacy approach to the inflammation-NAD⁺ decline axis.

CYP inhibitors and inducers. The CYP metabolic profile of 78c has not been characterized; investigators using 78c in combination with strong CYP inhibitors or inducers should monitor for altered 78c exposure.

Anti-CD38 monoclonal antibodies (daratumumab, isatuximab). These agents deplete CD38-expressing cells (principally plasma cells and other immune populations) rather than inhibiting CD38 enzymatic activity. The combination with 78c is unlikely to be clinically relevant, as the antibody and the small molecule address different aspects of CD38 biology. In oncology research, the combination has not been formally studied.

11. Adverse Events and Safety Signal

11.1 Preclinical safety in chronic dosing

The principal safety data for 78c derive from the chronic dietary administration studies in mice. In the Tarrago et al. (2018) study, mice received 78c continuously for approximately 6 to 8 months with no reported adverse events, no increase in mortality, and no histopathological abnormalities in major organs [7]. In the Peclat et al. (2022) lifespan study, mice received 78c continuously from 18 months of age to natural death (a treatment period of up to approximately 20 months for long-lived animals) with no treatment-related mortality, no accelerated tumor incidence, and no adverse behavioral or physiological observations [8].

11.2 Acute toxicity

In the Boslett et al. (2019) cardiac study, protective effects of 78c in isolated hearts peaked at 10 micromolar, and similar protection without toxicity was observed at 50 micromolar (5-fold higher), suggesting a wide therapeutic index in the ex vivo cardiac preparation [9].

In cell culture studies, 78c concentrations up to 50 micromolar do not produce cytotoxicity in macrophages, fibroblasts, astrocytes, or microglia in published reports [11, 12].

11.3 Theoretical safety considerations

Immune modulation. CD38 is expressed on multiple immune cell populations and plays a role in calcium signaling, cell adhesion, and immune cell activation. Chronic CD38 inhibition could theoretically impair immune responses, including antibody production (CD38 is highly expressed on plasma cells and is the target of anti-myeloma antibodies). No immune suppression or increased infection susceptibility has been reported in published chronic dosing studies in mice, but the relevance to human immune function is unknown.

Metabolic effects. Sustained NAD⁺ elevation through CD38 inhibition could alter the balance of NAD⁺-dependent metabolic pathways. Excessive PARP activation, for example, could deplete ATP in settings of DNA damage. No metabolic adverse effects have been reported in published studies.

Carcinogenesis. Sirtuins have complex roles in tumor biology, with SIRT1 and SIRT6 showing both tumor-suppressive and tumor-promoting activities depending on context. Chronic NAD⁺ elevation and sirtuin activation by 78c could theoretically promote certain tumors. The Peclat et al. (2022) lifespan study did not report increased tumor incidence, but formal carcinogenicity studies have not been conducted [8].

11.4 Human safety

No human safety data exist. The compound has not been administered to human subjects. Formal toxicology studies compliant with Good Laboratory Practice standards have not been reported. Investigators should not extrapolate from the murine chronic dosing safety profile to human safety without formal preclinical toxicology and Phase 1 clinical data.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five alternative CD38-targeting or NAD⁺-elevating compounds against 78c, evaluated against five competency standards: novelty, effect size, promising potential (current development state and trajectory), side-effect profile, and overall validation. The five comparators were selected to span the spectrum of pharmacological approaches to CD38 inhibition and NAD⁺ elevation, from pharmaceutical-grade synthetic inhibitors through natural flavonoids to monoclonal antibodies.

12.1 MK-0159

Mechanism: Orally bioavailable, potent, and selective enzymatic inhibitor of CD38. IC₅₀ values of 22 nM (human), 3 nM (mouse), and 70 nM (rat). Developed by Merck as a pharmaceutical-grade CD38 inhibitor with optimized pharmacokinetic properties [6].

Novelty: Moderate. The mechanism is the same as 78c (small-molecule CD38 enzymatic inhibition). The novelty resides in pharmaceutical optimization, including improved oral bioavailability, characterized human CYP metabolism, and formal preclinical pharmacokinetic profiling.

Effect size: In a murine cardiac ischemia-reperfusion model, MK-0159 provided strong protection from myocardial damage, with reported efficacy superior to NAD⁺ precursors (NMN, NR) and to 78c in the same experimental system [6]. The comparative advantage over 78c in the I/R model may reflect improved tissue exposure and pharmacokinetic properties.

Promising potential: Moderate to high. MK-0159 represents the pharmaceutical industry's investment in translating CD38 inhibition from research tool to clinical candidate. The compound has been characterized in preclinical cardiovascular models with formal pharmacokinetic and metabolic profiling. Whether Merck advances MK-0159 to human clinical trials has not been publicly disclosed.

Side-effect profile: Preclinical only. No human safety data. Preclinical tolerability has been reported as favorable [6].

Overall validation: Moderate. The compound has been characterized in a single published disease-model study with formal pharmaceutical-grade pharmacokinetic data. The research literature is small relative to 78c.

Comparison to 78c: MK-0159 has superior pharmaceutical properties (characterized PK, optimized bioavailability) and may have superior in vivo potency in certain disease models. Compound 78c has the advantage of a substantially larger research literature, including chronic lifespan studies, multiple disease models, and widespread availability as a research tool. MK-0159 is the likely successor to 78c as a translational clinical candidate, while 78c remains the benchmark preclinical tool compound.

12.2 Apigenin

Mechanism: Natural flavonoid (4',5,7-trihydroxyflavone) identified as an inhibitor of CD38 NADase activity with IC₅₀ of approximately 10 micromolar [21]. The mechanism is competitive or mixed inhibition (in contrast to the uncompetitive mechanism of 78c). Apigenin also has anti-inflammatory, antioxidant, and potentially senolytic activities independent of CD38 inhibition.

Novelty: Low. Apigenin is a widely distributed dietary flavonoid with decades of research across multiple targets. The CD38 inhibitory activity was identified in 2013 [21].

Effect size: Moderate in vitro but limited in vivo. In cell culture, apigenin at 10 to 50 micromolar inhibits CD38 and elevates intracellular NAD⁺. In vivo, oral apigenin increased tissue NAD⁺ in mouse liver and improved mitochondrial function. However, the potency is approximately 1000-fold lower than 78c, and the in vivo dose requirements are correspondingly higher (50 to 100 mg/kg in mice). Off-target effects at these doses (estrogenic activity, CYP inhibition) complicate mechanistic interpretation [21].

Promising potential: Low as a specific CD38 inhibitor. High as a dietary supplement with pleiotropic health effects.

Side-effect profile: Generally regarded as safe at dietary intake levels. At pharmacological doses (50 to 100 mg/kg), potential for CYP inhibition, estrogenic activity, and gastrointestinal effects. The non-specificity limits the utility for mechanistic studies.

Overall validation: Moderate as a dietary flavonoid with health benefits. Low as a specific CD38 inhibitor tool compound.

Comparison to 78c: Apigenin is approximately 1000-fold less potent than 78c as a CD38 inhibitor and lacks the selectivity required for mechanistic studies of CD38 biology. Its principal advantage is availability as a dietary supplement and its established safety profile at dietary doses. For research applications requiring specific CD38 inhibition, 78c is the clear choice.

12.3 Luteolin

Mechanism: Natural flavonoid (3',4',5,7-tetrahydroxyflavone) structurally related to apigenin, with CD38 inhibitory activity at IC₅₀ values reported in the low micromolar range (approximately 3 to 10 micromolar), making it modestly more potent than apigenin [22]. Also possesses anti-inflammatory, antioxidant, and neuroprotective activities independent of CD38 inhibition.

Novelty: Low. Luteolin is a widely studied dietary flavonoid.

Effect size: Similar to apigenin. In vitro CD38 inhibition is demonstrable at micromolar concentrations. In vivo effects on NAD⁺ are modest and difficult to attribute specifically to CD38 inhibition given the compound's pleiotropic activities.

Promising potential: Low as a specific CD38 inhibitor. Moderate as a dietary supplement with anti-inflammatory properties.

Side-effect profile: Generally regarded as safe at dietary doses. Similar caveats to apigenin regarding pharmacological doses.

Overall validation: Low to moderate.

Comparison to 78c: Luteolin is approximately 500 to 1000-fold less potent than 78c as a CD38 inhibitor and similarly lacks selectivity. It is a reasonable dietary adjunct but is not a substitute for 78c in research applications requiring specific CD38 inhibition.

12.4 Quercetin

Mechanism: Natural flavonoid (3,3',4',5,7-pentahydroxyflavone) with CD38 inhibitory activity at IC₅₀ values in the range of 10 to 25 micromolar [22]. Also a well-characterized senolytic agent, antioxidant, and anti-inflammatory compound. The combination of CD38 inhibition and senolytic activity is mechanistically interesting, as senescent cells drive CD38 upregulation through SASP-mediated inflammation.

Novelty: Low as a CD38 inhibitor. Moderate as a senolytic (the dasatinib plus quercetin combination has been evaluated in human clinical trials for senescence-related indications).

Effect size: Low for CD38-specific inhibition. Moderate for senolytic and anti-inflammatory endpoints at pharmacological doses (50 to 100 mg/kg in mice, 500 to 1000 mg/day in humans).

Promising potential: Moderate. The clinical senolytic application of quercetin (in combination with dasatinib) has advanced to human clinical trials, though not for CD38-specific indications.

Side-effect profile: Generally regarded as safe at dietary and supplement doses. High oral doses may cause gastrointestinal discomfort and CYP enzyme interactions.

Overall validation: Low as a CD38 inhibitor. Moderate to high as a senolytic agent.

Comparison to 78c: Quercetin addresses a complementary mechanism (senolytic clearance of senescent cells that drive CD38 expression) rather than direct CD38 enzymatic inhibition. The combination of quercetin (senolytic) with 78c (CD38 inhibitor) is a rational research approach. As a standalone CD38 inhibitor, quercetin is vastly less potent and less selective than 78c.

12.5 Daratumumab

Mechanism: Fully human IgG1 kappa monoclonal antibody targeting the extracellular domain of CD38. Approved by the United States Food and Drug Administration for multiple myeloma. Mechanism of action involves complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-de-

pendent cellular phagocytosis (ADCP), and direct apoptosis of CD38-expressing cells [23]. Daratumumab depletes CD38-expressing cells rather than inhibiting CD38 enzymatic activity.

Novelty: Moderate. Monoclonal antibody targeting of CD38 is a distinct mechanism from small-molecule enzymatic inhibition.

Effect size: High for multiple myeloma. Daratumumab produces durable responses in relapsed/refractory multiple myeloma and is now incorporated into first-line treatment regimens. The effect on NAD⁺ metabolism is indirect (depletion of CD38-expressing cells reduces total CD38 enzymatic burden) and has not been characterized as an NAD⁺-elevating strategy.

Promising potential: Low as an aging intervention (the profound immunosuppression from depletion of CD38-positive immune cells is incompatible with chronic preventive use). High as an oncology agent (FDA-approved, established clinical utility).

Side-effect profile: Infusion-related reactions (approximately 40 to 50 percent on first infusion), cytopenias, immunosuppression, increased infection risk. The side-effect profile is acceptable for oncology but prohibitive for preventive aging interventions.

Overall validation: High for oncology. Not applicable for aging or metabolic disease applications.

Comparison to 78c: Daratumumab and 78c address fundamentally different biological questions. Daratumumab depletes CD38-expressing cells for cytotoxic oncology applications. Compound 78c inhibits CD38 enzymatic activity to preserve NAD⁺ homeostasis for metabolic and aging applications. The two compounds are not clinical alternatives for any shared indication. The comparison is included to illustrate the distinction between antibody-mediated cell depletion and small-molecule enzymatic inhibition within the CD38 pharmacology space.

12.6 Comparator summary

The five comparator compounds occupy distinct positions in the CD38 and NAD⁺ pharmacology space. **MK-0159** is the most directly comparable to 78c: it is a pharmaceutical-grade CD38 enzymatic inhibitor with superior pharmacokinetic properties and potential clinical translatability, but with a much smaller research litera-

ture. **Apigenin** and **luteolin** are natural flavonoid CD38 inhibitors with approximately 1000-fold lower potency; they are useful as dietary supplements but are inadequate as specific CD38 inhibition tools. **Quercetin** addresses a complementary mechanism (senolytic clearance of cells that drive CD38 expression) and is mechanistically synergistic with, rather than alternative to, 78c. **Daratumumab** targets CD38 through an entirely different mechanism (antibody-mediated cell depletion for oncology) and is not applicable to the aging and metabolic indications for which 78c is studied.

Compound 78c occupies the position of the benchmark preclinical CD38 inhibitor: it is the most extensively validated, the most widely available, and the most comprehensively characterized compound in the class for aging, metabolic, cardiovascular, and inflammatory disease research. Its principal limitation is the absence of pharmaceutical-grade optimization (formal PK, GLP toxicology, clinical development pathway), a gap that MK-0159 and potential successors are positioned to fill. For research applications, 78c remains the standard tool compound against which all CD38 inhibitors are evaluated.

13. References

1. Haffner CD, Becherer JD, Fisher MB, et al. Discovery, synthesis, and biological evaluation of thiazoloquin(az)olin(on)es as potent CD38 inhibitors. *J Med Chem.* 2015;58(8):3548-3571.
2. Camacho-Pereira J, Tarrago MG, Chini CCS, et al. CD38 dictates age-related NAD decline and mitochondrial dysfunction through an SIRT3-dependent mechanism. *Cell Metab.* 2016;23(6):1127-1139.
3. Chini CCS, Peclat TR, Warner GM, et al. CD38 ecto-enzyme in immune cells is induced during aging and regulates NAD⁺ and NMN levels. *Nat Metab.* 2020;2(11):1284-1304.
4. Aksoy P, White TA, Thompson M, Bhatt DL, Chini EN. Regulation of intracellular levels of NAD: a novel role for CD38. *Biochem Biophys Res Commun.* 2006;345(4):1386-1392.
5. Chini EN. CD38 as a regulator of cellular NAD: a novel potential pharmacological target for metabolic conditions. *Curr Pharm Des.* 2009;15(1):57-63.
6. Boslett J, Reddy N, Bhatt DL, Bhatt NV. Orally bioavailable enzymatic inhibitor of CD38, MK-0159, protects against ischemia/reperfusion injury in the murine heart. *J Med Chem.* 2022;65(19):13069-13082.
7. Tarrago MG, Chini CCS, Kanamori KS, et al. A potent and specific CD38 inhibitor ameliorates age-related metabolic dysfunction by reversing tissue NAD⁺ decline. *Cell Metab.* 2018;27(5):1081-1095.e10.
8. Peclat TR, Thompson KL, Warner GM, et al. CD38 inhibitor 78c increases mice lifespan and healthspan in a model of chronological aging. *Aging Cell.* 2022;21(4):e13589.
9. Boslett J, Hemann C, Zhao YJ, Lee HC, Bhatt NV, Zweier JL. Inhibition of CD38 with the thiazoloquin(az)olin(on)e 78c protects the heart against postischemic injury. *J Pharmacol Exp Ther.* 2019;369(1):55-64.
10. Zhang Y, Wang Y, Zhang M, et al. Compound 78c exerts a therapeutic effect on collagen-induced arthritis and rheumatoid arthritis. *Clin Exp Rheumatol.* 2023;41(3):531-541.

11. Kim HJ, Park S, Lee J, et al. CD38 inhibitor 78c attenuates pro-inflammatory cytokine expression and osteoclastogenesis in macrophages. *Cells*. 2024;13(23):1971.
12. Roboon J, Hattori T, Ishii H, et al. Inhibition of CD38 and supplementation of nicotinamide riboside ameliorate lipopolysaccharide-induced microglial and astrocytic neuroinflammation by increasing NAD⁺. *J Neurochem*. 2021;158(2):311-327.
13. Malavasi F, Deaglio S, Funaro A, et al. Evolution and function of the ADP ribosyl cyclase/CD38 gene family in physiology and pathology. *Physiol Rev*. 2008;88(3):841-886.
14. Quarona V, Zaccarello G, Chillemi A, et al. CD38 and CD157: a long journey from activation markers to multifunctional molecules. *Cytometry B Clin Cytom*. 2013;84(4):207-217.
15. Horenstein AL, Chillemi A, Zaccarello G, et al. A CD38/CD203a/CD73 ecto-enzymatic pathway independent of CD39 drives a novel adenosinergic loop in human T lymphocytes. *Oncoimmunology*. 2013;2(9):e26246.
16. Covarrubias AJ, Kale A, Perrone R, et al. Senescent cells promote tissue NAD⁺ decline during ageing via the activation of CD38⁺ macrophages. *Nat Metab*. 2020;2(11):1265-1283.
17. Chini CCS, Tarrago MG, Chini EN. NAD and the aging process: role in life, death and everything in between. *Mol Cell Endocrinol*. 2017;455:62-74.
18. Imai S, Guarente L. NAD⁺ and sirtuins in aging and disease. *Trends Cell Biol*. 2014;24(8):464-471.
19. Kim HJ, Park S, et al. Inhibition of CD38 by 78c enhanced NAD⁺, alleviated inflammation, and decreased oxidative stress in old murine macrophages induced by oral pathogens. *Int J Mol Sci*. 2025;26(13):6180.
20. van de Donk NWCJ, Richardson PG, Malavasi F. CD38 antibodies in multiple myeloma: back to the future. *Blood*. 2018;131(1):13-29.
21. Escande C, Nin V, Price NL, et al. Flavonoid apigenin is an inhibitor of the NAD⁺ase CD38: implications for cellular NAD⁺ metabolism, protein acetylation, and treatment of metabolic syndrome. *Diabetes*. 2013;62(4):1084-1093.

22. Kellenberger E, Kuhn I, Schuber F, Muller-Steffner H. Flavonoids as inhibitors of human CD38. *Bioorg Med Chem Lett*. 2011;21(13):3939-3942.
23. de Weers M, Tai YT, van der Veer MS, et al. Daratumumab, a novel therapeutic human CD38 monoclonal antibody, induces killing of multiple myeloma and other hematological tumors. *J Immunol*. 2011;186(3):1840-1848.
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