

RESEARCH MONOGRAPH . COMPOUND PROFILE

P7C3-A20

A synthetic 3,6-dibromocarbazole derivative discovered through target-agnostic in vivo neurogenesis screening, distinguished by its activation of the NAD⁺ salvage enzyme NAMPT and broad neuroprotective efficacy across preclinical models of traumatic brain injury, ischemic stroke, Parkinson disease, amyotrophic lateral sclerosis, and Alzheimer disease.

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ABSTRACT

P7C3-A20, the fluorinated and methoxylated analog of the parent aminopropyl carbazole P7C3, is a synthetic neuroprotective compound identified through iterative structure-activity optimization of a chemical series originally discovered in a target-agnostic *in vivo* screen for enhancers of adult hippocampal neurogenesis conducted by Pieper, McKnight, and colleagues at the University of Texas Southwestern Medical Center [1]. The parent compound P7C3 was one of eight hits from a library of approximately 1,000 small molecules screened for their ability to augment the survival of newborn neurons in the subgranular zone of the murine dentate gyrus. Subsequent medicinal chemistry optimization, principally the replacement of the central hydroxyl with fluorine and the introduction of a methoxy substituent on the aniline ring, yielded P7C3-A20, which demonstrated approximately ten-fold greater proneurogenic potency than the parent compound while retaining favorable oral bioavailability, blood-brain barrier penetration, and tolerability in chronic dosing studies in rodents and nonhuman primates [2, 3]. The molecular target of P7C3-A20 was identified by Wang et al. (2014) as nicotinamide phosphoribosyltransferase (NAMPT), the rate-limiting enzyme in the nicotinamide adenine dinucleotide (NAD⁺) salvage pathway [4]. P7C3-A20 functions as a positive allosteric modulator of NAMPT, enhancing the conversion of nicotinamide to nicotinamide mononucleotide (NMN) and thereby augmenting intracellular NAD⁺ levels under conditions of metabolic stress without elevating NAD⁺ to supraphysiologic concentrations. This mechanism distinguishes P7C3-A20 from direct NAD⁺ precursor supplementation strategies (nicotinamide riboside, nicotinamide

mononucleotide) by preserving endogenous feedback regulation of the salvage pathway. The downstream consequences of NAMPT activation and NAD⁺ restoration include maintenance of sirtuin deacetylase activity (particularly SIRT1 and SIRT3), protection of mitochondrial bioenergetics, suppression of oxidative stress and DNA damage, attenuation of neuroinflammation through microglial modulation, and enhancement of the survival of newly generated neurons during adult hippocampal neurogenesis. The preclinical pharmacology of P7C3-A20 has been characterized across an unusually broad spectrum of neurodegenerative and neurotraumatic disease models. In the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model of Parkinson disease, P7C3-A20 substantially preserved dopaminergic neurons in the substantia nigra [5]. In the G93A-SOD1 transgenic mouse model of amyotrophic lateral sclerosis (ALS), P7C3-A20 reduced motor neuron cell death in the spinal cord [6]. In models of traumatic brain injury (TBI), P7C3-A20 blocked axonal degeneration and preserved neurological function when administered acutely [7], and, in a landmark 2020 study, restored blood-brain barrier integrity, arrested chronic neurodegeneration, and recovered normal cognitive function when treatment was initiated a full twelve months after the initial injury [8]. In rat models of focal ischemic stroke, P7C3-A20 promoted post-ischemic neurogenesis, restored cortical NAD⁺ levels, and improved chronic sensorimotor and cognitive outcomes [9]. In retinal degeneration models, the P7C3 class protected retinal ganglion cells from optic nerve injury [10]. In 2025, Vazquez-Rosa et al. published a study in *Cell Reports Medicine* demonstrating that P7C3-A20 treatment of 5xFAD and PS19 transgenic mice with advanced Alzheimer-like pathology produced comprehensive reversal of tau phosphorylation, blood-brain barrier deterioration, oxidative stress, DNA damage, and

neuroinflammation, with full cognitive recovery and normalization of the clinical biomarker p-tau217 [11]. P7C3-A20 has not entered human clinical trials as of the most recent monograph revision. The compound is not approved by any regulatory authority for any indication. It is available as a research-grade preparation from multiple chemical suppliers at high purity. This monograph reviews the chemistry, synthesis, and structure-activity relationships of P7C3-A20; the NAMPT-mediated mechanism of action; the preclinical pharmacokinetic profile; the extensive preclinical pharmacology across neurodegenerative and neurotraumatic models; the current clinical development status; sourcing and quality considerations; reconstitution and handling; stack interactions; the adverse-event and safety profile from preclinical studies; and a comparative assessment of five neuroprotective or NAD-augmenting compounds against P7C3-A20 on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

Common name: P7C3-A20.

Systematic chemical name: N-(3-(3,6-dibromo-9H-carbazol-9-yl)-2-fluoropropyl)-3-methoxyaniline.

Alternative designations: P7C3A20, compound A20. The designation "P7C3" reflects the compound's discovery order in the original Pieper et al. (2010) in vivo screen: pool 7, compound 3. The suffix "A20" denotes the twentieth analog in the first optimization series (A series) [1, 2].

Chemical Abstracts Service registry number: 1235481-90-9.

Molecular formula: C₂₂H₁₉Br₂FN₂O.

Molecular weight: 506.21 g/mol (exact mass 505.99 g/mol, monoisotopic).

PubChem CID: 71245370.

1.2 Structural class and chemistry

P7C3-A20 belongs to the aminopropyl carbazole structural class. The carbazole core is a tricyclic aromatic system consisting of two fused benzene rings bridged by a pyrrole nitrogen. In P7C3-A20, the carbazole is substituted at the 3- and 6-positions with bromine atoms and is connected through the pyrrole nitrogen (N-9) to a three-carbon propyl chain bearing a fluorine substituent at the 2-position (replacing the hydroxyl of the parent P7C3). The terminal nitrogen of the propyl chain is linked to a 3-methoxyaniline ring [2, 3].

Physical properties: Off-white to pale yellow solid. Soluble in dimethyl sulfoxide (DMSO) at concentrations up to 100 mM. Sparingly soluble in aqueous media; typically formulated in DMSO-containing vehicles or in cyclodextrin-based formulations for in vivo administration. Melting point is approximately 128 to 132 degrees Celsius.

Stereochemistry: The fluorine-bearing carbon at the 2-position of the propyl linker is a stereocenter. P7C3-A20 is typically supplied and studied as the racemic mixture. The related analog P7C3-S243, developed by De Brabander, Pieper, and Ready, is the resolved (S)-enantiomer of a closely related pyridyl variant with optimized druglike properties [12]. Investigators requiring enantiopure material should specify stereochemical configuration at procurement.

Key structural distinctions from the parent P7C3: The parent compound P7C3 bears a hydroxyl group at the 2-position of the propyl linker and an unsubstituted aniline ring. P7C3-A20 incorporates two modifications: (1) replacement of the hydroxyl with fluorine, which increases metabolic stability and membrane permeability; and (2) introduction of a 3-methoxy group on the aniline ring, which enhances proneurogenic potency. The combination of these two modifications produces a synergistic increase in activity relative to either single modification [2].

1.3 Synthesis

The original synthesis of P7C3-A20 followed a convergent route involving preparation of 3,6-dibromocarbazole, N-alkylation with an appropriately functionalized epifluorohydrin or fluorinated epoxide to install the fluorinated propyl linker, and reductive amination or nucleophilic coupling with 3-methoxyaniline [2]. Naidoo et al. (2013) reported a scalable synthesis of P7C3-A20 suitable for hundred-gram-scale production, eliminating the requirement for chromatographic purification of intermediates or the final product [13]. The scalable route proceeds through: (1) dibromination of carbazole at the 3- and 6-positions using N-bromosuccinimide in dimethylformamide; (2) N-alkylation of 3,6-dibromocarbazole with epifluorohydrin under basic conditions to yield the fluorinated epoxide intermediate; (3) regioselective ring opening of the epoxide with 3-methoxyaniline to afford P7C3-A20 as the racemic product; and (4) purification by recrystallization. Yields across the sequence are reported in the range of 50 to 70 percent for each step, with the final product obtained in greater than 98 percent purity by high-performance liquid chromatography [13].

2. Abstract

P7C3-A20 is a synthetic aminopropyl carbazole that functions as a positive allosteric modulator of nicotinamide phosphoribosyltransferase (NAMPT), the rate-limiting enzyme in the NAD⁺ salvage pathway [4]. The compound was derived through medicinal chemistry optimization of the parent compound P7C3, which was identified in a 2010 target-agnostic in vivo screen for small molecules capable of enhancing survival of newborn hippocampal neurons in adult mice [1]. Replacement of the central hydroxyl with fluorine and addition of a methoxy group to the aniline ring produced P7C3-A20, an analog with approximately ten-fold greater proneurogenic potency, improved metabolic stability, and retained oral bioavailability and blood-brain barrier penetration [2].

The mechanism of action was established by Wang et al. (2014), who demonstrated that P7C3-A20 binds NAMPT and enhances the enzymatic conversion of nicotinamide to NMN, thereby augmenting cellular NAD⁺ levels under conditions of metabolic stress [4]. Critically, P7C3-A20 acts as an allosteric modulator rather than a substrate, preserving endogenous negative feedback on the NAD⁺ salvage pathway and avoiding supraphysiologic NAD⁺ accumulation. The downstream neuroprotective consequences include maintained sirtuin (SIRT1, SIRT3) deacetylase activity, preserved mitochondrial bioenergetics, reduced oxidative stress and DNA damage, attenuated neuroinflammation, and enhanced survival of newborn neurons during adult hippocampal neurogenesis.

The preclinical pharmacology spans an exceptionally broad range of neurological disease models. Neuroprotective efficacy has been demonstrated in the MPTP model of Parkinson disease (preservation of substantia nigra dopaminergic neurons) [5]; the G93A-SOD1 model of ALS (reduced spinal motor neuron death) [6]; controlled cortical impact and blast-overpressure models of TBI (axonal preservation, blood-brain barrier repair, cognitive recovery even when treatment is initiated twelve months post-injury) [7, 8]; middle cerebral artery occlusion models of ischemic stroke (neurogenesis promotion, NAD⁺ restoration, chronic behavioral improvement) [9]; retinal ganglion cell injury (optic nerve protection) [10]; the P7C3 class in models of depression (antidepressant efficacy through hippocampal neurogenesis) [14]; paclitaxel-induced peripheral neuropathy (NAMPT-dependent axon protection) [15]; and, most recently, advanced Alzheimer disease in 5xFAD and PS19

transgenic mice (comprehensive reversal of tau phosphorylation, blood-brain barrier deterioration, oxidative stress, neuroinflammation, with full cognitive recovery) [11].

Pharmacokinetic studies in rodents demonstrate oral bioavailability, a plasma half-life of approximately 6 to 7 hours after intraperitoneal administration (characterized for the parent P7C3; P7C3-A20 has comparable or improved stability), and efficient blood-brain barrier penetration [1, 16]. In nonhuman primates, 38 weeks of daily oral P7C3-A20 at 10 mg/kg produced dramatic augmentation of hippocampal neurogenesis with no microscopic evidence of toxicity in any tissue examined [3].

P7C3-A20 has not entered human clinical trials. It is not approved by any regulatory authority. The compound is available as a research-grade preparation from multiple suppliers. Investigators should obtain analytical confirmation of identity and purity on every lot.

3. Discovery and Development History

3.1 Origin of the P7C3 chemical series

The P7C3 chemical series originated from a target-agnostic in vivo screen conducted by Andrew A. Pieper, Steven L. McKnight, and colleagues at the University of Texas Southwestern Medical Center, reported in *Cell* in 2010 [1]. The screen was designed to identify small molecules capable of enhancing the net magnitude of adult hippocampal neurogenesis in living mice, reasoning that the survival of newborn neurons in the dentate gyrus is a rate-limiting step in hippocampal neurogenesis and that chemical enhancers of this survival could have therapeutic relevance to neurodegenerative disease.

Approximately 1,000 small molecules were administered to adult C57BL/6 mice, and the number of surviving bromodeoxyuridine (BrdU)-labeled neurons in the subgranular zone of the dentate gyrus was quantified. Eight compounds enhanced neuronal survival above the vehicle control threshold. Among these, the most promising was an aminopropyl carbazole designated P7C3 (pool 7, compound 3). P7C3 demonstrated favorable oral bioavailability (approximately 32 percent), blood-brain barrier penetration, a plasma half-life of 6.7 hours after intraperitoneal injection, and tolerability in chronic dosing studies. Mechanistic studies established that P7C3 enhanced hippocampal neurogenesis not by increasing the proliferation of neural precursor cells but by protecting newborn neurons from apoptosis during the critical period of integration into hippocampal circuitry [1].

3.2 Development of P7C3-A20

Following the discovery of P7C3, the Pieper-McKnight-De Brabander-Ready team conducted systematic structure-activity relationship (SAR) studies across the aminopropyl carbazole scaffold. The carbazole core, the dibromination pattern, and the propyl linker were identified as essential pharmacophoric elements. Optimization of the linker and the aniline ring yielded multiple active analogs, among which P7C3-A20 (compound 12 in the published series) emerged as the most potent variant in the in vivo neurogenesis assay [2]. P7C3-A20 incorporates two key modifications relative to P7C3: conversion of the central hydroxyl to fluorine (im-

proving metabolic stability by eliminating a site of glucuronidation) and introduction of a 3-methoxy group on the aniline ring (enhancing target engagement). The combination produced a synergistic increase in proneurogenic potency of approximately ten-fold relative to the parent compound.

3.3 Identification of the molecular target

The molecular target of the P7C3 class was initially unknown, as the compounds were discovered through a phenotypic (target-agnostic) screen. In 2014, Wang et al. published a report in *Cell* establishing that P7C3 chemicals function by activating nicotinamide phosphoribosyltransferase (NAMPT), the rate-limiting enzyme in the NAD⁺ salvage pathway [4]. Using affinity chromatography, thermal shift assays, and enzymatic activity measurements with purified recombinant NAMPT, the investigators demonstrated that active P7C3 variants (including P7C3-A20) bind NAMPT and enhance its catalytic conversion of nicotinamide to NMN in a dose-responsive manner. Inactive structural analogs did not bind or activate NAMPT, confirming the structure-activity correlation. The identification of NAMPT as the target placed P7C3-A20 within the broader field of NAD⁺ biology and provided a molecular rationale for the observed neuroprotective effects: neurons under metabolic stress (from excitotoxicity, ischemia, oxidative damage, or proteinopathy) experience declining NAD⁺ levels, and pharmacological enhancement of the salvage pathway via NAMPT activation restores the bioenergetic and signaling capacity necessary for neuronal survival.

3.4 Expansion of preclinical indications

Between 2012 and 2025, the Pieper laboratory (which relocated from the University of Iowa to Case Western Reserve University and University Hospitals Cleveland) and collaborating groups extended the preclinical characterization of P7C3-A20 across a remarkably diverse set of neurological disease models. The chronological sequence of major publications is: Parkinson disease (MPTP model, De Jesus-Cortes et al. 2012) [5]; ALS (G93A-SOD1 model, Tesla et al. 2012) [6]; TBI acute neuroprotection (Yin et al. 2014) [7]; depression and neurogenesis (Walker et al. 2015) [14]; ischemic stroke (Loris et al. 2017) [9]; peripheral neuropathy (LoCoco et al. 2017) [15]; nonhuman primate neurogenesis (Baxter et al. 2018) [3]; chronic TBI repair twelve months post-injury (Vazquez-Rosa et al. 2020) [8]; and advanced Alzheimer disease reversal (Vazquez-Rosa et al. 2025) [11]. This trajectory is notable for the consis-

tency of the neuroprotective signal across mechanistically distinct disease models and for the progression from acute protection to disease reversal in chronic neurodegenerative states.

3.5 Scalable synthesis and clinical translation status

Naidoo et al. (2013) reported a scalable synthesis of P7C3-A20 capable of producing hundred-gram quantities without chromatographic purification, a prerequisite for IND-enabling studies and eventual clinical translation [13]. As of the most recent monograph revision, P7C3-A20 has not entered human clinical trials. The 2025 Vazquez-Rosa et al. Alzheimer disease study explicitly identified the compound as a candidate for clinical translation, and the investigators have indicated that human trials are under consideration [11]. The compound is not in active commercial pharmaceutical development by any disclosed entity.

4. Mechanism of Action

4.1 NAMPT activation and NAD⁺ salvage

The primary molecular target of P7C3-A20 is nicotinamide phosphoribosyltransferase (NAMPT), also known as pre-B-cell colony-enhancing factor (PBEF) or visfatin. NAMPT is the rate-limiting enzyme in the mammalian NAD⁺ salvage pathway, catalyzing the condensation of nicotinamide with 5-phosphoribosyl-1-pyrophosphate (PRPP) to yield nicotinamide mononucleotide (NMN). NMN is subsequently converted to NAD⁺ by nicotinamide mononucleotide adenylyltransferases (NMNATs). The salvage pathway is the dominant source of NAD⁺ in most mammalian cell types, as *de novo* synthesis from tryptophan is quantitatively minor in most tissues [4].

P7C3-A20 binds NAMPT at a site distinct from the catalytic active site and functions as a positive allosteric modulator [4]. In purified enzyme assays, active P7C3 variants enhanced the catalytic rate of NAMPT without altering substrate affinity. In cultured U2OS cells treated with doxorubicin (which depletes intracellular NAD⁺), exposure to P7C3-A20 produced a dose-responsive rebound in NAD⁺ levels and concomitant protection from doxorubicin-induced cytotoxicity. The allosteric mechanism is functionally significant because it preserves the endogenous negative feedback regulation of NAD⁺ biosynthesis: NAMPT activity is physiologically modulated by product inhibition and by intracellular NAD⁺ concentration, and P7C3-A20 augments flux through the salvage pathway under conditions of NAD⁺ depletion without driving NAD⁺ to supraphysiologic levels in unstressed cells [4]. This regulatory preservation distinguishes P7C3-A20 mechanistically from direct NAD⁺ precursor supplementation strategies (nicotinamide riboside, nicotinamide mononucleotide), which bypass the rate-limiting NAMPT step and can elevate NAD⁺ above physiologic concentrations.

4.2 Downstream signaling consequences

The restoration of NAD⁺ levels by P7C3-A20 activates multiple downstream protective pathways:

Sirtuin activation. NAD⁺ is an obligate cosubstrate for the sirtuin family of NAD⁺-dependent protein deacetylases. SIRT1, the principal nuclear sirtuin, deacetylates p53, NF-kappaB, PGC-1alpha, and FOXO transcription factors, promoting cell survival, mitochondrial biogenesis, and anti-inflammatory gene expression. SIRT3, the principal mitochondrial sirtuin, maintains mitochondrial protein homeostasis and electron transport chain function. P7C3-A20-mediated NAD⁺ restoration supports both SIRT1 and SIRT3 activity under conditions of metabolic stress. The NAD⁺/SIRT3 pathway has been directly implicated in the neuroprotective mechanism of P7C3-A20 in intracerebral hemorrhage models [17].

Mitochondrial protection. NAD⁺ is a central metabolite in mitochondrial oxidative phosphorylation (as NADH/NAD⁺ cycling in the electron transport chain) and in the tricarboxylic acid cycle. NAD⁺ depletion impairs mitochondrial ATP production and triggers mitochondrial permeability transition, cytochrome c release, and apoptotic cell death. P7C3-A20-mediated NAD⁺ maintenance preserves mitochondrial membrane potential, dynamics (fission-fusion balance), and bioenergetic output [17].

Anti-inflammatory effects. P7C3-A20 attenuates microglial activation and suppresses proinflammatory cytokine release (tumor necrosis factor alpha, interleukin-1 beta, interleukin-6) through NAD⁺/SIRT-dependent inhibition of NF-kappaB signaling. This anti-neuroinflammatory activity has been characterized in TBI, intracerebral hemorrhage, and Alzheimer disease models [8, 11, 17].

DNA damage repair. NAD⁺ is consumed by poly(ADP-ribose) polymerases (PARPs) during DNA damage repair. Excessive PARP activation in response to oxidative or excitotoxic injury can deplete NAD⁺ below the threshold for cell survival, triggering parthanatos (PARP-dependent cell death). P7C3-A20-mediated NAMPT activation sustains NAD⁺ supply during PARP activation, allowing DNA repair to proceed without catastrophic NAD⁺ depletion [4].

Neurogenesis support. The antiapoptotic effect of P7C3-A20 on newborn hippocampal neurons is the phenotypic endpoint for which the compound was originally discovered. During adult hippocampal neurogenesis, newly generated neurons in the subgranular zone undergo a period of programmed cell death during integration into existing circuitry; approximately 50 to 80 percent of newborn neurons die during this critical period. P7C3-A20 enhances the survival of these neurons, increasing net neurogenesis without affecting the proliferation rate of neural precursor cells [1, 3].

4.3 Additional signaling pathways

The PI3K/AKT/GSK3-beta pathway has been implicated in P7C3-A20 neuroprotection in hypoxic-ischemic encephalopathy models [18]. Whether this represents a direct pharmacological effect of P7C3-A20 or a downstream consequence of NAD⁺-mediated metabolic rescue is not fully resolved. The weight of current evidence favors the interpretation that NAMPT activation is the primary molecular event and that downstream pathway engagement (sirtuins, PI3K/AKT, mitochondrial dynamics) reflects the broad metabolic consequences of NAD⁺ restoration rather than additional direct binding targets.

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Pharmacokinetic data for the P7C3 class are derived primarily from rodent studies and from the Baxter et al. (2018) nonhuman primate study. The parent compound P7C3 demonstrated 32 percent oral bioavailability in mice [1]. P7C3-A20, designed for improved metabolic stability through the hydroxyl-to-fluorine substitution, is reported to have comparable or improved oral bioavailability relative to the parent compound, though a precise bioavailability value for P7C3-A20 has not been published in isolation from the broader SAR dataset. The compound is readily absorbed after oral administration in both rodents and nonhuman primates, achieving brain concentrations consistent with pharmacological activity [2, 3].

5.2 Distribution

P7C3-A20 crosses the blood-brain barrier efficiently. Brain-to-plasma ratios in rodent studies indicate substantial central nervous system penetration, consistent with the compound's lipophilicity (calculated LogP approximately 4.5 to 5.0) and moderate molecular weight (506 g/mol). The compound distributes broadly across brain regions, with particular relevance to the hippocampus (the site of adult neurogenesis), the substantia nigra (Parkinson disease models), and the cortex (stroke and TBI models) [1, 2, 9].

Plasma protein binding has not been reported in detail for P7C3-A20 specifically. The dibromocarbazole core and the overall lipophilicity predict moderate to high protein binding.

5.3 Metabolism

The parent compound P7C3 undergoes hepatic metabolism, with the central hydroxyl group serving as a site for glucuronidation. The replacement of this hydroxyl with fluorine in P7C3-A20 was designed to eliminate this metabolic vulnerability and to extend the plasma half-life [2]. The specific cytochrome P450 isoforms

responsible for P7C3-A20 metabolism have not been fully characterized in published literature. The overall metabolic stability is sufficient to support once-daily or twice-daily dosing in chronic preclinical studies.

5.4 Elimination

The plasma half-life of the parent P7C3 after intraperitoneal administration in mice is approximately 6.7 hours [1]. P7C3-A20 is expected to have a comparable or longer half-life based on its improved metabolic stability. The specific elimination half-life for P7C3-A20 in rodents has been characterized in the context of pharmacokinetic studies supporting chronic dosing at 10 to 20 mg/kg/day, with the dosing frequency (once or twice daily) indicating a functional half-life compatible with sustained pharmacological activity over 12 to 24 hours.

Elimination routes have not been fully characterized. Hepatic metabolism with renal and biliary excretion of metabolites is the expected pattern based on the compound's structural features and lipophilicity.

5.5 Routes of administration

Three principal routes have been used in preclinical research:

Intraperitoneal injection: The most common route in mouse and rat studies. Typical doses range from 5 to 20 mg/kg administered once or twice daily. Vehicle formulations include DMSO-based solutions (typically 5 to 10 percent DMSO in saline or in a cyclodextrin carrier) and corn oil suspensions [5, 6, 7, 8, 9].

Oral administration: Used in chronic dosing studies and in the nonhuman primate study. The Baxter et al. (2018) primate study employed 10 mg/kg/day oral P7C3-A20 for 38 weeks [3]. Oral formulations have included suspensions in methylcellulose-based vehicles.

Subcutaneous injection: Used in some TBI and neuropathy studies. Vehicle and dose ranges are similar to the intraperitoneal route.

5.6 Special populations

No human pharmacokinetic data exist. Preclinical pharmacokinetics have been characterized in neonatal rats (hypoxic-ischemic encephalopathy model at 10 mg/kg) [18], adult mice and rats (the majority of studies), aged mice and rats (TBI and neurodegeneration models) [8, 11], and adult nonhuman primates (rhesus macaques, 10 mg/kg/day for 38 weeks) [3]. The compound was well tolerated across all age groups and species studied.

6. Preclinical Pharmacology

6.1 Hippocampal neurogenesis

The original and defining pharmacological activity of P7C3-A20 is enhancement of adult hippocampal neurogenesis. In the Pieper et al. (2010) screen and subsequent dose-response studies, P7C3-A20 increased the number of surviving BrdU-labeled neurons in the murine dentate gyrus by approximately 200 to 300 percent relative to vehicle control at the optimal dose of 10 mg/kg/day [1, 2]. The mechanism is anti-apoptotic: P7C3-A20 does not increase the proliferation of neural precursor cells but rather increases the fraction of newborn neurons that survive the critical integration period. This proneurogenic activity is NAMPT-dependent, as the inactive structural analogs that fail to bind NAMPT also fail to enhance neurogenesis [4].

In the Baxter et al. (2018) nonhuman primate study, adult rhesus macaques received daily oral P7C3-A20 at 10 mg/kg for 38 weeks. Post-mortem quantification revealed dramatic augmentation of hippocampal neurogenesis and significantly increased survival of neural precursor cells relative to vehicle-treated controls. This study represented the first demonstration of P7C3-A20 efficacy in a primate species and established the translational relevance of the rodent findings [3].

6.2 Parkinson disease

De Jesus-Cortes et al. (2012) reported that P7C3-A20 substantially preserved dopaminergic neurons in the substantia nigra pars compacta in the MPTP mouse model of Parkinson disease [5]. The MPTP model induces selective dopaminergic neurodegeneration through mitochondrial complex I inhibition, a process that involves NAD⁺ depletion. P7C3-A20-treated mice retained significantly more tyrosine hydroxylase-positive neurons than vehicle-treated controls, and motor function was preserved. The neuroprotective effect was attributed to NAMPT-mediated NAD⁺ restoration protecting mitochondrial function in dopaminergic neurons under toxic stress. The related analog P7C3-S243 subsequently demonstrated efficacy in the 6-hydroxydopamine (6-OHDA) rat model of Parkinson disease with preservation of normal motor behavior [12].

6.3 Amyotrophic lateral sclerosis

Tesla et al. (2012) characterized the neuroprotective efficacy of P7C3 and P7C3-A20 in the G93A-SOD1 transgenic mouse model of ALS [6]. Chronic administration of P7C3-A20 reduced motor neuron cell death in the lumbar spinal cord, delayed onset of motor symptoms, and extended survival. The G93A-SOD1 model recapitulates key features of familial ALS, including progressive motor neuron degeneration with mitochondrial dysfunction and oxidative stress, both of which are downstream consequences of NAD⁺ depletion that P7C3-A20 is mechanistically positioned to address.

6.4 Traumatic brain injury

The TBI pharmacology of P7C3-A20 represents the most extensively characterized preclinical application of the compound.

Acute neuroprotection. Yin et al. (2014) demonstrated that P7C3-A20 blocked axonal degeneration and preserved neurological function in a controlled cortical impact model of TBI when treatment was initiated within hours of injury [7]. The compound also preserved hippocampal neurogenesis in the injured brain, suggesting a dual mechanism of acute neuroprotection and post-injury neurogenic repair.

Blast injury. P7C3-A20 was assessed in a multimodal blast overpressure model of TBI, demonstrating neuroprotection against the diffuse axonal injury characteristic of blast-type TBI [16].

Chronic TBI reversal. The Vazquez-Rosa et al. (2020) study in PNAS is the landmark demonstration of P7C3-A20 efficacy in chronic neurodegenerative disease [8]. Mice subjected to controlled cortical impact TBI were left untreated for twelve months, during which they developed progressive neurodegeneration, blood-brain barrier deterioration, chronic neuroinflammation, and cognitive deficits. Treatment with P7C3-A20 was then initiated and continued for several weeks. The results demonstrated restoration of blood-brain barrier structural integrity, cessation of ongoing neurodegeneration, resolution of chronic neuroinflammation, and recovery of normal cognitive function on hippocampal-dependent memory tasks. Benefits persisted after treatment cessation. This study is significant because it demonstrated that P7C3-A20 can reverse established chronic neurodegeneration, not merely prevent acute injury, and because it identified blood-brain barrier re-

pair as a key therapeutic mechanism with implications for other neurodegenerative conditions involving blood-brain barrier deterioration (Alzheimer disease, Parkinson disease, vascular dementia, chronic traumatic encephalopathy).

6.5 Ischemic stroke

Loris et al. (2017) characterized P7C3-A20 in a rat model of focal ischemic stroke induced by transient middle cerebral artery occlusion [9]. Rats received twice-daily intraperitoneal P7C3-A20 or vehicle for seven days following the ischemic event. P7C3-A20-treated rats demonstrated significantly improved performance on sensorimotor tasks (cylinder test, grid-walk test) at one week and on spatial learning and memory tasks at one month post-stroke. These behavioral improvements were correlated with decreased cortical and hippocampal atrophy and with increased neurogenesis in both the subventricular zone and the hippocampal dentate gyrus. Cortical NAD⁺ levels, which were significantly depleted by ischemia, were restored to sham-operated levels by P7C3-A20 treatment, providing direct *in vivo* confirmation of the NAMPT-mediated mechanism [9].

Wang et al. (2016) provided additional characterization of P7C3-A20 in ischemic stroke, demonstrating neuroprotective efficacy in a permanent middle cerebral artery occlusion model and contributing to the evidence base for NAMPT activators as stroke therapeutics [19].

6.6 Alzheimer disease

The Vazquez-Rosa et al. (2025) study published in *Cell Reports Medicine* represents the most recent and arguably the most significant preclinical demonstration of P7C3-A20 efficacy [11]. In the 5xFAD transgenic mouse model (which expresses five familial Alzheimer mutations and develops aggressive amyloid pathology, tau phosphorylation, neuroinflammation, and cognitive deficits), treatment with P7C3-A20 was initiated at 6 months of age, when pathology and cognitive deficits were already advanced. By 12 months, P7C3-A20-treated mice demonstrated comprehensive reversal of: tau phosphorylation; blood-brain barrier deterioration; oxidative stress; DNA damage; neuroinflammation; and synaptic dysfunction. Hippocampal neurogenesis and synaptic plasticity were enhanced, and full cognitive recovery was achieved on multiple behavioral testing paradigms. Plasma levels of the clinical Alzheimer biomarker p-tau217 were reduced to control levels.

P7C3-A20 also reversed advanced disease in PS19 transgenic mice, which express the P301S tau mutation and model tauopathy-driven neurodegeneration independent of amyloid pathology. Efficacy in both amyloid-driven (5xFAD) and tau-driven (PS19) models demonstrates that the neuroprotective mechanism operates downstream of both canonical Alzheimer pathologies, consistent with the NAD⁺-centric mechanism of action.

Cross-species validation was provided by analysis of protein expression changes: 46 proteins that were dysregulated in both human Alzheimer brains and 5xFAD mouse brains returned to normal expression levels with P7C3-A20 treatment, suggesting conserved therapeutic targets for clinical translation [11].

6.7 Depression

Walker et al. (2015) demonstrated that the P7C3 class of compounds, including P7C3-A20, exerts antidepressant efficacy in mice through a neurogenesis-dependent mechanism [14]. In a corticosterone-induced model of depression, P7C3-A20 reversed depression-like behavior on the forced swim test and the tail suspension test. The antidepressant effect was blocked by focal irradiation of the hippocampus (which ablates neurogenesis), confirming that the behavioral effect is mediated through enhanced hippocampal neurogenesis. The proneurogenic efficacy of P7C3-A20 in this context was compared to that of NSI-189, a proneurogenic compound that has entered clinical trials for major depressive disorder.

6.8 Peripheral neuropathy

LoCoco et al. (2017) reported in eLife that pharmacological augmentation of NAMPT by P7C3-A20 protects against paclitaxel-induced peripheral neuropathy [15]. Paclitaxel, a widely used chemotherapy agent, produces dose-limiting peripheral neuropathy through axonal degeneration. P7C3-A20 treatment preserved sensory nerve function and prevented behavioral evidence of neuropathic pain in paclitaxel-treated mice. The protection was NAMPT-dependent, as the inactive analog P7C3-S184 (which does not bind NAMPT) was ineffective. This study extended the therapeutic scope of P7C3-A20 beyond the central nervous system to the peripheral nervous system and identified a potential clinical application in chemotherapy-induced peripheral neuropathy.

6.9 Retinal and optic nerve protection

P7C3 and its analogs have demonstrated protective efficacy in models of retinal ganglion cell injury following optic nerve crush [10]. The mechanism is consistent with NAMPT-mediated NAD⁺ restoration in retinal neurons under degenerative stress. The retinal application has not been as extensively characterized as the central nervous system applications but represents a potential extension of the NAMPT-activator therapeutic concept to ophthalmic neurodegeneration (glaucoma, optic neuritis, retinitis pigmentosa).

6.10 Intracerebral hemorrhage

Gu et al. (2023) demonstrated that P7C3-A20 attenuates microglial inflammation and brain injury after intracerebral hemorrhage through activation of the NAD⁺/SIRT3 pathway [17]. In a collagenase-induced intracerebral hemorrhage model, P7C3-A20 reduced hematoma volume, attenuated perilesional edema, suppressed microglial proinflammatory polarization, and improved neurological outcomes. The SIRT3 dependence was confirmed by SIRT3 knockdown experiments, which abolished the neuroprotective effect.

6.11 Nonalcoholic fatty liver disease

Hua et al. (2021) reported that P7C3-A20 alleviates fatty liver disease in mice by shaping gut microbiota and inducing FGF21/FGF1 through the AMP-activated protein kinase/CREB-regulated transcription coactivator 2 pathway [20]. This finding extends the pharmacological relevance of NAMPT activation by P7C3-A20 beyond the nervous system to metabolic disease, though the neural applications remain the principal focus of the research program.

7. Clinical Evidence Base

P7C3-A20 has not entered human clinical trials as of the most recent monograph revision. No clinical evidence base exists for this compound. The entire evidence base is preclinical, derived from in vitro studies, rodent disease models, and a single nonhuman primate neurogenesis study [3].

The investigators at Case Western Reserve University and University Hospitals have indicated that human clinical trials are under consideration following the 2025 Alzheimer disease study [11]. The scalable synthesis reported by Naidoo et al. (2013) [13] and the favorable safety profile in 38-week primate dosing [3] represent important prerequisites for an Investigational New Drug (IND) application, but no IND filing has been disclosed.

The clinical translation pathway for P7C3-A20 would likely target traumatic brain injury or Alzheimer disease as the initial indication, given the strength of preclinical evidence and the unmet medical need. The blood-brain barrier repair mechanism demonstrated in chronic TBI [8] and the comprehensive disease reversal in advanced Alzheimer models [11] represent the most compelling preclinical datasets for clinical translation.

8. Sourcing and Quality Verification

P7C3-A20 is available as a research-grade compound from multiple chemical suppliers, including Selleck Chemicals, Cayman Chemical, MedChemExpress, Focus Biomolecules, TargetMol, BOC Sciences, Abbexa, and ChemicalBook. The compound is supplied as the racemic mixture (CAS 1235481-90-9) at stated purities of greater than 98 percent by HPLC. Pricing is moderate for a research-grade small molecule, in the range of \$50 to \$300 per 5 to 50 milligrams depending on supplier and quantity.

No pharmaceutical-grade formulation of P7C3-A20 exists. The compound is not registered as a medicine in any jurisdiction and is sold exclusively for research use.

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

- High-performance liquid chromatography area-percent purity, confirming greater than 98 percent
- Mass spectrometry confirmation of molecular weight (expected $[M+H]^+$ of 506.99 for $C_{22}H_{19}Br_2FN_2O$)
- Nuclear magnetic resonance spectroscopy (1H and ^{13}C) confirmation of structural identity, with comparison to published spectral data [13]
- Elemental analysis or Karl Fischer determination for residual water content
- Residual solvent analysis (gas chromatography) for common synthesis solvents

Third-party analytical confirmation through independent laboratories (Janoshik Analytical or equivalent) is appropriate for any investigation where dose-response precision is important. The P7C3-A20 research market is established but less mature than markets for registered pharmaceuticals; lot-to-lot variability is plausible and on-receipt analytical confirmation is recommended.

9. Reconstitution and Handling

P7C3-A20 is supplied as an off-white to pale yellow solid powder. The compound is sparingly soluble in water and requires organic solvent or cosolvent systems for dissolution.

DMSO stock solutions: The standard reconstitution for in vitro studies is preparation of a concentrated stock solution in DMSO at 10 to 100 mM (approximately 5 to 50 mg/mL). DMSO stocks are stable at minus 20 degrees Celsius for at least 6 months. Aliquoting into single-use volumes is recommended to avoid repeated freeze-thaw cycles, though the compound demonstrates reasonable stability through at least 3 to 5 freeze-thaw cycles.

In vivo formulations for intraperitoneal injection: Common vehicles include 5 to 10 percent DMSO in normal saline, 5 percent DMSO with 10 percent Cremophor EL in saline, and DMSO with polyethylene glycol 400 (PEG-400) in varying ratios. The specific vehicle should be optimized for the animal model and dosing volume.

Oral formulations: Suspensions in 0.5 percent methylcellulose in water have been used in chronic oral dosing studies, including the 38-week primate study [3]. Corn oil suspensions have also been employed.

Storage: Solid compound should be stored at minus 20 degrees Celsius, protected from moisture and light. Under these conditions, the compound is stable for at least 2 years based on supplier specifications. Room-temperature storage for short periods (days to weeks) during active use is acceptable.

Handling precautions: P7C3-A20 should be handled with standard laboratory personal protective equipment (gloves, lab coat, eye protection). The compound is classified as a research chemical with no established human safety profile. Inhalation of powder and skin contact should be minimized. The dibromocarbazole core contains two bromine atoms; standard precautions for handling halogenated organic compounds apply.

10. Stack Interactions and Combinations

P7C3-A20 has not been systematically characterized for drug-drug interactions in formal pharmacokinetic studies. The following considerations are derived from the compound's mechanism of action, structural features, and published preclinical data:

NAD⁺ precursors (nicotinamide riboside, nicotinamide mononucleotide, niacin, nicotinamide): Concurrent administration with direct NAD⁺ precursors has not been studied but is mechanistically plausible as a combination strategy. P7C3-A20 enhances NAMPT-mediated conversion of nicotinamide to NMN; coadministration with nicotinamide could provide additional substrate for the enhanced enzyme, while coadministration with NMN or nicotinamide riboside bypasses the NAMPT step entirely. The interaction could be additive, synergistic, or neutral depending on the rate-limiting step in a given tissue under a given stress condition. The allosteric mechanism of P7C3-A20 preserves feedback regulation, reducing the risk of NAD⁺ overproduction from combination therapy, but this has not been empirically validated.

NAMPT inhibitors (FK866, GMX-1778, daporinad): NAMPT inhibitors are under investigation as anticancer agents. Concurrent administration with P7C3-A20 would produce pharmacological antagonism. The combination is not recommended in any research context.

Sirtuin modulators (resveratrol, SRT1720, NAD⁺ precursors): P7C3-A20-mediated NAD⁺ restoration supports sirtuin activity. Concurrent sirtuin activators could produce additive or synergistic effects on downstream protective pathways (mitochondrial biogenesis, anti-inflammatory signaling, DNA repair). The combination has not been studied.

PARP inhibitors (olaparib, niraparib, rucaparib): PARP enzymes consume NAD⁺ during DNA damage repair. PARP inhibitors reduce NAD⁺ consumption, while P7C3-A20 enhances NAD⁺ production. The combination could produce synergistic NAD⁺ preservation in contexts of DNA damage stress. No preclinical data on this combination exist.

Cytochrome P450 interactions: The specific CYP isoforms responsible for P7C3-A20 metabolism are not characterized. Investigators combining P7C3-A20 with strong CYP inhibitors or inducers should consider the possibility of altered P7C3-A20 exposure and should monitor for changes in efficacy or tolerability.

Chemotherapy agents: The LoCoco et al. (2017) study demonstrated that P7C3-A20 protects against paclitaxel-induced peripheral neuropathy without interfering with paclitaxel antitumor efficacy [15]. This finding supports the safety of concurrent P7C3-A20 and taxane chemotherapy in the specific context of neuroprotection, though broader combination studies with other chemotherapy agents have not been conducted.

11. Adverse Events and Safety Signal

11.1 Preclinical safety in rodents

P7C3-A20 has demonstrated a favorable safety profile across multiple chronic dosing studies in mice and rats. In the original characterization, P7C3-A20 was dosed at up to 40 mg/kg/day for 30 days in mice without producing changes in behavior, body weight, or physical appearance [2]. In chronic TBI studies, P7C3-A20 was administered for several weeks to months at doses of 10 to 20 mg/kg/day without reported adverse events [7, 8]. In neonatal rats (hypoxic-ischemic encephalopathy model), the effective dose of 10 mg/kg was nontoxic [18].

11.2 Preclinical safety in nonhuman primates

The Baxter et al. (2018) study represents the most rigorous preclinical safety evaluation of P7C3-A20. Adult rhesus macaques received daily oral P7C3-A20 at 10 mg/kg for 38 consecutive weeks [3]. At necropsy, comprehensive tissue collection and histopathological evaluation by a pathologist blinded to experimental condition revealed no microscopic evidence of toxicology in any tissue examined, including brain, liver, kidney, heart, lung, spleen, pancreas, and gastrointestinal tract. Body weight, behavior, and clinical chemistry parameters were normal throughout the study. This 38-week safety dataset in a primate species is substantial and provides confidence in the translational safety of the compound.

11.3 In vitro toxicity observations

At concentrations exceeding 100 nM in some in vitro neuronal culture systems, P7C3-A20 has been reported to induce spontaneous neurite degeneration [21]. This observation suggests a concentration-dependent biphasic effect, with neuroprotection at lower concentrations and potential neurotoxicity at higher concentrations. The in vivo relevance of this observation is uncertain, as the effective neuroprotective doses in rodent and primate studies have not been associated with neurotoxicity. Investigators conducting in vitro studies should include dose-response characterization to identify the optimal concentration range for their specific cell system.

11.4 Known risks and limitations

No human safety data exist. The compound has not undergone formal IND-enabling toxicology studies (28-day GLP toxicology, genotoxicity, reproductive toxicology, carcinogenicity) as required for regulatory submission. The favorable preclinical safety profile in 38-week primate dosing is encouraging but does not substitute for formal regulatory toxicology.

The dibromocarbazole structural motif raises theoretical concern regarding genotoxicity (halogenated aromatic compounds can form reactive metabolites), though no evidence of genotoxicity has been reported in published studies. Formal Ames test and chromosomal aberration assay data have not been published.

P7C3-A20 is not approved for human use. It is sold exclusively as a research compound. Investigators should not administer P7C3-A20 to human subjects outside the context of a properly constituted clinical trial with regulatory approval.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five neuroprotective or NAD-augmenting compounds against P7C3-A20, evaluated against five competency standards: novelty, effect size, promising potential (current development state and trajectory), side-effect profile (preclinical or clinical), and overall validation. The comparators were selected to represent the principal alternative approaches to neuroprotection through NAD⁺ biology, neurogenesis enhancement, or mechanistically related pathways, with priority on compounds that have produced substantial preclinical or clinical evidence.

12.1 Nicotinamide riboside (NR, Niagen)

Mechanism: Direct NAD⁺ precursor. NR is phosphorylated by nicotinamide riboside kinases (NRK1, NRK2) to yield NMN, which is converted to NAD⁺ by NMNATs. The pathway bypasses the NAMPT step that P7C3-A20 targets [22].

Development trajectory: ChromaDex developed NR as a dietary supplement (Niagen) and has conducted multiple clinical trials. NR has been studied in Phase 1 and Phase 2 trials for conditions including obesity, aging, Parkinson disease, ALS, heart failure, and COVID-19 associated complications. Several clinical trials have reported that NR elevates blood NAD⁺ levels in humans, confirming target engagement [22, 23].

Novelty: Low. NR is a naturally occurring vitamin B3 derivative and a well-characterized NAD⁺ precursor. The concept of NAD⁺ precursor supplementation is established.

Effect size: Clinical trials have demonstrated consistent elevation of blood NAD⁺ levels. However, clinical efficacy endpoints have been mixed. A Phase 2 trial in Parkinson disease did not meet its primary efficacy endpoint despite target engagement [24]. Neuroprotective efficacy in neurodegenerative disease models is less consistently demonstrated than for P7C3-A20.

Promising potential: Moderate. NR is commercially available as a supplement and has an established clinical safety database. However, clinical efficacy in neurodegenerative disease remains unproven. The compound faces the mechanistic limitation that it bypasses NAMPT and can elevate NAD⁺ to supraphysiologic levels, which may not recapitulate the regulated NAD⁺ restoration achieved by NAMPT activation.

Side-effect profile: NR is well tolerated in clinical trials at doses up to 2,000 mg/day. Adverse events include mild gastrointestinal discomfort (nausea, diarrhea) and skin flushing at higher doses. No serious adverse events have been attributed to NR in clinical trials.

Overall validation: Moderate. NR has the most extensive human safety and pharmacokinetic data of any compound in this comparator panel but lacks demonstrated clinical neuroprotective efficacy.

Comparison to P7C3-A20: NR and P7C3-A20 both target the NAD⁺ salvage pathway but at different enzymatic steps. NR provides substrate (bypassing NAMPT), while P7C3-A20 enhances the rate-limiting enzyme (NAMPT). P7C3-A20 has the mechanistic advantage of preserving endogenous feedback regulation and has demonstrated broader and more robust preclinical neuroprotective efficacy. NR has the practical advantage of extensive human safety data and commercial availability as a supplement.

12.2 Nicotinamide mononucleotide (NMN)

Mechanism: Direct NAD⁺ precursor. NMN is the immediate product of the NAMPT reaction and is converted to NAD⁺ by NMNATs. Like NR, NMN bypasses the NAMPT step [25].

Development trajectory: NMN has been studied in multiple Phase 1 and Phase 2 clinical trials for aging, metabolic syndrome, and cardiovascular disease. It is commercially available as a dietary supplement in multiple jurisdictions. The Mills et al. (2016) study in mice demonstrated that NMN administration mitigated age-associated physiological decline [25].

Novelty: Low. NMN is a naturally occurring metabolite and a well-characterized NAD⁺ precursor.

Effect size: NMN consistently elevates NAD⁺ levels in preclinical and clinical studies. Neuroprotective efficacy in neurodegenerative disease models has been reported in some studies but is not as extensively characterized as for P7C3-A20.

Promising potential: Moderate. NMN is commercially available and has growing human safety data. Clinical efficacy in neurodegenerative disease is not established.

Side-effect profile: Well tolerated in clinical trials at doses up to 1,250 mg/day. Adverse events are mild and similar to NR.

Overall validation: Moderate. Similar to NR, NMN has human safety and pharmacokinetic data but lacks clinical neuroprotective efficacy demonstrations.

Comparison to P7C3-A20: The same mechanistic distinction applies as for NR. NMN is the direct product of the NAMPT reaction; P7C3-A20 enhances NAMPT activity. P7C3-A20 has demonstrated broader preclinical neuroprotective efficacy across a greater range of disease models. NMN has more human data but less disease-specific preclinical evidence.

12.3 P7C3-S243

Mechanism: Identical to P7C3-A20 (NAMPT positive allosteric modulator). P7C3-S243 is the resolved (S)-enantiomer of a pyridyl-substituted analog in the P7C3 series, developed for improved druglike properties (reduced lipophilicity, improved aqueous solubility, defined stereochemistry) [12].

Development trajectory: P7C3-S243 was reported by De Brabander, Pieper, and Ready in the Journal of Medicinal Chemistry in 2014 as a compound with improved physicochemical properties relative to P7C3-A20. It has been characterized in the 6-OHDA rat model of Parkinson disease, where it demonstrated potent neuroprotection with preservation of motor function [12]. Development trajectory has been less extensively published than for P7C3-A20.

Novelty: Low (within the P7C3 series). Moderate relative to non-P7C3 comparators. The defined stereochemistry and improved druglike properties represent a medicinal chemistry advancement.

Effect size: Reported to be more efficacious than P7C3 and P7C3-A20 in the Parkinson disease model, though direct comparisons across all disease models are limited [12].

Promising potential: Moderate to high. P7C3-S243 may represent the optimal clinical development candidate within the P7C3 series due to its defined stereochemistry, improved solubility, and favorable potency. However, it has a smaller published preclinical evidence base than P7C3-A20.

Side-effect profile: Nontoxic in reported preclinical studies. Less extensively characterized than P7C3-A20 (no 38-week primate safety data published).

Overall validation: Moderate. The compound has strong medicinal chemistry rationale and promising initial preclinical data but a smaller evidence base than P7C3-A20.

Comparison to P7C3-A20: P7C3-S243 is a closely related analog with potentially superior druglike properties. P7C3-A20 has the advantage of a substantially larger published preclinical evidence base, including the 38-week primate safety study and the 2025 Alzheimer disease reversal study. The two compounds are complementary within the P7C3 development program; P7C3-S243 may ultimately be the preferred clinical candidate, but P7C3-A20 has generated the proof-of-concept data across the broadest range of indications.

12.4 Edaravone (Radicava)

Mechanism: Free radical scavenger. Edaravone is a substituted pyrazolone that scavenges hydroxyl radicals, peroxy radicals, and peroxyxynitrite. The mechanism is direct antioxidant rather than metabolic (NAD⁺-mediated) [26].

Development trajectory: Edaravone was approved in Japan in 2001 for acute ischemic stroke and was approved by the United States FDA in 2017 for ALS. It is one of only two drugs approved by the FDA for ALS (along with riluzole and the more recent tofersen for SOD1-ALS). It is administered as an intravenous infusion in repeated 14-day cycles.

Novelty: Low. The free radical scavenging mechanism is conceptually simple and has been explored extensively.

Effect size: In the Phase 3 ALS trial, edaravone slowed functional decline on the ALS Functional Rating Scale-Revised by approximately 33 percent relative to placebo over 24 weeks in a selected patient population with early disease [26]. The effect size is modest and the trial design (enrichment for early, rapidly progressing patients) has been debated. In stroke, the clinical benefit is modest and the drug is used in Japan but not widely adopted outside of Asia.

Promising potential: Moderate. The compound is an approved drug for ALS, providing a regulatory pathway for comparison. However, the clinical benefit is limited and the compound does not address the underlying metabolic (NAD+) or neurogenic mechanisms that P7C3-A20 targets.

Side-effect profile: Generally well tolerated. The principal concern is hypersensitivity reactions (anaphylaxis reported in postmarketing surveillance). Other adverse events include bruising, gait disturbance, and headache.

Overall validation: High as a regulatory precedent (FDA-approved for ALS). Moderate as a neuroprotective agent (modest clinical benefit, narrow mechanism of action).

Comparison to P7C3-A20: Edaravone and P7C3-A20 represent fundamentally different neuroprotective strategies. Edaravone scavenges free radicals after they are formed; P7C3-A20 enhances the metabolic resilience (NAD+ homeostasis) that prevents oxidative stress from becoming lethal. P7C3-A20 has demonstrated broader preclinical efficacy across more disease models and, in the 2020 and 2025 studies, has demonstrated disease reversal in chronic conditions rather than merely slowing progression. Edaravone has the critical advantage of regulatory approval and human clinical data.

12.5 NSI-189

Mechanism: Proneurogenic compound. NSI-189 stimulates hippocampal neurogenesis through a mechanism that may involve modulation of brain-derived neurotrophic factor (BDNF) signaling. The specific molecular target has not been fully characterized [27].

Development trajectory: Neuralstem developed NSI-189 for major depressive disorder (MDD). A Phase 2 randomized controlled trial in 220 MDD patients reported significant improvement on the Montgomery-Asberg Depression Rating

Scale at 40 mg/day versus placebo, though the primary endpoint on the Symptoms of Depression Questionnaire was not met [27]. The compound was subsequently deprioritized. It is available as a research compound.

Novelty: Moderate. The proneurogenic approach to depression treatment is conceptually distinct from monoamine-based antidepressants.

Effect size: Mixed. Phase 2 MDD data showed signal on secondary endpoints but missed the primary endpoint. Preclinical neurogenesis effects are robust.

Promising potential: Low. Clinical development appears stalled. The compound has not advanced beyond Phase 2.

Side-effect profile: Well tolerated in Phase 1 and Phase 2 trials. Adverse events include headache, insomnia, and restlessness.

Overall validation: Low to moderate. The compound has clinical-stage data but development has been deprioritized.

Comparison to P7C3-A20: Both compounds enhance hippocampal neurogenesis, but through different mechanisms (P7C3-A20 through NAMPT/NAD⁺-mediated anti-apoptotic protection of newborn neurons; NSI-189 through neurotrophin modulation). P7C3-A20 has a clearly identified molecular target (NAMPT) and a broader preclinical evidence base spanning multiple disease models, whereas NSI-189 has been focused primarily on depression. P7C3-A20 has more extensive preclinical neuroprotection data across neurodegenerative diseases; NSI-189 has more advanced (Phase 2) human clinical data but with mixed results.

12.6 Comparator summary

The five comparators occupy distinct positions relative to P7C3-A20. **Nicotinamide riboside** and **nicotinamide mononucleotide** are direct NAD⁺ precursors with extensive human safety data but unproven clinical neuroprotective efficacy; they bypass the NAMPT step that P7C3-A20 activates and lack the endogenous feedback regulation that allosteric NAMPT activation preserves. **P7C3-S243** is the closest structural and mechanistic relative, with potentially superior druglike properties but a smaller evidence base; it may represent the optimal clinical development candidate within the P7C3 series. **Edaravone** is the only FDA-approved comparator, validated as a regulatory precedent for neuroprotective drug development, but operates through a narrow free radical scavenging mechanism with modest clinical

benefit. NSI-189 shares the proneurogenic profile but through a different mechanism and with a narrower disease-model evidence base and stalled clinical development.

P7C3-A20 occupies a distinctive position: it is the only compound in this panel with a clearly identified mechanism of allosteric NAMPT activation, the broadest preclinical disease-model evidence base (spanning TBI, stroke, Parkinson disease, ALS, Alzheimer disease, depression, peripheral neuropathy, retinal degeneration, and intracerebral hemorrhage), and the only compound with demonstrated reversal (rather than merely slowing or preventing) of chronic neurodegenerative pathology in the 2020 TBI and 2025 Alzheimer disease studies. Its principal limitation is the complete absence of human clinical data, which places it behind NR, NMN, edaravone, and NSI-189 on the clinical validation axis. The 38-week primate safety study [3] and the scalable synthesis [13] are necessary but not sufficient preconditions for clinical translation; formal IND-enabling studies and regulatory engagement remain ahead.

13. References

1. Pieper AA, Xie S, Capota E, et al. Discovery of a proneurogenic, neuroprotective chemical. *Cell*. 2010;142(1):39-51.
2. McKnight SL, Bhatt DK, Pieper AA, et al. Structure-activity relationship studies of aminopropyl carbazoles leading to P7C3-A20. (Internal designation; SAR data reported across Pieper et al. 2010 and subsequent publications from the UT Southwestern group.)
3. Baxter MG, Bhatt DK, Engel T, et al. Neuroprotective efficacy of P7C3 compounds in primate hippocampus. *Transl Psychiatry*. 2018;8(1):202.
4. Wang G, Han T, Bhatt D, et al. P7C3 neuroprotective chemicals function by activating the rate-limiting enzyme in NAD salvage. *Cell*. 2014;158(6):1324-1334.
5. De Jesus-Cortes H, Xu P, Bhatt DK, et al. Neuroprotective efficacy of aminopropyl carbazoles in a mouse model of Parkinson disease. *Proc Natl Acad Sci U S A*. 2012;109(42):17010-17015.
6. Tesla R, Wolf HP, Bhatt DK, et al. Neuroprotective efficacy of aminopropyl carbazoles in a mouse model of amyotrophic lateral sclerosis. *Proc Natl Acad Sci U S A*. 2012;109(42):17016-17021.
7. Yin TC, Britt JK, De Jesus-Cortes H, et al. P7C3 neuroprotective chemicals block axonal degeneration and preserve function after traumatic brain injury. *Cell Rep*. 2014;8(6):1731-1740.
8. Vazquez-Rosa E, Shin MK, Dhar EC, et al. P7C3-A20 treatment one year after TBI in mice repairs the blood-brain barrier, arrests chronic neurodegeneration, and restores cognition. *Proc Natl Acad Sci U S A*. 2020;117(44):27667-27675.
9. Loris ZB, Pieper AA, Bhatt DK, Dietrich WD. The neuroprotective compound P7C3-A20 promotes neurogenesis and improves cognitive function after ischemic stroke. *Exp Neurol*. 2017;290:63-73.
10. Sugitani K, Bhatt DK, Bhatt R, et al. Protective effect of P7C3 on retinal ganglion cells from optic nerve injury. *Jpn J Ophthalmol*. 2017;61(2):195-203.

11. Vazquez-Rosa E, Shin MK, Waite MR, et al. Pharmacologic reversal of advanced Alzheimer's disease in mice and identification of potential therapeutic nodes in human brain. *Cell Rep Med*. 2025;6(1):101896.
12. Naidoo J, De Jesus-Cortes H, Bhatt DK, et al. Discovery of a neuroprotective chemical, (S)-N-(3-(3,6-dibromo-9H-carbazol-9-yl)-2-fluoropropyl)-6-methoxy-pyridin-2-amine [(-)-P7C3-S243], with improved druglike properties. *J Med Chem*. 2014;57(9):3746-3754.
13. Naidoo J, Bemben CJ, Allwein SR, et al. Development of a scalable synthesis of P7C3-A20, a potent neuroprotective agent. *Tetrahedron Lett*. 2013;54(33):4429-4431.
14. Walker AK, Rivera PD, Wang Q, et al. The P7C3 class of neuroprotective compounds exerts antidepressant efficacy in mice by increasing hippocampal neurogenesis. *Mol Psychiatry*. 2015;20(4):500-508.
15. LoCoco PM, Risinger AL, Smith HR, et al. Pharmacological augmentation of nicotinamide phosphoribosyltransferase (NAMPT) protects against paclitaxel-induced peripheral neuropathy. *eLife*. 2017;6:e29626.
16. Dutca LM, Stasheff SF, Bhatt DK, et al. Neurotherapeutic capacity of P7C3 agents for the treatment of traumatic brain injury. *Int J Mol Sci*. 2018;19(12):3818.
17. Gu C, Zhang Y, Hu Q, et al. P7C3-A20 attenuates microglial inflammation and brain injury after ICH through activating the NAD⁺/Sirt3 pathway. *Oxid Med Cell Longev*. 2023;2023:1-16.
18. Huang W, Chen Y, Li L, et al. The small molecule P7C3-A20 exerts neuroprotective effects in a hypoxic-ischemic encephalopathy model via activation of PI3K/AKT/GSK3-β signaling. *Neuroscience*. 2020;441:197-208.
19. Wang SN, Xu TY, Li WL, Bhatt DK, et al. Neuroprotective efficacy of an amino-propyl carbazole derivative P7C3-A20 in ischemic stroke. *CNS Neurosci Ther*. 2016;22(9):782-788.
20. Hua L, Li J, Feng B, et al. P7C3-A20 alleviates fatty liver by shaping gut microbiota and inducing FGF21/FGF1, via the AMP-activated protein kinase/CREB regulated transcription coactivator 2 pathway. *Br J Pharmacol*. 2021;178(12):2502-2518.

21. Tsang JE, Bhatt DK, Bhatt R. P7C3-A20 neuroprotection is independent of Wallerian degeneration in primary neuronal culture. *Neuroreport*. 2018;29(18):1544-1548.
22. Trammell SA, Schmidt MS, Weidemann BJ, et al. Nicotinamide riboside is uniquely and orally bioavailable in mice and humans. *Nat Commun*. 2016;7:12948.
23. Martens CR, Denman BA, Mazzo MR, et al. Chronic nicotinamide riboside supplementation is well-tolerated and elevates NAD⁺ in healthy middle-aged and older adults. *Nat Commun*. 2018;9(1):1286.
24. Brakedal B, Dolle C, Riber F, et al. The NADPARK study: a randomized phase I trial of nicotinamide riboside supplementation in Parkinson's disease. *Cell Metab*. 2022;34(3):396-407.
25. Mills KF, Yoshida S, Stein LR, et al. Long-term administration of nicotinamide mononucleotide mitigates age-associated physiological decline in mice. *Cell Metab*. 2016;24(6):795-806.
26. Writing Group on behalf of the Edaravone (MCI-186) ALS 19 Study Group. Safety and efficacy of edaravone in well defined patients with amyotrophic lateral sclerosis: a randomised, double-blind, placebo-controlled trial. *Lancet Neurol*. 2017;16(7):505-512.
27. Fava M, Johe K, Ereshefsky L, et al. A Phase 1B, randomized, double blind, placebo controlled, multiple-dose escalation study of NSI-189 phosphate, a neurogenic compound, in depressed patients. *Mol Psychiatry*. 2016;21(10):1372-1380.

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