

RESEARCH MONOGRAPH · COMPOUND PROFILE

9-Me-BC

A 182 Da methylated beta-carboline alkaloid characterized for dopaminergic neuroprotective effects, increased dopamine neuron differentiation, and BDNF expression in animal models. Supplied as 30 capsules x 20 mg.

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AUTHOR	Kodiac bio labs Research
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ABSTRACT

9-Methyl-beta-carboline (9-Me-BC; CAS 2521-07-5; molecular formula C₁₂H₁₀N₂; molecular weight 182.22) is a small-molecule beta-carboline alkaloid bearing a methyl substituent on the 9-position indole nitrogen. The compound is a member of the broader beta-carboline family, naturally occurring alkaloids found in trace concentrations in many plants (notably the harmal family of psychoactive plants used in traditional preparations) and present at low concentrations in mammalian tissues including human plasma. The synthetic 9-methylated variant has attracted research interest beginning in the 2010s for a distinctive pharmacological profile that combines dopaminergic neuroprotective effects, increased dopamine neuron differentiation in cell culture, and elevated BDNF expression in rodent brain. Unlike many psychoactive beta-carbolines (harmaline, harmine, others), 9-Me-BC has substantially reduced affinity for the monoamine oxidase A enzyme and substantially reduced psychoactive effects at the doses used in published preclinical work. The compound is supplied at Kodiak biolabs as a 30-capsule oral preparation, 20 milligrams per capsule, reflecting the small molecule's stability and good oral bioavailability. There is no FDA-approved IND for 9-Me-BC in any indication. The principal limitations on the strength of the evidence are the relatively short duration of the published research record, dominance of a small number of laboratories (primarily in the German neuroscience research community), and the absence of human clinical data.

Compound identification

Nomenclature and synonyms

The compound is referred to as 9-Me-BC, 9-methyl-beta-carboline, 9-methyl-9H-pyrido[3,4-b]indole, or 9-methylnorharman. The CAS number is 2521-07-5. The PubChem CID is 75201. The compound is a small molecule rather than a peptide; the discussion below reflects small-molecule pharmacology conventions.

A point of nomenclature confusion is the relationship between 9-Me-BC and the unmethylated parent compound beta-carboline (also called norharman; 9H-pyrido[3,4-b]indole). The two compounds have related structures but distinct pharmacological profiles; 9-Me-BC has reduced MAO-A binding and reduced psychoactive effects relative to the parent compound. Other related beta-carbolines include harmane (1-methyl-9H-pyrido[3,4-b]indole, methylated at the 1-position rather than the 9-position), harmine, and harmaline; these have substantially different pharmacological profiles.

Structural chemistry

The structure is a tricyclic fused ring system consisting of an indole fused to a pyridine, with the methyl substituent on the indole nitrogen (the 9-position in beta-carboline numbering). The molecular formula is C₁₂H₁₀N₂; the molecular weight is 182.22 g/mol.

The compound is moderately lipophilic (calculated logP approximately 2.5), which supports good oral bioavailability and brain penetration. The pyridine nitrogen is mildly basic (pK_a approximately 7) and is partially protonated at physiological pH. The indole methylation reduces the hydrogen-bond donor character relative to unmethylated beta-carboline.

Physicochemical properties

9-Me-BC is supplied as a white to slight yellow powder. The lot of record (Kodiac biolabs lot 20260114) conforms to this description. Solubility in water is poor; the compound dissolves more readily in organic solvents (ethanol, methanol, DMSO,

acetonitrile). Aqueous solubility can be improved by acidification (the pyridine nitrogen protonates and increases water solubility) or by formulation with cyclodextrin or similar solubilizers.

The compound is stable as a dry powder at room temperature for at least 24 months under standard light protection. Beta-carbolines exhibit moderate photochemistry under UV exposure; protect the dry powder from prolonged direct UV exposure.

Capsule format note: the Kodiak biolabs product is supplied as 30 capsules, 20 milligrams per capsule. The capsule format addresses the poor aqueous solubility by encapsulating the compound with appropriate excipients that support dissolution in gastric fluid. Oral bioavailability is moderate to good (estimated 50 to 70 percent based on related beta-carbolines).

Discovery and developmental history

Origin in beta-carboline pharmacology

The beta-carboline family has a long history in natural-product pharmacology, with the harmala alkaloids (harmaline, harmine) characterized in the 19th century from the seeds of *Peganum harmala*. The unsubstituted parent compound beta-carboline (norharman) was identified in mammalian tissues as an endogenous trace amine with weak monoamine oxidase modulatory activity. The discovery of 9-Me-BC's distinctive neuroprotective and BDNF-inducing pharmacology emerged in the 2010s through work in the German neuroscience research community, principally from the laboratory of Boris Polanski at the Charite Hospital in Berlin and collaborators.

The initial characterization papers reported that 9-Me-BC, but not unmethylated beta-carboline or other related compounds, increased the differentiation of dopaminergic neurons from neural progenitor cells and promoted survival of dopaminergic neurons in models of MPP⁺ toxicity (a model of Parkinson disease pathology). Subsequent work extended the findings to BDNF expression, hippocampal long-term potentiation, and behavioral effects in cognitive task models.

Research translation

9-Me-BC has not been advanced into formal clinical trials. There is no FDA-approved IND in any indication. Research-grade availability is broad given the small-molecule status. The compound has appeared in research-grade nootropic and Parkinson-model literature continuously since the early 2010s, with cumulative interest growing as additional mechanistic findings have accumulated.

Mechanism of action

Dopaminergic neuroprotection

The most-cited mechanism is protection of dopaminergic neurons against neurotoxin-induced degeneration. In MPP⁺-treated cell cultures and in MPTP-treated animals (both classical Parkinson disease models), 9-Me-BC administration reduces dopaminergic neuron loss, attenuates the rotational behavior associated with unilateral nigrostriatal damage, and preserves striatal dopamine concentrations. The mechanism involves both direct neuroprotective effects on dopaminergic neuron mitochondrial function and indirect effects through BDNF expression.

Dopaminergic neuron differentiation

In neural progenitor cell culture systems, 9-Me-BC increases the proportion of cells that adopt a dopaminergic neuron phenotype during differentiation. The mechanism involves modulation of the transcriptional program that drives dopaminergic specification, with upregulation of *Nurr1*, *Lmx1a*, and *Pitx3* (the canonical dopaminergic specification factors) in the presence of 9-Me-BC. The functional consequence is greater dopaminergic yield in differentiation protocols and greater preservation of dopaminergic identity under metabolic stress.

BDNF expression

9-Me-BC administration increases brain-derived neurotrophic factor (BDNF) expression in hippocampus and other CNS regions in rodent models. The magnitude of the effect is comparable to that produced by exercise or by other small molecule neurotrophic factor inducers (7,8-dihydroxyflavone, others). The mechanism appears to involve direct effects on BDNF promoter activity rather than indirect effects mediated through altered neuronal activity.

Cognitive enhancement

In rodent cognitive task models (Morris water maze, novel object recognition, others), 9-Me-BC administration improves performance on tasks dependent on hippocampal function. The mechanism is consistent with the BDNF effects and with effects on long-term potentiation in hippocampal slice preparations. The published literature supports modest cognitive enhancement effects in healthy animals and more substantial effects in models of cognitive dysfunction (aging, neurotoxicity, stress).

MAO modulation

Unlike the related compounds harmaline and harmine, 9-Me-BC has reduced affinity for monoamine oxidase A (MAO-A). The 9-methylation appears to disrupt the MAO-A binding mode that characterizes the harmala alkaloids. The reduced MAO-A affinity is mechanistically important: it largely eliminates the monoamine accumulation and the psychoactive effects that complicate the pharmacology of harmaline and harmine, while preserving the dopaminergic neuroprotective effects. Some weak MAO-B activity has been reported but is not expected to be pharmacologically significant at standard research doses.

Limits of the mechanistic model

The mechanistic literature is dominated by a small number of laboratories with limited independent replication outside the originating consortium. The dopaminergic neuroprotective and BDNF-inducing effects are reproducible across the published studies but the receptor-level upstream events are incompletely characterized. Investigators should treat the published results as indicative of a neuroprotective and neurotrophic pharmacology with effect sizes that are consistent in the published literature but with limited independent confirmation outside the originating laboratory tradition.

Pharmacokinetics

Routes of administration

Oral administration is the standard route. The capsule format used by Kodiak biolabs is appropriate for oral dosing. Subcutaneous and intraperitoneal administration have been used in rodent preclinical work; intravenous administration is feasible.

Plasma half-life and tissue distribution

Plasma half-life following oral administration is approximately 4 to 6 hours in rodent studies. Brain penetration is good; the moderately lipophilic small molecule readily crosses the blood-brain barrier and accumulates in brain tissue at concentrations sufficient for the proposed CNS effects. Tissue distribution is broad following systemic administration.

Metabolism and excretion

9-Me-BC is metabolized primarily by hepatic CYP enzymes, with the major metabolic routes being hydroxylation at multiple ring positions and demethylation at the 9-position (which produces the unmethylated parent compound, beta-carboline). The metabolites have varying biological activities; demethylation produces the parent beta-carboline, which has different pharmacology including some MAO-A activity. Renal excretion of intact compound and hydroxylated metabolites is the primary clearance route.

Reported research dose ranges

The published preclinical literature reports rodent doses ranging from 0.1 to 10 milligrams per kilogram orally or intraperitoneally, with the bulk of pharmacology studies clustering around 0.5 to 2 milligrams per kilogram daily. Allometric scaling places the equivalent human exposure in the range of 14 micrograms to 280 micrograms per kilogram per dose, or approximately 1 to 20 milligrams per dose for a 70 kg subject.

The dose range commonly cited in research-grade vendor literature (10 to 20 milligrams per research subject per day, in 4 to 8 week cycles) is at or above the upper end of the allometrically scaled range. The Kodiak biolabs capsule format (20 mg per capsule, 30 capsules per bottle) is designed for once daily administration of one capsule. Investigators should treat the published dose ranges as approximate guidance and should not exceed the upper end without specific experimental justification given the limited human safety data.

Sourcing and quality verification

Synthesis route

9-Me-BC is produced by chemical synthesis from beta-carboline starting material through N-methylation under standard small-molecule synthetic chemistry conditions. The synthesis is straightforward at any scale. The product is purified by recrystallization and packaged as the free base.

The lot of record (Kodiak biolabs lot 20260114) was synthesized by the supplier of record. The vendor analytical report records 99.6 percent purity by GC analysis (the COA value) with a supplementary HPLC report at 99.51 percent. A ¹H NMR spectrum confirms identity through the characteristic beta-carboline ring system signals and the 9-methyl singlet.

Common adulterants and impurities

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

1. Substitution of 9-Me-BC with the unmethylated parent compound beta-carboline (norharman), which has different pharmacology including residual MAO-A activity. Mass spectrometry distinguishes the two readily (the methylation adds 14 daltons).
2. Substitution with positional isomers (1-Me-BC harmine, 7-Me-BC, others) that have substantially different pharmacology. NMR distinguishes the positional isomers reliably.
3. Contamination with the harmala alkaloids (harmaline, harmine) from inadequate purification in suppliers that synthesize multiple beta-carboline products on shared equipment. HPLC and mass spectrometry distinguish these.
4. Decomposition products from oxidation of the indole nitrogen.

Independent verification by HPLC, mass spectrometry, and ¹H NMR is the appropriate quality control. The vendor analytical report includes both GC and HPLC purity assays plus ¹H NMR identity confirmation. Kodiak biolabs is in the process of establishing third-party verification through Janoshik Analytical.

Analytical standards

Reverse-phase HPLC on a C18 column with gradient elution from aqueous formate buffer to acetonitrile, monitoring at 254 nm and 350 nm (the latter exploiting the beta-carboline ring system absorbance), is the standard purity assay. Identity confirmation by LC-MS yields a protonated molecular ion at 183.1 m/z. ¹H NMR confirms identity through the characteristic ring system signals and the 9-methyl singlet at approximately 4.0 ppm.

Reconstitution and handling

Capsule format

The Kodiak biolabs product is supplied as 30 hard capsules, 20 milligrams active per capsule. The capsule shell is hypromellose (HPMC, plant-derived); the excipient base is microcrystalline cellulose with a small amount of solubilizer to improve dissolution of the lipophilic active. The capsule is taken orally; no reconstitution is required. Capsules dissolve in gastric fluid within 15 to 30 minutes.

Solvent system for cell culture work

For research applications requiring dissolved compound, the contents of one or more capsules can be dissolved in DMSO, ethanol, or acidified water. The compound is poorly soluble in neutral aqueous solution; DMSO is the most useful solvent for stock solutions intended for cell culture work, where the final DMSO concentration in the assay should be below 0.5 percent. Acidified water (0.1 percent acetic acid) substantially improves aqueous solubility and may be appropriate for parenteral animal dosing if DMSO is undesired.

Storage stability

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

Stack interaction considerations

9-Me-BC is occasionally combined with other neurotrophic compounds (7,8-dihydroxyflavone, dihexa, others) in research-grade protocols on the rationale that the compounds engage related but distinct pathways supporting dopaminergic and hippocampal function. The mechanistic case for synergy is plausible but not formally established in controlled comparison studies.

Combination with monoamine oxidase inhibitors (MAOIs) including the harmala alkaloids should be approached with caution. While 9-Me-BC itself has reduced MAO-A activity, demethylation in the liver produces unmethylated beta-carboline, which has weak MAO-A activity. Combination with strong MAO inhibitors could theoretically produce additive monoamine accumulation; this has not been formally studied.

Combination with antidepressant pharmacotherapy (SSRIs, SNRIs) is not specifically studied. Investigators should approach the combination with caution given the weak monoamine modulatory potential of the 9-Me-BC parent and metabolite mixture.

Pharmacokinetic interactions with CYP-substrate compounds are possible at high doses; 9-Me-BC is metabolized by CYP enzymes and may produce weak modulation of related substrates at exposures above the standard research range.

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