

RESEARCH ARTICLE

Synthesis of Psilocin, Psilocybin and 5-MeO-DMT Succinate, All Labelled With Carbon-14 at the Indole 2-Position

Rodney Brown¹ | Niall M. Hamilton¹  | Connor Mallon¹ | James Stevenson¹ | Michael T. Faley² | Robert B. Kargbo² | Alexander M. Sherwood² | Balasubramaniam Upeandran¹

¹Isotope Chemistry Laboratories, Almac Sciences Ltd., Almac House, Seagoe Industrial Estate, Craigavon, UK | ²Usona Institute, Madison, Wisconsin, USA

Correspondence: Niall M. Hamilton (niall.hamilton@almacgroup.com)

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ABSTRACT

Three novel ¹⁴C-labelled isotopologues of the psychoactive agents psilocin, psilocybin and 5-methoxy-*N,N*-dimethyltryptamine (5-MeO-DMT) were synthesised, all labelled at the 2-position of the indole. The syntheses involved incorporating the 3-dimethylaminoethyl substituent common to all three substances onto a 4- or 5-substituted indole intermediate via successive treatments with oxalyl chloride, dimethylamine and reduction with lithium aluminium hydride.

Psilocybin-2-¹⁴C with a specific activity of 234 µCi/mg exhibited limited stability, but a 5.5-fold radio dilution with unlabelled psilocybin afforded material that maintained a radiochemical purity exceeding 97.5% after 1-month storage at ≤ −70°C. The stability of 5-MeO-DMT-2-¹⁴C succinate salt with a specific activity of 173 µCi/mg was assessed over a more extended storage period, and after 6 months at ≤ −70°C the radiochemical purity was 98.0%, supporting its use in long-term studies.

The radiolabelled psilocybin-2-¹⁴C and 5-MeO-DMT-2-¹⁴C succinate represent new tools for in vivo pharmacokinetic and metabolic studies with psychedelic tryptamines. These novel derivatives may offer enhanced metabolic stability and facilitate more precise ADME and mass balance studies. Future research will explore their behaviour in biological systems to support necessary studies toward regulatory approval of both psilocybin and 5-MeO-DMT for treating mental health disorders such as depression, anxiety and post-traumatic stress disorder.

1 | Introduction

The structures and psychoactive nature of psilocin [1], psilocybin [2] and 5-methoxy-*N,N*-dimethyltryptamine (5-MeO-DMT) [3] have been known for decades. There is now increased interest in exploring the therapeutic potential of these molecules for treating a wide range of mental health disorders, and several review articles have recently been published describing their use for the treatment of depression [4–10], anxiety [11], post-traumatic stress disorder (PTSD) [12] and other mental health conditions [13–15]. There is also evidence that subperceptual doses of these molecules may be efficacious, avoiding the pronounced psychoactive effects seen at higher doses [16].

To support further preclinical development, we report herein the carbon-14-labelled synthesis of psilocin, psilocybin and 5-MeO-DMT, all with ¹⁴C incorporated at the 2-position of the indole (Figure 1). These novel isotopologues will be useful tools for assessing the in vivo ADME properties of the parent molecules and their metabolites, adding to previously published synthesis [17] and mass balance studies [18, 19] with radiolabelled psilocin. The previous eight-step synthesis of ¹⁴C-psilocin reported by Poon et al. [17] has the ¹⁴C-label located in the sidechain (Figure 2). The procedures herein provide the first examples of psychedelic tryptamines containing isotopic ¹⁴C-labelling within the indole core, and a shorter seven-step synthesis to psilocin-2-¹⁴C. These isotopologues may offer enhanced

Summary

The potent psychoactive agents psilocin, psilocybin and 5-MeO-DMT were synthesised, all labelled with ^{14}C at the 2-position of the indole. The syntheses involved building a 4- or 5-substituted indole intermediate and then incorporating the 3-dimethylaminoethyl substituent common to all three substances via successive treatments with oxalyl chloride, dimethylamine and reduction with lithium aluminium hydride. The parent compounds of these novel isotopologues are controlled/scheduled substances owing to their abuse potential, but more recently, the CNS effects of these compounds are being investigated as potential treatments for depression, anxiety and post-traumatic stress disorder.

metabolic stability and facilitate more precise ADME and mass balance analysis, as opposed to the potentially metabolically labile sidechain [20].

2 | Results and Discussion

Recent advancements in synthetic methods for psilocin, psilocybin, and 5-MeO-DMT have been reported [21–23]. To prepare 5-MeO-DMT-2- ^{14}C , the methods described by Sherwood et al. [21, 23] were used, and the synthetic route is shown in Scheme 1, part B.

The preparation of unlabelled compound (3) in a single step through the reaction of 2-bromomethyl-4-methoxy-1-nitrobenzene with potassium cyanide was initially trialled using unlabelled materials to evaluate feasibility before introducing radiolabelled starting material (Scheme 1, Part A). However, the desired product rapidly reacted with starting material to give the dimeric product α -(5-methoxy-2-nitrophenyl)-5-methoxy-2-nitrobenzenepropanenitrile. The isolated chemical yield of unlabelled compound (3) was only 25%, and varying the solvent, temperature and order of addition all gave similar reaction profiles, so an improved method was sought. It was envisaged that the widely utilised vicarious nucleophilic substitution reaction, pioneered by Makosza and Winiarski [24] for nitroarenes, could be employed to synthesise compound (3). First, 1-chloro-4-(chloromethoxy)benzene

(1) was reacted with potassium cyanide- ^{14}C to produce 2-(4-chlorophenoxy)acetonitrile-1- ^{14}C (2) in 60% radiochemical yield. Then, the cyanomethyl group from (2) was added to 4-nitroanisole by vicarious nucleophilic substitution in the presence of potassium *tert*-butoxide in dimethylformamide, affording 5-methoxy-2-nitrobenzeneacetonitrile-1- ^{14}C (3) in 76% radiochemical yield. The overall radiochemical yield of 46% for these initial two steps was better than the 25% chemical yield obtained from the unlabelled reaction of 2-bromomethyl-4-methoxy-1-nitrobenzene with potassium cyanide. The preparation of 5-methoxy-1H-indole-2- ^{14}C (4) was achieved through catalytic hydrogenation of 5-methoxy-2-nitrobenzeneacetonitrile-1- ^{14}C (3) over palladium on activated charcoal. 5-Methoxy-1H-indole-2- ^{14}C (4) was subsequently converted to its oxoacetyl chloride derivative using oxalyl chloride in MTBE. This reactive intermediate was then transformed into 5-methoxy-*N,N*-dimethyl- α -oxo-1H-indole-3-acetamide-2- ^{14}C (6) by reaction with dimethylamine. Reduction of the ketone and amide groups using lithium aluminium hydride produced 5-MeO-DMT-2- ^{14}C (7), which was purified by semi-preparative HPLC. Finally, the succinate salt (8) was prepared by the reaction of the free base with succinic acid in acetone, yielding a highly stable crystalline solid.

The stability of the succinate salt was confirmed through radiochemical purity assessments over an extended storage period. After 6 months of storage at $\leq -70^\circ\text{C}$, the radiochemical purity was 98.0%; this still met the specification of $\geq 98\%$ and supports its use in long-term studies.

The synthesis of the novel isotopologues psilocin-2- ^{14}C (14) and psilocybin-2- ^{14}C (17) followed a similar strategy and is shown in Scheme 2. Following the published works of Czeskis et al. [25], the vicarious nucleophilic substitution reaction of 1-(benzyloxy)-3-nitrophenol and subsequent hydrogenation provided 4-hydroxyindole-2- ^{14}C (10).

Subsequent acetylation produced the protected indole (11), which was then reacted with oxalyl chloride and dimethylamine to yield *N,N*-dimethyl- α -oxo-1H-indole-3-acetamide-2- ^{14}C (13). Reduction of the ketone and amide groups with lithium aluminium hydride occurred in 85% radiochemical yield and afforded psilocin-2- ^{14}C (14) with 100% chemical and 98.3% radiochemical purity. The methodology minimised side-product formation through careful control of reaction conditions, paralleling the approach used for 5-MeO-DMT.

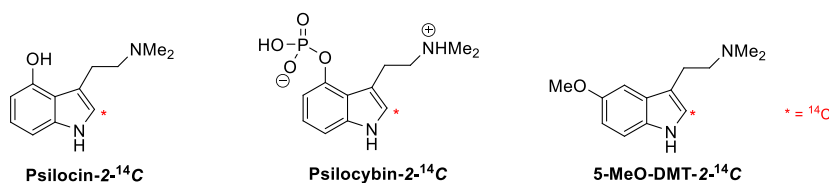


FIGURE 1 | Chemical structures of psilocin-2- ^{14}C , psilocybin-2- ^{14}C and 5-MeO-DMT-2- ^{14}C .

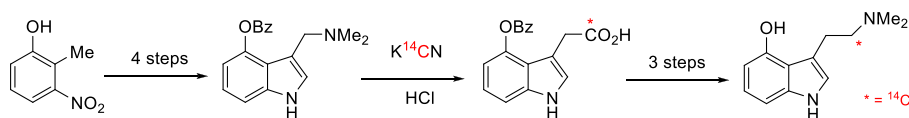
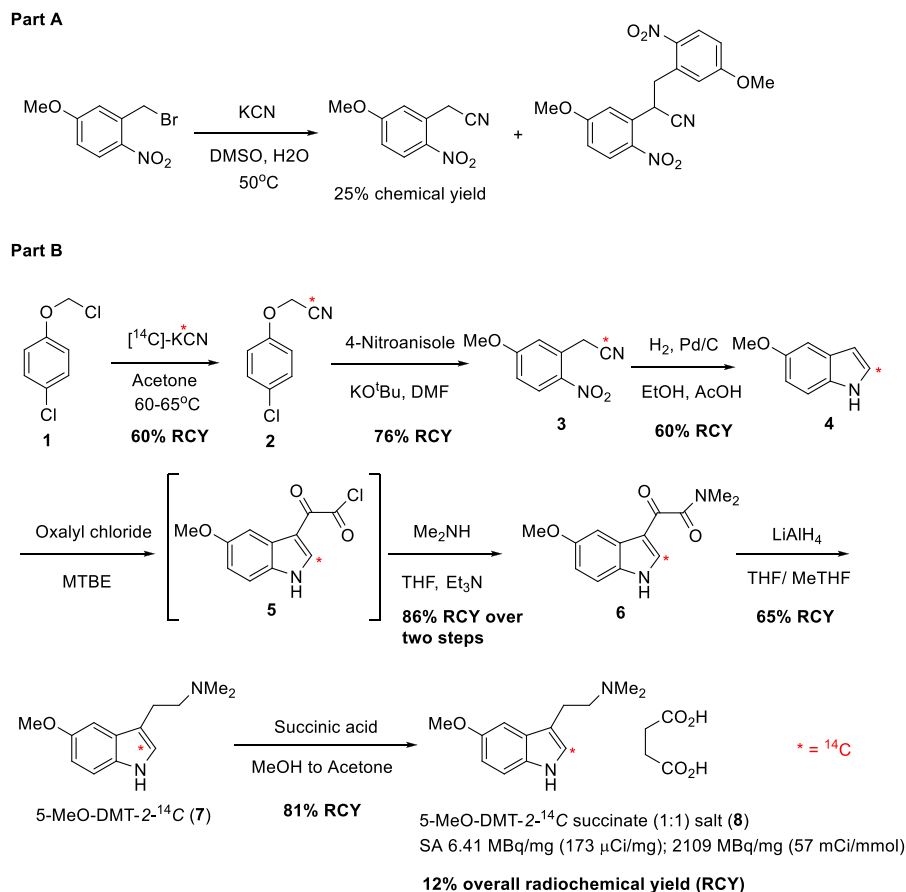


FIGURE 2 | Route to ^{14}C -psilocin reported by Poon et al. [17].



SCHEME 1 | Synthesis of 5-MeO-DMT-2- ^{14}C (7) and its succinate salt (8).

Conversion of psilocin-2- ^{14}C (14) to psilocybin-2- ^{14}C (17) required an additional phosphorylation step. Tetrabenzylpyrophosphate (TBPP) was used as the phosphorylating agent, and the reaction was facilitated by deprotonation of psilocin using *n*-BuLi in tetrahydrofuran. Similar to the synthetic approaches to psilocybin reported by Hofmann [26], Nichols and Frescas [27], Shirota et al. [28] and Sherwood et al. [21], the route proceeded through the benzyl-protected phosphate intermediate (15). Shirota first demonstrated that the neutral intermediate (15) tended to rearrange spontaneously to the corresponding zwitterionic isomer (16). Similarly, Sherwood employed this approach, first driving the benzyl rearrangement in methylene chloride and then isolating the poorly soluble zwitterion. In our hands, the rearrangement occurred during celite filtration in the reaction work-up. The zwitterionic product (16) was purified by silica-based chromatography, and subsequent deprotection via catalytic hydrogenation yielded psilocybin-2- ^{14}C (17).

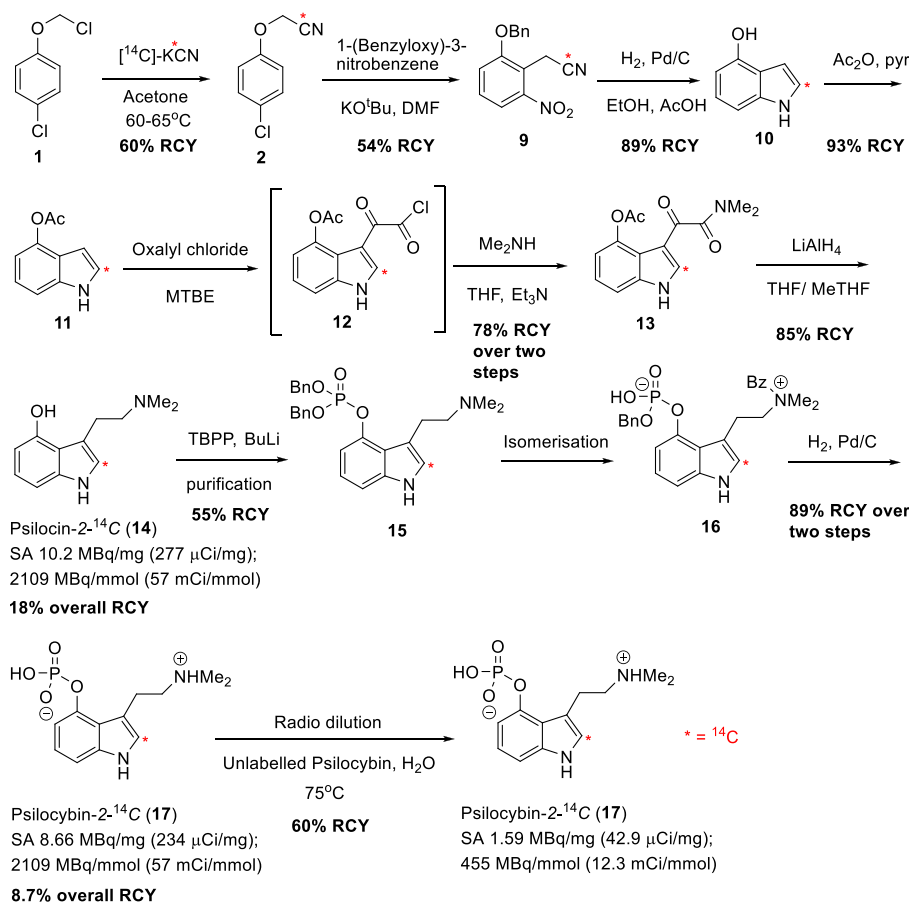
The psilocybin-2- ^{14}C (17) with a high specific activity (HSA) of 8.66 MBq/mg (234 $\mu\text{Ci}/\text{mg}$) demonstrated limited stability, showing approximately 10% degradation over 2 weeks, necessitating radio dilution with unlabelled psilocybin to improve storage properties. Fortunately, a combined recrystallisation and 5.5-fold radio dilution afforded psilocybin-2- ^{14}C (17) with a specific activity of 1.59 MBq/mg (43 $\mu\text{Ci}/\text{mg}$), and this material maintained a radiochemical purity exceeding 97.5% after 1-month storage at $\leq -70^\circ\text{C}$, supporting its utility for ADME studies.

The radiolabelled compounds synthesised in this study offer new tools for in vivo pharmacokinetic and metabolic studies with psychedelic tryptamines. Future research will explore their behaviour in biological systems to support necessary studies in the path toward regulatory approval of both psilocybin and 5-MeO-DMT for treating mental health disorders.

3 | Experimental Procedures

3.1 | Materials and Methods

The custom synthesis of 5-MeO-DMT-2- ^{14}C (7), its succinate salt (8) psilocin-2- ^{14}C (14) and psilocybin-2- ^{14}C (17), along with all associated radioactive experiments were carried out in the Isotope Chemistry Laboratories at Almac Sciences in specially designed fume hoods dedicated to carbon-14 only. Reactions were performed under an inert atmosphere using filtered nitrogen gas unless specified differently. Chemical reagents and solvents in the synthetic procedures were obtained from various chemical suppliers and used without further purification. Potassium [^{14}C]-cyanide was purchased from a commercial supplier with molar activity 2109 MBq/mmol (57 mCi/mmol). High-purity HPLC solvents were used. Intermediates and synthesised products were characterised based on proton-NMR spectra and recorded on a Bruker Avance Neo spectrometer with Prodigy BBO cryoprobe operating at 500 MHz. Chemical shifts were recorded in ppm (δ) from an internal tetramethylsilane



SCHEME 2 | Synthesis of psilocin-2-¹⁴C (14) and psilocybin-2-¹⁴C (17).

standard in either $\text{d}_6\text{-DMSO}$ or CDCl_3 and coupling constants (J) are reported in Hertz. The NMR peak patterns are reported as broad (br), singlets (s), doublets (d), triplets (t), quartets (q), septets (sep) and multiplets (m). Prepacked silica cartridges were used for flash column chromatography. TLC plates (pre-coated glass plates with silica gel 60F₂₅₄, 0.25-mm thickness) were used to monitor reactions and developed using the Cyclone Storage Phosphor System. Final products were dried on a high vacuum manifold. The radiochemical yield was determined by liquid scintillation counting using the Perkin-Elmer Tricarb 2900 Scintillation Analyzer. The purity of 5-MeO-DMT-2-¹⁴C succinate (**8**) was analysed using an Agilent 1100 HPLC system with UV and radiochemical detection; an X-Bridge Phenyl analytical HPLC column 4.6×250 mm, 5 μm . $T=58^\circ\text{C}$; eluents, Mobile Phase A, Phosphate Buffer pH6, Mobile Phase B, Methanol, gradient, 5% B to 80% B from 0 to 18.75 min; flow rate, 1.5 mL/min; injection volume 10 μL ; monitored at 225-nm wavelength. HPLC analyses are described as area%. The purity of psilocin-2-¹⁴C (**14**) and psilocybin-2-¹⁴C (**17**) was analysed using an Agilent 1100 HPLC system with UV and radiochemical detection using an Elysia Raytest Ramona Star HPLC radio-detector; a Waters Atlantis T3 analytical HPLC column, 4.6×150 mm, 3 μm . $T=30^\circ\text{C}$; eluents, Mobile Phase A, 0.1% TFA in water, Mobile Phase B, 0.1% TFA in acetonitrile, gradient, 5% B from 0 to 5 min, 5% B to 20% B from 5 to 15 min, 20% B to 90% B from 15 to 25 min; flow rate, 1 mL/min; injection volume 10 μL ; monitored at 220-nm wavelength. HPLC analyses are described as area%.

3.2 | Synthesis of 2-(4-Chlorophenoxy)acetonitrile-1-¹⁴C (2) [25]

To potassium [¹⁴C]-cyanide (500 mg, 7.45 mmol, 15,725 MBq, 425 mCi) was added a solution of 1-chloro-4-(chloromethoxy)benzene (1.30 g, 7.34 mmol) in acetone (10 mL, 20 vol). The reaction mixture was stirred and heated at reflux for 4 h. The reaction mixture was evaporated to an oil and transferred to a separating funnel using 5% sodium bicarbonate solution (2×15 mL) and diethyl ether (2×15 mL). The product was extracted using diethyl ether (5×50 mL). The organic layer was dried over anhydrous magnesium sulphate, filtered and evaporated to a thin oil. The oil was chromatographed on silica gel, and the product eluted using a gradient of heptane and ethyl acetate. Combined fractions were analysed by radio-HPLC, indicating 95% chemical purity and 99% radiochemical purity. The solution was counted and contained 9435 MBq (255 mCi), a radiochemical yield of 60%. The solution was concentrated on a rotary evaporator to give 2-(4-chlorophenoxy)acetonitrile-1-¹⁴C (**2**). ¹H NMR ($\text{d}_6\text{-DMSO}$, 500 MHz): δ 5.13 (2H, s), 7.12 (2H, AA'BB', m), 7.40 (2H, AA'BB', m).

3.3 | Synthesis of 5-Methoxy-2-nitrobenzeneacetonitrile-1-¹⁴C (3)

Potassium *tert*-butoxide (0.83 g, 7.41 mmol, 2.21 eq) was dissolved in DMF (12 mL, 20 vol) and cooled to -45°C .

2-(4-Chlorophenoxy)acetonitrile- $1\text{-}^{14}\text{C}$ (0.59 g, 6290 MBq, 170 mCi, 3.36 mmol, 1 eq) and 4-nitroanisole (0.58 g, 3.77 mmol, 1.1 eq) were dissolved in DMF (3 mL, 6 vol) and added dropwise to the cooled potassium *tert*-butoxide solution. Immediately, a purple solution formed. The reaction mixture was stirred for 15 min and analysis by radio-HPLC indicated reaction completion. The reaction was quenched by transferring the reaction mixture to a 500-mL conical flask containing ice (100 mL) and HCl (1 M, 10 mL). Upon addition, the dark purple reaction mixture became orange/yellow. The reaction flask was rinsed with ethyl acetate, and this was added to the ice/HCl mixture. The ice was allowed to melt, and the reaction mixture was extracted using ethyl acetate (4 $\times$ 75 mL). The organic layer was dried over anhydrous magnesium sulphate and evaporated to an orange oil. The oil was dissolved in ethyl acetate (50 mL) and washed with water (4 $\times$ 50 mL) and saturated brine solution (1 $\times$ 50 mL) to remove any residual DMF. The organic layer was evaporated to an orange oil. The oil was chromatographed on silica gel, and the product eluted using a gradient of heptane and ethyl acetate. Combined fractions were analysed by radio-HPLC, indicating 99% chemical and radiochemical purity. The solution was counted and contained 4810 MBq (130 mCi), a radiochemical yield of 76%. The solution was concentrated on a rotary evaporator to give 5-methoxy-2-nitrobenzeneacetonitrile- $1\text{-}^{14}\text{C}$ (**3**), with specific activity 10.9 MBq/mg (294 $\mu\text{Ci/mg}$) and molar activity 2109 MBq/mmol (57 mCi/mmol). For the nonradioactive compound (prepared in model experiment): ^1H NMR (d_6 -DMSO, 500 MHz): δ 3.92 (3H, s, CH_3O), 4.33 (2H, s, CH_2CN), 7.17 (1H, dd, J = 9.16 Hz, 2.84 Hz), 7.25 (1H, d, J = 2.8 Hz), 8.23 (1H, d, J = 9.2 Hz).

3.4 | Synthesis of 5-Methoxy-1H-indole-2- ^{14}C (**4**) [29]

A mixture of ethanol (35 mL), ethyl acetate (9.5 mL) and acetic acid (5.5 mL) was used to dissolve 5-methoxy-2-nitrobenzeneacetonitrile- $1\text{-}^{14}\text{C}$ (**3**) (0.61 g, 6660 MBq, 180 mCi, 3.15 mmol), while stirring under a nitrogen atmosphere. Palladium on activated charcoal (10% wt, 139 mg) was added, and the flask was evacuated and refilled with hydrogen gas three times. The mixture was stirred at ambient temperature overnight and analysed by HPLC, which showed reaction completion. Ethyl acetate (25 mL) was added to the reaction mixture, and the solution was filtered through celite, and the pad was washed with ethyl acetate. The filtrate was reduced to approximately 5 mL before charging to a 100-g silica cartridge and eluting with ethyl acetate to remove any residual palladium. The solvent was evaporated to afford a green oil, which was chromatographed on silica gel using a gradient of heptane and ethyl acetate. Combined fractions were analysed by radio-HPLC, indicating 94% chemical and 93% radiochemical purity. The solution was counted and contained 3996 MBq (108 mCi), a radiochemical yield of 60%. The solution was concentrated on a rotary evaporator to give 5-methoxy-1H-indole-2- ^{14}C (**4**), with specific activity 14.2 MBq/mg (383 $\mu\text{Ci/mg}$) and molar activity 2109 MBq/mmol (57 mCi/mmol). ^1H NMR (CDCl_3 , 500 MHz): δ 3.78 (3H, s, CH_3O), 6.41 (1H, m), 6.79 (1H, dd, J = 8.77 Hz, 2.41 Hz), 7.04 (1H, d, J = 2.41 Hz), 7.10 (1H, t, J = 2.71 Hz), 7.20 (1H, d, J = 8.77 Hz), 7.97 (1H, br s, NH).

3.5 | Synthesis of 5-Methoxy-*N,N*-dimethyl- α -oxo-1H-indole-3-acetamide-2- ^{14}C (**6**)

A mixture of TBME:THF (0.5 mL, 2.5 vol, 85:15 v/v) and oxalyl chloride (108 mg, 0.85 mmol, 1.4 equiv) was heated to 40°C. To this solution was added dropwise a solution of 5-methoxy-1H-indole-2- ^{14}C (**4**) (2701 MBq, 73 mCi, 191 mg, 1.29 mmol, 1 equiv) in TBME:THF (1 mL, 5 vol, 85:15 v/v). A bright orange precipitate was observed. The reaction mixture was stirred for 20 min before analysis by radio-HPLC showed the absence of starting material and formation of 2-(5-methoxy-1H-indol-3-yl-2- ^{14}C)-2-oxoacetyl chloride (**5**). The reaction mixture was cooled in an ice bath for 15 min, before dimethylamine (2 M in THF, 2.8 mL, 4.25 equiv, 5.46 mmol) was slowly added, leading to evolution of HCl gas. A very thick beige suspension formed, so more TBME:THF (1 mL, 85:15 v/v) was added to aid stirring. The suspension was allowed to warm to ambient temperature and stirred for 1 h. The slurry was filtered through a sintered funnel, and the solid washed with TBME:THF (2 $\times$ 2 mL, 85:15 v/v), then with heptane (3 $\times$ 2 mL). The solid was dissolved in acetone and evaporated to give a beige solid, which was then slurried in water (25 mL) for 2 h. The slurry was filtered through a sintered funnel and the solid washed with water (2 $\times$ 5 mL). The solid was redissolved in acetone. The total radioactivity was determined and the solution contained 2331 MBq (63 mCi), an 86% radiochemical yield. The solution was analysed by radio-HPLC, which indicated 95% chemical and radiochemical purity. The solution was evaporated to afford a solid and azeotropically dried twice with toluene to give 5-methoxy-*N,N*-dimethyl- α -oxo-1H-indole-3-acetamide-2- ^{14}C (**6**), with specific activity 8.5 MBq/mg (230 $\mu\text{Ci/mg}$) and molar activity 2109 MBq/mmol (57 mCi/mmol). For the nonradioactive compound (prepared in model experiment): ^1H NMR (d_6 -DMSO, 500 MHz): δ 2.91 (3H, s), 2.98 (3H, s), 3.80 (3H, s, CH_3O), 6.90 (1H, dd, J = 8.83 Hz, 2.61 Hz), 7.43 (1H, d, J = 8.81 Hz), 7.59 (1H, d, J = 2.3 Hz), 8.01 (1H, s), 12.3 (1H, br s, NH).

3.6 | Synthesis of 5-MeO-DMT-2- ^{14}C (**7**)

5-Methoxy-*N,N*-dimethyl- α -oxo-1H-indole-3-acetamide-2- ^{14}C (**6**) (2331 MBq, 63 mCi, 1.12 mmol, 275 mg) was slurried in 2-MeTHF (3 mL, 11 vol) by stirring in an ice bath for 10 min. Lithium aluminium hydride (2.3 M in 2-MeTHF, 2.1 mL, 4.25 equiv) was charged dropwise. A deep purple solution formed. The solution was allowed to stir at ambient temperature for 15 min and then stirred at 85°C for 1 h. A green suspension progressively formed. The reaction mixture was analysed by radio-HPLC, which indicated 95% conversion. The reaction mixture was cooled in an ice bath for 15 min, then THF:water (2.4 mL, 8.8 vol, 70:30 v/v) was added, which led to the evolution of a white gas. A very thick white slurry formed, which was thinned with more THF (3 mL). A grey suspension was observed, which was stirred overnight. The suspension was filtered through a sintered funnel, and the solid was washed with THF (3 mL, 11 vol). The filtrate was evaporated to an orange oil and chromatographed on silica gel using a gradient of ethyl acetate +1% triethylamine and methanol +1% triethylamine to elute the product. Combined fractions were analysed by radio-HPLC, indicating 96.7% chemical and 96.5% radiochemical purity. One impurity remained, amounting to 2.7%, which could not be removed using normal phase silica chromatography. The product was further purified

by preparative HPLC purification and afforded the product with 99.9% chemical purity and 99.4% radiochemical purity. The methanol was evaporated on a rotary evaporator, and the remaining aqueous solution was basified using 25% NaOH until pH 14 was reached. The product was extracted into MTBE. The total radioactivity was determined, and the solution contained 1517 MBq (41 mCi), a 65% radiochemical yield. The MTBE solution was evaporated to an oil to give 5-MeO-DMT-2-¹⁴C (**7**), with specific activity 9.6 MBq/mg (259 μ Ci/mg) and molar activity 2109 MBq/mmol (57 mCi/mmol). ¹H NMR (CDCl₃, 500 MHz): δ = 2.35 (6H, s), 2.63 (2H, m), 2.91 (2H, m), 3.87 (3H, s, CH₃O), 6.85 (1H, dd, J = 8.77 Hz, 2.42 Hz), 6.99 (1H, d, J = 2.14 Hz), 7.05 (1H, d, J = 2.43 Hz), 7.24 (1H, d, J = 8.82 Hz), 7.92 (1H, br s, NH).

3.7 | Synthesis of 5-MeO-DMT-2-¹⁴C Succinate (1:1) Salt (**8**), [5-Methoxy-N,N-Dimethyl-1H-indole-3-ethanamine-2-¹⁴C Butanedioic Acid (1:1) Salt]

5-MeO-DMT-2-¹⁴C (**7**) (1443 MBq, 39 mCi, 150 mg, 1 equiv, 0.68 mmol) was dissolved in methanol (4.5 mL, 30 vol) with stirring under nitrogen. To the solution was added succinic acid (83 mg, 0.71 mmol, 1.05 equiv) and the mixture stirred overnight. The solution was evaporated to dryness, and acetone was added and removed in 3-mL portions using a rotary evaporator until a white solid was observed. The solid was slurried in acetone for 1 h in an ice bath and filtered through a porosity 3-sintered funnel. The solid was washed with ice-cold acetone (3 $\times$ 1 mL) and dried under high vacuum to give 5-MeO-DMT-2-¹⁴C succinate (1:1) salt (**8**) (1166 MBq, 31.5 mCi, 182 mg, 6.41 MBq/mg, 173.3 μ Ci/mg, 2109 MBq/mmol, 57 mCi/mmol, 81% radiochemical yield). The solid was analysed by radio-HPLC which indicated a radiochemical purity of 99.7% and a chemical purity of 99.9%. ¹H NMR (MeOD, 500 MHz): δ 2.52 (4H, s, succinic acid), 2.85 (6H, s), 3.14 (2H, t, J = 7.49 Hz), 3.32 (2H, t, J = 7.49 Hz), 3.84 (3H, s, CH₃O), 6.79 (1H, dd, J = 8.84 Hz, 2.39 Hz), 7.07 (1H, d, J = 2.34 Hz), 7.15 (1H, s), 7.25 (1H, d, J = 8.77 Hz).

3.8 | Synthesis of 2-Nitro-6-(phenylmethoxy)-benzeneacetonitrile-cyano-¹⁴C (**9**) [25]

To a heat-dried flask under nitrogen was added potassium *tert*-butoxide (838 mg, 2.22 equiv, 7.47 mmol) and DMF (8.0 mL). The mixture was cooled to –30°C and stirred for 20 min. 2-(4-Chlorophenoxy)acetonitrile-1-¹⁴C (**2**) (7067 MBq, 191 mCi, 570 mg, 1 equiv, 3.36 mmol) was then added under nitrogen. Separately, 1-(benzyloxy)-3-nitrobenzene (860 mg, 1.12 equiv, 3.75 mmol) was dissolved in DMF (4.0 mL), and this solution was then added to the reaction mixture, dropwise, over 10 min at –36°C. The reaction mixture was stirred for 45 min, during which the temperature increased to –16°C. The reaction mixture was analysed by radio-HPLC, which confirmed reaction completion. The reaction mixture was quenched by careful addition onto a mixture of ice (100 mL) and 1 M HCl (10 mL). Ethyl acetate (50 mL) was used to effect transfer to the ice mixture, which turned the purple solution yellow and released white fumes. The ice was allowed to melt, and the mixture extracted with ethyl acetate (3 $\times$ 50 mL). The combined organic layers were washed with brine (20 mL), dried with over anhydrous magnesium sulphate, filtered and the solvent was removed on a rotary evaporator.

Three similar batches totaling 15,947 MBq (431 mCi) were processed and then combined using ethyl acetate to give 13,505 MBq (365 mCi), an 85% radiochemical recovery. The solvent was removed on a rotary evaporator at 35°C to yield a yellow/brown oil. The crude product was chromatographed on a 12-g silica cartridge using heptane and ethyl acetate to elute. The total radioactivity of the combined fractions was counted and contained 8621 MBq (233 mCi), a 54% radiochemical yield. The solution was analysed by radio-HPLC, which indicated 96% chemical and radiochemical purity. The solvent was removed on a rotary evaporator to give 2-nitro-6-(phenylmethoxy)-benzeneacetonitrile-cyano-¹⁴C (**9**) with specific activity 7.8 MBq/mg (211 μ Ci/mg) and molar activity 2109 MBq/mmol (57 mCi/mmol). ¹H NMR (d₆-DMSO, 500 MHz): δ 4.00 (2H, s), 5.35 (2H, s), 7.30–7.47 (4H, m), 7.53 (2H, d, J = 7.4 Hz), 7.58–7.67 (2H, m).

3.9 | Synthesis of 1H-Indol-4-ol-2-¹⁴C (**10**) [25]

To 2-Nitro-6-(phenylmethoxy)-benzeneacetonitrile-cyano-¹⁴C (**9**) (7511 MBq, 203 mCi, 962 mg, 1.0 equiv, 3.56 mmol) was added ethanol (26 mL) and ethyl acetate (6.5 mL). The flask was then warmed to 45°C and acetic acid (4 mL, 15.3 eq) was added to the solution, which completely dissolved the solids. The reaction mixture was cooled to room temperature and flushed with nitrogen for 10 min before adding palladium (10% wt, 470 mg) on activated charcoal. The flask was then evacuated and purged with hydrogen five times before allowing the mixture to stir at room temperature under hydrogen for 16 h. Radio-HPLC confirmed the absence of starting material and presence of 1H-indol-4-ol-2-¹⁴C with 84% chemical purity and 85% radiochemical purity. The reaction mixture was then diluted with ethyl acetate (50 mL), filtered through celite and the cake washed with ethyl acetate (500 mL). The solvent was then removed from the brown filtrate on a rotary evaporator to give a brown oil, which was chromatographed on a 100-g silica cartridge using 10% ethyl acetate in dichloromethane to elute the product. Combined fractions were analysed by radio-HPLC, indicating 98% radiochemical purity. The total radioactivity was counted and the solution contained 6660 MBq (180 mCi), a radiochemical yield of 89%. The solution was concentrated on a rotary evaporator to give 1H-indol-4-ol-2-¹⁴C, (**10**) with specific activity 15.6 MBq/mg (422 μ Ci/mg) and molar activity 2109 MBq/mmol (57 mCi/mmol) as a pink oil, which crystallised on standing. For the nonradioactive compound (prepared in model experiment): ¹H NMR (d₆-DMSO, 500 MHz): δ 6.33 (1H, dd, J = 6.41 Hz, 2.02 Hz), 6.45 (1H, m), 6.81–6.85 (2H, m), 7.13 (1H, m), 10.9 (1H, br s).

3.10 | Synthesis of 1H-Indol-4-ol-2-¹⁴C, 4-Acetate (**11**)

To 1H-indol-4-ol-2-¹⁴C (**10**) (5180 MBq, 140 mCi, 332 mg, 1.0 equiv, 2.46 mmol) and *N,N*-dimethylpyridin-4-amine (30.1 mg, 0.1 equiv, 246 μ mol) was added DCM (5.00 mL). A black precipitate was noted. This mixture was stirred at 0°C under nitrogen for 10 min before the dropwise addition of acetic anhydride (377 mg, 349 μ L, 1.5 equiv, 3.69 mmol), which caused a milky appearance. The reaction mixture was stirred at 0°C for 15 min, and then warmed to room temperature and stirred for

an additional hour. During this time, the black solid dissolved and HPLC confirmed no starting material remained.

Two similar batches totaling 6660 MBq (180 mCi) were combined using DCM, and a 5% aqueous solution of NaHCO₃ (20 mL) was added and stirred for 30 min. The layers were separated, and the aqueous layer was extracted with DCM (2 × 20 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL), then back-extracted with DCM (20 mL). The organic layer was dried using anhydrous magnesium sulphate, filtered and counted and contained 6216 MBq (168 mCi), a 93% radiochemical yield. The solution was analysed by radio-HPLC, which indicated 96.1% chemical purity and 96.4% radiochemical purity. The solvent was removed on a rotary evaporator at 35°C, yielding a brown oil that solidified and was then azeotropically dried with toluene (3 × 50 mL) on a rotary evaporator at 35°C, resulting in 1*H*-indol-4-yl-2-¹⁴C, 4-acetate (**11**) with specific activity 11.9 MBq/mg (322 μCi/mg) and molar activity 2109 MBq/mmol (57 mCi/mmol) as a red-brown solid (576 mg). ¹H NMR (d₆-DMSO, 500 MHz): δ 2.34 (3H, s), 6.30–6.34 (1H, m), 6.72 (1H, d, *J* = 7.47 Hz), 7.06 (1H, t, *J* = 7.76 Hz), 7.29 (1H, d, *J* = 8.13 Hz), 7.33 (1H, t, *J* = 2.69 Hz) 11.27 (3H, br s).

3.11 | Synthesis of 4-(Acetyloxy)-*N,N*-dimethyl- α -oxo-1*H*-indole-3-acetamide-2-¹⁴C, (**13**)

Oxalyl dichloride (353 mg, 238 μL, 1.2 equiv, 2.78 mmol) was added to THF (4.0 mL), and the mixture was heated to 40°C with stirring under nitrogen. After 20 min, a solution of 1*H*-indol-4-yl-2-¹⁴C, 4-acetate (**11**) (4884 MBq, 132 mCi, 410 mg, 1.0 equiv, 2.32 mmol) in THF (5.5 mL) was added dropwise to the reaction mixture over 15 min, resulting in a clear yellow solution. The reaction mixture was stirred at 40°C for 30 min, after which no starting material remained. The reaction mixture containing the intermediate 4-(acetyloxy)- α -oxo-1*H*-indole-3-acetyl chloride-2-¹⁴C (**12**) was then cooled to 0°C by immersing the flask in an ice bath for 5 min. Dimethylamine (444 mg, 4.92 mL, 2.0 M in THF, 4.25 equiv, 9.84 mmol) was added dropwise over 15 min, followed by the addition of triethylamine (288 mg, 398 μL, 1.23 equiv, 2.85 mmol). To facilitate stirring of the thick green/brown suspension, THF (4.00 mL) was added and the reaction mixture stirred overnight, after which no intermediate remained. The reaction mixture was dissolved in MeOH (~30 mL) and the solvent removed to leave a brown oil, which was chromatographed on a 100-g silica cartridge, using DCM/MeOH (50:1 v/v) to elute the product. Combined fractions were evaporated and redissolved in MeOH (25 mL). The total radioactivity was determined, and the solution contained 3811 MBq (103 mCi), a 78% radiochemical yield. This solution was analysed by radio-HPLC, indicating 99.1% chemical purity and 97% radiochemical purity. The solution was concentrated on a rotary evaporator to give 4-(acetyloxy)-*N,N*-dimethyl- α -oxo-1*H*-indole-3-acetamide-2-¹⁴C (**13**) with specific activity 7.6 MBq/mg (206 μCi/mg) and molar activity 2109 MBq/mmol (57 mCi/mmol) as a pink oil (521 mg), which crystallised on standing. For the nonradioactive compound (prepared in model experiment): ¹H NMR (d₆-DMSO, 500 MHz): δ 2.35 (3H, s), 2.85 (3H, s), 2.96 (3H, s), 6.92 (1H, dd, *J* = 7.69 Hz, 0.54 Hz), 7.29 (1H, t, *J* = 7.99 Hz), 7.45 (1H, dd, *J* = 8.14 Hz, 0.61 Hz), 8.10 (1H, d, *J* = 3.22 Hz), 12.54 (1H, br s).

3.12 | Synthesis of Psilocin-2-¹⁴C (**14**)

To 4-(acetyloxy)-*N,N*-dimethyl- α -oxo-1*H*-indole-3-acetamide-2-¹⁴C (**13**) (2531 MBq, 68.4 mCi, 332 mg, 1.0 equiv, 1.20 mmol) was added 2-MeTHF (3.98 mL). The reaction mixture was heated to 70°C under nitrogen, and LiAlH₄ in THF (190 mg, 2.50 mL, 2.00 M, 4.17 equiv, 5.00 mmol) was added dropwise over 10 min. The reaction mixture was stirred at 80°C for 3 h, turning from a yellow slurry into a clear yellow solution. More 2-MeTHF (2.32 mL) was added and stirred before cooling the reaction mixture to 0°C in an ice bath. THF:water (3.32 mL, 4:1, v/v) was added dropwise to quench the reaction with effervescence. Solids on the side of the flask were scraped into the quench solution, turning the yellow suspension blue/green. The mixture was stirred for 30 min, then filtered, and the residue was washed and agitated with THF:MeOH (20.0 mL, 99:1 v/v) five times. The solvent was removed from the filtrate to give a blue/black oily solid (395 mg), which was chromatographed on a 40-g silica cartridge using a gradient of ethyl acetate +1% triethylamine and methanol +1% triethylamine to elute the product. The total radioactivity of combined fractions was determined and contained 2146 MBq (58 mCi), an 85% radiochemical yield. This solution was analysed by radio-HPLC, showing psilocin-2-¹⁴C (**14**) with specific activity 10.2 MBq/mg (277 μCi/mg) and molar activity 2109 MBq/mmol (57 mCi/mmol), and with 100% chemical purity and 98.3% radiochemical purity. For the nonradioactive compound (prepared in model experiment): ¹H NMR (d₆-DMSO, 500 MHz): δ 2.23 (6H, s), 2.55 (2H, t, *J* = 6.83 Hz), 2.88 (2H, t, *J* = 6.71 Hz), 6.26 (1H, dd, *J* = 7.38 Hz, 0.97 Hz), 6.74 (1H, dd, *J* = 8.08 Hz, 0.94 Hz), 6.80 (1H, t, *J* = 7.57 Hz), 6.91 (1H, d, *J* = 2.21 Hz), 10.57 (1H, br s), 10.73 (1H, br s).

3.13 | Synthesis of 3-[2-(Dimethylamino)ethyl]-1*H*-indol-4-yl Bis(phenylmethyl) Phosphate-2-¹⁴C (**15**) and the Isomeric Zwitterion (**16**)

The step was performed in two batches, yielding 666 MBq (18 mCi) and 1480 MBq (40 mCi) of crude compound **15**, respectively—only one batch is described: to psilocin-2-¹⁴C (**14**) (1480 MBq, 40 mCi, 147 mg, 1 equiv, 712 μmol) was added anhydrous THF (4.5 mL) forming a clear orange solution. The reaction mixture was cooled to –60°C for 5 min. *n*-BuLi (55 mg, 342 μL, 2.5 M in hexane, 1.2 equiv, 855 μmol) was added dropwise, and the reaction mixture was stirred for 15 min before the dropwise addition of a solution of tetrabenzyl diphosphate (422 mg, 1.1 equiv, 784 μmol) in anhydrous THF (1.5 mL). The reaction mixture was stirred for 35 min, after which no starting material remained. The reaction mixture was quenched with EtOAc (5 mL) at –25°C and stirred for 30 min before the suspension was filtered through celite, and the cake was washed with EtOAc (100 mL). The solvent was removed under reduced pressure and analysed by HPLC. This showed the crude product (**15**) had rearranged via benzyl migration to the isomeric zwitterion (**16**). This material was then chromatographed on a 24-g silica cartridge using a gradient of ethyl acetate +1% triethylamine and methanol +1% triethylamine to elute the product. The total radioactivity of combined fractions from both batches was determined and contained 1184 MBq (32 mCi), a

55% radiochemical yield. This solution was analysed by radio-HPLC, indicating > 98% chemical purity and > 98% radiochemical purity for the isomeric zwitterion (**16**) with specific activity 4.5 MBq/mg (122 μ Ci/mg) and molar activity 2109 MBq/mmol (57 mCi/mmol). For the nonradioactive compound (prepared in model experiment): ^1H NMR (CD_3OD , 500 MHz): δ 3.09 (6H, s), 3.45–3.51 (2H, m), 3.61–3.67 (2H, m), 4.57 (2H, s), 4.96 (2H, d, J = 6.23 Hz), 7.01 (1H, t, J = 7.89 Hz), 7.07–7.14 (3H, m), 7.19–7.31 (5H, m), 7.45–7.57 (5H, m).

3.14 | Synthesis of Psilocybin-2- ^{14}C (**17**)

A stirred mixture of the isomeric zwitterion (**16**) (644 MBq, 17.4 mCi, 143 mg, 1 equiv, 0.306 mmol) [obtained from benzyl migration of 3-[2-(dimethylamino)ethyl]-1H-indol-4-yl-2- ^{14}C bis(phenylmethyl) phosphate (**15**)] in MeOH (8.95 mL) was flushed with nitrogen for 10 min. Pd/C (10% wt, 50% wet type, 28 mg, 0.086 equiv, 26.2 μ mol) was then added and the flask evacuated and filled with hydrogen five times via balloon before stirring under a hydrogen atmosphere for 2 h, after which radio-HPLC confirmed 98.9% conversion to the psilocybin product. The reaction mixture was filtered through a celite pad using MeOH and the filter cake washed with MeOH (100 mL). The celite plug was washed through with solvent until the Brehm probe indicated around 150–200 cps. The activity was then counted and the product analysed by HPLC, giving psilocybin-2- ^{14}C (**17**), 574 MBq (15.5 mCi), with specific activity 8.66 MBq/mg (234 μ Ci/mg) and molar activity 2109 MBq/mmol (57 mCi/mmol), in an 89% radiochemical yield and 98.2% radiochemical purity, respectively. Finally, the solvent was removed, and the product was placed in a -80°C freezer.

3.15 | Radio Dilution and Recrystallisation of Psilocybin-2- ^{14}C (**17**)

To a mixture of unlabelled psilocybin (390.5 mg, 1.37 mmol) and psilocybin-2- ^{14}C (**17**) (722 MBq, 19.5 mCi, 97.7 mg, 0.342 mmol) was added water (7.4 mL, 15.2 vol). The reaction mixture was heated to 75°C , and most of the solid dissolved. The reaction mixture was then filtered hot, under nitrogen, and the clear filtrate heated to 75°C with stirring. The mixture was allowed to cool to 65°C , and a psilocybin seed (~2 mg) was added. The seed did not dissolve and remained suspended in the black solution, which was allowed to cool slowly to room temperature. The mixture was then stirred overnight at room temperature, which resulted in the formation of a thick grey/white suspension. The mixture was cooled with stirring in an ice bath for a further hour, and then the solid was filtered off and the cake washed with ultrahigh-quality water (1 mL, 2 vol), and then washed with cold acetone (2×2 mL, 4 vol). The solid was dried under nitrogen for 30 min and then overnight under high vacuum. This afforded radio diluted psilocybin-2- ^{14}C (**17**) [435 MBq, 11.75 mCi, 274 mg, with specific activity 1.59 MBq/mg (42.9 μ Ci/mg) and molar activity 455 MBq/mmol (12.3 mCi/mmol), in 60% radiochemical yield]. ^1H NMR (D_2O , 500 MHz): δ 2.82 (6H, s), 3.23 (2H, t, J = 7.22 Hz), 3.39 (2H, t, J = 7.74 Hz), 6.95 (1H, d, J = 7.81 Hz), 7.09 (1H, t, J = 8 Hz), 7.14 (1H, s), 7.19 (1H, d, J = 7.99 Hz).

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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