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Syntheses of two isotopically labeled CB_1 receptor antagonists

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Synthesis of deuterium-labeled CB_1 receptor antagonist 2-d_9 was accomplished in three steps by alkylation of 2-nitrophenylacetonitrile with cyclopentyl-d_9 bromide, reductive cyclization of the resulting secondary nitrile into the 3-cyclopentyl indole-d_9 and its *N*-sulfonylation with corresponding *p*-amidosulfonyl chloride. Another, structurally related, CB_1 receptor antagonist 1 was radiolabeled with carbon-14 by oxidative cleavage of 3-cyclopentyl indole followed by the ring closure of *o*-acyl substituted *N*-formylaniline with potassium cyanide-[^{14}C], *in situ* reduction-elimination of the intermediate amino alcohol, and *N*-sulfonylation of the resulting 3-cyclopentyl indole-2-[^{14}C].

Keywords: CB_1 receptor antagonist; 3-cyclopentyl indole; deuterium labeled; carbon-14 labeled

Introduction

Interaction of endocannabinoids with neuronal CB_1 receptors stimulate appetite, whereas blocking of these receptors with CB_1 antagonists can be used for the prevention of excessive hunger and treatment of obesity.[1] Two structurally related CB_1 receptor antagonists, **1** and **2** (Figure 1), demonstrated significant potential as anti-obesity drug candidates[2] and were required to be isotopically labeled for protein binding and other ADME (Absorption, Distribution, Metabolism, Excretion) studies. The syntheses of deuterium-labeled **2** and carbon-14-labeled **1** are described herein.

Results and discussion

Retrosynthetic analysis of molecules **1** and **2** (Scheme 1) provides the opportunity of their construction by sulfonylation of 3-cyclopentyl indole (**3**) with corresponding substituted arylsulfonyl chlorides **4a, b**. The indole **3** could be obtained by reductive cyclization[3] of α-cyclopentyl-*o*-nitrobenzyl cyanide (**5**) that, in turn, could be prepared by the cyanation of a secondary halide **6** or alkylation of *o*-nitrobenzyl cyanide (**7**) with cyclopentyl halide.

After a number of unsuccessful approaches to **6**, including reaction of cyclopentylmagnesum chloride with 2-nitrobenzaldehyde, coupling of 2-nitrobenzyl bromide with cyclopentyl bromide in the presence of dilithium chlorocuprate, or α-alkylation of 2-nitrophenylacetic acid and its esters with cyclopentyl bromide, we decided to use nitrobenzyl cyanide **7** as a key intermediate in preparation of cyanide **5** (see retrosynthetic scheme 1). Nitrile **7** is known to be prepared by cyanation of the commercially available 2-nitrobenzyl bromide (**8**) using hydrogen cyanide, which is used directly or generated *in situ* from excess of sodium cyanide and trifluoroacetic acid.[4] The volatile hydrogen cyanide is not a convenient source of radioactivity for the synthesis of C-14-labeled isotopomer. Therefore, we investigated the reaction of bromide **8** with sodium cyanide as potential radioactive precursor. The use of anhydrous dimethyl sulfoxide (DMSO) as a solvent gave low yield of nitrile **7** (35%) in our hands (Scheme 2). The major product of this reaction was dimer **9** (the similar results were observed previously[4]). We found that the yield of **7** can be increased (to 52%) by performing the reaction homogeneously in aqueous DMSO.

The next step, alkylation of benzyl cyanide **7**, was attempted under few different conditions. A commonly accepted method for alkylation of phenylacetonitriles in the presence of sodium amide[5] was not successful in the case of **7**, probably due to the *ortho*-nitro group participation leading to the formation of a complex mixture containing neither starting material nor desired coupling product **5**. A reaction between **7** and cyclopentyl bromide failed under phase transfer catalysis conditions:[6] dichloromethane, aqueous sodium hydroxide, tetrabutylammonium bromide, or acetonitrile, potassium carbonate, and 18-crown-6. The alkylation product **5** was obtained in a modest yield (41%) when nitrobenzyl cyanide **7** reacted with cyclopentyl bromide in dimethylformamide in the presence of potassium carbonate and potassium iodide. The use of the cyclopentyl iodide in place of bromide increased the yield of **5** to 64% (Scheme 3).

The reductive cyclization of nitrobenzyl cyanide **5** was performed under palladium catalyzed hydrogenation conditions[3] to give 3-cyclopentyl indole **3** (Scheme 4). The reaction occurred under atmospheric pressure of hydrogen at room temperature. Initially, the reduction of nitro group takes place to form aminobenzyl cyanide **10** that could be isolated after the first 3 hours as the only product of the reaction. The subsequent reduction of the cyano group and cyclization required a higher temperature (30–40°C) or longer period (18 hours).

On the next step of *N*-sulfonylation of 3-cyclopentyl indole (**3**), the choice of a base appeared to be important (Scheme 5). When Lithium Diisopropylamide (LDA) was used in the reaction of **3** with sulfonyl chloride **4a**, the yield of **1** was just 13%, whereas replacement of LDA with potassium *tert*-butoxide increased the yield to 63%.

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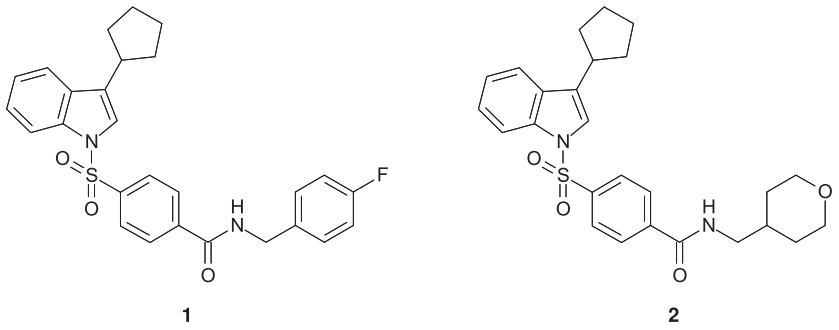
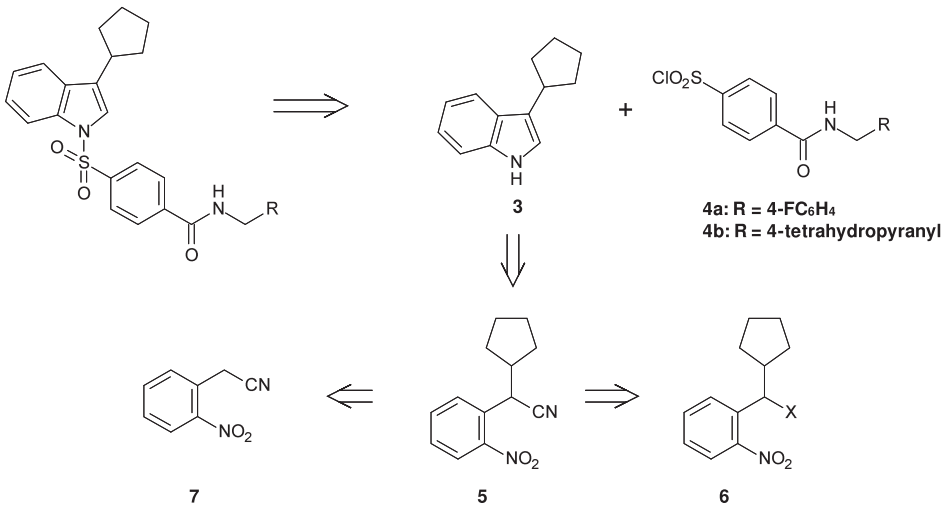
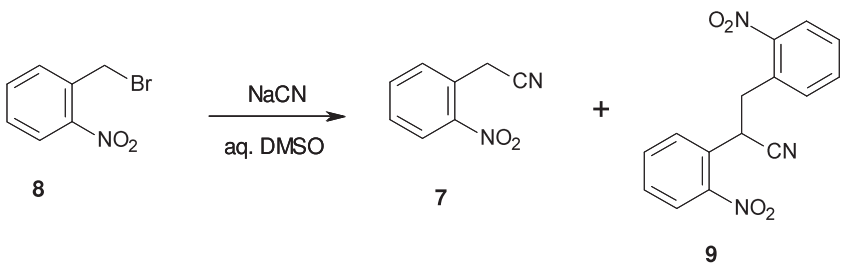


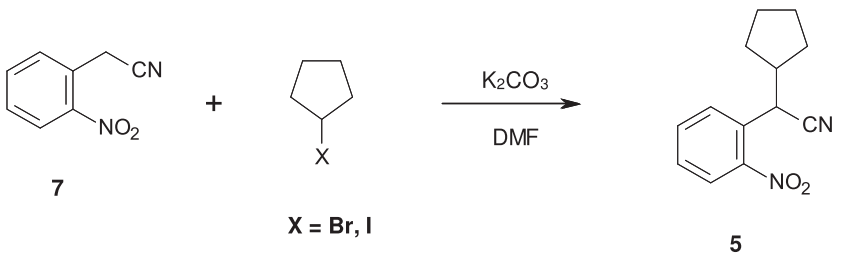
Figure 1. Structures of CB_1 receptor antagonists **1** and **2**.



Scheme 1. Retrosynthetic analysis for the synthesis of **1** and **2**.

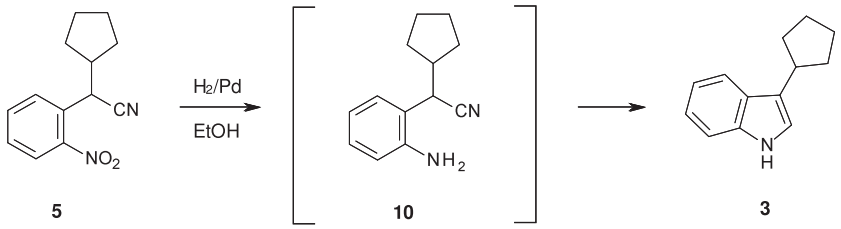


Scheme 2. Synthesis of nitrobenzyl cyanide **7**.

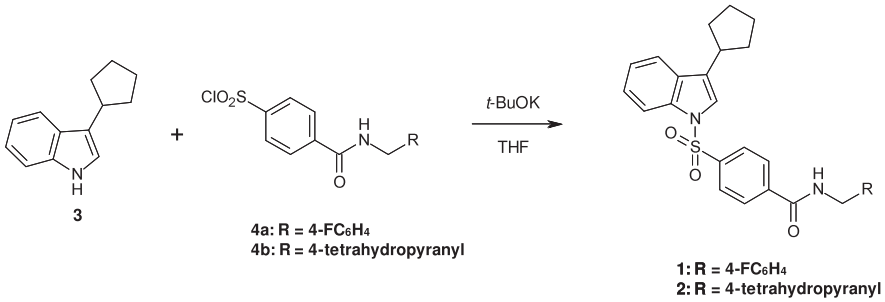


Scheme 3. Synthesis of **5** by alkylation of benzyl cyanide **7**.

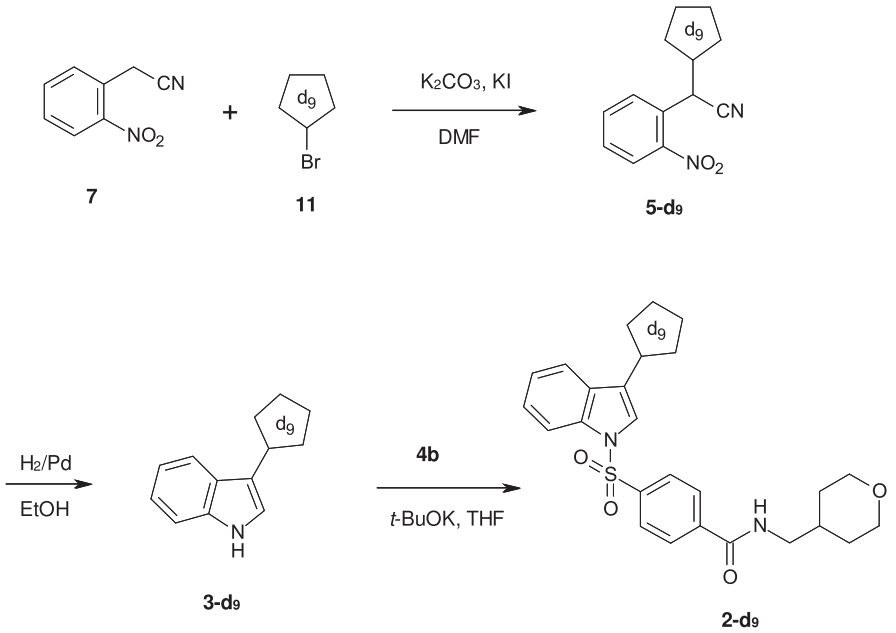
We used the method described earlier for the synthesis of deuterium-labeled material **2-d$_9$** from commercially available nonadeuterio cyclopentyl bromide (**11**) and 2-nitrophenylacetonitrile (**7**) (Scheme 6). Reaction of **7** with **11** in the presence of potassium carbonate and potassium iodide in dimethylformamide gave α-nonadeuterio cyclopentyl-*o*-nitrobenzyl cyanide (**5-d$_9$**) in the modest yield (32%). The lower yield probably resulted from secondary isotope effect of deuterium. Reductive cyclization of **5-d$_9$** by hydrogenation on palladium catalyst provided 3-nonadeuteriocyclopentyl indole (**3-d$_9$**). Finally,



Scheme 4. Reductive cyclization of **5** to form indole **3**.



Scheme 5. N-sulfonylation of indole **3**.

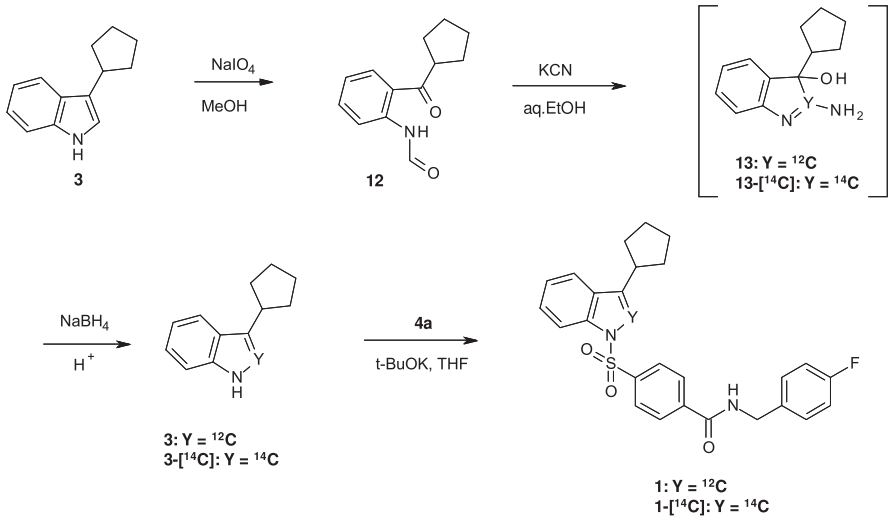


Scheme 6. Synthesis of **2-d$_9$**.

N-sulfonylation of **3-d$_9$** with amido phenylsulfonyl chloride **4b** afforded the target stable-labeled compound **2-d$_9$**.

Thus, just a three-step sequence from commercially available starting materials allowed the preparation of deuterium-labeled internal standard **2-d$_9$** for bioanalytical studies. The aforementioned method also could be used for the synthesis of C-14-labeled compound **1**. In that case, the radioactivity would be introduced on the first step of the synthesis during the preparation of 2-nitrobenzyl cyanide (**7**) from 2-nitrobenzyl bromide (**8**) (see Schemes 2–5).

We decided to investigate an alternative approach based on the oxidative cleavage of the indole ring followed by ring closure using potassium cyanide as a source of radioactivity[7] (Scheme 7). The starting material, cyclopentyl indole **3**, was treated with sodium periodate to form *N*-formyl-2-cyclopentylcarbonylaniline (**12**) in good yield (75%). The reaction of **12** with potassium cyanide in aqueous ethanol gave the cyclization product, amino alcohol **13** that was isolated simply by the evaporation of the reaction mixture. In accordance with known conditions,[7] the compound was redissolved in the mixture of tetrahydrofuran and acetic acid and treated with sodium borohydride to obtain the target cyclopentyl indole **3**. We found out, however, that the isolation and redissolving of the amino alcohol **13** were not necessary, and the addition of sodium borohydride could be performed directly to the reaction mixture after the cyclization with potassium cyanide is over. This method was



Scheme 7. Synthesis of **1** and **1-[^{14}C]**.

used for the short and efficient preparation of 3-cyclopentyl-2-[^{14}C]-indole (**3-[^{14}C]**) followed by its conversion into the target radiolabeled material **1-[^{14}C]**.

Conclusion

The isotopically labeled 3-cyclopentyl indoles **3-d$_9$** and **3-[^{14}C]** served as key intermediates in the preparation of isotopomers of two structurally related CB_1 receptor antagonists **2** and **1**. A short method for the preparation of deuterium-labeled **2** utilized a two-step construction of 3-cyclopentyl indole-d$_9$ (**3-d$_9$**) from commercially available 2-nitrophenylacetonitrile (**7**) and cyclopentyl-d$_9$ bromide (**11**). The efficient synthesis of C-14-labeled **1** included oxidative cleavage of non-labeled 3-cyclopentyl indole (**3**) followed by the ring closure with potassium cyanide-[^{14}C] and reduction-elimination to form 3-cyclopentyl-2-[^{14}C]-indole (**3-[^{14}C]**).

Experimental

The potassium cyanide-[^{14}C] was purchased from the American Radiolabeled Chemicals, Inc. The ^{1}H-NMR spectra were obtained in $CDCl_3$ on a Varian Mercury-400 at 400 MHz (Varian, Inc). Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane. Infrared (IR), Mass Spectra (MS), and microanalytical data were provided by the Physical Chemistry Department of the Lilly Research Laboratories. Flash chromatography was performed using Biotage Flash System (Biotage, Sweden). Thin layer chromatography (TLC) was conducted on precoated plates of silica gel 60 F_{254}. All ^{14}C-compounds were identified by TLC comparison with the corresponding non-radiolabeled isotopomers. The radiochemical purity of the final material **1-[^{14}C]** was determined by radio-HPLC: Polaris C18 (3 μm, 150 × 3 mm), column temperature 40°C, with gradient elution at 0.7 mL/min (Eluent A = 25 mM H_3PO_4 in water, Eluent B = 2% Eluent A / 98% 25 mM H_3PO_4 in acetonitrile) from 51% B to 97% B over 30 minutes and simultaneous radiochemical and UV (at 220 nm) detection.

2-Nitrophenylacetonitrile, 7

To a solution of sodium cyanide (196 mg, 4.0 mmol) in water (1 mL) and dimethyl sulfoxide (3 mL) at 0–5°C (ice bath), 2-nitrobenzyl bromide (**8**) (864 mg, 4.0 mmol) dropwise was added. The reaction mixture was stirred for 1 hour, diluted with water (3 mL), and extracted with ethyl acetate (20 mL). The extract was washed with brine (2 mL). The combined aqueous layers were re-extracted with ethyl acetate (5 mL). The combined organic extracts were dried over sodium sulfate and evaporated under vacuum. Biotage chromatography of the residue (column 12M, eluting with hexane/ethyl acetate, 85:15) gave **7** (338 mg, 52%) as a white solid. TLC (co-elutes with commercial sample of **7**): R_f = 0.23 (hexane/ethyl acetate, 80:20). ^{1}H-NMR (identical to ^{1}H-NMR of the commercial sample of **7**, $CDCl_3$): 4.22 (s, 2H), 7.58 (td, J = 8.3 and 1.3 Hz, 1H), 7.74 (m, 2H), 8.19 (dd, J = 8.3 and 1.3 Hz, 1H).

2-(Cyclopentyl)-2-(2-nitrophenyl)acetonitrile, 5

A mixture of benzyl cyanide **7** (324 mg, 2.0 mmol), cyclopentyl iodide (280 μL, 2.4 mmol), and potassium carbonate (995 mg, 7.2 mmol) in dimethylformamide (2.5 mL) was heated at 55°C for 3 hours, then cooled at room temperature, diluted with water (2 mL) and extracted with ethyl acetate (20 mL). The extract was washed with brine (2 mL). The combined aqueous layers were re-extracted with ethyl acetate (10 mL). The combined organic extracts were dried over sodium sulfate and evaporated under vacuum. Biotage chromatography of the residue (column 40S, eluting with hexanes/ethyl acetate, 85:15), gave **5** (296 mg, 64%) as a yellow oil. TLC: R_f 0.51 (hexanes/ethyl acetate 80:20). ^{1}H-NMR ($CDCl_3$): 1.42 (m, 1H), 1.60 (m, 3H), 1.80 (m, 4H), 2.38 (m, 1H), 4.89 (d, J = 6.2 Hz, 1H), 7.55 (td, J = 8.8 and 1.3 Hz, 1H), 7.72 (td, J = 7.5 and 1.3 Hz, 1H), 7.80 (dd, J = 7.9 and 1.3 Hz, 1H), 8.06 (dd, J = 8.4 and 1.3 Hz, 1H). IR (KBr, ν, cm^{-1}): 707, 745, 787, 862, 1191, 1349, 1446, 1529, 1576, 1609, 2239, 2870, 2958. UV (EtOH, λ_{max}, nm): 255 (ε 6113). MS (ES+): 248 (M + 1 + NH_3). MS (ES-): 229 (M-1). Analysis calculated for: $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.60; H, 6.21; N, 11.88.

2-(Nonadeuterio cyclopentyl)-2-(2-nitrophenyl) acetonitrile, 5-d$_9$

A mixture of benzyl cyanide **7** (585 mg, 3.61 mmol), nonadeuterio cyclopentyl bromide (**11**) (600 mg, 3.79 mmol), potassium iodide (630 mg, 3.79 mmol) and potassium carbonate (1.57 g, 11.36 mmol) in dimethylformamide (4.5 mL) was heated at 55–60°C for 6 hours, then cooled at room temperature, diluted with water (5 mL) and extracted with ethyl acetate (15 mL). The extract was washed with 10% aqueous sodium thiosulfate (3 mL), brine (3 mL), dried over sodium sulfate, and evaporated under vacuum. Biotage chromatography of the residue (column 40S, eluting with hexanes/ethyl acetate, 85:15), gave **5-d$_9$** (275 mg, 32%) as a yellow oil. TLC: the same as the one for **5**. ^{1}H-NMR ($CDCl_3$): 4.88 (s, 1H), 7.55 (td, J = 7.9 and 1.3 Hz, 1H), 7.72 (td, J = 7.9 and 1.3 Hz, 1H), 7.80 (dd, J = 7.9 and 1.3 Hz, 1H), 8.06 (dd, J = 8.3 and 1.3 Hz, 1H). IR (KBr, ν, cm^{-1}): 745, 787, 857, 1192, 1348, 1528, 1571, 1609, 2105,

2226. UV (EtOH, λ_{max}, nm): 271 (ε 12197). MS (ES+): 257 (M + 1 + NH_3). MS (ES-): 238 (M-1). Analysis calculated for: $C_{13}H_5D_9N_2O_2$: C, 65.27; H, 6.12; N, 11.71. Found: C, 65.44; H, 6.05; N, 11.61.

3-Cyclopentyl indole, 3 (from nitrile 5)

A mixture of nitrile **5** (291 mg, 1.26 mmol), 10% palladium on carbon (50 mg) and acetic acid (1.2 mL) in ethanol (5 mL) was vigorously stirred under atmospheric pressure of hydrogen for 18 hours, then diluted with ethyl acetate (5 mL) and filtered. The filtrate was evaporated under vacuum and subjected to Biotage chromatography on a 12M column. Eluting with hexanes/ethyl acetate (85:15) gave 3-cyclopentyl indole (**3**) (126 mg, 54%) as a white solid. TLC: R_f 0.41 (hexanes/ethyl acetate 90:10). ^{1}H-NMR ($CDCl_3$): 1.76 (m, 4H), 1.85 (m, 2H), 2.21 (m, 2H), 3.31 (m, 1H), 7.01 (s, 1H), 7.14 (td, *J* = 7.9 and 0.9 Hz, 1H), 7.22 (td, *J* = 7.9 and 0.9 Hz, 1H), 7.38 (dd, *J* = 7.9 and 0.9 Hz, 1H), 7.70 (d, *J* = 7.9 Hz, 1H), 7.90 (br.s, 1H). IR (KBr, ν, cm^{-1}): 493, 575, 743, 810, 1011, 1100, 1230, 1340, 1422, 1457, 1484, 1622, 2861, 2955, 3055, 3403. UV (EtOH, λ_{max}, nm): 223 (ε 32567), 282 (ε 5846). MS (ES+): 186 (M + 1). MS (ES-): 184 (M-1). Analysis calculated for: $C_{13}H_{15}N$: C, 84.28; H, 8.16; N, 7.56. Found: C, 84.06; H, 8.12; N, 7.61.

3-Nonadeuteriocyclopentyl indole, 3-d_9

In the same manner as described earlier, starting from nitrile (**5-d_9**) (193 mg, 0.81 mmol), 10% palladium on carbon (30 mg) and acetic acid (0.8 mL) in ethanol (3 mL), deuteriocyclopentyl indole **3-d_9** (89 mg, 57%) was obtained as a colorless solid. TLC: the same as the one for **3**. ^{1}H-NMR ($CDCl_3$): 7.01 (s, 1H), 7.14 (td, *J* = 7.9 and 0.9 Hz, 1H), 7.22 (td, *J* = 7.9 and 0.9 Hz, 1H), 7.38 (dd, *J* = 7.9 and 0.9 Hz, 1H), 7.70 (d, *J* = 7.9 Hz, 1H), 7.90 (br.s, 1H). IR (KBr, ν, cm^{-1}): 493, 575, 743, 816, 1011, 1099, 1247, 1333, 1417, 1456, 2100, 2222, 3403. UV (EtOH, λ_{max}, nm): 223 (ε 22415), 282 (ε 5828), 290 (ε 5138). MS (ES+): 195 (M + 1). MS (ES-): 193 (M-1). Analysis calculated for: $C_{13}H_6D_9N$: C, 80.39; H, 7.78; N, 7.21. Found: C, 79.72; H, 7.85; N, 7.20.

4-(Tetrahydropyran-4-ylmethylaminocarbonyl) phenylsulfonyl chloride, 4b

To a solution of 4-aminomethyltetrahydropyran (300 mg, 2.6 mmol), triethylamine (400 μL, 2.87 mmol) and 4-dimethylaminopyridine (15 mg. 0.12 mmol) in tetrahydrofuran (4 mL) at −78°C, a solution of 4-chloroformylphenylsulfonyl chloride (623 mg, 2.6 mmol) in tetrahydrofuran (5 mL) dropwise was added. The reaction mixture was allowed to reach 0°C, stirred for 3 hours at this temperature, then diluted with 1 *N*-hydrochloric acid (2 mL) and extracted with ethyl acetate (10 mL). The extract was washed with brine, dried over sodium sulfate, and evaporated under vacuum to give phenylsulfonyl chloride **4b** (760 mg, 92%) as a white solid (used in the next step without further purification). ^{1}H-NMR ($CDCl_3$): 1.43 (m, 2H), 1.70 (m, 2H), 1.95 (m, 1H), 3.43 (m, 4H), 4.03 (m, 2H), 6.35 (br.s, 1H), 7.69 (d, *J* = 8.3 Hz, 0.5H), 7.78 (d, *J* = 8.3 Hz, 0.5H), 7.90 (d, *J* = 8.3 Hz, 0.5H), 8.01 (d, *J* = 8.3 Hz, 1H), 8.07 (d, *J* = 8.3 Hz, 0.5H), 8.14 (d, *J* = 8.3 Hz, 1H). IR (KBr, ν, cm^{-1}): 564, 558, 625, 692, 807, 855, 904, 984, 1012, 1046, 1092, 1116, 1143, 1173, 1239, 1292, 1378, 1445, 1487, 1546, 1600, 1648, 1727, 1799, 2693, 2717, 2761, 2846, 2930, 3092, 3339. UV (EtOH, λ_{max}, nm): 230 (ε 14962). MS (ES+): 318 (M + 1). MS (ES-): 316 (M-1). Analysis calculated for: $C_{13}H_{16}ClNO_4S$: C, 49.13; H, 5.07; N, 4.41. Found: C, 50.10; H, 5.20; N, 4.33.

1-(4-(Tetrahydropyran-4-ylmethylaminocarbonyl) phenylsulfonyl)-3-cyclopentyl indole, 2

To a solution of 3-cyclopentyl indole (**3**) (50 mg, 0.27 mmol) and potassium *tert*-butoxide (37 mg, 0.33 mmol) in tetrahydrofuran (2 mL) at 0–5°C (ice bath), a solution of sulfonyl chloride **4b** (94 mg, 0.3 mmol) in tetrahydrofuran (0.5 mL) was added. The reaction mixture was allowed to reach room temperature, stirred for 16 hours, then diluted with aqueous 10% sodium bisulfate (2 mL) and extracted with ethyl acetate (20 mL). The extract was washed with brine, dried over sodium sulfate, and evaporated under vacuum. Biotage chromatography of the residue (12M column, eluting with hexanes/ethyl acetate, 30:70), gave **2** (56 mg, 44%) as a white solid, identical (TLC, NMR) to an authentic sample of **2**. TLC: R_f 0.38 (hexanes/ethyl acetate 30:70). ^{1}H-NMR ($CDCl_3$): 1.37 (m, 2H), 1.60–1.90 (m, 9H), 2.15 (m, 2H), 3.18 (m, 1H), 3.35 (m, 4H), 4.00 (m, 2H), 6.15 (br.s, 1H), 7.30 (m, 3H), 7.56 (d, *J* = 7.9 Hz, 1H), 7.79 (d, *J* = 8.3 Hz, 2H), 7.92 (d, *J* = 8.3 Hz, 2H), 8.00 (d, *J* = 8.3 Hz, 1H). MS (ES+): 467 (M + 1). MS (ES-): 465 (M-1).

1-(4-(Tetrahydropyran-4-ylmethylaminocarbonyl) phenylsulfonyl)-3-nonadeuteriocyclopentyl indole, 2-d_9

In the same manner as described earlier, starting from deuteriocyclopentyl indole **3-d_9** (73 mg, 0.376 mmol), potassium *tert*-butoxide (51 mg, 0.454 mmol) and sulfonyl chloride **4b** (130 mg, 0.409 mmol) in tetrahydrofuran (2.8 mL), **2-d_9** (60 mg, 34%) was obtained as a white solid. TLC: the same as the one for **2**. ^{1}H-NMR ($CDCl_3$): 1.37 (m, 2H), 1.65 (m, 2H), 1.87 (m, 1H), 3.38 (m, 4H), 3.99 (m, 2H), 6.14 (br.s, 1H), 7.30 (m, 3H), 7.55 (d, *J* = 7.9 Hz, 1H), 7.79 (d, *J* = 8.3 Hz, 2H), 7.93 (d, *J* = 8.3 Hz, 2H), 7.99 (d, *J* = 8.3 Hz, 1H). IR (KBr, ν, cm^{-1}): 569, 613, 745, 857, 980, 1011, 1093, 1128, 1179, 1302, 1373, 1447, 1541, 1646, 2105, 2223, 2843, 2928, 3428. UV (EtOH, λ_{max}, nm): 253. MS (ES+): 476 (M + 1). MS (ES-): 474 (M-1). Analysis calculated for: $C_{26}H_{21}D_9N_2O_4S$: C, 65.66; H, 6.36; N, 5.89. Found: C, 65.36; H, 6.34; N, 5.70.

N-Formyl-2-(cyclopentylcarbonyl)aniline, 12

To a solution of 3-cyclopentyl indole **3** (370 mg, 2.0 mmol) in methanol (40 mL), a solution of sodium periodate (1.70 g, 7.95 mmol) in water (17 mL) was added. The reaction mixture was stirred at room temperature for 16 hours and evaporated under vacuum at room temperature to remove methanol. The residue was diluted with saturated aqueous sodium bicarbonate (5 mL) and water (5 mL), extracted with ethyl acetate (20 mL), and filtered. The organic layer was separated and washed with brine (3 mL). The combined aqueous layers were re-extracted with ethyl acetate (10 mL). The combined organic extracts were dried over sodium sulfate and evaporated under vacuum. Biotage (40S) chromatography (eluting with hexane/ethyl acetate 85:15) gave ketone **12** (328 mg, 75%) as a yellow oil. TLC: R_f 0.37 (hexanes/ethyl acetate 80:20). ^{1}H-NMR ($CDCl_3$): 1.7 (m, 4H), 1.9 (m, 4H), 3.78 (quint, *J* = 7.5 Hz, 1H), 7.17 (t, *J* = 7.9 Hz, 1H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.96 (d, *J* = 7.9 Hz, 1H), 8.48 (s, 1H), 8.73 (d, *J* = 8.4 Hz, 1H), 11.67 (s, 1H). IR (KBr, ν, cm^{-1}): 750, 992, 1210, 1295, 1452, 1513, 1579, 1652, 1700, 2863, 2953, 3245. UV (EtOH, λ_{max}, nm): 230 (ε 25086), 260 (ε 11695), 319 (ε 4684). HRMS (AP+) calculated for $C_{13}H_{15}NO_2$: 217.1103. Found: 217.1120. Analysis calculated for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.76; H, 6.69; N, 6.23.

3-Cyclopentyl indole, 3 (from ketone 12)

(a) *With isolation of amino alcohol **13***:

To a solution of ketone **12** (221 mg, 1.02 mmol) in 95% ethanol (3 mL), a solution of potassium cyanide (66 mg, 1.01 mmol) in water (0.25 mL) and ethanol (2.5 mL) was added. The reaction mixture was stirred at room temperature for 4 hours and evaporated under vacuum to leave amino alcohol **13** as a white solid. TLC: R_f 0.50 (dichlomethane/methanol/ammonium hydroxide 85:15:1.5). ^{1}H-NMR (CD_3OD): 0.72 (m, 1H), 1.3–1.6 (m, 5H), 1.84 (q, *J* = 7.2 Hz, 2H), 2.38 (quint, *J* = 8.5 Hz, 1H), 6.88 (td, *J* = 7.5 and 0.9 Hz, 1H), 6.93 (d, *J* = 7.9 Hz, 1H), 7.16 (td, *J* = 7.5 and 1.3 Hz, 1H), 7.28 (d, *J* = 7.5 Hz, 1H), 8.55 (s, 1H). MS (ES+): 217 (M + 1). MS (ES-): 215 (M-1).To a solution of amino alcohol **13** in tetrahydrofuran (3 mL) and acetic acid (3 mL) at 0–5°C (ice bath), sodium borohydride (190 mg, 5.0 mmol) in portions over the period of 10 minutes was added. The reaction mixture was stirred for 2 hours and treated at 0–5°C (ice bath) by slow addition of 2*N*-hydrochloric

acid (2.5 mL). After 1.5 hours, the mixture was neutralized with 5*N*-sodium hydroxide and extracted with ethyl acetate (15 mL). The extract was washed with brine (2 mL). The combined aqueous layer was re-extracted with ethyl acetate (5 mL). The combined organic extract was dried over sodium sulfate, and evaporated under vacuum. Biotage (12M) chromatography (eluting with hexanes/ethyl acetate, 90:10) gave cyclopentyl indole **3** (137 mg, 73%) as a white solid. The compound was identical (TLC, NMR) to an authentic sample of 3-cyclopentyl indole.

(b) *Without isolation of aminoketone* ***13***:

To a solution of ketone **12** (324 mg, 1.49 mmol) in ethanol (5 mL), a solution of potassium cyanide (97 mg, 1.49 mmol) in water (0.4 mL) and ethanol (3 mL) was added. The reaction mixture was stirred at room temperature for 3 hours, where upon sodium borohydride (280 mg, 7.4 mmol) was added. The resulted mixture was stirred at room temperature for 1.5 hours, then placed in an ice bath and acidified with 1*N*-hydrochloric acid (7 mL) dropwise. The reaction mixture was stirred for 1.5 hours, then neutralized with 1*N*-aqueous sodium hydroxide (0.5 mL) and extracted with ethyl acetate (30 mL). The extract was washed with brine (3 mL). The combined aqueous layers were re-extracted with ethyl acetate (10 mL). The combined organic extracts were dried over sodium sulfate and evaporated under vacuum. Biotage (40S) chromatography (eluting with hexanes/ethyl acetate 90:10) gave cyclopentyl indole **3** (236 mg, 85%) as a white solid. The compound was identical (TLC, NMR) to an authentic sample of 3-cyclopentyl indole.

3-Cyclopentyl-2-[^{14}C]-indole, 3-[^{14}C]

To a solution of ketone **12** (261 mg, 1.2 mmol) in ethanol (4 mL), a solution of potassium cyanide-[^{14}C] (50 mCi, 55 mCi/mmol, 0.91 mmol) in water (0.2 mL) and ethanol (1.3 mL) was added. The vial was rinsed with a solution of potassium cyanide (19 mg, 0.29 mmol) in water (0.1 mL) and ethanol (0.7 mL). The reaction mixture was stirred at room temperature for 3.5 hours, whereupon sodium borohydride (225 mg, 5.95 mmol) was added in one portion. The resulting mixture was stirred at room temperature for 2.5 hours, then placed in an ice bath and acidified with 1*N*-hydrochloric acid (6.8 mL) dropwise over the period of 5 minutes. The reaction mixture was stirred for 1.5 hours, then neutralized with 1*N*-aqueous sodium hydroxide (0.4 mL) and extracted with ethyl acetate (20 mL). The extract was washed with brine (3 mL). The combined aqueous layers were re-extracted with ethyl acetate (10 mL). The combined organic extracts were dried over sodium sulfate and evaporated under vacuum. Biotage (40S) chromatography (eluting with hexanes/ethyl acetate 90:10) gave 3-cyclopentyl-2-[^{14}C]-indole (**3-[^{14}C]**) (167 mg, 74%) as a white solid.

1-(4-(4-Fluorophenylmethylaminocarbonyl)-phenylsulfonyl)-3-cyclopentyl indole, 1

To a solution of 3-cyclopentyl indole (**3**) (140 mg, 0.756 mmol) in tetrahydrofuran (3 mL), potassium *tert*-butoxide (104 mg, 0.93 mmol) was added. To the resulting solution, placed in an ice bath, a solution of sulfonyl chloride **4a** (275 mg, 0.84 mmol) in tetrahydrofuran (2.5 mL) dropwise was added. The reaction mixture was allowed to reach room temperature, stirred for 14 hours, then diluted with water (2 mL) and extracted with ethyl acetate (20 mL). The extract was washed with brine (5 mL). The combined aqueous layers were filtered and re-extracted with ethyl acetate (10 mL). The combined organic extracts were dried over sodium sulfate and evaporated under vacuum. Biotage (40S) chromatography (eluting with hexanes/ethyl acetate 70:30) gave **1** (227 mg, 63%) as a white solid, identical (TLC, NMR) to an authentic sample of **1**. TLC: R_f 0.30 (hexanes/ethyl acetate 30:70). ^{1}H-NMR ($CDCl_3$): 1.5–1.8 (m, 6H), 2.10 (m, 2H), 3.13 (quint, J = 8.3 Hz, 1H), 4.54 (d, J = 5.7 Hz, 2H), 6.31 (br.s, 1H), 7.00 (t, J = 8.3 Hz, 2H), 7.25 (m, 5H), 7.51 (d, J = 7.9 Hz, 1H), 7.77 (d, J = 8.3 Hz, 2H), 7.88 (d, J = 8.3 Hz, 2H), 7.94 (d, J = 8.3 Hz, 1H).

1-(4-(4-Fluorophenylmethylaminocarbonyl)-phenylsulfonyl)-3-cyclopentyl-2-[^{14}C]-indole, 1-[^{14}C]

In the same manner as described earlier, starting from cyclopentyl-2-[^{14}C]-indole **3-[^{14}C]** (156 mg, 0.83 mmol), potassium *tert*-butoxide (114 mg, 1.02 mmol) and sulfonyl chloride **4a** (300 mg, 0.915 mmol) in tetrahydrofuran (6 mL), **1-[^{14}C]** (208 mg, 52%, or 78% based on recovered starting material) was obtained as a white solid. The material had specific activity 79.5 μCi/mg and radiochemical purity 97% and co-eluted (HPLC, TLC) with an authentic sample of non-radioactive **1**.

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Conflict of Interest

The authors did not report any conflict of interest.

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