JOURNAL OF LABELLED COMPOUNDS AND RADIOPHARMACEUTICALS
J Label Compd Radiopharm 2006; **49**: 663–673.
Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/jlcr.1086

Research Article

Convergent synthesis of two ^{14}C-labeled β_3-adrenergic receptor agonists

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Summary

The synthesis of β_3-adrenergic receptor agonists **A** and **B** with radiolabeled amide fragment, required for drug disposition studies, was accomplished based on initial formation of 2-(4-(2-amino-2-methylpropyl)phenoxy)-5-[^{14}C]-cyanopyridine by the reaction of 2-bromo-5-iodopyridine with *para*-substituted phenol, and following cyanation of aromatic iodide with potassium cyanide-[^{14}C]. After the coupling of the resulted amine with glycidyl derivatives of 4-hydroxyindole and 4-hydroxycarbazole, the corresponding nitriles were hydrolyzed with basic hydrogen peroxide to obtain target amides **A** and **B**. Copyright © 2006 John Wiley & Sons, Ltd.

Received 27 April 2006; Revised 2 May 2006; Accepted 3 May 2006

Key Words: β_3-adrenergic receptor agonists; carbon-14 labeled

Introduction

It is well known that β_3-adrenergic receptor agonists potentially could be used for the treatment of obesity and diabetes.[1] Indole **A**[2] and carbazole **B**[3] belong to this class of receptor agonists (Figure 1).

For the metabolism and disposition studies ^{14}C-labeled materials were required. Preliminary findings suggested that one of the main metabolic routes leads to the cleavage of linear aliphatic parts of these molecules. Therefore, each molecule had to be radiolabeled in two 'side' positions. The syntheses of **A** with ^{14}C-labeled indole fragment,[4] and **B** containing ^{14}C-labeled carbazole fragment,[5] have been published recently. In this communication we describe the synthesis of both compounds with ^{14}C-labeled carbamide moiety.

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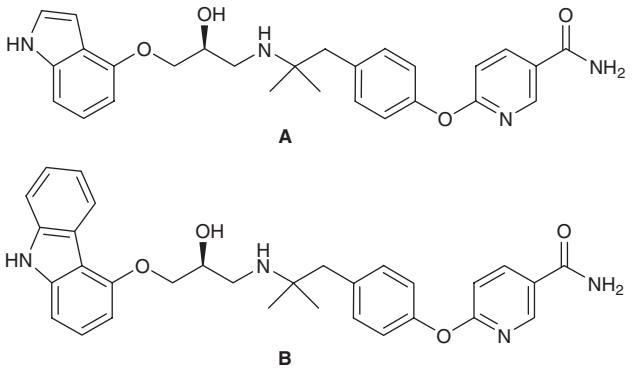


Figure 1.

Results and discussion

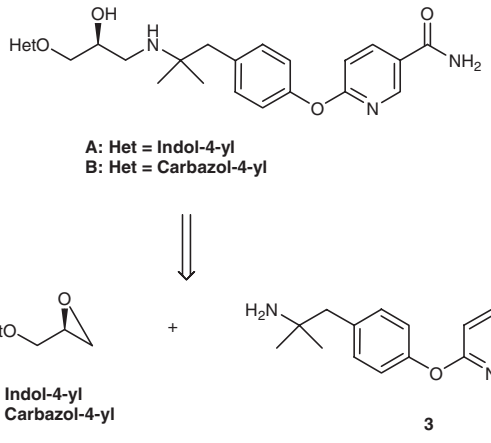
Retrosynthetic analysis of both molecules includes the coupling of corresponding epoxides **1** and **2** with primary amine **3** (Scheme 1).

Our initial intention was the introduction of radiocarbon on a penultimate step of the synthesis by cyanation of the iodide **8** (Scheme 2). For this purpose 2,5-diiodopyridine (**4**)[6] was coupled with aminophenol **6** to form ether **7** in 59% yield. Exclusive regioselectivity in substitution at position **2** of pyridine led us to attempt of replacement of diiodopyridine **4** by more stable 2-bromo-5-iodopyridine (**5**)[6]. Not only was the regioselectivity retained, but also the yield of the reaction was increased to 71%. Next step, the opening of epoxide **2** with amine **7**, went smoothly to give the desired adduct **8**. The attempts in the cyanation of iodide **8** were not satisfactory. The heating of **8** with potassium cyanide in the presence of copper (I) iodide in 1-methylpyrrolidinone (NMP)[7] gave a low yield (less than 20%) of the cyanide **9** as a mixture with 1-methylpyrrolidinone. A similar result was obtained when copper (I) cyanide alone[8] was used for the same reaction.

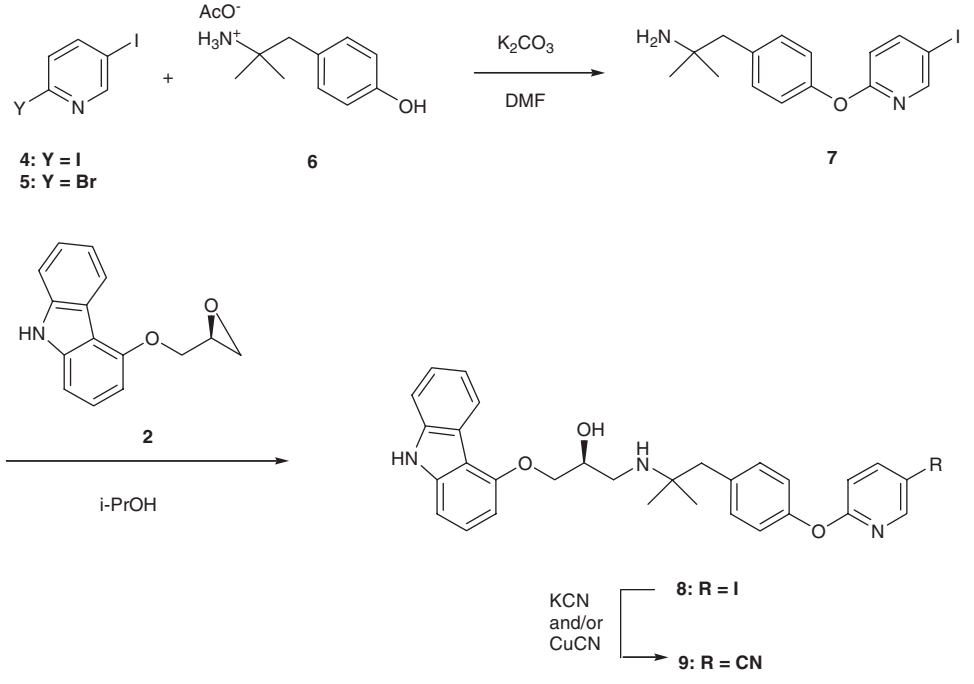
The unsuccessful conversion of **8** into **9** may be attributed to the instability of the substituted secondary alcohol fragment of the molecule under the high temperature required for the reaction. It was necessary therefore to move the cyanation to an earlier step of the synthesis. Indeed, the reaction of iodide **7** with potassium cyanide in the presence of copper (I) iodide in NMP proceeded without complications, and provided cyanide **10** in high yield (Scheme 3). The subsequent steps of coupling **10** with epoxides **1** and **2** leading to the corresponding nitriles **11** and **9**, and their hydrolysis with basic hydrogen peroxide, went smoothly to give the target products, which were converted to their salts **A** glycolate and **B** succinate.

The synthesis of radiolabeled compounds was accomplished using the same approach (Scheme 3). The reaction of iodide **7** with potassium cyanide-[^{14}**C**] in

DOI: 10.1002/jlcr



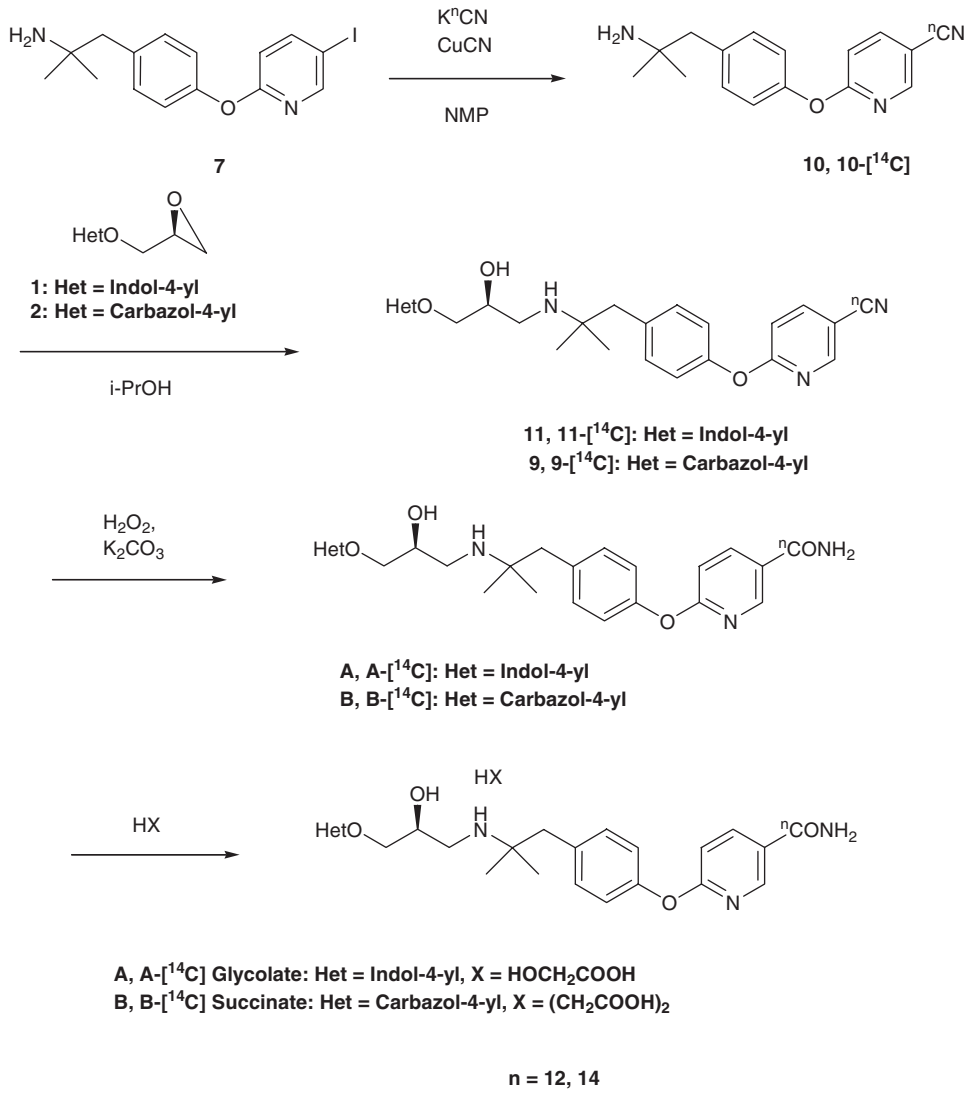
Scheme 1.



Scheme 2.

the presence of copper (I) iodide smoothly gave nitrile **10**-[^{14}**C**]. Condensation of its amino group with epoxides **1** and **2** led to the corresponding adducts **11**-[^{14}**C**] and **9**-[^{14}**C**]. They were converted into the amides **A**-[^{14}**C**] and **B**-[^{14}**C**]

DOI: 10.1002/jlcr



Scheme 3.

using hydrogen peroxide in the presence of potassium carbonate. On the final step, the salts **A**-[^{14}**C**] *glycolate and* **B**-[^{14}**C**] *succinate* were formed. High total chemical and radiochemical yields (more than 50%) from iodoamine **7** were achieved for both target materials.

In conclusion, the cyanation of 2-aryloxy-5-iodopyridine **7** with potassium cyanide-[^{14}C] quantitatively provided ^{14}C-labeled building block **10**-[^{14}**C**] that was used for the efficient preparation of radiolabeled β_3-adrenergic receptor agonists **A**-[^{14}**C**] and **B**-[^{14}**C**].

DOI: 10.1002/jlcr

Experimental

The potassium cyanide-[^{14}C]was purchased from American Radiolabeled Chemicals, Inc. The NMR spectra were obtained in $CDCl_3$ on a Varian Mercury-400 at 400 (^{1}H) and 100 (^{13}C) MHz. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane. Microanalytical, IR, and UV data were provided by Physical Chemistry Department of Lilly Research Laboratories. Flash column chromatography was performed using silica gel 60 (230–400mesh) or Biotage Flash System. TLC was conducted on precoated plates of silica gel 60 F_{254}. HPLC was conducted on a Hitachi instrument with UV detection at 230 nm at a flow rate of 1 ml/min; Conditions A: column Zorbax RX-C8 (4.6 mm × 25 cm); mobile phase: aqueous 0.1% trifluoroacetic acid/acetonitrile, 50:50; Conditions B: column Zorbax C8 (4.6 mm × 25 cm); mobile phase: aqueous 0.5% ammonium phosphate monobasic/acetonitrile, 45:55. The radiochemical purity of **A-[^{14}C]** glycolate was determined by radio-HPLC: column: Zorbax SB-Phenyl (4.6 × 250 mm) with gradient elution at 1.0 ml/min (Solvent A = 70% of 0.1% ifluoroacetic acid/30% of methanol, Solvent B = 40% of 0.1% trifluoroacetic acid/60% of methanol) from 0% B to 100% B over 30 min, and UV detection at 260 nm. The radiochemical purity of **B-[^{14}C]** succinate was determined by radio-HPLC: column Zorbax SB-Phenyl (4.6 × 250 mm) with gradient elution at 1.0 ml/min (Solvent A = 50% of 0.1% trifluoroacetic acid/50% of methanol, Solvent B = 25% of 0.1% trifluoroacetic acid/75% of methanol) from 0% B to 100% B over 32 min, and UV detection at 240 nm. All ^{14}C-compounds were identified by TLC and/or HPLC comparison with the corresponding non-radiolabeled isotopomers.

6-(4-(2-Amino-2-methylpropyl)phenoxy)-3-iodopyridine, **7**

To a solution of 2-bromo-5-iodopyridine (**5**)[6] (1.89 g, 6.66 mmol) in dimethylformamide (40 ml) were added 4-(2-amino-2-methylpropyl)phenol acetate (**6**) (1.5 g, 6.66 mmol) and potassium carbonate (2.77 g, 20 mmol). The reaction mixture was heated at 140°C (bath) for 16 h, and at 155°C (bath) for 4.5 h, then cooled to room temperature, diluted with ethyl acetate (40 ml), and filtered. The filtrate was evaporated under vacuum. Biotage chromatography of the residue (column 40M, eluting sequentially with 500 ml of dichlomethane/methanol, 90:10; 1000 ml of dichlomethane/methanol/ammonium hydroxide, 90:10:1; and 200 ml of dichlomethane/methanol/ammonium hydroxide, 85:15:1.5) gave **7** (1.75 g, 71%) as a pale solid. TLC: $R_f = 0.1$ (dichlomethane/methanol, 90:10). HPLC (conditions A): $R_t = 4.0$ *min*. NMR ($CDCl_3$, δ, ppm): 1.15 (s, 6H), 2.68 (s, 2H), 6.74 (d, $J = 8.8$ Hz, 1H), 7.05 (d, $J = 8.3$ Hz, 2H), 7.21 (d, $J = 8.3$ Hz, 2H), 7.90 (dd, $J = 8.8$ and 2.2 Hz, 1H), 8.36 (d, $J = 2.2$ Hz, 1H). IR (KBr, ν, cm^{-1}): 605, 757, 820, 837, 856, 996, 1076,

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1138, 1166, 1203, 1239, 1273, 1360, 1457, 1505, 1573, 2852, 2911, 2960, 3431. UV (EtOH, λ_{max}, nm): 290, 274, 236. MS (ES+, *m*/*z*, %): 369 (11, M + 1), 352 (100). Analysis calculated for $C_{15}H_{17}IN_2O$: C, 48.92; H, 4.62; I, 34.46; N, 7.61, found: C, 48.85; H, 4.69; I, 33.96; N, 7.64.

(S)-6-[4-[2-[3-(9H-Carbazol-4-yloxy)-2-hydroxypropylamino]-2-methylpropyl] phenoxy]-3-iodopyridine, **8**

A mixture of epoxide **2**[2,3,5] (53 mg, 0.22 mmol) and amine **8** (164 mg, 0.445 mmol) in 2-propanol (2.3 ml) was heated at 75–80°C (bath) for 24 h, and evaporated under vacuum. Biotage chromatography of the residue (column 12M, eluting with dichlomethane/methanol, 95:5) gave **8** (120 mg, 90%) as a white solid. TLC: $R_f = 0.39$ (dichlomethane/methanol, 95:5). HPLC (conditions A): $R_t = 9.7$ min. NMR ($CDCl_3$, δ, ppm): 1.12 (s, 3H), 1.14 (s, 3H), 2.70 (d_{AB}, $J = 3.5$ Hz, 1H), 2.73 (d_{AB}, $J = 3.5$ Hz, 1H), 2.99 (dd, $J = 11.9$ and 7.3 Hz, 1H), 3.11 (dd, $J = 11.9$ and 4.0 Hz, 1H), 4.14–4.26 (m, 2H), 4.32 (dd, $J = 9.2$ and 4.8 Hz, 1H), 6.69 (d, $J = 7.9$ Hz, 1H), 6.70 (d, $J = 8.3$ *Hz*, 1H), 6.95 (d, $J = 8.3$ Hz, 2H), 7.05 (d, $J = 7.9$ Hz, 1H), 7.17 (d, $J = 8.3$ Hz, 2H), 7.21 (t, $J = 7.9$ Hz, 1H), 7.32 (t, $J = 8.3$ Hz, 1H), 7.39 (m, 2H), 7.88 (dd, $J = 8.8$ and 2.5 Hz, 1H), 8.08 (br. s, 1H), 8.28 (d, $J = 7.9$ Hz, 1H), 8.34 (d, $J = 2.2$ Hz. 1H). IR (KBr, ν, cm^{-1}): 722, 753, 784, 828, 995, 1098, 1205, 1264, 1360, 1456, 1506, 1572, 1607, 2860, 2918, 2964, 3409. UV (EtOH, λ_{max}, nm): 332, 319, 286, 242. HRMS (AP+): calculated for $C_{30}H_{30}IN_3O_3$: 608.1410, found: 608.1379. Analysis for $C_{30}H_{30}IN_3O_3$: C, 59.31; H, 4.98; I, 20.89; N, 6.92; found: C, 59.18; H, 5.01; I, 20.87; N, 6.76.

(S)-6-[4-[2-[3-(9H-Carbazol-4-yloxy)-2-hydroxypropylamino]-2-methylpropyl] phenoxy]-3-cyanopyridine, **9** *(from iodide* **8** *)*

A mixture of iodide **8** (60 mg, 0.099 mmol), potassium cyanide (7 mg, 0.107 mmol), and copper (I) iodide (10 mg, 0.053 mmol) in 1-methyl-2 pyrrolidinone (0.25 ml) was heated at 190°C (bath) for 3.5 h, cooled to room temperature, diluted with 30% aqueous sodium cyanide (1 ml), stirred for 30 min, and extracted with ethyl acetate (20 ml). The extract was washed with 30% aqueous sodium cyanide (2 ml) and brine (2 ml). The combined aqueous layer was re-extracted with ethyl acetate (10 ml). The combined organic extract was dried over sodium sulfate, and evaporated under vacuum. Twice performed biotage chromatography of the residue (column 12M, eluting with dichlomethane/methanol, 90:10) gave **9** in a mixture (27 mg) with 1-methyl-2 pyrrolidinone in a ratio ~1:1 by NMR. For **9**:TLC:$R_f = 0.35$ (dichlomethane/methanol, 90:0). HPLC (conditions A): $R_t = 6.3$ min. NMR ($CDCl_3$, δ, ppm): 1.13 (s, 3H), 1.15 (s, 3H), 2.73 (d_{AB}, $J = 3.5$ Hz, 1H), 2.76 (d_{AB}, $J = 3.5$ *Hz*, 1H), 3.01 (dd, $J = 11.9$ and 7.3 Hz, 1H), 3.14 (dd, $J = 11.9$ and 4.0 Hz, 1H),

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4.16-4.26 (m, 2H), 4.32 (m, 1H), 6.68 (d, $J = 7.9$ Hz, 1H), 6.95 (d, $J = 8.3$ Hz, 1H), 6.98 (d, $J = 8.3$ Hz, 2H), 7.05 (d, $J = 8.3$ Hz, 1H), 7.20 (t, $J = 7.9$ Hz, 1H), 7.21 (d, $J = 8.3$ Hz, 2H), 7.31 (t, $J = 8.3$ Hz, 1H), 7.34–7.42 (m, 2H), 7.86 (dd, $J = 8.8$ and 2.2 Hz, 1H), 8.21 (br. s, 1H), 8.27 (d, $J = 7.9$ Hz, 1H), 8.42 (d, $J = 2.2$ Hz. 1H).

6-(4-(2-Amino-2-methylpropyl)phenoxy)-3-cyanopyridine, **10**

A mixture of iodide **7** (475 mg, 1.29 mmol), potassium cyanide (85 mg, 1.3 mmol), and copper (I) iodide (124 mg, 0.65 mmol) in 1-methyl-2 pyrrolidinone (2.9 ml) was heated at 190°C (bath) for 3.5 h, and at 200°C (bath) for 1 h, then cooled to room temperature, diluted with 30% aqueous sodium cyanide (4 ml), stirred for 40 min, and extracted with ethyl acetate (50 ml). The extract was washed with 30% aqueous sodium cyanide (5 ml) and brine (2×3 ml). The combined aqueous layer was re-extracted with ethyl acetate (10 ml). The combined organic extract was dried over sodium sulfate, and evaporated under vacuum. Biotage chromatography of the residue (column 40S, eluting with dichlomethane/methanol/ammonium hydroxide, 90:10:1) gave **10** (320 mg, 93%) as a grayish solid. TLC:$R_f = 0.31$ (dichlomethane/methanol/ammonium hydroxide, 90:10:1). HPLC (conditions A): $R_t = 3.2$ min. NMR ($CDCl_3$, δ, ppm): 1.15 (s, 6H), 2.69 (s, 2H), 7.01 (d, $J = 8.8$ Hz, 1H), 7.07 (d, $J = 8.3$ Hz, 2H), 7.25 (d, $J = 8.3$ Hz, 2H), 7.90 (dd, $J = 8.8$ and 2.2 Hz, 1H), 8.46 (d, $J = 2.2$ *Hz*, 1H). IR (KBr, ν, cm^{-1}): 550, 766, 841, 890, 1018, 1129, 1165, 1205, 1288, 1381, 1474, 1507, 1592, 2231, 2931, 2962, 3431. UV (EtOH, λ_{max}, nm): 463, 368, 238. MS (ES+, *m/z*, %): 268 (38, M + 1), 251 (100). HRMS (AP+): calculated for $C_{16}H_{17}N_3O$: 268.1450, found: 268.1437.

6-(4-(2-Amino-2-methylpropyl)phenoxy)-3-[^{14}c]-cyanopyridine, **10-[^{14}C]**

In the same manner as described above, starting from **7** (475 mg, 1.29 mmol), potassium cyanide-[^{14}C] (49.99 mCi, 55.1 mCi/mmol, 0.907 mmol), potassium cyanide (25 mg, 0.384 mmol), and copper (I) iodide (124 mg, 0.65 mmol) in 1-methyl-2 pyrrolidinone (2.9 ml), **10-[^{14}C]** (450 mg) was obtained.

(S)-6-[4-[2-[3-(Indol-4-yloxy)-2-hydroxypropylamino]-2-methylpropyl]phenoxy]-3-cyanopyridine, **11**

A mixture of amine **10** (93 mg, 0.35 mmol) and epoxide **1** (76 mg, 0.4 mmol) in 2-propanol (3 ml) was heated at 75–80°C (bath) for 18 h, and evaporated under vacuum. Flash chromatograpgy of the residue (silica gel column, eluting with chloroform/methanol, 90:10) gave **11** (748 mg, 68%) as a light brown solid. TLC:$R_f = 0.38$ (chloroform/methanol, 90:10). HPLC (conditions B): $R_t = 8.6$ min. NMR ($CDCl_3$, δ, ppm): 1.11 (s, 3H), 1.13 (s, 3H), 2.75

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(s, 2H), 2.89 (dd, $J = 11.7$ and 6.8 Hz, 1H), 3.02 (br. d, $J = 11.7$ *Hz*, 1H), 4.07–4.17 (m, 3H), 6.49 (d, $J = 7.8$ Hz, 1H), 6.59 (br. s 1H), 6.92–7.21 (m, 8H), 7.83 (dd, $J = 8.8$ and 2.4 Hz, 1H), 8.15 (br. s, 1H), 8.39 (br. s, 1H). The compound **11** is identical (TLC, HPLC, NMR) to an authentic sample of this material.[1]

(S)-6-[4-[2-[3-(Indol-4-yloxy)-2-hydroxypropylamino]-2-methylpropyl]phenoxy]-3-[^{14}C]-cyanopyridine, **11-[^{14}C]**

In the same manner as described above, starting from **10-[^{14}C]** (644 mg, 2.39 mmol), and epoxide **1** (520 mg, 2.75 mmol), in 2-propanol (20 ml), **11-[^{14}C]** (748 mg, 68%) was obtained.

(S)-6-[4-[2-[3-(9H-Carbazol-4-yloxy)-2-hydroxypropylamino]-2-methylpropyl] phenoxy]-3-cyanopyridine, **9** *(from amine* **10***)*

A mixture of amine **10** (281 mg, 1.05 mmol) and epoxide **2** (287 mg, 1.2 mmol) in 2-propanol (7 ml) was heated at 80–85°C (bath) for 17 h, and evaporated under vacuum. Biotage chromatography of the residue (column 40S, eluting with dichloromethane/methanol, 93:7) gave **9** (427 mg, 80%) as a white solid. TLC: $R_f = 0.32$ (dichloromethane/methanol, 93:7). HPLC (conditions A): $R_t = 6.2$ min. NMR ($CDCl_3$, δ, ppm): 1.14 (s, 3H), 1.15 (s, 3H), 2.73 (d_{AB}, $J = 3.5$ Hz, 1H), 2.76 (d_{AB}, $J = 3.5$ Hz, 1H), 3.00 (dd, $J = 11.9$ and 7.0 Hz, 1H), 3.13 (dd, $J = 11.9$ and 4.0 Hz, 1H), 4.18–4.25 (m, 2H), 4.32 (m, 1H), 6.68 (d, $J = 8.3$ Hz, 1H), 6.95 (d, $J = 8.3$ Hz, 1H), 6.98 (d, $J = 8.3$ Hz, 2H), 7.05 (d, $J = 7.9$ Hz, 1H), 7.21 (t, $J = 7.9$ Hz, 1H), 7.22 (d, $J = 8.3$ Hz, 2H), 7.32 (t, $J = 8.3$ Hz, 1H), 7.34–7.42 (m, 2H), 7.86 (dd, $J = 8.8$ and 2.2 Hz, 1H), 8.11 (br. s, 1H), 8.28 (d, $J = 7.9$ Hz, 1H), 8.43 (d, $J = 2.2$ Hz. 1H). IR (KBr, ν, cm^{-1}): 723, 883, 1015, 1089, 1283, 1380, 1474, 1592, 2229, 2918, 2957, 3408. UV (EtOH, λ_{max}, nm): 332, 320, 286, 243. MS (ES+, *m/z*, %): 507 (100, M + 1). HRMS (AP+): calculated for $C_{31}H_{30}N_4O_3$: 507.2396, found: 507.2395.

(S)-6-[4-[2-[3-(9H-Carbazol-4-yloxy)-2-hydroxypropylamino]-2-methylpropyl] phenoxy]-3-[^{14}C]-cyanopyridine, **9-[^{14}C]**

In the same manner as described above, starting from **10-[^{14}C]** (347 mg, 1.29 mmol), and epoxide **2** (350 mg, 1.46 mmol), in 2-propanol (9 ml), **9-[^{14}C]** (550 mg, 84%) was obtained.

(S)-6-[4-[2-[3-(Indol-4-yloxy)-2-hydroxypropylamino]-2-methylpropyl]phenoxy]-pyridine-3-carboxamide, **A**

To a solution of nitrile **11** (105 mg, 0.23 mmol) in dimethylsulfoxide (0.6 ml) were added potassium carbonate (17 mg, 0.12 mmol) and water (0.1 ml). After 15 min, 30% hydrogen peroxide (65 μL, 0.68 mmol) was added dropwise. The reaction mixture was stirred for 3.5 h at room temperature, then diluted with

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ethyl acetate (20 ml), washed with saturated aqueous sodium chloride (2×3 ml), dried over sodium sulfate, and evaporated under vacuum. Flash chromatography of the residue (silica gel column, eluting with chloroform/methanol/ammonium hydroxide, 85:15:1.5) gave **A** (100 mg, 92%) as a white solid. TLC: $R_f = 0.30$ (chloroform/methanol/ammonium hydroxide, 90:10:1). HPLC (conditions B): $R_t = 4.5$ min. NMR (CD_3OD, δ, ppm): 1.10 (s, 6H), 2.75 (d, $J = 5.4$ Hz, 2H), 2.85 (m, 1H), 2.99 (m, 1H), 4.05–4.15 (m, 3H), 6.45 (dd, $J = 4.9$ and 3.4 Hz, 1H), 6.49 (d, $J = 3.4$ Hz, 1H), 6.85–6.95 (m, 5H), 7.05 (d, $J = 2.9$ Hz, 1H), 7.23 (d, $J = 8.8$ Hz, 2H), 8.18 (dd, $J = 8.8$ and 2.4 Hz, 1H), 8.57 (d, $J = 2.4$ Hz, 1H). The compound is identical (TLC, HPLC, NMR) to an authentic sample of **A**.[1]

(S)-6-[4-[2-[3-(Indol-4-yloxy)-2-hydroxypropylamino]-2-methylpropyl]phenoxy]-pyridine-3-[^{14}C]-carboxamide, **A-[^{14}C]**

In the same manner as described above, starting from nitrile **11-[^{14}C]** (748 mg, 1.63 mmol), potassium carbonate (118 mg, 0.85 mmol), water (0.3 ml) and 30% hydrogen peroxide (0.46 ml, 4.79 mmol) in dimethylsulfoxide (4 ml), **A-[^{14}C]** (582 mg, 75%) was obtained.

(S)-6-[4-[2-[3-(9H-Carbazol-4-yloxy)-2-hydroxypropylamino]-2-methylpropyl] phenoxy]-pyridine-3-carboxamide, **B**

To a solution of nitrile **9** (396 mg, 0.78 mmol) in dimethylsulfoxide (2 ml) were added potassium carbonate (59 mg, 0.427 mmol) and water (0.1 ml). After 5 min, 30% hydrogen peroxide (250 µl) was added dropwise. The reaction mixture was stirred for 4 h at room temperature, then diluted with water (1 ml), and extracted with ethyl acetate (40 ml). The extract was washed with 10% aqueous sodium chloride (2 ml), brine (2 ml), dried over sodium sulfate, and evaporated under vacuum. Biotage chromatography of the residue (column 40S, eluting sequentially with 500 ml of dichloromethane/methanol, 90:10; and with 1000 ml of dichloromethane/methanol/ammonium hydroxide, 92:8:08) gave **B** (385 mg, 94%) as a white solid. TLC: $R_f = 0.24$ (dichloromethane/methanol/ammonium hydroxide, 92:8:08). HPLC (conditions A): $R_t = 3.8$ min. NMR ($CDCl_3$, δ, ppm): 1.13 (s, 3H), 1.15 (s, 3H), 2.72 (d_{AB}, $J = 3.5$ Hz, 1H), 2.74 (d_{AB}, $J = 3.5$ Hz, 1H), 3.00 (dd, $J = 11.9$ and 6.6 Hz, 1H), 3.12 (dd, $J = 11.9$and 4.0 Hz, 1H), 4.19–4.24 (m, 2H), 4.32 (m, 1H), 6.68 (d, $J = 7.9$ Hz, 1H), 6.90 (d, $J = 8.8$ Hz, 1H), 6.96 (d, $J = 8.8$ Hz, 2H), 7.04 (d, $J = 7.9$ Hz, 1H), 7.20 (t, $J = 7.9$ Hz, 1H), 7.21 (d, $J = 8.8$ Hz, 2H), 7.31 (t, $J = 7.9$ Hz, 1H), 7.34–7.41 (m, 2H), 8.12 (dd, $J = 8.8$ and 2.6 Hz, 1H), 8.16 (br. s, 1H), 8.29 (d, $J = 7.9$ Hz, 1H), 8.54 (d, $J = 2.6$ Hz. 1H). The compound is identical (TLC, HPLC, NMR) to an authentic sample of **B**.[2]

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(S)-6-[4-[2-[3-(9H-Carbazol-4-yloxy)-2-hydroxypropylamino]-2-methylpropyl] phenoxy]-pyridine-3-[^{14}C]-carboxamide, **B-[^{14}C]**

In the same manner as described above, starting from nitrile **9-[^{14}C]** (550 mg, 1.08 mmol), potassium carbonate (85 mg, 0.615 mmol), water (0.15 ml) and 30% hydrogen peroxide (0.35 ml) in dimethylsulfoxide (2.8 ml), **B-[^{14}C]** (370 mg, 65%) was obtained.

(S)-6-[4-[2-[3-(Indol-4-yloxy)-2-hydroxypropylamino]-2-methylpropyl]phenoxy]-pyridine-3-carboxamide glycolate, **A** *glycolate*

To a solution of **A** (85 mg, 0.179 mmol) in ethanol (0.55 ml) was added a solution of glycolic acid (14 mg, 0.184 mmol) in ethanol (0.37 ml) dropwise. The reaction mixture was stirred for 30 min at room temperature and evaporated under vacuum. The residue was triturated with ethyl ether (3×3 ml), and the supernatant liquid was decanted each time. After drying under vacuum obtained **A** glycolate (88 mg, 89%) as a white solid. HPLC (conditions B): $R_t = 4.5$ min. NMR: (DMSO-D_6, δ, ppm): 1.02 (s, 3H), 1.03 (s, 3H), 2.71 (s, 2H), 2.82 (m, 1H), 2.95 (m, 1H), 3.71 (s, 2H), 4.0.1 (m, 3H), 6.39 (br. s, 1H), 6.43 (dd, $J = 6.8$ and 1.9 Hz, 1H), 6.88–6.99 (m, 5H), 7.14 (br. s, 1H), 7.18 (d, $J = 8.3$ Hz, 2H), 7.42 (br. s, 1H), 7.97 (br. s, 1H), 8.18 (dd, $J = 8.8$ and 2.4 Hz, 1H), 8.56 (d, $J = 2.4$ Hz, 1H), 11.00 (s, 1H). The compound is identical (HPLC, NMR) to an authentic sample of **A** glycolate.[1]

(S)-6-[4-[2-[3-(Indol-4-yloxy)-2-hydroxypropylamino]-2-methylpropyl] phenoxy]-pyridine-3-[^{14}C]-carboxamide glycolate, **A-[^{14}C]** glycolate

In the same manner as described above, starting from A-[^{14}C] (203 mg, 0.426 mmol) in ethanol (1.3 ml), and glycolic acid (33 mg, 0.434 mmol) in ethanol (0.9 ml), **A-[^{14}C]** glycolate (191 mg, 81%) was obtained. The final sample had specific activity 62.9 μCi/mmol, and radiochemical purity 99.0%.

(S)-6-[4-[2-[3-(9H-Carbazol-4-yloxy)-2-hydroxypropylamino]-2-methylpropyl] phenoxy]-pyridine-3-carboxamide succinate, **B** *succinate*

To a solution of **B** (350 mg, 0.667 mmol) in ethyl acetate (2 ml) at 60°C (bath) was added a solution of succinic acid (40 mg, 0.339 mmol) in ethanol (1 ml) dropwise. The precipitate formed was dissolved by addition of ethanol (2×0.5 ml) followed by stirring at 70°C (bath) for 20 min. The reaction mixture was allowed to cool to room temperature, and evaporated under vacuum. The residual solid was triturated with ethyl ether (3 ml), filtered off, rinsed with ethyl ether (2×2 ml), and dried under vacuum to give **B** succinate (340 mg, 87%) as a white solid. HPLC (conditions A): $R_t = 3.8$ min. NMR (CD_3OD, δ, ppm): 1.28 (s, 6H), 2.51 (s, 2H), 2.92 (s, 2H), 3.25 (dd, $J = 12.3$ and 8.3 Hz, 1H), 3.40 (dd, $J = 12.3$ and 2.6 Hz, 1H), 4.26–4.29 (m, 2H),

DOI: 10.1002/jlcr

4.36 (m, 1H), 6.70 (d, $J = 7.9$ Hz, 1H), 6.97 (d, $J = 8.8$ Hz, 1H), 6.96 (d, $J = 8.3$ Hz, 2H), 7.05 (d, $J = 8.3$ Hz, 1H), 7.11 (t, $J = 7.9$ Hz, 1H), 7.26 (d, $J = 8.3$ Hz, 2H), 7.26–7.31 (m, 1H), 7.31 (t, $J = 7.9$ Hz, 1H), 7.40 d, $J = 7.9$ Hz, 1H), 8.24 (dd, $J = 8.8$ and 2.6 Hz, 1H), 8.29 (d, $J = 7.9$ Hz, 1H), 8.60 (d, $J = 2.6$ Hz. 1H).

(S)-6-[4-[2-[3-(9H-Carbazol-4-yloxy)-2-hydroxypropylamino]-2-methylpropyl] phenoxy]-pyridine-3-[^{14}C]-carboxamide succinate, **B-[^{14}C]** *succinate*

In the same manner as described above, starting from **B-[^{14}C]** (370 mg, 0.703 mmol) in ethyl acetate (1.5 ml), and succinic acid (42 mg, 0.356 mmol) in ethanol (1 ml), **B-[^{14}C]** succinate (378 mg, 92%) was obtained. The final sample had specific activity 51.8 μCi/mmol, and radiochemical purity 98.7%.

Acknowledgements

Authors are grateful to Chris Rito of Discovery Chemistry research, and Mary Peters of Chemical Process Research and Development for the supplying of some of the intermediates and experimental procedures.

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DOI: 10.1002/jlcr