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Synthesis of carbon-11 and fluorine-18 labeled *N*-acetyl-1-aryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline derivatives as new potential PET AMPA receptor ligands

Mingzhang Gao,[a] Deyuan Kong,[b] Abraham Clearfield[b] and Qi-Huang Zheng[a,*]

[a]*Department of Radiology, Indiana University School of Medicine, Indianapolis, IN 46202, USA*
[b]*Department of Chemistry, Texas A&M University, College Station, TX 77843, USA*

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Abstract—New carbon-11 and fluorine-18 labeled *N*-acetyl-1-aryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline derivatives were designed and synthesized as potential positron emission tomography AMPA (2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propionic acid) receptor ligands to image brain diseases. The single crystal structure of the most potent compound *N*-acetyl-1-(4′-chlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**5a**) is first reported.

The AMPA (2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propionic acid) receptor antagonists may be useful as potential neuroprotective agents in the treatment of neurological diseases such as epilepsy, ischemia, Parkinson's disease, and multiple sclerosis, since AMPA receptors are involved in learning, memory, neuronal degeneration, and even cell death. *N*-Acetyl-1-aryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline derivatives are novel and highly potent noncompetitive AMPA receptor antagonists recently developed by Gitto et al.[1] In vivo biomedical imaging technique positron emission tomography (PET) coupled with appropriate receptor radioligands has become a clinically valuable and accepted diagnostic tool to image brain diseases.[2] To further develop potential therapeutic drugs as diagnostic agents, we designed and synthesized carbon-11 and fluorine-18 labeled *N*-acetyl-1-aryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline derivatives.

The synthesis of reference standard and desmethylated precursors *N*-acetyl-1-aryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines (**5a**–**g**), *N*-acetyl-1-aryl-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinolines (**6a**–**c**), and *N*-acetyl-1-aryl-6-methoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinolines (**7a**–**b**) was performed using a modification of the literature procedure.[1] The synthetic approach is outlined in Scheme 1. Commercially available starting materials, suitable aromatic aldehydes (**2a**–**g**), were reacted with 2-(3′,4′-dimethoxyphenyl)ethylamine (**1**) to afford the desired imine benziliden[2-(3′,4′-dimethoxyphenyl)ethyl]amines (**3a**–**g**). The crude products were used for the next step reaction without further purification. The intramolecular cyclization reaction of the intermediate imines (**3a**–**g**) catalyzed by trifluoroacetic acid (TFA) formed the corresponding 1-aryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines (**4a**–**g**). The acetylation of the isoquinoline derivatives (**4a**–**g**) with acetyl chloride provided *N*-acetyl compounds (**5a**–**g**). The demethylation of the *N*-acetyl compounds (**5a**–**c**) with aluminium trichloride and ethanethiol[3] yielded monodesmethylated products 6-desmethylated isoquinoline derivatives (**6a**–**c**) and 7-desmethylated isoquinoline derivatives (**7a**–**b**).

The synthesis of target radioligands *N*-acetyl-1-aryl-6-[^{11}C]methoxy-7-methoxy-1,2,3,4-tetrahydroisoquinolines (6-[^{11}C]**5a**–**c**), *N*-acetyl-1-aryl-6-methoxy-7-[^{11}C]methoxy-1,2,3,4-tetrahydroisoquinolines (7-[^{11}C]**5a**–**b**), *N*-acetyl-1-(4′-[^{11}C]methoxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline ([^{11}C]**5e**), and *N*-acetyl-1-(4′-[^{18}F]fluorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline ([^{18}F]**5g**) is shown in Scheme 2. 6-Desmethylated isoquinoline derivatives (**6a**–**c**), 7-desmethylated

Keywords: *N*-Acetyl-1-aryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline derivatives; Carbon-11; Fluorine-18; Positron emission tomography; 2-Amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propionic acid receptor; Brain diseases.
* Corresponding author. Tel.: +1 317 278 4671; fax: +1 317 278 9711; e-mail: qzheng@iupui.edu

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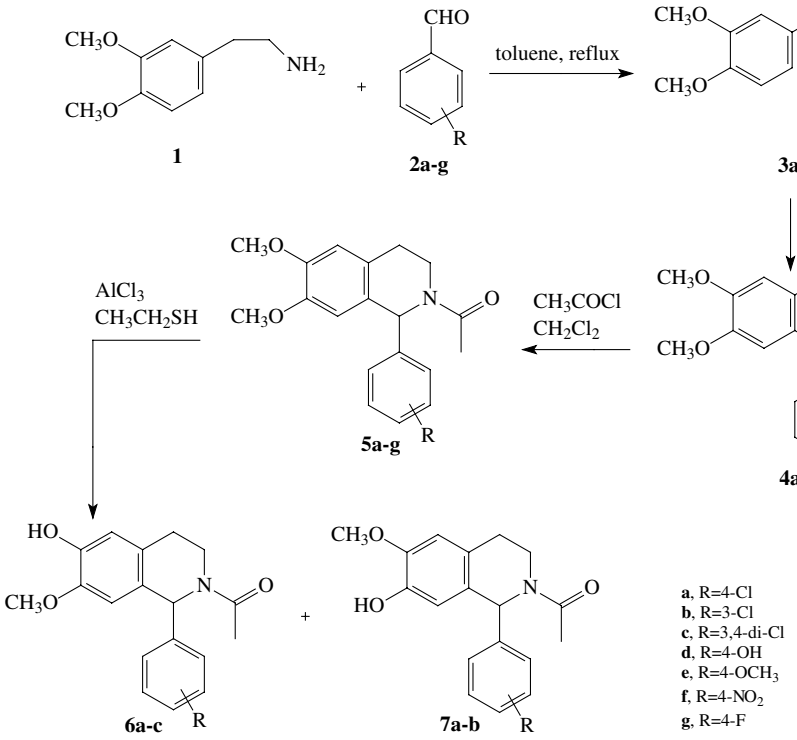
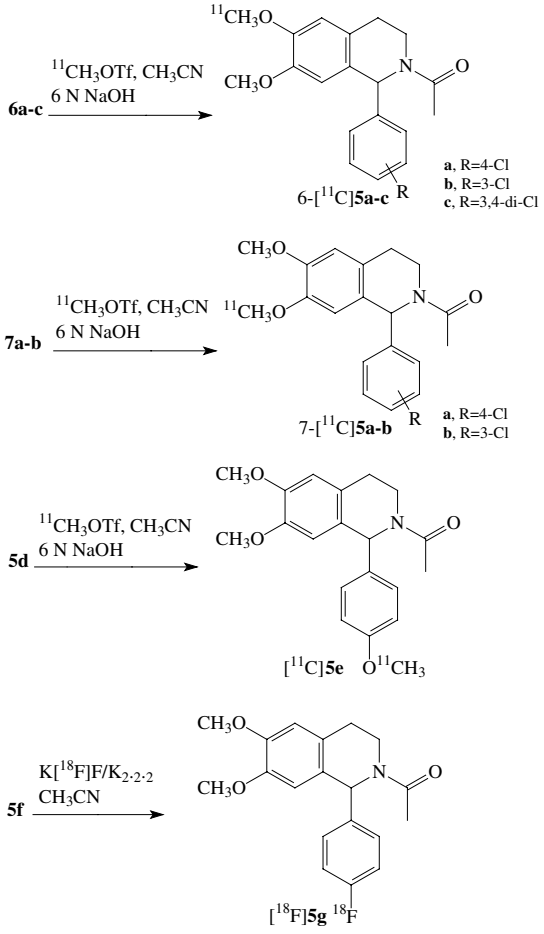


Scheme 1. Synthesis of isoquinoline derivatives.

isoquinoline derivatives (**7a**–**b**), and *N*-acetyl-1-(4′-hydroxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**5e**) were reacted with [^{11}C]methyl triflate ($^{11}CH_3OTf$)[4] under basic conditions through *O*-[^{11}C]methylation and isolated by solid-phase extraction (SPE) purification procedure using a C18 Sep-Pak cartridge[5] to give carbon-11 labeled isoquinoline derivative radiotracers 6-[^{11}C]**5a**–**c**, 7-[^{11}C]**5a**–**b**, and [^{11}C]**5e** in 30–45% radiochemical yields based on [^{11}C]CO_2, 15–20 min overall synthesis time from end of bombardment (EOB), >95% radiochemical purity, and >1.0 Ci/μmol specific activity at the end of synthesis (EOS) measured by analytical HPLC method.[6] *N*-Acetyl-1-(4′-nitrophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**5f**) was labeled by a conventional nucleophilic substitution with K^{18}F/Kryptofix 2.2.2 in acetonitrile at 120 °C for 15–20 min and purified by HPLC method[7] to afford fluorine-18 labeled isoquinoline derivative radiotracer [^{18}F]**5g** in 15-25% radiochemical yield at EOB. The specific activity was 1.0–1.2 Ci/μmol at EOS.

Compounds **5b**–**e** are new noncompetitive AMPA receptor antagonists first synthesized in this laboratory. Compound **5a** has been reported to be more potent than talampanel, a noncompetitive AMPA receptor antagonist currently being investigated in phase III trials as an antiepileptic agent, and a highly effective noncompetitive-type modulator of the AMPA receptor indicated by electrophysiological studies.[1] To better understand the structure of the new PET radioligands, the structure of the ligand **5a** was determined by X-ray crystallography. Compound **5a** was obtained in the form of air-stable, colorless crystals by slow evaporation from a solution of **5a** in ethyl acetate.



Scheme 2. Synthesis of carbon-11 and fluorine-18 labeled isoquinoline derivatives.

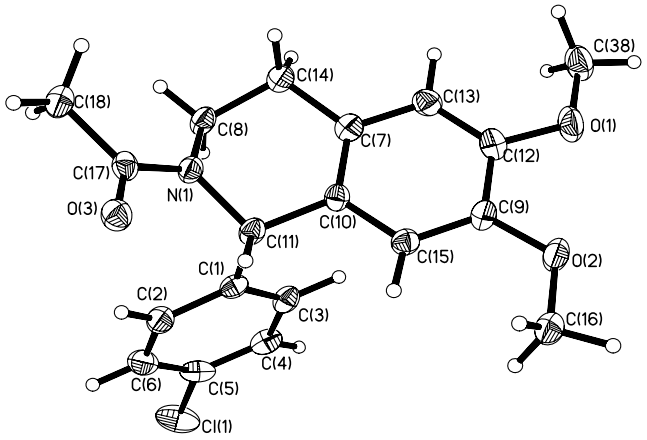


Figure 1. Molecular structure of compound **5a**.

The single crystal structure of compound **5a** is first reported, and the perspective view of **5a** is shown in Figure 1.

The characterization data for compounds **4a**–**g** and **5a**–**g**, experimental details, and characterization data for new compounds **6a**–**c** and **7a**–**b**, and new tracers 6-[^{11}C]**5a**–**c**, 7-[^{11}C]**5a**–**b**, [^{11}C]**5e**, and [^{18}F]**5g**, and crystal data for compound **5a** are given.[8]

In summary, an efficient and convenient chemical and radiochemical synthesis of the precursors, reference standards, and target tracers has been well developed. The chemistry result provides the foundation for further evaluation of carbon-11 and fluorine-18 labeled *N*-acetyl-1-aryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline derivatives as new potential PET radioligands for imaging AMPA receptors in brain diseases.

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8. (a) Experimental details and characterization data. General: All commercial reagents and solvents were used without further purification unless otherwise specified. The $^{11}CH_3OTf$ was made according to a literature procedure.[4] ^{1}H NMR spectra were recorded on a Bruker QE 300 NMR spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shift data for the proton resonances were reported in parts per million (δ) relative to internal standard TMS (δ 0.0). Low resolution mass spectra were obtained using a Bruker Biflex III MALDI-Tof mass spectrometer, and high resolution mass measurements were obtained using a Kratos MS80 mass spectrometer, in the Department of Chemistry at Indiana University. Chromatographic solvent proportions are expressed on a volume: volume basis. Thin layer chromatography was run using Analtech silica gel GF uniplates (5×10 cm^2). Plates were visualized by UV light. Normal phase flash chromatography was carried out on EM Science silica gel 60 (230–400 mesh) with a forced flow of the indicated solvent system in the proportions described below. All moisture-sensitive reactions were performed under a positive pressure of nitrogen maintained by a direct line from a nitrogen source. Analytical HPLC was performed using a Prodigy (Phenomenex) 5 μm C_{18} column, 4.6×250 mm; 3:1:3 CH_3CN:MeOH:20 mM, pH 6.7, $KHPO_4^-$ (buffer solution) mobile phase, flow rate 1.5 mL/min, and UV (254 nm) and γ-ray (NaI) flow detectors. Semi-preparative HPLC was performed using a Prodigy (Phenomenex) 5 μm C-18 column, 10×250 mm; 3:1:3 CH_3CN/MeOH/20 mM, pH 6.7 $KHPO_4^-$ mobile phase, 5.0 mL/min flow rate, UV (254 nm) and γ-ray (NaI) flow detectors. Semi-prep C_{18} silica guard cartridge column 1×1 cm was obtained from E. S. Industries, Berlin, NJ, and part number 300121-C18-BD 10μ. Semi-prep SiO_2 Sep-Pak type cartridge was obtained from Waters Corporate Headquarters, Milford, MA. Sterile vented Millex-GS 0.22 μm filter unit was obtained from Millipore Corporation, Bedford, MA; (b) Compounds (**4a**–**g**) were synthesized using a modification of the literature procedure[1] in about 90% yield. 1-(4′-Chlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**4a**). Mp: 112–114 °C. $R_f = 0.68$ (1:9 MeOH/CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.74 (s, 1H, NH), 2.73 (dt, $J = 4.82$, 15.45 Hz, 1H, C*H*H), 2.87–2.97 (m, 1H, CH*H*), 3.00–3.08 (m, 1H, C*H*H), 3.15–3.23 (m, 1H, CH*H*), 3.64 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 5.02 (s, 1H, H-1), 6.19 (s, 1H, H-5), 6.63 (s, 1H, H-8), 7.18–7.30 (m, 4H, ArH). 1-(3′-Chlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**4b**). Mp: 115–117 °C. $R_f = 0.27$ (EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.78 (s, 1H, NH), 2.72 (dt, $J = 5.14$, 16.17 Hz, 1H, C*H*H), 2.87–2.96 (m, 1H, CH*H*), 2.99–3.07 (m, 1H, C*H*H), 3.15–3.22 (m, 1H, CH*H*), 3.66 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 5.02 (s, 1H, H-1), 6.22 (s, 1H, H-5), 6.63 (s, 1H, H-8), 7.12–7.16 (m, 1H, ArH), 7.24–7.25 (m, 3H, ArH). 1-(3′,4′-Dichlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**4c**). Mp: 130–132 °C. $R_f = 0.48$ (1:9 MeOH/CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.76 (s, 1H, NH), 2.72 (dt, $J = 5.14$, 16.22 Hz, 1H, C*H*H), 2.86–2.99 (m, 1H, CH*H*), 3.01–3.07 (m, 1H, C*H*H), 3.12–3.20 (m, 1H, CH*H*), 3.65 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 5.00 (s, 1H, H-1), 6.19 (s, 1H, H-5), 6.63 (s, 1H, H-8), 7.08 (dd, $J = 2.20$, 8.09 Hz, 1H, ArH), 7.36–7.40 (m, 2H, ArH). 6,7-Dimethoxy-1-(4′-hydoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (**4d**). Mp: 195–197 °C. $R_f = 0.20$ (1:9 MeOH/CH_2Cl_2). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.62

(s, 1H, NH), 2.56–2.64 (m, 1H, C*H*H), 2.71–2.84 (m, 2H, CH_2), 2.95–3.02 (m, 1H, CH*H*), 3.47 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 4.77 (s, 1H, H-1), 6.16 (s, 1H, H-5), 6.68–6.98 (m, 3H, 2H, ArH and 1H, H-8), 6.98 (d, 2H, J = 8.82 Hz, 2H, ArH), 8.31 (s, 1H, ArOH). LRMS (EI): 285 (M^+, 89%), 284 [$(M-H)^+$, 100%]. HRMS (EI): calcd for $C_{17}H_{19}NO_3$ 285.1359, found 285.1346. 6,7-Dimethoxy-1-(4′-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (**4e**). Mp: 89–91 °C. R_f = 0.65 (1:9 MeOH/CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.04 (s, 1H, NH), 2.74 (dt, J = 5.14, 16.18 Hz, 1H, C*H*H), 2.88–3.07 (m, 2H, CH_2), 3.18–3.25 (m, 1H, CH*H*), 3.64 (s, 3H,4′-OCH_3), 3.80 (s, 3H, 6-OCH_3), 3.87 (s, 3H, 7-OCH_3), 5.00 (s, 1H, H-1), 6.25 (s, 1H, H-5), 6.62 (s, 1H, H-8), 6.83 (d, J = 8.83 Hz, 2H, ArH), 7.16 (d, J = 8.09 Hz, 2H, ArH). 6,7-Dimethoxy-1-(4′-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline (**4f**). Mp: 143–144 °C. R_f = 0.71 (1:9 MeOH/CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.76 (s, 1H, NH), 2.73 (dt, J = 5.14, 16.18 Hz, 1H, C*H*H), 2.88–2.97 (m, 1H, CH*H*), 3.01–3.09 (m, 1H, C*H*H), 3.12–3.20 (m, 1H, CH*H*), 3.63 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 5.14 (s, 1H, H-1), 6.14 (s, 1H, H-5), 6.65 (s, 1H, H-8), 7.42 (d, J = 8.83 Hz, 2H, ArH), 8.16 (d, J = 8.09 Hz, 2H, ArH). 6,7-Dimethoxy-1-(4′-fluorophenyl)-1,2,3,4-tetrahydroisoquinoline (**4g**). Mp: 84–86 °C. R_f = 0.66 (1:9 MeOH/CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.87 (s, 1H, NH), 2.73 (dt, J = 4.42, 16.18 Hz, 1H, C*H*H), 2.88–2.98 (m, 1H, CH*H*), 3.00–3.09 (m, 1H, C*H*H), 3.17–3.24 (m, 1H, CH*H*), 3.64 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 5.03 (s, 1H, H-1), 6.20 (s, 1H, H-5), 6.63 (s, 1H, H-8), 6.96–7.03 (m, 2H, ArH), 7.20–7.25 (m, 2H, ArH); (c) Compounds (**5a**–**g**) were synthesized using a modification of the literature procedure[1] in about 90% yield. *N*-Acetyl-1-(4′-chlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**5a**). Mp: 143–145 °C. R_f = 0.60 (EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.14 (s, 3H, $NCOCH_3$), 2.73 (dt, J = 3.30, 14.71 Hz, 1H, C*H*H), 2.89–3.00 (m, 1H, CH*H*), 3.29–3.39 (m, 1H, C*H*H), 3.68–3.75 (m, 1H, CH*H*), 3.75 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 6.48 (s, 1H, H-1), 6.66 (s, 1H, H-5), 6.83 (s, 1H, H-8), 7.16 (d, J = 8.09 Hz, 2H, ArH), 7.22 (d, J = 8.09 Hz, 2H, ArH). *N*-Acetyl-1-(3′-chlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**5b**). Mp: 194–195 °C. R_f = 0.66 (EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.17 (s, 3H, $NCOCH_3$), 2.73 (dt, J = 3.68, 15.44 Hz, 1H, C*H*H), 2.89–3.00 (m, 1H, CH*H*), 3.31–3.41 (m, 1H, C*H*H), 3.69–3.74 (m, 1H, CH*H*), 3.77 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 6.49 (s, 1H, H-1), 6.66 (s, 1H, H-5), 6.83 (s, 1H, H-8), 7.14–7.16 (m, 1H, ArH), 7.19–7.22 (m, 3H, ArH). LRMS (EI): 345 (M^+, 100%). HRMS (EI): calcd for $C_{19}H_{20}ClNO_3$ 345.1126, found 345.1126. *N*-Acetyl-1-(3′,4′-dichlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**5c**). Mp: 125–127 °C. R_f = 0.59 (EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.17 (s, 3H, $NCOCH_3$), 2.73 (dt, J = 3.50, 14.70 Hz, 1H, C*H*H), 2.89–3.00 (m, 1H, CH*H*), 3.29-3.39 (m, 1H, C*H*H), 3.69–3.75 (m, 1H, CH*H*), 3.77 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 6.46 (s, 1H, H-1), 6.67 (s, 1H, H-5), 6.80 (s, 1H, H-8), 7.10 (dd, J = 1.84, 8.09 Hz, 1H, ArH), 7.26–7.35 (m, 2H, ArH). LRMS (EI): 379 (M^+, 100%). HRMS (EI): calcd for $C_{19}H_{19}Cl_2NO_3$ 379.0737, found 379.0725. *N*-Acetyl-6,7-dimethoxy-1-(4′-hydroxyphenyl)-1,2,3,4-tetrahydroisoquinoline (**5d**). Mp: 208–210 °C. R_f = 0.70 (1:9 MeOH/CH_2Cl_2). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.06 (s, 3H, $NCOCH_3$), 2.60–2.70 (m, 1H, C*H*H), 2.79–2.90 (m, 1H, CH*H*), 3.19–3.27 (m, 1H, C*H*H), 3.61–3.65 (m, 1H, CH*H*), 3.61 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 6.55 (s, 1H, H-1), 6.60 (s, 1H, H-5), 6.63 (d, J = 8.09 Hz, 1H, ArH), 6.77 (s, 1H, H-8), 6.88 (d, J = 8.09 Hz, 2H, ArH), 9.32 (s, 1H, OH). LRMS (EI): 327 (M^+, 100%). HRMS (EI): calcd for $C_{19}H_{21}NO_4$ 327.1465, found 327.1460. *N*-Acetyl-6,7-dimethoxy-1-(4′-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline(**5e**). Mp: 110–112 °C. R_f = 0.57 (EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.14 (s, 3H, $NCOCH_3$), 2.71–2.76 (m, 1H, C*H*H), 2.88–2.99 (m, 1H, CH*H*), 3.32–3.42 (m, 1H, C*H*H), 3.65–3.70 (m, 1H, CH*H*), 3.74 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 6.50 (s, 1H, H-1), 6.64 (s, 1H, H-5), 6.78 (s, 1H, H-8), 6.80 (d, J = 8.09 Hz, 2H, ArH), 7.14 (d, J = 8.09 Hz, 2H, ArH). *N*-Acetyl-6,7-dimethoxy-1-(4′-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline (**5f**). Mp: 181–183 °C. R_f = 0.67 (EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.16 (s, 3H, $NCOCH_3$), 2.72 (dt, J = 3.38, 16.18 Hz, 1H, C*H*H), 2.91–3.02 (m, 1H, CH*H*), 3.29–3.39 (m, 1H, C*H*H), 3.71–3.76 (m, 1H, CH*H*), 3.76 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 6.47 (s, 1H, H-1), 6.69 (s, 1H, H-5), 6.90 (s, 1H, H-8), 7.41 (d, J = 8.09 Hz, 2H, ArH), 8.11 (d, J = 8.82 Hz, 2H, ArH). *N*-Acetyl-6,7-dimethoxy-1-(4′-fluorophenyl)-1,2,3,4-tetrahydroisoquinoline (**5g**). Mp: 162–164 °C. R_f = 0.66 (EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.16 (s, 3H, $NCOCH_3$), 2.72 (dt, J = 3.30, 14.71 Hz, 1H, C*H*H), 2.89–3.00 (m, 1H, CH*H*), 3.30–3.40 (m, 1H, C*H*H), 3.68–3.74 (m, 1H, CH*H*), 3.75 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 6.48 (s, 1H, H-1), 6.66 (s, 1H, H-5), 6.85 (s, 1H, H-8), 6.95 (t, J = 8.45 Hz, 2H, ArH), 7.21 (dd, J = 5.51, 8.09 Hz, 2H, ArH); (d) General procedure for preparation of compounds **6a**–**c** and compounds **7a**–**b** from mono-demethylation of compounds **5a**–**c**. To a stirred solution of **5** (1.5 mmol) in ethanethiol (1 mL) and dichloromethane (10 mL) cooled in an ice-water bath was added $AlCl_3$ (6.0 mmol, 0.8 g, 4 equiv of **5a**–**c**). The reaction mixture was kept to stir for 2 h. Subsequently the mixture was poured into water, extracted with dichloromethane, washed with brine, dried by Na_2SO_4, filtered, and then evaporated to give a crude product, which was purified by column chromatography (20% EtOAc/hexane) on silica gel to afford **6a**–**c** in about 40% yield and **7a**–**b** in about 25% yield. *N*-Acetyl-1-(4′-chlorophenyl)-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (**6a**). Mp: 168–169 °C. R_f = 0.67 (EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.13 (s, 3H, $NCOCH_3$), 2.73 (dt, J = 3.68, 16.18 Hz, 1H, C*H*H), 2.84–2.95 (m, 1H, CH*H*), 3.29-3.39 (m, 1H, C*H*H), 3.64–3.71 (ddd, J = 2.94, 5.14, 13.23 Hz, 1H, CH*H*), 3.77 (s, 3H, OCH_3), 5.68 (t, J = 3.62 Hz, 1H, OH), 6.47 (s, 1H, H-1), 6.74 (s, 1H, H-5), 6.82 (s, 1H, H-8), 7.16 (d, J = 8.82 Hz, 2H, ArH), 7.22 (d, J = 8.09 Hz, 2H, ArH). LRMS (EI): 331 (M^+, 100%). HRMS (EI): calcd for $C_{18}H_{18}ClNO_3$ 331.0970, found 331.0965. *N*-Acetyl-1-(3′-chlorophenyl)-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (**6b**). Mp: 173–175 °C. R_f = 0.67 (EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.16 (s, 3H, $NCOCH_3$), 2.69 (dt, J = 3.66, 16.15 Hz, 1H, C*H*H), 2.84–2.89 (m, 1H, CH*H*), 3.31–3.41 (m, 1H, C*H*H), 3.65–3.72 (ddd, J = 2.94, 5.14, 13.24 Hz, 1H, CH*H*), 3.78 (s, 3H, OCH_3), 5.69 (t, J = 4.68 Hz, 1H, OH), 6.49 (s, 1H, H-1), 6.74 (s, 1H, H-5), 6.82 (s, 1H, H-8), 7.11–7.15 (m, 1H, ArH), 7.17–7.25 (m, 3H, ArH). LRMS (EI): 331 (M^+, 100%). HRMS (EI): calcd for $C_{18}H_{18}ClNO_3$ 331.0970, found 331.0963. *N*-Acetyl-1-(3′,4′-dichlorophenyl)-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (**6c**). Mp: 197–199 °C. R_f = 0.63 (EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.14 (s, 3H, $NCOCH_3$), 2.70 (dt, J = 3.68, 16.18 Hz, 1H, C*H*H), 2.84-2.95 (m, 1H, CH*H*), 3.29-3.39 (m, 1H, C*H*H), 3.66–3.73 (ddd, J = 2.94, 5.15, 13.23 Hz, 1H, CH*H*), 3.78 (s, 3H, OCH_3), 5.69 (s, 1H, OH), 6.45 (s, 1H, H-1), 6.75 (s, 1H, H-5), 6.78 (s, 1H, H-8), 7.09 (dd, J = 1.84, 8.82 Hz, 1H, ArH), 7.26–7.35 (m, 2H, ArH). LRMS (EI): 365 (M^+, 100%). HRMS (EI): calcd for $C_{18}H_{17}Cl_2NO_3$ 365.0580, found 365.0577.*N*-Acetyl-1-(4′-chlorophenyl)-7-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline (**7a**). R_f = 0.58 (EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.14 (s, 3H, $NCOCH_3$), 2.73 (dt, J = 2.94,

12.51 Hz, 1H, C*H*H), 2.84–2.97 (m, 1H, CH*H*), 3.31–3.41 (m, 1H, C*H*H), 3.66-3.75 (m, 1H, CH*H*), 3.86 (s, 3H, OCH_3), 5.80 (s, 1H, OH), 6.58 (s, 1H, H-1), 6.64 (s, 1H, H-5), 6.74 (s, 1H, H-8), 7.13–7.20 (m, 4H, ArH). LRMS (EI): 331 (M^+, 100%). HRMS (EI): calcd for $C_{18}H_{18}ClNO_3$ 331.0970, found 331.0966. *N*-Acetyl-1-(3′-chlorophenyl)-7-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline (**7b**). $R_f = 0.62$ (EtOAc). ^1H NMR (300 MHz, $CDCl_3$): δ 2.15 (s, 3H, $NCOCH_3$), 2.73 (dt, $J = 3.68$, 16.18 Hz, 1H, C*H*H), 2.88–2.99 (m, 1H, CH*H*), 3.36-3.46 (m, 1H, C*H*H), 3.68–3.75 (m, 1H, CH*H*), 3.90 (s, 3H, OCH_3), 5.82 (s, 1H, OH), 6.61 (s, 1H, H-1), 6.66 (s, 1H, H-5), 6.77 (s, 1H, H-8), 7.17–7.21 (m, 4H, ArH). LRMS (EI): 331 (M^+, 100%). HRMS (EI): calcd for $C_{18}H_{18}ClNO_3$ 331.0970, found 331.0962; (e) Tracers 6-[^{11}C]**5a**–**c**, 7-[^{11}C]**5a**–**b**, and [^{11}C]**5e**, typical experimental procedure for the radiosynthesis: The precursor (**6a**–**c**, **7a**–**b**, or **5d**) (0.3-0.5 mg) was dissolved in CH_3CN (300 μL). To this solution was added 6 N NaOH (2-3 μL). The mixture was transferred to a small volume, three-necked reaction tube. $^{11}CH_3OTf$ was passed into the air-cooled reaction tube at −15 to −20 °C, which was generated by a Venturi cooling device powered with 100 psi compressed air, until radioactivity reached a maximum (~3 min), then the reaction tube was heated at 70–80 °C for 3 min. The contents of the reaction tube were diluted with $NaHCO_3$ (1 mL, 0.1 M). This solution was passed onto a C_{18} cartridge by gas pressure. The cartridge was washed with H_2O (2× 3 mL), and the aqueous washing was discarded. The product was eluted from the column with EtOH (2× 3 mL) and then passed onto a rotatory evaporator. The solvent was removed by evaporation under high vacuum. The labeled product 6-[^{11}C]**5a**–**c**, 7-[^{11}C]**5a**–**b**, or [^{11}C]**5e** was formulated with NaH_2PO_4 (50 mM), whose volume was dependent upon the use of the labeled product 6-[^{11}C]**5a**–**c**, 7-[^{11}C]**5a**–**b**, or [^{11}C]**5e** in tissue biodistribution studies (~6 mL, 3× 2 mL) or in micro-PET imaging studies (1–3 mL), sterile-filtered through a sterile vented Millex-GS 0.22 μm cellulose acetate membrane, and collected into a sterile vial. Total radioactivity was assayed and total volume was noted. The overall synthesis time was 15–20 min. The decay corrected radiochemical yield, from $^{11}CO_2$, was 30–45%, and the radiochemical purity was >95% by analytical HPLC. Retention times in the analytical HPLC system were: RT**6a**–**c**, **7a**–**b**, **5d** = 2.10–2.95 min, RT6-[^{11}C]**5a**–**c**, 7-[^{11}C]**5a**–**b**, [^{11}C]**5e** = 3.35–4.40 min. The chemical purities of the target tracers 6-[^{11}C]**5a**–**c**, 7-[^{11}C]**5a**–**b**, and [^{11}C]**5e** were >93%; (f) Tracer [^{18}F]**5g**: No-carrier-added (NCA) aqueous $H^{18}F$ (0.5 mL) prepared by $^{18}O(p,n)^{18}F$ nuclear reaction in a RDS-112 cyclotron on an enriched $H_2{}^{18}O$ water (95+%) target was added to a Pyrex vessel which contains K_2CO_3 (4 mg, in 0.2 mL H_2O) and Kryptofix 2.2.2 (10 mg, in 0.5 mL CH_3CN). Azeotropic distillation at 115 °C with HPLC grade CH_3CN (3× 1 mL) under a nitrogen steam efficiently removed water to form anhydrous $K^{18}F$-Kryptofix 2.2.2 complex. The nitro-precursor **5f** (2–3 mg, dissolved in 0.5 mL CH_3CN) was introduced to the $K^{18}F$-Kryptofix 2.2.2 complex. The radiolabeling reaction was monitored by analytical radio-HPLC method. Retention times (RTs) in the analytical HPLC system were: RT**5f** = 2.93 min, RT[^{18}F]**5g** = 3.68 min, and RT$K^{18}F$ = 1.88 min. The reaction mixture was sealed and heated at 120 °C for 15–20 min and was subsequently allowed to cool down, at which time the crude product was passed through a Silica Sep-Pak cartridge to remove Kryptofix 2.2.2 and unreacted $K^{18}F$. The Sep-Pak column was eluted with 15% MeOH/CH_2Cl_2 (5.0 mL), and the fractions were passed onto a rotatory evaporator. The solvent was removed by evaporation under high vacuum (0.1–1.0 mmHg) to give a crude product [^{18}F]**5g**. The mixture containing precursor and product was purified with semi-preparative HPLC method. The contents of the mixture residue were diluted with HPLC mobile phase 3:1:3 CH_3CN/MeOH/20 mM, pH 6.7 $KHPO_4^-$, and injected onto the semi-preparative HPLC column. The product fraction was collected, the solvent was removed by rotatory evaporation under vacuum, and the final product [^{18}F]**5g** was formulated in saline, sterile-filtered through a sterile vented Millex-GS 0.22 μm cellulose acetate membrane, and collected into a sterile vial. Total radioactivity was assayed and total volume was noted. The overall synthesis, purification, and formulation time was 60–70 min from EOB. RTs in the semi-preparative HPLC system were: RT**5f** = 4.57 min, RT[^{18}F]**5g** = 6.92 min. The radiochemical yield of [^{18}F]**5g** was 15–25%. Chemical purity, radiochemical purity, and specific radioactivity were determined by analytical HPLC method. The chemical purities of precursor **5f** and standard sample **5g** were >96%, the radiochemical purity of target radiotracer [^{18}F]**5g** was >99%, and the chemical purity of radiotracer [^{18}F]**5g** was ~92%; (g) X-ray crystallography. The crystallographic measurements were carried out on a Siemens P4 diffractometer with graphite-monochromated Mo-Kα radiation ($\lambda = 0.71073$ Å) and 12-kW rotating generator. The data were collected at 110 K. The structure was solved and refined using the programs SHELXS-97 (Sheldrick, 1997) and SHELXL (Sheldrick 1997). The program X-Seed (Barbour, 1999) was used as an interface to the SHELX programs. X-ray coordinates have been deposited with the Cambridge Crystallographic Data Centre (CCDC) for small molecules and the deposition number is CCDC 294643.