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Radiosynthesis of carbon-11-labeled camptothecin derivatives as potential positron emission tomography tracers for imaging of topoisomerase I in cancers

Mingzhang Gao,[a] Kathy D. Miller,[b] George W. Sledge[b] and Qi-Huang Zheng[a,*]

[a]*Department of Radiology, Indiana University School of Medicine, Indianapolis, IN 46202, USA*
[b]*Department of Medicine, Indiana University School of Medicine, Indianapolis, IN 46202, USA*

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Abstract—Four carbon-11-labeled camptothecin derivatives, 9-[^{11}C]methoxy-20(*S*)-camptothecin ([^{11}C]**5**), 10-[^{11}C]methoxy-20(*S*)-camptothecin ([^{11}C]**7**), 9-nitro-10-[^{11}C]methoxy-20(*S*)-camptothecin ([^{11}C]**9**), and 9-[([^{11}C]trimethylamino)methyl]-10-hydroxy-20(*S*)-camptothecin ([^{11}C]**11**), have been synthesized as potential positron emission tomography tracers for imaging of topoisomerase I in cancers.

The plant antitumor agent camptothecin is a cytotoxic pentacyclic ring alkaloid first isolated from the Chinese tree *Camptotheca acuminata* in 1966.[1] Camptothecin has been a target for synthesis because of its impressive antitumor activity and the paucity of naturally derived material, and many camptothecin analogues have been prepared.[2–4] Camptothecin and its derivatives such as 9-nitro-20(*S*)-camptothecin (9-NC, rubitecan) have been used as chemotherapeutic drugs to treat various cancers like breast cancer,[5] prostate cancer,[6] and lung cancer[7] due to their inhibition activity toward topoisomerase I. Topoisomerase I provides a target for in vivo biomedical imaging technique positron emission tomography (PET) to image cancers. We are interested in the development of novel cancer biomarkers for PET molecular imaging, and numerous PET cancer imaging agents have been synthesized in the laboratory and evaluated in cancer animal models of preclinical study.[8–14] These diagnostic agents target either receptors or enzymes in cancers.[15] To image topoisomerase I in cancers and to monitor the response to chemotherapeutic drug, 9-NC, we designed and synthesized a series of carbon-11-labeled camptothecin derivatives.

The synthesis of the precursor 9-hydroxy-20(*S*)-camptothecin (**4**) and the reference standard 9-methoxy-20(*S*)-camptothecin (**5**), as indicated in Scheme 1, was performed using a modification of the literature procedure.[2] Commercially available camptothecin (**1**) was nitrated with 61% nitric acid in concentrated sulfuric acid to give 9-nitro-20(*S*)-camptothecin (**2**) in 24% yield. Nitro compound **2** was reduced using two different methods, by H_2-Pd/C hydrogenation and by Sn–HCl reduction, to provide 9-amino-20(*S*)-camptothecin (**3**) in 48% and 81% yields, respectively. Amino compound **3** was converted into the hydroxyl derivative via diazonium salt with $NaNO_2/H_2SO_4$ to afford the precursor **4** in 36% yield. The methylation of the 9-hydroxyl precursor **4** with CH_2N_2 gave the reference standard **5** in 94% yield.

The synthesis of the precursor 10-hydroxy-20(*S*)-camptothecin (**6**) and the reference standard 10-methoxy-20(*S*)-camptothecin (**7**), as indicated in Scheme 2, was performed using a modification of the literature procedure.[4] The starting material **1** was converted into precursor **6** by a reduction–oxidation sequence using HOAc-H_2/PtO_2 and $Pb(OAc)_4$-HOAc in 51% yield. The methylation of the 10-hydroxyl precursor **6** with CH_2N_2 gave the reference standard **7** in 88% yield.

The synthesis of the precursor 9-nitro-10-hydroxy-20(*S*)-camptothecin (**8**) and the reference standard 9-nitro-10-methoxy-20(*S*)-camptothecin (**9**), as indicated in Scheme 3, was performed using a modification of the

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* Corresponding author. Tel.: +1 317 278 4671; fax: +1 317 278 9711; e-mail: qzheng@iupui.edu

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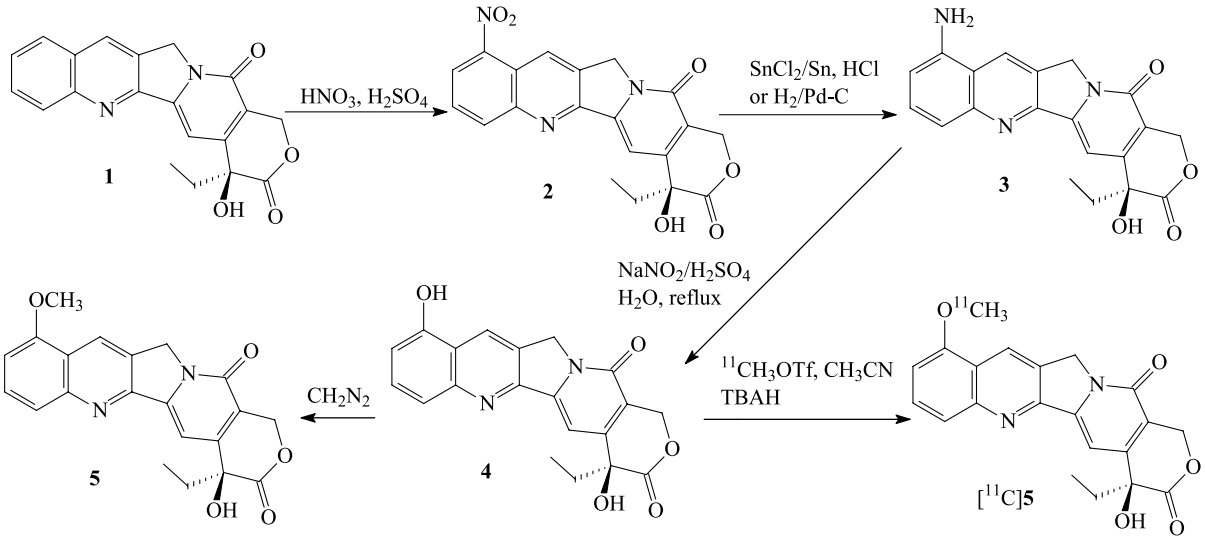
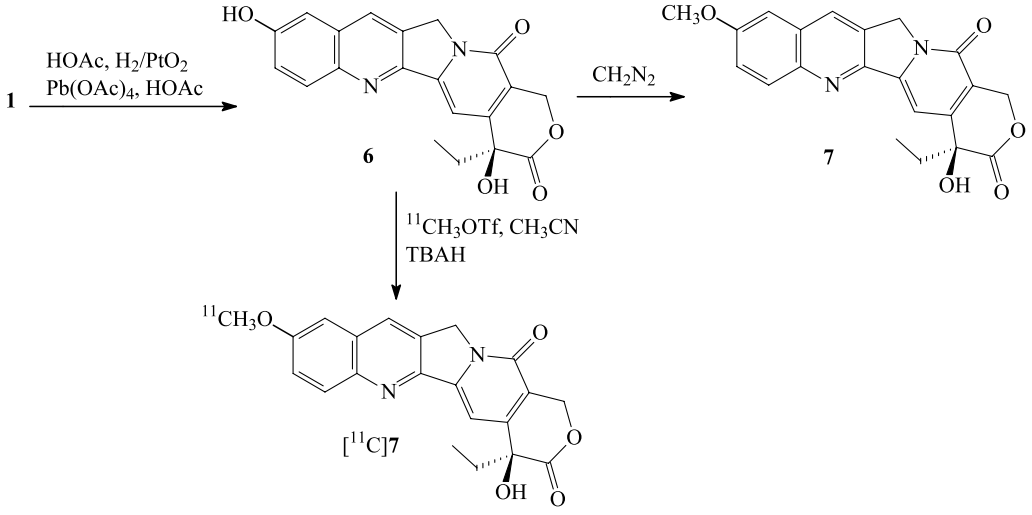


Scheme 1. Synthesis of 9-[^{11}C]methoxy-20(*S*)-camptothecin ([^{11}C]**5**).



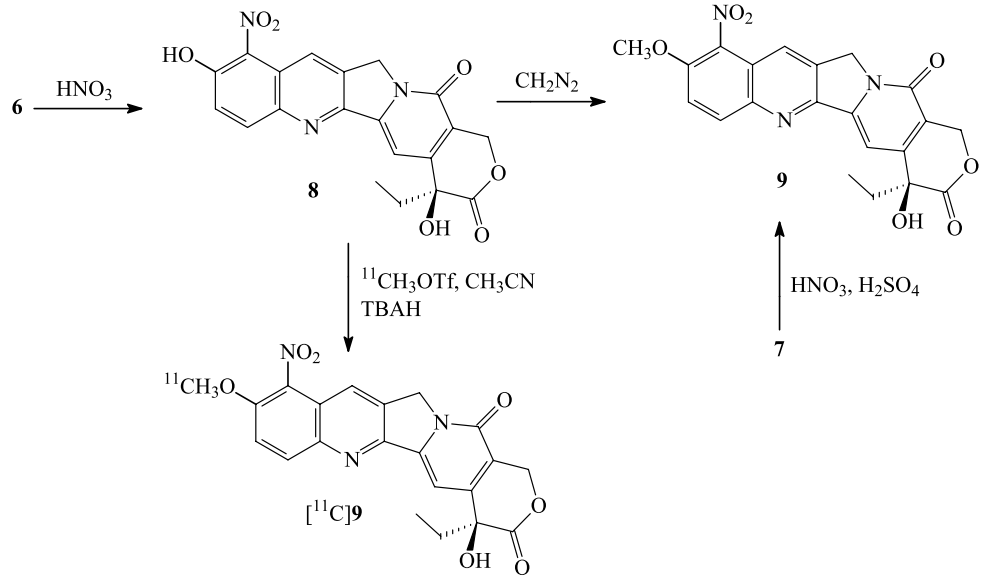
Scheme 2. Synthesis of 10-[^{11}C]methoxy-20(*S*)-camptothecin ([^{11}C]**7**).

literature procedure.[2] The 10-hydroxyl compound **6** was nitrated with HNO_3 to give the precursor **8** in 45% yield. The methylation of the 9-nitro-10-hydroxyl precursor **8** with CH_2N_2 gave the reference standard **9** in 90% yield. The direct nitration of the compound **7** also provided compound **9** in a similar yield with compound **8**.

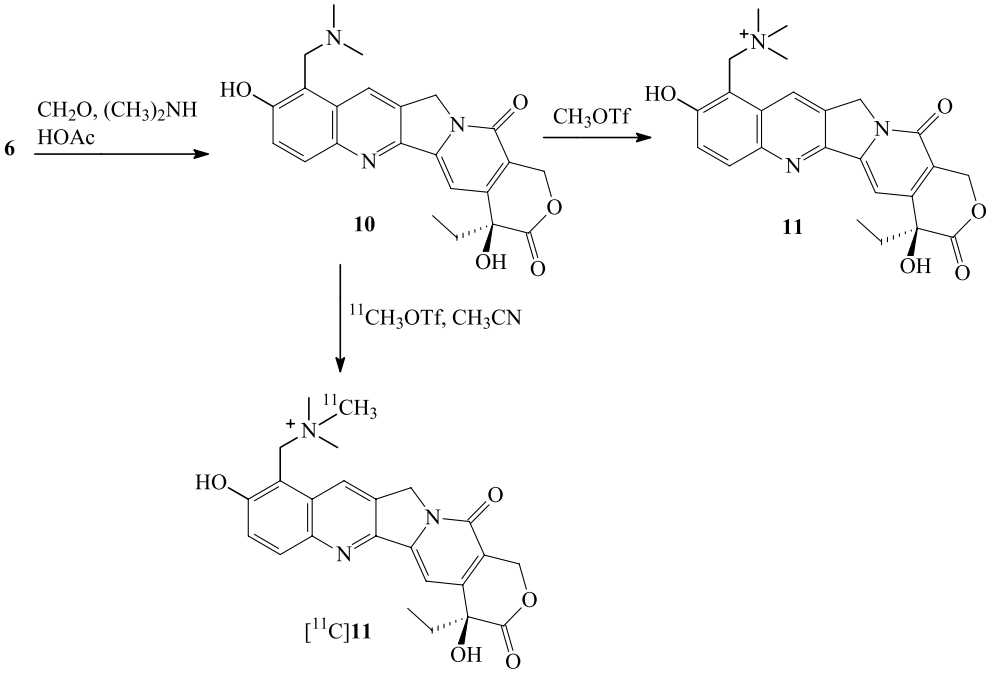
The synthesis of the precursor 9-[(dimethylamino)methyl]-10-hydroxy-20(*S*)-camptothecin (**10**) and the reference standard 9-[(trimethylamino)methyl]-10-methoxy-20(*S*)-camptothecin (**11**), as indicated in Scheme 4, was performed using a modification of the literature procedure.[3] The 10-hydroxyl compound **6** was converted into precursor **10** through Mannich reaction by treatment with dimethylamine, aqueous formaldehyde, and acetic acid in 65% yield. The methylation of the 9-[(dimethylamino)methyl]-10-hydroxyl precursor **10** with methyl triflate gave the reference standard **11** in 60% yield.

The key radioprecursor [^{11}C]methyl triflate ($^{11}CH_3OTf$) was produced by a fast, reliable, and easy-to-operate automated gas phase production method[16] starting from $^{11}CO_2$. Briefly, $^{11}CO_2$ was produced by the $^{14}N(p,\alpha)^{11}C$ nuclear reaction in research purity nitrogen (+3% O_2) using a Siemens RDS-112 cyclotron (11 MeV). Then $^{11}CO_2$ was reacted with 10% H_2 in N_2 at 120 °C to produce $^{11}CH_4$. The monohalogenation (bromination) of $^{11}CH_4$ with liquid Br_2 converted to gas phase $^{11}CH_3Br$. Finally, $^{11}CH_3Br$ gas was passed through a silver triflate (AgOTf) column to generate $^{11}CH_3OTf$. The overall radiochemical yield for $^{11}CH_3OTf$ is 67–71%, based on $^{11}CO_2$, decay corrected to end of bombardment (EOB). Carbon-11 PET radiotracers were synthesized using two kinds of general labeling strategies with [^{11}C]methyl triflate: *O*-[^{11}C]methylation method labeled at *O*-position and *N*-[^{11}C]methylation method labeled at *N*-position.

The target tracers 9-[^{11}C]methoxy-20(*S*)-camptothecin ([^{11}C]**5**), 10-[^{11}C]methoxy-20(*S*)-camptothecin ([^{11}C]**7**), and 9-nitro-10-[^{11}C]methoxy-20(*S*)-camptothecin ([^{11}C]**9**) were prepared by the *O*-[^{11}C]methylation of corresponding precursors **4**, **6**, and **8** using $^{11}CH_3OTf$ and isolated by C_{18} solid-phase extraction (SPE) puri-



Scheme 3. Synthesis of 9-nitro-10-[^{11}C]methoxy-20(*S*)-camptothecin ([^{11}C]**9**).



Scheme 4. Synthesis of 9-[([^{11}C]trimethylamino)methyl]-10-hydroxy-20(*S*)-camptothecin ([^{11}C]**11**).

fication[17,18] in 30–50% radiochemical yield based on [^{11}C]CO_2, 15–20 min overall synthesis time from EOB, >95% radiochemical purity, and >1.0 Ci/μmol specific activity at end of synthesis (EOS) measured by analytical HPLC method (Schemes 1–3). The large polarity difference between the hydroxyl precursor and the labeled methyl ether product permitted the use of an efficient SPE technique for the purification of the tracers [^{11}C]**5**, [^{11}C]**7**, and [^{11}C]**9**, which shortened total synthesis and formulation time, and afforded higher overall radiochemical yield. This is an important simplification for the fast routine production of carbon-11-labeled camptothecin derivatives. Since the precursor is more polar than the product, the SPE technique used in this kind of radiolabeling reaction is C_{18} SPE. The reaction mixture was loaded onto the C_{18} Sep-Pak cartridge by gas pressure. The cartridge was washed with water to remove unreacted hydroxyl precursor and $^{11}CH_3OTf$, and reaction solvent, and then the final labeled methyl ether product was eluted with ethanol. The HPLC confirm that there is no hydroxyl precursor contamination in the methylated product.

The target tracer 9-[([^{11}C]trimethylamino)methyl]-10-hydroxy-20(*S*)-camptothecin ([^{11}C]**11**) was prepared by the *N*-[^{11}C]methylation reaction of its corresponding precursor **10** with $^{11}CH_3OTf$ and isolated by SiO_2 SPE purifi-

cation procedure[18–20] in 40–65% radiochemical yield based on [^{11}C]CO_2, 10–15 min overall synthesis time from EOB, >99% radiochemical purity, and >1.0 Ci/μmol specific activity at EOS measured by HPLC (Scheme 4). A simple technique for convenient labeling and isolation of [N-^{11}C-methyl]quaternary amines[21] by *N*-[^{11}C]methylation method was employed in the radiosynthesis of [^{11}C]**11**. The key part in this technique is a SiO_2 Sep-Pak type cartridge, which contains ~0.5–2 g of adsorbent. The large polarity difference between tertiary amine precursor and the labeled [*N*-^{11}C-methyl]quaternary amine product permitted the use of SPE technique for fast purification of radiotracer from radiolabeling reaction mixture. Since the labeled quaternary amine product is more polar than the tertiary amine precursor, the SPE technique used in this kind of radiolabeling reaction is SiO_2 SPE. The reaction mixture was loaded onto the SiO_2 Sep-Pak cartridge by gas pressure. The cartridge was washed with ethanol to remove unreacted tertiary amine precursor and $^{11}CH_3OTf$, and reaction solvent, and then the final labeled product [*N*-^{11}C-methyl]quaternary amine was eluted with an aqueous solution of 2% acetic acid, which can also contain up to 8% ethanol to enhance recovery of some labeled products.

The experimental details are given for the new tracers [^{11}C]**5**, [^{11}C]**7**, [^{11}C]**9**, and [^{11}C]**11**, and only characterization data are given for other known compounds **2–11**.[22]

In summary, an efficient and convenient chemical and radiochemical synthesis of the precursors, reference standards, and target tracers have been well developed. The chemistry result provides the foundation for further evaluation of carbon-11-labeled camptothecin derivatives as new potential PET radiotracers for imaging enzyme topoisomerase I in cancers.

Acknowledgments

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22. Experimental details and characterization data. (a) General: All commercial reagents and solvents were used without further purification unless otherwise specified. The starting material camptothecin was purchased from the ChemPacific Corporation, Baltimore, MD, USA. The $^{11}CH_3OTf$ was made according to a literature procedure.[16] ^{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). 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 (240 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, USA. Sterile Millex-GS 0.22 μm vented filter unit was obtained from Millipore Corporation, Bedford, MA, USA. (b) Compound **2**: a yellow solid, yield 24%, mp 190–192 °C, R_f = 0.81 (1:9, MeOH/CH_2Cl_2). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.88 (t, *J* = 7.35 Hz, 3H, CH_3), 1.86 (dq, *J* = 4.41, 7.35 Hz, 2H, CH_2Me), 5.31 (s, 2H, H-17), 5.43 (s, 2H, H-5), 6.56 (s, 1H, 20-OH), 7.36 (s, 1H), 8.01 (t, *J* = 8.50 Hz, 1H), 8.51 (t, *J* = 8.50 Hz, 2H), 9.13 (s, 1H). (c) Compound **3**: a yellow solid, yield 48% (H_2-10%Pd/C), yield 81% ($SnCl_2$/Sn–HCl), mp 300 °C (dec.), R_f = 0.50 (1:9, MeOH/CH_2Cl_2). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.87 (t, *J* = 7.0 Hz, 3H, CH_3), 1.83–1.87 (m, 2H, CH_2Me), 5.25 (s, 2H, H-17), 5.41 (s, 2H, H-5), 6.11 (s, 2H, NH_2), 6.51 (s, 1H, 20-OH), 6.78 (d, *J* = 7.40 Hz, 1H), 7.29 (t, *J* = 6.26 Hz, 2H), 7.50 (t,*J* = 8.10 Hz, 1H), 8.83 (s, 1H). (d) Compound **4**: a yellow solid, yield 36%, mp 224–224 °C, R_f = 0.58 (1:9, MeOH/CH_2Cl_2). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.87 (t, *J* = 7.35 Hz, 3H, CH_3), 1.85 (dq, *J* = 4.41, 7.35 Hz, 2H, CH_2Me), 5.25 (s, 2H, H-17), 5.42 (s, 2H, H-5), 6.52 (s, 1H, 20-OH), 7.02 (d, *J* = 7.36 Hz, 1H), 7.03 (s, 1H), 7.57–7.66 (m, 2H), 8.81 (s, 1H), 10.72 (s, 1H, 9-OH). (e) Compound **5**: a yellow solid, yield 94%, mp 223–225 °C, R_f = 0.52 (1:19, MeOH/CH_2Cl_2). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.86 (t, *J* = 7.35 Hz, 3H, CH_3), 1.86 (dq, *J* = 5.15, 7.35 Hz, 2H, CH_2Me), 4.03 (s, 3H, OCH_3), 5.23 (s, 2H, H-17), 5.42 (s, 2H, H-5), 6.52 (s, 1H, 20-OH), 7.15 (d, *J* = 6.61 Hz, 1H), 7.30 (s, 1H), 7.68–7.75 (m, 2H), 8.82 (s, 1H). (f) Compound **6**: a yellow solid, yield 51%, mp 265–267 °C, R_f = 0.50 (1:9, MeOH/CH_2Cl_2). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.87 (t, *J* = 7.35 Hz, 3H, CH_3), 1.85 (dq, *J* = 4.40, 7.35 Hz, 2H, CH_2Me), 5.20 (s, 2H, H-17), 5.39 (s, 2H, H-5), 6.49 (s, 1H, 20-OH), 7.25 (t, *J* = 1 Hz, 2H), 7.41 (dd, *J* = 2.58, 9.18 Hz, 1H), 7.98 (d, *J* = 8.83 Hz, 1H), 8.42 (s, 1H), 10.31 (s, 1H, 10-OH). (g) Compound **7**: a yellow solid, yield 88%, mp 254–255 °C, R_f = 0.84 (1:9, MeOH/CH_2Cl_2). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.87 (t, *J* = 7.35 Hz, 3H, CH_3), 1.81–1.90 (m, 2H, CH_2Me), 3.92 (s, 3H, OCH_3), 5.21 (s, 2H, H-17), 5.40 (s, 2H, H-5), 6.50 (s, 1H, 20-OH), 7.25 (s, 1H), 7.45 (d, *J* = 6.62 Hz, 2H), 8.01 (d, *J* = 10.3 Hz, 1H), 8.50 (s, 1H). (h) Compound **8**: a yellow solid, yield 45%, mp 205–208 °C, R_f = 0.58 (1:9, MeOH/CH_2Cl_2). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.86 (t, *J* = 7.35 Hz, 3H, CH_3), 1.84 (dq, *J* = 4.41, 7.35 Hz, 2H, CH_2Me), 5.24 (s, 2H, H-17), 5.41 (s, 2H, H-5), 6.51 (s, 1H, 20-OH), 7.28 (s, 1H), 7.63 (d, *J* = 9.56 Hz, 1H), 8.24 (d, *J* = 9.56 Hz, 1H), 8.41 (s, 1H), 12.10 (s, 1H, 10-OH). (i) Compound **9**: a yellow solid, yield 90%, mp 218 °C (dec.), R_f = 0.86 (1:9, MeOH/CH_2Cl_2).^{1}H NMR (300 MHz, DMSO-d_6): δ 0.87 (t, *J* = 7.35 Hz, CH_3), 1.86 (dq, *J* = 4.41, 6.62 Hz, CH_2Me), 4.11 (s, 3H, OCH_3), 5.24 (s, 2H, H-17), 5.41 (s, 2H, H-5), 6.53 (s, 1H, 20-OH), 7.31 (s, 1H), 8.00 (d, *J* = 9.56 Hz, 1H), 8.43 (t, *J* = 4.83 Hz, 2 H). (j) Compound **10**: a hygroscopic yellow solid, yield 65%, R_f = 0.27 (1:9, MeOH/CH_2Cl_2). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.87 (t, *J* = 7.0 Hz, 3H, CH_3), 1.86 (q, *J* = 4.0 Hz, 2H, CH_2Me), 1.89 (s, 2H, CH_3CO_2), 2.29 (s, 6H, $(CH_3)_2$N), 3.99 (s, 2H, $ArCH_2$N), 5.22 (s, 2H, H-17), 5.40 (s, 2H, H-5), 7.24 (s, 1H), 7.39 (d, *J* = 8.83 Hz, 1H), 7.94 (d, *J* = 9.56 Hz, 1H), 8.58 (s, 1H). (k) Compound **11**: a hygroscopic yellow solid, yield 60%, R_f = 0.25 (1:9, MeOH/CH_2Cl_2). ^{1}H NMR (300 MHz, acetone-d_6): δ 0.95 (t, *J* = 7.35 Hz, 3H, CH_3), 1.93–1.97 (m, 2H, $MeCH_2$), 3.23 (s, 9H, $(CH_3)_3N^+$), 5.24 (s, 2H), 5.46 (d, *J* = 13.24 Hz, 2H), 5.56 (s, 2H), 7.93 (s, 1H), 8.12 (d, *J* = 9.56 Hz, 1H), 8.60 (d, *J* = 9.56 Hz, 1H), 9.88 (s, 1H), 11.32 (s, 1H, 10-OH). (l) Tracers [^{11}C]**5**, [^{11}C]**7**, and [^{11}C]**9**: typical experimental procedure for the radiosynthesis: the precursor (**4**, **6**, or **8**) (0.6–1.0 mg) was dissolved in CH_3CN (300 μL). To this solution was added tetrabutylammonium hydroxide (TBAH) (2–3 μL, 1 M solution in methanol). The mixture was transferred to a small volume, three-neck reaction tube. $^{11}CH_3OTf$ was passed into the air-cooled reaction tube at −15 °C 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 [^{11}C]**5**, [^{11}C]**7**, or [^{11}C]**9** was formulated with NaH_2PO_4 (50 mM), whose volume was dependent upon the use of the labeled product [^{11}C]**5**, [^{11}C]**7**, or [^{11}C]**9** in tissue biodistribution studies (∼6 mL, 3 × 2 mL) or in micro-PET imaging studies (1–3 mL) of cancer animal models,[8,11,12] 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 ∼20 min. The decay corrected radiochemical yield, from $^{11}CO_2$, was 30–50%, and the radiochemical purity was >95% by analytical HPLC. Retention times in the analytical HPLC system were: RT**4** = 1.67 min, RT**6** = 1.99 min, RT**8** = 1.64 min; RT[^{11}C]**5** = 2.49 min, RT[^{11}C]**7** = 2.91 min, RT[^{11}C]**9** = 2.33 min. The chemical purities of the target tracers [^{11}C]**5**, [^{11}C]**7**, and [^{11}C]**9** were >93%. (m) Tracer [^{11}C]**11**: the precursor **10** (0.6–1 mg) was dissolved in acetonitrile (250 μL). The mixture was transferred to a small volume, three-neck reaction tube. $^{11}CH_3OTf$ was passed into air-cooled reaction tube at −15 °C to −20 °C, which was generated by a Venturi cooling device powered with 100 psi compressed air, until radioactivity in solution reached a maximum (2–3 min), then reaction tube was isolated and heated at 70–80 °C for 2–3 min. The reaction tube was connected to the SiO_2 Sep-Pak. The product solution was passed onto the SiO_2 Sep-Pak for SPE purification by gas pressure. The reaction tube and Sep-Pak were washed with ethanol (5 mL), and the washing solution was discarded to a waste bottle. The product was eluted from the Sep-Pak with 90:8:2 H_2O/EtOH/HOAc (2–4 mL) and sterile-filtered through a 0.22 μm cellulose acetate membrane and collected in a sterile vial. The pH was adjusted to 5.5–7.0 with 2 M NaOH and 150 mM NaH_2PO_4 mixed solution (1/20, 0.2–0.4 mL). Total radioactivity was assayed and the total volume (2.5–5.0 mL) was noted. The overall synthesis time was 10–15 min. The decay corrected yields, from $^{11}CO_2$, were 40–65%, and the radiochemical purity was >99% by analytical HPLC. Retention times in the analytical HPLC system were RT**10** = 2.98 min and RT[^{11}C]**11** = 1.83 min. The chemical purity of the target tracer [^{11}C]**11** was >95%.