Available online at www.sciencedirect.com
ScienceDirect
Bioorganic & Medicinal Chemistry Letters 16 (2006) 5767–5772
Bioorganic & Medicinal Chemistry Letters

Synthesis of radiolabeled stilbene derivatives as new potential PET probes for aryl hydrocarbon receptor in cancers

Mingzhang Gao,[a] Min Wang,[a] Kathy D. Miller,[b] George W. Sledge,[b] Gary D. Hutchins[a] 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*

Received 31 July 2006; revised 16 August 2006; accepted 17 August 2006
Available online 6 September 2006

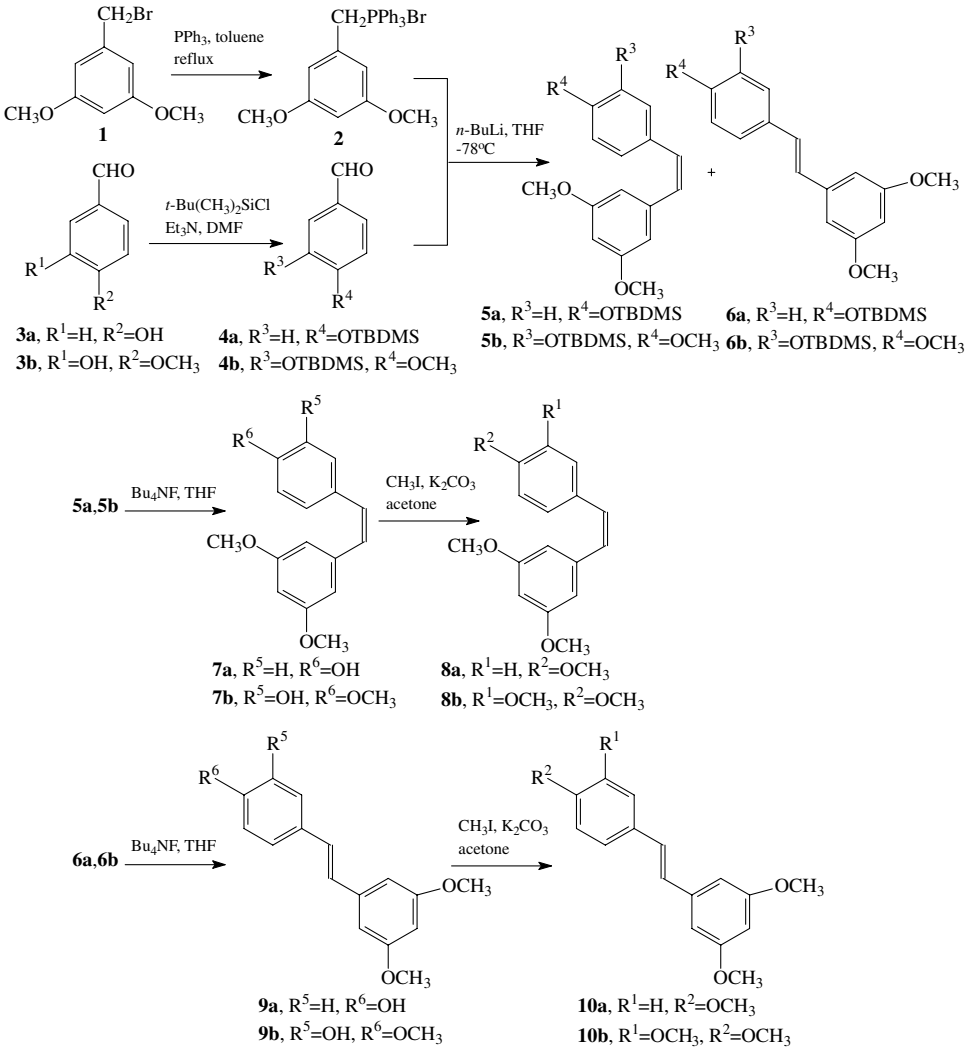
Abstract—New carbon-11 and fluorine-18 labeled stilbene derivatives, *cis*-3,5-dimethoxy-4′-[^{11}C]methoxystilbene (4′-[^{11}C]**8a**), *cis*-3,4′,5-trimethoxy-3′-[^{11}C]methoxystilbene (3′-[^{11}C]**8b**), *trans*-3,5-dimethoxy-4′-[^{11}C]methoxystilbene (4′-[^{11}C]**10a**), *trans*-3,4′,5-trimethoxy-3′-[^{11}C]methoxystilbene (3′-[^{11}C]**10b**), *cis*-3,5-dimethoxy-4′-[^{18}F]fluorostilbene (4′-[^{18}F]**12a**), and *trans*-3,5-dimethoxy-4′-[^{18}F]fluorostilbene (4′-[^{18}F]**13a**), were designed and synthesized as potential PET probes for aryl hydrocarbon receptor (AhR) in cancers.
© 2006 Elsevier Ltd. All rights reserved.

Fluorine-18 labeled stilbene derivatives have been developed by Kung and coworkers as non-invasive biomarkers for biomedical imaging technique positron emission tomography (PET) to image brain amyloid in Alzheimer's disease.[1,2] Stilbene derivatives exhibit a variety of useful biological properties such as anti-leukemic, anti-bacterial, anti-fungal, anti-platelet aggregation, and coronary vasodilator activities.[3–7] They also have strong anti-oxidative and anti-inflammatory activities as potential cancer chemopreventive agents based on their striking inhibitory effects on cellular events associated with cancer initiation, promotion, and progression. Resveratrol, 3,4′,5-trihydroxy-*trans*-stilbene, is a stilbene-based phytoalexin with multiple potencies in various pathologies including anti-oxidant potency, estrogenic potency, and antagonistic activity against the aryl hydrocarbon receptor (AhR), and resveratrol has been identified as an AhR mixed agonist/antagonist.[3] Therefore, stilbene derivatives of resveratrol are AhR mixed agonist/antagonists and could serve as new selective aryl hydrocarbon modulators. AhR is an intracellular, ligand-dependent, basic helix–loop–helix/PAS (per-arnt-sim) transcription factor and modulates the expression of various genes in a wide range of tissues and species.[3] AhR provides an attractive target for the development of receptor-based PET cancer imaging agents. Stilbene derivatives labeled with a positron emitting radionuclide carbon-11 or fluorine-18 may enable non-invasive monitoring AhR expression in cancers and cancer response to AhR agonist/antagonist therapy. Here, we report the design and synthesis of carbon-11 and fluorine-18 stilbene derivatives as PET probes for AhR in cancers.

The synthesis of *cis*- and *trans*-stilbene derivative reference standards and phenolic hydroxyl precursors for carbon-11 radiolabeling was performed using a modified method of the literature procedures.[1–7] The synthetic approach is outlined in Scheme 1. The commercially available starting material, 1-(bromomethyl)-3,5-dimethoxybenzene (**1**), was reacted with triphenylphosphine to provide 3,5-dimethoxybenzyltriphenylphosphonium bromide (**2**) in 90% yield. Starting materials 4-hydroxybenzaldehyde (**3a**) and 3-hydroxy-4-methoxybenzaldehyde (**3b**) were reacted with *tert*-butyldimethylsilyl chloride to afford corresponding products, 4-(*tert*-butyldimethylsilyloxy)benzaldehyde (**4a**) and 3-(*tert*-butyldimethylsilyloxy)-4-methoxybenzaldehyde (**4b**), in about 92% yield. The Wittig reactions of compounds **2** and **4a**,**b** were carried out to give *cis*-3,5-dimethoxy-4′-*tert*-butyldimethylsilyloxystilbene (**5a**) and *cis*-3,4′,5-trimethoxy-3′-*tert*-butyldimethylsilyloxystilbene (**5b**) in 30–50% yield, and *trans*-3,5-dimethoxy-4′-*tert*-butyldimethylsilyloxystilbene (**6a**) and *trans*-3,4′,5-trimethoxy-3′-*tert*-butyldimethylsilyloxystilbene (**6b**) in 30–60%

Keywords: Stilbene derivatives; Carbon-11; Fluorine-18; Positron emission tomography (PET); Aryl hydrocarbon receptor (AhR); Cancer.
* Corresponding author. Tel.: +1 317 278 4671; fax: +1 317 278 9711; e-mail: qzheng@iupui.edu

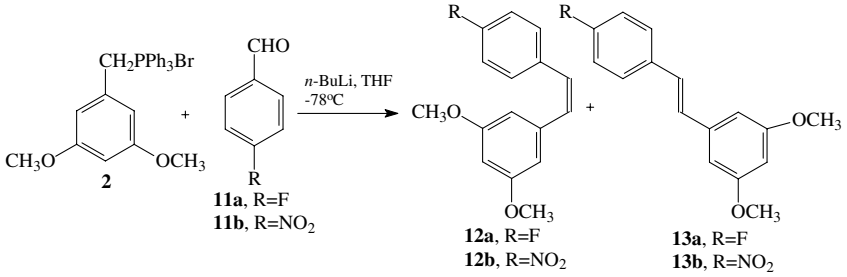
0960-894X/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2006.08.088



Scheme 1. Synthesis of *cis*- and *trans*-stilbene derivatives for carbon-11 radiolabeling.

yield, respectively. *cis*- and *trans*-Stilbene derivatives were separable by column chromatography. The deprotection reaction of silyloxy-protected stilbenes (**5a**,**b** and **6a**,**b**) using tetrabutylammonium fluoride gave *cis*-3,5-dimethoxy-4′-hydroxystilbene (**7a**) and *cis*-3,4′,5-trimethoxy-3′-hydroxystilbene (**7b**), and *trans*-3,5-dimethoxy-4′-hydroxystilbene (**9a**) and *trans*-3,4′,5-trimethoxy-3′-hydroxystilbene (**9b**), in about 90% yield, as precursors for radiolabeling. The methylation reaction of compounds **7a**,**b** and **9a**,**b** using methyl iodide produced *cis*-3,4′,5-trimethoxystilbene (**8a**) and *cis*-3,3′,4′,5-tetramethoxystilbene (**8b**), and *trans*-3,4′,5-trimethoxystilbene (**10a**) and *trans*-3,3′,4′,5-tetramethoxystilbene (**10b**), in about 92% yield, as reference standards.

The synthesis of *cis*- and *trans*-stilbene derivative reference standards and nitro precursors for fluorine-18 radiolabeling was performed using a modified method of the literature procedures.[1–7] The synthetic approach is outlined in Scheme 2. The Wittig reactions of compounds **2** with 4-fluorobenzaldehyde (**11a**) and 4-nitrobenzaldehyde (**11b**) were carried out to give



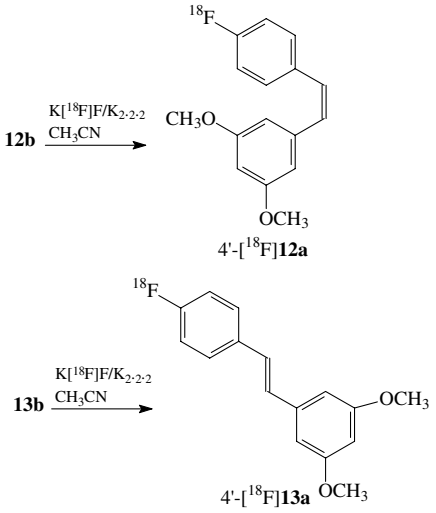
Scheme 2. Synthesis of *cis*- and *trans*-stilbene derivatives for fluorine-18 radiolabeling.

corresponding *cis*-3,5-dimethoxy-4′-fluorostilbene (**12a**) and *trans*-3,5-dimethoxy-4′-fluorostilbene (**13a**) as reference standards, and *cis*-3,5-dimethoxy-4′-nitrostilbene (**12b**) and *trans*-3,5-dimethoxy-4′-nitrostilbene (**13b**) as radiolabeling precursors, in 30–60% yield. Likewise, *cis*- and *trans*-stilbene derivatives were separated by column chromatography.

Compounds **8a**,**b**, **10a**,**b**, **12a**, and **13a** are AhR antagonists with high receptor binding activity, K_i (AhR, nM) 75 ± 3.2, 7.7 ± 0.2, 96 ± 3.4, and 3.1 ± 0.8 for compounds **8a**, **10a**, **12a**, and **13a**, respectively,[3] and nanomolar IC_{50} anti-tumor activity for compounds **8b** and **10b**.[6,8]

Synthesis of target radiotracers carbon-11 stilbenes is shown in Scheme 3. The phenolic hydroxyl precursors (**7a**,**b** and **9a**,**b**) were labeled with [^{11}C]methyl triflate ($^{11}CH_3OTf$)[9] under basic conditions through O-[^{11}C]methylation and isolated by solid-phase extraction (SPE) purification procedure using a C18 Sep-Pak cartridge[10] to give corresponding carbon-11 stilbene derivatives, *cis*-3,5-dimethoxy-4′-[^{11}C]methoxystilbene (4′-[^{11}C]**8a**) and *cis*-3,4′,5-trimethoxy-3′-[^{11}C]methoxystilbene (3′-[^{11}C]**8b**), and *trans*-3,5-dimethoxy-4′-[^{11}C]methoxystilbene (4′-[^{11}C]**10a**) and *trans*-3,4′,5-trimethoxy-3′-[^{11}C]methoxystilbene (3′-[^{11}C]**10b**), in 30–40% radiochemical yields based on [^{11}C]CO_2, 15–20 min overall synthesis time from end of bombardment (EOB), >95% radiochemical purity, and 1.0–2.0 Ci/μmol specific activity at end of synthesis (EOS) measured by analytical HPLC method.[11]

Synthesis of target radiotracers fluorine-18 stilbenes is shown in Scheme 4. The nitro precursors (**12b** and **13b**) were 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[12]

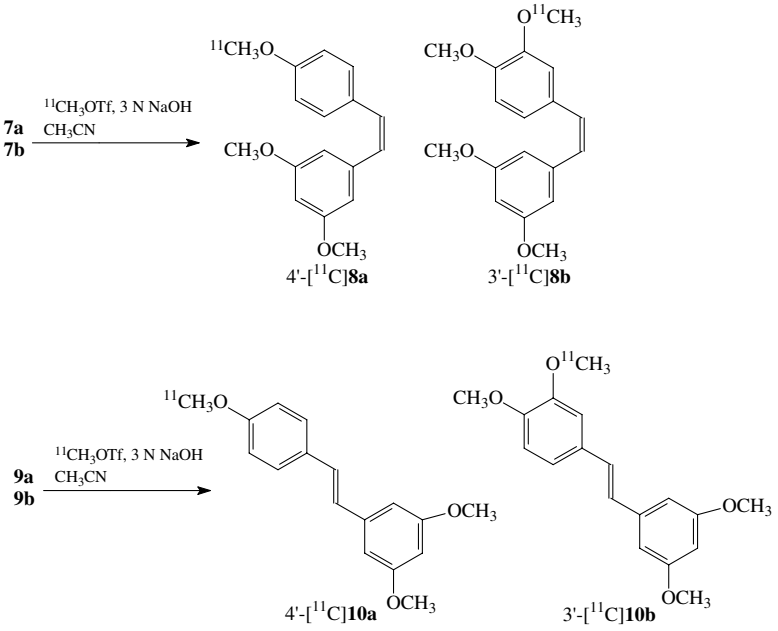


Scheme 4. Synthesis of fluorine-18 labeled stilbene derivatives.

to afford corresponding fluorine-18 stilbene derivatives, *cis*-3,5-dimethoxy-4′-[^{18}F]fluorostilbene (4′-[^{18}F]**12a**) and *trans*-3,5-dimethoxy-4′-[^{18}F]fluorostilbene (4′-[^{18}F]**13a**), in 15–20% radiochemical yield at EOB. The specific activity was 1.0–1.2 Ci/μmol at EOS.

The experimental details and characterization data for compounds **2**, **4a**,**b**, **5a**,**b**, **6a**,**b**, **7a**,**b**, **8a**,**b**, **9a**,**b**, **10a**,**b**, **12a**,**b**, and **13a**,**b**, and new tracers 4′-[^{11}C]**8a**, 3′-[^{11}C]**8b**, 4′-[^{11}C]**10a**, 3′-[^{11}C]**10b**, 4′-[^{18}F]**12a**, and 4′-[^{18}F]**13a** are given.[13]

In summary, an efficient and convenient chemical and radiochemical synthesis of the precursors, reference standards, and target tracers has been well developed. The synthetic methodology of carbon-11 and fluorine-18 labeled *cis*- and *trans*-stilbene derivatives employed



Scheme 3. Synthesis of carbon-11 labeled stilbene derivatives.

readily available benzyl bromides and benzyl aldehydes, featuring a stereo-divergent Wittig olefination, O-methylation with $^{11}CH_3OTf$, and nucleophilic aromatic substitution with $K^{18}F$/Kryptofix 2.2.2 under phase transfer catalysis. These reactions are mostly high yield, and the resulting stilbene derivatives were shown to have excellent radiochemical yields, and thus, given that they could serve as potential AhR antagonists, these agents should be useful as potential PET probes for imaging AhR in tumors. The chemistry result with reported in vitro binding data provides the foundation for further in vivo biological evaluation of carbon-11 and fluorine-18 labeled stilbene derivatives as new potential PET cancer AhR imaging agents.

Acknowledgments

This work was partially supported by the Susan G. Komen Breast Cancer Foundation, Breast Cancer Research Foundation, NIH/NINDS 5P50NS052606 and Indiana Genomics Initiative (INGEN) of Indiana University, which is supported in part by Lilly Endowment Inc. The authors thank Dr. Bruce H. Mock, Barbara E. Glick-Wilson, and Michael L. Sullivan for their assistance in production of $^{11}CH_3OTf$ and $K^{18}F$/Kryptofix 2.2.2. The referees' criticisms and editor's comments for the revision of the manuscript are greatly appreciated.

References and notes

1. Zhang, W.; Oya, S.; Kung, M.-P.; Hou, C.; Maier, D. L.; Kung, H. F. *J. Med. Chem.* **2005**, *48*, 5980.
2. Zhang, W.; Oya, S.; Kung, M.-P.; Hou, C.; Maier, D. L.; Kung, H. F. *Nucl. Med. Biol.* **2005**, *32*, 799.
3. de Medina, P.; Casper, R.; Savouret, J.-F.; Poirot, M. *J. Med. Chem.* **2005**, *48*, 287.
4. Lion, C. J.; Matthews, C. S.; Stevens, M. F. G.; Westwell, A. D. *J. Med. Chem.* **2005**, *48*, 1292.
5. Minutolo, F.; Sala, G.; Bagnacani, A.; Bertini, S.; Carboni, I.; Placanica, G.; Prota, G.; Rapposelli, S.; Sacchi, N.; Macchia, M.; Ghidoni, R. *J. Med. Chem.* **2005**, *48*, 6783.
6. Roberti, M.; Pizzirani, D.; Simoni, D.; Rondanin, R.; Baruchello, R.; Bonora, C.; Buscemi, F.; Grimaudo, S.; Tolomeo, M. *J. Med. Chem.* **2003**, *46*, 3546.
7. Pettit, G. R.; Grealish, M. P.; Jung, M. K.; Hamel, E.; Pettit, R. K.; Chapuis, J.-C.; Schmidt, J. M. *J. Med. Chem.* **2002**, *45*, 2534.
8. Kim, S.; Ko, H.; Park, J. E.; Jung, S.; Lee, S. K.; Chun, Y.-J. *J. Med. Chem.* **2002**, *45*, 160.
9. Mock, B. H.; Mulholland, G. K.; Vavrek, M. T. *Nucl. Med. Biol.* **1999**, *26*, 467.
10. Gao, M.; Miller, K. D.; Sledge, G. W.; Zheng, Q.-H. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3865.
11. Zheng, Q.-H.; Mock, B. H. *Biomed. Chromatogr.* **2005**, *19*, 671.
12. Wang, J.-Q.; Miller, K. D.; Sledge, G. W.; Zheng, Q.-H. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4380.
13. (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.[8] Melting points were determined on a MEL-TEMP II apparatus and are uncorrected. ^1H NMR spectra were recorded on a Bruker QE 300 FT-NMR spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shift data for the proton resonances were reported in parts per million (ppm, δ scale) relative to internal standard TMS (δ 0.0), and coupling constants (J) are reported in hertz (Hz). Chromatographic solvent proportions are expressed on a volume: volume basis. Thin-layer chromatography was run using Analtech silica gel GF uniplates ($5 \times 10\ cm^2$). 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- and/or air-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; 3:1:1 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; 3:1:1 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 10 μ. 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) Compound **2**. Compound **1** (11.6 g, 5.0 mmol) in toluene (180 mL) was added triphenylphosphine (13.2 g, 5.0 mmol). The mixture was heated at reflux for 14 h, and then the mixture was cooled down to room temperature. The resulting precipitate was filtered, washed with toluene, and recrystallized from ethanol to give a pure product **2** as a colorless solid (22.3 g, 90% yield). Mp 273–274 °C. ^1H NMR (300 MHz, DMSO-d_6): δ 3.50 (s, 6H, $2 \times CH_3$), 5.10 (t, J = 12.9 Hz, 2H, CH_2), 6.12 (dd, J = 2.5, 4.0 Hz, 2H, Ph-H), 6.42 (d, J = 2.2 Hz, 1H, Ph-H), 7.65–7.81 (m, 12H, Ph-H), 7.92 (t, J = 7.0 Hz, 3H, Ph-H); (c) General procedure for synthesis of compounds **4a**,**b**. To a solution of compound **3a** or **3b** (10 mmol) in DMF (120 mL) was added triethylamine (12.1 g, 12 mmol). Then *tert*-butyldimethylsilyl chloride (16.5 g, 11 mmol) in DMF (50 mL) was added slowly, and the reaction solution was stirred for overnight at room temperature. The reaction mixture was poured into water and extracted with ethyl acetate for three times, washed with brine for two times, and dried over $MgSO_4$. The solvent was removed under vacuum, and the crude product was purified by flash chromatography (1:19–1:4 EtOAc/hexanes) to give oily pure compound **4a** or **4b** in about 92% yield. Compound **4a**. R_f = 0.78 (1:6 EtOAc/hexanes). ^1H NMR (300 MHz, $CDCl_3$): δ 0.25 (s, 6H, Si–CH_3), 0.98 (s, 9H, C–CH_3), 6.93 (d, J = 8.5 Hz, 2H, Ph-H), 7.77 (d, J = 8.5 Hz, 2H, Ph-H), 9.88 (s, 1H, CHO). Compound **4b**. R_f = 0.60 (1:4, EtOAc/hexane). ^1H NMR (300 MHz, $CDCl_3$): δ 0.17 (s, 6H, Si–CH_3), 1.00 (s, 9H, C–CH_3), 3.89 (s, 3H, OCH_3), 6.94 (d, J = 8.5 Hz, 1H, Ph-H), 7.36 (d, J = 2.2 Hz, 1H, Ph-H), 7.46 (d, J = 8.5 Hz, 1H, Ph-H), 9.82 (s, 1H, CHO); (d) General procedure for synthesis of compounds **5a**,**b**, **6a**,**b**, **12a**,**b**, and **13a**,**b**. To the compound **2** (2.46 g, 5.0 mmol) in anhydrous THF (60 mL) at −78 °C was added *n*-butyllithium (2.1 mL, 2.5 M, 5.25 mmol), and the resulting red solution was

stirred for 3 h. A solution of the aldehyde (5.0 mmol, 1.0 equiv) in THF was added dropwise over 30 min. The reaction temperature was allowed to slowly rise to room temperature, and the mixture was stirred for another 5 h. The resulting cream suspension was poured into water and extracted with dichloromethane for three times. The organic phase was washed brine, dried over $MgSO_4$, and the solvent was removed under vacuum to afford crude product, which was separated and purified by flash chromatography (1:200–1:20 EtOAc/hexanes) to give two pure *cis*- and *trans*- products. The *cis*-stilbene eluted first in 30–50% yield, followed by the *trans*-isomer in 30–60% yield. Compound **5a**. $R_f = 0.52$ (1:19 EtOAc/hexanes). ^1H NMR (300 MHz, $CDCl_3$): δ 0.16 (s, 6H, Si–CH_3), 0.94 (s, 9H, C–CH_3), 3.65 (s, 6H, OCH_3), 6.31 (t, $J = 2.2$ Hz, 1H, Ph-H), 6.41 (d, $J = 6.1$ Hz, 1H, CH=C), 6.50 (d, $J = 6.1$ Hz, 1H, C=CH), 6.4 (d, $J = 2.2$ Hz, 2H, Ph-H), 6.99 (dd, $J = 2.0$, 6.6 Hz, 2H, Ph-H), 7.13 (d, $J = 8.8$ Hz, 2H, Ph-H). Compound **6a**. $R_f = 0.38$ (1:19 EtOAc/hexanes). ^1H NMR (300 MHz, $CDCl_3$): δ 0.21 (s, 6H, Si–CH_3), 0.99 (s, 9H, C–CH_3), 3.82 (s, 6H, OCH_3), 6.37 (t, $J = 2.2$ Hz, 1H, Ph-H), 6.64 (d, $J = 2.2$ Hz, 2H, Ph-H), 6.81 (d, $J = 8.8$ Hz, 2H, Ph-H), 6.86 (d, $J = 16.2$ Hz, 1H, CH=C), 6.92 (d, $J = 16.2$ Hz, 1H, C=CH), 7.36 (d, $J = 8.8$, 2H, Ph-H). Compound **5b**. $R_f = 0.32$ (1:19 EtOAc/hexanes). ^1H NMR (300 MHz, $CDCl_3$): δ 0.05 (s, 6H, Si–CH_3), 0.92 (s, 9H, C–CH_3), 3.67 (s, 6H, OCH_3), 3.77 (s, 3H, OCH_3), 6.30 (t, $J = 2.2$ Hz, 1H, Ph-H), 6.41 (d, $J = 2.2$ Hz, 2H, Ph-H), 6.45 (d, $J = 3.0$ Hz, 2H, Ph-H), 6.70 (d, $J = 8.8$ Hz, 1H, CH=C), 6.75 (d, $J = 2.2$ Hz, 1H, Ph-H), 6.81 (dd, $J = 2.2$, 8.8 Hz, 1H, C=CH). Compound **6b**. Yellow solid, mp 53–54 °C, $R_f = 0.24$ (1:19 EtOAc/hexanes). ^1H NMR (300 MHz, $CDCl_3$): δ 0.18 (s, 6H, Si–CH_3), 1.02 (s, 9H, C–CH_3), 3.81 (s, 3H, OCH_3), 3.82 (s, 6H, OCH_3), 6.37 (t, $J = 2.2$ Hz, 1H, Ph-H), 6.64 (d, $J = 2.2$ Hz, 2H, Ph-H), 6.81–6.87 (m, 2H, Ph-H and CH=C), 7.00–7.07 (m, 3H, Ph-H and C=CH). Compound **12a**. $R_f = 0.48$ (1:19 EtOAc/hexanes). ^1H NMR (300 MHz, $CDCl_3$): δ 3.65 (s, 6H, OCH_3), 6.32 (t, $J = 2.2$ Hz, 1H, Ph-H), 6.37 (d, $J = 2.2$ Hz, 2H, Ph-H), 6.48 (d, $J = 12.5$ Hz, 1H, CH=C), 6.53 (d, $J = 12.5$, 1H, C=CH), 6.91 (t, $J = 8.8$ Hz, 2H, Ph-H), 7.20–7.25 (m, 2H, Ph-H). Compound **13a**. Colorless solid, mp 42–44 °C, $R_f = 0.34$ (1:19 EtOAc/hexanes). ^1H NMR (300 MHz, $CDCl_3$): δ 3.83 (s, 6H, OCH_3), 6.40 (t, $J = 2.2$ Hz, 1H, Ph-H), 6.65 (d, $J = 2.2$ Hz, 2H, Ph-H), 6.91 (d, $J = 16.2$ Hz, 1H, CH=C), 6.96–7.07 (m, 3H, C=CH and Ph-H), 7.44–7.49 (m, 2H, Ph-H). Compound **12b**. Yellow solid, mp 71–72 °C, $R_f = 0.22$ (1:19 EtOAc/hexanes). ^1H NMR (300 MHz, $CDCl_3$): δ 3.84 (s, 6H, OCH_3), 6.46 (t, $J = 2.2$ Hz, 1H, Ph-H), 6.69 (d, $J = 2.2$ Hz, 2H, Ph-H), 7.08 (d, $J = 16.2$ Hz, 1H, CH=C), 7.17 (d, $J = 16.2$ Hz,1H, C=CH), 7.61 (d, $J = 8.8$ Hz, 2H, Ph-H), 8.20 (d, $J = 8.8$ Hz, 2H, Ph-H). Compound **13b**. Yellow solid, mp 134–135 °C, $R_f = 0.15$ (1:19 EtOAc/hexanes). ^1H NMR (300 MHz, $CDCl_3$): δ 3.67 (s, 6H, OCH_3), 6.34 (d, $J = 2.2$ Hz, 2H, Ph-H), 6.36 (t, $J = 2.2$ Hz, 1H, Ph-H), 6.58 (d, $J = 12.1$ Hz, 1H, CH=C), 6.73 (d, $J = 12.1$ Hz, 1H, C=CH), 7.38 (d, $J = 8.8$ Hz, 2H, Ph-H), 8.07 (d, $J = 8.8$ Hz, 2H, Ph-H); (e) General procedure for synthesis of compounds **7a**,**b** and **9a**,**b**. To a solution of compound **5a**, **5b**, **6a** or **6b** (1 equiv) in anhydrous THF (20 mL), tetrabutylammonium fluoride (1 M in THF, 3 equiv) was added. The yellow solution was stirred for 1 h at room temperature. Then the reaction mixture was poured into water, extracted with dichloromethane. Solvent was removed under vacuum to afford the crude product, which was purified by flash chromatography to give pure product **7a**, **7b**, **9a** or **9b** in about 90% yield. Compound **7a**. $R_f = 0.74$ (1:1 EtOAc/hexanes). ^1H NMR (300 MHz, $CDCl_3$): δ 3.66 (s, 6H, OCH_3), 5.10 (s, 1H, OH), 6.32 (t, $J = 2.2$ Hz, 1H, Ph-H), 6.43 (d, $J = 2.2$ Hz, 2H, Ph-H), 6.41 (d, $J = 12.5$ Hz, 1H, CH=C), 6.49 (d, $J = 12.5$ Hz, 1H, C=CH), 6.66 (dd, $J = 2.2$, 6.6 Hz, 2H, Ph-H), 7.13 (d, $J = 8.8$ Hz, 2H, Ph-H). Compound **9a**. Mp 87–88 °C, $R_f = 0.68$ (1:1 EtOAc/hexanes). ^1H NMR (300 MHz, $CDCl_3$): δ 3.82 (s, 6H, OCH_3), 5.05 (s, 1H, OH), 6.38 (t, $J = 2.2$ Hz, 1H, Ph-H), 6.65 (d, $J = 2.2$ Hz, 2H, Ph-H), 6.81 (dd, $J = 2.2$, 6.62 Hz, 2H, Ph-H), 6.86 (d, $J = 16.5$ Hz, 1H, CH=C), 6.99 (d, $J = 16.5$ Hz, 1H, C=CH), 7.38 (d, $J = 8.8$ Hz, 2H, Ph-H). Compound **7b**. $R_f = 0.46$ (1:4 EtOAc/hexanes). ^1H NMR (300 MHz, $CDCl_3$): δ 3.66 (s, 6H, OCH_3), 3.84 (s, 3H, OCH_3), 5.56 (s, 1H, OH), 6.31 (t, $J = 2.2$ Hz, 1H, Ph-H), 6.40–6.50 (m, 4H, CH=CH and Ph-H), 6.68 (d, $J = 8.8$ Hz, 1H, Ph-H), 6.76 (dd, $J = 2.2$, 8.80 Hz, 1H, Ph-H), 6.87 (d, $J = 2.2$, 1H, Ph-H). Compound **9b**. Mp 89–90 °C, $R_f = 0.42$ (1:4 EtOAc/hexanes). ^1H NMR (300 MHz, $CDCl_3$): δ 3.82 (s, 6H, OCH_3), 3.90 (s, 3H, OCH_3), 5.62 (s, 1H, OH), 6.37 (t, $J = 2.2$ Hz, 1H, Ph-H), 6.64 (d, $J = 2.2$ Hz, 2H, Ph-H), 6.81–6.91 (m, 2H), 6.96–7.01 (m, 2H), 7.13 (d, $J = 2.2$, 1H, Ph-H); (f) General procedure for synthesis of compounds **8a**,**b** and **10a**,**b**. To a solution of compounds **7a**, **7b**, **9a** or **9b** (1 equiv) in acetone (30 mL), potassium carbonate (1.2 equiv) and iodomethane (1.5 equiv) were added. The reaction mixture was heated at reflux for 5 h, and then the mixture was cooled down to room temperature and filtered. The organic phase was evaporated under vacuum, and the residue was purified by flash chromatography to obtain pure products **8a**, **8b**, **10a** or **10b** in about 92% yield. Compound **8a**. $R_f = 0.74$ (1:3 EtOAc/hexanes). ^1H NMR (300 MHz, $CDCl_3$): δ 3.65 (s, 6H, OCH_3), 3.76 (s, 3H, OCH_3), 6.31 (t, $J = 2.2$ Hz, 1H, Ph-H), 6.43 (d, $J = 2.2$ Hz, 2H, Ph-H), 6.41 (d, $J = 11.8$ Hz, 1H, CH=C), 6.49 (d, $J = 11.8$ Hz, 1H, C=CH), 6.74 (d, $J = 8.8$ Hz, 2H, Ph-H), 7.19 (d, $J = 8.8$ Hz, 2H, Ph-H). Compound **10a**. Mp 57 °C, $R_f = 0.68$ (1:3 EtOAc/hexanes). ^1H NMR (300 MHz, $CDCl_3$): δ 3.83 (s, 9H, OCH_3), 6.37 (t, $J = 2.2$ Hz, 1H, Ph-H), 6.65 (d, $J = 2.2$ Hz, 2H, Ph-H), 6.87 (d, $J = 8.8$ Hz, 2H, Ph-H), 6.87 (d, $J = 16.2$ Hz, 1H, CH=C), 7.01 (d, $J = 16.2$ Hz, 1H, C=CH), 7.42 (d, $J = 8.8$ Hz, 2H, Ph-H). Compound **8b**. $R_f = 0.56$ (1:4 EtOAc/hexanes). ^1H NMR (300 MHz, $CDCl_3$): δ 3.65 (s, 3H, OCH_3), 3.67 (s, 6H, OCH_3), 3.85 (s, 3H, OCH_3), 6.32 (t, $J = 2.2$ Hz, 1H, Ph-H), 6.45 (d, $J = 2.2$ Hz, 2H, Ph-H), 6.48 (d, $J = 11.1$ Hz, 1H, CH=C), 6.50 (d, $J = 11.1$ Hz, 1H, C=CH), 6.73 (d, $J = 8.8$ Hz, 1H, Ph-H), 6.83 (d, $J = 8.8$ Hz, 2H, Ph-H). Compound **10b**. $R_f = 0.50$ (1:4 EtOAc/hexanes). ^1H NMR (300 MHz, $CDCl_3$): δ 3.82 (s, 6H, OCH_3), 3.89 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 6.37 (t, $J = 2.2$ Hz, 1H, Ph-H), 6.65 (d, $J = 2.2$ Hz, 2H, Ph-H), 6.84 (d, $J = 8.1$ Hz, 1H, Ph-H), 6.92 (d, $J = 17.6$ Hz, 1H, CH=C), 7.00–7.06 (m, 3H, C=CH and Ph-H); (g) Typical experimental procedure for the radiosynthesis of C-11 tracer 4′-[^{11}C]**8a**, 3′-[^{11}C]**8b**, 4′-[^{11}C]**10a**, or 3′-[^{11}C]**10b**. The precursor (**7a**, **7b**, **9a** or **9b**) (0.3–0.5 mg) was dissolved in CH_3CN (300 μL). To this solution was added 3 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 4′-[^{11}C]**8a**, 3′-[^{11}C]**8b**, 4′-[^{11}C]**10a**, or 3′-[^{11}C]**10b** was formulated with saline, whose volume was dependent upon the use of the labeled product 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 30–40%, and the radiochemical purity was >95% by analytical HPLC. Retention times in the analytical HPLC system were: t_R **7a** = 3.50 min, t_R **8a** = 5.55 min, t_R 4′-[^{11}C]**8a** = 5.55 min; t_R **7b** = 3.66 min, t_R **8b** = 4.47 min, t_R 3′-[^{11}C]**8b** = 4.47 min; t_R **9a** = 3.17 min, t_R **10a** = 5.39 min, t_R 4′-[^{11}C]**10a** = 5.39 min; and t_R **9b** = 3.28 min, t_R **10b** = 4.22 min, t_R 3′-[^{11}C]**10b** = 4.22 min. The chemical purities of the target tracers 4′-[^{11}C]**8a**, 3′-[^{11}C]**8b**, 4′-[^{11}C]**10a** and 3′-[^{11}C]**10b** were >93%; (h) Typical experimental procedure for the radiosynthesis of F-18 tracer 4′-[^{18}F]**12a** or 4′-[^{18}F]**13a**. 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 **12b** or **13b** (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 in the analytical HPLC system were: t_R **12b** = 5.18 min, t_R **12a** = 6.09 min, t_R 4′-[^{18}F]**12a** = 6.09 min; t_R **13b** = 5.31 min, t_R **13a** = 5.79 min, t_R 4′-[^{18}F]**13a** = 5.79 min; and t_R 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 semi-prep SiO_2 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 4′-[^{18}F]**12a** or 4′-[^{18}F]**13a**. 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 3:1:1 CH_3CN/MeOH 20 mM, pH 6.7, $KHPO_4^-$, and injected onto the semi-preparative HPLC column with 2 mL injection loop. The product fraction was collected, the solvent was removed by rotatory evaporation under vacuum, and the final product 4′-[^{18}F]**12a** or 4′-[^{18}F]**13a** 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. Retention times in the semi-preparative HPLC system were: t_R **12b** = 7.28 min, t_R **12a** = 9.89 min, t_R 4′-[^{18}F]**12a** = 9.89 min; and t_R **13b** = 7.76 min, t_R **13a** = 9.35 min, t_R 4′-[^{18}F]**13a** = 9.35 min. The radiochemical yield of 4′-[^{18}F]**12a** or 4′-[^{18}F]**13a** was 15–20%. Chemical purity, radiochemical purity, and specific radioactivity were determined by analytical HPLC method. The chemical purities of precursors **12b** and **13b**, and standard samples **12a** and **13a** were >96%, the radiochemical purity of target radiotracer 4′-[^{18}F]**12a** or 4′-[^{18}F]**13a** was >99%, and the chemical purity of radiotracer 4′-[^{18}F]**12a** or 4′-[^{18}F]**13a** was >94%.