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Synthesis and Binding Affinity of a Fluorine-Substituted Peroxisome Proliferator-Activated Gamma (PPARγ) Ligand as a Potential Positron Emission Tomography (PET) Imaging Agent

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The peroxisome proliferator-activated receptor γ (PPARγ) is an important regulator of lipid metabolism and the differentiation of pre-adipocytes. Thus, imaging PPARγ in vivo using positron-emission tomography (PET) might be useful in assessing lipid metabolism disorders and identifying tumor cell differentiation. A fluorine-substituted PPARγ ligand from tyrosine-benzophenone class, compound **1**, has a very high affinity for PPARγ receptor (K_i = 0.14 nM). To develop this compound as a PPARγ PET imaging agent, we investigated synthetic routes suitable for its labeling with the short-lived PET radionuclide fluorine-18 ($t_{1/2}$ = 110 min). To obtain the high specific activity material needed for receptor imaging with this isotope, reactions need to proceed efficiently, within a short time, starting from fluoride ion at the tracer level. The most promising approach involves introduction of fluorine into a suitable benzophenone precursor, followed by efficient coupling of this intermediate with the heterocyclic tyrosine component using a copper-catalyzed Ullmann-type condensation.

INTRODUCTION

The nuclear hormone receptor, peroxisome proliferator-activated receptor γ (PPARγ) plays critical roles in adipogenesis and insulin-mediated glucose homeostasis, and in liposarcoma, PPARγ ligands can induce cancer cells to stop proliferating, lose their malignant character, and undergo terminal differentiation to adipocytes (*1*−*10*). PPARγ is also expressed in other tumor cells, including several breast cancer cell lines, as well as in animal models for breast cancer derived from primary and metastatic tumors, and recently, a number of laboratories have shown that PPARγ activation alters the growth characteristics of breast cancer cells (*6*, *9*). Thus, PPARγ is an attractive target for in vivo imaging that might be useful in assessing lipid metabolism disorders associated with obesity, type 2 diabetes, atherogenesis, and restenosis (*11*), and in identifying small metastatic tumors.

In previous work, our group has evaluated an initial set of fluorine-18 labeled compounds based on PPARγ ligands of the phenyl propanoic acid class, such as the fluorine-substituted analog of SB 213068 (Chart 1) (*12*). These compounds showed good binding affinities for PPARγ and good binding selectivity relative to the other receptor subtypes, PPARα and PPARδ. Though respectable, the PPARγ affinities of this set of compounds were not as high as would be desirable for imaging.

Since our prior work, ligands that have much higher affinity and selectivity for both PPARγ and PPARα have been discovered, largely through the efforts of researchers at Glaxo SmithKline (GSK) (*13*−*16*). In particular, members of the novel benzophenone-tyrosine class, exemplified by farglitazar (GI 262570), have a very high affinity for PPARγ, and they have high potency in vivo. Our group also recently prepared three fluorine-substituted members of the benzophenone−tyrosine class that retain high affinity and selectivity for PPARγ and thus appear to be attractive compounds to evaluate further as agents to be labeled with the short-lived positron-emitting radionuclide fluorine-18 ($t_{1/2}$ = 110 min) for imaging PPARγ in vivo using positron-emission tomography (PET).

In this work, we have selected one fluorine-substituted analog of farglitazar, namely, compound **1**, which was also previously described by GSK (*13*−*16*), and we have investigated synthetic routes by which it might be labeled with fluorine-18 in a manner that is rapid, efficient, and suitable for starting from fluoride ion at the tracer level, as would be needed to obtain the high specific activity material needed for receptor imaging with this radioisotope.

EXPERIMENTAL SECTION

Materials and Methods. Solvents and reagents were purchased from the following commercial sources: Aldrich, Fisher, or Acros. Anhydrous THF, Et_2O, and CH_2Cl_2 were collected using a solvent dispensing system built by J. C. Meyer based on a design described by Pahgborn (*17*). TLC was performed on Merck F_{254} silica plates. The chemical shifts were reported in parts per million downfield from tetramethylsilane and were referenced to the internal solvent peaks. Coupling constants were reported in hertz. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian U400 and U500 Instruments (Palo Alto, CA). Melting points were determined using a Thomas-Hoover capillary melting point apparatus (Philadelphia, PA) and are uncorrected. Low-resolution mass spectra (MS) were recorded on a Micromass 70-VSE, Finnigan MAT CH-5 and ZAB-SE spectrometers, respectively. High-resolution mass spectra were obtained on a VG 70-SE-4E spectrometer. Mass spectra were acquired in the positive ion mode under electron impact (EI, 70 eV), fast-atom bombardment mass (FAB), and electrospray ionization (ESI) methods. Microwave-assisted reactions were performed with model 520A Resonance Instruments, Inc. (Skokie, IL). N^{α}-*tert*-Butoxycarbonyl-L--tyrosine *tert*-butyl ester, 2-(5-methyl-2-phe-

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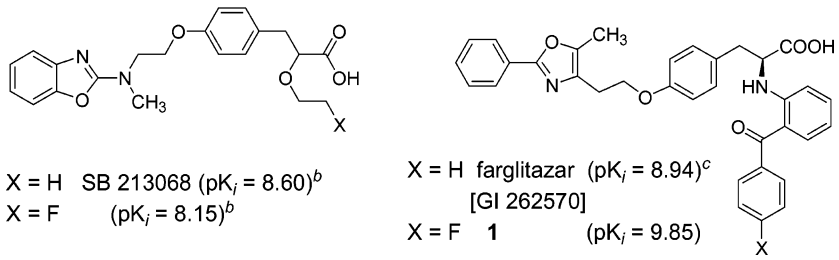
Chart 1. The Structure of PPARγ Ligands (SB 213068 and farglitazar [GI 262570]) and Fluorine-Substituted Analogs[a]



[a] pK_i: -log of the concentration of test compound required to achieve an apparent K_i value. [b] ref 12. [c] ref 14.

nyloxazol-4-yl)ethanol, and compound **11** were prepared according to the literature (*18*−*20*, respectively).

(2*S*)-[2-(4-Fluorobenzoyl)phenylamino]-3-(4-hydroxyphenyl)propionic Acid Methyl Ester (7). To a stirred solution of L--tyrosine methyl ester (1.90 g, 9.74 mmol) in toluene (10 mL) and 1,4-dioxane (10 mL) was added 2-(4-fluorobenzoyl)-cyclohexanone (2.41 g, 10.95 mmol). The reaction mixture was refluxed using a Dean−Stark trap for 12 h under nitrogen atmosphere. The resulting solution was evaporated, and anisole (20 mL) and an excess of 10% Pd/C were added. The reaction mixture was refluxed for 2 h. The resulting solution was evaporated and extracted with EtOAc (100 mL) and washed with H_2O (50 mL) and brine (50 mL). The organic layer was separated and dried with $MgSO_4$. Purification of this material by silica gel flash column chromatography using 20% EtOAc/hexane as eluant afforded 2.47 g (65%) of the title compound **7** as an orange oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.11 (dd, J = 14.0, 7.2 Hz, 1H), 3.18 (dd, J = 14.0, 5.6 Hz, 1H), 3.70 (s, 3H), 4.40 (t, J = 8.0 Hz, 1H), 6.59−6.70 (m, 4H), 7.07−7.13 (m, 4H), 7.33−7.38 (m, 1H), 7.42−7.45 (m, 1H), 7.59−7.63 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.84, 52.38, 57.84, 111.94, 115.04, 115.26, 115.53, 118.06, 127.50, 130.31, 131.65, 135.18, 136.02, 149.94, 155.10, 163.15, 165.65, 173.14, 198.14; MS (FAB) *m*/*z* 394 (M + H). HRMS calcd for $C_{23}H_{21}FNO_4$ 394.1455, found 394.1455.

(2*S*)-[2-(4-Nitrobenzoyl)phenylamino]-3-(4-hydroxyphenyl)-propionic Acid Methyl Ester (8). Prepared from L-tyrosine methyl ester and 2-(4-nitrobenzoyl)cyclohexanone by the method used to prepare compound **7** and obtained as an orange oil (10%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.13 (dd, J = 14.0, 7.2 Hz, 1H), 3.21 (dd, J = 13.6, 5.6 Hz, 1H), 3.73 (s, 3H), 4.43 (m, 1H), 6.57−6.66 (m, 2H), 6.72 (d, J = 8.4 Hz, 2H), 7.11 (d, J = 8.4 Hz, 2H), 7.30−7.40 (m, 2H), 7.70 (d, J = 8.8 Hz, 2H), 8.29 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.82, 52.46, 57.62, 112.06, 115.55, 116.95, 123.36, 127.62, 129.58, 130.39, 135.27, 136.05, 145.77, 148.78, 150.58, 154.99, 172.90, 197.13; MS (FAB) *m*/*z* 421 (M + H). HRMS calcd for $C_{23}H_{21}N_2O_6$ 421.1400, found 421.1399.

(2*S*)-[2-(4-Fluorobenzoyl)phenylamino]-3-{4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propionic Acid Methyl Ester (9). A stirred solution of compound **7** (193 mg, 0.49 mmol), 2-(5-methyl-2-phenyloxazol-4-yl)ethanol (100 mg, 0.49 mmol), and triphenylphosphine (129 mg, 0.49 mmol) in THF (30 mL) at room temperature was treated with diethyl azodicarboxylate (77 μL, 0.49 mmol) in THF (5 mL) via dropwise addition. The resulting solution was stirred for 16 h at room temperature, and then the solvent was removed in vacuo. The crude reaction mixture was purified by silica gel flash column chromatography using 30% EtOAc/hexane as eluant to afford 127 mg (45%) of the title compound **9** as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35 (s, 3H), 2.95 (t, J = 4.0 Hz, 2H), 3.11 (dd, J = 13.6, 7.2 Hz, 1H), 3.20 (dd, J = 13.6, 6.0 Hz, 1H), 3.69 (s, 3H), 4.20 (t, J = 4.0 Hz, 2H), 4.39 (m, 1H), 6.57−6.65 (m, 2H), 6.83 (d, J = 8.0 Hz, 2H), 7.10−7.18 (m, 4H), 7.31−7.35 (m, 1H), 7.40−7.45 (m, 4H), 7.61−7.65 (m, 2H), 7.98 (d, J = 8.0 Hz, 2H), 8.79 (d, J = 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.14, 26.20, 37.96, 52.16, 57.80, 66.48, 111.76, 114.53, 114.92, 115.03 (J = 21.0 Hz), 117.99, 125.80, 127.57, 128.16, 128.57, 129.70, 130.17, 131.53 (J = 8.0 Hz), 132.51, 134.86, 135.02, 136.19 (J = 4.0 Hz), 144.97, 149.97, 157.70, 159.334, 164.29 (J = 250.0 Hz), 172.87, 197.55; MS (FAB) *m*/*z* 579 (M + H). HRMS calcd for $C_{35}H_{32}FN_2O_5$ 579.2295, found 579.2295.

(2*S*)-[2-(4-Nitrobenzoyl)phenylamino]-3-{4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propionic Acid Methyl Ester (10). Prepared from **8** by the method used to prepare **9** and obtained as an orange oil (44%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.35 (s, 3H), 2.95 (t, J = 5.0 Hz, 2H), 3.13 (dd, J = 14.0, 7.5 Hz, 1H), 3.22 (dd, J = 14.0, 6.0 Hz, 1H), 3.71 (s, 3H), 4.20 (t, J = 5.0 Hz, 2H), 4.39−4.43 (m, 1H), 6.57 (t, J = 5.0 Hz, 1H), 6.64 (d, J = 10.0 Hz, 1H), 6.84 (d, J = 10.0 Hz, 2H), 7.17 (d, J = 10.0 Hz, 2H), 7.31 (d, J = 10.0 Hz, 2H), 7.34−7.43 (m, 4H), 7.71 (d, J = 10.0 Hz, 2H), 7.97 (d, J = 5.0 Hz, 2H), 8.29 (d, J = 10.0 Hz, 2H), 9.04 (d, J = 5.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 10.13, 26.35, 38.03, 52.21, 57.77, 66.70, 112.13, 114.77, 115.20, 117.14, 123.33, 125.92, 127.81, 128.15, 128.63, 129.62, 129.74, 130.26, 132.71, 135.10, 135.81, 144.96, 145.97, 148.93, 150.67, 158.00, 159.49, 172.65, 196.79; MS (FAB) *m*/*z* 606 (M + H). HRMS calcd for $C_{35}H_{32}N_3O_7$ 606.2240, found 606.2238.

(2*S*)-[2-(4-Fluorobenzoyl)phenylamino]-3-{4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propionic Acid (1). A stirred solution of compound **9** (50 mg, 0.086 mmol) in THF/MeOH (v/v = 3:1, 1.25 mL) was treated with 1.0 M LiOH (172 μL, 0.172 mmol). After the mixture was stirred at room temperature for 6 h, 1 N HCl (200 μL), water (1 mL), and EtOAc (5 mL) were added. The organic layer was separated and dried with sodium sulfate. The obtained organic layers were concentrated and purified by silica gel flash column chromatography using 5% MeOH/CH_2Cl_2 as eluant to afford 47 mg (96%) of the product **1** as a yellow solid: mp 140−145 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 2.30 (s, 3H), 2.90 (t, J = 6.8 Hz, 2H), 3.05 (dd, J = 13.8, 7 Hz, 1H), 3.22 (dd, J = 14, 5.2 Hz, 1H), 4.15 (t, J = 6.4 Hz, 2H), 4.42 (br, 1H), 6.56 (t, J = 7.6 Hz, 1H), 6.73−6.79 (m, 3H), 7.13 (d, J = 8.4 Hz, 2H), 7.18 (t, J = 8.4 Hz, 2H), 7.33−7.37 (m, 2H), 7.44−7.47 (m, 2H), 7.58−7.61 (m 2H), 7.91−7.93 (m, 2H);^{13}C NMR (100 MHz, DMSO-d_6) δ 9.84, 14.11, 25.56, 57.66, 59.79, 65.98, 112.62, 113.96, 115.10, 115.31, 116.84, 125.41, 127.11, 129.04, 130.05, 130.43, 131.36, 131.45, 132.65, 134.40, 134.79, 136.71, 145.05, 150.06, 156.73, 158.32, 162.31, 164.78, 196.24; MS (FAB) *m*/*z* 565 (M + H). HRMS calcd for $C_{34}H_{30}FN_2O_5$ 565.2139, found 565.2139.

2-Iodo-4′-dimethylaminobenzophenone (12). To a suspension of 2-iodo-*N*-phenyl benzamide **11** in *N*,*N*-dimethylaniline (5.49 mL, 43.33 mmol) was added phosphorus oxychloride (865 μL, 9.28 mmol) dropwise over 30 min at 50 °C. On completion of the addition, the resulting dark solution was heated to 150 °C for 4 h. After the reaction mixture was cooled to room temperature, HCl (8 mL, 50% aq) was added, and the

mixture was refluxed for 2 h. The cooled solution was poured into water (200 mL) and 2 M NaOH (50 mL) and extracted with dichloromethane (50 mL × 3). The organic layer was washed with 0.2 M NaOH (25 mL), 0.2 M HCl (25 mL), and water (25 mL), respectively. The organic layer was dried with sodium sulfate, and the solvent was removed to give the crude benzophenone. Purification of the material by silica gel flash column chromatography using 30% ethyl acetate/hexane as eluant afforded 1.72 g (79%) of the product **12** as a green solid: mp 121−125 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.07 (s, 6H), 6.63 (d, J = 9.2 Hz, 2H), 7.10−7.14 (m, 1H), 7.25−7.28 (m, 1H), 7.39−7.42 (m, 1H), 7.56 (d, J = 8.8 Hz, 2H), 7.88 (d, J = 8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.99, 92.52, 110.62, 123.02, 127.64, 127.94, 130.24, 132.82, 139.23, 145.64, 153.73, 195.38; MS (ESI) *m*/*z* 352 (M + H). HRMS calcd for $C_{15}H_{14}INO$ 352.0198, found 352.0215.

2-Iodo-4′-fluorobenzophenone (13). *Method A.* The flask was charged with $AlCl_3$ (644 mg, 4.82 mmol) and cat. $FeCl_3$ (5 mg, 0.03 mmol) in fluorobenzene (3 mL). The solution was then chilled thoroughly in an ice bath under nitrogen atmosphere. To this solution was added 2-iodobenzoylchloride (1.29 g, 4.82 mmol) in fluorobenzene (3 mL). The reaction mixture was allowed to stir overnight at room temperature. At the end of the reaction, the flask was placed again in an ice bath, and water (2 mL) was slowly added. The resulting two-phase mixture was stirred vigorously for 30 min. The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed in vacuo. Purification of the material by silica gel flash column chromatography using 10% ethyl acetate/hexane as eluant afforded the product **13** (1.39 g, 88%).

Method B. To a solution of compound **14** (100 mg, 0.19 mmol) in acetonirile (2 mL) was added 1 M TBAF in THF solution (210 μL, 0.21 mmol) at room temperature. The reaction mixture was heated at 90 °C for 1 h. The reaction mixture was poured into ethyl acetate (10 mL) and washed with water (10 mL) and brine (10 mL). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed in vacuo. Purification of the material by silica gel flash column chromatography using 10% ethyl acetate/hexane as eluant afforded the product **13** (59 mg, 96%) as a white solid: mp 50−52 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11−7.21 (m, 3H), 7.28 (dd, J = 7.6, 2 Hz, 1H), 7.43−7.47 (m, 1H), 7.81−7.85 (m, 2H), 7.92 (dd, J = 8.4, 2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 92.05, 115.88 (d, J = 22 Hz), 127.87, 128. 29, 131.20, 131.94 (d, J = 3 Hz), 133.09 (d, J = 9.9 Hz), 139.67, 144.01, 166.07 (d, J = 254.9 Hz), 195.66; MS (EI) *m*/*z* 327 (M + H). HRMS calcd for $C_{13}H_8FIO$ 326.9682, found 326.9676. Registry Number: 138504-31-1.

2-Iodo-4′-*N*,*N*,*N*-trimethylaminobenzophenone Triflate (14). To a solution compound **12** (500 mg, 1.42 mmol) in methylene chloride (10 mL) was added methyl trifluoromethanesulfonate (193 μL, 1.70 mmol) dropwise over 10 min at room temperature under argon atmosphere. Upon completion of the addition, the resulting dark brown solution was stirred at room temperature for 12 h. The reaction mixture was poured into diethyl ether (20 mL) and washed with water (10 mL). The residue was recrystallized from diethyl ether and methylene chloride to afford 380 mg (52%) of the product **14** as a white solid: mp 163−165 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 (s, 9H), 7.29−7.37 (m, 2H), 7.55−7.58 (m, 1H), 7.98−8.02 (m, 3H), 8.07−8.10 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 57.68, 92.42, 122.18, 123.36, 129.42, 129.63, 132.98, 133.25, 138.45, 141.06, 144.85, 151.97, 196.91; MS (ESI) *m*/*z* 366 (M − OTf). HRMS calcd for $C_{16}H_{17}INO$ 366.0355, found 366.0346.

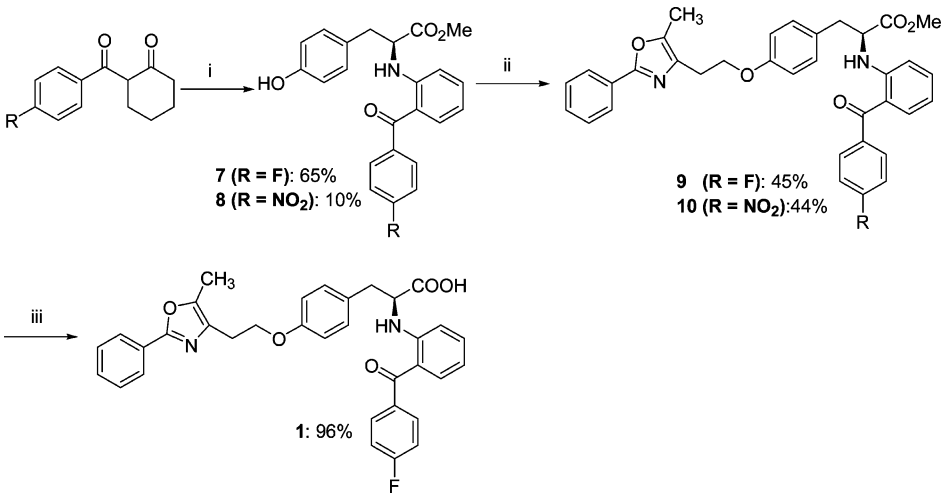
(*S*)-*tert*-Butoxycarbonylamino-3-{4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]-phenyl}propionic Acid *tert*-Butyl Ester (15). A stirred solution of N^{α}-*tert*-butoxycarbonyl-L-tyrosine *tert*-butyl ester (193 mg, 0.49 mmol), 2-(5-methyl-2-phenyloxazol-4-yl)ethanol (100 mg, 0.49 mmol), and triphenylphosphine (165 mg, 0.49 mmol) in tetrahydrofuran (30 mL) at room temperature was treated with diethyl azodicarboxylate (77 μL, 0.49 mmol) in tetrahydrofuran (5 mL) via dropwise addition. The resulting solution was stirred for 8 h at room temperature under nitrogen, and then the solvent was removed in vacuo. The crude reaction mixture was purified by silica gel flash column chromatography using 30% EtOAc/hexane as eluant to afford 140 mg (55%) of the product **15** as a white solid: mp 50−52 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (s, 9H), 1.37 (s, 9H), 2.30 (s, 3H), 2.90−3.00 (m, 4H), 4.17 (t. J = 6.6 Hz, 2H), 4.36 (q, J = 13.6 Hz, 1H), 5.04 (d, J = 8 Hz, 1H), 6.78 (d, J = 8.4 Hz, 2H), 7.02 (d, J = 8.4 Hz, 2H), 7.31−7.38 (m, 3H), 7.93 (d, J = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.96, 26.08, 27.70, 28.07, 37.22, 54.73, 66.36, 79.22, 81.54, 114.11, 125.62, 127.47, 128.14, 128.39, 129.51, 130.24, 132.44, 144.72, 154.86, 157.46, 159.17, 170.77; MS (ESI) *m*/*z* 523 (M + H, 100%), 467 (45%). HRMS calcd for $C_{30}H_{39}N_2O_6$ 523.2808, found 523.2815.

(*S*)-Amino-3-{4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]-phenyl}propionic Acid (16). A solution of (*S*)-*tert*-butoxycarbonylamino-3-{4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]-phenyl}propionic acid *tert*-butyl ester **15** (300 mg, 0.574 mmol) in trifluoroacetic acid and CH_2Cl_2 (v/v = 1:1, 6 mL) was stirred at room temperature for 6 h. The volume was reduced by evaporation of the solvent, whereupon some crystal formation occurred; then, diethyl ether was poured into the concentrated mixture. The white solid was filtered and washed with diethyl ether (5 mL) before being dried in vacuo. The trifluoroacetate was obtained as a white solid **16** (296 mg, 97%): mp 191−193 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 2.39 (s, 3H), 2.97 (t, J = 6.4, 2H), 3.01−3.25 (m, 2H), 4.10 (q, J = 8.0 Hz, 1H), 4.23 (t, J = 6.4 Hz, 2H), 6.92 (d, J = 8.4 Hz, 2H), 7.18 (d, J = 8.4 Hz, 2H), 7.46−7.49 (m, 3H), 7.93−7.96 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 10.03, 26.94, 36.61, 55.48, 67.62, 116.19, 126.94, 127.65, 128.49, 130.07, 131.51, 131.62, 133.77, 147.12, 159.94, 161.17, 171.60; MS (ESI) *m*/*z* 367 (M + H). HRMS calcd for $C_{21}H_{23}N_2O_4$ 367.1658, found 367.1650.

Ullmann-Type Condensation Procedure for (2*S*)-[2-(4-Fluorobenzoyl)phenylamino]-3-{4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propionic Acid (1). *Method A.* To a solution of compound **16** (73 mg, 0.15 mmol) and 2-iodo-4′-fluorobenzophenone **13** (50 mg, 10.4 μmol) in *N*,*N*-dimethylformamide (DMF, 3 mL) were added potassium carbonate (46 mg, 0.33 mmol), and CuI (3 mg, 0.015 mmol) under a nitrogen atmosphere. After the mixture was stirred at 100 °C for 4 h, the cooled solution was concentrated in vacuo. The residue was dissolved in water and acidified to pH 5 with 1 M HCl. After extraction with ethyl acetate (5 mL), the combined organic layers were dried, concentrated, and purified by silica gel flash column chromatography using 5% MeOH/CH_2Cl_2 as eluant to afford 43 mg (51%) of the product **1**.

Method B. To a solution of trifluoroacetate salt **16** (5.0 mg, 10.4 μmol) in acetonitrile (1 mL) was added tetrabutylammonium hydroxide (40% aq solution, 13 μL, 20.6 μmol). After sonication of the mixture, the clear solution was concentrated under reduced pressure. To the tetrabutylammonium salt were added 2-iodo-4′-fluorobenzophenone **13** (3.4 mg, 10.4 μmol), CuI (1 mg), and DMF (0.5 mL) under a nitrogen atmosphere. After the mixture was stirred at 100 °C for 20 min under nitrogen atmosphere, the cooled solution was concentrated in vacuo. The residue was dissolved in water and acidified to pH 5 with 1 M HCl. After extraction with ethyl acetate (1 mL), the combined organic layers were dried, concentrated, and purified

Scheme 1 [a]



[a] Reaction conditions: (i) (a) L-tyrosine methyl ester, 1,4-dioxane/toluene, 12 h; (b) anisole, 10% Pd/C, reflux, 2 h; (ii) 2-(5-methyl-2-phenyloxazol-4-yl)ethanol, Ph_3P, DEAD, THF, 0 °C ∼ rt, 12 h; (iii) **9**, LiOH, THF/MeOH (v/v = 3:1), rt, 6 h.

by short silica gel flash column chromatography using 5% MeOH/CH_2Cl_2 as eluant to afford 3.1 mg (53%) of the product **1**.

PPARγ Binding Assay. The binding of compound **1** to PPARγ was evaluated using a scintillation proximity assay (SPA) adapted from the method described by Sun et al. (*21*). Yttrium silicate (Ysi) copper His-Tag SPA beads (Amersham Biosciences, Piscataway, NJ), histidine-tagged human PPARγ ligand-binding domain (amino acids 195−477; Invitrogen, Carlsbad, CA), and the tritium ligand, [^{3}H]-rosiglitazone (American Radiolabeled Chemicals, St. Louis, MO) were obtained from the sources indicated.

[^{3}H]-Rosiglitazone and PPARγ protein were diluted to 23 μCi/mL and 50 ng/mL stock, respectively. Radioligand, protein and test compound at various concentrations (10 nM to 2 μM) were incubated at room temperature for 2 h. SPA beads were diluted and aliquoted into a clear bottom 96-well plate according to the manufacturer's specifications. Test the ligand, [^{3}H]-Rosiglitazone and protein were then added to the assay plate and incubated at room temperature for at least for 1 h before the plate was read by a Packard TopCount plate reader (Perkin-Elmer, Wellesley, MA). GW1929 (Cayman Chemical Co., Ann Arbor, MI), a potent PPARγ agonist, served as a positive control. The initial IC_{50} values of GW1929 and test compound were calculated by the *Prism* program (GraphPad Software, San Diego, CA). The reported compound IC_{50} value of the compound tested was normalized against GW1929 due to the variability of the assay (*22*). The normalized IC_{50} value is 0.14 ± 0.01 nM, which corresponds to a pK_i value of 9.85.

RESULTS AND DISCUSSION

Chemical Synthesis. We designed two synthetic routes to compound **1**, the first for preparation of an authentic sample of this compound and the second designed to proceed through precursor molecules that can be radiolabeled by fluoride ion displacement of a suitable leaving group for the eventual radiolabeling of this compound with fluorine-18.

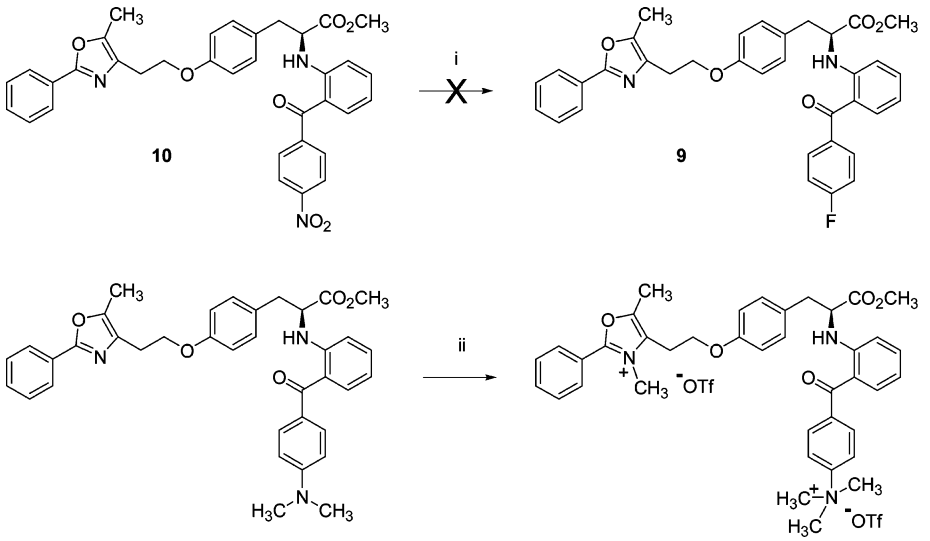
Synthesis of (2*S*)-[2-(4-fluorobenzoylphenylamino)-3-{4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propionic Acid (1). As shown in Scheme 1, an authentic sample of compound **1** was synthesized in three steps from 2-(4-fluorobenzoyl)-cyclohexanone, using a modification of known methods (*13*−*15*). 2-(4-Fluorobenzoyl)cyclohexanone (*23*) was attached to tyrosine methyl ester by an imine formation−aromatization sequence catalyzed by 10% Pd/C in anisole to produce compounds **7** and **8**. Under Mitsunobu conditions, the phenolic function in compound **7** was coupled to the known heterocyclic alcohol 2-(5-methyl-2-phenyloxazol-4-yl)ethanol (*19*) to provide compound **9**. Hydrolysis of this methyl ester with LiOH proceeded under mild conditions to give the desired fluorine-substituted PPARγ ligand **1**. Because it involves multiple steps following the introduction of the fluorine-containing component, this route is not suitable for labeling with the short-lived radionuclide fluorine-18.

An obvious approach for the direct labeling of compound **1** with fluorine would involve nucleophilic aromatic substitution by fluoride ion on a precursor of the final compound bearing a good leaving group on the para position of the benzophenone unit (i.e., compound **10**, Scheme 2). In many cases, a nitro group can function effectively as a leaving group in nucleophilic aromatic substitutions with fluoride ion, provided the system is adequately activated with electron withdrawing groups situated at ortho and/or para positions (*24*−*26*). Thus, we subjected compound **10**, the nitro analog of compound **1** that we had prepared previously, to various conditions typically used for such substitutions, but we failed to obtain any of the desired fluoro product. Although fluorine substitution of other nitrobenzophenones has been accomplished (*24*), we presume that the lack of reaction of compound **10** is due to the strongly electron donating ortho amino substituent on the other ring that can also hydrogen-bond with the benzophenone carbonyl group.

Our attempts to prepare the more reactive trimethylammonium analog of the nitro compound from the dimethyl amine analog using methyl triflate (Scheme 2) were thwarted by the dominant competitive N-methylation of the more nucleophilic oxazole ring in the tail of the molecule. Initial methylation took place on the heterocycle, so we could only obtain the bis-(ammonium) salt. Because of these difficulties with these direct fluorination approaches, we took an alternative, indirect approach to prepare target compound **1**, as outlined in Scheme 3.

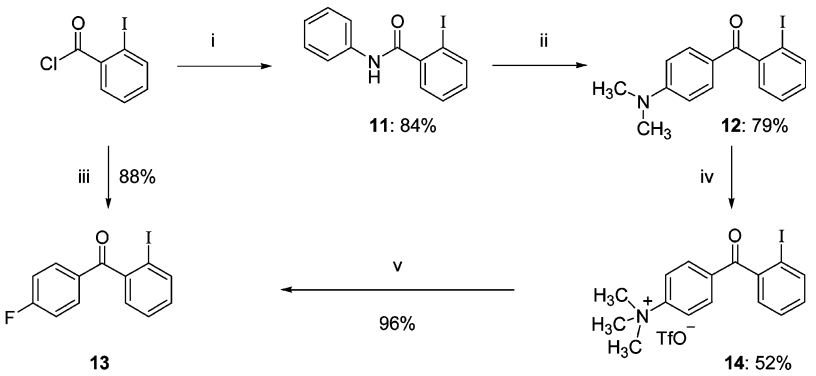
Synthesis of 2-iodo-4′-fluorobenzophenone (13). There is precedent for introducing fluoride ion by nucleophilic aromatic substitution at the para position of certain benzophenones bearing simple o,p′-substituents (*27*). We did not anticipate encountering problems in preparing the reactive p′-trimethylammonium group in the simpler benzophenone precursor **14**, because in this system this benzophenone is not attached to the nucleophilic oxazole. We imagined that fluoride ion substitution in compound **14** would proceed selectively by displacement of the more reactive p′-trimethylammonium leaving group rather

Scheme 2 [a]



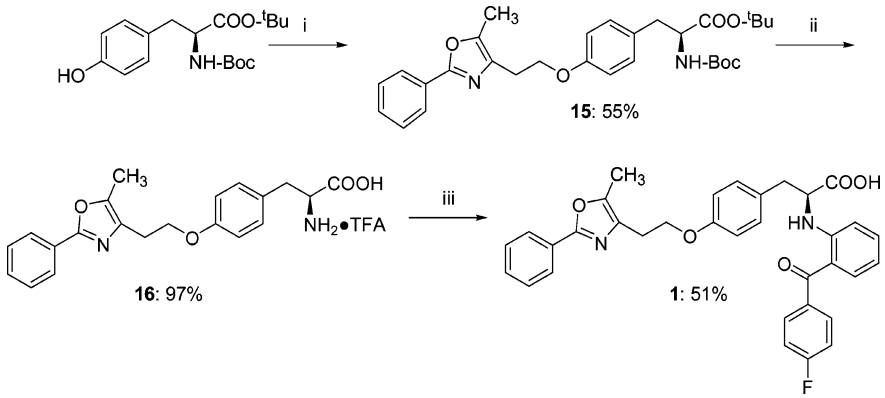
[a] Reaction conditions: (i) TBAF, DMSO, 130 °C or microwave; (ii) $CF_3SO_2OCH_3$, CH_2Cl_2, rt.

Scheme 3 [a]



[a] Reaction conditions: (i) aniline, pyridine, rt, 12 h; (ii) (1) $POCl_3$, *N*,*N*-dimethylaniline, 150 °C, 4 h, (2) 50% aq. HCl, 100 °C, 2 h; (iii) fluorobenzene, $AlCl_3$, $FeCl_3$, rt, 20 h; (iv) $CF_3SO_2OCH_3$, CH_2Cl_2, rt, 12 h; (v) TBAF, CH_3CN, 90 °C 1 h.

Scheme 4 [a]



[a] Reaction conditions: (i) 2-(5-methyl-2-phenyloxazol-4-yl)ethanol, PPh_3, DEAD, THF, 0 °C ∼ rt, 12 h; (ii) TFA/CH_2Cl_2, rt, 6 h; (iii) 13, K_2CO_3, CuI, DMF, 90 °C, 4 h.

than the o-iodo group (Scheme 3). This would leave as a final step in this approach the attachment of the *o*-iodo-*p*′-[^{18}F]-fluorobenzophenone system to the complex tyrosine unit by the displacement of the iodide using an Ullmann-type condensation (Scheme 4) (*28*, *29*). In this respect, our approach differs from earlier methods for achieving this coupling step, which involved imine formation with an *o*-benzoylcyclohexanone, followed by palladium-catalyzed aromatization (*13*, *15*).

An authentic sample of the o,p′-substituted benzophenone **13** was easily prepared by the Friedel−Crafts acylation of fluorobenzene with 2-iodobenzoyl chloride. The precursor for fluorine labeling, compound **14**, was prepared in three steps. 2-Iodo-4′-dimethylaminobenzophenone **12** was obtained in moderate yield by the Vilsmeier−Haack reaction of *N*,*N*-dimethylaniline with *N*-phenyl 2-iodo-benzamide (**11**), which was derived from the acylation of aniline with 2-iodo-

Scheme 5

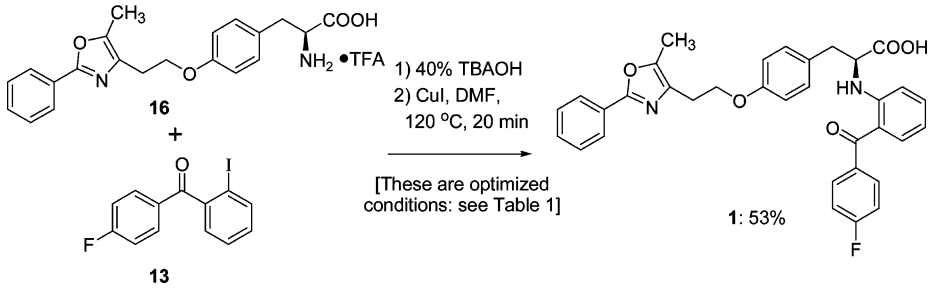


Table 1. Ullmann-Type C−N Coupling

entry	salt form	temperature	time	base	yields[f]
1[a]	TFA salt	100 °C	4 h	K_2CO_3	51%
2[b]	TFA salt	100 °C	2 h	K_2CO_3	13%
3[b]	TFA salt	120 °C	30 min	K_2CO_3	5%
4[c]	TFA salt	MW	5 min	K_2CO_3	trace
5[d]	TFA salt	MW	5 min	Cs_2CO_3 and TEA	trace
6[e]	TBA	120 °C	20 min	none	53%

[a−f] Reaction conditions: [a]Compound **16** (0.15 mmol), compound **13** (0.15 mmol), CuI (3 mg), K_2CO_3 (0.33 mmol), and DMF (3 mL); [b]Compound **16** (10.4 μmol), compound **13** (10.4 μmol), CuI (1 mg), K_2CO_3 (20.6 μmol), and DMF (500 μL); [c]Microwave irradiation (100 W, 5 min); [d]Compound **16** (10.4 μmol), compound **13** (10.4 μmol), CuI (1 mg), $Pd(Ph_3)_4$ (2 mg), Cs_2CO_3 (26.0 μmol), triethylamine (30 μL), tetrabutylammonium iodide (26.0 μmol), H_2O (10 μL), and DMF (500 μL); [e]Compound **16** (10.4 μmol), compound **13** (10.4 μmol), CuI (1 mg), tetrabutylammonium hydroxide (40% aqueous solution, 20.6 μmol), and DMF (500 μL). [f] Isolated yields.

benzoyl chloride using a catalytic amount of DMAP in pyridine (*20*, *30*, *31*). Treatment of the tertiary amine **12** with methyl trifluoromethanesulfonate produced the desired ammonium salt **14**, the key precursor for fluorine substitution. To demonstrate the effectiveness of the ammonium salt **14** as a precursor to the key intermediate **13**, we showed that the conversion of **14** to **13** occurred rapidly and in near quantitative yield when **14** was exposed to tetrabutylammonium fluoride in acetonitrile (Scheme 3).

As shown in Scheme 4, N^{α}-*tert*-butoxycarbonyl-L-tyrosine *tert*-butyl ester (*18*) was coupled to 2-[5-methyl-2-phenyloxazol-4-yl]ethanol under Mitsunobu conditions. Hydrolysis of the *tert*-butyl ester and Boc group in compound **15** with TFA in dichloromethane solution proceeded under mild conditions to give the desired phenyloxazole−tyrosine TFA salt **16**. The target compound **1** was then prepared using an Ullmann-type aryl amination of 2-iodo-4′-fluorobenzophene **13** with the amino group of the tyrosine ether **16** (Scheme 5). It is of note that this conversion can be done with the tyrosine unit **16** in its free acid form, rather than its ester derivative; this is a significant convenience for radiolabeling with short-lived isotopes, because it obviates ester hydrolysis as a final step.

Under conditions typical for Ullmann-type arylations, the conversion of **13** and **16** to **1** proceeded to only 51% yield after a 4 h reaction. We realized that this would be problematic for the synthesis of compound **1** labeled with the short-lived fluorine-18 ($t_{1/2}$ = 110 min), and thus we needed to find conditions for expediting this coupling reaction (Table 1).

While the mechanism of the Ullmann-type coupling reaction is not known, it is presumed to involve the coordination of copper ion with the aryl halide, followed by chelation with the carboxyl and/or amino groups in the coupling partner. The rate-determining step is then the intramolecular nucleophilic substitution of the aromatic ring by the amino group (*28*, *32*). Ullmann condensations typically proceed in higher yields under mild conditions, and we found the reaction yield to be strongly dependent on time. To explore how we might reduce the reaction time, we examined this reaction, when conducted on a micromolar scale (compound **16**, 5 mg, 10.4 μmol), under different conditions and using different reagents (Table 1).

When the phenyloxazole-tyrosine TFA salt **16** was reacted with the o,p′-substituted benzophenone **13** with CuI and K_2CO_3, under general Ullmann-type conditions, the reaction proceeded only slowly, with the yields of product **1** being very low at reaction times that would be applicable to labeling compound **1** with fluorine-18 (Table 1, entries 1−3). We also tried using a palladium/copper cocatalyst with microwave heating, conditions that have promoted other C−N cross couplings (*33*), but the reaction did not appear to be accelerated; yields were very low, and unknown side compounds were generated by the microwave heating (Table 1, entries 4 and 5). We noticed with interest that treatment of amino acid **16** with tetrabutylammonium hydroxide gave a TBA salt that was soluble in DMF (*34*). Interestingly, when this salt/solvent combination was used, the C−N coupling could be carried out in 20 min with 53% yield by heating to 120 °C, as shown in Table 1 (entry 6).

PPARγ Binding Affinity Determination. We retested the binding affinity of compound **1** for PPARγ in a competitive scintillation proximity radiometric binding assay, using a receptor preparation consisting of the ligand binding domain of PPARγ expressed in *E. coli* (*21*, *22*). The K_i value for compound **1** determined in this assay was 0.14 nM ($pK_i = 9.85$), consistent with the binding affinity for this compound reported earlier (*14*).

CONCLUSION

In this study, we have developed a method for introducing fluorine into a fluorine-substituted analog (compound **1**) of the high-affinity PPARγ ligand, farglitazar, that utilizes fluoride ion and that proceeds efficiently and rapidly under conditions suitable for labeling this molecule with the short-lived, positron-emitting radionuclide fluorine-18. The radiochemical synthesis of [^{18}F]compound **1** and an evaluation of its tissue distribution properties will be described in a future publication.

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