Supporting Information

4-[^{18}F]fluoro-*m*-hydroxyphenethylguanidine: a radiopharmaceutical for quantifying regional cardiac sympathetic nerve density with positron emission tomography

*Keun Sam Jang, Yong-Woon Jung, Guie Gu, Robert A. Koeppe, Phillip S. Sherman, Carole A. Quesada and David M. Raffel**

Division of Nuclear Medicine, Department of Radiology, 2276 Medical Sciences I Building, University of Michigan Medical School, Ann Arbor, Michigan 48109, USA

E-mail: raffel@umich.edu

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Chemistry. NMR spectra were obtained on a Varian Inova 500 (499.90 MHz for ^{1}H; 125.70 MHz for ^{13}C) spectrometer. ^{1}H and ^{13}C NMR chemical shifts (δ) are reported in parts per million (ppm) relative to internal standard TMS and coupling constants (*J*) are in Hz. High-resolution mass spectra were obtained on a VG (Micromass) 70-250S spectrometer using electrospray ionization (ESI) in positive ion mode, direct chemical ionization (DCI) or electron impact (EI) at 70 eV. Melting points were determined on a Mel-Temp capillary melting point apparatus in open capillary tubes. Flash column chromatography was performed with E. Merck 230-400 mesh silica gel. Analytical TLC was performed with Analtech 0.25 mm glass-backed plates with fluorescent background. Visualization was achieved by phosphomolybdic acid (PMA) or UV illumination. High pressure liquid chromatography (HPLC) was performed on a Hitachi pump L-7100 instrument equipped with Hitachi D-7500 integrator and Hitachi L-4000 UV detector. Radioactivity detection was done with Bioscan coincidence (model B-FC-4000) detector. Reverse-phase HPLC analysis of radiometabolite formation in plasma was performed on a Perkin-Elmer Series 410 LC instrument equipped with Ortec Model 905-4 NaI(Tl) radiodetector.

Reagents and solvents were purchased from commercial sources and used without further purification unless otherwise noted. 3-Benzyloxy-4-fluorophenethylamine hydrochloride (**16**) previously prepared in our laboratory was used to synthesize 3-benzyloxy-4-fluorophenethylamine *tert*-butylcarbamate (**15**).[1]

***3-Benzyloxy-4-iodobenzyl alcohol* (3).** K_2CO_3 (3.58 g, 25.8 mmol) and benzyl chloride (2.18 mL, 18.9 mmol) was added to a solution of 3-hydroxy-4-iodobenzyl alcohol **2** (4.3 g, 17.2 mmol) in DMF (30 mL) at room temperature and the reaction mixture was heated at 130 °C for 2 h. The cooled mixture was treated with saturated NH_4Cl solution (200 mL) and extracted with ethyl acetate (50 mL × 2). The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 30% ethyl acetate in hexane) to afford the desired alcohol **3** (5.39 g, 92%) as a white solid; mp 62-63 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.9 Hz, 1H), 7.52-7.50 (m, 2H), 7.41-7.40 (m, 2H), 7.39-7.31 (m, 1H), 6.91 (d, *J* = 1.8 Hz, 1H), 6.71 (dd, *J* = 8.0, 1.8 Hz, 1H), 5.15 (s, 2H), 4.63 (s, 2H), 1.76 (bs, 1H, OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.4, 142.8, 139.4, 136.4, 128.5, 127.9, 127.0, 121.0, 111.0, 85.4, 70.7, 64.7; MS (EI) *m*/*z* 339 (M^+). CAS Registry Number: 877064-78-3.

***3-Benzyloxy-4-iodobenzyl bromide* (4).** PBr_3 (26.0 mL, 1.0 M in dichloromethane, 26.0 mmol) was added dropwise to a solution of the alcohol **3** (4.37 g, 12.9 mmol) in CH_2Cl_2 (100 mL) at room temperature. The reaction mixture was stirred at room temperature for overnight, washed with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (100 mL × 2). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 20% ethyl acetate in hexane) to afford the bromide **4** (4.2 g, 81%) as a white solid; mp 88-90 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.8 Hz, 1H), 7.52-7.50 (m, 2H), 7.42-7.39 (m, 2H), 7.35-7.32 (m, 1H), 6.89 (d, *J* = 2.0 Hz, 1H), 6.76 (dd, *J* = 7.8, 2.0 Hz, 1H), 5.16 (s, 2H), 4.42 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.4, 139.7, 139.4, 136.1, 128.6, 128.0, 127.0, 123.2, 113.1, 86.9, 70.9, 32.8; MS (EI) *m*/*z* 401 (M^+). Anal. Calcd. For $C_{14}H_{12}BrIO$: C, 41.72; H, 3.00. Found: C, 41.95; H, 3.08.

***3-Benzyloxy-4-iodobenzyl cyanide* (5).** Sodium cyanide (174 mg, 3.5 mmol) was added to a solution of the bromide **4** (1.3 g, 3.2 mmol) in DMSO (12 mL) at room temperature. The mixture was stirred at room temperature for 3 h and then poured over ice water (100 mL). The aqueous solution was extracted with ethyl acetate (25 mL × 2). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 10% ethyl acetate in hexane) to afford the cyanide **5** (1.04 g, 92%) as a yellow solid; mp 48-50 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.8 Hz, 1H), 7.52-7.50 (m, 2H), 7.42-7.39 (m, 2H), 7.35-7.32 (m, 1H), 6.82 (d, *J* = 1.7 Hz, 1H), 6.68 (dd, *J* = 8.0, 1.8 Hz, 1H), 5.16 (s, 2H), 3.69 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.7, 140.0, 135.9, 131.4, 128.6, 128.0, 127.0, 122.2, 117.3, 112.0, 86.2, 70.9, 23.5; MS (EI) *m*/*z* 348 (M^+). HRMS (EI) calcd for $C_{15}H_{12}INO$ 348.9964, found 348.9968.

***3-Benzyloxy-4-iodophenethylamine hydrochloride* (6).** BH_3-THF (21.7 mL, 1.0 M solution in tetrahydrofuran, 21.7 mmol) was added dropwise to a solution of the cyanide **5** (2.7 g, 7.73 mmol) in anhydrous THF (70 mL) at room temperature under nitrogen atmosphere. The reaction mixture was refluxed for 2 h and excess BH_3 was decomposed by the cautious addition of methanol (20 mL) until effervescence ceased. After removing the solvent under reduced pressure, the residue was taken up in HCl solution (1.0 M HCl in Et_2O, 15 mL). The precipitate was filtered, washed with excess diethyl ether and dried *in vacuo* to give the desired product **6** (2.06 g, 69%) as a yellow solid. mp 146-148 °C; ^{1}H NMR (500 MHz, CD_3OD-d_4 + a drop of DMSO-d_6) 7.75 (d, *J* = 7.8 Hz, 1H), 7.53 (d, *J* = 7.4 Hz, 2H), 7.40-7.37 (m, 2H), 7.33-7.30 (m, 1H), 6.97 (d, *J* = 1.8 Hz, 1H), 6.69 (dd, *J* = 7.8, 1.8 Hz, 1H), 5.19 (s, 2H), 3.16 (t, *J* = 7.7 Hz, 2H), 2.92 (t, *J* = 7.7 Hz, 2H); ^{13}C NMR (125 MHz, CD_3OD-d_4 + a drop of DMSO-d_6) δ 159.0, 141.0, 140.1, 138.1, 129.5, 129.0, 128.3, 124.3, 114.6, 85.6, 71.8, 41.6, 34.3; MS (ESI) *m*/*z* 354 $(M+H)^+$. Anal. Calcd. For $C_{15}H_{17}ClINO$: C, 46.24; H, 4.40; N, 3.59. Found: C, 46.78; H, 4.32, N, 3.34.

***N,N'-Bis(tert-butoxycarbony)-N''-3-benzyloxy-4-iodophenethylguanidine* (7).** To a cooled (0 ^{o}C) solution of **6** (3.0 g, 7.7 mmol) and triethylamine (4.3 mL, 30.8 mmol) in anhydrous DMF (20 mL) was added in portion 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea (2.35 g, 8.08 mmol). The resulting mixture was stirred at 0 °C for 1 h, warmed to room temperature and stirred overnight. The mixture was diluted with ethyl acetate (50 mL), washed with saturated NH_4Cl solution (200 mL), and extracted with ethyl acetate (2 × 250 mL). The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 10% ethyl acetate in hexane) to afford the product (3.57 g, 78%) as a white solid. mp 104-108 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.5 (bs, 1H), 8.38-8.37 (m, 1H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.52-7.50 (m, 2 H), 7.41-7.38 (m, 2 H), 7.33-7.30 (m, 1H), 6.76 (d, *J* = 1.7 Hz, 1H), 6.60 (dd, *J* = 7.8, 1.9 Hz, 1H), 5.16 (s, 2H), 3.65 (q, *J* = 6.4 Hz, 2H), 2.81 (t, *J* = 7.0 Hz, 2H), 1.50 (s, 9H), 1.45 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.5, 157.3, 156.1, 153.2, 140.5, 139.5, 136.5, 128.5, 127.8, 127.0, 123.3, 113.3, 84.2, 83.2, 79.4, 70.8, 41.9, 35.1, 28.3, 28.0; MS (ESI) *m*/*z* 596 $(M+H)^+$. Anal. Calcd. For $C_{26}H_{34}IN_3O_5$: C, 52.44; H, 5.76; N, 7.06. Found: C, 52.46; H, 5.68; N, 6.96.

***N,N'-Bis(tert-butoxycarbonyl)-N''-3-benzyloxy-4-trimethylstannylphenethylguanidine* (8).** Hexamethylditin (0.84 mL, 4.03 mmol) was added to a solution of compound **7** (1.2 g, 2.0 mmol) and *tetrakis*(triphenylphosphine)palladium (117 mg, 0.1 mmol) in anhydrous toluene (8.0

mL) at room temperature under nitrogen atmosphere. The resulting mixture was heated to 130 °C for 30 min, cooled down to room temperature and filtered through a Celite pad. Celite pad was washed with ethyl acetate and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (silica gel, 5% to 10% ethyl acetate in hexane) to afford the product **8** (591 mg, 46%) as a white solid; mp 109-113 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.5 (s, 1H), 8.42 (s, 1H), 7.42-7.37 (m, 4H), 7.34-7.31 (m, 2H), 6.87-6.85 (m, 1H), 5.07 (s, 2H), 3.68 (q, *J* = 6.3 Hz, 2H), 2.87 (t, *J* = 7.0 Hz, 2H), 1.51 (s, 9H), 1.47 (s, 9H), 0.2 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.5, 163.2, 156.0, 153.1, 140.9, 137.0, 136.7, 128.4, 128.1, 127.6, 121.5, 110.7, 83.0, 79.2, 69.9, 42.3, 35.4, 28.3, 28.0, -9.2; MS (ESI) *m*/*z* 634 $(M+H)^+$. Anal. Calcd. For $C_{29}H_{43}N_3O_5Sn$: C, 55.08; H, 6.85; N, 6.64. Found: C, 55.17; H, 6.74, N, 6.59.

2-Benzyloxy-4-{2'-(N,N'-bis(tert-butoxycarbonyl)-N''-guanidinyl)ethyl}phenyl(2-thienyl)iodonium tosylate **(9).** A solution of 2-(diacetoxy)iodothiophene (132 mg, 0.4 mmol) in CH_2Cl_2 (1.5 mL) was added to a solution of *p*-toluenesulfonic acid hydrate (77 mg, 0.4 mmol) in MeCN (1.5 mL) at room temperature under nitrogen atmosphere. The white precipitate was immediately generated and the mixture was stirred for 1 h. A solution of compound **8** (254 mg, 0.4 mmol) in CH_2Cl_2 (1.5 mL) and MeCN (1.5 mL) was added slowly to the reaction mixture. After the white precipitate was disappeared, the mixture was stirred at room temperature for 20 h under nitrogen atmosphere. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (silica gel, 100% CH_2Cl_2 to 20:1=CH_2Cl_2:MeOH) to afford the product **9** (233 mg, 68%) as a yellow solid. mp 121-125 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.5 (s, 1H), 8.31 (t, *J* = 5.5 Hz, 1H), 8.25 (d, *J* = 8.1 Hz, 1H), 7.90-7.88 (m, 1H), 7.76-7.75 (m, 1H), 7.52-7.46 (m, 6H), 7.45-7.40 (m, 1H), 7.33 (bs, 1H), 7.12-7.09 (m, 3H), 6.98 (d, *J* = 8.3 Hz, 1H), 5.32 (s, 2H), 3.55 (q, *J* = 6.5 Hz, 2H), 2.88 (t, *J* = 7.0 Hz, 2H), 2.28 (s, 3H), 1.43 (s, 9H), 1.38 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.6, 155.8, 155.6, 152.6, 147.6, 146.1, 140.0, 138.3, 137.4, 137.0, 136.2, 129.8, 129.2, 129.0, 128.6, 128.5, 126.0, 124.5, 114.9, 108.1, 101.3, 83.5, 78.8, 71.5, 41.5, 39.5, 35.0, 28.5, 28.1, 21.3; MS (ESI) *m*/*z* 678 $(M\text{-}OTs)^+$. HRMS (EI) calcd for $C_{30}H_{37}IN_3O_5S$ 678.1493, found 678.1486.

2-Benzyloxy-4-{2'-(N,N'-bis(tert-butoxycarbonyl)-N''-guanidinyl)ethyl}phenyl(2-thienyl)iodonium bromide **(10).** A solution of KBr (72 mg, 0.6 mmol) in H_2O (1.0 mL) was added slowly to a solution of compound **9** (120 mg, 0.14 mmol) in MeCN (1.5 mL) at 60 °C. The reaction mixture was stirred at room temperature for 1 h. The precipitate was washed with ice H_2O (10 mL), filtered, washed further with Et_2O by several times and dried *in vacuo* to afford the product (94 mg, 89%) as a white solid. mp 141-144 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.5 (s, 1H), 8.33 (t, *J* = 5.4 Hz, 1H), 8.22 (d, *J* = 8.1 Hz, 1H), 7.84 (dd, *J* = 5.4, 1.3 Hz, 1H), 7.69 (dd, *J* = 3.9, 1.2 Hz, 1H), 7.51-7.38 (m, 5H), 7.29 (d, *J* = 1.2 Hz, 1H), 7.07-7.05 (m, 1H), 6.95 (dd, *J* = 8.1, 1.5 Hz, 1H), 5.30 (s, 2H), 3.55 (q, *J* = 6.5 Hz, 2H), 2.87 (t, *J* = 7.1 Hz, 2H), 1.43 (s, 9H), 1.38 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.6, 155.7, 155.5, 152.5, 139.1, 137.4, 136.3, 136.1, 129.5, 129.1, 128.9, 128.4, 124.4, 114.8, 109.7, 104.1, 83.5, 78.8, 71.4, 41.5, 35.0, 28.5, 28.1; MS (ESI) *m*/*z* 678 $(M\text{-}Br)^+$. Anal. Calcd. For $C_{30}H_{37}BrIN_3O_5S$: C, 47.50; H, 4.92; N, 5.54. Found: C, 47.42; H, 4.82, N, 5.54.

3-Benzyloxy-4-fluorophenethylamine tert-butylcarbamate **(15).** To a solution of 3-benzyloxy-4-fluorophenethylamine hydrochloride **16** (1.1 g, 2.8 mmol)[1] and triethylamine (1.6 mL, 11.3

mmol) in DMF (10 mL) was added $(Boc)_2O$ (650 mg, 3.0 mmol) at room temperature. The reaction mixture was heated at 120 °C for 1 h, cooled to room temperature, treated with saturated NH_4Cl solution (40 mL) and extracted with ethyl acetate (30 mL × 2). The combined organic layers were washed by brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 20% ethyl acetate in hexane) to afford the product (560 mg, 91%) as a white solid; mp 87-89 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45-7.31 (m, 5H), 7.03-6.99 (m, 1H), 6.84 (d, *J* = 7.5 Hz, 1H), 6.73-6.70 (m, 1H), 5.11 (s, 2H), 4.51 (bs, 1H), 3.32 (q, *J* = 6.4 Hz, 2H), 2.72 (t, *J* = 6.9 Hz, 2H), 1.44 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.7, 155.8, 151.7 (*J* = 243.6 Hz), 146.5 (*J* = 10.9 Hz), 136.4, 135.1, 128.6, 128.1, 127.5, 121.5, 116.1 (*J* = 18.1 Hz), 79.3, 71.4, 41.7, 35.7, 28.4; MS (ESI) *m*/*z* 368 $(M+Na)^+$. HRMS (EI) calcd for $C_{20}H_{24}FNO_3$ 368.1632, found 368.1634.

N,N'-Bis(tert-butoxycarbonyl)-N''-3-benzyloxy-4-fluorophenethylguanidine **(18).** To a solution of compound **16** (60 mg, 0.21 mmol) and triethylamine (0.12 mL, 0.85 mmol) in anhydrous DMF (2.0 mL) was added in portion 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea (68 mg, 0.23 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 1 h, warmed to room temperature and stirred overnight. The mixture was diluted with ethyl acetate (8.0 mL), washed with saturated NH_4Cl solution (10 mL) and extracted with ethyl acetate (2 × 10 mL). The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 10% to 25% ethyl acetate in hexane) to afford the product (95 mg, 91%) as a white liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.5 (s, 1H), 8.36-8.35 (m, 1H), 7.46-7.30 (m, 5H), 7.03-6.99 (m, 1H), 6.89 (dd, *J* = 8.1, 2.0 Hz, 1H), 6.75-6.72 (m, 1H), 5.13 (s, 2H), 3.65-3.61 (m, 2H), 2.79 (t, *J* = 7.0 Hz, 2H), 1.50 (s, 9H), 1.46 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.5, 156.1, 153.2, 146.6 (*J* = 11.0 Hz), 136.5, 134.8, 128.6, 128.1, 127.5, 121.4, 116.2 (*J* = 18.6 Hz), 116.0, 83.1, 79.3, 71.2, 42.1, 34.8, 28.3, 28.0; MS (ESI) *m*/*z* 488 $(M+H)^+$. HRMS (EI) calcd for $C_{26}H_{34}FN_3O_5$ 488.2555, found 488.2559.

Isolated rat heart studies. Hearts from male Sprague-Dawley rats (225 – 500 g) were perfused under moderate workload conditions (7.3 mmHg preload, 73 mmHg afterload) using a working heart preparation based on the system of Taegtmeyer et al.[2] Two separate perfusion circuits were used in parallel, connected to the left atrial cannula with a 3-way connector to allow for rapid switching from one perfusion circuit to the other. The perfusion medium was Krebs-Henseleit (KH) bicarbonate buffer (118 nM NaCl, 4.7 mM KCl, 2.55 mM $CaCl_2$, 1.2 mM $MgSO_4$, 1.2 mM $K_2H_2PO_4$, and 25 mM $NaHCO_3$) containing 5 mM glucose and oxygenated with a 95% O_2/5% CO_2 gas mixture. Corticosterone (54 μM) was added to the perfusate to block extraneuronal uptake (uptake-2) of the radiotracers into the rat myocardium.[3]

Radioactivity in the heart was measured externally using a pair of cesium fluoride (CsF) scintillation detectors (Crismatec 51Y51; Saint-Gobain, Nemours, France), with the front faces of the two CsF detectors directly opposing each other and the heart centered between them. Each detector was enclosed in a large cylindrical lead collimator (2 cm wall thickness, 25 cm long) to minimize detected counts originating from radioactive sources outside the heart. Two coincidence detection circuits were established between the detectors using standard Nuclear Instrumentation Module (NIM) electronic modules. One circuit measured total coincident events between the two detectors (true + random coincident events), and the second measured only

random coincident events. A computer-driven data acquisition system interfaced to the NIM-module coincidence circuits was used to acquire and record the whole-heart radioactivity data throughout the study.[4]

Hearts were initially perfused for a 30 min stabilization period using KH buffer in the first of the two perfusion circuits. During this time, [^{18}F]**1** was added to 1.0 L of KH buffer circulating in the second perfusion circuit and allowed to mix for several minutes. Three 1.0 mL aliquots were then drawn from the second perfusion circuit and counted in a gamma counter (Perkin-Elmer MINAXI AutoGamma 5500) to determine the radioactivity concentration in the perfusate (C_p). Radioactivity concentrations of around 2 μCi/mL perfusate were used. After initiating data acquisition from the CsF detectors, the heart was rapidly switched to the second perfusion circuit to begin a constant infusion of [^{18}F]**1**. After the 10 min constant infusion study, the heart was switched back to the first perfusion circuit for 120 min to measure clearance rates of the tracer from the heart.

The acquired whole-heart radioactivity data (counts per second; cps) at each time point were converted to an 'apparent distribution volume' (ADV; mL perfusate/g wet), by dividing by the perfusate radioactivity concentration C_p (μCi/mL perfusate), the external detection system calibration factor Z_{calib} (cps/μCi), and the measured wet mass of the heart M_w (g wet). Neuronal uptake rates of the radiotracers (K_{up}; mL perfusate/min/g wet) were calculated by fitting the ADV data between t = 1 min and t = 4 min of the 10 min constant infusion phase of the experiment to a line. Clearance rates were estimated by fitting the ADV data during the clearance phase of the study to multiple exponential decay processes. The exponential clearance rate constants (λ_i) were used to calculate corresponding clearance half-times ($T_{1/2} = \ln 2/\lambda_i$). The slowest estimated rate, associated with clearance from sympathetic neurons, is the rate reported for each compound.

References

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