Supplemental information

A Novel $^{18}$F-Labeling Method for the Synthesis of $[^{18}F]$-Piperidine-Containing Ligands as Potential PET Radiotracers for $\sigma$ Receptors

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I. General information

Glassware and stir bars were dried in an oven at 140 °C for at least 12 h and then cooled in a desiccator cabinet over Drierite prior to use. Unless otherwise noted, reactions were performed without exclusion of air or moisture. Plastic syringes or glass pipets were used to transfer liquid reagents. Reactions were stirred magnetically using Teflon-coated, magnetic stir bars.

All reagents and solvents were purchased from commercial sources and used as received unless otherwise stated. N-chlorosuccinimide (NCS) was recrystallized from boiling water then dried under a vacuum and stored in a desiccator. N-iodosuccinimide (NIS) was recrystallized from boiling dioxane and MTBE, crushed under a mortar and pestle, filtered, washed with hexanes, and then stored in a dark vial. Anhydrous THF and CH₂Cl₂ were obtained from a DriSolve purification system when necessary. Organic solutions were concentrated in vacuo using a rotary evaporator. Analytical thin-layer chromatography (TLC) was performed using aluminum plates pre-coated with 0.25 mm of 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light and/or exposure to KMnO₄ stain. Column chromatography was performed with silica gel (60 Å, standard grade).

Proton, carbon and fluorine nuclear magnetic resonance spectra were recorded at ambient temperature (unless otherwise stated) using a Varian INOVA 400 (400, 100, 376 MHz respectively) or Varian Unity (500, 125, 470 MHz respectively). All values for proton chemical shifts are reported in parts per million (δ) and are referenced to the residual protium in CDCl₃ (δ 7.24). All values for carbon chemical shifts are reported in parts per million (δ) and are referenced to the carbon resonances in CDCl₃ (δ 77.0). Chemical shifts for ¹⁹F NMR are reported in parts per million (δ) and are referenced to the fluorine resonances of CFCl₃ (δ 00.0). NMR data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constants (Hz), integration. Infrared spectroscopic data obtained using a Thermo Scientific Nicolet 380 and are reported in wavenumbers (cm⁻¹). High-resolution mass spectra were obtained through the Duke University Mass Spectrometry Facility using an Agilent 1100 Series liquid chromatography-electrospray ionization mass spectrometer. Melting points were determined in open capillary tubes using a Mel-Temp II apparatus and are uncorrected.
II. Experimental procedure for compound preparation and characterization data

2-(2’-(6”-Methoxy-3”’,4”’-dihydronaphthalen-1’’-yl)ethyl)-1,3-dioxolane (5).\textsuperscript{1-2} The flask charged with Mg\textsuperscript{o} turnings (2.01 g, 82.5 mmol, 5.5 equiv) was allowed to vigorously mechanical stirring for 24 h under a nitrogen atmosphere. To the flask was added THF (25 mL) followed by a single crystal of I\textsubscript{2}. After another 10 min, neat 2-(2-bromoethyl)-1,3-dioxolane (3.39 g, 18.75 mmol, 1.25 equiv) was added dropwise over 15 min followed by the dropwise addition of a solution of 4 (2.64 g, 15.0 mmol, 1.0 equiv) in THF (20 mL) over 15 min. The reaction mixture was allowed to reflux for 24 h and then was cooled to room temperature followed by the addition of a saturated aqueous solution of NH\textsubscript{4}Cl (20 mL) and EtOAc (50 mL) sequentially. The resulting suspension was filtered through Celite and the filtrate extracted with EtOAc (2 \times 75 mL). The organic layers were combined, washed with a saturated aqueous solution of NH\textsubscript{4}Cl (20 mL), brine (2 \times 25 mL), dried over Na\textsubscript{2}SO\textsubscript{4}, and filtered. The filtrate was concentrated in vacuo.

To the resulting residue was added AcOH (40 mL). The mixture was allowed to stir for 1.5 h and then was added H\textsubscript{2}O (20 mL). The resulting solution was extracted with hexanes (4 \times 50 mL). The hexanes layers were combined and washed with a saturated aqueous solution of NaHCO\textsubscript{3} (2 \times 50 mL), followed by brine (50 mL). The hexanes were removed in vacuo. The crude residue was purified by column chromatography (5% ethyl acetate–hexanes to 10% ethyl acetate–hexanes) to give 5 as a white solid (2.85 g, 73%). R\textsubscript{f} = 0.46 (25% ethyl acetate–hexanes); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \(\delta\) 7.20 (dd, \(J = 8.1, 0.9\) Hz, 1H), 6.74–6.69 (m, 2H), 5.76 (tt, \(J = 4.7, 1.2\) Hz, 1H), 4.96–4.94 (m, 1H), 4.02–3.96 (m, 2H), 3.93–3.86 (m, 2H), 3.80 (s, 3H), 2.71 (t, \(J = 8.0\) Hz, 2H), 2.57–2.51 (m, 2H), 2.26–2.20 (m, 2H), 1.92–1.86 (m, 2H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}): \(\delta\) 158.2, 138.5, 135.3, 127.8, 123.7, 122.4, 113.7, 110.8, 104.3, 64.9, 55.2, 32.7, 28.9, 26.9, 23.0; FTIR (thin film), cm\textsuperscript{-1} 1605, 1497, 1248, 1132, 1033, 821; HRMS-ESI (m/z) calcd. for C\textsubscript{16}H\textsubscript{21}O\textsubscript{3} ([M+H]\textsuperscript{+}): 261.1485; found: 261.1477.
3-(6′-Methoxynaphthalen-1′-yl)propanal (6). To a solution of 5 (1.95 g, 7.5 mmol, 1.0 equiv) in toluene (150 mL), was added DDQ (2.13 g, 9.375 mmol, 1.25 equiv) in one portion under nitrogen. The reaction mixture was stirred at room temperature for 2 h, then was filtered and washed with hexanes (150 mL). The organic layer was washed with an aqueous solution of NaOH (1.0 M, 2 × 50 mL), a saturated aqueous solution of NaHCO₃ (50 mL), and brine (50 mL). The organic layer was dried over Na₂SO₄ and filtered. The filtrate was concentrated in vacuo. The crude residue was purified by column chromatography (2% ethyl acetate–hexanes to 5% ethyl acetate–hexanes) to provide 2-(2′-(6′-methoxynaphthalen-1′-yl)ethyl)-1,3-dioxolane as a yellow oil (1.94 g, 97%). Rᵣ = 0.45 (25% ethyl acetate–hexanes); ¹H NMR (400 MHz, CDCl₃): δ 7.98 (dt, J = 9.1, 0.7 Hz, 1H), 7.61 (dd, J = 8.1, 0.7 Hz, 1H), 7.35 (dd, J = 8.1, 7.1 Hz, 1H), 7.23–7.15 (m, 3H), 4.99 (t, J = 4.6 Hz, 1H), 4.09–4.00 (m, 2H), 3.96–3.87 (m, 2H), 3.93 (s, 3H), 3.17 (m, 2H), 2.10 (m, 2H). ¹³C NMR (125 MHz, CDCl₃): δ 157.2, 137.8, 135.1, 127.2, 126.2, 125.6, 125.4, 123.8, 118.4, 106.6, 104.0, 65.0, 55.3, 34.9, 27.1; FTIR (thin film), cm⁻¹ 1624, 1257, 1131, 1030; HRMS-ESI (m/z) calcd. for C₁₆H₁₉O₃ ([M+H⁺]: 259.1329; found: 259.1332.

To 2-(2′-(6′-methoxynaphthalen-1′-yl)ethyl)-1,3-dioxolane (2.58 g, 10 mmol, 1.0 equiv) was added a solution of AcOH (120 mL) and H₂O (30 mL). The reaction mixture was stirred at 60 °C for 2 h and then was cooled down to room temperature. The solvent was removed in vacuo, providing the crude residue in approximately 20 mL. To the crude residue, was added an aqueous solution of NaOH (150 mL, 15%). The resulting mixture was extracted with MTBE (3 × 100 mL). The MTBE layers were combined, washed with brine (100 mL), dried over Na₂SO₄, and filtered. The filtrate was concentrated in vacuo. The crude material was purified by column chromatography (50% CH₂Cl₂–hexanes to 100% CH₂Cl₂) to give 6 (1.83 g, 86%) as an orange solid. Rᵣ = 0.54 (75% dichloromethane–hexanes); ¹H NMR (400 MHz, CDCl₃): δ 9.88 (t, J = 1.3 Hz, 1H), 7.89 (d, J = 9.1 Hz, 1H), 7.64 (d, J = 8.2 Hz, 1H), 7.36 (dd, J = 8.2, 7.2 Hz, 1H), 7.21–7.15 (m, 3H), 3.93 (s, 3H), 3.38 (t, J = 7.6 Hz, 2H), 2.90 (td, J = 7.6, 1.3 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃): δ 201.5, 157.3, 136.3, 135.2, 126.9, 126.2, 126.0, 124.8,
123.7, 118.7, 106.8, 55.2, 44.5, 25.1; FTIR (thin film), cm\(^{-1}\) 1721, 1625, 1435, 1256, 1221; HRMS-ESI (m/z) calcd. for C\(_{14}\)H\(_{15}\)O\(_2\) ([M+H]\(^+\)): 215.1067; found: 215.1068.

2,2-Dimethylpent-4-en-1-amine (7).\(^{3-4}\) To a solution of 2,2-dimethylpent-4-enal (2.05 mL, 15 mmol, 1.0 equiv) in MeOH (50 mL) and H\(_2\)O (6 mL) was added Na\(_2\)CO\(_3\) (1.91 g, 18 mmol, 1.2 equiv) and hydroxylamine hydrochloride (1.25 g, 18 mmol, 1.2 equiv). The reaction mixture was allowed to stir for 24 h and then was quenched by the addition of H\(_2\)O (50 mL). The resulting reaction mixture was extracted with Et\(_2\)O (3 \(\times\) 50 mL). The Et\(_2\)O layers were combined, washed with brine (2 \(\times\) 50 mL), dried over Na\(_2\)SO\(_4\), and filtered. The filtrate was concentrated in vacuo, providing 2,2-dimethylpent-4-enal oxime as a clear liquid (1.88 g, 99%). R\(_f\) = 0.55 (25% ethyl acetate–hexanes); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 8.01–7.72 (s, br, 1H), 7.34 (s, 1H), 5.76 (ddt, \(J\) = 16.9, 10.2, 7.4 Hz, 1H), 5.10–5.02 (m, 2H), 2.16 (dt, \(J\) = 7.4, 1.1 Hz, 2H), 1.09 (s, 6H). \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 158.5, 133.8, 118.1, 45.2, 36.6, 25.0; FTIR (neat), cm\(^{-1}\) 2965, 1384, 914, 652; HRMS-ESI (m/z) calcd. for C\(_7\)H\(_{14}\)NO ([M+H]\(^+\)): 128.1070; found: 128.1070.

To a mixture of LAH (418 mg, 11.0 mmol, 2.2 equiv) in THF (11 mL) at 0 °C, was added dropwise a solution of 2,2-dimethylpent-4-enal oxime (636 mg, 5.0 mmol, 1.0 equiv) in THF (2 mL) over 15 min under nitrogen. The reaction was warmed up to room temperature, allowed to stir at room temperature for 10 min, and then heated to reflux for 2 h. Next the reaction was cooled down to 0 °C, and quenched with H\(_2\)O (0.5 mL) and an aqueous solution of NaOH (0.5 mL, 15%). The mixture was allowed to stir for another 1 h, and then was diluted with H\(_2\)O (50 mL) and filtered. The filtrate was extracted with Et\(_2\)O (4 \(\times\) 25 mL). The organic layers were combined and extracted with an aqueous solution of HCl (4 \(\times\) 20 mL, 0.5 M). The aqueous layers were combined, basified with an aqueous solution of NaOH, and then extracted with Et\(_2\)O (3 \(\times\) 30 mL). The organic layers were combined, washed with brine (2 \(\times\) 25 mL), dried over Na\(_2\)SO\(_4\), and filtered. The filtrate was concentrated in vacuo to produce 7 as a clear liquid (403 mg, 71%). \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 5.85–5.76 (m, 1H), 5.04–4.99 (m, 2H), 2.44 (s, 2H), 1.96 (dt, \(J\) = 7.5, 1.1 Hz, 2H), 1.05–0.97 (s, br, 2H), 0.85 (s, 6H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 135.3,
116.9, 52.7, 44.0, 34.9, 24.6; FTIR (neat), cm\(^{-1}\) 2955, 1471, 996, 910, 810, 732; HRMS-ESI (m/z) calcd. for C\(_7\)H\(_{16}\)N ([M+H]\(^+\)): 114.1277; found: 114.1277.

4-Methyl-4-pentenamide (7').\(^5\) This reaction was performed at the 25 mmol scale in five separate 20 mL vials. To each vial was added the following: ethyl 4-methylpent-4-enoate (711 mg, 5.0 mmol, 1.0 equiv),\(^6\)\(^7\) concentrated aqueous ammonia (7.5 mL), sodium cyanide (24.5 mg, 0.5 mmol, 0.1 equiv), and MeOH (7.5 mL). The separate vials were sealed with paraffin film, heated to 45 °C, and stirred for 48 h. Then the vials were cooled to room temperature, combined, and concentrated in vacuo until approximately 25 mL of total volume remained. Brine (50 mL) was added and the resulting mixture extracted with CH\(_2\)Cl\(_2\) (4 \times 50 mL). The organic layers were combined, dried over Na\(_2\)SO\(_4\), and filtered. The filtrate was concentrated in vacuo. The remaining solid was filtered and washed with hexanes to give 7' as a white solid (1.85 g, 65%). \(R_f = 0.40\) (100% ethyl acetate); mp 84–85 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 5.47 (s, br, 2H), 4.79–4.77 (m, 1H), 4.74–4.71 (m, 1H), 2.42–2.32 (m, 4H), 1.76 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 175.2, 144.3, 110.5, 34.0, 33.0, 22.4; FTIR (neat), cm\(^{-1}\) 3348, 3177, 1627, 1414, 883, 646; HRMS-ESI (m/z) calcd. for C\(_6\)H\(_{11}\)NO ([M+H]\(^+\)): 114.0913; found: 114.0914.

\[ \text{Me} \quad \text{CO}_2\text{Et} \quad \xrightarrow{\text{NaCN, NH}_3\text{ (conc. aq)}} \quad \text{Me} \quad \text{H}_2\text{N} \quad \text{CO} \]

\(7'\)

\(N-(3'-(6''-\text{Methoxynaphthalen-1''-yl)propyl}-2,2-\text{dimethylpent-4-en-1-amine} \quad (8).\(^8\)}\) A solution of aldehyde 6 (429 mg, 2.0 mmol, 1.0 equiv) in MeOH/CH\(_2\)Cl\(_2\) (20 mL, 1:3) was added to a stirring solution of amine 7 (226 mg, 2.0 mmol, 1.0 equiv) in MeOH/CH\(_2\)Cl\(_2\) (20 mL, 1:3). The reaction mixture was allowed to stir for 24 h. Then the solvent was removed in vacuo. To
the residual liquid at 0 °C, was added MeOH/CH₂Cl₂ (40 mL, 1:1) followed by the addition of NaBH₄ (151 mg, 4.0 mmol, 2.0 equiv) in small portions over 5 min. The reaction was warmed up to room temperature and was allowed to stir for 12 h. The reaction was quenched by the addition of an aqueous solution of NaOH (2 mL, 15%). The mixture was extracted with EtOAc (100 mL). The organic layer was washed with a saturated aqueous solution of NaHCO₃ (20 mL), brine (2 × 20 mL), dried over Na₂SO₄, and filtered. The filtrate was concentrated in vacuo. Purification of the crude oil by column chromatography (1% MeOH–CH₂Cl₂ to 10% MeOH–CH₂Cl₂) yields 8 as a viscous, clear oil (468 mg, 75%).

\[ \text{R}_f = 0.08 \text{ (25% ethyl acetate–hexanes); } \]

\[ ^1H \text{ NMR (400 MHz, CDCl}_3): \delta 7.98 (dt, J = 8.8, 1.0 Hz, 1H), 7.60 (dd, J = 8.2, 1.0 Hz, 1H), 7.35 (dd, J = 8.2, 7.1 Hz, 1H), 7.20–7.14 (m, 3H), 5.87–5.77 (m, 1H), 5.04–4.98 (m, 2H), 3.93 (s, 3H), 3.08 (t, J = 7.7 Hz, 2H), 2.69 (t, J = 7.1 Hz, 2H), 2.35 (s, 2H), 2.01 (dt, J = 7.5, 1.2 Hz, 2H), 1.91 (tt, J = 7.7, 7.1 Hz, 2H), 1.20 (s, br, 1H), 0.89 (s, 6H); \]

\[ ^{13}C \text{ NMR (125 MHz, CDCl}_3): \delta 157.1, 138.6, 135.6, 135.1, 127.3, 126.2, 125.5, 125.4, 123.8, 118.2, 116.7, 106.6, 60.4, 55.2, 50.6, 44.8, 34.2, 31.2, 30.7, 25.5; \]

\[ \text{FTIR (thin film), cm}^{-1} 2951, 1626, 1434, 1220. \]

\[ \text{HRMS-ESI (m/z) calcd. for C}_{21}\text{H}_{30}\text{NO ([M+H]}^+): 312.2322; \text{found: 312.2322.} \]

\[ \text{-} \]

\[ \text{N-(3'}^\prime\text{-}(6''\text{-Methoxynaphthalen-1''-yl)propyl)-4-methylpent-4-en-1-amine (8'). To a mixture of LAH (418 mg, 11.0 mmol, 3.67 equiv) in THF (15 mL) at 0 °C, was added dropwise a solution of 7 (566 mg, 5.0 mmol, 1.67 equiv) in THF (5 mL) over 5 min under nitrogen. The reaction was allowed to stir at 0 °C for 10 min and then at room temperature for an additional 2 h. The reaction was then cooled down to 0 °C and quenched slowly with the addition of water (0.4 mL), an aqueous solution of NaOH (0.4 mL, 15%), and water (1.2 mL) sequentially. The mixture was stirred at room temperature for 1 h, then filtered, and washed with Et₂O (50 mL). The filtrate was dried over Na₂CO₃ and concentrated in vacuo (>100 Torr at 22 °C), providing a solution of amine intermediate which was used directly in the next step without further} \]
purification. The resulting solution of the amine intermediate was added to a solution of 6 (0.6423 g, 3.0 mmol, 1.0 equiv) in MeOH/CH₂Cl₂ (60 mL, 1:3). The reaction solution was allowed to stir overnight. Then the solvent was removed in vacuo. To the residue, was added MeOH/CH₂Cl₂ (60 mL, 1:1). To the resulting solution at 0 °C, was added NaBH₄ (227 mg, 6.0 mmol, 2.0 equiv). After 30 min, the reaction was warmed up to room temperature and allowed to stir for an additional 2 h. The reaction was quenched by the addition of an aqueous solution of NaOH (5 mL, 15%) and water (100 mL). The resulting solution was extracted with EtOAc (3 × 75 mL). The organic layers were combined, washed with a saturated aqueous solution of NaHCO₃ (100 mL) and brine (100 mL), dried over Na₂SO₄, and filtered. The filtrate was concentrated in vacuo. Preliminary treatment of the residue on silica followed by Kugelrohr distillation (0.4 Torr) yields 8’ as a viscous, clear oil (585 mg, 73%). Rᵣ = 0.08 (100% ethyl acetate on Et₃N/CH₂Cl₂-treated plate); ¹H NMR (400 MHz, CDCl₃): δ 7.96 (d, J = 9.2 Hz, 1H), 7.61 (d, J = 8.2 Hz, 1H), 7.35 (dd, J = 8.2, 7.1 Hz, 1H), 7.20–7.14 (m, 3H), 4.71–4.67 (m, 2H), 3.93 (s, 3H), 3.08 (t, J = 7.8 Hz, 2H), 2.72 (t, J = 7.2 Hz, 2H), 2.61 (t, J = 7.3 Hz, 2H), 2.04 (t, J = 7.6 Hz, 2H), 1.93 (tt, J = 7.8, 7.2 Hz, 2H), 1.72 (s, 3H), 1.63–1.52 (s, br, 1H), 1.63 (tt, J = 7.6, 7.3 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃): δ 157.2, 144.5, 137.2, 135.1, 127.1, 126.1, 125.7, 125.2, 123.8, 118.4, 110.6, 106.6, 55.2, 48.7, 48.6, 35.0, 30.3, 29.1, 25.9, 22.1; FTIR (thin film), cm⁻¹ 2952, 2769, 2359, 1626, 1443, 784; HRMS-ESI (m/z) calcd. for C₂₀H₂₈NO ([M+H]⁺): 298.2165; found: 298.2166.

1-(3’-(6’’-Methoxynaphthalen-1’’-yl)propyl)-3,3-dimethylpiperidine (3).⁹-¹⁰ A solution of 8 (31.1 mg, 0.1 mmol, 1.0 equiv) and NCS (13.4 mg, 0.1 mmol, 1.0 equiv) in MeCN (2 mL) was stirred at room temperature for one hour. Then NaI (0.7 mg, 0.005 mmol, 0.05 equiv) was added to the reaction and heated to 60 °C for 24 h. The reaction was cooled and directly purified by column chromatography (2% ethyl acetate–hexanes) to give 5-chloro-1-(3’-(6’’-}
methoxynaphthalen-1’’-yl)propyl)-3,3-dimethylpiperidine as a clear oil (27.7 mg, 80%). \( R_f = 0.41 \) (10% ethyl acetate–hexanes); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.97 (d, \( J = 8.8 \) Hz, 1H), 7.61 (d, \( J = 8.2 \) Hz, 1H), 7.36 (dd, \( J = 8.2, 7.1 \) Hz, 1H), 7.21–7.15 (m, 3H), 4.13 (ddt, \( J = 11.9, 10.6, 4.5 \) Hz, 1H), 3.93 (s, 3H), 3.18 (ddt, \( J = 10.6, 4.5, 1.7 \) Hz, 1H), 3.13–3.00 (m, 2H), 2.48–2.34 (m, 2H), 2.44 (dt, \( J = 11.1, 1.7 \) Hz, 1H), 1.97 (t, \( J = 10.6 \) Hz, 1H), 1.95 (ddt, \( J = 12.7, 4.5, 1.7 \) Hz, 1H), 1.91–1.84 (m, 2H), 1.71 (d, \( J = 11.1 \) Hz, 1H), 1.35 (t, \( J = 12.3 \) Hz, 1H), 1.09 (s, 3H), 0.93 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \( \delta \) 157.2, 138.5, 135.1, 127.3, 126.2, 125.5, 125.4, 124.0, 118.3, 106.6, 64.7, 62.4, 57.3, 55.3, 54.3, 48.4, 33.3, 30.5, 29.4, 28.2, 25.3; FTIR (thin film), cm\(^{-1}\) 2949, 1625, 1471, 1433, 1256, 1220; HRMS-ESI (m/z) calcd. for C\(_{21}\)H\(_{29}\)ClNO ([M+H]+): 346.1932; found: 346.1933.

To a stirring solution of 5-chloro-1-(3’-(6’’-methoxynaphthalen-1’’-yl)propyl)-3,3-dimethylpiperidine (27.7 mg, 0.08 mmol, 1.0 equiv) in THF (2 mL), was added solid LAH (30.4 mg, 0.8 mmol, 10.0 equiv) under nitrogen. The resulting mixture was heated to reflux for 24 h. The reaction was cooled down to room temperature and quenched with the sequential addition of H\(_2\)O (0.3 mL), aqueous NaOH (0.3 mL, 15%), and H\(_2\)O (0.6 mL). The resulting mixture was filtered and washed with Et\(_2\)O (20 mL). The filtrate was extracted with Et\(_2\)O (3 \( \times \) 15 mL). The organic layers were combined, washed with brine (15 mL), dried over Na\(_2\)SO\(_4\), and filtered. The filtrate was concentrated in vacuo. The crude residue was purified by column chromatography (2% methanol–dichloromethane) to give 3 as a clear oil (6.4 mg, 26%). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 8.00 (d, \( J = 9.0 \) Hz, 1H), 7.60 (d, \( J = 8.2 \) Hz, 1H), 7.35 (t, \( J = 7.6 \) Hz, 1H), 7.20–7.14 (m, 3H), 3.93 (s, 3H), 3.07 (t, \( J = 7.7 \) Hz, 2H), 2.42–2.25 (m, br, 4H), 2.10–2.00 (m, br, 2H), 1.93–1.86 (m, br, 2H), 1.25–1.21 (m, br, 2H), 0.97 (s, 6H). These data are consistent with published spectra.\(^{11}\)

![Chemical structure](image)

5-Fluoro-1-(3’-(6’’-methoxynaphthalen-1’’-yl)propyl)-3,3-dimethylpiperidine ([\(^{19}\)F]-3).\(^{10}\) To a stirring solution of 8 (31.1 mg, 0.1 mmol, 1.0 equiv) in \( \tau \)-BuOH (1 mL) was added a solution of
NIS (22.5 mg, 0.1 mmol, 1.0 equiv) in t-BuOH (1 mL) over 5 min. After 1 h, AgOTf (77.1 mg, 0.3 mmol, 3.0 equiv) and a solution of TBAF (0.3 mL, 3.0 equiv, 1.0 M in THF) were added at once to the reaction and the resulting mixture heated to 70 °C for 30 min. The reaction was cooled, filtered through Celite, washed with CH₂Cl₂, and then concentrated in vacuo. The crude residue was purified by column chromatography (5% ethyl acetate–hexanes) to give [¹⁹F]-3 as a clear oil (26.4 mg, 80%). \( R_f = 0.56 \) (25% ethyl acetate–hexanes); \(^1\)H NMR (400 MHz, CDCl₃): \( \delta \) 7.99 (d, \( J = 8.8 \) Hz, 1H), 7.61 (d, \( J = 8.2 \) Hz, 1H), 7.35 (dd, \( J = 8.2, 7.1 \) Hz, 1H), 7.21–7.15 (m, 3H), 4.76 (dtt, \( J = 48.9, 8.6, 4.4 \) Hz, 1H), 3.93 (s, 3H), 3.14–3.02 (m, 2H), 2.94–2.85 (m, 1H), 2.42 (t, \( J = 7.0 \) Hz, 2H), 2.24 (d, \( J = 11.2 \) Hz, 1H), 2.21–2.13 (m, 1H), 1.93–1.85 (m, 3H), 1.74 (td, \( J = 13.8, 4.6 \) Hz, 1H), 1.36 (td, \( J = 13.0, 9.0 \) Hz, 1H), 1.02 (s, 6H); \(^{13}\)C NMR (125 MHz, CDCl₃): \( \delta \) 157.2, 138.6, 135.1, 127.3, 126.2, 125.5, 125.4, 124.0, 124.0, 118.3, 106.6, 87.8 (d, \( ^1J_{F-C} \) = 169.9 Hz), 65.0, 58.5 (d, \( ^2J_{F-C} \) = 23.8 Hz), 57.4, 55.2, 43.4 (d, \( ^2J_{F-C} \) = 16.5 Hz), 31.8 (d, \( ^3J_{F-C} \) = 8.0 Hz), 30.4, 28.9, 28.2, 26.9; \(^{19}\)F NMR (376 MHz, CDCl₃) \( \delta \) −182.0 to −182.9 (br, m); FTIR (thin film), \( \text{cm}^{-1} \) 2948, 1625, 1472, 1256, 1219, 1002; HRMS-ESI (m/z) calcd. for C₂₁H₂₉FNO ([M+H]+): 330.2228; found: 330.2228.

\[ \text{[19F]-3' as a clear oil (11.5 mg, 37%).} \]

3-Fluoro-1-(3’-(6’’-methoxynaphthalen-1’’-yl)propyl)-3-methylpiperidine ([¹⁹F]-3’).\(^{10}\) To a stirring solution of 8’ (29.7 mg, 0.1 mmol, 1.0 equiv) in t-BuOH (0.75 mL) was added a solution of NIS (22.5 mg, 0.1 mmol, 1.0 equiv) in t-BuOH (0.75 mL) over 5 min. After 1 h, AgOTf (77.1 mg, 0.3 mmol, 3.0 equiv) and a solution of TBAF (0.3 mL, 3.0 equiv, 1.0 M in THF) were added at once to the reaction and the resulting mixture heated to 70 °C for 30 min. The reaction was cooled, filtered through Celite, washed with CH₂Cl₂, and then concentrated in vacuo. The crude residue was purified by column chromatography (5% ethyl acetate–hexanes to 50% ethyl acetate–1% methanol–49% hexanes) to give [¹⁹F]-3’ as a clear oil (11.5 mg, 37%). \( R_f = 0.15 \)
(50% ethyl acetate–hexanes); $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.98 (d, $J = 8.8$ Hz, 1H), 7.60 (d, $J = 8.2$ Hz, 1H), 7.35 (dd, $J = 8.2$, 7.0 Hz, 1H), 7.21–7.14 (m, 3H), 3.93 (s, 3H), 3.05 (td, $J = 7.6$, 2.6 Hz, 2H), 2.73–2.60 (br, m, 2H), 2.45 (t, $J = 7.6$ Hz, 2H), 2.20–2.11 (br, m, 1H), 1.93 (quintet, $J = 7.6$ Hz, 2H), 1.93–1.77 (m, 3H), 1.60–1.53 (m, 1H), 1.36 (d, $J = 21.6$ Hz, 3H), 0.98–0.85 (m, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$, 60 °C): $\delta$ 157.2, 138.5, 135.2, 127.4, 126.2, 125.6, 125.4, 123.9, 118.3, 106.7, 62.3 (d, $^2$J$_{F-C} = 22.6$ Hz), 58.1, 55.3, 53.3, 35.3 (d, $^2$J$_{F-C} = 21.2$ Hz), 30.7, 28.1 (d, $^3$J$_{F-C} = 4.1$ Hz), 25.2 (d, $^2$J$_{F-C} = 24.6$ Hz), 22.3, (note that a carbon peak for C-F could not be found); $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ −146.0 to −149.5 (br, m); FTIR (thin film), 1530, 1349, 1288, 1266, 1133; HRMS-ESI (m/z) calcd. for C$_{20}$H$_{27}$FNO ([M+H]$^+$): 316.2071; found: 316.2076.
III. Experimental procedure for radio-fluorination and in vivo PET imaging

General information for radiochemistry experiments.
All chemicals are analytical grade and used without further purification. Analytical reversed-phase high-performance liquid chromatography (HPLC) was accomplished on a SHIMADZU chromatography system (Model CBM-20A). The λ absorbance detector and the model 2200 scaler ratemeter radiation detector were added to the HPLC system. HPLC was performed on a Phenomenex, Kinetex® 5µm EVO C18 100 Å, 250 x 4.6 mm LC Column with a flow of 1 ml/min.

HPLC Method

Method A: Phenomenex, Kinetex® 5µm EVO C18 100 Å, 250 x 4.6 mm LC Column. Solvent A: 0.1%TFA water; Solvent B: 0.1%TFA acetonitrile; 0 to 2 min: isocratic elution at 5% solvent B, 2 to 22 min, 5% to 95% solvent B. Flow rate: 1 mL/min, column temperature: 19 to 21 °C.

Radio-fluorination experiments.
The radiolabeling reactions were performed using the following protocol. The alkene precursor 8 or 8' (6.5 µmol) was mixed with 1.5 equivalent of N-iodosuccinimide (NIS) in 25 µL of anhydrous MeCN. This reaction mixture was incubated at room temperature for 10 minutes. The resulting mixture was then combined with [18F]-TBAF in MeCN. After incubating at room temperature, 40 °C, 70 °C, or 100 °C for another 10 min, the reaction was quenched by adding 1 mL of 1:1 (v/v) water: MeCN. The mixture was passed through a Sep-Pak light alumina N cartridge. An aliquot of aqueous fraction was analyzed by HPLC using method A. The identity of the radiolabeled products ([18F]-3 and [18F]-3’) was confirmed by the comparison of their retention times with those of non-radiolabeled analogues ([19F]-3 and [19F]-3’).
Figure S1. Representative radio-HPLC profiles of Sep-Pak purified [\(^{18}\text{F}\)]-3 prepared at room temperature (A), 40 °C (B), 70 °C (C), and 100 °C (D).

Figure S2. Representative radio-HPLC profiles of Sep-Pak purified [\(^{18}\text{F}\)]-3’ prepared at room temperature (A), 40 °C (B), 70 °C (C), and 100 °C (D).
In vivo dynamic PET/CT Imaging

For dynamic PET/CT imaging, each nude mice was anesthetized using isoflurane (2% in oxygen), then placed on the imaging cradle with body temperature maintained. A baseline CT scan was obtained for localization and attenuation correction prior to radiotracer injection. When the 30-minute dynamic scan was started, $[^{18}\text{F}]-3$ or $[^{18}\text{F}]-3'$ (~ 0.2 mCi) in 1X PBS pH 7.5 (300 µL) was immediately injected intravenous into nude mice. The dynamic PET/CT acquisitions were then achieved and reconstructed for analysis.

Table S1. Brain accumulation of $[^{18}\text{F}]-3$ in nude mice at different time frames

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Figure S3. Dynamic PET/CT images of $[^{18}\text{F}]-3$ in nude mice at different time frames
**Table S2.** Brain accumulation of $[^{18}\text{F}]-3'$ in nude mice at different time frames

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**Figure S4.** Dynamic PET/CT images of $[^{18}\text{F}]-3'$ in nude mice at different time frames
IV. References


V. NMR spectra

\[
\text{MeO} \quad 5
\]

\[
\begin{array}{c}
\text{NMR Spectra}
\end{array}
\]
2-(2'-(6''-methoxynaphthalen-1''-yl)ethyl)-1,3-dioxolane
2-(2''-(6''-methoxynaphthalen-1''-yl)ethyl)-1,3-dioxolane
2,2-dimethylpent-4-enal oxime
2,2-dimethylpent-4-enal oxime
\[ \text{Diagram of a molecule with chemical shifts:} \]

- 5.85
- 5.82
- 5.81
- 5.00
- 5.03
- 5.02
- -2.44
- 1.97
- 1.96

- Number 7

- Chemical shifts in ppm

- t1 axis from 0.0 to 9.5
- t2 axis from 0.0 to 9.0
5-chloro-1-(3'-(6''-methoxynaphthalen-1''-yl)propyl)-3,3-dimethylpiperidine
5-chloro-1-(3′-(6″-methoxynaphthalen-1″-yl)propyl)-3,3-dimethylpiperidine