Supporting Information

Characterization and Optimization of Benzimidazopyrimidine and Pyridoimidazopyridine Derivatives as Tau-SPECT Probes

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1. Materials and Methods

1.1. General remarks

All reagents were obtained commercially and used without further purification unless otherwise indicated. All compounds were purified by Smart Flash EPCLC W-Prep 2XY (Yamazen Corporation, Osaka, Japan) unless otherwise stated. HPLC was performed with a Shimadzu system (an LC-20AD pump with an SPD-20A UV detector, λ = 254 nm; Shimadzu, Kyoto, Japan) using a Cosmosil C_{18} column ($5C_{18}$-AR-II, 4.6ID × 150 mm, Nacalai Tesque, Kyoto, Japan). ^{1}H NMR spectra were obtained on a JEOL JNM400 (JEOL, Tokyo, Japan) with TMS as an internal standard. Coupling constants are reported in hertz. Multiplicity was defined by s (singlet), d (doublet), t (triplet), q (quartet), br (broad), and m (multiplet). Mass spectra were obtained on a SHIMADZU LCMS-2020 EV. High-resolution mass spectrometry (HRMS) was carried out with LCMS-IT-TOF (Shimadzu).

1.2. Chemistry

6-Bromo-N-(tert-butoxycarbonyl)-pyrimidin-4-amine (1)

A mixture of 6-bromopyrimidine-4-amine (696 mg, 4.00 mmol), di-*tert*-butyl dicarbonate (1.31 g, 6.00 mmol), *N*,*N*-dimethylpyridine-4-amine (489 mg, 4.00 mmol), and Et_3N (647 μL, 4.80 mmol) in tetrahydrofuran (THF) (30 mL) was stirred for 80 min at room temperature. The solvent was removed and the residue was purified by silica gel chromatography (ethyl acetate/hexane = 1/2)

to give 445 mg of **1** (40.5%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.11 (s, 1H), 8.65 (s, 1H), 8.29 (s, 1H), 1.58 (s, 9H). MS (ESI) *m/z* calcd. for $C_9H_{12}BrN_3O_2$ (MH^+) 274.0, found 273.9 [MH^+].

2-Bromo-N-(tert-butoxycarbonyl)-pyridin-4-amine (2)

The same reaction described above to prepare **1** was used, and 531 mg of **2** was obtained from 2-bromopyridine-4-amine at a yield of 64.9%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 5.8 Hz, 1H), 7.70 (d, J = 1.4 Hz, 1H), 7.32 (s, 1H), 7.24 (dd, J = 5.5, 1.7 Hz, 1H), 1.51 (s, 9H). MS (ESI) *m/z* calcd. for $C_{10}H_{13}BrN_2O_2$ (MH^+) 273.0, found 272.9 [MH^+].

6-Bromo-N-(tert-butoxycarbonyl)-N-methylpyrimidin-4-amine (3)

To a solution of **1** (598 mg, 2.19 mmol) in *N*,*N*-dimethylformamide (DMF) (30 mL) were added NaH (78.8 mg, 3.29 mmol) and iodometane (266.8 μL, 3.29 mmol) on an ice bath. The mixture was stirred for 3 h at room temperature and then deionized water was added to quench the reaction. The mixture was extracted with ethyl acetate, and the organic phase was separated and dried over Na_2SO_4. The solvent was removed and the residue was purified by silica gel chromatography (ethyl acetate/hexane = 1/2) to give **3** (534 mg, 84.9%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, J = 1.2 Hz, 1H), 8.33 (d, J = 0.8 Hz, 1H), 3.44 (s, 3H), 1.58 (s, 9H). MS (ESI) *m/z* calcd. for $C_{10}H_{14}BrN_3O_2$ (MH^+) 288.0, found 287.9 [MH^+].

6-Bromo-N-(tert-butoxycarbonyl)-N-ethylpyrimidin-4-amine (4)

To a solution of **1** (495 mg, 1.81 mmol) in DMF (20 mL) were added NaH (65.2 mg, 2.72 mmol) and 1-iodoethane (373.9 μL, 3.62 mmol) on an ice bath. The mixture was stirred for 3 h at room temperature and then deionized water was added to quench the reaction. The mixture was extracted with ethyl acetate, and the organic phase was separated and dried over Na_2SO_4. The solvent was removed and the residue was purified by silica gel chromatography (ethyl acetate/hexane = 1/2) to give **4** (473 mg, 86.8%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, J = 0.8 Hz, 1H), 8.31 (d, J = 0.8 Hz, 1H), 4.08 (q, J = 7.2 Hz, 2H), 1.58 (s, 9H), 1.24 (t, J = 6.8 Hz, 3H). MS (ESI) *m/z* calcd. for $C_{11}H_{16}BrN_3O_2$ (MH^+) 302.0, found 301.8 [MH^+].

6-Bromo-N-(tert-butoxycarbonyl)-N-propylpyrimidin-4-amine (5)

To a solution of **1** (445 mg, 1.62 mmol) in DMF (30 mL) were added NaH (77.8 mg, 3.24 mmol) and 1-iodopropane (634 μL, 6.49 mmol) on an ice bath. The mixture was stirred for 1 h at room temperature and then deionized water was added to quench the reaction. The mixture was extracted with ethyl acetate, and the organic phase was separated and dried over Na_2SO_4. The solvent was removed and the residue was purified by silica gel chromatography (ethyl acetate/hexane = 1/2) to give **5** (467 mg, 91.1%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, J = 1.2 Hz, 1H), 8.29 (d, J = 1.2 Hz, 1H), 3.99-3.95 (m, 2H), 1.70-1.60 (m, 2H), 1.56 (s, 9H), 0.92 (t, J = 7.4 Hz, 3H). MS (ESI) *m/z* calcd. for $C_{12}H_{18}BrN_3O_2$ (MH^+) 316.1, found 315.9 [MH^+].

2-Bromo-N-(tert-butoxycarbonyl)-N-methylpyridin-4-amine (6)

The same reaction described above to prepare **3** was used, and 209 mg of **6** was obtained from **2** at a yield of 94.5%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, J = 5.5 Hz, 1H), 7.52 (d, J = 2.0 Hz, 1H), 7.29 (dd, J = 5.7, 2.2 Hz, 1H), 3.30 (s, 3H), 1.53 (s, 9H). MS (ESI) *m/z* calcd. for $C_{11}H_{15}BrN_2O_2$ (MH^+) 287.0, found 287.0 [MH^+].

2-Bromo-N-(tert-butoxycarbonyl)-N-ethylpyridin-4-amine (7)

The same reaction described above to prepare **4** was used, and 113 mg of **7** was obtained from **2** at a yield of 79.5%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, J = 5.5 Hz, 1H), 7.51 (d, J = 2.1 Hz, 1H), 7.25 (dd, J = 5.7, 2.1 Hz, 1H), 3.76 (q, J = 7.1 Hz, 2H), 1.52 (s, 9H), 1.25 (t, J = 7.0 Hz, 3H). MS (ESI) *m/z* calcd. for $C_{12}H_{17}BrN_2O_2$ (MH^+) 301.0, found 300.9 [MH^+].

2-Bromo-N-(tert-butoxycarbonyl)-N-propylpyridin-4-amine (8)

The same reaction described above to prepare **5** was used, and 579 mg of **8** was obtained from **2** at a yield of 93.2%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, J = 5.7 Hz, 1H), 7.49 (d, J = 2.1 Hz, 1H), 7.22 (dd, J = 5.7, 2.1 Hz, 1H), 3.66 (t, J = 7.6 Hz, 2H), 1.68-1.59 (m, 2H), 1.51 (s, 9H), 0.92 (t, J = 7.4 Hz, 3H). MS (ESI) *m/z* calcd. for $C_{13}H_{19}BrN_2O_2$ (MH^+) 315.1, found 315.1 [MH^+].

7-Bromo-N-(tert-butoxycarbonyl)-N-methylbenzo[4,5]imidazo[1,2-c]pyrimidin-3-amine (9)

A mixture of **3** (170 mg, 0.59 mmol), 2,5-dibromoaniline (223 mg, 0.89 mmol), CuI (22.8 mg, 0.12 mmol), Cs_2CO_3 (587 mg, 1.8 mmol), and 1,10-phenanthroline (43.3 mg, 0.24 mmol) in xylene (15 mL) was stirred under reflux for 23 h. The solvent was removed, and the residue was purified by silica gel chromatography (ethyl acetate/hexane = 1/2) to give **9** (17 mg, 7.7%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.12 (s, 1H), 8.09-8.06 (m, 1H), 8.00 (s, 1H), 7.83 (s, 1H), 7.51-7.43 (m, 1H), 3.46 (s, 3H), 1.58 (s, 9H). MS (ESI) *m/z* calcd. for $C_{16}H_{17}BrN_4O_2$ (MH^+) 377.0, found 376.9 [MH^+].

7-Bromo-N-(tert-butoxycarbonyl)-N-ethylbenzo[4,5]imidazo[1,2-c]pyrimidin-3-amine (10)

The same reaction described above to prepare **9** was used, and 39.3 mg of **10** was obtained from **4** at a yield of 7.4%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64-8.62 (m, 1H), 8.08 (d, J = 8.8 Hz, 1H), 7.69-7.67 (m, 1H), 7.48 (s, 1H), 6.93 (s, 1H), 4.04 (t, J = 6.8 Hz, 2H), 1.57 (s, 9H), 1.27-1.25 (m, 3H). MS (ESI) *m/z* calcd. for $C_{17}H_{19}BrN_4O_2$ (MH^+) 391.0, found 390.9 [MH^+].

7-Bromo-N-(tert-butoxycarbonyl)-N-propylbenzo[4,5]imidazo[1,2-c]pyrimidin-3-amine (11)

The same reaction described above to prepare **9** was used, and 15.3 mg of **11** was obtained from **5** at a yield of 8.0%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (s, 1H), 8.04 (d, J = 1.2 Hz, 1H), 7.99 (s, 1H), 7.83 (d, J = 8.4 Hz, 1H), 7.51 (dd, J = 8.7, 1.2 Hz, 1H), 3.99 (t, J = 7.4 Hz, 2H), 1.73-1.64

(m, 2H), 1.57 (s, 9H), 0.94 (t, J = 7.4 Hz, 3H). MS (ESI) *m/z* calcd. for $C_{18}H_{21}BrN_4O_2$ (MH^+) 405.1, found 404.9 [MH^+].

3-Bromo-N-(tert-butoxycarbonyl)-N-methylimidazo[1,2-a:5,4-b']dipyridin-7-amine (12).

A mixture of **6** (210 mg, 0.731 mmol), 2,5-dibromopyridine-3-amine (276 mg, 1.10 mmol), CuI (27.8 mg, 0.146 mmol), Cs_2CO_3 (476 mg, 1.46 mmol), and 1,10-phenanthroline (52.7 mg, 0.292 mmol) in xylene (20 mL) was stirred under reflux for 23 h. The solvent was removed, and the residue was purified by silica gel chromatography (ethyl acetate/hexane = 1/1) to give **12** (16.3 mg, 5.9%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (dd, J = 7.5, 0.9 Hz, 1H), 8.44 (d, J = 2.0 Hz, 1H), 8.26 (d, J = 2.0 Hz, 1H), 7.32 (d, J = 0.6 Hz, 1H), 7.30-7.27 (m, 1H), 3.42 (s, 3H), 1.54 (s, 9H). MS (ESI) *m/z* calcd. for $C_{16}H_{17}BrN_4O_2$ (MH^+) 377.1, found 377.1 [MH^+].

3-Bromo-N-(tert-butoxycarbonyl)-N-ethylimidazo[1,2-a:5,4-b']dipyridin-7-amine (13)

The same reaction described above to prepare **12** was used, and 48.6 mg of **13** was obtained from **7** at a yield of 10.1%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, J = 7.6 Hz, 1H), 8.44 (d, J = 2.1 Hz, 1H), 8.27 (d, J = 1.8 Hz, 1H), 7.38 (d, J = 1.4 Hz, 1H), 7.15 (dd, J = 7.6, 2.1 Hz, 1H), 3.86 (q, J = 7.1 Hz, 2H), 1.53 (s, 9H), 1.31 (t, J = 7.0 Hz, 3H). MS (ESI) *m/z* calcd. for $C_{17}H_{19}BrN_4O_2$ (MH^+) 391.1, found 390.9 [MH^+].

3-Bromo-N-(tert-butoxycarbonyl)-N-propylimidazo[1,2-a:5,4-b']dipyridin-7-amine (14)

The same reaction described above to prepare **12** was used, and 85.9 mg of **14** was obtained from **8** at a yield of 11.5%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, J = 7.5 Hz, 1H), 8.45 (d, J = 1.7 Hz, 1H), 8.27 (d, J = 2.0 Hz, 1H), 7.37 (dd, J = 2.0, 0.6 Hz, 1H), 7.13 (dd, J = 7.5, 2.0 Hz, 1H), 3.75 (t, J = 7.5 Hz, 2H), 1.75-1.65 (m, 2H), 1.52 (s, 9H), 0.94 (t, J = 7.5 Hz, 3H). MS (ESI) *m/z* calcd. for $C_{18}H_{21}BrN_4O_2$ (MH^+) 405.1, found 405.1 [MH^+].

N-(tert-Butoxycarbonyl)-N-methyl-7-(tributylstannyl)benzo[4,5]imidazo[1,2-c]pyrimidin-3-amine (15)

A mixture of **9** (54 mg, 0.14 mmol), bis(tributyltin) (143.9 μL, 0.28 mmol), and $Pd(PPh_3)_4$ (71.2 mg, 0.06 mmol) in a mixed solvent (dioxane/Et_3N = 2/1) was stirred under reflux for 4 h. The solvent was removed, and the residue was purified by silica gel chromatography (ethyl acetate/hexane = 1/2) to give **15** (6.7 mg, 8.0%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.16-9.15 (m, 1H), 8.07 (s, 1H), 8.02 (s, 1H), 7.76 (s, 1H), 7.47-7.45 (m, 1H), 3.46 (s, 3H), 1.56-0.71 (m, 36H). MS (ESI) *m/z* calcd. for $C_{28}H_{44}N_4O_2Sn$ (MH^+) 589.2, found 589.0 [MH^+].

N-(tert-Butoxycarbonyl)-N-ethyl-7-(tributylstannyl)benzo[4,5]imidazo[1,2-c]pyrimidin-3-amine (16)

The same reaction described above to prepare **15** was used, and 18.1 mg of **16** was obtained from **10** at a yield of 24.0%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.16 (s, 1H), 8.02 (s, 1H), 7.91 (d, J = 8.0 Hz, 1H), 7.74 (s, 1H), 7.45 (d, J = 8.4 Hz, 1H), 4.06-4.00 (m, 2H), 1.56 (s, 9H), 1.40-0.86 (m, 30H). MS (ESI) *m/z* calcd. for $C_{29}H_{46}N_4O_2Sn$ (MH^+) 603.3, found 603.1 [MH^+].

N-(tert-Butoxycarbonyl)-N-propyl-7-(tributylstannyl)benzo[4,5]imidazo[1,2-c]pyrimidin-3-amine (17)

The same reaction described above to prepare **15** was used, and 23.4 mg of **17** was obtained from **11** at a yield of 20.2%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.16 (d, J = 1.4 Hz, 1H), 8.02 (s, 1H), 7.90 (dd, J = 7.8, 0.6 Hz, 1H), 7.71 (d, J = 1.2 Hz, 1H), 7.45 (d, J = 7.8 Hz, 1H), 3.93 (t, J = 7.5 Hz, 2H), 1.73-1.63 (m, 2H), 1.61-1.49 (m, 15H), 1.39-1.30 (m, 6H), 1.16-1.10 (m, 6H), 0.93 (t, J = 7.4 Hz, 3H), 0.88 (t, J = 7.4 Hz, 9H). MS (ESI) *m/z* calcd. for $C_{30}H_{48}N_4O_2Sn$ (MH^+) 617.3, found 617.0 [MH^+].

N-(tert-Butoxycarbonyl)-N-methyl-3-(tributylstannyl)imidazo[1,2-a:5,4-b']dipyridin-7-amine (18)

The same reaction described above to prepare **15** was used, and 13.7 mg of **18** was obtained from **12** at a yield of 51.5%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, J = 7.5 Hz, 1H), 8.40 (s, 1H), 8.24 (s, 1H), 7.32 (s, 1H), 7.16 (d, J = 7.5 Hz, 1H), 3.40 (s, 3H), 1.69-1.56 (m, 6H), 1.53 (s, 9H),

1.40-1.25 (m, 6H), 1.19-1.14 (m, 6H), 0.94-0.87 (m, 9H). MS (ESI) *m/z* calcd. for $C_{28}H_{44}N_4O_2Sn$ (MH^+) 589.2, found 589.2 [MH^+].

N-(tert-Butoxycarbonyl)-N-ethyl-3-(tributylstannyl)imidazo[1,2-a:5,4-b']dipyridin-7-amine (19)

The same reaction described above to prepare **15** was used, and 27.1 mg of **19** was obtained from **13** at a yield of 36.2%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (dd, J = 7.5, 2.0 Hz, 1H), 8.41-8.40 (m, 1H), 8.26-8.25 (m, 1H), 7.38 (d, J = 2.0 Hz, 1H), 7.04 (dd, J = 7.4, 2.2 Hz, 1H), 3.85 (q, J = 7.1 Hz, 2H), 1.67-1.54 (m, 6H), 1.52 (s, 9H), 1.40-1.31 (m, 6H), 1.29 (t, J = 7.0 Hz, 3H), 1.20-1.14 (m, 6H), 0.92-0.86 (m, 9H). MS (ESI) *m/z* calcd. for $C_{29}H_{46}N_4O_2Sn$ (MH^+) 603.3, found 603.1 [MH^+].

N-(tert-Butoxycarbonyl)-N-propyl-3-(tributylstannyl)imidazo[1,2-a:5,4-b']dipyridin-7-amine (20)

The same reaction described above to prepare **15** was used, and 82.5 mg of **20** was obtained from **14** at a yield of 49.3%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, J = 7.4 Hz, 1H), 8.41 (d, J = 1.0 Hz, 1H), 8.25 (d, J = 1.0 Hz, 1H), 7.38 (d, J = 2.0 Hz, 1H), 7.03 (dd, J = 7.6, 1.8 Hz, 1H), 3.75 (t, J = 7.6 Hz, 2H), 1.73-1.54 (m, 8H), 1.51 (s, 9H), 1.41-1.30 (m, 6H), 1.21-1.15 (m, 6H), 0.98-0.87 (m, 12H). MS (ESI) *m/z* calcd. for $C_{30}H_{48}N_4O_2Sn$ (MH^+) 617.3, found 617.3 [MH^+].

7-Iodo-N-(tert-butoxycarbonyl)-N-methyylbenzo[4,5]imidazo[1,2-c]pyrimidin-3-amine (21)

A mixture of **15** (5.7 mg, 0.011 mmol) and iodine (3.3 mg, 0.013 mmol) in chloroform (8 mL) was stirred at room temperature for 4 h. Saturated $NaHSO_3$ aq. was added to quench the reaction. The mixture was extracted with chloroform after neutralization with saturated $NaHCO_3$ aq. and the organic phase was separated and dried over Na_2SO_4. The solvent was removed and the residue was purified by silica gel chromatography (ethyl acetate/hexane = 1/2) to give **21** (4.1 mg, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.14 (s, 1H), 8.30 (d, J = 7.6 Hz, 1H), 7.84 (s, 1H), 7.68 (d, J = 7.2 Hz, 1H), 6.94 (s, 1H), 3.46 (s, 3H), 1.56 (s, 9H). MS (ESI) *m/z* calcd. for $C_{16}H_{17}IN_4O_2$ (MH^+) 425.0, found 424.9 [MH^+].

7-Iodo-N-(tert-butoxycarbonyl)-N-ethyylbenzo[4,5]imidazo[1,2-c]pyrimidin-3-amine (22)

The same reaction described above to prepare **21** was used, and 7.2 mg of **22** was obtained from **16** at a yield of 49.6%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (s, 1H), 8.31 (s, 1H), 7.88-7.84 (m, 1H), 7.67 (d, J = 8.0 Hz, 1H), 6.94 (s, 1H), 4.05 (m, 2H), 1.56 (s, 9H), 0.88-0.86 (m, 3H). MS (ESI) *m/z* calcd. for $C_{17}H_{19}IN_4O_2$ (MH^+) 439.1, found 439.0 [MH^+].

7-Iodo-N-(tert-butoxycarbonyl)-N-propylbenzo[4,5]imidazo[1,2-c]pyrimidin-3-amine (23)

The same reaction described above to prepare **21** was used, and 7.2 mg of **23** was obtained from **17** at a yield of 87.2%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.12 (d, J = 1.4 Hz, 1H), 8.23-8.22 (m, 1H), 7.80 (d, J = 1.4 Hz, 1H), 7.69-7.62 (m, 2H), 3.95 (t, J = 7.5 Hz, 2H), 1.68 (td, J = 15.0, 7.6 Hz,

2H), 1.56 (s, 9H), 0.93 (t, J = 7.4 Hz, 3H). MS (ESI) *m/z* calcd. for $C_{18}H_{21}IN_4O_2$ (MH^+) 453.1, found 452.9 [MH^+].

3-Iodo-N-(tert-butoxycarbonyl)-N-methylimidazo[1,2-a:5,4-b']dipyridin-7-amine (24)

The same reaction described above to prepare **21** was used, and 34.9 mg of **24** was obtained from **18** at a yield of 84.7%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (dd, J = 7.5, 0.6 Hz, 1H), 8.57 (d, J = 1.7 Hz, 1H), 8.46 (d, J = 2.0 Hz, 1H), 7.31 (d, J = 1.4 Hz, 1H), 7.28 (dd, J = 7.1, 1.9 Hz, 1H), 3.41 (s, 3H), 1.54 (s, 9H). MS (ESI) *m/z* calcd. for $C_{16}H_{17}IN_4O_2$ (MH^+) 425.0, found 425.1 [MH^+].

3-Iodo-N-(tert-butoxycarbonyl)-N-ethylimidazo[1,2-a:5,4-b']dipyridin-7-amine (25)

The same reaction described above to prepare **21** was used, and 11.3 mg of **25** was obtained from **19** at a yield of 67.4%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, J = 7.5 Hz, 1H), 8.58 (d, J = 1.4 Hz, 1H), 8.47 (d, J = 1.4 Hz, 1H), 7.38 (d, J = 2.3 Hz, 1H), 7.15 (dd, J = 7.2, 1.7 Hz, 1H), 3.85 (q, J = 7.0 Hz, 2H), 1.53 (s, 9H), 1.30 (t, J = 7.1 Hz, 3H). MS (ESI) *m/z* calcd. for $C_{17}H_{19}IN_4O_2$ (MH^+) 439.1, found 438.9 [MH^+].

3-Iodo-N-(tert-butoxycarbonyl)-N-propylimidazo[1,2-a:5,4-b']dipyridin-7-amine (26)

The same reaction described above to prepare **21** was used, and 38.5 mg of **26** was obtained from **20** at a yield of 73.4%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (dd, J = 7.5, 0.6 Hz, 1H), 8.57 (d, J

= 1.7 Hz, 1H), 8.46 (d, *J* = 2.0 Hz, 1H), 7.37 (dd, *J* = 2.0, 0.6 Hz, 1H), 7.13 (dd, *J* = 7.5, 2.0 Hz, 1H), 3.76 (t, *J* = 7.7 Hz, 2H), 1.75-1.65 (m, 2H), 1.52 (s, 9H), 0.95 (t, *J* = 7.4 Hz, 3H). MS (ESI) *m/z* calcd. for $C_{18}H_{21}IN_4O_2$ (MH^+) 453.1, found 453.1 [MH^+].

7-Iodo-N-methylbenzo[4,5]imidazo[1,2-c]pyrimidin-3-amine (27: BIPM-NHMe)

To a solution of **21** (5.2 mg, 0.01 mmol) in dichloromethane (5 mL) was added TFA (3 mL) at room temperature. The mixture was stirred for 30 min, and after neutralization with saturated $NaHCO_3$ aq., the mixture was extracted with chloroform and the organic phase was separated and dried over Na_2SO_4. The solvent was removed and the residue was purified by silica gel chromatography (ethyl acetate/hexane = 1/1) to give **27** (2.3 mg, 57.9%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (s, 1H), 8.31-8.25 (m, 2H), 7.69-7.51 (m, 1H), 6.11 (s, 1H), 5.02 (s, 1H), 2.96 (d, *J* = 5.2 Hz, 3H). HRMS (ESI) *m/z* calcd. for $C_{11}H_9IN_4$ (MH^+) 324.9950, found 324.9926 [MH^+].

7-Iodo-N-ethylbenzo[4,5]imidazo[1,2-c]pyrimidin-3-amine (28:BIPM-NHEt)

The same reaction described above to prepare **27** was used, and 2.1 mg of **28** was obtained from **22** at a yield of 37.8%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (m, 1H), 8.08 (s, 1H), 7.96 (s, 1H), 7.54-7.44 (m, 1H), 5.88 (s, 1H), 5.27 (s, 1H), 3.39-3.30 (m, 2H), 1.93 (m, 3H). HRMS (ESI) *m/z* calcd. for $C_{12}H_{11}IN_4$ (MH^+) 339.0107, found 339.0084 [MH^+].

7-Iodo-N-propylbenzo[4,5]imidazo[1,2-c]pyrimidin-3-amine (29:BIPM-NHPr)

The same reaction described above to prepare **27** was used, and 3.9 mg of **29** was obtained from **23** at a yield of 77.0%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (d, J = 1.1 Hz, 1H), 8.03 (t, J = 0.9 Hz, 1H), 7.52-7.49 (m, 2H), 6.10 (d, J = 1.1 Hz, 1H), 4.99 (s, 1H), 3.20 (td, J = 7.0, 5.8 Hz, 2H), 1.78-1.68 (m, 2H), 1.04 (t, J = 7.3 Hz, 3H). HRMS (ESI) *m/z* calcd. for $C_{13}H_{13}IN_4$ (MH^+) 353.0263, found 353.0214 [MH^+].

3-Iodo-N-methylimidazo[1,2-a:5,4-b']dipyridin-7-amine (30:PIP-NHMe)

The same reaction described above to prepare **27** was used, and 18.7 mg of **30** was obtained from **24** at a yield of 70.2%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.46 (d, J = 7.6 Hz, 1H), 8.28 (dd, J = 1.8, 0.7 Hz, 1H), 8.18 (dd, J = 1.7, 0.6 Hz, 1H), 7.21 (d, J = 4.8 Hz, 1H), 6.56 (dd, J = 7.3, 2.1 Hz, 1H), 6.12 (d, J = 1.8 Hz, 1H), 2.80 (d, J = 4.8 Hz, 3H). HRMS (ESI) *m/z* calcd. for $C_{11}H_9IN_4$ (MH^+) 324.9950, found 324.9906 [MH^+].

3-Iodo-N-ethylimidazo[1,2-a:5,4-b']dipyridin-7-amine (31:PIP-NHEt)

The same reaction described above to prepare **27** was used, and 5.8 mg of **31** was obtained from **25** at a yield of 66.8%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 (d, J = 7.3 Hz, 1H), 8.29 (d, J = 1.6 Hz, 1H), 8.18 (d, J = 1.8 Hz, 1H), 7.13 (t, J = 4.9 Hz, 1H), 6.59 (dd, J = 7.4, 1.9 Hz, 1H), 6.16 (d,

J = 1.8 Hz, 1H), 3.21-3.15 (m, 2H), 1.23 (t, *J* = 7.2 Hz, 3H). HRMS (ESI) *m/z* calcd. for $C_{12}H_{11}IN_4$ (MH^+) 339.0107, found 339.0075 [MH^+].

3-Iodo-N-propylimidazo[1,2-a:5,4-b']dipyridin-7-amine (32:PIP-NHPr)

The same reaction described above to prepare **27** was used, and 10.2 mg of **32** was obtained from **26** at a yield of 34.1%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 (d, *J* = 7.3 Hz, 1H), 8.29 (d, *J* = 1.6 Hz, 1H), 8.18 (d, *J* = 1.6 Hz, 1H), 7.17 (t, *J* = 5.0 Hz, 1H), 6.61 (d, *J* = 7.6 Hz, 1H), 6.16 (s, 1H), 3.11 (q, *J* = 6.3 Hz, 2H), 1.68-1.59 (m, 2H), 0.98 (t, *J* = 7.3 Hz, 3H). HRMS (ESI) *m/z* calcd. for $C_{13}H_{13}IN_4$ (MH^+) 353.0263, found 353.0223 [MH^+].

6-Bromo-N,N-diethylpyrimidin-4-amine (33)

To a solution of 6-bromopyrimidine-4-amine (348 mg, 2.00 mmol) in DMF (15 mL) were added NaH (96.0 mg, 4.00 mmol) and iodoethane (482 μL, 6.00 mmol) on an ice bath. The mixture was stirred for 21 h at room temperature and then deionized water was added to quench the reaction. The mixture was extracted with ethyl acetate, and the organic phase was separated and dried over Na_2SO_4. The solvent was removed and the residue was purified by silica gel chromatography (ethyl acetate/hexane = 1/2) to give **33** (219 mg, 47.7%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 0.7 Hz, 1H), 6.55 (d, *J* = 0.9 Hz, 1H), 3.49 (br, 4H), 1.20 (t, *J* = 7.1 Hz, 6H). MS (ESI) *m/z* calcd. for $C_8H_{12}BrN_3$ (MH^+) 230.0, found 229.9 [MH^+].

2-Bromo-N,N-diethylpyridin-4-amine (34)

The same reaction described above to prepare **33** was used, and 174.5 mg of **34** was obtained from 2-bromopyridin-4-amine at a yield of 38.1%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 6.0 Hz, 1H), 6.50 (d, J = 2.5 Hz, 1H), 6.31 (dd, J = 6.1, 2.4 Hz, 1H), 3.23 (q, J = 7.2 Hz, 4H), 1.07 (t, J = 7.1 Hz, 6H). MS (ESI) *m/z* calcd. for $C_9H_{13}BrN_2$ (MH^+) 229.0, found 228.9 [MH^+].

7-Bromo-N,N-diethylbenzo[4,5]imidazo[1,2-c]pyrimidin-3-amine (35)

The same reaction described above to prepare **9** was used, and 38.3 mg of **35** was obtained from **33** at a yield of 9.3%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (s, 1H), 7.78 (d, J = 1.4 Hz, 1H), 7.60 (d, J = 8.5 Hz, 1H), 7.29-7.27 (m, 1H), 6.17 (s, 1H), 3.58 (q, J = 7.0 Hz, 4H), 1.24 (t, J = 7.0 Hz, 6H). MS (ESI) *m/z* calcd. for $C_{14}H_{15}BrN_4$ (MH^+) 319.0, found 318.9 [MH^+].

3-Bromo-N,N-diethylimidazo[1,2-a:5,4-b']dipyridin-7-amine (36)

The same reaction described above to prepare **12** was used, and 25.3 mg of **36** was obtained from **34** at a yield of 6.6%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, J = 7.8 Hz, 1H), 8.21 (d, J = 1.7 Hz, 1H), 8.02 (s, 1H), 6.58 (dd, J = 7.8, 2.0 Hz, 1H), 6.44 (d, J = 1.2 Hz, 1H), 3.49 (q, J = 7.2 Hz, 4H), 1.28 (t, J = 7.1 Hz, 6H). MS (ESI) *m/z* calcd. for $C_{14}H_{15}BrN_4$ (MH^+) 319.0, found 318.9 [MH^+].

N,N-Diethyl-7-(tributylstannyl)benzo[4,5]imidazo[1,2-c]pyrimidin-3-amine (37)

The same reaction described above to prepare **15** was used, and 34.2 mg of **37** was obtained from **35** at a yield of 34.4%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (d, J = 1.2 Hz, 1H), 7.80 (s, 1H), 7.73 (d, J = 7.8 Hz, 1H), 7.28-7.26 (m, 1H), 6.20 (s, 1H), 3.58 (q, J = 7.1 Hz, 4H), 1.77-1.52 (m, 6H), 1.41-1.28 (m, 6H), 1.24 (t, J = 7.0 Hz, 6H), 1.13-1.08 (m, 6H), 0.94-0.86 (m, 9H). MS (ESI) *m/z* calcd. for $C_{26}H_{42}N_4Sn$ (MH^+) 531.2, found 530.8 [MH^+].

N,N-Diethyl-3-(tributylstannyl)imidazo[1,2-a:5,4-b']dipyridin-7-amine (38)

The same reaction described above to prepare **15** was used, and 54.7 mg of **38** was obtained from **36** at a yield of 48.0%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, J = 7.8 Hz, 1H), 8.10 (s, 1H), 7.93 (s, 1H), 6.47 (dd, J = 7.8, 2.3 Hz, 1H), 6.36 (d, J = 2.3 Hz, 1H), 3.40 (q, J = 7.1 Hz, 4H), 1.67-1.42 (m, 6H), 1.33-1.23 (m, 6H), 1.19 (t, J = 7.2 Hz, 6H), 1.08-1.03 (m, 6H), 0.91-0.78 (m, 9H). MS (ESI) *m/z* calcd. for $C_{26}H_{42}N_4Sn$ (MH^+) 531.2, found 530.7 [MH^+].

7-Iodo-N,N-diethylbenzo[4,5]imidazo[1,2-c]pyrimidin-3-amine (39:BIPM-NEt$_2$)

The same reaction described above to prepare **21** was used, and 5.82 mg of **39** was obtained from **37** at a yield of 33.3%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (d, J = 1.2 Hz, 1H), 8.00 (d, J = 0.9 Hz, 1H), 7.51-7.45 (m, 2H), 6.17 (d, J = 1.2 Hz, 1H), 3.58 (q, J = 7.1 Hz, 4H), 1.24 (t, J = 7.1 Hz, 6H). HRMS (ESI) *m/z* calcd. for $C_{14}H_{15}IN_4$ (M^+) 367.0341, found 367.0328 [MH^+].

3-Iodo-N,N-diethylimidazo[1,2-a:5,4-b']dipyridin-7-amine (40:PIP-NEt$_2$)

The same reaction described above to prepare **21** was used, and 13.7 mg of **40** was obtained from **38** at a yield of 43.7%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, J = 8.1 Hz, 1H), 8.33 (d, J = 1.7 Hz, 1H), 8.20 (d, J = 1.7 Hz, 1H), 6.57 (dd, J = 7.8, 2.6 Hz, 1H), 6.42 (d, J = 2.3 Hz, 1H), 3.48 (q, J = 7.2 Hz, 4H), 1.27 (t, J = 7.1 Hz, 6H). HRMS (ESI) *m/z* calcd. for $C_{14}H_{15}IN_4$ (MH^+) 367.0341, found 367.0330 [MH^+].

1.3. Radiolabeling

Preparation of [^{125}I]27, [^{125}I]28, and [^{125}I]29

To the tributyltin precursors (**15**, **16**, and **17**) (1 mg/mL EtOH, 200 μL) was added a mixture of [^{125}I]NaI (3.70 - 7.40 MBq, molar activity: 81.4 TBq/mmol), 100 μL of 3% H_2O_2 aq., and 100 μL of 1 N HCl aq. in a sealed vial. The reaction to obtain radioiodinated ligands was allowed to proceed at room temperature for 10 min and terminated by the addition of saturated $NaHSO_3$ aq. (200 μL). After neutralization with saturated $NaHCO_3$ aq. (200 μL) and extraction with ethyl acetate, the organic phase was dried by passing through a column filled with anhydrous Na_2SO_4. The solution was gas-dried with a stream of nitrogen gas. To a solution of the residue in chloroform (250 μL) was added TFA (250 μL) at room temperature. The mixture was stirred for 10 min and the solution was

gas-dried with a stream of nitrogen gas. The crude radioiodinated ligands were purified by HPLC on a COSMOSIL 5C_{18}-AR-II column with an isocratic solvent of acetonitrile/H_2O (with TFA) at a flow rate of 1.0 mL/min.

Preparation of [^{125}I]30, [^{125}I]31, and [^{125}I]32

To the corresponding tributyltin precursors (**18**, **19**, and **20**) (0.5 mg/mL MeOH containing 1% acetic acid, 100 μL) were added *N*-chlorosuccinimide (0.5 mg/mL MeOH, 40 μL) and [^{125}I]NaI (3.70 - 7.40 MBq) in a sealed vial. The reaction to obtain radioiodinated ligands was allowed to proceed at room temperature for 13.5 min and terminated by the addition of saturated $NaHSO_3$ aq. (40 μL). After extraction with ethyl acetate, the organic phase was dried by passing through a column filled with anhydrous Na_2SO_4. The solution was gas-dried with a stream of nitrogen gas. To a solution of the residue in chloroform (250 μL) was added TFA (250 μL) at room temperature. The mixture was stirred for 10 min and the solution was gas-dried with a stream of nitrogen gas. The crude radioiodinated ligands were purified by HPLC on a COSMOSIL 5C_{18}-AR-II column with an isocratic solvent of acetonitrile/H_2O (with TFA) at a flow rate of 1.0 mL/min.

Preparation of [^{125}I]39 and [^{125}I]40

To the corresponding tributyltin precursors (**37** and **38**) (1 mg/mL EtOH, 200 μL) was added a mixture of [^{125}I]NaI (3.70 - 7.40 MBq), 100 μL of 3% H_2O_2 aq., and 100 μL of 1 N HCl aq.

in a sealed vial. The reaction to obtain radioiodinated ligands was allowed to proceed at room temperature for 10 min and terminated by the addition of saturated $NaHSO_3$ aq. (200 μL). After neutralization with saturated $NaHCO_3$ aq. (200 μL) and extraction with ethyl acetate, the organic phase was dried by passing through a column filled with anhydrous Na_2SO_4. The solution was gas-dried with a stream of nitrogen gas. The crude radioiodinated ligands were purified by HPLC on a COSMOSIL $5C_{18}$-AR-II column with an isocratic solvent of acetonitrile/H_2O (with TFA) at a flow rate of 1.0 mL/min.

1.4. Human brain tissue

Experiments using human subjects were performed in accordance with relevant guidelines and regulations and were approved by the Ethics Committee of Kyoto University. Informed consent was secured from all subjects in this study. Postmortem brain tissues from an autopsy-confirmed case of AD were obtained from the Graduate School of Medicine, Kyoto University.

1.5. *In vitro* autoradiography

Six-micrometer-thick serial sections of paraffin-embedded blocks were used for autoradiography. The sections were subjected to two 15-min incubations in xylene, two 1-min incubations in 100% EtOH, one 1-min incubation in 90% EtOH, and one 1-min incubation in 70%

EtOH to completely deparaffinize them, followed by two 2.5-min washes in water. The sections were incubated with radioiodinated ligands (370 kBq/mL in 10% EtOH) for 2 h at room temperature. They were then dipped in 50% EtOH for 1 h and washed with H_2O for 1 min. After drying, the ^{125}I-labeled sections were exposed to a BAS imaging plate (Fuji Film, Tokyo, Japan) overnight. Autoradiographic images were obtained using an American Typhoon scanner system (GE Healthcare Life Sciences, Illinois, USA).

1.6. Animals

Animal experiments were conducted in accordance with our institutional guidelines and were approved by the Kyoto University Animal Care Committee. Male normal ddY mice were purchased from Japan SLC, Inc. (Shizuoka, Japan). ddY mice were fed standard chow and had free access to water.

1.7. *In vivo* biodistribution assay in normal mice

A saline solution (100 μL) of each ^{125}I-labeled compound (27.8 kBq) containing EtOH (10 μL) and Tween 80 (0.1 μL) was injected intravenously directly into the tails of ddY mice (5 weeks old, male). The mice were sacrificed at various time-points postinjection. Organs including the brain

were removed and weighed, and the radioactivity was measured with an automatic γ counter (Wallac WIZARD 2470, PerkinElmer, Massachusetts, USA).

Table S1. Biodistribution of radioactivity after intravenous injection of radioiodinated BIPM and PIP derivatives in normal mice[a]

Tissue	Time after injection (min)			
	2	10	30	60
		[^{125}I]**27** ([^{125}I]BIPM-NHMe)		
Blood	4.88 (0.50)	3.05 (0.27)	1.76 (0.16)	1.40 (0.23)
Liver	11.8 (1.34)	10.7 (2.35)	4.81 (0.59)	3.28 (0.48)
Kidney	10.9 (1.07)	7.76 (1.20)	3.43 (0.45)	2.41 (0.69)
Intestine	3.63 (0.93)	10.0 (3.64)	16.3 (2.82)	16.9 (3.29)
Spleen	3.85 (0.85)	3.27 (0.37)	1.21 (0.09)	1.14 (0.11)
Pancreas	6.54 (0.69)	2.26 (0.34)	1.16 (0.18)	1.00 (0.15)
Heart	5.51 (0.56)	1.96 (0.20)	0.87 (0.10)	0.69 (0.12)
Lung	8.11 (1.23)	5.83 (3.33)	2.58 (0.50)	2.26 (0.62)
Stomach[b]	2.84 (0.73)	7.71 (2.52)	7.26 (1.87)	6.28 (0.97)
Brain	5.50 (0.41)	0.85 (0.08)	0.18 (0.02)	0.13 (0.03)
Thyroid[b]	0.07 (0.02)	0.06 (0.02)	0.10 (0.05)	0.21 (0.09)
		[^{125}I]**28** ([^{125}I]BIPM-NHEt)		
Blood	4.06 (0.52)	2.48 (0.62)	1.27 (0.27)	0.77 (0.08)
Liver	12.4 (2.98)	12.0 (1.45)	7.08 (1.38)	5.01 (0.59)
Kidney	9.82 (0.44)	7.32 (1.74)	3.67 (0.77)	2.08 (0.14)
Intestine	2.91 (0.85)	10.6 (0.87)	16.6 (3.21)	19.0 (1.42)
Spleen	3.40 (0.61)	3.16 (0.54)	0.99 (0.23)	0.74 (0.36)
Pancreas	5.01 (0.97)	2.11 (0.67)	1.10 (0.24)	0.78 (0.27)
Heart	4.93 (0.42)	1.82 (0.47)	0.73 (0.16)	0.45 (0.05)
Lung	6.28 (0.86)	3.37 (0.75)	1.60 (0.30)	0.93 (0.07)
Stomach[b]	2.46 (0.57)	6.28 (1.17)	7.30 (0.88)	7.35 (0.87)
Brain	3.98 (0.18)	0.83 (0.13)	0.22 (0.05)	0.11 (0.01)
Thyroid[b]	0.09 (0.02)	0.03 (0.01)	0.02 (0.02)	0.03 (0.01)
		[^{125}I]**29** ([^{125}I]BIPM-NHPr)		
Blood	3.84 (0.45)	2.25 (0.14)	1.27 (0.12)	0.75 (0.11)
Liver	12.59 (1.74)	11.29 (1.50)	5.69 (0.99)	3.88 (0.79)

Kidney	12.25 (2.17)	8.12 (0.70)	5.50 (1.17)	2.73 (1.97)
Intestine	3.50 (0.75)	12.11 (3.21)	17.69 (3.79)	23.02 (5.77)
Spleen	3.04 (0.95)	2.60 (0.10)	0.97 (0.12)	0.53 (0.04)
Pancreas	4.93 (1.03)	1.93 (0.16)	0.89 (0.10)	0.67 (0.22)
Heart	5.24 (0.70)	1.81 (0.10)	0.77 (0.07)	0.46 (0.09)
Lung	7.03 (2.45)	3.60 (0.28)	1.67 (0.12)	1.11 (0.28)
Stomach[b]	2.13 (0.55)	6.02 (2.84)	6.03 (0.59)	8.75 (1.12)
Brain	3.99 (0.63)	0.88 (0.04)	0.22 (0.02)	0.09 (0.01)
Thyroid[b]	0.09 (0.06)	0.05 (0.01)	0.09 (0.02)	0.07 (0.06)
		[^{125}I]**39** ([^{125}I]BIPM-NEt$_2$)		
Blood	4.52 (0.28)	2.78 (0.28)	1.89 (0.12)	1.18 (0.20)
Liver	13.48 (1.89)	11.44 (3.19)	5.59 (0.73)	4.30 (0.78)
Kidney	10.68 (0.94)	6.33 (0.65)	4.24 (1.36)	2.70 (1.08)
Intestine	2.84 (0.66)	9.07 (1.31)	15.71 (2.72)	21.79 (6.41)
Spleen	2.91 (0.67)	2.25 (0.46)	0.96 (0.17)	0.65 (0.15)
Pancreas	5.98 (0.56)	2.29 (0.37)	0.99 (0.29)	0.87 (0.54)
Heart	6.02 (0.65)	2.07 (0.45)	0.88 (0.13)	0.59 (0.07)
Lung	7.41 (0.86)	4.50 (2.09)	1.71 (0.30)	1.19 (0.16)
Stomach[b]	2.05 (0.30)	5.02 (1.41)	6.17 (1.21)	5.42 (1.42)
Brain	3.85 (0.39)	1.25 (0.20)	0.29 (0.04)	0.12 (0.02)
Thyroid[b]	0.08 (0.04)	0.04 (0.04)	0.04 (0.03)	0.07 (0.09)
		[^{125}I]**30** ([^{125}I]PIP-NHMe)		
Blood	6.20 (0.43)	4.03 (0.30)	1.98 (0.20)	1.73 (0.32)
Liver	11.16 (1.06)	7.57 (0.97)	2.02 (0.09)	1.71 (0.36)
Kidney	11.35 (0.82)	7.84 (0.83)	2.30 (0.21)	2.24 (1.28)
Intestine	4.31 (0.84)	10.97 (2.08)	13.55 (1.52)	15.73 (3.23)
Spleen	3.84 (0.65)	3.34 (0.32)	1.50 (0.20)	1.32 (0.31)
Pancreas	6.28 (0.50)	2.82 (0.26)	0.89 (0.06)	0.78 (0.20)
Heart	6.39 (1.03)	2.46 (0.06)	0.85 (0.05)	0.70 (0.12)
Lung	7.50 (0.61)	4.14 (0.30)	1.90 (0.18)	1.67 (0.31)
Stomach[b]	3.11 (0.62)	8.97 (0.72)	18.4 (2.75)	17.67 (2.95)
Brain	6.62 (0.84)	1.73 (0.13)	0.17 (0.01)	0.10 (0.02)

Thyroid[b]	0.12 (0.06)	0.21 (0.07)	0.27 (0.23)	0.76 (0.46)
		[^{125}I]**31** ([^{125}I]PIP-NHEt)		
Blood	4.84 (0.48)	3.84 (0.34)	2.23 (0.57)	1.71 (0.21)
Liver	9.90 (1.27)	6.92 (1.02)	4.05 (0.63)	2.76 (0.44)
Kidney	12.09 (1.73)	8.01 (0.97)	2.61 (0.53)	1.89 (0.48)
Intestine	3.78 (0.18)	8.98 (1.02)	13.40 (3.94)	16.61 (5.73)
Spleen	3.05 (0.53)	3.12 (0.33)	1.27 (0.20)	1.07 (0.35)
Pancreas	5.80 (0.84)	2.91 (0.19)	1.15 (0.21)	0.90 (0.07)
Heart	8.82 (1.12)	2.81 (0.18)	1.14 (0.25)	0.82 (0.31)
Lung	8.45 (2.30)	4.42 (0.39)	2.13 (0.34)	1.57 (0.32)
Stomach[b]	2.29 (0.54)	7.76 (1.17)	12.35 (2.00)	13.92 (1.39)
Brain	6.86 (0.96)	1.97 (0.17)	0.24 (0.03)	0.08 (0.01)
Thyroid[b]	0.08 (0.03)	0.14 (0.03)	0.37 (0.29)	0.17 (0.14)
		[^{125}I]**32** ([^{125}I]PIP-NHPr)		
Blood	5.25 (0.26)	3.95 (0.47)	2.50 (0.09)	1.96 (0.34)
Liver	11.85 (0.73)	8.87 (1.18)	4.80 (0.21)	3.10 (0.33)
Kidney	11.61 (1.07)	6.72 (0.68)	2.83 (0.59)	1.95 (0.23)
Intestine	3.80 (0.40)	8.26 (1.68)	12.72 (4.41)	14.77 (3.44)
Spleen	3.36 (0.55)	2.85 (0.44)	1.61 (0.28)	1.14 (0.18)
Pancreas	5.76 (0.51)	2.27 (0.21)	1.14 (0.12)	1.66 (1.24)
Heart	5.79 (0.23)	2.16 (0.21)	1.11 (0.14)	0.83 (0.11)
Lung	7.25 (0.75)	4.56 (0.73)	2.34 (0.14)	2.13 (0.62)
Stomach[b]	2.68 (0.34)	7.62 (1.29)	14.95 (2.12)	17.29 (1.01)
Brain	4.84 (0.39)	1.10 (0.13)	0.21 (0.00)	0.10 (0.01)
Thyroid[b]	0.05 (0.02)	0.08 (0.07)	0.29 (0.22)	0.25 (0.22)
		[^{125}I]**40** ([^{125}I]PIP-NEt$_2$)		
Blood	6.59 (0.34)	4.85 (0.46)	2.92 (0.20)	2.76 (0.41)
Liver	14.98 (1.58)	7.53 (0.73)	3.42 (0.20)	2.88 (0.44)
Kidney	12.76 (1.50)	6.48 (0.78)	2.74 (0.30)	2.52 (0.40)
Intestine	3.56 (0.62)	7.32 (0.77)	9.52 (2.35)	12.37 (2.63)
Spleen	5.53 (0.60)	5.16 (0.70)	1.90 (0.25)	1.78 (0.19)
Pancreas	6.29 (0.51)	3.17 (0.12)	1.93 (1.03)	1.37 (0.13)

Heart	6.24 (0.49)	2.76 (0.21)	1.21 (0.08)	1.10 (0.15)
Lung	11.61 (2.36)	5.87 (0.57)	2.73 (0.44)	2.48 (0.28)
Stomach[b]	2.94 (0.31)	9.47 (1.16)	20.67 (3.27)	18.75 (2.60)
Brain	4.54 (0.48)	1.55 (0.26)	0.23 (0.01)	0.13 (0.01)
Thyroid[b]	0.07 (0.03)	0.03 (0.01)	0.02 (0.01)	0.03 (0.01)

[a]Expressed as % ID/g. Each value represents the mean (SD) of 5 animals.

[b]Expressed as % ID.

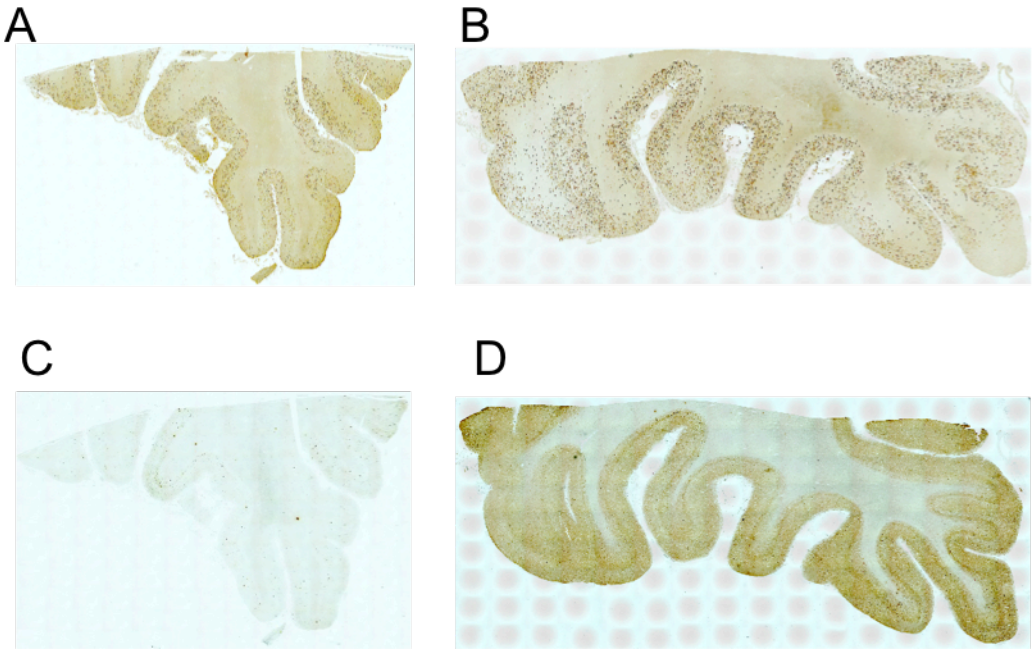

Figure S1. Immunohistochemical staining with antibodies against β-amyloid (A and B) and phosphorylated tau (C and D) of brain sections from patients with Alzheimer's disease. Adapted from reference.[1]

References

1. Watanabe, H.; Tatsumi, H.; Kaide, S.; Shimizu, Y.; Iikuni, S.; Ono, M., Structure-Activity Relationships of Radioiodinated 6,5,6-Tricyclic Compounds for the Development of Tau Imaging Probes. *ACS Med Chem Lett* **2020,** *11* (2), 120-126.