Supporting Information

Fluorinated Benzofuran Derivatives for PET Imaging of β-Amyloid Plaques in Alzheimer's Disease Brains

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Experimental Section

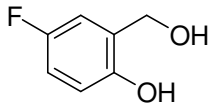
General remarks

All chemicals used in synthesis were commercial products used without further purification. ^{1}H-NMR spectra were obtained at 400 MHz on JEOL JNM-AL400 NMR spectrometers at room temperature with TMS as an internal standard. Chemical shifts are reported as δ values relative to the internal TMS. Coupling constants are reported in Hertz. Multiplicity is defined by s (singlet), d (doublet), t (triplet), and m (multiplet). Mass spectra were acquired with a Shimadzu GC-MS-QP2010 Plus (ESI). HPLC was performed with a Shimadzu system (a LC-10AT pump with a SPD-10A UV detector, λ = 254 nm) with a Cosmosil C18 column (Nakalai Tesque, 5C_{18}-AR-II,

4.6mm × 150mm) using acetonitrile/water (60:40) as the mobile phase at a flow rate of 1.0 mL/min. Fluorescent observation was performed by microscope (Nikon Eclipse 80i) with a BV-2A filter set (excitation, 400–440 nm; diachronic mirror, 455 nm; long pass filter, 470 nm). All key compounds were proven to show ≥98% purity by HPLC.

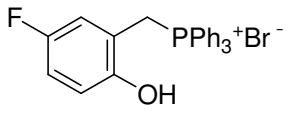
Synthesis

5-Fluoro-2-hydroxybenzyl alcohol (2).



Sodium borohydride (250 mg, 6.61 mmol) was added to a stirring solution of 5-fluoro-2-hydroxybenzaldehyde (1.8 g, 13.1 mmol) in ethanol (20 mL) in an ice bath. The reaction mixture was stirred at room temperature for 1 h. After the solvent was removed, a 1 N aqueous HCl solution (40 mL) was added to the residue and extracted with diethyl ether (40 mL). The organic phase was dried over Na_2SO_4 and filtered. The filtrate was concentrated to give 1.84 g of **2** (99.0%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.72 (s, 2H), 6.59 (s, 1H), 6.70-6.75 (m, 2H).

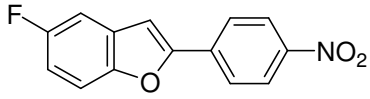
4-Fluoro-2-hydroxybenzyltriphenylphosphonium bromide (3).



A solution of **2** (1.84 g, 13.0 mmol) and triphenylphosphine hydrobromide (4.50 g, 13.1 mmol) in acetonitrile (40 mL) was stirred under reflux for 1 h. The solid that formed was filtered and washed with acetonitrile to give 4.27 g of **3** (70.5%). ^{1}H

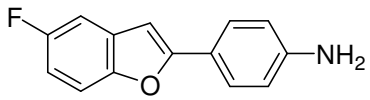
NMR (400 MHz, DMSO-d_6): δ 4.87 (d, 2H, J = 14.7 Hz), 6.33 (s, 1H), 6.65-6.71 (m, 2H), 7.67-7.89 (m, 15H), 9.34 (s, 1H).

5-Fluoro-2-(4-nitrophenyl)benzofuran (<u>4</u>).



A mixture of **<u>3</u>** (1.4 g, 3.0 mmol) and 4-nitrobenzoyl chloride (618 mg, 3.3mmol) in a mixed solvent (toluene 20 mL and triethylamine 0.5 mL) was stirred under reflux for 2 h. The precipitate was removed by filtration. The filtrate was concentrated, and the residue was recrystalized with ethyl acetate to give 238.4 mg of **<u>4</u>** (30.9%). ^{1}H NMR (400 MHz, $CDCl_3$) : δ 6.73 (d, 2H, J = 8.7 Hz), 6.76 (s, 1H), 6.88-6.93 (m, 1H), 7.16 (dd, 1H, J_1 = 11.2 Hz, J_2 = 2.4 Hz), 7.36 (dd, 1H, J_1 = 12.8 Hz, J_2 = 3.2 Hz), 7.67 (d, 2H, J = 8.7 Hz). MS: m/z 258 (M^++H).

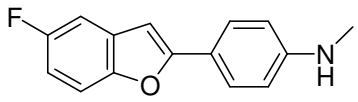
2-(4-Aminophenyl)-5-fluorobenzofuran (<u>5</u>).



A mixture of **<u>4</u>** (238 mg, 0.92 mmol), $SnCl_2$ (1.04 g, 5.5 mmol), and ethanol (20 mL) was stirred under reflux for 2 h. After the mixture cooled to room temperature, 1 M NaOH (20 mL) was added and extracted with ethyl acetate. The organic phase was dried over Na_2SO_4 and filtered. The filtrate was concentrated and the residue was purified by silica gel chromatography (hexane : ethyl acetate = 3 : 1) to give 194.4 mg of **<u>5</u>** (93.1%). ^{1}H NMR (400 MHz, $CDCl_3$) : δ 3.85 (s, 2H), 6.73 (d, 2H, J = 8.7 Hz),

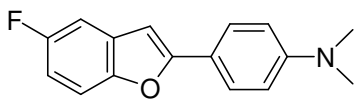
6.76 (s, 1H), 6.88-6.93 (m, 1H), 7.16 (dd, 1H, J_1 = 11.2 Hz, J_2 = 2.4 Hz), 7.36 (dd, 1H, J_1 = 12.8 Hz, J_2 = 3.2 Hz), 7.67 (d, 2H, J = 8.7 Hz). HRMS (EI): m/z calcd for $C_{14}H_{10}FNO$ (M^+) 227.0746, found 227.0753.

5-Fluoro-2-(4-methylaminophenyl)benzofuran (6).



A solution of NaOMe (28 wt % in MeOH, 0.48 mL) was added to a mixture of **5** (67 mg, 0.29 mmol) and paraformaldehyde (32 mg, 1.22 mmol) in methanol (5 mL) dropwise. The mixture was stirred under reflux for 1 h. After $NaBH_4$ (27 mg, 0.83 mmol) was added, the solution was heated under reflux for 2 h. 1 M NaOH (30 mL) was added to the cold mixture and extracted with $CHCl_3$ (30 mL). The organic phase was dried over Na_2SO_4 and filtered. The solvent was removed, and the residue was purified by silica gel chromatography (hexane : ethyl acetate = 5 : 1) to give 21.2 mg of **6** (30.3%). ^{1}H NMR (400 MHz, $CDCl_3$) : δ 2.93 (s, 3H), 3.98 (s, 1H), 6.65 (d, 2H, J = 8.7 Hz), 6.74 (s, 1H), 6.88-6.93 (m, 1H), 7.16 (dd, 1H, J_1 = 11.2 Hz, J_2 = 2.4 Hz), 7.36 (dd, 1H, J_1 = 12.8 Hz, J_2 = 3.2 Hz), 7.67 (d, 2H, J = 8.7 Hz). HRMS (EI): m/z calcd for $C_{15}H_{12}FNO$ (M^+) 241.0903, found 241.0910.

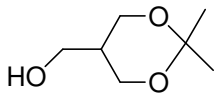
2-(4-Dimethylaminophenyl)-5-fluorobenzofuran (7).



A mixture of **3** (233 mg, 0.50 mmol) and 4-dimethylaminobenzoyl chloride (92.0 mg,

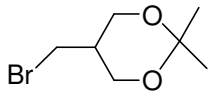
0.50 mmol) in a mixed solvent (toluene 20 mL and triethylamine 5 mL) was stirred under reflux for 6 h. The precipitate was removed by filtration. The filtrate was concentrated and the residue was recrystalized with ethyl acetate to give 70.3 mg of **7** (55.1%). ^{1}H NMR (400 MHz, $CDCl_3$) : δ 2.99 (s, 6H), 6.65 (d, 2H, J = 8.7 Hz), 6.74 (s, 1H), 6.88-6.93 (m, 1H), 7.16 (dd, 1H, J_1 = 11.2 Hz , J_2 = 2.4 Hz), 7.36 (dd, 1H, J_1 = 12.8 Hz, J_2 = 3.2 Hz), 7.67 (d, 2H, J = 8.7 Hz). HRMS (EI): m/z calcd for $C_{16}H_{14}FNO$ (M^+) 255.1059, found 255.1054.

(2,2-Dimethyl-[1,3]-dioxan-5-yl)methanol (9).



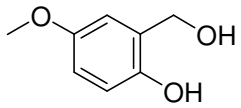
To a solution of 2-(hydroxymethyl)propane-1,3-diol (1.0 g, 9.1 mmol) and 4-toluenesulfonic acid monohydrate (54 mg, 0.28 mmol) in THF (30 mL) was added 2,2-dimethoxypropane (1.3 mL, 10.6 mmol). The solution was stirred for 2.5 h at room temperature and then neutralized by the addition of Et_3N (3 mL). The solvent was removed, and the residue was purified by silica gel chromatography (CH_3OH : $CHCl_3$ = 1 : 10) to give **9** (1.3 g, 99.8%) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 1.41 (s, 3H) , 1.45 (s, 3H), 1.75 (s, 1H) , 1.92-1.78 (m, 1H), 3.84-3.70 (m, 4H), 4.08-3.96 (m, 2H).

5-(Bromomethyl)-2,2-dimethyl-1,3-dioxane (10).



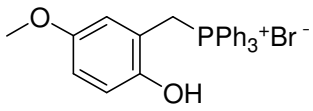
To a stirred solution of **9** (1.3 g, 8.8 mmol) in dry CH_2C1_2 (1.79 mL) and dry pyridine (0.64 mL) was added carbon tetrabromide (4.3 g, 13 mmol). To this solution was then added triphenylphosphine (0.67 g, 8.8 mmol) in dry CH_2CI_2 (2.5 mL) over 1.5 h under an argon atmosphere. After an additional hour, the mixture was poured into cold petroleum ether (290 mL), the suspension was filtered, and the filtrate was concentrated *in vacuo*. Purification by distillation (58-60˚C, 0.7 mm) afforded **10** (1.2 g, 71%) as a clear liquid: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.40 (s, 3H), 1.43 (s, 3H), 2.02-2.05 (m, 1H), 3.50 (d, 2H, J = 6.8 Hz), 3.75 (dd, 2H, J_1 = 12.0 Hz, J_2 = 5.6 Hz), 4.05 (dd, 2H, J_1 = 12.4Hz, J_2 = 4.0 Hz).

2-Hydroxy-5-methoxybenzyl alcohol (<u>12</u>).



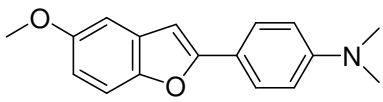
Sodium borohydride (250 mg, 6.61 mmol) was added to a stirring solution of 2-hydroxy-5-methoxybenzaldehyde (2.0 g, 13.1 mmol) in ethanol (20 mL) in an ice bath. The reaction mixture was stirred at room temperature for 1 h. After the solvent was removed, 1 N aqueous HCl solution (40 mL) was added to the residue and extracted with diethyl ether (40 mL). The organic phase was dried over Na_2SO_4 and filtered. The filtrate was concentrated to give 2.02 g of **<u>12</u>** (99.7%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.72 (s, 3H), 4.72 (s, 2H), 6.59 (s, 1H), 6.70-6.75 (m, 2H).

2-Hydroxy-4-methoxybenzyltriphenylphosphonium bromide (<u>13</u>).



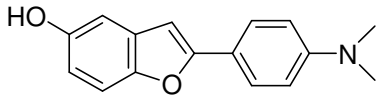
A solution of **12** (2.02 g, 13.1 mmol) and triphenylphosphine hydrobromide (4.50 g, 13.1 mmol) in acetonitrile (40 mL) was stirred under reflux for 1 h. The solid that formed was filtered and washed with acetonitrile to give 5.28 g of **13** (84.1%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.38 (s, 3H), 4.87 (d, 2H, J = 14.7 Hz), 6.33 (s, 1H), 6.65-6.71 (m, 2H), 7.67-7.89 (m, 15H), 9.34 (s, 1H).

2-(4-Dimethylaminophenyl)-5-methoxybenzofuran (14).



A mixture of **13** (5.28 g, 11.0 mmol) and 4-dimethylaminobenzoyl chloride (2.04 g, 11.1 mmol) in a mixed solvent (toluene 100 mL and triethylamine 25 mL) was stirred under reflux for 18 h. The precipitate was removed by filtration. The filtrate was concentrated and the residue was recrystalized with ethyl acetate to give 791 mg of **14** (26.9%). ^{1}H NMR (400 MHz, $CDCl_3$) : δ 3.03 (s, 6H), 3.85 (s, 3H), 6.70 (d, 2H, J = 8.0 Hz), 6.76 (s, 1H), 6.82 (dd, 1H, J_1 = 11.2 Hz , J_2 = 2.4 Hz), 7.01 (d, 1H, J = 2.4 Hz), 7.33 (d, 1H, J = 8.8 Hz), 7.71 (d, 2H, J = 8.0 Hz). MS: m/z 268 (M^++H).

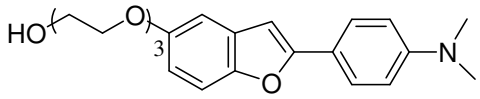
2-(4-Dimethylaminophenyl)-5-hydroxybenzofuran (15).



BBr_3 (15.4 mL, 1 M solution in CH_2Cl_2) was added to a solution of **14** (791 mg, 2.95 mmol) in CH_2Cl_2 (40 mL) dropwise in an ice bath. The mixture was allowed to warm

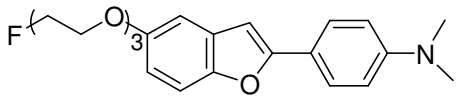
to room temperature and stirred for 1 h. Water (20 mL) was added while the reaction mixture was cooled in an ice bath. The mixture was extracted with ethyl acetate, and the organic phase was dried over Na_2SO_4 and filtered. The filtrate was concentrated, and the residue was purified by silica gel chromatography (hexane : ethyl acetate = 3 : 1) to give 541.5 mg of **15** (72.5%). ^{1}H NMR (400 MHz, $CDCl_3$) : δ 3.03 (s, 6H), 6.70 (d, 2H, J = 8.0 Hz), 6.76 (s, 1H), 6.82 (dd, 1H, J_1 = 11.2 Hz , J_2 = 2.4 Hz), 7.01 (d, 1H, J = 2.4 Hz), 7.33 (d, 1H, J = 8.8 Hz), 7.71 (d, 2H, J = 8.0 Hz). MS: m/z 254 (M^++H).

2-(2-(2-(2-(4-(Dimethylamino)phenyl)benzofuran-5-yloxy)ethoxy)ethoxy)ethanol (16).



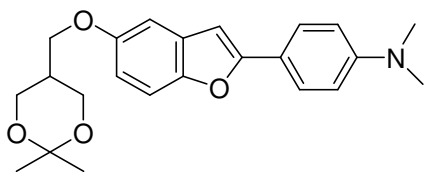
To a solution of **15** (167 mg, 0.66 mmol) and 2-[2-(2-chloroethoxy)-ethoxy]ethanol. (50 μL, 0.66 mmol) in DMF (5 mL) was added anhydrous K_2CO_3 (273 mg, 1.98 mmol). The reaction mixture was stirred for 18 h at 100˚C and then poured into water and extracted with chloroform. The organic layers were combined and dried over Na_2SO_4. Evaporation of the solvent afforded a residue, which was purified by silica gel chromatography (hexane : ethyl acetate = 1 : 1) to give 191.4 mg of **16** (75.3%). ^{1}H NMR (400 MHz, $CDCl_3$) : δ 3.03 (s, 6H), 3.74-3.80 (m, 6H), 3.86-3.89 (m, 2H), 4.11-4.18 (m, 2H), 4.49-4.51 (m, 1H), 4.61-4.63 (m, 1H), 6.70 (d, 2H, J = 8.0 Hz), 6.76 (s, 1H), 6.82 (dd, 1H, J_1 = 11.2 Hz , J_2 = 2.4 Hz), 7.01 (d, 1H, J = 2.4 Hz), 7.33 (d, 1H, J = 8.8 Hz), 7.71 (d, 2H, J = 8.0 Hz). MS: m/z 386 (M^++H).

4-(5-(2-(2-(2-Fluoroethoxy)ethoxy)ethoxy)benzofuran-2-yl)-*N,N*-dimethylbenzen amine (<u>17</u>).



To a solution of **16** (90 mg, 0.23 mmol) in 1,2-dimethoxyethane (DME) (5 mL) was added DAST (61 μL, 0.46 mmol) in a dry ice-acetone bath. The reaction mixture was stirred for 1 h at room temperature, poured into a saturated $NaHSO_3$ solution, and extracted with chloroform. The organic phase was separated, dried over Na_2SO_4, and filtered, and the residue was purified by preparative TLC (hexane : ethyl acetate = 1 : 1) to give 25.8 mg of **<u>17</u>** (28.9%). ^{1}H NMR (400 MHz, $CDCl_3$) : δ 3.03 (s, 6H), 3.74-3.80 (m, 6H), 3.86-3.89 (m, 2H), 4.11-4.18 (m, 2H), 4.49-4.51 (m, 1H), 4.61-4.63 (m, 1H), 6.70 (d, 2H, J = 8.0 Hz), 6.76 (s, 1H), 6.82 (dd, 1H, J_1 = 11.2 Hz , J_2 = 2.4 Hz), 7.01 (d, 1H, J = 2.4 Hz), 7.33 (d, 1H, J = 8.8 Hz), 7.71 (d, 2H, J = 8.0 Hz). HRMS (EI): m/z calcd for $C_{22}H_{26}FNO_4$ (M^+) 387.1846, found 387.1853.

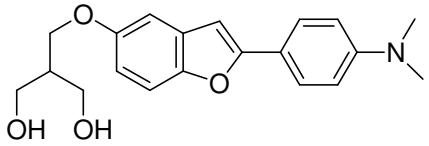
4-(5-(2,2-Dimethyl-1,3-dioxan-5-yloxy)benzofuran-2-yl)-*N,N*-dimethylbenzenami ne (<u>18</u>).



Under a nitrogen atmosphere, **<u>15</u>** (132 mg, 0.52 mmol) was dissolved in anhydrous DMF (5.0 mL). Potassium carbonate (196 mg, 1.4 mmol) was added to this solution followed by **10** (110 mg, 0.52 mmol). The mixture was heated to 100˚C and stirred

overnight. After cooling to room temperature, a standard workup with ethyl acetate was applied and the residue was purified by preparative TLC (hexane : ethyl acetate = 3 : 1) to afford **18** (158.5 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) : δ 1.44 (d, 6H, J = 8.8 Hz), 3.03 (s, 6H), 3.89-3.93 (m, 2H), 4.03-4.08 (m, 2H), 4.10-4.14 (m, 2H), 6.70 (d, 2H, J = 8.0 Hz), 6.76 (s, 1H), 6.82 (dd, 1H, J_1 = 11.2 Hz , J_2 = 2.4 Hz), 7.01 (d, 1H, J = 2.4 Hz), 7.33 (d, 1H, J = 8.8 Hz), 7.71 (d, 2H, J = 8.0 Hz). MS: m/z 382 (M^++H).

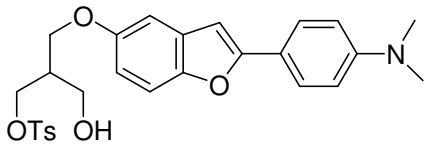
2-(2-(4-(Dimethylamino)phenyl)benzofuran-5-yloxy)propane-1,3-diol (19).



18 (158 mg, 0.41 mmol) was suspended in acetone (5.0 mL) and cooled to 0˚C with an ice bath. 1 N HCl (5.0 mL, 5.0 mmol) was slowly added over 20 min, during which time the suspension turned into a clear solution. The solution was stirred at 0˚C for an additional 1.5 h and then warmed to room temperature in 0.5 h. Saturated sodium bicarbonate was added to adjust the pH to 8-9. A standard workup with ethyl acetate was applied and the residue was purified by preparative TLC (hexane : ethyl acetate = 1 : 6) to afford **19** (95 mg, 67.5%). ^{1}H NMR (400 MHz, $CDCl_3$) : δ 3.03 (s, 6H), 3.89-3.93 (m, 2H), 4.03-4.08 (m, 2H), 4.10-4.14 (m, 2H), 6.70 (d, 2H, J = 8.0 Hz), 6.76 (s, 1H), 6.82 (dd, 1H, J_1 = 11.2 Hz , J_2 = 2.4 Hz), 7.01 (d, 1H, J = 2.4 Hz), 7.33 (d, 1H, J = 8.8 Hz), 7.71 (d, 2H, J = 8.0 Hz). MS: m/z 342 (M^++H).

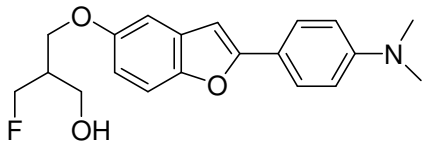
2-(2-(4-(Dimethylamino)phenyl)benzofuran-5-yloxy)-3-hydroxypropyl

4-methylbenzenesulfonate (<u>20</u>).



<u>19</u> (95 mg, 0.28 mmol) was dissolved in anhydrous pyridine (15 mL) and cooled to 0˚C with an ice bath. Tosyl chloride (76 mg, 0.40 mmol) was added, and the solution was stirred at 0˚C for 2 h. A standard workup with ethyl acetate was applied and the residue was purified by preparative TLC (hexane : ethyl acetate = 2 : 1) to afford the monotosylate compound **<u>20</u>** (62 mg, 45%). ^{1}H NMR (400 MHz, $CDCl_3$) :δ 2.40 (s, 3H), 3.03 (s, 6H), 3.89-3.93 (m, 2H), 4.03-4.08 (m, 2H), 4.10-4.14 (m, 2H), 6.70 (d, 2H, J = 8.0 Hz), 6.76 (s, 1H), 6.82 (dd, 1H, J_1 = 11.2 Hz , J_2 = 2.4 Hz), 7.01 (d, 1H, J = 2.4 Hz), 7.29 (d, 2H, J = 8.8 Hz), 7.33 (d, 1H, J = 8.8 Hz), 7.71 (d, 2H, J = 8.0 Hz), 7.80 (d, 2H, J = 8.8 Hz). MS: m/z 496 (M^++H).

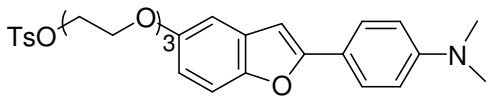
2-(2-(4-(Dimethylamino)phenyl)benzofuran-5-yloxy)-3-fluoropropane-1-ol (<u>21</u>).



<u>20</u> (33.3 mg, 0.067 mmol) was dissolved in anhydrous THF (5.0 mL). Under a nitrogen atmosphere, anhydrous 1 M TBAF in THF (0.4 mL, 0.4 mmol) was slowly added. The solution was then heated to reflux for 3 h. After cooling to room temperature, a standard workup with ethyl acetate was applied and the residue was purified by preparative TLC (hexane : ethyl acetate = 1 : 8) to afford **<u>21</u>** (13 mg, 55%). ^{1}H NMR (400 MHz, $CDCl_3$) : δ 3.03 (s, 6H), 3.89-3.93 (m, 2H), 4.03-4.08 (m, 2H),

4.10-4.14 (m, 2H), 6.70 (d, 2H, J = 8.0 Hz), 6.76 (s, 1H), 6.82 (dd, 1H, J_1 = 11.2 Hz, J_2 = 2.4 Hz), 7.01 (d, 1H, J = 2.4 Hz), 7.33 (d, 1H, J = 8.8 Hz), 7.71 (d, 2H, J = 8.0 Hz). HRMS (EI): m/z calcd for $C_{20}H_{22}FNO_3$ (M^+) 343.1584, found 343.1588.

2-(2-(2-(2-(4-(Dimethylamino)phenyl)benzofuran-5-yloxy)ethoxy)ethoxy)ethyl 4-methylbenzenesulfonate (<u>22</u>).



To a solution of **<u>16</u>** (100 mg, 0.26 mmol) in pyridine (3 mL) was added tosyl chloride (343.8 mg, 0.621 mmol). The reaction mixture was stirred for 3 h at room temperature. After water was added, the mixture was extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, and evaporation of the solvent afforded a residue, which was purified by preparative TLC (hexane : ethyl acetate = 1 : 1) to give 35.6 mg of **<u>22</u>** (25.4%). ^{1}H NMR (400 MHz, $CDCl_3$) : δ 2.40 (s, 3H), 3.03 (s, 6H), 3.74-3.80 (m, 6H), 3.86-3.89 (m, 2H), 4.11-4.18 (m, 2H), 4.49-4.51 (m, 1H), 4.61-4.63 (m, 1H), 6.70 (d, 2H, J = 8.0 Hz), 6.76 (s, 1H), 6.82 (dd, 1H, J_1 = 11.2 Hz, J_2 = 2.4 Hz), 7.01 (d, 1H, J = 2.4 Hz), 7.29 (d, 2H, J = 8.8 Hz), 7.33 (d, 1H, J = 8.8 Hz), 7.71 (d, 2H, J = 8.0 Hz), 7.80 (d, 2H, J = 8.8 Hz). MS: m/z 540 (M^++H).

Binding assays using the aggregated Aβ peptides in solution. Aβ(1-42) was purchased from Peptide Institute (Osaka, Japan). Aggregation was carried out by gently dissolving the peptide (0.25 mg/mL) in a buffer solution (pH 7.4) containing 10 mM sodium phosphate and 1 mM EDTA. The solution was incubated at 37˚C for

42 h with gentle and constant shaking. A mixture containing 50 μL of test compound (0.2 pM-400 μM in 10% EtOH), 50 μL of 0.02 nM [^{125}I]IMPY, 50 μL of Aβ(1-42) aggregates, and 850 μL of 10% EtOH was incubated at room temperature for 3 h. The mixture was then filtered through Whatman GF/B filters using a Brandel M-24 cell harvester, and the radioactivity of the filters containing the bound ^{125}I ligand was measured in a γ counter. Values for the half maximal inhibitory concentration (IC_{50}) were determined from displacement curves of three independent experiments using GraphPad Prism 5.0, and those for the inhibition constant (K_i) were calculated using the Cheng-Prusoff equation: $K_i = IC_{50}/(1 + [L]/K_d)$, where [L] is the concentration of [^{125}I]IMPY used in the assay and K_d is the dissociation constant of IMPY (4.2 nM).

Radiolabeling with ^{18}F. [^{18}F]Fluoride was produced by cyclotron (CYPRIS HM-18, Sumitomo Heavy Industries, Tokyo) via an ^{18}O (p,n)^{18}F reaction and passed through a Sep-Pak Light QMA cartridge (Waters) as an aqueous solution in ^{18}O-enriched water. The cartridge was dried by N_2, and the ^{18}F activity was eluted with 1.0 mL of a Kryptofix 222/K_2CO_3 solution (9.5 mg of Kryptofix 222 and 1.7 mg of K_2CO_3 in acetonitrile/water (96/ 4)). The solvent was removed at 120˚C under a stream of argon gas. The residue was azeotropically dried with 1 mL of anhydrous acetonitrile twice at 120˚C under a stream of nitrogen gas. A solution of tosyl precursor **22** (1.0 mg) in acetonitrile (200 μL) was added to the reaction vessel containing the ^{18}F activity. The mixture was heated at 120˚C for 10 min. Water (5 mL) was added, and the mixture was passed through a preconditioned Oasis HLB cartridge (3 cm^3) (Waters). The

cartridge was washed with 10 mL of water, and the labeled compound was eluted with 2 mL of acetonitrile. The eluted compound was purified by preparative HPLC [YMC-Pack Pro C18 column (20 mm× 150 mm), acetonitrile/water (70/30), flow rate 6.0 mL/min]. The retention time of the desired ^{18}F-labeled product is 23.7 min. The radiochemical purity and specific activity were determined by analytical HPLC [YMC-Pack Pro C18 column (4.6 mm × 150 mm), acetonitrile/ water (60/40), flow rate 1.0 mL/min], and [^{18}F]**17** was obtained in a radiochemical purity of >99% with specific activity of 242 GBq/μmol. Specific activity was estimated by comparing the UV peak intensity of the purified ^{18}F-labeled compound with a reference nonradioactive compound of known concentration.

Measurement of LogP values. The experimental determination of partition coefficients of [^{18}F]**17** was performed in 1-octanol and 0.02 M phosphate buffer at a pH of 7.4. The two phases were pre-saturated with each other. 1-Octanol (3.0 mL) and phosphate buffer (3.0 mL) were pipetted into a 12 mL-test tube containing 1.11 MBq of [^{18}F]**17**. The test tube was vortexed for 10 min, and centrifuged (5min, 1000 g). Aliquots (500 μL) from the 1-octanol and buffer phases were transferred into two test tubes for counting. One milliliter of the remaining 1-octanol phase was transferred into a new test tube. New 1-octanol (2.0 mL) and phosphate buffer (3.0 mL) were pipetted into the same test tube. The vortexing, centrifuging and counting were repeated. The amount of radioactivity in each tube was measured with a γ counter and corrected for decay. The partition coefficient was calculated using Eq. (1):

(counts / μL in 1-octanol)

$$\frac{}{\text{(counts / μL in buffer)}} = r \qquad (1)$$

Biodistribution in normal mice. Experiments with animals were conducted in accordance with our institutional guidelines and approved by the Kyoto University Animal Care Committee. While under anesthesia with isoflurane, ddY mice (22–25 g, male) were injected directly into the tail vein with 100 μL of a 0.1% BSA solution containing [^{18}F]**17** (185-370 kBq). The mice (n = 5 for each time point) were sacrificed at 2, 10, 30, and 60 min postinjection. The organs of interest were removed and weighed, and radioactivity was measured with an automatic gamma counter (COBRAII, Packard). The percentage dose per organ was calculated by a comparison of the tissue counts to suitably diluted aliquots of the injected material. The %dose/g of samples was calculated by comparing the sample counts with the count of the diluted initial dose.

In vitro autoradiography using brain sections from Tg2576 mice. Brain tissue from Tg2576 mice (male, 36 months old) was frozen in a dry ice/hexane bath and cut into 10-μm-thick sections. The sections were incubated with [^{18}F]**17** (200000–250000 cpm/200 μL) for 1 h at room temperature, then dipped in saturated Li_2CO_3 in 40% EtOH (two 2-min washes), washed with 40% EtOH (one 2-min wash), and rinsed with water for 30 s. After drying, the ^{18}F-labeled sections were exposed to a BAS imaging plate (Fuji Film, Tokyo, Japan) overnight. Autoradiographic images were obtained using a BAS5000 scanner system (Fuji Film). After autoradiographic

examination, the same sections were stained with thioflavin-S to confirm the presence of β–amyloid plaques. For the staining, sections were immersed in a 0.125% thioflavin-S solution containing 50% EtOH for 3 min and washed in 50% EtOH. After drying, the sections were examined using a microscope (Nikon, Eclipse 80i) equipped with a B-2A filter set (excitation, 450-490 nm; diachronic mirror, 505 nm; long-pass filter, 520 nm).

***In vivo* plaque labeling with [^{18}F]17.** The Tg2576 transgenic mice (36 months, male) and wild-type mice (36 months, male) were used as an Alzheimer's model and an age-matched control, respectively. Under anesthesia with 1% isoflurane, 9.29–11.1 MBq of [^{18}F]**17** in 200 μL of a 0.1% BSA solution was injected through a tail vein. The animals were allowed to recover for 30 min and then killed by decapitation. The brains were immediately removed and frozen in a dry ice/hexane bath. Sections of 20 μm were cut and exposed to a BAS imaging plate (Fuji Film, Tokyo, Japan) overnight. Autoradiograms were obtained.