Supporting Information

Structure-activity Relationships and in vivo Evaluation of Quinoxaline Derivatives for PET Imaging of β-Amyloid Plaques

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General remarks

All reagents were commercial products and used without further purification unless indicated otherwise. ^{1}H NMR spectra were recorded on a JEOL JNM-AL400 or JEOL JNM-ECS400 with TMS as an internal standard. Coupling constants are reported in Hertz. Multiplicity was defined as singlet (s), doublet (d), triplet (t), or multiplet (m). Mass spectra were obtained on a SHIMADZU LCMS-2010 EV. High-resolution mass spectrometry (HRMS) was conducted with a JEOL JMS-GC mate mass spectrometer. HPLC was performed with a Shimadzu system (a LC-20AT or LC-20AD pump with a SPD-20A UV detector, $\lambda = 254$ nm) using a Cosmosil C_{18} column (Nacalai Tesque, 5C_{18}-AR-II, 4.6×150 mm) and acetonitrile/water as the mobile phase at a flow rate of 1.0 mL/min. All key compounds were proven by this method to show ≥97% purity.

Synthesis

2,2-Dibromo-1-(4-(dimethylamino)phenyl)ethanone (1).

The solution of 1-(4-(dimethylamino)phenyl)ethanone (3.5 g, 21.46 mmol) in conc. H_2SO_4 (20 mL) was stirred for 0.5 h at 0°C. Bromine (1.12 mL, 21.83 mmol) was added

dropwise at 0ºC. The reaction mixture was stirred for 12 h at room temperature and poured into ice-cold water. The solid that formed was filtered and washed with ice-cold water to give 4.89 g of **1** (71.5 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.8 Hz, 2H), 6.69-6.66 (m, 3H), 3.10 (s, 6H).

2-Bromo-1-(4-(dimethylamino)phenyl)ethanone (2).

To a suspension of **1** (6.84 g, 21.5 mmol) in THF (40 mL) was added mixture diethyl phosphite (3 mL) and triethylamine (3.2 mL) in THF (25 mL) dropwise at 0ºC. The reaction mixture was stirred at room temperature for 11 h. Evaporation of the solvent afforded a residue, which was poured into ice-cold water and stirred for 0.5 h. The solid that formed was filtered and wash with ice-cold water to give 3.38 g of **2** (65.5%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.8 Hz, 2H), 6.66 (d, *J* = 8.8 Hz, 2H), 4.36 (s, 2H), 3.08 (s, 6H).

4-((*tert*-Butyldimethylsilyl)oxy)-2-nitroaniline (3).

A solution of 4-amino-3-nitrophenol (2.82 g, 18.3 mmol), TBSCl (3.6 g, 24 mmol) and

imidazole (2.00 g, 29.0 mmol) in THF (50 mL) was stirred for 1 h at room temperature. After extraction with Et_2O (100 mL x 3), the organic layer was dried over $MgSO_4$. Evaporation of the solvent afforded a residue, which was purified by silica gel chromatography (AcOEt / hexane = 1 / 3) to give 4.81 g of **3** (98.1%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 2.8 Hz, 1H), 6.97 (dd, *J* = 8.8, 2.8 Hz, 1H), 6.70 (d, *J* = 8.8 Hz, 1H), 5.79 (s, 2H), 0.98 (s, 9H), 0.19 (s, 6H).

4-((*tert*-Butyldimethylsilyl)oxy)benzene-1,2-diamine (4).

To a solution of **3** (9.57 g, 35.7 mmol) in mixture of MeOH (80 mL) and CH_2Cl_2 (40 mL) was added Pd/C (3.00 g). The reaction mixture was stirred for 7 h at room temperature under H_2 atmosphere. The mixture was filtered through celite, and then the filtrate was evaporated. The residue was purified by silica gel chromatography (AcOEt / hexane = 2 / 1) to give 7.28 g of **4** (85.6%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.55 (d, *J* = 8.0 Hz, 1H), 6.24 (d, *J* = 2.4 Hz, 1H), 6.18 (dd, *J* = 8.0, 2.4 Hz, 1H), 3.19 (s, 4H), 0.96 (s, 9H), 0.15 (s, 6H).

4-(7-((*tert*-Butyldimethylsilyl)oxy)quinoxalin-2-yl)-*N*,*N*-dimethylaniline (5).

A solution of **2** (482.0 mg, 2 mmol) and **4** (476.3 mg, 2 mmol) in DMSO (10 mL) was stirred for 4 h at room temperature. After extraction with AcOEt (100 mL x 2), the organic layer was dried over $MgSO_4$. Evaporation of the solvent afforded a residue, which was purified by silica gel chromatography (AcOEt / hexane = 1 / 3) to give 161.8 mg of **5** (21.3%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.12 (s, 1H), 8.10 (d, J = 8.8 Hz, 2H), 7.91 (d, J = 9.2 Hz, 1H), 7.42 (s, 1H), 7.23 (dd, J = 8.8, 2.4 Hz, 1H), 6.84 (d, J = 8.8 Hz, 2H), 3.07 (s, 6H), 1.04 (s, 9H), 0.30 (s, 6H). MS (APCI) m/z 380 [MH^+].

3-(4-(Dimethylamino)phenyl)quinoxalin-6-ol (6).

To a solution of **5** (161.8 mg, 0.427 mmol) in THF (10 mL) was added TBAF (1 M in THF, 512 μL) at 0°C. The solution was allowed to warm to room temperature and then stirred for 0.5 h. After extraction with AcOEt (60 mL x 2), the organic layer was dried over $MgSO_4$. Evaporation of the solvent afforded a residue, which was purified by silica gel chromatography (AcOEt / hexane = 1 / 1) to give 56.0 mg of **6** (49.5%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.22 (s, 1H), 8.17 (d, J = 8.8 Hz, 2H), 7.85 (d, J = 9.2 Hz,

1H), 7.26 (d, *J* = 8.4 Hz, 1H), 7.21 (s, 1H), 6.86 (d, *J* = 8.8 Hz, 2H), 3.02 (s, 6H). MS (APCI) m/z 266 [MH^+].

7-((*tert*-Butyldimethylsilyl)oxy)-2-(4-nitrophenyl)quinoxaline (7).

A solution of **4** (952.6 mg, 4 mmol) and 2-bromo-4'-nitroacetophenone (976.2 mg, 4 mmol) in DMSO (20 mL) was stirred for 2 h at room temperature. After extraction with AcOEt (200 mL x 2), the organic layer was dried over $MgSO_4$. Evaporation of the solvent afforded a residue, which was purified by silica gel chromatography (AcOEt / hexane = 1 / 3) to give 567.1 mg of **7** (37.2%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.22 (s, 1H), 8.43-8.36 (m, 4H), 8.03 (d, *J* = 8.8 Hz, 1H), 7.49 (d, *J* = 2.4 Hz, 1H), 7.40 (dd, *J* = 9.2, 2.4 Hz, 1H), 1.05 (s, 9H), 0.33 (s, 6H). MS (APCI) m/z 382 [MH^+].

3-(4-Nitrophenyl)quinoxalin-6-ol (8).

To a solution of **7** (398.8 mg, 1.05 mmol) in THF (15 mL) was added TBAF (1 M in THF, 1.26 mL) at 0°C. The mixture was stirred for 2 h at room temperature. After extraction with AcOEt (60 mL x 2), the organic layer was dried over $MgSO_4$.

Evaporation of the solvent afforded a residue, which was purified by silica gel chromatography (AcOEt / hexane = 1 / 1) to give 150.1 mg of **8** (53.7%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.7 (s, 1H), 9.44 (s, 1H), 8.57 (d, J = 8.8 Hz, 2H), 8.41 (d, J = 8.8 Hz, 2H), 8.00 (d, J = 9.2 Hz, 1H), 7.46 (dd, J = 9.2, 2.4 Hz, 1H), 7.36 (d, J = 2.4 Hz, 1H).

4-(7-(2-Fluoroethoxy)quinoxalin-2-yl)-*N*,*N*-dimethylaniline (9).

To a solution of **6** (56.0 mg, 0.211 mmol) in DMF (10 mL) was added K_2CO_3 (58.4 mg, 0.422 mmol). The reaction mixture was stirred for 0.5 h at 105ºC and then 2-fluoroethyl 4-methylbenzenesulfonate (50 μL) was added. The mixture was stirred for 1.5 h at 105ºC and then 2-fluoroethyl 4-methylbenzenesulfonate (30 μL) was added. The mixture was stirred for 3 h at 105ºC and then 2-fluoroethyl 4-methylbenzenesulfonate (40 μL) was added. The mixture was stirred for 0.5 h at 105ºC. The suspension was allowed to cool to room temperature and then extracted with AcOEt (60 mL x 2). The organic layers were combined and dried over $MgSO_4$. Evaporation of the solvent afforded a residue, which was purified by silica gel chromatography (AcOEt / hexane =

1 / 2) to give 33.4 mg of **9** (50.8%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.14 (s, 1H), 8.11 (d, *J* = 9.2 Hz, 2H), 7.95 (d, *J* = 9.2 Hz, 1H), 7.37-7.34 (m, 2H), 6.84 (d, *J* = 9.2 Hz, 2H), 4.93-4.79 (m, 2H), 4.44-4.35 (m, 2H), 3.07 (s, 6H). HRMS (EI) m/z calcd for $C_{18}H_{18}FN_3O$ (M^+) 311.1434, found 311.1439.

4-(7-(2-Fluoroethoxy)quinoxalin-2-yl)aniline (10).

To a solution of **8** (151.4 mg, 0.576 mmol) in DMF (10 mL) was added K_2CO_3 (159.2 mg, 1.152 mmol). The reaction mixture was stirred for 0.5 h at 105ºC and then 2-fluoroethyl 4-methylbenzenesulfonate (300 μL) was added. The solution was stirred for 4.5 h at 105ºC and then allowed to cool to room temperature. After extraction with AcOEt (60 mL x 2), the organic layer was dried over $MgSO_4$ and filtered. Evaporation of the solvent afforded a residue, which was dissolved in mixture of MeOH (40 mL) and CH_2Cl_2 (30 mL). To the solution Pd/C (100 mg) was added and stirred vigorously for 0.7 h at room temperature under H_2 atmosphere. The reaction mixture was filtered through celite, and then the filtration was evaporated. The residue was purified by silica gel chromatography (AcOEt / hexane = 1 / 1) to give 90.4 mg of **10** (55.4%). ^{1}H NMR

(400 MHz, $CDCl_3$) δ 9.12 (s, 1H), 8.04 (d, *J* = 8.4 Hz, 2H), 7.96 (d, *J* = 9.2 Hz, 1H), 7.40-7.37 (m, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 4.93-4.79 (m, 2H), 4.44-4.35 (m, 2H). HRMS (EI) m/z calcd for $C_{16}H_{14}FN_3O$ (M^+) 283.1121, found 283.1117.

4-(7-(2-Fluoroethoxy)quinoxalin-2-yl)-*N*-methylaniline (11).

To a suspension of **10** (90.4 mg, 0.319 mmol) and paraformaldehyde (51.7 mg, 1.72 mmol) in MeOH (35 mL) was added sodium methoxide (5 M in MeOH, 256 μL, 1.28 mmol) slowly at 0ºC. The mixture was heated to reflux for 1.5 h and then allowed to cool to room temperature. $NaBH_4$ (60.5 mg, 1.60 mmol) was added gently. The reaction mixture was brought to reflux again for 3 h and then quenched with sat. $NaHCO_3$ aq. MeOH was evaporated under reduced pressure, and the residue was extracted with AcOEt (60 mL x 2). The organic layers were combined and dried over $MgSO_4$. Evaporation of the solvent afforded a residue, which was purified by silica gel chromatography (AcOEt / hexane = 1 / 1) to give 19.4 mg of **11** (20.5%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (s, 1H), 8.07 (d, *J* = 8.8 Hz, 2H), 7.95 (d, *J* = 9.2 Hz, 1H), 7.38-7.35 (m, 2H), 6.74 (d, *J* = 8.8 Hz, 2H), 4.93-4.79 (m, 2H), 4.44-4.35 (m, 2H),

2.94 (s, 3H). HRMS (EI) m/z calcd for $C_{17}H_{16}FN_3O$ (M^+) 297.1277, found 297.1272.

2-((3-(4-(Dimethylamino)phenyl)quinoxalin-6-yl)oxy)ethanol (12).

To a solution of **6** (95.6 mg, 0.361 mmol) in DMF (10 mL) was added K_2CO_3 (99.8 mg, 0.722 mmol). The reaction mixture was stirred for 0.5 h at 105ºC and then 2-bromoethanol (51.2 μL, 0.722 mmol) was added. The solution was stirred for at 105ºC overnight. The solution was allowed to cool to room temperature and then extracted with AcOEt (60 mL x 2). The organic layers were combined and dried over $MgSO_4$. Evaporation of the solvent afforded a residue, which was purified by silica gel chromatography (AcOEt / hexane = 4 / 1) to give 59.3 mg of **12** (53.1%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (s, 1H), 8.11 (d, *J* = 9.2 Hz, 2H), 7.93 (d, *J* = 9.2 Hz, 1H), 7.39 (d, *J* = 2.8 Hz, 1H), 7.32 (dd, *J* = 9.2, 2.8 Hz, 1H), 6.84 (d, *J* = 9.2 Hz, 2H), 4.27 (t, *J* = 4.4 Hz, 2H), 4.08 (t, *J* = 4.0 Hz, 2H), 3.07 (s, 6H). MS (APCI) m/z 310 [MH^+].

7-(2-((*tert*-Butyldimethylsilyl)oxy)ethoxy)-2-(4-nitrophenyl)quinoxaline (13).

To a solution of **8** (150.1 mg, 0.562 mmol) in DMF (15 mL) was added K_2CO_3 (155.3

mg, 1.12 mmol). The suspension was stirred for 1 h at 80ºC and then (2-bromoethoxy)-*tert*-butyldimethylsilane (250 μL) was added. The reaction mixture was stirred at 80ºC overnight. The mixture was allowed to cool to room temperature and then extracted with AcOEt (60 mL x 2). The organic layers were combined and dried over $MgSO_4$. Evaporation of the solvent afforded a residue, which was purified by silica gel chromatography (AcOEt / hexane = 1 / 3) to give 203.8 mg of **13** (85.3%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.22 (s, 1H), 8.43-8.36 (m, 4H), 8.04 (d, J = 9.2 Hz, 1H), 7.50-7.46 (m, 2H), 4.26 (t, J = 4.8 Hz, 2H), 4.09 (t, J = 4.8 Hz, 2H), 0.93 (s, 9H), 0.14 (s, 6H). MS (APCI) m/z 426 [MH^+].

4-(7-(2-((*tert*-Butyldimethylsilyl)oxy)ethoxy)quinoxalin-2-yl)aniline (14).

To a solution of **13** (107.5 mg, 0.253 mmol) in mixture of MeOH (10 mL) and CH_2Cl_2 (5 mL) was added Pd/C (100 mg). The reaction mixture was stirred vigorously for 0.5 h at room temperature under H_2 atmosphere. The reaction mixture was filtered through celite, and then the filtrate was evaporated. The residue was purified by silica gel chromatography ($CHCl_3$ / MeOH = 40 / 1) to give 90.5 mg of **14** (90.6%). ^{1}H NMR

(400 MHz, $CDCl_3$) δ 9.09 (s, 1H), 8.03 (d, *J* = 8.8 Hz, 2H), 7.93 (d, *J* = 9.2 Hz, 1H), 7.37 (d, *J* = 2.8 Hz, 1H), 7.33 (dd, *J* = 9.2, 2.8 Hz, 1H), 6.82 (d, *J* = 8.8 Hz, 2H), 4.22 (t, *J* = 5.2 Hz, 2H), 4.07 (t, *J* = 5.2 Hz, 2H), 3.95 (s, 2H), 0.93 (s, 9H), 0.13 (s, 6H). MS (APCI) m/z 396 [MH^+].

4-(7-(2-((*tert*-Butyldimethylsilyl)oxy)ethoxy)quinoxalin-2-yl)-*N*-methylaniline (15).

To a suspension of **14** (215.1 mg, 0.544 mmol) and paraformaldehyde (88.3 mg, 2.94 mmol) in MeOH (40 mL) was slowly added sodium methoxide (5 M in MeOH, 436 μL, 2.18 mmol) at 0°C. The reaction mixture was heated to reflux for 4.5 h and then allowed to cool to room temperature. $NaBH_4$ (102.9 mg, 2.72 mmol) was added gently to the stirring solution. The reaction mixture was brought to reflux again for 1 h and then quenched with sat. $NaHCO_3$ aq. MeOH was evaporated under reduced pressure, and the residue was extracted with AcOEt (60 mL x 2). The organic layers were combined and dried over $MgSO_4$. Evaporation of the solvent afforded a residue, which was purified by silica gel chromatography (AcOEt / hexane = 1 / 1) to give 131.6 mg of **15** (59.1%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.10 (s, 1H), 8.07 (d, *J* = 8.8 Hz,

2H), 7.92 (d, *J* = 9.2 Hz, 1H), 7.37 (d, *J* = 2.8 Hz, 1H), 7.32 (dd, *J* = 9.2, 2.8 Hz, 1H), 6.74 (d, *J* = 8.8 Hz, 2H), 4.22 (t, *J* = 4.8 Hz, 2H), 4.07 (t, *J* = 4.8 Hz, 2H), 2.93 (s, 3H), 0.93 (s, 9H), 0.13 (s, 6H). MS (APCI) m/z 410 [MH^+].

2-((3-(4-(Dimethylamino)phenyl)quinoxalin-6-yl)oxy)ethyl 4-methylbenzenesulfonate (16).

To a solution of **12** (58.4 mg, 0.189 mmol) in pyridine (10 mL) was added *p*-toluenesulfonyl chloride (108.1 mg, 0.567 mmol) at 0 ºC. The reaction mixture was stirred at room temperature overnight. To the solution was added *p*-toluenesulfonyl chloride (108.1 mg, 0.567 mmol). The reaction mixture was stirred for 12 h at room temperature. Solvent was evaporated under reduced pressure, and the residue was extracted with AcOEt (60 mL x 2). The organic layers were combined and dried over $MgSO_4$. Evaporation of the solvent afforded a residue, which was purified by silica gel chromatography (AcOEt / hexane = 2 / 1) to give 22.2 mg of **16** (25.4%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (s, 1H), 8.10 (d, *J* = 8.8 Hz, 2H), 7.89 (d, *J* = 9.2 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 2.4 Hz, 1H), 7.16 (dd, *J* = 9.2, 2.8 Hz, 1H), 6.84 (d, *J* = 8.8 Hz, 2H), 4.48 (t, *J* = 4.8 Hz, 2H), 4.31 (t, *J* = 4.8 Hz,

2H), 3.07 (s, 6H), 2.43 (s, 3H). MS (APCI) m/z 464 [MH^+].

7-(2-((*tert*-Butyldimethylsilyl)oxy)ethoxy)-2-(*p*-di(*tert*-butoxycarbonyl)aminophenyl)quinoxaline (17).

A mixture of **14** (90.5 mg, 0.229 mmol), di-*tert*-butyl dicarbonate (499.8 mg, 2.29 mmol), DMAP (catalytic), and triethylamine (38.2 μL) was stirred under reflux for 1.5 h. The solution was allowed to cool to room temperature and then extracted with AcOEt (60 mL x 2). The organic layers were combined and dried over $MgSO_4$. Evaporation of the solvent afforded a residue, which was purified by silica gel chromatography (AcOEt / hexane = 1 / 3) to give 64.5 mg of **17** (47.3%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.18 (s, 1H), 8.19 (d, *J* = 8.8 Hz, 2H), 7.99 (d, *J* = 9.6 Hz, 1H), 7.44-7.41 (m, 2H), 7.33 (d, *J* = 8.8 Hz, 2H), 4.24 (t, *J* = 4.8 Hz, 2H), 4.08 (t, *J* = 4.8 Hz, 2H), 1.44 (s, 18H), 0.93 (s, 9H), 0.13 (s, 6H). MS (APCI) m/z 596 [MH^+].

***tert*-Butyl (4-(7-(2-((*tert*-butyldimethylsilyl)oxy)ethoxy)quinoxalin-2-yl)phenyl)(methyl)carba**

mate (18).

A solution of **15** (131.6 mg, 0.322 mmol) and di-*tert*-butyl dicarbonate (140.6 mg, 0.644 mmol) in THF (10 mL) was heated to reflux for 2 h. To the stirring solution was added di-*tert*-butyl dicarbonate (562.2 mg, 2.58 mmol), DMAP (catalytic) and triethylamine (54 μL). The reaction mixture was brought to reflux again for 5 h. The solution was allowed to cool to room temperature and then extracted with AcOEt (60 mL x 2). The organic layers were combined and dried over $MgSO_4$. Evaporation of the solvent afforded a residue, which was purified by silica gel chromatography (AcOEt / hexane = 1 / 2) to give 133.1 mg of **18** (81.2%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.15 (s, 1H), 8.14 (d, *J* = 8.8 Hz, 2H), 7.98 (d, *J* = 8.8 Hz, 1H), 7.46-7.39 (m, 4H), 4.24 (t, *J* = 4.8 Hz, 2H), 4.08 (t, *J* = 4.8 Hz, 2H), 3.34 (s, 3H), 1.49 (s, 9H), 0.93 (s, 9H), 0.13 (s, 6H). MS (APCI) m/z 510 [MH^+].

7-(2-Hydroxyethoxy)-2-(*p*-di(*tert*-butoxycarbonyl)aminophenyl)quinoxaline (19).

To a solution of **17** (64.5 mg, 0.108 mmol) in THF (5 mL) was added TBAF (1M in THF, 130 μL) at 0°C. The solution was allowed to warm to room temperature and

stirred overnight. After extraction with AcOEt (60 mL x 2), the organic layer was dried over $MgSO_4$. Evaporation of the solvent afforded a residue, which was purified by silica gel chromatography ($CHCl_3$ / MeOH = 20 / 1) to give 54.0 mg of **19** (quantitive yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.19 (s, 1H), 8.20 (d, *J* = 8.8 Hz, 2H), 8.02 (d, *J* = 9.6 Hz, 1H), 7.46-7.43 (m, 2H), 7.34 (d, *J* = 8.8 Hz, 2H), 4.30 (t, *J* = 4.8 Hz, 2H), 4.09 (t, *J* = 4.8 Hz, 2H), 1.44 (s, 18H). MS (APCI) m/z 482 [MH^+].

***tert*-Butyl (4-(7-(2-hydroxyethoxy)quinoxalin-2-yl)phenyl)(methyl)carbamate (20).**

To a solution of **18** (133.1 mg, 0.261 mmol) in THF (7 mL) was added TBAF (1 M in THF, 314 μL) at 0ºC. The solution was stirred for 2 h at room temperature. After extraction with AcOEt (60 mL x 2), the organic layer was dried over $MgSO_4$. Evaporation of the solvent afforded a residue, which was purified by silica gel chromatography ($CHCl_3$ / MeOH = 20 / 1) to give 104.1 mg of **20** (quantitative yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.17 (s, 1H), 8.14 (d, *J* = 8.8 Hz, 2H), 8.00 (d, *J* = 9.6 Hz, 1H), 7.46-7.40 (m, 4H), 4.78 (t, *J* = 4.8 Hz, 2H), 4.09 (t, *J* = 4.0 Hz, 2H), 3.34 (s, 3H), 1.49 (s, 9H). MS (APCI) m/z 396 [MH^+].

2-((3-(4-((Di-*tert*-butoxycarbonyl)amino)phenyl)quinoxalin-6-yl)oxy)ethyl 4-methylbenzenesulfonate (21).

To a solution of **19** (54.0 mg, 0.112 mmol) in pyridine (7 mL) was added *p*-toluenesulfonyl chloride (107.0 mg, 0.561 mmol) at 0ºC. The solution was allowed to warm to room temperature and then DMAP (catalytic) was added and stirred overnight. Solvent was evaporated under reduced pressure, and the residue was extracted with AcOEt (60 mL x 2). The organic layers were combined and dried over $MgSO_4$. Evaporation of the solvent afforded a residue, which was purified by silica gel chromatography (AcOEt / hexane = 1 / 1) to give 36.0 mg of **21** (50.6%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.19 (s, 1H), 8.19 (d, *J* = 8.8 Hz, 2H), 7.98 (d, *J* = 9.2 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 2H), 7.35-7.29 (m, 6H), 4.49 (t, *J* = 4.8 Hz, 2H), 4.34 (t, *J* = 4.8 Hz, 2H), 2.44 (s, 3H), 1.44 (s, 18H). MS (APCI) m/z 636 [MH^+].

2-((3-(4-((*tert*-Butoxycarbonyl)(methyl)amino)phenyl)quinoxalin-6-yl)oxy)ethyl 4-methylbenzenesulfonate (22).

To a solution of **20** (104.1 mg, 0.263 mmol) in pyridine (10 mL) was added *p*-toluenesulfonyl chloride (251.1 mg, 1.32 mmol) at 0ºC. The reaction mixture was allowed to warm to room temperature and stirred for 1 h. To the stirring solution was added DMAP (catalytic) and then stirred overnight. Solvent was evaporated under reduced pressure, and the residue was extracted with $CHCl_3$ (60 mL x 2). The organic layers were combined and dried over $MgSO_4$. Evaporation of the solvent afforded a residue, which was purified by silica gel chromatography (AcOEt / hexane = 1 / 1) to give 92.2 mg of **22** (63.9%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.17 (s, 1H), 8.14 (d, J = 8.4 Hz, 2H), 7.97 (d, J = 9.2 Hz, 1H), 7.85 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 8.8 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 2.8 Hz, 1H), 7.27 (dd, J = 8.8, 2.8 Hz, 1H), 4.49 (t, J = 4.4 Hz, 2H), 4.34 (t, J = 4.4 Hz, 2H), 3.34 (s, 3H), 2.43 (s, 3H), 1.50 (s, 9H). MS (APCI) m/z 550 [MH^+].

2-Chloroquinoxalin-6-ol (23).

6-Methoxy-2-chloroquinoxaline (97.3 mg, 0.5 mmol) was added to a suspension of $AlCl_3$ (160.0 mg, 1.2 mmol) in toluene (4 mL) at 0ºC. The reaction mixture was stirred

for 4 h at 80ºC. The mixture was cooled to 0ºC and then ice-cold water was added to quench the reaction. After extraction with AcOEt (60 mL x 2), the organic layer was dried over Na_2SO_4. Evaporation of the solvent afforded a residue, which was purified by silica gel chromatography ($CHCl_3$ / MeOH = 30 / 1) to give 59.3 mg of **23** (65.7%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.71 (s, 1H), 7.84 (d, *J* = 9.2 Hz, 1H), 7.44 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.32 (d, *J* = 2.8 Hz, 1H). MS (APCI) m/z 181 [MH^+].

2-Chloro-6-(2-fluoroethoxy)quinoxaline (24).

To a solution of **23** (194.2 mg, 1.08 mmol) in DMF (18 mL) was added K_2CO_3 (297.2 mg, 2.15 mmol). The reaction mixture was stirred for 0.5 h at 80ºC and then 2-fluoroethyl 4-methylbenzenesulfonate (460 μL) was added. The mixture was stirred for 1.5 h at 80ºC. The suspension was allowed to cool to room temperature and then extracted with AcOEt (60 mL x 2). The organic layers were combined and dried over $MgSO_4$. Evaporation of the solvent afforded a residue, which was purified by silica gel chromatography twice (AcOEt / hexane = 1 / 3 and $CHCl_3$ 100%) to give 133.0 mg of **24** (54.3%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1H), 7.93 (d, *J* = 9.2 Hz,

1H), 7.51 (dd, J = 9.2, 2.8 Hz, 1H), 7.39 (d, J = 2.8 Hz, 1H), 4.92-4.78 (m, 2H), 4.43-4.34 (m, 2H). MS (APCI) m/z 227 [MH^+].

4-(6-(2-Fluoroethoxy)quinoxalin-2-yl)-*N*,*N*-dimethylaniline (25).

To a solution of **24** (133.0 mg, 0.587 mmol) in mixture of toluene (5 mL) and EtOH (700 μL) were added *N*,*N*-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (159.6 mg, 0.646 mmol), $Pd(PPh_3)_4$ (20.3 mg, 0.0176 mmol) and K_2CO_3 (2.0 M in water, 645 μL). The reaction mixture was heated to reflux for 6.5 h. The solution was allowed to cool to room temperature and then extracted with AcOEt (50 mL x 2). The organic layers were combined and dried over $MgSO_4$. Evaporation of the solvent afforded a residue, which was purified by silica gel chromatography (AcOEt / hexane = 1 / 1) to give 113.5 mg of **25** (62.8%). ^1H NMR (400 MHz, $CDCl_3$) δ 9.20 (s, 1H), 8.10 (d, J = 9.2 Hz, 2H), 7.99 (d, J = 9.2 Hz, 1H), 7.44 (dd, J = 9.2, 2.8 Hz, 1H), 7.35 (d, J = 2.8 Hz, 1H), 6.85 (d, J = 9.2 Hz, 2H), 4.92-4.78 (m, 2H), 4.43-4.34 (m, 2H), 3.07 (s, 6H). HRMS (EI) m/z calcd for $C_{18}H_{18}FN_3O$ (M^+) 311.1434, found 311.1441.

4-(6-(2-Fluoroethoxy)quinoxalin-2-yl)aniline (26).

To a solution of **24** (829.8 mg, 3.66 mmol) in mixture of toluene (30 mL) and EtOH (4.2 mL) were added 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (882.9 mg, 4.03 mmol), $Pd(PPh_3)_4$ (127.1 mg, 0.110 mmol) and K_2CO_3 (2.0 M in water, 4.03 mL). The reaction mixture was heated to reflux for 3 h. The solution was allowed to cool to room temperature and then extracted with AcOEt (150 mL x 2). The organic layers were combined and dried over $MgSO_4$. Evaporation of the solvent afforded a residue, which was purified by silica gel chromatography twice ($CHCl_3$ / MeOH = 30 / 1 and AcOEt / hexane = 1 / 1) to give 173.0 mg of **26** (16.7%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.18 (s, 1H), 8.03-7.98 (m, 3H), 7.45 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.35 (d, *J* = 2.8 Hz, 1H), 6.83 (d, *J* = 8.4 Hz, 2H), 4.93-4.79 (m, 2H), 4.43-4.35 (m, 2H), 3.94 (s, 2H). HRMS (EI) m/z calcd for $C_{16}H_{14}FN_3O$ (M^+) 283.1121, found 283.1123.

4-(6-(2-Fluoroethoxy)quinoxalin-2-yl)-*N*-methylaniline (27).

A suspension of **26** (330.8 mg, 1.17 mmol) and paraformaldehyde (189.5 mg, 6.31

mmol) in MeOH (30 mL) was slowly added sodium methoxide (5 M in MeOH, 936 μL, 4.68 mmol) at 0°C. The mixture was heated to reflux for 2.5 h and then allowed to cool to room temperature. $NaBH_4$ (221.3 mg, 5.85 mmol) was added gently to the stirring solution. The reaction mixture was brought to reflux again for 1.5 h and then quenched with sat. $NaHCO_3$ aq. MeOH was evaporated under reduced pressure, and the residue was extracted with AcOEt (70 mL x 2). The organic layers were combined and dried over $MgSO_4$. Evaporation of the solvent afforded a residue, which was purified by silica gel chromatography (AcOEt / hexane = 1 / 1) to give 188.1 mg of **27** (54.1%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.19 (s, 1H), 8.05 (d, *J* = 8.4 Hz, 2H), 7.99 (d, *J* = 9.2 Hz, 1H), 7.44 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.35 (d, *J* = 2.8 Hz, 1H), 6.74 (d, *J* = 8.4 Hz, 2H), 4.92-4.79 (m, 2H), 4.43-4.34 (m, 2H), 4.05 (s, 1H), 2.93 (s, 3H). HRMS (EI) m/z calcd for $C_{17}H_{16}FN_3O$ (M^+) 297.1277, found 297.1280.

6-(2-((*tert*-Butyldimethylsilyl)oxy)ethoxy)-2-chloroquinoxaline (28).

To a solution of **23** (59.3 mg, 0.328 mmol) in DMF (7 mL) was added K_2CO_3 (90.8 mg, 0.657 mmol). The suspension was stirred for 0.5 h at 80°C and then

(2-bromoethoxy)-*tert*-butyldimethylsilane (140 μL) was added. The reaction mixture was stirred for 2.5 h at 80°C. The mixture was allowed to cool to room temperature and then extracted with AcOEt (60 mL x 2). The organic layers were combined and dried over $MgSO_4$. Evaporation of the solvent afforded a residue, which was purified by silica gel chromatography (AcOEt / hexane = 1 / 10) to give 101.5 mg of **28** (91.3%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 1H), 7.90 (d, *J* = 9.2 Hz, 1H), 7.47 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.39 (d, *J* = 2.8 Hz, 1H), 4.21 (t, *J* = 4.8 Hz, 2H), 4.06 (t, *J* = 4.8 Hz, 2H), 0.92 (s, 9H), 0.12 (s, 6H). MS (APCI) m/z 339 [MH^+].

4-(6-(2-((*tert*-Butyldimethylsilyl)oxy)ethoxy)quinoxalin-2-yl)-*N*,*N*-dimethylaniline (29).

To a solution of **28** (101.5 mg, 0.299 mmol) in mixture of toluene (2.5 mL) and EtOH (350 μL) were added *N*,*N*-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (81.3 mg, 0.329 mmol), $Pd(PPh_3)_4$ (10.4 mg, 0.00897 mmol) and K_2CO_3 (2.0 M in water, 329 μL). The reaction mixture was heated to reflux for 3 h. The solution was allowed to cool to room

temperature and then extracted with AcOEt (60 mL x 2). The organic layers were combined and dried over $MgSO_4$. Evaporation of the solvent afforded a residue, which was purified by silica gel chromatography (AcOEt / hexane = 1 / 3) to give 127.0 mg of **29** (quantitative yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.19 (s, 1H), 8.08 (d, *J* = 8.8 Hz, 2H), 7.96 (d, *J* = 9.2 Hz, 1H), 7.40 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.35 (d, *J* = 2.8 Hz, 1H), 6.84 (d, *J* = 9.2 Hz, 2H), 4.21 (t, *J* = 4.8 Hz, 2H), 4.06 (t, *J* = 4.8 Hz, 2H), 3.06 (s, 6H), 0.93 (s, 9H), 0.13 (s, 6H). MS (APCI) m/z 424 [MH^+].

4-(6-(2-((*tert*-Butyldimethylsilyl)oxy)ethoxy)quinoxalin-2-yl)aniline (30).

To a solution of **28** (1113 mg, 3.28 mmol) in mixture of toluene (28 mL) and EtOH (3.8 mL) were added 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (719.5 mg, 3.28 mmol), $Pd(PPh_3)_4$ (113.7 mg, 0.0984 mmol) and K_2CO_3 (2.0 M in water, 3.61 mL). The reaction mixture was heated to reflux for 3 h. $Pd(PPh_3)_4$ (113.7 mg, 0.0984 mmol) was added to the mixture. The reaction mixture was heated to reflux again for 1 h. The solution was allowed to cool to room temperature and then extracted with AcOEt (60 mL x 2). The organic layers were combined and dried over $MgSO_4$. Evaporation of the

solvent afforded a residue, which was purified by silica gel chromatography ($CHCl_3$ / MeOH = 40 / 1) to give 1425 mg of **30** (quantitative yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.17 (s, 1H), 8.02-7.96 (m, 3H), 7.41 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.36 (d, *J* = 2.8 Hz, 1H), 6.83 (d, *J* = 8.0 Hz, 2H), 4.21 (t, *J* = 4.8 Hz, 2H), 4.07 (t, *J* = 4.8 Hz, 2H), 3.95 (s, 2H), 0.93 (s, 9H), 0.13 (s, 6H).

4-(6-(2-((*tert*-Butyldimethylsilyl)oxy)ethoxy)quinoxalin-2-yl)-*N*-methylaniline (31).

To a suspension of **30** (712.0 mg, 1.8 mmol) and paraformaldehyde (291.9 mg, 9.72 mmol) in MeOH (40 mL) was added slowly sodium methoxide (5 M in MeOH, 1.44 mL, 7.2 mmol) at 0ºC. The reaction mixture was heated to reflux for 2.5 h and then allowed to cool to room temperature. $NaBH_4$ (340.5 mg, 9.0 mmol) was added gently. The reaction mixture was brought to reflux again for 1.5 h and then quenched with sat. $NaHCO_3$ aq. MeOH was evaporated under reduced pressure, and the residue was extracted with AcOEt (70 mL x 2). The organic layers were combined and dried over $MgSO_4$. Evaporation of the solvent afforded a residue, which was purified by silica gel chromatography (AcOEt / hexane = 1 / 2) to give 118.8 mg of **31** (16.1%). ^{1}H NMR

(400 MHz, $CDCl_3$) δ 9.18 (s, 1H), 8.04 (d, *J* = 8.4 Hz, 2H), 7.96 (d, *J* = 9.2 Hz, 1H), 7.42-7.39 (m, 2H), 6.74 (d, *J* = 8.4 Hz, 2H), 4.20 (t, *J* = 4.8 Hz, 2H), 4.07 (t, *J* = 4.8 Hz, 2H), 2.93 (s, 3H), 0.93 (s, 9H), 0.13 (s, 6H).

6-(2-((*tert*-Butyldimethylsilyl)oxy)ethoxy)-2-(*p*-di(*tert*-butoxycarbonyl)aminophenyl)quinoxaline (32).

A mixture of **30** (698.0 mg, 1.765 mmol), di-*tert*-butyl dicarbonate (3852 mg, 17.65 mmol), DMAP (21.6 mg, 0.177 mmol), and triethylamine (295 μL) in THF (18 mL) was stirred under reflux for 3 h. The solution was allowed to cool to room temperature and then extracted with AcOEt (70 mL x 2). The organic layers were combined and dried over $MgSO_4$. Evaporation of the solvent afforded a residue, which was purified by silica gel chromatography (AcOEt / hexane = 1 / 2) to give 528.7 mg of **32** (50.3%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.25 (s, 1H), 8.18 (d, *J* = 8.4 Hz, 2H), 8.03 (d, *J* = 9.2 Hz, 1H), 7.46 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.40 (d, *J* = 2.8, 1H), 7.32 (d, *J* = 8.4 Hz, 2H), 4.23 (t, *J* = 4.8 Hz, 2H), 4.08 (t, *J* = 4.8 Hz, 2H), 1.44 (s, 18H), 0.93 (s, 9H), 0.13 (s, 6H).

***tert*-Butyl**

(4-(6-(2-((*tert*-butyldimethylsilyl)oxy)ethoxy)quinoxalin-2-yl)phenyl)(methyl)carba

mate (33).

To a solution of **31** (118.8 mg, 0.290 mmol) in THF (8 mL) was added di-*tert*-butyl dicarbonate (632.9 mg, 2.90 mmol) and DMAP (3.54 mg, 0.0290 mmol) and triethylamine (48 μL). The reaction mixture was heated to reflux for 6 h. The solution was allowed to cool to room temperature and then extracted with AcOEt (60 mL x 2). The organic layers were combined and dried over $MgSO_4$. Evaporation of the solvent afforded a residue, which was purified by silica gel chromatography (AcOEt / hexane = 1 / 3) to give 111.2 mg of **33** (75.2%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23 (s, 1H), 8.13 (d, *J* = 8.4 Hz, 2H), 8.02 (d, *J* = 9.2 Hz, 1H), 7.47-7.39 (m, 4H), 4.23 (t, *J* = 4.8 Hz, 2H), 4.08 (t, *J* = 4.8 Hz, 2H), 3.33 (s, 3H), 1.49 (s, 9H), 0.93 (s, 9H), 0.13 (s, 6H). MS (APCI) m/z 510 [MH^+].

2-((2-(4-(Dimethylamino)phenyl)quinoxalin-6-yl)oxy)ethyl

4-methylbenzenesulfonate (34).

To a solution of **29** (127.0 mg, 0.300 mmol) in THF (5 mL) was added TBAF (1 M in THF, 360 μL) at 0ºC. The solution was allowed to warm to room temperature and stirred for 1 h. After extraction with AcOEt (60 mL x 2), the organic layer was dried over Na_2SO_4. Evaporation of the solvent afforded a residue, which was dissolved in pyridine (5 mL). To the solution were added *p*-toluenesulfonyl chloride (286.0 mg, 1.50 mmol) and DMAP (3.67 mg, 0.030 mmol). The mixture was stirred for 6 h at room temperature. Solvent was evaporated under reduced pressure, and the residue was extracted with AcOEt (60 mL x 2). The organic layers were combined and dried over $MgSO_4$. Evaporation of the solvent afforded a residue, which was purified by silica gel chromatography (AcOEt / hexane = 1 / 1) to give 64.0 mg of **34** (46.0%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.19 (s, 1H), 8.08 (d, *J* = 8.8 Hz, 2H), 7.94 (d, *J* = 9.2 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.25-7.21 (m, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 4.47 (t, *J* = 4.8 Hz, 2H), 4.30 (t, *J* = 4.8 Hz, 2H), 3.07 (s, 6H), 2.43 (s, 3H). MS (APCI) m/z 464 [MH^+].

2-((2-(4-((Di-*tert*-butoxycarbonyl)amino)phenyl)quinoxalin-6-yl)oxy)ethyl

4-methylbenzenesulfonate (35).

To a solution of **32** (528.7 mg, 0.887 mmol) in THF (10 mL) was added TBAF (1 M in THF, 1.06 mL) at 0ºC. The solution was allowed to warm to room temperature and then stirred for 2 h. After extraction with AcOEt (50 mL x 2), the organic layer was dried over $MgSO_4$. Evaporation of the solvent afforded a residue, which was dissolved in pyridine (10 mL). To the solution were added *p*-toluenesulfonyl chloride (845.5 mg, 4.44 mmol) and DMAP (10.8 mg, 0.0887 mmol). The mixture was stirred for 5 h at room temperature. Solvent was evaporated under reduced pressure, and the residue was extracted with AcOEt (70 mL x 2). The organic layers were combined and dried over $MgSO_4$. Evaporation of the solvent afforded a residue, which was purified by silica gel chromatography (AcOEt / hexane = 1 / 1) to give 338.2 mg of **35** (60.0%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.24 (s, 1H), 8.18 (d, *J* = 8.8 Hz, 2H), 8.01 (d, *J* = 9.2 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 2H), 7.34-7.28 (m, 6H), 4.49 (t, *J* = 4.8 Hz, 2H), 4.34 (t, *J* = 4.8 Hz, 2H), 2.42 (s, 3H), 1.44 (s, 18H). MS (APCI) m/z 636 [MH^+].

2-((2-(4-((*tert*-Butoxycarbonyl)(methyl)amino)phenyl)quinoxalin-6-yl)oxy)ethyl

4-methylbenzenesulfonate (36).

To a solution of **33** (111.2 mg, 0.218 mmol) in THF (5 mL) was added TBAF (1 M in THF, 262 μL) at 0ºC. The solution was allowed to warm to room temperature and then stirred for 3 h. After extraction with AcOEt (60 mL x 2), the organic layer was dried over Na_2SO_4. Evaporation of the solvent afforded a residue, which was dissolved in pyridine (5 mL). To the solution were added *p*-toluenesulfonyl chloride (207.8 mg, 1.09 mmol) and DMAP (2.7 mg, 0.0218 mmol). The mixture was stirred for 5 h at room temperature. Solvent was evaporated under reduced pressure, and the residue was extracted with AcOEt (50 mL x 2). The organic layers were combined and dried over $MgSO_4$. Evaporation of the solvent afforded a residue, which was purified by silica gel chromatography (AcOEt / hexane = 1 / 1) to give 72.6 mg of **36** (60.6%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.22 (s, 1H), 8.12 (d, *J* = 8.4 Hz, 2H), 8.00 (d, *J* = 9.2 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.34-7.28 (m, 4H), 4.48 (t, *J* = 4.8 Hz, 2H), 4.33 (t, *J* = 4.8 Hz, 2H), 3.33 (s, 3H), 2.42 (s, 3H), 1.49 (s, 9H). MS (APCI) m/z 550 [MH^+].

Radiolabeling with ^{18}F.

[^{18}F]Fluoride was produced by cyclotron (CYPRIS HM-12, 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 0.3 mL of 66 mM K_2CO_3 solution. Kryptofix222 (10 mg) was dissolved in the solution of [^{18}F]fluoride in water. The solvent was removed at 120˚C under a stream of argon gas. The residue was azeotropically dried with 300 μL of anhydrous acetonitrile three times at 120˚C under a stream of nitrogen gas. To prepare the desired ^{18}F-labeled dimethylated quinoxaline derivatives, a solution of tosylate precursor (1.0 mg) in acetonitrile (200 μL) was added to the reaction vessel containing the ^{18}F activity. The mixture was heated at 100°C for 10 min. The compound was purified by HPLC on a Cosmosil C_{18} column with an isocratic solvent of acetonitrile/H_2O (5 / 5) at a flow rate of 1.0 mL/min. To prepare the desired ^{18}F-labeled monomethylated and nonmethylated quinoxaline derivatives and AV-45, a solution of tosylate precursor (1.0 mg) in acetonitrile (200 μL) was added to the reaction vessel containing the ^{18}F activity. The mixture was heated at 100°C for 10 min and was cooled

down. 450 μL of 1N HCl was added and the mixture was heated at 100˚C again for 10 min. 500 μL of sat. $NaHCO_3$ aq. was added to adjust the pH. The mixture was extracted with ethyl acetate and the solvent was evaporated under reduced pressure. The residue was dissolved in acetonitrile (200 μL) and the solution was passed a filter. The radiofluorinated ligand was purified by HPLC on a Cosmosil C_{18} column with an isocratic solvent of acetonitrile/H_2O (4 / 6 for PQ derivatives and 5 / 5 for AV-45) at a flow rate of 1.0 mL/min. We calculated the radiochemical yields at the end of synthesis (EOS) for [^{18}F]PQ-1-6 as 25.9 ± 12.5% (n = 3), 20.1 ± 8.9% (n = 3), 31.3 ± 16.0% (n = 8), 34.0 ± 9.5% (n = 3), 22.7 ± 5.5% (n = 3), and 19.6 ± 11.4% (n = 5), respectively. The specific activity at the end of synthesis (EOS) for [^{18}F]PQ-1-6 was greater than 100 GBq/μmol. The total duration of the procedure was 90-120 min.

Measurement of log P-values.

The experimental determination of partition coefficients of [^{18}F]PQ1-6 were performed in 1-octanol and 0.01 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 0.35 MBq of [^{18}F]PQ1-6. The test tube was vortexed for 2 min, and centrifuged (5 min, 4,000 *g)*. Aliquots (500 μL) from the 1-octanol and buffer phases were transferred into two test tubes for counting. The remainder of the 1-octanol phase was transferred (1 mL) into a new test tube. 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)/(counts/μL in buffer) = r (1)

We calculated the values of partition coefficient of [^{18}F]PQ-1-6 and [^{18}F]AV-45 as 1.57, 1.80, 1.98, 1.59, 1.86, 1.99, and 1.82, respectively.

Binding assays using the aggregated Aβ peptides in solution.

A solid form of $A\beta_{1-42}$ was purchased from Peptide Institute (Osaka, Japan). Aggregation was carried out by gently dissolving the peptide (0.25 mg/mL) in PBS

solution (pH 7.4). The solution was incubated at 37˚C for 42 h with gentle and constant shaking. A mixture containing 50 μL of nonradioactive PQ derivative in EtOH (final conc., 0.5 pM-25 μM), 50 μL of [^{125}I]IMPY (final conc., 0.025nM), 50 μL of $A\beta_{1\text{-}42}$ aggregates (final conc., 0.125 μg/mL), and 850 μL of 10% EtOH was incubated at room temperature for 3 h. The mixture was then filtered through Whatman GF/B filters (Whatman, Kent, U.K.) using a Brandel M-24 cell harvester, and the radioactivity of the filters containing the bound ^{125}I ligand were measured in a γ counter (Wallac 1470 Wizard; Perkin Elmer). Values for the half maximal inhibitory concentration (IC_{50}) were determined from displacement curves 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).

In vitro **autoradiography using AD brain sections.**

Postmortem brain tissues from an autopsy-confirmed case of AD (a 78-year-old, female for [^{18}F]PQ3-6 and a 93-year-old, female for [^{18}F]PQ1-2) and a control (a 54-year-old,

male) were obtained from the Graduate School of Medicine, Kyoto University and BioChain Institute Inc., respectively. The presence and location of SPs in the sections were confirmed with immunohistochemical staining using anti $A\beta_{1-42}$ antibody. The sections were incubated with [^{18}F]tracer (370 kBq/100 μL) for 1 h at room temperature. They were then dipped in 50% EtOH (two 2-min washes) and washed with water (two 2-min washes). After drying, the ^{18}F-labeled sections were exposed to a BAS imaging plate (Fuji Film, Tokyo, Japan) for 1.5 h. Autoradiographic images were obtained using a BAS5000 scanner system (Fuji Film).

Immunohistochemical staining of SPs in human AD brain sections

Postmortem brain tissue from an autopsy-confirmed case of AD (a 78-year-old, female) was obtained from the Graduate School of Medicine, Kyoto University. Six-micrometer-thick serial sections of paraffin-embedded blocks were used for staining. The sections were subjected to two 15-min incubations in xylene, two 1-min incubations in 100% EtOH, two 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. They were then autoclaved for 15 min. in 0.01 M citric acid buffer (pH6.0) for antigen retrieval. After two 5-min incubations in PBS-Tween20, the sections were incubated at room temperature with 90% formic acid solution for 5 min for antigen retrieval. The sections were washed with flowing tap water for 5 min, followed by one 2-min incubatition in PBS-Tween20. The sections were incubated with mouse monoclonal $A\beta_{1\text{-}42}$ primary antibody overnight. After three 5-min incubations in PBS-Tween20, they were incubated with biotinylated goat anti-mouse IgG at room temperature for 1 h. After three 5-min incubations in PBS-Tween20, the sections were incubated with Streptavidin-Peroxidase complex at room temperature for 1 h. After two 5-min incubations in PBS-Tween20 and one 5-min incubation in TBS, they were incubated with DAB as a chromogen for 5 min. After being washed with water, the sections were observed under a microscope (BIOREVO BZ-9000, Keyence Corp., Osaka, Japan).

***In vivo* biodistribution in normal mice.**

A saline solution (100 μL) of [^{18}F]PQ-1-6 derivatives (23.4-48.2 kBq) containing

ethanol (10 μL) was injected intravenously directly into the tail of ddY mice (5-week-old, male). The mice (n = 5 for each time point) were sacrificed at 2, 10, 30, and 60 min post-injection. The organs of interest were removed and weighed, and the radioactivity was measured with a γ counter (Wallac 1480 Wizard 3; Perkin Elmer). 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. The results are presented in the following tables. All PQ derivatives displayed a high initial uptake (4.69-7.59%ID/g at 2 or 10 min postinjection) and washout with time from the brain (1.48-3.08%ID/g at 60 min postinjection), which is highly desirable for Aβ imaging. Furthermore, they also distributed to several other organs. The liver and kidney showed an initial uptake with washout, whereas the intestines showed sequential accumulation. In addition, no marked uptake of PQ derivatives in bone was observed (2.86-5.40%ID/g at 60 min), suggesting little defluorination in vivo by 60 min after the injection.

Table S1. Biodistribution of Radioactivity after Intravenous Injection of [^{18}F]PQ-1 in Mice[a)]

	Time after injection (min)			
Tissue	2	10	30	60
Blood	2.71 (0.20)	2.95 (0.14)	3.44 (0.24)	3.27 (0.22)
Liver	9.18 (1.45)	12.06 (1.82)	8.76 (1.01)	6.52 (0.93)
Kidney	11.14 (1.59)	6.36 (0.21)	5.00 (0.52)	3.30 (0.38)
Intestine	4.22 (0.33)	8.56 (1.29)	13.42 (1.45)	21.80 (5.00)
Spleen	3.77 (0.52)	4.86 (0.79)	3.94 (0.45)	3.72 (0.24)
Pancreas	6.13 (0.57)	4.98 (0.26)	3.60 (0.57)	2.73 (0.23)
Heart	8.76 (1.24)	5.30 (0.77)	4.52 (0.38)	4.53 (0.66)
Lung	8.18 (1.21)	5.67 (0.68)	4.70 (0.41)	4.05 (0.17)
Stomach[b)]	1.26 (0.05)	1.98 (0.15)	2.70 (0.53)	2.97 (1.57)
Brain	4.69 (0.46)	3.12 (0.10)	2.42 (0.22)	1.99 (0.08)
Bone	2.71 (0.53)	3.08 (0.45)	4.12 (0.41)	5.20 (1.67)

[a)]Expressed as % injected dose per gram. Each value represents the mean (SD) for 5

animals at each interval. [b)]Expressed as % injected dose per organ.

Table S2. Biodistribution of Radioactivity after Intravenous Injection of [^{18}F]PQ-2 in Mice[a)]

	Time after injection (min)			
Tissue	2	10	30	60
Blood	3.37 (0.46)	3.83 (1.24)	3.10 (0.34)	3.40 (0.32)
Liver	6.84 (1.50)	11.72 (0.58)	7.95 (1.32)	6.95 (0.68)
Kidney	11.78 (2.51)	7.55 (0.36)	3.92 (0.45)	3.12 (0.41)
Intestine	3.46 (0.75)	12.48 (2.77)	20.27 (2.55)	22.13 (2.95)
Spleen	2.71 (0.44)	4.53 (0.62)	3.33 (0.66)	3.17 (0.62)
Pancreas	5.42 (0.13)	4.91 (0.95)	2.60 (0.25)	2.73 (0.31)
Heart	7.42 (0.53)	4.41 (0.17)	8.53 (11.98)	3.92 (0.64)
Lung	6.71 (0.24)	4.98 (0.56)	3.34 (0.55)	4.06 (0.99)
Stomach*	1.13 (0.18)	2.11 (0.55)	1.56 (0.34)	2.73 (2.44)
Brain	5.96 (0.48)	3.77 (0.40)	2.18 (0.22)	1.91 (0.15)

Bone	1.86 (0.53)	2.67 (0.54)	4.84 (3.97)	5.35 (1.16)

[a)]Expressed as % injected dose per gram. Each value represents the mean (SD) for 5 animals at each interval. [b)]Expressed as % injected dose per organ.

Table S3. Biodistribution of Radioactivity after Intravenous Injection of [^{18}F]PQ-3 in Mice[a)]

	Time after injection (min)			
Tissue	2	10	30	60
Blood	2.26 (0.22)	1.92 (0.68)	2.43 (0.17)	2.38 (0.25)
Liver	11.93 (1.35)	11.67 (0.80)	7.11 (1.56)	5.30 (0.82)
Kidney	8.65 (0.88)	5.19 (0.88)	3.30 (0.27)	3.52 (1.21)
Intestine	3.24 (0.43)	7.95 (1.28)	16.17 (1.71)	17.9 (3.64)
Spleen	3.67 (0.40)	2.89 (0.37)	2.31 (0.21)	1.74 (0.05)
Pancreas	6.82 (0.80)	3.51 (0.25)	2.31 (0.19)	1.60 (0.18)
Heart	6.12 (0.79)	3.48 (0.56)	2.43 (0.12)	2.22 (0.08)
Lung	5.74 (0.48)	4.02 (0.32)	2.80 (0.15)	2.20 (0.15)

Stomach*	1.07 (0.20)	2.54 (0.88)	2.02 (0.63)	1.42 (0.22)
Brain	5.78 (0.60)	3.82 (0.33)	1.85 (0.09)	1.48 (0.07)
Bone	2.45 (0.43)	1.93 (0.09)	2.35 (0.39)	2.86 (0.36)

[a)]Expressed as % injected dose per gram. Each value represents the mean (SD) for 5 animals at each interval. [b)]Expressed as % injected dose per organ.

Table S4. Biodistribution of Radioactivity after Intravenous Injection of [^{18}F]PQ-4 in Mice[a)]

	Time after injection (min)			
Tissue	2	10	30	60
Blood	3.86 (0.48)	4.39 (0.49)	4.66 (0.13)	5.10 (0.36)
Liver	5.30 (1.33)	6.58 (0.47)	4.90 (0.29)	4.88 (0.30)
Kidney	11.92 (2.02)	7.08 (0.69)	4.67 (0.50)	3.93 (0.39)
Intestine	3.69 (0.44)	5.48 (0.85)	6.67 (0.52)	8.19 (0.69)
Spleen	3.54 (1.53)	5.36 (1.35)	4.55 (0.31)	4.81 (0.75)
Pancreas	6.21 (0.99)	5.08 (0.78)	3.76 (0.37)	3.94 (0.47)

Heart	7.55 (0.95)	5.35 (0.70)	5.07 (0.39)	6.10 (0.35)
Lung	8.28 (0.96)	5.60 (0.67)	5.21 (0.17)	5.56 (0.43)
Stomach*	1.68 (0.26)	2.67 (0.32)	3.31 (0.59)	2.71 (0.30)
Brain	7.59 (0.82)	5.63 (0.25)	3.50 (0.24)	3.08 (0.12)
Bone	2.01 (0.43)	2.57 (0.50)	3.23 (0.56)	5.40 (1.06)

[a)]Expressed as % injected dose per gram. Each value represents the mean (SD) for 5 animals at each interval. [b)]Expressed as % injected dose per organ.

Table S5. Biodistribution of Radioactivity after Intravenous Injection of [^{18}F]PQ-5 in Mice[a)]

	Time after injection (min)			
Tissue	2	10	30	60
Blood	3.91 (0.22)	3.35 (0.43)	3.83 (0.18)	4.15 (0.31)
Liver	8.81 (1.00)	9.29 (0.40)	7.07 (0.19)	6.10 (0.41)
Kidney	9.86 (0.77)	6.40 (0.62)	4.14 (0.31)	3.08 (0.21)
Intestine	3.40 (0.34)	8.06 (0.95)	12.13 (2.05)	13.37 (1.03)

Spleen	3.14 (0.55)	3.76 (0.55)	3.07 (0.32)	2.99 (0.21)
Pancreas	6.47 (0.75)	3.88 (0.52)	2.72 (0.29)	2.64 (0.34)
Heart	6.12 (0.45)	3.93 (0.40)	3.20 (0.32)	3.80 (0.22)
Lung	8.13 (1.13)	5.10 (0.74)	3.94 (0.33)	3.92 (0.11)
Stomach*	1.32 (0.21)	1.86 (0.38)	2.44 (0.62)	2.00 (0.76)
Brain	6.19 (0.30)	5.11 (0.28)	2.73 (0.16)	2.41 (0.12)
Bone	2.81 (0.52)	2.12 (0.11)	2.86 (0.45)	4.26 (0.29)

[a)]Expressed as % injected dose per gram. Each value represents the mean (SD) for 5 animals at each interval. [b)]Expressed as % injected dose per organ.

Table S6. Biodistribution of Radioactivity after Intravenous Injection of [^{18}F]PQ-6 in Mice[a)]

	Time after injection (min)			
Tissue	2	10	30	60
Blood	2.66 (0.50)	2.29 (0.25)	2.98 (0.29)	3.26 (0.37)
Liver	10.33 (1.00)	9.83 (0.22)	6.91 (0.81)	6.65 (0.90)

Kidney	10.65 (0.96)	6.66 (0.45)	4.19 (0.78)	3.30 (0.39)
Intestine	2.56 (0.10)	5.27 (0.27)	9.82 (1.43)	12.27 (0.79)
Spleen	2.86 (0.66)	4.09 (0.33)	2.66 (0.57)	3.07 (0.68)
Pancreas	6.55 (0.63)	4.74 (0.42)	2.73 (0.50)	2.74 (0.19)
Heart	8.50 (1.40)	4.19 (0.47)	3.29 (0.68)	3.74 (0.72)
Lung	8.94 (1.76)	4.59 (1.07)	3.51 (0.44)	3.39 (0.14)
Stomach*	1.09 (0.05)	1.64 (0.28)	1.98 (0.47)	2.06 (0.46)
Brain	5.67 (0.48)	6.39 (0.51)	3.73 (0.50)	2.61 (0.37)
Bone	2.65 (0.61)	2.34 (0.36)	2.97 (0.78)	4.22 (1.27)

[a)]Expressed as % injected dose per gram. Each value represents the mean (SD) for 5 animals at each interval. [b)]Expressed as % injected dose per organ.

Table S7. Biodistribution of Radioactivity after Intravenous Injection of [^{18}F]AV-45 in Mice[a)]

	Time after injection (min)			
Tissue	2	10	30	60

Blood	3.32 (0.56)	2.68 (0.45)	2.56 (0.22)	2.06 (0.16)
Liver	8.44 (1.21)	15.85 (2.75)	13.13 (1.40)	10.30 (1.28)
Kidney	10.63 (1.55)	8.72 (0.82)	9.17 (2.57)	5.91 (1.50)
Intestine	3.45 (0.53)	5.79 (0.51)	9.08 (1.52)	11.75 (2.56)
Spleen	2.45 (0.42)	2.20 (0.13)	1.78 (0.21)	1.49 (0.19)
Pancreas	4.57 (0.67)	3.20 (0.26)	2.52 (0.28)	1.77 (0.21)
Heart	6.70 (1.36)	3.07 (0.29)	2.12 (0.11)	1.17 (0.09)
Lung	6.54 (0.88)	3.75 (0.38)	2.99 (0.43)	2.35 (0.24)
Stomach*	1.83 (0.24)	5.10 (0.82)	5.95 (1.06)	6.84 (3.34)
Brain	4.90 (0.99)	2.52 (0.25)	1.65 (0.11)	1.29 (0.08)
Bone	1.48 (0.24)	1.30 (0.15)	2.01 (0.35)	3.48 (0.38)

[a)]Expressed as % injected dose per gram. Each value represents the mean (SD) for 5 animals at each interval. [b)]Expressed as % injected dose per organ.

Table S8. $Brain_{2\ min}$ / $Brain_{60\ min}$ Ratio

Compound	Ratio

[^{18}F]PQ-1	2.36
[^{18}F]PQ-2	3.12
[^{18}F]PQ-3	3.91
[^{18}F]PQ-4	2.46
[^{18}F]PQ-5	2.57
[^{18}F]PQ-6	2.45[a)]
[^{18}F]AV-45	3.80

[a)]Expressed as the $brain_{10\ min}$ / $brain_{60\ min}$ ratio.

Ex vivo **autoradiography using Tg2576 and wild-type mice.**

For [^{18}F]PQ-6, the Tg2576 transgenic mice (24 months, female) and wild-type mice (24 months, female) were used as an Alzheimer's model and an age-matched control, respectively. For [^{18}F]PQ-3, the Tg2576 transgenic mice (20 months, female) was used. A saline solution (200 μL) of [^{18}F]PQ-3 (55.5 MBq) or [^{18}F]PQ-6 (55.5 MBq) containing ethanol (20 μL) was injected through the tail vein. The animals were killed by decapitation at 1 h post injection. The brains were immediately removed, embedded

in carboxymethylcellulose solution and then frozen in dry ice/hexane bath. Sections of 30 μm were cut and exposed to a BAS imaging plate (Fuji Film, Tokyo, Japan) for 30 min. Autoradiographic images were obtained using a BAS5000 scanner system (Fuji Film). After autoradiographic examination, the same sections were stained by thioflavin-S to confirm the presence of β–amyloid plaques. For the staining of thioflavin-S, sections were immersed in a 200 μM thioflavin-S solution containing 50% EtOH and washed with water. After drying, the sections were then observed with the Keyence system (excitation filter, 450-490 nm; emission filter, 510-560 nm; DM filter; 495 nm). This experiment was performed under a fluorescence microscope (BIOREVO BZ-9000, Keyence Corp., Osaka, Japan).

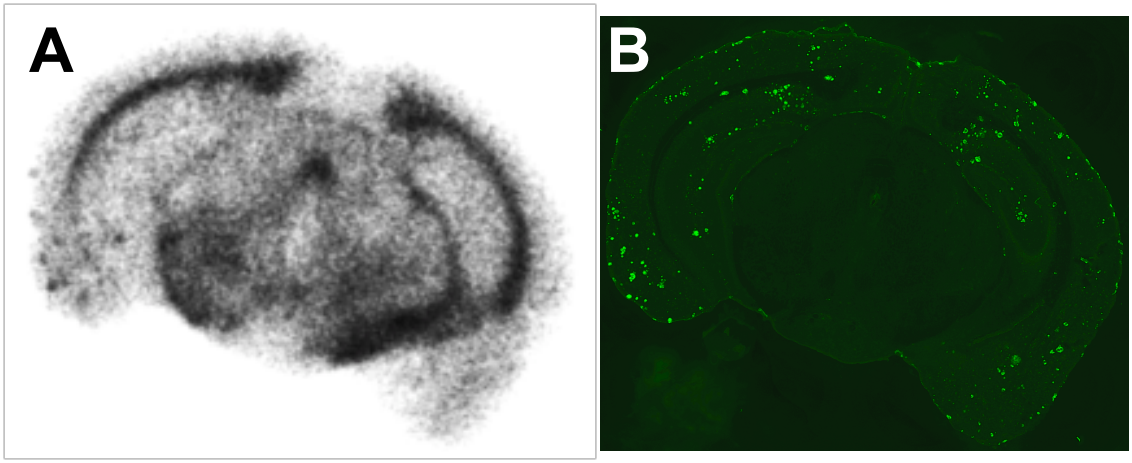

Figure S1. Ex vivo autoradiogram from a Tg2576 mouse (A) with [^{18}F]PQ-3. The same

sections were also stained with thioflavin-S (B).