Supplementary Information

Synthesis of *TEG*-substituted 4-(*N*-methyl-*N*-*Boc*-amino)styrylpyridine as Key Precursor for Monodentate and Multidentate Imaging Agents for $A\beta$ plaques

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1. General Information:

All commercially available reagents were used without further purification. Column chromatography was performed on silica gel (200-300 mesh). ^1H -NMR and ^{13}C -NMR spectra were recorded in CDCl_3 at 400 MHz on a Bruker NMR spectrometer. All chemical shifts are reported in ppm downfield to TMS and peak multiplicities are referred to as singlet (s), doublet (d), quartet (q), and multiplet (m).

2. Experimental Section:

(*E*)-2-chloro-5-(4-nitrostyryl)pyridine (**11**)

A solution of *p*-nitrobenzylbromide (**10**) (20 g, 93 mmol) in 40 mL $\text{P}(\text{OMe})_3$ was heated to reflux for 3.5 h. After cooling to r.t., the mixture was dissolved in 50 mL MeOH. To the solution 6-chloronicotinaldehyde (13.3 g, 93 mmol) was added. To the mixture MeONa (7.53 g, 139 mmol) was added *portionwise* at r.t. The mixture was heated to reflux for 1 h. After cooling to r.t., the mixture was filtered. The filter residue was washed by MeOH and dried to afford (*E*)-2-chloro-5-(4-nitrostyryl)pyridine (**11**) (19.0 g, yield: 80%) as a yellow solid. ^1H -NMR (CDCl_3): δ 8.53 (1H, *d*, $J = 2.4$ Hz), 8.25 (2H, *d*, $J = 8.8$ Hz), 7.85 (1H, *dd*, $J = 8.4$ Hz, $J = 2.4$ Hz), 7.65 (2H, *d*, $J = 8.8$ Hz), 7.36 (1H, *d*, $J = 8.4$ Hz), 7.19 (2H, s). HRMS (FAB) calcd for $\text{C}_{13}\text{H}_9\text{ClN}_2\text{O}_2$ (MH^+): 260.0353; found: 260.0352. The data are identical with those reported in literature [2f].

***mono-THP*-protected triethylene glycol (**12**)**

One drop of HCl was added to triethylene glycol (15 g, 0.1 mmol). To this mixture a solution of 3,4-dihydro-2*H*-pyran (4.2 g, 0.05 mmol) in 20 mL CH₂Cl₂ was added slowly. The mixture was stirred at r.t. for 12 h and the solvent was removed under vacuum. The residue was purified by column chromatography (SiO₂, PE/EtOAc = 1:2) to afford *mono-THP*-protected triethylene glycol (**12**) (12 g, yield: 52%) as a colorless oil. ¹H-NMR (CDCl₃): δ 4.58 (1H, *t*, *J* = 3.6 Hz), 3.84-3.78 (2H, *m*), 3.66-3.62 (8H, *m*), 3.58-3.53 (3H, *m*), 3.46-3.42 (1H, *m*), 2.81 (1H, *s*), 1.81-1.73 (1H, *m*), 1.70-1.64 (1H, *m*), 1.57-1.44 (4H, *m*). ¹³C-NMR (CDCl₃): δ 98.9, 72.5, 70.6, 70.5, 70.3, 66.5, 62.2, 61.7, 30.5, 25.4, 19.4. HRMS (FAB) calcd for C₁₁H₂₂O₅ (MH⁺): 234.1467; found: 234.1468.

Compound 13

To a solution of *mono-THP*-protected triethylene glycol (**12**) (1.83 g, 7.81 mmol) in 16 mL dioxane NaH (312 mg, 7.81 mmol) was added at r.t. The mixture was stirred for 3 h. To the mixture (*E*)-2-chloro-5-(4-nitrostyryl)pyridine (**11**) (750 mg, 2.92 mmol) was added. After stirred at r.t. for 12 h, the mixture was poured into water and extracted by EtOAc. The combined organic layer was dried over Na₂SO₄. After filtration, the filtrate was concentrated under vacuum and the residue was purified by column chromatography (SiO₂, PE/AcOEt = 1:1) to afford **13** (1.21 g, yield: 95%) as a yellow oil. ¹H-NMR (CDCl₃): δ 8.26 (1H, *s*), 8.22 (2H, *d*, *J* = 8.8 Hz), 7.87 (1H, *dd*, *J* = 8.8 Hz, *J* = 2.4 Hz), 7.62 (2H, *d*, *J* = 8.8 Hz), 7.19 (1H, *d*, *J* = 16.4 Hz), 7.04 (1H, *d*, *J* = 16.4 Hz), 6.89-6.88 (1H,

m), 4.63 (1H, *t*, *J* = 3.6 Hz), 4.57-4.53 (2H, *m*), 3.89-3.84 (4H, *m*), 3.73-3.67 (7H, *m*), 3.63-3.58 (1H, *m*), 1.86-1.78 (1H, *m*), 1.75-1.69 (1H, *m*), 1.61-1.52 (4H, *m*). ¹³C-NMR (CDCl₃): δ 163.9, 146.8, 143.7, 135.6, 129.5, 126.8, 125.7, 125.4, 124.2, 111.8, 99.0, 70.8, 70.7, 70.6, 70.6, 69.7, 66.7, 65.6, 62.3, 30.6, 25.5, 19.6. HRMS (FAB) calcd for C₂₄H₃₀N₂O₇ (MH⁺): 458.2053; found: 458.2055.

Compound 14

Compound **13** (1.0 g, 2.2 mmol) and Na₂S·10H₂O (1.72 g, 22 mmol) were dissolved in a mixture of EtOH and H₂O (15 mL, V_{EtOH}/V_{H₂O} = 2:1). The mixture was heated to reflux for 2 h. After cooling to r.t., the mixture was diluted with H₂O and extracted by EtOAc. The combined organic layer was dried over Na₂SO₄. After filtration, the filtrate was concentrated under vacuum and the residue was purified by column chromatography (SiO₂, PE/EtOAc = 1:1) to afford **14** (0.63 g, yield: 68%) as a yellow oil. ¹H-NMR (CDCl₃): δ 8.06 (1H, *d*, *J* = 2 Hz), 7.67 (1H, *dd*, *J* = 8.4 Hz, *J* = 2.0 Hz), 7.22 (2H, *d*, *J* = 8.0 Hz), 6.77 (2H, *q*, *J* = 16.0 Hz), 6.69 (1H, *d*, *J* = 8.8 Hz), 6.58 (2H, *d*, *J* = 8.4 Hz), 4.56 (1H, *t*, *J* = 3.6 Hz), 4.40 (2H, *t*, *J* = 4.8 Hz), 3.81-3.77 (4H, *m*), 3.74 (2H, *s*), 3.63-3.60 (6H, *m*), 3.56-3.51 (1H, *m*), 3.43-3.39 (1H, *m*), 1.78-1.71 (1H, *m*), 1.66-1.61 (1H, *m*), 1.55-1.41 (4H, *m*). ¹³C-NMR (CDCl₃): δ 162.7, 146.4, 145.1, 135.2, 128.2, 127.7, 127.7, 127.4, 121.0, 115.2, 111.4, 99.0, 70.8, 70.7, 70.7, 69.9, 66.7, 65.3, 62.3, 30.7, 25.5, 19.6. HRMS (FAB) calcd for C₂₄H₃₂N₂O₅ (MH⁺): 428.2311; found: 428.2310.

Compound 15

Compound **14** (500 mg, 0.25 mmol) and paraformaldehyde (120 mg, 0.30 mmol) in 10 mL MeOH was heated to reflux for 30 min. To the mixture 4-methylbenzenethiol (160 mg, 0.25 mmol) in 5 mL MeOH was added. After 2 h, the mixture was cooled to r.t. and MeOH was removed under vacuum. The residue was dissolved in 5 mL DME. To the solution NaBH₄ (100 mg, 0.76 mmol) was added and the mixture was heated to 100 °C for 1 h. After cooling to r.t., the mixture was poured into water. The mixture was extracted by EtOAc and the combined organic layer was dried over Na₂SO₄. After filtration, the filtrate was concentrated under vacuum and the residue was purified by column chromatography (SiO₂, PE/EtOAc = 1:1) to afford compound **15** (371 mg, yield: 65%) as yellow oil. ¹H-NMR (CDCl₃): δ 8.13 (1H, *d*, *J* = 2.4 Hz), 7.75 (1H, *dd*, *J* = 2.4 Hz, *J* = 8.8 Hz), 7.35 (2H, *d*, *J* = 8.8 Hz), 6.92-6.65 (5H, *m*), 4.63 (1H, *t*, *J* = 3.6 Hz), 4.47 (2H, *t*, *J* = 4.8 Hz), 3.88-3.83 (4H, *m*), 3.71-3.67 (7H, *m*), 3.63-3.58 (1H, *m*), 3.50-3.46 (1H, *m*), 2.87 (3H, *s*), 1.85-1.78 (1H, *m*), 1.74-1.68 (1H, *m*), 1.62-1.52 (4H, *m*). ¹³C-NMR (CDCl₃): δ 162.6, 149.2, 145.1, 135.1, 128.4, 127.7, 126.4, 120.3, 112.5, 111.4, 100.1, 99.1, 70.8, 70.8, 70.7, 69.9, 66.8, 65.3, 62.3, 58.3, 30.7, 25.6, 19.6. HRMS (FAB) calcd for C₂₅H₃₄N₂O₅ (MH⁺): 442.2468; found: 442.2469.

Compound 16

Compound **15** (600 mg, 1.5 mmol) and (Boc)₂O (410 mg, 2.2 mmol) were dissolved in a mixture of EtOH and H₂O (10 mL V_{EtOH}/V_{H₂O} = 2:1). The mixture was stirred at r.t. for 12 h. The mixture was

diluted with water and extracted by EtOAc. The combined organic layer was dried over Na₂SO₄.

After filtration, the filtrate was concentrated under vacuum and the residue was purified by column chromatography (SiO₂, PE/EtOAc =1:1) to afford compound **16** (500 mg, yield: 67%) as yellow oil.

¹H-NMR (CDCl₃): δ 8.16 (1H, *d*, *J* = 2.0 Hz), 7.77 (1H, *dd*, *J* = 2.0 Hz, *J* = 8.4 Hz), 7.43 (2H, *d*, *J* = 8.8 Hz), 7.21 (2H, *d*, *J* = 8.0 Hz), 6.99-6.90 (2H, *m*), 6.78 (1H, *d*, *J* = 8.8 Hz), 4.62 (1H, *t*, *J* = 3.6 Hz), 4.48 (2H, *t*, *J* = 4.8 Hz), 3.87-3.83 (4H, *m*), 3.70-3.66 (6H, *m*), 3.62-3.57 (1H, *m*), 3.49-3.45 (1H, *m*), 3.25 (3H, *s*), 1.89-1.78 (1H, *m*), 1.73-1.67 (1H, *m*), 1.62-1.53, (2H, *m*), 1.51-1.47 (2H, *m*), 1.45 (9H, *s*). ¹³C-NMR (CDCl₃): δ 163.2, 154.8, 145.8, 143.3, 135.4, 134.3, 127.4, 126.8, 126.6, 125.6, 124.6, 111.6, 99.1, 80.6, 70.9, 70.8, 70.7, 69.9, 66.8, 65.5, 62.3, 37.3, 30.7, 28.5, 25.6, 19.6. HRMS (FAB) calcd for C₃₀H₄₂N₂O₇ (MH⁺): 542.2992; found: 542.2993.

***TEG*-substituted 4-(*N*-methyl-*N*-*Boc*-amino)styrylpyridine (**5**)**

A mixture of compound **16** (1.5 g, 2.9 mmol) and CuSO₄·5H₂O (9.0 g, 36 mmol) in 20 mL MeOH was stirred at r.t. for 12 h. The mixture was diluted with water and extracted by EtOAc. The combined organic layer was dried over Na₂SO₄. After filtration, the filtrate was concentrated under vacuum and the residue was purified by column chromatography (SiO₂, EtOAc) to afford *TEG*-substituted 4-(*N*-methyl-*N*-*Boc*-amino)styrylpyridine (**5**) (1.2 g, yield: 72%) as a white solid.

¹H-NMR (CDCl₃): δ 8.15 (1H, *d*, *J* = 2.0 Hz), 7.76 (1H, *dd*, *J* = 2.4 Hz, *J* = 8.4 Hz), 7.41 (2H, *d*, *J* = 8.4 Hz), 7.20 (2H, *d*, *J* = 8.4 Hz), 6.98-6.89 (2H, *m*), 6.77 (1H, *d*, *J* = 8.8 Hz), 4.48 (2H, *t*, *J* = 4.8

Hz), 3.84 (2H, *t*, *J* = 4.8 Hz), 3.71-3.68 (6H, *m*), 3.60-3.58 (2H, *m*), 3.24 (3H, *s*), 2.71 (1H, *t*, *J* = 6.0 Hz), 1.44 (9H, *s*). ¹³C-NMR (CDCl₃): δ 163.1, 154.8, 145.7, 143.3, 135.5, 134.2, 127.4, 126.9, 126.6, 125.6, 124.6, 111.6, 80.6, 72.6, 70.8, 70.5, 69.8, 65.3, 61.9, 37.3, 28.5. HRMS (FAB) calcd for C₂₅H₃₄N₂O₆ (MH⁺): 458.2417; found: 458.2415. The data are identical with those reported in literature [3].

Compound 6 (AV-105)

To a solution of **5** (100 mg, 0.24 mmol) in 10 mL CH₂Cl₂ was added TsCl (90 mg, 0.47 mmol), Et₃N (238 mg, 2.36 mmol) and DMAP (2.9 mg, 0.024 mmol). The mixture was stirred at r.t. for 3 h. The mixture was poured into 30 mL water and extracted by CH₂Cl₂. The combined organic layer was dried over Na₂SO₄. After filtration, the filtrate was concentrated under vacuum and the residue was purified by column chromatography (SiO₂, PE/EtOAc = 1:1) to afford compound **6** (90 mg, 65%).

¹H-NMR (CDCl₃): δ 8.15 (1H, *d*, *J* = 2.4 Hz), 7.78-7.75 (3H, *m*), 7.42 (2H, *d*, *J* = 8.4 Hz), 7.29 (2H, *d*, *J* = 8.0 Hz), 7.20 (2H, *d*, *J* = 8.4 Hz), 6.94-6.89 (2H, *m*), 6.76=6.73 (1H, *m*), 4.44 (2H, *t*, *J* = 4.8 Hz), 4.13 (2H, *t*, *J* = 4.8 Hz), 3.79 (2H, *t*, *J* = 4.8 Hz), 3.66 (2H, *t*, *J* = 4.8 Hz), 3.62-3.57 (4H, *m*), 3.24 (3H, *s*), 2.39 (3H, *s*), 1.44 (9H, *s*). ¹³C-NMR (CDCl₃): δ 163.2, 154.8, 145.8, 144.9, 143.3, 135.5, 134.2, 133.1, 130.0, 128.1, 127.4, 127.1, 126.9, 126.6, 125.6, 124.6, 111.6, 80.6, 70.9, 70.7, 69.9, 69.4, 68.8, 65.4, 37.3, 28.5, 21.8. HRMS (FAB) calcd for C₃₂H₄₀N₂O₈S (MH⁺): 612.2505; found: 612.2506. The data are identical with those reported in literature [3].

Literatures:

[2f] Kung, M-P.; Kung, H. F. Pat. WO2007/126733 A2, 2007.

[3] Zha, Z.; Choi, S. R.; Ploessl, K.; Lieberman, B. P.; Qu, W.; Hefti, F.; Mintun, M.; Skovronsky, D.;

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mono-THP-protected triethylene glycol (12)

Compound 13

Compound 14

Compound 15

[illegible]

TEG-substituted 4-(*N*-methyl-*N*-Boc-amino)styrylpyridine (5)

Compound 6 (AV-105)