Supporting Information

Total Synthesis of Acetylcholinesterase Inhibitor Macakurzin C

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Preparation of Monobezoate Flavonol 6

To a solution of known tribenzoate 10 (2.437 g, 4.155 mmol) in pyridine (30 mL) was added K₂CO₃ (2.871 g, 20.78 mmol) at room temperature and the resulting mixture was stirred for 2 h at 160 °C before cooled to 0 °C and quenched with saturated aqueous NH₄Cl. The reaction mixture was diluted with EtOAc, the layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 3/1) to afford monobenzoate flavonol 6 (1.543 g, 80%) as a yellow solid: ¹H NMR (400 MHz, CDCl₃) δ 12.69 (s, 1H), 7.16 (d, J = 8.0 Hz, 2H), 7.95 (dd, J = 8.8, 2.0 Hz, 2H), 7.62 (dd, J = 8.8, 1.2 Hz, 1H), 7.50–7.39 (m, 5H), 7.28–7.21 (m, 5H), 6.90 (dd, J = 2.0, 1.6 Hz, 1H), 6.67 (dd, J = 1.6, 1.6 Hz, 1H), 5.08 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 179.2, 164.0, 161.7, 157.4, 156.0, 155.7, 138.1, 136.0, 134.0, 131.0, 130.2, 130.1, 128.7, 128.6, 128.3, 128.7, 128.5, 128.25, 128.24, 109.3, 104.9, 101.1, 74.5; HRMS (EI) found 464.1220 [calcd for C₂₉H₂₀O₆ [M]+ 464.1260].

Preparation of Flavonol 16

To a solution of monobenzoate flavonol 6 (1.327 g, 2.857 mmol) in MeOH (20 mL) was added K₂CO₃ (1.184 g, 8.571 mmol) at room temperature. After being stirred for 16 h at the same temperature, MeOH was evaporated in vacuo. The resulting residue was diluted H₂O and EtOAc, and acidified with 3 N HCl. The layers were separated, and the aqueous layer
was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na$_2$SO$_4$, and concentrated in vacuo. The residue was purified by column chromatography (silica gel; hexanes/EtOAc, 2/1 to 1/1) to afford known 1,3-diphenol 16 ($980.4$ mg, 92%): $^1$H NMR (400 MHz, DMSO-$_d$$_6$) $\delta$ 12.59 (s, 1H), 7.93 (dd, $J = 8.0$, 1.6 Hz, 2H), 7.56-7.49 (m, 3H), 7.33-7.27 (m, 5H), 6.45 (d, $J = 2.0$ Hz, 1H), 6.23 (d, $J = 2.0$ Hz, 1H), 5.05 (s, 2H); $^{13}$C NMR (100 MHz, DMSO-$_d$$_6$) $\delta$ 177.9, 164.2, 161.1, 156.4, 155.6, 137.1, 136.2, 130.8, 129.9, 128.31, 128.24, 128.18, 128.04, 127.94, 104.3, 98.7, 93.8, 73.6; IR (neat) 3183, 2321, 1650, 1164 cm$^{-1}$; HRMS (FAB) m/z: [M + H]$^+$ Calcd for C$_{22}$H$_{17}$O$_5$ 361.1076; Found 361.1072.

**Preparation of THP Ether 17**

To a solution of flavonol 16 (790.8 mg, 2.194 mmol) in CH$_2$Cl$_2$ (20 mL) were added DHP (1 mL, 10.95 mmol) and PPTS (165.4 mg, 0.658 mmol) at room temperature. After being stirred for 10 h at the same temperature, the reaction mixture was quenched saturated aqueous NaHCO$_3$. The layers were separated, and the aqueous layer was extracted with CH$_2$Cl$_2$. The combined organic layers were washed with brine, dried over anhydrous Na$_2$SO$_4$, and concentrated in vacuo. The residue was purified by column chromatography (silica gel; hexanes/EtOAc, 2/1 to 1/1) to afford THP protected Flavonol 17 (800.4 mg, 82%): $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 12.58 (s, 1H), 7.96 (ddd, $J = 6$, 1.6, 0.8 Hz, 2H), 7.47–7.42 (m, 3H), 7.30–7.23 (m, 5H), 6.64 (d, $J = 1.2$ Hz, 1H), 6.49 (d, $J = 2$ Hz, 1H), 5.51 (dd, $J = 3.2$, 2.8 Hz, 1H), 5.07 (s, 2H), 3.85 (ddd, $J = 11.2$, 11.2, 3.2 Hz, 1H), 3.65 (ddd, $J = 11.2$, 3.2, 3.2 Hz, 1H), 2.04–1.95 (m, 1H), 1.91–1.86 (m, 2H), 1.77–1.60 (m, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$
178.9, 162.9, 161.8, 156.7, 138.0, 136.3, 130.8, 130.6, 128.81, 128.77, 128.32, 128.26, 128.21, 106.7, 100.1, 96.5, 94.5, 74.5, 62.3, 30.2, 25.3 18.7; HRMS (EI) found 444.1505 [calcd for C_{27}H_{24}O_{6} (M^+)^{+} 444.1573].

**Preparation of Propargyl Ether 18**

To a suspension of flavonol 17 (499.5 mg, 1.124 mmol) in CH₃CN (20 mL) was added DBU (0.278 mL, 1.686 mmol) at room temperature. The resulting mixture was stirred until turned light red solution (ca. 30 min). The mixture was cooled to 0 °C and CuCl (7.6 mg, 0.056 mmol) and 3-chloro-3-methylbut-1-yne (0.26 mL, 2.248 mmol) were added. After being stirred for 16 h at the same temperature, the reaction mixture was quenched saturated aqueous NH₄Cl. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography (silica gel; hexanes/EtOAc, 5/1 to 3/1) to afford propargyl ether 18 (379.4 mg, 66%, 83% based on the recovered starting material) along with starting material 17 (100.3 mg): \(^1\)H NMR (400 MHz, CDCl₃) δ 7.93 (d, J = 7.6 Hz, 1H), 7.40–7.36 (m, 3H), 7.40–7.36 (m, 8H), 6.85 (d, J = 2 Hz, 1H), 5.50 (s, 1H), 5.06 (s, 2H), 3.88 (ddd, J = 11.2, 9.6, 2.8 Hz, 1H), 3.65 (dd, J = 7.2, 4.0 Hz, 1H), 2.64 (s, 1H), 2.56–1.97 (m, 1H), 1.90 (dd, J = 4.8, 3.2 Hz, 2H), 1.82 (s, 6H), 1.77–1.60 (m, 4H); \(^{13}\)C NMR (100 MHz, CDCl₃) δ 173.8, 160.3, 158.0, 156.8, 153.7, 140.0, 136.8, 131.0, 130.1, 128.8, 128.5, 128.1, 128.0, 127.8, 113.3, 106.7, 98.4, 96.7, 86.4, 74.7, 74.2, 74.2, 62.4, 30.3, 29.4, 29.3, 25.23, 18.8; HRMS (EI) found 510.2025 [calcd for C_{32}H_{30}O_{6} (M^+)^{+} 510.2042].
Preparation of Phenol 5

To a solution of flavonol 18 (315.5 mg, 0.626 mmol) in EtOH/THF (1:1, total 40 mL) was added PTSA (19 mg, 0.01 mmol) at room temperature. After being stirred for 12 h at the same temperature, the reaction mixture was quenched saturated aqueous NaHCO₃ and diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography (silica gel; hexanes/EtOAc, 2/1 to 1/1) to afford Flavonol 5 (258.2 mg, 97%): ¹H NMR (400 MHz, DMSO) δ 7.91 (dd, J = 4.4, 3.2 Hz, 2H), 7.47 (dd, J = 3.2, 1.6 Hz, 3H), 7.27 (dd, J = 4.8, 4.4 Hz, 5H), 6.98 (s, 1H), 6.61 (s, 1H), 5.73 (s, 1H), 4.97 (s, 2H), 3.72 (s, 1H), 1.70 (s, 6H); ¹³C NMR (100 MHz, DMSO) δ 172.1, 161.5, 157.7, 156.2, 152.3, 139.1, 136.7, 130.3, 130.2, 128.3, 128.1, 128.00, 127.98, 127.8, 110.7, 105.4, 97.4, 85.9, 77.0, 73.7, 73.0, 54.9, 29.0; HRMS (EI) found 426.1433 [calcd for C₂₇H₂₂O₅ (M⁺) 426.1467].

Preparation of Tricyclic Compound 14

A solution of aryl propargyl ether 5 (252.2 mg, 0.605 mmol) in diethylaniline (20 mL) was stirred at 270 ºC for 4 h. The reaction mixture was concentrated in vacuo and purified by
column chromatography (silica gel; hexanes/EtOAc, 10/1 to 5/1) to afford Claisen adduct 14 (240.8 mg, 93%): $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 12.9 (s, 1H), 7.93 (d, $J = 6.8$ Hz, 2H), 7.47-7.40 (m, 3H), 7.29–7.23 (m, 5H), 6.73 (d, $J = 9.6$ Hz, 1H), 6.35 (s, 1H), 5.62 (d, $J = 11.2$ Hz, 1H), 5.06 (s, 2H), 1.47 (s, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 178.9, 159.4, 156.5, 156.20, 156.18, 137.8, 136.3, 130.7, 130.6, 128.8, 128.7, 128.3, 128.2, 115.5, 106.0, 105.2, 94.9, 78.1, 74.5, 28.5; HRMS (FAB) found 426.1426 [calcd for C$_{27}$H$_{22}$O$_5$ (M$^+$) 426.1467].

**Preparation of Macakurzin C (3)**

To a cooled solution (0 °C) of 14 (240.8 mg, 0.565 mmol) in CH$_2$Cl$_2$ (10 mL) was added BCl$_3$ (1.2 mL, 1.0 M solution in heptane, 1.2 mmol) and the resulting mixture was stirred for 2 h at the same temperature before quenched with H$_2$O (100 mL) and diluted with EtOAc (50 mL). The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na$_2$SO$_4$, and concentrated in vacuo. The residue was purified by column chromatography (silica gel; hexanes/EtOAc, 4/1 to 2/1) to afford macakurzin C (3) (157.7 mg, 83%): $^1$H NMR (400 MHz, DMSO) $\delta$ 12.75 (s, 1H), 9.78 (s, 1H), 8.15(ddd, $J = 6.8$, 3.6, 1.6 Hz, 2H), 7.57-7.47 (m, 3H), 6.61 (d, $J = 10$ Hz, 1H), 6.56 (s, 1H), 5.80 (d, $J = 10.4$ Hz, 1H), 1.43 (s, 6H); $^{13}$C NMR (100 MHz, DMSO) $\delta$ 176.2, 158.5, 155.2, 154.5, 146.0, 137.1, 130.7, 129.9, 128.8, 128.4, 127.4, 114.3, 104.1, 104.0, 94.6, 77.9, 27.9; HRMS (FAB) found 336.0954 [calcd for C$_{20}$H$_{16}$O$_5$ (M$^+$) 336.0998].

**References**

400 MHz $^1$H NMR
CDCl$_3$
$^{1}$H NMR, 400 MHz, DMSO-d$_6$
400 MHz $^1$H NMR
CDCl$_3$
100 MHz $^{13}$C NMR
CDCl$_3$
Macakurzin C (3)
400 MHz $^1$H NMR
DMSO-$d_6$
Macakurzin C (3)
100 MHz $^{13}$C NMR
DMSO-d$_6$