

Synthesis of the pyridone analogues of territrem B

Yinghua Yang*, Lianli Sun, Shengyi Dong, Xiaoyu Wang, Leixiang Yang, Xiumei Wu, Hua Bai and Yu Zhao*

Selected spectral data

9a: Yield: 70%. White solid. M.p. 79–80 °C. R_f (petroleum ether (PET)/CH₃CO₂CH₂CH₃ (AcOEt) 9 : 1) 0.60; ¹H NMR (400 MHz, CDCl₃): 3.89 (s, 3H, MeO–C(3'')), 4.10 (s, 3H, MeO–C(2)), 4.65 (s, 2H, CH₂Cl–C(3)), 6.95 (d, 1H, $J = 8.4$, H–C(4'')), 7.34–7.39 (m, 2H, H–C(5), (5'')), 7.59–7.64 (m, 2H, H–C(2''), (6'')), 7.70 (d, 1H, $J = 8.4$, H–C(4)). ESI-MS: 264 ([M + 1]⁺). Calc. for C₁₄H₁₄ClNO₂, $M = 263.07$.

9b: Yield: 76%. white solid. M.p. 82–84 °C. R_f (PET/AcOEt 9 : 1) 0.65; ¹H NMR (400 MHz, CDCl₃): 3.87 (s, 3H, MeO–C(4'')), 4.10 (s, 3H, MeO–C(2)), 4.64 (s, 2H, CH₂Cl–C(3)), 6.98 (d, 2H, $J = 8.4$, H–C(3''), (5'')), 7.28 (d, 1H, $J = 8.0$, H–C(5)), 7.66 (d, 1H, $J = 8.0$, H–C(4)), 8.00 (d, 2H, $J = 8.4$, H–C(2''), (6'')). ¹³C NMR (100 MHz, CDCl₃): 41.1 (CH₂Cl–C(3)), 53.4 (MeO–C(4'')); 55.3 (MeO–C(2)), 111.8 (C(5)), 114.0 (C(3''), (5'')), 117.5 (C(3)), 128.0 (C(2''), (6'')), 131.2 (C(1'')), 139.4 (C(4)), 154.6 (C(6)), 160.5 (C(4'')), 160.9 (C(2)). ESI-MS: 264 ([M + 1]⁺). Calc. for C₁₄H₁₄ClNO₂, $M = 263.07$.

10a: Yield: 68%. White solid. M.p. 136–137 °C (CH₃CN). R_f (PET/AcOEt 3 : 1) 0.31; ¹H-NMR (400 MHz, CDCl₃): 2.52–2.57 (m, 8H, H–C(3'), (4'), (6'), (7')), 3.80 (s, 2H, H–C(1')), 3.87 (s, 3H, MeO–C(4'')), 4.03 (s, 3H, MeO–C(2)), 4.24 (s, 1H, H–C(8')), 6.98 (d, 1H, $J = 7.6$, H–C(5)), 7.15–7.30 (m, 8H, H–C(10'), (12'), (14'), (16'), (18'), (20'), (3''), (5'')), 7.39 (m, 4H, H–C(11'), (13'), (17'), (19')), 7.66 (d, 1H, $J = 7.6$, H–C(4)), 8.00 (d, 2H, $J = 8.6$, H–C(2''), (6'')). ESI-MS: 480 ([M + 1]⁺). Calc. for C₃₁H₃₃N₃O₂, $M = 479.26$.

10b: Yield: 59%. Yellow solid. M.p. 75–76 °C (EtOH). R_f (PET/AcOEt 3 : 1) 0.35; ¹H-NMR (400 MHz, CD₃COCD₃): 2.43 (brs, 8H, H–C(3'), (4'), (6'), (7')), 3.45 (s, 2H, H–C(8')), 3.47 (s, 2H, H–C(1')), 3.83 (s, 3H, MeO–C(4'')), 3.99 (s, 3H, MeO–C(2)), 6.86–7.07 (m, 4H, H–C(11'), (13'), (3''), (5'')), 7.32–7.34 (m, 2H, H–C(10'), (14')), 7.41 (d, 1H, $J = 7.6$, H–C(5)), 7.70 (d, 1H, $J = 7.6$, H–C(4)), 8.06 (d, 2H, $J = 6.4$, H–C(2''), (6'')). ESI-MS: 422 ([M + 1]⁺). Calc. for C₂₅H₂₈FN₃O₂, $M = 421.22$.

10c: Yield: 76%. White solid. M.p. 85–86 °C (EtOH). R_f (PET/AcOEt 3 : 1) 0.37; ¹H-NMR (400 MHz, CDCl₃): 2.70 (brs, 4H, H–C(3'), (7')), 3.15 (m, 4H, H–C(4'), (6'')), 3.62 (s, 2H, H–C(1')), 3.85 (s, 3H, MeO–C(4'')), 4.06 (s, 3H, MeO–C(2)), 6.86–6.90 (m, 2H, H–C(9'), (13'')), 6.94–6.99 (m, 4H, H–C(10'), (12'), (3''), (5'')), 7.29 (d, 1H, $J = 7.6$, H–C(5)), 7.69 (d, 1H, $J = 7.6$, H–C(4)), 8.01 (d, 2H, $J = 8.8$, H–C(2''), (6'')). ESI-MS: 408 ([M + 1]⁺). Calc. for C₂₄H₂₆FN₃O₂, $M = 407.20$.

10d: Yield: 58%. White solid. M.p. 89–90 °C (EtOH). R_f (PET/AcOEt 2 : 1) 0.31; ¹H-NMR (400 MHz, CDCl₃):

1.26 (t, 3H, $J = 7.2$, H-C(11')), 2.48 (brs, 4H, H-C(3'), (7')), 3.51 (brs, 4H, H-C(4'), (6')), 3.57 (s, 2H, H-C(1')), 3.87 (s, 3H, MeO-C(4'')), 4.04 (s, 3H, MeO-C(2)), 4.13 (q, 2H, $J = 7.2$, H-C(10')), 6.98 (d, 2H, $J = 8.8$, H-C(3''), (5'')), 7.28 (d, 1H, $J = 7.6$, H-C(5)), 7.64 (d, 1H, $J = 7.6$, H-C(4)), 8.01 (d, 2H, $J = 8.8$, H-C(2''), (6'')). ESI-MS: 386 ($[M + 1]^+$). Calc. for $C_{21}H_{27}N_3O_4$. $M = 385.20$.

10e: Yield: 69%. Yellow solid. M.p. 89–90 °C (EtOH). R_f (PET/AcOEt 3 : 1) 0.33; 1H -NMR (400 MHz, $CDCl_3$): 2.73 (brs, 4H, H-C(3'), (7')), 3.21 (brs, 4H, H-C(4'), (6')), 3.67 (s, 2H, H-C(1')), 3.87 (s, 3H, MeO-C(4'')), 4.05 (s, 3H, MeO-C(2)), 6.73 (dd, 1H, $J = 2.8, 8.8$, H-C(13')), 6.95–7.00 (m, 3H, H-C(9'), (3''), (5'')), 7.25–7.31 (m, 2H, H-C(5), (12')), 7.68 (d, 1H, $J = 7.6$, H-C(4)), 8.01 (d, 2H, $J = 8.8$, H-C(2''), (6'')). ESI-MS: 458 ($[M + 1]^+$). Calc. for $C_{24}H_{25}Cl_2N_3O_2$. $M = 457.13$.

10f: Yield: 78%. White solid. M.p. 74–75 °C (EtOH). R_f (PET/AcOEt 3 : 1) 0.36; 1H -NMR (400 MHz, CD_3COCD_3): 2.45 (brs, 4H, H-C(3'), (7')), 2.87 (brs, 4H, H-C(4'), (6')), 3.47 (d, 4H, H-C(1'), (8')), 3.83 (s, 3H, MeO-C(4'')), 3.99 (s, 3H, MeO-C(2)), 6.99 (d, 2H, $J = 8.8$, H-C(3''), (5'')), 7.21–7.32 (m, 5H, H-C(10'), (11'), (12'), (13'), (14')), 7.42 (d, 1H, $J = 7.6$, H-C(5)), 7.71 (d, 1H, $J = 7.6$, H-C(4)), 8.06 (d, 2H, $J = 8.8$, H-C(2''), (6'')). ESI-MS: 404 ($[M + 1]^+$). Calc. for $C_{25}H_{29}N_3O_2$. $M = 403.23$.

10g: Yield: 56%. Yellow solid. M.p. 39–41 °C (EtOH). R_f (PET/AcOEt 3 : 1) 0.45; 1H -NMR (400 MHz, CD_3COCD_3): 1.01 (t, 3H, $J = 7.2$, H-C(9')), 2.35 (q, 2H, $J = 7.2$, H-C(8')), 2.46 (brs, 6H, H-C(3'), (4'), (6'), (7')), 2.86 (brs, 2H, H-C(4'), (6')), 3.46 (s, 2H, H-C(1')), 3.83 (s, 3H, MeO-C(4'')), 3.99 (s, 3H, MeO-C(2)), 7.00 (d, 2H, $J = 8.8$, H-C(3''), (5'')), 7.42 (d, 1H, $J = 7.6$, H-C(5)), 7.71 (d, 1H, $J = 7.6$, H-C(4)), 8.06 (d, 2H, $J = 8.8$, H-C(2''), (6'')). ESI-MS: 342 ($[M + 1]^+$). Calc. for $C_{20}H_{27}N_3O_2$. $M = 341.21$.

10i: Yield: 78%. White solid. M.p. 79–80 °C (EtOH). R_f (PET/AcOEt 3 : 1) 0.35; 1H -NMR (400 MHz, $CDCl_3$): 1.08–1.90 (m, 10H, H-C(9'), (10'), (11'), (12'), (13')), 2.18–2.62 (m, 9H, H-C(3'), (4'), (6'), (7'), (8')), 3.55 (s, 2H, H-C(1')), 3.86 (s, 3H, MeO-C(4'')), 4.03 (s, 3H, MeO-C(2)), 6.97 (d, 2H, $J = 8.8$, H-C(3''), (5'')), 7.26 (d, 1H, $J = 7.2$, H-C(5)), 7.63 (d, 1H, $J = 7.2$, H-C(4)), 7.99 (d, 2H, $J = 8.8$, H-C(2''), (6'')). ESI-MS: 396 ($[M + 1]^+$). Calc. for $C_{24}H_{33}N_3O_2$. $M = 395.26$.

10k: Yield: 70%. colorless oil. R_f (PET/AcOEt 3 : 1) 0.33; 1H -NMR (400 MHz, $CDCl_3$): 2.70 (brs, 4H, H-C(3'), (7')), 3.15 (brs, 4H, H-C(4'), (6')), 3.62 (s, 2H, H-C(1')), 3.89 (s, 3H, MeO-C(3'')), 4.07 (s, 3H, MeO-C(2)), 6.86–6.90 (m, 2H, H-C(9'), (13')), 6.93–6.98 (m, 3H, H-C(10'), (12'), (5)), 7.35–7.37 (m, 2H, H-C(4''), (5'')), 7.61 (d, 1H, $J = 7.6$, H-C(4)), 7.66 (s, 1H, H-C(2'')), 7.72 (d, 1H, $J = 7.2$, H-C(6'')). ESI-MS: 408 ($[M + 1]^+$). Calc. for $C_{24}H_{26}FN_3O_2$. $M = 407.20$.

3a: Yield: 92.7%. White solid. M.p. 146–148 °C (CH_3CN). R_f (CH_2Cl_2 /MeOH 20 : 1) 0.28; 1H -NMR (400 MHz, $CDCl_3$): 2.39–2.58 (m, 8H, H-C(3'), (4'), (6'), (7')), 3.56 (s, 2H, H-C(1')), 3.85 (s, 3H, MeO-C(4'')), 4.22 (d, 1H, $J = 2.8$, H-C(8')), 6.53 (brd, 1H, $J = 7.2$, H-C(5)), 6.97 (d, 2H, $J = 8.8$, H-C(12'), (18')), 7.15–7.28 (m, 6H, H-C(10'), (14'), (16'), (20'), (3''), (5'')), 7.41 (m, 4H, H-C(11'), (13'), (17'), (19')), 7.48 (d, 1H, $J = 7.2$, H-C(4)),

7.67 (d, 2H, $J = 8.0$, H-C(2''), (6'')). ESI-MS: 466 ($[M + 1]^+$). Calc. for $C_{30}H_{31}N_3O_2$. $M = 465.24$.

3b: Yield: 91.5%. Pale yellow solid. M.p. 148–149 °C (CH₃CN). R_f (CH₂Cl₂/MeOH 20 : 1) 0.46; ¹H-NMR (400 MHz, CDCl₃): 2.49–2.58 (brd, 8H, H-C(3'), (4'), (6'), (7')), 3.48 (s, 2H, H-C(1')), 3.55 (s, 2H, H-C(8')), 3.86 (s, 3H, MeO-C(4'')), 6.53 (d, 1H, $J = 7.2$, H-C(5)), 6.99 (m, 4H, H-C(11'), (13'), (3''), (5'')), 7.26–7.29 (m, 2H, H-C(10'), (14')), 7.49 (d, 1H, $J = 7.2$, H-C(4)), 7.70 (d, 2H, $J = 8.4$, H-C(2''), (6'')). ESI-MS: 408 ($[M + 1]^+$). Calc. for $C_{24}H_{26}FN_3O_2$. $M = 407.20$.

3c: Yield: 93%. Pale yellow solid. M.p. 143–144 °C (CH₃CN). R_f (CH₂Cl₂/MeOH 20 : 1) 0.42; ¹H-NMR (400 MHz, CDCl₃): 2.74 (brs, 4H, H-C(3'), (7')), 3.15 (brs, 4H, H-C(4'), (6')), 3.60 (s, 2H, H-C(1')), 3.86 (s, 3H, MeO-C(4'')), 6.54 (d, 1H, $J = 7.2$, H-C(5)), 6.87 (m, 2H, H-C(9'), (13')), 6.95–7.02 (m, 4H, H-C(10'), (12'), (3''), (5'')), 7.56 (d, 1H, $J = 7.2$, H-C(4)), 7.66 (d, 2H, $J = 8.8$, H-C(2''), (6'')). ESI-MS: 394 ($[M + 1]^+$). Calc. for $C_{23}H_{24}FN_3O_2$. $M = 393.19$.

3d: Yield: 93%. Pale yellow solid. M.p. 111–112 °C (CH₃CN). R_f (CH₂Cl₂/MeOH 30 : 1) 0.46; ¹H-NMR (400 MHz, CDCl₃): 1.26 (t, 3H, $J = 7.2$, H-C(11')), 2.50 (brs, 4H, H-C(3'), (7')), 3.50 (s, 2H, H-C(1')), 3.53 (brs, 4H, H-C(4'), (6')), 3.87 (s, 3H, MeO-C(4'')), 4.13 (q, 2H, $J = 7.2$, H-C(10')), 6.49 (d, 1H, $J = 7.2$, H-C(5)), 6.99 (d, 2H, $J = 8.8$, H-C(3''), (5'')), 7.52 (d, 1H, $J = 7.2$, H-C(4)), 7.67 (d, 2H, $J = 8.8$, H-C(2''), (6'')). ESI-MS: 372 ($[M + 1]^+$). Calc. for $C_{20}H_{25}N_3O_4$. $M = 371.18$.

3e: Yield: 95%. Pale yellow solid. M.p. 141–142 °C (CH₃CN). R_f (CH₂Cl₂/MeOH 20 : 1) 0.41; ¹H-NMR (400 MHz, CDCl₃): 2.70 (brs, 4H, H-C(3'), (7')), 3.19 (brs, 4H, H-C(4'), (6')), 3.58 (s, 2H, H-C(1')), 3.85 (s, 3H, MeO-C(4'')), 6.50 (d, 1H, $J = 7.2$, H-C(5)), 6.73 (dd, 1H, $J = 2.8, 8.8$, H-C(13')), 6.94 (d, 1H, $J = 2.8$, H-C(9')), 6.99 (d, 2H, $J = 8.4$, H-C(3''), (5'')), 7.26 (d, 1H, $J = 8.8$, H-C(12')), 7.57 (d, 1H, $J = 7.2$, H-C(4)), 7.68 (d, 2H, $J = 8.4$, H-C(2''), (6'')). ESI-MS: 445 ($[M + 1]^+$). Calc. for $C_{23}H_{23}Cl_2N_3O_2$. $M = 443.12$.

3f: Yield: 93.5%. Pale yellow solid. M.p. 139–140 °C (CH₃CN). R_f (CH₂Cl₂/MeOH 20 : 1) 0.44; ¹H-NMR (400 MHz, CD₃COCD₃): 2.57 (brs, 4H, H-C(3'), (7')), 2.67 (brs, 4H, H-C(4'), (6')), 3.54 (s, 2H, H-C(8')), 3.62 (s, 2H, H-1'), 3.86 (s, 3H, MeO-C(4'')), 6.57 (d, 1H, $J = 7.2$, H-C(5)), 6.99 (d, 2H, $J = 8.8$, H-C(3''), (5'')), 7.23–7.32 (m, 5H, H-C(10'), (11'), (12'), (13'), (14')), 7.56 (d, 1H, $J = 7.2$, H-C(4)), 7.65 (d, 2H, $J = 8.8$, H-C(2''), (6'')). ESI-MS: 390 ($[M + 1]^+$). Calc. for $C_{24}H_{27}N_3O_2$. $M = 389.21$.

3g: Yield: 83.5%. Pale yellow solid. M.p. 101–103 °C (CH₃CN). R_f (CH₂Cl₂/MeOH 20 : 1) 0.28; ¹H-NMR (400 MHz, CD₃COCD₃): 1.08 (t, 3H, $J = 7.2$, H-C(9')), 2.42 (q, 2H, $J = 7.2$, H-C(8')), 2.46–2.62 (m, 8H, H-C(3'), (4'), (6'), (7')), 3.56 (s, 2H, H-C(1')), 3.86 (s, 3H, MeO-C(4'')), 6.55 (d, 1H, $J = 6.8$, H-C(5)), 6.98 (d, 2H, $J = 8.0$, H-C(3''), (5'')), 7.49 (d, 1H, $J = 6.8$, H-C(4)), 7.69 (d, 2H, $J = 8.0$, H-C(2''), (6'')). ESI-MS: 328 ($[M + 1]^+$). Calc. for $C_{19}H_{25}N_3O_2$. $M = 327.19$.