Supplementary Information

Synthesis of New Tandospirone Analogues Carrying 1-(3-(Trifluoromethyl)phenyl)piperazine

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List of contents page	Page
Title, author's name and address	1
Experimental Section	4
Spectral data for Products	4
¹ H NMR spectrum of 4	9
APT spectrum of 4	10
LC-MS spectrum of 4	11
¹ H NMR spectrum of 5a	12
APT spectrum of 5a	13
LC-MS spectrum of 5a	14
¹ H NMR spectrum of 5b	15
APT spectrum of 5b	16
LC-MS spectrum of 5b	17
¹ H NMR spectrum of 5c	18
APT spectrum of 5c	19
LC-MS spectrum of 5c	20
¹ H NMR spectrum of 5d	21
APT spectrum of 5d	22
LC-MS spectrum of 5d	23
¹ H NMR spectrum of 6	24
APT spectrum of 6	25
¹ H NMR spectrum of 7a	26
APT spectrum of 7a	27
¹ H NMR spectrum of 7b	28

List of contents page	Page
APT spectrum of 7b	29
¹ H NMR spectrum of 7c	30
APT spectrum of 7c	31
¹ H NMR spectrum of 7d	32
APT spectrum of 7d	33
¹ H NMR spectrum of 8	34
APT spectrum of 8	35
¹ H NMR spectrum of 9	36
APT spectrum of 9	37
LC-MS spectrum of 9	38
¹ H NMR spectrum of 10	39
APT spectrum of 10	40
LC-MS spectrum of 10	41

EXPERIMENTAL

N-{4-[3-(Trifluoromethyl)phenyl]piperazin-1-yl}butyl-5-(4-chloro-phenyl)bicyclo[2.2.1]heptane-2-endo,3-endo-dicarboximide (**5b**)

Yield: 509 mg (91 %). White crystal. M.p. 145-147 °C. R_f (CH₂Cl₂/MeOH 20:1) 0.61. IR (ATR): ν 3055, 2962, 2938, 2885, 2859, 2816, 2778, 1769, 1690, 1608, 1589, 1493, 1443, 1111, 730, 822 cm⁻¹. ¹H-NMR (500 MHz, CDCl₃): δ 1.46–1.52 (m, 3H); 1.56–1.62 (m, 3H); 1.67–1.72 (m, 1H); 1.74 (s, 1H); 2.35 (t, J = 7.3 Hz, 2H); 2.50 (t, J = 5.0 Hz, 4H); 2.68 (t, J = 6.1 Hz, 1H); 2.76 (d, J = 5.3 Hz, 1H); 2.83 (t, J = 4.2 Hz, 1H); 3.04–3.07 (m, 1H); 3.10 (s, 1H); 3.12 (t, J = 4.6 Hz, 4H); 3.48 (t, J = 6.9 Hz, 2H); 6.94 (dd, J = 2.3, 8.4 Hz, 1H); 6.98 (d, J = 7.4 Hz, 1H); 7.01 (s, 1H); 7.02 (d, J = 8.5 Hz, 2H); 7.17 (d, J = 8.5 Hz, 2H); 7.26 (t, J = 7.9 Hz, 1H) ppm. ¹³C NMR (125 MHz, CDCl₃): δ 24.5; 26.2; 32.7; 38.7; 39.6; 39.8; 41.6; 46.02; 48.4; 48.8; 49.0; 53.2 (x2); 58.1 (x2); 112.3; 116.0; 118.8; 128.6; 128.8 (x2); 129.7 (x2); 131.5; 131.7; 132.3; 143.0; 151.6; 178.1; 178.2 ppm. LC-MS: m/z 560.00 (M⁺). Anal. Calcd for C₃₀H₃₃ClF₃N₃O₂: C, 64.34; H, 5.94; N, 7.50%. Found: C, 64.58; H, 5.81; N, 7.39 %.

N-{4-[3-(Trifluoromethyl)phenyl]piperazin-1-yl}butyl-5-(6-chloro-3-pyridyl)bicyclo[2.2.1]heptane-2-endo,3-endo-dicarboximide (**5c**)

Yield: 403 mg (72 %). Colorless oil. R_f (CH₂Cl₂/MeOH 20:1) 0.57. IR (ATR): ν 3064, 2945, 2877, 2819, 2779, 1766, 1694, 1668, 1117, 787, 696 cm⁻¹. ¹H-NMR (500 MHz, CDCl₃): δ 1.49–1.55 (m, 3H); 1.58–1.77 (m, 4H); 2.39 (s, 1H); 2.43 (brs, 2H); 2.59 (brs, 4H); 2.77 (s, 1H); 2.87 (brs, 2H); 2.94–3.02 (m, 1H); 3.16–3.23 (m, 5H); 3.38 (brs, 2H); 7.10 (s, 2H); 7.23 (dd, J = 3.5, 7.9 Hz, 1H); 7.32–7.33 (m, 2H); 7.45 (dd, J = 4.8, 7.6 Hz, 1H); 8.22 (s, 1H) ppm. ¹³C NMR (125 MHz, CDCl₃): δ 24.2; 25.9; 32.6; 38.5; 39.3; 39.6; 44.9; 45.7; 48.0; 48.5 (x2); 48.6; 52.9 (x2); 57.8; 112.0; 118.6; 123.9; 129.5; 131.2; 134.4; 137.5; 138.7; 148.5; 151.3;

144.5; 151.6; 177.5; 177.6 ppm. LC-MS: m/z 560.90 (M^+). Calcd for $C_{29}H_{32}ClF_3N_4O_2$: C, 62.08; H, 5.75; N, 9.99%. Found: C, 61.92; H, 5.84; N, 10.21%.

***N*-{4-[3-(Trifluoromethyl)phenyl]piperazin-1-yl}butyl-5-(2-thienyl)bicyclo[2.2.1]heptane-2-endo,3-endo-dicarboximide (5d)**

Yield: 451 mg (85 %). Colorless oil. R_f ($CH_2Cl_2/MeOH$ 20:1) 0.46. IR (ATR): ν 3069, 2948, 2881, 2818, 2775, 1769, 1695, 1608, 1587, 1496, 1448, 1118, 729, 695 cm^{-1} . 1H -NMR (500 MHz, $CDCl_3$): δ 1.45-1.52 (m, 2H); 1.55-1.59 (m, 4H); 1.78 (d, $J = 7.4$ Hz, 1H); 1.87 (dt, $J = 2.5, 6.8$ Hz, 1H); 2.33 (dt, $J = 1.4, 10.5$ Hz, 2H); 2.50 (t, $J = 5.0$ Hz, 4H); 2.81 (d, $J = 5.3$ Hz, 2H); 2.93 (t, $J = 6.9$ Hz, 1H); 3.03 (dd, $J = 5.5, 9.9$ Hz, 1H); 3.09 (d, $J = 5.4$ Hz, 1H); 3.12 (t, $J = 4.8$ Hz, 4H); 3.48 (t, $J = 6.4$ Hz, 2H); 6.71 (dt, $J = 1.0, 3.4$ Hz, 1H); 6.83 (dd, $J = 3.4, 5.0$ Hz, 1H); 6.94 (dd, $J = 2.4, 8.5$ Hz, 1H); 6.98 (d, $J = 8.0$ Hz, 1H); 7.01 (s, 1H, ArH); 7.05 (dd, $J = 1.4, 5.3$ Hz, 1H); 7.25 (t, $J = 8.0$ Hz, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.2; 25.9; 34.9; 38.0; 38.5; 39.3; 39.7; 47.2; 48.0; 48.4; 48.5 (x2); 52.9 (x2); 57.8; 112.1; 115.7; 118.6; 123.5; 126.8; 129.5 (x2); 131.2; 131.5; 149.3; 151.4; 177.8; 177.9 ppm. LC-MS: m/z 531.60 (M^+). Calcd for $C_{28}H_{32}F_3N_3O_2S$: C, 63.26; H, 6.07; N, 7.90%. Found: C, 62.95; H, 5.88; N, 8.29%.

8-exo-phenyl-2-{4-[3-(trifluoromethyl)phenyl]piperazinylbutyl}-4,7-endomethylene-1H-isoindole (7a)

Yield: 328 mg (55 %). Yellow oil. R_f ($CH_2Cl_2/MeOH$ 10:1) 0.30. IR (ATR): ν 3050, 2943, 2779, 1608, 1495, 1448, 1119, 728, 695 cm^{-1} . 1H -NMR (500 MHz, $CDCl_3$): δ 1.39 (d, $J = 9.4$ Hz, 1H); 1.54-1.69 (m, 5H); 2.17-2.24 (m, 2H); 2.28 (brs, 1H); 2.34 (brd, $J = 4.4$, 1H); 2.43-2.48 (m, 5H); 2.52-2.55 (m, 2H); 2.58 (t, $J = 5.0$ Hz, 4H); 2.87 (d, $J = 9.8$ Hz, 1H); 2.97 (d, $J = 10.1$ Hz, 1H); 3.13-3.15 (m, 1H); 3.18 (t, $J = 5.0$ Hz, 4H); 3.34-3.36 (m, 1H); 7.01 (d, $J = 7.6$ Hz, 1H); 7.05-7.07 (m, 2H); 7.15 (t, $J = 7.2$ Hz, 1H); 7.23-7.29 (m, 4H); 7.33 (t, $J = 7.6$

Hz, 1H) ppm. ^{13}C NMR (125 MHz, CDCl_3): δ 24.4; 26.3; 32.2; 39.8; 40.2; 41.3; 43.3; 44.4; 47.2; 48.4 (x2); 53.0 (x2); 54.8; 55.2; 55.4; 58.4; 112.1; 115.7; 118.5; 125.2; 127.3 (x2); 128.2 (x2); 129.5; 132.5; 147.5; 151.3 (x2) ppm. GC-MS: m/z 497 (M^+). $\text{C}_{30}\text{H}_{38}\text{F}_3\text{N}_3$: C, 72.41; H, 7.70; N, 8.44%. Found: C, 72.55; H, 7.59; N, 8.71%.

8-exo-(4-chloro-phenyl)-2-{4-[3-(trifluoromethyl)phenyl]piperazinylbutyl}-4,7-endomethylene-1H-isoindole (7b)

Yield: 239 mg (45 %). Yellow oil. R_f ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 10:1) 0.18. IR (ATR): ν 2943, 2780, 1608, 1492, 1447, 1119, 783, 729, 694 cm^{-1} . ^1H -NMR (500 MHz, CDCl_3): δ 1.31 (d, $J = 9.4$, 1H); 1.47–1.59 (m, 5H); 2.11–2.17 (m, 4H); 2.35–2.42 (m, 5H); 2.48 (t, $J = 5.0$ Hz, 4H); 2.81 (d, $J = 9.8$ Hz, 1H); 2.93 (d, $J = 10.1$ Hz, 1H); 3.05 (t, $J = 5.0$ Hz, 5H); 3.20 (t, $J = 5.0$ Hz, 2H); 3.22–3.25 (m, 1H); 6.95–7.02 (m, 3H); 7.10–7.15 (m, 4H); 7.26 (d, $J = 7.6$ Hz, 1H) ppm. ^{13}C NMR (125 MHz, CDCl_3): δ 25.2 (x2); 27.3; 32.91; 40.5; 31.1; 42.6; 44.6 (x2); 45.8; 54.1 (x2); 55.8; 56.2; 56.5; 59.5 (x2); 112.8; 116.7; 120.2; 129.2 (x2); 130.0 (x2); 130.9; 132.1; 132.3; 132.5; 147.5; 152.9 ppm. LC-MS: m/z 532.00 (M^+). $\text{C}_{30}\text{H}_{37}\text{ClF}_3\text{N}_3$: C, 67.72; H, 7.01; N, 7.90%. Found: C, 67.99; H, 6.80; N, 7.74%.

8-exo-(6-chloro-3-pyridyl)-2-{4-[3-(trifluoromethyl)phenyl]piperazinylbutyl}-4,7-endomethylene-1H-isoindole (7c)

Yield: 330 mg (62 %). Yellow oil. R_f ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 10:1) 0.25. IR (ATR): ν 2948, 2775, 1608, 1584, 1495, 1454, 1102, 778, 729, 695 cm^{-1} . ^1H -NMR (500 MHz, CDCl_3): δ 1.41–1.57 (m, 6H); 2.17–2.43 (m, 6H); 2.56 (t, $J = 5.0$ Hz, 4H); 2.61–2.67 (m, 1H); 2.89 (d, $J = 9.8$ Hz, 1H); 3.01 (d, $J = 9.8$ Hz, 1H); 3.12 (t, $J = 5.0$ Hz, 2H); 3.18 (brs, 6H); 3.30–3.32 (m, 2H); 6.97 (d, $J = 7.2$ Hz, 1H); 7.01–7.05 (m, 2H); 7.27 (t, $J = 8.2$ Hz, 2H); 7.63 (dd, $J = 2.2, 8.2$ Hz, 1H); 8.15 (s, 1H) ppm. ^{13}C NMR (125 MHz, CDCl_3): δ 25.2; 27.0; 30.8; 32.9; 38.7; 40.8; 42.5; 44.5; 45.7; 46.9; 54.1; 55.6; 56.0; 56.5; 58.3; 59.3; 68.6; 113.0; 116.8; 120.3; 125.2;

125.6; 130.9; 132.2; 139.9; 143.6; 149.2; 151.2; 152.8 ppm. LC-MS: m/z 533.00 (M^+). $C_{29}H_{36}ClF_3N_4$: C, 65.34; H, 6.81; N, 10.51%. Found: C, 65.54; H, 7.09; N, 10.69%.

8-exo-(2-thienyl)-2-{4-[3-(trifluoromethyl)phenyl]piperazinylbutyl}-4,7-endomethylene-1H-isoindole (7d)

Yield: 186 mg (37 %). Yellow oil. R_f ($CH_2Cl_2/MeOH$ 10:1) 0.28. IR (ATR): ν 3020, 2943, 2779, 1608, 1587, 1495, 1447, 1119, 729, 691 cm^{-1} . 1H -NMR (500 MHz, $CDCl_3$): δ 1.36 (d, J = 9.8 Hz, 1H); 1.49–1.61 (m, 4H); 1.67 (d, J = 9.8 Hz, 1H); 2.20–2.26 (m, 2H); 2.35–2.39 (m, 6H); 2.42–2.49 (m, 1H); 2.53 (t, J = 5.0 Hz, 4H); 2.55–2.57 (m, 2H); 2.78 (d, J = 9.4 Hz, 1H); 2.88 (d, J = 9.8 Hz, 1H); 3.06–3.10 (m, 1H); 3.13 (t, J = 4.7 Hz, 4H); 3.44–3.46 (m, 1H); 6.70 (d, J = 3.5 Hz, 1H); 6.84 (dd, J = 3.5, 5.0 Hz, 1H); 6.94–7.03 (m, 4H); 7.26 (t, J = 7.9 Hz, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.4; 34.3; 36.5; 42.9 (x2); 44.1 (x2); 48.4 (x4); 53.0 (x4); 55.1; 58.4; 112.1; 115.7; 118.5; 122.4; 126.5; 129.5 (x2); 132.0; 143.57; 147.6; 151.3 ppm. LC-MS: m/z 503.60 (M^+). $C_{28}H_{36}F_3N_3S$: C, 66.77; H, 7.20; N, 8.34%. Found: C, 66.99; H, 7.03; N, 8.19%.

(8): In a sealed tube, a mixture of **2** (163 mg, 1 mmol), *N*-methylglycine (89 mg, 1 mmol), and ninhydrine (178.14 mg, 1 mmol) in EtOH/1,4-dioxane (1:1, 8 ml) was heated 65 °C for 24 h. After cooling to room temperature, the organic phase concentrated and the residue purified by column chromatography using $CH_2Cl_2/MeOH$ (20:1) as the eluent to give **8**. Yield: 227.5 mg (65 %). Yellow oil. R_f ($CH_2Cl_2/MeOH$ 20:1) 0.82. IR (ATR): ν 3158, 2993, 2953, 2868, 1755, 1696, 1402, 1350, 1121 cm^{-1} . 1H -NMR (500 MHz, $CDCl_3$): δ 1.44 (d, J = 10.4 Hz, 1H); 2.13 (s, 3H); 2.17 (d, J = 7.9 Hz, 1H); 2.54–2.58 (m, 2H); 2.69–2.70 (d, J = 5.0 Hz, 1H); 2.72–2.74 (d, J = 10.4 Hz, 1H); 2.91 (dd, J = 2.2, 9.4 Hz, 1H); 2.97 (dd, J = 5.3, 9.4 Hz, 1H); 3.05 (dd, J = 5.3, 9.4 Hz, 1H); 3.46 (t, J = 9.1 Hz, 1H); 7.80–7.84 (m, 3H); 7.89–7.91 (m, 1H); 8.06 (brs, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 35.7; 39.0; 41.9; 42.7; 45.0; 49.1; 49.6; 50.7; 60.8; 77.8; 123.3; 123.3; 136.4; 136.6; 136.6; 141.9; 177.5; 177.7; 200.5;

203.7 ppm. GC-MS: m/z 350 (M^+). Calcd for $C_{20}H_{18}N_2O_4$: C, 68.56; H, 5.18; N, 8.00%. Found: C, 68.75; H, 4.93; N, 8.31%.

(9): A solution of **8** (350 mg, 1 mmol) and anhydrous K_2CO_3 (276 mg, 2 mmol) in butanone (15 mL) was heated. Then a solution of 1,4-dibromobutane (648 mg, 3 mmol) in butanone (3 mL) was added to the mixture and refluxed for 20 h. After cooling to room temperature, K_2CO_3 was filtered, the organic phase concentrated and the residue purified by column chromatography using $CH_2Cl_2/MeOH$ (20:1) as the eluent to give **9**. Yield: 291 mg (60 %). Yellow oil. R_f ($CH_2Cl_2/MeOH$ 20:1) 0.86. IR (ATR): ν 3060, 2873, 1763, 1736, 1689, 1145 cm^{-1} . 1H -NMR (500 MHz, $CDCl_3$): δ 0.89 (p, $J = 7.2$ Hz, 2H); 1.54 (d, $J = 10.7$ Hz, 1H); 1.82 (p, $J = 7.2$ Hz, 2H); 2.04 (d, $J = 7.5$ Hz, 1H); 2.20 (s, 3H); 2.46 (t, $J = 8.2$ Hz, 1H); 2.64 (d, $J = 5.0$ Hz, 1H); 2.78–2.80 (m, 2H); 2.97 (dd, $J = 2.2, 9.7$ Hz, 1H); 3.02 (dd, $J = 5.7, 9.8$ Hz, 1H); 3.08 (dd, $J = 5.7, 9.8$ Hz, 1H); 3.40–3.47 (m, 4H); 3.50 (t, $J = 9.1$ Hz, 1H); 7.89–7.91 (m, 3H); 7.98–8.00 (m, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 26.4; 29.9; 32.7; 35.7; 37.6; 38.9; 41.8; 42.7; 44.6; 47.7; 48.2; 50.7; 52.3; 60.7; 123.2 (x2); 136.3; 136.5; 139.5; 141.9; 146.5; 177.4; 177.5; 200.1 ppm. LC-MS: m/z 485.00 (M^+). Calcd for $C_{24}H_{25}BrN_2O_4$: C, 59.39; H, 5.19; N, 5.77%. Found: C, 59.05; H, 5.33; N, 5.91%.

4

5a

5d