SUPPLEMENTARY MATERIAL TO

Synthesis and antimicrobial activity of azepine and thiepine derivatives

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ANALYTICAL AND SPECTRAL DATA OF THE COMPOUNDS

(2-Bromo-5-chlorophenyl)methanediyl diacetate. Yield: 1.31 g, 84 %; colourless powder; m.p.: 65–67 °C; IR (ATR, cm –1): 3077, 2995, 1759, 1466, 1435, 1374, 1234, 1202, 1140, 1096, 1068, 1032, 1006, 880; 1H-NMR (500 MHz, CDCl3, δ / ppm): 7.85 (1H, s), 7.54–7.50 (2H, m), 7.27–7.22 (1H, m), 2.16 (6H, s); 13C-NMR (125 MHz, CDCl3, δ / ppm): 168.23, 136.59, 134.30, 133.87, 131.12, 128.15, 120.33, 88.40, 20.66.

2-Bromo-5-chlorobenzaldehyde (19). White solid; m.p.; 72–74 °C; IR (ATR, cm–1): 3351, 3060, 2884, 1890, 1677, 1689, 1578, 1455, 1390, 1283, 1248, 1188, 1125, 1091, 1031, 899, 820; 1H-NMR (500 MHz, CDCl3, δ / ppm): 10.30 (1H, s), 7.88 (1H, d, J = 8.5 Hz), 7.60 (1H, d, J = 8.5 Hz), 7.43 (1H, dd, J = 2.5 Hz, J = 8.0 Hz); 13C-NMR (125 MHz, CDCl3, δ / ppm): 190.49, 135.12, 135.03, 134.61, 129.66, 124.61; GC-MS, RT 23 min (m/z (%)): 218.9 ([M+] (100)), 190.9 (24), 138.0 (14), 110.0 (29), 84.0 (5), 75.0 (47), 50.0 (15).

2-Bromo-5-methoxybenzaldehyde (21). Colourless solid; m.p.: 76–78 °C; IR (ATR, cm–1): 3339, 3095, 3074, 3008, 2981, 2944, 2876, 2845, 2746, 1890, 1677, 1689, 1600, 1570, 1471, 1419, 1384, 1301, 1281, 1243, 1200, 1169, 1136, 1061, 1014, 932, 866, 820; 1H-NMR (500 MHz, CDCl3, δ / ppm): 10.31 (1H, s), 7.52 (1H, d, J = 8.5 Hz), 7.42 (1H, d, J = 3.0 Hz), 7.03 (1H, dd, J = 3.0 Hz, J = 9.0 Hz), 3.84 (3H, s); 13C-NMR (125 MHz, CDCl3, δ / ppm): 191.77, 159.25, 134.54, 133.95, 123.11, 117.95, 112.66, 112.66, 112.66, 124.61; GC-MS, RT 14.92 min (m/z (%)): 213.9 ([M+] (100)), 184.9 (15), 171.9 (14), 156.9 (8), 144.9 (16), 134.0 (10), 106.0 (20), 92.0 (16), 75.0 (18), 63.0 (55), 50.0 (9).

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3-[(Z)-2-(2-Bromo-5-chlorophenyl)ethenyl]-4-chloropyridine (24). Colourless powder; m.p.: 65–67 °C; IR (ATR, cm⁻¹): 3107, 3081, 3054, 2967, 2928, 1754, 1732, 1639, 1572, 1546, 1471, 1449, 1404, 1386, 1309, 1267, 1224, 1204, 1166, 1109, 1087, 1023, 973, 936, 903, 882, 826; ¹H-NMR (500 MHz, CDCl₃, δ / ppm): 8.34 (1H, d, J = 5.5 Hz), 8.15 (1H, s), 7.51 (1H, d, J = 8.5 Hz), 7.34 (1H, d, J = 5.5 Hz), 7.07 (1H, dd, J = 2.0 Hz, J = 9.0 Hz), 6.92–6.89 (1H, m), 6.84 (1H, d, J = 11.5 Hz), 6.79 (1H, d, J = 12.0 Hz); ¹³C-NMR (125 MHz, CDCl₃, δ / ppm): 150.92, 149.18, 143.29, 138.12, 133.99, 133.27, 132.17, 130.97, 130.12, 129.37, 126.03, 124.41, 121.77; (+)ESI-HRMS m/z: calcd. for [M+H⁺]: 327.92899. Found: 327.92792.

3-[(Z)-2-(2-Bromo-5-methoxyphenyl)ethenyl]-4-chloropyridine (25). Colourless oil; IR (ATR, cm⁻¹): 3397, 3007, 2935, 2835, 2356, 1618, 1591, 1567, 1464, 1411, 1346, 1295, 1237, 1174, 1129, 1082, 1052, 1016, 934, 872, 821; ¹H-NMR (500 MHz, CDCl₃, δ / ppm): 8.32 (1H, d, J = 5.5 Hz), 8.21 (1H, s), 7.46 (1H, d, J = 8.5 Hz), 7.34 (1H, d, J = 5.5 Hz), 6.91 (1H, d, J = 12.0 Hz), 6.74 (1H, d, J = 12.0 Hz), 6.69–6.64 (1H, m), 6.46 (1H, d, J = 3.0 Hz), 3.53 (3H, s); ¹³C-NMR (125 MHz, CDCl₃, δ / ppm): 158.59, 150.82, 148.40, 143.60, 136.99, 133.63, 133.58, 131.75, 124.84, 124.42, 115.70, 115.56, 114.33, 55.24; (+)ESI-HRMS m/z: calcd. for [M + H⁺]: 323.97853. Found: 323.97699.

3-[(Z)-2-(2-Bromo-5-fluorophenyl)ethenyl]-4-chloropyridine (26). Colourless powder; m.p.: 109–110 °C; IR (ATR, cm⁻¹): 3403, 3041, 2924, 2850, 1632, 1599, 1574, 1550, 1460, 1413, 1344, 1275, 1211, 1177, 1143, 1102, 1082, 1032, 962, 882, 819; ¹H-NMR (500 MHz, CDCl₃, δ / ppm): 8.33 (1H, d, J = 5.5 Hz), 8.16 (1H, s), 7.54 (1H, dd, J = 5.5 Hz, J = 8.5 Hz), 7.34 (1H, d, J = 5.5 Hz), 6.90–6.75 (3H, m), 6.64 (1H, dd, J = 3.0 Hz, J = 9.0 Hz); ¹³C-NMR (125 MHz, CDCl₃, δ / ppm): 161.53 (d, J = 245.5 Hz), 150.98, 149.17, 143.29, 138.22 (d, J = 8.1 Hz), 134.18 (d, J = 8.1 Hz), 132.46, 131.04, 125.93, 124.41, 118.20, 117.26 (d, J = 23.5), 116.67 (d, J = 22.6 Hz); (+)ESI-HRMS m/z: calcd. for [M + H⁺]: 311.95854. Found: 311.95788.

5-[(3-Pyrrolidin-1-yl)propyl]-5H-pyrido[4,3-b][1]benzazepine (27). Yellow oil; IR (ATR, cm⁻¹): 3340, 3023, 2960, 2874, 2792, 1635, 1577, 1480, 1418, 1393, 1329, 1241, 1184, 1142, 1125, 1058, 912, 830; ¹H-NMR (500 MHz, CDCl₃, δ / ppm): 8.35 (1H, d, J = 5.5 Hz), 8.17 (1H, s), 7.29–7.23 (1H, m), 7.05–6.98 (2H, m), 6.94 (1H, d, J = 8.0 Hz), 6.81 (1H, d, J = 5.5 Hz), 6.74 (1H, d, J = 11.0 Hz), 6.60 (1H, d, J = 11.5 Hz), 3.81–3.73 (2H, m), 2.57–2.50 (2H, m), 2.46–2.37 (4H, m), 1.85–1.77 (2H, m), 1.76–1.69 (4H, m); ¹³C-NMR (125 MHz, CDCl₃, δ / ppm): 158.79, 150.45, 150.08, 149.09, 134.12, 133.59, 129.47, 129.30, 129.19, 129.06, 124.04, 121.08, 114.68, 54.23, 53.89, 48.50, 26.71, 23.37; (+)ESI-HRMS m/z: calcd. for [M + H⁺]: 316.19585. Found: 316.19578.

5-[(3-Pyrrolidin-1-yl)propyl]-5H-dipyrido[4,3-b:3',4'-f]azepine (28). Yellow oil; IR (ATR, cm⁻¹): 3330, 3028, 2958, 2858, 2803, 1732, 1645, 1580, 1483,
1398, 1335, 1248, 1178, 1063, 929, 831; ¹H-NMR (500 MHz, CDCl₃, δ / ppm): 8.39 (2H, d, J = 5.5 Hz), 8.16 (2H, s), 6.76 (2H, d, J = 5.5 Hz), 6.64 (2H, s), 3.82–3.75 (2H, m), 2.58–2.52 (2H, m), 2.47–2.39 (4H, m), 1.86–1.79 (2H, m), 1.78–1.71 (4H, m); ¹³C-NMR (125 MHz, CDCl₃, δ / ppm): 157.08, 150.76, 150.74, 131.19, 128.68, 115.41, 54.24, 53.60, 48.08, 26.42, 23.39; (+)ESI-HRMS m/z: calcd. for [M+H⁺]: 307.19172. Found: 307.19048.

3-(8-Chloro-5H-pyrido[4,3-b][1]benzazepin-5-yl)-N,N-dimethylpropan-1-amine (29). Yellow oil; IR (ATR, cm⁻¹): 3387, 3026, 2944, 2858, 2817, 1682, 1578, 150.42, 147.46, 135.26, 132.73, 130.50, 129.34, 128.98, 128.96, 128.66, 122.27, 114.72, 56.89, 48.29, 45.45, 25.23; (+)ESI-HRMS m/z: calcd. for [M+H⁺]: 314.14185. Found: 314.14336.

3-(8-Methoxy-5H-pyrido[4,3-b][1]benzazepin-5-yl)-N,N-dimethylpropan-1-amine (30). Yellow oil; IR (ATR, cm⁻¹): 3381, 2944, 2858, 2819, 2769, 1674, 1634, 1578, 1480, 1394, 1322, 1276, 1244, 1206, 1038, 972, 938, 876; ¹H-NMR (500 MHz, CDCl₃, δ / ppm): 8.34 (1H, d, J = 5.5 Hz), 8.17 (1H, s), 6.87 (1H, d, J = 9.0 Hz), 6.85–6.78 (2H, m), 6.71 (1H, d, J = 11.5 Hz), 6.62 (1H, d, J = 11.5 Hz), 6.57 (1H, d, J = 3.0 Hz), 3.76 (3H, s), 3.73–3.68 (2H, m), 2.44–2.36 (2H, m), 2.20–2.15 (6H, m), 1.79–1.70 (2H, m); ¹³C-NMR (125 MHz, CDCl₃, δ / ppm): 159.36, 156.12, 150.53, 150.05, 141.73, 134.76, 133.68, 121.96, 114.69, 114.37, 114.08, 57.07, 55.47, 48.32, 45.50, 25.40; (+)ESI-HRMS m/z: calcd. for [M+H⁺]: 310.19139. Found: 310.19142.

[1]Benzothiepin[3,2-c]pyridine (16). Colourless solid; ¹H-NMR (500 MHz, CDCl₃, δ / ppm): 8.49–8.42 (2H, m), 7.49–7.43 (1H, m), 7.38–7.29 (3H, m), 7.28–7.23 (1H, m), 7.13 (1H, d, J = 12.0 Hz), 6.99 (1H, d, J = 12.0 Hz); (+)ESI-HRMS m/z: calcd. for [M+H⁺]: 212.05354. Found: 212.05354.

Pyrido[3′:4′:6,7]thiepin[3,2-c]pyridine (17). Colourless solid; ¹H-NMR (500 MHz, CDCl₃, δ / ppm): 8.51 (2H, d, J = 5.5 Hz), 8.47 (2H, s), 7.32 (2H, s), 7.03 (2H, s). (+)ESI-HRMS m/z: calcd. for [M+H⁺]: 213.04810. Found: 213.04861.

8-Chloro[1]benzothiepin[3,2-c]pyridine (31). Colourless solid; m.p.: 132–136 °C; IR (ATR, cm⁻¹): 3965, 3356, 3080, 3048, 3021, 2959, 2928, 2855, 2024, 1989, 1952, 1894, 1852, 1812, 1754, 1676, 1630, 1569, 1546, 1468, 1395, 1362, 1306, 1273, 1195, 1163, 1099, 1053, 1027, 976, 946; ¹H-NMR (500 MHz, CDCl₃, δ / ppm): 8.48 (1H, d, J = 5.0 Hz), 8.46 (1H, s), 7.38 (1H, d, J = 8.5 Hz), 7.34 (1H, d, J = 5.0 Hz), 7.29 (1H, dd, J = 2.0 Hz, J = 8.0 Hz), 7.25–7.22 (1H, m), 3.03 (2H, s), 13C-NMR (125 MHz, CDCl₃, δ / ppm): 150.16, 141.73, 134.76, 133.68, 121.96, 114.69, 114.37, 114.08, 57.07, 55.47, 48.32, 45.50, 25.40; (+)ESI-HRMS m/z: calcd. for [M+H⁺]: 310.19139. Found: 310.19142.
8-Methoxy[1]benzothiepino[3,2-c]pyridine (32). Colourless oil; IR (ATR, cm–1): 3597, 3392, 3022, 2928, 2841, 1710, 1391, 1389, 1324, 1278, 1243, 1210, 1176, 1153, 1068, 1030, 926, 857, 829; 1H-NMR (500 MHz, CDCl3, δ ppm): 8.49–8.42 (2H, m), 7.38–7.32 (2H, m), 7.08 (1H, d, J = 12.5 Hz), 6.98 (1H, d, J = 12.0 Hz), 6.87 (1H, dd, J = 3.0 Hz, J = 8.5 Hz), 6.78 (1H, d, J = 3.0 Hz), 3.79 (3H, s); 13C-NMR (125 MHz, CDCl3, δ ppm): 160.12, 149.96, 149.74, 145.36, 140.92, 135.88, 134.14, 130.71, 126.05, 115.60, 114.72, 55.43; (+)ESI-HRMS m/z: calcd. for [M+H+]$: 246.01387. Found: 246.01318.

8-Fluoro[1]benzothiepino[3,2-c]pyridine (33). Colourless solid; m.p.: 110–112 °C; IR (ATR, cm –1): 3336, 2923, 2854, 1740, 1682, 1647, 1598, 1568, 1468, 1391, 1310, 1245, 1205, 1177, 1121, 1058; 1H-NMR (500 MHz, CDCl3, δ ppm): 8.48 (1H, d, J = 5.5 Hz), 8.47 (1H, s), 7.42 (1H, dd, J = 5.5 Hz, J = 8.5 Hz), 7.35 (1H, d, J = 5.0 Hz), 7.09–7.01 (3H, m), 6.96 (1H, dd, J = 2.5 Hz, J = 9.0 Hz); 13C-NMR (125 MHz, CDCl3, δ / ppm): 162.95 (d, J = 247.2 Hz), 150.12, 150.02, 144.73, 141.66 (d, J = 8.1 Hz), 135.13, 134.92, 134.62 (d, J = 8.1 Hz), 131.54, 127.88, 126.21, 116.81 (d, J = 21.8 Hz), 116.18 (d, J = 22.5 Hz); (+)ESI-HRMS m/z: calcd. for [M+H+]$: 230.04342. Found: 230.04321.

8-Chloro-2-methyl-1,2,3,4-tetrahydro[1]benzothiepino[3,2-c]pyridine (34). Pale yellow oil. IR (ATR, cm–1): 3012, 2922, 2844, 2784, 2384, 1735, 1636, 1575, 1546, 1461, 1375, 1290, 1263, 1188, 1150, 1128, 1097, 1065, 813; 1H-NMR (500 MHz, CDCl3, δ / ppm): 7.28–7.22 (2H, m), 7.16 (1H, s), 6.88 (1H, d, J = 12.5), 6.27 (1H, d, J = 12.0), 2.99 (2H, s), 2.52 (4H, s), 2.34 (3H, s); 13C-NMR (125 MHz, CDCl3, δ / ppm): 142.04, 135.71, 133.88, 133.42, 133.36, 133.33, 133.48, 129.68, 129.16, 128.24, 58.28, 52.12, 45.15, 34.51; (+)ESI-HRMS m/z: calcd. for [M+H+]$: 264.06082. Found: 264.06121.

8-Phenyl[1]benzothiepino[3,2-c]pyridine (35). Colourless foam; IR (ATR, cm–1): 3389, 3026, 2925, 2852, 1760, 1565, 1542, 1470, 1389, 1265, 1174, 1069, 1045, 836; 1H-NMR (500 MHz, CDCl3, δ / ppm): 8.51–8.44 (2H, m), 7.59–7.34 (9H, m), 7.19 (1H, d, J = 12.5), 7.03 (1H, d, J = 12.0); 13C-NMR (125 MHz, CDCl3, δ / ppm): 150.00, 149.90, 144.72, 141.95, 140.00, 139.71, 136.09, 135.40, 133.38, 131.59, 130.71, 128.90, 128.52, 128.41, 127.87, 127.04, 126.27; (+)ESI-HRMS m/z: calcd. for [M+H+]$: 288.08415. Found: 288.08543.
Fig. S-1. The $^1$H- and $^{13}$C-NMR spectra for (2-bromo-5-chlorophenyl)methanediyl diacetate.

Fig. S-2. The $^1$H- and $^{13}$C-NMR spectra for compound 19.
Fig. S-3. The $^1$H- and $^{13}$C-NMR spectra for compound 21.

Fig. S-4. The $^1$H- and $^{13}$C-NMR spectra for compound 24.
Fig. S-5. The $^1$H- and $^{13}$C-NMR spectra for compound 25.

Fig. S-6. The $^1$H- and $^{13}$C-NMR spectra for compound 26.
Fig. S-7. The $^1$H- and $^{13}$C-NMR spectra for compound 27.

Fig. S-8. The $^1$H- and $^{13}$C-NMR spectra for compound 28.
Fig. S-9. The $^1$H- and $^{13}$C-NMR spectra for compound 29.

Fig. S-10. The $^1$H- and $^{13}$C-NMR spectra for compound 30.
Fig. S-11. The $^1$H-NMR spectra for compounds 16 and 17.

Fig. S-12. The $^1$H- and $^{13}$C-NMR spectra for compound 31.
Fig. S-13. 2D $^1$H-$^{13}$C HSQC spectrum for compound 31.

Fig. S-14. The $^1$H- and $^{13}$C-NMR spectra for compound 32.
Fig. S-15. The $^1$H- and $^{13}$C-NMR spectra for compound 33.

Fig. S-16. The $^1$H- and $^{13}$C-NMR spectra for compound 34.
Supplementary Material

Fig. S-17. The $^1$H- and $^{13}$C-NMR spectra for compound 35.

HPLC Analyses for Purity

Compounds were analyzed for purity (HPLC) using a Agilent 1200 HPLC system equipped with Quat pump (G1311B), injector (G1329B) 1260 ALS, TCC 1260 (G1316A) and detector 1260 DAD VL + (G1315C). All compounds were >95 % pure. The HPLC analyses were performed in diverse systems:

**Method A**

Zorbax Eclipse Plus C18 4.6×150 mm, 1.8 µ, S.N. USWKY01594 was used as the stationary phase. The eluent was made from the following solvents: 0.2 % formic acid in water (A) and methanol (B). The analysis were performed at the UV max of the compounds (at 250 nm, 254 nm or 270 nm) to maximize selectivity. The compounds were dissolved in methanol; the final concentrations were ≈1 mg ml$^{-1}$. The flow rate was 0.5 ml min$^{-1}$.

Compounds 8–15, 27, 29, 30 and 34 were eluted using the gradient protocol: 0 – 1 min 95 % A, 1 – 5 min 95 % A → 5 % A, 5 – 14 min 5 % A, 14 – 15 min 5 % A → 95 % A, 15 – 16 min 95 % A.

Compounds 16, 17, 31, 32 and 33 were eluted using the gradient protocol: 0 – 1.5 min 95 % A, 1.5 – 5 min 95 % A → 5 % A, 5 – 16 min 5 % A, 16 – 18 min 5 % A → 95 % A.

**Compound 35** was eluted using gradient protocol: 0 – 1.5 min 50 % A, 1.5 – 3 min 50 % A → 30 % A, 3 – 6 min 30 % A → 0 % A, 6 – 9 min 0 % A → 50 % A, 9 – 12 min 50 % A.

**Method B**

Zorbax Eclipse Plus C18 4.6×150 mm, 1.8 µ, S.N. USWKY01594 was used as the stationary phase. The eluent was made from the following solvents: 0.2 % formic acid in water (A) and acetonitrile (B). The analyses were performed at the UV max of the compounds.
to maximize selectivity. The compounds were dissolved in methanol; the final concentrations were ≈1 mg ml⁻¹. The flow rate was 0.5 ml min⁻¹.

Compounds 8 – 15, 27–30 and 34 were eluted using the gradient protocol: 0 – 1 min 95 % A, 1 – 6 min 95 % A → 5 % A, 6 – 11 min 5 % A, 11 – 14 min 5 % A → 95 % A, 14 – 15 min 95 % A.

Compounds 31 and 32 were eluted using the gradient protocol: 0 – 1.5 min 95 % A, 1.5 – 5 min 95 % A → 5 % A, 5 – 16 min 5 % A, 16 – 18 min 5 % A → 95 % A, 18 – 21 min 95 % A.

Compounds 16, 17, 33 and 35 were eluted using the gradient protocol: 0 – 1.5 min 50 % A, 1.5 – 3 min 50 % A → 30 % A, 3 – 6 min 30 % A → 0 % A, 6 – 9 min 0 % A → 50 % A, 9 – 12 min 50 % A.

Method C

Zorbax Eclipse Plus C18 2.1 × 100 mm, 1.8 µ, was used as the stationary phase. The eluent was made from the following solvents: 0.2 % formic acid in water (A) and acetonitrile (B). The analysis was performed at the UV max of the compound to maximize selectivity. The compound was dissolved in methanol; the final concentrations were ≈1 mg ml⁻¹. The flow rate was 0.5 ml min⁻¹.

Compound 28 was eluted using gradient protocol: 0 – 1 min 95 % A, 1 – 6 min 95 % A→ 5 % A, 6 – 11 min 5 % A, 11 – 14 min 5 % A → 95 % A, 14 – 15 min 95 % A.
Fig. S-18. HPLC elution profiles for compound 27, upper method A and lower method B.
Fig. S-19. HPLC elution profiles for compound 28, upper method B and lower method C.
Fig. S-20. HPLC elution profiles for compound 29, upper method A and lower method B.
Fig. S-21. HPLC elution profiles for compound 30, upper method A and lower method B.
Fig. S-22. HPLC elution profiles for compound 16, upper method A and lower method B.
Fig. S-23. HPLC elution profiles for compound \textit{17}, upper method A and lower method B.
Fig. S-24. HPLC elution profiles for compound 31, upper method A and lower method B.
Fig. S-25. HPLC elution profiles for compound 32, upper method A and lower method B.
Fig. S-26. HPLC elution profiles for compound 33, upper method A and lower method B.
Fig. S-27. HPLC elution profiles for compound 34, upper method A and lower method B.
Fig. S-28. HPLC elution profiles for compound 35, upper method A and lower method B.