Electronic Supplementary Information (ESI)

Synthesis and cytotoxic activities of novel hybrid compounds of imidazole scaffold-based 2-substituted benzofurans

Wen-Jian Song, Xiao-Dong Yang *, Xiang-Hui Zeng, Xiao-Liang Xu,

Gao-Lan Zhang, Hong-Bin Zhang *

Key Laboratory of Medicinal Chemistry for Natural Resource (Yunnan University), Ministry of Education, School of Chemical Science and Technology, Yunnan University, Kunming, 650091, P. R. China

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^{*} Corresponding author. Tel.: +86-871-5031119; fax.: +86-871-5035538. *E-mail*: zhanghbyd@gmail.com, xdyang@ynu.edu.cn

1. General Experimental

Melting points were obtained on a XT-4 melting-point apparatus and were uncorrected. Proton nuclear magnetic resonance (¹H-NMR) spectra were recorded on a Bruker Avance 300 spectrometer at 300 MHz. Carbon-13 nuclear magnetic resonance (¹³C-NMR) was recorded on Bruker Avance 300 spectrometer at 75 MHz. Chemical shifts are reported as δ values in parts per million (ppm) relative to tetramethylsilane (TMS) for all recorded NMR spectra. Low-resolution Mass spectra were recorded on a VG Auto Spec-3000 magnetic sector MS spectrometer. High Resolution Mass spectra were taken on AB QSTAR Pulsar mass spectrometer. Element Analyses were taken on Vario EL III Elementar analyzer.

Silica gel (200–300 mesh) for column chromatography and silica GF_{254} for TLC were produced by Qingdao Marine Chemical Company (China). All air- or moisturesensitive reactions were conducted under an argon atmosphere. Starting materials and reagents used in reactions were obtained commercially from Acros, Aldrich, Fluka and were used without purification, unless otherwise indicated.

2. Analytical Data of Compound 4-24



White powder, yield 76%, mp 71–73 °C (CHCl₃). ¹H NMR (300 MHz, CDCl₃) δ 7.62(1H, s), 7.54 (1H, dd, J = 7.3, 1.0 Hz), 7.44 (1H, d, J = 7.8 Hz), 7.32-7.23(2H, m), 7.23(1H, s), 7.02(1H, s), 6.63(1H, s), 5.21(2H, s). ¹³C NMR (75 MHz, CDCl₃) δ 155.29 (C), 151.72 (C), 137.40 (CH), 129.92 (CH), 127.81 (CH), 125.03 (CH), 123.28 (CH), 121.35 (CH), 119.30 (CH), 111.45 (CH), 105.58 (CH), 44.22 (CH₂). HR-ESI-MS *m*/*z* Calcd for C₁₂H₁₀N₂O 198.0793, Found 198.0757.



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White powder, yield 72%, mp 76–78 °C (CHCl₃). ¹H NMR (300 MHz, CDCl₃) δ 7.53 (1H, dd, *J* = 7.2, 1.3 Hz), 7.44 (1H, d, *J* = 7.6 Hz), 7.29-7.22 (2H, m), 6.94 (2H, s), 6.52 (1H, s), 5.13 (2H, s), 2.47 (3H, s). ¹³C NMR (75 MHz, CDCl₃) δ 155.26 (C), 152.17 (C), 144.95 (C), 127.69 (CH), 124.88 (CH), 123.26 (CH), 121.27 (CH), 119.75 (CH), 111.43 (CH), 105.01 (CH), 43.58 (CH₂), 13.14 (CH₃). HR-ESI-MS *m*/*z* Calcd for C₁₃H₁₂N₂O 212.0950, Found 212.0919.



Yellow oil, yield 83%. ¹H NMR (300 MHz, CDCl₃) δ 7.52 (1H, dd, J = 7.3, 1.1 Hz), 7.43 (1H, d, J = 7.6 Hz), 7.29-7.22 (2H, m), 6.98 (1H, s), 6.93 (1H, s), 6.52 (1H, s),

5.14 (2H, s), 2.78 (2H, q, J = 15.0 Hz), 1.36 (3H, t, J = 7.5 Hz). ¹³C NMR (75 MHz, CDCl₃) δ 155.13 (C), 152.21 (C), 149.43 (C), 127.61 (CH), 124.76 (CH), 123.15 (CH), 121.16 (CH), 119.57 (CH), 111.32 (CH), 104.90 (CH), 43.09 (CH₂), 20.12 (CH₂), 11.99 (CH₃). HR-ESI-MS *m*/*z* Calcd for C₁₄H₁₄N₂O 226.1106, Found 226.1075.



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Brown oil, yield 54%. ¹H NMR (300 MHz, CDCl₃) δ 7.46-7.33 (3H, m), 7.20-7.13 (2H, m), 6.70, 6.63 (1H, s), 6.63, 6.42 (1H, s), 5.03 (2H, s), 2.13 (3H, s). ¹³C NMR (75 MHz, CDCl₃) δ 155.19 (C), 151.96 (C), 138.85 (C), 136.46 (CH), 127.81 (CH), 124.88 (CH), 123.18 (CH), 121.25 (CH), 115.67 (CH), 111.38 (CH), 105.36 (CH), 44.06 (CH₂), 13.71 (CH₃). HR-ESI-MS *m*/*z* Calcd for C₁₃H₁₂N₂O 212.0950, Found 212.0907.



White powder, yield 78%, mp 128–130 °C (CHCl₃). ¹H NMR (300 MHz, CDCl₃) δ 7.96 (1H, s), 7.84-7.81 (1H, m), 7.47-7.37 (3H, m), 7.28-7.17 (4H, m), 6.56 (1H, s), 5.32 (2H, s). ¹³C NMR (75 MHz, CDCl₃) δ 155.08 (C), 151.07 (C), 143.82 (C), 143.02 (CH), 133.66 (C), 127.69 (C), 124.86 (CH), 123.24 (CH), 122.42 (CH), 121.20 (CH), 120.47 (CH), 111.32 (CH), 109.77 (CH), 105.51 (CH), 42.18 (CH₂). HR-ESI-MS *m*/*z* Calcd for C₁₆H₁₂N₂O 248.0950, Found 248.0944. Anal. Calcd for C₁₆H₁₂N₂O: C, 77.40; H, 4.87; N, 11.28. Found: C, 77.33; H, 4.86; N, 10.95.



Yellow oil, yield 75%. ¹H NMR (300 MHz, CDCl₃) δ 7.45(1H, s), 7.27 (1H, d, *J* = 8.6 Hz), 6.95 (1H, s), 6.89 (1H, s), 6.84 (1H, d, *J* = 1.7 Hz), 6.75 (1H, dd, *J* = 8.6, 2.2 Hz), 6.45 (1H, s), 5.02 (2H, s), 3.69 (3H, s). ¹³C NMR (75 MHz, CDCl₃) δ 158.39 (C), 156.21 (C), 150.50 (C), 137.17 (CH), 129.47 (CH), 121.33 (CH), 120.86 (C), 119.18 (CH), 112.27 (CH), 105.47 (CH), 95.88 (CH), 55.65 (CH₃), 44.00 (CH₂). HR-ESI-MS *m/z* Calcd for C₁₃H₁₂N₂O₂ 228.0899, Found 228.0863.



Brown oil, yield 71%. ¹H NMR (300 MHz, CDCl₃) δ 7.29 (1H, d, *J* = 8.5 Hz), 6.88 (1H, d, *J* = 2.0 Hz), 6.85-6.83 (2H, m), 6.78 (1H, dd, *J* = 8.5, 2.0 Hz), 6.40 (1H, s), 4.99 (2H, s), 3.74(3H, s), 2.38(3H, s). ¹³C NMR (75 MHz, CDCl₃) δ 158.34 (C), 156.18 (C), 150.88 (C), 144.74 (C), 127.35 (CH), 121.21 (CH), 120.92 (C), 119.54 (CH), 112.21 (CH), 104.85 (CH), 95.95 (CH), 55.70 (CH₃), 43.39 (CH₂), 12.96 (CH₃). HR-ESI-MS *m*/*z* Calcd for C₁₄H₁₄N₂O₂ 242.1055, Found 242.1019



Brown oil, yield 80%. ¹H NMR (300 MHz, CDCl₃) δ 7.28 (1H, d, J = 8.5 Hz), 6.87 (2H, s), 6.82 (1H, d, J = 1.2 Hz), 6.77 (1H, dd, J = 8.5, 1.2 Hz), 6.39 (1H, s), 5.00 (2H, s), 3.73 (3H, s), 2.69 (2H, q, J = 15.0 Hz), 1.27 (3H, t, J = 7.5 Hz). ¹³C NMR (75 MHz, CDCl₃) δ 158.30 (C), 156.15 (C), 151.01 (C), 149.33 (C), 127.35 (CH), 121.20 (CH), 120.93 (C), 119.46 (CH), 112.19 (CH), 104.86 (CH), 95.93 (CH), 55.69 (CH₃),

43.00 (CH₂), 20.06 (CH₂), 11.97 (CH₃). HR-ESI-MS *m*/*z* Calcd for C₁₅H₁₆N₂O₂ 256.1212, Found 256.1178.



Brown oil, yield 70%. ¹H NMR (300 MHz, CDCl₃) δ 8.03 (1H, s), 7.76-7.73 (1H, m), 7.43-7.40 (1H, m), 7.30 (1H, d, J = 8.6 Hz), 7.26-7.21 (2H, m), 7.19 (1H, s), 6.87 (1H, d, J = 1.8 Hz), 6.78 (1H, dd, d, J = 8.6, 2.1 Hz), 6.54 (1H, s), 5.42 (2H, s), 3.83 (3H, s). ¹³C NMR (75 MHz, CDCl₃) δ 158.43 (C), 156.22 (C), 149.88 (C), 143.76 (C), 142.94 (CH), 123.25 (CH), 122.44 (CH), 121.29 (CH), 120.87 (C), 120.47 (CH), 112.35 (CH), 109.76 (CH), 105.59 (CH), 95.93 (CH), 55.70 (CH₃), 42.33 (CH₂). HR-ESI-MS *m/z* Calcd for C₁₇H₁₄N₂O₂ 278.1055, Found 278.1018.



Brown oil, yield 80%. ¹H NMR (300 MHz, CDCl₃) δ 7.55 (1H, s), 7.31 (1H, d, J = 7.5 Hz), 7.13-7.02 (3H, m), 6.96 (1H, s), 6.55 (1H, s), 6.00-5.89 (1H, m), 5.16 (2H, s), 5.09-5.01 (2H, m), 3.55 (2H, d, J = 6.6 Hz). ¹³C NMR (75 MHz, CDCl₃) δ 153.73 (C), 151.38 (C), 137.29 (CH), 135.62 (CH), 129.80 (CH), 127.50 (C), 124.95 (CH), 123.85 (CH), 123.39 (C), 119.22 (CH), 116.35 (CH₂), 105.71 (CH), 44.19 (CH₂), 33.77 (CH₂). HR-ESI-MS *m/z* Calcd for C₁₅H₁₄N₂O 238.1106, Found 238.1084.

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Brown oil, yield 73%. ¹H NMR (300 MHz, CDCl₃) δ 7.29 (1H, d, J = 7.5 Hz), 7.10-7.00 (2H, m), 6.84 (2H, s), 5.99-5.90 (1H, m), 5.08-4.99 (2H, m), 5.03 (2H, s), 3.53 (2H, d, J = 6.2 Hz), 2.39 (3H, s). ¹³C NMR (75 MHz, CDCl₃) δ 153.65 (C), 151.77 (C), 144.83 (C), 135.63 (CH), 127.54 (C), 127.34 (CH), 124.79 (CH), 123.77 (C), 123.36 (CH), 119.63 (CH), 119.15 (CH), 116.36 (CH₂), 105.13 (CH), 43.48 (CH₂), 33.81 (CH₂), 12.92 (CH₃). HR-ESI-MS *m*/*z* Calcd for C₁₆H₁₆N₂O 252.1263, Found 252.1221.



Brown oil, yield 78%. ¹H NMR (300 MHz, CDCl₃) δ 7.37 (1H, d, J = 7.3 Hz), 7.23-7.09 (2H, m), 6.96-6.93 (3H, m), 6.52 (1H, s), 6.09-5.96 (2H, m), 5.16-5.08 (2H, m), 5.14 (2H, s), 3.62 (2H, d, J = 6.2 Hz), 2.78 (3H, t, J = 7.5 Hz). ¹³C NMR (75 MHz, CDCl₃) δ 153.64 (C), 151.82 (C), 149.42 (C), 135.62 (CH), 127.53 (C), 127.27 (CH), 124.80 (CH), 123.77 (C), 123.37 (CH), 121.16 (CH), 119.62 (CH), 119.15 (CH), 116.34 (CH), 105.19 (CH₂), 43.13 (CH₂), 33.80 (CH₂), 21.74 (CH₂), 12.07 (CH₃). HR-ESI-MS *m*/*z* Calcd for C₁₇H₁₈N₂O 266.1419, 266.1395.



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Yellow powder, yield 70%, mp 48–50 °C. ¹H NMR (300 MHz, CDCl₃) δ 7.92(1H, s), 7.76-7.73 (1H, m), 7.41-7.39 (1H, m), 7.28-7.20 (3H, m), 7.06-6.99 (2H, m), 6.52 (1H, s), 5.96-5.85 (1H, m), 5.34 (2H, s), 5.05-4.97(2H, dd, J = 15.3, 8.4 Hz), 3.51 (2H, d, J = 6.3 Hz). ¹³C NMR (75 MHz, CDCl₃) δ 153.69 (C), 150.86 (C), 143.85 (C), 142.96 (CH), 135.60 (CH), 133.74 (C), 127.51 (C), 124.93 (CH), 123.85 (C), 123.41 (CH), 123.25 (CH), 122.44 (CH), 120.52 (CH), 119.21 (CH), 116.38 (CH2), 109.82 (CH), 105.81 (CH), 42.35 (CH₂), 33.81 (CH₂). HR-ESI-MS *m/z* Calcd for C₁₉H₁₆N₂O 288.1263, Found 288.1259.



Brown oil, yield 74%. ¹H NMR (300 MHz, CDCl₃) δ 7.59 (1H, s), 7.30 (1H, d, J = 8.6 Hz), 7.05 (1H, s), 6.99 (1H, s), 6.85 (1H, d, J = 8.6 Hz), 6.52 (1H, s), 6.05-5.96 (1H, m), 5.13 (2H, s), 5.06 (1H, d, J = 1.3 Hz), 4.98 (1H, d, J = 10.3 Hz), 3.84 (3H, s), 3.58 (2H, d, J = 6.2 Hz). ¹³C NMR (75 MHz, CDCl₃) δ 155.44 (C), 154.80 (C), 150.80 (C), 137.15 (CH), 135.67 (CH), 129.31 (CH), 121.28 (C), 119.26 (CH), 118.71 (CH), 115.07 (CH₂), 112.08 (C), 108.19 (CH), 105.55 (CH), 56.66 (CH₃), 44.12 (CH₂), 27.86 (CH₂). HR-ESI-MS *m/z* Calcd for C₁₆H₁₆N₂O₂ 268.1212, Found 268.1991.

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White powder, yield 68%, mp 118–120 °C (CHCl₃). ¹H NMR (300 MHz, CDCl₃) δ 7.99 (1H, s), 7.83-7.80 (1H, m), 7.50-7.47 (1H, m), 7.30 (2H, s), 7.29-7.26 (1H, m),

6.85-6.82 (1H, d, J = 8.6 Hz), 6.52 (1H, s), 6.03-5.94 (1H, m), 5.37 (2H, m), 5.05-4.94 (2H, m), 3.83 (3H, s), 3.58 (2H, d, J = 6.2 Hz). ¹³C NMR (75 MHz, CDCl₃) δ 155.44 (C), 154.78 (C), 150.35 (C), 143.80 (C), 142.94 (CH), 135.66 (CH), 133.75 (C), 123.19 (CH), 122.39 (CH), 121.30 (C), 120.43 (CH), 118.65 (CH), 115.10 (CH₂), 112.15 (C), 109.89 (CH), 108.18 (CH), 105.58 (CH), 56.69 (CH₃), 42.35 (CH₂), 27.93 (CH₂). HR-ESI-MS *m*/*z* Calcd for C₂₀H₁₈N₂O₂ 318.1368, Found 318.1353.



White powder, yield 90%, mp 176–178 °C (MeOH). ¹H NMR (300 MHz, MeOD) δ 9.42 (1H, s), 7.77 (1H, s), 7.48-7.41 (6H, m), 7.33-7.25 (2H, m), 7.13 (1H, s), 5.72 (2H, s), 5.48 (2H, s). ¹³C NMR (75 MHz, MeOD) δ 156.88 (C), 150.55 (C), 137.76 (CH), 135.12 (C), 130.49 (CH), 129.89 (CH), 129.03 (C), 126.72 (CH), 124.60 (CH), 124.27 (CH), 122.92 (CH), 112.36 (CH), 109.23 (CH), 54.40 (CH₂), 47.38 (CH₂). HR-ESI-MS *m/z* Calcd for C₁₉H₁₇N₂O [M-Br]⁺ 289.1335, Found 289.1325.



White powder, yield 92%, mp 175–177 °C (MeOH). ¹H NMR (300 MHz, MeOD) δ 6.38 (1H, s), 6.30-6.24 (2H, m), 6.14-5.91 (8H, m), 5.78 (1H, s), 4.35(2H, s), 4.13(2H, s), 1.49(3H, s). ¹³C NMR (75 MHz, MeOD) δ 155.41 (C), 149.31 (C), 145.12 (C), 133.53 (C), 129.08 (CH), 128.75 (CH), 127.80 (CH), 127.62 (C), 125.23 (CH), 123.20 (CH), 121.89 (CH), 121.46 (CH), 110.92 (CH), 107.37 (CH), 51.71 (CH₂), 44.97 (CH₂), 9.35 (CH₃). HR-ESI-MS *m*/*z* Calcd for C₂₀H₁₉N₂O 303.1492, Found 303.1486.



White powder, yield 88%, mp 179–181 °C (MeOH). ¹H NMR (300 MHz, MeOD) δ 7.59 (1H, d, J = 2.2 Hz), 7.53 (1H, d, J = 8.6 Hz), 7.46 (1H, d, J = 2.2 Hz), 7.35-7.31 (4H, m), 7.25-7.23 (3H, m), 7.14 (1H, s), 6.99 (1H, s), 5.57 (2H, s), 5.37 (2H, s), 3.21 (2H, q, J = 15.0 Hz), 1.05 (3H, t, J = 7.5 Hz). ¹³C NMR (75 MHz, MeOD) δ 155.37 (C), 149.32 (C), 148.78 (C), 133.85 (C), 129.08 (CH), 128.77 (CH), 127.75 (CH), 125.29 (CH), 123.24 (CH), 122.23 (CH), 121.92 (CH), 121.48 (CH), 110.90 (CH), 107.59 (CH), 51.58 (CH₂), 44.83 (CH₂), 16.89 (CH₂), 10.33 (CH₃). HR-ESI-MS *m/z* Calcd for C₂₁H₂₁N₂O [M-Br]⁺ 317.1648, Found 310.1641.



White powder, yield 85%, mp 219–221 °C (MeOH). ¹H NMR (300 MHz, MeOD) δ 7.76 (1H, d, *J* = 2.2 Hz), 7.66-7.60 (2H, m), 7.49-7.46 (2H, m), 7.39-7.29 (4H, m), 7.23-7.20 (1H, m), 7.18 (1H, s), 5.77 (2H, s), 5.55 (2H, s), 3.33 (2H, q, *J* = 15.0 Hz), 1.23 (3H, t, *J* = 7.5 Hz). ¹³C NMR (75 MHz, MeOD) δ 156.77 (C), 150.76 (C), 150.41 (C), 134.85 (CH), 133.95 (C), 132.52 (CH), 132.29 (CH), 130.96 (CH), 129.91 (CH), 129.04 (C), 126.77 (CH), 124.73 (C), 123.53 (CH), 123.27 (CH), 122.98 (CH), 112.37 (CH), 109.07 (CH), 53.23 (CH₂), 46.43(CH₂), 18.61(CH₂), 11.86(CH₃). HR-ESI-MS *m/z* Calcd for C₂₁H₂₀BrN₂O [M-Br]⁺ 395.0754, Found 395.0742.



White powder, yield 75%, mp 145–147 °C (MeOH). ¹H NMR (300 MHz, MeOD) δ

7.69-7.64 (3H, m), 7.48 (1H, d, J = 8.3 Hz), 7.36-7.28 (2H, m), 7.12 (1H, s), 5.68 (2H, s), 4.22 (2H, q, J = 15.0 Hz), 1.93-1.83 (2H, m), 1.51-1.38 (2H, m), 1.33 (3H, t, J = 7.5 Hz), 1.01 (3H, t, J = 7.5 Hz). ¹³C NMR (75 MHz, MeOD) δ 156.80 (C), 150.76 (C), 149.68 (C), 128.99 (C), 126.64 (CH), 124.61 (CH), 123.24 (CH), 122.91 (CH), 122.80 (CH), 112.22 (CH), 108.77 (CH), 48.75 (CH₂), 33.11 (CH₂), 20.66 (CH₂), 17.95 (CH₂), 13.89 (CH₃), 12.02 (CH₃). HR-ESI-MS *m*/*z* Calcd for C₁₈H₂₃N₂O [M-Br]⁺ 283.1805, Found 283.1794.



White powder, yield 89%, mp 218–220 °C (MeOH). ¹H NMR (300 MHz, MeOD) δ 8.39 (1H, s), 6.60 (1H, d, J = 7.6 Hz), 6.37 (1H, d, J = 7.6 Hz), 6.19-6.10 (3H, m), 6.01-5.91 (6H, m), 5.80-5.73 (2H, m), 5.70 (s, 1H), 4.52 (s, 2H), 4.27 (s, 2H). ¹³C NMR (75 MHz, MeOD) δ 148.74 (C), 142.01 (C), 133.02 (C), 131.42 (C), 129.04 (CH), 128.91 (CH), 128.04 (CH), 127.57 (C), 127.20 (CH), 127.09 (CH), 125.19 (CH), 123.12 (CH), 121.37 (CH), 113.67 (CH), 113.48 (CH), 110.81 (CH), 107.80 (CH), 50.77 (CH₂), 43.86 (CH₂). HR-ESI-MS *m*/*z* Calcd for C₂₃H₁₉N₂O [M-Br]⁺ 339.1492, Found 339.1483. Anal. Calcd for C₂₃H₁₉BrN₂O: C, 65.88; H, 4.57; N, 6.68. Found: C, 66.29; H, 4.57; N, 6.31.

Compound 8 ¹H NMR (300 MHz) and ¹³C NMR (75 MHz)





Compound 24 ${}^{1}HNMR$ (300 MHz) and ${}^{13}CNMR$ (75 MHz)





S15









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S16







Compound 5 ${}^{1}HNMR$ (300 MHz) and ${}^{13}CNMR$ (75 MHz)













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Compound 9





,N___ MeO



S25









MeO



Compound 12





Compound 13













Compound 15

^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz)







1

Compound 16 ${}^{1}HNMR$ (300 MHz) and ${}^{13}CNMR$ (75 MHz)







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S39









Compound 18

¹*H* NMR (300 MHz) and ¹³*C* NMR (75 MHz)









Compound 20 ${}^{1}HNMR$ (300 MHz) and ${}^{13}CNMR$ (75 MHz)





S47















5

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S51

Compound 23





