Design, Synthesis and Biological activity evaluation of Novel Allosteric Inhibitors of DENV NS2B-NS3 Protease

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Supporting information

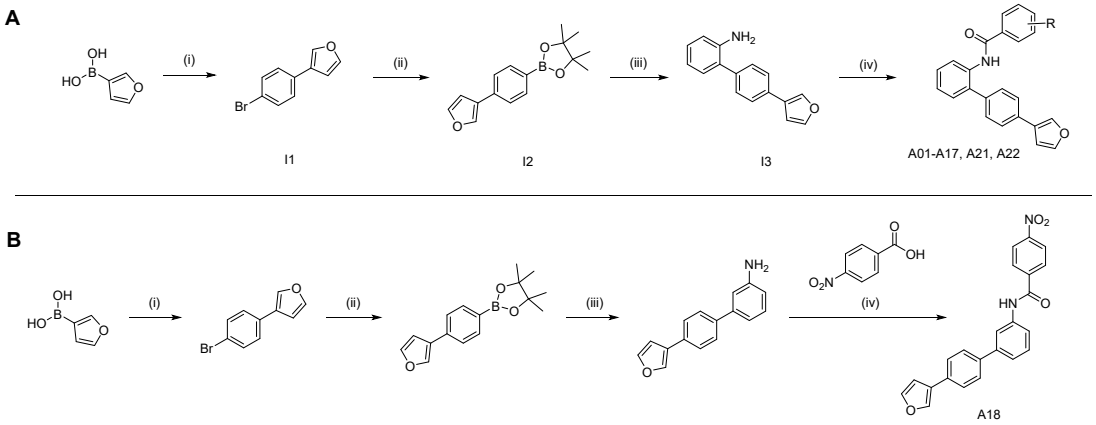
Table of contents:

1.Chemistry

1.1 General Chemistry

Commercially available solvents and reagents were used directly without further purification. Air-sensitive reactions were performed under a nitrogen atmosphere. Chromatographic separations utilized silica gel H60 (200-300 mesh) sourced from Qingdao Haiyang Chemical Co., Ltd. Thin-layer chromatography (TLC) was conducted using silica gel 60 GF254 and UV light for visualization. Mass spectrometry (MS) data were acquired on an Agilent 6120 Single Quadrupole LC/MS system, equipped with a photodiode array detector and employing electrospray ionization (ESI). Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AVANCE III HD spectrometer (5–650 MHz), with DMSO-d6 as the solvent and tetramethylsilane (TMS) as the internal standard.

1.2 General synthetic procedure for A01-A18, A21, A22.



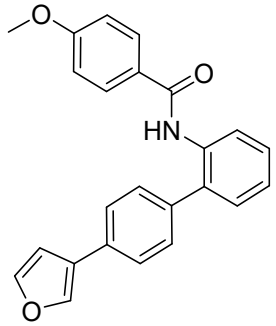
A mixture of 3-furanoboronic acid (2.37 g, 21.2 mmol), p-bromoiodobenzene (6 g, 21.2 mmol), and potassium acetate (6.24 g, 63.6 mmol) was dissolved in 150 mL of solvent (dioxane: H_2O= 4:1) under nitrogen. $PdCl_2$(pddf) (0.77 g, 1.06 mmol) was added, and the mixture was stirred at 95ºC for 12 hours. After TLC confirmed completion, 150 mL of ethyl acetate and 100 mL of water were added. The ethyl acetate layer was separated, washed with water and brine, and dried over Na_2SO_4. The drying agent was removed by filtration, and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (PE: EA = 15:1) to yield **I1** as a white solid (4.3 g, 50%).

To a solution of intermediate **I1** (1.4 g, 6.27 mmol), bis(pinacolato)diboron (1.9 g, 7.5 mmol), and potassium acetate (1.85 g, 18.8 mmol) in 100 mL of solvent (dioxane: H_2O= 4:1), $PdCl_2$(pddf) (0.2 g, 0.31 mmol) was added. The mixture was stirred at 95ºC for 12 hours under nitrogen. After TLC confirmed completion, 75 mL of ethyl acetate and 50 mL of water were added. The ethyl acetate layer was separated, washed with water and brine, dried over Na_2SO_4, and filtered. The solvent was evaporated, and the crude product was purified by column chromatography (PE: EA= 10:1) to yield **I2** as a white solid (0.88 g, 52%)[1].

To a solution of I2 (0.6 g, 2.2 mmol), 2-iodoaniline (0.48 g, 2.2 mmol), potassium acetate (0.65 g, 6.6 mmol) in 40 mL solvent (dioxane:water = 3:1) was added $PdCl_2$(pddf) (0.08 g, 0.11 mmol). The reaction was protected by nitrogen and stirred at 90ºC for 12 h. After the reaction was complete monitored by TLC, 30mL of ethyl acetate and 10 mL of water were added, the ethyl acetate layer was separated after stirring for 5 min, washed twice with water and saturated brine, and then dried over Na_2SO_4. Then the solvent was removed under reduced pressure to give to rude product which was purified by column chromatography (PE: EA = 5:1) to obtain pure **I3** as white solid (0.32 g, yield 62%).

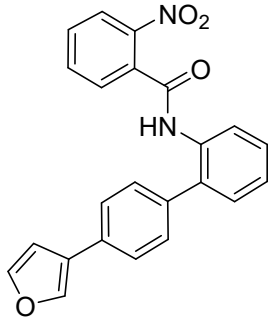
The mixture of **I3** (1 equiv), corresponding benzoic acid (1.25 equiv), HATU (1.5 equiv), DIPEA (3 equiv) and anhydrous DMF was stirred for 12 h at 50ºC. After the total consumption of I3, ethyl acetate and water were added to the reaction flask. The organic layer was dried with anhydrous Na_2SO_4 and removed in vacuo. Finally, the

residue was purified by column chromatography (PE: EA = 5:1) to afford the desired compounds.



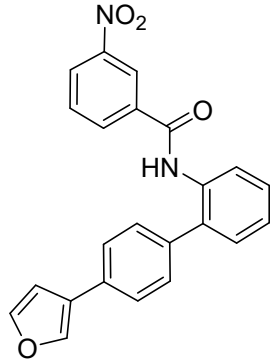
N-(4'-(furan-3-yl)-[1,1'-biphenyl]-2-yl)-2-nitrobenzamide (A01)

75% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.72 (s, 1H), 8.21 (t, J = 1.2 Hz, 1H), 7.82 (d, J = 8.8 Hz, 2H), 7.73 (t, J = 1.7 Hz, 1H), 7.63 (d, J = 8.3 Hz, 2H), 7.49 (dd, J = 7.7, 1.5 Hz, 1H), 7.46 (d, J = 8.3 Hz, 2H), 7.43 (dd, J = 7.2, 1.8 Hz, 1H), 7.41 (dd, J = 7.6, 1.9 Hz, 1H), 7.37 (td, J = 7.4, 1.5 Hz, 1H), 3.80 (s, 3H); ^{13}C NMR (151 MHz, DMSO) δ 165.16, 161.79, 144.32, 139.48, 137.76, 135.08, 130.74, 130.13, 129.38, 129.04, 128.47, 127.74, 126.60, 126.53, 125.46, 125.35, 113.59, 108.65, 55.37; ESI-MS *m/z*: 370.2 $[M+H]^+$



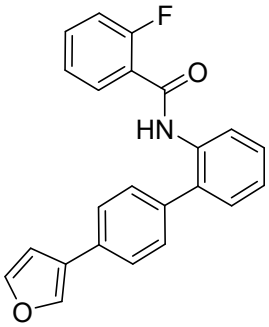
N-(4'-(furan-3-yl)-[1,1'-biphenyl]-2-yl)-2-nitrobenzamide (A02)

66% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.33 (s, 1H), 8.65 (s, 1H), 8.39 (dd, J = 8.3, 2.3 Hz, 1H), 8.27 (d, J = 7.7 Hz, 1H), 8.19 (t, J = 1.2 Hz, 1H), 7.78 (t, J = 8.0 Hz, 1H), 7.73 (t, J = 1.7 Hz, 1H), 7.66 – 7.62 (m, 2H), 7.51 (d, J = 7.1 Hz, 1H), 7.49 – 7.42 (m, 5H), 6.96 (d, J = 2.4 Hz, 1H); ^{13}C NMR (151 MHz, DMSO) δ 162.79, 146.75, 143.35, 138.48, 136.99, 136.60, 134.86, 133.40, 132.91, 129.90, 129.26, 128.01, 127.48, 126.92, 126.19, 125.13, 124.47, 124.45, 121.32, 107.65; ESI-MS *m/z*: 385.2 $[M+H]^+$.



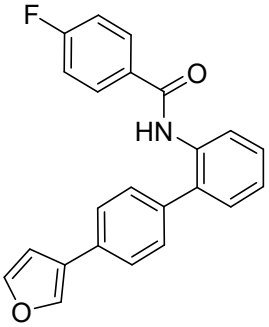
N-(4'-(furan-3-yl)-[1,1'-biphenyl]-2-yl)-3-nitrobenzamide (A03)

68% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.33 (s, 1H), 8.65 (s, 1H), 8.39 (dd, J = 8.3, 2.4 Hz, 1H), 8.26 (d, J = 7.7 Hz, 1H), 8.19 (t, J = 1.2 Hz, 1H), 7.79 (t, J = 8.0 Hz, 1H), 7.73 (t, J = 1.7 Hz, 1H), 7.67 – 7.61 (m, 2H), 7.51 (dd, J = 7.5, 1.6 Hz, 1H), 7.49 – 7.40 (m, 5H), 6.96 (d, J = 1.7 Hz, 1H); ^{13}C NMR (151 MHz, DMSO) δ 163.78, 147.75, 144.34, 139.48, 137.98, 137.59, 135.85, 134.40, 133.90, 130.89, 130.25, 129.00, 128.48, 127.92, 127.19, 126.12, 125.44, 122.31, 108.65; ESI-MS *m/z*: 385.2 $[M+H]^+$.



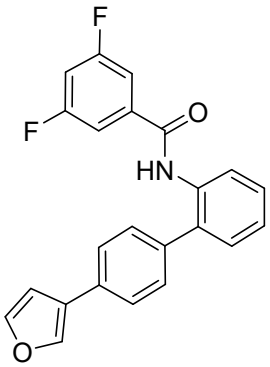
2-fluoro-N-(4'-(furan-3-yl)-[1,1'-biphenyl]-2-yl)benzamide (A04)

71% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.78 (s, 1H), 8.24 (t, J = 1.1 Hz, 1H), 7.76 (t, J = 1.7 Hz, 1H), 7.69 (d, J = 8.2 Hz, 2H), 7.66 (d, J = 8.1 Hz, 1H), 7.60 (t, J = 7.1 Hz, 1H), 7.52 (d, J = 6.8 Hz, 1H), 7.48 (d, J = 7.9 Hz, 2H), 7.42 (dd, J = 11.3, 3.5 Hz, 2H), 7.39 – 7.34 (m, 1H), 7.28 (t, J = 8.1 Hz, 3H), 7.01 (s, 1H); ^{13}C NMR (151 MHz, DMSO) δ 162.84, 159.14, 144.38, 139.53, 137.38, 136.85, 134.51, 132.70, 130.97, 130.28, 130.04, 129.24, 127.89, 126.95, 126.52, 125.49, 125.44, 124.53, 123.93, 116.19, 108.70; ESI-MS *m/z*: 380.1 $[M+Na]^+$.



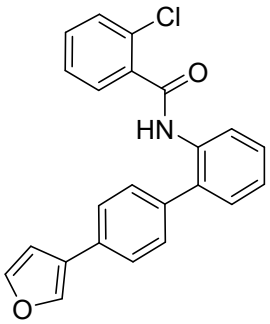
4-fluoro-N-(4'-(furan-3-yl)-[1,1'-biphenyl]-2-yl)benzamide (A05)

60% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.94 (s, 1H), 8.20 (s, 1H), 7.90 (t, J = 6.9 Hz, 2H), 7.73 (d, J = 1.8 Hz, 1H), 7.63 (d, J = 7.9 Hz, 2H), 7.50 – 7.37 (m, 6H), 7.30 (t, J = 8.7 Hz, 2H), 6.98 (d, J = 1.8 Hz, 1H); ^{13}C NMR (151 MHz, DMSO) δ 164.70, 164.02, 144.34, 139.50, 137.98, 137.71, 134.78, 130.87, 130.80, 130.19, 130.14, 129.01, 128.58, 127.82, 126.91, 125.44, 125.36, 115.34, 108.66; ESI-MS *m/z*: 355.9 $[M-H]^-$.



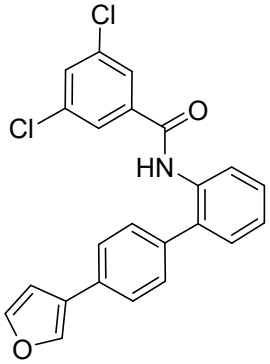
3,5-difluoro-N-(4'-(furan-3-yl)-[1,1'-biphenyl]-2-yl)benzamide (A06)

45% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.11 (s, 1H), 8.21 (s, 1H), 7.73 (t, J = 1.8 Hz, 1H), 7.64 (d, J = 8.2 Hz, 2H), 7.52 (d, J = 6.3 Hz, 2H), 7.49 – 7.39 (m, 7H), 6.98 (d, J = 1.9 Hz, 1H); ^{13}C NMR (151 MHz, DMSO) δ 163.20, 162.17, 144.36, 139.52, 138.04, 137.84, 137.55, 134.26, 130.88, 130.26, 128.98, 128.49, 127.90, 127.54, 127.23, 126.53, 125.42, 125.39, 110.91, 108.63, 107.06; ESI-MS *m/z*: 373.8 $[M-H]^-$.



2-chloro-N-(4'-(furan-3-yl)-[1,1'-biphenyl]-2-yl)benzamide (A07)

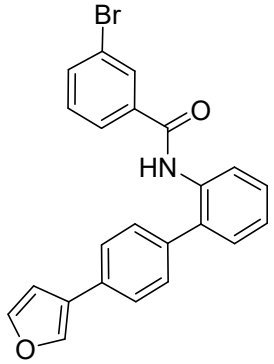
64% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.00 (s, 1H), 8.24 (d, J = 1.4 Hz, 1H), 7.76 (d, J = 1.7 Hz, 1H), 7.69 (d, J = 8.0 Hz, 2H), 7.57 (d, J = 7.8 Hz, 1H), 7.51 – 7.47 (m, 3H), 7.45 – 7.41 (m, 3H), 7.39 (dt, J = 7.2, 1.6 Hz, 3H), 7.01 (d, J = 1.8 Hz, 1H); ^{13}C NMR (151 MHz, DMSO) δ 165.54, 144.38, 139.46, 137.53, 136.77, 134.32, 130.94, 130.88, 130.25, 130.04, 129.65, 129.36, 128.62, 127.85, 127.83, 127.03, 126.81, 125.56, 125.41, 108.73; ESI-MS *m/z*: 396.0 $[M+Na]^+$.



3,5-dichloro-N-(4'-(furan-3-yl)-[1,1'-biphenyl]-2-yl)benzamide (A08)

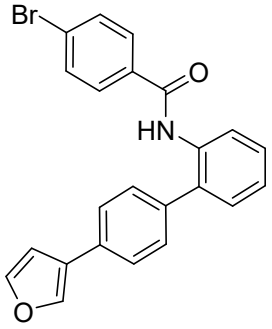
73% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.72 (s, 1H), 8.21 (t, J = 1.2 Hz, 1H), 7.82 (d, J = 8.8 Hz, 2H), 7.73 (t, J = 1.7 Hz, 1H), 7.63 (d, J = 8.3 Hz, 2H), 7.49 (dd, J = 7.7, 1.5 Hz, 1H), 7.46 (d, J = 8.3 Hz, 2H), 7.43 (dd, J = 7.2, 1.8 Hz, 1H), 7.41 (dd, J

= 7.6, 1.9 Hz, 1H), 7.37 (td, *J* = 7.4, 1.5 Hz, 1H), 3.80 (s, 3H); ^{13}C NMR (151 MHz, DMSO) δ 163.10, 144.36, 139.50, 137.93, 137.58, 137.57, 134.33, 134.27, 130.93, 130.90, 130.24, 128.98, 128.40, 127.90, 127.19, 126.36, 125.41, 108.64; ESI-MS *m/z*: 430.0 $[M+Na]^+$.



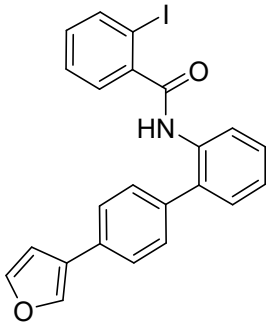
3-bromo-N-(4'-(furan-3-yl)-[1,1'-biphenyl]-2-yl)benzamide (A09)

59% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.05 (s, 1H), 8.20 (s, 1H), 7.99 (s, 1H), 7.82 (d, *J* = 7.8 Hz, 1H), 7.75 (d, *J* = 2.0 Hz, 1H), 7.73 (t, *J* = 1.9 Hz, 1H), 7.64 (d, *J* = 7.8 Hz, 2H), 7.50 – 7.37 (m, 7H), 6.98 (d, *J* = 1.8 Hz, 1H); ^{13}C NMR (151 MHz, DMSO) δ 164.31, 144.34, 139.49, 137.95, 137.66, 136.61, 134.57, 134.21, 130.85, 130.68, 130.20, 129.01, 128.48, 127.85, 127.02, 126.62, 125.44, 125.38, 121.69, 108.65. ESI-MS *m/z*: 417.7 $[M-H]^-$.



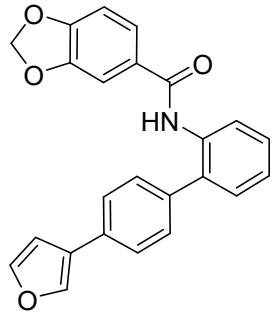
4-bromo-N-(4'-(furan-3-yl)-[1,1'-biphenyl]-2-yl)benzamide(A10)

73% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.01 (s, 1H), 8.20 (t, *J* = 1.2 Hz, 1H), 7.77 (d, *J* = 8.3 Hz, 2H), 7.73 (t, *J* = 1.7 Hz, 1H), 7.69 (d, *J* = 8.6 Hz, 2H), 7.62 (d, *J* = 8.3 Hz, 2H), 7.47 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.44 (dd, *J* = 8.8, 2.3 Hz, 3H), 7.43 – 7.38 (m, 2H), 6.97 (dd, *J* = 1.9, 0.9 Hz, 1H); ^{13}C NMR (151 MHz, DMSO) δ 164.84, 144.33, 139.50, 137.95, 137.65, 134.65, 133.49, 131.43, 130.82, 130.20, 129.61, 128.99, 128.53, 127.83, 126.97, 125.44, 125.37, 125.29, 108.66.; ESI-MS *m/z* : 420.1 $[M+H]^+$.



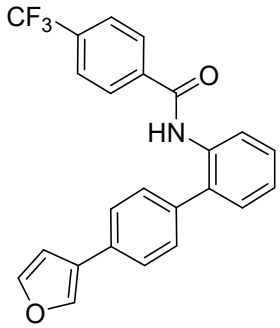
N-(4'-(furan-3-yl)-[1,1'-biphenyl]-2-yl)-2-iodobenzamide (A11)

80% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.94 (s, 1H), 8.23 (s, 1H), 7.89 (d, J = 7.9 Hz, 1H), 7.76 (s, 1H), 7.70 (d, J = 7.8 Hz, 2H), 7.59 (d, J = 7.8 Hz, 1H), 7.51 (d, J = 8.3 Hz, 2H), 7.47 – 7.40 (m, 3H), 7.41 – 7.36 (m, 1H), 7.28 (dd, J = 7.7, 1.8 Hz, 1H), 7.17 (td, J = 7.7, 1.7 Hz, 1H), 7.00 (d, J = 1.9 Hz, 1H); ^{13}C NMR (151 MHz, DMSO) δ 168.03, 144.38, 142.65, 139.45, 139.12, 137.52, 137.47, 134.40, 130.93, 130.88, 130.22, 129.40, 127.93, 127.79, 126.80, 125.56, 125.46, 108.73, 93.55; ESI-MS *m/z*: 487.9 $[M+Na]^+$.



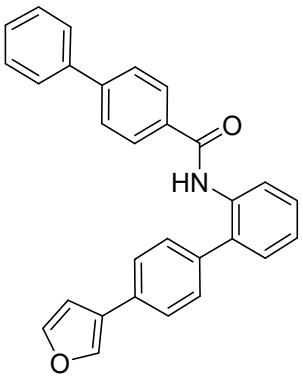
N-(4'-(furan-3-yl)-[1,1'-biphenyl]-2-yl)benzo[d][1,3]dioxole-5-carboxamide (A12)

72% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.72 (s, 1H), 8.21 (t, J = 1.2 Hz, 1H), 7.74 (t, J = 1.7 Hz, 1H), 7.63 (d, J = 8.2 Hz, 2H), 7.49 – 7.40 (m, 6H), 7.40 – 7.36 (m, 1H), 7.36 (s, 1H), 6.99 (d, J = 4.1 Hz, 1H), 6.98 (d, J = 2.2 Hz, 1H), 6.09 (s, 2H); ^{13}C NMR (151 MHz, DMSO) δ 165.26, 150.42, 147.80, 144.81, 139.97, 138.31, 138.22, 135.43, 130.62, 129.50, 128.97, 128.75, 128.23, 125.92, 125.82, 123.10, 109.12, 108.42, 107.97, 102.21; ESI-MS *m/z* : 384.1 $[M+H]^+$.



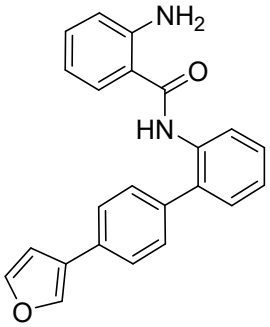
N-(4'-(furan-3-yl)-[1,1'-biphenyl]-2-yl)-4-(trifluoromethyl)benzamide (A13)

68% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.19 (s, 1H), 8.20 (s, 1H), 8.02 (d, J = 8.0 Hz, 2H), 7.86 (d, J = 8.0 Hz, 2H), 7.73 (t, J = 1.7 Hz, 1H), 7.63 (d, J = 7.9 Hz, 2H), 7.50 (d, J = 8.1 Hz, 1H), 7.46 (d, J = 8.0 Hz, 2H), 7.45 – 7.38 (m, 3H), 6.97 (d, J = 1.8 Hz, 1H); ^{13}C NMR (151 MHz, DMSO) δ 164.64, 144.34, 139.50, 138.30, 137.98, 137.66, 134.64, 131.32, 130.84, 130.24, 129.00, 128.47, 128.38, 127.87, 127.05, 125.44, 125.42, 125.38, 123.91, 108.67; ESI-MS *m/z*: 405.9 $[M-H]^-$.



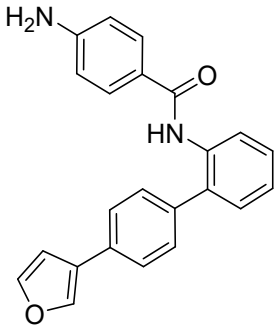
N-(4'-(furan-3-yl)-[1,1'-biphenyl]-2-yl)-[1,1'-biphenyl]-4-carboxamide (A14)

70% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.96 (s, 1H), 8.21 (s, 1H), 7.93 (d, J = 8.3 Hz, 2H), 7.77 (d, J = 8.4 Hz, 2H), 7.73 (t, J = 1.7 Hz, 2H), 7.72 (s, 1H), 7.65 (d, J = 8.3 Hz, 2H), 7.52 (dd, J = 7.7, 1.5 Hz, 1H), 7.48 (dd, J = 8.2, 2.6 Hz, 4H), 7.47 – 7.41 (m, 2H), 7.41 (ddd, J = 7.5, 6.0, 1.7 Hz, 2H), 6.98 (s, 1H); ^{13}C NMR (151 MHz, DMSO) δ 165.36, 144.33, 143.03, 139.50, 139.11, 137.88, 137.75, 134.91, 133.17, 130.79, 130.20, 129.04, 128.49, 128.20, 128.11, 127.81, 126.91, 126.80, 126.75, 126.71, 126.60, 125.46, 125.39, 108.66; ESI-MS *m/z* : 438.1 $[M+Na]^+$.



2-amino-N-(4'-(furan-3-yl)-[1,1'-biphenyl]-2-yl)benzamide (A15)

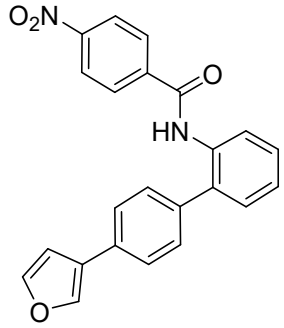
55% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.03 (s, 1H), 8.82 (d, J = 1.8 Hz, 1H), 8.60 (d, J = 1.8 Hz, 1H), 8.25 (t, J = 1.2 Hz, 1H), 8.12 (t, J = 1.9 Hz, 1H), 7.92 – 7.86 (m, 2H), 7.82 (dt, J = 7.8, 1.6 Hz, 1H), 7.77 (t, J = 1.7 Hz, 1H), 7.73 (d, J = 8.4 Hz, 2H), 7.67 (d, J = 8.4 Hz, 2H), 7.46 – 7.36 (m, 2H), 7.02 (dd, J = 1.9, 0.9 Hz, 1H), 6.90 (d, J = 8.8 Hz, 2H); ^{13}C NMR (151 MHz, DMSO) δ 165.32, 154.97, 144.41, 140.21, 140.02, 139.53, 138.63, 131.21, 129.18, 128.79, 126.97, 126.11, 125.43, 124.60, 121.29, 119.20, 118.24, 111.36, 108.70; ESI-MS *m/z*: 355.1 $[M+H]^+$.



4-amino-N-(4'-(furan-3-yl)-[1,1'-biphenyl]-2-yl)benzamide (A16)

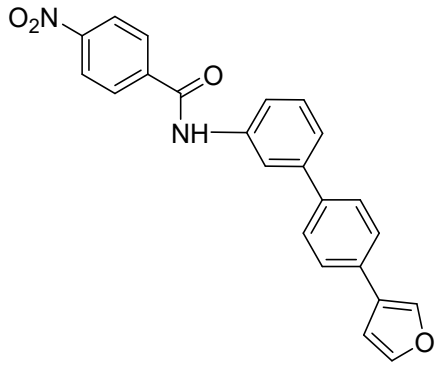
57% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.30 (s, 1H), 8.21 (s, 1H), 7.73 (s, 1H),

7.63 (d, *J* = 8.1 Hz, 2H), 7.55 (d, *J* = 8.5 Hz, 2H), 7.51 (d, *J* = 7.7 Hz, 1H), 7.45 (d, *J* = 8.2 Hz, 2H), 7.41 – 7.36 (m, 2H), 7.33 (t, *J* = 7.4 Hz, 1H), 6.99 (s, 1H), 6.52 (d, *J* = 8.5 Hz, 2H), 5.68 (s, 2H). ^{13}C NMR (151 MHz, DMSO) δ 165.54, 151.95, 144.33, 139.49, 137.79, 137.22, 135.53, 130.72, 130.03, 129.14, 129.10, 128.08, 127.65, 126.06, 125.47, 125.37, 120.83, 112.58, 108.65. ESI-MS *m/z* =355.1 $[M+H]^+$.



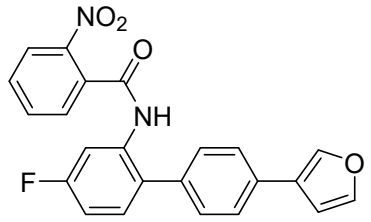
N-(4'-(furan-3-yl)-[1,1'-biphenyl]-2-yl)-4-nitrobenzamide (A17).

69% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.29 (s, 1H), 8.32 (d, *J* = 8.4 Hz, 2H), 8.20 (s, 1H), 8.05 (d, *J* = 8.3 Hz, 2H), 7.73 (t, *J* = 1.7 Hz, 1H), 7.63 (d, *J* = 8.0 Hz, 2H), 7.50 (d, *J* = 7.5 Hz, 1H), 7.48 – 7.41 (m, 5H), 6.97 (d, *J* = 1.8 Hz, 1H); ^{13}C NMR (151 MHz, DMSO) δ 164.21, 149.16, 144.36, 140.07, 139.51, 138.07, 137.60, 134.37, 130.88, 130.28, 128.97, 128.47, 127.92, 127.24, 125.42, 123.63, 108.6; ESI-MS *m/z* : 385.2 $[M+H]^+$.



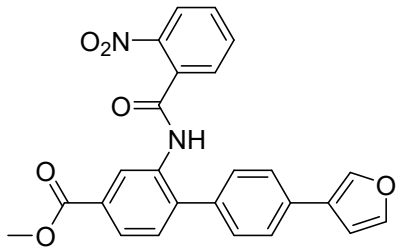
N-(4'-(furan-3-yl)-[1,1'-biphenyl]-3-yl)-4-nitrobenzamide (A18)

72% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.66 (s, 1H), 8.39 (d, *J* = 8.7 Hz, 2H), 8.26 (s, 1H), 8.23 (d, *J* = 8.8 Hz, 2H), 8.12 (s, 1H), 7.82 (td, *J* = 4.5, 2.1 Hz, 1H), 7.77 (t, *J* = 1.7 Hz, 1H), 7.74 (d, *J* = 8.3 Hz, 2H), 7.68 (d, *J* = 8.2 Hz, 2H), 7.48 (s, 1H), 7.48 (s, 1H), 7.02 (d, *J* = 1.8 Hz, 1H); ^{13}C NMR (151 MHz, DMSO) δ 163.99, 149.22, 144.42, 140.55, 140.24, 139.57, 139.34, 138.36, 131.35, 129.39, 129.25, 126.99, 126.15, 125.39, 123.61, 122.34, 119.47, 118.51, 108.67; ESI-MS *m/z*: 382.8 $[M-H]^-$.



N-(4-fluoro-4'-(furan-3-yl)-[1,1'-biphenyl]-2-yl)-2-nitrobenzamide (A21)

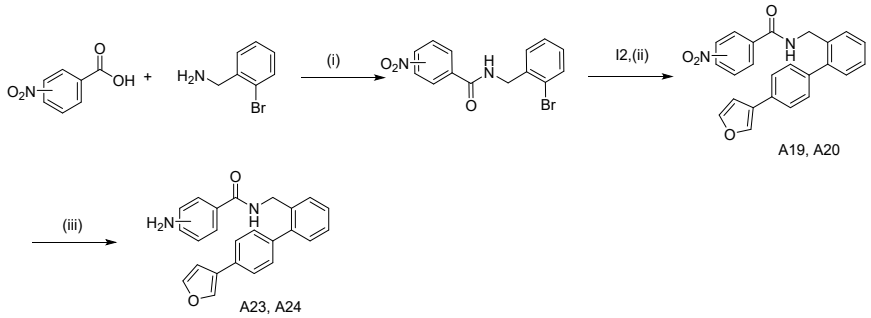
56% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.33 (s, 1H), 8.33 (d, J = 8.7 Hz, 2H), 8.21 – 8.20 (m, 1H), 8.04 (d, J = 8.3 Hz, 2H), 7.73 (t, J = 1.7 Hz, 1H), 7.64 (d, J = 8.4 Hz, 2H), 7.51 – 7.46 (m, 2H), 7.44 (d, J = 8.1 Hz, 2H), 7.27 (td, J = 8.4, 2.8 Hz, 1H), 6.97 (d, J = 1.8 Hz, 1H); ^{13}C NMR (151 MHz, DMSO) δ 164.25, 161.16, 149.24, 144.37, 139.81, 139.56, 136.62, 135.95, 134.02, 131.82, 131.01, 130.09, 129.06, 125.52, 125.40, 123.65, 114.73, 113.92, 108.66; ESI-MS *m/z* : 400.8 $[M-H]^-$.



Methyl 4'-(furan-3-yl)-2-(2-nitrobenzamido)-[1,1'-biphenyl]-4-carboxylate (A22)

68% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.44 (s, 1H), 8.33 (d, J = 8.8 Hz, 2H), 8.23 (t, J = 1.2 Hz, 1H), 8.11 (d, J = 1.8 Hz, 1H), 8.06 (d, J = 8.4 Hz, 2H), 7.97 (dd, J = 8.0, 1.8 Hz, 1H), 7.74 (t, J = 1.7 Hz, 1H), 7.67 (d, J = 8.3 Hz, 2H), 7.62 (d, J = 8.1 Hz, 1H), 7.51 (d, J = 8.2 Hz, 2H), 6.99 (dd, J = 1.9, 0.9 Hz, 1H), 3.90 (s, 4H); ^{13}C NMR (151 MHz, DMSO) δ 165.66, 164.35, 149.25, 144.43, 142.33, 139.79, 139.75, 136.50, 134.77, 131.62, 130.87, 129.08, 129.05, 128.93, 128.91, 127.59, 125.56, 125.32, 123.65, 108.64, 52.35; ESI-MS *m/z* : 465.0 $[M+Na]^+$.

1.3 General synthetic procedure for A19, A20, A23, A24.

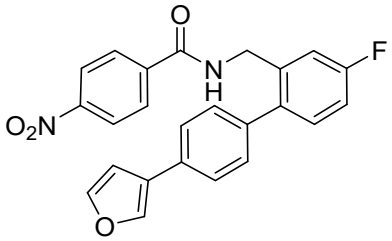


The mixture of 2-Bromobenzamine (1.01 g, 5.44 mmol), virous nitrobenzoic acid (1.0 g, 5.98 mmol), HATU (2.48 g, 6.53 mmol) was dissolved in 50 mL DMF. Then DIPEA (1.9 mL, 10.88 mmol) was added and the reaction was stirred at room temperature for 12 h. After the reaction was complete monitored by TLC, 50 mL ethyl acetate and 50 mL water were added to the flask, then separated from the organic layer through the separating funnel, and washed three times with 1M HCl, 5% NaOH and brine, and the yellow solid was obtained after removing the solvent. The product is used directly in the next step of the reaction without subsequent treatment.

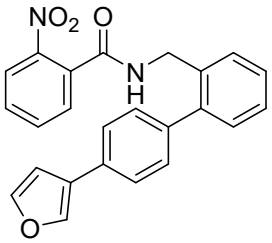
The In a 100 mL nightshade bottle, the product obtained above (0.675 g, 3.6 mmol),

condensation product obtained from the previous step (1.0 g, 3.0 mmol), potassium acetate (0.88 g, 9.0 mmol) were dissolved in 40 mL solvent (dioxane:water = 3:1). After adding $PdCl_2$(pddf) (0.08 g, 0.11 mmol), the reaction system was protected by nitrogen and heated to 90ºC for 12 h. After the reaction was complete monitored by TLC, 30mL of ethyl acetate and 20 mL of water were added, the ethyl acetate layer was separated after stirring for 5 ml, washed twice with water and brine, and then dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure after filtering the solid and purified by column chromatography (PE: EA = 5:1) to obtain the compound **A19** and **A20**.

Compound A20 (0.3 g, 0.75 mmol) was dissolved in 20 mL of tetrahydrofuran in a 50 mL round-bottom flask, and 1 drop of glacial acetic acid was added. 0.03 g of Pd/C (10% mol) was introduced to the solution. The air was replaced with hydrogen gas, and the mixture was stirred at room temperature for 12 hours. After completion of the reaction monitored by TLC, the solution was filtered to remove Pd/C, and the solvent was evaporated under vacuum. The crude product was purified by silica gel column chromatography (DCM: MeOH= 20:1) to yield A23. Compound A24 was obtained using the same synthesis method.

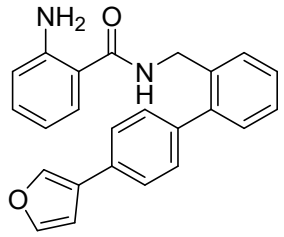


N-((4-fluoro-4'-(furan-3-yl)-[1,1'-biphenyl]-2-yl)methyl)-4-nitrobenzamide (A19)
56% yield. ^{1}H NMR (600 MHz, DMSO-d6) δ 9.27 (t, J = 5.5 Hz, 1H), 8.31 (d, J = 8.7 Hz, 2H), 8.25 (s, 1H), 8.09 (d, J = 8.7 Hz, 2H), 7.77 (s, 1H), 7.71 (d, J = 8.1 Hz, 2H), 7.48 (s, 1H), 7.45 (d, J = 8.1 Hz, 2H), 7.41 – 7.34 (m, 2H), 7.29 (d, J = 7.0 Hz, 1H), 7.02 (s, 1H), 4.50 (d, J = 5.4 Hz, 2H). ^{13}C NMR (151 MHz, DMSO) δ 164.66, 149.01, 144.37, 140.52, 139.94, 139.50, 138.88, 135.96, 130.88, 129.71, 129.56, 128.81, 127.77, 127.58, 127.05, 125.49, 125.46, 123.50, 41.03; ESI-MS *m/z* : 421.1 $[M+Na]^+$.



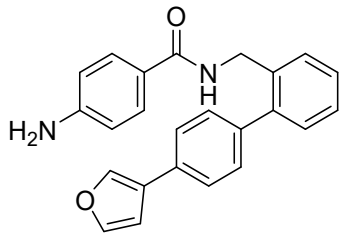
N-((4'-(furan-3-yl)-[1,1'-biphenyl]-2-yl)methyl)-2-nitrobenzamide (A20)
73% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.14 (t, *J* = 5.5 Hz, 1H), 8.26 (s, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.80 – 7.75 (m, 2H), 7.72 (d, *J* = 8.1 Hz, 2H), 7.70 – 7.66 (m, 1H), 7.57 (dd, *J* = 14.9, 7.5 Hz, 2H), 7.43 (d, *J* = 8.1 Hz, 2H), 7.42 – 7.40 (m, 1H), 7.37 (t, *J* = 7.2 Hz, 1H), 7.29 (d, *J* = 7.1 Hz, 1H), 7.03 (s, 1H), 4.43 (d, *J* = 5.5 Hz,

2H). ^{13}C NMR (151 MHz, DMSO) δ 165.46, 147.03, 144.39, 140.46, 139.52, 138.81, 135.67, 133.57, 132.42, 130.93, 130.72, 129.65, 129.59, 129.16, 128.03, 127.57, 127.13, 125.52, 124.06, 108.74, 40.75. ESI-MS *m/z* =399.3 $[M+H]^+$.



2-amino-N-((4'-(furan-3-yl)-[1,1'-biphenyl]-2-yl)methyl)benzamide (A23)

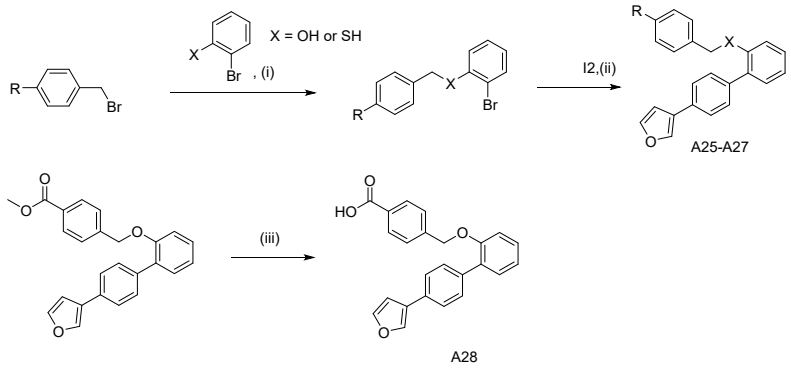
76% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.69 (t, *J* = 5.8 Hz, 1H), 8.26 (t, *J* = 1.2 Hz, 1H), 7.77 (t,n*J* = 1.7 Hz, 1H), 7.72 (d, *J* = 8.2 Hz, 2H), 7.55 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.45 (d, *J* = 8.2 Hz, 2H), 7.43 (d, *J* = 1.5 Hz, 1H), 7.35 (dtd, *J* = 22.3, 7.4, 1.5 Hz, 2H), 7.26 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.14 (ddd, *J* = 8.4, 7.1, 1.6 Hz, 1H), 7.03 (dd, *J* = 1.9, 0.9 Hz, 1H), 6.70 (dd, *J* = 8.3, 1.2 Hz, 1H), 6.52 (ddd, *J* = 8.1, 7.0, 1.3 Hz, 1H), 6.41 (s, 2H), 4.42 (d, *J* = 5.7 Hz, 2H); ^{13}C NMR (151 MHz, DMSO) δ 168.90, 149.71, 144.39, 140.26, 139.51, 139.02, 136.82, 131.78, 130.85, 129.62, 129.60, 128.20, 127.49, 127.31, 126.75, 125.55, 125.49, 116.38, 114.62, 114.50, 108.75, 40.25; ESI-MS *m/z* : 369.2 $[M+H]^+$.



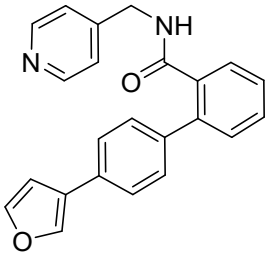
4-amino-N-((4'-(furan-3-yl)-[1,1'-biphenyl]-2-yl)methyl)benzamide (A24)

78% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.48 (t, *J* = 5.8 Hz, 1H), 8.25 (s, 1H), 7.77 (t, *J* = 1.7 Hz, 1H), 7.71 (d, *J* = 8.2 Hz, 2H), 7.62 (d, *J* = 8.7 Hz, 2H), 7.44 (d, *J* = 8.2 Hz, 2H), 7.41 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.35 (td, *J* = 7.4, 1.7 Hz, 1H), 7.31 (td, *J* = 7.3, 1.7 Hz, 1H), 7.25 (dd, *J* = 7.4, 1.7 Hz, 1H), 7.02 (dd, *J* = 1.9, 0.9 Hz, 1H), 6.55 (d, *J* = 8.6 Hz, 2H), 5.66 – 5.63 (m, 2H), 4.41 (d, *J* = 5.7 Hz, 2H); ^{13}C NMR (151 MHz, DMSO) δ 166.33, 151.65, 144.38, 140.18, 139.50, 139.06, 137.20, 130.82, 129.64, 129.53, 128.85, 127.44, 127.40, 126.65, 125.54, 125.46, 121.05, 112.58, 108.75, 40.38; ESI-MS *m/z*: 369.1 $[M+H]^+$.

1.4 General synthetic route of A25-A28

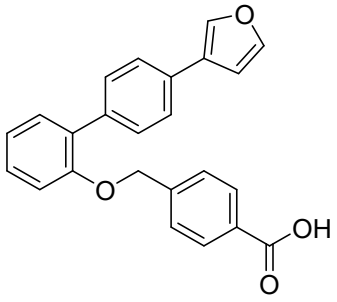


Compounds **A25-A27** were synthesized using the method previously described for A24, while compound 28 was obtained through hydrolysis. The specific steps are as follows: Intermediate (0.5 g, 1.3 mmol) and lithium hydroxide (0.16 g, 3.9 mmol) were dissolved in 20 mL of a methanol-water (3:1) mixture and stirred at 60ºC for 3 hours. The pH was adjusted to 3-4 with 1 M hydrochloric acid, then extracted with ethyl acetate and water. The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, and filtered. After solvent evaporation, the product was purified by column chromatography (PE: EA 5:1) to yield **A28**.



4'-(furan-3-yl)-N-(pyridin-4-ylmethyl)-[1,1'-biphenyl]-2-carboxamide (A25)

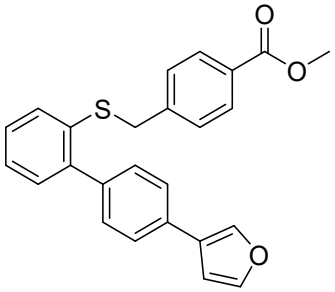
80% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.08 (t, J = 6.0 Hz, 1H), 8.75 (d, J = 6.7 Hz, 2H), 8.26 (t, J = 1.2 Hz, 1H), 7.79 (t, J = 1.7 Hz, 1H), 7.73 (d, J = 6.7 Hz, 2H), 7.61 (d, J = 8.2 Hz, 2H), 7.59 – 7.53 (m, 2H), 7.51 – 7.43 (m, 2H), 7.37 (d, J = 8.2 Hz, 2H), 7.02 (dd, J = 1.9, 0.9 Hz, 1H), 4.56 (d, J = 5.9 Hz, 2H); ^{13}C NMR (151 MHz, DMSO) δ 169.85, 159.44, 144.50, 141.45, 139.57, 138.94, 138.69, 136.32, 131.06, 129.89, 129.81, 128.94, 127.79, 127.24, 125.40, 125.35, 124.93, 108.67, 42.07; ESI-MS *m/z* : 355.3 $[M+H]^+$.



4-(((4'-(furan-3-yl)-[1,1'-biphenyl]-2-yl)oxy)methyl)benzoic acid (A26)

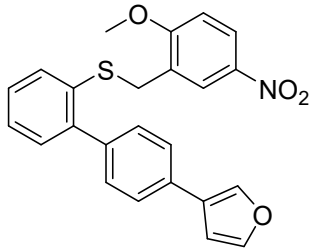
73% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.22 (t, J = 1.3 Hz, 1H), 8.14 (dd, J = 9.1, 2.9 Hz, 1H), 8.00 (d, J = 2.9 Hz, 1H), 7.76 (t, J = 1.7 Hz, 1H), 7.63 (d, J = 8.2 Hz, 2H), 7.50 (dd, J = 7.9, 1.3 Hz, 1H), 7.35 (td, J = 7.5, 1.7 Hz, 1H), 7.31 – 7.27 (m, 3H),

7.25 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.15 (d, *J* = 9.1 Hz, 1H), 6.99 (dd, *J* = 1.9, 0.9 Hz, 1H), 4.10 (s, 2H), 3.85 (s, 3H); ^{13}C NMR (151 MHz, DMSO) δ 162.31, 144.37, 141.68, 140.27, 139.50, 138.59, 134.01, 131.07, 130.04, 129.61, 129.33, 128.10, 126.39, 126.36, 125.49, 125.35, 125.18, 124.99, 111.40, 108.70, 56.57, 31.43; ESI-MS *m/z* : 440.0 $[M+Na]^+$.



Methyl 4-(((4'-(furan-3-yl)-[1,1'-biphenyl]-2-yl)thio)methyl)benzoate (A27)

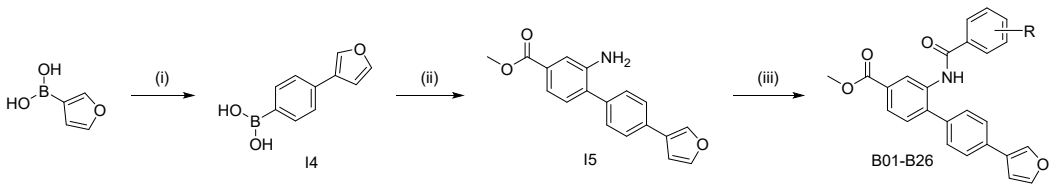
71% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.23 (t, *J* = 1.2 Hz, 1H), 7.84 (d, *J* = 8.3 Hz, 2H), 7.76 (t, *J* = 1.7 Hz, 1H), 7.65 (d, *J* = 8.2 Hz, 2H), 7.47 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.40 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 7.33 – 7.29 (m, 1H), 7.28 – 7.22 (m, 2H), 7.00 (dd, *J* = 1.9, 0.9 Hz, 1H), 4.18 (s, 2H), 3.82 (s, 3H); ^{13}C NMR (151 MHz, DMSO) δ 162.31, 144.37, 141.68, 140.27, 139.50, 138.59, 134.01, 131.07, 130.04, 129.61, 129.33, 128.10, 126.39, 126.36, 125.49, 125.35, 125.18, 124.99, 111.40, 108.70, 56.57, 31.43; ESI-MS *m/z* : 423.1 $[M+Na]^+$.



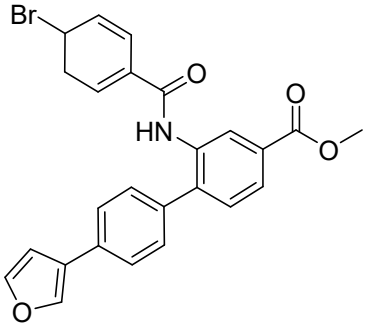
3-(2'-((2-methoxy-5-nitrobenzyl)thio)-[1,1'-biphenyl]-4-yl)furan (A28)

75% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.98 (s, 1H), 8.24 (t, *J* = 1.2 Hz, 1H), 7.95 (d, *J* = 8.3 Hz, 2H), 7.76 (t, *J* = 1.7 Hz, 1H), 7.67 (d, *J* = 8.3 Hz, 2H), 7.59 (d, *J* = 8.3 Hz, 2H), 7.51 (d, *J* = 8.3 Hz, 2H), 7.38 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.34 (ddd, *J* = 8.9, 7.5, 1.8 Hz, 1H), 7.19 (dd, *J* = 8.3, 1.1 Hz, 1H), 7.07 (td, *J* = 7.5, 1.1 Hz, 1H), 7.01 (dd, *J* = 1.9, 0.9 Hz, 1H), 5.24 (s, 2H). ^{13}C NMR (151 MHz, DMSO) δ 167.13, 154.99, 144.33, 142.25, 139.45, 136.57, 130.61, 130.50, 130.09, 129.81, 129.77, 129.47, 128.85, 127.05, 125.60, 125.18, 121.36, 113.25, 108.73, 69.10. ESI-MS *m/z*: 393.3 $[M+Na]^+$.

1.5 General synthetic route of B01-B26

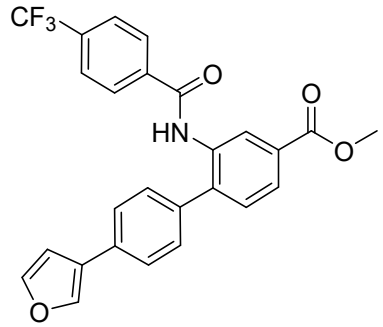


Intermediates **I4** (1.2 g, 2.2 mmol), 2-iodoaniline (0.96 g, 2.2 mmol), and potassium acetate (1.25 g, 6.6 mmol) were dissolved in 80 mL of solvent (dioxane: H_2O = 3:1) in a 250 mL round-bottom flask. After adding $PdCl_2$(dppf) (0.18 g, 0.11 mmol), the system was heated to 100ºC and reacted under nitrogen protection for 12 hours. Once the reaction was completed monitored by TLC, 60 mL of ethyl acetate and 30 mL of water were added. The ethyl acetate layer was separated after stirring for 5 minutes, extracted twice with water and brine, and dried with anhydrous Na_2SO_4. After standing overnight, the anhydrous sodium sulfate was removed by filtrating. The solvent was then evaporated under reduced pressure and the product was purified by column chromatography (PE: EA 5:1) to yield white solids (0.62 g, 59% yield). Target compounds **B01-B216** were obtained by condensation with substituted aniline.



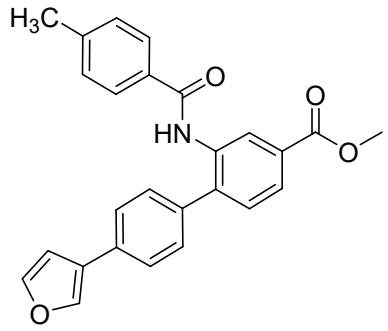
Methyl 2-(4-bromocyclohexa-1,5-diene-1-carboxamido)-4'-(furan-3-yl)-[1,1'-biphenyl]-4-carboxylate (B01)

68% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.15 (s, 1H), 8.23 (t, J = 1.2 Hz, 1H), 8.08 (d, J = 1.8 Hz, 1H), 7.95 (dd, J = 8.0, 1.8 Hz, 1H), 7.79 – 7.77 (m, 2H), 7.74 (t, J = 1.7 Hz, 1H), 7.71 – 7.69 (m, 2H), 7.67 – 7.65 (m, 2H), 7.60 (d, J = 8.1 Hz, 1H), 7.51 – 7.47 (m, 2H), 6.99 (dd, J = 1.9, 0.9 Hz, 1H), 3.90 (s, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 166.6, 165.4, 145.4, 142.7, 141.0, 137.0, 135.5, 133.7, 131.9, 131.3, 130.1, 129.4, 127.8, 125.9, 108.6, 61.3, 52.7; ESI-MS *m/z* : 500.4 $[M+Na]^+$.



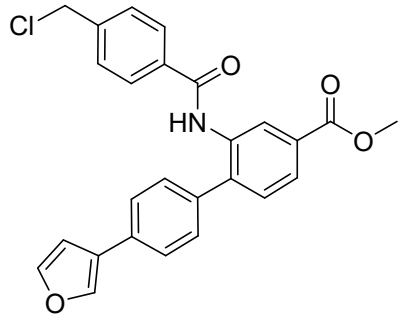
Methyl 4'-(furan-3-yl)-2-(4-(trifluoromethyl)benzamido)-[1,1'-biphenyl]-4-carboxylate (B02)

59% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.33 (s, 1H), 8.23 (t, J = 1.2 Hz, 1H), 8.11 (d, J = 1.8 Hz, 1H), 8.02 (d, J = 8.1 Hz, 2H), 7.97 (dd, J = 8.1, 1.8 Hz, 1H), 7.88 (d, J = 8.1 Hz, 2H), 7.74 (t, J = 1.7 Hz, 1H), 7.68 – 7.67 (m, 2H), 7.61 (d, J = 8.0 Hz, 1H), 7.52 – 7.50 (m, 2H), 6.99 – 6.99 (m, 1H), 3.90 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 166.1, 164.8, 145.3, 143.2, 140.2, 138.4, 136.9, 135.8, 132.0, 131.3, 129.3, 128.9, 127.9, 126.1, 125.8, 109.1, 52.7; ESI-MS *m/z* : 464.3 $[M-H]^-$.



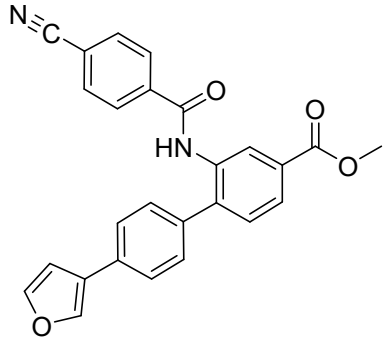
Methyl 4'-(furan-3-yl)-2-(4-methylbenzamido)-[1,1'-biphenyl]-4-carboxylate (B03)

61% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.94 (s, 1H), 8.23 (t, J = 1.2 Hz, 1H), 8.09 (d, J = 1.8 Hz, 1H), 7.94 (dd, J = 8.0, 1.8 Hz, 1H), 7.75 – 7.73 (m, 3H), 7.68 – 7.65 (m, 2H), 7.59 (d, J = 8.0 Hz, 1H), 7.51 – 7.49 (m, 2H), 7.28 (d, J = 7.9 Hz, 2H), 6.99 (dd, J = 1.9, 0.9 Hz, 1H), 3.90 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 166.2, 144.4, 142.2, 141.1, 137.1, 135.8, 132.8, 131.2, 129.4, 128.4, 126.4, 110.0, 52.2; ESI-MS *m/z*: 434.2 $[M+Na]^+$.



Methyl 2-(4-(chloromethyl)benzamido)-4'-(furan-3-yl)-[1,1'-biphenyl]-4-carboxylate (B04)

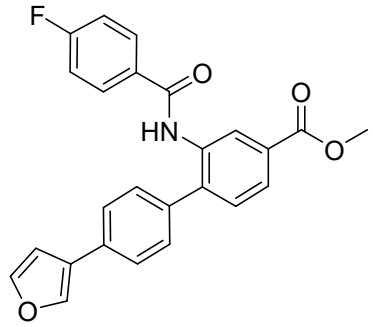
71% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.09 (s, 1H), 8.23 (t, J = 1.2 Hz, 1H), 8.10 (d, J = 1.8 Hz, 1H), 7.94 (dd, J = 8.0, 1.8 Hz, 1H), 7.83 (d, J = 8.0 Hz, 2H), 7.74 (t, J = 1.7 Hz, 1H), 7.68 – 7.66 (m, 2H), 7.60 (d, J = 8.1 Hz, 1H), 7.53 (d, J = 8.2 Hz, 2H), 7.51 – 7.49 (m, 2H), 6.99 (dd, J = 2.0, 0.9 Hz, 1H), 4.80 (s, 2H), 3.90 (s, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 166.2, 143.9, 142.6, 141.6, 140.2, 136.4, 134.4, 132.0, 129.2, 127.6, 125.9, 109.8, 52.8, 47.0; ESI-MS *m/z* : 468.2 $[M+Na]^+$



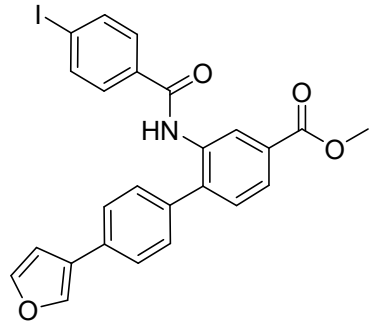
Methyl 2-(4-cyanobenzamido)-4'-(furan-3-yl)-[1,1'-biphenyl]-4-carboxylate (B05)

72% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.34 (s, 1H), 8.23 (t, J = 1.2 Hz, 1H), 8.10 (d, J = 1.8 Hz, 1H), 7.99 – 7.96 (m, 5H), 7.74 (t, J = 1.7 Hz, 1H), 7.69 – 7.66 (m,

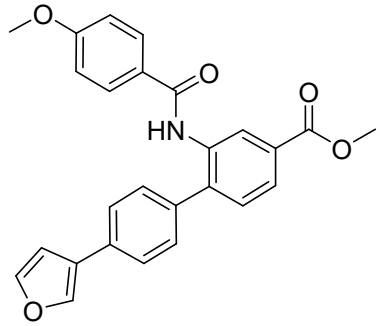
2H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.51 – 7.48 (m, 2H), 6.99 (dd, *J* = 1.9, 0.9 Hz, 1H), 3.90 (s, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 167.2, 145.3, 142.7, 140.2, 138.6, 136.9, 134.7, 133.0, 132.1, 131.3, 129.4, 128.8, 127.9, 126.0, 118.7, 113.4, 108.7, 52.4; ESI-MS *m/z*: 445.1 $[M+Na]^+$.



Methyl 2-(4-fluorobenzamido)-4'-(furan-3-yl)-[1,1'-biphenyl]-4-carboxylate (B06) 74% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.09 (s, 1H), 8.23 (t, *J* = 1.2 Hz, 1H), 8.09 (d, *J* = 1.8 Hz, 1H), 7.95 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.92 – 7.89 (m, 2H), 7.75 (t, *J* = 1.7 Hz, 1H), 7.68 – 7.66 (m, 2H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.51 – 7.49 (m, 2H), 7.34 – 7.31 (m, 2H), 6.99 (dd, *J* = 1.9, 0.9 Hz, 1H), 3.90 (s, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 166.2, 165.2, 144.8, 142.7, 139.3, 137.1, 135.6, 131.2, 130.7, 129.4, 128.6, 127.3, 125.9, 125.3, 115.8, 109.1, 53.2; ESI-MS *m/z*: 438.2 $[M+Na]^+$.

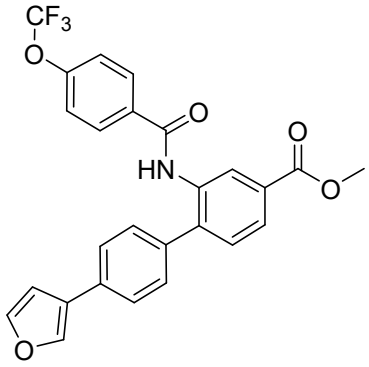


Methyl 4'-(furan-3-yl)-2-(4-iodobenzamido)-[1,1'-biphenyl]-4-carboxylate (B07) 76% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.13 (s, 1H), 8.23 (t, *J* = 1.2 Hz, 1H), 8.08 (d, *J* = 1.8 Hz, 1H), 7.95 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.89 – 7.87 (m, 2H), 7.75 (t, *J* = 1.7 Hz, 1H), 7.67 – 7.66 (m, 2H), 7.61 (dd, *J* = 9.6, 7.6 Hz, 3H), 7.50 – 7.48 (m, 2H), 7.00 – 6.99 (m, 1H), 3.90 (s, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 166.1, 165.2, 144.4, 142.6, 140.2, 137.8, 136.4, 135.5, 133.9, 132.1, 131.5, 131.2, 129.9, 129.4, 128.4, 125.9, 125.1, 110.5, 99.2, 52.8; ESI-MS *m/z*: 546.1 $[M+Na]^+$.



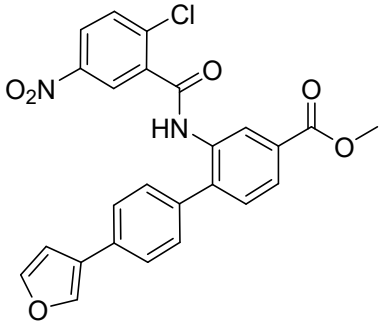
Methyl 4'-(furan-3-yl)-2-(4-methoxybenzamido)-[1,1'-biphenyl]-4-carboxylate (B08)

^{1}H NMR (600 MHz, DMSO-d_6) δ 9.86 (s, 1H), 8.23 (t, J = 1.1 Hz, 1H), 8.10 (d, J = 1.8 Hz, 1H), 7.92 (dd, J = 8.0, 1.8 Hz, 1H), 7.83 – 7.81 (m, 2H), 7.74 (t, J = 1.7 Hz, 1H), 7.67 – 7.65 (m, 2H), 7.58 (d, J = 8.1 Hz, 1H), 7.50 – 7.48 (m, 2H), 7.01 (d, J = 2.1 Hz, 1H), 7.00 – 6.99 (m, 2H), 3.89 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (151 MHz, DMSO-d6) δ 166.2, 165.7, 162.4, 144.8, 142.5, 140.2, 137.1, 135.9, 131.9, 131.2, 129.9, 129.4, 127.4, 126.6, 125.9, 114.1, 109.1, 55.8, 52.7; ESI-MS *m/z*: 450.1 $[M+Na]^+$.



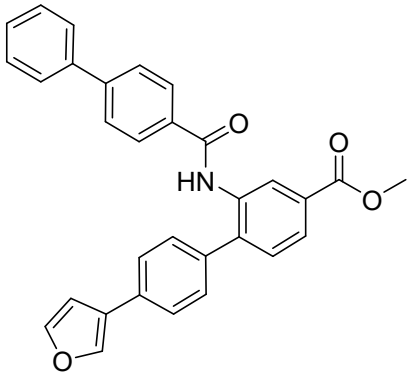
methyl 4'-(furan-3-yl)-2-(4-(trifluoromethoxy)benzamido)-[1,1'-biphenyl]-4-carboxylate (B09)

75% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.20 (s, 1H), 8.23 (t, J = 1.1 Hz, 1H), 8.10 (d, J = 1.8 Hz, 1H), 7.95 (dd, J = 8.0, 1.7 Hz, 3H), 7.74 (t, J = 1.7 Hz, 1H), 7.69 – 7.66 (m, 2H), 7.60 (d, J = 8.0 Hz, 1H), 7.50 (dd, J = 9.9, 8.0 Hz, 4H), 7.01 – 6.98 (m, 1H), 3.90 (s, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 166.9, 165.5, 150.9, 144.4, 142.2, 141.1, 137.0, 135.4, 133.7, 132.5, 131.3, 130.4, 129.4, 127.8, 126.0, 121.3, 110.1, 52.8; ESI-MS *m/z*: 480.2 $[M-H]^-$.



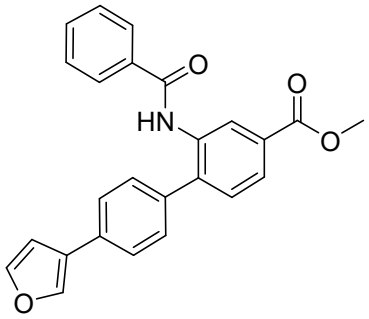
Methyl 2-(2-chloro-5-nitrobenzamido)-4'-(furan-3-yl)-[1,1'-biphenyl]-4-carboxylate (B10)

76% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.40 (s, 1H), 8.36 (d, J = 2.7 Hz, 1H), 8.29 (d, J = 2.1 Hz, 2H), 8.25 (t, J = 1.2 Hz, 1H), 7.96 (dd, J = 8.0, 1.8 Hz, 1H), 7.84 – 7.82 (m, 1H), 7.77 (t, J = 1.7 Hz, 1H), 7.74 – 7.71 (m, 2H), 7.59 (d, J = 8.0 Hz, 1H), 7.54 – 7.52 (m, 2H), 7.01 (dd, J = 1.9, 0.9 Hz, 1H), 3.92 (s, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 166.1, 164.0, 145.9, 145.3, 142.2, 140.7, 137.7, 136.6, 134.7, 131.7, 130.0, 125.8, 124.3, 109.1, 53.5; ESI-MS *m/z*: 475.2 $[M-H]^-$.



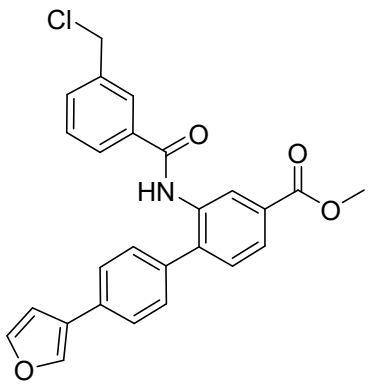
Methyl 2-([1,1'-biphenyl]-4-carboxamido)-4'-(furan-3-yl)-[1,1'-biphenyl]-4-carboxylate (B11)

62% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.11 (s, 1H), 8.23 (d, J = 1.5 Hz, 1H), 8.13 (d, J = 1.8 Hz, 1H), 7.95 – 7.93 (m, 3H), 7.79 (d, J = 6.3 Hz, 2H), 7.74 – 7.72 (m, 3H), 7.69 (d, J = 8.2 Hz, 2H), 7.61 (d, J = 8.0 Hz, 1H), 7.53 (d, J = 8.2 Hz, 2H), 7.48 (d, J = 7.7 Hz, 2H), 7.41 (d, J = 7.3 Hz, 1H), 7.00 (d, J = 1.9 Hz, 1H), 3.91 (s, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 166.2, 165.4, 144.8, 143.7, 142.6, 140.2, 139.5, 137.1, 134.9, 133.3, 132.0, 131.3, 127.4, 126.9, 126.0, 110.2, 53.5; ESI-MS *m/z*: 496.2 $[M+Na]^+$.



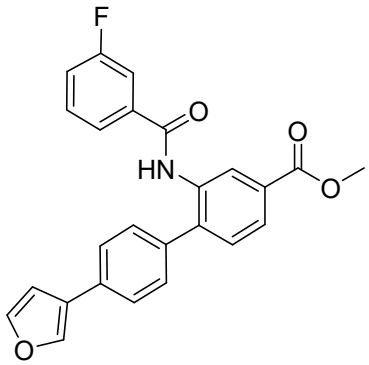
Methyl 2-benzamido-4'-(furan-3-yl)-[1,1'-biphenyl]-4-carboxylate (B12)

55% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.05 (s, 1H), 8.24 (s, 1H), 8.11 (d, J = 1.8 Hz, 1H), 7.95 (dd, J = 8.1, 1.8 Hz, 1H), 7.85 – 7.82 (m, 2H), 7.74 (t, J = 1.7 Hz, 1H), 7.69 – 7.67 (m, 2H), 7.60 (d, J = 8.0 Hz, 1H), 7.57 – 7.54 (m, 1H), 7.52 – 7.50 (m, 2H), 7.48 (dd, J = 8.3, 7.0 Hz, 2H), 7.00 (dd, J = 1.9, 0.9 Hz, 1H), 3.90 (s, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 166.3, 166.2, 144.8, 142.6, 140.1, 137.0, 135.4, 134.1, 132.1, 132.0, 131.3, 129.4, 128.8, 128.0, 125.9, 125.7, 109.0, 52.8; ESI-MS *m/z*: 420.1 $[M+Na]^+$.



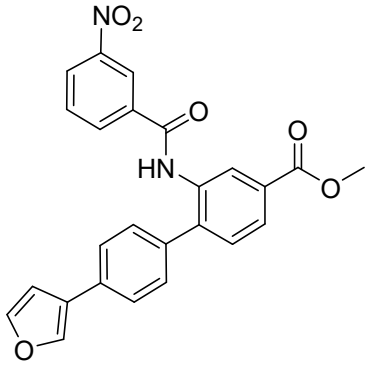
Methyl 2-(3-(chloromethyl)benzamido)-4'-(furan-3-yl)-[1,1'-biphenyl]-4-carboxylate (B13)

69% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.12 (s, 1H), 8.22 (t, J = 1.2 Hz, 1H), 8.10 (d, J = 1.8 Hz, 1H), 7.95 (dd, J = 8.0, 1.8 Hz, 1H), 7.90 (d, J = 1.8 Hz, 1H), 7.80 – 7.79 (m, 1H), 7.74 (t, J = 1.7 Hz, 1H), 7.69 – 7.66 (m, 2H), 7.60 (d, J = 8.1 Hz, 2H), 7.52 (s, 1H), 7.51 – 7.48 (m, 2H), 6.98 (dd, J = 1.8, 0.9 Hz, 1H), 4.80 (s, 2H), 3.90 (s, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 167.1, 144.1, 143.0, 140.1, 138.4, 137.0, 135.0, 132.8, 132.0, 129.2, 128.6, 125.9, 125.3, 109.1, 52.8, 46.6; ESI-MS *m/z*: 468.1 $[M+Na]^+$.



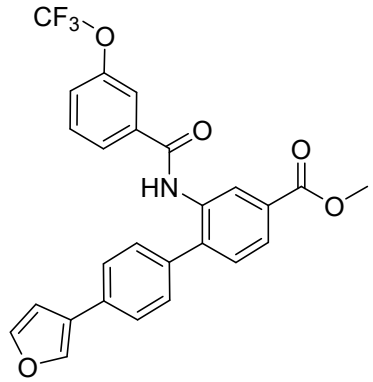
Methyl 2-(3-fluorobenzamido)-4'-(furan-3-yl)-[1,1'-biphenyl]-4-carboxylate (B14)

52% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.17 (s, 1H), 8.23 (d, J = 1.4 Hz, 1H), 8.09 (d, J = 1.8 Hz, 1H), 7.96 (dd, J = 8.1, 1.8 Hz, 1H), 7.74 (d, J = 2.0 Hz, 1H), 7.69 – 7.67 (m, 3H), 7.61 (dd, J = 11.9, 9.0 Hz, 2H), 7.55 – 7.53 (m, 1H), 7.50 (d, J = 8.1 Hz, 2H), 7.41 (td, J = 8.5, 2.6 Hz, 1H), 7.00 – 6.99 (m, 1H), 3.90 (s, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 166.1, 164.5, 163.1, 161.5, 144.8, 142.7, 140.6, 137.5, 135.4, 133.3, 131.2, 129.4, 127.3, 125.9, 123.8, 118.9, 114.7, 109.0, 53.5; ESI-MS *m/z*: 438.1 $[M+Na]^+$.



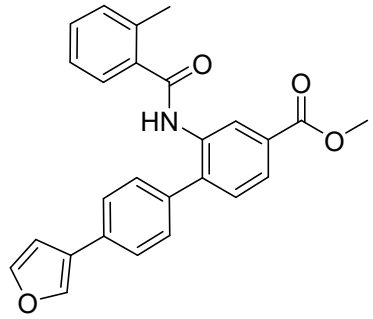
Methyl 4'-(furan-3-yl)-2-(3-nitrobenzamido)-[1,1'-biphenyl]-4-carboxylate (B15).

73% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.47 (s, 1H), 8.65 (s, 1H), 8.41 (dd, J = 8.2, 2.4 Hz, 1H), 8.26 (d, J = 7.3 Hz, 1H), 8.22 (s, 1H), 8.13 (d, J = 1.8 Hz, 1H), 7.97 (dd, J = 8.1, 1.8 Hz, 1H), 7.80 (t, J = 4.3 Hz, 1H), 7.74 (t, J = 1.7 Hz, 1H), 7.68 (d, J = 8.1 Hz, 2H), 7.62 (d, J = 7.9 Hz, 1H), 7.52 (d, J = 7.9 Hz, 2H), 6.98 (d, J = 1.9 Hz, 1H), 3.90 (s, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 166.1, 148.2, 145.5, 142.7, 140.8, 136.9, 136.0, 134.5, 132.8, 130.7, 129.3, 126.0, 122.8, 109.1, 52.2; ESI-MS *m/z*: 465.1 $[M+Na]^+$.



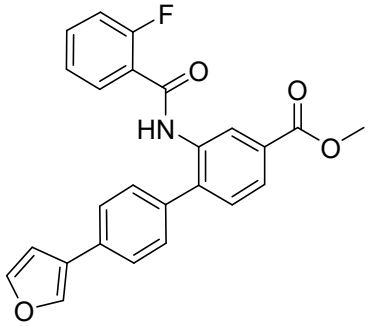
Methyl 4'-(furan-3-yl)-2-(3-(trifluoromethoxy)benzamido)-[1,1'-biphenyl]-4-carboxylate (B16)

64% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.24 (s, 1H), 8.22 (dd, J = 1.5, 0.9 Hz, 1H), 8.11 (d, J = 1.8 Hz, 1H), 7.96 (dd, J = 8.0, 1.8 Hz, 1H), 7.86 (d, J = 7.7 Hz, 1H), 7.75 (dt, J = 8.3, 1.7 Hz, 2H), 7.69 – 7.66 (m, 2H), 7.64 (t, J = 8.0 Hz, 1H), 7.61 (d, J = 8.0 Hz, 1H), 7.59 – 7.56 (m, 1H), 7.50 (d, J = 8.3 Hz, 2H), 6.98 (dd, J = 1.9, 0.9 Hz, 1H), 3.90 (s, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 166.1, 164.8, 148.7, 144.8, 142.7, 140.6, 137.4, 135.4, 132.7, 131.2, 129.6, 127.9, 127.1, 125.9, 120.5, 110.6, 52.7; ESI-MS *m/z*: 480.2 $[M-H]^-$.

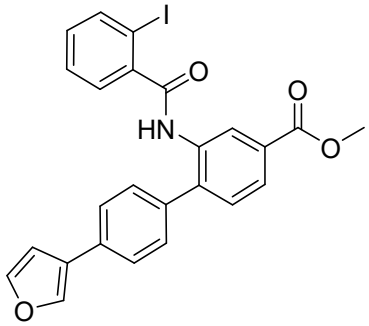


Methyl 4'-(furan-3-yl)-2-(2-methylbenzamido)-[1,1'-biphenyl]-4-carboxylate (B17)

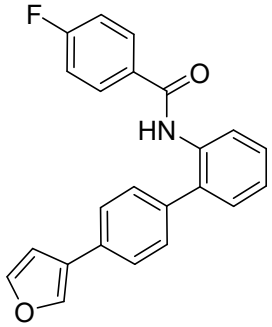
69% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.95 (s, 1H), 8.25 (t, J = 1.2 Hz, 1H), 8.13 – 8.12 (m, 1H), 7.94 (dd, J = 8.0, 1.8 Hz, 1H), 7.76 (t, J = 1.7 Hz, 1H), 7.72 – 7.70 (m, 2H), 7.56 (d, J = 8.0 Hz, 1H), 7.49 (d, J = 8.2 Hz, 2H), 7.38 (d, J = 7.7 Hz, 1H), 7.33 (td, J = 7.5, 1.4 Hz, 1H), 7.23 (dd, J = 7.5, 2.9 Hz, 2H), 7.01 (dd, J = 1.9, 0.9 Hz, 1H), 3.91 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 168.6, 166.2, 145.7, 142.8, 140.6, 137.7, 136.1, 135.7, 132.6, 130.9, 129.6, 128.9, 127.5, 127.4, 125.9, 109.1, 53.7, 20.1; ESI-MS *m/z*: 434.1 $[M+Na]^+$.



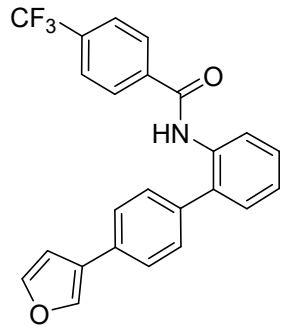
Methyl 2-(2-fluorobenzamido)-4'-(furan-3-yl)-[1,1'-biphenyl]-4-carboxylate (B18) 77% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.95 (d, J = 3.2 Hz, 1H), 8.29 (s, 1H), 8.27 (t, J = 1.3 Hz, 1H), 7.92 (dd, J = 8.0, 1.8 Hz, 1H), 7.76 (t, J = 1.7 Hz, 1H), 7.72 (d, J = 8.2 Hz, 2H), 7.64 (t, J = 7.5 Hz, 1H), 7.58 – 7.54 (m, 2H), 7.52 (d, J = 8.0 Hz, 2H), 7.29 (t, J = 7.8 Hz, 2H), 7.03 (d, J = 2.3 Hz, 1H), 3.91 (s, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 165.6, 144.9, 141.5, 140.2, 136.7, 135.3, 132.8, 132.1, 131.3, 130.5, 129.6, 127.4, 126.1, 116.7, 108.5, 52.8; ESI-MS *m/z*: 438.1 $[M+Na]^+$.



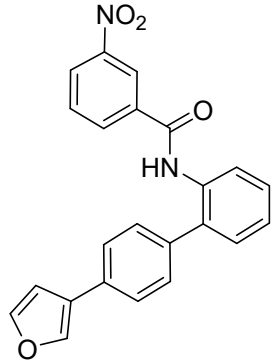
Methyl 4'-(furan-3-yl)-2-(2-iodobenzamido)-[1,1'-biphenyl]-4-carboxylate (B19) 63% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.13 (s, 1H), 8.26 (t, J = 1.2 Hz, 1H), 8.23 (d, J = 1.9 Hz, 1H), 7.94 (dd, J = 8.0, 1.8 Hz, 1H), 7.90 (dd, J = 7.9, 1.1 Hz, 1H), 7.76 (t, J = 1.7 Hz, 1H), 7.74 – 7.72 (m, 2H), 7.57 (d, J = 8.1 Hz, 1H), 7.56 – 7.54 (m, 2H), 7.45 (dt, J = 7.6, 2.3 Hz, 1H), 7.33 (dd, J = 7.6, 1.7 Hz, 1H), 7.18 (td, J = 7.7, 1.7 Hz, 1H), 7.01 (dd, J = 1.9, 0.9 Hz, 1H), 3.91 (s, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 168.5, 167.1, 145.5, 142.8, 142.1, 140.1, 139.5, 136.5, 135.2, 132.1, 131.4, 129.2, 128.3, 127.4, 125.9, 109.5, 93.9, 52.8; ESI-MS *m/z*: 546.0 $[M+Na]^+$.



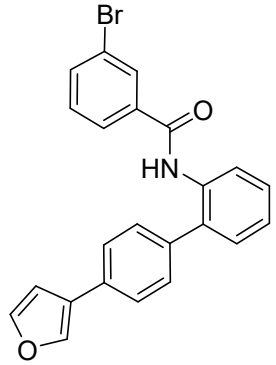
Methyl 4'-(furan-3-yl)-2-(2-nitrobenzamido)-[1,1'-biphenyl]-4-carboxylate (B20) 79% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.35 (s, 1H), 8.27 – 8.24 (m, 1H), 8.12 (t, J = 1.5 Hz, 1H), 8.10 – 8.06 (m, 2H), 7.81 (dt, J = 6.9, 2.3 Hz, 1H), 7.77 (t, J = 1.7 Hz, 1H), 7.75 – 7.72 (m, 2H), 7.70 – 7.64 (m, 2H), 7.48 – 7.44 (m, 2H), 7.41 – 7.37 (m, 2H), 7.02 (dd, J = 1.9, 0.9 Hz, 1H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 164.9, 144.8, 139.9, 138.1, 131.7, 130.8, 129.7, 122.3, 120.7, 118.8, 115.9, 109.1; ESI-MS *m/z*: 380.0 $[M+Na]^+$.



N-(4'-(furan-3-yl)-[1,1'-biphenyl]-2-yl)-4-(trifluoromethyl)benzamide (B21)
61% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.56 (s, 1H), 8.26 (s, 1H), 8.19 (d, J = 8.1 Hz, 2H), 8.13 (s, 1H), 7.94 (d, J = 8.1 Hz, 2H), 7.84 – 7.81 (m, 1H), 7.77 (t, J = 1.7 Hz, 1H), 7.74 (d, J = 8.3 Hz, 2H), 7.68 (d, J = 8.2 Hz, 2H), 7.47 (d, J = 5.0 Hz, 2H), 7.02 (d, J = 1.9 Hz, 1H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 164.9, 144.8, 141.0, 139.9, 138.8, 132.0, 130.2, 128.6, 127.2, 126.6, 122.2, 119.8, 118.9, 110.0; ESI-MS *m/z*: 406.2 $[M-H]^-$.

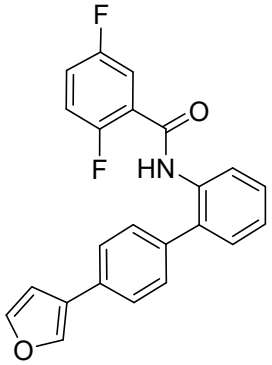


N-(4'-(furan-3-yl)-[1,1'-biphenyl]-2-yl)-3-nitrobenzamide (B22)
59% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.69 (s, 1H), 8.85 (t, J = 2.0 Hz, 1H), 8.47 – 8.45 (m, 2H), 8.26 (t, J = 1.2 Hz, 1H), 8.14 (q, J = 1.4 Hz, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.86 (s, 1H), 7.78 (t, J = 1.7 Hz, 1H), 7.76 – 7.73 (m, 2H), 7.70 (d, J = 8.3 Hz, 2H), 7.51 – 7.48 (m, 2H), 7.03 (d, J = 1.9 Hz, 1H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 164.2, 149.0, 144.8, 140.6, 140.1, 139.7, 138.3, 137.2, 134.6, 132.1, 130.6, 129.8, 127.4, 126.6, 125.8, 122.8, 120.0, 118.6, 109.1; ESI-MS *m/z*: 383.2 $[M-H]^-$.



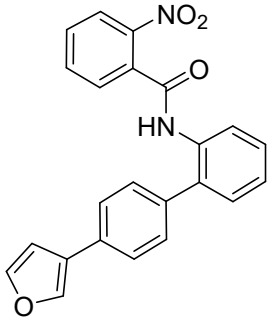
3-bromo-N-(4'-(furan-3-yl)-[1,1'-biphenyl]-2-yl)benzamide (B23)
77% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.43 (s, 1H), 8.25 (t, J = 1.2 Hz, 1H), 8.19 (t, J = 1.9 Hz, 1H), 8.10 (q, J = 1.4 Hz, 1H), 7.99 (dt, J = 7.8, 1.4 Hz, 1H), 7.82 – 7.80 (m, 2H), 7.77 (t, J = 1.7 Hz, 1H), 7.74 (d, J = 8.3 Hz, 2H), 7.68 (d, J = 8.4 Hz,

2H), 7.52 (t, *J* = 7.9 Hz, 1H), 7.48 – 7.44 (m, 2H), 7.02 (d, *J* = 2.2 Hz, 1H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 164.5, 146.6, 141.4, 140.0, 138.8, 137.1, 135.4, 131.1, 130.7, 130.2, 127.9, 126.5, 125.8, 122.1, 118.2, 108.7; ESI-MS *m/z*:418.9 $[M+H]^+$.



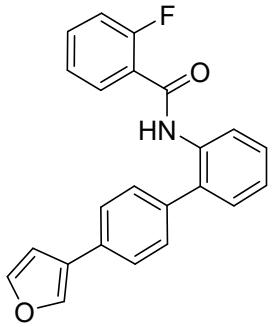
2,5-difluoro-N-(4'-(furan-3-yl)-[1,1'-biphenyl]-2-yl)benzamide (B24)

52% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.47 (s, 1H), 8.26 (s, 1H), 8.16 (s, 1H), 7.86 (t, *J* = 5.0 Hz, 1H), 7.80 – 7.74 (m, 5H), 7.70 (d, *J* = 8.0 Hz, 2H), 7.53 (t, *J* = 9.2 Hz, 1H), 7.48 (d, *J* = 4.7 Hz, 2H), 7.03 (s, 1H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 164.0, 161.9, 144.3, 140.6, 139.9, 133.9, 129.4, 127.5, 126.5, 123.1, 119.9, 118.9, 111.7, 108.7, 107.5; ESI-MS *m/z*: 374.2 $[M-H]^-$.



N-(4'-(furan-3-yl)-[1,1'-biphenyl]-2-yl)-2-nitrobenzamide (B25)

72% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.79 (s, 1H), 8.26 (d, *J* = 1.4 Hz, 1H), 8.17 (d, *J* = 8.2 Hz, 1H), 8.02 (d, *J* = 2.3 Hz, 1H), 7.90 (t, *J* = 7.5 Hz, 1H), 7.82 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.80 – 7.77 (m, 2H), 7.75 – 7.73 (m, 2H), 7.69 (dd, *J* = 6.1, 2.7 Hz, 1H), 7.66 (d, *J* = 8.2 Hz, 2H), 7.48 – 7.45 (m, 2H), 7.02 (d, *J* = 1.8 Hz, 1H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 165.2, 146.9, 144.8, 141.3, 140.2, 138.4, 134.6, 133.1, 131.5, 129.8, 126.6, 124.8, 124.5, 122.2, 119.1, 118.1, 109.1; ESI-MS *m/z*: 383.2 $[M-H]^-$.

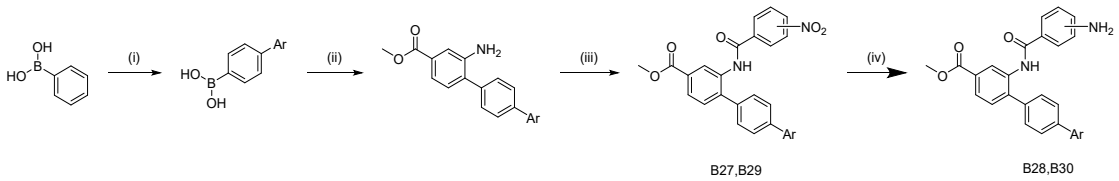


2-fluoro-N-(4'-(furan-3-yl)-[1,1'-biphenyl]-2-yl)benzamide (B26)

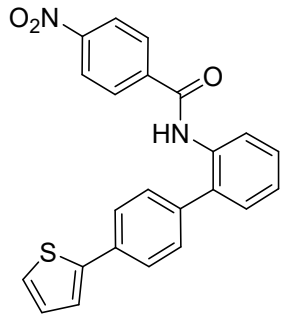
53% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.52 (s, 1H), 8.27 – 8.24 (m, 1H), 8.09 (d, *J* = 2.2 Hz, 1H), 7.77 (t, *J* = 1.7 Hz, 1H), 7.75 – 7.69 (m, 4H), 7.67 (d, *J* = 8.1 Hz,

2H), 7.62 – 7.56 (m, 1H), 7.53 – 7.43 (m, 2H), 7.40 – 7.32 (m, 2H), 7.02 (d, *J* = 1.9 Hz, 1H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 162.9, 160.2, 157.8, 144.8, 140.0, 138.9, 133.1, 131.8, 130.1, 127.5, 126.6, 125.4, 122.5, 118.2, 115.5, 109.6; ESI-MS *m/z*: 380.2 $[M+Na]^+$.

1.6 General synthetic route of B27-B30

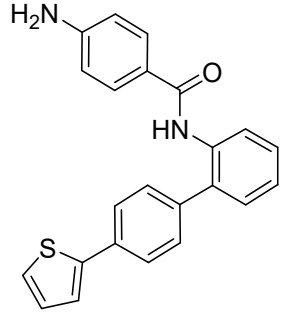


These compounds were synthesized through the similar procedure and the only difference is that the aromatic rings that are replaced are different.



4-nitro-N-(4'-(thiophen-2-yl)-[1,1'-biphenyl]-2-yl)benzamide (B27)

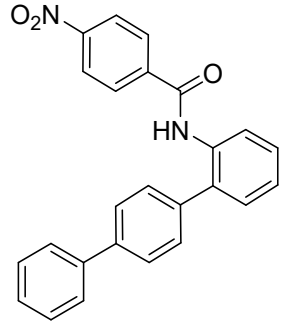
52% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.46 (s, 1H), 8.35 – 8.30 (m, 2H), 8.12 (d, *J* = 1.8 Hz, 1H), 8.06 (d, *J* = 8.4 Hz, 2H), 7.97 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.73 – 7.69 (m, 2H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.57 – 7.55 (m, 1H), 7.54 (d, *J* = 1.4 Hz, 1H), 7.53 (s, 1H), 7.14 (dd, *J* = 5.0, 3.7 Hz, 1H), 3.90 (s, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 166.1, 164.8, 149.6, 143.1, 142.4, 140.2, 137.6, 135.2, 133.7, 131.2, 129.6, 129.6, 129.5, 129.3, 129.1, 128.0, 126.5, 125.8, 124.6, 124.1, 52.8; ESI-MS *m/z*: 456.8 $[M-H]^-$.



4-amino-N-(4'-(thiophen-2-yl)-[1,1'-biphenyl]-2-yl)benzamide (B28)

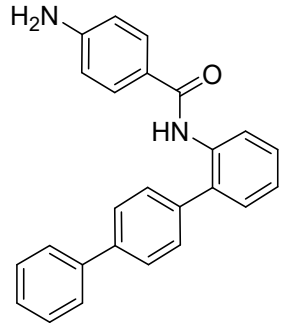
71% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.71 (s, 1H), 8.77 (d, *J* = 1.9 Hz, 1H), 8.56 (d, *J* = 1.8 Hz, 1H), 8.13 (d, *J* = 1.8 Hz, 1H), 7.91 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.72 (d, *J* = 2.3 Hz, 2H), 7.70 (d, *J* = 2.0 Hz, 2H), 7.61 – 7.57 (m, 1H), 7.57 – 7.54 (m, 2H), 7.54 – 7.51 (m, 2H), 7.14 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.86 – 6.78 (m, 2H), 3.89 (s, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 166.2, 166.0, 155.4, 143.2, 141.9, 137.8, 136.2,

133.6, 131.0, 129.7, 129.4, 129.1, 129.0, 127.6, 127.1, 126.4, 125.7, 124.5, 124.4, 111.8, 52.7; ESI-MS *m/z*: 429.1 $[M+H]^+$.



N-([1,1':4',1''-terphenyl]-2-yl)-4-nitrobenzamide (B29)

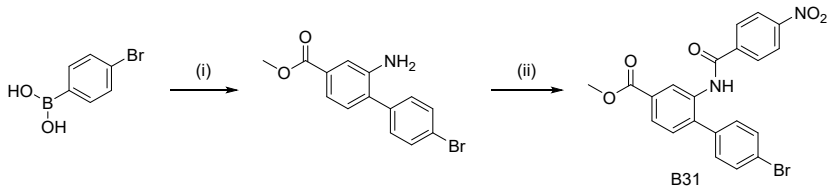
56% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.46 (s, 1H), 8.35 – 8.30 (m, 2H), 8.15 (d, *J* = 1.8 Hz, 1H), 8.06 (d, *J* = 8.3 Hz, 2H), 7.98 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.77 – 7.72 (m, 2H), 7.71 – 7.67 (m, 2H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.62 – 7.58 (m, 2H), 7.46 (t, *J* = 7.7 Hz, 2H), 7.39 – 7.35 (m, 1H), 3.91 (s, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 166.1, 164.9, 149.6, 142.5, 140.3, 140.0, 139.8, 137.5, 135.2, 131.3, 129.5 (d, *J* = 7.2 Hz), 129.5, 129.4, 129.5, 128.5, 128.0, 127.1 (d, *J* = 10.8 Hz), 124.1, 52.8; ESI-MS *m/z*: 450.9 $[M-H]^-$.



N-([1,1':4',1''-terphenyl]-2-yl)-4-aminobenzamide (B30)

65% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.50 (s, 1H), 8.16 (d, *J* = 1.8 Hz, 1H), 7.90 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.76 – 7.72 (m, 2H), 7.72 – 7.68 (m, 2H), 7.60 – 7.55 (m, 5H), 7.46 (t, *J* = 7.8 Hz, 2H), 7.39 – 7.35 (m, 1H), 6.57 – 6.54 (m, 2H), 5.81 (s, 2H), 3.89 (s, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 166.3, 166.1, 152.4, 141.7, 139.8, 137.8, 136.4, 131.1, 129.7, 129.6, 129.4, 129.3, 128.9, 128.1, 127.1, 127.0, 126.8, 121.1, 113.2, 52.7; ESI-MS *m/z*: 420.9 $[M-H]^-$.

General synthetic route of B31.



N-(4'-bromo-[1,1'-biphenyl]-2-yl)-4-nitrobenzamide (B31)

75% yield. 1H NMR (600 MHz, DMSO-d_6) δ 10.45 (s, 1H), 8.36 – 8.31 (m, 2H), 8.10 (d, *J* = 1.8 Hz, 1H), 8.03 (d, *J* = 8.4 Hz, 2H), 7.96 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.63 – 7.60 (m, 2H), 7.58 (d, *J* = 8.1 Hz, 1H), 7.46 – 7.42 (m, 2H), 3.90 (s, 3H);^{13}C NMR

(151 MHz, DMSO-d_6) δ 166.0, 164.7, 149.7, 141.8, 140.2, 137.8, 135.2, 131.8, 131.3, 130.9, 129.9, 129.5, 129.2, 128.0, 124.1, 121.9, 52.8; ESI-MS *m/z*: 452.9 $[M-H]^-$.

2.Biology

2.1 Inhibition rate test and IC50 value determination

For inhibition rate analysis, DENV NS2B-NS3 proteases were purchased from Sino-American Biotechnology Co., Ltd. Fluorescent substrate Bz-Nle-Lys-Arg-Arg-AMC were purchased from Nanjing Peptide Biotech Ltd. Aprotinins from bovine lung were purchased Shanghai McLean Biochemical Technology Co., Ltd. Enzyme labeling instrument (TECAN infinite f500, TECAN, Switzerland). Electronic analytical balance (ar1140; METTLER TOLEDO instrument (Shanghai) Co., Ltd.). Glass instruments were purchased from Beijing xinweier Glass Instrument Co., Ltd. Pipette guns were purchased from Fisher Scientific. An ultra-low temperature - 80 ℃ refrigerator was purchased from Qingdao Haier Co., Ltd.

The assay buffer consisted of 1 mM CHAPS, 50 mM Tris, and 20% glycerol at pH 7.5. 30 μL of DENV NS2B-NS3 protease (final 100 nM) and distributed into a 96-well plate, and 40 μL of compounds were added followed by a 60 min incubation at 37 °C temperature. The enzyme reaction was initiated by adding 30 μL of the substrate (final 3.6 μM). The fluorescence intensity was continuously monitored every min for 15 min at 37 °C using a fluorimeter (Tecan Infinite F500) with 380 nm excitation and 460 nm emission wavelengths. Aprotinin was used as a positive control for every plate. All compounds were tested in triplicate. The data of fluorescence intensity versus reaction time were linearly fitted to give the slope of the function, which was used to indicate the speed of hydrolysis in the presence or absence of inhibitors. Then, the inhibition rates were calculated by using the following formula:

$$Inhibition\ rate = (S_a - S_p)/S_a \quad (1)$$

S_a: the slope in the absence of inhibitor

S_p: the slope in the presence of inhibitor

IC_{50} values of optimized compounds (A16, A24, B08 and B14) were measured in the same concentration of enzyme and substrate as the above inhibition rate test with a series of compound concentrations (0.16 to 40 nM). The enzyme reaction was initiated by adding 30 μL of fluorogenic substrate (final 3.6 μM), and fluorogenic signals were continuously monitored every min for 15 min at 37 °C using a fluorimeter (Tecan Infinite F500) with 380 nm excitation and 460 nm emission wavelengths. Aprotinin was used as a positive control for every plate. All compounds were tested in triplicate[2, 3].

2.2 Enzyme Kinetics Assay

During the enzyme kinetics experiments, seven inhibitor concentrations (150, 100, 75, 50, 25, 12.5, 6.25 μM) and five substrate concentrations (180, 90, 45, 22.5, 11.25 μM)

were methodically selected. In each well of a 384-well microplate, 20 μL of inhibitor solution and 15 μL of DENV NS2B-NS3 protein were added, followed by a 30-minute incubation at 37°C. To initiate the enzymatic reaction, 15 μL of substrate solution was added. Fluorescence intensity was measured every 90 seconds at 37°C over a period of 22.5 minutes using a microplate reader, with excitation at 380 nm and emission at 460 nm. Each plate contained blank controls (substrate and buffer) and enzyme controls (substrate and enzyme), and each inhibitor condition was tested in triplicate. Post-experiment, a Lineweaver-Burk plot was constructed via double-reciprocal transformation of the raw data for comprehensive kinetic analysis[4].

2.3 Druglikeness evaluation

In order to evaluate the drug-likeness properties of compounds with strong activity, the main physicochemical properties and BOILED-Egg plot was generated using the online server at http://www.swissadme.ch/index.php[5]. Meanwhile, other services such as pharmacokinetic properties, druglike nature and medicinal chemistry friendliness of one or multiple small molecules could be served on this website.

3. Computational analyses

3.1 Molecular docking

Molecular docking calculations were performed using the Glide module in the Schrödinger suite. The .sdf files of the small molecules were prepared with the LigPrep module, optimizing bond angles, charge states under physiological conditions, and possible conformations. The protein structure (PDB code: 6MO1) was determined through X-ray diffraction at a resolution of 3.00 Å, with R-Value Free at 0.312, R-Value Work at 0.238, and R-Value Observed at 0.241. It was downloaded from the RCSB PDB website (http://www.rcsb.org/) and subsequently optimized using the Protein Preparation Wizard. This involved removing non-essential solvent molecules, ions, and crystallization aids, re-adding hydrogen atoms with the OPLS3 force field, deleting redundant segments, completing missing amino acid chains, and adjusting the conformation to avoid atomic overlaps. The protein pH was set to 7.3-7.4. A 10 Å × 10 Å × 10 Å box was created at the protein's allosteric site for docking. Finally, the Glide module docked the small molecules to the protein with XP precision.

3.2 Molecular dynamic simulation

To further investigate the protein-small molecule complexes obtained through molecular docking, molecular dynamics (MD) simulations were performed. MD simulations included system building, simulation, and results analysis. The docking structures were imported into Maestro and optimized using the Protein Preparation Wizard in the Schrödinger suite. The optimized protein structures were embedded in

an SPC solvent model and neutralized with counter ions. The system was placed in a 10 Å orthorhombic box using the OPLS_4e force field[6]. Further optimization was performed with the minimization module using the LBFGS algorithm, with a maximum of 2000 iterations and an energy convergence threshold of 1 kcal/mol/Å. MD simulations were conducted with an NPT ensemble, using a Nose-Hoover thermostat at 300 K and a Martyna-Tobias-Klein barostat[7]. After 2 ns equilibrium to stabilize the system, it started a 100 ns generation phase of molecular dynamics simulations, recording the energy every 1.0 ps as well as the orbital atomic coordinates every 100 ps. The RMSD, interactions, and other parameters were analyzed.

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