



Pyrido[2',1':2,3]imidazo[4,5-*c*]isoquinolin-5-amines as potential cytotoxic agents against human neuroblastoma

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Experimental Section

General procedure for synthesis of compounds 1a-1i, 2a-2j, 3a-3b, 4a-4b.

2-6

¹H NMR, ¹³C NMR Spectra of compounds 4a and 4b, other compounds were 7-8 described in reference [29] RSC Adv. 2015



General Procedures

9-Chloropyrido[2',1':2,3]imidazo[4,5-c]isoquinolin-5-amine (1a) [29]

Following the general *N*-deprotection-cyclization procedure with **S1** (187 mg, 0.49 mmol). Yellow solid (108 mg, 82 %); mp 278–279 °C; IR(neat, cm⁻¹): 765, 1084, 1273, 1324, 1427, 1625, 3177, 3300, 3444; ¹H NMR (400.13 MHz, DMSO-*d*₆): δ 7.20 (s, 2H), 7.35 (dd, *J* = 9.6, 2.1 Hz, 1H), 7.63 (t, *J* = 7.6 Hz, 1H), 7.71 (d, *J* = 9.6 Hz, 1H), 7.86 (t, *J* = 7.6 Hz, 1H), 8.43 (dd, *J* = 8.2, 3.1 Hz, 2H), 8.57 (d, *J* = 2.1 Hz, 1H); ¹³C NMR (101 MHz, DMSO-*d*₆): δ 118.0, 118.4, 118.4, 120.6, 120.6, 121.7, 125.6, 125.7, 126.1, 130.8, 130.9, 134.4, 140.8, 154.6; HRMS (ESI) [M+H]⁺: calcd for C₁₄H₁₀ClN₄: 269.0589, found: 269.0587.

9-Bromopyrido[2',1':2,3]imidazo[4,5-c]isoquinolin-5-amine (1b) [29]

Following the general *N*-deprotection-cyclization procedure with **S1** (181mg, 0.49 mmol). Yellow solid (135 mg, 88 %); mp 285–286 °C; IR (neat, cm⁻¹) : 777, 943, 1319, 1494, 1621, 3195, 3323, 3400; ¹H NMR (400.13 MHz, DMSO-*d*₆): δ 7.20 (s, 2H), 7.40 (d, *J* = 8.9 Hz, 1H), 7.58–7.67 (m, 2H), 7.85 (t, *J* = 7.4 Hz, 1H), 8.35–8.50 (m, 2H), 8.61 (s, 1H); ¹³C NMR (101 MHz, DMSO-*d*₆): δ 104.8, 118.5, 118.6, 121.8, 122.7, 125.5, 125.6, 125.7, 128.1, 130.7, 130.8, 134.2, 141.0, 154.6; HRMS (ESI) [M+H]⁺: calcd for C₁₄H₁₀BrN₄: 313.0083 [⁷⁹Br], 315.0064 [⁸¹Br], found: 313.0080 [⁷⁹Br], 315.0062 [⁸¹Br].

Methyl 5-aminopyrido[2',1':2,3]imidazo[4,5-c]isoquinoline-9-carboxylate (1c) [29]

Following the general *N*-deprotection-cyclization procedure with **S1** (171 mg, 0.49 mmol). Yellow solid (112 mg, 78 %); mp 296–297 °C; IR(neat, cm⁻¹): 760, 1099, 1275, 1418, 1643, 1716, 3184, 3315; ¹H NMR (400.13 MHz, DMSO-*d*₆): δ 3.93 (s, 3H), 7.31 (s, 2H), 7.58–7.75 (m, 3H), 7.87 (t, *J* = 7.5 Hz, 1H), 8.43 (d, *J* = 6.3 Hz, 2H), 9.12 (s, 1H); ¹³C NMR (101MHz, DMSO-*d*₆): δ 52.4, 114.0, 117.0, 118.5, 121.8, 123.8, 125.6, 125.8, 125.9, 126.9, 130.7, 131.0, 134.8, 142.4, 154.9, 164.9; HRMS (ESI) [M+H]⁺: calcd for C₁₆H₁₃N₄O₂: 293.1033, found: 293.1030.

5-Aminopyrido[2',1':2,3]imidazo[4,5-c]isoquinoline-9-carbonitrile (1d) [29]

Following the general *N*-deprotection-cyclization procedure with **S1** (154mg, 0.49 mmol). Yellow solid (117 mg, 92 %); mp 318–319 °C; IR (neat, cm⁻¹): 765, 1141, 1258, 1326, 1419, 1520, 1623, 2221 (CN), 3327, 3456; ¹H NMR (400.13 MHz, DMSO-*d*₆): δ 7.30 (s, 2H), 7.51 (dd, *J* = 9.5, 1.6 Hz, 1H), 7.66 (t, *J* = 7.7 Hz, 1H), 7.78 (d, *J* = 9.4 Hz, 1H), 7.88 (t, *J* = 7.5 Hz, 1H), 8.45 (t, *J* = 9.1 Hz, 2H), 9.17 (d, *J* = 1.3 Hz, 1H); ¹³C NMR (101 MHz, DMSO-*d*₆): δ 95.8, 117.4, 118.2, 118.6, 121.8, 124.6, 125.7, 125.9, 126.1, 130.6, 130.7, 131.1, 134.7, 141.3, 155.1; HRMS (ESI) [M+H]⁺: calcd for C₁₅H₁₀N₅: 260.0931, found: 260.0928.

9-Methylpyrido[2',1':2,3]imidazo[4,5-c]isoquinolin-5-amine (1e) [29]

Following the general *N*-deprotection-cyclization procedure with **S1** (149 mg, 0.49 mmol). Yellow solid (87.6 mg, 72 %); mp 247–248 °C; IR (neat, cm⁻¹): 787, 1026, 1324, 1416, 1508, 1624, 2920, 3176, 3330; ¹H NMR (400.13 MHz, DMSO-*d*₆): δ 2.37 (s, 3H), 7.03 (s, 2H), 7.20 (dd, *J* = 9.1, 1.7 Hz, 1H), 7.58 (t, *J* = 8.1 Hz, 2H), 7.83 (t, *J* = 7.4 Hz, 1H), 8.33 (s, 1H), 8.41 (d, *J* = 8.2 Hz, 2H); ¹³C NMR (101 MHz, DMSO-*d*₆): δ 17.7, 116.8, 118.1, 120.1, 120.2, 121.6, 125.1, 125.1, 125.5, 128.8, 130.5, 130.9, 134.1, 142.0, 154.0; HRMS (ESI) [M+H]⁺: calcd for C₁₅H₁₃N₄: 249.1135, found: 249.1132.

9-Methoxypyrido[2',1':2,3]imidazo[4,5-c]isoquinolin-5-amine (1f) [29]

Following the general *N*-deprotection-cyclization procedure with **S1** (157 mg, 0.49 mmol). Yellow-green solid (118mg, 91 %); mp 236–237 °C; IR (neat, cm⁻¹): 622, 793, 1242, 1322, 1429, 1512, 1623, 3151, 3300; ¹H NMR (400.13 MHz, DMSO-*d*₆): δ 3.88 (s, 3H), 7.09 (s, 2H), 7.13 (d, *J* = 8.3 Hz, 1H), 7.59 (t, *J* = 9.8 Hz, 2H), 7.83 (t, *J* = 6.9 Hz, 1H), 8.00 (s, 1H), 8.40 (d, *J* = 7.8 Hz, 2H); ¹³C NMR (101 MHz, DMSO-*d*₆): δ 55.9, 103.5, 117.9, 118.0, 120.9, 121.5, 125.1, 125.5, 125.6, 130.6, 131.1, 135.0, 140.2, 147.7, 154.0; HRMS (ESI) [M+H]⁺: calcd for C₁₅H₁₃N₄O: 265.1084, found: 265.1083.

**10-Methylpyrido[2',1':2,3]imidazo[4,5-c]isoquinolin-5-amine (1g) [29]**

Following the general *N*-deprotection-cyclization procedure with **S1** (149 mg, 0.49 mmol). Yellow solid (79 mg, 65%); mp 237–238 °C; IR (neat, cm⁻¹): 761, 850, 1161, 1306, 1370, 1460, 1627, 3194, 3319; ¹H NMR (400.13 MHz, DMSO-*d*₆): δ 2.42 (s, 3H), 6.82 (d, *J* = 6.9 Hz, 1H), 7.02 (s, 2H), 7.42 (s, 1H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.82 (t, *J* = 7.6 Hz, 1H), 8.39 (d, *J* = 8.4 Hz, 2H), 8.44 (d, *J* = 6.9 Hz, 1H); ¹³C NMR (101 MHz, DMSO-*d*₆): δ 21.2, 113.7, 115.3, 117.9, 121.6, 122.3, 124.6, 125.0, 125.5, 130.4, 130.8, 134.2, 136.4, 143.2, 153.7; HRMS (ESI) [*M*+*H*]⁺: calcd for C₁₅H₁₃N₄: 249.1135, found: 249.1132.

5-Aminopyrido[2',1':2,3]imidazo[4,5-c]isoquinoline-10-carbonitrile (1h) [29]

Following the general *N*-deprotection-cyclization procedure with **S1** (154 mg, 0.49 mmol). Yellow-orange solid (114 mg, 90 %); mp 340–341 °C; IR (neat, cm⁻¹): 658, 765, 1306, 1437, 1557, 1570, 1647, 2224 (CN), 3318, 3444; ¹H NMR (400.13 MHz, DMSO-*d*₆): δ 7.17 (d, *J* = 7.1 Hz, 1H), 7.46 (s, 2H), 7.67 (t, *J* = 7.7 Hz, 1H), 7.89 (t, *J* = 7.6 Hz, 1H), 8.38 (s, 1H), 8.46 (d, *J* = 7.7 Hz, 2H), 8.58 (d, *J* = 7.1 Hz, 1H); ¹³C NMR (101 MHz, DMSO-*d*₆): δ 105.7, 110.7, 118.4, 118.9, 122.0, 123.8, 124.3, 125.7, 126.5, 127.5, 130.5, 131.2, 135.0, 140.1, 155.7; HRMS (ESI) [*M*+*H*]⁺: calcd for C₁₅H₁₀N₅: 260.0931, found: 260.0931.

Pyrido[2',1':2,3]imidazo[4,5-c]isoquinolin-5-amine (1i) [29]

Following the general *N*-deprotection-cyclization procedure with **S1** (170 mg, 0.49 mmol). Yellow solid (91 mg, 80 %); mp 253–255 °C (lit 254–256 °C); IR (neat, cm⁻¹): 628, 929, 1279, 1279, 1505, 1623, 3120, 3450; ¹H NMR (400.13 MHz, CDCl₃): δ 5.26 (s, 2H), 6.87 (t, *J* = 6.7 Hz, 1H), 7.30 (t, *J* = 7.9 Hz, 1H), 7.58 (t, *J* = 7.7 Hz, 1H), 7.71 (d, *J* = 9.2 Hz, 1H), 7.83 (t, *J* = 7.6 Hz, 1H), 7.96 (d, *J* = 8.3 Hz, 1H), 8.58 (d, *J* = 6.8 Hz, 1H), 8.68 (d, *J* = 8.2 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃): δ 111.0, 118.0, 118.4, 123.0, 123.3, 124.0, 125.9, 126.4, 127.4, 131.0, 131.5, 134.1, 144.5, 152.5; HRMS (ESI) [*M*+*H*]⁺: calcd for C₁₄H₁₁N₄: 235.0978, found: 235.0984.

***N*-(4-(Trifluoromethyl)phenyl)pyrido[2',1':2,3]imidazo[4,5-c]isoquinoline-5-amine (2a) [29]**

Following the general Buchwald-Hartwig cross-coupling procedure with 1-iodo-4-(trifluoromethyl)benzene (62 μL, 0.426 mmol). (DCM/EA: 7:3). Yellow solid (129 mg, 80 %); mp 265–266 °C; IR (neat, cm⁻¹): 658, 768, 1064, 1110, 1319, 1522, 1626, 3333; ¹H NMR (400.13 MHz, DMSO-*d*₆): δ 7.06 (t, *J* = 6.6 Hz, 1H), 7.46 (t, *J* = 6.2 Hz, 1H), 7.67–7.79 (m, 4H), 7.93 (t, *J* = 7.4 Hz, 1H), 8.31 (d, *J* = 8.5 Hz, 2H), 8.56 (d, *J* = 8.0 Hz, 1H), 8.74 (d, *J* = 8.4 Hz, 1H), 8.80 (d, *J* = 6.7 Hz, 1H), 9.73 (s, 1H); ¹³C NMR (101 MHz, DMSO-*d*₆): δ 111.5, 117.3, 119.1 (2C), 119.3, 121.0 (q, C_q, *J*_{CF3} = 31.8 Hz), 122.0, 123.7, 124.8 (q, C_q, *J*_{CF3} = 271.0 Hz), 125.0, 125.7 (q, 2× CHar, *J*_{CF3} = 3.8 Hz), 126.1, 127.0, 127.2, 130.8, 132.6, 144.2, 145.0, 147.4 (2C_q); ¹⁹F NMR (376 MHz, DMSO-*d*₆): δ -61.69; HRMS (ESI) [*M*+*H*]⁺: calcd for C₂₁H₁₄F₃N₄: 379.1165, found: 379.1162.

***N*-(3-Nitrophenyl)pyrido[2',1':2,3]imidazo[4,5-c]isoquinolin-5-amine (2b) [29]**

Following the general Buchwald-Hartwig cross-coupling procedure with 1-iodo-3-nitrobenzene (106 mg, 0.426 mmol). (DCM/EA: 7:3). Red brick solid (100 mg, 66 %); mp 276–277 °C; IR (neat, cm⁻¹): 716, 821, 877, 1242, 1323, 1482, 1518, 1595, 1627, 3033, 3431; ¹H NMR (400.13 MHz, DMSO-*d*₆): δ 7.05 (t, *J* = 6.7 Hz, 1H), 7.42 (t, *J* = 6.9 Hz, 1H), 7.60 (t, *J* = 8.1 Hz, 1H), 7.65–7.72 (m, 2H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.88 (t, *J* = 7.5 Hz, 1H), 8.42–8.52 (m, 2H), 8.61 (d, *J* = 6.7 Hz, 1H), 8.67 (d, *J* = 8.5 Hz, 1H), 9.17 (s, 1H), 9.73 (s, 1H); ¹³C NMR (101 MHz, DMSO-*d*₆): δ 111.5, 113.4, 115.5, 117.4, 118.9, 122.0, 123.0, 124.7, 125.3, 125.9, 126.9, 127.0, 129.5, 130.7, 130.8, 132.3, 142.4, 144.1, 147.4, 147.9; HRMS (ESI) [*M*+*H*]⁺: calcd for C₂₀H₁₄N₅O₂: 356.1142, found: 356.1140.

***N*-(2-(Trifluoromethyl)phenyl)pyrido[2',1':2,3]imidazo[4,5-c]isoquinoline-5-amine (2c) [29]**

Following the general Buchwald-Hartwig cross-coupling procedure with 1-iodo-2-(trifluoromethyl)benzene (60 μL, 0.426 mmol). (DCM/EA: 7:3). Yellow solid (113 mg, 70 %); mp 180–181 °C; IR (neat, cm⁻¹): 645, 831, 1032, 1139, 1254, 1274, 1382, 1448, 1518, 1589, 1615, 2918, 3397; ¹H NMR (400.13 MHz, CDCl₃): δ 6.85 (t, *J* = 6.6 Hz, 1H), 7.13 (t, *J* = 7.5 Hz, 1H), 7.30 (dd, *J* = 9.0, 6.8 Hz, 1H), 7.56 (t, *J* = 7.9 Hz, 1H), 7.62 (t, *J* = 7.7 Hz, 1H), 7.63–7.73 (m, 3H), 7.83 (t, *J* = 7.5 Hz, 1H), 7.96 (d,



$J = 8.3$ Hz, 1H), 8.53 (d, $J = 6.2$ Hz, 1H), 8.60 (d, $J = 8.4$ Hz, 1H), 8.70 (d, $J = 8.1$ Hz, 1H); ^{13}C NMR (101 MHz, CDCl_3): δ 111.2, 117.8, 118.6 (q, $J = 29.1$ Hz), 119.6, 121.8, 122.0, 122.6

, 123.3, 123.4, 125.4 (q, $C_{\text{q}}, J_{\text{CF}_3} = 272.7$ Hz), 126.4 (q, $\text{CH}_{\text{ar}}, J = 5.5$ Hz), 126.6, 127.0, 128.3, 130.8, 131.6, 132.6, 133.2, 139.0, 145.2, 146.9; ^{19}F NMR (376 MHz, CDCl_3): δ -61.57; HRMS (ESI) $[\text{M}+\text{H}]^+$: calcd for $\text{C}_{21}\text{H}_{14}\text{F}_3\text{N}_4$: 379.1165, found: 379.1161.

N-Phenylpyrido[2',1':2,3]imidazo[4,5-c]isoquinolin-5-amine (2d) [29]

Following the general Buchwald-Hartwig cross-coupling procedure with iodobenzene (48 μL , 0.426 mmol). (DCM/EA: 7:3). Yellow solid (110 mg, 83 %); mp 213–214 °C (lit 212–214 °C); IR (neat, cm^{-1}): 661, 764, 1241, 1315, 1344, 1421, 1495, 1544, 1598, 3048, 3324; ^1H NMR (400.13 MHz, CDCl_3): δ 6.90 (t, $J = 6.7$ Hz, 1H), 7.11 (t, $J = 7.4$ Hz, 1H), 7.31–7.38 (m, 2H), 7.43 (t, $J = 7.9$ Hz, 2H), 7.63 (t, $J = 7.6$ Hz, 1H), 7.72 (d, $J = 9.2$ Hz, 1H), 7.83–7.86 (m, 3H), 8.09 (d, $J = 8.4$ Hz, 1H), 8.63 (d, $J = 6.8$ Hz, 1H), 8.72 (d, $J = 8.1$ Hz, 1H); ^{13}C NMR (101 MHz, CDCl_3): δ 111.2, 117.9, 119.4, 119.7 (2C), 122.7, 122.8, 123.3, 123.6, 126.3, 126.8, 127.6, 129.1 (2C), 130.7, 131.7, 133.7, 140.7, 144.9, 147.9; HRMS (m/z) $[\text{M}+\text{H}]^+$: calcd for $\text{C}_{20}\text{H}_{15}\text{N}_4$: 311.1291, found: 311.1289.

4-(Pyrido[2',1':2,3]imidazo[4,5-c]isoquinolin-5-ylamino)benzonitrile (2e) [29]

Following the general Buchwald-Hartwig cross-coupling procedure with 4-bromobenzonitrile (77.5 mg, 0.426 mmol). (DCM/EA: 7:3). Yellow solid (128 mg, 90 %); mp 279–280 °C; IR (neat, cm^{-1}): 650, 728, 810, 1170, 1244, 1320, 1404, 1496, 1506, 1600, 2209 (CN), 3360; ^1H NMR (400.13 MHz, $\text{DMSO}-d_6$): δ 7.11 (t, $J = 6.7$ Hz, 1H), 7.50 (t, $J = 6.5$ Hz, 1H), 7.73–7.84 (m, 4H), 7.97 (t, $J = 6.6$ Hz, 1H), 8.28 (d, $J = 8.7$ Hz, 2H), 8.59 (d, $J = 8.1$ Hz, 1H), 8.74 (d, $J = 8.5$ Hz, 1H), 8.82 (d, $J = 6.8$ Hz, 1H), 9.85 (s, 1H); ^{13}C NMR (101 MHz, $\text{DMSO}-d_6$): δ 102.2, 111.6, 117.4, 119.0 (2C), 119.4, 119.7, 122.1, 123.8, 125.1, 126.2, 127.4, 127.4, 130.8, 131.0, 132.6 (2C), 133.0, 144.4, 145.7, 146.9; HRMS (m/z) $[\text{M}+\text{H}]^+$: calcd for $\text{C}_{21}\text{H}_{14}\text{N}_5$: 336.1244, found: 336.1241.

N-(Pyridin-4-yl)pyrido[2',1':2,3]imidazo[4,5-c]isoquinolin-5-amine (2f) [29]

Following the general Buchwald-Hartwig cross-coupling procedure with 4-iodopyridine (87 mg, 0.426 mmol). (DCM/MeOH: 95:5). Yellow solid (91 mg, 69 %); mp 257–259 °C; IR (neat, cm^{-1}): 731, 827, 1212, 1251, 1349, 1504, 1538, 2923, 3078, 3304; ^1H NMR (400.13 MHz, CDCl_3): δ 7.00 (t, $J = 6.7$ Hz, 1H), 7.42 (ddd, $J = 9.0, 6.8, 1.3$ Hz, 1H), 7.52 (s, 1H), 7.70 (ddd, $J = 8.6, 7.1, 1.4$ Hz, 1H), 7.76–7.80 (m, 3H), 7.90 (t, $J = 7.6$ Hz, 1H), 8.12 (d, $J = 8.4$ Hz, 1H), 8.55 (d, $J = 5.3$ Hz, 2H), 8.71 (d, $J = 6.8$ Hz, 1H), 8.78 (d, $J = 8.1$ Hz, 1H); ^{13}C NMR (101 MHz, CDCl_3): δ 111.7, 112.9 (2C), 118.1, 119.6, 122.8, 123.5, 123.6, 126.7, 127.6, 128.7, 131.1, 131.6, 145.7, 146.1, 147.6, 150.6 (2C), 151.0; HRMS (ESI) $[\text{M}+\text{H}]^+$: Masse calcd for $\text{C}_{19}\text{H}_{14}\text{N}_5$: 312.1244, found: 312.1243.

N-(Pyridin-3-yl)pyrido[2',1':2,3]imidazo[4,5-c]isoquinolin-5-amine (2g) [29]

Following the general Buchwald-Hartwig cross-coupling procedure with 3-bromopyridine (41 μL , 0.426 mmol). (DCM/MeOH: 99:1). Yellow solid (95 mg, 72 %); mp 246–247 °C; IR (neat, cm^{-1}): 745, 930, 1251, 1348, 1415, 1521, 1582, 2930, 3080, 3314; ^1H NMR (400.13 MHz, CDCl_3): δ 6.90 (t, $J = 6.7$ Hz, 1H), 7.31–7.38 (m, 2H), 7.56 (s, 1H), 7.62 (t, $J = 7.6$ Hz, 1H), 7.71 (d, $J = 9.2$ Hz, 1H), 7.83 (t, $J = 7.5$ Hz, 1H), 8.13 (d, $J = 8.4$ Hz, 1H), 8.34 (d, $J = 5.8$ Hz, 2H), 8.59 (d, $J = 6.8$ Hz, 1H), 8.70 (d, $J = 8.1$ Hz, 1H), 9.07 (s, 1H); ^{13}C NMR (101 MHz, CDCl_3): δ 111.4, 117.9, 119.2, 122.8, 123.4, 123.5, 123.6, 126.4, 126.5, 127.1, 127.8, 130.8, 131.5, 133.3, 137.5, 141.7, 143.4, 145.1, 147.3. HRMS (ESI) $[\text{M}+\text{H}]^+$: calcd for $\text{C}_{19}\text{H}_{14}\text{N}_5$: 312.1244, found: 312.1243.

N-(Pyridin-2-yl)pyrido[2',1':2,3]imidazo[4,5-c]isoquinolin-5-amine (2h) [29]

Following the general Buchwald-Hartwig cross-coupling procedure with 2-bromopyridine (41 μL , 0.426 mmol). (DCM/acetone: 9:1). Yellow solid (92 mg, 70 %); mp 175–176 °C; IR (neat, cm^{-1}): 756, 771, 987, 1162, 1310, 1439, 1517, 1583, 3232; ^1H NMR (400.13 MHz, CDCl_3): δ 6.94 (t, $J = 6.7$ Hz, 1H), 7.00 (dd, $J = 7.2, 4.8$ Hz, 1H), 7.36 (ddd, $J = 9.2, 6.7, 1.3$ Hz, 1H), 7.66 (ddd, $J = 8.4, 6.9, 1.3$ Hz, 1H), 7.75 (d, $J = 9.2$ Hz, 1H), 7.79 (ddd, $J = 8.7, 7.1, 1.8$ Hz, 1H), 7.87 (t, $J = 7.6$ Hz, 1H), 8.18 (d, $J = 8.4$ Hz, 1H), 8.23 (s, 1H), 8.32–8.37 (m, 1H), 8.66 (d, $J = 6.8$ Hz, 1H), 8.70 (d, $J = 8.4$ Hz, 1H), 8.73



(d, $J = 8.2$ Hz, 1H); ^{13}C NMR (101 MHz, CDCl_3): δ 111.4, 112.7, 117.8, 118.0, 119.4, 123.0, 123.2, 123.4, 126.6, 127.0, 128.1, 130.9, 131.6, 133.3, 138.1, 145.2, 146.4, 148.2, 153.5; HRMS (ESI) $[\text{M}+\text{H}]^+$: calcd for $\text{C}_{19}\text{H}_{14}\text{N}_5$: 312.1244, found: 312.1243.

4-((9-Bromopyrido[2',1':2,3]imidazo[4,5-*c*]isoquinolin-5-yl)amino)benzonitrile (2i) [29]

Following the general Buchwald-Hartwig cross-coupling procedure with 4-bromobenzonitrile (77.5 mg, 0.426 mmol). (DCM/EA: 7:3). Yellow solid (127 mg, 72 %); mp 320–321 °C; IR (neat, cm^{-1}): 707, 769, 833, 1241, 1407, 1517, 1595, 2219 (CN), 3340; ^1H NMR (400.13 MHz, $\text{DMSO}-d_6$): δ 7.58 (dd, $J = 9.5, 1.9$ Hz, 1H), 7.75 (d, $J = 9.6$ Hz, 1H), 7.79 (t, $J = 7.6$ Hz, 1H), 7.83 (d, $J = 8.7$ Hz, 2H), 7.98 (t, $J = 7.6$ Hz, 1H), 8.30 (d, $J = 8.8$ Hz, 2H), 8.57 (d, $J = 8.0$ Hz, 1H), 8.75 (d, $J = 8.5$ Hz, 1H), 8.97 (d, $J = 1.9$ Hz, 1H), 9.87 (s, 1H); ^{13}C NMR (101 MHz, $\text{DMSO}-d_6$): δ 102.5, 105.5, 118.6, 119.3 (2C), 119.6, 119.7, 122.1, 123.6, 125.1, 126.5, 127.7, 130.1, 130.7, 131.3, 132.5, 133.0 (2C), 142.6, 145.4, 147.5; HRMS (m/z) $[\text{M}+\text{H}]^+$: calcd for $\text{C}_{21}\text{H}_{13}\text{BrN}_5$: 414.0349 ^{79}Br , 416.0331 ^{81}Br , found: 414.0350 ^{79}Br , 414.0349 ^{81}Br .

4-((9-Chloropyrido[2',1':2,3]imidazo[4,5-*c*]isoquinolin-5-yl)amino)benzonitrile (2j) [29]

Following the general Buchwald-Hartwig cross-coupling procedure with 4-bromobenzonitrile (77.5 mg, 0.426 mmol). (DCM/EA: 7:3). Yellow solid (116 mg, 74 %); mp 319–320 °C; IR (neat, cm^{-1}): 661, 765, 1089, 1173, 1244, 1511, 2212 (CN), 3376; ^1H NMR (400.13 MHz, $\text{DMSO}-d_6$): δ 7.49 (d, $J = 8.2$ Hz, 1H), 7.76–7.83 (m, 4H), 7.96 (t, $J = 7.4$ Hz, 1H), 8.29 (d, $J = 8.3$ Hz, 2H), 8.54 (d, $J = 8.1$ Hz, 1H), 8.72 (d, $J = 8.5$ Hz, 1H), 8.88 (s, 1H), 9.83 (s, 1H); ^{13}C NMR (101 MHz, $\text{DMSO}-d_6$): δ 102.5, 118.3, 118.6, 119.3 (2C), 119.5, 119.7, 121.6, 122.1, 125.1, 126.4, 127.9, 130.7, 131.2, 132.6, 133.0 (2C), 142.5, 145.4, 147.5, 147.7; HRMS (m/z) $[\text{M}+\text{H}]^+$: calcd for $\text{C}_{21}\text{H}_{13}\text{ClN}_5$: 370.0854, found: 370.0852.

9-Chloropyridazino[6',1':2,3]imidazo[4,5-*c*]isoquinolin-5-amine (3a) [29]

Following the general *N*-deprotection-cyclization procedure with S2 (159 mg, 0.49 mmol). Yellow orange solid (100 mg, 89 %); mp 299–300 °C; IR (neat, cm^{-1}): 708, 799, 1086, 1099, 1250, 1305, 1423, 1480, 1507, 3024, 3106, 3281; ^1H NMR (400.13 MHz, $\text{DMSO}-d_6$): δ 7.33 (d, $J = 9.5$ Hz, 1H), 7.47 (s, 2H), 7.67 (t, $J = 7.6$ Hz, 1H), 7.89 (t, $J = 7.5$ Hz, 1H), 8.24 (d, $J = 9.5$ Hz, 1H), 8.45 (t, $J = 8.3$ Hz, 2H). ^{13}C NMR (101 MHz, $\text{DMSO}-d_6$): δ 118.6, 118.8, 121.6, 125.6, 126.1, 126.4, 127.9, 130.7, 131.2, 135.8, 135.8, 145.3, 156.0; HRMS (ESI) $[\text{M}+\text{H}]^+$: calcd for $\text{C}_{13}\text{H}_9\text{ClN}_5$: 270.0541, found: 270.0540.

4-((9-Chloropyridazino[6',1':2,3]imidazo[4,5-*c*]isoquinolin-5-yl)amino)benzonitrile (3b) [29]

Following the general Buchwald-Hartwig cross-coupling procedure with 4-bromobenzonitrile (77.5 mg, 0.426 mmol). (DCM/EA: 7:3). Yellow solid (116 mg, 74 %); mp: 319–320 °C; IR (neat, cm^{-1}): 661, 765, 1089, 1173, 1244, 1511, 2212 (CN), 3376; ^1H NMR (400.13 MHz, $\text{DMSO}-d_6$): δ 7.49 (d, $J = 8.2$ Hz, 1H), 7.76–7.83 (m, 4H), 7.96 (t, $J = 7.4$ Hz, 1H), 8.29 (d, $J = 8.3$ Hz, 2H), 8.54 (d, $J = 8.1$ Hz, 1H), 8.72 (d, $J = 8.5$ Hz, 1H), 8.88 (s, 1H), 9.83 (s, 1H); ^{13}C NMR (101 MHz, $\text{DMSO}-d_6$): δ 102.5, 118.3, 118.6, 119.3 (2C), 119.5, 119.7, 121.6, 122.1, 125.1, 126.4, 127.9, 130.7, 131.2, 132.6, 133.0 (2C), 142.5, 145.4, 147.5, 147.7; HRMS (m/z) $[\text{M}+\text{H}]^+$: calcd for $\text{C}_{21}\text{H}_{13}\text{ClN}_5$: 370.0854, found: 370.0852.

6-Cyclohexylpyrido[2',1':2,3]imidazo[4,5-*c*]isoquinolin-5(6H)-imine (4a)

Following the general *N*-deprotection-cyclization procedure (84.0 mg, 0.265 mmol), DCM/MeOH (95/5), Yellow solid (84 mg, 80 %); mp: 172–173 °C, IR (neat, cm^{-1}): 671, 724, 797, 1128, 1186, 1448, 1631, 1669, 3359, 3439. NMR ^1H ($\text{DMSO}-d_6$, 400.13 MHz): δ 1.44–1.70 (m, 4H), 1.91–1.95 (m, 2H), 2.05–2.09 (m, 2H), 2.68–2.78 (m, 2H), 4.75–4.81 (m, 2H), 7.18 (t, $J = 6.8$ Hz, 1H), 7.44 (t, $J = 6.8$ Hz, 1H), 7.73 (t, $J = 7.9$ Hz, 1H), 7.79 (d, $J = 6.8$ Hz, 1H), 8.01 (t, $J = 7.9$ Hz, 1H), 8.28 (d, $J = 6.8$ Hz, 1H), 8.41 (d, $J = 7.9$ Hz, 1H), 8.71 (d, 1H, $J = 7.9$ Hz), 9.33 (s, 1H); NMR ^{13}C ($\text{DMSO}-d_6$, 101 MHz): δ 24.1, 25.9 (2C), 28.4 (2C), 63.9, 114.0, 116.2, 118.7, 119.2, 122.7, 125.3, 125.6, 126.1, 127.1, 128.5, 131.4, 134.8, 143.8, 157.2; HRMS (m/z) $[\text{M}+\text{H}]^+$: calcd for $\text{C}_{20}\text{H}_{21}\text{N}_4$: 317.1761, found: 317.1760.

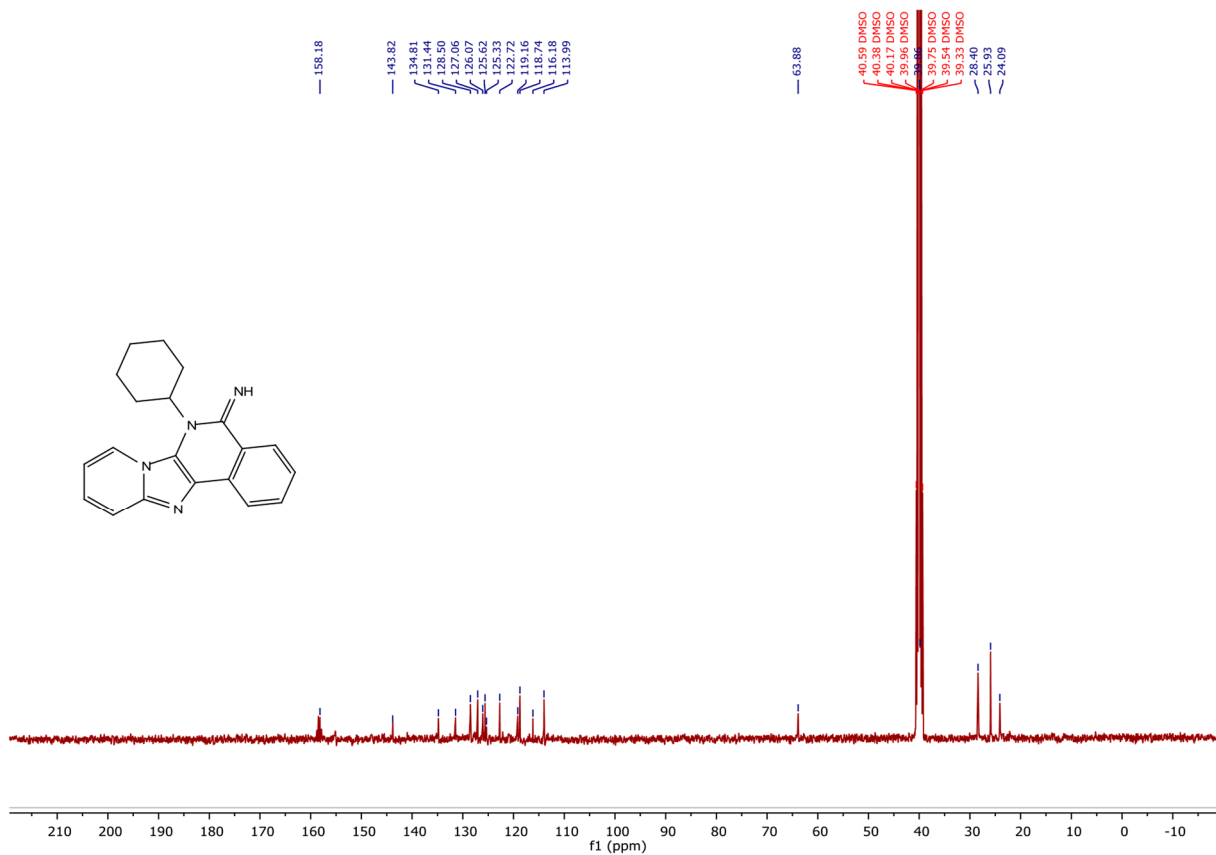
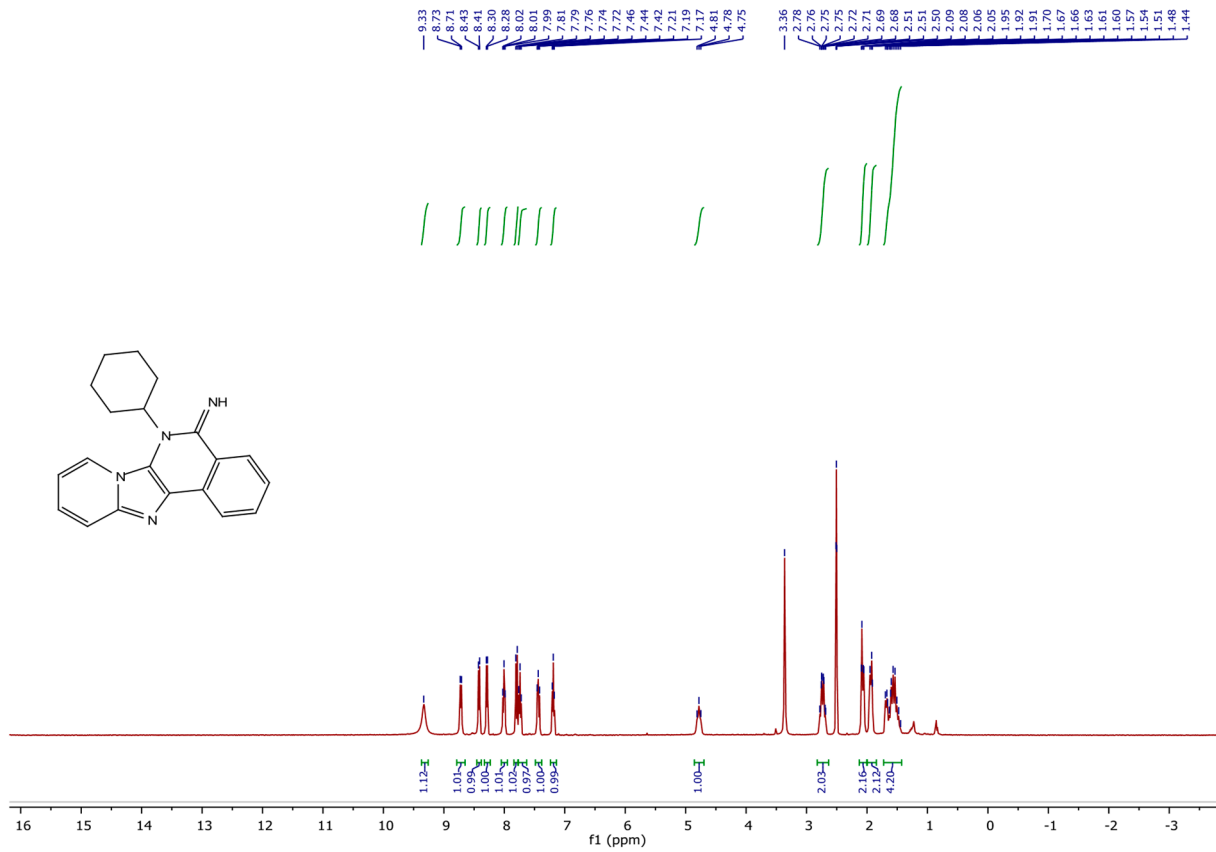
6-Benzylpyrido[2',1':2,3]imidazo[4,5-*c*]isoquinolin-5(6H)-imine (4b)

Following the general *N*-deprotection-cyclization procedure (83.0 mg, 0.256 mmol) DCM/MeOH (99/1). Yellow solid (83 mg, 78 %); mp: 174–175 °C; IR (neat, cm^{-1}): 663, 730, 898, 950, 1123, 1328, 1253, 1520, 1598,



1616, 3307; NMR ^1H (DMSO- d_6 , 400,13 MHz): δ 5.96 (s, 2H), 6.65 (t, J = 6.9 Hz, 1H), 7.03 (t, J = 6.9 Hz, 1H), 7.24 (t, J = 7.9 Hz, 1H), 7.27 – 7.37 (m, 4H), 7.56 – 7.46 (m, 2H), 7.72 (t, J = 7.9 Hz, 1H), 8.19 (d, J = 6.9 Hz, 1H), 8.22 (d, J = 7.9 Hz, 1H), 8.38 (d, J = 7.9 Hz, 1H), 8.60 (s, 1H); NMR ^{13}C (DMSO- d_6 , 101 MHz): δ 47.4, 112.0, 117.9, 121.8, 122.8, 122.9, 123.5, 123.7, 125.6 (2C), 126.1, 127.0, 127.0, 127.2, 128.8 (2C), 130.0, 131.6, 137.5, 141.5, 156.9; HRMS (m/z) HRMS (m/z) $[\text{M}+\text{H}]^+$: calcd for: $[\text{M}+\text{H}]^+$, $\text{C}_{21}\text{H}_{17}\text{N}_4$: 325.1448, found: 325.1149

6-cyclohexylpyrido[2',1':2,3]imidazo[4,5-c]isoquinolin-5(6H)-imine (4a)





6-benzylpyrido[2',1':2,3]imidazo[4,5-c]isoquinolin-5(6H)-imine (4b)

