Supporting information

Synthesis of 6-phenanthridinones and their heterocyclic analogues through palladium-catalyzed sequential aryl-aryl and N-aryl coupling

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General Considerations: Unless otherwise specified, all reagents and dry solvents (DMF, acetonitrile, CH₂Cl₂) were purchased from commercial suppliers and used without further purification.¹ 3-Bromothiophene-2-carboxylic acid,² 3-bromofuran-2-carboxylic acid,³ 2-bromofuran-3-carboxylic acid,⁴ 2-bromonicotinic acid,⁵ 3-bromobenzo[*b*]thiophene-2-carboxylic acid,² 2-bromo-*N*-methylbenzamide,⁶ *N*-benzyl-2-bromobenzamide⁷ and 2-chloro-*N*-methyl-nicotinamide⁸ were prepared according to reported procedures. The palladium-catalyzed reactions were run under nitrogen using standard Schlenk and vacuum line techniques. Melting points are uncorrected. ¹H and ¹³C NMR spectra of **5** and **6** were recorded in CDCl₃ on a Bruker 300-AMX spectrometer at 300 and 75 MHz, respectively. The reported ¹H NMR data of compounds **5** were obtained after treatment with D₂O. E. I. mass spectra were determined on a VG Analytical 7070 EQ mass spectrometer with an attached VG Analytical 11/250 data system. IR spectra were recorded with a Perkin-Elmer FT-IR 1725X spectrophotometer.

General procedure for the preparation of amides 5. A solution of carboxylic acid (4.38 mmol), a catalytic amount of anhydrous DMF (0.13 mmol, 10 μL), and thionyl chloride (10 mL) was heated at reflux for 3 h. The reaction mixture was cooled to room temperature and the excess of thionyl chloride was removed under reduced pressure. The acid chloride thus formed was dissolved in anhydrous CH₂Cl₂ (5 mL) and added dropwise to a CH₂Cl₂ (5 mL) solution of the amine (9.64 mmol) cooled at 0°C under stirring. The mixture was allowed to warm to room temperature and stirring was continued for additional 4 h. After treatment of the reaction mixture with a 10% solution of sodium hydroxide (5 mL) and separation of the organic layer, the aqueous phase was extracted with AcOEt (2 X 5 mL) to recover further product. The combined organic extracts were dried (Na₂SO₄) and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane-AcOEt).

3-Bromothiophene-2-carboxylic acid methylamide (5b) (R² = Me). Yield: 78%. M.p.: 60-61 °C (iPr₂O). ¹H NMR: δ 3.0 (s, 3H), 7.04 (d, *J* = 5.3 Hz, 1H), 7.44 (d, *J* = 5.3 Hz, 1H). ¹³C NMR: δ 26.6, 108.2, 129.8, 131.8, 135.0, 161.0. IR (nujol): ν 3419, 1636 cm⁻¹. MS *m/z* 221 (53), 219 (53), 191

(100), 189 (100), 140 (27), 82 (32). Anal. Calcd for C₆H₆BrNOS: C, 32.74; H, 2.75; N, 6.36. Found: C, 32.93; H, 2.78; N, 6.26.

3-Bromothiophene-2-carboxylic acid benzylamide (5b) (R² = Bn). Yield: 81%. M.p.: 104-105 °C (MeCN). ¹H NMR: δ 4.70 (s, 2H), 7.05 (d, *J* = 5.3 Hz, 1H), 7.30-7.40 (m, 5H), 7.48 (d, *J* = 5.3 Hz, 1H). ¹³C NMR: δ 44.0, 108.6, 127.6, 127.7, 128.7, 130.2, 131.9, 134.8, 137.7, 160.3. IR (nujol): ν 3361, 1623 cm⁻¹. MS *m/z* 297 (75), 295 (75), 216 (41), 191 (100), 189 (100), 106 (37), 91 (54). Anal. Calcd for C₁₂H₁₀BrNOS: C, 48.66; H, 3.40; N, 4.73. Found: C, 49.00; H, 3.49; N, 4.80.

3-Bromofuran-2-carboxylic acid methylamide (5c) (R² = Me). Yield: 81%. M.p.: 73-74 °C (*i*Pr₂O). ¹H NMR: δ 2.96 (s, 3H), 6.54 (d, *J* = 1.9 Hz, 1H), 7.38 (d, *J* = 1.9 Hz, 1H); ¹³C NMR: δ 25.7, 103.4, 116.3, 143.0, 143.4, 158.0. IR (nujol): ν 3298, 1640 cm⁻¹. MS *m/z* 205 (80), 203 (80), 175 (100), 173 (100), 124 (23). Anal. Calcd for C₆H₆BrNO₂: C, 35.32; H, 2.96; N, 6.87. Found: C, 35.46; H, 3.00; N, 7.13.

2-Bromofuran-3-carboxylic acid methylamide (5d) (R² = Me). Yield: 80%. M.p.: 94-95 °C (*i*Pr₂O). ¹H NMR: δ 2.96 (s, 3H), 6.79 (d, *J* = 2.1 Hz, 1H), 7.41 (d, *J* = 2.1 Hz, 1H). ¹³C NMR: δ 26.4, 112.7, 120.8, 122.4, 144.3, 161.6. IR (nujol): ν 3316, 1646 cm⁻¹. MS *m/z* 205 (40), 203 (40), 175 (100), 173 (100), 124 (40). Anal. Calcd for C₆H₆BrNO₂: C, 35.32; H, 2.96; N, 6.87. Found: C, 35.47; H, 2.89; N, 6.95.

N-Benzyl-2-chloronicotinamide (5e-Cl) (R² = Bn). Yield: 82%. M.p.: 122-123 °C (AcOEt). ¹H NMR: δ 4.67 (s, 2H), 7.30-7.40 (m, 6H), 8.13 (dd, *J* = 7.6, 2.0 Hz, 1H), 8.45 (dd, *J* = 4.8, 2.0 Hz, 1H). ¹³C NMR: δ 44.2, 122.6, 127.6, 127.7, 128.7, 131.2, 137.3, 139.4, 147.1, 150.7, 164.6. IR (nujol): ν 3262, 1649 cm⁻¹. MS *m/z* 248 (35), 246 (100), 211 (80), 142 (32), 140 (85), 114 (10), 112 (35), 91 (45). Anal. Calcd for C₁₃H₁₁ClN₂O: C, 63.29; H, 4.49; N, 11.36. Found: C, 63.09; H, 4.49; N, 11.26.

3-Bromobenzo[b]thiophene-2-carboxylic acid methylamide (5f) (R² = Me). Yield: 75 %. M.p.: 111-112 °C (*i*Pr₂O). ¹H NMR: δ 3.10 (s, 3H), 7.44-7.50 (m, 2H), 7.79-7.87 (m, 2H). ¹³C NMR: δ 26.8, 105.9, 122.5, 124.3, 125.4, 127.1, 134.8, 138.3, 151.5. IR (nujol): ν 3290, 1636 cm⁻¹. MS *m/z* 271 (62), 269 (67), 241 (100), 239 (97), 213 (20), 211 (17), 190 (15), 132 (65). Anal. Calcd for C₁₀H₈BrNOS: C, 44.46; H, 2.98; N, 5.18. Found: C, 44.67; H, 3.04; N, 5.91.

N-Benzyl-2-bromonicotinamide (5e-Br) (R² = Bn). A solution of 2-bromonicotinic acid (208 mg, 1.03 mmol) and 1,1'-carbonyldiimidazole (167 mg, 1.03 mmol) in anhydrous THF (10 mL) was stirred at r.t. for 2 h. Then, a solution of benzylamine (110 mg, 1.03 mmol) in anhydrous THF (4 mL) was added dropwise. The resulting reaction mixture was left under stirring overnight. After treatment with a saturated solution of NaHCO₃ (20 mL), the mixture was extracted with AcOEt (3 X 15 mL). The combined organic extracts were dried over Na₂SO₄. Removal of the solvent at

reduced pressure gave a crude which was purified by chromatography on silica gel (hexane/AcOEt 3/7). Yield: 300 mg, 69%. M.p.: 139-140 °C (AcOEt). ¹H NMR: δ 4.68 (s, 2H), 7.30-7.40 (m, 6H), 7.95 (dd, *J* = 7.6, 2.0 Hz, 1H), 8.43 (dd, *J* = 4.7, 2.0 Hz, 1H); ¹³C NMR: δ 44.4, 122.8, 127.8, 128.0, 128.8, 134.5, 137.1, 138.4, 138.6, 151.1, 165.5. IR (nujol): ν 3262, 1645 cm⁻¹. MS *m/z* 292 (100), 290 (100), 211 (85), 186 (80), 184 (80), 158 (40), 156 (40), 91 (90). Anal. Calcd for C₁₃H₁₁BrN₂O: C, 53.63; H, 3.81; N, 9.62. Found: C, 53.42; H, 3.75; N, 9.51.

Synthesis of 6. A Schlenk-type flask was charged under nitrogen with Pd(OAc)₂ (3.0 mg, 0.013 mmol), tri-2-furylphosphine (6.2 mg, 0.027 mmol), K₂CO₃ (72.3 mg, 0.52 mmol), the amide **5** (0.26 mmol), a solution of norbornene (26.9 mg, 0.286 mmol) in anhydrous solvent (5.8 mL), and the *o*-iodoarene **1** (0.26 mmol). The reaction mixture was heated under stirring at the temperature and for the time indicated in Table 2, then cooled to r. t. After addition of saturated NH₄Cl (30 mL) and extraction with AcOEt (3 X 15 mL), the combined organic extracts were washed with brine (30 mL) and dried over Na₂SO₄. Removal of the solvent under reduced pressure gave a crude which was purified by flash chromatography on silica gel (hexane-AcOEt).

4-Methyl-5*H*-phenanthridin-6-one (6a) (R¹ = Me, R² = H). M.p. 249-250 °C (MeCN). ¹H NMR: δ 2.5 (s, 3H), 7.20 (t, *J* = 7.7 Hz, 1H), 7.33 (d, *J* = 7.3 Hz, 1H), 7.60 (td, *J* = 8.0, 1.1 Hz, 1H), 7.79 (td, *J* = 8.0, 1.5 Hz, 1H), 8.10 (d, *J* = 8.0 Hz, 1H), 8.29 (d, *J* = 8.1 Hz, 1H), 8.52 (dd, *J* = 8.0, 1.5 Hz, 1H), 8.83 (br s, 1H). ¹³C NMR: δ 17.0, 118.4, 121.1, 122.3, 122.4, 123.1, 125.5, 127.8, 128.3, 130.8, 132.9, 134.3, 135.0, 161.9. IR (nujol): ν 3190, 1677 cm⁻¹. MS *m/z* 209 (100), 208 (39), 180 (27), 152 (17), 76 (16). Anal. Calcd for C₁₄H₁₁NO: C, 80.36; H, 5.30; N, 6.69. Found: C, 80.26; H, 5.32; N, 6.70.

4,5-Dimethyl-5*H*-phenanthridin-6-one (6a) (R¹, R² = Me). M.p.: 58-59 °C (*i*Pr₂O). ¹H NMR: δ 2.69 (s, 3H), 3.83 (s, 3H), 7.24 (t, *J* = 7.6 Hz, 1H), 7.34 (br d, 1H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.75 (td, *J* = 7.6, 1.3 Hz, 1H), 8.13 (d, *J* = 7.2 Hz, 1H), 8.25 (d, *J* = 8.2 Hz, 1H), 8.53 (dd, *J* = 8.0, 1.3 Hz, 1H). ¹³C NMR: δ 23.4, 38.2, 120.9, 121.2, 121.8, 122.8, 125.4, 126.1, 127.7, 128.4, 132.4, 133.7, 133.9, 139.5, 164.1. IR (nujol): ν 1636 cm⁻¹. MS *m/z* 223 (100), 208 (69), 194 (16), 165 (16), 152 (16). Anal. Calcd for C₁₅H₁₃NO: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.67; H, 5.77; N, 5.95.

5-Benzyl-4-methyl-5*H*-phenanthridin-6-one (6a) (R¹ = Me, R² = Bn). M.p.: 101-102 °C (AcOEt/*i*Pr₂O). ¹H NMR: δ 2.56 (s, 3H), 5.68 (s, 2H), 7.13-7.32 (m, 7H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.78 (td, *J* = 7.1, 1.3 Hz, 1H), 8.20 (dd, *J* = 7.6, 1.3 Hz, 1H), 8.30 (d, *J* = 8.2 Hz, 1H), 8.54 (dd, *J* = 7.9, 1.1 Hz, 1H). ¹³C NMR: δ 24.0, 51.5, 121.5, 121.9, 122.9, 125.3, 125.7, 125.9, 126.5, 128.0, 128.4, 128.9, 132.7, 134.2, 134.4, 138.6, 138.9, 164.1. IR (nujol): ν 1645 cm⁻¹. MS *m/z* 299 (65), 208 (100), 193 (45), 91 (90). Anal. Calcd for C₂₁H₁₇NO: C, 84.25; H, 5.72; N, 4.68. Found: C, 84.20; H, 5.89; N, 4.85.

4-Ethyl-5-methyl-5H-phenanthridin-6-one (6a) ($R^1 = \text{Et}$, $R^2 = \text{Me}$). M.p.: 82-83 °C (*i*Pr₂O). ¹H NMR: δ 1.31 (t, $J = 7.5$ Hz, 3H), 3.04 (q, $J = 7.5$ Hz, 2H), 3.81 (s, 3H), 7.28 (t, $J = 7.7$ Hz, 1H), 7.41 (d, $J = 7.4$ Hz, 1H), 7.57 (t, $J = 7.5$ Hz, 1H), 7.75 (td, $J = 7.7$, 1.2 Hz, 1H), 8.13 (d, $J = 7.9$ Hz, 1H), 8.24 (d, $J = 8.2$ Hz, 1H), 8.52 (dd, $J = 8.0$, 1.3 Hz, 1H). ¹³C NMR: δ 15.5, 28.1, 38.6, 120.8, 121.4, 121.8, 123.1, 125.3, 127.8, 128.4, 131.8, 132.4, 132.6, 134.0, 139.0, 164.2. IR (nujol): ν 1641 cm⁻¹. MS *m/z* 237 (100), 222 (90), 209 (20), 192 (50), 165 (25). Anal. Calcd for C₁₆H₁₅NO: C, 80.98; H, 6.37; N, 5.90. Found: C, 80.75; H, 6.47; N, 5.85.

4-Isopropyl-5-methyl-5H-phenanthridin-6-one (6a) ($R^1 = i\text{Pr}$, $R^2 = \text{Me}$). M.p.: 103-104 °C (*i*Pr₂O). ¹H NMR: δ 1.31 (d, $J = 6.7$ Hz, 6H), 3.53 (sept, $J = 6.7$ Hz, 1H), 3.75 (s, 3H), 7.29 (t, $J = 7.7$ Hz, 1H), 7.47 (dd, $J = 7.7$, 1.3 Hz, 1H), 7.53 (t, $J = 7.5$ Hz, 1H), 7.70 (td, $J = 7.7$, 1.4 Hz, 1H), 8.05 (dd, $J = 7.8$, 1.3 Hz, 1H), 8.19 (d, $J = 8.2$ Hz, 1H), 8.48 (dd, $J = 7.9$, 1.3 Hz, 1H). ¹³C NMR: δ 24.7, 29.8, 40.4, 120.3, 121.8, 123.3, 125.3, 127.7, 128.4, 132.4, 134.0, 137.9, 138.5, 164.5. IR (nujol): ν 1645 cm⁻¹. MS *m/z* 251 (95), 236 (100), 220 (35), 206 (35). Anal. Calcd for C₁₇H₁₇NO: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.27; H, 6.93; N, 5.64.

4-Methoxy-5-methyl-5H-phenanthridin-6-one (6a) ($R^1 = \text{OMe}$, $R^2 = \text{Me}$). M.p.: 128-129 °C (*i*Pr₂O). ¹H NMR: δ 3.96 (s, 3H), 3.98 (s, 3H), 7.11 (dd, $J = 8.0$, 1.2 Hz, 1H), 7.28 (t, $J = 8.1$ Hz, 1H), 7.6 (t further split, $J = 7.5$ Hz, 1H), 7.76 (td, $J = 7.7$, 1.4 Hz, 1H), 7.93 (dd, $J = 8.1$, 1.2 Hz, 1H), 8.26 (d, $J = 8.2$ Hz, 1H), 8.56 (dd, $J = 8.0$, 1.4 Hz, 1H). ¹³C NMR: δ 36.6, 56.5, 113.2, 115.7, 121.7, 122.0, 123.0, 125.7, 127.9, 128.6, 129.4, 132.2, 133.5, 149.4, 163.1. IR (nujol): ν 1645 cm⁻¹. MS *m/z* 239 (100), 224 (65), 209 (37), 194 (55), 166 (27). Anal. Calcd for C₁₅H₁₃NO₂: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.10; H, 5.29; N, 5.65.

5,6-Dimethyl-5H-thieno[2,3-*c*]quinolin-4-one (6b) ($R^1, R^2 = \text{Me}$). M.p.: 118-119 °C (AcOEt). ¹H NMR: δ 2.75 (s, 3H), 3.90 (s, 3H), 7.23 (t, $J = 7.6$ Hz, 1H), 7.35 (d, $J = 7.0$ Hz, 1H), 7.70 (d, $J = 5.2$ Hz, 1H), 7.77 (d, $J = 5.2$ Hz, 1H), 7.86 (dd, $J = 7.7$, 1.1 Hz, 1H); ¹³C NMR: δ 23.9, 37.3, 120.1, 122.4, 122.8, 126.1, 130.2, 133.0, 133.4, 140.0, 142.5, 160.3. IR (nujol): ν 1636 cm⁻¹. MS *m/z* 229 (100), 214 (73), 200 (13), 186 (10), 171 (9). Anal. Calcd for C₁₃H₁₁NOS: C, 68.09; H, 4.84; N, 6.11. Found: C, 67.79; H, 4.78; N, 6.09.

5-Benzyl-6-methyl-5H-thieno[2,3-*c*]quinolin-4-one (6b) ($R^1 = \text{Me}$, $R^2 = \text{Bn}$). M.p.: 171-172 °C (AcOEt). ¹H NMR: δ 2.58 (s, 3H), 5.76 (s, 2H), 7.07-7.09 (m, 2H), 7.15-7.28 (m, 5H), 7.73 (d, $J = 5.2$ Hz, 1H), 7.79 (d, $J = 5.2$ Hz, 1H), 7.90 (dd, $J = 7.5$, 1.9 Hz, 1H). ¹³C NMR: δ 24.3, 50.3, 120.4, 122.6, 122.9, 123.1, 125.6, 125.9, 126.6, 128.5, 133.5, 134.2, 138.6, 139.3, 143.0, 160.2. IR (nujol): ν 1634 cm⁻¹. MS *m/z* 305 (56), 214 (100), 199 (34), 91 (84). Anal. Calcd for C₁₉H₁₅NOS: C, 74.72; H, 4.95; N, 4.59. Found: C, 74.43; H, 4.95; N, 4.59.

5,6-Dimethyl-5*H*-furo[2,3-*c*]quinolin-4-one (6c) ($R^1, R^2 = \text{Me}$). M.p.: 149-150°C (AcOEt). ^1H NMR: δ 2.70 (s, 3H), 3.88 (s, 3H), 7.02 (d, $J = 2.0$ Hz, 1H), 7.22 (t, $J = 7.5$ Hz, 1H), 7.32 (br d, 1H), 7.67 (dd, $J = 7.6, 1.4$ Hz, 1H), 7.79 (d, $J = 2.0$ Hz, 1H). ^{13}C NMR: δ 24.0, 37.1, 105.9, 118.1, 122.4, 122.9, 126.3, 129.9, 133.2, 139.5, 142.0, 148.0, 155.8. IR (nujol): ν 1661 cm^{-1} . MS m/z 213 (100), 198 (84), 184 (14), 115 (18). Anal. Calcd for $\text{C}_{13}\text{H}_{11}\text{NO}_2$: C, 73.22; H, 5.20; N, 6.57. Found: C, 73.05; H, 5.28; N, 6.74.

5,6-Dimethyl-5*H*-furo[3,2-*c*]quinolin-4-one (6d) ($R^1, R^2 = \text{Me}$). M.p.: 87-88°C (*i*Pr₂O). ^1H NMR: δ 2.75 (s, 3H), 3.88 (s, 3H), 7.05 (d, $J = 1.8$ Hz, 1H), 7.22 (t, $J = 7.6$ Hz, 1H), 7.34 (d, $J = 7.4$ Hz, 1H), 7.61 (d, $J = 1.8$ Hz, 1H), 7.87 (d, $J = 7.7$ Hz, 1H). ^{13}C NMR: δ 24.1, 36.9, 108.1, 114.8, 119.3, 122.8, 126.0, 134.0, 139.6, 143.9, 155.9, 161.4. IR (nujol): ν 1662 cm^{-1} . MS m/z ; 213(100), 198(70), 184(15), 156(10), 128(10), 115(10). Anal. Calcd for $\text{C}_{13}\text{H}_{11}\text{NO}_2$: C, 73.22; H, 5.20; N, 6.57. Found: C, 73.00; H, 5.26; N, 6.37.

6,7-Dimethyl-6*H*-benzo[*h*][1,6]naphthyridin-5-one (6e) ($R^1, R^2 = \text{Me}$). M.p.: 156-157 °C (*i*Pr₂O). ^1H NMR: δ 2.71 (s, 3H), 3.86 (s, 3H), 7.3 (t, $J = 7.6$ Hz, 1H), 7.41 (br d, 1H), 7.48 (dd, $J = 8.0, 4.5$ Hz, 1H), 8.72 (dd, $J = 8.0, 1.8$ Hz, 1H), 8.78 (dd, $J = 7.8, 1.3$ Hz, 1H), 8.97 (dd, $J = 4.5, 1.8$ Hz, 1H). ^{13}C NMR: δ 23.5, 37.8, 120.5, 122.4, 122.8, 123.2, 125.5, 135.6, 136.3, 140.3, 150.5, 153.5, 163.7. IR (nujol): ν 1643 cm^{-1} . MS m/z 224 (100), 209 (74), 195 (13). Anal. Calcd for $\text{C}_{14}\text{H}_{12}\text{N}_2\text{O}$: C, 74.98; H, 5.39; N, 12.49. Found: C, 74.83; H, 5.47; N, 12.72

6-Benzyl-7-methyl-6*H*-benzo[*h*][1,6]naphthyridin-5-one (6e) ($R^1 = \text{Me}, R^2 = \text{Bn}$). M.p.: 164-166 °C (AcOEt). ^1H NMR: δ 2.59 (s, 3H), 5.72 (s, 2H), 7.14-7.39 (m, 7H), 7.51 (dd, $J = 8.0, 4.5$ Hz, 1H), 8.75 (dd, $J = 8.0, 1.9$ Hz, 1H), 8.92 (dd, $J = 7.8, 1.8$ Hz, 1H), 9.03 (dd, $J = 4.5, 1.9$ Hz, 1H). ^{13}C NMR: δ 24.0, 51.1, 120.4, 123.0, 122.8, 123.3, 123.8, 125.2, 125.6, 126.7, 128.6, 136.4, 136.7, 138.2, 139.8, 150.8, 153.9, 163.8. IR (nujol): ν 1650 cm^{-1} . MS m/z 300 (100), 209 (90), 194 (35), 91 (95). Anal. Calcd for $\text{C}_{20}\text{H}_{16}\text{N}_2\text{O}$: C, 79.98; H, 5.37; N, 9.33. Found: C, 79.86; H, 5.40; N, 9.60.

4,5-Dimethyl[1]benzothieno[2,3-*c*]quinolin-6(6*H*)-one (6f) ($R^1, R^2 = \text{Me}$). ^1H NMR: δ 2.75 (s, 3H), 3.92 (s, 3H), 7.32-7.40 (m, 2H), 7.56-7.60 (m, 2H), 8.02-8.05 (m, 1H), 8.54-8.58 (m, 1H), 8.67-8.7 (m, 1H). MS m/z 279 (M⁺).

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