Synthesis of Polysubstituted 4-Fluoroquinolinones

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Experimental Part

In a typical experimental procedure: solution of 2-(trifluoromethyl)aniline (**1**) (161 mg, 1 mmol) in 5 mL of dry THF was added *via* syringe to a vigorously stirred mixture of arylacetate (4 mmol) and LDA (6 mmol, freshly prepared from diisopropylamine and *n*-BuLi) in 20 mL of dry THF at -78°C under Ar. The mixture was allowed to warm to room temperature and stirred for an additional 4 h. The resulting solution was concentrated *in vacuo*. The residue was partitioned between EtOAc and concentrated aqueous NH₄Cl, and the aqueous layer was extracted with EtOAc. Combined organic extracts were dried over Na₂SO₄, concentrated *in vacuo*, and purified by column chromatography (Silica gel, hexane/EtOAc = 1:3) to afford analytically pure quinolinones **3**.

4-Fluoro-3-phenylhydroquinolin-2-one, 3a, 66% yield, m.p. 280°C (decomp.). ¹H NMR (400 MHz, dms_o-d₆): δ 7.23 (t, *J* = 7.6 Hz, 1H), 7.30-7.56 (m, 6H), 7.64 (dd, *J*₁ = 7.6 Hz, *J*₂ = 1.2 Hz, 1H), 7.82 (d, *J* = 7.6 Hz, 1H), 12.06 (br s, exch. D₂O, 1H); ¹⁹F NMR (400 MHz, dms_o-d₆): δ -112.2; ESI MS: (M+1) 240, (M-1) 238. Elemental analysis, calcd. for C₁₅H₁₀FNO: C, 75.30; H, 4.21; N, 5.85. Found: C, 75.13; H, 4.02; N, 5.61.

4-Fluoro-3-(3-pyridyl)hydroquinolin-2-one, 3b, 59% yield, m.p. 280°C (decomp.). ¹H NMR (400 MHz, dms_o-d₆): δ 7.26 (t, *J* = 7.6 Hz, 1H), 7.34 (d, *J* = 7.6 Hz, 1H), 7.43 (dd, *J*₁ = 7.6 Hz, *J*₂ = 1.2 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.82 (d, *J* = 7.6 Hz, 1H), 8.02 (d, *J* = 7.6 Hz, 1H), 8.64 (d, *J* = 1.2 Hz), 8.94 (s, 1H), 11.94 (br s, exch. D₂O, 1H); ¹⁹F NMR (400 MHz, dms_o-d₆): δ -111; ESI MS: (M+1) 241, (M-1) 239. Elemental analysis, calcd. for C₁₄H₉FN₂O: C, 69.99; H, 3.78; N, 11.66. Found: C, 69.81; H, 3.86; N, 11.52.

4-Fluoro-3-(4-methoxyphenyl)hydroquinolin-2-one, 3c, 71% yield, m.p. 280°C (decomp.). ¹H NMR (400 MHz, dms_o-d₆): δ 3.86 (s, 3H, OMe), 7.26 (t, *J* = 7.6 Hz, 1H), 6.96 (d, *J* = 7.6 Hz, 2H), 7.14 (d, *J* = 7.6 Hz, 1H), 7.22 (dd, *J*₁ = 7.6 Hz, *J*₂ = 1.2 Hz, 1H), 7.58 (d, *J* = 7.6 Hz, 2H), 7.76 (t, *J* = 7.6 Hz, 1H), 7.82 (d, *J* = 7.6 Hz, 1H), 12.04 (br s, exch. D₂O, 1H); ¹³C NMR (100 MHz, dms_o-d₆): δ 114.2, 115.6, 118.8, 122.6, 123.4, 123.8, 126.8, 133.1, 139.2, 149.2, 151.3, 160.2, 161.7, 163.7; ¹⁹F NMR (400 MHz, dms_o-d₆): δ -110.8; ESI

MS: (M+1) 270, (M-1) 268. Elemental analysis, calcd. for C₁₆H₁₂FNO₂: C, 71.37; H, 4.49; N, 5.20. Found: C, 71.15; H, 4.54; N, 5.02.

3-(3,5-dimethoxyphenyl)-4-fluorohydroquinolin-2-one, 3d, 63% yield, m.p. 280°C (decomp.). ¹H NMR (400 MHz, dms_o-d₆, 25°C): δ 3.64 (s, 3H, OMe), 3.68 (s, 3H, OMe), 6.82-7.06 (m, 3H), 7.12 (t, *J* = 7.6 Hz, 1H), 7.26 (dd, *J*₁ = 7.6 Hz, *J*₂ = 1.2 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.64 (d, *J* = 7.6 Hz, 1H), 11.86 (br s, exch. D₂O, 1H); ¹³C NMR (100 MHz, dms_o-d₆): δ 114.2, 115.6, 118.8, 122.6, 123.4, 123.8, 126.8, 133.1, 139.2, 149.2, 151.3, 160.2, 161.7, 163.7; ¹⁹F NMR (400 MHz, dms_o-d₆): δ -110.6; ESI MS: (M+1) 300, (M-1) 298. Elemental analysis, calcd. for C₁₇H₁₄FNO₃: C, 68.22; H, 4.71; N, 4.68. Found: C, 67.96; H, 4.84; N, 4.39.

4-Fluoro-3-(2-thienyl)hydroquinolin-2-one, 3e, 58% yield, m.p. 280°C (decomp.). ¹H NMR (400 MHz, dms_o-d₆): δ 6.98 (dd, *J*₁ = 7.6 Hz, *J*₂ = 1.2 Hz, 1H), 7.04 (t, *J* = 7.6 Hz, 1H), 7.18 (d, *J*₁ = 7.6 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 1H), 7.52 (d, *J* = 1.2 Hz, 1H), 7.64 (d, *J* = 7.6 Hz, 1H), 7.78 (d, *J* = 7.6 Hz, 1H), 11.96 (br s, exch. D₂O, 1H); ¹⁹F NMR (400 MHz, dms_o-d₆): δ -110.8; ESI MS: (M+1) 246, (M-1) 244. Elemental analysis, calcd. for C₁₃H₈FNOS: C, 63.66; H, 3.29; N, 5.71. Found: C, 63.30; H, 3.38; N, 5.58.

3-(3,4-dichlorophenyl)-4-fluorohydroquinolin-2-one, 3f, 72% yield, m.p. 280°C (decomp.). ¹H NMR (400 MHz, dms_o-d₆, 25°C): δ 7.15 (t, *J* = 7.6 Hz, 1H), 7.22 (dd, *J*₁ = 7.6 Hz, *J*₂ = 1.2 Hz, 1H), 7.33 (d, *J* = 7.6 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.75 (m, 2H), 12.08 (br s, exch. D₂O, 1H); ¹⁹F NMR (400 MHz, dms_o-d₆): δ

-112.2; ESI MS: (M+1) 309, (M-1) 307. Elemental analysis, calcd. for C₁₅H₈Cl₂FNO: C, 58.47; H, 2.62; N, 4.55. Found: C, 58.36; H, 2.50; N, 4.36.

3-[(3,4-demethoxyphenyl)methyl]-4-fluorohydroquinolin-2-one, 3g, 52% yield, m.p. 280°C (decomp.). ¹H NMR (400 MHz, dms_o-d₆): δ 3.82 (s, 6H, 2OMe), 3.92 (s, 2H, CH₂), 6.73 (t, *J* = 7.6 Hz, 1H), 6.91 (dd, *J*₁ = 7.6 Hz, *J*₂ = 1.2 Hz, 1H), 6.96 (s, 1H), 7.48 (t, *J* = 7.6 Hz, 1H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.74 (t, *J* = 7.6 Hz, 1H), 7.83 (d, *J* = 7.6 Hz, 1H), 11.98 (br s, exch. D₂O, 1H); ¹⁹F NMR (400 MHz, dms_o-d₆): δ -110.2; ESI MS: (M+1) 314, (M-1) 312. Elemental analysis, calcd. for C₁₈H₁₆FNO₃: C, 69.00; H, 5.15; N, 4.47. Found: C, 68.81; H, 5.24; N, 4.28.

4-Fluoro-3-(3-pyridyl)hydroquinolin-2-one, 3h, 59% yield, m.p. 280°C (decomp.). ¹H NMR (400 MHz, dms_o-d₆): δ 7.26-7.42 (m, 4H), 7.45 (d, *J* = 7.6 Hz, 1H), 7.69 (dd, *J*₁ = 7.6 Hz, *J*₂ = 1.2 Hz, 1H), 7.83 (d, *J* = 7.6 Hz, 1H), 12.13 (br s, exch. D₂O, 1H); ¹⁹F NMR (400 MHz, dms_o-d₆): δ -112.8; ESI MS: (M+1) 276, (M-1) 274. Elemental analysis, calcd. for C₁₅H₈F₃NO: C, 65.46; H, 2.93; N, 5.09. Found: C, 65.34; H, 2.82; N, 4.93.

4,6-Difluoro-3-(3-pyridyl)hydroquinolin-2-one, 3i, 72% yield, m.p. 280°C (decomp.). ¹H NMR (400 MHz, dms_o-d₆): δ 7.56-7.82 (m, 4H), 8.02 (d, *J* = 7.6 Hz, 1H), 8.70 (d, *J* = 1.2 Hz, 1H), 8.84 (s, 1H), 12.52 (br s, exch. D₂O, 1H); ¹⁹F NMR (400 MHz, dms_o-d₆): δ -113.5; ESI MS: (M+1) 259, (M-1) 257. Elemental analysis, calcd. for C₁₄H₈F₂N₂O: C, 65.12; H, 3.12; N, 10.85. Found: C, 64.84; H, 3.24; N, 10.61.

4,6-Difluoro-3-(1-naphthyl)hydroquinolin-2-one, 3j, 77% yield, m.p. 280°C (decomp.). ¹H NMR (400 MHz, dms_o-d₆): δ 7.32-7.72 (m, 7H), 7.76 (s, 1H), 7.92-7.94 (m, 2H), 12.14 (br s, exch. D₂O, 1H); ¹⁹F NMR (400 MHz, dms_o-d₆): δ -111.7; ESI MS: (M+1) 308, (M-1) 307. Elemental analysis, calcd. for C₁₉H₁₁F₂NO: C, 74.26; H, 3.61; N, 4.56. Found: C, 74.02; H, 3.45; N, 4.31.

4,6-Difluoro-3-(3-pyridyl)hydroquinolin-2-one, 3k, 78% yield, m.p. 280°C (decomp.). ¹H NMR (400 MHz, dms_o-d₆): δ 7.30-7.65 (m, 5H), 7.82 (d, *J* = 7.6 Hz, 1H), 8.64 (d, *J*

= 2.4 Hz, 1H), 12.26 (br s, exch. D₂O, 1H); ¹⁹F NMR (400 MHz, dms_o-d₆): δ -113.2; ESI MS: (M+1) 259, (M-1) 257. Elemental analysis, calcd. for C₁₄H₈F₂N₂O: C, 65.12; H, 3.12; N, 10.85. Found: C, 64.88; H, 3.27; N, 10.62.

3-(3,5-Dimethoxyphenyl)-4,6-difluorohydroquinolin-2-one, 3l, 74% yield, m.p. 280°C (decomp.). ¹H NMR (400 MHz, dms_o-d₆, 25°C): δ 3.98 (s, 3H, OMe), 4.04 (s, 3H, OMe), 7.12-7.28 (m, 2H), 7.30 (s, 1H), 7.54-7.80 (m, 3H), 12.28 (br s, exch. D₂O, 1H); ¹⁹F NMR (400 MHz, dms_o-d₆): δ -112.5; ESI MS: (M+1) 318, (M-1) 316. Elemental analysis, calcd. for C₁₇H₁₃F₂NO₃: C, 64.35; H, 4.13; N, 4.41. Found: C, 64.06; H, 4.22; N, 4.23.

4,6-Difluoro-3-(2-thienyl)hydroquinolin-2-one, 3m, 52% yield, m.p. 280°C (decomp.). ¹H NMR (400 MHz, dms_o-d₆): δ 7.48 (t, *J* = 7.6 Hz, 1H), 7.58-7.64 (m, 2H), 7.79 (dd, *J*₁ = 7.6 Hz, *J*₂ = 1.2 Hz, 1H), 7.88 (dd, *J*₁ = 7.6 Hz, *J*₂ = 1.2 Hz, 1H), 8.02 (d, *J* = 1.2 Hz, 1H), 12.34 (br s, exch. D₂O, 1H); ¹⁹F NMR (400 MHz, dms_o-d₆): δ -112.6; ESI MS: (M+1) 264, (M-1) 262. Elemental analysis, calcd. for C₁₃H₇F₂NOS: C, 59.31; H, 2.68; N, 5.32. Found: C, 59.06; H, 2.49; N, 5.13.

4,6-Difluoro-3-(4-methoxyphenyl)hydroquinolin-2-one, 3n, 57% yield, m.p. 280°C (decomp.). ¹H NMR (400 MHz, dms_o-d₆): δ 3.78 (s, 3H, OMe), 6.90 (d, *J* = 7.6 Hz, 2H), 7.30-7.66 (m, 3H), 7.54 (d, *J* = 7.6 Hz, 2H), 12.03 (br s, exch. D₂O, 1H); ¹⁹F NMR (400 MHz, dms_o-d₆): δ -111.4; ESI MS: (M+1) 288, (M-1) 286. Elemental analysis, calcd. for C₁₆H₁₁F₂NO₂: C, 66.90; H, 3.86; N, 4.88. Found: C, 66.76; H, 3.95; N, 4.69.

3-(3,4-Dichlorophenyl)-4,8-difluorohydroquinolin-2-one, 3o, 79% yield, m.p. 280°C (decomp.). ¹H NMR (400 MHz, dms_o-d₆): δ 7.29 (m, 1H), 7.33-7.40 (m, 2H), 7.64 (dd, *J*₁ = 7.6 Hz, *J*₂ = 1.2 Hz, 1H), 7.76 (d, *J* =

7.6 Hz, 1H), 7.85 (s, 1H), 12.28 (br s, exch. D₂O, 1H); ¹⁹F NMR (400 MHz, dms_o-d₆): δ -112.6; ESI MS: (M+1) 327, (M-1) 325. Elemental analysis, calcd. for C₁₅H₇Cl₂F₂NO: C, 55.24; H, 2.16; N, 4.29. Found: C, 55.02; H, 2.27; N, 4.11.

4,8-Difluoro-3-(1-naphthyl)hydroquinolin-2-one, 3p, 77% yield, m.p. 280°C (decomp.). ¹H NMR (400 MHz, dms_o-d₆): δ 7.22 (m, 1H), 7.40-7.66 (m, 6H), 7.69 (dd, $J_1 = 7.6$ Hz, $J_2 = 1.2$ Hz, 1H), 8.01 (m, 2H), 12.20 (br s, exch. D₂O, 1H); ¹⁹F NMR (400 MHz, dms_o-d₆): δ -112.0; ESI MS: (M+1) 308, (M-1) 306. Elemental analysis, calcd. for C₁₉H₁₁F₂NO: C, 74.26; H, 3.61; N, 4.56. Found: C, 74.03; H, 3.48; N, 4.33.

6-Bromo-4-fluoro-3-(4-methoxyphenyl)hydroquinolin-2-one, 3q, 63% yield, m.p. 280°C (decomp.). ¹H NMR (400 MHz, dms_o-d₆): δ 3.75 (s, 3H, OMe), 6.96 (d, $J = 7.6$ Hz, 2H), 7.22 (d, $J = 7.6$ Hz, 1H), 7.42 (d, $J = 7.6$ Hz, 2H), 7.56 (d, $J = 7.6$ Hz, 1H), 7.82 (s, 1H), 12.01 (br s, exch. D₂O, 1H); ¹⁹F NMR (400 MHz, dms_o-d₆): δ -111.2; ESI MS: (M+1) 349, (M-1) 347. Elemental analysis, calcd. for C₁₆H₁₁BrFNO₂: C, 55.20; H, 3.18; N, 4.02. Found: C, 54.94; H, 2.96; N, 3.73.

6-Bromo-4-fluoro-3-(3-thienyl)hydroquinolin-2-one, 3r, 55% yield, m.p. 280°C (decomp.). ¹H NMR (400 MHz, dms_o-d₆): δ 7.01 (dd, $J_1 = 7.6$ Hz, $J_2 = 1.2$ Hz, 1H), 7.13 (d, $J = 7.6$ Hz, 1H), 7.52-7.66 (m, 2H), 7.76 (s,

1H), 7.82 (s, 1H), 12.16 (br s, exch. D₂O, 1H); ¹⁹F NMR (400 MHz, dms_o-d₆): δ -111.9; ESI MS: (M+1) 325, (M-1) 323. Elemental analysis, calcd. for C₁₃H₇BrFNOS: C, 48.17; H, 2.18; N, 4.32. Found: C, 48.04; H, 2.06; N, 4.20.

6-Bromo-4-fluoro-3-(2-thienyl)hydroquinolin-2-one, 3s, 61% yield, m.p. 280°C (decomp.). ¹H NMR (400 MHz, dms_o-d₆): δ 7.21 (d, $J = 7.6$ Hz, 1H), 7.43 (d, $J = 1.2$ Hz, 1H), 7.48 (d, $J = 1.2$ Hz, 1H), 7.67 (dd, $J_1 = 7.6$ Hz, $J_2 = 1.2$ Hz, 1H), 7.86 (s, 1H), 8.06 (s, 1H), 12.20 (br s, exch. D₂O, 1H); ¹⁹F NMR (400 MHz, dms_o-d₆): δ -112.2; ESI MS: (M+1) 325, (M-1) 323. Elemental analysis, calcd. for C₁₃H₇BrFNOS: C, 48.17; H, 2.18; N, 4.32. Found: C, 47.89; H, 2.02; N, 4.11.

6-Bromo-4-fluoro-3-(4-pyridyl)hydroquinolin-2-one, 3t, 81% yield, m.p. 280°C (decomp.). ¹H NMR (400 MHz, dms_o-d₆): 7.22 (d, $J = 7.6$ Hz, 1H), 7.48 (d, $J = 7.6$ Hz,

2H), 7.64 (d, $J = 7.6$ Hz, 1H), 7.83 (s, 1H), 8.61 (d, $J = 7.6$ Hz, 2H), 12.18 (br s, exch. D₂O, 1H); ¹⁹F NMR (400 MHz, dms_o-d₆): δ -112.8; ESI MS: (M+1) 320, (M-1) 318. Elemental analysis, calcd. for C₁₄H₈BrFN₂O: C, 52.69; H, 2.53; N, 8.78. Found: C, 52.52; H, 2.63; N, 8.57.