An expedient route to 3-aryl substituted quinolin-2-one and 1,8-naphthyridin-2-one derivatives of pharmaceutical interest

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Experimental Procedures and Spectroscopic Data

General procedure for the preparation of 3-aryl-4-hydroxyquinolin-2(1*H*)-ones **4.** A solution of the appropriate arylacetic ester **2** (4.0 mmol) in anhydrous THF (10 mL) was added dropwise, under argon, to a solution of LDA (2.0M solution in THF/ethylbenzene/heptane; 4.0 mmol, 2.0 mL) in anhydrous THF (20 mL), at $-78\text{ }^{\circ}\text{C}$. The addition was completed in 20 min, the mixture stirred at $-78\text{ }^{\circ}\text{C}$ for 10 min and then a solution of benzoxazinone **1a** (or **1b**) (2.0 mmol) in anhydrous THF (20 mL) was added dropwise over 30 min and the mixture stirred at $-78\text{ }^{\circ}\text{C}$ for 30-40 min. After quenching with 10% hydrochloric acid (10 mL) the mixture was diluted with diethyl ether (15 mL), the organic phase separated and the aqueous layer extracted further with diethyl ether (15 mL). The mixture of the organic extracts was diluted with light petroleum (20 mL), the water separated removed and the organic phase dried over sodium sulfate and concentrated in vacuo to afford the crude acylated arylacetic ester **3** as a viscous oil. A solution of crude **3** in anhydrous toluene (5 mL) was added to a suspension of sodium methoxide [generated by the addition of methanol to a suspension of sodium hydride (60% in oil; 4.5 mmol, 0.18 g) in anhydrous toluene (20 mL)] and the mixture heated at reflux for 3 h. The insoluble salt was dissolved by the addition of water (*ca* 40 mL), the aqueous layer separated and the organic phase extracted further with water (10 mL). After washing with a small amount of light petroleum the mixture of the aqueous extracts was acidified with 10% hydrochloric acid under cooling at $0\text{ }^{\circ}\text{C}$ and the fine precipitate formed was filtered and washed with ice-cold water.

4-Hydroxy-3-phenylquinolin-2(1*H*)-one (4a**).** Starting from 2-methoxy-4*H*-3,1-benzoxazin-4-one (**1a**) (2.0 mmol, 0.36 g) and ethyl phenylacetate (**2a**), compound **4a** was obtained as a white solid (0.42 g, 89 %). Mp $>320\text{ }^{\circ}\text{C}$ (dec.), lit.¹ mp $318\text{--}320\text{ }^{\circ}\text{C}$ (dec.). ^1H NMR (300 MHz, DMSO-*d*₆) δ 7.16 (1 H, pseudotriplet, H-6), 7.25-7.45 (6 H, m, H-8, ArH), 7.49 (1 H, pseudotriplet, H-7), 7.93 (1 H, dd, $J = 8.3, 1.0$, H-5), 10.08 (1 H, br, OH), 11.47 (1 H, s, NH). ^{13}C NMR (75 MHz, DMSO-*d*₆) δ 112.8, 115.0, 115.5, 121.2, 123.3, 127.0, 127.8, 130.7, 131.3, 133.5, 138.2, 157.5, 162.8.

4-Hydroxy-3-(3-methoxyphenyl)quinolin-2(1H)-one (4b). Starting from 2-methoxy-4*H*-3,1-benzoxazin-4-one (**1a**) (2.0 mmol, 0.36 g) and ethyl 3-methoxyphenylacetate (**2b**), compound **4b** was obtained as a white solid (0.40 g, 75 %). Mp 309-312 °C (dec.). Anal Calcd for C₁₆H₁₃NO₃: C, 71.90, H, 4.90, N, 5.24. Found: C, 71.81, H, 4.96, N, 5.19. ¹H NMR (300 MHz, DMSO-*d*₆) δ 3.75 (3 H, s, Me), 6.85-6.95 (3 H, m, ArH), 7.15 (1 H, pseudotriplet, H-6), 7.25-7.35 (2 H, m, H-8, ArH), 7.49 (1 H, pseudotriplet, H-7), 7.91 (1 H, dd, *J* = 8.3, 1.3, H-5), 10.03 (1 H, br, OH), 11.44 (1 H, s, NH). ¹³C NMR (75 MHz, DMSO-*d*₆) δ 55.0, 112.6, 112.7, 115.0, 115.5, 117.0, 121.3, 123.3, 123.8, 128.9, 130.7, 134.7, 138.2, 157.6, 159.1, 162.8.

4-Hydroxy-3-(4-methoxyphenyl)quinolin-2(1H)-one (4c). Starting from 2-methoxy-4*H*-3,1-benzoxazin-4-one (**1a**) (2.0 mmol, 0.36 g) and methyl 4-methoxyphenylacetate (**2c**), compound **4c** was obtained as a white solid (0.42 g, 79 %). Mp >320 °C (dec.), lit.² mp 305-309 °C. ¹H NMR (300 MHz, DMSO-*d*₆) δ 3.77 (3 H, s, Me), 6.94 (2 H, d, *J* = 8.9, H-3'), 7.15 (1 H, pseudotriplet, H-6), 7.24-7.32 (3 H, m, H-8, H-2'), 7.47 (1 H, pseudotriplet, H-7), 7.91 (1 H, dd, *J* = 8.3, 1.3, H-5), 9.94 (1 H, br, OH), 11.43 (1 H, s, NH). ¹³C NMR (75 MHz, DMSO-*d*₆) δ 55.1, 112.3, 113.4, 115.0, 115.6, 121.2, 123.2, 125.4, 130.5, 132.5, 138.1, 157.3, 158.5, 163.0.

7-Chloro-4-hydroxy-3-phenylquinolin-2(1H)-one (4d). Starting from 7-chloro-2-ethoxy-4*H*-3,1-benzoxazin-4-one (**1b**) (2.0 mmol, 0.46 g) and ethyl phenylacetate (**2a**), compound **4d** was obtained as a white solid (0.45 g, 83 %). Mp >320 °C (from MeOH), lit.³ mp 315 °C (from EtOH). ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.20 (1 H, dd, *J* = 8.7, 2.0, H-6), 7.26-7.46 (6 H, m, ArH, H-8), 7.92 (1 H, d, *J* = 8.6, H-5), 10.27 (1 H, br, OH), 11.56 (1 H, s, NH). ¹³C NMR (75 MHz, DMSO-*d*₆) δ 113.0, 114.1, 114.6, 121.3, 125.4, 127.1, 127.9, 131.3, 133.1, 135.0, 139.1, 157.2, 162.9.

7-Chloro-4-hydroxy-3-(3-methoxyphenyl)quinolin-2(1H)-one (4e). Starting from 7-chloro-2-ethoxy-4*H*-3,1-benzoxazin-4-one (**1b**) (2.0 mmol, 0.46 g) and ethyl 3-methoxyphenylacetate (**2b**), compound **4e** was obtained as a white solid (0.52 g, 87 %). Mp >320 °C (dec.), lit.⁴ mp >320 °C (from DMF/H₂O). ¹H NMR (300 MHz, DMSO-*d*₆)

δ 3.74 (3 H, s, CH₃), 6.85-6.93 (3 H, m, ArH), 7.20 (1 H, dd, J = 8.6, 2.2, H-6), 7.26-7.33 (2 H, m, ArH, H-8), 7.90 (1 H, d, J = 8.9, H-5), 10.24 (1 H, br, OH), 11.54 (1 H, s, NH). ¹³C NMR (75 MHz, DMSO-*d*₆) δ 55.0, 112.8, 112.9, 114.2, 114.5, 116.8, 121.4, 123.6, 125.4, 128.9, 134.3, 135.1, 139.1, 157.1, 159.1, 162.8.

7-Chloro-4-hydroxy-3-(4-methoxyphenyl)quinolin-2(1*H*)-one (4f). Starting from 7-chloro-2-ethoxy-4*H*-3,1-benzoxazin-4-one (**1b**) (2.0 mmol, 0.46 g) and methyl 4-methoxyphenylacetate (**2c**), compound **4f** was obtained as a white solid (0.56 g, 93 %). Mp >320 °C (from DMF), lit.⁴ mp >350 °C (from DMF). ¹H NMR (300 MHz, DMSO-*d*₆) δ 3.77 (3 H, s, CH₃), 6.95 (2 H, d, J = 8.9, H-3'), 7.19 (1 H, dd, J = 8.9, 2.2, H-6), 7.89 (1 H, d, J = 8.9, H-5), 10.15 (1 H, br, OH), 11.53 (1 H, s, NH). ¹³C NMR (75 MHz, DMSO-*d*₆) δ 55.1, 112.6, 113.4, 114.1, 114.6, 121.4, 125.0, 125.3, 132.4, 134.9, 138.9, 156.9, 158.6, 163.0.

General procedure for the preparation of 1-acyl-4-hydroxy-3-phenyl-1,8-naphthyridin-2(1*H*)-ones 6. The appropriate ester **2** (3.0 mmol) was added dropwise, under argon, to a stirred solution of LDA (2.0M solution in THF/ethylbenzene/heptane; 3.0 mmol, 1.5 mL) in anhydrous THF (10 mL), at -78 °C, and the mixture stirred for 30 min. A solution of pyridoxazinone **1c** (or **1d**) (2.2 mmol) in anhydrous THF (10 mL) was added dropwise over 15 min and the mixture stirred at -78 °C for 1h, then allowed to reach rt and stirred further for 1h. The solvent was evaporated in vacuo, the residue dissolved in water and the aqueous mixture washed with diethyl ether. The aqueous solution was acidified with 10% hydrochloric acid and the precipitated solid collected by filtration.

1-Acetyl-4-hydroxy-3-phenyl-1,8-naphthyridin-2(1*H*)-one (6a). Starting from 2-methyl-4*H*-pyrido[2,3-*d*][1,3]oxazin-4-one (**1c**) (2.2 mmol, 0.35 g) and ethyl phenylacetate (**2a**) (3.0 mmol, 0.49 g), compound **6a** was obtained as a white solid (0.35 g, 57 %). Mp 220-222 °C (from dichloromethane-light petroleum ether). Anal. Calcd for C₁₆H₁₂O₃N₂: C, 68.56, H, 4.32, N, 10.00. Found: C, 68.50, H, 4.32, N, 10.03. $\nu_{\max}$ (Nujol)/cm⁻¹ 1710s, 1650m, 1530. ¹H NMR (300 MHz, CDCl₃) δ 2.45 (3 H, s, CH₃), 7.32-7.52 (6 H, m, Ph,

H-6), 8.88 (1 H, dd, $J = 7, 2$, H-5), 9.21 (1 H, dd, $J = 7, 2$, H-7), 16.39 (1 H, br, OH). ^{13}C NMR (75 MHz, CDCl_3) δ 22.9, 115.2, 117.9, 122.4, 128.5, 128.8, 130.2, 131.9, 133.2, 143.0, 148.4, 156.4, 158.9, 164.0.

1-Acetyl-4-hydroxy-3-methyl-1,8-naphthyridin-2(1H)-one (6b). Starting from 2-methyl-4H-pyrido[2,3-d][1,3]oxazin-4-one (**1c**) (2.2 mmol, 0.35 g) and ethyl propionate (**2d**) (3.0 mmol, 0.31 g), compound **6b** was obtained as a white solid (0.07 g, 14 %). Mp 209-211 °C (from dichloromethane-light petroleum ether). Anal. Calcd for $\text{C}_{11}\text{H}_{10}\text{O}_3\text{N}_2$: C, 60.54, H, 4.62, N, 12.84. Found: C, 60.49, H, 4.64, N, 12.81. $\nu_{\text{max}}(\text{Nujol})/\text{cm}^{-1}$ 1710s, 1650m, 1530. ^1H NMR (300 MHz, CDCl_3) δ 2.27 (3 H, s, CH_3), 2.55 (3 H, s, COCH_3), 7.29 (1 H, pseudotriplet, H-6), 8.79 (1 H, dd, $J = 7, 2$, H-5), 9.14 (1 H, dd, $J = 7, 2$, H-7), 16.46 (1 H, br, OH). ^{13}C NMR (75 MHz, CDCl_3) δ 11.8, 22.0, 112.8, 114.9, 122.2, 131.2, 141.9, 147.4, 157.2, 157.9, 164.1.

1-Benzoyl-4-hydroxy-3-phenyl-1,8-naphthyridin-2(1H)-one (6c). Starting from 2-phenyl-4H-pyrido[2,3-d][1,3]oxazin-4-one (**1d**) (2.2 mmol, 0.49 g) and ethyl phenylacetate (**2a**) (3.0 mmol, 0.49 g), compound **6c** was obtained as a white solid (0.31 g, 41 %). Mp 228-229 °C (from dichloromethane-light petroleum ether). Anal. Calcd for $\text{C}_{21}\text{H}_{14}\text{O}_3\text{N}_2$: C, 73.67, H, 4.12, N, 8.18. Found: C, 73.60, H, 4.09, N, 8.21. $\nu_{\text{max}}(\text{Nujol})/\text{cm}^{-1}$ 1720s, 1670m, 1560. ^1H NMR (300 MHz, CDCl_3) δ 7.24-7.41 (11 H, m, COPh , NCOPh , H-6), 8.91 (1 H, dd, $J = 7, 2$, H-5), 9.28 (1 H, dd, $J = 7, 2$, H-7), 16.27 (1 H, br, OH). ^{13}C NMR (75 MHz, CDCl_3) δ 115.5, 122.9, 128.2, 128.5, 129.0, 129.7, 130.0, 131.1, 131.8, 133.1, 136.7, 143.1, 148.6, 157.3, 158.0, 163.9.

1-Benzoyl-4-hydroxy-3-methyl-1,8-naphthyridin-2(1H)-one (6d). Starting from 2-phenyl-4H-pyrido[2,3-d][1,3]oxazin-4-one (**1d**) (2.2 mmol, 0.49 g) and ethyl propionate (**2d**) (3.0 mmol, 0.31 g), compound **6d** was obtained as a white solid (0.08 g, 13 %). Mp 192-195 °C (from dichloromethane-light petroleum ether). Anal. Calcd for $\text{C}_{16}\text{H}_{12}\text{O}_3\text{N}_2$: C, 68.56, H, 4.32, N, 10.00. Found: C, 68.47, H, 4.28, N, 10.12. $\nu_{\text{max}}(\text{Nujol})/\text{cm}^{-1}$ 1720s, 1670m, 1560. ^1H NMR (300 MHz, CDCl_3) δ 2.24 (3 H, s, CH_3), 7.31-7.41 (6 H, m, Ph , H-6), 8.90 (1 H, dd, $J = 7, 2$, H-5), 9.26 (1 H, dd, $J = 7, 2$, H-7), 16.13 (1 H, br, OH). ^{13}C

NMR (75 MHz, CDCl₃) δ 11.9, 113.7, 118.3, 124.6, 129.1, 131.0, 133.2, 136.5, 144.7, 149.1, 156.8, 159.1, 164.2.

General procedure for the reactions of pyridoxazinone 1c with alkyl substituted β -dicarbonyl compounds 7 (Method C). The appropriate malonate or acetoacetate **7** was added dropwise to a suspension of sodium hydride (55-60% in oil; 22 mmol, 0.88 g) in anhydrous THF (20 mL) and the mixture stirred at rt for 30 min. Pyridoxazinone **1c** (5.5 mmol, 0.89 g) was added, the mixture stirred at rt for 3 h and the solvent evaporated in vacuo. The residue was dissolved in water, the aqueous mixture washed with diethyl ether and acidified with 10% hydrochloric acid. The acidified mixture was extracted with dichloromethane and the mixture of the extracts dried over anhydrous sodium sulfate and evaporated in vacuo. The oily residue was treated with diethyl ether and the solid formed collected by filtration.

1-Acetyl-4-hydroxy-3-methyl-1,8-naphthyridin-2(1H)-one (6b). Starting from 2-methyl-4H-pyrido[2,3-d][1,3]oxazin-4-one (**1c**) (5.5 mmol, 0.89 g) and diethyl methylmalonate (**7a**) (11 mmol, 1.91 g), or methyl 2-methylacetoacetate (**7b**) (11 mmol, 1.43 g), compound **6b** was obtained as a white solid, in 38 % (0.46 g) and 41 % (0.49 g) yields, respectively. Mp 209-211 °C (from dichloromethane-light petroleum ether). $\nu_{\max}$ (Nujol)/cm⁻¹ 1710s, 1650m, 1530. ¹H NMR (300 MHz, CDCl₃) δ 2.27 (3 H, s, CH₃), 2.55 (3 H, s, COCH₃), 7.29 (1 H, pseudotriplet, H-6), 8.79 (1 H, dd, J = 7, 2, H-5), 9.14 (1 H, dd, J = 7, 2, H-7), 16.46 (1 H, br, OH). ¹³C NMR (75 MHz, CDCl₃) δ 11.8, 22.0, 112.8, 114.9, 122.2, 131.2, 141.9, 147.4, 157.2, 157.9, 164.1.

1-Acetyl-3-butyl-4-hydroxy-1,8-naphthyridin-2(1H)-one (6e). Starting from 2-methyl-4H-pyrido[2,3-d][1,3]oxazin-4-one (**1c**) (5.5 mmol, 0.89 g) and diethyl butylmalonate (**7c**) (11 mmol, 2.38 g), compound **6e** was obtained as a white solid (0.39 g, 27 %). Mp 237-238 °C (from dichloromethane-light petroleum ether). Anal. Calcd for C₁₄H₁₆O₃N₂: C, 64.60, H, 6.20, N, 10.76. Found: C, 64.62, H, 6.23, N, 10.78. $\nu_{\max}$ (Nujol)/cm⁻¹ 1710s, 1650m, 1530. ¹H NMR (300 MHz, CDCl₃) δ 0.96 (3 H, t, J = 7, CH₃), 1.50 [4 H, m, (CH₂)₂], 2.55 (3 H, s, COCH₃), 2.70 (2 H, t, J = 7, CH₂), 7.28 (1 H, pseudotriplet, H-6),

8.79 (1 H, dd, $J = 7, 2$, H-5), 9.13 (1 H, dd, $J = 7, 2$, H-7), 16.45 (1 H, br, OH). ^{13}C NMR (75 MHz, CDCl_3) δ 13.8, 21.5, 22.7, 26.3, 30.3, 114.8, 117.6, 122.2, 131.2, 141.9, 147.3, 157.0, 157.7, 164.2.

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