Supporting Information

Efficient Solid-Phase Synthesis of 2-Substituted-3-Hydroxy-4(1*H*)-Quinolinone-7-Carboxamides with Two Diversity Positions

Miroslav Soural[♣] and Viktor Krchňák*

Department of Chemistry and Biochemistry, 251 Nieuwland Science Center, University of Notre Dame, Notre Dame, Indiana 46556, USA

Material and Methods

Solvents were purchased from Fisher (Pittsburgh, PA, www.fishersci.com) and used without further purification. Chemicals were obtained from Aldrich (Milwaukee, IL, www.sigmaaldrich.com) and Alfa Aesar (Ward Hill, MA, www.alfa.com), the Rink resin (100-200 mesh, 1% DVB, 0.75 mmol/g), and the aminomethymethyl resin (100-200 mesh, 1% DVB, 0.88 mmol/g) from NovaBiochem (EMD Chemicals, San Diego, CA, www.emdbiosciences.com). Synthesis was carried out on Domino Blocks in disposable polypropylene reaction vessels (Torviq, Niles, MI, www.torviq.com). Labquake Tube Rotator (Thermolyne, Dubuque, IA, www.barnsteadthermolyne.com) was used for gentle but efficient tumbling of resin slurry.

All reactions were carried out at ambient temperature (21 ^{o}C) unless stated otherwise. The volume of wash solvent was 10 mL per 1 g of resin. For washing, resin slurry was shaken with the fresh solvent for at least 1 min before changing the solvent. After adding a reagent solution, the resin slurry was manually vigorously shaken to break any potential resin clumps. Resin-bound intermediates were dried by a stream of nitrogen for prolonged storage and/or quantitative analysis.

For the LC/MS analysis a sample of resin (~5 mg) was treated by TFA in DCM, the cleavage cocktail was evaporated by a stream of nitrogen, and cleaved compounds extracted into 1 mL of MeOH.

The LC/MS analyses were carried out on Waters ZQ instrument consisting of chromatography module Alliance HT, photodiode array detector 2996, and mass spectrometer Micromass ZQ, using a 3 x 50 mm Pro C18 YMC reverse phase column (Waters, Milford, MA, www.waters.com). Mobile phases: 10 mM ammonium acetate in HPLC grade water (A) and HPLC grade acetonitrile (B). A gradient was formed from 5% to 80% of B in 10 min at 0.7 mL/min. Target compounds were analyzed using 0.1% aqueous TFA (A) in a gradient from 5% to 90% of B in 6 min at 0.7 mL/min. The MS electrospray source operated at capillary voltage 3.5 kV and a desolvation temperature 300 ^{o}C.

Purification was carried out on SunFire Prep C18 OBD column 19 x 100 mm, 5 um particles (Waters, Milford, MA, www.waters.com), gradient was formed from 0.1% aqueous TFA and acetonitrile, flow rate 15 mL/min.

NMR ^{1}H/^{13}C spectra were obtained on a Varian Unity*Plus* (299.89 MHz, ^{1}H) instrument. NMR spectra were recorded at ambient temperature (21 ^{o}C) in DMSO-d_6 solutions and referenced to the resonance signal of DMSO at δ=2.50 ppm (^{1}H spectra) and δ=39.51 ppm (^{13}C spectra). Chemical shifts δ are reported in ppm and coupling constants *J* in Hz.

Reductive Alkylation (resins 6)

Polymer-supported secondary amines **6** were prepared according to the published procedure.[1]

♣ Current address: Department of Organic Chemistry, Faculty of Science, University of Palacký, 771 46 Olomouc, Czech Republic

Acylation with 1-methyl-2-aminoterephtalate (resins 1, 7)

A polypropylene 10-ml fritted syringe was charged with 500 mg of resin **6** (or Rink amide resin in the case of resin **1**), and the resin was swollen in 5 ml of DCM. Accordingly to the loading of the starting resin, the solution of 2 equivalents of 1-methyl-2-aminoterephtalate, 1-hydroxybenzotriazole and 1,3-diisopropylcarbodiimide in 5 ml DMF was added. Resin was kept on a tumbler overnight, then washed 3 three times with DMF, three times with DCM, three times with MeOH and dried.

Saponification of methylesters (resins 2, 8)

A polypropylene 10-ml fritted syringe was charged with 500 mg of resin **1** (or **7**) and solution of 150 mg TMSOK in 5 ml THF was added. The resin was shaken at room temperature for 5 h, acidified with 20% HAc/DMF, washed 3 three times with DMF, three times with DCM, three times with MeOH and dried.

Preparation of anthranilates (resins 3, 9)

A polypropylene 10-ml fritted syringe was charged with 200 mg of resin **2** (or **8**) and the resin was shaken with 5% TEA/DMF (2 ml) for 5 min. Then a solution of 50 mg phenacylbromide in 1 ml DMF was added, the resin was kept on a tumbler for 2 h, washed 3 three times with DMF, three times with DCM, three times with MeOH and dried.

Cleavage and cyclization to hydroxyquinolinones (5, 11, 12)

A polypropylene 5-ml fritted syringe was charged with 200 mg of resin **3** (or **9**) and 50% TFA in DCM was added (3 ml). The resin was shaken for 30 min, the cleavage cocktail was collected and the content of the syringe was washed 2 times with fresh 50% TFA in DCM. Combined washes were evaporated by a stream of nitrogen, the residual material was dissolved in a neat TFA and heated at 80 °C for 2 h. TFA was evaporated in a stream of nitrogen and residual oil was sonified in diethylether for 5 min. Precipitated solid was collected by suction, washed with fresh diethylether and dried.

2-(4-methyl-phenyl)-3-hydroxy-4(1*H*)-quinolinone-7-carboxamide (5)

Yield of the crude product 90 %, yield of the purified product 84%, purity of the purified product 98%. ESI-MS *m/z* = 295, $[M+H]^+$. ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 2.40 (s, 3 H) 7.38 (d, *J*=8.01 Hz, 2 H) 7.55 (br. s., 1 H) 7.64 - 7.79 (m, 3 H) 8.09 - 8.21 (m, 2 H) 8.24 (s, 1 H) 11.70 (br. s., 1 H); 13C NMR (300 MHz, DMSO-*d*6) δ ppm 21.0, 118.9, 120.1, 123.0, 124.6, 128.9, 129.1, 129.2, 132.4, 136.2, 137.4, 138.5, 139.0, 167.6, 169.5.

2-(4-methyl-phenyl)-3-hydroxy-4(1*H*)-quinolinone-7-carboxylic acid N-propylamide (11a)

Yield of the crude product 98 %, yield of the purified product 90%, purity of the purified product 99%. ESI-MS *m/z* = 337, $[M+H]^+$. ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 0.91 (t, *J*=7.46 Hz, 3 H) 1.45 - 1.65 (m, 2 H) 2.40 (s, 3 H) 3.25 (q, *J*=6.63 Hz, 2 H) 7.38 (d, *J*=8.01 Hz, 2 H) 7.66 (d, *J*=8.29 Hz, 1 H) 7.73 (d, *J*=8.01 Hz, 2 H) 8.13 - 8.27 (m, 2 H) 8.64 (t, *J*=5.52 Hz, 1 H) 11.69 (s, 1 H); 13C NMR (300 MHz, DMSO-*d*6) δ ppm 12.2, 21.7, 23.07, 41.9, 119.3, 120.4, 123.5, 125.3, 129.6, 129.8, 129.9, 133.1, 137.3, 138.1, 139.2, 139.8, 166.5, 170.2.

2-(4-methyl-phenyl)-3-hydroxy-4(1*H*)-quinolinone-7-carboxylic acid N-(2-hydroxyethyl)-amide (11b)

Yield of the crude product 85 %, yield of the purified product 76%, purity of the purified product 99%. ESI-MS *m/z* = 339, $[M+H]^+$. ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 2.40 (s, 3 H) 3.67 (q, *J*=5.43 Hz, 2 H) 4.55 (t, *J*=5.25 Hz, 2 H) 7.38 (d, *J*=8.01 Hz, 2 H) 7.64 (d, *J*=7.73 Hz, 1 H) 7.73 (d, *J*=8.01 Hz, 2 H) 8.16 - 8.27 (m, 2 H) 8.89 (t, *J*=5.11 Hz, 1 H) 11.74 (br. s., 1 H); 13C NMR

(300 MHz, DMSO-*d*6) δ ppm 21.0, 38.0, 59.7, 67.0, 118.8, 119.6, 123.0, 124.8, 128.8, 129.1, 129.2, 135.8, 137.4, 138.5, 139.1, 166.4, 169.4.

2-(4-methyl-phenyl)-3-hydroxy-4(1*H*)-quinolinone-7-carboxylic acid N-(4-methylbenzyl)-amide (11c)

Yield of the crude product 93 %, yield of the purified product 85%, purity of the purified product 99%, ESI-MS *m/z* = 399, $[M+H]^+$. ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 2.28 (s, 3 H) 2.40 (s, 3 H) 4.46 (d, *J*=6.08 Hz, 2 H) 7.14 (d, *J*=7.73 Hz, 2 H) 7.24 (d, *J*=8.01 Hz, 2 H) 7.38 (d, *J*=8.29 Hz, 2 H) 7.66 - 7.77 (m, 3 H) 8.20 (d, *J*=8.56 Hz, 1 H) 8.26 (s, 1 H) 9.19 (t, *J*=5.80 Hz, 1 H) 11.72 (s, 1 H); 13C NMR (300 MHz, DMSO-*d*6) δ ppm 21.4, 21.7, 43.2, 119.5, 120.5, 123.6, 125.4, 128.0, 129.6, 129.8, 129.9, 133.1, 136.6, 137.0, 137.2, 138.2, 139.2, 139.8, 141.5, 166.5, 170.2.

2-(4-methyl-phenyl)-3-hydroxy-4(1*H*)-quinolinone-7-carboxylic acid N-(1-imidazolylpropyl)-amide (11d)

Yield of the crude product 96 %, yield of the purified product 88%, purity of the purified product 97%, ESI-MS *m/z* = 403, $[M+H]^+$. ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 2.02 - 2.21 (m, 2 H) 2.41 (s, 3 H) 3.32 (q, *J*=6.08 Hz, 2 H) 4.28 (t, *J*=6.91 Hz, 2 H) 7.39 (d, *J*=8.01 Hz, 2 H) 7.62 - 7.77 (m, 3 H) 7.85 (s, 1 H) 8.21 (d, *J*=8.56 Hz, 2 H) 8.26 (s, 1 H) 8.78 (t, *J*=5.52 Hz, 1 H) 9.16 (s, 1 H) 11.73 (br. s., 1 H); 13C NMR (300 MHz, DMSO-*d*6) δ ppm 21.7, 30.3, 36.9, 47.3, 119.5, 120.4, 120.7, 122.8, 123.7, 125.4, 129.6, 129.8, 129.9, 136.2, 136.7, 138.2, 139.2, 139.8, 166.7.

2-(4-methyl-phenyl)-3-hydroxy-4(1*H*)-quinolinone-7-carboxylic acid N-(2-thienylmethyl)-amide (11e)

Yield of the crude product 60 %, yield of the purified product 52%, purity of the purified product 98%, ESI-MS *m/z* = 391, $[M+H]^+$. ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 2.40 (s, 3 H) 4.66 (d, *J*=5.52 Hz, 2 H) 6.94 - 7.00 (m, 1 H) 7.05 (d, *J*=3.59 Hz, 1 H) 7.34 - 7.43 (m, 3 H) 7.67 (d, *J*=8.84 Hz, 1 H) 7.73 (d, *J*=8.29 Hz, 2 H) 8.19 (d, *J*=7.46 Hz, 1 H) 8.25 (s, 1 H) 9.32 (t, *J*=5.94 Hz, 1 H) 11.70 (s, 1 H); 13C NMR (300 MHz, DMSO-*d*6) δ ppm 21.0, 37.9, 118.8, 119.6, 123.0, 124.8, 125.1, 125.5, 126.7, 128.9, 129.1, 129.2, 132.4, 138.5, 139.1, 142.4, 165.7, 169.5.

2-(4-methyl-phenyl)-3-hydroxy-4(1*H*)-quinolinone-7-carboxylic acid N-(1-piperidinylethyl)-amide (11f)

Yield of the crude product 90 %, yield of the purified product 83%, purity of the purified product 95%, ESI-MS *m/z* = 406, $[M+H]^+$. ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 1.57 - 1.75 (m, 4 H) 1.76 - 1.90 (m, 2 H) 2.40 (s, 3 H) 2.89 - 3.04 (m, 2 H) 3.28 (q, J=5.74 Hz, 2 H) 3.50 - 3.62 (m, 2 H) 3.67 (q, J=5.74 Hz, 2 H) 7.38 (d, J=8.13 Hz, 2 H) 7.65 - 7.77 (m, 3 H) 8.24 (d, J=8.61 Hz, 1 H) 8.31 (s, 1 H) 8.95 (t, J=5.74 Hz, 1 H) 11.72 (br. s., 1 H); 13C NMR (300 MHz, DMSO-*d*6) δ ppm 21.0, 21.2, 22.3, 34.4, 52.3, 55.1, 113.8, 117.6, 119.1, 119.9, 123.1, 124.7, 128.9, 129.1, 129.2, 133.2, 135.6, 137.4, 138.6, 139.3, 166.4.

2-(4-methoxy-phenyl)-3-hydroxy-4(1*H*)-quinolinone-7-carboxylic acid N-propylamide (12B)

Yield of the crude product 92 %, yield of the purified product 85%, purity of the purified product 99%, ESI-MS *m/z* = 353, $[M+H]^+$. ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 0.91 (t, *J*=7.32 Hz, 3 H) 1.46 - 1.66 (m, 2 H) 3.25 (q, *J*=6.17 Hz, 2 H) 3.85 (s, 3 H) 7.13 (d, *J*=8.56 Hz, 2 H) 7.65 (d, *J*=8.56 Hz, 1 H) 7.80 (d, *J*=8.56 Hz, 2 H) 8.18 (d, *J*=8.56 Hz, 1 H) 8.22 (s, 1 H) 8.64 (t, *J*=5.39 Hz, 1 H) 11.67 (s, 1 H); 13C NMR (300 MHz, DMSO-*d*6) δ ppm 11.5, 22.4, 41.1, 55.4, 113.8, 118.6, 118.7, 122.8, 124.2, 124.6, 130.7, 132.3, 136.5, 137.4, 138.3, 160.0, 165.8, 169.4.

2-(3-bromo-phenyl)-3-hydroxy-4(1*H*)-quinolinone-7-carboxylic acid N-propylamide (12C)

Yield of the crude product 90 %, yield of the purified product 82%, purity of the purified product 98%, ESI-MS *m/z* = 401, $[M+H]^+$. 1H NMR (300 MHz, DMSO-*d*6) δ ppm 0.41 (t, *J*=7.32 Hz, 3 H) 0.95 - 1.17 (m, 2 H) 2.75 (q, *J*=6.54 Hz, 2 H) 7.04 (t, *J*=7.87 Hz, 1 H) 7.17 (d, *J*=8.56 Hz, 1 H) 7.23 (d, *J*=8.56 Hz, 1 H) 7.34 (d, *J*=7.73 Hz, 1 H) 7.51 (s, 1 H) 7.63 - 7.76 (m, 2 H) 8.16 (t, *J*=5.11 Hz, 1 H) 11.29 (br. s., 1 H); 13C NMR (300 MHz, DMSO-*d*6) δ ppm 12.2, 23.1, 41.9, 119.3, 120.6, 122.2, 123.7, 125.4, 129.2, 131.2, 132.4, 132.8, 135.0, 137.5, 138.28., 139.4, 166.4, 170.0.

2-(3,5-dichloro-4-amino-phenyl)-3-hydroxy-4(1*H*)-quinolinone-7-carboxylic acid N-propyl-amide (12D)

Yield of the crude product 89 %, yield of the purified product 81%, purity of the purified product 98%, ESI-MS *m/z* = 406, $[M+H]^+$. ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 0.91 (t, *J*=7.32 Hz, 3 H) 1.46 - 1.66 (m, 2 H) 3.19 - 3.32 (q, *J*=6.08 Hz, 2 H) 6.04 (br. s., 2 H) 7.65 (d, *J*=8.56 Hz, 1 H) 7.81 (s, 2 H) 8.15 (d, *J*=8.56 Hz, 1 H) 8.21 (s, 1 H) 8.64 (t, *J*=5.66 Hz, 1 H) 11.55 (s, 1 H); 13C NMR (300 MHz, DMSO-*d*6) δ ppm 11.5, 22.4, 41.3, 117.4, 118.5, 119.7, 119.9, 122.7, 124.5, 128.7, 130.1, 136.5, 137.4, 138.3, 142.1, 165.7, 169.4.

2-(3-nitro-4-chloro-phenyl)-3-hydroxy-4(1*H*)-quinolinone-7-carboxylic acid N-propylamide (12E)

Yield of the crude product 85 %, yield of the purified product 78%, purity of the purified product 97 %, ESI-MS *m/z* = 402, $[M+H]^+$. ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 0.91 (t, *J*=7.32 Hz, 3 H) 1.47 - 1.67 (m, 2 H) 3.26 (q, *J*=6.08 Hz, 2 H) 7.69 (d, *J*=8.56 Hz, 1 H) 8.00 (d, *J*=8.01 Hz, 1 H) 8.12 - 8.25 (m, 3 H) 8.53 (s, 1 H) 8.69 (t, *J*=5.25 Hz, 1 H) 11.87 (br. s., 1 H); 13C NMR (300 MHz, DMSO-*d*6) δ ppm 12.2, 23.1, 41.9, 119.3, 120.7, 123.8, 125.5, 126.3, 126.9, 129.4, 132.3, 133.0, 135.2, 137.6, 138.4, 139.8, 140.1, 166.3.

2-(4-fluoro-phenyl)-3-hydroxy-4(1*H*)-quinolinone-7-carboxylic acid N-propylamide (12F)

Yield of the crude product 95 %, yield of the purified product 85%,purity of the purified product 98 %, ESI-MS *m/z* = 341, $[M+H]^+$. ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 0.91 (t, *J*=7.32 Hz, 3 H) 1.47 - 1.66 (m, 2 H) 3.25 (q, *J*=6.63 Hz, 2 H) 7.42 (t, *J*=8.84 Hz, 2 H) 7.67 (d, *J*=8.56 Hz, 1 H) 7.88 (dd, *J*=8.29, 5.52 Hz, 2 H) 8.14 - 8.25 (m, 2 H) 8.65 (t, *J*=4.70 Hz, 1 H) 11.76 (br. s., 1 H); 13C NMR (300 MHz, DMSO-*d*6) δ ppm 11.5, 22.4, 41.1, 115.2, 115.4, 118.6, 119.8, 123.0., 124.6, 131.4, 131.6, 131.7, 136.6, 137.5, 158.5, 165.7, 169.7.

2-(3-thienyl)-3-hydroxy-4(1*H*)-quinolinone-7-carboxylic acid N-propylamide (12G)

Yield of the crude product 95 %, yield of the purified product 87%, purity of the purified product 99 %, ESI-MS *m/z* = 329, $[M+H]^+$. ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 0.92 (t, *J*=7.32 Hz, 3 H) 1.41 - 1.70 (m, 2 H) 3.26 (q, *J*=6.26 Hz, 2 H) 7.66 (d, *J*=8.01 Hz, 1 H) 7.72 - 7.81 (m, 1 H) 7.86 (d, *J*=4.42 Hz, 1 H) 8.17 (d, *J*=8.56 Hz, 1 H) 8.23 - 8.38 (m, 2 H) 8.66 (t, *J*=5.52 Hz, 1 H) 11.49 (br. s., 1 H); 13C NMR (300 MHz, DMSO-*d*6) δ ppm 11.5, 22.4, 41.2, 118.6, 119.7, 122.6, 124.6, 126.4, 127.6, 127.7, 132.5, 136.7, 137.4, 138.5, 165.8, 169.7.

2-methyl-3-hydroxy-4(1*H*)-quinolinone-7-carboxylic acid N-propylamide (12H)

Yield of the crude product 92 %, yield of the purified product 83%, purity of the purified product 98 %, ESI-MS *m/z* = 261, $[M+H]^+$. ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 0.91 (t, *J*=7.32 Hz, 3 H) 1.45 - 1.65 (m, 2 H) 2.45 (s, 3 H) 3.25 (q, *J*=6.63 Hz, 2 H) 7.70 (d, *J*=8.56 Hz, 1 H) 8.05 (s, 1 H) 8.17 (d, *J*=8.56 Hz, 1 H) 8.68 (t, *J*=5.25 Hz, 1 H) 12.28 (br. s., 1 H); 13C NMR (300 MHz, DMSO-*d*6) δ ppm 11.5, 14.6, 22.4, 41.1, 117.9, 120.3, 123.0, 124.4, 135.7, 136.2, 136.3, 138.5, 165.5, 166.1.

Alkylation of resin 7a with ethyl-bromoacetate

To 50 mg of resin **7a** in 1 ml of dry NMP 28 μl of ethyl-bromoacetate and 44 μl of 2-tert-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine was added. The resin was heated at 50 °C for 48 h, washed 3 three times with DMF, three times with DCM, three times with MeOH and dried.

Alkylation of resin 7a with benzylbromide

To 50 mg of resin **7a** in 1 ml of dry NMP 40 μl of benzylbromide and 44 μl of 2-tert-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine was added. The resin was heated at 50 °C for 12 h, washed 3 three times with DMF, three times with DCM, three times with MeOH and dried.

Benzoylation of resin 7a

To 50 mg of resin **7a** was added 1 ml of pyridine and 50 μl of benzoylchloride. The resin was shaken at room temperature for 5 h, washed 3 three times with DMF, three times with DCM, three times with MeOH and dried.

References

1. Krchnak, V.; Smith, J.; Vagner, J. *Collect. Czech. Chem. Commun.* **2001**, *66*, 1078-1106.