Supporting Information for
Pd-catalyzed amidation of 2-chloro- and 2,7-dichloro-1,8-naphthyridines

G.B.W.L. Ligthart, H. Ohkawa, R.P. Sijbesma,^{*} E.W. Meijer

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Synthetic schemes:

Scheme 1: Synthesis of **S1**. (i) catalyst, ligand, base, dodecanoic amide, 1,4-dioxane, 100°C.

Scheme 2: Synthesis of **S2-S5**. (i) Pd(OAc)₂, Xantphos, K₂CO₃, amide, 1,4-dioxane, 100°C.

Scheme 3: Synthesis of **S6-S8**. (i) Pd(OAc)₂, Xantphos, Cs₂CO₃, amide, 1,4-dioxane, 80°C.

Scheme 4: Synthesis of **S9-S14**. (i) Pd(OAc)₂, Xantphos, K₂CO₃, amide, 1,4-dioxane, 100°C.

Scheme 4: Synthesis of **S15-S18**. (i) Pd(OAc)₂, Xantphos, K₂CO₃, amide, 1,4-dioxane, 100°C.

Scheme 5: Synthesis of **S19**. (i) pivaloyl chloride, pyridine, 110°C; 68%; (ii) POCl₃, 95°C, 80%; (iii) Pd(OAc)₂, Xantphos, K₂CO₃, 2-ethylhexanoic amide, 1,4-dioxane, 100°C.

Experimental details:

General methods. All synthetic procedures were performed under inert atmosphere of dry argon unless stated otherwise. Commercial solvents and reagents were used without purification unless stated otherwise. 1,4-Dioxane was distilled and pyridine was dried over 4Å molecular sieves prior to use. ¹H NMR and ¹³C NMR spectra were recorded on a 300, 400 or 500 MHz NMR spectrometer. Chemical shifts are reported in ppm relative to tetramethylsilane (TMS) and multiplicities as singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m). Matrix assisted laser desorption/ionization mass-time of flight (MALDI-TOF) were obtained using an acid α -cyanohydroxycinnamic acid (CHCA) or a neutral 2-[(2E)-3-(4-tert-Butylphenyl)-2-methylprop-2-enylidene]malononitrile (DCTB) matrix. Infrared (IR) spectra were recorded on a FT-IR spectrometer with an ATR sampling accessory. Elemental analysis was performed on a standard CHNS/O analyzer. Melting points were determined on a standard melting point apparatus.

Synthesis. 2,7-dichloro-1,8-naphthyridine and 7-amino-[1H]-2-oxo-1,8-naphthyridine were prepared as reported by Newkome *et al.*¹ 7-Acetamido-2-chloro-1,8-naphthyridine was prepared as reported by Zimmerman *et al.*² 7-(2-Ethyl-hexanoylamino)-2-chloro-1,8-naphthyridine was prepared as reported by Meijer *et al.*³ 2-n-Butylureido-6-methyl-4[1H]-pyrimidinone was prepared as reported by Beijer *et al.*⁴ Primary amides were synthesized according to literature procedures except the synthesis of 6-benzyloxyhexanoic amide which is described below.

(1) Newkome, G.R.; Garbis, S.J.; Majestic, V.K.; Fronczek, F.R.; Chiari, G. *J. Org. Chem.* **1981**, *46*, 833.

(2) Corbin, P.S.; Zimmerman, S.C.; Thiessen, P.A.; Hawryluk, N.A.; Murray, T.J. *J. Am. Chem. Soc.* **2001**, *124*, 10475.

(3) Ligthart, G.B.W.L.; Ohkawa, H.; Sijbesma, R.P.; Meijer, E.W. *J. Am. Chem. Soc.* **2005**, *127*, 810.

(4) Beijer, F. H.; Sijbesma, R. P.; Kooijman, H.; Spek, A. L.; Meijer, E. W. *J. Am. Chem. Soc.* **1998**, *120*, 6761-6769.

2,7-Bis-(dodecanoylamino)-1,8-naphthyridine, S1 (Table 1): Following the general procedure with 1.0 mmol 2,7-dichloro-1,8-naphthyridine using a ligand to base ratio of 2.0-2.1 gave a red residue. This residue was then recrystallized from EtOH, dried and recrystallized from toluene to yield the title compound as long white needles. Characterization of the compound was reported previously.³

2,7-Bis-(1-adamantanecarbonylamino)-1,8-naphthyridine, S2 (Table 2, entry 1): Following the general procedure with 0.5 mmol 2,7-dichloro-1,8-naphthyridine the resulting brownish residue was dissolved in chloroform followed by filtration. The title compound was purified by chromatography (SiO₂, chloroform / acetone 20:1 v/v) as a white powder (200 mg, 82%). M.P. 177-182 °C; ¹H NMR (CDCl₃): δ = 8.45 (d, 2H, *J* = 9 Hz), 8.31 (br, 2H), 8.11 (d, 2H, *J* = 9 Hz), 2.12 (m, 6H), 2.00 (m, 12H), 1.72- 1.81 (m, 12H) ppm; ¹³C NMR (CDCl₃): δ = 177.0, 154.0, 153.7, 138.8, 118.3, 138.9, 113.4, 42.0, 39.1, 36.3, 28.0 ppm; MALDI-TOF-MS: (m/z) calcd. 484.65; observed: 485.37 (M+H⁺), 507.35 (M+Na⁺), 523.33 (M+K⁺); FTR-IR (ATR): ν = 2905, 2852, 1690, 1609, 1529, 1498, 1454, 1378, 1308, 1284, 1260, 1206, 1177, 1133, 1079, 976, 930, 867, 855, 802 cm⁻¹; Anal. Calcd. for C₃₀H₃₆N₄O₂: C 74.35, H 7.49, N 11.56; found: C 74.62, H 7.61, N 11.20.

2,7-Bis-(10-undecenoylamino)-1,8-naphthyridine, S3 (Table 2, entry 2): Following the general procedure with 10 mmol 2,7-dichloro-1,8-naphthyridine the resulting red-brown residue was washed with *n*-heptane, filtered, dissolved in chloroform and filtered again. Evaporation gave an orange-colored crude product, which was recrystallized twice from ethanol to give the title compound as a fine white powder (4.38 g, 89%). M.P. 124-127 °C; ¹H NMR (CDCl₃): δ = 8.64 (br, 2H), 8.44 (d, 2H, *J* = 9 Hz), 8.11 (d, 2H, *J* = 9 Hz), 5.82-5.78 (m, 2H), 5.00-4.90 (m, 4H), 2.44 (t, 4H, *J* = 9 Hz), 2.01 (m, 4H), 1.70 (m, 4H), 1.35-1.26 (m, 20H) ppm; ¹³C NMR (CDCl₃): δ = 172.4, 154.0, 153.6, 139.1, 139.0, 118.3, 114.2, 113.5, 37.9, 33.7, 29.3-28.9 (multiple peaks), 25.2 ppm; MALDI-TOF-MS: (m/z) calcd. 492.35; observed: 493.31 (M+H⁺), 515.29 (M+Na⁺), 531.27 (M+K⁺); FTR-IR (ATR): ν = 3327, 2920, 2850, 1673, 1614, 1547, 1507, 1469, 1399, 1317, 1293, 1177, 1145, 994, 968, 910, 851, 803 cm⁻¹; Anal. Calcd. for C₃₀H₄₄N₄O₂: C 73.13, H 9.02, N 11.37; found: C 73.12, H 9.06, N 11.58.

2,7-Bis-(9-undecenoylamino)-1,8-naphthyridine, S3 isomer 20 mL of distilled toluene was added to 200 mL of Schlenk flask charged with 2,7-dichloro-1,8-naphthyridine (200 mg, 1.00 mmol), 10-undecenoic acid amide (369 mg, 2.00 mmol), K₂CO₃ (276 mg, 2.00 mmol), Pd(OAc)₂ (30.3mg, 0.136 mmol), and Xantphos (237 mg, 0.405 mmol). The resulting dispersion was immediately frozen by liquid-nitrogen, deoxygenated by a freeze-pump-thaw cycle, and backfilled with argon. The dispersion was stirred at reflux temperature for 32 hours. After

evaporation in vacuo, the brownish residue was washed with *n*-heptane and dissolved in chloroform. Insoluble matter was removed by silica-gel filtration, followed by a second evaporation. The orange-colored crude product was recrystallized twice from hot ethanol to give the almost fully isomerized compound as a fine pale-yellowish powder (82 mg, 17 %). M.P. 117-119 °C; ^1H NMR (CDCl_3): δ = 8.44 (d, 2H, J = 9 Hz), 8.39 (br, 2H), 8.12 (d, 2H, J = 9 Hz), 5.40 (m, 4H), 2.44 (t, 4H, J = 7 Hz), 2.04-1.95 (m, 4H), 1.72 (m, 4H), 1.63-1.58 (m, 6H), 1.36-1.29 (m, 16H) ppm; ^{13}C NMR (CDCl_3): δ = 172.3, 153.9, 153.7, 139.0, 131.5, 130.7, 124.7, 123.7, 118.3, 113.4, 38.0, 32.5, 29.5, 29.4, 29.2, 29.2, 29.1, 29.0, 28.9, 26.8, 25.2, 17.9 ppm; MALDI-TOF-MS: (m/z) calcd. 492.35; observed: 493.33 ($\text{M}+\text{H}^+$), 515.31 ($\text{M}+\text{Na}^+$), 531.28 ($\text{M}+\text{K}^+$); FTR-IR (ATR): ν = 3325, 3009, 2920, 2850, 1672, 1614, 1546, 1507, 1467, 1398, 1291, 1176, 1145, 963, 851, 818, 802 cm^{-1} .

6-Benzoyloxy-hexanoic amide 6-Benzoyloxy-hexanoic acid (4.5 g, 20.2 mmol) was converted to the acid chloride by oxalyl chloride (5 mL) with two drops of dimethylformamide (DMF) as a catalyst, followed by a dropwise addition into a large excess of concentrated ammonia solution (20 mL) to give a white precipitate. The precipitate was collected by filtration and washed with concentrated ammonia solution and water. The product was dried in vacuo overnight at 60 °C to yield the title compound as a white powder (4.15 g, 93%). M.P. 76-79 °C; ^1H NMR (CDCl_3): δ = 7.38-7.27 (m, 5H), 5.46 (br, 2H), 4.49 (s, 2H), 3.47 (t, 2H, J = 6 Hz), 2.22 (t, 2H, J = 8 Hz), 1.64 (m, 4H), 1.45 (m, 2H) ppm; ^{13}C NMR (CDCl_3): δ = 175.4, 138.6, 128.4, 127.6, 127.5, 72.9, 70.1, 35.8, 29.4, 25.8, 25.2 ppm; MALDI-TOF-MS: (m/z) calcd. 492.3; observed 493.3 ($\text{M}+1$), 515.3 ($\text{M}+\text{Na}^+$), 531.3 ($\text{M}+\text{K}^+$); FTR-IR (ATR): ν = 3357, 3180, 2942, 2856, 1659, 1630, 1464, 1453, 1414, 1359, 1345, 1102, 1050, 967 cm^{-1} .

2,7-Bis-(6-benzoyloxyhexanoylamino)-1,8-naphthyridine, S4 (Table 2, entry 3): Following the general procedure with 0.5 mmol 2,7-dichloro-1,8-naphthyridine, 21.6 μmol of $\text{Pd}_2(\text{dba})_3$ and 121 μmol of Xantphos gave a red-brown residue which was dissolved in chloroform and filtered. Evaporation gave a red-colored crude product, which was purified by chromatography (SiO_2 , chloroform / acetone 8:1 v/v) to yield the title compound as a yellowish gum (168 mg, 59 %). No reaction was observed when $\text{Pd}(\text{OAc})_2$ was used as a palladium source. ^1H NMR (CDCl_3): δ = 8.99 (br, 2H), 8.42 (d, 2H, J = 9 Hz), 8.09 (d, 2H, J = 9 Hz), 7.35-7.23 (m, 10H), 4.48 (s, 4H), 3.44 (t, 4H, J = 6 Hz), 2.42 (t, 4H, J = 8 Hz), 1.72-1.57 (m, 8H), 1.39 (m, 4H) ppm; ^{13}C NMR (CDCl_3): δ = 172.8, 154.1, 153.5, 139.0, 138.5, 128.4, 127.6, 127.5, 118.3, 113.5, 72.5, 70.9, 37.9, 29.4, 25.8, 25.2 ppm; MALDI-TOF-MS: (m/z) calcd. 568.30; observed: 569.18 ($\text{M}+\text{H}^+$),

591.16 (M+Na⁺), 607.13 (M+K⁺); FTR-IR (ATR): ν = 3327, 2925, 2852, 1669, 1618, 1547, 1507, 1469, 1399, 1351, 1317, 1293, 1177, 1145, 1102, 1024, 968, 910, 851, 803 cm⁻¹.

2,7-Bis-(2-(*tert*-butyldimethylsilyloxy)propanoylamino)-1,8-naphthyridine, S5 (Table 2, entry 4): Following the general procedure with 10 mmol 2,7-dichloro-1,8-naphthyridine the resulting red-brown residue was dissolved in dichloromethane and filtered. Evaporation gave a red-colored crude product, which was recrystallized twice from MeOH and finally from heptane to give the title compound as fine white needles (4.36 g, 82%). M.P. 110-111 °C; ¹H NMR (CDCl₃): δ = 9.32 (br, 2H), 8.49 (d, 2H, *J* = 9 Hz), 8.14 (d, 2H, *J* = 9 Hz), 4.40 (q, 2H, *J* = 7 Hz), 1.47 (d, 6H, *J* = 7 Hz), 0.97 (s, 18H), 0.17 (s, 12H) ppm; ¹³C NMR (CDCl₃): δ = 174.2, 153.7, 139.2, 119.0, 113.8, 70.9, 26.2, 22.5, 18.5, -4.4, -4.7 ppm; MALDI-TOF-MS: (*m/z*) calcd. 532.29; observed: 533.28 (M+H⁺), 555.27 (M+Na⁺), 571.24 (M+K⁺); FTR-IR (ATR): ν = 3388, 2957, 2928, 2857, 1697, 1612, 1528, 1506, 1463, 1390, 1312, 1292, 1255, 1120, 1070, 957, 925, 908, 830, 800 cm⁻¹; Anal. Calcd. for C₂₆H₄₄N₄O₄Si₂: C 58.61, H 8.32, N 10.52; found: C 58.41, H 8.29, N 10.36.

7-(2-Ethylhexanoylamino)-2-chloro-1,8-naphthyridine, S6 (Table 4, entry 1): Following the general procedure with 0.5 mmol 2,7-dichloro-1,8-naphthyridine the resulting red residue was dissolved in chloroform and 2-n-Butylureido-6-methyl-4[1H]-pyrimidinone (7.0 mg, 0.031 mmol) was added. The title compound was obtained as a white solid after purification by chromatography (SiO₂, 2 % acetone / chloroform) as a white powder (50 mg, 42 %). Characterization of the compound indicated > 99% purity.³

7-Dodecanoylamino-2-chloro-1,8-naphthyridine, S7 (Table 4, entry 2): Following the general procedure with 0.5 mmol 2,7-dichloro-1,8-naphthyridine the resulting brownish residue was dissolved in chloroform and 2-n-Butylureido-6-methyl-4[1H]-pyrimidinone (7.2 mg, 0.032 mmol) was added. The title compound was obtained as a white solid after purification by chromatography (SiO₂, 2 % acetone / chloroform) as a white powder (40 mg, 25 %). M.P. 147-149 °C; ¹H NMR (CDCl₃): δ = 9.12 (s, 1H), 8.58 (d, 1H, *J* = 9 Hz), 8.20 (d, 1H, *J* = 9 Hz), 8.05 (d, 1H, *J* = 9 Hz), 7.28 (d, 1H, *J* = 9 Hz), 2.45-2.49 (t, 2H, *J* = 6 Hz), 1.75-1.86 (q, 2H, *J* = 7 Hz), 1.18-1.43 (m, 16H), 0.87-0.92 (t, 3H, *J* = 6 Hz) ppm; ¹³C NMR (CDCl₃): δ = 176.2, 154.6, 154.2, 154.1, 139.0, 138.7, 121.9, 119.0, 115.8, 38.0, 31.2, 29.0-28.8 (multiple peaks), 25.0, 22.1, 13.7 ppm; MALDI-TOF-MS: (*m/z*) calcd. 361.92; observed: 362.52 (M+H⁺), 384.48 (M+Na⁺); FTR-IR (ATR): ν = 3182, 3131, 3062, 2961, 2922, 2870, 2850, 1685, 1610, 1597, 1490, 1400, 1345, 1265, 1185, 1154, 1142, 1007, 940, 853, 801; Anal. Calcd. for C₂₀H₂₈ClN₃O: C 66.37, H 7.80, N 11.61; found: C 66.10, H 7.63, 11.78.

7-(10-undecenoylamino)-2-chloro-1,8-naphthyridine, S8 (Table 4, entry 3): Following the general procedure with 0.5 mmol 2,7-dichloro-1,8-naphthyridine the resulting brownish residue

dissolved in chloroform and 2-n-Butylureido-6-methyl-4[1H]-pyrimidinone (7.6 mg, 0.034 mmol) was added. The title compound was obtained as a white solid after purification by chromatography (SiO₂, 2 % acetone / chloroform) as a white powder (35 mg, 22 %). M.P. 137-141 °C; ¹H NMR (CDCl₃): δ = 9.12 (s, 1H), 8.58 (d, 1H, *J* = 9 Hz), 8.20 (d, 1H, *J* = 9 Hz), 8.05 (d, 1H, *J* = 9 Hz), 7.28 (d, 1H, *J* = 9 Hz), 5.80-5.77 (m, 1H), 5.03-4.94 (m, 2H), 2.41 (t, 2H, *J* = 8 Hz), 2.04 (m, 2H), 1.68 (m, 2H), 1.40-1.28 (m, 10H) ppm; ¹³C NMR (CDCl₃): δ = 175.8, 154.7, 154.3, 154.1, 140.3, 139.0, 138.7, 121.9, 118.8, 115.2, 114.4, 38.0, 33.9, 29.4-28.8 (multiple peaks), 25.0 ppm; MALDI-TOF-MS: (m/z) calcd. 345.88; observed: 346.62 (M+H⁺), 368.57 (M+Na⁺); FTR-IR (ATR): ν = 3156, 3115, 3051, 2932, 2863, 1691, 1612, 1594, 1470, 1401, 1351, 1265, 1187, 1162, 1143, 999, 971, 912, 857, 804; Anal. Calcd. for C₁₉H₂₄ClN₃O: C 65.98, H 6.99, N 12.15; found: C 65.75, H 6.79, 12.19.

2-(2-Ethylhexanoylamino)-7-acetylamino-1,8-naphthyridine, S9 (Table 5, entry 1): Following the general procedure with 1.0 mmol 7-acetamido-2-chloro-1,8-naphthyridine the resulting red residue was dissolved in chloroform and n-hexane was added to precipitate. The crude product was filtered and purified by chromatography (SiO₂, ethyl acetate / hexane 2:1 v/v) to yield the title compound as a white powder (220 mg, 66 %). M.P. 117-122 °C; ¹H NMR (CDCl₃): δ = 9.80 (br, 1H), 8.98 (br, 1H), 8.49 (d, 2H, *J* = 9 Hz), 8.43 (d, 2H, *J* = 9 Hz), 8.10 (d, 1H, *J* = 9 Hz), 8.08 (d, 1H, *J* = 9 Hz), 2.25 (m, 1H), 2.21 (s, 3H), 1.75-1.48 (m, 4H), 1.28-1.26 (m, 4H), 0.96-0.82 (m, 6H) ppm; ¹³C NMR (CDCl₃): δ = 175.6, 169.8, 154.3, 154.0, 153.4, 139.0, 138.9, 118.1, 113.8, 113.7, 50.4, 32.2, 29.6, 25.8, 24.8, 22.6, 13.8, 11.9 ppm; MALDI-TOF-MS: (m/z) calcd. 328.19; observed: 329.31 (M+H⁺), 351.29 (M+Na⁺); FTR-IR (ATR): ν = 3212, 2959, 2929, 2860, 1689, 1607, 1542, 1498, 1436, 1378, 1312, 1283, 1231, 1170, 1134, 1118, 852, 802 cm⁻¹; Anal. Calcd. for C₁₈H₂₄N₄O₂: C 65.83, H 7.37, N 17.06; found: C 65.50, H 6.99, 16.75.

2-(Benzoylamino)-7-acetylamino-1,8-naphthyridine, S10 (Table 5, entry 2): Following the general procedure with 1.0 mmol 7-acetamido-2-chloro-1,8-naphthyridine the resulting red residue was purified by chromatography (SiO₂, 5 % methanol / chloroform) to yield the title compound as a yellow powder (157 mg, 51 %). M.P. 125-128 °C; ¹H NMR (CDCl₃): δ = 9.16 (br, 1H), 9.00 (br, 1H), 8.61 (d, 1H, *J* = 9 Hz), 8.43 (d, 2H, *J* = 9 Hz), 8.18 (d, 1H, *J* = 9 Hz), 8.15 (d, 1H, *J* = 9 Hz), 7.93 (d, 2H, *J* = 9 Hz), 7.57 (t, 1H, *J* = 6 Hz), 7.47 (t, 2H, *J* = 8 Hz), 2.26 (s, 3H) ppm; ¹³C NMR (CDCl₃): δ = 169.6, 166.2, 154.2, 153.6, 139.1, 133.9, 132.6, 128.9, 127.4, 118.4, 113.7, 25.0 ppm; MALDI-TOF-MS: (m/z) calcd. 306.11; observed: 307.27 (M+H⁺), 329.25 (M+Na⁺); FTR-IR (ATR): ν = 3213, 3057, 1682, 1606, 1539, 1496, 1376, 1282, 1246, 1135, 955,

894, 853, 801 cm^{-1} ; Anal. Calcd. for $\text{C}_{17}\text{H}_{14}\text{N}_4\text{O}_2$: C 66.66, H 4.61, N 18.29; found: C 66.78, H 4.60, N 16.95.

2-(1-Adamantanoylamino)-7-acetylamino-1,8-naphthyridine, S11 (Table 5, entry 3): Following the general procedure with 0.5 mmol 7-acetamido-2-chloro-1,8-naphthyridine the resulting red-brown residue was dissolved in chloroform and filtered. Evaporation yielded an orange-red product which was purified further by chromatography (SiO_2 , chloroform / acetone 8:1 v/v) followed by trituration with heptane to yield the title compound as a white powder (58 mg, 35 %). M.P. 152-155 $^\circ\text{C}$; ^1H NMR (CDCl_3): δ = 8.46 (d, 1H, J = 9 Hz), 8.41 (d, 1H, J = 9 Hz), 8.33 (br, 1H), 8.15 (br, 1H), 8.13 (d, 2H, J = 9 Hz), 2.27 (s, 3H), 2.12 (m, 3H), 2.00 (m, 6H), 1.76 (m, 6H) ppm; ^{13}C NMR (CDCl_3): δ = 177.0, 169.0, 154.2, 153.7, 153.6, 139.0, 138.9, 118.4, 113.6, 113.1, 42.0, 39.1, 36.3, 28.0, 25.1 ppm; MALDI-TOF-MS: (m/z) calcd. 364.45; observed: 365.24 ($\text{M}+\text{H}^+$), 387.23 ($\text{M}+\text{Na}^+$); FTR-IR (ATR): ν = 3307, 2904, 2851, 1691, 1608, 1535, 1500, 1378, 1311, 1283, 1231, 1211, 1178, 1136, 1082, 1040, 982, 853, 802 cm^{-1} ; Anal. Calcd. for $\text{C}_{21}\text{H}_{24}\text{N}_4\text{O}_2$: C 69.21, H 6.64, N 15.37; found: C 69.23, H 6.48, N 15.33.

2-(10-Undecenoylamino)-7-acetylamino-1,8-naphthyridine, S12 (Table 5, entry 4): Following the general procedure with 5.0 mmol 7-acetamido-2-chloro-1,8-naphthyridine the resulting red residue was purified by chromatography (SiO_2 , 3 % methanol/chloroform). Trituration with pentane gave the title compound as a white powder (1.62 mg, 88 %). M.P. 133-135 $^\circ\text{C}$; ^1H NMR (CDCl_3): δ = 8.43 (d, 1H, J = 9 Hz), 8.40 (d, 1H, J = 9 Hz), 8.13 (d, 2H, J = 9 Hz), 8.10 (br, 2H), 5.80 (m, 1H), 4.92 (m, 2H), 2.46 (t, 2H, J = 7 Hz), 2.28 (s, 3H), 2.03 (m, 2H), 1.75 (t, 2H, J = 7 Hz), 1.35-1.25 (m, 10H) ppm; ^{13}C NMR (CDCl_3): δ = 172.2, 169.1, 153.7, 153.6, 153.5, 139.1, 139.0, 138.9, 118.3, 114.1, 113.3, 113.2, 38.0, 33.7, 29.2, 29.0, 28.9, 28.8, 25.4, 25.1, 25.0 ppm; MALDI-TOF-MS: (m/z) calcd. 369.22; observed: 369.41 ($\text{M}+\text{H}^+$), 391.40 ($\text{M}+\text{Na}^+$); FTR-IR (ATR): ν = 3303, 2925, 2854, 1689, 1607, 1545, 1498, 1435, 1384, 1282, 1232, 1134, 1118, 990, 908, 854, 802 cm^{-1} ; Anal. Calcd. for $\text{C}_{21}\text{H}_{28}\text{N}_4\text{O}_2$: C 68.45, H 7.66, N 15.20; found: C 68.53, H 8.01, N 14.96.

2-(6-Benzyloxyhexanoylamino)-7-acetylamino-1,8-naphthyridine, S13 (Table 5, entry 5): Following the general procedure with 2.0 mmol 7-acetamido-2-chloro-1,8-naphthyridine and using $\text{Pd}_2(\text{dba})_3$ as the catalyst and Cs_2CO_3 as a base, the resulting red-brown residue was purified by chromatography (SiO_2 , 2 % ethanol / chloroform) to yield the title compound as a yellow powder (653 mg, 80 %). M.P. 146 $^\circ\text{C}$; ^1H NMR (CDCl_3): δ = 10.0 (br, 1H), 9.69 (br, 1H), 8.42 (d, 1H, J = 9 Hz), 8.41 (d, 1H, J = 9 Hz), 8.06 (d, 2H, J = 9 Hz), 4.46 (s, 2H), 3.41 (t, 2H, J = 6 Hz), 2.40 (t, 2H, J = 7 Hz), 2.17 (s, 3H), 1.64-1.50 (m, 4H), 1.38-1.30 (m, 2H) ppm; ^{13}C NMR

(CDCl₃): δ = 172.7, 169.9, 154.4, 153.3, 139.0, 138.9, 138.4, 128.2, 127.5, 127.4, 118.0, 113.7, 113.6, 72.8, 69.9, 29.3, 25.6, 24.8, 24.7 ppm; MALDI-TOF-MS: (m/z) calcd. 406.20; observed: 407.40 (M+H⁺), 429.38 (M+Na⁺), 445.35 (M+K⁺); FTR-IR (ATR): ν = 3213, 3032, 2933, 2857, 1694, 1606, 1542, 1496, 1454, 1379, 1312, 1282, 1232, 1134, 1115, 1090, 852, 802 cm⁻¹; Anal. Calcd. for C₂₃H₂₆N₄O₂: C 67.96, H 6.45, N 13.78; found: C 67.78, H 6.22, N 13.69.

2-(5-Methoxycarbonyl-hexanoylamino)-7-acetylamino-1,8-naphthyridine, S14 (Table 5, entry 6): Following the general procedure with 5.0 mmol 7-acetamido-2-chloro-1,8-naphthyridine and using Pd₂(dba)₃ as the catalyst and Cs₂CO₃ as a base, the resulting red-brown residue was purified by chromatography (SiO₂, 3 % methanol / chloroform) to yield the title compound as a white powder (1.32 g, 76 %). M.P. 93-95 °C; ¹H NMR (CDCl₃): δ = 8.41 (d, 2H, *J* = 8 Hz), 8.32 (br, 2H), 8.14 (d, 2H, *J* = 9 Hz), 3.68 (s, 3H), 2.48 (t, 2H, *J* = 7 Hz), 2.37 (t, 2H, *J* = 6Hz), 2.27 (s, 3H), 1.75 (m, 4H); ¹³C NMR (CDCl₃): δ = 173.7, 171.7, 169.2, 153.8, 153.5, 139.0, 118.3, 113.4, 113.3, 51.5, 37.3, 33.5, 25.0, 23.4, 24.2 ppm; MALDI-TOF-MS: (m/z) calcd. 344.15; observed: 345.32 (M+H⁺), 367.31 (M+Na⁺); FTR-IR (ATR): ν = 3241, 2950, 1739, 1705, 1614, 1548, 1507, 1418, 1376, 1314, 1290, 1258, 1234, 1198, 1155, 1132, 1118, 985, 884, 850 cm⁻¹; Anal. Calcd. for C₁₇H₂₀N₄O₄: C 59.29, H 5.85, N 16.27; found: C 58.95, H 5.63, N 18.31.

2,7-Bis-(2-ethylhexanoylamino)-1,8-naphthyridine, S15 (Table 6, entry 1): Following the general procedure with 1.0 mmol 7-(2-ethyl-hexanoyl)-amino-2-chloro-1,8-naphthyridine the resulting red residue was dissolved in heptane and filtered. Purification by chromatography (SiO₂, chloroform / acetone 8:1 v/v) gave the title compound as a white powder (360 mg, 89 %). M.P. 87-92 °C; ¹H NMR (CDCl₃): δ = 8.46 (d, 2H, *J* = 9 Hz), 8.35 (br, 2H), 8.13 (d, 2H, *J* = 9 Hz), 2.21 (m, 2H), 1.74-1.49 (m, 8H), 1.29 (m, 8H), 0.97-0.83 (m, 12H) ppm; ¹³C NMR (CDCl₃): δ = 175.4, 153.8, 153.3, 139.0, 118.4, 113.5, 50.9, 32.4, 29.7, 26.0, 22.7, 13.9, 12.0 ppm; MALDI-TOF-MS: (m/z) calcd. 412.58; observed: 413.35 (M+H⁺), 435.34 (M+Na⁺); FTR-IR (ATR): ν = 2959, 2929, 2860, 1684, 1608, 1537, 1500, 1460, 1392, 1377, 1310, 1282, 1169, 1134, 1116, 854, 803 cm⁻¹; Anal. Calcd. for C₂₄H₃₆N₄O₂: C 69.87, H 8.80, N 13.58; found: C 69.27, H 8.39, N 13.42.

2-(1-Adamantanoylamino)-7-(2-ethylhexanoylamino)-1,8-naphthyridine, S16 (Table 6, entry 2): Following the general procedure with 0.3 mmol 7-(2-ethyl-hexanoyl)-amino-2-chloro-1,8-naphthyridine the resulting red-brown residue was dissolved in chloroform and filtered. Evaporation yielded an orange-red product, which was purified further by chromatography (SiO₂, chloroform / acetone 20:1 v/v) followed by precipitation from heptane to yield the title compound as a white powder (68 mg, 47 %). M.P. 113-116 °C; ¹H NMR (CDCl₃): δ = 8.45 (d, 2H, *J* = 9 Hz),

8.31 (br, 1H), 8.13 (d, 2H, $J = 9$ Hz), 8.08 (br, 1H), 2.23 (m, 1H), 2.13 (m, 3H), 2.00 (m, 6H), 1.82-1.57 (m, 10H), 1.33 (m, 4H), 1.00-0.87 (m, 6H) ppm; ^{13}C NMR (CDCl_3): $\delta = 177.0, 175.3, 154.1, 153.8, 153.7, 139.0, 138.9, 118.3, 113.5, 113.4, 50.9, 41.9, 39.0, 36.3, 32.4, 29.7, 28.0, 26.0, 22.7, 14.1, 13.9, 12.0$ ppm; MALDI-TOF-MS: (m/z) calcd. 448.61; observed: 449.35 ($\text{M}+\text{H}^+$), 471.33 ($\text{M}+\text{Na}^+$); FTR-IR (ATR): $\nu = 2906, 2852, 1693, 1608, 1535, 1500, 1378, 1311, 1283, 1175, 1135, 1082, 854, 802\text{ cm}^{-1}$; Anal. Calcd. for $\text{C}_{27}\text{H}_{36}\text{N}_4\text{O}_2$: C 72.29, H 8.09, N 12.49; found: C 72.27, H 7.75, N 11.97.

7-(2-(*tert*-Butyldimethylsilyloxy)propanoylamino)-2-(2-ethylhexanoylamino)-1,8-

naphthyridine, S17 (Table 6, entry 3): Following the general procedure with 10.0 mmol 7-(2-ethyl-hexanoyl)-amino-2-chloro-1,8-naphthyridine the resulting red residue was further purified by chromatography (SiO_2 , 10 % ethyl acetate / hexane) to yield the title compound as a white powder (4.02 g, 85 %). M.P. 84 °C; ^1H NMR (CDCl_3): $\delta = 9.33$ (br, 1H), 9.18 (br, 1H), 8.38 (d, 1H, $J = 9$ Hz), 8.35 (d, 1H, $J = 9$ Hz), 8.02 (d, 1H, $J = 9$ Hz), 8.00 (d, 1H, $J = 9$ Hz), 4.25 (q, 1H, $J = 7$ Hz), 2.15 (m, 1H), 1.63-1.37 (m, 4H), 1.34 (d, 3H, $J = 7$ Hz), 1.15-1.04 (m, 4H), 0.83-0.63 (m, 15H), 0.10 (s, 6H) ppm; ^{13}C NMR (CDCl_3): $\delta = 175.6, 175.4, 173.4, 154.2, 154.1, 153.6, 153.1, 153.0, 138.8, 138.7, 118.3, 113.7, 113.0, 70.2, 50.1, 50.0, 32.0, 31.8, 29.4, 29.3, 25.7, 25.6, 25.9, 25.5, 22.5, 23.8, 21.8, 17.9, 13.7, 13.6, 11.8, 11.6, -4.9, -5.3$ ppm; MALDI-TOF-MS: (m/z) calcd. 472.29; observed: 473.21 ($\text{M}+\text{H}^+$), 495.19 ($\text{M}+\text{Na}^+$), 511.16 ($\text{M}+\text{K}^+$); FTR-IR (ATR): $\nu = 3380, 2931, 2859, 1703, 1608, 1530, 1500, 1380, 1311, 1283, 1253, 1172, 1134, 1118, 1061, 948, 910, 831, 803\text{ cm}^{-1}$; Anal. Calcd. for $\text{C}_{25}\text{H}_{40}\text{N}_4\text{O}_3\text{Si}$: C 63.52, H 8.53, N 11.85; found: C 63.32, H 8.58, N 11.82.

7-((6-Benzoyloxycarbonyl)amino-hexanoylamino)-2-(2-ethylhexanoylamino)-1,8-

naphthyridine, S18 (Table 6, entry 4): Following the general procedure with 1.0 mmol 7-(2-ethyl-hexanoyl)-amino-2-chloro-1,8-naphthyridine the resulting red-brown residue was purified by chromatography (SiO_2 , ethyl acetate / hexane 1:1 v/v) to yield the title compound as a yellow oil (330 mg, 65 %). ^1H NMR (CDCl_3): $\delta = 8.58$ (br, 1H), 8.47 (d, 2H, $J = 9$ Hz), 8.41 (br, 1H), 8.16 (d, 2H, $J = 9$ Hz), 8.14 (d, 2H, $J = 9$ Hz), 5.10 (s, 1H), 4.93 (s, 1H), 3.21 (q, 2H, $J = 7$ Hz), 2.43 (t, 2H, $J = 7$ Hz), 2.24 (m, 1H), 1.82-1.25 (m, 14H), 0.98-0.84 (m, 6H) ppm; ^{13}C NMR (CDCl_3): $\delta = 176.1, 172.7, 156.3, 154.5, 154.3, 139.0, 138.9, 136.6, 128.3, 127.9, 118.0, 113.9, 66.4, 49.8, 40.6, 36.9, 32.0, 29.5, 29.2, 25.9, 25.7, 24.3, 22.6, 13.8, 11.8$ ppm; MALDI-TOF-MS: (m/z) calcd. 533.26; observed: 534.26 ($\text{M}+\text{H}^+$), 556.25 ($\text{M}+\text{Na}^+$); FTR-IR (ATR): $\nu = 3301, 3035, 2930, 2860, 1684, 1607, 1537, 1498, 1456, 1380, 1311, 1282, 1166, 1134, 1027, 910, 853, 803\text{ cm}^{-1}$.

7-Pivaloylamino-[1H]-2-oxo-1,8-naphthyridine, S19A A mixture of 7-amino-[1H]-2-oxo-1,8-naphthyridine (5.07 g, 31.5 mmol) and pivaloyl chloride (6.03 g, 50.0 mmol) in 50 mL pyridine was heated to 110 °C and stirred for 20 hours. The reaction mixture was evaporated to dryness followed by co-evaporation with toluene. The black residue was dissolved in 200 mL hot ethyl acetate and filtered. Multiple crystallizations from ethyl acetate gave the title compound as white needles (1.55 g, 20 %). M.P. = 261 °C; ¹H-NMR (CDCl₃): δ = 11.32 (br, 1H), 9.74 (br, 1H), 8.22 (d, 1H, *J* = 9 Hz), 7.91 (d, 1H, *J* = 9 Hz), 7.71 (d, 1H, *J* = 9 Hz), 6.62 (d, 1H, *J* = 9 Hz), 1.39 (s, 9H) ppm. ¹³C-NMR (CDCl₃): δ = 179.0, 164.5, 154.0, 148.5, 139.5, 138.6, 120.4, 111.5, 111.3, 40.4, 27.1 ppm. MALDI-TOF-MS: (m/z) calcd. 245.12; observed: 246.27 (M+H⁺); FTR-IR (ATR): ν = 3177, 2976, 2910, 1687, 1659, 1617, 1574, 1511, 1476, 1461, 1398, 1374, 1339, 1304, 1282, 1246, 1153, 1141, 995, 939, 918, 847, 828, 801 cm⁻¹; Anal. Calcd. for C₁₆H₂₁N₃O₂: C 63.66, H 6.16, N 17.13 found: C 63.66, H 6.20, N 17.09.

7-Pivaloylamino-[1H]-(2-chloro-1,8-naphthyridine), S19B A mixture of 7-pivaloylamino-[1H]-2-oxo-1,8-naphthyridine **S19A** (1.55 g, 6.31 mmol) in 20 mL POCl₃ was stirred at 95 °C for 4 hours. The solution was allowed to cool to room temperature and some excess of POCl₃ was evaporated in vacuo. The remaining solution was slowly poured into 250 mL iced water under vigorous stirring followed by neutralization with concentrated aqueous NH₃ solution to pH = 8. The title compound was isolated as a white powder by filtration of the precipitate (1.34 g, 80 %). M.P. = 174 °C; ¹H-NMR (CDCl₃): δ = 8.59 (d, 1H, *J* = 9 Hz), 8.44 (br, 1H), 8.19 (d, 1H, *J* = 9 Hz), 8.07 (d, 1H, *J* = 9 Hz), 7.40 (d, 1H, *J* = 9 Hz), 1.36 (s, 9H) ppm; ¹³C-NMR (CDCl₃): δ = 177.6, 154.4, 154.3, 139.0, 138.6, 121.9, 119.0, 115.1, 40.0, 27.3 ppm; MALDI-TOF-MS: (m/z) calcd. 263.08; observed: 264.24 (M+H⁺), 286.22 (M+Na⁺). FTR-IR (ATR): ν = 3435, 3048, 2970, 1693, 1609, 1568, 1557, 1505, 1486, 1392, 1366, 1321, 1276, 1256, 1230, 1131, 988, 941, 906, 851, 792, 782 cm⁻¹; Anal. Calcd. for C₁₆H₂₀ClN₃O: C 59.21, H 5.35, N 15.93 found: C 59.23, H 5.45, N 16.17.

7-(Pivaloylamino)-2-(2-ethylhexanoylamino)-1,8-naphthyridine, S19 (Table 6, entry 5): Following the general procedure with 0.5 mmol 7-Pivaloylamino-2-chloro-1,8-naphthyridine **S19B** the resulting red residue was further purified by chromatography (SiO₂, 1 % methanol / chloroform) to yield the title compound as a white powder (100 mg, 54 %). M.P. 99-101 °C; ¹H NMR (CDCl₃): δ = 8.47 (d, 2H, *J* = 9 Hz), 8.45 (d, 2H, *J* = 9 Hz), 8.36 (br, 1H), 8.33 (br, 1H), 8.14 (d, 2H, *J* = 9 Hz), 2.23 (m, 1H), 1.75-1.58 (m, 4H), 1.36 (s, 12H), 1.35-1.32 (m, 4H), 0.98-0.86 (m, 6H) ppm; ¹³C NMR (CDCl₃): δ = 177.4, 175.2, 153.9, 153.6, 153.5, 138.9, 138.8, 118.2, 113.4, 113.2, 50.8, 39.9, 32.3, 29.6, 27.2, 25.9, 22.6, 13.8, 11.8 ppm; MALDI-TOF-MS: (m/z)

calcd. 370.24; observed: 371.20 ($M+H^+$), 393.18 ($M+Na^+$), 413.23 ($M+K^+$); FTIR-IR (ATR): ν = 3314, 2960, 2931, 2873, 1700, 1676, 1606, 1538, 1499, 1376, 1309, 1283, 1166, 1135, 854, 801 cm^{-1} ; Anal. Calcd. for $C_{21}H_{30}N_4O_2$: C 68.08, H 8.16, N 15.12; found: C 67.96, H 7.90, N 14.89.

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bw 16 fn
pw 7.0 not used
d1 3.000 werr
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nt 16 wit
stack n
gain not used
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il n
in n
dp n
DISPLAY y
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SD 3000.6
VE 269
SC 0
WC 250
WC 12.00
hzmm 10579.44
ts 748.6
rf1 ttfp
tff 2
tms 2.000
ims cdc ph

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1H NMR spectrum of compound 10. The x-axis represents chemical shift in ppm, ranging from 0 to 10. The spectrum shows several peaks: a broad peak at ~9.8 ppm (NH), a multiplet at ~8.2 ppm (10H), a multiplet at ~7.2 ppm (4H), a multiplet at ~6.2 ppm (4H), a multiplet at ~5.2 ppm (4H), a multiplet at ~4.2 ppm (4H), a multiplet at ~3.2 ppm (4H), a multiplet at ~2.2 ppm (2H), a multiplet at ~1.2 ppm (4H), and a multiplet at ~0.2 ppm (4H).