

Supporting Information

Synthesis of amino acid derivatives of quinolone antibiotics

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General methods. Melting points were determined on a capillary point apparatus equipped with a digital thermometer and are uncorrected. NMR spectra were recorded in DMSO-*d*₆ or CDCl₃ with TMS for ¹H (300 MHz) and ¹³C (75 MHz) as internal reference. HPLC analyses were performed using Chirobiotic T column (4.6 x 250 mm), detection at 220 nm, flow rate of 0.5 mL/min and MeOH/H₂O (50:50) as an eluting solvent.

3-(1*H*-Benzo[*d*][1,2,3]triazole-1-carbonyl)-1-ethyl-7-methyl-1,8-naphthyridin-4(1*H*)-one (6):

To a solution of 1*H*-benzotriazole (2.0 g, 16 mmol) in methylene-chloride was added thionyl chloride (0.5 g, 4.5 mmol) at 25°C. After 30 min. 1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (1.0 g, 4.3 mmol) was added and the stirring was continued for 2h. The precipitate was filtered off, and the filtrate was washed with water and evaporated to give yellow solid of 3-(1*H*-benzo[*d*][1,2,3]triazole-1-carbonyl)-1-ethyl-7-methyl-1,8-naphthyridin-4(1*H*)-one (1.3 g, 4.1 mmol, 90%) with the melting point of 169-171°C.

¹H NMR (300 MHz, CDCl₃) δ: 1.54 (t, *J* = 7.2 Hz, 3H), 2.70 (s, 3H), 4.54 (q, *J* = 7.1 Hz, 2H), 7.28 (d, *J* = 8.1 Hz, 1H), 7.50 (t, *J* = 8.1 Hz, 1H), 7.66 (t, *J* = 7.4 Hz, 1H), 8.11 (d, *J* = 8.2 Hz, 1H), 8.32 (d, *J* = 8.2 Hz, 1H), 8.50 (s, 1H), 8.62 (d, *J* = 8.0 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃) δ: 15.2, 25.1, 46.7, 114.4, 115.1, 120.0, 120.9, 121.3, 126.0, 130.0, 131.6, 136.8, 146.0, 147.5, 148.6, 163.1, 164.2, 174.5. C₁₈H₁₅N₅O₂·1/2 H₂O, Calculated: C, 63.15; H, 4.71; N, 20.46, Found: C, 62.78; H, 4.61; N, 20.06.

3-(1*H*-Benzo[*d*][1,2,3]triazole-1-carbonyl)-1-ethyl-[1,3]dioxolo[4,5-*g*]cinnolin-4(1*H*)-one (7):

To a solution of 1*H*-benzotriazole (0.55 g, 4.60 mmol) in methylene-chloride was added thionyl-chloride (0.13 ml, 1.70 mmol) at 25°C. After 30 min. 1-ethyl-4-oxo-1,4-dihydro-[1,3]dioxolo[4,5-*g*]cinnoline-3-carboxylic acid (0.3 g, 1.15 mmol) was added and stirring was continued for 2h. The reaction mixture was washed with water (1x), aq. sat. sodium-carbonate (3x),

and brine (1x), dried over sodium sulfate and the solvent was removed under reduced pressure, gave 3-(1*H*-benzo[*d*][1,2,3]triazole-1-carbonyl)-1-ethyl-[1,3]dioxolo[4,5-*g*]cinnolin-4(1*H*)-one (0.3 g, 80%) with the melting point of 221-223°C.

¹H NMR (300 MHz, DMSO-*d*₆) δ: 1.42 (t, *J* = 7.0 Hz, 3H), 4.59 (q, *J* = 7 Hz, 2H), 6.33 (s, 2H), 7.48 (s, 1H), 7.69 (t, *J* = 7.7 Hz, 2H), 7.87 (t, *J* = 7.7 Hz, 1H), 8.31 (dd, *J* = 2.5 & 8.0 Hz, 2H). ¹³C NMR (75 MHz, DMSO-*d*₆) δ: 13.8, 18.0, 47.8, 52.7, 95.7, 100.8, 103.4, 123.2, 135.1, 138.1, 148.1, 154.0, 161.2, 167.7, 173.9. C₁₈H₁₃N₅O₄·1/2 H₂O, Calculated: C, 58.06; H, 3.79; N, 18.81. Found: C, 58.06; H, 3.39; N, 18.71.

2-(1*H*-Benzo[*d*][1,2,3]triazole-1-carbonyl)-9-fluoro-5-methyl-6,7-dihydropyrido[3,2-*l*-*ij*]quinolin-1(5*H*)-one (8):

To a solution of 1*H*-benzotriazole (0.5 g, 4.4 mmol) in methylene-chloride was added thionyl chloride (0.2 g, 1.3 mmol) at 25°C. After 30 min. 9-fluoro-5-methyl-1-oxo-1,5,6,7-tetrahydropyrido[3,2-*l*-*ij*]quinoline-2-carboxylic acid (0.3 g, 1.1 mmol) was added and the stirring was continued for 2h. The precipitate was filtered off, and the filtrate was washed with water and evaporated to give yellow solid of 2-(1*H*-benzo[*d*][1,2,3]triazole-1-carbonyl)-9-fluoro-5-methyl-6,7-dihydropyrido[3,2-*l*-*ij*]quinolin-1(5*H*)-one (0.3 g, 0.83 mmol, 90%) with the melting point of 232-235°C.

¹H NMR (300 MHz, DMSO-*d*₆) δ: 1.43 (d, *J* = 6.7 Hz, 3H), 2.08-2.29 (m, 2H), 3.03-3.25 (m, 2H), 4.73 (bs, 1H), 7.58-7.68 (m, 2H), 7.69-7.89 (m, 2H), 8.20-8.34 (m, 2H), 8.77-8.88 (m, 1H). ¹³C NMR (75 MHz, DMSO-*d*₆) δ: 19.9, 21.5, 25.3, 56.5, 108.3, 108.6, 112.6, 113.6, 119.9, 120.4, 120.7, 126.3, 129.1, 129.2, 130.5, 130.9, 131.4, 131.5, 132.5, 145.4, 147.0, 160.4, 164.6, 172.3. C₂₀H₁₅FN₄O₂, Calculated: C, 66.29; H, 4.17; N, 15.46, Found: C, 66.19; H, 4.18; N, 15.14.

General procedure for oxolinic-amino acid conjugates (25-40):

A mixture of 7-(1*H*-benzo[*d*][1,2,3]triazole-1-carbonyl)-5-ethyl-[1,3]dioxolo[4,5-*g*]quinolin-8(5*H*)-one (181 mg, 0.5 mmol), amino acid (0.5 mmol) and triethylamine (101 mg, 0.13 mL, 1.0 mmol) in acetonitrile-water mixture (3.5 mL +1.5 mL) was stirred at room temperature for three hours. The acetonitrile was removed under vacuum and the residue was acidified with concentrated HCl. The precipitates was filtered and washed with cold water and dried under reduced pressure and recrystallized from aq. ethanol to gave the corresponding product.

2-(5-Ethyl-8-oxo-dihydro-[1,3]dioxolo[4,5-*g*]quinoline-7-carboxamido)acetate (25):

117 mg, 92%, mp. 296-298°C. ¹H NMR (300 MHz, DMSO-*d*₆) δ: 1.35 (t, *J* = 7.0 Hz, 3H), 4.06 (bs, 2H), 4.41-4.43 (m, 2H), 6.22 (s, 2H), 7.45 (s, 1H), 7.61 (s, 1H), 8.68 (s, 1H), 10.57 (d, *J* = 4.8 Hz, 1H). ¹³C NMR (75 MHz, DMSO-*d*₆) δ: 14.6, 40.9, 48.9, 96.7, 102.6, 102.8, 110.2, 123.1, 136.1, 146.1, 146.3, 152.6, 164.6, 171.5, 174.0. C₁₅H₁₄N₂O₆, Calculated: C, 56.60; H, 4.43; N, 8.80, Found: C, 56.35; H, 4.41; N, 8.56.

(*S*)-2-(5-Ethyl-8-oxo-dihydro-[1,3]dioxolo[4,5-*g*]quinoline-7-carboxamido)propanoate (26):

160 mg, 96%, mp. 257-259 °C. ¹H NMR (300 MHz, DMSO-*d*₆) δ: 1.32-1.41 (m, 6H), 4.13-4.52 (m, 3H), 6.23 (s, 2H), 7.47 (s, 1H), 7.60 (s, 1H), 8.69 (s, 1H), 10.48 (d, *J* = 7.0 Hz, 1H). ¹³C NMR (75 MHz, DMSO-*d*₆) δ: 14.6, 18.2, 47.5, 48.8, 96.6, 102.5, 102.7, 110.1, 123.1, 136.0, 146.0, 146.2, 152.5, 163.8, 174.1. C₁₆H₁₆N₂O₆, Calculated: C, 57.83; H, 4.85; N, 8.43, Found: C, 58.13; H, 4.84; N, 8.35.

2-(5-Ethyl-8-oxo-dihydro-[1,3]dioxolo[4,5-*g*]quinoline-7-carboxamido)propanoic acid (27):

140 mg, 84%, mp. 257-259 °C. ¹H NMR (300 MHz, DMSO-*d*₆) δ: 1.32-1.41 (m, 6H), 4.41-4.50 (m, 3H), 6.23 (s, 2H), 7.47 (s, 1H), 7.60 (s, 1H), 8.69 (s, 1H), 10.48 (d, *J* = 7.2 Hz, 1H). ¹³C NMR (75 MHz, DMSO-*d*₆) δ: 14.6, 18.3, 47.5, 48.8, 96.6, 102.5, 102.7, 110.1, 123.1, 136.0, 146.0, 146.2, 152.5,

163.8, 174.0, 174.1. C₁₆H₁₆N₂O₆, Calculated: C, 57.83; H, 4.85; N, 8.43, Found: C, 57.53; H, 4.92; N, 8.46.

(S)-2-(5-Ethyl-8-oxo-5,8-dihydro-[1,3]dioxolo[4,5-g]quinoline-7-carboxamido)-3-phenylpropanoate (28):

280 mg, 58%, mp. 213-215°C. ¹H NMR (300 MHz, DMSO-d₆) δ: 1.33 (t, *J* = 7.0 Hz, 3H), 3.00-3.08 (m, 1H), 3.15-3.22 (m, 1H), 4.40 (q, *J* = 6.0 Hz, 2H), 4.75 (q, *J* = 7.1 Hz, 1H), 6.23 (s, 2H), 7.19-7.30 (m, 5H), 7.46 (s, 1H), 7.60 (s, 1H), 8.67 (s, 1H), 10.49 (d, *J* = 7.6 Hz, 1H). ¹³C NMR (75 MHz, DMSO-d₆) δ: 14.6, 37.4, 48.8, 53.3, 96.6, 102.5, 102.7, 110.0, 123.0, 126.6, 128.3, 129.2, 136.0, 137.1, 146.1, 146.2, 152.5, 164.1, 172.8, 173.9. C₂₂H₂₀N₂O₆, Calculated: C, 64.70; H, 4.94; N, 6.86, Found: C, 64.34; H, 4.90; N, 6.85.

2-(5-Ethyl-8-oxo-dihydro-[1,3]dioxolo[4,5-g]quinoline-7-carboxamido)-3-phenylpropanoate (29):

180 mg, 88%, mp. 248-249 °C. ¹H NMR (300 MHz, DMSO-d₆) δ: 1.33 (t, *J* = 7.0 Hz, 3H), 3.04 (dd, *J* = 13.5 & 8.0 Hz 1H), 3.18 (dd, *J* = 13.5 & 8.0 Hz 1H), 4.41 (q, *J* = 7.0 Hz, 2H), 4.75-4.77 (m, 1H), 6.23 (s, 2H), 7.22-7.30 (m, 5H), 7.47 (s, 1H), 7.61 (s, 1H), 8.67 (s, 1H), 10.49 (d, *J* = 7.8 Hz, 1H). ¹³C NMR (75 MHz, DMSO-d₆) δ: 14.5, 37.4, 48.8, 53.3, 96.6, 102.5, 102.7, 110.0, 123.0, 126.6, 128.2, 129.2, 136.0, 137.1, 146.1, 146.2, 152.5, 164.1, 172.8, 174.0. C₂₂H₂₀N₂O₆, Calculated: C, 64.70; H, 4.94; N, 6.86, Found: C, 64.34; H, 4.90; N, 6.85.

(S)-2-(5-Ethyl-8-oxo-dihydro-[1,3]dioxolo[4,5-g]quinoline-7-carboxamido)-4-methylpentanoate (31):

165 mg, 88%, mp. 219-221°C. ¹H NMR (300 MHz, DMSO-d₆) δ: 0.92 (t, *J* = 6.9 Hz, 6H), 1.34 (t, *J* = 6.9 Hz, 3H), 1.62-1.75 (m, 3H), 4.42 (q, *J* = 6.9 Hz, 2H), 4.52 (q, *J* = 6.9 Hz, 1H), 6.23 (s, 2H), 7.47 (s, 1H), 7.61 (s, 1H), 8.70 (s, 1H), 10.46 (d, *J* = 7.8 Hz, 1H). ¹³C NMR (75 MHz, DMSO-d₆) δ: 14.6,

21.6, 22.9, 24.6, 41.0, 48.9, 50.2, 96.6, 102.5, 102.8, 110.1, 123.1, 136.0, 146.1, 146.2, 152.6, 164.2, 174.1. C₁₉H₂₂N₂O₆, Calculated: C, 60.95; H, 5.92; N, 7.48, Found: C, 60.67; H, 5.86; N, 7.14.

(2*S*,3*S*)-2-(5-Ethyl-8-oxo-dihydro-[1,3]dioxolo[4,5-*g*]quinoline-7-carboxamido)-3-methylpentanoate (32):

173 mg, 92%, mp. 225-228°C. ¹H NMR (300 MHz, DMSO-*d*₆) δ: 0.88-0.93 (m, 6H), 1.17-1.28 (m, 1H), 1.34 (t, *J* = 7.0 Hz, 3H), 1.44-1.53 (m, 1H), 1.92 (m, 1H), 4.40-4.51 (m, 3H), 6.24 (s, 2H), 7.50 (s, 1H), 7.65 (s, 1H), 8.71 (s, 1H), 10.56 (d, *J* = 8.4 Hz, 1H). ¹³C NMR (75 MHz, DMSO-*d*₆) δ: 11.5, 14.6, 15.9, 24.7, 36.9, 48.9, 56.1, 96.6, 102.6, 102.7, 110.2, 123.1, 136.1, 146.1, 146.2, 152.6, 164.2, 173.0, 174.2. C₁₉H₂₂N₂O₆, Calculated: C, 60.95, H, 5.92; N, 7.48, Found: C, 60.61; H, 5.95; N, 7.32 .

(*S*)-2-(5-Ethyl-8-oxo-dihydro-[1,3]dioxolo[4,5-*g*]quinoline-7-carboxamido)-3-(1*H*-indol-3-yl)propanoate (33):

162 mg, 72%, mp. 167-171 °C. ¹H NMR (300 MHz, DMSO-*d*₆) δ: 1.32 (t, *J* = 7.5 Hz, 3H), 3.17-3.33 (m, 2H), 4.40 (q, *J* = 7.5 Hz, 2H), 4.79-4.83 (m, 1H), 6.23 (s, 2H), 6.92-6.97 (m, 1H), 7.02-7.07 (m, 1H), 7.18 (s, 1H), 7.31-7.34 (m, 1H), 7.46 (s, 1H), 7.54-7.61 (m, 2H), 8.69 (s, 1H), 10.53 (d, *J* = 7.5 Hz, 1H), 10.91 (s, 1H). ¹³C NMR (75 MHz, DMSO-*d*₆) δ: 14.6, 27.7, 48.9, 52.7, 96.6, 102.5, 102.7, 109.4, 110.2, 111.4, 118.4, 121.0, 123.1, 123.6, 127.3, 136.0, 136.1, 146.1, 146.2, 152.5, 164.1, 173.3, 174.0. C₂₄H₂₁N₃O₆ · H₂O, Calculated: C, 61.93; H, 4.55; N, 9.03, Found: C, 61.71; H, 4.79; N, 9.35.

(*S*)-2-(5-Ethyl-8-oxo-dihydro-[1,3]dioxolo[4,5-*g*]quinoline-7-carboxamido)-3-hydroxypropanoate (34):

110 mg, 63%, mp. 246-248°C. ¹H NMR (300 MHz, DMSO-*d*₆) δ: 1.34 (t, *J* = 7.5 Hz, 3H), 3.79-3.80 (m, 2H), 4.03-4.04 (m, 2H), 4.41 (q, *J* = 7.5 Hz, 2H), 6.23 (s, 2H), 7.47 (s, 1H), 7.60 (s, 1H), 8.33 (bs, 1H), 8.69 (s, 1H), 10.37 (s, 1H). ¹³C NMR (75 MHz, DMSO-*d*₆) δ: 14.6, 42.0, 45.4, 48.9, 96.6, 102.5,

102.8, 110.4, 123.1, 136.0, 146.0, 146.2, 152.5, 164.5, 171.2, 173.9. C₁₆H₁₆N₂O₇, Calculated: C, 55.17; H, 4.63; N, 8.04, Found: C, 55.00; H, 4.57; N, 7.68.

(S)-2-(5-Ethyl-8-oxo-dihydro-[1,3]dioxolo[4,5-g]quinoline-7-carboxamido)-3-sulfanylpropanoate (35):

160 mg, 88%, mp. 218-220 °C. ¹H NMR (300 MHz, DMSO-d₆) δ: 1.38 (t, *J* = 7.2 Hz, 3H), 2.30 (t, *J* = 8.4 Hz, 1H), 3.02-3.06 (m, 2H), 4.48 (q, *J* = 7.5 Hz, 2H), 4.82-4.84 (m, 1H), 6.28 (s, 2H), 7.53 (s, 1H), 7.67 (s, 1H), 8.75 (s, 1H), 10.76 (d, *J* = 7.4 Hz, 1H). ¹³C NMR (75 MHz, DMSO-d₆) δ: 14.6, 26.2, 48.9, 53.6, 96.7, 102.6, 102.8, 107.1, 110.1, 123.1, 136.0, 146.2, 148.2, 152.6, 164.2, 171.5, 174.0. C₁₆H₁₆N₂O₆S·½H₂O, Calculated: C, 51.47; H, 4.59; N, 7.50, Found: C, 51.07; H, 4.54; N, 7.19 .

(S)-2-(5-Ethyl-8-oxo-dihydro-[1,3]dioxolo[4,5-g]quinoline-7-carboxamido)succinoate (36):

180 mg, 96%, mp. 238-239°C. ¹H NMR (300 MHz, DMSO-d₆) δ: 1.36 (t, *J* = 7.2 Hz, 3H), 2.73-2.89 (m, 2H), 4.43 (q, *J* = 7.2 Hz, 2H), 4.81 (m, 1H), 6.23 (s, 2H), 7.46 (s, 1H), 7.61 (s, 1H), 8.69 (s, 1H), 10.62 (d, *J* = 7.8 Hz, 1H). ¹³C NMR (75 MHz, DMSO-d₆) δ: 14.6, 36.6, 48.2, 48.9, 96.6, 102.5, 102.7, 110.1, 123.1, 136.0, 146.2, 152.5, 164.1, 171.9, 172.4, 173.9. C₁₇H₁₆N₂O₈, Calculated: C, 54.26; H, 4.29; N, 7.44, Found: C, 53.91; H, 4.29; N, 7.13 .

(S)-2-(5-Ethyl-8-oxo-dihydro-[1,3]dioxolo[4,5-g]quinoline-7-carboxamido)-3-methylbutanoate (37):

130 mg, 72%, mp. 225-227°C. ¹H NMR (300 MHz, DMSO-d₆) δ: 0.95 (d, *J* = 6.6 Hz, 6H), 1.35 (t, *J* = 7.0 Hz, 3H), 2.16-2.22 (m, 1H), 4.40-4.47 (m, 3H), 6.24 (s, 2H), 7.48 (s, 1H), 7.63 (s, 1H), 8.70 (s, 1H), 10.57 (d, *J* = 8.5 Hz, 1H). ¹³C NMR (75 MHz, DMSO-d₆) δ: 14.6, 17.7, 19.4, 30.3, 48.9, 56.8, 96.6, 102.6, 102.7, 110.2, 123.1, 136.0, 146.1, 146.2, 152.6, 164.4, 173.0, 174.2. C₁₈H₂₀N₂O₆·H₂O, Calculated: C, 57.14; H, 5.86; N, 7.40, Found: C, 57.56; H, 5.69; N, 7.35 .

(S)-2-(5-Ethyl-8-oxo-dihydro-[1,3]dioxolo[4,5-g]quinoline-7-carboxamido)-3-(*p*-hydroxyphenyl)propanoate (38):

190 mg, 90%, mp. 292-293°C ¹H NMR (300 MHz, DMSO-d₆) δ: 1.33 (t, *J* = 7.0 Hz, 3H), 2.91 (dd, *J* = 14.0 & 7.8 Hz, 1H), 3.05 (dd, *J* = 14.0 & 4.8 Hz, 1H), 4.41 (q, *J* = 6.6 Hz, 2H), 4.66 (m, 1H), 6.23 (s, 2H), 6.64 (d, *J* = 8.1 Hz, 2H), 7.00 (d, *J* = 8.1 Hz, 2H), 7.46 (s, 1H), 7.60 (s, 1H), 8.66 (s, 1H), 9.24 (s, 1H), 10.43 (d, *J* = 7.4 Hz, 1H). ¹³C NMR (75 MHz, DMSO-d₆) δ: 14.6, 36.6, 48.9, 53.6, 96.6, 102.8, 110.1, 115.1, 123.1, 127.1, 130.1, 136.0, 146.1, 146.2, 152.5, 156.0, 164.0, 172.9, 174.0. C₂₂H₂₀N₂O₇·1.5H₂O, Calculated: C, 58.53; H, 5.14; N, 6.21, Found: C, 58.66; H, 4.88; N, 5.91.

(2*S*,2'*S*)-3,3'-Disulfanediylbis[2-(5-Ethyl-8-oxo-dihydro-[1,3]dioxolo[4,5-g]quinoline-7-carboxamido)propanoate] (39):

105 mg, 58%, mp. 234-236°C. ¹H NMR (300 MHz, DMSO-d₆) δ: 1.32 (t, *J* = 6.6 Hz, 6H), 3.18-3.35 (m, 4H), 4.48 (q, *J* = 6.6 Hz, 4H), 4.81-4.85 (m, 2H), 6.21 (s, 4H), 7.40 (s, 2H), 7.53 (s, 2H), 8.65 (s, 2H), 10.64 (d, *J* = 7.7 Hz, 2H). ¹³C NMR (75 MHz, DMSO-d₆) δ: 14.6, 40.3, 48.9, 51.4, 96.5, 102.5, 102.8, 109.9, 123.0, 136.0, 146.2, 152.5, 164.3, 171.9, 173.9. C₃₂H₃₀N₄O₁₂S₂·H₂O, Calculated: C, 51.61; H, 4.33; N, 7.52, Found: C, 51.46; H, 4.32; N, 7.01.

2-[2-(5-Ethyl-8-oxo-dihydro-[1,3]dioxolo[4,5-g]quinoline-7-carboxamido)acetamido]-3-acetic acid (40):

170 mg, 90%, mp. 282-284 °C. ¹H NMR (300 MHz, DMSO-d₆) δ: 1.30 (t, *J* = 7.5 Hz, 3H), 3.68 (d, *J* = 9.0 Hz, 2H), 3.82 (d, *J* = 7.8 Hz, 2H), 4.37 (q, *J* = 7.5 Hz, 2H), 6.18 (s, 2H), 7.40 (s, 1H), 7.54 (s, 1H), 8.63 (s, 1H), 10.55 (d, *J* = 7.6 Hz, 1H). ¹³C NMR (75 MHz, DMSO-d₆) δ: 14.8, 48.9, 54.4, 61.8, 96.6, 102.6, 102.8, 110.4, 123.2, 136.0, 146.1, 146.2, 152.6, 164.2, 172.2, 174.0. C₁₇H₁₇N₃O₇, Calculated: C, 54.40; H, 4.57; N, 11.20, Found: C, 53.95; H, 4.98; N, 11.55.

General procedure for nalidixic-amino acid conjugates (41-51):

A mixture of 3-(1*H*-Benzo[*d*][1,2,3]triazole-1-carbonyl)-1-ethyl-7-methyl-1,8-naphthyridin-4(1*H*)-one (100 mg, 0.3 mmol), amino acid (0.3 mmol) and triethylamine (61 mg, 0.08 mL, 0.6 mmol) in acetonitrile-water mixture (2.1 mL + 0.9 mL) was stirred at room temperature for three hours. The acetonitrile was removed under vacuum and the residue was acidified with concentrated HCl. The precipitates was filtered and washed with cold water and dried under reduced pressure and recrystallized from aq. ethanol to gave the corresponding product.

2-(1-Ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxamido)acetate (41):

40 mg, 40%, mp. 256-260°C. ¹H NMR (300 MHz, DMSO-*d*₆) δ: 1.38 (t, *J* = 6.9 Hz, 3H), 2.66 (s, 3H), 4.08 (d, *J* = 5.4 Hz, 2H), 4.55-4.62 (m, 2H), 7.48 (d, *J* = 8.1 Hz, 1H), 8.55 (d, *J* = 8.1 Hz, 1H), 8.97 (s, 1H), 10.07 (s, 1H). ¹³C NMR (75 MHz, DMSO-*d*₆) δ: 15.0, 24.9, 40.9, 46.0, 111.7, 119.6, 121.5, 135.9, 148.0, 148.1, 163.2, 163.9, 171.3, 175.7. C₁₄H₁₅N₃O₄. Calculated: C, 58.13; H, 5.23; N, 14.53, Found: C, 58.44; H, 5.18; N, 14.33.

(*S*)-2-(1-Ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxamido)propanoate (42):

81 mg, 90%, mp. 251-253°C. ¹H NMR (300 MHz, DMSO-*d*₆) δ: 1.35-1.41 (m, 6H), 2.66 (s, 3H), 4.46-4.58 (m, 3H), 7.48 (d, *J* = 8.2 Hz, 1H), 8.54 (d, *J* = 8.1 Hz, 1H), 8.94 (s, 1H), 10.21 (d, *J* = 7.1 Hz, 1H). ¹³C NMR (75 MHz, DMSO-*d*₆) δ: 15.2, 18.4, 25.0, 46.2, 47.7, 111.7, 119.8, 121.7, 136.1, 148.2, 148.3, 163.5, 174.2, 176.0. C₁₅H₁₇N₃O₄·H₂O. Calculated: C, 56.07; H, 5.96; N, 13.08, Found: C, 56.40; H, 5.99; N, 13.05.

2-(1-Ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxamido)propanoate (43):

87 mg, 96%, mp. 252-254°C. ¹H NMR (300 MHz, DMSO-*d*₆) δ: 1.35-1.41 (m, 6H), 2.66 (s, 3H), 4.46-4.56 (m, 3H), 7.48 (d, *J* = 8.1 Hz, 1H), 8.54 (d, *J* = 8.1 Hz, 1H), 8.94 (s, 1H), 10.21 (d, *J* = 7.1 Hz, 1H). ¹³C NMR (75 MHz, DMSO-*d*₆) δ: 15.1, 18.3, 25.0, 46.2, 47.7, 111.7, 119.8, 121.7, 136.1,

148.2, 148.3, 163.5, 174.2, 176.0. C₁₅H₁₇N₃O₄ Calculated: C, 59.40; H, 5.65; N, 13.85, Found: C, 59.64; H, 5.63; N, 13.66.

(S)-2-(1-Ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxamido)-3-phenylpropanoate (44):

250 mg, 55%, mp. 213-215°C. ¹H NMR (300 MHz, DMSO-d₆) δ: 1.36 (t, *J* = 7.0 Hz, 3H), 2.63 (s, 3H), 3.06 (dd, *J* = 13.5 & 7.5 Hz, 1H), 3.20 (dd, *J* = 13.8 & 5.1 Hz, 1H), 4.52 (q, *J* = 7.0 Hz, 2H), 4.80 (q, *J* = 7.2 Hz, 1H), 7.18-7.30 (m, 5H), 7.42 (d, *J* = 8.1 Hz, 1H), 8.50 (d, *J* = 8.3 Hz, 1H), 8.93 (s, 1H), 10.19 (d, *J* = 7.4 Hz, 1H). ¹³C NMR (75 MHz, DMSO-d₆) δ: 15.0, 24.9, 37.3, 46.0, 53.3, 11.5, 119.6, 121.4, 126.6, 128.3, 129.2, 135.9, 137.0, 148.1, 163.1, 163.5, 172.7, 175.7. C₂₁H₂₁N₃O₄, Calculated: C, 66.48; H, 5.58; N, 11.07, Found: C, 66.21; H, 5.77; N, 11.17.

(S)-2-(1-Ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxamido)-4-methylsulfanylbutanoate (45):

70 mg, 64%, mp. 164-165°C. ¹H NMR (300 MHz, DMSO-d₆) δ: 1.33 (t, *J* = 6.9 Hz, 3H), 1.91-2.15 (m, 6H), 2.51 (m, 1H), 2.60 (s, 3H), 4.49 (q, *J* = 6.9 Hz, 2H), 4.59-4.66 (m, 1H), 7.39 (d, *J* = 8.1 Hz, 1H), 8.45 (d, *J* = 8.1 Hz, 1H), 8.91 (s, 1H), 10.21 (d, *J* = 7.7 Hz, 1H). ¹³C NMR (75 MHz, DMSO-d₆) δ: 14.6, 15.0, 24.8, 29.5, 31.6, 46.0, 50.9, 111.6, 119.6, 121.4, 135.8, 148.0, 163.2, 163.6, 173.1, 175.8. C₁₇H₂₁N₃O₄S, Calculated: C, 56.18; H, 5.82; N, 11.56, Found: C, 55.81; H, 5.82; N, 11.53.

(S)-2-(1-Ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxamido)-4-methylpentanoate (46):

70 mg, 67%, mp. 171-172°C. ¹H NMR (300 MHz, DMSO-d₆) δ: 0.90-0.94 (m, 6H), 1.37 (t, *J* = 6.6 Hz, 3H), 1.65-1.67 (m, 3H), 2.64 (s, 3H), 4.53-4.55 (m, 3H), 7.44 (d, *J* = 8.2 Hz, 1H), 8.50 (d, *J* = 8.1 Hz, 1H), 8.96 (s, 1H), 10.16 (d, *J* = 8.0 Hz, 1H). ¹³C NMR (75 MHz, DMSO-d₆) δ: 15.0, 21.6, 22.8,

24.6, 24.8, 40.3, 46.0, 50.2, 111.6, 119.6, 121.4, 135.8, 148.0, 163.2, 163.5, 173.9, 175.9. C₁₈H₂₃N₃O₄,
Calculated: C, 62.59; H, 6.71; N, 12.17, Found: C, 62.33; H, 6.73; N, 12.29.

(S)-2-(1-Ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxamido)-3-methylpentanoate (47):

80 mg, 77%, mp. 159-160°C. ¹H NMR (300 MHz, DMSO-d₆) δ: 0.89-0.99 (m, 6H), 1.15-1.31 (m, 1H), 1.39 (t, *J* = 6.6 Hz, 3H), 1.46-1.54 (m, 1H), 1.93 (m, 1H), 2.67 (s, 3H), 4.49-4.66 (m, 3H), 7.49 (d, *J* = 8.1, Hz, 1H), 8.57 (d, *J* = 8.1 Hz, 1H), 8.98 (s, 1H), 10.28 (d, *J* = 8.4 Hz, 1H). ¹³C NMR (75 MHz, DMSO-d₆) δ: 11.5, 15.0, 15.9, 24.7, 24.9, 36.9, 46.0, 56.1, 111.7, 119.7, 121.5, 136.0, 148.1, 163.2, 163.6, 172.9, 176.0. C₁₈H₂₃N₃O₄, Calculated: C, 62.59; H, 6.71; N, 12.17, Found: C, 61.23; H, 6.68; N, 11.83.

(S)-2-(1-Ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxamido)succinoate (48):

45 mg, 43%, mp. 238-239°C. ¹H NMR (300 MHz, DMSO-d₆) δ: 1.38 (t, *J* = 7.2 Hz, 3H), 2.66 (s, 3H), 2.74-2.92 (m, 2H), 4.56 (q *J* = 7.2 Hz, 2H), 4.79-4.86 (m, 1H), 7.47 (d, *J* = 8.1 Hz, 1H), 8.53 (d, *J* = 8.1 Hz, 1H), 8.96 (s, 1H), 10.38 (d, *J* = 8.0 Hz, 1H). ¹³C NMR (75 MHz, DMSO-d₆) δ: 15.0, 24.9, 36.5, 46.0, 48.2, 111.6, 119.7, 121.5, 135.9, 148.2, 163.2, 163.5, 171.9, 172.3, 175.7. C₁₆H₁₇N₃O₆,
Calculated: C, 55.33; H, 4.93; N, 12.10, Found: C, 55.48; H, 4.90; N, 12.30.

(S)-2-(1-Ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxamido)-3-methylbutanoate (49):

60 mg, 60%, mp. 182-185°C. ¹H NMR (300 MHz, DMSO-d₆) δ: 0.95 (d, *J* = 6.9 Hz, 6H), 1.39 (t, *J* = 7.0 Hz, 3H), 2.17-2.24 (m, 1H), 2.66 (s, 3H), 4.45-4.63 (m, 3H), 7.47 (d, *J* = 8.1 Hz, 1H), 8.55 (d, *J* = 8.1, 1H), 8.97 (s, 1H), 10.28 (d, *J* = 8.4 Hz, 1H). ¹³C NMR (75 MHz, DMSO-d₆) δ: 15.0, 17.6, 19.3, 24.9, 30.3, 46.0, 56.8, 111.7, 119.6, 121.5, 135.9, 148.0, 163.2, 163.8, 172.9, 176.0. C₁₇H₂₁N₃O₄,
Calculated: C, 62.59; H, 6.71; N, 12.17, Found: C, 62.33; H, 6.73; N, 12.29.

(S)-2-(1-Ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxamido)-3-(p-hydroxyphenyl)propanoate (50):

92 mg, 78%, mp. 140-142°C. ¹H NMR (300 MHz, DMSO-d₆) δ: 1.35 (t, *J* = 6.9 Hz, 3H), 2.62 (s, 3H), 2.91-3.10 (m, 2H), 4.51 (q, *J* = 6.9 Hz, 2H), 4.67-4.74 (m, 1H), 6.65 (d, *J* = 8.0 Hz, 2H), 7.02 (d, *J* = 8.0 Hz, 2H), 7.41 (d, *J* = 8.1 Hz, 1H), 8.48 (d, *J* = 8.1 Hz, 1H), 8.92 (s, 1H), 9.23 (s, 1H), 10.15 (d, *J* = 7.4 Hz, 1H). ¹³C NMR (75 MHz, DMSO-d₆) δ: 15.0, 24.8, 36.6, 46.0, 53.6, 111.6, 115.1, 119.6, 121.4, 127.0, 130.2, 135.9, 148.0, 148.1, 156.1, 163.1, 163.5, 172.8, 175.8. C₂₁H₂₁N₃O₅·H₂O, Calculated: C, 61.01; H, 5.61; N, 10.16, Found: C, 61.36; H, 5.32; N, 10.55.

2-[2-(1-Ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxamido)acetamido]acetate (51):

80 mg, 66%, mp. 246-247°C. ¹H NMR (300 MHz, DMSO-d₆) δ: 1.38 (t, *J* = 6.9 Hz, 3H), 2.65 (s, 3H), 3.80 (d, *J* = 5.4 Hz, 2H), 4.06 (d, *J* = 5.4 Hz, 2H), 4.56 (q, *J* = 6.9 Hz, 2H), 7.45 (d, *J* = 8.1 Hz, 1H), 8.25 (bs, 1H), 8.53 (d, *J* = 8.1 Hz, 1H), 8.95 (s, 1H), 10.08 (s, 1H). ¹³C NMR (75 MHz, DMSO-d₆) δ: 15.0, 24.8, 42.0, 46.0, 111.9, 119.6, 121.4, 135.9, 147.9, 148.1, 163.1, 163.9, 169.1, 171.2, 175.7. C₁₆H₁₈N₄O₅, Calculated: C, 55.49; H, 5.24; N, 16.18, Found: C, 54.96; H, 5.06; N, 15.91.

General procedure for cinoxacin-amino acid conjugates (52-54):

A mixture of 3-(1*H*-benzo[*d*][1,2,3]triazole-1-carbonyl)-1-ethyl-[1,3]dioxolo[4,5-*g*]cinnolin-4(1*H*)-one (100 mg, 0.3 mmol), amino acid (0.3 mmol) and triethylamine (61 mg, 0.08 mL, 0.6 mmol) in acetonitrile-water mixture (2.1 mL + 0.9 mL) was stirred at room temperature for three hours. The acetonitrile was removed under vacuum and the residue was acidified with concentrated HCl. The precipitates was filtered and washed with cold water and dried under reduced pressure and recrystallized from aq. ethanol to give the corresponding product.

(*S*)-2-(1-Ethyl-4-oxo-1,4-dihydro-[1,3]dioxolo[4,5-*g*]cinnoline-3-carboxamido)propanoate (52):

93 mg, 82%, mp. 236-238°C. ¹H NMR (300 MHz, DMSO-*d*₆) δ: 1.38-1.43 (m, 6H), 4.45-4.50 (m, 1H), 4.57-4.64 (m, 2H), 6.31 (s, 2H), 7.54 (s, 1H), 7.65 (s, 1H), 10.45 (d, *J* = 6.9 Hz, 1H). ¹³C NMR (75 MHz, DMSO-*d*₆) δ: 15.2, 18.4, 25.0, 46.3, 47.7, 111.7, 119.8, 121.8, 136.1, 148.2, 148.3, 163.5, 174.2, 176.0. C₁₅H₁₇N₃O₇·H₂O, Calculated: C, 51.28; H, 4.88; N, 11.96, Found: C, 51.49; H, 4.77; N, 11.92.

2-(1-Ethyl-4-oxo-1,4-dihydro-[1,3]dioxolo[4,5-*g*]cinnoline-3-carboxamido)-3-phenylpropanoate (53):

93 mg, 82%, mp. 266-268°C. ¹H NMR (300 MHz, DMSO-*d*₆) δ: 1.39 (t, *J* = 7.1 Hz, 3H), 3.03-3.10 (m, 1H), 3.20 (dd, *J* = 4.9 & 13.9 Hz, 1H), 4.58 (q, *J* = 7.0 Hz, 2H), 4.73-4.80 (m, 1H), 6.29 (s, 2H), 7.19-7.30 (m, 5H), 7.51 (s, 1H), 7.61 (s, 1H), 10.45 (d, *J* = 7.4 Hz, 1H). ¹³C NMR (75 MHz, DMSO-*d*₆) δ: 13.7, 37.1, 52.7, 53.5, 95.7, 100.8, 103.4, 123.2, 126.6, 128.3, 129.2, 134.8, 137.0, 138.1, 148.1, 153.9, 161.4, 167.7, 172.5. C₂₁H₁₉N₃O₆, Calculated: C, 61.61; H, 4.68; N, 10.26, Found: C, 61.28; H, 4.55; N, 10.21.

(S)-2-(1-Ethyl-4-oxo-1,4-dihydro-[1,3]dioxolo[4,5-g]cinnoline-3-carboxamido)-3-(1H-indol-3-yl)propanoate (54):

80 mg, 73%, mp. 179-181°C. ¹H NMR (300 MHz, DMSO-d₆) δ: 1.39 (t, *J* = 6.9 Hz, 3H), 3.26 (m, 2H), 4.59 (q, *J* = 6.9 Hz, 2H), 4.81 (q, *J* = 6.3 Hz, 1H), 6.30 (s, 2H), 6.94 (t, *J* = 7.4 Hz, 1H), 7.05 (t, *J* = 7.6 Hz, 1H), 7.19 (s, 1H), 7.32 (d, *J* = 8.1 Hz, 1H), 7.50 (bs, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.64 (s, 1H), 10.49 (d, *J* = 7.1 Hz, 1H), 10.90 (s, 1H). ¹³C NMR (75 MHz, DMSO-d₆) δ: 13.7, 52.7, 53.0, 95.7, 100.8, 103.4, 109.2, 111.4, 118.4, 121.0, 123.2, 123.7, 127.3, 135.0, 136.1, 138.1, 148.0, 154.0, 161.4, 167.7, 173.0. C₂₃H₂₂N₄O₇·H₂O Calculated: C, 59.22; H, 4.75; N, 12.01, Found: C, 59.47; H, 4.71; N, 12.50.

General procedure for flumequine-amino acid conjugates (55,56):

A mixture of 2-(1*H*-Benzo[*d*][1,2,3]triazole-1-carbonyl)-9-fluoro-5-methyl-6,7-dihydropyrido[3,2,1-*ij*]quinolin-1(5*H*)-one (100 mg, 0.3 mmol), amino acid (0.3 mmol) and triethylamine (61 mg, 0.08 mL, 0.6 mmol) in acetonitrile-water mixture (2.1 mL + 0.9 mL) was stirred at room temperature for three hours. The acetonitrile was removed under vacuum and the residue was acidified with concentrated HCl. The precipitates was filtered and washed with cold water and dried under reduced pressure and recrystallized from aq. ethanol to give the corresponding product.

(2S)-2-(9-Fluoro-5-methyl-1-oxo-1,5,6,7-tetrahydropyrido[3,2,1-*ij*]quinoline-2-carboxamido)-3-phenylpropanoate (55):

65 mg, 53%, mp. 175-176°C. ¹H NMR (300 MHz, DMSO-d₆) δ: 1.36 (d, *J* = 6.6 Hz, 3H), 2.09 (bs, 2H), 3.00-3.40 (m, 4H), 4.78-4.80 (m, 2H), 7.15-7.30 (m, 5H), 7.60 (dd, *J* = 9.0 & 3.0 Hz, 1H), 7.80 (dd, *J* = 8.7 & 2.7 Hz, 1H), 8.80, (s, 1H), 10.25 (d, *J* = 7 Hz, 1H). ¹³C NMR (75 MHz, DMSO-d₆) δ: 20.0, 21.5, 25.3, 37.3, 53.3, 53.4, 56.5, 108.1, 108.4, 109.8, 120.3, 120.6, 126.6, 128.3, 128.9, 129.2,

131.3, 131.4, 132.4, 137.0, 137.1, 146.3, 157.1, 160.3, 163.8, 163.9, 172.7, 174.6. C₂₃H₂₁FN₂O₄,
Calculated: C, 67.64; H, 5.18; N, 6.86, Found: C, 67.38; H, 5.18; N, 6.81.

(2*S*)-2-(9-Fluoro-5-methyl-1-oxo-1,5,6,7-tetrahydropyrido[3,2-*l*-*ij*]quinoline-2-carboxamido)-3-(1*H*-indol-3-yl)propanoic acid (56):

75 mg, 56%, mp. 202-203°C. ¹H NMR (300 MHz, DMSO-*d*₆) δ: 1.40 (d, *J* = 6.6 Hz, 3H), 2.14 (bs, 2H), 3.00-3.50 (m, 4H), 4.86 (m, 2H), 6.98 (t, *J* = 7.2 Hz, 1H), 7.08 (t, *J* = 7.2 Hz, 1H), 7.20 (s, 1H), 7.36 (d, *J* = 6.9 Hz, 1H), 7.58-7.66 (m, 2H), 7.81-7.84 (m, 1H), 8.85 (s, 1H), 10.39 (d, *J* = 7 Hz, 1H), 10.93 (s, 1H). ¹³C NMR (75 MHz, DMSO-*d*₆) δ: 20.0, 21.5, 25.3, 27.7, 52.7, 56.5, 108.0, 108.3, 109.3, 110.0, 111.4, 118.4, 120.3, 120.6, 121.0, 123.7, 127.3, 128.8, 128.9, 131.4, 131.5, 132.4, 136.1, 146.3, 157.1, 160.3, 163.9, 173.3, 174.5, 174.6. C₂₅H₂₂FN₃O₄·H₂O, Calculated: C, 64.51; H, 5.20; N, 9.03, Found: C, 64.44; H, 5.13; N, 8.84.













