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 CDCl$_3$ with TMS for $^1$H (300 MHz) and $^{13}$C (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/H$_2$O (50:50) as an eluting solvent.

**3-(1H-Benzotriazole-1-carbonyl)-1-ethyl-7-methyl-1,8-naphthyridin-4(1H)-one (6):**

To a solution of 1H-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-(1H-benzotriazole-1-carbonyl)-1-ethyl-7-methyl-1,8-naphthyridin-4(1H)-one (1.3 g, 4.1 mmol, 90%) with the melting point of 169-171°C.

$^1$H NMR (300 MHz, CDCl$_3$) 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). $^{13}$C NMR (75 MHz, CDCl$_3$) 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. C$_{18}$H$_{15}$N$_{5}$O$_{2}$·1/2 H$_2$O. Calculated: C, 63.15; H, 4.71; N, 20.46. Found: C, 62.78; H, 4.61; N, 20.06.

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

To a solution of 1H-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-
(1H-benzo[d][1,2,3]triazole-1-carbonyl)-1-ethyl-[1,3]dioxolo[4,5-g]cinnolin-4(1H)-one (0.3 g, 80%)
with the melting point of 221-223°C.

1H NMR (300 MHz, DMSO-d6) 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-d6) 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-(1H-Benzotriazol-1-yl)-9-fluoro-5-methyl-6,7-dihydropyrido[3,2,1-ij]quinolin-1(5H)-one (8):

To a solution of 1H-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-fluoror-5-methyl-1-oxo-1,5,6,7-tetrahydropyrido[3,2,1-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-(1H-benzo[d][1,2,3]triazole-1-carbonyl)-9-fluoro-5-methyl-6,7-
dihydropyrido[3,2,1-ij]quinolin-1(5H)-one (0.3 g, 0.83 mmol, 90%) with the melting point of 232-
235°C.

1H NMR (300 MHz, DMSO-d6) 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-d6) 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. C20H15F1N4O2,
General procedure for oxolinic-amino acid conjugates (25-40):

A mixture of 7-(1H-benzo[d][1,2,3]triazole-1-carbonyl)-5-ethyl-[1,3]dioxolo[4,5-g]quinolin-8(5H)-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. 296-298ºC. ¹H NMR (300 MHz, DMSO-d₆) 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-d₆) 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. C₁₅H₁₃N₂O₆. 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 ºC. ¹H NMR (300 MHz, DMSO-d₆) 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-d₆) 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 ºC. ¹H NMR (300 MHz, DMSO-d₆) 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-d₆) 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. C_{16}H_{16}N_{2}O_{6}, Calculated: C, 57.83; H, 4.85; N, 8.43, Found: C, 57.53; H, 4.92; N, 8.46.

(5)-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-d$_6$) 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-d$_6$) 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. C$_{22}$H$_{20}$N$_2$O$_6$, 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 ºC. ^1H NMR (300 MHz, DMSO-d$_6$) 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), 10.49 (d, J = 7.8 Hz, 1H). ^13C NMR (75 MHz, DMSO-d$_6$) 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. C$_{22}$H$_{20}$N$_2$O$_6$, 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-d$_6$) 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-d$_6$) 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. C$_{19}$H$_{22}$N$_2$O$_6$, Calculated: C, 60.95; H, 5.92; N, 7.48, Found: C, 60.67; H, 5.86; N, 7.14.

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

173 mg, 92%, mp. 225-228ºC. $^1$H 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). $^{13}$C 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. C$_{19}$H$_{22}$N$_2$O$_6$, 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-[(1H-indol-3-yl)propanoate (33):

162 mg, 72%, mp. 167-171 ºC. $^1$H 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). $^{13}$C 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. C$_{24}$H$_{21}$N$_3$O$_6$·H$_2$O, 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 ºC. $^1$H 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). $^{13}$C 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. C\textsubscript{16}H\textsubscript{16}N\textsubscript{2}O\textsubscript{7}, 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. \textsuperscript{1}H NMR (300 MHz, DMSO-\textsubscript{d}6) δ: 1.38 (t, \textit{J} = 7.2 Hz, 3H), 2.30 (t, \textit{J} = 8.4 Hz, 1H), 3.02-3.06 (m, 2H), 4.48 (q, \textit{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, \textit{J} = 7.4 Hz, 1H). \textsuperscript{13}C NMR (75 MHz, DMSO-\textsubscript{d}6) 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. C\textsubscript{16}H\textsubscript{16}N\textsubscript{2}O\textsubscript{7}S·\textsubscript{1/2}H\textsubscript{2}O, 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. \textsuperscript{1}H NMR (300 MHz, DMSO-\textsubscript{d}6) δ: 1.36 (t, \textit{J} = 7.2 Hz, 3H), 2.73-2.89 (m, 2H), 4.43 (q, \textit{J} = 7.2 Hz, 2H), 4.81 (m, 1H), 6.23 (s, 2H), 7.46 (s, 1H), 7.61 (s, 1H), 10.62 (d, \textit{J} = 7.8 Hz, 1H). \textsuperscript{13}C NMR (75 MHz, DMSO-\textsubscript{d}6) 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. C\textsubscript{17}H\textsubscript{18}N\textsubscript{2}O\textsubscript{8}, 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. \textsuperscript{1}H NMR (300 MHz, DMSO-\textsubscript{d}6) δ: 0.95 (d, \textit{J} = 6.6 Hz, 6H), 1.35 (t, \textit{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, \textit{J} = 8.5 Hz, 1H). \textsuperscript{13}C NMR (75 MHz, DMSO-\textsubscript{d}6) 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. C\textsubscript{18}H\textsubscript{20}N\textsubscript{2}O\textsubscript{6}H\textsubscript{2}O, 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. \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\): 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), 9.24 (s, 1H), 10.43 (d, \(J = 7.4\) Hz, 1H). \(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)) \(\delta\): 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, 172.9, 174.0. 

\(\text{C}_{22}\text{H}_{20}\text{N}_2\text{O}_7\cdot1.5\text{H}_2\text{O},\) Calculated: C, 58.53; H, 5.14; N, 6.21; Found: C, 58.66; H, 4.88; N, 5.91.

(2S,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. \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\): 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), 7.54 (s, 2H), 10.64 (d, \(J = 7.7\) Hz, 2H). \(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)) \(\delta\): 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. \(\text{C}_{32}\text{H}_{30}\text{N}_4\text{O}_{12}\text{S}_2\cdot\text{H}_2\text{O},\) 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. \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\): 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). \(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)) \(\delta\): 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. \(\text{C}_{17}\text{H}_{17}\text{N}_3\text{O}_7\), 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-(1H-Benzod[1,2,3]triazole-1-carbonyl)-1-ethyl-7-methyl-1,8-naphthyridin-4(1H)-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. $^1$H 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). $^{13}$C 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. C$_{14}$H$_{15}$N$_3$O$_4$, Calculated: C, 58.13; H, 5.23; N, 14.53, Found: C, 58.44; H, 5.18; N, 14.53.

(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. $^1$H 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). $^{13}$C 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. C$_{15}$H$_{17}$N$_3$O$_4$·H$_2$O. 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. $^1$H 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). $^{13}$C 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. C_{15}H_{17}N_{3}O_{4} 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. \(^1^H\) NMR (300 MHz, DMSO-d\(_6\)) \(\delta\): 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). \(^{13}\)C NMR (75 MHz, DMSO-d\(_6\)) \(\delta\): 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. C\(_{21}\)H\(_{21}\)N\(_3\)O\(_4\), 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. \(^1^H\) NMR (300 MHz, DMSO-d\(_6\)) \(\delta\): 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). \(^{13}\)C NMR (75 MHz, DMSO-d\(_6\)) \(\delta\): 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. C\(_{17}\)H\(_{21}\)N\(_3\)O\(_4\)S, 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. \(^1^H\) NMR (300 MHz, DMSO-d\(_6\)) \(\delta\): 0.90-0.94 (m, 6H), 1.37 (t, \(J = 6.6\) Hz, 3H), 1.65-1.67 (m, 3H), 2.64 (s, 3H), 4.53-455 (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). \(^{13}\)C NMR (75 MHz, DMSO-d\(_6\)) \(\delta\): 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. 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. $^1$H NMR (300 MHz, DMSO-d$_6$) 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). $^{13}$C NMR (75 MHz, DMSO-d$_6$) 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. Calculated: C, 62.59; H, 6.71; N, 12.17. Found: C, 62.59; H, 6.71; N, 12.17.

(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. $^1$H NMR (300 MHz, DMSO-d$_6$) 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). $^{13}$C NMR (75 MHz, DMSO-d$_6$) 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. 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. $^1$H NMR (300 MHz, DMSO-d$_6$) 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 Hz, 1H), 8.97 (s, 1H), 10.28 (d, $J$ = 8.4 Hz, 1H). $^{13}$C NMR (75 MHz, DMSO-d$_6$) 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. 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. $^1$H NMR (300 MHz, DMSO-$d_6$) 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). $^{13}$C NMR (75 MHz, DMSO-$d_6$) 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. C$_{21}$H$_{21}$N$_3$O$_5$·H$_2$O, 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. $^1$H NMR (300 MHz, DMSO-$d_6$) 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). $^{13}$C NMR (75 MHz, DMSO-$d_6$) 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. C$_{16}$H$_{18}$N$_4$O$_5$, 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-(1H-benzo[d][1,2,3]triazole-1-carbonyl)-1-ethyl-[1,3]dioxolo[4,5-g]cinnolin-4(1H)-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. $^1$H 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). $^{13}$C 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. C$_{15}$H$_{17}$N$_3$O$_7$·H$_2$O, 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. $^1$H 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). $^{13}$C 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. C$_{21}$H$_{19}$N$_3$O$_6$, 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. $^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$: 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). $^{13}$C NMR (75 MHz, DMSO-d$_6$) $\delta$: 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. C$_{23}$H$_{22}$N$_4$O$_7$·H$_2$O 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-(1H-Benzod[1,2,3]triazole-1-carbonyl)-9-fluoro-5-methyl-6,7-dihydropyrido[3,2,1-ij]quinolin-1(5H)-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. $^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$: 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). $^{13}$C NMR (75 MHz, DMSO-d$_6$) $\delta$: 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. C\textsubscript{23}H\textsubscript{21}FN\textsubscript{2}O\textsubscript{4}, Calculated: C, 67.64; H, 5.18; N, 6.86, Found: C, 67.38; H, 5.18; N, 6.81.

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

75 mg, 56%, mp. 202-203°C. \textsuperscript{1}H NMR (300 MHz, DMSO-d\textsubscript{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). \textsuperscript{13}C NMR (75 MHz, DMSO-d\textsubscript{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. C\textsubscript{25}H\textsubscript{22}FN\textsubscript{3}O\textsubscript{4}·H\textsubscript{2}O, Calculated: C, 64.51; H, 5.20; N, 9.03, Found: C, 64.44; H, 5.13; N, 8.84.