

Supporting Information

for

Cyclopropanation–ring expansion of 3-chloroindoles with α-halodiazoacetates: novel synthesis of 4-quinolone-3carboxylic acid and norfloxacin

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Synthetic procedures, spectroscopic data and copies of NMR spectra

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General Information

Solvents and chemicals were used as delivered from Sigma-Aldrich, VWR International AS and AK Scientific, unless stated otherwise. DCM, DMF and acetonitrile were dried using the MB SPS-800 solvent purification system from MBraun. Eluents used during flash chromatography were of technical grade. Technical grade hexane was distilled before used. NMR-solvents were used as delivered from Sigma-Aldrich and Cambridge Isotope Laboratories.

N-Chlorosuccinimide and N-bromosuccinimide were recrystallized before use.

Ethyl diazoacetate (EDA) – provided by Sigma Aldrich – contained \geq 13 wt % DCM according to the supplier. ¹H NMR analysis of EDA in CDCl₃ gave around 9 wt % DCM. In all reactions where EDA is used as reactant, the 9 wt % DCM was taken into account when calculating the yields.

Thin layer chromatography (TLC) was performed on 60 F254 silica coated alumina plates from Merck. Flash Chromatography was performed on silica gel from Merck (Silicagel 60, 40–0.60 μ m, 460–520 m²/g, pH 6.5–7.5) either manually or with an Isco Inc. CombiFlash Companion with PeakTrack software (v.1.4.10).

¹H, ¹³C and ¹⁹F NMR experiments were recorded in CDCl₃, methanol- d_4 , acetone- d_6 , TFA-d, DMSO- d_6 or acetonitrile- d_3 using either a Bruker Avance DPX200, DPX300, AVII400, AVIII400, DRX500 or AVII600 instrument with residual peaks as references (CDCl₃: 7.24 ppm/77.0 ppm, methanol- d_4 : 3.31 ppm/49.15 ppm, acetone- d_6 : 2.05 ppm/206.7 ppm, CF₃COOD: 11.5 ppm/164.2 ppm, DMSO- d_6 : 2.50 ppm/39.5 ppm or acetonitrile- d_3 : 1.94 ppm/118.7 ppm). Chemical shifts (δ) are given in parts per million (ppm) and coupling constants (J) are given in Hertz (Hz). Multiplicities are abbreviated as: s – singlet; bs – broad singlet; d – doublet; t – triplet; q – quartet; dd – doublet of doublets; dd – doublet of triplets; m – multiplet.

For new compounds, DEPT135, COSY and HSQC were recorded to assign ¹H and ¹³C-shift.

Mass spectra were obtained on Bruker Daltonik GmbH MAXIS II ETD (ESI) and SCION-TQ (EI) spectrometer by Osamu Sekiguchi. Melting points were measured on Büchi B-545-melting point instrument.

Synthetic procedures and spectroscopic data

CI-EDA and Br-EDA were synthesized from EDA according to a literature procedure.¹ We performed quantitative ¹H-NMR measurements and found the average yields of CI-EDA and Br-EDA to be 94%.

3-Cl-indole and 3-Cl-6,7-difluoro-indole were synthesized from commercially available indole and 6,7difluoro-indole according to a literature procedure.²

General procedure for the synthesis of ethyl 4-chloroquinoline-3-carboxylates from X-EDA and 3-chlororindoles.

X-EDA was synthesized according to a literature procedure.¹ This gave X-EDA in a cooled DCM solution (between 1.0 and 1.5 eqiuv). When desired, the solvent was swopped from DCM to toluene at 0 °C. The cooled X-EDA solution was transferred to an ice-cooled addition funnel (0 °C) and added slowly dropwise to a stirring solution of the desired 3-Cl-indole (1.0 equiv), Cs_2CO_3 (1.3 equiv) and $Rh_2(esp)_2$ (0.01 equiv) in DCM or toluene at ambient temperature. Upon addition, the solution color changed from green/purple to orange/brown. Addition time was around 30–60 min. After all X-EDA was added, the solution was stirred for 30 min. before the solvent was evaporated in vacuo. The crude product was dissolved in 30 mL EtOAc and washed with 3 mL H₂O and 3 mL saturated NaCl solution. The organic phase was dried with MgSO₄, filtered and the solvent evaporated in vacuo. The residue was purified using silica gel column chromatography.

General procedure for alcoholysis of ethyl 4-chloroquinoline-3-carboxylates to ethyl 4(1*H*)-oxoquinolone-3-carboxylates.³

To the desired ethyl 4-chloro-quinoline-3-carboxylate derivative (1 - 2 mmol) was added 5 mL dry ethanol. This solution was refluxed for 24 h or monitored by TLC analysis. The reaction mixture was cooled after the starting material was fully consumed (judged by TLC) and gave a white precipitation. The white solid was centrifuged, the liquid carefully removed and the solid was washed with EtOAc and centrifuged 2–3 times to leave a pure off-white solid.

General procedure for hydrolysis of ethyl 4-oxoquinolone-3-carboxylates to 4-oxoquinolone-3-carboxylic acids.

The ethyl 4(1*H*)-oxo-quinolone-3-carboxylate (1–2 mmol) was dissolved in 5 mL MeOH. LiOH·H₂O (3.0 equiv), dissolved in 1–2 mL H₂O, was added to the reaction mixture. The reaction mixture was stirred at ambient temperature overnight or monitored by TLC analysis. After the starting material was fully consumed (judged by TLC-analysis), the reaction volume was reduced to one third of its initial volume. The solution was acidified to pH 2–3 (pH-paper) with 1 M HCl. The resulting white solution was centrifuged and the liquid carefully removed. The remaining solid was washed with water and centrifuged twice, leaving a pure off-white solid.

Synthesis of ethyl 4-chloroquinoline-3-carboxylate (4)



Ethyl 4-chloroquinoline-3-carboxylate (4) was synthesized according to the general procedure.

Yield: 52% with Br-EDA; 50% with Cl-EDA.

TLC (silica plates; eluent EtOAc:DCM:Hexane 1:8:1): R_f = 0.42

¹**H NMR** (400 MHz, CDCl₃): δ 9.15 ppm (s, 1H, H-2), 8.33 ppm (dd, *J* = 1.5 Hz; 1.3 Hz, 1H, H-5), 8.03 - 8.12 ppm (m, 1H, H-8), 7.78 ppm (ddd, *J* = 8.4 Hz; 6.9 Hz; 1.4 Hz, 1H, H-6), 7.63 ppm (ddd, *J* = 8.4 Hz; 6.9 Hz; 1.3 Hz, 1H, H-7), 4.45 ppm (q, *J* = 7.2 Hz, 2H, H-10), 1.42 ppm (t, *J* = 7.1 Hz, 3H, H-11)

¹³**C NMR** (100 MHz, CDCl₃): δ 164.4 ppm (C-9), 149.9 ppm (C-4), 149.4 ppm (C-8a), 143.3 ppm (C-2), 131.7 ppm (C-7), 129.7 ppm (C-8), 128.2 ppm (C-6), 126.0 ppm (C-5), 125.3 ppm (C-4a), 122.8 ppm (C-3), 61.9 ppm (C-10), 14.2 ppm (C-11)

MS (EI, Methanol); m/z (relative intensity): 235 (*M*⁺, 44%), 237 (*M*⁺ + 2), 207 (35%), 209 (11%), 190 (100%), 192 (35%), 162 (41%), 164 (14%), 127 (19%)

HR-MS (ESI, Methanol): 258.0293 [M + Na⁺]; calculated value for C₁₂C₁₀ClNNaO₂: 258.0292 (Δ -0.2 ppm); 260.0264 [M + Na⁺ + 2]

Melting point: literature value: 46 – 47 °C; experimental value: 40 – 43 °C.

The compound is reported in literature.⁴

Synthesis of ethyl 4-oxo-1,4-dihydroquinoline-3-carboxylate (6)



Ethyl 4-oxo-1,4-dihydroquinoline-3-carboxylate (6) was synthesized according to the general procedure.

Yield: 65%

TLC (silica plates; eluent EtOAc:DCM:Hexane 1:8:1): R_{f (Substrate)} = 0.42; R_{f (Product)} = 0

¹**H NMR** (400 MHz, DMSO-*d*₆): δ 12.29 ppm (s, 1H, H-1), 8.53 ppm (s, 1H, H-2), 8.14 ppm (dd, *J* = 8.1 Hz; 1.5 Hz, 1H, H-5), 7.70 ppm (ddd, *J* = 8.4 Hz; 7.0 Hz; 1.6 Hz, 1H, H-7), 7.60 ppm (d, *J* = 7.1 Hz, 1H, H-

8), 7.40 ppm (ddd, *J* = 8.1 Hz; 7.0 Hz; 1.2 Hz, 1H, H-6), 4.20 ppm (q, *J* = 7.1 Hz, 2H, H-10), 1.27 ppm (t, *J* = 7.1 Hz, 3H, H-11)

¹³**C NMR** (101 MHz, DMSO-*d*₆): δ 173.4 ppm (C-4), 164.8 ppm (C-9),144.8 ppm (C-2), 138.9 ppm (C-8a), 132.4 ppm (C-7), 127.2 ppm (C-4a), 125.6 ppm (C-5), 124.6 ppm (C-6), 118.7 ppm (C-8), 109.8 ppm (C-3), 59.5 ppm (C-10), 14.3 ppm (C-11)

MS (ESI, Water); m/z (relative intensity): 240 (*M* + Na⁺, 100%), 218 (*M*⁺, 7%)

HR-MS (ESI, Water): 240.0631 [*M* + Na⁺]; calculated value for C₁₂H₁₁NNaO₃: 240.0631 (Δ -0.1 ppm)

The compound is reported in literature.⁵

Synthesis of 4-oxo-1,4-dihydroquinoline-3-carboxylic acid (7)



4-Oxo-1,4-dihydroquinoline-3-carboxylic (**7**) acid was synthesized according to the general procedure.

Yield: 87 %

TLC (silica plates; eluent EtOAc): R_{f (Product)} = 0

¹**H NMR** (400 MHz, DMSO-*d*₆): δ 15.34 ppm (s, 1H, H-10), 13.42 ppm (s, 1H, H-1), 8.90 ppm (s, 1H, H-2), 8.30 ppm (dd, *J* = 8.2 Hz; 1.4 Hz, 1H, H-5), 7.89 ppm (ddd, *J* = 8.4 Hz; 6.9 Hz; 1.5 Hz, 1H, H-7), 7.82 ppm (dd, *J* = 8.5 Hz; 1.2 Hz, 1H, H-8), 7.61 ppm (ddd, *J* = 8.2 Hz; 6.9 Hz; 1.2 Hz, 1H, H-6)

¹³**C NMR** (101 MHz, DMSO-*d₆*): δ 178.3 ppm (C-4), 166.4 ppm (C-9), 145.2 ppm (C-2), 139.5 ppm (C-8a), 133.9 ppm (C-7), 126.2 ppm (C-6), 125.0 ppm (C-5), 124.4 pp m (C-4a), 119.7 ppm (C-8), 107.6 ppm (C-3)

MS (EI, Water); m/z (relative intensity): 145 (100%), 117 (72%), 90 (39%)

HR-MS (ESI, Water): 212.0317 [*M* + Na⁺]; calculated value for C₁₀H₇NNaO₃: 212.0318 (Δ 0.3 ppm)

This compound is reported in literature.⁶

Synthesis of 3-chloro-5,6-difluoro-1H-indole (8)



3-Chloro-5,6-difluoro-1*H*-indole (8) was synthesized according to the general procedure

Yield: 87%

TLC (silica plates; eluent pure DCM): $R_{f(5,6-difluoroindole)} = 0.64$ (pink spot); $R_{f(Product)} = 0.64$ (green spot) when developed in 5% H₂SO₄/MeOH

¹**H NMR** (400 MHz, CDCl₃): δ 8.04 ppm (s, 1H, H-1), 7.35 ppm (dd, *J* = 10.1 Hz; 7.6 Hz, 1H, H-4), 7.18 ppm (d, *J* = 2.6 Hz, 1H, H-2), 7.14 ppm (dd, *J* = 10.3 Hz; 6.4 Hz, 1H, H-7)

¹³**C NMR** (101 MHz, CDCl₃): δ 148.8 ppm (dd, *J* = 243.4 Hz; 16.0 Hz, C-F, C-5), 147.1 ppm (dd, *J* = 237.4 Hz; 15.1 Hz, C-F, C-6), 129.7 ppm (d, *J* = 10.6 Hz, C, C-7a), 122.1 ppm (d, *J* = 3.9 Hz, CH, C-2), 120.9 ppm (dd, *J* = 8.6 Hz; 1.4 Hz, C, C-3a), 106.7 ppm (dd, *J* = 4.6 Hz; 1.9 Hz, C, C-3), 105.2 ppm (dd, *J* = 20.5 Hz; 1.4 Hz, CH, C-4), 99.6 ppm (d, *J* = 22.2 Hz, CH, C-7)

¹⁹**F NMR** (376 MHz, CDCl₃, decoupled ¹H): δ -141.9 ppm (d, *J* = 20.4 Hz, F-6), -145.6 ppm (d, *J* = 20.4 Hz, F-5)

¹⁹**F NMR** (376 MHz, CDCl₃, coupled ¹H): δ -141.9 ppm (ddd, *J* = 20.5 Hz; 10.2 Hz; 7.5 Hz, F-6), -145.6 ppm (ddd, *J* = 20.6 Hz; 10.1 Hz; 6.3 Hz, F-5)

MS (EI, Methanol); m/z (relative intensity): 187 (M⁺, 100%), 189 (M⁺+2, 33%), 152 (31%), 125 (51 %)

HR-MS (ESI, Methanol): 186.9995 [M^+]; calculated value for C₈H₄ClF₂N: 186.9995 (Δ -0.3 ppm)

Melting point: 77 – 80 °C.

Synthesis of ethyl 4-chloro-6,7-difluoroquinoline-3-carboxylate (9)



Ethyl 4-chloro-6,7-difluoroquinoline-3-carboxylate (9) was synthesized according to the general procedure.

Yield: 75% (with CI-EDA in toluene)

TLC (silica plates; eluent EtOAc:DCM:Hexane 1:8:1): R_{f (Substrate)} = 0.65; R_{f (Product)} = 0.47

¹**H NMR** (400 MHz, CDCl₃): δ 9.15 ppm (s, 1H, H-2), 8.13 ppm (dd, *J* = 10.9 Hz; 8.3 Hz, 1H, H-5), 7.87 ppm (dd, *J* = 10.5 Hz; 7.6 Hz, 1H, H-8), 4.48 ppm (q, *J* = 7.2 Hz, 2H, H-10), 1.44 ppm (t, *J* = 7.1 Hz, 3H, H-11)

¹³**C HMR** (101 MHz, CDCl₃): δ 164.0 ppm (s, C=O, C-9), 153.7 ppm (dd, *J* = 260.5 Hz; 16.0 Hz, C-F, C-6), 151.1 ppm (dd, *J* = 256.3 Hz; 15.7 Hz, C-F, C-7), 150.7 ppm (d, *J* = 2.9 Hz, CH, C-2), 146.9 ppm (dd, *J* = 11.2 Hz; 1.4 Hz, C, C-8a), 142.5 ppm (dd, *J* = 5.6 Hz; 2.2 Hz, C, C-4a), 123.7 ppm (d, *J* = 7.6 Hz, C, C-4), 123.2 ppm (d, *J* = 2.6 Hz, C, C-3), 116.3 ppm (dd, *J* = 17.0 Hz; 1.6 Hz, CH, C-8), 111.7 ppm (dd, *J* = 20.6 Hz; 2.0 Hz, CH, C-5), 62.3 ppm (s, CH₂, C-10), 14.2 ppm (s, CH₃, C-11)

¹⁹**F NMR** (377 MHz, CDCl₃, coupled to ¹H): δ -127.4 ppm (ddd, *J* = 21.0 Hz; 10.7 Hz; 8.2 Hz, F-7), -131.3 ppm (ddd, *J* = 21.1 Hz; 10.9 Hz; 7.5 Hz, F-6)

¹⁹**F NMR** (377 MHz, CDCl₃, decoupled to ¹H): δ -127.4 ppm (d, *J* = 21.0 Hz, F-7), -131.3 ppm (d, *J* = 21.1 Hz, F-6)

MS (EI, Methanol); m/z (relative intensity): 271 (*M*⁺, 28%), 273 (*M*⁺+2, 9%), 243 (39%), 245 (13%), 226 (100%), 228 (33%), 198 (48%), 200 (17%)

HR-MS (ESI, Methanol): 294.0104 [M + Na⁺]; calculated value for C₁₂H₈ClF₂NNaO₂: 294.0104 (Δ -0.1 ppm)

Melting point: 109 – 111 °C. No literature value reported.

This compound is reported in literature.⁷

Synthesis of ethyl 6,7-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate (10)



Ethyl 6,7-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate (**10**) was synthesized according to the general procedure.

Yield: 90%

TLC (silica plates; eluent EtOAc:Hexane 1:1): R_{f (Substrate)} = 0.56; R_{f (Product)} = 0

¹**H NMR** (300 MHz, CF₃COOD): δ 9.70 ppm (s, 1H, H-2), 8.78 ppm (dd, *J* = 9.1 Hz; 7.6 Hz, 1H, H-5), 8.39 ppm (dd, *J* = 9.1 Hz; 6.3 Hz, 1H, H-8), 5.06 ppm (q, *J* = 7.2 Hz, 2H, H-10), 1.90 ppm (t, *J* = 7.2 Hz, 3H, H-11)

¹³**C NMR** (101 MHz, CF₃COOD): δ 175.1 ppm (d, *J* = 4.2 Hz, C=O, C-4), 169.7 ppm (s, C=O, C-9), 160.1 ppm (dd, *J* = 271.7 Hz; 15.8 Hz, C-F, C-6), 154.8 ppm (dd, *J* = 263.6 Hz; 14.5 Hz, C-F, C-7), 148.1 ppm (s, CH, C-2), 139.9 ppm (d, *J* = 11.7 Hz, C, C-8a), 120,0 ppm (dd, *J* = 8.2 Hz; 1.7 Hz, C, C-4a), 114.5 ppm (dd, *J* = 20.9 Hz; 2.9 Hz, CH, C-5), 111.0 ppm (d, *J* = 22.5 Hz, CH, C-8), 107.7 ppm (s, C, C-3), 67.5 ppm (s, CH₂, C-10), 14.6 ppm (s, CH₃, C-11)

¹⁹**F NMR** (377 MHz, CF₃COOD, coupled to ¹H): δ -114.1 ppm (dd, *J* = 18.7 Hz; 8.9 Hz, F-6), -126.6 ppm (dt, *J* = 16.8 Hz; 7.6 Hz, F-7)

¹⁹**F NMR** (377 MHz, CF₃COOD, coupled to ¹H): δ -114.1 ppm (d, *J* = 19.2 Hz, F-6), -126.6 ppm (d, *J* = 19.5 Hz, F-7)

MS (EI, Methanol); m/z (relative intensity): 253 (M⁺, 30%), 208 (17%), 107 (100%), 180 (14%)

HR-MS (ESI, Methanol): 276.0443 [M + Na⁺]; calculated value for C₁₂H₉F₂NNaO₃: 276.0443 (Δ -0.2 ppm)

Melting point: The compound decomposes at 255 °C. No literature value reported.

This compound is reported in literature.⁸

Synthesis of ethyl 1-ethyl-6,7-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate⁹



Ethyl 6,7-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate (501.6 mg; 1.98 mmol; 1.0 equiv), K_2CO_3 (429.7 mg; 3.11 mmol; 1.6 equiv) and CH_3CH_2I (210 µL; 2.63 mmol; 1.33 equiv) were suspended in 7 mL dry DMF and the solution was heated at 90 °C for 24 h. The solution prior to heating was foggy white, after reflux transparent. 10 mL brine and 4 mL H₂O were added to the cold solution and the product was extracted with 4 x 10 mL EtOAc. The collected organic phases were washed with 4 x 10 mL brine and 2 x 10 mL H₂O, dried with Na₂SO₄ and evaporated in vacuo. The product was purified with flash chromatography on a silica plug with gradient elution from EtOAc:hexane (1:1) to pure EtOAc. This gave a white solid, 472.7 mg (1.68 mmol).

Yield: 85%

TLC (silica plates; eluent pure EtOAc): R_{f (Substrate)} = 0; R_{f (Product)} = 0.21

¹**H NMR** (400 MHz, CDCl₃): δ 8.47 ppm (s, 1H, H-2), 8.30 ppm (dd, *J* = 10.5 Hz; 8.8 Hz, 1H, H-5), 7.24 ppm (dd, *J* = 10.4 Hz; 6.3 Hz, 1H, H-8), 4.38 ppm (q, *J* = 7.1 Hz, 2H, H-10), 4.18 ppm (q, *J* = 7.3 Hz, 2H, H-12), 1.53 ppm (t, *J* = 7.3 Hz, 3H, H-13), 1.39 ppm (t, *J* = 7.1 Hz, 3H, H-11)

¹³**C NMR** (101 MHz, CDCl₃): δ 172.6 ppm (s, C=O, C-4), 165.5 ppm (s, C=O, C-9), 153.5 ppm (dd, *J* = 256 Hz; 15.3 Hz, C-F, C-7), 148.4 ppm (dd, *J* = 252 Hz; 13.3 Hz, C-F, C-6), 148.7 ppm (s, CH, C-2), 135.6 ppm (dd, *J* = 9.2 Hz; 1.9 Hz, C, C-8a), 126.7 ppm (dd, *J* = 4.8 Hz; 2.1 Hz, C, C-4a), 115.9 ppm (dd, *J* = 18.6 Hz; 2.5 Hz, CH, C-5), 111.2 ppm (s, C, C-3), 104.5 ppm (d, *J* = 22.5 Hz, CH, C-8), 61.1 ppm (s, CH₂, C-10), 49.3 ppm (s, CH₂, C-12), 14.4 ppm (s, CH₃, C-11), 14.3 ppm (s, CH₃, C-13)

¹⁹**F NMR** (376 MHz, CDCl₃, coupled to ¹H): δ (-127.3) – (-127.5) ppm (m, F-7), -138.7 ppm (ddd, J = 22.2 Hz; 10.3 Hz; 6.1 Hz, F-6)

¹⁹**F NMR** (376 MHz, CDCl₃, decoupled to ¹H): δ -127.4 ppm (d, *J* = 22.2 Hz, F-7), -138.7 ppm (d, *J* = 22.2 Hz, F-6)

MS (EI, Acetonitrile); m/z (relative intensity): 281 (*M*⁺, 6%), 236 (23%), 209 (100%), 208 (14%), 194 (34%)

HR-MS (ESI, Acetonitrile): 304.0755 [M + Na⁺]; calculated value for C₁₄H₁₃F₂NNaO₃: 304.0767 (Δ 0.2 ppm)

Melting point: Literature value: 154 - 155 °C; Experimental value: 149 - 153 °C

This compound is reported in literature.¹⁰

Synthesis of ethyl 1-ethyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate from piperazine and ethyl 6,7-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate



Ethyl 1-ethyl-6,7-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate (42.9 mg; 0.15 mmol; 1.0 equiv) and piperazine (60.6 mg; 0.70 mmol; 4.6 equiv) were dissolved in 1.0 mL MeCN, which gave an orange solution. The reaction was refluxed overnight (27 h), the solution cooled and the solvent was evaporated in vacuo to gave an off-white solid. Both ¹H and ¹⁹F NMR analysis indicated full conversion. Even though this reaction provided the desired target molecule, we found the purification and isolation difficult due to solubility and chromatographic complications. Hence, the yield was measured by internal standard (IS) using ¹H NMR.

Yield: 98% (IS)

TLC (silica plates; eluent pure EtOAc): R_{f (Substrate)} = 0.21; R_{f (Product)} = 0

¹**H NMR** (400 MHz, CDCl₃): δ 8.25 ppm (s, 1H, H-2), 7.88 ppm (d, *J* = 13.4 Hz, 1H, H-5), 6.61 ppm (d, *J* = 6.9 Hz, 1H, H-8), 4.25 ppm (q, *J* = 7.1 Hz, 2H, H-10), 4.09 ppm (q, *J* = 7.2 Hz, 2H, H-12), 3.10 ppm (dd, *J* = 6.3Hz; 3.4 Hz, 4H, H-14), 2.97 ppm (dd, *J* = 6.3 Hz; 3.5 Hz, 4H, H-15), 1.90 ppm (s, 1H, H-16), 1.42 ppm (t, *J* = 7.2 Hz, 3H, H-13), 1.29 ppm (t, *J* = 7.1 Hz, 3H, H-11)

¹³**C NMR** (101 MHz, CDCl₃): δ 172.8 ppm (d, *J* = 2.2 Hz, C=O, C-4), 165.4 ppm (s, C=O, C-9), 152.9 ppm (d, *J* = 248.7 Hz, C-F, C-6), 147.6 ppm (s, CH, C-2), 144.9 ppm (d, *J* = 10.6 Hz, C, C-7), 135.8 ppm (d, *J* = 1.3 Hz, C, C-8a), 123.3 ppm (d, *J* = 6.9 Hz, C, C-4a), 113.1 ppm (d, *J* = 23.1 Hz, CH, C-5), 109.9 ppm (s, C, C-3), 103.6 ppm (d, *J* = 3.1 Hz, CH, C-8), 60.5 ppm (s, CH₂, C-10), 51.0 ppm (d, *J* = 4.5 Hz, CH₂, C-14), 48.8 ppm (s, CH₂, C-12), 45.7 ppm (s, CH₂, C-15), 14.2 ppm (s, CH₃, C-11), 14.1 ppm (s, CH₃, C-13)

¹⁹**F NMR** (376 MHz, CDCl₃, coupled to ¹H): δ -123.5 ppm (dd, J = 13.5 Hz; 6.8 Hz, F-6)

¹⁹**F NMR** (376 MHz, CDCl₃, decoupled to ¹H): δ -123.5 ppm (s, F-6)

MS (EI, Water); m/z (relative intensity): 347 (M⁺, 13%), 305 (100%), 302 (6%), 275 (47%)

HR-MS (ESI, Water): 348.1718 [*M* + H⁺]; calculated value for C₁₈H₂₃FN₃O₃: 348.1718 (Δ 0.1 ppm)

The compound is reported in literature.¹¹

Synthesis of ethyl 7-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4dihydroquinoline-3-carboxylate (11)



Ethyl 6,7-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate (101.5 mg; 0.36 mmol; 1.0 equiv), Bocpiperazine (599.0 mg; 3.22 mmol; 8.9 equiv) and K_2CO_3 (153.1 mg; 1.11 mmol; 3.1 equiv) were dissolved in 2.0 mL MeCN and heated to reflux for 3 days. The solvent was evaporated in vacuo and ¹H NMR analysis of the crude products indicated over 95% conversion. The crude mixture was dissolved in 10 mL EtOAc and extracted with water (pH 4–5) until all Boc-piperazine was removed. The residue was purified with flash chromatography on a silica plug with gradient elution from pure EtOAc until 10% MeOH concentration. This gave **11** as an off-white solid 113.8 mg (0.25 mmol).

Yield: 70%

TLC (silica plates; eluent MeOH:EtOAc 1:20): R_{f (Substrate)} = 0.40; R_{f (Product)} = 0.27

¹**H NMR** (400 MHz, Acetone-*d*₆): δ 8.54 ppm (s, 1H, H-2), 7.90 ppm (d, *J* = 13.4 Hz, 1H, H-5), 7.17 ppm (d, *J* = 7.3 Hz, 1H, H-8), 4.47 ppm (q, *J* = 7.2 Hz, 2H, H-10), 4.24 ppm (q, *J* = 7.1 Hz, 2H, H-12), 3.61 ppm

(t, *J* = 5.1 Hz, 4H, H-14), 3.25 ppm (t, *J* = 5.1 Hz, 4H, H-15), 1.52 ppm (t, *J* = 7.2 Hz, 3H, H-11), 1.47 ppm (s, 9H, H-18) 1.30 ppm (t, *J* = 7.1 Hz, 3H, H-13)

¹³**C NMR** (101 MHz, Acetone-*d*₆): δ 172.5 ppm (d, *J* = 2.0 Hz, C=O, C-4), 165.7 ppm (s, C=O, C-9), 153.8 ppm (d, *J* = 247.1 Hz, C-F, C-6), 154.9 ppm (s, C=O, C-16), 149.2 ppm (s, CH, C-2), 145.3 ppm (d, *J* = 10.6 Hz, C, C-7), 137.3 ppm (s, C, C-8a), 124.5 ppm (dd, *J* = 6.2 Hz; 1.7 Hz, C, C-4a), 113.1 ppm (d, *J* = 22.8 Hz, CH, C-5), 111.0 ppm (s, C, C-3), 106.6 ppm (d, *J* = 2.2 Hz, CH, C-8), 79.9 ppm (s, C, C-17), 60.4 ppm (s, CH₂, C-12), 50.8 ppm (d, *J* = 4.0 Hz, CH₂, C-15), 49.3 ppm (s, CH₂, C-10), 44.3 ppm (d, *J* = 97.0 Hz, CH₂, C-14), 28.5 ppm (s, CH₃, C-18), 14.7 ppm (s, CH₃, C-11), 14.6 ppm (s, CH₃, C-13)

¹⁹**F NMR** (377 MHz, Acetone-*d*₆, coupled to ¹H): δ -126.3 ppm (dd, *J* = 13.5 Hz; 7.2 Hz, F-6)

¹⁹**F NMR** (377 MHz, Acetone- d_6 , decoupled to ¹H): δ -126.3 ppm (s, F-6)

MS (EI, Methanol); m/z (relative intensity): 347 (13 %), 346 (1 %), 305 (100 %), 302 (6%), 275 (47 %)

HR-MS (ESI, Methanol): 470.2061 [*M* + Na⁺]; calculated value for C₂₃H₃₀FN₃NaO₅: 470.2062 (Δ 0.1 ppm)

Melting point: Experimental value: 149-153 °C.

This compound is not reported in literature.

Synthesis of 7-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid



7-(4-(*tert*-Butoxycarbonyl)piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid was synthesized according to the general procedure. The ester substrate **11** (39.3 mg; 0.09 mmol; 1.0 equiv) and LiOH·H₂O (14.1 mg; 0.34 mmol; 3.8 equiv) in MeOH/H₂O gave 35.4 mg (0.08 mmol) of the carboxylic acid as white/yellow solid.

Yield: 96%

TLC (silica plates; eluent MeOH:EtOAc 1:20): R_{f (Substrate)} = 0.33 R_{f (Product)} = 0.09

¹**H NMR** (500 MHz, CDCl₃): δ 14.99 ppm (s, 1H, H-10), 8.67 ppm (s, 1H, H-2), 8.09 ppm (d, *J* = 12.9 Hz, 1H, H-5), 6.82 ppm (d, *J* = 6.9 Hz, 1H, H-8), 4.30 ppm (q, *J* = 7.3 Hz, 2H, H-11), 3.65 ppm (t, *J* = 4.9 Hz, 4H, H-13), 3.25 ppm (t, *J* = 5.1 Hz, 4H, H-14), 1.58 ppm (t, *J* = 7.3 Hz, 3H, H-12), 1.48 ppm (s, 9H, H-17)

¹³**C NMR** (101 MHz, CDCl₃): δ 176.9 ppm (s, C=O, C-4), 167.1 ppm (s, C=O, C-9), 153.5 ppm (d, *J* = 252.4 Hz, C-F, C-6), 154.5 ppm (s, C=O, C-15), 147.2 ppm (s, CH, C-2), 145.9 ppm (d, *J* = 10.6 Hz, C, C-7), 137.0 ppm (s, C, C-8a), 120.9 ppm (d, *J* = 7.8 Hz, C, C-4a), 112.9 ppm (d, *J* = 23.2 Hz, CH, C-5), 108.4 ppm (s, C, C-3), 104.0 ppm (d, *J* = 3.1 Hz, CH, C-8), 80.3 ppm (s, C, C-16), 49.8 ppm (s, CH₂, C-11 and C-14), 43.3 ppm (d, *J* = 82.0 Hz, CH₂, C-13), 28.4 ppm (s, CH₃, C-17), 14.5 ppm (s, CH₃, C-12)

¹⁹**F NMR** (376 MHz, CDCl₃, coupled to ¹H): δ -120.9 ppm (dd, *J* = 12.9 Hz; 6.8 Hz, F-6)

¹⁹F NMR (376 MHz, CDCl₃, decoupled to ¹H): δ -120.9 ppm (s, F-6)

MS (ESI, Methanol); m/z (relative intensity): 456 (100%), 442 (M + Na⁺, 98%), 413 (40%),

185 (10%)

HR-MS (ESI, Methanol): 442.1749 [M + Na⁺]; calculated value for C₂₁H₂₆FN₃NaO₅:

442.1749 (Δ = -0.0 ppm)

This compound is not reported in literature.

Synthesis of 4-(3-carboxy-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinolin-7-yl)piperazin-1-ium chloride – norfloxacin hydrochloride (12)



7-(4-(tert-Butoxycarbonyl)piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (23.1 mg; 0.05 mmol; 1.0 equiv) was dissolved in 2.5 mL dry DCM and gave a foggy pale-yellow solution. TFA (0.2 mL; 2.61 mmol; 47.49 equiv) was added to the solution and gave immediate color change to yellow. The reaction was stirred overnight at ambient temperature and the solvent removed *in vacuo*. Adding a small amount of methanol- d_4 for NMR analysis gave white/brown precipitation. ¹⁹F NMR analysis of the precipitate solution indicated full conversion to the trifluoroacetate salt of norfloxacin. It showed two ¹⁹F NMR peaks – one peak belonging to F-6 and one to trifluoroacetate counter ion. To the crude product dissolved in 2 mL H₂O, was added 2 mL 1 M HCl. The solvent was thereafter evaporated in vacuo. This was done a second time to ensure that most of the TFA was removed from the sample. This gave **12** as a white/yellow solid, 18.2 mg (0.05 mmol). ¹H and ¹⁹F NMR analysis indicated full conversion.

Yield: 99%

TLC (silica plates; eluent EtOAc): R_{f (Product)} = 0

¹**H NMR** (400 MHz, DMSO-*d*₆): δ 15.26 ppm (bs, 1H, H-10), 9.68 ppm (bs, 1H, H-15), 8.96 ppm (s, 1H, H-2), 7.94 ppm (d, *J* = 13.1 Hz, 1H, H-5), 7.26 ppm (d, *J* = 7.0 Hz, 1H, H-8), 4.62 ppm (q, *J* = 6.5 Hz, 1H, H-11), 3.58 ppm (s, 2H, H-13), 3.28 ppm (s, 2H, H-14), 1.41 ppm (t, *J* = 6.8 Hz, 3H, H-12)

¹³**C NMR** (101 MHz, DMSO-*d*₆): δ 176.1 ppm (s, C=O, C-4), 165.9 ppm (s, C=O, C-9), 152.7 ppm (d, *J* = 250.1 Hz, C-F, C-6), 148.7 ppm (s, CH, C-2), 144.4 ppm (d, *J* = 10.0 Hz, C, C-7), 137.1 ppm (s, C, C-8a), 119.9 ppm (s, C, C-4a), 111.4 ppm (d, *J* = 22.7 Hz, CH, C-5), 107.1 ppm (s, C, C-3), 106.5 ppm (s, CH, C-8), 49.1 ppm (s, CH₂, C-11), 46.4 ppm (s, CH₂, C-13), 42.4 ppm (s, CH₂, C-14), 14.5 ppm (s, CH₃, C-12)

¹⁹**F NMR** (376 MHz, DMSO-*d*₆, coupled ¹H): δ -121.7 ppm (dd, *J* = 13.2 Hz; 7.0 Hz, F-6)

¹⁹**F NMR** (376 MHz, DMSO-*d*₆, decoupled ¹H): δ -121.7 ppm (s, F-6)

MS (ESI, Water); m/z (relative intensity): 320 (*M*⁺, 100%), 301 (6%), 293 (10%), 250 (15%), 234 (7%)

HR-MS (ESI, Water): 320.1405 [M^+]; calculated value for C₁₆H₁₉FN₃O₃: 320.1405 (Δ = 0.0 ppm)

This compound is reported in the literature¹² and as its' non-salt form.¹³

NMR spectral data

Ethyl 4-chloroquinoline-3-carboxylate (4), 400 MHz, CDCl₃.



Ethyl-4-quinolone-3-carboxylate (6), 400 MHz, DMSO-d₆.



4-quinolone-3-carboxylic acid (7), 400 MHz, DMSO-*d*₆.



3-chloro-5,6-difluoro-1*H*-indole (8), 400 MHz, CDCl₃.



Ethyl 4-chloro-6,7-difluoroquinoline-3-carboxylate (9), 400 MHz, CDCl₃.



Ethyl 6,7-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate (10), 300 MHz, CF₃COOD.



Ethyl 1-ethyl-6,7-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate, 400 MHz, CDCl₃.



Ethyl 1-ethyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate, 400MHz, CDCl₃.



Ethyl 7-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate (**11**), 400MHz, acetone- d_6 .



7-(4-(*tert*-Butoxycarbonyl)piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid, 500 MHz, CDCl₃.



4-(3-carboxy-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinolin-7-yl)piperazin-1-ium chloride – norfloxacin hydrochloride (**12**), 400 MHz, DMSO-d₆.



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