

1 Autoinducer analogue-ciprofloxacin conjugates

The formation of biofilms can drastically increase MIC for many antibiotics.¹ For ciprofloxacin in *P. aeruginosa* the MIC increases by 16 fold according to Ceri et al.

Ganguly et al.² found the MICs of ciprofloxacin and a BHL analogue-ciprofloxacin **96** (see Figure 1) conjugate under standard planktonic conditions by introducing the compounds to liquid culture. The MICs were found to be ten times lower for ciprofloxacin vs. the conjugate **96** (5 vs 50 μ m). They then investigated the effect of the compounds on biofilms. The compounds were first cultured at 25 μ m, with PA liquid culture. As expected, the culture failed to grow and form biofilm in the presence of ciprofloxacin, but did grow in the presence of the conjugate **96**. They then cultured biofilm for 24 hours before adding the compounds, and found that, in contrast, the conjugate **96** disrupted the biofilm more effectively than ciprofloxacin. When the biofilm was cultured for 48 or 72 hours the conjugate similarly disruptive effects, whereas ciprofloxacin 'did not show any significant antibacterial activity'.

Ganguly et al. used Bac-Light Live/Dead staining and confocal microscopy to image the biofilms, whereas so far I have used crystal violet staining. Crystal violet does not differentiate between live or dead cells, and so might not pick up on the antibacterial effects of compounds. However, their confocal microscopy results show a quantifiable decrease in biofilm thickness, and it may be possible to detect this using crystal violet.

The conjugate **96** developed by Ganguly et al. contained a thiolactone AHL. The unconjugated thiolactone BHL **140** was shown to have 'either enhanced uptake or functional activity' when compared with BHL **2**. Therefore it seems possible that my compounds may not show enhanced antibiotic activity, where thiolactone analogues might.

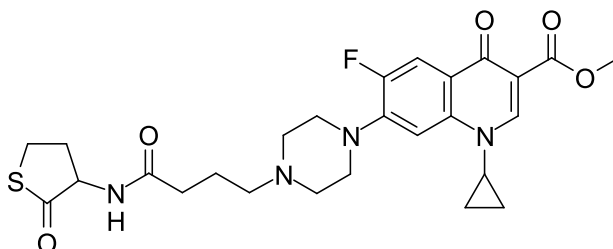


Figure 1

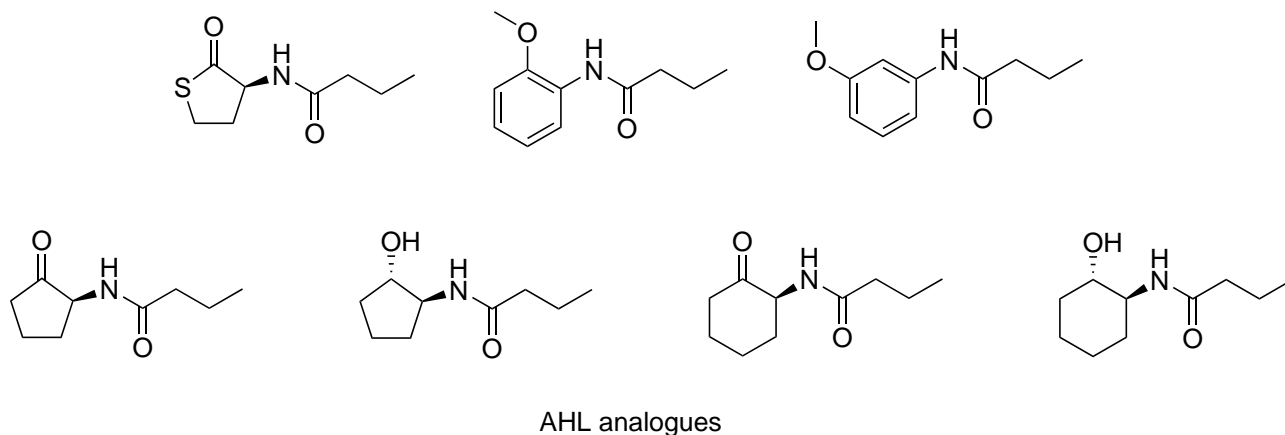
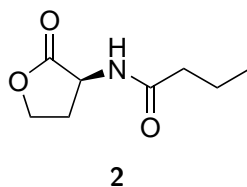
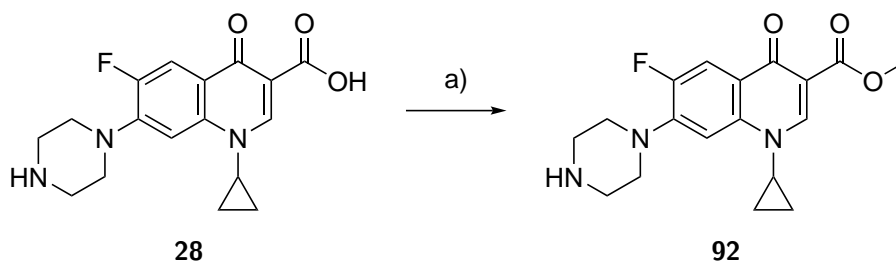


Figure 2

Introduce initial strategy of making bromide then azide, and diverting down the two different paths to make directly linked or triazole linked products.

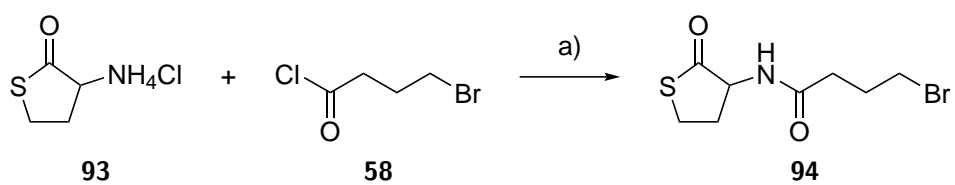
1.1 Synthesis of the C₄-homocysteine thiolactone derivatives

Methyl ciprofloxacin **92** was synthesised from ciprofloxacin **28** and MeOH in very good yield using *para*-toluenesulfonic acid as a catalyst.³

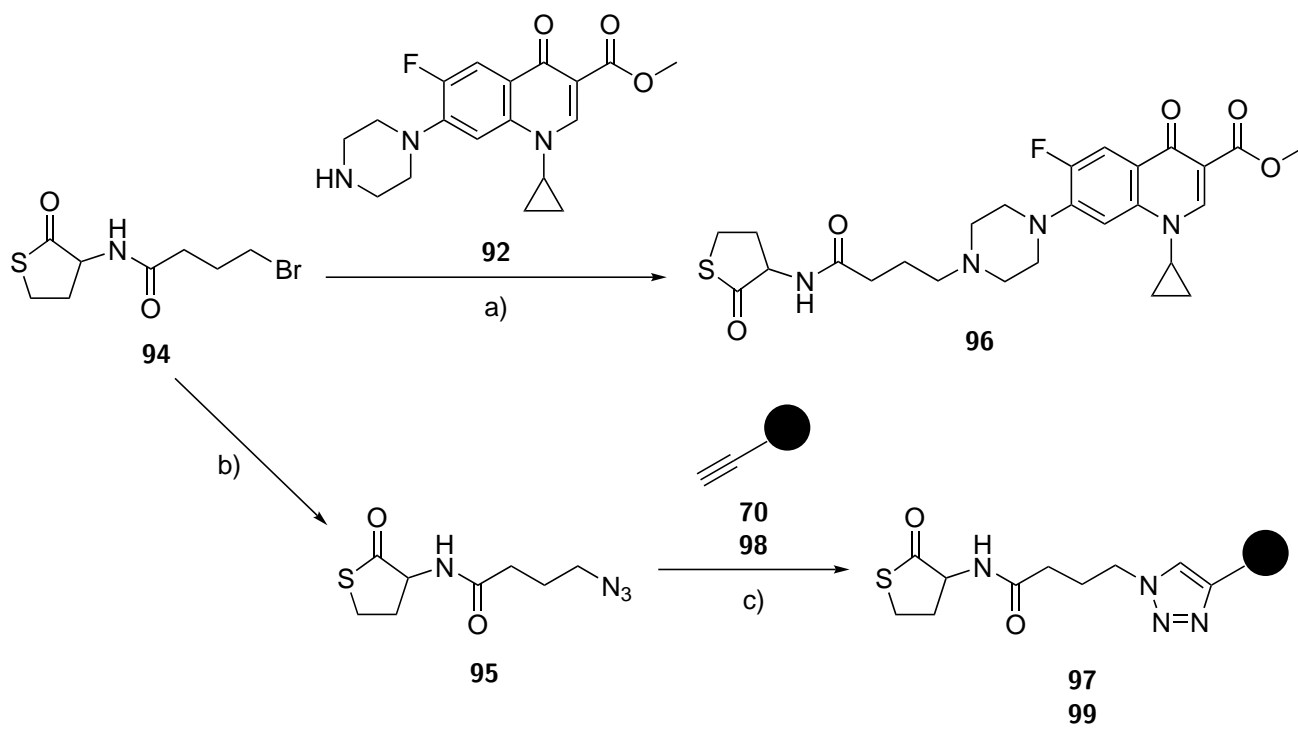


Scheme 1: a) *p*-TSA, MeOH, 72 h, reflux, 83.3 %.

Br-C₄-HCTL **94** was synthesised using the Schotten-Baumann conditions employed previously for the Br-C_{*n*}-HSL compounds **56**, **59** and **62**. Br-C₄-HCTL **94** was isolated in markedly higher yield than that achieved by Ganguly *et al.* (87.9 % vs. 25.0 %). It is possible that this was due to CH₂Cl₂ being used for the extraction, whereas Ganguly *et al.* used EtOAc.

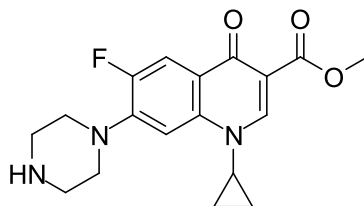


Scheme 2: a) NaHCO_3 , CH_2Cl_2 , H_2O , $0\text{ }^\circ\text{C}$, 1 h, 87.9 %.



Scheme 3: a) K_2CO_3 , acetonitrile, reflux, 24 h, 12.2 %. b) NaN_3 , acetonitrile, $80\text{ }^\circ\text{C}$, 1.5 h, 89.3 %.

1.2 Methyl 1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate **92**



Ciprofloxacin **28** (10.0 g, 30 mmol, 1 eq.) and *p*-toluenesulfonic acid (8.60 mg, 44.5 mmol, 1.5 eq.) were refluxed in methanol (500 ml) for 72 h. The mixture was cooled to room temperature and NaHCO₃ (sat., aq., 100 ml) and water (300 ml) were added. The product was extracted with CH₂Cl₂ (2×400 ml). The combined organic fractions were dried over MgSO₄ and evaporated under reduced pressure. **92** was obtained as a white amorphous solid (9.16 g, 26.5 mmol, 83.3 %).

TLC R_f = 0.13 (5 % MeOH/CH₂Cl₂)

IR (neat) ν_{max} / cm⁻¹ = 2947.9 (C-H), 2834.9 (C-H), 1720.9 (ester C=O), 1616.8 (quinolone C=O)

¹H NMR (400 MHz, MeOD) δ / ppm = 8.55 (s, 1 H, *ortho* to C(=O)OCH₃), 7.71 (d, J = 13.5 Hz, 1 H, *ortho* to F), 7.41 (d, J = 7.2 Hz, 1 H, *meta* to F), 3.83 (s, 3 H, CH₃), 3.62 (tt, J = 7.4, 3.5 Hz, 1 H, NCH(CH₂)₂), 3.24 - 3.29 (m, 4 H, HN(CH₂CH₂)CH₂CH₂), 3.02 - 3.10 (m, 4 H, HN(CH₂)CH₂), 1.31 - 1.38 (m, 2 H, NCH(CH₂)₂), 1.12 - 1.20 (m, 2 H, NCH(CH₂)₂)

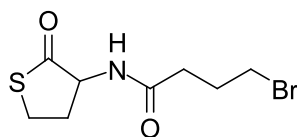
¹³C NMR (101 MHz, MeOD) δ / ppm = 175.2 (C(=O)CC(=O)OCH₃), 166.8 (C(=O)OCH₃), 154.9 (d, J = 248.0 Hz, *ipso* to F), 150.1 (C=CC(=O)OCH₃), 146.6 (d, J = 10.4 Hz, *ipso* to piperazine), 139.9 (*para* to F), 123.3 (d, J = 6.9 Hz, *para* to piperazine), 113.0 (d, J = 23.4 Hz, *ortho* to C=O and *ortho* to F), 110.1 (CC(=O)OCH₃), 107.1 (d, J = 3.5 Hz, *meta* to C=O and *meta* to F), 52.3 (CH₃), 51.7 (HN(CH₂CH₂)CH₂CH₂), 51.6 (HN(CH₂CH₂)CH₂CH₂), 46.5 (HN(CH₂)CH₂), 36.4 (NCH(CH₂)₂), 8.7 (NCH(CH₂)₂)

¹⁹F NMR (376.45 MHz, MeOD) δ / ppm = -124.8 (s, ciprofloxacin F)

HRMS (ESI⁺) m/z / Da = 346.1569, [M+H]⁺ found, [C₁₈H₂₁FN₃O₃]⁺ requires 346.1567

The data are consistent with the literature.³

1.3 4-Bromo-*N*-(2-oxotetrahydrothiophen-3-yl)butanamide **94**



3-Aminodihydrothiophen-2(3*H*)-one hydrochloride **93** (15.0 g, 97.6 mmol, 1 eq.) and NaHCO₃ (16.4 g, 195 mmol, 2 eq.) were added to CH₂Cl₂ (150 ml) and water (150 ml). 4-Bromobutyryl chloride **58** (11.3 ml, 107 mmol, 1.1 eq.) was added dropwise over 45 min at 0 °C and the mixture was stirred for a further 1 h. The

organic layer was separated and the aqueous layer was extracted with a second portion of CH_2Cl_2 (150 ml). The combined organic layers were dried over MgSO_4 and evaporated under reduced pressure. **94** was obtained as a white, amorphous solid (22.7 g, 85.8 mmol, 87.9 %).

TLC $R_f = 0.19$ (50 % EtOAc/PE)

IR (neat) $\nu_{\text{max}} / \text{cm}^{-1} = 3265.9$ (amide N-H), 3063.2 (amide N-H), 1694.3 (thiolactone C=O), 1650.5 (amide C=O)

^1H NMR (400 MHz, CDCl_3) $\delta / \text{ppm} = 6.08$ (d, $J = 6.1$ Hz, 1 H, NH), 4.54 (dt, $J = 12.9, 6.5$ Hz, 1 H, CHNH), 3.49 (t, $J = 6.4$ Hz, 2 H, CH_2Br), 3.37 (ddd, $J = 12.2, 11.5, 5.3$ Hz, 1 H, SCHH), 3.26 (ddd, $J = 11.5, 6.9, 1.3$ Hz, 1 H, SCHH), 2.91 (dddd, $J = 12.5, 6.7, 5.3, 1.3$ Hz, 1 H, SCH_2CHH), 2.45 (t, $J = 7.4$ Hz, 1 H, C(=O)CHH), 2.45 (t, $J = 6.8$ Hz, 1 H, C(=O)CHH), 2.20 (quin, $J = 6.7$ Hz, 1 H, $\text{C(=O)CH}_2\text{CH}_2$), 1.96 (dddd, $J = 12.7, 12.5, 12.2, 7.0$ Hz, 1 H, SCH_2CHH)

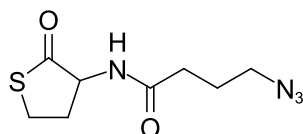
^{13}C NMR (101 MHz, CDCl_3) $\delta / \text{ppm} = 205.4$ (SC(=O)), 172.1 (NHC(=O)), 59.4 (CHNH), 34.1 (C(=O)CH_2), 33.1 (CH_2Br), 31.8 (SCH_2CH_2), 28.0 ($\text{C(=O)CH}_2\text{CH}_2$), 27.5 (SCH_2)

HRMS (ESI^+) $m/z / \text{Da} = ??$, $[\text{M}+\text{H}]^+$ found, $[??]^+$ requires ??

pick up

The compound has been synthesised previously^{2,4} but characterisation was not published.

1.4 4-Azido-*N*-(2-oxotetrahydrothiophen-3-yl)butanamide **95**



4-Bromo-*N*-(2-oxotetrahydrothiophen-3-yl)butanamide **94** (6.00 g, 27.0 mmol, 1 eq.) and NaN_3 (3.51 g, 54.1 mmol, 2 eq.) were refluxed in acetonitrile (120 ml) for 1.5 h. The solvent was evaporated under reduced pressure and the residue was partitioned between water (150 ml) and CH_2Cl_2 (150 ml). The aqueous layer was extracted twice more with CH_2Cl_2 (2×150 ml) and the combined organic fractions were dried with MgSO_4 and evaporated under reduced pressure. **95** was obtained as a yellow, sticky solid (4.60 g, 20.1 mmol, 89.3 %).

TLC $R_f = 0.19$ (50 % EtOAc/PE)

IR (neat) $\nu_{\text{max}} / \text{cm}^{-1} = 3285.6$ (N-H), 2963.9 (C-H), 2100.2 (azide), 1697.4 (thiolactone C=O), 1647.4 (amide C=O)

^1H NMR (400 MHz, CDCl_3) $\delta / \text{ppm} = 6.71$ (d, $J = 7.3$ Hz, 1 H, NH), 4.54 (dt, $J = 13.0, 7.0$ Hz, 1 H, CHNH), 3.30 (t, $J = 6.7$ Hz, 2 H, CH_2N_3), 3.31 (td, $J = 11.7, 5.3$ Hz, 1 H, 1 H, SCHH), 3.19 (ddd, $J = 11.3, 7.0, 1.2$ Hz, 1 H, SCHH), 2.70 (dddd, $J = 12.4, 6.8, 5.3, 1.2$ Hz, 1 H, SCH_2CHH), 2.29 (t, $J = 7.5$ Hz, 1 H, C(=O)CHH), 2.28 (t, $J = 7.1$ Hz, 1 H, C(=O)CHH), 1.97 (qd, $J = 12.4, 7.0$ Hz, 1 H, SCH_2CHH), 1.85 (quin, $J = 6.9$ Hz, 2 H, $\text{C(=O)CH}_2\text{CH}_2$)

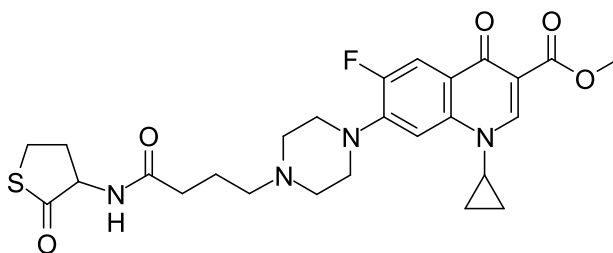
^{13}C NMR (101 MHz, CDCl_3) $\delta / \text{ppm} = 205.4$ (SC(=O)), 172.3 (NHC(=O)), 59.4 (CHNH), 50.6 (CH_2N_3),

32.8 (C(=O)CH₂), 31.8 (SCH₂CH₂), 27.5 (SCH₂), 24.6 (C(=O)CH₂CH₂)

HRMS (ESI⁺) m/z / Da = 251.0565, [M+Na]⁺ found, [C₈H₁₂N₄NaO₂S]⁺ requires 251.0573

The compound has not been reported previously.

1.5 Methyl 1-cyclopropyl-6-fluoro-4-oxo-7-(4-(4-oxo-4-((2-oxotetrahydrothiophen-3-yl)amino)butyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate **96**



Methyl 1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate **92** (50 mg, 0.145 mmol, 1 eq.), 4-bromo-*N*-(2-oxotetrahydrothiophen-3-yl)butanamide **94** (34.5 mg, 0.145 mmol, 1 eq.) and K₂CO₃ (20 mg, 0.145 mmol, 1 eq.) were stirred in acetonitrile (2 ml) at 50 °C under argon. After 24 h a further portion of **94** (34.5 mg, 0.145 mmol, 1 eq.) was added. After another 24 h a further portion was added (69.0 mg, 0.290 mmol, 2 eq.). After another 24 h the temperature was raised so the mixture was at reflux. After a final 24 h the precipitate was filtered off and the filtrate was purified by column chromatography (SiO₂, 5-10 % MeOH/CH₂Cl₂). **96** was obtained as a cream-coloured amorphous solid (9.4 mg, 0.018 mmol, 12.2 %).

TLC R_f = 0.47 (10 % MeOH/CH₂Cl₂)

IR (neat) ν_{max} / cm⁻¹ = 2944.2 (C-H), 2832.4 (C-H), 1722.4 (ester C=O), 1700.4 (thiolactone C=O), 1669.6 (amide C=O), 1617.3 (quinolone C=O)

¹H NMR (500 MHz, MeOD) δ / ppm = 8.53 (s, 1 H, *ortho* to C(=O)OCH₃), 7.68 (d, J=13.4 Hz, 1 H, *ortho* to F), 7.41 (d, J=7.3 Hz, 1 H, *meta* to F), 4.67 (dd, J=12.9, 6.9 Hz, 1 H, CHNH), 3.83 (s, 3 H, OCH₃), 3.61 (tt, J=6.9, 4.1 Hz, 1 H, NCH(CH₂)₂), 3.39 - 3.49 (m, 5 H, SCHH), 3.26 - 3.33 (m, 1 H, SCHH and CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 2.93 - 3.03 (m, 4 H, CH₂CH₂CH₂N(CH₂)CH₂), 2.79 (br. t, J=7.2, 7.2 Hz, 2 H, C(=O)CH₂CH₂CH₂), 2.59 (dddd, J=12.4, 6.9, 5.4, 1.4 Hz, 1 H, SCH₂CHH), 2.39 (t, J=7.20 Hz, 1 H, C(=O)CHH), 2.38 (t, J=6.94 Hz, 1 H, C(=O)CHH), 2.18 (qd, J=12.4, 7.0 Hz, 1 H, SCH₂CHH), 1.97 (quin, J=7.2 Hz, 2 H, C(=O)CH₂CH₂), 1.32 - 1.37 (m, 2 H, NCH(CHH)₂), 1.13 - 1.19 (m, 2 H, NCH(CHH)₂)

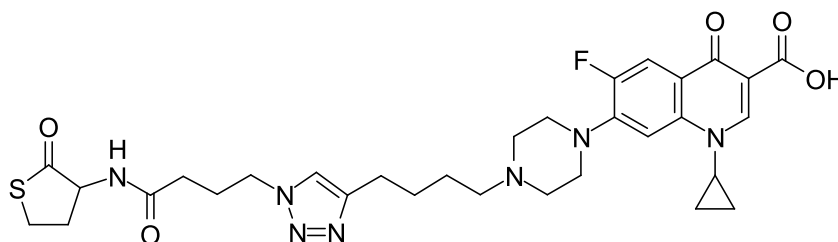
¹³C NMR (126 MHz, MeOD) δ / ppm = 207.0 (SC(=O)), 175.7 (NHC(=O)), 175.1 (C(=O)CC(=O)OCH₃), 166.6 (C(=O)OCH₃), 154.7 (d, J=249.0 Hz, *ipso* to F), 150.2 (s, CH=CC(=O)OCH₃), 145.6 (d, J=10.6 Hz, *ipso* to piperazine), 139.8 (*para* to F), 123.5 (d, J=6.9 Hz, *para* to piperazine), 113.1 (d, J=23.6 Hz, *ortho* to C=O and *ortho* to F), 110.0 (CC(=O)OCH₃), 107.4 (*meta* to C=O and *meta* to F), 60.2 (CHNH), 58.5 (C(=O)CH₂CH₂CH₂), 53.8 (CH₂CH₂CH₂N(CH₂)CH₂), 52.3 (OCH₃), 50.1 (CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 50.0 (CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 36.5 (NCH(CH₂)₂), 34.5 (C(=O)CH₂), 31.7 (SCH₂CH₂), 28.1 (SCH₂), 22.9 (C(=O)CH₂CH₂CH₂), 8.7 (NCH(CH₂)₂)

¹⁹F NMR (376.45 MHz, MeOD) δ / ppm = -125.4 (s, ciprofloxacin F)

HRMS (ESI⁺) m/z / Da = 531.2083, [M+H]⁺ found, [C₂₆H₃₂FN₄O₅S]⁺ requires 531.2077

The compound has been synthesised previously.^{2,4} Only HRMS characterisation was published, and this agrees with the result above.

1.6 1-Cyclopropyl-6-fluoro-4-oxo-7-(4-(4-(1-(4-oxo-4-((2-oxotetrahydrothiophen-3-yl)amino)butyl)-1*H*-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid **97**



1-Cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **70** (15 mg, 36.7 μ mol, 1 eq.) and 4-azido-*N*-(2-oxotetrahydrothiophen-3-yl)butanamide **95** (12.5 mg, 55.1 μ mol, 1.5 eq.) were dissolved in 1:9:10 water/*t*-BuOH/DMSO (3 ml), and the mixture was degassed by bubbling N₂ through it. A solution of CuSO₄ and THPTA (182 μ l, 18.2 μ mol, 0.5 eq. 100 mM, aq.) was added, followed by a solution of sodium ascorbate (367 μ l, 36.7 μ mol, 1 eq., 100 mM, aq.). The mixture was stirred at r.t. under argon for 7 d. Water (10 ml) and 10 % *i*-PrOH/CHCl₃ (10 ml) were added, the organic layer was separated and the aqueous layer was extracted again with 10 % *i*-PrOH/CHCl₃ (2 \times 10 ml). The combined organic layers were dried with MgSO₄ and evaporated under reduced pressure. The residue was purified by preparatory HPLC (5-95 % acetonitrile/water over 20 min). The combined pure fractions were evaporated under reduced pressure and then partitioned between NaHCO₃ (aq., sat., 50 ml) and 10 % *i*-PrOH/CHCl₃ (50 ml). The organic layer was dried with MgSO₄ and evaporated under reduced pressure. **97** was obtained as a white amorphous solid (16.5 mg, 25.9 μ mol, 70.6 %).

IR (neat) ν_{max} / cm⁻¹ = 2918.8 (C-H), 1712.7 (carboxylic acid C=O and thiolactone C=O), 1657.6 (amide C=O), 1626.8 (quinolone C=O), 1616.2 (triazole)

¹H NMR (500 MHz, DMSO d₆) δ / ppm = 15.23 (br s, 1 H, C(=O)OH), 8.66 (s, 1 H, *ortho* to C(=O)OH), 8.23 (d, J=8.5 Hz, 1 H, NH), 7.90 (d, J=13.4 Hz, 1 H, *ortho* to F), 7.84 (s, 1 H, CH=CCH₂), 7.56 (d, J=7.5 Hz, 1 H, *meta* to F), 4.59 (ddd, J=12.7, 8.4, 6.8 Hz, 1 H, CHNH), 4.31 (t, J=7.0 Hz, 2 H, CH₂NCH=C), 3.80 - 3.86 (6.9, 4.0 Hz, 1 H, NCH(CH₂)₂), 3.34 - 3.37 (m, 1 H, SCHH), 3.32 (br t, J=4.1 Hz, 4 H, CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 3.27 (ddd, J=11.1, 6.9, 1.4 Hz, 1 H, SCHH), 2.64 (t, J=7.6 Hz, 2 H, CH=CCH₂), 2.57 (br t, J=4.7 Hz, 4 H, CH₂CH₂CH₂N(CH₂)CH₂), 2.34 - 2.44 (m, 3 H, SCH₂CHH and CH=CCH₂CH₂CH₂CH₂), 2.12 (t, J=7.9 Hz, 1 H, C(=O)CHH), 2.12 (t, J=7.0 Hz, 1 H, C(=O)CHH), 2.04 (m, 3 H, SCH₂CHH and C(=O)CH₂CH₂), 1.64 (quin, J=7.5 Hz, 2 H, CH=CCH₂CH₂), 1.51 (quin, J=7.5 Hz, 2 H, CH=CCH₂CH₂CH₂), 1.28 - 1.34 (m, 2 H, NCH(CHH)₂), 1.15 - 1.20 (m, 2 H, NCH(CHH)₂)

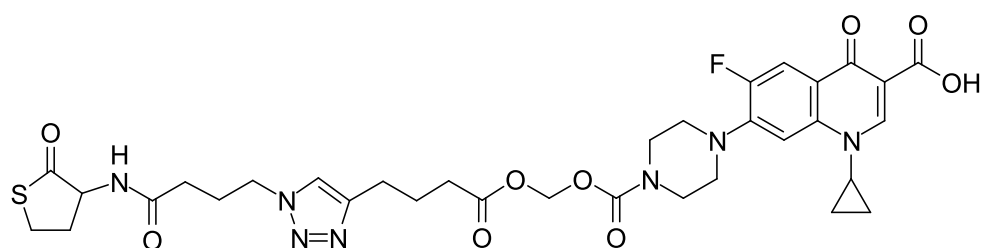
¹³C NMR (126 MHz, DMSO d₆) δ / ppm = 205.6 (SC(=O)), 176.4 (C(=O)CC(=O)OH), 171.4 (NHC(=O)), 166.0 (C(=O)OH), 153.1 (d, J=249.3 Hz, *ortho* to F), 148.0 (CH=CC(=O)OH), 146.9 (CH=CCH₂), 145.3 (d, J=10.1 Hz, *ipso* to piperazine), 139.2 (*para* to F), 121.8 (CH=CCH₂), 118.6 (d, J=7.7 Hz, *para* to piperazine), 111.0 (d, J=23.3 Hz, *ortho* to C=O and *ortho* to F), 106.7 (CC(=O)OH), 106.4 (d, J=2.9 Hz, *meta* to

C=O and *meta* to F), 58.2 (SC(=O)CHNH), 57.4 (CH=CCH₂CH₂CH₂CH₂N), 52.4 (CH₂CH₂CH₂N(CH₂)CH₂), 49.5 (CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 49.5 (CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 48.6 (CH₂NCH=C), 35.9 (NCH(CH₂)₂), 31.9 (NHC(=O)CH₂), 30.1 (CH₂CHNH), 26.9 (CH=CCH₂CH₂), 26.8 (SCH₂), 25.9 (NHC(=O)CH₂CH₂), 25.8 (CH=CCH₂CH₂CH₂), 25.0 (CH=CCH₂), 7.6 (NCH(CH₂)₂)

¹⁹F NMR (376.45 MHz, MeOD) δ / ppm = -124.9 (s, ciprofloxacin F)

HRMS (ESI⁺) m/z / Da = 640.2739, [M+H]⁺ found, [C₃₁H₃₉FN₇O₅S]⁺ requires 640.2712

1.7 1-Cyclopropyl-6-fluoro-4-oxo-7-(4-(((4-(1-(4-oxo-4-((2-oxotetrahydrothiophen-3-yl)amino)butyl)-1*H*-1,2,3-triazol-4-yl)butanoyl)oxy)methoxy)carbonyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid **99**



1-Cyclopropyl-6-fluoro-7-(4-(((hex-5-ynoyloxy)methoxy)carbonyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **98** (203 mg, 0.407 mmol, 1 eq.), 4-azido-*N*-(2-oxotetrahydrothiophen-3-yl)butanamide **95** (92.8 mg, 0.407 mmol, 1 eq.), CuI (40 mg, 0.190 mmol, 0.5 eq.) and DIPEA (0.356 ml, 0.264 mg, 2.04 mmol, 5 eq.) were stirred in CH₂Cl₂ (18.6 ml) at r.t. under Ar for 3 h. The mixture was filtered and the filtrate was dry-loaded onto SiO₂ and purified by column chromatography (SiO₂, 5-10 % MeOH/CH₂Cl₂). **99** was obtained as pale brown/yellow amorphous solid (14.7 mg, 20.2 μ mol, 5.0 %).

TLC R_f = 0.40 (5 % CH₂Cl₂/MeOH)

IR (neat) ν_{max} / cm⁻¹ = 3054.9 (C-H), 1715.8 (carboxylic acid C=O and ester C=O), 1696.2 (carbamate C=O and thiolactone C=O), 1651.2 (amide C=O), 1629.2 (quinolone C=O)

¹H NMR (400 MHz, DMSO d₆) δ / ppm = 15.16 (br s, 1 H, C(=O)OH), 8.65 (s, 1 H, *ortho* to C(=O)OH), 8.21 (d, J = 8.5 Hz, 1 H, NH), 7.89 (d, J = 13.1 Hz, 1 H, *ortho* to F), 7.85 (s, 1 H, CH=CCH₂), 7.57 (d, J = 7.4 Hz, 1 H, *meta* to F), 5.74 (s, 1 H, OCH₂O), 4.58 (ddd, J = 12.6, 8.1, 7.2 Hz, 1 H, CHNH), 4.30 (t, J = 6.9 Hz, 2 H, C(=O)CH₂CH₂CH₂N), 3.80 (tt, J = 6.9, 3.6 Hz, 1 H, NCH(CH₂)₂), 3.62 (br t, J = 5.2, 5.2 Hz, 4 H, C(=O)N(CH₂)CH₂), 3.38 (td, J = 11.4, 5.5 Hz, 1 H, SCHH), 3.34 (br. s, 4 H, C(=O)N(CH₂CH₂)CH₂CH₂), 3.27 (ddd, J = 11.0, 6.9, 1.6 Hz, 1 H, SCHH), 2.64 (t, J = 7.6 Hz, 2 H, CH=CCH₂), 2.44 (t, J = 7.5 Hz, 2 H, CH₂C(=O)O), 2.40 (dddd, J = 12.3, 6.8, 5.4, 1.4 Hz, 1 H, SCH₂CHH), 2.12 (t, J = 7.8 Hz, 1 H, NHC(=O)CHH), 2.12 (t, J = 6.8 Hz, 1 H, NHC(=O)CHH), 1.98 - 2.07 (m, 3 H, SCH₂CHH and NHC(=O)CH₂CH₂), 1.86 (quin, J = 7.5 Hz, 2 H, CH=CCH₂CH₂), 1.29 - 1.36 (m, 2 H, NCH(CH₂)₂), 1.14 - 1.21 (m, 2 H, NCH(CH₂)₂)

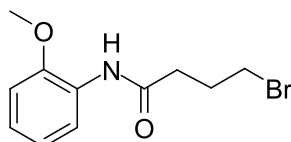
¹³C NMR (101 MHz, DMSO d₆) δ / ppm = 205.5 (SC(=O)), 176.4 (C(=O)CC(=O)OH), 171.8 (C(=O)OCH₂O), 171.3 (NHC(=O)), 165.9 (C(=O)OH), 152.8 (d, J = 249.7 Hz, *ipso* to F), 152.9 (OC(=O)N), 148.1 (CH=CC(=O)OH), 146.0 (CH=CCH₂), 144.9 (d, J = 9.6 Hz, *ipso* to piperazine), 139.1 (*para* to F), 122.0 (CH=CCH₂), 118.9 (d, J = 7.5 Hz, *para* to piperazine), 111.0 (d, J = 23.5 Hz, *ortho* to C=O and *ortho* to F), 106.8 (CC(=O)OH,

and *meta* to C=O and *meta* to F), 80.3 (OCH₂O), 58.2 (CHNH), 49.1 (C(=O)N(CH₂CH₂)CH₂CH₂), 49.1 (C(=O)N(CH₂CH₂)CH₂CH₂), 48.6 (C(=O)CH₂CH₂CH₂N), 43.4 (N(CH₂)CH₂), 43.0 (N(CH₂)CH₂), 35.9 (NCH(CH₂)₂), 32.7 (CH=CCH₂CH₂CH₂C(=O)), 31.8 (NHC(=O)CH₂), 30.1 (SCH₂CH₂), 26.8 (SCH₂), 25.8 (C(=O)CH₂CH₂CH₂N), 24.2 (CH=CCH₂CH₂CH₂C(=O)), 24.0 (CH=CCH₂CH₂CH₂C(=O)), 7.6 (NCH(CH₂)₂)

HRMS (ESI⁺) m/z / Da = 728.2502, [M+H]⁺ found, [C₃₃H₃₉FN₇O₉S]⁺ requires 728.2503

The compound has not been reported previously.

1.8 4-Bromo-*N*-(2-methoxyphenyl)butanamide **101**



2-Methoxyaniline **100** (9.12 ml, 10.0 g, 81.2 mmol, 1 eq.) and NaHCO₃ (8.19 g, 97.4 mmol, 1.2 eq.) were dissolved in water (100 ml) and CH₂Cl₂ (100 ml). The mixture was cooled to 0 °C and 4-bromobutyryl chloride **58** (9.40 ml, 15.1 g, 81.2 mmol, 1 eq.) was added dropwise over 15 min. The mixture was stirred at 0 °C for 1.5 h, then the aqueous layer was removed. The organic layer was dried with MgSO₄ and evaporated under reduced pressure. **101** was obtained as an initially colourless liquid which slowly turned blue then black if left out on the bench (11.0 g, 40.6 mmol, 50.0 %).

TLC R_f = 0.16 (10 % EtOAc/P.E.)

IR (neat) ν_{max} / cm⁻¹ = 3410.2 (N-H), 3313.4 (N-H), 2961.6 (C-H), 2939.5 (C-H), 2902.5 (C-H), 1676.4 (amide C=O)

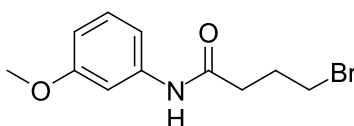
¹H NMR (400 MHz, CDCl₃ d₁) δ / ppm = 8.32 (dd, J = 8.0, 1.7 Hz, 1 H, *ortho* to NH), 7.85 (br s, 1 H, NH), 7.02 (td, J = 7.9, 1.7 Hz, 1 H, *para* to NH), 6.93 (td, J = 7.7, 1.4 Hz, 1 H, *para* to OCH₃), 6.85 (dd, J = 8.1, 1.5 Hz, 1 H, *ortho* to OCH₃), 3.85 (s, 3 H, CH₃), 3.50 (t, J = 6.4 Hz, 2 H, CH₂Br), 2.56 (t, J = 7.1 Hz, 2 H, C(=O)CH₂), 2.25 (quin, J = 6.7 Hz, 2 H, C(=O)CH₂CH₂)

¹³C NMR (101 MHz, CDCl₃ d₁) δ / ppm = 169.4 (C(=O)), 147.6 (*ipso* to OCH₃), 127.2 (*ipso* to NH), 123.5 (*para* to NH), 120.7 (*para* to OCH₃), 119.6 (*ortho* to NH and *meta* to OCH₃), 109.8 (*ortho* to OCH₃ and *meta* to NH), 55.5 (CH₃), 35.4 (C(=O)CH₂), 33.1 (CH₂Br), 27.9 (C(=O)CH₂CH₂)

HRMS (ESI⁺) m/z / Da = 272.0287, [M+H]⁺ found, [C₁₁H₁₅BrNO₂]⁺ requires 272.0286

The compound has not been reported previously.

1.9 4-Bromo-*N*-(3-methoxyphenyl)butanamide **103**



3-Methoxyaniline **102** (3.04 ml, 3.33 g, 27.1 mmol, 1 eq.) and NaHCO₃ (2.73 g, 32.5 mmol, 1.2 eq.) were dissolved in water (30 ml) and CH₂Cl₂ (30 ml). The mixture was cooled to 0 °C and 4-bromobutyryl chloride **58** (3.13 ml, 5.03 g, 27.1 mmol, 1 eq.) was added dropwise over 5 min. The mixture was stirred at 0 °C for 1 h, then the aqueous layer was removed. The organic layer was dry-loaded onto SiO₂ and purified by column chromatography using a Combiflash (SiO₂, 0-100 % EtOAc/P.E.). The combined pure fractions were dried with MgSO₄ and evaporated under reduced pressure. **103** was obtained as a pale pink amorphous solid (3.66 g, 13.5 mmol, 49.6 %).

TLC R_f = 0.18 (25 % EtOAc/P.E.)

IR (neat) ν_{max} / cm⁻¹ = 1670.9 (amide C=O)

¹H NMR (400 MHz, CDCl₃ d₁) δ / ppm = 8.45 (s, 1 H, NH), 7.27 (t, J = 2.2 Hz, 1 H, *ortho* to OCH₃ and *ortho* to NH), 7.14 (t, J = 8.1 Hz, 1 H, *meta* to OCH₃ and *meta* to NH), 7.02 (d, J = 8.3 Hz, 1 H, *para* to OCH₃), 6.62 (dd, J = 8.2, 2.1 Hz, 1 H, *para* to NH), 3.71 (s, 3 H, CH₃), 3.42 (t, J = 6.5 Hz, 2 H, CH₂Br), 2.51 (t, J = 6.9 Hz, 2 H, C(=O)CH₂), 2.19 (quin, J = 6.8 Hz, 2 H, C(=O)CH₂CH₂)

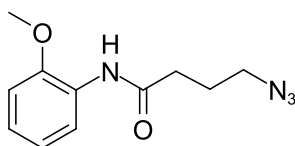
¹³C NMR (101 MHz, CDCl₃ d₁) δ / ppm = 170.3 (C(=O)), 159.9 (*ipso* to OCH₃), 139.0 (*ipso* to NH), 129.5 (*meta* to OCH₃ and *meta* to NH), 112.1 (*para* to OCH₃), 109.9 (*para* to NH), 105.7 (*ortho* to OCH₃ and *ortho* to NH), 55.2 (CH₃), 35.3 (C(=O)CH₂), 33.2 (CH₂Br), 28.0 (C(=O)CH₂CH₂)

HRMS (ESI⁺) m/z / Da = ??, [M+H]⁺ found, [??]⁺ requires ??

pick up

The compound has not been reported previously.

1.10 4-Azido-*N*-(2-methoxyphenyl)butanamide **104**



4-Bromo-*N*-(2-methoxyphenyl)butanamide **101** (2.05 g, 7.51 mmol, 1 eq.) and NaN₃ (1.17 g, 18.0 mmol, 2.4 eq.) were refluxed in acetonitrile (100 ml) for 2 h. The mixture was cooled and filtered, and the filtrate was dry-loaded onto SiO₂ and purified by column chromatography using a Combiflash (SiO₂, 8-14 % then hold at 14 % EtOAc/P.E.). **104** was obtained as an initially colourless liquid which slowly turned blue then black if left out on the bench (0.469 g, 2.00 mmol, 26.7 %).

TLC R_f = 0.20 (25 % EtOAc/P.E.)

IR (neat) ν_{max} / cm⁻¹ = 3419.7 (N-H), 3329.6 (N-H), 2094.8 (azide), 1672.3 (amide C=O)

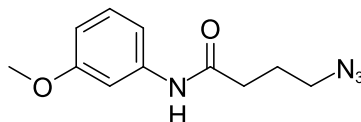
¹H NMR (400 MHz, CDCl₃ d₁) δ / ppm = 8.32 (dd, J = 7.9, 1.0 Hz, 1 H, *ortho* to NH), 7.86 (br s, 1 H, NH), 7.00 (td, J = 7.5, 1.5 Hz, 1 H, *para* to NH), 6.90 (td, J = 7.7, 1.1 Hz, 1 H, *para* to OCH₃), 6.83 (dd, J = 8.1, 1.4 Hz, 1 H, *ortho* to OCH₃), 3.81 (s, 3 H, CH₃), 3.33 (t, J = 6.7 Hz, 2 H, CH₂Br), 2.42 (t, J = 7.2 Hz, 2 H, C(=O)CH₂), 1.94 (quin, J = 6.9 Hz, 2 H, C(=O)CH₂CH₂)

^{13}C NMR (101 MHz, CDCl_3 d_1) δ / ppm = 169.5 ($\underline{\text{C}}(=\text{O})$), 147.6 (*ipso* to OCH_3), 127.1 (*ipso* to NH), 123.4 (*para* to NH), 120.5 (*para* to OCH_3), 119.5 (*ortho* to NH and *meta* to OCH_3), 109.6 (*ortho* to OCH_3 and *meta* to NH), 55.2 ($\underline{\text{CH}}_3$), 50.3 ($\underline{\text{CH}}_2\text{N}_3$), 33.9 ($\text{C}(=\text{O})\underline{\text{CH}}_2$), 24.3 ($\text{C}(=\text{O})\text{CH}_2\underline{\text{CH}}_2$)

HRMS (ESI^+) m/z / Da = 257.1010, $[\text{M}+\text{H}]^+$ found, $[\text{C}_{11}\text{H}_{14}\text{N}_4\text{NaO}_2]^+$ requires 257.1014

The data are consistent with the literature.⁵

1.11 4-Azido-*N*-(3-methoxyphenyl)butanamide **105**



4-Bromo-*N*-(3-methoxyphenyl)butanamide **103** (2.05 g, 7.51 mmol, 1 eq.) and NaN_3 (1.17 g, 18.0 mmol, 2.4 eq.) were refluxed in acetonitrile (100 ml) for 7 h. The mixture was cooled and filtered, and the filtrate was dry-loaded onto SiO_2 and purified by column chromatography using a Combiflash (SiO_2 , 0-100 % EtOAc/P.E.). The combined pure fractions were dried with MgSO_4 and evaporated under reduced pressure. **105** was obtained as a straw-coloured liquid (0.294 g, 1.25 mmol, 16.7 %).

TLC R_f = 0.37 (50 % EtOAc/P.E.)

IR (neat) ν_{max} / cm^{-1} = 3298.3 (N-H), 2094.7 (azide), 1661.7 (amide C=O)

^1H NMR (400 MHz, MeOD) δ / ppm = 8.63 (br s, 1 H, $\underline{\text{NH}}$), 7.26 (t, J = 2.3 Hz, 1 H, *ortho* to OCH_3 and *ortho* to NH), 7.15 (t, J = 8.1 Hz, 1 H, *meta* to OCH_3 and *meta* to NH), 7.01 (dd, J = 7.8, 1.6 Hz, 1 H, *para* to OCH_3), 6.63 (dd, J = 8.2, 1.9 Hz, 1 H, *para* to NH), 3.69 (s, 3 H, $\underline{\text{CH}}_3$), 3.28 (t, J = 6.7 Hz, 2 H, $\underline{\text{CH}}_2\text{N}_3$), 2.39 (t, J = 7.4 Hz, 2 H, $\text{C}(=\text{O})\underline{\text{CH}}_2$), 1.91 (quin, J = 7.0 Hz, 2 H, $\text{C}(=\text{O})\text{CH}_2\underline{\text{CH}}_2$)

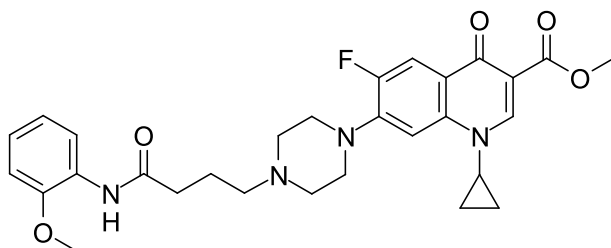
^{13}C NMR (101 MHz, MeOD) δ / ppm = 170.8 ($\underline{\text{C}}(=\text{O})$), 159.6 (*ipso* to OCH_3), 138.9 (*ipso* to NH), 129.2 (*meta* to OCH_3 and *meta* to NH), 112.3 (*para* to OCH_3), 109.5 (*para* to NH), 106.0 (*ortho* to OCH_3 and *ortho* to NH), 54.8 ($\underline{\text{CH}}_3$), 50.4 ($\underline{\text{CH}}_2\text{N}_3$), 33.6 ($\text{C}(=\text{O})\underline{\text{CH}}_2$), 24.4 ($\text{C}(=\text{O})\text{CH}_2\underline{\text{CH}}_2$)

HRMS (ESI^+) m/z / Da = ??, $[\text{M}+\text{H}]^+$ found, $[\text{?}]^+$ requires ??

pick up

The compound has not been reported previously.

1.12 Methyl 1-cyclopropyl-6-fluoro-7-(4-(4-((2-methoxyphenyl)amino)-4-oxobutyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate **106**



Methyl 1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate **92** (500 mg, 1.45 mmol, 1 eq.), 4-bromo-*N*-(2-methoxyphenyl)butanamide **101** (788 mg, 2.90 mmol, 2 eq.), DIPEA (1.28 ml, 950 mg, 7.35 mmol, 5 eq.), NaI (275 mg, 1.83 mmol, 1.3 eq.) and acetonitrile (10 ml) were stirred in a microwave reactor at 100 °C for 4 h. The mixture was dry-loaded onto SiO₂ and purified by column chromatography (SiO₂, 4 % MeOH/CH₂Cl₂). The combined pure fractions were dried with MgSO₄ and evaporated under reduced pressure. **106** was obtained as a bright pink glass (79.7 mg, 0.149 mmol, 10.2 %).

TLC R_f = 0.40 (10 % MeOH/CH₂Cl₂)

IR (neat) ν_{max} / cm⁻¹ = 2947.1 (C-H), 2833.7 (C-H), 1718.9 (ester C=O), 1685.3 (amide C=O), 1617.3 (quinolone C=O)

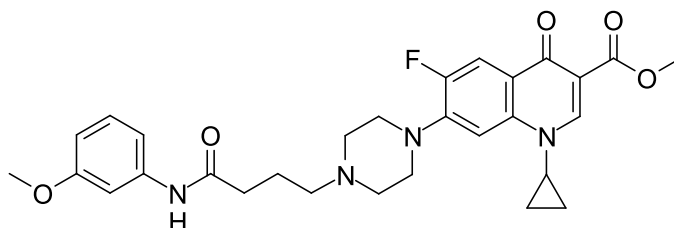
¹H NMR (400 MHz, CDCl₃ d₁) δ / ppm = 8.48 (s, 1 H, *ortho* to C(=O)OCH₃), 8.36 (d, J = 7.9 Hz, 1 H, *ortho* to NH), 7.87 - 7.99 (m, 2 H, *ortho* to F and NH), 7.19 (d, J = 6.5 Hz, 1 H, *meta* to F), 7.01 (t, J = 7.5 Hz, 1 H, *para* to NH), 6.93 (t, J = 7.7 Hz, 1 H, *para* to OCH₃), 6.85 (d, J = 7.9 Hz, 1 H, *ortho* to OCH₃), 3.88 (s, 3 H, C(=O)OCH₃), 3.85 (s, 3 H, aromatic OCH₃), 3.41 (tt, J = 6.9, 4.0 Hz, 1 H, NCH(CH₂)₂), 3.25 (br t, J = 5.0, 5.0 Hz, 4 H, C(=O)CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 2.67 (br t, J = 5.0, 5.0 Hz, 4 H, C(=O)CH₂CH₂CH₂N(CH₂)CH₂), 2.53 (t, J = 7.0 Hz, 2 H, C(=O)CH₂CH₂CH₂N), 2.47 (t, J = 7.1 Hz, 2 H, C(=O)CH₂CH₂CH₂N), 1.97 (quin, J = 6.8 Hz, 2 H, C(=O)CH₂CH₂CH₂N), 1.25 - 1.33 (m, 2 H, NCH(CH₂)₂), 1.07 - 1.14 (m, 2 H, NCH(CH₂)₂)

¹³C NMR (101 MHz, CDCl₃ d₁) δ / ppm = 172.9 (C(=O)CC(=O)OCH₃), 170.8 (NHC(=O)), 166.2 (C(=O)OCH₃), 153.3 (d, J = 248.0 Hz, *ipso* to F), 148.2 (C=CC(=O)OCH₃), 147.6 (*ipso* to OCH₃), 144.4 (d, J = 10.4 Hz, *ipso* to piperazine), 137.9 (*para* to F), 127.6 (*ipso* to NH), 123.4 (*para* to NH), 122.7 (d, J = 7.8 Hz, *para* to piperazine), 121.0 (*para* to OCH₃), 119.7 (*ortho* to NH and *meta* to OCH₃), 113.0 (d, J = 22.5 Hz, *ortho* to C=O and *ortho* to F), 109.8 (*ortho* to OCH₃ and *meta* to NH, and CC(=O)OCH₃), 104.7 (*meta* to C=O and *meta* to F), 57.2 (CH₂CH₂CH₂N), 55.6 (aromatic OCH₃), 52.7 (CH₂CH₂CH₂N(CH₂)CH₂), 51.9 (C(=O)OCH₃), 49.8 (CH₂CH₂CH₂N(CH₂)CH₂CH₂), 49.8 (CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 35.5 (CH₂CH₂CH₂N), 34.5 (NCH(CH₂)₂), 22.3 (CH₂CH₂CH₂N), 8.0 (NCH(CH₂)₂)

HRMS (ESI⁺) m/z / Da = 537.2523, [M+H]⁺ found, [C₂₉H₃₄FN₄O₅]⁺ requires 537.2513

The compound has not been reported previously.

1.13 Methyl 1-cyclopropyl-6-fluoro-7-(4-(4-((3-methoxyphenyl)amino)-4-oxobutyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate **107**



Methyl 1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate **92** (500 mg, 1.45 mmol, 1 eq.), 4-bromo-*N*-(3-methoxyphenyl)butanamide **103** (788 mg, 2.90 mmol, 2 eq.), DIPEA (1.28 ml, 950 mg, 7.35 mmol, 5 eq.), NaI (275 mg, 1.83 mmol, 1.3 eq.) and acetonitrile (10 ml) were stirred in a microwave reactor at 100 °C for 4 h. The mixture was evaporated under reduced pressure and partitioned between CH₂Cl₂ (50 ml) and water (50 ml). The organic layer was separated off and the aqueous layer was extracted again with CH₂Cl₂ (50 ml). The combined organic layers were dried with MgSO₄ and purified by column chromatography (SiO₂, 0-4 % MeOH/CH₂Cl₂). The combined pure fractions were dried with MgSO₄ and evaporated under reduced pressure. **107** was obtained as an off-white amorphous solid (81.7 mg, 0.152 mmol, 10.5 %).

TLC R_f = 0.38 (10 % MeOH/CH₂Cl₂)

IR (neat) ν_{max} / cm⁻¹ = 3270.8 (amide N-H) 2943.8 (C-H), 2817.0 (C-H), 1729.5 (ester C=O), 1682.0 (amide C=O), 1613.5 (quinolone C=O)

¹H NMR (400 MHz, CDCl₃) δ / ppm = 8.56 (s, 1 H, *ortho* to C(=O)OCH₃), 8.06 (d, J = 13.3 Hz, 1 H, *ortho* to F), 8.02 (br s, 1 H, NH), 7.34 (t, J = 1.7 Hz, 1 H, *ortho* to OCH₃ and *ortho* to NH), 7.25 (d, J = 7.0 Hz, 1 H, *meta* to F), 7.20 (t, J = 8.2 Hz, 1 H, *meta* to OCH₃ and *meta* to NH), 6.98 (dd, J = 7.8, 1.7 Hz, 1 H, *para* to OCH₃), 6.65 (dd, J = 8.2, 2.1 Hz, 1 H, *para* to NH), 3.93 (s, 3 H, C(=O)OCH₃), 3.80 (s, 3 H, aromatic OCH₃), 3.42 (tt, J = 6.8, 3.7 Hz, 1 H, NCH(CH₂)₂), 3.31 (br t, J = 4.3, 4.3 Hz, 4 H, C(=O)CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 2.73 (br t, J = 4.5, 4.5 Hz, 4 H, C(=O)CH₂CH₂CH₂N(CH₂)CH₂), 2.58 (t, J = 6.5 Hz, 2 H, C(=O)CH₂CH₂CH₂N), 2.48 (t, J = 6.8 Hz, 2 H, C(=O)CH₂CH₂CH₂N), 2.00 (quin, J = 6.8 Hz, 2 H, C(=O)CH₂CH₂CH₂N), 1.29 - 1.36 (m, 2 H, NCH(CH₂)₂), 1.11 - 1.17 (m, 2 H, NCH(CH₂)₂)

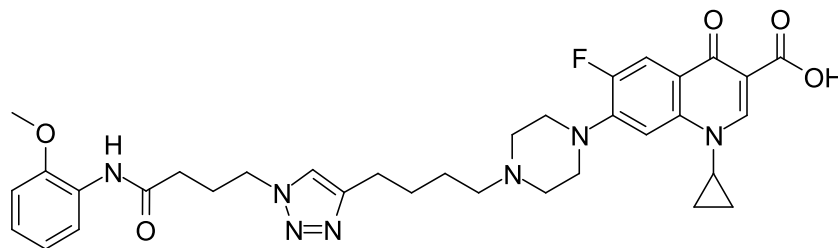
¹³C NMR (101 MHz, CDCl₃) δ / ppm = 173.1 (C(=O)CC(=O)OCH₃), 170.9 (NHC(=O)), 166.3 (C(=O)OCH₃), 160.1 (*ipso* to OCH₃), 153.3 (d, J =250.1 Hz, *ipso* to F), 148.4 (C=CC(=O)OCH₃), 144.1 (d, J =10.1 Hz, *ipso* to piperazine), 139.4 (*ipso* to NH), 138.0 (*para* to F), 129.6 (*meta* to NH and *meta* to OCH₃), 123.3 (d, J =6.4 Hz, *para* to piperazine), 113.4 (d, J =23.3 Hz, *ortho* to C=O and *ortho* to F), 111.8 (*para* to OCH₃), 110.0 (C(=O)OCH₃), 109.8 (*para* to NH), 105.5 (*ortho* to OCH₃ and *ortho* to NH), 105.0 (*meta* to C=O and *meta* to F), 57.0 (CH₂CH₂CH₂N), 55.3 (aromatic OCH₃), 52.6 (CH₂CH₂CH₂N(CH₂)CH₂), 52.1 (C(=O)OCH₃), 49.2 (CH₂CH₂CH₂N(CH₂)CH₂), 35.2 (CH₂CH₂CH₂N), 34.6 (NCH(CH₂)₂), 21.7 (CH₂CH₂CH₂N), 8.2 (NCH(CH₂)₂)

¹⁹F NMR (376.45 MHz, MeOD) δ / ppm = -123.5 (s, ciprofloxacin F)

HRMS (ESI⁺) m/z / Da = 537.2500, [M+H]⁺ found, [C₂₉H₃₄FN₄O₅]⁺ requires 537.2513

The compound has not been reported previously.

1.14 1-Cyclopropyl-6-fluoro-7-(4-(4-(1-(4-((2-methoxyphenyl)amino)-4-oxobutyl)-1*H*-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **108**



1-Cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **70** (24.1 mg, 58.6 μ mol, 1 eq.) and 4-azido-*N*-(2-methoxyphenyl)butanamide **104** (13.7 mg, 58.5 μ mol, 1 eq.) were dissolved in water (3 ml), *t*-BuOH (9 ml) and CH₂Cl₂ (9 ml), and the mixture was degassed by bubbling through N₂. A solution of CuSO₄ and THPTA (117 μ l, 5.85 μ mol, 0.1 eq., 50 mM, aq.) was added, followed by a solution of sodium ascorbate (234 μ l, 11.7 μ mol, 0.2 eq., 50 mM, aq.). The mixture was stirred at room temperature under argon for 16 h. Water (25 ml), CH₂Cl₂ (25 ml) and MeOH (5 ml) were added and the organic layer was separated off, dry-loaded onto SiO₂ and purified by column chromatography using a Combiflash (SiO₂, 3-23 % MeOH/CH₂Cl₂). The combined pure fractions were dried with MgSO₄ and evaporated under reduced pressure. **108** was obtained as a clear glass (14.7 mg, 22.8 μ mol, 39.0 %).

TLC R_f = 0.28 (10 % MeOH/CH₂Cl₂)

IR (neat) ν_{max} / cm⁻¹ = 2926.5 (C-H), 2846.6 (C-H), 1723.4 (carboxylic acid C=O), 1682.0 (amide C=O), 1625.8 (quinolone C=O), 1612.8 (triazole)

¹H NMR (400 MHz, CDCl₃) δ / ppm = 15.05 (br s, 1 H, C(=O)OH), 8.76 (s, 1 H, *ortho* to C(=O)OH), 8.31 (dd, J = 8.0, 1.7 Hz, 1 H, *ortho* to NH), 8.00 (d, J = 13.0 Hz, 1 H, *ortho* to F), 7.83 (br s, 1 H, NH), 7.37 (s, 1 H, CH=CCH₂), 7.35 (d, J = 7.2 Hz, 1 H, *meta* to F), 7.04 (td, J = 7.7, 1.7 Hz, 1 H, *para* to NH), 6.95 (td, J = 7.8, 1.5 Hz, 1 H, *para* to OCH₃), 6.88 (dd, J = 8.1, 1.4 Hz, 1 H, *ortho* to OCH₃), 4.47 (t, J = 6.7 Hz, 2 H, C(=O)CH₂CH₂CH₂N), 3.88 (s, 3 H, CH₃), 3.54 (tt, J = 6.9, 4.0 Hz, 1 H, NCH(CH₂)₂), 3.35 (br t, J = 4.7 Hz, 4 H, CH=CCH₂CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 2.76 (t, J = 7.5 Hz, 2 H, CH=CCH₂), 2.66 (t, J = 4.7 Hz, 4 H, CH=CCH₂CH₂CH₂CH₂N(CH₂)CH₂), 2.47 (t, J = 7.3 Hz, 2 H, CH=CCH₂CH₂CH₂CH₂N), 2.44 (t, J = 6.8 Hz, 2 H, C(=O)CH₂CH₂CH₂N), 2.32 (quin, J = 6.7 Hz, 2 H, C(=O)CH₂CH₂CH₂N), 1.75 (quin, J = 7.6 Hz, 2 H, CH=CCH₂CH₂CH₂CH₂N), 1.61 (quin, J = 7.5 Hz, 2 H, CH=CCH₂CH₂CH₂CH₂N), 1.35 - 1.42 (m, 2 H, NCH(CH₂)₂), 1.17 - 1.22 (m, 2 H, NCH(CH₂)₂)

¹³C NMR (101 MHz, CDCl₃) δ / ppm = 177.1 (C(=O)CC(=O)OH), 169.5 (NHC(=O)), 167.0 (C(=O)OH), 153.7 (d, J = 251.4 Hz, *ipso* to F), 148.1 (CH=CCH₂), 147.8 (*ipso* to OCH₃), 147.3 (C=CC(=O)OH), 145.9 (d, J = 10.4 Hz, *ipso* to piperazine), 139.1 (*para* to F), 127.3 (*ipso* to NH), 123.9 (*para* to NH), 121.0 (*para* to OCH₃), 120.9 (CH=CCH₂), 119.7 (*para* to piperazine, and *ortho* to NH and *meta* to OCH₃), 112.4 (d, J = 23.4 Hz, *ortho* to C=O and *ortho* to F), 109.9 (*ortho* to OCH₃ and *meta* to NH), 108.1 (CC(=O)OH), 104.7 (*meta* to C=O and *meta* to F), 58.1 (CH=CCH₂CH₂CH₂CH₂N), 55.6 (CH₃), 52.8 (CH=CCH₂CH₂CH₂CH₂N(CH₂)CH₂), 49.8 (CH=CCH₂CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 49.8 (CH=CCH₂CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 49.1

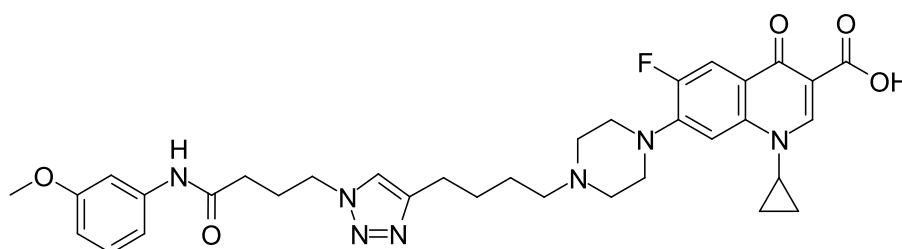
(C(=O)CH₂CH₂CH₂N), 35.2 (NCH(CH₂)₂), 33.8 (C(=O)CH₂CH₂CH₂N), 27.3 (CH=CCH₂CH₂CH₂CH₂N), 26.4 (CH=CCH₂CH₂CH₂CH₂N), 26.0 (C(=O)CH₂CH₂CH₂N), 25.5 (CH=CCH₂CH₂CH₂CH₂N), 8.2 (NCH(CH₂)₂)

¹⁹F NMR (376.45 MHz, CDCl₃) δ / ppm = -120.7 (s, ciprofloxacin F)

HRMS (ESI⁺) *m/z* / Da = 646.3132, [M+H]⁺ found, [C₃₄H₄₁FN₇O₅]⁺ requires 646.3153

The compound has not been reported previously.

1.15 1-Cyclopropyl-6-fluoro-7-(4-(4-(1-(4-((3-methoxyphenyl)amino)-4-oxobutyl)-1*H*-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **109**



1-Cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **70** (24.1 mg, 58.6 μmol, 1 eq.) and 4-azido-*N*-(3-methoxyphenyl)butanamide **105** (13.7 mg, 58.5 μmol, 1 eq.) were dissolved in water (1 ml), *t*-BuOH (9 ml) and CH₂Cl₂ (10 ml), and the mixture was degassed by bubbling through N₂. A solution of CuSO₄ and THPTA (58.5 μl, 5.85 μmol, 0.1 eq. 100 mM, aq.) was added, followed by a solution of sodium ascorbate (117 μl, 11.7 μmol, 0.2 eq., 100 mM, aq.). The mixture was stirred at room temperature under argon for 2 h, then the solvent was removed under reduced pressure. The residue was partitioned between water (15 ml) and CH₂Cl₂ (15 ml), and the aqueous layer was extracted a further four times with CH₂Cl₂ (4×15 ml). The combined organic layers were dried with MgSO₄, dry-loaded onto SiO₂ and purified by column chromatography (SiO₂, 0-10 % MeOH/CH₂Cl₂). The combined pure fractions were dried with MgSO₄ and evaporated under reduced pressure. **109** was obtained as a clear glass (1.9 mg, 2.9 μmol, 5.0 %).

TLC *R_f* = 0.22 (10 % MeOH/CH₂Cl₂)

IR (neat) *ν*_{max} / cm⁻¹ = 2922.8 (C-H), 2849.5 (C-H), 1725.8 (carboxylic acid C=O), 1684.7 (amide C=O), 1624.5 (quinolone C=O), 1612.2 (triazole)

¹H NMR (400 MHz, DMSO *d*₆) δ / ppm = 15.23 (br s, 1 H, C(=O)OH), 9.89 (s, 1 H, NH), 8.66 (s, 1 H, *ortho* to C(=O)OH), 7.90 (d, *J* = 13.4 Hz, 1 H, *ortho* to F), 7.88 (s, 1 H, CH=CCH₂), 7.55 (d, *J* = 7.6 Hz, 1 H, *meta* to F), 7.27 (t, *J* = 2.1 Hz, 1 H, *ortho* to C=O and *ortho* to F), 7.16 (t, *J* = 8.1 Hz, 1 H, *meta* to OCH₃ and *meta* to NH), 7.08 (d, *J* = 7.8 Hz, 1 H, *para* to OCH₃), 6.59 (ddd, *J* = 8.1, 2.4, 0.7 Hz, 1 H, *para* to NH), 4.36 (t, *J* = 6.9 Hz, 2 H, C(=O)CH₂CH₂CH₂N), 3.81 (tt, *J* = 6.7, 4.0 Hz, 1 H, NCH(CH₂)₂), 3.70 (s, 3 H, CH₃), 3.28 - 3.32 (m, 4 H, CH=CCH₂CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 2.64 (t, *J* = 7.5 Hz, 2 H, CH=CCH₂), 2.56 (m, *J* = 4.2, 4.2 Hz, 4 H, CH=CCH₂CH₂CH₂CH₂N(CH₂)CH₂), 2.38 (t, *J* = 7.3 Hz, 2 H, CH=CCH₂CH₂CH₂CH₂N), 2.30 (t, *J* = 7.4 Hz, 2 H, C(=O)CH₂CH₂CH₂N), 2.10 (quin, *J* = 7.1 Hz, 2 H, C(=O)CH₂CH₂CH₂N), 1.64 (quin, *J* = 7.5 Hz, 2 H, CH=CCH₂CH₂CH₂CH₂N), 1.51 (quin, *J* = 7.2 Hz, 2 H,

CH=CCH₂CH₂CH₂CH₂N), 1.27 - 1.33 (m, 2 H, NCH(CHH)₂), 1.15 - 1.20 (m, 2 H, NCH(CHH)₂)

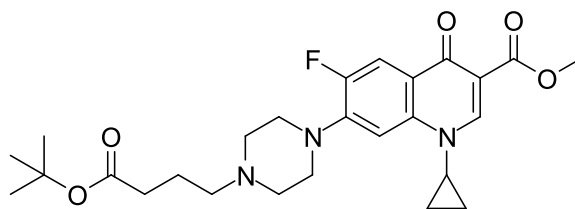
¹³C NMR (101 MHz, DMSO d₆) δ / ppm = 176.3 (C(=O)CC(=O)OH), 170.1 (NHC(=O)), 165.9 (C(=O)OH), 159.4 (*ipso* to OCH₃), 153.0 (d, *J* = 248.6 Hz, *ipso* to F), 148.0 (CH=CCH₂), 146.9 (C=CC(=O)OH), 145.2 (d, *J* = 10.7 Hz, *ipso* to piperazine), 140.3 (*para* to F), 139.2 (*ipso* to NH), 129.4 (*meta* to OCH₃ and *meta* to NH), 121.7 (CH=CCH₂), 118.5 (d, *J* = 7.5 Hz, *para* to piperazine), 111.3 (*para* to OCH₃), 110.9 (d, *J* = 22.4 Hz, *ortho* to C=O and *ortho* to F), 108.4 (*para* to NH), 106.7 (CC(=O)OH), 106.3 (*meta* to C=O and *meta* to F), 104.8 (*ortho* to OCH₃ and *ortho* to NH), 57.3 (CH=CCH₂CH₂CH₂CH₂N), 54.9 (CH₃), 52.4 (CH=CCH₂CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 49.5 (CH=CCH₂CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 49.4 (CH=CCH₂CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 48.7 (C(=O)CH₂CH₂CH₂N), 35.8 (NCH(CH₂)₂), 32.9 (C(=O)CH₂CH₂CH₂N), 26.8 (CH=CCH₂CH₂CH₂CH₂N), 25.7 (CH=CCH₂CH₂CH₂CH₂N), 25.5 (C(=O)CH₂CH₂CH₂N), 24.9 (CH=CCH₂CH₂CH₂CH₂N), 7.6 (NCH(CH₂)₂)

¹⁹F NMR (376.45 MHz, DMSO d₆) δ / ppm = -121.5 (s, ciprofloxacin F)

HRMS (ESI⁺) *m/z* / Da = 646.3159, [M+H]⁺ found, [C₃₄H₄₁FN₇O₅]⁺ requires 646.3153

The compound has not been reported previously.

1.16 Methyl 7-(4-(4-(*tert*-butoxy)-4-oxobutyl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate **111**



Methyl 1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate **92** (200 mg, 0.579 mmol, 1 eq.), *tert*-butyl 4-bromobutanoate **110** (103 μl, 130 mg, 0.581 mmol, 1 eq.), NaI (86.9 mg, 0.580 mmol, 1 eq.), TEA (316 μl, 229 mg, 2.27 mmol, 4 eq.) and acetonitrile (10 ml) were stirred in a microwave reactor at 100 °C for 8 h. A second portion of *tert*-butyl 4-bromobutanoate **141** (103 μl, 130 mg, 0.581 mmol, 1 eq.) was added, and the mixture was stirred in the microwave reactor at 100 °C for a further 8 h. The mixture was then dry-loaded onto SiO₂ and purified by column chromatography (SiO₂, 0-4 % MeOH/CH₂Cl₂). **111** was obtained as a white amorphous solid (141 mg, 0.289 mmol, 49.9 %).

TLC *R_f* = 0.12 (4 % MeOH/CH₂Cl₂)

IR (neat) ν_{max} / cm⁻¹ = 2961.6 (C-H), 2830.5 (C-H), 1732.2 (*t*-Bu ester C=O) 1717.2 (ciprofloxacin ester C=O), 1620.6 (quinolone C=O)

¹H NMR (400 MHz, CDCl₃) δ / ppm = 8.39 (s, 1 H, *ortho* to C(=O)OCH₃), 7.82 (d, *J* = 13.3 Hz, 1 H, *ortho* to F), 7.17 (d, *J* = 7.2 Hz, 1 H, *meta* to F), 3.83 (s, 3 H, CH₃), 3.40 (tt, *J* = 7.2, 3.6 Hz, 1 H, NCH(CH₂)₂), 3.22 (t, *J* = 4.3 Hz, 4 H, CH₂N(CH₂CH₂)CH₂CH₂), 2.63 (t, *J* = 4.4 Hz, 4 H, CH₂N(CH₂)CH₂), 2.41 (t, *J* = 7.3 Hz, 2 H, CH₂N(CH₂)CH₂), 2.25 (t, *J* = 7.4 Hz, 2 H, CH₂CH₂CH₂N(CH₂)CH₂), 1.78 (quin, *J* = 7.3 Hz, 2 H, CH₂CH₂N(CH₂)CH₂), 1.41 (s, 9 H, C((CH₃)₃)), 1.24 (m, 2 H, NCH(CHH)₂), 1.09 (m, 2 H, NCH(CHH)₂)

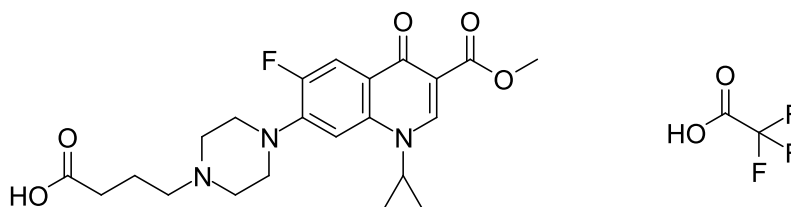
^{13}C NMR (101 MHz, CDCl_3) δ / ppm = 172.7 ($\text{C}(=\text{O})\text{CC}(=\text{O})\text{OCH}_3$), 172.6 ($\text{C}(=\text{O})\text{OC}(\text{CH}_3)_3$), 165.9 ($\text{C}(=\text{O})\text{OCH}_3$), 153.1 (d, J = 249.7 Hz, *ipso* to F), 148.1 ($\text{C}=\text{CC}(=\text{O})\text{OCH}_3$), 144.3 (d, J = 10.4 Hz, *ipso* to piperazine), 137.7 (*para* to F), 122.5 (d, J = 6.9 Hz, *para* to piperazine) 112.6 (d, J = 22.5 Hz, *ortho* to C=O and *ortho* to F), 109.5 ($\text{CC}(=\text{O})\text{OCH}_3$) 104.7 (*meta* to C=O and *meta* to F), 80.0 ($\text{C}(\text{CH}_3)_3$), 57.4 ($\text{C}(=\text{O})\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$), 52.7 ($\text{C}(=\text{O})\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2)\text{CH}_2$), 51.7 (CH_3), 49.7 ($\text{C}(=\text{O})\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)\text{CH}_2\text{CH}_2$), 49.7 ($\text{C}(=\text{O})\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)\text{CH}_2\text{CH}_2$), 34.4 ($\text{NCH}(\text{CH}_2)_2$), 33.2 ($\text{C}(=\text{O})\text{CH}_2$), 28.0 ($\text{C}(\text{CH}_3)_3$), 22.0 ($\text{C}(=\text{O})\text{CH}_2\text{CH}_2$), 7.9 ($\text{NCH}(\text{CH}_2)_2$)

^{19}F NMR (376.45 MHz, CDCl_3) δ / ppm = -123.5 (s, ciprofloxacin F)

HRMS (ESI^+) m/z / Da = 488.2562, $[\text{M}+\text{H}]^+$ found, $[\text{C}_{26}\text{H}_{35}\text{FN}_3\text{O}_5]^+$ requires 488.2561

The compound has not been reported previously.

1.17 4-(4-(1-Cyclopropyl-6-fluoro-3-(methoxycarbonyl)-4-oxo-1,4-dihydroquinolin-7-yl)piperazin-1-yl)butanoic acid trifluoroacetate **112**



Methyl 7-(4-(4-(*tert*-butoxy)-4-oxobutyl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate **111** (20 mg, 41.0 μmol) and TFA (0.2 ml) were stirred in CH_2Cl_2 (1.8 ml) at r.t. for 16 h then evaporated under reduced pressure. **112** was obtained as a white solid (21.4 mg, 39.2 μmol , 95.6 %).

mp T / $^\circ\text{C}$ = 225-231 (CH_2Cl_2 , decomposes)

IR (neat) ν_{max} / cm^{-1} = 1722.7 (ciprofloxacin ester C=O), 1699.0 (alkyl carboxylic acid C=O), 1673.3 (TFA C=O), 1614.6 (quinolone C=O)

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ / ppm = 8.47 (s, 1 H, *ortho* to $\text{C}(=\text{O})\text{OH}$), 7.80 (d, J = 13.2 Hz, 1 H, *ortho* to F), 7.47 (d, J = 7.4 Hz, 1 H, *meta* to F), 3.73 (s, 3 H, CH_3), 3.66 (tt, J = 7.2, 3.7 Hz, 1 H, $\text{NCH}(\text{CH}_2)_2$), 3.30 - 3.54 (br s, 8 H, $\text{CH}_2\text{N}(\text{CH}_2)\text{CH}_2$ and $\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)\text{CH}_2\text{CH}_2$) 3.13 - 3.22 (m, 2 H, $\text{CH}_2\text{N}(\text{CH}_2)\text{CH}_2$), 2.36 (t, J = 7.1 Hz, 2 H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2)\text{CH}_2$), 1.87 - 1.98 (m, 2 H, $\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2)\text{CH}_2$), 1.22 - 1.30 (m, 2 H, $\text{NCH}(\text{CH}_2)_2$), 1.06 - 1.15 (m, 2 H, $\text{NCH}(\text{CH}_2)_2$)

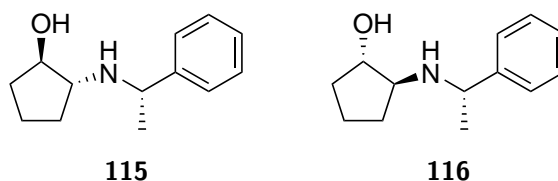
^{13}C NMR (101 MHz, $\text{DMSO}-d_6$) δ / ppm = 173.5 ($\text{CH}_2\text{C}(=\text{O})\text{OH}$), 171.6 ($\text{C}(=\text{O})\text{CC}(=\text{O})\text{OCH}_3$), 164.9 ($\text{C}(=\text{O})\text{OCH}_3$), 158.2 (q, J = 31.5 Hz, $\text{CF}_3\text{C}(=\text{O})\text{OH}$), 152.5 (d, J = 247.6 Hz, *ipso* to F), 148.5 ($\text{C}=\text{CC}(=\text{O})\text{OH}$), 142.3 (d, J = 10.7 Hz, *ipso* to piperazine), 138.0 (*para* to F), 122.6 (d, J = 6.4 Hz, *para* to piperazine), 117.2 (q, J = 299.8 Hz, CF_3), 111.9 (d, J = 22.4 Hz, *ortho* to C=O and *ortho* to F), 109.1 ($\text{CC}(=\text{O})\text{OCH}_3$), 106.9 (*meta* to C=O and *meta* to F), 55.1 ($\text{C}(=\text{O})\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$), 51.4 (CH_3), 50.8 ($\text{C}(=\text{O})\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2)\text{CH}_2$), 46.7 ($\text{C}(=\text{O})\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)\text{CH}_2\text{CH}_2$), 46.7 ($\text{C}(=\text{O})\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)\text{CH}_2\text{CH}_2$), 34.9 ($\text{NCH}(\text{CH}_2)_2$), 30.6 ($\text{C}(=\text{O})\text{CH}_2$), 19.1 ($\text{C}(=\text{O})\text{CH}_2\text{CH}_2$), 7.6 ($\text{NCH}(\text{CH}_2)_2$)

^{19}F NMR (376.45 MHz, DMSO d_6) δ / ppm = -73.6 (s, CF_3), -124.6 (s, ciprofloxacin F)

HRMS (ESI^+) m/z / Da = 432.1921, $[\text{M}+\text{H}]^+$ found, $[\text{C}_{22}\text{H}_{27}\text{FN}_3\text{O}_5]^+$ requires 432.1935

The compound has not been reported previously.

1.18 (1*R*,2*R*)-2-(((*S*)-1-Phenylethyl)amino)cyclopentan-1-ol **115** and (1*S*,2*S*)-2-(((*S*)-1-phenylethyl)amino)cyclopentan-1-ol **116**



(*S*)-1-Phenylethan-1-amine **113** (7.85 ml, 7.38 g, 60.9 mmol, 1 eq.) was dissolved in CH_2Cl_2 (50 ml) and stirred rapidly at 0 °C. A solution of AlMe_3 (31 ml, 2.0 M in heptane, 60.9 mmol) was added dropwise and the mixture was stirred at 0 °C for 1 h. A solution of cyclohexene oxide **114** (5.71 ml, 5.50 g, 65.4 mmol, 1.1 eq.) in CH_2Cl_2 (50 ml) was then added dropwise, and the mixture was stirred at 0 °C for a further 3 h, followed by 48 h at r.t.. The mixture was cooled to 0 °C and NaF (11 g, 262 mmol, 4.3 eq.) was added portionwise, followed by water (7.00 ml, 7.00 g, 389 mmol, 6.4 eq.) and CH_2Cl_2 (50 ml). The suspension was allowed to warm to r.t. and stirred for 1 h, then filtered through Celite and washed with CH_2Cl_2 (500 ml). The filtrate was dried with K_2CO_3 , concentrated under reduced pressure and purified by column chromatography (SiO_2 , 20:5:1 hexane:EtOAc:TEA). **115** was obtained as a pale yellow oil (4.08 g, 19.9 mmol, 32.6 %). **116** was obtained as pale yellow crystals (4.48 g, 21.8 mmol, 35.8 %).

(1*R*,2*R*)-2-(((*S*)-1-Phenylethyl)amino)cyclopentan-1-ol **115**

TLC R_f = 0.25 (15:5:1 hexane:EtOAc:TEA)

IR (neat) ν_{max} / cm^{-1} = 3300.0 (br, O-H), 2959.7 (C-H), 2870.1 (C-H)

^1H NMR (400 MHz, CDCl_3) δ / ppm = 7.28 - 7.38 (m, 4 H, *ortho* and *meta* to CHCH_3), 7.21 - 7.28 (m, 1 H, *para* to CHCH_3), 3.83 (q, J = 6.6 Hz, 1 H, CHCH_3), 3.78 (q, J = 7.0 Hz, 1 H, CHOH), 2.62 (dt, J = 8.2, 7.2 Hz, 1 H, CHNH), 1.97 (quin, J = 6.7 Hz, 1 H, CH_2CHNH), 1.90 (quin, J = 6.9 Hz, 1 H, CH_2CHOH), 1.56 - 1.68 (m, $\text{CH}_2\text{CH}_2\text{CHOH}$), 1.43 (dq, J = 12.5, 8.0 Hz, 1 H, CH_2CHOH), 1.37 (d, J = 6.6 Hz, 3 H, CH_3), 1.25 - 1.36 (m, 1 H, CH_2CHNH)

^{13}C NMR (101 MHz, CDCl_3) δ / ppm = 144.75 (*ipso* to CHCH_3), 128.26 (*meta* to CHCH_3), 126.72 (*para* to CHCH_3), 126.30 (*ortho* to CHCH_3), 77.65 (CHOH), 63.38 (CHNH), 56.20 (CHCH_3), 31.74 (CH_2CHOH), 29.22 (CH_2CHNH), 24.58 (CH_3), 19.57 ($\text{CH}_2\text{CH}_2\text{CHOH}$)

HRMS (ESI^+) m/z / Da = 206.1554, $[\text{M}+\text{H}]^+$ found, $[\text{C}_{13}\text{H}_{20}\text{NO}]^+$ requires 206.1545

$[\alpha]_D^{20}$ / $^{\circ}10^{-1}\text{cm}^2\text{g}^{-1}$ = -92.8 (c / $\text{g}(100\text{ ml})^{-1}$ = 1.19, MeOH)

(1*S*,2*S*)-2-(((*S*)-1-Phenylethyl)amino)cyclopentan-1-ol 116

TLC R_f = 0.36 (15:5:1 hexane:EtOAc:TEA)

mp T / °C = 66-71.5 (hexane, EtOAc, TEA)

IR (neat) ν_{max} / cm^{-1} = 3150.0 (br, O-H), 2950.9 (C-H), 2868.2 (C-H)

^1H NMR (400 MHz, CDCl_3) δ / ppm = 7.28 - 7.34 (m, 4 H, *ortho* and *meta* to CHCH_3), 7.20 - 7.26 (m, 1 H, *para* to CHCH_3), 3.86 (q, J = 6.6 Hz, 1 H, CHCH_3), 3.85 (q, J = 6.6 Hz, 1 H, CHOH), 2.83 (td, J = 7.6, 5.7 Hz, 1 H, CHNH), 1.85 - 1.97 (m, 1 H, CHHCHOH), 1.77 (dtd, J = 12.9, 7.9, 7.9, 4.9 Hz, 1 H, CHHCHNH), 1.55 - 1.68 (m, 2 H, $\text{CH}_2\text{CH}_2\text{CHOH}$), 1.47 - 1.55 (m, 1 H, CHHCHOH), 1.36 (d, J = 6.6 Hz, 3 H, CH_3), 1.12 (dq, J = 12.7, 8.1 Hz, 1 H, CHHCHNH)

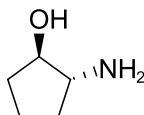
^{13}C NMR (101 MHz, CDCl_3) δ / ppm = 145.61 (*ipso* to CHCH_3), 128.08 (*meta* to CHCH_3), 126.61 (*para* to CHCH_3), 126.33 (*ortho* to CHCH_3), 77.43 (CHOH), 64.45 (CHNH), 56.62 (CHCH_3), 32.01 (CH_2CHOH), 30.56 (CH_2CHNH), 23.30 (CH_3), 20.06 ($\text{CH}_2\text{CH}_2\text{CHOH}$)

HRMS (ESI^+) m/z / Da = 206.1553, $[\text{M}+\text{H}]^+$ found, $[\text{C}_{13}\text{H}_{20}\text{NO}]^+$ requires 206.1545

$[\alpha]_D^{20}$ / $^{\circ}\text{10}^{-1}\text{cm}^2\text{g}^{-1}$ = -23.9 (c / g(100 ml)^{-1} = 0.96, MeOH)

The compounds have been synthesised previously,^{6,7} but NMR data were not published. The enantiomers of both compounds have also been synthesised previously, and the ^1H NMR data for these are consistent with the the above data.⁸

1.19 (1*R*,2*R*)-2-Aminocyclopentan-1-ol 117



(1*R*,2*R*)-2-(((*S*)-1-Phenylethyl)amino)cyclopentan-1-ol **115** (3.90 g, 19.0 mmol, 1 eq.), $\text{Pd}(\text{OH})_2$ (20 wt. % on C, moistened with 50 wt. % water, 1 g, 0.712 mmol, 0.04 eq.) and MeOH (50 ml) were stirred in a Paar hydrogenator at r.t. and 3 atm for 2 days. The mixture was then filtered through Celite and evaporated under reduced pressure. **117** was obtained as a yellow oil (1.92 g, 19.0 mmol, 100 %).

TLC R_f = 0.10 (10 % MeOH/ CH_2Cl_2)

IR (neat) ν_{max} / cm^{-1} = 3300.0 (br, O-H), 2958.3 (C-H), 2871.5 (C-H)

^1H NMR (400 MHz, MeOD) δ / ppm = 3.77 (ddd, J =6.6, 6.2, 5.6, 1 H, CHOH), 3.00 (td, J =7.3, 5.6 Hz, 1 H, CHNH_2), 2.00 (dtd, J =13.0, 7.7, 7.7, 5.6 Hz, 1 H, CHHCHNH_2), 1.97 (ddt, J =13.0, 8.7, 6.6, 6.6 Hz, 1 H, CHHCHOH), 1.63 - 1.77 (m, 2 H, $\text{CH}_2\text{CH}_2\text{CHOH}$), 1.53 (ddt, J =13.0, 9.5, 6.2, 6.2 Hz, 1 H, CHHCHOH), 1.37 (ddt, J =13.0, 8.3, 7.8, 7.8 Hz, 1 H, CHHCHNH_2)

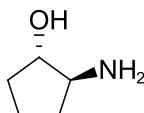
^{13}C NMR (101 MHz, MeOD) δ / ppm = 80.7 ($\underline{\text{C}}\text{HOH}$), 60.8 ($\underline{\text{C}}\text{HNH}_2$), 33.2 ($\underline{\text{C}}\text{H}_2\text{CHOH}$), 32.1 ($\underline{\text{C}}\text{H}_2\text{CHNH}_2$), 21.2 ($\underline{\text{C}}\text{H}_2\text{CH}_2\text{CHOH}$)

HRMS (ESI⁺) m/z / Da = 102.0917, $[\text{M}+\text{H}]^+$ found, $[\text{C}_5\text{H}_{12}\text{NO}]^+$ requires 102.0913

$[\alpha]_D^{20}$ / $^{\circ}\text{10}^{-1}\text{cm}^2\text{g}^{-1}$ = -30.9 (c / $\text{g}(100\text{ ml})^{-1}$ = 1.5, EtOH)

The data are consistent with the literature.^{7,9}

1.20 (1*S*,2*S*)-2-Aminocyclopentan-1-ol **118**



(1*S*,2*S*)-2-(((*S*)-1-Phenylethyl)amino)cyclopentan-1-ol **116** (3.00 g, 14.6 mmol, 1 eq.), Pd(OH)₂ (20 wt. % on C, moistened with 50 wt. % water, 0.5 g, 0.356 mmol, 0.025 eq.) and MeOH (50 ml) were stirred in a Paar hydrogenator at r.t. and 2.5 atm for 2 days. The mixture was then filtered through Celite and evaporated under reduced pressure. **118** was obtained as a yellow oil (1.48 g, 14.6 mmol, 100 %).

TLC R_f = 0.10 (10 % MeOH/ CH_2Cl_2)

IR (neat) ν_{max} / cm^{-1} = 3300.0 (O-H), 2969.2 (C-H), 2872.7 (C-H)

^1H NMR (400 MHz, MeOD) δ / ppm = 3.77 (ddd, J =6.6, 6.2, 5.6, 1 H, $\underline{\text{C}}\text{HOH}$), 3.00 (td, J = 7.4, 5.6 Hz, 1 H, $\underline{\text{C}}\text{HNH}_2$), 2.00 (dtd, J = 13.0, 7.7, 7.7, 5.6 Hz, 1 H, $\underline{\text{C}}\text{HHCHNH}_2$), 1.97 (ddt, J = 13.0, 8.7, 6.4, 6.4 Hz, 1 H, $\underline{\text{C}}\text{HHCHOH}$), 1.64 - 1.77 (m, 2 H, $\underline{\text{C}}\text{H}_2\text{CH}_2\text{CHOH}$), 1.53 (ddt, J = 13.0, 9.5, 6.2, 6.2 Hz, 1 H, $\underline{\text{C}}\text{HHCHOH}$), 1.37 (ddt, J = 12.8, 8.5, 7.7, 7.7 Hz, 1 H, $\underline{\text{C}}\text{HHCHNH}_2$)

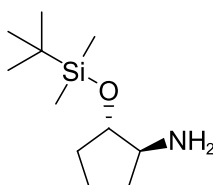
^{13}C NMR (101 MHz, MeOD) δ / ppm = 80.6 ($\underline{\text{C}}\text{HOH}$), 60.7 ($\underline{\text{C}}\text{HNH}_2$), 33.2 ($\underline{\text{C}}\text{H}_2\text{CHOH}$), 32.2 ($\underline{\text{C}}\text{H}_2\text{CHNH}_2$), 21.2 ($\underline{\text{C}}\text{H}_2\text{CH}_2\text{CHOH}$)

HRMS (ESI⁺) m/z / Da = 102.0915, $[\text{M}+\text{H}]^+$ found, $[\text{C}_5\text{H}_{12}\text{NO}]^+$ requires 102.0913

$[\alpha]_D^{20}$ / $^{\circ}\text{10}^{-1}\text{cm}^2\text{g}^{-1}$ = 33.4 (c / $\text{g}(100\text{ ml})^{-1}$ = 0.5, EtOH)

The data are consistent with the literature.^{7,9}

1.21 (1*S*,2*S*)-2-((*tert*-Butyldimethylsilyl)oxy)cyclopentan-1-amine **119**



(1*S*,2*S*)-2-Aminocyclopentan-1-ol **118** (0.480 g, 4.75 mmol) was stirred in dry CH₂Cl₂ (20 ml) under N₂ at 0 °C. TEA (3.14 ml, 2.28 g, 22.5 mmol, 5 eq.) was added dropwise, followed by TBSOTf (3 ml, 3.45 g, 13.1 mmol, 3 eq.) dropwise. The reaction was allowed to reach r.t. and stirred for 1 h. The reaction was quenched with NH₄Cl, diluted with CH₂Cl₂ (20 ml) and washed with water (20 ml). The organic phase was dried with Na₂SO₄, concentrated under reduced pressure and purified by column chromatography (SiO₂, 4 % MeOH/CH₂Cl₂). **119** was obtained as a yellow oil (1.00 g, 4.64 mmol, 97.7 %).

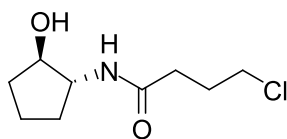
TLC R_f = 0.23 (10 % MeOH/CH₂Cl₂)

¹H NMR (400 MHz, CDCl₃) δ / ppm = 4.13 (q, J = 5.8 Hz, 1 H, CHOSi), 3.31 (td, J = 7.1, 5.2 Hz, 1 H, CHNH₂), 2.09 - 2.19 (m, 1 H, CHHCHNH₂), 1.97 (ddq, J = 8.8, 7.0, 6.0, 6.0, 6.0 Hz, 1 H, CHHCHOSi), 1.74 - 1.86 (m, 2 H, CH₂CH₂CHOSi), 1.64 - 1.74 (m, 1 H, CHHCHOSi), 1.58 (ddt, J = 13.2, 9.1, 6.0, 6.0 Hz, 1 H, CHHCHNH₂), 0.88 (s, 9 H, C(CH₃)₃), 0.09 (s, 3 H, SiCH₃), 0.07 (s, 3 H, SiCH₃)

¹³C NMR (101 MHz, CDCl₃) δ / ppm = 76.3 (CHOSi), 59.7 (CHNH), 32.2 (CH₂CHOSi), 26.8 (CH₂CHNH₂), 25.6 (C(CH₃)₃), 19.7 (CH₂CH₂CHOSi), 17.7 (C(CH₃)₃), -4.8 (SiCH₃), -5.2 (SiCH₃)

The compound has not been reported previously.

1.22 4-Chloro-*N*-((1*R*,2*R*)-2-hydroxycyclopentyl)butanamide **121**



(1*R*,2*R*)-2-Aminocyclopentan-1-ol **117** (500 mg, 4.94 mmol, 1 eq.), TEA (827 μ l, 600 mg, 5.93 mmol, 1.2 eq.) and CH₂Cl₂ (20 ml) were stirred at 0 °C and 4-chlorobutyryl chloride **120** (608 μ l, 766 mg, 5.43 mmol, 1.1 eq.) was added dropwise over 5 min. The mixture was stirred at 0 °C for 30 min, then water (50 ml) was added. The organic layer was separated off, and the aqueous layer was extracted with CH₂Cl₂ (7 \times 50 ml). The combined organic layers were dried with MgSO₄, concentrated under reduced pressure and purified by column chromatography (SiO₂, Et₂O). The combined pure fractions were dried with MgSO₄ and evaporated under reduced pressure. **121** was obtained as a white amorphous solid (651 mg, 3.16 mmol, 64.1 %).

TLC R_f = 0.35 (EtOAc)

IR (neat) ν_{max} / cm⁻¹ = 3277.6 (N-H and O-H), 2962.2 (C-H), 2876.0 (C-H), 1636.3 (amide C=O)

¹H NMR (400 MHz, CDCl₃) δ / ppm = 6.12 (br s, 1 H, NH), 4.42 (br s, 1 H, OH), 3.94 (q, J = 6.6 Hz, 1 H, CHOH), 3.82 (tt, J = 8.4, 5.3 Hz, 1 H, CHNH), 3.60 (t, J = 6.2 Hz, 2 H, CH₂Cl), 2.38 (t, J = 7.2 Hz, 2 H, CH₂C=O), 2.05 - 2.16 (m, 3 H, CHHCHNH and CH₂CH₂Cl), 1.96 - 2.04 (m, 1 H, CHHCHOH), 1.74 - 1.85 (m, 1 H, CHHCH₂CHOH), 1.58 - 1.73 (m, 2 H, CHHCH₂CHOH and CHHCHOH), 1.43 (dq, J = 12.7, 8.3 Hz, 1 H, CHHCHNH)

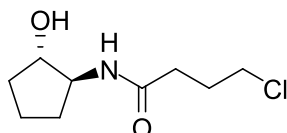
¹³C NMR (101 MHz, CDCl₃) δ / ppm = 173.8 (C=O), 79.4 (CHOH), 60.6 (CHNH), 44.4 (CH₂Cl), 32.8 (CH₂C=O), 32.4 (CH₂CHOH), 30.1 (CH₂CHNH), 28.0 (CH₂CH₂Cl), 21.1 (CH₂CH₂CHOH)

HRMS (ESI⁺) m/z / Da = 228.0787, [M+Na]⁺ found, [C₉H₁₆ClNNaO₂]⁺ requires 228.0762

$[\alpha]_D^{20}$ / °10⁻¹cm²g⁻¹ = -13.0 (c / g(100 ml)⁻¹ = 0.5, MeOH)

The compound has not been reported previously.

1.23 4-Chloro-*N*-((1*S*,2*S*)-2-hydroxycyclopentyl)butanamide **122**



(1*S*,2*S*)-2-Aminocyclopentan-1-ol **118** (72.3 mg, 716 μmol, 1 eq.), TEA (500 μl, 363 mg, 3.58 mmol, 5 eq.) and CH₂Cl₂ (5 ml) were stirred at 0 °C, and 4-chlorobutyryl chloride **120** (179 μl, 226 mg, 1.60 mmol, 1.1 eq.) was added dropwise over 5 min. The mixture was stirred at 0 °C for 30 min, then water (10 ml) was added. The organic layer was separated off, and the aqueous layer was extracted with 10 % *i*-PrOH/CHCl₃ (2×10 ml). The combined organic layers were dried with MgSO₄, concentrated under reduced pressure and purified by column chromatography (SiO₂, Et₂O). The combined pure fractions were dried with MgSO₄ and evaporated under reduced pressure. **122** was obtained as a white amorphous solid (35.6 mg, 173 μmol, 24.2 %).

TLC R_f = 0.35 (EtOAc)

¹H NMR (400 MHz, CDCl₃) δ / ppm = 6.05 (br s, 1 H, NH), 4.55 (br s, 1 H, OH), 3.95 (q, J=6.6 Hz, 1 H, CHOH), 3.82 (tt, J=8.4, 5.3 Hz, 1 H, CHNH), 3.60 (t, J=6.2 Hz, 2 H, CH₂Cl), 2.38 (t, J=7.0 Hz, 2 H, CH₂C=O), 2.05 - 2.17 (m, 3 H, CHHCHNH and CH₂CH₂Cl), 1.94 - 2.05 (m, 1 H, CHHCHOH), 1.74 - 1.86 (m, 1 H, CHHCH₂CHOH), 1.58 - 1.74 (m, 2 H, CHHCH₂CHOH and CHHCHOH), 1.42 (dq, J=12.5, 8.4 Hz, 1 H, CHHCHNH)

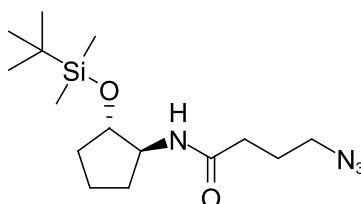
¹³C NMR (101 MHz, CDCl₃) δ / ppm = 173.8 (C=O), 79.4 (CHOH), 60.6 (CHNH), 44.4 (CH₂Cl), 32.8 (CH₂C=O), 32.4 (CH₂CHOH), 30.2 (CH₂CHNH), 28.0 (CH₂CH₂Cl), 21.2 (CH₂CH₂CHOH)

HRMS (ESI⁺) m/z / Da = 206.0939, [M+H]⁺ found, [C₉H₁₇ClNO₂]⁺ requires 206.0948

$[\alpha]_D^{20}$ / °10⁻¹cm²g⁻¹ = 10.0 (c / g(100 ml)⁻¹ = 0.05, MeOH)

The compound has not been reported previously.

1.24 4-Azido-*N*-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclopentyl)butanamide **123**



(1*S*,2*S*)-2-((*tert*-Butyldimethylsilyl)oxy)cyclopentan-1-amine **119** (50 mg, 0.232 mmol, 1 eq.) and NaHCO₃ (22.0 mg, 0.262 mmol, 1.1 eq.) were added to CH₂Cl₂ (3 ml) and water (3 ml) at 0 °C, and 4-bromobutyryl chloride (25.3 ml, 40.5 mg, 0.219 mmol, 0.95 eq.) was added dropwise. The mixture was stirred for 3 h at 0 °C. The aqueous layer was removed and NaN₃ (100 mg, 1.54 mmol, 6.6 eq.) and DMF (3 ml) were added. The mixture was then stirred at 40 °C for 6 h. The solvents were then evaporated using a N₂ stream and the residue was purified by column chromatography (SiO₂, 0.5 % MeOH/CH₂Cl₂). The combined pure fractions were dried with MgSO₄ and evaporated under reduced pressure. **123** was obtained as a clear liquid (71 mg, 0.217 mmol, 99.2 %).

TLC R_f = 0.84 (1 % MeOH/CH₂Cl₂)

IR (neat) ν_{max} / cm⁻¹ = 3287.9 (N-H), 2953.4 (C-H), 2933.2 (C-H), 2882.7 (C-H), 2857.1 (C-H), 2094.9 (azide), 1639.4 (amide C=O)

¹H NMR (400 MHz, CDCl₃) δ / ppm = 5.35 (d, J = 5.1 Hz, 1 H, NH), 3.97 - 4.01 (m, 1 H, CHOSi), 3.93 - 3.98 (m, 1 H, CHNH), 3.35 (t, J = 6.6 Hz, 2 H, CH₂N₃), 2.24 (t, J = 7.0 Hz, 2 H, CH₂C=O), 2.09 - 2.19 (m, 1 H, CHHCHNH), 1.89 - 1.97 (quin, J = 6.8 Hz, 2 H, CH₂CH₂N₃), 1.74 - 1.84 (m, 2 H, CHHCHOSi and CHHCH₂CHOSi), 1.60 - 1.70 (m, 1 H, CHHCH₂CHOSi), 1.51 - 1.61 (m, 1 H, CHHCHOSi), 1.31 - 1.39 (m, 1 H, CHHCHNH), 0.87 (s, 9 H, C(CH₃)₃), 0.08 (s, 3 H, SiCH₃), 0.06 (s, 3 H, SiCH₃)

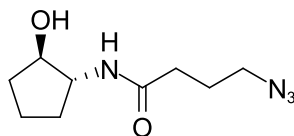
¹³C NMR (101 MHz, CDCl₃) δ / ppm = 171.17 (C=O), 77.80 (CHOSi), 58.36 (CHNH), 50.77 (CH₂N₃), 33.29 (CH₂C=O), 32.57 (CH₂CHOSi), 29.36 (CH₂CHNH), 25.72 (C(CH₃)₃), 24.77 (CH₂CH₂N₃), 20.40 (CH₂CH₂CHO Si), 17.95 (C(CH₃)₃), -4.75 (SiCH₃)

HRMS (ESI⁺) m/z / Da = 327.2221, [M+H]⁺ found, [C₁₅H₃₁N₄O₂Si]⁺ requires 327.2216

$[\alpha]_D^{20}$ / °10⁻¹cm²g⁻¹ = 12.4 (c / g(100 ml)⁻¹ = 0.5, MeOH)

The compound has not been reported previously.

1.25 4-Azido-*N*-((1*R*,2*R*)-2-hydroxycyclopentyl)butanamide **124**



4-Chloro-*N*-((1*R*,2*R*)-2-hydroxycyclopentyl)butanamide **121** (200 mg, 0.972 mmol, 1 eq.) and NaN₃ (126 mg, 1.94 mmol, 2 eq.) were stirred in acetonitrile (4 ml) at 50 °C for 16 h. The solvent was then evaporated under reduced pressure and the residue was partitioned between water (20 ml) and 10 % *i*-PrOH/CHCl₃ (20 ml). The aqueous layer was extracted again with 10 % *i*-PrOH/CHCl₃ (3×20 ml) and the combined organic fractions were dried with MgSO₄ and evaporated under reduced pressure. **124** was obtained as white needles (181 mg, 0.852 mmol, 87.6 %).

TLC R_f = 0.35 (EtOAc)

mp T / °C = 56.0-59.5 (*i*-PrOH, CHCl₃)

IR (neat) ν_{max} / cm^{-1} = 3279.9 (N-H and O-H), 2965.6 (C-H), 2875.4 (C-H), 2094.6 (azide), 1636.8 (amide C=O)

^1H NMR (400 MHz, CDCl_3) δ / ppm = 6.72 (d, J = 4.4 Hz, 1 H, NH), 4.82 (br. s., 1 H, OH), 3.88 (q, J = 6.6 Hz, 1 H, CHOH), 3.75 (tdd, J = 8.4, 8.4, 6.6, 4.4 Hz, 1 H, CHNH), 3.28 (t, J = 6.6 Hz, 2 H, CH_2N_3), 2.23 (t, J = 7.3 Hz, 2 H, $\text{CH}_2\text{C=O}$), 2.04 (dtd, J = 13.0, 8.0, 8.0, 4.9 Hz, 1 H, CHHCHNH), 1.92 (dtd, J = 13.0, 7.6, 7.6, 5.8 Hz, 1 H, CHHCHOH), 1.84 (quin, J = 7.0 Hz, 2 H, $\text{CH}_2\text{CH}_2\text{N}_3$), 1.59 - 1.77 (m, 2 H, $\text{CH}_2\text{CH}_2\text{CHOH}$), 1.54 (ddt, J = 12.7, 9.0, 6.7, 6.7 Hz, 1 H, CHHCHOH), 1.39 (dq, J = 12.9, 8.4 Hz, 1 H, CHHCHNH)

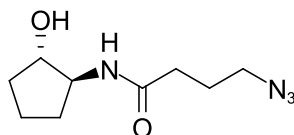
^{13}C NMR (101 MHz, CDCl_3) δ / ppm = 173.8 (C=O), 78.8 (CHOH), 59.9 (CHNH), 50.5 (CH_2N_3), 32.5 ($\text{CH}_2\text{C=O}$), 32.0 (CH_2CHOH), 29.5 (CH_2CHNH), 24.6 ($\text{CH}_2\text{CH}_2\text{N}_3$), 20.7 ($\text{CH}_2\text{CH}_2\text{CHOH}$)

HRMS (ESI^+) m/z / Da = 235.1174, $[\text{M}+\text{Na}]^+$ found, $[\text{C}_9\text{H}_{16}\text{N}_4\text{NaO}_2]^+$ requires 235.1171

$[\alpha]_D^{20}$ / $^{\circ}\text{10}^{-1}\text{cm}^2\text{g}^{-1}$ = -10.2 (c / g(100 ml)^{-1} = 0.5, MeOH)

The compound has not been reported previously.

1.26 4-Azido-*N*-((1*S*,2*S*)-2-hydroxycyclopentyl)butanamide **125**



4-Chloro-*N*-((1*S*,2*S*)-2-hydroxycyclopentyl)butanamide **122** (35.0 mg, 0.170 mmol, 1 eq.) and NaN_3 (22.1 mg, 0.340 mmol, 2 eq.) were stirred in acetonitrile (2 ml) at 50 $^{\circ}\text{C}$ for 24 h. The reaction mixture was then partitioned between water (20 ml) and 10 % *i*-PrOH/ CHCl_3 (5 ml). The aqueous layer was extracted again with 10 % *i*-PrOH/ CHCl_3 (2 \times 5 ml) and the combined organic fractions were dried with MgSO_4 and evaporated under reduced pressure. **125** was obtained as white needles (16.2 mg, 0.0764 mmol, 45.0 %).

TLC R_f = 0.35 (EtOAc)

IR (neat) ν_{max} / cm^{-1} = 3286.7 (N-H and O-H), 2957.6 (C-H), 2930.6 (C-H), 2860.7 (C-H), 2094.7 (azide), 1642.2 (amide C=O)

^1H NMR (400 MHz, CDCl_3) δ / ppm = 5.82 (br s, 1 H, NH), 4.45 (br. s., 1 H, OH), 3.96 (q, J =6.6 Hz, 1 H, CHOH), 3.83 (tdd, J =8.5, 8.5, 6.0, 4.6 Hz, 1 H, CHNH), 3.37 (t, J =6.4 Hz, 2 H, CH_2N_3), 2.31 (t, J =7.2 Hz, 2 H, $\text{CH}_2\text{C=O}$), 2.09 - 2.19 (m, 1 H, CHHCHNH), 1.99 - 2.06 (m, 1 H, CHHCHOH), 1.90 - 1.97 (m, 2 H, $\text{CH}_2\text{CH}_2\text{N}_3$), 1.60 - 1.85 (m, 3 H, $\text{CH}_2\text{CHHCHOH}$), 1.42 (dq, J =12.8, 8.3 Hz, 1 H, CHHCHNH)

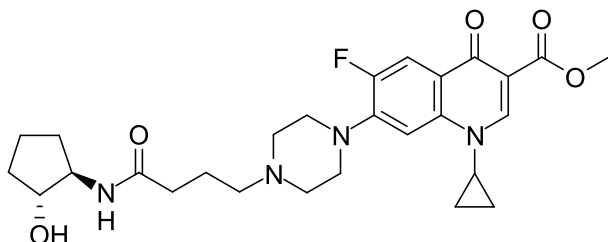
^{13}C NMR (101 MHz, CDCl_3) δ / ppm = 173.8 (C=O), 79.7 (CHOH), 61.0 (CHNH), 50.7 (CH_2N_3), 32.8 ($\text{CH}_2\text{C=O}$), 32.6 (CH_2CHOH), 30.5 (CH_2CHNH), 24.7 ($\text{CH}_2\text{CH}_2\text{N}_3$), 21.3 ($\text{CH}_2\text{CH}_2\text{CHOH}$)

HRMS (ESI^+) m/z / Da = 235.1178, $[\text{M}+\text{Na}]^+$ found, $[\text{C}_9\text{H}_{16}\text{N}_4\text{NaO}_2]^+$ requires 235.1171

$[\alpha]_D^{20}$ / $^{\circ}\text{10}^{-1}\text{cm}^2\text{g}^{-1}$ = 10.0 (c / g(100 ml)^{-1} = 0.01, MeOH)

The compound has not been reported previously.

1.27 Methyl 1-cyclopropyl-6-fluoro-7-(4-(4-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-4-oxobutyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate **126**



4-(4-(1-Cyclopropyl-6-fluoro-3-(methoxycarbonyl)-4-oxo-1,4-dihydroquinolin-7-yl)piperazin-1-yl)butanoic acid trifluoroacetate **112** (200 mg, 0.367 mmol, 1 eq.), (1*R*,2*R*)-2-aminocyclopentan-1-ol **117** (80 mg, 0.791 mmol, 2.1 eq.), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (112 mg, 0.584 mmol, 1.6 eq.), 1-hydroxybenzotriazole (96 mg, 0.710 mmol, 1.9 eq.) and DIPEA (192 μ l, 142 mg, 1.10 mmol, 3 eq.) were dissolved in DMF (5 ml) and stirred at r.t. for 16 h. The solvent was removed using a stream of N₂ and the residue was purified by preparatory HPLC (5-60 % acetonitrile/water over 12 min). The combined pure fractions were evaporated under reduced pressure and then partitioned between NaHCO₃ (aq., sat., 10 ml) and CH₂Cl₂ (10 ml). The organic layer was removed and the aqueous layer was extracted twice more with CH₂Cl₂ (2 \times 10 ml). The combined organic fractions were dried with MgSO₄ and evaporated under reduced pressure. **126** was obtained as a white amorphous solid (73.0 mg, 0.142 mmol, 38.7 %).

TLC R_f = 0.43 (30 % MeOH/EtOAc)

IR (neat) ν_{max} / cm⁻¹ = 2972.9 (C-H), 2901.5 (C-H), 1728.4 (ester C=O), 1656.3 (amide C=O), 1612.9 (quinolone C=O)

¹H NMR (400 MHz, DMSO d₆) δ / ppm = 8.44 (s, 1 H, *ortho* to C(=O)OCH₃), 7.75 (d, J = 13.5 Hz, 1 H, *ortho* to F), 7.70 (d, J = 7.2 Hz, 1 H, CHNH), 7.43 (d, J = 7.5 Hz, 1 H, *meta* to F), 4.74 (d, J = 4.0 Hz, 1 H, CHOH), 3.78 - 3.82 (m, 1 H, CHOH), 3.74 - 3.78 (m, 1 H, CHNH), 3.74 (s, 3 H, CH₃), 3.65 (tt, J = 7.2, 3.9 Hz, 1 H, NCH(CH₂)₂), 3.25 (t, J = 4.8 Hz, 4 H, CH₂N(CH₂CH₂)CH₂CH₂), 2.57 (br s, 4 H, CH₂N(CH₂)CH₂), 2.34 (t, J = 7.4 Hz, 2 H, CH₂N(CH₂)CH₂), 2.11 (t, J = 7.4 Hz, 2 H, CH₂CH₂CH₂N(CH₂)CH₂), 1.92 (dddd, J = 13.0, 8.7, 7.3, 6.0 Hz, 1 H, CHHCHNH), 1.78 (dddd, J = 12.6, 8.9, 6.3, 6.3 Hz, 1 H, CHHCHOH), 1.69 (quin, J = 7.3 Hz, 2 H, CH₂CH₂N(CH₂)CH₂), 1.54 - 1.65 (m, 2 H, CH₂CH₂CHOH), 1.42 (ddt, J = 13.1, 8.2, 5.3, 5.3 Hz, 1 H, CHHCHOH), 1.32 (dddd, J = 13.4, 8.5, 6.8, 5.8 Hz, 1 H, CHHCHNH), 1.21 - 1.29 (m, 2 H, NCH(CHH)₂), 1.07 - 1.13 (m, 2 H, NCH(CHH)₂)

¹³C NMR (101 MHz, DMSO d₆) δ / ppm = 171.9 (CH₂C(=O)NH), 171.6 (C(=O)CC(=O)OCH₃), 165.0 (C(=O)OCH₃), 152.6 (d, J = 246.5 Hz, *ipso* to F), 148.3 (C=CC(=O)OCH₃), 143.9 (d, J = 10.7 Hz, *ipso* to piperazine), 138.1 (*para* to F), 121.8 (d, J = 6.4 Hz, *para* to piperazine), 111.5 (d, J = 22.4 Hz, *ortho* to C=O and *ortho* to F), 109.0 (CC(=O)OCH₃), 106.2 (*meta* to C=O and *meta* to F), 76.3 (CHOH), 57.6 (CHNH), 57.2 (CH₂CH₂CH₂N), 52.4 (CH₂CH₂CH₂N(CH₂)CH₂), 51.3 (CH₃), 49.6 (CH₂CH₂CH₂N(CH₂)CH₂CH₂CH₂), 34.8 (NCH(CH₂)₂), 33.3 (C(=O)CH₂), 32.2 (CH₂CHOH), 29.5 (CH₂CHNH), 22.5 (C(=O)CH₂CH₂), 20.6 (CH₂CH₂CHOH), 7.6 (NCH(CH₂)₂)

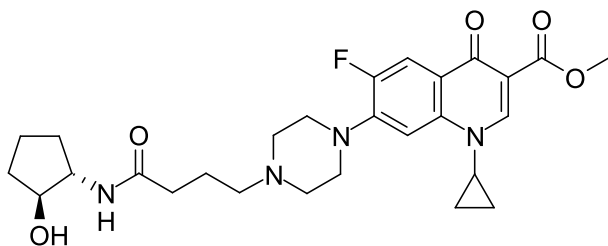
^{19}F NMR (376.45 MHz, DMSO d_6) δ / ppm = -124.3 (ciprofloxacin F)

HRMS (ESI $^+$) m/z / Da = 515.2661, $[\text{M}+\text{H}]^+$ found, $[\text{C}_{27}\text{H}_{36}\text{FN}_4\text{O}_5]^+$ requires 515.2670

$[\alpha]_D^{20}$ / $^{\circ}10^{-1}\text{cm}^2\text{g}^{-1}$ = -6.0 (c / $\text{g}(100\text{ ml})^{-1}$ = 0.05, MeOH)

The compound has not been reported previously.

1.28 Methyl 1-cyclopropyl-6-fluoro-7-(4-(4-(((1*S*,2*S*)-2-hydroxycyclopentyl)amino)-4-oxobutyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate **127**



4-(4-(1-Cyclopropyl-6-fluoro-3-(methoxycarbonyl)-4-oxo-1,4-dihydroquinolin-7-yl)piperazin-1-yl)butanoic acid trifluoroacetate **112** (52.1 mg, 95.5 μmol , 1 eq.), (1*S*,2*S*)-2-aminocyclopentan-1-ol **118** (19.5 mg, 193 μmol , 2 eq.), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (29.7 mg, 155 μmol , 1.6 eq.), 1-hydroxybenzotriazole (25.8 mg, 191 μmol , 2 eq.) and DIPEA (33.3 μl , 24.7 mg, 191 μmol , 2 eq.) were dissolved in DMF (2 ml) and stirred at r.t. for 16 h. The solvent was removed using a stream of N_2 and the residue was purified by preparatory HPLC (5-50 % acetonitrile/water over 15 min). The combined pure fractions were evaporated under reduced pressure and then partitioned between NaHCO_3 (aq., sat., 5 ml) and CH_2Cl_2 (5 ml). The organic layer was removed and the aqueous layer was extracted twice more with CH_2Cl_2 (2 \times 5 ml). The combined organic fractions were dried with MgSO_4 and evaporated under reduced pressure. **127** was obtained as a white amorphous solid (4.9 mg, 9.5 μmol , 9.9 %).

TLC R_f = 0.38 (30 % MeOH/ CH_2Cl_2)

IR (neat) ν_{max} / cm^{-1} = 2937.7 (C-H), 1721.4 (ester C=O), 1620.5 (amide C=O and quinolone C=O)

^1H NMR (500 MHz, DMSO d_6) δ / ppm = 8.44 (s, 1 H, *ortho* to C(=O)OCH $_3$), 7.75 (d, J =13.5 Hz, 1 H, *ortho* to F), 7.69 (d, J =6.9 Hz, 1 H, CHNH), 7.43 (d, J =7.6 Hz, 1 H, *meta* to F), 4.73 (br s, 1 H, CHOH), 3.77 - 3.81 (m, 1 H, CHOH), 3.74 - 3.77 (m, 1 H, CHNH), 3.73 (s, 3 H, CH $_3$), 3.65 (tt, J =6.9, 4.0 Hz, 1 H, NCH(CH $_2$) $_2$), 3.24 (br. t, J =4.2, 4.2 Hz, 4 H, CH $_2$ N(CH $_2$ CH $_2$)CH $_2$ CH $_2$), 2.55 (br t, J =5.0, 5.0 Hz, 4 H, CH $_2$ N(CH $_2$)CH $_2$), 2.32 (t, J =7.2 Hz, 2 H, CH $_2$ N(CH $_2$)CH $_2$), 2.10 (t, J =7.4 Hz, 2 H, CH $_2$ CH $_2$ CH $_2$ N(CH $_2$)CH $_2$), 1.92 (dddd, J =13.0, 8.7, 7.3, 6.0 Hz, 1 H, CHHCHNH), 1.77 (ddt, J =12.6, 8.9, 6.3, 6.3 Hz, 1 H, CHHCHOH), 1.68 (quin, J =7.4 Hz, 2 H, CH $_2$ CH $_2$ N(CH $_2$)CH $_2$), 1.53 - 1.64 (m, 2 H, CH $_2$ CH $_2$ CHOH), 1.42 (ddt, J =12.9, 8.4, 5.2, 5.2 Hz, 1 H, CHHCHOH), 1.31 (ddt, J =13.0, 8.6, 6.4, 6.4 Hz, 1 H, CHHCHNH), 1.22 - 1.28 (m, 2 H, NCH(CHH) $_2$), 1.06 - 1.12 (m, 2 H, NCH(CHH) $_2$)

^{13}C NMR (126 MHz, DMSO d_6) δ / ppm = 171.9 (NH $\underline{\text{C}}$ (=O)CH $_2$), 171.5 ($\underline{\text{C}}$ (=O)CC(=O)OCH $_3$), 165.0 ($\underline{\text{C}}$ (=O)OCH $_3$), 152.6 (d, J =247.4 Hz, *ipso* to F), 148.2 ($\underline{\text{C}}$ =CC(=O)OCH $_3$), 143.9 (d, J =10.3 Hz, *ipso* to piperazine), 138.1 (*para* to F), 121.7 (d, J =6.4 Hz, *para* to piperazine), 111.5 (d, J =23.0 Hz, *ortho* to C=O and

ortho to F), 109.0 ($\underline{\text{C}}\text{C}(=\text{O})\text{OCH}_3$), 106.2 (*meta* to C=O and *meta* to F), 76.2 ($\underline{\text{C}}\text{HOH}$), 57.6 ($\underline{\text{C}}\text{HNH}$), 57.2 ($\text{CH}_2\text{CH}_2\underline{\text{CH}_2\text{N}}$), 52.4 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\underline{\text{CH}_2}\underline{\text{C}}\underline{\text{H}_2})$), 51.3 ($\underline{\text{C}}\text{H}_3$), 49.6 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\underline{\text{C}}\underline{\text{H}_2})\text{CH}_2\text{CH}_2$), 49.6 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)\text{CH}_2\underline{\text{C}}\underline{\text{H}_2}$), 34.7 ($\text{N}\underline{\text{C}}\text{H}(\text{CH}_2)_2$), 33.2 ($\text{C}(=\text{O})\underline{\text{C}}\underline{\text{H}_2}$), 32.2 ($\underline{\text{C}}\underline{\text{H}_2}\text{CHOH}$), 29.5 ($\underline{\text{C}}\underline{\text{H}_2}\text{CHNH}$), 22.5 ($\text{C}(=\text{O})\text{CH}_2\underline{\text{C}}\underline{\text{H}_2}$), 20.6 ($\underline{\text{C}}\underline{\text{H}_2}\text{CH}_2\text{CHOH}$), 7.5 ($\text{NCH}(\underline{\text{C}}\underline{\text{H}_2})_2$)

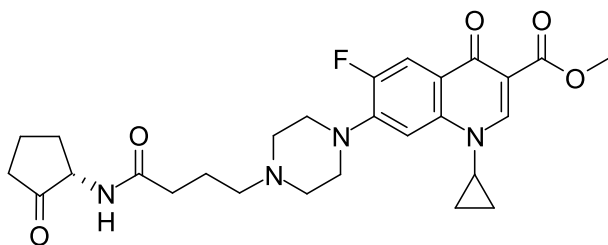
^{19}F NMR (376.45 MHz, MeOD) δ / ppm = -125.5

HRMS (ESI⁺) m/z / Da = 515.2667, $[\text{M}+\text{H}]^+$ found, $[\text{C}_{27}\text{H}_{36}\text{FN}_4\text{O}_5]^+$ requires 515.2670

$[\alpha]_D^{20}$ / $^\circ 10^{-1}\text{cm}^2\text{g}^{-1}$ = 8.0 (c / $\text{g}(100\text{ ml})^{-1}$ = 0.05, MeOH)

The compound has not been reported previously.

1.29 Methyl (*S*)-1-cyclopropyl-6-fluoro-4-oxo-7-(4-(4-oxo-4-((2-oxocyclopentyl)amino)butyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate **128**



Methyl 1-cyclopropyl-6-fluoro-7-(4-(4-(((1*S*,2*S*)-2-hydroxycyclopentyl)amino)-4-oxobutyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate **127** (20.0 mg, 38.9 μmol , 1 eq.) and Dess-Martin Periodane (32.8 mg, 77.4 μmol , 2 eq.) were stirred in CH_2Cl_2 (3 ml) for 6 h. The solvent was removed under reduced pressure and the residue was purified by preparatory HPLC (5-50 % acetonitrile/water over 10 min). The combined pure fractions were evaporated under reduced pressure, then NaHCO_3 (aq., sat., 30 ml) and 10 % *i*-PrOH/ CHCl_3 (30 ml) were added. The organic layer was removed and dried with MgSO_4 , then evaporated under reduced pressure. **128** was obtained as a white amorphous solid (11.3 mg, 22.0 μmol , 56.7 %).

^1H NMR (500 MHz, DMSO d_6) δ / ppm = 8.46 (s, 1 H, *ortho* to $\text{C}(=\text{O})\text{OCH}_3$), 7.78 (d, $J=13.5$ Hz, 1 H, *ortho* to F), 7.45 (d, $J=7.4$ Hz, 1 H, *meta* to F), 4.02 (dt, $J=11.1, 8.2$ Hz, 1 H, $\underline{\text{C}}\underline{\text{H}}\text{NH}$), 3.73 (s, 3 H, $\underline{\text{C}}\underline{\text{H}_3}$), 3.65 (tt, $J=6.9, 3.9$ Hz, 1 H, $\text{NCH}(\text{CH}_2)_2$), 3.40 (s, 10 H, $\text{CH}_2\text{CH}_2\underline{\text{CH}_2\text{N}}(\underline{\text{CH}_2}\underline{\text{C}}\underline{\text{H}_2})\underline{\text{C}}\underline{\text{H}_2}\underline{\text{C}}\underline{\text{H}_2}$), 2.05 - 2.29 (m, 5 H, $\text{NHC}(=\text{O})\underline{\text{C}}\underline{\text{H}_2}$, $\underline{\text{C}}\underline{\text{H}_2}\text{C}(=\text{O})\text{CHNH}$ and $\underline{\text{C}}\underline{\text{H}}\underline{\text{H}}\text{CHNH}$), 1.89 - 1.96 (m, 1 H, $\underline{\text{C}}\underline{\text{H}}\underline{\text{H}}\text{CH}_2\text{CHNH}$), 1.69 - 1.80 (m, 3 H, $\underline{\text{C}}\underline{\text{H}}\underline{\text{H}}\text{CH}_2\text{CHNH}$, $\underline{\text{C}}\underline{\text{H}}\underline{\text{H}}\text{CHNH}$ and $\text{NHC}(=\text{O})\text{CH}_2\underline{\text{C}}\underline{\text{H}_2}$), 1.24 - 1.29 (m, 2 H, $\text{NCH}(\underline{\text{C}}\underline{\text{H}}\underline{\text{H}})_2$), 1.07 - 1.12 (m, 2 H, $\text{NCH}(\underline{\text{C}}\underline{\text{H}}\underline{\text{H}})_2$)

^{13}C NMR (126 MHz, DMSO d_6) δ / ppm = 215.2 ($\underline{\text{C}}(=\text{O})\text{CHNH}$), 171.7 ($\text{NHC}(=\text{O})\underline{\text{C}}\underline{\text{H}_2}$), 171.7 ($\underline{\text{C}}(=\text{O})\text{CC}(=\text{O})\text{OCH}_3$), 165.1 ($\underline{\text{C}}(=\text{O})\text{OCH}_3$), 152.6 (d, $J=246.6$ Hz, *ipso* to F), 148.4 ($\underline{\text{C}}=\text{CC}(=\text{O})\text{OCH}_3$), 138.1 (*para* to F), 109.1 ($\underline{\text{C}}\text{C}(=\text{O})\text{OCH}_3$), 56.3 ($\underline{\text{C}}\underline{\text{H}}\text{NH}$), 51.4 ($\underline{\text{C}}\underline{\text{H}_3}$), 35.6 ($\underline{\text{C}}\underline{\text{H}_2}\text{C}(=\text{O})\text{CHNH}$), 34.8 ($\text{NCH}(\text{CH}_2)_2$), 28.8 ($\underline{\text{C}}\underline{\text{H}_2}\text{CHNH}$), 18.1 ($\underline{\text{C}}\underline{\text{H}_2}\text{CH}_2\text{CHNH}$), 7.6 ($\text{NCH}(\underline{\text{C}}\underline{\text{H}_2})_2$)

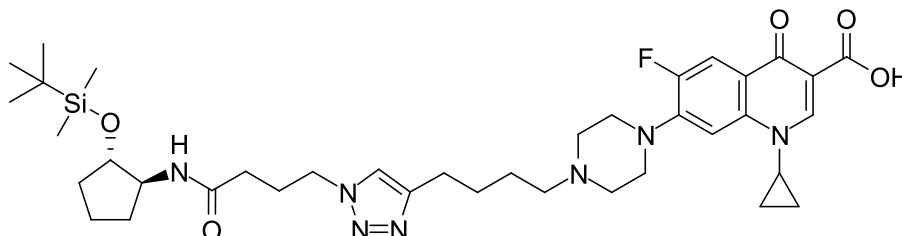
^{19}F NMR (376.45 MHz, MeOD) δ / ppm = -124.3

HRMS (ESI⁺) m/z / Da = 513.2495, $[\text{M}+\text{H}]^+$ found, $[\text{C}_{27}\text{H}_{34}\text{FN}_4\text{O}_5]^+$ requires 513.2513

$$[\alpha]_D^{20} / ^\circ 10^{-1} \text{cm}^2 \text{g}^{-1} = 6.7 \text{ (} c / \text{g(100 ml)}^{-1} = 0.075, \text{ MeOH)}$$

The compound has not been reported previously.

1.30 7-(4-(4-(1-(4-(((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclopentyl)amino)-4-oxobutyl)-1*H*-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **129**



1-Cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **70** (42.9 mg, 104 μmol , 1 eq.) and 4-azido-*N*-(((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclopentyl)butanamide **123** (33.9 mg, 104 μmol , 1 eq.) were dissolved in 10 % water/*t*-BuOH (3 ml), and the mixture was degassed by bubbling N_2 through it. A solution of CuSO_4 and THPTA (104 μl , 10.4 μmol , 0.1 eq. 100 mM, aq.) was added, followed by a solution of sodium ascorbate (208 μl , 20.8 μmol , 0.2 eq., 100 mM, aq.). The mixture was stirred at room temperature under argon for 16 h, then solvent was removed under reduced pressure. The residue was partitioned between water (10 ml) and CH_2Cl_2 (10 ml), the organic layer was separated and the aqueous layer was extracted again with CH_2Cl_2 (10 ml). The combined organic layers were dried with MgSO_4 and evaporated under reduced pressure. **129** was obtained as a clear glass (67.1 mg, 90.9 μmol , 87.4 %).

IR (neat) $\nu_{\text{max}} / \text{cm}^{-1} = 2951.3$ (C-H), 2929.2 (C-H), 2855.5 (C-H), 1741.0 (carboxylic acid C=O), 1640.3 (amide C=O), 1626.6 (quinolone C=O), 1612.3 (triazole)

^1H NMR (400 MHz, CDCl_3) $\delta / \text{ppm} = 8.67$ (s, 1 H, *ortho* to C(=O)OH), 7.87 (d, $J = 13.1$ Hz, 1 H, *ortho* to F), 7.34 (s, 1 H, $\text{CH}=\text{CCH}_2$), 7.33 (d, $J = 8.2$ Hz, 1 H, *meta* to F), 5.92 (t, $J = 6.6$ Hz, 1 H, CHNH), 4.35 (t, $J = 6.7$ Hz, 2 H, $\text{CH}_2\text{NCH}=\text{C}$), 3.96 - 4.02 (m, 1 H, CHOSi), 3.90 - 3.96 (m, 1 H, CHNH), 3.55 (tt, $J = 6.7, 4.0$ Hz, 1 H, $\text{NCH}(\text{CH}_2)_2$), 3.34 (br t, $J = 5.0$ Hz, 4 H, $\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)\text{CH}_2\text{CH}_2$), 2.71 (t, $J = 7.5$ Hz, 2 H, $\text{CH}=\text{CCH}_2$), 2.66 (br s, 4 H, $\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)\text{CH}_2$), 2.46 (t, $J = 7.3$ Hz, 2 H, $\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)\text{CH}_2$), 2.03 - 2.22 (m, 5 H, CHHCHNH , $\text{C}(=\text{O})\text{CH}_2$ and $\text{C}(=\text{O})\text{CH}_2\text{CH}_2$), 1.65 - 1.83 (m, 4 H, CHHCHOSi , $\text{CHHCH}_2\text{CHOSi}$ and $\text{NCH}=\text{CCH}_2\text{CH}_2$), 1.47 - 1.65 (m, 4 H, CHHCHOSi , $\text{CHHCH}_2\text{CHOSi}$ and $\text{NCH}=\text{CCH}_2\text{CH}_2\text{CH}_2$), 1.33 - 1.41 (m, 3 H, CHHCHNH and $\text{NCH}(\text{CHH})_2$), 1.14 - 1.20 (m, 2 H, $\text{NCH}(\text{CHH})_2$), 0.82 (s, 9 H, $\text{C}(\text{CH}_3)_3$), 0.03 (s, 3 H, SiCH_3), 0.01 (s, 3 H, SiCH_3)

^{13}C NMR (101 MHz, CDCl_3) $\delta / \text{ppm} = 176.9$ ($\text{C}(=\text{O})\text{CC}(=\text{O})\text{OH}$), 170.9 ($\text{CH}_2\text{C}(=\text{O})\text{NH}$), 166.9 ($\text{C}(=\text{O})\text{OH}$), 153.5 (d, $J = 251.4$ Hz, *ipso* to F), 147.9 ($\text{CH}=\text{CCH}_2$), 147.2 ($\text{C}=\text{CC}(=\text{O})\text{OH}$), 145.8 (d, $J = 10.4$ Hz, *ipso* to piperazine), 139.0 (*para* to F), 120.9 ($\text{NCH}=\text{CCH}_2$), 119.4 (d, $J = 7.8$ Hz, *para* to piperazine), 112.0 (d, $J = 23.4$ Hz, *ortho* to C=O and *ortho* to F), 107.7 ($\text{CC}(=\text{O})\text{OH}$), 104.7 (d, $J = 3.5$ Hz, *meta* to C=O and *meta* to F), 77.7 (CHOSi), 58.2 (CHNH), 57.9 ($\text{CH}=\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$), 52.6 ($\text{CH}=\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)\text{CH}_2\text{CH}_2$), 49.5 (d, $J = 6.1$ Hz, $\text{CH}=\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)\text{CH}_2\text{CH}_2$), 48.9 (d, $J = 3.5$ Hz, $\text{CH}_2\text{NCH}=\text{CCH}_2$), 35.3 ($\text{NCH}(\text{CH}_2)_2$), 32.6 ($\text{C}(=\text{O})\text{CH}_2$), 32.6 (CH_2CHOSi), 29.3 (CH_2CHNH), 27.2 ($\text{CH}=\text{CCH}_2\text{CH}_2$), 26.0 - 26.3 ($\text{C}(=\text{O})\text{CH}_2\text{CH}_2$ and $\text{CH}=\text{CCH}_2\text{CH}_2\text{CH}_2$), 25.6 ($\text{C}(\text{CH}_3)_3$), 25.4 ($\text{CH}=\text{CCH}_2$), 20.4 ($\text{CH}_2\text{CH}_2\text{CHOSi}$),

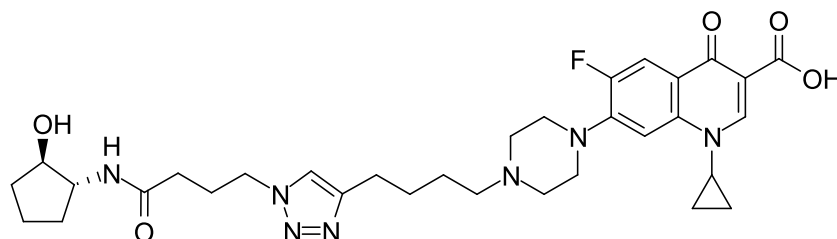
17.8 ($\underline{\text{C}}(\underline{\text{CH}}_3)_3$), 8.1 ($\text{NCH}(\underline{\text{CH}}_2)_2$), -4.8 ($\text{Si}\underline{\text{CH}}_3$)

HRMS (ESI^+) m/z / Da = 738.4164, $[\text{M}+\text{H}]^+$ found, $[\text{C}_{38}\text{H}_{57}\text{FN}_7\text{O}_5\text{Si}]^+$ requires 738.4169

$[\alpha]_D^{20} / ^\circ 10^{-1} \text{cm}^2 \text{g}^{-1} = 4.5$ ($c / \text{g}(100 \text{ ml})^{-1} = 0.2$, MeOH)

The compound has not been reported previously.

1.31 1-Cyclopropyl-6-fluoro-7-(4-(4-(1-(4-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-4-oxobutyl)-1*H*-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **130**



1-Cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **70** (42.9 mg, 104 μmol , 1 eq.) and 4-azido-*N*-(((1*R*,2*R*)-2-hydroxycyclopentyl)butanamide **124** (22.0 mg, 104 μmol , 1 eq.) were dissolved in 10 % water/*t*-BuOH (3 ml), and the mixture was degassed by bubbling N_2 through it. A solution of CuSO_4 and THPTA (104 μl , 10.4 μmol , 0.1 eq. 100 mM, aq.) was added, followed by a solution of sodium ascorbate (208 μl , 20.8 μmol , 0.2 eq., 100 mM, aq.). The mixture was stirred at room temperature under argon for 16 h. Water (30 ml) and CH_2Cl_2 (30 ml) were added, the organic layer was separated and the aqueous layer was extracted again with CH_2Cl_2 (4 \times 30 ml). The combined organic layers were dried with MgSO_4 and evaporated under reduced pressure. The residue was purified by preparatory HPLC (5-95 % acetonitrile/water over 20 min). The combined pure fractions were evaporated under reduced pressure and then partitioned between NaHCO_3 (aq., sat., 10 ml) and 10 % *i*-PrOH/ CHCl_3 (10 ml). The organic layer was dried with MgSO_4 and evaporated under reduced pressure. **130** was obtained as a white amorphous solid (17.6 mg, 28.2 μmol , 27.1 %).

IR (neat) $\nu_{\text{max}} / \text{cm}^{-1} = 2967.0$ (C-H), 2902.2 (C-H), 1721.4 (carboxylic acid C=O), 1646.7 (amide C=O), 1627.0 (quinolone C=O), 1613.0 (triazole)

^1H NMR (700 MHz, DMSO d_6) $\delta / \text{ppm} = 8.64$ (s, 1 H, *ortho* to C(=O)OH), 7.87 (d, $J = 13.3$ Hz, 1 H, *ortho* to F), 7.84 (s, 1 H, $\underline{\text{CH}}=\underline{\text{CCH}}_2$), 7.75 (d, $J = 7.1$ Hz, 1 H, $\underline{\text{CHNH}}$), 7.54 (d, $J = 7.5$ Hz, 1 H, *meta* to F), 4.73 (d, $J = 3.8$ Hz, 1 H, $\underline{\text{CHOH}}$), 4.29 (t, $J = 6.9$ Hz, 2 H, $\underline{\text{CH}}_2\text{NCH}=\text{C}$), 3.78 - 3.83 (m, 1 H, $\text{NCH}(\underline{\text{CH}}_2)_2$), 3.75 - 3.78 (m, 1 H, $\underline{\text{CHOH}}$), 3.71 - 3.75 (m, 1 H, $\underline{\text{CHNH}}$), 3.31 (br t, $J = 4.3$ Hz, 4 H, $\text{CH}_2\text{N}(\underline{\text{CH}}_2\text{CH}_2)\text{CH}_2\underline{\text{CH}}_2$), 2.63 (t, $J = 7.5$ Hz, 2 H, $\text{CH}=\underline{\text{CCH}}_2$), 2.56 (br t, $J = 4.2$ Hz, 4 H, $\text{CH}_2\text{N}(\underline{\text{CH}}_2)\text{CH}_2$), 2.37 (t, $J = 7.3$ Hz, 2 H, $\underline{\text{CH}}_2\text{N}(\text{CH}_2)\text{CH}_2$), 2.03 - 2.06 (m, 2 H, $\text{C}(=\text{O})\underline{\text{CH}}_2$), 1.97 - 2.02 (m, 2 H, $\text{C}(=\text{O})\text{CH}_2\underline{\text{CH}}_2$), 1.89 (dddd, $J = 13.1, 8.9, 7.4, 5.7$ Hz, 1 H, $\underline{\text{CHHCHNH}}$), 1.75 (ddt, $J = 13.0, 8.9, 6.4, 6.4$ Hz, 1 H, $\underline{\text{CHHCHOH}}$), 1.61 - 1.66 (m, 2 H, $\text{CH}=\underline{\text{CCH}}_2\underline{\text{CH}}_2$), 1.57 - 1.61 (m, 1 H, $\underline{\text{CHHCH}}_2\text{CHOH}$), 1.54 - 1.57 (m, 1 H, $\underline{\text{CHHCH}}_2\text{CHOH}$), 1.49 - 1.53 (m, 2 H, $\text{CH}=\underline{\text{CCH}}_2\text{CH}_2\underline{\text{CH}}_2$), 1.40 (ddt, $J = 13.0, 8.4, 5.3, 5.3$ Hz, 1 H, $\underline{\text{CHHCHOH}}$), 1.29 - 1.32 (m, 2 H, $\text{NCH}(\underline{\text{CHH}})_2$), 1.25 - 1.29 (m, 1 H, $\underline{\text{CHHCHNH}}$), 1.13 - 1.20 (m, 2 H, $\text{NCH}(\underline{\text{CHH}})_2$)

¹³C NMR (175 MHz, DMSO d₆) δ / ppm = 176.3 (C(=O)CC(=O)OH), 170.9 (NHC(=O)CH₂), 166.1 (C(=O)OH), 153.0 (d, J = 251.4 Hz, *ipso* to F), 147.9 (C=CC(=O)OH), 146.9 (CH=CCH₂), 145.2 (d, J = 8.7 Hz, *ipso* to piperazine), 139.2 (*para* to F), 121.7 (NCH=CCH₂), 118.7 (d, J = 5.8 Hz, *para* to piperazine), 111.0 (d, J = 23.3 Hz, *ortho* to C=O and *ortho* to F), 106.3 (*meta* to C=O and *meta* to F and CC(=O)OH), 76.2 (CHOH), 57.6 (CHNH), 57.4 (CH=CCH₂CH₂CH₂CH₂N(CH₂CH₂)), 52.5 (CH=CCH₂CH₂CH₂CH₂N(CH₂CH₂)), 49.5 (d, J = 4.4 Hz, CH=CCH₂CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 48.8 (CH₂NCH=CCH₂), 35.8 (NCH(CH₂)₂), 32.2 (CH₂CHOH), 32.0 (C(=O)CH₂), 29.5 (CH₂CHNH), 26.9 (CH=CCH₂CH₂), 26.0 (C(=O)CH₂CH₂), 25.8 (CH=CCH₂CH₂CH₂), 25.0 (CH=CCH₂), 20.5 (CH₂CH₂CHOH), 7.6 (NCH(CH₂)₂)

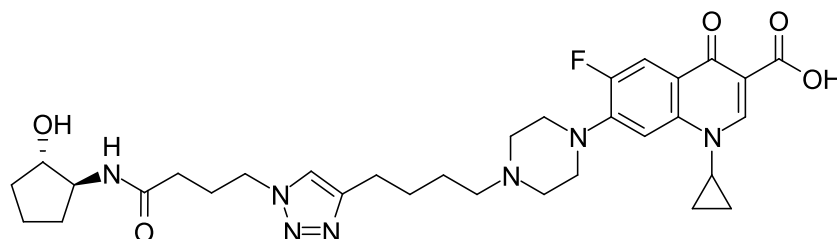
¹⁹F NMR (376.45 MHz, MeOD) δ / ppm = -122.1 (s, ciprofloxacin F)

HRMS (ESI⁺) m/z / Da = 624.3314, [M+H]⁺ found, [C₃₂H₄₃FN₇O₅]⁺ requires 624.3310

$[\alpha]_D^{20}$ / °10⁻¹cm²g⁻¹ = -3.6 (c / g(100 ml)⁻¹ = 0.0833, MeOH)

The compound has not been reported previously.

1.32 1-Cyclopropyl-6-fluoro-7-(4-(4-(1-(4-(((1*S*,2*S*)-2-hydroxycyclopentyl)amino)-4-oxobutyl)-1*H*-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **131**



1-Cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **70** (82.0 mg, 199 μ mol, 4 eq.) and 4-azido-*N*-((1*S*,2*S*)-2-hydroxycyclopentyl)butanamide **125** (11.0 mg, 51.8 μ mol, 1 eq.) were dissolved in 10 % water/*t*-BuOH (3 ml), and the mixture was degassed by bubbling N₂ through it. A solution of CuSO₄ and THPTA (156 μ l, 15.6 μ mol, 0.3 eq. 100 mM, aq.) was added, followed by a solution of sodium ascorbate (312 μ l, 31.2 μ mol, 0.6 eq., 100 mM, aq.). The mixture was stirred at room temperature under argon for 3 d. Water (10 ml) and 10 % *i*-PrOH/CHCl₃ (10 ml) were added, then the organic layer was separated and dried with MgSO₄ and evaporated under reduced pressure. The residue was purified by preparatory HPLC (5-95 % acetonitrile/water over 20 min). The combined pure fractions were evaporated under reduced pressure and then partitioned between NaHCO₃ (aq., sat., 10 ml) and 10 % *i*-PrOH/CHCl₃ (10 ml). The organic layer was dried with MgSO₄ and evaporated under reduced pressure. **131** was obtained as a white amorphous solid (7.2 mg, 11.5 μ mol, 22.2 %).

IR (neat) ν_{max} / cm⁻¹ = 2954.9 (C-H), 2917.9 (C-H), 2850.2 (C-H), 1722.1 (carboxylic acid C=O), 1647.3 (amide C=O), 1626.7 (quinolone C=O) 1611.9 (triazole)

¹H NMR (400 MHz, DMSO d₆) δ / ppm = 15.22 (br s, 1 H, C(=O)OH), 8.67 (s, 1 H, *ortho* to C(=O)OH), 7.91 (d, J =13.3 Hz, 1 H, *ortho* to F), 7.84 (s, 1 H, CH=CCH₂), 7.74 (d, J =6.7 Hz, 1 H, CHNH), 7.56 (d, J =7.4 Hz, 1 H, *meta* to F), 4.71 (d, J =3.7 Hz, 1 H, CHOH), 4.29 (t, J =6.6 Hz, 2 H, CH₂NCH=C),

3.82 (tt, $J=6.5, 4.3$ Hz, 1 H, $\text{NCH}(\underline{\text{CH}_2})_2$), 3.69 - 3.79 (m, 2 H, $\underline{\text{CHOH}}$ and $\underline{\text{CHNH}}$), 3.30 - 3.34 (m, 6 H, $\text{CH}=\underline{\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\underline{\text{CH}_2\text{CH}_2)}\underline{\text{CH}_2\text{CH}_2}$), 2.64 (t, $J=7.4$ Hz, 2 H, $\text{CH}=\underline{\text{CCH}_2}$), 1.95 - 2.08 (m, 4 H, $\text{C}(=\text{O})\underline{\text{CH}_2\text{CH}_2}$), 1.89 (dddd, $J=12.8, 8.9, 7.4, 5.8$ Hz, 1 H, $\underline{\text{CHHCHNH}}$), 1.75 (ddt, $J=12.7, 9.0, 6.2, 6.2$ Hz, 1 H, $\underline{\text{CHHCHOH}}$), 1.48 - 1.68 (m, 6 H, $\text{CH}=\underline{\text{CCH}_2\text{CH}_2\text{CH}_2}$ and $\underline{\text{CH}_2\text{CH}_2\text{CHOH}}$), 1.40 (ddt, $J=13.0, 8.3, 5.3, 5.3$ Hz, 1 H, $\underline{\text{CHHCHOH}}$), 1.28 - 1.35 (m, 2 H, $\text{NCH}(\underline{\text{CHH}})_2$), 1.24 - 1.31 (m, 1 H, $\underline{\text{CHHCHNH}}$), 1.15 - 1.21 (m, 2 H, $\text{NCH}(\underline{\text{CHH}})_2$)

^{13}C NMR (101 MHz, DMSO d_6) δ / ppm = 176.4 ($\underline{\text{C}}(=\text{O})\text{CC}(=\text{O})\text{OH}$), 170.9 ($\text{NHC}(\underline{\text{C}}(=\text{O}))\text{CH}_2$), 166.0 ($\underline{\text{C}}(=\text{O})\text{OH}$), 153.0 (d, $J=249.6$ Hz, *ipso* to F), 148.1 ($\underline{\text{C}}=\text{CC}(=\text{O})\text{OH}$), 146.7 ($\text{CH}=\underline{\text{CCH}_2}$), 145.2 (d, $J=8.3$ Hz, *ipso* to piperazine), 139.2 (*para* to F), 121.8 ($\text{NCH}=\text{CCH}_2$), 118.7 (*para* to piperazine), 111.0 (d, $J=23.2$ Hz, *ortho* to C=O and *ortho* to F), 106.7 ($\underline{\text{CC}}(=\text{O})\text{OH}$), 106.5 (*meta* to C=O and *meta* to F), 76.2 ($\underline{\text{CHOH}}$), 57.5 ($\underline{\text{CHNH}}$), 57.4 (br s, $\text{CH}=\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$), 52.3 (br s, $\text{CH}=\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\underline{\text{CH}_2\text{CH}_2)}\underline{\text{CH}_2\text{CH}_2}$), 49.3 (br s, $\text{CH}=\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\underline{\text{CH}_2\text{CH}_2)}\underline{\text{CH}_2\text{CH}_2}$), 48.8 ($\underline{\text{CH}_2\text{NCH}=\text{CCH}_2}$), 35.9 ($\text{NCH}(\text{CH}_2)_2$), 32.2 ($\underline{\text{CH}_2\text{CHOH}}$), 32.0 ($\text{C}(=\text{O})\underline{\text{CH}_2}$), 29.4 ($\underline{\text{CH}_2\text{CHNH}}$), 26.7 ($\text{CH}=\text{CCH}_2\text{CH}_2$), 26.0 ($\text{C}(=\text{O})\text{CH}_2\text{CH}_2$), 25.5 ($\text{CH}=\text{CCH}_2\text{CH}_2\text{CH}_2$), 24.9 ($\text{CH}=\text{CCH}_2$), 20.5 ($\underline{\text{CH}_2\text{CH}_2\text{CHOH}}$), 7.6 ($\text{NCH}(\underline{\text{CH}_2})_2$)

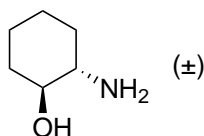
^{19}F NMR (376.45 MHz, MeOD) δ / ppm = -121.5

HRMS (ESI⁺) m/z / Da = 624.3298, $[\text{M}+\text{H}]^+$ found, $[\text{C}_{32}\text{H}_{43}\text{FN}_7\text{O}_5]^+$ requires 624.3310

$[\alpha]_D^{20}$ / $^{\circ}\text{10}^{-1}\text{cm}^2\text{g}^{-1}$ = -25.0 (c / g(100 ml)^{-1} = 0.08, MeOH)

The compound has not been reported previously.

1.33 (*trans*)-2-Aminocyclohexan-1-ol **133**



Cyclohexene oxide **132** (10 ml, 9.70 g, 98.8 mmol, 1 eq.), NH_3 (90 ml, 35 % w/w aq., 27.7 g, 791 mmol, 8 eq.) and MeOH (100 ml) were stirred at r.t. for 72 h. The solvent was removed by blowing a stream of N_2 over it, followed by evaporation under high vacuum. **133** was obtained as white needles (9.90 g, 85.2 mmol, 86.2 %)

TLC R_f = 0.04 (30 % MeOH/ CH_2Cl_2)

IR (neat) ν_{max} / cm^{-1} = 3350.4 (N-H), 3306.2 (br, O-H), 2926.9 (C-H), 2852.6 (C-H)

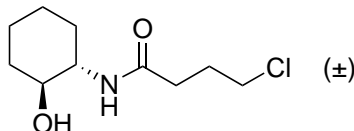
^1H NMR (400 MHz, CDCl_3) δ / ppm = 3.01 (td, $J = 9.4, 4.8$ Hz, 1 H, $\underline{\text{CHOH}}$), 2.80 - 2.92 (m, 2 H, $\underline{\text{OH}}$ and $\underline{\text{NH}_2}$), 2.35 (ddd, $J = 11.1, 9.1, 4.1$ Hz, 1 H, $\underline{\text{CHNH}_2}$), 1.77 - 1.84 (m, 1 H, $\underline{\text{CHHCHOH}}$), 1.69 - 1.76 (m, 1 H, $\underline{\text{CHHCHNH}_2}$), 1.56 - 1.66 (m, 1 H, $\underline{\text{CHHCH}_2\text{CHOH}}$), 1.45 - 1.56 (m, 1 H, $\underline{\text{CHHCH}_2\text{CHNH}_2}$), 1.07 - 1.19 (m, 3 H, $\underline{\text{CHHCH}_2\text{CHOH}}$, $\underline{\text{CHHCH}_2\text{CHNH}_2}$ and $\underline{\text{CHHCHOH}}$), 0.94 - 1.05 (m, 1 H, $\underline{\text{CHHCHNH}_2}$)

^{13}C NMR (101 MHz, CDCl_3) δ / ppm = 75.4 ($\underline{\text{CHOH}}$), 56.6 ($\underline{\text{CHN}_2}$), 33.8 ($\underline{\text{CH}_2\text{CHOH}}$ and $\underline{\text{CH}_2\text{CHN}_2}$), 24.7 ($\underline{\text{CH}_2\text{CH}_2\text{CHN}_2}$), 24.6 ($\underline{\text{CH}_2\text{CH}_2\text{CHOH}}$)

HRMS (ESI⁺) m/z / Da = 116.1070, [M+H]⁺ found, [C₆H₁₄NO]⁺ requires 116.1070

The data are consistent with the literature.¹⁰

1.34 4-Chloro-*N*-((*trans*)-2-hydroxycyclohexyl)butanamide **134**



(*trans*)-2-Aminocyclohexan-1-ol **133** (1.04 g, 9.03 mmol, 1 eq.), TEA (1.65 ml, 1.20 g, 11.8 mmol, 1.3 eq.) and CH₂Cl₂ (50 ml) were stirred at 0 °C. 4-Chlorobutyryl chloride **120** (1.22 ml, 1.54 g, 10.9 mmol, 1.2 eq.) was added dropwise over 5 min. The mixture was stirred at 0 °C for 30 min, then water (50 ml) was added. The organic layer was separated off, and the aqueous layer was extracted with 10 % *i*-PrOH/CHCl₃ (2×50 ml). The combined organic layers were dried with MgSO₄, concentrated under reduced pressure and purified by column chromatography (SiO₂, 0-100 % EtOAc/Et₂O). The combined organic fractions were dried with MgSO₄ and evaporated under reduced pressure. **134** was obtained as white needles (1.51 g, 6.87 mmol, 76.1 %).

TLC R_f = 0.19 (Et₂O)

mp T / °C = 72.5-75.7 (*i*-PrOH, CHCl₃)

IR (neat) ν_{max} / cm⁻¹ = 3289.9 (N-H), 3250.0 (O-H), 2927.6 (C-H), 2857.1 (C-H), 1629.2 (amide C=O)

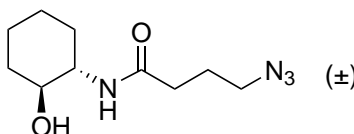
¹H NMR (400 MHz, MeOD) δ / ppm = 3.60 (t, J = 6.6 Hz, 2 H, CH₂Cl), 3.51 - 3.60 (m, 1 H, CHNH), 3.28 - 3.39 (m, 1 H, CHOH), 2.37 (td, J = 7.4, 2.3 Hz, 2 H, C(=O)CH₂), 2.06 (quin, J = 7.0 Hz, 2 H, C(=O)CH₂CH₂), 1.97 - 2.01 (m, 1 H, CHHCHOH), 1.85 - 1.93 (m, 1 H, CHHCHNH), 1.70 - 1.77 (m, 1 H, CHHCH₂CHOH), 1.64 - 1.70 (m, 1 H, CHHCH₂CHNH), 1.24 - 1.35 (m, 3 H, CHHCH₂CHOH, CHHCH₂CHNH and CHHCHOH), 1.13 - 1.25 (m, 1 H, CHHCHNH₂)

¹³C NMR (101 MHz, MeOD) δ / ppm = 175.0 (C(=O)), 74.1 (CHOH), 56.3 (CHNH), 45.3 (CH₂Cl), 35.6 (CH₂CHOH), 34.5 (C(=O)CH₂), 32.7 (CH₂CHNH), 30.1 (C(=O)CH₂CH₂), 25.8 (CH₂CH₂CHNH), 25.5 (CH₂CH₂CHOH)

HRMS (ESI⁺) m/z / Da = 242.0925, [M+Na]⁺ found, [C₁₀H₁₈ClNNaO₂]⁺ requires 242.0924

The compound has not been reported previously.

1.35 4-Azido-*N*-((*trans*)-2-hydroxycyclohexyl)butanamide **135**



4-Chloro-*N*-((*trans*)-2-hydroxycyclohexyl)butanamide **134** (345 mg, 1.57 mmol, 1 eq.) and NaN₃ (180 mg, 2.77 mmol, 1.75 eq.) were stirred in DMF (12 ml) at 50 °C for 16 h. Water (50 ml) and 10 % *i*-PrOH/CHCl₃ (50 ml) were added, and the organic layer was removed. The aqueous layer was extracted again with 10 % *i*-PrOH/CHCl₃ (50 ml) and the combined organic fractions were dried with MgSO₄. The solvent was evaporated under reduced pressure, and then by using a N₂ stream. **135** was obtained as large white prisms (347 mg, 1.53 mmol, 97.5 %).

TLC R_f = 0.23 (EtOAc)

mp T / °C = 74.5-75.7 (*i*-PrOH, CHCl₃)

IR (neat) ν_{max} / cm⁻¹ = 3299.0 (N-H), 3207.8 (O-H), 2944.3 (C-H), 2927.9 (C-H), 2859.2 (C-H), 2089.2 (azide), 1624.0 (amide C=O)

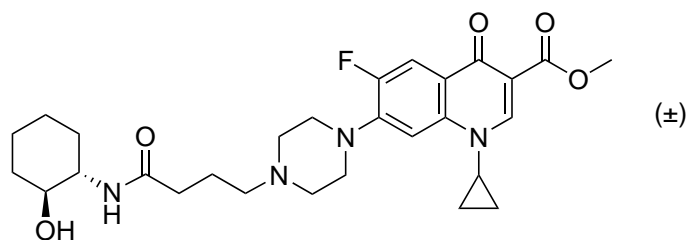
¹H NMR (400 MHz, MeOD) δ / ppm = 7.87 (d, J = 7.9 Hz, 1 H, NH), 5.27 (d, J = 4.3 Hz, 1 H, OH), 3.56 (td, J = 10.5, 4.4 Hz, 1 H, CHNH), 3.28 - 3.41 (m, 3 H, CHOH and CH₂N₃), 2.30 (td, J = 7.4, 2.7 Hz, 2 H, C(=O)CH₂), 1.95 - 2.03 (m, 1 H, CHHCHOH), 1.87 (m, 3 H, C(=O)CH₂CH₂ and CHHCHNH), 1.70 - 1.76 (m, 1 H, CHHCH₂CHOH), 1.63 - 1.70 (m, 1 H, CHHCH₂CHNH), 1.25 - 1.38 (m, 3 H, CHHCH₂CHOH, CHHCH₂CHNH and CHHCHOH), 1.14 - 1.24 (m, 1 H, CHHCHNH₂)

¹³C NMR (101 MHz, MeOD) δ / ppm = 175.1 (C(=O)), 74.0 (CHOH), 56.3 (CHNH), 52.0 (CH₂N₃), 35.5 (CH₂CHOH), 34.3 (C(=O)CH₂), 32.7 (CH₂CHNH), 26.3 (C(=O)CH₂CH₂), 25.8 (CH₂CH₂CHNH), 25.5 (CH₂CH₂CHOH)

HRMS (ESI⁺) m/z / Da = 249.1331, [M+Na]⁺ found, [C₁₀H₁₈N₄NaO₂]⁺ requires 249.1327

The compound has not been reported previously.

1.36 Methyl 1-cyclopropyl-6-fluoro-7-(4-(4-(((*trans*)-2-hydroxycyclohexyl)amino)-4-oxobutyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate **136**



4-(4-(1-Cyclopropyl-6-fluoro-3-(methoxycarbonyl)-4-oxo-1,4-dihydroquinolin-7-yl)piperazin-1-yl)butanoic acid trifluoroacetate **112** (200 mg, 0.367 mmol, 1 eq.), (*trans*)-2-aminocyclohexan-1-ol **133** (91.1 mg, 0.791 mmol, 2.1 eq.), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (112 mg, 0.584 mmol, 1.6 eq.), 1-hydroxybenzotriazole (96 mg, 0.710 mmol, 1.9 eq.) and DIPEA (192 μ l, 142 mg, 1.10 mmol, 3 eq.) were dissolved in DMF (5 ml) and stirred at r.t. for 16 h. The solvent was removed using a stream of N₂ and the residue was purified by preparatory HPLC (5-50 % acetonitrile/water over 10 min). The combined pure fractions were evaporated under reduced pressure and then partitioned between NaHCO₃ (aq., sat., 10 ml) and CH₂Cl₂ (10 ml). The organic layer was dried with MgSO₄ and evaporated under reduced pressure. **136** was obtained as a white amorphous

solid (73.0 mg, 0.142 mmol, 38.7 %).

IR (neat) ν_{max} / cm^{-1} = 3302.5 (N-H), 2929.8 (C-H), 2850.6 (C-H), 2832.9 (C-H), 1698.1 (ester C=O), 1646.4 (amide C=O), 1613.8 (quinolone C=O)

^1H NMR (400 MHz, MeOD) δ / ppm = 8.60 (s, 1 H, *ortho* to C(=O)OCH₃), 7.79 (d, J = 13.5 Hz, 1 H, *ortho* to F), 7.46 (d, J = 7.2 Hz, 1 H, *meta* to F), 3.84 (s, 3 H, CH₃), 3.62 - 3.68 (m, 1 H, NCH(CH₂)₂), 3.58 (td, J = 10.3, 4.2 Hz, 1 H, CHNH), 3.38 (br s, 4 H, CH₂N(CH₂CH₂)CH₂CH₂), 3.32 - 3.36 (m, 1 H, CHOH), 2.83 (br s, 4 H, CH₂N(CH₂)CH₂), 2.60 (t, J = 7.3 Hz, 2 H, C(=O)CH₂CH₂CH₂N), 2.32 (td, J = 7.1, 3.1 Hz, 2 H, C(=O)CH₂), 1.96 - 2.04 (m, 1 H, CHHCHOH), 1.87 - 1.96 (m, 3 H, CHHCHNH and C(=O)CH₂CH₂), 1.72 - 1.77 (m, 1 H, CHHCH₂CHOH), 1.66 - 1.72 (m, 1 H, CHHCH₂CHNH), 1.25 - 1.39 (m, 5 H, CHHCHOH, CHHCH₂CHOH, CHHCH₂CHNH and NCH(CHH)₂), 1.15 - 1.25 (m, 3 H, CHHCHOH and NCH(CHH)₂)

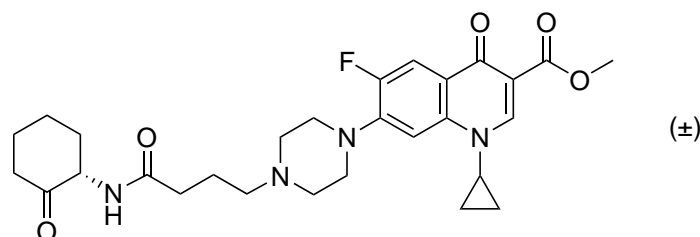
^{13}C NMR (101 MHz, MeOD) δ / ppm = 175.8 (CH₂C(=O)NH), 175.3 (C(=O)CC(=O)OCH₃), 166.8 (C(=O)OCH₃), 154.9 (d, J = 248.8 Hz, *ipso* to F), 150.2 (C=CC(=O)OCH₃), 146.1 (d, J = 10.8 Hz, *ipso* to piperazine), 139.9 (*para* to F), 123.5 (d, J = 7.5 Hz, *para* to piperazine), 113.2 (d, J = 23.2 Hz, *ortho* to C=O and *ortho* to F), 110.2 (CC(=O)OCH₃), 107.2 (*meta* to C=O and *meta* to F), 74.1 (CHOH), 58.9 (C(=O)CH₂CH₂CH₂N), 56.4 (CHNH), 54.0 (C(=O)CH₂CH₂CH₂N(CH₂)CH₂), 52.3 (CH₃), 50.5 (d, J = 5.0 Hz, C(=O)CH₂CH₂CH₂N(CH₂)CH₂CH₂), 36.4 (NCH(CH₂)₂), 35.7 (CH₂CHOH), 35.1 (C(=O)CH₂), 32.8 (CH₂CHNH), 25.9 (CH₂CH₂CHNH), 25.5 (CH₂CH₂CHOH), 23.5 (C(=O)CH₂CH₂), 8.7 (NCH(CH₂)₂)

^{19}F NMR (376.45 MHz, MeOD) δ / ppm = -124.7 (ciprofloxacin F)

HRMS (ESI⁺) m/z / Da = 529.2827, [M+H]⁺ found, [C₂₈H₃₈FN₄O₅]⁺ requires 529.2826

The compound has not been reported previously.

1.37 Methyl 1-cyclopropyl-6-fluoro-4-oxo-7-(4-(4-oxo-4-((2-oxocyclohexyl)amino)-butyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate **137**



Methyl 1-cyclopropyl-6-fluoro-7-(4-(4-(((*trans*)-2-hydroxycyclohexyl)amino)-4-oxobutyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate **136** (5.2 mg, 9.84 μmol , 1 eq.) and Dess-Martin periodane (16.4 mg, 38.7 μmol , 4 eq.) were stirred in CH₂Cl₂ (3 ml) for 6 h. The solvent was removed under reduced pressure and the residue was purified by preparatory HPLC (5-95 % acetonitrile/water over 20 min). The combined pure fractions were evaporated under reduced pressure to a volume of 20 ml, then NaHCO₃ (aq., sat., 30 ml) and 10 % *i*-PrOH/CHCl₃ (30 ml) were added. The organic layer was dried with MgSO₄ and evaporated under reduced pressure. **137** was obtained as a white amorphous solid (3.6 mg, 6.8 μmol , 69.1 %).

TLC R_f = 0.74 (30 % MeOH/CH₂Cl₂)

IR (neat) ν_{max} / cm^{-1} = 2921.2 (C-H), 2851.6 (C-H), 1721.4 (ketone C=O), 1698.0 (ester C=O), 1639.3 (amide C=O), 1620.0 (quinolone C=O)

^1H NMR (400 MHz, DMSO d_6) δ / ppm = 8.45 (s, 1 H, *ortho* to C(=O)OCH₃), 7.87 (d, J = 6.2 Hz, 1 H, NH), 7.76 (d, J = 13.4 Hz, 1 H, *ortho* to F), 7.44 (d, J = 7.5 Hz, 1 H, *meta* to F), 4.42 (dddd, J = 13.0, 7.6, 6.0, 1.0 Hz, 1 H, CHNH), 3.73 (s, 3 H, CH₃), 3.65 (tt, J = 7.1, 3.9 Hz, 1 H, NCH(CH₂)₂), 3.25 (br s, 4 H, CH₂N(CH₂CH₂)CH₂CH₂), 2.58 (br s, 4 H, CH₂N(CH₂)CH₂), 2.45 - 2.53 (m, 1 H, CHHC(=O)CHNH), 2.36 (br s, 2 H, C(=O)CH₂CH₂CH₂N), 2.26 (dtt, J = 13.4, 2.6, 2.6, 1.6, 1.6 Hz, 1 H, CHHC(=O)CHNH), 2.16 - 2.22 (m, 2 H, C(=O)CH₂CH₂CH₂N), 2.12 (ddq, J = 12.7, 6.0, 2.8, 2.8, 2.8 Hz, 1 H, CHHCHNH), 2.00 (ddquin, J = 13.2, 6.0, 2.9, 2.9, 2.9, 2.9 Hz, 1 H, CHHCH₂C(=O)), 1.65 - 1.83 (m, 4 H, CH₂CH₂CHNH), 1.41 - 1.56 (m, 2 H, CHHCHNH and CHHCH₂C(=O)), 1.20 - 1.30 (m, 2 H, NCH(CH₂)₂), 1.05 - 1.13 (m, 2 H, NCH(CH₂)₂)

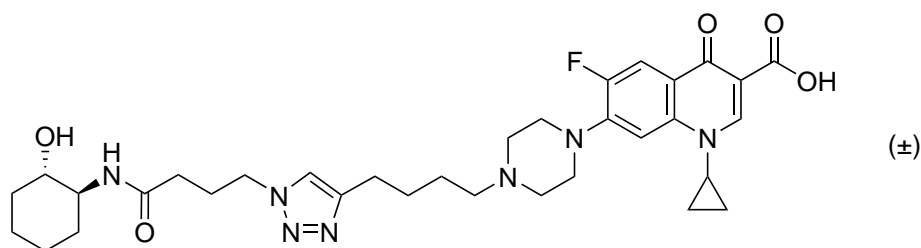
^{13}C NMR (101 MHz, DMSO d_6) δ / ppm = 207.5 (C(=O)CHNH), 171.7 (C(=O)CC(=O)OCH₃), 171.6 (CH₂C(=O)NH), 165.0 (C(=O)OCH₃), 152.6 (d, J = 247.6 Hz, *ipso* to F), 148.3 (C=CC(=O)OCH₃), 143.9 (br s, *ipso* to piperazine), 138.1 (*para* to F), 121.8 (d, J = 6.4 Hz, *para* to piperazine), 111.5 (d, J = 22.4 Hz, *ortho* to C=O and *ortho* to F), 109.0 (CC(=O)OCH₃), 106.3 (*meta* to C=O and *meta* to F), 57.0 (CHNH and C(=O)CH₂CH₂CH₂N), 52.3 (br s, C(=O)CH₂CH₂CH₂N(CH₂)CH₂), 51.3 (CH₃), 49.5 (br s, C(=O)CH₂CH₂CH₂N(CH₂)CH₂CH₂), 40.6 (CH₂C(=O)CHNH), 34.8 (NCH(CH₂)₂), 33.9 (CH₂CHNH), 32.9 (C(=O)CH₂CH₂CH₂N), 27.2 (CH₂CH₂C(=O)CHNH), 23.8 (CH₂CH₂CHNH), 22.4 (br s, C(=O)CH₂CH₂CH₂N), 7.6 (NCH(CH₂)₂)

^{19}F NMR (376.45 MHz, DMSO d_6) δ / ppm = -124.3 (ciprofloxacin F)

HRMS (ESI⁺) m/z / Da = 527.2654, [M+H]⁺ found, [C₂₈H₃₆FN₄O₅]⁺ requires 527.2670

The compound has not been reported previously.

1.38 1-Cyclopropyl-6-fluoro-7-(4-(4-(1-(4-(((*trans*)-2-hydroxycyclohexyl)amino)-4-oxobutyl)-1*H*-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **138**



1-Cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **70** (40 mg, 97.2 μmol , 1 eq.) and 4-azido-*N*-(((*trans*)-2-hydroxycyclohexyl)butanamide **135** (22.0 mg, 97.2 μmol , 1 eq.) were dissolved in 10 % water/*t*-BuOH (3 ml), and the mixture was degassed by bubbling N₂ through it. A solution of CuSO₄ and THPTA (97.2 μl , 9.72 μmol , 0.1 eq. 100 mM, aq.) was added, followed by a solution of sodium ascorbate (194 μl , 19.4 μmol , 0.2 eq., 100 mM, aq.). The mixture was stirred at r.t. under argon for 16 h. Water (50 ml) and 10 % *i*-PrOH/CHCl₃ (50 ml) were added, then the organic layer was separated, dried with MgSO₄ and evaporated under reduced pressure. The residue was purified by preparatory HPLC (5-70 % acetonitrile/water over 15 min). The combined pure fractions were evaporated under reduced pressure and then

partitioned between NaHCO₃ (aq., sat., 50 ml) and 10 % *i*-PrOH/CHCl₃ (50 ml). The organic layer was dried with MgSO₄ and evaporated under reduced pressure. **138** was obtained as a white amorphous solid (30.3 mg, 47.5 μmol, 48.9 %).

IR (neat) ν_{max} / cm⁻¹ = 3345.4 (N-H), 2927.6 (C-H), 2859.6 (C-H), 2814.7 (C-H), 1727.0 (carboxylic acid C=O), 1641.7 (amide C=O), 1625.8 (quinolone C=O), 1619.0 (triazole)

¹H NMR (400 MHz, DMSO d₆) δ / ppm = 8.64 (s, 1 H, *ortho* to C(=O)OH), 7.86 (d, *J* = 13.9 Hz, 1 H, *ortho* to F), 7.84 (s, 1 H, CH=CCH₂), 7.64 (d, *J* = 8.1 Hz, 1 H, NH), 7.54 (d, *J* = 7.5 Hz, 1 H, *meta* to F), 4.54 (d, *J* = 4.7 Hz, 1 H, OH), 4.30 (t, *J* = 6.8 Hz, 2 H, C(=O)CH₂CH₂CH₂N), 3.77 - 3.86 (m, 1 H, NCH(CH₂)₂), 3.33 - 3.40 (m, 1 H, CHNH), 3.31 (br t, *J* = 4.8, 4.8 Hz, 4 H, CH=CCH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 3.14 - 3.24 (m, 1 H, CHOH), 2.63 (t, *J* = 7.4 Hz, 2 H, CH=CCH₂), 2.56 (br t, *J* = 4.6, 4.6 Hz, 4 H, CH=CCH₂CH₂CH₂N(CH₂)CH₂), 2.38 (t, *J* = 6.9 Hz, 2 H, CH=CCH₂CH₂CH₂CH₂N), 2.04 - 2.08 (m, 2 H, C(=O)CH₂CH₂CH₂N), 1.96 - 2.04 (m, 2 H, C(=O)CH₂CH₂CH₂N), 1.78 - 1.87 (m, 1 H, CHHCHOH), 1.69 - 1.78 (m, 1 H, CHHCHNH), 1.63 (quin, *J* = 7.5 Hz, 2 H, CH=CCH₂CH₂CH₂CH₂N), 1.54 - 1.60 (m, 1 H, CHHCH₂OH), 1.51 (quin, *J* = 7.4 Hz, 2 H, CH=CCH₂CH₂CH₂CH₂N), 1.28 - 1.35 (m, 1 H, NCH(CHH)₂), 1.11 - 1.22 (m, 5 H, NCH(CHH)₂, CHHCHOH, CHHCH₂CHOH and CH₂CH₂CHNH), 1.04 - 1.13 (m, 1 H, CHHCHNH)

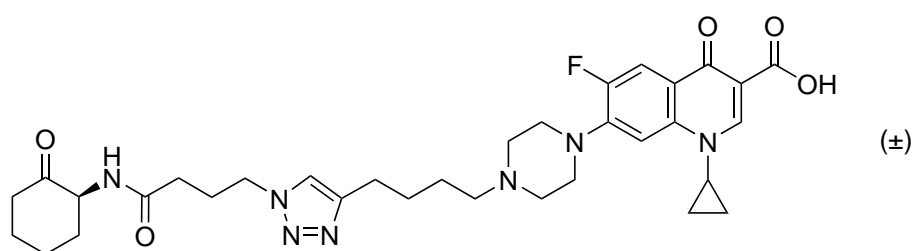
¹³C NMR (101 MHz, DMSO d₆) δ / ppm = 176.4 (C(=O)CC(=O)OH), 170.9 (CH₂C(=O)NH), 166.0 (C(=O)OH), 153.1 (d, *J* = 252.1 Hz, *ipso* to F), 148.0 (C=CC(=O)OH), 146.9 (CH=CCH₂), 145.3 (d, *J* = 10.0 Hz, *ipso* to piperazine), 139.2 (*para* to F), 121.8 (NCH=CCH₂), 118.5 (d, *J* = 8.3 Hz, *para* to piperazine), 110.9 (d, *J* = 23.2 Hz, *ortho* to C=O and *ortho* to F), 106.7 (CC(=O)OH), 106.3 (d, *J* = 3.3 Hz, *meta* to C=O and *meta* to F), 71.4 (CHOH), 57.4 (CH=CCH₂CH₂CH₂CH₂N), 54.2 (CHNH), 52.4 (CH=CCH₂CH₂CH₂CH₂N(CH₂)CH₂), 49.5 (CH=CCH₂CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 49.5 (CH=CCH₂CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 48.8 (C(=O)CH₂CH₂CH₂NCH=C), 35.9 (NCH(CH₂)₂), 34.1 (CH₂CHOH), 32.3 (C(=O)CH₂CH₂CH₂NCH=C), 31.1 (CH₂CHNH), 26.9 (CH=CCH₂CH₂CH₂CH₂N), 26.1 (C(=O)CH₂CH₂CH₂NCH=C), 25.8 (CH=CCH₂CH₂CH₂CH₂N), 25.0 (CH=CCH₂CH₂CH₂CH₂N), 24.2 (CH₂CH₂CHNH), 23.8 (CH₂CH₂CHOH), 7.6 (NCH(CH₂)₂)

¹⁹F NMR (376.45 MHz, DMSO d₆) δ / ppm = -121.4 (ciprofloxacin F)

HRMS (ESI⁺) *m/z* / Da = 638.3480, [M+H]⁺ found, [C₃₃H₄₅FN₇O₅]⁺ requires 638.3466

The compound has not been reported previously.

1.39 1-Cyclopropyl-6-fluoro-4-oxo-7-(4-(4-(1-(4-oxo-4-((2-oxocyclohexyl)amino)butyl)-1*H*-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid **139**



1-Cyclopropyl-6-fluoro-7-(4-(4-(1-(4-(((*trans*)-2-hydroxycyclohexyl)amino)-4-oxobutyl)-1H-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **138** (15.0 mg, 23.6 mmol, 1 eq.) and Dess-Martin periodane (35.0 mg, 82.5 mmol, 3.5 eq.) were stirred in CH₂Cl₂ (3 ml) for 4 h. The solvent was removed under reduced pressure and the residue was purified by preparatory HPLC (5-70 % acetonitrile/water over 15 min). The combined pure fractions were evaporated under reduced pressure, then NaHCO₃ (aq., sat., 30 ml) and 10 % *i*-PrOH/CHCl₃ (30 ml) were added. The organic layer was dried with MgSO₄ and evaporated under reduced pressure. **139** was obtained as a clear gum (11.7 mg, 18.4 μmol, 78.0 %).

IR (neat) ν_{max} / cm⁻¹ = 2941.2 (C-H), 2859.8 (C-H), 1719.8 (carboxylic acid C=O and ketone C=O), 1656.8 (amide C=O), 1625.6 (quinolone C=O), 1613.5 (triazole)

¹H NMR (500 MHz, DMSO d₆) δ / ppm = 8.65 (s, 1 H, *ortho* to C(=O)OH), 7.94 (d, J=7.7 Hz, 1 H, NH), 7.88 (d, J=13.4 Hz, 1 H, *ortho* to F), 7.85 (s, 1 H, CH=CCH₂), 7.55 (d, J=7.3 Hz, 1 H, *meta* to F), 4.40 (dddd, J=12.8, 7.6, 6.1, 1.1 Hz, 1 H), 4.31 (t, J=7.0 Hz, 1 H, C(=O)CH₂CH₂CHHN), 4.31 (t, J=6.9 Hz, 1 H, C(=O)CH₂CH₂CHH₂N), 3.74 - 3.84 (m, 1 H, NCH(CH₂)₂), 3.31 (br. s, 4 H, CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 2.64 (t, J=7.5 Hz, 2 H, CH=CCH₂), 2.56 (br t, J=5.0, 5.0 Hz, 4 H, CH₂CH₂CH₂N(CH₂)CH₂), 2.45 - 2.52 (m, 1 H, CHHC(=O)), 2.38 (t, J=7.1 Hz, 2 H, CH=CCH₂CH₂CH₂CH₂N), 2.25 (dt, J=13.4, 2.6, 2.6, 1.6, 1.6 Hz, 1 H, CHHC(=O)), 2.07 - 2.17 (m, 3 H, C(=O)CH₂CH₂CH₂N and CHHCHNH), 1.96 - 2.05 (m, 3 H, C(=O)CH₂CH₂CH₂N and CHHCH₂C(=O)), 1.68 - 1.81 (m, 2 H, CHHCH₂CHNH), 1.64 (quin, J=7.5 Hz, 2 H, CH=CCH₂CH₂CH₂CH₂N), 1.40 - 1.56 (m, 5 H, CHHCH₂C(=O), CHHCHNH and CH=CCH₂CH₂CH₂CH₂N), 1.27 - 1.34 (m, 2 H, NCH(CH₂)₂), 1.13 - 1.20 (m, 2 H, NCH(CH₂)₂)

¹³C NMR (126 MHz, DMSO d₆) δ / ppm = 207.4 (C(=O)CHNH), 176.3 (C(=O)CC(=O)OH), 170.8 (CH₂C(=O)NH), 166.0 (C(=O)OH), 153.0 (d, J=246.4 Hz, *ipso* to F), 147.9 (C=CC(=O)OH), 146.8 (CH=CCH₂), 145.1 (d, J=10.1 Hz, *ipso* to piperazine), 139.1 (*para* to F), 121.7 (NCH=CCH₂), 118.7 (d, J=6.9 Hz, *para* to piperazine), 110.9 (d, J=23.0 Hz, *ortho* to C=O and *ortho* to F), 106.3 (CC(=O)OH, and *meta* to C=O and *meta* to F), 57.3 (CH=CCH₂CH₂CH₂CH₂N), 57.0 (CHNH), 52.4 (CH₂CH₂CH₂N(CH₂)CH₂), 49.5 (CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 49.5 (CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 48.7 (C(=O)CH₂CH₂CH₂NCH=C), 40.5 (CH₂C(=O)), 35.8 (NCH(CH₂)₂), 33.7 (CH₂CHNH), 31.8 (C(=O)CH₂CH₂CH₂NCH=C), 27.1 (CH₂CH₂C(=O)), 26.9 (CH=CCH₂CH₂CH₂CH₂N), 26.0 (C(=O)CH₂CH₂CH₂NCH=C), 25.7 (CH=CCH₂CH₂CH₂CH₂N), 24.9 (CH=CCH₂CH₂CH₂CH₂N), 23.8 (CH₂CH₂CHNH), 7.6 (NCH(CH₂)₂)

¹⁹F NMR (376 MHz, DMSO d₆) δ / ppm = -121.7 (s, ciprofloxacin F)

HRMS (ESI⁺) m/z / Da = 636.3303, [M+H]⁺ found, [C₃₃H₄₃FN₇O₅]⁺ requires 636.3310

The compound has not been reported previously.

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