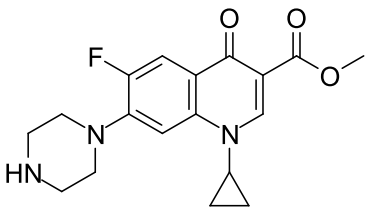
Contents

0.1 Methyl 1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate 124



Ciprofloxacin **97** (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 $NaHCO_3$ (sat., aq., 100 ml) and water (300 ml) were added. The product was extracted with CH_2Cl_2 (2 × 400 ml), which was dried over $MgSO_4$ and evaporated under reduced pressure. **124** was obtained as a white amorphous solid (9.16 g, 26.5 mmol, 83.3 %).

TLC R_f = 0.13 (5 % MeOH/CH_2Cl_2)

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

^{1}**H NMR** (400 MHz, MeOD) δ / ppm = 8.55 (s, 1 H, *ortho* to C(=O)OCH_3), 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, C$\underline{H}_3$), 3.62 (tt, J = 7.4, 3.5 Hz, 1 H, NC$\underline{H}(CH_2)_2$), 3.24 - 3.29 (m, 4 H, HN($CH_2C\underline{H}_2$)$CH_2C\underline{H}_2$), 3.02 - 3.10 (m, 4 H, HN($C\underline{H}_2$)$C\underline{H}_2$), 1.31 - 1.38 (m, 2 H, NCH($C\underline{H}H$)$_2$), 1.12 - 1.20 (m, 2 H, NCH($CH\underline{H}$)$_2$)

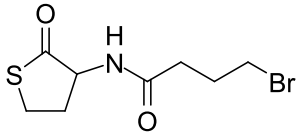
^{13}**C NMR** (101 MHz, MeOD) δ / ppm = 175.2 ($\underline{C}$(=O)CC(=O)OCH_3), 166.8 ($\underline{C}$(=O)OCH_3), 154.9 (d, J = 248.0 Hz, *ipso* to F), 150.1 ($\underline{C}$=CC(=O)OCH_3), 146.6 (d, J = 10.4 Hz, *ipso* to piperazine), 139.9 (*para* to F), 123.3 (d, J = 6.9 Hz, *para* to piperazine), 113.0 (d, J = 23.4 Hz, *ortho* to C=O and *ortho* to F), 110.1 ($\underline{C}$C(=O)OCH_3), 107.1 (d, J = 3.5 Hz, *meta* to C=O and *meta* to F), 52.3 ($\underline{C}H_3$), 51.7 (HN($CH_2\underline{C}H_2$)CH_2CH_2), 51.6 (HN(CH_2CH_2)$CH_2\underline{C}H_2$), 46.5 (HN($\underline{C}H_2$)$\underline{C}H_2$), 36.4 (N$\underline{C}H(CH_2)_2$), 8.7 (NCH($\underline{C}H_2$)$_2$)

^{19}**F NMR** (376.45 MHz, MeOD) δ / ppm = -124.8 (s, ciprofloxacin $\underline{F}$)

HRMS (ESI$^+$) m/z / Da = 346.1569, $[M+H]^+$ found, $[C_{18}H_{21}FN_3O_3]^+$ requires 346.1567

The data are consistent with the literature.[?]

0.2 4-Bromo-*N*-(2-oxotetrahydrothiophen-3-yl)butanamide 125



3-Aminodihydrothiophen-2(3H)-one hydrochloride **163** (15.0 g, 97.6 mmol, 1 eq.) and $NaHCO_3$ (16.4 g, 195 mmol, 2 eq.) were added to CH_2Cl_2 (150 ml) and water (150 ml). 4-Bromobutyryl chloride **42** (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. **125** 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) ν_{max} / cm^{-1} = 3265.9 (amide N-H), 3063.2 (amide N-H), 1694.3 (thiolactone C=O), 1650.5 (amide C=O)

^{1}H NMR (400 MHz, $CDCl_3$) δ / 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, $C(=O)CH_2CH_2$), 1.96 (dddd, J = 12.7, 12.5, 12.2, 7.0 Hz, 1 H, SCH_2CHH)

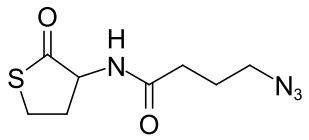
Orientatio are not unam- biguous without noesy.

^{13}C NMR (101 MHz, $CDCl_3$) δ / 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 ($C(=O)CH_2CH_2$), 27.5 (SCH_2)

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

The compound has been synthesised previously[?,?] but characterisation was not published.

0.3 4-Azido-*N*-(2-oxotetrahydrothiophen-3-yl)butanamide 126



4-Bromo-*N*-(2-oxotetrahydrothiophen-3-yl)butanamide **125** (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. **126** 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) ν_{max} / cm^{-1} = 3285.6 (N-H), 2963.9 (C-H), 2100.2 (azide), 1697.4 (thiolactone C=O), 1647.4 (amide C=O)

^{1}H NMR (400 MHz, $CDCl_3$) δ / 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, $C(=O)CH_2CH_2$)

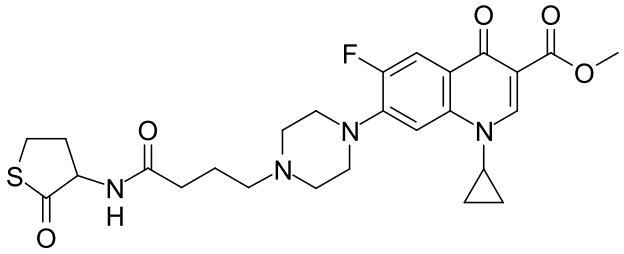
^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 205.4 (SC(=O)), 172.3 (NHC(=O)), 59.4 (CHNH), 50.6 (CH_2N_3),

32.8 (C(=O)$\underline{C}H_2$), 31.8 (SCH$_2\underline{C}H_2$), 27.5 (S$\underline{C}H_2$), 24.6 (C(=O)CH$_2\underline{C}H_2$)

HRMS (ESI$^+$) m/z / Da = 251.0565, [M+Na]$^+$ found, [$C_8H_{12}N_4NaO_2S$]$^+$ requires 251.0573

The compound has not been reported previously.

0.4 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 127



Methyl 1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate **124** (50 mg, 0.145 mmol, 1 eq.), 4-bromo-*N*-(2-oxotetrahydrothiophen-3-yl)butanamide **125** (34.5 mg, 0.145 mmol, 1 eq.) and K_2CO_3 (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 **125** (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 (SiO_2, 5-10 % MeOH/CH_2Cl_2). **127** was obtained as a cream-coloured amorphous solid (9.4 mg, 0.018 mmol, 12.2 %).

TLC R_f = 0.47 (10 % MeOH/CH_2Cl_2)

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)

^{1}**H NMR** (500 MHz, MeOD) δ / ppm = 8.53 (s, 1 H, *ortho* to C(=O)OCH$_3$), 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, C$\underline{H}$NH), 3.83 (s, 3 H, OC$\underline{H}_3$), 3.61 (tt, J=6.9, 4.1 Hz, 1 H, NC$\underline{H}$(CH$_2$)$_2$), 3.39 - 3.49 (m, 5 H, SC$\underline{H}$H), 3.26 - 3.33 (m, 1 H, SCH$\underline{H}$ and CH$_2$CH$_2$CH$_2$N(CH$_2$C$\underline{H}_2$)CH$_2$C$\underline{H}_2$), 2.93 - 3.03 (m, 4 H, CH$_2$CH$_2$CH$_2$N(C$\underline{H}_2$)C$\underline{H}_2$), 2.79 (br. t, J=7.2, 7.2 Hz, 2 H, C(=O)CH$_2$CH$_2$C$\underline{H}_2$), 2.59 (dddd, J=12.4, 6.9, 5.4, 1.4 Hz, 1 H, SCH$_2$C$\underline{H}$H), 2.39 (t, J=7.20 Hz, 1 H, C(=O)C$\underline{H}$H), 2.38 (t, J=6.94 Hz, 1 H, C(=O)CH$\underline{H}$), 2.18 (qd, J=12.4, 7.0 Hz, 1 H, SCH$_2$CH$\underline{H}$), 1.97 (quin, J=7.2 Hz, 2 H, C(=O)CH$_2$C$\underline{H}_2$), 1.32 - 1.37 (m, 2 H, NCH(C$\underline{H}$H)$_2$), 1.13 - 1.19 (m, 2 H, NCH(CH$\underline{H}$)$_2$)

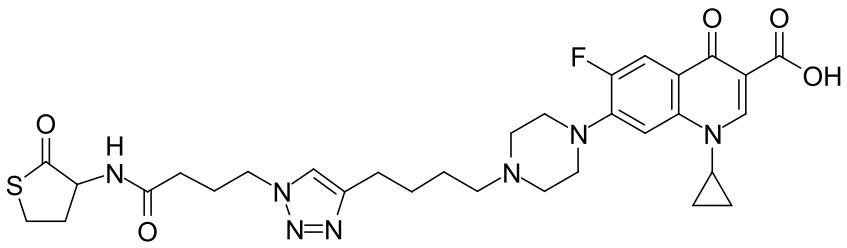
^{13}**C NMR** (126 MHz, MeOD) δ / ppm = 207.0 (S$\underline{C}$(=O)), 175.7 (NH$\underline{C}$(=O)), 175.1 ($\underline{C}$(=O)CC(=O)OCH$_3$), 166.6 ($\underline{C}$(=O)OCH$_3$), 154.7 (d, J=249.0 Hz, *ipso* to F), 150.2 (s, $\underline{C}$H=CC(=O)OCH$_3$), 145.6 (d, J=10.6 Hz, *ipso* to piperazine), 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 ($\underline{C}$C(=O)OCH$_3$), 107.4 (*meta* to C=O and *meta* to F), 60.2 ($\underline{C}$HNH), 58.5 (C(=O)CH$_2$CH$_2$C$\underline{H}_2$), 53.8 (CH$_2$CH$_2$CH$_2$N($\underline{C}$H$_2$)$\underline{C}$H$_2$), 52.3 (O$\underline{C}$H$_3$), 50.1 (CH$_2$CH$_2$CH$_2$N(CH$_2\underline{C}$H$_2$)CH$_2$CH$_2$), 50.0 (CH$_2$CH$_2$CH$_2$N(CH$_2$CH$_2$)CH$_2\underline{C}$H$_2$), 36.5 (N$\underline{C}$H(CH$_2$)$_2$), 34.5 (C(=O)$\underline{C}$H$_2$), 31.7 (SCH$_2\underline{C}$H$_2$), 28.1 (S$\underline{C}$H$_2$), 22.9 (C(=O)CH$_2\underline{C}$H$_2$CH$_2$), 8.7 (NCH($\underline{C}$H$_2$)$_2$)

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

HRMS (ESI$^+$) m/z / Da = 531.2083, $[M+H]^+$ found, $[C_{26}H_{32}FN_4O_5S]^+$ requires 531.2077

The compound has been synthesised previously.[?,?] Only HRMS characterisation was published, and this agrees with the result above. check??

0.5 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 128



1-Cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **164** (15 mg, 36.7 μmol, 1 eq.) and 4-azido-*N*-(2-oxotetrahydrothiophen-3-yl)butanamide **126** (12.5 mg, 55.1 μmol, 1.5 eq.) were dissolved in 1:9:10 % water/*t*-BuOH/DMSO (3 ml), and the mixture was degassed by bubbling N_2 through it. A solution of $CuSO_4$ and THPTA (182 μl, 18.2 μmol, 0.5 eq. 100 mM, aq.) was added, followed by a solution of sodium ascorbate (367 μl, 36.7 μmol, 1 eq., 100 mM, aq.). The mixture was stirred at r.t. under argon for 7 d. Water (50 ml) and 10 % *i*-PrOH/$CHCl_3$ (10 ml) were added, the organic layer was separated and the aqueous layer was extracted again with 10 % *i*-PrOH/$CHCl_3$ (2 × 10 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., 50 ml) and 10 % *i*-PrOH/$CHCl_3$ (50 ml). The organic layer was dried with $MgSO_4$ and evaporated under reduced pressure. **128** was obtained as a white amorphous solid (16.5 mg, 25.9 μmol, 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)

^{1}**H NMR** (500 MHz, DMSO d_6) δ / ppm = 15.23 (br s, 1 H, C(=O)O$\underline{H}$), 8.66 (s, 1 H, *ortho* to C(=O)OH), 8.23 (d, J=8.5 Hz, 1 H, N$\underline{H}$), 7.90 (d, J=13.4 Hz, 1 H, *ortho* to F), 7.84 (s, 1 H, C$\underline{H}$=CCH$_2$), 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, C$\underline{H}$NH), 4.31 (t, J=7.0 Hz, 2 H, C$\underline{H}_2$NCH=C), 3.80 - 3.86 (6.9, 4.0 Hz, 1 H, NC$\underline{H}$(CH$_2$)$_2$), 3.34 - 3.37 (m, 1 H, SC$\underline{H}$H), 3.32 (br t, J=4.1 Hz, 4 H, CH$_2$CH$_2$CH$_2$N(CH$_2$C$\underline{H}_2$)CH$_2$C$\underline{H}_2$), 3.27 (ddd, J=11.1, 6.9, 1.4 Hz, 1 H, SCH$\underline{H}$), 2.64 (t, J=7.6 Hz, 2 H, CH=CC$\underline{H}_2$), 2.57 (br t, J=4.7 Hz, 4 H, CH$_2$CH$_2$CH$_2$N(C$\underline{H}_2$)C$\underline{H}_2$), 2.34 - 2.44 (m, 3 H, SCH$_2$C$\underline{H}$H and CH=CCH$_2$CH$_2$CH$_2$C$\underline{H}_2$), 2.12 (t, J=7.9 Hz, 1 H, C(=O)C$\underline{H}$H), 2.12 (t, J=7.0 Hz, 1 H, C(=O)CH$\underline{H}$), 2.04 (m, 3 H, SCH$_2$CH$\underline{H}$ and C(=O)CH$_2$C$\underline{H}_2$), 1.64 (quin, J=7.5 Hz, 2 H, CH=CCH$_2$C$\underline{H}_2$), 1.51 (quin, J=7.5 Hz, 2 H, CH=CCH$_2$CH$_2$C$\underline{H}_2$), 1.28 - 1.34 (m, 2 H, NCH(C$\underline{H}$H)$_2$), 1.15 - 1.20 (m, 2 H, NCH(CH$\underline{H}$)$_2$)

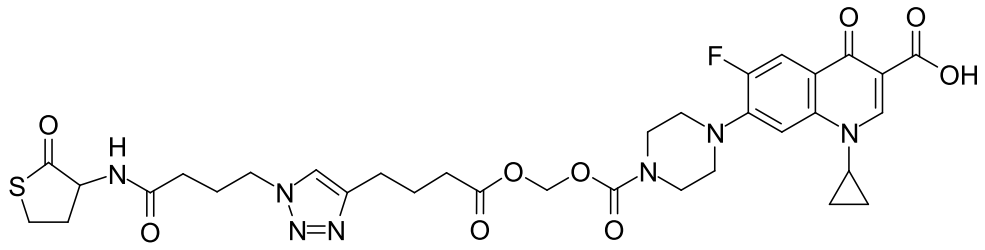
^{13}**C NMR** (126 MHz, DMSO d_6) δ / ppm = 205.6 (S$\underline{C}$(=O)), 176.4 ($\underline{C}$(=O)CC(=O)OH), 171.4 (NH$\underline{C}$(=O)), 166.0 ($\underline{C}$(=O)OH), 153.1 (d, J=249.3 Hz, *ortho* to F), 148.0 ($\underline{C}$H=CC(=O)OH), 146.9 (CH=$\underline{C}$CH$_2$), 145.3 (d, J=10.1 Hz, *ipso* to piperazine), 139.2 (*para* to F), 121.8 ($\underline{C}$H=CCH$_2$), 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 ($\underline{C}$C(=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=CCH$_2$CH$_2$CH$_2$CH$_2$N), 52.4 (CH$_2$CH$_2$CH$_2$N(CH$_2$)CH$_2$), 49.5 (CH$_2$CH$_2$CH$_2$N(CH$_2$CH$_2$)CH$_2$CH$_2$), 49.5 (CH$_2$CH$_2$CH$_2$N(CH$_2$CH$_2$)CH$_2$CH$_2$), 48.6 (CH$_2$NCH=C), 35.9 (NCH(CH$_2$)$_2$), 31.9 (NHC(=O)CH$_2$), 30.1 (CH$_2$CHNH), 26.9 (CH=CCH$_2$CH$_2$), 26.8 (SCH$_2$), 25.9 (NHC(=O)CH$_2$CH$_2$), 25.8 (CH=CCH$_2$CH$_2$CH$_2$), 25.0 (CH=CCH$_2$), 7.6 (NCH(CH$_2$)$_2$)

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

HRMS (ESI$^+$) m/z / Da = 640.2739, $[M+H]^+$ found, $[C_{31}H_{39}FN_7O_5S]^+$ requires 640.2712

0.6 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)butanoyl)oxy)methoxy)carbonyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid 129



1-Cyclopropyl-6-fluoro-7-(4-(((hex-5-ynoyloxy)methoxy)carbonyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **165** (203 mg, 0.407 mmol, 1 eq.), 4-azido-*N*-(2-oxotetrahydrothiophen-3-yl)butanamide **126** (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 CH_2Cl_2 (18.6 ml) at r.t. under Ar for 3 h. The mixture was fitered and the filtrate was dry-loaded onto SiO_2 and purified by column chromatography (SiO_2, 5-10 % MeOH/CH_2Cl_2). **129** was obtained as pale brown/yellow amorphous solid (14.7 mg, 20.2 μmol, 5.0 %).

TLC R_f = 0.40 (5 % CH_2Cl_2/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)

^{1}H NMR (400 MHz, DMSO d_6) 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=CCH$_2$), 7.57 (d, J = 7.4 Hz, 1 H, *meta* to F), 5.74 (s, 1 H, OCH$_2$O), 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)CH$_2$CH$_2$CH$_2$N), 3.80 (tt, J = 6.9, 3.6 Hz, 1 H, NCH(CH$_2$)$_2$), 3.62 (br t, J = 5.2, 5.2 Hz, 4 H, C(=O)N(CH$_2$)CH$_2$), 3.38 (td, J = 11.4, 5.5 Hz, 1 H, SCHH), 3.34 (br. s, 4 H, C(=O)N(CH$_2$CH$_2$)CH$_2$CH$_2$), 3.27 (ddd, J = 11.0, 6.9, 1.6 Hz, 1 H, SCHH), 2.64 (t, J = 7.6 Hz, 2 H, CH=CCH$_2$), 2.44 (t, J = 7.5 Hz, 2 H, CH$_2$C(=O)O), 2.40 (dddd, J = 12.3, 6.8, 5.4, 1.4 Hz, 1 H, SCH$_2$CHH), 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, SCH$_2$CHH and NHC(=O)CH$_2$CH$_2$), 1.86 (quin, J = 7.5 Hz, 2 H, CH=CCH$_2$CH$_2$), 1.29 - 1.36 (m, 2 H, NCH(CHH)$_2$), 1.14 - 1.21 (m, 2 H, NCH(CHH)$_2$)

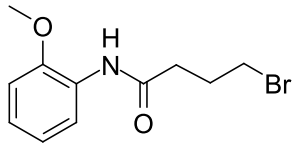
^{13}C NMR (101 MHz, DMSO d_6) δ / ppm = 205.5 (SC(=O)), 176.4 (C(=O)CC(=O)OH), 171.8 (C(=O)OCH$_2$O), 171.3 (NHC(=O)), 165.9 (C(=O)OH), 152.8 (d, J = 249.7 Hz, *ipso* to F), 152.9 (OC(=O)N), 148.1 (CH=CC(=O)OH), 146.0 (CH=CCH$_2$), 144.9 (d, J = 9.6 Hz, *ipso* to piperazine), 139.1 (*para* to F), 122.0 (CH=CCH$_2$), 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 (O$\underline{C}H_2O$), 58.2 ($\underline{C}$HNH), 49.1 (C(=O)N($CH_2\underline{C}H_2$)CH_2CH_2), 49.1 (C(=O)N(CH_2CH_2)$CH_2\underline{C}H_2$), 48.6 (C(=O)$CH_2CH_2\underline{C}H_2$N), 43.4 (N($\underline{C}H_2$)CH_2), 43.0 (N(CH_2)$\underline{C}H_2$), 35.9 (N$\underline{C}$H(CH_2)$_2$), 32.7 (CH=C$CH_2CH_2\underline{C}H_2$C(=O)), 31.8 (NH$\underline{C}$(=O)$\underline{C}H_2$), 30.1 (S$CH_2\underline{C}H_2$), 26.8 (S$\underline{C}H_2$), 25.8 (C(=O)$CH_2\underline{C}H_2CH_2$N), 24.2 (CH=C$\underline{C}H_2CH_2CH_2$C(=O)), 24.0 (CH=C$CH_2\underline{C}H_2CH_2$C(=O)), 7.6 (NCH($\underline{C}H_2$)$_2$)

HRMS (ESI$^+$) m/z / Da = 728.2502, $[M+H]^+$ found, $[C_{33}H_{39}FN_7O_9S]^+$ requires 728.2503

The compound has not been reported previously.

0.7 4-Bromo-*N*-(2-methoxyphenyl)butanamide 130



2-Methoxyaniline **166** (9.12 ml, 10.0 g, 81.2 mmol, 1 eq.) and $NaHCO_3$ (8.19 g, 97.4 mmol, 1.2 eq.) were dissolved in water (100 ml) and CH_2Cl_2 (100 ml). The mixture was cooled to 0 °C and 4-bromobutyryl chloride **42** (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 $MgSO_4$ and evaporated under reduced pressure. **130** 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)

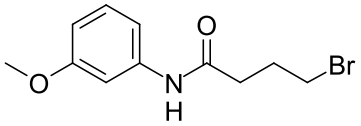
^{1}**H NMR** (400 MHz, $CDCl_3$ d_1) δ / ppm = 8.32 (dd, J = 8.0, 1.7 Hz, 1 H, *ortho* to NH), 7.85 (br s, 1 H, N$\underline{H}$), 7.02 (td, J = 7.9, 1.7 Hz, 1 H, *para* to NH), 6.93 (td, J = 7.7, 1.4 Hz, 1 H, *para* to OCH_3), 6.85 (dd, J = 8.1, 1.5 Hz, 1 H, *ortho* to OCH_3), 3.85 (s, 3 H, C$\underline{H}_3$), 3.50 (t, J = 6.4 Hz, 2 H, C$\underline{H}_2$Br), 2.56 (t, J = 7.1 Hz, 2 H, C(=O)C$\underline{H}_2$), 2.25 (quin, J = 6.7 Hz, 2 H, C(=O)CH_2C$\underline{H}_2$)

^{13}**C NMR** (101 MHz, $CDCl_3$ d_1) δ / ppm = 169.4 ($\underline{C}$(=O)), 147.6 (*ipso* to OCH_3), 127.2 (*ipso* to NH), 123.5 (*para* to NH), 120.7 (*para* to OCH_3), 119.6 (*ortho* to NH and *meta* to OCH_3), 109.8 (*ortho* to OCH_3 and *meta* to NH), 55.5 ($\underline{C}H_3$), 35.4 (C(=O)$\underline{C}H_2$), 33.1 ($\underline{C}H_2$Br), 27.9 (C(=O)$CH_2\underline{C}H_2$)

HRMS (ESI$^+$) m/z / Da = 272.0287, $[M+H]^+$ found, $[C_{11}H_{15}BrNO_2]^+$ requires 272.0286

The compound has not been reported previously.

0.8 4-Bromo-*N*-(3-methoxyphenyl)butanamide 131



3-Methoxyaniline **167** (3.04 ml, 3.33 g, 27.1 mmol, 1 eq.) and $NaHCO_3$ (2.73 g, 32.5 mmol, 1.2 eq.) were dissolved in water (30 ml) and CH_2Cl_2 (30 ml). The mixture was cooled to 0 °C and 4-bromobutyryl chloride **42** (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 SiO_2 and purified by column chromatography using a Combiflash (SiO_2, 0-100 % EtOAc/P.E.). **131** was obtained as a pale pink amorphous solid (3.66 g, 13.5 mmol, 49.6 %). how to report?

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

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

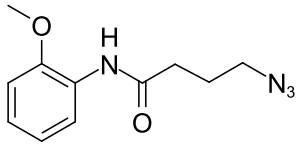
^{1}H NMR (400 MHz, $CDCl_3$ d_1) δ / ppm = 8.45 (s, 1 H, NH), 7.27 (t, J = 2.2 Hz, 1 H, *ortho* to OCH_3 and *ortho* to NH), 7.14 (t, J = 8.1 Hz, 1 H, *meta* to OCH_3 and *meta* to NH), 7.02 (d, J = 8.3 Hz, 1 H, *para* to OCH_3), 6.62 (dd, J = 8.2, 2.1 Hz, 1 H, *para* to NH), 3.71 (s, 3 H, CH_3), 3.42 (t, J = 6.5 Hz, 2 H, CH_2Br), 2.51 (t, J = 6.9 Hz, 2 H, C(=O)CH_2), 2.19 (quin, J = 6.8 Hz, 2 H, C(=O)CH_2CH_2)

^{13}C NMR (101 MHz, $CDCl_3$ d_1) δ / ppm = 170.3 (C(=O)), 159.9 (*ipso* to OCH_3), 139.0 (*ipso* to NH), 129.5 (*meta* to OCH_3 and *meta* to NH), 112.1 (*para* to OCH_3), 109.9 (*para* to NH), 105.7 (*ortho* to OCH_3 and *ortho* to NH), 55.2 (CH_3), 35.3 (C(=O)CH_2), 33.2 (CH_2Br), 28.0 (C(=O)CH_2CH_2)

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

The compound has not been reported previously.

0.9 4-Azido-*N*-(2-methoxyphenyl)butanamide 132



4-Bromo-*N*-(2-methoxyphenyl)butanamide **130** (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 2 h. The mixture was cooled and filtered, and the fitrate was dry-loaded onto SiO_2 and purified by column chromatography using a Combiflash (SiO_2, 8-14 % then hold at 14 % EtOAc/P.E.). **132** 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 %). how to report?

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)

^{1}H NMR (400 MHz, $CDCl_3$ d_1) 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 OCH_3), 6.83 (dd, J = 8.1, 1.4 Hz, 1 H, *ortho* to OCH_3), 3.81 (s, 3 H, CH_3), 3.33 (t, J = 6.7 Hz, 2 H, CH_2Br), 2.42 (t, J = 7.2 Hz, 2 H, C(=O)CH_2), 1.94 (quin, J = 6.9 Hz, 2 H, C(=O)CH_2CH_2)

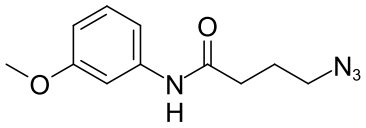
^{13}C NMR (101 MHz, $CDCl_3$ d_1) δ / ppm = 169.5 (C(=O)), 147.6 (*ipso* to OCH_3), 127.1 (*ipso* to NH), 123.4

(*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 ($\underline{C}H_3$), 50.3 ($\underline{C}H_2N_3$), 33.9 (C(=O)$\underline{C}H_2$), 24.3 (C(=O)$CH_2\underline{C}H_2$)

HRMS (ESI$^+$) m/z / Da = 257.1010, $[M+H]^+$ found, $[C_{11}H_{14}N_4NaO_2]^+$ requires 257.1014

The data are consistent with the literature.[?]

0.10 4-Azido-*N*-(3-methoxyphenyl)butanamide 133



4-Bromo-*N*-(3-methoxyphenyl)butanamide **131** (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 fitrate was dry-loaded onto SiO_2 and purified by column chromatography using a Combiflash (SiO_2, 0-100 % EtOAc/P.E.). **133** was obtained as an straw-coloured liquid (0.294 g, 1.25 mmol, 16.7 %).

how to report?

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)

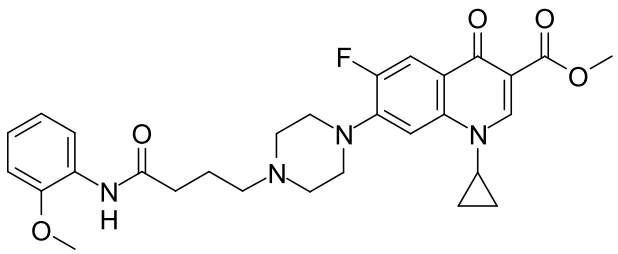
^{1}H NMR (400 MHz, MeOD) δ / ppm = 8.63 (br s, 1 H, N$\underline{H}$), 7.26 (t, J = 2.3 Hz, 1 H, *ortho* to OCH_3 and *ortho* to NH), 7.15 (t, J = 8.1 Hz, 1 H, *meta* to OCH_3 and *meta* to NH), 7.01 (dd, J = 7.8, 1.6 Hz, 1 H, *para* to OCH_3), 6.63 (dd, J = 8.2, 1.9 Hz, 1 H, *para* to NH), 3.69 (s, 3 H, C$\underline{H}_3$), 3.28 (t, J = 6.7 Hz, 2 H, C$\underline{H}_2N_3$), 2.39 (t, J = 7.4 Hz, 2 H, C(=O)C$\underline{H}_2$), 1.91 (quin, J = 7.0 Hz, 2 H, C(=O)CH_2C$\underline{H}_2$)

^{13}C NMR (101 MHz, MeOD) δ / ppm = 170.8 ($\underline{C}$(=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 ($\underline{C}H_3$), 50.4 ($\underline{C}H_2N_3$), 33.6 (C(=O)$\underline{C}H_2$), 24.4 (C(=O)$CH_2\underline{C}H_2$)

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

The compound has not been reported previously.

0.11 Methyl 1-cyclopropyl-6-fluoro-7-(4-(4-((2-methoxyphenyl)amino)-4-oxobutyl) piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 134



Methyl 1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate **124** (500 mg, 1.45 mmol, 1 eq.), 4-bromo-*N*-(2-methoxyphenyl)butanamide **130** (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 SiO_2 and purified by column chromatography (SiO_2, 4 % MeOH/CH_2Cl_2). **134** was obtained as a bright pink glass (79.7 mg, 0.149 mmol, 10.2 %).

how to report?

TLC R_f = 0.40 (10 % MeOH/CH_2Cl_2)

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)

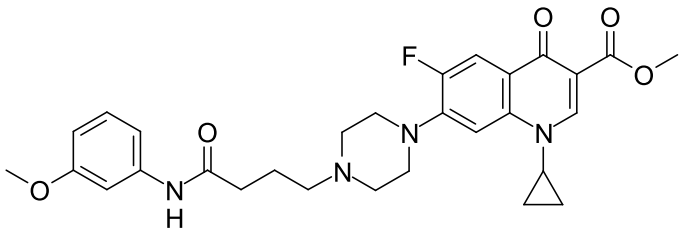
^{1}**H NMR** (400 MHz, $CDCl_3$ d_1) δ / ppm = 8.48 (s, 1 H, *ortho* to C(=O)OCH_3), 8.36 (d, J = 7.9 Hz, 1 H, *ortho* to NH), 7.87 - 7.99 (m, 2 H, *ortho* to F and NH), 7.19 (d, J = 6.5 Hz, 1 H, *meta* to F), 7.01 (t, J = 7.5 Hz, 1 H, *para* to NH), 6.93 (t, J = 7.7 Hz, 1 H, *para* to OCH_3), 6.85 (d, J = 7.9 Hz, 1 H, *ortho* to OCH_3), 3.88 (s, 3 H, C(=O)OCH_3), 3.85 (s, 3 H, aromatic OCH_3), 3.41 (tt, J = 6.9, 4.0 Hz, 1 H, NCH$(CH_2)_2$), 3.25 (br t, J = 5.0, 5.0 Hz, 4 H, C(=O)$CH_2CH_2CH_2$N$(CH_2CH_2)CH_2CH_2$), 2.67 (br t, J = 5.0, 5.0 Hz, 4 H, C(=O)$CH_2CH_2CH_2$N$(CH_2)CH_2$), 2.53 (t, J = 7.0 Hz, 2 H, C(=O)$CH_2CH_2CH_2$N), 2.47 (t, J = 7.1 Hz, 2 H, C(=O)$CH_2CH_2CH_2$N), 1.97 (quin, J = 6.8 Hz, 2 H, C(=O)$CH_2CH_2CH_2$N), 1.25 - 1.33 (m, 2 H, NCH$(CHH)_2$), 1.07 - 1.14 (m, 2 H, NCH$(CHH)_2$)

^{13}**C NMR** (101 MHz, $CDCl_3$ d_1) δ / ppm = 172.9 (C(=O)CC(=O)OCH_3), 170.8 (NHC(=O)), 166.2 (C(=O)O CH_3), 153.3 (d, J = 248.0 Hz, *ipso* to F), 148.2 (C=CC(=O)OCH_3), 147.6 (*ipso* to OCH_3), 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 OCH_3), 119.7 (*ortho* to NH and *meta* to OCH_3), 113.0 (d, J = 22.5 Hz, *ortho* to C=O and *ortho* to F), 109.8 (*ortho* to OCH_3 and *meta* to NH, and CC(=O)OCH_3), 104.7 (*meta* to C=O and *meta* to F), 57.2 ($CH_2CH_2CH_2$N), 55.6 (aromatic OCH_3), 52.7 ($CH_2CH_2CH_2$N$(CH_2)CH_2$), 51.9 (C(=O)OCH_3), 49.8 ($CH_2CH_2CH_2$N$(CH_2CH_2)CH_2CH_2$), 49.8 ($CH_2CH_2CH_2$N$(CH_2CH_2)CH_2CH_2$), 35.5 (CH_2 CH_2CH_2N), 34.5 (NCH$(CH_2)_2$), 22.3 ($CH_2CH_2CH_2$N), 8.0 (NCH$(CH_2)_2$)

HRMS (ESI$^+$) m/z / Da = 537.2523, $[M+H]^+$ found, $[C_{29}H_{34}FN_4O_5]^+$ requires 537.2513

The compound has not been reported previously.

0.12 Methyl 1-cyclopropyl-6-fluoro-7-(4-(4-((3-methoxyphenyl)amino)-4-oxobutyl) piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 135



Methyl 1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate **124** (500 mg, 1.45 mmol, 1 eq.), 4-bromo-*N*-(3-methoxyphenyl)butanamide **131** (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 mi-

crowave reactor at 100 °C for 4 h. The mixture was evaporated under reduced pressure and partitioned between how to report? CH_2Cl_2 (50 ml) and water (50 ml). The organic layer was separated off and the aqueous layer was extracted again with CH_2Cl_2 (50 ml). The combined organic layers were dried with $MgSO_4$ and purified by column chromatography (SiO_2, 0-4 % MeOH/CH_2Cl_2). **135** was obtained as an off-white amorphous solid (81.7 mg, 0.152 mmol, 10.5 %).

TLC R_f = 0.38 (10 % MeOH/CH_2Cl_2)

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)

^{1}**H NMR** (400 MHz, $CDCl_3$) δ / ppm = 8.56 (s, 1 H, *ortho* to C(=O)OCH_3), 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 OCH_3 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 OCH_3 and *meta* to NH), 6.98 (dd, J = 7.8, 1.7 Hz, 1 H, *para* to OCH_3), 6.65 (dd, J = 8.2, 2.1 Hz, 1 H, *para* to NH), 3.93 (s, 3 H, C(=O)OCH$_3$), 3.80 (s, 3 H, aromatic OCH$_3$), 3.42 (tt, J = 6.8, 3.7 Hz, 1 H, NCH$(CH_2)_2$), 3.31 (br t, J = 4.3, 4.3 Hz, 4 H, C(=O)$CH_2CH_2CH_2$N$(CH_2CH_2)CH_2CH_2$), 2.73 (br t, J = 4.5, 4.5 Hz, 4 H, C(=O)$CH_2CH_2CH_2$N$(CH_2)CH_2$), 2.58 (t, J = 6.5 Hz, 2 H, C(=O)$CH_2CH_2CH_2$N), 2.48 (t, J = 6.8 Hz, 2 H, C(=O)$CH_2CH_2CH_2$N), 2.00 (quin, J = 6.8 Hz, 2 H, C(=O)$CH_2CH_2CH_2$N), 1.29 - 1.36 (m, 2 H, NCH$(CHH)_2$), 1.11 - 1.17 (m, 2 H, NCH$(CHH)_2$)

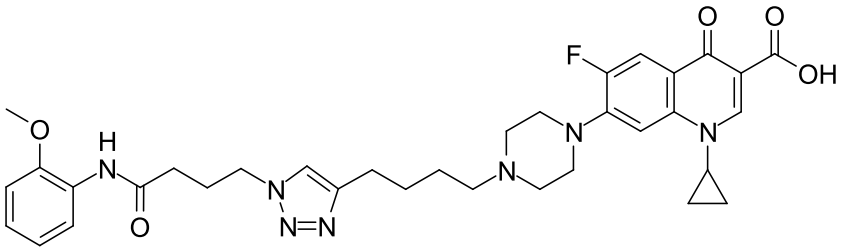
^{13}**C NMR** (101 MHz, $CDCl_3$) δ / ppm = 173.1 (C(=O)CC(=O)OCH_3), 170.9 (NHC(=O)), 166.3 (C(=O)OCH_3), 160.1 (*ipso* to OCH_3), 153.3 (d, J=250.1 Hz, *ipso* to F), 148.4 (C=CC(=O)OCH_3), 144.1 (d, J=10.1 Hz, *ipso* to piperazine), 139.4 (*ipso* to NH), 138.0 (*para* to F), 129.6 (*meta* to NH and *meta* to OCH_3), 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 OCH_3), 110.0 (CC(=O)OCH_3), 109.8 (*para* to NH), 105.5 (*ortho* to OCH_3 and *ortho* to NH), 105.0 (*meta* to C=O and *meta* to F), 57.0 ($CH_2CH_2CH_2$N), 55.3 (aromatic OCH_3), 52.6 ($CH_2CH_2CH_2$N$(CH_2)CH_2$), 52.1 (C(=O)OCH_3), 49.2 ($CH_2CH_2CH_2$N$(CH_2CH_2)CH_2CH_2$), 35.2 ($CH_2CH_2CH_2$N), 34.6 (NCH$(CH_2)_2$), 21.7 ($CH_2CH_2CH_2$N), 8.2 (NCH$(CH_2)_2$)

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

HRMS (ESI$^+$) m/z / Da = 537.2500, $[M+H]^+$ found, $[C_{29}H_{34}FN_4O_5]^+$ requires 537.2513

The compound has not been reported previously.

0.13 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 136



1-Cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **164** (24.1 mg, 58.6 μmol, 1 eq.) and 4-azido-*N*-(2-methoxyphenyl)butanamide **132** (13.7 mg, 58.5 μmol, 1 eq.) were dissolved in water (3 ml), *t*-BuOH (9 ml) and CH_2Cl_2 (9 ml), and the mixture was degassed by bubbling through N_2. A solution of $CuSO_4$ and THPTA (117 μl, 5.85 μmol, 0.1 eq., 50 mM, aq.) was added, followed by a solution of sodium ascorbate (234 μl, 11.7 μmol, 0.2 eq., 50 mM, aq.). The mixture was stirred at room temperature under argon for 16 h. Water (25 ml), CH_2Cl_2 (25 ml) and MeOH (5 ml) were added and the organic layer was separated off, dry-loaded onto SiO_2 and purified by column chromatography using a Combiflash (SiO_2, 3-23 % MeOH/CH_2Cl_2). **136** was obtained as a clear glass (14.7 mg, 22.8 μmol, 39.0 %).

how to phrase this?

how to report??

TLC R_f = 0.28 (10 % MeOH/CH_2Cl_2)

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)

^{1}**H NMR** (400 MHz, $CDCl_3$) 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=CCH_2), 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 OCH_3), 6.88 (dd, J = 8.1, 1.4 Hz, 1 H, *ortho* to OCH_3), 4.47 (t, J = 6.7 Hz, 2 H, C(=O)$CH_2CH_2CH_2$N), 3.88 (s, 3 H, CH_3), 3.54 (tt, J = 6.9, 4.0 Hz, 1 H, NCH(CH_2)$_2$), 3.35 (br t, J = 4.7 Hz, 4 H, CH=$CCH_2CH_2CH_2CH_2$N(CH_2CH_2)CH_2CH_2), 2.76 (t, J = 7.5 Hz, 2 H, CH=CCH_2), 2.66 (t, J = 4.7 Hz, 4 H, CH=$CCH_2CH_2CH_2CH_2$N(CH_2)CH_2), 2.47 (t, J = 7.3 Hz, 2 H, CH=$CCH_2CH_2CH_2CH_2$N), 2.44 (t, J = 6.8 Hz, 2 H, C(=O)$CH_2CH_2CH_2$N), 2.32 (quin, J = 6.7 Hz, 2 H, C(=O)$CH_2CH_2CH_2$N), 1.75 (quin, J = 7.6 Hz, 2 H, CH=$CCH_2CH_2CH_2CH_2$N), 1.61 (quin, J = 7.5 Hz, 2 H, CH=$CCH_2CH_2CH_2CH_2$N), 1.35 - 1.42 (m, 2 H, NCH(CHH)$_2$), 1.17 - 1.22 (m, 2 H, NCH(CHH)$_2$)

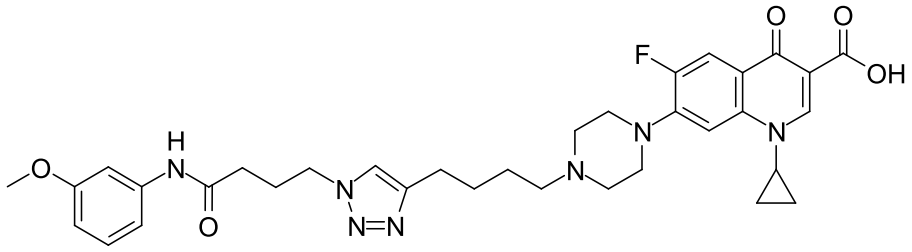
^{13}**C NMR** (101 MHz, $CDCl_3$) δ / ppm = 177.1 (C(=O)CC(=O)OH), 169.5 (NHC(=O)), 167.0 (C(=O)OH), 153.7 (d, J = 251.4 Hz, *ipso* to F), 148.1 (CH=CCH_2), 147.8 (*ipso* to OCH_3), 147.3 (C=CC(=O)OH), 145.9 (d, J = 10.4 Hz, *ipso* to piperazine), 139.1 (*para* to F), 127.3 (*ipso* to NH), 123.9 (*para* to NH), 121.0 (*para* to OCH_3), 120.9 (CH=CCH_2), 119.7 (*para* to piperazine, and *ortho* to NH and *meta* to OCH_3), 112.4 (d, J = 23.4 Hz, *ortho* to C=O and *ortho* to F), 109.9 (*ortho* to OCH_3 and *meta* to NH), 108.1 (CC(=O)OH), 104.7 (*meta* to C=O and *meta* to F), 58.1 (CH=$CCH_2CH_2CH_2CH_2$N), 55.6 (CH_3), 52.8 (CH=$CCH_2CH_2CH_2CH_2$N(CH_2)CH_2), 49.8 (CH=$CCH_2CH_2CH_2CH_2$N(CH_2CH_2)CH_2CH_2), 49.8 (CH=$CCH_2CH_2CH_2CH_2$N(CH_2CH_2)CH_2CH_2), 49.1 (C(=O)$CH_2CH_2CH_2$N), 35.2 (NCH(CH_2)$_2$), 33.8 (C(=O)$CH_2CH_2CH_2$N), 27.3 (CH=$CCH_2CH_2CH_2CH_2$N), 26.4 (CH=$CCH_2CH_2CH_2CH_2$N), 26.0 (C(=O)$CH_2CH_2CH_2$N), 25.5 (CH=C$CH_2CH_2CH_2CH_2$N), 8.2 (NCH(CH_2)$_2$)

^{19}**F NMR** (376.45 MHz, $CDCl_3$) δ / ppm = -120.7 (s, ciprofloxacin F)

HRMS (ESI$^+$) m/z / Da = 646.3132, $[M+H]^+$ found, $[C_{34}H_{41}FN_7O_5]^+$ requires 646.3153

The compound has not been reported previously.

0.14 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 137



1-Cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **164** (24.1 mg, 58.6 μmol, 1 eq.) and 4-azido-*N*-(3-methoxyphenyl)butanamide **133** (13.7 mg, 58.5 μmol, 1 eq.) were dissolved in water (1 ml), *t*-BuOH (9 ml) and CH_2Cl_2 (10 ml), and the mixture was degassed by bubbling through N_2. A solution of $CuSO_4$ 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 resudue was partitioned between water (15 ml) and CH_2Cl_2 (15 ml), and the aqueous layer was extracted a further four times with CH_2Cl_2 (4 $\times$ 15 ml). The combined organic layers were dried with $MgSO_4$, dry-loaded onto SiO_2 and purified by column chromatography (SiO_2, 0-10 % MeOH/CH_2Cl_2). **137** was obtained as a clear glass (1.9 mg, 2.9 μmol, 5.0 %).

TLC R_f = 0.22 (10 % MeOH/CH_2Cl_2)

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)

^{1}**H NMR** (400 MHz, DMSO d_6) δ / ppm = 15.23 (br s, 1 H, C(=O)O<u>H</u>), 9.89 (s, 1 H, N<u>H</u>), 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, C<u>H</u>=CCH$_2$), 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 OCH_3 and *meta* to NH), 7.08 (d, J = 7.8 Hz, 1 H, *para* to OCH_3), 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)CH$_2$CH$_2$C<u>H$_2$</u>N), 3.81 (tt, J = 6.7, 4.0 Hz, 1 H, NC<u>H</u>(CH$_2$)$_2$), 3.70 (s, 3 H, C<u>H$_3$</u>), 3.28 - 3.32 (m, 4 H, CH=CCH$_2$CH$_2$CH$_2$CH$_2$N(CH$_2$C<u>H$_2$</u>)CH$_2$C<u>H$_2$</u>), 2.64 (t, J = 7.5 Hz, 2 H, CH=C<u>C</u>H$_2$), 2.56 (m, J = 4.2, 4.2 Hz, 4 H, CH=CCH$_2$CH$_2$CH$_2$CH$_2$N(C<u>H$_2$</u>)C<u>H$_2$</u>), 2.38 (t, J = 7.3 Hz, 2 H, CH=CCH$_2$CH$_2$CH$_2$C<u>H$_2$</u>N), 2.30 (t, J = 7.4 Hz, 2 H, C(=O)C<u>H$_2$</u>CH$_2$CH$_2$N), 2.10 (quin, J = 7.1 Hz, 2 H, C(=O)CH$_2$C<u>H$_2$</u>CH$_2$N), 1.64 (quin, J = 7.5 Hz, 2 H, CH=CCH$_2$C<u>H$_2$</u>CH$_2$CH$_2$N), 1.51 (quin, J = 7.2 Hz, 2 H, CH=CCH$_2$CH$_2$C<u>H$_2$</u>CH$_2$N), 1.27 - 1.33 (m, 2 H, NCH(C<u>H</u>H)$_2$), 1.15 - 1.20 (m, 2 H, NCH(CH<u>H</u>)$_2$)

^{13}**C NMR** (101 MHz, DMSO d_6) δ / ppm = 176.3 (<u>C</u>(=O)CC(=O)OH), 170.1 (NH<u>C</u>(=O)), 165.9 (<u>C</u>(=O)OH), 159.4 (*ipso* to OCH_3), 153.0 (d, J = 248.6 Hz, *ipso* to F), 148.0 (CH=<u>C</u>CH$_2$), 146.9 (<u>C</u>=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 OCH_3 and *meta* to NH), 121.7 (<u>C</u>H=CCH$_2$), 118.5 (d, J = 7.5 Hz, *para* to piperazine), 111.3 (*para* to OCH_3), 110.9 (d, J = 22.4 Hz, *ortho* to C=O and *ortho* to F), 108.4 (*para* to NH), 106.7 (<u>C</u>C(=O)OH), 106.3 (*meta* to C=O and *meta* to F), 104.8 (*ortho* to OCH_3 and *ortho* to NH), 57.3 (CH=CCH$_2$CH$_2$CH$_2$<u>C</u>H$_2$N), 54.9 (<u>C</u>H$_3$), 52.4 (CH=CCH$_2$CH$_2$CH$_2$CH$_2$N(<u>C</u>H$_2$)<u>C</u>H$_2$), 49.5 (CH=CCH$_2$CH$_2$CH$_2$CH$_2$N(CH$_2$<u>C</u>H$_2$)CH$_2$CH$_2$), 49.4 (CH=CCH$_2$CH$_2$CH$_2$CH$_2$N(CH$_2$CH$_2$)CH$_2$<u>C</u>H$_2$), 48.7 (C(=O)CH$_2$CH$_2$<u>C</u>H$_2$N), 35.8 (N<u>C</u>H(CH$_2$)$_2$), 32.9 (C(=O)<u>C</u>H$_2$CH$_2$CH$_2$N), 26.8 (CH=CCH$_2$<u>C</u>H$_2$CH$_2$CH$_2$N), 25.7 (CH=CCH$_2$CH$_2$<u>C</u>H$_2$CH$_2$N), 25.5 (C(=O)CH$_2$<u>C</u>H$_2$CH$_2$

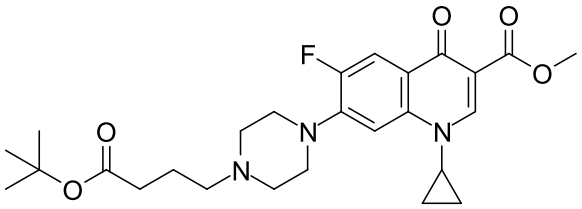
N), 24.9 (CH=C$\underline{C}$H$_2$CH$_2$CH$_2$CH$_2$N), 7.6 (NCH($\underline{C}$H$_2$)$_2$)

^{19}**F NMR** (376.45 MHz, DMSO d$_6$) δ / ppm = -121.5 (s, ciprofloxacin F)

HRMS (ESI$^+$) m/z / Da = 646.3159, [M+H]$^+$ found, [$C_{34}H_{41}FN_7O_5$]$^+$ requires 646.3153

The compound has not been reported previously.

0.15 Methyl 7-(4-(4-(*tert*-butoxy)-4-oxobutyl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate 138



Methyl 1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate **124** (200 mg, 0.579 mmol, 1 eq.), *tert*-butyl 4-bromobutanoate **168** (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 **168** (103 μl, 130 mg, 0.581 mmol, 1 eq.) was added, and the mixture was stirred in a microwave reactor at 100 °C for a further 8 h. The mixture was then dry-loaded onto SiO_2 and purified by column chromatography (SiO_2, 0-4 % MeOH/CH_2Cl_2). **138** was obtained as a white amorphous solid (141 mg, 0.289 mmol, 49.9 %).

how to report?

how to report?

TLC R_f = 0.12 (4 % MeOH/CH_2Cl_2)

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)

^{1}**H NMR** (400 MHz, $CDCl_3$) δ / ppm = 8.39 (s, 1 H, *ortho* to C(=O)OCH$_3$), 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, C$\underline{H}_3$), 3.40 (tt, J = 7.2, 3.6 Hz, 1 H, NC$\underline{H}$(CH$_2$)$_2$), 3.22 (t, J = 4.3 Hz, 4 H, CH$_2$N(CH$_2$C$\underline{H}_2$)CH$_2$C$\underline{H}_2$), 2.63 (t, J = 4.4 Hz, 4 H, CH$_2$N(C$\underline{H}_2$)C$\underline{H}_2$), 2.41 (t, J=7.3 Hz, 2 H, C$\underline{H}_2$N(CH$_2$)CH$_2$), 2.25 (t, J=7.4 Hz, 2 H, C$\underline{H}_2$CH$_2$CH$_2$N(CH$_2$)CH$_2$), 1.78 (quin, J=7.3 Hz, 2 H, C$\underline{H}_2$CH$_2$N(CH$_2$)CH$_2$), 1.41 (s, 9 H, C((C$\underline{H}$)$_3$)$_3$), 1.24 (m, 2 H, NCH(C$\underline{H}$H)$_2$), 1.09 (m, 2 H, NCH(CH$\underline{H}$)$_2$)

should be ranges ideally, go back if time

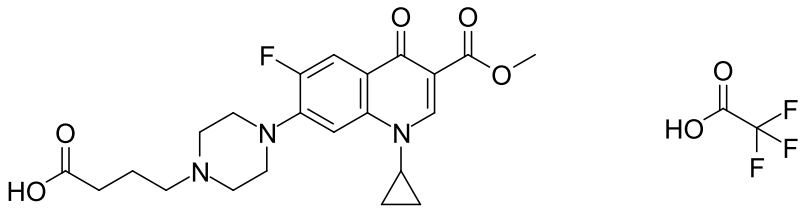
^{13}**C NMR** (101 MHz, $CDCl_3$) δ / ppm = 172.7 ($\underline{C}$(=O)CC(=O)OCH$_3$), 172.6 ($\underline{C}$(=O)OC(CH$_3$)$_3$), 165.9 ($\underline{C}$(=O)OCH$_3$), 153.1 (d, J = 249.7 Hz, *ipso* to F), 148.1 ($\underline{C}$=CC(=O)OCH$_3$), 144.3 (d, J = 10.4 Hz, *ipso* to piperazine), 137.7 (*para* 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 ($\underline{C}$C(=O)OCH$_3$) 104.7 (*meta* to C=O and *meta* to F), 80.0 ($\underline{C}$(CH$_3$)$_3$), 57.4 (C(=O)CH$_2$CH$_2$$\underline{C}H_2$N), 52.7 (C(=O)CH$_2CH_2CH_2$N($\underline{C}H_2$)$\underline{C}H_2$), 51.7 ($\underline{C}H_3$), 49.7 (C(=O)CH$_2CH_2CH_2$N(CH$_2$$\underline{C}H_2$)CH$_2CH_2$), 49.7 (C(=O)CH$_2CH_2CH_2$N(CH$_2CH_2$)CH$_2$$\underline{C}H_2$), 34.4 (N$\underline{C}$H(CH$_2$)$_2$), 33.2 (C(=O)$\underline{C}H_2$), 28.0 (C($\underline{C}H_3$)$_3$), 22.0 (C(=O)CH$_2$$\underline{C}H_2$), 7.9 (NCH($\underline{C}H_2$)$_2$)

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

HRMS (ESI$^+$) m/z / Da = 488.2562, $[M+H]^+$ found, $[C_{26}H_{35}FN_3O_5]^+$ requires 488.2561

The compound has not been reported previously.

0.16 4-(4-(1-Cyclopropyl-6-fluoro-3-(methoxycarbonyl)-4-oxo-1,4-dihydroquinolin-7-yl)piperazin-1-yl)butanoic acid, trifluoroacetic acid salt 139



Methyl 7-(4-(4-(*tert*-butoxy)-4-oxobutyl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate **169** (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. **139** was obtained as a white solid (21.4 mg, 39.2 μmol, 95.6 %).

not sure how to draw/nam this?

mp T / °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)

^{1}**H NMR** (400 MHz, DMSO d_6) δ / ppm = 8.47 (s, 1 H, *ortho* to C(=O)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, C$\underline{H}_3$), 3.66 (tt, J = 7.2, 3.7 Hz, 1 H, NC$\underline{H}(CH_2)_2$), 3.30 - 3.54 (br s, 8 H, $CH_2N(C\underline{H}_2)C\underline{H}_2$ and $CH_2N(CH_2C\underline{H}_2)CH_2C\underline{H}_2$) 3.13 - 3.22 (m, 2 H, C$\underline{H}_2N(CH_2)CH_2$), 2.36 (t, J = 7.1 Hz, 2 H, C$\underline{H}_2CH_2CH_2N(CH_2)CH_2$), 1.87 - 1.98 (m, 2 H, C$\underline{H}_2CH_2N(CH_2)CH_2$), 1.22 - 1.30 (m, 2 H, NCH(C$\underline{H}$H)$_2$), 1.06 - 1.15 (m, 2 H, NCH(CH$\underline{H}$)$_2$)

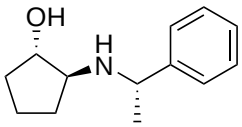
^{13}**C NMR** (101 MHz, DMSO d_6) δ / ppm = 173.5 ($CH_2\underline{C}$(=O)OH), 171.6 ($\underline{C}$(=O)CC(=O)OCH_3), 164.9 ($\underline{C}$(=O)OCH_3), 158.2 (q, J = 31.5 Hz, $CF_3\underline{C}$(=O)OH), 152.5 (d, J = 247.6 Hz, *ipso* to F), 148.5 ($\underline{C}$=CC(=O)OH), 142.3 (d, J = 10.7 Hz, *ipso* to piperazine), 138.0 (*para* to F), 122.6 (d, J = 6.4 Hz, *para* to piperazine), 117.2 (q, J = 299.8 Hz, $\underline{C}F_3$), 111.9 (d, J = 22.4 Hz, *ortho* to C=O and *ortho* to F), 109.1 ($\underline{C}C$(=O)OCH_3), 106.9 (*meta* to C=O and *meta* to F), 55.1 (C(=O)$CH_2CH_2\underline{C}H_2N$), 51.4 ($\underline{C}H_3$), 50.8 (C(=O)$CH_2CH_2CH_2N(\underline{C}H_2)\underline{C}H_2$), 46.7 (C(=O)$CH_2CH_2CH_2N(CH_2\underline{C}H_2)CH_2CH_2$), 46.7 (C(=O)$CH_2CH_2CH_2N(CH_2CH_2)CH_2\underline{C}H_2$), 34.9 (N$\underline{C}H(CH_2)_2$), 30.6 (C(=O)$\underline{C}H_2$), 19.1 (C(=O)$CH_2\underline{C}H_2$), 7.6 (NCH($\underline{C}H_2)_2$)

^{19}**F NMR** (376.45 MHz, DMSO d_6) δ / ppm = -73.6 (s, C$\underline{F}_3$), -124.6 (s, ciprofloxacin $\underline{F}$)

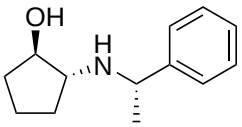
HRMS (ESI$^+$) m/z / Da = 432.1921, $[M+H]^+$ found, $[C_{22}H_{27}FN_3O_5]^+$ requires 432.1935

The compound has not been reported previously.

0.17 (1*S*,2*S*)-2-(((*S*)-1-Phenylethyl)amino)cyclopentan-1-ol 140 and (1*R*,2*R*)-2-(((*S*)-1-phenylethyl)amino)cyclopentan-1-ol 141



147



148

(*S*)-1-phenylethan-1-amine **170** (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 solution was stirred at 0 °C for 1 h. A solution of cyclohexene oxide **171** (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). **140** was obtained as a pale yellow oil (4.08 g, 19.9 mmol, 32.6 %). **141** was obtained as pale yellow crystals (4.48 g, 21.8 mmol, 35.8 %).

fix image sizes

(1*S*,2*S*)-2-(((*S*)-1-Phenylethyl)amino)cyclopentan-1-ol 140

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

fix spacings for subtitles

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

^{1}H 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, C<u>H</u>CH_3), 3.78 (q, J = 7.0 Hz, 1 H, C<u>H</u>OH), 2.62 (dt, J = 8.2, 7.2 Hz, 1 H, C<u>H</u>NH), 1.97 (quin, J = 6.7 Hz, 1 H, C<u>H</u>$_2$CHNH), 1.90 (quin, J = 6.9 Hz, 1 H, C<u>H</u>$_2$CHOH), 1.56 - 1.68 (m, C<u>H</u>$_2$CH$_2$CHOH), 1.43 (dq, J = 12.5, 8.0 Hz, 1 H, C<u>H</u>$_2$CHOH), 1.37 (d, J = 6.6 Hz, 3 H, C<u>H</u>$_3$), 1.25 - 1.36 (m, 1 H, C<u>H</u>$_2$CHNH)

^{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 (<u>C</u>HOH), 63.38 (<u>C</u>HNH), 56.20 (<u>C</u>HCH_3), 31.74 (<u>C</u>H_2CHOH), 29.22 (<u>C</u>H_2CHNH), 24.58 (<u>C</u>H_3), 19.57 (<u>C</u>H_2CH_2CHOH)

HRMS (ESI^+) m/z / Da = 206.1554, $[M+H]^+$ found, $[C_{13}H_{20}NO]^+$ requires 206.1545 $[\alpha]_D^{20}$ / $°10^{-1}cm^2g^{-1}$ = -92.8 (c / g(100 ml)$^{-1}$ = 1.19, MeOH)

(1*R*,2*R*)-2-(((*S*)-1-Phenylethyl)amino)cyclopentan-1-ol 141

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)

^{1}H 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, C<u>H</u>CH_3), 3.85 (q, J = 6.6 Hz, 1 H, C<u>H</u>OH), 2.83 (td, J = 7.6, 5.7 Hz, 1 H, C<u>H</u>NH), 1.85 - 1.97 (m, 1 H, C<u>H</u>HCHOH), 1.77 (dtd, J = 12.9, 7.9, 7.9, 4.9 Hz, 1 H, C<u>H</u>HCHNH), 1.55 - 1.68 (m, 2 H, C<u>H</u>$_2$$CH_2$CHOH), 1.47 - 1.55 (m, 1 H, CH<u>H</u>CHOH), 1.36 (d, J = 6.6 Hz, 3 H, C<u>H</u>$_3$), 1.12 (dq, J = 12.7, 8.1 Hz, 1 H, CH<u>H</u>CHNH)

^{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 (<u>C</u>HOH), 64.45 (<u>C</u>HNH), 56.62 (<u>C</u>HCH_3), 32.01 (<u>C</u>H_2CHOH), 30.56 (<u>C</u>H_2CHNH), 23.30 (<u>C</u>H_3), 20.06 (<u>C</u>$H_2$$CH_2$CHOH)

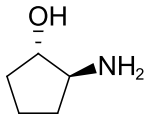
HRMS (ESI$^+$) m/z / Da = 206.1553, $[M+H]^+$ found, $[C_{13}H_{20}NO]^+$ requires 206.1545

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

The compounds have been synthesised previously,[?,?,?] but NMR data were not published.

consistenc with other data?

0.18 (1*S*,2*S*)-2-Aminocyclopentan-1-ol 142



(1*S*,2*S*)-2-(((*S*)-1-Phenylethyl)amino)cyclopentan-1-ol **140** (3.90 g, 19.0 mmol, 1 eq.), $Pd(OH)_2$ (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. **142** 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)

^{1}H NMR (400 MHz, MeOD) δ / ppm = 3.77 (ddd, J=6.6, 6.2, 5.6, 1 H, C<u>H</u>OH), 3.00 (td, J=7.3, 5.6 Hz, 1 H, C<u>H</u>NH_2), 2.00 (dtd, J=13.0, 7.7, 7.7, 5.6 Hz, 1 H, C<u>H</u>HCHNH_2), 1.97 (ddt, J=13.0, 8.7, 6.6, 6.6 Hz, 1 H, C<u>H</u>HCHOH), 1.63 - 1.77 (m, 2 H, C<u>H</u>$_2$$CH_2$CHOH), 1.53 (ddt, J=13.0, 9.5, 6.2, 6.2 Hz, 1 H, CH<u>H</u>CHOH), 1.37 (ddt, J=13.0, 8.3, 7.8, 7.8 Hz, 1 H, CH<u>H</u>CHNH_2)

^{13}C NMR (101 MHz, MeOD) δ / ppm = 80.7 (<u>C</u>HOH), 60.8 (<u>C</u>HNH_2), 33.2 (<u>C</u>H_2CHOH), 32.1 (<u>C</u>H_2CHNH_2), 21.2 (<u>C</u>$H_2$$CH_2$CHOH)

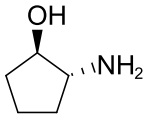
HRMS (ESI$^+$) m/z / Da = 102.0917, $[M+H]^+$ found, $[C_5H_{12}NO]^+$ requires 102.0913

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

The data are consistent with the literature.[?,?]

check

0.19 (1*R*,2*R*)-2-Aminocyclopentan-1-ol 143



(1*R*,2*R*)-2-(((*S*)-1-Phenylethyl)amino)cyclopentan-1-ol **141** (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. **143** 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)

^{1}H NMR (400 MHz, MeOD) δ / ppm = 3.77 (ddd, J=6.6, 6.2, 5.6, 1 H, C<u>H</u>OH), 3.00 (td, J = 7.4, 5.6 Hz, 1 H, C<u>H</u>NH_2), 2.00 (dtd, J = 13.0, 7.7, 7.7, 5.6 Hz, 1 H, C<u>H</u>HCHNH_2), 1.97 (ddt, J = 13.0, 8.7, 6.4, 6.4 Hz, 1 H, C<u>H</u>HCHOH), 1.64 - 1.77 (m, 2 H, C<u>H$_2$</u>CH_2CHOH), 1.53 (ddt, J = 13.0, 9.5, 6.2, 6.2 Hz, 1 H, CH<u>H</u>CHOH), 1.37 (ddt, J = 12.8, 8.5, 7.7, 7.7 Hz, 1 H, CH<u>H</u>CHNH_2)

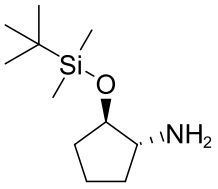
^{13}C NMR (101 MHz, MeOD) δ / ppm = 80.6 (<u>C</u>HOH), 60.7 (<u>C</u>HNH_2), 33.2 (<u>C</u>H_2CHOH), 32.2 (<u>C</u>H_2CHNH_2), 21.2 (<u>C</u>$H_2$$CH_2$CHOH)

HRMS (ESI^+) m/z / Da = 102.0915, $[M+H]^+$ found, $[C_5H_{12}NO]^+$ requires 102.0913

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

The data are consistent with the literature.[?,?]

0.20 (1*R*,2*R*)-2-((*tert*-butyldimethylsilyl)oxy)cyclopentan-1-amine 144



(1*R*,2*R*)-2-aminocyclopentan-1-ol **143** (0.480 g, 4.75 mmol) was stirred in dry CH_2Cl_2 (20 ml) under N_2 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 NH_4Cl, diluted with CH_2Cl_2 (20 ml) and washed with water (20 ml). The organic phase was dried with Na_2SO_4, concentrated under reduced pressure and purified by column chromatography (SiO_2, 4 % $MeOH/CH_2Cl_2$). **172**(RR) was obtained as a yellow oil (1.00 g, 4.64 mmol, 97.7 %).

TLC R_f = 0.23 (10 % $MeOH/CH_2Cl_2$, ninhydrin stain)

check stains for others

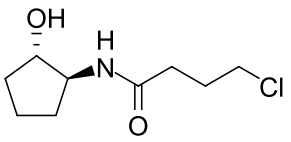
^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 4.13 (q, J = 5.8 Hz, 1 H, C$\underline{H}$OSi), 3.31 (td, J = 7.1, 5.2 Hz, 1 H, C$\underline{H}NH_2$), 2.09 - 2.19 (m, 1 H, C$\underline{H}$HCHNH$_2$), 1.97 (ddq, J = 8.8, 7.0, 6.0, 6.0, 6.0 Hz, 1 H, C$\underline{H}$HCHOSi), 1.74 - 1.86 (m, 2 H, C$\underline{H}_2$CH$_2$CHOSi), 1.64 - 1.74 (m, 1 H, CH$\underline{H}$CHOSi), 1.58 (ddt, J = 13.2, 9.1, 6.0, 6.0 Hz, 1 H, CH$\underline{H}$CHNH$_2$), 0.88 (s, 9 H, C(C$\underline{H}_3$)$_3$), 0.09 (s, 3 H, SiC$\underline{H}_3$), 0.07 (s, 3 H, SiC$\underline{H}_3$)

^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 76.3 (C$\underline{H}$OSi), 59.7 (C$\underline{H}$NH), 32.2 (C$\underline{H}_2$CHOSi), 26.8 (C$\underline{H}_2$CHNH$_2$), 25.6 (C(C$\underline{H}_3$)$_3$), 19.7 (C$\underline{H}_2$CH$_2$CHOSi), 17.7 (C(CH$_3$)$_3$), -4.8 (SiCH$_3$), -5.2 (SiCH$_3$)

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

$[\boldsymbol{\alpha}]_D^{20}$ / °10^{-1}cm^{2}g^{-1} = ?? (c / g(100 ml)$^{-1}$ = ? , MeOH)

0.21 4-Chloro-*N*-((1*S*,2*S*)-2-hydroxycyclopentyl)butanamide 145



(1*S*,2*S*)-2-aminocyclopentan-1-ol **142** (500 mg, 4.94 mmol, 1 eq.), TEA (827 μl, 600 mg, 5.93 mmol, 1.2 eq.) and CH_2Cl_2 (20 ml) were stirred at 0°C. 4-Chlorobutyryl chloride **173**(608 μl, 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 CH_2Cl_2 (7×50 ml). The combined organic layers were dried with $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (SiO_2, Et_2O). **174**(SS) was obtained as a white amorphous solid (651 mg, 3.16 mmol, 64.1 %).

TLC R_f = 0.35 (EtOAc, ninhydrin stain)

check stains for others

mp T / °C = ?? (??)

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)

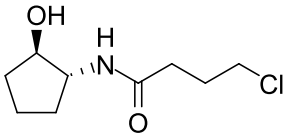
^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 6.12 (br s, 1 H, N$\underline{H}$), 4.42 (br s, 1 H, O$\underline{H}$), 3.94 (q, J = 6.6 Hz, 1 H, C$\underline{H}$OH), 3.82 (tt, J = 8.4, 5.3 Hz, 1 H, C$\underline{H}$NH), 3.60 (t, J = 6.2 Hz, 2 H, C$\underline{H}_2$Cl), 2.38 (t, J = 7.2 Hz, 2 H, C$\underline{H}_2$C=O), 2.05 - 2.16 (m, 3 H, C$\underline{H}$HCHNH and C$\underline{H}_2$CH$_2$Cl), 1.96 - 2.04 (m, 1 H, C$\underline{H}$HCHOH), 1.74 - 1.85 (m, 1 H, C$\underline{H}$HCH$_2$CHOH), 1.58 - 1.73 (m, 2 H, CH$\underline{H}$CH$_2$CHOH and CH$\underline{H}$CHOH), 1.43 (dq, J = 12.7, 8.3 Hz, 1 H, CH$\underline{H}$CHNH)

^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 173.8 (C$\underline{=}$O), 79.4 (C$\underline{H}$OH), 60.6 (C$\underline{H}$NH), 44.4 (C$\underline{H}_2$Cl), 32.8 (C$\underline{H}_2$C=O), 32.4 (C$\underline{H}_2$CHOH), 30.1 (C$\underline{H}_2$CHNH), 28.0 (C$\underline{H}_2$CH$_2$Cl), 21.1 (C$\underline{H}_2$CH$_2$CHOH)

HRMS (ESI$^+$) m/z / Da = 228.0787, [M+Na]$^+$ found, [$C_9H_{16}ClNNaO_2$]$^+$ requires 228.0762

$[\boldsymbol{\alpha}]_D^{20}$ / °10^{-1}cm^{2}g^{-1} = -13.0 (c / g(100 ml)$^{-1}$ = 0.5, MeOH)

0.22 4-Chloro-*N*-((1*R*,2*R*)-2-hydroxycyclopentyl)butanamide 146



(1*R*,2*R*)-2-aminocyclopentan-1-ol **143** (72.3 mg, 716 μmol, 1 eq.), TEA (500 μl, 363 mg, 3.58 mmol, 5 eq.) and CH_2Cl_2 (5 ml) were stirred at 0°C. 4-Chlorobutyryl chloride **173**(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/$CHCl_3$ (2 × 10 ml). The combined organic layers were dried with $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (SiO_2, Et_2O). **146** was obtained as a white amorphous solid (35.6 mg, 173 μmol, 24.2 %).

times with spaces?

TLC R_f = 0.35 (EtOAc)

mp T / °C = ?? (??)

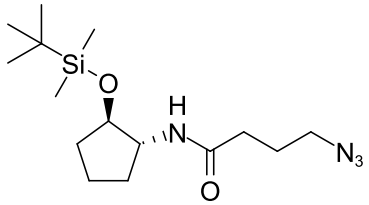
^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 6.05 (br s, 1 H, NH), 4.55 (br s, 1 H, OH), 3.95 (q, J=6.6 Hz, 1 H, CHOH), 3.82 (tt, J=8.4, 5.3 Hz, 1 H, CHNH), 3.60 (t, J=6.2 Hz, 2 H, CH_2Cl), 2.38 (t, J=7.0 Hz, 2 H, CH_2C=O), 2.05 - 2.17 (m, 3 H, CHHCHNH and CH_2CH_2Cl), 1.94 - 2.05 (m, 1 H, CHHCHOH), 1.74 - 1.86 (m, 1 H, CHHCH$_2$CHOH), 1.58 - 1.74 (m, 2 H, CHHCH$_2$CHOH and CHHCHOH), 1.42 (dq, J=12.5, 8.4 Hz, 1 H, CHHCHNH)

^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 173.8 (C=O), 79.4 (CHOH), 60.6 (CHNH), 44.4 (CH_2Cl), 32.8 (CH_2C=O), 32.4 (CH_2CHOH), 30.2 (CH_2CHNH), 28.0 (CH_2CH_2Cl), 21.2 (CH_2CH_2CHOH)

HRMS (ESI$^+$) m/z / Da = 206.0939, $[M+H]^+$ found, $[C_9H_{17}ClNO_2]^+$ requires 206.0948

$[\alpha]_D^{20}$ / °10^{-1}cm^{2}g^{-1} = 10.0 (c / g(100 ml)$^{-1}$ = 0.05, MeOH)

0.23 4-Azido-*N*-((1*R*,2*R*)-2-((*tert*-butyldimethylsilyl)oxy)cyclopentyl)butanamide 147



(1*R*,2*R*)-2-((*tert*-butyldimethylsilyl)oxy)cyclopentan-1-amine **144** (50 mg, 0.232 mmol, 1 eq.) and $NaHCO_3$ (22.0 mg, 0.262 mmol, 1.1 eq.) were added to CH_2Cl_2 (3 ml) and water (3 ml). 4-Bromobutyryl chloride (25.3 ml, 40.5 mg, 0.219 mmol, 0.95 eq.) was added dropwise at 0 °C and the mixture was stirred for 3 h. The aqueous layer was removed and NaN_3 (100 mg, 1.54 mmol, 6.6 eq.) and DMF (3 ml) were added. The mixture was stirred

check brackets inside for all

at 40 °C for 6 h. The solvents were then evaporated using a N_2 stream and the residue was purified by column chromatography (SiO_2, 0.5 % MeOH/CH_2Cl_2). **175**(RR) was obtained as a clear liquid (71 mg, 0.217 mmol, 99.2 %).

TLC R_f = 0.84 (1 % MeOH/CH_2Cl_2)

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)

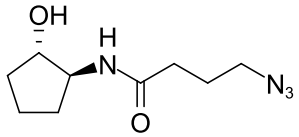
^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 5.35 (d, J = 5.1 Hz, 1 H, NH), 3.97 - 4.01 (m, 1 H, CHOSi), 3.93 - 3.98 (m, 1 H, CHNH), 3.35 (t, J = 6.6 Hz, 2 H, CH_2N_3), 2.24 (t, J = 7.0 Hz, 2 H, CH_2C=O), 2.09 - 2.19 (m, 1 H, CHHCHNH), 1.89 - 1.97 (quin, J = 6.8 Hz, 2 H, $CH_2CH_2N_3$), 1.74 - 1.84 (m, 2 H, CHHCHOSi and CHHCH$_2$CHOSi), 1.60 - 1.70 (m, 1 H, CHHCH$_2$CHOSi), 1.51 - 1.61 (m, 1 H, CHHCHOSi), 1.31 - 1.39 (m, 1 H, CHHCHNH), 0.87 (s, 9 H, C(CH_3)$_3$), 0.08 (s, 3 H, SiCH_3), 0.06 (s, 3 H, SiCH_3)

^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 171.17 (C=O), 77.80 (CHOSi), 58.36 (CHNH), 50.77 (CH_2N_3), 33.29 (CH_2C=O), 32.57 (CH_2CHOSi), 29.36 (CH_2CHNH), 25.72 (C(CH_3)$_3$), 24.77 ($CH_2CH_2N_3$), 20.40 (CH_2CH_2CHOSi), 17.95 (C(CH_3)$_3$), -4.75 (SiCH_3)

HRMS (ESI^+) m/z / Da = 327.2221, $[M+H]^+$ found, $[C_{15}H_{31}N_4O_2Si]^+$ requires 327.2216

$[\alpha]_D^{20}$ / $°10^{-1}cm^2g^{-1}$ = 12.4 (c / g(100 ml)$^{-1}$ = 0.5, MeOH)

0.24 4-Azido-*N*-((1*S*,2*S*)-2-hydroxycyclopentyl)butanamide 148



4-Chloro-*N*-((1*S*,2*S*)-2-hydroxycyclopentyl)butanamide **145** (200 mg, 0.972 mmol, 1 eq.) and NaN_3 (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/$CHCl_3$ (20 ml). The aqueous layer was extracted again with 10 % *i*-PrOH/$CHCl_3$ (3 × 20 ml) and the combined organic fractions were dried with $MgSO_4$ and evaporated under reduced pressure. **148** was obtained as white needles (181 mg, 0.852 mmol, 87.6 %).

TLC R_f = 0.35 (EtOAc, ninhydrin stain)

check stains for others

mp T / °C = 56-59.5 (*i*-PrOH, $CHCl_3$)

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)

^{1}H 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

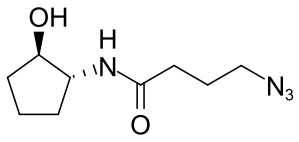
Hz, 1 H, C<u>H</u>OH), 3.75 (tdd, J = 8.4, 8.4, 6.6, 4.4 Hz, 1 H, C<u>H</u>NH), 3.28 (t, J = 6.6 Hz, 2 H, C<u>H</u>$_2$N$_3$), 2.23 (t, J = 7.3 Hz, 2 H, C<u>H</u>$_2$C=O), 2.04 (dtd, J = 13.0, 8.0, 8.0, 4.9 Hz, 1 H, C<u>H</u>HCHNH), 1.92 (dtd, J = 13.0, 7.6, 7.6, 5.8 Hz, 1 H, C<u>H</u>HCHOH), 1.84 (quin, J = 7.0 Hz, 2 H, C<u>H</u>$_2$CH$_2$N$_3$), 1.59 - 1.77 (m, 2 H, C<u>H</u>$_2$CH$_2$CHOH), 1.54 (ddt, J = 12.7, 9.0, 6.7, 6.7 Hz, 1 H, CH<u>H</u>CHOH), 1.39 (dq, J = 12.9, 8.4 Hz, 1 H, CH<u>H</u>CHNH)

^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 173.8 (<u>C</u>=O), 78.8 (<u>C</u>HOH), 59.9 (<u>C</u>HNH), 50.5 (<u>C</u>H$_2$N$_3$), 32.5 (<u>C</u>H$_2$C=O), 32.0 (<u>C</u>H$_2$CHOH), 29.5 (<u>C</u>H$_2$CHNH), 24.6 (<u>C</u>H$_2$CH$_2$N$_3$), 20.7 (<u>C</u>H$_2$CH$_2$CHOH)

HRMS (ESI$^+$) m/z / Da = 235.1174, $[M+Na]^+$ found, $[C_9H_{16}N_4NaO_2]^+$ requires 235.1171

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

0.25 4-Azido-*N*-((1*R*,2*R*)-2-hydroxycyclopentyl)butanamide 149



4-Chloro-*N*-((1*S*,2*S*)-2-hydroxycyclopentyl)butanamide **145** (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 °C for 24 h. The reaction mixtures 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 × 5 ml) and the combined organic fractions were dried with $MgSO_4$ and evaporated under reduced pressure. **148** was obtained as a white solid (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)

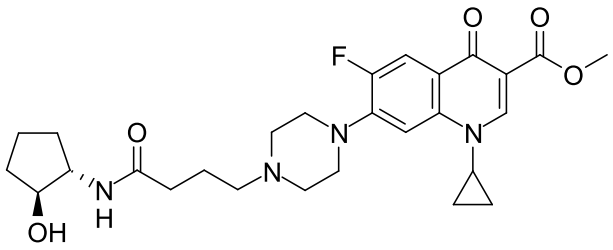
^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 5.82 (br s, 1 H, N<u>H</u>), 4.45 (br. s., 1 H, O<u>H</u>), 3.96 (q, J=6.6 Hz, 1 H, C<u>H</u>OH), 3.83 (tdd, J=8.5, 8.5, 6.0, 4.6 Hz, 1 H, C<u>H</u>NH), 3.37 (t, J=6.4 Hz, 2 H, C<u>H</u>$_2$N$_3$), 2.31 (t, J=7.2 Hz, 2 H, C<u>H</u>$_2$C=O), 2.09 - 2.19 (m, 1 H,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

^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 173.8 (<u>C</u>=O), 79.7 (<u>C</u>HOH), 61.0 (<u>C</u>HNH), 50.7 (<u>C</u>H$_2$N$_3$), 32.8 (<u>C</u>H$_2$C=O), 32.6 (<u>C</u>H$_2$CHOH), 30.5 (<u>C</u>H$_2$CHNH), 24.7 (<u>C</u>H$_2$CH$_2$N$_3$), 21.3 (<u>C</u>H$_2$CH$_2$CHOH)

HRMS (ESI$^+$) m/z / Da = 235.1178, $[M+Na]^+$ found, $[C_9H_{16}N_4NaO_2]^+$ requires 235.1171

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

0.26 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 150



139 (200 mg, 0.367 mmol, 1 eq.), **142** (80 mg, 0.791 mmol, 2.1 eq.), 1-ethyl-3-(3-dimethylaminopropyl)carbodiim ide hydrochloride (112 mg, 0.584 mmol, 1.6 eq.), 1-hydroxybenzotriazole (96 mg, 0.710 mmol, 1.9 eq.) and DIPEA (192 μl, 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 N_2 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 $NaHCO_3$ (aq., sat., 10 ml) and CH_2Cl_2 (10 ml). The organic layer was removed and the aqueous layer was extracted twice more with CH_2Cl_2 (2 × 10 ml). The combined organic fractions were dried with $MgSO_4$ and evaporated under reduced pressure. **150** 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)

^{1}H NMR (400 MHz, DMSO d_6) δ / ppm = 8.44 (s, 1 H, *ortho* to C(=O)OC$\underline{H}_3$), 7.75 (d, J = 13.5 Hz, 1 H, *ortho* to F), 7.70 (d, J = 7.2 Hz, 1 H, CHN$\underline{H}$), 7.43 (d, J = 7.5 Hz, 1 H, *meta* to F), 4.74 (d, J = 4.0 Hz, 1 H, CHO$\underline{H}$), 3.78 - 3.82 (m, 1 H, C$\underline{H}$OH), 3.74 - 3.78 (m, 1 H, C$\underline{H}$NH), 3.74 (s, 3 H, C$\underline{H}_3$), 3.65 (tt, J = 7.2, 3.9 Hz, 1 H, NC$\underline{H}$(CH_2)$_2$), 3.25 (t, J = 4.8 Hz, 4 H, CH_2N(CH_2C$\underline{H}_2$)CH_2C$\underline{H}_2$), 2.57 (br s, 4 H, CH_2N(C$\underline{H}_2$)C$\underline{H}_2$), 2.34 (t, J = 7.4 Hz, 2 H, C$\underline{H}_2$N(CH_2)CH_2), 2.11 (t, J = 7.4 Hz, 2 H, C$\underline{H}_2$$CH_2$$CH_2$N($CH_2$)$CH_2$), 1.92 (dddd, J = 13.0, 8.7, 7.3, 6.0 Hz, 1 H, C$\underline{H}$HCHNH), 1.78 (dddd, J = 12.6, 8.9, 6.3, 6.3 Hz, 1 H, C$\underline{H}$HCHOH), 1.69 (quin, J = 7.3 Hz, 2 H, C$\underline{H}_2$$CH_2$N($CH_2$)$CH_2$), 1.54 - 1.65 (m, 2 H, C$\underline{H}_2$$CH_2$CHOH), 1.42 (ddt, J = 13.1, 8.2, 5.3, 5.3 Hz, 1 H, CH$\underline{H}$CHOH), 1.32 (dddd, J = 13.4, 8.5, 6.8, 5.8 Hz, 1 H, CH$\underline{H}$CHNH), 1.21 - 1.29 (m, 2 H, NCH(C$\underline{H}$H)$_2$), 1.07 - 1.13 (m, 2 H, NCH(CH$\underline{H}$)$_2$)

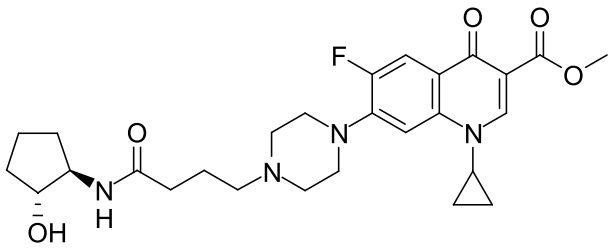
^{13}C NMR (101 MHz, DMSO d_6) δ / ppm = 171.9 ($CH_2$$\underline{C}$(=O)NH), 171.6 ($\underline{C}$(=O)CC(=O)$OCH_3$), 165.0 ($\underline{C}$(=O)$OCH_3$), 152.6 (d, J = 246.5 Hz, *ipso* to F), 148.3 ($\underline{C}$=CC(=O)OCH_3), 143.9 (d, J = 10.7 Hz, *ipso* to piperazine), 138.1 (*para* to F), 121.8 (d, J = 6.4 Hz, *para* to piperazine), 111.5 (d, J = 22.4 Hz, *ortho* to C=O and *ortho* to F), 109.0 ($\underline{C}$C(=O)OCH_3), 106.2 (*meta* to C=O and *meta* to F), 76.3 ($\underline{C}$HOH), 57.6 ($\underline{C}$HNH), 57.2 ($CH_2CH_2\underline{C}H_2$N), 52.4 ($CH_2CH_2CH_2$N($\underline{C}H_2$)$\underline{C}H_2$), 51.3 ($\underline{C}H_3$), 49.6 ($CH_2CH_2CH_2$N($CH_2\underline{C}H_2$)$CH_2\underline{C}H_2$), 34.8 (N$\underline{C}$H(CH_2)$_2$), 33.3 (C(=O)$\underline{C}H_2$), 32.2 ($\underline{C}H_2$CHOH), 29.5 ($\underline{C}H_2$CHNH), 22.5 (C(=O)$CH_2\underline{C}H_2$), 20.6 ($\underline{C}H_2CH_2$CHOH), 7.6 (NCH($\underline{C}H_2$)$_2$)

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

HRMS (ESI$^+$) m/z / Da = 515.2661, $[M+H]^+$ found, $[C_{27}H_{36}FN_4O_5]^+$ requires 515.2670

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

0.27 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 151



139 (52.1 mg, 95.5 μmol, 1 eq.), **143** (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 partitionedbetween $NaHCO_3$ (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 × 5 ml). The combined organic fractions were dried with $MgSO_4$ and evaporated under reduced pressure. **150** was obtained as a white amorphous solid (4.9 mg, 9.5 μmol, 9.9 %).

not done yet?

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)

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

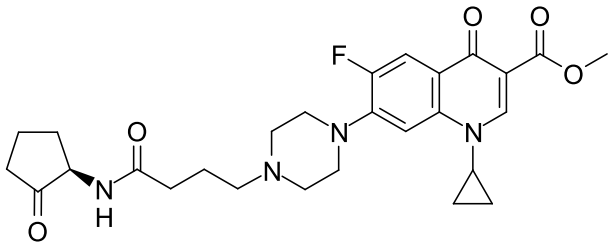
^{13}**C NMR** (126 MHz, DMSO d_6) δ / ppm = 171.9 (NH<u>C</u>(=O)CH$_2$), 171.5 (<u>C</u>(=O)CC(=O)OCH$_3$), 165.0 (<u>C</u>(=O)OCH$_3$), 152.6 (d, J=247.4 Hz, *ipso* to F), 148.2 (<u>C</u>=CC(=O)OCH$_3$), 143.9 (d, J=10.3 Hz, *ipso* to piperazine), 138.1 (*para* to F), 121.7 (d, J=6.4 Hz, *para* to piperazine), 111.5 (d, J=23.0 Hz, *ortho* to C=O and *ortho* to F), 109.0 (<u>C</u>C(=O)OCH$_3$), 106.2 (*meta* to C=O and *meta* to F), 76.2 (<u>C</u>HOH), 57.6 (<u>C</u>HNH), 57.2 (CH$_2$CH$_2$<u>C</u>H$_2$N), 52.4 (CH$_2$CH$_2$CH$_2$N(<u>C</u>H$_2$)<u>C</u>H$_2$), 51.3 (<u>C</u>H$_3$), 49.6 (CH$_2$CH$_2$CH$_2$N(CH$_2$<u>C</u>H$_2$)CH$_2$CH$_2$), 49.6 (CH$_2$CH$_2$CH$_2$N(CH$_2$CH$_2$)CH$_2$<u>C</u>H$_2$), 34.7 (N<u>C</u>H(CH$_2$)$_2$), 33.2 (C(=O)<u>C</u>H$_2$), 32.2 (<u>C</u>H$_2$CHOH), 29.5 (<u>C</u>H$_2$CH NH), 22.5 (C(=O)CH$_2$<u>C</u>H$_2$), 20.6 (<u>C</u>H$_2$CH$_2$CHOH), 7.5 (NCH(<u>C</u>H$_2$)$_2$)

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

HRMS (ESI$^+$) m/z / Da = 515.2667, $[M+H]^+$ found, $[C_{27}H_{36}FN_4O_5]^+$ requires 515.2670

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

0.28 Methyl (*R*)-1-cyclopropyl-6-fluoro-4-oxo-7-(4-(4-oxo-4-((2-oxocyclopentyl)amino)butyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate 152



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 **151** (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. **152** was obtained as a white amorphous solid (11.3 mg, 22.0 μmol, 56.7 %).

^{1}**H NMR** (500 MHz, DMSO d_6) δ / ppm = 8.46 (s, 1 H, *ortho* to C(=O)OC$\underline{H}_3$), 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, C$\underline{H}$NH), 3.73 (s, 3 H, C$\underline{H}_3$), 3.65 (tt, J=6.9, 3.9 Hz, 1 H, NC$\underline{H}(CH_2)_2$), 3.40 (s, 10 H, $CH_2CH_2C\underline{H}_2N(C\underline{H}_2C\underline{H}_2)C\underline{H}_2C\underline{H}_2$), 2.05 - 2.29 (m, 5 H, NHC(=O)C$\underline{H}_2$, C$\underline{H}_2$C(=O)CHNH and C$\underline{H}$HCHNH), 1.89 - 1.96 (m, 1 H, C$\underline{H}$HCH$_2$CHNH), 1.69 - 1.80 (m, 3 H, CH$\underline{H}$CH$_2$CHNH, CH$\underline{H}$CHNH and NHC(=O)CH$_2$C$\underline{H}_2$), 1.24 - 1.29 (m, 2 H, NCH(C$\underline{H}$H)$_2$), 1.07 - 1.12 (m, 2 H, NCH(CH$\underline{H}$)$_2$)

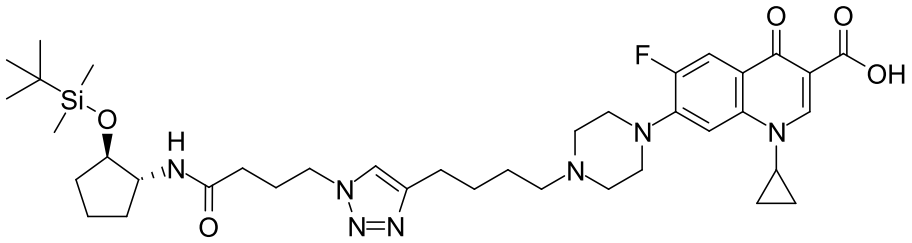
^{13}**C NMR** (126 MHz, DMSO d_6) δ / ppm = 215.2 ($\underline{C}$(=O)CHNH), 171.7 (NH$\underline{C}$(=O)CH$_2$), 171.7 ($\underline{C}$(=O)CC(=O)OCH$_3$), 165.1 ($\underline{C}$(=O)OCH$_3$), 152.6 (d, J=246.6 Hz, *ipso* to F), 148.4 ($\underline{C}$=CC(=O)OCH$_3$), 138.1 (*para* to F), 109.1 ($\underline{C}$C(=O)OCH$_3$),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

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

HRMS (ESI$^+$) m/z / Da = 513.2495, $[M+H]^+$ found, $[C_{27}H_{34}FN_4O_5]^+$ requires 513.2513

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

0.29 7-(4-(4-(1-(4-(((1*R*,2*R*)-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 153



1-Cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **164** (42.9 mg, 104 μmol, 1 eq.) and 4-azido-*N*-((1*R*,2*R*)-2-((*tert*-butyldimethylsilyl)oxy)cyclopentyl)butanamide **175**(RR) (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 resudue was partitioned between water (10 ml) and CH_2Cl_2 (10 ml), the organic layer was separated and the aqeous layer was extracted again with CH_2Cl_2 (10 ml). The combined organic layers were dried with $MgSO_4$ and evaporated under reduced pressure. **153** was obtained as a clear glass (67.1 mg, 90.9 μmol, 87.4 %).

IR (neat) ν_{max} / 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)

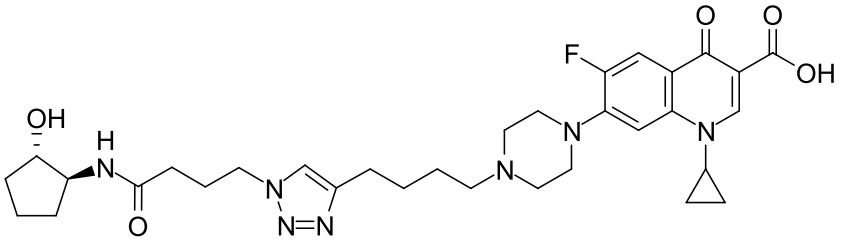
^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 8.67 (s, 1 H, *ortho* to C(=O)OH), 7.87 (d, J = 13.1 Hz, 1 H, *ortho* to F), 7.34 (s, 1 H, C$\underline{H}$=CCH$_2$), 7.33 (d, J = 8.2 Hz, 1 H, *meta* to F), 5.92 (t, J = 6.6 Hz, 1 H, CHN$\underline{H}$), 4.35 (t, J = 6.7 Hz, 2 H, C$\underline{H}_2$NCH=C), 3.96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

^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 176.9 (C(=O)CC(=O)OH), 170.9 (CH$_2$C(=O)NH), 166.9 (C(=O)OH), 153.5 (d, J = 251.4 Hz, *ipso* to F), 147.9 (CH=CCH$_2$), 147.2 (C=CC(=O)OH), 145.8 (d, J = 10.4 Hz, *ipso* to piperazine), 139.0 (*para* to F), 120.9 (NCH=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 (CC(=O)OH), 104.7 (d, J = 3.5 Hz, *meta* to C=O and *meta* to F), 77.7 (CHOSi), 58.2 (CHNH), 57.9 (CH=CCH$_2$CH$_2$CH$_2$CH$_2$N), 52.6 (CH=CCH$_2$CH$_2$CH$_2$CH$_2$N(CH$_2$)CH$_2$), 49.5 (d, J = 6.1 Hz, CH=CCH$_2$CH$_2$CH$_2$CH$_2$N(CH$_2$CH$_2$)CH$_2$CH$_2$), 48.9 (d, J = 3.5 Hz, CH$_2$NCH=CCH$_2$), 35.3 (NCH(CH$_2$)$_2$), 32.6 (C(=O)CH$_2$), 32.6 (CH$_2$CHOSi), 29.3 (CH$_2$CHNH), 27.2 (CH=CCH$_2$CH$_2$), 26.0 - 26.3 (C(=O)CH$_2$CH$_2$ and CH=CCH$_2$CH$_2$CH$_2$), 25.6 (C(CH$_3$)$_3$), 25.4 (CH=CCH$_2$), 20.4 (CH$_2$CH$_2$CHOSi), 17.8 (C(CH$_3$)$_3$), 8.1 (NCH(CH$_2$)$_2$), -4.8 (SiCH$_3$)

HRMS (ESI$^+$) m/z / Da = 738.4164, $[M+H]^+$ found, $[C_{38}H_{57}FN_7O_5Si]^+$ requires 738.4169

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

0.30 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 154



1-Cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **164** (42.9 mg, 104 μmol, 1 eq.) and 4-azido-*N*-((1*S*,2*S*)-2-hydroxycyclopentyl)butanamide **148** (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 × 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. **154** was obtained as a white amorphous solid (17.6 mg, 28.2 μmol, 27.1 %).

IR (neat) ν_{max} / 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)

^{1}H NMR (700 MHz, DMSO d_6) δ / 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, C$\underline{\mathrm{H}}$=CCH$_2$), 7.75 (d, J = 7.1 Hz, 1 H, CHN$\underline{\mathrm{H}}$), 7.54 (d, J = 7.5 Hz, 1 H, *meta* to F), 4.73 (d, J = 3.8 Hz, 1 H, CHO$\underline{\mathrm{H}}$), 4.29 (t, J = 6.9 Hz, 2 H, C$\underline{\mathrm{H}}_2$NCH=C), 3.78 - 3.83 (m, 1 H, NC$\underline{\mathrm{H}}$(CH$_2$)$_2$), 3.75 - 3.78 (m, 1 H, C$\underline{\mathrm{H}}$OH), 3.71 - 3.75 (m, 1 H, C$\underline{\mathrm{H}}$NH), 3.31 (br t, J = 4.3 Hz, 4 H, CH$_2$N(CH$_2$C$\underline{\mathrm{H}}_2$)CH$_2$C$\underline{\mathrm{H}}_2$), 2.63 (t, J = 7.5 Hz, 2 H, CH=CC$\underline{\mathrm{H}}_2$), 2.56 (br t, J = 4.2 Hz, 4 H, CH$_2$N(C$\underline{\mathrm{H}}_2$)C$\underline{\mathrm{H}}_2$), 2.37 (t, J = 7.3 Hz, 2 H, C$\underline{\mathrm{H}}_2$N(CH$_2$)CH$_2$), 2.03 - 2.06 (m, 2 H, C(=O)C$\underline{\mathrm{H}}_2$), 1.97 - 2.02 (m, 2 H, C(=O)CH$_2$C$\underline{\mathrm{H}}_2$), 1.89 (dddd, J = 13.1, 8.9, 7.4, 5.7 Hz, 1 H, C$\underline{\mathrm{H}}$HCHNH), 1.75 (ddt, J = 13.0, 8.9, 6.4, 6.4 Hz, 1 H, C$\underline{\mathrm{H}}$HCHOH), 1.61 - 1.66 (m, 2 H, CH=CCH$_2$C$\underline{\mathrm{H}}_2$), 1.57 - 1.61 (m, 1 H, C$\underline{\mathrm{H}}$HCH$_2$CHOH), 1.54 - 1.57 (m, 1 H, CH$\underline{\mathrm{H}}$CH$_2$CHOH), 1.49 - 1.53 (m, 2 H, CH=CCH$_2$CH$_2$C$\underline{\mathrm{H}}_2$), 1.40 (ddt, J = 13.0, 8.4, 5.3, 5.3 Hz, 1 H, CH$\underline{\mathrm{H}}$CHOH), 1.29 - 1.32 (m, 2 H, NCH(C$\underline{\mathrm{H}}$H)$_2$), 1.25 - 1.29 (m, 1 H, CH$\underline{\mathrm{H}}$CHNH), 1.13 - 1.20 (m, 2 H, NCH(CH$\underline{\mathrm{H}}$)$_2$)

^{13}C NMR (175 MHz, DMSO d_6) δ / ppm = 176.3 ($\underline{\mathrm{C}}$(=O)CC(=O)OH), 170.9 (NH$\underline{\mathrm{C}}$(=O)CH$_2$), 166.1 ($\underline{\mathrm{C}}$(=O)OH), 153.0 (d, J = 251.4 Hz, *ipso* to F), 147.9 ($\underline{\mathrm{C}}$=CC(=O)OH), 146.9 (CH=$\underline{\mathrm{C}}$CH$_2$), 145.2 (d, J = 8.7 Hz, *ipso* to piperazine), 139.2 (*para* to F), 121.7 (N$\underline{\mathrm{C}}$H=CCH$_2$), 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 $\underline{\mathrm{C}}$C(=O)OH),

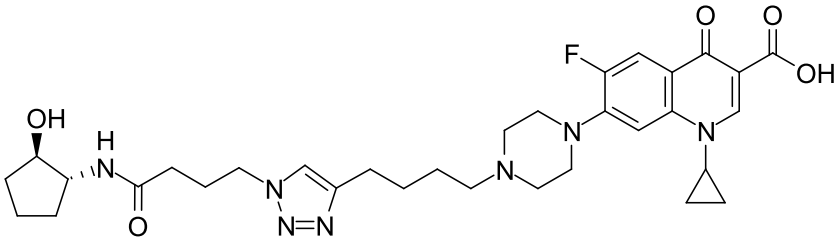
76.2 (CHOH), 57.6 (CHNH), 57.4 ($CH{=}CCH_2CH_2CH_2CH_2N$), 52.5 ($CH{=}CCH_2CH_2CH_2CH_2N(CH_2)CH_2$), 49.5 (d, J = 4.4 Hz, $CH{=}CCH_2CH_2CH_2CH_2N(CH_2CH_2)CH_2CH_2$), 48.8 ($CH_2NCH{=}CCH_2$), 35.8 ($NCH(CH_2)_2$), 32.2 ($CH_2CHOH$), 32.0 ($C(=O)CH_2$), 29.5 ($CH_2CHNH$), 26.9 ($CH{=}CCH_2CH_2$), 26.0 ($C(=O)CH_2CH_2$), 25.8 ($CH{=}CCH_2CH_2CH_2$), 25.0 ($CH{=}CCH_2$), 20.5 ($CH_2CH_2CHOH$), 7.6 ($NCH(CH_2)_2$)

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

HRMS (ESI$^+$) m/z / Da = 624.3314, $[M+H]^+$ found, $[C_{32}H_{43}FN_7O_5]^+$ requires 624.3310

$[\alpha]_D^{20}$ / $^\circ 10^{-1}$cm^{2}g^{-1} = -3.6 (c / g(100 ml)$^{-1}$ = 0.0833, MeOH)

0.31 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 155



1-Cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **164** (82.0 mg, 199 μmol, 4 eq.) and 4-azido-*N*-((1*R*,2*R*)-2-hydroxycyclopentyl)butanamide **149** (11.0 mg, 51.8 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 (156 μl, 15.6 μmol, 0.3 eq. 100 mM, aq.) was added, followed by a solution of sodium ascorbate (312 μl, 31.2 μmol, 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/$CHCl_3$ (10 ml) were added, then the organic layer was separated and 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. **155** was obtained as a white amorphous solid (7.2 mg, 11.5 μmol, 22.2 %).

high?

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)

^{1}H NMR (400 MHz, DMSO d_6) 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, $CH{=}CCH_2$), 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, $CH_2NCH{=}C$), 3.82 (tt, J=6.5, 4.3 Hz, 1 H, $NCH(CH_2)_2$), 3.69 - 3.79 (m, 2 H, CHOH and CHNH), 3.30 - 3.34 (m, 6 H, $CH{=}CCH_2CH_2CH_2CH_2N(CH_2CH_2)CH_2CH_2$), 2.64 (t, J=7.4 Hz, 2 H, $CH{=}CCH_2$), 1.95 - 2.08 (m, 4 H, $C(=O)CH_2CH_2$), 1.89 (dddd, J=12.8, 8.9, 7.4, 5.8 Hz, 1 H, CHHCHNH), 1.75 (ddt, J=12.7, 9.0, 6.2, 6.2 Hz, 1 H, CHHCHOH), 1.48 - 1.68 (m, 6 H, $CH{=}CCH_2CH_2CH_2$ and CH_2CH_2CHOH), 1.40 (ddt, J=13.0, 8.3, 5.3, 5.3

Hz, 1 H, CHHCHOH), 1.28 - 1.35 (m, 2 H, NCH(CHH)$_2$), 1.24 - 1.31 (m, 1 H, CHHCHNH), 1.15 - 1.21 (m, 2 H, NCH(CHH)$_2$)

^{13}C NMR (101 MHz, DMSO d_6) δ / ppm = 176.4 (C(=O)CC(=O)OH), 170.9 (NHC(=O)CH_2), 166.0 (C(=O)OH), 153.0 (d, J=249.6 Hz, *ipso* to F), 148.1 (C=CC(=O)OH), 146.7 (CH=CCH_2), 145.2 (d, J=8.3 Hz, *ipso* to piperazine), 139.2 (*para* to F), 121.8 (NCH=CCH_2), 118.7 (*para* to piperazine), 111.0 (d, J=23.2 Hz, *ortho* to C=O and *ortho* to F), 106.7 (CC(=O)OH), 106.5 (*meta* to C=O and *meta* to F), 76.2 (CHOH), 57.5 (CHNH), 57.4 (br s, CH=C$CH_2CH_2CH_2CH_2$N), 52.3 (br s, CH=C$CH_2CH_2CH_2CH_2$N(CH_2)CH_2), 49.3 (br s, CH=C$CH_2CH_2CH_2CH_2$N(CH_2CH_2)CH_2CH_2), 48.8 (CH_2NCH=CCH_2), 35.9 (NCH(CH_2)$_2$), 32.2 (CH_2CHOH), 32.0 (C(=O)CH_2), 29.4 (CH_2CHNH), 26.7 (CH=CCH_2CH_2), 26.0 (C(=O)CH_2CH_2), 25.5 (CH=C$CH_2CH_2CH_2$), 24.9 (CH=CCH_2), 20.5 (CH_2CH_2CHOH), 7.6 (NCH(CH_2)$_2$)

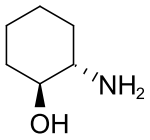
^{19}F NMR (376.45 MHz, MeOD) δ / ppm = -121.5

HRMS (ESI$^+$) m/z / Da = 624.3298, $[M+H]^+$ found, $[C_{32}H_{43}FN_7O_5]^+$ requires 624.3310

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

explain discrepancy

0.32 (*trans*)-2-Aminocyclohexan-1-ol 156



Cyclohexene oxide **176** (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

TLC R_f = 0.04 (30 % MeOH/CH_2Cl_2)

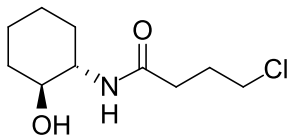
IR (neat) ν_{max} / cm^{-1} = 3350.4 (N-H), 3306.2 (br, O-H), 2926.9 (C-H), 2852.6 (C-H)

^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 3.01 (td, J = 9.4, 4.8 Hz, 1 H, CHOH), 2.80 - 2.92 (m, 2 H, OH and NH_2), 2.35 (ddd, J = 11.1, 9.1, 4.1 Hz, 1 H, CHNH_2), 1.77 - 1.84 (m, 1 H, CHHCHOH), 1.69 - 1.76 (m, 1 H, CHHCHNH_2), 1.56 - 1.66 (m, 1 H, CHHCH_2CHOH), 1.45 - 1.56 (m, 1 H, CHHCH_2CHNH_2), 1.07 - 1.19 (m, 3 H, CHHCH_2CHOH, CHHCH_2CHNH_2 and CHHCHOH), 0.94 - 1.05 (m, 1 H, CHHCHNH_2)

^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 75.4 (CHOH), 56.6 (CHN_2), 33.8 (CH_2CHOH and CH_2CHN_2), 24.7 (CH_2CH_2CHN_2), 24.6 (CH_2CH_2CHOH)

HRMS (ESI$^+$) m/z / Da = 116.1070, $[M+H]^+$ found, $[C_6H_{14}NO]^+$ requires 116.1070

0.33 4-Chloro-*N*-((*trans*)-2-hydroxycyclohexyl)butanamide 157



(Trans)-2-aminocyclohexan-1-ol **156** (1.04 g, 9.03 mmol, 1 eq.), TEA (1.65 ml, 1.20 g, 11.8 mmol, 1.3 eq.) and CH_2Cl_2 (50 ml) were stirred at 0°C. 4-Chlorobutyryl chloride **173** (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/$CHCl_3$ (2 × 50 ml). The combined organic layers were dried with $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (SiO_2, 0-100 % EtOAc/Et_2O). **157** was obtained as white needles (1.51 g, 6.87 mmol, 76.1 %).

TLC R_f = 0.19 (Et_2O)

mp T / °C = 72.5-75.7 (*i*-PrOH, $CHCl_3$)

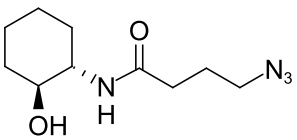
IR (neat) ν_{max} / cm^{-1} = 3289.9 (N-H), 3250.0 (O-H), 2927.6 (C-H), 2857.1 (C-H), 1629.2 (amide C=O)

^{1}H NMR (400 MHz, MeOD) δ / ppm = 3.60 (t, J = 6.6 Hz, 2 H, C$\underline{H}_2$Cl), 3.51 - 3.60 (m, 1 H, C$\underline{H}$NH), 3.28 - 3.39 (m, 1 H, C$\underline{H}$OH), 2.37 (td, J = 7.4, 2.3 Hz, 2 H, C(=O)C$\underline{H}_2$), 2.06 (quin, J = 7.0 Hz, 2 H, C(=O)CH$_2$C$\underline{H}_2$), 1.97 - 2.01 (m, 1 H, C$\underline{H}$HCHOH), 1.85 - 1.93 (m, 1 H, C$\underline{H}$HCHNH), 1.70 - 1.77 (m, 1 H, C$\underline{H}$HCH$_2$CHOH), 1.64 - 1.70 (m, 1 H, C$\underline{H}$HCH$_2$CHNH), 1.24 - 1.35 (m, 3 H, CH$\underline{H}$CH$_2$CHOH, CH$\underline{H}$CH$_2$CHNH and CH$\underline{H}$CHOH), 1.13 - 1.25 (m, 1 H, CH$\underline{H}$CHNH$_2$)

^{13}C NMR (101 MHz, MeOD) δ / ppm = 175.0 ($\underline{C}$(=O)), 74.1 ($\underline{C}$HOH), 56.3 ($\underline{C}$HNH), 45.3 ($\underline{C}$H$_2$Cl), 35.6 ($\underline{C}$H$_2$CHOH), 34.5 (C(=O)$\underline{C}$H$_2$), 32.7 ($\underline{C}$H$_2$CHNH), 30.1 (C(=O)CH$_2\underline{C}$H$_2$), 25.8 ($\underline{C}$H$_2$CH$_2$CHNH), 25.5 ($\underline{C}$H$_2$CH$_2$CHOH)

HRMS (ESI$^+$) m/z / Da = 242.0925, $[M+Na]^+$ found, $[C_{10}H_{18}ClNNaO_2]^+$ requires 242.0924

0.34 4-Azido-*N*-((*trans*)-2-hydroxycyclohexyl)butanamide 158



4-Chloro-*N*-((trans)-2-hydroxycyclohexyl)butanamide **157** (345 mg, 1.57 mmol, 1 eq.) and NaN_3 (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/$CHCl_3$ (50 ml) were added, and the organic layer was removed. The aqueous layer was extracted again with 10 % *i*-PrOH/$CHCl_3$ (50 ml) and the combined organic fractions were dried with $MgSO_4$. The solvent was evaporated under reduced pressure, and then by using a N_2 stream. **177** 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, $CHCl_3$)

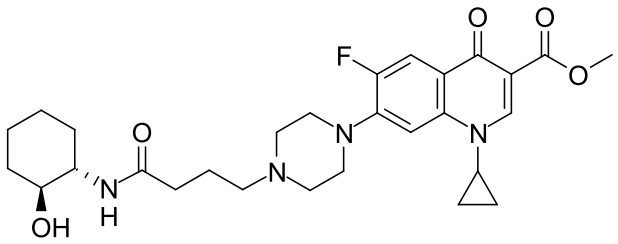
IR (neat) ν_{max} / cm^{-1} = 3299.0 (N-H), 3207.8 (O-H), 2944.3 (C-H), 2927.9 (C-H), 2859.2 (C-H), 2089.2 (azide), 1624.0 (amide C=O)

^{1}H 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 CH_2N_3), 2.30 (td, J = 7.4, 2.7 Hz, 2 H, C(=O)CH_2), 1.95 - 2.03 (m, 1 H, CHHCHOH), 1.87 (m, 3 H, C(=O)CH_2CH_2 and CHHCHNH), 1.70 - 1.76 (m, 1 H, $CHHCH_2$CHOH), 1.63 - 1.70 (m, 1 H, $CHHCH_2$CHNH), 1.25 - 1.38 (m, 3 H, $CHHCH_2$CHOH, $CHHCH_2$CHNH and CHHCHOH), 1.14 - 1.24 (m, 1 H, $CHHCHNH_2$)

^{13}C NMR (101 MHz, MeOD) δ / ppm = 175.1 (C(=O)), 74.0 (CHOH), 56.3 (CHNH), 52.0 (CH_2N_3), 35.5 (CH_2CHOH), 34.3 (C(=O)CH_2), 32.7 (CH_2CHNH), 26.3 (C(=O)CH_2CH_2), 25.8 (CH_2CH_2CHNH), 25.5 (CH_2CH_2CHOH)

HRMS (ESI^+) m/z / Da = 249.1331, $[M+Na]^+$ found, $[C_{10}H_{18}N_4NaO_2]^+$ requires 249.1327

0.35 Methyl 1-cyclopropyl-6-fluoro-7-(4-(4-(((*trans*)-2-hydroxycyclohexyl)amino)-4-oxobutyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 159



139 (200 mg, 0.367 mmol, 1 eq.), **156** (91.1 mg, 0.791 mmol, 2.1 eq.), 1-ethyl-3-(3-dimethylaminopropyl)carbodi imide hydrochloride (112 mg, 0.584 mmol, 1.6 eq.), 1-hydroxybenzotriazole (96 mg, 0.710 mmol, 1.9 eq.) and DIPEA (192 μl, 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 N_2 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 $NaHCO_3$ (aq., sat., 10 ml) and CH_2Cl_2 (10 ml). The organic layer was dried with $MgSO_4$ and evaporated under reduced pressure. **150** 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)

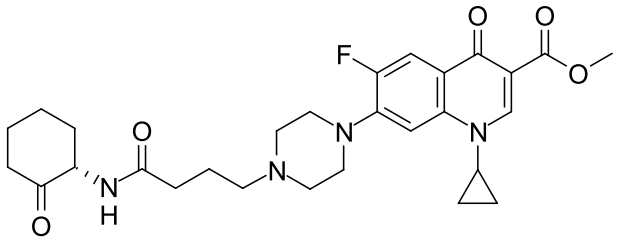
^{1}H NMR (400 MHz, MeOD) δ / ppm = 8.60 (s, 1 H, *ortho* to C(=O)OCH$_3$), 7.79 (d, J = 13.5 Hz, 1 H, *ortho* to F), 7.46 (d, J = 7.2 Hz, 1 H, *meta* to F), 3.84 (s, 3 H, CH$_3$), 3.62 - 3.68 (m, 1 H, NCH$(CH_2)_2$), 3.58 (td, J = 10.3, 4.2 Hz, 1 H, CHNH), 3.38 (br s, 4 H, $CH_2N(CH_2CH_2)CH_2CH_2$), 3.32 - 3.36 (m, 1 H, CHOH), 2.83 (br s, 4 H, $CH_2N(CH_2)CH_2$), 2.60 (t, J = 7.3 Hz, 2 H, C(=O)$CH_2CH_2CH_2$N), 2.32 (td, J = 7.1, 3.1 Hz, 2 H, C(=O)CH_2), 1.96 - 2.04 (m, 1 H, CHHCHOH), 1.87 - 1.96 (m, 3 H, CHHCHNH and C(=O)CH_2CH_2), 1.72 - 1.77 (m, 1 H, $CHHCH_2$CHOH), 1.66 - 1.72 (m, 1 H, $CHHCH_2$CHNH), 1.25 - 1.39 (m, 5 H, CHHCHOH, $CHHCH_2$CHOH, $CHHCH_2$CHNH 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 ($CH_2\underline{C}(=O)NH$), 175.3 ($\underline{C}(=O)CC(=O)OCH_3$), 166.8 ($\underline{C}(=O)OCH_3$), 154.9 (d, J = 248.8 Hz, *ipso* to F), 150.2 ($\underline{C}=CC(=O)OCH_3$), 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 ($\underline{C}C(=O)OCH_3$), 107.2 (*meta* to C=O and *meta* to F), 74.1 ($\underline{C}HOH$), 58.9 ($C(=O)CH_2CH_2\underline{C}H_2N$), 56.4 ($\underline{C}HNH$), 54.0 ($C(=O)CH_2CH_2CH_2N(\underline{C}H_2)\underline{C}H_2$), 52.3 ($\underline{C}H_3$), 50.5 (d, J = 5.0 Hz, $C(=O)CH_2CH_2CH_2N(CH_2\underline{C}H_2)CH_2\underline{C}H_2$), 36.4 ($N\underline{C}H(CH_2)_2$), 35.7 ($\underline{C}H_2CHOH$), 35.1 ($C(=O)\underline{C}H_2$), 32.8 ($\underline{C}H_2CHNH$), 25.9 ($\underline{C}H_2CH_2CHNH$), 25.5 ($\underline{C}H_2CH_2CHOH$), 23.5 ($C(=O)CH_2\underline{C}H_2$), 8.7 ($NCH(\underline{C}H_2)_2$)

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

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

0.36 Methyl 1-cyclopropyl-6-fluoro-4-oxo-7-(4-(4-oxo-4-((2-oxocyclohexyl)amino)-butyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate 160



Methyl 1-cyclopropyl-6-fluoro-7-(4-(4-(((trans)-2-hydroxycyclohexyl)amino)-4-oxobutyl)piperazin-1-yl)-4-oxo-1, 4-dihydroquinoline-3-carboxylate **159** (5.2 mg, 9.84 μmol, 1 eq.) and Dess-Martin Periodane (16.4 mg, 38.7 μmol, 4 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 (5-95 % acetonitrile/water over ??)

TLC R_f = 0.74 (30 % MeOH/CH_2Cl_2)

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)

^{1}**H NMR** (400 MHz, DMSO d_6) δ / ppm = 8.45 (s, 1 H, *ortho* to $C(=O)OC\underline{H}_3$), 7.87 (d, J = 6.2 Hz, 1 H, $N\underline{H}$), 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, $C\underline{H}NH$), 3.73 (s, 3 H, $C\underline{H}_3$), 3.65 (tt, J = 7.1, 3.9 Hz, 1 H, $NC\underline{H}(CH_2)_2$), 3.25 (br s, 4 H, $CH_2N(CH_2C\underline{H}_2)CH_2C\underline{H}_2$), 2.58 (br s, 4 H, $CH_2N(C\underline{H}_2)C\underline{H}_2$), 2.45 - 2.53 (m, 1 H, $C\underline{H}HC(=O)CHNH$), 2.36 (br s, 2 H, $C(=O)CH_2CH_2C\underline{H}_2N$), 2.26 (dtt, J = 13.4, 2.6, 2.6, 1.6, 1.6 Hz, 1 H, $CH\underline{H}C(=O)CHNH$), 2.16 - 2.22 (m, 2 H, $C(=O)C\underline{H}_2CH_2CH_2N$), 2.12 (ddq, J = 12.7, 6.0, 2.8, 2.8, 2.8 Hz, 1 H, $C\underline{H}HCHNH$), 2.00 (ddquin, J = 13.2, 6.0, 2.9, 2.9, 2.9, 2.9 Hz, 1 H, $C\underline{H}HCH_2C(=O)$), 1.65 - 1.83 (m, 4 H, $C\underline{H}_2CH_2CHNH$), 1.41 - 1.56 (m, 2 H, $CH\underline{H}CHNH$ and $CH\underline{H}CH_2C(=O)$), 1.20 - 1.30 (m, 2 H, $NCH(C\underline{H}H)_2$), 1.05 - 1.13 (m, 2 H, $NCH(CH\underline{H})_2$)

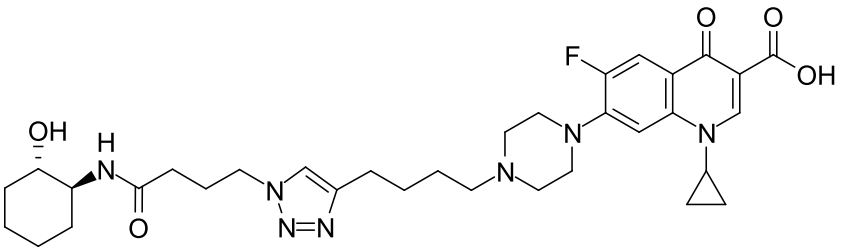
^{13}**C NMR** (101 MHz, DMSO d_6) δ / ppm = 207.5 ($\underline{C}(=O)CHNH$), 171.7 ($\underline{C}(=O)CC(=O)OCH_3$), 171.6 ($CH_2\underline{C}(=O)NH$), 165.0 ($\underline{C}(=O)OCH_3$), 152.6 (d, J = 247.6 Hz, *ipso* to F), 148.3 ($\underline{C}=CC(=O)OCH_3$), 143.9 (br s, *ipso* to piperazine), 138.1 (*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 ($\underline{C}C(=O)OCH_3$), 106.3 (*meta* to C=O and *meta* to F), 57.0 ($\underline{C}HNH$ and $C(=O)CH_2CH_2\underline{C}H_2N$), 52.3 (br s, $C(=O)CH_2CH_2CH_2N(\underline{C}H_2)\underline{C}H_2$), 51.3 ($\underline{C}H_3$), 49.5 (br

s, C(=O)$CH_2CH_2CH_2N(CH_2\underline{C}H_2)CH_2\underline{C}H_2$), 40.6 ($C\underline{H}_2C(=O)CHNH$), 34.8 ($N\underline{C}H(CH_2)_2$), 33.9 ($C\underline{H}_2CHNH$), 32.9 ($C(=O)\underline{C}H_2CH_2CH_2N$), 27.2 ($C\underline{H}_2CH_2C(=O)CHNH$), 23.8 ($C\underline{H}_2CH_2CHNH$), 22.4 (br s, $C(=O)CH_2\underline{C}H_2$ CH_2N), 7.6 ($NCH(\underline{C}H_2)_2$)

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

HRMS (ESI^+) m/z / Da = 527.2654, $[M+H]^+$ found, $[C_{28}H_{36}FN_4O_5]^+$ requires 527.2670

0.37 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 161



1-Cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **164** (40 mg, 97.2 μmol, 1 eq.) and 4-azido-*N*-((trans)-2-hydroxycyclohexyl)butanamide **158** (22.0 mg, 97.2 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 (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/$CHCl_3$ (50 ml) were added, then the organic layer was separated and dried with $MgSO_4$ 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 $NaHCO_3$ (aq., sat., 50 ml) and 10 % *i*-PrOH/$CHCl_3$ (50 ml). The organic layer was dried with $MgSO_4$ and evaporated under reduced pressure. **161** 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)

^{1}H NMR (400 MHz, DMSO d_6) 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, $C\underline{H}{=}CCH_2$), 7.64 (d, J = 8.1 Hz, 1 H, $N\underline{H}$), 7.54 (d, J = 7.5 Hz, 1 H, *meta* to F), 4.54 (d, J = 4.7 Hz, 1 H, $O\underline{H}$), 4.30 (t, J = 6.8 Hz, 2 H, $C(=O)CH_2CH_2C\underline{H}_2N$), 3.77 - 3.86 (m, 1 H, $NC\underline{H}(CH_2)_2$), 3.33 - 3.40 (m, 1 H, $C\underline{H}NH$), 3.31 (br t, J = 4.8, 4.8 Hz, 4 H, $CH{=}CCH_2CH_2CH_2N(CH_2C\underline{H}_2)CH_2C\underline{H}_2$), 3.14 - 3.24 (m, 1 H, $C\underline{H}OH$), 2.63 (t, J = 7.4 Hz, 2 H, $CH{=}CC\underline{H}_2$), 2.56 (br t, J = 4.6, 4.6 Hz, 4 H, $CH{=}CCH_2CH_2CH_2N(C\underline{H}_2)C\underline{H}_2$), 2.38 (t, J = 6.9 Hz, 2 H, $CH{=}CCH_2CH_2CH_2C\underline{H}_2N$), 2.04 - 2.08 (m, 2 H, $C(=O)C\underline{H}_2CH_2CH_2N$), 1.96 - 2.04 (m, 2 H, $C(=O)CH_2C\underline{H}_2CH_2N$), 1.78 - 1.87 (m, 1 H, $C\underline{H}HCHOH$), 1.69 - 1.78 (m, 1 H, $C\underline{H}HCHNH$), 1.63 (quin, J = 7.5 Hz, 2 H, $CH{=}CCH_2C\underline{H}_2CH_2CH_2N$), 1.54 - 1.60 (m, 1 H, $C\underline{H}HCH_2OH$), 1.51 (quin, J = 7.4 Hz, 2 H, $CH{=}CCH_2CH_2C\underline{H}_2CH_2N$), 1.28 - 1.35 (m, 1 H, $NCH(C\underline{H}H)_2$), 1.11 - 1.22 (m, 5 H, $NCH(CH\underline{H})_2$, $CH\underline{H}CHOH$, $CH\underline{H}CH_2CHOH$ and $C\underline{H}_2CH_2CHNH$), 1.04 - 1.13 (m, 1 H, $CH\underline{H}CHNH$)

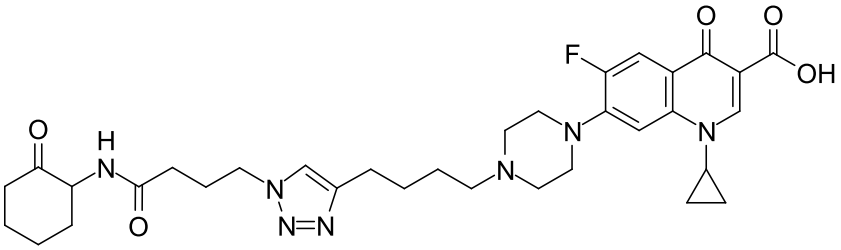
^{13}C NMR (101 MHz, DMSO d_6) δ / ppm = 176.4 ($\underline{C}(=O)CC(=O)OH$), 170.9 ($CH_2\underline{C}(=O)NH$), 166.0

(C(=O)OH), 153.1 (d, J = 252.1 Hz, *ipso* to F), 148.0 (C=CC(=O)OH), 146.9 (CH=CCH$_2$), 145.3 (d, J = 10.0 Hz, *ipso* to piperazine), 139.2 (*para* to F), 121.8 (NCH=CCH$_2$), 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=CCH$_2$CH$_2$CH$_2$CH$_2$N), 54.2 (CHNH), 52.4 (CH=CCH$_2$CH$_2$CH$_2$CH$_2$N(CH$_2$)CH$_2$), 49.5 (CH=CCH$_2$CH$_2$CH$_2$CH$_2$N(CH$_2$CH$_2$)CH$_2$CH$_2$), 49.5 (CH=CCH$_2$CH$_2$CH$_2$CH$_2$N(CH$_2$CH$_2$)CH$_2$CH$_2$), 48.8 (C(=O)CH$_2$CH$_2$CH$_2$NCH=C), 35.9 (NCH(CH$_2$)$_2$), 34.1 (CH$_2$CHOH), 32.3 (C(=O)CH$_2$CH$_2$CH$_2$NCH=C), 31.1 (CH$_2$CHNH), 26.9 (CH=CCH$_2$CH$_2$CH$_2$CH$_2$N), 26.1 (C(=O)CH$_2$CH$_2$CH$_2$NCH=C), 25.8 (CH=CCH$_2$CH$_2$CH$_2$ CH$_2$N), 25.0 (CH=CCH$_2$CH$_2$CH$_2$CH$_2$N), 24.2 (CH$_2$CH$_2$CHNH), 23.8 (CH$_2$CH$_2$CHOH), 7.6 (NCH(CH$_2$)$_2$)

^{19}F NMR (376.45 MHz, DMSO d$_6$) δ / ppm = -121.4 (ciprofloxacin F)

HRMS (ESI$^+$) m/z / Da = 638.3480, [M+H]$^+$ found, [C$_{33}$H$_{45}$FN$_7$O$_5$]$^+$ requires 638.3466

0.38 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 162



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 **161** (15.0 mg, 23.6 mmol, 1 eq.) and Dess-Martin Periodane (35.0 mg, 82.5 mmol, 3.5 eq.) were stirred in CH$_2$Cl$_2$ (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 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)

^{1}H NMR (500 MHz, DMSO d$_6$) 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=CCH$_2$), 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)CH$_2$CH$_2$CHHN), 4.31 (t, J=6.9 Hz, 1 H, C(=O)CH$_2$CH$_2$CHH$_2$N), 3.74 - 3.84 (m, 1 H, NCH(CH$_2$)$_2$), 3.31 (br. s, 4 H, CH$_2$CH$_2$CH$_2$N(CH$_2$CH$_2$)CH$_2$CH$_2$), 2.64 (t, J=7.5 Hz, 2 H, CH=CCH$_2$), 2.56 (br t, J=5.0, 5.0 Hz, 4 H, CH$_2$CH$_2$CH$_2$N(CH$_2$)CH$_2$), 2.45 - 2.52 (m, 1 H, CHHC(=O)), 2.38 (t, J=7.1 Hz, 2 H, CH=CCH$_2$CH$_2$CH$_2$CH$_2$N), 2.25 (dtt, 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)CH$_2$CH$_2$CH$_2$N and CHHCHNH), 1.96 - 2.05 (m, 3 H, C(=O)CH$_2$CH$_2$CH$_2$N and CHHCH$_2$C(=O)), 1.68 - 1.81 (m, 2 H, CHHCH$_2$CHNH), 1.64 (quin, J=7.5 Hz, 2 H, CH=CCH$_2$CH$_2$CH$_2$CH$_2$N), 1.40 - 1.56 (m, 5 H, CHHCH$_2$C(=O), CHHCHNH and CH=CCH$_2$CH$_2$CH$_2$CH$_2$N), 1.27 - 1.34 (m, 2 H, NCH(CHH)$_2$), 1.13 - 1.20 (m, 2 H, NCH(CHH)$_2$)

^{13}C NMR (126 MHz, DMSO d$_6$) δ / ppm = 207.4 (C(=O)CHNH), 176.3 (C(=O)CC(=O)OH), 170.8 (CH$_2$C (=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=CCH$_2$),

145.1 (d, J=10.1 Hz, *ipso* to piperazine), 139.1 (*para* to F), 121.7 (N$\underline{C}$H=CCH$_2$), 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 ($\underline{C}$C(=O)OH, and *meta* to C=O and *meta* to F), 57.3 (CH=CCH$_2$CH$_2$CH$_2\underline{C}$H$_2$N), 57.0 ($\underline{C}$HNH), 52.4 (CH$_2$CH$_2$CH$_2$N($\underline{C}$H$_2$)$\underline{C}$H$_2$), 49.5 (CH$_2$CH$_2$CH$_2$N(CH$_2\underline{C}$H$_2$)CH$_2$CH$_2$), 49.5 (CH$_2$CH$_2$CH$_2$N(CH$_2$CH$_2$)CH$_2\underline{C}$H$_2$), 48.7 (C(=O)CH$_2$CH$_2\underline{C}$H$_2$NCH=C), 40.5 ($\underline{C}$H$_2$C(=O)), 35.8 (N$\underline{C}$H(CH$_2$)$_2$), 33.7 ($\underline{C}$H$_2$CHNH), 31.8 (C(=O)$\underline{C}$H$_2$CH$_2$CH$_2$NCH=C), 27.1 ($\underline{C}$H$_2$CH$_2$C(=O)), 26.9 (CH=CCH$_2\underline{C}$H$_2$CH$_2$CH$_2$N), 26.0 (C(=O)CH$_2\underline{C}$H$_2$CH$_2$NCH=C), 25.7 (CH=CCH$_2$CH$_2\underline{C}$H$_2$CH$_2$N), 24.9 (CH=C$\underline{C}$H$_2$CH$_2$CH$_2$CH$_2$N), 23.8 ($\underline{C}$H$_2$CH$_2$CHNH), 7.6 (NCH($\underline{C}$H$_2$)$_2$)

^{19}F NMR (376 MHz, DMSO d$_6$) δ / ppm = -121.7 (s, ciprofloxacin F)

some TFA

HRMS (ESI$^+$) m/z / Da = 636.3303, [M+H]$^+$ found, [$C_{33}H_{43}FN_7O_5$]$^+$ requires 636.3310