Contents

1 Experimental

1.1 General

Unless otherwise stated, reactions were performed in air-dried glassware under argon with dry, freshly distilled solvents. THF was distilled from $LiAlH_4$ in the presence of triphenyl methane indicator. CH_2Cl_2, hexane, MeOH and MeCN were distilled from calcium hydride. All other chemicals were used as obtained from commercial sources.

Reactions using microwave heating were performed in sealed vials using a CEM Discover SP microwave reactor.

Thin Layer Chromatography (TLC) was performed using Merck pre-coated 0.23 mm thick plates of Keisel-gel 60 F254 and visualised using UV (λ = 254 or 366 nm) or by staining with $KMnO_4$ or ninhydrin. All retention factors (R_f) are given to 0.01. All column chromatography was carried out using Merck 9385 Keisel-gel 60 silica gel (230-400 mesh) or using a CombiFlash® EZ Prep with RediSep® normal-phase silica flash columns. Preparative High Pressure Liquid Chromatography was run on an Agilent 1260 Infinity machine, using a Supelcosil™ ABZ+PLUS column (250 mm × 21.2 mm, 5 μm) with a linear gradient system (solvent A: 0.1 % (v/v) TFA/water, solvent B: 0.05 % (v/v) TFA/acetonitrile) at a flow rate of 20 mL min^{-1}, visualised by UV absorbance (λ_{max} = 254 nm)

Nuclear Magnetic Resonance (NMR) spectra were recorded using an internal deuterium lock at ambient probe temperatures on Bruker DPX-400, Bruker Avance DRX-400, Bruker Avance 500 BB-ATM or Bruker Avance 500 Cryo Ultrashield spectrometers. Data were processed using NMR Processor Academic Edition version 12 (ADC Labs) or TopSpin version 3.5 (Bruker). ^{1}H and ^{1}3C spectra were assigned using DEPT, COSY, HMQC and HMQC spectra where necessary, or by analogy to fully interpreted spectra of related compounds. The following abbreviations are used to indicate the multiplicity of signals: s singlet, d doublet, t triplet, q quartet, quin quintet, m multiplet and br broad.

^{1}H chemical shifts (δ) are quoted to the nearest 0.01 ppm and are referenced relative to the residual solvent peak.[1] Coupling constants (J) are given to the nearest 0.1 Hz. Diastereotopic protons are assigned as C<u>H</u>H and CH<u>H</u>, where the latter designates the lower-field proton. Data are reported as follows: <chemical shift> (<multiplicity>, <coupling constant(s) (if any)>, <integration>, <assignment>).

^{13}C chemical shifts (δ) are quoted to the nearest 0.1 ppm and are referenced relative to the deuterated solvent peak.[1] Data are reported as follows: <chemical shift> (<multiplicity (if not s)>, <coupling constant(s) (if any)>, <assignment>).

^{19}F chemical shifts (δ) are quoted to the nearest 0.1 ppm. Data are reported as follows: <chemical shift> (<assignment>).

High Resolution Mass Spectra (HRMS) were recorded using either a Micromass Q-TOF or a Micromass LCT Premier spectrometer and reported mass values are within ± 5 ppm mass units. Low Resolution Mass Spectra (LRMS) were recorded on an Agilent 1200 series LC with an ESCi Multi-Mode Ionisation Waters ZQ spectrometer or a Waters ACQUITY H-Class UPLC with an ESCi Multi-Mode Ionisation Waters SQ Detector 2 spectrometer.

Infra Red (IR) spectra were recorded using neat sample on a PerkinElmer 1600 FT IR spectrometer. Selected absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}). Broad peaks are marked br.

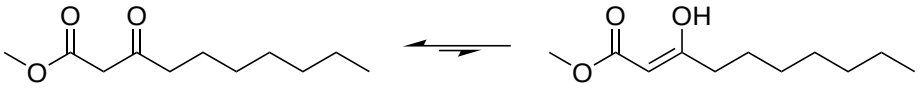
Melting points (m.p.) were measured using a Buchi B-545 melting point apparatus and are uncorrected.

Optical rotations ($[\alpha]_D^T$) were recorded on a PerkinElmer 343 polarimeter or an Anton-Paar MCP 100 polarimeter. $[\alpha]_D^T$ values are reported in $^\circ 10^{-1} cm^2 g^{-1}$ at 589 nm and concentration (c) is given in g (100 mL)$^{-1}$.

The Open Access Accurate Mass system is a self-service system utilising an Agilent 1100 pump and autosampler with a Waters LCT Premier TOF (Time of Flight) mass spectrometer.

Waters Vion IMS Qtof, Small molecules direct infusion, Low energy, High energy

1.2 Methyl 3-oxodecanoate 35/36



35
92 %

36
8 %

Meldrum's acid **33** (9.0 g, 63 mmol, 1 eq.) was dissolved in anhydrous CH_2Cl_2 (150 ml) in an oven-dried flask and cooled to 0 °C. Pyridine (10.2 ml, 126 mmol, 2 eq.) was added dropwise over 20 min. Octanoyl chloride **34** (11.7 ml, 69 mmol, 1.1 eq.) was then added and the mixture was stirred at 0 °C for a further 4 h. The mixture was allowed to warm to r.t., diluted with CH_2Cl_2 (20 ml) and poured into a mixture of ice (~30 g) and HCl (2 N, 90 ml). The solution was washed with NaCl (sat., aq., 150 ml) and dried over $MgSO_4$. The solvent was removed under vacuum to give an orange-brown oil. The oil was refluxed in anhydrous MeOH (150 ml) for 5 h and the solvent was removed under vacuum. The resulting residue was purified by column chromatography (SiO_2, 5 % Et_2O/40-60 P.E.). A tautomeric mixture of **35** and **36** was obtained as a colourless oil (8.34 g, 41.6 mmol, 66 %, 92 % **35** as determined by ^{1}H NMR).

Keto form 35

TLC R_f = 0.12 (5 % EtO_2/PE)

IR (neat) ν_{max} / cm^{-1} = 2927.8 (C-H), 2856.3 (C-H), 1746.9 (ester C=O), 1716.7 (ketone C=O)

^{1}**H NMR** (400 MHz, $CDCl_3$) δ / ppm = 3.74 (s, 3 H, OC$\underline{H}_3$), 3.45 (s, 2 H, C(=O)C$\underline{H}_2$C(=O)), 2.53 (t, J = 7.4 Hz, 2 H, C(=O)C$\underline{H}_2$CH$_2$), 1.60 (quin, J = 7.1 Hz, 2 H, C(=O)CH$_2$C$\underline{H}_2$), 1.39 - 1.19 (m, 8 H, C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}_2$CH$_3$), 0.88 (t, J = 6.8 Hz, 3 H, CH$_2$C$\underline{H}_3$)

^{13}**C NMR** (101 MHz, $CDCl_3$) δ / ppm = 202.3 (CH$_3$OC(=O)CH$_2$$\underline{C}$(=O)), 167.3 (CH$_3O\underline{C}$(=O)CH$_2$C(=O)), 51.7 (O$\underline{C}H_3$), 48.5 (CH$_3$OC(=O)$\underline{C}H_2$C(=O)), 42.5 (C(=O)$\underline{C}H_2CH_2$), 31.3 ($\underline{C}H_2$), 28.7 ($\underline{C}H_2$), 28.6 ($\underline{C}H_2$), 23.1 ($\underline{C}H_2$), 22.2 ($\underline{C}H_2$), 13.6 (CH$_2$$\underline{C}H_3$)

Enol form 36

TLC R_f = 0.12 (5 % EtO_2/PE)

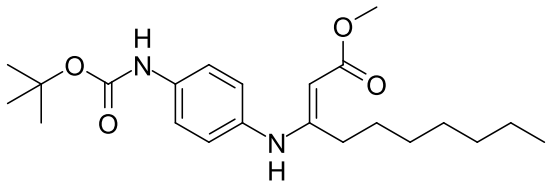
IR (neat) ν_{max} / cm^{-1} = 2927.8 (C-H), 2856.3 (C-H), 1653.8 (C=C), 1629.2 (α,β unsaturated C=O)

^{1}**H NMR** (400 MHz, $CDCl_3$) δ / ppm = 12.02 (s, 1 H, CO$\underline{H}$), 4.99 (s, 1 H, C(=O)C$\underline{H}$=COH), 3.73 (s, 3 H, OC$\underline{H}_3$), 2.20 (t, J = 7.4 Hz, 2 H, COHC$\underline{H}_2$), 1.76 - 1.72 (m, 2 H, COHCH$_2$C$\underline{H}_2$), 1.39 - 1.19 (m, 8 H, C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}_2$CH$_3$), 0.88 (t, J = 6.8 Hz, 3 H, CH$_2$C$\underline{H}_3$)

^{13}**C NMR** (101 MHz, $CDCl_3$) δ / ppm = 178.7 (CH$_3$OC(=O)CH=$\underline{C}$OH), 172.7 (CH$_3$O$\underline{C}$(=O)CH=COH), 88.2 (CH$_3$OC(=O)$\underline{C}$H=COH), 50.5 (O$\underline{C}$H$_3$), 37.9 (COH$\underline{C}$H$_2$CH$_2$), 34.6 ($\underline{C}$H$_2$), 31.2 ($\underline{C}$H$_2$), 29.0 ($\underline{C}$H$_2$), 25.9 ($\underline{C}$H$_2$), 22.3 ($\underline{C}$H$_2$), 13.6 (CH$_2$$\underline{C}H_3$)

Spectroscopic data are consistent with the literature.[2,3]

1.3 Methyl (*E*)-3-((4-((*tert*-butoxycarbonyl)amino)phenyl)amino)dec-2-enoate 38



Methyl 3-oxodecanoate **35** (500 mg, 2.50 mmol, 1.00 eq.) and *O*-*tert*-butyl *N*-(4-aminophenyl)carbamate **37** (520 mg, 2.50 mmol, 1.00 eq.) were dissolved in MeOH (10 ml) and refluxed for 18 h. The solvent was removed under vacuum and the resulting residue was purified by column chromatography (SiO_2, gradient of 0 to 20 % Et_2O/40-60 P.E.). **38** was obtained as a white amorphous solid (0.169 mg, 0.480 mmol, 19 %).

TLC R_f = 0.30 (30 % Et_2O/40-60 P.E.)

mp T / °C = 78.8 (Et_2O/40-60 P.E.)

IR (neat) ν_{max} / cm^{-1} = 3337.0 (N-H), 2927.7 (C-H), 2857.1 (C-H), 1723.7 (carbamate C=O), 1634.5 (α,β unsaturated C=O), 1610.7 (C=C), 1580.9 (N-H bend)

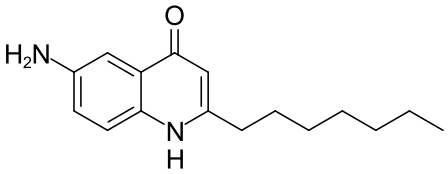
^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 10.16 (s, 1 H, N$\underline{H}$C(C_7H_{15})=C), 7.35 (d, J = 8.6 Hz, 2 H, *meta* to NHBoc), 7.02 (d, J = 8.7 Hz, 2 H, *meta* to enamine), 6.60 (br s, 1 H, N$\underline{H}$Boc), 4.71 (s, 1 H, C=C$\underline{H}$), 3.70 (s, 3 H, OC$\underline{H}_3$), 2.23 (t, J = 7.7 Hz, 2 H, C$\underline{H}_2$$CH_2CH_2CH_2CH_2CH_2CH_3$), 1.54 (s, 9 H, C(C$\underline{H}_3$)$_3$), 1.40 (quin, J = 7.3 Hz, 2 H, CH_2C$\underline{H}_2$$CH_2CH_2CH_2CH_2CH_3$), 1.33 - 1.16 (m, 8 H, CH_2CH_2C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}_2$$CH_3$), 0.86 (t, J = 7.1 Hz, 3 H, $CH_2CH_2CH_2CH_2CH_2CH_2$C$\underline{H}_3$)

^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 171.1 (C(=O)CH=C), 164.3 (C(=O)CH=C), 152.7 (OC(=O)NH), 136.0 (*para* to NHBoc), 134.1 (CNHBoc), 126.3 (*meta* to NHBoc), 119.1 (*ortho* to NHBoc), 83.8 (C(=O)CH=C), 80.7 (C(CH_3)$_3$), 50.2 (OCH_3), 32.2 (CH_2), 31.6 (CH_2), 29.1 (CH_2), 28.8 (CH_2), 28.3 (C(CH_3)$_3$), 28.0 (CH_2), 22.6 (CH_2), 14.0 (CH_3)

HRMS (ESI$^+$) m/z / Da = 391.2589, $[M+H]^+$, $[C_{22}H_{35}N_2O_4]^+$ requires 391.2591

Spectroscopic data are consistent with the literature.[4]

1.4 6-Amino-2-heptylquinolin-4-ol 39



Methyl (*E*)-3-((4-((*tert*-butoxycarbonyl)amino)phenyl)amino)dec-2-enoate **38** (168 mg, 0.649 mmol, 1 eq.) and polyphosphoric acid (5 g) were heated to 90 °C for 1 h. The reaction mixture was then poured into $NaHCO_3$ (sat., aq., 50 ml) cooled with ice. The precipitate was collected by vacuum filtration, washed with water (50 ml) and dried under high vacuum. **39** was obtained as a pale yellow amorphous solid (121 mg, 0.468 mmol, 72 %).

mp T / °C = 249 (H_2O)

IR (neat) ν_{max} / cm^{-1} = 3336.5 (N-H), 2926.5 (C-H), 2856.9 (C-H), 1634.5 (C=O),

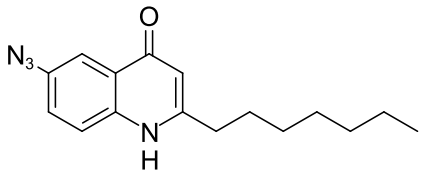
^{1}H NMR (400 MHz, DMSO-d_6) δ / ppm = 7.26 (d, J = 8.7 Hz, 1 H, *meta* to NH_2), 7.15 (d, J = 2.6 Hz, 1 H, *ortho* to C(=O)), 6.95 (dd, J = 2.7, 8.8 Hz, 1 H, *para* to C(=O)), 5.74 (s, 1 H, *ortho* to CH_2), 5.16 (s, 2 H, $N\underline{H}_2$), 2.52 (t, J = 7.4 Hz, 2 H, $CC\underline{H}_2$), 1.64 (quin, J = 7.6 Hz, 2 H, $CCH_2C\underline{H}_2$), 1.36 - 1.19 (m, 8 H, $C\underline{H}_2C\underline{H}_2C\underline{H}_2C\underline{H}_2CH_3$), 0.86 (t, J = 7.0 Hz, 3 H, $\underline{H}_3$)

^{13}C NMR (101 MHz, DMSO-d_6) δ / ppm = 176.7 ($\underline{C}$(=O)), 151.7 ($\underline{C}CH_2$), 145.1 (*para* to NH_2 or *ipso* to C(=O)), 132.4 (*ipso* to NH_2), 126.6 (*para* to NH_2 or *ipso* to C(=O)), 121.1 (*para* to C(=O)), 119.0 (*meta* to NH_2 and *meta* to C(=O)), 106.2 ($\underline{C}H$=CCH_2), 105.9 (*ortho* to NH_2 and *ortho* to C(=O)), 33.6 ($C\underline{C}H_2$), 31.6 ($\underline{C}H_2CH_2CH_3$), 29.0 ($\underline{C}H_2$), 29.0 ($\underline{C}H_2$), 28.9 ($\underline{C}H_2$), 22.5 ($\underline{C}H_2CH_3$), 14.4 ($\underline{C}H_3$)

HRMS (ESI^+) m/z / Da = 259.1810, $[M+H]^+$, $[C_{16}H_{23}N_2O]^+$ requires 259.1803

Spectroscopic data are consistent with the literature.[4]

1.5 6-Azido-2-heptylquinolin-4-ol 40



6-Amino-2-heptylquinolin-4-ol **39** (50 mg, 0.194 mmol, 1 eq) was dissolved in HCl (conc., aq., 1.20 ml), water (1.80 ml) and MeOH (2.00 ml) and cooled to 0 °C. A solution of $NaNO_2$ (16.0 mg, 0.232 mmol, 1.2 eq.) in water (0.300 ml) was added dropwise over 10 min and the mixture was stirred for 1 h. A solution of NaN_3 (15.1 mg, 0.232 mmol, 1.2 eq.) in water (0.300 ml) was then added. The mixture was warmed to room temperature and stirred for a further 4 h. The resultant precipitate was filtered off and dried under reduced pressure. **40** was obtained as a pale cream amorphous solid (25.6 mg, 0.0900 mmol, 46.5 %).

TLC R_f = 0.40 (5 % MeOH/CH_2Cl_2)

IR (neat) ν_{max} / cm^{-1} = 3249.3 (N-H), 3065.1 (N-H), 2916.6 (C-H), 2852.6 (C-H), 2728.1 (C-H), 2106.8 (azide), 1634.5 (C=O)

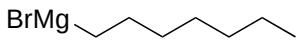
^{1}H NMR (400 MHz, MeOD) δ / ppm = 7.73 (d, J = 8.6 Hz, 1 H, *ortho* to NH), 7.71 (d, J = 2.8 Hz, 1 H, *ortho* to N_3 and *ortho* to C(=O)), 7.47 (dd, J = 8.9, 2.7 Hz, 1 H, *para* to C(=O)), 6.24 (s, 1 H, C(=O)C$\underline{H}$), 2.69 (t, J = 7.7 Hz, 2 H, $CC\underline{H}_2$), 1.68 (quin, J = 7.6 Hz, 2 H, $CCH_2C\underline{H}_2$), 1.28 - 1.39 (m, 4 H, $CCH_2CH_2C\underline{H}_2C\underline{H}_2$), 1.18 - 1.28 (m, 4 H, $C\underline{H}_2C\underline{H}_2CH_3$), 0.85 (t, J = 6.8 Hz, 3 H, $C\underline{H}_3$)

^{13}C NMR (101 MHz, MeOD) δ / ppm = 172.3 ($\underline{C}$(=O)), 155.5 ($NH\underline{C}CH_2$), 137.4 ($\underline{C}N_3$), 135.6 (*para* to N_3), 124.6 (*para* to C(=O)), 124.1 (*ipso* to C(=O)), 120.7 (*meta* to N_3 and *meta* to C(=O)), 112.8 (*ortho* to N_3 and *ortho* to C(=O)), 107.0 (C(=O)$\underline{C}$H), 33.3 ($NHC\underline{C}H_2$), 31.2 ($\underline{C}H_2CH_2CH_3$), 28.3 - 28.5 ($\underline{C}H_2\underline{C}H_2\underline{C}H_2CH_2CH_2CH_3$), 22.1 ($\underline{C}H_2CH_3$), 14.0 ($\underline{C}H_3$)

HRMS (ESI$^+$) m/z / Da = 285.1728, $[M+H]^+$ found, $[C_{16}H_{21}N_4O]^+$ requires 285.1715

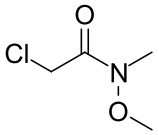
Spectroscopic data are not consistent with the literature.[4] ????

1.6 Heptyl magnesium bromide 42



Magnesium turnings (352 mg, 14.5 mmol, 1 eq.) were added to an oven-dried flask under argon. THF (15 ml) was added, followed by bromoheptane **41** (2.40 ml, 14.5 mmol, 1 eq.) dropwise. The mixture was stirred at r.t. for 2 h followed by heating to reflux for 2 h. Heptyl magnesium bromide **42** was obtained as a pale grey suspension (15 ml, ~ 1 M) which was used without further purification.

1.7 2-Chloro-*N*-methoxy-*N*-methylacetamide 45



N,*O*-Dimethylhydroxyl amine hydrochloride **43** (6.00 g, 61.5 mmol, 1 eq.) and toluene (75 ml) were added successively to a stirred solution of potassium carbonate (22.4 g, 162 mmol, 2.63 eq.) in water (75 ml) at 0 °C under argon. The mixture was cooled to - 5 °C and chloroacetyl chloride **44** (5.88 ml, 73.8 mmol, 1.20 eq.) was added dropwise over 5 min. The mixture was allowed to warm to r.t. over 30 min, then the organic layer was separated and the aqueous layer was extracted with toluene (3×20 ml). The combined organic extracts were dried with $MgSO_4$ and the solvent was removed by rotary evaporation followed by high vacuum. **45** was obtained as white, prism-like crystals (7.24 g, 52.6 mmol, 71 %).

mp T / °C = 38.8 (toluene)

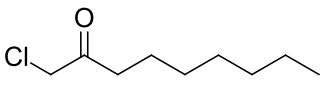
IR (neat) ν_{max} / cm^{-1} = 3016.7 (C-H), 2966.4 (C-H), 2946.7 (C-H), 2827.7 (C-H), 1666.2 (C=O)

^{1}**H NMR** (400 MHz, $CDCl_3$) δ / ppm = 4.20 (s, 2 H, ClC$\underline{H}_2$C=O), 3.71 (m, 3 H, OC$\underline{H}_3$), 3.18 (s, 3 H, NC$\underline{H}_3$)

^{13}**C NMR** (101 MHz, $CDCl_3$) δ / ppm = 167.4 (C=O), 61.6 (O$\underline{C}H_3$), 40.9 (Cl$\underline{C}H_2$C=O), 32.6 (N$\underline{C}H_3$)

Spectroscopic data are consistent with the literature.[5]

1.8 1-Chlorononan-2-one 46



2-Chloro-*N*-methoxy-*N*-methylacetamide **45** (1.00 g, 7.26 mmol, 1 eq.) was added to a dry flask under argon. THF (20 ml) was added and the flask cooled to 0 °C. Heptyl magnesium bromide **42** (~ 1 M, 15.0 ml, 15.0

mmol, 2.07 eq.) was added dropwise over 5 min, then the mixture was allowed to warm to r.t. and stirred for 15 h. The reaction mixture was then poured into HCl (aq., 2 N, 60 ml) at 0 °C and stirred for 10 min. The mixture was extracted with toluene (30 ml) and the aqueous layer discarded. The organic layer was washed with brine and dried with $MgSO_4$, and the solvent was removed by rotary evaporation. **46** was obtained as a colourless oil (1.23 g, 6.96 mmol, 96 %).

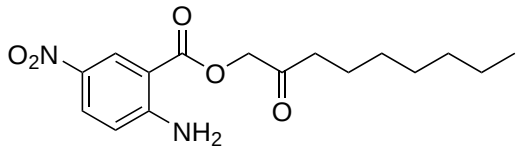
IR (neat) ν_{max} / cm^{-1} = 2951.7 (C-H), 2925.0 (C-H), 2855.5 (C-H), 1720.4 (C=O)

^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 4.05 (s, 2 H, ClC$\underline{H}_2$C(=O)), 2.54 (t, J = 7.4 Hz, 2 H, C(=O)C$\underline{H}_2$$CH_2$), 1.59 (quin, J = 7.0 Hz, 2 H, C(=O)CH_2C$\underline{H}_2$), 1.34 - 1.21 (m, 8 H, C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}_2$$CH_3$), 0.87 (t, J = 6.8 Hz, 3 H, C$\underline{H}_3$)

^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 202.6 ($\underline{C}$(=O)), 48.1 ($\underline{C}H_2$Cl), 39.6 (C(=O)$\underline{C}H_2$$CH_2$), 31.5 ($\underline{C}H_2$$CH_2$ CH_3), 28.9 ($\underline{C}H_2$), 28.9 ($\underline{C}H_2$), 23.5 (C(=O)$CH_2$$\underline{C}H_2$), 22.5 ($\underline{C}H_2$$CH_3$), 13.9 ($\underline{C}H_3$)

Spectroscopic data are consistent with the literature.[5]

1.9 2-Oxononyl 2-amino-5-nitrobenzoate 48



5-Nitroanthranilic acid **47** (500 mg, 2.75 mmol, 1.38 eq.) and potassium carbonate (270 mg, 2.00 mmol, 1 eq.) were dissolved in DMF (5 ml). The mixture was heated under argon to 90 °C and stirred for 1 h then cooled to r.t.. 1-Chlorononan-2-one **46** (353 mg, 2.00 mmol, 1 eq.) was added and the mixture was stirred for 15 h. The solution was poured into Na_2HCO_3 (aq., 10 %, 50 ml) and ice (~ 20 g). The precipitate was collected by vacuum filtration, washed with water and dried under high vacuum. **48** was obtained as a yellow amorphous solid (0.674 g, 2.00 mmol, 100 %).

mp T / °C = 135 (H_2O)

IR (neat) ν_{max} / cm^{-1} = 3453.3 (N-H), 3350.5 (N-H), 2924.9 (C-H), 2853.9 (C-H), 1720.1 (ester C=O) 1703.9 (ketone C=O) 1626.1 (N-H bend) 1602.7 (aromatic) 1572.5 (N-O) 1506.6 (N-O)

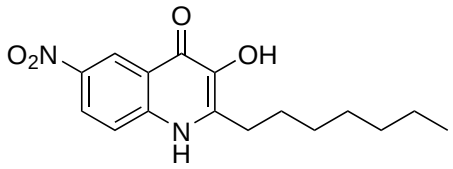
^{1}H NMR (400 MHz, DMSO-d_6) δ / ppm = 8.66 (d, J = 2.8 Hz, 1 H, *ortho* to C(=O)), 8.12 (dd, J = 2.8, 9.4 Hz, 1 H, *para* to C(=O)), 6.93 (d, J = 9.4 Hz, 1 H, *meta* to C(=O)), 5.05 (s, 2 H, OC$\underline{H}_2$C(=O)), 2.49 (t, J = 7.4 Hz, 2 H, C(=O)C$\underline{H}_2$$CH_2$), 1.52 (quin, J = 7.2 Hz, 2 H, C(=O)CH_2C$\underline{H}_2$), 1.32 - 1.20 (m, 8 H, C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}_2$$CH_3$), 0.86 (t, J = 6.8 Hz, 3 H, C$\underline{H}_3$)

^{13}C NMR (101 MHz, DMSO-d_6) δ / ppm = 204.4 (OC$H_2$$\underline{C}$(=O)), 165.6 ($\underline{C}$(=O)O), 156.3 (*ipso* to NH_2), 135.7 (*ipso* to NO_2), 129.6 (*para* to C(=O)), 128.9 (*ortho* to C(=O)), 117.4 (*meta* to C(=O)), 107.5 (*ipso* to C(=O)), 68.8 (O$\underline{C}H_2$C(=O)), 38.3 (C(=O)$\underline{C}H_2$$CH_2$), 31.6 ($\underline{C}H_2$$CH_2$$CH_3$), 28.9 ($\underline{C}H_2$), 28.9 ($\underline{C}H_2$), 23.2 (C(=O)$CH_2$$\underline{C}H_2$), 22.5 ($\underline{C}H_2$$CH_3$), 14.4 ($\underline{C}H_3$)

HRMS (ESI$^+$) m/z / Da = 323.1610, $[M+H]^+$, $[C_{16}H_{23}N_2O_5]^+$ requires 323.1607

Spectroscopic data are consistent with the literature.[4]

1.10 6-Nitro-2-heptyl-3-hydroxyquinolin-4(1*H*)-one 49



2-Oxononyl 2-amino-5-nitrobenzoate **48** (100 mg, 0.340 mmol, 1 eq.) and polyphosphoric acid (300 mg) were stirred for 5.5 h at 90 °C under argon. The mixture was then poured into $NaHCO_3$ (sat., aq., 50 ml) cooled on ice. The precipitate was collected by vacuum filtration, washed with water (50 ml) and dried under high vacuum. **49** was obtained as a yellow-brown amorphous solid (44 mg, 0.145 mmol, 43 %).

mp T / °C = 223 (H_2O, EtOAc)

IR (neat) ν_{max} / cm^{-1} = 3436.0 (N-H), 3000.0 (O-H, br), 2955.4 (C-H), 2925.8 (C-H), 2850.9 (C-H), 1648.2 (C=O), 1570.7 (N-O), 1536.4 (N-O)

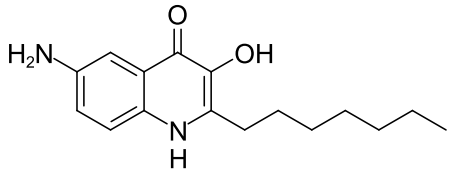
^{1}H NMR (400 MHz, DMSO-d_6) δ / ppm = 12.00 (s, 1 H, N$\underline{H}$), 8.91 (d, J = 2.8 Hz, 1 H, *ortho* to C=O), 8.29 (dd, J = 2.7, 9.2 Hz, 1 H, *para* to C=O), 7.70 (d, J = 9.3 Hz, 1 H, *meta* to C=O), 2.75 (t, J = 7.7 Hz, 2 H, CC$\underline{H}_2$), 1.67 (quin, J = 7.3 Hz, 2 H, $CCH_2C\underline{H}_2$), 1.36 - 1.23 (m, 8 H, $C\underline{H}_2C\underline{H}_2C\underline{H}_2C\underline{H}_2CH_3$), 0.85 (t, J = 7.0 Hz, 3 H, $C\underline{H}_3$)

^{13}C NMR (101 MHz, DMSO-d_6) δ / ppm = 169.7 ($\underline{C}$=O), 141.9 (*para* to NO_2), 140.7 (*ipso* to NO_2), 139.6 (*ipso* to OH), 137.3 ($\underline{C}$=COH), 124.3 (*para* to C=O), 122.3 (*ortho* to NO_2 and *ortho* to C=O), 121.5 (*ipso* to C=O), 120.0 (*meta* to NO_2 and *meta* to C=O), 31.6 ($\underline{C}H_2CH_2CH_3$), 29.2 ($\underline{C}H_2$), 28.9 ($\underline{C}H_2$), 28.5 ($C\underline{C}H_2$), 28.1 ($CCH_2\underline{C}H_2$), 22.5 ($\underline{C}H_2CH_3$), 14.4 ($\underline{C}H_3$)

HRMS (ESI^+) m/z / Da = 305.1501, $[M+H]^+$, $[C_{16}H_{21}N_2O_4]^+$ requires 305.1500

Spectroscopic data are consistent with the literature.[4]

1.11 6-Amino-2-heptyl-3-hydroxyquinolin-4(1*H*)-one 50



6-Nitro-2-heptyl-3-hydroxyquinolin-4(1*H*)-one **49** (20 mg, 0.0658 mmol, 1 eq.) and PtO_2 (2 mg, 10 weight %) were stirred in MeOH (1 ml) under a H_2 atmosphere for 45 min at room temperature and pressure. The reaction mixture was then filtered through celite and the solvent was removed under vacuum. **50** was obtained as a yellow-brown amorphous solid (14.5 mg, 0.0529 mmol, 80 %).

mp (MeOH) T / °C = 176

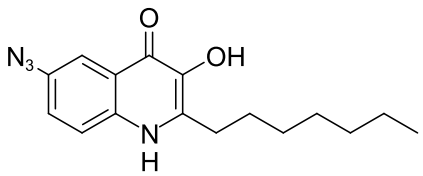
IR (neat) ν_{max} / cm^{-1} = 3000.00 (O-H, br) 2925.41 (C-H), 2854.09 (C-H), 1613.43 (C=O)

^{1}H NMR (400 MHz, MeOD) δ / ppm = 11.12 (s, 1 H, NH), 7.47 (d, J = 8.9 Hz, 1 H, *meta* to C=O), 7.40 (d, J = 2.4 Hz, 1 H, *ortho* to C=O), 7.16 (dd, J = 2.6, 9.0 Hz, 1 H, *para* to C=O), 2.86 (t, J = 7.5 Hz, 2 H, CCH_2), 1.75 (quin, J = 7.8 Hz, 2 H, CCH_2CH_2), 1.48 - 1.22 (m, J = 5.4 Hz, 8 H, $CH_2CH_2CH_2CH_2CH_3$), 0.89 (t, J = 6.7 Hz, 3 H, CH_3)

^{13}C NMR (101 MHz, MeOD) δ / ppm = 166.8 (C(=O)), 144.8 (*para* to NH_2 or *ipso* to C(=O)), 140.5 (*ipso* to COH), 138.6 (C=COH), 132.6 (*ipso* to NH_2), 124.8 (*para* to NH_2 or *ipso* to C(=O)), 123.8 (*para* to C(=O)), 107.7 (*meta* to NH_2 and *meta* to C(=O)), 106.4 (*ortho* to NH_2 and *ortho* to C(=O)), 33.0 ($CH_2CH_2CH_3$), 29.5 - 31.0 ($CCH_2CH_2CH_2CH_2$), 23.8 (CH_2CH_3), 14.5 (CH_3)

HRMS (ESI$^+$) m/z / Da = 275.1760, $[M+H]^+$, $[C_{16}H_{23}N_2O_2]^+$ requires 275.1762 Spectroscopic data are not consistent with the literature.[4] It is possible that Baker's product is a Zn adduct.

1.12 6-Azido-2-heptyl-3-hydroxyquinolin-4(1*H*)-one 51



6-Amino-2-heptyl-3-hydroxyquinolin-4(1*H*)-one **50** (18.2 mg, 0.0664 mmol, 1 eq.) was dissolved in HCl (conc., aq., 0.8 ml) and MeOH (0.5 ml) at 0 °C. $NaNO_2$ (5.0 mg, 0.0725 mmol, 1.09 eq.) in H_2O (0.2 ml) was added dropwise over 2 min and the mixture was stirred at 0 °C for 50 min, during which time the solution turned from yellow to orange. NaN_3 (4.9 mg, 0.0754 mmol, 1.14 eq.) in H_2O (0.2 ml) was then added and the mixture was allowed to warm to r.t. and stirred for 4 h. The reaction mixture was then filtered and the solid was dried under reduced pressure. **51** was obtained as a brown amorphous solid (5.5 mg, 0.0183 mmol, 28 %).

IR (neat) ν_{max} / cm^{-1} = pending — don't have?

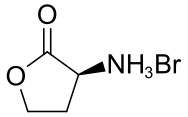
^{1}H NMR (400 MHz, DMSO-d_6) δ / ppm = 7.74 (s, 1 H, *ortho* to C=O), 7.65 (d, J = 6.9 Hz, 1 H, *meta* to C(=O)), 7.32 (d, J = 7.4 Hz, 1 H, *para* to C(=O)), 2.75 (t, J = 7.5 Hz, 2 H, CCH_2), 1.67 (quin, J = 6.4 Hz, 2 H, CCH_2CH_2), 1.43 - 1.13 (m, 8 H, $CH_2CH_2CH_2CH_2CH_3$), 0.85 (t, J = 6.8 Hz, 3 H, CH_3)

^{13}C NMR (101 MHz, DMSO-d_6) δ / ppm = pending — don't have?

HRMS (ESI$^+$) m/z / Da = pending, $[M+H]^+$, $[C_{16}H_{21}N_4O_2]^+$ requires 301.1659 — try?

Spectroscopic data are consistent with the literature.[4]

1.13 (*S*)-3-Aminodihydrofuran-2(3*H*)-one hydrobromide 54



L-Methionine **52** (3.04 g, 20.4 mmol, 1 eq.) and bromoacetic acid **53** (3.08 g, 22.2 mmol, 1.09 eq.) were dissolved in *i*-PrOH (12.5 ml), H_2O (12.5 ml) and AcOH (5 ml). The reaction was refluxed for 15 h then concentrated under vacuum. The resulting brown oil was added to a mixture of *i*-PrOH (16 ml) and HBr (33 % in AcOH, 4 ml), causing the precipitation of a pale pink amorphous solid. The precipitate was collected by filtration and washed with *i*-PrOH (20 ml). The filtrate was concentrated under vacuum and precipitated again using the same procedure. The two crops of precipitate were combined. **54** was obtained as a pale pink amorphous solid (1.73 g, 9.50 mmol, 41 % yield).

mp T / °C = 242 (*i*-PrOH/AcOH, gas evolved)

IR (neat) ν_{max} / cm^{-1} = 2972.1 (N-H), 2877.5 (N-H), 1771.8 (C=O), 1585.1 (N-H bend), 1572.2 (N-H bend)

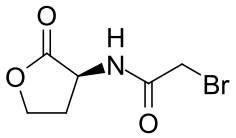
^{1}H NMR (400 MHz, DMSO-d_6) δ / ppm = 8.59 (br s, 3 H, $N\underline{H}_3^+$), 4.46 (dt, J = 1.3, 8.9 Hz, 1 H, $OC\underline{H}H$), 4.37 (dd, J = 8.8, 11.4 Hz, 1 H, $C\underline{H}NH_3^+$), 4.29 (ddd, J = 6.1, 8.8, 10.9 Hz, 1 H, $OCH\underline{H}$), 2.57 (dddd, J = 1.2, 6.1, 8.9, 12.3 Hz, 1 H, $OCH_2C\underline{H}H$), 2.26 (dtd, J = 9.0, 11.2, 12.2 Hz, 1 H, $OCH_2CH\underline{H}$)

^{13}C NMR (101 MHz, DMSO-d_6) δ / ppm = 173.3 ($\underline{C}$=O), 66.2 (O$\underline{C}H_2$), 47.8 ($\underline{C}HNH_3^+$), 27.0 ($OCH_2\underline{C}H_2$)

$[\boldsymbol{\alpha}]_D^{20}$ / °$10^{-1}cm^2g^{-1}$ = -30.0, lit. = -25.0 (c / g(100 ml)$^{-1}$ = 0.0200, DMSO)

The data are consistent with the literature.[6]

1.14 (*S*)-2-Bromo-*N*-(2-oxotetrahydrofuran-3-yl)acetamide 56



(*S*)-3-Aminodihydrofuran-2(3*H*)-one hydrobromide **54** (100 mg, 0.549 mmol, 1.08 eq.) and $NaHCO_3$ (84.9 mg, 1.01 mmol, 2.00 eq.) were dissolved in CH_2Cl_2 (2 ml) and H_2O (2 ml). Bromoacetyl bromide **55** (44.0 μL, 102 mg, 0.505 mmol, 1.00 eq.) was then added dropwise. The reaction mixture was stirred for 24 h, after which the CH_2Cl_2 was removed under vacuum. The aqueous phase was extracted with EtOAc (4×10 ml). The combined organic layers were dried with $MgSO_4$ and the solvent was removed under reduced pressure. **56** was obtained as white, needle-like crystals (88.0 mg, 0.396 mmol, 74 %).

mp T / °C = 132 (EtOAc)

IR (neat) ν_{max} / cm^{-1} = 3255.7 (N-H), 3066.6 (C-H), 1763.0 (lactone C=O), 1658.0 (amide C=O), 1552.7 (N-H bend)

^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 6.94 (br s, 1 H, N<u>H</u>), 4.57 (ddd, J = 11.7, 8.6, 5.9 Hz, 1 H, C<u>H</u>NH), 4.51 (td, J = 9.2, 1.0 Hz, 1 H, OC<u>H</u>H), 4.32 (ddd, J = 11.3, 9.4, 5.9 Hz, 1 H, OCH<u>H</u>), 3.93 (s, 1 H, C<u>H</u>HBr), 3.93 (s, 1 H, CH<u>H</u>Br), 2.87 (dddd, J = 12.6, 8.6, 5.9, 1.3 Hz, 1 H, OCH_2C<u>H</u>H), 2.22 (dtd, J = 12.6, 11.5, 11.5, 8.9 Hz, 1 H, OCH_2CH<u>H</u>)

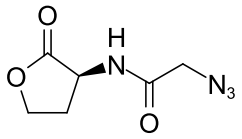
^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 174.6 (O<u>C</u>=O), 166.4 (<u>C</u>(=O)NH), 66.1 (O<u>C</u>H_2), 49.8 (<u>C</u>HNHC=O), 29.9 (OCH_2<u>C</u>H_2), 28.2 (O=C<u>C</u>H_2Br)

HRMS The compound does not ionise.

$[\boldsymbol{\alpha}]_D^{20}$ / °10^{-1}cm^{2}g^{-1} = 27.0, lit. = 20.5 (c / g(100 ml)$^{-1}$ = 0.00740, $CHCl_3$)

The data are consistent with the literature.[6,7]

1.15 (*S*)-2-Azido-*N*-(2-oxotetrahydrofuran-3-yl)acetamide 57



(3*S*)-2-Oxotetrahydrofuran-3-aminium bromide **54** (100 mg, 0.552 mmol, 1.08 eq.), NaN_3 (85.7 mg, 1.32 mmol, 2.61 eq.) and $NaHCO_3$ (84.9 mg, 1.01 mmol, 2.00 eq.) were dissolved in CH_2Cl_2 (2 ml) and H_2O (2 ml). Bromoacetyl bromide **55** (44.0 μL, 102 mg, 0.505 mmol, 1.00 eq.) was then added dropwise. The reaction mixture was stirred for 48 h, after which the CH_2Cl_2 was removed under vacuum. The aqueous phase was extracted with EtOAc (4×10 ml). The combined organic layers were dried with $MgSO_4$ and the solvent was removed under reduced pressure. **57** was obtained as white, needle-like crystals (38.4 mg, 0.209 mmol, 41 %).

mp T / °C = 87 (EtOAc)

IR (neat) ν_{max} / cm^{-1} = 3283.5 (N-H), 2923.3 (C-H), 2853.0 (C-H), 2129.7 (N_3), 1782.9 (lactone C=O), 1661.4 (amide C=O), 1536.8 (N-H bend)

^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 7.05 (br d, J = 6.5 Hz, 1 H, N<u>H</u>), 4.64 (ddd, J = 11.6, 8.7, 6.8 Hz, 1 H, C<u>H</u>NH), 4.48 (td, J = 9.1, 1.3 Hz, 1 H, OC<u>H</u>H), 4.30 (ddd, J = 11.2, 9.2, 6.0 Hz, 1 H, OCH<u>H</u>), 4.04 (s, 2 H, C<u>H$_2$</u>N_3), 2.76 (dddd, J = 12.5, 8.8, 6.0, 1.4 Hz, 1 H, OCH_2C<u>H</u>H), 2.25 (dtd, J = 12.5, 11.4, 11.4, 8.9 Hz, 1 H, OCH_2CH<u>H</u>)

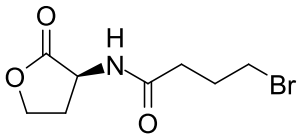
^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 174.9 (O<u>C</u>=O), 167.5 (<u>C</u>=ONH), 66.0 (O<u>C</u>H_2), 52.2 (O=C<u>C</u>H_2N_3), 48.9 (<u>C</u>HNHC=O), 29.7 (OCH_2<u>C</u>H_2)

HRMS The compound does not ionise.

$[\boldsymbol{\alpha}]_D^{20}$ / °10^{-1}cm^{2}g^{-1} = -32.6, lit. = -24.4 (c / g(100 ml)$^{-1}$ = 0.0430, DMSO)

The data are consistent with the literature.[6]

1.16 (*S*)-4-Bromo-*N*-(2-oxotetrahydrofuran-3-yl)butanamide 59



(*S*)-3-Aminodihydrofuran-2(3*H*)-one hydrobromide **54** (200 mg, 1.10 mmol, 1.00 eq.) and $NaHCO_3$ (170 mg, 2.02 mmol, 1.84 eq.) were dissolved in CH_2Cl_2 (2 ml) and H_2O (2 ml). Bromobutyryl chloride **58** (140 μL, 224 mg, 1.21 mmol, 1.10 eq.) was then added dropwise. The reaction mixture was stirred for 1 h, after which the CH_2Cl_2 was removed under vacuum. The aqueous phase was extracted with EtOAc (7×5 ml) and the combined organic layers were dried with $MgSO_4$. The solvent was removed under vacuum to give white crystals which were recrystallised from EtOAc. **59** was obtained as white, needle-like crystals (219 mg, 0.878 mmol, 80 %).

mp T / °C = 105 (EtOAc)

IR (neat) ν_{max} / cm^{-1} = 3307.9 (N-H), 3073.9 (C-H), 2948.9 (C-H), 1773.7 (lactone C=O), 1643.5 (amide C=O), 1541.4 (N-H bend)

^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 6.31 (br d, J = 5.5 Hz, 1 H, NH), 4.59 (ddd, J = 6.2, 8.7, 11.5 Hz, 1 H, CHNH), 4.48 (dt, J = 1.2, 8.9 Hz, 1 H, OCHH), 4.30 (ddd, J = 5.8, 9.3, 11.3 Hz, 1 H, OCHH), 3.49 (t, J = 6.3 Hz, 2 H, CH_2Br), 2.82 (dddd, J = 1.3, 5.9, 8.7, 12.5 Hz, 1 H, OCH_2CHH), 2.47 (t, J = 7.3 Hz, 2 H, C(=O)CH_2), 2.26 - 2.15 (m, 3 H, OCH_2CHH and CH_2CH_2Br)

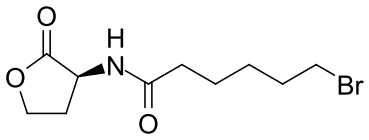
^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 175.4 (OC=O), 172.3 (C(=O)NH), 66.1 (OCH_2), 49.3 (CHNHC=O), 33.9 (C(=O)CH_2), 33.1 (CH_2Br), 30.3 (OCH_2CH_2), 27.9 (C(=O)CH_2CH_2)

HRMS The compound does not ionise.

$[\alpha]_D^{26.6}$ / °$10^{-1}cm^2g^{-1}$ = -78 (c / g(100 ml)$^{-1}$ = 0.0833, MeOH)

The compound has not been reported previously.

1.17 (*S*)-6-Bromo-*N*-(2-oxotetrahydrofuran-3-yl)hexanamide 62



(*S*)-3-Aminodihydrofuran-2(3*H*)-one hydrobromide **54** (100 mg, 0.549 mmol, 1.00 eq.) and $NaHCO_3$ (84.9 mg, 1.01 mmol, 1.84 eq.) were dissolved in CH_2Cl_2 (2 ml) and H_2O (2 ml) at r.t.. Bromohexanoyl chloride **61** (93.0 μL, 130 mg, 0.608 mmol, 1.11 eq.) was then added dropwise. The reaction mixture was stirred for 4 h, after which the CH_2Cl_2 was removed under vacuum. The mixture was then filtered, washed with H_2O (10 ml) and dried under high vacuum. **62** was obtained as white, needle-like crystals (101 mg, 0.362 mmol, 66 %).

mp T / °C = 106 (CH_2Cl_2/H_2O)

IR (neat) ν_{max} / cm^{-1} = 3300.3 (N-H), 3067.6 (C-H), 2937.4 (C-H), 2856.7 (C-H), 1784.8 (lactone C=O), 1639.3 (amide C=O), 1539.9 (N-H bend)

^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 6.09 (br d, J = 5.7 Hz, 1 H, NH), 4.57 (ddd, J = 5.9, 8.6, 11.6 Hz, 1 H, CHNH), 4.50 (dt, J = 1.3, 9.1 Hz, 1 H, OCHH), 4.31 (ddd, J = 5.9, 9.3, 11.3 Hz, 1 H, OCHH), 3.43 (t, J = 6.7 Hz, 2 H, CH_2Br), 2.88 (dddd, J = 1.3, 5.9, 8.6, 12.6 Hz, 1 H, OCH_2CHH), 2.30 (dt, J = 1.8, 7.5 Hz, 2 H, C(=O)CH_2), 2.16 (dtd, J = 8.9, 11.5, 12.5 Hz, 1 H, OCH_2CHH), 1.90 (quin, J = 7.2 Hz, 2 H, CH_2CH_2Br), 1.71 (quin, J = 7.6 Hz, 2 H, C(=O)CH_2CH_2), 1.59 - 1.46 (m, 2 H, C(=O)$CH_2CH_2CH_2$)

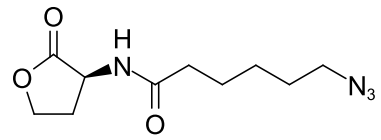
^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 175.5 (OC=O), 173.3 (C(=O)NH), 66.1 (OCH_2), 49.3 (CHNHC=O), 35.8 (CH_2Br), 33.5 (C(=O)CH_2), 32.3 (CH_2CH_2Br), 30.5 (OCH_2CH_2), 27.6 (C(=O)CH_2CH_2), 24.4 (C(=O)CH_2 CH_2CH_2)

HRMS (ESI^+) m/z / Da = 278.0381, $[M+H]^+$, $[C_{10}H_{17}BrNO_3]^+$ requires 278.0386

$[\alpha]_D^{26.6}$ / $°10^{-1}cm^2g^{-1}$ = -16 (c / g(100 ml)$^{-1}$ = 0.208, MeOH)

The compound has not been reported previously.

1.18 (*S*)-6-Azido-*N*-(2-oxotetrahydrofuran-3-yl)hexanamide 63



(*S*)-6-Bromo-*N*-(2-oxotetrahydrofuran-3-yl)hexanamide **62** (80 mg, 0.320 mmol, 1.00 eq.) and NaN_3 (26.3 mg, 0.405 mmol, 1.27 eq.) were heated in DMF (0.5 ml) for 5 h at 100 °C. The reaction mixture was then partitioned between CH_2Cl_2 (5 ml) and H_2O (5 ml). The aqueous phase was extracted twice more with CH_2Cl_2 (2×5 ml) and the organic layers were combined and dried over $MgSO_4$. The solvent was removed by rotary evaporation followed by high vacuum. **63** was obtained as white, needle-like crystals (42.7 mg, 0.178 mmol, 56 %).

mp T / °C = 90.0 (CH_2Cl_2)

IR (neat) ν_{max} / cm^{-1} = 3314.0 (N-H), 2931.6 (C-H), 2862.9 (C-H), 2095.1 (N_3), 1775.4 (lactone C=O), 1643.1 (amide C=O), 1547.9 (N-H bend)

^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 5.96 (d, J = 4.2 Hz, 1 H, NH), 4.54 (ddd, J = 11.7, 8.6, 5.7 Hz, 1 H, CHNH), 4.49 (td, J = 9.1, 1.0 Hz, 1 H, OCHH), 4.30 (ddd, J = 11.3, 9.4, 5.8 Hz, 1 H, OCHH), 3.29 (t, J = 6.9 Hz, 2 H, CH_2N_3), 2.88 (dddd, J = 12.5, 8.6, 5.8, 1.1 Hz, 1 H, OCH_2CHH), 2.28 (t, J = 7.5 Hz, 1 H, C(=O)CHH), 2.28 (t, J = 7.4 Hz, 1 H, C(=O)CHH), 2.14 (dtd, J = 12.3, 11.5, 11.5, 8.8 Hz, 1 H, OCH_2CHH), 1.70 (quin, J = 7.6 Hz, 2 H, $CH_2CH_2N_3$), 1.63 (quin, J = 7.2 Hz, 2 H, C(=O)CH_2CH_2), 1.38 - 1.49 (m, 2 H, C(=O)$CH_2CH_2CH_2$)

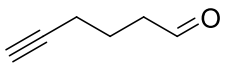
^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 175.4 (OC=O), 172.2 (C(=O)NH), 66.1 (OCH_2), 51.2 (CH_2N_3), 49.4 (CHNHC=O), 35.9 (C(=O)CH_2), 30.7 (OCH_2CH_2), 28.6 ($CH_2CH_2N_3$), 26.3 (C(=O)CH_2CH_2), 24.8 (C(=O)CH_2 CH_2CH_2)

HRMS (ESI$^+$) m/z / Da = 241.1289, $[M+H]^+$, $[C_{10}H_{17}N_4O_3]^+$ requires 241.1295

$[\alpha]_D^{26.6}$ / $^\circ 10^{-1} cm^2 g^{-1}$ = -16 (c / g(100 ml)$^{-1}$ = 0.208, MeOH)

The compound has not been reported previously.

1.19 Hex-5-ynal 65



Pyridinium chlorochromate (14.6 g, 68.1 mmol, 1.50 eq) and DCM (500 ml) were stirred at r.t. under argon. 5-Hexyn-1-ol **64** (5.00 ml, 45.4 mmol, 1 eq.) was added and the reaction mixture was stirred for 5 h followed by addition of Et_2O (125 ml) and silica gel (62.5 g). The suspension was stirred for 1 h then filtered through a pad of silica (100 g) and washed with Et_2O. The solvent was removed by rotary evaporation. **65** was obtained as a pale yellow-green oil (4.72 g, 49.1 mmol, 72 %).

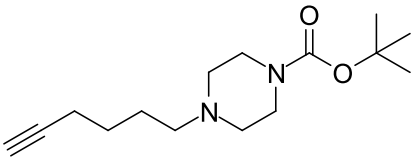
IR (neat) ν_{max} / cm^{-1} = 3292.7 (alkyne C-H), 2943.3 (alkane C-H), 2830.9 (aldehyde C-H), 2728.6 (aldehyde C-H), 1720.3 (aldehyde C=O)

^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 9.80 (s, 1 H, C(=O)$\underline{H}$), 2.60 (t, J = 7.1 Hz, 2 H, C$\underline{H}_2$C(=O)H), 2.26 (dt, J = 2.6, 6.8 Hz, 2 H, HC≡CC$\underline{H}_2$), 1.98 (t, J = 2.7 Hz, 1 H, $\underline{H}$C≡C), 1.85 (quin, J = 7.0 Hz, 2 H, HC≡CCH$_2$C$\underline{H}_2$)

^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 201.6 ($\underline{C}$(=O)), 83.1 (HC≡$\underline{C}$), 69.3 (H$\underline{C}$≡C), 42.4 ($\underline{C}$H$_2$C(=O)), 20.7 ($\underline{C}$H$_2$CH$_2$C(=O)), 17.6 (HC≡C$\underline{C}$H$_2$)

Spectroscopic data are consistent with the literature.[8]

1.20 *tert*-Butyl 4-(hex-5-yn-1-yl)piperazine-1-carboxylate 67



Hex-5-ynal **65** (0.407 g, 4.24 mmol, 1.00 eq.) and *tert*-butyl piperazine-1-carboxylate **66** (0.791 g, 4.24 mmol, 1.00 eq.) were stirred under a N_2 atmosphere in 1,2-dichloroethane (20 ml) for 2.5 h followed by addition of sodium triacetoxyborohydride (6.25 g, 29.5 mmol, 7 eq.) in four portions over 4 d. The mixture was stirred for a further day then $NaHCO_3$ (sat., aq., 120 ml) was added and the product extracted with EtOAc (2×100 ml). The solvent was dried over $MgSO_4$ and removed by rotary evaporation. **67** was obtained as a colourless liquid (1.12 g, 4.21 mmol, 99 %).

TLC R_f (10 % MeOH/CH_2Cl_2) = 0.55

IR (neat) ν_{max} / cm^{-1} = 3303.6 (alkyne C-H), 2940.0 (alkane C-H), 2865.2 (C-H), 2810.4 (C-H), 1691.3

(carbamate C=O)

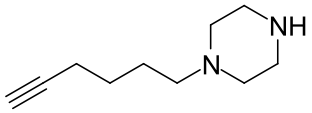
^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 3.44 (t, J = 5.2 Hz, 4 H, $CH_2CH_2CH_2N(CH_2C\underline{H}_2)CH_2C\underline{H}_2$), 2.39 (t, J = 5.1 Hz, 4 H, $CH_2CH_2CH_2N(C\underline{H}_2)C\underline{H}_2$), 2.37 (t, J = 7.3 Hz, 2 H, $CH_2CH_2C\underline{H}_2N$), 2.23 (dt, J = 2.7, 6.8 Hz, 2 H, $HC{\equiv}CC\underline{H}_2$), 1.96 (t, J = 2.7 Hz, 1 H, $\underline{H}C{\equiv}C$), 1.65 - 1.53 (m, 4 H, $HC{\equiv}CCH_2C\underline{H}_2C\underline{H}_2$), 1.47 (s, 9 H, $C\underline{H}_3$)

^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 154.7 ($N\underline{C}(=O)O$), 84.2 ($HC{\equiv}\underline{C}$), 79.6 ($\underline{C}(CH_3)_3$), 68.5 ($H\underline{C}{\equiv}C$), 60.4 ($CH_2CH_2\underline{C}H_2N$), 58.0 ($CH_2CH_2CH_2N(\underline{C}H_2)\underline{C}H_2$), 53.0 ($CH_2CH_2CH_2N(CH_2\underline{C}H_2)CH_2\underline{C}H_2$), 28.4 ($C(\underline{C}H_3)_3$), 26.3 ($\underline{C}H_2CH_2N$), 25.7 ($HC{\equiv}CCH_2\underline{C}H_2$), 18.3 ($HC{\equiv}C\underline{C}H_2$)

HRMS (ESI$^+$) m/z / Da = 267.2073, $[M+H]^+$, $[C_{15}H_{27}N_2O_2]^+$ requires 267.2064

The compound has not been reported previously.

1.21 1-(Hex-5-yn-1-yl)piperazine 68



tert-Butyl 4-(hex-5-yn-1-yl)piperazine-1-carboxylate **67** (763 mg, 2.86 mmol) was stirred in TFA (10 ml) at r.t. for 2 h. The TFA was removed under vacuum followed by co-evaporation with CH_2Cl_2 (2×20 ml). The oil was diluted with H_2O (10 ml) and the pH adjusted to 14 with NaOH (10 % aq.). This mixture was extracted with CH_2Cl_2 (2×20 ml) and the combined organic layers were dried over $MgSO_4$. The solvent was removed under vacuum and purified by column chromatography (SiO_2 MeOH/CH_2Cl_2 3:7). **68** was obtained as a colourless liquid (476 mg, 2.86 mmol, 100 %).

TLC R_f (30 % MeOH/CH_2Cl_2) = 0.20

IR (neat) ν_{max} / cm^{-1} = 3295.9 (alkyne C-H), 2941.1 (alkane C-H), 2810.6 (alkane C-H), 1637.2 (N-H bend)

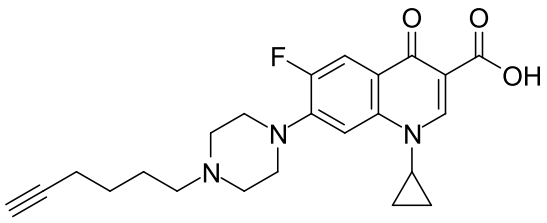
^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 2.88 (t, J = 4.9 Hz, 4 H, $CH_2CH_2CH_2N(CH_2C\underline{H}_2)CH_2C\underline{H}_2$), 2.39 (m, 4 H, $CH_2CH_2CH_2N(C\underline{H}_2)C\underline{H}_2$), 2.31 (t, J = 7.1 Hz, 2 H, $HC{\equiv}CCH_2CH_2CH_2C\underline{H}_2N$), 2.20 (dt, J = 2.7, 6.8 Hz, 2 H, $HC{\equiv}CC\underline{H}_2$), 2.05 (br s, 1 H, $N\underline{H}$), 1.93 (t, J = 2.7 Hz, 1 H, $\underline{H}C{\equiv}C$), 1.65 - 1.48 (m, 4 H, $HC{\equiv}CCH_2C\underline{H}_2C\underline{H}_2$-$CH_2N$)

^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 84.3 ($HC{\equiv}\underline{C}$), 68.4 ($H\underline{C}{\equiv}C$), 58.6 ($CH_2CH_2\underline{C}H_2N$), 54.5 ($CH_2CH_2CH_2N(\underline{C}H_2)\underline{C}H_2$), 46.0 ($CH_2CH_2CH_2N(CH_2\underline{C}H_2)CH_2\underline{C}H_2$), 26.4 ($CH_2\underline{C}H_2CH_2N$), 25.7 ($HC{\equiv}CCH_2\underline{C}H_2$), 18.3 ($HC{\equiv}C\underline{C}H_2$)

HRMS (ESI$^+$) m/z / Da = 167.1548, $[M+H]^+$, $[C_{10}H_{19}N_2]^+$ requires 167.1548

The compound has not been reported previously.

1.22 1-Cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 70



7-Chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquino-line-3-carboxylic acid **69** (1.27 g, 4.51 mmol, 1 eq.), 1-(hex-5-yn-1-yl)piperazine **68** (1.5 g, 9.02 mmol, 2 eq.) and *N*-methyl-2-pyrrolidone (10 ml) were stirred in a microwave reactor at 115 °C for 24 h. The reaction mixture was cooled to r.t. and water (80 ml) was added. The mixture was stirred for 3 h and then filtered, and residue was washed with MeOH (50 ml). The resulting solid (0.571 g) was further purified by recrystalisation from EtOAc (50 ml). **70** was obtained as off-white crystals (0.219 g, 0.531 mmol, 11.8 %).

TLC R_f = 0.02 (10 % MeOH/CH_2Cl_2)

mp T / °C = 220 (MeOH, decomposes)

IR (neat) ν_{max} / cm^{-1} = 3212.0 (alkyne C-H), 2459.3 (O-H), 1722.6 (carboxylic acid C=O), 1626.8 (quinolone C=O)

^{1}**H NMR** (500 MHz, DMSO-d_6) δ / ppm = 15.12 (br s, 1 H, C(=O)O$\underline{H}$), 8.69 (s, 1 H, *ortho* to C(=O)OH), 7.96 (d, J = 13.0 Hz, 1 H, *ortho* to F), 7.61 (d, J = 7.6 Hz, 1 H, *meta* to F), 3.82 - 3.92 (m, 3 H, NC$\underline{H}$$(CH_2)_2$ and $CH_2CH_2CH_2N(CH_2C\underline{H}_2)CH_2CH_2$), 3.54 - 3.68 (br m, 2 H, $CH_2CH_2CH_2N(C\underline{H}_2)CH_2$), 3.45 (br. t, J = 11.6 Hz, 2 H, $CH_2CH_2CH_2N(CH_2CH_2)CH_2C\underline{H}_2$), 3.21 - 3.29 (br m, 2 H, $CH_2CH_2CH_2N(CH_2CH_2)CH_2C\underline{H}_2$), 3.11 - 3.20 (br m, 2 H, $CH_2CH_2CH_2N(CH_2)C\underline{H}_2$), 2.84 (t, J = 2.7 Hz, 1 H, $\underline{H}$C≡C), 2.24 (td, J = 7.0, 2.7 Hz, 2 H, HC≡C$C\underline{H}_2$), 1.83 (br. quin, J = 7.5 Hz, 2 H, HC≡$CCH_2CH_2C\underline{H}_2$), 1.52 (quin, J = 7.4 Hz, 2 H, HC≡$CCH_2C\underline{H}_2$), 1.29 - 1.36 (m, 2 H, NCH($C\underline{H}H)_2$), 1.16 - 1.23 (m, 2 H, NCH($CH\underline{H})_2$)

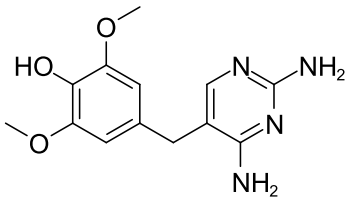
^{13}**C NMR** (126 MHz, DMSO-d_6) δ / ppm = 176.4 ($\underline{C}$(=O)CC(=O)OH), 165.8 ($\underline{C}$(=O)OH), 152.8 (d, J = 248.5 Hz, *ipso* to F), 148.2 ($\underline{C}$HCC(=O)OH), 143.7 (d, J = 11.1 Hz, *para* to C(=O)), 139.1 (*para* to F), 119.4 (d, J = 6.9 Hz, *ipso* to C(=O)), 111.2 (d, J = 22.5 Hz, *ortho* to F and *ortho* to C(=O)), 106.9 (*meta* to F and *meta* to C(=O)), 106.9 (C(=O)$\underline{C}$C(=O)OH), 83.9 (HC≡$\underline{C}$), 71.8 (H$\underline{C}$≡C), 55.0 ($CH_2CH_2\underline{C}H_2N$), 50.5 ($CH_2CH_2CH_2N(\underline{C}H_2)\underline{C}H_2$), 46.3 ($CH_2CH_2CH_2N(CH_2\underline{C}H_2)CH_2\underline{C}H_2$), 36.0 (N$\underline{C}H(CH_2)_2$), 25.2 (HC≡$CCH_2\underline{C}H_2$), 22.3 (HC≡$CCH_2CH_2\underline{C}H_2$), 17.4 (HC≡C$\underline{C}H_2$), 7.6 (NCH($\underline{C}H_2)_2$)

^{19}**F NMR** (376.45 MHz, MeOD) δ / ppm = -121.8 (s, ciprofloxacin F)

HRMS (ESI$^+$) m/z / Da = 412.2036, $[M+H]^+$, $[C_{23}H_{27}N_3O_3F]^+$ requires 412.2030

The compound has not been reported previously.

1.23 4-((2,4-Diaminopyrimidin-5-yl)methyl)-2,6-dimethoxyphenol 71



Hydrobromic acid (48 % w/w, aq., 50 ml) was heated to 100 °C. Trimethoprim **30** (5.00 g, 17.2 mmol) was added, and the suspension was stirred for 40 min under Ar. The mixture was removed from the heat, and NaOH (50 % w/w, aq., 15 ml) was added dropwise. The reaction mixture was then cooled slowly to 0 °C, and the resulting crystals were filtered out and washed with cold water. The crystals were then dissolved in hot water (80 ml), neutralized with NH_4OH (sat., aq.) and cooled slowly to 0 °C. The resulting crystals were filtered out, washed with cold water and dried under vacuum. **71** was obtained as pale pink prisms (2.06 g, 7.46 mmol, 43.4 %).

TLC R_f = 0.04 (5 % MeOH/$CHCl_2$)

mp T / °C = 238 (H_2O, decomposes)

IR (neat) ν_{max} / cm^{-1} = 3314.0 (N-H), 3137.4 (N-H), 3045.3 (C-H), 3000.9 (C-H), 2938.1 (C-H), 2838.7 (C-H), 1662.9 (pyrimidine), 1645.2 (pyrimidine), 1626.6 (pyrimidine)

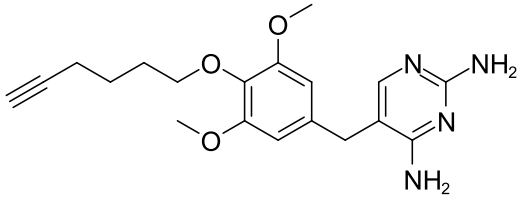
^{1}H NMR (400 MHz, MeOD) δ / ppm = 7.21 (s, 1 H, C$\underline{H}$N), 6.54 (s, 2 H, *meta* to OCH_2), 4.87 (br s, 5 H, OH, $NH_2 \times 2$), 3.82 (s, 6 H, OC$\underline{H}_3$), 3.63 (s, 2 H, CC$\underline{H}_2$C)

^{13}C NMR (101 MHz, MeOD) δ / ppm = 166.4 ($CH_2C\underline{C}NH_2$), 162.0 (CHN$\underline{C}NH_2$), 156.2 ($\underline{C}HNCNH_2$), 149.8 (*ipso* to OCH_3), 135.9 (*ipso* to OH), 128.2 (*para* to OH), 111.7 ($CH_2\underline{C}CNH_2$), 107.5 (*meta* to OH), 57.0 (O$\underline{C}H_3$), 33.9 (C$\underline{C}H_2$C)

HRMS (ESI$^+$) m/z / Da = 277.1295, $[M+H]^+$ found, $[C_{13}H_{17}N_4O_3]^+$ requires 277.1301

The data are consistent with the literature.[9]

1.24 5-(4-(Hex-5-yn-1-yloxy)-3,5-dimethoxybenzyl)pyrimidine-2,4-diamine 73



4-((2,4-Diaminopyrimidin-5-yl)methyl)-2,6-dimethoxyphenol **71** (1.00 g, 3.62 mmol, 1 eq.), 6-chloro-1-hexyne **72** (0.524 ml, 0.420 g, 4.34 mmol, 1.2 eq.), Cs_2CO_3 (2.36 g, 7.24 mmol, 2 eq.) and anhydrous DMF (30 ml) were stirred at 70 °C for 7 h. The solvent was removed under reduced pressure, then CH_2Cl_2 (30 ml) was

added and the mixture filtured. The filtrate was concentrated under reduced pressure and purified by column chromatography using a Combiflash (SiO_2, 5 % MeOH/CH_2Cl_2). **73** was obtained as a pale cream amorphous solid (0.327 g, 0.917 mmol, 25.3 %).

TLC R_f = 0.14 (5 % MeOH/CH_2Cl_2)

IR (neat) ν_{max} / cm^{-1} = 3451.4 (alkyne C-H), 3313.4 (N-H), 3136.7 (N-H), 3113.9 (N-H), 2944.2 (C-H), 2839.0 (C-H), 1635.1 (pyrimidine)

^{1}H NMR (400 MHz, MeOD) δ / ppm = 7.77 (s, 1 H, C<u>H</u>N), 6.37 (s, 2 H, *meta* to OCH_2), 4.83 (br s, 2 H, CHNCN<u>H</u>$_2$), 4.63 (br s, 2 H, CH_2CCN<u>H</u>$_2$), 3.95 (t, J = 6.3 Hz, 2 H, C<u>H</u>$_2$O), 3.79 (s, 6 H, OC<u>H</u>$_3$), 3.65 (s, 2 H, CC<u>H</u>$_2$C), 2.28 (td, J = 7.1, 2.6 Hz, 2 H, HC≡CC<u>H</u>$_2$), 1.94 (t, J = 2.7 Hz, 1 H, <u>H</u>C≡C), 1.81 - 1.90 (m, 2 H, C<u>H</u>$_2$$CH_2$O), 1.71 - 1.80 (m, 2 H, C<u>H</u>$_2$$CH_2$$CH_2$O)

^{13}C NMR (101 MHz, MeOD) δ / ppm = 162.7 (CH_2C<u>C</u>NH$_2$), 162.0 (CHN<u>C</u>NH$_2$), 156.4 (<u>C</u>HNCNH$_2$), 153.8 (*ipso* to OCH_3), 136.0 (*ipso* to OCH_2), 133.6 (*para* to OCH_2), 106.5 (CH_2<u>C</u>CNH$_2$), 105.0 (*meta* to OCH_2), 84.5 (HC≡<u>C</u>), 72.6 (<u>C</u>H$_2$O), 68.3 (H<u>C</u>≡C), 56.1 (O<u>C</u>H$_3$), 34.7 (C<u>C</u>H$_2$C), 29.1 (<u>C</u>H$_2$$CH_2$O), 24.9 (<u>C</u>H$_2$$CH_2$$CH_2$O), 18.0 (HC≡C<u>C</u>H$_2$)

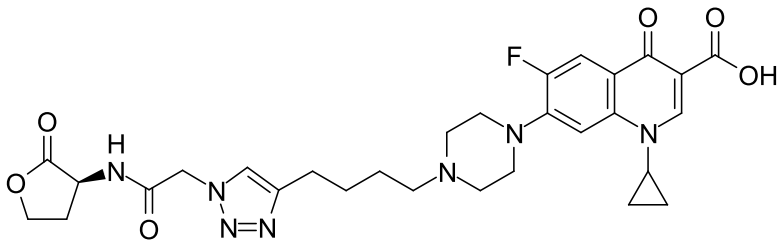
HRMS (ESI$^+$) m/z / Da = 357.1920, $[M+H]^+$ found, $[C_{19}H_{25}N_4O_3]^+$ requires 357.1927

The compound has not been reported previously.

1.25 Optimised general procedure for the click reaction

Azide (1 eq.) and alkyne (1 eq.) were dissolved in 50 % *t*-BuOH/water in a round-bottomed flask with a stirrer bar, closed with a *new* septum. The mixture was degassed by bubbling through N_2. The mixture was placed under positive pressure of Ar using a balloon. Equimolar amounts of $CuSO_4 \cdot 5\,H_2O$ and THPTA **76** were dissolved in similar water to make a 50 mM solution and similarly degassed. Sodium ascorbate was dissolved in water to make a 100 mM solution and similarly degassed. The Cu/THPTA solution (0.05 eq.) was added to the reaction mixture, followed by the sodium ascorbate solution (0.1 eq.). The mixture was stirred for 2 h and monitored using LCMS. HL derivative conjugates were dry-loaded onto SiO_2 and purified by column chromatography (SiO_2, 0-20 % MeOH/CH_2Cl_2). Other conjugates were purified by preparative HPLC (5-95 % acetonitrile (0.1 % TFA)/water (0.05 % TFA) over 20 min).

1.26 (*S*)-1-Cyclopropyl-6-fluoro-4-oxo-7-(4-(4-(1-(2-oxo-2-((2-oxotetrahydrofuran-3-yl)amino)ethyl)-1*H*-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid 74



50 % water/*t*-BuOH (2 ml) was degassed by bubbling N_2 through it. This was then added to a mixture of 1-cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **70** (20.6 mg, 50.0 μmol, 1 eq.) and (*S*)-2-azido-*N*-(2-oxotetrahydrofuran-3-yl)acetamide **57** (9.2 mg, 50.0 μmol, 1 eq.). A similarly degassed solution of $CuSO_4 \cdot 5\,H_2O$ (624 μg, 2.5 μmol, 0.05 eq. 50 mM), THPTA (1.09 mg, 2.5 μmol, 0.05 eq. 50 mM) and sodium ascorbate (991 μg, 5 μmol, 0.1 eq., 100 mM) in 50 % water/*t*-BuOH (50 μl) was then added. The mixture was stirred at r.t. under argon for 3 h. On observation that the reaction had stalled, the reaction was degassed again, and a further portion of cataylst solution (50 μl) was added. After a further 3 h the reaction mixture was dry-loaded onto SiO_2 and purified by column chromatography using a Combiflash (SiO_2, 0-20 % MeOH/CH_2Cl_2 over 15 min). The combined pure fractions were dried with $MgSO_4$ and evaporated under reduced pressure. **74** was obtained as a white amorphous solid (8.8 mg, 14.8 μmol, 29.6 %).

IR (neat) ν_{max} / cm^{-1} = 3266.3 (N-H), 2949.0 (C-H), 2934.8 (C-H), 2827.2 (C-H), 1778.0 (lactone C=O), 1724.9 (carboxylic acid C=O), 1665.0 (amide C=O), 1625.5 (quinolone C=O)

^{1}H NMR (400 MHz, DMSO d_6) δ / ppm = 15.23 (s, 1 H, C(=O)O<u>H</u>), 8.84 (d, J = 7.9 Hz, 1 H, N<u>H</u>), 8.66 (s, 1 H, *ortho* to C(=O)OH), 7.90 (d, J = 13.3 Hz, 1 H, *ortho* to F), 7.82 (s, 1 H, C<u>H</u>=CCH_2), 7.57 (d, J = 7.6 Hz, 1 H, *meta* to F), 5.13 (s, 1 H, C(=O)C<u>H</u>HN), 5.12 (s, 1 H, C(=O)CH<u>H</u>N), 4.64 (ddd, J = 10.9, 9.0, 7.8 Hz, 1 H, C<u>H</u>NH), 4.36 (td, J = 8.9, 1.7 Hz, 1 H, OC<u>H</u>H), 4.23 (ddd, J = 10.6, 8.8, 6.4 Hz, 1 H, OCH<u>H</u>), 3.83 (tt, J = 7.0, 4.0 Hz, 1 H, NC<u>H</u>$(CH_2)_2$), 3.32 (br s, 4 H, $CH_2CH_2CH_2N(CH_2C\underline{H}_2)CH_2C\underline{H}_2$), 2.67 (t, J = 7.4 Hz, 2 H, CH=CC<u>H_2</u>), 2.58 (br t, J = 5.0 Hz, 4 H, $CH_2CH_2CH_2N(C\underline{H}_2)C\underline{H}_2$), 2.42 - 2.49 (m, 1 H, $OCH_2C\underline{H}H$), 2.40 (t, J = 7.1 Hz, 2 H, CH=$CCH_2CH_2CH_2C\underline{H}_2$), 2.17 (dtd, J = 11.7, 10.8, 9.0 Hz, 1 H, $OCH_2CH\underline{H}$), 1.66 (quin, J = 7.2 Hz, 2 H, CH=$CCH_2C\underline{H}_2$), 1.53 (quin, J = 7.2 Hz, 2 H, CH=$CCH_2CH_2C\underline{H}_2$), 1.28 - 1.35 (m, 2 H, $NCH(C\underline{H}H)_2$), 1.16 - 1.21 (m, 2 H, $NCH(CH\underline{H})_2$)

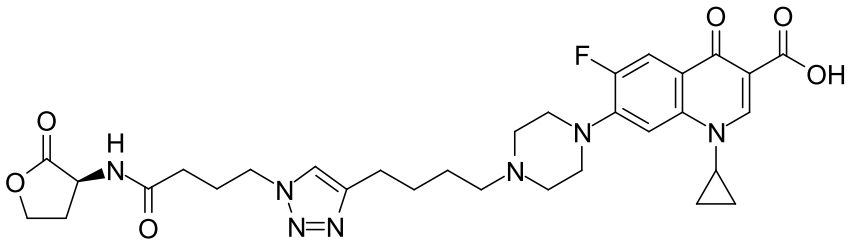
^{13}C NMR (101 MHz, DMSO d_6) δ / ppm = 176.4 (<u>C</u>(=O)CC(=O)OH), 174.9 (O<u>C</u>(=O)), 166.0 (<u>C</u>(=O)OH), 165.9 (NH<u>C</u>(=O)), 153.1 (d, J = 250.8 Hz, *ipso* to F), 148.0 (<u>C</u>H=CC(=O)OH), 146.6 (CH=<u>C</u>CH_2), 145.3 (d, J = 9.6 Hz, *ipso* to piperazine), 139.2 (*para* to F), 123.4 (<u>C</u>H=CCH_2), 118.5 (d, J = 7.5 Hz, *para* to piperazine), 110.9 (d, J = 23.5 Hz, *ortho* to C=O and *ortho* to F), 106.7 (<u>C</u>C(=O)OH), 106.4 (d, J = 3.2 Hz, *meta* to C=O and *meta* to F), 65.4 (O<u>C</u>H_2), 57.3 ($CH=CCH_2CH_2CH_2\underline{C}H_2N$), 52.4 ($CH_2CH_2CH_2N(\underline{C}H_2)\underline{C}H_2$), 51.2 (C(=O)<u>C</u>$H_2$N), 49.5 ($CH_2CH_2CH_2N(CH_2\underline{C}H_2)CH_2CH_2$), 49.5 ($CH_2CH_2CH_2N(CH_2CH_2)CH_2\underline{C}H_2$), 48.2 (<u>C</u>HNH), 35.9 (N<u>C</u>$H(CH_2)_2$), 28.2 (<u>C</u>H_2CHNH), 26.8 ($CH=CCH_2\underline{C}H_2$), 25.7 ($CH=CCH_2CH_2\underline{C}H_2$), 24.9 (CH=C<u>C</u>$H_2$), 7.6 ($NCH(\underline{C}H_2)_2$)

HRMS (ESI^+) m/z / Da = 596.2627, $[M+H]^+$ found, $[C_{29}H_{35}FN_7O_6]^+$ requires 596.2633

$[\boldsymbol{\alpha}]_D^{20}$ / $^\circ 10^{-1} cm^2 g^{-1}$ = -3.5 (c / g(100 ml)$^{-1}$ = 0.0575 , MeOH)

The compound has not been reported previously.

1.27 (*S*)-1-Cyclopropyl-6-fluoro-4-oxo-7-(4-(4-(1-(4-oxo-4-((2-oxotetrahydrofuran-3-yl)amino)butyl)-1*H*-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid 79



50 % water/*t*-BuOH (2 ml) was degassed by bubbling N_2 through it. This was then added to a mixture of 1-cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **70** (20.6 mg, 50.0 μmol, 1 eq.) and (*S*)-4-azido-*N*-(2-oxotetrahydrofuran-3-yl)butanamide **60** (10.6 mg, 50.0 μmol, 1 eq.). A similarly degassed solution of $CuSO_4 \cdot 5\,H_2O$ (624 μg, 2.5 μmol, 0.05 eq. 50 mM), THPTA (1.09 mg, 2.5 μmol, 0.05 eq. 50 mM) and sodium ascorbate (991 μg, 5 μmol, 0.1 eq., 100 mM) in 50 % water/*t*-BuOH (50 μl) was then added. The mixture was stirred at r.t. under argon for 3 h, then dry-loaded onto SiO_2 and purified by column chromatography using a Combiflash (SiO_2, 0-20 % MeOH/CH_2Cl_2 over 15 min). The combined pure fractions were dried with $MgSO_4$ and evaporated under reduced pressure. **79** was obtained as a white amorphous solid (14.6 mg, 23.4 μmol, 46.8 %).

IR (neat) ν_{max} / cm^{-1} = 3286.7 (N-H), 2949.7 (C-H), 2820.6 (C-H), 2778.0 (C-H), 1778.1 (lactone C=O), 1725.6 (carboxylic acid C=O), 1663.7 (amide C=O), 1625.8 (quinolone C=O)

^{1}H NMR (500 MHz, DMSO d_6) δ / ppm = 15.22 (br s, 1 H, C(=O)O<u>H</u>), 8.65 (s, 1 H, *ortho* to C(=O)OH), 8.40 (d, J = 8.0 Hz, 1 H, N<u>H</u>), 7.88 (d, J = 13.4 Hz, 1 H, *ortho* to F), 7.85 (s, 1 H, C<u>H</u>=CCH$_2$), 7.55 (d, J = 7.5 Hz, 1 H, *meta* to F), 4.53 (ddd, J = 10.9, 9.0, 8.1 Hz, 1 H, C<u>H</u>NH), 4.33 (td, J = 8.9, 1.8 Hz, 1 H, OC<u>H</u>H), 4.31 (t, J = 7.0 Hz, 2 H, C<u>H$_2$</u>NCH=C), 4.20 (ddd, J = 10.5, 8.8, 6.5 Hz, 1 H, OCH<u>H</u>), 3.82 (tt, J = 6.9, 4.0 Hz, 1 H, NC<u>H</u>(CH$_2$)$_2$), 3.32 (br. t, J = 4.2 Hz, 4 H, 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 = 7.4 Hz, 2 H, CH=CC<u>H$_2$</u>), 2.57 (br. t, J = 5.0 Hz, 2 H, CH$_2$CH$_2$CH$_2$N(C<u>H$_2$</u>)C<u>H$_2$</u>), 2.34 - 2.42 (m, 3 H, OCH$_2$C<u>H</u>H and CH=CCH$_2$CH$_2$CH$_2$C<u>H$_2$</u>), 2.09 - 2.19 (m, 3 H, OCH$_2$CH<u>H</u> and C(=O)C<u>H$_2$</u>), 2.02 (quin, J = 7.2 Hz, 2 H, C(=O)CH$_2$C<u>H$_2$</u>), 1.64 (quin, J = 7.6 Hz, 2 H, CH=CCH$_2$C<u>H$_2$</u>), 1.52 (quin, J = 7.2 Hz, 2 H, CH=CCH$_2$CH$_2$C<u>H$_2$</u>), 1.29 - 1.34 (m, 2 H, NCH(C<u>H</u>H)$_2$), 1.15 - 1.21 (m, 2 H, NCH(CH<u>H</u>)$_2$)

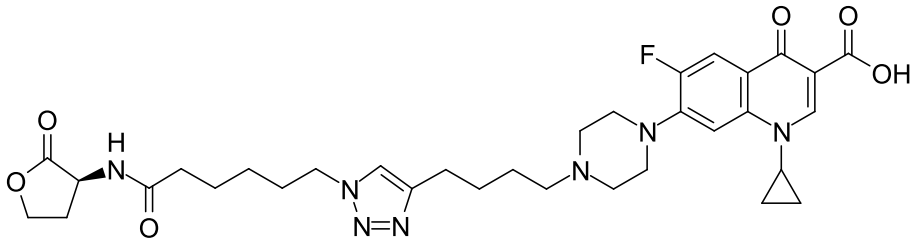
^{13}C NMR (126 MHz, DMSO d_6) δ / ppm = 176.3 (<u>C</u>(=O)CC(=O)OH), 175.4 (O<u>C</u>(=O)), 171.2 (NH<u>C</u>(=O)), 166.0 (<u>C</u>(=O)OH), 153.0 (d, J = 248.6 Hz, *ortho* to F), 148.0 (<u>C</u>H=CC(=O)OH), 146.8 (CH=<u>C</u>CH$_2$), 145.2 (d, J = 9.6 Hz, *ipso* to piperazine), 139.2 (*para* to F), 121.7 (<u>C</u>H=CCH$_2$), 118.5 (d, J = 7.5 Hz, *para* to piperazine), 110.9 (d, J = 22.4 Hz, *ortho* to C=O and *ortho* to F), 106.7 (<u>C</u>C(=O)OH), 106.3 (d, J = 3.2 Hz, *meta* to C=O and *meta* to F), 65.3 (O<u>C</u>H$_2$), 57.3 (CH=CCH$_2$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$_2$), 49.5 (CH$_2$CH$_2$CH$_2$N(CH$_2$<u>C</u>H$_2$)CH$_2$CH$_2$), 49.4 (CH$_2$CH$_2$CH$_2$N(CH$_2$CH$_2$)CH$_2$<u>C</u>H$_2$), 48.6 (<u>C</u>H$_2$NCH=C), 47.9 (OC(=O)<u>C</u>HNH), 35.9 (N<u>C</u>H(CH$_2$)$_2$), 31.7 (NHC(=O)<u>C</u>H$_2$), 28.2 (<u>C</u>H$_2$CHNH), 26.9 (CH=CCH$_2$<u>C</u>H$_2$), 25.8 (NHC(=O)CH$_2$<u>C</u>H$_2$ and CH=CCH$_2$CH$_2$<u>C</u>H$_2$), 24.9 (CH=C<u>C</u>H$_2$), 7.6 (NCH(<u>C</u>H$_2$)$_2$)

HRMS (ESI$^+$) m/z / Da = 624.2928, $[M+H]^+$ found, $[C_{31}H_{39}FN_7O_6]^+$ requires 624.2946

$[\alpha]_D^{20}$ / $^\circ 10^{-1} cm^2 g^{-1}$ = -10.6 (c / g(100 ml)$^{-1}$ = 0.094 , MeOH)

The compound has not been reported previously.

1.28 (*S*)-1-Cyclopropyl-6-fluoro-4-oxo-7-(4-(4-(1-(6-oxo-6-((2-oxotetrahydrofuran-3-yl)amino)hexyl)-1*H*-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid 80



50 % water/*t*-BuOH (2 ml) was degassed by bubbling N_2 through it. This was then added to a mixture of 1-cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **70** (20.6 mg, 50.0 μmol, 1 eq.) and (*S*)-6-azido-*N*-(2-oxotetrahydrofuran-3-yl)hexanamide **63** (12.0 mg, 50.0 μmol, 1 eq.). A similarly degassed solution of $CuSO_4 \cdot 5\,H_2O$ (624 μg, 2.5 μmol, 0.05 eq. 50 mM), THPTA (1.09 mg, 2.5 μmol, 0.05 eq. 50 mM) and sodium ascorbate (991 μg, 5 μmol, 0.1 eq., 100 mM) in 50 % water/*t*-BuOH (50 μl) was then added. The mixture was stirred at r.t. under argon for 3 h, then dry-loaded onto SiO_2 and purified by column chromatography using a Combiflash (SiO_2, 0-20 % MeOH/CH_2Cl_2 over 15 min) The combined pure fractions were dried with $MgSO_4$ and evaporated under reduced pressure. **80** was obtained as a white amorphous solid (12.4 mg, 19.0 μmol, 38.0 %).

TLC R_f = 0.30 (30 % MeOH/CH_2Cl_2)

IR (neat) ν_{max} / cm^{-1} = 3301.8 (N-H), 2939.7 (C-H), 2857.5 (C-H), 1784.6 (lactone C=O), 1728.5 (carboxylic acid C=O), 1658.2 (amide C=O), 1625.5 (quinolone C=O)

^{1}H NMR (500 MHz, DMSO d_6) δ / ppm = 15.22 (br s, 1 H, C(=O)O<u>H</u>), 8.65 (s, 1 H, *ortho* to C(=O)OH), 8.32 (d, J = 8.0 Hz, 1 H, N<u>H</u>), 7.89 (d, J = 13.3 Hz, 1 H, *ortho* to F), 7.84 (s, 1 H, C<u>H</u>=CCH$_2$), 7.55 (d, J = 7.6 Hz, 1 H, *meta* to F), 4.51 (ddd, J = 10.9, 9.1, 7.9 Hz, 1 H, C<u>H</u>NH), 4.33 (td, J = 8.8, 1.8 Hz, 1 H, OC<u>H</u>H), 4.28 (t, J = 7.1 Hz, 2 H, C<u>H$_2$</u>NCH=C), 4.19 (ddd, J = 10.5, 8.7, 6.6 Hz, 1 H, OCH<u>H</u>), 3.82 (tt, J = 7.0, 4.0 Hz, 1 H, NC<u>H</u>(CH$_2$)$_2$), 3.32 (br t, J = 4.5, 4 H, CH$_2$CH$_2$CH$_2$N(CH$_2$C<u>H$_2$</u>)CH$_2$C<u>H$_2$</u>), 2.63 (t, J = 7.5 Hz, 2 H, CH=CC<u>H$_2$</u>), 2.57 (br t, J = 4.2 Hz, 4 H, CH$_2$CH$_2$CH$_2$N(C<u>H$_2$</u>)C<u>H$_2$</u>), 2.33 - 2.41 (m, 3 H, OCH$_2$C<u>H</u>H and CH=CCH$_2$CH$_2$CH$_2$C<u>H$_2$</u>), 2.06 - 2.16 (m, 3 H, OCH$_2$CH<u>H</u> and C(=O)C<u>H$_2$</u>), 1.79 (quin, J = 7.4 Hz, 2 H, C(=O)CH$_2$CH$_2$CH$_2$C<u>H$_2$</u>), 1.63 (quin, J = 7.5 Hz, 2 H, CH=CCH$_2$C<u>H$_2$</u>), 1.45 - 1.56 (m, 4 H, C(=O)CH$_2$C<u>H$_2$</u> and CH=CCH$_2$CH$_2$C<u>H$_2$</u>), 1.29 - 1.34 (m, 2 H, NCH(C<u>H</u>H)$_2$), 1.19 - 1.25 (m, 2 H, C(=O)CH$_2$CH$_2$C<u>H$_2$</u>), 1.15 - 1.19 (m, 2 H, NCH(CH<u>H</u>)$_2$)

^{13}C NMR (126 MHz, DMSO d_6) δ / ppm = 176.4 (<u>C</u>(=O)CC(=O)OH), 175.4 (O<u>C</u>(=O)), 172.1 (NH<u>C</u>(=O)), 166.0 (<u>C</u>(=O)OH), 153.0 (d, J = 250.2 Hz, *ipso* to F), 148.0 (<u>C</u>H=CC(=O)OH), 146.8 (CH=<u>C</u>CH$_2$), 145.2 (d, J = 9.6 Hz, *ipso* to piperazine), 139.2 (*para* to F), 121.6 (<u>C</u>H=CCH$_2$), 118.5 (d, J = 8.0 Hz, *para* to piperazine), 110.9 (d, J = 23.5 Hz, *ortho* to C=O and *ortho* to F), 106.7 (<u>C</u>C(=O)OH), 106.3 (d, J = 2.1 Hz, *meta* to C=O and *meta* to F), 65.3 (O<u>C</u>H$_2$), 57.4 (CH=CCH$_2$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$_2$), 49.5 (CH$_2$CH$_2$CH$_2$N(CH$_2$<u>C</u>H$_2$)CH$_2$CH$_2$), 49.5 (CH$_2$CH$_2$CH$_2$N(CH$_2$CH$_2$)CH$_2$<u>C</u>H$_2$), 49.0 (<u>C</u>H$_2$NCH=C), 47.8 (<u>C</u>HNH), 35.9 (N<u>C</u>H(CH$_2$)$_2$), 34.8 (NHC(=O)<u>C</u>H$_2$), 29.5 (<u>C</u>H$_2$CH$_2$NCH=C), 28.3 (<u>C</u>H$_2$CHNH), 26.9 (CH=C

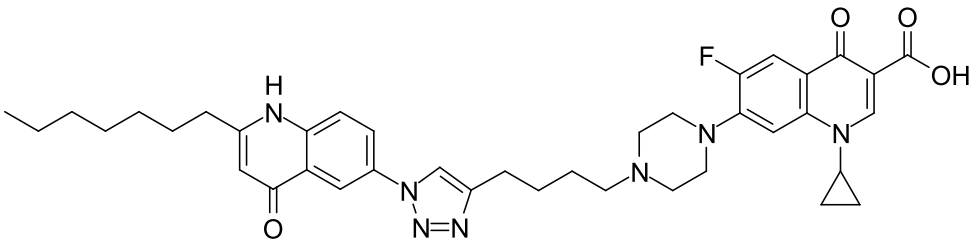
$CH_2\underline{C}H_2$), 25.7 (CH=CCH$_2$CH$_2\underline{C}$H$_2$), 25.4 (NHC(=O)CH$_2$CH$_2\underline{C}$H$_2$), 24.9 (CH=C$\underline{C}$H$_2$), 24.5 (NHC(=O)CH$_2\underline{C}$H$_2$), 7.6 (NCH($\underline{C}$H$_2$)$_2$)

HRMS (ESI$^+$) m/z / Da = 652.3254, $[M+H]^+$ found, $[C_{33}H_{43}FN_7O_6]^+$ requires 652.3248

$[\alpha]_D^{20}$ / °10^{-1}cm^{2}g^{-1} = -8.5 (c / g(100 ml)$^{-1}$ = 0.106 , MeOH)

The compound has not been reported previously.

1.29 1-Cyclopropyl-6-fluoro-7-(4-(4-(1-(2-heptyl-4-oxo-1,4-dihydroquinolin-6-yl)-1*H*-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 82



50 % water/t-BuOH (1 ml) was degassed by bubbling N_2 through it. This was then added to a mixture of 1-cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **70** (4.1 mg, 10.0 μmol, 1 eq.) and 6-azido-2-heptylquinolin-4(1H)-one **40** (2.8 mg, 10.0 μmol, 1 eq.). A similarly degassed solution of $CuSO_4 \cdot 5\,H_2O$ (125 μg, 0.5 μmol, 0.05 eq. 50 mM), THPTA (218 μg, 0.5 μmol, 0.05 eq. 50 mM) and sodium ascorbate (198 μg, 1 μmol, 0.1 eq., 100 mM) in 50 % water/t-BuOH (10 μl) was then added. The mixture was stirred at r.t. under argon for 1.5 h, then the reaction mixture was evaporated under reduced pressure. The residue was purified by preparative HPLC (50-100 % 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. **82** was obtained as a white amorphous solid (8.6 mg, 2.7 μmol, 27.0 %).

IR (neat) ν_{max} / cm^{-1} = 2927.0 (C-H), 2865.5 (C-H), 1715.5 (carboxylic acid C=O), 1631.0 (ciprofloxacin quinolone C=O and HHQ C=O)

^{1}H NMR (500 MHz, DMSO d$_6$) 15.12 (br s, 1 H, $\underline{C}$(=O)OH), 11.79 (s, 1 H, N$\underline{H}$), 8.75 (s, 1 H, NC$\underline{H}$=CCH$_2$), 8.71 (s, 1 H, *ortho* to C(=O)OH), 8.40 (d, J = 2.7 Hz, 1 H, *ortho* to C(=O) and *ortho* to N), 8.18 (dd, J = 8.9, 2.6 Hz, 1 H, *para* to C(=O) and *ortho* to N), 7.99 (d, J = 13.0 Hz, 1 H, *ortho* to F), 7.75 (d, J = 9.0 Hz, 1 H, *meta* to C(=O) and *meta* to N), 7.62 (d, J = 7.8 Hz, 1 H, *meta* to F), 6.02 (s, 1 H, NHC=C$\underline{H}$C(=O)), 3.85 (tt, J = 7.0, 4.0 Hz, 1 H, NC$\underline{H}$(CH$_2$)$_2$), 3.23 - 3.30 (m, 10 H, C$\underline{H}_2$N(C$\underline{H}_2$C$\underline{H}_2$)C$\underline{H}_2$C$\underline{H}_2$), 2.82 (t, J = 5.9 Hz, 2 H, NCH=CC$\underline{H}_2$), 2.63 (t, J = 7.9 Hz, 2 H, C$\underline{H}_2$C=CHC(=O)), 1.76 - 1.81 (m, 4 H, NCH=CCH$_2$C$\underline{H}_2$C$\underline{H}_2$), 1.70 (quin, J = 7.2 Hz, 2 H, C$\underline{H}_2$CH$_2$C=CHC(=O)), 1.15 - 1.38 (m, 12 H, CH$_3$C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}_2$, NCH(C$\underline{H}$H)$_2$ and NCH(CH$\underline{H}$)$_2$), 0.87 (t, J = 6.9 Hz, 3 H, C$\underline{H}_3$)

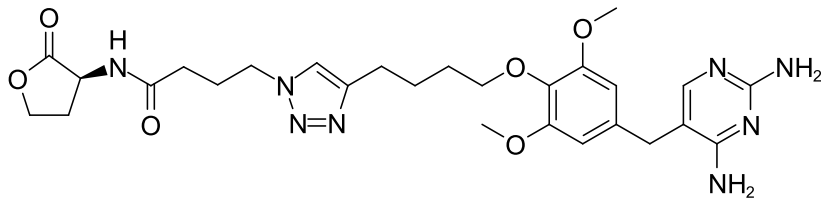
^{13}C NMR (126 MHz, DMSO d$_6$) δ / ppm = 176.4 ($\underline{C}$(=O)CC(=O)OH), 176.3 (CH$\underline{C}$(=O)), 165.8 ($\underline{C}$(=O)OH), 154.3 (CCH$\underline{C}$(=O)), 152.9 (d, J = 240.1 Hz, *ipso* to F), 148.3 ($\underline{C}$H=CC(=O)OH), 147.5 (NCH$\underline{C}$CH$_2$), 143.3 (d, J = 8.5 Hz, *ortho* to F and *ipso* to N), 139.6 (*ipso* to NH), 139.0 (*para* to F), 132.0 (*para* to NH), 124.9 (*ipso*

to C(=O) and *ortho* to NH), 123.6 (*para* to C(=O) and *meta* to NH), 120.5 (NCH=CCH_2), 120.0 (*meta* to C(=O) and *meta* to N), 119.6 (d, J = 9.6 Hz, *ipso* to C(=O) and *para* to N), 115.1 (*ortho* to C(=O) and *ortho* to N), 111.3 (d, J = 28.8 Hz, *ortho* to F and *ortho* to C(=O)), 107.9 (*meta* to F and *meta* to C(=O)), 107.2 (CHC(=O)), 106.9 (CC(=O)OH), 55.4 (CH=$CCH_2CH_2CH_2CH_2N$), 50.6 ($CH_2CH_2CH_2N(CH_2)CH_2$), 46.5 ($CH_2CH_2CH_2N(CH_2CH_2)CH_2CH_2$), 46.5 ($CH_2CH_2CH_2N(CH_2CH_2)CH_2CH_2$), 36.0 ($NCH(CH_2)_2$), 33.2 ($CH_2CNH$), 31.2 ($CH_3CH_2CH_2$), 28.3 - 28.5 ($CH_3CH_2CH_2CH_2CH_2CH_2$), 25.6 (CH=$CCH_2CH_2$), 24.4 (CH=C CH_2), 22.7 (CH=$CCH_2CH_2CH_2$), 22.0 (CH_3CH_2), 13.9 (CH_3), 7.6 ($NCH(CH_2)_2$)

HRMS (ESI^+) m/z / Da = 696.3667, $[M+H]^+$ found, $[C_{39}H_{47}FN_7O_4]^+$ requires 696.3668

The compound has not been reported previously.

1.30 (*S*)-4-(4-(4-(4-((2,4-Diaminopyrimidin-5-yl)methyl)-2,6-dimethoxyphenoxy) butyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(2-oxotetrahydrofuran-3-yl)butanamide 86



50 % water/*t*-BuOH (2 ml) was degassed by bubbling N_2 through it. This was then added to a mixture of 5-(4-(hex-5-yn-1-yloxy)-3,5-dimethoxybenzyl)pyrimidine-2,4-diamine **73** (20.6 mg, 50.0 μmol, 1 eq.) and (*S*)-4-azido-*N*-(2-oxotetrahydrofuran-3-yl)butanamide **60** (15.9 mg, 75.0 μmol, 1.5 eq.). Similarly degassed solutions of $CuSO_4 \cdot 5\,H_2O$ (624 μg, 2.5 μmol, 0.05 eq. 50 mM), THPTA (1.09 mg, 2.5 μmol, 0.05 eq. 50 mM) and sodium ascorbate (991 μg, 5 μmol, 0.1 eq., 100 mM) in water (50 μl) were then added. An extra portion of **60** (10.6 mg, 50.0 μmol, 1 eq.) was added after 4 d. Extra portions of the catalysts were added after 9 d. After 2 weeks, the reaction mixture was extracted with CH_2Cl_2 (6×10 ml) then dry-loaded onto SiO_2 and purified by column chromatography using a Combiflash (SiO_2, 0-20 % MeOH/CH_2Cl_2).The combined pure fractions were dried with $MgSO_4$ and evaporated under reduced pressure. **86** was obtained as a pale brown gum (4.8 mg, 8.4 μmol, 16.8 %).

TLC R_f = 0.30 (30 % MeOH/CH_2Cl_2)

IR (neat) ν_{max} / cm^{-1} = 3340.5 (N-H), 3303.3 (N-H), 3182.5 (N-H), 2933.8 (C-H), 1774.2 (lactone C=O), 1659.7 (amide C=O and pyrimidine)

^{1}H NMR (500 MHz, DMSO d_6) δ / ppm = 8.43 (d, J = 8.0 Hz, 1 H, NH), 7.80 (s, 1 H, NCH=CCH_2), 7.46 (s, 1 H, CHN=CNH_2), 6.68 (br s, 2 H, CH_2CCNH_2), 6.53 (s, 2 H, *meta* to CH_2), 6.21 (br s, 2 H, CHN=CNH_2), 4.49 (dt, J = 10.7, 8.6 Hz, 1 H, CHNH), 4.32 (td, J = 8.7, 1.6 Hz, 1 H, CHHOC(=O)), 4.29 (t, J = 6.8 Hz, 2 H, CH_2N), 4.19 (ddd, J = 10.6, 8.7, 6.5 Hz, 1 H, CHHOC(=O)), 3.79 (t, J = 6.2 Hz, 2 H, $CH_2CH_2CH_2O$), 3.68 (s, 6 H, CH_3), 3.53 (br s, 2 H, CCH_2C), 2.63 (t, J = 7.5 Hz, 2 H, CH=CCH_2), 2.37 (dddd, J = 12.2, 8.9, 6.7, 1.8 Hz, 1 H, CHHCHNH), 2.08 - 2.15 (m, 3 H, CHHCHNH and C(=O)CH_2), 2.00 (quin, J = 7.2 Hz, 2 H, CH_2CH_2N), 1.72 (quin, J = 7.3 Hz, 2 H, CH=CCH_2CH_2), 1.61 (quin, J = 6.7 Hz, 2 H, CH_2CH_2O)

^{13}C NMR (126 MHz, DMSO d_6) δ / ppm = 175.8 (OC=O), 171.9 (NHC=O), 163.1 ($CC(NH_2)N$), 159.7

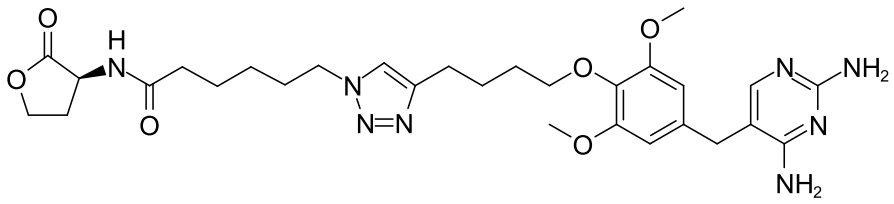
(br s, N<u>C</u>(NH_2)N), 153.2 (*ipso* to OCH_3), 150.5 (br s, <u>C</u>HNC(NH_2)N), 147.3 (NCH=<u>C</u>CH_2CH_2), 135.2 (*para* to CH_2O), 135.0 (*ipso* to CH_2O), 122.1 (<u>C</u>H=CCH_2CH_2), 107.3 (CH_2<u>C</u>C(NH_2)=N), 106.2 (*meta* to CH_2O), 72.3 (CH_2CH_2<u>C</u>H_2O), 65.7 (O<u>C</u>H_2CH_2CHNH), 56.2 (O<u>C</u>H_3), 48.9 (<u>C</u>H_2N), 48.3 (<u>C</u>HNH), 32.9 (C<u>C</u>H_2C), 32.0 (C(=O)<u>C</u>H_2), 29.3 (CH_2<u>C</u>H_2CH_2O), 28.4 (OCH_2<u>C</u>H_2CHNH), 26.0 (<u>C</u>H_2CH_2N), 25.7 (CH=CCH_2<u>C</u>H_2), 24.9 (CH=C<u>C</u>H_2CH_2)

HRMS (ESI$^+$) m/z / Da = 569.2834, $[M+H]^+$ found, $[C_{27}H_{37}N_8O_6]^+$ requires 569.2836

$[\boldsymbol{\alpha}]_D^{20}$ / $^\circ 10^{-1}$cm^{2}g^{-1} = -4.6 (c / g(100 ml)$^{-1}$ = 0.0433 , MeOH)

The compound has not been reported previously.

1.31 (*S*)-6-(4-(4-(4-((2,4-Diaminopyrimidin-5-yl)methyl)-2,6-dimethoxyphenoxy) butyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(2-oxotetrahydrofuran-3-yl)hexanamide 87



50 % water/*t*-BuOH (2 ml) was degassed by bubbling N_2 through it. This was then added to a mixture of 5-(4-(hex-5-yn-1-yloxy)-3,5-dimethoxybenzyl)pyrimidine-2,4-diamine **73** (20.6 mg, 50.0 μmol, 1 eq.) and (*S*)-6-azido-*N*-(2-oxotetrahydrofuran-3-yl)hexanamide **63** (18.0 mg, 75.0 μmol, 1.5 eq.). Similarly degassed solutions of $CuSO_4 \cdot 5\,H_2O$ (624 μg, 2.5 μmol, 0.05 eq. 50 mM), THPTA (1.09 mg, 2.5 μmol, 0.05 eq. 50 mM) and sodium ascorbate (991 μg, 5 μmol, 0.1 eq., 100 mM) in water (50 μl) were then added. An extra portion of **63** (12.0 mg, 50.0 μmol, 1 eq.) was added after was added after 4 d. Extra portions of the catalysts were added after 9 d. After 2 weeks, the After 2 weeks, the reaction mixture was extracted with CH_2Cl_2 (6×10 ml) then dry-loaded onto SiO_2 and purified by column chromatography using a Combiflash (SiO_2, 0-20 % MeOH/CH_2Cl_2).The combined pure fractions were dried with $MgSO_4$ and evaporated under reduced pressure. **87** was obtained as a clear gum (8.0 mg, 13.4 μmol, 26.8 %).

TLC R_f = 0.35 (30 % MeOH/CH_2Cl_2)

IR (neat) ν_{max} / cm^{-1} = 3336.0 (N-H), 3208.7 (N-H), 2941.1 (C-H), 2869.2 (C-H), 1775.2 (lactone C=O), 1657.3 (amide C=O and pyrimidine)

^{1}H NMR (500 MHz, DMSO d_6) δ / ppm = 8.34 (d, J = 8.0 Hz, 1 H, N<u>H</u>), 7.83 (s, 1 H, NC<u>H</u>=CCH_2), 7.50 (s, 1 H, C<u>H</u>N=CNH_2), 6.54 (s, 2 H, *meta* to CH_2), 6.17 (br s, 2 H, CH_2CCN<u>H</u>$_2$), 5.77 (br s, 2 H, CHN=CN<u>H</u>$_2$), 4.51 (ddd, J = 11.0, 9.0, 8.1 Hz, 1 H, C<u>H</u>NH), 4.33 (td, J = 8.8, 1.9 Hz, 1 H, C<u>H</u>HOC(=O)), 4.27 (t, J = 7.1 Hz, 2 H, C<u>H</u>$_2$N), 4.19 (ddd, J = 10.5, 8.7, 6.5 Hz, 1 H, CH<u>H</u>OC(=O)), 3.80 (t, J = 6.3 Hz, 2 H, CH_2CH_2C<u>H</u>$_2$O), 3.70 (s, 6 H, C<u>H</u>$_3$), 3.52 (s, 2 H, CC<u>H</u>$_2$C), 2.64 (t, J = 7.5 Hz, 2 H, CH=CC<u>H</u>$_2$), 2.36 (dddd, J = 12.1, 8.9, 6.7, 1.8 Hz, 1 H, C<u>H</u>HCHNH), 2.06 - 2.16 (m, 3 H, CH<u>H</u>CHNH and C(=O)C<u>H</u>$_2$), 1.78 (quin, J = 7.4 Hz, 2 H, C<u>H</u>$_2CH_2$N), 1.73 (quin, J = 7.7 Hz, 2 H, CH=CCH_2C<u>H</u>$_2$), 1.63 (quin, J = 6.8 Hz, 2 H, C<u>H</u>$_2CH_2$O), 1.52 (quin, J = 7.5 Hz, 2 H, C(=O)CH_2C<u>H</u>$_2$), 1.17 - 1.27 (m, 2 H, C(=O)CH_2CH_2C<u>H</u>$_2$)

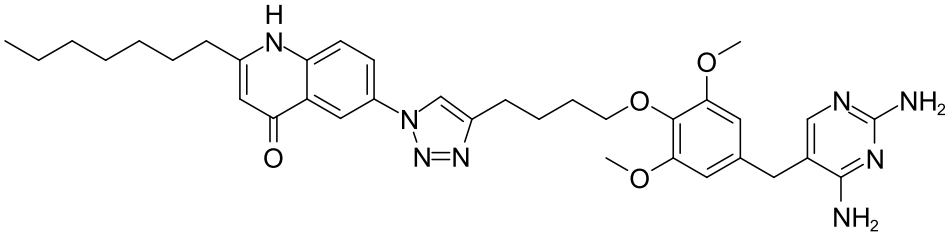
^{13}**C NMR** (125 MHz, DMSO d_6) δ / ppm = 175.4 (O<u>C</u>=O), 172.0 (NH<u>C</u>=O), 162.2 (C<u>C</u>(NH_2)N), 161.8 (N<u>C</u>(NH_2)N), 154.8 (<u>C</u>HNC(NH_2)N), 152.8 (*ipso* to OCH_3), 146.7 (CH=<u>C</u>CH_2CH_2), 135.5 (*para* to CH_2O), 134.8 (*ipso* to CH_2O), 121.6 (<u>C</u>H=CCH_2CH_2), 105.9 (CH_2<u>C</u>C(NH_2)=N), 105.8 (*meta* to CH_2O), 71.9 (CH_2CH_2 <u>C</u>H_2O), 65.2 (O<u>C</u>H_2CH_2CHNH), 55.8 (O<u>C</u>H_3), 49.0 (<u>C</u>H_2N), 47.8 (<u>C</u>HNH), 34.8 (C(=O)<u>C</u>H_2), 32.9 (C<u>C</u>H_2C), 29.4 (<u>C</u>H_2CH_2N), 29.1 (CH_2<u>C</u>H_2CH_2O), 28.2 (OCH_2<u>C</u>H_2CHNH), 25.5 (CH=CCH_2<u>C</u>H_2), 25.3 (C(=O)CH_2CH_2 <u>C</u>H_2), 24.7 (CH=C<u>C</u>H_2CH_2), 24.4 (C(=O)CH_2<u>C</u>H_2)

HRMS (ESI$^+$) m/z / Da = 597.3149, $[M+H]^+$ found, $[C_{29}H_{41}N_8O_6]^+$ requires 597.3144

$[\alpha]_D^{20}$ / $^\circ 10^{-1}$cm^{2}g^{-1} = -3.6 (c / g(100 ml)$^{-1}$ = 0.11 , MeOH)

The compound has not been reported previously.

1.32 6-(4-(4-(4-((2,4-Diaminopyrimidin-5-yl)methyl)-2,6-dimethoxyphenoxy)butyl)-1*H*-1,2,3-triazol-1-yl)-2-heptylquinolin-4(1*H*)-one 89



50 % water/*t*-BuOH (1 ml) was degassed by bubbling N_2 through it. This was then added to a mixture of 5-(4-(hex-5-yn-1-yloxy)-3,5-dimethoxybenzyl)pyrimidine-2,4-diamine **73** (3.6 mg, 10.0 μmol, 1 eq.) and 6-azido-2-heptylquinolin-4(1*H*)-one **40** (2.8 mg, 10.0 μmol, 1 eq.). A similarly degassed solution of $CuSO_4 \cdot 5\,H_2O$ (125 μg, 0.5 μmol, 0.05 eq. 50 mM), THPTA (218 μg, 0.5 μmol, 0.05 eq. 50 mM) and sodium ascorbate (198 μg, 1 μmol, 0.1 eq., 100 mM) in water (10 μl) was then added. The mixture was stirred at r.t. under argon for 1.5 h, then evaporated under reduced pressure. The residue was purified by preparative HPLC (5-100 % 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. **89** was obtained as a clear gum (2.6 mg, 4.1 μmol, 41.0 %).

TLC R_f = 0.17 (20 % MeOH/CH_2Cl_2)

IR (neat) ν_{max} / cm^{-1} = 2927.7 (C-H), 2855.5 (C-H), 1664.1 (pyrimidine), 1645.4 (pyrimidine and HHQ C=O),

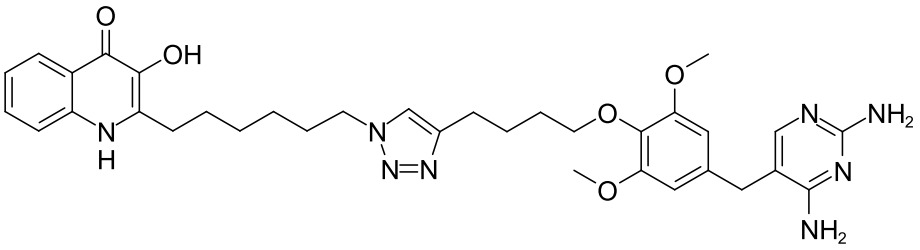
^{1}**H NMR** (500 MHz, DMSO d_6) δ / ppm = 11.80 (s, 1 H, N<u>H</u>), 8.69 (s, 1 H, NC<u>H</u>=CCH_2), 8.41 (d, J = 2.7 Hz, 1 H, *ortho* to C=O), 8.17 (dd, J = 9.0, 2.6 Hz, 1 H, *para* to C=O), 7.73 (d, J = 9.0 Hz, 1 H, <u>ortho</u> to NH), 7.51 (br s, 4 H, NH_2), 7.41 (s, 1 H, C<u>H</u>N=CNH_2), 6.61 (s, 2 H, *meta* to CH_2), 6.02 (d, J = 1.8 Hz, 1 H, C(=O)C<u>H</u>), 3.86 (t, J = 6.3 Hz, 2 H, C<u>H</u>$_2$O), 3.73 (s, 6 H, OC<u>H</u>$_3$), 3.57 - 3.62 (m, 2 H, CC<u>H</u>$_2$C), 2.78 (t, J = 7.5 Hz, 2 H, CH=CC<u>H</u>$_2$), 2.63 (t, J = 7.3 Hz, 2 H, HNCC<u>H</u>$_2$), 1.85 (quin, J = 7.5 Hz, 2 H, CH=CCH_2C<u>H</u>$_2$), 1.61 - 1.78 (m, 4 H, HNCCH_2C<u>H</u>$_2$ and CH=CCH_2CH_2C<u>H</u>$_2$), 1.31 - 1.40 (m, 4 H, HNCCH_2CH_2C<u>H</u>$_2$C<u>H</u>$_2$), 1.25 - 1.31 (m, 4 H, CH_3C<u>H</u>$_2$C<u>H</u>$_2$), 0.86 (t, J = 7.2 Hz, 3 H, C<u>H</u>$_3CH_2$)

^{13}C NMR (125 MHz, DMSO d_6) δ / ppm = 176.4 (C=O), 164.1 (CC(NH_2)N), 154.3 (HNC), 154.2 (NC(NH_2)N), 153.1 (*ipso* to OCH_3), 148.3 (CH=CCH_2CH_2), 140.2 (CHNC(NH_2)N), 139.6 (*ipso* to NH), 135.4 (*ipso* to CH_2O), 132.8 (*para* to CH_2O), 132.1 (*para* to NH), 124.9 (*ipso* to C=O), 123.7 (*para* to C=O), 120.3 (CH=CCH_2CH_2), 120.0 (*meta* to C=O and *ortho* to NH), 115.1 (*ortho* to C=O and *meta* to NH), 109.0 (CH_2CC(NH_2)=N), 108.0 (C(=O)CH), 106.3 (*meta* to CH_2O), 72.0 ($CH_2CH_2CH_2O$), 56.0 (OCH_3), 33.3 (HNCCH_2), 32.1 (CCH_2C), 31.2 ($CH_3CH_2CH_2$), 29.1 (CH_2CH_2O), 28.3 - 28.6 ($CH_3CH_2CH_2CH_2CH_2CH_2$), 25.3 ($CH_2CH_2CH_2O$), 24.7 (CH=CCH_2), 22.1 (CH_3CH_2), 14.0 (CH_3CH_2)

HRMS (ESI$^+$) m/z / Da = 641.3557, $[M+H]^+$ found, $[C_{35}H_{45}N_8O_4]^+$ 641.3558

The compound has not been reported previously.

1.33 2-(6-(4-(4-(4-((2,4-Diaminopyrimidin-5-yl)methyl)-2,6-dimethoxyphenoxy)butyl)-1*H*-1,2,3-triazol-1-yl)hexyl)-3-hydroxyquinolin-4(1*H*)-one 91



50 % water/*t*-BuOH (1 ml) was degassed by bubbling N_2 through it. This was then added to a mixture of 5-(4-(hex-5-yn-1-yloxy)-3,5-dimethoxybenzyl)pyrimidine-2,4-diamine **73** (14.2 mg, 39.8 μmol, 1 eq.) and 2-(6-azidohexyl)-3-hydroxyquinolin-4(1H)-one **19** (11.4 mg, 39.8 μmol, 1 eq.). A similarly degassed solution of $CuSO_4 \cdot 5\,H_2O$ (1.25 mg, 5 μmol, 0.125 eq. 50 mM), THPTA (2.18 mg, 5 μmol, 0.125 eq. 50 mM) and sodium ascorbate (1.98 mg, 10 μmol, 0.25 eq., 100 mM) in water (100 μl) was then added. The mixture was stirred at r.t. under argon for 3 h, then MeOH (1 ml) was added and the reaction mixture was dry-loaded onto SiO_2 and purified by column chromatography (SiO_2, 0-20 % MeOH/CH_2Cl_2). The combined pure fractions were dried with $MgSO_4$ and evaporated under reduced pressure. **91** was obtained as a pale brown amorphous solid (4.7 mg, 7.3 μmol, 18.3 %).

TLC R_f = 0.21 (20 % MeOH/CH_2Cl_2)

IR (neat) ν_{max} / cm^{-1} = 2924.8 (C-H), 2853.4 (C-H), 1660.0 (pyrimidine), 1638.8 (pyrimidine and PQS C=O),

^{1}H NMR (500 MHz, DMSO d_6) δ / ppm = 11.53 (br s, 1 H, NH), 8.09 (d, J = 8.0 Hz, 1 H, *ortho* to C=O), 7.83 (s, 1 H, NCH=CCH_2), 7.48 - 7.57 (m, 3 H, *para* to C=O, *ortho* to NH and CHN=CNH_2), 7.21 (ddd, J = 8.0, 6.3, 1.5 Hz, 1 H, *para* to NH), 6.55 (s, 2 H, *meta* to CH_2), 4.28 (t, J = 7.1 Hz, 2 H, CH_2N), 3.80 (t, J = 6.2 Hz, 2 H, CH_2O), 3.70 (s, 6 H, CH_3), 3.53 (d, J = 0.3 Hz, 2 H, CCH_2C), 2.73 (t, J = 7.5 Hz, 2 H, HNCCH_2), 2.64 (t, J = 7.4 Hz, 2 H, CH=CCH_2), 1.80 (quin, J = 7.4 Hz, 2 H, CH_2CH_2N), 1.73 (quin, J = 7.5 Hz, 2 H, CH=CCH_2CH_2), 1.66 (quin, J = 7.2 Hz, 2 H, HNCCH_2CH_2), 1.62 (quin, J = 6.8 Hz, 2 H, CH_2CH_2O), 1.33 - 1.40 (m, 2 H, HNCCH_2CH_2CH_2), 1.27 - 1.32 (m, 2 H, HNC$CH_2CH_2CH_2$CH_2)

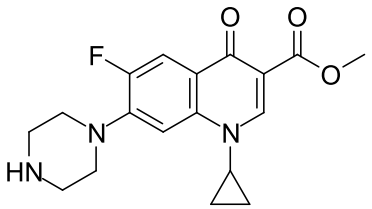
^{13}C NMR (125 MHz, DMSO d_6) δ / ppm = 168.9 (C=O), 162.5 (CC(NH_2)N), 162.5 (NC(NH_2)N), 152.9 (CHNC(NH_2)N), 152.8 (*ipso* to OCH_3), 146.8 (CH=CCH_2CH_2), 137.7 (COH), 137.3 (*para* to OH), 135.4

(HN$\underline{C}$), 135.1 (*para* to CH_2O), 134.8 (*ipso* to CH_2O), 129.9 (*para* to C=O), 124.4 (*ortho* to C=O and *meta* to NH), 122.1 (*ipso* to C=O), 121.5 (*para* to NH), 121.4 ($\underline{C}H{=}CCH_2CH_2$), 117.7 (*meta* to C=O and *ortho* to NH), 106.2 ($CH_2\underline{C}C(NH_2){=}N$), 105.8 (*meta* to CH_2O), 71.9 ($CH_2CH_2\underline{C}H_2O$), 55.8 ($O\underline{C}H_3$), 49.0 ($\underline{C}H_2N$), 32.8 ($C\underline{C}H_2C$), 29.5 ($\underline{C}H_2CH_2N$), 29.0 ($\underline{C}H_2CH_2O$), 28.1 ($HNCCH_2CH_2\underline{C}H_2$), 27.9 ($HNC\underline{C}H_2$), 27.6 ($HNCCH_2\underline{C}H_2$), 25.6 ($\underline{C}H_2CH_2CH_2N$), 25.4 ($\underline{C}H_2CH_2CH_2O$), 24.6 ($CH{=}C\underline{C}H_2CH_2$)

HRMS (ESI$^+$) m/z / Da = 643.3365, $[M+H]^+$ found, $[C_{34}H_{43}N_8O_5]^+$ requires 643.3351

The compound has not been reported previously.

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



Ciprofloxacin **28** (10.0 g, 30 mmol, 1 eq.) and *p*-toluenesulfonic acid (8.60 mg, 44.5 mmol, 1.5 eq.) were refluxed in methanol (500 ml) for 72 h. The mixture was cooled to room temperature and $NaHCO_3$ (sat., aq., 100 ml) and water (300 ml) were added. The product was extracted with CH_2Cl_2 (2×400 ml). The combined organic fractions were dried over $MgSO_4$ and evaporated under reduced pressure. **92** was obtained as a white amorphous solid (9.16 g, 26.5 mmol, 83.3 %).

TLC R_f = 0.13 (5 % MeOH/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, $NCH(CH\underline{H})_2$)

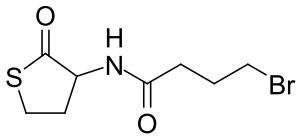
^{13}C NMR (101 MHz, MeOD) δ / ppm = 175.2 ($\underline{C}(=O)CC(=O)OCH_3$), 166.8 ($\underline{C}(=O)OCH_3$), 154.9 (d, J = 248.0 Hz, *ipso* to F), 150.1 ($\underline{C}{=}CC(=O)OCH_3$), 146.6 (d, J = 10.4 Hz, *ipso* to piperazine), 139.9 (*para* to F), 123.3 (d, J = 6.9 Hz, *para* to piperazine), 113.0 (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 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.[10]

1.35 4-Bromo-*N*-(2-oxotetrahydrothiophen-3-yl)butanamide 94



3-Aminodihydrothiophen-2(3*H*)-one hydrochloride **93** (15.0 g, 97.6 mmol, 1 eq.) and $NaHCO_3$ (16.4 g, 195 mmol, 2 eq.) were added to CH_2Cl_2 (150 ml) and water (150 ml). 4-Bromobutyryl chloride **58** (11.3 ml, 107 mmol, 1.1 eq.) was added dropwise over 45 min at 0 °C and the mixture was stirred for a further 1 h. The organic layer was separated and the aqueous layer was extracted with a second portion of CH_2Cl_2 (150 ml). The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. **94** was obtained as a white, amorphous solid (22.7 g, 85.8 mmol, 87.9 %).

TLC R_f = 0.19 (50 % EtOAc/PE)

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

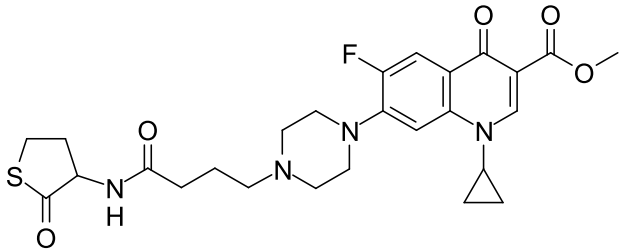
^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 6.08 (d, J = 6.1 Hz, 1 H, NH), 4.54 (dt, J = 12.9, 6.5 Hz, 1 H, CHNH), 3.49 (t, J = 6.4 Hz, 2 H, CH_2Br), 3.37 (ddd, J = 12.2, 11.5, 5.3 Hz, 1 H, SCHH), 3.26 (ddd, J = 11.5, 6.9, 1.3 Hz, 1 H, SCHH), 2.91 (dddd, J = 12.5, 6.7, 5.3, 1.3 Hz, 1 H, SCH_2CHH), 2.45 (t, 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)

^{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^+) The compound does not ionise.

The compound has been synthesised previously[11,12] but characterisation was not published.

1.36 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 95



Methyl 1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate **92** (50 mg, 0.145 mmol, 1 eq.), 4-bromo-*N*-(2-oxotetrahydrothiophen-3-yl)butanamide **94** (34.5 mg, 0.145 mmol, 1 eq.) and 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 **94** (34.5 mg, 0.145 mmol, 1 eq.) was added. After another 24 h a further portion was added (69.0 mg,

0.290 mmol, 2 eq.). After another 24 h the temperature was raised so the mixture was at reflux. After a final 24 h the precipitate was filtered off and the filtrate was purified by column chromatography (SiO_2, 5-10 % MeOH/CH_2Cl_2) followed by preparative HPLC (5-95 % acetonitrile/water over 20 min). **95** 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, 1 H, SC$\underline{H}$H), 3.26 - 3.33 (m, 5 H, SCH$\underline{H}$ and $CH_2CH_2CH_2N(CH_2C\underline{H}_2)CH_2C\underline{H}_2$), 2.93 - 3.03 (m, 4 H, $CH_2CH_2CH_2N(C\underline{H}_2)C\underline{H}_2$), 2.79 (br. t, J = 7.2, 7.2 Hz, 2 H, C(=O)$CH_2CH_2C\underline{H}_2$), 2.59 (dddd, J = 12.4, 6.9, 5.4, 1.4 Hz, 1 H, $SCH_2C\underline{H}$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, $SCH_2CH\underline{H}$), 1.97 (quin, J = 7.2 Hz, 2 H, C(=O)$CH_2C\underline{H}_2$), 1.32 - 1.37 (m, 2 H, NCH(C$\underline{H}$H)$_2$), 1.13 - 1.19 (m, 2 H, NCH(CH$\underline{H}$)$_2$)

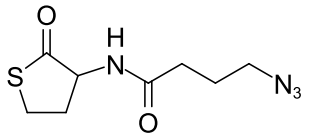
^{13}**C NMR** (126 MHz, MeOD) δ / ppm = 207.0 (S$\underline{C}$(=O)), 175.7 (NH$\underline{C}$(=O)), 175.1 ($\underline{C}$(=O)CC(=O)OCH_3), 166.6 ($\underline{C}$(=O)OCH_3), 154.7 (d, J = 249.0 Hz, *ipso* to F), 150.2 (s, $\underline{C}$H=CC(=O)OCH_3), 145.6 (d, J = 10.6 Hz, *ipso* to piperazine), 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)$CH_2CH_2\underline{C}H_2$), 53.8 ($CH_2CH_2CH_2N(\underline{C}H_2)\underline{C}H_2$), 52.3 (O$\underline{C}H_3$), 50.1 ($CH_2CH_2CH_2N(CH_2\underline{C}H_2)CH_2CH_2$), 50.0 ($CH_2CH_2CH_2N(CH_2CH_2)CH_2\underline{C}H_2$), 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)$CH_2\underline{C}H_2CH_2$), 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.[11,12] Only HRMS characterisation was published, and this agrees with the result above.

1.37 4-Azido-*N*-(2-oxotetrahydrothiophen-3-yl)butanamide 96



4-Bromo-*N*-(2-oxotetrahydrothiophen-3-yl)butanamide **94** (6.00 g, 27.0 mmol, 1 eq.) and NaN_3 (3.51 g, 54.1 mmol, 2 eq.) were refluxed in acetonitrile (120 ml) for 1.5 h. The solvent was evaporated under reduced pressure and the residue was partitioned between water (150 ml) and CH_2Cl_2 (150 ml). The aqueous layer was extracted twice more with CH_2Cl_2 (2×150 ml) and the combined organic fractions were dried with $MgSO_4$ and evaporated under reduced pressure. **96** 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)

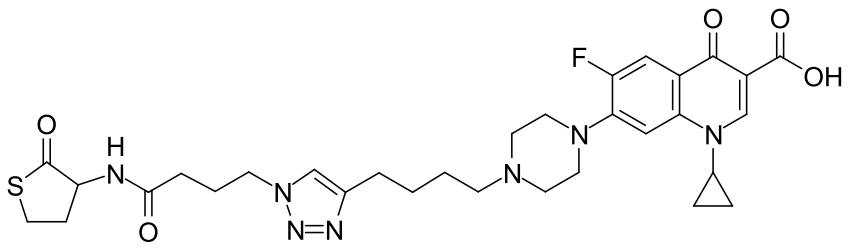
^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 6.71 (d, J = 7.3 Hz, 1 H, N<u>H</u>), 4.54 (dt, J = 13.0, 7.0 Hz, 1 H, C<u>H</u>NH), 3.30 (t, J = 6.7 Hz, 2 H, C<u>H$_2$</u>N$_3$), 3.31 (td, J = 11.7, 5.3 Hz, 1 H, SC<u>H</u>H), 3.19 (ddd, J = 11.3, 7.0, 1.2 Hz, 1 H, SCH<u>H</u>), 2.70 (dddd, J = 12.4, 6.8, 5.3, 1.2 Hz, 1 H, SCH$_2$C<u>H</u>H), 2.29 (t, J = 7.5 Hz, 1 H, C(=O)C<u>H</u>H), 2.28 (t, J = 7.1 Hz, 1 H, C(=O)CH<u>H</u>), 1.97 (qd, J = 12.4, 7.0 Hz, 1 H, SCH$_2$CH<u>H</u>), 1.85 (quin, J = 6.9 Hz, 2 H, C(=O)CH$_2$C<u>H$_2$</u>)

^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 205.4 (S<u>C</u>(=O)), 172.3 (NH<u>C</u>(=O)), 59.4 (<u>C</u>HNH), 50.6 (<u>C</u>H$_2$N$_3$), 32.8 (C(=O)<u>C</u>H$_2$), 31.8 (SCH$_2$<u>C</u>H$_2$), 27.5 (S<u>C</u>H$_2$), 24.6 (C(=O)CH$_2$<u>C</u>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.

1.38 1-Cyclopropyl-6-fluoro-4-oxo-7-(4-(4-(1-(4-oxo-4-((2-oxotetrahydrothiophen-3-yl)amino)butyl)-1*H*-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid 97



1-Cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **70** (15 mg, 36.7 μmol, 1 eq.) and 4-azido-*N*-(2-oxotetrahydrothiophen-3-yl)butanamide **96** (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 4 d. Water (10 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 preparative 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. **97** 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<u>H</u>), 8.66 (s, 1 H, *ortho* to C(=O)OH), 8.23 (d, J = 8.5 Hz, 1 H, N<u>H</u>), 7.90 (d, J = 13.4 Hz, 1 H, *ortho* to F), 7.84 (s, 1 H, C<u>H</u>=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<u>H</u>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, $CH_2CH_2CH_2N(CH_2C\underline{H}_2)CH_2C\underline{H}_2$), 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, $CH_2CH_2CH_2N(C\underline{H}_2)C\underline{H}_2$), 2.34 - 2.44 (m, 3 H, $SCH_2C\underline{H}H$ and $CH{=}CCH_2CH_2CH_2C\underline{H}_2$), 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, $SCH_2CH\underline{H}$ and $C(=O)CH_2C\underline{H}_2$), 1.64 (quin, J = 7.5 Hz, 2 H, $CH{=}CCH_2C\underline{H}_2$), 1.51 (quin, J = 7.5 Hz, 2 H, $CH{=}CCH_2CH_2C\underline{H}_2$), 1.28 - 1.34 (m, 2 H, NCH(C$\underline{H}$H)$_2$), 1.15 - 1.20 (m, 2 H, NCH(CH$\underline{H}$)$_2$)

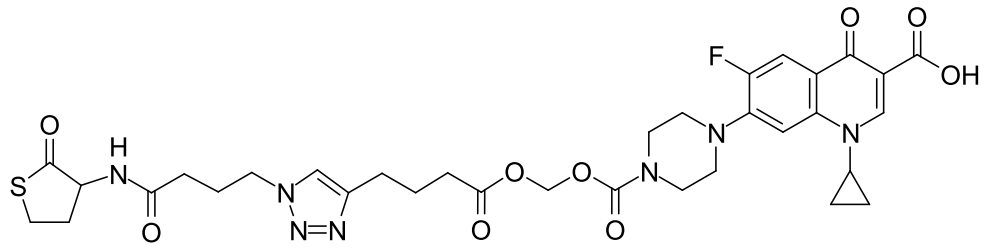
^{13}C NMR (126 MHz, DMSO d_6) δ / ppm = 205.6 (S$\underline{C}$(=O)), 176.4 ($\underline{C}$(=O)CC(=O)OH), 171.4 (NH$\underline{C}$(=O)), 166.0 ($\underline{C}$(=O)OH), 153.1 (d, J = 249.3 Hz, *ortho* to F), 148.0 ($\underline{C}$H=CC(=O)OH), 146.9 (CH=$\underline{C}CH_2$), 145.3 (d, J = 10.1 Hz, *ipso* 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)$\underline{C}$HNH), 57.4 ($CH{=}CCH_2CH_2CH_2\underline{C}H_2N$), 52.4 ($CH_2CH_2CH_2N(\underline{C}H_2)\underline{C}H_2$), 49.5 ($CH_2CH_2CH_2N(CH_2\underline{C}H_2)CH_2CH_2$), 49.5 ($CH_2CH_2CH_2N(CH_2CH_2)CH_2\underline{C}H_2$), 48.6 ($\underline{C}H_2NCH{=}C$), 35.9 (N$\underline{C}$H($CH_2$)$_2$), 31.9 (NHC(=O)$\underline{C}H_2$), 30.1 ($\underline{C}H_2CHNH$), 26.9 ($CH{=}CCH_2\underline{C}H_2$), 26.8 (S$\underline{C}H_2$), 25.9 (NHC(=O)$CH_2\underline{C}H_2$), 25.8 ($CH{=}CCH_2CH_2\underline{C}H_2$), 25.0 (CH=C$\underline{C}H_2$), 7.6 (NCH($\underline{C}H_2$)$_2$)

^{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

The compound has not been reported previously.

1.39 1-Cyclopropyl-6-fluoro-4-oxo-7-(4-((((4-(1-(4-oxo-4-((2-oxotetrahydrothiophen-3-yl)amino)butyl)-1*H*-1,2,3-triazol-4-yl)butanoyl)oxy)methoxy)carbonyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid 99



1-Cyclopropyl-6-fluoro-7-(4-(((hex-5-ynoyloxy)methoxy)carbonyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **98** (203 mg, 0.407 mmol, 1 eq.), 4-azido-*N*-(2-oxotetrahydrothiophen-3-yl)butanamide **96** (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). **99** 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)O$\underline{H}$), 8.65 (s, 1 H, *ortho* to C(=O)OH),

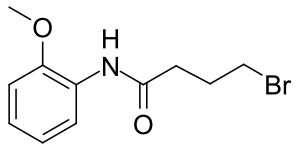
8.21 (d, J = 8.5 Hz, 1 H, N$\underline{H}$), 7.89 (d, J = 13.1 Hz, 1 H, *ortho* to F), 7.85 (s, 1 H, C$\underline{H}$=CCH$_2$), 7.57 (d, J = 7.4 Hz, 1 H, *meta* to F), 5.74 (s, 1 H, OC$\underline{H}_2$O), 4.58 (ddd, J = 12.6, 8.1, 7.2 Hz, 1 H, C$\underline{H}$NH), 4.30 (t, J = 6.9 Hz, 2 H, C(=O)CH$_2$CH$_2$C$\underline{H}_2$N), 3.80 (tt, J = 6.9, 3.6 Hz, 1 H, NC$\underline{H}$(CH$_2$)$_2$), 3.62 (br t, J = 5.2 Hz, 4 H, C(=O)N(C$\underline{H}_2$)C$\underline{H}_2$), 3.38 (td, J = 11.4, 5.5 Hz, 1 H, SC$\underline{H}$H), 3.34 (br. s, 4 H, C(=O)N(CH$_2$C$\underline{H}_2$)CH$_2$C$\underline{H}_2$), 3.27 (ddd, J = 11.0, 6.9, 1.6 Hz, 1 H, SCH$\underline{H}$), 2.64 (t, J = 7.6 Hz, 2 H, CH=CC$\underline{H}_2$), 2.44 (t, J = 7.5 Hz, 2 H, C$\underline{H}_2$C(=O)O), 2.40 (dddd, J = 12.3, 6.8, 5.4, 1.4 Hz, 1 H, SCH$_2$C$\underline{H}$H), 2.12 (t, J = 7.8 Hz, 1 H, NHC(=O)C$\underline{H}$H), 2.12 (t, J = 6.8 Hz, 1 H, NHC(=O)CH$\underline{H}$), 1.98 - 2.07 (m, 3 H, SCH$_2$C$\underline{H}$H and NHC(=O)CH$_2$C$\underline{H}_2$), 1.86 (quin, J = 7.5 Hz, 2 H, CH=CCH$_2$C$\underline{H}_2$), 1.29 - 1.36 (m, 2 H, NCH(C$\underline{H}$H)$_2$), 1.14 - 1.21 (m, 2 H, NCH(CH$\underline{H}$)$_2$)

^{13}C NMR (101 MHz, DMSO d$_6$) δ / ppm = 205.5 (S$\underline{C}$(=O)), 176.4 ($\underline{C}$(=O)CC(=O)OH), 171.8 ($\underline{C}$(=O)OCH$_2$O), 171.3 (NH$\underline{C}$(=O)), 165.9 ($\underline{C}$(=O)OH), 152.8 (d, J = 249.7 Hz, *ipso* to F), 152.9 (O$\underline{C}$(=O)N), 148.1 ($\underline{C}$H=CC(=O)OH), 146.0 (CH=$\underline{C}$CH$_2$), 144.9 (d, J = 9.6 Hz, *ipso* to piperazine), 139.1 (*para* to F), 122.0 ($\underline{C}$H=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 ($\underline{C}$C(=O)OH, and *meta* to C=O and *meta* to F), 80.3 (O$\underline{C}$H$_2$O), 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$$\underline{C}H_2$N), 43.4 (N($\underline{C}H_2$)CH$_2$), 43.0 (N(CH$_2$)$\underline{C}H_2$), 35.9 (N$\underline{C}$H(CH$_2$)$_2$), 32.7 (CH=CCH$_2CH_2$$\underline{C}H_2$C(=O)), 31.8 (NH$\underline{C}$(=O)$\underline{C}H_2$), 30.1 (SCH$_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$C(=O)), 24.0 (CH=CCH$_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$_7$O$_9$S]$^+$ requires 728.2503

The compound has not been reported previously.

1.40 4-Bromo-*N*-(2-methoxyphenyl)butanamide 101



2-Methoxyaniline **100** (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$_2$Cl$_2$ (100 ml). The mixture was cooled to 0 °C and 4-bromobutyryl chloride **58** (9.40 ml, 15.1 g, 81.2 mmol, 1 eq.) was added dropwise over 15 min. The mixture was stirred at 0 °C for 1.5 h, then the aqueous layer was removed. The organic layer was dried with MgSO$_4$ and purified by column chromatography (SiO$_2$, 5-25 % EtOAc/P.E.). The combined pure fractions were dried with MgSO$_4$ and evaporated under reduced pressure. **101** was obtained as an initially colourless liquid which slowly turned blue then black if left out on the bench (11.0 g, 40.6 mmol, 50.0 %).

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

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

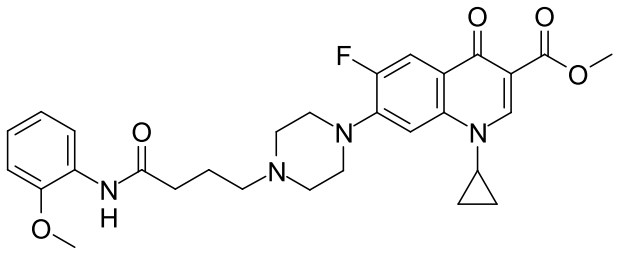
^{1}H NMR (400 MHz, CDCl$_3$ d$_1$) δ / ppm = 8.32 (dd, J = 8.0, 1.7 Hz, 1 H, *ortho* to NH), 7.85 (br s, 1 H, N$\underline{H}$), 7.02 (td, J = 7.9, 1.7 Hz, 1 H, *para* to NH), 6.93 (td, J = 7.7, 1.4 Hz, 1 H, *para* to OCH$_3$), 6.85 (dd, J = 8.1, 1.5 Hz, 1 H, *ortho* to OCH$_3$), 3.85 (s, 3 H, C$\underline{H}_3$), 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$_2$C$\underline{H}_2$)

^{13}**C NMR** (101 MHz, $CDCl_3$ d_1) δ / ppm = 169.4 (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 (CH_3), 35.4 (C(=O)CH_2), 33.1 (CH_2Br), 27.9 (C(=O)CH_2CH_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.

1.41 Methyl 1-cyclopropyl-6-fluoro-7-(4-(4-((2-methoxyphenyl)amino)-4-oxobutyl) piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 102



Methyl 1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate **92** (500 mg, 1.45 mmol, 1 eq.), 4-bromo-*N*-(2-methoxyphenyl)butanamide **101** (788 mg, 2.90 mmol, 2 eq.), DIPEA (1.28 ml, 950 mg, 7.35 mmol, 5 eq.), NaI (275 mg, 1.83 mmol, 1.3 eq.) and acetonitrile (10 ml) were stirred in a microwave reactor at 100 °C for 4 h. The mixture was dry-loaded onto SiO_2 and purified by column chromatography (SiO_2, 4 % $MeOH/CH_2Cl_2$). The combined pure fractions were dried with $MgSO_4$ and evaporated under reduced pressure. **102** was obtained as a bright pink amorphous solid (79.7 mg, 0.149 mmol, 10.2 %).

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)$CH_2CH_2CH_2N(CH_2CH_2)CH_2CH_2$), 2.67 (br t, J = 5.0 Hz, 4 H, C(=O)$CH_2CH_2CH_2N(CH_2)CH_2$), 2.53 (t, J = 7.0 Hz, 2 H, C(=O)$CH_2CH_2CH_2N$), 2.47 (t, J = 7.1 Hz, 2 H, C(=O)$CH_2CH_2CH_2N$), 1.97 (quin, J = 6.8 Hz, 2 H, C(=O)$CH_2CH_2CH_2N$), 1.25 - 1.33 (m, 2 H, NCH$(CHH)_2$), 1.07 - 1.14 (m, 2 H, NCH$(CHH)_2$)

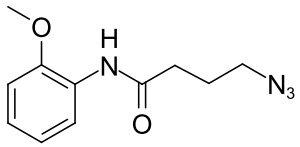
^{13}**C NMR** (101 MHz, $CDCl_3$ d_1) δ / ppm = 172.9 (C(=O)CC(=O)OCH_3), 170.8 (NHC(=O)), 166.2 (C(=O)O CH_3), 153.3 (d, J = 248.0 Hz, *ipso* to F), 148.2 (C=CC(=O)OCH_3), 147.6 (*ipso* to OCH_3), 144.4 (d, J = 10.4 Hz, *ipso* to piperazine), 137.9 (*para* to F), 127.6 (*ipso* to NH), 123.4 (*para* 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 ($CH_2CH_2CH_2N$), 55.6 (aromatic OCH_3), 52.7 ($CH_2CH_2CH_2N(CH_2)CH_2$), 51.9 (C(=O)OCH_3), 49.8 ($CH_2CH_2CH_2N(CH_2CH_2)CH_2CH_2$), 49.8 ($CH_2CH_2CH_2N(CH_2CH_2)CH_2CH_2$), 35.5 ($CH_2$

CH_2CH_2N), 34.5 (N$\underline{C}$H$(CH_2)_2$), 22.3 ($CH_2\underline{C}H_2CH_2N$), 8.0 (NCH($\underline{C}H_2)_2$)

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.

1.42 4-Azido-*N*-(2-methoxyphenyl)butanamide 103



4-Bromo-*N*-(2-methoxyphenyl)butanamide **101** (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.). **103** was obtained as an initially colourless liquid which slowly turned blue then black if left out on the bench (0.469 g, 2.00 mmol, 26.7 %).

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

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

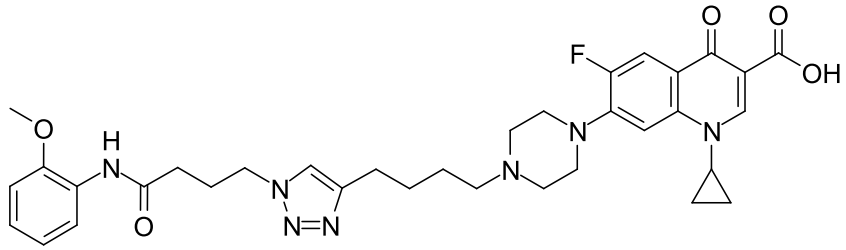
^{1}H NMR (400 MHz, $CDCl_3$ d_1) δ / ppm = 8.32 (dd, J = 7.9, 1.0 Hz, 1 H, *ortho* to NH), 7.86 (br s, 1 H, N$\underline{H}$), 7.00 (td, J = 7.5, 1.5 Hz, 1 H, *para* to NH), 6.90 (td, J = 7.7, 1.1 Hz, 1 H, *para* to OCH_3), 6.83 (dd, J = 8.1, 1.4 Hz, 1 H, *ortho* to OCH_3), 3.81 (s, 3 H, C$\underline{H}_3$), 3.33 (t, J = 6.7 Hz, 2 H, C$\underline{H}_2$Br), 2.42 (t, J = 7.2 Hz, 2 H, C(=O)C$\underline{H}_2$), 1.94 (quin, J = 6.9 Hz, 2 H, C(=O)CH_2C$\underline{H}_2$)

^{13}C NMR (101 MHz, $CDCl_3$ d_1) δ / ppm = 169.5 ($\underline{C}$(=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.[13]

1.43 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 104



1-Cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **70** (24.1 mg, 58.6 μmol, 1 eq.) and 4-azido-*N*-(2-methoxyphenyl)butanamide **103** (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). The combined pure fractions were dried with $MgSO_4$ and evaporated under reduced pressure. **104** was obtained as a clear amorphous solid (14.7 mg, 22.8 μmol, 39.0 %).

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)O$\underline{H}$), 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, N$\underline{H}$), 7.37 (s, 1 H, C$\underline{H}$=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$_2$CH$_2$C$\underline{H}_2$N), 3.88 (s, 3 H, C$\underline{H}_3$), 3.54 (tt, J = 6.9, 4.0 Hz, 1 H, NC$\underline{H}$(CH$_2$)$_2$), 3.35 (br t, J = 4.7 Hz, 4 H, CH=CCH$_2$CH$_2$CH$_2$CH$_2$N(CH$_2$C$\underline{H}_2$)CH$_2$C$\underline{H}_2$), 2.76 (t, J = 7.5 Hz, 2 H, CH=C$\underline{C}$H$_2$), 2.66 (t, J = 4.7 Hz, 4 H, CH=CCH$_2$CH$_2$CH$_2$CH$_2$N(C$\underline{H}_2$)C$\underline{H}_2$), 2.47 (t, J = 7.3 Hz, 2 H, CH=CCH$_2$CH$_2$CH$_2$C$\underline{H}_2$N), 2.44 (t, J = 6.8 Hz, 2 H, C(=O)C$\underline{H}_2$CH$_2$CH$_2$N), 2.32 (quin, J = 6.7 Hz, 2 H, C(=O)CH$_2$C$\underline{H}_2$CH$_2$N), 1.75 (quin, J = 7.6 Hz, 2 H, CH=CCH$_2$C$\underline{H}_2$CH$_2$CH$_2$N), 1.61 (quin, J = 7.5 Hz, 2 H, CH=CCH$_2$CH$_2$C$\underline{H}_2$CH$_2$N), 1.35 - 1.42 (m, 2 H, NCH(C$\underline{H}$H)$_2$), 1.17 - 1.22 (m, 2 H, NCH(CH$\underline{H}$)$_2$)

^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 177.1 ($\underline{C}$(=O)CC(=O)OH), 169.5 (NH$\underline{C}$(=O)), 167.0 ($\underline{C}$(=O)OH), 153.7 (d, J = 251.4 Hz, *ipso* to F), 148.1 (CH=$\underline{C}$CH$_2$), 147.8 (*ipso* to OCH_3), 147.3 ($\underline{C}$=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 ($\underline{C}$H=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 ($\underline{C}\underline{C}$(=O)OH), 104.7 (*meta* to C=O and *meta* to F), 58.1 (CH=CCH$_2$CH$_2$CH$_2\underline{C}$H$_2$N), 55.6 ($\underline{C}$H$_3$), 52.8 (CH=CCH$_2$CH$_2$CH$_2$CH$_2$N($\underline{C}$H$_2$)$\underline{C}$H$_2$), 49.8 (CH=CCH$_2$CH$_2$CH$_2$CH$_2$N(CH$_2\underline{C}$H$_2$)CH$_2$CH$_2$), 49.8 (CH=CCH$_2$CH$_2$CH$_2$CH$_2$N(CH$_2$CH$_2$)CH$_2\underline{C}$H$_2$), 49.1 (C(=O)CH$_2$CH$_2\underline{C}$H$_2$N), 35.2 (N$\underline{C}$H(CH$_2$)$_2$), 33.8 (C(=O)$\underline{C}$H$_2$CH$_2$CH$_2$N), 27.3 (CH=CCH$_2\underline{C}$H$_2$CH$_2$CH$_2$N), 26.4 (CH=CCH$_2$CH$_2\underline{C}$H$_2$CH$_2$N), 26.0 (C(=O)CH$_2\underline{C}$H$_2$CH$_2$N), 25.5 (CH=C$\underline{C}$H$_2$CH$_2$CH$_2$CH$_2$N), 8.2 (NCH

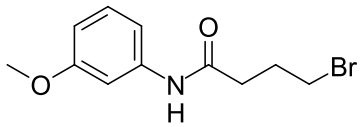
($\underline{C}H_2)_2$)

^{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.

1.44 4-Bromo-*N*-(3-methoxyphenyl)butanamide 106



3-Methoxyaniline **105** (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 **58** (3.13 ml, 5.03 g, 27.1 mmol, 1 eq.) was added dropwise over 5 min. The mixture was stirred at 0 °C for 1 h, then the aqueous layer was removed. The organic layer was dry-loaded onto SiO_2 and purified by column chromatography using a Combiflash (SiO_2, 0-100 % EtOAc/P.E.). The combined pure fractions were dried with $MgSO_4$ and evaporated under reduced pressure. **106** was obtained as a pale pink amorphous solid (3.66 g, 13.5 mmol, 49.6 %).

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

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

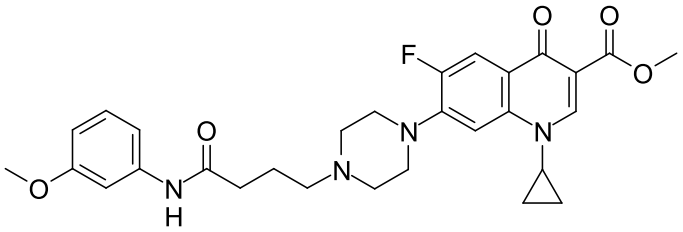
^{1}H NMR (400 MHz, $CDCl_3$ d_1) δ / ppm = 8.45 (s, 1 H, N$\underline{H}$), 7.27 (t, J = 2.2 Hz, 1 H, *ortho* to OCH_3 and *ortho* to NH), 7.14 (t, J = 8.1 Hz, 1 H, *meta* to OCH_3 and *meta* to NH), 7.02 (d, J = 8.3 Hz, 1 H, *para* to OCH_3), 6.62 (dd, J = 8.2, 2.1 Hz, 1 H, *para* to NH), 3.71 (s, 3 H, C$\underline{H}_3$), 3.42 (t, J = 6.5 Hz, 2 H, C$\underline{H}_2$Br), 2.51 (t, J = 6.9 Hz, 2 H, C(=O)C$\underline{H}_2$), 2.19 (quin, J = 6.8 Hz, 2 H, C(=O)CH$_2$C$\underline{H}_2$)

^{13}C NMR (101 MHz, $CDCl_3$ d_1) δ / ppm = 170.3 ($\underline{C}$(=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 ($\underline{C}H_3$), 35.3 (C(=O)$\underline{C}H_2$), 33.2 ($\underline{C}H_2$Br), 28.0 (C(=O)CH$_2\underline{C}H_2$)

HRMS (ESI$^+$) The compound does not ionise.

The compound has not been reported previously.

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



Methyl 1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate **92** (500 mg, 1.45 mmol, 1 eq.), 4-bromo-*N*-(3-methoxyphenyl)butanamide **106** (788 mg, 2.90 mmol, 2 eq.), DIPEA (1.28 ml, 950 mg, 7.35 mmol, 5 eq.), NaI (275 mg, 1.83 mmol, 1.3 eq.) and acetonitrile (10 ml) were stirred in a microwave reactor at 100 °C for 4 h. The mixture was evaporated under reduced pressure and partitioned between 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). The combined pure fractions were dried with $MgSO_4$ and evaporated under reduced pressure. **107** was obtained as an off-white amorphous solid (81.7 mg, 0.152 mmol, 10.5 %).

TLC R_f = 0.38 (10 % MeOH/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, N$\underline{H}$), 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)OC$\underline{H}_3$), 3.80 (s, 3 H, aromatic OC$\underline{H}_3$), 3.42 (tt, J = 6.8, 3.7 Hz, 1 H, NC$\underline{H}$(CH_2)$_2$), 3.31 (br t, J = 4.3 Hz, 4 H, C(=O)$CH_2CH_2CH_2$N($CH_2C\underline{H}_2$)$CH_2C\underline{H}_2$), 2.73 (br t, J = 4.5 Hz, 4 H, C(=O)$CH_2CH_2CH_2$N($C\underline{H}_2$)$C\underline{H}_2$), 2.58 (t, J = 6.5 Hz, 2 H, C(=O)$CH_2CH_2C\underline{H}_2$N), 2.48 (t, J = 6.8 Hz, 2 H, C(=O)$C\underline{H}_2CH_2CH_2$N), 2.00 (quin, J = 6.8 Hz, 2 H, C(=O)$CH_2C\underline{H}_2CH_2$N), 1.29 - 1.36 (m, 2 H, NCH(C$\underline{H}$H)$_2$), 1.11 - 1.17 (m, 2 H, NCH(CH$\underline{H}$)$_2$)

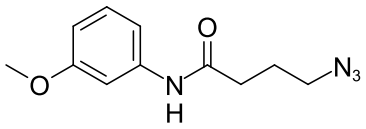
^{13}**C NMR** (101 MHz, $CDCl_3$) δ / ppm = 173.1 ($\underline{C}$(=O)CC(=O)OCH_3), 170.9 (NH$\underline{C}$(=O)), 166.3 ($\underline{C}$(=O)OCH_3), 160.1 (*ipso* to OCH_3), 153.3 (d, J = 250.1 Hz, *ipso* to F), 148.4 ($\underline{C}$=CC(=O)OCH_3), 144.1 (d, J = 10.1 Hz, *ipso* to piperazine), 139.4 (*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 ($\underline{C}$C(=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 ($CH_2CH_2\underline{C}H_2$N), 55.3 (aromatic O$\underline{C}H_3$), 52.6 ($CH_2CH_2CH_2$N($\underline{C}H_2$)$\underline{C}H_2$), 52.1 (C(=O)O$\underline{C}H_3$), 49.2 ($CH_2CH_2CH_2$N($CH_2\underline{C}H_2$)$CH_2\underline{C}H_2$), 35.2 ($\underline{C}H_2CH_2CH_2$N), 34.6 (N$\underline{C}$H(CH_2)$_2$), 21.7 ($CH_2\underline{C}H_2CH_2$N), 8.2 (NCH($\underline{C}H_2$)$_2$)

^{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.

1.46 4-Azido-*N*-(3-methoxyphenyl)butanamide 108



4-Bromo-*N*-(3-methoxyphenyl)butanamide **106** (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.). The combined pure fractions were dried with $MgSO_4$ and evaporated under reduced pressure. **108** was obtained as an straw-coloured liquid (0.294 g, 1.25 mmol, 16.7 %).

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

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

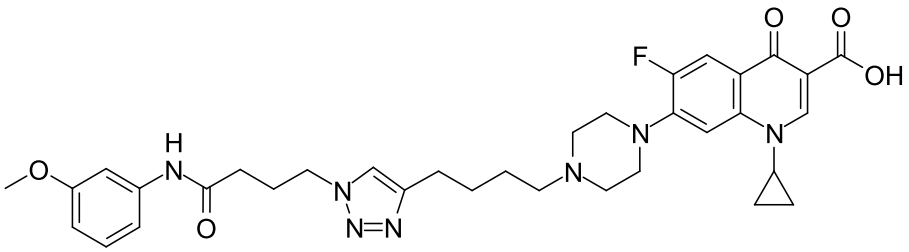
^{1}H NMR (400 MHz, MeOD) δ / ppm = 8.63 (br s, 1 H, N$\underline{H}$), 7.26 (t, J = 2.3 Hz, 1 H, *ortho* to OCH_3 and *ortho* to NH), 7.15 (t, J = 8.1 Hz, 1 H, *meta* to OCH_3 and *meta* to NH), 7.01 (dd, J = 7.8, 1.6 Hz, 1 H, *para* to OCH_3), 6.63 (dd, J = 8.2, 1.9 Hz, 1 H, *para* to NH), 3.69 (s, 3 H, C$\underline{H}_3$), 3.28 (t, J = 6.7 Hz, 2 H, C$\underline{H}_2$$N_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 (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^+) The compound does not ionise.

The compound has not been reported previously.

1.47 1-Cyclopropyl-6-fluoro-7-(4-(4-(1-(4-((3-methoxyphenyl)amino)-4-oxobutyl)-1*H*-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 109



1-Cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **70** (24.1 mg, 58.6 μmol, 1 eq.) and 4-azido-*N*-(3-methoxyphenyl)butanamide **108** (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 (4×15 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). The combined pure fractions were dried with $MgSO_4$ and evaporated under reduced pressure. **109** was obtained as a clear amorphous solid (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_2CH_2C<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=$CCH_2CH_2CH_2CH_2N(CH_2C$<u>H_2</u>$)CH_2C$<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=$CCH_2CH_2CH_2CH_2N(C$<u>H_2</u>$)C$<u>H_2</u>), 2.38 (t, J = 7.3 Hz, 2 H, CH=$CCH_2CH_2CH_2C$<u>H_2</u>N), 2.30 (t, J = 7.4 Hz, 2 H, C(=O)C<u>H_2</u>CH_2CH_2N), 2.10 (quin, J = 7.1 Hz, 2 H, C(=O)CH_2C<u>H_2</u>CH_2N), 1.64 (quin, J = 7.5 Hz, 2 H, CH=CCH_2C<u>H_2</u>CH_2CH_2N), 1.51 (quin, J = 7.2 Hz, 2 H, CH=CCH_2CH_2C<u>H_2</u>CH_2N), 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>)$_2$)

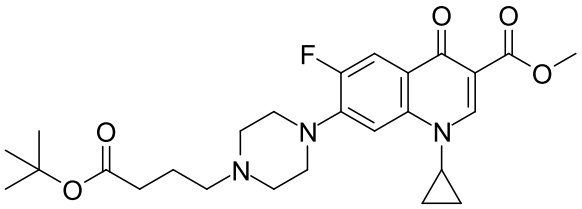
^{13}**C NMR** (101 MHz, DMSO d_6) δ / ppm = 176.3 (<u>C</u>(=O)CC(=O)OH), 170.1 (NH<u>C</u>(=O)), 165.9 (<u>C</u>(=O)OH), 159.4 (*ipso* to OCH_3), 153.0 (d, J = 248.6 Hz, *ipso* to F), 148.0 (CH=<u>C</u>CH_2), 146.9 (<u>C</u>=CC(=O)OH), 145.2 (d, J = 10.7 Hz, *ipso* to piperazine), 140.3 (*para* to 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=$CCH_2CH_2CH_2$<u>C</u>H_2N), 54.9 (<u>C</u>H_3), 52.4 (CH=$CCH_2CH_2CH_2CH_2N$(<u>C</u>H_2)<u>C</u>H_2), 49.5 (CH=$CCH_2CH_2CH_2CH_2N(CH_2$<u>C</u>H_2)CH_2CH_2), 49.4 (CH=$CCH_2CH_2CH_2CH_2N(CH_2CH_2)CH_2$<u>C</u>$H_2$), 48.7 (C(=O)$CH_2CH_2$<u>C</u>$H_2$N), 35.8 (N<u>C</u>H$(CH_2)_2$), 32.9 (C(=O)<u>C</u>$H_2CH_2CH_2$N), 26.8 (CH=$CCH_2$<u>C</u>$H_2CH_2CH_2$N), 25.7 (CH=$CCH_2CH_2$<u>C</u>$H_2CH_2$N), 25.5 (C(=O)$CH_2$<u>C</u>$H_2CH_2$N), 24.9 (CH=C<u>C</u>$H_2CH_2CH_2CH_2$N), 7.6 (NCH(<u>C</u>$H_2)_2$)

^{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.

1.48 Methyl 7-(4-(4-(*tert*-butoxy)-4-oxobutyl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate 136



Methyl 1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate **92** (200 mg, 0.579 mmol, 1 eq.), *tert*-butyl 4-bromobutanoate **135** (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 **150** (103 μl, 130 mg, 0.581 mmol, 1 eq.) was added, and the mixture was stirred in the microwave reactor at 100 °C for a further 8 h. The mixture was then dry-loaded onto SiO_2 and purified by column chromatography (SiO_2, 0-4 % MeOH/CH_2Cl_2). **136** was obtained as a white amorphous solid (141 mg, 0.289 mmol, 49.9 %).

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, $CH_2N(CH_2C\underline{H}_2)CH_2C\underline{H}_2$), 2.63 (t, J = 4.4 Hz, 4 H, $CH_2N(C\underline{H}_2)C\underline{H}_2$), 2.41 (t, J=7.3 Hz, 2 H, $C\underline{H}_2N(CH_2)CH_2$), 2.25 (t, J=7.4 Hz, 2 H, $C\underline{H}_2CH_2CH_2N(CH_2)CH_2$), 1.78 (quin, J=7.3 Hz, 2 H, $C\underline{H}_2CH_2N(CH_2)CH_2$), 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, $NCH(CH\underline{H})_2$)

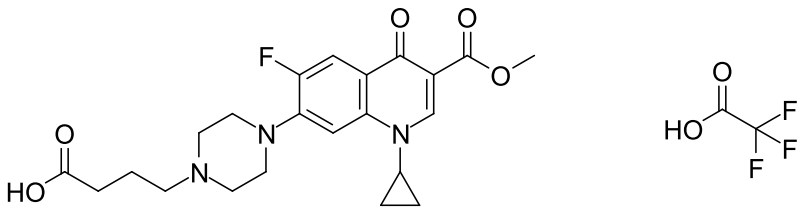
^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 172.7 ($\underline{C}$(=O)CC(=O)OCH_3), 172.6 ($\underline{C}$(=O)$OC(CH_3)_3$), 165.9 ($\underline{C}$(=O)OCH_3), 153.1 (d, J = 249.7 Hz, *ipso* to F), 148.1 ($\underline{C}$=CC(=O)OCH_3), 144.3 (d, J = 10.4 Hz, *ipso* to piperazine), 137.7 (*para* to F), 122.5 (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 ($C(=O)CH_2CH_2\underline{C}H_2N$), 52.7 ($C(=O)CH_2CH_2CH_2N(\underline{C}H_2)\underline{C}H_2$), 51.7 ($\underline{C}H_3$), 49.7 ($C(=O)CH_2CH_2CH_2N(CH_2\underline{C}H_2)CH_2CH_2$), 49.7 ($C(=O)CH_2CH_2CH_2N(CH_2CH_2)CH_2\underline{C}H_2$), 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.

1.49 4-(4-(1-Cyclopropyl-6-fluoro-3-(methoxycarbonyl)-4-oxo-1,4-dihydroquinolin-7-yl)piperazin-1-yl)butanoic acid trifluoroacetate 137



Methyl 7-(4-(4-(*tert*-butoxy)-4-oxobutyl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate **136** (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. **137** was obtained as a white solid (21.4 mg, 39.2 μmol, 95.6 %).

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$\underline{H})_2$)

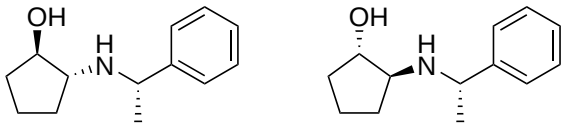
^{13}C NMR (101 MHz, DMSO d_6) δ / ppm = 173.5 ($CH_2\underline{C}$(=O)OH), 171.6 ($\underline{C}$(=O)CC(=O)OCH_3), 164.9 ($\underline{C}$(=O)OCH_3), 158.2 (q, J = 31.5 Hz, $CF_3\underline{C}$(=O)OH), 152.5 (d, J = 247.6 Hz, *ipso* to F), 148.5 ($\underline{C}$=CC(=O)OH), 142.3 (d, J = 10.7 Hz, *ipso* 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 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.

1.50 (1*R*,2*R*)-2-(((*S*)-1-Phenylethyl)amino)cyclopentan-1-ol 113 and (1*S*,2*S*)-2-(((*S*)-1-phenylethyl)amino)cyclopentan-1-ol 112



113 **112**

(*S*)-1-Phenylethan-1-amine **111** (7.85 ml, 7.38 g, 60.9 mmol, 1 eq.) was dissolved in CH_2Cl_2 (50 ml) and stirred rapidly at 0 °C. A solution of $AlMe_3$ (31 ml, 2.0 M in heptane, 60.9 mmol) was added dropwise and the mixture was stirred at 0 °C for 1 h. A solution of cyclohexene oxide **110** (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). **113** was obtained as a pale yellow oil (4.08 g, 19.9 mmol, 32.6 %). **112** was obtained as pale yellow crystals (4.48 g, 21.8 mmol, 35.8 %).

(1*R*,2*R*)-2-(((*S*)-1-Phenylethyl)amino)cyclopentan-1-ol 113

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

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

^{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_2$$CH_2$CHOH)

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

$[\boldsymbol{\alpha}]_D^{20}$ / $°10^{-1}cm^2g^{-1}$ = -92.8, lit. = -76.8 (c / g(100 ml)$^{-1}$ = 1.19, MeOH)

(1*S*,2*S*)-2-(((*S*)-1-Phenylethyl)amino)cyclopentan-1-ol 112

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$\underline{H}CH_3$), 3.85 (q, J = 6.6 Hz, 1 H, C$\underline{H}$OH), 2.83 (td, J = 7.6, 5.7 Hz, 1 H, C$\underline{H}$NH), 1.85 - 1.97 (m, 1 H, C$\underline{H}$HCHOH), 1.77 (dtd, J = 12.9, 7.9, 4.9 Hz, 1 H, C$\underline{H}$HCHNH), 1.55 - 1.68 (m, 2 H, C$\underline{H}_2CH_2CHOH$), 1.47 - 1.55 (m, 1 H, CH$\underline{H}$CHOH), 1.36 (d, J = 6.6 Hz, 3 H, C$\underline{H}_3$), 1.12 (dq, J = 12.7, 8.1 Hz, 1 H, CH$\underline{H}$CHNH)

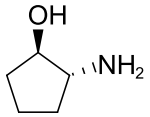
^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 145.61 (*ipso* to $CHCH_3$), 128.08 (*meta* to $CHCH_3$), 126.61 (*para* to $CHCH_3$), 126.33 (*ortho* to $CHCH_3$), 77.43 (C$\underline{H}$OH), 64.45 (C$\underline{H}$NH), 56.62 (C$\underline{H}CH_3$), 32.01 ($\underline{C}H_2$CHOH), 30.56 ($\underline{C}H_2$CHNH), 23.30 ($\underline{C}H_3$), 20.06 ($\underline{C}H_2CH_2$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, lit. = -22.1 (c / g(100 ml)$^{-1}$ = 0.96 , MeOH)

The compounds have been synthesised previously,[14,15] but NMR data were not published. The enantiomers of both compounds have also been synthesised previously, and the ^{1}H NMR data for these are consistent with the the above data.[16]

1.51 (1*R*,2*R*)-2-Aminocyclopentan-1-ol 115



(1*R*,2*R*)-2-(((*S*)-1-Phenylethyl)amino)cyclopentan-1-ol **113** (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. **115** 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$\underline{H}$OH), 3.00 (td, J = 7.3, 5.6 Hz, 1 H, C$\underline{H}NH_2$), 2.00 (dtd, J = 13.0, 7.7, 5.6 Hz, 1 H, C$\underline{H}$HCHNH$_2$), 1.97 (ddt, J = 13.0, 8.7, 6.6 Hz, 1 H, C$\underline{H}$HCHOH), 1.63 - 1.77 (m, 2 H, C$\underline{H}_2CH_2$CHOH), 1.53 (ddt, J = 13.0, 9.5, 6.2 Hz, 1 H, CH$\underline{H}$CHOH), 1.37 (ddt, J = 13.0, 8.3, 7.8 Hz, 1 H, CH$\underline{H}$CHNH$_2$)

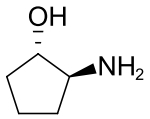
^{13}C NMR (101 MHz, MeOD) δ / ppm = 80.7 (C$\underline{H}$OH), 60.8 (C$\underline{H}NH_2$), 33.2 ($\underline{C}H_2$CHOH), 32.1 ($\underline{C}H_2$CHNH$_2$), 21.2 ($\underline{C}H_2CH_2$CHOH)

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, lit. = -32.9 (c / g(100 ml)$^{-1}$ = 1.5 , EtOH)

The data are consistent with the literature.[15,17]

1.52 (1*S*,2*S*)-2-Aminocyclopentan-1-ol 114



(1*S*,2*S*)-2-(((*S*)-1-Phenylethyl)amino)cyclopentan-1-ol **112** (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. **114** 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, 5.6 Hz, 1 H, C<u>H</u>HCHNH_2), 1.97 (ddt, J = 13.0, 8.7, 6.4 Hz, 1 H, C<u>H</u>HCHOH), 1.64 - 1.77 (m, 2 H, C<u>H</u>$_2$$CH_2$CHOH), 1.53 (ddt, J = 13.0, 9.5, 6.2 Hz, 1 H, CH<u>H</u>CHOH), 1.37 (ddt, J = 12.8, 8.5, 7.7 Hz, 1 H, CH<u>H</u>CHNH_2)

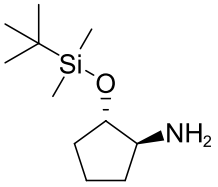
^{13}C NMR (101 MHz, MeOD) δ / ppm = 80.6 (<u>C</u>HOH), 60.7 (<u>C</u>HNH_2), 33.2 (<u>C</u>H$_2$CHOH), 32.2 (<u>C</u>H$_2$CHNH_2), 21.2 (<u>C</u>H$_2$$CH_2$CHOH)

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, lit. = 29.7 (c / g(100 ml)$^{-1}$ = 0.5, EtOH)

The data are consistent with the literature.[15,17]

1.53 (1*S*,2*S*)-2-((*tert*-Butyldimethylsilyl)oxy)cyclopentan-1-amine 125



(1*S*,2*S*)-2-Aminocyclopentan-1-ol **114** (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 TBDMSOTf (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). **125** was obtained as a yellow oil (1.00 g, 4.64 mmol, 97.7 %).

TLC R_f = 0.23 (10 % MeOH/CH_2Cl_2)

IR (neat) ν_{max} / cm^{-1} = 2953.6 (C-H), 2931.1 (C-H), 2888.4 (C-H), 2858.8 (C-H), 1625.2 (N-H bend)

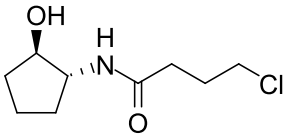
^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 4.13 (q, J = 5.8 Hz, 1 H, C<u>H</u>OSi), 3.31 (td, J = 7.1, 5.2 Hz, 1 H, C<u>H</u>NH_2), 2.09 - 2.19 (m, 1 H, C<u>H</u>HCHNH_2), 1.97 (ddq, J = 8.8, 7.0, 6.0 Hz, 1 H, C<u>H</u>HCHOSi), 1.74 - 1.86 (m, 2 H, C<u>H</u>$_2$$CH_2$CHOSi), 1.64 - 1.74 (m, 1 H, CH<u>H</u>CHOSi), 1.58 (ddt, J = 13.2, 9.1, 6.0 Hz, 1 H, CH<u>H</u>CHNH_2), 0.88 (s, 9 H, C(C<u>H</u>$_3$)$_3$), 0.09 (s, 3 H, SiC<u>H</u>$_3$), 0.07 (s, 3 H, SiC<u>H</u>$_3$)

^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 76.3 (<u>C</u>HOSi), 59.7 (<u>C</u>HNH), 32.2 (<u>C</u>H_2CHOSi), 26.8 (<u>C</u>H_2CHNH_2), 25.6 (C(<u>C</u>H_3)$_3$), 19.7 (<u>C</u>$H_2$$CH_2$CHOSi), 17.7 (<u>C</u>$(CH_3)_3$), -4.8 (Si<u>C</u>$H_3$), -5.2 (Si<u>C</u>$H_3$)

HRMS (ESI$^+$) m/z / Da = 216.1785, $[M+H]^+$ found, $[C_{11}H_{26}NOSi]^+$ requires 216.1784

The compound has not been reported previously.

1.54 4-Chloro-*N*-((1*R*,2*R*)-2-hydroxycyclopentyl)butanamide 141



(1*R*,2*R*)-2-Aminocyclopentan-1-ol **115** (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 and 4-chlorobutyryl chloride **139** (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). The combined pure fractions were dried with $MgSO_4$ and evaporated under reduced pressure. **141** was obtained as a white amorphous solid (651 mg, 3.16 mmol, 64.1 %).

TLC R_f = 0.35 (EtOAc)

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

^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 6.12 (br s, 1 H, N<u>H</u>), 4.42 (br s, 1 H, O<u>H</u>), 3.94 (q, J = 6.6 Hz, 1 H, C<u>H</u>OH), 3.82 (tt, J = 8.4, 5.3 Hz, 1 H, C<u>H</u>NH), 3.60 (t, J = 6.2 Hz, 2 H, C<u>H</u>$_2$Cl), 2.38 (t, J = 7.2 Hz, 2 H, C<u>H</u>$_2$C=O), 2.05 - 2.16 (m, 3 H, C<u>H</u>HCHNH and C<u>H</u>$_2$$CH_2$Cl), 1.96 - 2.04 (m, 1 H, C<u>H</u>HCHOH), 1.74 - 1.85 (m, 1 H, C<u>H</u>HCH_2CHOH), 1.58 - 1.73 (m, 2 H, CH<u>H</u>CH_2CHOH and CH<u>H</u>CHOH), 1.43 (dq, J = 12.7, 8.3 Hz, 1 H, CH<u>H</u>CHNH)

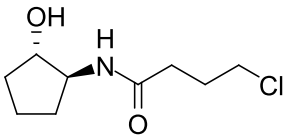
^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 173.8 (<u>C</u>=O), 79.4 (<u>C</u>HOH), 60.6 (<u>C</u>HNH), 44.4 (<u>C</u>H_2Cl), 32.8 (<u>C</u>H_2C=O), 32.4 (<u>C</u>H_2CHOH), 30.1 (<u>C</u>H_2CHNH), 28.0 (<u>C</u>$H_2$$CH_2$Cl), 21.1 (<u>C</u>$H_2$$CH_2$CHOH)

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

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

The compound has not been reported previously.

1.55 4-Chloro-*N*-((1*S*,2*S*)-2-hydroxycyclopentyl)butanamide 140



(1*S*,2*S*)-2-Aminocyclopentan-1-ol **114** (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, and 4-chlorobutyryl chloride **139** (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). The combined pure fractions were dried with $MgSO_4$ and evaporated under reduced pressure. **140** was obtained as a white amorphous solid (35.6 mg, 173 μmol, 24.2 %).

TLC R_f = 0.35 (EtOAc)

^{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_2CHOH), 1.58 - 1.74 (m, 2 H, CHHCH_2CHOH and CHHCHOH), 1.42 (dq, J = 12.5, 8.4 Hz, 1 H, CHHCHNH)

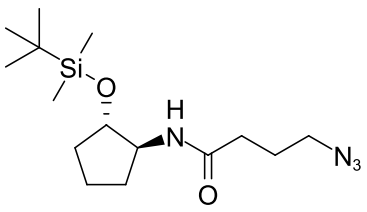
^{13}**C NMR** (101 MHz, $CDCl_3$) δ / ppm = 173.8 (C=O), 79.4 (CHOH), 60.6 (CHNH), 44.4 (CH_2Cl), 32.8 (CH_2C=O), 32.4 (CH_2CHOH), 30.2 (CH_2CHNH), 28.0 (CH_2CH_2Cl), 21.2 (CH_2CH_2CHOH)

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)

The compound has not been reported previously.

1.56 4-Azido-*N*-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclopentyl)butanamide 129



(1*S*,2*S*)-2-((*tert*-Butyldimethylsilyl)oxy)cyclopentan-1-amine **125** (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) at 0 °C, and 4-bromobutyryl chloride (25.3 ml, 40.5 mg, 0.219 mmol, 0.95 eq.) was added dropwise. The mixture was stirred for 3 h at 0 °C. The aqueous layer was removed and NaN_3 (100 mg, 1.54 mmol, 6.6 eq.) and DMF (3 ml) were added. The mixture was then stirred at 40 °C for 6 h. The solvents were then evaporated using a N_2 stream and the residue was

purified by column chromatography (SiO_2, 0.5 % MeOH/CH_2Cl_2). The combined pure fractions were dried with $MgSO_4$ and evaporated under reduced pressure. **129** 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, N<u>H</u>), 3.97 - 4.01 (m, 1 H, C<u>H</u>OSi), 3.93 - 3.98 (m, 1 H, C<u>H</u>NH), 3.35 (t, J = 6.6 Hz, 2 H, C<u>H$_2$</u>N_3), 2.24 (t, J = 7.0 Hz, 2 H, C<u>H$_2$</u>C=O), 2.09 - 2.19 (m, 1 H, C<u>H</u>HCHNH), 1.89 - 1.97 (quin, J = 6.8 Hz, 2 H, C<u>H$_2$</u>CH_2N_3), 1.74 - 1.84 (m, 2 H, C<u>H</u>HCHOSi and C<u>H</u>HCH$_2$CHOSi), 1.60 - 1.70 (m, 1 H, CH<u>H</u>CH$_2$CHOSi), 1.51 - 1.61 (m, 1 H, CH<u>H</u>CHOSi), 1.31 - 1.39 (m, 1 H, CH<u>H</u>CHNH), 0.87 (s, 9 H, C(C<u>H$_3$</u>)$_3$), 0.08 (s, 3 H, SiC<u>H$_3$</u>), 0.06 (s, 3 H, SiC<u>H$_3$</u>)

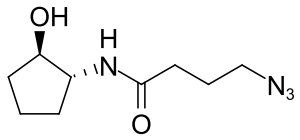
^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 171.17 (<u>C</u>=O), 77.80 (<u>C</u>HOSi), 58.36 (<u>C</u>HNH), 50.77 (<u>C</u>H$_2$$N_3$), 33.29 (<u>C</u>H$_2$C=O), 32.57 (<u>C</u>H$_2$CHOSi), 29.36 (<u>C</u>H$_2$CHNH), 25.72 (C(<u>C</u>H$_3$)$_3$), 24.77 (<u>C</u>H$_2$$CH_2N_3$), 20.40 (<u>C</u>H$_2CH_2$CHO Si), 17.95 (<u>C</u>(CH$_3$)$_3$), -4.75 (Si<u>C</u>H$_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)

The compound has not been reported previously.

1.57 4-Azido-*N*-((1*R*,2*R*)-2-hydroxycyclopentyl)butanamide 119



4-Chloro-*N*-((1*R*,2*R*)-2-hydroxycyclopentyl)butanamide **141** (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. **119** was obtained as white needles (181 mg, 0.852 mmol, 87.6 %).

TLC R_f = 0.35 (EtOAc)

mp T / °C = 56.0-59.5 (*i*-PrOH, $CHCl_3$)

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, N<u>H</u>), 4.82 (br. s., 1 H, O<u>H</u>), 3.88 (q, J =

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

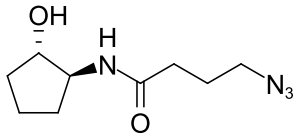
^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 173.8 (<u>C</u>=O), 78.8 (<u>C</u>HOH), 59.9 (<u>C</u>HNH), 50.5 (<u>C</u>H$_2$N$_3$), 32.5 (<u>C</u>H$_2$C=O), 32.0 (<u>C</u>H$_2$CHOH), 29.5 (<u>C</u>H$_2$CHNH), 24.6 (<u>C</u>H$_2$CH$_2$N$_3$), 20.7 (<u>C</u>H$_2$CH$_2$CHOH)

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)

The compound has not been reported previously.

1.58 4-Azido-*N*-((1*S*,2*S*)-2-hydroxycyclopentyl)butanamide 118



4-Chloro-*N*-((1*S*,2*S*)-2-hydroxycyclopentyl)butanamide **140** (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 mixture was then partitioned between water (20 ml) and 10 % *i*-PrOH/$CHCl_3$ (5 ml). The aqueous layer was extracted again with 10 % *i*-PrOH/$CHCl_3$ (2×5 ml) and the combined organic fractions were dried with $MgSO_4$ and evaporated under reduced pressure. **118** was obtained as white needles (16.2 mg, 0.0764 mmol, 45.0 %).

TLC R_f = 0.35 (EtOAc)

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

^{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, 6.0, 4.6 Hz, 1 H, C<u>H</u>NH), 3.37 (t, J = 6.4 Hz, 2 H, C<u>H$_2$</u>N$_3$), 2.31 (t, J = 7.2 Hz, 2 H, C<u>H$_2$</u>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$_2$</u>CH$_2$N$_3$), 1.60 - 1.85 (m, 3 H, C<u>H$_2$</u>CH<u>H</u>CHOH), 1.42 (dq, J = 12.8, 8.3 Hz, 1 H, CH<u>H</u>CHNH)

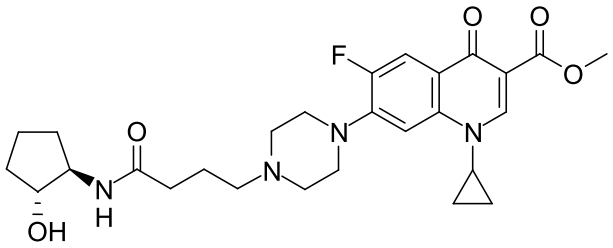
^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 173.8 (<u>C</u>=O), 79.7 (<u>C</u>HOH), 61.0 (<u>C</u>HNH), 50.7 (<u>C</u>H$_2$N$_3$), 32.8 (<u>C</u>H$_2$C=O), 32.6 (<u>C</u>H$_2$CHOH), 30.5 (<u>C</u>H$_2$CHNH), 24.7 (<u>C</u>H$_2$CH$_2$N$_3$), 21.3 (<u>C</u>H$_2$CH$_2$CHOH)

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)

The compound has not been reported previously.

1.59 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 121



4-(4-(1-Cyclopropyl-6-fluoro-3-(methoxycarbonyl)-4-oxo-1,4-dihydroquinolin-7-yl)piperazin-1-yl)butanoic acid trifluoroacetate **137** (200 mg, 0.367 mmol, 1 eq.), (1*R*,2*R*)-2-aminocyclopentan-1-ol **115** (80 mg, 0.791 mmol, 2.1 eq.), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (112 mg, 0.584 mmol, 1.6 eq.), 1-hydroxybenzotriazole (96 mg, 0.710 mmol, 1.9 eq.) and DIPEA (192 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 preparative 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. **121** 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$CHOH), 1.42 (ddt, J = 13.1, 8.2, 5.3 Hz, 1 H, CH$\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}\underline{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$)

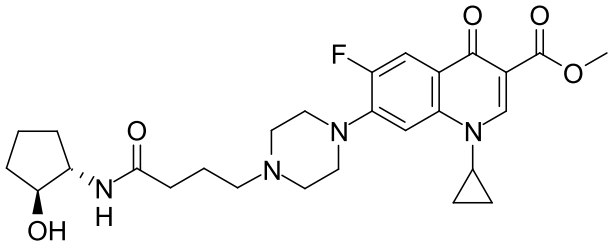
^{19}F NMR (376.45 MHz, DMSO d_6) δ / ppm = -124.3 (ciprofloxacin F)

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

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

The compound has not been reported previously.

1.60 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 120



4-(4-(1-Cyclopropyl-6-fluoro-3-(methoxycarbonyl)-4-oxo-1,4-dihydroquinolin-7-yl)piperazin-1-yl)butanoic acid trifluoroacetate **137** (52.1 mg, 95.5 μmol, 1 eq.), (1*S*,2*S*)-2-aminocyclopentan-1-ol **114** (19.5 mg, 193 μmol, 2 eq.), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (29.7 mg, 155 μmol, 1.6 eq.), 1-hydroxyben zotriazole (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 preparative HPLC (5-50 % acetonitrile/water over 15 min). The combined pure fractions were evaporated under reduced pressure and then partitioned between $NaHCO_3$ (aq., sat., 5 ml) and CH_2Cl_2 (5 ml). The organic layer was removed and the aqueous layer was extracted twice more with CH_2Cl_2 (2×5 ml). The combined organic fractions were dried with $MgSO_4$ and evaporated under reduced pressure. **120** was obtained as a white amorphous solid (4.9 mg, 9.5 μmol, 9.9 %).

TLC R_f = 0.38 (30 % MeOH/CH_2Cl_2)

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

^{1}**H NMR** (500 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), 7.69 (d, J = 6.9 Hz, 1 H, CHN$\underline{H}$), 7.43 (d, J = 7.6 Hz, 1 H, *meta* to F), 4.73 (br s, 1 H, CHO$\underline{H}$), 3.77 - 3.81 (m, 1 H, C$\underline{H}$OH), 3.74 - 3.77 (m, 1 H, C$\underline{H}$NH), 3.73 (s, 3 H, C$\underline{H}_3$), 3.65 (tt, J = 6.9, 4.0 Hz, 1 H, NC$\underline{H}$(CH$_2$)$_2$), 3.24 (br. t, J = 4.2 Hz, 4 H, CH$_2$N(CH$_2$C$\underline{H}_2$)CH$_2$C$\underline{H}_2$), 2.55 (br t, J = 5.0 Hz, 4 H, CH$_2$N(C$\underline{H}_2$)C$\underline{H}_2$), 2.32 (t, J = 7.2 Hz, 2 H, C$\underline{H}_2$N(CH$_2$)CH$_2$), 2.10 (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, CH$\underline{H}$HCHNH), 1.77 (ddt, J = 12.6, 8.9, 6.3 Hz, 1 H, CH$\underline{H}$HCHOH), 1.68 (quin, J = 7.4 Hz, 2 H, C$\underline{H}_2$CH$_2$N(CH$_2$)CH$_2$), 1.53 - 1.64 (m, 2 H, C$\underline{H}_2$CH$_2$CHOH), 1.42 (ddt, J = 12.9, 8.4, 5.2 Hz, 1 H, CH$\underline{H}$CHOH), 1.31 (ddt, J = 13.0, 8.6, 6.4 Hz, 1 H, CH$\underline{H}$CHNH), 1.22 - 1.28 (m, 2 H, NCH(C$\underline{H}$H)$_2$), 1.06 - 1.12 (m, 2 H, NCH(CH$\underline{H}$)$_2$)

^{13}**C NMR** (126 MHz, DMSO d_6) δ / ppm = 171.9 (NH$\underline{C}$(=O)CH$_2$), 171.5 ($\underline{C}$(=O)CC(=O)OCH$_3$), 165.0 ($\underline{C}$(=O)OCH$_3$), 152.6 (d, J = 247.4 Hz, *ipso* to F), 148.2 ($\underline{C}$=CC(=O)OCH$_3$), 143.9 (d, J = 10.3 Hz, *ipso* to piperazine), 138.1 (*para* to F), 121.7 (d, J = 6.4 Hz, *para* to piperazine), 111.5 (d, J = 23.0 Hz, *ortho* to C=O and *ortho* to F), 109.0 ($\underline{C}$C(=O)OCH$_3$), 106.2 (*meta* to C=O and *meta* to F), 76.2 ($\underline{C}$HOH), 57.6 ($\underline{C}$HNH), 57.2 (CH$_2$CH$_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$)CH$_2CH_2$), 49.6

($CH_2CH_2CH_2N(CH_2CH_2)CH_2\underline{C}H_2$), 34.7 ($N\underline{C}H(CH_2)_2$), 33.2 ($C(=O)\underline{C}H_2$), 32.2 ($\underline{C}H_2CHOH$), 29.5 ($\underline{C}H_2CH$ NH), 22.5 ($C(=O)CH_2\underline{C}H_2$), 20.6 ($\underline{C}H_2CH_2CHOH$), 7.5 ($NCH(\underline{C}H_2)_2$)

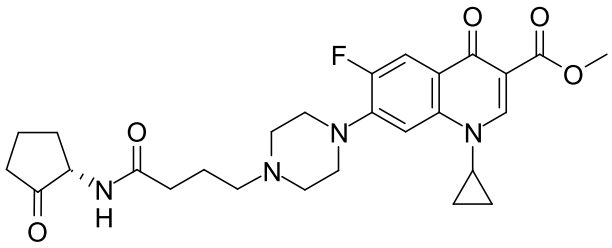
^{19}F NMR (376.45 MHz, MeOD) δ / ppm = -125.5

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

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

The compound has not been reported previously.

1.61 Methyl (*S*)-1-cyclopropyl-6-fluoro-4-oxo-7-(4-(4-oxo-4-((2-oxocyclopentyl)amino)butyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate 122



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 **120** (20.0 mg, 38.9 μmol, 1 eq.) and Dess-Martin periodinane (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 preparative 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. **122** was obtained as a white amorphous solid (11.3 mg, 22.0 μmol, 56.7 %).

remove unless very active as not fully characterised

^{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, $NHC(=O)C\underline{H}_2$, $C\underline{H}_2C(=O)CHNH$ and $C\underline{H}HCHNH$), 1.89 - 1.96 (m, 1 H, $C\underline{H}HCH_2CHNH$), 1.69 - 1.80 (m, 3 H, $CH\underline{H}CH_2CHNH$, $CH\underline{H}CHNH$ and $NHC(=O)CH_2C\underline{H}_2$), 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 ($\underline{C}H_2C(=O)CHNH$), 34.8 ($N\underline{C}H(CH_2)_2$), 28.8 ($\underline{C}H_2CHNH$), 18.1 ($\underline{C}H_2CH_2CHNH$), 7.6 ($NCH(\underline{C}H_2)_2$)

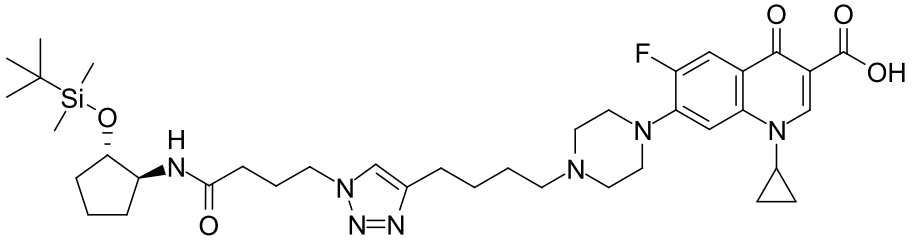
^{19}F NMR (376.45 MHz, MeOD) δ / ppm = -124.3

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

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

The compound has not been reported previously.

1.62 7-(4-(4-(1-(4-(((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclopentyl)amino)-4-oxobutyl)-1*H*-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 133



1-Cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **70** (42.9 mg, 104 μmol, 1 eq.) and 4-azido-*N*-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclopentyl)butanamide **129** (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 aqueous layer was extracted again with CH_2Cl_2 (10 ml). The combined organic layers were dried with $MgSO_4$ and evaporated under reduced pressure. **133** was obtained as a clear amorphous solid (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$\underline{H}_3$)

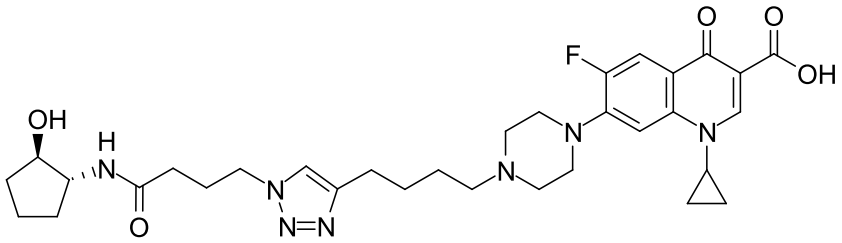
^{13}**C NMR** (101 MHz, $CDCl_3$) δ / ppm = 176.9 ($\underline{C}$(=O)CC(=O)OH), 170.9 (CH$_2\underline{C}$(=O)NH), 166.9 ($\underline{C}$(=O)OH), 153.5 (d, J = 251.4 Hz, *ipso* to F), 147.9 (CH=$\underline{C}$CH$_2$), 147.2 ($\underline{C}$=CC(=O)OH), 145.8 (d, J = 10.4 Hz, *ipso* to piperazine), 139.0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

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

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

The compound has not been reported previously.

1.63 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 124



1-Cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **70** (42.9 mg, 104 μmol, 1 eq.) and 4-azido-*N*-((1*R*,2*R*)-2-hydroxycyclopentyl)butanamide **119** (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 preparative 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. **124** 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$\underline{\text{H}}$=CCH$_2$), 7.75 (d, J = 7.1 Hz, 1 H, CHN$\underline{\text{H}}$), 7.54 (d, J = 7.5 Hz, 1 H, *meta* to F), 4.73 (d, J = 3.8 Hz, 1 H, CHO$\underline{\text{H}}$), 4.29 (t, J = 6.9 Hz, 2 H, C$\underline{\text{H}}_2$NCH=C), 3.78 - 3.83 (m, 1 H, NC$\underline{\text{H}}$(CH$_2$)$_2$), 3.75 - 3.78 (m, 1 H, C$\underline{\text{H}}$OH), 3.71 - 3.75 (m, 1 H, C$\underline{\text{H}}$NH), 3.31 (br t, J = 4.3 Hz, 4 H, CH$_2$N(CH$_2$C$\underline{\text{H}}_2$)CH$_2$C$\underline{\text{H}}_2$), 2.63 (t, J = 7.5 Hz, 2 H, CH=CC$\underline{\text{H}}_2$), 2.56 (br t, J = 4.2 Hz, 4 H, CH$_2$N(C$\underline{\text{H}}_2$)C$\underline{\text{H}}_2$), 2.37 (t, J = 7.3 Hz, 2 H, C$\underline{\text{H}}_2$N(CH$_2$)CH$_2$), 2.03 - 2.06 (m, 2 H, C(=O)C$\underline{\text{H}}_2$), 1.97 - 2.02 (m, 2 H, C(=O)CH$_2$C$\underline{\text{H}}_2$), 1.89 (dddd, J = 13.1, 8.9, 7.4, 5.7 Hz, 1 H, C$\underline{\text{H}}$HCHNH), 1.75 (ddt, J = 13.0, 8.9, 6.4, 6.4 Hz, 1 H, C$\underline{\text{H}}$HCHOH), 1.61 - 1.66 (m, 2 H, CH=CCH$_2$C$\underline{\text{H}}_2$), 1.57 - 1.61 (m, 1 H, C$\underline{\text{H}}$HCH$_2$CHOH), 1.54 - 1.57 (m, 1 H, CH$\underline{\text{H}}$CH$_2$CHOH), 1.49 - 1.53 (m, 2 H, CH=CCH$_2$CH$_2$C$\underline{\text{H}}_2$), 1.40 (ddt, J = 13.0, 8.4, 5.3, 5.3 Hz, 1 H, CH$\underline{\text{H}}$CHOH), 1.29 - 1.32 (m, 2 H, NCH(C$\underline{\text{H}}\text{H}$)$_2$), 1.25 - 1.29 (m, 1 H, CH$\underline{\text{H}}$CHNH), 1.13 - 1.20 (m, 2 H, NCH(CH$\underline{\text{H}}$)$_2$)

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

= 8.7 Hz, *ipso* to piperazine), 139.2 (*para* to F), 121.7 (N$\underline{C}$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 $\underline{C}$C(=O)OH), 76.2 ($\underline{C}$HOH), 57.6 ($\underline{C}$HNH), 57.4 (CH=CCH$_2$CH$_2$CH$_2\underline{C}$H$_2$N), 52.5 (CH=CCH$_2$CH$_2$CH$_2$CH$_2$N($\underline{C}$H$_2$)$\underline{C}$H$_2$), 49.5 (d, J = 4.4 Hz, CH=CCH$_2$CH$_2$CH$_2$CH$_2$N(CH$_2\underline{C}$H$_2$)CH$_2\underline{C}$H$_2$), 48.8 ($\underline{C}$H$_2$NCH=CCH$_2$), 35.8 (N$\underline{C}$H(CH$_2$)$_2$), 32.2 ($\underline{C}$H$_2$CHOH), 32.0 (C(=O)$\underline{C}$H$_2$), 29.5 ($\underline{C}$H$_2$CHNH), 26.9 (CH=CCH$_2\underline{C}$H$_2$), 26.0 (C(=O)CH$_2\underline{C}$H$_2$), 25.8 (CH=CCH$_2$CH$_2\underline{C}$H$_2$), 25.0 (CH=C$\underline{C}$H$_2$), 20.5 ($\underline{C}$H$_2$CH$_2$CHOH), 7.6 (NCH($\underline{C}$H$_2$)$_2$)

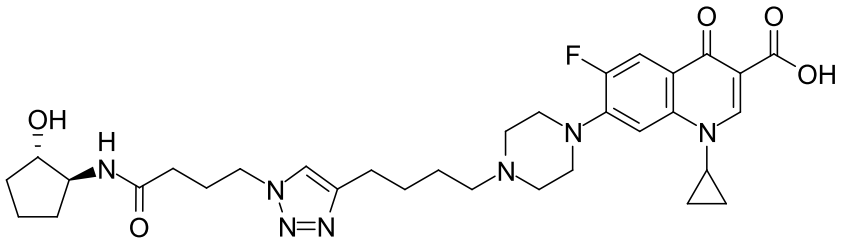
^{19}**F NMR** (376.45 MHz, MeOD) δ / ppm = -122.1 (s, ciprofloxacin F)

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

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

The compound has not been reported previously.

1.64 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 123



1-Cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **70** (82.0 mg, 199 μmol, 4 eq.) and 4-azido-*N*-((1*S*,2*S*)-2-hydroxycyclopentyl)butanamide **118** (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 preparative 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. **123** was obtained as a white amorphous solid (7.2 mg, 11.5 μmol, 22.2 %).

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

^{1}**H NMR** (400 MHz, DMSO d_6) δ / ppm = 15.22 (br s, 1 H, C(=O)O$\underline{H}$), 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, C$\underline{H}$=CCH$_2$), 7.74 (d, J = 6.7 Hz, 1 H, CHN$\underline{H}$), 7.56 (d, J = 7.4 Hz, 1 H, *meta* to F), 4.71 (d, J = 3.7 Hz, 1 H, CHO$\underline{H}$), 4.29 (t, J = 6.6 Hz, 2 H, C$\underline{H}_2$NCH=C), 3.82 (tt, J = 6.5, 4.3 Hz, 1 H, NC$\underline{H}$(CH$_2$)$_2$), 3.69 - 3.79 (m, 2 H, C$\underline{H}$OH and C$\underline{H}$NH), 3.30 - 3.34 (m, 6 H, CH=CCH$_2$CH$_2$CH$_2$C$\underline{H}_2$N(C$\underline{H}_2$C$\underline{H}_2$)C$\underline{H}_2$C$\underline{H}_2$), 2.64 (t, J = 7.4 Hz, 2 H, CH=CC$\underline{H}_2$), 1.95 - 2.08 (m, 4 H,

C(=O)C$\underline{H}_2$C$\underline{H}_2$), 1.89 (dddd, J = 12.8, 8.9, 7.4, 5.8 Hz, 1 H, C$\underline{H}$HCHNH), 1.75 (ddt, J = 12.7, 9.0, 6.2 Hz, 1 H, C$\underline{H}$HCHOH), 1.48 - 1.68 (m, 6 H, CH=CCH$_2$C$\underline{H}_2$C$\underline{H}_2$ and C$\underline{H}_2$CH$_2$CHOH), 1.40 (ddt, J = 13.0, 8.3, 5.3 Hz, 1 H, CH$\underline{H}$CHOH), 1.28 - 1.35 (m, 2 H, NCH(C$\underline{H}$H)$_2$), 1.24 - 1.31 (m, 1 H, CH$\underline{H}$CHNH), 1.15 - 1.21 (m, 2 H, NCH(CH$\underline{H}$)$_2$)

^{13}C NMR (101 MHz, DMSO d$_6$) δ / ppm = 176.4 ($\underline{C}$(=O)CC(=O)OH), 170.9 (NH$\underline{C}$(=O)CH$_2$), 166.0 ($\underline{C}$(=O)OH), 153.0 (d, J = 249.6 Hz, *ipso* to F), 148.1 ($\underline{C}$=CC(=O)OH), 146.7 (CH=$\underline{C}$CH$_2$), 145.2 (d, J = 8.3 Hz, *ipso* to piperazine), 139.2 (*para* to F), 121.8 (N$\underline{C}$H=CCH$_2$), 118.7 (*para* to piperazine), 111.0 (d, J = 23.2 Hz, *ortho* to C=O and *ortho* to F), 106.7 ($\underline{C}$C(=O)OH), 106.5 (*meta* to C=O and *meta* to F), 76.2 ($\underline{C}$HOH), 57.5 ($\underline{C}$HNH), 57.4 (br s, CH=CCH$_2$CH$_2$CH$_2$C$\underline{H}_2$N), 52.3 (br s, CH=CCH$_2$CH$_2$CH$_2$CH$_2$N($\underline{C}$H$_2$)C$\underline{H}_2$), 49.3 (br s, CH=CCH$_2$CH$_2$CH$_2$CH$_2$N(CH$_2$$\underline{C}H_2$)CH$_2C\underline{H}_2$), 48.8 ($\underline{C}H_2$NCH=CCH$_2$), 35.9 (N$\underline{C}$H(CH$_2$)$_2$), 32.2 ($\underline{C}H_2$CHOH), 32.0 (C(=O)$\underline{C}H_2$), 29.4 ($\underline{C}H_2$CHNH), 26.7 (CH=CCH$_2$$\underline{C}H_2$), 26.0 (C(=O)CH$_2$$\underline{C}H_2$), 25.5 (CH=CCH$_2CH_2$$\underline{C}H_2$), 24.9 (CH=C$\underline{C}H_2$), 20.5 ($\underline{C}H_2CH_2$CHOH), 7.6 (NCH($\underline{C}H_2$)$_2$)

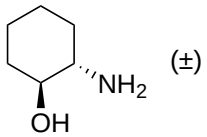
^{19}F NMR (376.45 MHz, MeOD) δ / ppm = -121.5

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

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

The compound has not been reported previously.

1.65 (*trans*)-2-Aminocyclohexan-1-ol 143



(±)

Cyclohexene oxide **142** (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.**143** was obtained as a white amorphous solid (9.90 g, 85.2 mmol, 86.2 %)

TLC R_f = 0.04 (30 % MeOH/CH_2Cl_2)

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

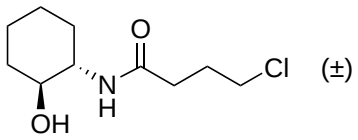
^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 3.01 (td, J = 9.4, 4.8 Hz, 1 H, C$\underline{H}$OH), 2.80 - 2.92 (m, 2 H, O$\underline{H}$ and N$\underline{H}_2$), 2.35 (ddd, J = 11.1, 9.1, 4.1 Hz, 1 H, C$\underline{H}$NH$_2$), 1.77 - 1.84 (m, 1 H, C$\underline{H}$HCHOH), 1.69 - 1.76 (m, 1 H, C$\underline{H}$HCHNH$_2$),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

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

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

The data are consistent with the literature.[18]

1.66 4-Chloro-*N*-((*trans*)-2-hydroxycyclohexyl)butanamide 144



(*trans*)-2-Aminocyclohexan-1-ol **143** (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 **139** (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). The combined organic fractions were dried with $MgSO_4$ and evaporated under reduced pressure. **144** 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)

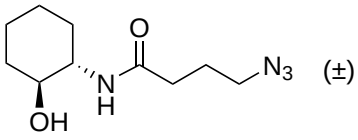
^{1}H NMR (400 MHz, MeOD) δ / ppm = 3.60 (t, J = 6.6 Hz, 2 H, C$\underline{H}_2$Cl), 3.51 - 3.60 (m, 1 H, C$\underline{H}$NH), 3.28 - 3.39 (m, 1 H, C$\underline{H}$OH), 2.37 (td, J = 7.4, 2.3 Hz, 2 H, C(=O)C$\underline{H}_2$), 2.06 (quin, J = 7.0 Hz, 2 H, C(=O)CH_2C$\underline{H}_2$), 1.97 - 2.01 (m, 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_2CHOH), 1.64 - 1.70 (m, 1 H, C$\underline{H}$HCH_2CHNH), 1.24 - 1.35 (m, 3 H, CH$\underline{H}$CH_2CHOH, CH$\underline{H}$CH_2CHNH 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 (C(=O)), 74.1 (C$\underline{H}$OH), 56.3 (C$\underline{H}$NH), 45.3 (C$\underline{H}_2$Cl), 35.6 (C$\underline{H}_2$CHOH), 34.5 (C(=O)C$\underline{H}_2$), 32.7 (C$\underline{H}_2$CHNH), 30.1 (C(=O)CH_2C$\underline{H}_2$), 25.8 (C$\underline{H}_2$CH_2CHNH), 25.5 (C$\underline{H}_2$CH_2CHOH)

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

The compound has not been reported previously.

1.67 4-Azido-*N*-((*trans*)-2-hydroxycyclohexyl)butanamide 145



4-Chloro-*N*-((*trans*)-2-hydroxycyclohexyl)butanamide **144** (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. **145** 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)

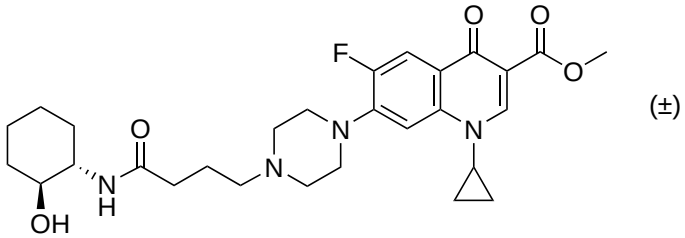
^{1}H NMR (400 MHz, MeOD) δ / ppm = 7.87 (d, J = 7.9 Hz, 1 H, NH), 5.27 (d, J = 4.3 Hz, 1 H, OH), 3.56 (td, J = 10.5, 4.4 Hz, 1 H, CHNH), 3.28 - 3.41 (m, 3 H, CHOH and CH_2N_3), 2.30 (td, J = 7.4, 2.7 Hz, 2 H, C(=O)CH_2), 1.95 - 2.03 (m, 1 H, CHHCHOH), 1.87 (m, 3 H, C(=O)CH_2CH_2 and CHHCHNH), 1.70 - 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

The compound has not been reported previously.

1.68 Methyl 1-cyclopropyl-6-fluoro-7-(4-(4-(((*trans*)-2-hydroxycyclohexyl)amino)-4-oxobutyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 146



(±)

4-(4-(1-Cyclopropyl-6-fluoro-3-(methoxycarbonyl)-4-oxo-1,4-dihydroquinolin-7-yl)piperazin-1-yl)butanoic acid trifluoroacetate **137** (200 mg, 0.367 mmol, 1 eq.), (*trans*)-2-aminocyclohexan-1-ol **143** (91.1 mg, 0.791 mmol, 2.1 eq.), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (112 mg, 0.584 mmol, 1.6 eq.), 1-hydroxybenzotriazole (96 mg, 0.710 mmol, 1.9 eq.) and DIPEA (192 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 preparative 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. **146** 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)OC$\underline{H}_3$), 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, C$\underline{H}_3$), 3.62 - 3.68 (m, 1 H, NC$\underline{H}$(CH_2)$_2$), 3.58 (td, J = 10.3, 4.2 Hz, 1 H, C$\underline{H}$NH), 3.38 (br s, 4 H, $CH_2N(CH_2C\underline{H}_2)CH_2C\underline{H}_2$), 3.32 - 3.36 (m, 1 H, C$\underline{H}$OH), 2.83 (br s, 4 H, $CH_2N(C\underline{H}_2)C\underline{H}_2$), 2.60 (t, J = 7.3 Hz, 2 H, C(=O)$CH_2CH_2C\underline{H}_2$N), 2.32 (td, J = 7.1, 3.1 Hz, 2 H, C(=O)C$\underline{H}_2$), 1.96 - 2.04 (m, 1 H, C$\underline{H}$HCHOH), 1.87 - 1.96 (m, 3 H, C$\underline{H}$HCHNH and C(=O)$CH_2C\underline{H}_2$), 1.72 - 1.77 (m, 1 H, C$\underline{H}$HCH_2CHOH), 1.66 - 1.72 (m, 1 H, C$\underline{H}$HCH_2CHNH), 1.25 - 1.39 (m, 5 H, CH$\underline{H}$CHOH, CH$\underline{H}CH_2$CHOH, CH$\underline{H}CH_2$CHNH and NCH(C$\underline{H}$H)$_2$), 1.15 - 1.25 (m, 3 H, CH$\underline{H}$CHOH and NCH(CH$\underline{H}$)$_2$)

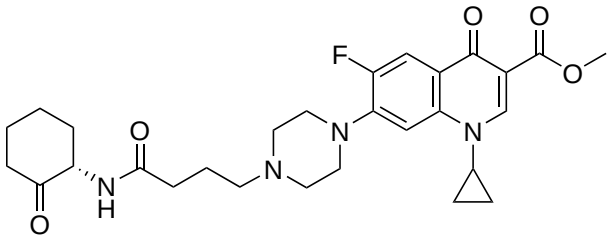
^{13}C NMR (101 MHz, MeOD) δ / ppm = 175.8 ($CH_2\underline{C}$(=O)NH), 175.3 ($\underline{C}$(=O)CC(=O)OCH_3), 166.8 ($\underline{C}$(=O)OCH_3), 154.9 (d, J = 248.8 Hz, *ipso* to F), 150.2 ($\underline{C}$=CC(=O)OCH_3), 146.1 (d, J = 10.8 Hz, *ipso* to piperazine), 139.9 (*para* to F), 123.5 (d, J = 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)$CH_2CH_2\underline{C}H_2$N), 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 ($\underline{C}H_2$CHOH), 35.1 (C(=O)$\underline{C}H_2$), 32.8 ($\underline{C}H_2$CHNH), 25.9 ($\underline{C}H_2CH_2$CHNH), 25.5 ($\underline{C}H_2CH_2$CHOH), 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 F)

HRMS (ESI$^+$) m/z / Da = 529.2827, $[M+H]^+$ found, $[C_{28}H_{38}FN_4O_5]^+$ requires 529.2826

The compound has not been reported previously.

1.69 Methyl 1-cyclopropyl-6-fluoro-4-oxo-7-(4-(4-oxo-4-((2-oxocyclohexyl)amino)-butyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate 147



Methyl 1-cyclopropyl-6-fluoro-7-(4-(4-(((*trans*)-2-hydroxycyclohexyl)amino)-4-oxobutyl)piperazin-1-yl)-4-oxo-1, 4-dihydroquinoline-3-carboxylate **146** (5.2 mg, 9.84 μmol, 1 eq.) and Dess-Martin periodinane (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 preparative HPLC (5-95 % acetonitrile/water over 20 min). The combined pure fractions were evaporated under reduced pressure to a volume of 20 ml, then $NaHCO_3$ (aq., sat., 30 ml) and 10 % *i*-PrOH/$CHCl_3$ (30 ml) were added. The organic layer was dried with $MgSO_4$ and evaporated under reduced pressure. **147** was obtained as a white amorphous solid (3.6 mg, 6.8 μmol, 69.1 %).

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<u>H</u>$_3$), 7.87 (d, J = 6.2 Hz, 1 H, N<u>H</u>), 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<u>H</u>NH), 3.73 (s, 3 H, C<u>H</u>$_3$), 3.65 (tt, J = 7.1, 3.9 Hz, 1 H, NC<u>H</u>$(CH_2)_2$), 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<u>H</u>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, 1.6 Hz, 1 H, CH<u>H</u>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 Hz, 1 H, C<u>H</u>HCHNH), 2.00 (ddquin, J = 13.2, 6.0, 2.9 Hz, 1 H, C<u>H</u>H$CH_2C(=O)$), 1.65 - 1.83 (m, 4 H, $C\underline{H}_2CH_2CHNH$), 1.41 - 1.56 (m, 2 H, CH<u>H</u>CHNH and CH<u>H</u>$CH_2C(=O)$), 1.20 - 1.30 (m, 2 H, NCH(C<u>H</u>H)$_2$), 1.05 - 1.13 (m, 2 H, NCH(CH<u>H</u>)$_2$)

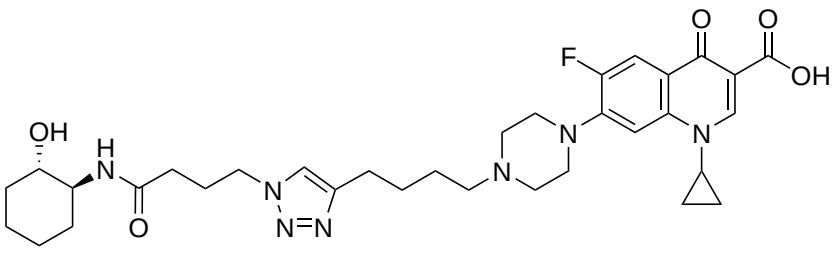
^{13}C NMR (101 MHz, DMSO d_6) δ / ppm = 207.5 (<u>C</u>(=O)CHNH), 171.7 (<u>C</u>(=O)CC(=O)OCH_3), 171.6 (CH_2<u>C</u>(=O)NH), 165.0 (<u>C</u>(=O)OCH_3), 152.6 (d, J = 247.6 Hz, *ipso* to F), 148.3 (<u>C</u>=CC(=O)OCH_3), 143.9 (br s, *ipso* to piperazine), 138.1 (*para* to F), 121.8 (d, J = 6.4 Hz, *para* to piperazine), 111.5 (d, J = 22.4 Hz, *ortho* to C=O and *ortho* to F), 109.0 (<u>C</u>C(=O)OCH_3), 106.3 (*meta* to C=O and *meta* to F), 57.0 (<u>C</u>HNH and $C(=O)CH_2CH_2C\underline{H}_2N$), 52.3 (br s, $C(=O)CH_2CH_2CH_2N(\underline{C}H_2)\underline{C}H_2$), 51.3 (<u>C</u>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 ($C\underline{H}_2$C(=O)CHNH), 34.8 (N<u>C</u>H$(CH_2)_2$), 33.9 ($C\underline{H}_2$CHNH), 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(<u>C</u>H$_2)_2$)

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

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

The compound has not been reported previously.

1.70 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 148



(±)

1-Cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **70** (40 mg, 97.2 μmol, 1 eq.) and 4-azido-*N*-((*trans*)-2-hydroxycyclohexyl)butanamide **145** (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, dried with $MgSO_4$ and evaporated under reduced pressure. The residue was purified by preparative 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. **148** 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$_2$CH$_2$C$\underline{H}_2$N), 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 Hz, 4 H, CH=CCH$_2$CH$_2$CH$_2$N(CH$_2$C$\underline{H}_2$)CH$_2$C$\underline{H}_2$), 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 Hz, 4 H, CH=CCH$_2$CH$_2$CH$_2$N(C$\underline{H}_2$)C$\underline{H}_2$), 2.38 (t, J = 6.9 Hz, 2 H, CH=CCH$_2$CH$_2$CH$_2$C$\underline{H}_2$N), 2.04 - 2.08 (m, 2 H, C(=O)C$\underline{H}_2$CH$_2$CH$_2$N), 1.96 - 2.04 (m, 2 H, C(=O)CH$_2$C$\underline{H}_2$CH$_2$N), 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$_2$C$\underline{H}_2$CH$_2$CH$_2$N), 1.54 - 1.60 (m, 2 H, C$\underline{H}$HCH$_2$OH), 1.51 (quin, J = 7.4 Hz, 2 H, CH=CCH$_2$CH$_2$C$\underline{H}_2$CH$_2$N), 1.28 - 1.35 (m, 2 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$_2$CHOH and C$\underline{H}_2$CH$_2$CHNH), 1.04 - 1.13 (m, 1 H, CH$\underline{H}$CHNH)

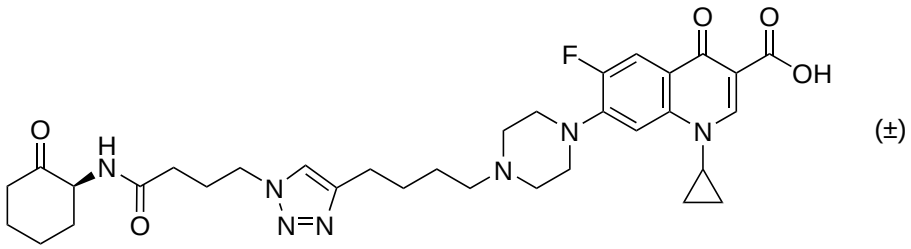
^{13}**C NMR** (101 MHz, DMSO d_6) δ / ppm = 176.4 (C(=O)CC(=O)OH), 170.9 (CH$_2$C(=O)NH), 166.0 (C(=O)OH), 153.1 (d, J = 252.1 Hz, *ipso* to F), 148.0 (C=CC(=O)OH), 146.9 (CH=CCH$_2$), 145.3 (d, J = 10.0 Hz, *ipso* to piperazine), 139.2 (*para* to F), 121.8 (NCH=CCH$_2$), 118.5 (d, J = 8.3 Hz, *para* 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, $[C_{33}H_{45}FN_7O_5]^+$ requires 638.3466

The compound has not been reported previously.

1.71 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 149



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 **148** (15.0 mg, 23.6 mmol, 1 eq.) and Dess-Martin

periodinane (35.0 mg, 82.5 mmol, 3.5 eq.) were stirred in CH_2Cl_2 (3 ml) for 4 h. The solvent was removed under reduced pressure and the residue was purified by preparative HPLC (5-70 % acetonitrile/water over 15 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 dried with $MgSO_4$ and evaporated under reduced pressure. **149** was obtained as a clear gum (11.7 mg, 18.4 μmol, 78.0 %).

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

^{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, N$\underline{H}$), 7.88 (d, J = 13.4 Hz, 1 H, *ortho* to F), 7.85 (s, 1 H, C$\underline{H}$=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, $C(=O)CH_2CH_2C\underline{H}HN$), 4.31 (t, J = 6.9 Hz, 1 H, $C(=O)CH_2CH_2CH\underline{H}_2N$), 3.74 - 3.84 (m, 1 H, $NC\underline{H}(CH_2)_2$), 3.31 (br. s, 4 H, $CH_2CH_2CH_2N(CH_2C\underline{H}_2)CH_2C\underline{H}_2$), 2.64 (t, J = 7.5 Hz, 2 H, $CH{=}CC\underline{H}_2$), 2.56 (br t, J = 5.0, 5.0 Hz, 4 H, $CH_2CH_2CH_2N(C\underline{H}_2)C\underline{H}_2$), 2.45 - 2.52 (m, 1 H, C$\underline{H}$HC(=O)), 2.38 (t, J = 7.1 Hz, 2 H, $CH{=}CCH_2CH_2CH_2C\underline{H}_2N$), 2.25 (dtt, J = 13.4, 2.6, 1.6 Hz, 1 H, CH$\underline{H}$C(=O)), 2.07 - 2.17 (m, 3 H, $C(=O)C\underline{H}_2CH_2CH_2N$ and C$\underline{H}$HCHNH), 1.96 - 2.05 (m, 3 H, $C(=O)CH_2C\underline{H}_2CH_2N$ and C$\underline{H}$HCH_2C(=O)), 1.68 - 1.81 (m, 2 H, C$\underline{H}$HCH_2CHNH), 1.64 (quin, J = 7.5 Hz, 2 H, $CH{=}CCH_2C\underline{H}_2CH_2CH_2N$), 1.40 - 1.56 (m, 5 H, CH$\underline{H}CH_2$C(=O), CH$\underline{H}$CHNH and $CH{=}CCH_2CH_2C\underline{H}_2CH_2N$), 1.27 - 1.34 (m, 2 H, $NCH(C\underline{H}H)_2$), 1.13 - 1.20 (m, 2 H, $NCH(CH\underline{H})_2$)

^{13}**C NMR** (126 MHz, DMSO d_6) δ / ppm = 207.4 ($\underline{C}$(=O)CHNH), 176.3 ($\underline{C}$(=O)CC(=O)OH), 170.8 ($CH_2\underline{C}$(=O)NH), 166.0 ($\underline{C}$(=O)OH), 153.0 (d, J = 246.4 Hz, *ipso* to F), 147.9 ($\underline{C}$=CC(=O)OH), 146.8 (CH=$\underline{C}CH_2$), 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 ($CH{=}CCH_2CH_2CH_2\underline{C}H_2N$), 57.0 ($\underline{C}$HNH), 52.4 ($CH_2CH_2CH_2N(\underline{C}H_2)\underline{C}H_2$), 49.5 ($CH_2CH_2CH_2N(CH_2\underline{C}H_2)CH_2CH_2$), 49.5 ($CH_2CH_2CH_2N(CH_2CH_2)CH_2\underline{C}H_2$), 48.7 ($C(=O)CH_2CH_2\underline{C}H_2NCH{=}C$), 40.5 ($\underline{C}H_2C(=O)$), 35.8 ($N\underline{C}H(CH_2)_2$), 33.7 ($\underline{C}H_2CHNH$), 31.8 ($C(=O)\underline{C}H_2CH_2CH_2NCH{=}C$), 27.1 ($\underline{C}H_2CH_2C(=O)$), 26.9 ($CH{=}CCH_2\underline{C}H_2CH_2CH_2N$), 26.0 ($C(=O)CH_2\underline{C}H_2CH_2NCH{=}C$), 25.7 ($CH{=}CCH_2CH_2\underline{C}H_2CH_2N$), 24.9 ($CH{=}C\underline{C}H_2CH_2CH_2CH_2N$), 23.8 ($\underline{C}H_2CH_2CHNH$), 7.6 ($NCH(\underline{C}H_2)_2$)

^{19}**F NMR** (376 MHz, DMSO d_6) δ / ppm = -121.7 (s, ciprofloxacin F)

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

The compound has not been reported previously.

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