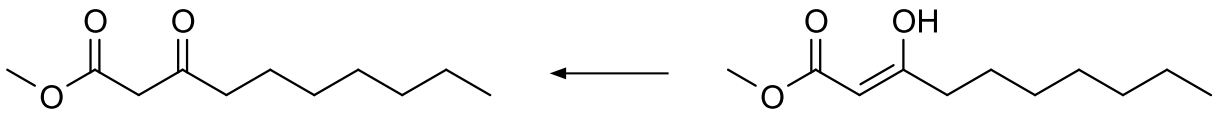
Contents

1 Experimental

1.1 Methyl 3-oxodecanoate 21

fix eps



Meldrum's acid (9.0 g, 63 mmol, 1 eq.) was dissolved in anhydrous CH_2Cl_2 (150 mL) and cooled to 0 °C. Pyridine (10.2 mL, 126 mmol, 2 eq.) was added dropwise over 20 min. Octanoyl chloride (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 Mg_2SO_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.) to give a tautomeric mixture of **21** and **22** as a colourless oil (8.34 g, 41.6 mmol, 66 %, 92 % **21** as determined by NMR).

Keto form 21

TLC R_f = 0.12 (5 % EtO_2/PE)

IR (neat) ν_{max} / cm^{-1} = 2927.84 (C-H), 2856.26 (C-H), 1746.86 (ester C=O), 1716.70 (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, $C(=O)C\underline{H}_2C(=O)$), 2.53 (t, J = 7.4 Hz, 2 H, $C\underline{H}_2CH_2CH_2CH_2CH_2CH_3$), 1.60 (quin, J = 7.1 Hz, 2 H, $CH_2C\underline{H}_2CH_2CH_2CH_2CH_3$), 1.39 - 1.19 (m, 8 H, $CH_2CH_2C\underline{H}_2C\underline{H}_2C\underline{H}_2C\underline{H}_2CH_3$), 0.88 (t, J = 6.8 Hz, 3 H, $CH_2CH_2CH_2CH_2CH_2CH_2C\underline{H}_3$)

^{13}**C NMR** (101 MHz, $CDCl_3$) δ / ppm = 202.3 ($CH_3OC(=O)CH_2\underline{C}(=O)$), 167.3 ($CH_3O\underline{C}(=O)CH_2C(=O)$), 51.7 ($O\underline{C}H_3$), 48.5 ($CH_3OC(=O)\underline{C}H_2C(=O)$), 42.5 ($\underline{C}H_2$), 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 ($\underline{C}H_3$)

Enol form 22

TLC R_f = 0.12 (5 % EtO_2/PE)

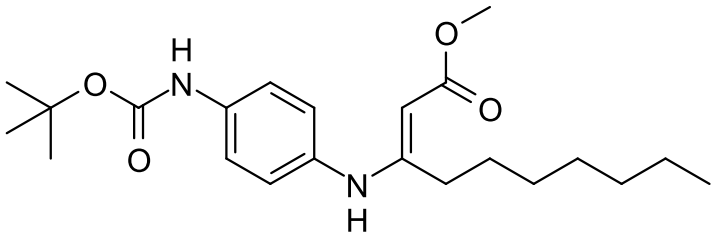
IR (neat) ν_{max} / cm^{-1} = 2927.84 (C-H), 2856.26 (C-H), 1653.80 (C=C), 1629.21 (α,β unsaturated C=O)

^{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, $C\underline{H}_2CH_2CH_2CH_2CH_2CH_3$), 1.76 - 1.72 (m, 2 H, $CH_2C\underline{H}_2CH_2CH_2CH_2CH_2CH_3$), 1.39 - 1.19 (m, 8 H, $CH_2CH_2C\underline{H}_2C\underline{H}_2C\underline{H}_2C\underline{H}_2CH_3$), 0.88 (t, J = 6.8 Hz, 3 H, $CH_2CH_2CH_2CH_2CH_2CH_2C\underline{H}_3$)

^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 178.7 ($CH_3OC(=O)CH=\underline{C}OH$), 172.7 ($CH_3O\underline{C}(=O)CH=COH$), 88.2 ($CH_3OC(=O)\underline{C}H=COH$), 50.5 ($O\underline{C}H_3$), 37.9 ($\underline{C}H_2$), 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 ($\underline{C}H_3$)

Spectroscopic data are consistent with the literature.[1,2]

1.2 Methyl (*E*)-3-((4-((*tert*-butoxycarbonyl)amino)phenyl)amino)dec-2-enoate 24



Methyl 3-oxodecanoate **21** (500 mg, 2.50 mmol, 1.00 eq.) and *tert*-butyl (4-aminophenyl)carbamate **174** (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.) to give a white powder (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} = 3336.97 (N-H), 2927.71 (C-H), 2857.14 (C-H), 1723.71 (carbamate C=O), 1634.49 (α,β unsaturated C=O), 1610.73 (C=C), 1580.85 (N-H bend)

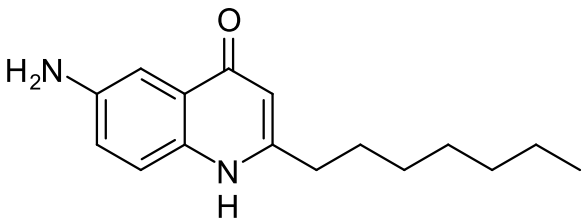
^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 10.16 (s, 1 H, $N\underline{H}C(C_7H_{15})=C$), 7.35 (d, J = 8.6 Hz, 2 H, *meta* to NHBoc), 7.02 (d, J = 8.7 Hz, 2 H, *meta* to enamine), 6.60 (br s, 1 H, $N\underline{H}Boc$), 4.71 (s, 1 H, $C=C\underline{H}$), 3.70 (s, 3 H, $OC\underline{H}_3$), 2.23 (t, J = 7.7 Hz, 2 H, $C\underline{H}_2CH_2CH_2CH_2CH_2CH_2CH_3$), 1.54 (s, 9 H, $C(C\underline{H}_3)_3$), 1.40 (quin, J = 7.3 Hz, 2 H, $CH_2C\underline{H}_2CH_2CH_2CH_2CH_2CH_3$), 1.33 - 1.16 (m, 8 H, $CH_2CH_2C\underline{H}_2C\underline{H}_2C\underline{H}_2C\underline{H}_2CH_3$), 0.86 (t, J = 7.1 Hz, 3 H, $CH_2CH_2CH_2CH_2CH_2CH_2C\underline{H}_3$)

^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 171.1 ($\underline{C}(=O)CH=C$), 164.3 ($C(=O)CH=\underline{C}$), 152.7 ($O\underline{C}(=O)NH$), 136.0 (*para* to NHBoc), 134.1 ($\underline{C}NHBoc$), 126.3 (*meta* to NHBoc), 119.1 (*ortho* to NHBoc), 83.8 ($C(=O)\underline{C}H=C$), 80.7 ($\underline{C}(CH_3)_3$), 50.2 ($O\underline{C}H_3$), 32.2 ($\underline{C}H_2$), 31.6 ($\underline{C}H_2$), 29.1 ($\underline{C}H_2$), 28.8 ($\underline{C}H_2$), 28.3 ($C(\underline{C}H_3)_3$), 28.0 ($\underline{C}H_2$), 22.6 ($\underline{C}H_2$), 14.0 ($\underline{C}H_3$)

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

1.3 6-Amino-2-heptylquinolin-4-ol 25

NMR wrong? not tautomer?



Methyl (*E*)-3-((4-((tert-butoxycarbonyl)amino)phenyl)amino)dec-2-enoate **24** (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 to give a pale yellow powder (121 mg, 0.468 mmol, 72 %).

check for consistent prod reporting

mp T / °C = 249 (H_2O)

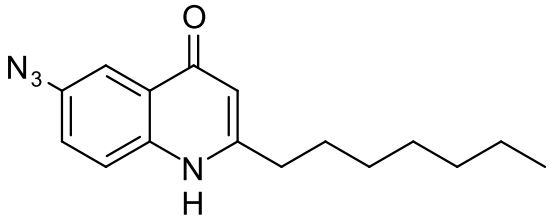
IR (neat) ν_{max} / cm^{-1} = 3336.52 (N-H), 2926.47 (C-H), 2856.89 (C-H), 1723.88 (aromatic), 1634.48 (aromatic), 1610.84 (aromatic), 1583.26 (aromatic), 1519.06 (aromatic)

^{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, *para* to COH), 6.95 (dd, J = 2.7, 8.8 Hz, 1 H, *ortho* to COH), 5.74 (s, 1 H, *ortho* to OH), 5.16 (s, 2 H, $N\underline{H}_2$), 2.52 (t, J = 7.4 Hz, 2 H, $C\underline{H}_2CH_2CH_2CH_2CH_2CH_2CH_3$), 1.64 (quin, J = 7.6 Hz, 2 H, $CH_2C\underline{H}_2CH_2CH_2CH_2CH_2CH_3$), 1.36 - 1.19 (m, 8 H, $CH_2CH_2C\underline{H}_2C\underline{H}_2C\underline{H}_2C\underline{H}_2CH_3$), 0.86 (t, J = 7.0 Hz, 3 H, $CH_2CH_2CH_2CH_2CH_2CH_2C\underline{H}_3$)

^{13}C NMR (101 MHz, DMSO-d_6) δ / ppm = 176.7 ($\underline{C}OH$), 151.7 ($\underline{C}CH_2CH_2CH_2CH_2CH_2CH_2CH_3$), 145.1 ($\underline{C}NH_2$), 132.4 (*para* to NH_2), 126.6 (*para* to $CH_2CH_2CH_2CH_2CH_2CH_2CH_3$), 121.1 (*ortho* to NH_2 and *para* to COH), 119.0 (*meta* to NH_2 and *meta* to COH), 106.2 (*ortho* to NH_2 and *ortho* to COH), 105.9 (*ortho* to $CH_2CH_2CH_2CH_2CH_2CH_2CH_3$ and *ortho* to OH), 33.6 ($\underline{C}H_2$), 31.6 ($\underline{C}H_2$), 29.0 ($\underline{C}H_2$), 29.0 ($\underline{C}H_2$), 28.9 ($\underline{C}H_2$), 22.5 ($\underline{C}H_2$), 14.4 ($\underline{C}H_3$)

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

1.4 6-Azido-2-heptylquinolin-4-ol 26



6-Amino-2-heptylquinolin-4-ol **25** (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. **26** 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)

mp T / °C = ?? (??)

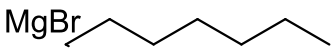
IR (neat) ν_{max} / cm^{-1} = ??

^{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, NHCC$\underline{H}_2$), 1.68 (quin, J = 7.6 Hz, 2 H, NHCCH_2C$\underline{H}_2$), 1.28 - 1.39 (m, 4 H, NHCCH_2CH_2C$\underline{H}_2$C$\underline{H}_2$), 1.18 - 1.28 (m, 4 H, C$\underline{H}_2$C$\underline{H}_2$CH_3), 0.85 (t, J = 6.8 Hz, 3 H, C$\underline{H}_3$)

^{13}C NMR (101 MHz, MeOD) δ / ppm = 172.3 (C(=O)), 155.5 (NHCCH_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 ($\underline{C}H_3$)

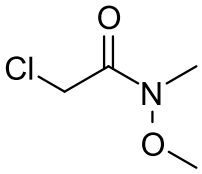
HRMS (ESI$^+$) m/z / Da = ??, $[M+H]^+$ found, $[??]^+$ requires ??

1.5 Heptyl magnesium bromide 28



Magnesium turnings (352 mg, 14.5 mmol, 1 eq.) were added to a dry flask under argon. THF (15 mL) was added, followed by bromoheptane (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 to give the Grignard reagent as a pale grey suspension (15 mL, ~ 1 M) which was used without further purification.

1.6 2-Chloro-*N*-methoxy-*N*-methylacetamide 30



N,O-Dimethylhydroxyl amine hydrochloride (6.00 g, 61.5 mmol, 1 eq.) and toluene (75 mL) were added successively to a 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 (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 four combined organic extracts were dried with $MgSO_4$ and the solvent was removed by rotary evaporation followed by high vacuum to give white, prism-like crystals (7.24 g, 52.6 mmol, 71 %).

mp T / °C = 38.8 (toluene)

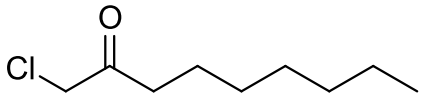
IR (neat) ν_{max} / cm^{-1} = 3016.69 (C-H), 2966.38 (C-H), 2946.75 (C-H), 2827.73 (C-H), 1666.20 (C=O)

^{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.[3]

1.7 1-Chlorononan-2-one 31



2-Chloro-*N*-methoxy-*N*-methylacetamide (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 (~ 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 $MgSO_4$. The solvent was removed by rotary evaporation to give a colourless oil (1.23 g, 6.96 mmol, 96 %).

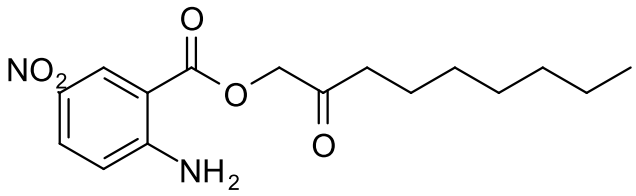
IR (neat) ν_{max} / cm^{-1} = 2951.65 (C-H), 2924.99 (C-H), 2855.46 (C-H), 1720.39 (C=O)

^{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$$CH_2CH_2$-$CH_2CH_2CH_2CH_2CH_3$), 1.59 (quin, J = 7.0 Hz, 2 H, C(=O)CH_2C$\underline{H}_2$$CH_2CH_2CH_2CH_2CH_2CH_3$), 1.34 - 1.21 (m, 8 H, C(=O)CH_2CH_2C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}_2$$CH_3$), 0.87 (t, J = 6.8 Hz, 3 H, C(=O)$CH_2CH_2CH_2CH_2CH_2CH_2$C$\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)$\underline{C}H_2$), 31.5 ($\underline{C}H_2CH_2CH_3$)), 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_2CH_3$), 13.9 ($\underline{C}H_3$)

Spectroscopic data are consistent with the literature.[3]

1.8 2-Oxononyl 2-amino-5-nitrobenzoate 33



5-Nitroanthranilic acid (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 **31** (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 to give a yellow powder (0.674 g, 2.00 mmol, 100 %).

mp T / °C = 135 (H_2O)

IR (neat) ν_{max} / cm^{-1} = 3453.32 (N-H), 3350.52 (N-H), 2924.93 (C-H), 2853.87 (C-H), 1720.10 (ester C=O)

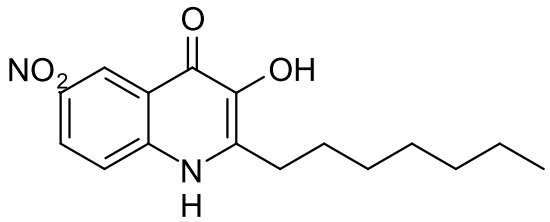
1703.91 (ketone C=O) 1626.14 (N-H bend) 1602.74 (aromatic) 1572.48 (N-O) 1506.58 (N-O)

^{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_2CH_2CH_2CH_2CH_3$), 1.52 (quin, J = 7.2 Hz, 2 H, $C(=O)CH_2C\underline{H}_2CH_2CH_2CH_2CH_2CH_3$), 1.32 - 1.20 (m, 8 H, $C(=O)CH_2CH_2C\underline{H}_2C\underline{H}_2C\underline{H}_2C\underline{H}_2CH_3$), 0.86 (t, J = 6.8 Hz, 3 H, $C(=O)CH_2CH_2CH_2CH_2$-$CH_2CH_2C\underline{H}_3$)

^{13}C NMR (101 MHz, DMSO-d_6) δ / ppm = 204.4 ($OCH_2\underline{C}(=O)$), 165.6 ($\underline{C}(=O)O$), 156.3 ($\underline{C}NH_2$), 135.7 ($\underline{C}NO_2$), 129.6 (*para* to C=O), 128.9 (*ortho* to C=O), 117.4 (*meta* to C=O), 107.5 ($\underline{C}C(=O)O$), 68.8 ($O\underline{C}H_2C$-(=O)), 38.3 ($\underline{C}H_2$), 31.6 ($\underline{C}H_2$), 28.9 ($\underline{C}H_2$), 28.9 ($\underline{C}H_2$), 23.2 ($\underline{C}H_2$), 22.5 ($\underline{C}H_2$), 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

1.9 6-Nitro-2-heptyl-3-hydroxyquinolin-4(1*H*)-one 34



2-Oxononyl 2-amino-5-nitrobenzoate (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 to give a yellow-brown powder (44 mg, 0.145 mmol, 43 %) which could be recrystallised from EtOAc to give yellow-brown plate-like crystals.

mp T / °C = 223 (H_2O)

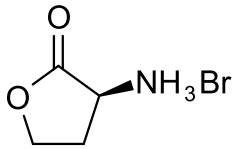
IR (neat) ν_{max} / cm^{-1} = 3436.01 (N-H), 3000.00 (O-H, br), 2955.37 (C-H), 2925.76 (C-H), 2850.93 (C-H), 1648.18 (aromatic), 1606.05 (aromatic), 1570.67 (N-O), 1536.35 (N-O)

^{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, $C\underline{H}_2CH_2CH_2CH_2CH_2CH_3$), 1.67 (quin, J = 7.3 Hz, 2 H, $CH_2C\underline{H}_2CH_2CH_2CH_2CH_2CH_3$), 1.36 - 1.23 (m, 8 H, $CH_2CH_2C\underline{H}_2C\underline{H}_2C\underline{H}_2C\underline{H}_2CH_3$), 0.85 (t, J = 7.0 Hz, 3 H, $CH_2CH_2CH_2CH_2CH_2CH_2C\underline{H}_3$)

^{13}C NMR (101 MHz, DMSO-d_6) δ / ppm = 169.7 ($\underline{C}$=O), 141.9 ($\underline{C}$OH), 140.7 (*para* to NO_2), 139.6 ($\underline{C}NO_2$), 137.3 (CH$\underline{C}$C=O), 124.3 (*ortho* to NO_2 and *ortho* to C=O), 122.3 (*ortho* to NO_2 and *para* to C=O), 121.5 ($\underline{C}CH_2CH_2CH_2CH_2CH_2CH_3$), 120.0 (*meta* to NO_2 and *meta* to C=O), 31.6 ($\underline{C}H_2$), 29.2 ($\underline{C}H_2$), 28.9 ($\underline{C}H_2$), 28.5 ($\underline{C}H_2$), 28.1 ($\underline{C}H_2$), 22.5 ($\underline{C}H_2$), 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

1.10 (*S*)-3-Aminodihydrofuran-2(3*H*)-one hydrobromide 38



L-Methionine (3.04 g, 20.4 mmol, 1 eq.) and bromoacetic acid (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 powder. 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 to give a pale pink powder (1.73 g, 9.50 mmol, 41 % yield).

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

IR (neat) ν_{max} / cm^{-1} = 2972.09 (N-H), 2877.54 (N-H), 1771.77 (C=O), 1585.05 (N-H bend), 1572.24 (N-H bend)

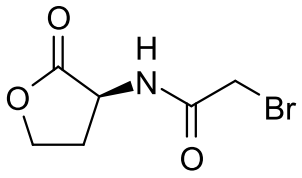
^{1}H NMR (400 MHz, DMSO-d_6) δ / ppm = 8.59 (br s, 3 H, $N\underline{H}_3^+$), 4.46 (dt, J = 1.3, 8.9 Hz, 1 H, $OC\underline{H}_2$), 4.37 (dd, J = 8.8, 11.4 Hz, 1 H, $C\underline{H}NH_3^+$), 4.29 (ddd, J = 6.1, 8.8, 10.9 Hz, 1 H, $OC\underline{H}_2$), 2.57 (dddd, J = 1.2, 6.1, 8.9, 12.3 Hz, 1 H, $OCH_2C\underline{H}_2$), 2.26 (dtd, J = 9.0, 11.2, 12.2 Hz, 1 H, $OCH_2C\underline{H}_2$)

^{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 (c / g(100 mL)$^{-1}$ = 0.02 , DMSO)

The data are consistent with the literature.[4]

1.11 (*S*)-2-Bromo-*N*-(2-oxotetrahydrofuran-3-yl)acetamide 40



(*S*)-3-Aminodihydrofuran-2(3*H*)-one hydrobromide **38** (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 (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) and the combined organic layers were dried with $MgSO_4$. The solvent was removed under vacuum to give white, needle-like crystals (88.0 mg, 0.396 mmol, 74 %).

mp T / °C = 132 (EtOAc)

IR (neat) ν_{max} / cm^{-1} = 3255.69 (N-H), 3066.58 (C-H), 1763.02 (lactone C=O), 1657.99 (amide C=O), 1552.67

(N-H bend)

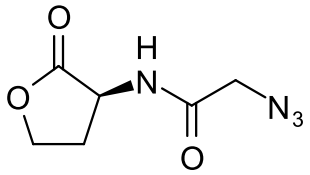
^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 6.95 (br d, 1 H, N<u>H</u>), 4.58 (ddd, J = 5.9, 8.6, 11.7 Hz, 1 H, C<u>H</u>NHC=O), 4.53 (dt, J = 1.0, 9.2 Hz, 1 H, OC<u>H$_2$</u>), 4.33 (ddd, J = 5.9, 9.4, 11.3 Hz, 1 H, OC<u>H$_2$</u>), 3.95 (d, J = 1.3 Hz, 2 H, C(=O)C<u>H$_2$</u>Br), 2.88 (dddd, J = 1.3, 5.9, 8.6, 12.6 Hz, 1 H, OCH$_2$C<u>H$_2$</u>), 2.24 (dtd, J = 8.9, 11.5, 12.6 Hz, 1 H, OCH$_2$C<u>H$_2$</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$_2$Br)

$[\boldsymbol{\alpha}]_D^{20}$ / °10^{-1}cm^{2}g^{-1} = 27.0 (c / g(100 mL)$^{-1}$ = 0.0074 , $CHCl_3$)

The data are consistent with the literature.[4,5]

1.12 (*S*)-2-Azido-*N*-(2-oxotetrahydrofuran-3-yl)acetamide 41



(3*S*)-2-Oxotetrahydrofuran-3-aminium bromide **38** (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 (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) and the combined organic layers were dried with $MgSO_4$. The solvent was removed under vacuum to give white, needle-like crystals (38.4 mg, 0.209 mmol, 41 %).

mp T / °C = 87 (EtOAc)

IR (neat) ν_{max} / cm^{-1} = 3283.47 (N-H), 2923.28 (C-H), 2852.99 (C-H), 2129.69 (N_3), 1782.86 (lactone C=O), 1661.40 (amide C=O), 1536.81 (N-H bend)

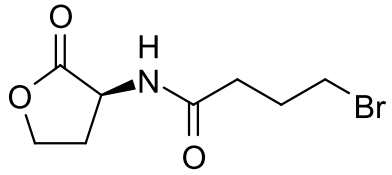
^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 7.07 (br d, J = 5.1 Hz, 1 H, N<u>H</u>), 4.65 (ddd, J = 6.8, 8.7, 11.6 Hz, 1 H, C<u>H</u>NHC=O), 4.49 (dt, J = 1.3, 9.1 Hz, 1 H, OC<u>H$_2$</u>), 4.31 (ddd, J = 6.0, 9.2, 11.2 Hz, 1 H, OC<u>H$_2$</u>), 4.05 (s, 2 H, C(=O)C<u>H$_2$</u>N$_3$), 2.77 (dddd, J = 1.4, 6.0, 8.8, 12.5 Hz, 1 H, OCH$_2$C<u>H$_2$</u>), 2.26 (dq, J = 8.9, 11.8 Hz, 1 H, OCH$_2$C<u>H$_2$</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$_2$N$_3$), 48.9 (<u>C</u>HNHC=O), 29.7 (OCH$_2$<u>C</u>H$_2$)

$[\boldsymbol{\alpha}]_D^{20}$ / °10^{-1}cm^{2}g^{-1} = -32.6 (c / g(100 mL)$^{-1}$ = 0.043 , DMSO)

The data are consistent with the literature.[4]

1.13 (*S*)-4-Bromo-*N*-(2-oxotetrahydrofuran-3-yl)butanamide 44



(*S*)-3-Aminodihydrofuran-2(3*H*)-one hydrobromide **38** (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 (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 to give white, needle-like crystals (219 mg, 0.878 mmol, 80 %).

mp T / °C = 105 (EtOAc)

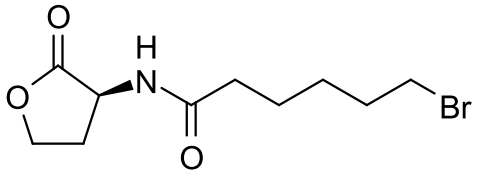
IR (neat) ν_{max} / cm^{-1} = 3307.92 (N-H), 3073.85 (C-H), 2948.93 (C-H), 1773.66 (lactone C=O), 1643.46 (amide C=O), 1541.39 (N-H bend)

^{1}**H NMR** (400 MHz, $CDCl_3$) δ / ppm = 6.31 (br d, J = 5.5 Hz, 1 H, N$\underline{H}$), 4.59 (ddd, J = 6.2, 8.7, 11.5 Hz, 1 H, C$\underline{H}$NHC=O), 4.48 (dt, J = 1.2, 8.9 Hz, 1 H, OC$\underline{H}_2$), 4.30 (ddd, J = 5.8, 9.3, 11.3 Hz, 1 H, OC$\underline{H}_2$), 3.49 (t, J = 6.3 Hz, 2 H, C$\underline{H}_2$Br), 2.82 (dddd, J = 1.3, 5.9, 8.7, 12.5 Hz, 1 H, $OCH_2C\underline{H}_2$), 2.47 (t, J = 7.3 Hz, 2 H, C(=O)C$\underline{H}_2$), 2.26 - 2.15 (m, 3 H, $OCH_2C\underline{H}_2$ and $C(=O)CH_2C\underline{H}_2CH_2Br$)

^{13}**C NMR** (101 MHz, $CDCl_3$) δ / ppm = 175.4 (O$\underline{C}$=O), 172.3 ($\underline{C}$(=O)NH), 66.1 (O$\underline{C}H_2$), 49.3 ($\underline{C}$HNHC=O), 33.9 (C(=O)$\underline{C}H_2$), 33.1 ($\underline{C}H_2$Br), 30.3 ($OCH_2\underline{C}H_2$), 27.9 ($C(=O)CH_2\underline{C}H_2CH_2Br$)

$[\boldsymbol{\alpha}]_D^{26.6}$ / $°10^{-1}cm^2g^{-1}$ = - 78 (c / g(100 mL)$^{-1}$ = 0.08333 , MeOH)

1.14 (*S*)-6-Bromo-*N*-(2-oxotetrahydrofuran-3-yl)hexanamide 45



(*S*)-3-Aminodihydrofuran-2(3*H*)-one hydrobromide **38** (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). Bromohexanoyl chloride (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 to give 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} = 3300.30 (N-H), 3067.62 (C-H), 2937.37 (C-H), 2856.67 (C-H), 1784.83 (lactone C=O),

1639.33 (amide C=O), 1539.87 (N-H bend)

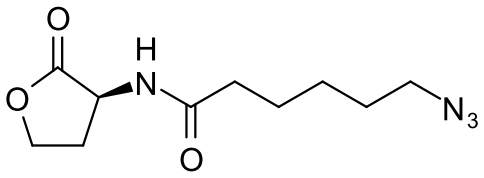
^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 6.09 (br d, J = 5.7 Hz, 1 H, N$\underline{H}$), 4.57 (ddd, J = 5.9, 8.6, 11.6 Hz, 1 H, C$\underline{H}$NHC=O), 4.50 (dt, J = 1.3, 9.1 Hz, 1 H, OC$\underline{H}_2$), 4.31 (ddd, J = 5.9, 9.3, 11.3 Hz, 1 H, OC$\underline{H}_2$), 3.43 (t, J = 6.7 Hz, 2 H, C(=O)$CH_2CH_2CH_2CH_2C\underline{H}_2$Br), 2.88 (dddd, J = 1.3, 5.9, 8.6, 12.6 Hz, 1 H, $OCH_2C\underline{H}_2$), 2.30 (dt, J = 1.8, 7.5 Hz, 2 H, C(=O)C$\underline{H}_2CH_2CH_2CH_2CH_2$Br), 2.16 (dtd, J = 8.9, 11.5, 12.5 Hz, 1 H, $OCH_2C\underline{H}_2$), 1.90 (quin, J = 7.2 Hz, 2 H, C(=O)$CH_2CH_2CH_2C\underline{H}_2CH_2$Br), 1.71 (quin, J = 7.6 Hz, 2 H, C(=O)$CH_2C\underline{H}_2CH_2CH_2CH_2$Br), 1.59 - 1.46 (m, 2 H, C(=O)$CH_2CH_2C\underline{H}_2CH_2CH_2$Br)

^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 175.5 (O$\underline{C}$=O), 173.3 ($\underline{C}$(=O)NH), 66.1 (O$\underline{C}H_2$), 49.3 ($\underline{C}$HNHC=O), 35.8 (C(=O)$CH_2CH_2CH_2CH_2\underline{C}H_2$Br), 33.5 (C(=O)$\underline{C}H_2CH_2CH_2CH_2CH_2$Br), 32.3 (C(=O)$CH_2CH_2CH_2\underline{C}H_2$-$CH_2$Br), 30.5 ($OCH_2\underline{C}H_2$), 27.6 (C(=O)$CH_2\underline{C}H_2CH_2CH_2CH_2$Br), 24.4 (C(=O)$CH_2CH_2\underline{C}H_2CH_2CH_2$Br)

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

$[\boldsymbol{\alpha}]_D^{26.6}$ / °10^{-1}cm^{2}g^{-1} = - 16 (c / g(100 mL)$^{-1}$ = 0.20833 , MeOH)

1.15 (*S*)-6-Azido-*N*-(2-oxotetrahydrofuran-3-yl)hexanamide 47



(*S*)-6-Bromo-*N*-(2-oxotetrahydrofuran-3-yl)hexanamide (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 to give 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} = 3314.00 (N-H), 2931.56 (C-H), 2862.89 (C-H), 2095.06 (N_3), 1775.38 (lactone C=O), 1643.14 (amide C=O), 1547.90 (N-H bend)

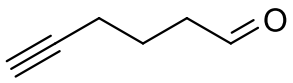
^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 5.97 (br d, J = 4.2 Hz, 1 H, N$\underline{H}$), 4.56 (ddd, J = 5.7, 8.6, 11.7 Hz, 1 H, C$\underline{H}$NHC=O), 4.50 (dt, J = 1.0, 9.1 Hz, 1 H, OC$\underline{H}_2$), 4.31 (ddd, J = 5.8, 9.4, 11.3 Hz, 1 H, OC$\underline{H}_2$), 3.31 (t, J = 6.9 Hz, 2 H, C$\underline{H}_2N_3$), 2.90 (dddd, J = 1.1, 5.8, 8.6, 12.5 Hz, 1 H, $OCH_2C\underline{H}_2$), 2.30 (dt, J = 1.8, 7.4 Hz, 2 H, O=CC$\underline{H}_2$), 2.15 (dtd, J = 8.8, 11.5, 12.3 Hz, 1 H, $OCH_2C\underline{H}_2$), 1.72 (quin, J = 7.6 Hz, 2 H, O=$CCH_2CH_2CH_2C\underline{H}_2CH_2N_3$), 1.65 (quin, J = 7.2 Hz, 2 H, O=$CCH_2C\underline{H}_2CH_2CH_2CH_2N_3$) 1.46 (m, 2 H, O=$CCH_2CH_2C\underline{H}_2CH_2CH_2N_3$)

^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 175.4 (O$\underline{C}$=O), 172.2 ($\underline{C}$(=O)NH), 66.1 (O$\underline{C}H_2$), 51.2 (C(=O)CH_2CH_2-$CH_2CH_2\underline{C}H_2N_3$), 49.4 ($\underline{C}$HNHC=O), 35.9 (C(=O)$\underline{C}H_2CH_2CH_2CH_2CH_2N_3$), 30.7 ($OCH_2\underline{C}H_2$), 28.6 (C(=O)$CH_2$-$CH_2CH_2\underline{C}H_2CH_2N_3$), 26.3 (C(=O)$CH_2\underline{C}H_2CH_2CH_2CH_2N_3$), 24.8 (C(=O)$CH_2CH_2\underline{C}H_2CH_2CH_2N_3$)

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)$^{-1}$ = 0.20833 , MeOH)

1.16 Hex-5-ynal 49



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 (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 to give a pale yellow-green oil (4.72 g, 49.1 mmol, 72 %).

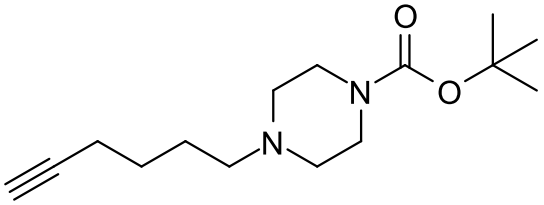
IR (neat) ν_{max} / cm^{-1} = 3292.68 (alkyne C-H), 2943.26 (alkane C-H), 2830.88 (aldehyde C-H), 2728.56 (aldehyde C-H), 1720.29 (aldehyde C=O)

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

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

Spectroscopic data are consistent with the literature.[6]

1.17 *tert*-Butyl 4-(hex-5-yn-1-yl)piperazine-1-carboxylate 51



Hex-5-ynal **49** (0.407 g, 4.24 mmol, 1.00 eq.) and *tert*-butyl piperazine-1-carboxylate (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, 6.96 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 to give a colourless liquid (1.12 g, 4.21 mmol, 99 %).

TLC R_f (10 % MeOH/CH_2Cl_2) = 0.55

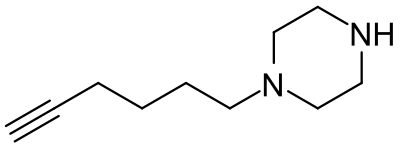
IR (neat) ν_{max} / cm^{-1} = 3303.59 (alkyne C-H), 2939.96 (alkane C-H), 2865.23 (C-H), 2810.42 (C-H), 1691.29 (carbamate C=O)

^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 3.44 (t, J = 5.2 Hz, 4 H, BocN(C$\underline{H}_2$)C$\underline{H}_2$), 2.39 (t, J = 5.1 Hz, 4 H, HC≡CCH$_2$CH$_2$CH$_2$CH$_2$N(C$\underline{H}_2$)C$\underline{H}_2$), 2.37 (t, J = 7.3 Hz, 2 H, HC≡CCH$_2$CH$_2$CH$_2$C$\underline{H}_2$N), 2.23 (dt, J = 2.7, 6.8 Hz, 2 H, HC≡CC$\underline{H}_2$CH$_2$CH$_2$CH$_2$N), 1.96 (t, J = 2.7 Hz, 1 H, $\underline{H}$C≡CCH$_2$CH$_2$CH$_2$CH$_2$N), 1.65 - 1.53 (m, 4 H, HC≡CCH$_2$C$\underline{H}_2$C$\underline{H}_2$CH$_2$N), 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≡$\underline{C}$), 79.6 ($\underline{C}$(CH$_3$)$_3$), 68.5 (H$\underline{C}$≡C), 60.4 (HC≡CCH$_2$CH$_2$CH$_2\underline{C}$H$_2$N), 58.0 (HC≡CCH$_2$CH$_2$CH$_2$CH$_2$N($\underline{C}$H$_2$)$\underline{C}$H$_2$), 53.0 (BocN($\underline{C}$H$_2$)$\underline{C}$H$_2$), 28.4 (C-($\underline{C}$H$_3$)$_3$), 26.3 (HC≡CCH$_2$CH$_2\underline{C}$H$_2$CH$_2$N), 25.7 (HC≡CCH$_2\underline{C}$H$_2$CH$_2$CH$_2$N), 18.3 (HC≡C$\underline{C}$H$_2$CH$_2$CH$_2$CH$_2$N)

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

1.18 1-(Hex-5-yn-1-yl)piperazine 52



tert-Butyl 4-(hex-5-yn-1-yl)piperazine-1-carboxylate **51** (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) to give a colourless liquid (476 mg, 2.86 mmol, 100 %).

TLC R_f (30 % MeOH/CH_2Cl_2) = 0.20

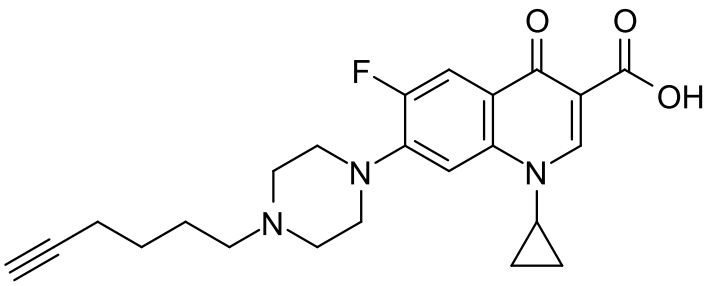
IR (neat) ν_{max} / cm^{-1} = 3295.87 (alkyne C-H), 2941.07 (alkane C-H), 2810.64 (alkane C-H), 1637.22 (N-H bend)

^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 2.88 (t, J = 4.9 Hz, 4 H, HN(C$\underline{H}_2$)C$\underline{H}_2$), 2.39 (m, 4 H, HC≡CCH$_2$CH$_2$-CH$_2$CH$_2$N(C$\underline{H}_2$)C$\underline{H}_2$), 2.31 (t, J = 7.1 Hz, 2 H, HC≡CCH$_2$CH$_2$CH$_2$C$\underline{H}_2$N), 2.20 (dt, J = 2.7, 6.8 Hz, 2 H, HC≡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≡C), 1.65 - 1.48 (m, 4 H, HC≡CCH$_2$C$\underline{H}_2$C$\underline{H}_2$-CH$_2$N)

^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 84.3 (HC≡$\underline{C}$), 68.4 (H$\underline{C}$≡C), 58.6 (HC≡CCH$_2$CH$_2$CH$_2\underline{C}$H$_2$N), 54.5 (HC≡CCH$_2$CH$_2$CH$_2$CH$_2$N($\underline{C}$H$_2$)$\underline{C}$H$_2$), 46.0 (HN($\underline{C}$H$_2$)$\underline{C}$H$_2$), 26.4 (HC≡CCH$_2$CH$_2\underline{C}$H$_2$CH$_2$N), 25.7 (HC≡C-CH$_2\underline{C}$H$_2$CH$_2$CH$_2$N), 18.3 (HC≡C$\underline{C}$H$_2$CH$_2$CH$_2$CH$_2$N)

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

1.19 1-Cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 54



7-Chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquino-line-3-carboxylic acid **53** (1.27 g, 4.51 mmol, 1 eq.), 1-(hex-5-yn-1-yl)piperazine **52** (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). **54** 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} = 3211.99 (alkyne C-H), 2459.32 (O-H), 1722.63 (carboxylic acid C=O), 1626.76 (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($CH\underline{H})_2$)

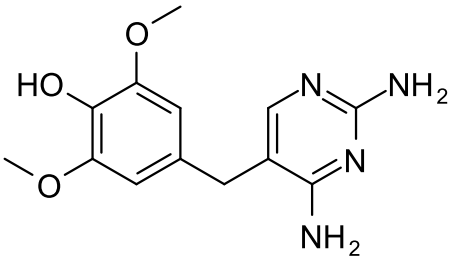
^{13}**C NMR** (126 MHz, DMSO-d_6) δ / ppm = 176.4 ($\underline{C}$(=O)CC(=O)OH), 165.8 ($\underline{C}$(=O)OH), 152.8 (d, J=248.5 Hz, *ipso* to F), 148.2 ($\underline{C}$HCC(=O)OH), 143.7 (d, J=11.1 Hz, *para* to C(=O)), 139.1 (*para* to F), 119.4 (d, J=6.9 Hz, *ipso* to C(=O)), 111.2 (d, J=22.5 Hz, *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 = -121.82 (s, ciprofloxacin F)

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

go through Cips and check pip C is two peaks not doublet

1.20 4-((2,4-Diaminopyrimidin-5-yl)methyl)-2,6-dimethoxyphenol 124



Hydrobromic acid (48 % w/w, aq., 50 ml) was heated to 100 °C, then trimethoprim (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. **124** 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)

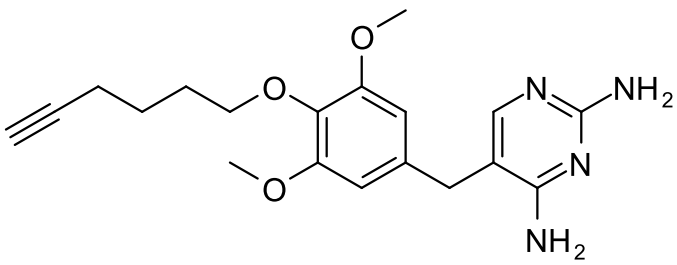
^{1}H NMR (400 MHz, MeOD) δ / ppm = 7.21 (s, 1 H, C$\underline{H}$N), 6.54 (s, 2 H, *meta* to OCH_2), 4.87 (br. s., 5 H, OH, $NH_2 \times 2$), 3.82 (s, 6 H, OC$\underline{H}_3$), 3.63 (s, 2 H, CC$\underline{H}_2$C)

^{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.[7]

1.21 5-(4-(Hex-5-yn-1-yloxy)-3,5-dimethoxybenzyl)pyrimidine-2,4-diamine 125



4-((2,4-Diaminopyrimidin-5-yl)methyl)-2,6-dimethoxyphenol **124** (1.00 g, 3.62 mmol, 1 eq.), 6-chloro-1-hexyne **175** (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 °CC 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). **125** was obtained as a pale cream amorphous solid (0.253 g, 0.709 mmol, 19.6 %).

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)

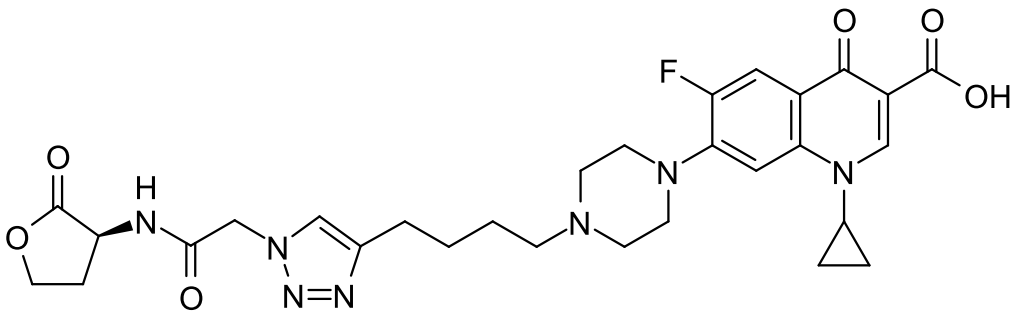
^{1}**H NMR** (400 MHz, MeOD) δ / ppm = 7.77 (s, 1 H, C$\underline{H}$N), 6.37 (s, 2 H, *meta* to OCH_2), 4.83 (br. s., 2 H, CHNCN$\underline{H}_2$), 4.63 (br. s., 2 H, CH_2CCN$\underline{H}_2$), 3.95 (t, J = 6.3 Hz, 2 H, C$\underline{H}_2$O), 3.79 (s, 6 H, OC$\underline{H}_3$), 3.65 (s, 2 H, CC$\underline{H}_2$C),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

^{13}**C NMR** (101 MHz, MeOD) δ / ppm = 162.7 (CH_2C$\underline{C}$NH_2), 162.0 (CHN$\underline{C}$NH_2), 156.4 ($\underline{C}$HNCNH_2), 153.8 (*ipso* to OCH_3), 136.0 (*ipso* to OCH_2), 133.6 (*para* to OCH_2), 106.5 ($CH_2$$\underline{C}CNH_2$), 105.0 (*meta* to OCH_2), 84.5 (HC≡$\underline{C}$), 72.6 ($\underline{C}$$H_2$O), 68.3 (H$\underline{C}$≡C), 56.1 (O$\underline{C}$$H_3$), 34.7 (C$\underline{C}$$H_2$C), 29.1 ($\underline{C}$$H_2$$CH_2$O), 24.9 ($\underline{C}$$H_2$$CH_2$$CH_2$O), 18.0 (HC≡C$\underline{C}$$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.

1.22 (*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 126



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 **176** (20.6 mg, 50.0 μmol, 1 eq.) and (*S*)-2-azido-*N*-(2-oxotetrahydrofuran-3-yl)acetamide **41** (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 3h. 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 3h

the reaction mixture was evaporated under reduced pressure. The residue was purified by preparatory HPLC(?? % acetonitrile/water over 15 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. **126** was obtained as a white amorphous solid (8.8 mg, 14.8 μmol, 29.6 %).

IDK what happened after this, check, weigh etc.

column? equipment?

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)

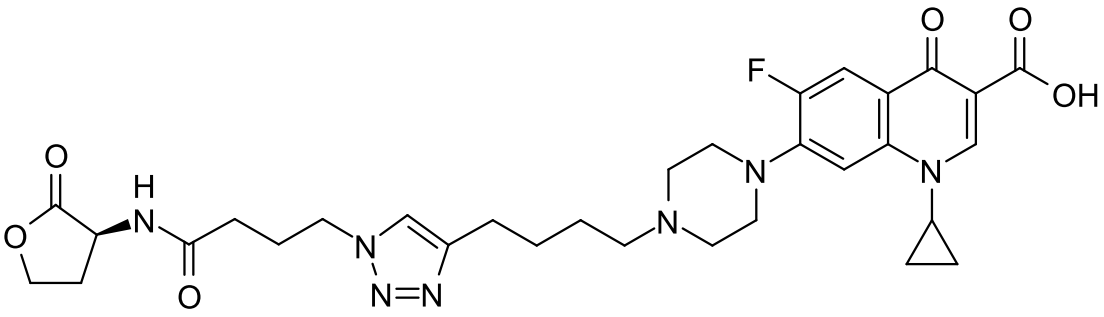
^{1}**H NMR** (400 MHz, DMSO d_6) δ / ppm = 15.23 (s, 1 H, C(=O)OH), 8.84 (d, J = 7.9 Hz, 1 H, NH), 8.66 (s, 1 H, *ortho* to C(=O)OH), 7.90 (d, J = 13.3 Hz, 1 H, *ortho* to F), 7.82 (s, 1 H, CH=CCH_2), 7.57 (d, J = 7.6 Hz, 1 H, *meta* to F), 5.13 (s, 1 H, C(=O)CHHN), 5.12 (s, 1 H, C(=O)CHHN), 4.64 (ddd, J = 10.9, 9.0, 7.8 Hz, 1 H, CHNH), 4.36 (td, J = 8.9, 1.7 Hz, 1 H, OCHH), 4.23 (ddd, J = 10.6, 8.8, 6.4 Hz, 1 H, OCHH), 3.83 (tt, J = 7.0, 4.0 Hz, 1 H, NCH$(CH_2)_2$), 3.32 (br s, 4 H, $CH_2CH_2CH_2N(CH_2CH_2)CH_2CH_2$), 2.67 (t, J = 7.4 Hz, 2 H, CH=CCH_2), 2.58 (br t, J = 5.0 Hz, 4 H, $CH_2CH_2CH_2N(CH_2)CH_2$), 2.42 - 2.49 (m, 1 H, OCH_2CHH), 2.40 (t, J = 7.1 Hz, 1 H, $CH{=}CCH_2CH_2CH_2CH_2$), 2.17 (dtd, J = 11.7, 10.8, 10.8, 9.0 Hz, 1 H, OCH_2CHH), 1.66 (quin, J = 7.2 Hz, 1 H, $CH{=}CCH_2CH_2CH_2$), 1.53 (quin, J = 7.2 Hz, 1 H, $CH{=}CCH_2CH_2CH_2$), 1.28 - 1.35 (m, 1 H, NCH$(CHH)_2$), 1.16 - 1.21 (m, 1 H, NCH$(CHH)_2$)

^{13}**C NMR** (101 MHz, DMSO d_6) δ / ppm = 176.4 (C(=O)CC(=O)OH), 174.9 (OC(=O)), 166.0 (C(=O)OH), 165.9 (NHC(=O)), 153.1 (d, J = 250.8 Hz, *ipso* to F), 148.0 (CH=CC(=O)OH), 146.6 (CH=CCH_2), 145.3 (d, J = 9.6 Hz, *ipso* to piperazine), 139.2 (*para* to F), 123.4 (CH=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 (CC(=O)OH), 106.4 (d, J = 3.2 Hz, *meta* to C=O and *meta* to F), 65.4 (OCH_2), 57.3 ($CH{=}CCH_2CH_2CH_2CH_2N$), 52.4 ($CH_2CH_2CH_2N(CH_2)CH_2$), 51.2 (C(=O)CH_2N), 49.5 (d, J = 4.3 Hz, $CH_2CH_2CH_2N(CH_2CH_2)CH_2CH_2$), 48.2 (CHNH), 35.9 (NCH$(CH_2)_2$), 28.2 (CH_2CHNH), 26.8 ($CH{=}CCH_2CH_2$), 25.7 ($CH{=}CCH_2CH_2CH_2$), 24.9 ($CH{=}CCH_2$), 7.6 (NCH$(CH_2)_2$)

^{19}**F NMR** (376.45 MHz, DMSO d_6) δ / ppm = ??

HRMS (ESI^+) m/z / Da = 596.2627, $[M+H]^+$ found, $[C_{29}H_{35}FN_7O_6]^+$ requires 596.2633 $[\alpha]_D^{20}$ / $°10^{-1}cm^2g^{-1}$ = -3.5 (c / g(100 mL)$^{-1}$ = 0.0575 , MeOH)

1.23 (*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 127



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 **176** (20.6 mg, 50.0 μmol, 1 eq.) and (*S*)-4-azido-*N*-(2-oxotetrahydrofuran-3-yl)butanamide **46** (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 3h, then the reaction mixture was evaporated under reduced pressure. The residue was purified by preparatory HPLC(% acetonitrile/water over 15 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. **127** was obtained as a white amorphous solid (14.6 mg, 23.4 μmol, 46.8 %).

IDK what happened after this, was it prep or combi-flash?, check, weigh etc.

column? equipment?

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)

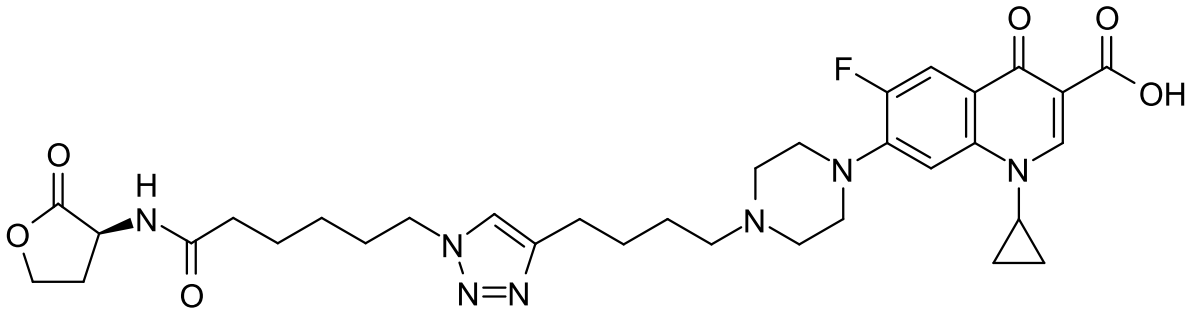
^{1}H NMR (500 MHz, DMSO d_6) δ / ppm = 15.22 (br s, 1 H, C(=O)O<u>H</u>), 8.65 (s, 1 H, *ortho* to C(=O)OH), 8.40 (d, J = 8.0 Hz, 1 H, N<u>H</u>), 7.88 (d, J = 13.4 Hz, 1 H, *ortho* to F), 7.85 (s, 1 H, C<u>H</u>=CCH$_2$), 7.55 (d, J = 7.5 Hz, 1 H, *meta* to F), 4.53 (ddd, J = 10.9, 9.0, 8.1 Hz, 1 H, 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, 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, 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 (NHC(=O)CH$_2$<u>C</u>H$_2$), 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$_2$)$_2$)

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

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)

1.24 (*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 128



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 **176** (20.6 mg, 50.0 μmol, 1 eq.) and (*S*)-6-azido-*N*-(2-oxotetrahydrofuran-3-yl)hexanamide **47** (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 3h, then 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). The combined pure fractions were dried with $MgSO_4$ and evaporated under reduced pressure. **126** was obtained as a white amorphous solid (12.4 mg, 19.0 μmol, 38.0 %).

how to report?

IDK what happened after this, check, weigh etc.

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)OH), 8.65 (s, 1 H, *ortho* to C(=O)OH), 8.32 (d, J = 8.0 Hz, 1 H, NH), 7.89 (d, J = 13.3 Hz, 1 H, *ortho* to F), 7.84 (s, 1 H, CH=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, CHNH), 4.33 (td, J = 8.8, 1.8 Hz, 1 H, OCHH), 4.28 (t, J = 7.1 Hz, 2 H, CH_2NCH=C), 4.19 (ddd, J = 10.5, 8.7, 6.6 Hz, 1 H, OCHH), 3.82 (tt, J = 7.0, 4.0 Hz, 1 H, NCH(CH_2)$_2$), 3.32 (br t, J = 4.5, 4 H, $CH_2CH_2CH_2N(CH_2CH_2)CH_2CH_2$), 2.63 (t, J = 7.5 Hz, 2 H, CH=CCH_2), 2.57 (br t, J = 4.2, 4.2 Hz, 4 H, $CH_2CH_2CH_2N(CH_2)CH_2$), 2.33 - 2.41 (m, 3 H, OCH_2CHH and $CH=CCH_2CH_2CH_2CH_2$), 2.06 - 2.16 (m, 3 H, OCH_2CHH and C(=O)CH_2), 1.79 (quin, J = 7.4 Hz, 2 H, $C(=O)CH_2CH_2CH_2CH_2$), 1.63 (quin, J = 7.5 Hz, 2 H, $CH=CCH_2CH_2$), 1.45 - 1.56 (m, 4 H, $C(=O)CH_2CH_2$ and $CH=CCH_2CH_2CH_2CH_2$), 1.29 - 1.34 (m, 2 H, NCH(CHH)$_2$), 1.19 - 1.25 (m, 2 H, $C(=O)CH_2CH_2CH_2$), 1.15 - 1.19 (m, 2 H, NCH(CHH)$_2$)

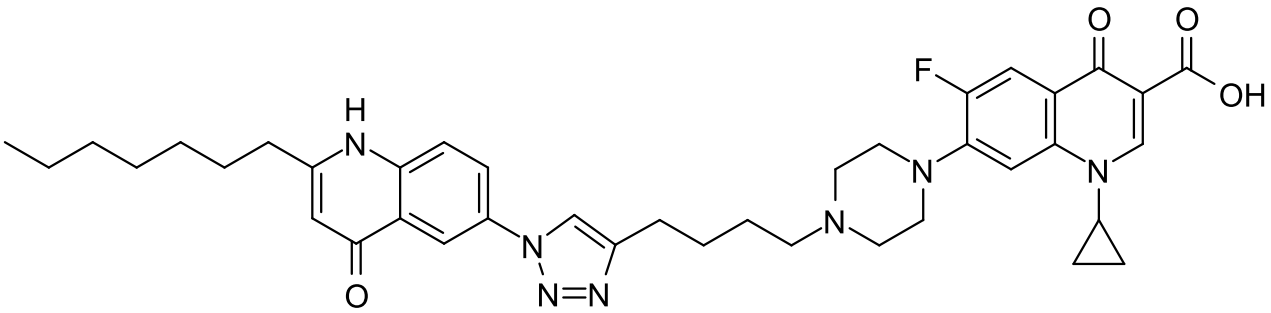
^{13}**C NMR** (126 MHz, DMSO d_6) δ / ppm = 176.4 (C(=O)CC(=O)OH), 175.4 (OC(=O)), 172.1 (NHC(=O)), 166.0 (C(=O)OH), 153.0 (d, J = 250.2 Hz, *ipso* to F), 148.0 (CH=CC(=O)OH), 146.8 (CH=CCH_2), 145.2 (d, J = 9.6 Hz, *ipso* to piperazine), 139.2 (*para* to F), 121.6 (CH=CCH_2), 118.5 (d, J = 8.0 Hz, *para* to piperazine), 110.9 (d, J = 23.5 Hz, *ortho* to C=O and *ortho* to F), 106.7 (CC(=O)OH), 106.3 (d, J = 2.1 Hz, *meta* to C=O and *meta* to F), 65.3 (OCH_2), 57.4 ($CH=CCH_2CH_2CH_2CH_2N$), 52.4 ($CH_2CH_2CH_2N(CH_2)CH_2$), 49.5 (d, J = 3.2 Hz, $CH_2CH_2CH_2N(CH_2CH_2)CH_2CH_2$), 49.0 ($CH_2NCH=C$), 47.8 (CHNH), 35.9 (NCH(CH_2)$_2$), 34.8 ($NHC(=O)CH_2$), 29.5 ($CH_2CH_2NCH=C$), 28.3 (CH_2CHNH), 26.9 ($CH=CCH_2CH_2$), 25.7 ($CH=CCH_2CH_2CH_2$),

25.4 (NHC(=O)$CH_2CH_2\underline{C}H_2$), 24.9 (CH=C$\underline{C}H_2$), 24.5 (NHC(=O)$CH_2\underline{C}H_2$), 7.6 (NCH($\underline{C}H_2)_2$)

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

HRMS (ESI$^+$) m/z / Da = 652.3254, $[M+H]^+$ found, $[C_{33}H_{43}FN_7O_6]^+$ requires 652.3248 $[\alpha]_D^{20}$ / $°10^{-1}cm^2g^{-1}$ = -8.5 (c / g(100 mL)$^{-1}$ = 0.106 , MeOH)

1.25 1-Cyclopropyl-6-fluoro-7-(4-(4-(1-(2-heptyl-4-oxo-1,4-dihydroquinolin-6-yl)-1H-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 129



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 **176** (4.1 mg, 10.0 μmol, 1 eq.) and 6-azido-2-heptylquinolin-4(1H)-one **26** (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 preparatory HPLC (50-100 % acetonitrile/water over ??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. **129** was obtained as a white amorphous solid (8.6 mg, 2.7 μmol, 27.0 %).

check

column? equip-ment?

needs desalt-ing

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)

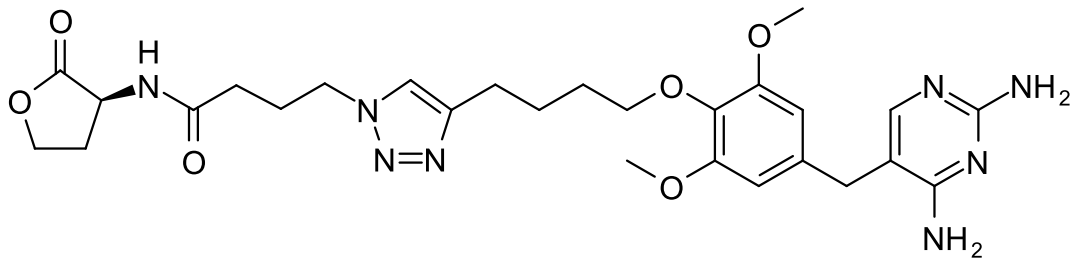
^{1}H NMR (400 MHz, MeOD) δ / ppm = ??

^{13}C NMR (101 MHz, MeOD) δ / ppm = ??

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

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

1.26 (*S*)-4-(4-(4-((2,4-Diaminopyrimidin-5-yl)methyl)-2,6-dimethoxyphenoxy)butyl)-1H-1,2,3-triazol-1-yl)-*N*-(2-oxotetrahydrofuran-3-yl)butanamide 130



Method?? pale brown gum 4.8 mg, 8.4 μmol

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)

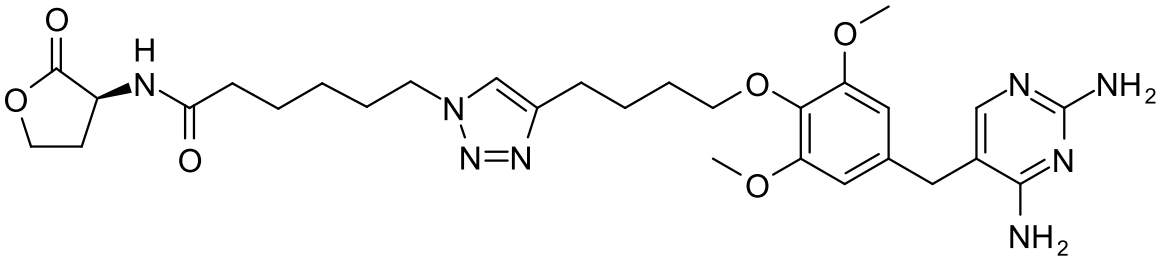
^{1}**H NMR** (400 MHz, MeOD) δ / ppm = ??

^{13}**C NMR** (101 MHz, MeOD) δ / ppm = ??

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

HRMS (ESI^+) m/z / Da = 569.2834, $[M+H]^+$ found, $[C_{27}H_{37}N_8O_6]^+$ requires 569.2836 $[\alpha]_D^{20}$ / $°10^{-1}cm^2g^{-1}$ = -4.6 (c / g(100 mL)$^{-1}$ = 0.0433 , MeOH)

1.27 (*S*)-6-(4-(4-(4-((2,4-Diaminopyrimidin-5-yl)methyl)-2,6-dimethoxyphenoxy)butyl)-1H-1,2,3-triazol-1-yl)-*N*-(2-oxotetrahydrofuran-3-yl)hexanamide 131



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 **125** (20.6 mg, 50.0 μmol, 1 eq.) and (*S*)-6-azido-*N*-(2-oxotetrahydrofuran-3-yl)hexanamide **47** (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 **47** (12.0 mg, 50.0 μmol, 1 eq.) was added after 1 d. . **131** was obtained as a clear gum (8.0 mg, 13.4 μmol, 26.8 %).

IDK what happened after this, check,

TLC R_f = 0.35 (30 % MeOH/CH_2Cl_2)

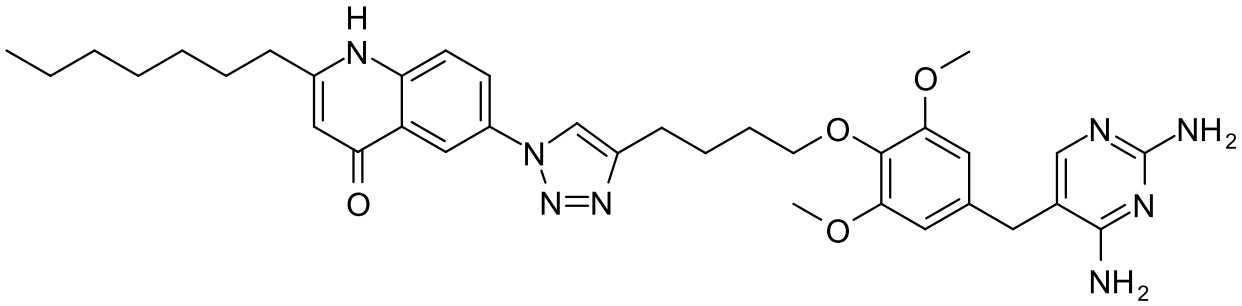
IR (neat) ν_{max} / cm^{-1} = 3336.0 (N-H), 3208.7 (N-H), 2941.1 (C-H), 2869.2 (C-H), 1775.2 (lactone C=O), 1657.3 (amide C=O and pyrimidine)

^{1}H NMR (500 MHz, DMSO d_6) δ / ppm = 8.34 (d, J = 8.0 Hz, 1 H, NH), 7.83 (s, 1 H, NCH=CCH_2), 7.50 (s, 1 H, CHN=CNH_2), 6.54 (s, 2 H, *meta* to CH_2), 6.17 (br s, 2 H, CH_2CCNH_2), 5.77 (br s, 2 H, CHN=CNH_2), 4.51 (ddd, J = 11.0, 9.0, 8.1 Hz, 1 H, CHNH), 4.33 (td, J = 8.8, 1.9 Hz, 1 H, CHHOC(=O)), 4.27 (t, J = 7.1 Hz, 2 H, CH_2N), 4.19 (ddd, J = 10.5, 8.7, 6.5 Hz, 1 H, CHHOC(=O)), 3.80 (t, J = 6.3 Hz, 2 H, CH_2O), 3.70 (s, 6 H, CH_3), 3.52 (s, 2 H, CCH_2C), 2.64 (t, J = 7.5 Hz, 2 H, CH=CCH_2), 2.36 (dddd, J = 12.1, 8.9, 6.7, 1.8 Hz, 1 H, CHHCHNH), 2.06 - 2.16 (m, 3 H, CHHCHNH and C(=O)CH_2), 1.78 (quin, J = 7.4 Hz, 2 H, CH_2CH_2N), 1.73 (quin, J = 7.7 Hz, 2 H, $CH{=}CCH_2CH_2$), 1.63 (quin, J = 6.8 Hz, 2 H, CH_2CH_2O), 1.52 (quin, J = 7.5 Hz, 2 H, $C(=O)CH_2CH_2$), 1.17 - 1.27 (m, 2 H, $C(=O)CH_2CH_2CH_2$)

^{13}C NMR (125 MHz, DMSO d_6) δ / ppm = 175.4 (OC=O), 172.0 (NHC=O), 162.2 ($CC(NH_2)N$), 161.8 ($NC(NH_2)N$), 154.8 (CHNC(NH_2)N), 152.8 (*ipso* to OCH_3), 146.7 ($CH{=}CCH_2CH_2$), 135.5 (*para* to CH_2O), 134.8 (*ipso* to CH_2O), 121.6 ($CH{=}CCH_2CH_2$), 105.9 ($CH_2CC(NH_2){=}N$), 105.8 (*meta* to CH_2O), 71.9 ($CH_2CH_2CH_2O$), 65.2 (OCH_2CH_2CHNH), 55.8 (OCH_3), 49.0 (CH_2N), 47.8 (CHNH), 34.8 ($C(=O)CH_2$), 32.9 (CCH_2C), 29.4 (CH_2CH_2N), 29.1 ($CH_2CH_2CH_2O$), 28.2 (OCH_2CH_2CHNH), 25.5 ($CH{=}CCH_2CH_2$), 25.3 ($C(=O)CH_2CH_2CH_2$), 24.7 ($CH{=}CCH_2CH_2$), 24.4 ($C(=O)CH_2CH_2$)

HRMS (ESI^+) m/z / Da = 597.3149, $[M+H]^+$ found, $[C_{29}H_{41}N_8O_6]^+$ requires 597.3144 $[\alpha]_D^{20}$ / $°10^{-1}cm^2g^{-1}$ = -3.6 (c / g(100 mL)$^{-1}$ = 0.11 , MeOH)

1.28 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 132



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 **125** (3.6 mg, 10.0 μmol, 1 eq.) and 6-azido-2-heptylquinolin-4(1*H*)-one **26** (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 the reaction mixture was evaporated under reduced pressure. The residue was purified by preparatory HPLC (5-100 % acetonitrile/water over 20 min). The combined pure fractions were evaporated under reduced pressure. **132** was obtained as a clear gum (2.6 mg, 4.1 μmol, 41.0 %).

column? equipment?

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),

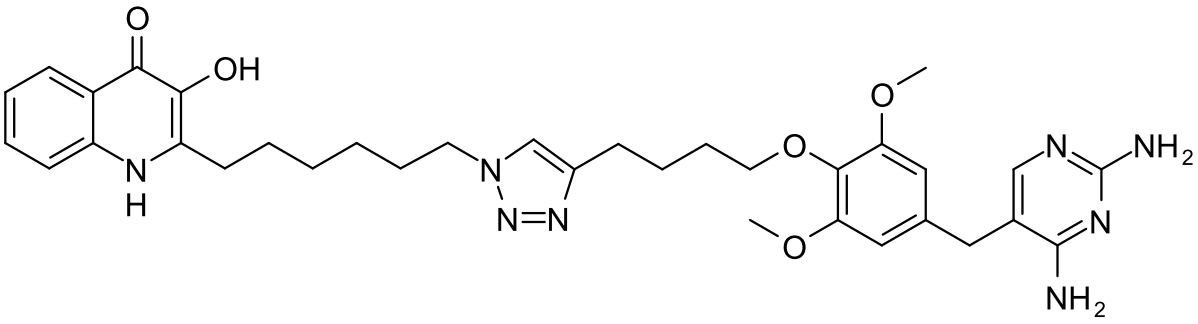
^{1}H NMR (500 MHz, DMSO d_6) δ / ppm = 11.80 (s, 1 H, NH), 8.69 (s, 1 H, NCH=CCH$_2$), 8.41 (d, J = 2.7 Hz, 1 H, *ortho* to C=O), 8.17 (dd, J = 9.0, 2.6 Hz, 1 H, *para* to C=O), 7.73 (d, J = 9.0 Hz, 1 H, ortho to NH), 7.51 (br s, 4 H, NH$_2$), 7.41 (s, 1 H, CHN=CNH$_2$), 6.61 (s, 2 H, *meta* to CH$_2$), 6.02 (d, J = 1.8 Hz, 1 H, C(=O)CH), 3.86 (t, J = 6.3 Hz, 2 H, CH$_2$O), 3.73 (s, 6 H, OCH$_3$), 3.57 - 3.62 (m, 2 H, CCH$_2$C), 2.78 (t, J = 7.5 Hz, 2 H, CH=CCH$_2$), 2.63 (t, J = 7.3 Hz, 2 H, HNCCH$_2$), 1.85 (quin, J = 7.5 Hz, 2 H, CH=CCH$_2$CH$_2$), 1.61 - 1.78 (m, 4 H, HNCCH$_2$CH$_2$ and CH=CCH$_2$CH$_2$CH$_2$), 1.31 - 1.40 (m, 4 H, HNCCH$_2$CH$_2$CH$_2$CH$_2$), 1.25 - 1.31 (m, 4 H, CH$_3$CH$_2$CH$_2$), 0.86 (t, J = 7.2 Hz, 3 H, CH$_3$CH$_2$)

check all frequencies

^{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$_2$CH$_2$), 140.2 (CHNC(NH$_2$)N), 139.6 (*ipso* to NH), 135.4 (*ipso* to CH$_2$O), 132.8 (*para* to CH$_2$O), 132.1 (*para* to NH), 124.9 (*ipso* to C=O), 123.7 (*para* to C=O), 120.3 (CH=CCH$_2$CH$_2$), 120.0 (*meta* to C=O and *ortho* to NH), 115.1 (*ortho* to C=O and *meta* to NH), 109.0 (CH$_2$CC(NH$_2$)=N), 108.0 (C(=O)CH), 106.3 (*meta* to CH$_2$O), 72.0 (CH$_2$CH$_2$CH$_2$O), 56.0 (OCH$_3$), 33.3 (HNCCH$_2$), 32.1 (CCH$_2$C), 31.2 (CH$_3$CH$_2$CH$_2$), 29.1 (CH$_2$CH$_2$O), 28.3 - 28.6 (CH$_3$CH$_2$CH$_2$CH$_2$CH$_2$CH$_2$), 25.3 (CH$_2$CH$_2$CH$_2$O), 24.7 (CH=CCH$_2$), 22.1 (CH$_3$CH$_2$), 14.0 (CH$_3$CH$_2$)

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

1.29 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 133



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 **125** (14.2 mg, 39.8 μmol, 1 eq.) and 2-(6-azidohexyl)-3-hydroxyquinolin-4(1H)-one **70** (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. **133** 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),

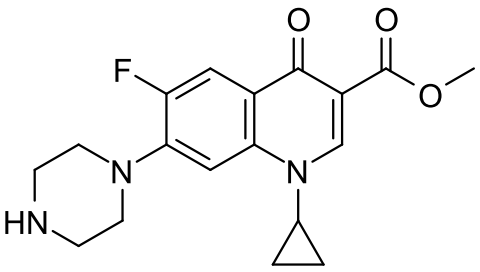
^{1}H NMR (500 MHz, DMSO d_6) δ / ppm = 11.53 (br s, 1 H, NH), 8.09 (d, J = 8.0 Hz, 1 H, *ortho* to C=O), 7.83 (s, 1 H, NCH=CCH$_2$), 7.48 - 7.57 (m, 3 H, *para* to C=O, *ortho* to NH and CHN=CNH$_2$), 7.21 (ddd, J =

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, $C\underline{H}_2N$), 3.80 (t, J = 6.2 Hz, 2 H, $C\underline{H}_2O$), 3.70 (s, 6 H, $C\underline{H}_3$), 3.53 (d, J = 0.3 Hz, 2 H, $CC\underline{H}_2C$), 2.73 (t, J = 7.5 Hz, 2 H, $HNCC\underline{H}_2$), 2.64 (t, J = 7.4 Hz, 2 H, $CH{=}CC\underline{H}_2$), 1.80 (quin, J = 7.4 Hz, 2 H, $C\underline{H}_2CH_2N$), 1.73 (quin, J = 7.5 Hz, 2 H, $CH{=}CCH_2C\underline{H}_2$), 1.66 (quin, J = 7.2 Hz, 2 H, $HNCCH_2C\underline{H}_2$), 1.62 (quin, J = 6.8 Hz, 2 H, $C\underline{H}_2CH_2O$), 1.33 - 1.40 (m, 2 H, $HNCCH_2CH_2C\underline{H}_2$), 1.27 - 1.32 (m, 2 H, $HNCCH_2CH_2CH_2C\underline{H}_2$)

^{13}C NMR (125 MHz, DMSO d_6) δ / ppm = 168.9 ($\underline{C}{=}O$), 162.5 ($C\underline{C}(NH_2)N$), 162.5 ($N\underline{C}(NH_2)N$), 152.9 ($\underline{C}HNC(NH_2)N$), 152.8 (*ipso* to OCH_3), 146.8 ($CH{=}\underline{C}CH_2CH_2$), 137.7 ($\underline{C}OH$), 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

1.30 Methyl 1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate 134



Ciprofloxacin **97** (10.0 g, 30 mmol, 1 eq.) and *p*-toluenesulfonic acid (8.60 mg, 44.5 mmol, 1.5 eq.) were refluxed in methanol (500 ml) for 72 h. The mixture was cooled to room temperature and $NaHCO_3$ (sat., aq., 100 ml) and water (300 ml) were added. The product was extracted with CH_2Cl_2 (2 × 400 ml), which was dried over $MgSO_4$ and evaporated under reduced pressure. **134** was obtained as a white amorphous solid (9.16 g, 26.5 mmol, 83.3 %).

TLC R_f = 0.13 (5 % MeOH/CH_2Cl_2)

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

^{1}**H NMR** (400 MHz, MeOD) δ / ppm = 8.55 (s, 1 H, *ortho* to C(=O)OCH_3), 7.71 (d, J = 13.5 Hz, 1 H, *ortho* to F), 7.41 (d, J = 7.2 Hz, 1 H, *meta* to F), 3.83 (s, 3 H, C$\underline{H}_3$), 3.62 (tt, J = 7.4, 3.5 Hz, 1 H, NC$\underline{H}(CH_2)_2$), 3.24 - 3.29 (m, 4 H, HN($CH_2C\underline{H}_2$)$CH_2C\underline{H}_2$), 3.02 - 3.10 (m, 4 H, HN($C\underline{H}_2$)$C\underline{H}_2$), 1.31 - 1.38 (m, 2 H, NCH($C\underline{H}H$)$_2$), 1.12 - 1.20 (m, 2 H, NCH($CH\underline{H}$)$_2$)

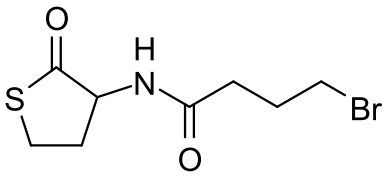
^{13}**C NMR** (101 MHz, MeOD) δ / ppm = 175.2 ($\underline{C}$(=O)CC(=O)OCH_3), 166.8 ($\underline{C}$(=O)OCH_3), 154.9 (d, J = 248.0 Hz, *ipso* to F), 150.1 ($\underline{C}$=CC(=O)OCH_3), 146.6 (d, J = 10.4 Hz, *ipso* to piperazine), 139.9 (*para* to F), 123.3 (d, J = 6.9 Hz, *para* to piperazine),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

^{19}**F NMR** (376.45 MHz, MeOD) δ / ppm = -124.8 (s, ciprofloxacin $\underline{F}$) 1dp

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.[8]

1.31 4-Bromo-*N*-(2-oxotetrahydrothiophen-3-yl)butanamide 135



3-Aminodihydrothiophen-2(3H)-one hydrochloride **177** (15.0 g, 97.6 mmol, 1 eq.) and $NaHCO_3$ (16.4 g, 195 mmol, 2 eq.) were added to CH_2Cl_2 (150 ml) and water (150 ml). 4-Bromobutyryl chloride **42** (11.3 ml, 107 mmol, 1.1 eq.) was added dropwise over 45 min at 0 °C and the mixture was stirred for a further 1 h. The organic layer was separated and the aqueous layer was extracted with a second portion of CH_2Cl_2 (150 ml). The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. **135** was obtained as a white, amorphous solid (22.7 g, 85.8 mmol, 87.9 %)

TLC R_f = 0.19 (50 % EtOAc/PE)

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

^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 6.08 (d, J = 6.1 Hz, 1 H, NH), 4.54 (dt, J = 12.9, 6.5 Hz, 1 H, CHNH), 3.49 (t, J = 6.4 Hz, 2 H, CH_2Br), 3.37 (ddd, J = 12.2, 11.5, 5.3 Hz, 1 H, SCHH), 3.26 (ddd, J = 11.5, 6.9, 1.3 Hz, 1 H, SCHH), 2.91 (dddd, J = 12.5, 6.7, 5.3, 1.3 Hz, 1 H, SCH_2CHH), 2.45 (t, J = 7.4 Hz, 1 H, C(=O)CHH), 2.45 (t, J = 6.8 Hz, 1 H, C(=O)CHH), 2.20 (quin, J = 6.7 Hz, 1 H, C(=O)CH_2CH$_2$), 1.96 (dddd, J = 12.7, 12.5, 12.2, 7.0 Hz, 1 H, SCH_2CHH)

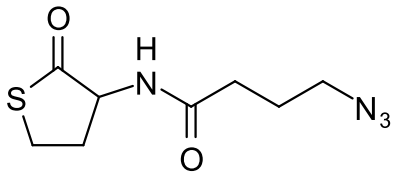
Orientatio are not unam- biguous without noesy.

^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 205.4 (SC(=O)), 172.1 (NHC(=O)), 59.4 (CHNH), 34.1 (C(=O)CH_2), 33.1 (CH_2Br), 31.8 (SCH_2CH_2), 28.0 (C(=O)CH_2CH_2), 27.5 (SCH_2)

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

The compound has been synthesised previously[9,10] but characterisation was not published.

1.32 4-Azido-*N*-(2-oxotetrahydrothiophen-3-yl)butanamide 136



4-Bromo-*N*-(2-oxotetrahydrothiophen-3-yl)butanamide **135** (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. **136** was obtained as a yellow, sticky solid (4.60 g, 20.1 mmol, 89.3 %).

TLC R_f = 0.19 (50 % EtOAc/PE)

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

^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 6.71 (d, J = 7.3 Hz, 1 H, NH), 4.54 (dt, J = 13.0, 7.0 Hz, 1 H, CHNH), 3.30 (t, J = 6.7 Hz, 2 H, CH_2N_3), 3.31 (td, J = 11.7, 5.3 Hz, 1 H, 1 H, SCHH), 3.19 (ddd, J = 11.3, 7.0, 1.2 Hz, 1 H, SCHH), 2.70 (dddd, J = 12.4, 6.8, 5.3, 1.2 Hz, 1 H, SCH_2CHH), 2.29 (t, J = 7.5 Hz, 1 H,

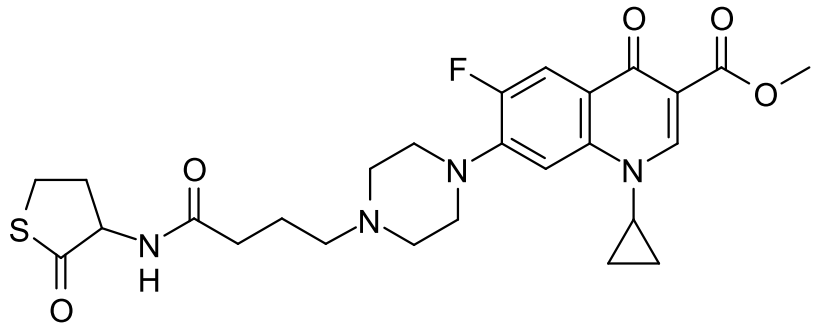
C(=O)C<u>H</u><u>H</u>), 2.28 (t, J = 7.1 Hz, 1 H, C(=O)CH<u>H</u>), 1.97 (qd, J = 12.4, 7.0 Hz, 1 H, $SCH_2CH\underline{H}$), 1.85 (quin, J = 6.9 Hz, 2 H, $C(=O)CH_2C\underline{H}_2$)

^{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 ($\underline{C}H_2N_3$), 32.8 ($C(=O)\underline{C}H_2$), 31.8 ($SCH_2\underline{C}H_2$), 27.5 ($S\underline{C}H_2$), 24.6 ($C(=O)CH_2\underline{C}H_2$)

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

The compound has not been reported previously.

1.33 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 137



Methyl 1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate **134** (50 mg, 0.145 mmol, 1 eq.), 4-bromo-*N*-(2-oxotetrahydrothiophen-3-yl)butanamide **135** (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 **135** (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 % $MeOH/CH_2Cl_2$). **137** 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<u>H</u>NH), 3.83 (s, 3 H, $OC\underline{H}_3$), 3.61 (tt, J=6.9, 4.1 Hz, 1 H, $NC\underline{H}(CH_2)_2$), 3.39 - 3.49 (m, 5 H, SC<u>H</u>H), 3.26 - 3.33 (m, 1 H, SCH<u>H</u> 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<u>H</u><u>H</u>), 2.38 (t, J=6.94 Hz, 1 H, C(=O)CH<u>H</u>), 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<u>C</u>(=O)), 175.7 (NH<u>C</u>(=O)), 175.1 (<u>C</u>(=O)CC(=O)OCH_3), 166.6 (<u>C</u>(=O)OCH_3), 154.7 (d, J=249.0 Hz, *ipso* to F), 150.2 (s, <u>C</u>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*

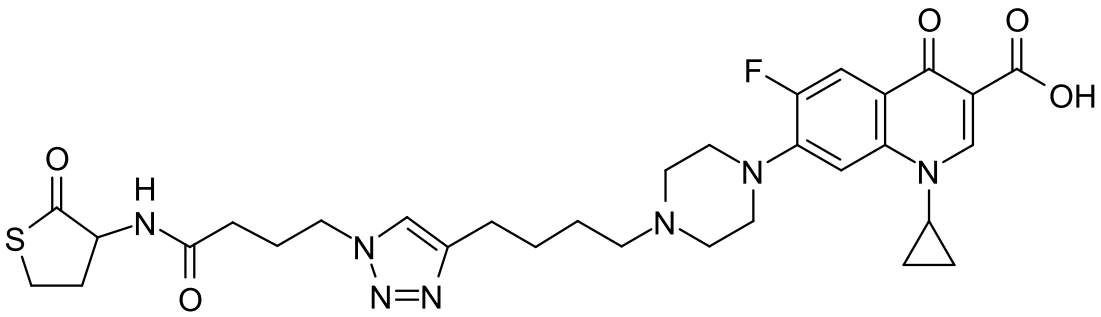
to C=O and *ortho* to F), 110.0 (C(=O)OCH$_3$), 107.4 (*meta* to C=O and *meta* to F), 60.2 (CHNH), 58.5 (C(=O)CH$_2$CH$_2$CH$_2$), 53.8 (C(=O)CH$_2$CH$_2$CH$_2$N(CH$_2$)CH$_2$), 52.3 (OCH$_3$), 50.1 (C(=O)CH$_2$CH$_2$CH$_2$N(CH$_2$CH$_2$)CH$_2$CH$_2$), 50.0 (C(=O)CH$_2$CH$_2$CH$_2$N(CH$_2$CH$_2$)CH$_2$CH$_2$), 36.5 (NCH(CH$_2$)$_2$), 34.5 (C(=O)CH$_2$), 31.7 (SCH$_2$CH$_2$), 28.1 (SCH$_2$), 22.9 (C(=O)CH$_2$CH$_2$CH$_2$), 8.7 (NCH(CH$_2$)$_2$)

^{19}F NMR (376.45 MHz, MeOD) δ / ppm = -125.35 (s, ciprofloxacin F)

HRMS (ESI$^+$) m/z / Da = 531.2083, [M+H]$^+$ found, [C$_{26}$H$_{32}$FN$_4$O$_5$S]$^+$ requires 531.2077

The compound has been synthesised previously.[9,10] Only HRMS characterisation was published, and this agrees with the result above. check??

1.34 1-Cyclopropyl-6-fluoro-4-oxo-7-(4-(4-(1-(4-oxo-4-((2-oxotetrahydrothiophen-3-yl)amino)butyl)-1H-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid 138



1-Cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **176** (12.9 mg, 31.4 μmol, 1 eq.), 4-azido-*N*-(2-oxotetrahydrothiophen-3-yl)butanamide **136** (7.2 mg, 31.4 μmol, 1 eq.), CuI (3.6 mg, 18.9 μmol, 0.6 eq.) and DIPEA (8.00 μl, 5.9 mg, 45.9 μmol, 1.5 eq.) were stirred in CH$_2$Cl$_2$ (1.4 ml) at r.t. under Ar for 3 h. Water (10 ml) was added, and the organic layer was separated off. The aqueous layer was further extracted with 10 % *i*-PrOH/CHCl$_3$ (3 × 10 ml), and the combined organic layers were dried with MgSO$_4$ and concentrated under reduced pressure. **138** was obtained as a white amorphous solid (16.5 mg, 25.9 μmol, 82.5 %).

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)

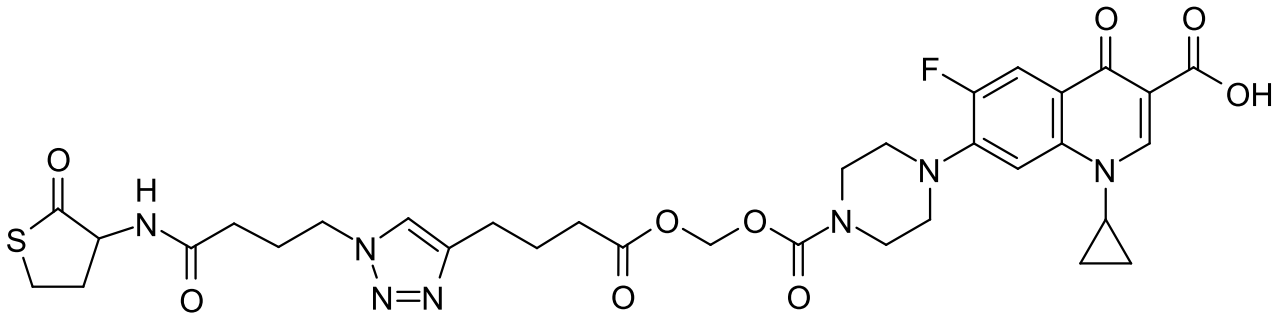
^{1}H NMR (400 MHz, MeOD) δ / ppm = ??

^{13}C NMR (101 MHz, MeOD) δ / ppm = ??

^{19}F NMR (376.45 MHz, MeOD) δ / ppm = -124.86 (s, ciprofloxacin F)

HRMS (ESI$^+$) m/z / Da = 640.2739, [M+H]$^+$ found, [C$_{31}$H$_{39}$FN$_7$O$_5$S]$^+$ requires 640.2712

1.35 1-Cyclopropyl-6-fluoro-4-oxo-7-(4-((((4-(1-(4-oxo-4-((2-oxotetrahydrothiophen-3-yl)amino)butyl)-1H-1,2,3-triazol-4-yl)butanoyl)oxy)methoxy)carbonyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid 139



1-Cyclopropyl-6-fluoro-7-(4-(((hex-5-ynoyloxy)methoxy)carbonyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **178** (203 mg, 0.407 mmol, 1 eq.), 4-azido-*N*-(2-oxotetrahydrothiophen-3-yl)butanamide **136** (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). **139** was obtained as pale brown/yellow amorphous solid (14.7 mg, 20.2 μmol, 5.0 %).

TLC R_f = 0.40 (5 % CH_2Cl_2/MeOH)

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

^{1}H NMR (400 MHz, DMSO d_6) δ / ppm = 15.16 (br. s., 1 H, C(=O)OH), 8.65 (s, 1 H, *ortho* to C(=O)OH), 8.21 (d, J = 8.5 Hz, 1 H, NH), 7.89 (d, J = 13.1 Hz, 1 H, *ortho* to F), 7.85 (s, 1 H, CH=CCH_2), 7.57 (d, J = 7.4 Hz, 1 H, *meta* to F), 5.74 (s, 1 H, OCH_2O), 4.58 (ddd, J = 12.6, 8.1, 7.2 Hz, 1 H, CHNH), 4.30 (t, J = 6.9 Hz, 2 H, $C(=O)CH_2CH_2CH_2N$), 3.80 (tt, J = 6.9, 3.6 Hz, 1 H, $NCH(CH_2)_2$), 3.62 (br t, J = 5.2, 5.2 Hz, 4 H, $C(=O)N(CH_2)CH_2$), 3.38 (td, J = 11.4, 5.5 Hz, 1 H, SCHH), 3.34 (br. s, 4 H, $C(=O)N(CH_2CH_2)CH_2CH_2$), 3.27 (ddd, J = 11.0, 6.9, 1.6 Hz, 1 H, SCHH), 2.64 (t, J = 7.6 Hz, 2 H, $CH=CCH_2$), 2.44 (t, J = 7.5 Hz, 2 H, $CH_2C(=O)O$), 2.40 (dddd, J = 12.3, 6.8, 5.4, 1.4 Hz, 1 H, SCH_2CHH), 2.12 (t, J = 7.8 Hz, 1 H, NHC(=O)CHH), 2.12 (t, J = 6.8 Hz, 1 H, NHC(=O)CHH), 1.98 - 2.07 (m, 3 H, SCH_2CHH and $NHC(=O)CH_2CH_2$), 1.86 (quin, J = 7.5 Hz, 2 H, $CH=CCH_2CH_2$), 1.29 - 1.36 (m, 2 H, $NCH(CHH)_2$), 1.14 - 1.21 (m, 2 H, $NCH(CHH)_2$)

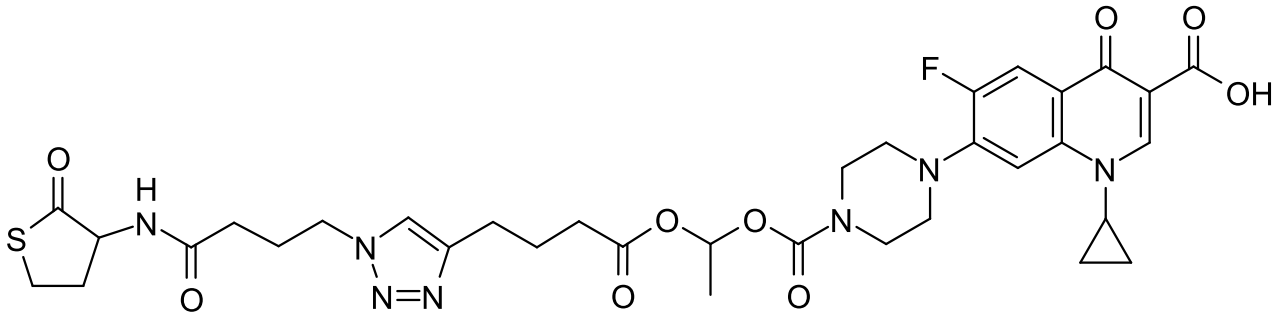
^{13}C NMR (101 MHz, DMSO d_6) δ / ppm = 205.5 (SC(=O)), 176.4 (C(=O)CC(=O)OH), 171.8 ($C(=O)OCH_2O$), 171.3 ($NHC(=O)$), 165.9 (C(=O)OH), 152.8 (d, J = 249.7 Hz, *ipso* to F), 152.9 ($OC(=O)N$), 148.1 (CH=CC(=O)OH), 146.0 ($CH=CCH_2$), 144.9 (d, J = 9.6 Hz, *ipso* to piperazine), 139.1 (*para* to F), 122.0 ($CH=CCH_2$), 118.9 (d, J = 7.5 Hz, *para* to piperazine), 111.0 (d, J = 23.5 Hz, *ortho* to C=O and *ortho* to F), 106.8 (CC(=O)OH, and *meta* to C=O and *meta* to F), 80.3 (OCH_2O), 58.2 (CHNH), 49.1 ($C(=O)N(CH_2CH_2)CH_2CH_2$), 49.1 ($C(=O)N(CH_2CH_2)CH_2CH_2$), 48.6 ($C(=O)CH_2CH_2CH_2N$), 43.4 ($N(CH_2)CH_2$), 43.0 ($N(CH_2)CH_2$), 35.9 ($NCH(CH_2)_2$), 32.7 ($CH=CCH_2CH_2CH_2C(=O)$), 31.8 ($NHC(=O)CH_2$), 30.1 (SCH_2CH_2), 26.8 (SCH_2), 25.8 ($C(=O)CH_2CH_2CH_2N$), 24.2 ($CH=CCH_2CH_2CH_2C(=O)$), 24.0 ($CH=CCH_2CH_2CH_2C(=O)$), 7.6 ($NCH(CH_2)_2$)

^{19}F NMR (376.45 MHz, DMSO d_6) δ / ppm = ?? no F

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

The compound has not been reported previously.

1.36 1-Cyclopropyl-6-fluoro-4-oxo-7-(4-((1-((4-(1-(4-oxo-4-((2-oxotetrahydrothiophen-3-yl)amino)butyl)-1H-1,2,3-triazol-4-yl)butanoyl)oxy)ethoxy)carbonyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid 140



Method?? white amorphous solid 1.2 mg, 1.6 μmol

TLC R_f = 0.33 (10 % MeOH/CH_2Cl_2)

IR (neat) ν_{max} / cm^{-1} = ??

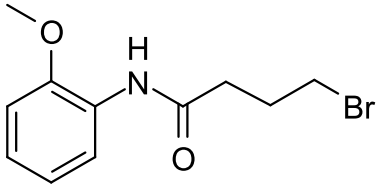
^{1}**H NMR** (400 MHz, MeOD) δ / ppm = ??

^{13}**C NMR** (101 MHz, MeOD) δ / ppm = ??

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

HRMS (ESI$^+$) m/z / Da = 742.2670, $[M+H]^+$ found, $[C_{34}H_{41}FN_7O_9S]^+$ requires 742.2671

1.37 4-Bromo-*N*-(2-methoxyphenyl)butanamide 141



2-Methoxyaniline **179** (9.12 ml, 10.0 g, 81.2 mmol, 1 eq.) and $NaHCO_3$ (8.19 g, 97.4 mmol, 1.2 eq.) were dissolved in water (100 ml) and CH_2Cl_2 (100 ml). The mixture was cooled to 0 °C and 4-bromobutyryl chloride **42** (9.40 ml, 15.1 g, 81.2 mmol, 1 eq.) was added dropwise over 15 min. The mixture was stirred at 0 °C for 1.5 h, then the aqueous layer was removed. The organic layer was dried with $MgSO_4$ and evaporated under reduced pressure. **141** 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)

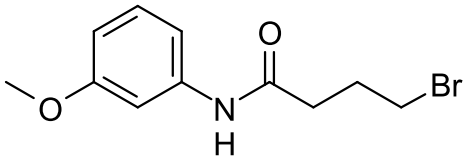
^{1}H NMR (400 MHz, $CDCl_3$ d_1) δ / ppm = 8.32 (dd, J = 8.0, 1.7 Hz, 1 H, *ortho* to NH), 7.85 (br s, 1 H, NH), 7.02 (td, J = 7.9, 1.7 Hz, 1 H, *para* to NH), 6.93 (td, J = 7.7, 1.4 Hz, 1 H, *para* to OCH_3), 6.85 (dd, J = 8.1, 1.5 Hz, 1 H, *ortho* to OCH_3), 3.85 (s, 3 H, CH_3), 3.50 (t, J = 6.4 Hz, 2 H, CH_2Br), 2.56 (t, J = 7.1 Hz, 2 H, C(=O)CH_2), 2.25 (quin, J = 6.7 Hz, 2 H, C(=O)CH_2CH_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.

1.38 4-Bromo-*N*-(3-methoxyphenyl)butanamide 142



3-Methoxyaniline **180** (3.04 ml, 3.33 g, 27.1 mmol, 1 eq.) and $NaHCO_3$ (2.73 g, 32.5 mmol, 1.2 eq.) were dissolved in water (30 ml) and CH_2Cl_2 (30 ml). The mixture was cooled to 0 °C and 4-bromobutyryl chloride **42** (3.13 ml, 5.03 g, 27.1 mmol, 1 eq.) was added dropwise over 5 min. The mixture was stirred at 0 °C for 1 h, then the aqueous layer was removed. The organic layer was dry-loaded onto SiO_2 and purified by column chromatography using a Combiflash (SiO_2, 0-100 % EtOAc/P.E.). **142** was obtained as a pale pink amorphous solid (3.66 g, 13.5 mmol, 49.6 %).

how to report?

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

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

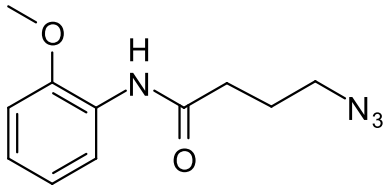
^{1}H NMR (400 MHz, $CDCl_3$ d_1) δ / ppm = 8.45 (s, 1 H, NH), 7.27 (t, J = 2.2 Hz, 1 H, *ortho* to OCH_3 and *ortho* to NH), 7.14 (t, J = 8.1 Hz, 1 H, *meta* to OCH_3 and *meta* to NH), 7.02 (d, J = 8.3 Hz, 1 H, *para* to OCH_3), 6.62 (dd, J = 8.2, 2.1 Hz, 1 H, *para* to NH), 3.71 (s, 3 H, CH_3), 3.42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

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

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

The compound has not been reported previously.

1.39 4-Azido-*N*-(2-methoxyphenyl)butanamide 143



4-Bromo-*N*-(2-methoxyphenyl)butanamide **141** (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.). **143** was obtained as an initially colourless liquid which slowly turned blue then black if left out on the bench (0.469 g, 2.00 mmol, 26.7 %).

how to report?

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

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

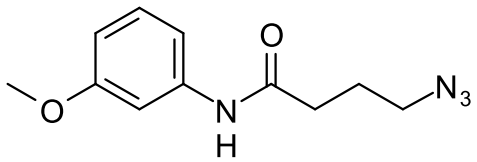
^{1}H NMR (400 MHz, $CDCl_3$ d_1) δ / ppm = 8.32 (dd, J = 7.9, 1.0 Hz, 1 H, *ortho* to NH), 7.86 (br s, 1 H, N$\underline{H}$), 7.00 (td, J = 7.5, 1.5 Hz, 1 H, *para* to NH), 6.90 (td, J = 7.7, 1.1 Hz, 1 H, *para* to OCH_3), 6.83 (dd, J = 8.1, 1.4 Hz, 1 H, *ortho* to OCH_3), 3.81 (s, 3 H, C$\underline{H}_3$), 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 (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.[11]

1.40 4-Azido-*N*-(3-methoxyphenyl)butanamide 144



4-Bromo-*N*-(3-methoxyphenyl)butanamide **142** (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.). **144** was obtained as an straw-coloured liquid (0.294 g, 1.25 mmol, 16.7 %).

how to report?

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

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

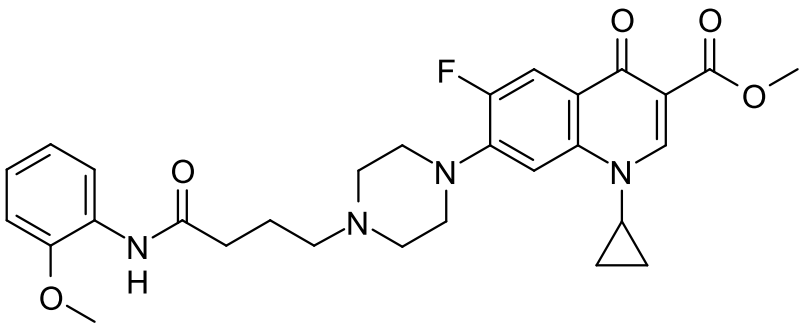
^{1}H NMR (400 MHz, MeOD) δ / ppm = 8.63 (br s, 1 H, N<u>H</u>), 7.26 (t, J = 2.3 Hz, 1 H, *ortho* to OCH_3 and *ortho* to NH), 7.15 (t, J = 8.1 Hz, 1 H, *meta* to OCH_3 and *meta* to NH), 7.01 (dd, J = 7.8, 1.6 Hz, 1 H, *para* to OCH_3), 6.63 (dd, J = 8.2, 1.9 Hz, 1 H, *para* to NH), 3.69 (s, 3 H, C<u>H</u>$_3$), 3.28 (t, J = 6.7 Hz, 2 H, C<u>H</u>$_2$$N_3$), 2.39 (t, J = 7.4 Hz, 2 H, C(=O)C<u>H</u>$_2$), 1.91 (quin, J = 7.0 Hz, 2 H, C(=O)CH_2C<u>H</u>$_2$)

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

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

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 145



Methyl 1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate **134** (500 mg, 1.45 mmol, 1 eq.), 4-bromo-*N*-(2-methoxyphenyl)butanamide **141** (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). **145** was obtained as a bright pink glass (79.7 mg, 0.149 mmol, 10.2 %).

how to report?

TLC R_f = 0.40 (10 % MeOH/CH_2Cl_2)

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

^{1}H NMR (400 MHz, $CDCl_3$ d_1) δ / ppm = 8.48 (s, 1 H, *ortho* to C(=O)OCH_3), 8.36 (d, J = 7.9 Hz, 1 H, *ortho* to NH), 7.87 - 7.99 (m, 2 H, *ortho* to F and N<u>H</u>), 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)OC<u>H</u>$_3$), 3.85 (s, 3 H, aromatic OC<u>H</u>$_3$), 3.41 (tt, J = 6.9, 4.0 Hz, 1 H, NC<u>H</u>$(CH_2)_2$), 3.25 (br t, J = 5.0, 5.0 Hz, 4 H, C(=O)$CH_2CH_2CH_2N(CH_2$C<u>H</u>$_2)CH_2$C<u>H</u>$_2$), 2.67 (br t, J = 5.0, 5.0 Hz, 4 H, C(=O)$CH_2CH_2CH_2N(CH_2$<u>H</u>$_2)$C<u>H</u>$_2$), 2.53 (t, J = 7.0 Hz, 2 H, C(=O)$CH_2CH_2CH_2$<u>H</u>$_2$N), 2.47 (t, J = 7.1 Hz, 2 H, C(=O)C<u>H</u>$_2CH_2CH_2$N), 1.97 (quin, J = 6.8 Hz, 2 H, C(=O)CH_2C<u>H</u>$_2CH_2$N), 1.25 - 1.33 (m, 2 H, NCH(C<u>H</u>H)$_2$), 1.07 - 1.14 (m, 2 H, NCH(CH<u>H</u>)$_2$)

^{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)OCH_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 ($CH_2CH_2CH_2N$), 34.5 ($NCH(CH_2)_2$), 22.3 ($CH_2CH_2CH_2N$), 8.0 ($NCH(CH_2)_2$)

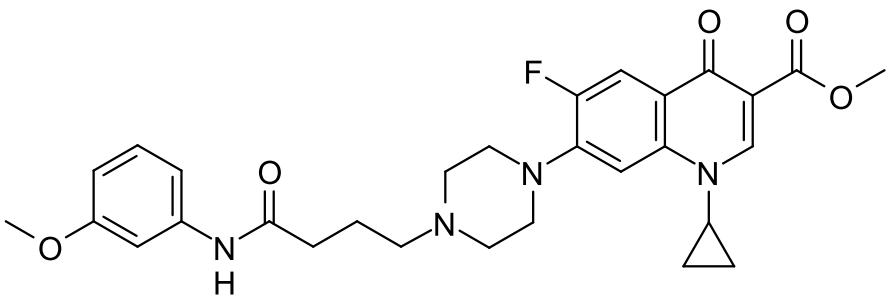
^{19}F NMR (376.45 MHz, $CDCl_3$ d_1) δ / ppm = ??

Check for F

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 Methyl 1-cyclopropyl-6-fluoro-7-(4-(4-((3-methoxyphenyl)amino)-4-oxobutyl)-piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 146



Methyl 1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate **134** (500 mg, 1.45 mmol, 1 eq.), 4-bromo-*N*-(3-methoxyphenyl)butanamide **142** (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). **146** was obtained as an off-white amorphous solid (81.7 mg, 0.152 mmol, 10.5 %).

how to report?

TLC R_f = 0.38 (10 % MeOH/CH_2Cl_2)

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

^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 8.56 (s, 1 H, *ortho* to C(=O)OCH_3), 8.06 (d, J = 13.3 Hz, 1 H, *ortho* to F), 8.02 (br s, 1 H, NH), 7.34 (t, J = 1.7 Hz, 1 H, *ortho* to OCH_3 and *ortho* to NH), 7.25 (d, J = 7.0 Hz, 1 H, *meta* to F), 7.20 (t, J = 8.2 Hz, 1 H, *meta* to OCH_3 and *meta* to NH), 6.98 (dd, J = 7.8, 1.7 Hz, 1 H, *para* to OCH_3), 6.65 (dd, J = 8.2, 2.1 Hz, 1 H, *para* to NH), 3.93 (s, 3 H, C(=O)OCH_3), 3.80 (s, 3 H, aromatic OCH_3), 3.42 (tt, J = 6.8, 3.7 Hz, 1 H, NCH$(CH_2)_2$), 3.31 (br t, J = 4.3, 4.3 Hz, 4 H, C(=O)$CH_2CH_2CH_2N(CH_2CH_2)CH_2CH_2$), 2.73 (br t, J = 4.5, 4.5 Hz, 4 H, C(=O)$CH_2CH_2CH_2N(CH_2)CH_2$),

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$\underline{H}$)$_2$)

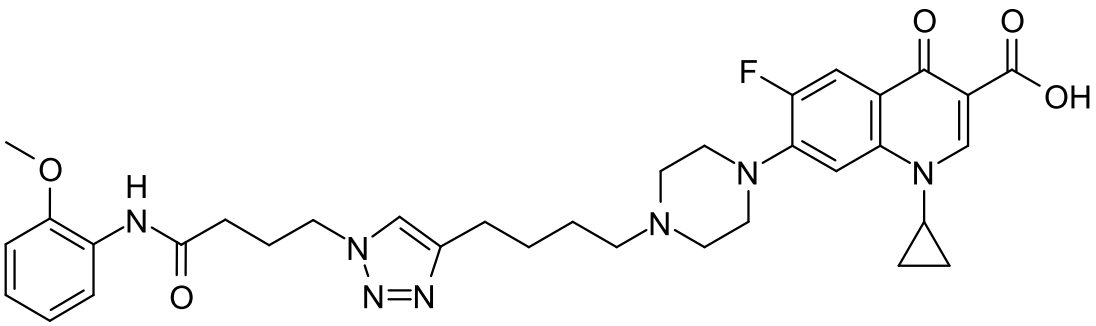
^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 173.1 ($\underline{C}$(=O)CC(=O)OCH_3), 170.9 (NH$\underline{C}$(=O)), 166.3 ($\underline{C}$(=O)OCH_3), 160.1 (*ipso* to OCH_3), 153.3 (d, J=250.1 Hz, *ipso* to F), 148.4 ($\underline{C}$=CC(=O)OCH_3), 144.1 (d, J=10.1 Hz, *ipso* to piperazine), 139.4 (*ipso* 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 ($CH_2CH_2CH_2N(\underline{C}H_2)\underline{C}H_2$), 52.1 (C(=O)O$\underline{C}H_3$), 49.2 ($CH_2CH_2CH_2N(CH_2\underline{C}H_2)CH_2\underline{C}H_2$), 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.

1.43 1-Cyclopropyl-6-fluoro-7-(4-(4-(1-(4-((2-methoxyphenyl)amino)-4-oxobutyl)-1H-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 147



1-Cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **176** (24.1 mg, 58.6 μmol, 1 eq.) and 4-azido-*N*-(2-methoxyphenyl)butanamide **143** (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). **147** was obtained as a clear glass (14.7 mg, 22.8 μmol, 39.0 %).

how to phrase this?

how to report??

TLC R_f = 0.28 (10 % MeOH/CH_2Cl_2)

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

^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 15.05 (br s, 1 H, C(=O)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$\underline{H}$)$_2$)

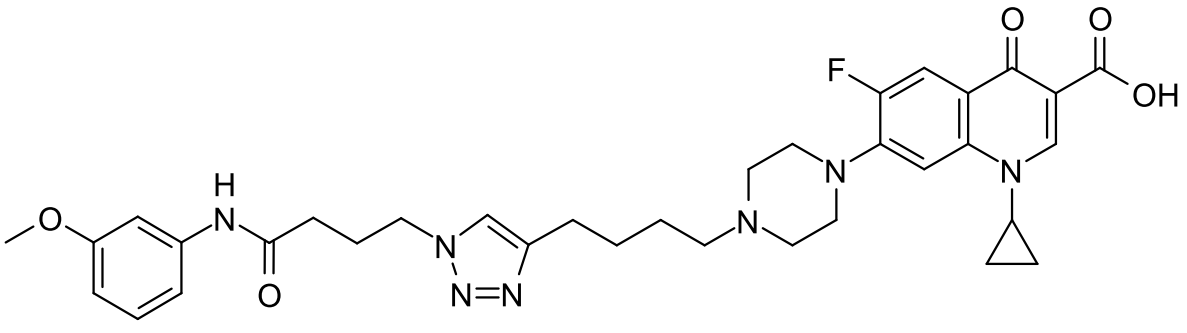
^{13}**C NMR** (101 MHz, $CDCl_3$) δ / ppm = 177.1 ($\underline{C}$(=O)CC(=O)OH), 169.5 (NH$\underline{C}$(=O)), 167.0 ($\underline{C}$(=O)OH), 153.7 (d, J = 251.4 Hz, *ipso* to F), 148.1 (CH=$\underline{C}$CH$_2$), 147.8 (*ipso* to OCH$_3$), 147.3 ($\underline{C}$=CC(=O)OH), 145.9 (d, J = 10.4 Hz, *ipso* 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 ($\underline{C}$C(=O)OH), 104.7 (*meta* to C=O and *meta* to F), 58.1 (CH=CCH$_2$CH$_2$CH$_2$$\underline{C}H_2$N), 55.6 ($\underline{C}H_3$), 52.8 (CH=CCH$_2CH_2CH_2CH_2$N($\underline{C}H_2$)$\underline{C}H_2$), 49.8 (CH=CCH$_2CH_2CH_2CH_2$N(CH$_2$$\underline{C}H_2$)CH$_2CH_2$), 49.8 (CH=CCH$_2CH_2CH_2CH_2$N(CH$_2CH_2$)CH$_2$$\underline{C}H_2$), 49.1 (C(=O)CH$_2CH_2$$\underline{C}H_2$N), 35.2 (N$\underline{C}$H(CH$_2$)$_2$), 33.8 (C(=O)$\underline{C}H_2CH_2CH_2$N), 27.3 (CH=CCH$_2$$\underline{C}H_2CH_2CH_2$N), 26.4 (CH=CCH$_2CH_2$$\underline{C}H_2CH_2$N), 26.0 (C(=O)CH$_2$$\underline{C}H_2CH_2$N), 25.5 (CH=C$\underline{C}H_2CH_2CH_2CH_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 1-Cyclopropyl-6-fluoro-7-(4-(4-(1-(4-((3-methoxyphenyl)amino)-4-oxobutyl)-1H-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 **176** (24.1 mg, 58.6 μmol, 1 eq.) and 4-azido-*N*-(3-methoxyphenyl)butanamide **144** (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). **148** was obtained as a clear glass (1.9 mg, 2.9 μmol, 5.0 %).

TLC R_f = 0.22 (10 % MeOH/CH_2Cl_2)

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

^{1}H NMR (400 MHz, DMSO d_6) δ / ppm = 15.23 (br s, 1 H, C(=O)O<u>H</u>), 9.89 (s, 1 H, N<u>H</u>), 8.66 (s, 1 H, *ortho* to C(=O)OH), 7.90 (d, J = 13.4 Hz, 1 H, *ortho* to F), 7.88 (s, 1 H, C<u>H</u>=CCH_2), 7.55 (d, J = 7.6 Hz, 1 H, *meta* to F), 7.27 (t, J = 2.1 Hz, 1 H, *ortho* to C=O and *ortho* to F), 7.16 (t, J = 8.1 Hz, 1 H, *meta* to OCH_3 and *meta* to NH), 7.08 (d, J = 7.8 Hz, 1 H, *para* to OCH_3), 6.59 (ddd, J = 8.1, 2.4, 0.7 Hz, 1 H, *para* to NH), 4.36 (t, J = 6.9 Hz, 2 H, C(=O)CH_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>)$_2$)

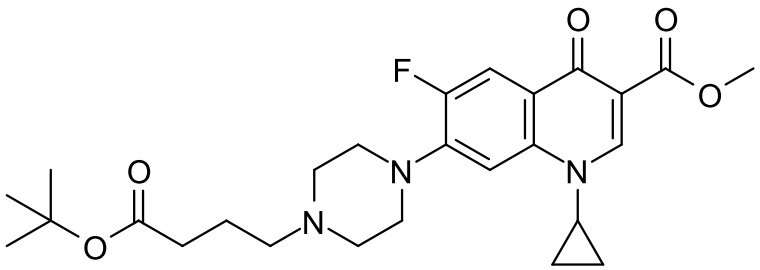
^{13}C NMR (101 MHz, DMSO d_6) δ / ppm = 176.3 (<u>C</u>(=O)CC(=O)OH), 170.1 (NH<u>C</u>(=O)), 165.9 (<u>C</u>(=O)OH), 159.4 (*ipso* to OCH_3), 153.0 (d, J = 248.6 Hz, *ipso* to F), 148.0 (CH=<u>C</u>CH_2), 146.9 (<u>C</u>=CC(=O)OH), 145.2 (d, J = 10.7 Hz, *ipso* to piperazine), 140.3 (*para* to F), 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.

1.45 Methyl 7-(4-(4-(*tert*-butoxy)-4-oxobutyl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate 149



Methyl 1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate **134** (200 mg, 0.579 mmol, 1 eq.), *tert*-butyl 4-bromobutanoate **181** (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 **181** (103 μl, 130 mg, 0.581 mmol, 1 eq.) was added, and the mixture was stirred in a microwave reactor at 100 °C for a further 8 h. The mixture was then dry-loaded onto SiO_2 and purified by column chromatography (SiO_2, 0-4 % MeOH/CH_2Cl_2). **149** was obtained as a white amorphous solid (141 mg, 0.289 mmol, 49.9 %).

how to report?

how to report?

TLC R_f = 0.12 (4 % MeOH/CH_2Cl_2)

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

^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 8.39 (s, 1 H, *ortho* to C(=O)OCH_3), 7.82 (d, J = 13.3 Hz, 1 H, *ortho* to F), 7.17 (d, J = 7.2 Hz, 1 H, *meta* to F), 3.83 (s, 3 H, C$\underline{H}_3$), 3.40 (tt, J = 7.2, 3.6 Hz, 1 H, NC$\underline{H}$(CH_2)$_2$), 3.22 (t, J = 4.3 Hz, 4 H, $CH_2N(CH_2C\underline{H}_2)CH_2C\underline{H}_2$), 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$\underline{H}_2$N(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$\underline{H}$)$_2$)

should be ranges ideally, go back if time

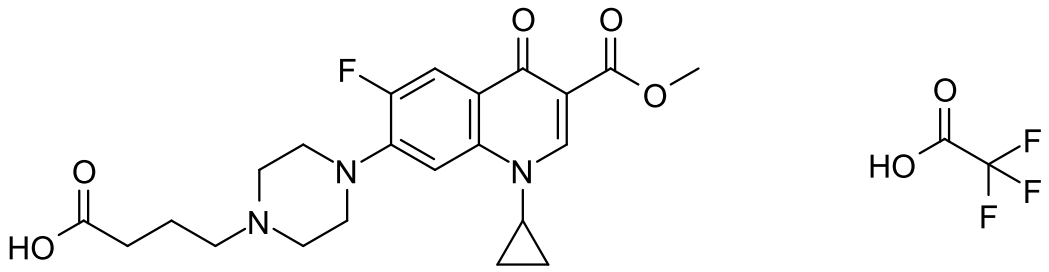
^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 172.7 (C(=O)CC(=O)OCH_3), 172.6 (C(=O)OC(CH_3)$_3$), 165.9 (C(=O)OCH_3), 153.1 (d, J = 249.7 Hz, *ipso* to F), 148.1 (C=CC(=O)OCH_3), 144.3 (d, J = 10.4 Hz, *ipso* to piperazine), 137.7 (*para* to F), 122.5 (d, J = 6.9 Hz, *para* to piperazine) 112.6 (d, J = 22.5 Hz, *ortho* to C=O and *ortho* to F), 109.5 (CC(=O)OCH_3) 104.7 (*meta* to C=O and *meta* to F), 80.0 (C(CH_3)$_3$), 57.4 ($C(=O)CH_2CH_2CH_2N$), 52.7 ($C(=O)CH_2CH_2CH_2N(CH_2)CH_2$), 51.7 ($CH_3$), 49.7 ($C(=O)CH_2CH_2CH_2N(CH_2CH_2)CH_2CH_2$), 49.7 ($C(=O)CH_2CH_2CH_2N(CH_2CH_2)CH_2CH_2$), 34.4 (NCH($CH_2$)$_2$), 33.2 ($C(=O)CH_2$), 28.0 (C($CH_3$)$_3$), 22.0 ($C(=O)CH_2CH_2$), 7.9 (NCH($CH_2$)$_2$)

^{19}F NMR (376.45 MHz, $CDCl_3$) δ / ppm = -123.50 (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.

1.46 4-(4-(1-Cyclopropyl-6-fluoro-3-(methoxycarbonyl)-4-oxo-1,4-dihydroquinolin-7-yl)piperazin-1-yl)butanoic acid, trifluoroacetic acid salt 150



Methyl 7-(4-(4-(*tert*-butoxy)-4-oxobutyl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate **149** (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. **150** was obtained as a white solid (21.4 mg, 39.2 μmol, 95.6 %).

not sure how to draw/nam this?

mp T / °C = 225-231 (CH_2Cl_2, decomposes)

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

^{1}H NMR (400 MHz, DMSO d_6) δ / ppm = 8.47 (s, 1 H, *ortho* to C(=O)OH), 7.80 (d, J = 13.2 Hz, 1 H, *ortho* to F), 7.47 (d, J = 7.4 Hz, 1 H, *meta* to F), 3.73 (s, 3 H, $C\underline{H}_3$), 3.66 (tt, J = 7.2, 3.7 Hz, 1 H, $NC\underline{H}(CH_2)_2$), 3.30 - 3.54 (br s, 8 H, $CH_2N(C\underline{H}_2)C\underline{H}_2$ and $CH_2N(CH_2C\underline{H}_2)CH_2C\underline{H}_2$) 3.13 - 3.22 (m, 2 H, $C\underline{H}_2N(CH_2)CH_2$), 2.36 (t, J = 7.1 Hz, 2 H, $C\underline{H}_2CH_2CH_2N(CH_2)CH_2$), 1.87 - 1.98 (m, 2 H, $C\underline{H}_2CH_2N(CH_2)CH_2$), 1.22 - 1.30 (m, 2 H, $NCH(C\underline{H}H)_2$), 1.06 - 1.15 (m, 2 H, $NCH(CH\underline{H})_2$)

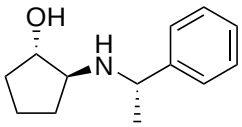
^{13}C NMR (101 MHz, DMSO d_6) δ / ppm = 173.5 ($CH_2\underline{C}(=O)OH$), 171.6 ($\underline{C}(=O)CC(=O)OCH_3$), 164.9 ($\underline{C}(=O)OCH_3$), 158.2 (q, J = 31.5 Hz, $CF_3\underline{C}(=O)OH$), 152.5 (d, J = 247.6 Hz, *ipso* to F), 148.5 ($\underline{C}=CC(=O)OH$), 142.3 (d, J = 10.7 Hz, *ipso*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

^{19}F NMR (376.45 MHz, DMSO d_6) δ / ppm = -73.62 (s, $C\underline{F}_3$), -124.61 (s, ciprofloxacin $\underline{F}$)

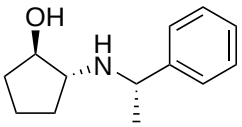
HRMS (ESI^+) m/z / Da = 432.1921, $[M+H]^+$ found, $[C_{22}H_{27}FN_3O_5]^+$ requires 432.1935

The compound has not been reported previously.

1.47 (1*S*,2*S*)-2-(((*S*)-1-Phenylethyl)amino)cyclopentan-1-ol 151 and (1*R*,2*R*)-2-(((*S*)-1-phenylethyl)amino)cyclopentan-1-ol 152



160



161

(*S*)-1-phenylethan-1-amine **182** (7.85 ml, 7.38 g, 60.9 mmol, 1 eq.) was dissolved in CH_2Cl_2 (50 ml) and stirred rapidly at 0 °C. A solution of $AlMe_3$ (31 ml, 2.0 M in heptane, 60.9 mmol) was added dropwise and the solution was stirred at 0 °C for 1 h. A solution of cyclohexene oxide **183** (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). **151** was obtained as a pale yellow oil (4.08 g, 19.9 mmol, 32.6 %). **152** was obtained as pale yellow crystals (4.48 g, 21.8 mmol, 35.8 %).

fix image sizes

(1*S*,2*S*)-2-(((*S*)-1-Phenylethyl)amino)cyclopentan-1-ol 151

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

fix spacings for subtitles

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

^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 7.28 - 7.38 (m, 4 H, *ortho* and *meta* to $CHCH_3$), 7.21 - 7.28 (m, 1 H, *para* to $CHCH_3$), 3.83 (q, J = 6.6 Hz, 1 H, C<u>H</u>CH_3), 3.78 (q, J = 7.0 Hz, 1 H, C<u>H</u>OH), 2.62 (dt, J = 8.2, 7.2 Hz, 1 H, C<u>H</u>NH), 1.97 (quin, J = 6.7 Hz, 1 H, C<u>H</u>$_2$CHNH), 1.90 (quin, J = 6.9 Hz, 1 H, C<u>H</u>$_2$CHOH), 1.56 - 1.68 (m, C<u>H</u>$_2$CH$_2$CHOH), 1.43 (dq, J = 12.5, 8.0 Hz, 1 H, C<u>H</u>$_2$CHOH), 1.37 (d, J = 6.6 Hz, 3 H, C<u>H</u>$_3$), 1.25 - 1.36 (m, 1 H, C<u>H</u>$_2$CHNH)

^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 144.75 (*ipso* to $CHCH_3$), 128.26 (*meta* to $CHCH_3$), 126.72 (*para* to $CHCH_3$), 126.30 (*ortho* to $CHCH_3$), 77.65 (<u>C</u>HOH), 63.38 (<u>C</u>HNH), 56.20 (<u>C</u>HCH_3), 31.74 (<u>C</u>H_2CHOH), 29.22 (<u>C</u>H_2CHNH), 24.58 (<u>C</u>H_3), 19.57 (<u>C</u>H_2CH_2CHOH)

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

(1*R*,2*R*)-2-(((*S*)-1-Phenylethyl)amino)cyclopentan-1-ol 152

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

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

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

^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 7.28 - 7.34 (m, 4 H, *ortho* and *meta* to $CHCH_3$), 7.20 - 7.26 (m, 1 H, *para* to $CHCH_3$), 3.86 (q, J = 6.6 Hz, 1 H, C<u>H</u>CH_3), 3.85 (q, J = 6.6 Hz, 1 H, C<u>H</u>OH), 2.83 (td, J = 7.6, 5.7 Hz, 1 H, C<u>H</u>NH), 1.85 - 1.97 (m, 1 H, C<u>H</u>HCHOH), 1.77 (dtd, J = 12.9, 7.9, 7.9, 4.9 Hz, 1 H, C<u>H</u>HCHNH), 1.55 - 1.68 (m, 2 H, C<u>H</u>$_2$$CH_2$CHOH), 1.47 - 1.55 (m, 1 H, CH<u>H</u>CHOH), 1.36 (d, J = 6.6 Hz, 3 H, C<u>H</u>$_3$), 1.12 (dq, J = 12.7, 8.1 Hz, 1 H, CH<u>H</u>CHNH)

^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 145.61 (*ipso* to $CHCH_3$), 128.08 (*meta* to $CHCH_3$), 126.61 (*para* to $CHCH_3$), 126.33 (*ortho* to $CHCH_3$), 77.43 (<u>C</u>HOH), 64.45 (<u>C</u>HNH), 56.62 (<u>C</u>HCH_3), 32.01 (<u>C</u>H_2CHOH), 30.56 (<u>C</u>H_2CHNH), 23.30 (<u>C</u>H_3), 20.06 (<u>C</u>H_2CH_2CHOH)

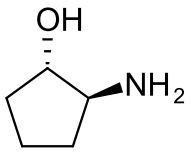
HRMS (ESI$^+$) m/z / Da = 206.1553, $[M+H]^+$ found, $[C_{13}H_{20}NO]^+$ requires 206.1545

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

The compounds have been synthesised previously,[12–14] but NMR data were not published.

consistenc with other data?

1.48 (1*S*,2*S*)-2-Aminocyclopentan-1-ol 153



(1*S*,2*S*)-2-(((*S*)-1-Phenylethyl)amino)cyclopentan-1-ol **151** (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. **153** was obtained as a yellow oil (1.92 g, 19.0 mmol, 100 %).

TLC R_f = 0.10 (10 % MeOH/CH_2Cl_2)

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

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

^{13}C NMR (101 MHz, MeOD) δ / ppm = 80.7 (<u>C</u>HOH), 60.8 (<u>C</u>HNH_2), 33.2 (<u>C</u>H_2CHOH), 32.1 (<u>C</u>H_2CHNH_2), 21.2 (<u>C</u>H_2CH_2CHOH)

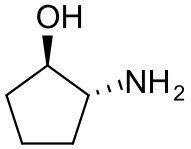
HRMS (ESI$^+$) m/z / Da = 102.0917, $[M+H]^+$ found, $[C_5H_{12}NO]^+$ requires 102.0913

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

The data are consistent with the literature.[13,15]

check

1.49 (1*R*,2*R*)-2-Aminocyclopentan-1-ol 154



(1*R*,2*R*)-2-(((*S*)-1-Phenylethyl)amino)cyclopentan-1-ol **152** (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. **154** 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$\underline{H}$OH), 3.00 (td, J = 7.4, 5.6 Hz, 1 H, C$\underline{H}NH_2$), 2.00 (dtd, J = 13.0, 7.7, 7.7, 5.6 Hz, 1 H, C$\underline{H}$HCHNH$_2$), 1.97 (ddt, J = 13.0, 8.7, 6.4, 6.4 Hz, 1 H, C$\underline{H}$HCHOH), 1.64 - 1.77 (m, 2 H, C$\underline{H}_2CH_2$CHOH), 1.53 (ddt, J = 13.0, 9.5, 6.2, 6.2 Hz, 1 H, CH$\underline{H}$CHOH), 1.37 (ddt, J = 12.8, 8.5, 7.7, 7.7 Hz, 1 H, CH$\underline{H}$CHNH$_2$)

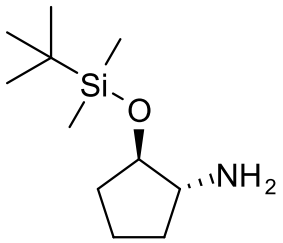
^{13}C NMR (101 MHz, MeOD) δ / ppm = 80.6 ($\underline{C}$HOH), 60.7 ($\underline{C}HNH_2$), 33.2 ($\underline{C}H_2$CHOH), 32.2 ($\underline{C}H_2$CHNH$_2$), 21.2 ($\underline{C}H_2CH_2$CHOH)

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

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

The data are consistent with the literature.[13,15]

1.50 (1*R*,2*R*)-2-((*tert*-butyldimethylsilyl)oxy)cyclopentan-1-amine 155



(1*R*,2*R*)-2-aminocyclopentan-1-ol **154** (0.480 g, 4.75 mmol) was stirred in dry CH_2Cl_2 (20 ml) under N_2 at 0 °C. TEA (3.14 ml, 2.28 g, 22.5 mmol, 5 eq.) was added dropwise, followed by TBSOTf (3 ml, 3.45 g, 13.1 mmol, 3 eq.) dropwise. The reaction was allowed to reach r.t. and stirred for 1 h. The reaction was quenched with NH_4Cl, diluted with CH_2Cl_2 (20 ml) and washed with water (20 ml). The organic phase was dried with Na_2SO_4, concentrated under reduced pressure and purified by column chromatography (SiO_2, 4 % $MeOH/CH_2Cl_2$). **184**(RR) was obtained as a yellow oil (1.00 g, 4.64 mmol, 97.7 %).

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

check stains for others

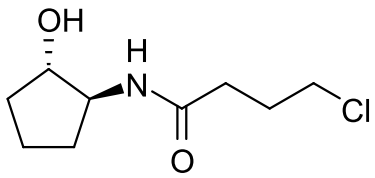
^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 4.13 (q, J = 5.8 Hz, 1 H, C<u>H</u>OSi), 3.31 (td, J = 7.1, 5.2 Hz, 1 H, C<u>H</u>NH_2), 2.09 - 2.19 (m, 1 H, C<u>H</u>HCHNH_2), 1.97 (ddq, J = 8.8, 7.0, 6.0, 6.0, 6.0 Hz, 1 H, C<u>H</u>HCHOSi), 1.74 - 1.86 (m, 2 H, C<u>H</u>$_2$$CH_2$CHOSi), 1.64 - 1.74 (m, 1 H, CH<u>H</u>CHOSi), 1.58 (ddt, J = 13.2, 9.1, 6.0, 6.0 Hz, 1 H, CH<u>H</u>CHNH_2), 0.88 (s, 9 H, C(C<u>H</u>$_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 = 76.29 (<u>C</u>HOSi), 59.69 (<u>C</u>HNH), 32.18 (<u>C</u>H$_2$CHOSi), 26.78 (<u>C</u>H$_2$CHNH_2), 25.62 (C(<u>C</u>H$_3$)$_3$), 19.73 (<u>C</u>H$_2$CH$_2$CHOSi), 17.74 (<u>C</u>(CH$_3$)$_3$), -4.82 (Si<u>C</u>H$_3$), -5.23 (Si<u>C</u>H$_3$)

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

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

1.51 4-Chloro-*N*-((1*S*,2*S*)-2-hydroxycyclopentyl)butanamide 156



(1*S*,2*S*)-2-aminocyclopentan-1-ol **153** (500 mg, 4.94 mmol, 1 eq.), TEA (827 μl, 600 mg, 5.93 mmol, 1.2 eq.) and CH_2Cl_2 (20 ml) were stirred at 0°C. 4-Chlorobutyryl chloride **185**(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). **186**(SS) was obtained as a white amorphous solid (651 mg, 3.16 mmol, 64.1 %).

TLC R_f = 0.35 (EtOAc, ninhydrin stain)

check stains for others

mp T / °C = ?? (??)

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

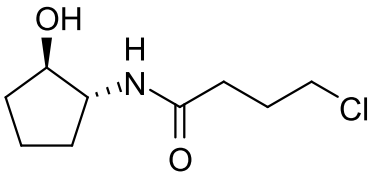
^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 6.12 (br s, 1 H, N<u>H</u>), 4.42 (br s, 1 H, O<u>H</u>), 3.94 (q, J = 6.6 Hz, 1 H, C<u>H</u>OH), 3.82 (tt, J = 8.4, 5.3 Hz, 1 H, C<u>H</u>NH), 3.60 (t, J = 6.2 Hz, 2 H, C<u>H</u>$_2$Cl), 2.38 (t, J = 7.2 Hz, 2 H, C<u>H</u>$_2$C=O), 2.05 - 2.16 (m, 3 H, C<u>H</u>HCHNH 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$_2$CHOH), 1.58 - 1.73 (m, 2 H, CH<u>H</u>CH$_2$CHOH 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$_2$Cl), 32.8 (<u>C</u>H$_2$C=O), 32.4 (<u>C</u>H$_2$CHOH), 30.1 (<u>C</u>H$_2$CHNH), 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^{2}g^{-1} = -13.0 (c / g(100 mL)$^{-1}$ = 0.5, MeOH)

1.52 4-Chloro-*N*-((1*R*,2*R*)-2-hydroxycyclopentyl)butanamide 157



(1*R*,2*R*)-2-aminocyclopentan-1-ol **154** (72.3 mg, 716 μmol, 1 eq.), TEA (500 μl, 363 mg, 3.58 mmol, 5 eq.) and CH_2Cl_2 (5 ml) were stirred at 0°C. 4-Chlorobutyryl chloride **185**(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). **157** was obtained as a white amorphous solid (35.6 mg, 173 μmol, 24.2 %).

times with spaces?

TLC R_f = 0.35 (EtOAc)

mp T / °C = ?? (??)

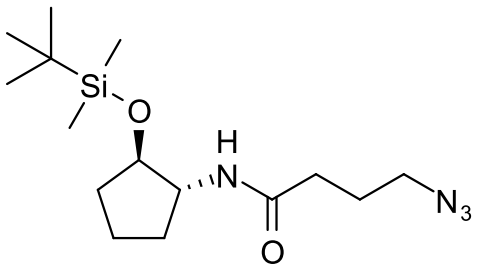
^{1}**H NMR** (400 MHz, $CDCl_3$) δ / ppm = 6.05 (br s, 1 H, NH), 4.55 (br s, 1 H, OH), 3.95 (q, J=6.6 Hz, 1 H, CHOH), 3.82 (tt, J=8.4, 5.3 Hz, 1 H, CHNH), 3.60 (t, J=6.2 Hz, 2 H, CH_2Cl), 2.38 (t, J=7.0 Hz, 2 H, CH_2C=O), 2.05 - 2.17 (m, 3 H, CHHCHNH and CH_2CH_2Cl), 1.94 - 2.05 (m, 1 H, CHHCHOH), 1.74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

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

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

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

1.53 4-Azido-*N*-((1*R*,2*R*)-2-((*tert*-butyldimethylsilyl)oxy)cyclopentyl)butanamide 158



(1*R*,2*R*)-2-((*tert*-butyldimethylsilyl)oxy)cyclopentan-1-amine **155** (50 mg, 0.232 mmol, 1 eq.) and $NaHCO_3$ (22.0 mg, 0.262 mmol, 1.1 eq.) were added to CH_2Cl_2 (3 ml) and water (3 ml). 4-Bromobutyryl chloride (25.3 ml, 40.5 mg, 0.219 mmol, 0.95 eq.) was added dropwise at 0 °C and the mixture was stirred for 3 h. The aqueous layer was removed and NaN_3 (100 mg, 1.54 mmol, 6.6 eq.) and DMF (3 ml) were added. The mixture was stirred 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). **187**(RR) was obtained as a clear liquid (71 mg, 0.217 mmol, 99.2 %).

check brackets inside for all

TLC R_f = 0.84 (1 % MeOH/CH_2Cl_2)

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

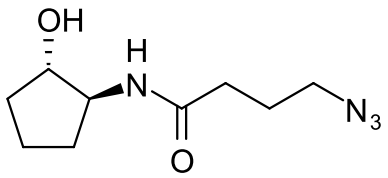
^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 5.35 (d, J = 5.1 Hz, 1 H, NH), 3.97 - 4.01 (m, 1 H, CHOSi), 3.93 - 3.98 (m, 1 H, CHNH), 3.35 (t, J = 6.6 Hz, 2 H, CH_2N_3), 2.24 (t, J = 7.0 Hz, 2 H, CH_2C=O), 2.09 - 2.19 (m, 1 H, CHHCHNH), 1.89 - 1.97 (quin, J = 6.8 Hz, 2 H, $CH_2CH_2N_3$), 1.74 - 1.84 (m, 2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

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

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

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

1.54 4-Azido-*N*-((1*S*,2*S*)-2-hydroxycyclopentyl)butanamide 159



4-Chloro-*N*-((1*S*,2*S*)-2-hydroxycyclopentyl)butanamide **156** (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. **159** was obtained as white needles (181 mg, 0.852 mmol, 87.6 %).

TLC R_f = 0.35 (EtOAc, ninhydrin stain)

check stains for others

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

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

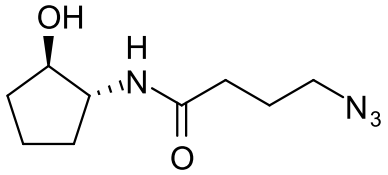
^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 6.72 (d, J = 4.4 Hz, 1 H, NH), 4.82 (br. s., 1 H, OH), 3.88 (q, J = 6.6 Hz, 1 H, CHOH), 3.75 (tdd, J = 8.4, 8.4, 6.6, 4.4 Hz, 1 H, CHNH), 3.28 (t, J = 6.6 Hz, 2 H, CH_2N_3), 2.23 (t, J = 7.3 Hz, 2 H, CH_2C=O), 2.04 (dtd, J = 13.0, 8.0, 8.0, 4.9 Hz, 1 H, CHHCHNH), 1.92 (dtd, J = 13.0, 7.6, 7.6, 5.8 Hz, 1 H, CHHCHOH), 1.84 (quin, J = 7.0 Hz, 2 H, $CH_2CH_2N_3$), 1.59 - 1.77 (m, 2 H, CH_2CH_2CHOH), 1.54 (ddt, J = 12.7, 9.0, 6.7, 6.7 Hz, 1 H, CHHCHOH), 1.39 (dq, J = 12.9, 8.4 Hz, 1 H, CHHCHNH)

^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 173.8 (C=O), 78.8 (CHOH), 59.9 (CHNH), 50.5 (CH_2N_3), 32.5 (CH_2C=O), 32.0 (CH_2CHOH), 29.5 (CH_2CHNH), 24.6 ($CH_2CH_2N_3$), 20.7 (CH_2CH_2CHOH)

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

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

1.55 4-Azido-*N*-((1*R*,2*R*)-2-hydroxycyclopentyl)butanamide 160



4-Chloro-*N*-((1*S*,2*S*)-2-hydroxycyclopentyl)butanamide **156** (35.0 mg, 0.170 mmol, 1 eq.) and NaN_3 (22.1 mg, 0.340 mmol, 2 eq.) were stirred in acetonitrile (2 ml) at 50 °C for 24 h. The reaction mixtures was then partitioned between water (20 ml) and 10 % *i*-PrOH/$CHCl_3$ (5 ml). The aqueous layer was extracted again with 10 % *i*-PrOH/$CHCl_3$ (2 × 5 ml) and the combined organic fractions were dried with $MgSO_4$ and evaporated under reduced pressure. **159** was obtained as a white solid (16.2 mg, 0.0764 mmol, 45.0 %).

TLC R_f = 0.35 (EtOAc)

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

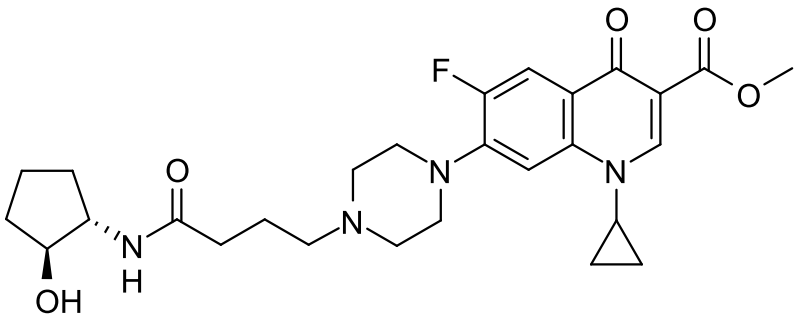
^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 5.82 (br s, 1 H, NH), 4.45 (br. s., 1 H, OH), 3.96 (q, J=6.6 Hz, 1 H, CHOH), 3.83 (tdd, J=8.5, 8.5, 6.0, 4.6 Hz, 1 H, CHNH), 3.37 (t, J=6.4 Hz, 2 H, CH_2N_3), 2.31 (t, J=7.2 Hz, 2 H, CH_2C=O), 2.09 - 2.19 (m, 1 H, CHHCHNH), 1.99 - 2.06 (m, 1 H, CHHCHOH), 1.90 - 1.97 (m, 2 H, $CH_2CH_2N_3$), 1.60 - 1.85 (m, 3 H, $CH_2CHHCHOH$), 1.42 (dq, J=12.8, 8.3 Hz, 1 H, CHHCHNH)

^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 173.8 (C=O), 79.7 (CHOH), 61.0 (CHNH), 50.7 (CH_2N_3), 32.8 (CH_2C=O), 32.6 (CH_2CHOH), 30.5 (CH_2CHNH), 24.7 ($CH_2CH_2N_3$), 21.3 (CH_2CH_2CHOH)

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

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

1.56 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 161



150 (200 mg, 0.367 mmol, 1 eq.), **153** (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 preparatory HPLC (5-60 % acetonitrile/water over 12 min). The combined pure fractions were evaporated under reduced pressure and then partitioned between $NaHCO_3$ (aq., sat., 10 ml) and CH_2Cl_2 (10 ml). The organic layer was removed and the aqueous layer was extracted twice more with CH_2Cl_2 (2 × 10 ml). The combined organic fractions were dried with $MgSO_4$ and evaporated under reduced pressure. **161** 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$\underline{\mathrm{H}}_3$), 7.75 (d, J = 13.5 Hz, 1 H, *ortho* to F), 7.70 (d, J = 7.2 Hz, 1 H, CHN$\underline{\mathrm{H}}$), 7.43 (d, J = 7.5 Hz, 1 H, *meta* to F), 4.74 (d, J = 4.0 Hz, 1 H, CHO$\underline{\mathrm{H}}$), 3.78 - 3.82 (m, 1 H, C$\underline{\mathrm{H}}$OH), 3.74 - 3.78 (m, 1 H, C$\underline{\mathrm{H}}$NH), 3.74 (s, 3 H, C$\underline{\mathrm{H}}_3$), 3.65 (tt, J = 7.2, 3.9 Hz, 1 H, NC$\underline{\mathrm{H}}$(CH$_2$)$_2$), 3.25 (t, J = 4.8 Hz, 4 H, CH$_2$N(CH$_2$C$\underline{\mathrm{H}}_2$)CH$_2$C$\underline{\mathrm{H}}_2$), 2.57 (br s, 4 H, CH$_2$N(C$\underline{\mathrm{H}}_2$)C$\underline{\mathrm{H}}_2$), 2.34 (t, J = 7.4 Hz, 2 H, C$\underline{\mathrm{H}}_2$N(CH$_2$)CH$_2$), 2.11 (t, J = 7.4 Hz, 2 H, C$\underline{\mathrm{H}}_2$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$\underline{\mathrm{H}}$HCHNH), 1.78 (dddd, J = 12.6, 8.9, 6.3, 6.3 Hz, 1 H, C$\underline{\mathrm{H}}$HCHOH), 1.69 (quin, J = 7.3 Hz, 2 H, C$\underline{\mathrm{H}}_2$CH$_2$N(CH$_2$)CH$_2$), 1.54 - 1.65 (m, 2 H, C$\underline{\mathrm{H}}_2$CH$_2$CHOH), 1.42 (ddt, J = 13.1, 8.2, 5.3, 5.3 Hz, 1 H, CH$\underline{\mathrm{H}}$CHOH), 1.32 (dddd, J = 13.4, 8.5, 6.8, 5.8 Hz, 1 H, CH$\underline{\mathrm{H}}$CHNH), 1.21 - 1.29 (m, 2 H, NCH(C$\underline{\mathrm{H}}\mathrm{H}$)$_2$), 1.07 - 1.13 (m, 2 H, NCH(CH$\underline{\mathrm{H}}$)$_2$)

^{13}**C NMR** (101 MHz, DMSO d_6) δ / ppm = 171.9 (CH$_2\underline{\mathrm{C}}$(=O)NH), 171.6 ($\underline{\mathrm{C}}$(=O)CC(=O)OCH$_3$), 165.0 ($\underline{\mathrm{C}}$(=O)OCH$_3$), 152.6 (d, J = 246.5 Hz, *ipso* to F), 148.3 ($\underline{\mathrm{C}}$=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 ($\underline{\mathrm{C}}$C(=O)OCH$_3$), 106.2 (*meta* to C=O and *meta* to F), 76.3 ($\underline{\mathrm{C}}$HOH), 57.6 ($\underline{\mathrm{C}}$HNH), 57.2 (C(=O)CH$_2$CH$_2\underline{\mathrm{C}}$H$_2$N), 52.4 (C(=O)CH$_2$CH$_2$CH$_2$N($\underline{\mathrm{C}}$H$_2$)$\underline{\mathrm{C}}$H$_2$), 51.3 ($\underline{\mathrm{C}}$H$_3$), 49.6 (C(=O)CH$_2$CH$_2$CH$_2$N(CH$_2\underline{\mathrm{C}}$H$_2$)CH$_2\underline{\mathrm{C}}$H$_2$)

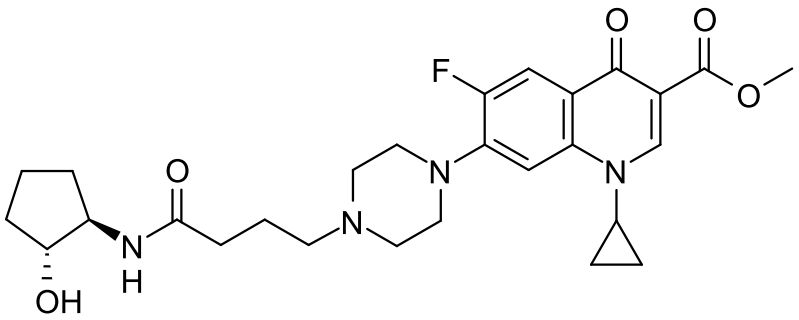
34.8 (N<u>C</u>H(CH_2)$_2$), 33.3 (C(=O)<u>C</u>H_2), 32.2 (<u>C</u>H_2CHOH), 29.5 (<u>C</u>H_2CHNH), 22.5 (C(=O)CH_2<u>C</u>H_2), 20.6 (<u>C</u>H_2CH_2CHOH), 7.6 (NCH(<u>C</u>H_2)$_2$)

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

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

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

1.57 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 162



150 (52.1 mg, 95.5 μmol, 1 eq.), **154** (19.5 mg, 193 μmol, 2 eq.), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (29.7 mg, 155 μmol, 1.6 eq.), 1-hydroxybenzotriazole (25.8 mg, 191 μmol, 2 eq.) and DIPEA (33.3 μl, 24.7 mg, 191 μmol, 2 eq.) were dissolved in DMF (2 ml) and stirred at r.t. for 16 h. The solvent was removed using a stream of N_2 and the residue was purified by preparatory HPLC (5-50 % acetonitrile/water over 15 min). The combined pure fractions were evaporated under reduced pressure and then partitionedbetween $NaHCO_3$ (aq., sat., 5 ml) and CH_2Cl_2 (5 ml). The organic layer was removed and the aqueous layer was extracted twice more with CH_2Cl_2 (2 × 5 ml). The combined organic fractions were dried with $MgSO_4$ and evaporated under reduced pressure. **161** was obtained as a white amorphous solid (4.9 mg, 9.5 μmol, 9.9 %).

not done yet?

TLC R_f = 0.38 (30 % MeOH/CH_2Cl_2)

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

^{1}H NMR (500 MHz, DMSO d_6) δ / ppm = 8.44 (s, 1 H, *ortho* to C(=O)OC<u>H</u>$_3$), 7.75 (d, J=13.5 Hz, 1 H, *ortho* to F), 7.69 (d, J=6.9 Hz, 1 H, CHN<u>H</u>), 7.43 (d, J=7.6 Hz, 1 H, *meta* to F), 4.73 (br s, 1 H, CHO<u>H</u>), 3.77 - 3.81 (m, 1 H, C<u>H</u>OH), 3.74 - 3.77 (m, 1 H, C<u>H</u>NH), 3.73 (s, 3 H, C<u>H</u>$_3$), 3.65 (tt, J=6.9, 4.0 Hz, 1 H, NC<u>H</u>(CH$_2$)$_2$), 3.24 (br. t, J=4.2, 4.2 Hz, 4 H, CH_2N(CH_2C<u>H</u>$_2$)CH_2C<u>H</u>$_2$), 2.55 (br t, J=5.0, 5.0 Hz, 4 H, CH_2N(C<u>H</u>$_2$)C<u>H</u>$_2$), 2.32 (t, J=7.2 Hz, 2 H, C<u>H</u>$_2$N(CH_2)CH_2), 2.10 (t, J=7.4 Hz, 2 H, C<u>H</u>$_2$$CH_2$$CH_2$N($CH_2$)$CH_2$), 1.92 (dddd, J=13.0, 8.7, 7.3, 6.0 Hz, 1 H, C<u>H</u>HCHNH), 1.77 (ddt, J=12.6, 8.9, 6.3, 6.3 Hz, 1 H, C<u>H</u>HCHOH), 1.68 (quin, J=7.4 Hz, 2 H, C<u>H</u>$_2$$CH_2$N($CH_2$)$CH_2$), 1.53 - 1.64 (m, 2 H, C<u>H</u>$_2$$CH_2$CHOH), 1.42 (ddt, J=12.9, 8.4, 5.2, 5.2 Hz, 1 H, CH<u>H</u>CHOH), 1.31 (ddt, J=13.0, 8.6, 6.4, 6.4 Hz, 1 H, CH<u>H</u>CHNH), 1.22 - 1.28 (m, 2 H, NCH(C<u>H</u>H)$_2$), 1.06 - 1.12 (m, 2 H, NCH(CH<u>H</u>)$_2$)

^{13}**C NMR** (126 MHz, DMSO d_6) δ / ppm = 171.9 ($CH_2\underline{C}(=O)NH$), 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 ($C(=O)CH_2CH_2\underline{C}H_2N$), 52.4 ($C(=O)CH_2CH_2CH_2N(\underline{C}H_2)\underline{C}H_2$), 51.3 ($\underline{C}H_3$), 49.6 ($C(=O)CH_2CH_2CH_2N(CH_2\underline{C}H_2)CH_2CH_2$), 49.6 ($C(=O)CH_2CH_2CH_2N(CH_2CH_2)CH_2\underline{C}H_2$), 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 ($\underline{C}H_2CHNH$), 22.5 ($C(=O)CH_2\underline{C}H_2$), 20.6 ($\underline{C}H_2CH_2CHOH$), 7.5 ($NCH(\underline{C}H_2)_2$)

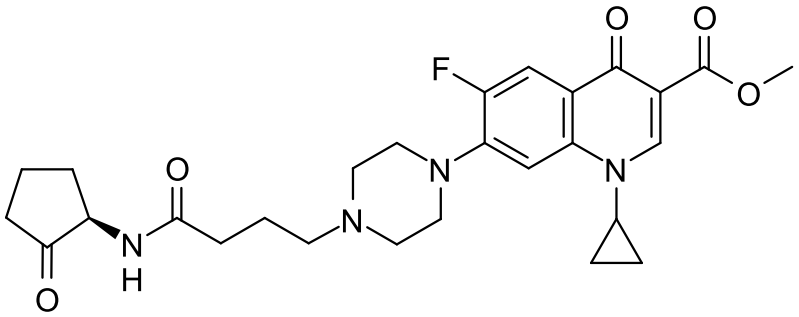
^{19}**F NMR** (376.45 MHz, MeOD) δ / ppm = -125.47

still TFA present after desalt attempt

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

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

1.58 Methyl (*R*)-1-cyclopropyl-6-fluoro-4-oxo-7-(4-(4-oxo-4-((2-oxocyclopentyl)amino)butyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate 163



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 **162** (20.0 mg, 38.9 μmol, 1 eq.) and Dess-Martin Periodane (32.8 mg, 77.4 μmol, 2 eq.) were stirred in CH_2Cl_2 (3 ml) for 6 h. The solvent was removed under reduced pressure and the residue was purified by preparatory HPLC (5-50 % acetonitrile/water over 10 min). The combined pure fractions were evaporated under reduced pressure, then $NaHCO_3$ (aq., sat., 30 ml) and 10 % *i*-PrOH/$CHCl_3$ (30 ml) were added. The organic layer was removed and dried with $MgSO_4$, then evaporated under reduced pressure. **163** was obtained as a white amorphous solid (11.3 mg, 22.0 μmol, 56.7 %).

^{1}**H NMR** (400 MHz, MeOD) δ / ppm = ??

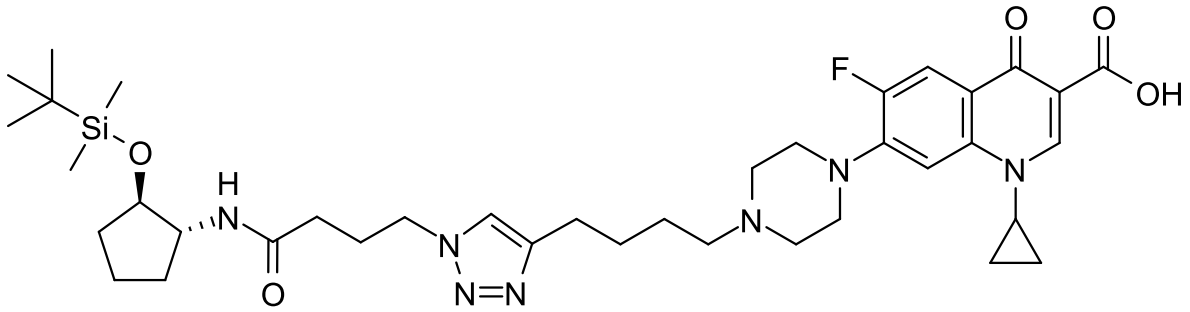
^{13}**C NMR** (101 MHz, MeOD) δ / ppm = ??

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

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

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

1.59 7-(4-(4-(1-(4-(((1*R*,2*R*)-2-((*tert*-butyldimethylsilyl)oxy)cyclopentyl)amino)-4-oxobutyl)-1H-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 164



1-Cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **176** (42.9 mg, 104 μmol, 1 eq.) and 4-azido-*N*-((1*R*,2*R*)-2-((*tert*-butyldimethylsilyl)oxy)cyclopentyl)butanamide **187**(RR) (33.9 mg, 104 μmol, 1 eq.) were dissolved in 10 % water/*t*-BuOH (3 ml), and the mixture was degassed by bubbling N_2 through it. A solution of $CuSO_4$ and THPTA (104 μl, 10.4 μmol, 0.1 eq. 100 mM, aq.) was added, followed by a solution of sodium ascorbate (208 μl, 20.8 μmol, 0.2 eq., 100 mM, aq.). The mixture was stirred at room temperature under argon for 16 h, then solvent was removed under reduced pressure. The resudue was partitioned between water (10 ml) and CH_2Cl_2 (10 ml), the organic layer was separated and the aqeous layer was extracted again with CH_2Cl_2 (10 ml). The combined organic layers were dried with $MgSO_4$ and evaporated under reduced pressure. **164** was obtained as a clear glass (67.1 mg, 90.9 μmol, 87.4 %).

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

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

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

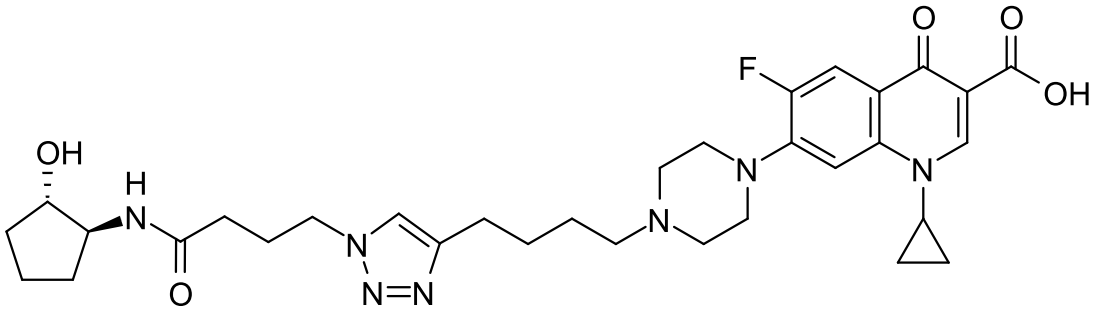
17.8 ($\underline{C}(CH_3)_3$), 8.1 (NCH($\underline{C}H_2)_2$), -4.8 (Si$\underline{C}H_3$)

^{19}F NMR (376.45 MHz, $CDCl_3$) δ / ppm = ?? F??

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

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

1.60 1-Cyclopropyl-6-fluoro-7-(4-(4-(1-(4-(((1*S*,2*S*)-2-hydroxycyclopentyl)amino)-4-oxobutyl)-1H-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 165



1-Cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **176** (42.9 mg, 104 μmol, 1 eq.) and 4-azido-*N*-((1*S*,2*S*)-2-hydroxycyclopentyl)butanamide **159** (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 M, aq.). The mixture was stirred at room temperature under argon for 16 h. Water (30 ml) and CH_2Cl_2 (30 ml) were added, the organic layer was separated and the aqueous layer was extracted again with CH_2Cl_2 (4 × 30 ml). The combined organic layers were dried with $MgSO_4$ and evaporated under reduced pressure. The residue was purified by preparatory HPLC (5-95 % acetonitrile/water over 20 min). The combined pure fractions were evaporated under reduced pressure and then partitioned between $NaHCO_3$ (aq., sat., 10 ml) and 10 % *i*-PrOH/$CHCl_3$ (10 ml). The organic layer was dried with $MgSO_4$ and evaporated under reduced pressure. **164** 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$\underline{H}$=CCH$_2$), 7.75 (d, J = 7.1 Hz, 1 H, CHN$\underline{H}$), 7.54 (d, J = 7.5 Hz, 1 H, *meta* to F), 4.73 (d, J = 3.8 Hz, 1 H, CHO$\underline{H}$), 4.29 (t, J = 6.9 Hz, 2 H, C$\underline{H}_2$NCH=C), 3.78 - 3.83 (m, 1 H, NC$\underline{H}$(CH$_2$)$_2$), 3.75 - 3.78 (m, 1 H, C$\underline{H}$OH), 3.71 - 3.75 (m, 1 H, C$\underline{H}$NH), 3.31 (br t, J = 4.3 Hz, 4 H, CH$_2$N(CH$_2$C$\underline{H}_2$)CH$_2$C$\underline{H}_2$), 2.63 (t, J = 7.5 Hz, 2 H, CH=CC$\underline{H}_2$), 2.56 (br t, J = 4.2 Hz, 4 H, CH$_2$N(C$\underline{H}_2$)C$\underline{H}_2$), 2.37 (t, J = 7.3 Hz, 2 H, C$\underline{H}_2$N(CH$_2$)CH$_2$), 2.03 - 2.06 (m, 2 H, C(=O)C$\underline{H}_2$), 1.97 - 2.02 (m, 2 H, C(=O)CH$_2$C$\underline{H}_2$), 1.89 (dddd, J = 13.1, 8.9, 7.4, 5.7 Hz, 1 H, C$\underline{H}$HCHNH), 1.75 (ddt, J = 13.0, 8.9, 6.4, 6.4 Hz, 1 H, C$\underline{H}$HCHOH), 1.61 - 1.66

(m, 2 H, CH=CCH$_2$CH$_2$), 1.57 - 1.61 (m, 1 H, CHHCH$_2$CHOH), 1.54 - 1.57 (m, 1 H, CHHCH$_2$CHOH), 1.49 - 1.53 (m, 2 H, CH=CCH$_2$CH$_2$CH$_2$), 1.40 (ddt, J = 13.0, 8.4, 5.3, 5.3 Hz, 1 H, CHHCHOH), 1.29 - 1.32 (m, 2 H, NCH(CHH)$_2$), 1.25 - 1.29 (m, 1 H, CHHCHNH), 1.13 - 1.20 (m, 2 H, NCH(CHH)$_2$)

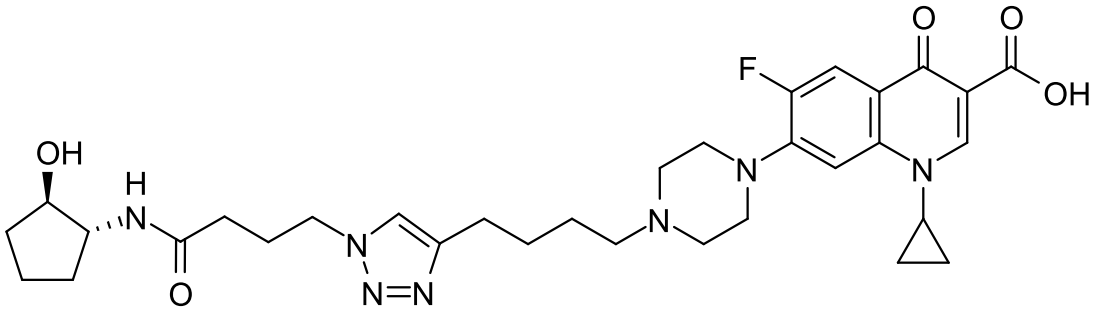
^{13}C NMR (175 MHz, DMSO d$_6$) δ / ppm = 176.3 (C(=O)CC(=O)OH), 170.9 (CH$_2$C(=O)NH), 166.1 (C(=O)OH), 153.0 (d, J = 251.4 Hz, *ipso* to F), 147.9 (C=CC(=O)OH), 146.9 (CH=CCH$_2$), 145.2 (d, J = 8.7 Hz, *ipso* to piperazine), 139.2 (*para* to F), 121.7 (NCH=CCH$_2$), 118.7 (d, J = 5.8 Hz, *para* to 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 CC(=O)OH), 76.2 (CHOH), 57.6 (CHNH), 57.4 (CH=CCH$_2$CH$_2$CH$_2$CH$_2$N), 52.5 (CH=CCH$_2$CH$_2$CH$_2$CH$_2$N(CH$_2$)CH$_2$), 49.5 (d, J = 4.4 Hz, CH=CCH$_2$CH$_2$CH$_2$CH$_2$N(CH$_2$CH$_2$)CH$_2$CH$_2$), 48.8 (CH$_2$NCH=CCH$_2$), 35.8 (NCH(CH$_2$)$_2$), 32.2 (CH$_2$CHOH), 32.0 (C(=O)CH$_2$), 29.5 (CH$_2$CHNH), 26.9 (CH=CCH$_2$CH$_2$), 26.0 (C(=O)CH$_2$CH$_2$), 25.8 (CH=CCH$_2$CH$_2$CH$_2$), 25.0 (CH=CCH$_2$), 20.5 (CH$_2$CH$_2$CHOH), 7.6 (NCH(CH$_2$)$_2$)

^{19}F NMR (376.45 MHz, MeOD) δ / ppm = -122.12 (s, ciprofloxacin F)

HRMS (ESI$^+$) m/z / Da = 624.3314, [M+H]$^+$ found, [C$_{32}$H$_{43}$FN$_7$O$_5$]$^+$ requires 624.3310

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

1.61 1-Cyclopropyl-6-fluoro-7-(4-(4-(1-(4-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-4-oxobutyl)-1H-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 166



Method?? white amorphous solid 7.2 mg, 11.5 μmol

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, MeOD) δ / ppm = ??

^{13}C NMR (101 MHz, MeOD) δ / ppm = ??

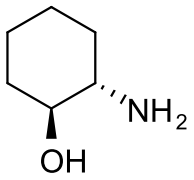
^{19}F NMR (376.45 MHz, MeOD) δ / ppm = ??

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

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

explain discrepancy

1.62 (*trans*)-2-Aminocyclohexan-1-ol 167



Cyclohexene oxide **188** (10 ml, 9.70 g, 98.8 mmol, 1 eq.), NH_3 (90 ml, 35 % w/w aq., 27.7 g, 791 mmol, 8 eq.) and MeOH (100 ml) were stirred at r.t. for 72 h. The solvent was removed by blowing a stream of N_2 over it, followed by evaporation under high vacuum

TLC R_f = 0.04 (30 % MeOH/CH_2Cl_2)

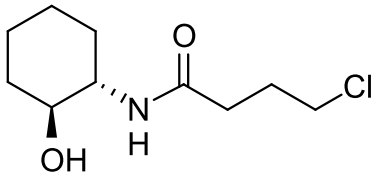
IR (neat) ν_{max} / cm^{-1} = 3350.4 (N-H), 3306.2 (br, O-H), 2926.9 (C-H), 2852.6 (C-H)

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

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

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

1.63 4-Chloro-*N*-((*trans*)-2-hydroxycyclohexyl)butanamide 168



(Trans)-2-aminocyclohexan-1-ol **167** (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 **185** (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). **168** was obtained as white needles (1.51 g, 6.87 mmol, 76.1 %).

TLC R_f = 0.19 (Et_2O)

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

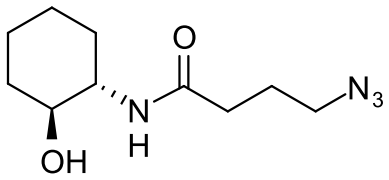
IR (neat) ν_{max} / cm^{-1} = 3289.9 (N-H), 3250.0 (O-H), 2927.6 (C-H), 2857.1 (C-H), 1629.2 (amide C=O)

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

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

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

1.64 4-Azido-*N*-((*trans*)-2-hydroxycyclohexyl)butanamide 169



4-Chloro-*N*-((trans)-2-hydroxycyclohexyl)butanamide **168** (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. **189** 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, $CHCl_3$)

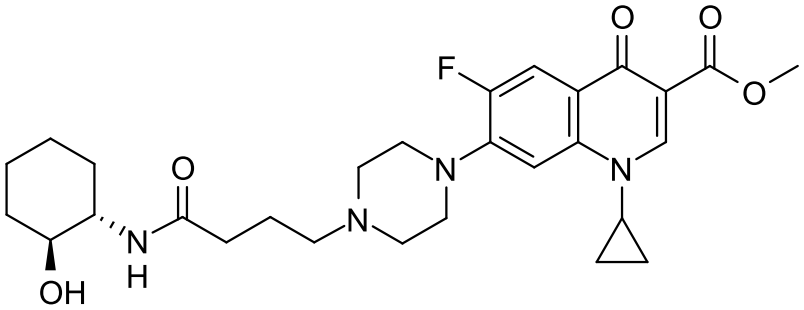
IR (neat) ν_{max} / cm^{-1} = 3299.0 (N-H), 3207.8 (O-H), 2944.3 (C-H), 2927.9 (C-H), 2859.2 (C-H), 2089.2 (azide), 1624.0 (amide C=O)

^{1}H NMR (400 MHz, MeOD) δ / ppm = 7.87 (d, J = 7.9 Hz, 1 H, N$\underline{H}$), 5.27 (d, J = 4.3 Hz, 1 H, O$\underline{H}$), 3.56 (td, J = 10.5, 4.4 Hz, 1 H, C$\underline{H}$NH), 3.28 - 3.41 (m, 3 H, C$\underline{H}$OH and C$\underline{H}_2$N$_3$), 2.30 (td, J = 7.4, 2.7 Hz, 2 H, C(=O)C$\underline{H}_2$), 1.95 - 2.03 (m, 1 H, C$\underline{H}$HCHOH), 1.87 (m, 3 H, C(=O)CH$_2$C$\underline{H}_2$ and C$\underline{H}$HCHNH), 1.70 - 1.76 (m, 1 H, C$\underline{H}$HCH$_2$CHOH), 1.63 - 1.70 (m, 1 H, C$\underline{H}$HCH$_2$CHNH), 1.25 - 1.38 (m, 3 H, CH$\underline{H}$CH$_2$CHOH, CH$\underline{H}$CH$_2$CHNH and CH$\underline{H}$CHOH), 1.14 - 1.24 (m, 1 H, CH$\underline{H}$CHNH$_2$)

^{13}C NMR (101 MHz, MeOD) δ / ppm = 175.1 ($\underline{C}$(=O)), 74.0 ($\underline{C}$HOH), 56.3 ($\underline{C}$HNH), 52.0 ($\underline{C}$H$_2$N$_3$), 35.5 ($\underline{C}$H$_2$CHOH), 34.3 (C(=O)$\underline{C}$H$_2$), 32.7 ($\underline{C}$H$_2$CHNH), 26.3 (C(=O)CH$_2\underline{C}$H$_2$), 25.8 ($\underline{C}$H$_2$CH$_2$CHNH), 25.5 ($\underline{C}$H$_2$CH$_2$CHOH)

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

1.65 Methyl 1-cyclopropyl-6-fluoro-7-(4-(4-(((*trans*)-2-hydroxycyclohexyl)amino)-4-oxobutyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 170



150 (200 mg, 0.367 mmol, 1 eq.), **167** (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 preparatory HPLC (5-50 % acetonitrile/water over 10 min). The combined pure fractions were evaporated under reduced pressure and then partitioned between $NaHCO_3$ (aq., sat., 10 ml) and CH_2Cl_2 (10 ml). The organic layer was dried with $MgSO_4$ and evaporated under reduced pressure. **161** 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)

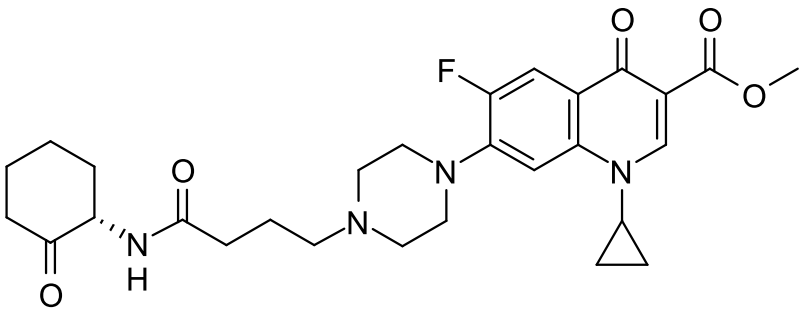
^{1}**H NMR** (400 MHz, MeOD) δ / ppm = 8.60 (s, 1 H, *ortho* to C(=O)OC$\underline{H}_3$), 7.79 (d, J = 13.5 Hz, 1 H, *ortho* to F), 7.46 (d, J = 7.2 Hz, 1 H, *meta* to F), 3.84 (s, 3 H, C$\underline{H}_3$), 3.62 - 3.68 (m, 1 H, NC$\underline{H}$(CH$_2$)$_2$), 3.58 (td, J = 10.3, 4.2 Hz, 1 H, C$\underline{H}$NH), 3.38 (br s, 4 H, CH$_2$N(CH$_2$C$\underline{H}_2$)CH$_2$C$\underline{H}_2$), 3.32 - 3.36 (m, 1 H, C$\underline{H}$OH), 2.83 (br s, 4 H, CH$_2$N(C$\underline{H}_2$)C$\underline{H}_2$), 2.60 (t, J = 7.3 Hz, 2 H, C(=O)CH$_2$CH$_2$C$\underline{H}_2$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$_2$C$\underline{H}_2$), 1.72 - 1.77 (m, 1 H, C$\underline{H}$HCH$_2$CHOH), 1.66 - 1.72 (m, 1 H, C$\underline{H}$HCH$_2$CHNH), 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$$\underline{C}$(=O)NH), 175.3 ($\underline{C}$(=O)CC(=O)OCH$_3$), 166.8 ($\underline{C}$(=O)OCH$_3$), 154.9 (d, J = 248.8 Hz, *ipso* to F), 150.2 ($\underline{C}$=CC(=O)OCH$_3$), 146.1 (d, J = 10.8 Hz, *ipso* to piperazine), 139.9 (*para* to F), 123.5 (d, J = 7.5 Hz, *para* to piperazine), 113.2 (d, J = 23.2 Hz, *ortho* to C=O and *ortho* to F), 110.2 ($\underline{C}$C(=O)OCH$_3$), 107.2 (*meta* to C=O and *meta* to F), 74.1 ($\underline{C}$HOH), 58.9 (C(=O)CH$_2$CH$_2$$\underline{C}H_2$N), 56.4 ($\underline{C}$HNH), 54.0 (C(=O)CH$_2CH_2CH_2$N($\underline{C}H_2$)$\underline{C}H_2$), 52.3 ($\underline{C}H_3$), 50.5 (d, J = 5.0 Hz, C(=O)CH$_2$CH$_2$CH$_2$N(CH$_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 $\underline{F}$)

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

1.66 Methyl 1-cyclopropyl-6-fluoro-4-oxo-7-(4-(4-oxo-4-((2-oxocyclohexyl)amino)-butyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate 171



Methyl 1-cyclopropyl-6-fluoro-7-(4-(4-(((trans)-2-hydroxycyclohexyl)amino)-4-oxobutyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate **170** (5.2 mg, 9.84 μmol, 1 eq.) and Dess-Martin Periodane (16.4 mg, 38.7 μmol, 4 eq.) were stirred in CH_2Cl_2 (3 ml) for 6 h. The solvent was removed under reduced pressure and the residue was purified by preparatory HPLC (5-95 % acetonitrile/water over ??)

TLC R_f = 0.74 (30 % MeOH/CH_2Cl_2)

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

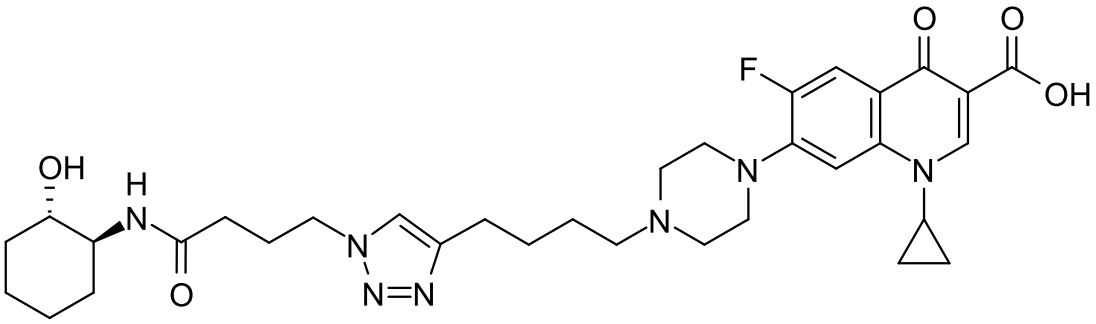
^{1}H NMR (400 MHz, DMSO d_6) δ / ppm = 8.45 (s, 1 H, *ortho* to C(=O)OC$\underline{H}_3$), 7.87 (d, J = 6.2 Hz, 1 H, N$\underline{H}$), 7.76 (d, J = 13.4 Hz, 1 H, *ortho* to F), 7.44 (d, J = 7.5 Hz, 1 H, *meta* to F), 4.42 (dddd, J = 13.0, 7.6, 6.0, 1.0 Hz, 1 H, C$\underline{H}$NH), 3.73 (s, 3 H, C$\underline{H}_3$), 3.65 (tt, J = 7.1, 3.9 Hz, 1 H, NC$\underline{H}(CH_2)_2$), 3.25 (br s, 4 H, $CH_2N(CH_2C\underline{H}_2)CH_2C\underline{H}_2$), 2.58 (br s, 4 H, $CH_2N(C\underline{H}_2)C\underline{H}_2$), 2.45 - 2.53 (m, 1 H, C$\underline{H}$HC(=O)CHNH), 2.36 (br s, 2 H, $C(=O)CH_2CH_2C\underline{H}_2N$), 2.26 (dtt, J = 13.4, 2.6, 2.6, 1.6, 1.6 Hz, 1 H, CH$\underline{H}$C(=O)CHNH), 2.16 - 2.22 (m, 2 H, $C(=O)C\underline{H}_2CH_2CH_2N$), 2.12 (ddq, J = 12.7, 6.0, 2.8, 2.8, 2.8 Hz, 1 H, C$\underline{H}$HCHNH), 2.00 (ddquin, J = 13.2, 6.0, 2.9, 2.9, 2.9, 2.9 Hz, 1 H, C$\underline{H}$HCH_2C(=O)), 1.65 - 1.83 (m, 4 H, $C\underline{H}_2CH_2CHNH$), 1.41 - 1.56 (m, 2 H, CH$\underline{H}$CHNH and CH$\underline{H}$CH_2C(=O)), 1.20 - 1.30 (m, 2 H, NCH(C$\underline{H}\underline{H}$)$_2$), 1.05 - 1.13 (m, 2 H, NCH(CH$\underline{H}$)$_2$)

^{13}C NMR (101 MHz, DMSO d_6) δ / ppm = 207.5 ($\underline{C}$(=O)CHNH), 171.7 ($\underline{C}$(=O)CC(=O)OCH_3), 171.6 ($CH_2\underline{C}$(=O)NH), 165.0 ($\underline{C}$(=O)OCH_3), 152.6 (d, J = 247.6 Hz, *ipso* to F), 148.3 ($\underline{C}$=CC(=O)OCH_3), 143.9 (br s, *ipso* to piperazine), 138.1 (*para* to F), 121.8 (d, J = 6.4 Hz, *para* to piperazine), 111.5 (d, J = 22.4 Hz, *ortho* to C=O and *ortho* to F), 109.0 (C$\underline{C}$(=O)OCH_3), 106.3 (*meta* to C=O and *meta* to F), 57.0 ($\underline{C}$HNH and $C(=O)CH_2CH_2\underline{C}H_2N$), 52.3 (br s, $C(=O)CH_2CH_2CH_2N(\underline{C}H_2)\underline{C}H_2$), 51.3 ($\underline{C}H_3$), 49.5 (br s, $C(=O)CH_2CH_2CH_2N(CH_2\underline{C}H_2)CH_2\underline{C}H_2$), 40.6 ($C\underline{H}_2C(=O)CHNH$), 34.8 (N$\underline{C}H(CH_2)_2$), 33.9 ($C\underline{H}_2CHNH$), 32.9 ($C(=O)\underline{C}H_2CH_2CH_2N$), 27.2 ($C\underline{H}_2CH_2C(=O)CHNH$), 23.8 ($C\underline{H}_2CH_2CHNH$), 22.4 (br s, $C(=O)CH_2\underline{C}H_2CH_2N$), 7.6 (NCH($\underline{C}H_2$)$_2$)

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

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

1.67 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 172



1-Cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **176** (40 mg, 97.2 μmol, 1 eq.) and 4-azido-*N*-((trans)-2-hydroxycyclohexyl)butanamide **169** (22.0 mg, 97.2 μmol, 1 eq.) were dissolved in 10 % water/*t*-BuOH (3 ml), and the mixture was degassed by bubbling N_2 through it. A solution of $CuSO_4$ and THPTA (97.2 μl, 9.72 μmol, 0.1 eq. 100 mM, aq.) was added, followed by a solution of sodium ascorbate (194 μl, 19.4 μmol, 0.2 eq., 100 mM, aq.). The mixture was stirred at r.t. under argon for 16 h. Water (50 ml) and 10 % *i*-PrOH/$CHCl_3$ (50 ml) were added, then the organic layer was separated and dried with $MgSO_4$ and evaporated under reduced pressure. The residue was purified by preparatory HPLC (5-70 % acetonitrile/water over 15 min). The combined pure fractions were evaporated under reduced pressure and then partitioned between $NaHCO_3$ (aq., sat., 50 ml) and 10 % *i*-PrOH/$CHCl_3$ (50 ml). The organic layer was dried with $MgSO_4$ and evaporated under reduced pressure. **172** 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, 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, 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, 1 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, 1 H, NCH(C$\underline{H}$H)$_2$), 1.11 - 1.22 (m, 5 H, NCH(CH$\underline{H}$)$_2$, CH$\underline{H}$CHOH, CH$\underline{H}$CH$_2$CHOH and C$\underline{H}_2$CH$_2$CHNH), 1.04 - 1.13 (m, 1 H, CH$\underline{H}$CHNH)

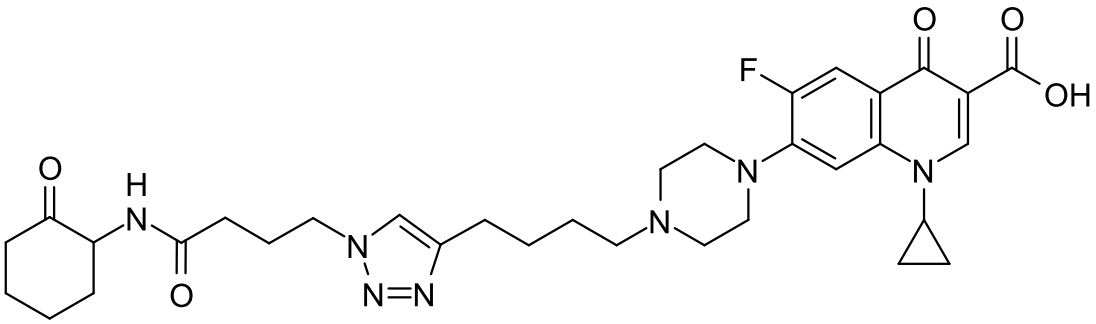
^{13}C NMR (101 MHz, DMSO d_6) δ / ppm = 176.4 (C(=O)CC(=O)OH), 170.9 (CH$_2$C(=O)NH), 166.0 (C(=O)OH), 153.1 (d, J = 252.1 Hz, *ipso* to F), 148.0 (C=CC(=O)OH), 146.9 (CH=CCH$_2$), 145.3 (d, J = 10.0 Hz, *ipso* to piperazine), 139.2 (*para* to F), 121.8 (NCH=CCH$_2$), 118.5 (d, J = 8.3 Hz, *para* to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

(C$\underline{H}_2$CHNH), 26.9 (CH=CCH$_2$C$\underline{H}_2$CH$_2$CH$_2$N), 26.1 (C(=O)CH$_2$C$\underline{H}_2$CH$_2$NCH=C), 25.8 (CH=CCH$_2$CH$_2$C$\underline{H}_2$CH$_2$N), 25.0 (CH=C$\underline{C}$H$_2$CH$_2$CH$_2$CH$_2$N), 24.2 (C$\underline{H}_2$CH$_2$CHNH), 23.8 (C$\underline{H}_2$CH$_2$CHOH), 7.6 (NCH($\underline{C}$H$_2$)$_2$)

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

HRMS (ESI$^+$) m/z / Da = 638.3480, [M+H]$^+$ found, [$C_{33}H_{45}FN_7O_5$]$^+$ requires 638.3466

1.68 1-Cyclopropyl-6-fluoro-4-oxo-7-(4-(4-(1-(4-oxo-4-((2-oxocyclohexyl)amino)butyl)-1H-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid 173



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 **172** (15.0 mg, 23.6 mmol, 1 eq.) and Dess-Martin Periodane (35.0 mg, 82.5 mmol, 3.5 eq.) were stirred in CH_2Cl_2 (3 ml) for 4 h. The solvent was removed under reduced pressure and the residue was purified by preparatory HPLC (5-70 % acetonitrile/water over 15 min). The combined pure fractions were evaporated under reduced pressure clear gum (11.7 mg, 18.4 μmol, 78.0 %).

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

^{1}**H NMR** (500 MHz, DMSO d$_6$) δ / ppm = 8.65 (s, 1 H, *ortho* to C(=O)OH), 7.94 (d, J=7.7 Hz, 1 H, 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$_2$CH$_2$C$\underline{H}$HN), 4.31 (t, J=6.9 Hz, 1 H, C(=O)CH$_2$CH$_2$CH$\underline{H}_2$N), 3.74 - 3.84 (m, 1 H, NC$\underline{H}$(CH$_2$)$_2$), 3.31 (br. s, 4 H, CH=CCH$_2$CH$_2$CH$_2$N(CH$_2$C$\underline{H}_2$)CH$_2$C$\underline{H}_2$), 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=CCH$_2$CH$_2$CH$_2$N(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$_2$CH$_2$CH$_2$C$\underline{H}_2$N), 2.25 (dtt, J=13.4, 2.6, 2.6, 1.6, 1.6 Hz, 1 H, CH$\underline{H}$C(=O)), 2.07 - 2.17 (m, 3 H, C(=O)C$\underline{H}_2$CH$_2$CH$_2$N and C$\underline{H}$HCHNH), 1.96 - 2.05 (m, 3 H, C(=O)CH$_2$C$\underline{H}_2$CH$_2$N and C$\underline{H}$HCH$_2$C(=O)), 1.68 - 1.81 (m, 2 H, C$\underline{H}$HCH$_2$CHNH), 1.64 (quin, J=7.5 Hz, 2 H, CH=CCH$_2$C$\underline{H}_2$CH$_2$CH$_2$N), 1.40 - 1.56 (m, 5 H, CH$\underline{H}$CH$_2$C(=O), CH$\underline{H}$CHNH and CH=CCH$_2$CH$_2$C$\underline{H}_2$CH$_2$N), 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$_2$CH$_2$CH$_2\underline{C}$H$_2$N), 57.0 ($\underline{C}$HNH), 52.4 (CH=CCH$_2$CH$_2$CH$_2$CH$_2$N($\underline{C}$H$_2$)$\underline{C}$H$_2$), 49.5 (CH=CCH$_2$CH$_2$CH$_2$CH$_2$N(CH$_2\underline{C}$H$_2$)CH$_2$CH$_2$), 49.5 (CH=CCH$_2$CH$_2$CH$_2$CH$_2$N(CH$_2$CH$_2$)CH$_2\underline{C}$H$_2$), 48.7 (C(=O)CH$_2$CH$_2\underline{C}$

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 = -121.67 (s, ciprofloxacin F)

some TFA

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

2 References

[1] Y. Baker. Novel Affinity Based Probes for Use in Chemical Proteomic Studies. 2012.

[2] J. D. Scribner, D. L. Smith and J. A. McCloskey. Meldrum's Acid in Organic Synthesis. 2. A General and Versatile Synthesis of β-Keto Esters. *The Journal of Organic Chemistry*, 43(10):2087–2088. 1978.

[3] J. T. Hodgkinson. The synthesis of Pseudomonas Quinolone Signal analogues and their effects on quinolone signalling in *Pseudomonas aeruginosa*. PhD thesis, University of Cambridge. 2011.

[4] D. M. Stacy, S. T. Le Quement, C. L. Hansen, J. W. Clausen, T. Tolker-Nielsen, J. W. Brummond, M. Givskov, T. E. Nielsen and H. E. Blackwell. Synthesis and biological evaluation of triazole-containing N-acyl homoserine lactones as quorum sensing modulators. *Organic & Biomolecular Chemistry*, 11(6):938–954. 2013.

[5] T. Persson, T. H. Hansen, T. B. Rasmussen, M. E. Skindersø, M. Givskov and J. Nielsen. Rational design and synthesis of new quorum-sensing inhibitors derived from acylated homoserine lactones and natural products from garlic. 38:253–262. 2005.

[6] L. S. Kocsis, E. Benedetti and K. M. Brummond. LETTERS A Thermal Dehydrogenative Diels À Alder Reaction of Styrenes for the Concise Synthesis of Functionalized Naphthalenes. *Organic Letters*, 14(17):4430–4433. 2012.

[7] S. Information, F. Tmp, H. Signal, B. Intracellular, L. Cell, I. Chaoran, V. W. Cornish, N. W. C. Building, N. York, C. Molecular, S. Chemistry, D. Mutagenesis, C. B. Methods, F. Characterization and C. Jing. A fluorogenic TMP-tag for high signal-to-background intracellular live cell imaging. *ACS chemical biology*, 8(8):1704–12. 2013.

[8] K. Sachin, E.-M. Kim, S.-J. Cheong, H.-J. Jeong, S. T. Lim, M.-H. Sohn and D. W. Kim. Synthesis of N_4'-[^{18}F]fluoroalkylated ciprofloxacin as a potential bacterial infection imaging agent for PET study. *Bioconjugate chemistry*, 21(12):2282–2288. 2010.

[9] K. Ganguly, R. Wu, M. Ollivault-Shiflett, P. M. Goodwin, L. A. Silks and R. Iyer. Design, synthesis, and a novel application of quorum-sensing agonists as potential drug-delivery vehicles. *Journal of drug targeting*, 19(7):528–539. 2011.

[10] R. Iyer, K. Ganguly and L. A. Silks. Synthetic analogs of bacterial quorum sensors. 2012.

[11] R. Srinivasan, L. P. Tan, H. Wu, P.-Y. Yang, K. A. Kalesh and S. Q. Yao. High-throughput synthesis of azide libraries suitable for direct "click" chemistry and in situ screening. *Organic & Biomolecular Chemistry*, 7(9):1821. 2009.

[12] J. Aubé, Michael S. Wolfe, R. K. Yantiss, S. M. Cook, F. Takusagawa, M. S. Wolfe, R. K. Yantiss, S. M. Cook and F. Takusagawa. Synthesis of Enantiopure N-tert-Butoxycarbonyl-2- aminocycloalkanones. *Synthetic Communications*, 22(20):3003–3012. 1992.

[13] L. E. Overman, S. Sugai, L. E. Overman and S. Sugai. A Convenient Method for Obtaining trans -2-Aminocyclohexanol and trans -2-Aminocyclopentanol in Enantiomerically Pure Form. *The Journal of Organic Chemistry*, 50:4154–4155. 1985.

[14] L. E. Overman and S. Sugai. Total Synthesis of (-)-Crinine. Use of Tandem Cationic Aza-Cope Rearrangement/Mannich Cyclizations for the Synthesis of Enantiomerically Pure Amaryllidaceae Alkaloids. *Helvetica Chimica Acta*, 68(3):745–749. 1985.

[15] I. Schiffers, T. Rantanen, F. Schmidt, W. Bergmans, L. Zani and C. Bolm. Resolution of racemic 2-aminocyclohexanol derivatives and their application as ligands in asymmetric catalysis. *The Journal of organic chemistry*, 71(1):2320–2331. 2006.