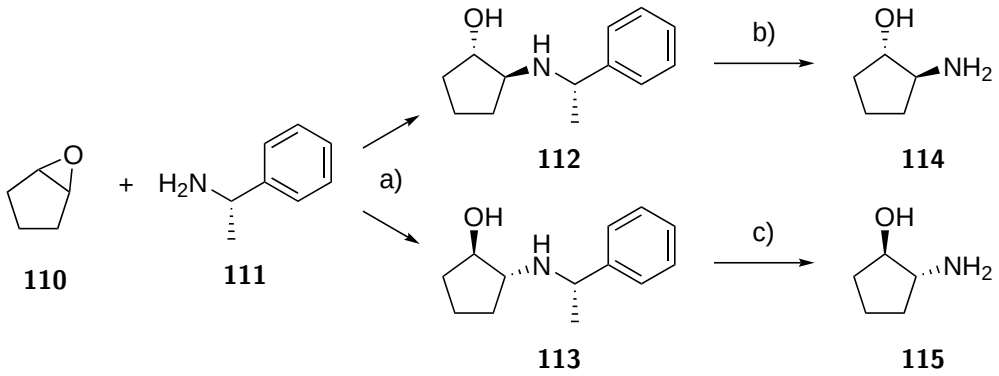
Contents

0.1 Cyclopentanol derivatives

0.1.1 Synthesis of the cyclopentanol head groups

Synthesis of the cyclopentanol derivatives began with the synthesis of (1*S*,2*S*)-2-aminocyclopentan-1-ol **114** and (1*R*,2*R*)-2-aminocyclopentan-1-ol **115** (see Scheme 1), using a procedure reported by Overman and Sugai.[14–16] These precursors were synthesised by opening cyclopentene oxide **110** using (*S*)-1-phenylethan-1-amine **111** to give approximately equal amounts of two diastereomers, **112** and **113**, which were separated using column chromatography. The removal of the methylbenzyl groups proved more difficult than expected, with the conditions reported by Overman and Sugai[15] yielding only a salt of the starting material. After several attempts under various conditions (including using the free amine vs. the salt, varying the temperature, ensuring the dryness of the reagents and adding acetic acid), an approach using H_2 gas was attempted (see Table 1). This proceeded smoothly at 5 atm to give the two enantiomers of 2-aminocyclopentan-1-ol, **114** and **115**, both in quantitative yield.



Scheme 1: Synthesis of (1*S*,2*S*)-2-aminocyclopentan-1-ol **114** and (1*R*,2*R*)-2-aminocyclopentan-1-ol **115** a) $AlMe_3$, CH_2Cl_2, 0 °C, **112** (*SSS*): 35.2 %, **113** (*RRS*): 32.1 %. b) See Table 1. c) $Pd(OH)_2$, MeOH, H_2, 5 atm, r.t., 1 d, 100 %.

Conditions	Temperature and pressure	Time	Result
112·HCl, ammonium formate, 10 % Pd/C, DMF	r.t., 1 atm	2 d	**112** salt
112, ammonium formate, 10 % Pd/C, DMF	r.t., 1 atm	2 d	**112** salt
112·HCl, ammonium formate, 10 % Pd/C, dry DMF	r.t., 1 atm	2 d	**112** salt
113, ammonium formate, 10 % Pd/C, dry DMF	r.t., 1 atm	2 d	**113** salt
112, ammonium formate, 10 % Pd/C, dry DMF	70 °C, 1 atm	1 d	**112** salt
112, ammonium formate, 10 % Pd/C, dry DMF, AcOH	70 °C, 1 atm	1 d	Complex mixture
112·HCl, dry ammonium formate, 10 % Pd/C, dry DMF	120 °C, 1 atm	7 d	Complex mixture
112·HCl, $Pd(OH)_2$, MeOH, H_2	r.t., 1 atm	1 d	**112** salt
112·HCl, $Pd(OH)_2$, MeOH, H_2	r.t., 3.4 atm	1 d	**114** salt, **112** salt, and an unidentified compound (approx. 7:2:10 by ^{1}H NMR)
112, $Pd(OH)_2$, MeOH, H_2	r.t., 5 atm	1 d	**114**, 100 % yield

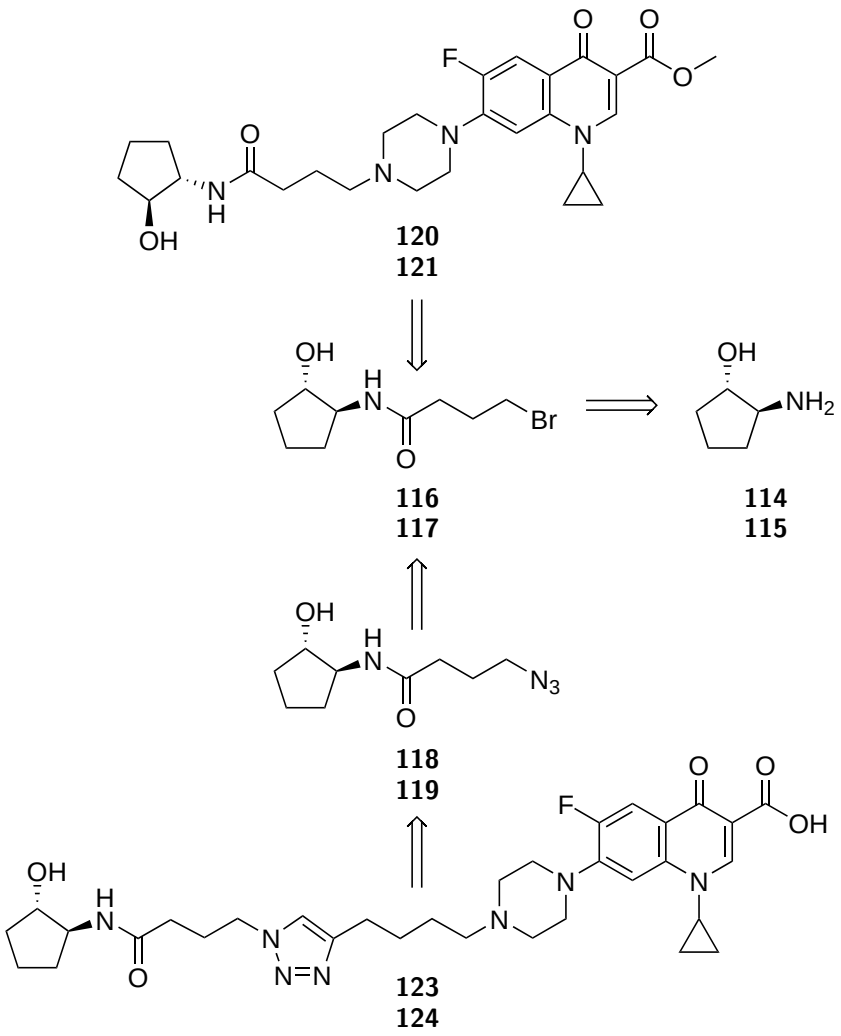
Table 1: Conditions attempted for the synthesis of (1*S*,2*S*)-2-aminocyclopentan-1-ol **114** and (1*R*,2*R*)-2-aminocyclopentan-1-ol **115** (see Scheme 1).

0.1.2 Initial branching strategy

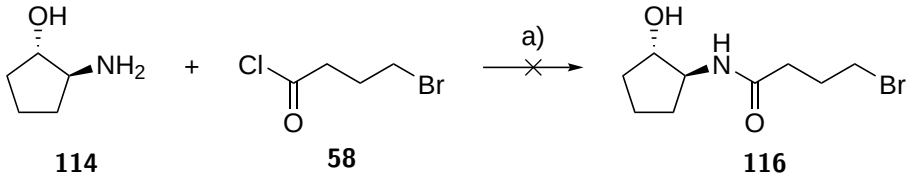
An initial retrosynthesis of the conjugates is shown in Scheme 2, and follows a similar path to previous conjugates.

Synthesis of Br-C_4-cyclopentanol-(*SS*) **116** from (1*S*,2*S*)-2-aminocyclopentan-1-ol **114** and 4-bromobutyryl chloride **58** was attempted using Schotten-Baumann conditions (see Scheme 3). However, a large number of impurities were observed by LCMS (see Figure 1), and so three new strategies were attempted: protection of

the alcohol (see 0.1.3), installing the linker on methyl ciprofloxacin **92** and then attaching the head group by peptide coupling (see 0.1.4), and using 4-chlorobutyryl chloride **139** as the linker instead of 4-bromobutyryl chloride **58** (see 0.1.5).



Scheme 2: Retrosynthesis of the cyclopentanol-CipMe conjugates **120** (*SS*) and **121** (*RR*), and the cyclopentanol-Cip triazole conjugates **123** (*SS*) and **124** (*RR*). *SS* enantiomers are shown, but both will be synthesised.



Scheme 3: Synthesis of Br-C_4-cyclopentanol-(*SS*) **116**. a) $NaHCO_3$, CH_2Cl_2, H_2O, 0 °C, 2 h.

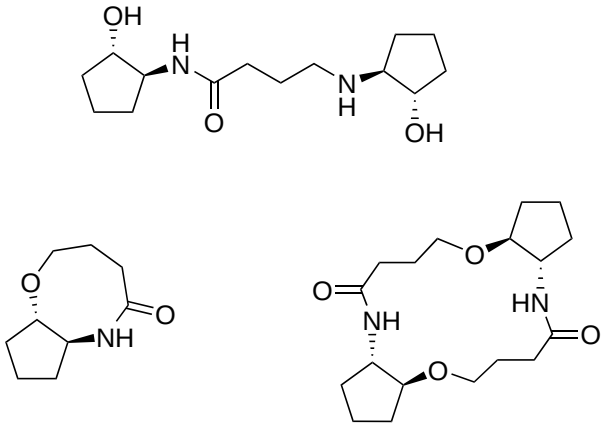
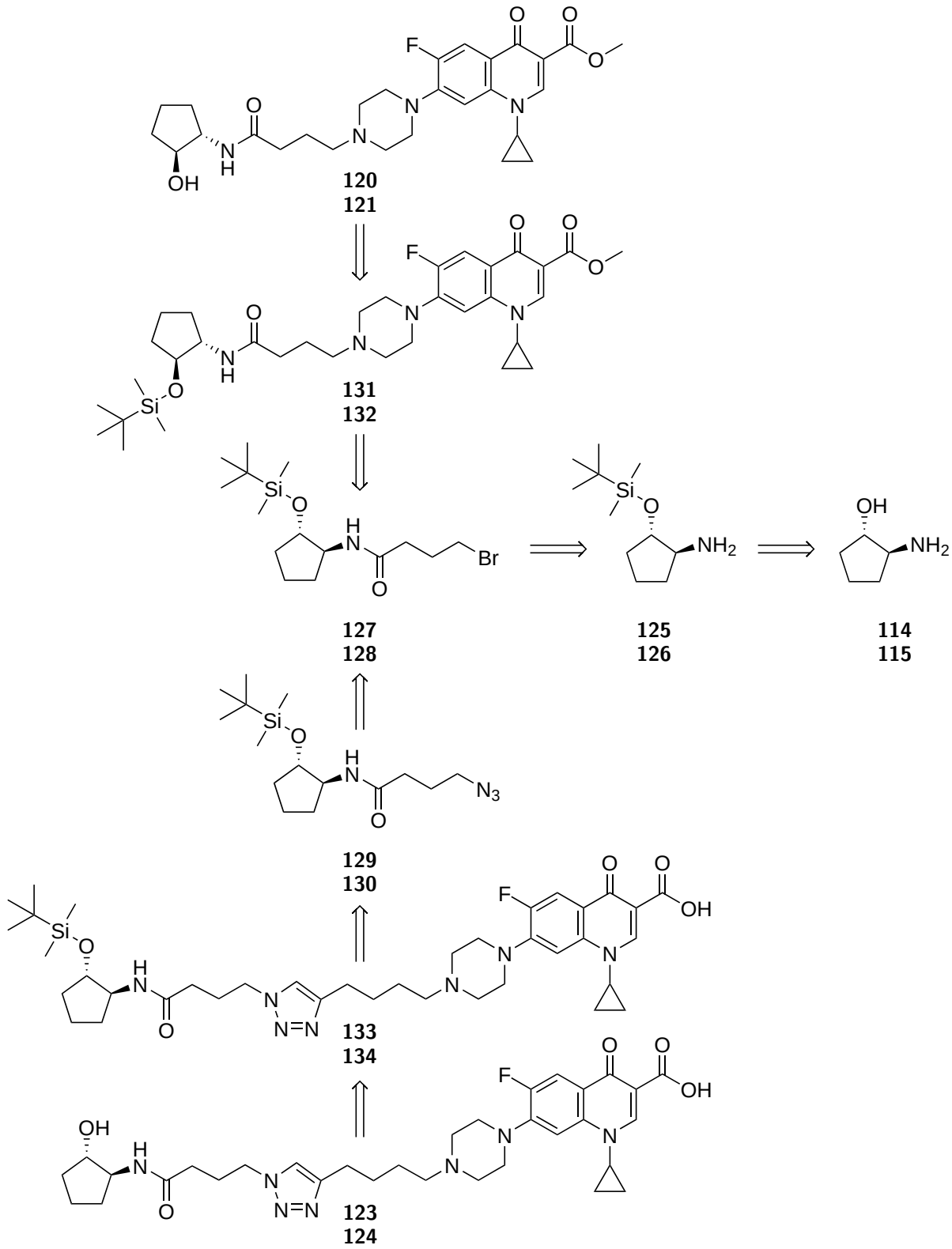


Figure 1: Impurities observed by LCMS during the synthesis of Br-C_4-cyclopentanol-(*SS*) **116**. Regiochemistry is speculative.

0.1.3 TBDMS protection of the alcohol

0.1.3.1 Initial protection strategy

The first attempt at an alternative strategy for the synthesis of the conjugates involved TBDMS protection of the alcohol (see Scheme 4). It was envisaged that protection would eliminate enough of the side reactions with products shown in Figure 1 that intermediates Br-C_4-cyclopentanol-(*SS*) **116** and N_3-C_4-cyclopentanol-(*SS*) **118** could be purified. The TBDMS group could be removed later in the synthesis using TBAF or acid.

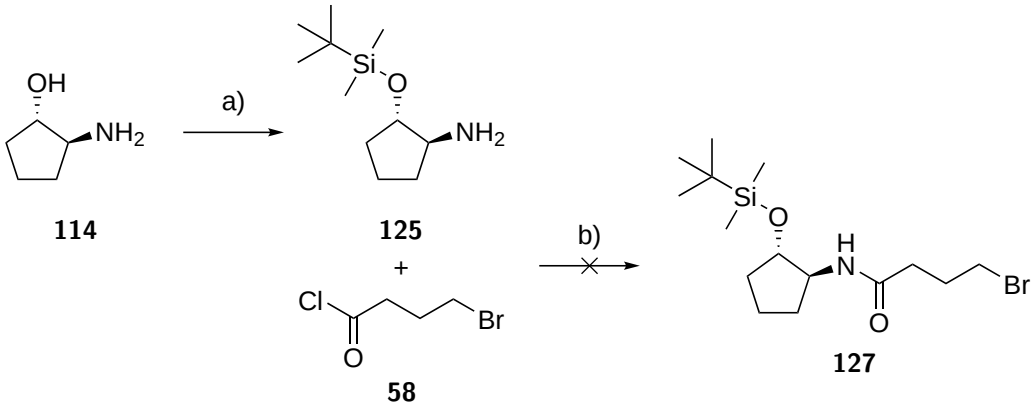


Scheme 4: Retrosynthesis of the cyclopentanol-CipMe conjugates **120** (*SS*) and **121** (*RR*), and the cyclopentanol-Cip triazole conjugates **123** (*SS*) and **124** (*RR*) using a TBDMS protection strategy. *SS* enantiomers are shown, but both will be synthesised.

The synthesis began with the optimisation of the protection of (1*S*,2*S*)-2-aminocyclopentan-1-ol **114** with a TBDMS group on the alcohol (see Scheme 5).

Opt.

OTf[?] Cl[?] DBU[?]



Scheme 5: The attempted synthesis of Br-C_4-cyclopentanol-TBDMS-(*SS*) **127**. a) See Table 2. b) $NaHCO_3$, CH_2Cl_2, H_2O, 0 °C, 2 h.

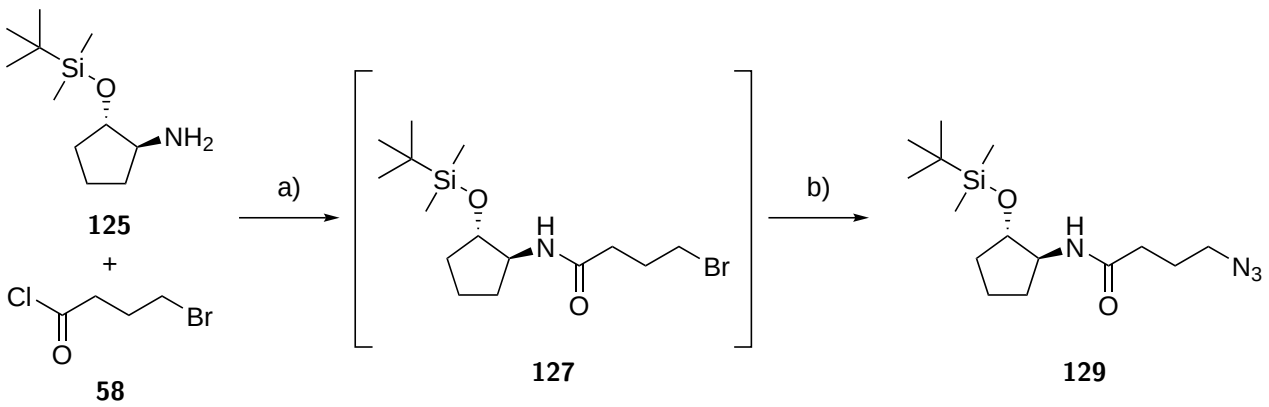
Conditions	Temperature	Time	Result
TBDMSCl, DMAP, TEA, CH_2Cl_2	r.t.	18 h	Trace of **125**, mostly **114**
TBDMSCl, DMAP, TEA, CH_2Cl_2	r.t.	1 d	Didn't go to completion, lost on prep TLC
TBDMSCl, imidazole, CH_2Cl_2	0 °C	1 h	**114**
TBDMSCl, DBU, MeCN	0 °C	1 d	**114**
TBDMSOTf, TEA, CH_2Cl_2	0 °C	4 h	**125** possibly seen but lost in workup
TBDMSOTf in 2 portions, TEA, CH_2Cl_2, NH_4Cl workup	0 °C	6 h	**125** salt
TBDMSOTf in 2 portions, TEA, CH_2Cl_2, aq. workup then column	0 °C	6 h	**125**, 85 % yield

Table 2: Conditions attempted for the synthesis of (1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclopentan-1-amine **125** (see Scheme 5).

Still get side-reactions when adding tail — come back to

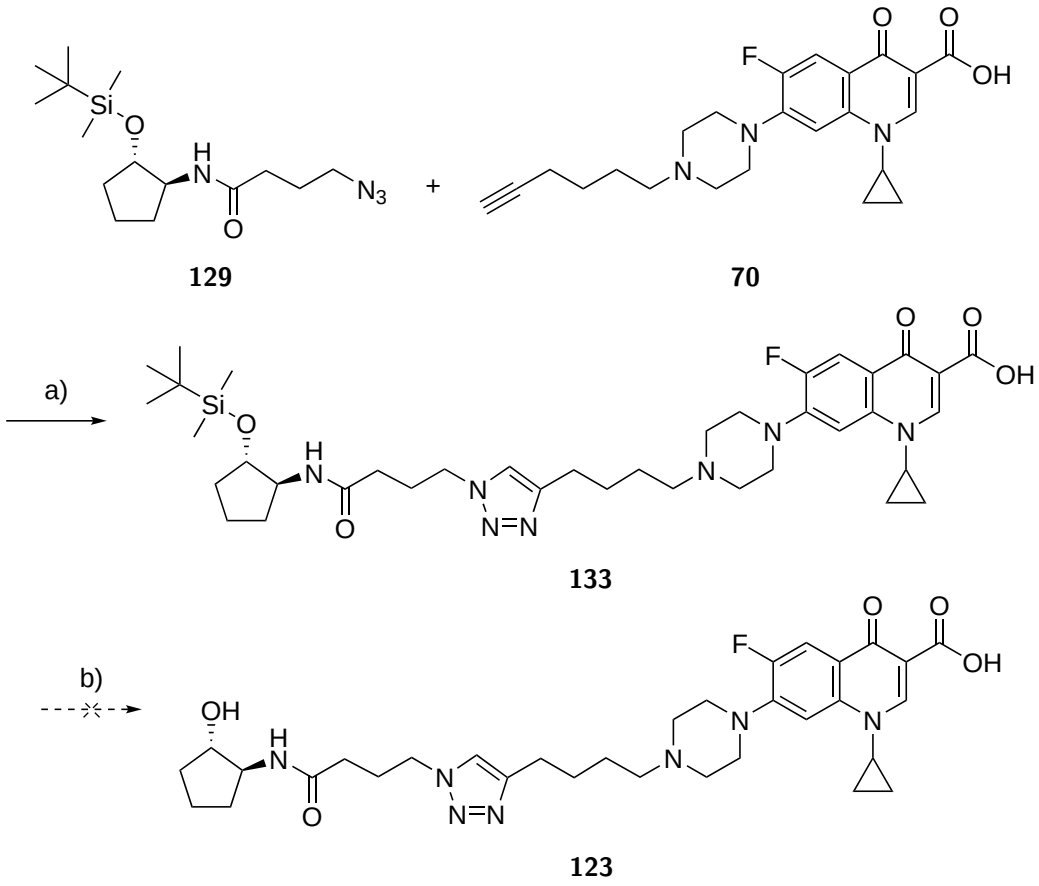
0.1.3.2 Triazoles by two-step reaction

Talk about moving to two-step reaction. — come back to



Scheme 6: a) $NaHCO_3$, CH_2Cl_2, H_2O, 0 °C, 3 h. b) NaN_3, DMF, CH_2Cl_2, r.t., 3 h. 99.2 % over 2 steps.

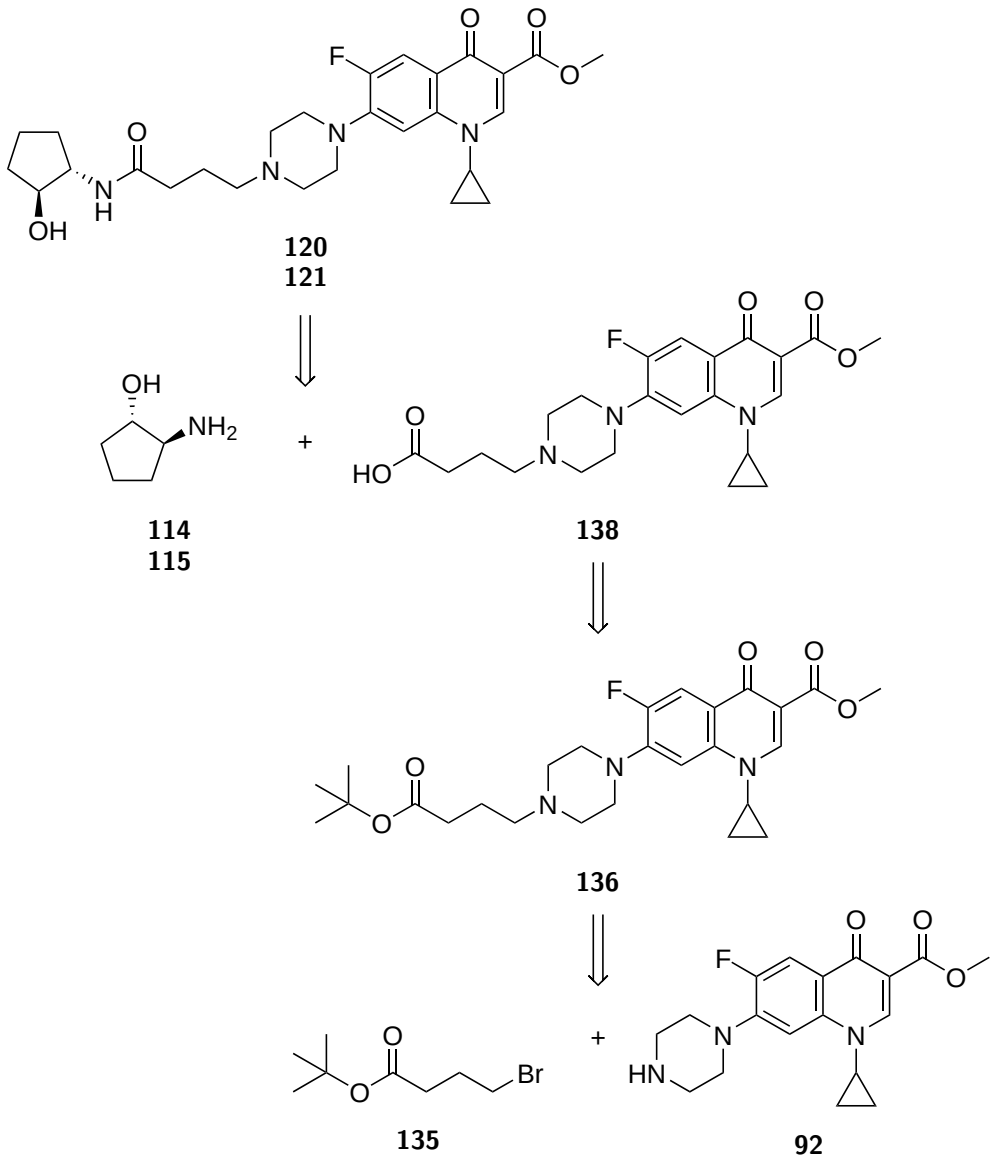
N_3-C_4-cyclopentanol-TBDMS-(*SS*) **129** and the alkynyl ciprofloxacin derivative **70** were subjected to standard click conditions, and the TBDMS-protected (*SS*)-cyclopentanol-Cip triazole conjugate **133** was synthesised in very good yield. However, removal of the TBDMS group proved difficult. Deprotection using 1.5 eq. TBAF in THF proceeded slowly, reaching completion in 5 d. Increasing the amount of TBAF to 8 eq. allowed the reaction to proceed overnight. Purification of the final conjugate **123** by column chromatography was not successful due to streaking and poor separation. Purification using DOWEX resin and $CaCO_3$ was attempted, but the product could not be recovered from the resin. The purification method could probably be optimised, e.g. by varying the solvent used with the resin, but ultimately this route was abandoned due to the reduction in number of steps afforded by the two methods described below.



Scheme 7: a) $CuSO_4$, sodium ascorbate, THPTA, H_2O, *t*-BuOH, r.t., 87.4 %. b) TBAF, THF, r.t., 16 h.

0.1.4 Peptide coupling route

Given the side-reactions and low yields associated with the literate synthesis of the S_N2 conjugates proposed by Ganguly et. al,[11] an alternative synthesis was investigated, involving building up the linker on the ciprofloxacin side before coupling with the head group (see Scheme 8).



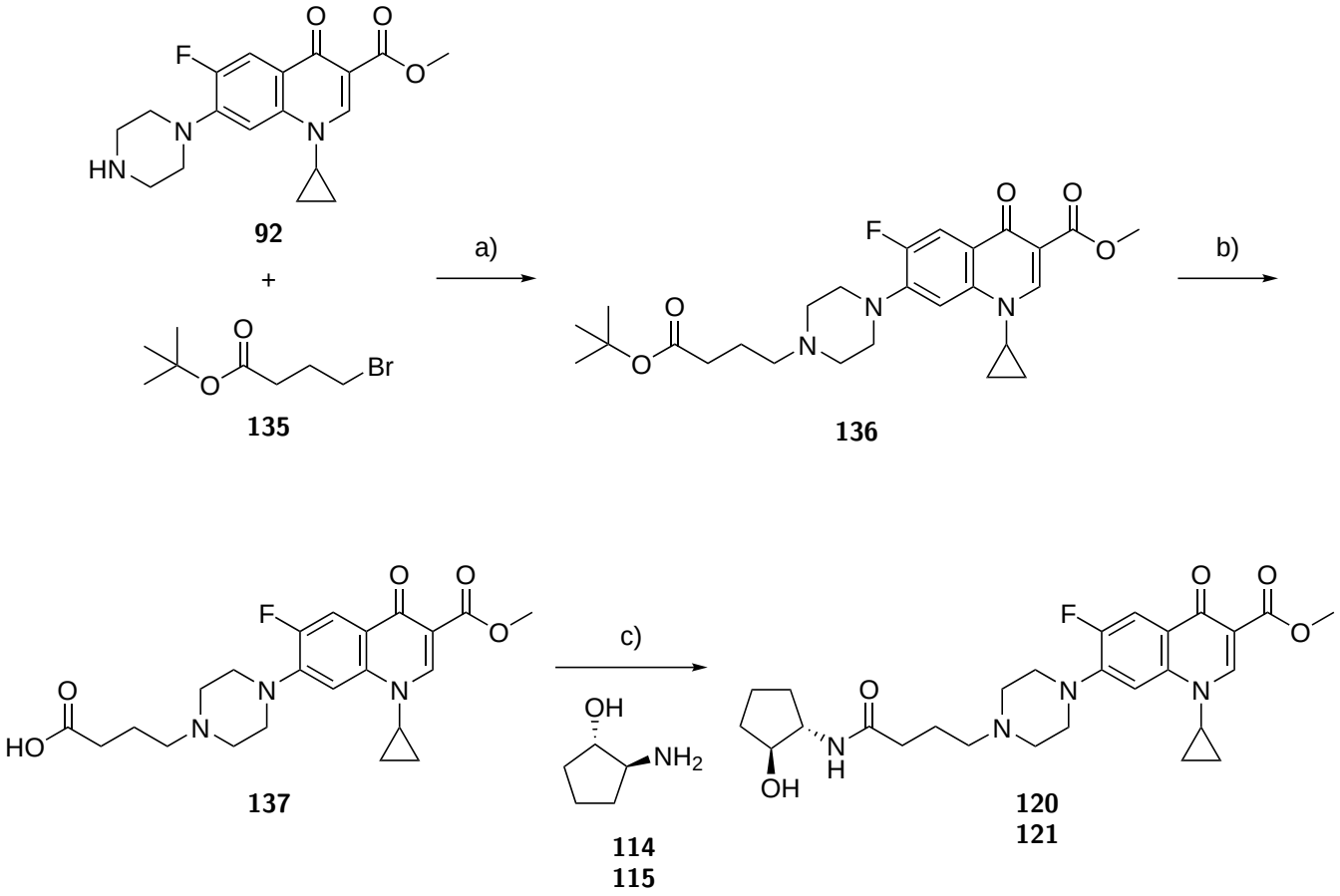
Scheme 8: Retrosynthesis of the cyclopentanol-CipMe conjugates **120** (*SS*) and **121** (*RR*). *SS* enantiomers are shown, but both will be synthesised.

The first step of the synthesis was an S_N2 reaction between Boc-protected 4-bromobutyric acid **135** methyl ciprofloxacin **92** (see Scheme 9). This reaction used fairly harsh conditions (16 h at 100 °C), but early on in the synthesis before the head group was installed. Hence the possibility of side reactions between the bromide and the amine was removed. Intermediate **136** was obtained in acceptable yield after column chromatography (49.9 %). Intermediate **136** was deprotected in excellent yield using TFA in CH_2Cl_2 to give carboxylic acid **138**. Scale-up of this reaction allowed the easy synthesis of 600 mg of this useful intermediate, which can be coupled with various amine head-groups to create a library. Carboxylic acid **138** was first coupled with (1*R*,2*R*)-2-aminocyclopentan-1-ol **115** using standard peptide coupling conditions to give cyclopentanol-CipMe conjugate **121**. Purification by column chromatography was attempted twice with poor results, before moving on to using preparative HPLC, which gave **121** cleanly in 38.7 % yield. Coupling was also performed with (1*S*,2*S*)-2-aminocyclopentan-1-ol **114** to give the enantiomer **120** in 54.7 % yield.

Direct comparisons of routes are not possible without repeating syntheses using this new method, but if it is assumed that peptide coupling of homocysteine thiolactone hydrochloride **93** to carboxylic acid **138** would have a similar yield to the coupling with (1*R*,2*R*)-2-aminocyclopentan-1-ol **115**, approximate comparisons can be made. The synthesis described in **??** has an overall yield of 10.7 %, whereas the route shown in Scheme 9 for

120 has an overall yield of 26.1 %. Moreover, if the yield starting from the head group (which may be expensive, difficult to synthesise and/or unstable) is considered, the yield is 54.7 % vs. 10.7 %. Therefore, this route is recommended for further investigation if the library is to be expanded.

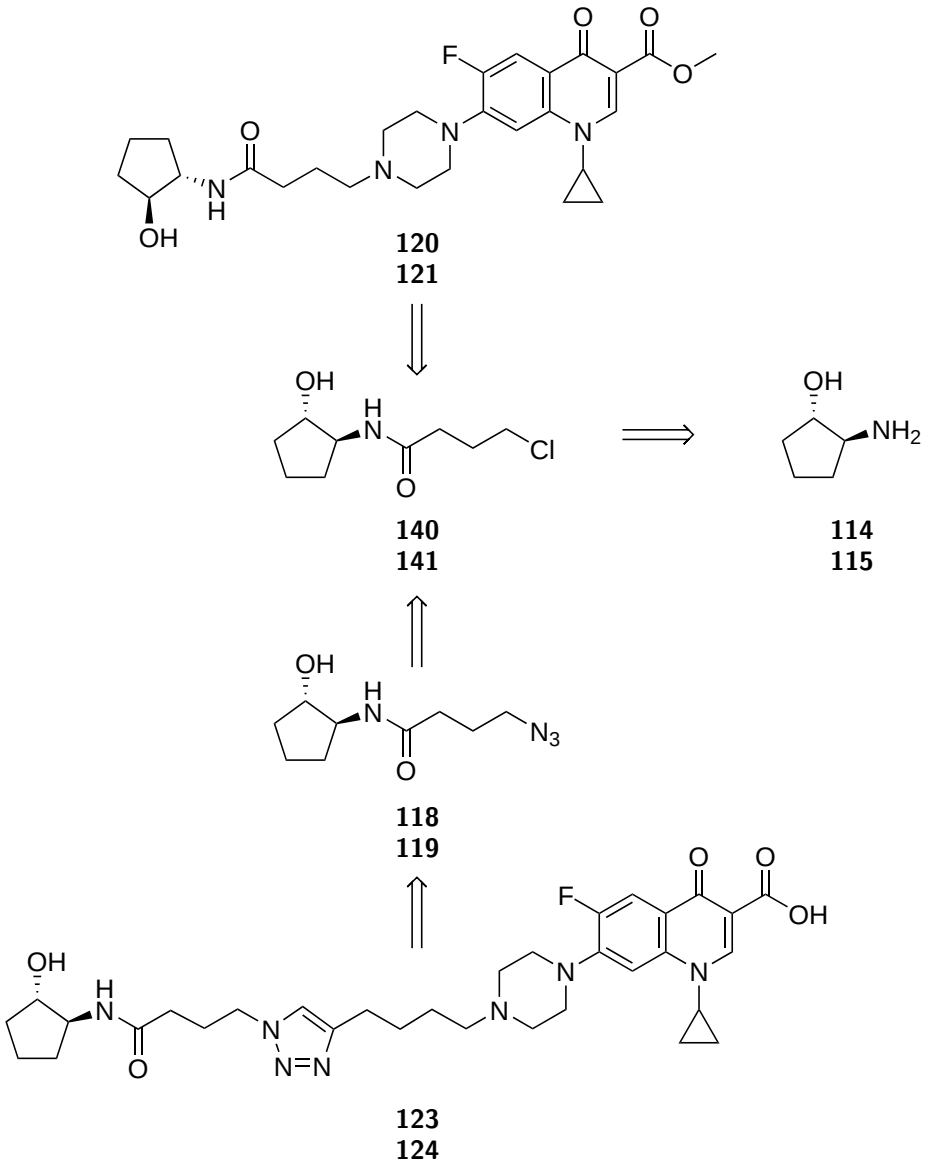
A downside to this route is that it cannot branch towards the triazole-coupled library in the same way that the route in **??**. A carboxylic acid intermediate with a triazole in the chain could presumably be synthesised, but this would be rather pointless given that the triazole library was initially proposed so that the two sides could be joined by the 'click' reaction. Therefore, an alternative route to the azide was proposed, via a more stable chloride intermediate (see 0.1.5).



Scheme 9: Synthesis of the cyclopentanol-CipMe conjugates **120** (*SS*) and **121** (*RR*) by peptide coupling. *SS* enantiomers are shown, but both were synthesised. a) NaI, TEA, acetonitrile, 100 °C, 16 h, 49.9 %. b) TFA, CH_2Cl_2, r.t., 18 h, 95.6 %. c) EDC, HOBt, DIPEA, DMF, r.t., 16 h, **120** (*SS*): 54.7 %, **121** (*RR*): 38.7 %.

0.1.5 Triazoles from chlorides

A final attempt at a branching strategy was attempted, via a chloride rather than a bromide intermediate (see Scheme 10 and Scheme 2 for comparison). The bromide intermediate was initially chosen as it was used by Ganguly et. al,[11] but it was hoped that using a chloride would cut out some of the side reactions seen with the more reactive bromide.



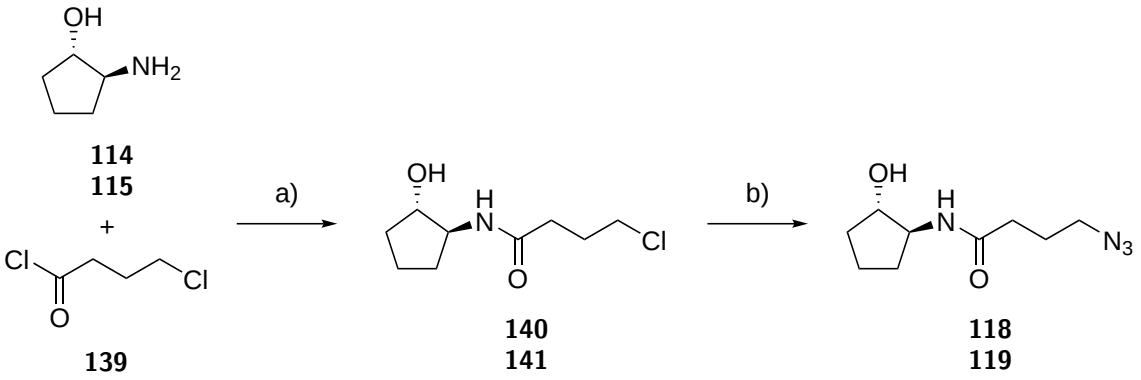
Scheme 10: Retrosynthesis of the cyclopentanol-CipMe conjugates **120** (*SS*) and **121** (*RR*), and the cyclopentanol-Cip triazole conjugates **123** (*SS*) and **124** (*RR*) via Cl-C_4-cyclopentanol intermediates **140** (*SS*) and **141** (*RR*). *SS* enantiomers are shown, but both will be synthesised.

Attempts at this route began with the synthesis of Cl-C_4-cyclopentanol-(*RR*) **141**. Standard Schotten-Baumann conditions failed to produce significant amounts of product. If prolonged reaction times were allowed, degradation of the acid chloride to the carboxylic acid was observed. The reason for this is unclear, but it is possible that bromide ions present in small amounts in previous reactions were helping to catalyse the reaction of the acid chloride. Archer et al.[?] propose that bromide ions can react with acid chlorides to form acid bromides, which are then more susceptible to nucleophilic attack. As no bromide ions are present in this reaction, different conditions were sought in order to increase the rate.

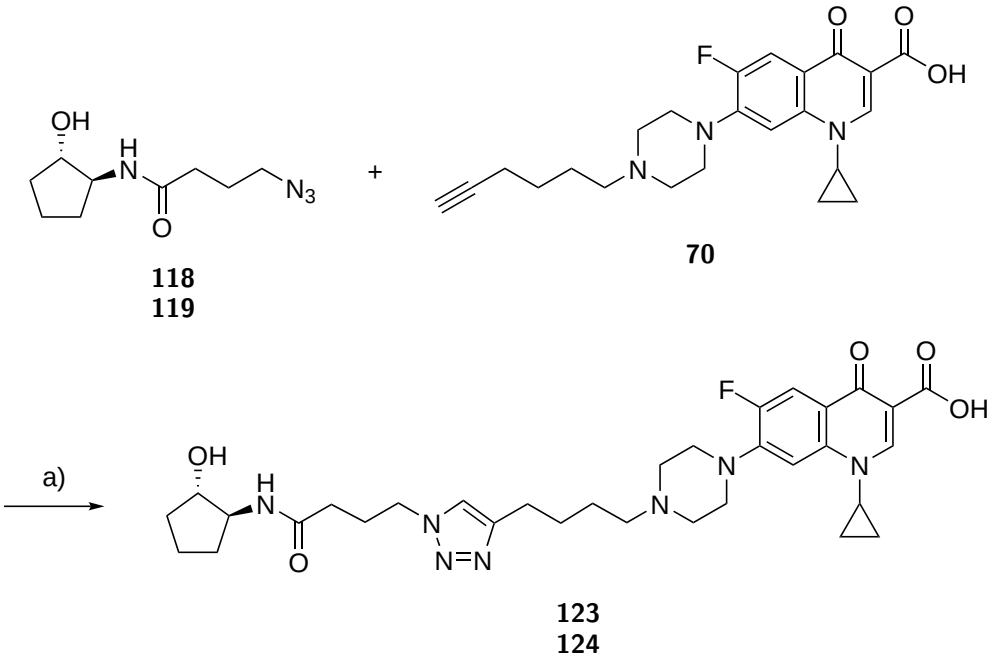
As (1*R*,2*R*)-2-aminocyclopentan-1-ol **115** is fairly polar, it is likely that it was staying in the aqueous layer to some extent even when deprotonated, thus keeping the two reactants apart. Therefore, the solvent system and base were changed to neat CH_2Cl_2 and TEA. This produced Cl-C_4-cyclopentanol-(*RR*) **141** in good yield (64.1 %). Unlike the bromide **116**, the chloride **141** was stable when concentrated.

Cl-C_4-cyclopentanol-(*RR*) **141** was converted to N_3-C_4-cyclopentanol-(*RR*) **119** by reaction with sodium azide. The reaction was slower than with previous bromides (~16 h vs. ~2 h), but much cleaner than with Br-C_4-cyclopentanol-(*SS*) **116** (see 0.1.2).

The enantiomer Cl-C_4-cyclopentanol-(*SS*) **140** was synthesised in lower yield, in part because



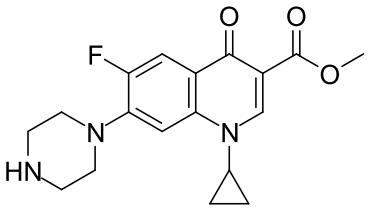
Scheme 11: Synthesis of N_3-C_4-cyclopentanol-(*SS*) **118** and N_3-C_4-cyclopentanol-(*RR*) **119**. *SS* enantiomers are shown, but both were synthesised. a) TEA, CH_2Cl_2, 0 °C, 2 h, **140** (*SS*): 24.2 %, **141** (*RR*): 64.1 %. b) NaN_3, acetonitrile, 50 °C, 16 h, **118** (*SS*): 45.0 %, **119** (*RR*): 87.6 %.



Scheme 12: Synthesis of the cyclopentanol-Cip triazole conjugates **123** (*SS*) and **124** (*RR*). *SS* enantiomers are shown, but both were synthesised. a) $CuSO_4$, THPTA, sodium ascorbate, H_2O, *t*-BuOH, CH_2Cl_2, r.t., 3 d, **123** (*SS*): 22.2 %, **124** (*RR*): 27.1 %.

This worked. Mention Sn2 attempt

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



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

TLC R_f = 0.13 (5 % MeOH/CH_2Cl_2)

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

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

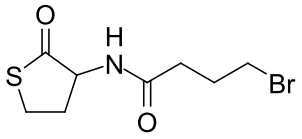
^{13}**C NMR** (101 MHz, MeOD) δ / ppm = 175.2 ($\underline{C}$(=O)CC(=O)OCH_3), 166.8 ($\underline{C}$(=O)OCH_3), 154.9 (d, J = 248.0 Hz, *ipso* to F), 150.1 ($\underline{C}$=CC(=O)OCH_3), 146.6 (d, J = 10.4 Hz, *ipso* to piperazine), 139.9 (*para* to F), 123.3 (d, J = 6.9 Hz, *para* to piperazine),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

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

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

The data are consistent with the literature.[10]

0.3 4-Bromo-*N*-(2-oxotetrahydrothiophen-3-yl)butanamide 94



3-Aminodihydrothiophen-2(3*H*)-one hydrochloride **93** (15.0 g, 97.6 mmol, 1 eq.) and $NaHCO_3$ (16.4 g, 195 mmol, 2 eq.) were added to CH_2Cl_2 (150 ml) and water (150 ml). 4-Bromobutyryl chloride **58** (11.3 ml, 107 mmol, 1.1 eq.) was added dropwise over 45 min at 0 °C and the mixture was stirred for a further 1 h. The

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

TLC R_f = 0.19 (50 % EtOAc/PE)

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

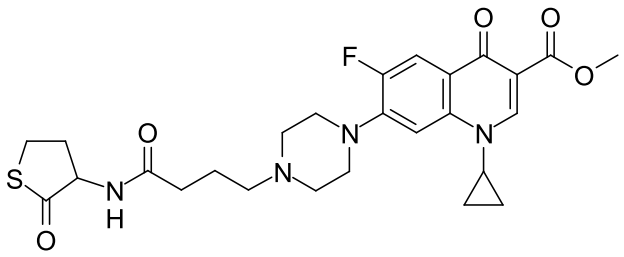
^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 6.08 (d, J = 6.1 Hz, 1 H, NH), 4.54 (dt, J = 12.9, 6.5 Hz, 1 H, CHNH), 3.49 (t, J = 6.4 Hz, 2 H, CH_2Br), 3.37 (ddd, J = 12.2, 11.5, 5.3 Hz, 1 H, SCHH), 3.26 (ddd, J = 11.5, 6.9, 1.3 Hz, 1 H, SCHH), 2.91 (dddd, J = 12.5, 6.7, 5.3, 1.3 Hz, 1 H, SCH_2CHH), 2.45 (t, J = 7.4 Hz, 1 H, C(=O)CHH), 2.45 (t, J = 6.8 Hz, 1 H, C(=O)CHH), 2.20 (quin, J = 6.7 Hz, 1 H, $C(=O)CH_2CH_2$), 1.96 (dddd, J = 12.7, 12.5, 12.2, 7.0 Hz, 1 H, SCH_2CHH)

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

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

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

0.4 Methyl 1-cyclopropyl-6-fluoro-4-oxo-7-(4-(4-oxo-4-((2-oxotetrahydrothiophen-3-yl)amino)butyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate 95



Methyl 1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate **92** (50 mg, 0.145 mmol, 1 eq.), 4-bromo-*N*-(2-oxotetrahydrothiophen-3-yl)butanamide **94** (34.5 mg, 0.145 mmol, 1 eq.) and K_2CO_3 (20 mg, 0.145 mmol, 1 eq.) were stirred in acetonitrile (2 ml) at 50 °C under argon. After 24 h a further portion of **94** (34.5 mg, 0.145 mmol, 1 eq.) was added. After another 24 h a further portion was added (69.0 mg, 0.290 mmol, 2 eq.). After another 24 h the temperature was raised so the mixture was at reflux. After a final 24 h the precipitate was filtered off and the filtrate was purified by column chromatography (SiO_2, 5-10 % MeOH/CH_2Cl_2) followed by preparative HPLC (5-95 % acetonitrile/water over 20 min). **95** was obtained as a cream-coloured amorphous solid (9.4 mg, 0.018 mmol, 12.2 %).

TLC R_f = 0.47 (10 % MeOH/CH_2Cl_2)

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

^{1}H NMR (500 MHz, MeOD) δ / ppm = 8.53 (s, 1 H, *ortho* to C(=O)OCH_3), 7.68 (d, J = 13.4 Hz, 1 H, *ortho* to F), 7.41 (d, J = 7.3 Hz, 1 H, *meta* to F), 4.67 (dd, J = 12.9, 6.9 Hz, 1 H, C$\underline{H}$NH), 3.83 (s, 3 H, O$C\underline{H}_3$), 3.61 (tt, J = 6.9, 4.1 Hz, 1 H, NC$\underline{H}(CH_2)_2$), 3.39 - 3.49 (m, 1 H, SC$\underline{H}$H), 3.26 - 3.33 (m, 5 H, SCH$\underline{H}$ and $CH_2CH_2CH_2N(CH_2C\underline{H}_2)CH_2C\underline{H}_2$), 2.93 - 3.03 (m, 4 H, $CH_2CH_2CH_2N(C\underline{H}_2)C\underline{H}_2$), 2.79 (br. t, J = 7.2, 7.2 Hz, 2 H, C(=O)$CH_2CH_2C\underline{H}_2$), 2.59 (dddd, J = 12.4, 6.9, 5.4, 1.4 Hz, 1 H, $SCH_2C\underline{H}$H), 2.39 (t, J = 7.20 Hz, 1 H, C(=O)C$\underline{H}$H), 2.38 (t, J = 6.94 Hz, 1 H, C(=O)CH$\underline{H}$), 2.18 (qd, J = 12.4, 7.0 Hz, 1 H, $SCH_2CH\underline{H}$), 1.97 (quin, J = 7.2 Hz, 2 H, C(=O)$CH_2C\underline{H}_2$), 1.32 - 1.37 (m, 2 H, NCH(C$\underline{H}$H)$_2$), 1.13 - 1.19 (m, 2 H, NCH(CH$\underline{H}$)$_2$)

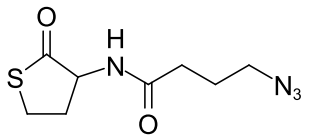
^{13}C NMR (126 MHz, MeOD) δ / ppm = 207.0 (S$\underline{C}$(=O)), 175.7 (NH$\underline{C}$(=O)), 175.1 ($\underline{C}$(=O)CC(=O)OCH_3), 166.6 ($\underline{C}$(=O)OCH_3), 154.7 (d, J = 249.0 Hz, *ipso* to F), 150.2 (s, $\underline{C}$H=CC(=O)OCH_3), 145.6 (d, J = 10.6 Hz, *ipso* to piperazine), 139.8 (*para* to F), 123.5 (d, J = 6.9 Hz, *para* to piperazine), 113.1 (d, J = 23.6 Hz, *ortho* to C=O and *ortho* to F), 110.0 ($\underline{C}$C(=O)OCH_3), 107.4 (*meta* to C=O and *meta* to F), 60.2 ($\underline{C}$HNH), 58.5 (C(=O)$CH_2CH_2\underline{C}H_2$), 53.8 ($CH_2CH_2CH_2N(\underline{C}H_2)\underline{C}H_2$), 52.3 (O$\underline{C}H_3$), 50.1 ($CH_2CH_2CH_2N(CH_2\underline{C}H_2)CH_2CH_2$), 50.0 ($CH_2CH_2CH_2N(CH_2CH_2)CH_2\underline{C}H_2$), 36.5 (N$\underline{C}H(CH_2)_2$), 34.5 (C(=O)$\underline{C}H_2$), 31.7 ($SCH_2\underline{C}H_2$), 28.1 (S$\underline{C}H_2$), 22.9 (C(=O)$CH_2\underline{C}H_2CH_2$), 8.7 (NCH($\underline{C}H_2)_2$)

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

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

The compound has been synthesised previously.[11,12] Only HRMS characterisation was published, and this agrees with the result above.

0.5 4-Azido-*N*-(2-oxotetrahydrothiophen-3-yl)butanamide 96



4-Bromo-*N*-(2-oxotetrahydrothiophen-3-yl)butanamide **94** (6.00 g, 27.0 mmol, 1 eq.) and NaN_3 (3.51 g, 54.1 mmol, 2 eq.) were refluxed in acetonitrile (120 ml) for 1.5 h. The solvent was evaporated under reduced pressure and the residue was partitioned between water (150 ml) and CH_2Cl_2 (150 ml). The aqueous layer was extracted twice more with CH_2Cl_2 (2×150 ml) and the combined organic fractions were dried with $MgSO_4$ and evaporated under reduced pressure. **96** was obtained as a yellow, sticky solid (4.60 g, 20.1 mmol, 89.3 %).

TLC R_f = 0.19 (50 % EtOAc/PE)

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

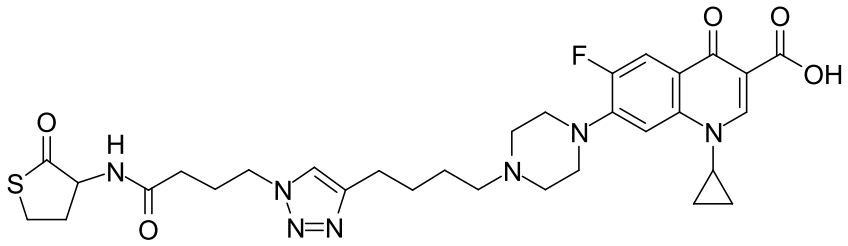
^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 6.71 (d, J = 7.3 Hz, 1 H, N$\underline{H}$), 4.54 (dt, J = 13.0, 7.0 Hz, 1 H, C$\underline{H}$NH), 3.30 (t, J = 6.7 Hz, 2 H, $C\underline{H}_2N_3$), 3.31 (td, J = 11.7, 5.3 Hz, 1 H, SC$\underline{H}$H), 3.19 (ddd, J = 11.3, 7.0, 1.2 Hz, 1 H, SCH$\underline{H}$), 2.70 (dddd, J = 12.4, 6.8, 5.3, 1.2 Hz, 1 H, $SCH_2C\underline{H}$H), 2.29 (t, J = 7.5 Hz, 1 H, C(=O)C$\underline{H}$H), 2.28 (t, J = 7.1 Hz, 1 H, C(=O)CH$\underline{H}$), 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 (<u>C</u>H_2N_3), 32.8 (C(=O)<u>C</u>H_2), 31.8 (SCH_2<u>C</u>H_2), 27.5 (S<u>C</u>H_2), 24.6 ($C(=O)CH_2$<u>C</u>H_2)

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

The compound has not been reported previously.

0.6 1-Cyclopropyl-6-fluoro-4-oxo-7-(4-(4-(1-(4-oxo-4-((2-oxotetrahydrothiophen-3-yl)amino)butyl)-1*H*-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid 97



1-Cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **70** (15 mg, 36.7 μmol, 1 eq.) and 4-azido-*N*-(2-oxotetrahydrothiophen-3-yl)butanamide **96** (12.5 mg, 55.1 μmol, 1.5 eq.) were dissolved in 1:9:10 water/*t*-BuOH/DMSO (3 ml), and the mixture was degassed by bubbling N_2 through it. A solution of $CuSO_4$ and THPTA (182 μl, 18.2 μmol, 0.5 eq. 100 mM, aq.) was added, followed by a solution of sodium ascorbate (367 μl, 36.7 μmol, 1 eq., 100 mM, aq.). The mixture was stirred at r.t. under argon for 4 d. Water (10 ml) and 10 % *i*-PrOH/$CHCl_3$ (10 ml) were added, the organic layer was separated and the aqueous layer was extracted again with 10 % *i*-PrOH/$CHCl_3$ (2×10 ml). The combined organic layers were dried with $MgSO_4$ and evaporated under reduced pressure. The residue was purified by preparative HPLC (5-95 % acetonitrile/water over 20 min). The combined pure fractions were evaporated under reduced pressure and then partitioned between $NaHCO_3$ (aq., sat., 50 ml) and 10 % *i*-PrOH/$CHCl_3$ (50 ml). The organic layer was dried with $MgSO_4$ and evaporated under reduced pressure. **97** was obtained as a white amorphous solid (16.5 mg, 25.9 μmol, 70.6 %).

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

^{1}**H NMR** (500 MHz, DMSO d_6) δ / ppm = 15.23 (br s, 1 H, C(=O)O<u>H</u>), 8.66 (s, 1 H, *ortho* to C(=O)OH), 8.23 (d, J = 8.5 Hz, 1 H, N<u>H</u>), 7.90 (d, J = 13.4 Hz, 1 H, *ortho* to F), 7.84 (s, 1 H, C<u>H</u>=CCH_2), 7.56 (d, J = 7.5 Hz, 1 H, *meta* to F), 4.59 (ddd, J = 12.7, 8.4, 6.8 Hz, 1 H, C<u>H</u>NH), 4.31 (t, J = 7.0 Hz, 2 H, CH_2NCH=C), 3.80 - 3.86 (6.9, 4.0 Hz, 1 H, NC<u>H</u>$(CH_2)_2$), 3.34 - 3.37 (m, 1 H, SC<u>H</u>H), 3.32 (br t, J = 4.1 Hz, 4 H, $CH_2CH_2CH_2N(CH_2CH_2)CH_2CH_2$), 3.27 (ddd, J = 11.1, 6.9, 1.4 Hz, 1 H, SCH<u>H</u>), 2.64 (t, J = 7.6 Hz, 2 H, CH=CCH_2), 2.57 (br t, J = 4.7 Hz, 4 H, $CH_2CH_2CH_2N(CH_2)CH_2$), 2.34 - 2.44 (m, 3 H, SCH_2C<u>H</u>H and CH=$CCH_2CH_2CH_2CH_2$), 2.12 (t, J = 7.9 Hz, 1 H, C(=O)C<u>H</u>H), 2.12 (t, J = 7.0 Hz, 1 H, C(=O)CH<u>H</u>), 2.04 (m, 3 H, SCH_2CH<u>H</u> and $C(=O)CH_2CH_2$), 1.64 (quin, J = 7.5 Hz, 2 H, CH=CCH_2CH_2), 1.51 (quin, J = 7.5 Hz, 2 H, CH=$CCH_2CH_2CH_2$), 1.28 - 1.34 (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** (126 MHz, DMSO d_6) δ / ppm = 205.6 (S<u>C</u>(=O)), 176.4 (<u>C</u>(=O)CC(=O)OH), 171.4 (NH<u>C</u>(=O)), 166.0 (<u>C</u>(=O)OH), 153.1 (d, J = 249.3 Hz, *ortho* to F), 148.0 (<u>C</u>H=CC(=O)OH), 146.9 (CH=<u>C</u>CH_2), 145.3 (d, J

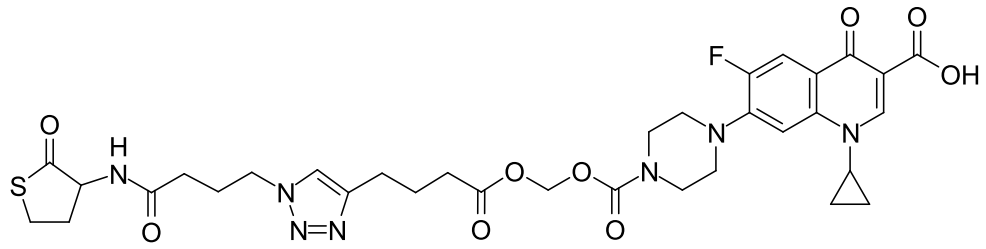
= 10.1 Hz, *ipso* to piperazine), 139.2 (*para* to F), 121.8 (C̲H=CCH$_2$), 118.6 (d, J = 7.7 Hz, *para* to piperazine), 111.0 (d, J = 23.3 Hz, *ortho* to C=O and *ortho* to F), 106.7 (C̲C(=O)OH), 106.4 (d, J = 2.9 Hz, *meta* to C=O and *meta* to F), 58.2 (SC(=O)C̲HNH), 57.4 (CH=CCH$_2$CH$_2$CH$_2$C̲H$_2$N), 52.4 (CH$_2$CH$_2$CH$_2$N(C̲H$_2$)C̲H$_2$), 49.5 (CH$_2$CH$_2$CH$_2$N(CH$_2$C̲H$_2$)CH$_2$CH$_2$), 49.5 (CH$_2$CH$_2$CH$_2$N(CH$_2$CH$_2$)CH$_2$C̲H$_2$), 48.6 (C̲H$_2$NCH=C), 35.9 (NC̲H(CH$_2$)$_2$), 31.9 (NHC(=O)C̲H$_2$), 30.1 (C̲H$_2$CHNH), 26.9 (CH=CCH$_2$C̲H$_2$), 26.8 (SC̲H$_2$), 25.9 (NHC(=O)CH$_2$C̲H$_2$), 25.8 (CH=CCH$_2$CH$_2$C̲H$_2$), 25.0 (CH=CC̲H$_2$), 7.6 (NCH(C̲H$_2$)$_2$)

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

HRMS (ESI$^+$) m/z / Da = 640.2739, [M+H]$^+$ found, [$C_{31}H_{39}FN_7O_5S$]$^+$ requires 640. 2712

The compound has not been reported previously.

0.7 1-Cyclopropyl-6-fluoro-4-oxo-7-(4-((((4-(1-(4-oxo-4-((2-oxotetrahydrothiophen-3-yl)amino)butyl)-1*H*-1,2,3-triazol-4-yl)butanoyl)oxy)methoxy)carbonyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid 99



1-Cyclopropyl-6-fluoro-7-(4-(((hex-5-ynoyloxy)methoxy)carbonyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **98** (203 mg, 0.407 mmol, 1 eq.), 4-azido-*N*-(2-oxotetrahydrothiophen-3-yl)butanamide **96** (92.8 mg, 0.407 mmol, 1 eq.), CuI (40 mg, 0.190 mmol, 0.5 eq.) and DIPEA (0.356 ml, 0.264 mg, 2.04 mmol, 5 eq.) were stirred in CH_2Cl_2 (18.6 ml) at r.t. under Ar for 3 h. The mixture was fitered and the filtrate was dry-loaded onto SiO_2 and purified by column chromatography (SiO_2, 5-10 % MeOH/CH_2Cl_2). **99** was obtained as pale brown/yellow amorphous solid (14.7 mg, 20.2 μmol, 5.0 %).

TLC R_f = 0.40 (5 % CH_2Cl_2/MeOH)

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

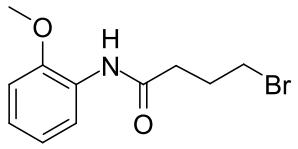
^{1}H NMR (400 MHz, DMSO d_6) δ / ppm = 15.16 (br s, 1 H, C(=O)OH̲), 8.65 (s, 1 H, *ortho* to C(=O)OH), 8.21 (d, J = 8.5 Hz, 1 H, NH̲), 7.89 (d, J = 13.1 Hz, 1 H, *ortho* to F), 7.85 (s, 1 H, CH̲=CCH$_2$), 7.57 (d, J = 7.4 Hz, 1 H, *meta* to F), 5.74 (s, 1 H, OCH̲$_2$O), 4.58 (ddd, J = 12.6, 8.1, 7.2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

^{13}C NMR (101 MHz, DMSO d_6) δ / ppm = 205.5 (S<u>C</u>(=O)), 176.4 (<u>C</u>(=O)CC(=O)OH), 171.8 (<u>C</u>(=O)OCH$_2$O), 171.3 (NH<u>C</u>(=O)), 165.9 (<u>C</u>(=O)OH), 152.8 (d, J = 249.7 Hz, *ipso* to F), 152.9 (O<u>C</u>(=O)N), 148.1 (<u>C</u>H=CC(=O)OH), 146.0 (CH=<u>C</u>CH$_2$), 144.9 (d, J = 9.6 Hz, *ipso* to piperazine), 139.1 (*para* to F), 122.0 (<u>C</u>H=CCH$_2$), 118.9 (d, J = 7.5 Hz, *para* to piperazine), 111.0 (d, J = 23.5 Hz, *ortho* to C=O and *ortho* to F), 106.8 (<u>C</u>C(=O)OH, and *meta* to C=O and *meta* to F), 80.3 (O<u>C</u>H$_2$O), 58.2 (<u>C</u>HNH), 49.1 (C(=O)N(CH$_2$<u>C</u>H$_2$)CH$_2$CH$_2$), 49.1 (C(=O)N(CH$_2$CH$_2$)CH$_2$<u>C</u>H$_2$), 48.6 (C(=O)CH$_2$CH$_2$<u>C</u>H$_2$N), 43.4 (N(<u>C</u>H$_2$)CH$_2$), 43.0 (N(CH$_2$)<u>C</u>H$_2$), 35.9 (N<u>C</u>H(CH$_2$)$_2$), 32.7 (CH=CCH$_2$CH$_2$<u>C</u>H$_2$C(=O)), 31.8 (NH<u>C</u>(=O)<u>C</u>H$_2$), 30.1 (SCH$_2$<u>C</u>H$_2$), 26.8 (S<u>C</u>H$_2$), 25.8 (C(=O)CH$_2$<u>C</u>H$_2$CH$_2$N), 24.2 (CH=C<u>C</u>H$_2$CH$_2$CH$_2$C(=O)), 24.0 (CH=CCH$_2$<u>C</u>H$_2$CH$_2$C(=O)), 7.6 (NCH(<u>C</u>H$_2$)$_2$)

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

The compound has not been reported previously.

0.8 4-Bromo-*N*-(2-methoxyphenyl)butanamide 101



2-Methoxyaniline **100** (9.12 ml, 10.0 g, 81.2 mmol, 1 eq.) and $NaHCO_3$ (8.19 g, 97.4 mmol, 1.2 eq.) were dissolved in water (100 ml) and CH_2Cl_2 (100 ml). The mixture was cooled to 0 °C and 4-bromobutyryl chloride **58** (9.40 ml, 15.1 g, 81.2 mmol, 1 eq.) was added dropwise over 15 min. The mixture was stirred at 0 °C for 1.5 h, then the aqueous layer was removed. The organic layer was dried with $MgSO_4$ and purified by column chromatography (SiO_2, 5-25 % EtOAc/P.E.). The combined pure fractions were dried with $MgSO_4$ and evaporated under reduced pressure. **101** was obtained as an initially colourless liquid which slowly turned blue then black if left out on the bench (11.0 g, 40.6 mmol, 50.0 %).

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

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

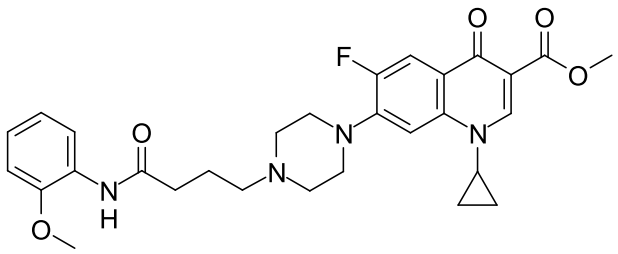
^{1}H NMR (400 MHz, $CDCl_3$ d_1) δ / ppm = 8.32 (dd, J = 8.0, 1.7 Hz, 1 H, *ortho* to NH), 7.85 (br s, 1 H, N<u>H</u>), 7.02 (td, J = 7.9, 1.7 Hz, 1 H, *para* to NH), 6.93 (td, J = 7.7, 1.4 Hz, 1 H, *para* to OCH_3), 6.85 (dd, J = 8.1, 1.5 Hz, 1 H, *ortho* to OCH_3), 3.85 (s, 3 H, C<u>H</u>$_3$), 3.50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

^{13}C NMR (101 MHz, $CDCl_3$ d_1) δ / ppm = 169.4 (<u>C</u>(=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 (<u>C</u>H$_3$), 35.4 (C(=O)<u>C</u>H$_2$), 33.1 (<u>C</u>H$_2$Br), 27.9 (C(=O)CH$_2$<u>C</u>H$_2$)

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

The compound has not been reported previously.

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



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

TLC R_f = 0.40 (10 % $MeOH/CH_2Cl_2$)

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

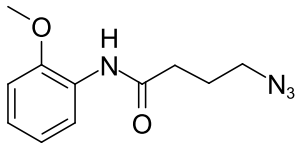
^{1}**H NMR** (400 MHz, $CDCl_3$ d_1) δ / ppm = 8.48 (s, 1 H, *ortho* to $C(=O)OCH_3$), 8.36 (d, J = 7.9 Hz, 1 H, *ortho* to NH), 7.87 - 7.99 (m, 2 H, *ortho* to F and N$\underline{H}$), 7.19 (d, J = 6.5 Hz, 1 H, *meta* to F), 7.01 (t, J = 7.5 Hz, 1 H, *para* to NH), 6.93 (t, J = 7.7 Hz, 1 H, *para* to OCH_3), 6.85 (d, J = 7.9 Hz, 1 H, *ortho* to OCH_3), 3.88 (s, 3 H, $C(=O)OC\underline{H}_3$), 3.85 (s, 3 H, aromatic $OC\underline{H}_3$), 3.41 (tt, J = 6.9, 4.0 Hz, 1 H, $NC\underline{H}(CH_2)_2$), 3.25 (br t, J = 5.0, 5.0 Hz, 4 H, $C(=O)CH_2CH_2CH_2N(CH_2C\underline{H}_2)CH_2C\underline{H}_2$), 2.67 (br t, J = 5.0 Hz, 4 H, $C(=O)CH_2CH_2CH_2N(C\underline{H}_2)C\underline{H}_2$), 2.53 (t, J = 7.0 Hz, 2 H, $C(=O)CH_2CH_2C\underline{H}_2N$), 2.47 (t, J = 7.1 Hz, 2 H, $C(=O)C\underline{H}_2CH_2CH_2N$), 1.97 (quin, J = 6.8 Hz, 2 H, $C(=O)CH_2C\underline{H}_2CH_2N$), 1.25 - 1.33 (m, 2 H, $NCH(C\underline{H}H)_2$), 1.07 - 1.14 (m, 2 H, $NCH(CH\underline{H})_2$)

^{13}**C NMR** (101 MHz, $CDCl_3$ d_1) δ / ppm = 172.9 ($\underline{C}(=O)CC(=O)OCH_3$), 170.8 ($NH\underline{C}(=O)$), 166.2 ($\underline{C}(=O)O CH_3$), 153.3 (d, J = 248.0 Hz, *ipso* to F), 148.2 ($\underline{C}=CC(=O)OCH_3$), 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 $\underline{C}C(=O)OCH_3$), 104.7 (*meta* to C=O and *meta* to F), 57.2 ($CH_2CH_2\underline{C}H_2N$), 55.6 (aromatic $O\underline{C}H_3$), 52.7 ($CH_2CH_2CH_2N(\underline{C}H_2)\underline{C}H_2$), 51.9 ($C(=O)O\underline{C}H_3$), 49.8 ($CH_2CH_2CH_2N(CH_2\underline{C}H_2)CH_2CH_2$), 49.8 ($CH_2CH_2CH_2N(CH_2CH_2)CH_2\underline{C}H_2$), 35.5 ($\underline{C}H_2 CH_2CH_2N$), 34.5 ($N\underline{C}H(CH_2)_2$), 22.3 ($CH_2\underline{C}H_2CH_2N$), 8.0 ($NCH(\underline{C}H_2)_2$)

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

The compound has not been reported previously.

0.10 4-Azido-*N*-(2-methoxyphenyl)butanamide 103



4-Bromo-*N*-(2-methoxyphenyl)butanamide **101** (2.05 g, 7.51 mmol, 1 eq.) and NaN_3 (1.17 g, 18.0 mmol, 2.4 eq.) were refluxed in acetonitrile (100 ml) for 2 h. The mixture was cooled and filtered, and the fitrate was dry-loaded onto SiO_2 and purified by column chromatography using a Combiflash (SiO_2, 8-14 % then hold at 14 % EtOAc/P.E.). **103** was obtained as an initially colourless liquid which slowly turned blue then black if left out on the bench (0.469 g, 2.00 mmol, 26.7 %).

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

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

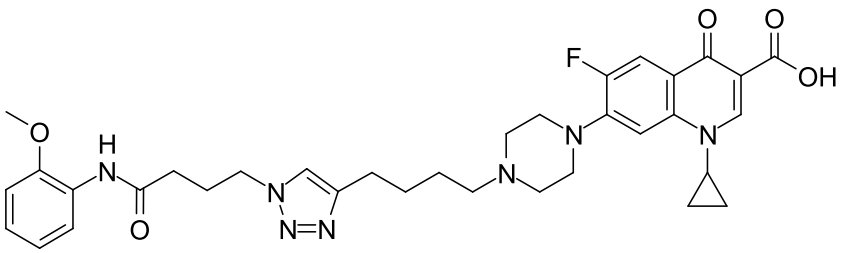
^{1}H NMR (400 MHz, $CDCl_3$ d_1) δ / ppm = 8.32 (dd, J = 7.9, 1.0 Hz, 1 H, *ortho* to NH), 7.86 (br s, 1 H, N$\underline{H}$), 7.00 (td, J = 7.5, 1.5 Hz, 1 H, *para* to NH), 6.90 (td, J = 7.7, 1.1 Hz, 1 H, *para* to OCH_3), 6.83 (dd, J = 8.1, 1.4 Hz, 1 H, *ortho* to OCH_3), 3.81 (s, 3 H, C$\underline{H}_3$),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

^{13}C NMR (101 MHz, $CDCl_3$ d_1) δ / ppm = 169.5 (C(=O)), 147.6 (*ipso* to OCH_3), 127.1 (*ipso* to NH), 123.4 (*para* to NH), 120.5 (*para* to OCH_3), 119.5 (*ortho* to NH and *meta* to OCH_3), 109.6 (*ortho* to OCH_3 and *meta* to NH), 55.2 ($\underline{C}H_3$), 50.3 ($\underline{C}H_2N_3$), 33.9 (C(=O)$\underline{C}H_2$), 24.3 (C(=O)$CH_2\underline{C}H_2$)

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

The data are consistent with the literature.[13]

0.11 1-Cyclopropyl-6-fluoro-7-(4-(4-(1-(4-((2-methoxyphenyl)amino)-4-oxobutyl)-1*H*-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 104



1-Cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **70** (24.1 mg, 58.6 μmol, 1 eq.) and 4-azido-*N*-(2-methoxyphenyl)butanamide **103** (13.7 mg, 58.5 μmol, 1 eq.) were dissolved in water (3 ml), *t*-BuOH (9 ml) and CH_2Cl_2 (9 ml), and the mixture was degassed by bubbling through N_2. A solution of $CuSO_4$ and THPTA (117 μl, 5.85 μmol, 0.1 eq., 50 mM, aq.) was added, followed by a solution

of sodium ascorbate (234 μl, 11.7 μmol, 0.2 eq., 50 mM, aq.). The mixture was stirred at room temperature under argon for 16 h. Water (25 ml), CH_2Cl_2 (25 ml) and MeOH (5 ml) were added and the organic layer was separated off, dry-loaded onto SiO_2 and purified by column chromatography using a Combiflash (SiO_2, 3-23 % $MeOH/CH_2Cl_2$). The combined pure fractions were dried with $MgSO_4$ and evaporated under reduced pressure. **104** was obtained as a clear amorphous solid (14.7 mg, 22.8 μmol, 39.0 %).

TLC R_f = 0.28 (10 % $MeOH/CH_2Cl_2$)

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

^{1}**H NMR** (400 MHz, $CDCl_3$) δ / ppm = 15.05 (br s, 1 H, C(=O)O<u>H</u>), 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<u>H</u>), 7.37 (s, 1 H, C<u>H</u>=CCH_2), 7.35 (d, J = 7.2 Hz, 1 H, *meta* to F), 7.04 (td, J = 7.7, 1.7 Hz, 1 H, *para* to NH), 6.95 (td, J = 7.8, 1.5 Hz, 1 H, *para* to OCH_3), 6.88 (dd, J = 8.1, 1.4 Hz, 1 H, *ortho* to OCH_3), 4.47 (t, J = 6.7 Hz, 2 H, C(=O)CH_2CH_2C<u>H</u>$_2$N), 3.88 (s, 3 H, C<u>H</u>$_3$), 3.54 (tt, J = 6.9, 4.0 Hz, 1 H, NC<u>H</u>$(CH_2)_2$), 3.35 (br t, J = 4.7 Hz, 4 H, CH=$CCH_2CH_2CH_2CH_2$N$(CH_2C$<u>H</u>$_2)CH_2C$<u>H</u>$_2$), 2.76 (t, J = 7.5 Hz, 2 H, CH=C<u>C</u>H_2), 2.66 (t, J = 4.7 Hz, 4 H, CH=$CCH_2CH_2CH_2CH_2$N$(C$<u>H</u>$_2)C$<u>H</u>$_2$), 2.47 (t, J = 7.3 Hz, 2 H, CH=$CCH_2CH_2CH_2C$<u>H</u>$_2$N), 2.44 (t, J = 6.8 Hz, 2 H, C(=O)C<u>H</u>$_2CH_2CH_2$N), 2.32 (quin, J = 6.7 Hz, 2 H, C(=O)CH_2C<u>H</u>$_2CH_2$N), 1.75 (quin, J = 7.6 Hz, 2 H, CH=CCH_2C<u>H</u>$_2CH_2CH_2$N), 1.61 (quin, J = 7.5 Hz, 2 H, CH=CCH_2CH_2C<u>H</u>$_2CH_2$N), 1.35 - 1.42 (m, 2 H, NCH(C<u>H</u>H)$_2$), 1.17 - 1.22 (m, 2 H, NCH(CH<u>H</u>)$_2$)

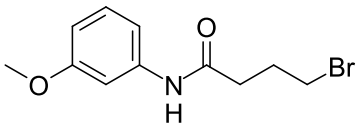
^{13}**C NMR** (101 MHz, $CDCl_3$) δ / ppm = 177.1 (<u>C</u>(=O)CC(=O)OH), 169.5 (NH<u>C</u>(=O)), 167.0 (<u>C</u>(=O)OH), 153.7 (d, J = 251.4 Hz, *ipso* to F), 148.1 (CH=<u>C</u>CH_2), 147.8 (*ipso* to OCH_3), 147.3 (<u>C</u>=CC(=O)OH), 145.9 (d, J = 10.4 Hz, *ipso* to piperazine), 139.1 (*para* to F), 127.3 (*ipso* to NH), 123.9 (*para* to NH), 121.0 (*para* to OCH_3), 120.9 (<u>C</u>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 (<u>C</u>C(=O)OH), 104.7 (*meta* to C=O and *meta* to F), 58.1 (CH=$CCH_2CH_2CH_2$<u>C</u>H_2N), 55.6 (<u>C</u>H_3), 52.8 (CH=$CCH_2CH_2CH_2CH_2$N(<u>C</u>H_2)<u>C</u>H_2), 49.8 (CH=$CCH_2CH_2CH_2CH_2$N$(CH_2$<u>C</u>$H_2)CH_2CH_2$), 49.8 (CH=$CCH_2CH_2CH_2CH_2$N$(CH_2CH_2)CH_2$<u>C</u>H_2), 49.1 (C(=O)CH_2CH_2<u>C</u>H_2N), 35.2 (N<u>C</u>H$(CH_2)_2$), 33.8 (C(=O)<u>C</u>$H_2CH_2CH_2$N), 27.3 (CH=CCH_2<u>C</u>$H_2CH_2CH_2$N), 26.4 (CH=CCH_2CH_2<u>C</u>H_2CH_2N), 26.0 (C(=O)CH_2<u>C</u>H_2CH_2N), 25.5 (CH=C<u>C</u>$H_2CH_2CH_2CH_2$N), 8.2 (NCH(<u>C</u>$H_2)_2$)

^{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.

0.12 4-Bromo-*N*-(3-methoxyphenyl)butanamide 106



3-Methoxyaniline **105** (3.04 ml, 3.33 g, 27.1 mmol, 1 eq.) and $NaHCO_3$ (2.73 g, 32.5 mmol, 1.2 eq.) were dissolved in water (30 ml) and CH_2Cl_2 (30 ml). The mixture was cooled to 0 °C and 4-bromobutyryl chloride **58** (3.13 ml, 5.03 g, 27.1 mmol, 1 eq.) was added dropwise over 5 min. The mixture was stirred at 0 °C for 1 h, then the aqueous layer was removed. The organic layer was dry-loaded onto SiO_2 and purified by column chromatography using a Combiflash (SiO_2, 0-100 % EtOAc/P.E.). The combined pure fractions were dried with $MgSO_4$ and evaporated under reduced pressure. **106** was obtained as a pale pink amorphous solid (3.66 g, 13.5 mmol, 49.6 %).

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

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

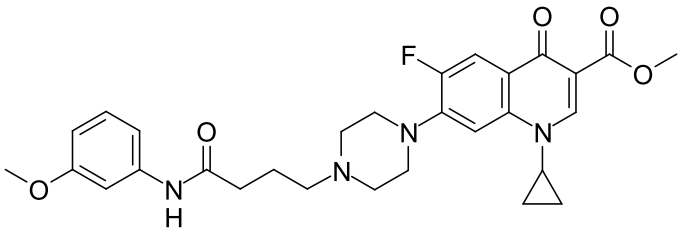
^{1}H NMR (400 MHz, $CDCl_3$ d_1) δ / ppm = 8.45 (s, 1 H, N<u>H</u>), 7.27 (t, J = 2.2 Hz, 1 H, *ortho* to OCH_3 and *ortho* to NH), 7.14 (t, J = 8.1 Hz, 1 H, *meta* to OCH_3 and *meta* to NH), 7.02 (d, J = 8.3 Hz, 1 H, *para* to OCH_3), 6.62 (dd, J = 8.2, 2.1 Hz, 1 H, *para* to NH), 3.71 (s, 3 H, C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

^{13}C NMR (101 MHz, $CDCl_3$ d_1) δ / ppm = 170.3 (<u>C</u>(=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 (<u>C</u>H$_3$), 35.3 (C(=O)<u>C</u>H$_2$), 33.2 (<u>C</u>H$_2$Br), 28.0 (C(=O)CH$_2$<u>C</u>H$_2$)

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

The compound has not been reported previously.

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



Methyl 1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate **92** (500 mg, 1.45 mmol, 1 eq.), 4-bromo-*N*-(3-methoxyphenyl)butanamide **106** (788 mg, 2.90 mmol, 2 eq.), DIPEA (1.28 ml, 950 mg, 7.35 mmol, 5 eq.), NaI (275 mg, 1.83 mmol, 1.3 eq.) and acetonitrile (10 ml) were stirred in a microwave reactor at 100 °C for 4 h. The mixture was evaporated under reduced pressure and partitioned between CH_2Cl_2 (50 ml) and water (50 ml). The organic layer was separated off and the aqueous layer was extracted again with CH_2Cl_2 (50 ml). The combined organic layers were dried with $MgSO_4$ and purified by column chromatography (SiO_2, 0-4 % MeOH/CH_2Cl_2). The combined pure fractions were dried with $MgSO_4$ and evaporated under reduced pressure. **107** was obtained as an off-white amorphous solid (81.7 mg, 0.152 mmol, 10.5 %).

TLC R_f = 0.38 (10 % MeOH/CH_2Cl_2)

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

^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 8.56 (s, 1 H, *ortho* to C(=O)OCH_3), 8.06 (d, J = 13.3 Hz, 1 H, *ortho* to F), 8.02 (br s, 1 H, N$\underline{H}$), 7.34 (t, J = 1.7 Hz, 1 H, *ortho* to OCH_3 and *ortho* to NH), 7.25 (d, J = 7.0 Hz, 1 H, *meta* to F), 7.20 (t, J = 8.2 Hz, 1 H, *meta* to OCH_3 and *meta* to NH), 6.98 (dd, J = 7.8, 1.7 Hz, 1 H, *para* to OCH_3), 6.65 (dd, J = 8.2, 2.1 Hz, 1 H, *para* to NH), 3.93 (s, 3 H, C(=O)O$C\underline{H}_3$), 3.80 (s, 3 H, aromatic O$C\underline{H}_3$), 3.42 (tt, J = 6.8, 3.7 Hz, 1 H, N$C\underline{H}(CH_2)_2$), 3.31 (br t, J = 4.3 Hz, 4 H, $C(=O)CH_2CH_2CH_2N(CH_2C\underline{H}_2)CH_2C\underline{H}_2$), 2.73 (br t, J = 4.5 Hz, 4 H, $C(=O)CH_2CH_2CH_2N(C\underline{H}_2)C\underline{H}_2$), 2.58 (t, J = 6.5 Hz, 2 H, $C(=O)CH_2CH_2C\underline{H}_2N$), 2.48 (t, J = 6.8 Hz, 2 H, $C(=O)C\underline{H}_2CH_2CH_2N$), 2.00 (quin, J = 6.8 Hz, 2 H, $C(=O)CH_2C\underline{H}_2CH_2N$), 1.29 - 1.36 (m, 2 H, $NCH(C\underline{H}H)_2$), 1.11 - 1.17 (m, 2 H, $NCH(CH\underline{H})_2$)

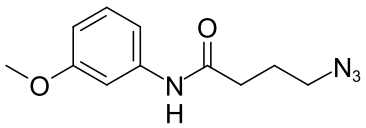
^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 173.1 ($\underline{C}(=O)CC(=O)OCH_3$), 170.9 ($NH\underline{C}(=O)$), 166.3 ($\underline{C}(=O)O CH_3$), 160.1 (*ipso* to OCH_3), 153.3 (d, J = 250.1 Hz, *ipso* to F), 148.4 ($\underline{C}=CC(=O)OCH_3$), 144.1 (d, J = 10.1 Hz, *ipso* to piperazine), 139.4 (*ipso* 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 ($CH_2CH_2\underline{C}H_2N$), 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 ($\underline{C}H_2CH_2CH_2N$), 34.6 ($N\underline{C}H(CH_2)_2$), 21.7 ($CH_2\underline{C}H_2CH_2N$), 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.

0.14 4-Azido-*N*-(3-methoxyphenyl)butanamide 108



4-Bromo-*N*-(3-methoxyphenyl)butanamide **106** (2.05 g, 7.51 mmol, 1 eq.) and NaN_3 (1.17 g, 18.0 mmol, 2.4 eq.) were refluxed in acetonitrile (100 ml) for 7 h. The mixture was cooled and filtered, and the fitrate was dry-loaded onto SiO_2 and purified by column chromatography using a Combiflash (SiO_2, 0-100 % EtOAc/P.E.). The combined pure fractions were dried with $MgSO_4$ and evaporated under reduced pressure. **108** was obtained as an straw-coloured liquid (0.294 g, 1.25 mmol, 16.7 %).

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

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

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

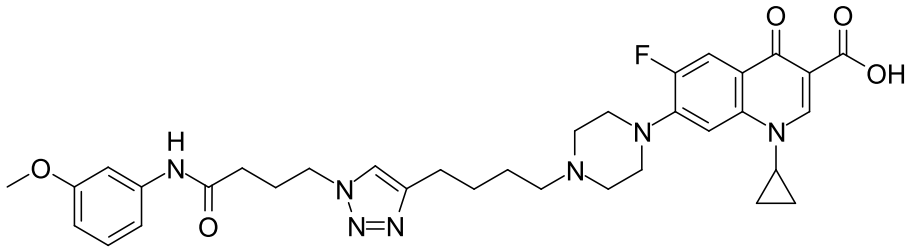
2.39 (t, J = 7.4 Hz, 2 H, C(=O)C$\underline{H}_2$), 1.91 (quin, J = 7.0 Hz, 2 H, C(=O)CH$_2$C$\underline{H}_2$)

^{13}C NMR (101 MHz, MeOD) δ / ppm = 170.8 (C(=O)), 159.6 (*ipso* to OCH_3), 138.9 (*ipso* to NH), 129.2 (*meta* to OCH_3 and *meta* to NH), 112.3 (*para* to OCH_3), 109.5 (*para* to NH), 106.0 (*ortho* to OCH_3 and *ortho* to NH), 54.8 ($\underline{C}H_3$), 50.4 ($\underline{C}H_2N_3$), 33.6 (C(=O)$\underline{C}H_2$), 24.4 (C(=O)CH$_2\underline{C}H_2$)

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

The compound has not been reported previously.

0.15 1-Cyclopropyl-6-fluoro-7-(4-(4-(1-(4-((3-methoxyphenyl)amino)-4-oxobutyl)-1*H*-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 109



1-Cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **70** (24.1 mg, 58.6 μmol, 1 eq.) and 4-azido-*N*-(3-methoxyphenyl)butanamide **108** (13.7 mg, 58.5 μmol, 1 eq.) were dissolved in water (1 ml), *t*-BuOH (9 ml) and CH_2Cl_2 (10 ml), and the mixture was degassed by bubbling through N_2. A solution of $CuSO_4$ and THPTA (58.5 μl, 5.85 μmol, 0.1 eq. 100 mM, aq.) was added, followed by a solution of sodium ascorbate (117 μl, 11.7 μmol, 0.2 eq., 100 mM, aq.). The mixture was stirred at room temperature under argon for 2 h, then the solvent was removed under reduced pressure. The resudue was partitioned between water (15 ml) and CH_2Cl_2 (15 ml), and the aqueous layer was extracted a further four times with CH_2Cl_2 (4×15 ml). The combined organic layers were dried with $MgSO_4$, dry-loaded onto SiO_2 and purified by column chromatography (SiO_2, 0-10 % MeOH/CH_2Cl_2). The combined pure fractions were dried with $MgSO_4$ and evaporated under reduced pressure. **109** was obtained as a clear amorphous solid (1.9 mg, 2.9 μmol, 5.0 %).

TLC R_f = 0.22 (10 % MeOH/CH_2Cl_2)

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

^{1}H NMR (400 MHz, DMSO d_6) δ / ppm = 15.23 (br s, 1 H, C(=O)O$\underline{H}$), 9.89 (s, 1 H, N$\underline{H}$), 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$\underline{H}$=CCH$_2$), 7.55 (d, J = 7.6 Hz, 1 H, *meta* to F), 7.27 (t, J = 2.1 Hz, 1 H, *ortho* to C=O and *ortho* to F), 7.16 (t, J = 8.1 Hz, 1 H, *meta* to OCH_3 and *meta* to NH), 7.08 (d, J = 7.8 Hz, 1 H, *para* to OCH_3), 6.59 (ddd, J = 8.1, 2.4, 0.7 Hz, 1 H, *para* to NH), 4.36 (t, J = 6.9 Hz, 2 H, C(=O)CH$_2$CH$_2$C$\underline{H}_2$N), 3.81 (tt, J = 6.7, 4.0 Hz, 1 H, NC$\underline{H}$(CH$_2$)$_2$), 3.70 (s, 3 H, C$\underline{H}_3$), 3.28 - 3.32 (m, 4 H, CH=CCH$_2$CH$_2$CH$_2$CH$_2$N(CH$_2$C$\underline{H}_2$)CH$_2$C$\underline{H}_2$), 2.64 (t, J = 7.5 Hz, 2 H, CH=C$\underline{C}$H$_2$), 2.56 (m, J = 4.2, 4.2 Hz, 4 H, CH=CCH$_2$CH$_2$CH$_2$CH$_2$N(C$\underline{H}_2$)C$\underline{H}_2$), 2.38 (t, J = 7.3 Hz, 2 H, CH=CCH$_2$CH$_2$CH$_2$C$\underline{H}_2$N), 2.30 (t, J = 7.4 Hz, 2 H, C(=O)C$\underline{H}_2$CH$_2$CH$_2$N), 2.10 (quin, J = 7.1 Hz, 2 H, C(=O)CH$_2$C$\underline{H}_2$CH$_2$N), 1.64 (quin, J = 7.5 Hz, 2 H, CH=CCH$_2$C$\underline{H}_2$CH$_2$CH$_2$N), 1.51 (quin, J = 7.2 Hz, 2 H,

CH=CCH$_2$CH$_2$C$\underline{\text{H}}_2$CH$_2$N), 1.27 - 1.33 (m, 2 H, NCH(C$\underline{\text{H}}$H)$_2$), 1.15 - 1.20 (m, 2 H, NCH(CH$\underline{\text{H}}$)$_2$)

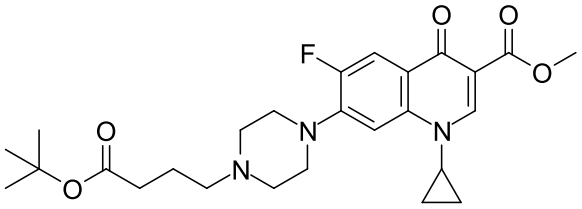
^{13}C NMR (101 MHz, DMSO d$_6$) δ / ppm = 176.3 ($\underline{\text{C}}$(=O)CC(=O)OH), 170.1 (NH$\underline{\text{C}}$(=O)), 165.9 ($\underline{\text{C}}$(=O)OH), 159.4 (*ipso* to OCH$_3$), 153.0 (d, J = 248.6 Hz, *ipso* to F), 148.0 (CH=$\underline{\text{C}}$CH$_2$), 146.9 ($\underline{\text{C}}$=CC(=O)OH), 145.2 (d, J = 10.7 Hz, *ipso* to piperazine), 140.3 (*para* to F), 139.2 (*ipso* to NH), 129.4 (*meta* to OCH$_3$ and *meta* to NH), 121.7 ($\underline{\text{C}}$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 ($\underline{\text{C}}$C(=O)OH), 106.3 (*meta* to C=O and *meta* to F), 104.8 (*ortho* to OCH$_3$ and *ortho* to NH), 57.3 (CH=CCH$_2$CH$_2$CH$_2\underline{\text{C}}$H$_2$N), 54.9 ($\underline{\text{C}}$H$_3$), 52.4 (CH=CCH$_2$CH$_2$CH$_2$CH$_2$N($\underline{\text{C}}$H$_2$)$\underline{\text{C}}$H$_2$), 49.5 (CH=CCH$_2$CH$_2$CH$_2$CH$_2$N(CH$_2\underline{\text{C}}$H$_2$)CH$_2$CH$_2$), 49.4 (CH=CCH$_2$CH$_2$CH$_2$CH$_2$N(CH$_2$CH$_2$)CH$_2\underline{\text{C}}$H$_2$), 48.7 (C(=O)CH$_2$CH$_2\underline{\text{C}}$H$_2$N), 35.8 (N$\underline{\text{C}}$H(CH$_2$)$_2$), 32.9 (C(=O)$\underline{\text{C}}$H$_2$CH$_2$CH$_2$N), 26.8 (CH=CCH$_2\underline{\text{C}}$H$_2$CH$_2$CH$_2$N), 25.7 (CH=CCH$_2$CH$_2\underline{\text{C}}$H$_2$CH$_2$N), 25.5 (C(=O)CH$_2\underline{\text{C}}$H$_2$CH$_2$N), 24.9 (CH=C$\underline{\text{C}}$H$_2$CH$_2$CH$_2$CH$_2$N), 7.6 (NCH($\underline{\text{C}}$H$_2$)$_2$)

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

HRMS (ESI$^+$) m/z / Da = 646.3159, [M+H]$^+$ found, [C$_{34}$H$_{41}$FN$_7$O$_5$]$^+$ requires 646.3153

The compound has not been reported previously.

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



Methyl 1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate **92** (200 mg, 0.579 mmol, 1 eq.), *tert*-butyl 4-bromobutanoate **135** (103 μl, 130 mg, 0.581 mmol, 1 eq.), NaI (86.9 mg, 0.580 mmol, 1 eq.), TEA (316 μl, 229 mg, 2.27 mmol, 4 eq.) and acetonitrile (10 ml) were stirred in a microwave reactor at 100 °C for 8 h. A second portion of *tert*-butyl 4-bromobutanoate **150** (103 μl, 130 mg, 0.581 mmol, 1 eq.) was added, and the mixture was stirred in the microwave reactor at 100 °C for a further 8 h. The mixture was then dry-loaded onto SiO$_2$ and purified by column chromatography (SiO$_2$, 0-4 % MeOH/CH$_2$Cl$_2$). **136** was obtained as a white amorphous solid (141 mg, 0.289 mmol, 49.9 %).

TLC R_f = 0.12 (4 % MeOH/CH$_2$Cl$_2$)

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$\underline{\text{H}}_3$), 3.40 (tt, J = 7.2, 3.6 Hz, 1 H, NC$\underline{\text{H}}$(CH$_2$)$_2$), 3.22 (t, J = 4.3 Hz, 4 H, CH$_2$N(CH$_2$C$\underline{\text{H}}_2$)CH$_2$C$\underline{\text{H}}_2$), 2.63 (t, J = 4.4 Hz, 4 H, CH$_2$N(C$\underline{\text{H}}_2$)C$\underline{\text{H}}_2$), 2.41 (t, J=7.3 Hz, 2 H, C$\underline{\text{H}}_2$N(CH$_2$)CH$_2$), 2.25 (t, J=7.4 Hz, 2 H, C$\underline{\text{H}}_2$CH$_2$CH$_2$N(CH$_2$)CH$_2$), 1.78 (quin, J=7.3 Hz, 2 H, C$\underline{\text{H}}_2$CH$_2$N(CH$_2$)CH$_2$), 1.41 (s, 9 H, C((C$\underline{\text{H}}$)$_3$)$_3$), 1.24 (m, 2 H, NCH(C$\underline{\text{H}}$H)$_2$), 1.09 (m, 2 H, NCH(CH$\underline{\text{H}}$)$_2$)

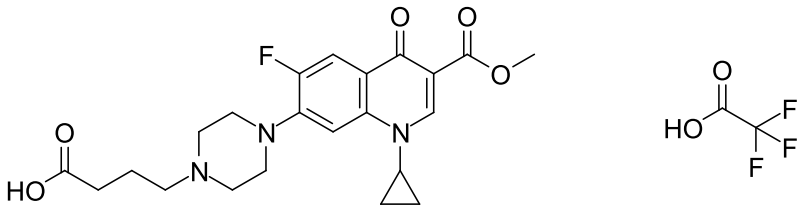
^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 172.7 ($\underline{C}$(=O)CC(=O)OCH_3), 172.6 ($\underline{C}$(=O)$OC(CH_3)_3$), 165.9 ($\underline{C}$(=O)OCH_3), 153.1 (d, J = 249.7 Hz, *ipso* to F), 148.1 ($\underline{C}$=CC(=O)OCH_3), 144.3 (d, J = 10.4 Hz, *ipso* to piperazine), 137.7 (*para* to F), 122.5 (d, J = 6.9 Hz, *para* to piperazine) 112.6 (d, J = 22.5 Hz, *ortho* to C=O and *ortho* to F), 109.5 ($\underline{C}$C(=O)OCH_3) 104.7 (*meta* to C=O and *meta* to F), 80.0 ($\underline{C}(CH_3)_3$), 57.4 (C(=O)$CH_2CH_2\underline{C}H_2$N), 52.7 (C(=O)$CH_2CH_2CH_2$N($\underline{C}H_2$)$\underline{C}H_2$), 51.7 ($\underline{C}H_3$), 49.7 (C(=O)$CH_2CH_2CH_2$N($CH_2\underline{C}H_2$)CH_2CH_2), 49.7 (C(=O)$CH_2CH_2CH_2$N(CH_2CH_2)$CH_2\underline{C}H_2$), 34.4 (N$\underline{C}$H$(CH_2)_2$), 33.2 (C(=O)$\underline{C}H_2$), 28.0 ($C(\underline{C}H_3)_3$), 22.0 (C(=O)$CH_2\underline{C}H_2$), 7.9 (NCH($\underline{C}H_2)_2$)

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

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

The compound has not been reported previously.

0.17 4-(4-(1-Cyclopropyl-6-fluoro-3-(methoxycarbonyl)-4-oxo-1,4-dihydroquinolin-7-yl)piperazin-1-yl)butanoic acid trifluoroacetate 137



Methyl 7-(4-(4-(*tert*-butoxy)-4-oxobutyl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate **136** (20 mg, 41.0 μmol) and TFA (0.2 ml) were stirred in CH_2Cl_2 (1.8 ml) at r.t. for 16 h then evaporated under reduced pressure. **137** was obtained as a white solid (21.4 mg, 39.2 μmol, 95.6 %).

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

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

^{1}H NMR (400 MHz, DMSO d_6) δ / ppm = 8.47 (s, 1 H, *ortho* to C(=O)OH), 7.80 (d, J = 13.2 Hz, 1 H, *ortho* to F), 7.47 (d, J = 7.4 Hz, 1 H, *meta* to F), 3.73 (s, 3 H, C$\underline{H}_3$), 3.66 (tt, J = 7.2, 3.7 Hz, 1 H, NC$\underline{H}(CH_2)_2$), 3.30 - 3.54 (br s, 8 H, CH_2N(C$\underline{H}_2$)C$\underline{H}_2$ and CH_2N(CH_2C$\underline{H}_2$)CH_2C$\underline{H}_2$) 3.13 - 3.22 (m, 2 H, C$\underline{H}_2$N(CH_2)CH_2), 2.36 (t, J = 7.1 Hz, 2 H, C$\underline{H}_2CH_2CH_2$N(CH_2)CH_2), 1.87 - 1.98 (m, 2 H, C$\underline{H}_2CH_2$N(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$\underline{H}$)$_2$)

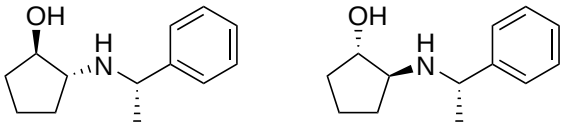
^{13}C NMR (101 MHz, DMSO d_6) δ / ppm = 173.5 ($CH_2\underline{C}$(=O)OH), 171.6 ($\underline{C}$(=O)CC(=O)OCH_3), 164.9 ($\underline{C}$(=O)OCH_3), 158.2 (q, J = 31.5 Hz, $CF_3\underline{C}$(=O)OH), 152.5 (d, J = 247.6 Hz, *ipso* to F), 148.5 ($\underline{C}$=CC(=O)OH), 142.3 (d, J = 10.7 Hz, *ipso* 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)$CH_2CH_2\underline{C}H_2$N), 51.4 ($\underline{C}H_3$), 50.8 (C(=O)$CH_2CH_2CH_2$N($\underline{C}H_2$)$\underline{C}H_2$), 46.7 (C(=O)$CH_2CH_2CH_2$N($CH_2\underline{C}H_2$)CH_2CH_2), 46.7 (C(=O)$CH_2CH_2CH_2$N(CH_2CH_2)$CH_2\underline{C}H_2$), 34.9 (N$\underline{C}$H$(CH_2)_2$), 30.6 (C(=O)$\underline{C}H_2$), 19.1 (C(=O)$CH_2\underline{C}H_2$), 7.6 (NCH($\underline{C}H_2)_2$)

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

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

The compound has not been reported previously.

0.18 (1*R*,2*R*)-2-(((*S*)-1-Phenylethyl)amino)cyclopentan-1-ol 113 and (1*S*,2*S*)-2-(((*S*)-1-phenylethyl)amino)cyclopentan-1-ol 112



113 **112**

(*S*)-1-Phenylethan-1-amine **111** (7.85 ml, 7.38 g, 60.9 mmol, 1 eq.) was dissolved in CH_2Cl_2 (50 ml) and stirred rapidly at 0 °C. A solution of $AlMe_3$ (31 ml, 2.0 M in heptane, 60.9 mmol) was added dropwise and the mixture was stirred at 0 °C for 1 h. A solution of cyclohexene oxide **110** (5.71 ml, 5.50 g, 65.4 mmol, 1.1 eq.) in CH_2Cl_2 (50 ml) was then added dropwise, and the mixture was stirred at 0 °C for a further 3 h, followed by 48 h at r.t.. The mixture was cooled to 0 °C and NaF (11 g, 262 mmol, 4.3 eq.) was added portionwise, followed by water (7.00 ml, 7.00 g, 389 mmol, 6.4 eq.) and CH_2Cl_2 (50 ml). The suspension was allowed to warm to r.t. and stirred for 1 h, then filtered through Celite and washed with CH_2Cl_2 (500 ml). The filtrate was dried with K_2CO_3, concentrated under reduced pressure and purified by column chromatography (SiO_2, 20:5:1 hexane:EtOAc:TEA). **113** was obtained as a pale yellow oil (4.08 g, 19.9 mmol, 32.6 %). **112** was obtained as pale yellow crystals (4.48 g, 21.8 mmol, 35.8 %).

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

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

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

^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 7.28 - 7.38 (m, 4 H, *ortho* and *meta* to $CHCH_3$), 7.21 - 7.28 (m, 1 H, *para* to $CHCH_3$), 3.83 (q, J = 6.6 Hz, 1 H, C$\underline{H}CH_3$), 3.78 (q, J = 7.0 Hz, 1 H, C$\underline{H}$OH), 2.62 (dt, J = 8.2, 7.2 Hz, 1 H, C$\underline{H}$NH), 1.97 (quin, J = 6.7 Hz, 1 H, C$\underline{H}_2$CHNH), 1.90 (quin, J = 6.9 Hz, 1 H, C$\underline{H}_2$CHOH), 1.56 - 1.68 (m, C$\underline{H}_2CH_2$CHOH), 1.43 (dq, J = 12.5, 8.0 Hz, 1 H, C$\underline{H}_2$CHOH), 1.37 (d, J = 6.6 Hz, 3 H, C$\underline{H}_3$), 1.25 - 1.36 (m, 1 H, C$\underline{H}_2$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 ($\underline{C}$HOH), 63.38 ($\underline{C}$HNH), 56.20 ($\underline{C}$HCH$_3$), 31.74 ($\underline{C}H_2$CHOH), 29.22 ($\underline{C}H_2$CHNH), 24.58 ($\underline{C}H_3$), 19.57 ($\underline{C}H_2CH_2$CHOH)

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

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

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

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

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

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

^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 7.28 - 7.34 (m, 4 H, *ortho* and *meta* to $CHCH_3$), 7.20 - 7.26 (m, 1 H, *para* to $CHCH_3$), 3.86 (q, J = 6.6 Hz, 1 H, C<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, 4.9 Hz, 1 H, C<u>H</u>HCHNH), 1.55 - 1.68 (m, 2 H, C<u>H</u>$_2$$CH_2$CHOH), 1.47 - 1.55 (m, 1 H, CH<u>H</u>CHOH), 1.36 (d, J = 6.6 Hz, 3 H, C<u>H</u>$_3$), 1.12 (dq, J = 12.7, 8.1 Hz, 1 H, CH<u>H</u>CHNH)

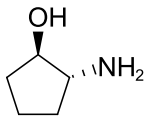
^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 145.61 (*ipso* to $CHCH_3$), 128.08 (*meta* to $CHCH_3$), 126.61 (*para* to $CHCH_3$), 126.33 (*ortho* to $CHCH_3$), 77.43 (<u>C</u>HOH), 64.45 (<u>C</u>HNH), 56.62 (<u>C</u>HCH_3), 32.01 (<u>C</u>H_2CHOH), 30.56 (<u>C</u>H_2CHNH), 23.30 (<u>C</u>H_3), 20.06 (<u>C</u>$H_2$$CH_2$CHOH)

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

$[\alpha]_D^{20}$ / $°10^{-1}cm^2g^{-1}$ = -23.9, lit. = -22.1 (c / g(100 ml)$^{-1}$ = 0.96 , MeOH)

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

0.19 (1*R*,2*R*)-2-Aminocyclopentan-1-ol 115



(1*R*,2*R*)-2-(((*S*)-1-Phenylethyl)amino)cyclopentan-1-ol **113** (3.90 g, 19.0 mmol, 1 eq.), $Pd(OH)_2$ (20 wt. % on C, moistened with 50 wt. % water, 1 g, 0.712 mmol, 0.04 eq.) and MeOH (50 ml) were stirred in a Paar hydrogenator at r.t. and 3 atm for 2 days. The mixture was then filtered through Celite and evaporated under reduced pressure. **115** was obtained as a yellow oil (1.92 g, 19.0 mmol, 100 %).

TLC R_f = 0.10 (10 % MeOH/CH_2Cl_2)

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

^{1}H NMR (400 MHz, MeOD) δ / ppm = 3.77 (ddd, J = 6.6, 6.2, 5.6, 1 H, C<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, 5.6 Hz, 1 H, C<u>H</u>HCHNH_2), 1.97 (ddt, J = 13.0, 8.7, 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 Hz, 1 H, CH<u>H</u>CHOH), 1.37 (ddt, J = 13.0, 8.3, 7.8 Hz, 1 H, CH<u>H</u>CHNH_2)

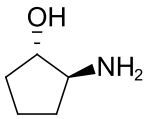
^{13}**C NMR** (101 MHz, MeOD) δ / ppm = 80.7 (C$\underline{\text{H}}$OH), 60.8 (C$\underline{\text{H}}$NH$_2$), 33.2 (C$\underline{\text{H}}_2$CHOH), 32.1 (C$\underline{\text{H}}_2$CHNH$_2$), 21.2 (C$\underline{\text{H}}_2$CH$_2$CHOH)

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

$[\boldsymbol{\alpha}]_D^{20}$ / $^\circ 10^{-1}$cm^{2}g^{-1} = -30.9, lit. = -32.9 (c / g(100 ml)$^{-1}$ = 1.5 , EtOH)

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

0.20 (1*S*,2*S*)-2-Aminocyclopentan-1-ol 114



(1*S*,2*S*)-2-(((*S*)-1-Phenylethyl)amino)cyclopentan-1-ol **112** (3.00 g, 14.6 mmol, 1 eq.), Pd(OH)$_2$ (20 wt. % on C, moistened with 50 wt. % water, 0.5 g, 0.356 mmol, 0.025 eq.) and MeOH (50 ml) were stirred in a Paar hydrogenator at r.t. and 2.5 atm for 2 days. The mixture was then filtered through Celite and evaporated under reduced pressure. **114** was obtained as a yellow oil (1.48 g, 14.6 mmol, 100 %).

TLC R_f = 0.10 (10 % MeOH/CH_2Cl_2)

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

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

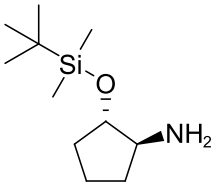
^{13}**C NMR** (101 MHz, MeOD) δ / ppm = 80.6 (C$\underline{\text{H}}$OH), 60.7 (C$\underline{\text{H}}$NH$_2$), 33.2 (C$\underline{\text{H}}_2$CHOH), 32.2 (C$\underline{\text{H}}_2$CHNH$_2$), 21.2 (C$\underline{\text{H}}_2$CH$_2$CHOH)

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

$[\boldsymbol{\alpha}]_D^{20}$ / $^\circ 10^{-1}$cm^{2}g^{-1} = 33.4, lit. = 29.7 (c / g(100 ml)$^{-1}$ = 0.5, EtOH)

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

0.21 (1*S*,2*S*)-2-((*tert*-Butyldimethylsilyl)oxy)cyclopentan-1-amine 125



(1*S*,2*S*)-2-Aminocyclopentan-1-ol **114** (0.480 g, 4.75 mmol) was stirred in dry CH_2Cl_2 (20 ml) under N_2 at 0 °C. TEA (3.14 ml, 2.28 g, 22.5 mmol, 5 eq.) was added dropwise, followed by TBDMSOTf (3 ml, 3.45 g, 13.1 mmol, 3 eq.) dropwise. The reaction was allowed to reach r.t. and stirred for 1 h. The reaction was quenched with NH_4Cl, diluted with CH_2Cl_2 (20 ml) and washed with water (20 ml). The organic phase was dried with Na_2SO_4, concentrated under reduced pressure and purified by column chromatography (SiO_2, 4 % MeOH/CH_2Cl_2). **125** was obtained as a yellow oil (1.00 g, 4.64 mmol, 97.7 %).

TLC R_f = 0.23 (10 % MeOH/CH_2Cl_2)

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

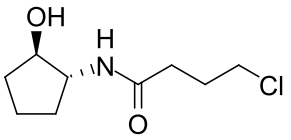
^{1}**H NMR** (400 MHz, $CDCl_3$) δ / ppm = 4.13 (q, J = 5.8 Hz, 1 H, C<u>H</u>OSi), 3.31 (td, J = 7.1, 5.2 Hz, 1 H, C<u>H</u>NH_2), 2.09 - 2.19 (m, 1 H, C<u>H</u>HCHCNH_2), 1.97 (ddq, J = 8.8, 7.0, 6.0 Hz, 1 H, C<u>H</u>HCHOSi), 1.74 - 1.86 (m, 2 H, C<u>H</u>$_2$$CH_2$CHOSi), 1.64 - 1.74 (m, 1 H, CH<u>H</u>CHOSi), 1.58 (ddt, J = 13.2, 9.1, 6.0 Hz, 1 H, CH<u>H</u>CHNH_2), 0.88 (s, 9 H, C(C<u>H</u>$_3$)$_3$), 0.09 (s, 3 H, SiC<u>H</u>$_3$), 0.07 (s, 3 H, SiC<u>H</u>$_3$)

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

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

The compound has not been reported previously.

0.22 4-Chloro-*N*-((1*R*,2*R*)-2-hydroxycyclopentyl)butanamide 141



(1*R*,2*R*)-2-Aminocyclopentan-1-ol **115** (500 mg, 4.94 mmol, 1 eq.), TEA (827 μl, 600 mg, 5.93 mmol, 1.2 eq.) and CH_2Cl_2 (20 ml) were stirred at 0 °C and 4-chlorobutyryl chloride **139** (608 μl, 766 mg, 5.43 mmol, 1.1 eq.) was added dropwise over 5 min. The mixture was stirred at 0 °C for 30 min, then water (50 ml) was added. The organic layer was separated off, and the aqueous layer was extracted with CH_2Cl_2 (7×50 ml). The combined organic layers were dried with $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (SiO_2, Et_2O). The combined pure fractions were dried with $MgSO_4$ and evaporated under reduced pressure. **141** was obtained as a white amorphous solid (651 mg, 3.16 mmol, 64.1 %).

TLC R_f = 0.35 (EtOAc)

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

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

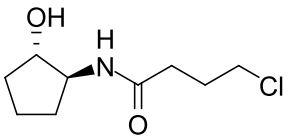
^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 173.8 (C=O), 79.4 (CHOH), 60.6 (CHNH), 44.4 (CH_2Cl), 32.8 (CH_2C=O), 32.4 (CH_2CHOH), 30.1 (CH_2CHNH), 28.0 (CH_2CH_2Cl), 21.1 (CH_2CH_2CHOH)

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

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

The compound has not been reported previously.

0.23 4-Chloro-*N*-((1*S*,2*S*)-2-hydroxycyclopentyl)butanamide 140



(1*S*,2*S*)-2-Aminocyclopentan-1-ol **114** (72.3 mg, 716 μmol, 1 eq.), TEA (500 μl, 363 mg, 3.58 mmol, 5 eq.) and CH_2Cl_2 (5 ml) were stirred at 0 °C, and 4-chlorobutyryl chloride **139** (179 μl, 226 mg, 1.60 mmol, 1.1 eq.) was added dropwise over 5 min. The mixture was stirred at 0 °C for 30 min, then water (10 ml) was added. The organic layer was separated off, and the aqueous layer was extracted with 10 % *i*-PrOH/$CHCl_3$ (2×10 ml). The combined organic layers were dried with $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (SiO_2, Et_2O). The combined pure fractions were dried with $MgSO_4$ and evaporated under reduced pressure. **140** was obtained as a white amorphous solid (35.6 mg, 173 μmol, 24.2 %).

TLC R_f = 0.35 (EtOAc)

^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 6.05 (br s, 1 H, NH), 4.55 (br s, 1 H, OH), 3.95 (q, J = 6.6 Hz, 1 H, CHOH), 3.82 (tt, J = 8.4, 5.3 Hz, 1 H, CHNH), 3.60 (t, J = 6.2 Hz, 2 H, CH_2Cl), 2.38 (t, J = 7.0 Hz, 2 H, CH_2C=O), 2.05 - 2.17 (m, 3 H, CHHCHNH and CH_2CH_2Cl), 1.94 - 2.05 (m, 1 H, CHHCHOH), 1.74 - 1.86 (m, 1 H, CHHCH_2CHOH), 1.58 - 1.74 (m, 2 H, CHHCH_2CHOH and CHHCHOH), 1.42 (dq, J = 12.5, 8.4 Hz, 1 H, CHHCHNH)

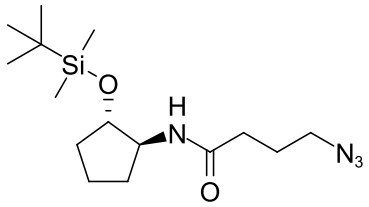
^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 173.8 (C=O), 79.4 (CHOH), 60.6 (CHNH), 44.4 (CH_2Cl), 32.8 (CH_2C=O), 32.4 (CH_2CHOH), 30.2 (CH_2CHNH), 28.0 (CH_2CH_2Cl), 21.2 (CH_2CH_2CHOH)

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

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

The compound has not been reported previously.

0.24 4-Azido-*N*-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclopentyl)butanamide 129



(1*S*,2*S*)-2-((*tert*-Butyldimethylsilyl)oxy)cyclopentan-1-amine **125** (50 mg, 0.232 mmol, 1 eq.) and $NaHCO_3$ (22.0 mg, 0.262 mmol, 1.1 eq.) were added to CH_2Cl_2 (3 ml) and water (3 ml) at 0 °C, and 4-bromobutyryl chloride (25.3 ml, 40.5 mg, 0.219 mmol, 0.95 eq.) was added dropwise. The mixture was stirred for 3 h at 0 °C. The aqueous layer was removed and NaN_3 (100 mg, 1.54 mmol, 6.6 eq.) and DMF (3 ml) were added. The mixture was then stirred at 40 °C for 6 h. The solvents were then evaporated using a N_2 stream and the residue was purified by column chromatography (SiO_2, 0.5 % MeOH/CH_2Cl_2). The combined pure fractions were dried with $MgSO_4$ and evaporated under reduced pressure. **129** was obtained as a clear liquid (71 mg, 0.217 mmol, 99.2 %).

TLC R_f = 0.84 (1 % MeOH/CH_2Cl_2)

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

^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 5.35 (d, J = 5.1 Hz, 1 H, 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)

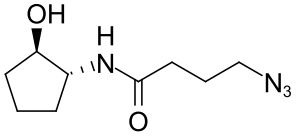
^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 171.17 (C=O), 77.80 (CHOSi), 58.36 (CHNH), 50.77 (CH_2N_3), 33.29 (CH_2C=O), 32.57 (CH_2CHOSi), 29.36 (CH_2CHNH), 25.72 (C(CH_3)$_3$), 24.77 ($CH_2CH_2N_3$), 20.40 (CH_2CH_2CHOSi), 17.95 (C(CH_3)$_3$), -4.75 (SiCH_3)

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

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

The compound has not been reported previously.

0.25 4-Azido-*N*-((1*R*,2*R*)-2-hydroxycyclopentyl)butanamide 119



4-Chloro-*N*-((1*R*,2*R*)-2-hydroxycyclopentyl)butanamide **141** (200 mg, 0.972 mmol, 1 eq.) and NaN_3 (126 mg, 1.94 mmol, 2 eq.) were stirred in acetonitrile (4 ml) at 50 °C for 16 h. The solvent was then evaporated under reduced pressure and the residue was partitioned between water (20 ml) and 10 % *i*-PrOH/$CHCl_3$ (20 ml). The aqueous layer was extracted again with 10 % *i*-PrOH/$CHCl_3$ (3×20 ml) and the combined organic fractions were dried with $MgSO_4$ and evaporated under reduced pressure. **119** was obtained as white needles (181 mg, 0.852 mmol, 87.6 %).

TLC R_f = 0.35 (EtOAc)

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

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

^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 6.72 (d, J = 4.4 Hz, 1 H, NH), 4.82 (br. s., 1 H, OH), 3.88 (q, J = 6.6 Hz, 1 H, CHOH), 3.75 (tdd, J = 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, 4.9 Hz, 1 H, CHHCHNH), 1.92 (dtd, J = 13.0, 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 Hz, 1 H, CHHCHOH), 1.39 (dq, J = 12.9, 8.4 Hz, 1 H, CHHCHNH)

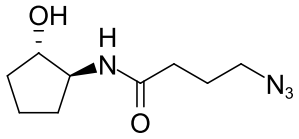
^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 173.8 (C=O), 78.8 (CHOH), 59.9 (CHNH), 50.5 (CH_2N_3), 32.5 (CH_2C=O), 32.0 (CH_2CHOH), 29.5 (CH_2CHNH), 24.6 ($CH_2CH_2N_3$), 20.7 (CH_2CH_2CHOH)

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)

The compound has not been reported previously.

0.26 4-Azido-*N*-((1*S*,2*S*)-2-hydroxycyclopentyl)butanamide 118



4-Chloro-*N*-((1*S*,2*S*)-2-hydroxycyclopentyl)butanamide **140** (35.0 mg, 0.170 mmol, 1 eq.) and NaN_3 (22.1 mg, 0.340 mmol, 2 eq.) were stirred in acetonitrile (2 ml) at 50 °C for 24 h. The reaction mixture was then partitioned between water (20 ml) and 10 % *i*-PrOH/$CHCl_3$ (5 ml). The aqueous layer was extracted again with 10 % *i*-PrOH/$CHCl_3$ (2×5 ml) and the combined organic fractions were dried with $MgSO_4$ and evaporated under reduced pressure. **118** was obtained as white needles (16.2 mg, 0.0764 mmol, 45.0 %).

TLC R_f = 0.35 (EtOAc)

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

^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 5.82 (br s, 1 H, NH), 4.45 (br. s., 1 H, OH), 3.96 (q, J = 6.6 Hz, 1 H, CHOH), 3.83 (tdd, J = 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)

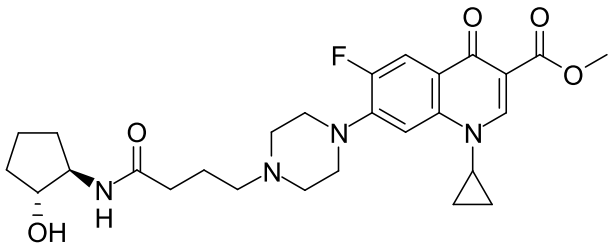
^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 173.8 (C=O), 79.7 (CHOH), 61.0 (CHNH), 50.7 (CH_2N_3), 32.8 ($CH_2C{=}O$), 32.6 (CH_2CHOH), 30.5 (CH_2CHNH), 24.7 ($CH_2CH_2N_3$), 21.3 (CH_2CH_2CHOH)

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

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

The compound has not been reported previously.

0.27 Methyl 1-cyclopropyl-6-fluoro-7-(4-(4-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-4-oxobutyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 121



4-(4-(1-Cyclopropyl-6-fluoro-3-(methoxycarbonyl)-4-oxo-1,4-dihydroquinolin-7-yl)piperazin-1-yl)butanoic acid trifluoroacetate **137** (200 mg, 0.367 mmol, 1 eq.), (1*R*,2*R*)-2-aminocyclopentan-1-ol **115** (80 mg, 0.791 mmol, 2.1 eq.), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (112 mg, 0.584 mmol, 1.6 eq.), 1-hydroxybenzotriazole (96 mg, 0.710 mmol, 1.9 eq.) and DIPEA (192 μl, 142 mg, 1.10 mmol, 3 eq.) were dissolved in DMF (5 ml) and stirred at r.t. for 16 h. The solvent was removed using a stream of N_2 and the residue was purified by preparative HPLC (5-60 % acetonitrile/water over 12 min). The combined pure fractions were evaporated under reduced pressure and then partitioned between $NaHCO_3$ (aq., sat., 10 ml) and CH_2Cl_2 (10 ml). The organic layer was removed and the aqueous layer was extracted twice more with CH_2Cl_2 (2×10 ml). The combined organic fractions were dried with $MgSO_4$ and evaporated under reduced pressure. **121** was obtained as a white amorphous solid (73.0 mg, 0.142 mmol, 38.7 %).

TLC R_f = 0.43 (30 % MeOH/EtOAc)

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

^{1}H NMR (400 MHz, DMSO d_6) δ / ppm = 8.44 (s, 1 H, *ortho* to C(=O)OCH$_3$), 7.75 (d, J = 13.5 Hz, 1 H, *ortho* to F), 7.70 (d, J = 7.2 Hz, 1 H, CHNH), 7.43 (d, J = 7.5 Hz, 1 H, *meta* to F), 4.74 (d, J = 4.0 Hz, 1 H, CHOH), 3.78 - 3.82 (m, 1 H, CHOH), 3.74 - 3.78 (m, 1 H, CHNH), 3.74 (s, 3 H, CH_3), 3.65 (tt, J = 7.2, 3.9 Hz, 1 H, $NCH(CH_2)_2$), 3.25 (t, J = 4.8 Hz, 4 H, $CH_2N(CH_2CH_2)CH_2CH_2$), 2.57 (br s, 4 H, $CH_2N(CH_2)CH_2$), 2.34 (t, J = 7.4 Hz, 2 H, $CH_2N(CH_2)CH_2$), 2.11 (t, J = 7.4 Hz, 2 H, $CH_2CH_2CH_2N(CH_2)CH_2$), 1.92 (dddd, J = 13.0, 8.7, 7.3, 6.0 Hz, 1 H, CHHCHNH), 1.78 (dddd, J = 12.6, 8.9, 6.3, 6.3 Hz, 1 H, CHHCHOH), 1.69 (quin, J

= 7.3 Hz, 2 H, C$\underline{H}_2$CH$_2$N(CH$_2$)CH$_2$), 1.54 - 1.65 (m, 2 H, C$\underline{H}_2$CH$_2$CHOH), 1.42 (ddt, J = 13.1, 8.2, 5.3 Hz, 1 H, CH$\underline{H}$CHOH), 1.32 (dddd, J = 13.4, 8.5, 6.8, 5.8 Hz, 1 H, CH$\underline{H}$CHNH), 1.21 - 1.29 (m, 2 H, NCH(C$\underline{H}$H)$_2$), 1.07 - 1.13 (m, 2 H, NCH(CH$\underline{H}$)$_2$)

^{13}C NMR (101 MHz, DMSO d$_6$) δ / ppm = 171.9 (CH$_2\underline{C}$(=O)NH), 171.6 ($\underline{C}$(=O)CC(=O)OCH$_3$), 165.0 ($\underline{C}$(=O)OCH$_3$), 152.6 (d, J = 246.5 Hz, *ipso* to F), 148.3 ($\underline{C}$=CC(=O)OCH$_3$), 143.9 (d, J = 10.7 Hz, *ipso* to piperazine), 138.1 (*para* to F), 121.8 (d, J = 6.4 Hz, *para* to piperazine), 111.5 (d, J = 22.4 Hz, *ortho* to C=O and *ortho* to F), 109.0 ($\underline{C}$C(=O)OCH$_3$), 106.2 (*meta* to C=O and *meta* to F), 76.3 ($\underline{C}$HOH), 57.6 ($\underline{C}$HNH), 57.2 (CH$_2$CH$_2\underline{C}$H$_2$N), 52.4 (CH$_2$CH$_2$CH$_2$N($\underline{C}$H$_2$)$\underline{C}$H$_2$), 51.3 ($\underline{C}$H$_3$), 49.6 (CH$_2$CH$_2$CH$_2$N(CH$_2\underline{C}$H$_2$)CH$_2\underline{C}$H$_2$), 34.8 (N$\underline{C}$H(CH$_2$)$_2$), 33.3 (C(=O)$\underline{C}$H$_2$), 32.2 ($\underline{C}$H$_2$CHOH), 29.5 ($\underline{C}$H$_2$CHNH), 22.5 (C(=O)CH$_2\underline{C}$H$_2$), 20.6 ($\underline{C}$H$_2$CH$_2$CHOH), 7.6 (NCH($\underline{C}$H$_2$)$_2$)

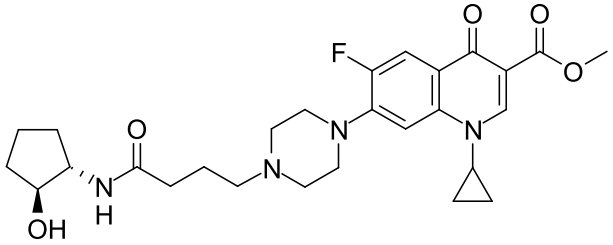
^{19}F NMR (376.45 MHz, DMSO d$_6$) δ / ppm = -124.3 (ciprofloxacin F)

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

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

The compound has not been reported previously.

0.28 Methyl 1-cyclopropyl-6-fluoro-7-(4-(4-(((1*S*,2*S*)-2-hydroxycyclopentyl)amino)-4-oxobutyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 120



4-(4-(1-Cyclopropyl-6-fluoro-3-(methoxycarbonyl)-4-oxo-1,4-dihydroquinolin-7-yl)piperazin-1-yl)butanoic acid trifluoroacetate **137** (52.1 mg, 95.5 μmol, 1 eq.), (1*S*,2*S*)-2-aminocyclopentan-1-ol **114** (19.5 mg, 193 μmol, 2 eq.), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (29.7 mg, 155 μmol, 1.6 eq.), 1-hydroxyben zotriazole (25.8 mg, 191 μmol, 2 eq.) and DIPEA (33.3 μl, 24.7 mg, 191 μmol, 2 eq.) were dissolved in DMF (2 ml) and stirred at r.t. for 16 h. The solvent was removed using a stream of N_2 and the residue was purified by preparative HPLC (5-50 % acetonitrile/water over 15 min). The combined pure fractions were evaporated under reduced pressure and then partitioned between $NaHCO_3$ (aq., sat., 5 ml) and CH_2Cl_2 (5 ml). The organic layer was removed and the aqueous layer was extracted twice more with CH_2Cl_2 (2×5 ml). The combined organic fractions were dried with $MgSO_4$ and evaporated under reduced pressure. **120** was obtained as a white amorphous solid (26.9 mg, 52.3 μmol, 54.7 %).

TLC R_f = 0.38 (30 % MeOH/CH_2Cl_2)

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

^{1}H NMR (500 MHz, DMSO d$_6$) δ / ppm = 8.44 (s, 1 H, *ortho* to C(=O)OC$\underline{H}_3$), 7.75 (d, J = 13.5 Hz, 1 H, *ortho*

to F), 7.69 (d, J = 6.9 Hz, 1 H, CHN$\underline{H}$), 7.43 (d, J = 7.6 Hz, 1 H, *meta* to F), 4.73 (br s, 1 H, CHO$\underline{H}$), 3.77 - 3.81 (m, 1 H, C$\underline{H}$OH), 3.74 - 3.77 (m, 1 H, C$\underline{H}$NH), 3.73 (s, 3 H, C$\underline{H}_3$), 3.65 (tt, J = 6.9, 4.0 Hz, 1 H, NC$\underline{H}(CH_2)_2$), 3.24 (br. t, J = 4.2 Hz, 4 H, $CH_2N(CH_2C\underline{H}_2)CH_2C\underline{H}_2$), 2.55 (br t, J = 5.0 Hz, 4 H, $CH_2N(C\underline{H}_2)C\underline{H}_2$), 2.32 (t, J = 7.2 Hz, 2 H, $C\underline{H}_2N(CH_2)CH_2$), 2.10 (t, J = 7.4 Hz, 2 H, $C\underline{H}_2CH_2CH_2N(CH_2)CH_2$), 1.92 (dddd, J = 13.0, 8.7, 7.3, 6.0 Hz, 1 H, C$\underline{H}$HCHNH), 1.77 (ddt, J = 12.6, 8.9, 6.3 Hz, 1 H, C$\underline{H}$HCHOH), 1.68 (quin, J = 7.4 Hz, 2 H, $C\underline{H}_2CH_2N(CH_2)CH_2$), 1.53 - 1.64 (m, 2 H, $C\underline{H}_2CH_2CHOH$), 1.42 (ddt, J = 12.9, 8.4, 5.2 Hz, 1 H, CH$\underline{H}$CHOH), 1.31 (ddt, J = 13.0, 8.6, 6.4 Hz, 1 H, CH$\underline{H}$CHNH), 1.22 - 1.28 (m, 2 H, NCH(C$\underline{H}\underline{H})_2$), 1.06 - 1.12 (m, 2 H, NCH(CH$\underline{H})_2$)

^{13}**C NMR** (126 MHz, DMSO d_6) δ / ppm = 171.9 (NH$\underline{C}$(=O)CH_2), 171.5 ($\underline{C}$(=O)CC(=O)OCH_3), 165.0 ($\underline{C}$(=O)OCH_3), 152.6 (d, J = 247.4 Hz, *ipso* to F), 148.2 ($\underline{C}$=CC(=O)OCH_3), 143.9 (d, J = 10.3 Hz, *ipso* to piperazine), 138.1 (*para* to F), 121.7 (d, J = 6.4 Hz, *para* to piperazine), 111.5 (d, J = 23.0 Hz, *ortho* to C=O and *ortho* to F), 109.0 ($\underline{C}$C(=O)OCH_3), 106.2 (*meta* to C=O and *meta* to F), 76.2 ($\underline{C}$HOH), 57.6 ($\underline{C}$HNH), 57.2 ($CH_2CH_2\underline{C}H_2N$), 52.4 ($CH_2CH_2CH_2N(\underline{C}H_2)\underline{C}H_2$), 51.3 ($\underline{C}H_3$), 49.6 ($CH_2CH_2CH_2N(CH_2\underline{C}H_2)CH_2CH_2$), 49.6 ($CH_2CH_2CH_2N(CH_2CH_2)CH_2\underline{C}H_2$), 34.7 (N$\underline{C}H(CH_2)_2$), 33.2 (C(=O)$\underline{C}H_2$), 32.2 ($\underline{C}H_2$CHOH), 29.5 ($\underline{C}H_2$CH NH), 22.5 (C(=O)$CH_2\underline{C}H_2$), 20.6 ($\underline{C}H_2CH_2$CHOH), 7.5 (NCH($\underline{C}H_2)_2$)

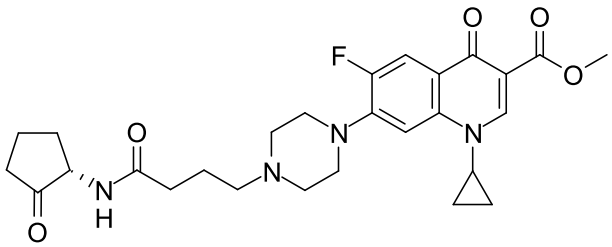
^{19}**F NMR** (376.45 MHz, MeOD) δ / ppm = -125.5

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

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

The compound has not been reported previously.

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



Methyl 1-cyclopropyl-6-fluoro-7-(4-(4-(((1*S*,2*S*)-2-hydroxycyclopentyl)amino)-4-oxobutyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate **120** (20.0 mg, 38.9 μmol, 1 eq.) and Dess-Martin periodinane (32.8 mg, 77.4 μmol, 2 eq.) were stirred in CH_2Cl_2 (3 ml) for 6 h. The solvent was removed under reduced pressure and the residue was purified by preparative HPLC (5-50 % acetonitrile/water over 10 min). The combined pure fractions were evaporated under reduced pressure, then $NaHCO_3$ (aq., sat., 30 ml) and 10 % *i*-PrOH/$CHCl_3$ (30 ml) were added. The organic layer was removed and dried with $MgSO_4$, then evaporated under reduced pressure. **122** was obtained as a white amorphous solid (11.3 mg, 22.0 μmol, 56.7 %).

remove unless very active as not fully characterised

^{1}**H NMR** (500 MHz, DMSO d_6) δ / ppm = 8.46 (s, 1 H, *ortho* to C(=O)OC$\underline{H}_3$), 7.78 (d, J = 13.5 Hz, 1 H, *ortho* to F), 7.45 (d, J = 7.4 Hz, 1 H, *meta* to F), 4.02 (dt, J = 11.1, 8.2 Hz, 1 H, C$\underline{H}$NH), 3.73 (s, 3 H, C$\underline{H}_3$), 3.65 (tt, J = 6.9, 3.9 Hz, 1 H, NC$\underline{H}(CH_2)_2$), 3.40 (s, 10 H, $CH_2CH_2C\underline{H}_2N(C\underline{H}_2C\underline{H}_2)C\underline{H}_2C\underline{H}_2$), 2.05 - 2.29 (m, 5

H, NHC(=O)C$\underline{H}_2$, C$\underline{H}_2$C(=O)CHNH and C$\underline{H}$HCHNH), 1.89 - 1.96 (m, 1 H, C$\underline{H}$HCH$_2$CHNH), 1.69 - 1.80 (m, 3 H, CH$\underline{H}$CH$_2$CHNH, CH$\underline{H}$CHNH and NHC(=O)CH$_2$C$\underline{H}_2$), 1.24 - 1.29 (m, 2 H, NCH(C$\underline{H}$H)$_2$), 1.07 - 1.12 (m, 2 H, NCH(CH$\underline{H}$)$_2$)

^{13}**C NMR** (126 MHz, DMSO d$_6$) δ / ppm = 215.2 ($\underline{C}$(=O)CHNH), 171.7 (NH$\underline{C}$(=O)CH$_2$), 171.7 ($\underline{C}$(=O)CC(=O)OCH$_3$), 165.1 ($\underline{C}$(=O)OCH$_3$), 152.6 (d, J = 246.6 Hz, *ipso* to F), 148.4 ($\underline{C}$=CC(=O)OCH$_3$), 138.1 (*para* to F), 109.1 ($\underline{C}$C(=O)OCH$_3$), 56.3 ($\underline{C}$HNH), 51.4 ($\underline{C}$H$_3$), 35.6 ($\underline{C}$H$_2$C(=O)CHNH), 34.8 (N$\underline{C}$H(CH$_2$)$_2$), 28.8 ($\underline{C}$H$_2$CHNH), 18.1 ($\underline{C}$H$_2$CH$_2$CHNH), 7.6 (NCH($\underline{C}$H$_2$)$_2$)

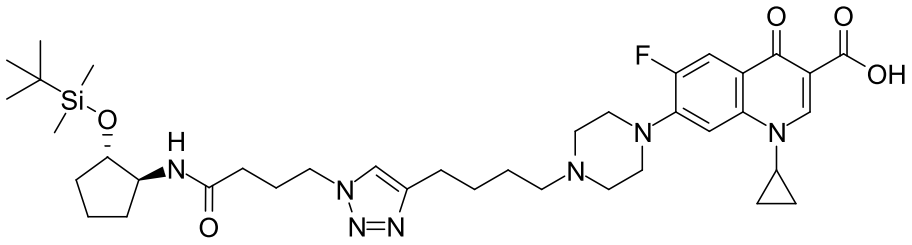
^{19}**F NMR** (376.45 MHz, MeOD) δ / ppm = -124.3

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

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

The compound has not been reported previously.

0.30 7-(4-(4-(1-(4-(((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclopentyl)amino)-4-oxobutyl)-1*H*-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 133



1-Cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **70** (42.9 mg, 104 μmol, 1 eq.) and 4-azido-*N*-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclopentyl)butanamide **129** (33.9 mg, 104 μmol, 1 eq.) were dissolved in 10 % water/*t*-BuOH (3 ml), and the mixture was degassed by bubbling N_2 through it. A solution of $CuSO_4$ and THPTA (104 μl, 10.4 μmol, 0.1 eq. 100 mM, aq.) was added, followed by a solution of sodium ascorbate (208 μl, 20.8 μmol, 0.2 eq., 100 mM, aq.). The mixture was stirred at room temperature under argon for 16 h, then solvent was removed under reduced pressure. The resudue was partitioned between water (10 ml) and CH_2Cl_2 (10 ml), the organic layer was separated and the aqueous layer was extracted again with CH_2Cl_2 (10 ml). The combined organic layers were dried with $MgSO_4$ and evaporated under reduced pressure. **133** was obtained as a clear amorphous solid (67.1 mg, 90.9 μmol, 87.4 %).

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

^{1}**H NMR** (400 MHz, $CDCl_3$) δ / ppm = 8.67 (s, 1 H, *ortho* to C(=O)OH), 7.87 (d, J = 13.1 Hz, 1 H, *ortho* to F), 7.34 (s, 1 H, C$\underline{H}$=CCH$_2$), 7.33 (d, J = 8.2 Hz, 1 H, *meta* to F), 5.92 (t, J = 6.6 Hz, 1 H, CHN$\underline{H}$), 4.35 (t, J = 6.7 Hz, 2 H, C$\underline{H}_2$NCH=C), 3.96 - 4.02 (m, 1 H, C$\underline{H}$OSi), 3.90 - 3.96 (m, 1 H, C$\underline{H}$NH), 3.55 (tt, J = 6.7, 4.0 Hz, 1 H, NC$\underline{H}$(CH$_2$)$_2$), 3.34 (br t, J = 5.0 Hz, 4 H, CH$_2$N(CH$_2$C$\underline{H}_2$)CH$_2$C$\underline{H}_2$), 2.71 (t, J = 7.5 Hz, 2 H, CH=CC$\underline{H}_2$), 2.66 (br s, 4 H, CH$_2$N(C$\underline{H}_2$)C$\underline{H}_2$), 2.46 (t, J = 7.3 Hz, 2 H, C$\underline{H}_2$N(CH$_2$)CH$_2$), 2.03 - 2.22

(m, 5 H, CHHCHNH, C(=O)CH$_2$ and C(=O)CH$_2$CH$_2$), 1.65 - 1.83 (m, 4 H, CHHCHOSi, CHHCH$_2$CHOSi and NCH=CCH$_2$CH$_2$), 1.47 - 1.65 (m, 4 H, CHHCHOSi, CHHCH$_2$CHOSi and NCH=CCH$_2$CH$_2$CH$_2$CH$_2$), 1.33 - 1.41 (m, 3 H, CHHCHNH and NCH(CHH)$_2$), 1.14 - 1.20 (m, 2 H, NCH(CHH)$_2$), 0.82 (s, 9 H, C(CH$_3$)$_3$), 0.03 (s, 3 H, SiCH$_3$), 0.01 (s, 3 H, SiCH$_3$)

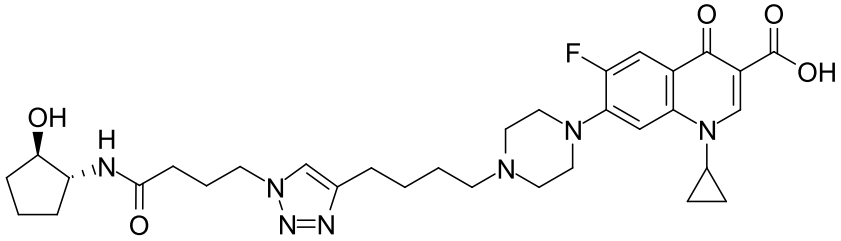
^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 176.9 (C(=O)CC(=O)OH), 170.9 (CH$_2$C(=O)NH), 166.9 (C(=O)OH), 153.5 (d, J = 251.4 Hz, *ipso* to F), 147.9 (CH=CCH$_2$), 147.2 (C=CC(=O)OH), 145.8 (d, J = 10.4 Hz, *ipso* to piperazine), 139.0 (*para* to F), 120.9 (NCH=CCH$_2$), 119.4 (d, J = 7.8 Hz, *para* to piperazine), 112.0 (d, J = 23.4 Hz, *ortho* to C=O and *ortho* to F), 107.7 (CC(=O)OH), 104.7 (d, J = 3.5 Hz, *meta* to C=O and *meta* to F), 77.7 (CHOSi), 58.2 (CHNH), 57.9 (CH=CCH$_2$CH$_2$CH$_2$CH$_2$N), 52.6 (CH=CCH$_2$CH$_2$CH$_2$CH$_2$N(CH$_2$)CH$_2$), 49.5 (d, J = 6.1 Hz, CH=CCH$_2$CH$_2$CH$_2$CH$_2$N(CH$_2$CH$_2$)CH$_2$CH$_2$), 48.9 (d, J = 3.5 Hz, CH$_2$NCH=CCH$_2$), 35.3 (NCH(CH$_2$)$_2$), 32.6 (C(=O)CH$_2$), 32.6 (CH$_2$CHOSi), 29.3 (CH$_2$CHNH), 27.2 (CH=CCH$_2$CH$_2$), 26.0 - 26.3 (C(=O)CH$_2$CH$_2$ and CH=CCH$_2$CH$_2$CH$_2$), 25.6 (C(CH$_3$)$_3$), 25.4 (CH=CCH$_2$), 20.4 (CH$_2$CH$_2$CHOSi), 17.8 (C(CH$_3$)$_3$), 8.1 (NCH(CH$_2$)$_2$), -4.8 (SiCH$_3$)

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

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

The compound has not been reported previously.

0.31 1-Cyclopropyl-6-fluoro-7-(4-(4-(1-(4-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-4-oxobutyl)-1*H*-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 124



1-Cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **70** (42.9 mg, 104 μmol, 1 eq.) and 4-azido-*N*-((1*R*,2*R*)-2-hydroxycyclopentyl)butanamide **119** (22.0 mg, 104 μmol, 1 eq.) were dissolved in 10 % water/*t*-BuOH (3 ml), and the mixture was degassed by bubbling N_2 through it. A solution of $CuSO_4$ and THPTA (104 μl, 10.4 μmol, 0.1 eq. 100 mM, aq.) was added, followed by a solution of sodium ascorbate (208 μl, 20.8 μmol, 0.2 eq., 100 mM, aq.). The mixture was stirred at room temperature under argon for 16 h. Water (30 ml) and CH_2Cl_2 (30 ml) were added, the organic layer was separated and the aqueous layer was extracted again with CH_2Cl_2 (4×30 ml). The combined organic layers were dried with $MgSO_4$ and evaporated under reduced pressure. The residue was purified by preparative HPLC (5-95 % acetonitrile/water over 20 min). The combined pure fractions were evaporated under reduced pressure and then partitioned between $NaHCO_3$ (aq., sat., 10 ml) and 10 % *i*-PrOH/$CHCl_3$ (10 ml). The organic layer was dried with $MgSO_4$ and evaporated under reduced pressure. **124** was obtained as a white amorphous solid (17.6 mg, 28.2 μmol, 27.1 %).

IR (neat) ν_{max} / cm^{-1} = 2967.0 (C-H), 2902.2 (C-H), 1721.4 (carboxylic acid C=O), 1646.7 (amide C=O),

1627.0 (quinolone C=O), 1613.0 (triazole)

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

^{13}C NMR (175 MHz, DMSO d_6) δ / ppm = 176.3 (<u>C</u>(=O)CC(=O)OH), 170.9 (NH<u>C</u>(=O)CH$_2$), 166.1 (<u>C</u>(=O)OH), 153.0 (d, J = 251.4 Hz, *ipso* to F), 147.9 (<u>C</u>=CC(=O)OH), 146.9 (CH=<u>C</u>CH$_2$), 145.2 (d, J = 8.7 Hz, *ipso* to piperazine), 139.2 (*para* to F), 121.7 (N<u>C</u>H=CCH$_2$), 118.7 (d, J = 5.8 Hz, *para* to piperazine), 111.0 (d, J = 23.3 Hz, *ortho* to C=O and *ortho* to F), 106.3 (*meta* to C=O and *meta* to F and <u>C</u>C(=O)OH), 76.2 (<u>C</u>HOH), 57.6 (<u>C</u>HNH), 57.4 (CH=CCH$_2$CH$_2$CH$_2$<u>C</u>H$_2$N), 52.5 (CH=CCH$_2$CH$_2$CH$_2$CH$_2$N(<u>C</u>H$_2$)<u>C</u>H$_2$), 49.5 (d, J = 4.4 Hz, CH=CCH$_2$CH$_2$CH$_2$CH$_2$N(CH$_2$<u>C</u>H$_2$)CH$_2$<u>C</u>H$_2$), 48.8 (<u>C</u>H$_2$NCH=CCH$_2$), 35.8 (N<u>C</u>H(CH$_2$)$_2$), 32.2 (<u>C</u>H$_2$CHOH), 32.0 (C(=O)<u>C</u>H$_2$), 29.5 (<u>C</u>H$_2$CHNH), 26.9 (CH=CCH$_2$<u>C</u>H$_2$), 26.0 (C(=O)CH$_2$<u>C</u>H$_2$), 25.8 (CH=CCH$_2$CH$_2$<u>C</u>H$_2$), 25.0 (CH=C<u>C</u>H$_2$), 20.5 (<u>C</u>H$_2$CH$_2$CHOH), 7.6 (NCH(<u>C</u>H$_2$)$_2$)

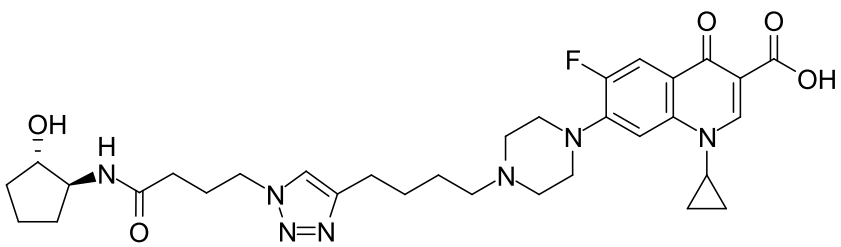
^{19}F NMR (376.45 MHz, MeOD) δ / ppm = -122.1 (s, ciprofloxacin F)

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

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

The compound has not been reported previously.

0.32 1-Cyclopropyl-6-fluoro-7-(4-(4-(1-(4-(((1*S*,2*S*)-2-hydroxycyclopentyl)amino)-4-oxobutyl)-1*H*-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 123



1-Cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **70** (82.0 mg, 199 μmol, 4 eq.) and 4-azido-*N*-((1*S*,2*S*)-2-hydroxycyclopentyl)butanamide **118** (11.0 mg, 51.8 μmol, 1 eq.) were dissolved in 10 % water/*t*-BuOH (3 ml), and the mixture was degassed by bubbling N_2 through it. A solution of $CuSO_4$ and THPTA (156 μl, 15.6 μmol, 0.3 eq. 100 mM, aq.) was added, followed by a solution of sodium ascorbate (312 μl, 31.2 μmol, 0.6 eq., 100 mM, aq.). The mixture was stirred at room temperature under

argon for 3 d. Water (10 ml) and 10 % *i*-PrOH/$CHCl_3$ (10 ml) were added, then the organic layer was separated and dried with $MgSO_4$ and evaporated under reduced pressure. The residue was purified by preparative HPLC (5-95 % acetonitrile/water over 20 min). The combined pure fractions were evaporated under reduced pressure and then partitioned between $NaHCO_3$ (aq., sat., 10 ml) and 10 % *i*-PrOH/$CHCl_3$ (10 ml). The organic layer was dried with $MgSO_4$ and evaporated under reduced pressure. **123** was obtained as a white amorphous solid (7.2 mg, 11.5 μmol, 22.2 %).

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

^{1}**H NMR** (400 MHz, DMSO d_6) δ / ppm = 15.22 (br s, 1 H, C(=O)OH), 8.67 (s, 1 H, *ortho* to C(=O)OH), 7.91 (d, J = 13.3 Hz, 1 H, *ortho* to F), 7.84 (s, 1 H, CH=CCH_2), 7.74 (d, J = 6.7 Hz, 1 H, CHNH), 7.56 (d, J = 7.4 Hz, 1 H, *meta* to F), 4.71 (d, J = 3.7 Hz, 1 H, CHOH), 4.29 (t, J = 6.6 Hz, 2 H, CH_2NCH=C), 3.82 (tt, J = 6.5, 4.3 Hz, 1 H, NCH$(CH_2)_2$), 3.69 - 3.79 (m, 2 H, CHOH and CHNH), 3.30 - 3.34 (m, 6 H, CH=$CCH_2CH_2CH_2CH_2N(CH_2CH_2)CH_2CH_2$), 2.64 (t, J = 7.4 Hz, 2 H, CH=CCH_2), 1.95 - 2.08 (m, 4 H, C(=O)CH_2CH_2), 1.89 (dddd, J = 12.8, 8.9, 7.4, 5.8 Hz, 1 H, CHHCHNH), 1.75 (ddt, J = 12.7, 9.0, 6.2 Hz, 1 H, CHHCHOH), 1.48 - 1.68 (m, 6 H, CH=$CCH_2CH_2CH_2$ and CH_2CH_2CHOH), 1.40 (ddt, J = 13.0, 8.3, 5.3 Hz, 1 H, CHHCHOH), 1.28 - 1.35 (m, 2 H, NCH$(CHH)_2$), 1.24 - 1.31 (m, 1 H, CHHCHNH), 1.15 - 1.21 (m, 2 H, NCH$(CHH)_2$)

^{13}**C NMR** (101 MHz, DMSO d_6) δ / ppm = 176.4 (C(=O)CC(=O)OH), 170.9 (NHC(=O)CH_2), 166.0 (C(=O)OH), 153.0 (d, J = 249.6 Hz, *ipso* to F), 148.1 (C=CC(=O)OH), 146.7 (CH=CCH_2), 145.2 (d, J = 8.3 Hz, *ipso* to piperazine), 139.2 (*para* to F), 121.8 (NCH=CCH_2), 118.7 (*para* to piperazine), 111.0 (d, J = 23.2 Hz, *ortho* to C=O and *ortho* to F), 106.7 (CC(=O)OH), 106.5 (*meta* to C=O and *meta* to F), 76.2 (CHOH), 57.5 (CHNH), 57.4 (br s, CH=$CCH_2CH_2CH_2CH_2N$), 52.3 (br s, CH=$CCH_2CH_2CH_2CH_2N(CH_2)CH_2$), 49.3 (br s, CH=$CCH_2CH_2CH_2CH_2N(CH_2CH_2)CH_2CH_2$), 48.8 ($CH_2$NCH=$CCH_2$), 35.9 (NCH$(CH_2)_2$), 32.2 ($CH_2$CHOH), 32.0 (C(=O)$CH_2$), 29.4 ($CH_2$CHNH), 26.7 (CH=$CCH_2CH_2$), 26.0 (C(=O)$CH_2CH_2$), 25.5 (CH=$CCH_2CH_2CH_2$), 24.9 (CH=$CCH_2$), 20.5 ($CH_2CH_2$CHOH), 7.6 (NCH$(CH_2)_2$)

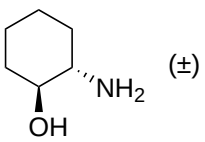
^{19}**F NMR** (376.45 MHz, MeOD) δ / ppm = -121.5

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

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

The compound has not been reported previously.

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



(±)

Cyclohexene oxide **142** (10 ml, 9.70 g, 98.8 mmol, 1 eq.), NH_3 (90 ml, 35 % w/w aq., 27.7 g, 791 mmol, 8 eq.) and MeOH (100 ml) were stirred at r.t. for 72 h. The solvent was removed by blowing a stream of N_2 over it, followed by evaporation under high vacuum.**143** was obtained as a white amorphous solid (9.90 g, 85.2 mmol,

86.2 %)

TLC R_f = 0.04 (30 % MeOH/CH_2Cl_2)

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

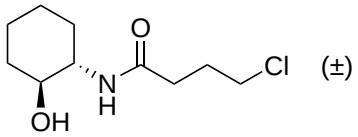
^{1}H NMR (400 MHz, $CDCl_3$) δ / ppm = 3.01 (td, J = 9.4, 4.8 Hz, 1 H, C<u>H</u>OH), 2.80 - 2.92 (m, 2 H, O<u>H</u> and N<u>H</u>$_2$), 2.35 (ddd, J = 11.1, 9.1, 4.1 Hz, 1 H, C<u>H</u>NH$_2$), 1.77 - 1.84 (m, 1 H, C<u>H</u>HCHOH), 1.69 - 1.76 (m, 1 H, C<u>H</u>HCHNH$_2$), 1.56 - 1.66 (m, 1 H, C<u>H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

The data are consistent with the literature.[18]

0.34 4-Chloro-*N*-((*trans*)-2-hydroxycyclohexyl)butanamide 144



(*trans*)-2-Aminocyclohexan-1-ol **143** (1.04 g, 9.03 mmol, 1 eq.), TEA (1.65 ml, 1.20 g, 11.8 mmol, 1.3 eq.) and CH_2Cl_2 (50 ml) were stirred at 0 °C. 4-Chlorobutyryl chloride **139** (1.22 ml, 1.54 g, 10.9 mmol, 1.2 eq.) was added dropwise over 5 min. The mixture was stirred at 0 °C for 30 min, then water (50 ml) was added. The organic layer was separated off, and the aqueous layer was extracted with 10 % *i*-PrOH/$CHCl_3$ (2×50 ml). The combined organic layers were dried with $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (SiO_2, 0-100 % EtOAc/Et_2O). The combined organic fractions were dried with $MgSO_4$ and evaporated under reduced pressure. **144** was obtained as white needles (1.51 g, 6.87 mmol, 76.1 %).

TLC R_f = 0.19 (Et_2O)

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

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

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

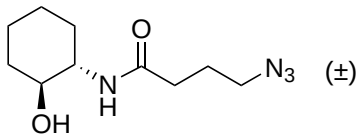
^{13}C NMR (101 MHz, MeOD) δ / ppm = 175.0 (<u>C</u>(=O)), 74.1 (<u>C</u>HOH), 56.3 (<u>C</u>HNH), 45.3 (<u>C</u>H$_2$Cl), 35.6 (<u>C</u>H$_2$CHOH), 34.5 (C(=O)<u>C</u>H$_2$), 32.7 (<u>C</u>H$_2$CHNH), 30.1 (C(=O)CH$_2$<u>C</u>H$_2$), 25.8 (<u>C</u>H$_2$CH$_2$CHNH), 25.5

($\underline{C}H_2CH_2CHOH$)

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

The compound has not been reported previously.

0.35 4-Azido-*N*-((*trans*)-2-hydroxycyclohexyl)butanamide 145



4-Chloro-*N*-((*trans*)-2-hydroxycyclohexyl)butanamide **144** (345 mg, 1.57 mmol, 1 eq.) and NaN_3 (180 mg, 2.77 mmol, 1.75 eq.) were stirred in DMF (12 ml) at 50 °C for 16 h. Water (50 ml) and 10 % *i*-PrOH/$CHCl_3$ (50 ml) were added, and the organic layer was removed. The aqueous layer was extracted again with 10 % *i*-PrOH/$CHCl_3$ (50 ml) and the combined organic fractions were dried with $MgSO_4$. The solvent was evaporated under reduced pressure, and then by using a N_2 stream. **145** was obtained as large white prisms (347 mg, 1.53 mmol, 97.5 %).

TLC R_f = 0.23 (EtOAc)

mp T / °C = 74.5-75.7 (*i*-PrOH, $CHCl_3$)

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

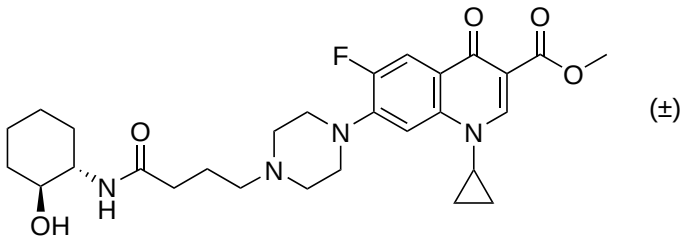
^{1}**H NMR** (400 MHz, MeOD) δ / ppm = 7.87 (d, J = 7.9 Hz, 1 H, N$\underline{H}$), 5.27 (d, J = 4.3 Hz, 1 H, O$\underline{H}$), 3.56 (td, J = 10.5, 4.4 Hz, 1 H, C$\underline{H}$NH), 3.28 - 3.41 (m, 3 H, C$\underline{H}$OH and C$\underline{H}_2$N$_3$), 2.30 (td, J = 7.4, 2.7 Hz, 2 H, C(=O)C$\underline{H}_2$), 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 ($\underline{C}H_2N_3$), 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 ($\underline{C}H_2CH_2$CHNH), 25.5 ($\underline{C}H_2CH_2$CHOH)

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

The compound has not been reported previously.

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



4-(4-(1-Cyclopropyl-6-fluoro-3-(methoxycarbonyl)-4-oxo-1,4-dihydroquinolin-7-yl)piperazin-1-yl)butanoic acid trifluoroacetate **137** (200 mg, 0.367 mmol, 1 eq.), (*trans*)-2-aminocyclohexan-1-ol **143** (91.1 mg, 0.791 mmol, 2.1 eq.), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (112 mg, 0.584 mmol, 1.6 eq.), 1-hydroxyben zotriazole (96 mg, 0.710 mmol, 1.9 eq.) and DIPEA (192 μl, 142 mg, 1.10 mmol, 3 eq.) were dissolved in DMF (5 ml) and stirred at r.t. for 16 h. The solvent was removed using a stream of N_2 and the residue was purified by preparative HPLC (5-50 % acetonitrile/water over 10 min). The combined pure fractions were evaporated under reduced pressure and then partitioned between $NaHCO_3$ (aq., sat., 10 ml) and CH_2Cl_2 (10 ml). The organic layer was dried with $MgSO_4$ and evaporated under reduced pressure. **146** was obtained as a white amorphous solid (73.0 mg, 0.142 mmol, 38.7 %).

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

^{1}**H NMR** (400 MHz, MeOD) δ / ppm = 8.60 (s, 1 H, *ortho* to C(=O)OC$\underline{H}_3$), 7.79 (d, J = 13.5 Hz, 1 H, *ortho* to F), 7.46 (d, J = 7.2 Hz, 1 H, *meta* to F), 3.84 (s, 3 H, C$\underline{H}_3$), 3.62 - 3.68 (m, 1 H, NC$\underline{H}$(CH$_2$)$_2$), 3.58 (td, J = 10.3, 4.2 Hz, 1 H, C$\underline{H}$NH), 3.38 (br s, 4 H, CH$_2$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$\underline{H}$)$_2$)

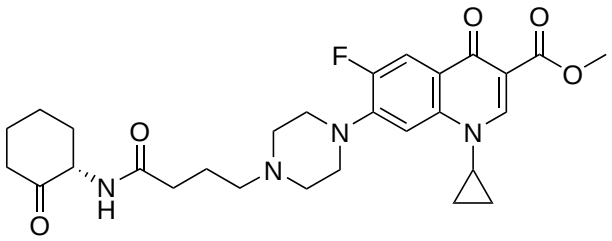
^{13}**C NMR** (101 MHz, MeOD) δ / ppm = 175.8 (CH$_2$$\underline{C}$(=O)NH), 175.3 ($\underline{C}$(=O)CC(=O)OCH$_3$), 166.8 ($\underline{C}$(=O)OCH$_3$), 154.9 (d, J = 248.8 Hz, *ipso* to F), 150.2 ($\underline{C}$=CC(=O)OCH$_3$), 146.1 (d, J = 10.8 Hz, *ipso* to piperazine), 139.9 (*para* to F), 123.5 (d, J = 7.5 Hz, *para* to piperazine), 113.2 (d, J = 23.2 Hz, *ortho* to C=O and *ortho* to F), 110.2 ($\underline{C}$C(=O)OCH$_3$), 107.2 (*meta* to C=O and *meta* to F), 74.1 ($\underline{C}$HOH), 58.9 (C(=O)CH$_2$CH$_2$$\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 F)

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

The compound has not been reported previously.

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



(±)

Methyl 1-cyclopropyl-6-fluoro-7-(4-(4-(((*trans*)-2-hydroxycyclohexyl)amino)-4-oxobutyl)piperazin-1-yl)-4-oxo-1, 4-dihydroquinoline-3-carboxylate **146** (5.2 mg, 9.84 μmol, 1 eq.) and Dess-Martin periodinane (16.4 mg, 38.7 μmol, 4 eq.) were stirred in CH_2Cl_2 (3 ml) for 6 h. The solvent was removed under reduced pressure and the residue was purified by preparative HPLC (5-95 % acetonitrile/water over 20 min). The combined pure fractions were evaporated under reduced pressure to a volume of 20 ml, then $NaHCO_3$ (aq., sat., 30 ml) and 10 % *i*-PrOH/$CHCl_3$ (30 ml) were added. The organic layer was dried with $MgSO_4$ and evaporated under reduced pressure. **147** was obtained as a white amorphous solid (3.6 mg, 6.8 μmol, 69.1 %).

TLC R_f = 0.74 (30 % MeOH/CH_2Cl_2)

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

^{1}H NMR (400 MHz, DMSO d_6) δ / ppm = 8.45 (s, 1 H, *ortho* to C(=O)OC$\underline{H}_3$), 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, 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 Hz, 1 H, C$\underline{H}$HCHNH), 2.00 (ddquin, J = 13.2, 6.0, 2.9 Hz, 1 H, C$\underline{H}$HCH_2C(=O)), 1.65 - 1.83 (m, 4 H, $C\underline{H}_2CH_2$CHNH), 1.41 - 1.56 (m, 2 H, CH$\underline{H}$CHNH and CH$\underline{H}$CH_2C(=O)), 1.20 - 1.30 (m, 2 H, NCH(C$\underline{H}$H)$_2$), 1.05 - 1.13 (m, 2 H, NCH(CH$\underline{H}$)$_2$)

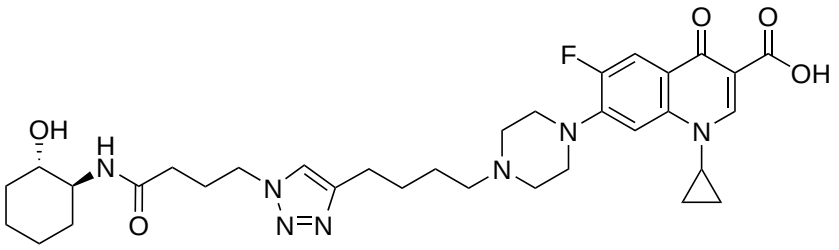
^{13}C NMR (101 MHz, DMSO d_6) δ / ppm = 207.5 ($\underline{C}$(=O)CHNH), 171.7 ($\underline{C}$(=O)CC(=O)OCH_3), 171.6 ($CH_2\underline{C}$(=O)NH), 165.0 ($\underline{C}$(=O)OCH_3), 152.6 (d, J = 247.6 Hz, *ipso* to F), 148.3 ($\underline{C}$=CC(=O)OCH_3), 143.9 (br s, *ipso* to piperazine), 138.1 (*para* to F), 121.8 (d, J = 6.4 Hz, *para* to piperazine), 111.5 (d, J = 22.4 Hz, *ortho* to C=O and *ortho* to F), 109.0 ($\underline{C}$C(=O)OCH_3), 106.3 (*meta* to C=O and *meta* to F), 57.0 ($\underline{C}$HNH and $C(=O)CH_2CH_2\underline{C}H_2N$), 52.3 (br s, $C(=O)CH_2CH_2CH_2N(\underline{C}H_2)\underline{C}H_2$), 51.3 ($\underline{C}H_3$), 49.5 (br s, $C(=O)CH_2CH_2CH_2N(CH_2\underline{C}H_2)CH_2\underline{C}H_2$), 40.6 ($C\underline{H}_2C(=O)$CHNH), 34.8 ($N\underline{C}H(CH_2)_2$), 33.9 ($C\underline{H}_2$CHNH), 32.9 ($C(=O)\underline{C}H_2CH_2CH_2N$), 27.2 ($C\underline{H}_2CH_2C(=O)$CHNH), 23.8 ($C\underline{H}_2CH_2$CHNH), 22.4 (br s, $C(=O)CH_2\underline{C}H_2$ CH_2N), 7.6 ($NCH(\underline{C}H_2)_2$)

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

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

The compound has not been reported previously.

0.38 1-Cyclopropyl-6-fluoro-7-(4-(4-(1-(4-(((*trans*)-2-hydroxycyclohexyl)amino)-4-oxobutyl)-1*H*-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 148



(±)

1-Cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **70** (40 mg, 97.2 μmol, 1 eq.) and 4-azido-*N*-((*trans*)-2-hydroxycyclohexyl)butanamide **145** (22.0 mg, 97.2 μmol, 1 eq.) were dissolved in 10 % water/*t*-BuOH (3 ml), and the mixture was degassed by bubbling N_2 through it. A solution of $CuSO_4$ and THPTA (97.2 μl, 9.72 μmol, 0.1 eq. 100 mM, aq.) was added, followed by a solution of sodium ascorbate (194 μl, 19.4 μmol, 0.2 eq., 100 mM, aq.). The mixture was stirred at r.t. under argon for 16 h. Water (50 ml) and 10 % *i*-PrOH/$CHCl_3$ (50 ml) were added, then the organic layer was separated, dried with $MgSO_4$ and evaporated under reduced pressure. The residue was purified by preparative HPLC (5-70 % acetonitrile/water over 15 min). The combined pure fractions were evaporated under reduced pressure and then partitioned between $NaHCO_3$ (aq., sat., 50 ml) and 10 % *i*-PrOH/$CHCl_3$ (50 ml). The organic layer was dried with $MgSO_4$ and evaporated under reduced pressure. **148** was obtained as a white amorphous solid (30.3 mg, 47.5 μmol, 48.9 %).

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

^{1}H NMR (400 MHz, DMSO d_6) δ / ppm = 8.64 (s, 1 H, *ortho* to C(=O)OH), 7.86 (d, J = 13.9 Hz, 1 H, *ortho* to F), 7.84 (s, 1 H, C<u>H</u>=CCH_2), 7.64 (d, J = 8.1 Hz, 1 H, N<u>H</u>), 7.54 (d, J = 7.5 Hz, 1 H, *meta* to F), 4.54 (d, J = 4.7 Hz, 1 H, O<u>H</u>), 4.30 (t, J = 6.8 Hz, 2 H, C(=O)$CH_2CH_2C\underline{H}_2$N), 3.77 - 3.86 (m, 1 H, NC<u>H</u>$(CH_2)_2$), 3.33 - 3.40 (m, 1 H, C<u>H</u>NH), 3.31 (br t, J = 4.8 Hz, 4 H, CH=$CCH_2CH_2CH_2N(CH_2C\underline{H}_2)CH_2C\underline{H}_2$), 3.14 - 3.24 (m, 1 H, C<u>H</u>OH), 2.63 (t, J = 7.4 Hz, 2 H, CH=$CC\underline{H}_2$), 2.56 (br t, J = 4.6 Hz, 4 H, CH=$CCH_2CH_2CH_2N(C\underline{H}_2)C\underline{H}_2$), 2.38 (t, J = 6.9 Hz, 2 H, CH=$CCH_2CH_2CH_2C\underline{H}_2$N), 2.04 - 2.08 (m, 2 H, C(=O)$C\underline{H}_2CH_2CH_2$N), 1.96 - 2.04 (m, 2 H, C(=O)$CH_2C\underline{H}_2CH_2$N), 1.78 - 1.87 (m, 1 H, C<u>H</u>HCHOH), 1.69 - 1.78 (m, 1 H, C<u>H</u>HCHNH), 1.63 (quin, J = 7.5 Hz, 2 H, CH=$CCH_2C\underline{H}_2CH_2CH_2$N), 1.54 - 1.60 (m, 2 H, C<u>H</u>HCH_2OH), 1.51 (quin, J = 7.4 Hz, 2 H, CH=$CCH_2CH_2C\underline{H}_2CH_2$N), 1.28 - 1.35 (m, 2 H, NCH(C<u>H</u>H)$_2$), 1.11 - 1.22 (m, 5 H, NCH(CH<u>H</u>)$_2$, CH<u>H</u>CHOH, CH<u>H</u>CH_2CHOH and $C\underline{H}_2CH_2$CHNH), 1.04 - 1.13 (m, 1 H, CH<u>H</u>CHNH)

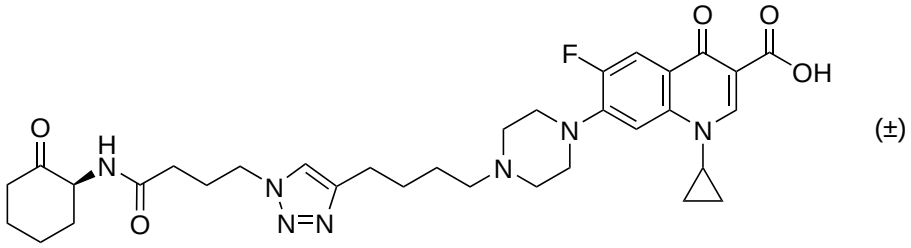
^{13}C NMR (101 MHz, DMSO d_6) δ / ppm = 176.4 (<u>C</u>(=O)CC(=O)OH), 170.9 (CH_2<u>C</u>(=O)NH), 166.0 (<u>C</u>(=O)OH), 153.1 (d, J = 252.1 Hz, *ipso* to F), 148.0 (<u>C</u>=CC(=O)OH), 146.9 (CH=<u>C</u>CH_2), 145.3 (d, J = 10.0 Hz, *ipso* to piperazine), 139.2 (*para* to F), 121.8 (NC<u>H</u>=CCH_2), 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 (<u>C</u>C(=O)OH), 106.3 (d, J = 3.3 Hz, *meta* to C=O and *meta* to F), 71.4 (<u>C</u>HOH), 57.4 (CH=$CCH_2CH_2CH_2C\underline{H}_2$N), 54.2 (<u>C</u>HNH), 52.4 (CH=$CCH_2CH_2CH_2CH_2N(\underline{C}H_2)\underline{C}H_2$), 49.5 (CH=$CCH_2CH_2CH_2CH_2N(CH_2\underline{C}H_2)CH_2CH_2$), 49.5 (CH=$CCH_2CH_2CH_2CH_2N(CH_2CH_2)CH_2\underline{C}H_2$), 48.8 (C(=O)$CH_2CH_2\underline{C}H_2$NCH=C), 35.9 (NC<u>H</u>$(CH_2)_2$), 34.1 ($C\underline{H}_2$CHOH), 32.3 (C(=O)<u>C</u>$H_2CH_2CH_2$NCH=C), 31.1 ($C\underline{H}_2$CHNH), 26.9 (CH=$CCH_2\underline{C}H_2CH_2CH_2$N), 26.1 (C(=O)$CH_2\underline{C}H_2CH_2$NCH=C), 25.8 (CH=$CCH_2CH_2\underline{C}H_2$ CH_2N), 25.0 (CH=C<u>C</u>$H_2CH_2CH_2CH_2$N), 24.2 ($C\underline{H}_2CH_2$CHNH), 23.8 ($C\underline{H}_2CH_2$CHOH), 7.6 (NCH(<u>C</u>$H_2)_2$)

^{19}**F NMR** (376.45 MHz, DMSO d_6) δ / ppm = -121.4 (ciprofloxacin F)

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

The compound has not been reported previously.

0.39 1-Cyclopropyl-6-fluoro-4-oxo-7-(4-(4-(1-(4-oxo-4-((2-oxocyclohexyl)amino)butyl)-1*H*-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid 149



1-Cyclopropyl-6-fluoro-7-(4-(4-(1-(4-(((*trans*)-2-hydroxycyclohexyl)amino)-4-oxobutyl)-1H-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **148** (15.0 mg, 23.6 mmol, 1 eq.) and Dess-Martin periodinane (35.0 mg, 82.5 mmol, 3.5 eq.) were stirred in CH_2Cl_2 (3 ml) for 4 h. The solvent was removed under reduced pressure and the residue was purified by preparative HPLC (5-70 % acetonitrile/water over 15 min). The combined pure fractions were evaporated under reduced pressure, then $NaHCO_3$ (aq., sat., 30 ml) and 10 % *i*-PrOH/$CHCl_3$ (30 ml) were added. The organic layer was dried with $MgSO_4$ and evaporated under reduced pressure. **149** was obtained as a clear gum (11.7 mg, 18.4 μmol, 78.0 %).

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

^{1}**H NMR** (500 MHz, DMSO d_6) δ / ppm = 8.65 (s, 1 H, *ortho* to C(=O)OH), 7.94 (d, J = 7.7 Hz, 1 H, N$\underline{H}$), 7.88 (d, J = 13.4 Hz, 1 H, *ortho* to F), 7.85 (s, 1 H, C$\underline{H}$=CCH$_2$), 7.55 (d, J = 7.3 Hz, 1 H, *meta* to F), 4.40 (dddd, J = 12.8, 7.6, 6.1, 1.1 Hz, 1 H), 4.31 (t, J = 7.0 Hz, 1 H, C(=O)CH$_2$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$_2$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$_2$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, 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 (C(=O)CHNH), 176.3 (C(=O)CC(=O)OH), 170.8 (CH$_2$C(=O)NH), 166.0 (C(=O)OH), 153.0 (d, J = 246.4 Hz, *ipso* to F), 147.9 (C=CC(=O)OH), 146.8 (CH=CCH$_2$), 145.1 (d, J = 10.1 Hz, *ipso* to piperazine), 139.1 (*para* to F), 121.7 (NCH=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 (CC(=O)OH, and *meta* to C=O and *meta* to F), 57.3 (CH=CCH$_2$CH$_2$CH$_2$CH$_2$N), 57.0 (CHNH), 52.4 (CH$_2$CH$_2$CH$_2$N(CH$_2$)CH$_2$), 49.5 (CH$_2$CH$_2$CH$_2$N(CH$_2$CH$_2$)CH$_2$CH$_2$), 49.5 (CH$_2$CH$_2$CH$_2$N(CH$_2$CH$_2$)CH$_2$CH$_2$), 48.7 (C(=O)CH$_2$CH$_2$CH$_2$NCH=C), 40.5 (CH$_2$C(=O)), 35.8 (NCH(CH$_2$)$_2$), 33.7 (CH$_2$CHNH), 31.8 (C(=O)CH$_2$CH$_2$CH$_2$NCH=C), 27.1 (CH$_2$CH$_2$C(=O)),

26.9 (CH=CCH$_2$<u>C</u>H$_2$CH$_2$CH$_2$N), 26.0 (C(=O)CH$_2$<u>C</u>H$_2$CH$_2$NCH=C), 25.7 (CH=CCH$_2$CH$_2$<u>C</u>H$_2$CH$_2$N), 24.9 (CH=C<u>C</u>H$_2$CH$_2$CH$_2$CH$_2$N), 23.8 (<u>C</u>H$_2$CH$_2$CHNH), 7.6 (NCH(<u>C</u>H$_2$)$_2$)

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

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

The compound has not been reported previously.

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