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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	15
0.5	4-Azido- <i>N</i> -(2-oxotetrahydrothiophen-3-yl)butanamide 96	16
0.6	1-Cyclopropyl-6-fluoro-4-oxo-7-(4-(4-(1-(4-oxo-4-((2-oxotetrahydrothiophen-3-yl)amino)butyl)-1 <i>H</i> -1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid 97	16
0.7	1-Cyclopropyl-6-fluoro-4-oxo-7-(4-(((4-(1-(4-oxo-4-((2-oxotetrahydrothiophen-3-yl)amino)butyl)-1 <i>H</i> -1,2,3-triazol-4-yl)butanoyl)oxy)methoxy)carbonyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid 99	18
0.8	4-Bromo- <i>N</i> -(2-methoxyphenyl)butanamide 101	19
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	19
0.10	4-Azido- <i>N</i> -(2-methoxyphenyl)butanamide 103	20
0.11	1-Cyclopropyl-6-fluoro-7-(4-(4-(1-(4-((2-methoxyphenyl)amino)-4-oxobutyl)-1 <i>H</i> -1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 104	21
0.12	4-Bromo- <i>N</i> -(3-methoxyphenyl)butanamide 106	22
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	23
0.14	4-Azido- <i>N</i> -(3-methoxyphenyl)butanamide 108	24
0.15	1-Cyclopropyl-6-fluoro-7-(4-(4-(1-(4-((3-methoxyphenyl)amino)-4-oxobutyl)-1 <i>H</i> -1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 109	25
0.16	Methyl 7-(4-(4-(<i>tert</i> -butoxy)-4-oxobutyl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate 136	26
0.17	4-(4-(1-Cyclopropyl-6-fluoro-3-(methoxycarbonyl)-4-oxo-1,4-dihydroquinolin-7-yl)piperazin-1-yl)butanoic acid trifluoroacetate 137	27
0.18	(1 <i>R</i> ,2 <i>R</i>)-2-(((<i>S</i>)-1-Phenylethyl)amino)cyclopentan-1-ol 113 and (1 <i>S</i> ,2 <i>S</i>)-2-(((<i>S</i>)-1-phenylethyl)amino)cyclopentan-1-ol 112	28
0.19	(1 <i>R</i> ,2 <i>R</i>)-2-Aminocyclopentan-1-ol 115	29
0.20	(1 <i>S</i> ,2 <i>S</i>)-2-Aminocyclopentan-1-ol 114	30
0.21	(1 <i>S</i> ,2 <i>S</i>)-2-((<i>tert</i> -Butyldimethylsilyl)oxy)cyclopentan-1-amine 125	30
0.22	4-Chloro- <i>N</i> -((1 <i>R</i> ,2 <i>R</i>)-2-hydroxycyclopentyl)butanamide 141	31
0.23	4-Chloro- <i>N</i> -((1 <i>S</i> ,2 <i>S</i>)-2-hydroxycyclopentyl)butanamide 140	32
0.24	4-Azido- <i>N</i> -((1 <i>S</i> ,2 <i>S</i>)-2-((<i>tert</i> -butyldimethylsilyl)oxy)cyclopentyl)butanamide 129	32

0.25	4-Azido- <i>N</i> -((1 <i>R</i> ,2 <i>R</i>)-2-hydroxycyclopentyl)butanamide 119	33
0.26	4-Azido- <i>N</i> -((1 <i>S</i> ,2 <i>S</i>)-2-hydroxycyclopentyl)butanamide 118	34
0.27	Methyl 1-cyclopropyl-6-fluoro-7-(4-(4-(((1 <i>R</i> ,2 <i>R</i>)-2-hydroxycyclopentyl)amino)-4-oxobutyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 121	35
0.28	Methyl 1-cyclopropyl-6-fluoro-7-(4-(4-(((1 <i>S</i> ,2 <i>S</i>)-2-hydroxycyclopentyl)amino)-4-oxobutyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 120	36
0.29	Methyl (<i>S</i>)-1-cyclopropyl-6-fluoro-4-oxo-7-(4-(4-oxo-4-((2-oxocyclopentyl)amino)butyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate 122	37
0.30	7-(4-(4-(1-(4-(((1 <i>S</i> ,2 <i>S</i>)-2-((<i>tert</i> -butyldimethylsilyl)oxy)cyclopentyl)amino)-4-oxobutyl)-1 <i>H</i> -1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 133	38
0.31	1-Cyclopropyl-6-fluoro-7-(4-(4-(1-(4-(((1 <i>R</i> ,2 <i>R</i>)-2-hydroxycyclopentyl)amino)-4-oxobutyl)-1 <i>H</i> -1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 124	39
0.32	1-Cyclopropyl-6-fluoro-7-(4-(4-(1-(4-(((1 <i>S</i> ,2 <i>S</i>)-2-hydroxycyclopentyl)amino)-4-oxobutyl)-1 <i>H</i> -1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 123	40
0.33	(<i>trans</i>)-2-Aminocyclohexan-1-ol 143	41
0.34	4-Chloro- <i>N</i> -((<i>trans</i>)-2-hydroxycyclohexyl)butanamide 144	42
0.35	4-Azido- <i>N</i> -((<i>trans</i>)-2-hydroxycyclohexyl)butanamide 145	42
0.36	Methyl 1-cyclopropyl-6-fluoro-7-(4-(4-(((<i>trans</i>)-2-hydroxycyclohexyl)amino)-4-oxobutyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 146	43
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	44
0.38	1-Cyclopropyl-6-fluoro-7-(4-(4-(1-(4-(((<i>trans</i>)-2-hydroxycyclohexyl)amino)-4-oxobutyl)-1 <i>H</i> -1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 148	45
0.39	1-Cyclopropyl-6-fluoro-4-oxo-7-(4-(4-(1-(4-oxo-4-((2-oxocyclohexyl)amino)butyl)-1 <i>H</i> -1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid 149	46

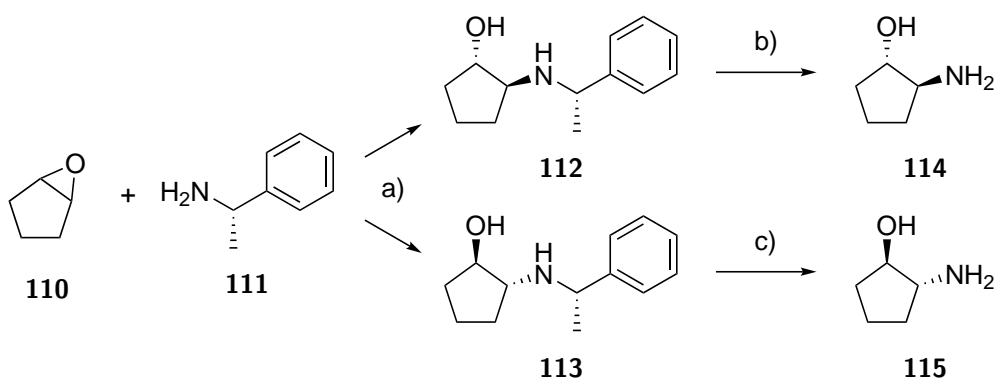
1 References

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0.1 Cyclopentyl alcohol derivatives

0.1.1 Synthesis of the cyclopentyl alcohol head groups

Synthesis of the cyclopentyl alcohol 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 Sugai¹⁵ 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 H₂ 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**: 35.2 %, **113**: 32.1 %. b) See Table 1. c) $\text{Pd}(\text{OH})_2$, 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, $\text{Pd}(\text{OH})_2$, MeOH, H_2	r.t., 1 atm	1 d	112 salt
112 ·HCl, $\text{Pd}(\text{OH})_2$, MeOH, H_2	r.t., 3.4 atm	1 d	114 salt, 112 salt, and an unidentified compound (approx. 7:2:10 by ^1H NMR)
112 , $\text{Pd}(\text{OH})_2$, MeOH, H_2	r.t., 5 atm	1 d	114 , 100 % yield

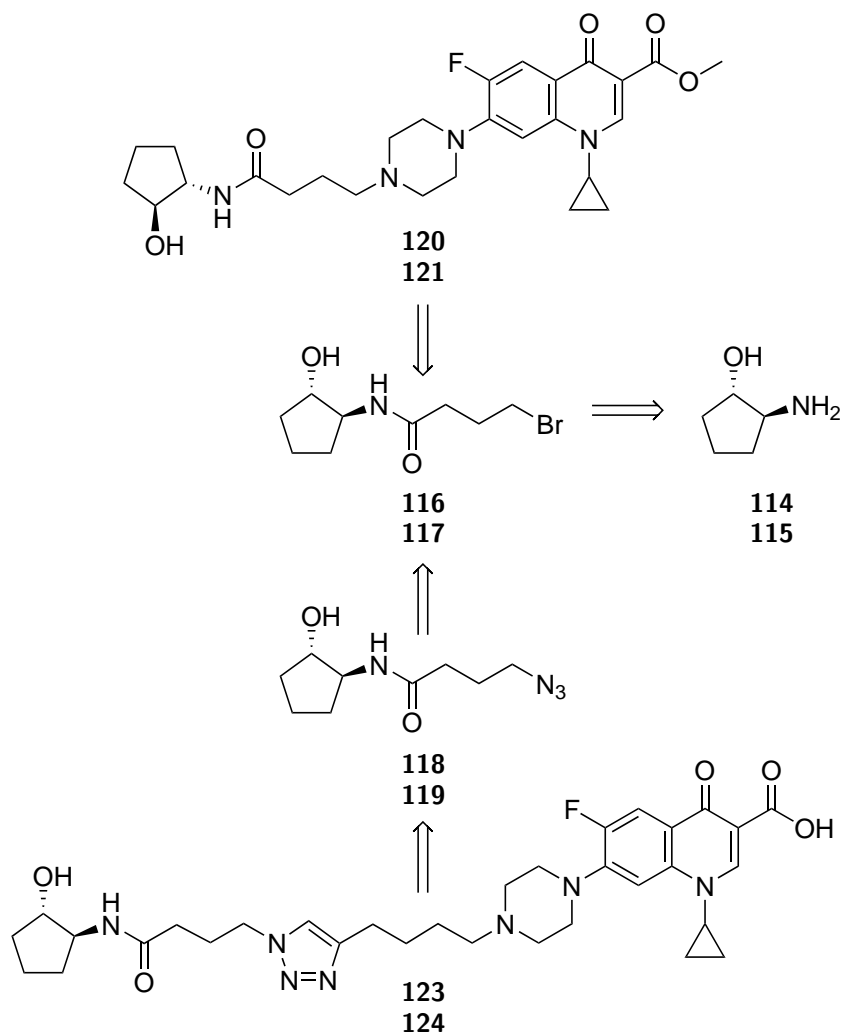
Table 1: Conditions attempted for the synthesis of (1*S*,2*S*)-2-aminocyclopentan-1-ol **114** and (1*R*,2*R*)-2-aminocyclopentan-1-ol **115** (see Scheme 1).

0.1.2 Initial branching strategy

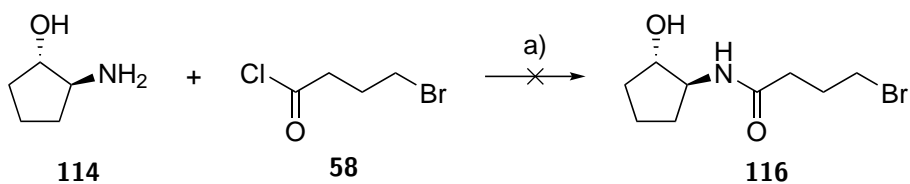
An initial retrosynthesis of the conjugates is shown in Scheme 2, and follows a similar path to previous conjugates.

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 cyclopentyl alcohol-CipMe conjugates **120** (*SS*) and **121** (*RR*), and the cyclopentyl alcohol-Cip triazole conjugates **123** (*SS*) and **124** (*RR*). *SS* enantiomers are shown, but both will be synthesised.



Scheme 3: Synthesis of Br-C₄-cyclopentanol-(*SS*) **116**. a) NaHCO₃, CH₂Cl₂, H₂O, 0 °C, 2 h.

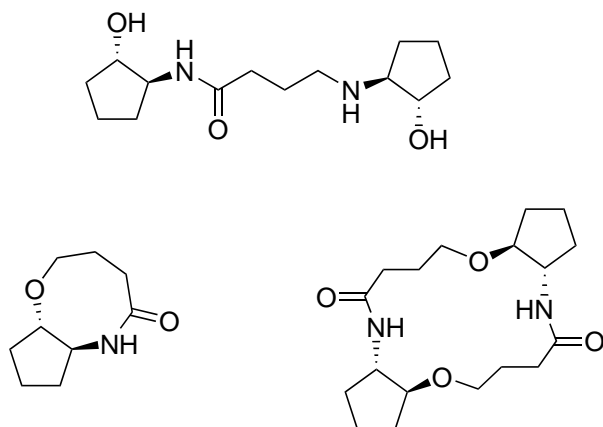
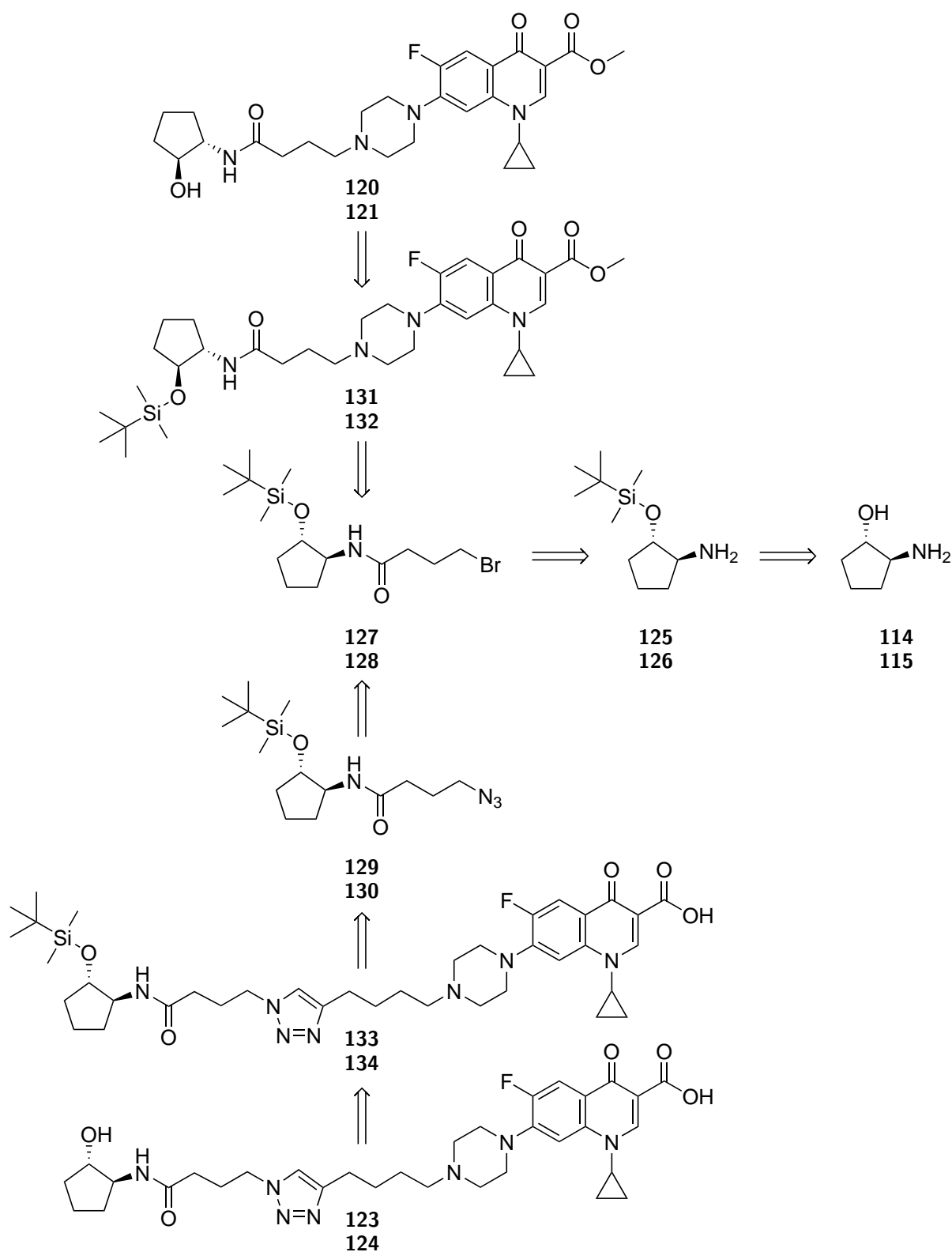


Figure 1: Impurities observed by LCMS during the synthesis of Br-C₄-cyclopentanol-(*SS*) **116**. Regiochemistry is speculative.

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-C₄-cyclopentanol-(*SS*) **116** and N₃-C₄-cyclopentanol-(*SS*) **118** could be purified. The TBDMS group could be removed later in the synthesis using TBAF or acid.

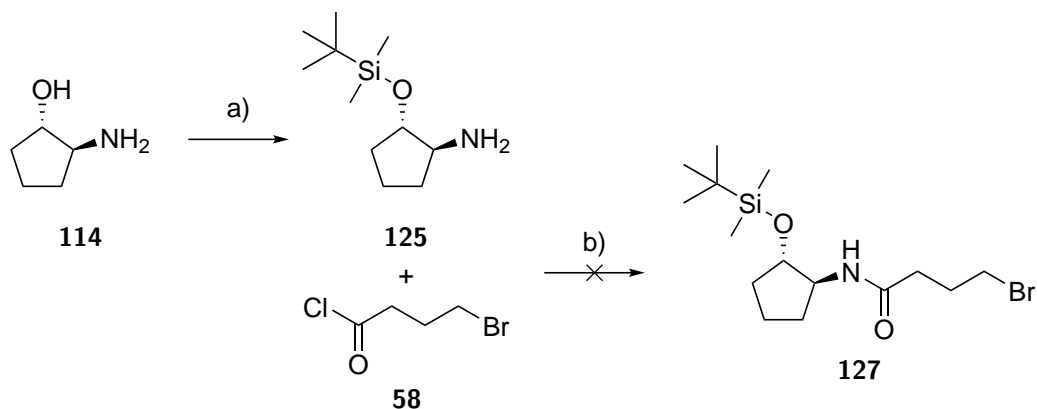


Scheme 4: Retrosynthesis of the cyclopentyl alcohol-CipMe conjugates **120** (*SS*) and **121** (*RR*), and the cyclopentyl alcohol-Cip triazole conjugates **123** (*SS*) and **124** (*RR*) using a TBDMS protection strategy. *SS* enantiomers are shown, but both will be synthesised.

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

Opt.

OTf? Cl? DBU?



Scheme 5: The attempted synthesis of Br-C₄-cyclopentanol-TBDMS-(*SS*) **127**. a) See Table 2. b) NaHCO₃, CH₂Cl₂, H₂O, 0 °C, 2 h.

Conditions	Temperature	Time	Result
TBDMSCl, DMAP, TEA, CH ₂ Cl ₂	r.t.	18 h	Trace of 125 , mostly 114
TBDMSCl, DMAP, TEA, CH ₂ Cl ₂	r.t.	1 d	Didn't go to completion, lost on prep TLC
TBDMSCl, imidazole, CH ₂ Cl ₂	0 °C	1 h	114
TBDMSCl, DBU, MeCN	0 °C	1 d	114
TBDMSOTf, TEA, CH ₂ Cl ₂	0 °C	4 h	125 possibly seen but lost in workup
TBDMSOTf in 2 portions, TEA, CH ₂ Cl ₂ , NH ₄ Cl workup	0 °C	6 h	125 salt
TBDMSOTf in 2 portions, TEA, CH ₂ Cl 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).

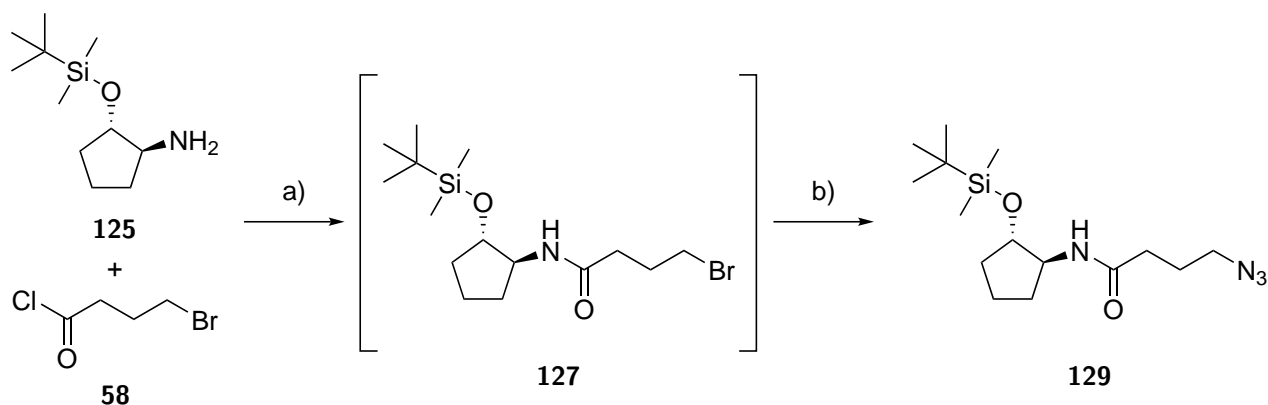
Still get side-reactions when adding tail

come
back to

0.1.3.2 Triazoles by two-step reaction

Talk about moving to two-step reaction.

come
back to

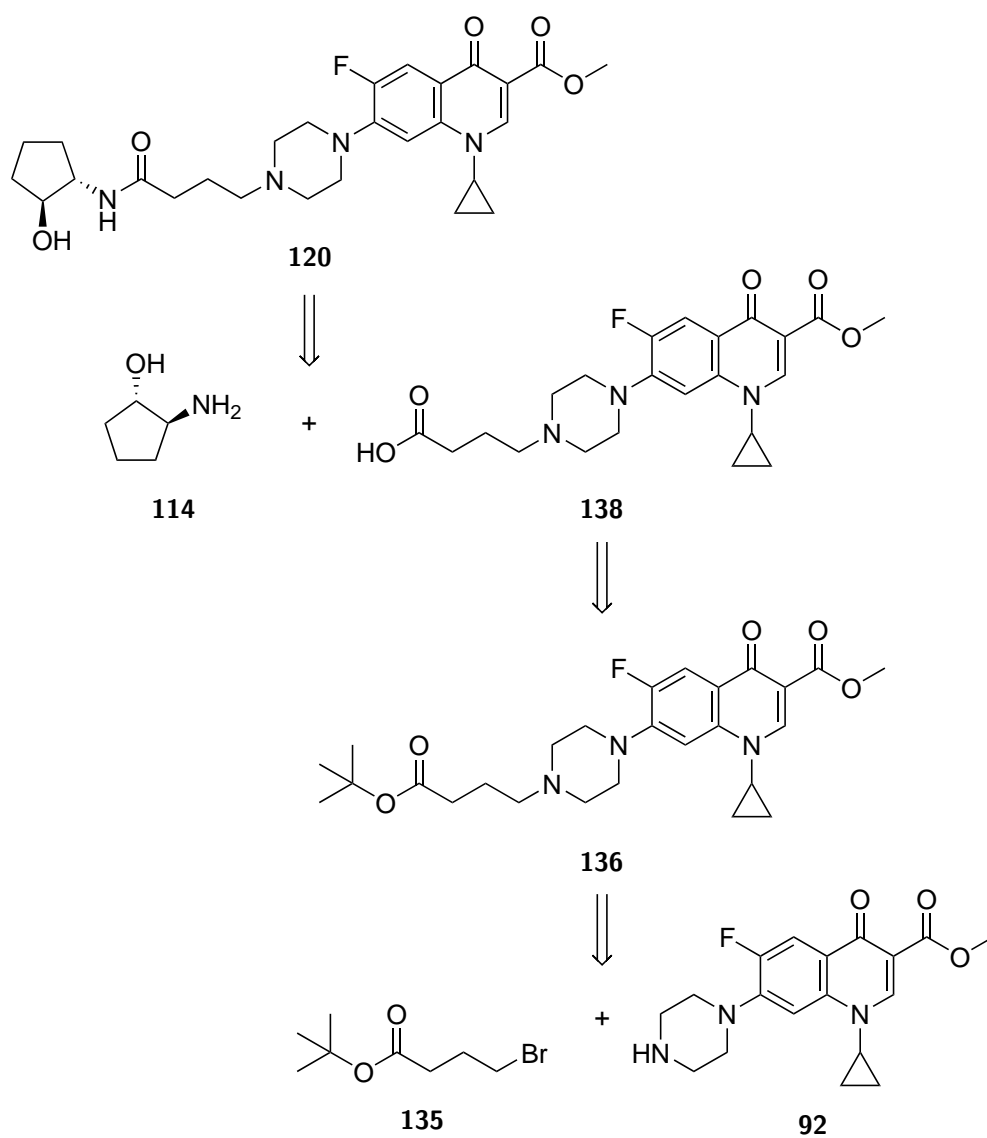


Scheme 6: a) NaHCO₃, CH₂Cl₂, H₂O, 0 °C, 3 h. b) NaN₃, DMF, CH₂Cl₂, r.t., 3 h. 99.2 % over 2 steps.

N₃-C₄-cyclopentanol-TBDMS-(*SS*) **129** and the alkynyl ciprofloxacin derivative **70** were subjected to standard click conditions, and the TBDMS-protected (*SS*)-cyclopentyl alcohol-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 CaCO₃ 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.

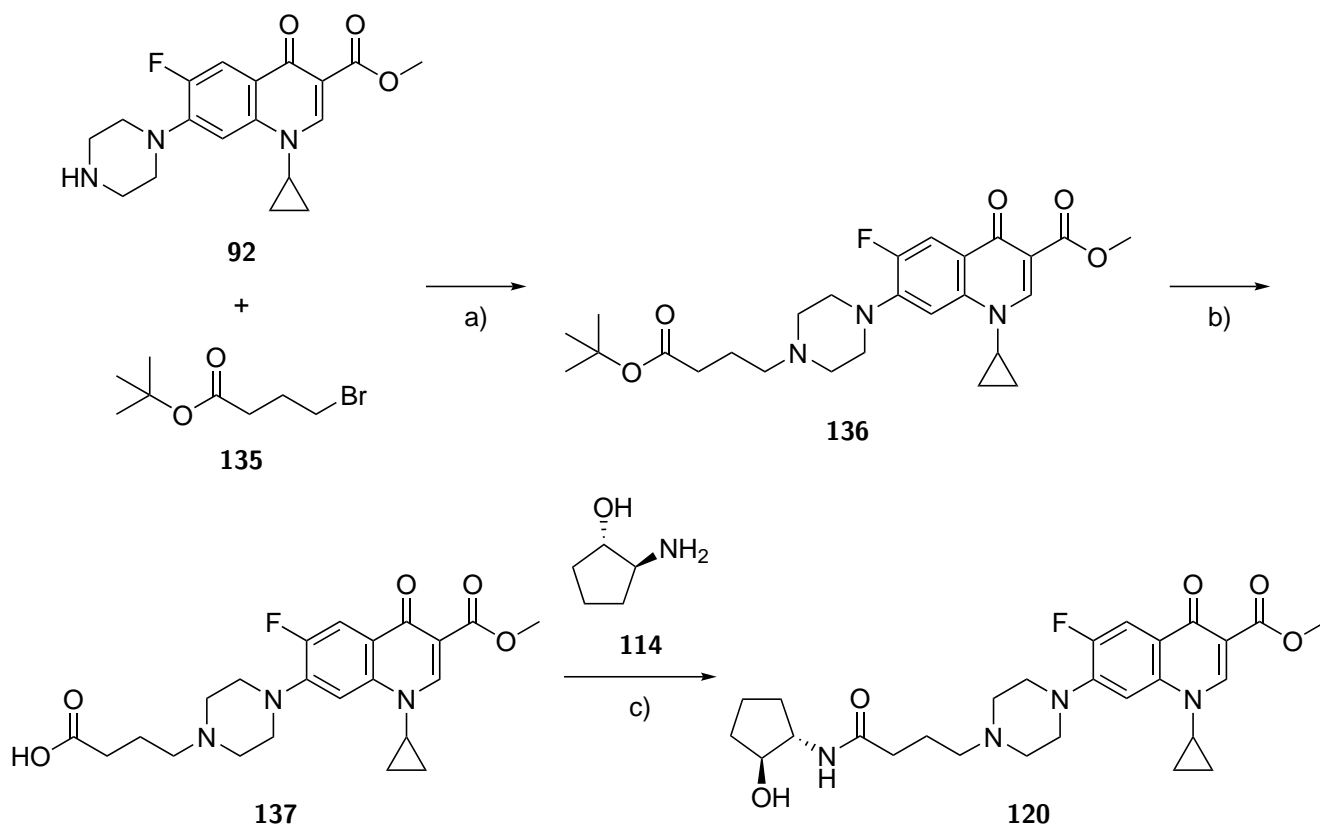
Scheme 7: a) CuSO_4 , sodium ascorbate, THPTA, H_2O , *t*-BuOH, r.t., 87.4 %. b) TBAF, THF, r.t., 16 h.

Given the side-reactions and low yields associated with the literature 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 ??).



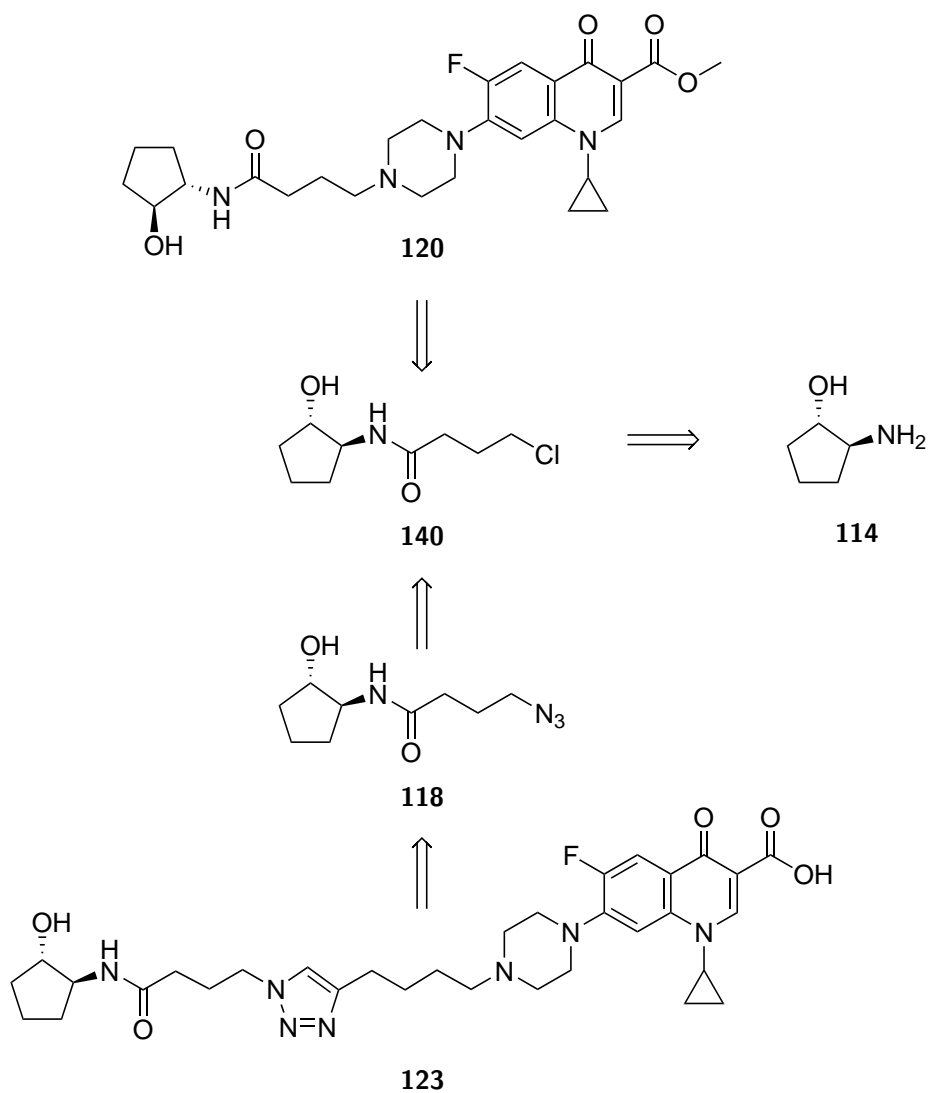
Scheme 8: Retrosynthesis of the cyclopentyl alcohol-CipMe conjugates (*RR*) **121** and (*SS*) **120**. *SS* enantiomers are shown, but both will be synthesised.

0.1.4.1 Synthesis of methyl-protected ciprofloxacin with linker with terminal carboxylate

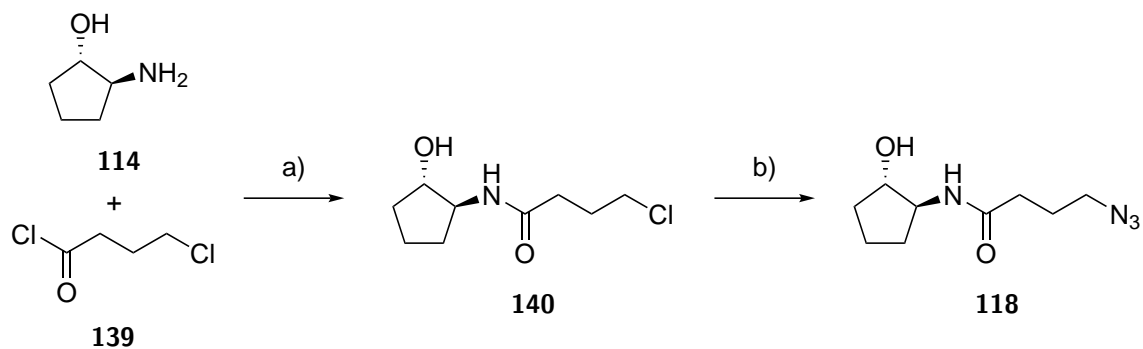


Scheme 9: Synthesis of **120**. a) NaI, TEA, MeCN, 100°C, 16h, 50 %. b) TFA, CH₂Cl₂, r.t., 18h, 96 %. c) EDC, HOBT, DIPEA, DMF, 35 %.

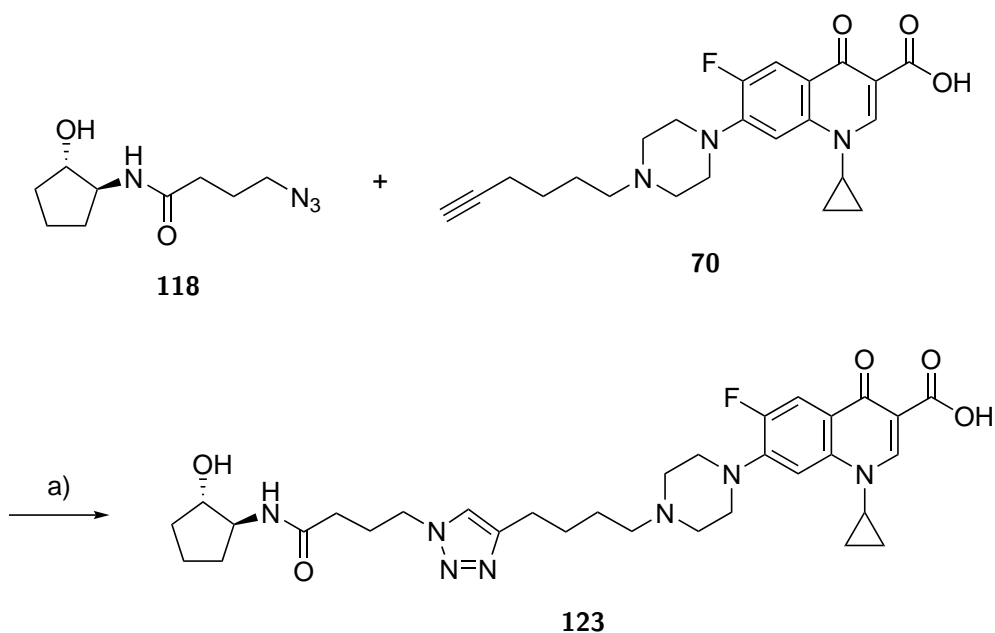
0.1.5 Triazoles from the chloride



Scheme 10: Retrosynthesis of the cyclopentyl alcohol-CipMe conjugates (*RR*) **121** and (*SS*) **120**, and the cyclopentyl alcohol-Cip triazole conjugates (*RR*) **124** and (*SS*) **123** using Cl-C₄-cyclopentanol-(*SS*) **140**. *SS* enantiomers are shown, but both will be synthesised.



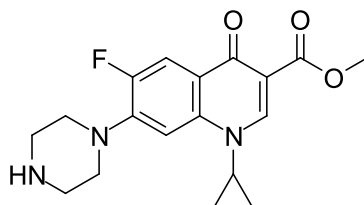
Scheme 11: Synthesis of N₃-C₄-cyclopentanol-(*SS*) **118**. a) TEA, CH₂Cl₂, 0 °C, 2 h. b) NaN₃, acetonitrile, 50 °C, 24 h, 45.0 %.



Scheme 12: Synthesis of the cyclopentyl alcohol-Cip triazole conjugate **123**. a) CuSO₄, THPTA, sodium ascorbate, H₂O, *t*-BuOH, CH₂Cl₂, r.t., 3 d, 22.2 %.

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 NaHCO₃ (sat., aq., 100 ml) and water (300 ml) were added. The product was extracted with CH₂Cl₂ (2×400 ml). The combined organic fractions were dried over MgSO₄ and evaporated under reduced pressure. **92** was obtained as a white amorphous solid (9.16 g, 26.5 mmol, 83.3 %).

TLC R_f = 0.13 (5 % MeOH/CH₂Cl₂)

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

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

¹³C NMR (101 MHz, MeOD) δ / ppm = 175.2 (C(=O)CC(=O)OCH₃), 166.8 (C(=O)OCH₃), 154.9 (d, J

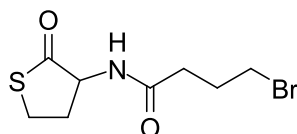
= 248.0 Hz, *ipso* to F), 150.1 ($\underline{\text{C}}=\text{CC}(=\text{O})\text{OCH}_3$), 146.6 (d, $J = 10.4$ Hz, *ipso* to piperazine), 139.9 (*para* to F), 123.3 (d, $J = 6.9$ Hz, *para* to piperazine), 113.0 (d, $J = 23.4$ Hz, *ortho* to C=O and *ortho* to F), 110.1 ($\underline{\text{C}}\text{C}(=\text{O})\text{OCH}_3$), 107.1 (d, $J = 3.5$ Hz, *meta* to C=O and *meta* to F), 52.3 ($\underline{\text{C}}\text{H}_3$), 51.7 ($\text{HN}(\underline{\text{C}}\text{H}_2\underline{\text{C}}\text{H}_2)\text{CH}_2\text{CH}_2$), 51.6 ($\text{HN}(\text{CH}_2\underline{\text{C}}\text{H}_2)\text{CH}_2$), 46.5 ($\text{HN}(\underline{\text{C}}\text{H}_2)\underline{\text{C}}\text{H}_2$), 36.4 ($\text{NCH}(\text{CH}_2)_2$), 8.7 ($\text{NCH}(\underline{\text{C}}\text{H}_2)_2$)

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

HRMS (ESI^+) m/z / Da = 346.1569, $[\text{M}+\text{H}]^+$ found, $[\text{C}_{18}\text{H}_{21}\text{FN}_3\text{O}_3]^+$ 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)

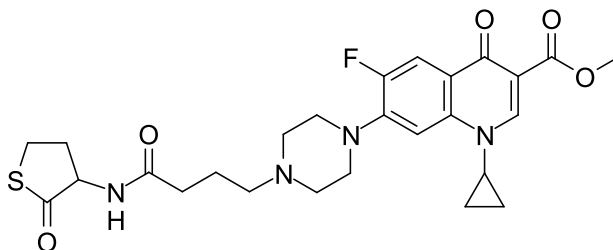
^1H NMR (400 MHz, CDCl_3) δ / ppm = 6.08 (d, $J = 6.1$ Hz, 1 H, $\underline{\text{NH}}$), 4.54 (dt, $J = 12.9, 6.5$ Hz, 1 H, $\underline{\text{CHNH}}$), 3.49 (t, $J = 6.4$ Hz, 2 H, $\underline{\text{CH}_2}\text{Br}$), 3.37 (ddd, $J = 12.2, 11.5, 5.3$ Hz, 1 H, $\text{SCH}\underline{\text{H}}$), 3.26 (ddd,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

^{13}C NMR (101 MHz, CDCl_3) δ / ppm = 205.4 ($\text{SC}(=\text{O})$), 172.1 ($\text{NHC}(=\text{O})$), 59.4 ($\underline{\text{CHNH}}$), 34.1 ($\text{C}(=\text{O})\underline{\text{C}}\text{H}_2$), 33.1 ($\underline{\text{C}}\text{H}_2\text{Br}$), 31.8 ($\text{SCH}_2\underline{\text{C}}\text{H}_2$), 28.0 ($\text{C}(=\text{O})\text{CH}_2\underline{\text{C}}\text{H}_2$), 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)

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

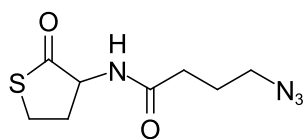
^{13}C NMR (126 MHz, MeOD) δ / ppm = 207.0 (SC(=O)), 175.7 (NHC(=O)), 175.1 (C(=O)CC(=O)OCH₃), 166.6 (C(=O)OCH₃), 154.7 (d, J = 249.0 Hz, *ipso* to F), 150.2 (s, CH=CC(=O)OCH₃), 145.6 (d, J = 10.6 Hz, *ipso* to piperazine), 139.8 (*para* to F), 123.5 (d, J = 6.9 Hz, *para* to piperazine), 113.1 (d, J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

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

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

The compound has been synthesised previously.^{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 NaN₃ (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 CH₂Cl₂ (150 ml). The aqueous layer was extracted twice more with CH₂Cl₂ (2×150 ml) and the combined organic fractions were dried with MgSO₄ 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)

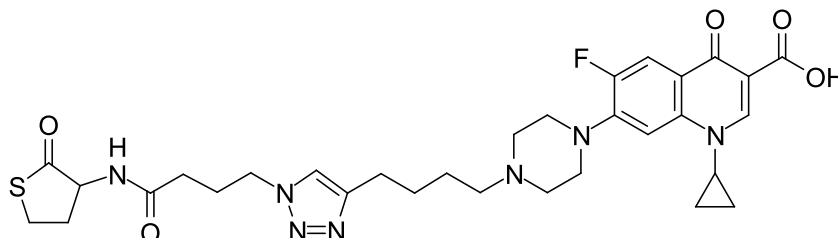
¹H NMR (400 MHz, CDCl₃) δ / ppm = 6.71 (d, J = 7.3 Hz, 1 H, NH), 4.54 (dt, J = 13.0, 7.0 Hz, 1 H, CHNH), 3.30 (t, J = 6.7 Hz, 2 H, CH₂N₃), 3.31 (td, J = 11.7, 5.3 Hz, 1 H, SCHH), 3.19 (ddd, J = 11.3, 7.0, 1.2 Hz, 1 H, SCHH), 2.70 (dddd, J = 12.4, 6.8, 5.3, 1.2 Hz, 1 H, SCH₂CHH), 2.29 (t, J = 7.5 Hz, 1 H, C(=O)CHH), 2.28 (t, J = 7.1 Hz, 1 H, C(=O)CHH), 1.97 (qd, J = 12.4, 7.0 Hz, 1 H, SCH₂CHH), 1.85 (quin, J = 6.9 Hz, 2 H, C(=O)CH₂CH₂)

¹³C NMR (101 MHz, CDCl₃) δ / ppm = 205.4 (SC(=O)), 172.3 (NHC(=O)), 59.4 (CHNH), 50.6 (CH₂N₃), 32.8 (C(=O)CH₂), 31.8 (SCH₂CH₂), 27.5 (SCH₂), 24.6 (C(=O)CH₂CH₂)

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

The compound has not been reported previously.

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 μ mol, 1 eq.) and 4-azido-*N*-(2-oxotetrahydrothiophen-3-yl)butanamide **96** (12.5 mg, 55.1 μ mol, 1.5 eq.) were dissolved in 1:9:10 water/*t*-BuOH/DMSO (3 ml), and the mixture was degassed by bubbling N₂ through it. A solution of CuSO₄ and THPTA (182 μ l, 18.2 μ mol, 0.5 eq. 100 mM, aq.) was added, followed by

a solution of sodium ascorbate (367 μ l, 36.7 μ mol, 1 eq., 100 mM, aq.). The mixture was stirred at r.t. under argon for 4 d. Water (10 ml) and 10 % *i*-PrOH/CHCl₃ (10 ml) were added, the organic layer was separated and the aqueous layer was extracted again with 10 % *i*-PrOH/CHCl₃ (2 \times 10 ml). The combined organic layers were dried with MgSO₄ and evaporated under reduced pressure. The residue was purified by preparative HPLC (5-95 % acetonitrile/water over 20 min). The combined pure fractions were evaporated under reduced pressure and then partitioned between NaHCO₃ (aq., sat., 50 ml) and 10 % *i*-PrOH/CHCl₃ (50 ml). The organic layer was dried with MgSO₄ and evaporated under reduced pressure. **97** was obtained as a white amorphous solid (16.5 mg, 25.9 μ mol, 70.6 %).

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

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

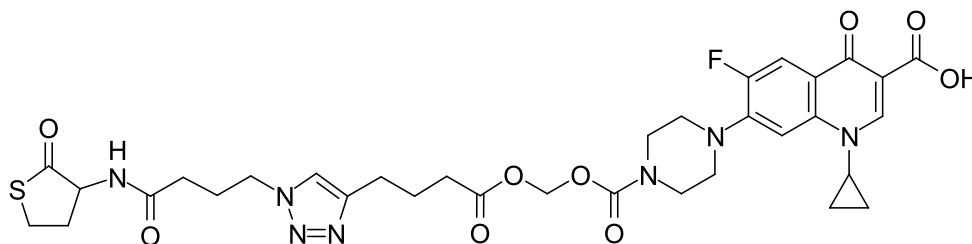
¹³C NMR (126 MHz, DMSO d₆) δ / ppm = 205.6 (SC(=O)), 176.4 (C(=O)CC(=O)OH), 171.4 (NHC(=O)), 166.0 (C(=O)OH), 153.1 (d, J = 249.3 Hz, *ortho* to F), 148.0 (CH=CC(=O)OH), 146.9 (CH=CCH₂), 145.3 (d, J = 10.1 Hz, *ipso* to piperazine), 139.2 (*para* to F), 121.8 (CH=CCH₂), 118.6 (d, J = 7.7 Hz, *para* to piperazine), 111.0 (d, J = 23.3 Hz, *ortho* to C=O and *ortho* to F), 106.7 (CC(=O)OH), 106.4 (d, J = 2.9 Hz, *meta* to C=O and *meta* to F), 58.2 (SC(=O)CHNH), 57.4 (CH=CCH₂CH₂CH₂CH₂N), 52.4 (CH₂CH₂CH₂N(CH₂)CH₂), 49.5 (CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 49.5 (CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 48.6 (CH₂NCH=C), 35.9 (NCH(CH₂)₂), 31.9 (NHC(=O)CH₂), 30.1 (CH₂CHNH), 26.9 (CH=CCH₂CH₂), 26.8 (SCH₂), 25.9 (NHC(=O)CH₂CH₂), 25.8 (CH=CCH₂CH₂CH₂), 25.0 (CH=CCH₂), 7.6 (NCH(CH₂)₂)

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

HRMS (ESI⁺) m/z / Da = 640.2739, [M+H]⁺ found, [C₃₁H₃₉FN₇O₅S]⁺ requires 640. 2712

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 CH₂Cl₂ (18.6 ml) at r.t. under Ar for 3 h. The mixture was filtered and the filtrate was dry-loaded onto SiO₂ and purified by column chromatography (SiO₂, 5-10 % MeOH/CH₂Cl₂). **99** was obtained as pale brown/yellow amorphous solid (14.7 mg, 20.2 μmol, 5.0 %).

TLC R_f = 0.40 (5 % CH₂Cl₂/MeOH)

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

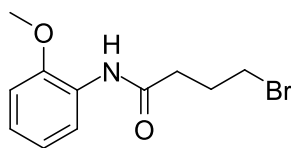
¹H NMR (400 MHz, DMSO d₆) δ / ppm = 15.16 (br s, 1 H, C(=O)OH), 8.65 (s, 1 H, *ortho* to C(=O)OH), 8.21 (d, J = 8.5 Hz, 1 H, NH), 7.89 (d, J = 13.1 Hz, 1 H, *ortho* to F), 7.85 (s, 1 H, CH=CCH₂), 7.57 (d, J = 7.4 Hz, 1 H, *meta* to F), 5.74 (s, 1 H, OCH₂O), 4.58 (ddd, J = 12.6, 8.1, 7.2 Hz, 1 H, CHNH),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

¹³C NMR (101 MHz, DMSO d₆) δ / ppm = 205.5 (SC(=O)), 176.4 (C(=O)CC(=O)OH), 171.8 (C(=O)OCH₂O), 171.3 (NHC(=O)), 165.9 (C(=O)OH), 152.8 (d, J = 249.7 Hz, *ipso* to F), 152.9 (OC(=O)N), 148.1 (CH=CC(=O)OH), 146.0 (CH=CCH₂), 144.9 (d, J = 9.6 Hz, *ipso* to piperazine), 139.1 (*para* to F), 122.0 (CH=CCH₂), 118.9 (d, J = 7.5 Hz, *para* to piperazine), 111.0 (d, J = 23.5 Hz, *ortho* to C=O and *ortho* to F), 106.8 (CC(=O)OH, and *meta* to C=O and *meta* to F), 80.3 (OCH₂O), 58.2 (CHNH), 49.1 (C(=O)N(CH₂CH₂)CH₂CH₂), 49.1 (C(=O)N(CH₂CH₂)CH₂CH₂), 48.6 (C(=O)CH₂CH₂CH₂N), 43.4 (N(CH₂)CH₂), 43.0 (N(CH₂)CH₂), 35.9 (NCH(CH₂)₂), 32.7 (CH=CCH₂CH₂CH₂C(=O)), 31.8 (NHC(=O)CH₂), 30.1 (SCH₂CH₂), 26.8 (SCH₂), 25.8 (C(=O)CH₂CH₂CH₂N), 24.2 (CH=CCH₂CH₂CH₂C(=O)), 24.0 (CH=CCH₂CH₂CH₂C(=O)), 7.6 (NCH(CH₂)₂)

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

The compound has not been reported previously.

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



2-Methoxyaniline **100** (9.12 ml, 10.0 g, 81.2 mmol, 1 eq.) and NaHCO₃ (8.19 g, 97.4 mmol, 1.2 eq.) were dissolved in water (100 ml) and CH₂Cl₂ (100 ml). The mixture was cooled to 0 °C and 4-bromobutyryl chloride **58** (9.40 ml, 15.1 g, 81.2 mmol, 1 eq.) was added dropwise over 15 min. The mixture was stirred at 0 °C for 1.5 h, then the aqueous layer was removed. The organic layer was dried with MgSO₄ and purified by column chromatography (SiO₂, 5-25 % EtOAc/P.E.). The combined pure fractions were dried with MgSO₄ and evaporated under reduced pressure. **101** was obtained as an initially colourless liquid which slowly turned blue then black if left out on the bench (11.0 g, 40.6 mmol, 50.0 %).

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

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

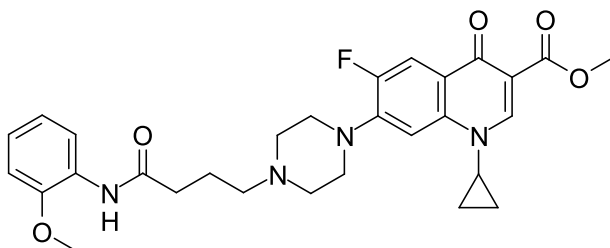
¹H NMR (400 MHz, CDCl₃ d₁) δ / ppm = 8.32 (dd, J = 8.0, 1.7 Hz, 1 H, *ortho* to NH), 7.85 (br s, 1 H, NH), 7.02 (td, J = 7.9, 1.7 Hz, 1 H, *para* to NH), 6.93 (td, J = 7.7, 1.4 Hz, 1 H, *para* to OCH₃), 6.85 (dd, J = 8.1, 1.5 Hz, 1 H, *ortho* to OCH₃), 3.85 (s, 3 H, CH₃), 3.50 (t, J = 6.4 Hz, 2 H, CH₂Br),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

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

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

The compound has not been reported previously.

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 SiO₂ and purified by column chromatography (SiO₂, 4 % MeOH/CH₂Cl₂). The combined pure fractions were dried with MgSO₄ 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/CH₂Cl₂)

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

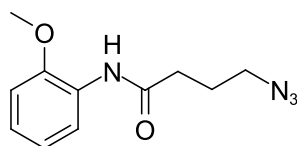
¹H NMR (400 MHz, CDCl₃ d₁) δ / ppm = 8.48 (s, 1 H, *ortho* to C(=O)OCH₃), 8.36 (d, J = 7.9 Hz, 1 H, *ortho* to NH), 7.87 - 7.99 (m, 2 H, *ortho* to F and NH), 7.19 (d, J = 6.5 Hz, 1 H, *meta* to F), 7.01 (t, J = 7.5 Hz, 1 H, *para* to NH), 6.93 (t, J = 7.7 Hz, 1 H, *para* to OCH₃), 6.85 (d, J = 7.9 Hz,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

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

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

The compound has not been reported previously.

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 NaN₃ (1.17 g, 18.0 mmol, 2.4 eq.) were refluxed in acetonitrile (100 ml) for 2 h. The mixture was cooled and filtered, and the filtrate was dry-loaded onto SiO₂ and purified by column chromatography using a Combiflash (SiO₂, 8-14 % then hold at 14 % EtOAc/P.E.). **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)

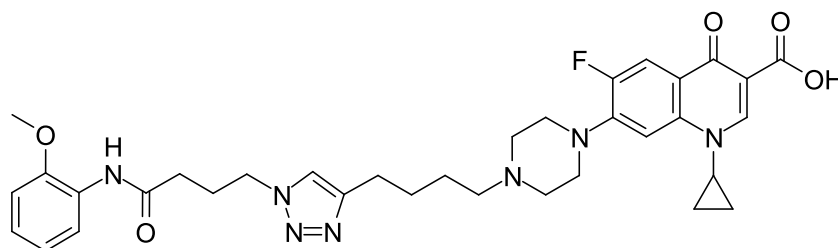
^1H NMR (400 MHz, CDCl_3 d_1) δ / ppm = 8.32 (dd, J = 7.9, 1.0 Hz, 1 H, *ortho* to NH), 7.86 (br s, 1 H, NH), 7.00 (td, J = 7.5, 1.5 Hz, 1 H, *para* to NH), 6.90 (td, J = 7.7, 1.1 Hz, 1 H, *para* to OCH_3), 6.83 (dd, J = 8.1, 1.4 Hz, 1 H, *ortho* to OCH_3), 3.81 (s, 3 H, CH_3), 3.33 (t, J = 6.7 Hz, 2 H, CH_2Br), 2.42 (t, J = 7.2 Hz, 2 H, C(=O)CH_2), 1.94 (quin, J = 6.9 Hz, 2 H, $\text{C(=O)CH}_2\text{CH}_2$)

^{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 (CH_3), 50.3 (CH_2N_3), 33.9 (C(=O)CH_2), 24.3 ($\text{C(=O)CH}_2\text{CH}_2$)

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

The data are consistent with the literature.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 % $\text{MeOH}/\text{CH}_2\text{Cl}_2$). 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 % $\text{MeOH}/\text{CH}_2\text{Cl}_2$)

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)

^1H NMR (400 MHz, CDCl_3) δ / ppm = 15.05 (br s, 1 H, C(=O)OH), 8.76 (s, 1 H, *ortho* to C(=O)OH), 8.31 (dd, J = 8.0, 1.7 Hz, 1 H, *ortho* to NH), 8.00 (d, J = 13.0 Hz, 1 H, *ortho* to F), 7.83 (br s, 1 H, NH), 7.37 (s, 1 H, $\text{CH}=\text{CCH}_2$), 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, $\text{C(=O)CH}_2\text{CH}_2\text{CH}_2\text{N}$), 3.88 (s, 3 H, CH_3), 3.54 (tt, J = 6.9, 4.0 Hz, 1 H, $\text{NCH}(\text{CH}_2)_2$), 3.35 (br t, J = 4.7

H_z, 4 H, CH=CCH₂CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 2.76 (t, *J* = 7.5 Hz, 2 H, CH=CCH₂), 2.66 (t, *J* = 4.7 Hz, 4 H, CH=CCH₂CH₂CH₂CH₂N(CH₂)CH₂), 2.47 (t, *J* = 7.3 Hz, 2 H, CH=CCH₂CH₂CH₂CH₂N), 2.44 (t, *J* = 6.8 Hz, 2 H, C(=O)CH₂CH₂CH₂N), 2.32 (quin, *J* = 6.7 Hz, 2 H, C(=O)CH₂CH₂CH₂N), 1.75 (quin, *J* = 7.6 Hz, 2 H, CH=CCH₂CH₂CH₂CH₂N), 1.61 (quin, *J* = 7.5 Hz, 2 H, CH=CCH₂CH₂CH₂CH₂N), 1.35 - 1.42 (m, 2 H, NCH(CH₂)₂), 1.17 - 1.22 (m, 2 H, NCH(CH₂)₂)

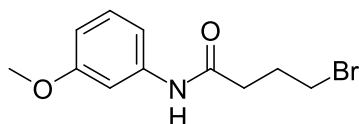
¹³C NMR (101 MHz, CDCl₃) δ / ppm = 177.1 (C(=O)CC(=O)OH), 169.5 (NHC(=O)), 167.0 (C(=O)OH), 153.7 (d, *J* = 251.4 Hz, *ipso* to F), 148.1 (CH=CCH₂), 147.8 (*ipso* to OCH₃), 147.3 (C=CC(=O)OH), 145.9 (d, *J* = 10.4 Hz, *ipso* to piperazine), 139.1 (*para* to F), 127.3 (*ipso* to NH), 123.9 (*para* to NH), 121.0 (*para* to OCH₃), 120.9 (CH=CCH₂), 119.7 (*para* to piperazine, and *ortho* to NH and *meta* to OCH₃), 112.4 (d, *J* = 23.4 Hz, *ortho* to C=O and *ortho* to F), 109.9 (*ortho* to OCH₃ and *meta* to NH), 108.1 (CC(=O)OH), 104.7 (*meta* to C=O and *meta* to F), 58.1 (CH=CCH₂CH₂CH₂CH₂N), 55.6 (CH₃), 52.8 (CH=CCH₂CH₂CH₂CH₂N(CH₂)CH₂), 49.8 (CH=CCH₂CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 49.8 (CH=CCH₂CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 49.1 (C(=O)CH₂CH₂CH₂N), 35.2 (NCH(CH₂)₂), 33.8 (C(=O)CH₂CH₂CH₂N), 27.3 (CH=CCH₂CH₂CH₂CH₂N), 26.4 (CH=CCH₂CH₂CH₂CH₂N), 26.0 (C(=O)CH₂CH₂CH₂N), 25.5 (CH=CCH₂CH₂CH₂CH₂N), 8.2 (NCH(CH₂)₂)

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

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

The compound has not been reported previously.

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



3-Methoxyaniline **105** (3.04 ml, 3.33 g, 27.1 mmol, 1 eq.) and NaHCO₃ (2.73 g, 32.5 mmol, 1.2 eq.) were dissolved in water (30 ml) and CH₂Cl₂ (30 ml). The mixture was cooled to 0 °C and 4-bromobutyryl chloride **58** (3.13 ml, 5.03 g, 27.1 mmol, 1 eq.) was added dropwise over 5 min. The mixture was stirred at 0 °C for 1 h, then the aqueous layer was removed. The organic layer was dry-loaded onto SiO₂ and purified by column chromatography using a Combiflash (SiO₂, 0-100 % EtOAc/P.E.). The combined pure fractions were dried with MgSO₄ and evaporated under reduced pressure. **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)

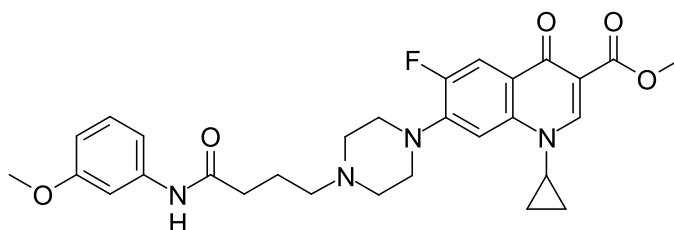
¹H NMR (400 MHz, CDCl₃ d₁) δ / ppm = 8.45 (s, 1 H, NH), 7.27 (t, *J* = 2.2 Hz, 1 H, *ortho* to OCH₃ and *ortho* to NH), 7.14 (t, *J* = 8.1 Hz, 1 H, *meta* to OCH₃ and *meta* to NH), 7.02 (d, *J* = 8.3 Hz, 1 H, *para* to OCH₃), 6.62 (dd, *J* = 8.2, 2.1 Hz, 1 H, *para* to NH), 3.71 (s, 3 H, CH₃), 3.42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

^{13}C NMR (101 MHz, CDCl_3 d₁) δ / ppm = 170.3 ($\text{C}(=\text{O})$), 159.9 (*ipso* to OCH_3), 139.0 (*ipso* to NH), 129.5 (*meta* to OCH_3 and *meta* to NH), 112.1 (*para* to OCH_3), 109.9 (*para* to NH), 105.7 (*ortho* to OCH_3 and *ortho* to NH), 55.2 (CH_3), 35.3 ($\text{C}(=\text{O})\text{CH}_2$), 33.2 (CH_2Br), 28.0 ($\text{C}(=\text{O})\text{CH}_2\text{CH}_2$)

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 % $\text{MeOH}/\text{CH}_2\text{Cl}_2$). 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 % $\text{MeOH}/\text{CH}_2\text{Cl}_2$)

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

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

^{13}C NMR (101 MHz, CDCl_3) δ / ppm = 173.1 ($\text{C}(=\text{O})\text{CC}(=\text{O})\text{OCH}_3$), 170.9 ($\text{NHC}(=\text{O})$), 166.3 ($\text{C}(=\text{O})\text{OCH}_3$), 160.1 (*ipso* to OCH_3), 153.3 (d, J = 250.1 Hz, *ipso* to F), 148.4 ($\text{C}=\text{CC}(=\text{O})\text{OCH}_3$), 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 $\text{C}=\text{O}$ and *ortho* to F), 111.8 (*para* to OCH_3), 110.0 ($\text{CC}(=\text{O})\text{OCH}_3$), 109.8 (*para* to NH), 105.5 (*ortho* to OCH_3 and *ortho* to NH), 105.0 (*meta* to $\text{C}=\text{O}$ and

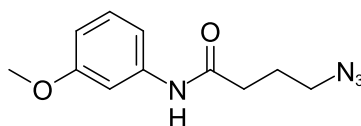
meta to F), 57.0 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$), 55.3 (aromatic OCH_3), 52.6 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)$), 52.1 ($\text{C}(=\text{O})\text{OCH}_3$), 49.2 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)\text{CH}_2\text{CH}_2$), 35.2 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$), 34.6 ($\text{NCH}(\text{CH}_2)_2$), 21.7 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$), 8.2 ($\text{NCH}(\text{CH}_2)_2$)

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

HRMS (ESI^+) m/z / Da = 537.2500, $[\text{M}+\text{H}]^+$ found, $[\text{C}_{29}\text{H}_{34}\text{FN}_4\text{O}_5]^+$ 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 filtrate was dry-loaded onto SiO_2 and purified by column chromatography using a Combiflash (SiO_2 , 0-100 % EtOAc/P.E.). The combined pure fractions were dried with MgSO_4 and evaporated under reduced pressure. **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)

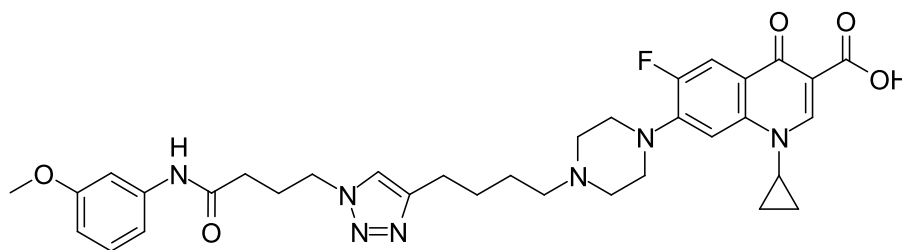
^1H NMR (400 MHz, MeOD) δ / ppm = 8.63 (br s, 1 H, NH), 7.26 (t, J = 2.3 Hz, 1 H, *ortho* to OCH_3 and *ortho* to NH), 7.15 (t, J = 8.1 Hz, 1 H, *meta* to OCH_3 and *meta* to NH), 7.01 (dd, J = 7.8, 1.6 Hz, 1 H, *para* to OCH_3), 6.63 (dd, J = 8.2, 1.9 Hz, 1 H, *para* to NH), 3.69 (s, 3 H, CH_3), 3.28 (t, J = 6.7 Hz, 2 H, CH_2N_3), 2.39 (t, J = 7.4 Hz, 2 H, $\text{C}(=\text{O})\text{CH}_2$), 1.91 (quin, J = 7.0 Hz, 2 H, $\text{C}(=\text{O})\text{CH}_2\text{CH}_2$)

^{13}C NMR (101 MHz, MeOD) δ / ppm = 170.8 ($\text{C}(=\text{O})$), 159.6 (*ipso* to OCH_3), 138.9 (*ipso* to NH), 129.2 (*meta* to OCH_3 and *meta* to NH), 112.3 (*para* to OCH_3), 109.5 (*para* to NH), 106.0 (*ortho* to OCH_3 and *ortho* to NH), 54.8 (CH_3), 50.4 (CH_2N_3), 33.6 ($\text{C}(=\text{O})\text{CH}_2$), 24.4 ($\text{C}(=\text{O})\text{CH}_2\text{CH}_2$)

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 μ mol, 1 eq.) and 4-azido-*N*-(3-methoxyphenyl)butanamide **108** (13.7 mg, 58.5 μ mol, 1 eq.) were dissolved in water (1 ml), *t*-BuOH (9 ml) and CH₂Cl₂ (10 ml), and the mixture was degassed by bubbling through N₂. A solution of CuSO₄ and THPTA (58.5 μ l, 5.85 μ mol, 0.1 eq. 100 mM, aq.) was added, followed by a solution of sodium ascorbate (117 μ l, 11.7 μ mol, 0.2 eq., 100 mM, aq.). The mixture was stirred at room temperature under argon for 2 h, then the solvent was removed under reduced pressure. The residue was partitioned between water (15 ml) and CH₂Cl₂ (15 ml), and the aqueous layer was extracted a further four times with CH₂Cl₂ (4 \times 15 ml). The combined organic layers were dried with MgSO₄, dry-loaded onto SiO₂ and purified by column chromatography (SiO₂, 0-10 % MeOH/CH₂Cl₂). The combined pure fractions were dried with MgSO₄ and evaporated under reduced pressure. **109** was obtained as a clear amorphous solid (1.9 mg, 2.9 μ mol, 5.0 %).

TLC R_f = 0.22 (10 % MeOH/CH₂Cl₂)

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

¹H NMR (400 MHz, DMSO d₆) δ / ppm = 15.23 (br s, 1 H, C(=O)OH), 9.89 (s, 1 H, NH), 8.66 (s, 1 H, *ortho* to C(=O)OH), 7.90 (d, J = 13.4 Hz, 1 H, *ortho* to F), 7.88 (s, 1 H, CH=CCH₂), 7.55 (d, J = 7.6 Hz, 1 H, *meta* to F), 7.27 (t, J = 2.1 Hz, 1 H, *ortho* to C=O and *ortho* to F), 7.16 (t, J = 8.1 Hz, 1 H, *meta* to OCH₃ and *meta* to NH), 7.08 (d, J = 7.8 Hz, 1 H, *para* to OCH₃), 6.59 (ddd, J = 8.1, 2.4, 0.7 Hz, 1 H, *para* to NH), 4.36 (t, J = 6.9 Hz, 2 H, C(=O)CH₂CH₂CH₂N), 3.81 (tt, J = 6.7, 4.0 Hz, 1 H, NCH(CH₂)₂), 3.70 (s, 3 H, CH₃), 3.28 - 3.32 (m, 4 H, CH=CCH₂CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 2.64 (t, J = 7.5 Hz, 2 H, CH=CCH₂), 2.56 (m, J = 4.2, 4.2 Hz, 4 H, CH=CCH₂CH₂CH₂CH₂N(CH₂)CH₂), 2.38 (t, J = 7.3 Hz, 2 H, CH=CCH₂CH₂CH₂CH₂N), 2.30 (t, J = 7.4 Hz, 2 H, C(=O)CH₂CH₂CH₂N), 2.10 (quin, J = 7.1 Hz, 2 H, C(=O)CH₂CH₂CH₂N), 1.64 (quin, J = 7.5 Hz, 2 H, CH=CCH₂CH₂CH₂CH₂N), 1.51 (quin, J = 7.2 Hz, 2 H, CH=CCH₂CH₂CH₂CH₂N), 1.27 - 1.33 (m, 2 H, NCH(CH₂)₂), 1.15 - 1.20 (m, 2 H, NCH(CH₂)₂)

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

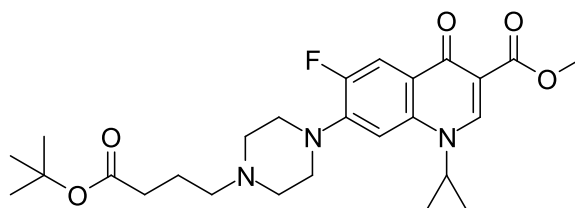
$\underline{\text{CH}_2\text{CH}_2\text{CH}_2\text{N}}$), 26.8 ($\text{CH}=\text{CCH}_2\underline{\text{CH}_2\text{CH}_2\text{CH}_2\text{N}}$), 25.7 ($\text{CH}=\text{CCH}_2\text{CH}_2\underline{\text{CH}_2\text{CH}_2\text{N}}$), 25.5 ($\text{C}(=\text{O})\text{CH}_2\underline{\text{CH}_2\text{CH}_2\text{N}}$), 24.9 ($\text{CH}=\text{C}\underline{\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}}$), 7.6 ($\text{NCH}(\underline{\text{CH}_2})_2$)

^{19}F NMR (376.45 MHz, DMSO d_6) δ / ppm = -121.5 (s, ciprofloxacin F)

HRMS (ESI^+) m/z / Da = 646.3159, $[\text{M}+\text{H}]^+$ found, $[\text{C}_{34}\text{H}_{41}\text{FN}_7\text{O}_5]^+$ 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_2Cl_2). **136** was obtained as a white amorphous solid (141 mg, 0.289 mmol, 49.9 %).

TLC R_f = 0.12 (4 % MeOH/ CH_2Cl_2)

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

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

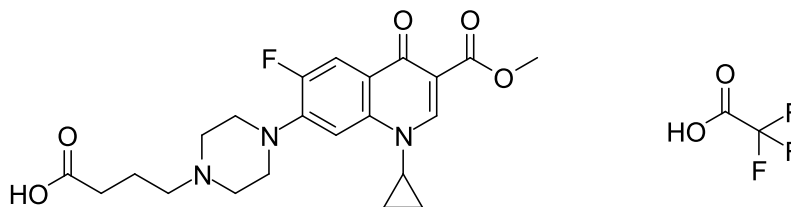
^{13}C NMR (101 MHz, CDCl_3) δ / ppm = 172.7 ($\underline{\text{C}}(=\text{O})\text{CC}(=\text{O})\text{OCH}_3$), 172.6 ($\underline{\text{C}}(=\text{O})\text{OC}(\text{CH}_3)_3$), 165.9 ($\underline{\text{C}}(=\text{O})\text{OCH}_3$), 153.1 (d, J = 249.7 Hz, *ipso* to F), 148.1 ($\underline{\text{C}}=\text{CC}(=\text{O})\text{OCH}_3$),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

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

HRMS (ESI⁺) m/z / Da = 488.2562, [M+H]⁺ found, [C₂₆H₃₅FN₃O₅]⁺ 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 μ mol) and TFA (0.2 ml) were stirred in CH₂Cl₂ (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 μ mol, 95.6 %).

mp T / °C = 225-231 (CH₂Cl₂, decomposes)

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

¹H NMR (400 MHz, DMSO d₆) 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, CH₃), 3.66 (tt, J = 7.2, 3.7 Hz, 1 H, NCH(CH₂)₂), 3.30 - 3.54 (br s, 8 H, CH₂N(CH₂)CH₂ and CH₂N(CH₂CH₂)CH₂CH₂) 3.13 - 3.22 (m, 2 H, CH₂N(CH₂)CH₂), 2.36 (t, J = 7.1 Hz, 2 H, CH₂CH₂CH₂N(CH₂)CH₂), 1.87 - 1.98 (m, 2 H, CH₂CH₂N(CH₂)CH₂), 1.22 - 1.30 (m, 2 H, NCH(CH₂)₂), 1.06 - 1.15 (m, 2 H, NCH(CH₂)₂)

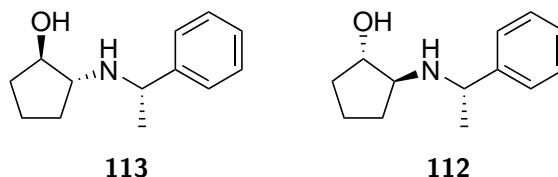
¹³C NMR (101 MHz, DMSO d₆) δ / ppm = 173.5 (CH₂C(=O)OH), 171.6 (C(=O)CC(=O)OCH₃), 164.9 (C(=O)OCH₃), 158.2 (q, J = 31.5 Hz, CF₃C(=O)OH), 152.5 (d, J = 247.6 Hz, *ipso* to F), 148.5 (C=CC(=O)OH), 142.3 (d, J = 10.7 Hz, *ipso* to piperazine), 138.0 (*para* to F), 122.6 (d, J = 6.4 Hz, *para* to piperazine), 117.2 (q, J = 299.8 Hz, CF₃), 111.9 (d, J = 22.4 Hz, *ortho* to C=O and *ortho* to F), 109.1 (CC(=O)OCH₃), 106.9 (*meta* to C=O and *meta* to F), 55.1 (C(=O)CH₂CH₂CH₂N), 51.4 (CH₃), 50.8 (C(=O)CH₂CH₂CH₂N(CH₂)CH₂), 46.7 (C(=O)CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 46.7 (C(=O)CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 34.9 (NCH(CH₂)₂), 30.6 (C(=O)CH₂), 19.1 (C(=O)CH₂CH₂), 7.6 (NCH(CH₂)₂)

¹⁹F NMR (376.45 MHz, DMSO d₆) δ / ppm = -73.6 (s, CF₃), -124.6 (s, ciprofloxacin F)

HRMS (ESI⁺) m/z / Da = 432.1921, [M+H]⁺ found, [C₂₂H₂₇FN₃O₅]⁺ 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



(*S*)-1-Phenylethan-1-amine **111** (7.85 ml, 7.38 g, 60.9 mmol, 1 eq.) was dissolved in CH₂Cl₂ (50 ml) and stirred rapidly at 0 °C. A solution of AlMe₃ (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 CH₂Cl₂ (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 CH₂Cl₂ (50 ml). The suspension was allowed to warm to r.t. and stirred for 1 h, then filtered through Celite and washed with CH₂Cl₂ (500 ml). The filtrate was dried with K₂CO₃, concentrated under reduced pressure and purified by column chromatography (SiO₂, 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)

¹H NMR (400 MHz, CDCl₃) δ / ppm = 7.28 - 7.38 (m, 4 H, *ortho* and *meta* to CHCH₃), 7.21 - 7.28 (m, 1 H, *para* to CHCH₃), 3.83 (q, J = 6.6 Hz, 1 H, CHCH₃), 3.78 (q, J = 7.0 Hz, 1 H, CHOH), 2.62 (dt, J = 8.2, 7.2 Hz, 1 H, CHNH), 1.97 (quin, J = 6.7 Hz, 1 H, CH₂CHNH), 1.90 (quin, J = 6.9 Hz, 1 H, CH₂CHOH), 1.56 - 1.68 (m, CH₂CH₂CHOH), 1.43 (dq, J = 12.5, 8.0 Hz, 1 H, CH₂CHOH), 1.37 (d, J = 6.6 Hz, 3 H, CH₃), 1.25 - 1.36 (m, 1 H, CH₂CHNH)

¹³C NMR (101 MHz, CDCl₃) δ / ppm = 144.75 (*ipso* to CHCH₃), 128.26 (*meta* to CHCH₃), 126.72 (*para* to CHCH₃), 126.30 (*ortho* to CHCH₃), 77.65 (CHOH), 63.38 (CHNH), 56.20 (CHCH₃), 31.74 (CH₂CHOH), 29.22 (CH₂CHNH), 24.58 (CH₃), 19.57 (CH₂CH₂CHOH)

HRMS (ESI⁺) m/z / Da = 206.1554, [M+H]⁺ found, [C₁₃H₂₀NO]⁺ requires 206.1545

$[\alpha]_D^{20}$ / °10⁻¹cm²g⁻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)

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

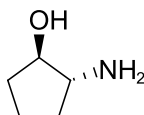
^{13}C NMR (101 MHz, CDCl_3) δ / ppm = 145.61 (*ipso* to CHCH_3), 128.08 (*meta* to CHCH_3), 126.61 (*para* to CHCH_3), 126.33 (*ortho* to CHCH_3), 77.43 (CHOH), 64.45 (CHNH), 56.62 (CHCH_3), 32.01 (CH_2CHOH), 30.56 (CH_2CHNH), 23.30 (CH_3), 20.06 ($\text{CH}_2\text{CH}_2\text{CHOH}$)

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

$[\alpha]_D^{20}$ / $^\circ 10^{-1}\text{cm}^2\text{g}^{-1}$ = -23.9, lit. = -22.1 (c / $\text{g}(100\text{ ml})^{-1}$ = 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 ^1H 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.), $\text{Pd}(\text{OH})_2$ (20 wt. % on C, moistened with 50 wt. % water, 1 g, 0.712 mmol, 0.04 eq.) and MeOH (50 ml) were stirred in a Paar hydrogenator at r.t. and 3 atm for 2 days. The mixture was then filtered through Celite and evaporated under reduced pressure. **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)

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

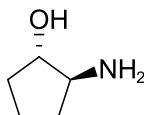
^{13}C NMR (101 MHz, MeOD) δ / ppm = 80.7 (CHOH), 60.8 (CHNH_2), 33.2 (CH_2CHOH), 32.1 (CH_2CHNH_2), 21.2 ($\text{CH}_2\text{CH}_2\text{CHOH}$)

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

$[\alpha]_D^{20}$ / $^\circ 10^{-1}\text{cm}^2\text{g}^{-1}$ = -30.9, lit. = -32.9 (c / $\text{g}(100\text{ ml})^{-1}$ = 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/CH₂Cl₂)

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

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

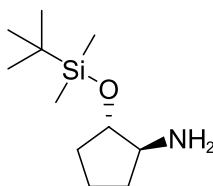
¹³C NMR (101 MHz, MeOD) δ / ppm = 80.6 ($\underline{\text{C}}\text{HOH}$), 60.7 ($\underline{\text{C}}\text{NH}_2$), 33.2 ($\underline{\text{C}}\text{H}_2\text{CHOH}$), 32.2 ($\underline{\text{C}}\text{H}_2\text{CHNH}_2$), 21.2 ($\underline{\text{C}}\text{H}_2\text{CH}_2\text{CHOH}$)

HRMS (ESI⁺) m/z / Da = 102.0915, [M+H]⁺ found, [C₅H₁₂NO]⁺ requires 102.0913

$[\alpha]_D^{20}$ / °10⁻¹cm²g⁻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 CH₂Cl₂ (20 ml) under N₂ at 0 °C. TEA (3.14 ml, 2.28 g, 22.5 mmol, 5 eq.) was added dropwise, followed by 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 NH₄Cl, diluted with CH₂Cl₂ (20 ml) and washed with water (20 ml). The organic phase was dried with Na₂SO₄, concentrated under reduced pressure and purified by column chromatography (SiO₂, 4 % MeOH/CH₂Cl₂). **125** was obtained as a yellow oil (1.00 g, 4.64 mmol, 97.7 %).

TLC R_f = 0.23 (10 % MeOH/CH₂Cl₂)

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)

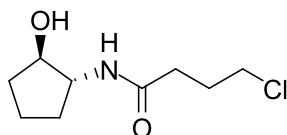
^1H NMR (400 MHz, CDCl_3) δ / ppm = 4.13 (q, J = 5.8 Hz, 1 H, CHOSi), 3.31 (td, J = 7.1, 5.2 Hz, 1 H, CHNH_2), 2.09 - 2.19 (m, 1 H, CHHCHNH_2), 1.97 (ddq, J = 8.8, 7.0, 6.0 Hz, 1 H, CHHCHOSi), 1.74 - 1.86 (m, 2 H, $\text{CH}_2\text{CH}_2\text{CHOSi}$), 1.64 - 1.74 (m, 1 H, CHHCHOSi), 1.58 (ddt, J = 13.2, 9.1, 6.0 Hz, 1 H, CHHCHNH_2), 0.88 (s, 9 H, $\text{C}(\text{CH}_3)_3$), 0.09 (s, 3 H, SiCH_3), 0.07 (s, 3 H, SiCH_3)

^{13}C NMR (101 MHz, CDCl_3) δ / ppm = 76.3 (CHOSi), 59.7 (CHNH), 32.2 (CH_2CHOSi), 26.8 (CH_2CHNH_2), 25.6 ($\text{C}(\text{CH}_3)_3$), 19.7 ($\text{CH}_2\text{CH}_2\text{CHOSi}$), 17.7 ($\text{C}(\text{CH}_3)_3$), -4.8 (SiCH_3), -5.2 (SiCH_3)

HRMS (ESI^+) m/z / Da = 216.1785, $[\text{M}+\text{H}]^+$ found, $[\text{C}_{11}\text{H}_{26}\text{NOSi}]^+$ 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 \times 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)

^1H NMR (400 MHz, CDCl_3) δ / ppm = 6.12 (br s, 1 H, NH), 4.42 (br s, 1 H, OH), 3.94 (q, J = 6.6 Hz, 1 H, CHOH), 3.82 (tt, J = 8.4, 5.3 Hz, 1 H, CHNH), 3.60 (t, J = 6.2 Hz, 2 H, CH_2Cl), 2.38 (t, J = 7.2 Hz, 2 H, $\text{CH}_2\text{C=O}$), 2.05 - 2.16 (m, 3 H, CHHCHNH and $\text{CH}_2\text{CH}_2\text{Cl}$), 1.96 - 2.04 (m, 1 H, CHHCHOH), 1.74 - 1.85 (m, 1 H, $\text{CHHCH}_2\text{CHOH}$), 1.58 - 1.73 (m, 2 H, $\text{CHHCH}_2\text{CHOH}$ and CHHCHOH), 1.43 (dq, J = 12.7, 8.3 Hz, 1 H, CHHCHNH)

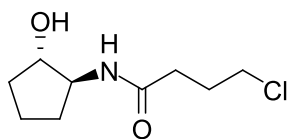
^{13}C NMR (101 MHz, CDCl_3) δ / ppm = 173.8 (C=O), 79.4 (CHOH), 60.6 (CHNH), 44.4 (CH_2Cl), 32.8 ($\text{CH}_2\text{C=O}$), 32.4 (CH_2CHOH), 30.1 (CH_2CHNH), 28.0 ($\text{CH}_2\text{CH}_2\text{Cl}$), 21.1 ($\text{CH}_2\text{CH}_2\text{CHOH}$)

HRMS (ESI^+) m/z / Da = 228.0787, $[\text{M}+\text{Na}]^+$ found, $[\text{C}_9\text{H}_{16}\text{ClNNaO}_2]^+$ requires 228.0762

$[\alpha]_D^{20}$ / $^{\circ}\text{10}^{-1}\text{cm}^2\text{g}^{-1}$ = -13.0 (c / $\text{g}(100\text{ ml})^{-1}$ = 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 μ mol, 1 eq.), TEA (500 μ l, 363 mg, 3.58 mmol, 5 eq.) and CH_2Cl_2 (5 ml) were stirred at 0 °C, and 4-chlorobutyryl chloride **139** (179 μ l, 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 \times 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 μ mol, 24.2 %).

TLC R_f = 0.35 (EtOAc)

^1H 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, $\text{CH}_2\text{C=O}$), 2.05 - 2.17 (m, 3 H, CHHCHNH and $\text{CH}_2\text{CH}_2\text{Cl}$), 1.94 - 2.05 (m, 1 H, CHHCHOH), 1.74 - 1.86 (m, 1 H, $\text{CHHCH}_2\text{CHOH}$), 1.58 - 1.74 (m, 2 H, $\text{CHHCH}_2\text{CHOH}$ and CHHCHOH), 1.42 (dq, J = 12.5, 8.4 Hz, 1 H, CHHCHNH)

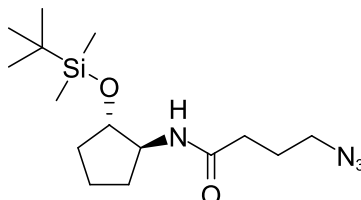
^{13}C NMR (101 MHz, CDCl_3) δ / ppm = 173.8 (C=O), 79.4 (CHOH), 60.6 (CHNH), 44.4 (CH_2Cl), 32.8 ($\text{CH}_2\text{C=O}$), 32.4 (CH_2CHOH), 30.2 (CH_2CHNH), 28.0 ($\text{CH}_2\text{CH}_2\text{Cl}$), 21.2 ($\text{CH}_2\text{CH}_2\text{CHOH}$)

HRMS (ESI^+) m/z / Da = 206.0939, $[\text{M}+\text{H}]^+$ found, $[\text{C}_9\text{H}_{17}\text{ClNO}_2]^+$ requires 206.0948

$[\alpha]_D^{20}$ / $^{\circ}\text{10}^{-1}\text{cm}^2\text{g}^{-1}$ = 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 (SiO₂, 0.5 % MeOH/CH₂Cl₂). The combined pure fractions were dried with MgSO₄ 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/CH₂Cl₂)

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

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

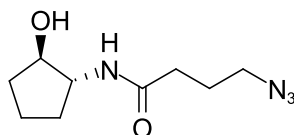
¹³C NMR (101 MHz, CDCl₃) δ / ppm = 171.17 (C=O), 77.80 (CHOSi), 58.36 (CHNH), 50.77 (CH₂N₃), 33.29 (CH₂C=O), 32.57 (CH₂CHOSi), 29.36 (CH₂CHNH), 25.72 (C(CH₃)₃), 24.77 (CH₂CH₂N₃), 20.40 (CH₂CH₂CHO Si), 17.95 (C(CH₃)₃), -4.75 (SiCH₃)

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

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

The compound has not been reported previously.

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 NaN₃ (126 mg, 1.94 mmol, 2 eq.) were stirred in acetonitrile (4 ml) at 50 °C for 16 h. The solvent was then evaporated under reduced pressure and the residue was partitioned between water (20 ml) and 10 % *i*-PrOH/CHCl₃ (20 ml). The aqueous layer was extracted again with 10 % *i*-PrOH/CHCl₃ (3×20 ml) and the combined organic fractions were dried with MgSO₄ and evaporated under reduced pressure. **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, CHCl₃)

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

¹H NMR (400 MHz, CDCl₃) 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, $\underline{\text{CHOH}}$), 3.75 (tdd, $J = 8.4, 6.6, 4.4$ Hz, 1 H, $\underline{\text{CHNH}}$), 3.28 (t, $J = 6.6$ Hz, 2 H, $\underline{\text{CH}_2\text{N}_3}$), 2.23 (t, $J = 7.3$ Hz, 2 H, $\underline{\text{CH}_2\text{C=O}}$), 2.04 (dtd, $J = 13.0, 8.0, 4.9$ Hz, 1 H, $\underline{\text{CHHCHNH}}$), 1.92 (dtd, $J = 13.0, 7.6, 5.8$ Hz, 1 H, $\underline{\text{CHHCHOH}}$), 1.84 (quin, $J = 7.0$ Hz, 2 H, $\underline{\text{CH}_2\text{CH}_2\text{N}_3}$), 1.59 - 1.77 (m, 2 H, $\underline{\text{CH}_2\text{CH}_2\text{CHOH}}$), 1.54 (ddt, $J = 12.7, 9.0, 6.7$ Hz, 1 H, $\underline{\text{CHHCHOH}}$), 1.39 (dq, $J = 12.9, 8.4$ Hz, 1 H, $\underline{\text{CHHCHNH}}$)

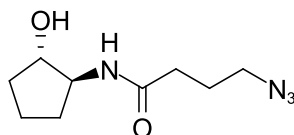
^{13}C NMR (101 MHz, CDCl_3) δ / ppm = 173.8 ($\underline{\text{C=O}}$), 78.8 ($\underline{\text{CHOH}}$), 59.9 ($\underline{\text{CHNH}}$), 50.5 ($\underline{\text{CH}_2\text{N}_3}$), 32.5 ($\underline{\text{CH}_2\text{C=O}}$), 32.0 ($\underline{\text{CH}_2\text{CHOH}}$), 29.5 ($\underline{\text{CH}_2\text{CHNH}}$),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

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

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

The compound has not been reported previously.

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 $^{\circ}\text{C}$ for 24 h. The reaction mixture was then partitioned between water (20 ml) and 10 % *i*-PrOH/ CHCl_3 (5 ml). The aqueous layer was extracted again with 10 % *i*-PrOH/ CHCl_3 (2 \times 5 ml) and the combined organic fractions were dried with MgSO_4 and evaporated under reduced pressure. **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)

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

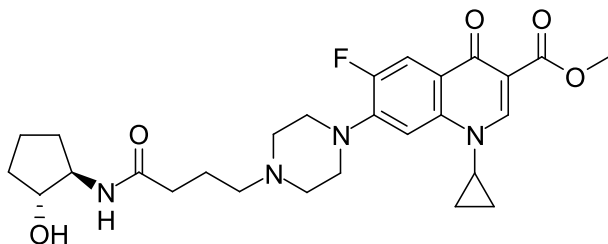
^{13}C NMR (101 MHz, CDCl_3) δ / ppm = 173.8 ($\underline{\text{C=O}}$), 79.7 ($\underline{\text{CHOH}}$), 61.0 ($\underline{\text{CHNH}}$), 50.7 ($\underline{\text{CH}_2\text{N}_3}$), 32.8 ($\underline{\text{CH}_2\text{C=O}}$), 32.6 ($\underline{\text{CH}_2\text{CHOH}}$), 30.5 ($\underline{\text{CH}_2\text{CHNH}}$),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

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

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

The compound has not been reported previously.

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 μ l, 142 mg, 1.10 mmol, 3 eq.) were dissolved in DMF (5 ml) and stirred at r.t. for 16 h. The solvent was removed using a stream of N₂ and the residue was purified by preparative HPLC (5-60 % acetonitrile/water over 12 min). The combined pure fractions were evaporated under reduced pressure and then partitioned between NaHCO₃ (aq., sat., 10 ml) and CH₂Cl₂ (10 ml). The organic layer was removed and the aqueous layer was extracted twice more with CH₂Cl₂ (2 \times 10 ml). The combined organic fractions were dried with MgSO₄ and evaporated under reduced pressure. **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)

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

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

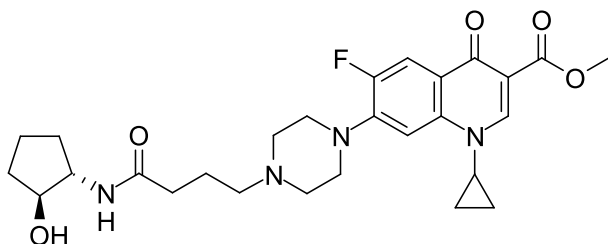
¹⁹F NMR (376.45 MHz, DMSO d₆) δ / ppm = -124.3 (ciprofloxacin F)

HRMS (ESI⁺) m/z / Da = 515.2661, [M+H]⁺ found, [C₂₇H₃₆FN₄O₅]⁺ requires 515.2670

$[\alpha]_D^{20}$ / °10⁻¹cm²g⁻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-hydroxybenzotriazole (25.8 mg, 191 μmol, 2 eq.) and DIPEA (33.3 μl, 24.7 mg, 191 μmol, 2 eq.) were dissolved in DMF (2 ml) and stirred at r.t. for 16 h. The solvent was removed using a stream of N₂ 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 NaHCO₃ (aq., sat., 5 ml) and CH₂Cl₂ (5 ml). The organic layer was removed and the aqueous layer was extracted twice more with CH₂Cl₂ (2×5 ml). The combined organic fractions were dried with MgSO₄ and evaporated under reduced pressure. **120** was obtained as a white amorphous solid (4.9 mg, 9.5 μmol, 9.9 %).

TLC R_f = 0.38 (30 % MeOH/CH₂Cl₂)

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

¹H NMR (500 MHz, DMSO d₆) δ / ppm = 8.44 (s, 1 H, *ortho* to C(=O)OCH₃), 7.75 (d, J = 13.5 Hz, 1 H, *ortho* to F), 7.69 (d, J = 6.9 Hz, 1 H, CHNH), 7.43 (d, J = 7.6 Hz, 1 H, *meta* to F), 4.73 (br s, 1 H, CHOH), 3.77 - 3.81 (m, 1 H, CHOH), 3.74 - 3.77 (m, 1 H, CHNH), 3.73 (s, 3 H, CH₃), 3.65 (tt, J = 6.9, 4.0 Hz, 1 H, NCH(CH₂)₂), 3.24 (br. t, J = 4.2 Hz, 4 H, CH₂N(CH₂CH₂)CH₂CH₂), 2.55 (br t, J = 5.0 Hz, 4 H, CH₂N(CH₂)CH₂), 2.32 (t, J = 7.2 Hz, 2 H, CH₂N(CH₂)CH₂), 2.10 (t, J = 7.4 Hz, 2 H, CH₂CH₂CH₂N(CH₂)CH₂), 1.92 (dddd, J = 13.0, 8.7, 7.3, 6.0 Hz, 1 H, CHHCHNH), 1.77 (ddt, J = 12.6, 8.9, 6.3 Hz, 1 H, CHHCHOH), 1.68 (quin, J = 7.4 Hz, 2 H, CH₂CH₂N(CH₂)CH₂), 1.53 - 1.64 (m, 2 H, CH₂CH₂CHOH), 1.42 (ddt, J = 12.9, 8.4, 5.2 Hz, 1 H, CHHCHOH), 1.31 (ddt, J = 13.0, 8.6, 6.4 Hz, 1 H, CHHCHNH), 1.22 - 1.28 (m, 2 H, NCH(CHH)₂), 1.06 - 1.12 (m, 2 H, NCH(CHH)₂)

¹³C NMR (126 MHz, DMSO d₆) δ / ppm = 171.9 (NHC(=O)CH₂), 171.5 (C(=O)CC(=O)OCH₃), 165.0 (C(=O)OCH₃), 152.6 (d, J = 247.4 Hz, *ipso* to F), 148.2 (C=CC(=O)OCH₃), 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 (CC(=O)OCH₃), 106.2 (*meta* to C=O and *meta* to F), 76.2 (CHOH), 57.6 (CHNH), 57.2 (CH₂CH₂CH₂N), 52.4 (CH₂CH₂CH₂N(CH₂)CH₂), 51.3 (CH₃), 49.6 (CH₂CH₂CH₂N(CH₂)CH₂)

(CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 34.7 (NCH(CH₂)₂), 33.2 (C(=O)CH₂), 32.2 (CH₂CHOH), 29.5 (CH₂CHNH), 22.5 (C(=O)CH₂CH₂), 20.6 (CH₂CH₂CHOH), 7.5 (NCH(CH₂)₂)

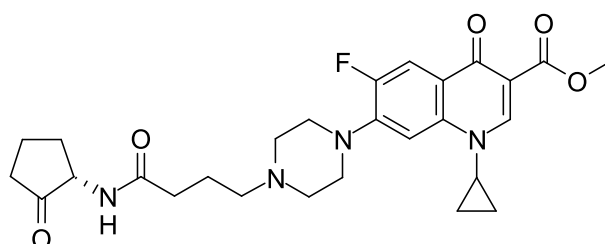
¹⁹F NMR (376.45 MHz, MeOD) δ / ppm = -125.5

HRMS (ESI⁺) *m/z* / Da = 515.2667, [M+H]⁺ found, [C₂₇H₃₆FN₄O₅]⁺ requires 515.2670

[α]_D²⁰ / °10⁻¹cm²g⁻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 CH₂Cl₂ (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 NaHCO₃ (aq., sat., 30 ml) and 10 % *i*-PrOH/CHCl₃ (30 ml) were added. The organic layer was removed and dried with MgSO₄, then evaporated under reduced pressure. **122** was obtained as a white amorphous solid (11.3 mg, 22.0 μmol, 56.7 %).

¹H NMR (500 MHz, DMSO d₆) δ / ppm = 8.46 (s, 1 H, *ortho* to C(=O)OCH₃), 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, CHNH), 3.73 (s, 3 H, CH₃), 3.65 (tt, *J* = 6.9, 3.9 Hz, 1 H, NCH(CH₂)₂), 3.40 (s, 10 H, CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 2.05 - 2.29 (m, 5 H, NHC(=O)CH₂, CH₂C(=O)CHNH and CHHCHNH), 1.89 - 1.96 (m, 1 H, CHHCH₂CHNH), 1.69 - 1.80 (m, 3 H, CHHCH₂CHNH, CHHCHNH and NHC(=O)CH₂CH₂), 1.24 - 1.29 (m, 2 H, NCH(CH₂)₂), 1.07 - 1.12 (m, 2 H, NCH(CH₂)₂)

¹³C NMR (126 MHz, DMSO d₆) δ / ppm = 215.2 (C(=O)CHNH), 171.7 (NHC(=O)CH₂), 171.7 (C(=O)CC(=O)OCH₃), 165.1 (C(=O)OCH₃), 152.6 (d, *J* = 246.6 Hz, *ipso* to F), 148.4 (C=CC(=O)OCH₃), 138.1 (*para* to F), 109.1 (CC(=O)OCH₃), 56.3 (CHNH), 51.4 (CH₃), 35.6 (CH₂C(=O)CHNH), 34.8 (NCH(CH₂)₂), 28.8 (CH₂CHNH), 18.1 (CH₂CH₂CHNH), 7.6 (NCH(CH₂)₂)

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

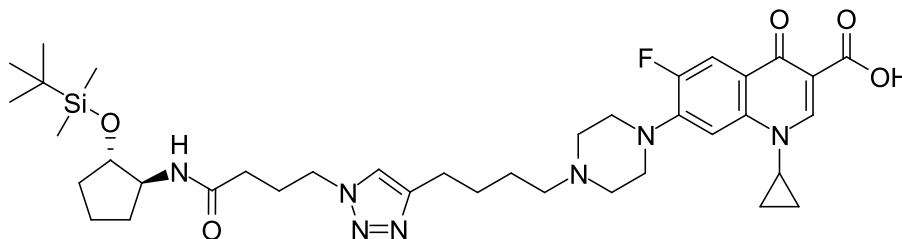
HRMS (ESI⁺) *m/z* / Da = 513.2495, [M+H]⁺ found, [C₂₇H₃₄FN₄O₅]⁺ requires 513.2513

[α]_D²⁰ / °10⁻¹cm²g⁻¹ = 6.7 (*c* / g(100 ml)⁻¹ = 0.075, MeOH)

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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 μ mol, 1 eq.) and 4-azido-*N*-(((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclopentyl)butanamide **129** (33.9 mg, 104 μ mol, 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 μ l, 10.4 μ mol, 0.1 eq. 100 mM, aq.) was added, followed by a solution of sodium ascorbate (208 μ l, 20.8 μ mol, 0.2 eq., 100 mM, aq.). The mixture was stirred at room temperature under argon for 16 h, then solvent was removed under reduced pressure. The residue was partitioned between water (10 ml) and CH_2Cl_2 (10 ml), the organic layer was separated and the aqueous layer was extracted again with CH_2Cl_2 (10 ml). The combined organic layers were dried with $MgSO_4$ and evaporated under reduced pressure. **133** was obtained as a clear amorphous solid (67.1 mg, 90.9 μ mol, 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)

1H 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, $CH=CCH_2$), 7.33 (d, J = 8.2 Hz, 1 H, *meta* to F), 5.92 (t, J = 6.6 Hz, 1 H, $CHNH$), 4.35 (t, J = 6.7 Hz, 2 H, $CH_2NCH=C$), 3.96 - 4.02 (m, 1 H, $CHOSi$), 3.90 - 3.96 (m, 1 H, $CHNH$), 3.55 (tt, J = 6.7, 4.0 Hz, 1 H, $NCH(CH_2)_2$), 3.34 (br t, J = 5.0 Hz, 4 H, $CH_2N(CH_2CH_2)CH_2CH_2$), 2.71 (t, J = 7.5 Hz, 2 H, $CH=CCH_2$), 2.66 (br s, 4 H, $CH_2N(CH_2CH_2)$), 2.46 (t, J = 7.3 Hz, 2 H, $CH_2N(CH_2)CH_2$), 2.03 - 2.22 (m, 5 H, $CHHCHNH$, C(=O) CH_2 and C(=O) CH_2CH_2), 1.65 - 1.83 (m, 4 H, $CHHCHOSi$, $CHHCH_2CHOSi$ and $NCH=CCH_2CH_2CH_2$), 1.47 - 1.65 (m, 4 H, $CHHCHOSi$, $CHHCH_2CHOSi$ and $NCH=CCH_2CH_2CH_2$), 1.33 - 1.41 (m, 3 H, $CHHCHNH$ and $NCH(CH_2)_2$), 1.14 - 1.20 (m, 2 H, $NCH(CH_2)_2$), 0.82 (s, 9 H, $C(CH_3)_3$), 0.03 (s, 3 H, $SiCH_3$), 0.01 (s, 3 H, $SiCH_3$)

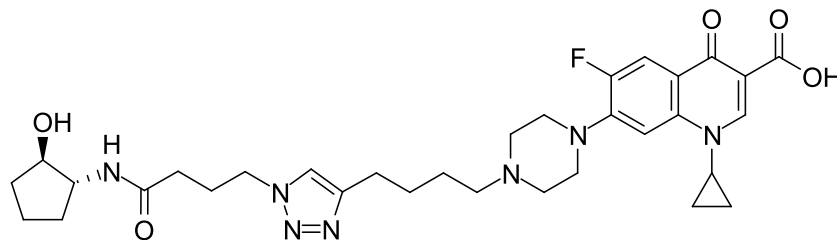
^{13}C NMR (101 MHz, $CDCl_3$) δ / ppm = 176.9 (C(=O)CC(=O)OH), 170.9 ($CH_2C(=O)NH$), 166.9 (C(=O)OH), 153.5 (d, J = 251.4 Hz, *ipso* to F), 147.9 ($CH=CCH_2$), 147.2 (C=CC(=O)OH), 145.8 (d, J = 10.4 Hz, *ipso* to piperazine), 139.0 (*para* to F), 120.9 ($NCH=CCH_2$), 119.4 (d, J = 7.8 Hz, *para* to piperazine), 112.0 (d, J = 23.4 Hz, *ortho* to C=O and *ortho* to F), 107.7 (C(=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 ($CH=CCH_2CH_2CH_2CH_2N$), 52.6 ($CH=CCH_2CH_2CH_2CH_2N(CH_2)CH_2$), 49.5 (d, J = 6.1 Hz, $CH=CCH_2CH_2CH_2CH_2N(CH_2)CH_2CH_2$), 48.9 (d, J = 3.5 Hz, $CH_2NCH=CCH_2$), 35.3 ($NCH(CH_2)_2$), 32.6 (C(=O) CH_2), 32.6 (CH_2CHOSi), 29.3 (CH_2CHNH), 27.2 ($CH=CCH_2CH_2$), 26.0 - 26.3 (C(=O) CH_2CH_2 and $CH=CCH_2CH_2CH_2$), 25.6 ($C(CH_3)_3$), 25.4 ($CH=CCH_2$), 20.4 (CH_2CH_2CHOSi), 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, [C₃₈H₅₇FN₇O₅Si]⁺ requires 738.4169

$[\alpha]_D^{20}$ / °10⁻¹cm²g⁻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 μ mol, 1 eq.) and 4-azido-*N*-(((1*R*,2*R*)-2-hydroxycyclopentyl)butanamide **119** (22.0 mg, 104 μ mol, 1 eq.) were dissolved in 10 % water/*t*-BuOH (3 ml), and the mixture was degassed by bubbling N₂ through it. A solution of CuSO₄ and THPTA (104 μ l, 10.4 μ mol, 0.1 eq. 100 mM, aq.) was added, followed by a solution of sodium ascorbate (208 μ l, 20.8 μ mol, 0.2 eq., 100 mM, aq.). The mixture was stirred at room temperature under argon for 16 h. Water (30 ml) and CH₂Cl₂ (30 ml) were added, the organic layer was separated and the aqueous layer was extracted again with CH₂Cl₂ (4×30 ml). The combined organic layers were dried with MgSO₄ 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 NaHCO₃ (aq., sat., 10 ml) and 10 % *i*-PrOH/CHCl₃ (10 ml). The organic layer was dried with MgSO₄ and evaporated under reduced pressure. **124** was obtained as a white amorphous solid (17.6 mg, 28.2 μ mol, 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)

¹H NMR (700 MHz, DMSO d₆) 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, CH=CCH₂), 7.75 (d, J = 7.1 Hz, 1 H, CHNH), 7.54 (d, J = 7.5 Hz, 1 H, *meta* to F), 4.73 (d, J = 3.8 Hz, 1 H, CHOH), 4.29 (t, J = 6.9 Hz, 2 H, CH₂NCH=C), 3.78 - 3.83 (m, 1 H, NCH(CH₂)₂), 3.75 - 3.78 (m, 1 H, CHOH), 3.71 - 3.75 (m, 1 H, CHNH), 3.31 (br t, J = 4.3 Hz, 4 H, CH₂N(CH₂CH₂)CH₂CH₂), 2.63 (t, J = 7.5 Hz, 2 H, CH=CCH₂), 2.56 (br t, J = 4.2 Hz, 4 H, CH₂N(CH₂)CH₂), 2.37 (t, J = 7.3 Hz, 2 H, CH₂N(CH₂)CH₂), 2.03 - 2.06 (m, 2 H, C(=O)CH₂), 1.97 - 2.02 (m, 2 H, C(=O)CH₂CH₂), 1.89 (dddd, J = 13.1, 8.9, 7.4, 5.7 Hz, 1 H, CHHCHNH), 1.75 (ddt, J = 13.0, 8.9, 6.4, 6.4 Hz, 1 H, CHHCHOH), 1.61 - 1.66 (m, 2 H, CH=CCH₂CH₂), 1.57 - 1.61 (m, 1 H, CHHCH₂CHOH), 1.54 - 1.57 (m, 1 H, CHHCH₂CHOH), 1.49 - 1.53 (m, 2 H, CH=CCH₂CH₂CH₂), 1.40 (ddt, J = 13.0, 8.4, 5.3, 5.3 Hz, 1 H, CHHCHOH), 1.29 - 1.32 (m, 2 H, NCH(CHH)₂), 1.25 - 1.29 (m, 1 H, CHHCHNH), 1.13 - 1.20 (m, 2 H, NCH(CHH)₂)

¹³C NMR (175 MHz, DMSO d₆) δ / ppm = 176.3 (C(=O)CC(=O)OH), 170.9 (NHC(=O)CH₂), 166.1 (C(=O)OH), 153.0 (d, J = 251.4 Hz, *ipso* to F), 147.9 (C=CC(=O)OH), 146.9 (CH=CCH₂), 145.2 (d, J

= 8.7 Hz, *ipso* to piperazine), 139.2 (*para* to F), 121.7 (NCH=CCH₂), 118.7 (d, *J* = 5.8 Hz, *para* to piperazine), 111.0 (d, *J* = 23.3 Hz, *ortho* to C=O and *ortho* to F), 106.3 (*meta* to C=O and *meta* to F and C=C(O)OH), 76.2 (CHOH), 57.6 (CHNH), 57.4 (CH=CCH₂CH₂CH₂CH₂N), 52.5 (CH=CCH₂CH₂CH₂CH₂N(CH₂CH₂CH₂CH₂), 49.5 (d, *J* = 4.4 Hz, CH=CCH₂CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 48.8 (CH₂NCH=CCH₂), 35.8 (NCH(CH₂)₂), 32.2 (CH₂CHOH), 32.0 (C(=O)CH₂), 29.5 (CH₂CHNH), 26.9 (CH=CCH₂CH₂), 26.0 (C(=O)CH₂CH₂), 25.8 (CH=CCH₂CH₂CH₂), 25.0 (CH=CCH₂), 20.5 (CH₂CH₂CHOH), 7.6 (NCH(CH₂)₂)

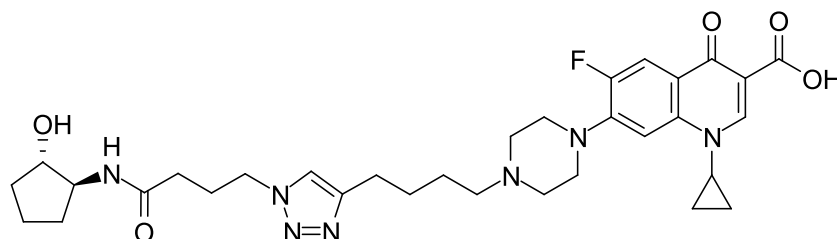
¹⁹F NMR (376.45 MHz, MeOD) δ / ppm = -122.1 (s, ciprofloxacin F)

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

[α]_D²⁰ / °10⁻¹cm²g⁻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 N₂ through it. A solution of CuSO₄ 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/CHCl₃ (10 ml) were added, then the organic layer was separated and dried with MgSO₄ and evaporated under reduced pressure. The residue was purified by preparative HPLC (5-95 % acetonitrile/water over 20 min). The combined pure fractions were evaporated under reduced pressure and then partitioned between NaHCO₃ (aq., sat., 10 ml) and 10 % *i*-PrOH/CHCl₃ (10 ml). The organic layer was dried with MgSO₄ and evaporated under reduced pressure. **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)

¹H NMR (400 MHz, DMSO d₆) δ / ppm = 15.22 (br s, 1 H, C(=O)OH), 8.67 (s, 1 H, *ortho* to C(=O)OH), 7.91 (d, *J* = 13.3 Hz, 1 H, *ortho* to F), 7.84 (s, 1 H, CH=CCH₂), 7.74 (d, *J* = 6.7 Hz, 1 H, CHNH), 7.56 (d, *J* = 7.4 Hz, 1 H, *meta* to F), 4.71 (d, *J* = 3.7 Hz, 1 H, CHOH), 4.29 (t, *J* = 6.6 Hz, 2 H, CH₂NCH=C), 3.82 (tt, *J* = 6.5, 4.3 Hz, 1 H, NCH(CH₂)₂), 3.69 - 3.79 (m, 2 H, CHOH and CHNH), 3.30 - 3.34 (m, 6 H, CH=CCH₂CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 2.64 (t, *J* = 7.4 Hz, 2 H, CH=CCH₂), 1.95 - 2.08 (m, 4 H,

C(=O)CH₂CH₂), 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=CCH₂CH₂CH₂ and CH₂CH₂CHOH), 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)

¹³C NMR (101 MHz, DMSO d₆) δ / ppm = 176.4 (C(=O)CC(=O)OH), 170.9 (NHC(=O)CH₂), 166.0 (C(=O)OH), 153.0 (d, $J = 249.6$ Hz, *ipso* to F), 148.1 (C=CC(=O)OH), 146.7 (CH=CCH₂), 145.2 (d, $J = 8.3$ Hz, *ipso* to piperazine), 139.2 (*para* to F), 121.8 (NCH=CCH₂), 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=CCH₂CH₂CH₂CH₂N), 52.3 (br s, CH=CCH₂CH₂CH₂CH₂N(CH₂CH₂), 49.3 (br s, CH=CCH₂CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 48.8 (CH₂NCH=CCH₂), 35.9 (NCH(CH₂)₂), 32.2 (CH₂CHOH), 32.0 (C(=O)CH₂), 29.4 (CH₂CHNH), 26.7 (CH=CCH₂CH₂), 26.0 (C(=O)CH₂CH₂), 25.5 (CH=CCH₂CH₂CH₂), 24.9 (CH=CCH₂), 20.5 (CH₂CH₂CHOH), 7.6 (NCH(CH₂)₂)

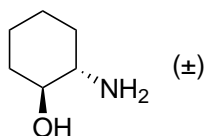
¹⁹F NMR (376.45 MHz, MeOD) δ / ppm = -121.5

HRMS (ESI⁺) m/z / Da = 624.3298, [M+H]⁺ found, [C₃₂H₄₃FN₇O₅]⁺ requires 624.3310

$[\alpha]_D^{20}$ / °10⁻¹cm²g⁻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.), NH₃ (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 N₂ 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/CH₂Cl₂)

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

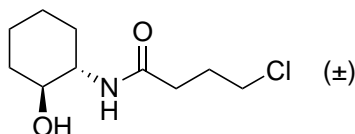
¹H NMR (400 MHz, CDCl₃) δ / ppm = 3.01 (td, $J = 9.4, 4.8$ Hz, 1 H, CHOH), 2.80 - 2.92 (m, 2 H, OH and NH₂), 2.35 (ddd, $J = 11.1, 9.1, 4.1$ Hz, 1 H, CHNH₂), 1.77 - 1.84 (m, 1 H, CHHCHOH), 1.69 - 1.76 (m, 1 H, CHHCHNH₂), 1.56 - 1.66 (m, 1 H, CHHCH₂CHOH), 1.45 - 1.56 (m, 1 H, CHHCH₂CHNH₂), 1.07 - 1.19 (m, 3 H, CHHCH₂CHOH, CHHCH₂CHNH₂ and CHHCHOH), 0.94 - 1.05 (m, 1 H, CHHCHNH₂)

¹³C NMR (101 MHz, CDCl₃) δ / ppm = 75.4 (CHOH), 56.6 (CHNH₂), 33.8 (CH₂CHOH and CH₂CHNH₂), 24.7 (CH₂CH₂CHNH₂), 24.6 (CH₂CH₂CHOH)

HRMS (ESI⁺) m/z / Da = 116.1070, [M+H]⁺ found, [C₆H₁₄NO]⁺ 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 CH₂Cl₂ (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/CHCl₃ (2×50 ml). The combined organic layers were dried with MgSO₄, concentrated under reduced pressure and purified by column chromatography (SiO₂, 0-100 % EtOAc/Et₂O). The combined organic fractions were dried with MgSO₄ and evaporated under reduced pressure. **144** was obtained as white needles (1.51 g, 6.87 mmol, 76.1 %).

TLC R_f = 0.19 (Et₂O)

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

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

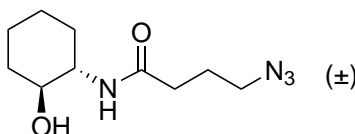
¹H NMR (400 MHz, MeOD) δ / ppm = 3.60 (t, J = 6.6 Hz, 2 H, CH₂Cl), 3.51 - 3.60 (m, 1 H, CHNH), 3.28 - 3.39 (m, 1 H, CHOH), 2.37 (td, J = 7.4, 2.3 Hz, 2 H, C(=O)CH₂), 2.06 (quin, J = 7.0 Hz, 2 H, C(=O)CH₂CH₂), 1.97 - 2.01 (m, 1 H, CHHCHOH), 1.85 - 1.93 (m, 1 H, CHHCHNH), 1.70 - 1.77 (m, 1 H, CHHCH₂CHOH),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

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

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

The compound has not been reported previously.

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 NaN₃ (180 mg, 2.77 mmol, 1.75 eq.) were stirred in DMF (12 ml) at 50 °C for 16 h. Water (50 ml) and 10 % *i*-PrOH/CHCl₃

(50 ml) were added, and the organic layer was removed. The aqueous layer was extracted again with 10 % *i*-PrOH/CHCl₃ (50 ml) and the combined organic fractions were dried with MgSO₄. The solvent was evaporated under reduced pressure, and then by using a N₂ stream. **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, CHCl₃)

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

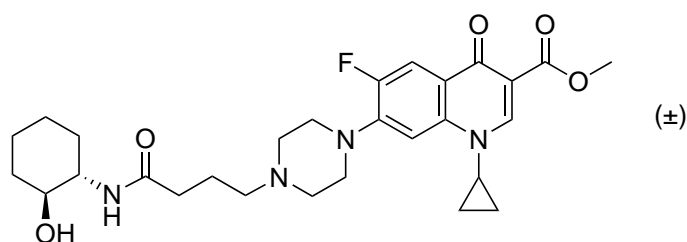
¹H NMR (400 MHz, MeOD) δ / ppm = 7.87 (d, J = 7.9 Hz, 1 H, NH), 5.27 (d, J = 4.3 Hz, 1 H, OH), 3.56 (td, J = 10.5, 4.4 Hz, 1 H, CHNH), 3.28 - 3.41 (m, 3 H, CHOH and CH₂N₃), 2.30 (td, J = 7.4, 2.7 Hz, 2 H, C(=O)CH₂), 1.95 - 2.03 (m, 1 H, CHHCHOH), 1.87 (m, 3 H, C(=O)CH₂CH₂ and CHHCHNH), 1.70 - 1.76 (m,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

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

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

The compound has not been reported previously.

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-hydroxybenzotriazole (96 mg, 0.710 mmol, 1.9 eq.) and DIPEA (192 μ l, 142 mg, 1.10 mmol, 3 eq.) were dissolved in DMF (5 ml) and stirred at r.t. for 16 h. The solvent was removed using a stream of N₂ and the residue was purified by preparative HPLC (5-50 % acetonitrile/water over 10 min). The combined pure fractions were evaporated under reduced pressure and then partitioned between NaHCO₃ (aq., sat., 10 ml) and CH₂Cl₂ (10 ml). The organic layer was dried with MgSO₄ and evaporated under reduced pressure. **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)

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

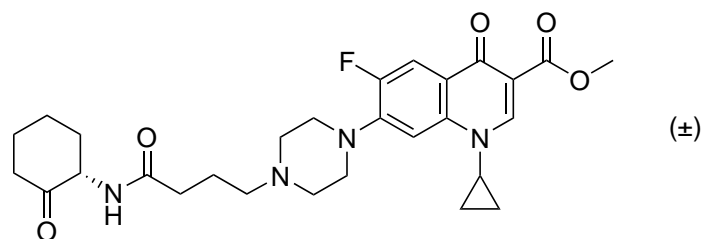
^{13}C NMR (101 MHz, MeOD) δ / ppm = 175.8 (CH₂C(=O)NH), 175.3 (C(=O)CC(=O)OCH₃), 166.8 (C(=O)OCH₃), 154.9 (d, J = 248.8 Hz, *ipso* to F), 150.2 (C=CC(=O)OCH₃), 146.1 (d, J = 10.8 Hz, *ipso* to piperazine), 139.9 (*para* to F), 123.5 (d, J = 7.5 Hz, *para* to piperazine), 113.2 (d, J = 23.2 Hz, *ortho*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

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

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

The compound has not been reported previously.

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 CH₂Cl₂ (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 NaHCO₃ (aq., sat., 30 ml) and 10 % *i*-PrOH/CHCl₃ (30 ml) were added. The organic layer was dried with MgSO₄ and evaporated under reduced pressure. **147** was obtained as a white amorphous solid (3.6 mg, 6.8 μmol , 69.1 %).

TLC R_f = 0.74 (30 % MeOH/CH₂Cl₂)

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

C=O), 1620.0 (quinolone C=O)

¹H NMR (400 MHz, DMSO d₆) δ / ppm = 8.45 (s, 1 H, *ortho* to C(=O)OCH₃), 7.87 (d, J = 6.2 Hz, 1 H, NH), 7.76 (d, J = 13.4 Hz, 1 H, *ortho* to F), 7.44 (d, J = 7.5 Hz, 1 H, *meta* to F), 4.42 (dddd, J = 13.0, 7.6, 6.0, 1.0 Hz, 1 H, CHNH), 3.73 (s, 3 H, CH₃), 3.65 (tt, J = 7.1, 3.9 Hz, 1 H, NCH(CH₂)₂), 3.25 (br s, 4 H, CH₂N(CH₂CH₂)CH₂CH₂), 2.58 (br s, 4 H, CH₂N(CH₂)CH₂), 2.45 - 2.53 (m, 1 H, CHHC(=O)CHNH), 2.36 (br s, 2 H, C(=O)CH₂CH₂CH₂N), 2.26 (dtt, J = 13.4, 2.6, 1.6 Hz, 1 H, CHHC(=O)CHNH), 2.16 - 2.22 (m, 2 H, C(=O)CH₂CH₂CH₂N), 2.12 (ddq, J = 12.7, 6.0, 2.8 Hz, 1 H, CHHCHNH), 2.00 (ddquin, J = 13.2, 6.0, 2.9 Hz, 1 H, CHHCH₂C(=O)), 1.65 - 1.83 (m, 4 H, CH₂CH₂CHNH), 1.41 - 1.56 (m, 2 H, CHHCHNH and CHHCH₂C(=O)), 1.20 - 1.30 (m, 2 H, NCH(CHH)₂), 1.05 - 1.13 (m, 2 H, NCH(CHH)₂)

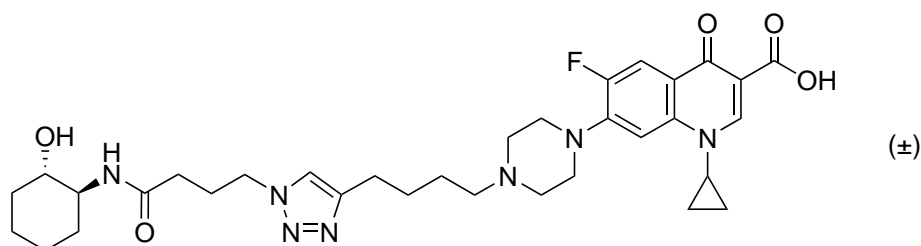
¹³C NMR (101 MHz, DMSO d₆) δ / ppm = 207.5 (C(=O)CHNH), 171.7 (C(=O)CC(=O)OCH₃), 171.6 (CH₂C(=O)NH), 165.0 (C(=O)OCH₃), 152.6 (d, J = 247.6 Hz, *ipso* to F), 148.3 (C=CC(=O)OCH₃), 143.9 (br s, *ipso* to piperazine), 138.1 (*para* to F), 121.8 (d, J = 6.4 Hz, *para* to piperazine), 111.5 (d, J = 22.4 Hz, *ortho* to C=O and *ortho* to F), 109.0 (CC(=O)OCH₃), 106.3 (*meta* to C=O and *meta* to F), 57.0 (CHNH and C(=O)CH₂CH₂CH₂N), 52.3 (br s, C(=O)CH₂CH₂CH₂N(CH₂)CH₂), 51.3 (CH₃), 49.5 (br s, C(=O)CH₂CH₂CH₂N(CH₂)CH₂CH₂), 40.6 (CH₂C(=O)CHNH), 34.8 (NCH(CH₂)₂), 33.9 (CH₂CHNH), 32.9 (C(=O)CH₂CH₂CH₂N), 27.2 (CH₂CH₂C(=O)CHNH), 23.8 (CH₂CH₂CHNH), 22.4 (br s, C(=O)CH₂CH₂CH₂N), 7.6 (NCH(CH₂)₂)

¹⁹F NMR (376.45 MHz, DMSO d₆) δ / ppm = -124.3 (ciprofloxacin F)

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

The compound has not been reported previously.

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 μ mol, 1 eq.) and 4-azido-*N*-(((*trans*)-2-hydroxycyclohexyl)butanamide **145** (22.0 mg, 97.2 μ mol, 1 eq.) were dissolved in 10 % water/*t*-BuOH (3 ml), and the mixture was degassed by bubbling N₂ through it. A solution of CuSO₄ and THPTA (97.2 μ l, 9.72 μ mol, 0.1 eq. 100 mM, aq.) was added, followed by a solution of sodium ascorbate (194 μ l, 19.4 μ mol, 0.2 eq., 100 mM, aq.). The mixture was stirred at r.t. under argon for 16 h. Water (50 ml) and 10 % *i*-PrOH/CHCl₃ (50 ml) were added, then the organic layer was separated, dried with MgSO₄ and evaporated under reduced pressure. The residue was purified by preparative HPLC (5-70 % acetonitrile/water over 15 min). The combined pure fractions were evaporated under reduced pressure and then partitioned between NaHCO₃ (aq., sat., 50 ml) and 10 % *i*-PrOH/CHCl₃ (50 ml). The organic layer was dried

with 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)

^1H NMR (400 MHz, $\text{DMSO-}d_6$) 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, $\text{CH}=\text{CCH}_2$), 7.64 (d, J = 8.1 Hz, 1 H, NH), 7.54 (d, J = 7.5 Hz, 1 H, *meta* to F), 4.54 (d, J = 4.7 Hz, 1 H, OH), 4.30 (t, J = 6.8 Hz, 2 H, $\text{C(=O)CH}_2\text{CH}_2\text{CH}_2\text{N}$), 3.77 - 3.86 (m, 1 H, $\text{NCH(CH}_2)_2$), 3.33 - 3.40 (m, 1 H, CHNH), 3.31 (br t, J = 4.8 Hz, 4 H, $\text{CH}=\text{CCH}_2\text{CH}_2\text{CH}_2\text{N(CH}_2\text{CH}_2)\text{CH}_2\text{CH}_2$), 3.14 - 3.24 (m, 1 H, CHOH), 2.63 (t, J = 7.4 Hz, 2 H, $\text{CH}=\text{CCH}_2$), 2.56 (br t, J = 4.6 Hz, 4 H, $\text{CH}=\text{CCH}_2\text{CH}_2\text{CH}_2\text{N(CH}_2\text{CH}_2)\text{CH}_2$), 2.38 (t, J = 6.9 Hz, 2 H, $\text{CH}=\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$), 2.04 - 2.08 (m, 2 H, $\text{C(=O)CH}_2\text{CH}_2\text{CH}_2\text{N}$), 1.96 - 2.04 (m, 2 H, $\text{C(=O)CH}_2\text{CH}_2\text{CH}_2\text{N}$), 1.78 - 1.87 (m, 1 H, CHHCHOH), 1.69 - 1.78 (m, 1 H, CHHCHNH), 1.63 (quin, J = 7.5 Hz, 2 H, $\text{CH}=\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$), 1.54 - 1.60 (m, 2 H, CHHCH_2OH), 1.51 (quin, J = 7.4 Hz, 2 H, $\text{CH}=\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$), 1.28 - 1.35 (m, 2 H, $\text{NCH(CH}_2)_2$), 1.11 - 1.22 (m, 5 H, $\text{NCH(CH}_2)_2$, CHHCHOH , $\text{CHHCH}_2\text{CHOH}$ and $\text{CH}_2\text{CH}_2\text{CHNH}$), 1.04 - 1.13 (m, 1 H, CHHCHNH)

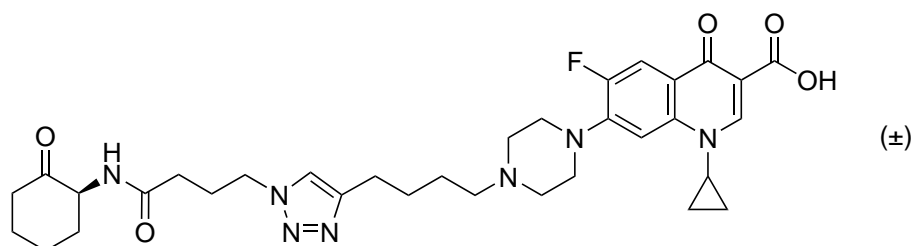
^{13}C NMR (101 MHz, $\text{DMSO-}d_6$) δ / ppm = 176.4 (C(=O)CC(=O)OH), 170.9 ($\text{CH}_2\text{C(=O)NH}$), 166.0 (C(=O)OH), 153.1 (d, J = 252.1 Hz, *ipso* to F), 148.0 ($\text{C}=\text{CC(=O)OH}$), 146.9 ($\text{CH}=\text{CCH}_2$), 145.3 (d, J = 10.0 Hz, *ipso* to piperazine), 139.2 (*para* to F), 121.8 ($\text{NCH}=\text{CCH}_2$), 118.5 (d, J = 8.3 Hz, *para* to piperazine), 110.9 (d, J = 23.2 Hz, *ortho* to C=O and *ortho* to F), 106.7 (CC(=O)OH), 106.3 (d, J = 3.3 Hz, *meta* to C=O and *meta* to F), 71.4 (CHOH), 57.4 ($\text{CH}=\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$), 54.2 (CHNH), 52.4 ($\text{CH}=\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N(CH}_2\text{CH}_2)\text{CH}_2$), 49.5 ($\text{CH}=\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N(CH}_2\text{CH}_2)\text{CH}_2\text{CH}_2$), 49.5 ($\text{CH}=\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N(CH}_2\text{CH}_2)\text{CH}_2\text{CH}_2$), 48.8 ($\text{C(=O)CH}_2\text{CH}_2\text{CH}_2\text{NCH}=\text{C}$), 35.9 ($\text{NCH(CH}_2)_2$), 34.1 (CH_2CHOH), 32.3 ($\text{C(=O)CH}_2\text{CH}_2\text{CH}_2\text{NCH}=\text{C}$), 31.1 (CH_2CHNH), 26.9 ($\text{CH}=\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$), 26.1 ($\text{C(=O)CH}_2\text{CH}_2\text{CH}_2\text{NCH}=\text{C}$), 25.8 ($\text{CH}=\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$), 25.0 ($\text{CH}=\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$), 24.2 ($\text{CH}_2\text{CH}_2\text{CHNH}$), 23.8 ($\text{CH}_2\text{CH}_2\text{CHOH}$), 7.6 ($\text{NCH(CH}_2)_2$)

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

HRMS (ESI^+) m/z / Da = 638.3480, $[\text{M}+\text{H}]^+$ found, $[\text{C}_{33}\text{H}_{45}\text{FN}_7\text{O}_5]^+$ 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)-1*H*-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)

^1H NMR (500 MHz, DMSO d_6) δ / ppm = 8.65 (s, 1 H, *ortho* to C(=O)OH), 7.94 (d, J = 7.7 Hz, 1 H, NH), 7.88 (d, J = 13.4 Hz, 1 H, *ortho* to F), 7.85 (s, 1 H, $\text{CH}=\text{CCH}_2$), 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) $\text{CH}_2\text{CH}_2\text{CHHN}$), 4.31 (t, J = 6.9 Hz, 1 H, C(=O) $\text{CH}_2\text{CH}_2\text{CHH}_2\text{N}$), 3.74 - 3.84 (m, 1 H, $\text{NCH}(\text{CH}_2)_2$), 3.31 (br. s, 4 H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)\text{CH}_2\text{CH}_2$), 2.64 (t, J = 7.5 Hz, 2 H, $\text{CH}=\text{CCH}_2$), 2.56 (br t, J = 5.0, 5.0 Hz, 4 H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2)\text{CH}_2$), 2.45 - 2.52 (m, 1 H, $\text{CHHC}(\text{=O})$), 2.38 (t, J = 7.1 Hz, 2 H, $\text{CH}=\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$), 2.25 (dt, J = 13.4, 2.6, 1.6 Hz, 1 H, $\text{CHHC}(\text{=O})$), 2.07 - 2.17 (m, 3 H, C(=O) $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$ and CHHCHNH), 1.96 - 2.05 (m, 3 H, C(=O) $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$ and $\text{CHHCH}_2\text{C}(\text{=O})$), 1.68 - 1.81 (m, 2 H, $\text{CHHCH}_2\text{CHNH}$), 1.64 (quin, J = 7.5 Hz, 2 H, $\text{CH}=\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$), 1.40 - 1.56 (m, 5 H, $\text{CHHCH}_2\text{C}(\text{=O})$, CHHCHNH and $\text{CH}=\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$), 1.27 - 1.34 (m, 2 H, $\text{NCH}(\text{CHH})_2$), 1.13 - 1.20 (m, 2 H, $\text{NCH}(\text{CHH})_2$)

^{13}C NMR (126 MHz, DMSO d_6) δ / ppm = 207.4 ($\text{C}(\text{=O})\text{CHNH}$), 176.3 ($\text{C}(\text{=O})\text{CC}(\text{=O})\text{OH}$), 170.8 ($\text{CH}_2\text{C}(\text{=O})\text{NH}$), 166.0 ($\text{C}(\text{=O})\text{OH}$), 153.0 (d, J = 246.4 Hz, *ipso* to F), 147.9 ($\text{C}=\text{CC}(\text{=O})\text{OH}$), 146.8 ($\text{CH}=\text{CCH}_2$), 145.1 (d, J = 10.1 Hz, *ipso* to piperazine), 139.1 (*para* to F), 121.7 ($\text{NCH}=\text{CCH}_2$), 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 ($\text{CC}(\text{=O})\text{OH}$, and *meta* to C=O and *meta* to F), 57.3 ($\text{CH}=\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$), 57.0 (CHNH), 52.4 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2)\text{CH}_2$), 49.5 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)\text{CH}_2\text{CH}_2$), 49.5 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)\text{CH}_2\text{CH}_2$), 48.7 (C(=O) $\text{CH}_2\text{CH}_2\text{CH}_2\text{NCH}=\text{C}$), 40.5 ($\text{CH}_2\text{C}(\text{=O})$), 35.8 ($\text{NCH}(\text{CH}_2)_2$), 33.7 (CH_2CHNH), 31.8 (C(=O) $\text{CH}_2\text{CH}_2\text{CH}_2\text{NCH}=\text{C}$), 27.1 ($\text{CH}_2\text{CH}_2\text{C}(\text{=O})$), 26.9 ($\text{CH}=\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$), 26.0 (C(=O) $\text{CH}_2\text{CH}_2\text{CH}_2\text{NCH}=\text{C}$), 25.7 ($\text{CH}=\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$), 24.9 ($\text{CH}=\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$), 23.8 ($\text{CH}_2\text{CH}_2\text{CHNH}$), 7.6 ($\text{NCH}(\text{CH}_2)_2$)

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

HRMS (ESI^+) m/z / Da = 636.3303, $[\text{M}+\text{H}]^+$ found, $[\text{C}_{33}\text{H}_{43}\text{FN}_7\text{O}_5]^+$ requires 636.3310

The compound has not been reported previously.

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Todo list

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