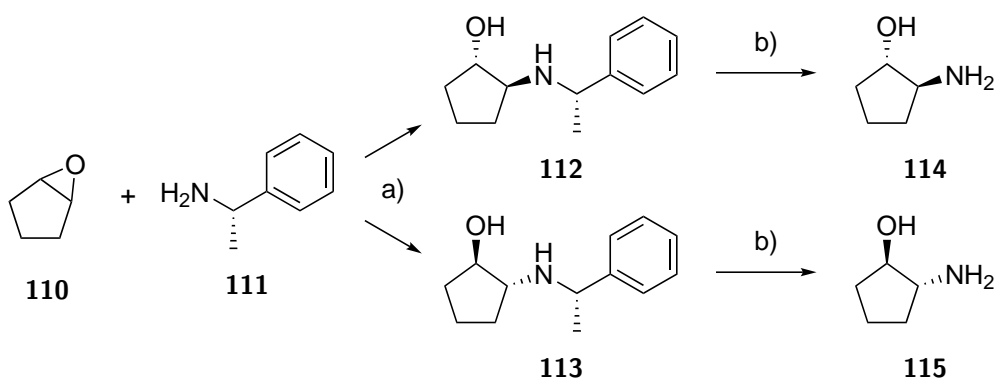


## 0.1 Cyclopentyl alcohol derivatives

### 0.1.1 Synthesis of the cyclopentyl alcohol head groups

Synthesis of the cyclopentyl alcohol derivatives began with the synthesis of (1*R*,2*R*)-2-aminocyclopentan-1-ol **115** and (1*S*,2*S*)-2-aminocyclopentan-1-ol **114** (see ??). These were synthesised by opening cyclopentene oxide using (*S*)-1-phenylethan-1-amine **111** to give approximately equal amounts of two diastereomers, **113** and **112**, which were separated using column chromatography.<sup>1-3</sup> The methylbenzyl group was then removed by hydrogenation to give the two enantiomers of 2-aminocyclopentan-1-ol, **115** and **114**, both in quantitative yield.

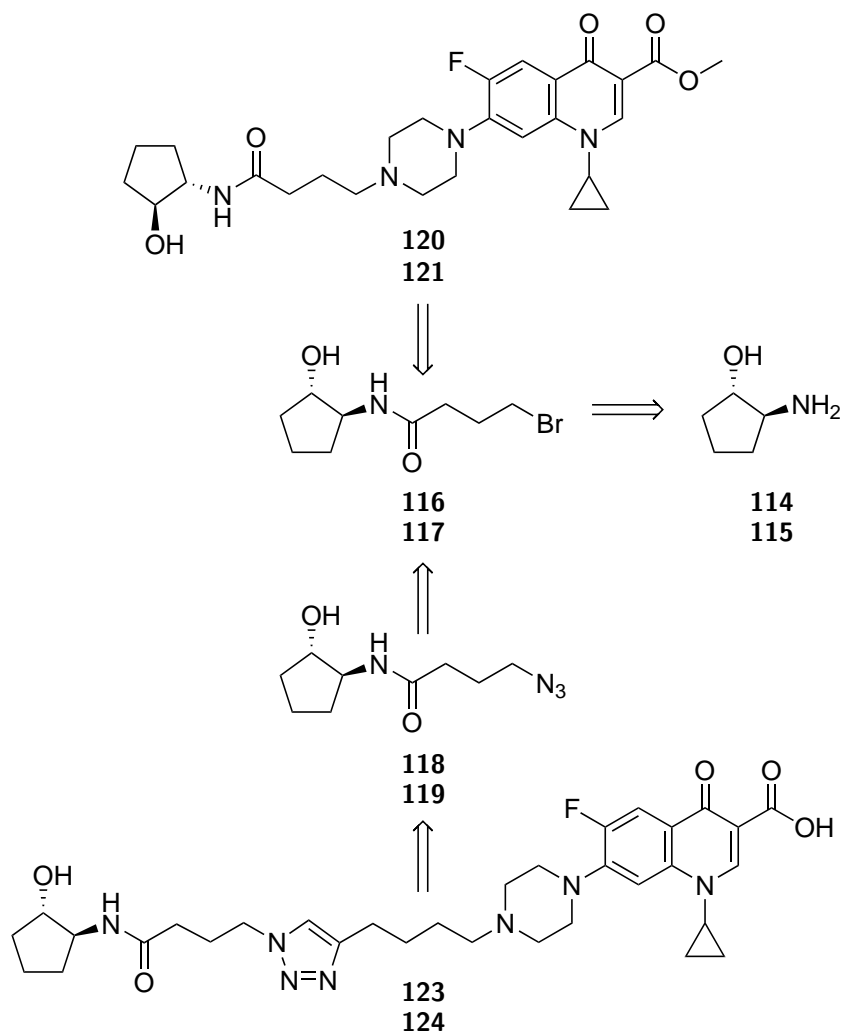


this was optimised, maybe add that?

Scheme 1: Synthesis of (1*S*,2*S*)-2-aminocyclopentan-1-ol **114** and (1*R*,2*R*)-2-aminocyclopentan-1-ol **115** a)  $\text{AlMe}_3$ ,  $\text{CH}_2\text{Cl}_2$ , 0 °C. **112** : 35.2 %, **113** : 32.1 %. b)  $\text{Pd}(\text{OH})_2$ , MeOH,  $\text{H}_2$ , 5 atm, r.t., 1 d, **114** : 100 %, **115** : 100 %.

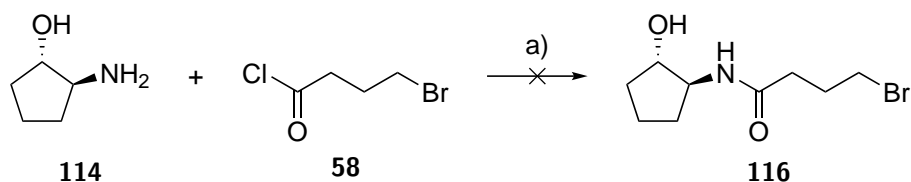
### 0.1.2 Initial branching strategy

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



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

Synthesis of Br-C<sub>4</sub>-cyclopentanol(*SS*) **116** from (1*S*,2*S*)-2-aminocyclopentanol-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 3: Synthesis of Br-C<sub>4</sub>-cyclopentanol(*SS*) **116**. a) NaHCO<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, H<sub>2</sub>O, 0 °C, 2 h.

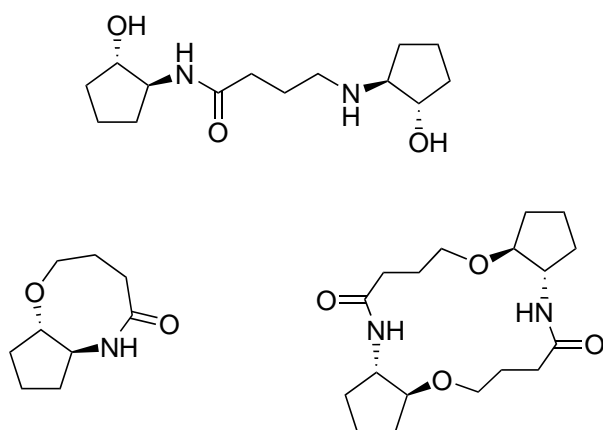
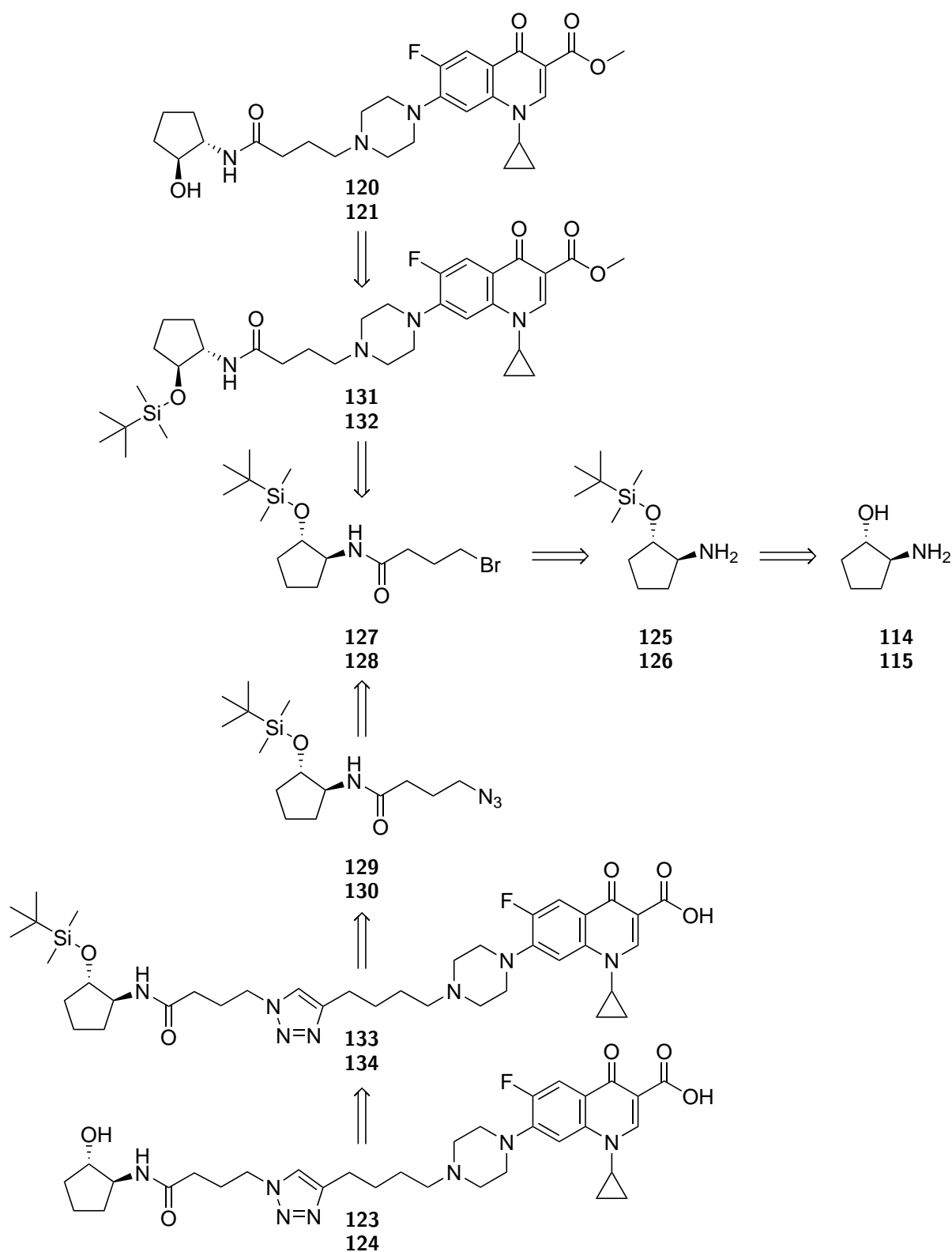


Figure 1: Impurities formed during the synthesis of Br-C<sub>4</sub>-cyclopentanol(*SS*) **116**.

### 0.1.3 TBS protection strategy

#### 0.1.3.1 Initial

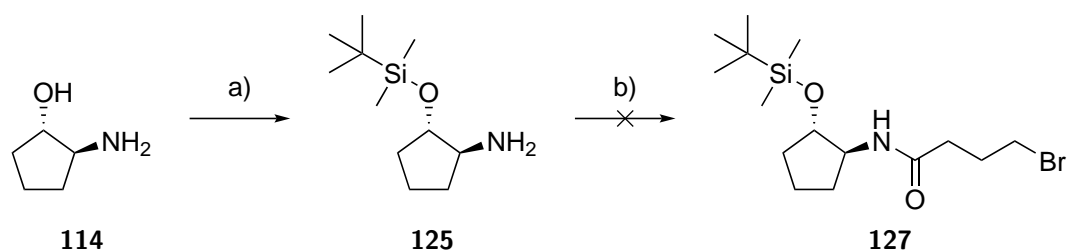
Want to protect alcohol to stop side reactions



Scheme 4: 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 a TBS protection strategy. *SS* enantiomers are shown, but both will be synthesised.

Conditions	Temperature	Time	Result
TBDMSCl, DMAP, TEA, CH <sub>2</sub> Cl <sub>2</sub>	r.t.	18 h	Trace of product?
TBDMSCl, DMAP, TEA, CH <sub>2</sub> Cl <sub>2</sub>	r.t.	1 d	Didn't go to completion, lost on prep TLC
TBDMSCl, imidazole, CH <sub>2</sub> Cl <sub>2</sub>	0 °C	1 h	S.M. salt in aq layer?
TBDMSCl, DBU, MeCN	0 °C	1 d	S.M.
TBDMSOTf, TEA	0 °C	4 h	Product possibly seen but lost in workup
TBDMSOTf, in 2 portions TEA, NH <sub>4</sub> Cl workup	0 °C	6 h	Product salt?
TBDMSOTf, in 2 portions TEA, aq workup then column	0 °C	6 h	Product! 85 %

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



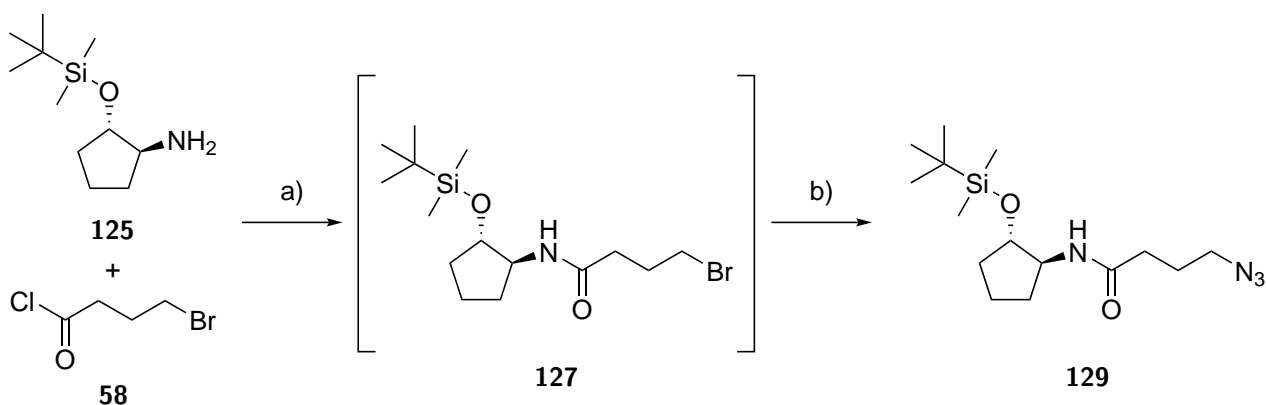
Scheme 5: The synthesis of Br-C<sub>4</sub>-cyclopentanol-TBS(*SS*) **127** (see Table 1).

Protection optimisation

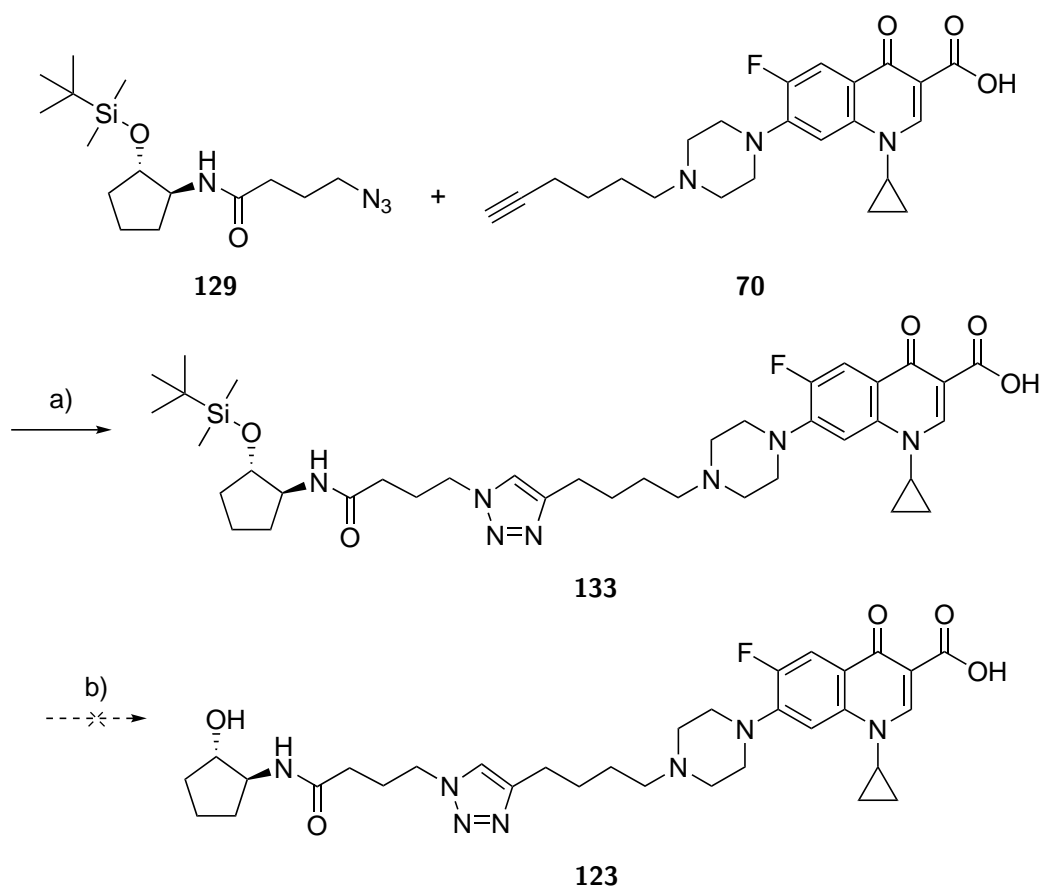
Still get side-reactions when adding tail

### 0.1.3.2 Triazoles by two-step reaction

Talk about moving to two-step reaction.



Scheme 6

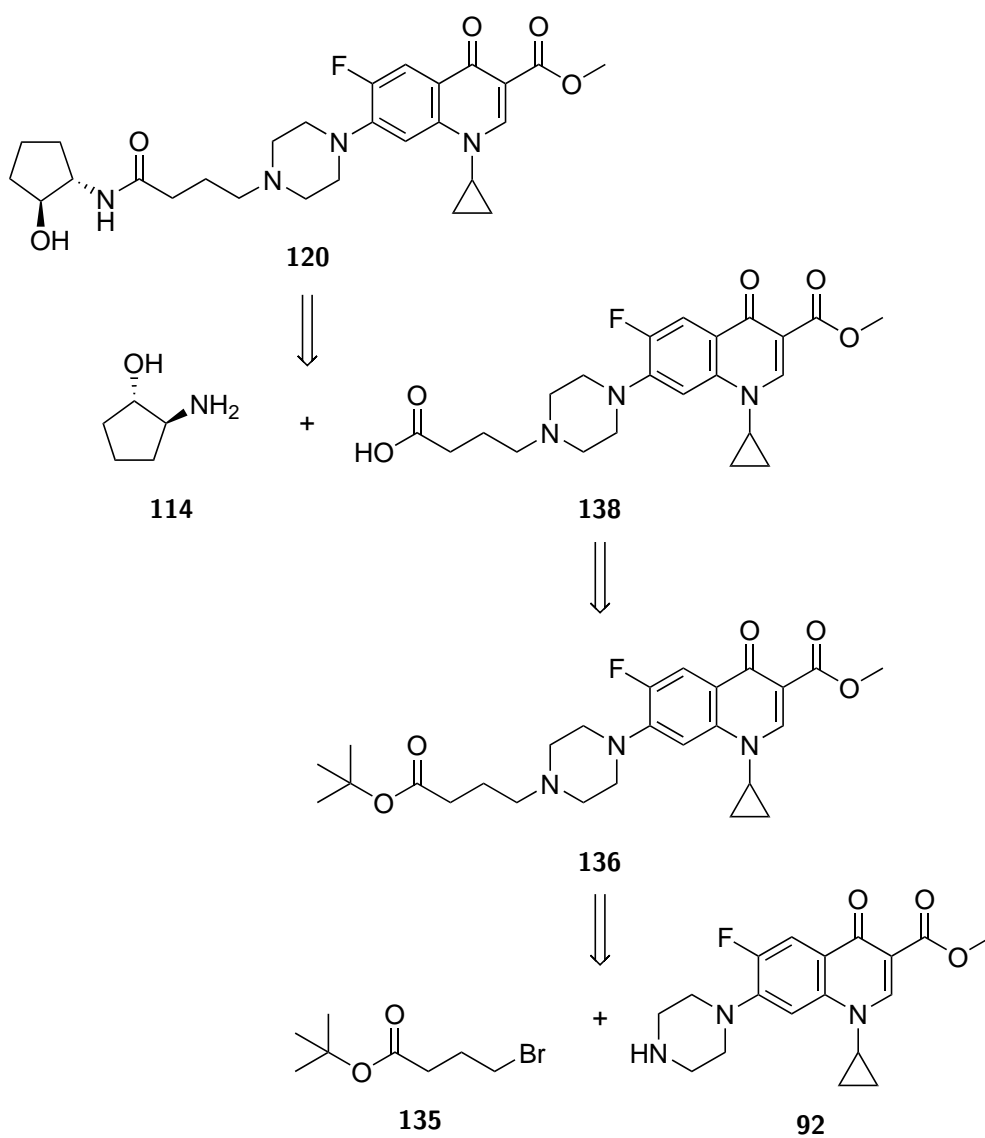


Scheme 7

Did click, then failed to deprotect.

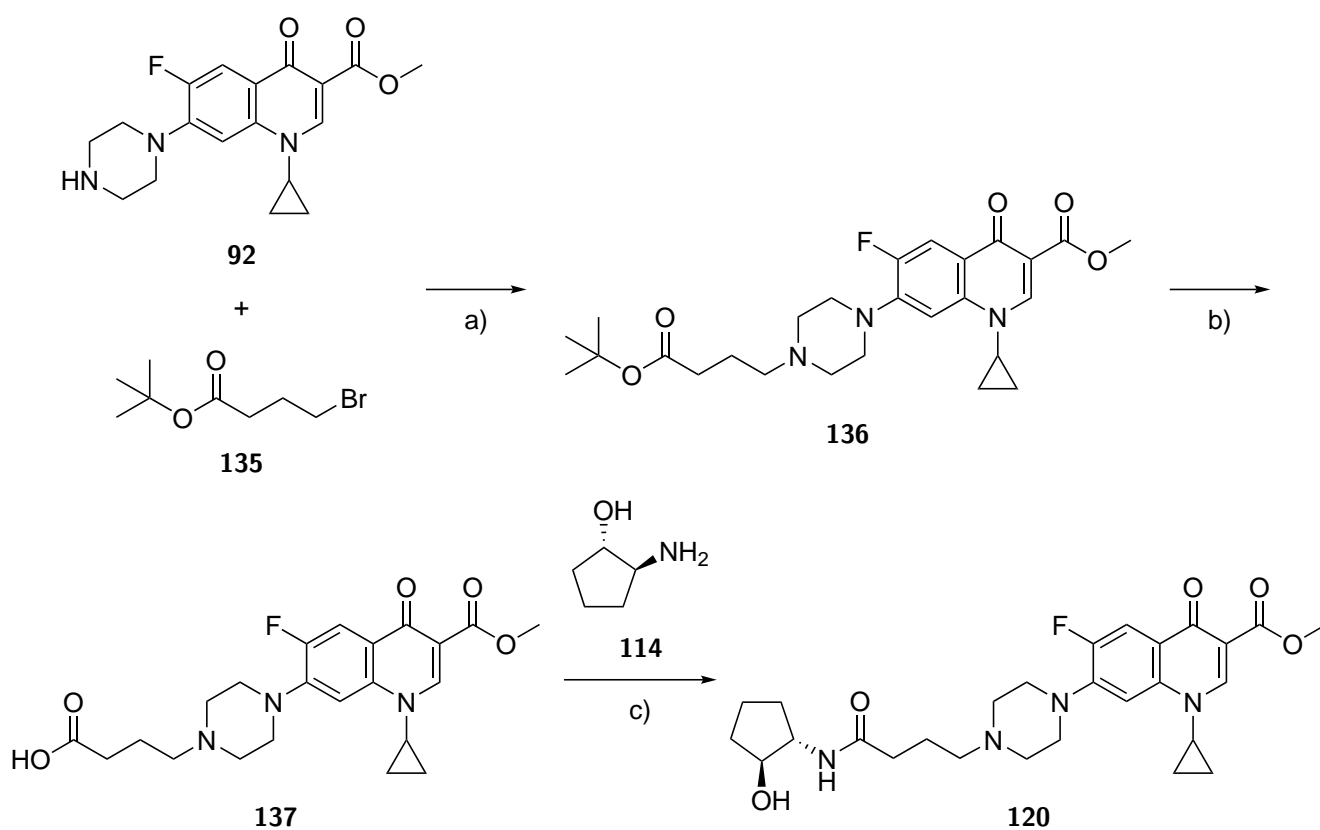
#### 0.1.4 Attaching the linker to ciprofloxacin first

Given the side-reactions and low yields associated with the literature synthesis of the  $S_N2$  conjugates proposed by Ganguly et. al,<sup>4</sup> we investigated a second synthesis, 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.

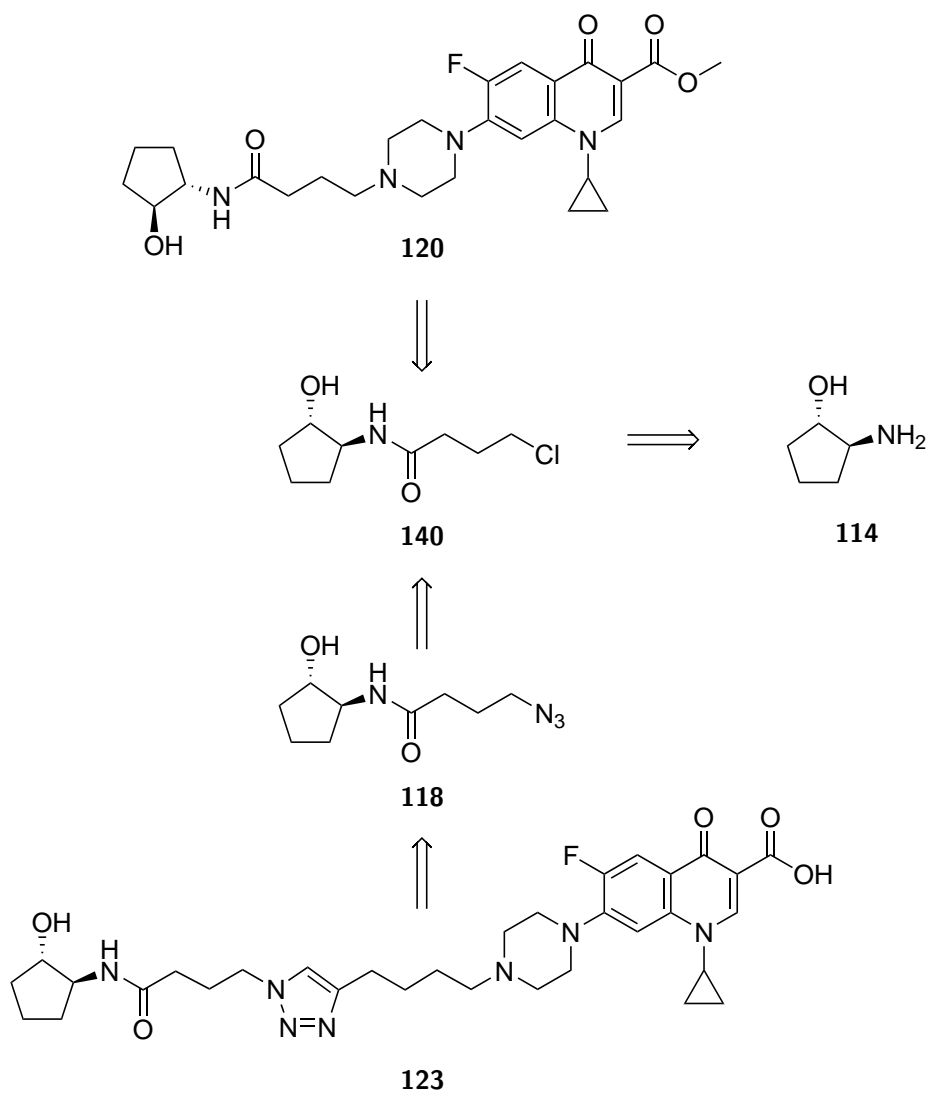
#### 0.1.4.1 Synthesis of methyl-protected ciprofloxacin with linker with terminal carboxylate



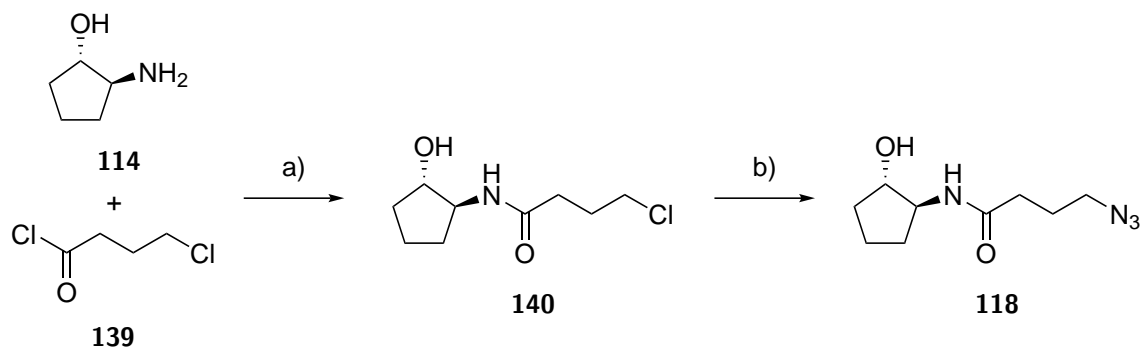
Scheme 9: Synthesis of **120**. a) .



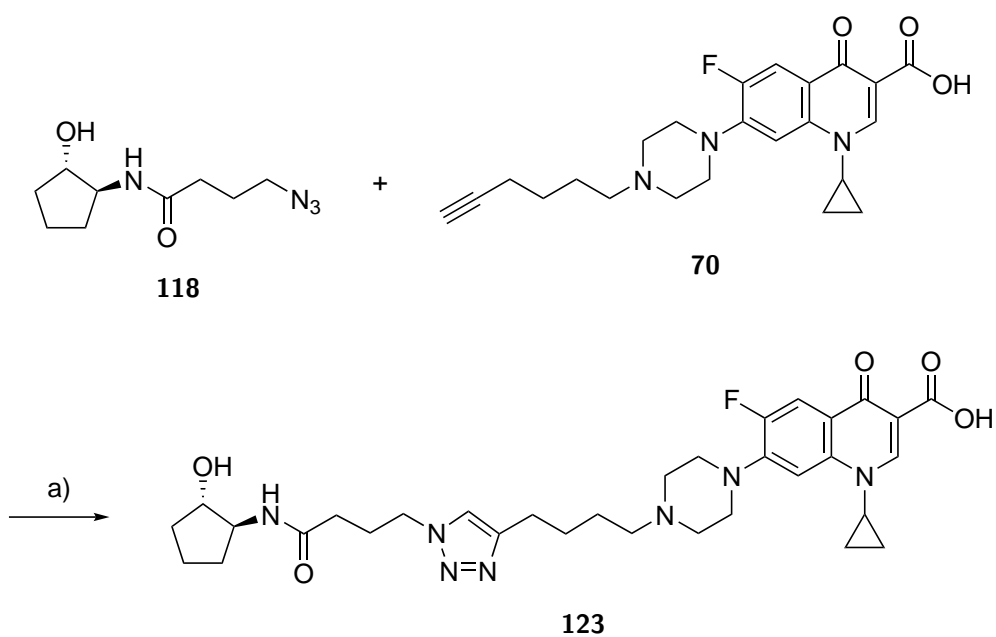
### 0.1.5 Triazoles from the chloride



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-C<sub>4</sub>-cyclopentanol(*SS*) **140**. *SS* enantiomers are shown, but both will be synthesised.



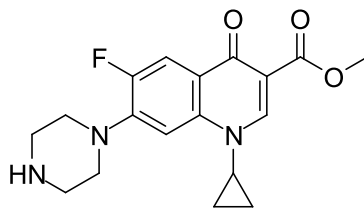
Scheme 11: Synthesis of N<sub>3</sub>-C<sub>4</sub>-cyclopentanol(*SS*) **118**. a) TEA, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 2 h. b) NaN<sub>3</sub>, acetonitrile, 50 °C, 24 h, 45.0 %.



Scheme 12: Synthesis of the cyclopentyl alcohol-Cip triazole conjugate **123**. a) CuSO<sub>4</sub>, THPTA, sodium ascorbate, H<sub>2</sub>O, *t*-BuOH, CH<sub>2</sub>Cl<sub>2</sub>, r.t., 3 d, 22.2 %.

This worked.

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



Ciprofloxacin **28** (10.0 g, 30 mmol, 1 eq.) and *p*-toluenesulfonic acid (8.60 mg, 44.5 mmol, 1.5 eq.) were refluxed in methanol (500 ml) for 72 h. The mixture was cooled to room temperature and NaHCO<sub>3</sub> (sat., aq., 100 ml) and water (300 ml) were added. The product was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2×400 ml). The combined organic fractions were dried over MgSO<sub>4</sub> and evaporated under reduced pressure. **92** was obtained as a white amorphous solid (9.16 g, 26.5 mmol, 83.3 %).

**TLC**  $R_f$  = 0.13 (5 % MeOH/CH<sub>2</sub>Cl<sub>2</sub>)

**IR** (neat)  $\nu_{max}$  / cm<sup>-1</sup> = 2947.9 (C-H), 2834.9 (C-H), 1720.9 (ester C=O), 1616.8 (quinolone C=O)

**<sup>1</sup>H NMR** (400 MHz, MeOD)  $\delta$  / ppm = 8.55 (s, 1 H, *ortho* to C(=O)OCH<sub>3</sub>), 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, CH<sub>3</sub>), 3.62 (tt,  $J$  = 7.4, 3.5 Hz, 1 H, NCH(CH<sub>2</sub>)<sub>2</sub>), 3.24 - 3.29 (m, 4 H, HN(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 3.02 - 3.10 (m, 4 H, HN(CH<sub>2</sub>)CH<sub>2</sub>), 1.31 - 1.38 (m, 2 H, NCH(CH<sub>2</sub>)<sub>2</sub>), 1.12 - 1.20 (m, 2 H, NCH(CH<sub>2</sub>)<sub>2</sub>)

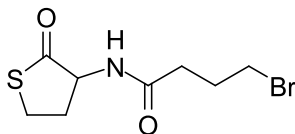
**<sup>13</sup>C NMR** (101 MHz, MeOD)  $\delta$  / ppm = 175.2 (C(=O)CC(=O)OCH<sub>3</sub>), 166.8 (C(=O)OCH<sub>3</sub>), 154.9 (d,  $J$  = 248.0 Hz, *ipso* to F), 150.1 (C=CC(=O)OCH<sub>3</sub>), 146.6 (d,  $J$  = 10.4 Hz, *ipso* to piperazine), 139.9 (*para* to F), 123.3 (d,  $J$  = 6.9 Hz, *para* to piperazine), 113.0 (d,  $J$  = 23.4 Hz, *ortho* to C=O and *ortho* to F), 110.1 (CC(=O)OCH<sub>3</sub>), 107.1 (d,  $J$  = 3.5 Hz, *meta* to C=O and *meta* to F), 52.3 (CH<sub>3</sub>), 51.7 (HN(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 51.6 (HN(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 46.5 (HN(CH<sub>2</sub>)CH<sub>2</sub>), 36.4 (NCH(CH<sub>2</sub>)<sub>2</sub>), 8.7 (NCH(CH<sub>2</sub>)<sub>2</sub>)

**<sup>19</sup>F NMR** (376.45 MHz, MeOD)  $\delta$  / ppm = -124.8 (s, ciprofloxacin F)

**HRMS** (ESI<sup>+</sup>)  $m/z$  / Da = 346.1569, [M+H]<sup>+</sup> found, [C<sub>18</sub>H<sub>21</sub>FN<sub>3</sub>O<sub>3</sub>]<sup>+</sup> requires 346.1567

The data are consistent with the literature.<sup>5</sup>

## 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<sub>3</sub> (16.4 g, 195 mmol, 2 eq.) were added to CH<sub>2</sub>Cl<sub>2</sub> (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<sub>2</sub>Cl<sub>2</sub> (150 ml). The combined organic layers were dried over MgSO<sub>4</sub> 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)  $\nu_{max}$  / cm<sup>-1</sup> = 3265.9 (amide N-H), 3063.2 (amide N-H), 1694.3 (thiolactone C=O), 1650.5 (amide C=O)

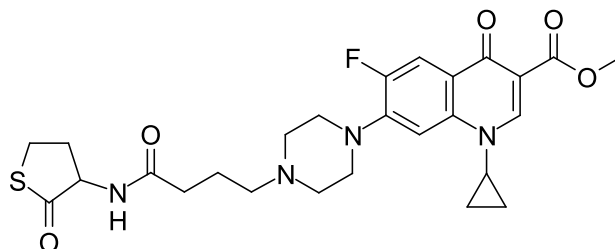
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  / ppm = 6.08 (d,  $J$  = 6.1 Hz, 1 H, NH), 4.54 (dt,  $J$  = 12.9, 6.5 Hz, 1 H, CHNH), 3.49 (t,  $J$  = 6.4 Hz, 2 H, CH<sub>2</sub>Br), 3.37 (ddd,  $J$  = 12.2, 11.5, 5.3 Hz, 1 H, SCHH), 3.26 (ddd,  $J$  = 11.5, 6.9, 1.3 Hz, 1 H, SCHH), 2.91 (dddd,  $J$  = 12.5, 6.7, 5.3, 1.3 Hz, 1 H, SCH<sub>2</sub>CHH), 2.45 (t,  $J$  = 7.4 Hz, 1 H, C(=O)CHH), 2.45 (t,  $J$  = 6.8 Hz, 1 H, C(=O)CHH), 2.20 (quin,  $J$  = 6.7 Hz, 1 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>), 1.96 (dddd,  $J$  = 12.7, 12.5, 12.2, 7.0 Hz, 1 H, SCH<sub>2</sub>CHH)

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  / ppm = 205.4 (SC(=O)), 172.1 (NHC(=O)), 59.4 (CHNH), 34.1 (C(=O)CH<sub>2</sub>), 33.1 (CH<sub>2</sub>Br), 31.8 (SCH<sub>2</sub>CH<sub>2</sub>), 28.0 (C(=O)CH<sub>2</sub>CH<sub>2</sub>), 27.5 (SCH<sub>2</sub>)

**HRMS** (ESI<sup>+</sup>) The compound does not ionise.

The compound has been synthesised previously<sup>4,6</sup> 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<sub>2</sub>CO<sub>3</sub> (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<sub>2</sub>, 5-10 % MeOH/CH<sub>2</sub>Cl<sub>2</sub>) followed by preparatory 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<sub>2</sub>Cl<sub>2</sub>)

**IR** (neat)  $\nu_{max}$  / cm<sup>-1</sup> = 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)

**<sup>1</sup>H NMR** (500 MHz, MeOD)  $\delta$  / ppm = 8.53 (s, 1 H, *ortho* to C(=O)OCH<sub>3</sub>), 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, OCH<sub>3</sub>), 3.61 (tt, J=6.9, 4.1 Hz, 1 H, NCH(CH<sub>2</sub>)<sub>2</sub>), 3.39 - 3.49 (m, 5 H, SCHH), 3.26 - 3.33 (m, 1 H, SCHH and CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 2.93 - 3.03 (m, 4 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 2.79 (br. t, J=7.2, 7.2 Hz, 2 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 2.59 (dddd, J=12.4, 6.9, 5.4, 1.4 Hz, 1 H, SCH<sub>2</sub>CHH), 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, SCH<sub>2</sub>CHH), 1.97 (quin, J=7.2 Hz, 2 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>), 1.32 - 1.37 (m, 2 H, NCH(CHH)<sub>2</sub>), 1.13 - 1.19 (m, 2 H, NCH(CHH)<sub>2</sub>)

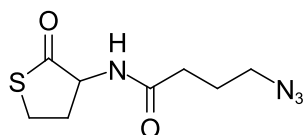
**<sup>13</sup>C NMR** (126 MHz, MeOD)  $\delta$  / ppm = 207.0 (SC(=O)), 175.7 (NHC(=O)), 175.1 (C(=O)CC(=O)OCH<sub>3</sub>), 166.6 (C(=O)OCH<sub>3</sub>), 154.7 (d, J=249.0 Hz, *ipso* to F), 150.2 (s, CH=CC(=O)OCH<sub>3</sub>), 145.6 (d, J=10.6 Hz, *ipso* to piperazine), 139.8 (*para* to F), 123.5 (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)OCH<sub>3</sub>), 107.4 (*meta* to C=O and *meta* to F), 60.2 (CHNH), 58.5 (C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 53.8 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 52.3 (OCH<sub>3</sub>), 50.1 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 50.0 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 36.5 (NCH(CH<sub>2</sub>)<sub>2</sub>), 34.5 (C(=O)CH<sub>2</sub>), 31.7 (SCH<sub>2</sub>CH<sub>2</sub>), 28.1 (SCH<sub>2</sub>), 22.9 (C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 8.7 (NCH(CH<sub>2</sub>)<sub>2</sub>)

**<sup>19</sup>F NMR** (376.45 MHz, MeOD)  $\delta$  / ppm = -125.4 (s, ciprofloxacin F)

**HRMS** (ESI<sup>+</sup>)  $m/z$  / Da = 531.2083, [M+H]<sup>+</sup> found, [C<sub>26</sub>H<sub>32</sub>FN<sub>4</sub>O<sub>5</sub>S]<sup>+</sup> requires 531.2077

The compound has been synthesised previously.<sup>4,6</sup> Only HRMS characterisation was published, and this agrees with the result above.

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



4-Bromo-*N*-(2-oxotetrahydrothiophen-3-yl)butanamide **94** (6.00 g, 27.0 mmol, 1 eq.) and NaN<sub>3</sub> (3.51 g, 54.1 mmol, 2 eq.) were refluxed in acetonitrile (120 ml) for 1.5 h. The solvent was evaporated under reduced pressure and the residue was partitioned between water (150 ml) and CH<sub>2</sub>Cl<sub>2</sub> (150 ml). The aqueous layer was extracted twice more with CH<sub>2</sub>Cl<sub>2</sub> (2×150 ml) and the combined organic fractions were dried with MgSO<sub>4</sub> 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)  $\nu_{max}$  / cm<sup>-1</sup> = 3285.6 (N-H), 2963.9 (C-H), 2100.2 (azide), 1697.4 (thiolactone C=O), 1647.4 (amide C=O)

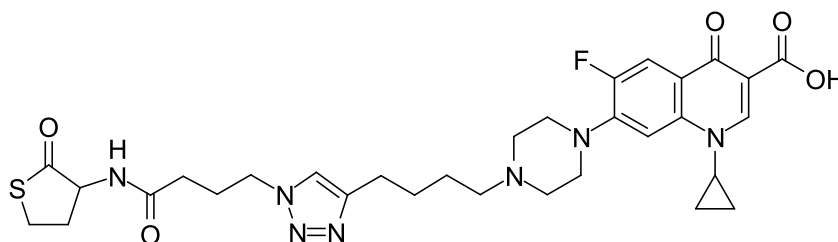
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  / ppm = 6.71 (d,  $J$  = 7.3 Hz, 1 H, NH), 4.54 (dt,  $J$  = 13.0, 7.0 Hz, 1 H, CHNH), 3.30 (t,  $J$  = 6.7 Hz, 2 H, CH<sub>2</sub>N<sub>3</sub>), 3.31 (td,  $J$  = 11.7, 5.3 Hz, 1 H, 1 H, SCHH), 3.19 (ddd,  $J$  = 11.3, 7.0, 1.2 Hz, 1 H, SCHH), 2.70 (dddd,  $J$  = 12.4, 6.8, 5.3, 1.2 Hz, 1 H, SCH<sub>2</sub>CHH), 2.29 (t,  $J$  = 7.5 Hz, 1 H, C(=O)CHH), 2.28 (t,  $J$  = 7.1 Hz, 1 H, C(=O)CHH), 1.97 (qd,  $J$  = 12.4, 7.0 Hz, 1 H, SCH<sub>2</sub>CHH), 1.85 (quin,  $J$  = 6.9 Hz, 2 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>)

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  / ppm = 205.4 ( $\text{SC}(=\text{O})$ ), 172.3 ( $\text{NHC}(=\text{O})$ ), 59.4 ( $\text{CHNH}$ ), 50.6 ( $\text{CH}_2\text{N}_3$ ), 32.8 ( $\text{C}(=\text{O})\text{CH}_2$ ), 31.8 ( $\text{SCH}_2\text{CH}_2$ ), 27.5 ( $\text{SCH}_2$ ), 24.6 ( $\text{C}(=\text{O})\text{CH}_2\text{CH}_2$ )

HRMS ( $\text{ESI}^+$ )  $m/z$  / Da = 251.0565,  $[\text{M}+\text{Na}]^+$  found,  $[\text{C}_8\text{H}_{12}\text{N}_4\text{NaO}_2\text{S}]^+$  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  $\mu\text{mol}$ , 1 eq.) and 4-azido-*N*-(2-oxotetrahydrothiophen-3-yl)butanamide **96** (12.5 mg, 55.1  $\mu\text{mol}$ , 1.5 eq.) were dissolved in 1:9:10 water/*t*-BuOH/DMSO (3 ml), and the mixture was degassed by bubbling  $\text{N}_2$  through it. A solution of  $\text{CuSO}_4$  and THPTA (182  $\mu\text{l}$ , 18.2  $\mu\text{mol}$ , 0.5 eq. 100 mM, aq.) was added, followed by a solution of sodium ascorbate (367  $\mu\text{l}$ , 36.7  $\mu\text{mol}$ , 1 eq., 100 mM, aq.). The mixture was stirred at r.t. under argon for 4 d. Water (10 ml) and 10 % *i*-PrOH/ $\text{CHCl}_3$  (10 ml) were added, the organic layer was separated and the aqueous layer was extracted again with 10 % *i*-PrOH/ $\text{CHCl}_3$  ( $2 \times 10$  ml). The combined organic layers were dried with  $\text{MgSO}_4$  and evaporated under reduced pressure. The residue was purified by preparatory HPLC (5-95 % acetonitrile/water over 20 min). The combined pure fractions were evaporated under reduced pressure and then partitioned between  $\text{NaHCO}_3$  (aq., sat., 50 ml) and 10 % *i*-PrOH/ $\text{CHCl}_3$  (50 ml). The organic layer was dried with  $\text{MgSO}_4$  and evaporated under reduced pressure. **97** was obtained as a white amorphous solid (16.5 mg, 25.9  $\mu\text{mol}$ , 70.6 %).

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

$^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  / ppm = 15.23 (br s, 1 H,  $\text{C}(=\text{O})\text{OH}$ ), 8.66 (s, 1 H, *ortho* to  $\text{C}(=\text{O})\text{OH}$ ), 8.23 (d,  $J=8.5$  Hz, 1 H,  $\text{NH}$ ), 7.90 (d,  $J=13.4$  Hz, 1 H, *ortho* to F), 7.84 (s, 1 H,  $\text{CH}=\text{CCH}_2$ ), 7.56 (d,  $J=7.5$  Hz, 1 H, *meta* to F), 4.59 (ddd,  $J=12.7, 8.4, 6.8$  Hz, 1 H,  $\text{CHNH}$ ), 4.31 (t,  $J=7.0$  Hz, 2 H,  $\text{CH}_2\text{NCH}=\text{C}$ ), 3.80 - 3.86 (6.9, 4.0 Hz, 1 H,  $\text{NCH}(\text{CH}_2)_2$ ), 3.34 - 3.37 (m, 1 H,  $\text{SCHH}$ ), 3.32 (br t,  $J=4.1$  Hz, 4 H,  $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)\text{CH}_2\text{CH}_2$ ), 3.27 (ddd,  $J=11.1, 6.9, 1.4$  Hz, 1 H,  $\text{SCHH}$ ), 2.64 (t,  $J=7.6$  Hz, 2 H,  $\text{CH}=\text{CCH}_2$ ), 2.57 (br t,  $J=4.7$  Hz, 4 H,  $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2)\text{CH}_2$ ), 2.34 - 2.44 (m, 3 H,  $\text{SCH}_2\text{CHH}$  and  $\text{CH}=\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2$ ), 2.12 (t,  $J=7.9$  Hz, 1 H,  $\text{C}(=\text{O})\text{CHH}$ ), 2.12 (t,  $J=7.0$  Hz, 1 H,  $\text{C}(=\text{O})\text{CHH}$ ), 2.04 (m, 3 H,  $\text{SCH}_2\text{CHH}$  and  $\text{C}(=\text{O})\text{CH}_2\text{CH}_2$ ), 1.64 (quin,  $J=7.5$  Hz, 2 H,  $\text{CH}=\text{CCH}_2\text{CH}_2$ ), 1.51 (quin,  $J=7.5$  Hz, 2 H,  $\text{CH}=\text{CCH}_2\text{CH}_2\text{CH}_2$ ), 1.28 - 1.34 (m, 2 H,  $\text{NCH}(\text{CHH})_2$ ), 1.15 - 1.20 (m, 2 H,  $\text{NCH}(\text{CHH})_2$ )

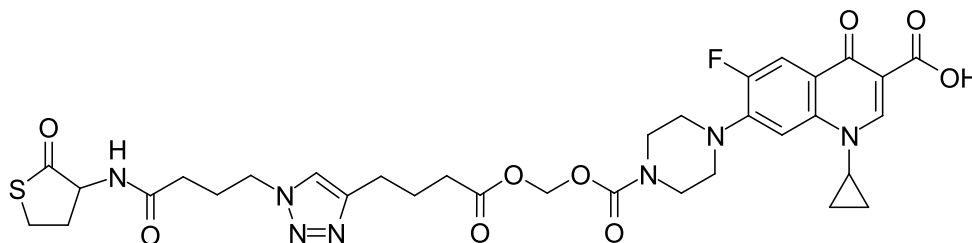
$^{13}\text{C}$  NMR (126 MHz,  $\text{DMSO}-d_6$ )  $\delta$  / ppm = 205.6 ( $\text{SC}(=\text{O})$ ), 176.4 ( $\text{C}(=\text{O})\text{CC}(=\text{O})\text{OH}$ ), 171.4 ( $\text{NHC}(=\text{O})$ ), 166.0 ( $\text{C}(=\text{O})\text{OH}$ ), 153.1 (d,  $J=249.3$  Hz, *ortho* to F), 148.0 ( $\text{CH}=\text{CC}(=\text{O})\text{OH}$ ), 146.9 ( $\text{CH}=\text{CCH}_2$ ), 145.3

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

$^{19}\text{F}$  NMR (376.45 MHz, MeOD)  $\delta$  / ppm = -124.9 (s, ciprofloxacin F)

HRMS ( $\text{ESI}^+$ )  $m/z$  / Da = 640.2739,  $[\text{M}+\text{H}]^+$  found,  $[\text{C}_{31}\text{H}_{39}\text{FN}_7\text{O}_5\text{S}]^+$  requires 640. 2712

## 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  $\text{CH}_2\text{Cl}_2$  (18.6 ml) at r.t. under Ar for 3 h. The mixture was filtered and the filtrate was dry-loaded onto  $\text{SiO}_2$  and purified by column chromatography ( $\text{SiO}_2$ , 5-10 % MeOH/ $\text{CH}_2\text{Cl}_2$ ). **99** was obtained as pale brown/yellow amorphous solid (14.7 mg, 20.2  $\mu\text{mol}$ , 5.0 %).

TLC  $R_f$  = 0.40 (5 %  $\text{CH}_2\text{Cl}_2$ /MeOH)

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

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

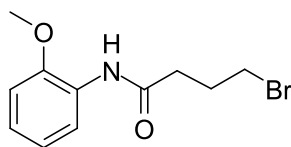
$^{13}\text{C}$  NMR (101 MHz, DMSO  $d_6$ )  $\delta$  / ppm = 205.5 ( $\text{SC}(=\text{O})$ ), 176.4 ( $\text{C}(=\text{O})\text{CC}(=\text{O})\text{OH}$ ), 171.8 ( $\text{C}(=\text{O})\text{OCH}_2\text{O}$ ), 171.3 ( $\text{NHC}(=\text{O})$ ), 165.9 ( $\text{C}(=\text{O})\text{OH}$ ), 152.8 (d,  $J = 249.7$  Hz, *ipso* to F), 152.9 ( $\text{OC}(=\text{O})\text{N}$ ), 148.1 ( $\text{CH}=\text{CC}(=\text{O})$ )

OH), 146.0 (CH=CCH<sub>2</sub>), 144.9 (d,  $J$  = 9.6 Hz, *ipso* to piperazine), 139.1 (*para* to F), 122.0 (CH=CCH<sub>2</sub>), 118.9 (d,  $J$  = 7.5 Hz, *para* to piperazine), 111.0 (d,  $J$  = 23.5 Hz, *ortho* to C=O and *ortho* to F), 106.8 (CC(=O)OH, and *meta* to C=O and *meta* to F), 80.3 (OCH<sub>2</sub>O), 58.2 (CHNH), 49.1 (C(=O)N(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 49.1 (C(=O)N(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 48.6 (C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 43.4 (N(CH<sub>2</sub>)CH<sub>2</sub>), 43.0 (N(CH<sub>2</sub>)CH<sub>2</sub>), 35.9 (NCH(CH<sub>2</sub>)<sub>2</sub>), 32.7 (CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>C(=O)), 31.8 (NHC(=O)CH<sub>2</sub>), 30.1 (SCH<sub>2</sub>CH<sub>2</sub>), 26.8 (SCH<sub>2</sub>), 25.8 (C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 24.2 (CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>C(=O)), 24.0 (CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>C(=O)), 7.6 (NCH(CH<sub>2</sub>)<sub>2</sub>)

**HRMS** (ESI<sup>+</sup>)  $m/z$  / Da = 728.2502, [M+H]<sup>+</sup> found, [C<sub>33</sub>H<sub>39</sub>FN<sub>7</sub>O<sub>9</sub>S]<sup>+</sup> requires 728.2503

The compound has not been reported previously.

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



2-Methoxyaniline **100** (9.12 ml, 10.0 g, 81.2 mmol, 1 eq.) and NaHCO<sub>3</sub> (8.19 g, 97.4 mmol, 1.2 eq.) were dissolved in water (100 ml) and CH<sub>2</sub>Cl<sub>2</sub> (100 ml). The mixture was cooled to 0 °C and 4-bromobutyryl chloride **58** (9.40 ml, 15.1 g, 81.2 mmol, 1 eq.) was added dropwise over 15 min. The mixture was stirred at 0 °C for 1.5 h, then the aqueous layer was removed. The organic layer was dried with MgSO<sub>4</sub> and purified by column chromatography (SiO<sub>2</sub>, 5-25 % EtOAc/P.E.). The combined pure fractions were dried with MgSO<sub>4</sub> 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)  $\nu_{max}$  / cm<sup>-1</sup> = 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)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub> d<sub>1</sub>)  $\delta$  / ppm = 8.32 (dd,  $J$  = 8.0, 1.7 Hz, 1 H, *ortho* to NH), 7.85 (br s, 1 H, NH), 7.02 (td,  $J$  = 7.9, 1.7 Hz, 1 H, *para* to NH), 6.93 (td,  $J$  = 7.7, 1.4 Hz, 1 H, *para* to OCH<sub>3</sub>), 6.85 (dd,  $J$  = 8.1, 1.5 Hz, 1 H, *ortho* to OCH<sub>3</sub>), 3.85 (s, 3 H, CH<sub>3</sub>), 3.50 (t,  $J$  = 6.4 Hz, 2 H, CH<sub>2</sub>Br), 2.56 (t,  $J$  = 7.1 Hz, 2 H, C(=O)CH<sub>2</sub>), 2.25 (quin,  $J$  = 6.7 Hz, 2 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>)

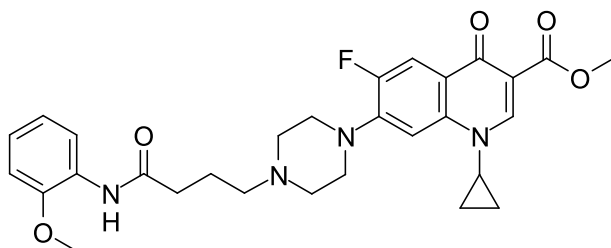
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub> d<sub>1</sub>)  $\delta$  / ppm = 169.4 (C(=O)), 147.6 (*ipso* to OCH<sub>3</sub>), 127.2 (*ipso* to NH), 123.5 (*para* to NH), 120.7 (*para* to OCH<sub>3</sub>), 119.6 (*ortho* to NH and *meta* to OCH<sub>3</sub>), 109.8 (*ortho* to OCH<sub>3</sub> and *meta* to NH), 55.5 (CH<sub>3</sub>), 35.4 (C(=O)CH<sub>2</sub>), 33.1 (CH<sub>2</sub>Br), 27.9 (C(=O)CH<sub>2</sub>CH<sub>2</sub>)

**HRMS** (ESI<sup>+</sup>)  $m/z$  / Da = 272.0287, [M+H]<sup>+</sup> found, [C<sub>11</sub>H<sub>15</sub>BrNO<sub>2</sub>]<sup>+</sup> requires 272.0286

The compound has not been reported previously.



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



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

**TLC**  $R_f$  = 0.40 (10 % MeOH/CH<sub>2</sub>Cl<sub>2</sub>)

**IR** (neat)  $\nu_{max}$  / cm<sup>-1</sup> = 2947.1 (C-H), 2833.7 (C-H), 1718.9 (ester C=O), 1685.3 (amide C=O), 1617.3 (quinolone C=O)

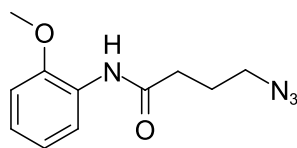
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub> d<sub>1</sub>)  $\delta$  / ppm = 8.48 (s, 1 H, *ortho* to C(=O)OCH<sub>3</sub>), 8.36 (d,  $J$  = 7.9 Hz, 1 H, *ortho* to NH), 7.87 - 7.99 (m, 2 H, *ortho* to F and NH), 7.19 (d,  $J$  = 6.5 Hz, 1 H, *meta* to F), 7.01 (t,  $J$  = 7.5 Hz, 1 H, *para* to NH), 6.93 (t,  $J$  = 7.7 Hz, 1 H, *para* to OCH<sub>3</sub>), 6.85 (d,  $J$  = 7.9 Hz, 1 H, *ortho* to OCH<sub>3</sub>), 3.88 (s, 3 H, C(=O)OCH<sub>3</sub>), 3.85 (s, 3 H, aromatic OCH<sub>3</sub>), 3.41 (tt,  $J$  = 6.9, 4.0 Hz, 1 H, NCH(CH<sub>2</sub>)<sub>2</sub>), 3.25 (br t,  $J$  = 5.0, 5.0 Hz, 4 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 2.67 (br t,  $J$  = 5.0, 5.0 Hz, 4 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 2.53 (t,  $J$  = 7.0 Hz, 2 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 2.47 (t,  $J$  = 7.1 Hz, 2 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 1.97 (quin,  $J$  = 6.8 Hz, 2 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 1.25 - 1.33 (m, 2 H, NCH(CH<sub>2</sub>)<sub>2</sub>), 1.07 - 1.14 (m, 2 H, NCH(CH<sub>2</sub>)<sub>2</sub>)

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub> d<sub>1</sub>)  $\delta$  / ppm = 172.9 (C(=O)CC(=O)OCH<sub>3</sub>), 170.8 (NHC(=O)), 166.2 (C(=O)OCH<sub>3</sub>), 153.3 (d,  $J$  = 248.0 Hz, *ipso* to F), 148.2 (C=CC(=O)OCH<sub>3</sub>), 147.6 (*ipso* to OCH<sub>3</sub>), 144.4 (d,  $J$  = 10.4 Hz, *ipso* to piperazine), 137.9 (*para* to F), 127.6 (*ipso* to NH), 123.4 (*para* to NH), 122.7 (d,  $J$  = 7.8 Hz, *para* to piperazine), 121.0 (*para* to OCH<sub>3</sub>), 119.7 (*ortho* to NH and *meta* to OCH<sub>3</sub>), 113.0 (d,  $J$  = 22.5 Hz, *ortho* to C=O and *ortho* to F), 109.8 (*ortho* to OCH<sub>3</sub> and *meta* to NH, and CC(=O)OCH<sub>3</sub>), 104.7 (*meta* to C=O and *meta* to F), 57.2 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 55.6 (aromatic OCH<sub>3</sub>), 52.7 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 51.9 (C(=O)OCH<sub>3</sub>), 49.8 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 49.8 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 35.5 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 34.5 (NCH(CH<sub>2</sub>)<sub>2</sub>), 22.3 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 8.0 (NCH(CH<sub>2</sub>)<sub>2</sub>)

**HRMS** (ESI<sup>+</sup>)  $m/z$  / Da = 537.2523, [M+H]<sup>+</sup> found, [C<sub>29</sub>H<sub>34</sub>FN<sub>4</sub>O<sub>5</sub>]<sup>+</sup> requires 537.2513

The compound has not been reported previously.

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



4-Bromo-*N*-(2-methoxyphenyl)butanamide **101** (2.05 g, 7.51 mmol, 1 eq.) and NaN<sub>3</sub> (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 SiO<sub>2</sub> and purified by column chromatography using a Combiflash (SiO<sub>2</sub>, 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)  $\nu_{max}$  / cm<sup>-1</sup> = 3419.7 (N-H), 3329.6 (N-H), 2094.8 (azide), 1672.3 (amide C=O)

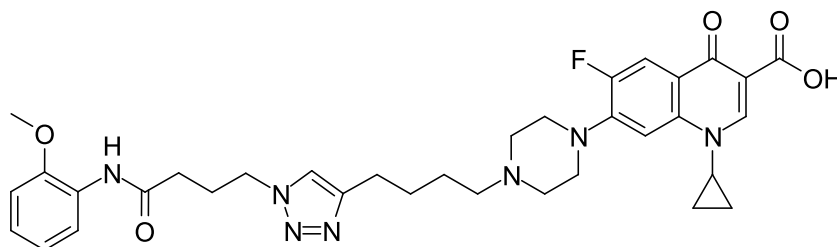
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub> d<sub>1</sub>)  $\delta$  / ppm = 8.32 (dd,  $J$  = 7.9, 1.0 Hz, 1 H, *ortho* to NH), 7.86 (br s, 1 H, NH), 7.00 (td,  $J$  = 7.5, 1.5 Hz, 1 H, *para* to NH), 6.90 (td,  $J$  = 7.7, 1.1 Hz, 1 H, *para* to OCH<sub>3</sub>), 6.83 (dd,  $J$  = 8.1, 1.4 Hz, 1 H, *ortho* to OCH<sub>3</sub>), 3.81 (s, 3 H, CH<sub>3</sub>), 3.33 (t,  $J$  = 6.7 Hz, 2 H, CH<sub>2</sub>Br), 2.42 (t,  $J$  = 7.2 Hz, 2 H, C(=O)CH<sub>2</sub>), 1.94 (quin,  $J$  = 6.9 Hz, 2 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>)

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub> d<sub>1</sub>)  $\delta$  / ppm = 169.5 (C(=O)), 147.6 (*ipso* to OCH<sub>3</sub>), 127.1 (*ipso* to NH), 123.4 (*para* to NH), 120.5 (*para* to OCH<sub>3</sub>), 119.5 (*ortho* to NH and *meta* to OCH<sub>3</sub>), 109.6 (*ortho* to OCH<sub>3</sub> and *meta* to NH), 55.2 (CH<sub>3</sub>), 50.3 (CH<sub>2</sub>N<sub>3</sub>), 33.9 (C(=O)CH<sub>2</sub>), 24.3 (C(=O)CH<sub>2</sub>CH<sub>2</sub>)

**HRMS** (ESI<sup>+</sup>)  $m/z$  / Da = 257.1010, [M+H]<sup>+</sup> found, [C<sub>11</sub>H<sub>14</sub>N<sub>4</sub>NaO<sub>2</sub>]<sup>+</sup> requires 257.1014

The data are consistent with the literature.<sup>7</sup>

## 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  $\mu$ mol, 1 eq.) and 4-azido-*N*-(2-methoxyphenyl)butanamide **103** (13.7 mg, 58.5  $\mu$ mol, 1 eq.) were dissolved in water (3 ml), *t*-BuOH (9 ml) and CH<sub>2</sub>Cl<sub>2</sub> (9 ml), and the mixture was degassed by bubbling through N<sub>2</sub>. A solution of CuSO<sub>4</sub> and THPTA (117  $\mu$ l, 5.85  $\mu$ mol, 0.1 eq., 50 mM, aq.) was added, followed by a solution

of sodium ascorbate (234  $\mu$ l, 11.7  $\mu$ mol, 0.2 eq., 50 mM, aq.). The mixture was stirred at room temperature under argon for 16 h. Water (25 ml),  $\text{CH}_2\text{Cl}_2$  (25 ml) and MeOH (5 ml) were added and the organic layer was separated off, dry-loaded onto  $\text{SiO}_2$  and purified by column chromatography using a Combiflash ( $\text{SiO}_2$ , 3-23 % MeOH/ $\text{CH}_2\text{Cl}_2$ ). The combined pure fractions were dried with  $\text{MgSO}_4$  and evaporated under reduced pressure. **104** was obtained as a clear glass (14.7 mg, 22.8  $\mu$ mol, 39.0 %).

**TLC**  $R_f$  = 0.28 (10 % MeOH/ $\text{CH}_2\text{Cl}_2$ )

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

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  / 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  $\text{OCH}_3$ ), 6.88 (dd,  $J$  = 8.1, 1.4 Hz, 1 H, *ortho* to  $\text{OCH}_3$ ), 4.47 (t,  $J$  = 6.7 Hz, 2 H, C(=O) $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$ ), 3.88 (s, 3 H,  $\text{CH}_3$ ), 3.54 (tt,  $J$  = 6.9, 4.0 Hz, 1 H,  $\text{NCH}(\text{CH}_2)_2$ ), 3.35 (br t,  $J$  = 4.7 Hz, 4 H,  $\text{CH}=\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)\text{CH}_2\text{CH}_2$ ), 2.76 (t,  $J$  = 7.5 Hz, 2 H,  $\text{CH}=\text{CCH}_2$ ), 2.66 (t,  $J$  = 4.7 Hz, 4 H,  $\text{CH}=\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)\text{CH}_2\text{CH}_2$ ), 2.47 (t,  $J$  = 7.3 Hz, 2 H,  $\text{CH}=\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$ ), 2.44 (t,  $J$  = 6.8 Hz, 2 H, C(=O) $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$ ), 2.32 (quin,  $J$  = 6.7 Hz, 2 H, C(=O) $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$ ), 1.75 (quin,  $J$  = 7.6 Hz, 2 H,  $\text{CH}=\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$ ), 1.61 (quin,  $J$  = 7.5 Hz, 2 H,  $\text{CH}=\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$ ), 1.35 - 1.42 (m, 2 H,  $\text{NCH}(\text{CH}_2)_2$ ), 1.17 - 1.22 (m, 2 H,  $\text{NCH}(\text{CH}_2)_2$ )

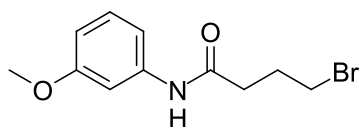
**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  / ppm = 177.1 (C(=O)CC(=O)OH), 169.5 ( $\text{NHC}(=\text{O})$ ), 167.0 (C(=O)OH), 153.7 (d,  $J$  = 251.4 Hz, *ipso* to F), 148.1 ( $\text{CH}=\text{CCH}_2$ ), 147.8 (*ipso* to  $\text{OCH}_3$ ), 147.3 (C=CC(=O)OH), 145.9 (d,  $J$  = 10.4 Hz, *ipso* to piperazine), 139.1 (*para* to F), 127.3 (*ipso* to NH), 123.9 (*para* to NH), 121.0 (*para* to  $\text{OCH}_3$ ), 120.9 ( $\text{CH}=\text{CCH}_2$ ), 119.7 (*para* to piperazine, and *ortho* to NH and *meta* to  $\text{OCH}_3$ ), 112.4 (d,  $J$  = 23.4 Hz, *ortho* to C=O and *ortho* to F), 109.9 (*ortho* to  $\text{OCH}_3$  and *meta* to NH), 108.1 (C(=O)OH), 104.7 (*meta* to C=O and *meta* to F), 58.1 ( $\text{CH}=\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$ ), 55.6 ( $\text{CH}_3$ ), 52.8 ( $\text{CH}=\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)\text{CH}_2\text{CH}_2$ ), 49.8 ( $\text{CH}=\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)\text{CH}_2\text{CH}_2$ ), 49.1 (C(=O) $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$ ), 35.2 ( $\text{NCH}(\text{CH}_2)_2$ ), 33.8 (C(=O) $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$ ), 27.3 ( $\text{CH}=\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$ ), 26.4 ( $\text{CH}=\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$ ), 26.0 (C(=O) $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$ ), 25.5 ( $\text{CH}=\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$ ), 8.2 ( $\text{NCH}(\text{CH}_2)_2$ )

**$^{19}\text{F}$  NMR** (376.45 MHz,  $\text{CDCl}_3$ )  $\delta$  / ppm = -120.7 (s, ciprofloxacin F)

**HRMS** ( $\text{ESI}^+$ )  $m/z$  / Da = 646.3132,  $[\text{M}+\text{H}]^+$  found,  $[\text{C}_{34}\text{H}_{41}\text{FN}_7\text{O}_5]^+$  requires 646.3153

The compound has not been reported previously.

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



3-Methoxyaniline **105** (3.04 ml, 3.33 g, 27.1 mmol, 1 eq.) and NaHCO<sub>3</sub> (2.73 g, 32.5 mmol, 1.2 eq.) were dissolved in water (30 ml) and CH<sub>2</sub>Cl<sub>2</sub> (30 ml). The mixture was cooled to 0 °C and 4-bromobutyryl chloride **58** (3.13 ml, 5.03 g, 27.1 mmol, 1 eq.) was added dropwise over 5 min. The mixture was stirred at 0 °C for 1 h, then the aqueous layer was removed. The organic layer was dry-loaded onto SiO<sub>2</sub> and purified by column chromatography using a Combiflash (SiO<sub>2</sub>, 0-100 % EtOAc/P.E.). The combined pure fractions were dried with MgSO<sub>4</sub> 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)  $\nu_{max}$  / cm<sup>-1</sup> = 1670.9 (amide C=O)

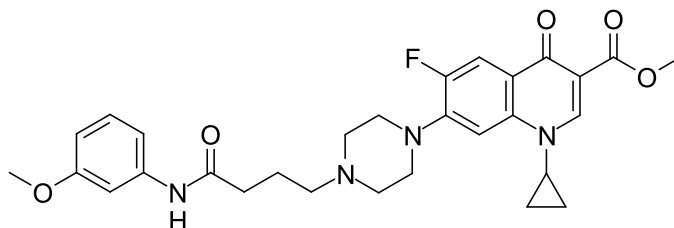
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub> d<sub>1</sub>)  $\delta$  / ppm = 8.45 (s, 1 H, NH), 7.27 (t,  $J$  = 2.2 Hz, 1 H, *ortho* to OCH<sub>3</sub> and *ortho* to NH), 7.14 (t,  $J$  = 8.1 Hz, 1 H, *meta* to OCH<sub>3</sub> and *meta* to NH), 7.02 (d,  $J$  = 8.3 Hz, 1 H, *para* to OCH<sub>3</sub>), 6.62 (dd,  $J$  = 8.2, 2.1 Hz, 1 H, *para* to NH), 3.71 (s, 3 H, CH<sub>3</sub>), 3.42 (t,  $J$  = 6.5 Hz, 2 H, CH<sub>2</sub>Br), 2.51 (t,  $J$  = 6.9 Hz, 2 H, C(=O)CH<sub>2</sub>), 2.19 (quin,  $J$  = 6.8 Hz, 2 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>)

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub> d<sub>1</sub>)  $\delta$  / ppm = 170.3 (C(=O)), 159.9 (*ipso* to OCH<sub>3</sub>), 139.0 (*ipso* to NH), 129.5 (*meta* to OCH<sub>3</sub> and *meta* to NH), 112.1 (*para* to OCH<sub>3</sub>), 109.9 (*para* to NH), 105.7 (*ortho* to OCH<sub>3</sub> and *ortho* to NH), 55.2 (CH<sub>3</sub>), 35.3 (C(=O)CH<sub>2</sub>), 33.2 (CH<sub>2</sub>Br), 28.0 (C(=O)CH<sub>2</sub>CH<sub>2</sub>)

**HRMS** (ESI<sup>+</sup>) 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<sub>2</sub>Cl<sub>2</sub> (50 ml) and water (50 ml). The organic layer was separated off and the aqueous layer was extracted again with CH<sub>2</sub>Cl<sub>2</sub> (50 ml). The combined organic layers were dried with MgSO<sub>4</sub> and purified by column chromatography (SiO<sub>2</sub>, 0-4 % MeOH/CH<sub>2</sub>Cl<sub>2</sub>). The combined pure fractions were dried with MgSO<sub>4</sub> and evaporated under reduced pressure. **107** was obtained as an off-white amorphous solid (81.7 mg, 0.152 mmol, 10.5 %).

**TLC**  $R_f$  = 0.38 (10 % MeOH/CH<sub>2</sub>Cl<sub>2</sub>)

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

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

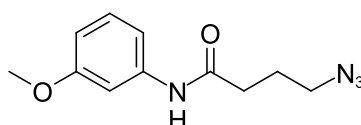
**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  / ppm = 173.1 (C(=O)CC(=O)OCH<sub>3</sub>), 170.9 (NHC(=O)), 166.3 (C(=O)OCH<sub>3</sub>), 160.1 (*ipso* to OCH<sub>3</sub>), 153.3 (d,  $J$ =250.1 Hz, *ipso* to F), 148.4 (C=CC(=O)OCH<sub>3</sub>), 144.1 (d,  $J$ =10.1 Hz, *ipso* to piperazine), 139.4 (*ipso* to NH), 138.0 (*para* to F), 129.6 (*meta* to NH and *meta* to OCH<sub>3</sub>), 123.3 (d,  $J$ =6.4 Hz, *para* to piperazine), 113.4 (d,  $J$ =23.3 Hz, *ortho* to C=O and *ortho* to F), 111.8 (*para* to OCH<sub>3</sub>), 110.0 (CC(=O)OCH<sub>3</sub>), 109.8 (*para* to NH), 105.5 (*ortho* to OCH<sub>3</sub> and *ortho* to NH), 105.0 (*meta* to C=O and *meta* to F), 57.0 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 55.3 (aromatic OCH<sub>3</sub>), 52.6 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 52.1 (C(=O)OCH<sub>3</sub>), 49.2 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 35.2 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 34.6 (NCH(CH<sub>2</sub>)<sub>2</sub>), 21.7 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 8.2 (NCH(CH<sub>2</sub>)<sub>2</sub>)

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

**HRMS** (ESI<sup>+</sup>)  $m/z$  / Da = 537.2500, [M+H]<sup>+</sup> found, [C<sub>29</sub>H<sub>34</sub>FN<sub>4</sub>O<sub>5</sub>]<sup>+</sup> 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<sub>3</sub> (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<sub>2</sub> and purified by column chromatography using a Combiflash (SiO<sub>2</sub>, 0-100 % EtOAc/P.E.). The combined pure fractions were dried with MgSO<sub>4</sub> 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)  $\nu_{max}$  /  $\text{cm}^{-1}$  = 3298.3 (N-H), 2094.7 (azide), 1661.7 (amide C=O)

**$^1\text{H}$  NMR** (400 MHz, MeOD)  $\delta$  / ppm = 8.63 (br s, 1 H, NH), 7.26 (t,  $J$  = 2.3 Hz, 1 H, *ortho* to OCH<sub>3</sub> and *ortho* to NH), 7.15 (t,  $J$  = 8.1 Hz, 1 H, *meta* to OCH<sub>3</sub> and *meta* to NH), 7.01 (dd,  $J$  = 7.8, 1.6 Hz, 1 H, *para* to OCH<sub>3</sub>), 6.63 (dd,  $J$  = 8.2, 1.9 Hz, 1 H, *para* to NH), 3.69 (s, 3 H, CH<sub>3</sub>), 3.28 (t,  $J$  = 6.7 Hz, 2 H, CH<sub>2</sub>N<sub>3</sub>),

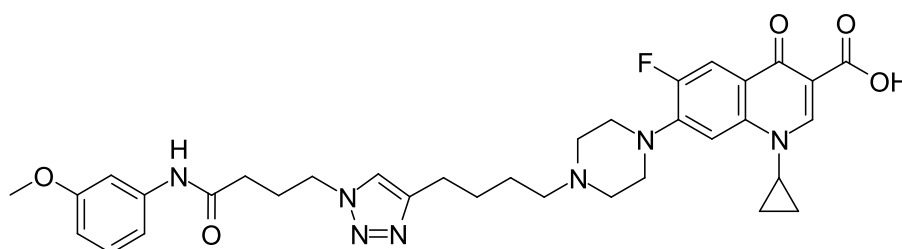
2.39 (t,  $J = 7.4$  Hz, 2 H, C(=O)CH<sub>2</sub>), 1.91 (quin,  $J = 7.0$  Hz, 2 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>)

<sup>13</sup>C NMR (101 MHz, MeOD)  $\delta$  / ppm = 170.8 (C(=O)), 159.6 (*ipso* to OCH<sub>3</sub>), 138.9 (*ipso* to NH), 129.2 (*meta* to OCH<sub>3</sub> and *meta* to NH), 112.3 (*para* to OCH<sub>3</sub>), 109.5 (*para* to NH), 106.0 (*ortho* to OCH<sub>3</sub> and *ortho* to NH), 54.8 (CH<sub>3</sub>), 50.4 (CH<sub>2</sub>N<sub>3</sub>), 33.6 (C(=O)CH<sub>2</sub>), 24.4 (C(=O)CH<sub>2</sub>CH<sub>2</sub>)

**HRMS** (ESI<sup>+</sup>) 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  $\mu$ mol, 1 eq.) and 4-azido-*N*-(3-methoxyphenyl)butanamide **108** (13.7 mg, 58.5  $\mu$ mol, 1 eq.) were dissolved in water (1 ml), *t*-BuOH (9 ml) and CH<sub>2</sub>Cl<sub>2</sub> (10 ml), and the mixture was degassed by bubbling through N<sub>2</sub>. A solution of CuSO<sub>4</sub> and THPTA (58.5  $\mu$ l, 5.85  $\mu$ mol, 0.1 eq. 100 mM, aq.) was added, followed by a solution of sodium ascorbate (117  $\mu$ l, 11.7  $\mu$ 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 CH<sub>2</sub>Cl<sub>2</sub> (15 ml), and the aqueous layer was extracted a further four times with CH<sub>2</sub>Cl<sub>2</sub> (4 $\times$ 15 ml). The combined organic layers were dried with MgSO<sub>4</sub>, dry-loaded onto SiO<sub>2</sub> and purified by column chromatography (SiO<sub>2</sub>, 0-10 % MeOH/CH<sub>2</sub>Cl<sub>2</sub>). The combined pure fractions were dried with MgSO<sub>4</sub> and evaporated under reduced pressure. **109** was obtained as a clear glass (1.9 mg, 2.9  $\mu$ mol, 5.0 %).

**TLC**  $R_f = 0.22$  (10 % MeOH/CH<sub>2</sub>Cl<sub>2</sub>)

**IR** (neat)  $\nu_{max}$  / cm<sup>-1</sup> = 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)

<sup>1</sup>H NMR (400 MHz, DMSO d<sub>6</sub>)  $\delta$  / 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=CCH<sub>2</sub>), 7.55 (d,  $J = 7.6$  Hz, 1 H, *meta* to F), 7.27 (t,  $J = 2.1$  Hz, 1 H, *ortho* to C=O and *ortho* to F), 7.16 (t,  $J = 8.1$  Hz, 1 H, *meta* to OCH<sub>3</sub> and *meta* to NH), 7.08 (d,  $J = 7.8$  Hz, 1 H, *para* to OCH<sub>3</sub>), 6.59 (ddd,  $J = 8.1, 2.4, 0.7$  Hz, 1 H, *para* to NH), 4.36 (t,  $J = 6.9$  Hz, 2 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 3.81 (tt,  $J = 6.7, 4.0$  Hz, 1 H, NCH(CH<sub>2</sub>)<sub>2</sub>), 3.70 (s, 3 H, CH<sub>3</sub>), 3.28 - 3.32 (m, 4 H, CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 2.64 (t,  $J = 7.5$  Hz, 2 H, CH=CCH<sub>2</sub>), 2.56 (m,  $J = 4.2, 4.2$  Hz, 4 H, CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 2.38 (t,  $J = 7.3$  Hz, 2 H, CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 2.30 (t,  $J = 7.4$  Hz, 2 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 2.10 (quin,  $J = 7.1$  Hz, 2 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 1.64 (quin,  $J = 7.5$  Hz, 2 H, CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 1.51 (quin,  $J = 7.2$  Hz, 2 H,

CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 1.27 - 1.33 (m, 2 H, NCH(CHH)<sub>2</sub>), 1.15 - 1.20 (m, 2 H, NCH(CHH)<sub>2</sub>)

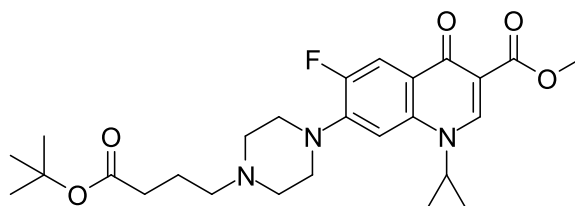
<sup>13</sup>C NMR (101 MHz, DMSO d<sub>6</sub>) δ / ppm = 176.3 (C(=O)CC(=O)OH), 170.1 (NHC(=O)), 165.9 (C(=O)OH), 159.4 (*ipso* to OCH<sub>3</sub>), 153.0 (d, *J* = 248.6 Hz, *ipso* to F), 148.0 (CH=CCH<sub>2</sub>), 146.9 (C=CC(=O)OH), 145.2 (d, *J* = 10.7 Hz, *ipso* to piperazine), 140.3 (*para* to F), 139.2 (*ipso* to NH), 129.4 (*meta* to OCH<sub>3</sub> and *meta* to NH), 121.7 (CH=CCH<sub>2</sub>), 118.5 (d, *J* = 7.5 Hz, *para* to piperazine), 111.3 (*para* to OCH<sub>3</sub>), 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 OCH<sub>3</sub> and *ortho* to NH), 57.3 (CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 54.9 (CH<sub>3</sub>), 52.4 (CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 49.5 (CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 49.4 (CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 48.7 (C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 35.8 (NCH(CH<sub>2</sub>)<sub>2</sub>), 32.9 (C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 26.8 (CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 25.7 (CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 25.5 (C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 24.9 (CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 7.6 (NCH(CH<sub>2</sub>)<sub>2</sub>)

<sup>19</sup>F NMR (376.45 MHz, DMSO d<sub>6</sub>) δ / ppm = -121.5 (s, ciprofloxacin F)

HRMS (ESI<sup>+</sup>) *m/z* / Da = 646.3159, [M+H]<sup>+</sup> found, [C<sub>34</sub>H<sub>41</sub>FN<sub>7</sub>O<sub>5</sub>]<sup>+</sup> 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<sub>2</sub> and purified by column chromatography (SiO<sub>2</sub>, 0-4 % MeOH/CH<sub>2</sub>Cl<sub>2</sub>). **136** was obtained as a white amorphous solid (141 mg, 0.289 mmol, 49.9 %).

TLC *R<sub>f</sub>* = 0.12 (4 % MeOH/CH<sub>2</sub>Cl<sub>2</sub>)

IR (neat) ν<sub>max</sub> / cm<sup>-1</sup> = 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)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ / ppm = 8.39 (s, 1 H, *ortho* to C(=O)OCH<sub>3</sub>), 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, CH<sub>3</sub>), 3.40 (tt, *J* = 7.2, 3.6 Hz, 1 H, NCH(CH<sub>2</sub>)<sub>2</sub>), 3.22 (t, *J* = 4.3 Hz, 4 H, CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 2.63 (t, *J* = 4.4 Hz, 4 H, CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 2.41 (t, *J* = 7.3 Hz, 2 H, CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 2.25 (t, *J* = 7.4 Hz, 2 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 1.78 (quin, *J* = 7.3 Hz, 2 H, CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 1.41 (s, 9 H, C((CH<sub>3</sub>)<sub>3</sub>)), 1.24 (m, 2 H, NCH(CHH)<sub>2</sub>), 1.09 (m, 2 H, NCH(CHH)<sub>2</sub>)

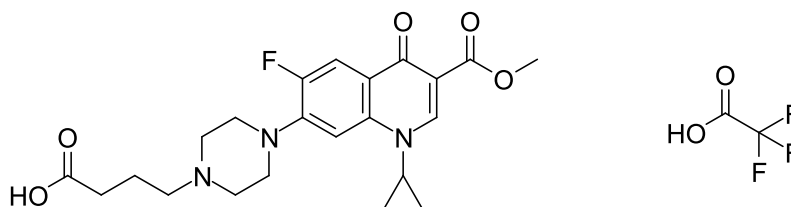
**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  / ppm = 172.7 ( $\text{C}(=\text{O})\text{CC}(=\text{O})\text{OCH}_3$ ), 172.6 ( $\text{C}(=\text{O})\text{OC}(\text{CH}_3)_3$ ), 165.9 ( $\text{C}(=\text{O})\text{OCH}_3$ ), 153.1 (d,  $J$  = 249.7 Hz, *ipso* to F), 148.1 ( $\text{C}=\text{CC}(=\text{O})\text{OCH}_3$ ), 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 ( $\text{CC}(=\text{O})\text{OCH}_3$ ) 104.7 (*meta* to C=O and *meta* to F), 80.0 ( $\text{C}(\text{CH}_3)_3$ ), 57.4 ( $\text{C}(=\text{O})\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$ ), 52.7 ( $\text{C}(=\text{O})\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2)\text{CH}_2$ ), 51.7 ( $\text{CH}_3$ ), 49.7 ( $\text{C}(=\text{O})\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)\text{CH}_2\text{CH}_2$ ), 49.7 ( $\text{C}(=\text{O})\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)\text{CH}_2\text{CH}_2$ ), 34.4 ( $\text{NCH}(\text{CH}_2)_2$ ), 33.2 ( $\text{C}(=\text{O})\text{CH}_2$ ), 28.0 ( $\text{C}(\text{CH}_3)_3$ ), 22.0 ( $\text{C}(=\text{O})\text{CH}_2\text{CH}_2$ ), 7.9 ( $\text{NCH}(\text{CH}_2)_2$ )

**$^{19}\text{F}$  NMR** (376.45 MHz,  $\text{CDCl}_3$ )  $\delta$  / ppm = -123.5 (s, ciprofloxacin F)

**HRMS** ( $\text{ESI}^+$ )  $m/z$  / Da = 488.2562,  $[\text{M}+\text{H}]^+$  found,  $[\text{C}_{26}\text{H}_{35}\text{FN}_3\text{O}_5]^+$  requires 488.2561

The compound has not been reported previously.

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



Methyl 7-(4-(4-(*tert*-butoxy)-4-oxobutyl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate **136** (20 mg, 41.0  $\mu\text{mol}$ ) and TFA (0.2 ml) were stirred in  $\text{CH}_2\text{Cl}_2$  (1.8 ml) at r.t. for 16 h then evaporated under reduced pressure. **137** was obtained as a white solid (21.4 mg, 39.2  $\mu\text{mol}$ , 95.6 %).

**mp**  $T$  /  $^\circ\text{C}$  = 225-231 ( $\text{CH}_2\text{Cl}_2$ , decomposes)

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

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

**$^{13}\text{C}$  NMR** (101 MHz,  $\text{DMSO}-d_6$ )  $\delta$  / ppm = 173.5 ( $\text{CH}_2\text{C}(=\text{O})\text{OH}$ ), 171.6 ( $\text{C}(=\text{O})\text{CC}(=\text{O})\text{OCH}_3$ ), 164.9 ( $\text{C}(=\text{O})\text{OCH}_3$ ), 158.2 (q,  $J$  = 31.5 Hz,  $\text{CF}_3\text{C}(=\text{O})\text{OH}$ ), 152.5 (d,  $J$  = 247.6 Hz, *ipso* to F), 148.5 ( $\text{C}=\text{CC}(=\text{O})\text{OH}$ ), 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,  $\text{CF}_3$ ), 111.9 (d,  $J$  = 22.4 Hz, *ortho* to C=O and *ortho* to F), 109.1 ( $\text{CC}(=\text{O})\text{OCH}_3$ ), 106.9 (*meta* to C=O and *meta* to F), 55.1 ( $\text{C}(=\text{O})\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$ ), 51.4 ( $\text{CH}_3$ ), 50.8 ( $\text{C}(=\text{O})\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2)\text{CH}_2$ ), 46.7 ( $\text{C}(=\text{O})\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)\text{CH}_2\text{CH}_2$ ), 46.7 ( $\text{C}(=\text{O})\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)\text{CH}_2\text{CH}_2$ ), 34.9 ( $\text{NCH}(\text{CH}_2)_2$ ), 30.6 ( $\text{C}(=\text{O})\text{CH}_2$ ), 19.1 ( $\text{C}(=\text{O})\text{CH}_2\text{CH}_2$ ), 7.6 ( $\text{NCH}(\text{CH}_2)_2$ )

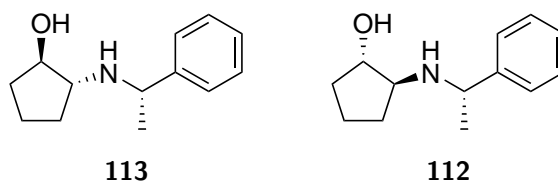


$^{19}\text{F}$  NMR (376.45 MHz, DMSO  $d_6$ )  $\delta$  / ppm = -73.6 (s,  $\text{CF}_3$ ), -124.6 (s, ciprofloxacin F)

HRMS ( $\text{ESI}^+$ )  $m/z$  / Da = 432.1921,  $[\text{M}+\text{H}]^+$  found,  $[\text{C}_{22}\text{H}_{27}\text{FN}_3\text{O}_5]^+$  requires 432.1935

The compound has not been reported previously.

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



(*S*)-1-Phenylethan-1-amine **111** (7.85 ml, 7.38 g, 60.9 mmol, 1 eq.) was dissolved in  $\text{CH}_2\text{Cl}_2$  (50 ml) and stirred rapidly at 0 °C. A solution of  $\text{AlMe}_3$  (31 ml, 2.0 M in heptane, 60.9 mmol) was added dropwise and the mixture was stirred at 0 °C for 1 h. A solution of cyclohexene oxide **110** (5.71 ml, 5.50 g, 65.4 mmol, 1.1 eq.) in  $\text{CH}_2\text{Cl}_2$  (50 ml) was then added dropwise, and the mixture was stirred at 0 °C for a further 3 h, followed by 48 h at r.t.. The mixture was cooled to 0 °C and NaF (11 g, 262 mmol, 4.3 eq.) was added portionwise, followed by water (7.00 ml, 7.00 g, 389 mmol, 6.4 eq.) and  $\text{CH}_2\text{Cl}_2$  (50 ml). The suspension was allowed to warm to r.t. and stirred for 1 h, then filtered through Celite and washed with  $\text{CH}_2\text{Cl}_2$  (500 ml). The filtrate was dried with  $\text{K}_2\text{CO}_3$ , concentrated under reduced pressure and purified by column chromatography ( $\text{SiO}_2$ , 20:5:1 hexane:EtOAc:TEA). **113** was obtained as a pale yellow oil (4.08 g, 19.9 mmol, 32.6 %). **112** was obtained as pale yellow crystals (4.48 g, 21.8 mmol, 35.8 %).

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

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

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

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  / ppm = 7.28 - 7.38 (m, 4 H, *ortho* and *meta* to  $\text{CHCH}_3$ ), 7.21 - 7.28 (m, 1 H, *para* to  $\text{CHCH}_3$ ), 3.83 (q,  $J$  = 6.6 Hz, 1 H,  $\text{CHCH}_3$ ), 3.78 (q,  $J$  = 7.0 Hz, 1 H,  $\text{CHOH}$ ), 2.62 (dt,  $J$  = 8.2, 7.2 Hz, 1 H,  $\text{CHNH}$ ), 1.97 (quin,  $J$  = 6.7 Hz, 1 H,  $\text{CH}_2\text{CHNH}$ ), 1.90 (quin,  $J$  = 6.9 Hz, 1 H,  $\text{CH}_2\text{CHOH}$ ), 1.56 - 1.68 (m,  $\text{CH}_2\text{CH}_2\text{CHOH}$ ), 1.43 (dq,  $J$  = 12.5, 8.0 Hz, 1 H,  $\text{CH}_2\text{CHOH}$ ), 1.37 (d,  $J$  = 6.6 Hz, 3 H,  $\text{CH}_3$ ), 1.25 - 1.36 (m, 1 H,  $\text{CH}_2\text{CHNH}$ )

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  / ppm = 144.75 (*ipso* to  $\text{CHCH}_3$ ), 128.26 (*meta* to  $\text{CHCH}_3$ ), 126.72 (*para* to  $\text{CHCH}_3$ ), 126.30 (*ortho* to  $\text{CHCH}_3$ ), 77.65 ( $\text{CHOH}$ ), 63.38 ( $\text{CHNH}$ ), 56.20 ( $\text{CHCH}_3$ ), 31.74 ( $\text{CH}_2\text{CHOH}$ ), 29.22 ( $\text{CH}_2\text{CHNH}$ ), 24.58 ( $\text{CH}_3$ ), 19.57 ( $\text{CH}_2\text{CH}_2\text{CHOH}$ )

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

$[\alpha]_D^{20}$  /  $^{\circ}10^{-1}\text{cm}^2\text{g}^{-1}$  = -92.8 ( $c$  /  $\text{g}(100\text{ ml})^{-1}$  = 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)  $\nu_{max}$  /  $\text{cm}^{-1}$  = 3150.0 (br, O-H), 2950.9 (C-H), 2868.2 (C-H)

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  / ppm = 7.28 - 7.34 (m, 4 H, *ortho* and *meta* to  $\text{CHCH}_3$ ), 7.20 - 7.26 (m, 1 H, *para* to  $\text{CHCH}_3$ ), 3.86 (q,  $J$  = 6.6 Hz, 1 H,  $\text{CHCH}_3$ ), 3.85 (q,  $J$  = 6.6 Hz, 1 H,  $\text{CHOH}$ ), 2.83 (td,  $J$  = 7.6, 5.7 Hz, 1 H,  $\text{CHNH}$ ), 1.85 - 1.97 (m, 1 H,  $\text{CHHCHOH}$ ), 1.77 (dtd,  $J$  = 12.9, 7.9, 7.9, 4.9 Hz, 1 H,  $\text{CHHCHNH}$ ), 1.55 - 1.68 (m, 2 H,  $\text{CH}_2\text{CH}_2\text{CHOH}$ ), 1.47 - 1.55 (m, 1 H,  $\text{CHHCHOH}$ ), 1.36 (d,  $J$  = 6.6 Hz, 3 H,  $\text{CH}_3$ ), 1.12 (dq,  $J$  = 12.7, 8.1 Hz, 1 H,  $\text{CHHCHNH}$ )

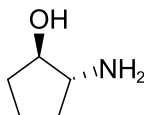
**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  / ppm = 145.61 (*ipso* to  $\text{CHCH}_3$ ), 128.08 (*meta* to  $\text{CHCH}_3$ ), 126.61 (*para* to  $\text{CHCH}_3$ ), 126.33 (*ortho* to  $\text{CHCH}_3$ ), 77.43 ( $\text{CHOH}$ ), 64.45 ( $\text{CHNH}$ ), 56.62 ( $\text{CHCH}_3$ ), 32.01 ( $\text{CH}_2\text{CHOH}$ ), 30.56 ( $\text{CH}_2\text{CHNH}$ ), 23.30 ( $\text{CH}_3$ ), 20.06 ( $\text{CH}_2\text{CH}_2\text{CHOH}$ )

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

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

The compounds have been synthesised previously,<sup>1,2</sup> but NMR data were not published. The enantiomers of both compounds have also been synthesised previously, and the  $^1\text{H}$  NMR data for these are consistent with the the above data.<sup>3</sup>

**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/ $\text{CH}_2\text{Cl}_2$ )

**IR** (neat)  $\nu_{max}$  /  $\text{cm}^{-1}$  = 3300.0 (br, O-H), 2958.3 (C-H), 2871.5 (C-H)

**$^1\text{H}$  NMR** (400 MHz, MeOD)  $\delta$  / ppm = 3.77 (ddd,  $J$ =6.6, 6.2, 5.6, 1 H,  $\text{CHOH}$ ), 3.00 (td,  $J$ =7.3, 5.6 Hz, 1 H,  $\text{CHNH}_2$ ), 2.00 (dtd,  $J$ =13.0, 7.7, 7.7, 5.6 Hz, 1 H,  $\text{CHHCHNH}_2$ ), 1.97 (ddt,  $J$ =13.0, 8.7, 6.6, 6.6 Hz, 1 H,  $\text{CHHCHOH}$ ), 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, 6.2 Hz, 1 H,  $\text{CHHCHOH}$ ), 1.37 (ddt,  $J$ =13.0, 8.3, 7.8, 7.8 Hz, 1 H,  $\text{CHHCHNH}_2$ )

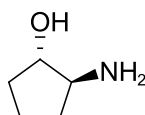
$^{13}\text{C}$  NMR (101 MHz, MeOD)  $\delta$  / ppm = 80.7 ( $\underline{\text{C}}\text{HOH}$ ), 60.8 ( $\underline{\text{C}}\text{HNH}_2$ ), 33.2 ( $\underline{\text{C}}\text{H}_2\text{CHOH}$ ), 32.1 ( $\underline{\text{C}}\text{H}_2\text{CHNH}_2$ ), 21.2 ( $\underline{\text{C}}\text{H}_2\text{CH}_2\text{CHOH}$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

HRMS (ESI<sup>+</sup>)  $m/z$  / 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 ( $c$  /  $\text{g}(100\text{ ml})^{-1}$  = 1.5, EtOH)

The data are consistent with the literature.<sup>2,8</sup>

## 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)<sub>2</sub> (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/ $\text{CH}_2\text{Cl}_2$ )

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

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

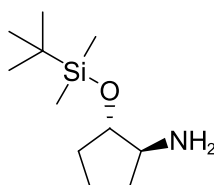
$^{13}\text{C}$  NMR (101 MHz, MeOD)  $\delta$  / ppm = 80.6 ( $\underline{\text{C}}\text{HOH}$ ), 60.7 ( $\underline{\text{C}}\text{HNH}_2$ ), 33.2 ( $\underline{\text{C}}\text{H}_2\text{CHOH}$ ), 32.2 ( $\underline{\text{C}}\text{H}_2\text{CHNH}_2$ ), 21.2 ( $\underline{\text{C}}\text{H}_2\text{CH}_2\text{CHOH}$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

HRMS (ESI<sup>+</sup>)  $m/z$  / Da = 102.0915,  $[\text{M}+\text{H}]^+$  found,  $[\text{C}_5\text{H}_{12}\text{NO}]^+$  requires 102.0913

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

The data are consistent with the literature.<sup>2,8</sup>

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



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

**TLC**  $R_f$  = 0.23 (10 % MeOH/CH<sub>2</sub>Cl<sub>2</sub>)

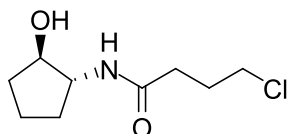
**IR** (neat)  $\nu_{max}$  / cm<sup>-1</sup> = 2953.6 (C-H), 2931.1 (C-H), 2888.4 (C-H), 2858.8 (C-H), 1625.2 (N-H bend)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  / ppm = 4.13 (q,  $J$  = 5.8 Hz, 1 H, CHOSi), 3.31 (td,  $J$  = 7.1, 5.2 Hz, 1 H, CHNH<sub>2</sub>), 2.09 - 2.19 (m, 1 H, CHHCHNH<sub>2</sub>), 1.97 (ddq,  $J$  = 8.8, 7.0, 6.0, 6.0, 6.0 Hz, 1 H, CHHCHOSi), 1.74 - 1.86 (m, 2 H, CH<sub>2</sub>CH<sub>2</sub>CHOSi), 1.64 - 1.74 (m, 1 H, CHHCHOSi), 1.58 (ddt,  $J$  = 13.2, 9.1, 6.0, 6.0 Hz, 1 H, CHHCHNH<sub>2</sub>), 0.88 (s, 9 H, C(CH<sub>3</sub>)<sub>3</sub>), 0.09 (s, 3 H, SiCH<sub>3</sub>), 0.07 (s, 3 H, SiCH<sub>3</sub>)

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  / ppm = 76.3 (CHOSi), 59.7 (CHNH), 32.2 (CH<sub>2</sub>CHOSi), 26.8 (CH<sub>2</sub>CHNH<sub>2</sub>), 25.6 (C(CH<sub>3</sub>)<sub>3</sub>), 19.7 (CH<sub>2</sub>CH<sub>2</sub>CHOSi), 17.7 (C(CH<sub>3</sub>)<sub>3</sub>), -4.8 (SiCH<sub>3</sub>), -5.2 (SiCH<sub>3</sub>)

**HRMS** (ESI<sup>+</sup>)  $m/z$  / Da = 216.1785, [M+H]<sup>+</sup> found, [C<sub>11</sub>H<sub>26</sub>NOSi]<sup>+</sup> 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  $\mu$ l, 600 mg, 5.93 mmol, 1.2 eq.) and CH<sub>2</sub>Cl<sub>2</sub> (20 ml) were stirred at 0 °C and 4-chlorobutyl chloride **139** (608  $\mu$ l, 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<sub>2</sub>Cl<sub>2</sub> (7×50 ml). The combined organic layers were dried with MgSO<sub>4</sub>, concentrated under reduced pressure and purified by column chromatography (SiO<sub>2</sub>, Et<sub>2</sub>O). The combined pure fractions were dried with MgSO<sub>4</sub> 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)  $\nu_{max}$  / cm<sup>-1</sup> = 3277.6 (N-H and O-H), 2962.2 (C-H), 2876.0 (C-H), 1636.3 (amide C=O)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  / 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<sub>2</sub>Cl), 2.38 (t,  $J$  = 7.2 Hz, 2 H, CH<sub>2</sub>C=O), 2.05 - 2.16 (m, 3 H, CHHCHNH and CH<sub>2</sub>CH<sub>2</sub>Cl), 1.96 - 2.04 (m, 1 H, CHHCHOH), 1.74 - 1.85 (m, 1 H, CHHCH<sub>2</sub>CHOH), 1.58 - 1.73 (m, 2 H, CHHCH<sub>2</sub>CHOH and CHHCHOH), 1.43 (dq,  $J$  = 12.7, 8.3 Hz, 1 H, CHHCHNH)

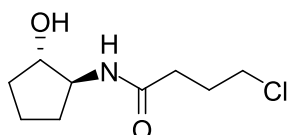
**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  / ppm = 173.8 ( $\text{C=O}$ ), 79.4 ( $\text{CHOH}$ ), 60.6 ( $\text{CHNH}$ ), 44.4 ( $\text{CH}_2\text{Cl}$ ), 32.8 ( $\text{CH}_2\text{C=O}$ ), 32.4 ( $\text{CH}_2\text{CHOH}$ ), 30.1 ( $\text{CH}_2\text{CHNH}$ ), 28.0 ( $\text{CH}_2\text{CH}_2\text{Cl}$ ), 21.1 ( $\text{CH}_2\text{CH}_2\text{CHOH}$ )

**HRMS** ( $\text{ESI}^+$ )  $m/z$  / 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 ( $c$  /  $\text{g(100 ml)}^{-1}$  = 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-Aminocyclopentanol **114** (72.3 mg, 716  $\mu\text{mol}$ , 1 eq.), TEA (500  $\mu\text{l}$ , 363 mg, 3.58 mmol, 5 eq.) and  $\text{CH}_2\text{Cl}_2$  (5 ml) were stirred at 0  $^{\circ}\text{C}$ , and 4-chlorobutyryl chloride **139** (179  $\mu\text{l}$ , 226 mg, 1.60 mmol, 1.1 eq.) was added dropwise over 5 min. The mixture was stirred at 0  $^{\circ}\text{C}$  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/ $\text{CHCl}_3$  (2 $\times$ 10 ml). The combined organic layers were dried with  $\text{MgSO}_4$ , concentrated under reduced pressure and purified by column chromatography ( $\text{SiO}_2$ ,  $\text{Et}_2\text{O}$ ). The combined pure fractions were dried with  $\text{MgSO}_4$  and evaporated under reduced pressure. **140** was obtained as a white amorphous solid (35.6 mg, 173  $\mu\text{mol}$ , 24.2 %).

**TLC**  $R_f$  = 0.35 ( $\text{EtOAc}$ )

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  / ppm = 6.05 (br s, 1 H,  $\text{NH}$ ), 4.55 (br s, 1 H,  $\text{OH}$ ), 3.95 (q,  $J=6.6$  Hz, 1 H,  $\text{CHOH}$ ), 3.82 (tt,  $J=8.4$ , 5.3 Hz, 1 H,  $\text{CHNH}$ ), 3.60 (t,  $J=6.2$  Hz, 2 H,  $\text{CH}_2\text{Cl}$ ), 2.38 (t,  $J=7.0$  Hz, 2 H,  $\text{CH}_2\text{C=O}$ ), 2.05 - 2.17 (m, 3 H,  $\text{CHHCHNH}$  and  $\text{CH}_2\text{CH}_2\text{Cl}$ ), 1.94 - 2.05 (m, 1 H,  $\text{CHHCHOH}$ ), 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  $\text{CHHCHOH}$ ), 1.42 (dq,  $J=12.5$ , 8.4 Hz, 1 H,  $\text{CHHCHNH}$ )

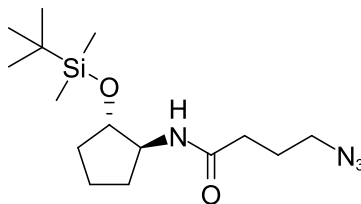
**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  / ppm = 173.8 ( $\text{C=O}$ ), 79.4 ( $\text{CHOH}$ ), 60.6 ( $\text{CHNH}$ ), 44.4 ( $\text{CH}_2\text{Cl}$ ), 32.8 ( $\text{CH}_2\text{C=O}$ ), 32.4 ( $\text{CH}_2\text{CHOH}$ ), 30.2 ( $\text{CH}_2\text{CHNH}$ ), 28.0 ( $\text{CH}_2\text{CH}_2\text{Cl}$ ), 21.2 ( $\text{CH}_2\text{CH}_2\text{CHOH}$ )

**HRMS** ( $\text{ESI}^+$ )  $m/z$  / 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 ( $c$  /  $\text{g(100 ml)}^{-1}$  = 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<sub>3</sub> (22.0 mg, 0.262 mmol, 1.1 eq.) were added to CH<sub>2</sub>Cl<sub>2</sub> (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<sub>3</sub> (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<sub>2</sub> stream and the residue was purified by column chromatography (SiO<sub>2</sub>, 0.5 % MeOH/CH<sub>2</sub>Cl<sub>2</sub>). The combined pure fractions were dried with MgSO<sub>4</sub> and evaporated under reduced pressure. **129** was obtained as a clear liquid (71 mg, 0.217 mmol, 99.2 %).

**TLC**  $R_f$  = 0.84 (1 % MeOH/CH<sub>2</sub>Cl<sub>2</sub>)

**IR** (neat)  $\nu_{max}$  / cm<sup>-1</sup> = 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)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  / ppm = 5.35 (d,  $J$  = 5.1 Hz, 1 H, NH), 3.97 - 4.01 (m, 1 H, CHOSi), 3.93 - 3.98 (m, 1 H, CHNH), 3.35 (t,  $J$  = 6.6 Hz, 2 H, CH<sub>2</sub>N<sub>3</sub>), 2.24 (t,  $J$  = 7.0 Hz, 2 H, CH<sub>2</sub>C=O), 2.09 - 2.19 (m, 1 H, CHHCHNH), 1.89 - 1.97 (quin,  $J$  = 6.8 Hz, 2 H, CH<sub>2</sub>CH<sub>2</sub>N<sub>3</sub>), 1.74 - 1.84 (m, 2 H, CHHCHOSi and CHHCH<sub>2</sub>CHOSi), 1.60 - 1.70 (m, 1 H, CHHCH<sub>2</sub>CHOSi), 1.51 - 1.61 (m, 1 H, CHHCHOSi), 1.31 - 1.39 (m, 1 H, CHHCHNH), 0.87 (s, 9 H, C(CH<sub>3</sub>)<sub>3</sub>), 0.08 (s, 3 H, SiCH<sub>3</sub>), 0.06 (s, 3 H, SiCH<sub>3</sub>)

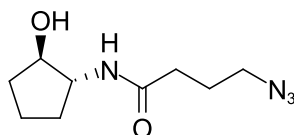
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  / ppm = 171.17 (C=O), 77.80 (CHOSi), 58.36 (CHNH), 50.77 (CH<sub>2</sub>N<sub>3</sub>), 33.29 (CH<sub>2</sub>C=O), 32.57 (CH<sub>2</sub>CHOSi), 29.36 (CH<sub>2</sub>CHNH), 25.72 (C(CH<sub>3</sub>)<sub>3</sub>), 24.77 (CH<sub>2</sub>CH<sub>2</sub>N<sub>3</sub>), 20.40 (CH<sub>2</sub>CH<sub>2</sub>CHO Si), 17.95 (C(CH<sub>3</sub>)<sub>3</sub>), -4.75 (SiCH<sub>3</sub>)

**HRMS** (ESI<sup>+</sup>)  $m/z$  / Da = 327.2221, [M+H]<sup>+</sup> found, [C<sub>15</sub>H<sub>31</sub>N<sub>4</sub>O<sub>2</sub>Si]<sup>+</sup> requires 327.2216

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

The compound has not been reported previously.

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



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

**TLC**  $R_f$  = 0.35 (EtOAc)

**mp**  $T$  / °C = 56.0-59.5 (*i*-PrOH, CHCl<sub>3</sub>)

**IR** (neat)  $\nu_{max}$  / cm<sup>-1</sup> = 3279.9 (N-H and O-H), 2965.6 (C-H), 2875.4 (C-H), 2094.6 (azide), 1636.8 (amide C=O)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  / ppm = 6.72 (d,  $J$  = 4.4 Hz, 1 H, NH), 4.82 (br. s., 1 H, OH), 3.88 (q,  $J$  = 6.6 Hz, 1 H, CHOH), 3.75 (tdd,  $J$  = 8.4, 8.4, 6.6, 4.4 Hz, 1 H, CHNH), 3.28 (t,  $J$  = 6.6 Hz, 2 H, CH<sub>2</sub>N<sub>3</sub>), 2.23 (t,  $J$  = 7.3 Hz, 2 H, CH<sub>2</sub>C=O), 2.04 (dtd,  $J$  = 13.0, 8.0, 8.0, 4.9 Hz, 1 H, CHHCHNH), 1.92 (dtd,  $J$  = 13.0, 7.6, 7.6, 5.8 Hz, 1 H, CHHCHOH), 1.84 (quin,  $J$  = 7.0 Hz, 2 H, CH<sub>2</sub>CH<sub>2</sub>N<sub>3</sub>), 1.59 - 1.77 (m, 2 H, CH<sub>2</sub>CH<sub>2</sub>CHOH), 1.54 (ddt,  $J$  = 12.7, 9.0, 6.7, 6.7 Hz, 1 H, CHHCHOH), 1.39 (dq,  $J$  = 12.9, 8.4 Hz, 1 H, CHHCHNH)

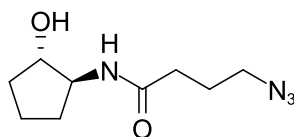
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  / ppm = 173.8 (C=O), 78.8 (CHOH), 59.9 (CHNH), 50.5 (CH<sub>2</sub>N<sub>3</sub>), 32.5 (CH<sub>2</sub>C=O), 32.0 (CH<sub>2</sub>CHOH), 29.5 (CH<sub>2</sub>CHNH), 24.6 (CH<sub>2</sub>CH<sub>2</sub>N<sub>3</sub>), 20.7 (CH<sub>2</sub>CH<sub>2</sub>CHOH)

**HRMS** (ESI<sup>+</sup>)  $m/z$  / Da = 235.1174, [M+Na]<sup>+</sup> found, [C<sub>9</sub>H<sub>16</sub>N<sub>4</sub>NaO<sub>2</sub>]<sup>+</sup> requires 235.1171

$[\alpha]_D^{20}$  / °10<sup>-1</sup>cm<sup>2</sup>g<sup>-1</sup> = -10.2 ( $c$  / g(100 ml)<sup>-1</sup> = 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<sub>3</sub> (22.1 mg, 0.340 mmol, 2 eq.) were stirred in acetonitrile (2 ml) at 50 °C for 24 h. The reaction mixture was then partitioned between water (20 ml) and 10 % *i*-PrOH/CHCl<sub>3</sub> (5 ml). The aqueous layer was extracted again with 10 % *i*-PrOH/CHCl<sub>3</sub> (2×5 ml) and the combined organic fractions were dried with MgSO<sub>4</sub> 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)  $\nu_{max}$  / cm<sup>-1</sup> = 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)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  / ppm = 5.82 (br s, 1 H, NH), 4.45 (br. s., 1 H, OH), 3.96 (q, J=6.6 Hz, 1 H, CHOH), 3.83 (tdd, J=8.5, 8.5, 6.0, 4.6 Hz, 1 H, CHNH), 3.37 (t, J=6.4 Hz, 2 H, CH<sub>2</sub>N<sub>3</sub>), 2.31 (t, J=7.2 Hz, 2 H, CH<sub>2</sub>C=O), 2.09 - 2.19 (m, 1 H, CHHCHNH), 1.99 - 2.06 (m, 1 H, CHHCHOH), 1.90 - 1.97 (m, 2 H, CH<sub>2</sub>CH<sub>2</sub>N<sub>3</sub>), 1.60 - 1.85 (m, 3 H, CH<sub>2</sub>CHHCHOH), 1.42 (dq, J=12.8, 8.3 Hz, 1 H, CHHCHNH)

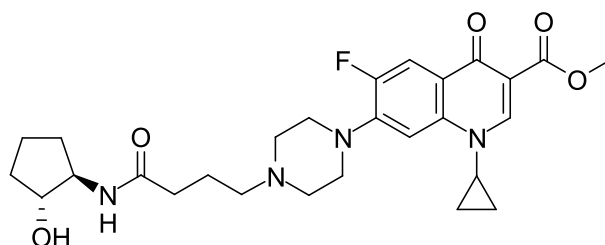
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  / ppm = 173.8 (C=O), 79.7 (CHOH), 61.0 (CHNH), 50.7 (CH<sub>2</sub>N<sub>3</sub>), 32.8 (CH<sub>2</sub>C=O), 32.6 (CH<sub>2</sub>CHOH), 30.5 (CH<sub>2</sub>CHNH), 24.7 (CH<sub>2</sub>CH<sub>2</sub>N<sub>3</sub>), 21.3 (CH<sub>2</sub>CH<sub>2</sub>CHOH)

**HRMS** (ESI<sup>+</sup>)  $m/z$  / Da = 235.1178, [M+Na]<sup>+</sup> found, [C<sub>9</sub>H<sub>16</sub>N<sub>4</sub>NaO<sub>2</sub>]<sup>+</sup> requires 235.1171

$[\alpha]_D^{20}$  / °10<sup>-1</sup>cm<sup>2</sup>g<sup>-1</sup> = 10.0 ( $c$  / g(100 ml)<sup>-1</sup> = 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  $\mu$ 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 N<sub>2</sub> and the residue was purified by preparatory HPLC (5-60 % acetonitrile/water over 12 min). The combined pure fractions were evaporated under reduced pressure and then partitioned between NaHCO<sub>3</sub> (aq., sat., 10 ml) and CH<sub>2</sub>Cl<sub>2</sub> (10 ml). The organic layer was removed and the aqueous layer was extracted twice more with CH<sub>2</sub>Cl<sub>2</sub> (2×10 ml). The combined organic fractions were dried with MgSO<sub>4</sub> 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)  $\nu_{max}$  / cm<sup>-1</sup> = 2972.9 (C-H), 2901.5 (C-H), 1728.4 (ester C=O), 1656.3 (amide C=O), 1612.9 (quinolone C=O)

**<sup>1</sup>H NMR** (400 MHz, DMSO d<sub>6</sub>)  $\delta$  / ppm = 8.44 (s, 1 H, *ortho* to C(=O)OCH<sub>3</sub>), 7.75 (d,  $J$  = 13.5 Hz, 1 H, *ortho* to F), 7.70 (d,  $J$  = 7.2 Hz, 1 H, CHNH), 7.43 (d,  $J$  = 7.5 Hz, 1 H, *meta* to F), 4.74 (d,  $J$  = 4.0 Hz, 1 H, CHOH), 3.78 - 3.82 (m, 1 H, CHOH), 3.74 - 3.78 (m, 1 H, CHNH), 3.74 (s, 3 H, CH<sub>3</sub>), 3.65 (tt,  $J$  = 7.2, 3.9 Hz, 1 H, NCH(CH<sub>2</sub>)<sub>2</sub>), 3.25 (t,  $J$  = 4.8 Hz, 4 H, CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 2.57 (br s, 4 H, CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 2.34 (t,  $J$  = 7.4 Hz, 2 H, CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 2.11 (t,  $J$  = 7.4 Hz, 2 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 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,  $\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)_2$ ), 1.54 - 1.65 (m, 2 H,  $\text{CH}_2\text{CH}_2\text{CHOH}$ ), 1.42 (ddt,  $J = 13.1, 8.2, 5.3, 5.3$  Hz, 1 H,  $\text{CHHCHOH}$ ), 1.32 (dddd,  $J = 13.4, 8.5, 6.8, 5.8$  Hz, 1 H,  $\text{CHHCHNH}$ ), 1.21 - 1.29 (m, 2 H,  $\text{NCH}(\text{CHH})_2$ ), 1.07 - 1.13 (m, 2 H,  $\text{NCH}(\text{CHH})_2$ )

$^{13}\text{C}$  NMR (101 MHz, DMSO  $d_6$ )  $\delta$  / ppm = 171.9 ( $\text{CH}_2\text{C}(=\text{O})\text{NH}$ ), 171.6 ( $\text{C}(=\text{O})\text{CC}(=\text{O})\text{OCH}_3$ ), 165.0 ( $\text{C}(=\text{O})\text{OCH}_3$ ), 152.6 (d,  $J = 246.5$  Hz, *ipso* to F), 148.3 ( $\text{C}=\text{CC}(=\text{O})\text{OCH}_3$ ), 143.9 (d,  $J = 10.7$  Hz, *ipso* to piperazine), 138.1 (*para* to F), 121.8 (d,  $J = 6.4$  Hz, *para* to piperazine), 111.5 (d,  $J = 22.4$  Hz, *ortho* to C=O and *ortho* to F), 109.0 ( $\text{CC}(=\text{O})\text{OCH}_3$ ), 106.2 (*meta* to C=O and *meta* to F), 76.3 ( $\text{CHOH}$ ), 57.6 ( $\text{CHNH}$ ), 57.2 ( $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$ ), 52.4 ( $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)_2$ ), 51.3 ( $\text{CH}_3$ ), 49.6 ( $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)_2$ ), 34.8 ( $\text{NCH}(\text{CH}_2)_2$ ), 33.3 ( $\text{C}(=\text{O})\text{CH}_2$ ), 32.2 ( $\text{CH}_2\text{CHOH}$ ), 29.5 ( $\text{CH}_2\text{CHNH}$ ), 22.5 ( $\text{C}(=\text{O})\text{CH}_2\text{CH}_2$ ), 20.6 ( $\text{CH}_2\text{CH}_2\text{CHOH}$ ), 7.6 ( $\text{NCH}(\text{CH}_2)_2$ )

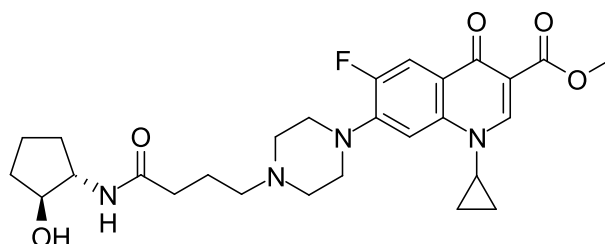
$^{19}\text{F}$  NMR (376.45 MHz, DMSO  $d_6$ )  $\delta$  / ppm = -124.3 (ciprofloxacin F)

HRMS (ESI $^+$ )  $m/z$  / Da = 515.2661,  $[\text{M}+\text{H}]^+$  found,  $[\text{C}_{27}\text{H}_{36}\text{FN}_4\text{O}_5]^+$  requires 515.2670

$[\alpha]_D^{20}$  /  $^{\circ}\text{10}^{-1}\text{cm}^2\text{g}^{-1}$  = -6.0 ( $c$  /  $\text{g}(100\text{ ml})^{-1}$  = 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  $\mu\text{mol}$ , 1 eq.), (1*S*,2*S*)-2-aminocyclopentan-1-ol **114** (19.5 mg, 193  $\mu\text{mol}$ , 2 eq.), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (29.7 mg, 155  $\mu\text{mol}$ , 1.6 eq.), 1-hydroxybenzotriazole (25.8 mg, 191  $\mu\text{mol}$ , 2 eq.) and DIPEA (33.3  $\mu\text{l}$ , 24.7 mg, 191  $\mu\text{mol}$ , 2 eq.) were dissolved in DMF (2 ml) and stirred at r.t. for 16 h. The solvent was removed using a stream of  $\text{N}_2$  and the residue was purified by preparatory HPLC (5-50 % acetonitrile/water over 15 min). The combined pure fractions were evaporated under reduced pressure and then partitioned between  $\text{NaHCO}_3$  (aq., sat., 5 ml) and  $\text{CH}_2\text{Cl}_2$  (5 ml). The organic layer was removed and the aqueous layer was extracted twice more with  $\text{CH}_2\text{Cl}_2$  (2 $\times$ 5 ml). The combined organic fractions were dried with  $\text{MgSO}_4$  and evaporated under reduced pressure. **120** was obtained as a white amorphous solid (4.9 mg, 9.5  $\mu\text{mol}$ , 9.9 %).

TLC  $R_f$  = 0.38 (30 % MeOH/ $\text{CH}_2\text{Cl}_2$ )

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

$^1\text{H}$  NMR (500 MHz, DMSO  $d_6$ )  $\delta$  / ppm = 8.44 (s, 1 H, *ortho* to  $\text{C}(=\text{O})\text{OCH}_3$ ), 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, CH<sub>3</sub>), 3.65 (tt, J=6.9, 4.0 Hz, 1 H, NCH(CH<sub>2</sub>)<sub>2</sub>), 3.24 (br. t, J=4.2, 4.2 Hz, 4 H, CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 2.55 (br t, J=5.0, 5.0 Hz, 4 H, CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 2.32 (t, J=7.2 Hz, 2 H, CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 2.10 (t, J=7.4 Hz, 2 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 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, 6.3 Hz, 1 H, CHHCHOH), 1.68 (quin, J=7.4 Hz, 2 H, CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 1.53 - 1.64 (m, 2 H, CH<sub>2</sub>CH<sub>2</sub>CHOH), 1.42 (ddt, J=12.9, 8.4, 5.2, 5.2 Hz, 1 H, CHHCHOH), 1.31 (ddt, J=13.0, 8.6, 6.4, 6.4 Hz, 1 H, CHHCHNH), 1.22 - 1.28 (m, 2 H, NCH(CHH)<sub>2</sub>), 1.06 - 1.12 (m, 2 H, NCH(CHH)<sub>2</sub>)

<sup>13</sup>C NMR (126 MHz, DMSO d<sub>6</sub>) δ / ppm = 171.9 (NHC(=O)CH<sub>2</sub>), 171.5 (C(=O)CC(=O)OCH<sub>3</sub>), 165.0 (C(=O)OCH<sub>3</sub>), 152.6 (d, J=247.4 Hz, *ipso* to F), 148.2 (C=CC(=O)OCH<sub>3</sub>), 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)OCH<sub>3</sub>), 106.2 (*meta* to C=O and *meta* to F), 76.2 (CHOH), 57.6 (CHNH), 57.2 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 52.4 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 51.3 (CH<sub>3</sub>), 49.6 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 49.6 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 34.7 (NCH(CH<sub>2</sub>)<sub>2</sub>), 33.2 (C(=O)CH<sub>2</sub>), 32.2 (CH<sub>2</sub>CHOH), 29.5 (CH<sub>2</sub>CHNH), 22.5 (C(=O)CH<sub>2</sub>CH<sub>2</sub>), 20.6 (CH<sub>2</sub>CH<sub>2</sub>CHOH), 7.5 (NCH(CH<sub>2</sub>)<sub>2</sub>)

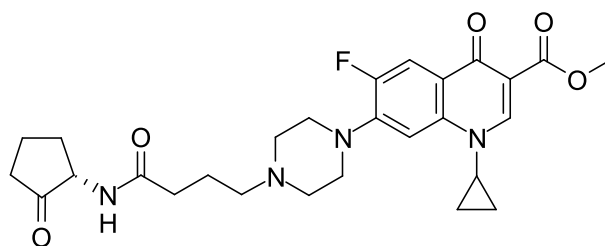
<sup>19</sup>F NMR (376.45 MHz, MeOD) δ / ppm = -125.5

HRMS (ESI<sup>+</sup>) *m/z* / Da = 515.2667, [M+H]<sup>+</sup> found, [C<sub>27</sub>H<sub>36</sub>FN<sub>4</sub>O<sub>5</sub>]<sup>+</sup> requires 515.2670

[α]<sub>D</sub><sup>20</sup> / °10<sup>-1</sup>cm<sup>2</sup>g<sup>-1</sup> = 8.0 (*c* / g(100 ml)<sup>-1</sup> = 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 Periodane (32.8 mg, 77.4 μmol, 2 eq.) were stirred in CH<sub>2</sub>Cl<sub>2</sub> (3 ml) for 6 h. The solvent was removed under reduced pressure and the residue was purified by preparatory HPLC (5-50 % acetonitrile/water over 10 min). The combined pure fractions were evaporated under reduced pressure, then NaHCO<sub>3</sub> (aq., sat., 30 ml) and 10 % *i*-PrOH/CHCl<sub>3</sub> (30 ml) were added. The organic layer was removed and dried with MgSO<sub>4</sub>, then evaporated under reduced pressure. **122** was obtained as a white amorphous solid (11.3 mg, 22.0 μmol, 56.7 %).

<sup>1</sup>H NMR (500 MHz, DMSO d<sub>6</sub>) δ / ppm = 8.46 (s, 1 H, *ortho* to C(=O)OCH<sub>3</sub>), 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, CH<sub>3</sub>), 3.65 (tt, J=6.9, 3.9 Hz, 1 H, NCH(CH<sub>2</sub>)<sub>2</sub>), 3.40 (s, 10 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 2.05 - 2.29 (m, 5

H, NHC(=O)CH<sub>2</sub>, CH<sub>2</sub>C(=O)CHNH and CHHCHNH), 1.89 - 1.96 (m, 1 H, CHHCH<sub>2</sub>CHNH), 1.69 - 1.80 (m, 3 H, CHHCH<sub>2</sub>CHNH, CHHCHNH and NHC(=O)CH<sub>2</sub>CH<sub>2</sub>), 1.24 - 1.29 (m, 2 H, NCH(CHH)<sub>2</sub>), 1.07 - 1.12 (m, 2 H, NCH(CHH)<sub>2</sub>)

<sup>13</sup>C NMR (126 MHz, DMSO d<sub>6</sub>) δ / ppm = 215.2 (C(=O)CHNH), 171.7 (NHC(=O)CH<sub>2</sub>), 171.7 (C(=O)CC(=O)OCH<sub>3</sub>), 165.1 (C(=O)OCH<sub>3</sub>), 152.6 (d, J=246.6 Hz, *ipso* to F), 148.4 (C=CC(=O)OCH<sub>3</sub>), 138.1 (*para* to F), 109.1 (CC(=O)OCH<sub>3</sub>), 56.3 (CHNH), 51.4 (CH<sub>3</sub>), 35.6 (CH<sub>2</sub>C(=O)CHNH), 34.8 (NCH(CH<sub>2</sub>)<sub>2</sub>), 28.8 (CH<sub>2</sub>CHNH), 18.1 (CH<sub>2</sub>CH<sub>2</sub>CHNH), 7.6 (NCH(CH<sub>2</sub>)<sub>2</sub>)

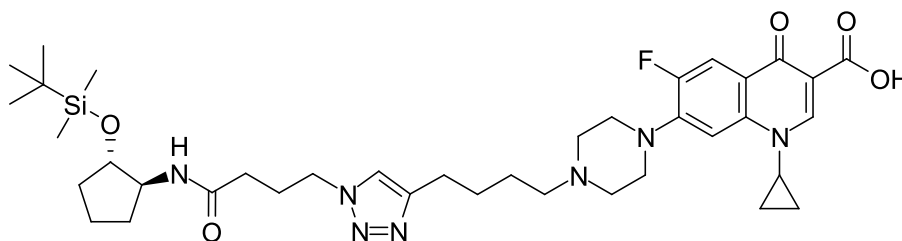
<sup>19</sup>F NMR (376.45 MHz, MeOD) δ / ppm = -124.3

HRMS (ESI<sup>+</sup>) *m/z* / Da = 513.2495, [M+H]<sup>+</sup> found, [C<sub>27</sub>H<sub>34</sub>FN<sub>4</sub>O<sub>5</sub>]<sup>+</sup> requires 513.2513

[α]<sub>D</sub><sup>20</sup> / °10<sup>-1</sup>cm<sup>2</sup>g<sup>-1</sup> = 6.7 (*c* / g(100 ml)<sup>-1</sup> = 0.075, MeOH)

The compound has not been reported previously.

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



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

IR (neat) ν<sub>max</sub> / cm<sup>-1</sup> = 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)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 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<sub>2</sub>), 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<sub>2</sub>NCH=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<sub>2</sub>)<sub>2</sub>), 3.34 (br t, *J* = 5.0 Hz, 4 H, CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 2.71 (t, *J* = 7.5 Hz, 2 H, CH=CCH<sub>2</sub>), 2.66 (br s, 4 H, CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 2.46 (t, *J* = 7.3 Hz, 2 H, CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 2.03 - 2.22



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

**<sup>1</sup>H NMR** (700 MHz, DMSO d<sub>6</sub>)  $\delta$  / 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=CCH<sub>2</sub>), 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, CH<sub>2</sub>NCH=C), 3.78 - 3.83 (m, 1 H, NCH(CH<sub>2</sub>)<sub>2</sub>), 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, CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 2.63 (t,  $J$  = 7.5 Hz, 2 H, CH=CCH<sub>2</sub>), 2.56 (br t,  $J$  = 4.2 Hz, 4 H, CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 2.37 (t,  $J$  = 7.3 Hz, 2 H, CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 2.03 - 2.06 (m, 2 H, C(=O)CH<sub>2</sub>), 1.97 - 2.02 (m, 2 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>), 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=CCH<sub>2</sub>CH<sub>2</sub>), 1.57 - 1.61 (m, 1 H, CHHCH<sub>2</sub>CHOH), 1.54 - 1.57 (m, 1 H, CHHCH<sub>2</sub>CHOH), 1.49 - 1.53 (m, 2 H, CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 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)<sub>2</sub>), 1.25 - 1.29 (m, 1 H, CHHCHNH), 1.13 - 1.20 (m, 2 H, NCH(CHH)<sub>2</sub>)

**<sup>13</sup>C NMR** (175 MHz, DMSO d<sub>6</sub>)  $\delta$  / ppm = 176.3 (C(=O)CC(=O)OH), 170.9 (NHC(=O)CH<sub>2</sub>), 166.1 (C(=O)OH), 153.0 (d,  $J$  = 251.4 Hz, *ipso* to F), 147.9 (C=CC(=O)OH), 146.9 (CH=CCH<sub>2</sub>), 145.2 (d,  $J$  = 8.7 Hz, *ipso* to piperazine), 139.2 (*para* to F), 121.7 (NCH=CCH<sub>2</sub>), 118.7 (d,  $J$  = 5.8 Hz, *para* to piperazine), 111.0 (d,  $J$  = 23.3 Hz, *ortho* to C=O and *ortho* to F), 106.3 (*meta* to C=O and *meta* to F and CC(=O)OH), 76.2 (CHOH), 57.6 (CHNH), 57.4 (CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 52.5 (CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 49.5 (d,  $J$  = 4.4 Hz, CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 48.8 (CH<sub>2</sub>NCH=CCH<sub>2</sub>), 35.8 (NCH(CH<sub>2</sub>)<sub>2</sub>), 32.2 (CH<sub>2</sub>CHOH), 32.0 (C(=O)CH<sub>2</sub>), 29.5 (CH<sub>2</sub>CHNH), 26.9 (CH=CCH<sub>2</sub>CH<sub>2</sub>), 26.0 (C(=O)CH<sub>2</sub>CH<sub>2</sub>), 25.8 (CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 25.0 (CH=CCH<sub>2</sub>), 20.5 (CH<sub>2</sub>CH<sub>2</sub>CHOH), 7.6 (NCH(CH<sub>2</sub>)<sub>2</sub>)

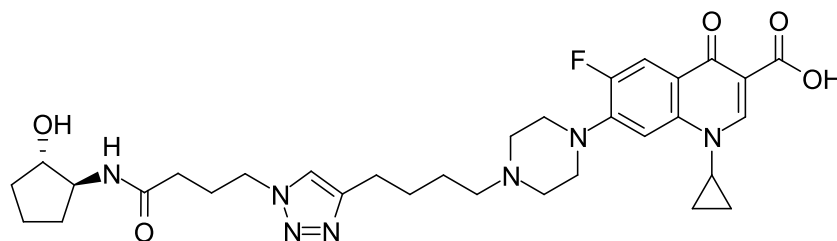
**<sup>19</sup>F NMR** (376.45 MHz, MeOD)  $\delta$  / ppm = -122.1 (s, ciprofloxacin F)

**HRMS** (ESI<sup>+</sup>)  $m/z$  / Da = 624.3314, [M+H]<sup>+</sup> found, [C<sub>32</sub>H<sub>43</sub>FN<sub>7</sub>O<sub>5</sub>]<sup>+</sup> requires 624.3310

$[\alpha]_D^{20}$  / °10<sup>-1</sup>cm<sup>2</sup>g<sup>-1</sup> = -3.6 ( $c$  / g(100 ml)<sup>-1</sup> = 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  $\mu$ mol, 4 eq.) and 4-azido-*N*-(((1*S*,2*S*)-2-hydroxycyclopentyl)butanamide **118** (11.0 mg, 51.8  $\mu$ mol, 1 eq.) were dissolved in 10 % water/*t*-BuOH (3 ml), and the mixture was degassed by bubbling N<sub>2</sub> through it. A solution of CuSO<sub>4</sub> and THPTA (156  $\mu$ l, 15.6  $\mu$ mol, 0.3 eq. 100 mM, aq.) was added, followed by a solution of sodium ascorbate (312  $\mu$ l, 31.2  $\mu$ mol, 0.6 eq., 100 mM, aq.). The mixture was stirred at room temperature under

argon for 3 d. Water (10 ml) and 10 % *i*-PrOH/CHCl<sub>3</sub> (10 ml) were added, then the organic layer was separated and dried with MgSO<sub>4</sub> and evaporated under reduced pressure. The residue was purified by preparatory HPLC (5-95 % acetonitrile/water over 20 min). The combined pure fractions were evaporated under reduced pressure and then partitioned between NaHCO<sub>3</sub> (aq., sat., 10 ml) and 10 % *i*-PrOH/CHCl<sub>3</sub> (10 ml). The organic layer was dried with MgSO<sub>4</sub> and evaporated under reduced pressure. **123** was obtained as a white amorphous solid (7.2 mg, 11.5 μmol, 22.2 %).

**IR** (neat)  $\nu_{max}$  / cm<sup>-1</sup> = 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)

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

**<sup>13</sup>C NMR** (101 MHz, DMSO d<sub>6</sub>)  $\delta$  / ppm = 176.4 (C(=O)CC(=O)OH), 170.9 (NHC(=O)CH<sub>2</sub>), 166.0 (C(=O)OH), 153.0 (d, J=249.6 Hz, *ipso* to F), 148.1 (C=CC(=O)OH), 146.7 (CH=CCH<sub>2</sub>), 145.2 (d, J=8.3 Hz, *ipso* to piperazine), 139.2 (*para* to F), 121.8 (NCH=CCH<sub>2</sub>), 118.7 (*para* to piperazine), 111.0 (d, J=23.2 Hz, *ortho* to C=O and *ortho* to F), 106.7 (CC(=O)OH), 106.5 (*meta* to C=O and *meta* to F), 76.2 (CHOH), 57.5 (CHNH), 57.4 (br s, CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 52.3 (br s, CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 49.3 (br s, CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 48.8 (CH<sub>2</sub>NCH=CCH<sub>2</sub>), 35.9 (NCH(CH<sub>2</sub>)<sub>2</sub>), 32.2 (CH<sub>2</sub>CHOH), 32.0 (C(=O)CH<sub>2</sub>), 29.4 (CH<sub>2</sub>CHNH), 26.7 (CH=CCH<sub>2</sub>CH<sub>2</sub>), 26.0 (C(=O)CH<sub>2</sub>CH<sub>2</sub>), 25.5 (CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 24.9 (CH=CCH<sub>2</sub>), 20.5 (CH<sub>2</sub>CH<sub>2</sub>CHOH), 7.6 (NCH(CH<sub>2</sub>)<sub>2</sub>)

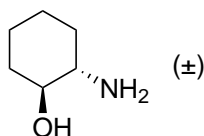
**<sup>19</sup>F NMR** (376.45 MHz, MeOD)  $\delta$  / ppm = -121.5

**HRMS** (ESI<sup>+</sup>)  $m/z$  / Da = 624.3298, [M+H]<sup>+</sup> found, [C<sub>32</sub>H<sub>43</sub>FN<sub>7</sub>O<sub>5</sub>]<sup>+</sup> requires 624.3310

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

The compound has not been reported previously.

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



Cyclohexene oxide **142** (10 ml, 9.70 g, 98.8 mmol, 1 eq.), NH<sub>3</sub> (90 ml, 35 % w/w aq., 27.7 g, 791 mmol, 8 eq.) and MeOH (100 ml) were stirred at r.t. for 72 h. The solvent was removed by blowing a stream of N<sub>2</sub> over it, followed by evaporation under high vacuum. **143** was obtained as a white amorphous solid (9.90 g, 85.2 mmol,

86.2 %)

**TLC**  $R_f$  = 0.04 (30 % MeOH/CH<sub>2</sub>Cl<sub>2</sub>)

**IR** (neat)  $\nu_{max}$  / cm<sup>-1</sup> = 3350.4 (N-H), 3306.2 (br, O-H), 2926.9 (C-H), 2852.6 (C-H)

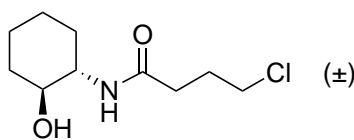
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  / ppm = 3.01 (td,  $J$  = 9.4, 4.8 Hz, 1 H, CHOH), 2.80 - 2.92 (m, 2 H, OH and NH<sub>2</sub>), 2.35 (ddd,  $J$  = 11.1, 9.1, 4.1 Hz, 1 H, CHNH<sub>2</sub>), 1.77 - 1.84 (m, 1 H, CHHCHOH), 1.69 - 1.76 (m, 1 H, CHHCHNH<sub>2</sub>), 1.56 - 1.66 (m, 1 H, CHHCH<sub>2</sub>CHOH), 1.45 - 1.56 (m, 1 H, CHHCH<sub>2</sub>CHNH<sub>2</sub>), 1.07 - 1.19 (m, 3 H, CHHCH<sub>2</sub>CHOH, CHHCH<sub>2</sub>CHNH<sub>2</sub> and CHHCHOH), 0.94 - 1.05 (m, 1 H, CHHCHNH<sub>2</sub>)

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  / ppm = 75.4 (CHOH), 56.6 (CHN<sub>2</sub>), 33.8 (CH<sub>2</sub>CHOH and CH<sub>2</sub>CHN<sub>2</sub>), 24.7 (CH<sub>2</sub>CH<sub>2</sub>CHN<sub>2</sub>), 24.6 (CH<sub>2</sub>CH<sub>2</sub>CHOH)

**HRMS** (ESI<sup>+</sup>)  $m/z$  / Da = 116.1070, [M+H]<sup>+</sup> found, [C<sub>6</sub>H<sub>14</sub>NO]<sup>+</sup> requires 116.1070

The data are consistent with the literature.<sup>9</sup>

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



(*trans*)-2-Aminocyclohexan-1-ol **143** (1.04 g, 9.03 mmol, 1 eq.), TEA (1.65 ml, 1.20 g, 11.8 mmol, 1.3 eq.) and CH<sub>2</sub>Cl<sub>2</sub> (50 ml) were stirred at 0 °C. 4-Chlorobutyryl chloride **139** (1.22 ml, 1.54 g, 10.9 mmol, 1.2 eq.) was added dropwise over 5 min. The mixture was stirred at 0 °C for 30 min, then water (50 ml) was added. The organic layer was separated off, and the aqueous layer was extracted with 10 % *i*-PrOH/CHCl<sub>3</sub> (2×50 ml). The combined organic layers were dried with MgSO<sub>4</sub>, concentrated under reduced pressure and purified by column chromatography (SiO<sub>2</sub>, 0-100 % EtOAc/Et<sub>2</sub>O). The combined organic fractions were dried with MgSO<sub>4</sub> and evaporated under reduced pressure. **144** was obtained as white needles (1.51 g, 6.87 mmol, 76.1 %).

**TLC**  $R_f$  = 0.19 (Et<sub>2</sub>O)

**mp**  $T$  / °C = 72.5-75.7 (*i*-PrOH, CHCl<sub>3</sub>)

**IR** (neat)  $\nu_{max}$  / cm<sup>-1</sup> = 3289.9 (N-H), 3250.0 (O-H), 2927.6 (C-H), 2857.1 (C-H), 1629.2 (amide C=O)

**<sup>1</sup>H NMR** (400 MHz, MeOD)  $\delta$  / ppm = 3.60 (t,  $J$  = 6.6 Hz, 2 H, CH<sub>2</sub>Cl), 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)CH<sub>2</sub>), 2.06 (quin,  $J$  = 7.0 Hz, 2 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>), 1.97 - 2.01 (m, 1 H, CHHCHOH), 1.85 - 1.93 (m, 1 H, CHHCHNH), 1.70 - 1.77 (m, 1 H, CHHCH<sub>2</sub>CHOH), 1.64 - 1.70 (m, 1 H, CHHCH<sub>2</sub>CHNH), 1.24 - 1.35 (m, 3 H, CHHCH<sub>2</sub>CHOH, CHHCH<sub>2</sub>CHNH and CHHCHOH), 1.13 - 1.25 (m, 1 H, CHHCHNH<sub>2</sub>)

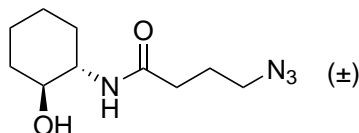
**<sup>13</sup>C NMR** (101 MHz, MeOD)  $\delta$  / ppm = 175.0 (C(=O)), 74.1 (CHOH), 56.3 (CHNH), 45.3 (CH<sub>2</sub>Cl), 35.6 (CH<sub>2</sub>CHOH), 34.5 (C(=O)CH<sub>2</sub>), 32.7 (CH<sub>2</sub>CHNH), 30.1 (C(=O)CH<sub>2</sub>CH<sub>2</sub>), 25.8 (CH<sub>2</sub>CH<sub>2</sub>CHNH), 25.5

(CH<sub>2</sub>CH<sub>2</sub>CHOH)

**HRMS** (ESI<sup>+</sup>)  $m/z$  / Da = 242.0925, [M+Na]<sup>+</sup> found, [C<sub>10</sub>H<sub>18</sub>ClNNaO<sub>2</sub>]<sup>+</sup> requires 242.0924

The compound has not been reported previously.

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



4-Chloro-*N*-((*trans*)-2-hydroxycyclohexyl)butanamide **144** (345 mg, 1.57 mmol, 1 eq.) and NaN<sub>3</sub> (180 mg, 2.77 mmol, 1.75 eq.) were stirred in DMF (12 ml) at 50 °C for 16 h. Water (50 ml) and 10 % *i*-PrOH/CHCl<sub>3</sub> (50 ml) were added, and the organic layer was removed. The aqueous layer was extracted again with 10 % *i*-PrOH/CHCl<sub>3</sub> (50 ml) and the combined organic fractions were dried with MgSO<sub>4</sub>. The solvent was evaporated under reduced pressure, and then by using a N<sub>2</sub> stream. **145** was obtained as large white prisms (347 mg, 1.53 mmol, 97.5 %).

**TLC**  $R_f$  = 0.23 (EtOAc)

**mp**  $T$  / °C = 74.5-75.7 (*i*-PrOH, CHCl<sub>3</sub>)

**IR** (neat)  $\nu_{max}$  / cm<sup>-1</sup> = 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)

**<sup>1</sup>H NMR** (400 MHz, MeOD)  $\delta$  / ppm = 7.87 (d,  $J$  = 7.9 Hz, 1 H, NH), 5.27 (d,  $J$  = 4.3 Hz, 1 H, OH), 3.56 (td,  $J$  = 10.5, 4.4 Hz, 1 H, CHNH), 3.28 - 3.41 (m, 3 H, CHOH and CH<sub>2</sub>N<sub>3</sub>), 2.30 (td,  $J$  = 7.4, 2.7 Hz, 2 H, C(=O)CH<sub>2</sub>), 1.95 - 2.03 (m, 1 H, CHHCHOH), 1.87 (m, 3 H, C(=O)CH<sub>2</sub>CH<sub>2</sub> and CHHCHNH), 1.70 - 1.76 (m, 1 H, CHHCH<sub>2</sub>CHOH), 1.63 - 1.70 (m, 1 H, CHHCH<sub>2</sub>CHNH), 1.25 - 1.38 (m, 3 H, CHHCH<sub>2</sub>CHOH, CHHCH<sub>2</sub>CHNH and CHHCHOH), 1.14 - 1.24 (m, 1 H, CHHCHNH<sub>2</sub>)

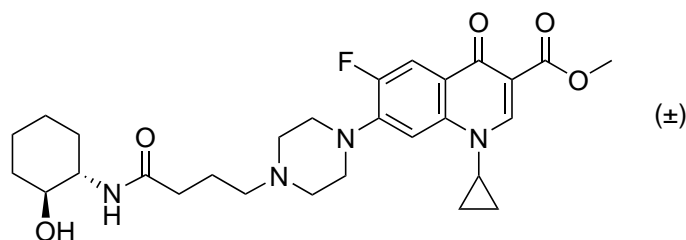
**<sup>13</sup>C NMR** (101 MHz, MeOD)  $\delta$  / ppm = 175.1 (C(=O)), 74.0 (CHOH), 56.3 (CHNH), 52.0 (CH<sub>2</sub>N<sub>3</sub>), 35.5 (CH<sub>2</sub>CHOH), 34.3 (C(=O)CH<sub>2</sub>), 32.7 (CH<sub>2</sub>CHNH), 26.3 (C(=O)CH<sub>2</sub>CH<sub>2</sub>), 25.8 (CH<sub>2</sub>CH<sub>2</sub>CHNH), 25.5 (CH<sub>2</sub>CH<sub>2</sub>CHOH)

**HRMS** (ESI<sup>+</sup>)  $m/z$  / Da = 249.1331, [M+Na]<sup>+</sup> found, [C<sub>10</sub>H<sub>18</sub>N<sub>4</sub>NaO<sub>2</sub>]<sup>+</sup> 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  $\mu$ 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 N<sub>2</sub> and the residue was purified by preparatory HPLC (5-50 % acetonitrile/water over 10 min). The combined pure fractions were evaporated under reduced pressure and then partitioned between NaHCO<sub>3</sub> (aq., sat., 10 ml) and CH<sub>2</sub>Cl<sub>2</sub> (10 ml). The organic layer was dried with MgSO<sub>4</sub> and evaporated under reduced pressure. **146** was obtained as a white amorphous solid (73.0 mg, 0.142 mmol, 38.7 %).

**IR** (neat)  $\nu_{max}$  / cm<sup>-1</sup> = 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)

**<sup>1</sup>H NMR** (400 MHz, MeOD)  $\delta$  / ppm = 8.60 (s, 1 H, *ortho* to C(=O)OCH<sub>3</sub>), 7.79 (d, *J* = 13.5 Hz, 1 H, *ortho* to F), 7.46 (d, *J* = 7.2 Hz, 1 H, *meta* to F), 3.84 (s, 3 H, CH<sub>3</sub>), 3.62 - 3.68 (m, 1 H, NCH(CH<sub>2</sub>)<sub>2</sub>), 3.58 (td, *J* = 10.3, 4.2 Hz, 1 H, CHNH), 3.38 (br s, 4 H, CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 3.32 - 3.36 (m, 1 H, CHOH), 2.83 (br s, 4 H, CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 2.60 (t, *J* = 7.3 Hz, 2 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 2.32 (td, *J* = 7.1, 3.1 Hz, 2 H, C(=O)CH<sub>2</sub>), 1.96 - 2.04 (m, 1 H, CHHCHOH), 1.87 - 1.96 (m, 3 H, CHHCHNH and C(=O)CH<sub>2</sub>CH<sub>2</sub>), 1.72 - 1.77 (m, 1 H, CHHCH<sub>2</sub>CHOH), 1.66 - 1.72 (m, 1 H, CHHCH<sub>2</sub>CHNH), 1.25 - 1.39 (m, 5 H, CHHCHOH, CHHCH<sub>2</sub>CHOH, CHHCH<sub>2</sub>CHNH and NCH(CHH)<sub>2</sub>), 1.15 - 1.25 (m, 3 H, CHHCHOH and NCH(CHH)<sub>2</sub>)

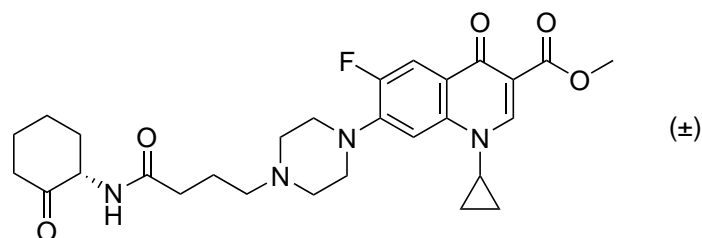
**<sup>13</sup>C NMR** (101 MHz, MeOD)  $\delta$  / ppm = 175.8 (CH<sub>2</sub>C(=O)NH), 175.3 (C(=O)CC(=O)OCH<sub>3</sub>), 166.8 (C(=O)OCH<sub>3</sub>), 154.9 (d, *J* = 248.8 Hz, *ipso* to F), 150.2 (C=CC(=O)OCH<sub>3</sub>), 146.1 (d, *J* = 10.8 Hz, *ipso* to piperazine), 139.9 (*para* to F), 123.5 (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)OCH<sub>3</sub>), 107.2 (*meta* to C=O and *meta* to F), 74.1 (CHOH), 58.9 (C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 56.4 (CHNH), 54.0 (C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 52.3 (CH<sub>3</sub>), 50.5 (d, *J* = 5.0 Hz, C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 36.4 (NCH(CH<sub>2</sub>)<sub>2</sub>), 35.7 (CH<sub>2</sub>CHOH), 35.1 (C(=O)CH<sub>2</sub>), 32.8 (CH<sub>2</sub>CHNH), 25.9 (CH<sub>2</sub>CH<sub>2</sub>CHNH), 25.5 (CH<sub>2</sub>CH<sub>2</sub>CHOH), 23.5 (C(=O)CH<sub>2</sub>CH<sub>2</sub>), 8.7 (NCH(CH<sub>2</sub>)<sub>2</sub>)

**<sup>19</sup>F NMR** (376.45 MHz, MeOD)  $\delta$  / ppm = -124.7 (ciprofloxacin F)

**HRMS** (ESI<sup>+</sup>) *m/z* / Da = 529.2827, [M+H]<sup>+</sup> found, [C<sub>28</sub>H<sub>38</sub>FN<sub>4</sub>O<sub>5</sub>]<sup>+</sup> 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  $\mu$ mol, 1 eq.) and Dess-Martin periodane (16.4 mg, 38.7  $\mu$ mol, 4 eq.) were stirred in  $\text{CH}_2\text{Cl}_2$  (3 ml) for 6 h. The solvent was removed under reduced pressure and the residue was purified by preparatory HPLC (5-95 % acetonitrile/water over 20 min). The combined pure fractions were evaporated under reduced pressure to a volume of 20 ml, then  $\text{NaHCO}_3$  (aq., sat., 30 ml) and 10 % *i*-PrOH/ $\text{CHCl}_3$  (30 ml) were added. The organic layer was dried with  $\text{MgSO}_4$  and evaporated under reduced pressure. **147** was obtained as a white amorphous solid (3.6 mg, 6.8  $\mu$ mol, 69.1 %).

**TLC**  $R_f$  = 0.74 (30 % MeOH/ $\text{CH}_2\text{Cl}_2$ )

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

**$^1\text{H}$  NMR** (400 MHz, DMSO  $d_6$ )  $\delta$  / ppm = 8.45 (s, 1 H, *ortho* to C(=O)OCH<sub>3</sub>), 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, CH<sub>3</sub>), 3.65 (tt,  $J$  = 7.1, 3.9 Hz, 1 H, NCH(CH<sub>2</sub>)<sub>2</sub>), 3.25 (br s, 4 H, CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 2.58 (br s, 4 H, CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 2.45 - 2.53 (m, 1 H, CHHC(=O)CHNH), 2.36 (br s, 2 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 2.26 (dtt,  $J$  = 13.4, 2.6, 2.6, 1.6, 1.6 Hz, 1 H, CHHC(=O)CHNH), 2.16 - 2.22 (m, 2 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 2.12 (ddq,  $J$  = 12.7, 6.0, 2.8, 2.8, 2.8 Hz, 1 H, CHHCHNH), 2.00 (ddquin,  $J$  = 13.2, 6.0, 2.9, 2.9, 2.9, 2.9 Hz, 1 H, CHHCH<sub>2</sub>C(=O)), 1.65 - 1.83 (m, 4 H, CH<sub>2</sub>CH<sub>2</sub>CHNH), 1.41 - 1.56 (m, 2 H, CHHCHNH and CHHCH<sub>2</sub>C(=O)), 1.20 - 1.30 (m, 2 H, NCH(CH<sub>2</sub>)<sub>2</sub>), 1.05 - 1.13 (m, 2 H, NCH(CH<sub>2</sub>)<sub>2</sub>)

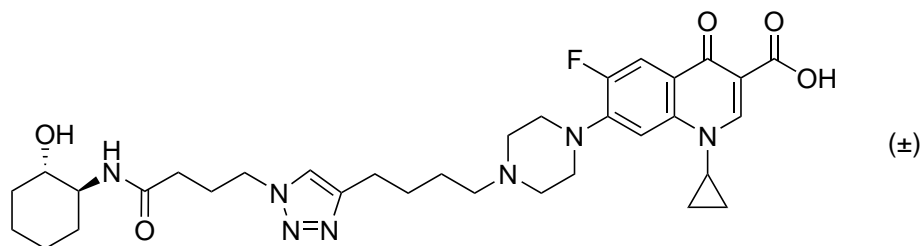
**$^{13}\text{C}$  NMR** (101 MHz, DMSO  $d_6$ )  $\delta$  / ppm = 207.5 (C(=O)CHNH), 171.7 (C(=O)CC(=O)OCH<sub>3</sub>), 171.6 (CH<sub>2</sub>C(=O)NH), 165.0 (C(=O)OCH<sub>3</sub>), 152.6 (d,  $J$  = 247.6 Hz, *ipso* to F), 148.3 (C=CC(=O)OCH<sub>3</sub>), 143.9 (br s, *ipso* to piperazine), 138.1 (*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)OCH<sub>3</sub>), 106.3 (*meta* to C=O and *meta* to F), 57.0 (CHNH and C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 52.3 (br s, C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 51.3 (CH<sub>3</sub>), 49.5 (br s, C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 40.6 (CH<sub>2</sub>C(=O)CHNH), 34.8 (NCH(CH<sub>2</sub>)<sub>2</sub>), 33.9 (CH<sub>2</sub>CHNH), 32.9 (C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 27.2 (CH<sub>2</sub>CH<sub>2</sub>C(=O)CHNH), 23.8 (CH<sub>2</sub>CH<sub>2</sub>CHNH), 22.4 (br s, C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 7.6 (NCH(CH<sub>2</sub>)<sub>2</sub>)

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

**HRMS** (ESI<sup>+</sup>)  $m/z$  / Da = 527.2654,  $[\text{M}+\text{H}]^+$  found,  $[\text{C}_{28}\text{H}_{36}\text{FN}_4\text{O}_5]^+$  requires 527.2670

The compound has not been reported previously.

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



1-Cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **70** (40 mg, 97.2  $\mu$ mol, 1 eq.) and 4-azido-*N*-(((*trans*)-2-hydroxycyclohexyl)butanamide **145** (22.0 mg, 97.2  $\mu$ mol, 1 eq.) were dissolved in 10 % water/*t*-BuOH (3 ml), and the mixture was degassed by bubbling N<sub>2</sub> through it. A solution of CuSO<sub>4</sub> and THPTA (97.2  $\mu$ l, 9.72  $\mu$ mol, 0.1 eq. 100 mM, aq.) was added, followed by a solution of sodium ascorbate (194  $\mu$ l, 19.4  $\mu$ 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/CHCl<sub>3</sub> (50 ml) were added, then the organic layer was separated, dried with MgSO<sub>4</sub> and evaporated under reduced pressure. The residue was purified by preparatory HPLC (5-70 % acetonitrile/water over 15 min). The combined pure fractions were evaporated under reduced pressure and then partitioned between NaHCO<sub>3</sub> (aq., sat., 50 ml) and 10 % *i*-PrOH/CHCl<sub>3</sub> (50 ml). The organic layer was dried with MgSO<sub>4</sub> and evaporated under reduced pressure. **148** was obtained as a white amorphous solid (30.3 mg, 47.5  $\mu$ mol, 48.9 %).

**IR** (neat)  $\nu_{max}$  / cm<sup>-1</sup> = 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)

**<sup>1</sup>H NMR** (400 MHz, DMSO d<sub>6</sub>)  $\delta$  / 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, CH=CCH<sub>2</sub>), 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, C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 3.77 - 3.86 (m, 1 H, NCH(CH<sub>2</sub>)<sub>2</sub>), 3.33 - 3.40 (m, 1 H, CHNH), 3.31 (br t, *J* = 4.8, 4.8 Hz, 4 H, CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 3.14 - 3.24 (m, 1 H, CHOH), 2.63 (t, *J* = 7.4 Hz, 2 H, CH=CCH<sub>2</sub>), 2.56 (br t, *J* = 4.6, 4.6 Hz, 4 H, CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 2.38 (t, *J* = 6.9 Hz, 2 H, CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 2.04 - 2.08 (m, 2 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 1.96 - 2.04 (m, 2 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>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, CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 1.54 - 1.60 (m, 1 H, CHHCH<sub>2</sub>OH), 1.51 (quin, *J* = 7.4 Hz, 2 H, CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 1.28 - 1.35 (m, 1 H, NCH(CHH)<sub>2</sub>), 1.11 - 1.22 (m, 5 H, NCH(CHH)<sub>2</sub>, CHHCHOH, CHHCH<sub>2</sub>CHOH and CH<sub>2</sub>CH<sub>2</sub>CHNH), 1.04 - 1.13 (m, 1 H, CHHCHNH)

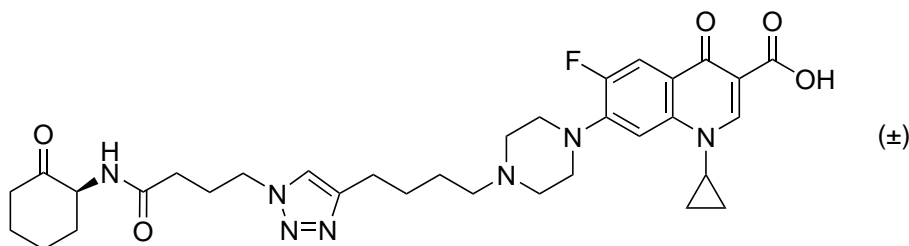
**<sup>13</sup>C NMR** (101 MHz, DMSO d<sub>6</sub>)  $\delta$  / ppm = 176.4 (C(=O)CC(=O)OH), 170.9 (CH<sub>2</sub>C(=O)NH), 166.0 (C(=O)OH), 153.1 (d, *J* = 252.1 Hz, *ipso* to F), 148.0 (C=CC(=O)OH), 146.9 (CH=CCH<sub>2</sub>), 145.3 (d, *J* = 10.0 Hz, *ipso* to piperazine), 139.2 (*para* to F), 121.8 (NCH=CCH<sub>2</sub>), 118.5 (d, *J* = 8.3 Hz, *para* to piperazine), 110.9 (d, *J* = 23.2 Hz, *ortho* to C=O and *ortho* to F), 106.7 (CC(=O)OH), 106.3 (d, *J* = 3.3 Hz, *meta* to C=O and *meta* to F), 71.4 (CHOH), 57.4 (CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 54.2 (CHNH), 52.4 (CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 49.5 (CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 49.5 (CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 48.8 (C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>NCH=C), 35.9 (NCH(CH<sub>2</sub>)<sub>2</sub>), 34.1 (CH<sub>2</sub>CHOH), 32.3 (C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>NCH=C), 31.1 (CH<sub>2</sub>CHNH), 26.9 (CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 26.1 (C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>NCH=C), 25.8 (CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 25.0 (CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 24.2 (CH<sub>2</sub>CH<sub>2</sub>CHNH), 23.8 (CH<sub>2</sub>CH<sub>2</sub>CHOH), 7.6 (NCH(CH<sub>2</sub>)<sub>2</sub>)

<sup>19</sup>F NMR (376.45 MHz, DMSO d<sub>6</sub>) δ / ppm = -121.4 (ciprofloxacin F)

HRMS (ESI<sup>+</sup>) *m/z* / Da = 638.3480, [M+H]<sup>+</sup> found, [C<sub>33</sub>H<sub>45</sub>FN<sub>7</sub>O<sub>5</sub>]<sup>+</sup> 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 periodane (35.0 mg, 82.5 mmol, 3.5 eq.) were stirred in CH<sub>2</sub>Cl<sub>2</sub> (3 ml) for 4 h. The solvent was removed under reduced pressure and the residue was purified by preparatory HPLC (5-70 % acetonitrile/water over 15 min). The combined pure fractions were evaporated under reduced pressure, then NaHCO<sub>3</sub> (aq., sat., 30 ml) and 10 % *i*-PrOH/CHCl<sub>3</sub> (30 ml) were added. The organic layer was dried with MgSO<sub>4</sub> and evaporated under reduced pressure. **149** was obtained as a clear gum (11.7 mg, 18.4 μmol, 78.0 %).

IR (neat)  $\nu_{max}$  / cm<sup>-1</sup> = 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)

<sup>1</sup>H NMR (500 MHz, DMSO d<sub>6</sub>) δ / ppm = 8.65 (s, 1 H, *ortho* to C(=O)OH), 7.94 (d, J=7.7 Hz, 1 H, NH), 7.88 (d, J=13.4 Hz, 1 H, *ortho* to F), 7.85 (s, 1 H, CH=CCH<sub>2</sub>), 7.55 (d, J=7.3 Hz, 1 H, *meta* to F), 4.40 (dddd, J=12.8, 7.6, 6.1, 1.1 Hz, 1 H), 4.31 (t, J=7.0 Hz, 1 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>CHHN), 4.31 (t, J=6.9 Hz, 1 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 3.74 - 3.84 (m, 1 H, NCH(CH<sub>2</sub>)<sub>2</sub>), 3.31 (br. s, 4 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 2.64 (t, J=7.5 Hz, 2 H, CH=CCH<sub>2</sub>), 2.56 (br t, J=5.0, 5.0 Hz, 4 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 2.45 - 2.52 (m, 1 H, CHHC(=O)), 2.38 (t, J=7.1 Hz, 2 H, CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 2.25 (dt, J=13.4, 2.6, 2.6, 1.6, 1.6 Hz, 1 H, CHHC(=O)), 2.07 - 2.17 (m, 3 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N and CHHCNH), 1.96 - 2.05 (m, 3 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N and CHHCCH<sub>2</sub>C(=O)), 1.68 - 1.81 (m, 2 H, CHHCCH<sub>2</sub>CHNH), 1.64 (quin, J=7.5 Hz, 2 H, CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 1.40 - 1.56 (m, 5 H, CHHCCH<sub>2</sub>C(=O), CHHCNH and CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 1.27 - 1.34 (m, 2 H, NCH(CH<sub>2</sub>)<sub>2</sub>), 1.13 - 1.20 (m, 2 H, NCH(CH<sub>2</sub>)<sub>2</sub>)

<sup>13</sup>C NMR (126 MHz, DMSO d<sub>6</sub>) δ / ppm = 207.4 (C(=O)CHNH), 176.3 (C(=O)CC(=O)OH), 170.8 (CH<sub>2</sub>C(=O)NH), 166.0 (C(=O)OH), 153.0 (d, J=246.4 Hz, *ipso* to F), 147.9 (C=CC(=O)OH), 146.8 (CH=CCH<sub>2</sub>), 145.1 (d, J=10.1 Hz, *ipso* to piperazine), 139.1 (*para* to F), 121.7 (NCH=CCH<sub>2</sub>), 118.7 (d, J=6.9 Hz, *para* to piperazine), 110.9 (d, J=23.0 Hz, *ortho* to C=O and *ortho* to F), 106.3 (CC(=O)OH, and *meta* to C=O and *meta* to F), 57.3 (CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 57.0 (CHNH), 52.4 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 49.5 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 49.5 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 48.7 (C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>NCH=C), 40.5 (CH<sub>2</sub>C(=O)), 35.8 (NCH(CH<sub>2</sub>)<sub>2</sub>), 33.7 (CH<sub>2</sub>CHNH), 31.8 (C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>NCH=C), 27.1 (CH<sub>2</sub>CH<sub>2</sub>C(=O)),

26.9 (CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 26.0 (C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>NCH=C), 25.7 (CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 24.9 (CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 23.8 (CH<sub>2</sub>CH<sub>2</sub>CHNH), 7.6 (NCH(CH<sub>2</sub>)<sub>2</sub>)

**<sup>19</sup>F NMR** (376 MHz, DMSO d<sub>6</sub>)  $\delta$  / ppm = -121.7 (s, ciprofloxacin F)

**HRMS** (ESI<sup>+</sup>)  $m/z$  / Da = 636.3303, [M+H]<sup>+</sup> found, [C<sub>33</sub>H<sub>43</sub>FN<sub>7</sub>O<sub>5</sub>]<sup>+</sup> requires 636.3310

The compound has not been reported previously.

## 1 References

- [1] J. Aubé, Michael S. Wolfe, R. K. Yantiss, S. M. Cook, F. Takusagawa, M. S. Wolfe, R. K. Yantiss, S. M. Cook and F. Takusagawa. Synthesis of Enantiopure N-tert-Butoxycarbonyl-2- aminocycloalkanones. *Synthetic Communications*, 22(20):3003–3012. 1992.
- [2] L. E. Overman, S. Sugai, L. E. Overman and S. Sugai. A Convenient Method for Obtaining trans -2-Aminocyclohexanol and trans -2-Aminocyclopentanol in Enantiomerically Pure Form. *The Journal of Organic Chemistry*, 50:4154–4155. 1985.
- [3] L. E. Overman and S. Sugai. Total Synthesis of (-)-Crinine. Use of Tandem Cationic Aza-Cope Rearrangement/Mannich Cyclizations for the Synthesis of Enantiomerically Pure Amaryllidaceae Alkaloids. *Helvetica Chimica Acta*, 68(3):745–749. 1985.
- [4] K. Ganguly, R. Wu, M. Ollivault-Shiflett, P. M. Goodwin, L. A. Silks and R. Iyer. Design, synthesis, and a novel application of quorum-sensing agonists as potential drug-delivery vehicles. *Journal of Drug Targeting*, 19(7):528–539. 2011.
- [5] K. Sachin, E.-M. Kim, S.-J. Cheong, H.-J. Jeong, S. T. Lim, M.-H. Sohn and D. W. Kim. Synthesis of  $N_4'$ - $[^{18}F]$ fluoroalkylated ciprofloxacin as a potential bacterial infection imaging agent for PET study. *Bioconjugate Chemistry*, 21(12):2282–2288. 2010.
- [6] R. Iyer, K. Ganguly and L. A. Silks. Synthetic analogs of bacterial quorum sensors. Los Alamos National Laboratory. 2012.
- [7] R. Srinivasan, L. P. Tan, H. Wu, P.-Y. Yang, K. A. Kalesh and S. Q. Yao. High-throughput synthesis of azide libraries suitable for direct "click" chemistry and in situ screening. *Organic & Biomolecular Chemistry*, 7(9):1821. 2009.
- [8] I. Schiffrers, T. Rantanen, F. Schmidt, W. Bergmans, L. Zani and C. Bolm. Resolution of racemic 2-aminocyclohexanol derivatives and their application as ligands in asymmetric catalysis. *The Journal of Organic Chemistry*, 71(1):2320–2331. 2006.
- [9] F. Xue and C. T. Seto. Structure-activity studies of cyclic ketone inhibitors of the serine protease plasmin: Design, synthesis, and biological activity. *Bioorganic & Medicinal Chemistry*, 14:8467–8487. 2006.

## Todo list

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