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0.21	(1 <i>S</i> ,2 <i>S</i> )-2-(( <i>tert</i> -Butyldimethylsilyl)oxy)cyclopentan-1-amine <b>125</b> . . . . .	30
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0.23	4-Chloro- <i>N</i> -((1 <i>S</i> ,2 <i>S</i> )-2-hydroxycyclopentyl)butanamide <b>139</b> . . . . .	32
0.24	4-Azido- <i>N</i> -((1 <i>S</i> ,2 <i>S</i> )-2-(( <i>tert</i> -butyldimethylsilyl)oxy)cyclopentyl)butanamide <b>129</b> . . . . .	33
0.25	4-Azido- <i>N</i> -((1 <i>R</i> ,2 <i>R</i> )-2-hydroxycyclopentyl)butanamide <b>119</b> . . . . .	33

0.26	4-Azido- <i>N</i> -((1 <i>S</i> ,2 <i>S</i> )-2-hydroxycyclopentyl)butanamide <b>118</b>	34
0.27	Methyl 1-cyclopropyl-6-fluoro-7-(4-(4-(((1 <i>R</i> ,2 <i>R</i> )-2-hydroxycyclopentyl)amino)-4-oxobutyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate <b>121</b>	35
0.28	Methyl 1-cyclopropyl-6-fluoro-7-(4-(4-(((1 <i>S</i> ,2 <i>S</i> )-2-hydroxycyclopentyl)amino)-4-oxobutyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate <b>120</b>	36
0.29	Methyl ( <i>S</i> )-1-cyclopropyl-6-fluoro-4-oxo-7-(4-(4-oxo-4-((2-oxocyclopentyl)amino)butyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate <b>122</b>	37
0.30	7-(4-(4-(1-(4-(((1 <i>S</i> ,2 <i>S</i> )-2-(( <i>tert</i> -butyldimethylsilyl)oxy)cyclopentyl)amino)-4-oxobutyl)-1 <i>H</i> -1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid <b>133</b>	38
0.31	1-Cyclopropyl-6-fluoro-7-(4-(4-(1-(4-(((1 <i>R</i> ,2 <i>R</i> )-2-hydroxycyclopentyl)amino)-4-oxobutyl)-1 <i>H</i> -1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid <b>124</b>	39
0.32	1-Cyclopropyl-6-fluoro-7-(4-(4-(1-(4-(((1 <i>S</i> ,2 <i>S</i> )-2-hydroxycyclopentyl)amino)-4-oxobutyl)-1 <i>H</i> -1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid <b>123</b>	40
0.33	( <i>trans</i> )-2-Aminocyclohexan-1-ol <b>142</b>	41
0.34	Methyl 1-cyclopropyl-6-fluoro-7-(4-(4-((( <i>trans</i> )-2-hydroxycyclohexyl)amino)-4-oxobutyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate <b>143</b>	42
0.35	Methyl 1-cyclopropyl-6-fluoro-4-oxo-7-(4-(4-oxo-4-((2-oxocyclohexyl)amino)-butyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate <b>144</b>	43
0.36	4-Chloro- <i>N</i> -(( <i>trans</i> )-2-hydroxycyclohexyl)butanamide <b>145</b>	44
0.37	4-Azido- <i>N</i> -(( <i>trans</i> )-2-hydroxycyclohexyl)butanamide <b>146</b>	45
0.38	1-Cyclopropyl-6-fluoro-7-(4-(4-(1-(4-((( <i>trans</i> )-2-hydroxycyclohexyl)amino)-4-oxobutyl)-1 <i>H</i> -1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid <b>147</b>	46
0.39	1-Cyclopropyl-6-fluoro-4-oxo-7-(4-(4-(1-(4-oxo-4-((2-oxocyclohexyl)amino)butyl)-1 <i>H</i> -1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid <b>148</b>	47

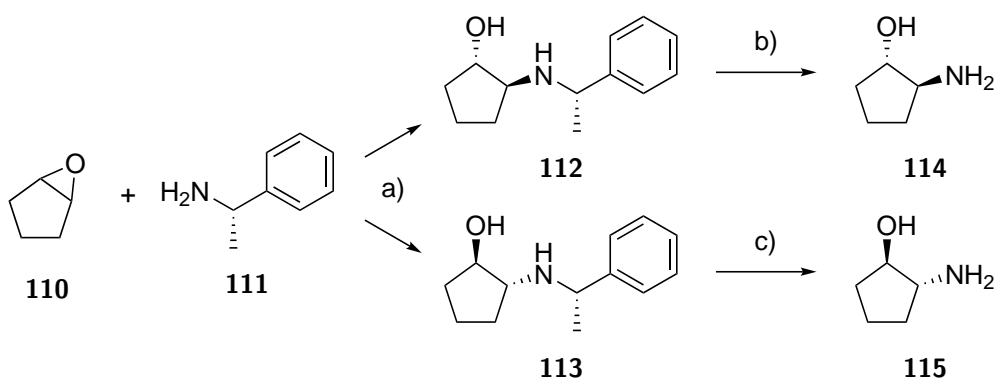
## 1 References

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### 0.1 Cyclopentanol derivatives

#### 0.1.1 Synthesis of the 2-aminocyclopentan-1-ol head groups

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



Scheme 1: Synthesis of (1*S*,2*S*)-2-aminocyclopentan-1-ol **114** and (1*R*,2*R*)-2-aminocyclopentan-1-ol **115**. a) AlMe<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, **112** (*SSS*): 35.2 %, **113** (*RRS*): 32.1 %. b) See Table 1. c) Pd(OH)<sub>2</sub>, MeOH, H<sub>2</sub>, 5 atm, r.t., 1 d, 100 %.

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

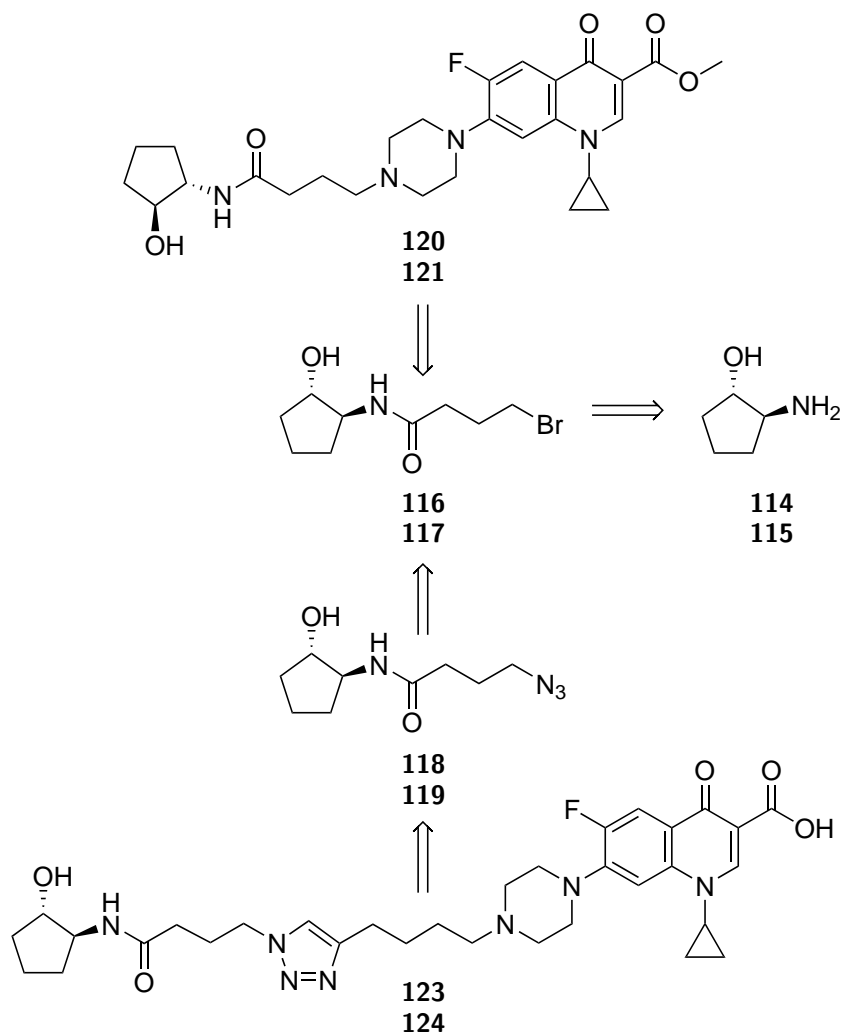
Table 1: Conditions attempted for the synthesis of (1*S*,2*S*)-2-aminocyclopentan-1-ol **114** and (1*R*,2*R*)-2-aminocyclopentan-1-ol **115** (see Scheme 1).

### 0.1.2 Initial branching strategy

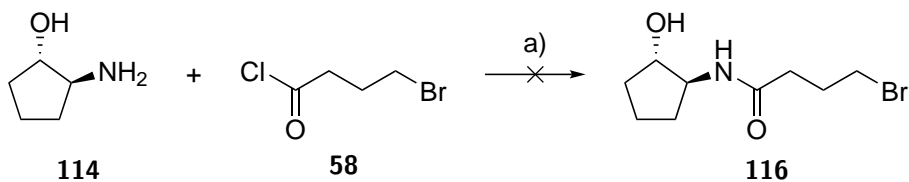
An initial retrosynthesis of the conjugates is shown in Scheme 2, and follows a similar path to previous conjugates.

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

the alcohol (see 0.1.3), installing the linker on methyl ciprofloxacin **92** and then attaching the head group by peptide coupling (see 0.1.4), and using 4-chlorobutyryl chloride **138** as the linker instead of 4-bromobutyryl chloride **58** (see 0.1.5).



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



Scheme 3: Synthesis of Br-C<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.

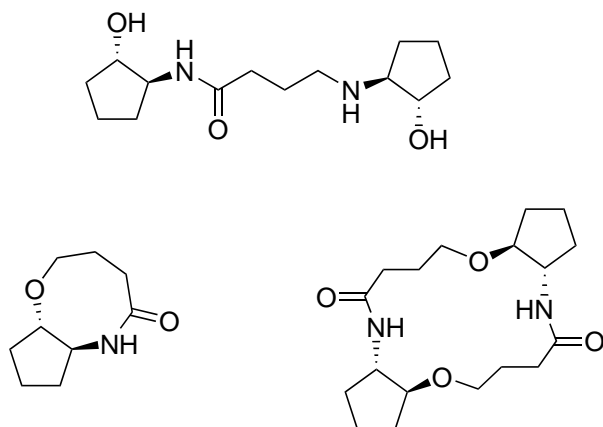
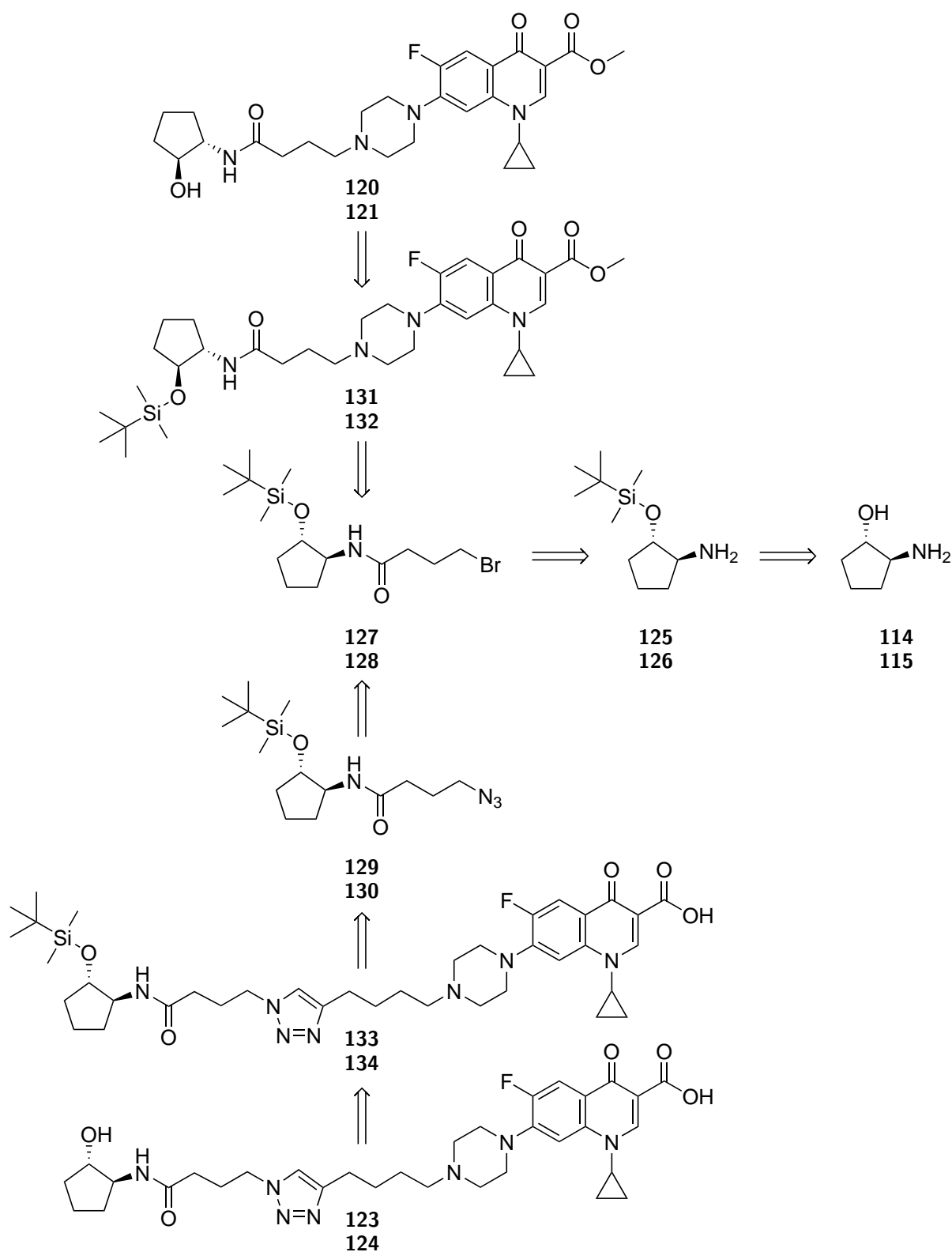


Figure 1: Impurities observed by LCMS during the synthesis of Br-C<sub>4</sub>-cyclopentanol-(*SS*) **116**. Regiochemistry is speculative.

### 0.1.3 TBDMS protection of the alcohol

#### 0.1.3.1 Initial protection strategy

The first attempt at an alternative strategy for the synthesis of the conjugates involved TBDMS protection of the alcohol (see Scheme 4). It was envisaged that protection would eliminate enough of the side reactions with products shown in Figure 1 that intermediates Br-C<sub>4</sub>-cyclopentanol-(*SS*) **116** and N<sub>3</sub>-C<sub>4</sub>-cyclopentanol-(*SS*) **118** could be purified. The TBDMS group could be removed later in the synthesis using TBAF or acid.

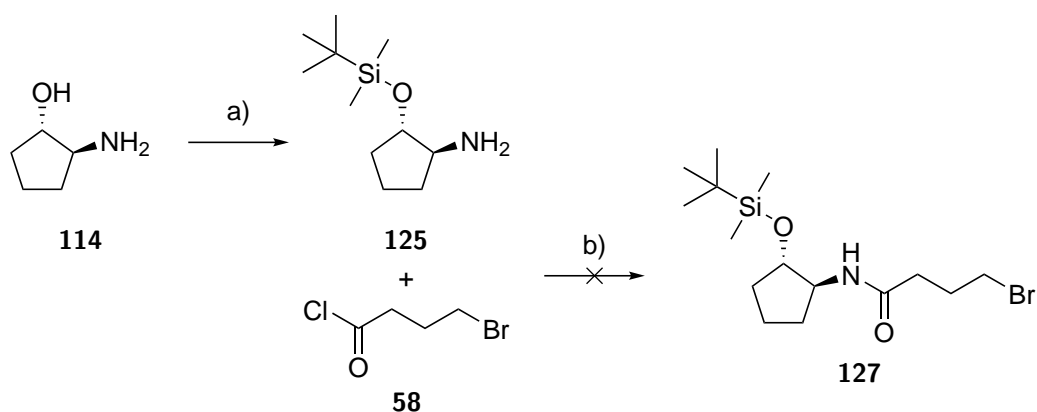


Scheme 4: Retrosynthesis of the cyclopentanol-CipMe conjugates **120** (*SS*) and **121** (*RR*), and the cyclopentanol-Cip triazole conjugates **123** (*SS*) and **124** (*RR*) using a TBDMMS protection strategy. *SS* enantiomers are shown, but both will be synthesised.

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

Opt.

OTf? Cl? DBU?



Scheme 5: The attempted synthesis of Br-C<sub>4</sub>-cyclopentanol-TBDMS-(*SS*) **127**. a) See Table 2. b) NaHCO<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, H<sub>2</sub>O, 0 °C, 2 h.

Conditions	Temperature	Time	Result
TBDMSCl, DMAP, TEA, CH <sub>2</sub> Cl <sub>2</sub>	r.t.	18 h	Trace of <b>125</b> , mostly <b>114</b>
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	<b>114</b>
TBDMSCl, DBU, MeCN	0 °C	1 d	<b>114</b>
TBDMSOTf, TEA, CH <sub>2</sub> Cl <sub>2</sub>	0 °C	4 h	<b>125</b> possibly seen but lost in workup
TBDMSOTf in 2 portions, TEA, CH <sub>2</sub> Cl <sub>2</sub> , NH <sub>4</sub> Cl workup	0 °C	6 h	<b>125</b> salt
TBDMSOTf in 2 portions, TEA, CH <sub>2</sub> Cl <sub>2</sub> , aq. workup then column	0 °C	6 h	<b>125</b> , 85 % yield

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

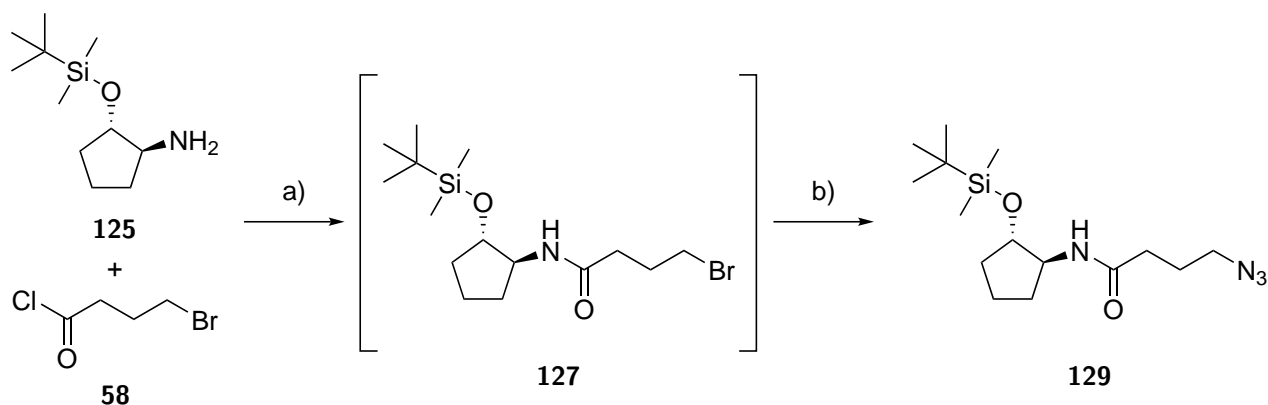
Still get side-reactions when adding tail

come  
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### 0.1.3.2 Triazoles by two-step reaction

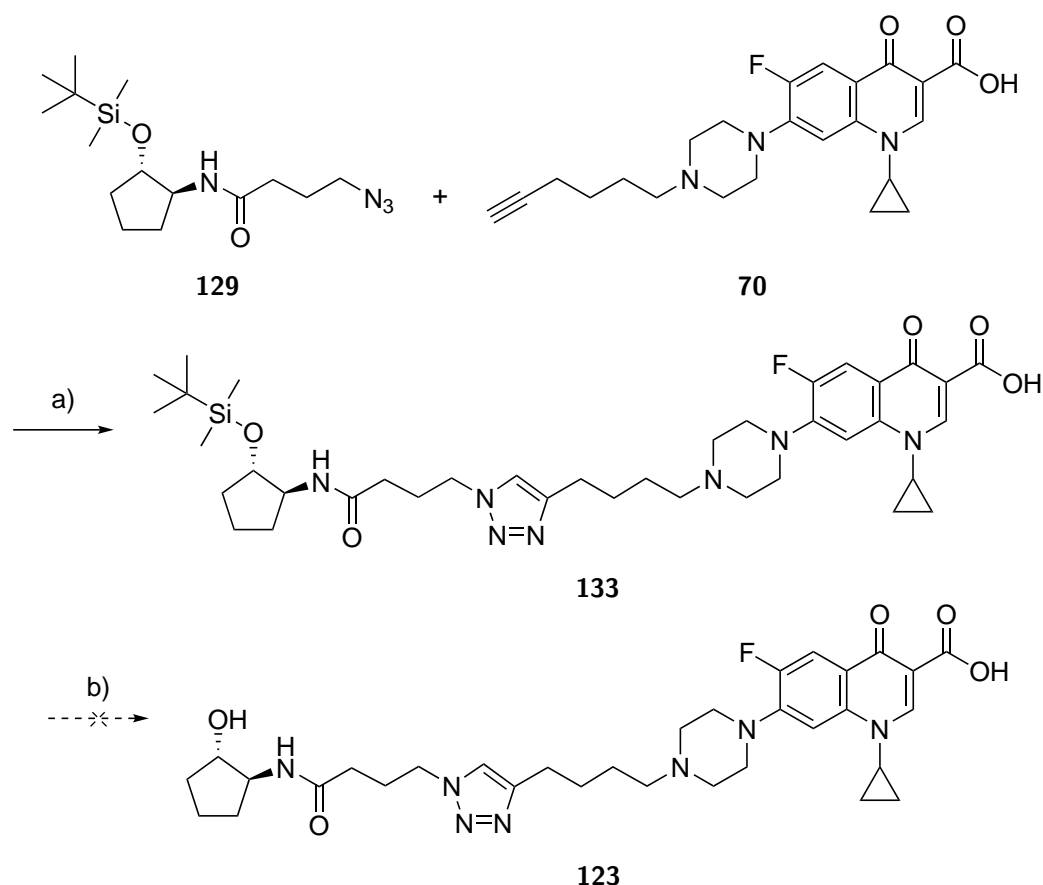
Talk about moving to two-step reaction.

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Scheme 6: a) NaHCO<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, H<sub>2</sub>O, 0 °C, 3 h. b) NaN<sub>3</sub>, DMF, CH<sub>2</sub>Cl<sub>2</sub>, r.t., 3 h. 99.2 % over 2 steps.

$N_3$ -C<sub>4</sub>-cyclopentanol-TBDMS-(*SS*) **129** and the alkynyl ciprofloxacin derivative **70** were subjected to standard click conditions (see ??), and the TBDMS-protected (*SS*)-cyclopentanol-Cip triazole conjugate **133** was synthesised in very good yield. However, removal of the TBDMS group proved difficult. Deprotection using 1.5 eq. TBAF in THF proceeded slowly, reaching completion in 5 d. Increasing the amount of TBAF to 8 eq. allowed the reaction to proceed overnight. Purification of the final conjugate **123** by column chromatography was not successful due to streaking and poor separation. Purification using DOWEX resin and CaCO<sub>3</sub> was attempted, but the product could not be recovered from the resin. The purification method could probably be optimised, e.g. by varying the solvent used with the resin, but ultimately this route was abandoned due to the reduction in number of steps afforded by the two methods described below.

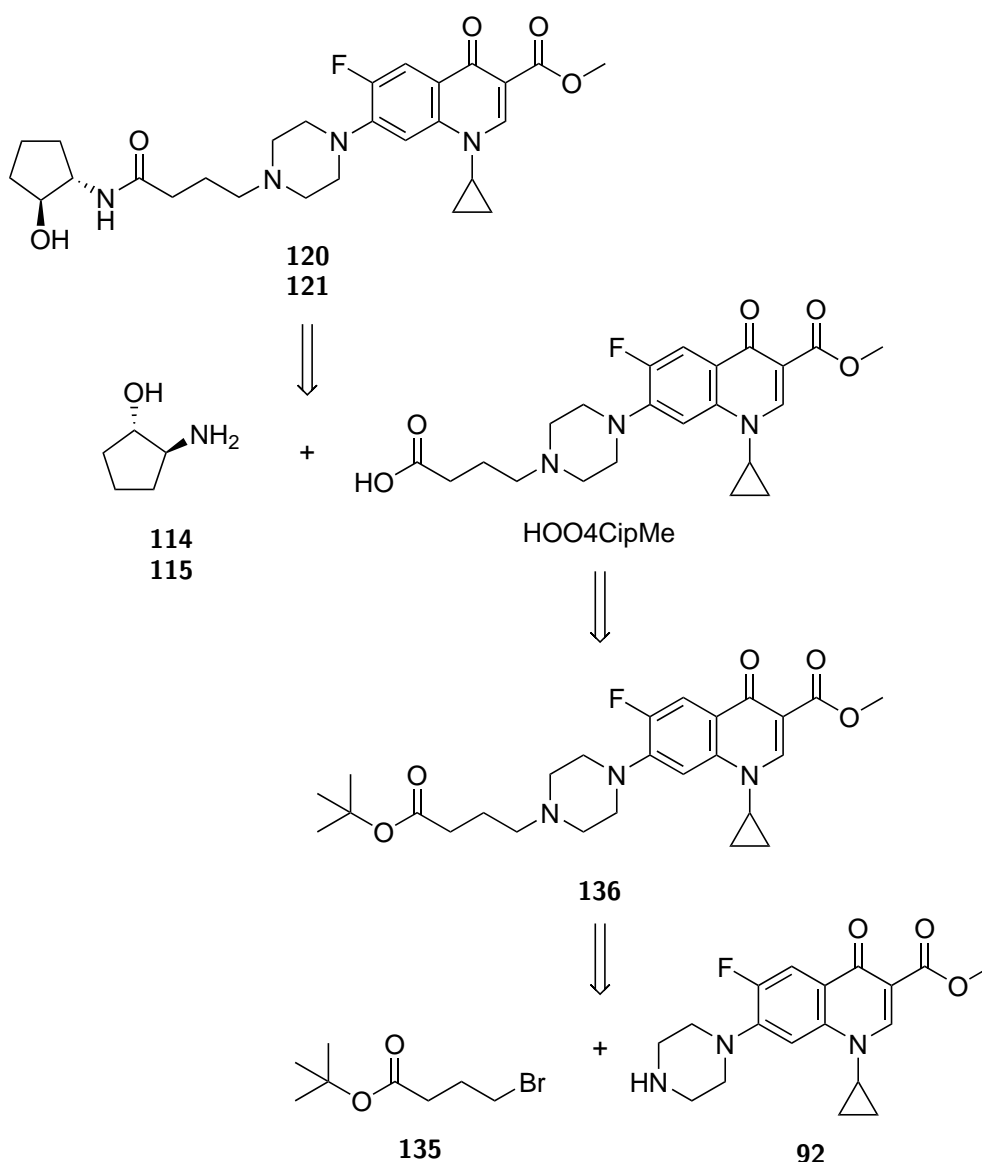


Scheme 7: a) CuSO<sub>4</sub>, sodium ascorbate, THPTA, H<sub>2</sub>O, *t*-BuOH, r.t., 87.4 %. b) TBAF, THF, r.t., 16 h.

#### 0.1.4 Peptide coupling route

Given the side-reactions and low yields associated with the literature synthesis of the S<sub>N</sub>2 conjugates proposed by Ganguly et. al,<sup>11</sup> an alternative synthesis was investigated, involving building up the linker on the ciprofloxacin side before coupling with the head group (see Scheme 8).





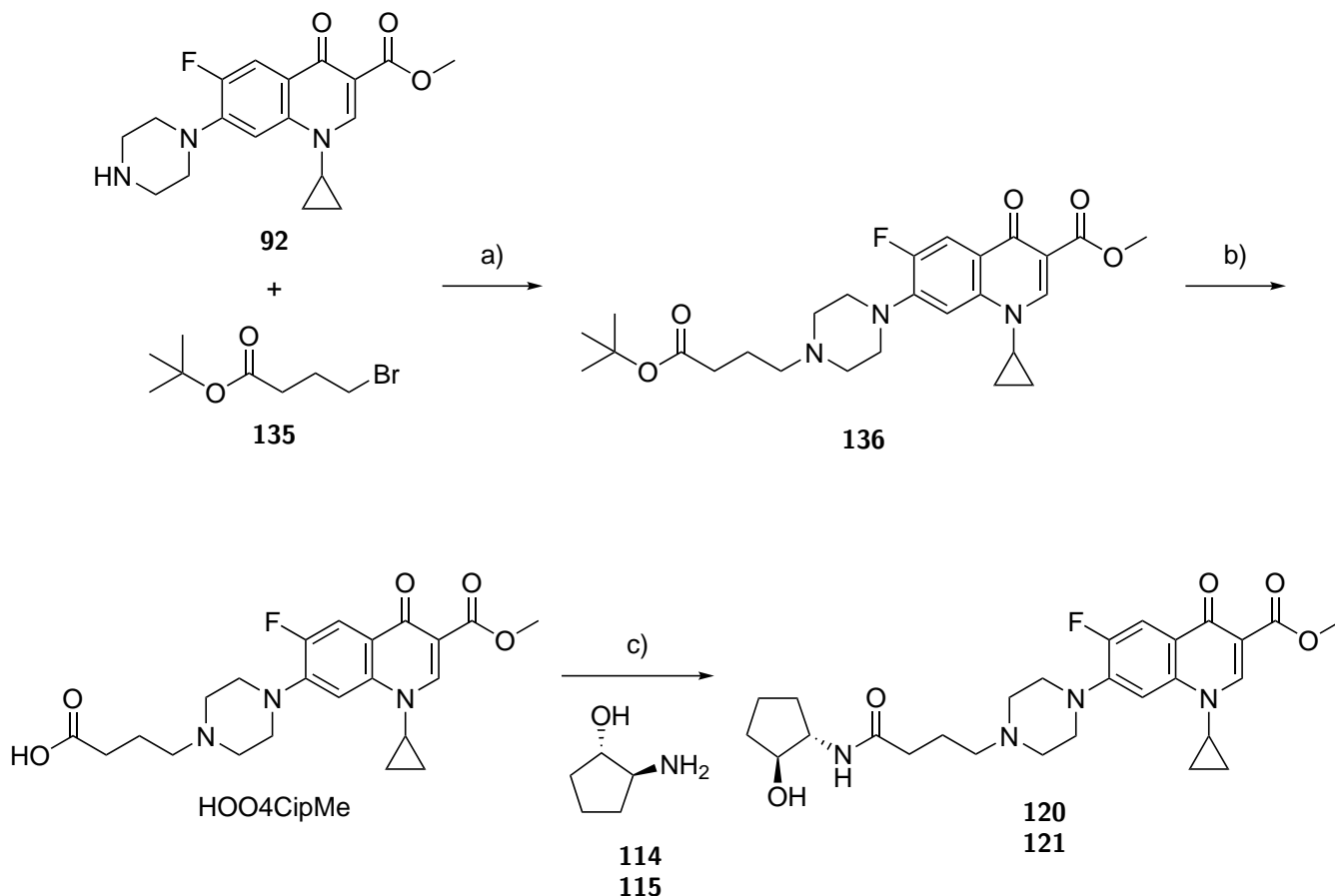
Scheme 8: Retrosynthesis of the cyclopentanol-CipMe conjugates **120** (*SS*) and **121** (*RR*). *SS* enantiomers are shown, but both will be synthesised.

The first step of the synthesis was an  $S_N2$  reaction between Boc-protected 4-bromobutyric acid **135** methyl ciprofloxacin **92** (see Scheme 9). This reaction used fairly harsh conditions (16 h at 100 °C), but early on in the synthesis before the head group was installed. Hence the possibility of side reactions between the bromide and the amine was removed. Intermediate **136** was obtained in acceptable yield after column chromatography (49.9 %). Intermediate **136** was deprotected in excellent yield using TFA in  $\text{CH}_2\text{Cl}_2$  to give carboxylic acid **137**. Scale-up of this reaction allowed the easy synthesis of 600 mg of this useful intermediate, which can be coupled with various amine head-groups to create a library. Carboxylic acid **137** was first coupled with (1*R*,2*R*)-2-aminocyclopentan-1-ol **115** using standard peptide coupling conditions to give cyclopentanol-CipMe conjugate **121**. Purification by column chromatography was attempted twice with poor results, before moving on to using preparative HPLC, which gave **121** cleanly in 38.7 % yield. Coupling was also performed with (1*S*,2*S*)-2-aminocyclopentan-1-ol **114** to give the enantiomer **120** in 54.7 % yield.

Direct comparisons of routes are not possible without repeating syntheses using this new method, but if it is assumed that peptide coupling of homocysteine thiolactone hydrochloride **93** to carboxylic acid **137** would have a similar yield to the coupling with (1*R*,2*R*)-2-aminocyclopentan-1-ol **115**, approximate comparisons can be made. The synthesis described in ?? has an overall yield of 10.7 %, whereas the route shown in Scheme 9 for

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

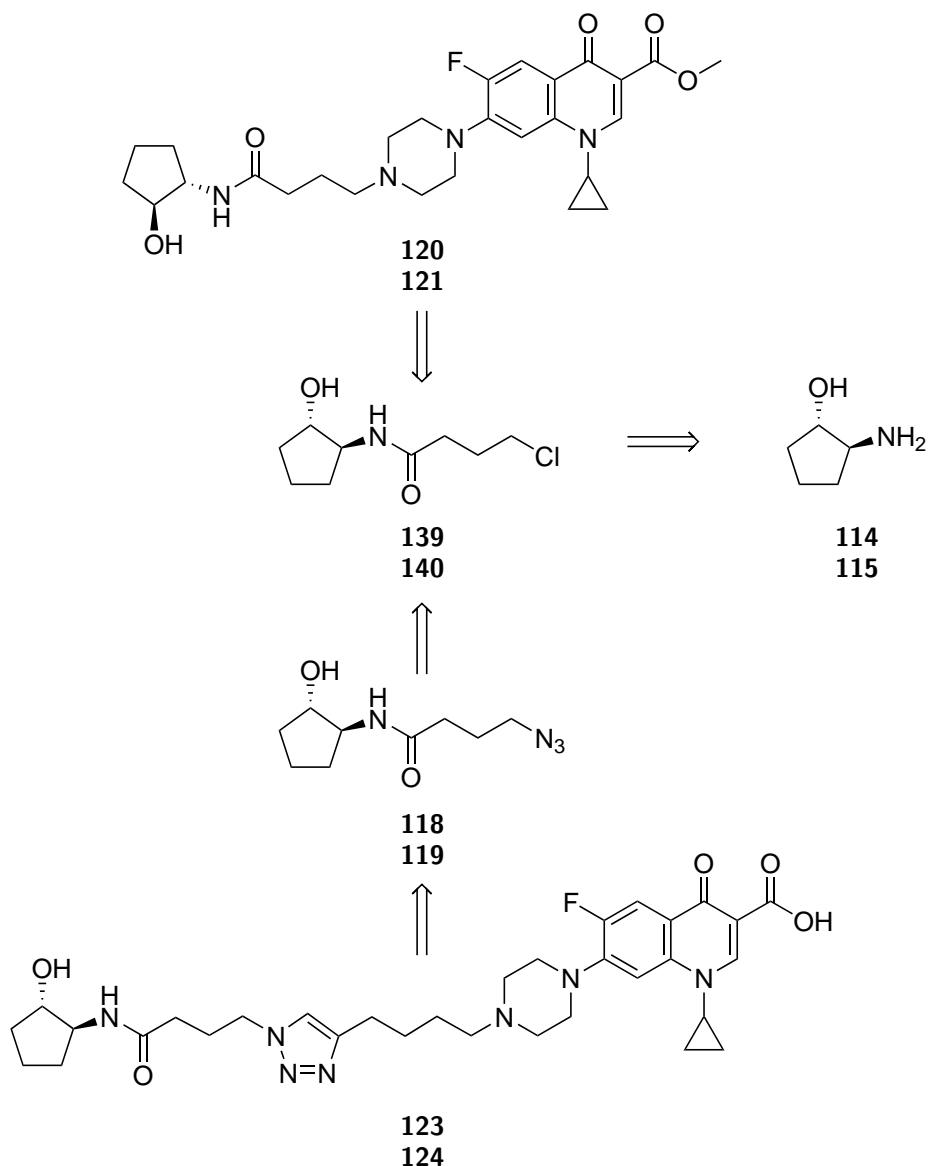
A downside to this route is that it cannot branch towards the triazole-coupled library in the same way that the route in ???. A carboxylic acid intermediate with a triazole in the chain could presumably be synthesised, but this would be rather pointless given that the triazole library was initially proposed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



Scheme 9: Synthesis of the cyclopentanol-CipMe conjugates **120** (*SS*) and **121** (*RR*) by peptide coupling. *SS* enantiomers are shown, but both were synthesised. a) NaI, TEA, acetonitrile, 100 °C, 16 h, 49.9 %. b) TFA, CH<sub>2</sub>Cl<sub>2</sub>, r.t., 18 h, 95.6 %. c) EDC, HOBT, DIPEA, DMF, r.t., 16 h, **120** (*SS*): 54.7 %, **121** (*RR*): 38.7 %.

### 0.1.5 Triazoles from chlorides

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



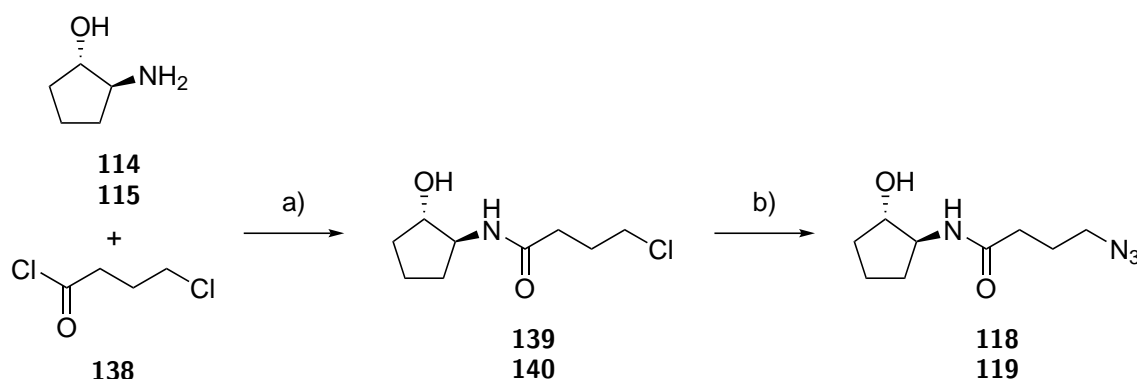
Scheme 10: Retrosynthesis of the cyclopentanol-CipMe conjugates **120** (*SS*) and **121** (*RR*), and the cyclopentanol-Cip triazole conjugates **123** (*SS*) and **124** (*RR*) via Cl-C<sub>4</sub>-cyclopentanol intermediates **139** (*SS*) and **140** (*RR*). *SS* enantiomers are shown, but both will be synthesised.

Attempts at this route began with the synthesis of Cl-C<sub>4</sub>-cyclopentanol-(*RR*) **140**. Standard Schotten-Baumann conditions failed to produce significant amounts of product. If prolonged reaction times were allowed, degradation of the acid chloride to the carboxylic acid was observed. The reason for this is unclear, but it is possible that bromide ions present in small amounts in previous reactions were helping to catalyse the reaction of the acid chloride. Archer et al.<sup>7</sup> propose that bromide ions can react with acid chlorides to form acid bromides, which are then more susceptible to nucleophilic attack. As no bromide ions are present in this reaction, different conditions were sought in order to increase the rate.

As (1*R*,2*R*)-2-aminocyclopentanol-1-ol **115** is fairly polar, it is likely that it was staying in the aqueous layer to some extent even when deprotonated, thus keeping the two reactants apart. Therefore, the solvent system and base were changed to neat CH<sub>2</sub>Cl<sub>2</sub> and TEA. This produced Cl-C<sub>4</sub>-cyclopentanol-(*RR*) **140** in good yield (64.1 %). Unlike the bromide **116**, the chloride **140** was stable when concentrated.

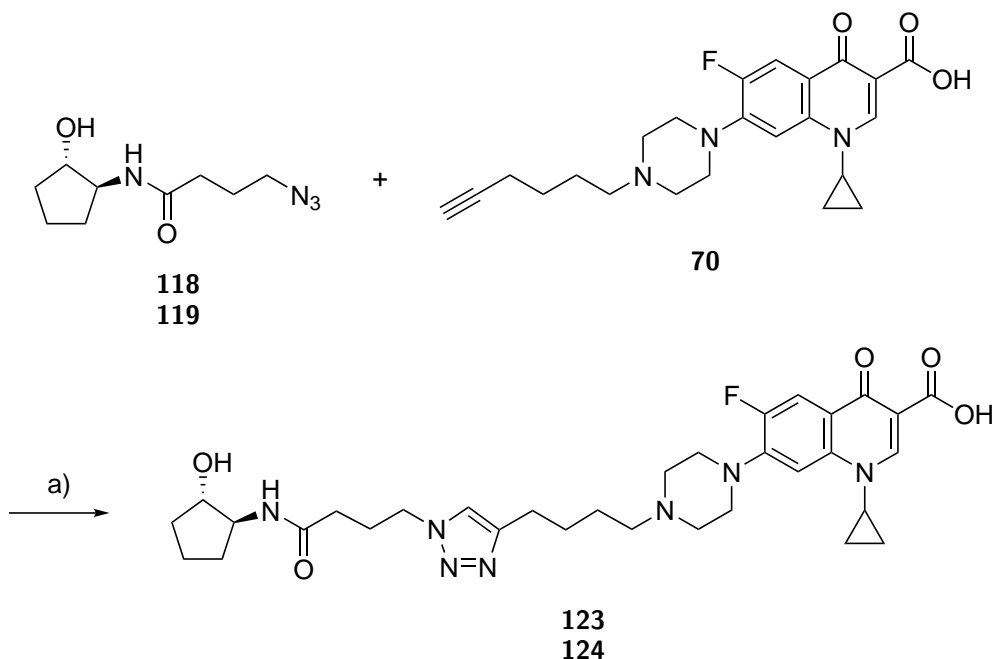
Cl-C<sub>4</sub>-cyclopentanol-(*RR*) **140** was converted to N<sub>3</sub>-C<sub>4</sub>-cyclopentanol-(*RR*) **119** by reaction with sodium azide. The reaction was slower than with previous bromides (~16 h vs. ~2 h), but much cleaner than with Br-C<sub>4</sub>-cyclopentanol-(*SS*) **116** (see 0.1.2).

The enantiomers Cl-C<sub>4</sub>-cyclopentanol-(*SS*) **139** and N<sub>3</sub>-C<sub>4</sub>-cyclopentanol-(*SS*) **118** were synthesised in lower yields, in part because of the smaller amounts being used.



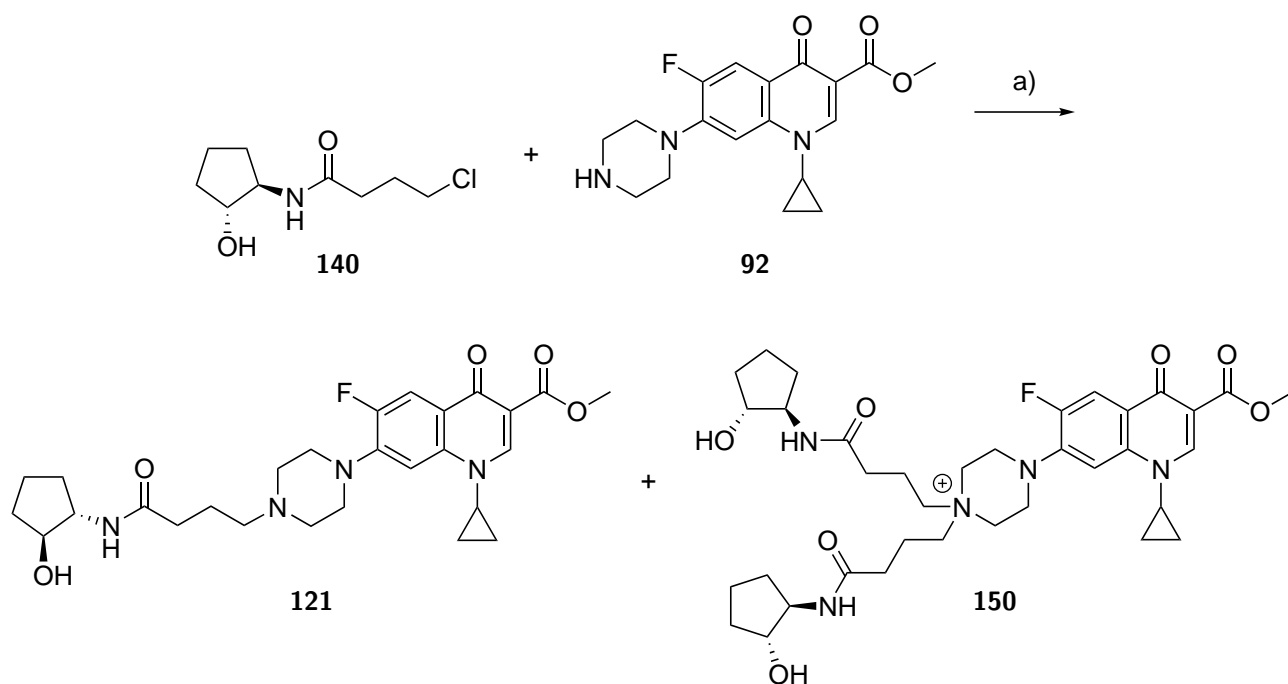
Scheme 11: Synthesis of N<sub>3</sub>-C<sub>4</sub>-cyclopentanol-(*SS*) **118** and N<sub>3</sub>-C<sub>4</sub>-cyclopentanol-(*RR*) **119**. *SS* enantiomers are shown, but both were synthesised. a) TEA, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 2 h, **139** (*SS*): 24.2 %, **140** (*RR*): 64.1 %. b) NaN<sub>3</sub>, acetonitrile, 50 °C, 16 h, **118** (*SS*): 45.0 %, **119** (*RR*): 87.6 %.

The cyclopentanol-Cip triazole conjugates **123** (*SS*) and **124** (*RR*) were synthesised using standard click conditions (see ??). Yields were poor primarily due to problems with purification, including losses on the preparative HPLC column and high polarity leading to losses during extraction from aqueous solvents. However, as enough of the compounds was obtained for biological testing the purification was not optimised further.



Scheme 12: Synthesis of the cyclopentanol-Cip triazole conjugates **123** (*SS*) and **124** (*RR*). *SS* enantiomers are shown, but both were synthesised. a) CuSO<sub>4</sub>, THPTA, sodium ascorbate, H<sub>2</sub>O, *t*-BuOH, r.t., 16 h, **123** (*SS*): 22.2 %, **124** (*RR*): 27.1 %.

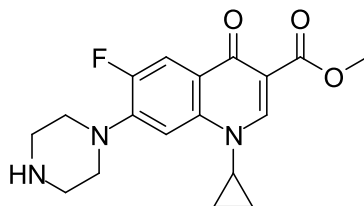
The S<sub>N</sub>2 reaction of Cl-C<sub>4</sub>-cyclopentanol-(*RR*) **140** and methyl ciprofloxacin **92** was attempted (see Scheme 13) using the microwave conditions described previously (see ??), to see if the chloride produced better results compared with the bromide. However, as was seen with the other microwave reactions, a substantial amount of the disubstituted product **149** was seen by LCMS (in an approx 1:1 ratio with the desired product **150**). As a higher-yielding route had already been found (see 0.1.4), this route was abandoned.



Scheme 13: Attempted synthesis of the cyclopentanol-CipMe-(*RR*) conjugate **121**. a) NaI, DIPEA, acetonitrile, microwave reactor, 100 °C.

With (unfortunately not branching) routes to the  $S_N2$  and click conjugates established (see 0.1.4 and 0.1.5 respectively), attention was turned to the cyclohexanol derivatives.

## 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>)

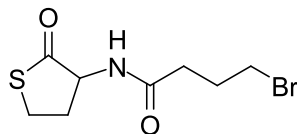
**<sup>13</sup>C NMR** (101 MHz, MeOD)  $\delta$  / ppm = 175.2 (C(=O)CC(=O)OCH<sub>3</sub>), 166.8 (C(=O)OCH<sub>3</sub>), 154.9 (d,  $J$  = 248.0 Hz, *ipso* to F), 150.1 (C=CC(=O)OCH<sub>3</sub>), 146.6 (d,  $J$  = 10.4 Hz, *ipso* to piperazine), 139.9 (*para* to F), 123.3 (d,  $J$  = 6.9 Hz, *para* 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>10</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)

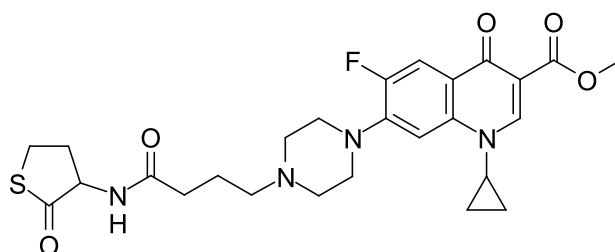
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  / ppm = 6.08 (d,  $J$  = 6.1 Hz, 1 H, NH), 4.54 (dt,  $J$  = 12.9, 6.5 Hz, 1 H, CHNH), 3.49 (t,  $J$  = 6.4 Hz, 2 H, CH<sub>2</sub>Br), 3.37 (ddd,  $J$  = 12.2, 11.5, 5.3 Hz, 1 H, SCHH), 3.26 (ddd,  $J$  = 11.5, 6.9, 1.3 Hz, 1 H, SCHH), 2.91 (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>11,12</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 preparative HPLC (5-95 % acetonitrile/water over 20 min). **95** was obtained as a cream-coloured amorphous solid (9.4 mg, 0.018 mmol, 12.2 %).

**TLC**  $R_f$  = 0.47 (10 % MeOH/CH<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)

works  
in  
LCMS  
see  
Lois283

**<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, 1 H, SCHH), 3.26 - 3.33 (m, 5 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>)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>)

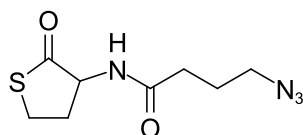
**<sup>13</sup>C NMR** (126 MHz, MeOD)  $\delta$  / ppm = 207.0 (SC(=O)), 175.7 (NHC(=O)), 175.1 (C(=O)CC(=O)OCH<sub>3</sub>), 166.6 (C(=O)OCH<sub>3</sub>), 154.7 (d,  $J$  = 249.0 Hz, *ipso* to F), 150.2 (s, CH=CC(=O)OCH<sub>3</sub>), 145.6 (d,  $J$  = 10.6 Hz, *ipso* to piperazine), 139.8 (*para* to 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>)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>11,12</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, 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>)

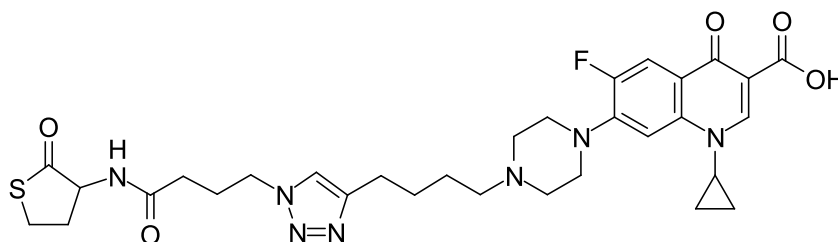


$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  / ppm = 205.4 ( $\text{SC}(=\text{O})$ ), 172.3 ( $\text{NHC}(=\text{O})$ ), 59.4 ( $\text{CHNH}$ ), 50.6 ( $\text{CH}_2\text{N}_3$ ), 32.8 ( $\text{C}(=\text{O})\text{CH}_2$ ), 31.8 ( $\text{SCH}_2\text{CH}_2$ ), 27.5 ( $\text{SCH}_2$ ), 24.6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

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 preparative 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,  $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)\text{CH}_2$ ), 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,  $J$

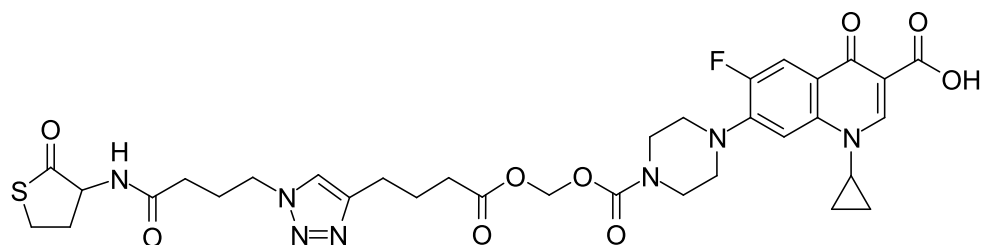
= 10.1 Hz, *ipso* to piperazine), 139.2 (*para* to F), 121.8 ( $\underline{\text{CH}}=\text{CCH}_2$ ), 118.6 (d,  $J = 7.7$  Hz, *para* to piperazine), 111.0 (d,  $J = 23.3$  Hz, *ortho* to C=O and *ortho* to F), 106.7 ( $\underline{\text{C}}\text{C}(=\text{O})\text{OH}$ ), 106.4 (d,  $J = 2.9$  Hz,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

$^{19}\text{F}$  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

The compound has not been reported previously.

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



1-Cyclopropyl-6-fluoro-7-(4-(((hex-5-ynoyloxy)methoxy)carbonyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **98** (203 mg, 0.407 mmol, 1 eq.), 4-azido-*N*-(2-oxotetrahydrothiophen-3-yl)butanamide **96** (92.8 mg, 0.407 mmol, 1 eq.), CuI (40 mg, 0.190 mmol, 0.5 eq.) and DIPEA (0.356 ml, 0.264 mg, 2.04 mmol, 5 eq.) were stirred in  $\text{CH}_2\text{Cl}_2$  (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)

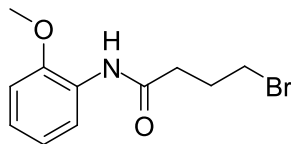
$^1\text{H}$  NMR (400 MHz, DMSO  $d_6$ )  $\delta$  / ppm = 15.16 (br s, 1 H,  $\text{C}(=\text{O})\text{OH}$ ), 8.65 (s, 1 H, *ortho* to  $\text{C}(=\text{O})\text{OH}$ ), 8.21 (d,  $J = 8.5$  Hz, 1 H,  $\underline{\text{NH}}$ ), 7.89 (d,  $J = 13.1$  Hz, 1 H, *ortho* to F), 7.85 (s, 1 H,  $\underline{\text{CH}}=\text{CCH}_2$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

**<sup>13</sup>C NMR** (101 MHz, DMSO d<sub>6</sub>)  $\delta$  / ppm = 205.5 (SC(=O)), 176.4 (C(=O)CC(=O)OH), 171.8 (C(=O)OCH<sub>2</sub>O), 171.3 (NHC(=O)), 165.9 (C(=O)OH), 152.8 (d,  $J$  = 249.7 Hz, *ipso* to F), 152.9 (OC(=O)N), 148.1 (CH=CC(=O)OH), 146.0 (CH=CCH<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)

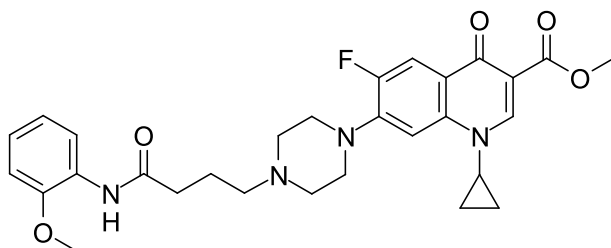
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub> d<sub>1</sub>)  $\delta$  / ppm = 8.32 (dd,  $J$  = 8.0, 1.7 Hz, 1 H, *ortho* to NH), 7.85 (br s, 1 H, NH), 7.02 (td,  $J$  = 7.9, 1.7 Hz, 1 H, *para* to NH), 6.93 (td,  $J$  = 7.7, 1.4 Hz, 1 H, *para* to OCH<sub>3</sub>), 6.85 (dd,  $J$  = 8.1, 1.5 Hz, 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 amorphous solid (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)

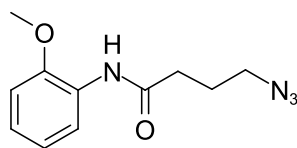
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub> d<sub>1</sub>)  $\delta$  / ppm = 8.48 (s, 1 H, *ortho* to C(=O)OCH<sub>3</sub>), 8.36 (d,  $J$  = 7.9 Hz, 1 H, *ortho* to NH), 7.87 - 7.99 (m, 2 H, *ortho* to F and NH), 7.19 (d,  $J$  = 6.5 Hz, 1 H, *meta* to F), 7.01 (t,  $J$  = 7.5 Hz, 1 H, *para* 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 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>), 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)

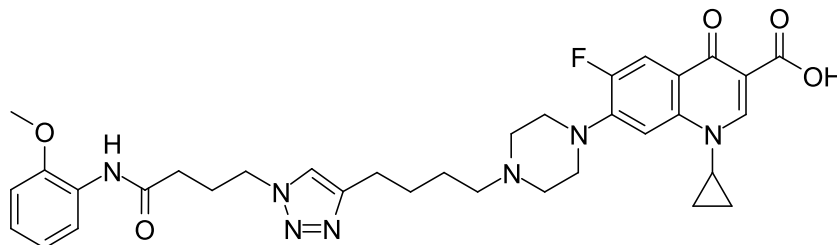
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub> d<sub>1</sub>)  $\delta$  / ppm = 8.32 (dd,  $J$  = 7.9, 1.0 Hz, 1 H, *ortho* to NH), 7.86 (br s, 1 H, NH), 7.00 (td,  $J$  = 7.5, 1.5 Hz, 1 H, *para* to NH), 6.90 (td,  $J$  = 7.7, 1.1 Hz, 1 H, *para* to OCH<sub>3</sub>), 6.83 (dd,  $J$  = 8.1, 1.4 Hz, 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>13</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 amorphous solid (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,  $\text{CH}=\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)\text{CH}_2$ ), 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,  $\text{NCH}(\text{CH}_2)_2$ )

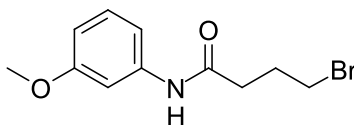
**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  / ppm = 177.1 (C(=O)CC(=O)OH), 169.5 ( $\text{NHC}(=\text{O})$ ), 167.0 (C(=O)OH), 153.7 (d,  $J$  = 251.4 Hz, *ipso* to F), 148.1 ( $\text{CH}=\text{CCH}_2$ ), 147.8 (*ipso* to  $\text{OCH}_3$ ), 147.3 (C=CC(=O)OH), 145.9 (d,  $J$  = 10.4 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 ( $\text{CH}=\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)\text{CH}_2$ ), 49.8 ( $\text{CH}=\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)\text{CH}_2\text{CH}_2$ ), 49.8 ( $\text{CH}=\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)\text{CH}_2\text{CH}_2$ ), 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)

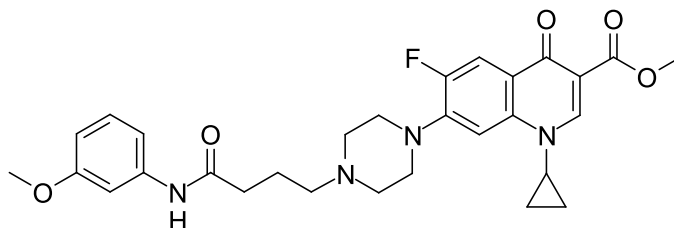
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub> d<sub>1</sub>)  $\delta$  / ppm = 8.45 (s, 1 H, NH), 7.27 (t,  $J$  = 2.2 Hz, 1 H, *ortho* to OCH<sub>3</sub> and *ortho* to NH), 7.14 (t,  $J$  = 8.1 Hz, 1 H, *meta* to OCH<sub>3</sub> and *meta* to NH), 7.02 (d,  $J$  = 8.3 Hz, 1 H, *para* to OCH<sub>3</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 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 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>), 2.58 (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>)

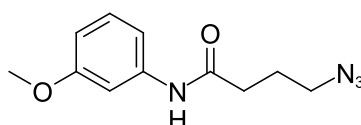
**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  / ppm = 173.1 (C(=O)CC(=O)OCH<sub>3</sub>), 170.9 (NHC(=O)), 166.3 (C(=O)OCH<sub>3</sub>), 160.1 (*ipso* to OCH<sub>3</sub>), 153.3 (d,  $J$  = 250.1 Hz, *ipso* to F), 148.4 (C=CC(=O)OCH<sub>3</sub>), 144.1 (d,  $J$  = 10.1 Hz, *ipso* to 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>), 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>),



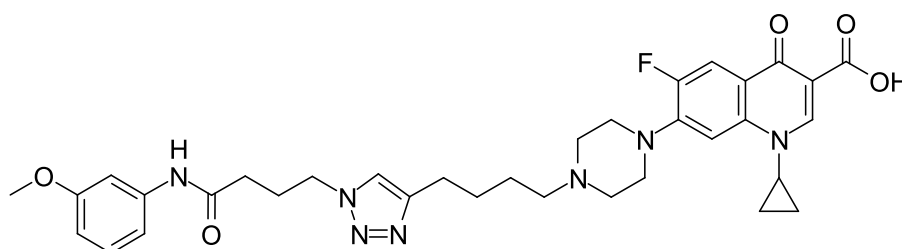
2.39 (t,  $J = 7.4$  Hz, 2 H, C(=O)CH<sub>2</sub>), 1.91 (quin,  $J = 7.0$  Hz, 2 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>)

<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 amorphous solid (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>)

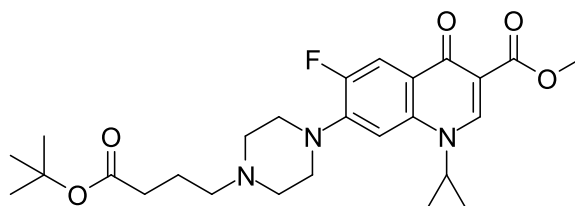
**<sup>13</sup>C NMR** (101 MHz, DMSO d<sub>6</sub>) δ / ppm = 176.3 (C(=O)CC(=O)OH), 170.1 (NHC(=O)), 165.9 (C(=O)OH), 159.4 (*ipso* to OCH<sub>3</sub>), 153.0 (d, *J* = 248.6 Hz, *ipso* to F), 148.0 (CH=CCH<sub>2</sub>), 146.9 (C=CC(=O)OH), 145.2 (d, *J* = 10.7 Hz, *ipso* to piperazine), 140.3 (*para* 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 **151** (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>)

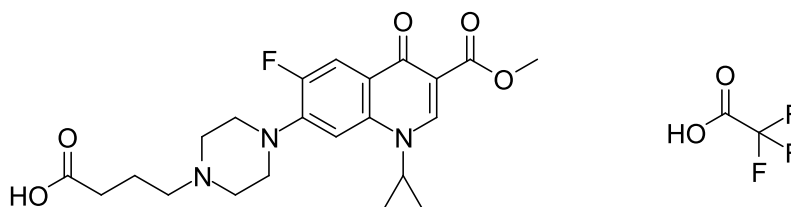
**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  / ppm = 172.7 ( $\text{C}(=\text{O})\text{CC}(=\text{O})\text{OCH}_3$ ), 172.6 ( $\text{C}(=\text{O})\text{OC}(\text{CH}_3)_3$ ), 165.9 ( $\text{C}(=\text{O})\text{OCH}_3$ ), 153.1 (d,  $J$  = 249.7 Hz, *ipso* to F), 148.1 ( $\text{C}=\text{CC}(=\text{O})\text{OCH}_3$ ), 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,  $\text{NCH}(\text{CH}_2)_2$ )

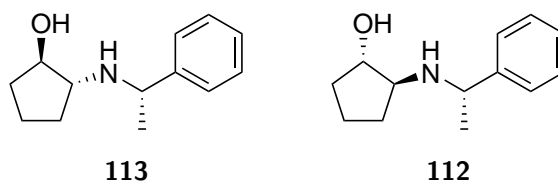
**$^{13}\text{C}$  NMR** (101 MHz,  $\text{DMSO}-d_6$ )  $\delta$  / ppm = 173.5 ( $\text{CH}_2\text{C}(=\text{O})\text{OH}$ ), 171.6 ( $\text{C}(=\text{O})\text{CC}(=\text{O})\text{OCH}_3$ ), 164.9 ( $\text{C}(=\text{O})\text{OCH}_3$ ), 158.2 (q,  $J$  = 31.5 Hz,  $\text{CF}_3\text{C}(=\text{O})\text{OH}$ ), 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, lit. = -76.8 ( $c$  /  $\text{g}(100\text{ ml})^{-1}$  = 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, 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,  $\text{CHHCHNH}$ )

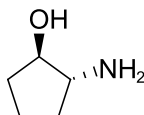
**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  / ppm = 145.61 (*ipso* to  $\text{CHCH}_3$ ), 128.08 (*meta* to  $\text{CHCH}_3$ ), 126.61 (*para* to  $\text{CHCH}_3$ ), 126.33 (*ortho* to  $\text{CHCH}_3$ ), 77.43 ( $\text{CHOH}$ ), 64.45 ( $\text{CHNH}$ ), 56.62 ( $\text{CHCH}_3$ ), 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, lit. = -22.1 ( $c$  /  $\text{g(100 ml)}^{-1}$  = 0.96, MeOH)

The compounds have been synthesised previously,<sup>14,15</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 above data.<sup>16</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, 5.6 Hz, 1 H,  $\text{CHHCHNH}_2$ ), 1.97 (ddt,  $J$  = 13.0, 8.7, 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 Hz, 1 H,  $\text{CHHCHOH}$ ), 1.37 (ddt,  $J$  = 13.0, 8.3, 7.8 Hz, 1 H,  $\text{CHHCHNH}_2$ )

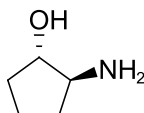
$^{13}\text{C}$  NMR (101 MHz, MeOD)  $\delta$  / ppm = 80.7 ( $\underline{\text{C}}\text{HOH}$ ), 60.8 ( $\underline{\text{C}}\text{HNH}_2$ ), 33.2 ( $\underline{\text{C}}\text{H}_2\text{CHOH}$ ), 32.1 ( $\underline{\text{C}}\text{H}_2\text{CHNH}_2$ ), 21.2 ( $\underline{\text{C}}\text{H}_2\text{CH}_2\text{CHOH}$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

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

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

The data are consistent with the literature.<sup>15,17</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) $_2$  (20 wt. % on C, moistened with 50 wt. % water, 0.5 g, 0.356 mmol, 0.025 eq.) and MeOH (50 ml) were stirred in a Paar hydrogenator at r.t. and 2.5 atm for 2 days. The mixture was then filtered through Celite and evaporated under reduced pressure. **114** was obtained as a yellow oil (1.48 g, 14.6 mmol, 100 %).

TLC  $R_f$  = 0.10 (10 % MeOH/ $\text{CH}_2\text{Cl}_2$ )

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, 5.6 Hz, 1 H,  $\underline{\text{C}}\text{HHCHNH}_2$ ), 1.97 (ddt,  $J$  = 13.0, 8.7, 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 Hz, 1 H,  $\underline{\text{C}}\text{HHCHOH}$ ), 1.37 (ddt,  $J$  = 12.8, 8.5, 7.7 Hz, 1 H,  $\underline{\text{C}}\text{HHCHNH}_2$ )

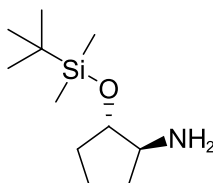
$^{13}\text{C}$  NMR (101 MHz, MeOD)  $\delta$  / ppm = 80.6 ( $\underline{\text{C}}\text{HOH}$ ), 60.7 ( $\underline{\text{C}}\text{HNH}_2$ ), 33.2 ( $\underline{\text{C}}\text{H}_2\text{CHOH}$ ), 32.2 ( $\underline{\text{C}}\text{H}_2\text{CHNH}_2$ ), 21.2 ( $\underline{\text{C}}\text{H}_2\text{CH}_2\text{CHOH}$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

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

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

The data are consistent with the literature.<sup>15,17</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)

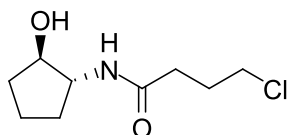
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  / ppm = 4.13 (q,  $J$  = 5.8 Hz, 1 H, CHOSi), 3.31 (td,  $J$  = 7.1, 5.2 Hz, 1 H, CHNH<sub>2</sub>), 2.09 - 2.19 (m, 1 H, CHHCHNH<sub>2</sub>), 1.97 (ddq,  $J$  = 8.8, 7.0, 6.0 Hz, 1 H, CHHCHOSi), 1.74 - 1.86 (m, 2 H, CH<sub>2</sub>CH<sub>2</sub>CHOSi), 1.64 - 1.74 (m, 1 H, CHHCHOSi), 1.58 (ddt,  $J$  = 13.2, 9.1, 6.0 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 **140**



(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 **138** (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. **140** 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)

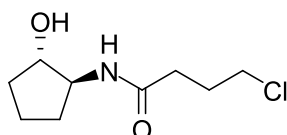
**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  / ppm = 173.8 ( $\text{C}=\text{O}$ ), 79.4 ( $\text{CHOH}$ ), 60.6 ( $\text{CHNH}$ ), 44.4 ( $\text{CH}_2\text{Cl}$ ), 32.8 ( $\text{CH}_2\text{C}=\text{O}$ ), 32.4 ( $\text{CH}_2\text{CHOH}$ ), 30.1 ( $\text{CH}_2\text{CHNH}$ ), 28.0 ( $\text{CH}_2\text{CH}_2\text{Cl}$ ), 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 **139**



(1*S*,2*S*)-2-Aminocyclopentan-1-ol **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 **138** (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. **139** was obtained as a white amorphous solid (35.6 mg, 173  $\mu\text{mol}$ , 24.2 %).

**TLC**  $R_f$  = 0.35 (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,  $\text{CH}_2\text{C}=\text{O}$ ), 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 ( $\text{C}=\text{O}$ ), 79.4 ( $\text{CHOH}$ ), 60.6 ( $\text{CHNH}$ ), 44.4 ( $\text{CH}_2\text{Cl}$ ), 32.8 ( $\text{CH}_2\text{C}=\text{O}$ ), 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 ( $\text{CH}_2\text{CH}_2\text{CHOH}$ )

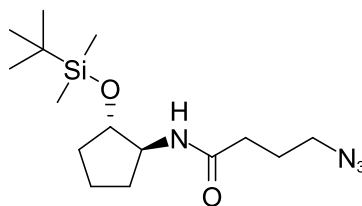
**HRMS** ( $\text{ESI}^+$ )  $m/z$  / Da = 206.0939,  $[\text{M}+\text{H}]^+$  found,  $[\text{C}_9\text{H}_{17}\text{ClNO}_2]^+$  requires 206.0948

$[\alpha]_D^{20}$  /  $^{\circ}\text{10}^{-1}\text{cm}^2\text{g}^{-1}$  = 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>)

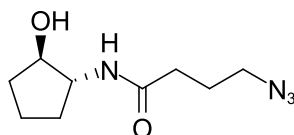
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  / ppm = 171.17 (C=O), 77.80 (CHOSi), 58.36 (CHNH), 50.77 (CH<sub>2</sub>N<sub>3</sub>), 33.29 (CH<sub>2</sub>C=O), 32.57 (CH<sub>2</sub>CHOSi), 29.36 (CH<sub>2</sub>CHNH), 25.72 (C(CH<sub>3</sub>)<sub>3</sub>), 24.77 (CH<sub>2</sub>CH<sub>2</sub>N<sub>3</sub>), 20.40 (CH<sub>2</sub>CH<sub>2</sub>CHOSi), 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 **140** (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, 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, 4.9 Hz, 1 H, CHHCHNH), 1.92 (dtd,  $J$  = 13.0, 7.6, 5.8 Hz, 1 H, CHHCHOH), 1.84 (quin,  $J$  = 7.0 Hz, 2 H, CH<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 Hz, 1 H, CHHCHOH), 1.39 (dq,  $J$  = 12.9, 8.4 Hz, 1 H, CHHCHNH)

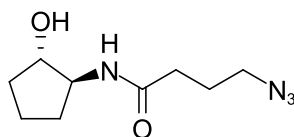
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  / ppm = 173.8 (C=O), 78.8 (CHOH), 59.9 (CHNH), 50.5 (CH<sub>2</sub>N<sub>3</sub>), 32.5 (CH<sub>2</sub>C=O), 32.0 (CH<sub>2</sub>CHOH), 29.5 (CH<sub>2</sub>CHNH), 24.6 (CH<sub>2</sub>CH<sub>2</sub>N<sub>3</sub>), 20.7 (CH<sub>2</sub>CH<sub>2</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 **139** (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, 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)

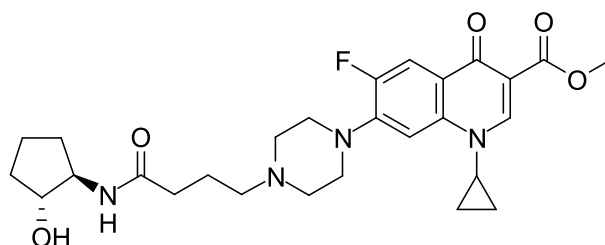
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  / ppm = 173.8 (C=O), 79.7 (CHOH), 61.0 (CHNH), 50.7 (CH<sub>2</sub>N<sub>3</sub>), 32.8 (CH<sub>2</sub>C=O), 32.6 (CH<sub>2</sub>CHOH), 30.5 (CH<sub>2</sub>CHNH), 24.7 (CH<sub>2</sub>CH<sub>2</sub>N<sub>3</sub>), 21.3 (CH<sub>2</sub>CH<sub>2</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 preparative 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,  $\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2)\text{CH}_2$ ), 1.54 - 1.65 (m, 2 H,  $\text{CH}_2\text{CH}_2\text{CHOH}$ ), 1.42 (ddt,  $J = 13.1, 8.2, 5.3$  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 ( $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2)\text{CH}_2$ ), 51.3 ( $\text{CH}_3$ ), 49.6 ( $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)\text{CH}_2\text{CH}_2$ ), 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 ( $\text{NCH}(\text{CH}_2)_2$ )

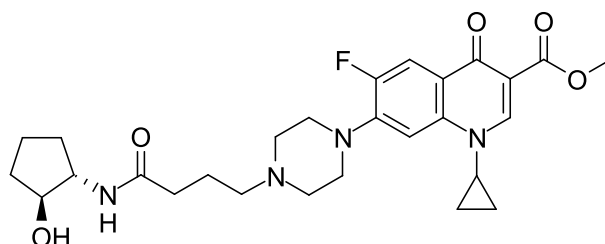
$^{19}\text{F}$  NMR (376.45 MHz, DMSO  $d_6$ )  $\delta$  / ppm = -124.3 (ciprofloxacin F)

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 preparative 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 (26.9 mg, 52.3  $\mu\text{mol}$ , 54.7 %).

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,  $J = 4.2$  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,  $J = 5.0$  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,  $J = 12.6, 8.9, 6.3$  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,  $J = 12.9, 8.4, 5.2$  Hz, 1 H, CHHCHOH), 1.31 (ddt,  $J = 13.0, 8.6, 6.4$  Hz, 1 H, CHHCHNH), 1.22 - 1.28 (m, 2 H, NCH(CHH)<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>)  $\delta$  / 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>)

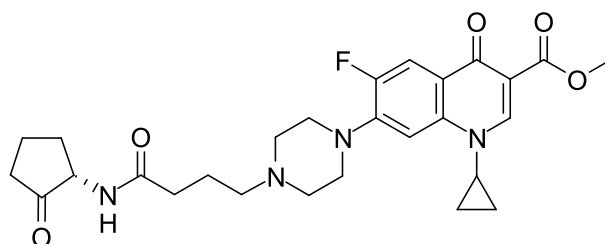
<sup>19</sup>F NMR (376.45 MHz, MeOD)  $\delta$  / ppm = -125.5

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

$[\alpha]_D^{20}$  / °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  $\mu$ mol, 1 eq.) and Dess-Martin periodinane (32.8 mg, 77.4  $\mu$ mol, 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 preparative 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  $\mu$ mol, 56.7 %).

<sup>1</sup>H NMR (500 MHz, DMSO d<sub>6</sub>)  $\delta$  / 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>)

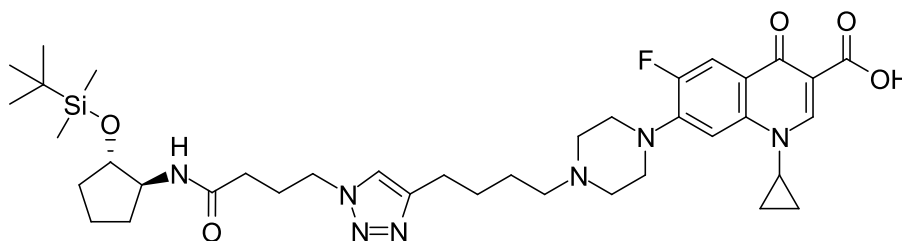
<sup>19</sup>F NMR (376.45 MHz, MeOD) δ / ppm = -124.3

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 amorphous solid (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>)

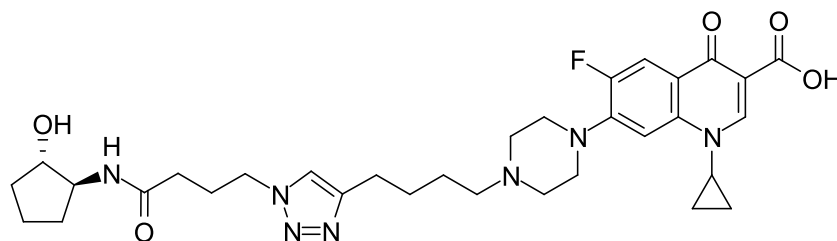
**<sup>19</sup>F NMR** (376.45 MHz, MeOD)  $\delta$  / ppm = -122.1 (s, ciprofloxacin F)

**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 preparative 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 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 Hz, 1 H, CHHCHOH), 1.28 - 1.35 (m, 2 H, NCH(CH<sub>2</sub>)<sub>2</sub>), 1.24 - 1.31 (m, 1 H, CHHCHNH), 1.15 - 1.21 (m, 2 H, NCH(CH<sub>2</sub>)<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>)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>)

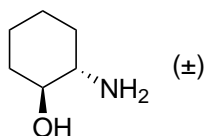
**<sup>19</sup>F NMR** (376.45 MHz, MeOD)  $\delta$  / ppm = -121.5

**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 **142**



Cyclohexene oxide **141** (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. **142** 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)

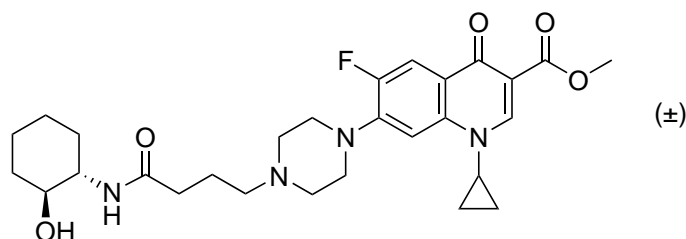
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  / ppm = 3.01 (td,  $J$  = 9.4, 4.8 Hz, 1 H, CHOH), 2.80 - 2.92 (m, 2 H, OH and NH<sub>2</sub>), 2.35 (ddd,  $J$  = 11.1, 9.1, 4.1 Hz, 1 H, CHNH<sub>2</sub>), 1.77 - 1.84 (m, 1 H, CHHCHOH), 1.69 - 1.76 (m, 1 H, CHHCHNH<sub>2</sub>), 1.56 - 1.66 (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>CHNH<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>18</sup>

### 0.34 Methyl 1-cyclopropyl-6-fluoro-7-(4-(4-(((*trans*)-2-hydroxycyclohexyl)amino)-4-oxobutyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate **143**



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 **142** (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 preparative 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. **143** was obtained as a white amorphous solid (61.2 mg, 0.116 mmol, 31.7 %).

**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,  $\text{CHHCH}_2\text{CHOH}$ ), 1.66 - 1.72 (m, 1 H,  $\text{CHHCH}_2\text{CHNH}$ ), 1.25 - 1.39 (m, 5 H,  $\text{CHHCHOH}$ ,  $\text{CHHCH}_2\text{CHOH}$ ,  $\text{CHHCH}_2\text{CHNH}$  and  $\text{NCH}(\text{CHH})_2$ ), 1.15 - 1.25 (m, 3 H,  $\text{CHHCHOH}$  and  $\text{NCH}(\text{CHH})_2$ )

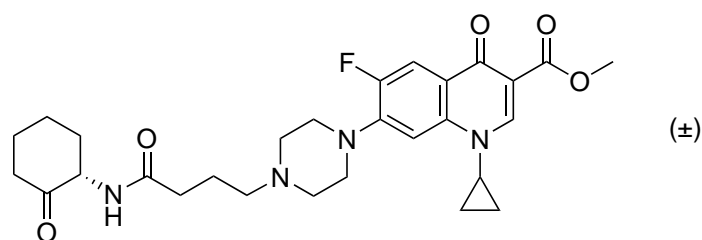
$^{13}\text{C}$  NMR (101 MHz, MeOD)  $\delta$  / ppm = 175.8 ( $\text{CH}_2\text{C}(=\text{O})\text{NH}$ ), 175.3 ( $\text{C}(=\text{O})\text{CC}(=\text{O})\text{OCH}_3$ ), 166.8 ( $\text{C}(=\text{O})\text{OCH}_3$ ), 154.9 (d,  $J$  = 248.8 Hz, *ipso* to F), 150.2 ( $\text{C}=\text{CC}(=\text{O})\text{OCH}_3$ ), 146.1 (d,  $J$  = 10.8 Hz, *ipso* to piperazine), 139.9 (*para* to F), 123.5 (d,  $J$  = 7.5 Hz, *para* to piperazine), 113.2 (d,  $J$  = 23.2 Hz, *ortho* to C=O and *ortho* to F), 110.2 ( $\text{CC}(=\text{O})\text{OCH}_3$ ), 107.2 (*meta* to C=O and *meta* to F), 74.1 ( $\text{CHOH}$ ), 58.9 ( $\text{C}(=\text{O})\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$ ), 56.4 ( $\text{CHNH}$ ), 54.0 ( $\text{C}(=\text{O})\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)\text{CH}_2\text{CH}_2$ ), 52.3 ( $\text{CH}_3$ ), 50.5 (d,  $J$  = 5.0 Hz,  $\text{C}(=\text{O})\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)\text{CH}_2\text{CH}_2$ ), 36.4 ( $\text{NCH}(\text{CH}_2)_2$ ), 35.7 ( $\text{CH}_2\text{CHOH}$ ), 35.1 ( $\text{C}(=\text{O})\text{CH}_2$ ), 32.8 ( $\text{CH}_2\text{CHNH}$ ), 25.9 ( $\text{CH}_2\text{CH}_2\text{CHNH}$ ), 25.5 ( $\text{CH}_2\text{CH}_2\text{CHOH}$ ), 23.5 ( $\text{C}(=\text{O})\text{CH}_2\text{CH}_2$ ), 8.7 ( $\text{NCH}(\text{CH}_2)_2$ )

$^{19}\text{F}$  NMR (376.45 MHz, MeOD)  $\delta$  / ppm = -124.7 (ciprofloxacin F)

HRMS (ESI<sup>+</sup>)  $m/z$  / Da = 529.2827,  $[\text{M}+\text{H}]^+$  found,  $[\text{C}_{28}\text{H}_{38}\text{FN}_4\text{O}_5]^+$  requires 529.2826

The compound has not been reported previously.

### 0.35 Methyl 1-cyclopropyl-6-fluoro-4-oxo-7-(4-(4-oxo-4-((2-oxocyclohexyl)amino)-butyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate **144**



Methyl 1-cyclopropyl-6-fluoro-7-(4-(4-(((*trans*)-2-hydroxycyclohexyl)amino)-4-oxobutyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate **143** (5.2 mg, 9.84  $\mu\text{mol}$ , 1 eq.) and Dess-Martin periodinane (16.4 mg, 38.7  $\mu\text{mol}$ , 4 eq.) were stirred in  $\text{CH}_2\text{Cl}_2$  (3 ml) at r.t. for 6 h. The solvent was removed under reduced pressure and the residue was purified by preparative HPLC (5-95 % acetonitrile/water over 20 min). The combined pure fractions were evaporated under reduced pressure to a volume of 20 ml, then  $\text{NaHCO}_3$  (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. **144** was obtained as a white amorphous solid (3.6 mg, 6.8  $\mu\text{mol}$ , 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  $\text{C}(=\text{O})\text{OCH}_3$ ), 7.87 (d,  $J$  = 6.2 Hz, 1 H,  $\text{NH}$ ), 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,  $\text{CHNH}$ ), 3.73 (s, 3 H,  $\text{CH}_3$ ), 3.65 (tt,  $J$  = 7.1, 3.9 Hz, 1 H,  $\text{NCH}(\text{CH}_2)_2$ ), 3.25 (br s, 4 H,  $\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)\text{CH}_2\text{CH}_2$ ), 2.58 (br s, 4 H,  $\text{CH}_2\text{N}(\text{CH}_2)\text{CH}_2$ ), 2.45 - 2.53 (m, 1 H,  $\text{CHHC}(=\text{O})\text{CHNH}$ ), 2.36 (br s, 2 H,  $\text{C}(=\text{O})\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$ ), 2.26 (dtt,  $J$  = 13.4, 2.6, 1.6 Hz, 1 H,  $\text{CHHC}(=\text{O})\text{CHNH}$ ), 2.16 - 2.22 (m, 2 H,  $\text{C}(=\text{O})\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$ ), 2.12 (ddq,  $J$  = 12.7, 6.0, 2.8 Hz, 1 H,  $\text{CHHCHNH}$ ), 2.00 (ddquin,  $J$  = 13.2,

6.0, 2.9 Hz, 1 H,  $\text{CHHCH}_2\text{C(=O)}$ ), 1.65 - 1.83 (m, 4 H,  $\text{CH}_2\text{CH}_2\text{CHNH}$ ), 1.41 - 1.56 (m, 2 H,  $\text{CHHCHNH}$  and  $\text{CHHCH}_2\text{C(=O)}$ ), 1.20 - 1.30 (m, 2 H,  $\text{NCH(CHH)}_2$ ), 1.05 - 1.13 (m, 2 H,  $\text{NCH(CHH)}_2$ )

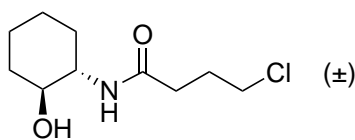
**$^{13}\text{C}$  NMR** (101 MHz, DMSO  $d_6$ )  $\delta$  / ppm = 207.5 ( $\text{C(=O)CHNH}$ ), 171.7 ( $\text{C(=O)CC(=O)OCH}_3$ ), 171.6 ( $\text{CH}_2\text{C(=O)NH}$ ), 165.0 ( $\text{C(=O)OCH}_3$ ), 152.6 (d,  $J$  = 247.6 Hz, *ipso* to F), 148.3 ( $\text{C=CC(=O)OCH}_3$ ), 143.9 (br s, *ipso* to piperazine), 138.1 (*para* to F), 121.8 (d,  $J$  = 6.4 Hz, *para* to piperazine), 111.5 (d,  $J$  = 22.4 Hz, *ortho* to C=O and *ortho* to F), 109.0 ( $\text{CC(=O)OCH}_3$ ), 106.3 (*meta* to C=O and *meta* to F), 57.0 ( $\text{CHNH}$  and  $\text{C(=O)CH}_2\text{CH}_2\text{CH}_2\text{N}$ ), 52.3 (br s,  $\text{C(=O)CH}_2\text{CH}_2\text{CH}_2\text{N(CH}_2\text{CH}_2\text{CH}_2\text{N)}$ ), 51.3 ( $\text{CH}_3$ ), 49.5 (br s,  $\text{C(=O)CH}_2\text{CH}_2\text{CH}_2\text{N(CH}_2\text{CH}_2\text{CH}_2\text{N)}$ ), 40.6 ( $\text{CH}_2\text{C(=O)CHNH}$ ), 34.8 ( $\text{NCH(CH}_2)_2$ ), 33.9 ( $\text{CH}_2\text{CHNH}$ ), 32.9 ( $\text{C(=O)CH}_2\text{CH}_2\text{CH}_2\text{N}$ ), 27.2 ( $\text{CH}_2\text{CH}_2\text{C(=O)CHNH}$ ), 23.8 ( $\text{CH}_2\text{CH}_2\text{CHNH}$ ), 22.4 (br s,  $\text{C(=O)CH}_2\text{CH}_2\text{CH}_2\text{N}$ ), 7.6 ( $\text{NCH(CH}_2)_2$ )

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

**HRMS** ( $\text{ESI}^+$ )  $m/z$  / 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.

### 0.36 4-Chloro-*N*-((*trans*)-2-hydroxycyclohexyl)butanamide **145**



(*trans*)-2-Aminocyclohexan-1-ol **142** (1.04 g, 9.03 mmol, 1 eq.), TEA (1.65 ml, 1.20 g, 11.8 mmol, 1.3 eq.) and  $\text{CH}_2\text{Cl}_2$  (50 ml) were stirred at 0 °C. 4-Chlorobutyryl chloride **138** (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/ $\text{CHCl}_3$  ( $2 \times 50$  ml). The combined organic layers were dried with  $\text{MgSO}_4$ , concentrated under reduced pressure and purified by column chromatography ( $\text{SiO}_2$ , 0-100 % EtOAc/ $\text{Et}_2\text{O}$ ). The combined organic fractions were dried with  $\text{MgSO}_4$  and evaporated under reduced pressure. **145** was obtained as white needles (1.51 g, 6.87 mmol, 76.1 %).

**TLC**  $R_f$  = 0.19 ( $\text{Et}_2\text{O}$ )

**mp**  $T$  / °C = 72.5-75.7 (*i*-PrOH,  $\text{CHCl}_3$ )

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

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

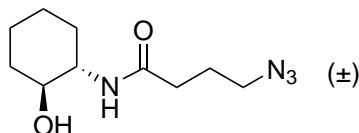
**$^{13}\text{C}$  NMR** (101 MHz, MeOD)  $\delta$  / ppm = 175.0 ( $\text{C(=O)}$ ), 74.1 ( $\text{CHOH}$ ), 56.3 ( $\text{CHNH}$ ), 45.3 ( $\text{CH}_2\text{Cl}$ ), 35.6 ( $\text{CH}_2\text{CHOH}$ ), 34.5 ( $\text{C(=O)CH}_2$ ), 32.7 ( $\text{CH}_2\text{CHNH}$ ), 30.1 ( $\text{C(=O)CH}_2\text{CH}_2$ ), 25.8 ( $\text{CH}_2\text{CH}_2\text{CHNH}$ ), 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.

### 0.37 4-Azido-*N*-((*trans*)-2-hydroxycyclohexyl)butanamide **146**



4-Chloro-*N*-((*trans*)-2-hydroxycyclohexyl)butanamide **145** (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. **146** 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)

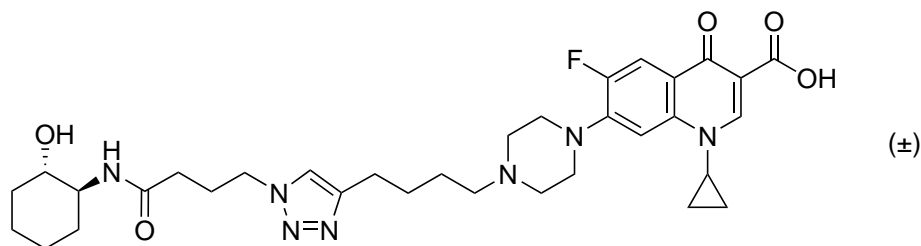
**<sup>1</sup>H NMR** (400 MHz, MeOD)  $\delta$  / ppm = 7.87 (d,  $J$  = 7.9 Hz, 1 H, NH), 5.27 (d,  $J$  = 4.3 Hz, 1 H, OH), 3.56 (td,  $J$  = 10.5, 4.4 Hz, 1 H, CHNH), 3.28 - 3.41 (m, 3 H, CHOH and CH<sub>2</sub>N<sub>3</sub>), 2.30 (td,  $J$  = 7.4, 2.7 Hz, 2 H, C(=O)CH<sub>2</sub>), 1.95 - 2.03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

**0.38 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 **147****



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 **146** (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 preparative 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. **147** 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 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 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, 2 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, 2 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)

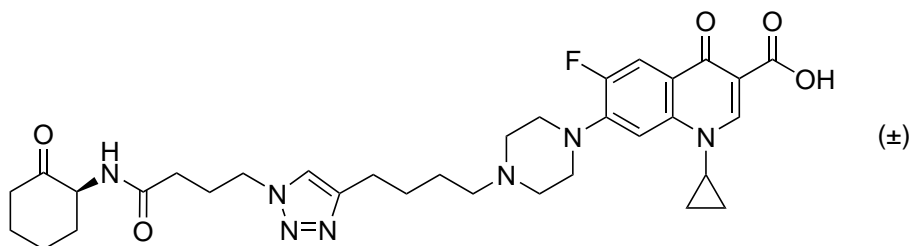
**<sup>13</sup>C NMR** (101 MHz, DMSO d<sub>6</sub>)  $\delta$  / ppm = 176.4 (C(=O)CC(=O)OH), 170.9 (CH<sub>2</sub>C(=O)NH), 166.0 (C(=O)OH), 153.1 (d, *J* = 252.1 Hz, *ipso* to F), 148.0 (C=CC(=O)OH), 146.9 (CH=CCH<sub>2</sub>), 145.3 (d, *J* = 10.0 Hz, *ipso* to piperazine), 139.2 (*para* to F), 121.8 (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 **148****



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 **147** (15.0 mg, 23.6 mmol, 1 eq.) and Dess-Martin periodinane (35.0 mg, 82.5 mmol, 3.5 eq.) were stirred in CH<sub>2</sub>Cl<sub>2</sub> (3 ml) at r.t. for 4 h. The solvent was removed under reduced pressure and the residue was purified by preparative HPLC (5-70 % acetonitrile/water over 15 min). The combined pure fractions were evaporated under reduced pressure, then NaHCO<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. **148** 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>CHNH), 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 (dtt, *J* = 13.4, 2.6, 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.



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