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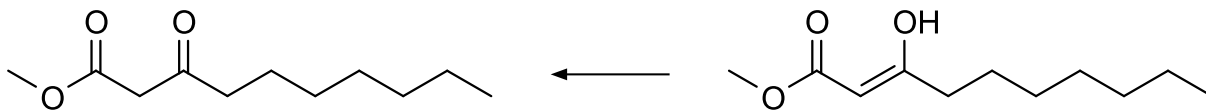
## 2 References

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# 1 Experimental

## 1.1 Methyl 3-oxodecanoate **21**

fix eps



Meldrum's acid (9.0 g, 63 mmol, 1 eq.) was dissolved in anhydrous  $\text{CH}_2\text{Cl}_2$  (150 mL) and cooled to 0 °C. Pyridine (10.2 mL, 126 mmol, 2 eq.) was added dropwise over 20 min. Octanoyl chloride (11.7 mL, 69 mmol, 1.1 eq.) was then added and the mixture was stirred at 0 °C for a further 4 h. The mixture was allowed to warm to r.t., diluted with  $\text{CH}_2\text{Cl}_2$  (20 mL) and poured into a mixture of ice (~ 30 g) and HCl (2 N, 90 mL). The solution was washed with NaCl (sat., aq., 150 mL) and dried over  $\text{MgSO}_4$ . The solvent was removed under vacuum to give an orange-brown oil. The oil was refluxed in anhydrous MeOH (150 mL) for 5 h and the solvent was removed under vacuum. The resulting residue was purified by column chromatography ( $\text{SiO}_2$ , 5 %  $\text{Et}_2\text{O}$ /40-60 P.E.) to give a tautomeric mixture of **21** and **22** as a colourless oil (8.34 g, 41.6 mmol, 66 %, 92 % **21** as determined by NMR).

### Keto form **21**

**TLC**  $R_f$  = 0.12 (5 %  $\text{EtO}_2$ /PE)

**IR** (neat)  $\nu_{\text{max}}$  /  $\text{cm}^{-1}$  = 2927.84 (C-H), 2856.26 (C-H), 1746.86 (ester C=O), 1716.70 (ketone C=O)

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  / ppm = 3.74 (s, 3 H,  $\text{OCH}_3$ ), 3.45 (s, 2 H,  $\text{C}(=\text{O})\text{CH}_2\text{C}(=\text{O})$ ), 2.53 (t,  $J$  = 7.4 Hz, 2 H,  $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 1.60 (quin,  $J$  = 7.1 Hz, 2 H,  $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 1.39 - 1.19 (m, 8 H,  $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 0.88 (t,  $J$  = 6.8 Hz, 3 H,  $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ )

**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  / ppm = 202.3 ( $\text{CH}_3\text{OC}(=\text{O})\text{CH}_2\text{C}(=\text{O})$ ), 167.3 ( $\text{CH}_3\text{OC}(=\text{O})\text{CH}_2\text{C}(=\text{O})$ ), 51.7 ( $\text{OCH}_3$ ), 48.5 ( $\text{CH}_3\text{OC}(=\text{O})\text{CH}_2\text{C}(=\text{O})$ ), 42.5 ( $\text{CH}_2$ ), 31.3 ( $\text{CH}_2$ ), 28.7 ( $\text{CH}_2$ ), 28.6 ( $\text{CH}_2$ ), 23.1 ( $\text{CH}_2$ ), 22.2 ( $\text{CH}_2$ ), 13.6 ( $\text{CH}_3$ )

### Enol form **22**

**TLC**  $R_f$  = 0.12 (5 %  $\text{EtO}_2$ /PE)

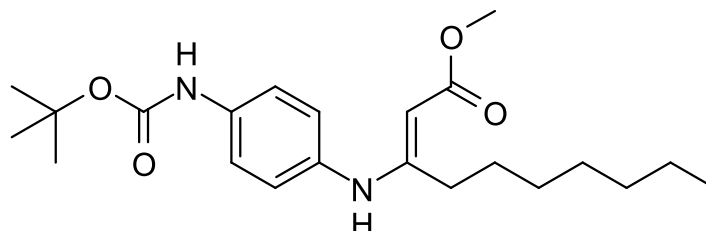
**IR** (neat)  $\nu_{\text{max}}$  /  $\text{cm}^{-1}$  = 2927.84 (C-H), 2856.26 (C-H), 1653.80 (C=C), 1629.21 ( $\alpha,\beta$  unsaturated C=O)

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  / ppm = 12.02 (s, 1 H,  $\text{COH}$ ), 4.99 (s, 1 H,  $\text{C}(=\text{O})\text{CH}=\text{COH}$ ), 3.73 (s, 3 H,  $\text{OCH}_3$ ), 2.20 (t,  $J$  = 7.4 Hz, 2 H,  $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 1.76 - 1.72 (m, 2 H,  $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 1.39 - 1.19 (m, 8 H,  $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 0.88 (t,  $J$  = 6.8 Hz, 3 H,  $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ )

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  / ppm = 178.7 ( $\text{CH}_3\text{OC}(=\text{O})\text{CH}=\underline{\text{C}}\text{OH}$ ), 172.7 ( $\text{CH}_3\text{OC}(=\text{O})\text{CH}=\text{COH}$ ), 88.2 ( $\text{CH}_3\text{OC}(=\text{O})\underline{\text{C}}\text{H}=\text{COH}$ ), 50.5 ( $\text{OC}\underline{\text{H}}_3$ ), 37.9 ( $\underline{\text{C}}\text{H}_2$ ), 34.6 ( $\underline{\text{C}}\text{H}_2$ ), 31.2 ( $\underline{\text{C}}\text{H}_2$ ), 29.0 ( $\underline{\text{C}}\text{H}_2$ ), 25.9 ( $\underline{\text{C}}\text{H}_2$ ), 22.3 ( $\underline{\text{C}}\text{H}_2$ ), 13.6 ( $\underline{\text{C}}\text{H}_3$ )

Spectroscopic data are consistent with the literature.<sup>1,2</sup>

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



Methyl 3-oxodecanoate **21** (500 mg, 2.50 mmol, 1.00 eq.) and *tert*-butyl (4-aminophenyl)carbamate **174** (520 mg, 2.50 mmol, 1.00 eq.) were dissolved in MeOH (10 mL) and refluxed for 18 h. The solvent was removed under vacuum and the resulting residue was purified by column chromatography ( $\text{SiO}_2$ , gradient of 0 to 20 %  $\text{Et}_2\text{O}/40\text{-}60$  P.E.) to give a white powder (0.169 mg, 0.480 mmol, 19 %).

TLC  $R_f$  = 0.30 (30 %  $\text{Et}_2\text{O}/40\text{-}60$  P.E.)

mp  $T$  /  $^\circ\text{C}$  = 78.8 ( $\text{Et}_2\text{O}/40\text{-}60$  P.E.)

IR (neat)  $\nu_{\text{max}}$  /  $\text{cm}^{-1}$  = 3336.97 (N-H), 2927.71 (C-H), 2857.14 (C-H), 1723.71 (carbamate C=O), 1634.49 ( $\alpha,\beta$  unsaturated C=O), 1610.73 (C=C), 1580.85 (N-H bend)

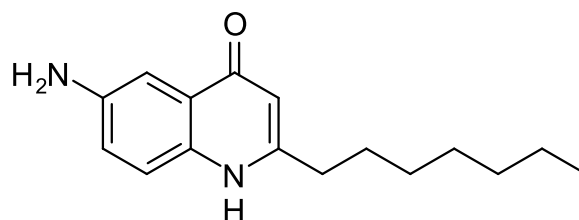
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  / ppm = 10.16 (s, 1 H,  $\text{NH}\underline{\text{C}}(\text{C}_7\text{H}_{15})=\text{C}$ ), 7.35 (d,  $J$  = 8.6 Hz, 2 H, *meta* to NHBoc), 7.02 (d,  $J$  = 8.7 Hz, 2 H, *meta* to enamine), 6.60 (br s, 1 H,  $\text{NH}\underline{\text{B}}\text{oc}$ ), 4.71 (s, 1 H,  $\text{C}=\underline{\text{C}}\text{H}$ ), 3.70 (s, 3 H,  $\text{OC}\underline{\text{H}}_3$ ), 2.23 (t,  $J$  = 7.7 Hz, 2 H,  $\underline{\text{C}}\text{H}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 1.54 (s, 9 H,  $\text{C}(\underline{\text{C}}\text{H}_3)_3$ ), 1.40 (quin,  $J$  = 7.3 Hz, 2 H,  $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 1.33 - 1.16 (m, 8 H,  $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 0.86 (t,  $J$  = 7.1 Hz, 3 H,  $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ )

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  / ppm = 171.1 ( $\underline{\text{C}}(=\text{O})\text{CH}=\text{C}$ ), 164.3 ( $\text{C}(=\text{O})\text{CH}=\underline{\text{C}}$ ), 152.7 ( $\text{OC}(=\text{O})\text{NH}$ ), 136.0 (*para* to NHBoc), 134.1 ( $\underline{\text{C}}\text{NHBoc}$ ), 126.3 (*meta* to NHBoc), 119.1 (*ortho* to NHBoc), 83.8 ( $\text{C}(=\text{O})\underline{\text{C}}\text{H}=\text{C}$ ), 80.7 ( $\underline{\text{C}}(\text{CH}_3)_3$ ), 50.2 ( $\text{OC}\underline{\text{H}}_3$ ), 32.2 ( $\underline{\text{C}}\text{H}_2$ ), 31.6 ( $\underline{\text{C}}\text{H}_2$ ), 29.1 ( $\underline{\text{C}}\text{H}_2$ ), 28.8 ( $\underline{\text{C}}\text{H}_2$ ), 28.3 ( $\text{C}(\underline{\text{C}}\text{H}_3)_3$ ), 28.0 ( $\underline{\text{C}}\text{H}_2$ ), 22.6 ( $\underline{\text{C}}\text{H}_2$ ), 14.0 ( $\underline{\text{C}}\text{H}_3$ )

HRMS ( $\text{ESI}^+$ )  $m/z$  / Da = 391.2589,  $[\text{M}+\text{H}]^+$ ,  $[\text{C}_{22}\text{H}_{35}\text{N}_2\text{O}_4]^+$  requires 391.2591

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

NMR  
wrong?  
not  
tau-  
tomer?



Methyl (*E*)-3-((4-((tert-butoxycarbonyl)amino)phenyl)amino)dec-2-enoate **24** (168 mg, 0.649 mmol, 1 eq.) and polyphosphoric acid (5 g) were heated to 90 °C for 1 h. The reaction mixture was then poured into NaHCO<sub>3</sub> (sat., aq., 50 mL) cooled with ice. The precipitate was collected by vacuum filtration, washed with water (50 mL) and dried under high vacuum to give a pale yellow powder (121 mg, 0.468 mmol, 72 %).

**mp** *T* / °C = 249 (H<sub>2</sub>O)

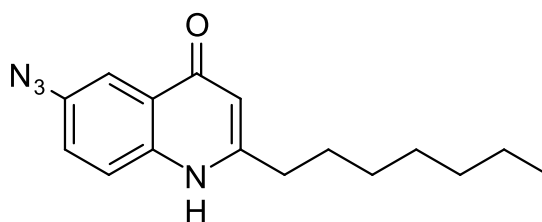
**IR** (neat)  $\nu_{max}$  / cm<sup>-1</sup> = 3336.52 (N-H), 2926.47 (C-H), 2856.89 (C-H), 1723.88 (aromatic), 1634.48 (aromatic), 1610.84 (aromatic), 1583.26 (aromatic), 1519.06 (aromatic)

**<sup>1</sup>H NMR** (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  / ppm = 7.26 (d, *J* = 8.7 Hz, 1 H, *meta* to NH<sub>2</sub>), 7.15 (d, *J* = 2.6 Hz, 1 H, *para* to COH), 6.95 (dd, *J* = 2.7, 8.8 Hz, 1 H, *ortho* to COH), 5.74 (s, 1 H, *ortho* to OH), 5.16 (s, 2 H, NH<sub>2</sub>), 2.52 (t, *J* = 7.4 Hz, 2 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.64 (quin, *J* = 7.6 Hz, 2 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.36 - 1.19 (m, 8 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 0.86 (t, *J* = 7.0 Hz, 3 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>)

**<sup>13</sup>C NMR** (101 MHz, DMSO-d<sub>6</sub>)  $\delta$  / ppm = 176.7 (C=O), 151.7 (CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 145.1 (C=NH<sub>2</sub>), 132.4 (*para* to NH<sub>2</sub>), 126.6 (*para* to CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 121.1 (*ortho* to NH<sub>2</sub> and *para* to COH), 119.0 (*meta* to NH<sub>2</sub> and *meta* to COH), 106.2 (*ortho* to NH<sub>2</sub> and *ortho* to COH), 105.9 (*ortho* to CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub> and *ortho* to OH), 33.6 (CH<sub>2</sub>), 31.6 (CH<sub>2</sub>), 29.0 (CH<sub>2</sub>), 29.0 (CH<sub>2</sub>), 28.9 (CH<sub>2</sub>), 22.5 (CH<sub>2</sub>), 14.4 (CH<sub>3</sub>)

**HRMS** (ESI<sup>+</sup>) *m/z* / Da = 259.1810, [M+H]<sup>+</sup>, [C<sub>16</sub>H<sub>23</sub>N<sub>2</sub>O]<sup>+</sup> requires 259.1803

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



6-Amino-2-heptylquinolin-4-ol **25** (50 mg, 0.194 mmol, 1 eq) was dissolved in HCl (conc., aq., 1.20 ml), water (1.80 ml) and MeOH (2.00 ml) and cooled to 0 °C. A solution of NaNO<sub>2</sub> (16.0 mg, 0.232 mmol, 1.2 eq.) in water (0.300 ml) was added dropwise over 10 min and the mixture was stirred for 1 h. A solution of NaN<sub>3</sub> (15.1 mg, 0.232 mmol, 1.2 eq.) in water (0.300 ml) was then added. The mixture was warmed to room temperature and stirred for a further 4 h. The resultant precipitate was filtered off and dried under reduced pressure. **26** was obtained as a pale cream amorphous solid (25.6 mg, 0.0900 mmol, 46.5 %).

**TLC** *R<sub>f</sub>* = 0.40 (5 % MeOH/CH<sub>2</sub>Cl<sub>2</sub>)

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**mp**  $T / ^\circ\text{C} = ??$  (??)

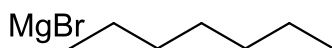
**IR** (neat)  $\nu_{\text{max}} / \text{cm}^{-1} = ??$

**$^1\text{H}$  NMR** (400 MHz, MeOD)  $\delta / \text{ppm} = 7.73$  (d,  $J = 8.6$  Hz, 1 H, *ortho* to NH), 7.71 (d,  $J = 2.8$  Hz, 1 H, *ortho* to  $\text{N}_3$  and *ortho* to  $\text{C}(=\text{O})$ ), 7.47 (dd,  $J = 8.9, 2.7$  Hz, 1 H, *para* to  $\text{C}(=\text{O})$ ), 6.24 (s, 1 H,  $\text{C}(=\text{O})\text{CH}$ ), 2.69 (t,  $J = 7.7$  Hz, 2 H,  $\text{NHCCH}_2$ ), 1.68 (quin,  $J = 7.6$  Hz, 2 H,  $\text{NHCCH}_2\text{CH}_2$ ), 1.28 - 1.39 (m, 4 H,  $\text{NHCCH}_2\text{CH}_2\text{CH}_2\text{CH}_2$ ), 1.18 - 1.28 (m, 4 H,  $\text{CH}_2\text{CH}_2\text{CH}_3$ ), 0.85 (t,  $J = 6.8$  Hz, 3 H,  $\text{CH}_3$ )

**$^{13}\text{C}$  NMR** (101 MHz, MeOD)  $\delta / \text{ppm} = 172.3$  ( $\text{C}(=\text{O})$ ), 155.5 ( $\text{NHCCH}_2$ ), 137.4 ( $\text{CN}_3$ ), 135.6 (*para* to  $\text{N}_3$ ), 124.6 (*para* to  $\text{C}(=\text{O})$ ), 124.1 (*ipso* to  $\text{C}(=\text{O})$ ), 120.7 (*meta* to  $\text{N}_3$  and *meta* to  $\text{C}(=\text{O})$ ), 112.8 (*ortho* to  $\text{N}_3$  and *ortho* to  $\text{C}(=\text{O})$ ), 107.0 ( $\text{C}(=\text{O})\text{CH}$ ), 33.3 ( $\text{NHCCH}_2$ ), 31.2 ( $\text{CH}_2\text{CH}_2\text{CH}_3$ ), 28.3 - 28.5 ( $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 22.1 ( $\text{CH}_2\text{CH}_3$ ), 14.0 ( $\text{CH}_3$ )

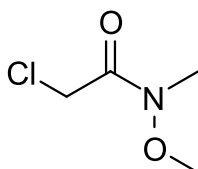
**HRMS** ( $\text{ESI}^+$ )  $m/z / \text{Da} = ??$ ,  $[\text{M}+\text{H}]^+$  found,  $[??]^+$  requires ??

## 1.5 Heptyl magnesium bromide 28



Magnesium turnings (352 mg, 14.5 mmol, 1 eq.) were added to a dry flask under argon. THF (15 mL) was added, followed by bromoheptane (2.40 mL, 14.5 mmol, 1 eq.) dropwise. The mixture was stirred at r.t. for 2 h followed by heating to reflux for 2 h to give the Grignard reagent as a pale grey suspension (15 mL,  $\sim 1$  M) which was used without further purification.

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



*N*,*O*-Dimethylhydroxyl amine hydrochloride (6.00 g, 61.5 mmol, 1 eq.) and toluene (75 mL) were added successively to a solution of potassium carbonate (22.4 g, 162 mmol, 2.63 eq.) in water (75 mL) at  $0^\circ\text{C}$  under argon. The mixture was cooled to  $-5^\circ\text{C}$  and chloroacetyl chloride (5.88 mL, 73.8 mmol, 1.20 eq.) was added dropwise over 5 min. The mixture was allowed to warm to r.t. over 30 min, then the organic layer was separated and the aqueous layer was extracted with toluene ( $3 \times 20$  mL). The four combined organic extracts were dried with  $\text{MgSO}_4$  and the solvent was removed by rotary evaporation followed by high vacuum to give white, prism-like crystals (7.24 g, 52.6 mmol, 71 %).

**mp**  $T / ^\circ\text{C} = 38.8$  (toluene)

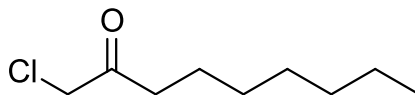
**IR** (neat)  $\nu_{\text{max}} / \text{cm}^{-1} = 3016.69$  (C-H), 2966.38 (C-H), 2946.75 (C-H), 2827.73 (C-H), 1666.20 (C=O)

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta / \text{ppm} = 4.20$  (s, 2 H,  $\text{ClCH}_2\text{C}(=\text{O})$ ), 3.71 (m, 3 H,  $\text{OCH}_3$ ), 3.18 (s, 3 H,  $\text{NCH}_3$ )

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  / ppm = 167.4 (C=O), 61.6 ( $\text{OCH}_3$ ), 40.9 ( $\text{ClCH}_2\text{C=O}$ ), 32.6 ( $\text{NCH}_3$ )

Spectroscopic data are consistent with the literature.<sup>3</sup>

## 1.7 1-Chlorononan-2-one **31**



2-Chloro-*N*-methoxy-*N*-methylacetamide (1.00 g, 7.26 mmol, 1 eq.) was added to a dry flask under argon. THF (20 mL) was added and the flask cooled to 0 °C. Heptyl magnesium bromide (~ 1 M, 15.0 mL, 15.0 mmol, 2.07 eq.) was added dropwise over 5 min, then the mixture was allowed to warm to r.t. and stirred for 15 h. The reaction mixture was then poured into HCl (aq., 2 N, 60 mL) at 0 °C and stirred for 10 min. The mixture was extracted with toluene (30 mL) and the aqueous layer discarded. The organic layer was washed with brine and dried with  $\text{MgSO}_4$ . The solvent was removed by rotary evaporation to give a colourless oil (1.23 g, 6.96 mmol, 96 %).

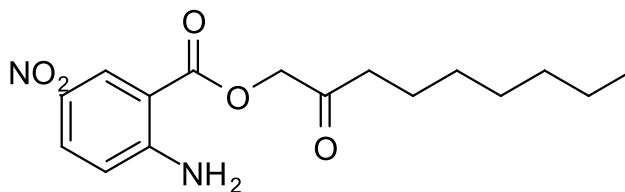
IR (neat)  $\nu_{\text{max}}$  /  $\text{cm}^{-1}$  = 2951.65 (C-H), 2924.99 (C-H), 2855.46 (C-H), 1720.39 (C=O)

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  / ppm = 4.05 (s, 2 H,  $\text{ClCH}_2\text{C(=O)}$ ), 2.54 (t,  $J$  = 7.4 Hz, 2 H,  $\text{C(=O)CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 1.59 (quin,  $J$  = 7.0 Hz, 2 H,  $\text{C(=O)CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 1.34 - 1.21 (m, 8 H,  $\text{C(=O)CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 0.87 (t,  $J$  = 6.8 Hz, 3 H,  $\text{C(=O)CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ )

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  / ppm = 202.6 ( $\text{C=O}$ ), 48.1 ( $\text{CH}_2\text{Cl}$ ), 39.6 ( $\text{C(=O)CH}_2$ ), 31.5 ( $\text{CH}_2\text{CH}_2\text{CH}_3$ ), 28.9 ( $\text{CH}_2$ ), 28.9 ( $\text{CH}_2$ ), 23.5 ( $\text{C(=O)CH}_2\text{CH}_2$ ), 22.5 ( $\text{CH}_2\text{CH}_3$ ), 13.9 ( $\text{CH}_3$ )

Spectroscopic data are consistent with the literature.<sup>3</sup>

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



5-Nitroanthranilic acid (500 mg, 2.75 mmol, 1.38 eq.) and potassium carbonate (270 mg, 2.00 mmol, 1 eq.) were dissolved in DMF (5 ml). The mixture was heated under argon to 90 °C and stirred for 1 h then cooled to r.t.. 1-chlorononan-2-one **31** (353 mg, 2.00 mmol, 1 eq.) was added and the mixture was stirred for 15 h. The solution was poured into  $\text{Na}_2\text{HCO}_3$  (aq., 10 %, 50 ml) and ice (~ 20 g). The precipitate was collected by vacuum filtration, washed with water and dried under high vacuum to give a yellow powder (0.674 g, 2.00 mmol, 100 %).

mp  $T$  / °C = 135 ( $\text{H}_2\text{O}$ )

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



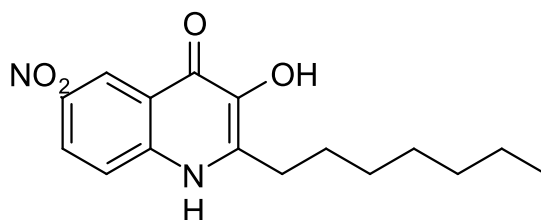
1703.91 (ketone C=O) 1626.14 (N-H bend) 1602.74 (aromatic) 1572.48 (N-O) 1506.58 (N-O)

**<sup>1</sup>H NMR** (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  / ppm = 8.66 (d,  $J$  = 2.8 Hz, 1 H, *ortho* to C(=O)), 8.12 (dd,  $J$  = 2.8, 9.4 Hz, 1 H, *para* to C(=O)), 6.93 (d,  $J$  = 9.4 Hz, 1 H, *meta* to C(=O)), 5.05 (s, 2 H, OCH<sub>2</sub>C(=O)), 2.49 (t,  $J$  = 7.4 Hz, 2 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.52 (quin,  $J$  = 7.2 Hz, 2 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.32 - 1.20 (m, 8 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 0.86 (t,  $J$  = 6.8 Hz, 3 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>)

**<sup>13</sup>C NMR** (101 MHz, DMSO-d<sub>6</sub>)  $\delta$  / ppm = 204.4 (OCH<sub>2</sub>C(=O)), 165.6 (C(=O)O), 156.3 (C(NH<sub>2</sub>)), 135.7 (CNO<sub>2</sub>), 129.6 (*para* to C=O), 128.9 (*ortho* to C=O), 117.4 (*meta* to C=O), 107.5 (CC(=O)O), 68.8 (OCH<sub>2</sub>C(=O)), 38.3 (CH<sub>2</sub>), 31.6 (CH<sub>2</sub>), 28.9 (CH<sub>2</sub>), 28.9 (CH<sub>2</sub>), 23.2 (CH<sub>2</sub>), 22.5 (CH<sub>2</sub>), 14.4 (CH<sub>3</sub>)

**HRMS** (ESI<sup>+</sup>)  $m/z$  / Da = 323.1610, [M+H]<sup>+</sup>, [C<sub>16</sub>H<sub>23</sub>N<sub>2</sub>O<sub>5</sub>]<sup>+</sup> requires 323.1607

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



2-Oxononyl 2-amino-5-nitrobenzoate (100 mg, 0.340 mmol, 1 eq.) and polyphosphoric acid (300 mg) were stirred for 5.5 h at 90 °C under argon. The mixture was then poured into NaHCO<sub>3</sub> (sat., aq., 50 mL) cooled on ice. The precipitate was collected by vacuum filtration, washed with water (50 mL) and dried under high vacuum to give a yellow-brown powder (44 mg, 0.145 mmol, 43 %) which could be recrystallised from EtOAc to give yellow-brown plate-like crystals.

**mp**  $T$  / °C = 223 (H<sub>2</sub>O)

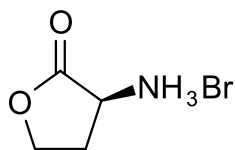
**IR** (neat)  $\nu_{max}$  / cm<sup>-1</sup> = 3436.01 (N-H), 3000.00 (O-H, br), 2955.37 (C-H), 2925.76 (C-H), 2850.93 (C-H), 1648.18 (aromatic), 1606.05 (aromatic), 1570.67 (N-O), 1536.35 (N-O)

**<sup>1</sup>H NMR** (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  / ppm = 12.00 (s, 1 H, NH), 8.91 (d,  $J$  = 2.8 Hz, 1 H, *ortho* to C=O), 8.29 (dd,  $J$  = 2.7, 9.2 Hz, 1 H, *para* to C=O), 7.70 (d,  $J$  = 9.3 Hz, 1 H, *meta* to C=O), 2.75 (t,  $J$  = 7.7 Hz, 2 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.67 (quin,  $J$  = 7.3 Hz, 2 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.36 - 1.23 (m, 8 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 0.85 (t,  $J$  = 7.0 Hz, 3 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>)

**<sup>13</sup>C NMR** (101 MHz, DMSO-d<sub>6</sub>)  $\delta$  / ppm = 169.7 (C=O), 141.9 (COH), 140.7 (*para* to NO<sub>2</sub>), 139.6 (CNO<sub>2</sub>), 137.3 (CHCC=O), 124.3 (*ortho* to NO<sub>2</sub> and *ortho* to C=O), 122.3 (*ortho* to NO<sub>2</sub> and *para* to C=O), 121.5 (CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 120.0 (*meta* to NO<sub>2</sub> and *meta* to C=O), 31.6 (CH<sub>2</sub>), 29.2 (CH<sub>2</sub>), 28.9 (CH<sub>2</sub>), 28.5 (CH<sub>2</sub>), 28.1 (CH<sub>2</sub>), 22.5 (CH<sub>2</sub>), 14.4 (CH<sub>3</sub>)

**HRMS** (ESI<sup>+</sup>)  $m/z$  / Da = 305.1501, [M+H]<sup>+</sup>, [C<sub>16</sub>H<sub>21</sub>N<sub>2</sub>O<sub>4</sub>]<sup>+</sup> requires 305.1500

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



L-Methionine (3.04 g, 20.4 mmol, 1 eq.) and bromoacetic acid (3.08 g, 22.2 mmol, 1.09 eq.) were dissolved in *i*-PrOH (12.5 mL), H<sub>2</sub>O (12.5 mL) and AcOH (5 mL). The reaction was refluxed for 15 h then concentrated under vacuum. The resulting brown oil was added to a mixture of *i*-PrOH (16 mL) and HBr (33 % in AcOH, 4 mL), causing the precipitation of a pale pink powder. The precipitate was collected by filtration and washed with *i*-PrOH (20 mL). The filtrate was concentrated under vacuum and precipitated again using the same procedure. The two crops of precipitate were combined to give a pale pink powder (1.73 g, 9.50 mmol, 41 % yield).

**mp**  $T / ^\circ\text{C} = 242$  (*i*-PrOH/AcOH, gas evolved)

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

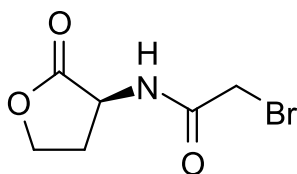
**<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta / \text{ppm} = 8.59$  (br s, 3 H,  $\text{NH}_3^+$ ), 4.46 (dt,  $J = 1.3, 8.9$  Hz, 1 H,  $\text{OCH}_2$ ), 4.37 (dd,  $J = 8.8, 11.4$  Hz, 1 H,  $\text{CHNH}_3^+$ ), 4.29 (ddd,  $J = 6.1, 8.8, 10.9$  Hz, 1 H,  $\text{OCH}_2$ ), 2.57 (dddd,  $J = 1.2, 6.1, 8.9, 12.3$  Hz, 1 H,  $\text{OCH}_2\text{CH}_2$ ), 2.26 (dtd,  $J = 9.0, 11.2, 12.2$  Hz, 1 H,  $\text{OCH}_2\text{CH}_2$ )

**<sup>13</sup>C NMR** (101 MHz, DMSO-*d*<sub>6</sub>)  $\delta / \text{ppm} = 173.3$  ( $\text{C}=\text{O}$ ), 66.2 ( $\text{OCH}_2$ ), 47.8 ( $\text{CHNH}_3^+$ ), 27.0 ( $\text{OCH}_2\text{CH}_2$ )

$[\alpha]_D^{20} / ^\circ 10^{-1} \text{cm}^2 \text{g}^{-1} = -30.0$  ( $c / \text{g}(100 \text{ mL})^{-1} = 0.02$ , DMSO)

The data are consistent with the literature.<sup>4</sup>

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



(*S*)-3-Aminodihydrofuran-2(3*H*)-one hydrobromide **38** (100 mg, 0.549 mmol, 1.08 eq.) and NaHCO<sub>3</sub> (84.9 mg, 1.01 mmol, 2.00 eq.) were dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) and H<sub>2</sub>O (2 mL). Bromoacetyl bromide (44.0  $\mu\text{L}$ , 102 mg, 0.505 mmol, 1.00 eq.) was then added dropwise. The reaction mixture was stirred for 24 h, after which the CH<sub>2</sub>Cl<sub>2</sub> was removed under vacuum. The aqueous phase was extracted with EtOAc (4  $\times$  10 mL) and the combined organic layers were dried with MgSO<sub>4</sub>. The solvent was removed under vacuum to give white, needle-like crystals (88.0 mg, 0.396 mmol, 74 %).

**mp**  $T / ^\circ\text{C} = 132$  (EtOAc)

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

(N-H bend)

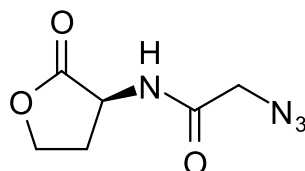
$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  / ppm = 6.95 (br d, 1 H,  $\text{NH}$ ), 4.58 (ddd,  $J = 5.9, 8.6, 11.7$  Hz, 1 H,  $\text{CHNHC=O}$ ), 4.53 (dt,  $J = 1.0, 9.2$  Hz, 1 H,  $\text{OCH}_2$ ), 4.33 (ddd,  $J = 5.9, 9.4, 11.3$  Hz, 1 H,  $\text{OCH}_2$ ), 3.95 (d,  $J = 1.3$  Hz, 2 H,  $\text{C(=O)CH}_2\text{Br}$ ), 2.88 (dddd,  $J = 1.3, 5.9, 8.6, 12.6$  Hz, 1 H,  $\text{OCH}_2\text{CH}_2$ ), 2.24 (dtd,  $J = 8.9, 11.5, 12.6$  Hz, 1 H,  $\text{OCH}_2\text{CH}_2$ )

$^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  / ppm = 174.6 ( $\text{OC=O}$ ), 166.4 ( $\text{C(=O)NH}$ ), 66.1 ( $\text{OCH}_2$ ), 49.8 ( $\text{CHNHC=O}$ ), 29.9 ( $\text{OCH}_2\text{CH}_2$ ), 28.2 ( $\text{O=CCH}_2\text{Br}$ )

$[\alpha]_D^{20} / ^\circ 10^{-1} \text{cm}^2 \text{g}^{-1} = 27.0$  ( $c / \text{g}(100 \text{ mL})^{-1} = 0.0074$ ,  $\text{CHCl}_3$ )

The data are consistent with the literature.<sup>4,5</sup>

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



(3*S*)-2-Oxotetrahydrofuran-3-aminium bromide **38** (100 mg, 0.552 mmol, 1.08 eq.),  $\text{NaN}_3$  (85.7 mg, 1.32 mmol, 2.61 eq.) and  $\text{NaHCO}_3$  (84.9 mg, 1.01 mmol, 2.00 eq.) were dissolved in  $\text{CH}_2\text{Cl}_2$  (2 mL) and  $\text{H}_2\text{O}$  (2 mL). Bromoacetyl bromide (44.0  $\mu\text{L}$ , 102 mg, 0.505 mmol, 1.00 eq.) was then added dropwise. The reaction mixture was stirred for 48 h, after which the  $\text{CH}_2\text{Cl}_2$  was removed under vacuum. The aqueous phase was extracted with EtOAc ( $4 \times 10 \text{ mL}$ ) and the combined organic layers were dried with  $\text{MgSO}_4$ . The solvent was removed under vacuum to give white, needle-like crystals (38.4 mg, 0.209 mmol, 41 %).

mp  $T / ^\circ\text{C} = 87$  (EtOAc)

**IR** (neat)  $\nu_{\text{max}} / \text{cm}^{-1} = 3283.47$  (N-H), 2923.28 (C-H), 2852.99 (C-H), 2129.69 ( $\text{N}_3$ ), 1782.86 (lactone  $\text{C=O}$ ), 1661.40 (amide  $\text{C=O}$ ), 1536.81 (N-H bend)

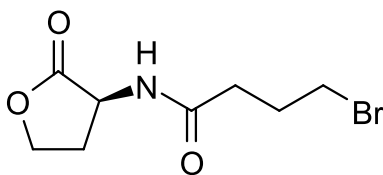
$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  / ppm = 7.07 (br d,  $J = 5.1$  Hz, 1 H,  $\text{NH}$ ), 4.65 (ddd,  $J = 6.8, 8.7, 11.6$  Hz, 1 H,  $\text{CHNHC=O}$ ), 4.49 (dt,  $J = 1.3, 9.1$  Hz, 1 H,  $\text{OCH}_2$ ), 4.31 (ddd,  $J = 6.0, 9.2, 11.2$  Hz, 1 H,  $\text{OCH}_2$ ), 4.05 (s, 2 H,  $\text{C(=O)CH}_2\text{N}_3$ ), 2.77 (dddd,  $J = 1.4, 6.0, 8.8, 12.5$  Hz, 1 H,  $\text{OCH}_2\text{CH}_2$ ), 2.26 (dq,  $J = 8.9, 11.8$  Hz, 1 H,  $\text{OCH}_2\text{CH}_2$ )

$^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  / ppm = 174.9 ( $\text{OC=O}$ ), 167.5 ( $\text{C=ONH}$ ), 66.0 ( $\text{OCH}_2$ ), 52.2 ( $\text{O=CCH}_2\text{N}_3$ ), 48.9 ( $\text{CHNHC=O}$ ), 29.7 ( $\text{OCH}_2\text{CH}_2$ )

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

The data are consistent with the literature.<sup>4</sup>

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



(*S*)-3-Aminodihydrofuran-2(3*H*)-one hydrobromide **38** (200 mg, 1.10 mmol, 1.00 eq.) and NaHCO<sub>3</sub> (170 mg, 2.02 mmol, 1.84 eq.) were dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) and H<sub>2</sub>O (2 mL). Bromobutyl chloride (140 μL, 224 mg, 1.21 mmol, 1.10 eq.) was then added dropwise. The reaction mixture was stirred for 1 h, after which the CH<sub>2</sub>Cl<sub>2</sub> was removed under vacuum. The aqueous phase was extracted with EtOAc (7 × 5 mL) and the combined organic layers were dried with MgSO<sub>4</sub>. The solvent was removed under vacuum to give white crystals which were recrystallised from EtOAc to give white, needle-like crystals (219 mg, 0.878 mmol, 80 %).

**mp** *T* / °C = 105 (EtOAc)

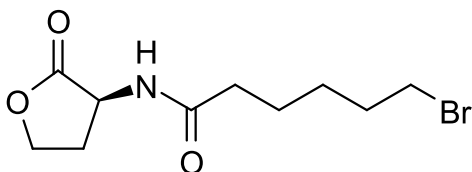
**IR** (neat)  $\nu_{max}$  / cm<sup>-1</sup> = 3307.92 (N-H), 3073.85 (C-H), 2948.93 (C-H), 1773.66 (lactone C=O), 1643.46 (amide C=O), 1541.39 (N-H bend)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  / ppm = 6.31 (br d, *J* = 5.5 Hz, 1 H, NH), 4.59 (ddd, *J* = 6.2, 8.7, 11.5 Hz, 1 H, CHNH<sub>2</sub>C=O), 4.48 (dt, *J* = 1.2, 8.9 Hz, 1 H, OCH<sub>2</sub>), 4.30 (ddd, *J* = 5.8, 9.3, 11.3 Hz, 1 H, OCH<sub>2</sub>), 3.49 (t, *J* = 6.3 Hz, 2 H, CH<sub>2</sub>Br), 2.82 (dddd, *J* = 1.3, 5.9, 8.7, 12.5 Hz, 1 H, OCH<sub>2</sub>CH<sub>2</sub>), 2.47 (t, *J* = 7.3 Hz, 2 H, C(=O)CH<sub>2</sub>), 2.26 - 2.15 (m, 3 H, OCH<sub>2</sub>CH<sub>2</sub> and C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>Br)

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  / ppm = 175.4 (OC=O), 172.3 (C(=O)NH), 66.1 (OCH<sub>2</sub>), 49.3 (CHNH<sub>2</sub>C=O), 33.9 (C(=O)CH<sub>2</sub>), 33.1 (CH<sub>2</sub>Br), 30.3 (OCH<sub>2</sub>CH<sub>2</sub>), 27.9 (C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>Br)

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

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



(*S*)-3-Aminodihydrofuran-2(3*H*)-one hydrobromide **38** (100 mg, 0.549 mmol, 1.00 eq.) and NaHCO<sub>3</sub> (84.9 mg, 1.01 mmol, 1.84 eq.) were dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) and H<sub>2</sub>O (2 mL). Bromohexanoyl chloride (93.0 μL, 130 mg, 0.608 mmol, 1.11 eq.) was then added dropwise. The reaction mixture was stirred for 4 h, after which the CH<sub>2</sub>Cl<sub>2</sub> was removed under vacuum. The mixture was then filtered, washed with H<sub>2</sub>O (10 mL) and dried under high vacuum to give white, needle-like crystals (101 mg, 0.362 mmol, 66 %).

**mp** *T* / °C = 106 (CH<sub>2</sub>Cl<sub>2</sub>/H<sub>2</sub>O)

**IR** (neat)  $\nu_{max}$  / cm<sup>-1</sup> = 3300.30 (N-H), 3067.62 (C-H), 2937.37 (C-H), 2856.67 (C-H), 1784.83 (lactone C=O),

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

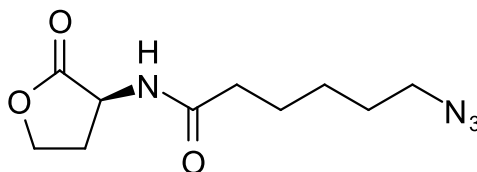
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  / ppm = 6.09 (br d,  $J$  = 5.7 Hz, 1 H, NH), 4.57 (ddd,  $J$  = 5.9, 8.6, 11.6 Hz, 1 H, CHNH<sub>2</sub>C=O), 4.50 (dt,  $J$  = 1.3, 9.1 Hz, 1 H, OCH<sub>2</sub>), 4.31 (ddd,  $J$  = 5.9, 9.3, 11.3 Hz, 1 H, OCH<sub>2</sub>), 3.43 (t,  $J$  = 6.7 Hz, 2 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>Br), 2.88 (dddd,  $J$  = 1.3, 5.9, 8.6, 12.6 Hz, 1 H, OCH<sub>2</sub>CH<sub>2</sub>), 2.30 (dt,  $J$  = 1.8, 7.5 Hz, 2 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>Br), 2.16 (dtd,  $J$  = 8.9, 11.5, 12.5 Hz, 1 H, OCH<sub>2</sub>CH<sub>2</sub>), 1.90 (quin,  $J$  = 7.2 Hz, 2 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>Br), 1.71 (quin,  $J$  = 7.6 Hz, 2 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>Br), 1.59 - 1.46 (m, 2 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>Br)

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  / ppm = 175.5 (OC=O), 173.3 (C(=O)NH), 66.1 (OCH<sub>2</sub>), 49.3 (CHNH<sub>2</sub>C=O), 35.8 (C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>Br), 33.5 (C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>Br), 32.3 (C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>Br), 30.5 (OCH<sub>2</sub>CH<sub>2</sub>), 27.6 (C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>Br), 24.4 (C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>Br)

**HRMS** (ESI<sup>+</sup>)  $m/z$  / Da = 278.0381, [M+H]<sup>+</sup>, [C<sub>10</sub>H<sub>17</sub>BrNO<sub>3</sub>]<sup>+</sup> requires 278.0386

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

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



(*S*)-6-Bromo-*N*-(2-oxotetrahydrofuran-3-yl)hexanamide (80 mg, 0.320 mmol, 1.00 eq.) and NaN<sub>3</sub> (26.3 mg, 0.405 mmol, 1.27 eq.) were heated in DMF (0.5 mL) for 5 h at 100 °C. The reaction mixture was then partitioned between CH<sub>2</sub>Cl<sub>2</sub> (5 mL) and H<sub>2</sub>O (5 mL). The aqueous phase was extracted twice more with CH<sub>2</sub>Cl<sub>2</sub> (2 × 5 mL) and the organic layers were combined and dried over MgSO<sub>4</sub>. The solvent was removed by rotary evaporation followed by high vacuum to give white, needle-like crystals (42.7 mg, 0.178 mmol, 56 %).

**mp**  $T$  / °C = 90.0 (CH<sub>2</sub>Cl<sub>2</sub>)

**IR** (neat)  $\nu_{max}$  / cm<sup>-1</sup> = 3314.00 (N-H), 2931.56 (C-H), 2862.89 (C-H), 2095.06 (N<sub>3</sub>), 1775.38 (lactone C=O), 1643.14 (amide C=O), 1547.90 (N-H bend)

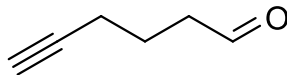
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  / ppm = 5.97 (br d,  $J$  = 4.2 Hz, 1 H, NH), 4.56 (ddd,  $J$  = 5.7, 8.6, 11.7 Hz, 1 H, CHNH<sub>2</sub>C=O), 4.50 (dt,  $J$  = 1.0, 9.1 Hz, 1 H, OCH<sub>2</sub>), 4.31 (ddd,  $J$  = 5.8, 9.4, 11.3 Hz, 1 H, OCH<sub>2</sub>), 3.31 (t,  $J$  = 6.9 Hz, 2 H, CH<sub>2</sub>N<sub>3</sub>), 2.90 (dddd,  $J$  = 1.1, 5.8, 8.6, 12.5 Hz, 1 H, OCH<sub>2</sub>CH<sub>2</sub>), 2.30 (dt,  $J$  = 1.8, 7.4 Hz, 2 H, O=CCH<sub>2</sub>), 2.15 (dtd,  $J$  = 8.8, 11.5, 12.3 Hz, 1 H, OCH<sub>2</sub>CH<sub>2</sub>), 1.72 (quin,  $J$  = 7.6 Hz, 2 H, O=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N<sub>3</sub>), 1.65 (quin,  $J$  = 7.2 Hz, 2 H, O=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N<sub>3</sub>), 1.46 (m, 2 H, O=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N<sub>3</sub>)

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  / ppm = 175.4 (OC=O), 172.2 (C(=O)NH), 66.1 (OCH<sub>2</sub>), 51.2 (C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N<sub>3</sub>), 49.4 (CHNH<sub>2</sub>C=O), 35.9 (C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N<sub>3</sub>), 30.7 (OCH<sub>2</sub>CH<sub>2</sub>), 28.6 (C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N<sub>3</sub>), 26.3 (C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N<sub>3</sub>), 24.8 (C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N<sub>3</sub>)

**HRMS** (ESI<sup>+</sup>)  $m/z$  / Da = 241.1289, [M+H]<sup>+</sup>, [C<sub>10</sub>H<sub>17</sub>N<sub>4</sub>O<sub>3</sub>]<sup>+</sup> requires 241.1295

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

### 1.16 Hex-5-ynal **49**



Pyridinium chlorochromate (14.6 g, 68.1 mmol, 1.50 eq) and DCM (500 mL) were stirred at r.t. under argon. 5-hexyn-1-ol (5.00 mL, 45.4 mmol, 1 eq.) was added and the reaction mixture was stirred for 5 h followed by addition of Et<sub>2</sub>O (125 mL) and silica gel (62.5 g). The suspension was stirred for 1 h then filtered through a pad of silica (100 g) and washed with Et<sub>2</sub>O. The solvent was removed by rotary evaporation to give a pale yellow-green oil (4.72 g, 49.1 mmol, 72 %).

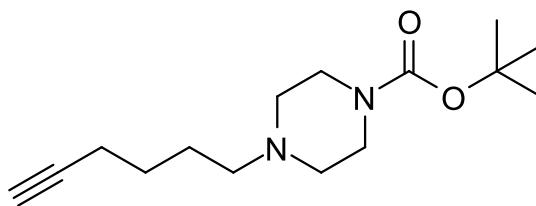
**IR** (neat)  $\nu_{max}$  / cm<sup>-1</sup> = 3292.68 (alkyne C-H), 2943.26 (alkane C-H), 2830.88 (aldehyde C-H), 2728.56 (aldehyde C-H), 1720.29 (aldehyde C=O)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  / ppm = 9.80 (s, 1 H, C(=O)H), 2.60 (t,  $J$  = 7.1 Hz, 2 H, CH<sub>2</sub>C(=O)H), 2.26 (dt,  $J$  = 2.6, 6.8 Hz, 2 H, HC≡CCH<sub>2</sub>), 1.98 (t,  $J$  = 2.7 Hz, 1 H, HC≡C), 1.85 (quin,  $J$  = 7.0 Hz, 2 H, HC≡CCH<sub>2</sub>CH<sub>2</sub>)

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  / ppm = 201.6 (C=O), 83.1 (HC≡C), 69.3 (HC≡C), 42.4 (CH<sub>2</sub>C=O), 20.7 (HC≡CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>C=O), 17.6 (HC≡CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>C=O)

Spectroscopic data are consistent with the literature.<sup>6</sup>

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



Hex-5-ynal **49** (0.407 g, 4.24 mmol, 1.00 eq.) and *tert*-butyl piperazine-1-carboxylate (0.791 g, 4.24 mmol, 1.00 eq.) were stirred under a N<sub>2</sub> atmosphere in 1,2-dichloroethane (20 mL) for 2.5 h followed by addition of sodium triacetoxyborohydride (6.25 g, 29.5 mmol, 6.96 eq.) in four portions over 4 d. The mixture was stirred for a further day then NaHCO<sub>3</sub> (sat., aq., 120 mL) was added and the product extracted with EtOAc (2 × 100 mL). The solvent was dried over MgSO<sub>4</sub>, and removed by rotary evaporation to give a colourless liquid (1.12 g, 4.21 mmol, 99 %).

**TLC**  $R_f$  (10 % MeOH/CH<sub>2</sub>Cl<sub>2</sub>) = 0.55

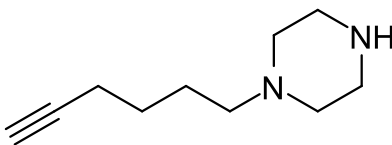
**IR** (neat)  $\nu_{max}$  / cm<sup>-1</sup> = 3303.59 (alkyne C-H), 2939.96 (alkane C-H), 2865.23 (C-H), 2810.42 (C-H), 1691.29 (carbamate C=O)

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  / ppm = 3.44 (t,  $J$  = 5.2 Hz, 4 H,  $\text{BocN}(\underline{\text{CH}_2})\underline{\text{CH}_2}$ ), 2.39 (t,  $J$  = 5.1 Hz, 4 H,  $\text{HC}\equiv\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\underline{\text{CH}_2})\underline{\text{CH}_2}$ ), 2.37 (t,  $J$  = 7.3 Hz, 2 H,  $\text{HC}\equiv\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$ ), 2.23 (dt,  $J$  = 2.7, 6.8 Hz, 2 H,  $\text{HC}\equiv\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$ ), 1.96 (t,  $J$  = 2.7 Hz, 1 H,  $\underline{\text{H}}\text{C}\equiv\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$ ), 1.65 - 1.53 (m, 4 H,  $\text{HC}\equiv\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$ ), 1.47 (s, 9 H,  $\underline{\text{CH}_3}$ )

**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  / ppm = 154.7 ( $\text{NC}(=\text{O})\text{O}$ ), 84.2 ( $\text{HC}\equiv\text{C}$ ), 79.6 ( $\text{C}(\text{CH}_3)_3$ ), 68.5 ( $\text{HC}\equiv\text{C}$ ), 60.4 ( $\text{HC}\equiv\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$ ), 58.0 ( $\text{HC}\equiv\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\underline{\text{CH}_2})\underline{\text{CH}_2}$ ), 53.0 ( $\text{BocN}(\underline{\text{CH}_2})\underline{\text{CH}_2}$ ), 28.4 ( $\text{C}(\underline{\text{CH}_3})_3$ ), 26.3 ( $\text{HC}\equiv\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$ ), 25.7 ( $\text{HC}\equiv\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$ ), 18.3 ( $\text{HC}\equiv\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$ )

**HRMS** ( $\text{ESI}^+$ )  $m/z$  / Da = 267.2073,  $[\text{M}+\text{H}]^+$ ,  $[\text{C}_{15}\text{H}_{27}\text{N}_2\text{O}_2]^+$  requires 267.2064

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



*tert*-Butyl 4-(hex-5-yn-1-yl)piperazine-1-carboxylate **51** (763 mg, 2.86 mmol) was stirred in TFA (10 mL) at r.t. for 2 h. The TFA was removed under vacuum followed by co-evaporation with  $\text{CH}_2\text{Cl}_2$  ( $2 \times 20$  mL). The oil was diluted with  $\text{H}_2\text{O}$  (10 mL) and the pH adjusted to 14 with NaOH (10 % aq.). This mixture was extracted with  $\text{CH}_2\text{Cl}_2$  ( $2 \times 20$  mL) and the combined organic layers were dried over  $\text{MgSO}_4$ . The solvent was removed under vacuum and purified by column chromatography ( $\text{SiO}_2$  MeOH/ $\text{CH}_2\text{Cl}_2$  3:7) to give a colourless liquid (476 mg, 2.86 mmol, 100 %).

**TLC**  $R_f$  (30 % MeOH/ $\text{CH}_2\text{Cl}_2$ ) = 0.20

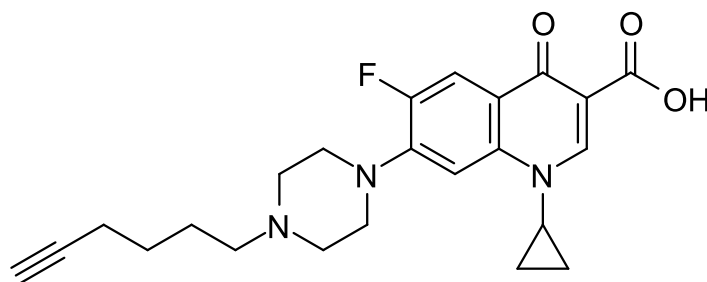
**IR** (neat)  $\nu_{\text{max}}$  /  $\text{cm}^{-1}$  = 3295.87 (alkyne C-H), 2941.07 (alkane C-H), 2810.64 (alkane C-H), 1637.22 (N-H bend)

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  / ppm = 2.88 (t,  $J$  = 4.9 Hz, 4 H,  $\text{HN}(\underline{\text{CH}_2})\underline{\text{CH}_2}$ ), 2.39 (m, 4 H,  $\text{HC}\equiv\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\underline{\text{CH}_2})\underline{\text{CH}_2}$ ), 2.31 (t,  $J$  = 7.1 Hz, 2 H,  $\text{HC}\equiv\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$ ), 2.20 (dt,  $J$  = 2.7, 6.8 Hz, 2 H,  $\text{HC}\equiv\text{CCH}_2$ ), 2.05 (br s, 1 H,  $\underline{\text{NH}}$ ), 1.93 (t,  $J$  = 2.7 Hz, 1 H,  $\underline{\text{H}}\text{C}\equiv\text{C}$ ), 1.65 - 1.48 (m, 4 H,  $\text{HC}\equiv\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$ )

**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  / ppm = 84.3 ( $\text{HC}\equiv\text{C}$ ), 68.4 ( $\text{HC}\equiv\text{C}$ ), 58.6 ( $\text{HC}\equiv\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$ ), 54.5 ( $\text{HC}\equiv\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\underline{\text{CH}_2})\underline{\text{CH}_2}$ ), 46.0 ( $\text{HN}(\underline{\text{CH}_2})\underline{\text{CH}_2}$ ), 26.4 ( $\text{HC}\equiv\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$ ), 25.7 ( $\text{HC}\equiv\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$ ), 18.3 ( $\text{HC}\equiv\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$ )

**HRMS** ( $\text{ESI}^+$ )  $m/z$  / Da = 167.1548,  $[\text{M}+\text{H}]^+$ ,  $[\text{C}_{10}\text{H}_{19}\text{N}_2]^+$  requires 167.1548

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



7-Chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **53** (1.27 g, 4.51 mmol, 1 eq.), 1-(hex-5-yn-1-yl)piperazine **52** (1.5 g, 9.02 mmol, 2 eq.) and *N*-methyl-2-pyrrolidone (10 mL) were stirred in a microwave reactor at 115 °C for 24 h. The reaction mixture was cooled to r.t. and water (80 ml) was added. The mixture was stirred for 3 h and then filtered, and residue was washed with MeOH (50 ml). The resulting solid (0.571 g) was further purified by recrystallisation from EtOAc (50 ml). **54** was obtained as off-white crystals (0.219 g, 0.531 mmol, 11.8 %).

**TLC**  $R_f$  = 0.02 (10 % MeOH/CH<sub>2</sub>Cl<sub>2</sub>)

**mp**  $T$  / °C = 220 (MeOH, decomposes)

**IR** (neat)  $\nu_{max}$  / cm<sup>-1</sup> = 3211.99 (alkyne C-H), 2459.32 (O-H), 1722.63 (carboxylic acid C=O), 1626.76 (quinolone C=O)

**<sup>1</sup>H NMR** (500 MHz, DMSO-d<sub>6</sub>)  $\delta$  / ppm = 15.12 (br. s., 1 H, C(=O)OH), 8.69 (s, 1 H, *ortho* to C(=O)OH), 7.96 (d, J=13.0 Hz, 1 H, *ortho* to F), 7.61 (d, J=7.6 Hz, 1 H, *meta* to F), 3.82 - 3.92 (m, 3 H, NCH(CH<sub>2</sub>)<sub>2</sub> 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>), 3.54 - 3.68 (br. m, 2 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 3.45 (br. t, J=11.6 Hz, 2 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>), 3.21 - 3.29 (br. m, 2 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>), 3.11 - 3.20 (br. m, 2 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 2.84 (t, J=2.7 Hz, 1 H, HC≡C), 2.24 (td, J=7.0, 2.7 Hz, 2 H, HC≡CCH<sub>2</sub>), 1.83 (br. quin, J=7.5 Hz, 2 H, HC≡CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 1.52 (quin, J=7.4 Hz, 2 H, HC≡CCH<sub>2</sub>CH<sub>2</sub>), 1.29 - 1.36 (m, 2 H, NCH(CH<sub>2</sub>)<sub>2</sub>), 1.16 - 1.23 (m, 2 H, NCH(CH<sub>2</sub>)<sub>2</sub>)

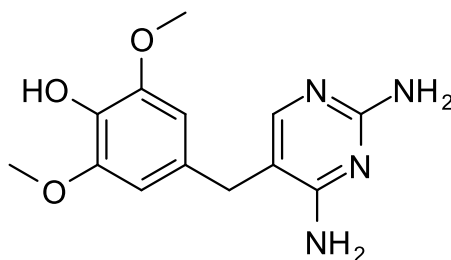
**<sup>13</sup>C NMR** (126 MHz, DMSO-d<sub>6</sub>)  $\delta$  / ppm = 176.4 (C(=O)CC(=O)OH), 165.8 (C(=O)OH), 152.8 (d, J=248.5 Hz, *ipso* to F), 148.2 (CHCC(=O)OH), 143.7 (d, J=11.1 Hz, *para* to C(=O)), 139.1 (*para* to F), 119.4 (d, J=6.9 Hz, *ipso* to C(=O)), 111.2 (d, J=22.5 Hz, *ortho* to F and *ortho* to C(=O)), 106.9 (*meta* to F and *meta* to C(=O)), 106.9 (C(=O)CC(=O)OH), 83.9 (HC≡C), 71.8 (HC≡C), 55.0 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 50.5 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 46.3 (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>), 36.0 (NCH(CH<sub>2</sub>)<sub>2</sub>), 25.2 (HC≡CCH<sub>2</sub>CH<sub>2</sub>), 22.3 (HC≡CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 17.4 (HC≡CCH<sub>2</sub>), 7.6 (NCH(CH<sub>2</sub>)<sub>2</sub>)

**<sup>19</sup>F NMR** (376.45 MHz, MeOD)  $\delta$  / ppm = -121.82 (s, ciprofloxacin F)

**HRMS** (ESI<sup>+</sup>)  $m/z$  / Da = 412.2036, [M+H]<sup>+</sup>, [C<sub>23</sub>H<sub>27</sub>N<sub>3</sub>O<sub>3</sub>F]<sup>+</sup> requires 412.2030



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



Hydrobromic acid (48 % w/w, aq., 50 ml) was heated to 100 °C, then trimethoprim (5.00 g, 17.2 mmol) was added, and the suspension was stirred for 40 min under Ar. The mixture was removed from the heat, and NaOH (50 % w/w, aq., 15 ml) was added dropwise. The reaction mixture was then cooled slowly to 0 °C, and the resulting crystals were filtered out and washed with cold water. The crystals were then dissolved in hot water (80 ml), neutralized with NH<sub>4</sub>OH (sat., aq.) and cooled slowly to 0 °C. The resulting crystals were filtered out, washed with cold water and dried under vacuum. **124** was obtained as pale pink prisms (2.06 g, 7.46 mmol, 43.4 %).

**TLC**  $R_f$  = 0.04 (5 % MeOH/CHCl<sub>2</sub>)

**mp**  $T$  / °C = 238 (H<sub>2</sub>O, decomposes)

**IR** (neat)  $\nu_{max}$  / cm<sup>-1</sup> = 3314.0 (N-H), 3137.4 (N-H), 3045.3 (C-H), 3000.9 (C-H), 2938.1 (C-H), 2838.7 (C-H), 1662.9 (pyrimidine), 1645.2 (pyrimidine), 1626.6 (pyrimidine)

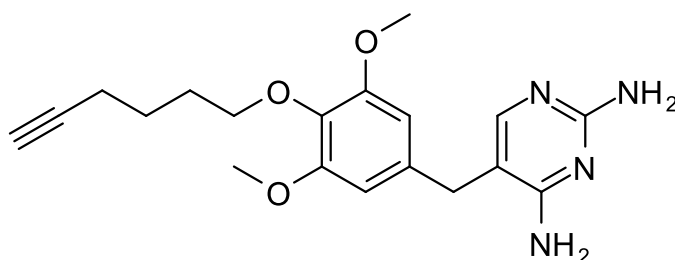
**<sup>1</sup>H NMR** (400 MHz, MeOD)  $\delta$  / ppm = 7.21 (s, 1 H, CHN), 6.54 (s, 2 H, *meta* to OCH<sub>2</sub>), 4.87 (br. s., 5 H, OH, NH<sub>2</sub> × 2), 3.82 (s, 6 H, OCH3), 3.63 (s, 2 H, CCH2C)

**<sup>13</sup>C NMR** (101 MHz, MeOD)  $\delta$  / ppm = 166.4 (CH<sub>2</sub>CCNH<sub>2</sub>), 162.0 (CHNCNH<sub>2</sub>), 156.2 (CHNCNH<sub>2</sub>), 149.8 (*ipso* to OCH<sub>3</sub>), 135.9 (*ipso* to OH), 128.2 (*para* to OH), 111.7 (CH<sub>2</sub>CCNH<sub>2</sub>), 107.5 (*meta* to OH), 57.0 (OCH3), 33.9 (CCH<sub>2</sub>C)

**HRMS** (ESI<sup>+</sup>)  $m/z$  / Da = 277.1295, [M+H]<sup>+</sup> found, [C<sub>13</sub>H<sub>17</sub>N<sub>4</sub>O<sub>3</sub>]<sup>+</sup> requires 277.1301

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

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



4-((2,4-Diaminopyrimidin-5-yl)methyl)-2,6-dimethoxyphenol **124** (1.00 g, 3.62 mmol, 1 eq.), 6-chloro-1-hexyne **175** (0.524 ml, 0.420 g, 4.34 mmol, 1.2 eq.), Cs<sub>2</sub>CO<sub>3</sub> (2.36 g, 7.24 mmol, 2 eq.) and anhydrous DMF (30 ml) were stirred at 70 °C for 7 h. The solvent was removed under reduced pressure, then CH<sub>2</sub>Cl<sub>2</sub> (30 ml) was added and the mixture filtered. The filtrate was concentrated under reduced pressure and purified by column chromatography using a Combiflash (SiO<sub>2</sub>, 5 % MeOH/CH<sub>2</sub>Cl<sub>2</sub>). **125** was obtained as a pale cream amorphous solid (0.253 g, 0.709 mmol, 19.6 %).

**TLC**  $R_f$  = 0.14 (5 % MeOH/CH<sub>2</sub>Cl<sub>2</sub>)

**IR** (neat)  $\nu_{max}$  / cm<sup>-1</sup> = 3451.4 (alkyne C-H), 3313.4 (N-H), 3136.7 (N-H), 3113.9 (N-H), 2944.2 (C-H), 2839.0 (C-H), 1635.1 (pyrimidine)

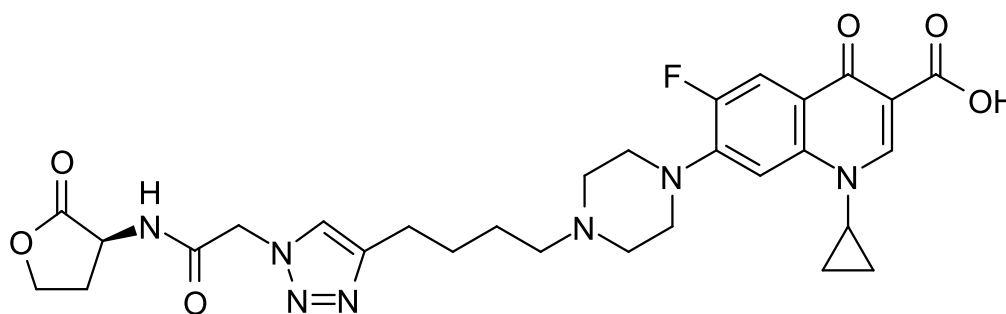
**<sup>1</sup>H NMR** (400 MHz, MeOD)  $\delta$  / ppm = 7.77 (s, 1 H, CHN), 6.37 (s, 2 H, *meta* to OCH<sub>2</sub>), 4.83 (br. s., 2 H, CHNCNH<sub>2</sub>), 4.63 (br. s., 2 H, CH<sub>2</sub>CCNH<sub>2</sub>), 3.95 (t,  $J$  = 6.3 Hz, 2 H, CH<sub>2</sub>O), 3.79 (s, 6 H, OCH<sub>3</sub>), 3.65 (s, 2 H, CCH<sub>2</sub>C), 2.28 (td,  $J$  = 7.1, 2.6 Hz, 2 H, HC≡CCH<sub>2</sub>), 1.94 (t,  $J$  = 2.7 Hz, 1 H, HC≡C), 1.81 - 1.90 (m, 2 H, CH<sub>2</sub>CH<sub>2</sub>O), 1.71 - 1.80 (m, 2 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>O)

**<sup>13</sup>C NMR** (101 MHz, MeOD)  $\delta$  / ppm = 162.7 (CH<sub>2</sub>CCNH<sub>2</sub>), 162.0 (CHNCNH<sub>2</sub>), 156.4 (CHNCNH<sub>2</sub>), 153.8 (*ipso* to OCH<sub>3</sub>), 136.0 (*ipso* to OCH<sub>2</sub>), 133.6 (*para* to OCH<sub>2</sub>), 106.5 (CH<sub>2</sub>CCNH<sub>2</sub>), 105.0 (*meta* to OCH<sub>2</sub>), 84.5 (HC≡C), 72.6 (CH<sub>2</sub>O), 68.3 (HC≡C), 56.1 (OCH<sub>3</sub>), 34.7 (CCH<sub>2</sub>C), 29.1 (CH<sub>2</sub>CH<sub>2</sub>O), 24.9 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>O), 18.0 (HC≡CCH<sub>2</sub>)

**HRMS** (ESI<sup>+</sup>)  $m/z$  / Da = 357.1920, [M+H]<sup>+</sup> found, [C<sub>19</sub>H<sub>25</sub>N<sub>4</sub>O<sub>3</sub>]<sup>+</sup> requires 357.1927

The compound has not been reported previously.

## 1.22 (*S*)-1-Cyclopropyl-6-fluoro-4-oxo-7-(4-(4-(1-(2-oxo-2-((2-oxotetrahydrofuran-3-yl)amino)ethyl)-1*H*-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid **126**



50 % water/*t*-BuOH (2 ml) was degassed by bubbling N<sub>2</sub> through it. This was then added to a mixture of 1-cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **176** (20.6 mg, 50.0  $\mu$ mol, 1 eq.) and (*S*)-2-azido-*N*-(2-oxotetrahydrofuran-3-yl)acetamide **41** (9.2 mg, 50.0  $\mu$ mol, 1 eq.). A similarly degassed solution of CuSO<sub>4</sub> · 5 H<sub>2</sub>O (624  $\mu$ g, 2.5  $\mu$ mol, 0.05 eq. 50 mM), THPTA (1.09 mg, 2.5  $\mu$ mol, 0.05 eq. 50 mM) and sodium ascorbate (991  $\mu$ g, 5  $\mu$ mol, 0.1 eq., 100 mM) in 50 % water/*t*-BuOH (50  $\mu$ l) was then added. The mixture was stirred at r.t. under argon for 3h. On observation that the reaction had stalled, the reaction was degassed again, and a further portion of catalyst solution (50  $\mu$ l) was added. After a further 3h

the reaction mixture was evaporated under reduced pressure. The residue was purified by preparatory HPLC(?? % acetonitrile/water over 15 min). The combined pure fractions were evaporated under reduced pressure and then partitioned between NaHCO<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. **126** was obtained as a white amorphous solid (8.8 mg, 14.8 μmol, 29.6 %).

**IR** (neat)  $\nu_{max}$  / cm<sup>-1</sup> = 3266.3 (N-H), 2949.0 (C-H), 2934.8 (C-H), 2827.2 (C-H), 1778.0 (lactone C=O), 1724.9 (carboxylic acid C=O), 1665.0 (amide C=O), 1625.5 (quinolone C=O)

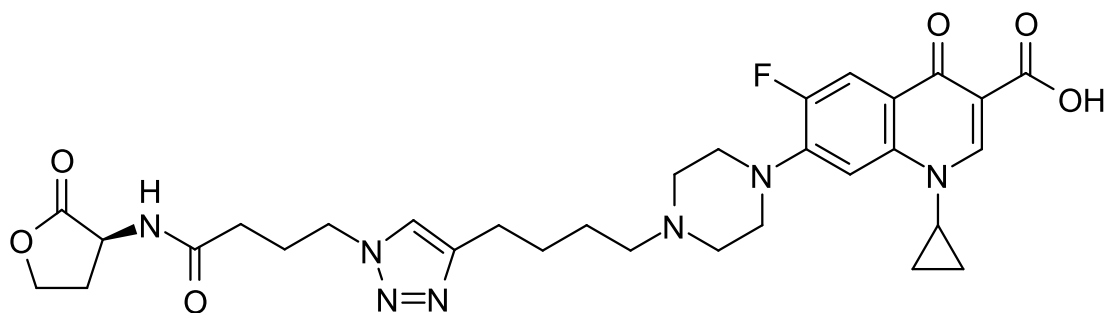
**<sup>1</sup>H NMR** (400 MHz, DMSO d<sub>6</sub>)  $\delta$  / ppm = 15.23 (s, 1 H, C(=O)OH), 8.84 (d,  $J$  = 7.9 Hz, 1 H, NH), 8.66 (s, 1 H, *ortho* to C(=O)OH), 7.90 (d,  $J$  = 13.3 Hz, 1 H, *ortho* to F), 7.82 (s, 1 H, CH=CCH<sub>2</sub>), 7.57 (d,  $J$  = 7.6 Hz, 1 H, *meta* to F), 5.13 (s, 1 H, C(=O)CHHN), 5.12 (s, 1 H, C(=O)CHHN), 4.64 (ddd,  $J$  = 10.9, 9.0, 7.8 Hz, 1 H, CHNH), 4.36 (td,  $J$  = 8.9, 1.7 Hz, 1 H, OCHH), 4.23 (ddd,  $J$  = 10.6, 8.8, 6.4 Hz, 1 H, OCHH), 3.83 (tt,  $J$  = 7.0, 4.0 Hz, 1 H, NCH(CH<sub>2</sub>)<sub>2</sub>), 3.32 (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>), 2.67 (t,  $J$  = 7.4 Hz, 2 H, CH=CCH<sub>2</sub>), 2.58 (br t,  $J$  = 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>)CH<sub>2</sub>CH<sub>2</sub>), 2.42 - 2.49 (m, 1 H, OCH<sub>2</sub>CHH), 2.40 (t,  $J$  = 7.1 Hz, 1 H, CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 2.17 (dtd,  $J$  = 11.7, 10.8, 10.8, 9.0 Hz, 1 H, OCH<sub>2</sub>CHH), 1.66 (quin,  $J$  = 7.2 Hz, 1 H, CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 1.53 (quin,  $J$  = 7.2 Hz, 1 H, CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 1.28 - 1.35 (m, 1 H, NCH(CHH)<sub>2</sub>), 1.16 - 1.21 (m, 1 H, NCH(CHH)<sub>2</sub>)

**<sup>13</sup>C NMR** (101 MHz, DMSO d<sub>6</sub>)  $\delta$  / ppm = 176.4 (C(=O)CC(=O)OH), 174.9 (OC(=O)), 166.0 (C(=O)OH), 165.9 (NH<sub>2</sub>C(=O)), 153.1 (d,  $J$  = 250.8 Hz, *ipso* to F), 148.0 (CH=CC(=O)OH), 146.6 (CH=CCH<sub>2</sub>), 145.3 (d,  $J$  = 9.6 Hz, *ipso* to piperazine), 139.2 (*para* to F), 123.4 (CH=CCH<sub>2</sub>), 118.5 (d,  $J$  = 7.5 Hz, *para* to piperazine), 110.9 (d,  $J$  = 23.5 Hz, *ortho* to C=O and *ortho* to F), 106.7 (CC(=O)OH), 106.4 (d,  $J$  = 3.2 Hz, *meta* to C=O and *meta* to F), 65.4 (OCH<sub>2</sub>), 57.3 (CH=CCH<sub>2</sub>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>)CH<sub>2</sub>CH<sub>2</sub>), 51.2 (C(=O)CH<sub>2</sub>N), 49.5 (d,  $J$  = 4.3 Hz, 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>), 48.2 (CHNH), 35.9 (NCH(CH<sub>2</sub>)<sub>2</sub>), 28.2 (CH<sub>2</sub>CHNH), 26.8 (CH=CCH<sub>2</sub>CH<sub>2</sub>), 25.7 (CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 24.9 (CH=CCH<sub>2</sub>), 7.6 (NCH(CH<sub>2</sub>)<sub>2</sub>)

**<sup>19</sup>F NMR** (376.45 MHz, DMSO d<sub>6</sub>)  $\delta$  / ppm = ??

**HRMS** (ESI<sup>+</sup>)  $m/z$  / Da = 596.2627, [M+H]<sup>+</sup> found, [C<sub>29</sub>H<sub>35</sub>FN<sub>7</sub>O<sub>6</sub>]<sup>+</sup> requires 596.2633 [ $\alpha$ ]<sub>D</sub><sup>20</sup> / °10<sup>-1</sup>cm<sup>2</sup>g<sup>-1</sup> = -3.5 ( $c$  / g(100 mL)<sup>-1</sup> = 0.0575, MeOH)

### 1.23 (*S*)-1-Cyclopropyl-6-fluoro-4-oxo-7-(4-(4-(1-(4-oxo-4-((2-oxotetrahydrofuran-3-yl)amino)butyl)-1*H*-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid **127**



IDK  
what  
happened  
after  
this,  
check,  
weigh  
etc.

column?  
equipment?

50 % water/*t*-BuOH (2 ml) was degassed by bubbling N<sub>2</sub> through it. This was then added to a mixture of 1-cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **176** (20.6 mg, 50.0 μmol, 1 eq.) and (*S*)-4-azido-*N*-(2-oxotetrahydrofuran-3-yl)butanamide **46** (10.6 mg, 50.0 μmol, 1 eq.). A similarly degassed solution of CuSO<sub>4</sub> · 5 H<sub>2</sub>O (624 μg, 2.5 μmol, 0.05 eq. 50 mM), THPTA (1.09 mg, 2.5 μmol, 0.05 eq. 50 mM) and sodium ascorbate (991 μg, 5 μmol, 0.1 eq., 100 mM) in 50 % water/*t*-BuOH (50 μl) was then added. The mixture was stirred at r.t. under argon for 3h, then the reaction mixture was evaporated under reduced pressure. The residue was purified by preparatory HPLC( % acetonitrile/water over 15 min). The combined pure fractions were evaporated under reduced pressure and then partitioned between NaHCO<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. **127** was obtained as a white amorphous solid (14.6 mg, 23.4 μmol, 46.8 %).

**IR** (neat)  $\nu_{max}$  / cm<sup>-1</sup> = 3286.7 (N-H), 2949.7 (C-H), 2820.6 (C-H), 2778.0 (C-H), 1778.1 (lactone C=O), 1725.6 (carboxylic acid C=O), 1663.7 (amide C=O), 1625.8 (quinolone C=O)

**<sup>1</sup>H NMR** (500 MHz, DMSO d<sub>6</sub>)  $\delta$  / ppm = 15.22 (br s, 1 H, C(=O)OH), 8.65 (s, 1 H, *ortho* to C(=O)OH), 8.40 (d, *J* = 8.0 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* = 7.5 Hz, 1 H, *meta* to F), 4.53 (ddd, *J* = 10.9, 9.0, 8.1 Hz, 1 H, CHNH), 4.33 (td, *J* = 8.9, 1.8 Hz, 1 H, OCHH), 4.31 (t, *J* = 7.0 Hz, 2 H, CH<sub>2</sub>NCH=C), 4.20 (ddd, *J* = 10.5, 8.8, 6.5 Hz, 1 H, OCHH), 3.82 (tt, *J* = 6.9, 4.0 Hz, 1 H, NCH(CH<sub>2</sub>)<sub>2</sub>), 3.32 (br. t, *J* = 4.2, 4.2 Hz, 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* = 7.4 Hz, 2 H, CH=CCH<sub>2</sub>), 2.57 (br. t, *J* = 5.0, 5.0 Hz, 2 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>), 2.34 - 2.42 (m, 3 H, OCH<sub>2</sub>CHH and CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 2.09 - 2.19 (m, 3 H, OCH<sub>2</sub>CHH and C(=O)CH<sub>2</sub>), 2.02 (quin, *J* = 7.2 Hz, 2 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>), 1.64 (quin, *J* = 7.6 Hz, 2 H, CH=CCH<sub>2</sub>CH<sub>2</sub>), 1.52 (quin, *J* = 7.2 Hz, 2 H, CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 1.29 - 1.34 (m, 2 H, NCH(CHH)<sub>2</sub>), 1.15 - 1.21 (m, 2 H, NCH(CHH)<sub>2</sub>)

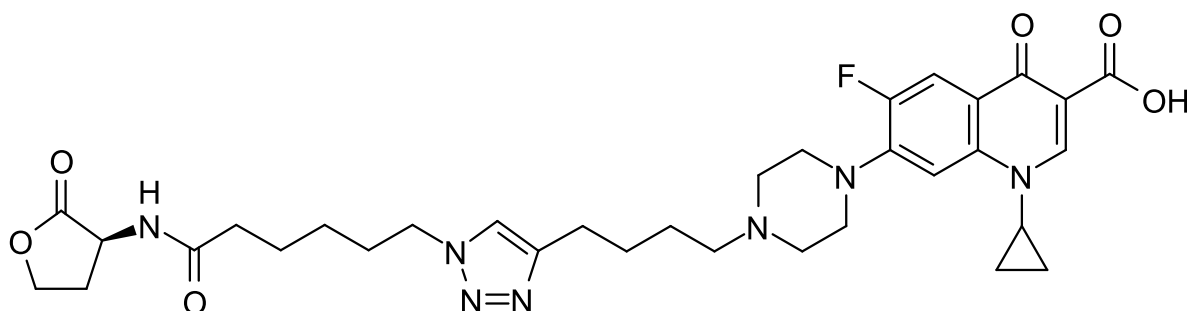
**<sup>13</sup>C NMR** (126 MHz, DMSO d<sub>6</sub>)  $\delta$  / ppm = 176.3 (C(=O)CC(=O)OH), 175.4 (OC(=O)), 171.2 (NHC(=O)), 166.0 (C(=O)OH), 153.0 (d, *J* = 248.6 Hz, *ortho* to F), 148.0 (CH=CC(=O)OH), 146.8 (CH=CCH<sub>2</sub>), 145.2 (d, *J* = 9.6 Hz, *ipso* to piperazine), 139.2 (*para* to F), 121.7 (CH=CCH<sub>2</sub>), 118.5 (d, *J* = 7.5 Hz, *para* to piperazine), 110.9 (d, *J* = 22.4 Hz, *ortho* to C=O and *ortho* to F), 106.7 (CC(=O)OH), 106.3 (d, *J* = 3.2 Hz, *meta* to C=O and *meta* to F), 65.3 (OCH<sub>2</sub>), 57.3 (CH=CCH<sub>2</sub>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>), 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>), 49.4 (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>), 48.6 (CH<sub>2</sub>NCH=C), 47.9 (OC(=O)CHNH), 35.9 (NCH(CH<sub>2</sub>)<sub>2</sub>), 31.7 (NHC(=O)CH<sub>2</sub>), 28.2 (CH<sub>2</sub>CHNH), 26.9 (CH=CCH<sub>2</sub>CH<sub>2</sub>), 25.8 (NHC(=O)CH<sub>2</sub>CH<sub>2</sub> and CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 24.9 (CH=CCH<sub>2</sub>), 7.6 (NCH(CH<sub>2</sub>)<sub>2</sub>)

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

**HRMS** (ESI<sup>+</sup>) *m/z* / Da = 624.2928, [M+H]<sup>+</sup> found, [C<sub>31</sub>H<sub>39</sub>FN<sub>7</sub>O<sub>6</sub>]<sup>+</sup> requires 624.2946 [ $\alpha$ ]<sub>D</sub><sup>20</sup> / °10<sup>-1</sup>cm<sup>2</sup>g<sup>-1</sup> = -10.6 (*c* / g(100 mL)<sup>-1</sup> = 0.094, MeOH)

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**1.24 (S)-1-Cyclopropyl-6-fluoro-4-oxo-7-(4-(4-(1-(6-oxo-6-((2-oxotetrahydrofuran-3-yl)amino)hexyl)-1H-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid **128****



50 % water/*t*-BuOH (2 ml) was degassed by bubbling N<sub>2</sub> through it. This was then added to a mixture of 1-cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **176** (20.6 mg, 50.0 μmol, 1 eq.) and (*S*)-6-azido-*N*-(2-oxotetrahydrofuran-3-yl)hexanamide **47** (12.0 mg, 50.0 μmol, 1 eq.). A similarly degassed solution of CuSO<sub>4</sub> · 5 H<sub>2</sub>O (624 μg, 2.5 μmol, 0.05 eq. 50 mM), THPTA (1.09 mg, 2.5 μmol, 0.05 eq. 50 mM) and sodium ascorbate (991 μg, 5 μmol, 0.1 eq., 100 mM) in 50 % water/*t*-BuOH (50 μl) was then added. The mixture was stirred at r.t. under argon for 3h, then the reaction mixture was dry-loaded onto SiO<sub>2</sub> and purified by column chromatography using a Combiflash (SiO<sub>2</sub>, 0-20 % 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. **126** was obtained as a white amorphous solid (12.4 mg, 19.0 μmol, 38.0 %).

**TLC** *R<sub>f</sub>* = 0.30 (30 % MeOH/CH<sub>2</sub>Cl<sub>2</sub>)

**IR** (neat)  $\nu_{max}$  / cm<sup>-1</sup> = 3301.8 (N-H), 2939.7 (C-H), 2857.5 (C-H), 1784.6 (lactone C=O), 1728.5 (carboxylic acid C=O), 1658.2 (amide C=O), 1625.5 (quinolone C=O)

**<sup>1</sup>H NMR** (500 MHz, DMSO d<sub>6</sub>)  $\delta$  / ppm = 15.22 (br s, 1 H, C(=O)OH), 8.65 (s, 1 H, *ortho* to C(=O)OH), 8.32 (d, *J* = 8.0 Hz, 1 H, NH), 7.89 (d, *J* = 13.3 Hz, 1 H, *ortho* to F), 7.84 (s, 1 H, CH=CCH<sub>2</sub>), 7.55 (d, *J* = 7.6 Hz, 1 H, *meta* to F), 4.51 (ddd, *J* = 10.9, 9.1, 7.9 Hz, 1 H, CHNH), 4.33 (td, *J* = 8.8, 1.8 Hz, 1 H, OCHH), 4.28 (t, *J* = 7.1 Hz, 2 H, CH<sub>2</sub>NCH=C), 4.19 (ddd, *J* = 10.5, 8.7, 6.6 Hz, 1 H, OCHH), 3.82 (tt, *J* = 7.0, 4.0 Hz, 1 H, NCH(CH<sub>2</sub>)<sub>2</sub>), 3.32 (br t, *J* = 4.5, 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>), 2.63 (t, *J* = 7.5 Hz, 2 H, CH=CCH<sub>2</sub>), 2.57 (br t, *J* = 4.2, 4.2 Hz, 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>), 2.33 - 2.41 (m, 3 H, OCH<sub>2</sub>CHH and CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 2.06 - 2.16 (m, 3 H, OCH<sub>2</sub>CHH and C(=O)CH<sub>2</sub>), 1.79 (quin, *J* = 7.4 Hz, 2 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 1.63 (quin, *J* = 7.5 Hz, 2 H, CH=CCH<sub>2</sub>CH<sub>2</sub>), 1.45 - 1.56 (m, 4 H, C(=O)CH<sub>2</sub>CH<sub>2</sub> and CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 1.29 - 1.34 (m, 2 H, NCH(CH<sub>2</sub>)<sub>2</sub>), 1.19 - 1.25 (m, 2 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 1.15 - 1.19 (m, 2 H, NCH(CH<sub>2</sub>)<sub>2</sub>)

**<sup>13</sup>C NMR** (126 MHz, DMSO d<sub>6</sub>)  $\delta$  / ppm = 176.4 (C(=O)CC(=O)OH), 175.4 (OC(=O)), 172.1 (NHC(=O)), 166.0 (C(=O)OH), 153.0 (d, *J* = 250.2 Hz, *ipso* to F), 148.0 (CH=CC(=O)OH), 146.8 (CH=CCH<sub>2</sub>), 145.2 (d, *J* = 9.6 Hz, *ipso* to piperazine), 139.2 (*para* to F), 121.6 (CH=CCH<sub>2</sub>), 118.5 (d, *J* = 8.0 Hz, *para* to piperazine), 110.9 (d, *J* = 23.5 Hz, *ortho* to C=O and *ortho* to F), 106.7 (CC(=O)OH), 106.3 (d, *J* = 2.1 Hz, *meta* to C=O and *meta* to F), 65.3 (OCH<sub>2</sub>), 57.4 (CH=CCH<sub>2</sub>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>)CH<sub>2</sub>CH<sub>2</sub>), 49.5 (d, *J* = 3.2 Hz, 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>), 49.0 (CH<sub>2</sub>NCH=C), 47.8 (CHNH), 35.9 (NCH(CH<sub>2</sub>)<sub>2</sub>), 34.8 (NHC(=O)CH<sub>2</sub>), 29.5 (CH<sub>2</sub>CH<sub>2</sub>NCH=C), 28.3 (CH<sub>2</sub>CHNH), 26.9 (CH=CCH<sub>2</sub>CH<sub>2</sub>), 25.7 (CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>),

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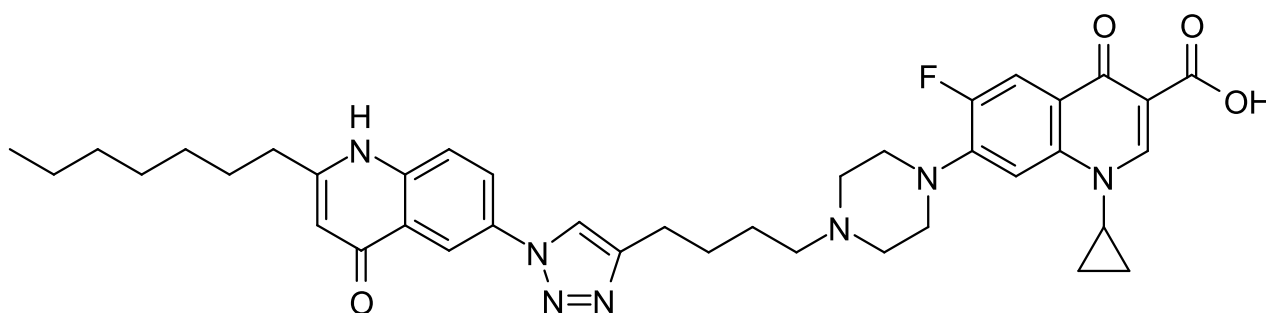
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25.4 (NHC(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 24.9 (CH=CCH<sub>2</sub>), 24.5 (NHC(=O)CH<sub>2</sub>CH<sub>2</sub>), 7.6 (NCH(CH<sub>2</sub>)<sub>2</sub>)

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

HRMS (ESI<sup>+</sup>) *m/z* / Da = 652.3254, [M+H]<sup>+</sup> found, [C<sub>33</sub>H<sub>43</sub>FN<sub>7</sub>O<sub>6</sub>]<sup>+</sup> requires 652.3248 [α]<sub>D</sub><sup>20</sup> / °10<sup>-1</sup>cm<sup>2</sup>g<sup>-1</sup> = -8.5 (c / g(100 mL)<sup>-1</sup> = 0.106, MeOH)

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



50 % water/*t*-BuOH (1 ml) was degassed by bubbling N<sub>2</sub> through it. This was then added to a mixture of 1-cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **176** (4.1 mg, 10.0 μmol, 1 eq.) and 6-azido-2-heptylquinolin-4(1*H*)-one **26** (2.8 mg, 10.0 μmol, 1 eq.). A similarly degassed solution of CuSO<sub>4</sub> · 5H<sub>2</sub>O (125 μg, 0.5 μmol, 0.05 eq. 50 mM), THPTA (218 μg, 0.5 μmol, 0.05 eq. 50 mM) and sodium ascorbate (198 μg, 1 μmol, 0.1 eq., 100 mM) in 50 % water/*t*-BuOH (10 μl) was then added. The mixture was stirred at r.t. under argon for 1.5 h, then the reaction mixture was evaporated under reduced pressure. The residue was purified by preparatory HPLC (50-100 % acetonitrile/water over ??min). The combined pure fractions were evaporated under reduced pressure and then partitioned between NaHCO<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. **129** was obtained as a white amorphous solid (8.6 mg, 2.7 μmol, 27.0 %).

IR (neat) ν<sub>max</sub> / cm<sup>-1</sup> = 2927.0 (C-H), 2865.5 (C-H), 1715.5 (carboxylic acid C=O), 1631.0 (ciprofloxacin quinolone C=O and HHQ C=O)

<sup>1</sup>H NMR (500 MHz, DMSO d<sub>6</sub>) 15.12 (br s, C(=O)OH), 11.79 (s, 1 H, NH), 8.75 (s, 1 H, NCH=CCH<sub>2</sub>), 8.71 (s, 1 H, *ortho* to C(=O)OH), 8.40 (d, J=2.7 Hz, 1 H, *ortho* to C(=O) and *ortho* to N), 8.18 (dd, J=8.9, 2.6 Hz, 1 H, *para* to C(=O) and *ortho* to N), 7.99 (d, J=13.0 Hz, 1 H, *ortho* to F), 7.75 (d, J=9.0 Hz, 1 H, *meta* to C(=O) and *meta* to N), 7.62 (d, J=7.8 Hz, 1 H, *meta* to F), 6.02 (s, 1 H, NHC=CHC(=O)), 3.85 (tt, J=7.0, 4.0 Hz, 1 H, NCH(CH<sub>2</sub>)<sub>2</sub>), 3.23 - 3.30 (m, 6 H, CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 2.82 (t, J=5.9 Hz, 2 H, NCH=CCH<sub>2</sub>), 2.63 (t, J=7.9 Hz, 2 H, CH<sub>2</sub>C=CHC(=O)), 1.76 - 1.81 (m, 4 H, NCH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 1.70 (quin, J=7.2 Hz, 2 H, CH<sub>2</sub>CH<sub>2</sub>C=CHC(=O)), 1.15 - 1.38 (m, 12 H, CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>, NCH(CH<sub>2</sub>)<sub>2</sub> and NCH(CH<sub>2</sub>)<sub>2</sub>), 0.87 (t, J=6.9 Hz, 3 H, CH<sub>3</sub>)

<sup>13</sup>C NMR (126 MHz, DMSO d<sub>6</sub>) δ / ppm = 176.4 (C(=O)CC(=O)OH), 176.3 (CHC(=O)), 165.8 (C(=O)OH), 154.3 (CCHC(=O)), 152.9 (d, J=240.1 Hz, *ipso* to F), 148.3 (CH=CC(=O)OH), 147.5 (NCHCCH<sub>2</sub>), 143.3 (d, J=8.5 Hz, *ortho* to F and *ipso* to N), 139.6 (*ipso* to NH), 139.0 (*para* to F), 132.0 (*para* to NH), 124.9 (*ipso*

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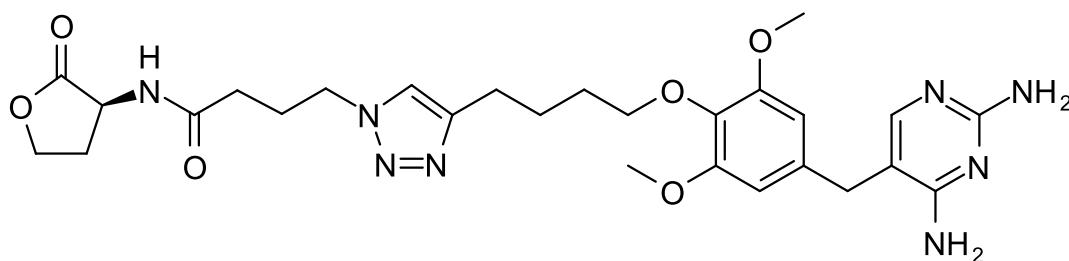
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to C(=O) and *ortho* to NH), 123.6 (*para* to C(=O) and *meta* to NH), 120.5 (NCH=CCH<sub>2</sub>), 120.0 (*meta* to C(=O) and *meta* to N), 119.6 (d, J=9.6 Hz, *ipso* to C(=O) and *para* to N), 115.1 (*ortho* to C(=O) and *ortho* to N), 111.3 (d, J=28.8 Hz, *ortho* to F and *ortho* to C(=O)), 107.9 (*meta* to F and *meta* to C(=O)), 107.2 (CHC(=O)), 106.9 (CC(=O)OH), 55.4 (CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 50.6 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>)), 46.5 (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>), 36.0 (NCH(CH<sub>2</sub>)<sub>2</sub>), 33.2 (CH<sub>2</sub>CNH), 31.2 (CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>), 28.3 - 28.5 (CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 25.6 (CH=CCH<sub>2</sub>CH<sub>2</sub>), 24.4 (CH=CCH<sub>2</sub>), 22.7 (CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 22.0 (CH<sub>3</sub>CH<sub>2</sub>), 13.9 (CH<sub>3</sub>), 7.6 (NCH(CH<sub>2</sub>)<sub>2</sub>)

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

HRMS (ESI<sup>+</sup>) *m/z* / Da = 696.3667, [M+H]<sup>+</sup> found, [C<sub>39</sub>H<sub>47</sub>FN<sub>7</sub>O<sub>4</sub>]<sup>+</sup> requires 696.3668

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



Method?? pale brown gum 4.8 mg, 8.4 μmol

TLC *R<sub>f</sub>* = 0.30 (30 % MeOH/CH<sub>2</sub>Cl<sub>2</sub>)

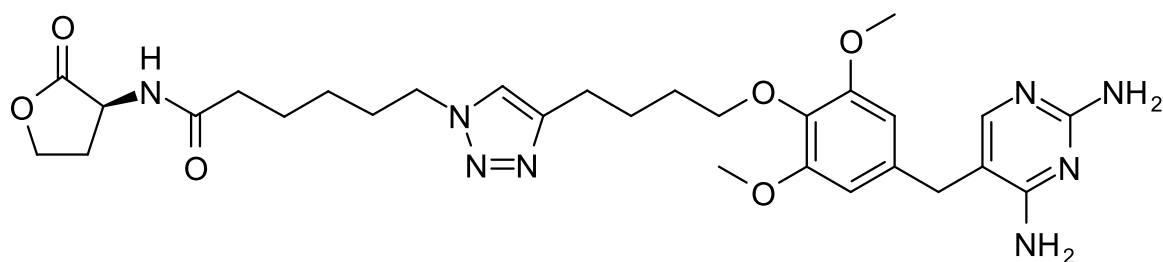
IR (neat)  $\nu_{max}$  / cm<sup>-1</sup> = 3340.5 (N-H), 3303.3 (N-H), 3182.5 (N-H), 2933.8 (C-H), 1774.2 (lactone C=O), 1659.7 (amide C=O and pyrimidine)

<sup>1</sup>H NMR (500 MHz, DMSO d<sub>6</sub>) δ / ppm = 8.43 (d, J=8.0 Hz, 1 H, NH), 7.80 (s, 1 H, NCH=CCH<sub>2</sub>), 7.46 (s, 1 H, CHN=CNH<sub>2</sub>), 6.68 (br s, 2 H, CH<sub>2</sub>CCNH<sub>2</sub>), 6.53 (s, 2 H, *meta* to CH<sub>2</sub>), 6.21 (br s, 2 H, CHN=CNH<sub>2</sub>), 4.49 (dt, J=10.7, 8.6 Hz, 1 H, CHNH), 4.32 (td, J=8.7, 1.6 Hz, 1 H, CHHOC(=O)), 4.29 (t, J=6.8 Hz, 2 H, CH<sub>2</sub>N), 4.19 (ddd, J=10.6, 8.7, 6.5 Hz, 1 H, CHHOC(=O)), 3.79 (t, J=6.2 Hz, 2 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>O), 3.68 (s, 6 H, CH<sub>3</sub>), 3.53 (br s, 2 H, CCH<sub>2</sub>C), 2.63 (t, J=7.5 Hz, 2 H, CH=CCH<sub>2</sub>), 2.37 (dddd, J=12.2, 8.9, 6.7, 1.8 Hz, 1 H, CHHCHNH), 2.08 - 2.15 (m, 3 H, CHHCHNH and C(=O)CH<sub>2</sub>), 2.00 (quin, J=7.2 Hz, 2 H, CH<sub>2</sub>CH<sub>2</sub>N), 1.72 (quin, J=7.3 Hz, 2 H, CH=CCH<sub>2</sub>CH<sub>2</sub>), 1.61 (quin, J=6.7 Hz, 2 H, CH<sub>2</sub>CH<sub>2</sub>O)

<sup>13</sup>C NMR (126 MHz, DMSO d<sub>6</sub>) δ / ppm = 175.8 (OC=O), 171.9 (NHC=O), 163.1 (CC(NH<sub>2</sub>)N), 159.7 (br s, NC(NH<sub>2</sub>)N), 153.2 (*ipso* to OCH<sub>3</sub>), 150.5 (br s, CHNC(NH<sub>2</sub>)N), 147.3 (NCH=CCH<sub>2</sub>CH<sub>2</sub>), 135.2 (*para* to CH<sub>2</sub>O), 135.0 (*ipso* to CH<sub>2</sub>O), 122.1 (CH=CCH<sub>2</sub>CH<sub>2</sub>), 107.3 (CH<sub>2</sub>CC(NH<sub>2</sub>)=N), 106.2 (*meta* to CH<sub>2</sub>O), 72.3 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>O), 65.7 (OCH<sub>2</sub>CH<sub>2</sub>CHNH), 56.2 (OCH<sub>3</sub>), 48.9 (CH<sub>2</sub>N), 48.3 (CHNH), 32.9 (CCH<sub>2</sub>C), 32.0 (C(=O)CH<sub>2</sub>), 29.3 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>O), 28.4 (OCH<sub>2</sub>CH<sub>2</sub>CHNH), 26.0 (CH<sub>2</sub>CH<sub>2</sub>N), 25.7 (CH=CCH<sub>2</sub>CH<sub>2</sub>), 24.9 (CH=CCH<sub>2</sub>CH<sub>2</sub>)

HRMS (ESI<sup>+</sup>) *m/z* / Da = 569.2834, [M+H]<sup>+</sup> found, [C<sub>27</sub>H<sub>37</sub>N<sub>8</sub>O<sub>6</sub>]<sup>+</sup> requires 569.2836 [α]<sub>D</sub><sup>20</sup> / °10<sup>-1</sup>cm<sup>2</sup>g<sup>-1</sup> = -4.6 (c / g(100 mL)<sup>-1</sup> = 0.0433, MeOH)

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



50 % water/*t*-BuOH (2 ml) was degassed by bubbling N<sub>2</sub> through it. This was then added to a mixture of 5-(4-(hex-5-yn-1-yloxy)-3,5-dimethoxybenzyl)pyrimidine-2,4-diamine **125** (20.6 mg, 50.0 μmol, 1 eq.) and (*S*)-6-azido-*N*-(2-oxotetrahydrofuran-3-yl)hexanamide **47** (18.0 mg, 75.0 μmol, 1.5 eq.). Similarly degassed solutions of CuSO<sub>4</sub> · 5 H<sub>2</sub>O (624 μg, 2.5 μmol, 0.05 eq. 50 mM), THPTA (1.09 mg, 2.5 μmol, 0.05 eq. 50 mM) and sodium ascorbate (991 μg, 5 μmol, 0.1 eq., 100 mM) in water (50 μl) were then added. An extra portion of **47** (12.0 mg, 50.0 μmol, 1 eq.) was added after 1 d. . **131** was obtained as a clear gum (8.0 mg, 13.4 μmol, 26.8 %).

**TLC** *R<sub>f</sub>* = 0.35 (30 % MeOH/CH<sub>2</sub>Cl<sub>2</sub>)

**IR** (neat)  $\nu_{max}$  / cm<sup>-1</sup> = 3336.0 (N-H), 3208.7 (N-H), 2941.1 (C-H), 2869.2 (C-H), 1775.2 (lactone C=O), 1657.3 (amide C=O and pyrimidine)

**<sup>1</sup>H NMR** (500 MHz, DMSO d<sub>6</sub>)  $\delta$  / ppm = 8.34 (d, *J* = 8.0 Hz, 1 H, NH), 7.83 (s, 1 H, NCH=CCH<sub>2</sub>), 7.50 (s, 1 H, CHN=CNH<sub>2</sub>), 6.54 (s, 2 H, *meta* to CH<sub>2</sub>), 6.17 (br s, 2 H, CH<sub>2</sub>CCNH<sub>2</sub>), 5.77 (br s, 2 H, CHN=CNH<sub>2</sub>), 4.51 (ddd, *J* = 11.0, 9.0, 8.1 Hz, 1 H, CHNH), 4.33 (td, *J* = 8.8, 1.9 Hz, 1 H, CHHOC(=O)), 4.27 (t, *J* = 7.1 Hz, 2 H, CH<sub>2</sub>N), 4.19 (ddd, *J* = 10.5, 8.7, 6.5 Hz, 1 H, CHHOC(=O)), 3.80 (t, *J* = 6.3 Hz, 2 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>O), 3.70 (s, 6 H, CH<sub>3</sub>), 3.52 (s, 2 H, CCH<sub>2</sub>C), 2.64 (t, *J* = 7.5 Hz, 2 H, CH=CCH<sub>2</sub>), 2.36 (dddd, *J* = 12.1, 8.9, 6.7, 1.8 Hz, 1 H, CHHCHNH), 2.06 - 2.16 (m, 3 H, CHHCHNH and C(=O)CH<sub>2</sub>), 1.78 (quin, *J* = 7.4 Hz, 2 H, CH<sub>2</sub>CH<sub>2</sub>N), 1.73 (quin, *J* = 7.7 Hz, 2 H, CH=CCH<sub>2</sub>CH<sub>2</sub>), 1.63 (quin, *J* = 6.8 Hz, 2 H, CH<sub>2</sub>CH<sub>2</sub>O), 1.52 (quin, *J* = 7.5 Hz, 2 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>), 1.17 - 1.27 (m, 2 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>)

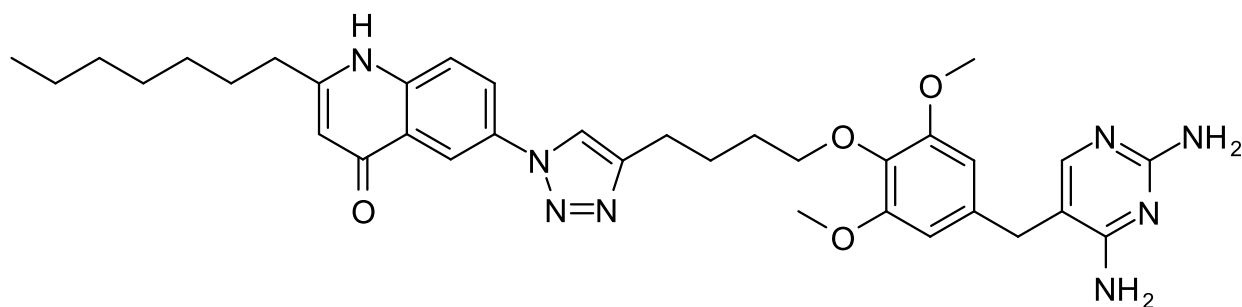
**<sup>13</sup>C NMR** (125 MHz, DMSO d<sub>6</sub>)  $\delta$  / ppm = 175.4 (OC=O), 172.0 (NHC=O), 162.2 (CC(NH<sub>2</sub>)N), 161.8 (NC(NH<sub>2</sub>)N), 154.8 (CHNC(NH<sub>2</sub>)N), 152.8 (*ipso* to OCH<sub>3</sub>), 146.7 (CH=CCH<sub>2</sub>CH<sub>2</sub>), 135.5 (*para* to CH<sub>2</sub>O), 134.8 (*ipso* to CH<sub>2</sub>O), 121.6 (CH=CCH<sub>2</sub>CH<sub>2</sub>), 105.9 (CH<sub>2</sub>CC(NH<sub>2</sub>)=N), 105.8 (*meta* to CH<sub>2</sub>O), 71.9 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>O), 65.2 (OCH<sub>2</sub>CH<sub>2</sub>CHNH), 55.8 (OCH<sub>3</sub>), 49.0 (CH<sub>2</sub>N), 47.8 (CHNH), 34.8 (C(=O)CH<sub>2</sub>), 32.9 (CCH<sub>2</sub>C), 29.4 (CH<sub>2</sub>CH<sub>2</sub>N), 29.1 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>O), 28.2 (OCH<sub>2</sub>CH<sub>2</sub>CHNH), 25.5 (CH=CCH<sub>2</sub>CH<sub>2</sub>), 25.3 (C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 24.7 (CH=CCH<sub>2</sub>CH<sub>2</sub>), 24.4 (C(=O)CH<sub>2</sub>CH<sub>2</sub>)

**HRMS** (ESI<sup>+</sup>) *m/z* / Da = 597.3149, [M+H]<sup>+</sup> found, [C<sub>29</sub>H<sub>41</sub>N<sub>8</sub>O<sub>6</sub>]<sup>+</sup> requires 597.3144 [ $\alpha$ ]<sub>D</sub><sup>20</sup> / °10<sup>-1</sup>cm<sup>2</sup>g<sup>-1</sup> = -3.6 (*c* / g(100 mL)<sup>-1</sup> = 0.11, MeOH)

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**1.28 6-(4-(4-(4-((2,4-Diaminopyrimidin-5-yl)methyl)-2,6-dimethoxyphenoxy)butyl)-1*H*-1,2,3-triazol-1-yl)-2-heptylquinolin-4(1*H*)-one 132**



50 % water/*t*-BuOH (1 ml) was degassed by bubbling N<sub>2</sub> through it. This was then added to a mixture of 5-(4-(hex-5-yn-1-yloxy)-3,5-dimethoxybenzyl)pyrimidine-2,4-diamine **125** (3.6 mg, 10.0 μmol, 1 eq.) and 6-azido-2-heptylquinolin-4(1*H*)-one **26** (2.8 mg, 10.0 μmol, 1 eq.). A similarly degassed solution of CuSO<sub>4</sub> · 5 H<sub>2</sub>O (125 μg, 0.5 μmol, 0.05 eq. 50 mM), THPTA (218 μg, 0.5 μmol, 0.05 eq. 50 mM) and sodium ascorbate (198 μg, 1 μmol, 0.1 eq., 100 mM) in water (10 μl) was then added. The mixture was stirred at r.t. under argon for 1.5 h, then the reaction mixture was evaporated under reduced pressure. The residue was purified by preparatory HPLC (5-100 % acetonitrile/water over 20 min). The combined pure fractions were evaporated under reduced pressure. **132** was obtained as a clear gum (2.6 mg, 4.1 μmol, 41.0 %).

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**TLC** *R<sub>f</sub>* = 0.17 (20 % MeOH/CH<sub>2</sub>Cl<sub>2</sub>)

**IR** (neat)  $\nu_{max}$  / cm<sup>-1</sup> = 2927.7 (C-H), 2855.5 (C-H), 1664.1 (pyrimidine), 1645.4 (pyrimidine and HHQ C=O),

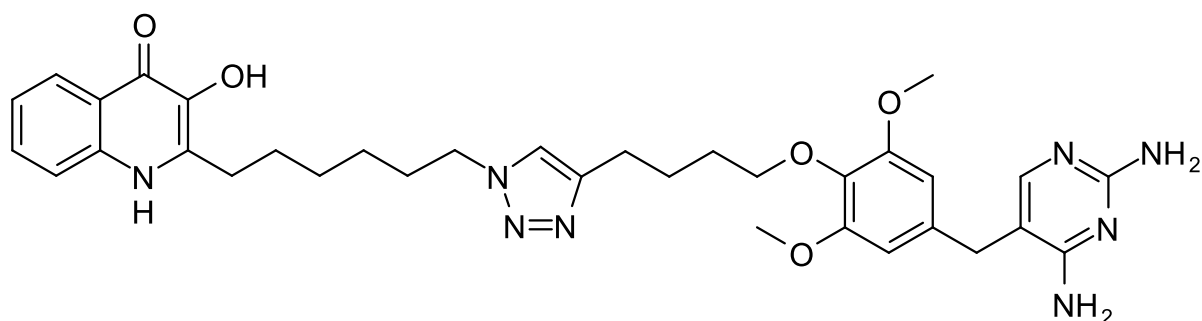
**<sup>1</sup>H NMR** (500 MHz, DMSO d<sub>6</sub>)  $\delta$  / ppm = 11.80 (s, 1 H, NH), 8.69 (s, 1 H, NCH=CCH<sub>2</sub>), 8.41 (d, *J* = 2.7 Hz, 1 H, *ortho* to C=O), 8.17 (dd, *J* = 9.0, 2.6 Hz, 1 H, *para* to C=O), 7.73 (d, *J* = 9.0 Hz, 1 H, *ortho* to NH), 7.51 (br s, 4 H, NH<sub>2</sub>), 7.41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

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**<sup>13</sup>C NMR** (125 MHz, DMSO d<sub>6</sub>)  $\delta$  / ppm = 176.4 (C=O), 164.1 (CC(NH<sub>2</sub>)N), 154.3 (HNC), 154.2 (NC(NH<sub>2</sub>)N), 153.1 (*ipso* to OCH<sub>3</sub>), 148.3 (CH=CCH<sub>2</sub>CH<sub>2</sub>), 140.2 (CHNC(NH<sub>2</sub>)N), 139.6 (*ipso* to NH), 135.4 (*ipso* to CH<sub>2</sub>O), 132.8 (*para* to CH<sub>2</sub>O), 132.1 (*para* to NH), 124.9 (*ipso* to C=O), 123.7 (*para* to C=O), 120.3 (CH=CCH<sub>2</sub>CH<sub>2</sub>), 120.0 (*meta* to C=O and *ortho* to NH), 115.1 (*ortho* to C=O and *meta* to NH), 109.0 (CH<sub>2</sub>CC(NH<sub>2</sub>)=N), 108.0 (C(=O)CH), 106.3 (*meta* to CH<sub>2</sub>O), 72.0 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>O), 56.0 (OCH<sub>3</sub>), 33.3 (HNCCH<sub>2</sub>), 32.1 (CCH<sub>2</sub>C), 31.2 (CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>), 29.1 (CH<sub>2</sub>CH<sub>2</sub>O), 28.3 - 28.6 (CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 25.3 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>O), 24.7 (CH=CCH<sub>2</sub>), 22.1 (CH<sub>3</sub>CH<sub>2</sub>), 14.0 (CH<sub>3</sub>CH<sub>2</sub>)

**HRMS** (ESI<sup>+</sup>) *m/z* / Da = 641.3557, [M+H]<sup>+</sup> found, [C<sub>35</sub>H<sub>45</sub>N<sub>8</sub>O<sub>4</sub>]<sup>+</sup> 641.3558

**1.29 2-(6-(4-(4-(4-((2,4-Diaminopyrimidin-5-yl)methyl)-2,6-dimethoxyphenoxy)butyl)-1*H*-1,2,3-triazol-1-yl)hexyl)-3-hydroxyquinolin-4(1*H*)-one **133****



50 % water/*t*-BuOH (1 ml) was degassed by bubbling N<sub>2</sub> through it. This was then added to a mixture of 5-(4-(hex-5-yn-1-yloxy)-3,5-dimethoxybenzyl)pyrimidine-2,4-diamine **125** (14.2 mg, 39.8 μmol, 1 eq.) and 2-(6-azidoethyl)-3-hydroxyquinolin-4(1*H*)-one **70** (11.4 mg, 39.8 μmol, 1 eq.). A similarly degassed solution of CuSO<sub>4</sub> · 5 H<sub>2</sub>O (1.25 mg, 5 μmol, 0.125 eq. 50 mM), THPTA (2.18 mg, 5 μmol, 0.125 eq. 50 mM) and sodium ascorbate (1.98 mg, 10 μmol, 0.25 eq., 100 mM) in water (100 μl) was then added. The mixture was stirred at r.t. under argon for 3 h, then MeOH (1 ml) was added and the reaction mixture was dry-loaded onto SiO<sub>2</sub> and purified by column chromatography (SiO<sub>2</sub>, 0-20 % 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. **133** was obtained as a pale brown amorphous solid (4.7 mg, 7.3 μmol, 18.3 %).

**TLC** *R<sub>f</sub>* = 0.21 (20 % MeOH/CH<sub>2</sub>Cl<sub>2</sub>)

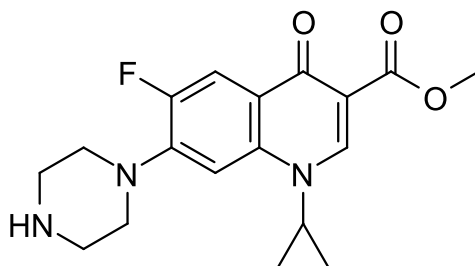
**IR** (neat)  $\nu_{max}$  / cm<sup>-1</sup> = 2924.8 (C-H), 2853.4 (C-H), 1660.0 (pyrimidine), 1638.8 (pyrimidine and PQS C=O),

**<sup>1</sup>H NMR** (500 MHz, DMSO d<sub>6</sub>)  $\delta$  / ppm = 11.53 (br s, 1 H, NH), 8.09 (d, *J* = 8.0 Hz, 1 H, *ortho* to C=O), 7.83 (s, 1 H, NCH=CCH<sub>2</sub>), 7.48 - 7.57 (m, 3 H, *para* to C=O, *ortho* to NH and CHN=CNH<sub>2</sub>), 7.21 (ddd, *J* = 8.0, 6.3, 1.5 Hz, 1 H, *para* to NH), 6.55 (s, 2 H, *meta* to CH<sub>2</sub>), 4.28 (t, *J* = 7.1 Hz, 2 H, CH<sub>2</sub>N), 3.80 (t, *J* = 6.2 Hz, 2 H, CH<sub>2</sub>O), 3.70 (s, 6 H, CH<sub>3</sub>), 3.53 (d, *J* = 0.3 Hz, 2 H, CCH<sub>2</sub>C), 2.73 (t, *J* = 7.5 Hz, 2 H, HNCCH<sub>2</sub>), 2.64 (t, *J* = 7.4 Hz, 2 H, CH=CCH<sub>2</sub>), 1.80 (quin, *J* = 7.4 Hz, 2 H, CH<sub>2</sub>CH<sub>2</sub>N), 1.73 (quin, *J* = 7.5 Hz, 2 H, CH=CCH<sub>2</sub>CH<sub>2</sub>), 1.66 (quin, *J* = 7.2 Hz, 2 H, HNCCH<sub>2</sub>CH<sub>2</sub>), 1.62 (quin, *J* = 6.8 Hz, 2 H, CH<sub>2</sub>CH<sub>2</sub>O), 1.33 - 1.40 (m, 2 H, HNCCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 1.27 - 1.32 (m, 2 H, HNCCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>)

**<sup>13</sup>C NMR** (125 MHz, DMSO d<sub>6</sub>)  $\delta$  / ppm = 168.9 (C=O), 162.5 (CC(NH<sub>2</sub>)N), 162.5 (NC(NH<sub>2</sub>)N), 152.9 (CHNC(NH<sub>2</sub>)N), 152.8 (*ipso* to OCH<sub>3</sub>), 146.8 (CH=CCH<sub>2</sub>CH<sub>2</sub>), 137.7 (COH), 137.3 (*para* to OH), 135.4 (HNC), 135.1 (*para* to CH<sub>2</sub>O), 134.8 (*ipso* to CH<sub>2</sub>O), 129.9 (*para* to C=O), 124.4 (*ortho* to C=O and *meta* to NH), 122.1 (*ipso* to C=O), 121.5 (*para* to NH), 121.4 (CH=CCH<sub>2</sub>CH<sub>2</sub>), 117.7 (*meta* to C=O and *ortho* to NH), 106.2 (CH<sub>2</sub>CC(NH<sub>2</sub>)=N), 105.8 (*meta* to CH<sub>2</sub>O), 71.9 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>O), 55.8 (OCH<sub>3</sub>), 49.0 (CH<sub>2</sub>N), 32.8 (CCH<sub>2</sub>C), 29.5 (CH<sub>2</sub>CH<sub>2</sub>N), 29.0 (CH<sub>2</sub>CH<sub>2</sub>O), 28.1 (HNCCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 27.9 (HNCCH<sub>2</sub>), 27.6 (HNCCH<sub>2</sub>CH<sub>2</sub>), 25.6 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 25.4 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>O), 24.6 (CH=CCH<sub>2</sub>CH<sub>2</sub>)

**HRMS** (ESI<sup>+</sup>) *m/z* / Da = 643.3365, [M+H]<sup>+</sup> found, [C<sub>34</sub>H<sub>43</sub>N<sub>8</sub>O<sub>5</sub>]<sup>+</sup> requires 643.3351

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



Ciprofloxacin **97** (10.0 g, 30 mmol, 1 eq.) and *p*-toluenesulfonic acid (8.60 mg, 44.5 mmol, 1.5 eq.) were refluxed in methanol (500 ml) for 72 h. The mixture was cooled to room temperature and NaHCO<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), which was dried over MgSO<sub>4</sub> and evaporated under reduced pressure. **134** was obtained as a white amorphous solid (9.16 g, 26.5 mmol, 83.3 %).

**TLC**  $R_f$  = 0.13 (5 % MeOH/CH<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>), 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(CHH)<sub>2</sub>), 1.12 - 1.20 (m, 2 H, NCH(CHH)<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>)

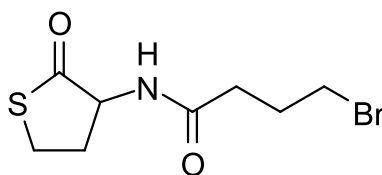
**<sup>19</sup>F NMR** (376.45 MHz, MeOD)  $\delta$  / ppm = -124.8 (s, ciprofloxacin F)

1dp

**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>8</sup>

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



3-Aminodihydrothiophen-2(3H)-one hydrochloride **177** (15.0 g, 97.6 mmol, 1 eq.) and NaHCO<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 **42** (11.3 ml, 107 mmol, 1.1 eq.) was added dropwise over 45 min at 0 °C and the mixture was stirred for a further 1 h. The organic layer was separated and the aqueous layer was extracted with a second portion of CH<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. **135** was obtained as a white, amorphous solid (22.7 g, 85.8 mmol, 87.9 %)

**TLC**  $R_f$  = 0.19 (50 % EtOAc/PE)

**IR** (neat)  $\nu_{max}$  / cm<sup>-1</sup> = 3265.9 (amide N-H), 3063.2 (amide N-H), 1694.3 (thiolactone C=O), 1650.5 (amide C=O)

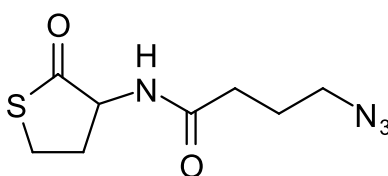
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  / ppm = 6.08 (d,  $J$  = 6.1 Hz, 1 H, NH), 4.54 (dt,  $J$  = 12.9, 6.5 Hz, 1 H, CHNH), 3.49 (t,  $J$  = 6.4 Hz, 2 H, CH<sub>2</sub>Br), 3.37 (ddd,  $J$  = 12.2, 11.5, 5.3 Hz, 1 H, SCHH), 3.26 (ddd,  $J$  = 11.5, 6.9, 1.3 Hz, 1 H, SCHH), 2.91 (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>)  $m/z$  / Da = ??, [M+H]<sup>+</sup> found, [??]<sup>+</sup> requires ??

The compound has been synthesised previously<sup>9,10</sup> but characterisation was not published.

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



4-Bromo-*N*-(2-oxotetrahydrothiophen-3-yl)butanamide **135** (6.00 g, 27.0 mmol, 1 eq.) and NaN<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. **136** was obtained as a yellow, sticky solid (4.60 g, 20.1 mmol, 89.3 %).

**TLC**  $R_f$  = 0.19 (50 % EtOAc/PE)

**IR** (neat)  $\nu_{max}$  / cm<sup>-1</sup> = 3285.6 (N-H), 2963.9 (C-H), 2100.2 (azide), 1697.4 (thiolactone C=O), 1647.4 (amide C=O)

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

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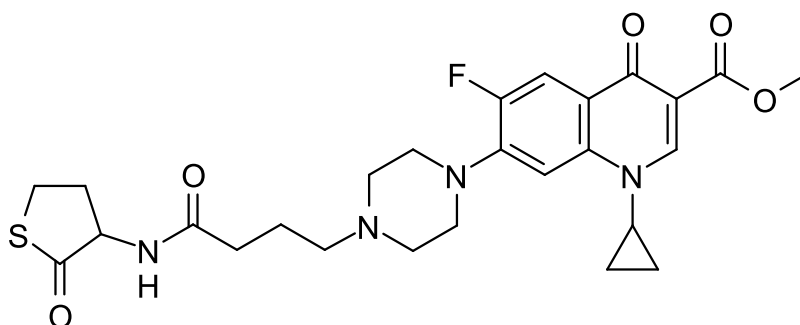
C(=O)CHH), 2.28 (t,  $J = 7.1$  Hz, 1 H, C(=O)CHH), 1.97 (qd,  $J = 12.4, 7.0$  Hz, 1 H, SCH<sub>2</sub>CHH), 1.85 (quin,  $J = 6.9$  Hz, 2 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>)

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  / ppm = 205.4 (SC(=O)), 172.3 (NHC(=O)), 59.4 (CHNH), 50.6 (CH<sub>2</sub>N<sub>3</sub>), 32.8 (C(=O)CH<sub>2</sub>), 31.8 (SCH<sub>2</sub>CH<sub>2</sub>), 27.5 (SCH<sub>2</sub>), 24.6 (C(=O)CH<sub>2</sub>CH<sub>2</sub>)

HRMS (ESI<sup>+</sup>)  $m/z$  / Da = 251.0565, [M+Na]<sup>+</sup> found, [C<sub>8</sub>H<sub>12</sub>N<sub>4</sub>NaO<sub>2</sub>S]<sup>+</sup> requires 251.0573

The compound has not been reported previously.

### 1.33 Methyl 1-cyclopropyl-6-fluoro-4-oxo-7-(4-(4-oxo-4-((2-oxotetrahydrothiophen-3-yl)amino)butyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate **137**



Methyl 1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate **134** (50 mg, 0.145 mmol, 1 eq.), 4-bromo-*N*-(2-oxotetrahydrothiophen-3-yl)butanamide **135** (34.5 mg, 0.145 mmol, 1 eq.) and K<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 **135** (34.5 mg, 0.145 mmol, 1 eq.) was added. After another 24 h a further portion was added (69.0 mg, 0.290 mmol, 2 eq.). After another 24 h the temperature was raised so the mixture was at reflux. After a final 24 h the precipitate was filtered off and the filtrate was purified by column chromatography (SiO<sub>2</sub>, 5-10 % MeOH/CH<sub>2</sub>Cl<sub>2</sub>). **137** was obtained as a cream-coloured amorphous solid (9.4 mg, 0.018 mmol, 12.2 %).

TLC  $R_f$  = 0.47 (10 % MeOH/CH<sub>2</sub>Cl<sub>2</sub>)

IR (neat)  $\nu_{max}$  / cm<sup>-1</sup> = 2944.2 (C-H), 2832.4 (C-H), 1722.4 (ester C=O), 1700.4 (thiolactone C=O), 1669.6 (amide C=O), 1617.3 (quinolone C=O)

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

<sup>13</sup>C NMR (126 MHz, MeOD)  $\delta$  / ppm = 207.0 (SC(=O)), 175.7 (NHC(=O)), 175.1 (C(=O)CC(=O)OCH<sub>3</sub>), 166.6 (C(=O)OCH<sub>3</sub>), 154.7 (d,  $J=249.0$  Hz, *ipso* to F), 150.2 (s, CH=CC(=O)OCH<sub>3</sub>), 145.6 (d,  $J=10.6$  Hz, *ipso* to piperazine), 139.8 (*para* to F), 123.5 (d,  $J=6.9$  Hz, *para* to piperazine), 113.1 (d,  $J=23.6$  Hz, *ortho*

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

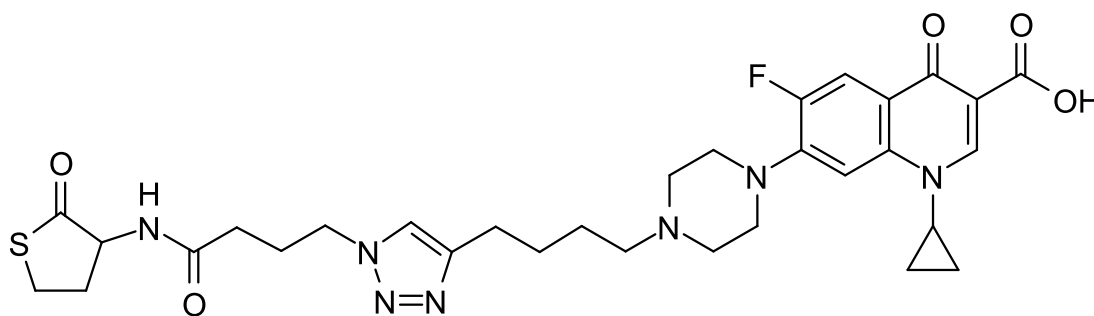
$^{19}\text{F}$  NMR (376.45 MHz, MeOD)  $\delta$  / ppm = -125.35 (s, ciprofloxacin F)

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

The compound has been synthesised previously.<sup>9,10</sup> Only HRMS characterisation was published, and this agrees with the result above.

check??

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



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

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)

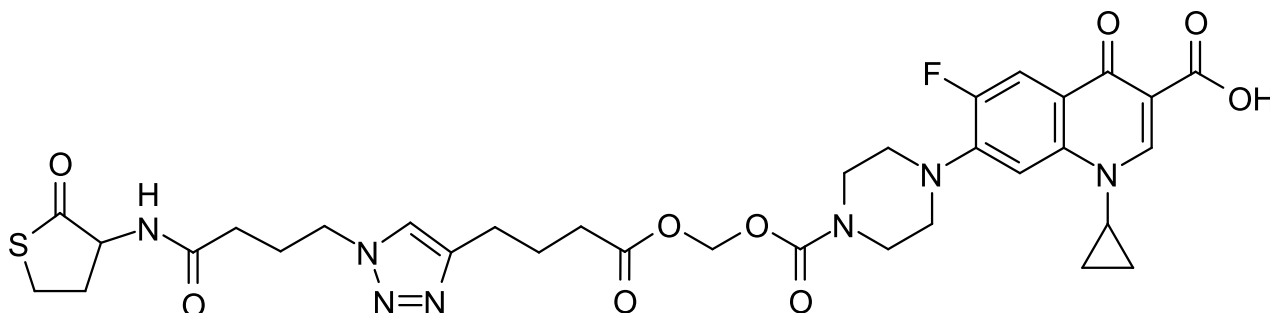
$^1\text{H}$  NMR (500 MHz, DMSO  $d_6$ )  $\delta$  / ppm = 15.23 (br s, 1 H,  $\text{C}(=\text{O})\text{OH}$ ), 8.66 (s, 1 H, *ortho* to  $\text{C}(=\text{O})\text{OH}$ ), 8.23 (d,  $J=8.5$  Hz, 1 H,  $\text{NH}$ ), 7.90 (d,  $J=13.4$  Hz, 1 H, *ortho* to F), 7.84 (s, 1 H,  $\text{CH}=\text{CCH}_2$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

**<sup>13</sup>C NMR** (126 MHz, DMSO d<sub>6</sub>)  $\delta$  / ppm = 205.6 (SC(=O)), 176.4 (C(=O)CC(=O)OH), 171.4 (NHC(=O)), 166.0 (C(=O)OH), 153.1 (d,  $J$ =249.3 Hz, *ortho* to F), 148.0 (CH=CC(=O)OH), 146.9 (CH=CCH<sub>2</sub>), 145.3 (d,  $J$ =10.1 Hz, *ipso* to piperazine), 139.2 (*para* to F), 121.8 (CH=CCH<sub>2</sub>), 118.6 (d,  $J$ =7.7 Hz, *para* to piperazine), 111.0 (d,  $J$ =23.3 Hz, *ortho* to C=O and *ortho* to F), 106.7 (CC(=O)OH), 106.4 (d,  $J$ =2.9 Hz, *meta* to C=O and *meta* to F), 58.2 (SC(=O)CHNH), 57.4 (CH=CCH<sub>2</sub>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>), 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>), 48.6 (CH<sub>2</sub>NCH=C), 35.9 (NCH(CH<sub>2</sub>)<sub>2</sub>), 31.9 (NHC(=O)CH<sub>2</sub>), 30.1 (CH<sub>2</sub>CHNH), 26.9 (CH=CCH<sub>2</sub>CH<sub>2</sub>), 26.8 (SCH<sub>2</sub>), 25.9 (NHC(=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>), 7.6 (NCH(CH<sub>2</sub>)<sub>2</sub>)

**<sup>19</sup>F NMR** (376.45 MHz, MeOD)  $\delta$  / ppm = -124.86 (s, ciprofloxacin F)

**HRMS** (ESI<sup>+</sup>)  $m/z$  / Da = 640.2739, [M+H]<sup>+</sup> found, [C<sub>31</sub>H<sub>39</sub>FN<sub>7</sub>O<sub>5</sub>S]<sup>+</sup> requires 640.2712

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



1-Cyclopropyl-6-fluoro-7-(4-((((hex-5-ynoyloxy)methoxy)carbonyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **178** (203 mg, 0.407 mmol, 1 eq.), 4-azido-*N*-(2-oxotetrahydrothiophen-3-yl)butanamide **136** (92.8 mg, 0.407 mmol, 1 eq.), CuI (40 mg, 0.190 mmol, 0.5 eq.) and DIPEA (0.356 ml, 0.264 mg, 2.04 mmol, 5 eq.) were stirred in CH<sub>2</sub>Cl<sub>2</sub> (18.6 ml) at r.t. under Ar for 3 h. The mixture was filtered and the filtrate was dry-loaded onto SiO<sub>2</sub> and purified by column chromatography (SiO<sub>2</sub>, 5-10 % MeOH/CH<sub>2</sub>Cl<sub>2</sub>). **139** was obtained as pale brown/yellow amorphous solid (14.7 mg, 20.2  $\mu$ mol, 5.0 %).

**TLC**  $R_f$  = 0.40 (5 % CH<sub>2</sub>Cl<sub>2</sub>/MeOH)

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

**<sup>1</sup>H NMR** (400 MHz, DMSO d<sub>6</sub>)  $\delta$  / ppm = 15.16 (br s, 1 H, C(=O)OH), 8.65 (s, 1 H, *ortho* to C(=O)OH), 8.21 (d,  $J$  = 8.5 Hz, 1 H, NH), 7.89 (d,  $J$  = 13.1 Hz, 1 H, *ortho* to F), 7.85 (s, 1 H, CH=CCH<sub>2</sub>), 7.57 (d,  $J$  = 7.4 Hz, 1 H, *meta* to F), 5.74 (s, 1 H, OCH<sub>2</sub>O), 4.58 (ddd,  $J$  = 12.6, 8.1, 7.2 Hz, 1 H, CHNH), 4.30 (t,  $J$  = 6.9 Hz, 2 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 3.80 (tt,  $J$  = 6.9, 3.6 Hz, 1 H, NCH(CH<sub>2</sub>)<sub>2</sub>), 3.62 (br t,  $J$  = 5.2, 5.2 Hz, 4 H, C(=O)N(CH<sub>2</sub>)CH<sub>2</sub>), 3.38 (td,  $J$  = 11.4, 5.5 Hz, 1 H, SCHH), 3.34 (br. s, 4 H, C(=O)N(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 3.27 (ddd,  $J$  = 11.0, 6.9, 1.6 Hz, 1 H, SCHH), 2.64 (t,  $J$  = 7.6 Hz, 2 H, CH=CCH<sub>2</sub>), 2.44 (t,  $J$  = 7.5 Hz, 2 H, CH<sub>2</sub>C(=O)O), 2.40 (dddd,  $J$  = 12.3, 6.8, 5.4, 1.4 Hz, 1 H, SCH<sub>2</sub>CHH), 2.12 (t,  $J$  = 7.8 Hz, 1 H, NHC(=O)CHH), 2.12 (t,  $J$  = 6.8 Hz, 1 H, NHC(=O)CHH), 1.98 - 2.07 (m, 3 H, SCH<sub>2</sub>CHH and NHC(=O)CH<sub>2</sub>CH<sub>2</sub>), 1.86 (quin,

$J = 7.5$  Hz, 2 H,  $\text{CH}=\text{CCH}_2\text{CH}_2$ ), 1.29 - 1.36 (m, 2 H,  $\text{NCH}(\text{CHH})_2$ ), 1.14 - 1.21 (m, 2 H,  $\text{NCH}(\text{CHH})_2$ )

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

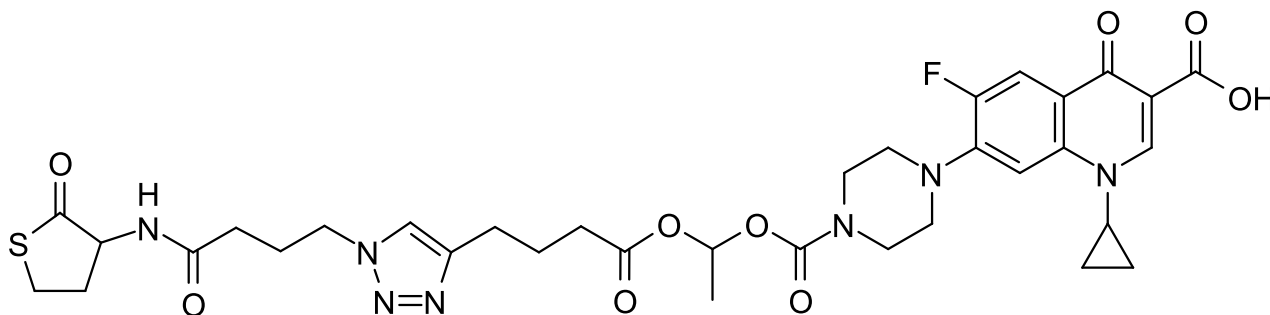
**$^{19}\text{F}$  NMR** (376.45 MHz, DMSO  $d_6$ )  $\delta$  / ppm = ??

no F

**HRMS** ( $\text{ESI}^+$ )  $m/z$  / Da = 728.2502,  $[\text{M}+\text{H}]^+$  found,  $[\text{C}_{33}\text{H}_{39}\text{FN}_7\text{O}_9\text{S}]^+$  requires 728.2503

The compound has not been reported previously.

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



Method?? white amorphous solid 1.2 mg, 1.6  $\mu\text{mol}$

**TLC**  $R_f = 0.33$  (10 % MeOH/ $\text{CH}_2\text{Cl}_2$ )

**IR** (neat)  $\nu_{\text{max}}$  /  $\text{cm}^{-1} = ??$

**$^1\text{H}$  NMR** (400 MHz, MeOD)  $\delta$  / ppm = ??

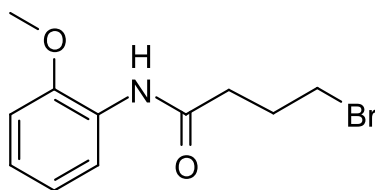
**$^{13}\text{C}$  NMR** (101 MHz, MeOD)  $\delta$  / ppm = ??

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

**HRMS** ( $\text{ESI}^+$ )  $m/z$  / Da = 742.2670,  $[\text{M}+\text{H}]^+$  found,  $[\text{C}_{34}\text{H}_{41}\text{FN}_7\text{O}_9\text{S}]^+$  requires 742.2671



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



2-Methoxyaniline **179** (9.12 ml, 10.0 g, 81.2 mmol, 1 eq.) and NaHCO<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 **42** (9.40 ml, 15.1 g, 81.2 mmol, 1 eq.) was added dropwise over 15 min. The mixture was stirred at 0 °C for 1.5 h, then the aqueous layer was removed. The organic layer was dried with MgSO<sub>4</sub> and evaporated under reduced pressure. **141** was obtained as an initially colourless liquid which slowly turned blue then black if left out on the bench (11.0 g, 40.6 mmol, 50.0 %).

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

**IR** (neat)  $\nu_{max}$  / 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)

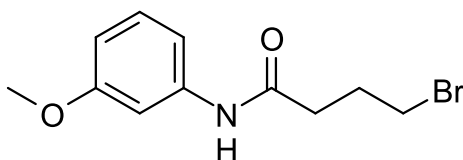
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub> d<sub>1</sub>)  $\delta$  / ppm = 8.32 (dd,  $J$  = 8.0, 1.7 Hz, 1 H, *ortho* to NH), 7.85 (br s, 1 H, NH), 7.02 (td,  $J$  = 7.9, 1.7 Hz, 1 H, *para* to NH), 6.93 (td,  $J$  = 7.7, 1.4 Hz, 1 H, *para* to OCH<sub>3</sub>), 6.85 (dd,  $J$  = 8.1, 1.5 Hz,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

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



3-Methoxyaniline **180** (3.04 ml, 3.33 g, 27.1 mmol, 1 eq.) and NaHCO<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 **42** (3.13 ml, 5.03 g, 27.1 mmol, 1 eq.) was added dropwise over 5 min. The mixture was stirred at 0 °C for 1 h, then the aqueous layer was removed. The organic layer was dry-loaded onto SiO<sub>2</sub> and purified by column chromatography using a Combiflash (SiO<sub>2</sub>, 0-100 % EtOAc/P.E.). **142** was obtained as a pale pink amorphous solid (3.66 g, 13.5 mmol, 49.6 %).

how to  
report?

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

**IR** (neat)  $\nu_{max} / \text{cm}^{-1} = 1670.9$  (amide C=O)

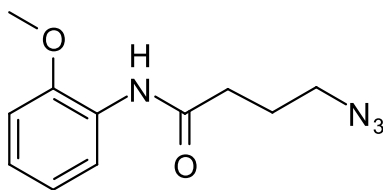
**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$   $d_1$ )  $\delta / \text{ppm} = 8.45$  (s, 1 H,  $\text{NH}$ ), 7.27 (t,  $J = 2.2$  Hz, 1 H, *ortho* to  $\text{OCH}_3$  and *ortho* to NH), 7.14 (t,  $J = 8.1$  Hz, 1 H, *meta* to  $\text{OCH}_3$  and *meta* to NH), 7.02 (d,  $J = 8.3$  Hz, 1 H, *para*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

**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$   $d_1$ )  $\delta / \text{ppm} = 170.3$  ( $\text{C(=O)}$ ), 159.9 (*ipso* to  $\text{OCH}_3$ ), 139.0 (*ipso* to NH), 129.5 (*meta* to  $\text{OCH}_3$  and *meta* to NH), 112.1 (*para* to  $\text{OCH}_3$ ), 109.9 (*para* to NH), 105.7 (*ortho* to  $\text{OCH}_3$  and *ortho* to NH), 55.2 ( $\text{CH}_3$ ), 35.3 ( $\text{C(=O)CH}_2$ ), 33.2 ( $\text{CH}_2\text{Br}$ ), 28.0 ( $\text{C(=O)CH}_2\text{CH}_2$ )

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

The compound has not been reported previously.

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



4-Bromo-*N*-(2-methoxyphenyl)butanamide **141** (2.05 g, 7.51 mmol, 1 eq.) and  $\text{NaN}_3$  (1.17 g, 18.0 mmol, 2.4 eq.) were refluxed in acetonitrile (100 ml) for 2 h. The mixture was cooled and filtered, and the filtrate was dry-loaded onto  $\text{SiO}_2$  and purified by column chromatography using a Combiflash ( $\text{SiO}_2$ , 8-14 % then hold at 14 % EtOAc/P.E.). **143** was obtained as an initially colourless liquid which slowly turned blue then black if left out on the bench (0.469 g, 2.00 mmol, 26.7 %).

how to report?

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

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

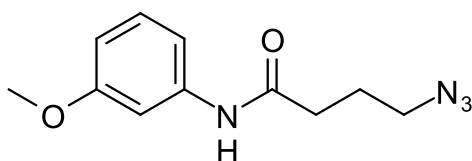
**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$   $d_1$ )  $\delta / \text{ppm} = 8.32$  (dd,  $J = 7.9, 1.0$  Hz, 1 H, *ortho* to NH), 7.86 (br s, 1 H,  $\text{NH}$ ), 7.00 (td,  $J = 7.5, 1.5$  Hz, 1 H, *para* to NH), 6.90 (td,  $J = 7.7, 1.1$  Hz, 1 H, *para* to  $\text{OCH}_3$ ), 6.83 (dd,  $J =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

**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$   $d_1$ )  $\delta / \text{ppm} = 169.5$  ( $\text{C(=O)}$ ), 147.6 (*ipso* to  $\text{OCH}_3$ ), 127.1 (*ipso* to NH), 123.4 (*para* to NH), 120.5 (*para* to  $\text{OCH}_3$ ), 119.5 (*ortho* to NH and *meta* to  $\text{OCH}_3$ ), 109.6 (*ortho* to  $\text{OCH}_3$  and *meta* to NH), 55.2 ( $\text{CH}_3$ ), 50.3 ( $\text{CH}_2\text{N}_3$ ), 33.9 ( $\text{C(=O)CH}_2$ ), 24.3 ( $\text{C(=O)CH}_2\text{CH}_2$ )

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

The data are consistent with the literature.<sup>11</sup>

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



4-Bromo-*N*-(3-methoxyphenyl)butanamide **142** (2.05 g, 7.51 mmol, 1 eq.) and NaN<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.). **144** was obtained as a straw-coloured liquid (0.294 g, 1.25 mmol, 16.7 %).

how to report?

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

**IR** (neat)  $\nu_{max}$  / cm<sup>-1</sup> = 3298.3 (N-H), 2094.7 (azide), 1661.7 (amide C=O)

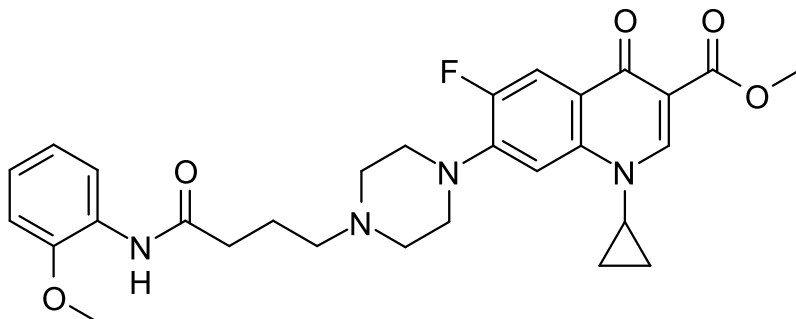
**<sup>1</sup>H NMR** (400 MHz, MeOD)  $\delta$  / ppm = 8.63 (br s, 1 H, NH), 7.26 (t,  $J$  = 2.3 Hz, 1 H, *ortho* to OCH<sub>3</sub> and *ortho* to NH), 7.15 (t,  $J$  = 8.1 Hz, 1 H, *meta* to OCH<sub>3</sub> and *meta* to NH), 7.01 (dd,  $J$  = 7.8, 1.6 Hz, 1 H, *para* to OCH<sub>3</sub>), 6.63 (dd,  $J$  = 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>)  $m/z$  / Da = ??, [M+H]<sup>+</sup> found, [??]<sup>+</sup> requires ??

The compound has not been reported previously.

#### 1.41 Methyl 1-cyclopropyl-6-fluoro-7-(4-(4-((2-methoxyphenyl)amino)-4-oxobutyl)-piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate **145**



Methyl 1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate **134** (500 mg, 1.45 mmol, 1 eq.), 4-bromo-*N*-(2-methoxyphenyl)butanamide **141** (788 mg, 2.90 mmol, 2 eq.), DIPEA (1.28 ml, 950 mg, 7.35 mmol, 5 eq.), NaI (275 mg, 1.83 mmol, 1.3 eq.) and acetonitrile (10 ml) were stirred in a microwave reactor at 100 °C for 4 h. The mixture was dry-loaded onto SiO<sub>2</sub> and purified by column chromatography (SiO<sub>2</sub>,

how to report?

4 % MeOH/CH<sub>2</sub>Cl<sub>2</sub>). **145** was obtained as a bright pink glass (79.7 mg, 0.149 mmol, 10.2 %).

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

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

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

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

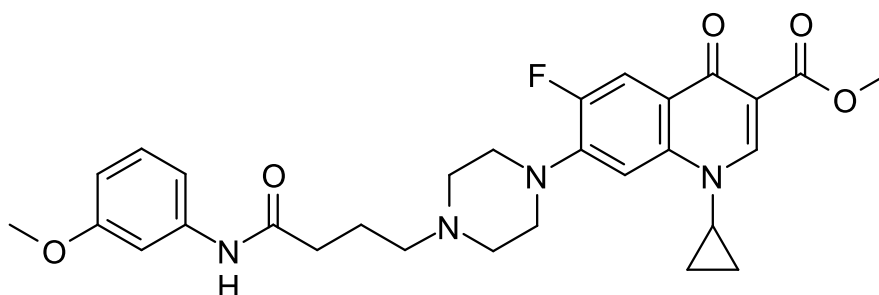
**<sup>19</sup>F NMR** (376.45 MHz, CDCl<sub>3</sub> d<sub>1</sub>)  $\delta$  / ppm = ??

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**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.

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



Methyl 1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate **134** (500 mg, 1.45 mmol, 1 eq.), 4-bromo-*N*-(3-methoxyphenyl)butanamide **142** (788 mg, 2.90 mmol, 2 eq.), DIPEA (1.28 ml, 950 mg, 7.35 mmol, 5 eq.), NaI (275 mg, 1.83 mmol, 1.3 eq.) and acetonitrile (10 ml) were stirred in a microwave reactor at 100 °C for 4 h. The mixture was evaporated under reduced pressure and partitioned between

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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>). **146** 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)  $\nu_{max}$  / cm<sup>-1</sup> = 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)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  / ppm = 8.56 (s, 1 H, *ortho* to C(=O)OCH<sub>3</sub>), 8.06 (d,  $J$  = 13.3 Hz, 1 H, *ortho* to F), 8.02 (br s, 1 H, NH), 7.34 (t,  $J$  = 1.7 Hz, 1 H, *ortho* to OCH<sub>3</sub> and *ortho* to NH), 7.25 (d,  $J$  = 7.0 Hz, 1 H, *meta* to F), 7.20 (t,  $J$  = 8.2 Hz, 1 H, *meta* to OCH<sub>3</sub> and *meta* to NH), 6.98 (dd,  $J$  = 7.8, 1.7 Hz, 1 H, *para* to OCH<sub>3</sub>), 6.65 (dd,  $J$  = 8.2, 2.1 Hz, 1 H, *para* to NH), 3.93 (s, 3 H, C(=O)OCH<sub>3</sub>), 3.80 (s, 3 H, aromatic OCH<sub>3</sub>), 3.42 (tt,  $J$  = 6.8, 3.7 Hz, 1 H, NCH(CH<sub>2</sub>)<sub>2</sub>), 3.31 (br t,  $J$  = 4.3, 4.3 Hz, 4 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 2.73 (br t,  $J$  = 4.5, 4.5 Hz, 4 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 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>)

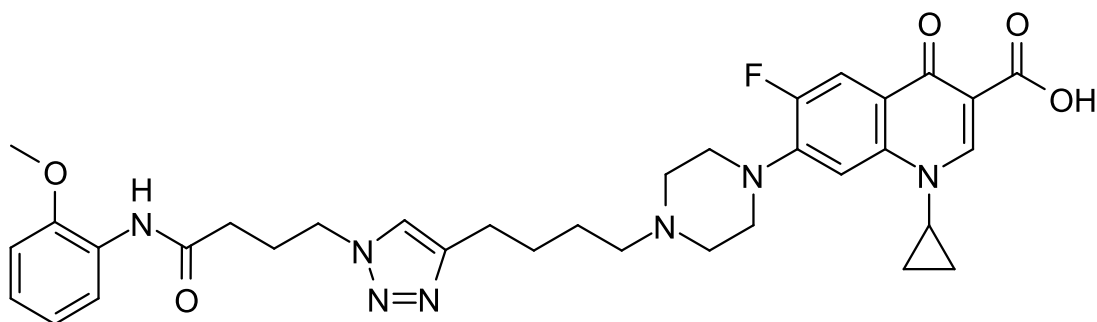
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  / ppm = 173.1 (C(=O)CC(=O)OCH<sub>3</sub>), 170.9 (NHC(=O)), 166.3 (C(=O)OCH<sub>3</sub>), 160.1 (*ipso* to OCH<sub>3</sub>), 153.3 (d,  $J$ =250.1 Hz, *ipso* to F), 148.4 (C=CC(=O)OCH<sub>3</sub>), 144.1 (d,  $J$ =10.1 Hz, *ipso* to piperazine),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

**<sup>19</sup>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.

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



1-Cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **176** (24.1 mg, 58.6  $\mu$ mol, 1 eq.) and 4-azido-*N*-(2-methoxyphenyl)butanamide **143** (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), CH<sub>2</sub>Cl<sub>2</sub> (25 ml) and MeOH (5 ml) were added and the organic layer was separated off, dry-loaded onto SiO<sub>2</sub> and purified by column chromatography using a Combiflash (SiO<sub>2</sub>, 3-23 % MeOH/CH<sub>2</sub>Cl<sub>2</sub>). **147** was obtained as a clear glass (14.7 mg, 22.8  $\mu$ mol, 39.0 %).

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**TLC**  $R_f$  = 0.28 (10 % MeOH/CH<sub>2</sub>Cl<sub>2</sub>)

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

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  / 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, CH=CCH<sub>2</sub>), 7.35 (d,  $J$  = 7.2 Hz, 1 H, *meta* to F), 7.04 (td,  $J$  = 7.7, 1.7 Hz, 1 H, *para* to NH), 6.95 (td,  $J$  = 7.8, 1.5 Hz, 1 H, *para* to OCH<sub>3</sub>), 6.88 (dd,  $J$  = 8.1, 1.4 Hz, 1 H, *ortho* to OCH<sub>3</sub>), 4.47 (t,  $J$  = 6.7 Hz, 2 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 3.88 (s, 3 H, CH<sub>3</sub>), 3.54 (tt,  $J$  = 6.9, 4.0 Hz, 1 H, NCH(CH<sub>2</sub>)<sub>2</sub>), 3.35 (br t,  $J$  = 4.7 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>)CH<sub>2</sub>CH<sub>2</sub>), 2.76 (t,  $J$  = 7.5 Hz, 2 H, CH=CCH<sub>2</sub>), 2.66 (t,  $J$  = 4.7 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>), 2.47 (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), 2.44 (t,  $J$  = 6.8 Hz, 2 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 2.32 (quin,  $J$  = 6.7 Hz, 2 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 1.75 (quin,  $J$  = 7.6 Hz, 2 H, CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 1.61 (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), 1.35 - 1.42 (m, 2 H, NCH(CH<sub>2</sub>)<sub>2</sub>), 1.17 - 1.22 (m, 2 H, NCH(CH<sub>2</sub>)<sub>2</sub>)

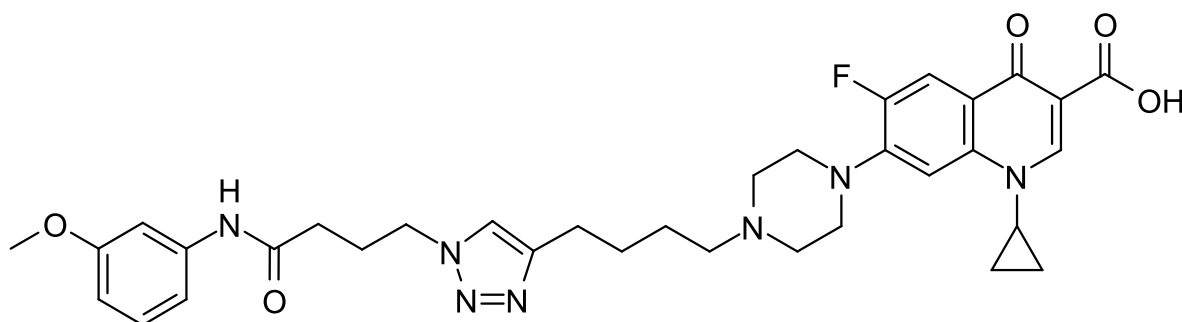
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  / ppm = 177.1 (C(=O)CC(=O)OH), 169.5 (NHC(=O)), 167.0 (C(=O)OH), 153.7 (d,  $J$  = 251.4 Hz, *ipso* to F), 148.1 (CH=CCH<sub>2</sub>), 147.8 (*ipso* to OCH<sub>3</sub>), 147.3 (C=CC(=O)OH), 145.9 (d,  $J$  = 10.4 Hz, *ipso* to piperazine), 139.1 (*para* to F), 127.3 (*ipso* to NH), 123.9 (*para* to NH), 121.0 (*para* to OCH<sub>3</sub>), 120.9 (CH=CCH<sub>2</sub>), 119.7 (*para* to piperazine, and *ortho* to NH and *meta* to OCH<sub>3</sub>), 112.4 (d,  $J$  = 23.4 Hz, *ortho* to C=O and *ortho* to F), 109.9 (*ortho* to OCH<sub>3</sub> and *meta* to NH), 108.1 (CC(=O)OH), 104.7 (*meta* to C=O and *meta* to F), 58.1 (CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 55.6 (CH<sub>3</sub>), 52.8 (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>), 49.8 (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>), 49.8 (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>), 49.1 (C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 35.2 (NCH(CH<sub>2</sub>)<sub>2</sub>), 33.8 (C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 27.3 (CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 26.4 (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>N), 25.5 (CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 8.2 (NCH(CH<sub>2</sub>)<sub>2</sub>)

**<sup>19</sup>F NMR** (376.45 MHz, CDCl<sub>3</sub>)  $\delta$  / ppm = -120.7 (s, ciprofloxacin F)

**HRMS** (ESI<sup>+</sup>)  $m/z$  / Da = 646.3132, [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.

**1.44 1-Cyclopropyl-6-fluoro-7-(4-(4-(1-(4-((3-methoxyphenyl)amino)-4-oxobutyl)-1H-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **148****



1-Cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **176** (24.1 mg, 58.6  $\mu\text{mol}$ , 1 eq.) and 4-azido-*N*-(3-methoxyphenyl)butanamide **144** (13.7 mg, 58.5  $\mu\text{mol}$ , 1 eq.) were dissolved in water (1 ml), *t*-BuOH (9 ml) and  $\text{CH}_2\text{Cl}_2$  (10 ml), and the mixture was degassed by bubbling through  $\text{N}_2$ . A solution of  $\text{CuSO}_4$  and THPTA (58.5  $\mu\text{l}$ , 5.85  $\mu\text{mol}$ , 0.1 eq. 100 mM, aq.) was added, followed by a solution of sodium ascorbate (117  $\mu\text{l}$ , 11.7  $\mu\text{mol}$ , 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  $\text{CH}_2\text{Cl}_2$  (15 ml), and the aqueous layer was extracted a further four times with  $\text{CH}_2\text{Cl}_2$  ( $4 \times 15$  ml). The combined organic layers were dried with  $\text{MgSO}_4$ , dry-loaded onto  $\text{SiO}_2$  and purified by column chromatography ( $\text{SiO}_2$ , 0-10 % MeOH/ $\text{CH}_2\text{Cl}_2$ ). **148** was obtained as a clear glass (1.9 mg, 2.9  $\mu\text{mol}$ , 5.0 %).

**TLC**  $R_f$  = 0.22 (10 % MeOH/ $\text{CH}_2\text{Cl}_2$ )

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

**$^1\text{H}$  NMR** (400 MHz, DMSO  $d_6$ )  $\delta$  / 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(CH<sub>2</sub>)<sub>2</sub>), 1.15 - 1.20 (m, 2 H, NCH(CH<sub>2</sub>)<sub>2</sub>)

**$^{13}\text{C}$  NMR** (101 MHz, DMSO  $d_6$ )  $\delta$  / 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>), 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>), 49.4

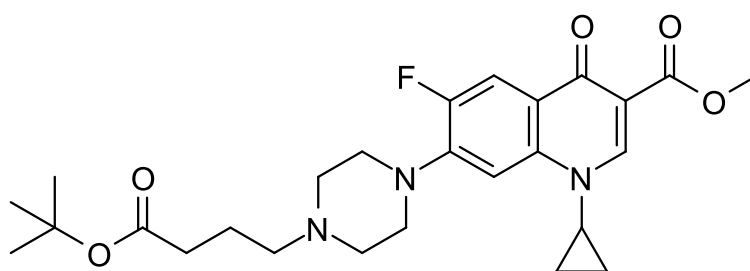
(CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 48.7 (C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 35.8 (NCH(CH<sub>2</sub>)<sub>2</sub>), 32.9 (C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 26.8 (CH=CCH<sub>2</sub>CH<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.

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



Methyl 1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate **134** (200 mg, 0.579 mmol, 1 eq.), *tert*-butyl 4-bromobutanoate **181** (103 μl, 130 mg, 0.581 mmol, 1 eq.), NaI (86.9 mg, 0.580 mmol, 1 eq.), TEA (316 μl, 229 mg, 2.27 mmol, 4 eq.) and acetonitrile (10 ml) were stirred in a microwave reactor at 100 °C for 8 h. A second portion of *tert*-butyl 4-bromobutanoate **181** (103 μl, 130 mg, 0.581 mmol, 1 eq.) was added, and the mixture was stirred in a microwave reactor at 100 °C for a further 8 h. The mixture was then dry-loaded onto SiO<sub>2</sub> and purified by column chromatography (SiO<sub>2</sub>, 0-4 % MeOH/CH<sub>2</sub>Cl<sub>2</sub>). **149** was obtained as a white amorphous solid (141 mg, 0.289 mmol, 49.9 %).

how to report?

how to report?

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(CH<sub>2</sub>)<sub>2</sub>), 1.09 (m, 2 H, NCH(CH<sub>2</sub>)<sub>2</sub>)

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ / ppm = 172.7 (C(=O)CC(=O)OCH<sub>3</sub>), 172.6 (C(=O)OC(CH<sub>3</sub>)<sub>3</sub>), 165.9 (C(=O)OCH<sub>3</sub>), 153.1 (d, *J* = 249.7 Hz, *ipso* to F), 148.1 (C=CC(=O)OCH<sub>3</sub>), 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 (C(=O)OCH<sub>3</sub>) 104.7 (*meta* to C=O and *meta* to F), 80.0 (C(CH<sub>3</sub>)<sub>3</sub>), 57.4 (C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 52.7 (C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 51.7 (CH<sub>3</sub>), 49.7 (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>), 49.7 (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>), 34.4 (NCH(CH<sub>2</sub>)<sub>2</sub>), 33.2 (C(=O)CH<sub>2</sub>), 28.0

should be ranges ideally, go back if time



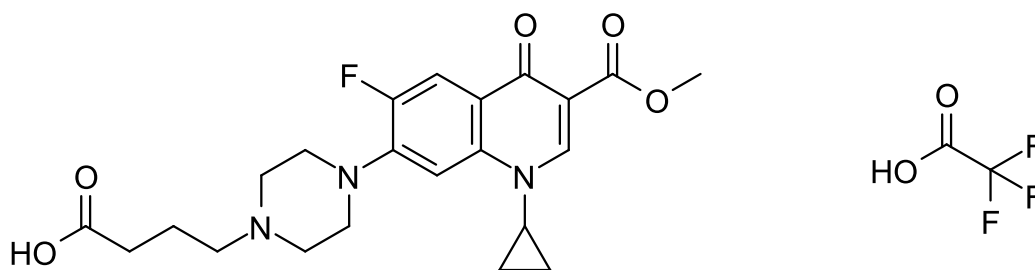
(C(CH<sub>3</sub>)<sub>3</sub>), 22.0 (C(=O)CH<sub>2</sub>CH<sub>2</sub>), 7.9 (NCH(CH<sub>2</sub>)<sub>2</sub>)

<sup>19</sup>F NMR (376.45 MHz, CDCl<sub>3</sub>) δ / ppm = -123.50 (s, ciprofloxacin F)

HRMS (ESI<sup>+</sup>) *m/z* / Da = 488.2562, [M+H]<sup>+</sup> found, [C<sub>26</sub>H<sub>35</sub>FN<sub>3</sub>O<sub>5</sub>]<sup>+</sup> requires 488.2561

The compound has not been reported previously.

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



Methyl 7-(4-(4-(*tert*-butoxy)-4-oxobutyl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate **149** (20 mg, 41.0 μmol) and TFA (0.2 ml) were stirred in CH<sub>2</sub>Cl<sub>2</sub> (1.8 ml) at r.t. for 16 h then evaporated under reduced pressure. **150** was obtained as a white solid (21.4 mg, 39.2 μmol, 95.6 %).

mp *T* / °C = 225-231 (CH<sub>2</sub>Cl<sub>2</sub>, decomposes)

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

<sup>1</sup>H NMR (400 MHz, DMSO *d*<sub>6</sub>) δ / ppm = 8.47 (s, 1 H, *ortho* to C(=O)OH), 7.80 (d, *J* = 13.2 Hz, 1 H, *ortho* to F), 7.47 (d, *J* = 7.4 Hz, 1 H, *meta* to F), 3.73 (s, 3 H, CH<sub>3</sub>), 3.66 (tt, *J* = 7.2, 3.7 Hz, 1 H, NCH(CH<sub>2</sub>)<sub>2</sub>), 3.30 - 3.54 (br s, 8 H, CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub> and CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>) 3.13 - 3.22 (m, 2 H, CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 2.36 (t, *J* = 7.1 Hz, 2 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 1.87 - 1.98 (m, 2 H, CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 1.22 - 1.30 (m, 2 H, NCH(CH<sub>2</sub>)<sub>2</sub>), 1.06 - 1.15 (m, 2 H, NCH(CH<sub>2</sub>)<sub>2</sub>)

<sup>13</sup>C NMR (101 MHz, DMSO *d*<sub>6</sub>) δ / ppm = 173.5 (CH<sub>2</sub>C(=O)OH), 171.6 (C(=O)CC(=O)OCH<sub>3</sub>), 164.9 (C(=O)OCH<sub>3</sub>), 158.2 (q, *J* = 31.5 Hz, CF<sub>3</sub>C(=O)OH), 152.5 (d, *J* = 247.6 Hz, *ipso* to F), 148.5 (C=CC(=O)OH), 142.3 (d, *J* = 10.7 Hz, *ipso* to piperazine), 138.0 (*para* to F), 122.6 (d, *J* = 6.4 Hz, *para* to piperazine), 117.2 (q, *J* = 299.8 Hz, CF<sub>3</sub>), 111.9 (d, *J* = 22.4 Hz, *ortho* to C=O and *ortho* to F), 109.1 (CC(=O)OCH<sub>3</sub>), 106.9 (*meta* to C=O and *meta* to F), 55.1 (C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 51.4 (CH<sub>3</sub>), 50.8 (C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 46.7 (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>), 46.7 (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>), 34.9 (NCH(CH<sub>2</sub>)<sub>2</sub>), 30.6 (C(=O)CH<sub>2</sub>), 19.1 (C(=O)CH<sub>2</sub>CH<sub>2</sub>), 7.6 (NCH(CH<sub>2</sub>)<sub>2</sub>)

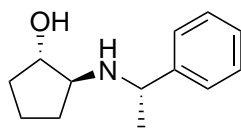
<sup>19</sup>F NMR (376.45 MHz, DMSO *d*<sub>6</sub>) δ / ppm = -73.62 (s, CF<sub>3</sub>), -124.61 (s, ciprofloxacin F)

HRMS (ESI<sup>+</sup>) *m/z* / Da = 432.1921, [M+H]<sup>+</sup> found, [C<sub>22</sub>H<sub>27</sub>FN<sub>3</sub>O<sub>5</sub>]<sup>+</sup> requires 432.1935

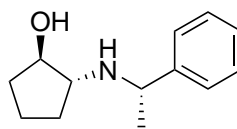
The compound has not been reported previously.

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this?

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



**160**



**161**

(*S*)-1-phenylethan-1-amine **182** (7.85 ml, 7.38 g, 60.9 mmol, 1 eq.) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (50 ml) and stirred rapidly at 0 °C. A solution of AlMe<sub>3</sub> (31 ml, 2.0 M in heptane, 60.9 mmol) was added dropwise and the solution was stirred at 0 °C for 1 h. A solution of cyclohexene oxide **183** (5.71 ml, 5.50 g, 65.4 mmol, 1.1 eq.) in CH<sub>2</sub>Cl<sub>2</sub> (50 ml) was then added dropwise, and the mixture was stirred at 0 °C for a further 3 h, followed by 48 h at r.t.. The mixture was cooled to 0 °C and NaF (11 g, 262 mmol, 4.3 eq.) was added portionwise, followed by water (7.00 ml, 7.00 g, 389 mmol, 6.4 eq.) and CH<sub>2</sub>Cl<sub>2</sub> (50 ml). The suspension was allowed to warm to r.t. and stirred for 1 h, then filtered through Celite and washed with CH<sub>2</sub>Cl<sub>2</sub> (500 ml). The filtrate was dried with K<sub>2</sub>CO<sub>3</sub>, concentrated under reduced pressure and purified by column chromatography (SiO<sub>2</sub>, 20:5:1 hexane:EtOAc:TEA). **151** was obtained as a pale yellow oil (4.08 g, 19.9 mmol, 32.6 %). **152** was obtained as pale yellow crystals (4.48 g, 21.8 mmol, 35.8 %).

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

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

**IR** (neat)  $\nu_{max}$  / cm<sup>-1</sup> = 3300.0 (br, O-H), 2959.7 (C-H), 2870.1 (C-H)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  / ppm = 7.28 - 7.38 (m, 4 H, *ortho* and *meta* to CHCH<sub>3</sub>), 7.21 - 7.28 (m, 1 H, *para* to CHCH<sub>3</sub>), 3.83 (q,  $J$  = 6.6 Hz, 1 H, CHCH<sub>3</sub>), 3.78 (q,  $J$  = 7.0 Hz, 1 H, CHOH), 2.62 (dt,  $J$  = 8.2, 7.2 Hz, 1 H, CHNH), 1.97 (quin,  $J$  = 6.7 Hz, 1 H, CH<sub>2</sub>CHNH), 1.90 (quin,  $J$  = 6.9 Hz, 1 H, CH<sub>2</sub>CHOH), 1.56 - 1.68 (m, CH<sub>2</sub>CH<sub>2</sub>CHOH), 1.43 (dq,  $J$  = 12.5, 8.0 Hz, 1 H, CH<sub>2</sub>CHOH), 1.37 (d,  $J$  = 6.6 Hz, 3 H, CH<sub>3</sub>), 1.25 - 1.36 (m, 1 H, CH<sub>2</sub>CHNH)

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  / ppm = 144.75 (*ipso* to CHCH<sub>3</sub>), 128.26 (*meta* to CHCH<sub>3</sub>), 126.72 (*para* to CHCH<sub>3</sub>), 126.30 (*ortho* to CHCH<sub>3</sub>), 77.65 (CHOH), 63.38 (CHNH), 56.20 (CHCH<sub>3</sub>), 31.74 (CH<sub>2</sub>CHOH), 29.22 (CH<sub>2</sub>CHNH), 24.58 (CH<sub>3</sub>), 19.57 (CH<sub>2</sub>CH<sub>2</sub>CHOH)

**HRMS** (ESI<sup>+</sup>)  $m/z$  / Da = 206.1554, [M+H]<sup>+</sup> found, [C<sub>13</sub>H<sub>20</sub>NO]<sup>+</sup> requires 206.1545 [ $\alpha$ ]<sub>D</sub><sup>20</sup> / °10<sup>-1</sup>cm<sup>2</sup>g<sup>-1</sup> = -92.8 ( $c$  / g(100 mL)<sup>-1</sup> = 1.19, MeOH)

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

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

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

**IR** (neat)  $\nu_{max}$  / cm<sup>-1</sup> = 3150.0 (br, O-H), 2950.9 (C-H), 2868.2 (C-H)

fix spacings for subtitles

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

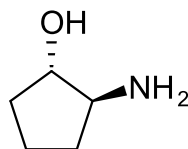
**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  / ppm = 145.61 (*ipso* to  $\text{CHCH}_3$ ), 128.08 (*meta* to  $\text{CHCH}_3$ ), 126.61 (*para* to  $\text{CHCH}_3$ ), 126.33 (*ortho* to  $\text{CHCH}_3$ ), 77.43 ( $\text{CHOH}$ ), 64.45 ( $\text{CHNH}$ ), 56.62 ( $\text{CHCH}_3$ ),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

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

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

The compounds have been synthesised previously,<sup>12-14</sup> but NMR data were not published.

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



(1*S*,2*S*)-2-(((*S*)-1-Phenylethyl)amino)cyclopentan-1-ol **151** (3.90 g, 19.0 mmol, 1 eq.),  $\text{Pd}(\text{OH})_2$  (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. **153** 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)  $\nu_{\text{max}}$  /  $\text{cm}^{-1}$  = 3300.0 (br, O-H), 2958.3 (C-H), 2871.5 (C-H)

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

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

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

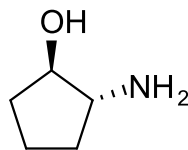
$[\alpha]_D^{20}$  /  $^\circ 10^{-1}\text{cm}^2\text{g}^{-1}$  = -30.9 ( $c$  /  $\text{g}(100\text{ mL})^{-1}$  = 1.5, EtOH)

The data are consistent with the literature.<sup>13,15</sup>

consistent  
with  
other  
data?

check

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



(1*R*,2*R*)-2-(((*S*)-1-Phenylethyl)amino)cyclopentan-1-ol **152** (3.00 g, 14.6 mmol, 1 eq.), Pd(OH)<sub>2</sub> (20 wt. % on C, moistened with 50 wt. % water, 0.5 g, 0.356 mmol, 0.025 eq.) and MeOH (50 ml) were stirred in a Paar hydrogenator at r.t. and 2.5 atm for 2 days. The mixture was then filtered through Celite and evaporated under reduced pressure. **154** was obtained as a yellow oil (1.48 g, 14.6 mmol, 100 %).

**TLC**  $R_f$  = 0.10 (10 % MeOH/CH<sub>2</sub>Cl<sub>2</sub>)

**IR** (neat)  $\nu_{max}$  / cm<sup>-1</sup> = 3300.0 (O-H), 2969.2 (C-H), 2872.7 (C-H)

**<sup>1</sup>H NMR** (400 MHz, MeOD)  $\delta$  / ppm = 3.77 (ddd,  $J$ =6.6, 6.2, 5.6, 1 H, CHOH), 3.00 (td,  $J$  = 7.4, 5.6 Hz, 1 H, CHNH<sub>2</sub>), 2.00 (dtd,  $J$  = 13.0, 7.7, 7.7, 5.6 Hz, 1 H, CHHCHNH<sub>2</sub>), 1.97 (ddt,  $J$  = 13.0, 8.7, 6.4, 6.4 Hz, 1 H, CHHCHOH), 1.64 - 1.77 (m, 2 H, CH<sub>2</sub>CH<sub>2</sub>CHOH), 1.53 (ddt,  $J$  = 13.0, 9.5, 6.2, 6.2 Hz, 1 H, CHHCHOH), 1.37 (ddt,  $J$  = 12.8, 8.5, 7.7, 7.7 Hz, 1 H, CHHCHNH<sub>2</sub>)

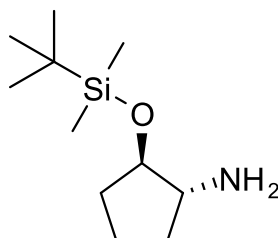
**<sup>13</sup>C NMR** (101 MHz, MeOD)  $\delta$  / ppm = 80.6 (CHOH), 60.7 (CHNH<sub>2</sub>), 33.2 (CH<sub>2</sub>CHOH), 32.2 (CH<sub>2</sub>CHNH<sub>2</sub>), 21.2 (CH<sub>2</sub>CH<sub>2</sub>CHOH)

**HRMS** (ESI<sup>+</sup>)  $m/z$  / Da = 102.0915, [M+H]<sup>+</sup> found, [C<sub>5</sub>H<sub>12</sub>NO]<sup>+</sup> requires 102.0913

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

The data are consistent with the literature.<sup>13,15</sup>

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



(1*R*,2*R*)-2-aminocyclopentan-1-ol **154** (0.480 g, 4.75 mmol) was stirred in dry CH<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 TBSOTf (3 ml, 3.45 g, 13.1 mmol, 3 eq.) dropwise. The reaction was allowed to reach r.t. and stirred for 1 h. The reaction was quenched with NH<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>). **155**(RR) 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>, ninhydrin stain)

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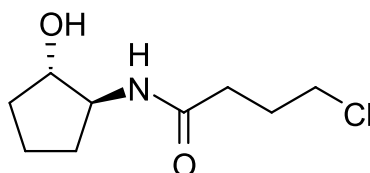
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  / ppm = 4.13 (q,  $J = 5.8$  Hz, 1 H, CH<sub>2</sub>OSi), 3.31 (td,  $J = 7.1, 5.2$  Hz, 1 H, CHNH<sub>2</sub>), 2.09 - 2.19 (m, 1 H, CH<sub>2</sub>CHNH<sub>2</sub>), 1.97 (ddq,  $J = 8.8, 7.0, 6.0, 6.0, 6.0$  Hz, 1 H, CH<sub>2</sub>CHOSi), 1.74 - 1.86 (m, 2 H, CH<sub>2</sub>CH<sub>2</sub>CHOSi), 1.64 - 1.74 (m, 1 H, CH<sub>2</sub>CHOSi), 1.58 (ddt,  $J = 13.2, 9.1, 6.0, 6.0$  Hz, 1 H, CH<sub>2</sub>CHNH<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 = 76.29 (CHOSi), 59.69 (CHNH), 32.18 (CH<sub>2</sub>CHOSi), 26.78 (CH<sub>2</sub>CHNH<sub>2</sub>), 25.62 (C(CH<sub>3</sub>)<sub>3</sub>), 19.73 (CH<sub>2</sub>CH<sub>2</sub>CHOSi), 17.74 (C(CH<sub>3</sub>)<sub>3</sub>), -4.82 (SiCH<sub>3</sub>), -5.23 (SiCH<sub>3</sub>)

**HRMS** (ESI<sup>+</sup>)  $m/z$  / Da = ??, [M+H]<sup>+</sup> found, [??]<sup>+</sup> requires ??

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

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



(1*S*,2*S*)-2-aminocyclopentan-1-ol **153** (500 mg, 4.94 mmol, 1 eq.), TEA (827  $\mu$ 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. 4-Chlorobutyryl chloride **185** (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). **186**(SS) was obtained as a white amorphous solid (651 mg, 3.16 mmol, 64.1 %).

**TLC**  $R_f = 0.35$  (EtOAc, ninhydrin stain)

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**mp**  $T$  / °C = ?? (??)

**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)

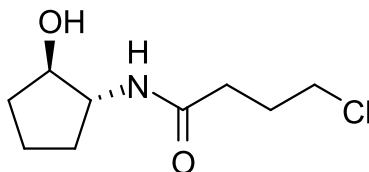
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  / ppm = 6.12 (br s, 1 H, NH), 4.42 (br s, 1 H, OH), 3.94 (q,  $J = 6.6$  Hz, 1 H, CHOH), 3.82 (tt,  $J = 8.4, 5.3$  Hz, 1 H, CHNH), 3.60 (t,  $J = 6.2$  Hz, 2 H, CH<sub>2</sub>Cl), 2.38 (t,  $J = 7.2$  Hz, 2 H, CH<sub>2</sub>C=O), 2.05 - 2.16 (m, 3 H, CH<sub>2</sub>CHNH and CH<sub>2</sub>CH<sub>2</sub>Cl), 1.96 - 2.04 (m, 1 H, CH<sub>2</sub>CHOH), 1.74 - 1.85 (m, 1 H, CH<sub>2</sub>CH<sub>2</sub>CHOH), 1.58 - 1.73 (m, 2 H, CH<sub>2</sub>CH<sub>2</sub>CHOH and CH<sub>2</sub>CHOH), 1.43 (dq,  $J = 12.7, 8.3$  Hz, 1 H, CH<sub>2</sub>CHNH)

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  / ppm = 173.8 (C=O), 79.4 (CHOH), 60.6 (CHNH), 44.4 (CH<sub>2</sub>Cl), 32.8 (CH<sub>2</sub>C=O), 32.4 (CH<sub>2</sub>CHOH), 30.1 (CH<sub>2</sub>CHNH), 28.0 (CH<sub>2</sub>CH<sub>2</sub>Cl), 21.1 (CH<sub>2</sub>CH<sub>2</sub>CHOH)

**HRMS** (ESI<sup>+</sup>)  $m/z$  / Da = 228.0787, [M+Na]<sup>+</sup> found, [C<sub>9</sub>H<sub>16</sub>ClNNaO<sub>2</sub>]<sup>+</sup> requires 228.0762

$[\alpha]_D^{20}$  / °10<sup>-1</sup>cm<sup>2</sup>g<sup>-1</sup> = -13.0 ( $c$  / g(100 mL)<sup>-1</sup> = 0.5, MeOH)

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



(1*R*,2*R*)-2-aminocyclopentan-1-ol **154** (72.3 mg, 716  $\mu$ mol, 1 eq.), TEA (500  $\mu$ l, 363 mg, 3.58 mmol, 5 eq.) and  $\text{CH}_2\text{Cl}_2$  (5 ml) were stirred at 0°C. 4-Chlorobutyryl chloride **185** (179  $\mu$ l, 226 mg, 1.60 mmol, 1.1 eq.) was added dropwise over 5 min. The mixture was stirred at 0°C for 30 min, then water (10 ml) was added. The organic layer was separated off, and the aqueous layer was extracted with 10 % *i*-PrOH/ $\text{CHCl}_3$  ( $2 \times 10$  ml). The combined organic layers were dried with  $\text{MgSO}_4$ , concentrated under reduced pressure and purified by column chromatography ( $\text{SiO}_2$ ,  $\text{Et}_2\text{O}$ ). **157** was obtained as a white amorphous solid (35.6 mg, 173  $\mu$ mol, 24.2 %).

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

**mp**  $T$  / °C = ?? (??)

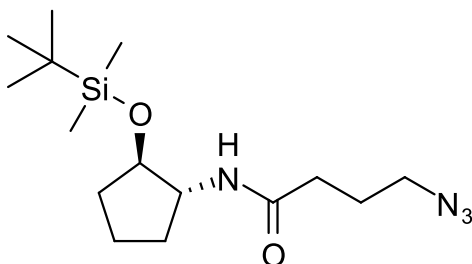
**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  / ppm = 6.05 (br s, 1 H,  $\text{NH}$ ), 4.55 (br s, 1 H,  $\text{OH}$ ), 3.95 (q,  $J=6.6$  Hz, 1 H,  $\text{CHOH}$ ), 3.82 (tt,  $J=8.4, 5.3$  Hz, 1 H,  $\text{CHNH}$ ), 3.60 (t,  $J=6.2$  Hz, 2 H,  $\text{CH}_2\text{Cl}$ ), 2.38 (t,  $J=7.0$  Hz, 2 H,  $\text{CH}_2\text{C=O}$ ), 2.05 - 2.17 (m, 3 H,  $\text{CHHCHNH}$  and  $\text{CH}_2\text{CH}_2\text{Cl}$ ), 1.94 - 2.05 (m, 1 H,  $\text{CHHCHOH}$ ), 1.74 - 1.86 (m, 1 H,  $\text{CHHCH}_2\text{CHOH}$ ), 1.58 - 1.74 (m, 2 H,  $\text{CHHCH}_2\text{CHOH}$  and  $\text{CHHCHOH}$ ), 1.42 (dq,  $J=12.5, 8.4$  Hz, 1 H,  $\text{CHHCHNH}$ )

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

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

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

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



(1*R*,2*R*)-2-((*tert*-butyldimethylsilyl)oxy)cyclopentan-1-amine **155** (50 mg, 0.232 mmol, 1 eq.) and NaHCO<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). 4-Bromobutyryl chloride (25.3 ml, 40.5 mg, 0.219 mmol, 0.95 eq.) was added dropwise at 0 °C and the mixture was stirred for 3 h. The aqueous layer was removed and NaN<sub>3</sub> (100 mg, 1.54 mmol, 6.6 eq.) and DMF (3 ml) were added. The mixture was stirred at 40 °C for 6 h. The solvents were then evaporated using a N<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>). **187**(RR) was obtained as a clear liquid (71 mg, 0.217 mmol, 99.2 %).

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**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)

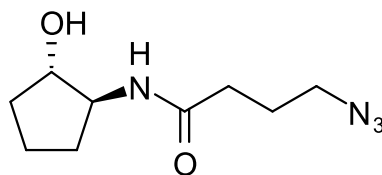
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  / ppm = 5.35 (d,  $J$  = 5.1 Hz, 1 H, NH), 3.97 - 4.01 (m, 1 H, CHOSi), 3.93 - 3.98 (m, 1 H, CHNH), 3.35 (t,  $J$  = 6.6 Hz, 2 H, CH<sub>2</sub>N<sub>3</sub>), 2.24 (t,  $J$  = 7.0 Hz, 2 H, CH<sub>2</sub>C=O), 2.09 - 2.19 (m, 1 H, CHHCHNH), 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)

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



4-Chloro-*N*-((1*S*,2*S*)-2-hydroxycyclopentyl)butanamide **156** (200 mg, 0.972 mmol, 1 eq.) and NaN<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. **159** was obtained as white needles (181 mg, 0.852 mmol, 87.6 %).

**TLC**  $R_f$  = 0.35 (EtOAc, ninhydrin stain)

**mp**  $T$  / °C = 56-59.5 (*i*-PrOH, CHCl<sub>3</sub>)

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for others

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

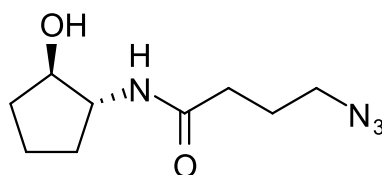
**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  / ppm = 6.72 (d,  $J$  = 4.4 Hz, 1 H,  $\text{NH}$ ), 4.82 (br. s., 1 H,  $\text{OH}$ ), 3.88 (q,  $J$  = 6.6 Hz, 1 H,  $\text{CHOH}$ ), 3.75 (tdd,  $J$  = 8.4, 8.4, 6.6, 4.4 Hz, 1 H,  $\text{CHNH}$ ), 3.28 (t,  $J$  = 6.6 Hz, 2 H,  $\text{CH}_2\text{N}_3$ ), 2.23 (t,  $J$  = 7.3 Hz, 2 H,  $\text{CH}_2\text{C=O}$ ), 2.04 (dtd,  $J$  = 13.0, 8.0, 8.0, 4.9 Hz, 1 H,  $\text{CHHCHNH}$ ), 1.92 (dtd,  $J$  = 13.0, 7.6, 7.6, 5.8 Hz, 1 H,  $\text{CHHCHOH}$ ), 1.84 (quin,  $J$  = 7.0 Hz, 2 H,  $\text{CH}_2\text{CH}_2\text{N}_3$ ), 1.59 - 1.77 (m, 2 H,  $\text{CH}_2\text{CH}_2\text{CHOH}$ ), 1.54 (ddt,  $J$  = 12.7, 9.0, 6.7, 6.7 Hz, 1 H,  $\text{CHHCHOH}$ ), 1.39 (dq,  $J$  = 12.9, 8.4 Hz, 1 H,  $\text{CHHCHNH}$ )

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

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

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

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



4-Chloro-*N*-((1*S*,2*S*)-2-hydroxycyclopentyl)butanamide **156** (35.0 mg, 0.170 mmol, 1 eq.) and  $\text{NaN}_3$  (22.1 mg, 0.340 mmol, 2 eq.) were stirred in acetonitrile (2 ml) at 50  $^{\circ}\text{C}$  for 24 h. The reaction mixtures was then partitioned between water (20 ml) and 10 % *i*-PrOH/ $\text{CHCl}_3$  (5 ml). The aqueous layer was extracted again with 10 % *i*-PrOH/ $\text{CHCl}_3$  ( $2 \times 5$  ml) and the combined organic fractions were dried with  $\text{MgSO}_4$  and evaporated under reduced pressure. **159** was obtained as a white solid (16.2 mg, 0.0764 mmol, 45.0 %).

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

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

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

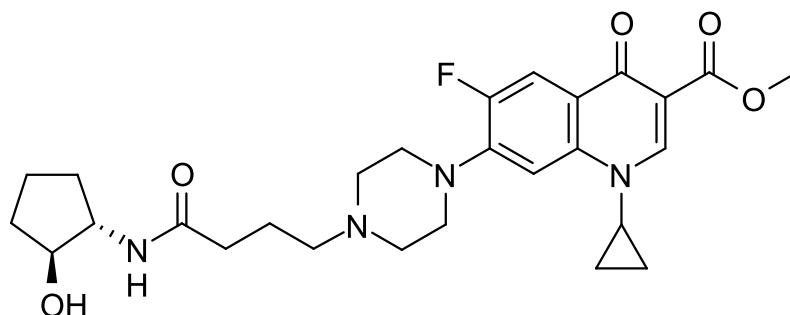
**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  / ppm = 173.8 ( $\text{C=O}$ ), 79.7 ( $\text{CHOH}$ ), 61.0 ( $\text{CHNH}$ ), 50.7 ( $\text{CH}_2\text{N}_3$ ), 32.8 ( $\text{CH}_2\text{C=O}$ ), 32.6 ( $\text{CH}_2\text{CHOH}$ ), 30.5 ( $\text{CH}_2\text{CHNH}$ ), 24.7 ( $\text{CH}_2\text{CH}_2\text{N}_3$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

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



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

**1.56 Methyl 1-cyclopropyl-6-fluoro-7-(4-(4-(((1*S*,2*S*)-2-hydroxycyclopentyl)amino)-4-oxobutyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate **161****



**150** (200 mg, 0.367 mmol, 1 eq.), **153** (80 mg, 0.791 mmol, 2.1 eq.), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (112 mg, 0.584 mmol, 1.6 eq.), 1-hydroxybenzotriazole (96 mg, 0.710 mmol, 1.9 eq.) and DIPEA (192  $\mu$ l, 142 mg, 1.10 mmol, 3 eq.) were dissolved in DMF (5 ml) and stirred at r.t. for 16 h. The solvent was removed using a stream of N<sub>2</sub> and the residue was purified by preparatory HPLC (5-60 % acetonitrile/water over 12 min). The combined pure fractions were evaporated under reduced pressure and then partitioned between NaHCO<sub>3</sub> (aq., sat., 10 ml) and CH<sub>2</sub>Cl<sub>2</sub> (10 ml). The organic layer was removed and the aqueous layer was extracted twice more with CH<sub>2</sub>Cl<sub>2</sub> (2  $\times$  10 ml). The combined organic fractions were dried with MgSO<sub>4</sub> and evaporated under reduced pressure. **161** was obtained as a white amorphous solid (73.0 mg, 0.142 mmol, 38.7 %).

**TLC**  $R_f$  = 0.43 (30 % MeOH/EtOAc)

**IR** (neat)  $\nu_{max}$  / 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, CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 1.54 - 1.65 (m, 2 H, CH<sub>2</sub>CH<sub>2</sub>CHOH), 1.42 (ddt,  $J$  = 13.1, 8.2, 5.3, 5.3 Hz, 1 H, CHHCHOH), 1.32 (dddd,  $J$  = 13.4, 8.5, 6.8, 5.8 Hz, 1 H, CHHCHNH), 1.21 - 1.29 (m, 2 H, NCH(CH<sub>2</sub>)<sub>2</sub>), 1.07 - 1.13 (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 = 171.9 (CH<sub>2</sub>C(=O)NH), 171.6 (C(=O)CC(=O)OCH<sub>3</sub>), 165.0 (C(=O)OCH<sub>3</sub>), 152.6 (d,  $J$  = 246.5 Hz, *ipso* to F), 148.3 (C=CC(=O)OCH<sub>3</sub>), 143.9 (d,  $J$  = 10.7 Hz, *ipso* to piperazine), 138.1 (*para* to F), 121.8 (d,  $J$  = 6.4 Hz, *para* to piperazine), 111.5 (d,  $J$  = 22.4 Hz, *ortho* to C=O and *ortho* to F), 109.0 (CC(=O)OCH<sub>3</sub>), 106.2 (*meta* to C=O and *meta* to F), 76.3 (CHOH), 57.6 (CHNH), 57.2 (C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 52.4 (C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>), 51.3 (CH<sub>3</sub>), 49.6 (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>)

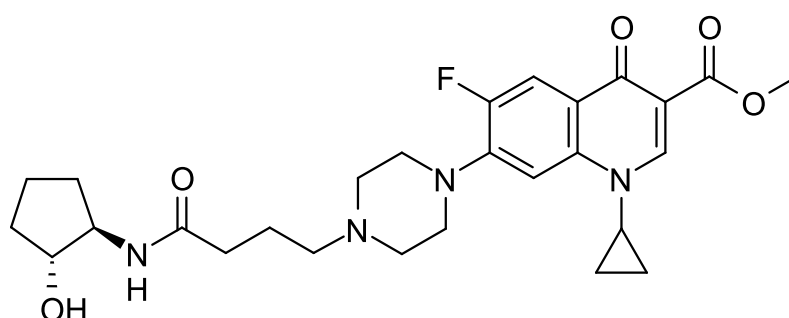
34.8 ( $\text{NCH}(\text{CH}_2)_2$ ), 33.3 ( $\text{C}(=\text{O})\text{CH}_2$ ), 32.2 ( $\text{CH}_2\text{CHOH}$ ), 29.5 ( $\text{CH}_2\text{CHNH}$ ), 22.5 ( $\text{C}(=\text{O})\text{CH}_2\text{CH}_2$ ), 20.6 ( $\text{CH}_2\text{CH}_2\text{CHOH}$ ), 7.6 ( $\text{NCH}(\text{CH}_2)_2$ )

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

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

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

### 1.57 Methyl 1-cyclopropyl-6-fluoro-7-(4-(4-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-4-oxobutyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate **162**



**150** (52.1 mg, 95.5  $\mu\text{mol}$ , 1 eq.), **154** (19.5 mg, 193  $\mu\text{mol}$ , 2 eq.), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (29.7 mg, 155  $\mu\text{mol}$ , 1.6 eq.), 1-hydroxybenzotriazole (25.8 mg, 191  $\mu\text{mol}$ , 2 eq.) and DIPEA (33.3  $\mu\text{l}$ , 24.7 mg, 191  $\mu\text{mol}$ , 2 eq.) were dissolved in DMF (2 ml) and stirred at r.t. for 16 h. The solvent was removed using a stream of  $\text{N}_2$  and the residue was purified by preparatory HPLC (5-50 % acetonitrile/water over 15 min). The combined pure fractions were evaporated under reduced pressure and then partitioned between  $\text{NaHCO}_3$  (aq., sat., 5 ml) and  $\text{CH}_2\text{Cl}_2$  (5 ml). The organic layer was removed and the aqueous layer was extracted twice more with  $\text{CH}_2\text{Cl}_2$  ( $2 \times 5 \text{ ml}$ ). The combined organic fractions were dried with  $\text{MgSO}_4$  and evaporated under reduced pressure. **161** was obtained as a white amorphous solid (4.9 mg, 9.5  $\mu\text{mol}$ , 9.9 %).

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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,  $J=13.5 \text{ Hz}$ , 1 H, *ortho* to F), 7.69 (d,  $J=6.9 \text{ Hz}$ , 1 H,  $\text{CHNH}$ ), 7.43 (d,  $J=7.6 \text{ Hz}$ , 1 H, *meta* to F), 4.73 (br s, 1 H,  $\text{CHOH}$ ), 3.77 - 3.81 (m, 1 H,  $\text{CHOH}$ ), 3.74 - 3.77 (m, 1 H,  $\text{CHNH}$ ), 3.73 (s, 3 H,  $\text{CH}_3$ ), 3.65 (tt,  $J=6.9, 4.0 \text{ Hz}$ , 1 H,  $\text{NCH}(\text{CH}_2)_2$ ), 3.24 (br. t,  $J=4.2, 4.2 \text{ Hz}$ , 4 H,  $\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)\text{CH}_2\text{CH}_2$ ), 2.55 (br t,  $J=5.0, 5.0 \text{ Hz}$ , 4 H,  $\text{CH}_2\text{N}(\text{CH}_2)\text{CH}_2$ ), 2.32 (t,  $J=7.2 \text{ Hz}$ , 2 H,  $\text{CH}_2\text{N}(\text{CH}_2)\text{CH}_2$ ), 2.10 (t,  $J=7.4 \text{ Hz}$ , 2 H,  $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2)\text{CH}_2$ ), 1.92 (dddd,  $J=13.0, 8.7, 7.3, 6.0 \text{ Hz}$ , 1 H,  $\text{CHHCHNH}$ ), 1.77 (ddt,  $J=12.6, 8.9, 6.3, 6.3 \text{ Hz}$ , 1 H,  $\text{CHHCHOH}$ ), 1.68 (quin,  $J=7.4 \text{ Hz}$ , 2 H,  $\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2)\text{CH}_2$ ), 1.53 - 1.64 (m, 2 H,  $\text{CH}_2\text{CH}_2\text{CHOH}$ ), 1.42 (ddt,  $J=12.9, 8.4, 5.2, 5.2 \text{ Hz}$ , 1 H,  $\text{CHHCHOH}$ ), 1.31 (ddt,  $J=13.0, 8.6, 6.4, 6.4 \text{ Hz}$ , 1 H,  $\text{CHHCHNH}$ ), 1.22 - 1.28 (m, 2 H,  $\text{NCH}(\text{CHH})_2$ ), 1.06 - 1.12 (m, 2 H,  $\text{NCH}(\text{CHH})_2$ )

**$^{13}\text{C}$  NMR** (126 MHz, DMSO  $d_6$ )  $\delta$  / ppm = 171.9 ( $\text{CH}_2\text{C}(=\text{O})\text{NH}$ ), 171.5 ( $\text{C}(=\text{O})\text{CC}(=\text{O})\text{OCH}_3$ ), 165.0 ( $\text{C}(=\text{O})\text{OCH}_3$ ), 152.6 (d,  $J=247.4$  Hz, *ipso* to F), 148.2 ( $\text{C}=\text{CC}(=\text{O})\text{OCH}_3$ ), 143.9 (d,  $J=10.3$  Hz, *ipso* to piperazine), 138.1 (*para* to F), 121.7 (d,  $J=6.4$  Hz, *para* to piperazine), 111.5 (d,  $J=23.0$  Hz, *ortho* to C=O and *ortho* to F), 109.0 ( $\text{CC}(=\text{O})\text{OCH}_3$ ), 106.2 (*meta* to C=O and *meta* to F), 76.2 ( $\text{CHOH}$ ), 57.6 ( $\text{CHNH}$ ), 57.2 ( $\text{C}(=\text{O})\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$ ), 52.4 ( $\text{C}(=\text{O})\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)$ ), 51.3 ( $\text{CH}_3$ ), 49.6 ( $\text{C}(=\text{O})\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)\text{CH}_2\text{CH}_2$ ), 49.6 ( $\text{C}(=\text{O})\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)\text{CH}_2\text{CH}_2$ ), 34.7 ( $\text{NCH}(\text{CH}_2)_2$ ), 33.2 ( $\text{C}(=\text{O})\text{CH}_2$ ), 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 ( $\text{CH}_2\text{CH}_2\text{CHOH}$ ), 7.5 ( $\text{NCH}(\text{CH}_2)_2$ )

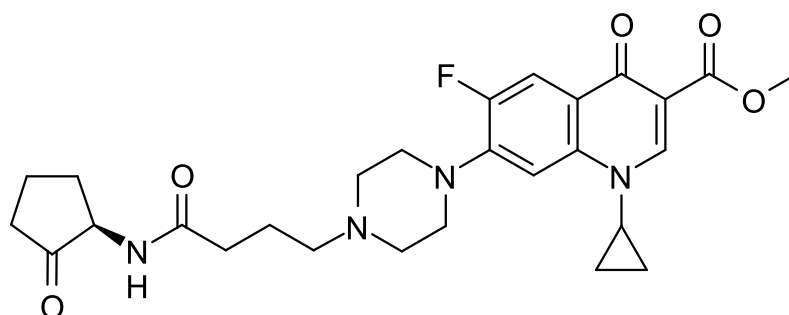
**$^{19}\text{F}$  NMR** (376.45 MHz, MeOD)  $\delta$  / ppm = -125.47

**HRMS** (ESI $^+$ )  $m/z$  / Da = 515.2667,  $[\text{M}+\text{H}]^+$  found,  $[\text{C}_{27}\text{H}_{36}\text{FN}_4\text{O}_5]^+$  requires 515.2670

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

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



Methyl 1-cyclopropyl-6-fluoro-7-(4-(4-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-4-oxobutyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate **162** (20.0 mg, 38.9  $\mu\text{mol}$ , 1 eq.) and Dess-Martin Periodane (32.8 mg, 77.4  $\mu\text{mol}$ , 2 eq.) were stirred in  $\text{CH}_2\text{Cl}_2$  (3 ml) for 6 h. The solvent was removed under reduced pressure and the residue was purified by preparatory HPLC (5-50 % acetonitrile/water over 10 min). The combined pure fractions were evaporated under reduced pressure, then  $\text{NaHCO}_3$  (aq., sat., 30 ml) and 10 % *i*-PrOH/ $\text{CHCl}_3$  (30 ml) were added. The organic layer was removed and dried with  $\text{MgSO}_4$ , then evaporated under reduced pressure. **163** was obtained as a white amorphous solid (11.3 mg, 22.0  $\mu\text{mol}$ , 56.7 %).

**$^1\text{H}$  NMR** (400 MHz, MeOD)  $\delta$  / ppm = ??

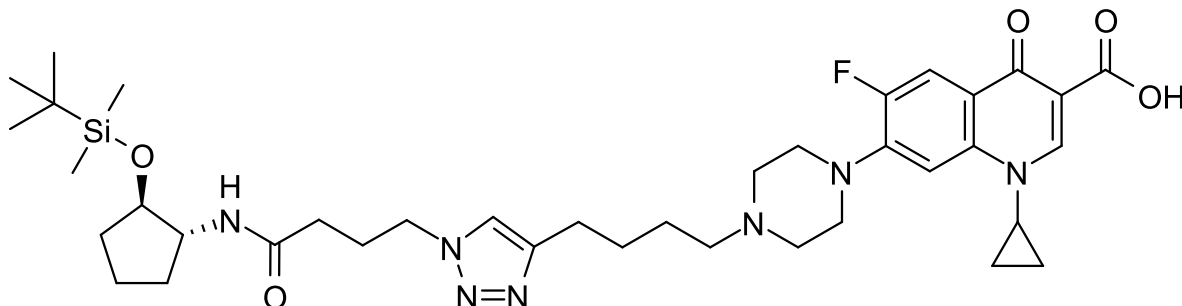
**$^{13}\text{C}$  NMR** (101 MHz, MeOD)  $\delta$  / ppm = ??

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

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

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

**1.59 7-(4-(4-(1-(4-(((1*R*,2*R*)-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 **164****



1-Cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **176** (42.9 mg, 104  $\mu\text{mol}$ , 1 eq.) and 4-azido-*N*-(((1*R*,2*R*)-2-((*tert*-butyldimethylsilyl)oxy)cyclopentyl)butanamide **187** (RR) (33.9 mg, 104  $\mu\text{mol}$ , 1 eq.) were dissolved in 10 % water/*t*-BuOH (3 ml), and the mixture was degassed by bubbling  $\text{N}_2$  through it. A solution of  $\text{CuSO}_4$  and THPTA (104  $\mu\text{l}$ , 10.4  $\mu\text{mol}$ , 0.1 eq. 100 mM, aq.) was added, followed by a solution of sodium ascorbate (208  $\mu\text{l}$ , 20.8  $\mu\text{mol}$ , 0.2 eq., 100 mM, aq.). The mixture was stirred at room temperature under argon for 16 h, then solvent was removed under reduced pressure. The residue was partitioned between water (10 ml) and  $\text{CH}_2\text{Cl}_2$  (10 ml), the organic layer was separated and the aqueous layer was extracted again with  $\text{CH}_2\text{Cl}_2$  (10 ml). The combined organic layers were dried with  $\text{MgSO}_4$  and evaporated under reduced pressure. **164** was obtained as a clear glass (67.1 mg, 90.9  $\mu\text{mol}$ , 87.4 %).

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

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  / 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,  $\text{CH}=\text{CCH}_2$ ), 7.33 (d,  $J$  = 8.2 Hz, 1 H, *meta* to F), 5.92 (t,  $J$  = 6.6 Hz, 1 H,  $\text{CHNH}$ ), 4.35 (t,  $J$  = 6.7 Hz, 2 H,  $\text{CH}_2\text{NCH}=\text{C}$ ), 3.96 - 4.02 (m, 1 H,  $\text{CHOSi}$ ), 3.90 - 3.96 (m, 1 H,  $\text{CHNH}$ ), 3.55 (tt,  $J$  = 6.7, 4.0 Hz, 1 H,  $\text{NCH}(\text{CH}_2)_2$ ), 3.34 (br t,  $J$  = 5.0 Hz, 4 H,  $\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)\text{CH}_2\text{CH}_2$ ), 2.71 (t,  $J$  = 7.5 Hz, 2 H,  $\text{CH}=\text{CCH}_2$ ), 2.66 (br s, 4 H,  $\text{CH}_2\text{N}(\text{CH}_2)\text{CH}_2$ ), 2.46 (t,  $J$  = 7.3 Hz, 2 H,  $\text{CH}_2\text{N}(\text{CH}_2)\text{CH}_2$ ), 2.03 - 2.22 (m, 5 H,  $\text{CHHCHNH}$ ,  $\text{C}(=\text{O})\text{CH}_2$  and  $\text{C}(=\text{O})\text{CH}_2\text{CH}_2$ ), 1.65 - 1.83 (m, 4 H,  $\text{CHHCHOSi}$ ,  $\text{CHHCH}_2\text{CHOSi}$  and  $\text{NCH}=\text{CCH}_2\text{CH}_2$ ), 1.47 - 1.65 (m, 4 H,  $\text{CHHCHOSi}$ ,  $\text{CHHCH}_2\text{CHOSi}$  and  $\text{NCH}=\text{CCH}_2\text{CH}_2$ ), 1.33 - 1.41 (m, 3 H,  $\text{CHHCHNH}$  and  $\text{NCH}(\text{CHH})_2$ ), 1.14 - 1.20 (m, 2 H,  $\text{NCH}(\text{CHH})_2$ ), 0.82 (s, 9 H,  $\text{C}(\text{CH}_3)_3$ ), 0.03 (s, 3 H,  $\text{SiCH}_3$ ), 0.01 (s, 3 H,  $\text{SiCH}_3$ )

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

17.8 ( $\underline{\text{C}}(\underline{\text{CH}}_3)_3$ ), 8.1 ( $\text{NCH}(\underline{\text{CH}}_2)_2$ ), -4.8 ( $\text{Si}\underline{\text{CH}}_3$ )

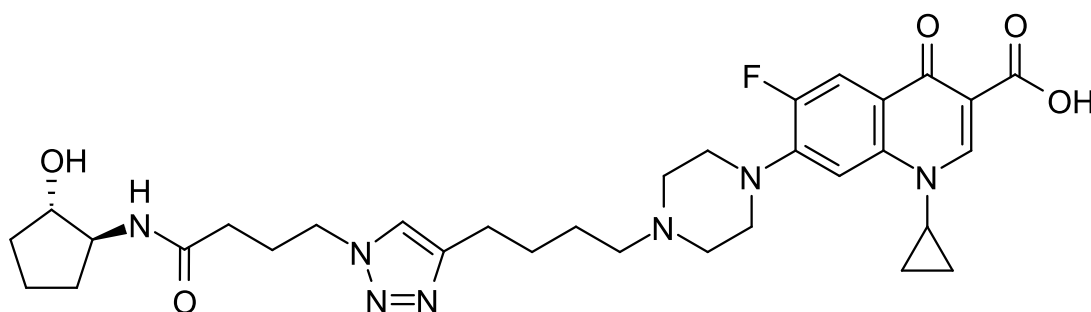
$^{19}\text{F}$  NMR (376.45 MHz,  $\text{CDCl}_3$ )  $\delta$  / ppm = ??

F??

HRMS ( $\text{ESI}^+$ )  $m/z$  / Da = 738.4164,  $[\text{M}+\text{H}]^+$  found,  $[\text{C}_{38}\text{H}_{57}\text{FN}_7\text{O}_5\text{Si}]^+$  requires 738.4169

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

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



1-Cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **176** (42.9 mg, 104  $\mu\text{mol}$ , 1 eq.) and 4-azido-*N*-((1*S*,2*S*)-2-hydroxycyclopentyl)butanamide **159** (22.0 mg, 104  $\mu\text{mol}$ , 1 eq.) were dissolved in 10 % water/*t*-BuOH (3 ml), and the mixture was degassed by bubbling  $\text{N}_2$  through it. A solution of  $\text{CuSO}_4$  and THPTA (104  $\mu\text{l}$ , 10.4  $\mu\text{mol}$ , 0.1 eq. 100 mM, aq.) was added, followed by a solution of sodium ascorbate (208  $\mu\text{l}$ , 20.8  $\mu\text{mol}$ , 0.2 eq., 100 mM, aq.). The mixture was stirred at room temperature under argon for 16 h. Water (30 ml) and  $\text{CH}_2\text{Cl}_2$  (30 ml) were added, the organic layer was separated and the aqueous layer was extracted again with  $\text{CH}_2\text{Cl}_2$  (4  $\times$  30 ml). The combined organic layers were dried with  $\text{MgSO}_4$  and evaporated under reduced pressure. The residue was purified by preparatory HPLC (5-95 % acetonitrile/water over 20 min). The combined pure fractions were evaporated under reduced pressure and then partitioned between  $\text{NaHCO}_3$  (aq., sat., 10 ml) and 10 % *i*-PrOH/ $\text{CHCl}_3$  (10 ml). The organic layer was dried with  $\text{MgSO}_4$  and evaporated under reduced pressure. **164** was obtained as a white amorphous solid (17.6 mg, 28.2  $\mu\text{mol}$ , 27.1 %).

IR (neat)  $\nu_{\text{max}}$  /  $\text{cm}^{-1}$  = 2967.0 (C-H), 2902.2 (C-H), 1721.4 (carboxylic acid C=O), 1646.7 (amide C=O), 1627.0 (quinolone C=O), 1613.0 (triazole)

$^1\text{H}$  NMR (700 MHz,  $\text{DMSO}-d_6$ )  $\delta$  / 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,  $\underline{\text{CH}}=\underline{\text{CCH}}_2$ ), 7.75 (d,  $J$  = 7.1 Hz, 1 H,  $\text{CHN}\underline{\text{H}}$ ), 7.54 (d,  $J$  = 7.5 Hz, 1 H, *meta* to F), 4.73 (d,  $J$  = 3.8 Hz, 1 H,  $\text{CHO}\underline{\text{H}}$ ), 4.29 (t,  $J$  = 6.9 Hz, 2 H,  $\underline{\text{CH}}_2\text{NCH}=\text{C}$ ), 3.78 - 3.83 (m, 1 H,  $\text{NCH}(\underline{\text{CH}}_2)_2$ ), 3.75 - 3.78 (m, 1 H,  $\underline{\text{CH}}\text{OH}$ ), 3.71 - 3.75 (m, 1 H,  $\text{CHN}\underline{\text{H}}$ ), 3.31 (br t,  $J$  = 4.3 Hz, 4 H,  $\text{CH}_2\text{N}(\underline{\text{CH}}_2\underline{\text{CH}}_2)\underline{\text{CH}}_2\underline{\text{CH}}_2$ ), 2.63 (t,  $J$  = 7.5 Hz, 2 H,  $\text{CH}=\underline{\text{CCH}}_2$ ), 2.56 (br t,  $J$  = 4.2 Hz, 4 H,  $\text{CH}_2\text{N}(\underline{\text{CH}}_2)\underline{\text{CH}}_2$ ), 2.37 (t,  $J$  = 7.3 Hz, 2 H,  $\underline{\text{CH}}_2\text{N}(\underline{\text{CH}}_2)\underline{\text{CH}}_2$ ), 2.03 - 2.06 (m, 2 H,  $\text{C}(=\text{O})\underline{\text{CH}}_2$ ), 1.97 - 2.02 (m, 2 H,  $\text{C}(=\text{O})\underline{\text{CH}}_2\underline{\text{CH}}_2$ ), 1.89 (dddd,  $J$  = 13.1, 8.9, 7.4, 5.7 Hz, 1 H,  $\underline{\text{CH}}\text{HCHN}\underline{\text{H}}$ ), 1.75 (ddt,  $J$  = 13.0, 8.9, 6.4, 6.4 Hz, 1 H,  $\underline{\text{CH}}\text{HCH}\text{OH}$ ), 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>)

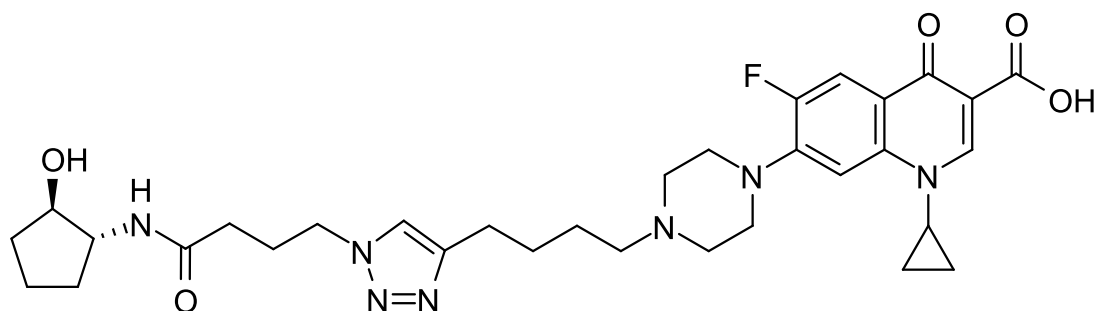
<sup>13</sup>C NMR (175 MHz, DMSO d<sub>6</sub>)  $\delta$  / ppm = 176.3 (C(=O)CC(=O)OH), 170.9 (CH<sub>2</sub>C(=O)NH), 166.1 (C(=O)OH), 153.0 (d, *J* = 251.4 Hz, *ipso* to F), 147.9 (C=CC(=O)OH), 146.9 (CH=CCH<sub>2</sub>), 145.2 (d, *J* = 8.7 Hz, *ipso* to piperazine), 139.2 (*para* to F), 121.7 (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>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 = -122.12 (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)

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



Method?? white amorphous solid 7.2 mg, 11.5 μmol

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, MeOD)  $\delta$  / ppm = ??

<sup>13</sup>C NMR (101 MHz, MeOD)  $\delta$  / ppm = ??

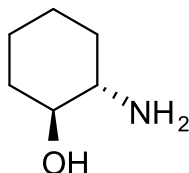
<sup>19</sup>F NMR (376.45 MHz, MeOD)  $\delta$  / ppm = ??

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

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

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



Cyclohexene oxide **188** (10 ml, 9.70 g, 98.8 mmol, 1 eq.),  $\text{NH}_3$  (90 ml, 35 % w/w aq., 27.7 g, 791 mmol, 8 eq.) and MeOH (100 ml) were stirred at r.t. for 72 h. The solvent was removed by blowing a stream of  $\text{N}_2$  over it, followed by evaporation under high vacuum

**TLC**  $R_f = 0.04$  (30 % MeOH/ $\text{CH}_2\text{Cl}_2$ )

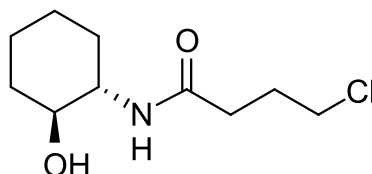
**IR** (neat)  $\nu_{\text{max}} / \text{cm}^{-1} = 3350.4$  (N-H), 3306.2 (br, O-H), 2926.9 (C-H), 2852.6 (C-H)

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta / \text{ppm} = 3.01$  (td,  $J = 9.4, 4.8$  Hz, 1 H,  $\text{CH(OH)}$ ), 2.80 - 2.92 (m, 2 H,  $\text{OH}$  and  $\text{NH}_2$ ), 2.35 (ddd,  $J = 11.1, 9.1, 4.1$  Hz, 1 H,  $\text{CHNH}_2$ ), 1.77 - 1.84 (m, 1 H,  $\text{CHHCHOH}$ ), 1.69 - 1.76 (m, 1 H,  $\text{CHHCHNH}_2$ ), 1.56 - 1.66 (m, 1 H,  $\text{CHHCH}_2\text{CHOH}$ ), 1.45 - 1.56 (m, 1 H,  $\text{CHHCH}_2\text{CHNH}_2$ ), 1.07 - 1.19 (m, 3 H,  $\text{CHHCH}_2\text{CHOH}$ ,  $\text{CHHCH}_2\text{CHNH}_2$  and  $\text{CHHCHOH}$ ), 0.94 - 1.05 (m, 1 H,  $\text{CHHCHNH}_2$ )

**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta / \text{ppm} = 75.4$  ( $\text{CHOH}$ ), 56.6 ( $\text{CHN}_2$ ), 33.8 ( $\text{CH}_2\text{CHOH}$  and  $\text{CH}_2\text{CHN}_2$ ), 24.7 ( $\text{CH}_2\text{CH}_2\text{CHN}_2$ ), 24.6 ( $\text{CH}_2\text{CH}_2\text{CHOH}$ )

**HRMS** ( $\text{ESI}^+$ )  $m/z / \text{Da} = 116.1070$ ,  $[\text{M}+\text{H}]^+$  found,  $[\text{C}_6\text{H}_{14}\text{NO}]^+$  requires 116.1070

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



(*Trans*)-2-aminocyclohexan-1-ol **167** (1.04 g, 9.03 mmol, 1 eq.), TEA (1.65 ml, 1.20 g, 11.8 mmol, 1.3 eq.) and  $\text{CH}_2\text{Cl}_2$  (50 ml) were stirred at  $0^\circ\text{C}$ . 4-Chlorobutyryl chloride **185** (1.22 ml, 1.54 g, 10.9 mmol, 1.2 eq.) was added dropwise over 5 min. The mixture was stirred at  $0^\circ\text{C}$  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/ $\text{Et}_2\text{O}$ ). **168** was obtained as white needles (1.51 g, 6.87 mmol, 76.1 %).

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

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

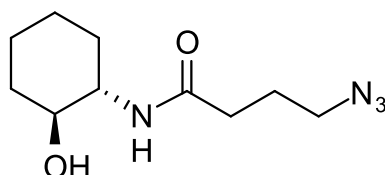
**IR** (neat)  $\nu_{\text{max}} / \text{cm}^{-1} = 3289.9$  (N-H), 3250.0 (O-H), 2927.6 (C-H), 2857.1 (C-H), 1629.2 (amide C=O)

**$^1\text{H}$  NMR** (400 MHz, MeOD)  $\delta / \text{ppm} = 3.60$  (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)  $\delta / \text{ppm} = 175.0$  ( $\text{C(=O)}$ ), 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 ( $\text{CH}_2\text{CH}_2\text{CHOH}$ )

**HRMS** ( $\text{ESI}^+$ )  $m/z / \text{Da} = 242.0925$ ,  $[\text{M}+\text{Na}]^+$  found,  $[\text{C}_{10}\text{H}_{18}\text{ClNNaO}_2]^+$  requires 242.0924

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



4-Chloro-*N*-((*trans*)-2-hydroxycyclohexyl)butanamide **168** (345 mg, 1.57 mmol, 1 eq.) and  $\text{NaN}_3$  (180 mg, 2.77 mmol, 1.75 eq.) were stirred in DMF (12 ml) at  $50^\circ\text{C}$  for 16 h. Water (50 ml) and 10 % *i*-PrOH/ $\text{CHCl}_3$  (50 ml) were added, and the organic layer was removed. The aqueous layer was extracted again with 10 % *i*-PrOH/ $\text{CHCl}_3$  (50 ml) and the combined organic fractions were dried with  $\text{MgSO}_4$ . The solvent was evaporated under reduced pressure, and then by using a  $\text{N}_2$  stream. **189** was obtained as large white prisms (347 mg, 1.53 mmol, 97.5 %).

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

**mp**  $T / ^\circ\text{C} = 74.5\text{-}75.7$  (*i*-PrOH,  $\text{CHCl}_3$ )

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

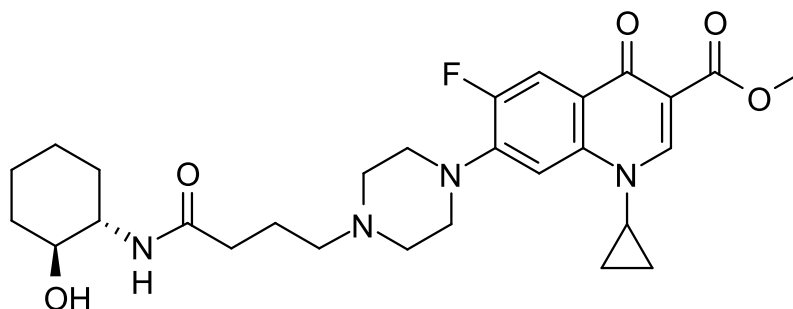
**$^1\text{H}$  NMR** (400 MHz, MeOD)  $\delta / \text{ppm} = 7.87$  (d,  $J = 7.9$  Hz, 1 H,  $\text{NH}$ ), 5.27 (d,  $J = 4.3$  Hz, 1 H,  $\text{OH}$ ), 3.56 (td,  $J = 10.5, 4.4$  Hz, 1 H,  $\text{CHNH}$ ), 3.28 - 3.41 (m, 3 H,  $\text{CHOH}$  and  $\text{CH}_2\text{N}_3$ ), 2.30 (td,  $J = 7.4,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

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



**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

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



**150** (200 mg, 0.367 mmol, 1 eq.), **167** (91.1 mg, 0.791 mmol, 2.1 eq.), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (112 mg, 0.584 mmol, 1.6 eq.), 1-hydroxybenzotriazole (96 mg, 0.710 mmol, 1.9 eq.) and DIPEA (192  $\mu$ l, 142 mg, 1.10 mmol, 3 eq.) were dissolved in DMF (5 ml) and stirred at r.t. for 16 h. The solvent was removed using a stream of N<sub>2</sub> and the residue was purified by preparatory HPLC (5-50 % acetonitrile/water over 10 min). The combined pure fractions were evaporated under reduced pressure and then partitioned between NaHCO<sub>3</sub> (aq., sat., 10 ml) and CH<sub>2</sub>Cl<sub>2</sub> (10 ml). The organic layer was dried with MgSO<sub>4</sub> and evaporated under reduced pressure. **161** was obtained as a white amorphous solid (73.0 mg, 0.142 mmol, 38.7 %).

**IR** (neat)  $\nu_{max}$  / cm<sup>-1</sup> = 3302.5 (N-H), 2929.8 (C-H), 2850.6 (C-H), 2832.9 (C-H), 1698.1 (ester C=O), 1646.4 (amide C=O), 1613.8 (quinolone C=O)

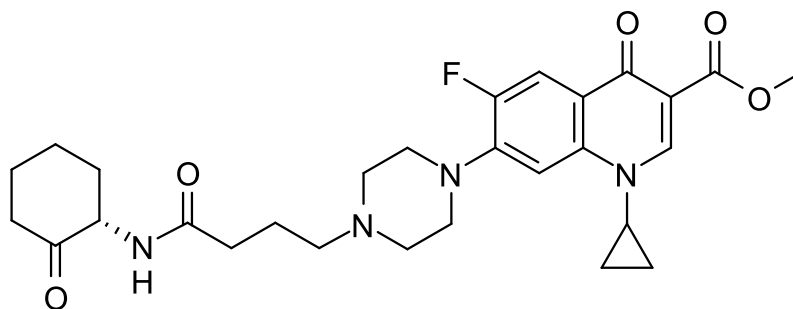
**<sup>1</sup>H NMR** (400 MHz, MeOD)  $\delta$  / ppm = 8.60 (s, 1 H, *ortho* to C(=O)OCH<sub>3</sub>), 7.79 (d,  $J$  = 13.5 Hz, 1 H, *ortho* to F), 7.46 (d,  $J$  = 7.2 Hz, 1 H, *meta* to F), 3.84 (s, 3 H, CH<sub>3</sub>), 3.62 - 3.68 (m, 1 H, NCH(CH<sub>2</sub>)<sub>2</sub>), 3.58 (td,  $J$  = 10.3,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

**<sup>13</sup>C NMR** (101 MHz, MeOD)  $\delta$  / ppm = 175.8 (CH<sub>2</sub>C(=O)NH), 175.3 (C(=O)CC(=O)OCH<sub>3</sub>), 166.8 (C(=O)OCH<sub>3</sub>), 154.9 (d,  $J$  = 248.8 Hz, *ipso* to F), 150.2 (C=CC(=O)OCH<sub>3</sub>), 146.1 (d,  $J$  = 10.8 Hz, *ipso* to piperazine), 139.9 (*para* to F), 123.5 (d,  $J$  = 7.5 Hz, *para* to piperazine), 113.2 (d,  $J$  = 23.2 Hz, *ortho* to C=O and *ortho* to F), 110.2 (CC(=O)OCH<sub>3</sub>), 107.2 (*meta* to C=O and *meta* to F), 74.1 (CHOH), 58.9 (C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 56.4 (CHNH), 54.0 (C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 52.3 (CH<sub>3</sub>), 50.5 (d,  $J$  = 5.0 Hz, C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 36.4 (NCH(CH<sub>2</sub>)<sub>2</sub>), 35.7 (CH<sub>2</sub>CHOH), 35.1 (C(=O)CH<sub>2</sub>), 32.8 (CH<sub>2</sub>CHNH), 25.9 (CH<sub>2</sub>CH<sub>2</sub>CHNH), 25.5 (CH<sub>2</sub>CH<sub>2</sub>CHOH), 23.5 (C(=O)CH<sub>2</sub>CH<sub>2</sub>), 8.7 (NCH(CH<sub>2</sub>)<sub>2</sub>)

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

**HRMS** (ESI<sup>+</sup>)  $m/z$  / Da = 529.2827, [M+H]<sup>+</sup> found, [C<sub>28</sub>H<sub>38</sub>FN<sub>4</sub>O<sub>5</sub>]<sup>+</sup> requires 529.2826

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



Methyl 1-cyclopropyl-6-fluoro-7-(4-(4-(((trans)-2-hydroxycyclohexyl)amino)-4-oxobutyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate **170** (5.2 mg, 9.84  $\mu$ mol, 1 eq.) and Dess-Martin Periodane (16.4 mg, 38.7  $\mu$ mol, 4 eq.) were stirred in  $\text{CH}_2\text{Cl}_2$  (3 ml) for 6 h. The solvent was removed under reduced pressure and the residue was purified by preparatory HPLC (5-95 % acetonitrile/water over ??)

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

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

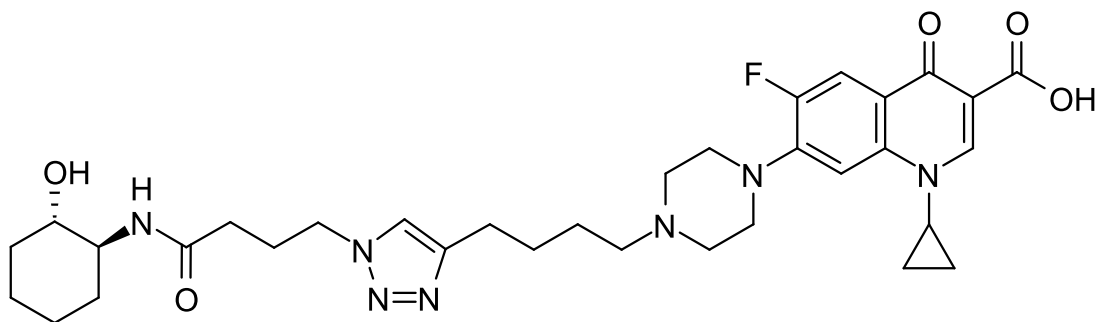
**$^1\text{H}$  NMR** (400 MHz, DMSO  $d_6$ )  $\delta$  / ppm = 8.45 (s, 1 H, *ortho* to C(=O)OCH<sub>3</sub>), 7.87 (d,  $J$  = 6.2 Hz, 1 H, NH), 7.76 (d,  $J$  = 13.4 Hz, 1 H, *ortho* to F), 7.44 (d,  $J$  = 7.5 Hz, 1 H, *meta* to F), 4.42 (dddd,  $J$  = 13.0, 7.6, 6.0, 1.0 Hz, 1 H, CHNH), 3.73 (s, 3 H, CH<sub>3</sub>), 3.65 (tt,  $J$  = 7.1, 3.9 Hz, 1 H, NCH(CH<sub>2</sub>)<sub>2</sub>), 3.25 (br s, 4 H, CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 2.58 (br s, 4 H, CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 2.45 - 2.53 (m, 1 H, CHHC(=O)CHNH), 2.36 (br s, 2 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 2.26 (dt,  $J$  = 13.4, 2.6, 2.6, 1.6, 1.6 Hz, 1 H, CHHC(=O)CHNH), 2.16 - 2.22 (m, 2 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 2.12 (ddq,  $J$  = 12.7, 6.0, 2.8, 2.8, 2.8 Hz, 1 H, CHHCHNH), 2.00 (ddquin,  $J$  = 13.2, 6.0, 2.9, 2.9, 2.9, 2.9 Hz, 1 H, CHHCH<sub>2</sub>C(=O)), 1.65 - 1.83 (m, 4 H, CH<sub>2</sub>CH<sub>2</sub>CHNH), 1.41 - 1.56 (m, 2 H, CHHCHNH and CHHCH<sub>2</sub>C(=O)), 1.20 - 1.30 (m, 2 H, NCH(CH<sub>2</sub>)<sub>2</sub>), 1.05 - 1.13 (m, 2 H, NCH(CH<sub>2</sub>)<sub>2</sub>)

**$^{13}\text{C}$  NMR** (101 MHz, DMSO  $d_6$ )  $\delta$  / ppm = 207.5 (C(=O)CHNH), 171.7 (C(=O)CC(=O)OCH<sub>3</sub>), 171.6 (CH<sub>2</sub>C(=O)NH), 165.0 (C(=O)OCH<sub>3</sub>), 152.6 (d,  $J$  = 247.6 Hz, *ipso* to F), 148.3 (C=CC(=O)OCH<sub>3</sub>), 143.9 (br s, *ipso* to piperazine), 138.1 (*para* to F), 121.8 (d,  $J$  = 6.4 Hz, *para* to piperazine), 111.5 (d,  $J$  = 22.4 Hz, *ortho* to C=O and *ortho* to F), 109.0 (CC(=O)OCH<sub>3</sub>), 106.3 (*meta* to C=O and *meta* to F), 57.0 (CHNH and C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 52.3 (br s, C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 51.3 (CH<sub>3</sub>), 49.5 (br s, C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 40.6 (CH<sub>2</sub>C(=O)CHNH), 34.8 (NCH(CH<sub>2</sub>)<sub>2</sub>), 33.9 (CH<sub>2</sub>CHNH), 32.9 (C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 27.2 (CH<sub>2</sub>CH<sub>2</sub>C(=O)CHNH), 23.8 (CH<sub>2</sub>CH<sub>2</sub>CHNH), 22.4 (br s, C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 7.6 (NCH(CH<sub>2</sub>)<sub>2</sub>)

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

**HRMS** (ESI<sup>+</sup>)  $m/z$  / Da = 527.2654, [M+H]<sup>+</sup> found, [C<sub>28</sub>H<sub>36</sub>FN<sub>4</sub>O<sub>5</sub>]<sup>+</sup> requires 527.2670

**1.67 1-Cyclopropyl-6-fluoro-7-(4-(4-(1-(4-(((*trans*)-2-hydroxycyclohexyl)amino)-4-oxobutyl)-1H-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **172****



1-Cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **176** (40 mg, 97.2  $\mu$ mol, 1 eq.) and 4-azido-*N*-((*trans*)-2-hydroxycyclohexyl)butanamide **169** (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 and dried with MgSO<sub>4</sub> and evaporated under reduced pressure. The residue was purified by preparatory HPLC (5-70 % acetonitrile/water over 15 min). The combined pure fractions were evaporated under reduced pressure and then partitioned between NaHCO<sub>3</sub> (aq., sat., 50 ml) and 10 % *i*-PrOH/CHCl<sub>3</sub> (50 ml). The organic layer was dried with MgSO<sub>4</sub> and evaporated under reduced pressure. **172** was obtained as a white amorphous solid (30.3 mg, 47.5  $\mu$ mol, 48.9 %).

**IR** (neat)  $\nu_{max}$  / cm<sup>-1</sup> = 3345.4 (N-H), 2927.6 (C-H), 2859.6 (C-H), 2814.7 (C-H), 1727.0 (carboxylic acid C=O), 1641.7 (amide C=O), 1625.8 (quinolone C=O), 1619.0 (triazole)

**<sup>1</sup>H NMR** (400 MHz, DMSO d<sub>6</sub>)  $\delta$  / ppm = 8.64 (s, 1 H, *ortho* to C(=O)OH), 7.86 (d, *J* = 13.9 Hz, 1 H, *ortho* to F), 7.84 (s, 1 H, CH=CCH<sub>2</sub>), 7.64 (d, *J* = 8.1 Hz, 1 H, NH), 7.54 (d, *J* = 7.5 Hz, 1 H, *meta* to F), 4.54 (d, *J* = 4.7 Hz, 1 H, OH), 4.30 (t, *J* = 6.8 Hz, 2 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 3.77 - 3.86 (m, 1 H, NCH(CH<sub>2</sub>)<sub>2</sub>), 3.33 - 3.40 (m, 1 H, CHNH), 3.31 (br t, *J* = 4.8, 4.8 Hz, 4 H, CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 3.14 - 3.24 (m, 1 H, CHOH), 2.63 (t, *J* = 7.4 Hz, 2 H, CH=CCH<sub>2</sub>), 2.56 (br t, *J* = 4.6, 4.6 Hz, 4 H, CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 2.38 (t, *J* = 6.9 Hz, 2 H, CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 2.04 - 2.08 (m, 2 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 1.96 - 2.04 (m, 2 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 1.78 - 1.87 (m, 1 H, CHHCHOH), 1.69 - 1.78 (m, 1 H, CHHCHNH), 1.63 (quin, *J* = 7.5 Hz, 2 H, CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 1.54 - 1.60 (m, 1 H, CHHCH<sub>2</sub>OH), 1.51 (quin, *J* = 7.4 Hz, 2 H, CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 1.28 - 1.35 (m, 1 H, NCH(CH<sub>2</sub>)<sub>2</sub>), 1.11 - 1.22 (m, 5 H, NCH(CH<sub>2</sub>)<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)

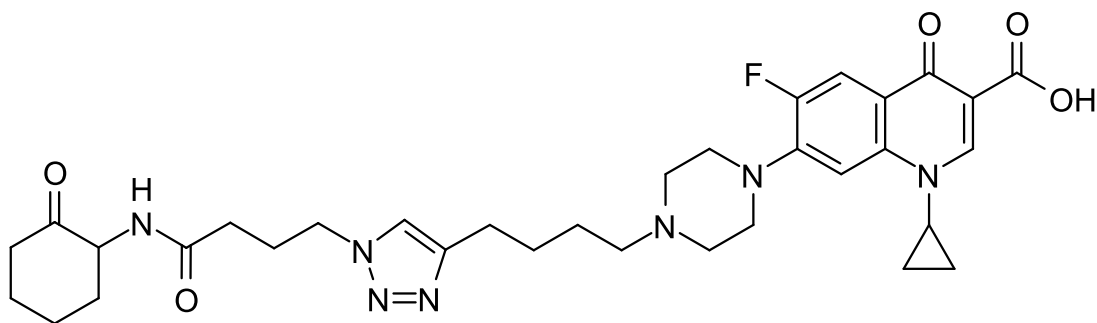
**<sup>13</sup>C NMR** (101 MHz, DMSO d<sub>6</sub>)  $\delta$  / ppm = 176.4 (C(=O)CC(=O)OH), 170.9 (CH<sub>2</sub>C(=O)NH), 166.0 (C(=O)OH), 153.1 (d, *J* = 252.1 Hz, *ipso* to F), 148.0 (C=CC(=O)OH), 146.9 (CH=CCH<sub>2</sub>), 145.3 (d, *J* = 10.0 Hz, *ipso* to piperazine), 139.2 (*para* to F), 121.8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

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



1-Cyclopropyl-6-fluoro-7-(4-(4-(1-(4-(((trans)-2-hydroxycyclohexyl)amino)-4-oxobutyl)-1H-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **172** (15.0 mg, 23.6 mmol, 1 eq.) and Dess-Martin Periodane (35.0 mg, 82.5 mmol, 3.5 eq.) were stirred in CH<sub>2</sub>Cl<sub>2</sub> (3 ml) for 4 h. The solvent was removed under reduced pressure and the residue was purified by preparatory HPLC (5-70 % acetonitrile/water over 15 min). The combined pure fractions were evaporated under reduced pressure 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=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>), 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=CCH<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, 2.6, 1.6, 1.6 Hz, 1 H, CHHC(=O)), 2.07 - 2.17 (m, 3 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N and CHHCNH), 1.96 - 2.05 (m, 3 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N and CHHCCH<sub>2</sub>C(=O)), 1.68 - 1.81 (m, 2 H, CHHCCH<sub>2</sub>CHNH), 1.64 (quin, J=7.5 Hz, 2 H, CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 1.40 - 1.56 (m, 5 H, CHHCCH<sub>2</sub>C(=O), CHHCNH and CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 1.27 - 1.34 (m, 2 H, NCH(CH<sub>2</sub>)<sub>2</sub>), 1.13 - 1.20 (m, 2 H, NCH(CH<sub>2</sub>)<sub>2</sub>)

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

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>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>) δ / ppm = -121.67 (s, ciprofloxacin F)

some  
TFA

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

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