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# 1 Experimental

## 1.1 General

Unless otherwise stated, reactions were performed in air-dried glassware under argon with dry, freshly distilled solvents. THF was distilled from LiAlH<sub>4</sub> in the presence of triphenyl methane indicator. CH<sub>2</sub>Cl<sub>2</sub>, hexane, MeOH and MeCN were distilled from calcium hydride. All other chemicals were used as obtained from commercial sources.

Reactions using microwave heating were performed in sealed vials using a CEM Discover SP microwave reactor.

Thin Layer Chromatography (TLC) was performed using Merck pre-coated 0.23 mm thick plates of Keiselgel 60 F254 and visualised using UV ( $\lambda = 254$  or  $366$  nm) or by staining with KMnO<sub>4</sub> or ninhydrin. All retention factors ( $R_f$ ) are given to 0.01. All column chromatography was carried out using Merck 9385 Keiselgel 60 silica gel (230-400 mesh) or using a CombiFlash® EZ Prep with RediSep® normal-phase silica flash columns. Preparative High Pressure Liquid Chromatography (Prep HPLC) was run on an Agilent 1260 Infinity machine, using a Supelcosil™ ABZ+PLUS column (250 mm  $\times$  21.2 mm, 5  $\mu$ m) with a linear gradient system (solvent A: 0.1 % (v/v) TFA/water, solvent B: 0.05 % (v/v) TFA/acetonitrile) at a flow rate of 20 mL min<sup>-1</sup>, visualised by UV absorbance ( $\lambda_{max} = 254$  nm)

Nuclear Magnetic Resonance (NMR) spectra were recorded using an internal deuterium lock at ambient probe temperatures on Bruker DPX-400, Bruker Avance DRX-400, Bruker Avance 500 BB-ATM or Bruker Avance 500 Cryo Ultrashield spectrometers. Data were processed using NMR Processor Academic Edition version 12 (ADC Labs) or TopSpin version 3.5 (Bruker). <sup>1</sup>H and <sup>13</sup>C spectra were assigned using DEPT, COSY, HMQC and HMQC spectra where necessary, or by analogy to fully interpreted spectra of related compounds. The following abbreviations are used to indicate the multiplicity of signals: s singlet, d doublet, t triplet, q quartet, quin quintet, m multiplet and br broad.

<sup>1</sup>H chemical shifts ( $\delta$ ) are quoted to the nearest 0.01 ppm and are referenced relative to the residual solvent peak.<sup>1</sup> Coupling constants ( $J$ ) are given to the nearest 0.1 Hz. Diastereotopic protons are assigned as CHH and CHH̄, where the latter designates the lower-field proton. Data are reported as follows: <chemical shift> (<multiplicity>, <coupling constant(s) (if any)>, <integration>, <assignment>).

<sup>13</sup>C chemical shifts ( $\delta$ ) are quoted to the nearest 0.1 ppm and are referenced relative to the deuterated solvent peak.<sup>1</sup> Data are reported as follows: <chemical shift> (<multiplicity (if not s)>, <coupling constant(s) (if any)>, <assignment>).

<sup>19</sup>F chemical shifts ( $\delta$ ) are quoted to the nearest 0.1 ppm. Data are reported as follows: <chemical shift> (<assignment>).

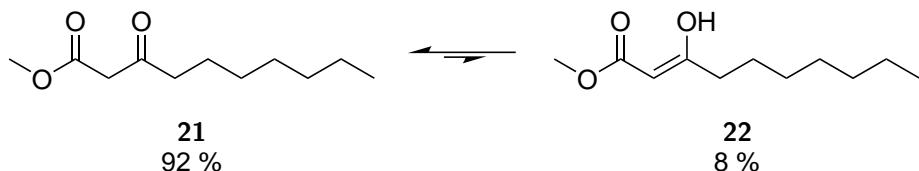
High Resolution Mass Spectra (HRMS) were recorded using either a Micromass Q-TOF or a Micromass LCT Premier spectrometer and reported mass values are within  $\pm 5$  ppm mass units. Low Resolution Mass Spectra (LRMS) were recorded on an Agilent 1200 series LC with an ESCi Multi-Mode Ionisation Waters ZQ spectrometer or a Waters ACQUITY H-Class UPLC with an ESCi Multi-Mode Ionisation Waters SQ Detector 2 spectrometer.

Infra Red (IR) spectra were recorded using neat sample on a PerkinElmer 1600 FT IR spectrometer. Selected absorption maxima ( $\nu_{max}$ ) are reported in wavenumbers (cm<sup>-1</sup>). Broad peaks are marked br.

Melting points (m.p.) were measured using a Buchi B-545 melting point apparatus and are uncorrected.

Optical rotations ( $[\alpha]_D^T$ ) were recorded on a PerkinElmer 343 polarimeter or an Anton-Paar MCP 100 polarimeter.  $[\alpha]_D^T$  values are reported in  ${}^\circ 10^{-1}\text{cm}^2\text{g}^{-1}$  at 589 nm and concentration ( $c$ ) is given in g (100 mL)<sup>-1</sup>.

## 1.2 Methyl 3-oxodecanoate **21**/22



Meldrum's acid (9.0 g, 63 mmol, 1 eq.) was dissolved in anhydrous  $\text{CH}_2\text{Cl}_2$  (150 ml) in an oven-dried flask 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 %  $\text{Et}_2\text{O}/40\text{-}60$  P.E.). A tautomeric mixture of **21** and **22** was obtained as a colourless oil (8.34 g, 41.6 mmol, 66 %, 92 % **21** as determined by  $^1\text{H}$  NMR).

### Keto form **21**

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

**IR** (neat)  $\nu_{max}$  /  $\text{cm}^{-1}$  = 2927.8 (C-H), 2856.3 (C-H), 1746.9 (ester C=O), 1716.7 (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,  $\text{C}(=\text{O})\text{CH}_2\text{CH}_2$ ), 1.60 (quin,  $J$  = 7.1 Hz, 2 H,  $\text{C}(=\text{O})\text{CH}_2\text{CH}_2$ ), 1.39 - 1.19 (m, 8 H,  $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 0.88 (t,  $J$  = 6.8 Hz, 3 H,  $\text{CH}_2\text{CH}_3$ )

**$^{13}\text{C}$  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 ( $\text{C}(=\text{O})\text{CH}_2\text{CH}_2$ ), 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 ( $\text{CH}_2\text{CH}_3$ )

### Enol form **22**

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

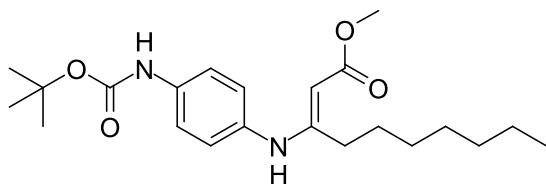
**IR** (neat)  $\nu_{max}$  /  $\text{cm}^{-1}$  = 2927.8 (C-H), 2856.3 (C-H), 1653.8 (C=C), 1629.2 ( $\alpha,\beta$  unsaturated C=O)

**$^1\text{H}$  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,  $\text{COHCH}_2$ ), 1.76 - 1.72 (m, 2 H,  $\text{COHCH}_2\text{CH}_2$ ), 1.39 - 1.19 (m, 8 H,  $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 0.88 (t,  $J$  = 6.8 Hz, 3 H,  $\text{CH}_2\text{CH}_3$ )

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

Spectroscopic data are consistent with the literature.<sup>2,3</sup>

### 1.3 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 *O*-*tert*-butyl *N*-(4-aminophenyl)carbamate **90** (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 (SiO<sub>2</sub>, gradient of 0 to 20 % Et<sub>2</sub>O/40-60 P.E.). **24** was obtained as a white amorphous solid (0.169 mg, 0.480 mmol, 19 %).

**TLC**  $R_f$  = 0.30 (30 % Et<sub>2</sub>O/40-60 P.E.)

**mp**  $T$  / °C = 78.8 (Et<sub>2</sub>O/40-60 P.E.)

**IR** (neat)  $\nu_{max}$  / cm<sup>-1</sup> = 3337.0 (N-H), 2927.7 (C-H), 2857.1 (C-H), 1723.7 (carbamate C=O), 1634.5 ( $\alpha,\beta$  unsaturated C=O), 1610.7 (C=C), 1580.9 (N-H bend)

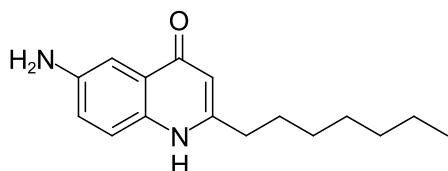
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  / ppm = 10.16 (s, 1 H, NHC(C<sub>7</sub>H<sub>15</sub>)=C), 7.35 (d,  $J$  = 8.6 Hz, 2 H, *meta* to NH<sub>Boc</sub>), 7.02 (d,  $J$  = 8.7 Hz, 2 H, *meta* to enamine), 6.60 (br s, 1 H, NH<sub>Boc</sub>), 4.71 (s, 1 H, C=CH), 3.70 (s, 3 H, OCH<sub>3</sub>), 2.23 (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>3</sub>), 1.54 (s, 9 H, C(CH<sub>3</sub>)<sub>3</sub>), 1.40 (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>3</sub>), 1.33 - 1.16 (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,  $J$  = 7.1 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>3</sub>)

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  / ppm = 171.1 (C(=O)CH=C), 164.3 (C(=O)CH=C), 152.7 (OC(=O)NH), 136.0 (*para* to NH<sub>Boc</sub>), 134.1 (CNH<sub>Boc</sub>), 126.3 (*meta* to NH<sub>Boc</sub>), 119.1 (*ortho* to NH<sub>Boc</sub>), 83.8 (C(=O)CH=C), 80.7 (C(CH<sub>3</sub>)<sub>3</sub>), 50.2 (OCH<sub>3</sub>), 32.2 (CH<sub>2</sub>), 31.6 (CH<sub>2</sub>), 29.1 (CH<sub>2</sub>), 28.8 (CH<sub>2</sub>), 28.3 (C(CH<sub>3</sub>)<sub>3</sub>), 28.0 (CH<sub>2</sub>), 22.6 (CH<sub>2</sub>), 14.0 (CH<sub>3</sub>)

**HRMS** (ESI<sup>+</sup>)  $m/z$  / Da = 391.2589, [M+H]<sup>+</sup>, [C<sub>22</sub>H<sub>35</sub>N<sub>2</sub>O<sub>4</sub>]<sup>+</sup> requires 391.2591

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

### 1.4 6-Amino-2-heptylquinolin-4-ol 25



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. **25** was obtained as 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> = 3336.5 (N-H), 2926.5 (C-H), 2856.9 (C-H), 1723.9 (C=O), 1634.5 (aromatic), 1610.8 (aromatic), 1583.3 (aromatic), 1519.1 (aromatic)

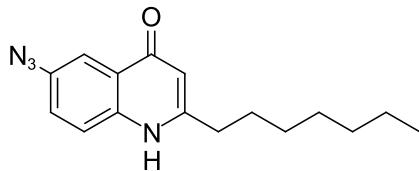
**<sup>1</sup>H NMR** (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  / ppm = 7.26 (d,  $J$  = 8.7 Hz, 1 H, *meta* to NH<sub>2</sub>), 7.15 (d,  $J$  = 2.6 Hz, 1 H, *ortho* to C(=O)), 6.95 (dd,  $J$  = 2.7, 8.8 Hz, 1 H, *para* to C(=O)), 5.74 (s, 1 H, *ortho* to CH<sub>2</sub>), 5.16 (s, 2 H, NH<sub>2</sub>), 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>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>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>3</sub>), 0.86 (t,  $J$  = 7.0 Hz, 3 H, H<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>), 145.1 (*para* to NH<sub>2</sub>), 132.4 (*ipso* to NH<sub>2</sub>), 126.6 (*para* to CH<sub>2</sub>), 121.1 (*para* to C(=O)), 119.0 (*meta* to NH<sub>2</sub> and *meta* to C(=O)), 106.2 (CH=CCH<sub>2</sub>), 105.9 (*ortho* to NH<sub>2</sub> and *ortho* to C(=O)), 33.6 (CCH<sub>2</sub>), 31.6 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</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>CH<sub>3</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

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

## 1.5 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**  $R_f$  = 0.40 (5 % MeoH/CH<sub>2</sub>Cl<sub>2</sub>)

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

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

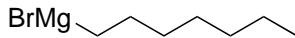
**<sup>13</sup>C NMR** (101 MHz, MeOD)  $\delta$  / ppm = 172.3 (C(=O)), 155.5 (NHCC<sub>2</sub>), 137.4 (CN<sub>3</sub>), 135.6 (*para* to N<sub>3</sub>), 124.6 (*para* to C(=O)), 124.1 (*ipso* to C(=O)), 120.7 (*meta* to N<sub>3</sub> and *meta* to C(=O)), 112.8 (*ortho* to N<sub>3</sub> and *ortho* to C(=O)), 107.0 (C(=O)CH), 33.3 (NHCC<sub>2</sub>), 31.2 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 28.3 - 28.5 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 22.1 (CH<sub>2</sub>CH<sub>3</sub>), 14.0 (CH<sub>3</sub>)

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

Spectroscopic data are not consistent with the literature.<sup>4</sup>

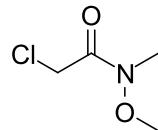
????

## 1.6 Heptyl magnesium bromide 28



Magnesium turnings (352 mg, 14.5 mmol, 1 eq.) were added to an oven-dried 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, ~1 M) which was used without further purification.

## 1.7 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 stirred solution of potassium carbonate (22.4 g, 162 mmol, 2.63 eq.) in water (75 ml) at 0 °C under argon. The mixture was cooled to - 5 °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 (3×20 ml). The combined organic extracts were dried with MgSO<sub>4</sub> and the solvent was removed by rotary evaporation followed by high vacuum. **30** was obtained as white, prism-like crystals (7.24 g, 52.6 mmol, 71 %).

mp  $T$  / °C = 38.8 (toluene)

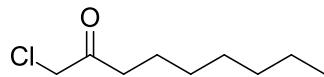
**IR** (neat)  $\nu_{max}$  /  $\text{cm}^{-1}$  = 3016.7 (C-H), 2966.4 (C-H), 2946.7 (C-H), 2827.7 (C-H), 1666.2 (C=O)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  / ppm = 4.20 (s, 2 H, ClCH<sub>2</sub>C=O), 3.71 (m, 3 H, OCH<sub>3</sub>), 3.18 (s, 3 H, NCH<sub>3</sub>)

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ / ppm = 167.4 (C=O), 61.6 (OCH<sub>3</sub>), 40.9 (ClCH<sub>2</sub>C=O), 32.6 (NCH<sub>3</sub>)

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

## 1.8 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 MgSO<sub>4</sub>, and the solvent was removed by rotary evaporation. **31** was obtained as a colourless oil (1.23 g, 6.96 mmol, 96 %).

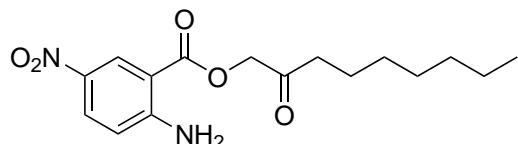
IR (neat)  $\nu_{max}$  / cm<sup>-1</sup> = 2951.7 (C-H), 2925.0 (C-H), 2855.5 (C-H), 1720.4 (C=O)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  / ppm = 4.05 (s, 2 H, ClCH<sub>2</sub>C(=O)), 2.54 (t,  $J$  = 7.4 Hz, 2 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>), 1.59 (quin,  $J$  = 7.0 Hz, 2 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>), 1.34 - 1.21 (m, 8 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 0.87 (t,  $J$  = 6.8 Hz, 3 H, CH<sub>3</sub>)

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ / ppm = 202.6 (C(=O)), 48.1 (CH<sub>2</sub>Cl), 39.6 (C(=O)CH<sub>2</sub>CH<sub>2</sub>), 31.5 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 28.9 (CH<sub>2</sub>), 28.9 (CH<sub>2</sub>), 23.5 (C(=O)CH<sub>2</sub>CH<sub>2</sub>), 22.5 (CH<sub>2</sub>CH<sub>3</sub>), 13.9 (CH<sub>3</sub>)

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

## 1.9 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 Na<sub>2</sub>HCO<sub>3</sub> (aq., 10 %, 50 ml) and ice (~ 20 g). The precipitate was collected by vacuum filtration, washed with water and dried under high vacuum. **33** was obtained as a yellow amorphous solid (0.674 g, 2.00 mmol, 100 %).

mp  $T$  / °C = 135 (H<sub>2</sub>O)

**IR (neat)  $\nu_{max}$  / cm<sup>-1</sup>** = 3453.3 (N-H), 3350.5 (N-H), 2924.9 (C-H), 2853.9 (C-H), 1720.1 (ester C=O) 1703.9 (ketone C=O) 1626.1 (N-H bend) 1602.7 (aromatic) 1572.5 (N-O) 1506.6 (N-O)

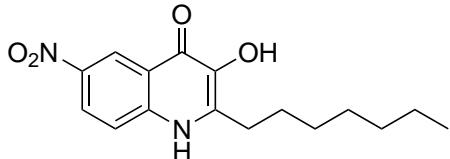
**<sup>1</sup>H NMR** (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  / ppm = 8.66 (d,  $J$  = 2.8 Hz, 1 H, *ortho* to C(=O)), 8.12 (dd,  $J$  = 2.8, 9.4 Hz, 1 H, *para* to C(=O)), 6.93 (d,  $J$  = 9.4 Hz, 1 H, *meta* to C(=O)), 5.05 (s, 2 H, OCCH<sub>2</sub>C(=O)), 2.49 (t,  $J$  = 7.4 Hz, 2 H, C(=O)CH2CH<sub>2</sub>), 1.52 (quin,  $J$  = 7.2 Hz, 2 H, C(=O)CH<sub>2</sub>CH2), 1.32 - 1.20 (m, 8 H, 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, CH3)

**<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 (*ipso* to NH<sub>2</sub>), 135.7 (*ipso* to NO<sub>2</sub>), 129.6 (*para* to C(=O)), 128.9 (*ortho* to C(=O)), 117.4 (*meta* to C(=O)), 107.5 (*ipso* to C(=O)), 68.8 (OCH<sub>2</sub>C(=O)), 38.3 (C(=O)CH<sub>2</sub>CH<sub>2</sub>), 31.6 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 28.9 (CH<sub>2</sub>), 28.9 (CH<sub>2</sub>), 23.2 (C(=O)CH<sub>2</sub>CH<sub>2</sub>), 22.5 (CH<sub>2</sub>CH<sub>3</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

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

### 1.10 6-Nitro-2-heptyl-3-hydroxyquinolin-4(1*H*)-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. **34** was obtained as a yellow-brown amorphous solid (44 mg, 0.145 mmol, 43 %).

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

**IR** (neat)  $\nu_{max}$  / cm<sup>-1</sup> = 3436.0 (N-H), 3000.0 (O-H, br), 2955.4 (C-H), 2925.8 (C-H), 2850.9 (C-H), 1648.2 (C=O), 1606.1 (aromatic), 1570.7 (N-O), 1536.4 (N-O)

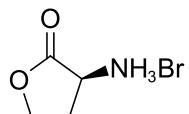
**<sup>1</sup>H NMR** (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  / ppm = 12.00 (s, 1 H, NH), 8.91 (d,  $J$  = 2.8 Hz, 1 H, *ortho* to C=O), 8.29 (dd,  $J$  = 2.7, 9.2 Hz, 1 H, *para* to C=O), 7.70 (d,  $J$  = 9.3 Hz, 1 H, *meta* to C=O), 2.75 (t,  $J$  = 7.7 Hz, 2 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>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>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>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>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 (CCH<sub>2</sub>), 28.1 (CCH<sub>2</sub>CH<sub>2</sub>), 22.5 (CH<sub>2</sub>CH<sub>3</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

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

### 1.11 (*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. **38** was obtained as a pale pink amorphous solid (1.73 g, 9.50 mmol, 41 % yield).

**mp**  $T$  / °C = 242 (*i*-PrOH/AcOH, gas evolved)

**IR** (neat)  $\nu_{max}$  / cm<sup>-1</sup> = 2972.1 (N-H), 2877.5 (N-H), 1771.8 (C=O), 1585.1 (N-H bend), 1572.2 (N-H bend)

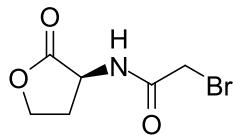
**<sup>1</sup>H NMR** (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  / ppm = 8.59 (br s, 3 H, NH<sub>3</sub><sup>+</sup>), 4.46 (dt,  $J$  = 1.3, 8.9 Hz, 1 H, OCHH), 4.37 (dd,  $J$  = 8.8, 11.4 Hz, 1 H, CHNH<sub>3</sub><sup>+</sup>), 4.29 (ddd,  $J$  = 6.1, 8.8, 10.9 Hz, 1 H, OCHH), 2.57 (dddd,  $J$  = 1.2, 6.1, 8.9, 12.3 Hz, 1 H, OCH<sub>2</sub>CHH), 2.26 (dtd,  $J$  = 9.0, 11.2, 12.2 Hz, 1 H, OCH<sub>2</sub>CHH)

**<sup>13</sup>C NMR** (101 MHz, DMSO-d<sub>6</sub>)  $\delta$  / ppm = 173.3 (C=O), 66.2 (OCH<sub>2</sub>), 47.8 (CHNH<sub>3</sub><sup>+</sup>), 27.0 (OCH<sub>2</sub>CH<sub>2</sub>)

$[\alpha]_D^{20}$  / °10<sup>-1</sup>cm<sup>2</sup>g<sup>-1</sup> = -30.0 ( $c$  / g(100 ml)<sup>-1</sup> = 0.0200, DMSO)

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

### 1.12 (*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  $\mu$ 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). The combined organic layers were dried with MgSO<sub>4</sub> and the solvent was removed under reduced pressure. **40** was obtained as white, needle-like crystals (88.0 mg, 0.396 mmol, 74 %).

**mp**  $T$  / °C = 132 (EtOAc)

**IR** (neat)  $\nu_{max}$  / cm<sup>-1</sup> = 3255.7 (N-H), 3066.6 (C-H), 1763.0 (lactone C=O), 1658.0 (amide C=O), 1552.7 (N-H bend)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  / ppm = 6.94 (br s, 1 H, NH), 4.57 (ddd,  $J$  = 11.7, 8.6, 5.9 Hz, 1 H, CHNH), 4.51 (td,  $J$  = 9.2, 1.0 Hz, 1 H, OCHH), 4.32 (ddd,  $J$  = 11.3, 9.4, 5.9 Hz, 1 H, OCHH), 3.93 (s, 1 H, CHHBr), 3.93 (s, 1 H, CHHBr), 2.87 (dddd,  $J$  = 12.6, 8.6, 5.9, 1.3 Hz, 1 H, OCH<sub>2</sub>CHH), 2.22 (dtd,  $J$  = 12.6, 11.5, 11.5, 8.9 Hz, 1 H, OCH<sub>2</sub>CHH)

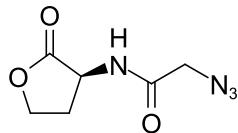
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  / ppm = 174.6 (OC=O), 166.4 (C(=O)NH), 66.1 (OCH<sub>2</sub>), 49.8 (CHNH<sub>2</sub>CO), 29.9 (OCH<sub>2</sub>CH<sub>2</sub>), 28.2 (O=CCH<sub>2</sub>Br)

**HRMS** The compound does not ionise.

$$[\alpha]_D^{20} / {}^\circ 10^{-1} \text{cm}^2 \text{g}^{-1} = 27.0 \ (c / \text{g}(100 \text{ ml})^{-1} = 0.00740, \text{CHCl}_3)$$

The data are consistent with the literature.<sup>6,7</sup>

### 1.13 (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.), NaN<sub>3</sub> (85.7 mg, 1.32 mmol, 2.61 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  $\mu$ L, 102 mg, 0.505 mmol, 1.00 eq.) was then added dropwise. The reaction mixture was stirred for 48 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). The combined organic layers were dried with MgSO<sub>4</sub> and the solvent was removed under reduced pressure. **41** was obtained as white, needle-like crystals (38.4 mg, 0.209 mmol, 41 %).

**mp** *T* / °C = 87 (EtOAc)

**IR** (neat)  $\nu_{max}$  / cm<sup>-1</sup> = 3283.5 (N-H), 2923.3 (C-H), 2853.0 (C-H), 2129.7 (N<sub>3</sub>), 1782.9 (lactone C=O), 1661.4 (amide C=O), 1536.8 (N-H bend)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  / ppm = 7.05 (br d, *J* = 6.5 Hz, 1 H, NH), 4.64 (ddd, *J* = 11.6, 8.7, 6.8 Hz, 1 H, CHNH), 4.48 (td, *J* = 9.1, 1.3 Hz, 1 H, OCHH), 4.30 (ddd, *J* = 11.2, 9.2, 6.0 Hz, 1 H, OCHH), 4.04 (s, 2 H, CH<sub>2</sub>N<sub>3</sub>), 2.76 (dddd, *J* = 12.5, 8.8, 6.0, 1.4 Hz, 1 H, OCH<sub>2</sub>CHH), 2.25 (dtd, *J* = 12.5, 11.4, 11.4, 8.9 Hz, 1 H, OCH<sub>2</sub>CHH)

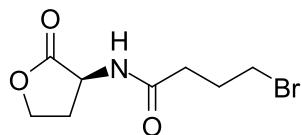
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  / ppm = 174.9 (OC=O), 167.5 (C=ONH), 66.0 (OCH<sub>2</sub>), 52.2 (O=CCH<sub>2</sub>N<sub>3</sub>), 48.9 (CHNHC=O), 29.7 (OCH<sub>2</sub>CH<sub>2</sub>)

**HRMS** The compound does not ionise.

$$[\alpha]_D^{20} / {}^\circ 10^{-1} \text{cm}^2 \text{g}^{-1} = -32.6 \ (c / \text{g}(100 \text{ ml})^{-1} = 0.0430, \text{DMSO})$$

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

### 1.14 (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). Bromobutyryl chloride (140  $\mu$ L, 224 mg, 1.21 mmol, 1.10 eq.) was then added dropwise. The reaction mixture was stirred for 1 h, after which the

$\text{CH}_2\text{Cl}_2$  was removed under vacuum. The aqueous phase was extracted with  $\text{EtOAc}$  ( $7 \times 5 \text{ ml}$ ) and the combined organic layers were dried with  $\text{MgSO}_4$ . The solvent was removed under vacuum to give white crystals which were recrystallised from  $\text{EtOAc}$ . **44** was obtained as white, needle-like crystals (219 mg, 0.878 mmol, 80 %).

**mp**  $T / ^\circ\text{C} = 105$  ( $\text{EtOAc}$ )

**IR** (neat)  $\nu_{max} / \text{cm}^{-1} = 3307.9$  (N-H), 3073.9 (C-H), 2948.9 (C-H), 1773.7 (lactone C=O), 1643.5 (amide C=O), 1541.4 (N-H bend)

**$^1\text{H NMR}$**  (400 MHz,  $\text{CDCl}_3$ )  $\delta / \text{ppm} = 6.31$  (br d,  $J = 5.5 \text{ Hz}$ , 1 H,  $\text{NH}$ ), 4.59 (ddd,  $J = 6.2, 8.7, 11.5 \text{ Hz}$ , 1 H,  $\text{CHNH}$ ), 4.48 (dt,  $J = 1.2, 8.9 \text{ Hz}$ , 1 H,  $\text{OCHH}$ ), 4.30 (ddd,  $J = 5.8, 9.3, 11.3 \text{ Hz}$ , 1 H,  $\text{OCHH}$ ), 3.49 (t,  $J = 6.3 \text{ Hz}$ , 2 H,  $\text{CH}_2\text{Br}$ ), 2.82 (dddd,  $J = 1.3, 5.9, 8.7, 12.5 \text{ Hz}$ , 1 H,  $\text{OCH}_2\text{CHH}$ ), 2.47 (t,  $J = 7.3 \text{ Hz}$ , 2 H,  $\text{C}(=\text{O})\text{CH}_2$ ), 2.26 - 2.15 (m, 3 H,  $\text{OCH}_2\text{CHH}$  and  $\text{CH}_2\text{CH}_2\text{Br}$ )

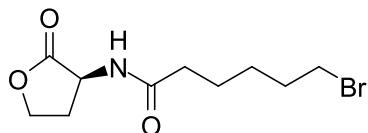
**$^{13}\text{C NMR}$**  (101 MHz,  $\text{CDCl}_3$ )  $\delta / \text{ppm} = 175.4$  ( $\text{OC=O}$ ), 172.3 ( $\text{C}(=\text{O})\text{NH}$ ), 66.1 ( $\text{OCH}_2$ ), 49.3 ( $\text{CHNHC=O}$ ), 33.9 ( $\text{C}(=\text{O})\text{CH}_2$ ), 33.1 ( $\text{CH}_2\text{Br}$ ), 30.3 ( $\text{OCH}_2\text{CH}_2$ ), 27.9 ( $\text{C}(=\text{O})\text{CH}_2\text{CH}_2$ )

**HRMS** The compound does not ionise.

$[\alpha]_D^{26.6} / ^\circ\text{10}^{-1}\text{cm}^2\text{g}^{-1} = -78$  ( $c / \text{g}(100 \text{ ml})^{-1} = 0.0833$ , MeOH)

The compound has not been reported previously.

### 1.15 (*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  $\text{NaHCO}_3$  (84.9 mg, 1.01 mmol, 1.84 eq.) were dissolved in  $\text{CH}_2\text{Cl}_2$  (2 ml) and  $\text{H}_2\text{O}$  (2 ml) at r.t.. Bromohexanoyl chloride (93.0  $\mu\text{L}$ , 130 mg, 0.608 mmol, 1.11 eq.) was then added dropwise. The reaction mixture was stirred for 4 h, after which the  $\text{CH}_2\text{Cl}_2$  was removed under vacuum. The mixture was then filtered, washed with  $\text{H}_2\text{O}$  (10 ml) and dried under high vacuum. **45** was obtained as white, needle-like crystals (101 mg, 0.362 mmol, 66 %).

**mp**  $T / ^\circ\text{C} = 106$  ( $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ )

**IR** (neat)  $\nu_{max} / \text{cm}^{-1} = 3300.3$  (N-H), 3067.6 (C-H), 2937.4 (C-H), 2856.7 (C-H), 1784.8 (lactone C=O), 1639.3 (amide C=O), 1539.9 (N-H bend)

**$^1\text{H NMR}$**  (400 MHz,  $\text{CDCl}_3$ )  $\delta / \text{ppm} = 6.09$  (br d,  $J = 5.7 \text{ Hz}$ , 1 H,  $\text{NH}$ ), 4.57 (ddd,  $J = 5.9, 8.6, 11.6 \text{ Hz}$ , 1 H,  $\text{CHNH}$ ), 4.50 (dt,  $J = 1.3, 9.1 \text{ Hz}$ , 1 H,  $\text{OCHH}$ ), 4.31 (ddd,  $J = 5.9, 9.3, 11.3 \text{ Hz}$ , 1 H,  $\text{OCHH}$ ), 3.43 (t,  $J = 6.7 \text{ Hz}$ , 2 H,  $\text{CH}_2\text{Br}$ ), 2.88 (dddd,  $J = 1.3, 5.9, 8.6, 12.6 \text{ Hz}$ , 1 H,  $\text{OCH}_2\text{CHH}$ ), 2.30 (dt,  $J = 1.8, 7.5 \text{ Hz}$ , 2 H,  $\text{C}(=\text{O})\text{CH}_2$ ), 2.16 (td,  $J = 8.9, 11.5, 12.5 \text{ Hz}$ , 1 H,  $\text{OCH}_2\text{CHH}$ ), 1.90 (quin,  $J = 7.2 \text{ Hz}$ , 2 H,  $\text{CH}_2\text{CH}_2\text{Br}$ ), 1.71 (quin,  $J = 7.6 \text{ Hz}$ , 2 H,  $\text{C}(=\text{O})\text{CH}_2\text{CH}_2$ ), 1.59 - 1.46 (m, 2 H,  $\text{C}(=\text{O})\text{CH}_2\text{CH}_2\text{CH}_2$ )

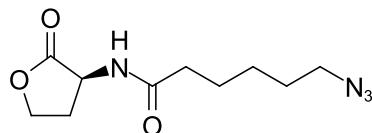
**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  / ppm = 175.5 ( $\text{OC=O}$ ), 173.3 ( $\text{C(=O)NH}$ ), 66.1 ( $\text{OCH}_2$ ), 49.3 ( $\text{CHNHC=O}$ ), 35.8 ( $\text{CH}_2\text{Br}$ ), 33.5 ( $\text{C(=O)CH}_2$ ), 32.3 ( $\text{CH}_2\text{CH}_2\text{Br}$ ), 30.5 ( $\text{OCH}_2\text{CH}_2$ ), 27.6 ( $\text{C(=O)CH}_2\text{CH}_2$ ), 24.4 ( $\text{C(=O)CH}_2\text{CH}_2\text{CH}_2$ )

**HRMS** (ESI $^+$ )  $m/z$  / Da = 278.0381,  $[\text{M}+\text{H}]^+$ ,  $[\text{C}_{10}\text{H}_{17}\text{BrNO}_3]^+$  requires 278.0386

$[\alpha]_D^{26.6} / {}^\circ\text{10}^{-1}\text{cm}^2\text{g}^{-1} = -16$  ( $c$  / g(100 ml) $^{-1}$  = 0.208, MeOH)

The compound has not been reported previously.

### 1.16 (*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  $\text{NaN}_3$  (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  $\text{CH}_2\text{Cl}_2$  (5 ml) and  $\text{H}_2\text{O}$  (5 ml). The aqueous phase was extracted twice more with  $\text{CH}_2\text{Cl}_2$  ( $2 \times 5$  ml) and the organic layers were combined and dried over  $\text{MgSO}_4$ . The solvent was removed by rotary evaporation followed by high vacuum. **47** was obtained as white, needle-like crystals (42.7 mg, 0.178 mmol, 56 %).

**mp**  $T$  / °C = 90.0 ( $\text{CH}_2\text{Cl}_2$ )

**IR** (neat)  $\nu_{max}$  /  $\text{cm}^{-1}$  = 3314.0 (N-H), 2931.6 (C-H), 2862.9 (C-H), 2095.1 ( $\text{N}_3$ ), 1775.4 (lactone C=O), 1643.1 (amide C=O), 1547.9 (N-H bend)

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  / ppm = 5.96 (d,  $J$  = 4.2 Hz, 1 H,  $\text{NH}$ ), 4.54 (ddd,  $J$  = 11.7, 8.6, 5.7 Hz, 1 H,  $\text{CHNH}$ ), 4.49 (td,  $J$  = 9.1, 1.0 Hz, 1 H,  $\text{OCHHH}$ ), 4.30 (ddd,  $J$  = 11.3, 9.4, 5.8 Hz, 1 H,  $\text{OCHH}$ ), 3.29 (t,  $J$  = 6.9 Hz, 2 H,  $\text{CH}_2\text{N}_3$ ), 2.88 (dddd,  $J$  = 12.5, 8.6, 5.8, 1.1 Hz, 1 H,  $\text{OCH}_2\text{CHHH}$ ), 2.28 (t,  $J$  = 7.5 Hz, 1 H,  $\text{C(=O)CHH}$ ), 2.28 (t,  $J$  = 7.4 Hz, 1 H,  $\text{C(=O)CHH}$ ), 2.14 (dtd,  $J$  = 12.3, 11.5, 11.5, 8.8 Hz, 1 H,  $\text{OCH}_2\text{CHH}$ ), 1.70 (quin,  $J$  = 7.6 Hz, 2 H,  $\text{CH}_2\text{CH}_2\text{N}_3$ ), 1.63 (quin,  $J$  = 7.2 Hz, 2 H,  $\text{C(=O)CH}_2\text{CH}_2$ ), 1.38 - 1.49 (m, 2 H,  $\text{C(=O)CH}_2\text{CH}_2\text{CH}_2$ )

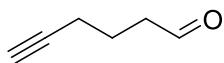
**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  / ppm = 175.4 ( $\text{OC=O}$ ), 172.2 ( $\text{C(=O)NH}$ ), 66.1 ( $\text{OCH}_2$ ), 51.2 ( $\text{CH}_2\text{N}_3$ ), 49.4 ( $\text{CHNHC=O}$ ), 35.9 ( $\text{C(=O)CH}_2$ ), 30.7 ( $\text{OCH}_2\text{CH}_2$ ), 28.6 ( $\text{CH}_2\text{CH}_2\text{N}_3$ ), 26.3 ( $\text{C(=O)CH}_2\text{CH}_2$ ), 24.8 ( $\text{C(=O)CH}_2\text{CH}_2\text{CH}_2$ )

**HRMS** (ESI $^+$ )  $m/z$  / Da = 241.1289,  $[\text{M}+\text{H}]^+$ ,  $[\text{C}_{10}\text{H}_{17}\text{N}_4\text{O}_3]^+$  requires 241.1295

$[\alpha]_D^{26.6} / {}^\circ\text{10}^{-1}\text{cm}^2\text{g}^{-1} = -16$  ( $c$  / g(100 ml) $^{-1}$  = 0.208, MeOH)

The compound has not been reported previously.

## 1.17 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 **48** (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. **49** was obtained as a pale yellow-green oil (4.72 g, 49.1 mmol, 72 %).

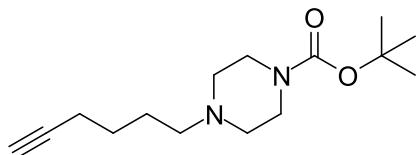
**IR** (neat)  $\nu_{max}$  / cm<sup>-1</sup> = 3292.7 (alkyne C-H), 2943.3 (alkane C-H), 2830.9 (aldehyde C-H), 2728.6 (aldehyde C-H), 1720.3 (aldehyde C=O)

**<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 (CH<sub>2</sub>CH<sub>2</sub>C(=O)), 17.6 (HC≡CCH<sub>2</sub>)

Spectroscopic data are consistent with the literature.<sup>8</sup>

## 1.18 *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. **51** was obtained as 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> = 3303.6 (alkyne C-H), 2940.0 (alkane C-H), 2865.2 (C-H), 2810.4 (C-H), 1691.3 (carbamate C=O)

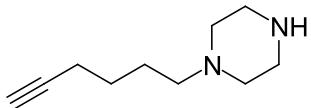
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  / ppm = 3.44 (t,  $J$  = 5.2 Hz, 4 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 2.39 (t,  $J$  = 5.1 Hz, 4 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 2.37 (t,  $J$  = 7.3 Hz, 2 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 2.23 (dt,  $J$  = 2.7, 6.8 Hz, 2 H, HC≡CCH<sub>2</sub>), 1.96 (t,  $J$  = 2.7 Hz, 1 H, HC≡C), 1.65 - 1.53 (m, 4 H, HC≡CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 1.47 (s, 9 H, CH<sub>3</sub>)

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  / ppm = 154.7 (NC(=O)O), 84.2 (HC≡C), 79.6 (C(CH<sub>3</sub>)<sub>3</sub>), 68.5 (HC≡C), 60.4 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 58.0 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 53.0 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 28.4 (C(CH<sub>3</sub>)<sub>3</sub>), 26.3 (CH<sub>2</sub>CH<sub>2</sub>N), 25.7 (HC≡CCH<sub>2</sub>CH<sub>2</sub>), 18.3 (HC≡CCH<sub>2</sub>)

**HRMS** (ESI<sup>+</sup>)  $m/z$  / Da = 267.2073, [M+H]<sup>+</sup>, [C<sub>15</sub>H<sub>27</sub>N<sub>2</sub>O<sub>2</sub>]<sup>+</sup> requires 267.2064

The compound has not been reported previously.

### 1.19 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 CH<sub>2</sub>Cl<sub>2</sub> (2×20 ml). The oil was diluted with H<sub>2</sub>O (10 ml) and the pH adjusted to 14 with NaOH (10 % aq.). This mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2×20 ml) and the combined organic layers were dried over MgSO<sub>4</sub>. The solvent was removed under vacuum and purified by column chromatography (SiO<sub>2</sub> MeOH/CH<sub>2</sub>Cl<sub>2</sub> 3:7). **52** was obtained as a colourless liquid (476 mg, 2.86 mmol, 100 %).

**TLC**  $R_f$  (30 % MeOH/CH<sub>2</sub>Cl<sub>2</sub>) = 0.20

**IR** (neat)  $\nu_{max}$  / cm<sup>-1</sup> = 3295.9 (alkyne C-H), 2941.1 (alkane C-H), 2810.6 (alkane C-H), 1637.2 (N-H bend)

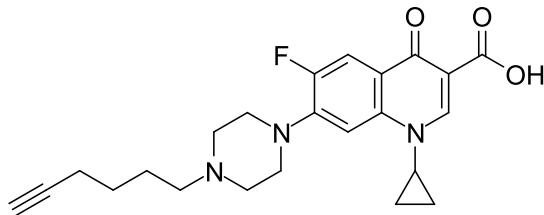
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  / ppm = 2.88 (t,  $J$  = 4.9 Hz, 4 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 2.39 (m, 4 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 2.31 (t,  $J$  = 7.1 Hz, 2 H, HC≡CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 2.20 (dt,  $J$  = 2.7, 6.8 Hz, 2 H, HC≡CCH<sub>2</sub>), 2.05 (br s, 1 H, NH), 1.93 (t,  $J$  = 2.7 Hz, 1 H, HC≡C), 1.65 - 1.48 (m, 4 H, HC≡CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N)

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  / ppm = 84.3 (HC≡C), 68.4 (HC≡C), 58.6 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 54.5 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 46.0 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 26.4 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 25.7 (HC≡CCH<sub>2</sub>CH<sub>2</sub>), 18.3 (HC≡CCH<sub>2</sub>)

**HRMS** (ESI<sup>+</sup>)  $m/z$  / Da = 167.1548, [M+H]<sup>+</sup>, [C<sub>10</sub>H<sub>19</sub>N<sub>2</sub>]<sup>+</sup> requires 167.1548

The compound has not been reported previously.

**1.20 1-Cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid 91**



7-Chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquino-line-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). **91** 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> = 3212.0 (alkyne C-H), 2459.3 (O-H), 1722.6 (carboxylic acid C=O), 1626.8 (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>)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(CHH)<sub>2</sub>), 1.16 - 1.23 (m, 2 H, NCH(CHH)<sub>2</sub>)

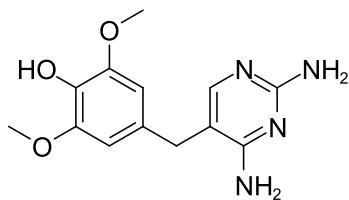
**<sup>13</sup>C NMR** (126 MHz, DMSO-d<sub>6</sub>)  $\delta$  / ppm = 176.4 (C(=O)CC(=O)OH), 165.8 (C(=O)OH), 152.8 (d,  $J$  = 248.5 Hz, *ipso* to F), 148.2 (CHCC(=O)OH), 143.7 (d,  $J$  = 11.1 Hz, *para* to C(=O)), 139.1 (*para* to F), 119.4 (d,  $J$  = 6.9 Hz, *ipso* to C(=O)), 111.2 (d,  $J$  = 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 = -121.8 (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

The compound has not been reported previously.

## 1.21 4-((2,4-Diaminopyrimidin-5-yl)methyl)-2,6-dimethoxyphenol 92



Hydrobromic acid (48 % w/w, aq., 50 ml) was heated to 100 °C. Trimethoprim **78** (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. **92** 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)

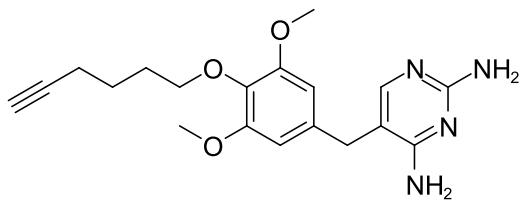
**<sup>1</sup>H NMR** (400 MHz, MeOD)  $\delta$  / ppm = 7.21 (s, 1 H, CHN), 6.54 (s, 2 H, *meta* to OCH<sub>2</sub>), 4.87 (br s, 5 H, OH, NH<sub>2</sub> × 2), 3.82 (s, 6 H, OCH<sub>3</sub>), 3.63 (s, 2 H, CCH<sub>2</sub>C)

**<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 (OCH<sub>3</sub>), 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>9</sup>

## 1.22 5-(4-(Hex-5-yn-1-yloxy)-3,5-dimethoxybenzyl)pyrimidine-2,4-diamine 94



4-((2,4-Diaminopyrimidin-5-yl)methyl)-2,6-dimethoxyphenol **92** (1.00 g, 3.62 mmol, 1 eq.), 6-chloro-1-hexyne **93** (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>). **94** 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)

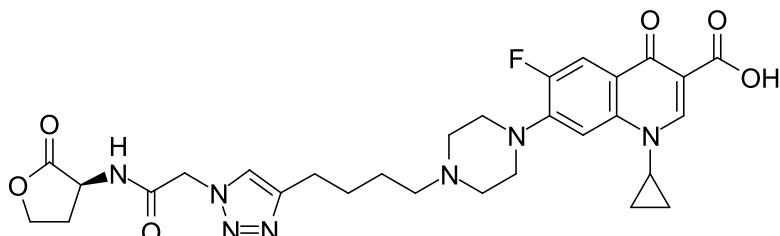
**<sup>1</sup>H NMR** (400 MHz, MeOD)  $\delta$  / ppm = 7.77 (s, 1 H, CHN), 6.37 (s, 2 H, *meta* to OCH<sub>2</sub>), 4.83 (br s, 2 H, CHNCNH<sub>2</sub>), 4.63 (br s, 2 H, CH<sub>2</sub>CCNH<sub>2</sub>), 3.95 (t,  $J$  = 6.3 Hz, 2 H, CH<sub>2</sub>O), 3.79 (s, 6 H, OCH<sub>3</sub>), 3.65 (s, 2 H, 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.

**1.23 (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 95**



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 **91** (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 3 h. 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 3 h 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> over 15 min). The combined pure fractions were dried with MgSO<sub>4</sub> and evaporated under reduced pressure. **95** was obtained as a white amorphous solid (8.8 mg, 14.8  $\mu$ mol, 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)

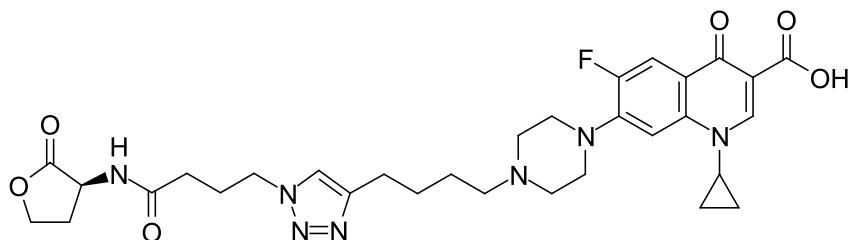
**<sup>1</sup>H NMR** (400 MHz, DMSO d<sub>6</sub>) δ / ppm = 15.23 (s, 1 H, C(=O)OH), 8.84 (d, *J* = 7.9 Hz, 1 H, NH), 8.66 (s, 1 H, *ortho* to C(=O)OH), 7.90 (d, *J* = 13.3 Hz, 1 H, *ortho* to F), 7.82 (s, 1 H, CH=CCH<sub>2</sub>), 7.57 (d, *J* = 7.6 Hz, 1 H, *meta* to F), 5.13 (s, 1 H, C(=O)CHHN), 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>), 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>), 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>) δ / ppm = 176.4 (C(=O)CC(=O)OH), 174.9 (OC(=O)), 166.0 (C(=O)OH), 165.9 (NHC(=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>N), 52.4 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 51.2 (C(=O)CH<sub>2</sub>N), 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>), 48.2 (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>)

**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

[\mathbf{\alpha}]\_D^{20} / ^\circ 10^{-1} \text{cm}^2 \text{g}^{-1} = -3.5 (c / \text{g} (100 \text{ ml})^{-1} = 0.0575, \text{MeOH})

**1.24 (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 96**



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 **91** (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 3 h, then 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> over 15 min). The combined pure fractions were dried with MgSO<sub>4</sub> and evaporated under reduced pressure. **96** was obtained as a white amorphous solid (14.6 mg, 23.4 μmol, 46.8 %).

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

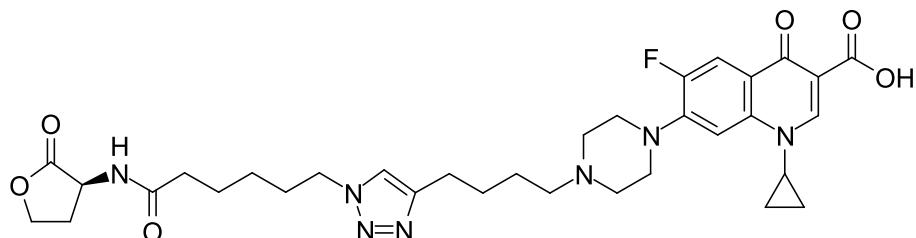
**$^1\text{H NMR}$**  (500 MHz, DMSO d<sub>6</sub>)  $\delta$  / ppm = 15.22 (br s, 1 H, C(=O)OH), 8.65 (s, 1 H, *ortho* to C(=O)OH), 8.40 (d,  $J$  = 8.0 Hz, 1 H, NH), 7.88 (d,  $J$  = 13.4 Hz, 1 H, *ortho* to F), 7.85 (s, 1 H, CH=CCH<sub>2</sub>), 7.55 (d,  $J$  = 7.5 Hz, 1 H, *meta* to F), 4.53 (ddd,  $J$  = 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>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>)

**$^{13}\text{C NMR}$**  (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>)

**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

$[\alpha]_D^{20}$  /  ${}^\circ\text{10}^{-1}\text{cm}^2\text{g}^{-1}$  = -10.6 ( $c$  / g(100 ml)<sup>-1</sup> = 0.094, MeOH)

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



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 **91** (20.6 mg, 50.0  $\mu\text{mol}$ , 1 eq.) and (S)-6-azido-*N*-(2-oxotetrahydrofuran-3-yl)hexanamide **47** (12.0 mg, 50.0  $\mu\text{mol}$ , 1 eq.). A similarly degassed solution of CuSO<sub>4</sub> · 5 H<sub>2</sub>O (624  $\mu\text{g}$ , 2.5  $\mu\text{mol}$ , 0.05 eq. 50 mM), THPTA (1.09 mg, 2.5  $\mu\text{mol}$ , 0.05 eq. 50 mM) and sodium ascorbate (991  $\mu\text{g}$ , 5  $\mu\text{mol}$ , 0.1 eq., 100 mM) in 50 % water/t-BuOH (50  $\mu\text{l}$ ) was then added. The mixture was stirred at r.t. under argon for 3 h, then 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> over 15 min) The combined pure fractions were dried with MgSO<sub>4</sub> and evaporated under reduced pressure. **97** was obtained as a white amorphous solid (12.4 mg, 19.0  $\mu\text{mol}$ , 38.0 %).

**TLC**  $R_f = 0.30$  (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)

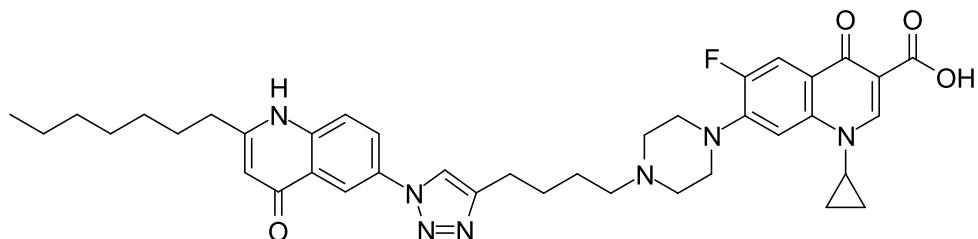
**<sup>1</sup>H NMR** (500 MHz, DMSO d<sub>6</sub>)  $\delta$  / ppm = 15.22 (br s, 1 H, C(=O)OH), 8.65 (s, 1 H, *ortho* to C(=O)OH), 8.32 (d,  $J$  = 8.0 Hz, 1 H, NH), 7.89 (d,  $J$  = 13.3 Hz, 1 H, *ortho* to F), 7.84 (s, 1 H, CH=CCH<sub>2</sub>), 7.55 (d,  $J$  = 7.6 Hz, 1 H, *meta* to F), 4.51 (ddd,  $J$  = 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>)), 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(CHH)<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(CHH)<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>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>)), 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>), 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>), 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>)

**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

$[\alpha]_D^{20}$  / °10<sup>-1</sup>cm<sup>2</sup>g<sup>-1</sup> = -8.5 (c / g(100 ml)<sup>-1</sup> = 0.106, MeOH)

**1.26 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 98**



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 **91** (4.1 mg, 10.0  $\mu$ mol, 1 eq.) and 6-azido-2-heptylquinolin-4(1H)-one **26** (2.8 mg, 10.0  $\mu$ mol, 1 eq.). A similarly degassed solution of CuSO<sub>4</sub> · 5 H<sub>2</sub>O (125  $\mu$ g, 0.5  $\mu$ mol, 0.05 eq. 50 mM), THPTA (218  $\mu$ g, 0.5  $\mu$ mol, 0.05 eq. 50 mM) and sodium ascorbate (198  $\mu$ g, 1  $\mu$ mol, 0.1 eq., 100 mM) in 50 % water/t-BuOH (10  $\mu$ l) 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 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/CHCl<sub>3</sub> (10 ml). The organic layer was dried with MgSO<sub>4</sub> and evaporated under reduced pressure. **98** was obtained as a white amorphous solid (8.6 mg, 2.7  $\mu\text{mol}$ , 27.0 %).

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

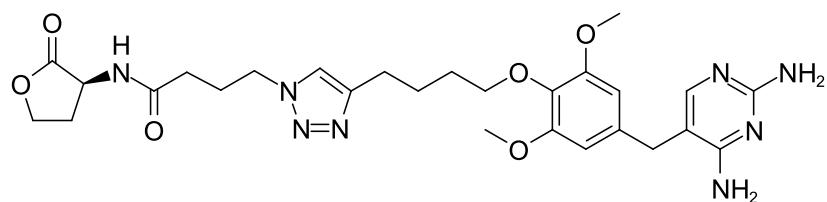
**<sup>1</sup>H NMR** (500 MHz, DMSO d<sub>6</sub>) 15.12 (br s,  $\underline{\text{C}}(\text{=O})\text{OH}$ ), 11.79 (s, 1 H,  $\underline{\text{NH}}$ ), 8.75 (s, 1 H,  $\text{NCH}=\text{CCH}_2$ ), 8.71 (s, 1 H, *ortho* to C(=O)OH), 8.40 (d,  $J$  = 2.7 Hz, 1 H, *ortho* to C(=O) and *ortho* to N), 8.18 (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,  $\text{NHC}=\underline{\text{CH}}(\text{=O})$ ), 3.85 (tt,  $J$  = 7.0, 4.0 Hz, 1 H,  $\text{NCH}(\text{CH}_2)_2$ ), 3.23 - 3.30 (m, 6 H,  $\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)\text{CH}_2\text{CH}_2$ ), 2.82 (t,  $J$  = 5.9 Hz, 2 H,  $\text{NCH}=\text{CCH}_2$ ), 2.63 (t,  $J$  = 7.9 Hz, 2 H,  $\text{CH}_2\text{C}=\text{CH}(\text{=O})$ ), 1.76 - 1.81 (m, 4 H,  $\text{NCH}=\text{CCH}_2\text{CH}_2\text{CH}_2$ ), 1.70 (quin,  $J$  = 7.2 Hz, 2 H,  $\text{CH}_2\text{CH}_2\text{C}=\text{CH}(\text{=O})$ ), 1.15 - 1.38 (m, 12 H,  $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$ ,  $\text{NCH}(\text{CHH})_2$  and  $\text{NCH}(\text{CHH}_2)_2$ ), 0.87 (t,  $J$  = 6.9 Hz, 3 H,  $\text{CH}_3$ )

**<sup>13</sup>C NMR** (126 MHz, DMSO d<sub>6</sub>)  $\delta$  / ppm = 176.4 ( $\underline{\text{C}}(\text{=O})\text{CC}(\text{=O})\text{OH}$ ), 176.3 ( $\text{CH}\underline{\text{C}}(\text{=O})$ ), 165.8 ( $\underline{\text{C}}(\text{=O})\text{OH}$ ), 154.3 ( $\text{CCH}\underline{\text{C}}(\text{=O})$ ), 152.9 (d,  $J$  = 240.1 Hz, *ipso* to F), 148.3 ( $\underline{\text{CH}}=\text{CC}(\text{=O})\text{OH}$ ), 147.5 ( $\text{NCH}\underline{\text{CCH}}_2$ ), 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* to C(=O) and *ortho* to NH), 123.6 (*para* to C(=O) and *meta* to NH), 120.5 ( $\text{N}\underline{\text{CH}}=\text{CCH}_2$ ), 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 ( $\underline{\text{CH}}(\text{=O})$ ), 106.9 ( $\underline{\text{CC}}(\text{=O})\text{OH}$ ), 55.4 ( $\text{CH}=\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$ ), 50.6 ( $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2)\underline{\text{CH}}_2$ ), 46.5 ( $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)\text{CH}_2\underline{\text{CH}}_2$ ), 36.0 ( $\text{N}\underline{\text{CH}}(\text{CH}_2)_2$ ), 33.2 ( $\text{CH}_2\text{CNH}$ ), 31.2 ( $\text{CH}_3\text{CH}_2\underline{\text{CH}}_2$ ), 28.3 - 28.5 ( $\text{CH}_3\text{CH}_2\text{CH}_2\underline{\text{CH}}_2\text{CH}_2\underline{\text{CH}}_2$ ), 25.6 ( $\text{CH}=\text{CCH}_2\underline{\text{CH}}_2$ ), 24.4 ( $\text{CH}=\underline{\text{CH}}_2$ ), 22.7 ( $\text{CH}=\text{CCH}_2\text{CH}_2\underline{\text{CH}}_2$ ), 22.0 ( $\text{CH}_3\underline{\text{CH}}_2$ ), 13.9 ( $\underline{\text{CH}}_3$ ), 7.6 ( $\text{NCH}(\underline{\text{CH}}_2)_2$ )

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

**1.27 (S)-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 99**



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 **94** (20.6 mg, 50.0  $\mu\text{mol}$ , 1 eq.) and (*S*)-4-azido-*N*-(2-oxotetrahydrofuran-3-yl)butanamide **46** (15.9 mg, 75.0  $\mu\text{mol}$ , 1.5 eq.). Similarly degassed solutions of CuSO<sub>4</sub> · 5 H<sub>2</sub>O (624  $\mu\text{g}$ , 2.5  $\mu\text{mol}$ , 0.05 eq. 50 mM), THPTA (1.09 mg, 2.5  $\mu\text{mol}$ , 0.05 eq. 50 mM) and sodium

ascorbate (991  $\mu$ g, 5  $\mu$ mol, 0.1 eq., 100 mM) in water (50  $\mu$ l) were then added. An extra portion of **46** (10.6 mg, 50.0  $\mu$ mol, 1 eq.) was added after 4 d. Extra portions of the catalysts were added after 9 d. After 2 weeks, the reaction mixture was extracted with  $\text{CH}_2\text{Cl}_2$  ( $6 \times 10$  ml) then dry-loaded onto  $\text{SiO}_2$  and purified by column chromatography using a Combiflash ( $\text{SiO}_2$ , 0-20 %  $\text{MeOH}/\text{CH}_2\text{Cl}_2$ ). The combined pure fractions were dried with  $\text{MgSO}_4$  and evaporated under reduced pressure. **99** was obtained as a pale brown gum (4.8 mg, 8.4  $\mu$ mol, 16.8 %).

**TLC**  $R_f = 0.30$  (30 %  $\text{MeOH}/\text{CH}_2\text{Cl}_2$ )

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

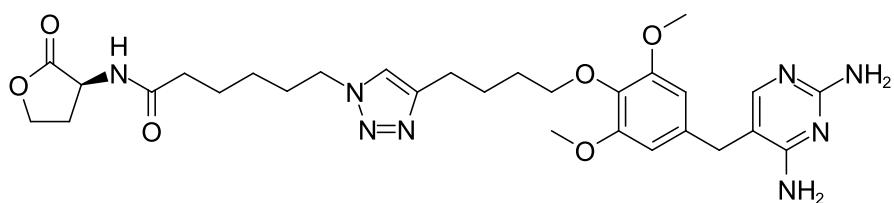
**$^1\text{H NMR}$**  (500 MHz, DMSO d<sub>6</sub>)  $\delta$  / ppm = 8.43 (d,  $J = 8.0$  Hz, 1 H, NH), 7.80 (s, 1 H,  $\text{NCH}=\text{CCH}_2$ ), 7.46 (s, 1 H,  $\text{CHN}=\text{CNH}_2$ ), 6.68 (br s, 2 H,  $\text{CH}_2\text{CCN}\text{H}_2$ ), 6.53 (s, 2 H, *meta* to CH<sub>2</sub>), 6.21 (br s, 2 H,  $\text{CHN}=\text{CNH}_2$ ), 4.49 (dt,  $J = 10.7, 8.6$  Hz, 1 H,  $\text{CHNH}$ ), 4.32 (td,  $J = 8.7, 1.6$  Hz, 1 H,  $\text{CHHOC}(=\text{O})$ ), 4.29 (t,  $J = 6.8$  Hz, 2 H,  $\text{CH}_2\text{N}$ ), 4.19 (ddd,  $J = 10.6, 8.7, 6.5$  Hz, 1 H,  $\text{CHHOC}(=\text{O})$ ), 3.79 (t,  $J = 6.2$  Hz, 2 H,  $\text{CH}_2\text{CH}_2\text{CH}_2\text{O}$ ), 3.68 (s, 6 H,  $\text{CH}_3$ ), 3.53 (br s, 2 H,  $\text{CCH}_2\text{C}$ ), 2.63 (t,  $J = 7.5$  Hz, 2 H,  $\text{CH}=\text{CCH}_2$ ), 2.37 (dddd,  $J = 12.2, 8.9, 6.7, 1.8$  Hz, 1 H,  $\text{CHHCHNH}$ ), 2.08 - 2.15 (m, 3 H,  $\text{CHHCHNH}$  and  $\text{C}(=\text{O})\text{CH}_2$ ), 2.00 (quin,  $J = 7.2$  Hz, 2 H,  $\text{CH}_2\text{CH}_2\text{N}$ ), 1.72 (quin,  $J = 7.3$  Hz, 2 H,  $\text{CH}=\text{CCH}_2\text{CH}_2$ ), 1.61 (quin,  $J = 6.7$  Hz, 2 H,  $\text{CH}_2\text{CH}_2\text{O}$ )

**$^{13}\text{C NMR}$**  (126 MHz, DMSO d<sub>6</sub>)  $\delta$  / ppm = 175.8 ( $\text{OC}=\text{O}$ ), 171.9 ( $\text{NHC}=\text{O}$ ), 163.1 ( $\text{CC}(\text{NH}_2)\text{N}$ ), 159.7 (br s,  $\text{NC}(\text{NH}_2)\text{N}$ ), 153.2 (*ipso* to  $\text{OCH}_3$ ), 150.5 (br s,  $\text{CHNC}(\text{NH}_2)\text{N}$ ), 147.3 ( $\text{NCH}=\text{CCH}_2\text{CH}_2$ ), 135.2 (*para* to  $\text{CH}_2\text{O}$ ), 135.0 (*ipso* to  $\text{CH}_2\text{O}$ ), 122.1 ( $\text{CH}=\text{CCH}_2\text{CH}_2$ ), 107.3 ( $\text{CH}_2\text{CC}(\text{NH}_2)=\text{N}$ ), 106.2 (*meta* to  $\text{CH}_2\text{O}$ ), 72.3 ( $\text{CH}_2\text{CH}_2\text{CH}_2\text{O}$ ), 65.7 ( $\text{OCH}_2\text{CH}_2\text{CHNH}$ ), 56.2 ( $\text{OCH}_3$ ), 48.9 ( $\text{CH}_2\text{N}$ ), 48.3 ( $\text{CHNH}$ ), 32.9 ( $\text{CCH}_2\text{C}$ ), 32.0 ( $\text{C}(=\text{O})\text{CH}_2$ ), 29.3 ( $\text{CH}_2\text{CH}_2\text{CH}_2\text{O}$ ), 28.4 ( $\text{OCH}_2\text{CH}_2\text{CHNH}$ ), 26.0 ( $\text{CH}_2\text{CH}_2\text{N}$ ), 25.7 ( $\text{CH}=\text{CCH}_2\text{CH}_2$ ), 24.9 ( $\text{CH}=\text{CCH}_2\text{CH}_2$ )

**HRMS** (ESI<sup>+</sup>)  $m/z$  / Da = 569.2834, [M+H]<sup>+</sup> found,  $[\text{C}_{27}\text{H}_{37}\text{N}_8\text{O}_6]^{+}$  requires 569.2836

$[\alpha]_D^{20}$  /  ${}^\circ\text{10}^{-1}\text{cm}^2\text{g}^{-1}$  = -4.6 ( $c$  / g(100 ml)<sup>-1</sup> = 0.0433, MeOH)

## 1.28 (*S*)-6-(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)hexanamide 100



50 % water/t-BuOH (2 ml) was degassed by bubbling  $\text{N}_2$  through it. This was then added to a mixture of 5-(4-(hex-5-yn-1-yloxy)-3,5-dimethoxybenzyl)pyrimidine-2,4-diamine **94** (20.6 mg, 50.0  $\mu$ mol, 1 eq.) and (*S*)-6-azido-*N*-(2-oxotetrahydrofuran-3-yl)hexanamide **47** (18.0 mg, 75.0  $\mu$ mol, 1.5 eq.). Similarly degassed solutions of  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  (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 water (50  $\mu$ l) were then added. An extra portion of **47** (12.0 mg, 50.0  $\mu$ mol, 1 eq.) was added after was added after 4 d. Extra portions of the catalysts were added after 9 d. After

2 weeks, the reaction mixture was extracted with  $\text{CH}_2\text{Cl}_2$  ( $6 \times 10$  ml) then dry-loaded onto  $\text{SiO}_2$  and purified by column chromatography using a Combiflash ( $\text{SiO}_2$ , 0-20 %  $\text{MeOH}/\text{CH}_2\text{Cl}_2$ ). The combined pure fractions were dried with  $\text{MgSO}_4$  and evaporated under reduced pressure. **100** was obtained as a clear gum (8.0 mg, 13.4  $\mu\text{mol}$ , 26.8 %).

**TLC**  $R_f = 0.35$  (30 %  $\text{MeOH}/\text{CH}_2\text{Cl}_2$ )

**IR** (neat)  $\nu_{max}$  /  $\text{cm}^{-1} = 3336.0$  (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)

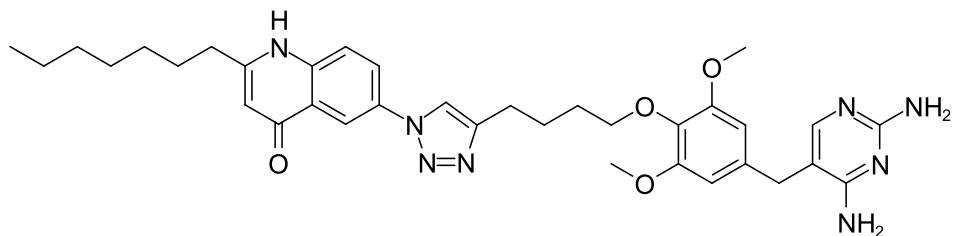
**$^1\text{H NMR}$**  (500 MHz, DMSO d<sub>6</sub>)  $\delta$  / ppm = 8.34 (d,  $J = 8.0$  Hz, 1 H, NH), 7.83 (s, 1 H,  $\text{NCH}=\text{CCH}_2$ ), 7.50 (s, 1 H,  $\text{CHN}=\text{CNH}_2$ ), 6.54 (s, 2 H, *meta* to  $\text{CH}_2$ ), 6.17 (br s, 2 H,  $\text{CH}_2\text{CCN}\underline{\text{H}}_2$ ), 5.77 (br s, 2 H,  $\text{CHN}=\text{CNH}_2$ ), 4.51 (ddd,  $J = 11.0, 9.0, 8.1$  Hz, 1 H,  $\text{CHNH}$ ), 4.33 (td,  $J = 8.8, 1.9$  Hz, 1 H,  $\text{CHHOC}(=\text{O})$ ), 4.27 (t,  $J = 7.1$  Hz, 2 H,  $\text{CH}_2\text{N}$ ), 4.19 (ddd,  $J = 10.5, 8.7, 6.5$  Hz, 1 H,  $\text{CHHOC}(=\text{O})$ ), 3.80 (t,  $J = 6.3$  Hz, 2 H,  $\text{CH}_2\text{CH}_2\text{CH}_2\text{O}$ ), 3.70 (s, 6 H,  $\text{CH}_3$ ), 3.52 (s, 2 H,  $\text{CCH}_2\text{C}$ ), 2.64 (t,  $J = 7.5$  Hz, 2 H,  $\text{CH}=\text{CCH}_2$ ), 2.36 (dddd,  $J = 12.1, 8.9, 6.7, 1.8$  Hz, 1 H,  $\text{CHHCHNH}$ ), 2.06 - 2.16 (m, 3 H,  $\text{CHHCHNH}$  and  $\text{C}(=\text{O})\text{CH}_2$ ), 1.78 (quin,  $J = 7.4$  Hz, 2 H,  $\text{CH}_2\text{CH}_2\text{N}$ ), 1.73 (quin,  $J = 7.7$  Hz, 2 H,  $\text{CH}=\text{CCH}_2\text{CH}_2$ ), 1.63 (quin,  $J = 6.8$  Hz, 2 H,  $\text{CH}_2\text{CH}_2\text{O}$ ), 1.52 (quin,  $J = 7.5$  Hz, 2 H,  $\text{C}(=\text{O})\text{CH}_2\text{CH}_2$ ), 1.17 - 1.27 (m, 2 H,  $\text{C}(=\text{O})\text{CH}_2\text{CH}_2\text{CH}_2$ )

**$^{13}\text{C NMR}$**  (125 MHz, DMSO d<sub>6</sub>)  $\delta$  / ppm = 175.4 ( $\text{OC}=\text{O}$ ), 172.0 ( $\text{NHC}=\text{O}$ ), 162.2 ( $\text{CC}(\text{NH}_2)\text{N}$ ), 161.8 ( $\text{NC}(\text{NH}_2)\text{N}$ ), 154.8 ( $\text{CHNC}(\text{NH}_2)\text{N}$ ), 152.8 (*ipso* to  $\text{OCH}_3$ ), 146.7 ( $\text{CH}=\text{CCH}_2\text{CH}_2$ ), 135.5 (*para* to  $\text{CH}_2\text{O}$ ), 134.8 (*ipso* to  $\text{CH}_2\text{O}$ ), 121.6 ( $\text{CH}=\text{CCH}_2\text{CH}_2$ ), 105.9 ( $\text{CH}_2\text{CC}(\text{NH}_2)=\text{N}$ ), 105.8 (*meta* to  $\text{CH}_2\text{O}$ ), 71.9 ( $\text{CH}_2\text{CH}_2\text{CH}_2\text{O}$ ), 65.2 ( $\text{OCH}_2\text{CH}_2\text{CHNH}$ ), 55.8 ( $\text{OCH}_3$ ), 49.0 ( $\text{CH}_2\text{N}$ ), 47.8 ( $\text{CHNH}$ ), 34.8 ( $\text{C}(=\text{O})\text{CH}_2$ ), 32.9 ( $\text{CCH}_2\text{C}$ ), 29.4 ( $\text{CH}_2\text{CH}_2\text{N}$ ), 29.1 ( $\text{CH}_2\text{CH}_2\text{CH}_2\text{O}$ ), 28.2 ( $\text{OCH}_2\text{CH}_2\text{CHNH}$ ), 25.5 ( $\text{CH}=\text{CCH}_2\text{CH}_2$ ), 25.3 ( $\text{C}(=\text{O})\text{CH}_2\text{CH}_2\text{CH}_2$ ), 24.7 ( $\text{CH}=\text{CCH}_2\text{CH}_2$ ), 24.4 ( $\text{C}(=\text{O})\text{CH}_2\text{CH}_2$ )

**HRMS** (ESI<sup>+</sup>)  $m/z$  / Da = 597.3149, [M+H]<sup>+</sup> found,  $[\text{C}_{29}\text{H}_{41}\text{N}_8\text{O}_6]^+$  requires 597.3144

$[\alpha]_D^{20}$  /  ${}^\circ 10^{-1}\text{cm}^2\text{g}^{-1} = -3.6$  ( $c$  / g(100 ml)<sup>-1</sup> = 0.11, MeOH)

**1.29 6-(4-(4-((2,4-Diaminopyrimidin-5-yl)methyl)-2,6-dimethoxyphenoxy)butyl)-1*H*-1,2,3-triazol-1-yl)-2-heptylquinolin-4(*1H*)-one 101**



50 % water/t-BuOH (1 ml) was degassed by bubbling  $\text{N}_2$  through it. This was then added to a mixture of 5-(4-(hex-5-yn-1-yloxy)-3,5-dimethoxybenzyl)pyrimidine-2,4-diamine **94** (3.6 mg, 10.0  $\mu\text{mol}$ , 1 eq.) and 6-azido-2-heptylquinolin-4(*1H*)-one **26** (2.8 mg, 10.0  $\mu\text{mol}$ , 1 eq.). A similarly degassed solution of  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  (125  $\mu\text{g}$ , 0.5  $\mu\text{mol}$ , 0.05 eq. 50 mM), THPTA (218  $\mu\text{g}$ , 0.5  $\mu\text{mol}$ , 0.05 eq. 50 mM) and sodium ascorbate (198  $\mu\text{g}$ , 1  $\mu\text{mol}$ , 0.1 eq., 100 mM) in water (10  $\mu\text{l}$ ) was then added. The mixture was stirred at r.t. under argon for 1.5 h, then evaporated under reduced pressure. The residue was purified by preparatory HPLC (5-100 % ace-

tonitrile/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/CHCl<sub>3</sub> (10 ml). The organic layer was dried with MgSO<sub>4</sub> and evaporated under reduced pressure. **101** was obtained as a clear gum (2.6 mg, 4.1  $\mu\text{mol}$ , 41.0 %).

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

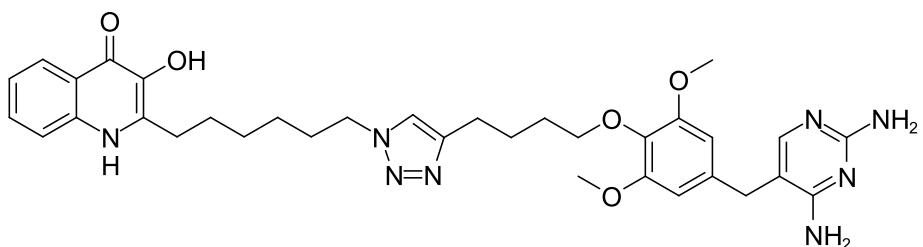
**IR** (neat)  $\nu_{max}$  / cm<sup>-1</sup> = 2927.7 (C-H), 2855.5 (C-H), 1664.1 (pyrimidine), 1645.4 (pyrimidine and HHQ C=O),

**<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>)

**<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

### 1.30 2-(6-(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 **102**



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 **94** (14.2 mg, 39.8  $\mu\text{mol}$ , 1 eq.) and 2-(6-azidohexyl)-3-hydroxyquinolin-4(1*H*)-one **56** (11.4 mg, 39.8  $\mu\text{mol}$ , 1 eq.). A similarly degassed solution of CuSO<sub>4</sub> · 5 H<sub>2</sub>O (1.25 mg, 5  $\mu\text{mol}$ , 0.125 eq. 50 mM), THPTA (2.18 mg, 5  $\mu\text{mol}$ , 0.125 eq. 50 mM) and sodium ascorbate (1.98 mg, 10  $\mu\text{mol}$ , 0.25 eq., 100 mM) in water (100  $\mu\text{l}$ ) 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. **102** was obtained as a pale brown amorphous solid (4.7 mg, 7.3  $\mu\text{mol}$ , 18.3 %).

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

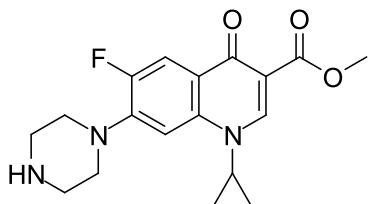
**IR** (neat)  $\nu_{max} / \text{cm}^{-1} = 2924.8$  (C-H), 2853.4 (C-H), 1660.0 (pyrimidine), 1638.8 (pyrimidine and PQS C=O),

**<sup>1</sup>H NMR** (500 MHz, DMSO d<sub>6</sub>)  $\delta / \text{ppm} = 11.53$  (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 C<sub>HN</sub>=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>)  $\delta / \text{ppm} = 168.9$  (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>)  $m/z / \text{Da} = 643.3365$ , [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

### 1.31 Methyl 1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate 103



Ciprofloxacin **76** (10.0 g, 30 mmol, 1 eq.) and *p*-toluenesulfonic acid (8.60 mg, 44.5 mmol, 1.5 eq.) were refluxed in methanol (500 ml) for 72 h. The mixture was cooled to room temperature and NaHCO<sub>3</sub> (sat., aq., 100 ml) and water (300 ml) were added. The product was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2×400 ml). The combined organic fractions were dried over MgSO<sub>4</sub> and evaporated under reduced pressure. **103** 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)  $\nu_{max} / \text{cm}^{-1} = 2947.9$  (C-H), 2834.9 (C-H), 1720.9 (ester C=O), 1616.8 (quinolone C=O)

**<sup>1</sup>H NMR** (400 MHz, MeOD)  $\delta / \text{ppm} = 8.55$  (s, 1 H, *ortho* to C(=O)OCH<sub>3</sub>), 7.71 (d,  $J = 13.5$  Hz, 1 H, *ortho* to F), 7.41 (d,  $J = 7.2$  Hz, 1 H, *meta* to F), 3.83 (s, 3 H, CH<sub>3</sub>), 3.62 (tt,  $J = 7.4, 3.5$  Hz, 1 H, NCH(CH<sub>2</sub>)<sub>2</sub>), 3.24 - 3.29 (m, 4 H, HN(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 3.02 - 3.10 (m, 4 H, HN(CH<sub>2</sub>)CH<sub>2</sub>), 1.31 - 1.38 (m, 2 H, NCH(CHH)<sub>2</sub>), 1.12 - 1.20 (m, 2 H, NCH(CHH)<sub>2</sub>)

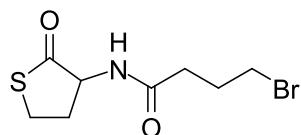
**<sup>13</sup>C NMR** (101 MHz, MeOD)  $\delta$  / ppm = 175.2 ( $\underline{\text{C}}(\text{=O})\text{CC}(\text{=O})\text{OCH}_3$ ), 166.8 ( $\underline{\text{C}}(\text{=O})\text{OCH}_3$ ), 154.9 (d,  $J$  = 248.0 Hz, *ipso* to F), 150.1 ( $\underline{\text{C}}=\text{CC}(\text{=O})\text{OCH}_3$ ), 146.6 (d,  $J$  = 10.4 Hz, *ipso* to piperazine), 139.9 (*para* to F), 123.3 (d,  $J$  = 6.9 Hz, *para* to piperazine), 113.0 (d,  $J$  = 23.4 Hz, *ortho* to C=O and *ortho* to F), 110.1 ( $\underline{\text{C}}\text{C}(\text{=O})\text{OCH}_3$ ), 107.1 (d,  $J$  = 3.5 Hz, *meta* to C=O and *meta* to F), 52.3 ( $\underline{\text{CH}_3}$ ), 51.7 ( $\text{HN}(\text{CH}_2\text{CH}_2)\text{CH}_2\text{CH}_2$ ), 51.6 ( $\text{HN}(\text{CH}_2\text{CH}_2)\text{CH}_2\text{CH}_2$ ), 46.5 ( $\text{HN}(\underline{\text{CH}_2})\text{CH}_2$ ), 36.4 ( $\text{NCH}(\text{CH}_2)_2$ ), 8.7 ( $\text{NCH}(\underline{\text{CH}_2})_2$ )

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

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

The data are consistent with the literature.<sup>10</sup>

### 1.32 4-Bromo-*N*-(2-oxotetrahydrothiophen-3-yl)butanamide 105



3-Aminodihydrothiophen-2(3H)-one hydrochloride **104** (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. **105** 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)

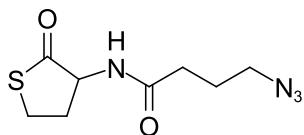
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  / ppm = 205.4 (SC(=O)), 172.1 (NHC(=O)), 59.4 (CHNH), 34.1 (C(=O)CH<sub>2</sub>), 33.1 (CH<sub>2</sub>Br), 31.8 (SCH<sub>2</sub>CH<sub>2</sub>), 28.0 (C(=O)CH<sub>2</sub>CH<sub>2</sub>), 27.5 (SCH<sub>2</sub>)

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

**pick up**

The compound has been synthesised previously<sup>11,12</sup> but characterisation was not published.

### 1.33 4-Azido-*N*-(2-oxotetrahydrothiophen-3-yl)butanamide 106



4-Bromo-*N*-(2-oxotetrahydrothiophen-3-yl)butanamide **105** (6.00 g, 27.0 mmol, 1 eq.) and  $\text{NaN}_3$  (3.51 g, 54.1 mmol, 2 eq.) were refluxed in acetonitrile (120 ml) for 1.5 h. The solvent was evaporated under reduced pressure and the residue was partitioned between water (150 ml) and  $\text{CH}_2\text{Cl}_2$  (150 ml). The aqueous layer was extracted twice more with  $\text{CH}_2\text{Cl}_2$  ( $2 \times 150$  ml) and the combined organic fractions were dried with  $\text{MgSO}_4$  and evaporated under reduced pressure. **106** 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)  $\nu_{max}$  /  $\text{cm}^{-1}$  = 3285.6 (N-H), 2963.9 (C-H), 2100.2 (azide), 1697.4 (thiolactone C=O), 1647.4 (amide C=O)

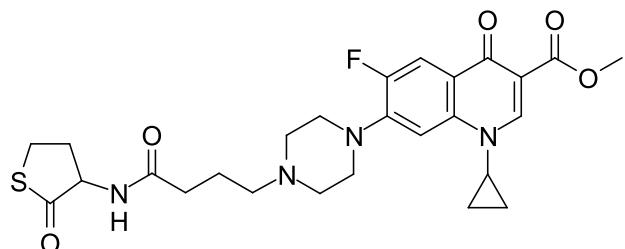
**$^1\text{H NMR}$**  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  / ppm = 6.71 (d,  $J$  = 7.3 Hz, 1 H, NH), 4.54 (dt,  $J$  = 13.0, 7.0 Hz, 1 H,  $\text{CHNH}$ ), 3.30 (t,  $J$  = 6.7 Hz, 2 H,  $\text{CH}_2\text{N}_3$ ), 3.31 (td,  $J$  = 11.7, 5.3 Hz, 1 H, 1 H,  $\text{SCHH}$ ), 3.19 (ddd,  $J$  = 11.3, 7.0, 1.2 Hz, 1 H,  $\text{SCHH}$ ), 2.70 (dddd,  $J$  = 12.4, 6.8, 5.3, 1.2 Hz, 1 H,  $\text{SCH}_2\text{CHH}$ ), 2.29 (t,  $J$  = 7.5 Hz, 1 H, C(=O)CHH), 2.28 (t,  $J$  = 7.1 Hz, 1 H, C(=O)CHH), 1.97 (qd,  $J$  = 12.4, 7.0 Hz, 1 H,  $\text{SCH}_2\text{CHH}$ ), 1.85 (quin,  $J$  = 6.9 Hz, 2 H, C(=O)CH $_2$ CH $_2$ )

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

**HRMS (ESI $^+$ )**  $m/z$  / Da = 251.0565, [M+Na] $^+$  found,  $[\text{C}_8\text{H}_{12}\text{N}_4\text{NaO}_2\text{S}]^+$  requires 251.0573

The compound has not been reported previously.

### 1.34 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 107



Methyl 1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate **103** (50 mg, 0.145 mmol, 1 eq.), 4-bromo-*N*-(2-oxotetrahydrothiophen-3-yl)butanamide **105** (34.5 mg, 0.145 mmol, 1 eq.) and  $\text{K}_2\text{CO}_3$  (20 mg, 0.145 mmol, 1 eq.) were stirred in acetonitrile (2 ml) at 50 °C under argon. After 24 h a further portion of **105** (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 ( $\text{SiO}_2$ , 5-10 %  $\text{MeOH}/\text{CH}_2\text{Cl}_2$ ). **107** 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, CH<sub>2</sub>NH), 3.83 (s, 3 H, OCH<sub>3</sub>), 3.61 (tt,  $J$ =6.9, 4.1 Hz, 1 H, NCH<sub>2</sub>(CH<sub>2</sub>)<sub>2</sub>), 3.39 - 3.49 (m, 5 H, SCH<sub>2</sub>H), 3.26 - 3.33 (m, 1 H, SCH<sub>2</sub>H 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)CH<sub>2</sub>), 2.18 (qd,  $J$ =12.4, 7.0 Hz, 1 H, SCH<sub>2</sub>CH<sub>2</sub>), 1.97 (quin,  $J$ =7.2 Hz, 2 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>), 1.32 - 1.37 (m, 2 H, NCH(CHH)<sub>2</sub>), 1.13 - 1.19 (m, 2 H, NCH(CHH)<sub>2</sub>)

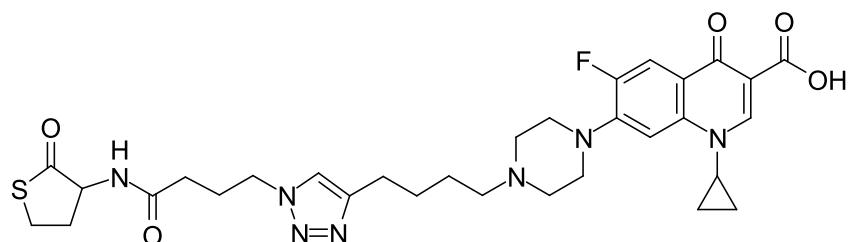
**<sup>13</sup>C NMR** (126 MHz, MeOD)  $\delta$  / ppm = 207.0 (SC(=O)), 175.7 (NHC(=O)), 175.1 (C(=O)CC(=O)OCH<sub>3</sub>), 166.6 (C(=O)OCH<sub>3</sub>), 154.7 (d,  $J$ =249.0 Hz, *ipso* to F), 150.2 (s, CH=CC(=O)OCH<sub>3</sub>), 145.6 (d,  $J$ =10.6 Hz, *ipso* to piperazine), 139.8 (*para* to F), 123.5 (d,  $J$ =6.9 Hz, *para* to piperazine), 113.1 (d,  $J$ =23.6 Hz, *ortho* to C=O and *ortho* to F), 110.0 (CC(=O)OCH<sub>3</sub>), 107.4 (*meta* to C=O and *meta* to F), 60.2 (CHNH), 58.5 (C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 53.8 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 52.3 (OCH<sub>3</sub>), 50.1 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 50.0 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 36.5 (NCH(CH<sub>2</sub>)<sub>2</sub>), 34.5 (C(=O)CH<sub>2</sub>), 31.7 (SCH<sub>2</sub>CH<sub>2</sub>), 28.1 (SCH<sub>2</sub>), 22.9 (C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 8.7 (NCH(CH<sub>2</sub>)<sub>2</sub>)

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

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

The compound has been synthesised previously.<sup>11,12</sup> Only HRMS characterisation was published, and this agrees with the result above.

1.35 1-Cyclopropyl-6-fluoro-4-oxo-7-(4-(4-(1-(4-oxo-4-((2-oxotetrahydrothiophen-3-yl)amino)butyl)-1*H*-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid 108



1-Cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **91** (15 mg, 36.7  $\mu$ mol, 1 eq.) and 4-azido-*N*-(2-oxotetrahydrothiophen-3-yl)butanamide **106** (12.5 mg, 55.1  $\mu$ mol, 1.5 eq.) were dissolved in 1:9:10 water/*t*-BuOH/DMSO (3 ml), and the mixture was degassed by bubbling  $\text{N}_2$  through it. A solution of  $\text{CuSO}_4$  and THPTA (182  $\mu$ l, 18.2  $\mu$ mol, 0.5 eq. 100 mM, aq.) was added, followed by

a solution of sodium ascorbate (367  $\mu$ l, 36.7  $\mu$ mol, 1 eq., 100 mM, aq.). The mixture was stirred at r.t. under argon for 7 d. Water (10 ml) and 10 % *i*-PrOH/CHCl<sub>3</sub> (10 ml) were added, the organic layer was separated and the aqueous layer was extracted again with 10 % *i*-PrOH/CHCl<sub>3</sub> (2×10 ml). The combined organic layers were dried with MgSO<sub>4</sub> and evaporated under reduced pressure. The residue was purified by preparatory HPLC (5-95 % acetonitrile/water over 20 min). The combined pure fractions were evaporated under reduced pressure and then partitioned between NaHCO<sub>3</sub> (aq., sat., 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. **108** was obtained as a white amorphous solid (16.5 mg, 25.9  $\mu$ mol, 70.6 %).

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

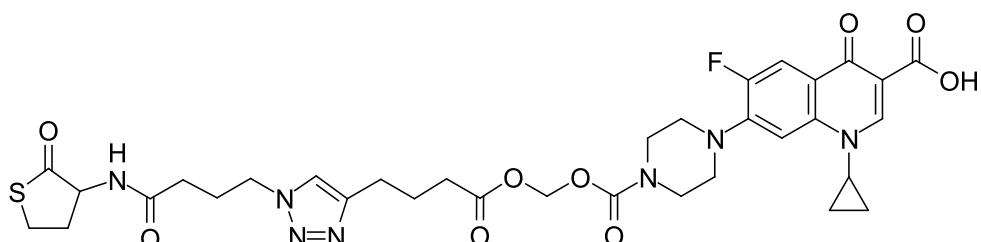
**<sup>1</sup>H NMR** (500 MHz, DMSO d<sub>6</sub>)  $\delta$  / ppm = 15.23 (br s, 1 H, C(=O)OH), 8.66 (s, 1 H, *ortho* to C(=O)OH), 8.23 (d, J=8.5 Hz, 1 H, NH), 7.90 (d, J=13.4 Hz, 1 H, *ortho* to F), 7.84 (s, 1 H, CH=CCH<sub>2</sub>), 7.56 (d, J=7.5 Hz, 1 H, *meta* to F), 4.59 (ddd, J=12.7, 8.4, 6.8 Hz, 1 H, CHNH), 4.31 (t, J=7.0 Hz, 2 H, CH<sub>2</sub>NCH=C), 3.80 - 3.86 (6.9, 4.0 Hz, 1 H, NCH(CH<sub>2</sub>)<sub>2</sub>), 3.34 - 3.37 (m, 1 H, SCHH), 3.32 (br t, J=4.1 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>), 3.27 (ddd, J=11.1, 6.9, 1.4 Hz, 1 H, SCHH), 2.64 (t, J=7.6 Hz, 2 H, CH=CCH<sub>2</sub>), 2.57 (br t, J=4.7 Hz, 4 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 2.34 - 2.44 (m, 3 H, SCH<sub>2</sub>CHH and CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 2.12 (t, J=7.9 Hz, 1 H, C(=O)CHH), 2.12 (t, J=7.0 Hz, 1 H, C(=O)CHH), 2.04 (m, 3 H, SCH<sub>2</sub>CHH and C(=O)CH<sub>2</sub>CH<sub>2</sub>), 1.64 (quin, J=7.5 Hz, 2 H, CH=CCH<sub>2</sub>CH<sub>2</sub>), 1.51 (quin, J=7.5 Hz, 2 H, CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 1.28 - 1.34 (m, 2 H, NCH(CHH)<sub>2</sub>), 1.15 - 1.20 (m, 2 H, NCH(CHH)<sub>2</sub>)

**<sup>13</sup>C NMR** (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>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 = -124.9 (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

### 1.36 1-Cyclopropyl-6-fluoro-4-oxo-7-(4-(((4-(1-(4-oxo-4-((2-oxotetrahydrothiophen-3-yl)amino)butyl)-1*H*-1,2,3-triazol-4-yl)butanoyl)oxy)methoxy)carbonyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid **110**



1-Cyclopropyl-6-fluoro-7-((hex-5-ynoyloxy)methoxy)carbonylpiperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **109** (203 mg, 0.407 mmol, 1 eq.), 4-azido-*N*-(2-oxotetrahydrothiophen-3-yl)butanamide **106** (92.8 mg, 0.407 mmol, 1 eq.), CuI (40 mg, 0.190 mmol, 0.5 eq.) and DIPEA (0.356 ml, 0.264 mg, 2.04 mmol, 5 eq.) were stirred in  $\text{CH}_2\text{Cl}_2$  (18.6 ml) at r.t. under Ar for 3 h. The mixture was filtered and the filtrate was dry-loaded onto  $\text{SiO}_2$  and purified by column chromatography ( $\text{SiO}_2$ , 5-10 % MeOH/ $\text{CH}_2\text{Cl}_2$ ). **110** was obtained as pale brown/yellow amorphous solid (14.7 mg, 20.2  $\mu\text{mol}$ , 5.0 %).

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

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

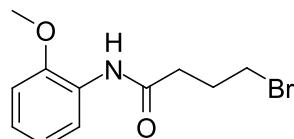
**$^1\text{H NMR}$**  (400 MHz, DMSO d<sub>6</sub>)  $\delta$  / ppm = 15.16 (br s, 1 H, C(=O)OH), 8.65 (s, 1 H, *ortho* to C(=O)OH), 8.21 (d,  $J$  = 8.5 Hz, 1 H, NH), 7.89 (d,  $J$  = 13.1 Hz, 1 H, *ortho* to F), 7.85 (s, 1 H, CH=CCH<sub>2</sub>), 7.57 (d,  $J$  = 7.4 Hz, 1 H, *meta* to F), 5.74 (s, 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, CH=CCH<sub>2</sub>CH<sub>2</sub>), 1.29 - 1.36 (m, 2 H, NCH(CHH)<sub>2</sub>), 1.14 - 1.21 (m, 2 H, NCH(CHH)<sub>2</sub>)

**$^{13}\text{C NMR}$**  (101 MHz, DMSO d<sub>6</sub>)  $\delta$  / ppm = 205.5 (SC(=O)), 176.4 (C(=O)CC(=O)OH), 171.8 (C(=O)OCH<sub>2</sub>O), 171.3 (NHC(=O)), 165.9 (C(=O)OH), 152.8 (d,  $J$  = 249.7 Hz, *ipso* to F), 152.9 (OC(=O)N), 148.1 (CH=CC(=O)OH), 146.0 (CH=CCH<sub>2</sub>), 144.9 (d,  $J$  = 9.6 Hz, *ipso* to piperazine), 139.1 (para to F), 122.0 (CH=CCH<sub>2</sub>), 118.9 (d,  $J$  = 7.5 Hz, *para* to piperazine), 111.0 (d,  $J$  = 23.5 Hz, *ortho* to C=O and *ortho* to F), 106.8 (CC(=O)OH, and *meta* to C=O and *meta* to F), 80.3 (OCH<sub>2</sub>O), 58.2 (CHNH), 49.1 (C(=O)N(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 49.1 (C(=O)N(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 48.6 (C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 43.4 (N(CH<sub>2</sub>)CH<sub>2</sub>), 43.0 (N(CH<sub>2</sub>)CH<sub>2</sub>), 35.9 (NCH(CH<sub>2</sub>)<sub>2</sub>), 32.7 (CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>C(=O)), 31.8 (NHC(=O)CH<sub>2</sub>), 30.1 (SCH<sub>2</sub>CH<sub>2</sub>), 26.8 (SCH<sub>2</sub>), 25.8 (C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 24.2 (CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>C(=O)), 24.0 (CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>C(=O)), 7.6 (NCH(CH<sub>2</sub>)<sub>2</sub>)

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

The compound has not been reported previously.

### 1.37 4-Bromo-*N*-(2-methoxyphenyl)butanamide **112**



2-Methoxyaniline **111** (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  $\text{CH}_2\text{Cl}_2$  (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. **112** 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)  $\nu_{max} / \text{cm}^{-1} = 3410.2$  (N-H), 3313.4 (N-H), 2961.6 (C-H), 2939.5 (C-H), 2902.5 (C-H), 1676.4 (amide C=O)

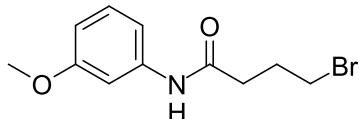
**$^1\text{H NMR}$**  (400 MHz,  $\text{CDCl}_3$  d<sub>1</sub>)  $\delta / \text{ppm} = 8.32$  (dd,  $J = 8.0, 1.7$  Hz, 1 H, *ortho* to NH), 7.85 (br s, 1 H, NH), 7.02 (td,  $J = 7.9, 1.7$  Hz, 1 H, *para* to NH), 6.93 (td,  $J = 7.7, 1.4$  Hz, 1 H, *para* to OCH<sub>3</sub>), 6.85 (dd,  $J = 8.1,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

**$^{13}\text{C NMR}$**  (101 MHz,  $\text{CDCl}_3$  d<sub>1</sub>)  $\delta / \text{ppm} = 169.4$  (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>)  $m/z / \text{Da} = 272.0287$ , [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 114



3-Methoxyaniline **113** (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.). The combined pure fractions were dried with MgSO<sub>4</sub> and evaporated under reduced pressure. **114** was obtained as a pale pink amorphous solid (3.66 g, 13.5 mmol, 49.6 %).

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

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

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

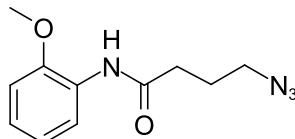
**$^{13}\text{C NMR}$**  (101 MHz,  $\text{CDCl}_3$  d<sub>1</sub>)  $\delta / \text{ppm} = 170.3$  (C(=O)), 159.9 (*ipso* to OCH<sub>3</sub>), 139.0 (*ipso* to NH), 129.5 (*meta* to OCH<sub>3</sub> and *meta* to NH), 112.1 (*para* to OCH<sub>3</sub>), 109.9 (*para* to NH), 105.7 (*ortho* to OCH<sub>3</sub> and *ortho* to NH), 55.2 (CH<sub>3</sub>), 35.3 (C(=O)CH<sub>2</sub>), 33.2 (CH<sub>2</sub>Br), 28.0 (C(=O)CH<sub>2</sub>CH<sub>2</sub>)

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

pick up

The compound has not been reported previously.

### 1.39 4-Azido-*N*-(2-methoxyphenyl)butanamide 115



4-Bromo-*N*-(2-methoxyphenyl)butanamide **112** (2.05 g, 7.51 mmol, 1 eq.) and NaN<sub>3</sub> (1.17 g, 18.0 mmol, 2.4 eq.) were refluxed in acetonitrile (100 ml) for 2 h. The mixture was cooled and filtered, and the filtrate was dry-loaded onto SiO<sub>2</sub> and purified by column chromatography using a Combiflash (SiO<sub>2</sub>, 8-14 % then hold at 14 % EtOAc/P.E.). **115** was obtained as an initially colourless liquid which slowly turned blue then black if left out on the bench (0.469 g, 2.00 mmol, 26.7 %).

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

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

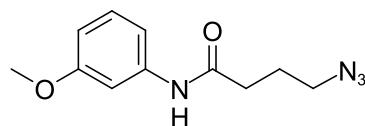
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub> d<sub>1</sub>)  $\delta$  / ppm = 8.32 (dd, *J* = 7.9, 1.0 Hz, 1 H, *ortho* to NH), 7.86 (br s, 1 H, NH), 7.00 (td, *J* = 7.5, 1.5 Hz, 1 H, *para* to NH), 6.90 (td, *J* = 7.7, 1.1 Hz, 1 H, *para* to OCH<sub>3</sub>), 6.83 (dd, *J* = 8.1, 1.4 Hz, 1 H, *ortho*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

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

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

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

### 1.40 4-Azido-*N*-(3-methoxyphenyl)butanamide 116



4-Bromo-*N*-(3-methoxyphenyl)butanamide **114** (2.05 g, 7.51 mmol, 1 eq.) and NaN<sub>3</sub> (1.17 g, 18.0 mmol, 2.4 eq.) were refluxed in acetonitrile (100 ml) for 7 h. The mixture was cooled and filtered, and the filtrate was dry-loaded onto SiO<sub>2</sub> and purified by column chromatography using a Combiflash (SiO<sub>2</sub>, 0-100 % EtOAc/P.E.). The combined pure fractions were dried with MgSO<sub>4</sub> and evaporated under reduced pressure. **116** was obtained as an straw-coloured liquid (0.294 g, 1.25 mmol, 16.7 %).

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

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

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

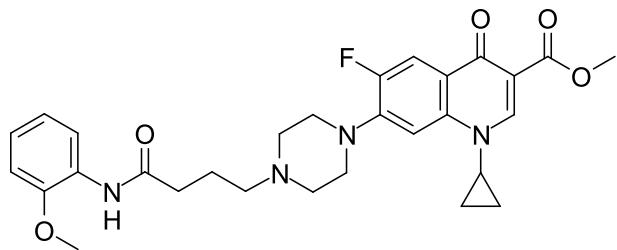
**$^{13}\text{C NMR}$**  (101 MHz, MeOD)  $\delta$  / ppm = 170.8 (C(=O)), 159.6 (*ipso* to OCH<sub>3</sub>), 138.9 (*ipso* to NH), 129.2 (*meta* to OCH<sub>3</sub> and *meta* to NH), 112.3 (*para* to OCH<sub>3</sub>), 109.5 (*para* to NH), 106.0 (*ortho* to OCH<sub>3</sub> and *ortho* to NH), 54.8 (CH<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 ??

**pick up**

The compound has not been reported previously.

#### 1.41 Methyl 1-cyclopropyl-6-fluoro-7-(4-((2-methoxyphenyl)amino)-4-oxobutyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 117



Methyl 1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate **103** (500 mg, 1.45 mmol, 1 eq.), 4-bromo-*N*-(2-methoxyphenyl)butanamide **112** (788 mg, 2.90 mmol, 2 eq.), DIPEA (1.28 ml, 950 mg, 7.35 mmol, 5 eq.), NaI (275 mg, 1.83 mmol, 1.3 eq.) and acetonitrile (10 ml) were stirred in a microwave reactor at 100 °C for 4 h. The mixture was dry-loaded onto SiO<sub>2</sub> and purified by column chromatography (SiO<sub>2</sub>, 4 % MeOH/CH<sub>2</sub>Cl<sub>2</sub>). The combined pure fractions were dried with MgSO<sub>4</sub> and evaporated under reduced pressure. **117** 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)  $\nu_{max}$  /  $\text{cm}^{-1} = 2947.1$  (C-H), 2833.7 (C-H), 1718.9 (ester C=O), 1685.3 (amide C=O), 1617.3 (quinolone C=O)

**$^1\text{H NMR}$**  (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>)<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>)<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>),

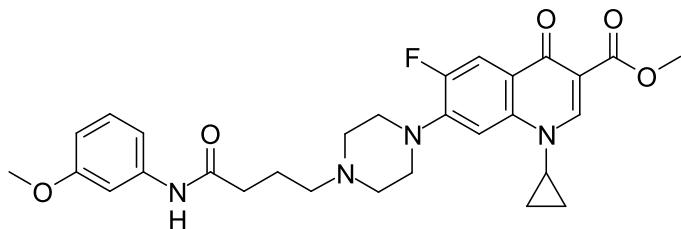
1.07 - 1.14 (m, 2 H,  $\text{NCH}(\text{CH}_2)_2$ )

**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$  d<sub>1</sub>)  $\delta$  / ppm = 172.9 ( $\text{C}(=\text{O})\text{CC}(=\text{O})\text{OCH}_3$ ), 170.8 ( $\text{NHC}(=\text{O})$ ), 166.2 ( $\text{C}(=\text{O})\text{O}$   $\text{CH}_3$ ), 153.3 (d,  $J$  = 248.0 Hz, *ipso* to F), 148.2 ( $\text{C}=\text{CC}(=\text{O})\text{OCH}_3$ ), 147.6 (*ipso* to  $\text{OCH}_3$ ), 144.4 (d,  $J$  = 10.4 Hz, *ipso* to piperazine), 137.9 (*para* to F), 127.6 (*ipso* to NH), 123.4 (*para* to NH), 122.7 (d,  $J$  = 7.8 Hz, *para* to piperazine), 121.0 (*para* to  $\text{OCH}_3$ ), 119.7 (*ortho* to NH and *meta* to  $\text{OCH}_3$ ), 113.0 (d,  $J$  = 22.5 Hz, *ortho* to  $\text{C}=\text{O}$  and *ortho* to F), 109.8 (*ortho* to  $\text{OCH}_3$  and *meta* to NH, and  $\text{CC}(=\text{O})\text{OCH}_3$ ), 104.7 (*meta* to  $\text{C}=\text{O}$  and *meta* to F), 57.2 ( $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$ ), 55.6 (aromatic  $\text{OCH}_3$ ), 52.7 ( $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2)\text{CH}_2$ ), 51.9 ( $\text{C}(=\text{O})\text{OCH}_3$ ), 49.8 ( $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)\text{CH}_2\text{CH}_2$ ), 49.8 ( $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)\text{CH}_2\text{CH}_2$ ), 35.5 ( $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$ ), 34.5 ( $\text{NCH}(\text{CH}_2)_2$ ), 22.3 ( $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$ ), 8.0 ( $\text{NCH}(\text{CH}_2)_2$ )

**HRMS** (ESI<sup>+</sup>)  $m/z$  / Da = 537.2523, [M+H]<sup>+</sup> found,  $[\text{C}_{29}\text{H}_{34}\text{FN}_4\text{O}_5]^{+}$  requires 537.2513

The compound has not been reported previously.

#### 1.42 Methyl 1-cyclopropyl-6-fluoro-7-(4-((3-methoxyphenyl)amino)-4-oxobutyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 118



Methyl 1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate **103** (500 mg, 1.45 mmol, 1 eq.), 4-bromo-*N*-(3-methoxyphenyl)butanamide **114** (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  $\text{CH}_2\text{Cl}_2$  (50 ml) and water (50 ml). The organic layer was separated off and the aqueous layer was extracted again with  $\text{CH}_2\text{Cl}_2$  (50 ml). The combined organic layers were dried with  $\text{MgSO}_4$  and purified by column chromatography ( $\text{SiO}_2$ , 0-4 % MeOH/ $\text{CH}_2\text{Cl}_2$ ). The combined pure fractions were dried with  $\text{MgSO}_4$  and evaporated under reduced pressure. **118** was obtained as an off-white amorphous solid (81.7 mg, 0.152 mmol, 10.5 %).

**TLC**  $R_f$  = 0.38 (10 % MeOH/ $\text{CH}_2\text{Cl}_2$ )

**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)

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

*J* = 6.8 Hz, 2 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 1.29 - 1.36 (m, 2 H, NCH(CHH)<sub>2</sub>), 1.11 - 1.17 (m, 2 H, NCH(CHH)<sub>2</sub>)

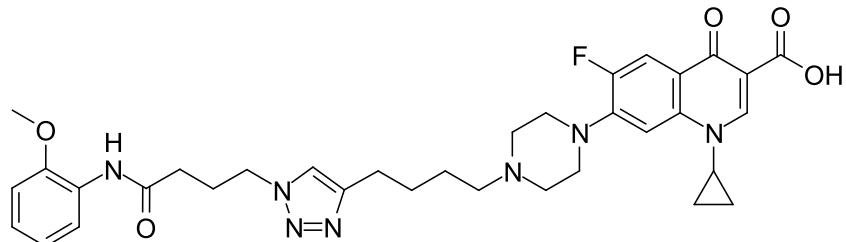
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  / ppm = 173.1 (C(=O)CC(=O)OCH<sub>3</sub>), 170.9 (NHC(=O)), 166.3 (C(=O)OCH<sub>3</sub>), 160.1 (*ipso* to OCH<sub>3</sub>), 153.3 (d, *J*=250.1 Hz, *ipso* to F), 148.4 (C=CC(=O)OCH<sub>3</sub>), 144.1 (d, *J*=10.1 Hz, *ipso* to piperazine), 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>N), 55.3 (aromatic OCH<sub>3</sub>), 52.6 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>)), 52.1 (C(=O)OCH<sub>3</sub>), 49.2 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 35.2 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 34.6 (NCH(CH<sub>2</sub>)<sub>2</sub>), 21.7 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 8.2 (NCH(CH<sub>2</sub>)<sub>2</sub>)

**<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)-1*H*-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 119**



1-Cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **91** (24.1 mg, 58.6  $\mu$ mol, 1 eq.) and 4-azido-*N*-(2-methoxyphenyl)butanamide **115** (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>). The combined pure fractions were dried with MgSO<sub>4</sub> and evaporated under reduced pressure. **119** was obtained as a clear glass (14.7 mg, 22.8  $\mu$ mol, 39.0 %).

**TLC** *R<sub>f</sub>* = 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(CHH)<sub>2</sub>), 1.17 - 1.22 (m, 2 H, NCH(CHH)<sub>2</sub>)

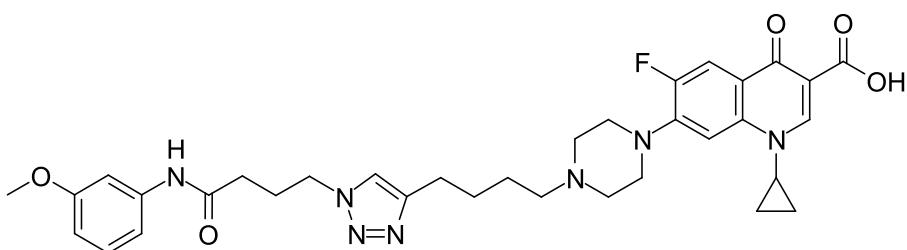
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  / ppm = 177.1 (C(=O)CC(=O)OH), 169.5 (NH<sub>2</sub>C(=O)), 167.0 (C(=O)OH), 153.7 (d, *J* = 251.4 Hz, *ipso* to F), 148.1 (CH=CCH<sub>2</sub>), 147.8 (*ipso* to OCH<sub>3</sub>), 147.3 (C=CC(=O)OH), 145.9 (d, *J* = 10.4 Hz, *ipso* to piperazine), 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)-1*H*-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 120**



1-Cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **91** (24.1 mg, 58.6  $\mu$ mol, 1 eq.) and 4-azido-*N*-(3-methoxyphenyl)butanamide **116** (13.7 mg, 58.5  $\mu$ mol, 1 eq.) were dissolved in water (1 ml), *t*-BuOH (9 ml) and CH<sub>2</sub>Cl<sub>2</sub> (10 ml), and the mixture was degassed by bubbling through N<sub>2</sub>. A solution of CuSO<sub>4</sub> and THPTA (58.5  $\mu$ l, 5.85  $\mu$ mol, 0.1 eq. 100 mM, aq.) was added, followed by a solution of sodium ascorbate (117  $\mu$ l, 11.7  $\mu$ mol, 0.2 eq., 100 mM, aq.). The mixture was stirred at room temperature under argon for 2 h, then the solvent was removed under reduced pressure. The residue was partitioned between water (15 ml) and CH<sub>2</sub>Cl<sub>2</sub> (15 ml), and the aqueous layer was extracted a further four times with CH<sub>2</sub>Cl<sub>2</sub> (4  $\times$  15 ml). The combined organic layers were dried with MgSO<sub>4</sub>, dry-loaded onto SiO<sub>2</sub> and purified by column chromatography (SiO<sub>2</sub>, 0-10 % MeOH/CH<sub>2</sub>Cl<sub>2</sub>). The combined pure fractions were dried with MgSO<sub>4</sub> and evaporated under reduced pressure. **120** was obtained as a clear glass (1.9 mg, 2.9  $\mu$ mol, 5.0 %).

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

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

**<sup>1</sup>H NMR** (400 MHz, DMSO d<sub>6</sub>)  $\delta$  / ppm = 15.23 (br s, 1 H, C(=O)OH), 9.89 (s, 1 H, NH), 8.66 (s, 1 H, *ortho* to C(=O)OH), 7.90 (d,  $J$  = 13.4 Hz, 1 H, *ortho* to F), 7.88 (s, 1 H, CH=CCH<sub>2</sub>), 7.55 (d,  $J$  = 7.6 Hz, 1 H, *meta* to F), 7.27 (t,  $J$  = 2.1 Hz, 1 H, *ortho* to C=O and *ortho* to F), 7.16 (t,  $J$  = 8.1 Hz, 1 H, *meta* to OCH<sub>3</sub> and *meta* to NH), 7.08 (d,  $J$  = 7.8 Hz, 1 H, *para* to OCH<sub>3</sub>), 6.59 (ddd,  $J$  = 8.1, 2.4, 0.7 Hz, 1 H, *para* to NH), 4.36 (t,  $J$  = 6.9 Hz, 2 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 3.81 (tt,  $J$  = 6.7, 4.0 Hz, 1 H, NCH(CH<sub>2</sub>)<sub>2</sub>), 3.70 (s, 3 H, CH<sub>3</sub>), 3.28 - 3.32 (m, 4 H, CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(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>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>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>N), 1.51 (quin,  $J$  = 7.2 Hz, 2 H, CH=CCH<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>)

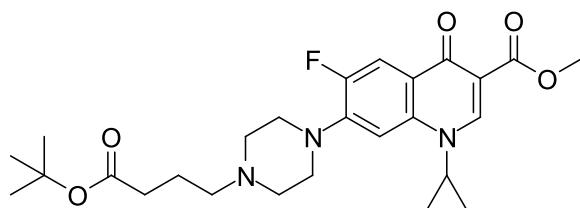
**<sup>13</sup>C NMR** (101 MHz, DMSO d<sub>6</sub>)  $\delta$  / ppm = 176.3 (C(=O)CC(=O)OH), 170.1 (NHC(=O)), 165.9 (C(=O)OH), 159.4 (*ipso* to OCH<sub>3</sub>), 153.0 (d,  $J$  = 248.6 Hz, *ipso* to F), 148.0 (CH=CCH<sub>2</sub>), 146.9 (C=CC(=O)OH), 145.2 (d,  $J$  = 10.7 Hz, *ipso* to piperazine), 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>N), 54.9 (CH<sub>3</sub>), 52.4 (CH=CCH<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>N(CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>)), 48.7 (C(=O)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>N), 26.8 (CH=CCH<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>N), 25.5 (C(=O)CH<sub>2</sub>CH<sub>2</sub>N), 24.9 (CH=CCH<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>)  $\delta$  / 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-(*tert*-butoxy)-4-oxobutyl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate 122



Methyl 1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate **103** (200 mg, 0.579 mmol, 1 eq.), *tert*-butyl 4-bromobutanoate **121** (103  $\mu$ l, 130 mg, 0.581 mmol, 1 eq.), NaI (86.9 mg, 0.580 mmol, 1 eq.), TEA (316  $\mu$ l, 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 **153** (103  $\mu$ l, 130 mg, 0.581 mmol, 1 eq.) was

added, and the mixture was stirred in the microwave reactor at 100 °C for a further 8 h. The mixture was then dry-loaded onto  $\text{SiO}_2$  and purified by column chromatography ( $\text{SiO}_2$ , 0-4 %  $\text{MeOH}/\text{CH}_2\text{Cl}_2$ ). **122** was obtained as a white amorphous solid (141 mg, 0.289 mmol, 49.9 %).

**TLC**  $R_f = 0.12$  (4 %  $\text{MeOH}/\text{CH}_2\text{Cl}_2$ )

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

**$^1\text{H NMR}$**  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  / 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>2</sub>)<sub>3</sub>)<sub>3</sub>), 1.24 (m, 2 H, NCH(CHH)<sub>2</sub>), 1.09 (m, 2 H, NCH(CHH)<sub>2</sub>)

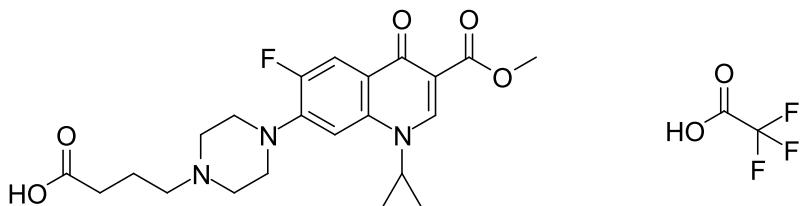
**$^{13}\text{C NMR}$**  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  / ppm = 172.7 (C(=O)CC(=O)OCH<sub>3</sub>), 172.6 (C(=O)OC(CH<sub>3</sub>)<sub>3</sub>), 165.9 (C(=O)OCH<sub>3</sub>), 153.1 (d,  $J = 249.7$  Hz, *ipso* to F), 148.1 (C=CC(=O)OCH<sub>3</sub>), 144.3 (d,  $J = 10.4$  Hz, *ipso* to piperazine), 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 (CC(=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>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 (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>)

**$^{19}\text{F NMR}$**  (376.45 MHz,  $\text{CDCl}_3$ )  $\delta$  / ppm = -123.5 (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 trifluoroacetate **123**



Methyl 7-(4-(4-(*tert*-butoxy)-4-oxobutyl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate **122** (20 mg, 41.0  $\mu\text{mol}$ ) and TFA (0.2 ml) were stirred in  $\text{CH}_2\text{Cl}_2$  (1.8 ml) at r.t. for 16 h then evaporated under reduced pressure. **123** was obtained as a white solid (21.4 mg, 39.2  $\mu\text{mol}$ , 95.6 %).

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

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

**<sup>1</sup>H NMR** (400 MHz, DMSO d<sub>6</sub>)  $\delta$  / 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(CHH)<sub>2</sub>), 1.06 - 1.15 (m, 2 H, NCH(CHH)<sub>2</sub>)

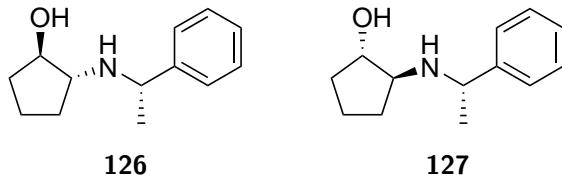
**<sup>13</sup>C NMR** (101 MHz, DMSO d<sub>6</sub>)  $\delta$  / ppm = 173.5 (CH<sub>2</sub>C(=O)OH), 171.6 (C(=O)CC(=O)OCH<sub>3</sub>), 164.9 (C(=O)OCH<sub>3</sub>), 158.2 (q,  $J$  = 31.5 Hz, CF<sub>3</sub>C(=O)OH), 152.5 (d,  $J$  = 247.6 Hz, *ipso* to F), 148.5 (C=CC(=O)OH), 142.3 (d,  $J$  = 10.7 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>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>)  $\delta$  / ppm = -73.6 (s, CF<sub>3</sub>), -124.6 (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.

**1.47 (1*R*,2*R*)-2-(((*S*)-1-Phenylethyl)amino)cyclopentan-1-ol 126 and (1*S*,2*S*)-2-((*S*)-1-phenylethyl)amino)cyclopentan-1-ol 127**



(*S*)-1-Phenylethan-1-amine **124** (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 mixture was stirred at 0 °C for 1 h. A solution of cyclohexene oxide **125** (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). **126** was obtained as a pale yellow oil (4.08 g, 19.9 mmol, 32.6 %). **127** was obtained as pale yellow crystals (4.48 g, 21.8 mmol, 35.8 %).

**(1*R*,2*R*)-2-(((*S*)-1-Phenylethyl)amino)cyclopentan-1-ol 126**

**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

$[\alpha]_D^{20}$  / °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*S*,2*S*)-2-((*S*)-1-Phenylethyl)amino)cyclopentan-1-ol 127**

TLC *R<sub>f</sub>* = 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)

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

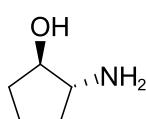
<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  / ppm = 145.61 (*ipso* to CHCH<sub>3</sub>), 128.08 (*meta* to CHCH<sub>3</sub>), 126.61 (*para* to CHCH<sub>3</sub>), 126.33 (*ortho* to CHCH<sub>3</sub>), 77.43 (CHOH), 64.45 (CHNH), 56.62 (CHCH<sub>3</sub>), 32.01 (CH<sub>2</sub>CHOH), 30.56 (CH<sub>2</sub>CHNH), 23.30 (CH<sub>3</sub>), 20.06 (CH<sub>2</sub>CH<sub>2</sub>CHOH)

HRMS (ESI<sup>+</sup>) *m/z* / Da = 206.1553, [M+H]<sup>+</sup> found, [C<sub>13</sub>H<sub>20</sub>NO]<sup>+</sup> requires 206.1545

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

The compounds have been synthesised previously,<sup>14,15</sup> but NMR data were not published. The enantiomers of both compounds have also been synthesised previously, and the <sup>1</sup>H NMR data for these are consistent with the the above data.<sup>16</sup>

**1.48 (1*R*,2*R*)-2-Aminocyclopentan-1-ol 128**



(1*R*,2*R*)-2-(((*S*)-1-Phenylethyl)amino)cyclopentan-1-ol **126** (3.90 g, 19.0 mmol, 1 eq.), Pd(OH)<sub>2</sub> (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. **128** was obtained as a yellow oil (1.92 g, 19.0 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 (br, O-H), 2958.3 (C-H), 2871.5 (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*=7.3, 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, 6.6, 6.6 Hz, 1 H, CHHCHOH), 1.63 - 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*=13.0, 8.3, 7.8, 7.8 Hz, 1 H, CHHCHNH<sub>2</sub>)

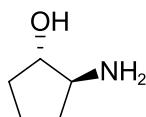
**<sup>13</sup>C NMR** (101 MHz, MeOD)  $\delta$  / ppm = 80.7 (CHOH), 60.8 (CHNH<sub>2</sub>), 33.2 (CH<sub>2</sub>CHOH), 32.1 (CH<sub>2</sub>CHNH<sub>2</sub>), 21.2 (CH<sub>2</sub>CH<sub>2</sub>CHOH)

**HRMS** (ESI<sup>+</sup>) *m/z* / Da = 102.0917, [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> = -30.9 (*c* / g(100 ml)<sup>-1</sup> = 1.5, EtOH)

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

#### 1.49 (1*S*,2*S*)-2-Aminocyclopentan-1-ol **129**



(1*S*,2*S*)-2-(((*S*)-1-Phenylethyl)amino)cyclopentan-1-ol **127** (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. **129** 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>)

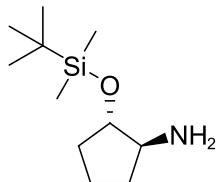
**<sup>13</sup>C NMR** (101 MHz, MeOD)  $\delta$  / ppm = 80.6 (CHOH), 60.7 (CHNH<sub>2</sub>), 33.2 (CH<sub>2</sub>CHOH), 32.2 (CH<sub>2</sub>CHNH<sub>2</sub>), 21.2 (CH<sub>2</sub>CH<sub>2</sub>CHOH)

**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

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

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

### 1.50 (1*S*,2*S*)-2-((*tert*-Butyldimethylsilyl)oxy)cyclopentan-1-amine 130



(1*S*,2*S*)-2-Aminocyclopentan-1-ol **129** (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>). **130** was obtained as a yellow oil (1.00 g, 4.64 mmol, 97.7 %).

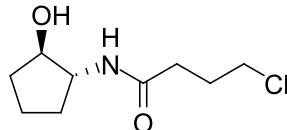
**TLC**  $R_f = 0.23$  (10 % MeOH/CH<sub>2</sub>Cl<sub>2</sub>)

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

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

The compound has not been reported previously.

### 1.51 4-Chloro-*N*-((1*R*,2*R*)-2-hydroxycyclopentyl)butanamide 132



(1*R*,2*R*)-2-Aminocyclopentan-1-ol **128** (500 mg, 4.94 mmol, 1 eq.), TEA (827  $\mu$ l, 600 mg, 5.93 mmol, 1.2 eq.) and CH<sub>2</sub>Cl<sub>2</sub> (20 ml) were stirred at 0 °C and 4-chlorobutyryl chloride **131** (608  $\mu$ l, 766 mg, 5.43 mmol, 1.1 eq.) was added dropwise over 5 min. The mixture was stirred at 0 °C for 30 min, then water (50 ml) was added. The organic layer was separated off, and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (7×50 ml). The combined organic layers were dried with MgSO<sub>4</sub>, concentrated under reduced pressure and purified by column chromatography (SiO<sub>2</sub>, Et<sub>2</sub>O). The combined pure fractions were dried with MgSO<sub>4</sub> and evaporated under

reduced pressure. **132** was obtained as a white amorphous solid (651 mg, 3.16 mmol, 64.1 %).

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

**IR** (neat)  $\nu_{max} / \text{cm}^{-1} = 3277.6$  (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>)  $\delta / \text{ppm} = 6.12$  (br s, 1 H, NH), 4.42 (br s, 1 H, OH), 3.94 (q,  $J = 6.6$  Hz, 1 H, CH<sub>OH</sub>), 3.82 (tt,  $J = 8.4, 5.3$  Hz, 1 H, CHNH), 3.60 (t,  $J = 6.2$  Hz, 2 H, CH<sub>2</sub>Cl), 2.38 (t,  $J = 7.2$  Hz, 2 H, CH<sub>2</sub>C=O), 2.05 - 2.16 (m, 3 H, CHHCHNH and CH<sub>2</sub>CH<sub>2</sub>Cl), 1.96 - 2.04 (m, 1 H, CHHCHOH), 1.74 - 1.85 (m, 1 H, CHHCH<sub>2</sub>CHOH), 1.58 - 1.73 (m, 2 H, CHHCH<sub>2</sub>CHOH and CHHCHOH), 1.43 (dq,  $J = 12.7, 8.3$  Hz, 1 H, CHHCHNH)

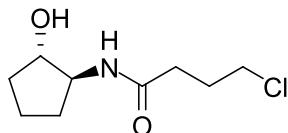
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta / \text{ppm} = 173.8$  (C=O), 79.4 (CHOH), 60.6 (CHNH), 44.4 (CH<sub>2</sub>Cl), 32.8 (CH<sub>2</sub>C=O), 32.4 (CH<sub>2</sub>CHOH), 30.1 (CH<sub>2</sub>CHNH), 28.0 (CH<sub>2</sub>CH<sub>2</sub>Cl), 21.1 (CH<sub>2</sub>CH<sub>2</sub>CHOH)

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

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

The compound has not been reported previously.

## 1.52 4-Chloro-*N*-(*(1S,2S)*-2-hydroxycyclopentyl)butanamide **133**



(*1S,2S*)-2-Aminocyclopentan-1-ol **129** (72.3 mg, 716  $\mu\text{mol}$ , 1 eq.), TEA (500  $\mu\text{l}$ , 363 mg, 3.58 mmol, 5 eq.) and CH<sub>2</sub>Cl<sub>2</sub> (5 ml) were stirred at 0 °C, and 4-chlorobutyryl chloride **131** (179  $\mu\text{l}$ , 226 mg, 1.60 mmol, 1.1 eq.) was added dropwise over 5 min. The mixture was stirred at 0 °C for 30 min, then water (10 ml) was added. The organic layer was separated off, and the aqueous layer was extracted with 10 % *i*-PrOH/CHCl<sub>3</sub> (2×10 ml). The combined organic layers were dried with MgSO<sub>4</sub>, concentrated under reduced pressure and purified by column chromatography (SiO<sub>2</sub>, Et<sub>2</sub>O). The combined pure fractions were dried with MgSO<sub>4</sub> and evaporated under reduced pressure. **133** was obtained as a white amorphous solid (35.6 mg, 173  $\mu\text{mol}$ , 24.2 %).

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

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta / \text{ppm} = 6.05$  (br s, 1 H, NH), 4.55 (br s, 1 H, OH), 3.95 (q,  $J=6.6$  Hz, 1 H, CH<sub>OH</sub>), 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,  $J=7.0$  Hz, 2 H, CH<sub>2</sub>C=O), 2.05 - 2.17 (m, 3 H, CHHCHNH and CH<sub>2</sub>CH<sub>2</sub>Cl), 1.94 - 2.05 (m, 1 H, CHHCHOH), 1.74 - 1.86 (m, 1 H, CHHCH<sub>2</sub>CHOH), 1.58 - 1.74 (m, 2 H, CHHCH<sub>2</sub>CHOH and CHHCHOH), 1.42 (dq,  $J=12.5, 8.4$  Hz, 1 H, CHHCHNH)

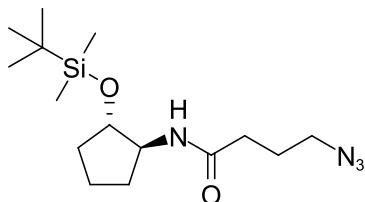
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta / \text{ppm} = 173.8$  (C=O), 79.4 (CHOH), 60.6 (CHNH), 44.4 (CH<sub>2</sub>Cl), 32.8 (CH<sub>2</sub>C=O), 32.4 (CH<sub>2</sub>CHOH), 30.2 (CH<sub>2</sub>CHNH), 28.0 (CH<sub>2</sub>CH<sub>2</sub>Cl), 21.2 (CH<sub>2</sub>CH<sub>2</sub>CHOH)

**HRMS** (ESI<sup>+</sup>)  $m/z$  / Da = 206.0939, [M+H]<sup>+</sup> found, [C<sub>9</sub>H<sub>17</sub>ClNO<sub>2</sub>]<sup>+</sup> 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)

The compound has not been reported previously.

**1.53 4-Azido-*N*-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclopentyl)butanamide 134**



(1*S*,2*S*)-2-((*tert*-Butyldimethylsilyl)oxy)cyclopentan-1-amine **130** (50 mg, 0.232 mmol, 1 eq.) and NaHCO<sub>3</sub> (22.0 mg, 0.262 mmol, 1.1 eq.) were added to CH<sub>2</sub>Cl<sub>2</sub> (3 ml) and water (3 ml) at 0 °C, and 4-bromobutyryl chloride (25.3 ml, 40.5 mg, 0.219 mmol, 0.95 eq.) was added dropwise. The mixture was stirred for 3 h at 0 °C. The aqueous layer was removed and NaN<sub>3</sub> (100 mg, 1.54 mmol, 6.6 eq.) and DMF (3 ml) were added. The mixture was then stirred at 40 °C for 6 h. The solvents were then evaporated using a N<sub>2</sub> stream and the residue was purified by column chromatography (SiO<sub>2</sub>, 0.5 % MeOH/CH<sub>2</sub>Cl<sub>2</sub>). The combined pure fractions were dried with MgSO<sub>4</sub> and evaporated under reduced pressure. **134** was obtained as a clear liquid (71 mg, 0.217 mmol, 99.2 %).

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

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

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta / \text{ppm} = 5.35$  (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>)

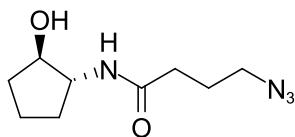
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta / \text{ppm} = 171.17$  (C=O), 77.80 (CHOSi), 58.36 (CHNH), 50.77 (CH<sub>2</sub>N<sub>3</sub>), 33.29 (CH<sub>2</sub>C=O), 32.57 (CH<sub>2</sub>CHOSi), 29.36 (CH<sub>2</sub>CHNH), 25.72 (C(CH<sub>3</sub>)<sub>3</sub>), 24.77 (CH<sub>2</sub>CH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

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

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

The compound has not been reported previously.

## 1.54 4-Azido-*N*-(*(1R,2R)*-2-hydroxycyclopentyl)butanamide 135



4-Chloro-*N*-(*(1R,2R)*-2-hydroxycyclopentyl)butanamide **132** (200 mg, 0.972 mmol, 1 eq.) and  $\text{NaN}_3$  (126 mg, 1.94 mmol, 2 eq.) were stirred in acetonitrile (4 ml) at 50 °C for 16 h. The solvent was then evaporated under reduced pressure and the residue was partitioned between water (20 ml) and 10 % *i*-PrOH/CHCl<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. **135** was obtained as white needles (181 mg, 0.852 mmol, 87.6 %).

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

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

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

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

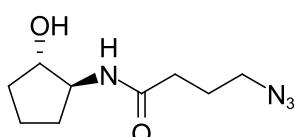
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  / ppm = 173.8 (C=O), 78.8 (CHOH), 59.9 (CHNH), 50.5 (CH<sub>2</sub>N<sub>3</sub>), 32.5 (CH<sub>2</sub>C=O), 32.0 (CH<sub>2</sub>CHOH), 29.5 (CH<sub>2</sub>CHNH), 24.6 (CH<sub>2</sub>CH<sub>2</sub>N<sub>3</sub>), 20.7 (CH<sub>2</sub>CH<sub>2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

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

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

The compound has not been reported previously.

## 1.55 4-Azido-*N*-(*(1S,2S)*-2-hydroxycyclopentyl)butanamide 136



4-Chloro-*N*-(*(1S,2S)*-2-hydroxycyclopentyl)butanamide **133** (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 °C for 24 h. The reaction mixture was then partitioned between water (20 ml) and 10 % *i*-PrOH/CHCl<sub>3</sub> (5 ml). The aqueous layer was extracted again with 10 % *i*-PrOH/CHCl<sub>3</sub> (2×5 ml) and the combined organic fractions were dried with MgSO<sub>4</sub> and evaporated under

reduced pressure. **136** was obtained as white needles (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, NH), 4.45 (br. s., 1 H, OH), 3.96 (q,  $J=6.6$  Hz, 1 H,  $\text{CH}_2\text{OH}$ ), 3.83 (td,  $J=8.5, 8.5, 6.0, 4.6$  Hz, 1 H,  $\text{CH}_2\text{NH}$ ), 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,  $\text{CH}_2\text{CH}_2\text{NH}$ ), 1.99 - 2.06 (m, 1 H,  $\text{CH}_2\text{CH}_2\text{OH}$ ), 1.90 - 1.97 (m, 2 H,  $\text{CH}_2\text{CH}_2\text{N}_3$ ), 1.60 - 1.85 (m, 3 H,  $\text{CH}_2\text{CH}_2\text{CHOH}$ ), 1.42 (dq,  $J=12.8, 8.3$  Hz, 1 H,  $\text{CH}_2\text{CH}_2\text{NH}$ )

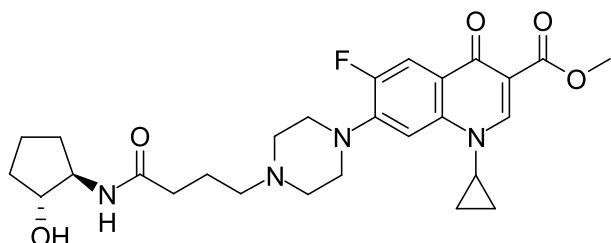
**$^{13}\text{C NMR}$**  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  / ppm = 173.8 (C=O), 79.7 (CHOH), 61.0 (CHNH), 50.7 (CH<sub>2</sub>N<sub>3</sub>), 32.8 (CH<sub>2</sub>C=O), 32.6 (CH<sub>2</sub>CHOH), 30.5 (CH<sub>2</sub>CHNH), 24.7 (CH<sub>2</sub>CH<sub>2</sub>N<sub>3</sub>), 21.3 (CH<sub>2</sub>CH<sub>2</sub>CHOH)

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

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

The compound has not been reported previously.

### 1.56 Methyl 1-cyclopropyl-6-fluoro-7-(4-((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-4-oxobutyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate **137**



4-(4-(1-Cyclopropyl-6-fluoro-3-(methoxycarbonyl)-4-oxo-1,4-dihydroquinolin-7-yl)piperazin-1-yl)butanoic acid trifluoroacetate **123** (200 mg, 0.367 mmol, 1 eq.), (1*R*,2*R*)-2-aminocyclopentan-1-ol **128** (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  $\mu\text{l}$ , 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  $\text{N}_2$  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  $\text{NaHCO}_3$  (aq., sat., 10 ml) and  $\text{CH}_2\text{Cl}_2$  (10 ml). The organic layer was removed and the aqueous layer was extracted twice more with  $\text{CH}_2\text{Cl}_2$  (2  $\times$  10 ml). The combined organic fractions were dried with  $\text{MgSO}_4$  and evaporated under reduced pressure. **137** 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)  $\nu_{max}$  /  $\text{cm}^{-1} = 2972.9$  (C-H), 2901.5 (C-H), 1728.4 (ester C=O), 1656.3 (amide C=O), 1612.9 (quinolone C=O)

**<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, CHO<sub>H</sub>), 3.78 - 3.82 (m, 1 H, CHO<sub>H</sub>), 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(CHH)<sub>2</sub>), 1.07 - 1.13 (m, 2 H, NCH(CHH)<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 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 52.4 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 51.3 (CH<sub>3</sub>), 49.6 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 34.8 (NCH(CH<sub>2</sub>)<sub>2</sub>), 33.3 (C(=O)CH<sub>2</sub>), 32.2 (CH<sub>2</sub>CHOH), 29.5 (CH<sub>2</sub>CHNH), 22.5 (C(=O)CH<sub>2</sub>CH<sub>2</sub>), 20.6 (CH<sub>2</sub>CH<sub>2</sub>CHOH), 7.6 (NCH(CH<sub>2</sub>)<sub>2</sub>)

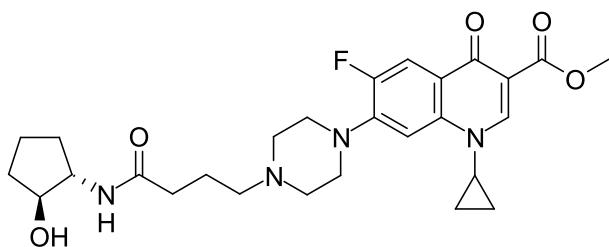
**<sup>19</sup>F NMR** (376.45 MHz, DMSO d<sub>6</sub>)  $\delta$  / ppm = -124.3 (ciprofloxacin F)

**HRMS (ESI<sup>+</sup>)** *m/z* / Da = 515.2661, [M+H]<sup>+</sup> found, [C<sub>27</sub>H<sub>36</sub>FN<sub>4</sub>O<sub>5</sub>]<sup>+</sup> requires 515.2670

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

The compound has not been reported previously.

### 1.57 Methyl 1-cyclopropyl-6-fluoro-7-(4-((1*S*,2*S*)-2-hydroxycyclopentyl)amino)-4-oxobutyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 138



4-(4-(1-Cyclopropyl-6-fluoro-3-(methoxycarbonyl)-4-oxo-1,4-dihydroquinolin-7-yl)piperazin-1-yl)butanoic acid trifluoroacetate **123** (52.1 mg, 95.5  $\mu$ mol, 1 eq.), (1*S*,2*S*)-2-aminocyclopentan-1-ol **129** (19.5 mg, 193  $\mu$ mol, 2 eq.), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (29.7 mg, 155  $\mu$ mol, 1.6 eq.), 1-hydroxybenzotriazole (25.8 mg, 191  $\mu$ mol, 2 eq.) and DIPEA (33.3  $\mu$ l, 24.7 mg, 191  $\mu$ 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 N<sub>2</sub> 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 NaHCO<sub>3</sub> (aq., sat., 5 ml) and CH<sub>2</sub>Cl<sub>2</sub> (5 ml). The organic layer was removed and the aqueous layer was extracted twice more with CH<sub>2</sub>Cl<sub>2</sub> (2  $\times$  5 ml). The combined organic fractions were dried with MgSO<sub>4</sub> and evaporated under reduced pressure. **138** was obtained as a white amorphous solid (4.9 mg, 9.5  $\mu$ mol, 9.9 %).

**TLC**  $R_f = 0.38$  (30 % MeOH/CH<sub>2</sub>Cl<sub>2</sub>)

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

**<sup>1</sup>H NMR** (500 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), 7.69 (d, J=6.9 Hz, 1 H, CHNH), 7.43 (d, J=7.6 Hz, 1 H, *meta* to F), 4.73 (br s, 1 H, CHOH), 3.77 - 3.81 (m, 1 H, CHOH), 3.74 - 3.77 (m, 1 H, CHNH), 3.73 (s, 3 H, CH<sub>3</sub>), 3.65 (tt, J=6.9, 4.0 Hz, 1 H, NCH(CH<sub>2</sub>)<sub>2</sub>), 3.24 (br. t, J=4.2, 4.2 Hz, 4 H, CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 2.55 (br t, J=5.0, 5.0 Hz, 4 H, CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 2.32 (t, J=7.2 Hz, 2 H, CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 2.10 (t, J=7.4 Hz, 2 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 1.92 (dddd, J=13.0, 8.7, 7.3, 6.0 Hz, 1 H, CHHCHNH), 1.77 (ddt, J=12.6, 8.9, 6.3, 6.3 Hz, 1 H, CHHCHOH), 1.68 (quin, J=7.4 Hz, 2 H, CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 1.53 - 1.64 (m, 2 H, CH<sub>2</sub>CH<sub>2</sub>CHOH), 1.42 (ddt, J=12.9, 8.4, 5.2, 5.2 Hz, 1 H, CHHCHOH), 1.31 (ddt, J=13.0, 8.6, 6.4, 6.4 Hz, 1 H, CHHCHNH), 1.22 - 1.28 (m, 2 H, NCH(CHH)<sub>2</sub>), 1.06 - 1.12 (m, 2 H, NCH(CHH)<sub>2</sub>)

**<sup>13</sup>C NMR** (126 MHz, DMSO d<sub>6</sub>)  $\delta$  / ppm = 171.9 (NHC(=O)CH<sub>2</sub>), 171.5 (C(=O)CC(=O)OCH<sub>3</sub>), 165.0 (C(=O)OCH<sub>3</sub>), 152.6 (d, J=247.4 Hz, *ipso* to F), 148.2 (C=CC(=O)OCH<sub>3</sub>), 143.9 (d, J=10.3 Hz, *ipso* to piperazine), 138.1 (*para* to F), 121.7 (d, J=6.4 Hz, *para* to piperazine), 111.5 (d, J=23.0 Hz, *ortho* to C=O and *ortho* to F), 109.0 (CC(=O)OCH<sub>3</sub>), 106.2 (*meta* to C=O and *meta* to F), 76.2 (CHOH), 57.6 (CHNH), 57.2 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 52.4 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 51.3 (CH<sub>3</sub>), 49.6 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 49.6 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 34.7 (NCH(CH<sub>2</sub>)<sub>2</sub>), 33.2 (C(=O)CH<sub>2</sub>), 32.2 (CH<sub>2</sub>CHOH), 29.5 (CH<sub>2</sub>CH NH), 22.5 (C(=O)CH<sub>2</sub>CH<sub>2</sub>), 20.6 (CH<sub>2</sub>CH<sub>2</sub>CHOH), 7.5 (NCH(CH<sub>2</sub>)<sub>2</sub>)

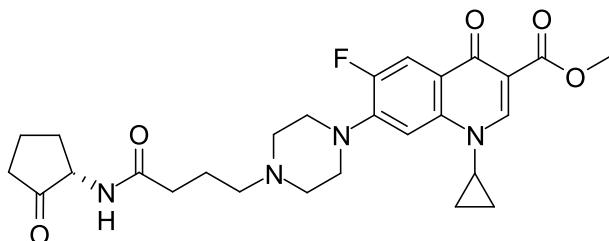
**<sup>19</sup>F NMR** (376.45 MHz, MeOD)  $\delta$  / ppm = -125.5

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

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

The compound has not been reported previously.

**1.58 Methyl (S)-1-cyclopropyl-6-fluoro-4-oxo-7-(4-(4-oxo-4-((2-oxocyclopentyl)amino)butyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate 139**



Methyl 1-cyclopropyl-6-fluoro-7-(4-((1*S*,2*S*)-2-hydroxycyclopentyl)amino)-4-oxobutyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate **138** (20.0 mg, 38.9  $\mu$ mol, 1 eq.) and Dess-Martin Periodane (32.8 mg, 77.4  $\mu$ mol, 2 eq.) were stirred in CH<sub>2</sub>Cl<sub>2</sub> (3 ml) for 6 h. The solvent was removed under reduced pressure and the residue was purified by preparatory HPLC (5-50 % acetonitrile/water over 10 min). The combined pure fractions were evaporated under reduced pressure, then NaHCO<sub>3</sub> (aq., sat., 30 ml) and 10 % *i*-PrOH/CHCl<sub>3</sub> (30 ml) were added. The organic layer was removed and dried with MgSO<sub>4</sub>, then evaporated under reduced pressure.

**139** was obtained as a white amorphous solid (11.3 mg, 22.0  $\mu\text{mol}$ , 56.7 %).

**<sup>1</sup>H NMR** (500 MHz, DMSO d<sub>6</sub>)  $\delta$  / ppm = 8.46 (s, 1 H, *ortho* to C(=O)OCH<sub>3</sub>), 7.78 (d, J=13.5 Hz, 1 H, *ortho* to F), 7.45 (d, J=7.4 Hz, 1 H, *meta* to F), 4.02 (dt, J=11.1, 8.2 Hz, 1 H, CHNH), 3.73 (s, 3 H, CH<sub>3</sub>), 3.65 (tt, J=6.9, 3.9 Hz, 1 H, NCH(CH<sub>2</sub>)<sub>2</sub>), 3.40 (s, 10 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 2.05 - 2.29 (m, 5 H, NHC(=O)CH<sub>2</sub>, CH<sub>2</sub>C(=O)CHNH and CHHCHNH), 1.89 - 1.96 (m, 1 H, CHHCH<sub>2</sub>CHNH), 1.69 - 1.80 (m, 3 H, CHHCH<sub>2</sub>CHNH, CHHCHNH and NHC(=O)CH<sub>2</sub>CH<sub>2</sub>), 1.24 - 1.29 (m, 2 H, NCH(CHH)<sub>2</sub>), 1.07 - 1.12 (m, 2 H, NCH(CHH)<sub>2</sub>)

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

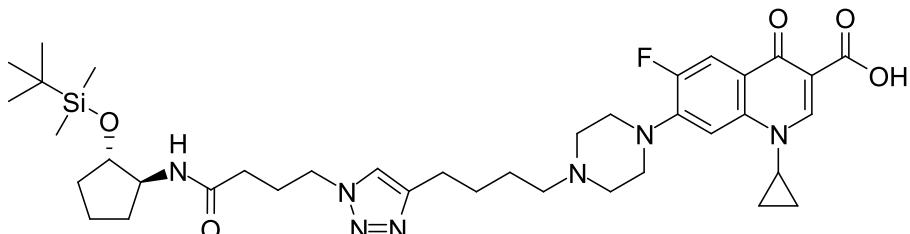
**<sup>19</sup>F NMR** (376.45 MHz, MeOD)  $\delta$  / ppm = -124.3

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

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

The compound has not been reported previously.

**1.59 7-(4-(1-(4-(((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclopentyl)amino)-4-oxobutyl)-1*H*-1,2,3-triazol-4-ylbutyl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 140**



1-Cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **91** (42.9 mg, 104  $\mu\text{mol}$ , 1 eq.) and 4-azido-*N*-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclopentyl)butanamide **134** (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 N<sub>2</sub> through it. A solution of CuSO<sub>4</sub> 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 CH<sub>2</sub>Cl<sub>2</sub> (10 ml), the organic layer was separated and the aqueous layer was extracted again with CH<sub>2</sub>Cl<sub>2</sub> (10 ml). The combined organic layers were dried with MgSO<sub>4</sub> and evaporated under reduced pressure. **140** was obtained as a clear glass (67.1 mg, 90.9  $\mu\text{mol}$ , 87.4 %).

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

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

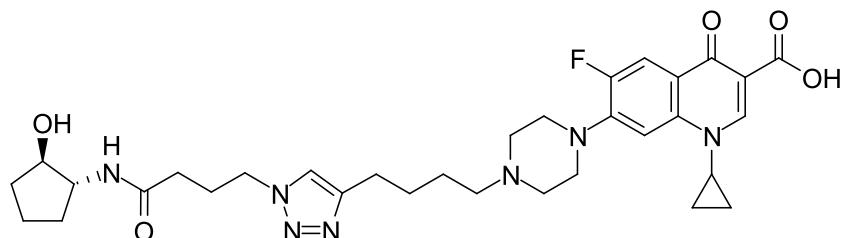
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  / ppm = 176.9 (C(=O)CC(=O)OH), 170.9 (CH<sub>2</sub>C(=O)NH), 166.9 (C(=O)OH), 153.5 (d,  $J$  = 251.4 Hz, *ipso* to F), 147.9 (CH=CCH<sub>2</sub>), 147.2 (C=CC(=O)OH), 145.8 (d,  $J$  = 10.4 Hz, *ipso* to piperazine), 139.0 (*para* to F), 120.9 (NCH=CCH<sub>2</sub>), 119.4 (d,  $J$  = 7.8 Hz, *para* to piperazine), 112.0 (d,  $J$  = 23.4 Hz, *ortho* to C=O and *ortho* to F), 107.7 (CC(=O)OH), 104.7 (d,  $J$  = 3.5 Hz, *meta* to C=O and *meta* to F), 77.7 (CHOSi), 58.2 (CHNH), 57.9 (CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 52.6 (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,  $J$  = 6.1 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>), 48.9 (d,  $J$  = 3.5 Hz, CH<sub>2</sub>NCH=CCH<sub>2</sub>), 35.3 (NCH(CH<sub>2</sub>)<sub>2</sub>), 32.6 (C(=O)CH<sub>2</sub>), 32.6 (CH<sub>2</sub>CHOSi), 29.3 (CH<sub>2</sub>CHNH), 27.2 (CH=CCH<sub>2</sub>CH<sub>2</sub>), 26.0 - 26.3 (C(=O)CH<sub>2</sub>CH<sub>2</sub> and CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 25.6 (C(CH<sub>3</sub>)<sub>3</sub>), 25.4 (CH=CCH<sub>2</sub>), 20.4 (CH<sub>2</sub>CH<sub>2</sub>CHOSi), 17.8 (C(CH<sub>3</sub>)<sub>3</sub>), 8.1 (NCH(CH<sub>2</sub>)<sub>2</sub>), -4.8 (SiCH<sub>3</sub>)

**HRMS (ESI<sup>+</sup>)**  $m/z$  / Da = 738.4164, [M+H]<sup>+</sup> found, [C<sub>38</sub>H<sub>57</sub>FN<sub>7</sub>O<sub>5</sub>Si]<sup>+</sup> requires 738.4169

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

The compound has not been reported previously.

**1.60 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 141**



1-Cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **91** (42.9 mg, 104  $\mu$ mol, 1 eq.) and 4-azido-*N*-(*1R,2R*)-2-hydroxycyclopentyl)butanamide **135** (22.0 mg, 104  $\mu$ 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 (104  $\mu$ l, 10.4  $\mu$ mol, 0.1 eq. 100 mM, aq.) was added, followed by a solution of sodium ascorbate (208  $\mu$ l, 20.8  $\mu$ mol, 0.2 eq., 100 mM, aq.). The mixture was stirred at room temperature under argon for 16 h. Water (30 ml) and CH<sub>2</sub>Cl<sub>2</sub> (30 ml) were added, the organic layer was separated and the aqueous layer was extracted again with CH<sub>2</sub>Cl<sub>2</sub> (4×30 ml). The combined organic layers were dried with MgSO<sub>4</sub> and evaporated under reduced pressure. The residue was purified by preparatory HPLC (5-95 % acetonitrile/water over 20 min). The combined pure fractions were evaporated under reduced pressure and then

partitioned between  $\text{NaHCO}_3$  (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. **141** was obtained as a white amorphous solid (17.6 mg, 28.2  $\mu\text{mol}$ , 27.1 %).

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

**<sup>1</sup>H NMR** (700 MHz, DMSO d<sub>6</sub>)  $\delta$  / ppm = 8.64 (s, 1 H, *ortho* to C(=O)OH), 7.87 (d,  $J$  = 13.3 Hz, 1 H, *ortho* to F), 7.84 (s, 1 H, CH=CCH<sub>2</sub>), 7.75 (d,  $J$  = 7.1 Hz, 1 H, CHNH), 7.54 (d,  $J$  = 7.5 Hz, 1 H, *meta* to F), 4.73 (d,  $J$  = 3.8 Hz, 1 H, CHOH), 4.29 (t,  $J$  = 6.9 Hz, 2 H, CH<sub>2</sub>NCH=C), 3.78 - 3.83 (m, 1 H, NCH(CH<sub>2</sub>)<sub>2</sub>), 3.75 - 3.78 (m, 1 H, CHOH), 3.71 - 3.75 (m, 1 H, CHNH), 3.31 (br t,  $J$  = 4.3 Hz, 4 H, CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH2), 2.63 (t,  $J$  = 7.5 Hz, 2 H, CH=CCH<sub>2</sub>), 2.56 (br t,  $J$  = 4.2 Hz, 4 H, CH<sub>2</sub>N(CH<sub>2</sub>)CH2), 2.37 (t,  $J$  = 7.3 Hz, 2 H, CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 2.03 - 2.06 (m, 2 H, C(=O)CH<sub>2</sub>), 1.97 - 2.02 (m, 2 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>), 1.89 (dd,  $J$  = 13.1, 8.9, 7.4, 5.7 Hz, 1 H, CHHCHNH), 1.75 (ddt,  $J$  = 13.0, 8.9, 6.4, 6.4 Hz, 1 H, CHHCHOH), 1.61 - 1.66 (m, 2 H, CH=CCH<sub>2</sub>CH<sub>2</sub>), 1.57 - 1.61 (m, 1 H, CH2HCH<sub>2</sub>CHOH), 1.54 - 1.57 (m, 1 H, CH2HCH<sub>2</sub>CHOH), 1.49 - 1.53 (m, 2 H, CH=CCH<sub>2</sub>CH<sub>2</sub>CH2), 1.40 (ddt,  $J$  = 13.0, 8.4, 5.3, 5.3 Hz, 1 H, CH2HCHOH), 1.29 - 1.32 (m, 2 H, NCH(CHH)<sub>2</sub>), 1.25 - 1.29 (m, 1 H, CH2HCHNH), 1.13 - 1.20 (m, 2 H, NCH(CHH)<sub>2</sub>)

**<sup>13</sup>C NMR** (175 MHz, DMSO d<sub>6</sub>)  $\delta$  / ppm = 176.3 (C(=O)CC(=O)OH), 170.9 (NHC(=O)CH<sub>2</sub>), 166.1 (C(=O)OH), 153.0 (d,  $J$  = 251.4 Hz, *ipso* to F), 147.9 (C=CC(=O)OH), 146.9 (CH=CCH<sub>2</sub>), 145.2 (d,  $J$  = 8.7 Hz, *ipso* to piperazine), 139.2 (*para* to F), 121.7 (NCH=CCH<sub>2</sub>), 118.7 (d,  $J$  = 5.8 Hz, *para* to piperazine), 111.0 (d,  $J$  = 23.3 Hz, *ortho* to C=O and *ortho* to F), 106.3 (*meta* to C=O and *meta* to F and CC(=O)OH), 76.2 (CHOH), 57.6 (CHNH), 57.4 (CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 52.5 (CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 49.5 (d,  $J$  = 4.4 Hz, CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH2), 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>CH2), 25.0 (CH=CCH<sub>2</sub>), 20.5 (CH<sub>2</sub>CH<sub>2</sub>CHOH), 7.6 (NCH(CH<sub>2</sub>)<sub>2</sub>)

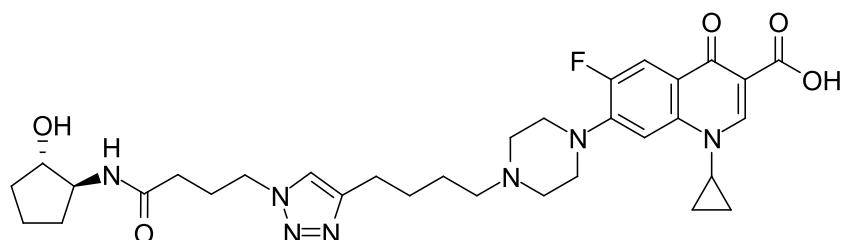
**<sup>19</sup>F NMR** (376.45 MHz, MeOD)  $\delta$  / ppm = -122.1 (s, ciprofloxacin F)

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

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

The compound has not been reported previously.

**1.61 1-Cyclopropyl-6-fluoro-7-(4-(4-((1*S*,2*S*)-2-hydroxycyclopentyl)amino)-4-oxobutyl)-1*H*-1,2,3-triazol-4-ylbutyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **142****



1-Cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **91** (82.0 mg, 199  $\mu$ mol, 4 eq.) and 4-azido-*N*-((1*S*,2*S*)-2-hydroxycyclopentyl)butanamide **136** (11.0 mg, 51.8  $\mu$ mol, 1 eq.) were dissolved in 10 % water/*t*-BuOH (3 ml), and the mixture was degassed by bubbling  $N_2$  through it. A solution of CuSO<sub>4</sub> and THPTA (156  $\mu$ l, 15.6  $\mu$ mol, 0.3 eq. 100 mM, aq.) was added, followed by a solution of sodium ascorbate (312  $\mu$ l, 31.2  $\mu$ mol, 0.6 eq., 100 mM, aq.). The mixture was stirred at room temperature under argon for 3 d. Water (10 ml) and 10 % *i*-PrOH/CHCl<sub>3</sub> (10 ml) were added, then the organic layer was separated and dried with MgSO<sub>4</sub> and evaporated under reduced pressure. The residue was purified by preparatory HPLC (5-95 % acetonitrile/water over 20 min). The combined pure fractions were evaporated under reduced pressure and then partitioned between NaHCO<sub>3</sub> (aq., sat., 10 ml) and 10 % *i*-PrOH/CHCl<sub>3</sub> (10 ml). The organic layer was dried with MgSO<sub>4</sub> and evaporated under reduced pressure. **142** was obtained as a white amorphous solid (7.2 mg, 11.5  $\mu$ mol, 22.2 %).

**IR** (neat)  $\nu_{max}$  / cm<sup>-1</sup> = 2954.9 (C-H), 2917.9 (C-H), 2850.2 (C-H), 1722.1 (carboxylic acid C=O), 1647.3 (amide C=O), 1626.7 (quinolone C=O) 1611.9 (triazole)

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

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

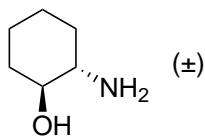
**<sup>19</sup>F NMR** (376.45 MHz, MeOD)  $\delta$  / ppm = -121.5

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

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

The compound has not been reported previously.

## 1.62 (*trans*)-2-Aminocyclohexan-1-ol 144



Cyclohexene oxide **143** (10 ml, 9.70 g, 98.8 mmol, 1 eq.), NH<sub>3</sub> (90 ml, 35 % w/w aq., 27.7 g, 791 mmol, 8 eq.) and MeOH (100 ml) were stirred at r.t. for 72 h. The solvent was removed by blowing a stream of N<sub>2</sub> over it, followed by evaporation under high vacuum. **144** was obtained as white needles (9.90 g, 85.2 mmol, 86.2 %)

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

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

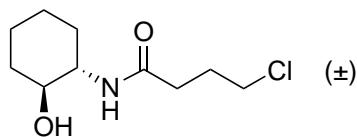
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  / ppm = 3.01 (td,  $J$  = 9.4, 4.8 Hz, 1 H, CHOH), 2.80 - 2.92 (m, 2 H, OH and NH<sub>2</sub>), 2.35 (ddd,  $J$  = 11.1, 9.1, 4.1 Hz, 1 H, CHNH<sub>2</sub>), 1.77 - 1.84 (m, 1 H, CHHCHOH), 1.69 - 1.76 (m, 1 H, CHHCHNH<sub>2</sub>), 1.56 - 1.66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

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

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

The data are consistent with the literature.<sup>18</sup>

## 1.63 4-Chloro-*N*-((*trans*)-2-hydroxycyclohexyl)butanamide 145



(*trans*)-2-Aminocyclohexan-1-ol **144** (1.04 g, 9.03 mmol, 1 eq.), TEA (1.65 ml, 1.20 g, 11.8 mmol, 1.3 eq.) and CH<sub>2</sub>Cl<sub>2</sub> (50 ml) were stirred at 0 °C. 4-Chlorobutyryl chloride **131** (1.22 ml, 1.54 g, 10.9 mmol, 1.2 eq.) was added dropwise over 5 min. The mixture was stirred at 0 °C for 30 min, then water (50 ml) was added. The organic layer was separated off, and the aqueous layer was extracted with 10 % *i*-PrOH/CHCl<sub>3</sub> (2×50 ml). The combined organic layers were dried with MgSO<sub>4</sub>, concentrated under reduced pressure and purified by column chromatography (SiO<sub>2</sub>, 0-100 % EtOAc/Et<sub>2</sub>O). The combined organic fractions were dried with MgSO<sub>4</sub> and evaporated under reduced pressure. **145** was obtained as white needles (1.51 g, 6.87 mmol, 76.1 %).

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

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

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

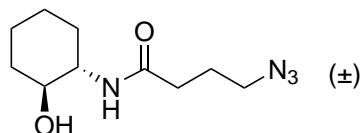
**<sup>1</sup>H NMR** (400 MHz, MeOD)  $\delta$  / ppm = 3.60 (t,  $J$  = 6.6 Hz, 2 H,  $\text{CH}_2\text{Cl}$ ), 3.51 - 3.60 (m, 1 H,  $\text{CH}_\text{NH}$ ), 3.28 - 3.39 (m, 1 H,  $\text{CHOH}$ ), 2.37 (td,  $J$  = 7.4, 2.3 Hz, 2 H,  $\text{C}(=\text{O})\text{CH}_2$ ), 2.06 (quin,  $J$  = 7.0 Hz, 2 H,  $\text{C}(=\text{O})\text{CH}_2\text{CH}_2$ ), 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,  $\text{CHHCHNH}_2$ )

**<sup>13</sup>C NMR** (101 MHz, MeOD)  $\delta$  / ppm = 175.0 ( $\text{C}(=\text{O})$ ), 74.1 ( $\text{CHOH}$ ), 56.3 ( $\text{CHNH}$ ), 45.3 ( $\text{CH}_2\text{Cl}$ ), 35.6 ( $\text{CH}_2\text{CHOH}$ ), 34.5 ( $\text{C}(=\text{O})\text{CH}_2$ ), 32.7 ( $\text{CH}_2\text{CHNH}$ ), 30.1 ( $\text{C}(=\text{O})\text{CH}_2\text{CH}_2$ ), 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 = 242.0925, [M+Na]<sup>+</sup> found, [C<sub>10</sub>H<sub>18</sub>ClNNaO<sub>2</sub>]<sup>+</sup> requires 242.0924

The compound has not been reported previously.

### 1.64 4-Azido-*N*-((*trans*)-2-hydroxycyclohexyl)butanamide 146



4-Chloro-*N*-((*trans*)-2-hydroxycyclohexyl)butanamide **145** (345 mg, 1.57 mmol, 1 eq.) and NaN<sub>3</sub> (180 mg, 2.77 mmol, 1.75 eq.) were stirred in DMF (12 ml) at 50 °C for 16 h. Water (50 ml) and 10 % *i*-PrOH/CHCl<sub>3</sub> (50 ml) were added, and the organic layer was removed. The aqueous layer was extracted again with 10 % *i*-PrOH/CHCl<sub>3</sub> (50 ml) and the combined organic fractions were dried with MgSO<sub>4</sub>. The solvent was evaporated under reduced pressure, and then by using a N<sub>2</sub> stream. **146** was obtained as large white prisms (347 mg, 1.53 mmol, 97.5 %).

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

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

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

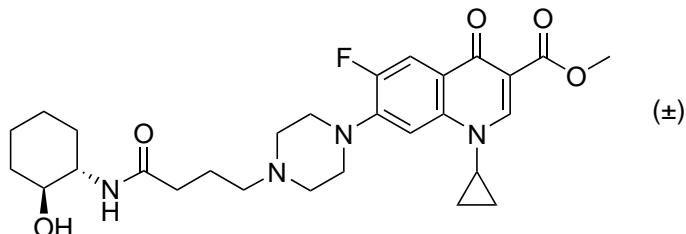
**<sup>1</sup>H NMR** (400 MHz, MeOD)  $\delta$  / ppm = 7.87 (d,  $J$  = 7.9 Hz, 1 H, NH), 5.27 (d,  $J$  = 4.3 Hz, 1 H, OH), 3.56 (td,  $J$  = 10.5, 4.4 Hz, 1 H, CHNH), 3.28 - 3.41 (m, 3 H, CHOH and CH<sub>2</sub>N<sub>3</sub>), 2.30 (td,  $J$  = 7.4, 2.7 Hz, 2 H, C(=O)CH<sub>2</sub>), 1.95 - 2.03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

**<sup>13</sup>C NMR** (101 MHz, MeOD)  $\delta$  / ppm = 175.1 ( $\text{C}(=\text{O})$ ), 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 ( $\text{C}(=\text{O})\text{CH}_2$ ), 32.7 ( $\text{CH}_2\text{CHNH}$ ), 26.3 ( $\text{C}(=\text{O})\text{CH}_2\text{CH}_2$ ), 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

The compound has not been reported previously.

**1.65 Methyl 1-cyclopropyl-6-fluoro-7-(4-((*trans*)-2-hydroxycyclohexyl)amino)-4-oxobutyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 147**



4-(4-(1-Cyclopropyl-6-fluoro-3-(methoxycarbonyl)-4-oxo-1,4-dihydroquinolin-7-yl)piperazin-1-yl)butanoic acid trifluoroacetate **123** (200 mg, 0.367 mmol, 1 eq.), (*trans*)-2-aminocyclohexan-1-ol **144** (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  $N_2$  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  $NaHCO_3$  (aq., sat., 10 ml) and  $CH_2Cl_2$  (10 ml). The organic layer was dried with  $MgSO_4$  and evaporated under reduced pressure. **147** was obtained as a white amorphous solid (73.0 mg, 0.142 mmol, 38.7 %).

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

**$^1H$  NMR** (400 MHz, MeOD)  $\delta$  / 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>)

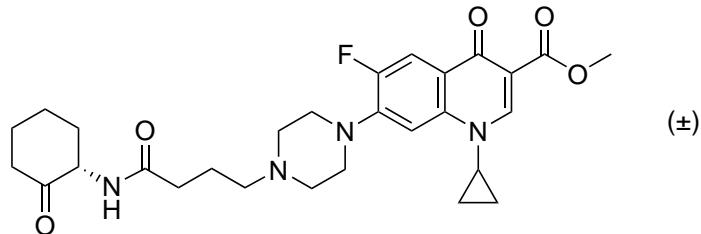
**$^{13}C$  NMR** (101 MHz, MeOD)  $\delta$  / ppm = 175.8 (CH<sub>2</sub>C(=O)NH), 175.3 (C(=O)CC(=O)OCH<sub>3</sub>), 166.8 (C(=O)OCH<sub>3</sub>), 154.9 (d,  $J$  = 248.8 Hz, *ipso* to F), 150.2 (C=CC(=O)OCH<sub>3</sub>), 146.1 (d,  $J$  = 10.8 Hz, *ipso* to piperazine), 139.9 (*para* to F), 123.5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

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

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

The compound has not been reported previously.

**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 148**



Methyl 1-cyclopropyl-6-fluoro-7-(4-((*trans*)-2-hydroxycyclohexyl)amino)-4-oxobutyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate **147** (5.2 mg, 9.84  $\mu$ mol, 1 eq.) and Dess-Martin periodane (16.4 mg, 38.7  $\mu$ mol, 4 eq.) were stirred in  $\text{CH}_2\text{Cl}_2$  (3 ml) for 6 h. The solvent was removed under reduced pressure and the residue was purified by preparatory HPLC (5-95 % acetonitrile/water over 20 min). The combined pure fractions were evaporated under reduced pressure to a volume of 20 ml, then  $\text{NaHCO}_3$  (aq., sat., 30 ml) and 10 % *i*-PrOH/ $\text{CHCl}_3$  (30 ml) were added. The organic layer was dried with  $\text{MgSO}_4$  and evaporated under reduced pressure. **148** was obtained as a white amorphous solid (3.6 mg, 6.8  $\mu$ mol, 69.1 %).

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

**IR** (neat)  $\nu_{max}$  /  $\text{cm}^{-1}$  = 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<sub>6</sub>)  $\delta$  / 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, CH<sub>2</sub>NH), 3.73 (s, 3 H, CH<sub>3</sub>), 3.65 (tt,  $J$  = 7.1, 3.9 Hz, 1 H, NCH<sub>2</sub>(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, CH<sub>2</sub>C(=O)CHNH), 2.36 (br s, 2 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 2.26 (dtt,  $J$  = 13.4, 2.6, 2.6, 1.6, 1.6 Hz, 1 H, CH<sub>2</sub>C(=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, CH<sub>2</sub>C(=O)CHNH), 2.00 (ddquin,  $J$  = 13.2, 6.0, 2.9, 2.9, 2.9 Hz, 1 H, CH<sub>2</sub>C(=O)CHNH), 1.65 - 1.83 (m, 4 H, CH<sub>2</sub>CH<sub>2</sub>CHNH), 1.41 - 1.56 (m, 2 H, CH<sub>2</sub>CHNH and CH<sub>2</sub>C(=O)CHNH), 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>)

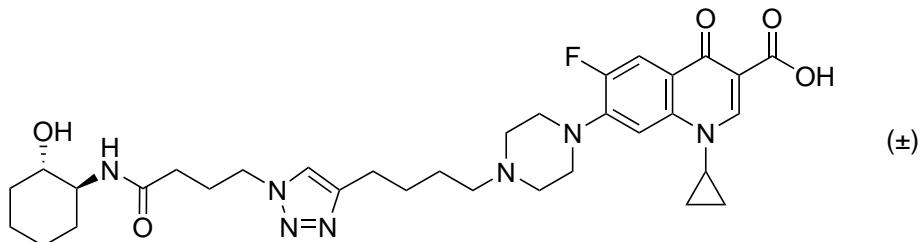
**$^{13}\text{C NMR}$**  (101 MHz, DMSO d<sub>6</sub>)  $\delta$  / ppm = 207.5 (C(=O)CHNH), 171.7 (C(=O)CC(=O)OCH<sub>3</sub>), 171.6 (CH<sub>2</sub>C(=O)NH), 165.0 (C(=O)OCH<sub>3</sub>), 152.6 (d,  $J$  = 247.6 Hz, *ipso* to F), 148.3 (C=CC(=O)OCH<sub>3</sub>), 143.9 (br s, *ipso* to piperazine), 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 (CH<sub>2</sub>NH 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<sub>6</sub>)  $\delta$  / 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

The compound has not been reported previously.

**1.67 1-Cyclopropyl-6-fluoro-7-(4-(4-(1-(4-((*trans*)-2-hydroxycyclohexyl)amino)-4-oxobutyl)-1*H*-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 149**



1-Cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **91** (40 mg, 97.2  $\mu$ mol, 1 eq.) and 4-azido-*N*-((*trans*)-2-hydroxycyclohexyl)butanamide **146** (22.0 mg, 97.2  $\mu$ mol, 1 eq.) were dissolved in 10 % water/*t*-BuOH (3 ml), and the mixture was degassed by bubbling  $N_2$  through it. A solution of CuSO<sub>4</sub> and THPTA (97.2  $\mu$ l, 9.72  $\mu$ mol, 0.1 eq. 100 mM, aq.) was added, followed by a solution of sodium ascorbate (194  $\mu$ l, 19.4  $\mu$ mol, 0.2 eq., 100 mM, aq.). The mixture was stirred at r.t. under argon for 16 h. Water (50 ml) and 10 % *i*-PrOH/CHCl<sub>3</sub> (50 ml) were added, then the organic layer was separated, dried with MgSO<sub>4</sub> and evaporated under reduced pressure. The residue was purified by preparatory HPLC (5-70 % acetonitrile/water over 15 min). The combined pure fractions were evaporated under reduced pressure and then partitioned between NaHCO<sub>3</sub> (aq., sat., 50 ml) and 10 % *i*-PrOH/CHCl<sub>3</sub> (50 ml). The organic layer was dried with MgSO<sub>4</sub> and evaporated under reduced pressure. **149** was obtained as a white amorphous solid (30.3 mg, 47.5  $\mu$ mol, 48.9 %).

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

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

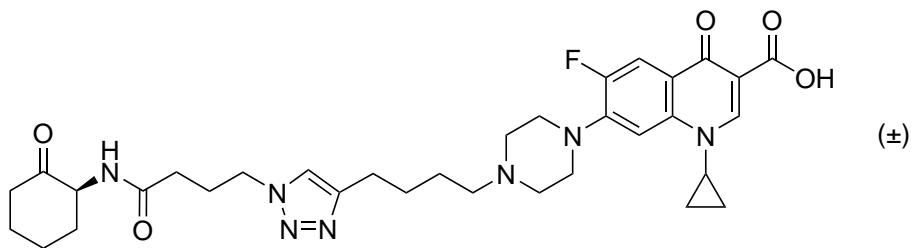
**<sup>13</sup>C NMR** (101 MHz, DMSO d<sub>6</sub>)  $\delta$  / ppm = 176.4 (C(=O)CC(=O)OH), 170.9 (CH<sub>2</sub>C(=O)NH), 166.0 (C(=O)OH), 153.1 (d,  $J$  = 252.1 Hz, *ipso* to F), 148.0 (C=CC(=O)OH), 146.9 (CH=CCH<sub>2</sub>), 145.3 (d,  $J$  = 10.0 Hz, *ipso* to piperazine), 139.2 (para to F), 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 (CC(=O)OH), 106.3 (d,  $J$  = 3.3 Hz, *meta* to C=O and *meta* to F), 71.4 (CHOH), 57.4 (CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 54.2 (CHNH), 52.4 (CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)), 49.5 (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>), 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>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>)  $\delta$  / ppm = -121.4 (ciprofloxacin F)

HRMS (ESI<sup>+</sup>) *m/z* / Da = 638.3480, [M+H]<sup>+</sup> found, [C<sub>33</sub>H<sub>45</sub>FN<sub>7</sub>O<sub>5</sub>]<sup>+</sup> requires 638.3466

The compound has not been reported previously.

**1.68 1-Cyclopropyl-6-fluoro-4-oxo-7-(4-(4-(1-(4-oxo-4-((2-oxocyclohexyl)amino)butyl)-1*H*-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid 151**



1-Cyclopropyl-6-fluoro-7-(4-(4-(1-(4-((*trans*)-2-hydroxycyclohexyl)amino)-4-oxobutyl)-1*H*-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **149** (15.0 mg, 23.6 mmol, 1 eq.) and Dess-Martin periodane (35.0 mg, 82.5 mmol, 3.5 eq.) were stirred in CH<sub>2</sub>Cl<sub>2</sub> (3 ml) for 4 h. The solvent was removed under reduced pressure and the residue was purified by preparatory HPLC (5-70 % acetonitrile/water over 15 min). The combined pure fractions were evaporated under reduced pressure, then NaHCO<sub>3</sub> (aq., sat., 30 ml) and 10 % *i*-PrOH/CHCl<sub>3</sub> (30 ml) were added. The organic layer was dried with MgSO<sub>4</sub> and evaporated under reduced pressure. **151** was obtained as a clear gum (11.7 mg, 18.4  $\mu$ mol, 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>)  $\delta$  / 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 (dd, *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>CH<sub>2</sub>NH), 4.31 (t, *J*=6.9 Hz, 1 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>NH), 3.74 - 3.84 (m, 1 H, NCH(CH<sub>2</sub>)<sub>2</sub>), 3.31 (br. s, 4 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 2.64 (t, *J*=7.5 Hz, 2 H, CH=CCH<sub>2</sub>), 2.56 (br t, *J*=5.0, 5.0 Hz, 4 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 2.45 - 2.52 (m, 1 H, CHHC(=O)), 2.38 (t, *J*=7.1 Hz, 2 H, CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>NH), 2.25 (dt, *J*=13.4, 2.6, 2.6, 1.6, 1.6 Hz, 1 H, CHHC(=O)), 2.07 - 2.17 (m, 3 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N and CHHCHNH), 1.96 - 2.05 (m, 3 H, C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N and CHHCH<sub>2</sub>C(=O)), 1.68 - 1.81 (m, 2 H, CHHCH<sub>2</sub>CH<sub>2</sub>NH), 1.64 (quin, *J*=7.5 Hz, 2 H, CH=CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>NH), 1.40 - 1.56 (m, 5 H, CHHCH<sub>2</sub>C(=O), CHHCHNH 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>)  $\delta$  / 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>NH), 57.0 (CHNH), 52.4 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 49.5 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 49.5 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 48.7 (C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>NCH=C), 40.5 (CH<sub>2</sub>C(=O)), 35.8 (NCH(CH<sub>2</sub>)<sub>2</sub>), 33.7 (CH<sub>2</sub>CHNH), 31.8 (C(=O)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>NCH=C), 27.1 (CH<sub>2</sub>CH<sub>2</sub>C(=O)),

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

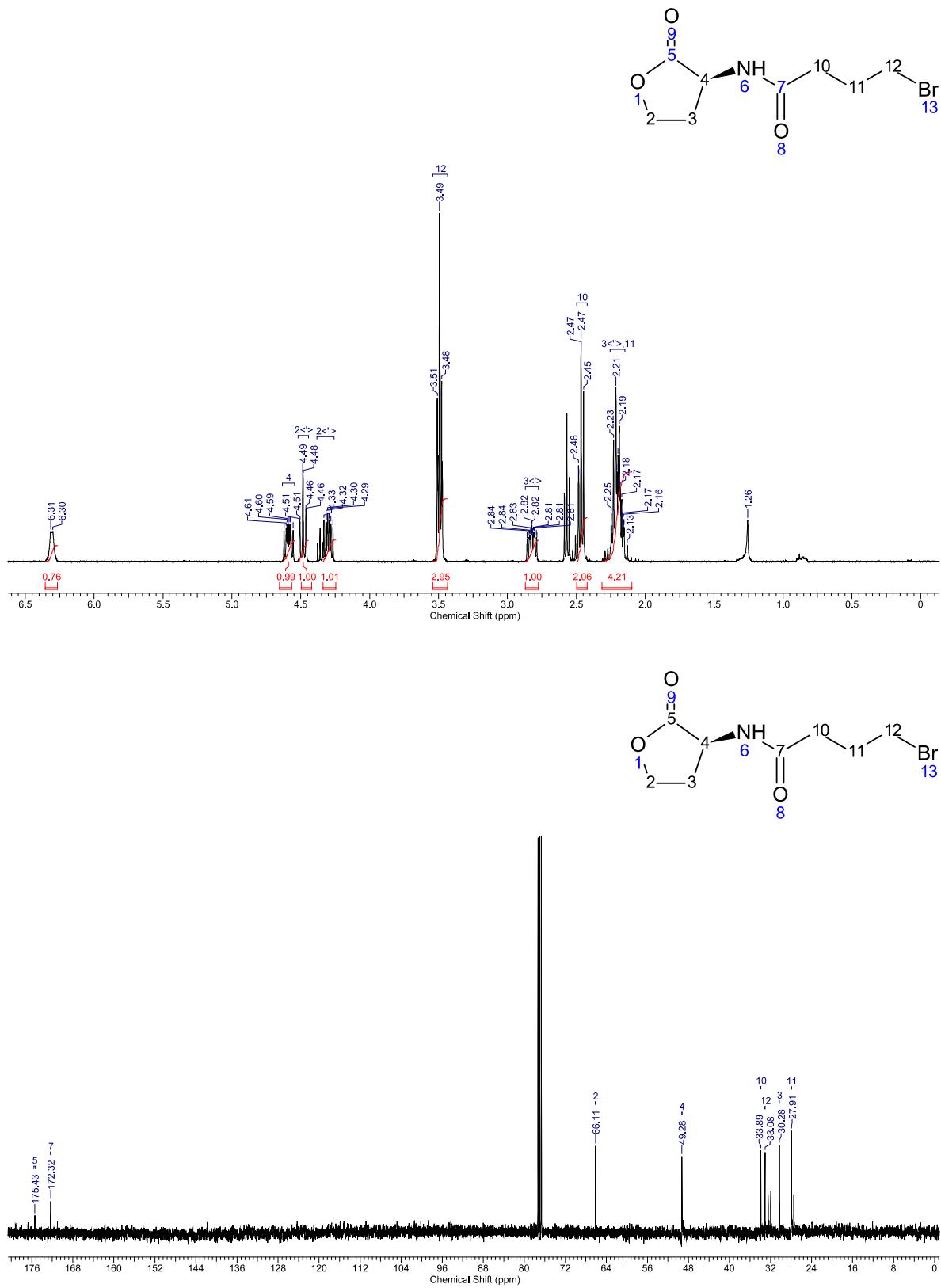
**<sup>19</sup>F NMR** (376 MHz, DMSO d<sub>6</sub>)  $\delta$  / ppm = -121.7 (s, ciprofloxacin F)

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

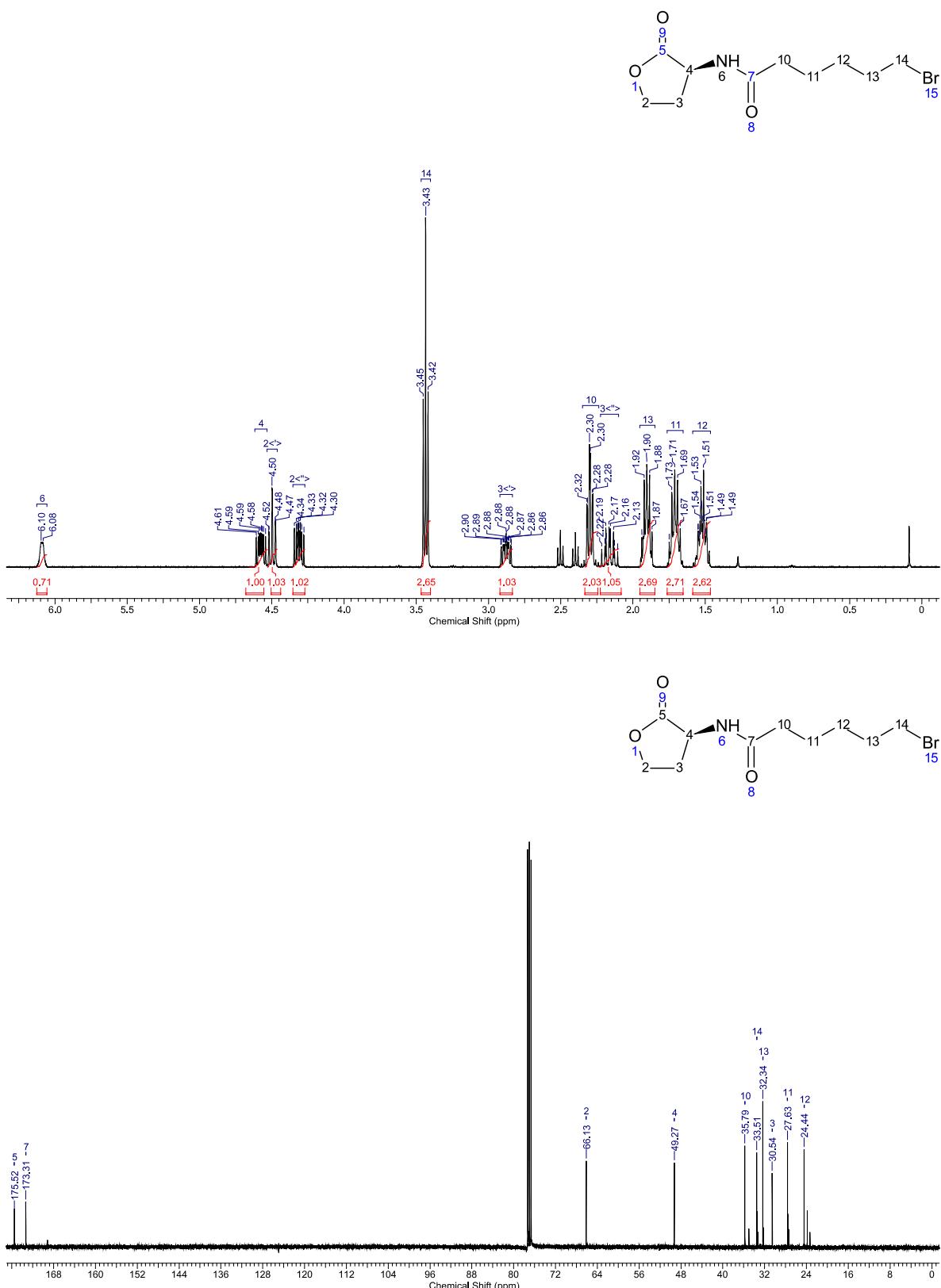
The compound has not been reported previously.

## 2 NMR spectra

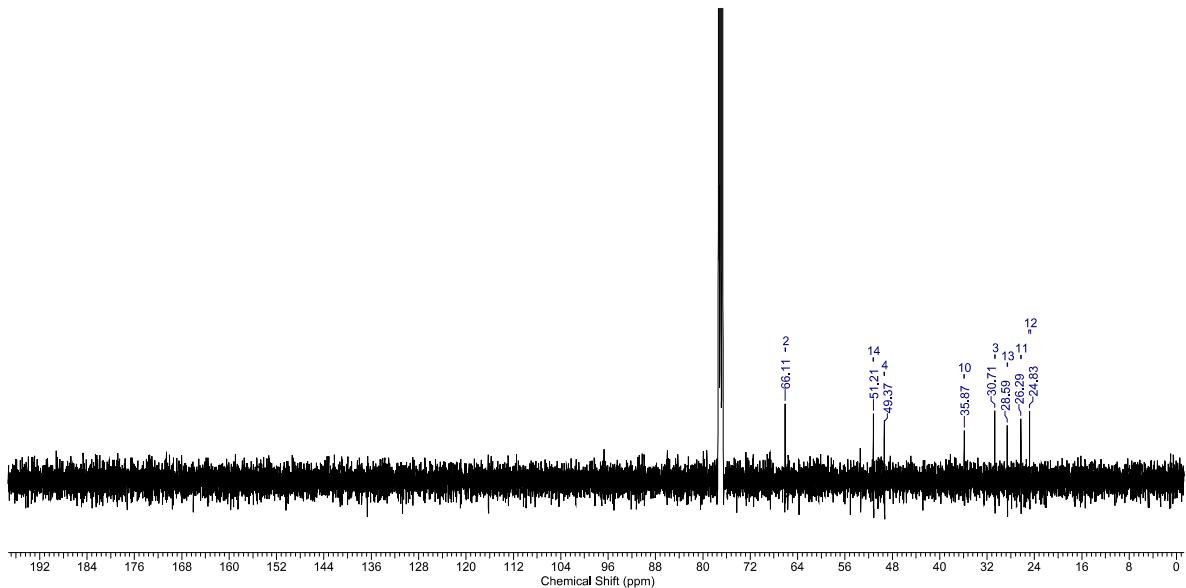
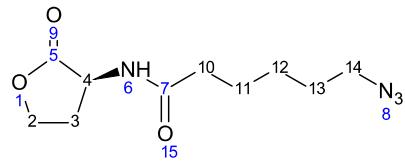
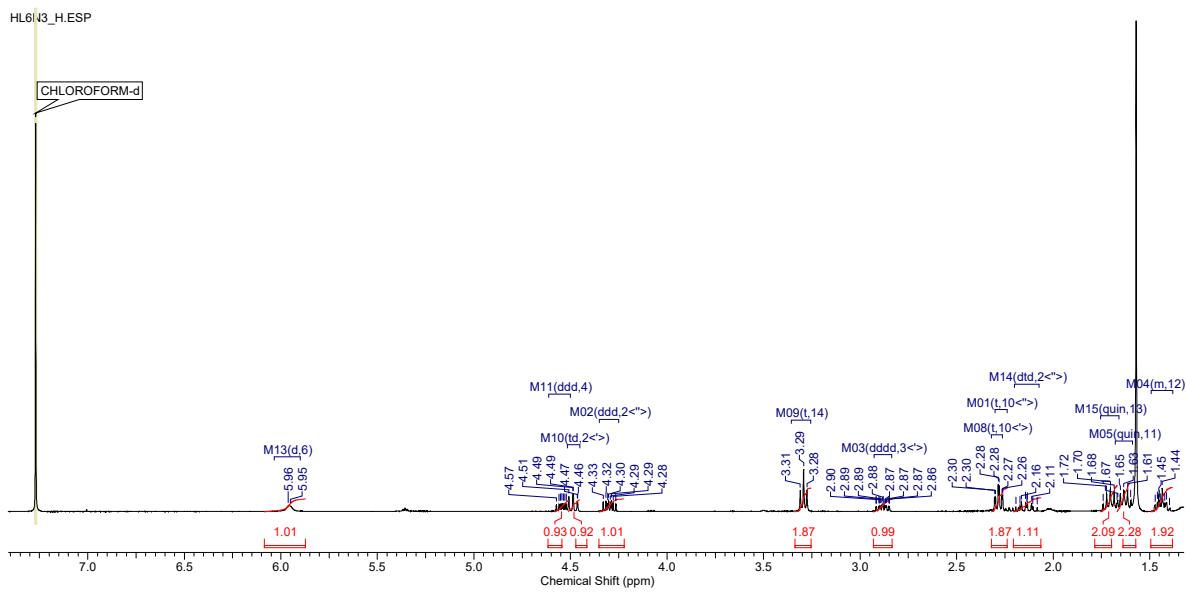
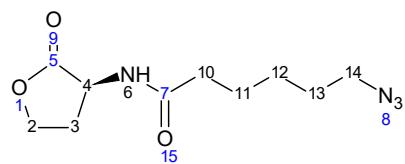
## 2.1 (S)-4-Bromo-N-(2-oxotetrahydrofuran-3-yl)butanamide 44



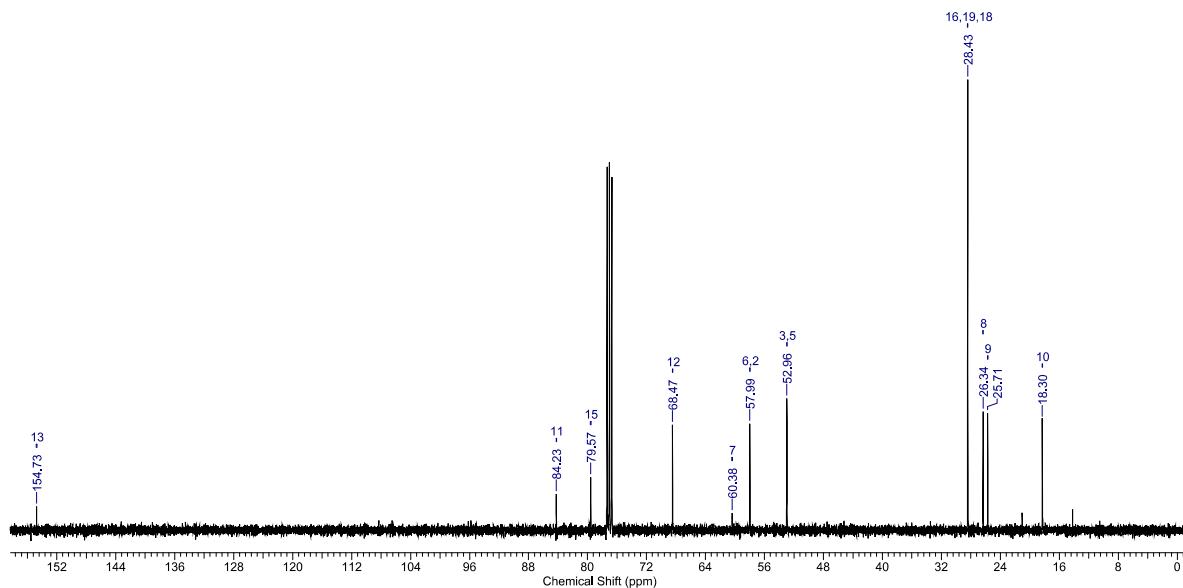
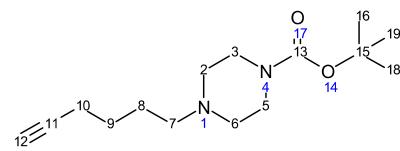
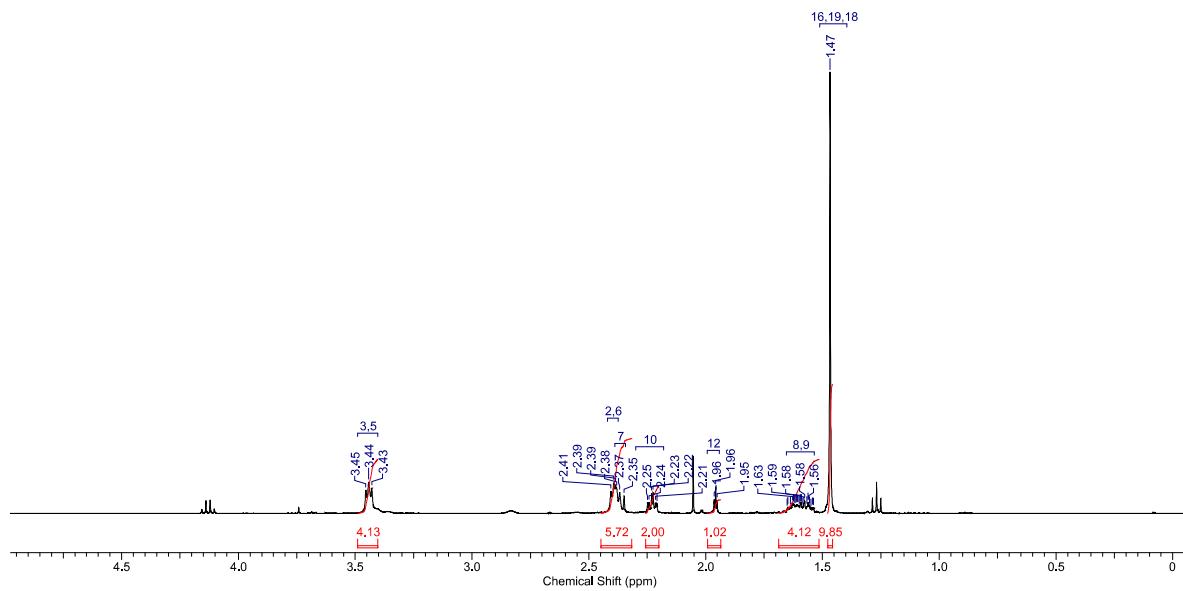
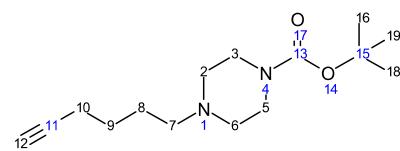
## 2.2 (*S*)-6-Bromo-*N*-(2-oxotetrahydrofuran-3-yl)hexanamide 45



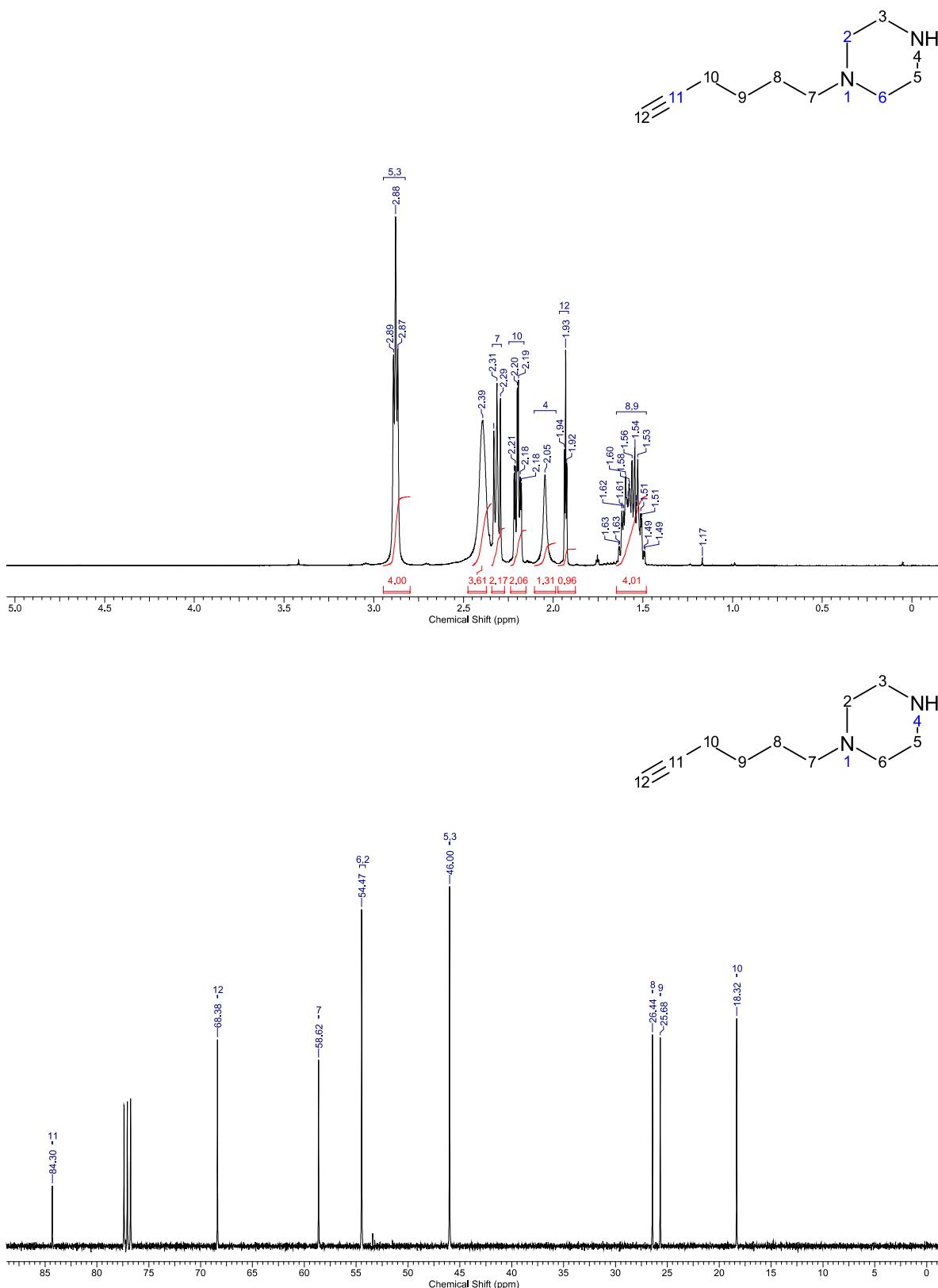
### 2.3 (S)-6-Azido-*N*-(2-oxotetrahydrofuran-3-yl)hexanamide 47



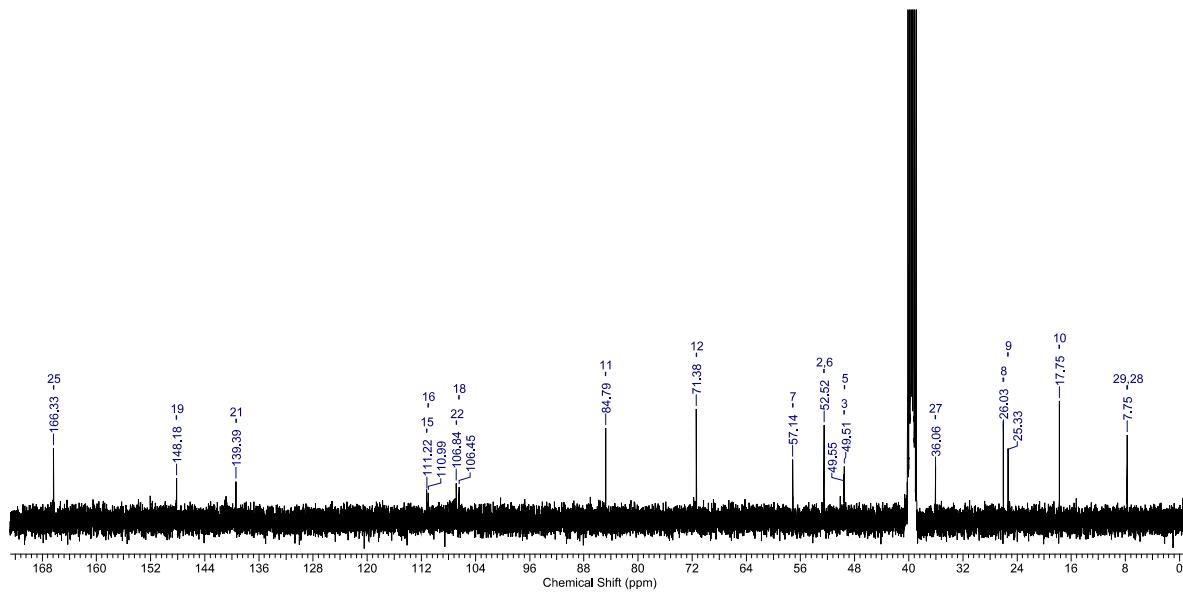
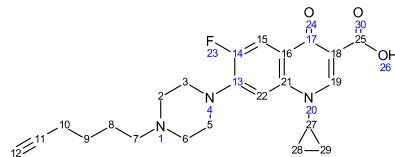
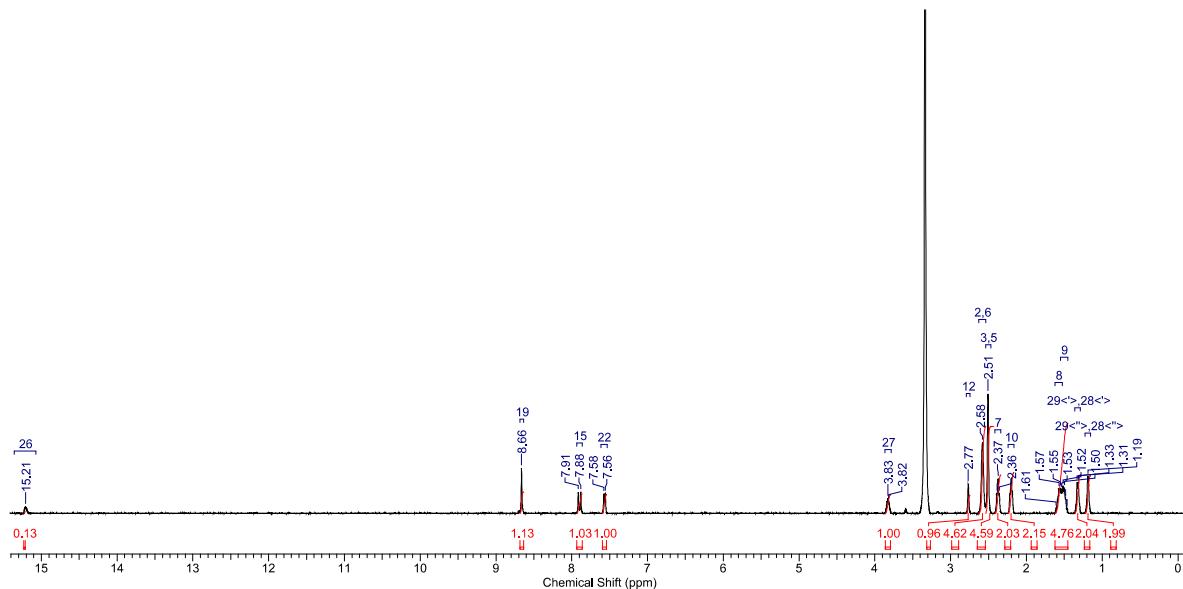
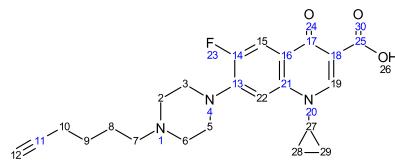
## 2.4 *tert*-Butyl 4-(hex-5-yn-1-yl)piperazine-1-carboxylate 51



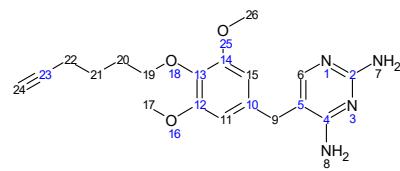
## 2.5 1-(Hex-5-yn-1-yl)piperazine 52



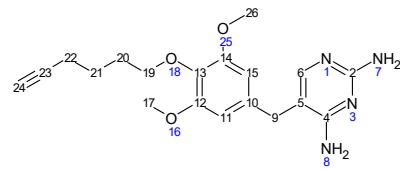
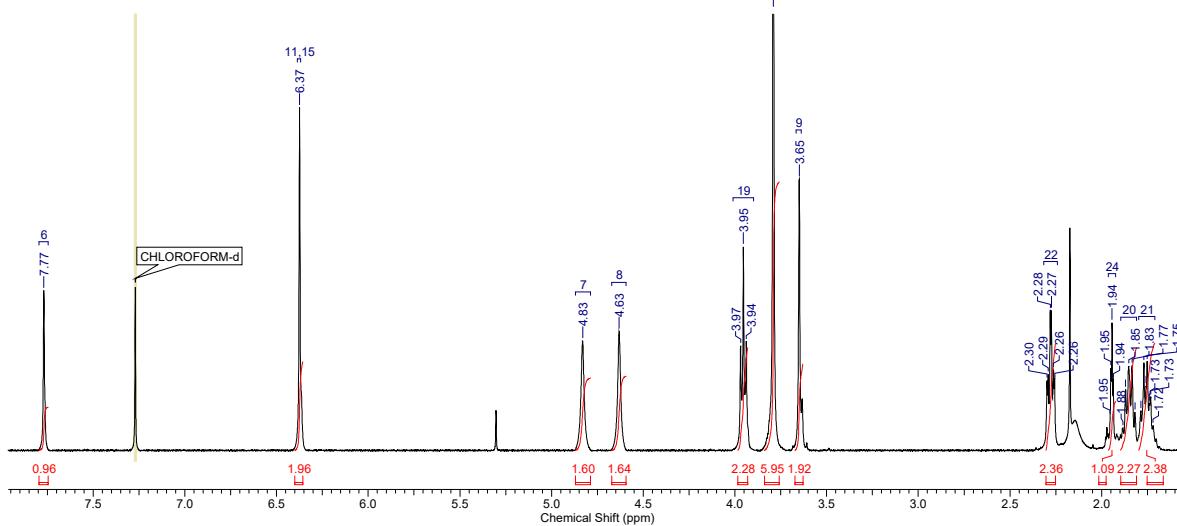
## 2.6 1-Cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 54



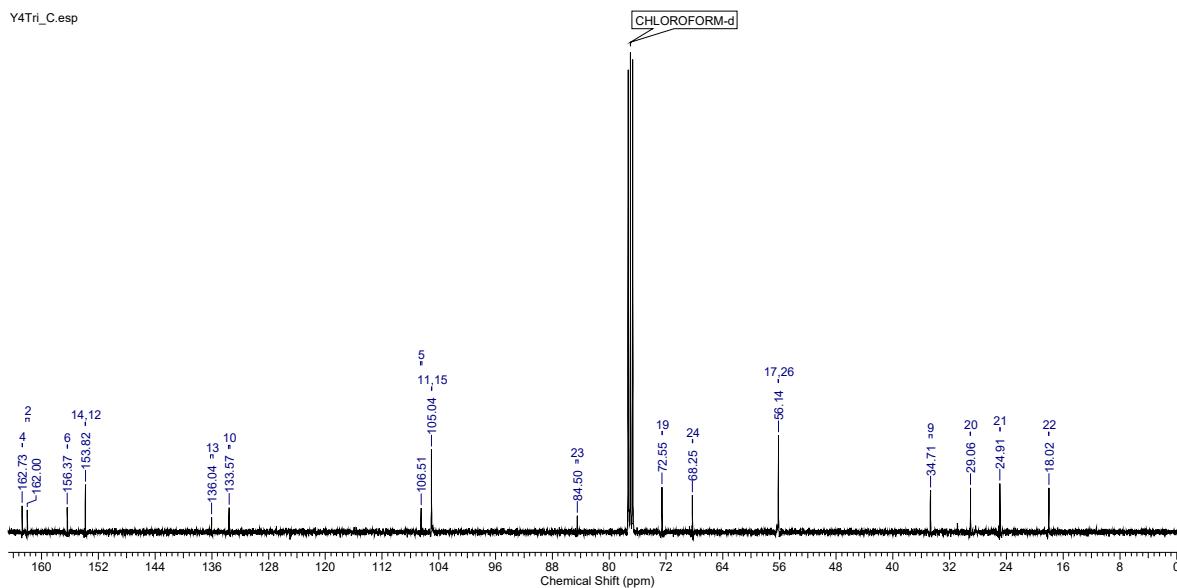
## 2.7 5-(4-(Hex-5-yn-1-yloxy)-3,5-dimethoxybenzyl)pyrimidine-2,4-diamine 94



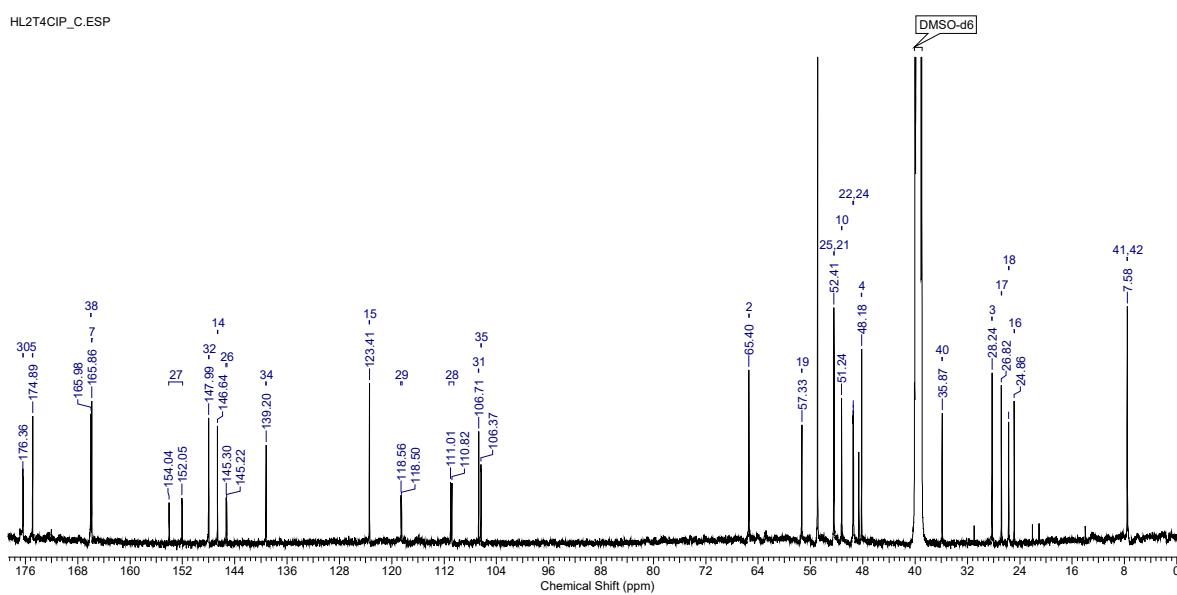
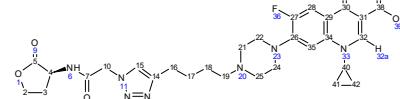
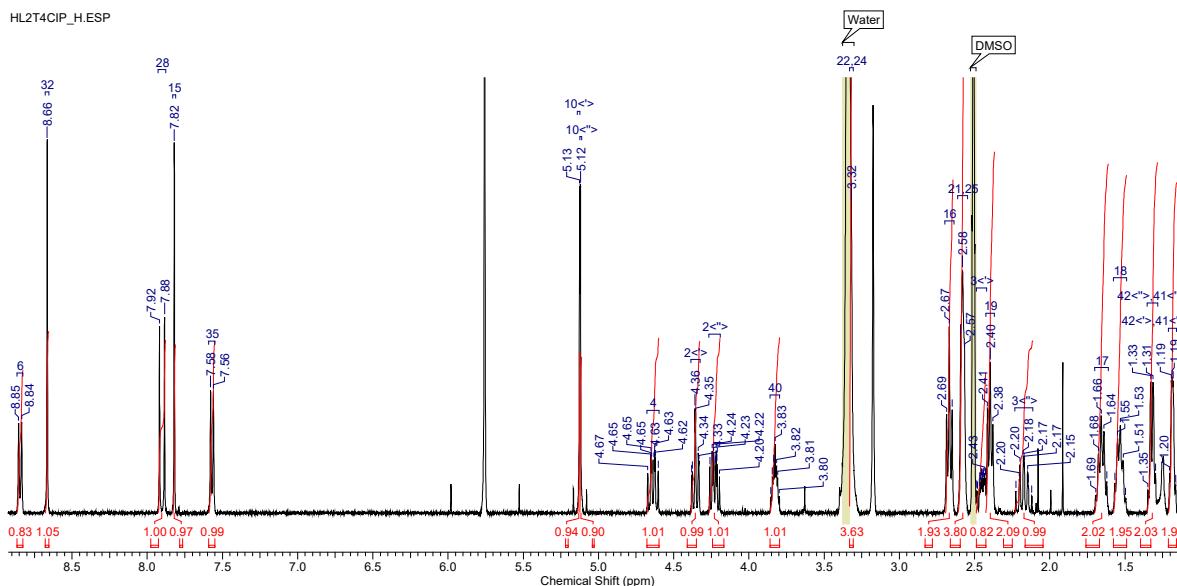
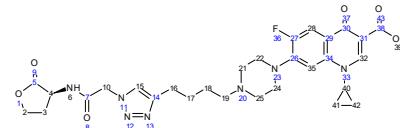
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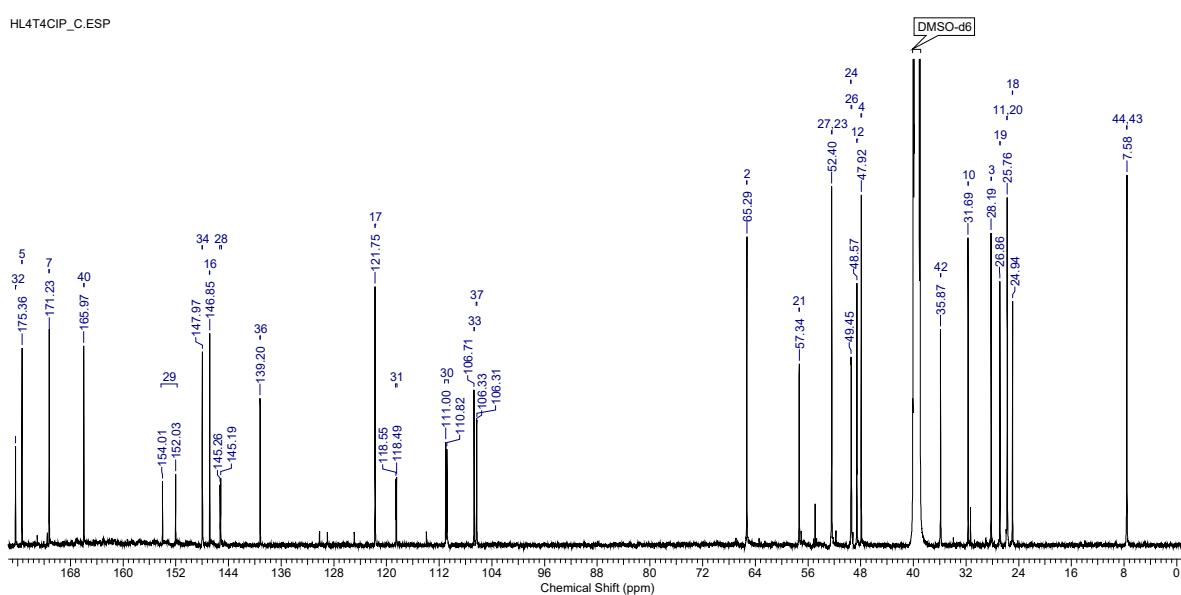
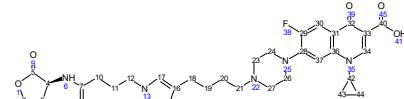
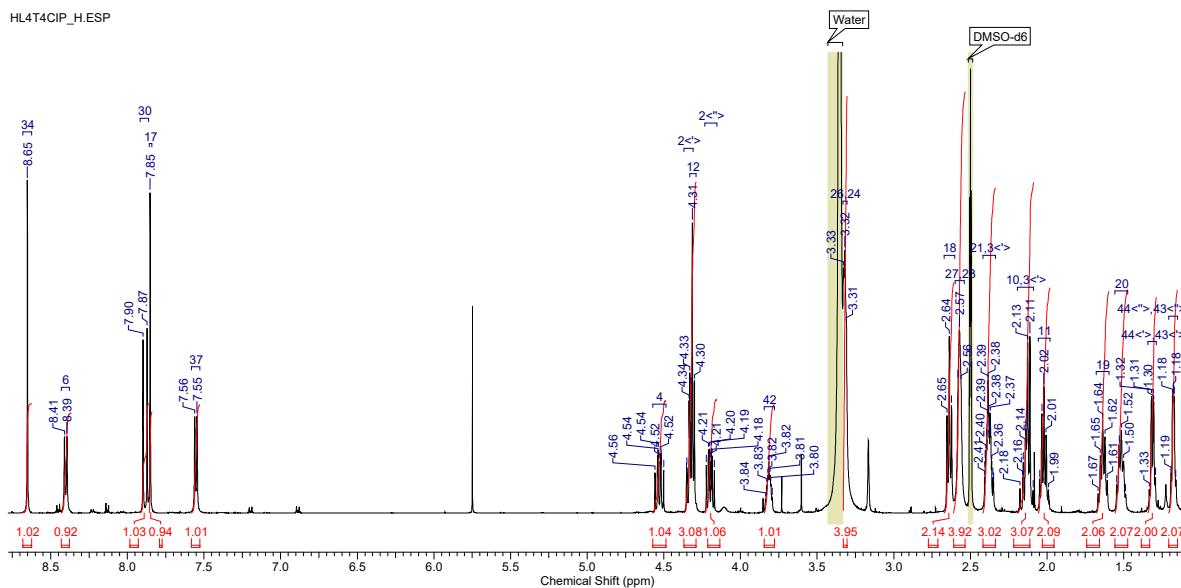
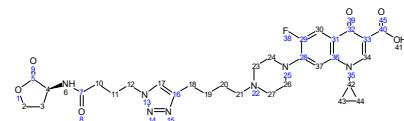
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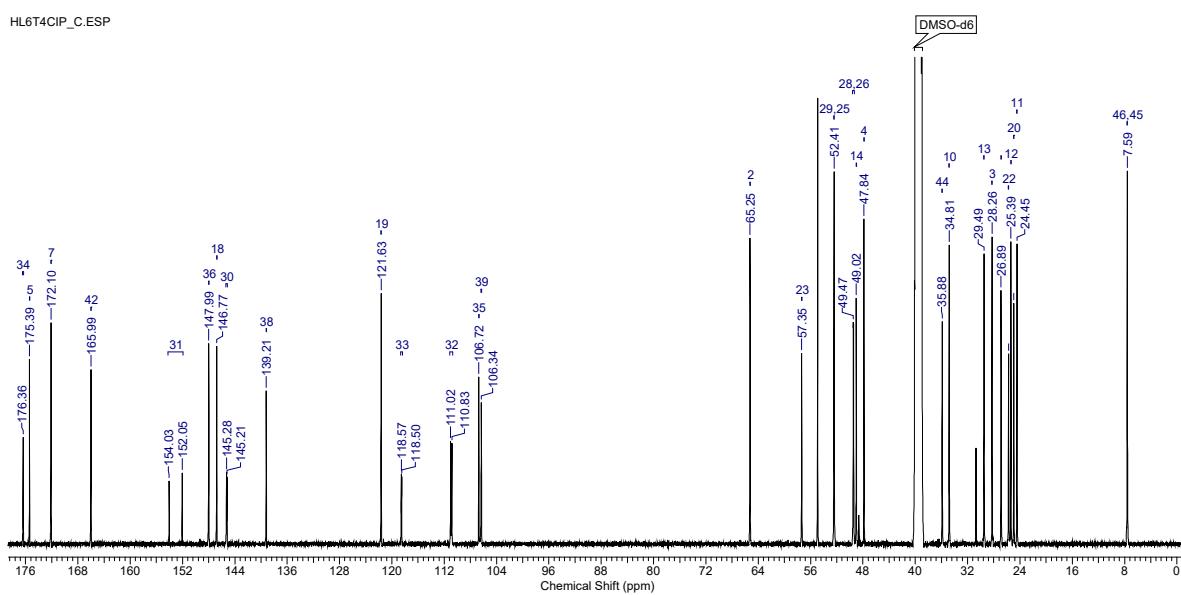
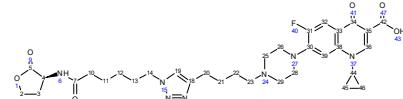
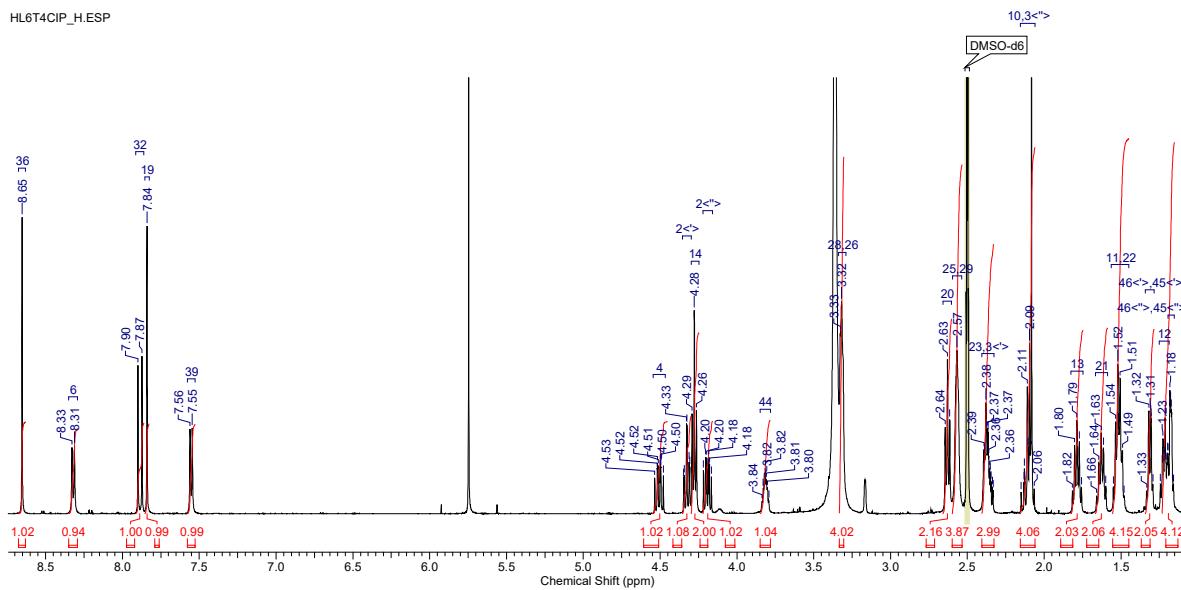
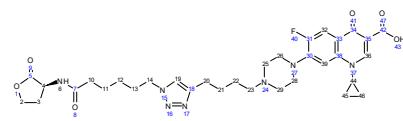
2.8 (S)-1-Cyclopropyl-6-fluoro-4-oxo-7-(4-(4-(1-(2-oxo-2-((2-oxotetrahydrofuran-3-yl)amino)ethyl)-1*H*-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid 95



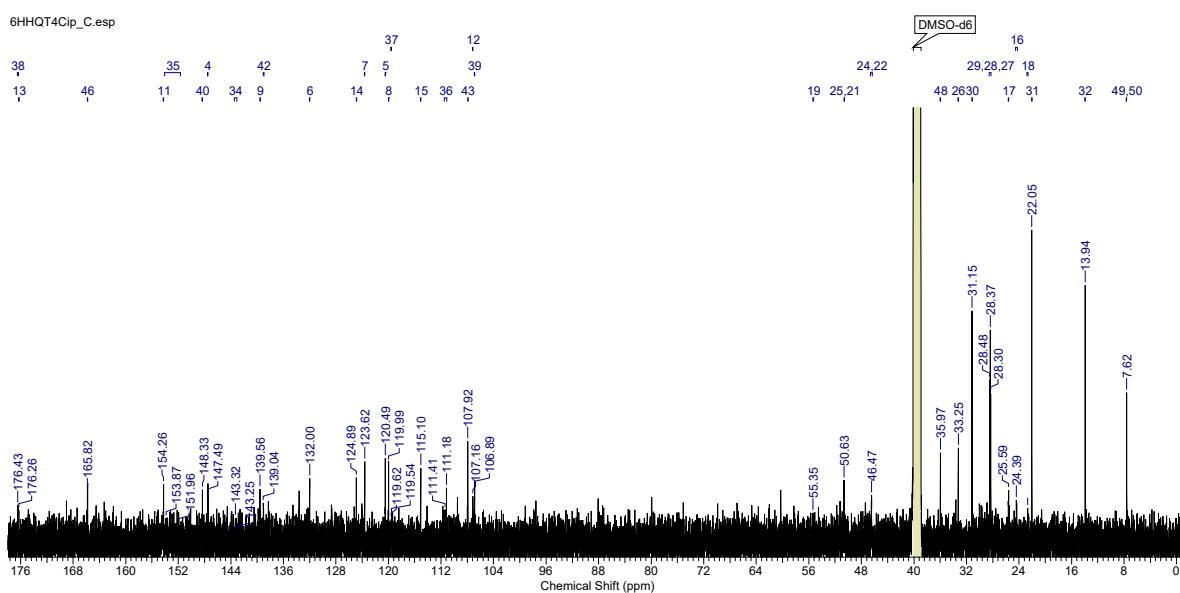
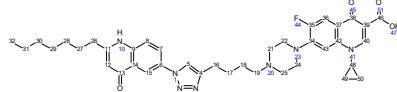
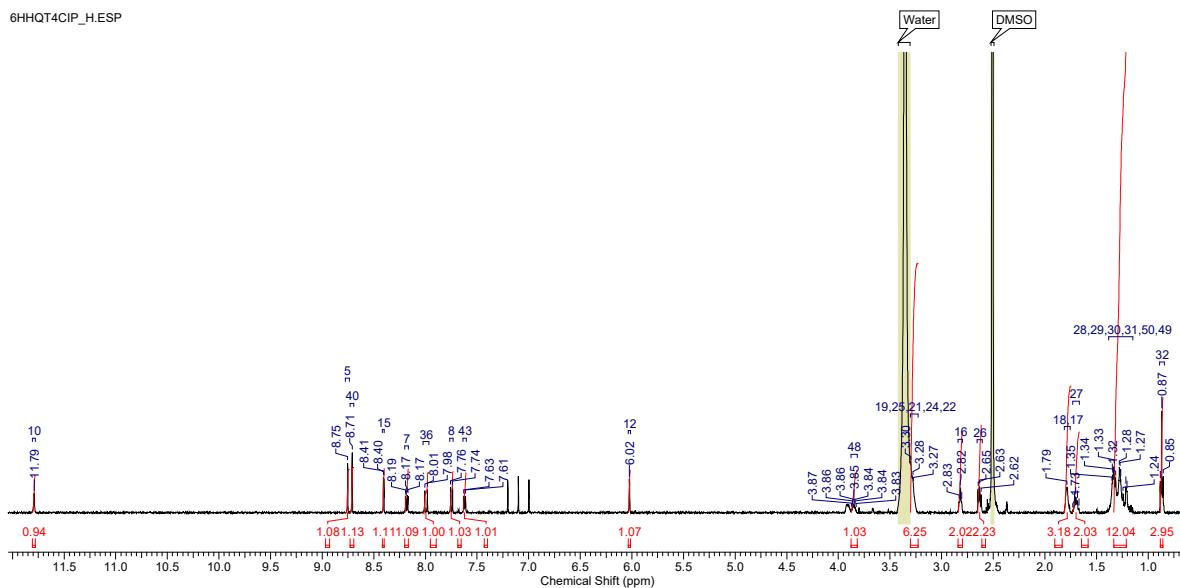
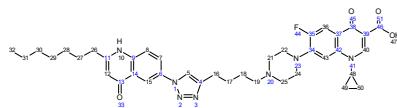
2.9 (*S*)-1-Cyclopropyl-6-fluoro-4-oxo-7-(4-(4-(1-(4-oxo-4-((2-oxotetrahydrofuran-3-yl)amino)butyl)-1*H*-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid 96



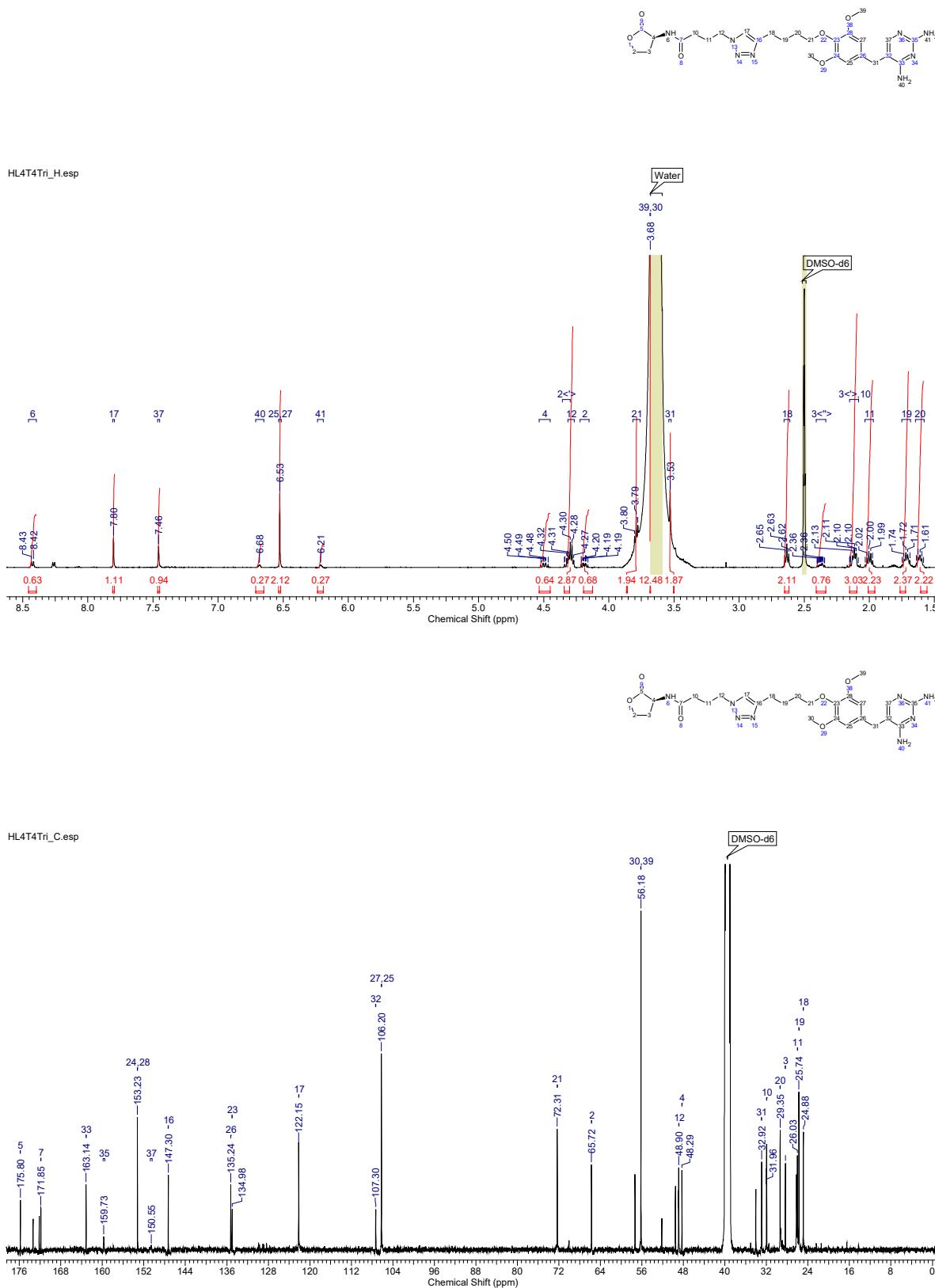
2.10 (*S*)-1-Cyclopropyl-6-fluoro-4-oxo-7-(4-(4-(1-(6-oxo-6-((2-oxotetrahydrofuran-3-yl)amino)hexyl)-1*H*-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid 97



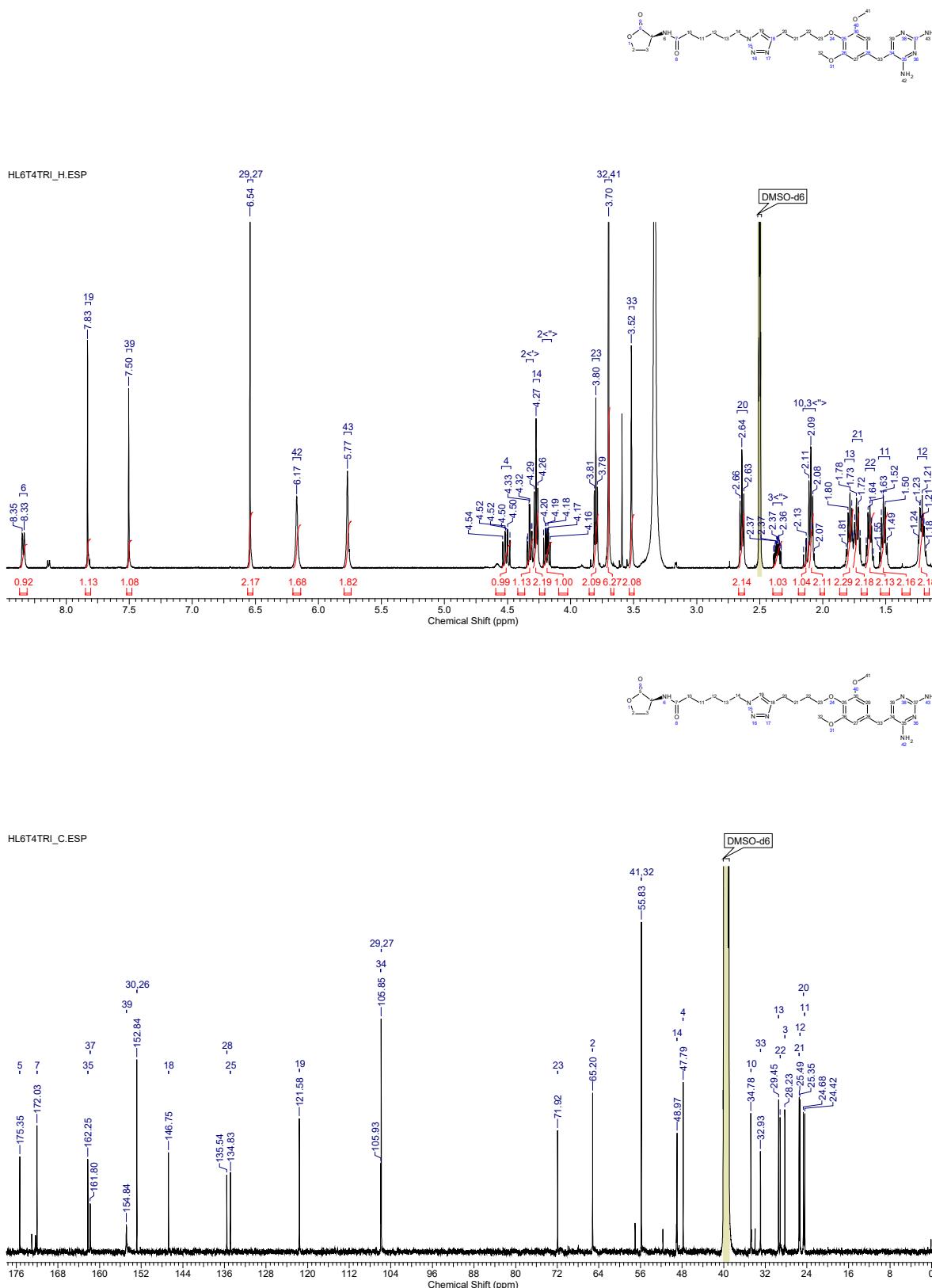
2.11 1-Cyclopropyl-6-fluoro-7-(4-(4-(1-(2-heptyl-4-oxo-1,4-dihydroquinolin-6-yl)-1*H*-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 98



**2.12 (S)-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 99**

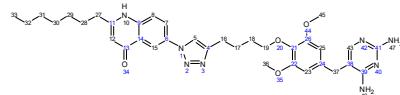


**2.13 (S)-6-(4-((2,4-Diaminopyrimidin-5-yl)methyl)-2,6-dimethoxyphenoxy)butyl-1*H*-1,2,3-triazol-1-yl)-*N*-(2-oxotetrahydrofuran-3-yl)hexanamide 100**

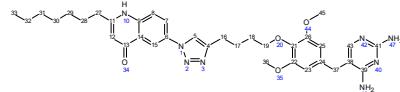
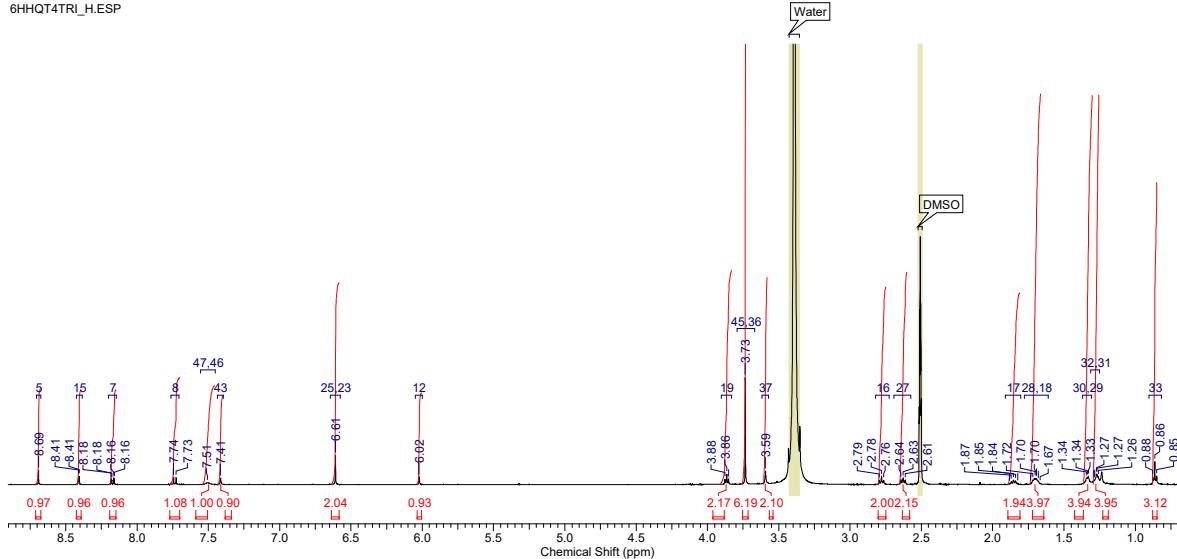


**2.14 6-(4-(4-((2,4-Diaminopyrimidin-5-yl)methyl)-2,6-dimethoxyphenoxy)butyl)-1*H*-1,2,3-triazol-1-yl)-2-heptylquinolin-4(*H*)-one 101**

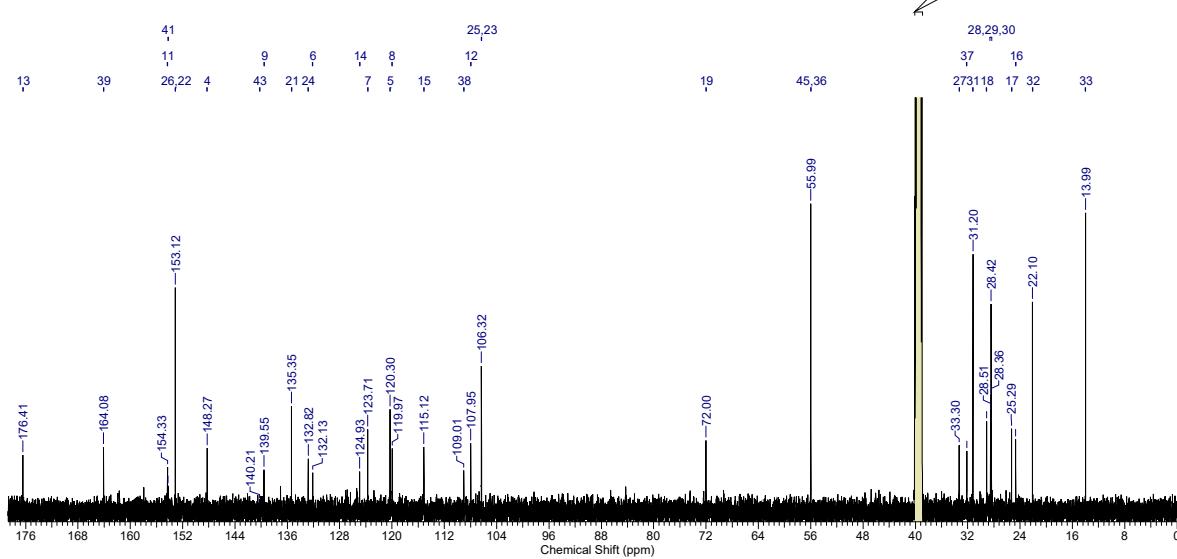
**User Notes** Some guesses



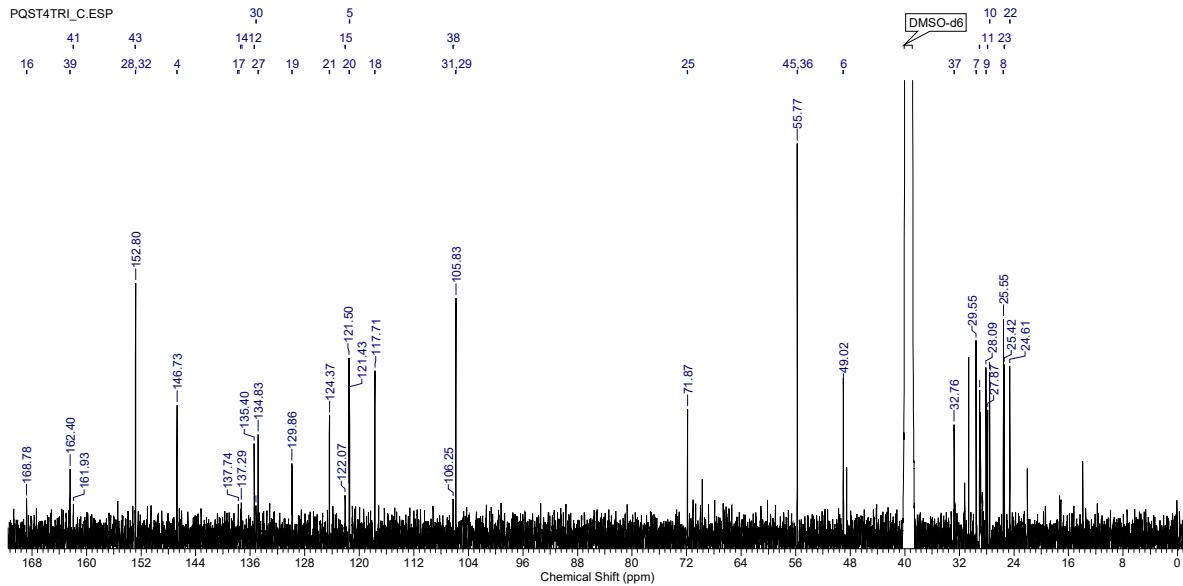
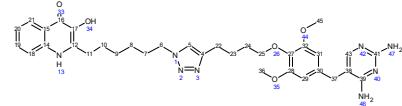
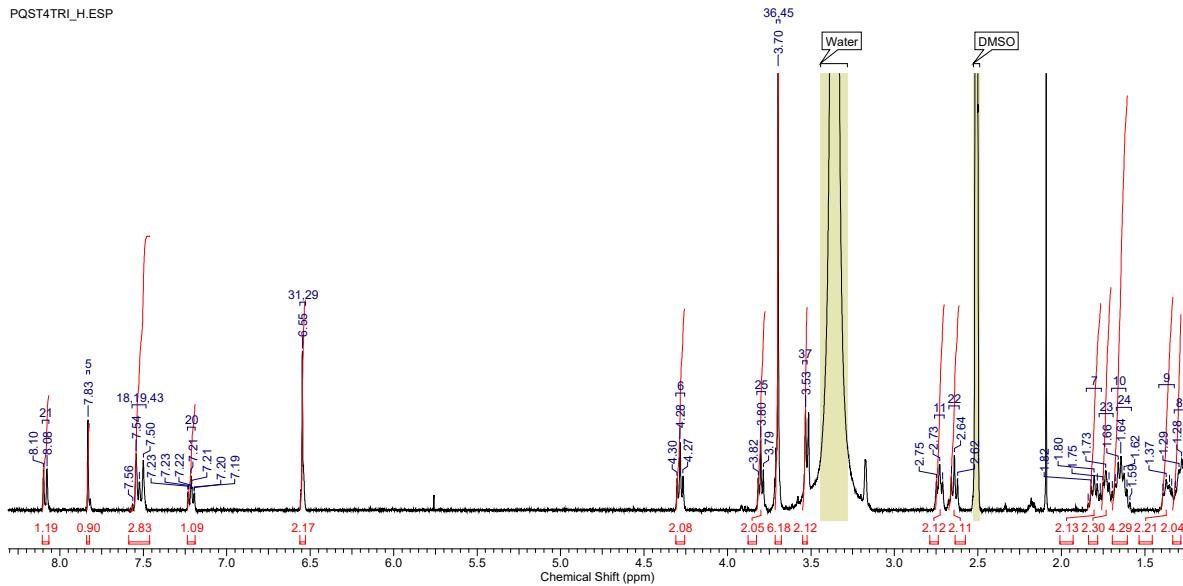
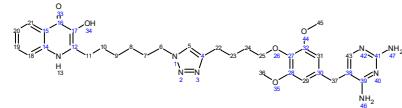
6HHQT4TRI H.ESP



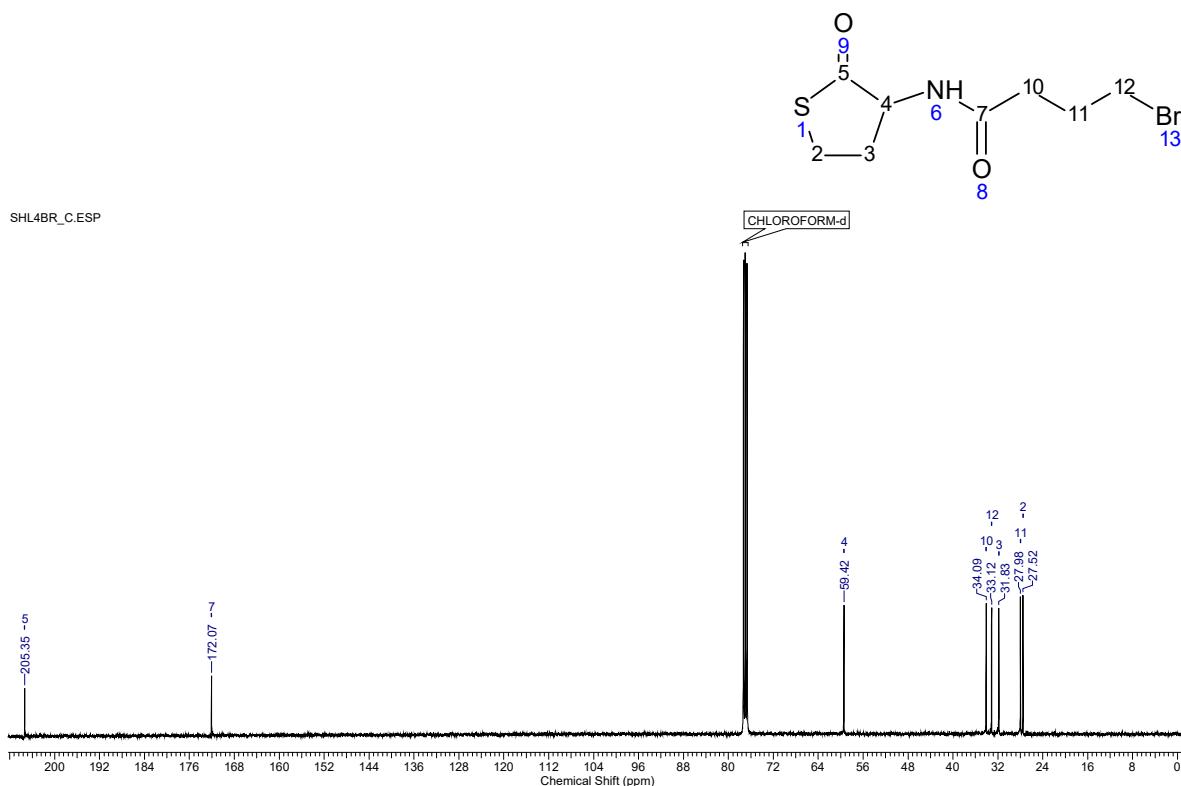
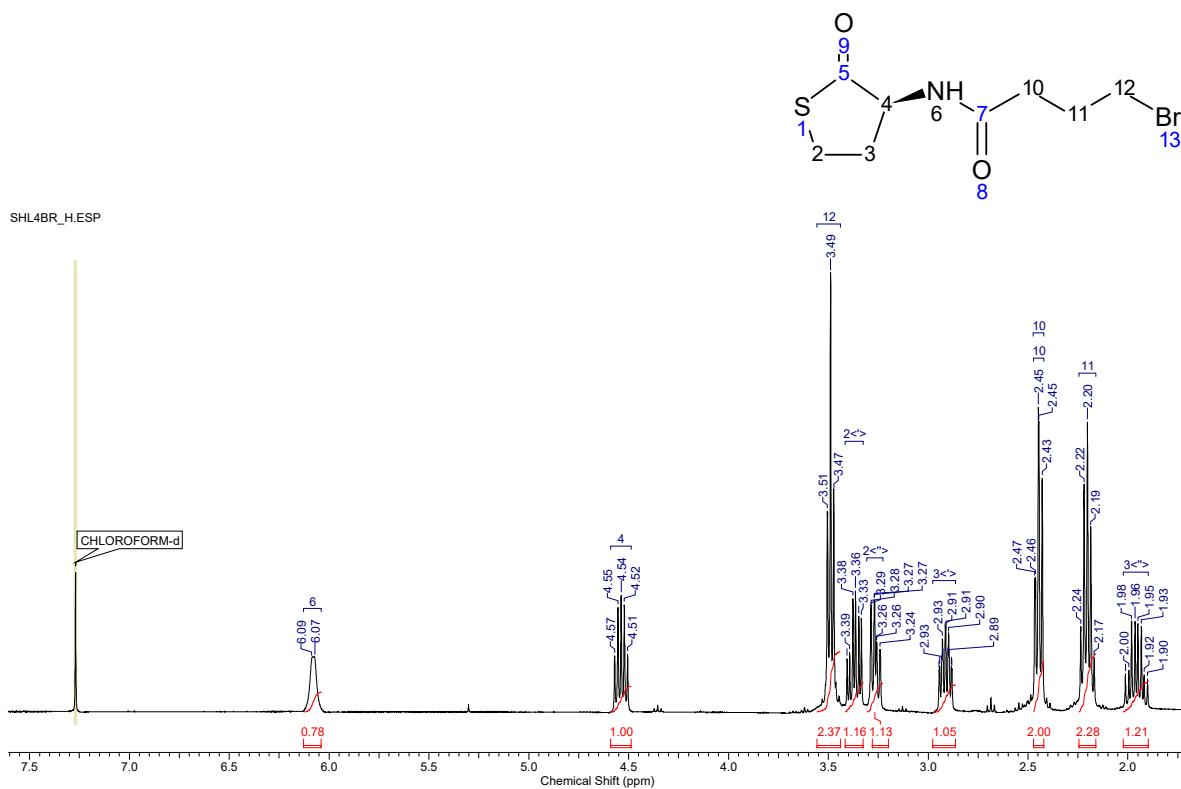
6HHQT4TRI\_C.ESP



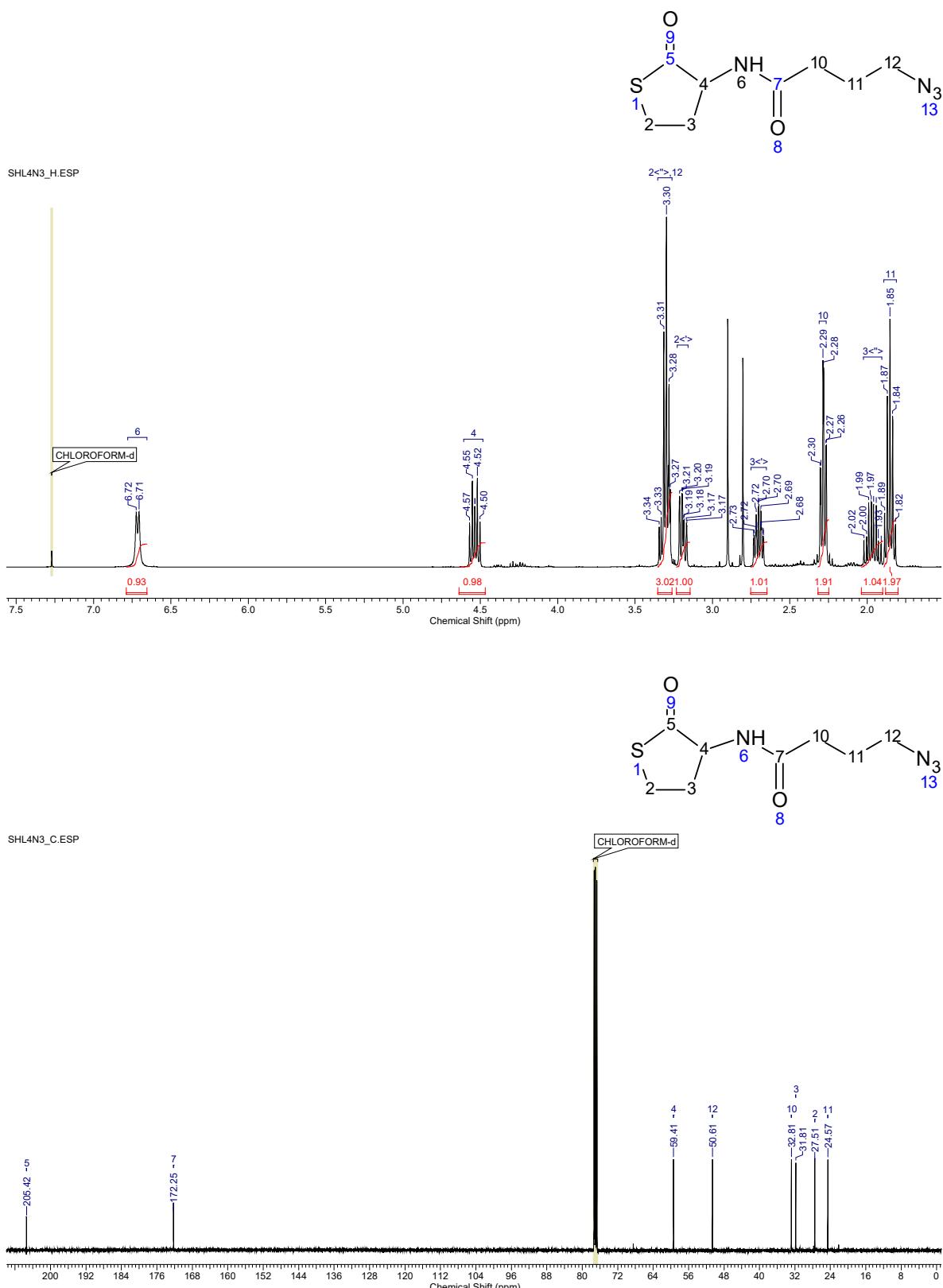
**2.15 2-(6-(4-(4-((2,4-Diaminopyrimidin-5-yl)methyl)-2,6-dimethoxyphenoxy)butyl)-1*H*-1,2,3-triazol-1-yl)hexyl)-3-hydroxyquinolin-4(*H*)-one 102**



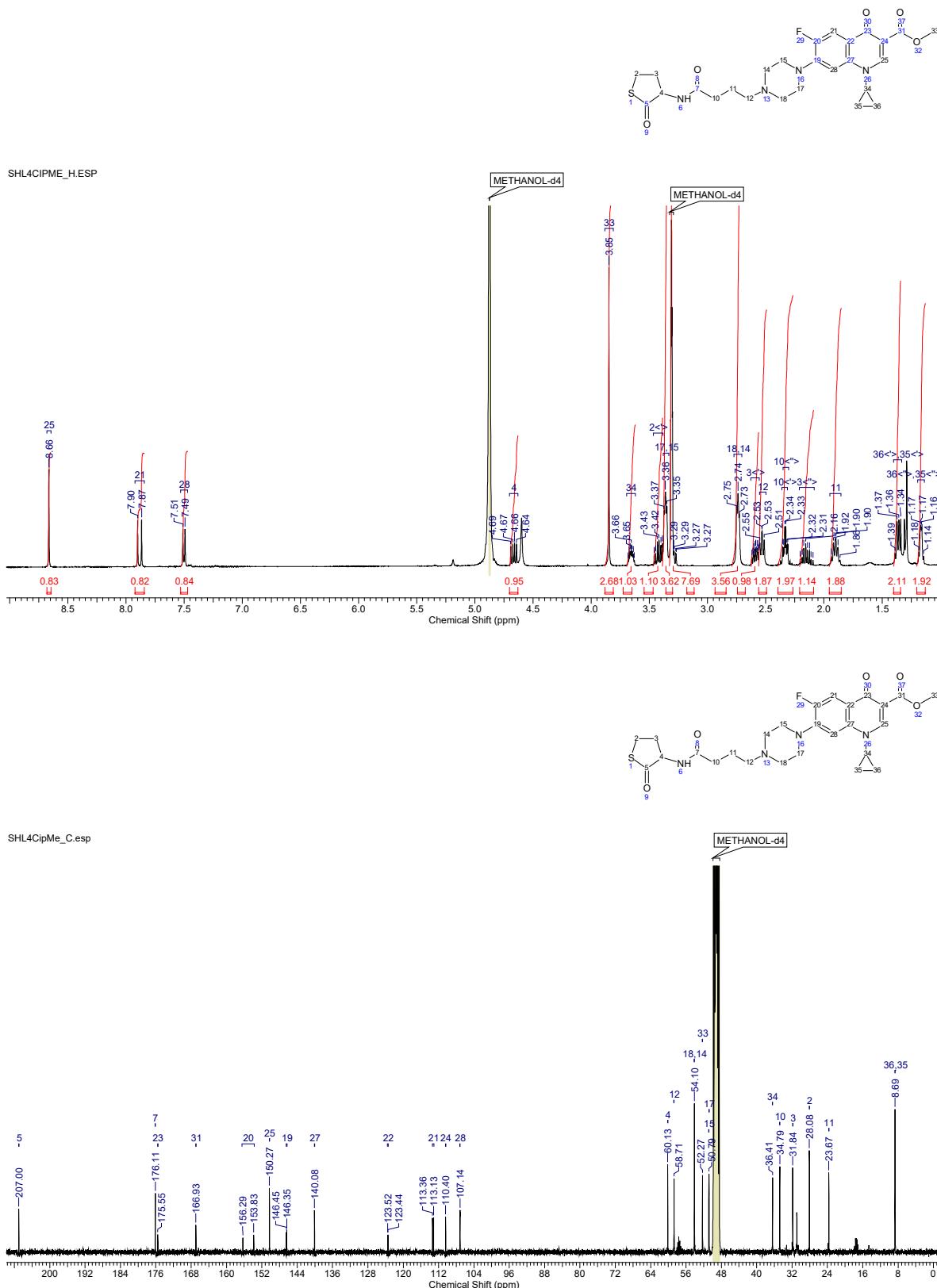
## 2.16 4-Bromo-*N*-(2-oxotetrahydrothiophen-3-yl)butanamide 105



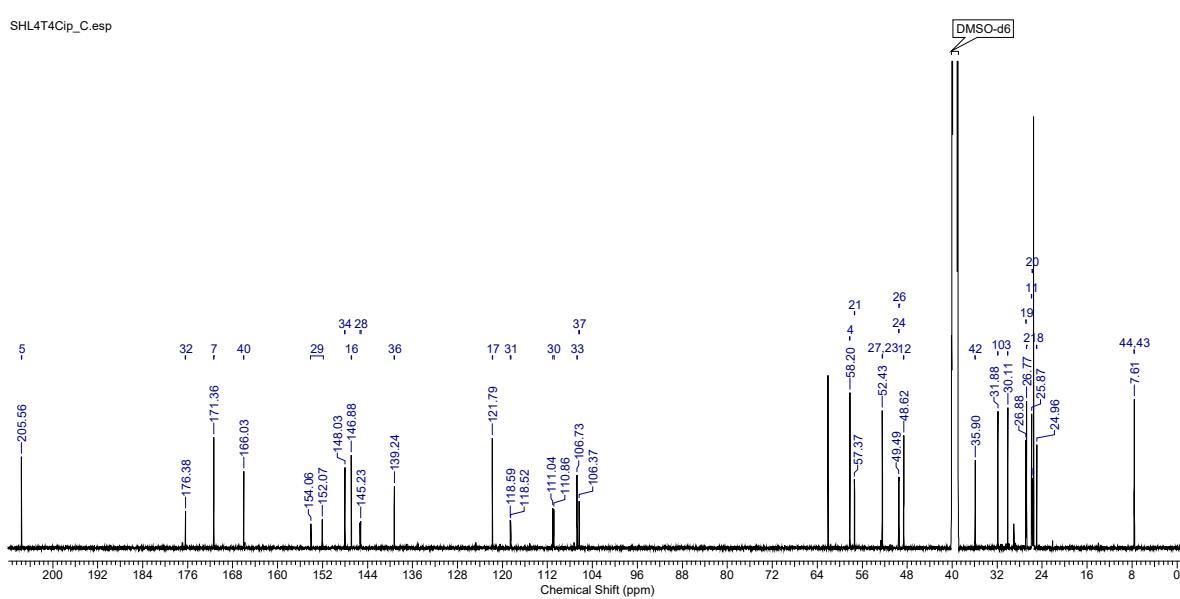
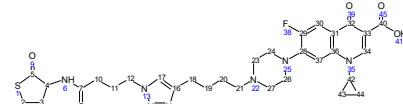
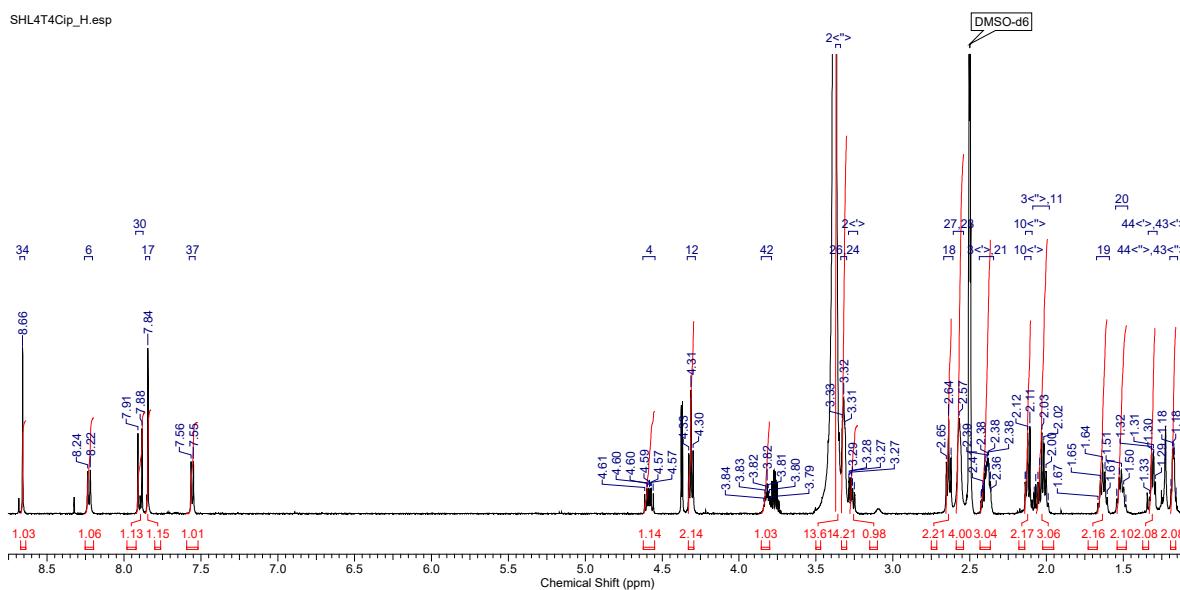
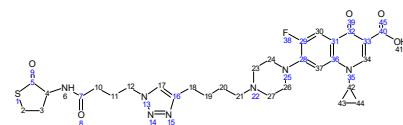
2.17 4-Azido-*N*-(2-oxotetrahydrothiophen-3-yl)butanamide 106



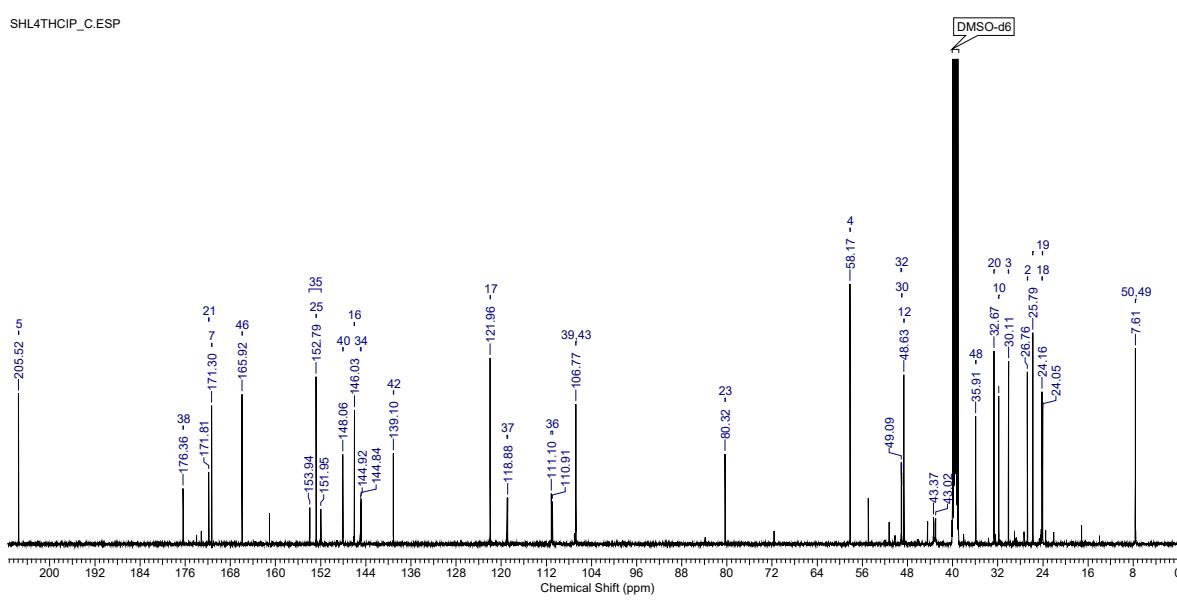
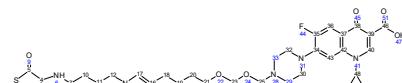
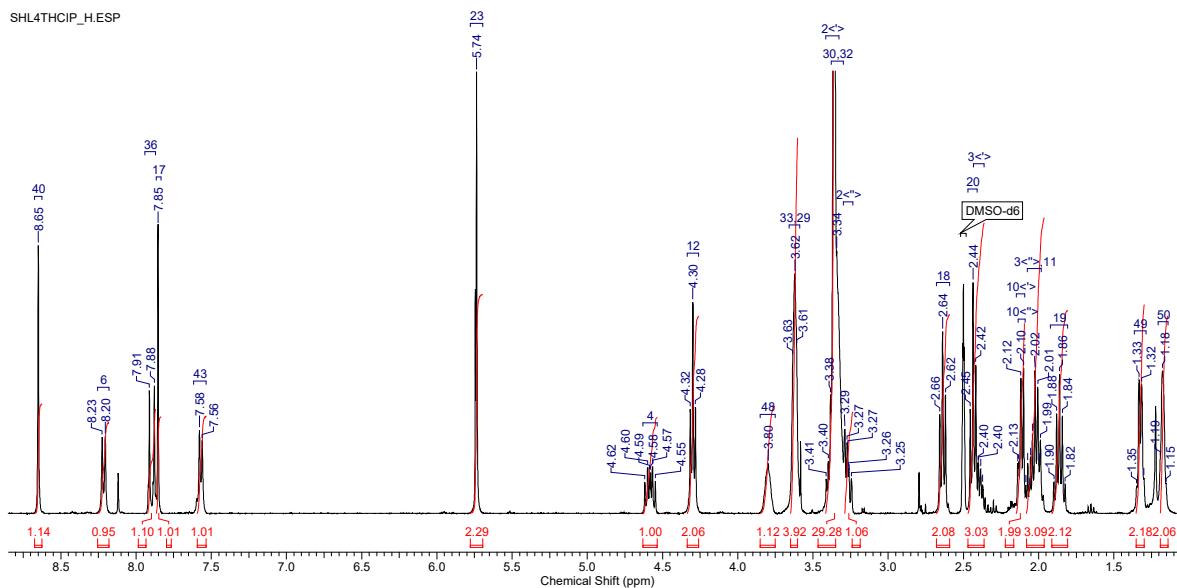
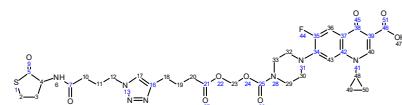
2.18 Methyl 1-cyclopropyl-6-fluoro-4-oxo-7-(4-(4-oxo-4-((2-oxotetrahydrothiophen-3-yl)amino)butyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate 107



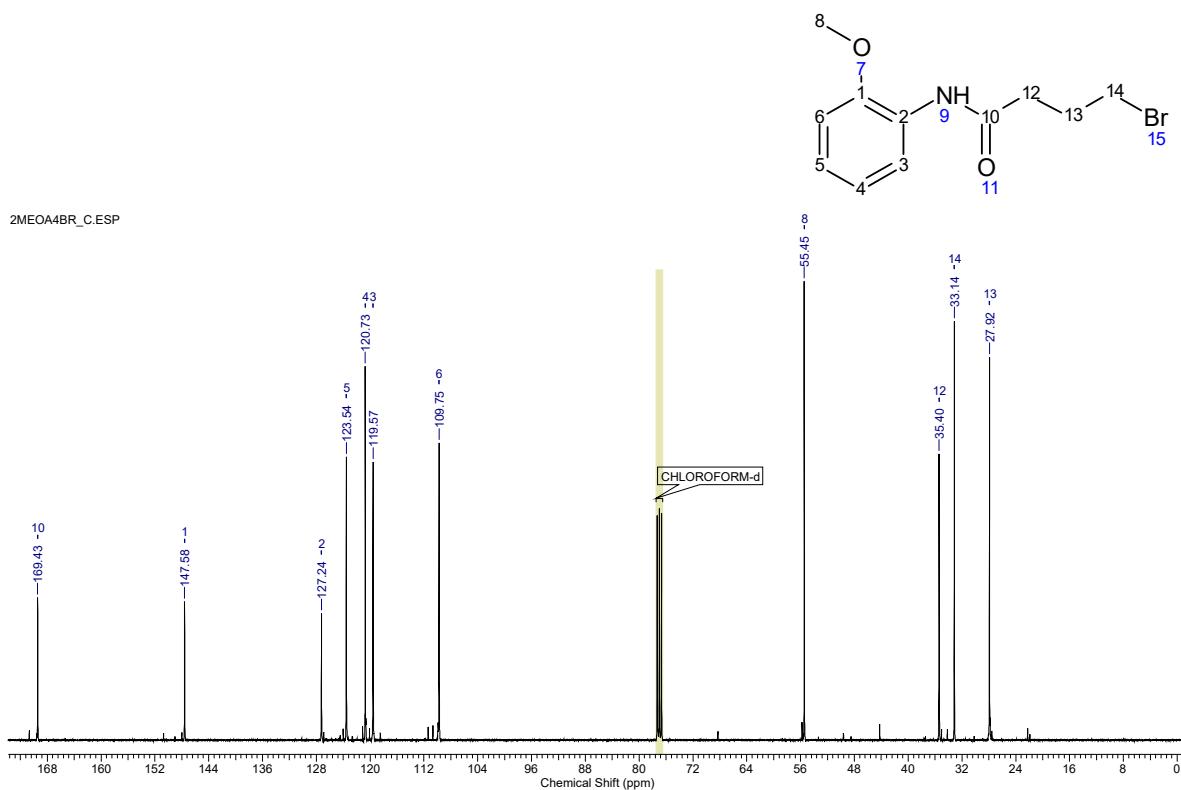
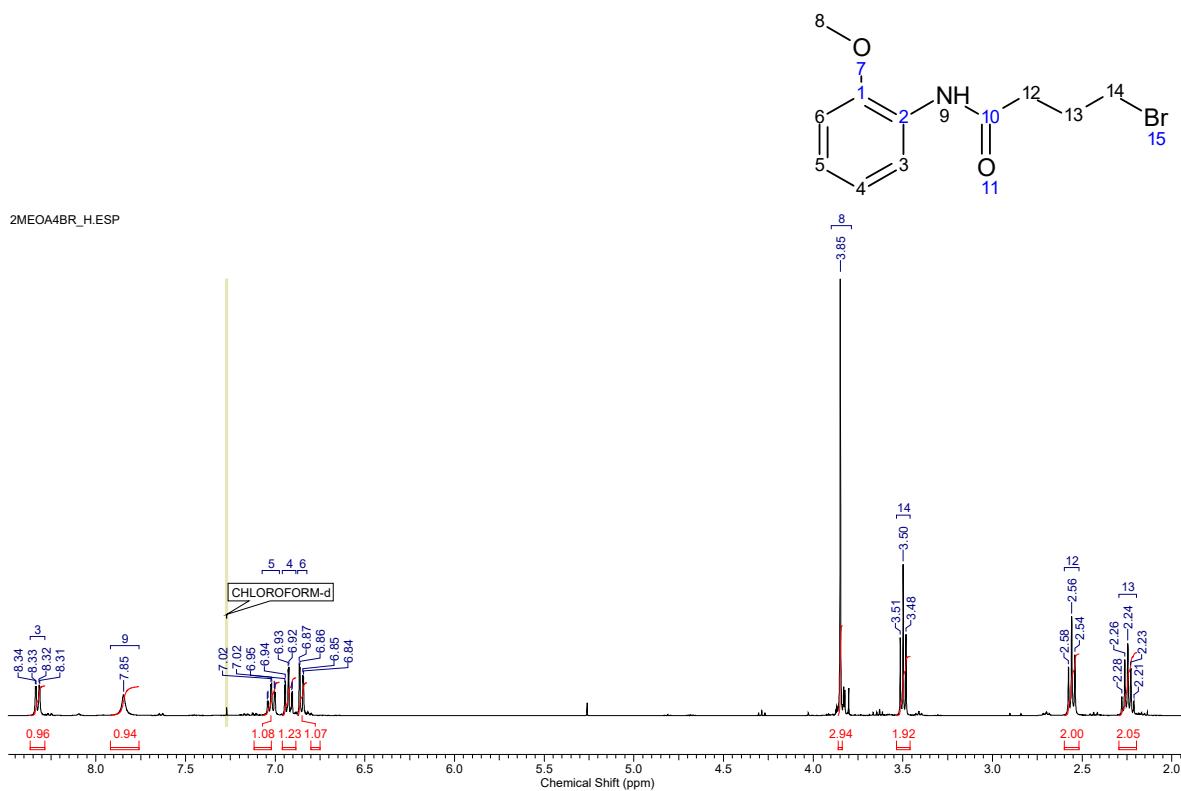
2.19 1-Cyclopropyl-6-fluoro-4-oxo-7-(4-(4-(1-(4-oxo-4-((2-oxotetrahydrothiophen-3-yl)amino)butyl)-1*H*-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid 108



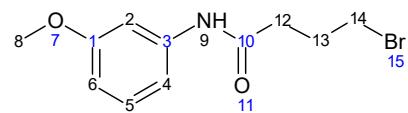
2.20 1-Cyclopropyl-6-fluoro-4-oxo-7-(((4-(1-(4-oxo-4-((2-oxotetrahydrothiophen-3-yl)amino)butyl)-1*H*-1,2,3-triazol-4-yl)butanoyl)oxy)methoxy)carbonyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid 110



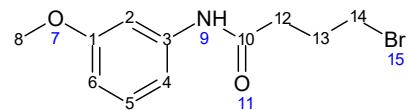
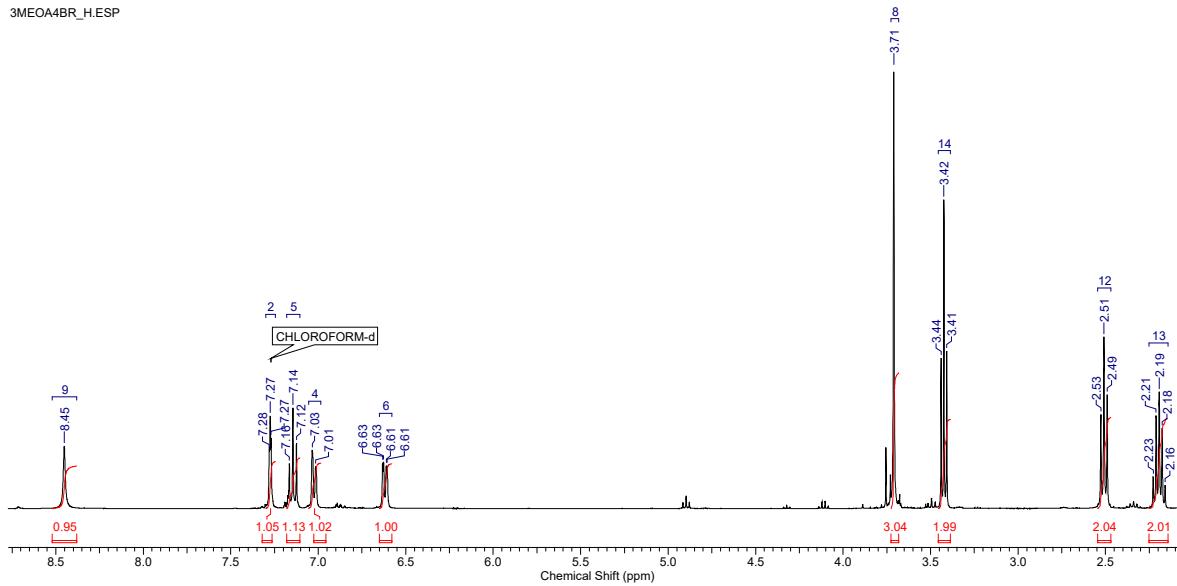
## 2.21 4-Bromo-N-(2-methoxyphenyl)butanamide 112



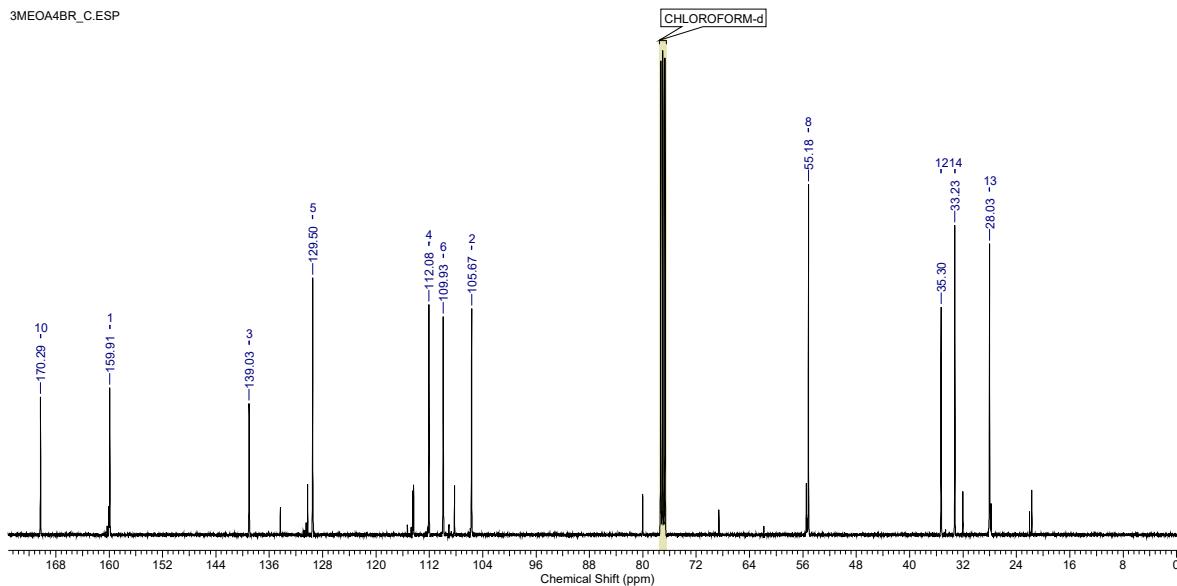
## 2.22 4-Bromo-N-(3-methoxyphenyl)butanamide 114



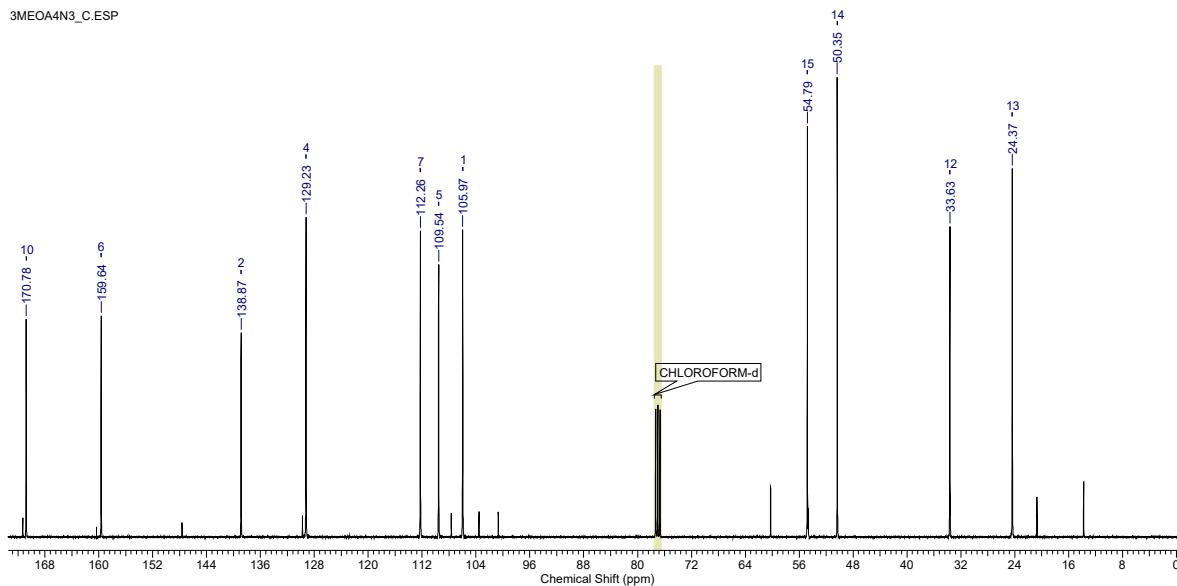
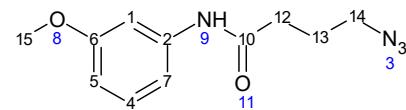
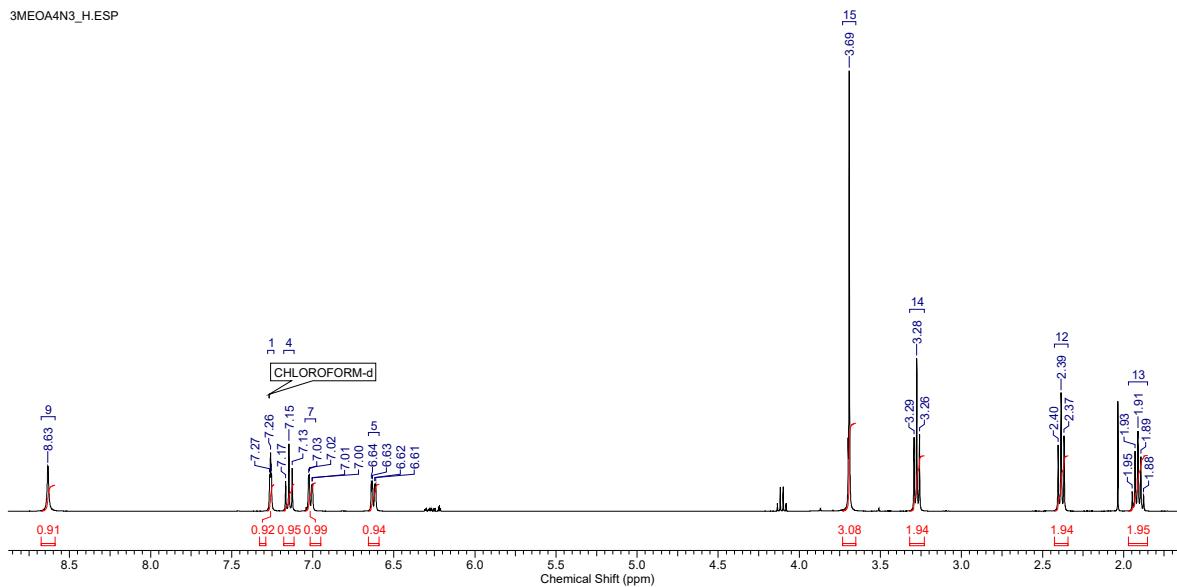
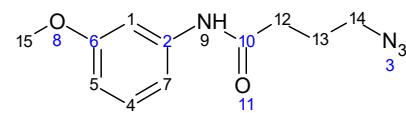
3MEOA4BR\_H.ESP



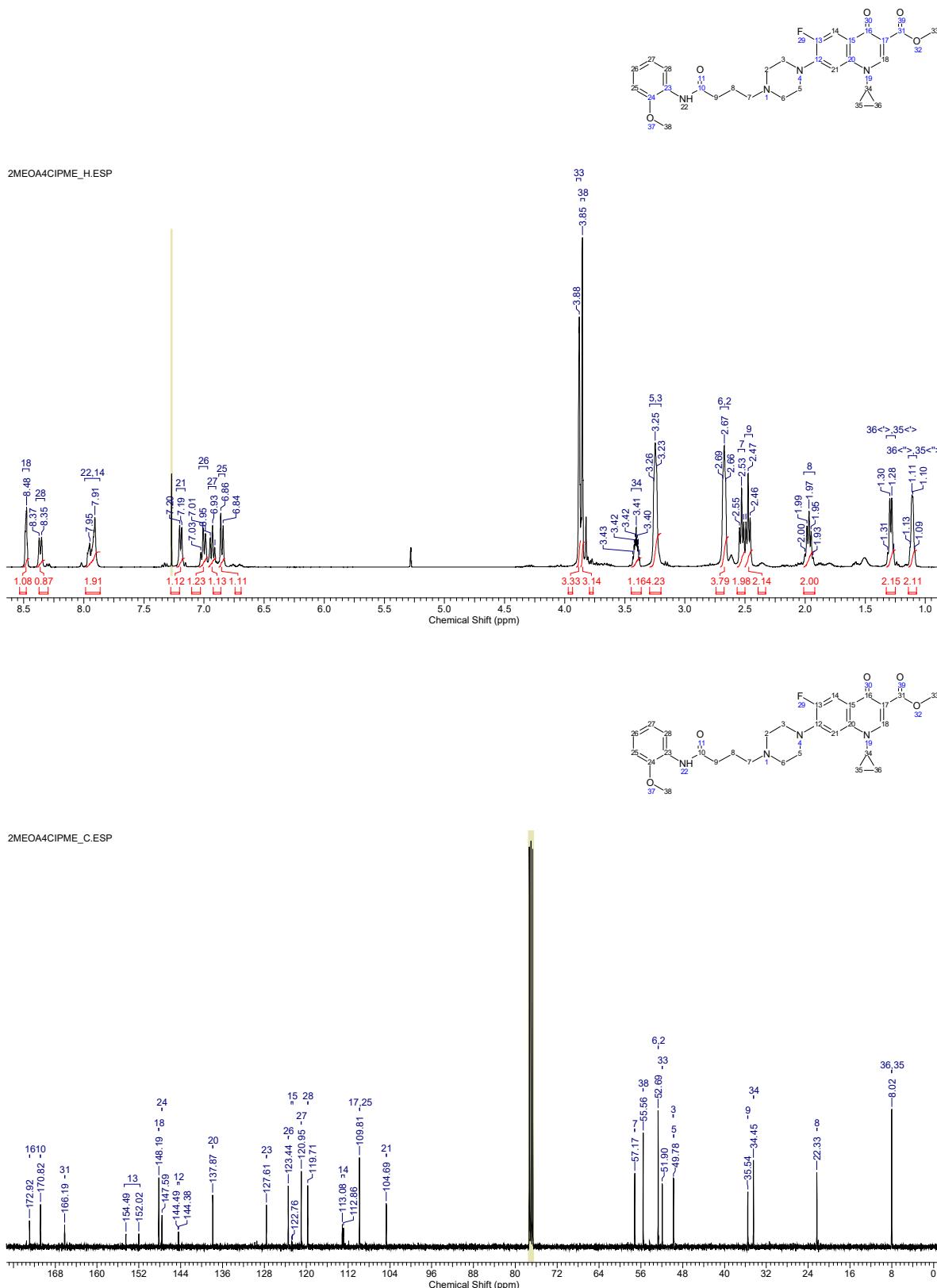
3MEOA4BR\_C.ESP



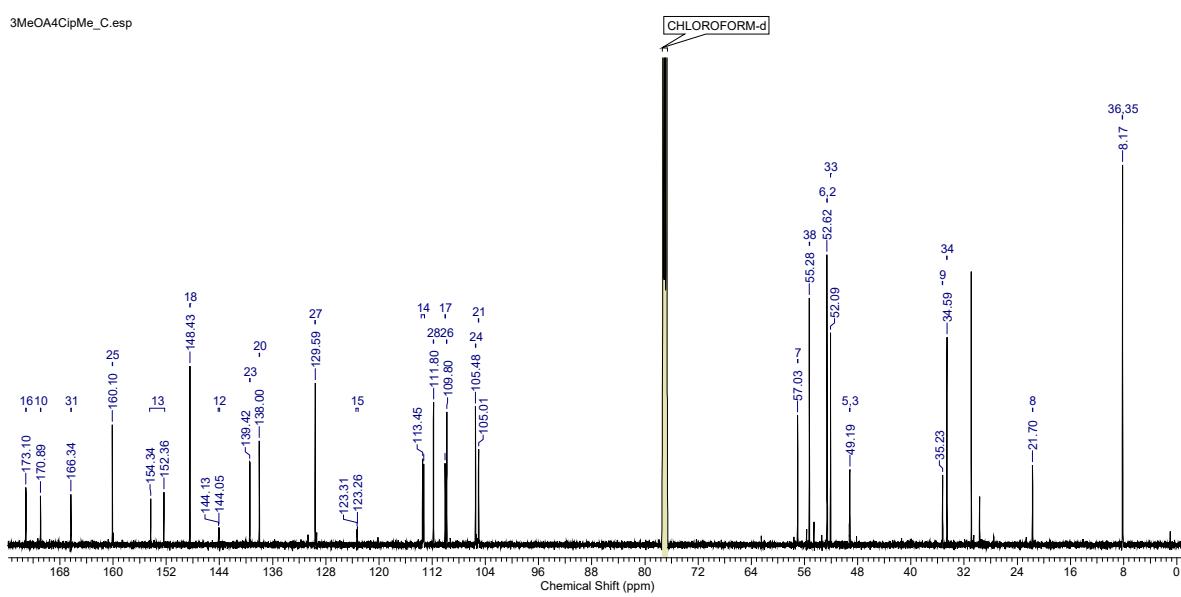
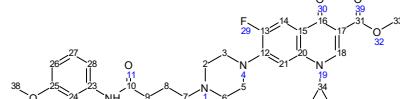
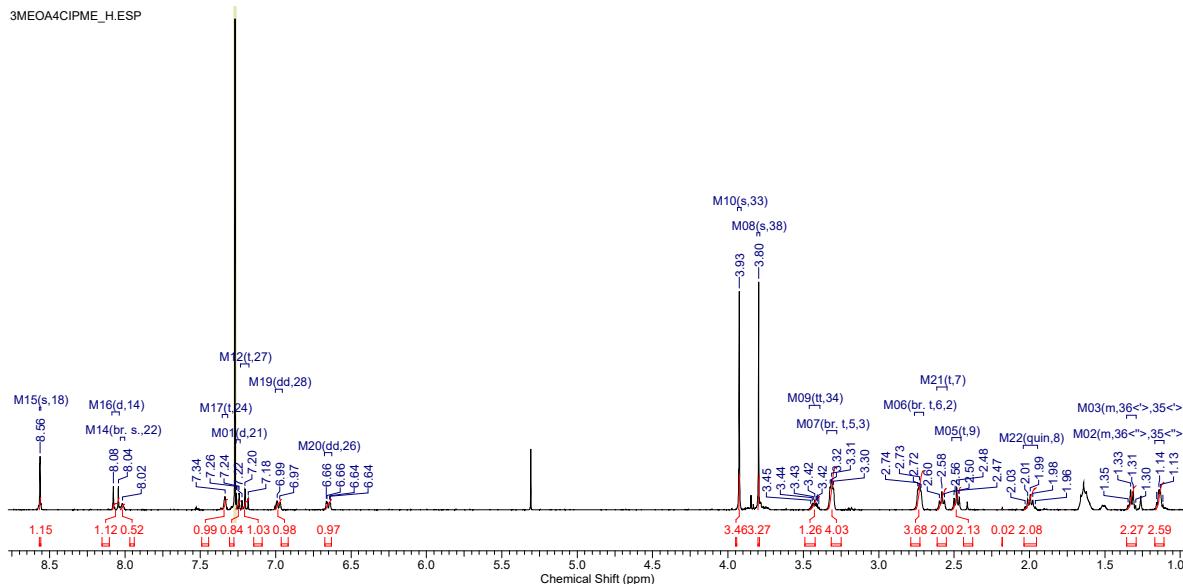
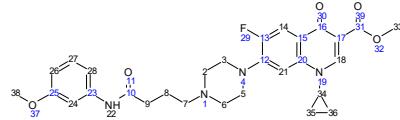
2.23 4-Azido-*N*-(3-methoxyphenyl)butanamide 116



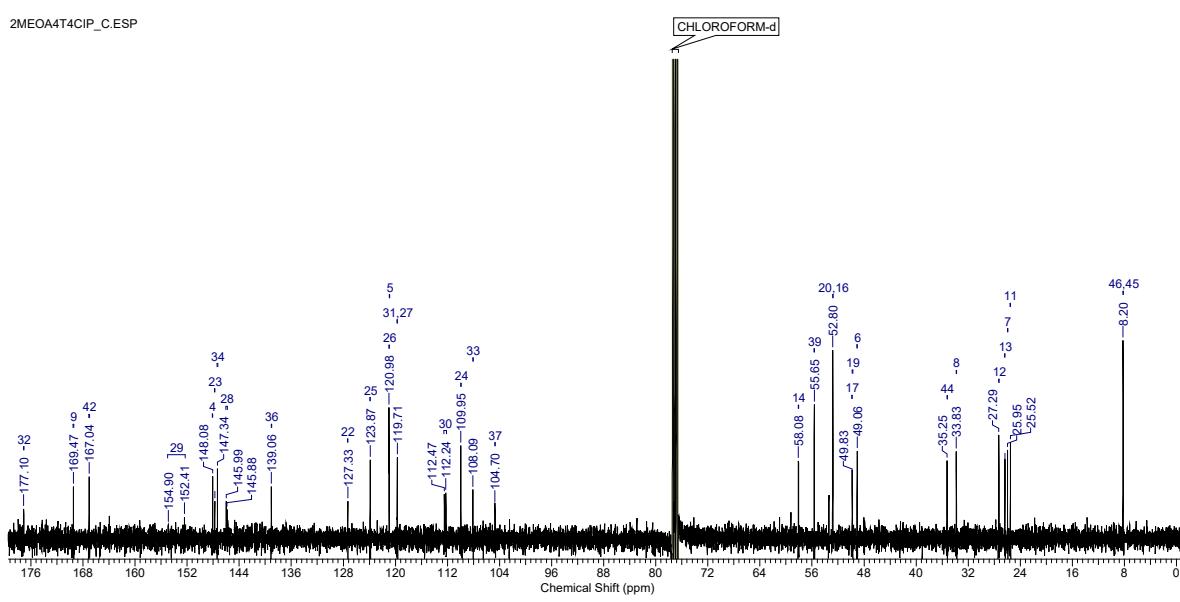
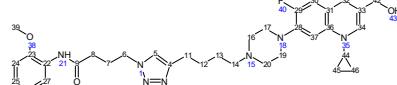
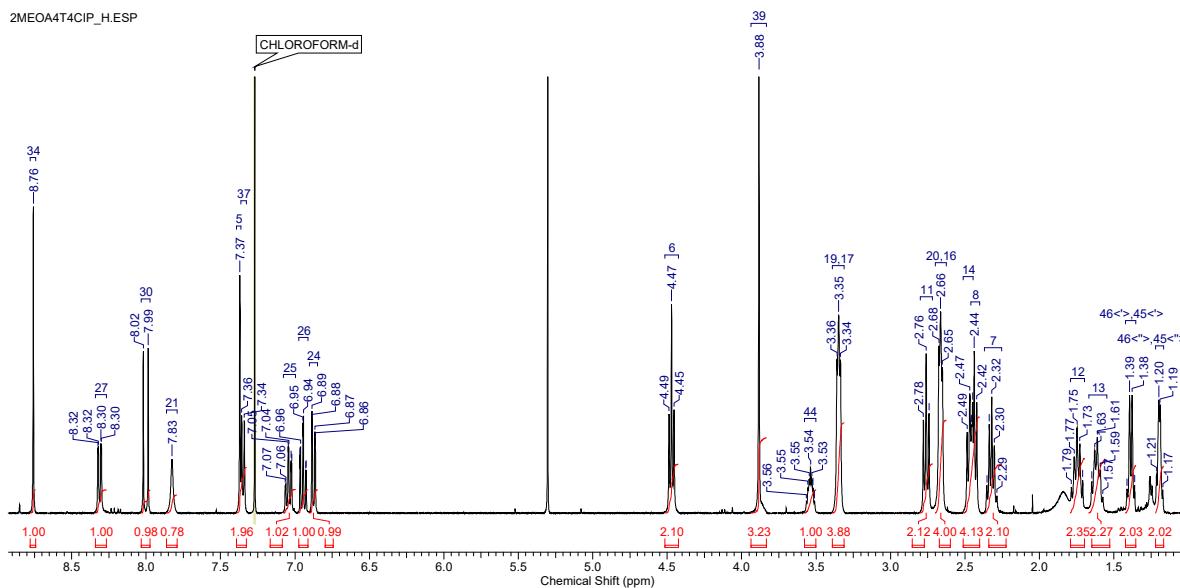
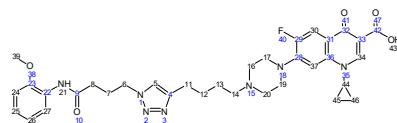
**2.24 Methyl 1-cyclopropyl-6-fluoro-7-(4-((2-methoxyphenyl)amino)-4-oxobutyl)-piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 117**



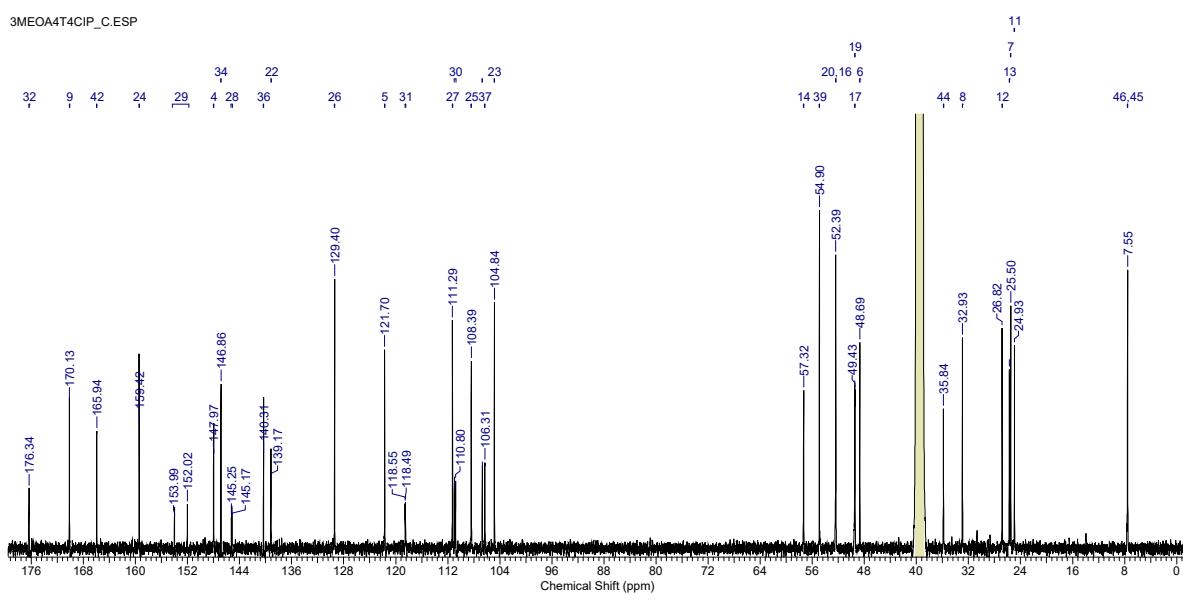
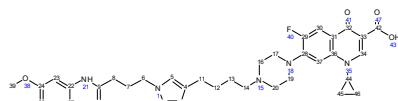
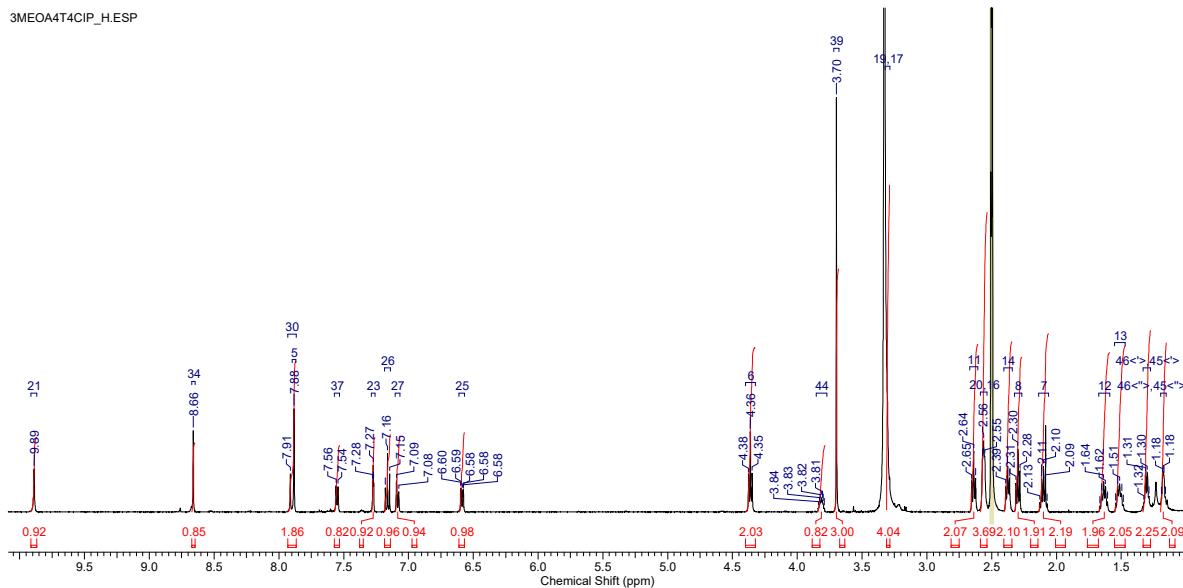
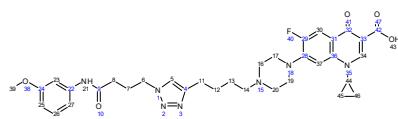
2.25 Methyl 1-cyclopropyl-6-fluoro-7-(4-(4-((3-methoxyphenyl)amino)-4-oxobutyl)-piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 118



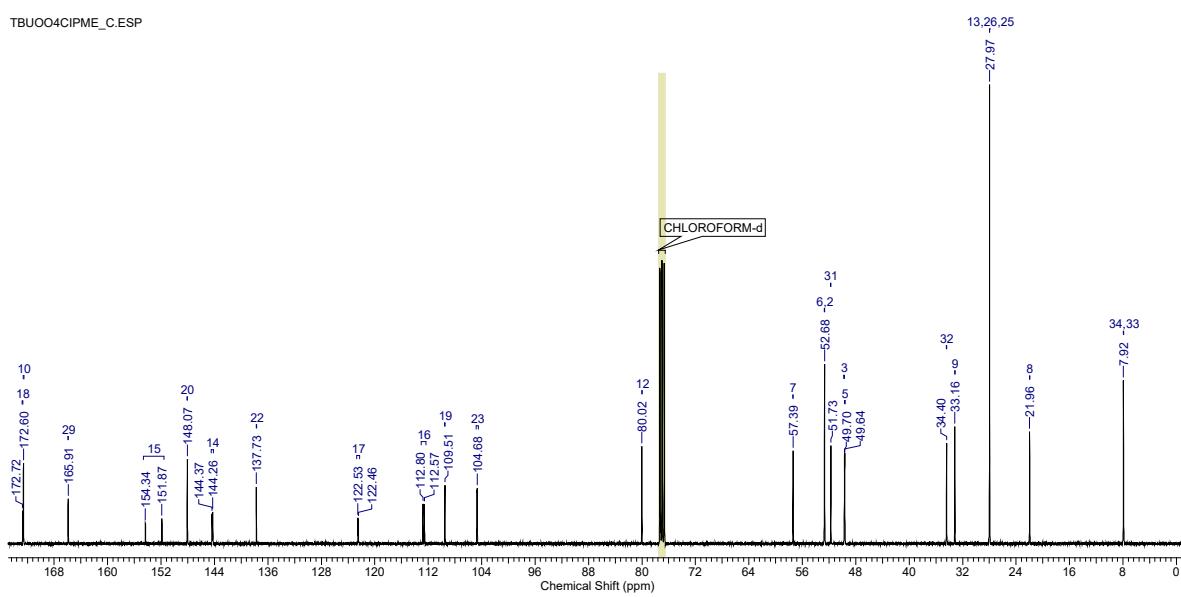
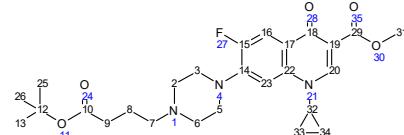
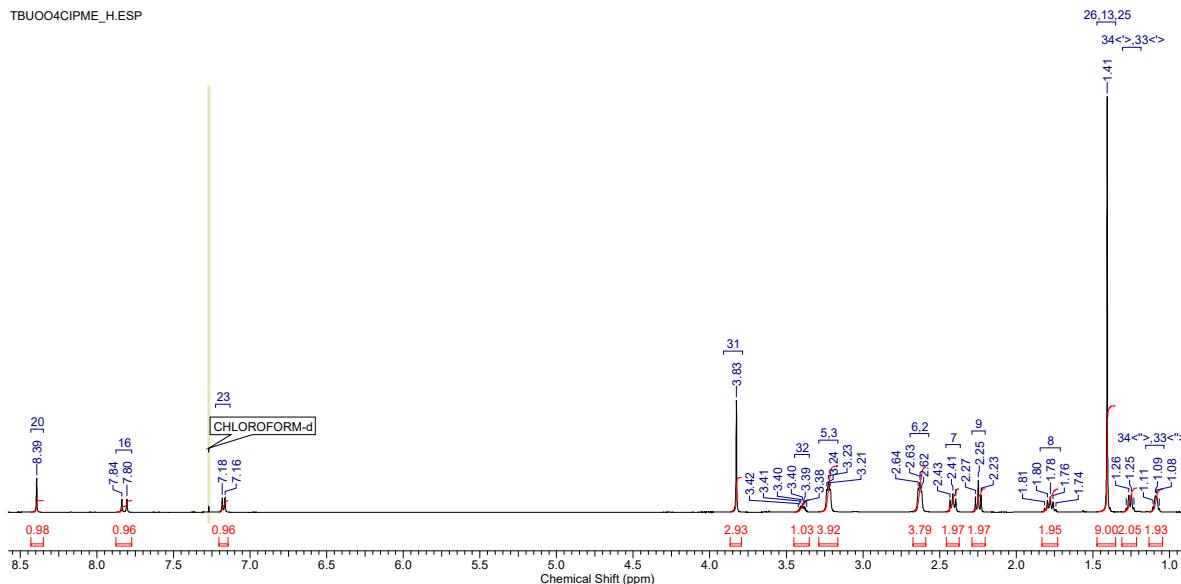
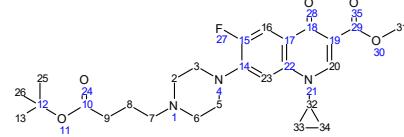
2.26 1-Cyclopropyl-6-fluoro-7-(4-(1-(4-((2-methoxyphenyl)amino)-4-oxobutyl)-1*H*-1,2,3-triazol-4-yl)butyl) piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 119



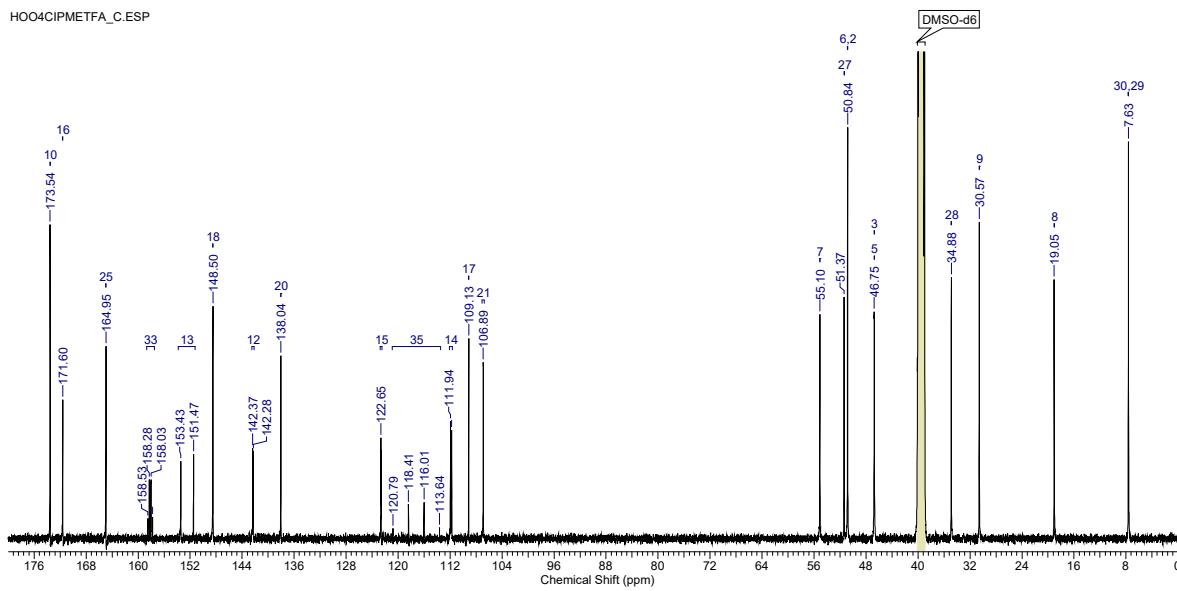
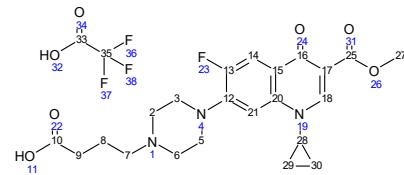
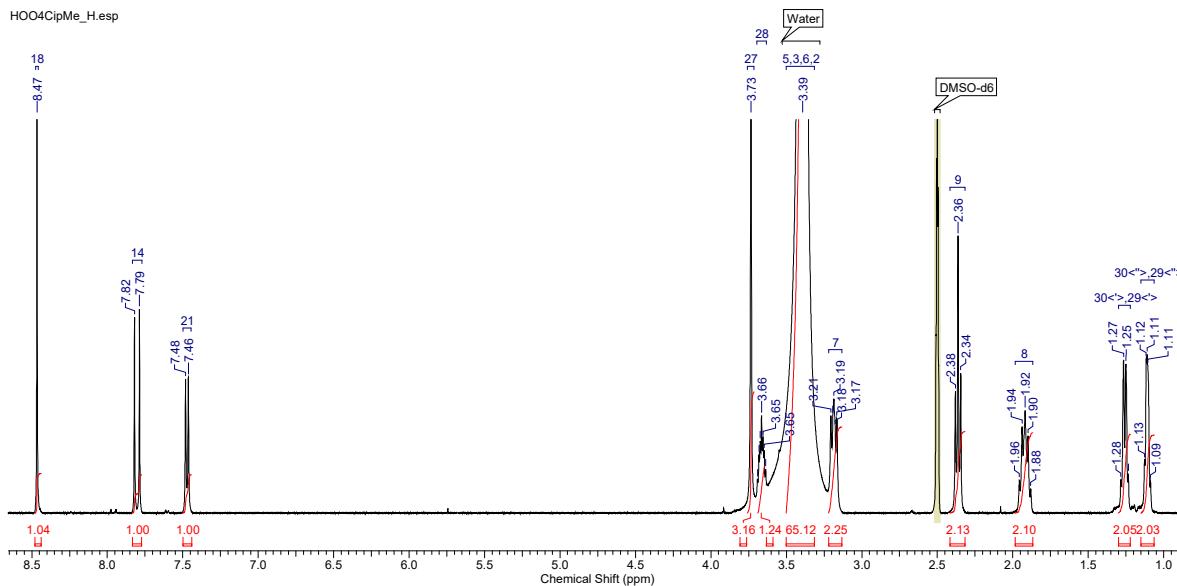
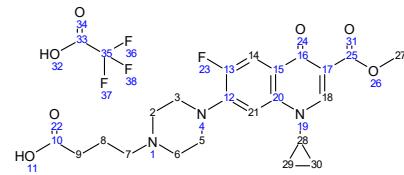
2.27 1-Cyclopropyl-6-fluoro-7-(4-(1-(4-((3-methoxyphenyl)amino)-4-oxobutyl)-1*H*-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 120



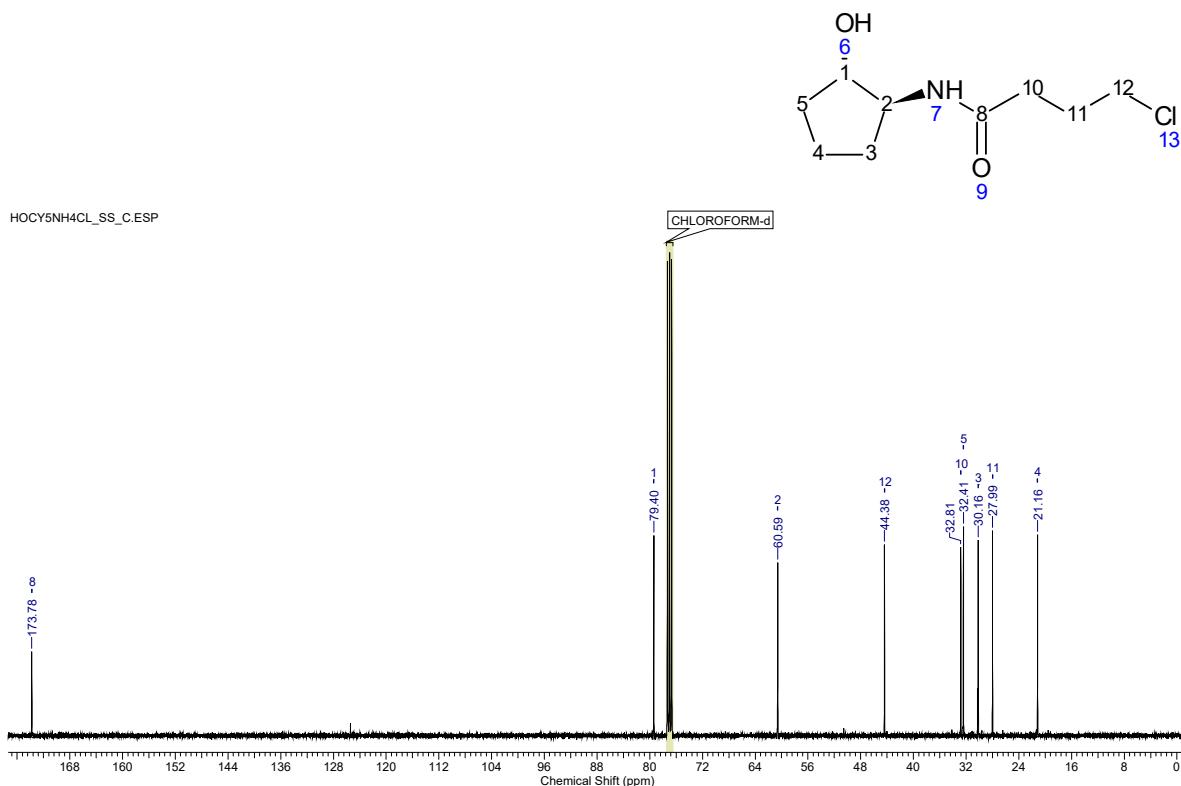
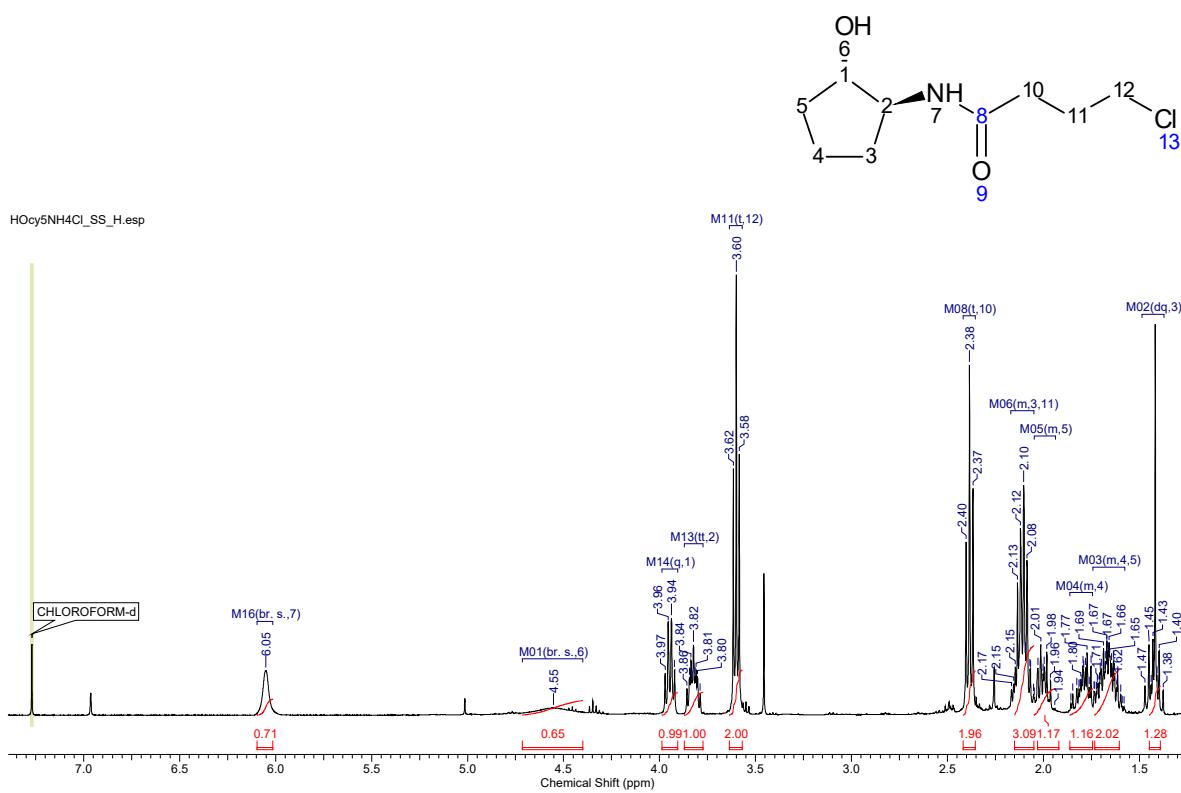
**2.28 Methyl 7-(4-(*tert*-butoxy)-4-oxobutyl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate 122**



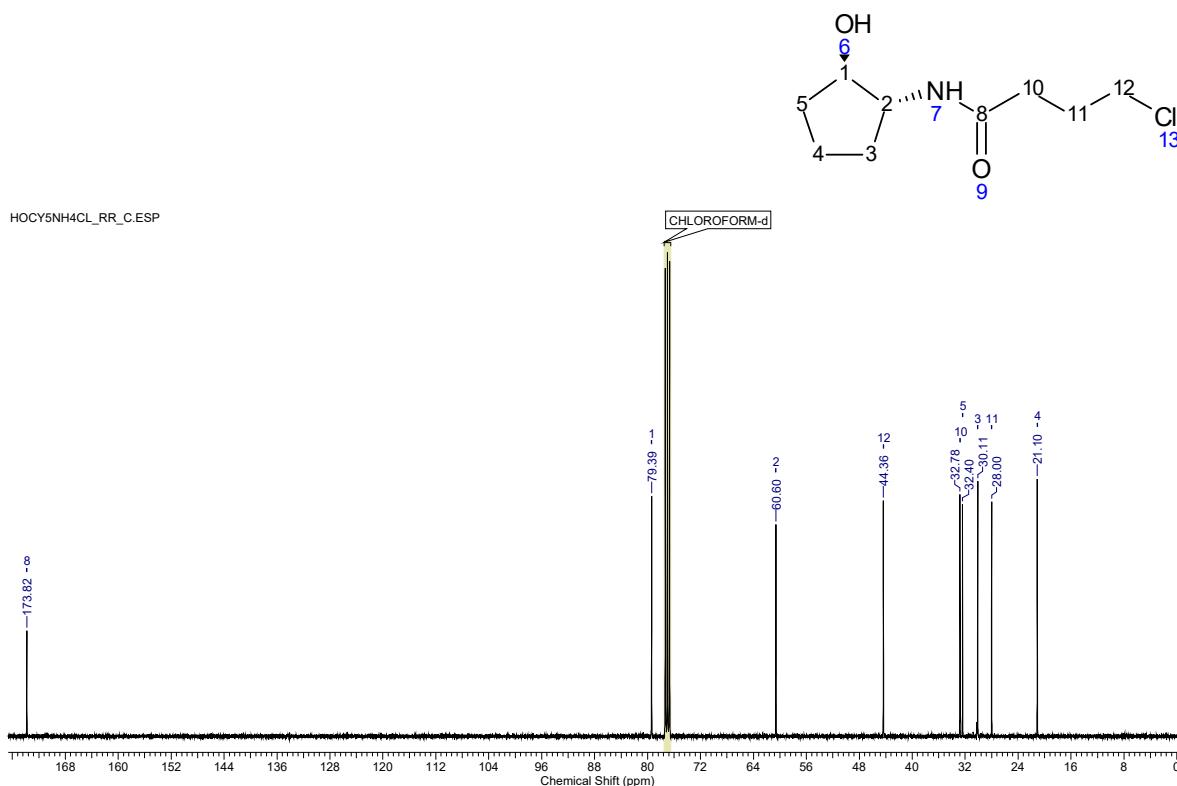
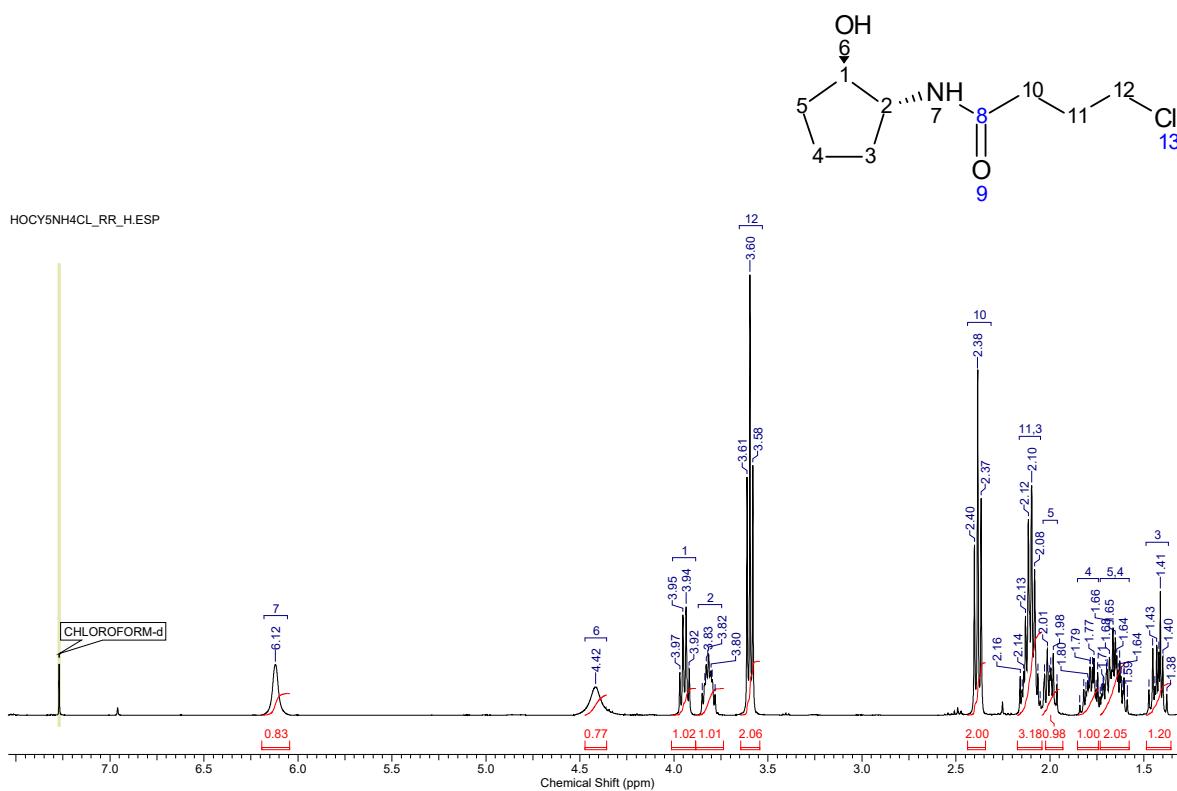
**2.29 4-(4-(1-Cyclopropyl-6-fluoro-3-(methoxycarbonyl)-4-oxo-1,4-dihydroquinolin-7-yl)piperazin-1-yl)butanoic acid, trifluoroacetic acid salt 123**



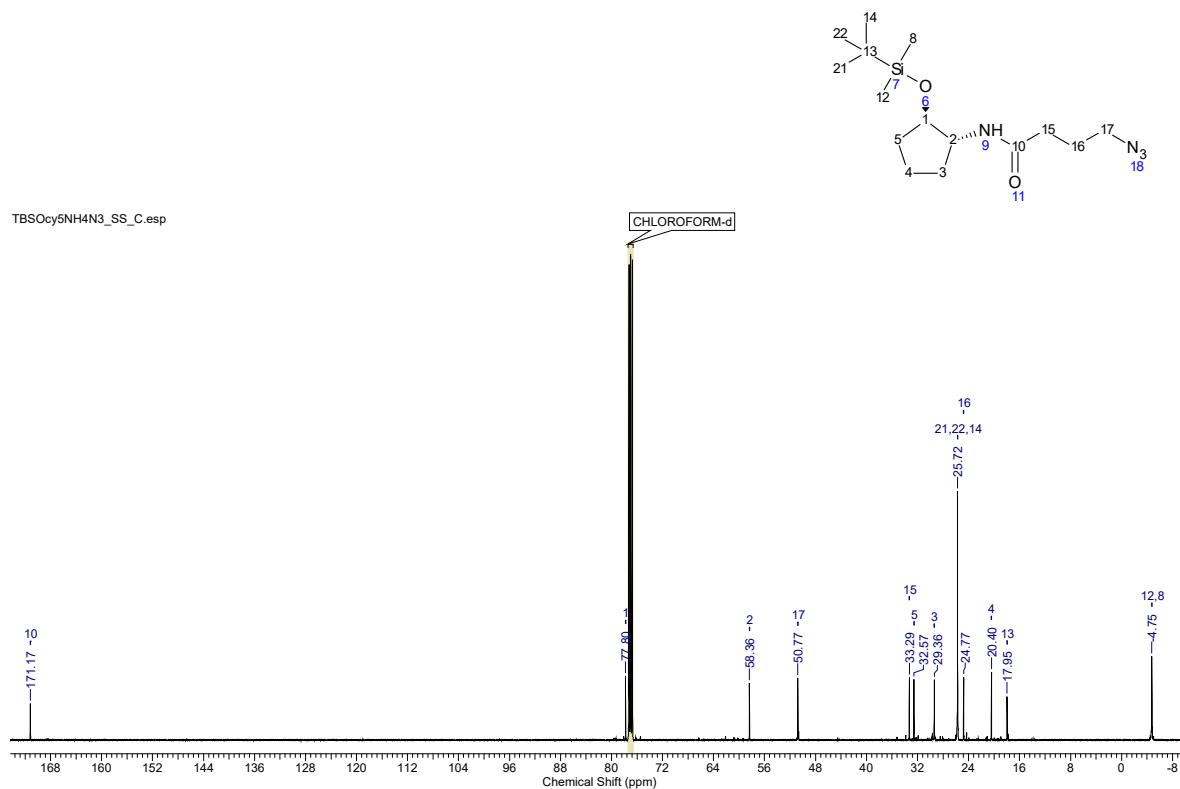
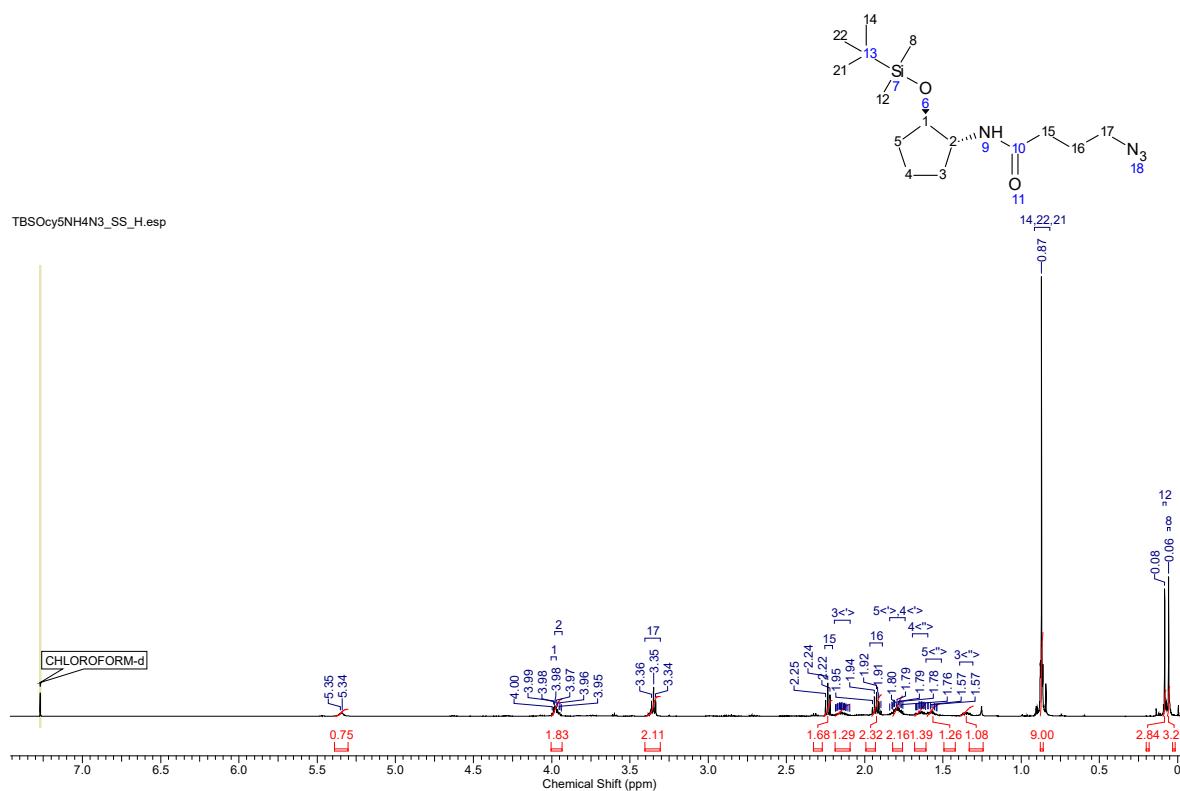
## 2.30 4-Chloro-*N*-((1*S*,2*S*)-2-hydroxycyclopentyl)butanamide 133



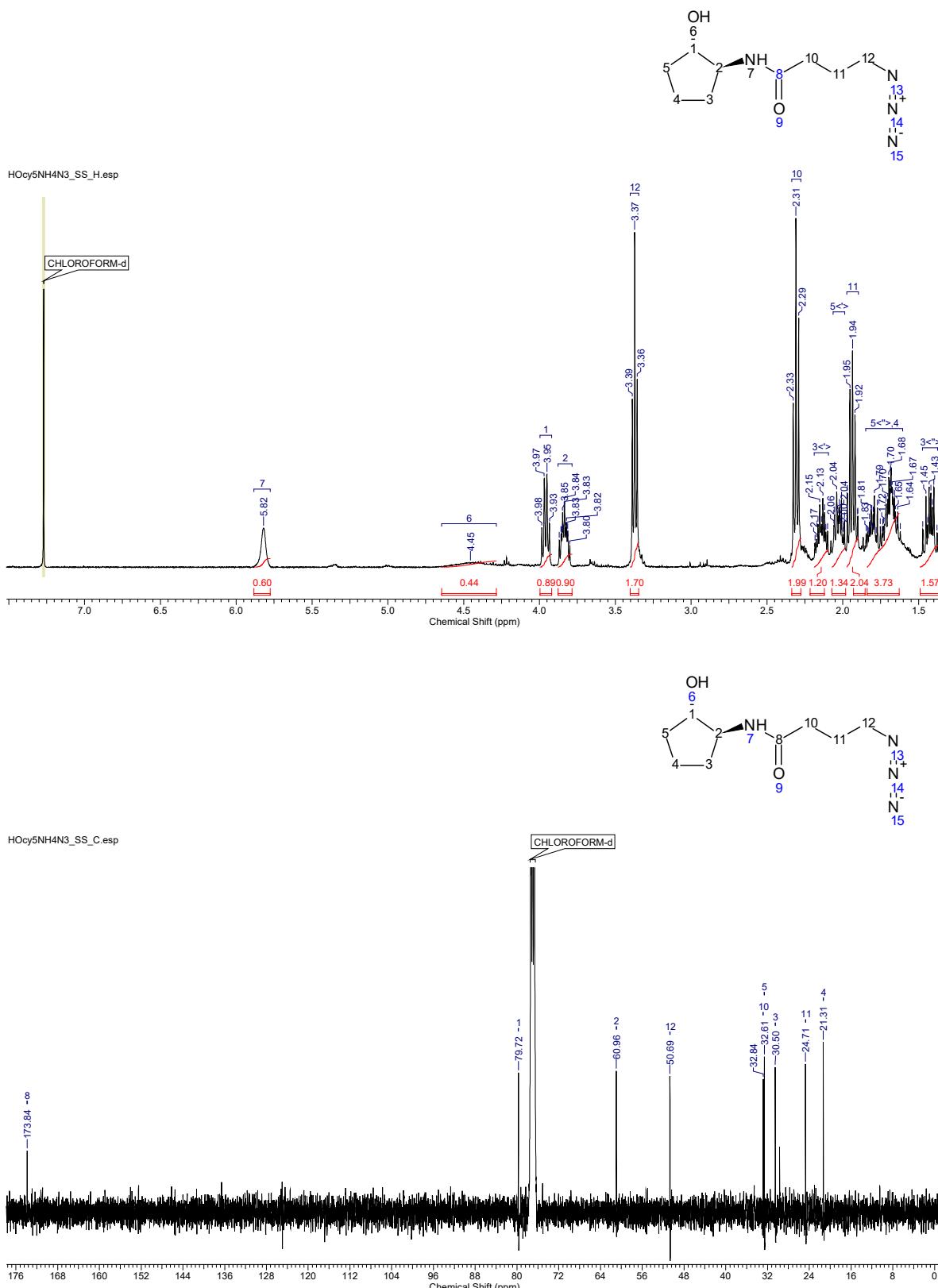
2.31 4-Chloro-*N*-(*1R,2R*)-2-hydroxycyclopentyl)butanamide 132



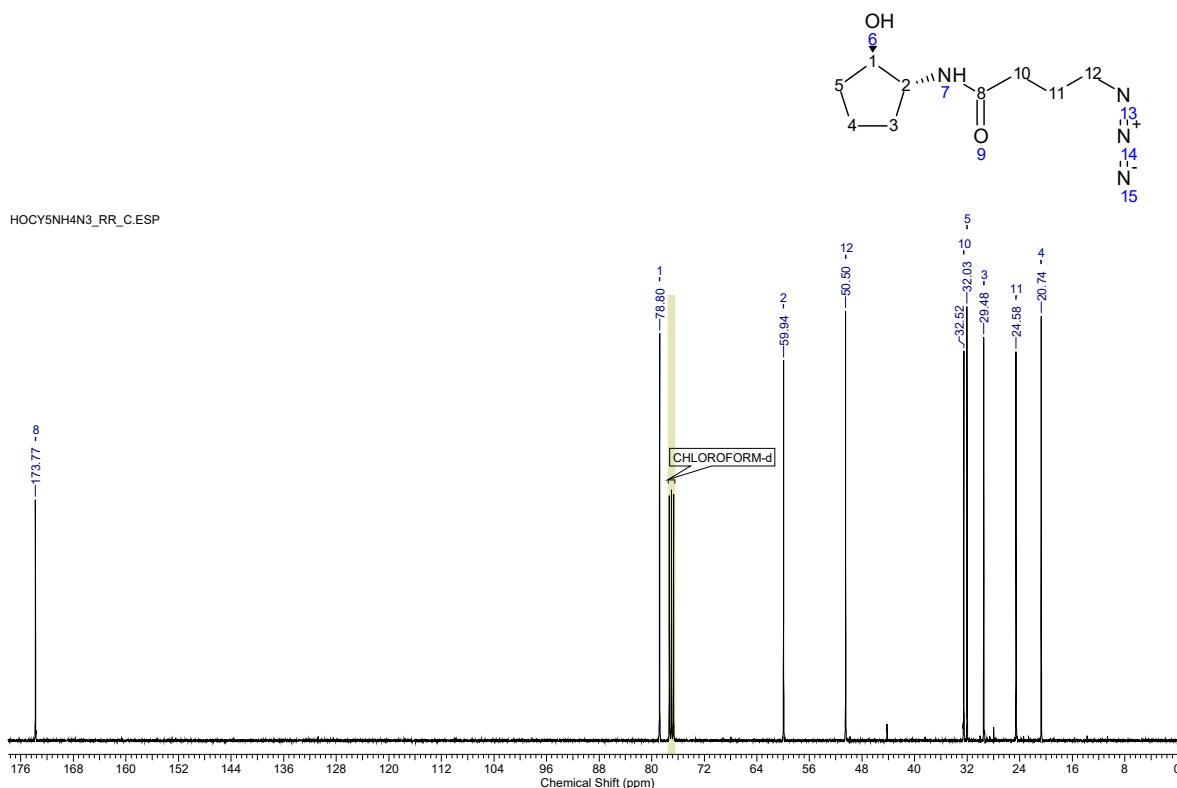
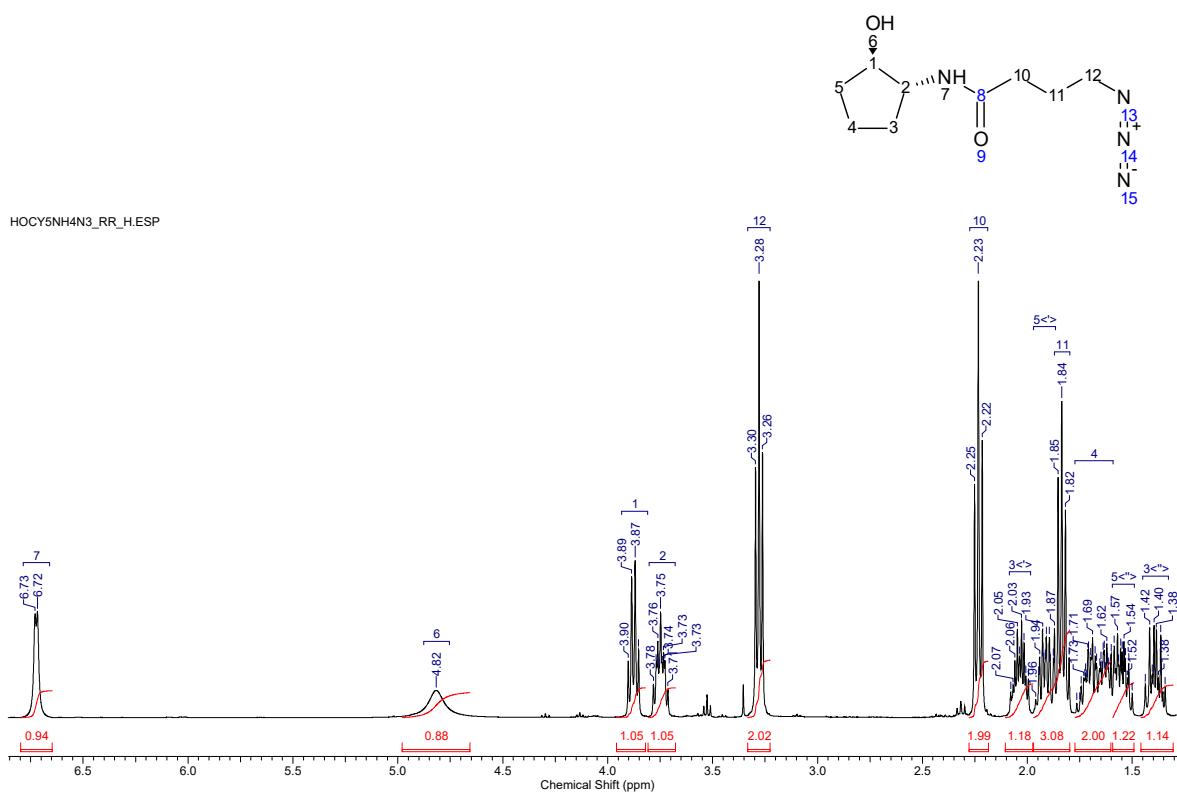
2.32 4-Azido-*N*-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclopentyl)butanamide  
134



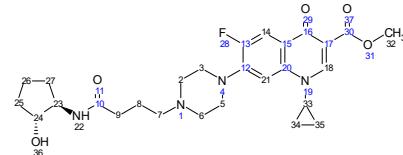
2.33 4-Azido-*N*-(*(1S,2S)*-2-hydroxycyclopentyl)butanamide 136



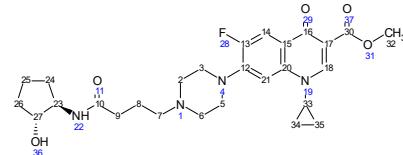
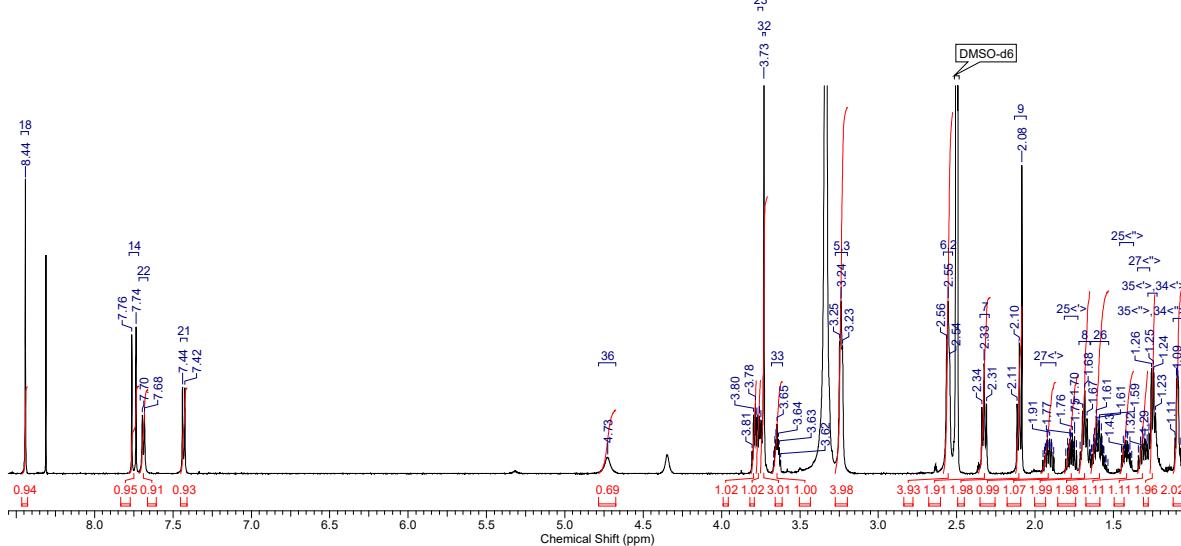
2.34 4-Azido-*N*-(*(1R,2R)*-2-hydroxycyclopentyl)butanamide 135



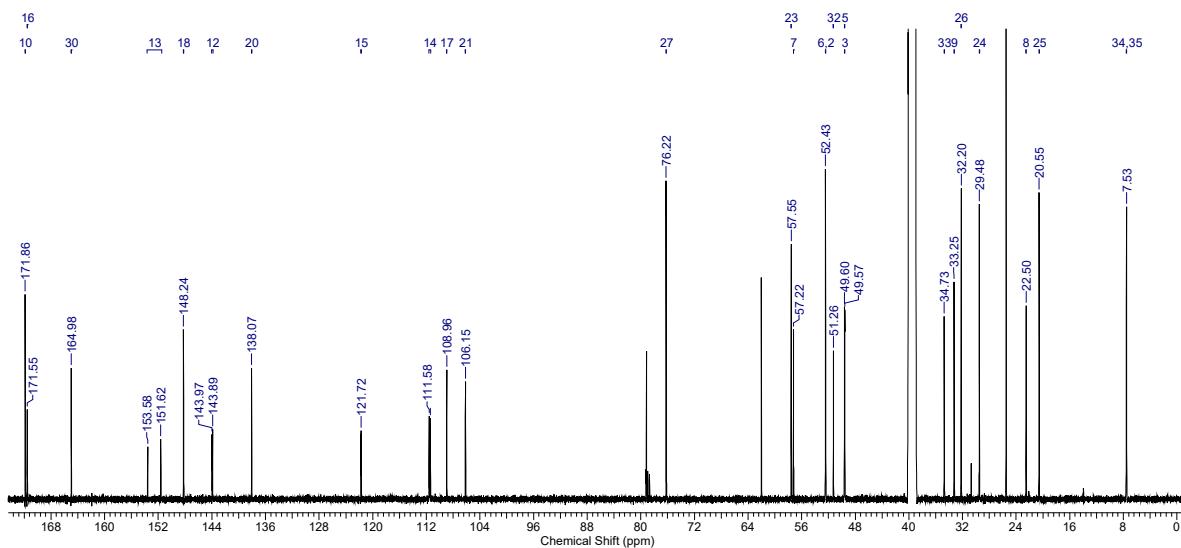
2.35 Methyl 1-cyclopropyl-6-fluoro-7-(4-((1*S*,2*S*)-2-hydroxycyclopentyl)amino)-4-oxobutyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 138



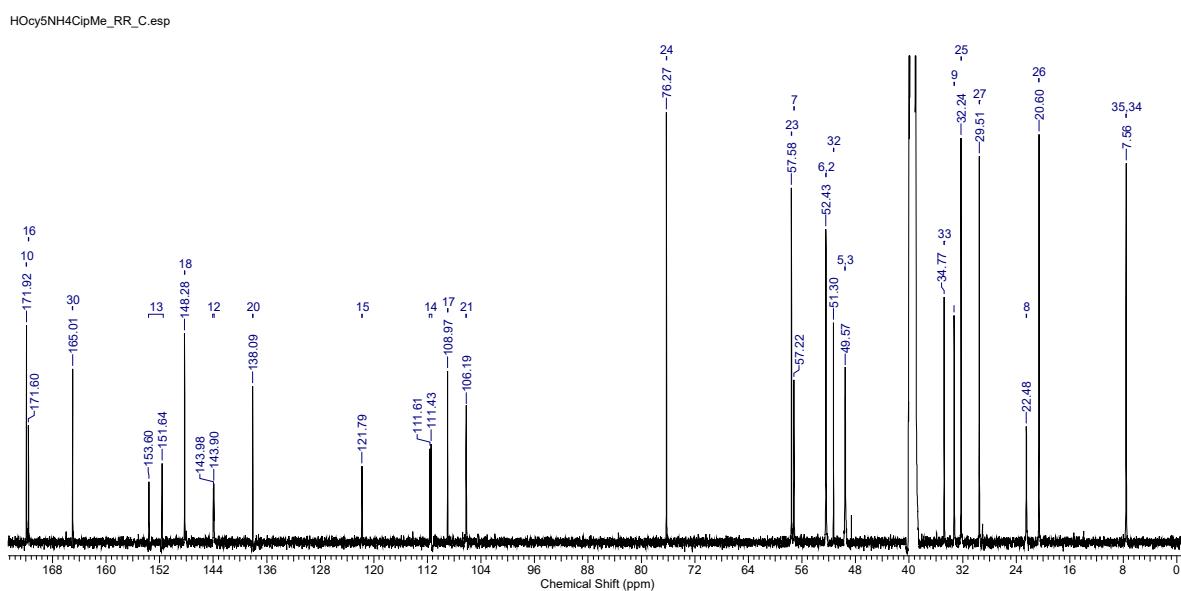
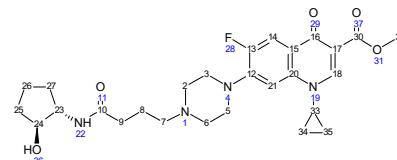
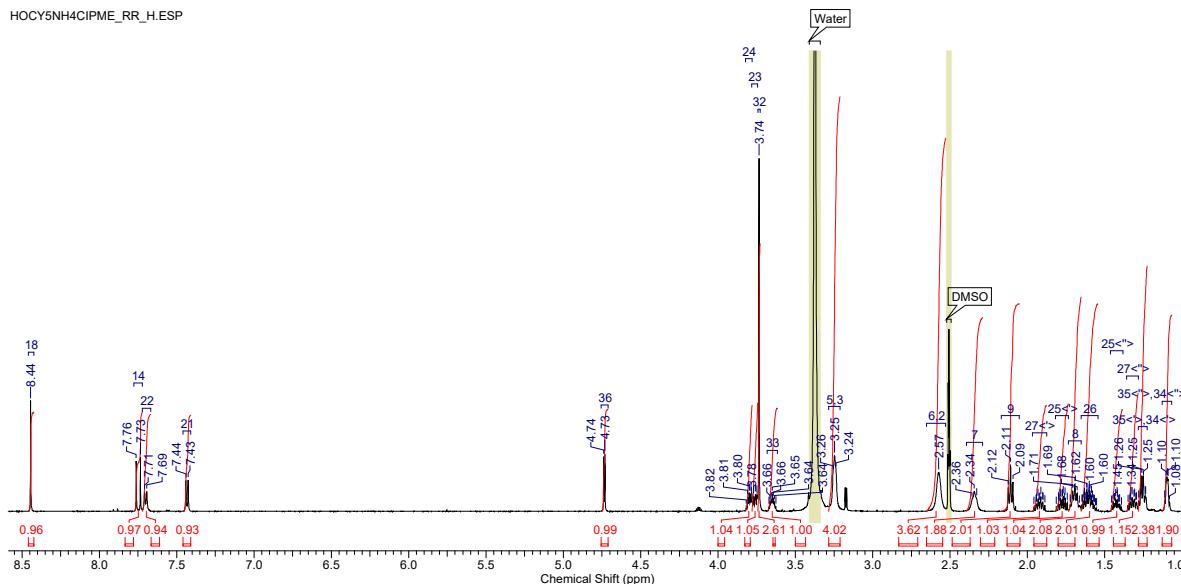
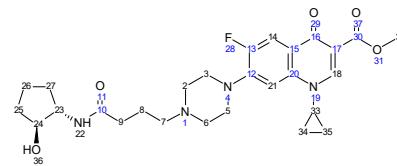
HOcy5NH4CipMe\_SS\_H.esp



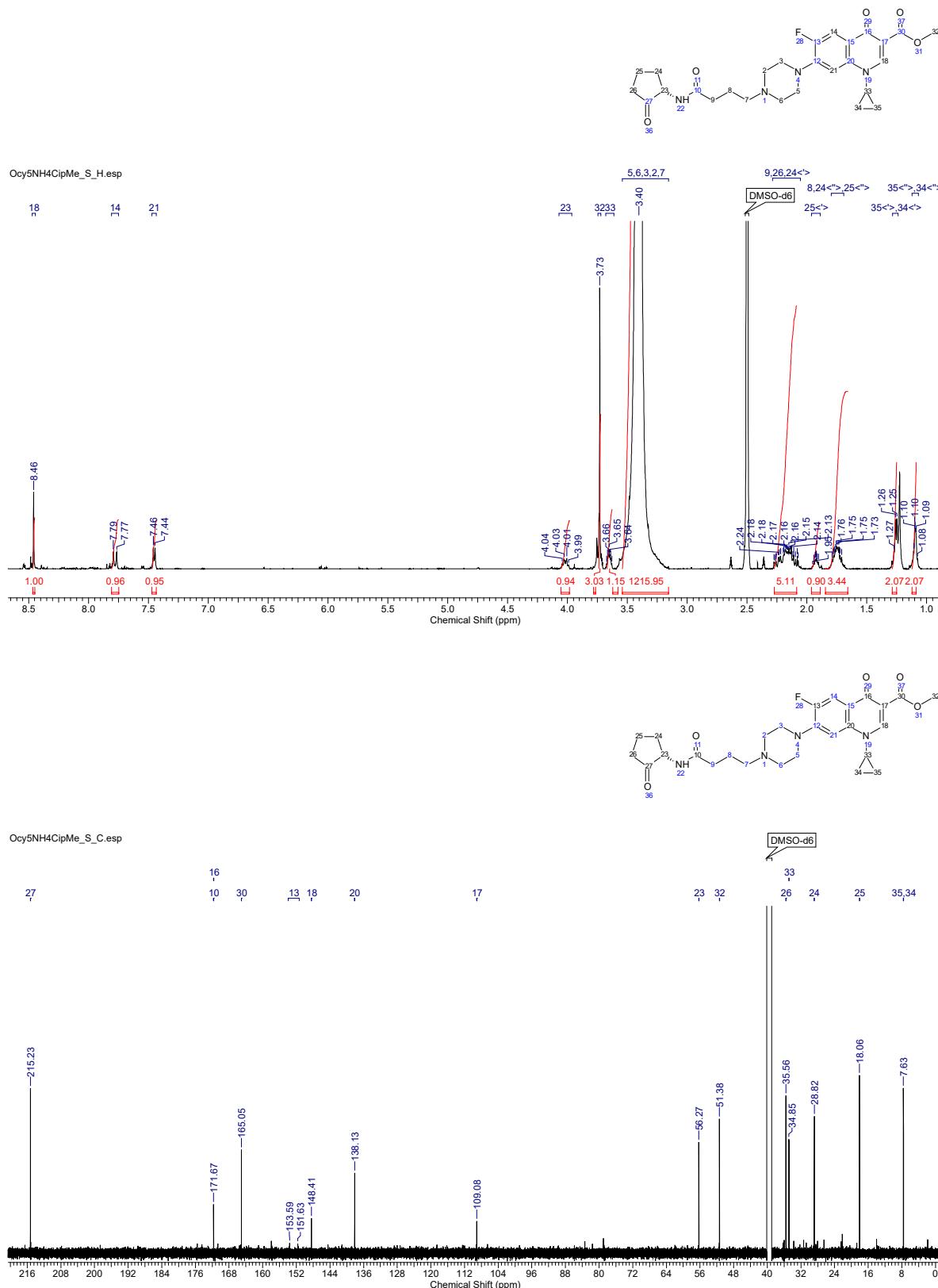
HOcy5NH4CipMe\_SS\_C.esp



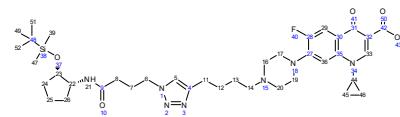
2.36 Methyl 1-cyclopropyl-6-fluoro-7-(4-((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-4-oxobutyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 137



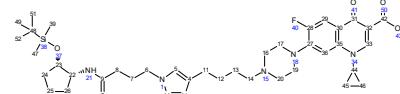
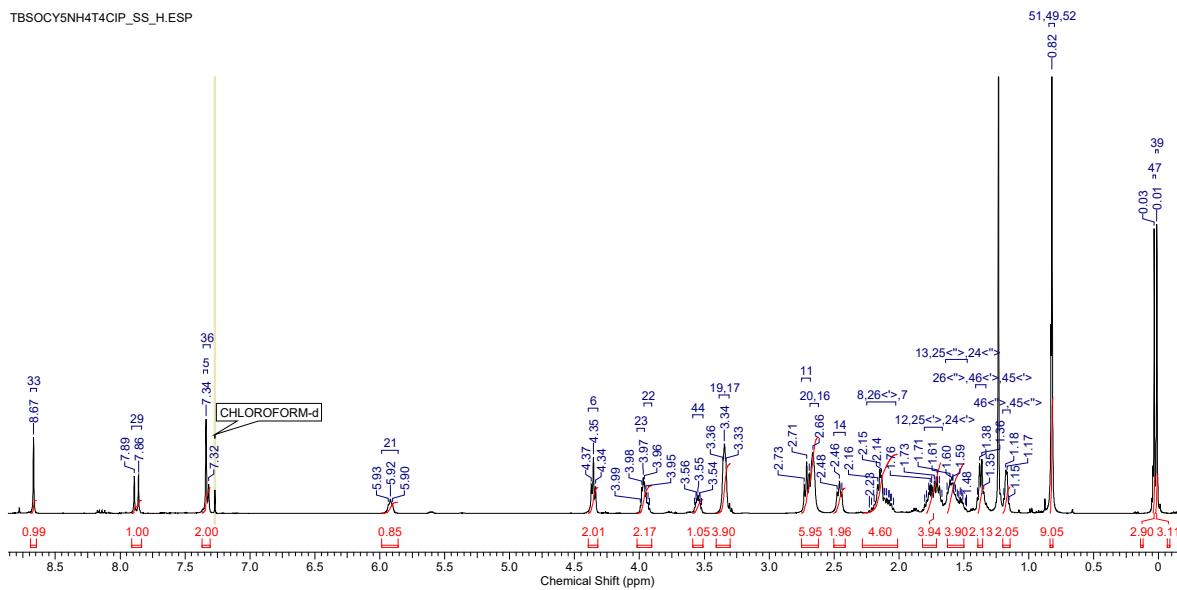
**2.37 Methyl (S)-1-cyclopropyl-6-fluoro-4-oxo-7-(4-(4-oxo-4-((2-oxocyclopentyl)amino)butyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate 152**



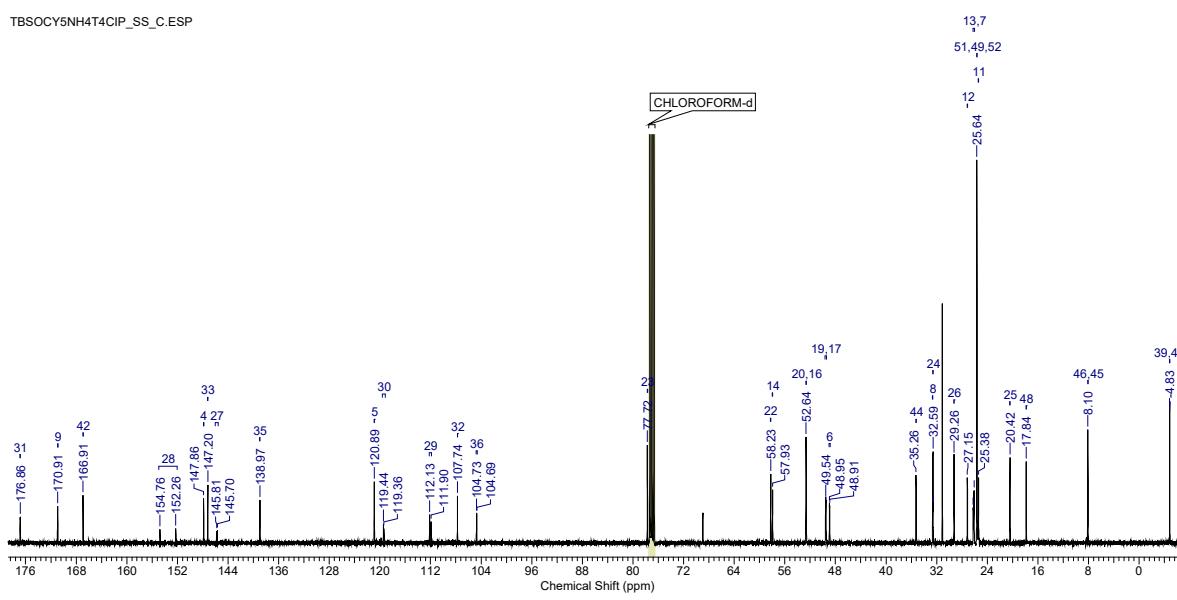
2.38 7-(4-(4-(1-(4-(((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclopentyl)amino)-4-oxobutyl)-1*H*-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 140



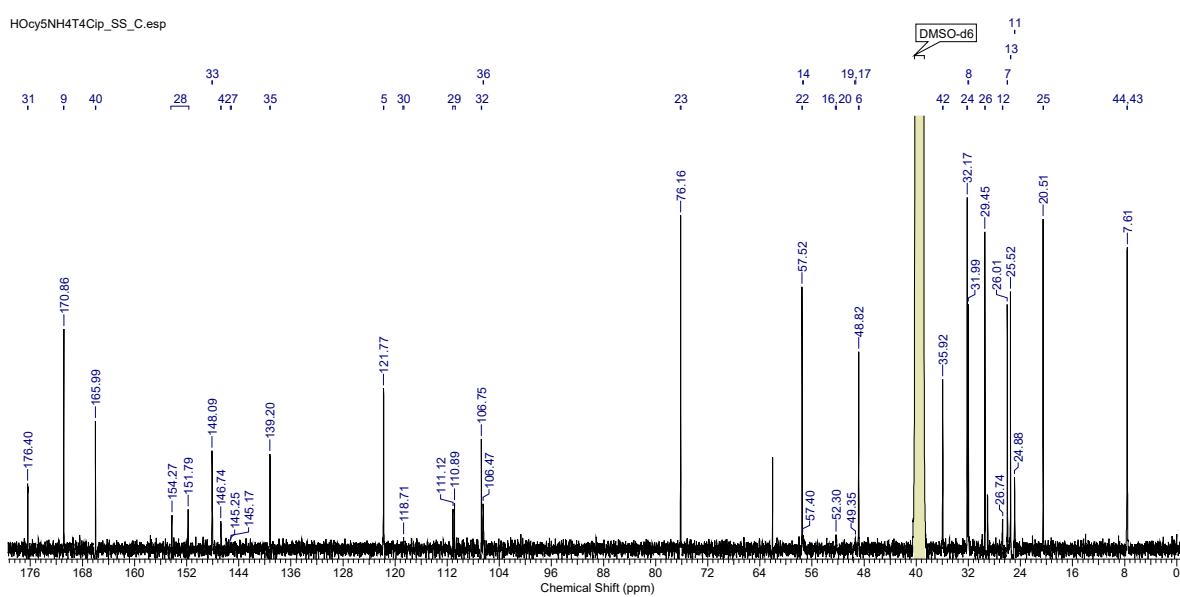
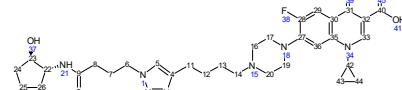
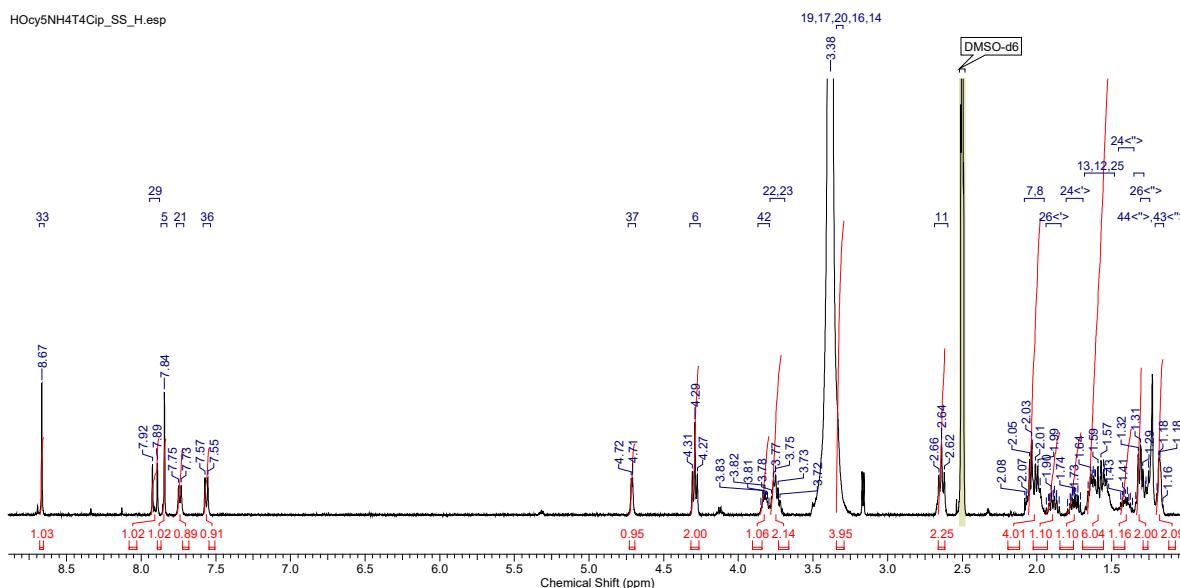
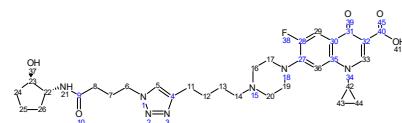
TBSOCY5NH4T4CIP\_SS\_H.ESP



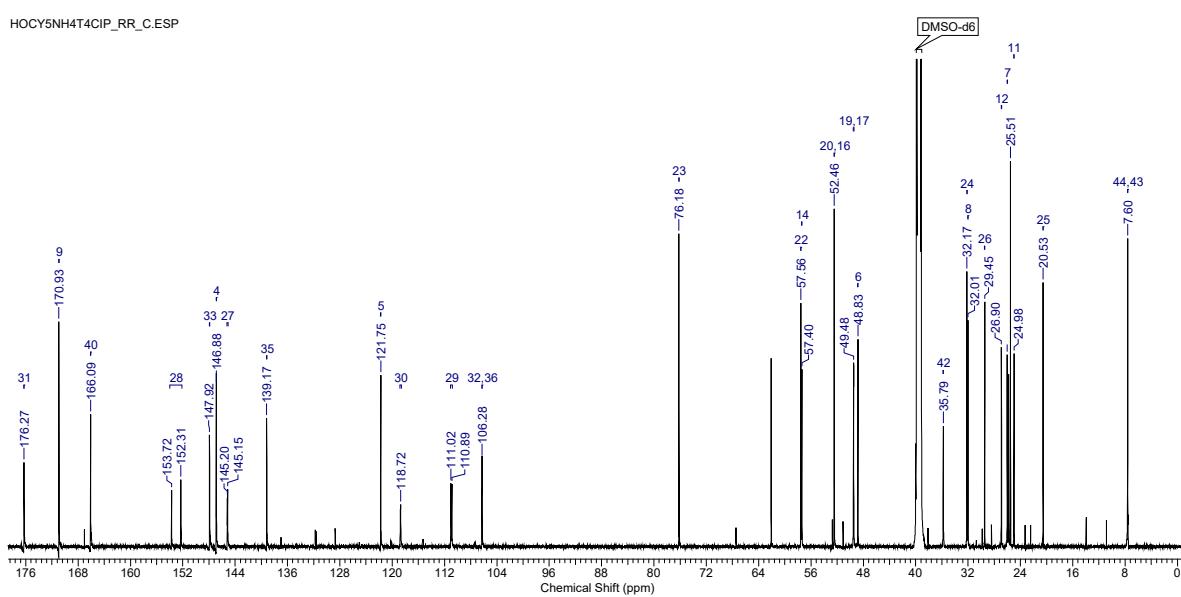
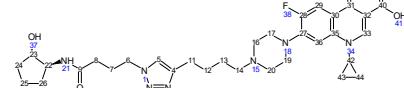
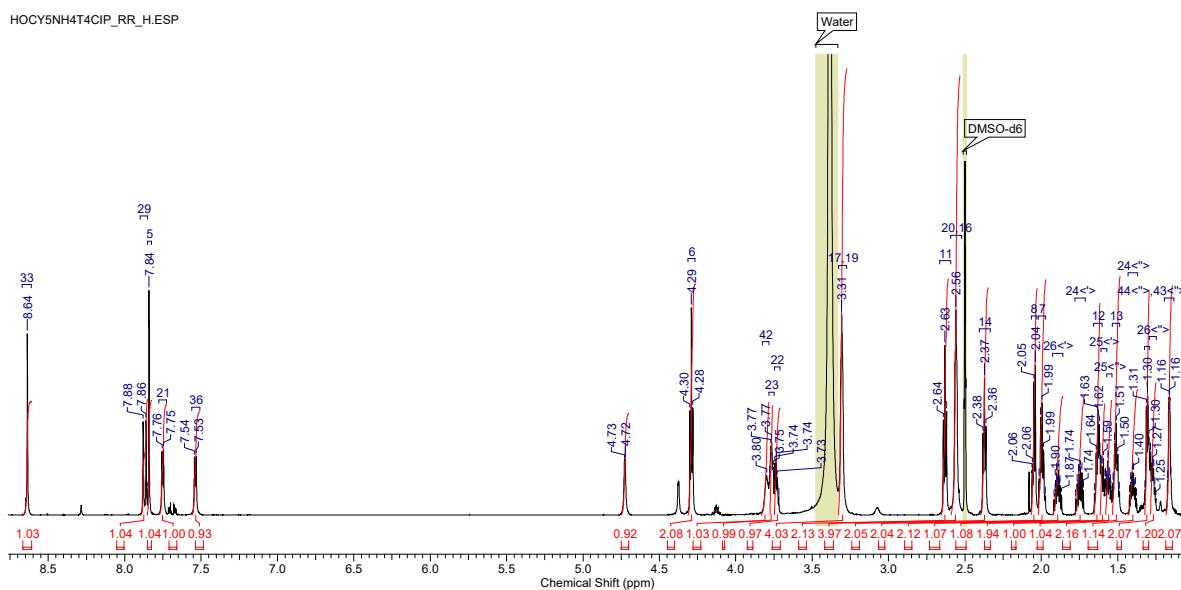
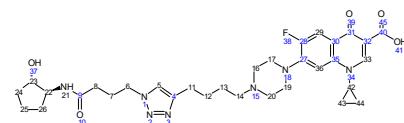
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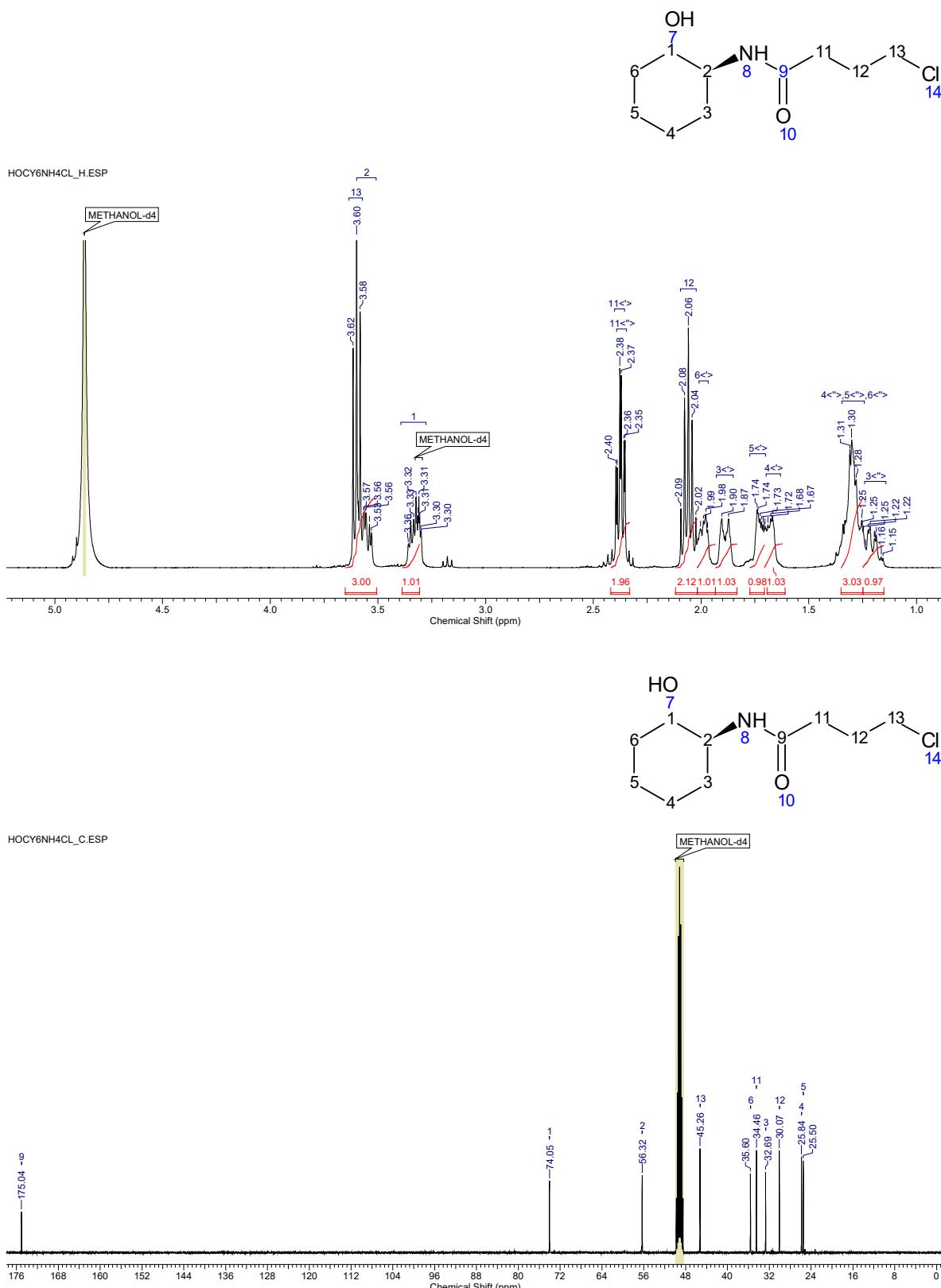
2.39 1-Cyclopropyl-6-fluoro-7-(4-(1-(4-(((1*S*,2*S*)-2-hydroxycyclopentyl)amino)-4-oxobutyl)-1*H*-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-4-oxo-1,4-dihydroquino-line-3-carboxylic acid 142



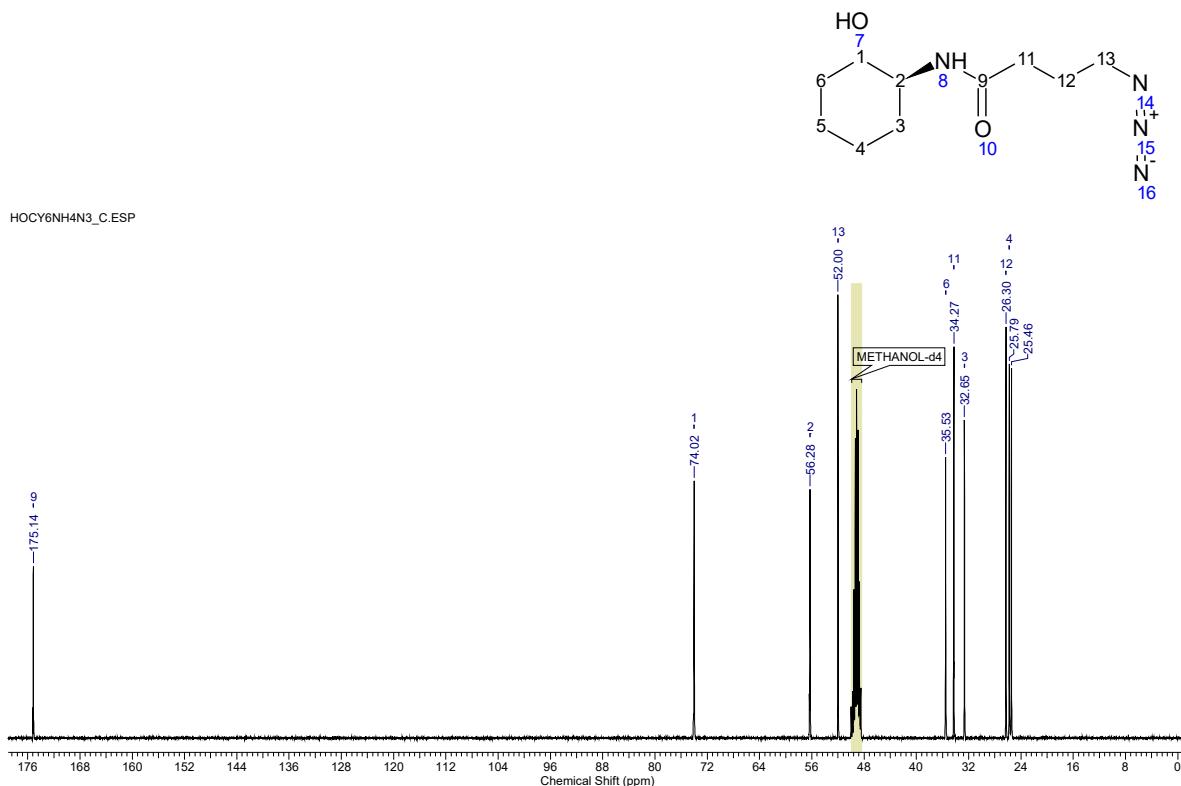
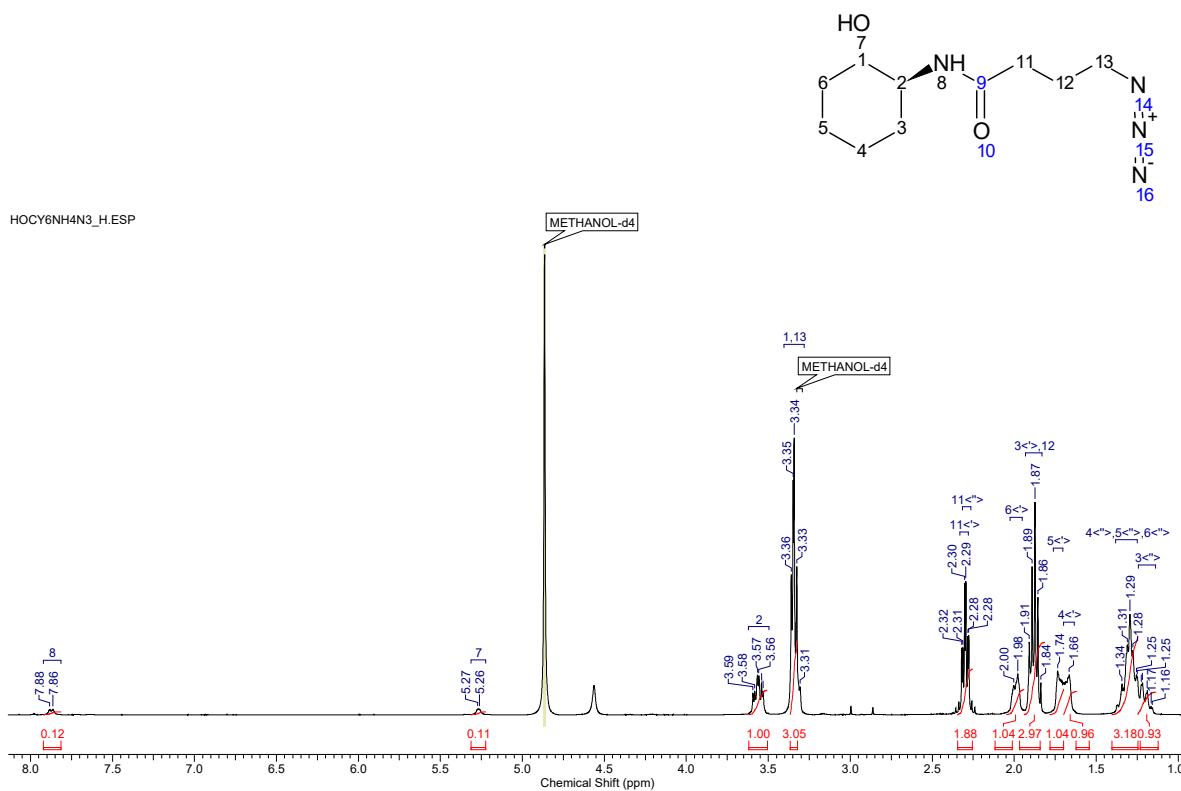
2.40 1-Cyclopropyl-6-fluoro-7-(4-(1-(4-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-4-oxobutyl)-1*H*-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-4-oxo-1,4-dihydroquino-line-3-carboxylic acid 141



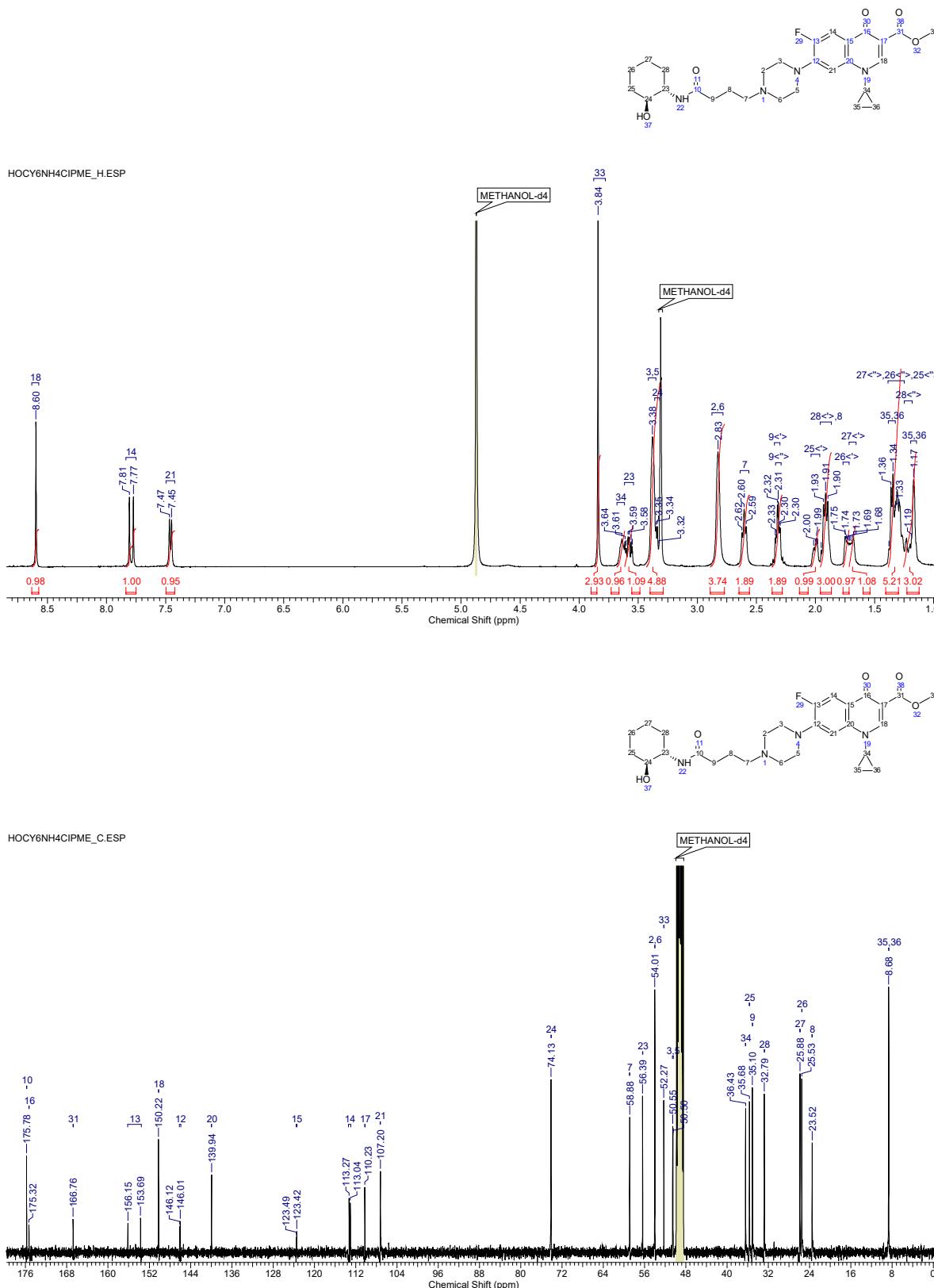
2.41 4-Chloro-*N*-((*trans*)-2-hydroxycyclohexyl)butanamide 145



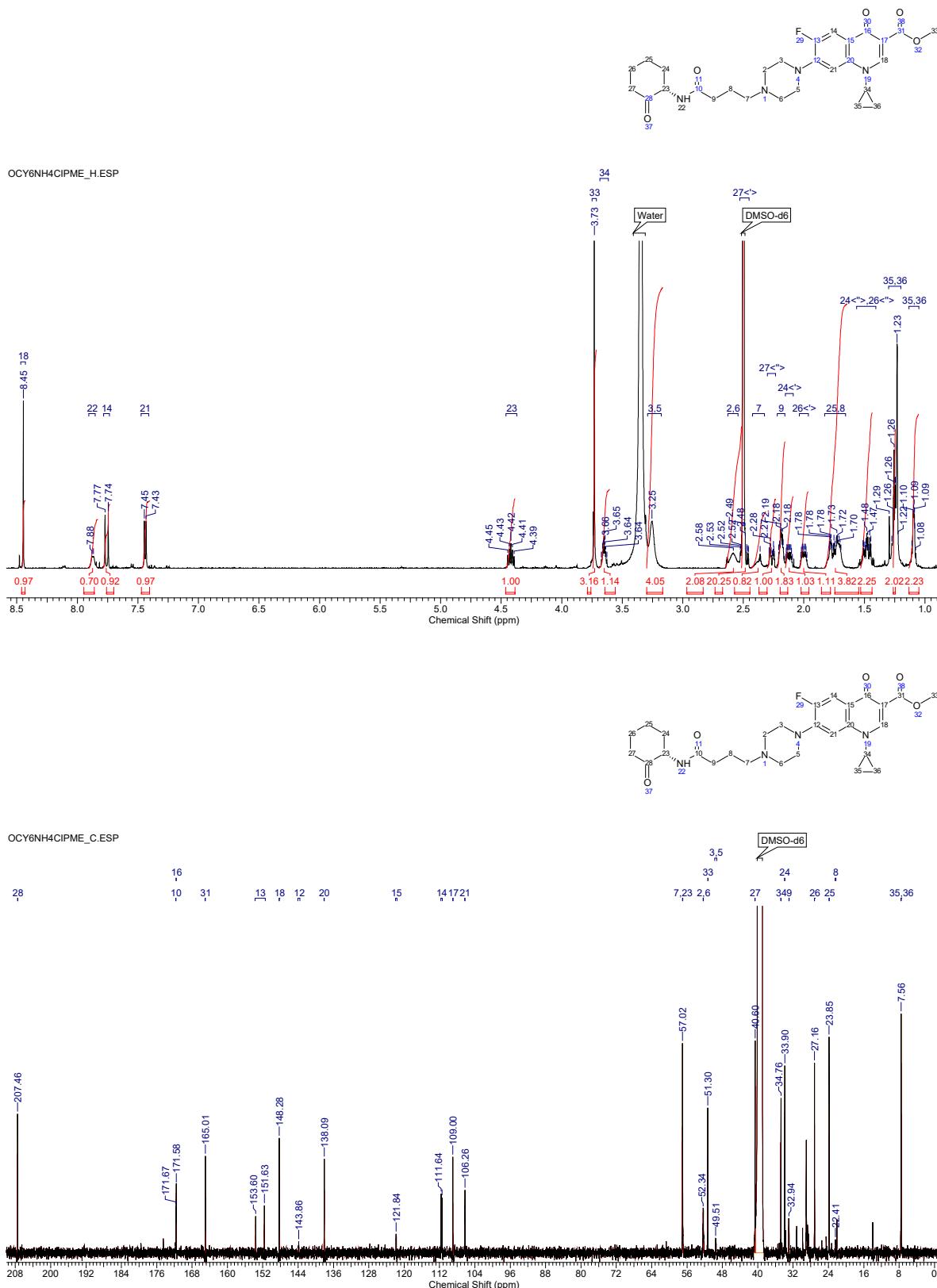
2.42 4-Azido-*N*-((*trans*)-2-hydroxycyclohexyl)butanamide 146



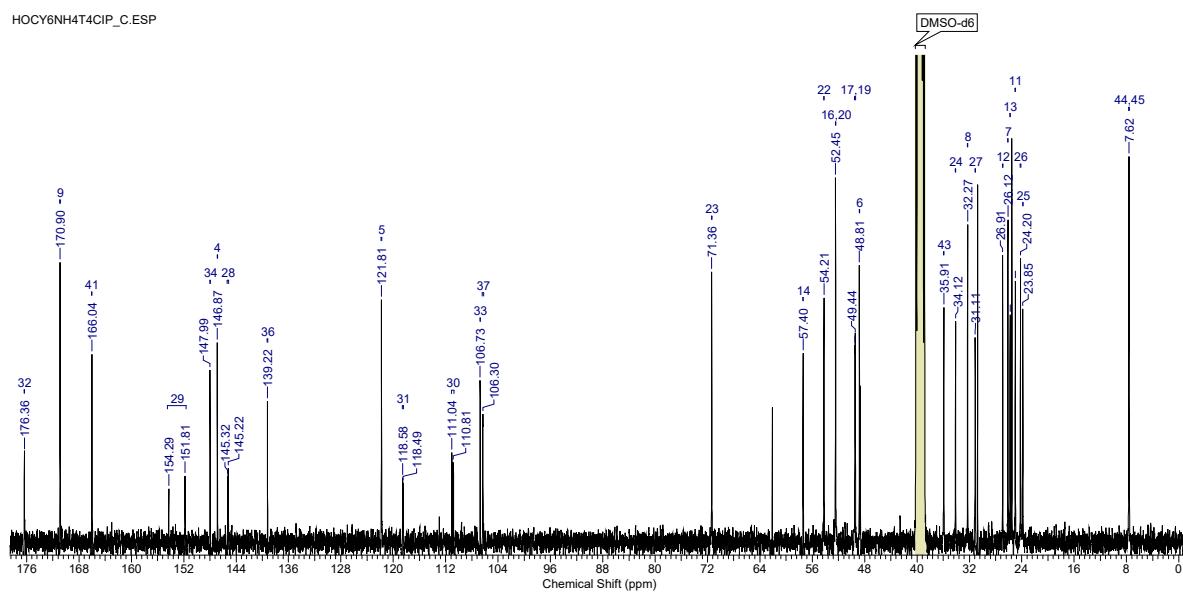
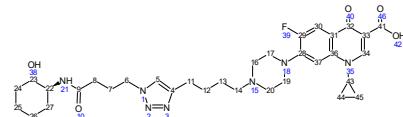
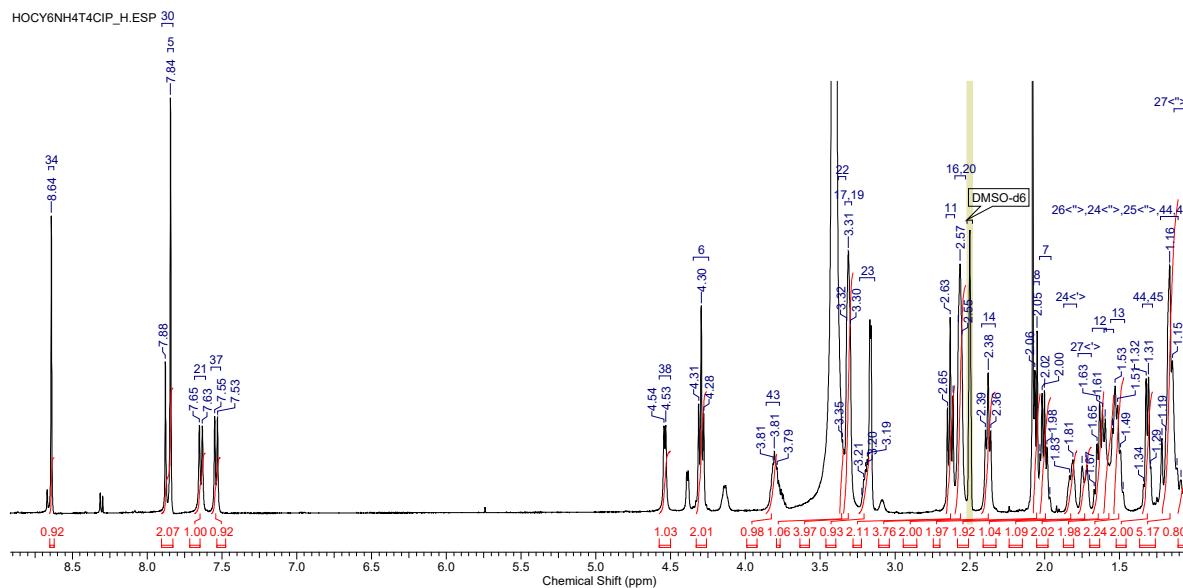
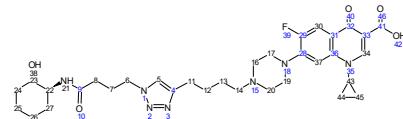
2.43 Methyl 1-cyclopropyl-6-fluoro-7-(4-((*trans*)-2-hydroxycyclohexyl)amino)-4-oxobutyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 147



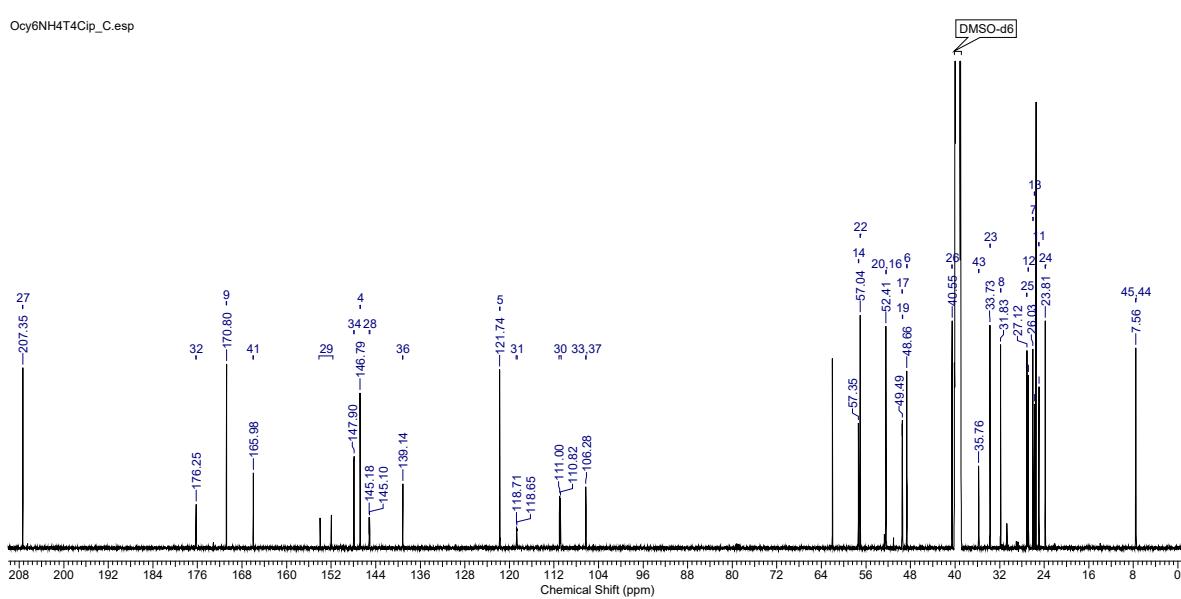
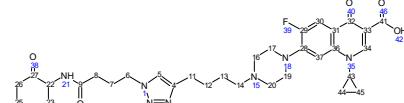
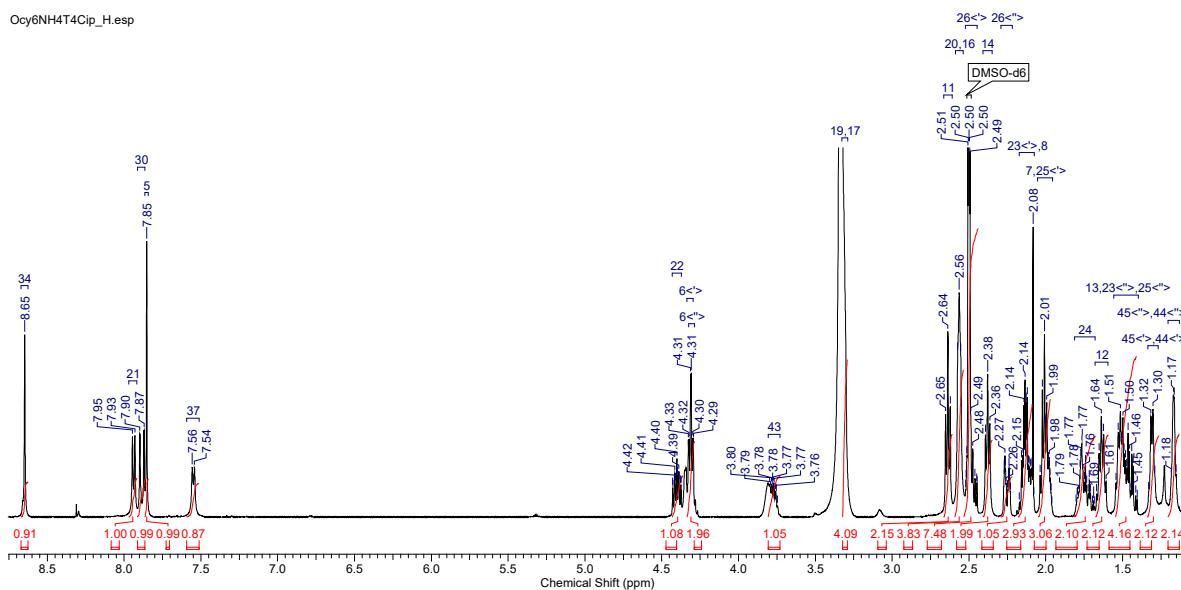
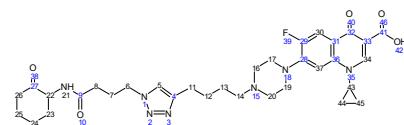
**2.44 Methyl 1-cyclopropyl-6-fluoro-4-oxo-7-(4-(4-oxo-4-((2-oxocyclohexyl)amino)-butyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate 148**



2.45 1-Cyclopropyl-6-fluoro-7-(4-(1-(4-(((trans)-2-hydroxycyclohexyl)amino)-4-oxobutyl)-1*H*-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-4-oxo-1,4-dihydroquino-line-3-carboxylic acid 149



2.46 1-Cyclopropyl-6-fluoro-4-oxo-7-(4-(4-(1-(4-oxo-4-((2-oxocyclohexyl)amino)butyl)-1*H*-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid 151



### 3 References

- [1] H. E. Gottlieb, V. Kotlyar and A. Nudelman. NMR Chemical Shifts of Common Laboratory Solvents as Trace Impurities. *The Journal of Organic Chemistry*, 62(21):7512–7515. 1997.
- [2] Y. R. Baker. Novel Affinity Based Probes for Use in Chemical Proteomic Studies. CPGS thesis. University of Cambridge. 2012.
- [3] J. D. Scribner, D. L. Smith and J. A. McCloskey. Meldrum's Acid in Organic Synthesis. 2. A General and Versatile Synthesis of  $\beta$ -Keto Esters. *The Journal of Organic Chemistry*, 43(10):2087–2088. 1978.
- [4] Y. R. Baker. Investigating quinolone based quorum sensing in *Pseudomonas aeruginosa* using a chemical proteomics approach. PhD thesis, University of Cambridge. 2015.
- [5] J. T. Hodgkinson. The synthesis of *Pseudomonas* Quinolone Signal analogues and their effects on quinolone signalling in *Pseudomonas aeruginosa*. PhD thesis, University of Cambridge. 2011.
- [6] D. M. Stacy, S. T. Le Quement, C. L. Hansen, J. W. Clausen, T. Tolker-Nielsen, J. W. Brummond, M. Givskov, T. E. Nielsen and H. E. Blackwell. Synthesis and biological evaluation of triazole-containing N-acyl homoserine lactones as quorum sensing modulators. *Organic & Biomolecular Chemistry*, 11(6):938–954. 2013.
- [7] T. Persson, T. H. Hansen, T. B. Rasmussen, M. E. Skindersø, M. Givskov and J. Nielsen. Rational design and synthesis of new quorum-sensing inhibitors derived from acylated homoserine lactones and natural products from garlic. *Organic & Biomolecular Chemistry*, 3(2):253–262. 2005.
- [8] L. S. Kocsis, E. Benedetti and K. M. Brummond. A Thermal Dehydrogenative Diels-Alder Reaction of Styrenes for the Concise Synthesis of Functionalized Naphthalenes. *Organic Letters*, 14(17):4430–4433. 2012.
- [9] S. Information, F. Tmp, H. Signal, B. Intracellular, L. Cell, I. Chaoran, V. W. Cornish, N. W. C. Building, N. York, C. Molecular, S. Chemistry, D. Mutagenesis, C. B. Methods, F. Characterization and C. Jing. A fluorogenic TMP-tag for high signal-to-background intracellular live cell imaging. *ACS Chemical Biology*, 8(8):1704–12. 2013.
- [10] K. Sachin, E.-M. Kim, S.-J. Cheong, H.-J. Jeong, S. T. Lim, M.-H. Sohn and D. W. Kim. Synthesis of N<sub>4</sub>'-[<sup>18</sup>F]fluoroalkylated ciprofloxacin as a potential bacterial infection imaging agent for PET study. *Bioconjugate Chemistry*, 21(12):2282–2288. 2010.
- [11] K. Ganguly, R. Wu, M. Ollivault-Shiflett, P. M. Goodwin, L. A. Silks and R. Iyer. Design, synthesis, and a novel application of quorum-sensing agonists as potential drug-delivery vehicles. *Journal of Drug Targeting*, 19(7):528–539. 2011.
- [12] R. Iyer, K. Ganguly and L. A. Silks. Synthetic analogs of bacterial quorum sensors. Los Alamos National Laboratory. 2012.
- [13] R. Srinivasan, L. P. Tan, H. Wu, P.-Y. Yang, K. A. Kalesh and S. Q. Yao. High-throughput synthesis of azide libraries suitable for direct "click" chemistry and in situ screening. *Organic & Biomolecular Chemistry*, 7(9):1821. 2009.
- [14] J. Aubé, Michael S. Wolfe, R. K. Yantiss, S. M. Cook, F. Takusagawa, M. S. Wolfe, R. K. Yantiss, S. M. Cook and F. Takusagawa. Synthesis of Enantiopure N-tert-Butoxycarbonyl-2- aminocycloalkanones. *Synthetic Communications*, 22(20):3003–3012. 1992.

- [15] L. E. Overman, S. Sugai, L. E. Overman and S. Sugai. A Convenient Method for Obtaining trans - 2-Aminocyclohexanol and trans -2-Aminocyclopentanol in Enantiomerically Pure Form. *The Journal of Organic Chemistry*, 50:4154–4155. 1985.
- [16] L. E. Overman and S. Sugai. Total Synthesis of (-)-Crinine. Use of Tandem Cationic Aza-Cope Rearrangement/Mannich Cyclizations for the Synthesis of Enantiomerically Pure Amaryllidaceae Alkaloids. *Helvetica Chimica Acta*, 68(3):745–749. 1985.
- [17] I. Schiffers, T. Rantanen, F. Schmidt, W. Bergmans, L. Zani and C. Bolm. Resolution of racemic 2-aminocyclohexanol derivatives and their application as ligands in asymmetric catalysis. *The Journal of Organic Chemistry*, 71(1):2320–2331. 2006.
- [18] F. Xue and C. T. Seto. Structure-activity studies of cyclic ketone inhibitors of the serine protease plasmin: Design, synthesis, and biological activity. *Bioorganic & Medicinal Chemistry*, 14:8467–8487. 2006.