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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 LiAlH₄ in the presence of triphenyl methane indicator. CH₂Cl₂, 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 KMnO₄ 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 μ 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⁻¹, 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). ¹H and ¹³C 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.

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

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

¹⁹F chemical shifts (δ) are quoted to the nearest 0.1 ppm. Data are reported as follows: <chemical shift> (<assignment>).

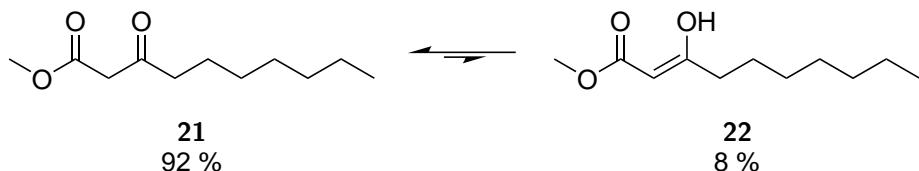
High Resolution Mass Spectra (HRMS) were recorded using either a Micromass Q-TOF or a Micromass LCT Premier spectrometer and reported mass values are within ± 5 ppm mass units. Low Resolution Mass Spectra (LRMS) were recorded on an Agilent 1200 series LC with an ESCi Multi-Mode Ionisation Waters ZQ spectrometer 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 (ν_{max}) are reported in wavenumbers (cm⁻¹). 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)⁻¹.

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



Meldrum's acid (9.0 g, 63 mmol, 1 eq.) was dissolved in anhydrous CH_2Cl_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 CH_2Cl_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 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 (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 ^1H NMR).

Keto form **21**

TLC R_f = 0.12 (5 % EtO_2/PE)

IR (neat) ν_{max} / cm^{-1} = 2927.8 (C-H), 2856.3 (C-H), 1746.9 (ester C=O), 1716.7 (ketone C=O)

^1H NMR (400 MHz, CDCl_3) δ / ppm = 3.74 (s, 3 H, 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, CH_2CH_3)

^{13}C NMR (101 MHz, CDCl_3) δ / 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 (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 (CH_2), 28.7 (CH_2), 28.6 (CH_2), 23.1 (CH_2), 22.2 (CH_2), 13.6 (CH_2CH_3)

Enol form **22**

TLC R_f = 0.12 (5 % EtO_2/PE)

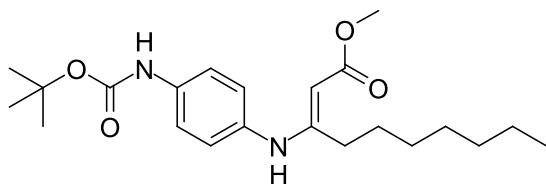
IR (neat) ν_{max} / cm^{-1} = 2927.8 (C-H), 2856.3 (C-H), 1653.8 (C=C), 1629.2 (α,β unsaturated C=O)

^1H NMR (400 MHz, CDCl_3) δ / ppm = 12.02 (s, 1 H, COH), 4.99 (s, 1 H, $\text{C}(=\text{O})\text{CH}=\text{COH}$), 3.73 (s, 3 H, OCH_3), 2.20 (t, J = 7.4 Hz, 2 H, 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, CH_2CH_3)

^{13}C NMR (101 MHz, CDCl_3) δ / 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 (OCH_3), 37.9 ($\text{COHCH}_2\text{CH}_2$), 34.6 (CH_2), 31.2 (CH_2), 29.0 (CH_2), 25.9 (CH_2), 22.3 (CH_2), 13.6 (CH_2CH_3)

Spectroscopic data are consistent with the literature.^{2,3}

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 (SiO₂, gradient of 0 to 20 % Et₂O/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 % Et₂O/40-60 P.E.)

mp T / °C = 78.8 (Et₂O/40-60 P.E.)

IR (neat) ν_{max} / cm⁻¹ = 3337.0 (N-H), 2927.7 (C-H), 2857.1 (C-H), 1723.7 (carbamate C=O), 1634.5 (α,β unsaturated C=O), 1610.7 (C=C), 1580.9 (N-H bend)

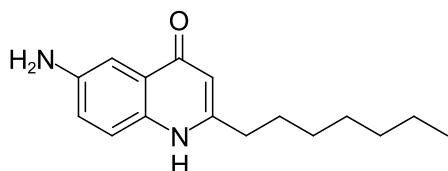
¹H NMR (400 MHz, CDCl₃) δ / ppm = 10.16 (s, 1H, NH(C₇H₁₅)=C), 7.35 (d, J = 8.6 Hz, 2 H, *meta* to NHBOC), 7.02 (d, J = 8.7 Hz, 2 H, *meta* to enamine), 7.60 (br s, 1 H, NHBOC), 4.71 (s, 1 H, C=CH), 3.70 (s, 3 H, OCH₃), 2.23 (t, J = 7.7 Hz, 2 H, CH₂CH₂CH₂CH₂CH₂CH₃), 1.54 (s, 9 H, C(CH₃)₃), 1.40 (quin, J = 7.3 Hz, 2 H, CH₂CH₂CH₂CH₂CH₂CH₃), 1.33 - 1.16 (m, 8 H, CH₂CH₂CH₂CH₂CH₂CH₃), 0.86 (t, J = 7.1 Hz, 3 H, CH₂CH₂CH₂CH₂CH₂CH₃)

¹³C NMR (101 MHz, CDCl₃) δ / ppm = 171.1 (C(=O)CH=C), 164.3 (C(=O)CH=C), 152.7 (OC(=O)NH), 136.0 (*para* to NHBOC), 134.1 (CNHBOC), 126.3 (*meta* to NHBOC), 119.1 (*ortho* to NHBOC), 83.8 (C(=O)CH=C), 80.7 (C(CH₃)₃), 50.2 (OCH₃), 32.2 (CH₂), 31.6 (CH₂), 29.1 (CH₂), 28.8 (CH₂), 28.3 (C(CH₃)₃), 28.0 (CH₂), 22.6 (CH₂), 14.0 (CH₃)

HRMS (ESI⁺) m/z / Da = 391.2589, [M+H]⁺, [C₂₂H₃₅N₂O₄]⁺ requires 391.2591

Spectroscopic data are consistent with the literature.⁴

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 NaHCO₃ (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 (H₂O)

IR (neat) ν_{max} / cm⁻¹ = 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)

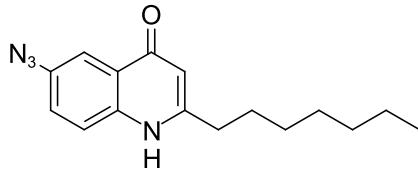
¹H NMR (400 MHz, DMSO-d₆) δ / ppm = 7.26 (d, J = 8.7 Hz, 1 H, *meta* to NH₂), 7.15 (d, J = 2.6 Hz, 1 H, *ortho* to C(=O)), 6.95 (dd, J = 2.7, 8.8 Hz, 1 H, *para* to C(=O)), 5.74 (s, 1 H, *ortho* to CH₂), 5.16 (s, 2 H, NH₂), 2.52 (t, J = 7.4 Hz, 2 H, CH₂CH₂CH₂CH₂CH₂CH₃), 1.64 (quin, J = 7.6 Hz, 2 H, CH₂CH₂CH₂CH₂CH₂CH₃), 1.36 - 1.19 (m, 8 H, CH₂CH₂CH₂CH₂CH₃), 0.86 (t, J = 7.0 Hz, 3 H, H₃)

¹³C NMR (101 MHz, DMSO-d₆) δ / ppm = 176.7 (C(=O)), 151.7 (CCH₂), 145.1 (*para* to NH₂), 132.4 (*ipso* to NH₂), 126.6 (*para* to CH₂), 121.1 (*para* to C(=O)), 119.0 (*meta* to NH₂ and *meta* to C(=O)), 106.2 (CH=CCH₂), 105.9 (*ortho* to NH₂ and *ortho* to C(=O)), 33.6 (CCH₂), 31.6 (CH₂CH₂CH₃), 29.0 (CH₂), 29.0 (CH₂), 28.9 (CH₂), 22.5 (CH₂CH₃), 14.4 (CH₃) 

HRMS (ESI⁺) m/z / Da = 259.1810, [M+H]⁺, [C₁₆H₂₃N₂O]⁺ requires 259.1803

Spectroscopic data are consistent with the literature.⁴

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 NaNO₂ (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 NaN₃ (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/CH₂Cl₂)

IR (neat) ν_{max} / cm⁻¹ = ?? 

¹H NMR (400 MHz, MeOD) δ / ppm = 7.73 (d, J = 8.6 Hz, 1 H, *ortho* to NH), 7.71 (d, J = 2.8 Hz, 1 H, *ortho* to N₃ 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, NHCC₂), 1.68 (quin, J = 7.6 Hz, 2 H, NHCC₂CH₂), 1.28 - 1.39 (m, 4 H, NHCC₂CH₂CH₂CH₂), 1.18 - 1.28 (m, 4 H, CH₂CH₂CH₃), 0.85 (t, J = 6.8 Hz, 3 H, CH₃)

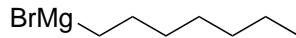
¹³C NMR (101 MHz, MeOD) δ / ppm = 172.3 (C(=O)), 155.5 (NHCC₂), 137.4 (CN₃), 135.6 (*para* to N₃), 124.6 (*para* to C(=O)), 124.1 (*ipso* to C(=O)), 120.7 (*meta* to N₃ and *meta* to C(=O)), 112.8 (*ortho* to N₃ and *ortho* to C(=O)), 107.0 (C(=O)CH), 33.3 (NHCC₂), 31.2 (CH₂CH₂CH₃), 28.3 - 28.5 (CH₂CH₂CH₂CH₂CH₃), 22.1 (CH₂CH₃), 14.0 (CH₃)

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

Spectroscopic data are not consistent with the literature.⁴

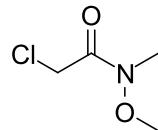
????

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 MgSO₄ 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)

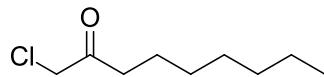
IR (neat) ν_{max} / cm^{-1} = 3016.7 (C-H), 2966.4 (C-H), 2946.7 (C-H), 2827.7 (C-H), 1666.2 (C=O)

¹H NMR (400 MHz, CDCl₃) δ / ppm = 4.20 (s, 2 H, ClCH₂C=O), 3.71 (m, 3 H, OCH₃), 3.18 (s, 3 H, NCH₃)

¹³C NMR (101 MHz, CDCl₃) δ / ppm = 167.4 (C=O), 61.6 (OCH₃), 40.9 (ClCH₂C=O), 32.6 (NCH₃)

Spectroscopic data are consistent with the literature.⁵

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 MgSO₄, and the solvent was removed by rotary evaporation. **31** was obtained as a colourless oil (1.23 g, 6.96 mmol, 96 %).

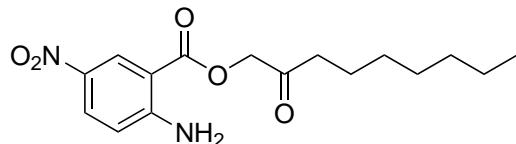
IR (neat) ν_{max} / cm⁻¹ = 2951.7 (C-H), 2925.0 (C-H), 2855.5 (C-H), 1720.4 (C=O)

¹H NMR (400 MHz, CDCl₃) δ / ppm = 4.05 (s, 2 H, ClCH₂C(=O)), 2.54 (t, J = 7.4 Hz, 2 H, C(=O)CH₂CH₂), 1.59 (quin, J = 7.0 Hz, 2 H, C(=O)CH₂CH₂), 1.34 - 1.21 (m, 8 H, CH₂CH₂CH₂CH₂CH₃), 0.87 (t, J = 6.8 Hz, 3 H, CH₃)

¹³C NMR (101 MHz, CDCl₃) δ / ppm = 202.6 (C(=O)), 48.1 (CH₂Cl), 39.6 (C(=O)CH₂CH₂), 31.5 (CH₂CH₂CH₃), 28.9 (CH₂), 28.9 (CH₂), 23.5 (C(=O)CH₂CH₂), 22.5 (CH₂CH₃), 13.9 (CH₃)

Spectroscopic data are consistent with the literature.⁵

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 Na₂HCO₃ (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 (H₂O)

IR (neat) ν_{max} / cm⁻¹ = 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)

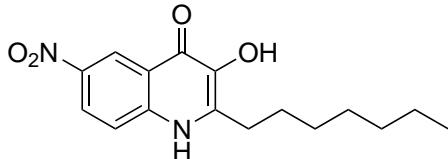
¹H NMR (400 MHz, DMSO-d₆) δ / ppm = 8.66 (d, J = 2.8 Hz, 1 H, *ortho* to C(=O)), 8.12 (dd, J = 2.8, 9.4 Hz, 1 H, *para* to C(=O)), 6.93 (d, J = 9.4 Hz, 1 H, *meta* to C(=O)), 5.05 (s, 2 H, OCH₂C(=O)), 2.49 (t, J = 7.4 Hz, 2 H, C(=O)CH₂CH₂), 1.52 (quin, J = 7.2 Hz, 2 H, C(=O)CH₂CH₂), 1.32 - 1.20 (m, 8 H, CH₂CH₂CH₂CH₂CH₃), 0.86 (t, J = 6.8 Hz, 3 H, CH₃)

¹³C NMR (101 MHz, DMSO-d₆) δ / ppm = 204.4 (OCH₂C(=O)), 165.6 (C(=O)O), 156.3 (*ipso* to NH₂), 135.7 (*ipso* to NO₂), 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 (OCH₂C(=O)), 38.3 (C(=O)CH₂CH₂), 31.6 (CH₂CH₂CH₃), 28.9 (CH₂), 28.9 (CH₂), 23.2 (C(=O)CH₂CH₂), 22.5 (CH₂CH₃), 14.4 (CH₃)

HRMS (ESI⁺) m/z / Da = 323.1610, [M+H]⁺, [C₁₆H₂₃N₂O₅]⁺ requires 323.1607

Spectroscopic data are consistent with the literature.⁴

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 NaHCO₃ (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 (H₂O, EtOAc)

IR (neat) ν_{max} / cm⁻¹ = 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)

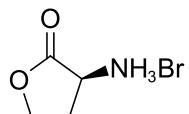
¹H NMR (400 MHz, DMSO-d₆) δ / ppm = 12.00 (s, 1 H, NH), 8.91 (d, J = 2.8 Hz, 1 H, *ortho* to C=O), 8.29 (dd, J = 2.7, 9.2 Hz, 1 H, *para* to C=O), 7.70 (d, J = 9.3 Hz, 1 H, *meta* to C=O), 2.75 (t, J = 7.7 Hz, 2 H, CH₂CH₂CH₂CH₂CH₂CH₃), 1.67 (quin, J = 7.3 Hz, 2 H, CH₂CH₂CH₂CH₂CH₂CH₃), 1.36 - 1.23 (m, 8 H, CH₂CH₂CH₂CH₂CH₂CH₂CH₃), 0.85 (t, J = 7.0 Hz, 3 H, CH₂CH₂CH₂CH₂CH₂CH₃)

¹³C NMR (101 MHz, DMSO-d₆) δ / ppm = 169.7 (C=O), 141.9 (COH), 140.7 (*para* to NO₂), 139.6 (CNO₂), 137.3 (CHCC=O), 124.3 (*ortho* to NO₂ and *ortho* to C=O), 122.3 (*ortho* to NO₂ and *para* to C=O), 121.5 (CCH₂CH₂CH₂CH₂CH₂CH₃), 120.0 (*meta* to NO₂ and *meta* to C=O), 31.6 (CH₂), 29.2 (CH₂), 28.9 (CH₂), 28.5 (CCH₂), 28.1 (CCH₂CH₂), 22.5 (CH₂CH₃), 14.4 (CH₃)

HRMS (ESI⁺) m/z / Da = 305.1501, [M+H]⁺, [C₁₆H₂₁N₂O₄]⁺ requires 305.1500

Spectroscopic data are consistent with the literature.⁴

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), H₂O (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 $T / ^\circ\text{C} = 242$ (*i*-PrOH/AcOH, gas evolved)

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

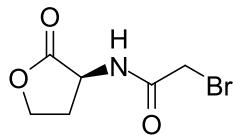
$^1\text{H NMR}$ (400 MHz, DMSO-d₆) $\delta / \text{ppm} = 8.59$ (br s, 3 H, NH₃⁺), 4.46 (dt, $J = 1.3, 8.9$ Hz, 1 H, OCHH), 4.37 (dd, $J = 8.8, 11.4$ Hz, 1 H, CHNH₃⁺), 4.29 (ddd, $J = 6.1, 8.8, 10.9$ Hz, 1 H, OCHH), 2.57 (dddd, $J = 1.2, 6.1, 8.9, 12.3$ Hz, 1 H, OCH₂CHH), 2.26 (dtd, $J = 9.0, 11.2, 12.2$ Hz, 1 H, OCH₂CHH)

$^{13}\text{C NMR}$ (101 MHz, DMSO-d₆) $\delta / \text{ppm} = 173.3$ (C=O), 66.2 (OCH₂), 47.8 (CHNH₃⁺), 27.0 (OCH₂CH₂)

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

The data are consistent with the literature.⁶

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 NaHCO₃ (84.9 mg, 1.01 mmol, 2.00 eq.) were dissolved in CH₂Cl₂ (2 ml) and H₂O (2 ml). Bromoacetyl bromide (44.0 μL , 102 mg, 0.505 mmol, 1.00 eq.) was then added dropwise. The reaction mixture was stirred for 24 h, after which the CH₂Cl₂ was removed under vacuum. The aqueous phase was extracted with EtOAc (4 \times 10 ml). The combined organic layers were dried with MgSO₄ and the solvent was removed under reduced pressure. **40** was obtained as white, needle-like crystals (88.0 mg, 0.396 mmol, 74 %).

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

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

$^1\text{H NMR}$ (400 MHz, CDCl₃) $\delta / \text{ppm} = 6.94$ (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, OCH₂CHH), 2.22 (dtd, $J = 12.6, 11.5, 11.5, 8.9$ Hz, 1 H, OCH₂CHH)

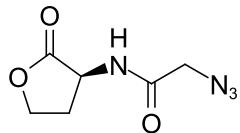
$^{13}\text{C NMR}$ (101 MHz, CDCl₃) $\delta / \text{ppm} = 174.6$ (OC=O), 166.4 (C(=O)NH), 66.1 (OCH₂), 49.8 (CHNH₂), 29.9 (OCH₂CH₂), 28.2 (O=CCH₂Br)

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.^{6,7}

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.), NaN₃ (85.7 mg, 1.32 mmol, 2.61 eq.) and NaHCO₃ (84.9 mg, 1.01 mmol, 2.00 eq.) were dissolved in CH₂Cl₂ (2 ml) and H₂O (2 ml). Bromoacetyl bromide (44.0 μ L, 102 mg, 0.505 mmol, 1.00 eq.) was then added dropwise. The reaction mixture was stirred for 48 h, after which the CH₂Cl₂ was removed under vacuum. The aqueous phase was extracted with EtOAc (4 \times 10 ml). The combined organic layers were dried with MgSO₄ 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) ν_{max} / cm⁻¹ = 3283.5 (N-H), 2923.3 (C-H), 2853.0 (C-H), 2129.7 (N₃), 1782.9 (lactone C=O), 1661.4 (amide C=O), 1536.8 (N-H bend)

¹H NMR (400 MHz, CDCl₃) δ / 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, CH₂N₃), 2.76 (dddd, *J* = 12.5, 8.8, 6.0, 1.4 Hz, 1 H, OCH₂CHH), 2.25 (dtd, *J* = 12.5, 11.4, 11.4, 8.9 Hz, 1 H, OCH₂CHH)

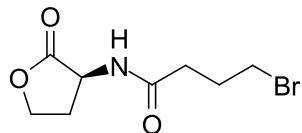
¹³C NMR (101 MHz, CDCl₃) δ / ppm = 174.9 (OC=O), 167.5 (C=ONH), 66.0 (OCH₂), 52.2 (O=CCH₂N₃), 48.9 (CHNHC=O), 29.7 (OCH₂CH₂)

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.⁶

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 NaHCO₃ (170 mg, 2.02 mmol, 1.84 eq.) were dissolved in CH₂Cl₂ (2 ml) and H₂O (2 ml). Bromobutyryl chloride (140 μ L, 224 mg, 1.21 mmol, 1.10 eq.) was then added dropwise. The reaction mixture was stirred for 1 h, after which the

CH_2Cl_2 was removed under vacuum. The aqueous phase was extracted with EtOAc ($7 \times 5 \text{ ml}$) and the combined organic layers were dried with MgSO_4 . The solvent was removed under vacuum to give white crystals which were recrystallised from EtOAc . **44** was obtained as white, needle-like crystals (219 mg, 0.878 mmol, 80 %).

mp $T / ^\circ\text{C} = 105$ (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, CDCl_3) $\delta / \text{ppm} = 6.31$ (br d, $J = 5.5 \text{ Hz}$, 1 H, NH), 4.59 (ddd, $J = 6.2, 8.7, 11.5 \text{ Hz}$, 1 H, CHNH), 4.48 (dt, $J = 1.2, 8.9 \text{ Hz}$, 1 H, OCHH), 4.30 (ddd, $J = 5.8, 9.3, 11.3 \text{ Hz}$, 1 H, OCHH), 3.49 (t, $J = 6.3 \text{ Hz}$, 2 H, CH₂Br), 2.82 (dddd, $J = 1.3, 5.9, 8.7, 12.5 \text{ Hz}$, 1 H, OCH₂CHH), 2.47 (t, $J = 7.3 \text{ Hz}$, 2 H, C(=O)CH₂), 2.26 - 2.15 (m, 3 H, OCH₂CHH and CH₂CH₂Br)

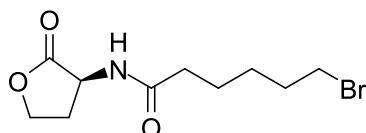
$^{13}\text{C NMR}$ (101 MHz, CDCl_3) $\delta / \text{ppm} = 175.4$ (OC=O), 172.3 (C(=O)NH), 66.1 (OCH₂), 49.3 (CHNHC=O), 33.9 (C(=O)CH₂), 33.1 (CH₂Br), 30.3 (OCH₂CH₂), 27.9 (C(=O)CH₂CH₂)

HRMS The compound does not ionise. 

$[\alpha]_D^{26.6} / ^\circ 10^{-1} \text{cm}^2 \text{g}^{-1} = -78$ ($c / \text{g}(100 \text{ ml})^{-1} = 0.0833$, 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 NaHCO_3 (84.9 mg, 1.01 mmol, 1.84 eq.) were dissolved in CH_2Cl_2 (2 ml) and H_2O (2 ml) at r.t.. Bromohexanoyl chloride (93.0 μL , 130 mg, 0.608 mmol, 1.11 eq.) was then added dropwise. The reaction mixture was stirred for 4 h, after which the CH_2Cl_2 was removed under vacuum. The mixture was then filtered, washed with H_2O (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, CDCl_3) $\delta / \text{ppm} = 6.09$ (br d, $J = 5.7 \text{ Hz}$, 1 H, NH), 4.57 (ddd, $J = 5.9, 8.6, 11.6 \text{ Hz}$, 1 H, CHNH), 4.50 (dt, $J = 1.3, 9.1 \text{ Hz}$, 1 H, OCHH), 4.31 (ddd, $J = 5.9, 9.3, 11.3 \text{ Hz}$, 1 H, OCHH), 3.43 (t, $J = 6.7 \text{ Hz}$, 2 H, CH₂Br), 2.88 (dddd, $J = 1.3, 5.9, 8.6, 12.6 \text{ Hz}$, 1 H, OCH₂CHH), 2.30 (dt, $J = 1.8, 7.5 \text{ Hz}$, 2 H, C(=O)CH₂), 2.16 (td, $J = 8.9, 11.5, 12.5 \text{ Hz}$, 1 H, OCH₂CHH), 1.90 (quin, $J = 7.2 \text{ Hz}$, 2 H, CH₂CH₂Br), 1.71 (quin, $J = 7.6 \text{ Hz}$, 2 H, C(=O)CH₂CH₂), 1.59 - 1.46 (m, 2 H, C(=O)CH₂CH₂CH₂)

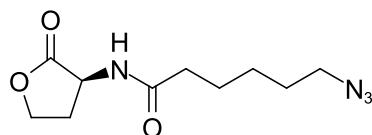
^{13}C NMR (101 MHz, CDCl_3) δ / ppm = 175.5 (OC=O), 173.3 (C(=O)NH), 66.1 (OCH_2), 49.3 (CHNHC=O), 35.8 (CH_2Br), 33.5 (C(=O)CH_2), 32.3 ($\text{CH}_2\text{CH}_2\text{Br}$), 30.5 (OCH_2CH_2), 27.6 ($\text{C(=O)CH}_2\text{CH}_2$), 24.4 ($\text{C(=O)CH}_2\text{CH}_2\text{CH}_2$)

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 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 CH_2Cl_2 (5 ml) and H_2O (5 ml). The aqueous phase was extracted twice more with CH_2Cl_2 (2×5 ml) and the organic layers were combined and dried over 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 (CH_2Cl_2)

IR (neat) ν_{max} / cm^{-1} = 3314.0 (N-H), 2931.6 (C-H), 2862.9 (C-H), 2095.1 (N_3), 1775.4 (lactone C=O), 1643.1 (amide C=O), 1547.9 (N-H bend)

^1H NMR (400 MHz, CDCl_3) δ / ppm = 5.96 (d, J = 4.2 Hz, 1 H, NH), 4.54 (ddd, J = 11.7, 8.6, 5.7 Hz, 1 H, CHNH), 4.49 (td, J = 9.1, 1.0 Hz, 1 H, OCHHH), 4.30 (ddd, J = 11.3, 9.4, 5.8 Hz, 1 H, OCHH), 3.29 (t, J = 6.9 Hz, 2 H, CH_2N_3), 2.88 (dddd, J = 12.5, 8.6, 5.8, 1.1 Hz, 1 H, OCH_2CHHH), 2.28 (t, J = 7.5 Hz, 1 H, C(=O)CHH), 2.28 (t, J = 7.4 Hz, 1 H, C(=O)CHH), 2.14 (dtd, J = 12.3, 11.5, 11.5, 8.8 Hz, 1 H, OCH_2CHH), 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, $\text{C(=O)CH}_2\text{CH}_2\text{CH}_2$)

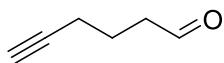
^{13}C NMR (101 MHz, CDCl_3) δ / ppm = 175.4 (OC=O), 172.2 (C(=O)NH), 66.1 (OCH_2), 51.2 (CH_2N_3), 49.4 (CHNHC=O), 35.9 (C(=O)CH_2), 30.7 (OCH_2CH_2), 28.6 ($\text{CH}_2\text{CH}_2\text{N}_3$), 26.3 ($\text{C(=O)CH}_2\text{CH}_2$), 24.8 ($\text{C(=O)CH}_2\text{CH}_2\text{CH}_2$)

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 Et₂O (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 Et₂O. The solvent was removed by rotary evaporation. **49** was obtained as a pale yellow-green oil (4.72 g, 49.1 mmol, 72 %).

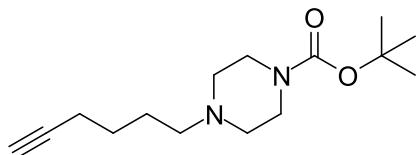
IR (neat) ν_{max} / cm⁻¹ = 3292.7 (alkyne C-H), 2943.3 (alkane C-H), 2830.9 (aldehyde C-H), 2728.6 (aldehyde C-H), 1720.3 (aldehyde C=O)

¹H NMR (400 MHz, CDCl₃) δ / ppm = 9.80 (s, 1 H, C(=O)H), 2.60 (t, J = 7.1 Hz, 2 H, CH₂C(=O)H), 2.26 (dt, J = 2.6, 6.8 Hz, 2 H, HC≡CCH₂), 1.98 (t, J = 2.7 Hz, 1 H, HC≡C), 1.85 (quin, J = 7.0 Hz, 2 H, HC≡CCH₂CH₂)

¹³C NMR (101 MHz, CDCl₃) δ / ppm = 201.6 (C(=O)), 83.1 (HC≡C), 69.3 (HC≡C), 42.4 (CH₂C(=O)), 20.7 (CH₂CH₂C(=O)), 17.6 (HC≡CCH₂)

Spectroscopic data are consistent with the literature.⁸

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 N₂ 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 NaHCO₃ (sat., aq., 120 ml) was added and the product extracted with EtOAc (2×100 ml). The solvent was dried over MgSO₄ and removed by rotary evaporation. **51** was obtained as a colourless liquid (1.12 g, 4.21 mmol, 99 %).

TLC R_f (10 % MeOH/CH₂Cl₂) = 0.55

IR (neat) ν_{max} / cm⁻¹ = 3303.6 (alkyne C-H), 2940.0 (alkane C-H), 2865.2 (C-H), 2810.4 (C-H), 1691.3 (carbamate C=O)

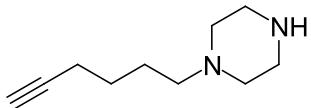
¹H NMR (400 MHz, CDCl₃) δ / ppm = 3.44 (t, J = 5.2 Hz, 4 H, CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 2.39 (t, J = 5.1 Hz, 4 H, CH₂CH₂CH₂N(CH₂)CH₂), 2.37 (t, J = 7.3 Hz, 2 H, CH₂CH₂CH₂N), 2.23 (dt, J = 2.7, 6.8 Hz, 2 H, HC≡CCH₂), 1.96 (t, J = 2.7 Hz, 1 H, HC≡C), 1.65 - 1.53 (m, 4 H, HC≡CCH₂CH₂CH₂), 1.47 (s, 9 H, CH₃)

¹³C NMR (101 MHz, CDCl₃) δ / ppm = 154.7 (NC(=O)O), 84.2 (HC≡C), 79.6 (C(CH₃)₃), 68.5 (HC≡C), 60.4 (CH₂CH₂CH₂N), 58.0 (CH₂CH₂CH₂N(CH₂)CH₂), 53.0 (CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 28.4 (C(CH₃)₃), 26.3 (CH₂CH₂N), 25.7 (HC≡CCH₂CH₂), 18.3 (HC≡CCH₂)

HRMS (ESI⁺) m/z / Da = 267.2073, [M+H]⁺, [C₁₅H₂₇N₂O₂]⁺ 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 CH₂Cl₂ (2×20 ml). The oil was diluted with H₂O (10 ml) and the pH adjusted to 14 with NaOH (10 % aq.). This mixture was extracted with CH₂Cl₂ (2×20 ml) and the combined organic layers were dried over MgSO₄. The solvent was removed under vacuum and purified by column chromatography (SiO₂ MeOH/CH₂Cl₂ 3:7). **52** was obtained as a colourless liquid (476 mg, 2.86 mmol, 100 %).

TLC R_f (30 % MeOH/CH₂Cl₂) = 0.20

IR (neat) ν_{max} / cm⁻¹ = 3295.9 (alkyne C-H), 2941.1 (alkane C-H), 2810.6 (alkane C-H), 1637.2 (N-H bend)

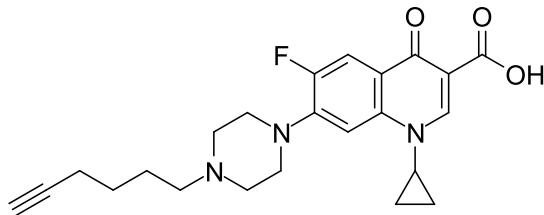
¹H NMR (400 MHz, CDCl₃) δ / ppm = 2.88 (t, J = 4.9 Hz, 4 H, CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 2.39 (m, 4 H, CH₂CH₂CH₂N(CH₂)CH₂), 2.31 (t, J = 7.1 Hz, 2 H, HC≡CCH₂CH₂CH₂N), 2.20 (dt, J = 2.7, 6.8 Hz, 2 H, HC≡CCH₂), 2.05 (br s, 1 H, NH), 1.93 (t, J = 2.7 Hz, 1 H, HC≡C), 1.65 - 1.48 (m, 4 H, HC≡CCH₂CH₂CH₂N)

¹³C NMR (101 MHz, CDCl₃) δ / ppm = 84.3 (HC≡C), 68.4 (HC≡C), 58.6 (CH₂CH₂CH₂N), 54.5 (CH₂CH₂CH₂N(CH₂)CH₂), 46.0 (CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 26.4 (CH₂CH₂CH₂N), 25.7 (HC≡CCH₂CH₂), 18.3 (HC≡CCH₂)

HRMS (ESI⁺) m/z / Da = 167.1548, [M+H]⁺, [C₁₀H₁₉N₂]⁺ 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/CH₂Cl₂)

mp T / °C = 220 (MeOH, decomposes)

IR (neat) ν_{max} / cm⁻¹ = 3212.0 (alkyne C-H), 2459.3 (O-H), 1722.6 (carboxylic acid C=O), 1626.8 (quinolone C=O)

¹H NMR (500 MHz, DMSO-d₆) δ / 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(CH₂)₂ and CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 3.54 - 3.68 (br m, 2 H, CH₂CH₂CH₂N(CH₂CH₂)CH₂), 3.45 (br. t, J = 11.6 Hz, 2 H, CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 3.21 - 3.29 (br m, 2 H, CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 3.11 - 3.20 (br m, 2 H, CH₂CH₂CH₂N(CH₂CH₂)), 2.84 (t, J = 2.7 Hz, 1 H, HC≡C), 2.24 (td, J = 7.0, 2.7 Hz, 2 H, HC≡CCH₂), 1.83 (br. quin, J = 7.5 Hz, 2 H, HC≡CCH₂CH₂CH₂), 1.52 (quin, J = 7.4 Hz, 2 H, HC≡CCH₂CH₂), 1.29 - 1.36 (m, 2 H, NCH(CHH)₂), 1.16 - 1.23 (m, 2 H, NCH(CHH)₂)

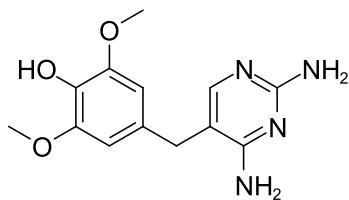
¹³C NMR (126 MHz, DMSO-d₆) δ / ppm = 176.4 (C(=O)CC(=O)OH), 165.8 (C(=O)OH), 152.8 (d, J = 248.5 Hz, *ipso* to F), 148.2 (CHCC(=O)OH), 143.7 (d, J = 11.1 Hz, *para* to C(=O)), 139.1 (*para* to F), 119.4 (d, J = 6.9 Hz, *ipso* to C(=O)), 111.2 (d, J = 22.5 Hz, *ortho* to F and *ortho* to C(=O)), 106.9 (*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 (CH₂CH₂CH₂N), 50.5 (CH₂CH₂CH₂N(CH₂CH₂)), 46.3 (CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 36.0 (NCH(CH₂)₂), 25.2 (HC≡CCH₂CH₂), 22.3 (HC≡CCH₂CH₂CH₂), 17.4 (HC≡CCH₂), 7.6 (NCH(CH₂)₂)

¹⁹F NMR (376.45 MHz, MeOD) δ / ppm = -121.8 (s, ciprofloxacin F)

HRMS (ESI⁺) m/z / Da = 412.2036, [M+H]⁺, [C₂₃H₂₇N₃O₃F]⁺ 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 NH₄OH (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/CHCl₂)

mp T / °C = 238 (H₂O, decomposes)

IR (neat) ν_{max} / cm⁻¹ = 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)

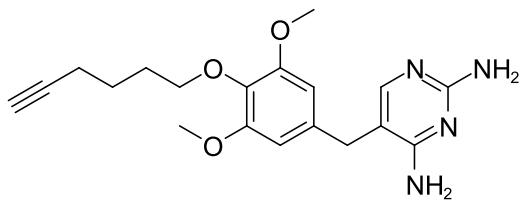
¹H NMR (400 MHz, MeOD) δ / ppm = 7.21 (s, 1 H, CHN), 6.54 (s, 2 H, *meta* to OCH₂), 4.87 (br s, 5 H, OH, NH₂ × 2), 3.82 (s, 6 H, OCH₃), 3.63 (s, 2 H, CCH₂C)

¹³C NMR (101 MHz, MeOD) δ / ppm = 166.4 (CH₂CCNH₂), 162.0 (CHNCNH₂), 156.2 (CHNCNH₂), 149.8 (*ipso* to OCH₃), 135.9 (*ipso* to OH), 128.2 (*para* to OH), 111.7 (CH₂CCNH₂), 107.5 (*meta* to OH), 57.0 (OCH₃), 33.9 (CCH₂C)

HRMS (ESI⁺) m/z / Da = 277.1295, [M+H]⁺ found, [C₁₃H₁₇N₄O₃]⁺ requires 277.1301

The data are consistent with the literature.⁹

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.), Cs₂CO₃ (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 CH₂Cl₂ (30 ml) was added and the mixture filtered. The filtrate was concentrated under reduced pressure and purified by column

chromatography using a CombiFlash (SiO₂, 5 % MeOH/CH₂Cl₂). **94** was obtained as a pale cream amorphous solid (0.253 g, 0.709 mmol, 19.6 %).

TLC R_f = 0.14 (5 % MeOH/CH₂Cl₂)

IR (neat) ν_{max} / cm⁻¹ = 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)

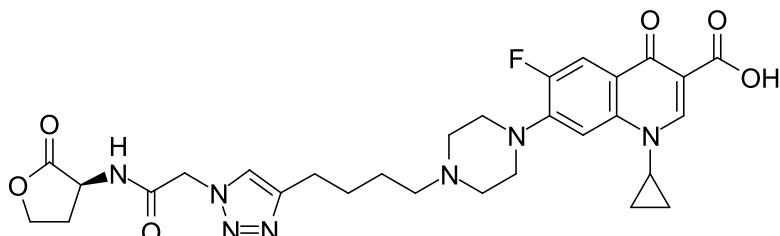
¹H NMR (400 MHz, MeOD) δ / ppm = 7.77 (s, 1 H, CHN), 6.37 (s, 2 H, *meta* to OCH₂), 4.83 (br s, 2 H, CHNCNH₂), 4.63 (br s, 2 H, CH₂CCNH₂), 3.95 (t, J = 6.3 Hz, 2 H, CH₂O), 3.79 (s, 6 H, OCH₃), 3.65 (s, 2 H, CCH₂C), 2.28 (td, J = 7.1, 2.6 Hz, 2 H, HC≡CCH₂), 1.94 (t, J = 2.7 Hz, 1 H, HC≡C), 1.81 - 1.90 (m, 2 H, CH₂CH₂O), 1.71 - 1.80 (m, 2 H, CH₂CH₂CH₂O)

¹³C NMR (101 MHz, MeOD) δ / ppm = 162.7 (CH₂CCNH₂), 162.0 (CHNCNH₂), 156.4 (CHNCNH₂), 153.8 (*ipso* to OCH₃), 136.0 (*ipso* to OCH₂), 133.6 (*para* to OCH₂), 106.5 (CH₂CCNH₂), 105.0 (*meta* to OCH₂), 84.5 (HC≡C), 72.6 (CH₂O), 68.3 (HC≡C), 56.1 (OCH₃), 34.7 (CCH₂C), 29.1 (CH₂CH₂O), 24.9 (CH₂CH₂CH₂O), 18.0 (HC≡CCH₂)

HRMS (ESI⁺) m/z / Da = 357.1920, [M+H]⁺ found, [C₁₉H₂₅N₄O₃]⁺ 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 N₂ 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 μ mol, 1 eq.) and (*S*)-2-azido-*N*-(2-oxotetrahydrofuran-3-yl)acetamide **41** (9.2 mg, 50.0 μ mol, 1 eq.). A similarly degassed solution of CuSO₄ · 5 H₂O (624 μ g, 2.5 μ mol, 0.05 eq. 50 mM), THPTA (1.09 mg, 2.5 μ mol, 0.05 eq. 50 mM) and sodium ascorbate (991 μ g, 5 μ mol, 0.1 eq., 100 mM) in 50 % water/*t*-BuOH (50 μ 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 μ l) was added. After a further 3 h the reaction mixture was dry-loaded onto SiO₂ and purified by column chromatography using a CombiFlash (SiO₂, 0-20 % MeOH/CH₂Cl₂ over 15 min). The combined pure fractions were dried with MgSO₄ and evaporated under reduced pressure. **95** was obtained as a white amorphous solid (8.8 mg, 14.8 μ mol, 29.6 %).

IR (neat) ν_{max} / cm⁻¹ = 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)

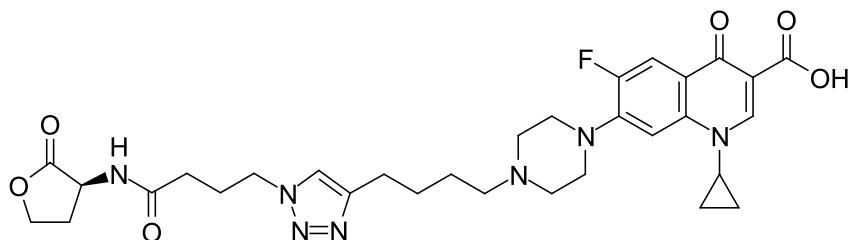
¹H NMR (400 MHz, DMSO d₆) δ / ppm = 15.23 (s, 1 H, C(=O)OH), 8.84 (d, *J* = 7.9 Hz, 1 H, NH), 8.66 (s, 1 H, *ortho* to C(=O)OH), 7.90 (d, *J* = 13.3 Hz, 1 H, *ortho* to F), 7.82 (s, 1 H, CH=CCH₂), 7.57 (d, *J* = 7.6 Hz, 1 H, *meta* to F), 5.13 (s, 1 H, C(=O)CHHN), 5.12 (s, 1 H, C(=O)CHHN), 4.64 (ddd, *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(CH₂)₂), 3.32 (br s, 4 H, CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 2.67 (t, *J* = 7.4 Hz, 2 H, CH=CCH₂), 2.58 (br t, *J* = 5.0 Hz, 4 H, CH₂CH₂CH₂N(CH₂)CH₂), 2.42 - 2.49 (m, I, OCH₂CHH), 2.40 (t, *J* = 7.1 Hz, 1 H, CH=CCH₂CH₂CH₂CH₂), 2.17 (td, *J* = 11.7, 10.8, 10.8, 9.0 Hz, I, OCH₂CHH), 1.66 (quin, *J* = 7.2 Hz, 1 H, CH=CCH₂CH₂), 1.53 (quin, *J* = 7.2 Hz, 1 H, CH=CCH₂CH₂CH₂), 1.28 - 1.35 (m, 1 H, NCH(CHH)₂), 1.16 - 1.21 (m, 1 H, NCH(CHH)₂)

¹³C NMR (101 MHz, DMSO d₆) 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=CCH₂), 145.3 (d, *J* = 9.6 Hz, *ipso* to piperazine), 139.2 (para to F), 123.4 (CH=CCH₂), 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 (OCH₂), 57.3 (CH=CCH₂CH₂CH₂N), 52.4 (CH₂CH₂CH₂N(CH₂)CH₂), 51.2 (C(=O)CH₂N), 49.5 (CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 49.5 (CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 48.2 (CHNH), 35.9 (NCH(CH₂)₂), 28.2 (CH₂CHNH), 26.8 (CH=CCH₂CH₂), 25.7 (CH=CCH₂CH₂CH₂), 24.9 (CH=CCH₂), 7.6 (NCH(CH₂)₂)

HRMS (ESI⁺) *m/z* / Da = 596.2627, [M+H]⁺ found, [C₂₉H₃₅FN₇O₆]⁺ requires 596.2633

[\alpha]_D²⁰ / °10⁻¹cm²g⁻¹ = -3.5 (c / g(100 ml)⁻¹ = 0.0575, 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 N₂ 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 CuSO₄ · 5 H₂O (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 SiO₂ and purified by column chromatography using a CombiFlash (SiO₂, 0-20 % MeOH/CH₂Cl₂ over 15 min). The combined pure fractions were dried with MgSO₄ and evaporated under reduced pressure. **96** was obtained as a white amorphous solid (14.6 mg, 23.4 μmol, 46.8 %).

IR (neat) ν_{max} / 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)

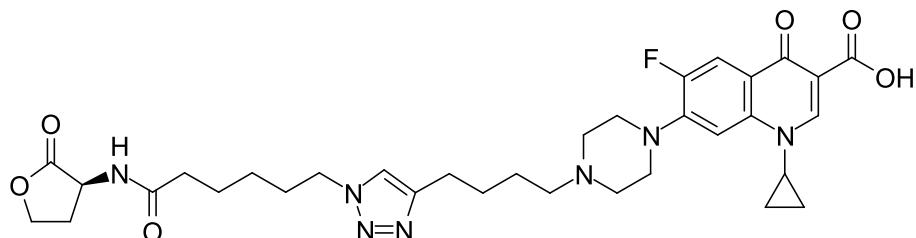
$^1\text{H NMR}$ (500 MHz, DMSO d₆) δ / ppm = 15.22 (br s, 1 H, C(=O)OH), 8.65 (s, 1 H, *ortho* to C(=O)OH), 8.40 (d, J = 8.0 Hz, 1 H, NH), 7.88 (d, J = 13.4 Hz, 1 H, *ortho* to F), 7.85 (s, 1 H, CH=CCH₂), 7.55 (d, J = 7.5 Hz, 1 H, *meta* to F), 4.53 (ddd, J = 10.9, 9.0, 8.1 Hz, 1 H, CHNH), 4.33 (td, J = 8.9, 1.8 Hz, 1 H, OCHH), 4.31 (t, J = 7.0 Hz, 2 H, CH₂NCH=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(CH₂)₂), 3.32 (br. t, J = 4.2, 4.2 Hz, 4 H, CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 2.64 (t, J = 7.4 Hz, 2 H, CH=CCH₂), 2.57 (br. t, J = 5.0, 5.0 Hz, 2 H, CH₂CH₂CH₂N(CH₂)CH₂), 2.34 - 2.42 (m, 3 H, OCH₂CHH and CH=CCH₂CH₂CH₂CH₂CH₂), 2.09 - 2.19 (m, 3 H, OCH₂CHH and C(=O)CH₂), 2.02 (quin, J = 7.2 Hz, 2 H, C(=O)CH₂CH₂), 1.64 (quin, J = 7.6 Hz, 2 H, CH=CCH₂CH₂), 1.52 (quin, J = 7.2 Hz, 2 H, CH=CCH₂CH₂CH₂), 1.29 - 1.34 (m, 2 H, NCH(CHH)₂), 1.15 - 1.21 (m, 2 H, NCH(CHH)₂)

$^{13}\text{C NMR}$ (126 MHz, DMSO d₆) δ / 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=CCH₂), 145.2 (d, J = 9.6 Hz, *ipso* to piperazine), 139.2 (*para* to F), 121.7 (CH=CCH₂), 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 (OCH₂), 57.3 (CH=CCH₂CH₂CH₂CH₂N), 52.4 (CH₂CH₂CH₂N(CH₂)CH₂), 49.5 (CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 49.4 (CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 48.6 (CH₂NCH=C), 47.9 (OC(=O)CHNH), 35.9 (NCH(CH₂)₂), 31.7 (NHC(=O)CH₂), 28.2 (CH₂CHNH), 26.9 (CH=CCH₂CH₂), 25.8 (NHC(=O)CH₂CH₂ and CH=CCH₂CH₂CH₂), 24.9 (CH=CCH₂), 7.6 (NCH(CH₂)₂)

HRMS (ESI⁺) m/z / Da = 624.2928, [M+H]⁺ found, [C₃₁H₃₉FN₇O₆]⁺ requires 624.2946

$[\alpha]_D^{20}$ / ${}^\circ 10^{-1}\text{cm}^2\text{g}^{-1}$ = -10.6 (c / g(100 ml)⁻¹ = 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 N₂ 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)-6-azido-N-(2-oxotetrahydrofuran-3-yl)hexanamide **47** (12.0 mg, 50.0 μmol , 1 eq.). A similarly degassed solution of CuSO₄ · 5 H₂O (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 SiO₂ and purified by column chromatography using a CombiFlash (SiO₂, 0-20 % MeOH/CH₂Cl₂ over 15 min) The combined pure fractions were dried with MgSO₄ and evaporated under reduced pressure. **97** was obtained as a white amorphous solid (12.4 mg, 19.0 μmol , 38.0 %).

TLC $R_f = 0.30$ (30 % MeOH/CH₂Cl₂)

IR (neat) ν_{max} / cm⁻¹ = 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)

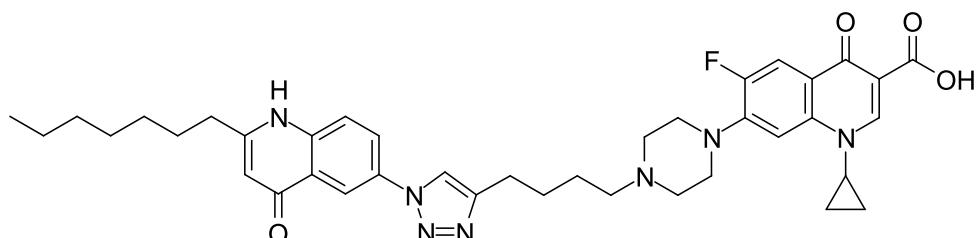
¹H NMR (500 MHz, DMSO d₆) δ / ppm = 15.22 (br s, 1 H, C(=O)OH), 8.65 (s, 1 H, *ortho* to C(=O)OH), 8.32 (d, J = 8.0 Hz, 1 H, NH), 7.89 (d, J = 13.3 Hz, 1 H, *ortho* to F), 7.84 (s, 1 H, CH=CCH₂), 7.55 (d, J = 7.6 Hz, 1 H, *meta* to F), 4.51 (ddd, J = 10.9, 9.1, 7.9 Hz, 1 H, CHNH), 4.33 (td, J = 8.8, 1.8 Hz, 1 H, OCHH), 4.28 (t, J = 7.1 Hz, 2 H, CH₂NCH=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(CH₂)₂), 3.32 (br t, J = 4.5, 4 H, CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 2.63 (t, J = 7.5 Hz, 2 H, CH=CCH₂), 2.57 (br t, J = 4.2, 4.2 Hz, 4 H, CH₂CH₂CH₂N(CH₂CH₂)), 2.33 - 2.41 (m, 3 H, OCH₂CHH and CH=CCH₂CH₂CH₂CH₂), 2.06 - 2.16 (m, 3 H, OCH₂CHH and C(=O)CH₂), 1.79 (quin, J = 7.4 Hz, 2 H, C(=O)CH₂CH₂CH₂CH₂), 1.63 (quin, J = 7.5 Hz, 2 H, CH=CCH₂CH₂), 1.45 - 1.56 (m, 4 H, C(=O)CH₂CH₂ and CH=CCH₂CH₂CH₂), 1.29 - 1.34 (m, 2 H, NCH(CHH)₂), 1.19 - 1.25 (m, 2 H, C(=O)CH₂CH₂CH₂), 1.15 - 1.19 (m, 2 H, NCH(CHH)₂)

¹³C NMR (126 MHz, DMSO d₆) δ / 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=CCH₂), 145.2 (d, J = 9.6 Hz, *ipso* to piperazine), 139.2 (para to F), 121.6 (CH=CCH₂), 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 (OCH₂), 57.4 (CH=CCH₂CH₂CH₂N), 52.4 (CH₂CH₂CH₂N(CH₂CH₂)CH₂), 49.5 (CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 49.5 (CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 49.0 (CH₂NCH=C), 47.8 (CHNH), 35.9 (NCH(CH₂)₂), 34.8 (NHC(=O)CH₂), 29.5 (CH₂CH₂NCH=C), 28.3 (CH₂CHNH), 26.9 (CH=CCH₂CH₂), 25.7 (CH=CCH₂CH₂CH₂), 25.4 (NHC(=O)CH₂CH₂CH₂), 24.9 (CH=CCH₂), 24.5 (NHC(=O)CH₂CH₂), 7.6 (NCH(CH₂)₂)

HRMS (ESI⁺) m/z / Da = 652.3254, [M+H]⁺ found, [C₃₃H₄₃FN₇O₆]⁺ requires 652.3248

$[\alpha]_D^{20}$ / °10⁻¹cm²g⁻¹ = -8.5 (c / g(100 ml)⁻¹ = 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 N₂ 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 μ mol, 1 eq.) and 6-azido-2-heptylquinolin-4(1H)-one **26** (2.8 mg, 10.0 μ mol, 1 eq.). A similarly degassed solution of CuSO₄ · 5 H₂O (125 μ g, 0.5 μ mol, 0.05 eq. 50 mM), THPTA (218 μ g, 0.5 μ mol, 0.05 eq. 50 mM) and sodium ascorbate (198 μ g, 1 μ mol, 0.1 eq., 100 mM) in 50 % water/t-BuOH (10 μ 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 NaHCO_3 (aq., sat., 10 ml) and 10 % *i*-PrOH/CHCl₃ (10 ml). The organic layer was dried with MgSO_4 and evaporated under reduced pressure. **98** was obtained as a white amorphous solid (8.6 mg, 2.7 μmol , 27.0 %).

IR (neat) ν_{max} / cm^{-1} = 2927.0 (C-H), 2865.5 (C-H), 1715.5 (carboxylic acid C=O), 1631.0 (ciprofloxacin quinolone C=O and HHQ C=O)

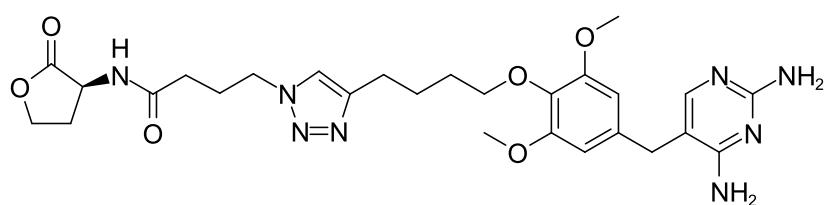
¹H NMR (500 MHz, DMSO d₆) 15.12 (br s, $\text{C}(=\text{O})\text{OH}$), 11.79 (s, 1 H, NH), 8.75 (s, 1 H, $\text{NCH}=\text{CCH}_2$), 8.71 (s, 1 H, *ortho* to C(=O)OH), 8.40 (d, J = 2.7 Hz, 1 H, *ortho* to C(=O) and *ortho* to N), 8.18 (dd, J = 8.9, 2.6 Hz, 1 H, *para* to C(=O) and *ortho* to N), 7.99 (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, $\text{NHC}=\text{CH}(\text{C}(=\text{O}))$), 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, $\text{CH}_2\text{C}=\text{CH}(\text{C}(=\text{O}))$), 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, $\text{CH}_2\text{CH}_2\text{C}=\text{CH}(\text{C}(=\text{O}))$) 

¹³C NMR (126 MHz, DMSO d₆) δ / ppm = 176.4 ($\text{C}(=\text{O})\text{CC}(=\text{O})\text{OH}$), 176.3 ($\text{CHC}(=\text{O})$), 165.8 ($\text{C}(=\text{O})\text{OH}$), 154.3 ($\text{CCHC}(=\text{O})$), 152.9 (d, J = 240.1 Hz, *ipso* to F), 148.3 ($\text{CH}=\text{CC}(=\text{O})\text{OH}$), 147.5 (NCHCCH_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 ($\text{NCH}=\text{CCH}_2$), 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 ($\text{CHC}(=\text{O})$), 106.9 ($\text{CC}(=\text{O})\text{OH}$), 55.4 ($\text{CH}=\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$), 50.6 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2)\text{CH}_2$), 46.5 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)\text{CH}_2\text{CH}_2$), 36.0 ($\text{NCH}(\text{CH}_2)_2$), 33.2 (CH_2CNH), 31.2 ($\text{CH}_3\text{CH}_2\text{CH}_2$), 28.3 - 28.5 ($\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$), 25.6 ($\text{CH}=\text{CCH}_2\text{CH}_2$), 24.4 ($\text{CH}=\text{CCH}_2$), 22.7 ($\text{CH}=\text{CCH}_2\text{CH}_2\text{CH}_2$), 22.0 (CH_3CH_2), 13.9 (CH_3), 7.6 ($\text{NCH}(\text{CH}_2)_2$)

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

HRMS (ESI⁺) m/z / Da = 696.3667, [M+H]⁺ found, [C₃₉H₄₇FN₇O₄]⁺ 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_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 μmol , 1 eq.) and (*S*)-4-azido-*N*-(2-oxotetrahydrofuran-3-yl)butanamide **46** (15.9 mg, 75.0 μmol , 1.5 eq.). Similarly degassed solutions of $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (624 μg , 2.5 μmol , 0.05 eq. 50 mM), THPTA (1.09 mg, 2.5 μmol , 0.05 eq. 50 mM) and sodium

ascorbate (991 μg , 5 μmol , 0.1 eq., 100 mM) in water (50 μl) were then added. An extra portion of **46** (10.6 mg, 50.0 μmol , 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 CH_2Cl_2 ($6 \times 10 \text{ ml}$) then dry-loaded onto SiO_2 and purified by column chromatography using a Combiflash (SiO_2 , 0-20 % $\text{MeOH}/\text{CH}_2\text{Cl}_2$). The combined pure fractions were dried with MgSO_4 and evaporated under reduced pressure. **99** was obtained as a pale brown gum (4.8 mg, 8.4 μmol , 16.8 %).

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

IR (neat) ν_{max} / 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)

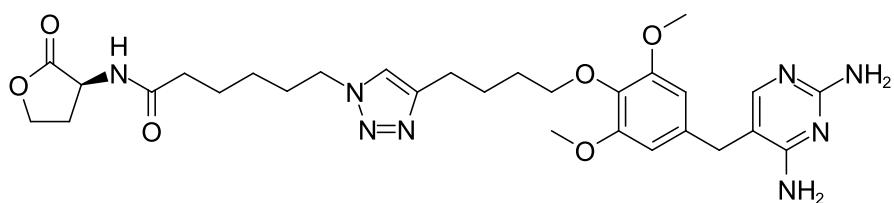
$^1\text{H NMR}$ (500 MHz, DMSO d₆) δ / ppm = 8.43 (d, $J = 8.0 \text{ Hz}$, 1 H, NH), 7.80 (s, 1 H, $\text{NCH}=\text{CCH}_2$), 7.46 (s, 1 H, $\text{CHN}=\text{CNH}_2$), 6.68 (br s, 2 H, CH_2CCNH_2), 6.53 (s, 2 H, *meta* to CH₂), 6.21 (br s, 2 H, $\text{CHN}=\text{CNH}_2$), 4.49 (dt, $J = 10.7, 8.6 \text{ Hz}$, 1 H, CHNH), 4.32 (td, $J = 8.7, 1.6 \text{ Hz}$, 1 H, $\text{CHHOC}(=\text{O})$), 4.29 (t, $J = 6.8 \text{ Hz}$, 2 H, CH_2N), 4.19 (ddd, $J = 10.6, 8.7, 6.5 \text{ Hz}$, 1 H, $\text{CHHOC}(=\text{O})$), 3.79 (t, $J = 6.2 \text{ Hz}$, 2 H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{O}$), 3.68 (s, 6 H, CH_3), 3.53 (br s, 2 H, CCH_2C), 2.63 (t, $J = 7.5 \text{ Hz}$, 2 H, $\text{CH}=\text{CCH}_2$), 2.37 (dddd, $J = 12.2, 8.9, 6.7, 1.8 \text{ Hz}$, 1 H, CHHCHNH), 2.08 - 2.15 (m, 3 H, CHHCHNH and $\text{C}(=\text{O})\text{CH}_2$), 2.00 (quin, $J = 7.2 \text{ Hz}$, 2 H, $\text{CH}_2\text{CH}_2\text{N}$), 1.72 (quin, $J = 7.3 \text{ Hz}$, 2 H, $\text{CH}=\text{CCH}_2\text{CH}_2$), 1.61 (quin, $J = 6.7 \text{ Hz}$, 2 H, $\text{CH}_2\text{CH}_2\text{O}$)

$^{13}\text{C NMR}$ (126 MHz, DMSO d₆) δ / 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 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 CH_2O), 135.0 (*ipso* to CH_2O), 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 CH_2O), 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 (OCH_3), 48.9 (CH_2N), 48.3 (CHNH), 32.9 (CCH_2C), 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⁺) m/z / Da = 569.2834, [M+H]⁺ found, $[\text{C}_{27}\text{H}_{37}\text{N}_8\text{O}_6]^+$ requires 569.2836

$[\alpha]_D^{20}$ / ${}^\circ 10^{-1}\text{cm}^2\text{g}^{-1}$ = -4.6 (c / g(100 ml)⁻¹ = 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 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 μmol , 1 eq.) and (*S*)-6-azido-*N*-(2-oxotetrahydrofuran-3-yl)hexanamide **47** (18.0 mg, 75.0 μmol , 1.5 eq.). Similarly degassed solutions of $\text{CuSO}_4 \cdot 5 \text{ H}_2\text{O}$ (624 μg , 2.5 μmol , 0.05 eq. 50 mM), THPTA (1.09 mg, 2.5 μmol , 0.05 eq. 50 mM) and sodium ascorbate (991 μg , 5 μmol , 0.1 eq., 100 mM) in water (50 μl) were then added. An extra portion of **47** (12.0 mg, 50.0 μmol , 1 eq.) was added after was added after 4 d. Extra portions of the catalysts were added after 9 d. After

2 weeks, the reaction mixture was extracted with CH_2Cl_2 (6×10 ml) then dry-loaded onto SiO_2 and purified by column chromatography using a Combiflash (SiO_2 , 0-20 % $\text{MeOH}/\text{CH}_2\text{Cl}_2$). The combined pure fractions were dried with MgSO_4 and evaporated under reduced pressure. **100** was obtained as a clear gum (8.0 mg, 13.4 μmol , 26.8 %).

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

IR (neat) ν_{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)

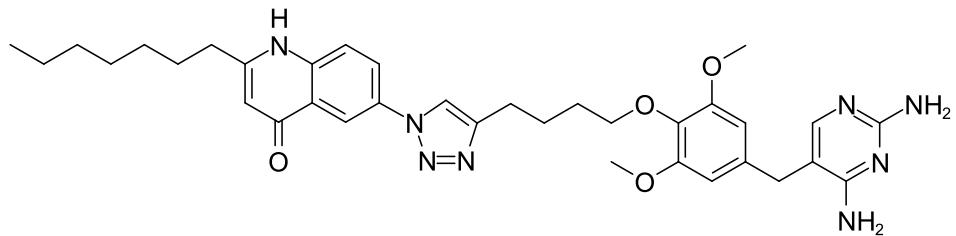
$^1\text{H NMR}$ (500 MHz, DMSO d₆) δ / ppm = 8.34 (d, $J = 8.0$ Hz, 1 H, NH), 7.83 (s, 1 H, $\text{NCH}=\text{CCH}_2$), 7.50 (s, 1 H, $\text{CHN}=\text{CNH}_2$), 6.54 (s, 2 H, *meta* to CH_2), 6.17 (br s, 2 H, $\text{CH}_2\text{CCN}\underline{\text{H}}_2$), 5.77 (br s, 2 H, $\text{CHN}=\text{CNH}_2$), 4.51 (ddd, $J = 11.0, 9.0, 8.1$ Hz, 1 H, 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, CH_2N), 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, CH_3), 3.52 (s, 2 H, CCH_2C), 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, CHHCHNH), 2.06 - 2.16 (m, 3 H, 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 d₆) δ / 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 OCH_3), 146.7 ($\text{CH}=\text{CCH}_2\text{CH}_2$), 135.5 (*para* to CH_2O), 134.8 (*ipso* to CH_2O), 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 CH_2O), 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 (OCH_3), 49.0 (CH_2N), 47.8 (CHNH), 34.8 ($\text{C}(=\text{O})\text{CH}_2$), 32.9 (CCH_2C), 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⁺) m/z / Da = 597.3149, [M+H]⁺ found, $[\text{C}_{29}\text{H}_{41}\text{N}_8\text{O}_6]^+$ requires 597.3144

$[\alpha]_D^{20}$ / ${}^\circ\text{10}^{-1}\text{cm}^2\text{g}^{-1} = -3.6$ (c / g(100 ml)⁻¹ = 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 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 μmol , 1 eq.) and 6-azido-2-heptylquinolin-4(*1H*)-one **26** (2.8 mg, 10.0 μmol , 1 eq.). A similarly degassed solution of $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (125 μg , 0.5 μmol , 0.05 eq. 50 mM), THPTA (218 μg , 0.5 μmol , 0.05 eq. 50 mM) and sodium ascorbate (198 μg , 1 μmol , 0.1 eq., 100 mM) in water (10 μl) was then added. The mixture was stirred at r.t. under argon for 1.5 h, then 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 NaHCO_3 (aq., sat., 10 ml) and 10 % *i*-PrOH/CHCl₃ (10 ml). The organic layer was dried with MgSO₄ and evaporated under reduced pressure. **101** was obtained as a clear gum (2.6 mg, 4.1 μmol , 41.0 %).

TLC R_f = 0.17 (20 % MeOH/CH₂Cl₂)

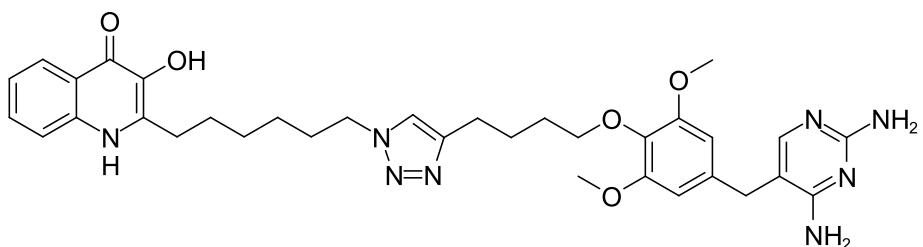
IR (neat) ν_{max} / cm⁻¹ = 2927.7 (C-H), 2855.5 (C-H), 1664.1 (pyrimidine), 1645.4 (pyrimidine and HHQ C=O),

¹H NMR (500 MHz, DMSO d₆) δ / ppm = 11.80 (s, 1 H, NH), 8.69 (s, 1 H, NCH=CCH₂), 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, NH₂), 7.41 (s, 1 H, CHN=CNH₂), 6.61 (s, 2 H, *meta* to CH₂), 6.02 (d, J = 1.8 Hz, 1 H, C(=O)CH), 3.86 (t, J = 6.3 Hz, 2 H, CH₂O), 3.73 (s, 6 H, OCH₃), 3.57 - 3.62 (m, 2 H, CCH₂C), 2.78 (t, J = 7.5 Hz, 2 H, CH=CCH₂), 2.63 (t, J = 7.3 Hz, 2 H, HNCCH₂), 1.85 (quin, J = 7.5 Hz, 2 H, CH=CCH₂CH₂), 1.61 - 1.78 (m, 4 H, HNCCH₂CH₂ and CH=CCH₂CH₂CH₂), 1.31 - 1.40 (m, 4 H, HNCCH₂CH₂CH₂CH₂), 1.25 - 1.31 (m, 4 H, CH₃CH₂CH₂), 0.86 (t, J = 7.2 Hz, 3 H, CH₃CH₂)

¹³C NMR (125 MHz, DMSO d₆) δ / ppm = 176.4 (C=O), 164.1 (CC(NH₂)N), 154.3 (HNC), 154.2 (NC(NH₂)N), 153.1 (*ipso* to OCH₃), 148.3 (CH=CCH₂CH₂), 140.2 (CHNC(NH₂)N), 139.6 (*ipso* to NH), 135.4 (*ipso* to CH₂O), 132.8 (*para* to CH₂O), 132.1 (*para* to NH), 124.9 (*ipso* to C=O), 123.7 (*para* to C=O), 120.3 (CH=CCH₂CH₂), 120.0 (*meta* to C=O and *ortho* to NH), 115.1 (*ortho* to C=O and *meta* to NH), 109.0 (CH₂CC(NH₂)=N), 108.0 (C(=O)CH), 106.3 (*meta* to CH₂O), 72.0 (CH₂CH₂CH₂O), 56.0 (OCH₃), 33.3 (HNCCH₂), 32.1 (CCH₂C), 31.2 (CH₃CH₂CH₂), 29.1 (CH₂CH₂O), 28.3 - 28.6 (CH₃CH₂CH₂CH₂CH₂CH₂), 25.3 (CH₂CH₂CH₂O), 24.7 (CH=CCH₂), 22.1 (CH₃CH₂), 14.0 (CH₃CH₂)

HRMS (ESI⁺) m/z / Da = 641.3557, [M+H]⁺ found, [C₃₅H₄₅N₈O₄]⁺ 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 N₂ 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 μmol , 1 eq.) and 2-(6-azidohexyl)-3-hydroxyquinolin-4(1*H*)-one **56** (11.4 mg, 39.8 μmol , 1 eq.). A similarly degassed solution of CuSO₄ · 5 H₂O (1.25 mg, 5 μmol , 0.125 eq. 50 mM), THPTA (2.18 mg, 5 μmol , 0.125 eq. 50 mM) and sodium ascorbate (1.98 mg, 10 μmol , 0.25 eq., 100 mM) in water (100 μl) was then added. The mixture was stirred at r.t. under argon for 3 h, then MeOH (1 ml) was added and the reaction mixture was dry-loaded onto SiO₂ and purified by column chromatography (SiO₂, 0-20 % MeOH/CH₂Cl₂). The combined pure fractions were dried with MgSO₄ and evaporated under reduced pressure. **102** was obtained as a pale brown amorphous solid (4.7 mg, 7.3 μmol , 18.3 %).

TLC $R_f = 0.21$ (20 % MeOH/CH₂Cl₂)

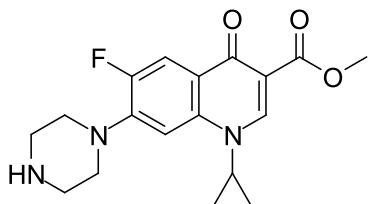
IR (neat) $\nu_{max} / \text{cm}^{-1} = 2924.8$ (C-H), 2853.4 (C-H), 1660.0 (pyrimidine), 1638.8 (pyrimidine and PQS C=O),

¹H NMR (500 MHz, DMSO d₆) $\delta / \text{ppm} = 11.53$ (br s, 1 H, NH), 8.09 (d, $J = 8.0$ Hz, 1 H, *ortho* to C=O), 7.83 (s, 1 H, NCH=CCH₂), 7.48 - 7.57 (m, 3 H, *para* to C=O, *ortho* to NH and C_{HN}=CNH₂), 7.21 (ddd, $J = 8.0, 6.3, 1.5$ Hz, 1 H, *para* to NH), 6.55 (s, 2 H, *meta* to CH₂), 4.28 (t, $J = 7.1$ Hz, 2 H, CH₂N), 3.80 (t, $J = 6.2$ Hz, 2 H, CH₂O), 3.70 (s, 6 H, CH₃), 3.53 (d, $J = 0.3$ Hz, 2 H, CCH₂C), 2.73 (t, $J = 7.5$ Hz, 2 H, HNCCH₂), 2.64 (t, $J = 7.4$ Hz, 2 H, CH=CCH₂), 1.80 (quin, $J = 7.4$ Hz, 2 H, CH₂CH₂N), 1.73 (quin, $J = 7.5$ Hz, 2 H, CH=CCH₂CH₂), 1.66 (quin, $J = 7.2$ Hz, 2 H, HNCCH₂CH₂), 1.62 (quin, $J = 6.8$ Hz, 2 H, CH₂CH₂O), 1.33 - 1.40 (m, 2 H, HNCCH₂CH₂CH₂), 1.27 - 1.32 (m, 2 H, HNCCH₂CH₂CH₂CH₂)

¹³C NMR (125 MHz, DMSO d₆) $\delta / \text{ppm} = 168.9$ (C=O), 162.5 (CC(NH₂)N), 162.5 (NC(NH₂)N), 152.9 (CHNC(NH₂)N), 152.8 (*ipso* to OCH₃), 146.8 (CH=CCH₂CH₂), 137.7 (COH), 137.3 (*para* to OH), 135.4 (HNC), 135.1 (*para* to CH₂O), 134.8 (*ipso* to CH₂O), 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=CCH₂CH₂), 117.7 (*meta* to C=O and *ortho* to NH), 106.2 (CH₂CC(NH₂)=N), 105.8 (*meta* to CH₂O), 71.9 (CH₂CH₂CH₂O), 55.8 (OCH₃), 49.0 (CH₂N), 32.8 (CCH₂C), 29.5 (CH₂CH₂N), 29.0 (CH₂CH₂O), 28.1 (HNCCH₂CH₂CH₂), 27.9 (HNCCH₂), 27.6 (HNCCH₂CH₂), 25.6 (CH₂CH₂CH₂N), 25.4 (CH₂CH₂CH₂O), 24.6 (CH=CCH₂CH₂)

HRMS (ESI⁺) $m/z / \text{Da} = 643.3365$, [M+H]⁺ found, [C₃₄H₄₃N₈O₅]⁺ 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 NaHCO₃ (sat., aq., 100 ml) and water (300 ml) were added. The product was extracted with CH₂Cl₂ (2×400 ml). The combined organic fractions were dried over MgSO₄ and evaporated under reduced pressure. **103** was obtained as a white amorphous solid (9.16 g, 26.5 mmol, 83.3 %).

TLC $R_f = 0.13$ (5 % MeOH/CH₂Cl₂)

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

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

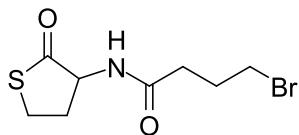
¹³C NMR (101 MHz, MeOD) δ / ppm = 175.2 ($\underline{\text{C}}(\text{=O})\text{CC}(\text{=O})\text{OCH}_3$), 166.8 ($\underline{\text{C}}(\text{=O})\text{OCH}_3$), 154.9 (d, J = 248.0 Hz, *ipso* to F), 150.1 ($\underline{\text{C}}=\text{CC}(\text{=O})\text{OCH}_3$), 146.6 (d, J = 10.4 Hz, *ipso* to piperazine), 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 ($\text{NCH}(\underline{\text{CH}_2})_2$)

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

HRMS (ESI⁺) m/z / Da = 346.1569, [M+H]⁺ found, [C₁₈H₂₁FN₃O₃]⁺ requires 346.1567

The data are consistent with the literature.¹⁰

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 NaHCO₃ (16.4 g, 195 mmol, 2 eq.) were added to CH₂Cl₂ (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 CH₂Cl₂ (150 ml). The combined organic layers were dried over MgSO₄ 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) ν_{max} / cm⁻¹ = 3265.9 (amide N-H), 3063.2 (amide N-H), 1694.3 (thiolactone C=O), 1650.5 (amide C=O)

¹H NMR (400 MHz, CDCl₃) δ / 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, CH₂Br), 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, SCH₂CHH), 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)CH₂CH₂), 1.96 (dddd, J = 12.7, 12.5, 12.2, 7.0 Hz, 1 H, SCH₂CHH)

¹³C NMR (101 MHz, CDCl₃) δ / ppm = 205.4 (SC(=O)), 172.1 (NHC(=O)), 59.4 (CHNH), 34.1 (C(=O)CH₂), 33.1 (CH₂Br), 31.8 (SCH₂CH₂), 28.0 (C(=O)CH₂CH₂), 27.5 (SCH₂)

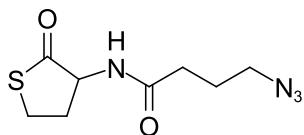
HRMS (ESI⁺) m/z / Da = ??, [M+H]⁺ found, [??]⁺ requires ??



pick up

The compound has been synthesised previously^{11,12} 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 NaN₃ (3.51 g, 54.1 mmol, 2 eq.) were refluxed in acetonitrile (120 ml) for 1.5 h. The solvent was evaporated under reduced pressure and the residue was partitioned between water (150 ml) and CH₂Cl₂ (150 ml). The aqueous layer was extracted twice more with CH₂Cl₂ (2×150 ml) and the combined organic fractions were dried with MgSO₄ and evaporated under reduced pressure. **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) ν_{max} / cm⁻¹ = 3285.6 (N-H), 2963.9 (C-H), 2100.2 (azide), 1697.4 (thiolactone C=O), 1647.4 (amide C=O)

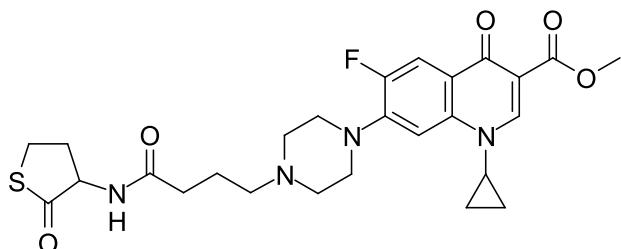
¹H NMR (400 MHz, CDCl₃) δ / ppm = 6.71 (d, J = 7.3 Hz, 1 H, NH), 4.54 (dt, J = 13.0, 7.0 Hz, 1 H, CHNH), 3.30 (t, J = 6.7 Hz, 2 H, CH₂N₃), 3.31 (td, J = 11.7, 5.3 Hz, 1 H, ~~H~~, SCHH), 3.19 (ddd, J = 11.3, 7.0, 1.2 Hz, 1 H, SCHH), 2.70 (dddd, J = 12.4, 6.8, 5.3, 1.2 Hz, 1 H, SCH₂CHH), 2.29 (t, J = 7.5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

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

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

The compound has not been reported previously.

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 K₂CO₃ (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 (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 % $\text{MeOH}/\text{CH}_2\text{Cl}_2$)

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

$^1\text{H NMR}$ (500 MHz, MeOD) δ / ppm = 8.53 (s, 1 H, *ortho* to C(=O)OCH₃), 7.68 (d, $J=13.4$ Hz, 1 H, *ortho* to F), 7.41 (d, $J=7.3$ Hz, 1 H, *meta* to F), 4.67 (dd, $J=12.9, 6.9$ Hz, 1 H, CH₂NH), 3.83 (s, 3 H, OCH₃), 3.61 (tt, $J=6.9, 4.1$ Hz, 1 H, NCH(CH₂)₂), 3.39 - 3.49 (m, 5 H, SCH₂H), 3.26 - 3.33 (m, 1 H, SCH₂H and CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 2.93 - 3.03 (m, 4 H, CH₂CH₂CH₂N(CH₂CH₂)CH₂), 2.79 (br. t, $J=7.2, 7.2$ Hz, 2 H, C(=O)CH₂CH₂CH₂), 2.59 (dd, $J=12.4, 6.9, 5.4, 1.4$ Hz, 1 H, SCH₂CH₂H), 2.39 (t, $J=7.20$ Hz, 1 H, C(=O)CH₂CH₂H), 2.38 (t, $J=6.94$ Hz, 1 H, C(=O)CH₂H), 2.18 (qd, $J=12.4, 7.0$ Hz, 1 H, SCH₂CH₂H), 1.97 (quin, $J=7.2$ Hz, 2 H, C(=O)CH₂CH₂), 1.32 - 1.37 (m, 2 H, NCH(CH₂CH₂)₂), 1.13 - 1.19 (m, 2 H, NCH(CH₂CH₂)₂)

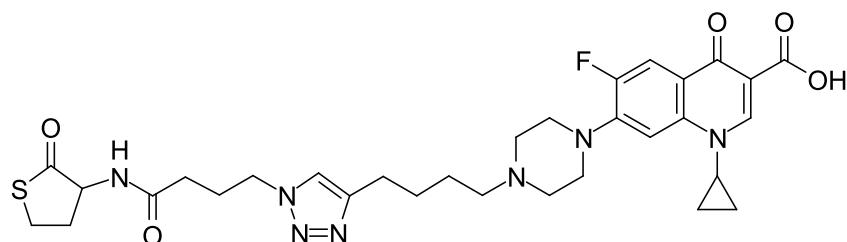
$^{13}\text{C NMR}$ (126 MHz, MeOD) δ / ppm = 207.0 (SC(=O)), 175.7 (NHC(=O)), 175.1 (C(=O)CC(=O)OCH₃), 166.6 (C(=O)OCH₃), 154.7 (d, $J=249.0$ Hz, *ipso* to F), 150.2 (s, CH=CC(=O)OCH₃), 145.6 (d, $J=10.6$ Hz, *ipso* to piperazine), 139.8 (*para* to F), 123.5 (d, $J=6.9$ Hz, *para* to piperazine), 113.1 (d, $J=23.6$ Hz, *ortho* to C=O and *ortho* to F), 110.0 (CC(=O)OCH₃), 107.4 (*meta* to C=O and *meta* to F), 60.2 (CH₂NH), 58.5 (C(=O)CH₂CH₂CH₂), 53.8 (CH₂CH₂CH₂N(CH₂CH₂)CH₂), 52.3 (OCH₃), 50.1 (CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 50.0 (CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 36.5 (NCH(CH₂CH₂)₂), 34.5 (C(=O)CH₂), 31.7 (SCH₂CH₂), 28.1 (SCH₂), 22.9 (C(=O)CH₂CH₂CH₂), 8.7 (NCH(CH₂CH₂)₂)

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

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

The compound has been synthesised previously.^{11,12} Only HRMS characterisation was published, and this agrees with the result above.

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 μmol , 1 eq.) and 4-azido-*N*-(2-oxotetrahydrothiophen-3-yl)butanamide **106** (12.5 mg, 55.1 μmol , 1.5 eq.) were dissolved in 1:9:10 water/*t*-BuOH/DMSO (3 ml), and the mixture was degassed by bubbling N_2 through it. A solution of CuSO₄ and THPTA (182 μl , 18.2 μmol , 0.5 eq. 100 mM, aq.) was added, followed by

a solution of sodium ascorbate (367 μ l, 36.7 μ mol, 1 eq., 100 mM, aq.). The mixture was stirred at r.t. under argon for 7 d. Water (10 ml) and 10 % *i*-PrOH/CHCl₃ (10 ml) were added, the organic layer was separated and the aqueous layer was extracted again with 10 % *i*-PrOH/CHCl₃ (2×10 ml). The combined organic layers were dried with MgSO₄ 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 NaHCO₃ (aq., sat., 50 ml) and 10 % *i*-PrOH/CHCl₃ (50 ml). The organic layer was dried with MgSO₄ and evaporated under reduced pressure. **108** was obtained as a white amorphous solid (16.5 mg, 25.9 μ mol, 70.6 %).

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

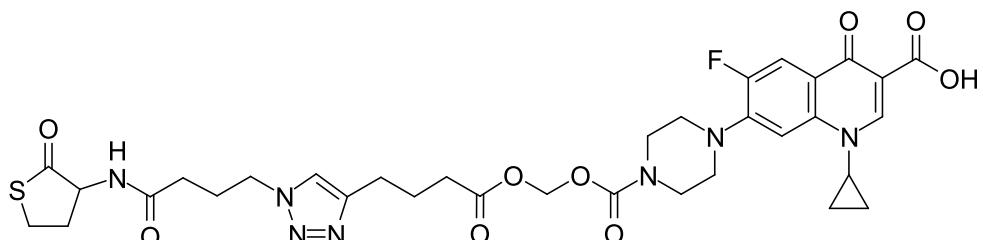
¹H NMR (500 MHz, DMSO d₆) δ / ppm = 15.23 (br s, 1 H, C(=O)OH), 8.66 (s, 1 H, *ortho* to C(=O)OH), 8.23 (d, J=8.5 Hz, 1 H, NH), 7.90 (d, J=13.4 Hz, 1 H, *ortho* to F), 7.84 (s, 1 H, CH=CCH₂), 7.56 (d, J=7.5 Hz, 1 H, *meta* to F), 4.59 (ddd, J=12.7, 8.4, 6.8 Hz, 1 H, CHNH), 4.31 (t, J=7.0 Hz, 2 H, CH₂NCH=C),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

¹³C NMR (126 MHz, DMSO d₆) δ / ppm = 205.6 (SC(=O)), 176.4 (C(=O)CC(=O)OH), 171.4 (NHC(=O)), 166.0 (C(=O)OH), 153.1 (d, J=249.3 Hz, *ortho* to F), 148.0 (CH=CC(=O)OH), 146.9 (CH=CCH₂), 145.3 (d, J=10.1 Hz, *ipso* to piperazine), 139.2 (para to F), 121.8 (CH=CCH₂), 118.6 (d, J=7.7 Hz, para to piperazine), 111.0 (d, J=23.3 Hz, *ortho* to C=O and *ortho* to F), 106.7 (CC(=O)OH), 106.4 (d, J=2.9 Hz, *meta* to C=O and *meta* to F), 58.2 (SC(=O)CHNH), 57.4 (CH=CCH₂CH₂CH₂N), 52.4 (CH₂CH₂CH₂N(CH₂)CH₂), 49.5 (CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 49.5 (CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 48.6 (CH₂NCH=C), 35.9 (NCH(CH₂)₂), 31.9 (NHC(=O)CH₂), 30.1 (CH₂CHNH), 26.9 (CH=CCH₂CH₂), 26.8 (SCH₂), 25.9 (NHC(=O)CH₂CH₂), 25.8 (CH=CCH₂CH₂CH₂), 25.0 (CH=CCH₂), 7.6 (NCH(CH₂)₂)

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

HRMS (ESI⁺) *m/z* / Da = 640.2739, [M+H]⁺ found, [C₃₁H₃₉FN₇O₅S]⁺ requires 640.2712

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 CH_2Cl_2 (18.6 ml) at r.t. under Ar for 3 h. The mixture was filtered and the filtrate was dry-loaded onto SiO_2 and purified by column chromatography (SiO_2 , 5-10 % MeOH/ CH_2Cl_2). **110** was obtained as pale brown/yellow amorphous solid (14.7 mg, 20.2 μmol , 5.0 %).

TLC R_f = 0.40 (5 % CH_2Cl_2 /MeOH)

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

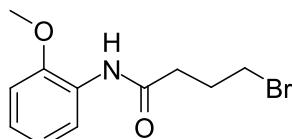
$^1\text{H NMR}$ (400 MHz, DMSO d₆) δ / ppm = 15.16 (br s, 1 H, C(=O)OH), 8.65 (s, 1 H, *ortho* to C(=O)OH), 8.21 (d, J = 8.5 Hz, 1 H, NH), 7.89 (d, J = 13.1 Hz, 1 H, *ortho* to F), 7.85 (s, 1 H, CH=CCH₂), 7.57 (d, J = 7.4 Hz, 1 H, *meta* to F), 5.74 (s, 1 H, OCH₂O), 4.58 (ddd, J = 12.6, 8.1, 7.2 Hz,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

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

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

The compound has not been reported previously. 

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



2-Methoxyaniline **111** (9.12 ml, 10.0 g, 81.2 mmol, 1 eq.) and NaHCO₃ (8.19 g, 97.4 mmol, 1.2 eq.) were dissolved in water (100 ml) and CH_2Cl_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 MgSO₄ 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)

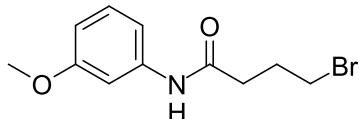
$^1\text{H NMR}$ (400 MHz, CDCl_3 d₁) $\delta / \text{ppm} = 8.32$ (dd, $J = 8.0, 1.7$ Hz, 1 H, *ortho* to NH), 7.85 (br s, 1 H, NH), 7.02 (td, $J = 7.9, 1.7$ Hz, 1 H, *para* to NH), 6.93 (td, $J = 7.7, 1.4$ Hz, 1 H, *para* to OCH₃), 6.85 (dd, $J = 8.1, 1.5$ Hz, 1 H, *ortho* to OCH₃), 3.85 (s, 3 H, CH₃), 3.50 (t, $J = 6.4$ Hz, 2 H, CH₂Br), 2.56 (t, $J = 7.1$ Hz, 2 H, C(=O)CH₂), 2.25 (quin, $J = 6.7$ Hz, 2 H, C(=O)CH₂CH₂)

$^{13}\text{C NMR}$ (101 MHz, CDCl_3 d₁) $\delta / \text{ppm} = 169.4$ (C(=O)), 147.6 (*ipso* to OCH₃), 127.2 (*ipso* to NH), 123.5 (*para* to NH), 120.7 (*para* to OCH₃), 119.6 (*ortho* to NH and *meta* to OCH₃), 109.8 (*ortho* to OCH₃ and *meta* to NH), 55.5 (CH₃), 35.4 (C(=O)CH₂), 33.1 (CH₂Br), 27.9 (C(=O)CH₂CH₂)

HRMS (ESI⁺) $m/z / \text{Da} = 272.0287$, [M+H]⁺ found, [C₁₁H₁₅BrNO₂]⁺ 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 NaHCO₃ (2.73 g, 32.5 mmol, 1.2 eq.) were dissolved in water (30 ml) and CH₂Cl₂ (30 ml). The mixture was cooled to 0 °C and 4-bromobutyryl chloride **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 SiO₂ and purified by column chromatography using a CombiFlash (SiO₂, 0-100 % EtOAc/P.E.). The combined pure fractions were dried with MgSO₄ and evaporated under reduced pressure. **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, CDCl_3 d₁) $\delta / \text{ppm} = 8.45$ (s, 1 H, NH), 7.27 (t, $J = 2.2$ Hz, 1 H, *ortho* to OCH₃ and *ortho* to NH), 7.14 (t, $J = 8.1$ Hz, 1 H, *meta* to OCH₃ and *meta* to NH), 7.02 (d, $J = 8.3$ Hz, 1 H, *para* to OCH₃), 6.62 (dd, $J = 8.2, 2.1$ Hz, 1 H, *para* to NH), 3.71 (s, 3 H, CH₃), 3.42 (t, $J = 6.5$ Hz, 2 H, CH₂Br), 2.51 (t, $J = 6.9$ Hz, 2 H, C(=O)CH₂), 2.19 (quin, $J = 6.8$ Hz, 2 H, C(=O)CH₂CH₂)

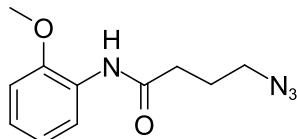
$^{13}\text{C NMR}$ (101 MHz, CDCl_3 d₁) $\delta / \text{ppm} = 170.3$ (C(=O)), 159.9 (*ipso* to OCH₃), 139.0 (*ipso* to NH), 129.5 (*meta* to OCH₃ and *meta* to NH), 112.1 (*para* to OCH₃), 109.9 (*para* to NH), 105.7 (*ortho* to OCH₃ and *ortho* to NH), 55.2 (CH₃), 35.3 (C(=O)CH₂), 33.2 (CH₂Br), 28.0 (C(=O)CH₂CH₂)

HRMS (ESI⁺) m/z / Da = ??, [M+H]⁺ found, [??]⁺ 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 NaN₃ (1.17 g, 18.0 mmol, 2.4 eq.) were refluxed in acetonitrile (100 ml) for 2 h. The mixture was cooled and filtered, and the filtrate was dry-loaded onto SiO₂ and purified by column chromatography using a Combiflash (SiO₂, 8-14 % then hold at 14 % EtOAc/P.E.). **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) ν_{max} / cm⁻¹ = 3419.7 (N-H), 3329.6 (N-H), 2094.8 (azide), 1672.3 (amide C=O)

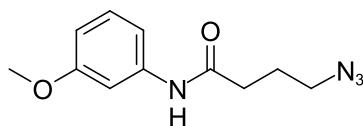
¹H NMR (400 MHz, CDCl₃ d₁) δ / ppm = 8.32 (dd, *J* = 7.9, 1.0 Hz, 1 H, *ortho* to NH), 7.86 (br s, 1 H, NH), 7.00 (td, *J* = 7.5, 1.5 Hz, 1 H, *para* to NH), 6.90 (td, *J* = 7.7, 1.1 Hz, 1 H, *para* to OCH₃), 6.83 (dd, *J* = 8.1, 1.4 Hz, 1 H, *ortho* to OCH₃), 3.81 (s, 3 H, CH₃), 3.33 (t, *J* = 6.7 Hz, 2 H, CH₂Br), 2.42 (t, *J* = 7.2 Hz, 2 H, C(=O)CH₂), 1.94 (quin, *J* = 6.9 Hz, 2 H, C(=O)CH₂CH₂)

¹³C NMR (101 MHz, CDCl₃ d₁) δ / ppm = 169.5 (C(=O)), 147.6 (*ipso* to OCH₃), 127.1 (*ipso* to NH), 123.4 (*para* to NH), 120.5 (*para* to OCH₃), 119.5 (*ortho* to NH and *meta* to OCH₃), 109.6 (*ortho* to OCH₃ and *meta* to NH), 55.2 (CH₃), 50.3 (CH₂N₃), 33.9 (C(=O)CH₂), 24.3 (C(=O)CH₂CH₂)

HRMS (ESI⁺) m/z / Da = 257.1010, [M+H]⁺ found, [C₁₁H₁₄N₄NaO₂]⁺ requires 257.1014

The data are consistent with the literature.¹³

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 NaN₃ (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 SiO₂ and purified by column chromatography using a Combiflash (SiO₂, 0-100 % EtOAc/P.E.). The combined pure fractions were dried with MgSO₄ and evaporated under reduced pressure. **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) ν_{max} / $\text{cm}^{-1} = 3298.3$ (N-H), 2094.7 (azide), 1661.7 (amide C=O)

$^1\text{H NMR}$ (400 MHz, MeOD) δ / ppm = 8.63 (br s, 1 H, NH), 7.26 (t, $J = 2.3$ Hz, 1 H, *ortho* to OCH₃ and *ortho* to NH), 7.15 (t, $J = 8.1$ Hz, 1 H, *meta* to OCH₃ and *meta* to NH), 7.01 (dd, $J = 7.8, 1.6$ Hz, 1 H, *para* to OCH₃), 6.63 (dd, $J = 8.2, 1.9$ Hz, 1 H, *para* to NH), 3.69 (s, 3 H, CH₃), 3.28 (t, $J = 6.7$ Hz, 2 H, CH₂N₃), 2.39 (t, $J = 7.4$ Hz, 2 H, C(=O)CH₂), 1.91 (quin, $J = 7.0$ Hz, 2 H, C(=O)CH₂CH₂)

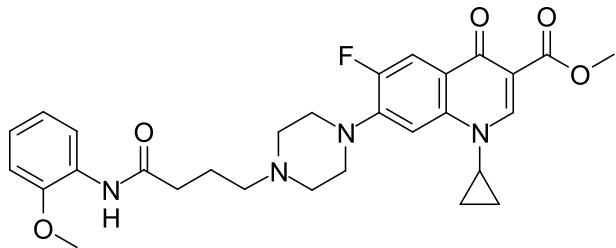
$^{13}\text{C NMR}$ (101 MHz, MeOD) δ / ppm = 170.8 (C(=O)), 159.6 (*ipso* to OCH₃), 138.9 (*ipso* to NH), 129.2 (*meta* to OCH₃ and *meta* to NH), 112.3 (*para* to OCH₃), 109.5 (*para* to NH), 106.0 (*ortho* to OCH₃ and *ortho* to NH), 54.8 (CH₃), 50.4 (CH₂N₃), 33.6 (C(=O)CH₂), 24.4 (C(=O)CH₂CH₂)

HRMS (ESI⁺) m/z / Da = ??, [M+H]⁺ found, [??]⁺ 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 SiO₂ and purified by column chromatography (SiO₂, 4 % MeOH/CH₂Cl₂). The combined pure fract^{on} were dried with MgSO₄ 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/CH₂Cl₂)

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

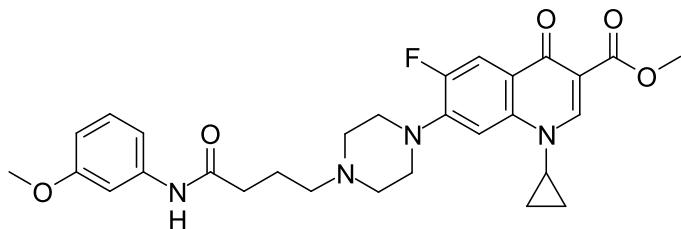
1.07 - 1.14 (m, 2 H, NCH(CH₂)₂)

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

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

The compound has not been reported previously.

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 CH₂Cl₂ (50 ml) and water (50 ml). The organic layer was separated off and the aqueous layer was extracted again with CH₂Cl₂ (50 ml). The combined organic layers were dried with MgSO₄ and purified by column chromatography (SiO₂, 0-4 % MeOH/CH₂Cl₂). The combined pure fractions were dried with MgSO₄ 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/CH₂Cl₂)

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

¹H NMR (400 MHz, CDCl₃) δ / ppm = 8.56 (s, 1 H, *ortho* to C(=O)OCH₃), 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 OCH₃ 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 OCH₃ and *meta* to NH), 6.98 (dd, *J* = 7.8, 1.7 Hz, 1 H, *para* to OCH₃), 6.65 (dd, *J* = 8.2, 2.1 Hz, 1 H, *para* to NH), 3.93 (s, 3 H, C(=O)OCH₃), 3.80 (s, 3 H, aromatic OCH₃), 3.42 (tt, *J* = 6.8, 3.7 Hz, 1 H, NCH(CH₂)₂), 3.31 (br t, *J* = 4.3, 4.3 Hz, 4 H, C(=O)CH₂CH₂CH₂N(CH₂)CH₂), 2.73 (br t, *J* = 4.5, 4.5 Hz, 4 H, C(=O)CH₂CH₂N(CH₂)CH₂), 2.58 (t, *J* = 6.5 Hz, 2 H, C(=O)CH₂CH₂CH₂N), 2.48 (t, *J* = 6.8 Hz, 2 H, C(=O)CH₂CH₂CH₂N), 2.00 (quin,

J = 6.8 Hz, 2 H, C(=O)CH₂CH₂CH₂N), 1.29 - 1.36 (m, 2 H, NCH(CHH)₂), 1.11 - 1.17 (m, 2 H, NCH(CHH)₂)

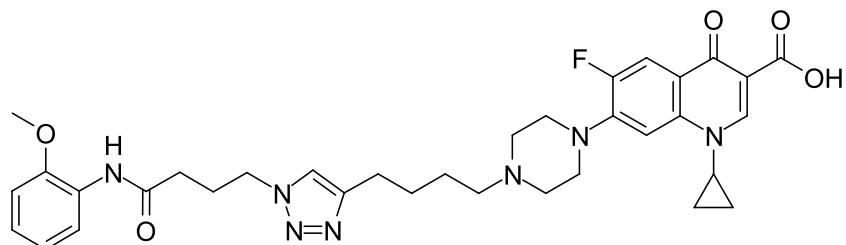
¹³C NMR (101 MHz, CDCl₃) δ / ppm = 173.1 (C(=O)CC(=O)OCH₃), 170.9 (NHC(=O)), 166.3 (C(=O)OCH₃), 160.1 (*ipso* to OCH₃), 153.3 (d, *J*=250.1 Hz, *ipso* to F), 148.4 (C=CC(=O)OCH₃), 144.1 (d, *J*=10.1 Hz, *ipso* to piperazine), 139.4 (*ipso* to NH), 138.0 (*para* to F), 129.6 (*meta* to NH and *meta* to OCH₃), 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 OCH₃), 110.0 (CC(=O)OCH₃), 109.8 (*para* to NH), 105.5 (*ortho* to OCH₃ and *ortho* to NH), 105.0 (*meta* to C=O and *meta* to F), 57.0 (CH₂CH₂N), 55.3 (aromatic OCH₃), 52.6 (CH₂CH₂CH₂N(CH₂CH₂)), 52.1 (C(=O)OCH₃), 49.2 (CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 35.2 (CH₂CH₂CH₂N), 34.6 (NCH(CH₂)₂), 21.7 (CH₂CH₂CH₂N), 8.2 (NCH(CH₂)₂)

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

HRMS (ESI⁺) *m/z* / Da = 537.2500, [M+H]⁺ found, [C₂₉H₃₄FN₄O₅]⁺ 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 μ mol, 1 eq.) and 4-azido-*N*-(2-methoxyphenyl)butanamide **115** (13.7 mg, 58.5 μ mol, 1 eq.) were dissolved in water (3 ml), *t*-BuOH (9 ml) and CH₂Cl₂ (9 ml), and the mixture was degassed by bubbling through N₂. A solution of CuSO₄ and THPTA (117 μ l, 5.85 μ mol, 0.1 eq., 50 mM, aq.) was added, followed by a solution of sodium ascorbate (234 μ l, 11.7 μ mol, 0.2 eq., 50 mM, aq.). The mixture was stirred at room temperature under argon for 16 h. Water (25 ml), CH₂Cl₂ (25 ml) and MeOH (5 ml) were added and the organic layer was separated off, dry-loaded onto SiO₂ and purified by column chromatography using a CombiFlash (SiO₂, 3-23 % MeOH/CH₂Cl₂). The combined pure fractions were dried with MgSO₄ and evaporated under reduced pressure. **119** was obtained as a clear glass (14.7 mg, 22.8 μ mol, 39.0 %).

TLC *R_f* = 0.28 (10 % MeOH/CH₂Cl₂)

IR (neat) ν_{max} / cm⁻¹ = 2926.5 (C-H), 2846.6 (C-H), 1723.4 (carboxylic acid C=O), 1682.0 (amide C=O), 1625.8 (quinolone C=O), 1612.8 (triazole)

¹H NMR (400 MHz, CDCl₃) δ / ppm = 15.05 (br s, 1 H, C(=O)OH), 8.76 (s, 1 H, *ortho* to C(=O)OH), 8.31 (dd, *J* = 8.0, 1.7 Hz, 1 H, *ortho* to NH), 8.00 (d, *J* = 13.0 Hz, 1 H, *ortho* to F), 7.83 (br s, 1 H, NH), 7.37 (s, 1 H, CH=CCH₂), 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 OCH₃), 6.88 (dd, *J* = 8.1, 1.4 Hz, 1 H, *ortho* to OCH₃), 4.47 (t, *J* = 6.7 Hz, 2 H, C(=O)CH₂CH₂CH₂N), 3.88 (s, 3 H, CH₃), 3.54 (tt, *J* = 6.9, 4.0 Hz, 1 H, NCH(CH₂)₂), 3.35 (br t, *J* = 4.7 Hz, 4 H, CH=CCH₂CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 2.76 (t, *J* = 7.5 Hz, 2 H, CH=CCH₂), 2.66 (t, *J* = 4.7 Hz, 4 H, CH=CCH₂CH₂CH₂CH₂N(CH₂)CH₂), 2.47 (t, *J* = 7.3 Hz, 2 H, CH=CCH₂CH₂CH₂CH₂N), 2.44 (t, *J* = 6.8 Hz, 2 H, C(=O)CH₂CH₂CH₂N), 2.32 (quin, *J* = 6.7 Hz, 2 H, C(=O)CH₂CH₂CH₂N), 1.75 (quin, *J* = 7.6 Hz, 2 H, CH=CCH₂CH₂CH₂CH₂N), 1.61 (quin, *J* = 7.5 Hz, 2 H, CH=CCH₂CH₂CH₂CH₂N), 1.35 - 1.42 (m, 2 H, NCH(CHH)₂), 1.17 - 1.22 (m, 2 H, NCH(CHH)₂)

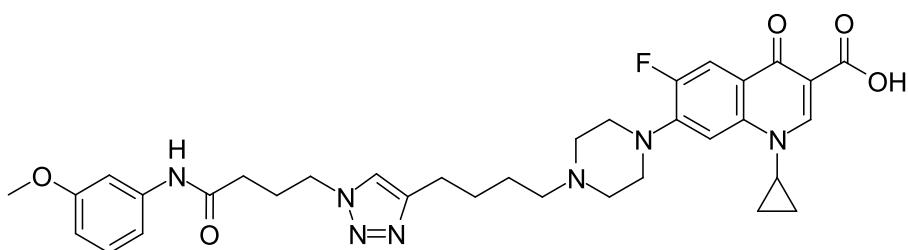
¹³C NMR (101 MHz, CDCl₃) δ / ppm = 177.1 (C(=O)CC(=O)OH), 169.5 (NH₂C(=O)), 167.0 (C(=O)OH), 153.7 (d, *J* = 251.4 Hz, *ipso* to F), 148.1 (CH=CCH₂), 147.8 (*ipso* to OCH₃), 147.3 (C=CC(=O)OH), 145.9 (d, *J* = 10.4 Hz, *ipso* to piperazine), 139.1 (*para* to F), 127.3 (*ipso* to NH), 123.9 (*para* to NH), 121.0 (*para* to OCH₃), 120.9 (CH=CCH₂), 119.7 (*para* to piperazine, and *ortho* to NH and *meta* to OCH₃), 112.4 (d, *J* = 23.4 Hz, *ortho* to C=O and *ortho* to F), 109.9 (*ortho* to OCH₃ and *meta* to NH), 108.1 (CC(=O)OH), 104.7 (*meta* to C=O and *meta* to F), 58.1 (CH=CCH₂CH₂CH₂CH₂N), 55.6 (CH₃), 52.8 (CH=CCH₂CH₂CH₂CH₂N(CH₂CH₂)), 49.8 (CH=CCH₂CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 49.8 (CH=CCH₂CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 49.1 (C(=O)CH₂CH₂CH₂N), 35.2 (NCH(CH₂)₂), 33.8 (C(=O)CH₂CH₂CH₂N), 27.3 (CH=CCH₂CH₂CH₂CH₂N), 26.4 (CH=CCH₂CH₂CH₂CH₂N), 26.0 (C(=O)CH₂CH₂CH₂N), 25.5 (CH=CCH₂CH₂CH₂CH₂N), 8.2 (NCH(CH₂)₂)

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

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

The compound has not been reported previously.

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 μ mol, 1 eq.) and 4-azido-*N*-(3-methoxyphenyl)butanamide **116** (13.7 mg, 58.5 μ mol, 1 eq.) were dissolved in water (1 ml), *t*-BuOH (9 ml) and CH₂Cl₂ (10 ml), and the mixture was degassed by bubbling through N₂. A solution of CuSO₄ and THPTA (58.5 μ l, 5.85 μ mol, 0.1 eq. 100 mM, aq.) was added, followed by a solution of sodium ascorbate (117 μ l, 11.7 μ mol, 0.2 eq., 100 mM, aq.). The mixture was stirred at room temperature under argon for 2 h, then the solvent was removed under reduced pressure. The residue was partitioned between water (15 ml) and CH₂Cl₂ (15 ml), and the aqueous layer was extracted a further four times with CH₂Cl₂ (4 \times 15 ml). The combined organic layers were dried with MgSO₄, dry-loaded onto SiO₂ and purified by column chromatography (SiO₂, 0-10 % MeOH/CH₂Cl₂). The combined pure fractions were dried with MgSO₄ and evaporated under reduced pressure. **120** was obtained as a clear glass (1.9 mg, 2.9 μ mol, 5.0 %).

TLC $R_f = 0.22$ (10 % MeOH/CH₂Cl₂)

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

¹H NMR (400 MHz, DMSO d₆) δ / ppm = 15.23 (br s, 1 H, C(=O)OH), 9.89 (s, 1 H, NH), 8.66 (s, 1 H, *ortho* to C(=O)OH), 7.90 (d, J = 13.4 Hz, 1 H, *ortho* to F), 7.88 (s, 1 H, CH=CCH₂), 7.55 (d, J = 7.6 Hz, 1 H, *meta* to F), 7.27 (t, J = 2.1 Hz, 1 H, *ortho* to C=O and *ortho* to F), 7.16 (t, J = 8.1 Hz, 1 H, *meta* to OCH₃ and *meta* to NH), 7.08 (d, J = 7.8 Hz, 1 H, *para* to OCH₃), 6.59 (ddd, J = 8.1, 2.4, 0.7 Hz, 1 H, *para* to NH), 4.36 (t, J = 6.9 Hz, 2 H, C(=O)CH₂CH₂CH₂N), 3.81 (tt, J = 6.7, 4.0 Hz, 1 H, NCH(CH₂)₂), 3.70 (s, 3 H, CH₃), 3.28 - 3.32 (m, 4 H, CH=CCH₂CH₂CH₂N(CH₂CH₂)CH₂), 2.64 (t, J = 7.5 Hz, 2 H, CH=CCH₂), 2.56 (m, J = 4.2, 4.2 Hz, 4 H, CH=CCH₂CH₂CH₂N(CH₂CH₂)), 2.38 (t, J = 7.3 Hz, 2 H, CH=CCH₂CH₂CH₂N), 2.30 (t, J = 7.4 Hz, 2 H, C(=O)CH₂CH₂CH₂N), 2.10 (quin, J = 7.1 Hz, 2 H, C(=O)CH₂CH₂CH₂N), 1.64 (quin, J = 7.5 Hz, 2 H, CH=CCH₂CH₂CH₂N), 1.51 (quin, J = 7.2 Hz, 2 H, CH=CCH₂CH₂CH₂N), 1.27 - 1.33 (m, 2 H, NCH(CH₂)₂), 1.15 - 1.20 (m, 2 H, NCH(CH₂)₂)

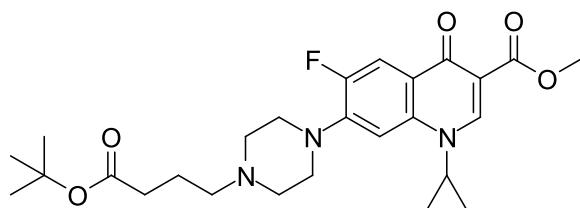
¹³C NMR (101 MHz, DMSO d₆) δ / ppm = 176.3 (C(=O)CC(=O)OH), 170.1 (NHC(=O)), 165.9 (C(=O)OH), 159.4 (*ipso* to OCH₃), 153.0 (d, J = 248.6 Hz, *ipso* to F), 148.0 (CH=CCH₂), 146.9 (C=CC(=O)OH), 145.2 (d, J = 10.7 Hz, *ipso* to piperazine), 140.3 (*para* to F), 139.2 (*ipso* to NH), 129.4 (*meta* to OCH₃ and *meta* to NH), 121.7 (CH=CCH₂), 118.5 (d, J = 7.5 Hz, *para* to piperazine), 111.3 (*para* to OCH₃), 110.9 (d, J = 22.4 Hz, *ortho* to C=O and *ortho* to F), 108.4 (*para* to NH), 106.7 (CC(=O)OH), 106.3 (*meta* to C=O and *meta* to F), 104.8 (*ortho* to OCH₃ and *ortho* to NH), 57.3 (CH=CCH₂CH₂CH₂N), 54.9 (CH₃), 52.4 (CH=CCH₂CH₂CH₂N(CH₂CH₂)), 49.5 (CH=CCH₂CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 49.4 (CH=CCH₂CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 48.7 (C(=O)CH₂CH₂CH₂N), 35.8 (NCH(CH₂)₂), 32.9 (C(=O)CH₂CH₂CH₂N), 26.8 (CH=CCH₂CH₂CH₂CH₂N), 25.7 (CH=CCH₂CH₂CH₂CH₂N), 25.5 (C(=O)CH₂CH₂CH₂N), 24.9 (CH=CCH₂CH₂CH₂CH₂N), 7.6 (NCH(CH₂)₂)

¹⁹F NMR (376.45 MHz, DMSO d₆) δ / ppm = -121.5 (s, ciprofloxacin F)

HRMS (ESI⁺) m/z / Da = 646.3159, [M+H]⁺ found, [C₃₄H₄₁FN₇O₅]⁺ 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 μ l, 130 mg, 0.581 mmol, 1 eq.), NaI (86.9 mg, 0.580 mmol, 1 eq.), TEA (316 μ 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 μ 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 SiO_2 and purified by column chromatography (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) ν_{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, CDCl_3) δ / ppm = 8.39 (s, 1 H, *ortho* to C(=O)OCH₃), 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, CH₃), 3.40 (tt, $J = 7.2, 3.6$ Hz, 1 H, NCH(CH₂)₂), 3.22 (t, $J = 4.3$ Hz, 4 H, CH₂N(CH₂CH₂)CH₂CH₂), 2.63 (t, $J = 4.4$ Hz, 4 H, CH₂N(CH₂)CH₂), 2.41 (t, $J = 7.3$ Hz, 2 H, CH₂N(CH₂)CH₂), 2.25 (t, $J = 7.4$ Hz, 2 H, CH₂CH₂CH₂N(CH₂)CH₂), 1.78 (quin, $J = 7.3$ Hz, 2 H, CH₂CH₂N(CH₂)CH₂), 1.41 (s, 9 H, C((CH₂)₃)₃), 1.24 (m, 2 H, NCH(CHH)₂), 1.09 (m, 2 H, NCH(CHH)₂)

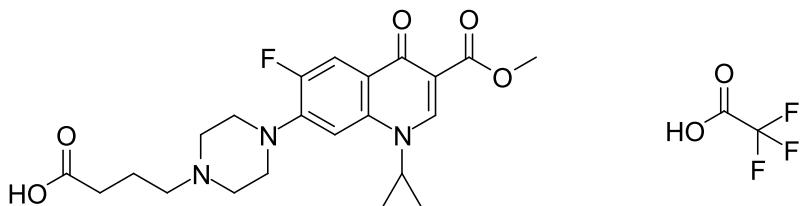
$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ / ppm = 172.7 (C(=O)CC(=O)OCH₃), 172.6 (C(=O)OC(CH₃)₃), 165.9 (C(=O)OCH₃), 153.1 (d, $J = 249.7$ Hz, *ipso* to F), 148.1 (C=CC(=O)OCH₃), 144.3 (d, $J = 10.4$ Hz, *ipso* to piperazine), 137.7 (*para* to F), 122.5 (d, $J = 6.9$ Hz, *para* to piperazine) 112.6 (d, $J = 22.5$ Hz, *ortho* to C=O and *ortho* to F), 109.5 (CC(=O)OCH₃) 104.7 (*meta* to C=O and *meta* to F), 80.0 (C(CH₃)₃), 57.4 (C(=O)CH₂CH₂CH₂N), 52.7 (C(=O)CH₂CH₂CH₂N(CH₂)CH₂), 51.7 (CH₃), 49.7 (C(=O)CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 49.7 (C(=O)CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 34.4 (NCH(CH₂)₂), 33.2 (C(=O)CH₂), 28.0 (C(CH₃)₃), 22.0 (C(=O)CH₂CH₂), 7.9 (NCH(CH₂)₂)

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

HRMS (ESI⁺) m/z / Da = 488.2562, [M+H]⁺ found, [C₂₆H₃₅FN₃O₅]⁺ requires 488.2561

The compound has not been reported previously.

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 μmol) and TFA (0.2 ml) were stirred in CH_2Cl_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 μmol , 95.6 %).

mp T / °C = 225-231 (CH_2Cl_2 , decomposes)

IR (neat) ν_{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)

¹H NMR (400 MHz, DMSO d₆) δ / ppm = 8.47 (s, 1 H, *ortho* to C(=O)OH), 7.80 (d, J = 13.2 Hz, 1 H, *ortho* to F), 7.47 (d, J = 7.4 Hz, 1 H, *meta* to F), 3.73 (s, 3 H, CH₃), 3.66 (tt, J = 7.2, 3.7 Hz, 1 H, NCH(CH₂)₂), 3.30 - 3.54 (br s, 8 H, CH₂N(CH₂)CH₂ and CH₂N(CH₂CH₂)CH₂CH₂) 3.13 - 3.22 (m, 2 H, CH₂N(CH₂)CH₂), 2.36 (t, J = 7.1 Hz, 2 H, CH₂CH₂CH₂N(CH₂)CH₂), 1.87 - 1.98 (m, 2 H, CH₂CH₂N(CH₂)CH₂), 1.22 - 1.30 (m, 2 H, NCH(CHH)₂), 1.06 - 1.15 (m, 2 H, NCH(CHH)₂)

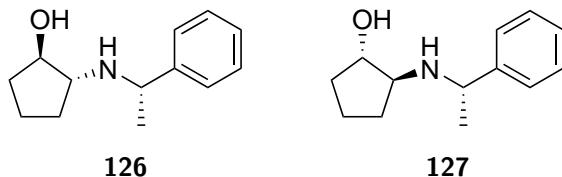
¹³C NMR (101 MHz, DMSO d₆) δ / ppm = 173.5 (CH₂C(=O)OH), 171.6 (C(=O)CC(=O)OCH₃), 164.9 (C(=O)OCH₃), 158.2 (q, J = 31.5 Hz, CF₃C(=O)OH), 152.5 (d, J = 247.6 Hz, *ipso* to F), 148.5 (C=CC(=O)OH), 142.3 (d, J = 10.7 Hz, *ipso* to piperazine), 138.0 (*para* to F), 122.6 (d, J = 6.4 Hz, *para* to piperazine),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

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

HRMS (ESI⁺) *m/z* / Da = 432.1921, [M+H]⁺ found, [C₂₂H₂₇FN₃O₅]⁺ requires 432.1935

The compound has not been reported previously.

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 CH₂Cl₂ (50 ml) and stirred rapidly at 0 °C. A solution of AlMe₃ (31 ml, 2.0 M in heptane, 60.9 mmol) was added dropwise and the mixture was stirred at 0 °C for 1 h. A solution of cyclohexene oxide **125** (5.71 ml, 5.50 g, 65.4 mmol, 1.1 eq.) in CH₂Cl₂ (50 ml) was then added dropwise, and the mixture was stirred at 0 °C for a further 3 h, followed by 48 h at r.t.. The mixture was cooled to 0 °C and NaF (11 g, 262 mmol, 4.3 eq.) was added portionwise, followed by water (7.00 ml, 7.00 g, 389 mmol, 6.4 eq.) and CH₂Cl₂ (50 ml). The suspension was allowed to warm to r.t. and stirred for 1 h, then filtered through Celite and washed with CH₂Cl₂ (500 ml). The filtrate was dried with K₂CO₃, concentrated under reduced pressure and purified by column chromatography (SiO₂, 20:5:1 hexane:EtOAc:TEA). **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) ν_{max} / cm⁻¹ = 3300.0 (br, O-H), 2959.7 (C-H), 2870.1 (C-H)

¹H NMR (400 MHz, CDCl₃) δ / ppm = 7.28 - 7.38 (m, 4 H, *ortho* and *meta* to CHCH₃), 7.21 - 7.28 (m, 1 H,

para to CHCH₃), 3.83 (q, *J* = 6.6 Hz, 1 H, CHCH₃), 3.78 (q, *J* = 7.0 Hz, 1 H, CHOH), 2.62 (dt, *J* = 8.2, 7.2 Hz, 1 H, CHNH), 1.97 (quin, *J* = 6.7 Hz, 1 H, CH₂CHNH), 1.90 (quin, *J* = 6.9 Hz, 1 H, CH₂CHOH), 1.56 - 1.68 (m, CH₂CH₂CHOH), 1.43 (dq, *J* = 12.5, 8.0 Hz, 1 H, CH₂CHOH), 1.37 (d, *J* = 6.6 Hz, 3 H, CH₃), 1.25 - 1.36 (m, 1 H, CH₂CHNH)

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

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

$[\alpha]_D^{20}$ / °10⁻¹cm²g⁻¹ = -92.8 (c / g(100 ml)⁻¹ = 1.19, MeOH)

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

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

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

IR (neat) ν_{max} / cm⁻¹ = 3150.0 (br, O-H), 2950.9 (C-H), 2868.2 (C-H)

¹H NMR (400 MHz, CDCl₃) δ / ppm = 7.28 - 7.34 (m, 4 H, *ortho* and *meta* to CHCH₃), 7.20 - 7.26 (m, 1 H, *para* to CHCH₃), 3.86 (q, *J* = 6.6 Hz, 1 H, CHCH₃), 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, CH₂CHOH), 1.77 (dtd, *J* = 12.9, 7.9, 7.9, 4.9 Hz, 1 H, CH₂CHNH), 1.55 - 1.68 (m, 2 H, CH₂CH₂CHOH), 1.47 - 1.55 (m, 1 H, CH₂CHOH), 1.36 (d, *J* = 6.6 Hz, 3 H, CH₃), 1.12 (dq, *J* = 12.7, 8.1 Hz, 1 H, CH₂CHNH)

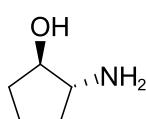
¹³C NMR (101 MHz, CDCl₃) δ / ppm = 145.61 (*ipso* to CHCH₃), 128.08 (*meta* to CHCH₃), 126.61 (*para* to CHCH₃), 126.33 (*ortho* to CHCH₃), 77.43 (CHOH), 64.45 (CHNH), 56.62 (CHCH₃), 32.01 (CH₂CHOH), 30.56 (CH₂CHNH), 23.30 (CH₃), 20.06 (CH₂CH₂CHOH)

HRMS (ESI⁺) *m/z* / Da = 206.1553, [M+H]⁺ found, [C₁₃H₂₀NO]⁺ requires 206.1545

$[\alpha]_D^{20}$ / °10⁻¹cm²g⁻¹ = -23.9 (c / g(100 ml)⁻¹ = 0.96, MeOH)

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

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)₂ (20 wt. % on C, moistened with 50 wt. % water, 1 g, 0.712 mmol, 0.04 eq.) and MeOH (50 ml) were stirred in a Paar hydrogenator at r.t. and 3 atm for 2 days. The mixture was then filtered through Celite and evaporated under reduced pressure. **128** was obtained as a yellow oil (1.92 g, 19.0 mmol, 100 %).

TLC R_f = 0.10 (10 % MeOH/CH₂Cl₂)

IR (neat) ν_{max} / cm⁻¹ = 3300.0 (br, O-H), 2958.3 (C-H), 2871.5 (C-H)

¹H NMR (400 MHz, MeOD) δ / ppm = 3.77 (ddd, *J*=6.6, 6.2, 5.6, 1 H, CHOH), 3.00 (td, *J*=7.3, 5.6 Hz, 1 H, CHNH₂), 2.00 (dtd, *J*=13.0, 7.7, 7.7, 5.6 Hz, 1 H, CHHCHNH₂), 1.97 (ddt, *J*=13.0, 8.7, 6.6, 6.6 Hz, 1 H, CHHCHOH), 1.63 - 1.77 (m, 2 H, CH₂CH₂CHOH), 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, CHHCHNH₂)

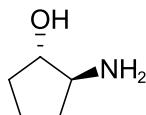
¹³C NMR (101 MHz, MeOD) δ / ppm = 80.7 (CHOH), 60.8 (CHNH₂), 33.2 (CH₂CHOH), 32.1 (CH₂CHNH₂), 21.2 (CH₂CH₂CHOH)

HRMS (ESI⁺) *m/z* / Da = 102.0917, [M+H]⁺ found, [C₅H₁₂NO]⁺ requires 102.0913

$[\alpha]_D^{20}$ / °10⁻¹cm²g⁻¹ = -30.9 (*c* / g(100 ml)⁻¹ = 1.5, EtOH)

The data are consistent with the literature.^{15,17}

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)₂ (20 wt. % on C, moistened with 50 wt. % water, 0.5 g, 0.356 mmol, 0.025 eq.) and MeOH (50 ml) were stirred in a Paar hydrogenator at r.t. and 2.5 atm for 2 days. The mixture was then filtered through Celite and evaporated under reduced pressure. **129** was obtained as a yellow oil (1.48 g, 14.6 mmol, 100 %).

TLC R_f = 0.10 (10 % MeOH/CH₂Cl₂)

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

¹H NMR (400 MHz, MeOD) δ / ppm = 3.77 (ddd, *J*=6.6, 6.2, 5.6, 1 H, CHOH), 3.00 (td, *J* = 7.4, 5.6 Hz, 1 H, CHNH₂), 2.00 (dtd, *J* = 13.0, 7.7, 7.7, 5.6 Hz, 1 H, CHHCHNH₂), 1.97 (ddt, *J* = 13.0, 8.7, 6.4, 6.4 Hz, 1 H, CHHCHOH), 1.64 - 1.77 (m, 2 H, CH₂CH₂CHOH), 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, CHHCHNH₂)

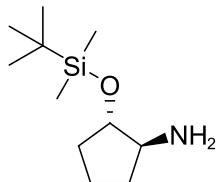
¹³C NMR (101 MHz, MeOD) δ / ppm = 80.6 (CHOH), 60.7 (CHNH₂), 33.2 (CH₂CHOH), 32.2 (CH₂CHNH₂), 21.2 (CH₂CH₂CHOH)

HRMS (ESI⁺) m/z / Da = 102.0915, [M+H]⁺ found, [C₅H₁₂NO]⁺ 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.^{15,17}

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 CH₂Cl₂ (20 ml) under N₂ at 0 °C. TEA (3.14 ml, 2.28 g, 22.5 mmol, 5 eq.) was added dropwise, followed by 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 NH₄Cl, diluted with CH₂Cl₂ (20 ml) and washed with water (20 ml). The organic phase was dried with Na₂SO₄, concentrated under reduced pressure and purified by column chromatography (SiO₂, 4 % MeOH/CH₂Cl₂). **130** was obtained as a yellow oil (1.00 g, 4.64 mmol, 97.7 %).

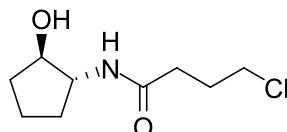
TLC $R_f = 0.23$ (10 % MeOH/CH₂Cl₂)

¹H NMR (400 MHz, CDCl₃) δ / ppm = 4.13 (q, $J = 5.8$ Hz, 1 H, CHOSi), 3.31 (t, $J = 7.1, 5.2$ Hz, 1 H, CHNH₂), 2.09 - 2.19 (m, 1 H, CHHCHNH₂), 1.97 (ddq, $J = 8.8, 7.0, 6.0, 6.0$ Hz, 1 H, CHHCH₂), 1.74 - 1.86 (m, 2 H, CH₂CH₂CHOSi), 1.64 - 1.74 (m, 1 H, CHHCHOSi), 1.58 (ddt, $J = 13.2, 9.1, 6.0, 6.0$ Hz, 1 H, CHHCHNH₂), 0.88 (s, 9 H, C(CH₃)₃), 0.09 (s, 3 H, SiCH₃), 0.07 (s, 3 H, SiCH₃)

¹³C NMR (101 MHz, CDCl₃) δ / ppm = 76.3 (CHOSi), 59.7 (CHNH), 32.2 (CH₂CHOSi), 26.8 (CH₂CHNH₂), 25.6 (C(CH₃)₃), 19.7 (CH₂CH₂CHOSi), 17.7 (C(CH₃)₃), -4.8 (SiCH₃), -5.2 (SiCH₃)

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 μ l, 600 mg, 5.93 mmol, 1.2 eq.) and CH₂Cl₂ (20 ml) were stirred at 0 °C and 4-chlorobutyryl chloride **131** (608 μ 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 CH₂Cl₂ (7×50 ml). The combined organic layers were dried with MgSO₄, concentrated under reduced pressure and purified by column chromatography (SiO₂, Et₂O). The combined pure fractions were dried with MgSO₄ 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)

¹H NMR (400 MHz, CDCl₃) $\delta / \text{ppm} = 6.12$ (br s, 1 H, NH), 4.42 (br s, 1 H, OH), 3.94 (q, $J = 6.6$ Hz, 1 H, CH_{OH}), 3.82 (tt, $J = 8.4, 5.3$ Hz, 1 H, CHNH), 3.60 (t, $J = 6.2$ Hz, 2 H, CH₂Cl), 2.38 (t, $J = 7.2$ Hz, 2 H, CH₂C=O), 2.05 - 2.16 (m, 3 H, CHHCHNH and CH₂CH₂Cl), 1.96 - 2.04 (m, 1 H, CHHCHOH), 1.74 - 1.85 (m, 1 H, CHHCH₂CHOH), 1.58 - 1.73 (m, 2 H, CHHCH₂CHOH and CHHCHOH), 1.43 (dq, $J = 12.7, 8.3$ Hz, 1 H, CHHCHNH)

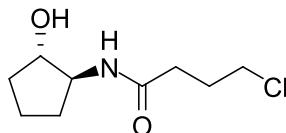
¹³C NMR (101 MHz, CDCl₃) $\delta / \text{ppm} = 173.8$ (C=O), 79.4 (CHOH), 60.6 (CHNH), 44.4 (CH₂Cl), 32.8 (CH₂C=O), 32.4 (CH₂CHOH), 30.1 (CH₂CHNH), 28.0 (CH₂CH₂Cl), 21.1 (CH₂CH₂CHOH)

HRMS (ESI⁺) $m/z / \text{Da} = 228.0787$, [M+Na]⁺ found, [C₉H₁₆ClNNaO₂]⁺ requires 228.0762

$[\alpha]_D^{20} / {}^\circ 10^{-1} \text{cm}^2 \text{g}^{-1} = -13.0$ ($c / \text{g} (100 \text{ ml})^{-1} = 0.5$, 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 μmol , 1 eq.), TEA (500 μl , 363 mg, 3.58 mmol, 5 eq.) and CH₂Cl₂ (5 ml) were stirred at 0 °C, and 4-chlorobutyryl chloride **131** (179 μl , 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/CHCl₃ (2×10 ml). The combined organic layers were dried with MgSO₄, concentrated under reduced pressure and purified by column chromatography (SiO₂, Et₂O). The combined pure fractions were dried with MgSO₄ and evaporated under reduced pressure. **133** was obtained as a white amorphous solid (35.6 mg, 173 μmol , 24.2 %).

TLC $R_f = 0.35$ (EtOAc)

¹H NMR (400 MHz, CDCl₃) $\delta / \text{ppm} = 6.05$ (br s, 1 H, NH), 4.55 (br s, 1 H, OH), 3.95 (q, $J=6.6$ Hz, 1 H, CH_{OH}), 3.82 (tt, $J=8.4, 5.3$ Hz, 1 H, CHNH), 3.60 (t, $J=6.2$ Hz, 2 H, CH₂Cl), 2.38 (t, $J=7.0$ Hz, 2 H, CH₂C=O), 2.05 - 2.17 (m, 3 H, CHHCHNH and CH₂CH₂Cl), 1.94 - 2.05 (m, 1 H, CHHCHOH), 1.74 - 1.86 (m, 1 H, CHHCH₂CHOH), 1.58 - 1.74 (m, 2 H, CHHCH₂CHOH and CHHCHOH), 1.42 (dq, $J=12.5, 8.4$ Hz, 1 H, CHHCHNH)

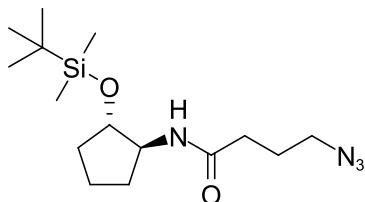
¹³C NMR (101 MHz, CDCl₃) $\delta / \text{ppm} = 173.8$ (C=O), 79.4 (CHOH), 60.6 (CHNH), 44.4 (CH₂Cl), 32.8 (CH₂C=O), 32.4 (CH₂CHOH), 30.2 (CH₂CHNH), 28.0 (CH₂CH₂Cl), 21.2 (CH₂CH₂CHOH)

HRMS (ESI⁺) m/z / Da = 206.0939, [M+H]⁺ found, [C₉H₁₇ClNO₂]⁺ 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 NaHCO₃ (22.0 mg, 0.262 mmol, 1.1 eq.) were added to CH₂Cl₂ (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 NaN₃ (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 N₂ stream and the residue was purified by column chromatography (SiO₂, 0.5 % MeOH/CH₂Cl₂). The combined pure fractions were dried with MgSO₄ and evaporated under reduced pressure. **134** was obtained as a clear liquid (71 mg, 0.217 mmol, 99.2 %).

TLC $R_f = 0.84$ (1 % MeOH/CH₂Cl₂)

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)

¹H NMR (400 MHz, CDCl₃) $\delta / \text{ppm} = 5.35$ (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, CH₂N₃), 2.24 (t, $J = 7.0$ Hz, 2 H, CH₂C=O), 2.09 - 2.19 (m, 1 H, CHHCHNH), 1.89 - 1.97 (quin, $J = 6.8$ Hz, 2 H, CH₂CH₂N₃), 1.74 - 1.84 (m, 2 H, CHHCHOSi and CHHCH₂CHOSi), 1.60 - 1.70 (m, 1 H, CHHCH₂CHOSi), 1.51 - 1.61 (m, 1 H, CHHCHOSi), 1.31 - 1.39 (m, 1 H, CHHCHNH), 0.87 (s, 9 H, C(CH₃)₃), 0.08 (s, 3 H, SiCH₃), 0.06 (s, 3 H, SiCH₃)

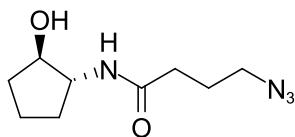
¹³C NMR (101 MHz, CDCl₃) $\delta / \text{ppm} = 171.17$ (C=O), 77.80 (CHOSi), 58.36 (CHNH), 50.77 (CH₂N₃), 33.29 (CH₂C=O), 32.57 (CH₂CHOSi), 29.36 (CH₂CHNH), 25.72 (C(CH₃)₃), 24.77 (CH₂CH₂N₃), 20.40 (CH₂CH₂CHO Si), 17.95 (C(CH₃)₃), -4.75 (SiCH₃)

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

$[\alpha]_D^{20} / {}^\circ 10^{-1} \text{cm}^2 \text{g}^{-1} = 12.4$ ($c / \text{g}(100 \text{ ml})^{-1} = 0.5$, 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 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/CHCl₃ (20 ml). The aqueous layer was extracted again with 10 % *i*-PrOH/CHCl₃ (3×20 ml) and the combined organic fractions were dried with MgSO₄ and evaporated under reduced pressure. **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, CHCl₃)

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

¹H NMR (400 MHz, CDCl₃) δ / ppm = 6.72 (d, J = 4.4 Hz, 1 H, NH), 4.82 (br. s., 1 H, OH), 3.88 (q, J = 6.6 Hz, 1 H, 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, CH₂N₃), 2.23 (t, J = 7.3 Hz, 2 H, CH₂C=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, CH₂CH₂N₃), 1.59 - 1.77 (m, 2 H, CH₂CH₂CHOH), 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)

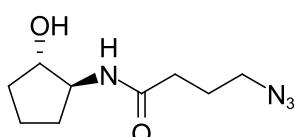
¹³C NMR (101 MHz, CDCl₃) δ / ppm = 173.8 (C=O), 78.8 (CHOH), 59.9 (CHNH), 50.5 (CH₂N₃), 32.5 (CH₂C=O), 32.0 (CH₂CHOH), 29.5 (CH₂CHNH), 24.6 (CH₂CH₂N₃), 20.7 (CH₂CH₂CHOH)

HRMS (ESI⁺) m/z / Da = 235.1174, [M+Na]⁺ found, [C₉H₁₆N₄NaO₂]⁺ requires 235.1171

$[\alpha]_D^{20}$ / °10⁻¹cm²g⁻¹ = -10.2 (c / g(100 ml)⁻¹ = 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 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/CHCl₃ (5 ml). The aqueous layer was extracted again with 10 % *i*-PrOH/CHCl₃ (2×5 ml) and the combined organic fractions were dried with MgSO₄ 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) ν_{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, CDCl_3) δ / ppm = 5.82 (br s, 1 H, NH), 4.45 (br. s., 1 H, OH), 3.96 (q, $J=6.6$ Hz, 1 H, CH_2OH), 3.83 (td, $J=8.5, 8.5, 6.0, 4.6$ Hz, 1 H, CH_2NH), 3.37 (t, $J=6.4$ Hz, 2 H, CH_2N_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, $\text{CH}_2\text{CH}_2\text{NH}$)

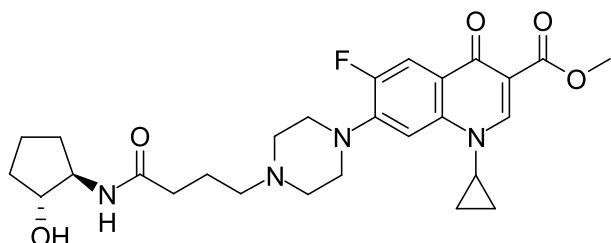
$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ / ppm = 173.8 (C=O), 79.7 (CHOH), 61.0 (CHNH), 50.7 (CH₂N₃), 32.8 (CH₂C=O), 32.6 (CH₂CHOH), 30.5 (CH₂CHNH), 24.7 (CH₂CH₂N₃), 21.3 (CH₂CH₂CHOH)

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

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

The compound has not been reported previously.

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 μl , 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 (5-60 % acetonitrile/water over 12 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 removed and the aqueous layer was extracted twice more with CH_2Cl_2 (2 \times 10 ml). The combined organic fractions were dried with 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) ν_{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)

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

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

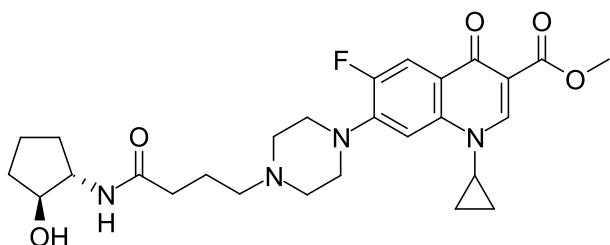
¹⁹F NMR (376.45 MHz, DMSO d₆) δ / ppm = -124.3 (ciprofloxacin F)

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

$[\alpha]_D^{20} / {}^\circ 10^{-1} \text{cm}^2 \text{g}^{-1} = -6.0$ (*c* / g(100 ml)⁻¹ = 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 μ mol, 1 eq.), (1*S*,2*S*)-2-aminocyclopentan-1-ol **129** (19.5 mg, 193 μ mol, 2 eq.), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (29.7 mg, 155 μ mol, 1.6 eq.), 1-hydroxybenzotriazole (25.8 mg, 191 μ mol, 2 eq.) and DIPEA (33.3 μ l, 24.7 mg, 191 μ 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 N₂ 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 NaHCO₃ (aq., sat., 5 ml) and CH₂Cl₂ (5 ml). The organic layer was removed and the aqueous layer was extracted twice more with CH₂Cl₂ (2×5 ml). The combined organic fractions were dried with MgSO₄ and evaporated under reduced pressure. **138** was obtained as a white amorphous solid (4.9 mg, 9.5 μ mol, 9.9 %).

TLC $R_f = 0.38$ (30 % MeOH/CH₂Cl₂)

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

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

¹³C NMR (126 MHz, DMSO d₆) δ / ppm = 171.9 (NHC(=O)CH₂), 171.5 (C(=O)CC(=O)OCH₃), 165.0 (C(=O)OCH₃), 152.6 (d, J=247.4 Hz, *ipso* to F), 148.2 (C=CC(=O)OCH₃), 143.9 (d, J=10.3 Hz, *ipso* to piperazine), 138.1 (*para* to F), 121.7 (d, J=6.4 Hz, *para* to piperazine), 111.5 (d, J=23.0 Hz, *ortho* to C=O and *ortho* to F), 109.0 (CC(=O)OCH₃), 106.2 (*meta* to C=O and *meta* to F), 76.2 (CHOH), 57.6 (CHNH), 57.2 (CH₂CH₂CH₂N), 52.4 (CH₂CH₂CH₂N(CH₂)CH₂), 51.3 (CH₃), 49.6 (CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 49.6 (CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 34.7 (NCH(CH₂)₂), 33.2 (C(=O)CH₂), 32.2 (CH₂CHOH), 29.5 (CH₂CH NH), 22.5 (C(=O)CH₂CH₂), 20.6 (CH₂CH₂CHOH), 7.5 (NCH(CH₂)₂)

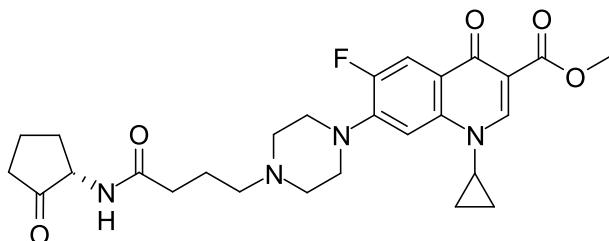
¹⁹F NMR (376.45 MHz, MeOD) δ / ppm = -125.5

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

$[\alpha]_D^{20}$ / °10⁻¹cm²g⁻¹ = 8.0 (c / g(100 ml)⁻¹ = 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 μ mol, 1 eq.) and Dess-Martin **Periodane** (32.8 mg, 77.4 μ mol, 2 eq.) were stirred in CH₂Cl₂ (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 NaHCO₃ (aq., sat., 30 ml) and 10 % *i*-PrOH/CHCl₃ (30 ml) were added. The organic layer was removed and dried with MgSO₄, then evaporated under reduced pressure.

139 was obtained as a white amorphous solid (11.3 mg, 22.0 μmol , 56.7 %).

^1H NMR (500 MHz, DMSO d₆) δ / ppm = 8.46 (s, 1 H, *ortho* to C(=O)OCH₃), 7.78 (d, $J=13.5$ Hz, 1 H, *ortho* to F), 7.45 (d, $J=7.4$ Hz, 1 H, *meta* to F), 4.02 (dt, $J=11.1, 8.2$ Hz, 1 H, CHNH), 3.73 (s, 3 H, CH₃), 3.65 (tt, $J=6.9, 3.9$ Hz, 1 H, NCH(CH₂)₂), 3.40 (s, 10 H, CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 2.05 - 2.29 (m, 5 H, NHC(=O)CH₂, CH₂C(=O)CHNH and CHHCHNH), 1.89 - 1.96 (m, 1 H, CHHCH₂CHNH), 1.69 - 1.80 (m, 3 H, CHHCH₂CHNH, CHHCHNH and NHC(=O)CH₂CH₂), 1.24 - 1.29 (m, 2 H, NCH(CHH)₂), 1.07 - 1.12 (m, 2 H, NCH(CHH)₂)

^{13}C NMR (126 MHz, DMSO d₆) δ / ppm = 215.2 (C(=O)CHNH), 171.7 (NHC(=O)CH₂), 171.7 (C(=O)CC(=O)OCH₃), 165.1 (C(=O)OCH₃), 152.6 (d, $J=246.6$ Hz, *ipso* to F), 148.4 (C=CC(=O)OCH₃), 138.1 (*para* to F), 109.1 (CC(=O)OCH₃), 56.3 (CHNH), 51.4 (CH₃) , 25.6 (CH₂C(=O)CHNH), 34.8 (NCH(CH₂)₂), 28.8 (CH₂CHNH), 18.1 (CH₂CH₂CHNH), 7.6 (NCH(CH₂)₂)

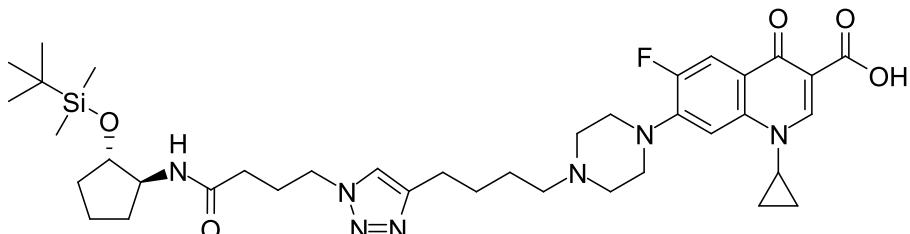
^{19}F NMR (376.45 MHz, MeOD) δ / ppm = -124.3

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

$[\alpha]_D^{20}$ / $^{\circ}10^{-1}\text{cm}^2\text{g}^{-1}$ = 6.7 (c / g(100 ml)⁻¹ = 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 μmol , 1 eq.) and 4-azido-*N*-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclopentyl)butanamide **134** (33.9 mg, 104 μmol , 1 eq.) were dissolved in 10 % water/t-BuOH (3 ml), and the mixture was degassed by bubbling N₂ through it. A solution of CuSO₄ and THPTA (104 μl , 10.4 μmol , 0.1 eq. 100 mM, aq.) was added, followed by a solution of sodium ascorbate (208 μl , 20.8 μmol , 0.2 eq., 100 mM, aq.). The mixture was stirred at room temperature under argon for 16 h, then solvent was removed under reduced pressure. The residue was partitioned between water (10 ml) and CH₂Cl₂ (10 ml), the organic layer was separated and the aqueous layer was extracted again with CH₂Cl₂ (10 ml). The combined organic layers were dried with MgSO₄ and evaporated under reduced pressure. **140** was obtained as a clear glass (67.1 mg, 90.9 μmol , 87.4 %).

IR (neat) ν_{max} / cm⁻¹ = 2951.3 (C-H), 2929.2 (C-H), 2855.5 (C-H), 1741.0 (carboxylic acid C=O), 1640.3 (amide C=O), 1626.6 (quinolone C=O), 1612.3 (triazole)

¹H NMR (400 MHz, CDCl₃) δ / ppm = 8.67 (s, 1 H, *ortho* to C(=O)OH), 7.87 (d, J = 13.1 Hz, 1 H, *ortho* to F), 7.34 (s, 1 H, CH=CCH₂), 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, CH₂NCH=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(CH₂)₂), 3.34 (br t, J = 5.0 Hz, 4 H, CH₂N(CH₂CH₂)CH₂CH₂), 2.71 (t, J = 7.5 Hz, 2 H, CH=CCH₂), 2.66 (br s, 4 H, CH₂N(CH₂)CH₂), 2.46 (t, J = 7.3 Hz, 2 H, CH₂N(CH₂)CH₂), 2.03 - 2.22 (m, 5 H, CHHCHNH, C(=O)CH₂ and C(=O)CH₂CH₂), 1.65 - 1.83 (m, 4 H, CHHCHOSi, CHHCH₂CHOSi and NCH=CCH₂CH₂), 1.47 - 1.65 (m, 4 H, CHHCHOSi, CHHCH₂CHOSi and NCH=CCH₂CH₂CH₂), 1.33 - 1.41 (m, 3 H, CHHCHNH and NCH(CHH)₂), 1.14 - 1.20 (m, 2 H, NCH(CHH)₂), 0.82 (s, 9 H, C(CH₃)₃), 0.03 (s, 3 H, SiCH₃), 0.01 (s, 3 H, SiCH₃)

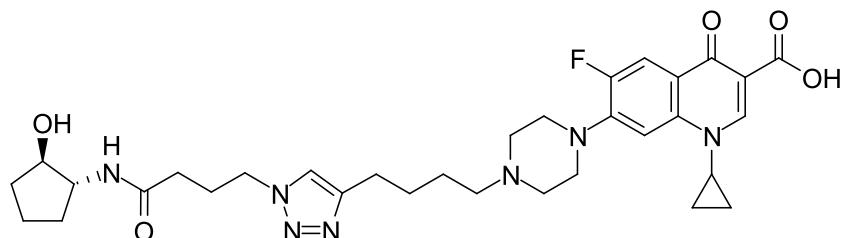
¹³C NMR (101 MHz, CDCl₃) δ / ppm = 176.9 (C(=O)CC(=O)OH), 170.9 (CH₂C(=O)NH), 166.9 (C(=O)OH), 153.5 (d, J = 251.4 Hz, *ipso* to F), 147.9 (CH=CCH₂), 147.2 (C=CC(=O)OH), 145.8 (d, J = 10.4 Hz, *ipso* to piperazine), 139.0 (*para* to F), 120.9 (NCH=CCH₂), 119.4 (d, J = 7.8 Hz, *para* to piperazine), 112.0 (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=CCH₂CH₂CH₂CH₂N), 52.6 (CH=CCH₂CH₂CH₂CH₂N(CH₂)CH₂), 49.5 (d, J = 6.1 Hz, CH=CCH₂CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 48.9 (d, J = 3.5 Hz, CH₂NCH=CCH₂), 35.3 (NCH(CH₂)₂), 32.6 (C(=O)CH₂), 32.6 (CH₂CHOSi), 29.3 (CH₂CHNH), 27.2 (CH=CCH₂CH₂), 26.0 - 26.3 (C(=O)CH₂CH₂ and CH=CCH₂CH₂CH₂), 25.6 (C(CH₃)₃), 25.4 (CH=CCH₂), 20.4 (CH₂CH₂CHOSi), 17.8 (C(CH₃)₃), 8.1 (NCH(CH₂)₂), -4.8 (SiCH₃)

HRMS (ESI⁺) m/z / Da = 738.4164, [M+H]⁺ found, [C₃₈H₅₇FN₇O₅Si]⁺ requires 738.4169

$[\alpha]_D^{20} / {}^\circ 10^{-1} \text{cm}^2 \text{g}^{-1} = 4.5$ (c / g(100 ml)⁻¹ = 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 μ mol, 1 eq.) and 4-azido-*N*-(*1R,2R*)-2-hydroxycyclopentyl)butanamide **135** (22.0 mg, 104 μ mol, 1 eq.) were dissolved in 10 % water/*t*-BuOH (3 ml), and the mixture was degassed by bubbling N₂ through it. A solution of CuSO₄ and THPTA (104 μ l, 10.4 μ mol, 0.1 eq. 100 mM, aq.) was added, followed by a solution of sodium ascorbate (208 μ l, 20.8 μ mol, 0.2 eq., 100 mM, aq.). The mixture was stirred at room temperature under argon for 16 h. Water (30 ml) and CH₂Cl₂ (30 ml) were added, the organic layer was separated and the aqueous layer was extracted again with CH₂Cl₂ (4×30 ml). The combined organic layers were dried with MgSO₄ and evaporated under reduced pressure. The residue was purified by preparatory HPLC (5-95 % acetonitrile/water over 20 min). The combined pure fractions were evaporated under reduced pressure and then

partitioned between NaHCO_3 (aq., sat., 10 ml) and 10 % *i*-PrOH/CHCl₃ (10 ml). The organic layer was dried with MgSO₄ and evaporated under reduced pressure. **141** was obtained as a white amorphous solid (17.6 mg, 28.2 μmol , 27.1 %).

IR (neat) ν_{max} / cm⁻¹ = 2967.0 (C-H), 2902.2 (C-H), 1721.4 (carboxylic acid C=O), 1646.7 (amide C=O), 1627.0 (quinolone C=O), 1613.0 (triazole)

¹H NMR (700 MHz, DMSO d₆) δ / ppm = 8.64 (s, 1 H, *ortho* to C(=O)OH), 7.87 (d, J = 13.3 Hz, 1 H, *ortho* to F), 7.84 (s, 1 H, CH=CCH₂), 7.75 (d, J = 7.1 Hz, 1 H, CHNH), 7.54 (d, J = 7.5 Hz, 1 H, *meta* to F), 4.73 (d, J = 3.8 Hz, 1 H, CHOH), 4.29 (t, J = 6.9 Hz, 2 H, CH₂NCH=C), 3.78 - 3.83 (m, 1 H, NCH(CH₂)₂), 3.75 - 3.78 (m, 1 H, CHOH), 3.71 - 3.75 (m, 1 H, CHNH), 3.31 (br t, J = 4.3 Hz, 4 H, CH₂N(CH₂CH₂)CH₂CH2), 2.63 (t, J = 7.5 Hz, 2 H, CH=CCH₂), 2.56 (br t, J = 4.2 Hz, 4 H, CH₂N(CH₂)CH2), 2.37 (t, J = 7.3 Hz, 2 H, CH₂N(CH₂)CH₂), 2.03 - 2.06 (m, 2 H, C(=O)CH₂), 1.97 - 2.02 (m, 2 H, C(=O)CH₂CH₂), 1.89 (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=CCH₂CH₂), 1.57 - 1.61 (m, 1 H, CH2HCH₂CHOH), 1.54 - 1.57 (m, 1 H, CH2HCH₂CHOH), 1.49 - 1.53 (m, 2 H, CH=CCH₂CH₂CH2), 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)₂), 1.25 - 1.29 (m, 1 H, CH2HCHNH), 1.13 - 1.20 (m, 2 H, NCH(CHH)₂)

¹³C NMR (175 MHz, DMSO d₆) δ / ppm = 176.3 (C(=O)CC(=O)OH), 170.9 (NHC(=O)CH₂), 166.1 (C(=O)OH), 153.0 (d, J = 251.4 Hz, *ipso* to F), 147.9 (C=CC(=O)OH), 146.9 (CH=CCH₂), 145.2 (d, J = 8.7 Hz, *ipso* to piperazine), 139.2 (*para* to F), 121.7 (NCH=CCH₂), 118.7 (d, J = 5.8 Hz, *para* to piperazine), 111.0 (d, J = 23.3 Hz, *ortho* to C=O and *ortho* to F), 106.3 (*meta* to C=O and *meta* to F and CC(=O)OH), 76.2 (CHOH), 57.6 (CHNH), 57.4 (CH=CCH₂CH₂CH₂CH₂N), 52.5 (CH=CCH₂CH₂CH₂CH₂N(CH₂)CH₂), 49.5 (d, J = 4.4 Hz, CH=CCH₂CH₂CH₂N(CH₂CH₂)CH₂CH2), 48.8 (CH₂NCH=CCH₂), 35.8 (NCH(CH₂)₂), 32.2 (CH₂CHOH), 32.0 (C(=O)CH₂), 29.5 (CH₂CHNH), 26.9 (CH=CCH₂CH₂), 26.0 (C(=O)CH₂CH₂), 25.8 (CH=CCH₂CH₂CH2), 25.0 (CH=CCH₂), 20.5 (CH₂CH₂CHOH), 7.6 (NCH(CH₂)₂)

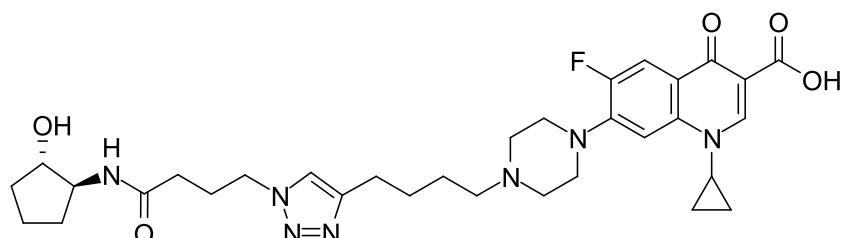
¹⁹F NMR (376.45 MHz, MeOD) δ / ppm = -122.1 (s, ciprofloxacin F)

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

$[\alpha]_D^{20}$ / °10⁻¹cm²g⁻¹ = -3.6 (c / g(100 ml)⁻¹ = 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 μ mol, 4 eq.) and 4-azido-*N*-((1*S*,2*S*)-2-hydroxycyclopentyl)butanamide **136** (11.0 mg, 51.8 μ mol, 1 eq.) were dissolved in 10 % water/*t*-BuOH (3 ml), and the mixture was degassed by bubbling N_2 through it. A solution of CuSO₄ and THPTA (156 μ l, 15.6 μ mol, 0.3 eq. 100 mM, aq.) was added, followed by a solution of sodium ascorbate (312 μ l, 31.2 μ 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/CHCl₃ (10 ml) were added, then the organic layer was separated and dried with MgSO₄ and evaporated under reduced pressure. The residue was purified by preparatory HPLC (5-95 % acetonitrile/water over 20 min). The combined pure fractions were evaporated under reduced pressure and then partitioned between NaHCO₃ (aq., sat., 10 ml) and 10 % *i*-PrOH/CHCl₃ (10 ml). The organic layer was dried with MgSO₄ and evaporated under reduced pressure. **142** was obtained as a white amorphous solid (7.2 mg, 11.5 μ mol, 22.2 %).

IR (neat) ν_{max} / cm⁻¹ = 2954.9 (C-H), 2917.9 (C-H), 2850.2 (C-H), 1722.1 (carboxylic acid C=O), 1647.3 (amide C=O), 1626.7 (quinolone C=O) 1611.9 (triazole)

¹H NMR (400 MHz, DMSO d₆) δ / ppm = 15.22 (br s, 1 H, C(=O)OH), 8.67 (s, 1 H, *ortho* to C(=O)OH), 7.91 (d, J=13.3 Hz, 1 H, *ortho* to F), 7.84 (s, 1 H, CH=CCH₂), 7.74 (d, J=6.7 Hz, 1 H, CHNH), 7.56 (d, J=7.4 Hz, 1 H, *meta* to F), 4.71 (d, J=3.7 Hz, 1 H, CHOH), 4.29 (t, J=6.6 Hz, 2 H, CH₂NCH=C), 3.82 (tt, J=6.5, 4.3 Hz, 1 H, NCH(CH₂)₂), 3.69 - 3.79 (m, 2 H, CHOH and CHNH), 3.30 - 3.34 (m, 6 H, CH=CCH₂CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 2.64 (t, J=7.4 Hz, 2 H, CH=CCH₂), 1.95 - 2.08 (m, 4 H, C(=O)CH₂CH₂), 1.89 (dddd, J=12.8, 8.9, 7.4, 5.8 Hz, 1 H, CHHCHNH), 1.75 (ddt, J=12.7, 9.0, 6.2, 6.2 Hz, 1 H, CHHCHOH), 1.48 - 1.68 (m, 6 H, CH=CCH₂CH₂CH₂ and CH₂CH₂CHOH), 1.40 (ddt, J=13.0, 8.3, 5.3, 5.3 Hz, 1 H, CHHCHOH), 1.28 - 1.35 (m, 2 H, NCH(CHH)₂), 1.24 - 1.31 (m, 1 H, CHHCHNH), 1.15 - 1.21 (m, 2 H, NCH(CHH)₂)

¹³C NMR (101 MHz, DMSO d₆) δ / ppm = 176.4 (C(=O)CC(=O)OH), 170.9 (NHC(=O)CH₂), 166.0 (C(=O)OH), 153.0 (d, J=249.6 Hz, *ipso* to F), 148.1 (C=CC(=O)OH), 146.7 (CH=CCH₂), 145.2 (d, J=8.3 Hz, *ipso* to piperazine), 139.2 (*para* to F), 121.8 (NCH=CCH₂), 118.7 (*para* to piperazine), 111.0 (d, J=23.2 Hz, *ortho* to C=O and *ortho* to F), 106.7 (CC(=O)OH), 106.5 (*meta* to C=O and *meta* to F), 76.2 (CHOH), 57.5 (CHNH), 57.4 (br s, CH=CCH₂CH₂CH₂N), 52.3 (br s, CH=CCH₂CH₂CH₂N(CH₂)CH₂), 49.3 (br s, CH=CCH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 48.8 (CH₂NCH=CCH₂), 35.9 (NCH(CH₂)₂), 32.2 (CH₂CHOH), 32.0 (C(=O)CH₂), 29.4 (CH₂CHNH), 26.7 (CH=CCH₂CH₂), 26.0 (C(=O)CH₂CH₂), 25.5 (CH=CCH₂CH₂CH₂), 24.9 (CH=CCH₂CH₂), 20.5 (CH₂CH₂CHOH), 7.6 (NCH(CH₂)₂)

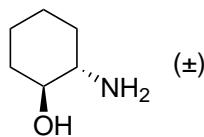
¹⁹F NMR (376.45 MHz, MeOD) δ / ppm = -121.5

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

$[\alpha]_D^{20}$ / °10⁻¹cm²g⁻¹ = -25.0 (*c* / g(100 ml)⁻¹ = 0.08, MeOH) 

The compound has not been reported previously.

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



Cyclohexene oxide **143** (10 ml, 9.70 g, 98.8 mmol, 1 eq.), NH₃ (90 ml, 35 % w/w aq., 27.7 g, 791 mmol, 8 eq.) and MeOH (100 ml) were stirred at r.t. for 72 h. The solvent was removed by blowing a stream of N₂ over it, followed by evaporation under high vacuum. **144** was obtained as white needles (9.90 g, 85.2 mmol, 86.2 %)

TLC R_f = 0.04 (30 % MeOH/CH₂Cl₂)

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

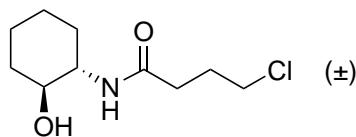
¹H NMR (400 MHz, CDCl₃) δ / ppm = 3.01 (td, J = 9.4, 4.8 Hz, 1 H, CHOH), 2.80 - 2.92 (m, 2 H, OH and NH₂), 2.35 (ddd, J = 11.1, 9.1, 4.1 Hz, 1 H, CHNH₂), 1.77 - 1.84 (m, 1 H, CHHCHOH), 1.69 - 1.76 (m, 1 H, CHHCHNH₂), 1.56 - 1.66 (m, 1 H, CHHCH₂CHOH), 1.45 - 1.56 (m, 1 H, CHHCH₂CHNH₂), 1.07 - 1.19 (m,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

¹³C NMR (101 MHz, CDCl₃) δ / ppm = 75.4 (CHOH), 56.6 (CHN₂), 33.8 (CH₂CHOH and CH₂CHNH₂), 24.7 (CH₂CH₂CHNH₂), 24.6 (CH₂CH₂CHOH)

HRMS (ESI⁺) m/z / Da = 116.1070, [M+H]⁺ found, [C₆H₁₄NO]⁺ requires 116.1070

The data are consistent with the literature.¹⁸

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 CH₂Cl₂ (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/CHCl₃ (2×50 ml). The combined organic layers were dried with MgSO₄, concentrated under reduced pressure and purified by column chromatography (SiO₂, 0-100 % EtOAc/Et₂O). The combined organic fractions were dried with MgSO₄ and evaporated under reduced pressure. **145** was obtained as white needles (1.51 g, 6.87 mmol, 76.1 %).

TLC R_f = 0.19 (Et₂O)

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

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

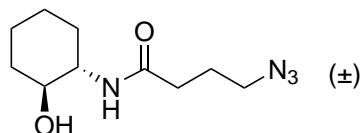
¹H NMR (400 MHz, MeOD) δ / ppm = 3.60 (t, J = 6.6 Hz, 2 H, CH_2Cl), 3.51 - 3.60 (m, 1 H, CH_2NH), 3.28 - 3.39 (m, 1 H, CHOH), 2.37 (td, J = 7.4, 2.3 Hz, 2 H, $\text{C}(=\text{O})\text{CH}_2$), 2.06 (quin, J = 7.0 Hz, 2 H, $\text{C}(=\text{O})\text{CH}_2\text{CH}_2$), 1.97 - 2.01 (m, 1 H, CH_2CHOH), 1.85 - 1.93 (m, 1 H, CH_2CHNH), 1.70 - 1.77 (m, 1 H, $\text{CH}_2\text{CH}_2\text{CHOH}$), 1.64 - 1.70 (m, 1 H, $\text{CH}_2\text{CH}_2\text{CHNH}$), 1.24 - 1.35 (m, 3 H, $\text{CH}_2\text{CH}_2\text{CHOH}$, $\text{CH}_2\text{CH}_2\text{CHNH}$ and $\text{CH}_2\text{CH}_2\text{CHOH}$), 1.13 - 1.25 (m, 1 H, CH_2CHNH_2)

¹³C NMR (101 MHz, MeOD) δ / ppm = 175.0 ($\text{C}(=\text{O})$), 74.1 (CHOH), 56.3 (CHNH), 45.3 (CH_2Cl), 35.6 (CH_2CHOH), 34.5 ($\text{C}(=\text{O})\text{CH}_2$), 32.7 (CH_2CHNH), 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⁺) m/z / Da = 242.0925, [M+Na]⁺ found, [C₁₀H₁₈ClNNaO₂]⁺ 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 NaN₃ (180 mg, 2.77 mmol, 1.75 eq.) were stirred in DMF (12 ml) at 50 °C for 16 h. Water (50 ml) and 10 % *i*-PrOH/CHCl₃ (50 ml) were added, and the organic layer was removed. The aqueous layer was extracted again with 10 % *i*-PrOH/CHCl₃ (50 ml) and the combined organic fractions were dried with MgSO₄. The solvent was evaporated under reduced pressure, and then by using a N₂ stream. **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, CHCl₃)

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

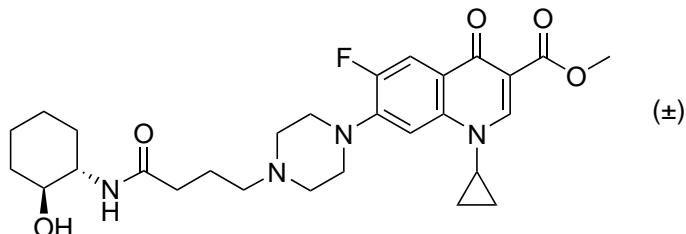
¹H NMR (400 MHz, MeOD) δ / ppm = 7.87 (d, J = 7.9 Hz, 1 H, NH), 5.27 (d, J = 4.3 Hz, 1 H, OH), 3.56 (td, J = 10.5, 4.4 Hz, 1 H, CHNH), 3.28 - 3.41 (m, 3 H, CHOH and CH₂N₃), 2.30 (td, J = 7.4, 2.7 Hz, 2 H, C(=O)CH₂), 1.95 - 2.03 (m, 1 H, CH₂CHOH), 1.87 (m, 3 H, C(=O)CH₂CH₂ and CH₂CHNH), 1.70 - 1.76 (m, 1 H, CH₂CH₂CHOH), 1.63 - 1.70 (m, 1 H, CH₂CH₂CHNH), 1.25 - 1.38 (m, 3 H, CH₂CH₂CHOH, CH₂CH₂CHNH and CH₂CH₂CHOH), 1.14 - 1.24 (m, 1 H, CH₂CHNH₂)

¹³C NMR (101 MHz, MeOD) δ / ppm = 175.1 ($\text{C}(=\text{O})$), 74.0 (CHOH), 56.3 (CHNH), 52.0 (CH_2N_3), 35.5 (CH_2CHOH), 34.3 ($\text{C}(=\text{O})\text{CH}_2$), 32.7 (CH_2CHNH), 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⁺) m/z / Da = 249.1331, [M+Na]⁺ found, [C₁₀H₁₈N₄NaO₂]⁺ 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 μ l, 142 mg, 1.10 mmol, 3 eq.) were dissolved in DMF (5 ml) and stirred at r.t. for 16 h. The solvent was removed using a stream of 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) ν_{max} / cm^{-1} = 3302.5 (N-H), 2929.8 (C-H), 2850.6 (C-H), 2832.9 (C-H), 1698.1 (ester C=O), 1646.4 (amide C=O), 1613.8 (quinolone C=O)

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

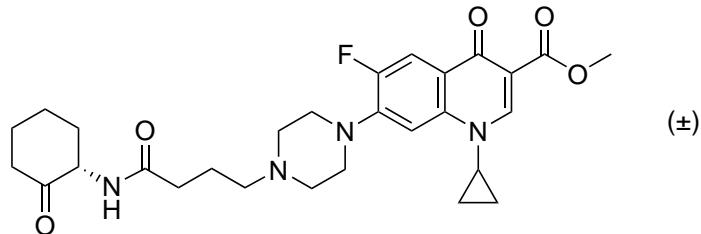
^{13}C NMR (101 MHz, MeOD) δ / ppm = 175.8 (CH₂C(=O)NH), 175.3 (C(=O)CC(=O)OCH₃), 166.8 (C(=O)OCH₃), 154.9 (d, J = 248.8 Hz, *ipso* to F), 150.2 (C=CC(=O)OCH₃), 146.1 (d, J = 10.8 Hz, *ipso* to piperazine), 139.9 (*para* to F), 123.5 (d, J = 7.5 Hz, *para* to piperazine), 113.2 (d, J = 23.2 Hz, *ortho* to C=O and *ortho* to F), 110.2 (C(=O)OCH₃), 107.2 (*meta* to C=O and *meta* to F), 74.1 (CHOH), 58.9 (C(=O)CH₂CH₂CH₂N), 56.4 (CHNH), 54.0 (C(=O)CH₂CH₂CH₂N(CH₂CH₂)), 52.3 (CH₃), 50.5 (d, J = 5.0 Hz, C(=O)CH₂CH₂CH₂N(CH₂CH₂CH₂)), 36.4 (NCH(CH₂)₂), 35.7 (CH₂CHOH), 35.1 (C(=O)CH₂), 32.8 (CH₂CHNH), 25.9 (CH₂CH₂CHNH), 25.5 (CH₂CH₂CHOH), 23.5 (C(=O)CH₂CH₂), 8.7 (NCH(CH₂)₂)

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

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

The compound has not been reported previously.

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 μ mol, 1 eq.) and Dess-Martin periodane (16.4 mg, 38.7 μ mol, 4 eq.) were stirred in CH_2Cl_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 NaHCO_3 (aq., sat., 30 ml) and 10 % *i*-PrOH/ CHCl_3 (30 ml) were added. The organic layer was dried with MgSO_4 and evaporated under reduced pressure. **148** was obtained as a white amorphous solid (3.6 mg, 6.8 μ mol, 69.1 %).

TLC R_f = 0.74 (30 % MeOH/ CH_2Cl_2)

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

$^1\text{H NMR}$ (400 MHz, DMSO d₆) δ / ppm = 8.45 (s, 1 H, *ortho* to C(=O)OCH₃), 7.87 (d, J = 6.2 Hz, 1 H, NH), 7.76 (d, J = 13.4 Hz, 1 H, *ortho* to F), 7.44 (d, J = 7.5 Hz, 1 H, *meta* to F), 4.42 (dddd, J = 13.0, 7.6, 6.0, 1.0 Hz, 1 H, CH₂NH), 3.73 (s, 3 H, CH₃), 3.65 (tt, J = 7.1, 3.9 Hz, 1 H, NCH₂(CH₂)₂), 3.25 (br s, 4 H, CH₂N(CH₂CH₂)CH₂CH₂), 2.58 (br s, 4 H, CH₂N(CH₂)CH₂), 2.45 - 2.53 (1 H, CH₂C(=O)CHNH), 2.36 (br s, 2 H, C(=O)CH₂CH₂CH₂N), 2.26 (dtt, J = 13.4, 2.6, 2.6, 1.6, 1.6 Hz, CH₂, CH₂C(=O)CHNH), 2.16 - 2.22 (m, 2 H, C(=O)CH₂CH₂CH₂N), 2.12 (ddq, J = 12.7, 6.0, 2.8, 2.8, 2.8 Hz, 1 H, CH₂CH₂CH₂N), 2.00 (ddquin, J = 13.2, 6.0, 2.9, 2.9, 2.9 Hz, 1 H, CH₂CH₂C(=O)), 1.65 - 1.83 (m, 4 H, CH₂CH₂CH₂N), 1.41 - 1.56 (m, 2 H, CH₂CH₂CH₂N and CH₂CH₂C(=O)), 1.20 - 1.30 (m, 2 H, NCH(CH₂)₂), 1.05 - 1.13 (m, 2 H, NCH(CH₂)₂)

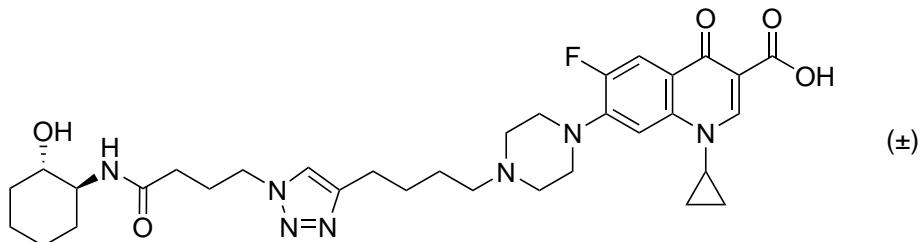
$^{13}\text{C NMR}$ (101 MHz, DMSO d₆) δ / ppm = 207.5 (C(=O)CHNH), 171.7 (C(=O)CC(=O)OCH₃), 171.6 (CH₂C(=O)NH), 165.0 (C(=O)OCH₃), 152.6 (d, J = 247.6 Hz, *ipso* to F), 148.3 (C=CC(=O)OCH₃), 143.9 (br s, *ipso* to piperazine), 138.1 (para to F), 121.8 (d, J = 6.4 Hz, para to piperazine), 111.5 (d, J = 22.4 Hz, *ortho* to C=O and *ortho* to F), 109.0 (CC(=O)OCH₃), 106.3 (meta to C=O and meta to F), 57.0 (CH₂NH and C(=O)CH₂CH₂CH₂N), 52.3 (br s, C(=O)CH₂CH₂CH₂N(CH₂)CH₂), 51.3 (CH₃), 49.5 (br s, C(=O)CH₂CH₂CH₂N(CH₂CH₂)CH₂), 40.6 (CH₂C(=O)CHNH), 34.8 (NCH(CH₂)₂), 33.9 (CH₂CH₂CH₂N), 32.9 (C(=O)CH₂CH₂CH₂N), 27.2 (CH₂CH₂C(=O)CHNH), 23.8 (CH₂CH₂CH₂N), 22.4 (br s, C(=O)CH₂CH₂CH₂N), 7.6 (NCH(CH₂)₂)

$^{19}\text{F NMR}$ (376.45 MHz, DMSO d₆) δ / ppm = -124.3 (ciprofloxacin F)

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

The compound has not been reported previously.

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 μ mol, 1 eq.) and 4-azido-*N*-((*trans*)-2-hydroxycyclohexyl)butanamide **146** (22.0 mg, 97.2 μ mol, 1 eq.) were dissolved in 10 % water/*t*-BuOH (3 ml), and the mixture was degassed by bubbling N_2 through it. A solution of $CuSO_4$ and THPTA (97.2 μ l, 9.72 μ mol, 0.1 eq. 100 mM, aq.) was added, followed by a solution of sodium ascorbate (194 μ l, 19.4 μ mol, 0.2 eq., 100 mM, aq.). The mixture was stirred at r.t. under argon for 16 h. Water (50 ml) and 10 % *i*-PrOH/CHCl₃ (50 ml) were added, then the organic layer was separated, dried with MgSO₄ and evaporated under reduced pressure. The residue was purified by preparatory HPLC (5-70 % acetonitrile/water over 15 min). The combined pure fractions were evaporated under reduced pressure and then partitioned between NaHCO₃ (aq., sat., 50 ml) and 10 % *i*-PrOH/CHCl₃ (50 ml). The organic layer was dried with MgSO₄ and evaporated under reduced pressure. **149** was obtained as a white amorphous solid (30.3 mg, 47.5 μ mol, 48.9 %).

IR (neat) ν_{max} / cm⁻¹ = 3345.4 (N-H), 2927.6 (C-H), 2859.6 (C-H), 2814.7 (C-H), 1727.0 (carboxylic acid C=O), 1641.7 (amide C=O), 1625.8 (quinolone C=O), 1619.0 (triazole)

¹H NMR (400 MHz, DMSO d₆) δ / ppm = 8.64 (s, 1 H, *ortho* to C(=O)OH), 7.86 (d, J = 13.9 Hz, 1 H, *ortho* to F), 7.84 (s, 1 H, CH=CCH₂), 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)CH₂CH₂CH₂N), 3.77 - 3.86 (m, 1 H, NCH(CH₂)₂), 3.33 - 3.40 (m, 1 H, CHNH), 3.31 (br t, J = 4.8, 4.8 Hz, 4 H, CH=CCH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 3.14 - 3.24 (m, 1 H, CHOH), 2.63 (t, J = 7.4 Hz, 2 H, CH=CCH₂), 2.56 (br t, J = 4.6, 4.6 Hz, 4 H, CH=CCH₂CH₂CH₂N(CH₂)CH₂), 2.38 (t, J = 6.9 Hz, 2 H, CH=CCH₂CH₂CH₂CH₂N), 2.04 - 2.08 (m, 2 H, C(=O)CH₂CH₂CH₂N), 1.96 - 2.04 (m, 2 H, C(=O)CH₂CH₂CH₂N), 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=CCH₂CH₂CH₂CH₂N), 1.54 - 1.60 (m, 1 H, CHHCH₂OH), 1.51 (quin, J = 7.4 Hz, 2 H, CH=CCH₂CH₂CH₂CH₂N), 1.28 - 1.35 (m, 1 H, NCH(CH₂)₂), 1.11 - 1.22 (m, 5 H, NCH(CH₂)₂, CHHCHOH, CHHCH₂CHOH and CH₂CH₂CHNH), 1.04 - 1.13 (m, 1 H, CHHCHNH)

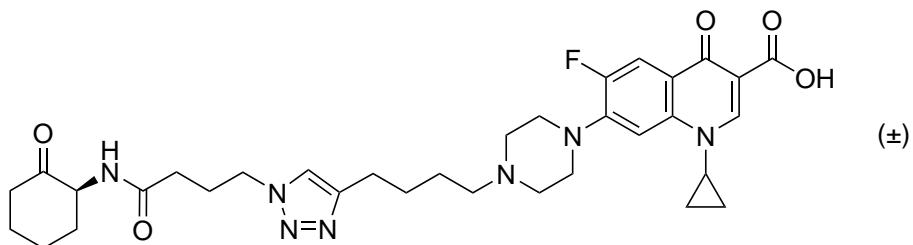
¹³C NMR (101 MHz, DMSO d₆) δ / ppm = 176.4 (C(=O)CC(=O)OH), 170.9 (CH₂C(=O)NH), 166.0 (C(=O)OH), 153.1 (d, J = 252.1 Hz, *ipso* to F), 148.0 (C=CC(=O)OH), 146.9 (CH=CCH₂), 145.3 (d, J = 10.0 Hz, *ipso* to piperazine), 139.2 (para to F), 121.8 (NCH=CCH₂), 118.5 (d, J = 8.3 Hz, para to piperazine), 110.9 (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=CCH₂CH₂CH₂N), 54.2 (CHNH), 52.4 (CH=CCH₂CH₂CH₂N(CH₂)), 49.5 (CH=CCH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 49.5 (CH=CCH₂CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 48.8 (C(=O)CH₂CH₂CH₂NCH=C), 35.9 (NCH(CH₂)₂), 34.1 (CH₂CHOH), 32.3 (C(=O)CH₂CH₂CH₂NCH=C), 31.1 (CH₂CHNH), 26.9 (CH=CCH₂CH₂CH₂N), 26.1 (C(=O)CH₂CH₂CH₂NCH=C), 25.8 (CH=CCH₂CH₂CH₂N), 25.0 (CH=CCH₂CH₂CH₂N), 24.2 (CH₂CH₂CHNH), 23.8 (CH₂CH₂CHOH), 7.6 (NCH(CH₂)₂)

¹⁹F NMR (376.45 MHz, DMSO d₆) δ / ppm = -121.4 (ciprofloxacin F)

HRMS (ESI⁺) *m/z* / Da = 638.3480, [M+H]⁺ found, [C₃₃H₄₅FN₇O₅]⁺ 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-(*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 CH₂Cl₂ (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 NaHCO₃ (aq., sat., 30 ml) and 10 % *i*-PrOH/CHCl₃ (30 ml) were added. The organic layer was dried with MgSO₄ and evaporated under reduced pressure. **151** was obtained as a clear gum (11.7 mg, 18.4 μmol, 78.0 %).

IR (neat) ν_{max} / cm⁻¹ = 2941.2 (C-H), 2859.8 (C-H), 1719.8 (carboxylic acid C=O and ketone C=O), 1656.8 (amide C=O), 1625.6 (quinolone C=O), 1613.5 (triazole)

¹H NMR (500 MHz, DMSO d₆) δ / ppm = 8.65 (s, 1 H, *ortho* to C(=O)OH), 7.94 (d, J=7.7 Hz, 1 H, NH), 7.88 (d, J=13.4 Hz, 1 H, *ortho* to F), 7.85 (s, 1 H, CH=CCH₂), 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)CH₂CH₂CH₂NH), 4.31 (t, J=6.9 Hz, 1 H, C(=O)CH₂CH₂CH₂NH), 3.74 - 3.84 (m, 1 H, NCH(CH₂)₂), 3.31 (br. s, 4 H, CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 2.64 (t, J=7.5 Hz, 2 H, CH=CCH₂), 2.56 (br t, J=5.0, 5.0 Hz, 4 H, CH₂CH₂CH₂N(CH₂)CH₂), 2.45 - 2.52 (m, 1 H, CHHC(=O)), 2.38 (t, J=7.1 Hz, 2 H, CH=CCH₂CH₂CH₂NH), 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)CH₂CH₂CH₂N and CHHCHNH), 1.96 - 2.05 (m, 3 H, C(=O)CH₂CH₂CH₂N and CHHCH₂C(=O)), 1.68 - 1.81 (m, 2 H, CHHCH₂CH₂NH), 1.64 (quin, J=7.5 Hz, 2 H, CH=CCH₂CH₂CH₂NH), 1.40 - 1.56 (m, 5 H, CHHCH₂C(=O), CHHCHNH and CH=CCH₂CH₂CH₂CH₂N), 1.27 - 1.34 (m, 2 H, NCH(CH₂)₂), 1.13 - 1.20 (m, 2 H, NCH(CH₂)₂)

¹³C NMR (126 MHz, DMSO d₆) δ / ppm = 207.4 (C(=O)CHNH), 176.3 (C(=O)CC(=O)OH), 170.8 (CH₂C(=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=CCH₂), 145.1 (d, J=10.1 Hz, *ipso* to piperazine), 139.1 (para to F), 121.7 (NCH=CCH₂), 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=CCH₂CH₂CH₂NH), 57.0 (CHNH), 52.4 (CH₂CH₂CH₂N(CH₂)CH₂), 49.5 (CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 49.5 (CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 48.7 (C(=O)CH₂CH₂CH₂NCH=C), 40.5 (CH₂C(=O)), 35.8 (NCH(CH₂)₂), 33.7 (CH₂CHNH), 31.8 (C(=O)CH₂CH₂CH₂NCH=C), 27.1 (CH₂CH₂C(=O)),

26.9 (CH=CCH₂CH₂CH₂CH₂N), 26.0 (C(=O)CH₂CH₂CH₂NCH=C), 25.7 (CH=CCH₂CH₂CH₂CH₂N), 24.9 (CH=CCH₂CH₂CH₂CH₂N), 23.8 (CH₂CH₂CHNH), 7.6 (NCH(CH₂)₂)

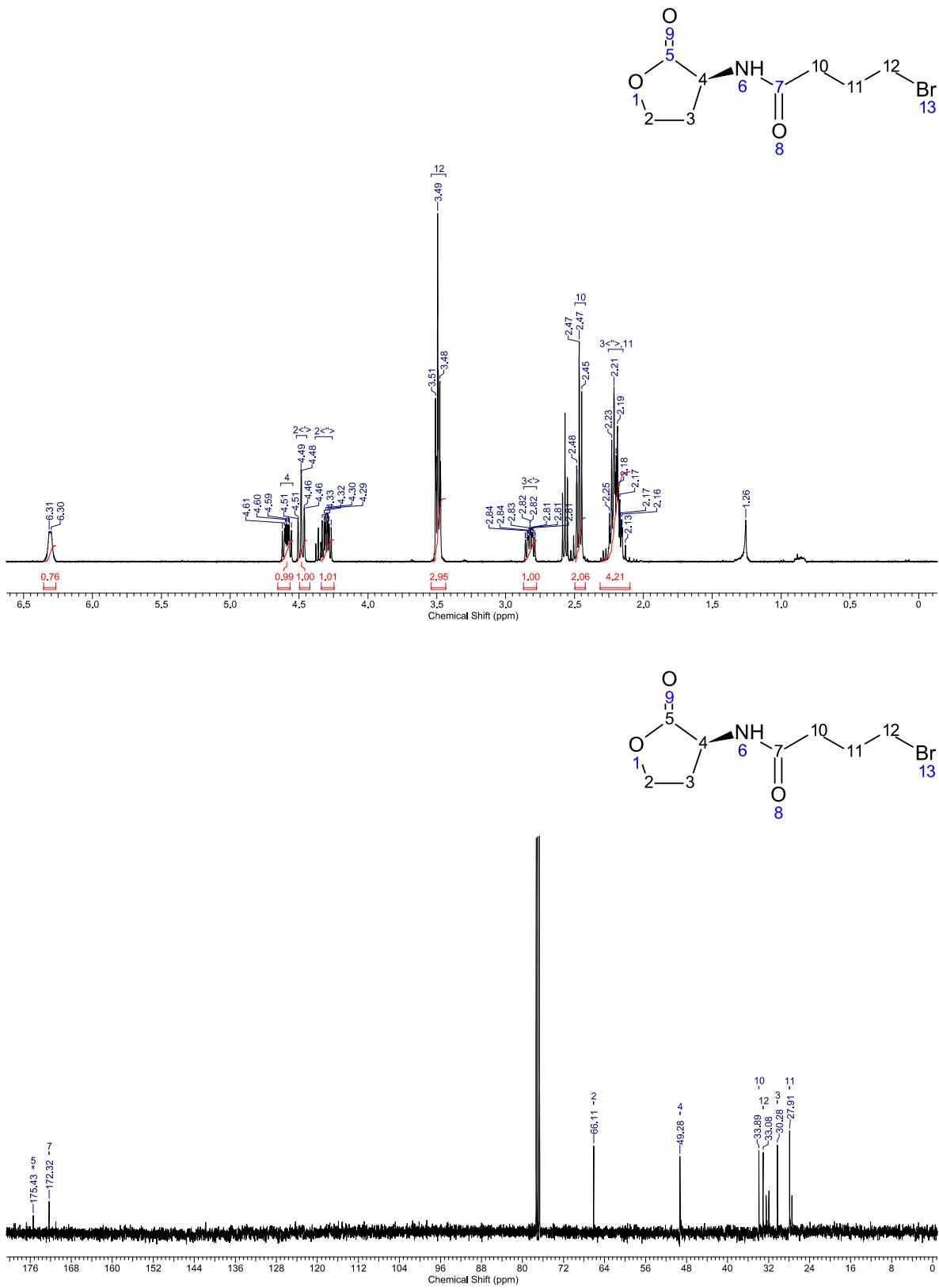
¹⁹F NMR (376 MHz, DMSO d₆) δ / ppm = -121.7 (s, ciprofloxacin F)

HRMS (ESI⁺) *m/z* / Da = 636.3303, [M+H]⁺ found, [C₃₃H₄₃FN₇O₅]⁺ requires 636.3310

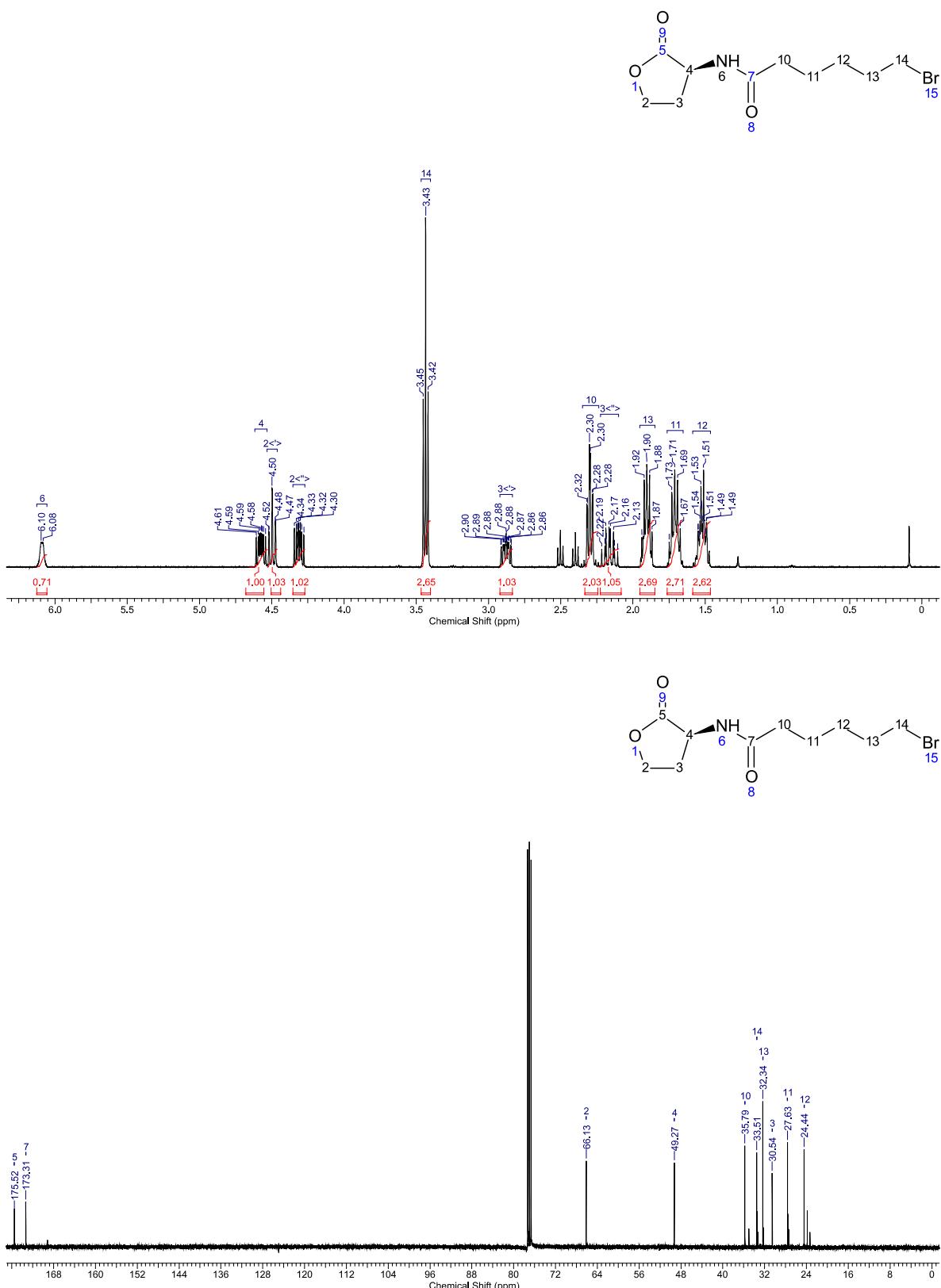
The compound has not been reported previously.

2 NMR spectra

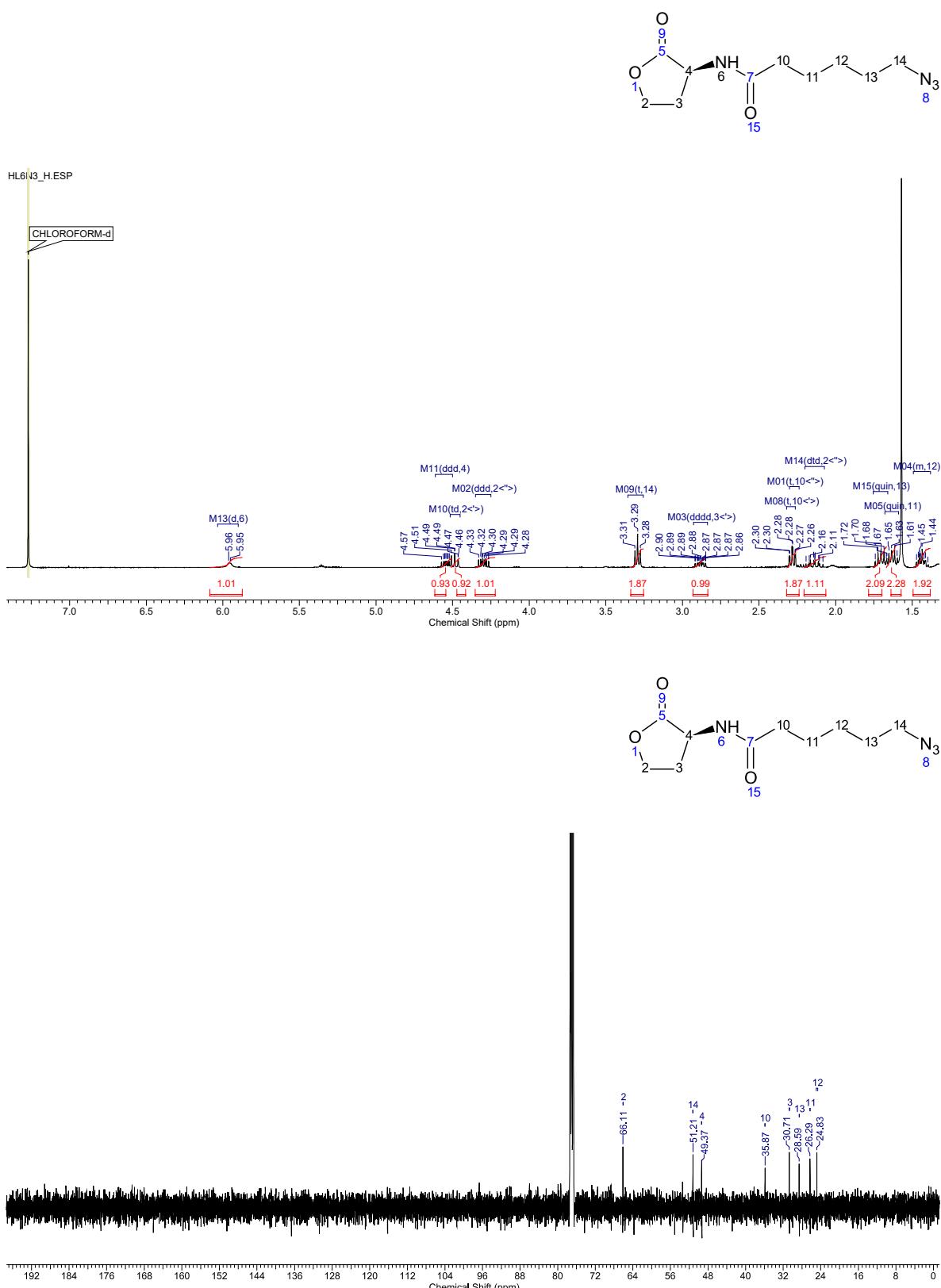
2.1 (S)-4-Bromo-N-(2-oxotetrahydrofuran-3-yl)butanamide 44



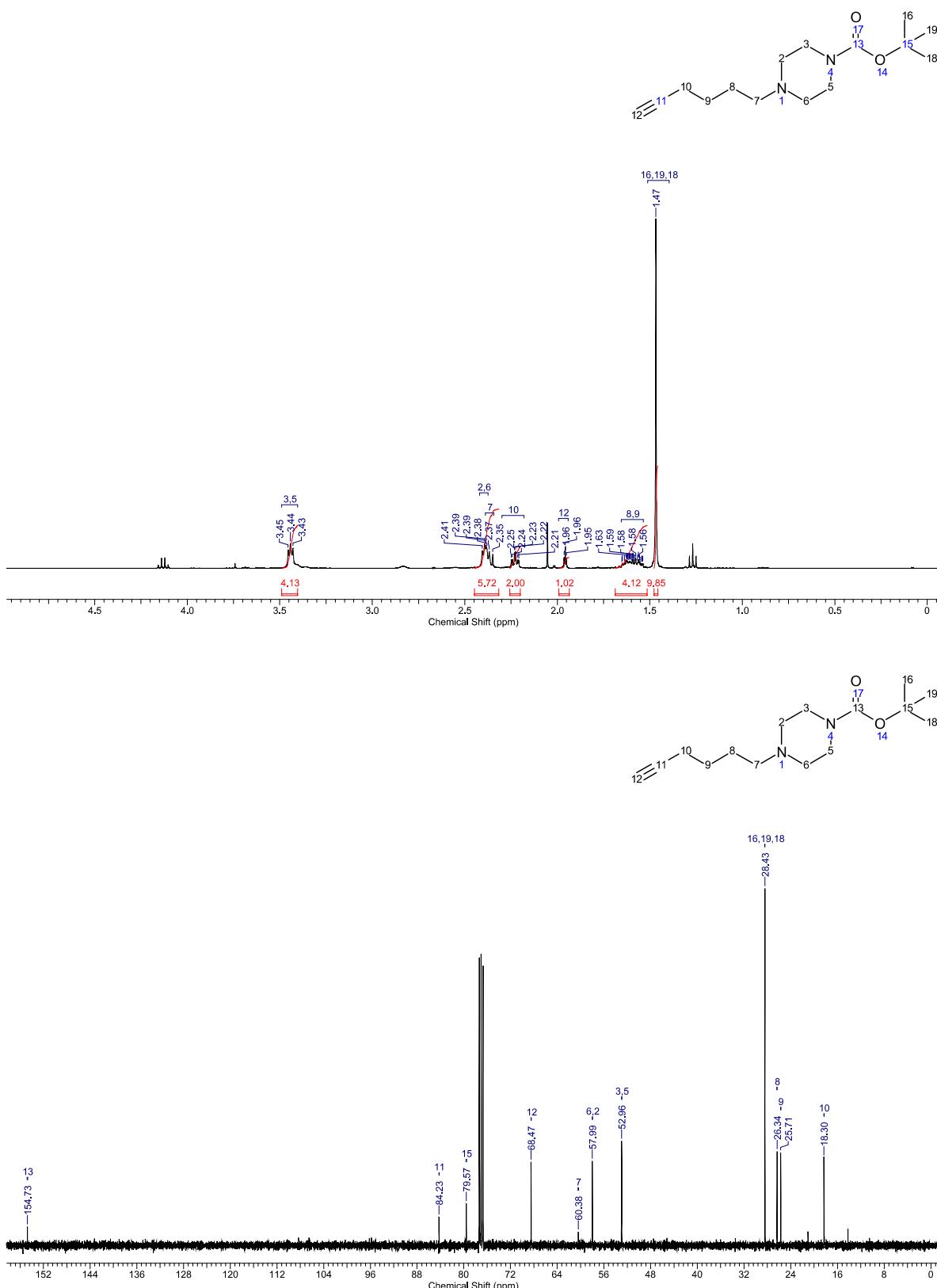
2.2 (*S*)-6-Bromo-*N*-(2-oxotetrahydrofuran-3-yl)hexanamide 45



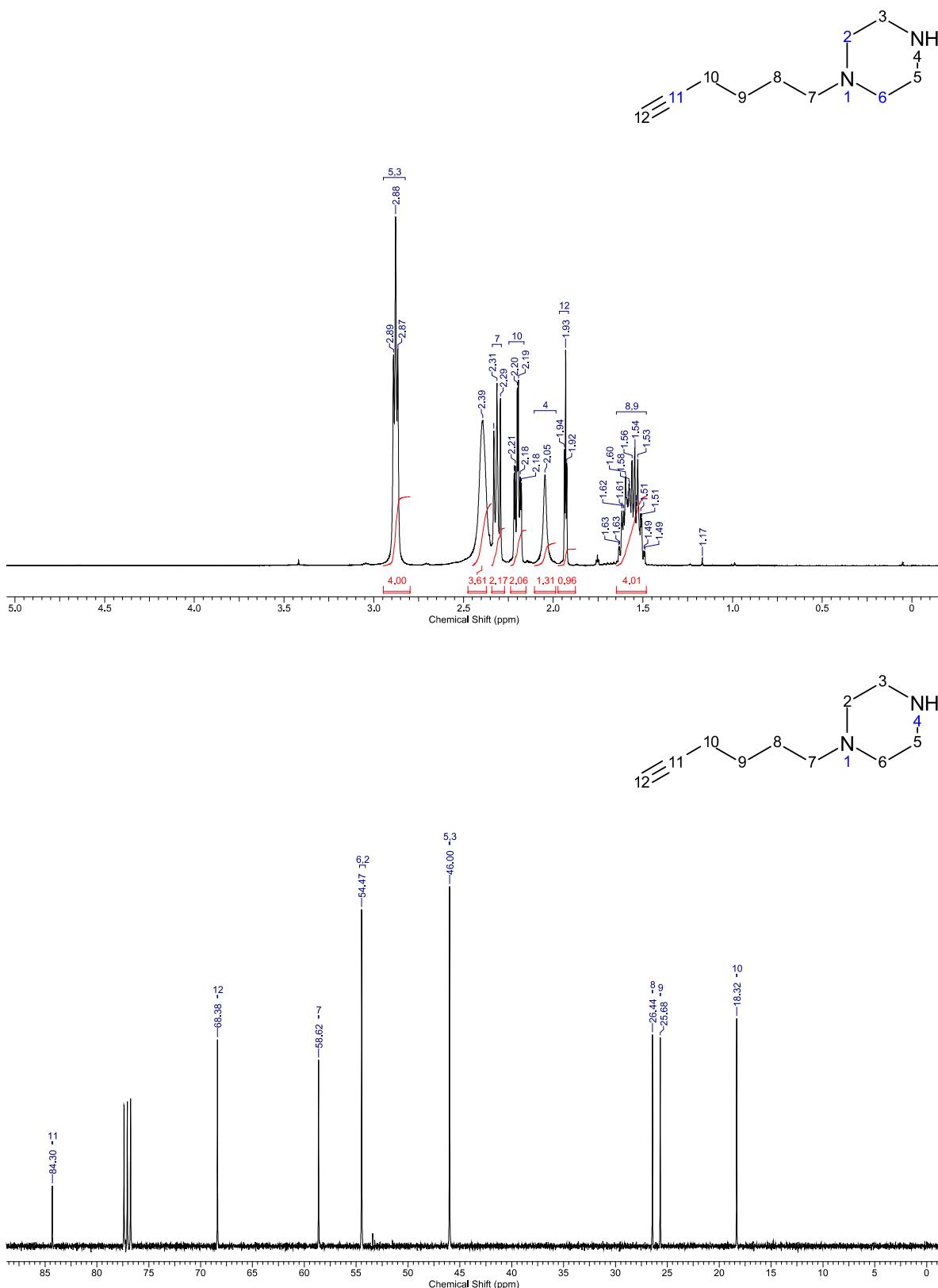
2.3 (*S*)-6-Azido-*N*-(2-oxotetrahydrofuran-3-yl)hexanamide 47



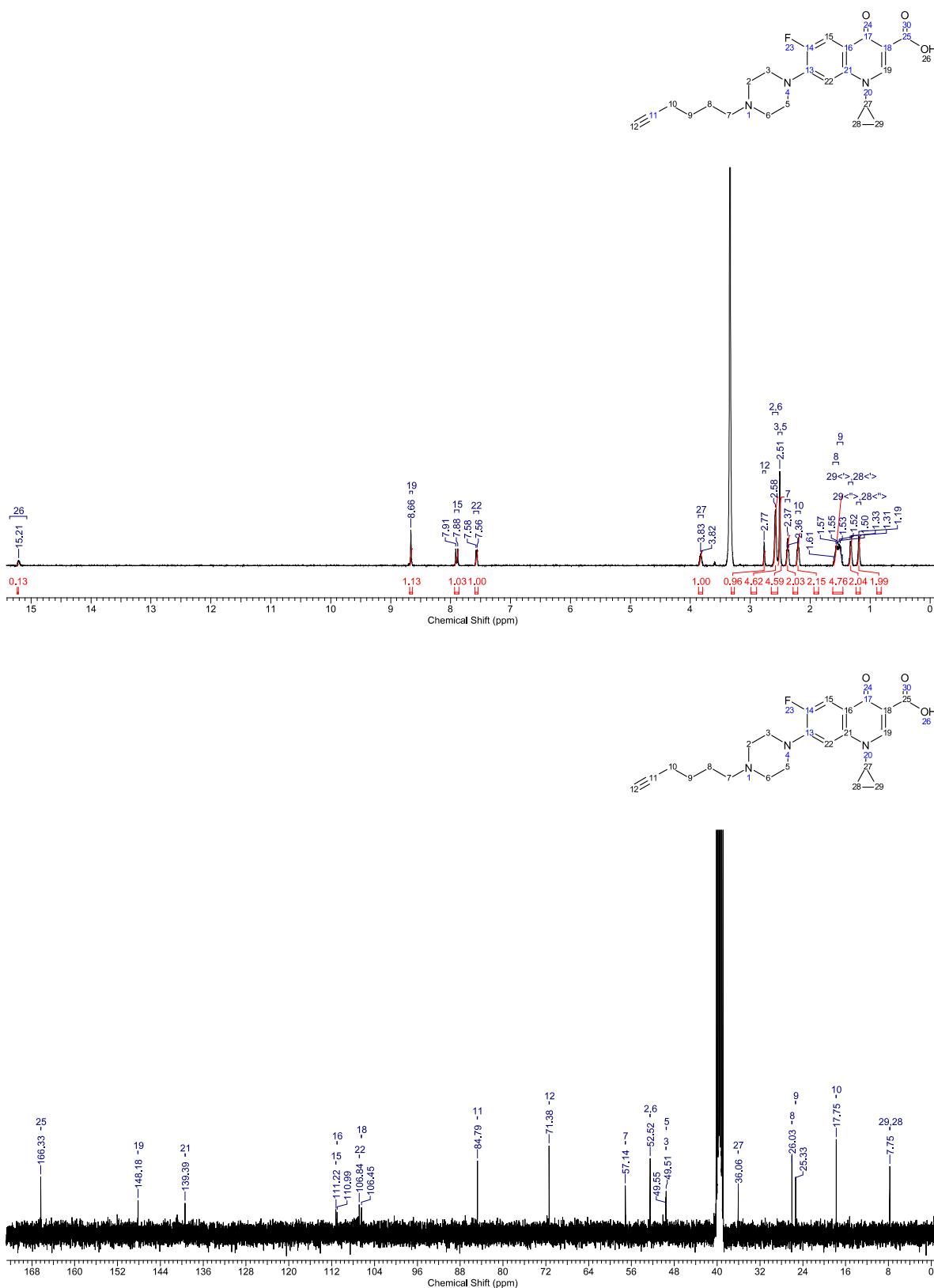
2.4 *tert*-Butyl 4-(hex-5-yn-1-yl)piperazine-1-carboxylate 51



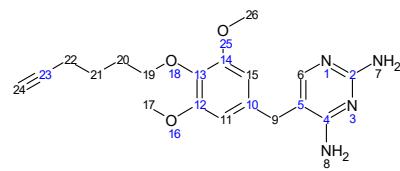
2.5 1-(Hex-5-yn-1-yl)piperazine 52



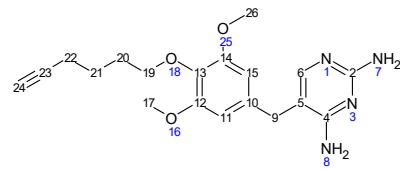
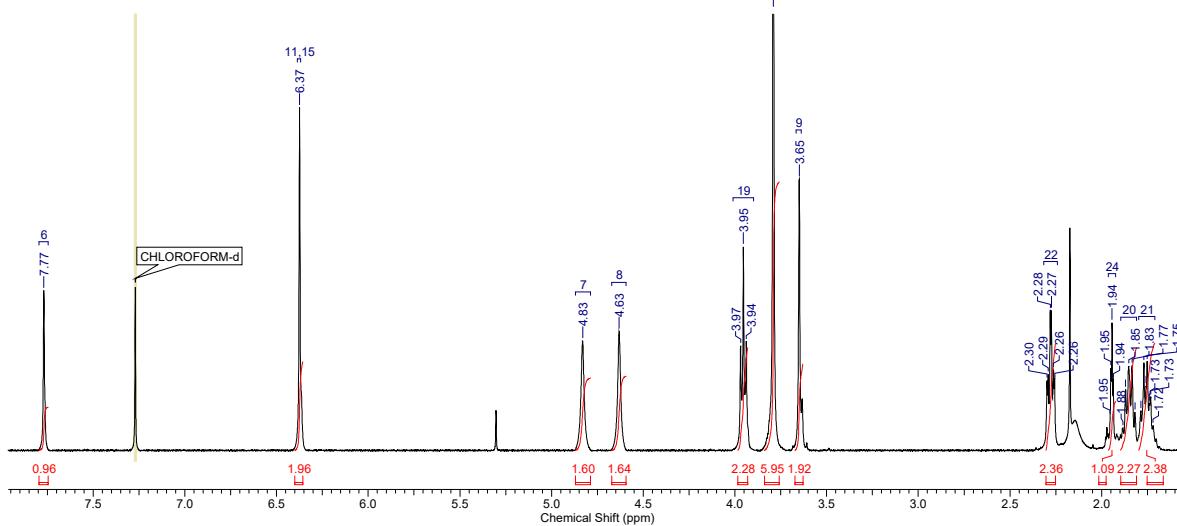
2.6 1-Cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 54



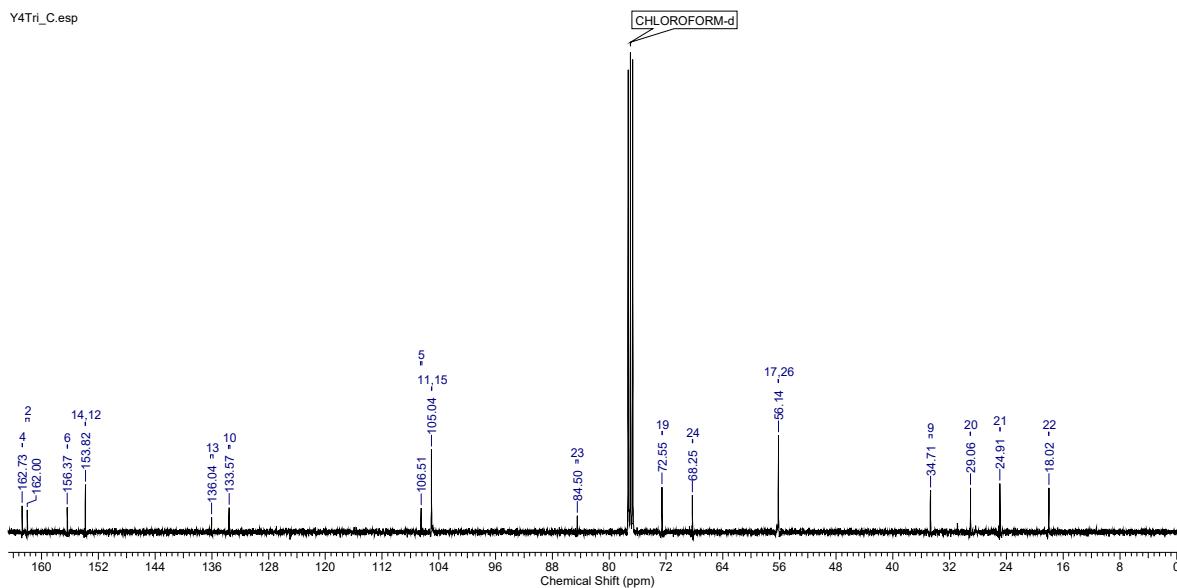
2.7 5-(4-(Hex-5-yn-1-yloxy)-3,5-dimethoxybenzyl)pyrimidine-2,4-diamine 94



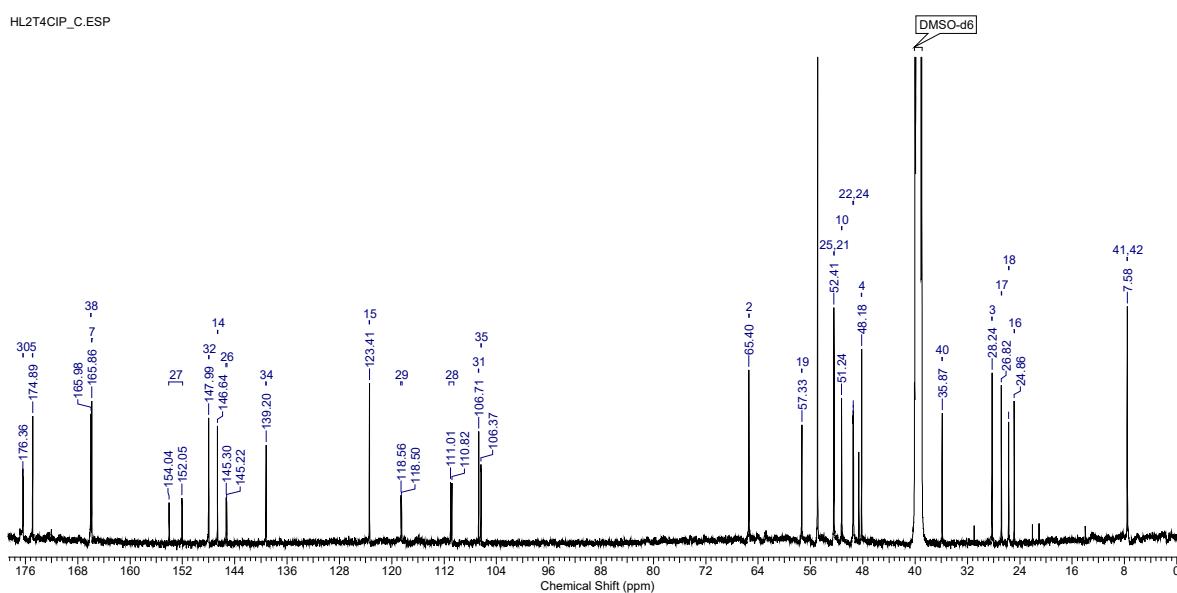
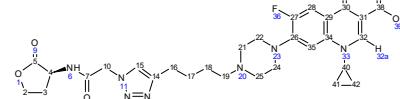
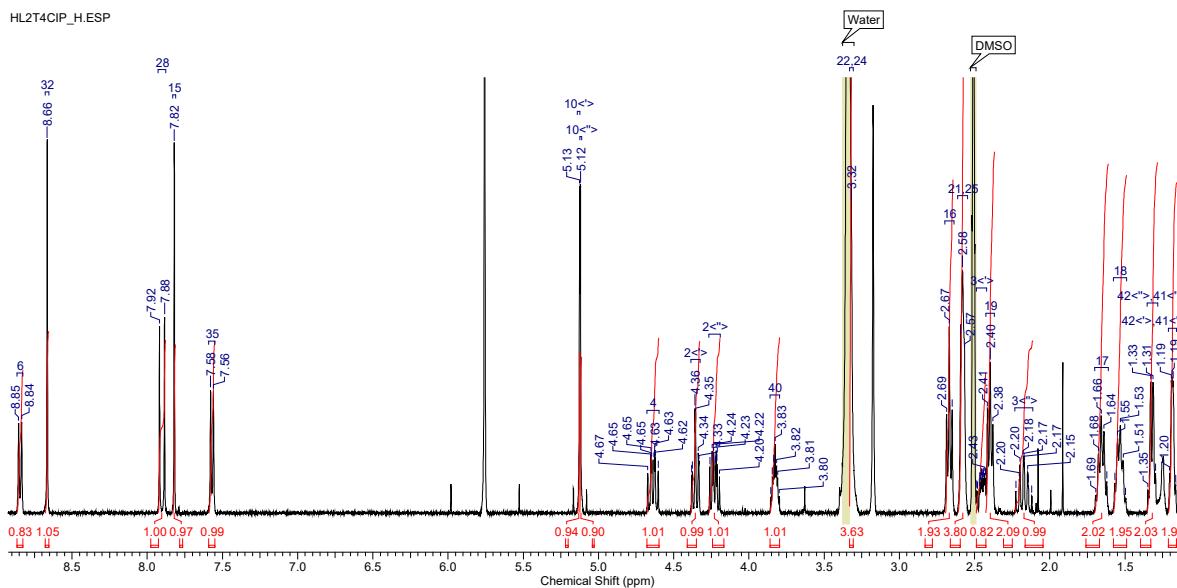
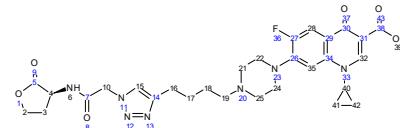
Y4Tri_H.esp



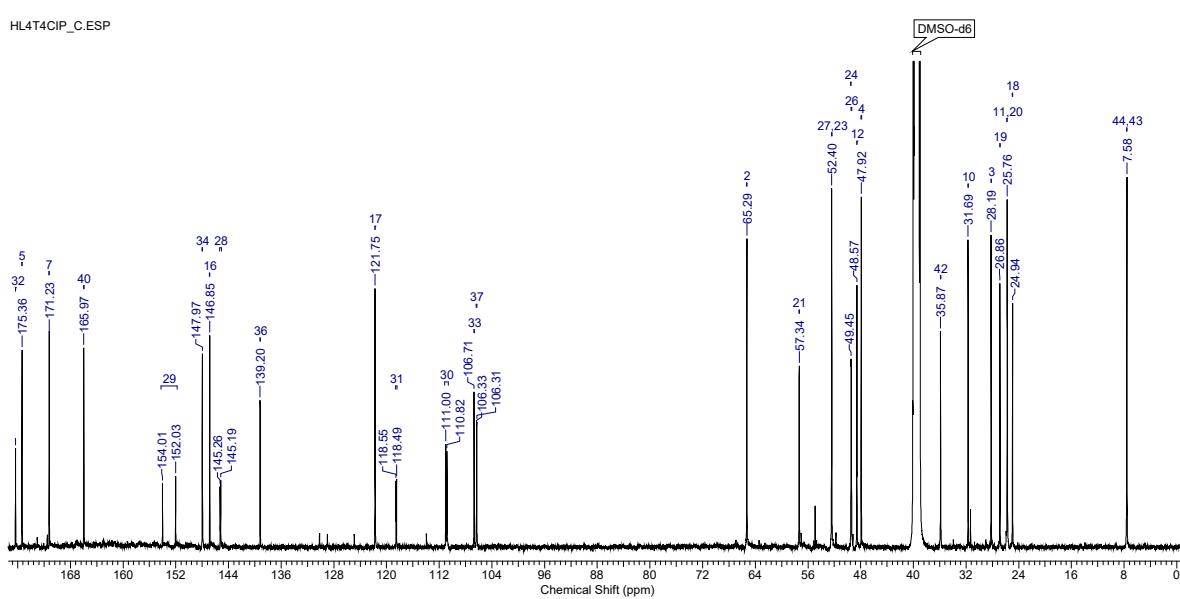
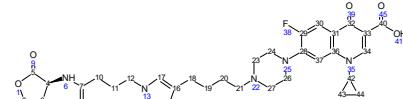
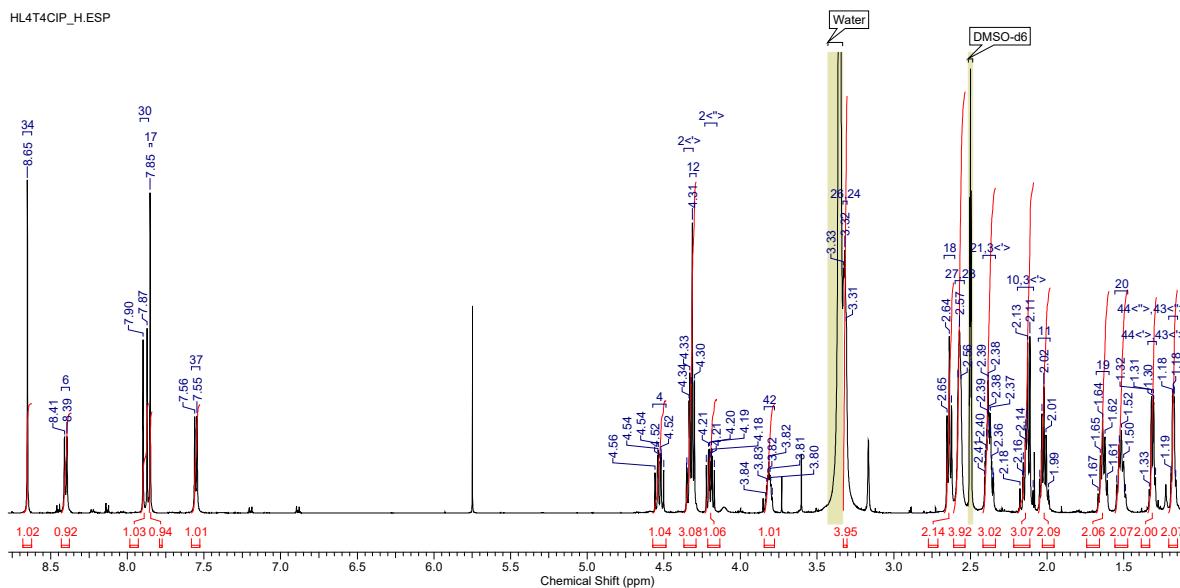
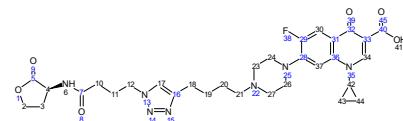
Y4Tri_C.esp



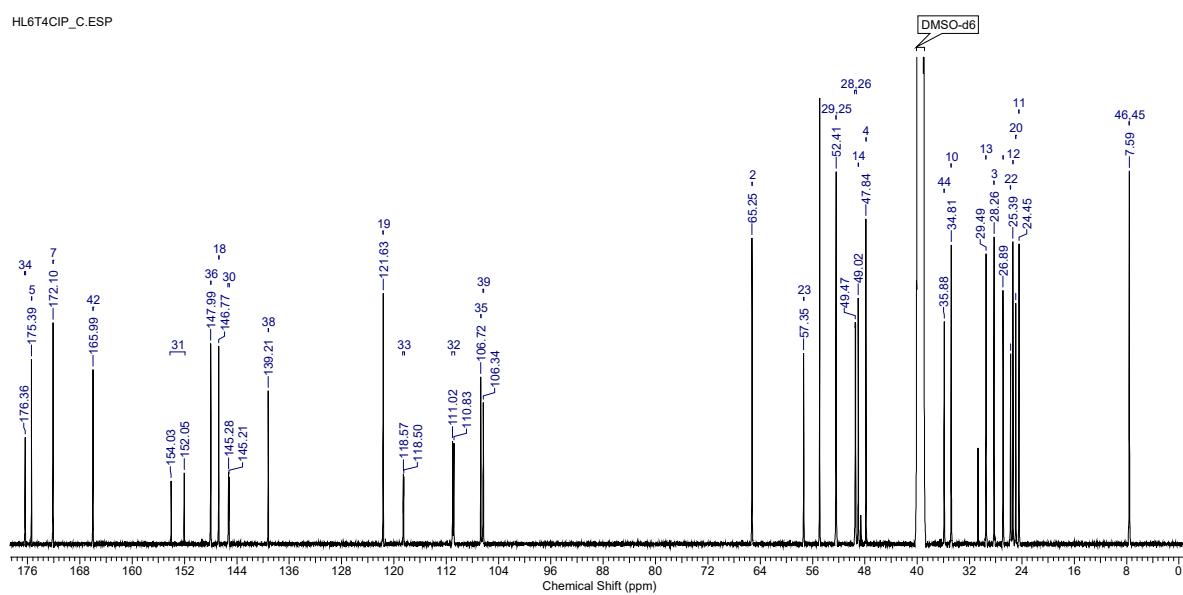
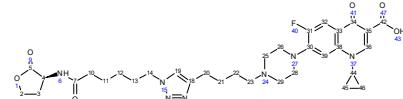
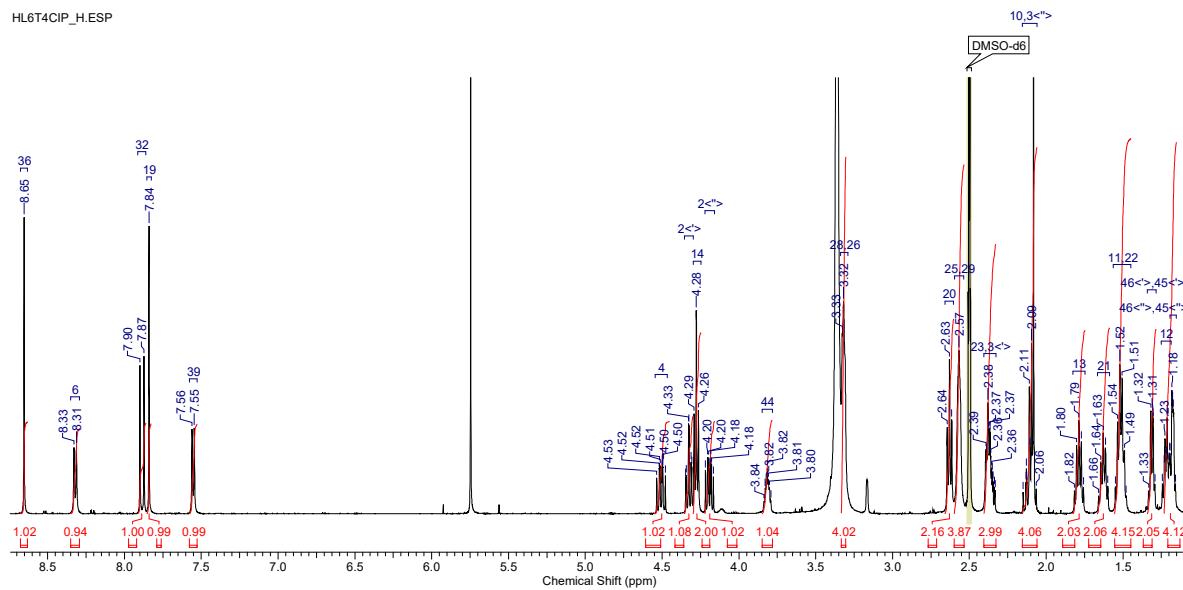
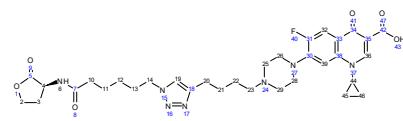
2.8 (S)-1-Cyclopropyl-6-fluoro-4-oxo-7-(4-(4-(1-(2-oxo-2-((2-oxotetrahydrofuran-3-yl)amino)ethyl)-1*H*-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid 95



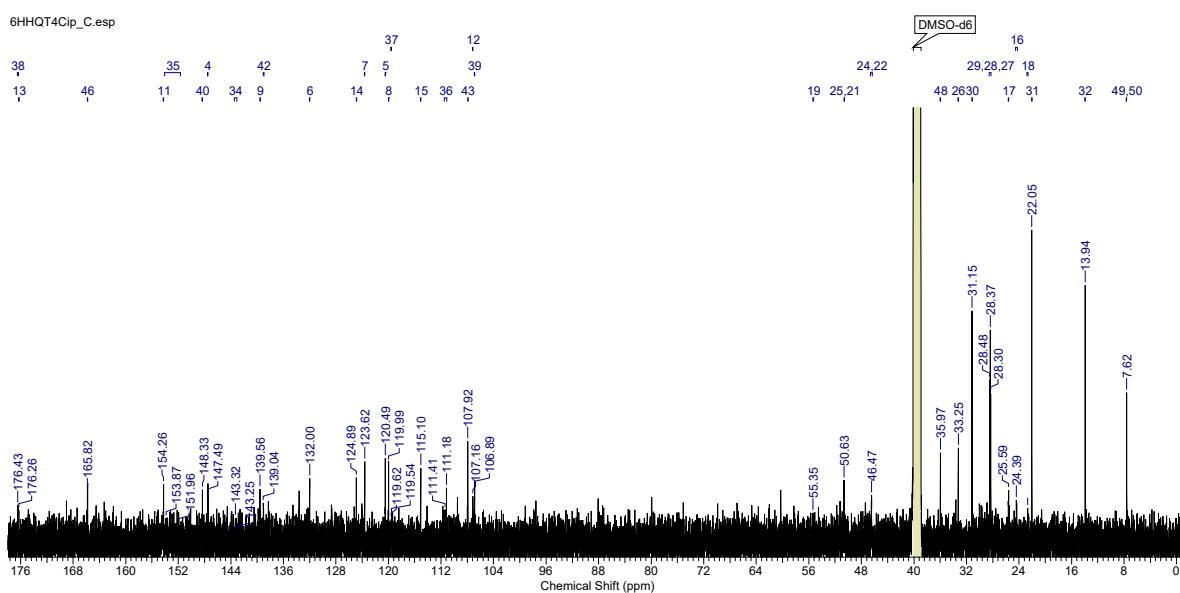
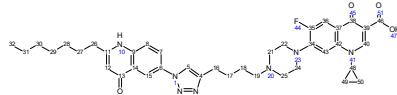
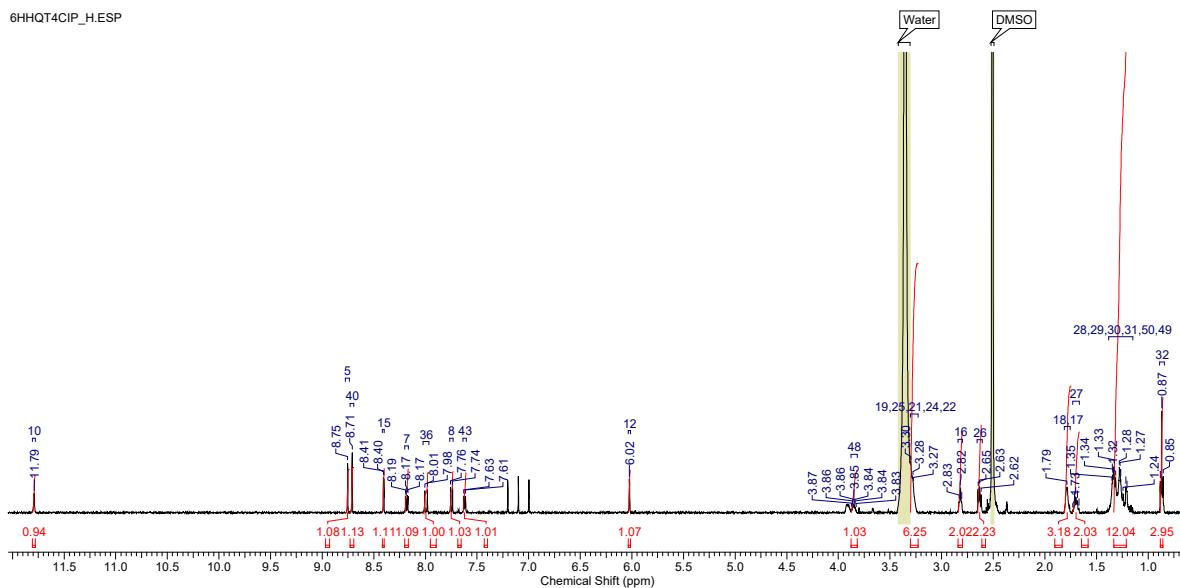
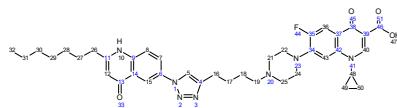
2.9 (*S*)-1-Cyclopropyl-6-fluoro-4-oxo-7-(4-(4-(1-(4-oxo-4-((2-oxotetrahydrofuran-3-yl)amino)butyl)-1*H*-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid 96



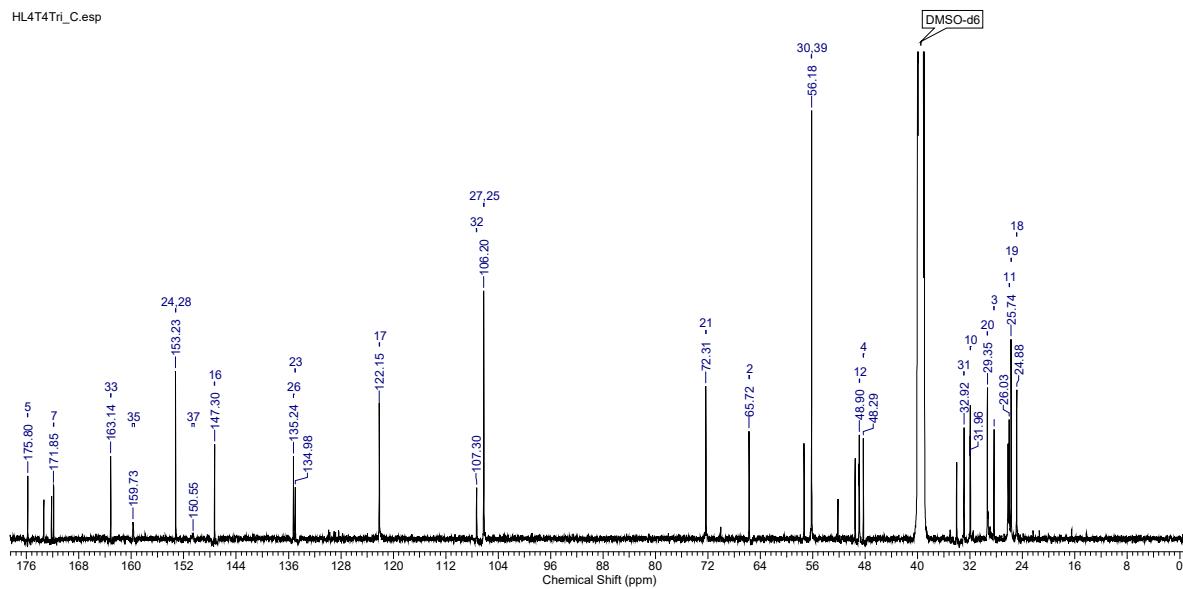
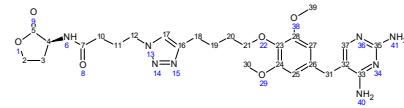
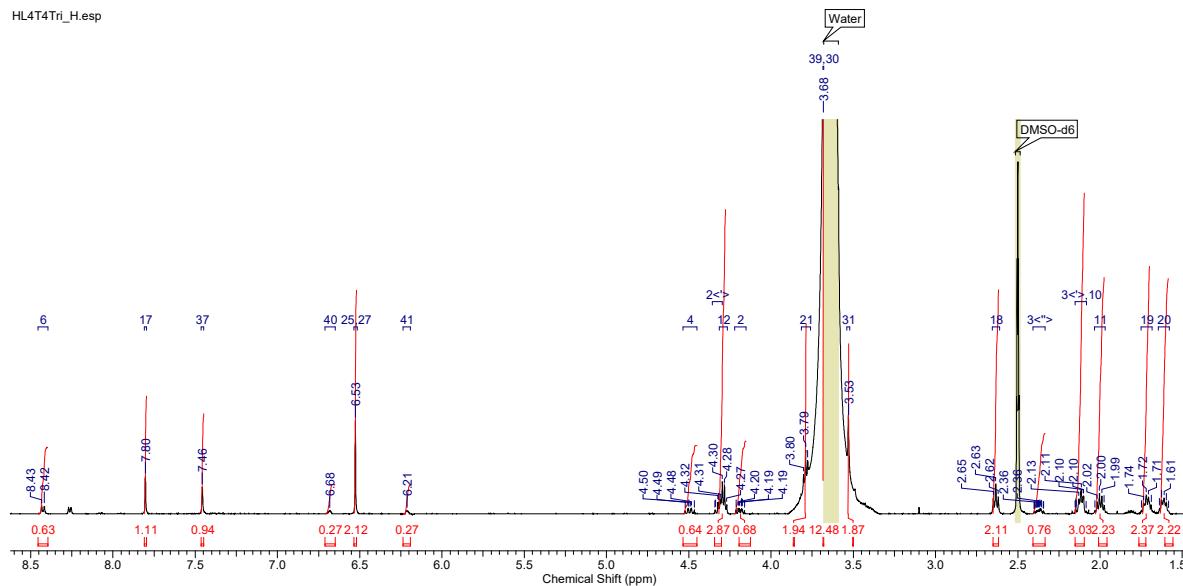
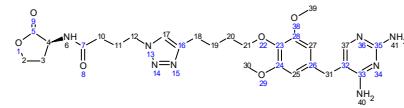
2.10 (*S*)-1-Cyclopropyl-6-fluoro-4-oxo-7-(4-(4-(1-(6-oxo-6-((2-oxotetrahydrofuran-3-yl)amino)hexyl)-1*H*-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid 97



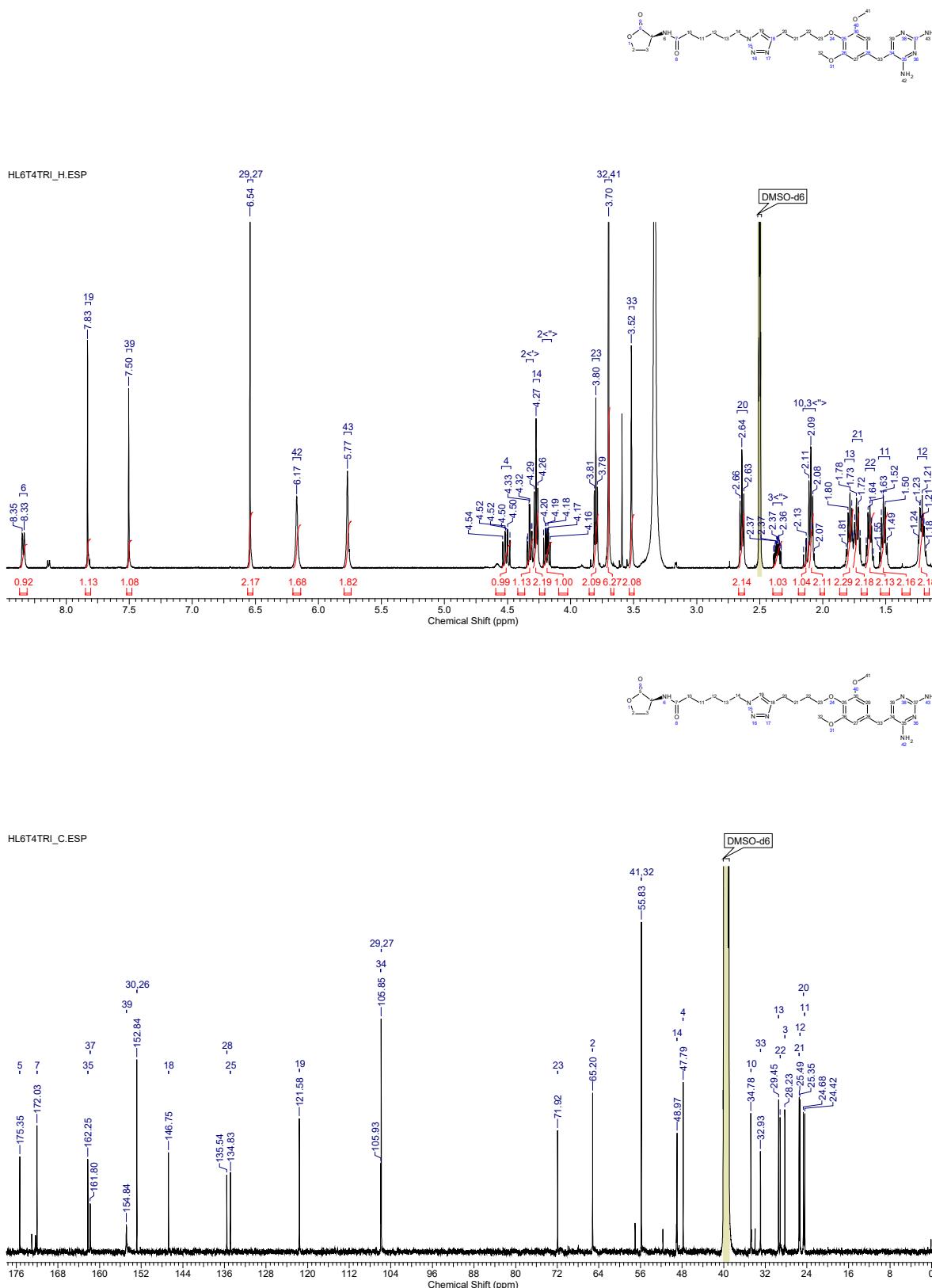
2.11 1-Cyclopropyl-6-fluoro-7-(4-(4-(1-(2-heptyl-4-oxo-1,4-dihydroquinolin-6-yl)-1*H*-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 98



2.12 (*S*)-4-(4-(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

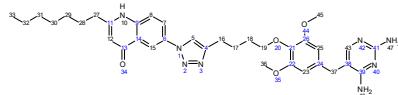


2.13 (S)-6-(4-((2,4-Diaminopyrimidin-5-yl)methyl)-2,6-dimethoxyphenoxy)butyl-1*H*-1,2,3-triazol-1-yl)-*N*-(2-oxotetrahydrofuran-3-yl)hexanamide 100

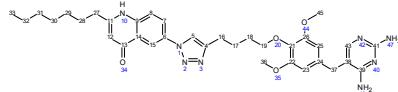
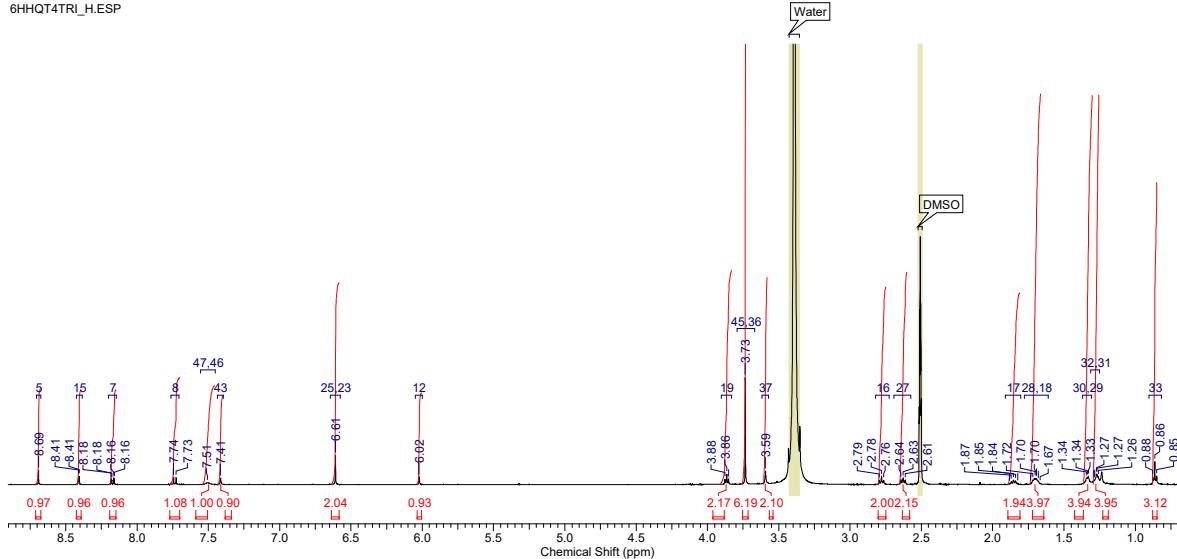


2.14 6-(4-(4-((2,4-Diaminopyrimidin-5-yl)methyl)-2,6-dimethoxyphenoxy)butyl)-1*H*-1,2,3-triazol-1-yl)-2-heptylquinolin-4(*H*)-one 101

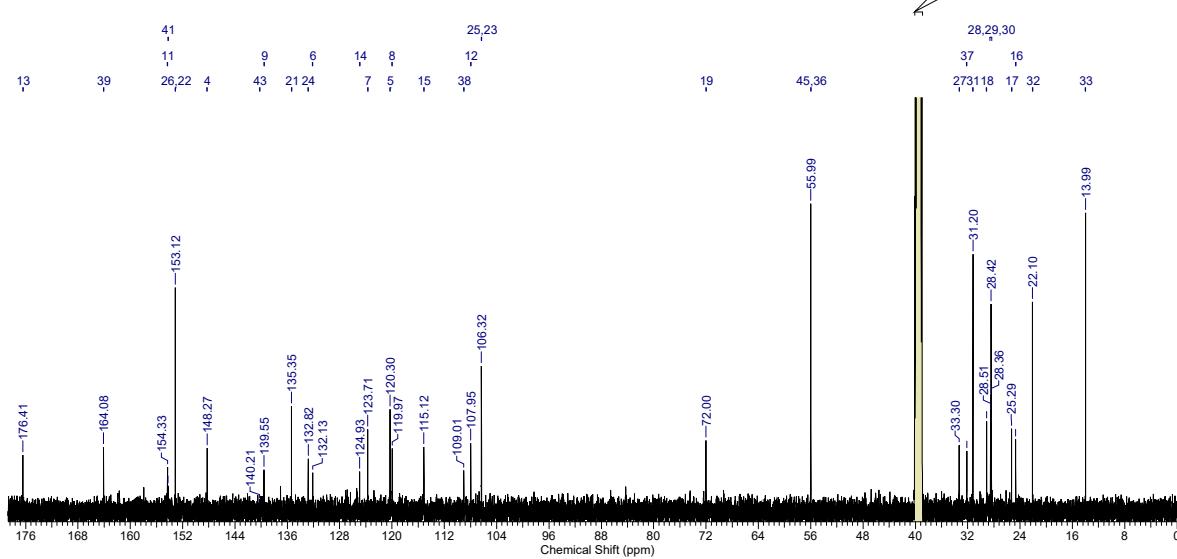
User Notes Some guesses



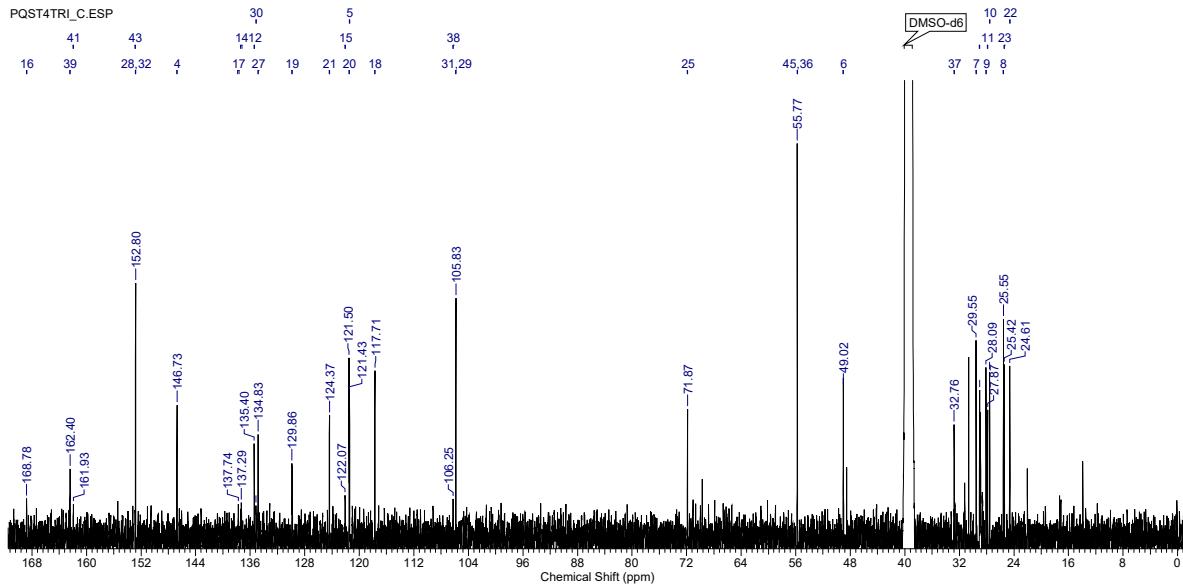
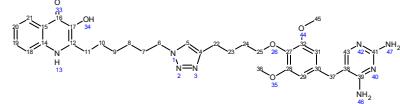
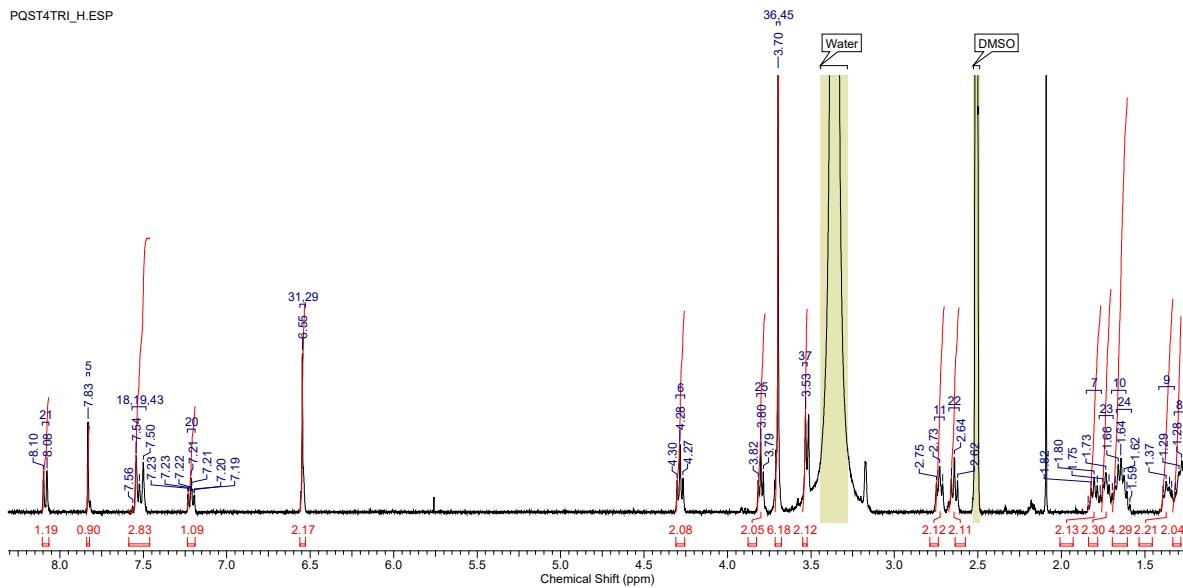
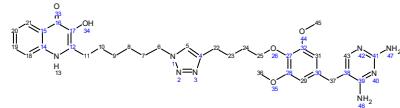
6HHQT4TRI H.ESP



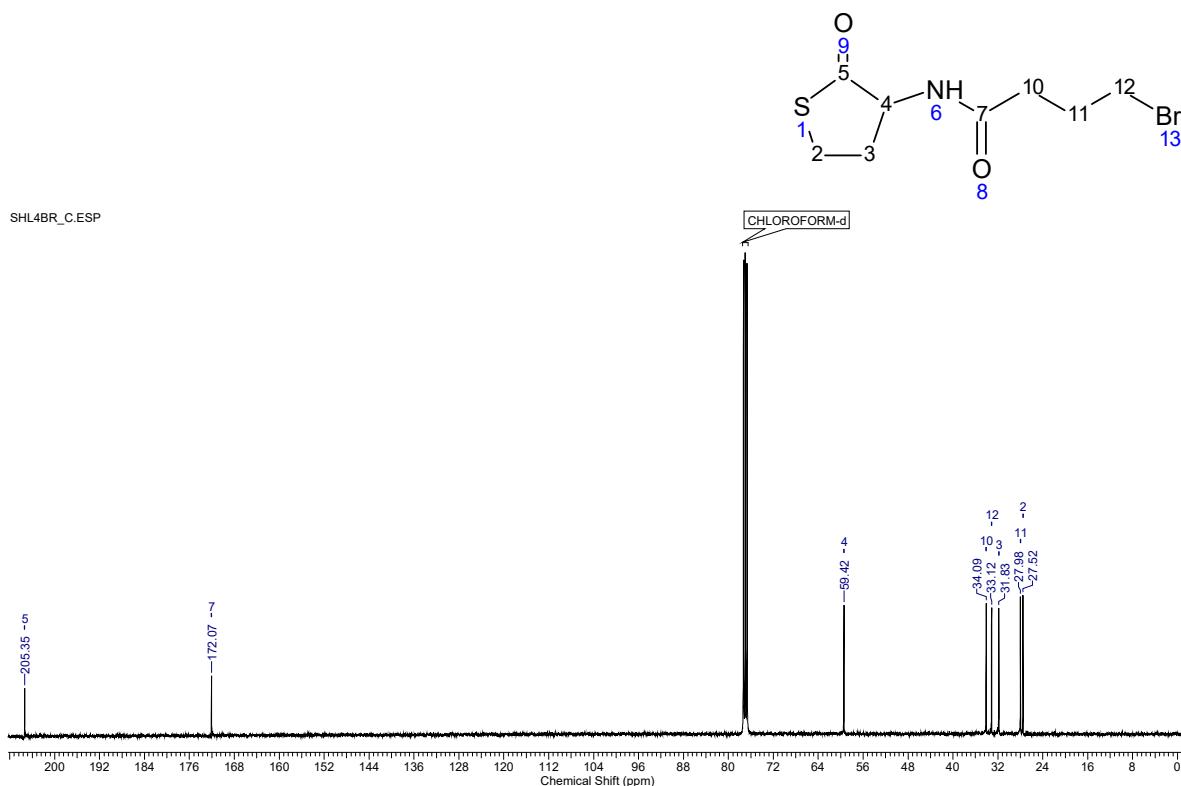
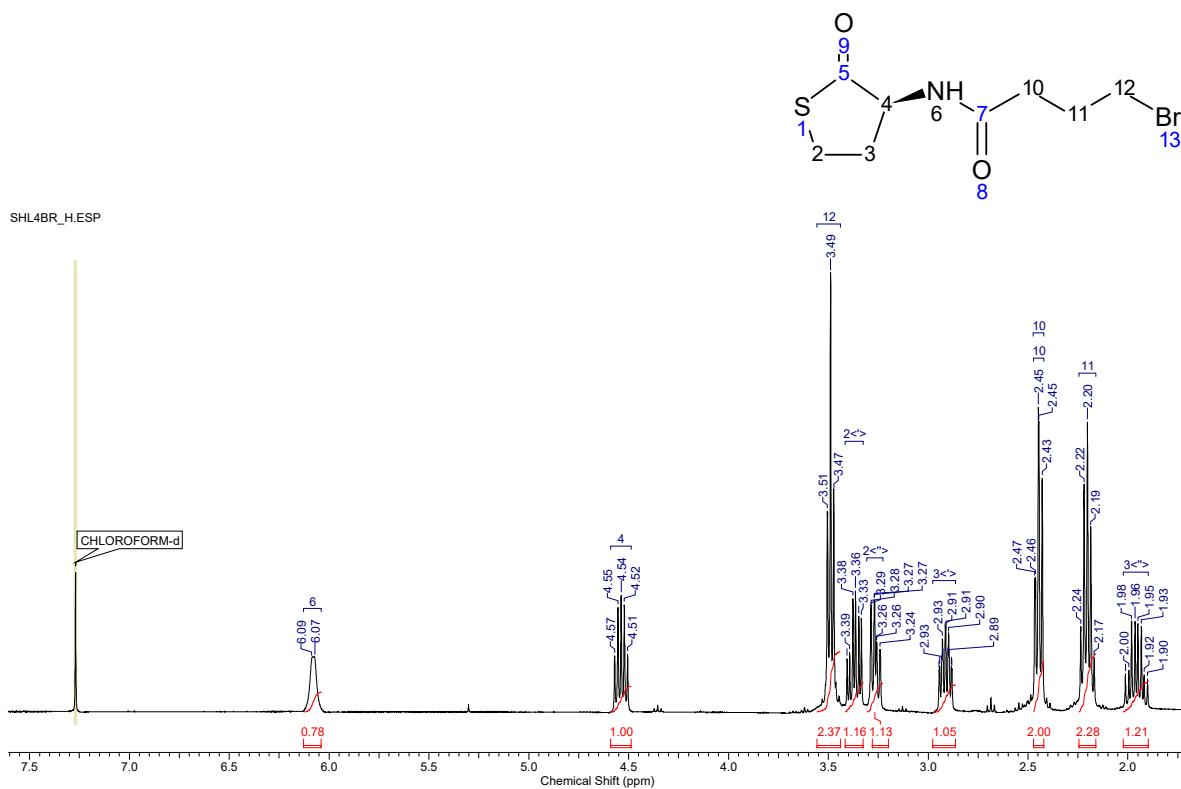
6HHQT4TRI_C.ESP



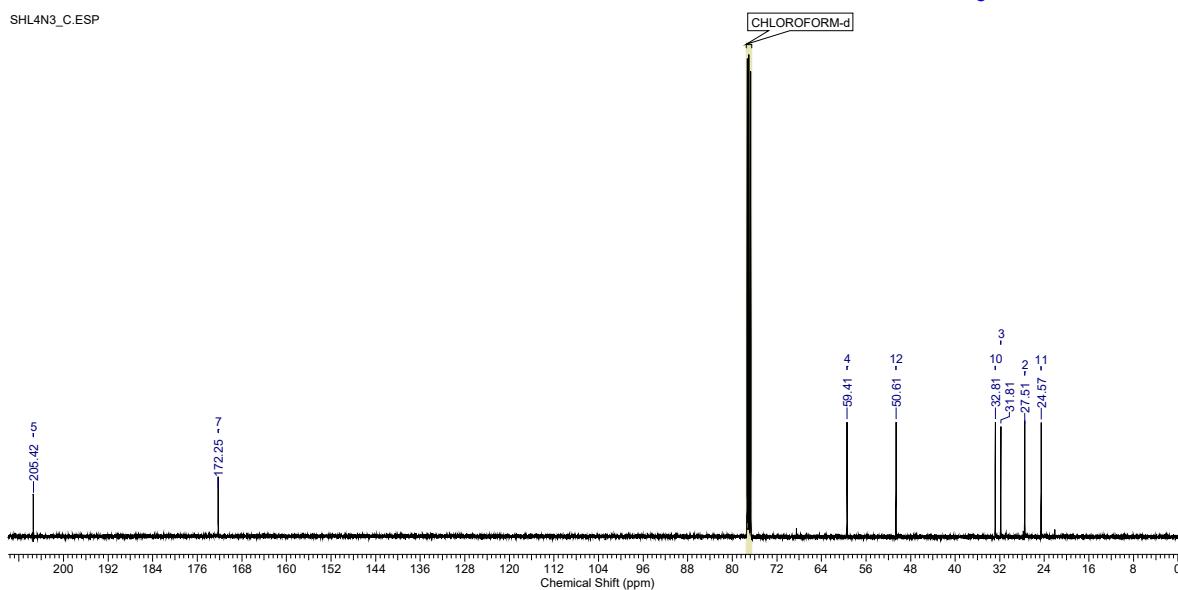
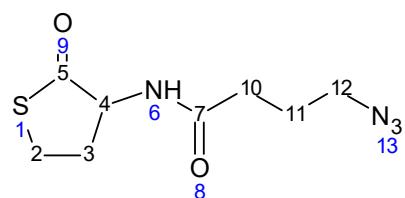
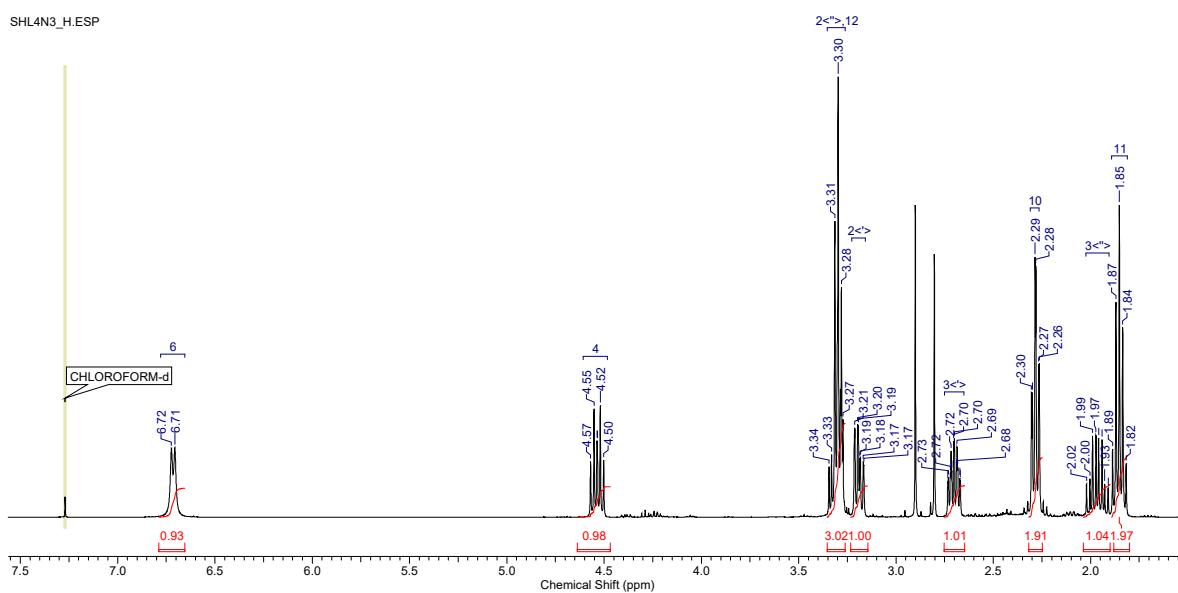
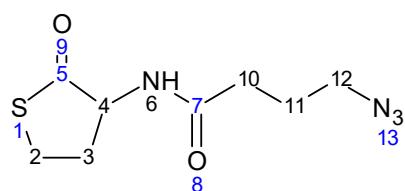
2.15 2-(6-(4-(4-((2,4-Diaminopyrimidin-5-yl)methyl)-2,6-dimethoxyphenoxy)butyl)-1*H*-1,2,3-triazol-1-yl)hexyl)-3-hydroxyquinolin-4(*H*)-one 102



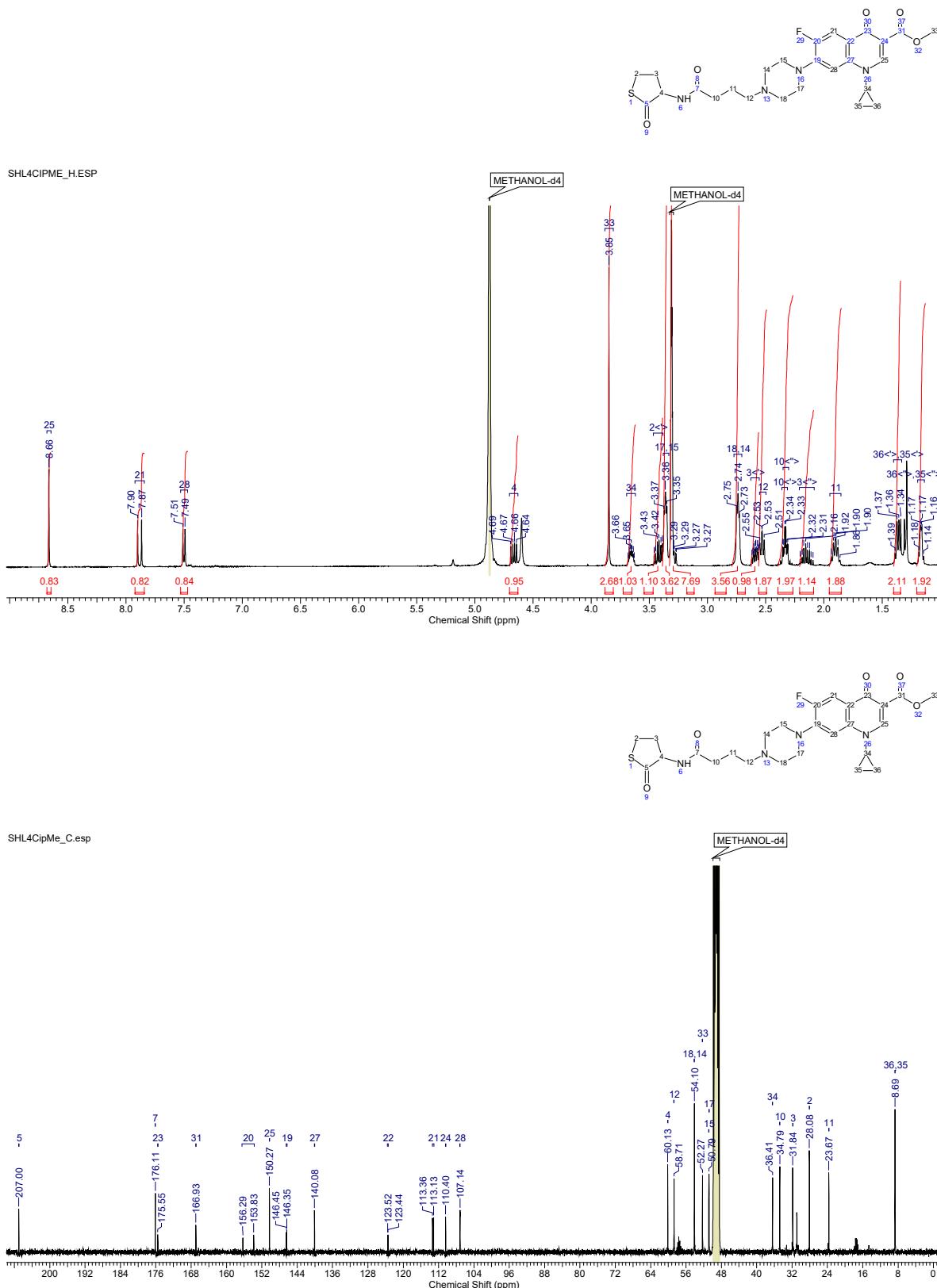
2.16 4-Bromo-*N*-(2-oxotetrahydrothiophen-3-yl)butanamide 105



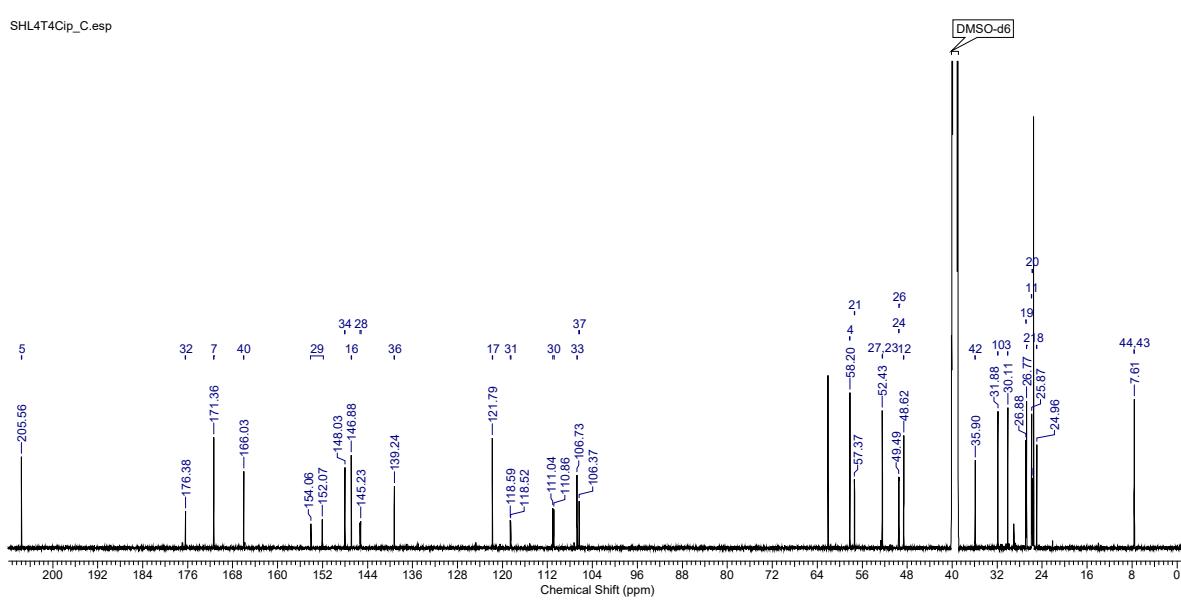
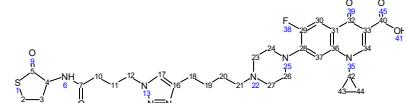
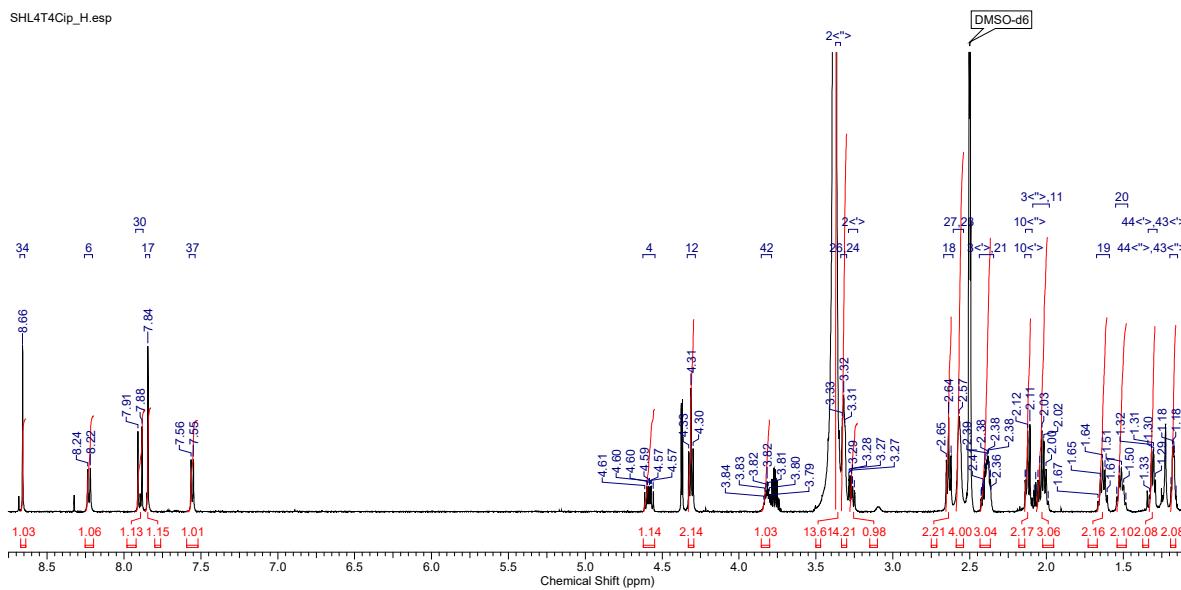
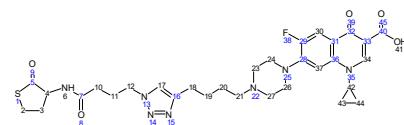
2.17 4-Azido-*N*-(2-oxotetrahydrothiophen-3-yl)butanamide 106



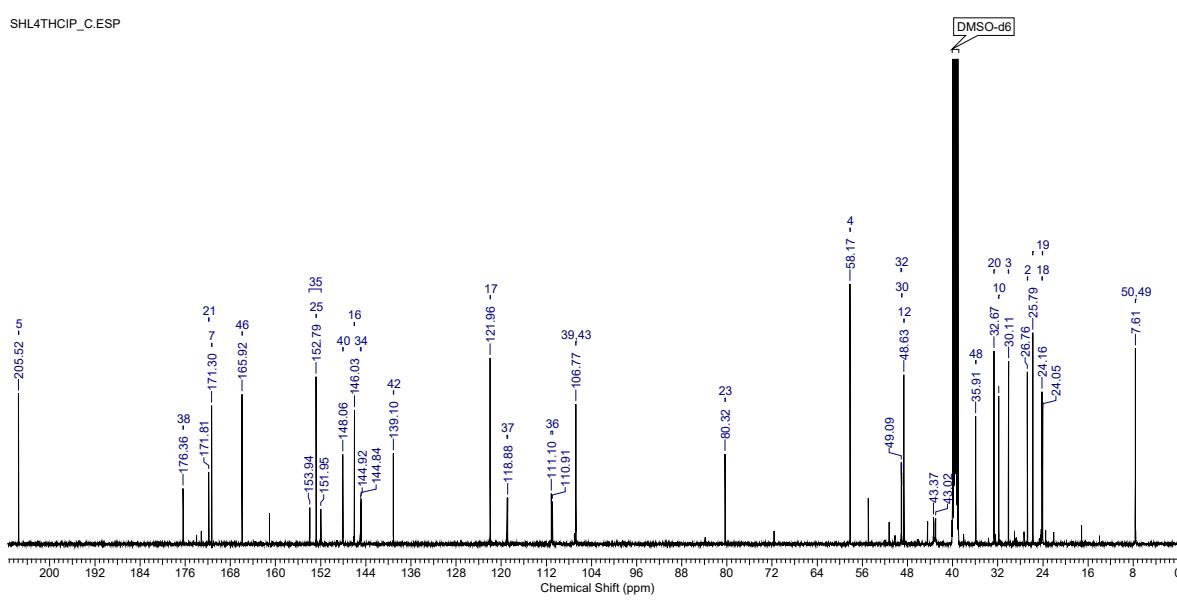
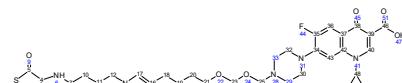
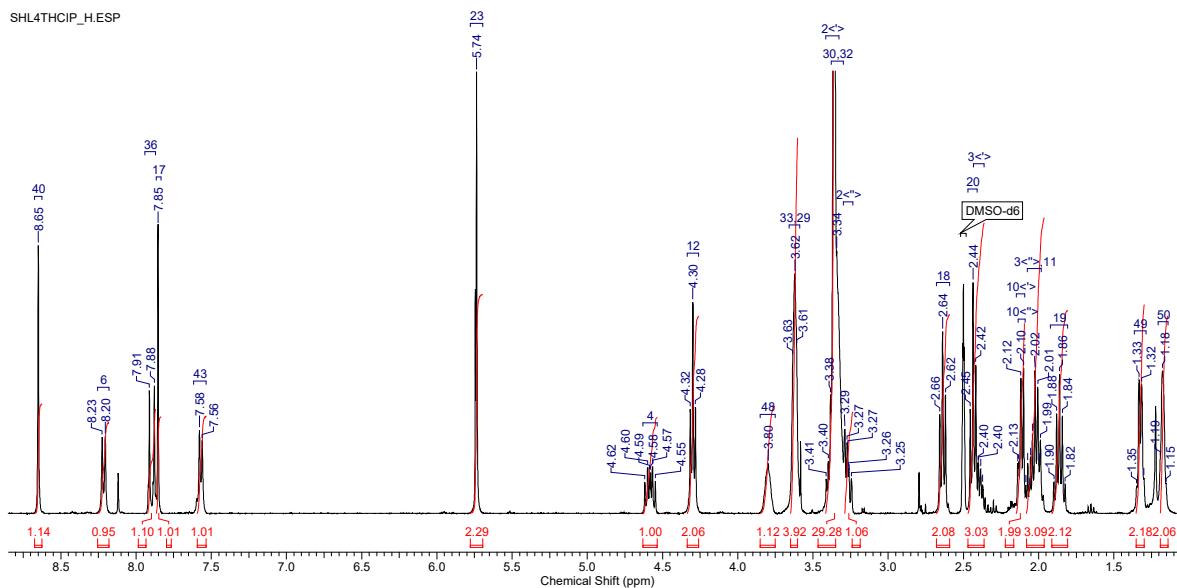
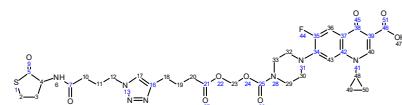
2.18 Methyl 1-cyclopropyl-6-fluoro-4-oxo-7-(4-(4-oxo-4-((2-oxotetrahydrothiophen-3-yl)amino)butyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate 107



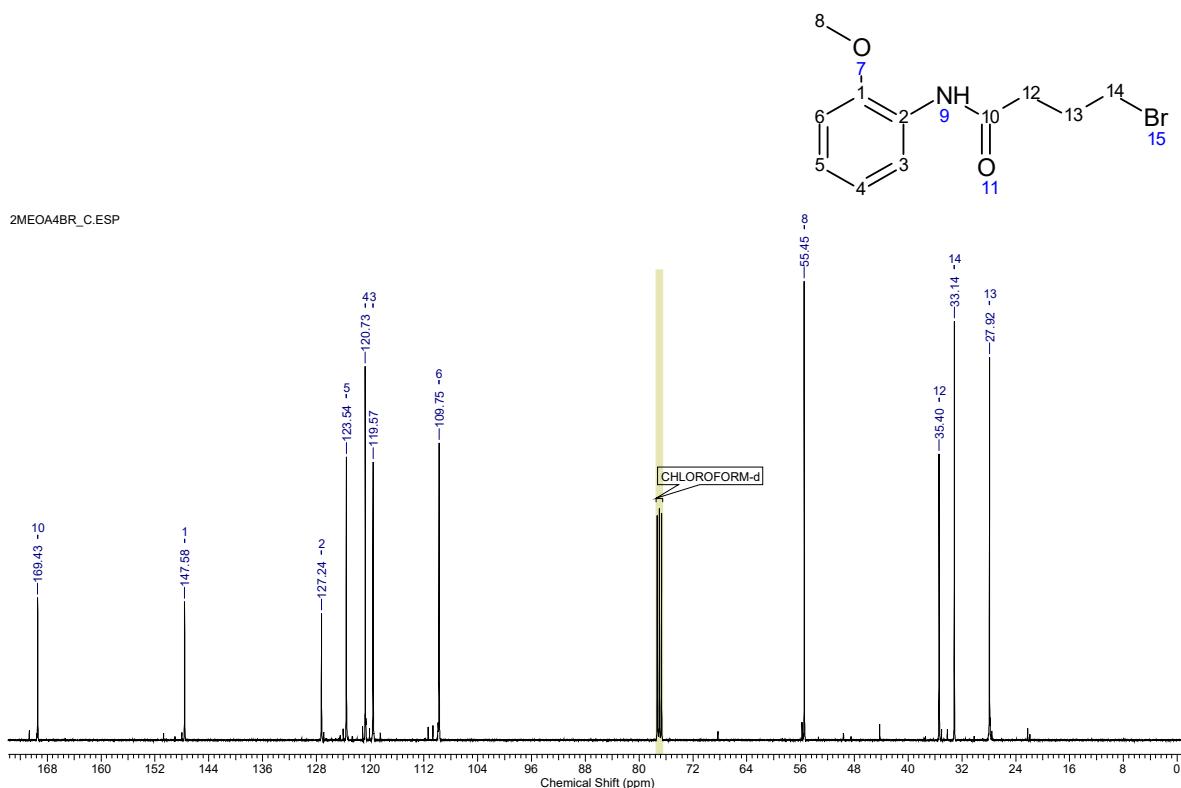
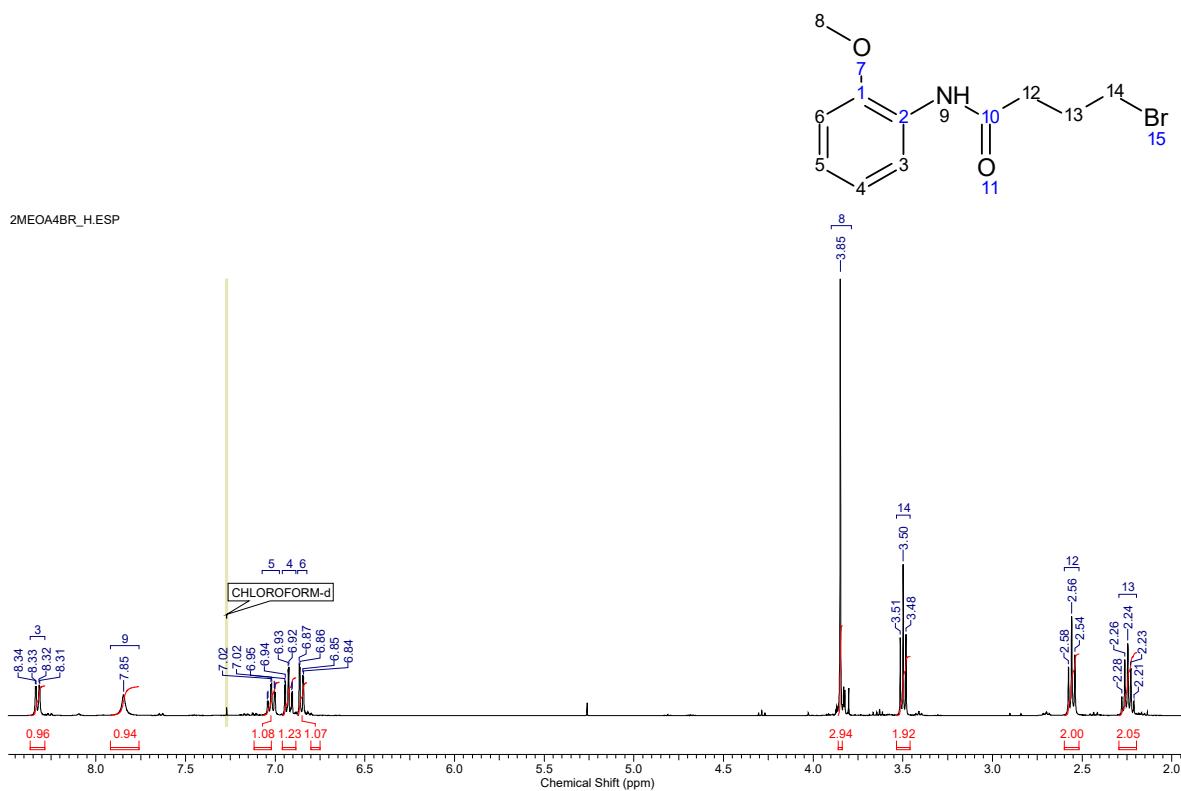
2.19 1-Cyclopropyl-6-fluoro-4-oxo-7-(4-(4-(1-(4-oxo-4-((2-oxotetrahydrothiophen-3-yl)amino)butyl)-1*H*-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid 108



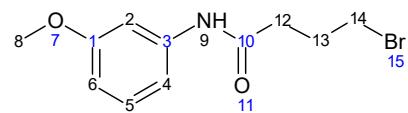
2.20 1-Cyclopropyl-6-fluoro-4-oxo-7-(((4-(1-(4-oxo-4-((2-oxotetrahydrothiophen-3-yl)amino)butyl)-1*H*-1,2,3-triazol-4-yl)butanoyl)oxy)methoxy)carbonyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid 110



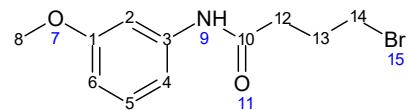
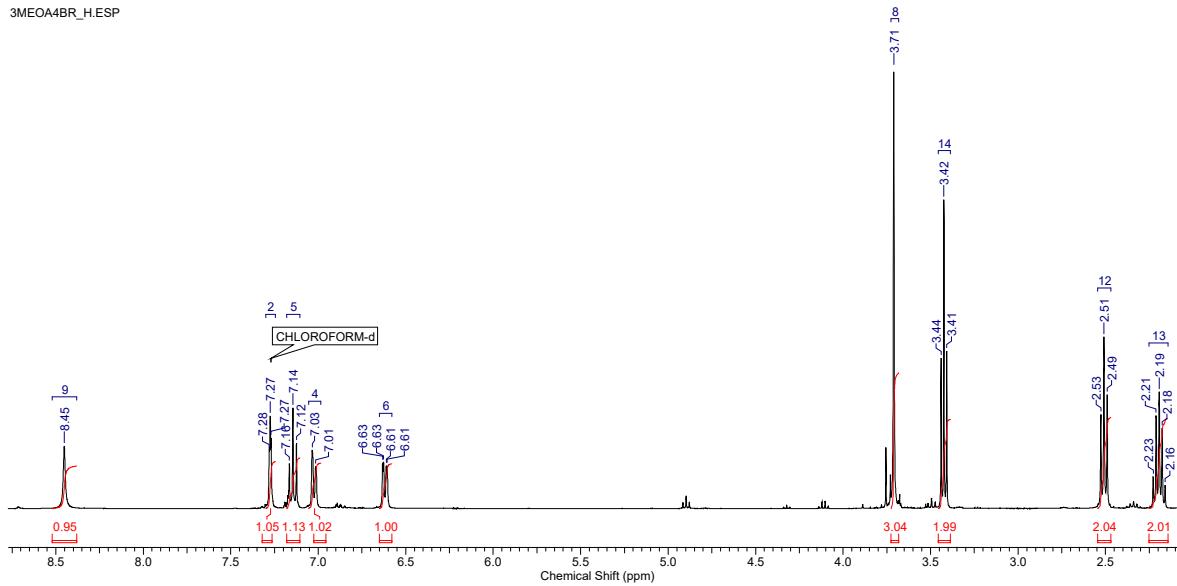
2.21 4-Bromo-N-(2-methoxyphenyl)butanamide 112



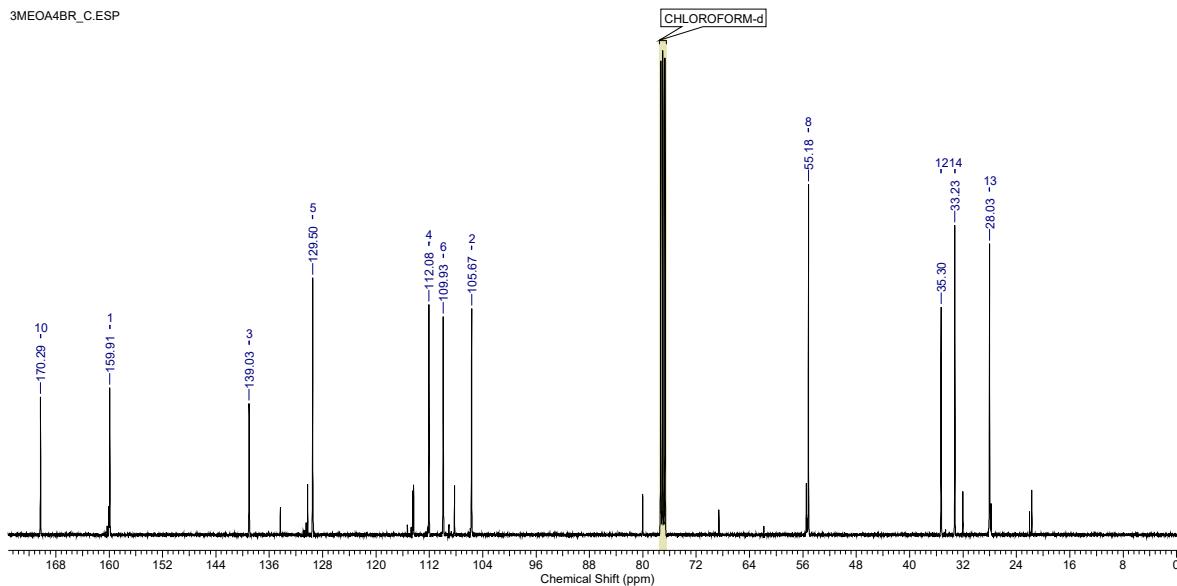
2.22 4-Bromo-N-(3-methoxyphenyl)butanamide 114



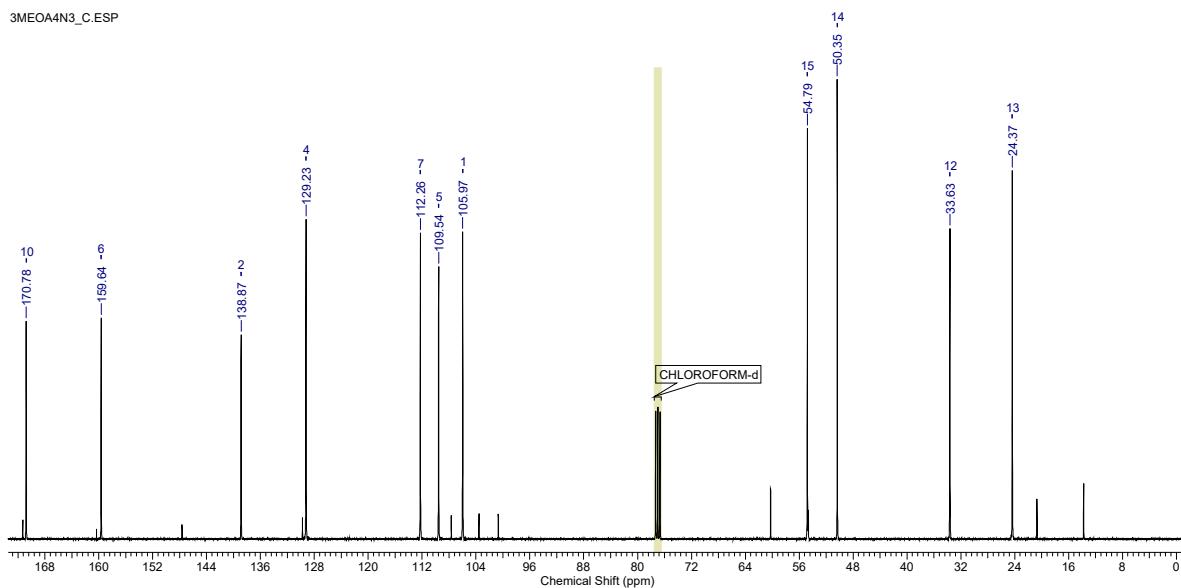
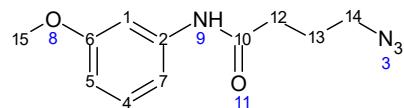
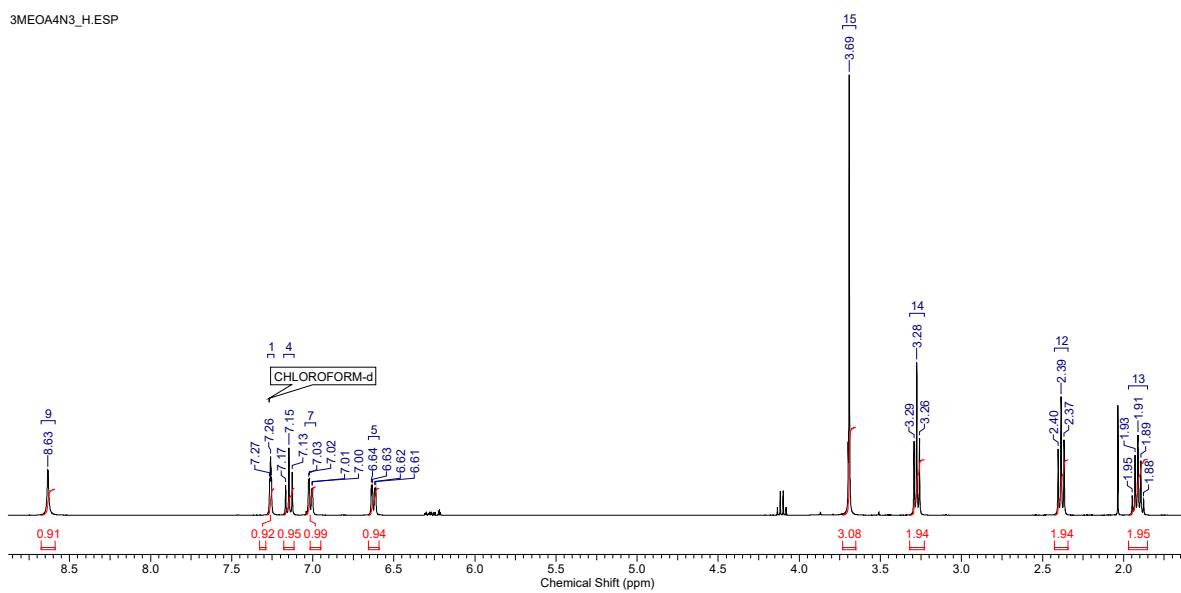
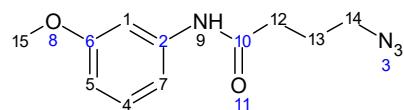
3MEOA4BR_H.ESP



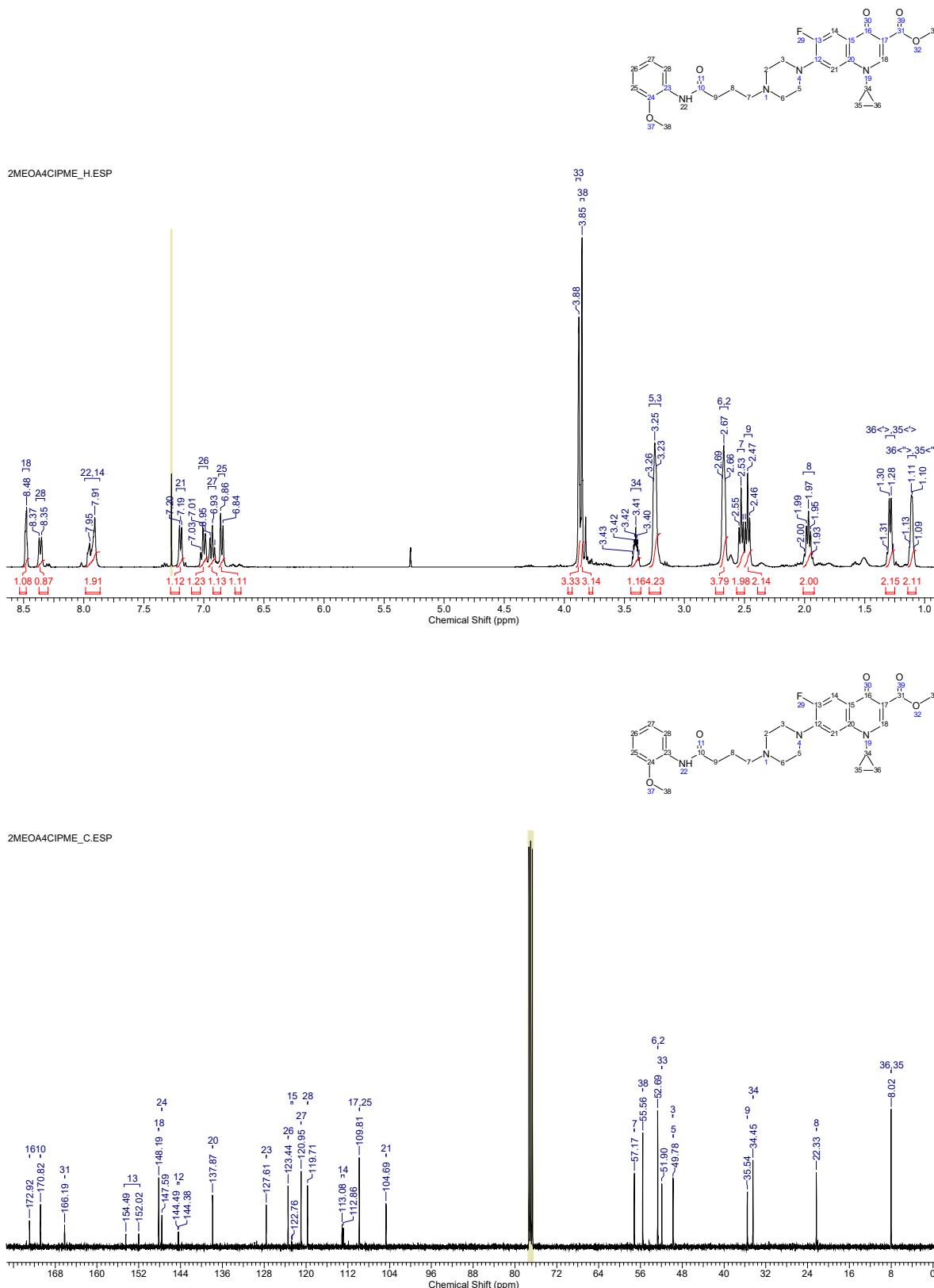
3MEOA4BR_C.ESP



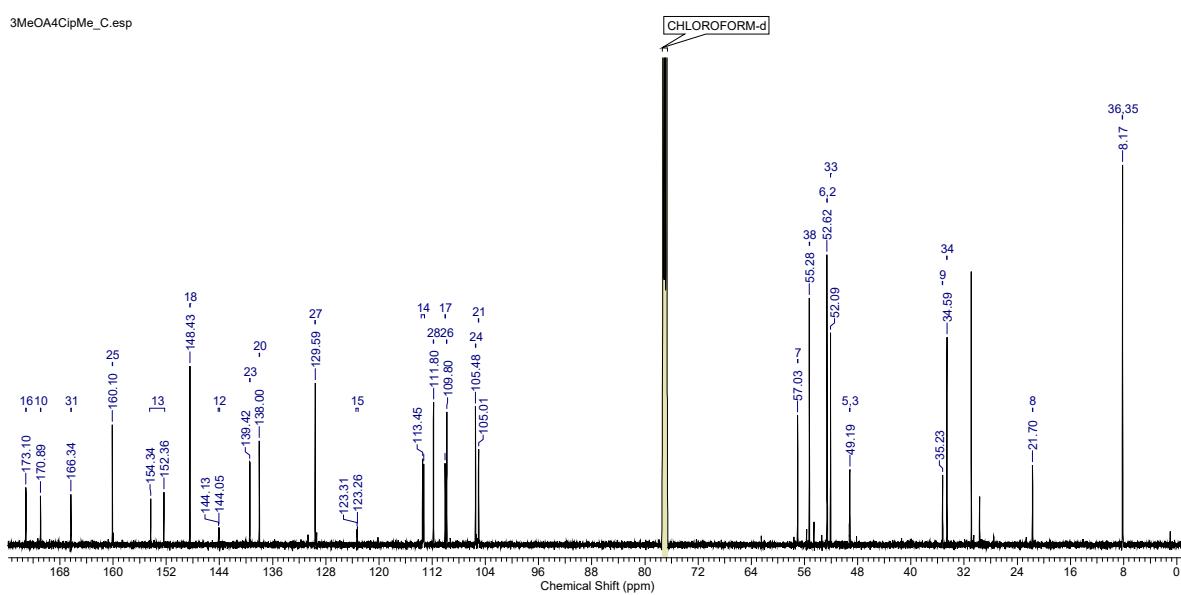
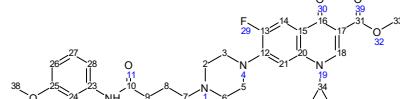
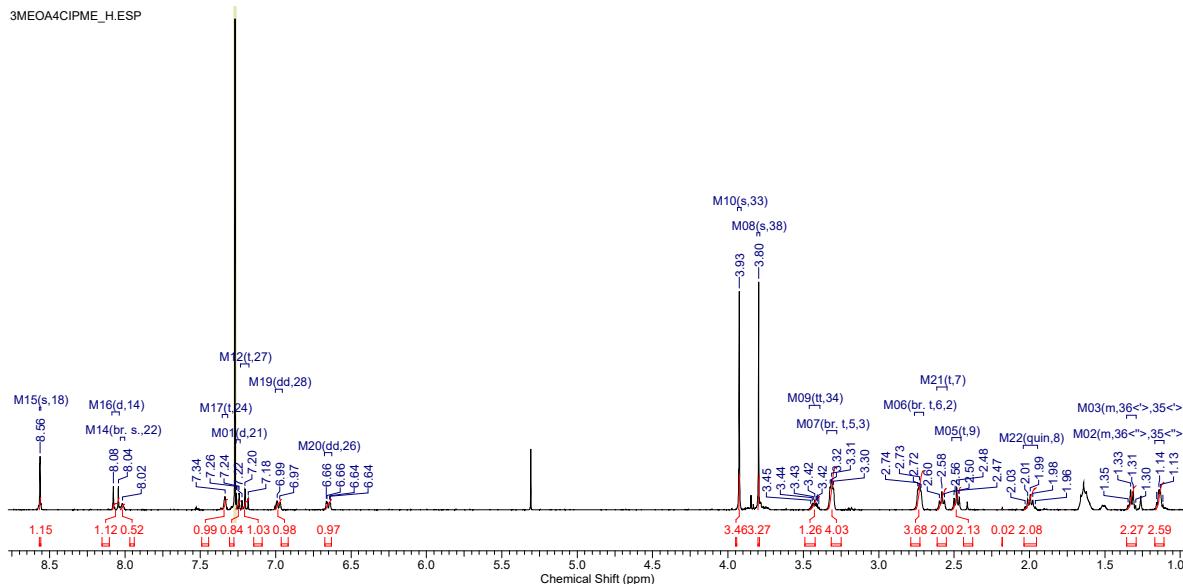
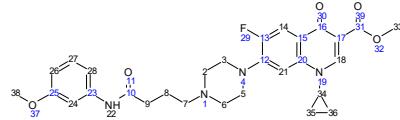
2.23 4-Azido-*N*-(3-methoxyphenyl)butanamide 116



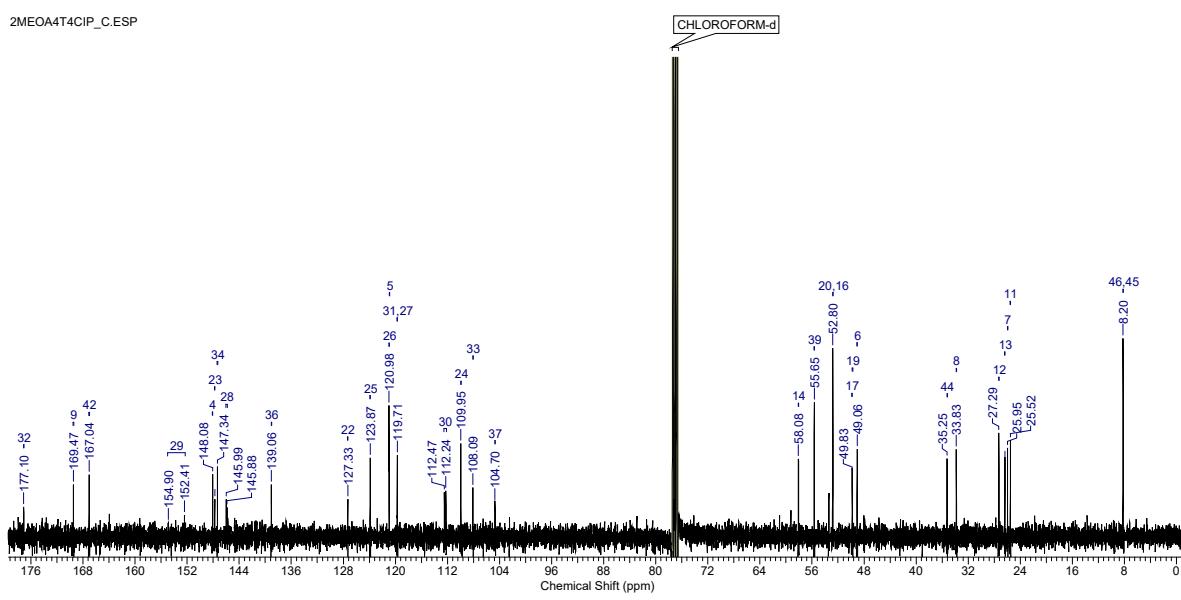
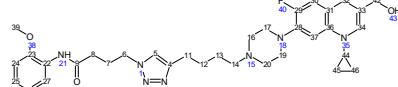
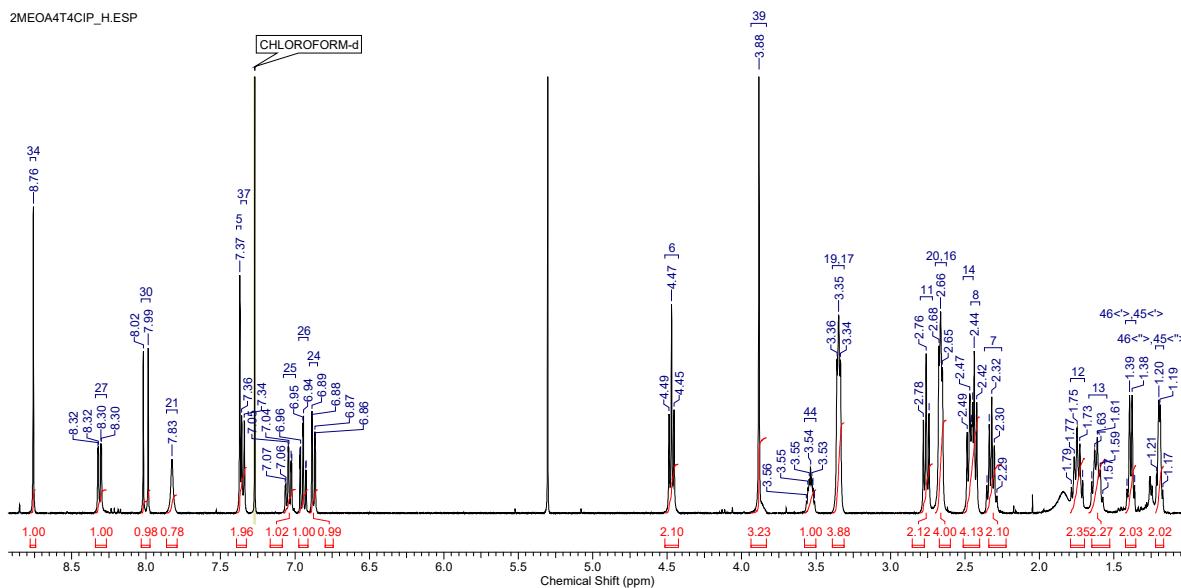
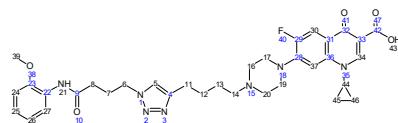
2.24 Methyl 1-cyclopropyl-6-fluoro-7-(4-((2-methoxyphenyl)amino)-4-oxobutyl)-piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 117



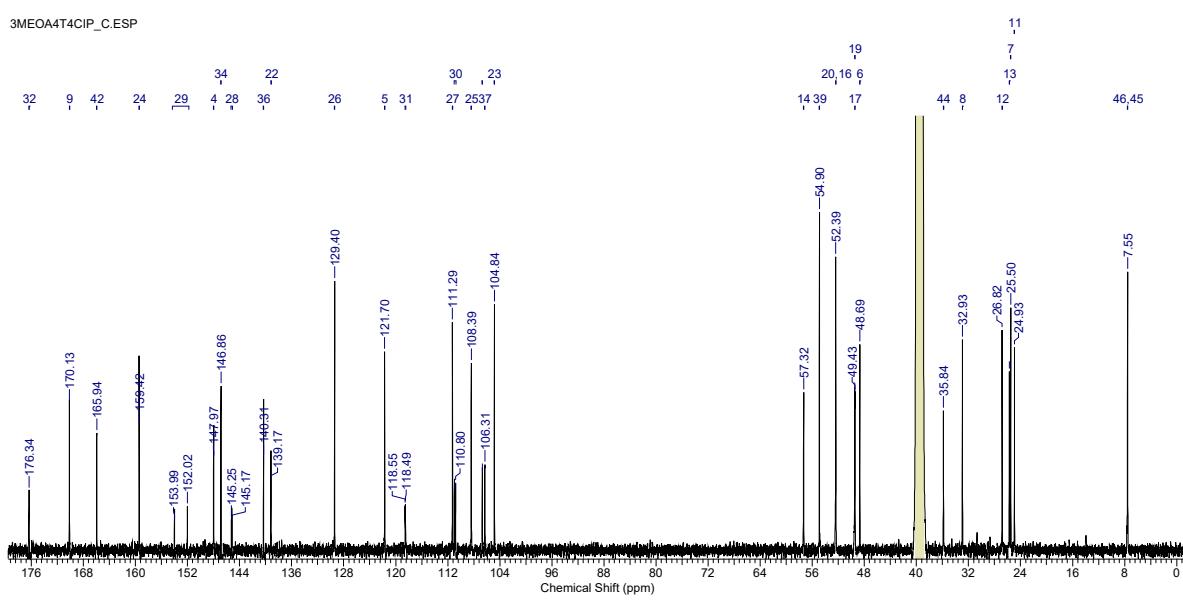
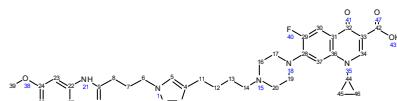
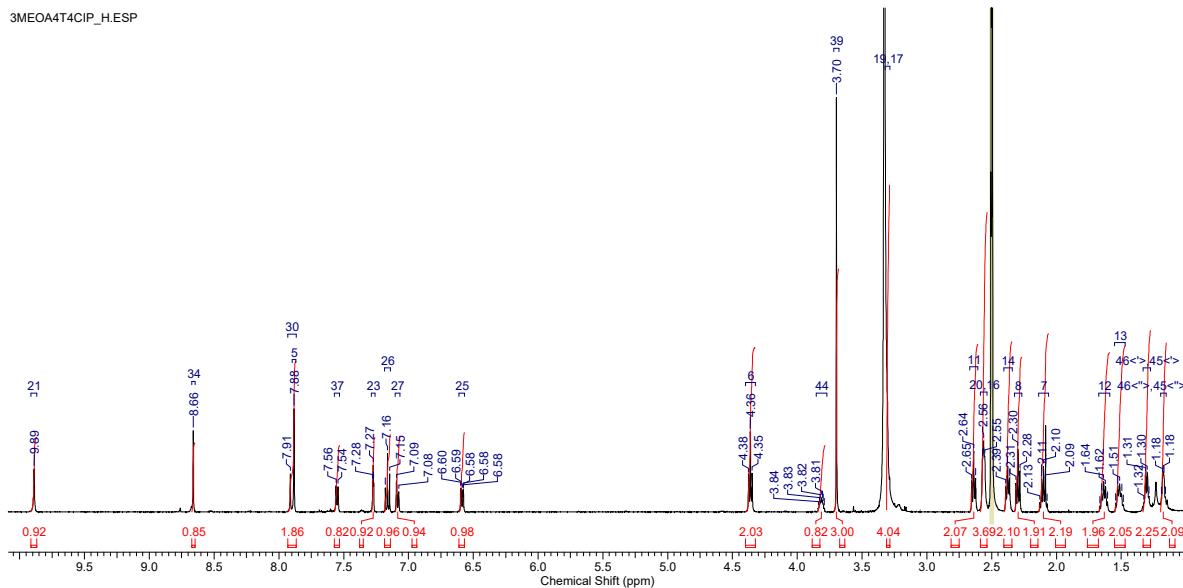
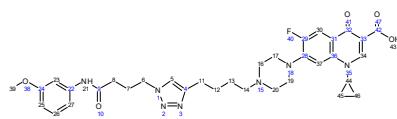
2.25 Methyl 1-cyclopropyl-6-fluoro-7-(4-(4-((3-methoxyphenyl)amino)-4-oxobutyl)-piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 118



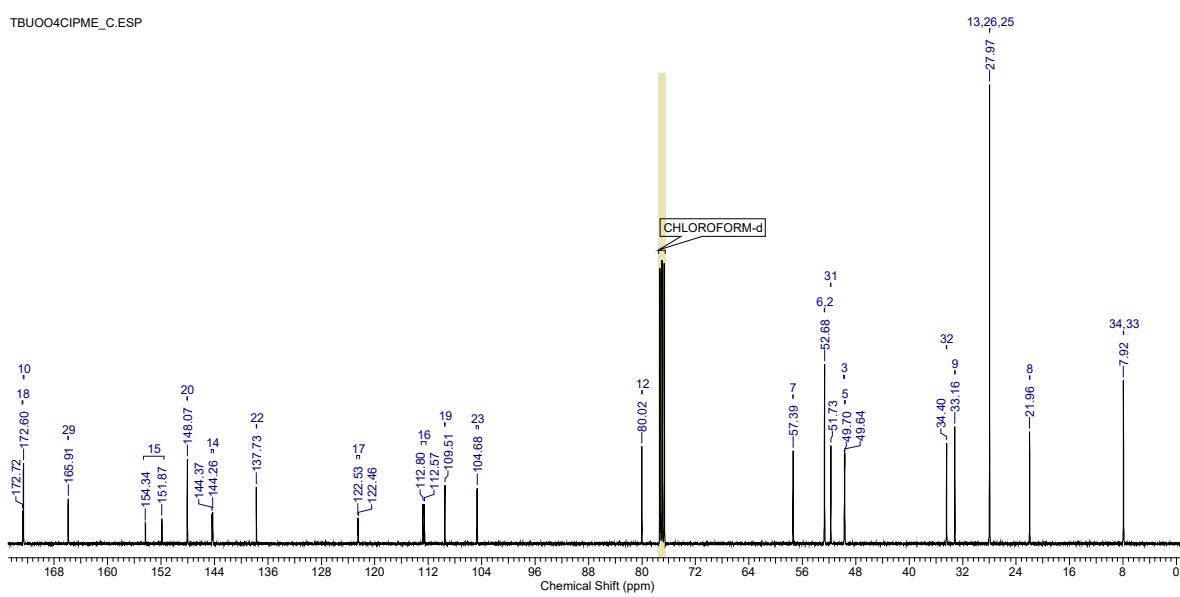
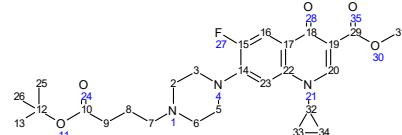
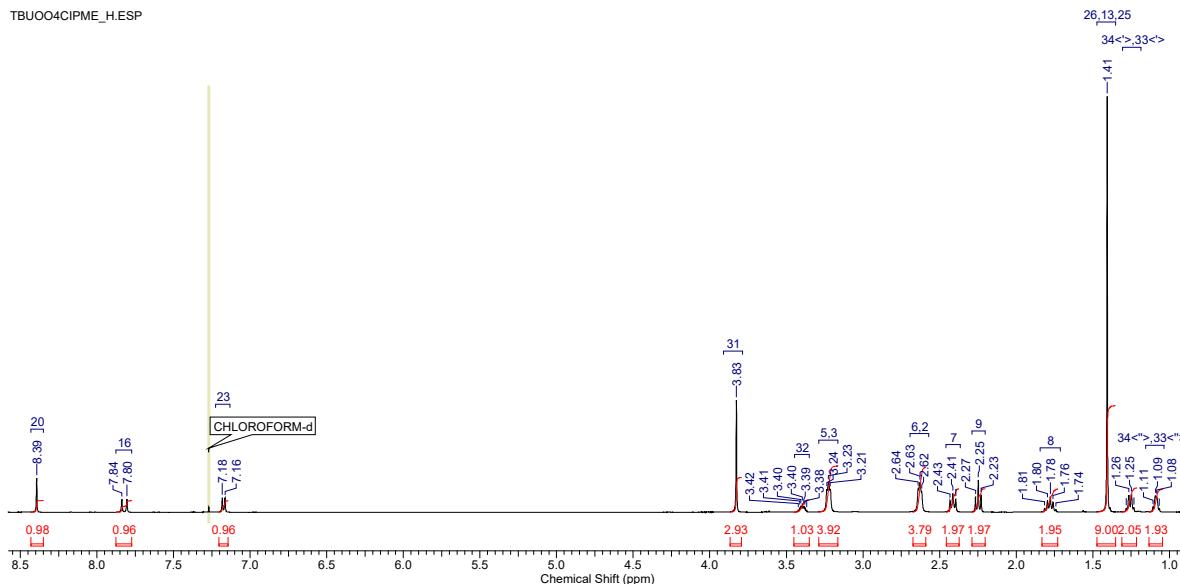
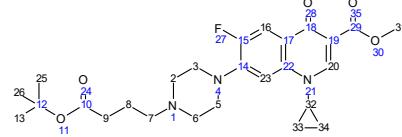
2.26 1-Cyclopropyl-6-fluoro-7-(4-(1-(4-((2-methoxyphenyl)amino)-4-oxobutyl)-1*H*-1,2,3-triazol-4-yl)butyl) piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 119



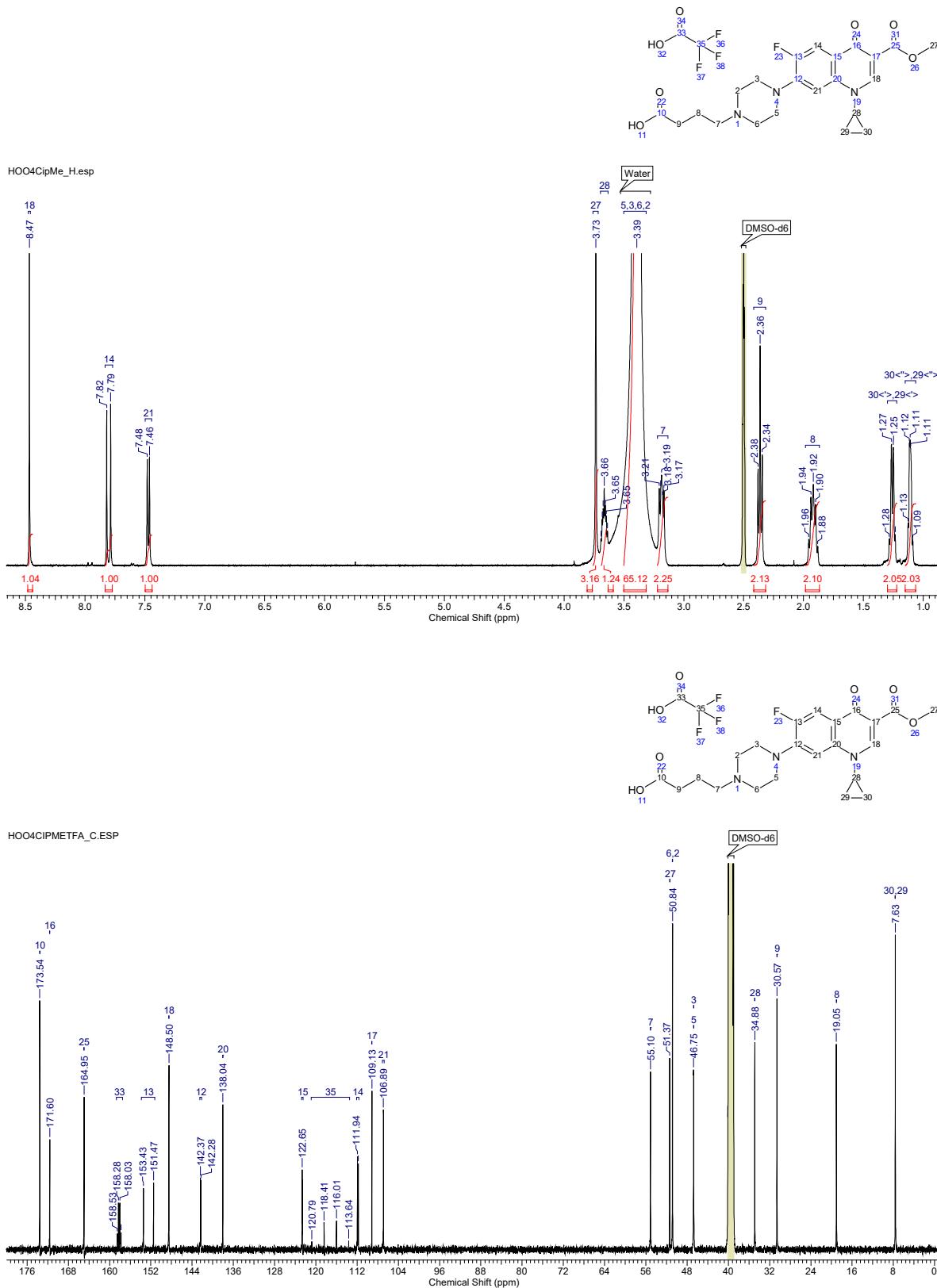
2.27 1-Cyclopropyl-6-fluoro-7-(4-(1-(4-((3-methoxyphenyl)amino)-4-oxobutyl)-1*H*-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 120



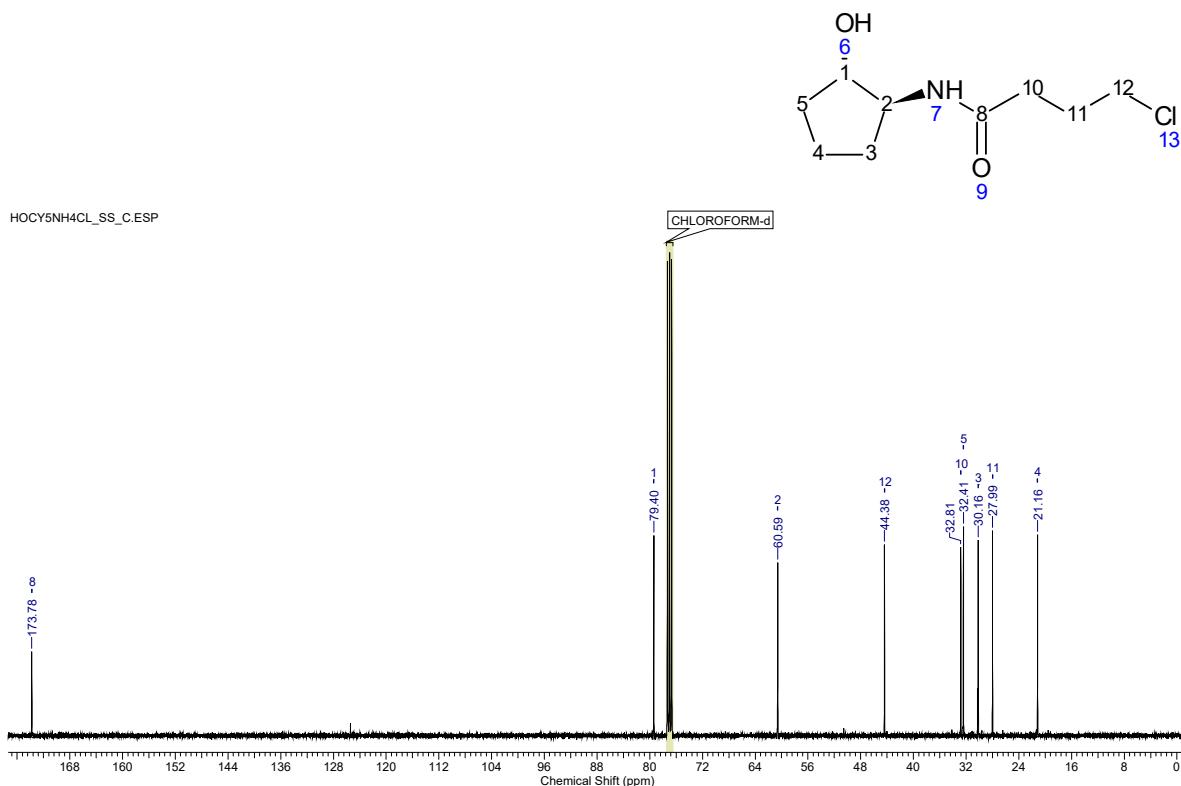
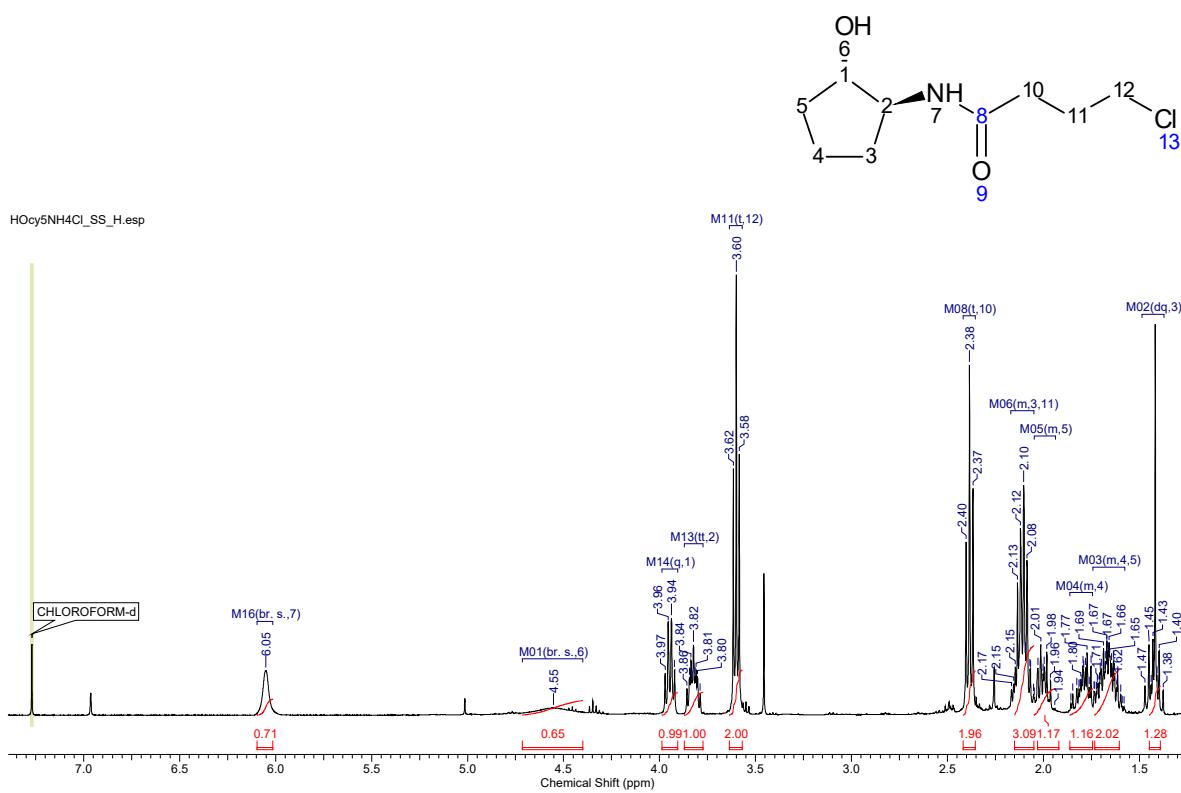
2.28 Methyl 7-(4-(*tert*-butoxy)-4-oxobutyl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate 122



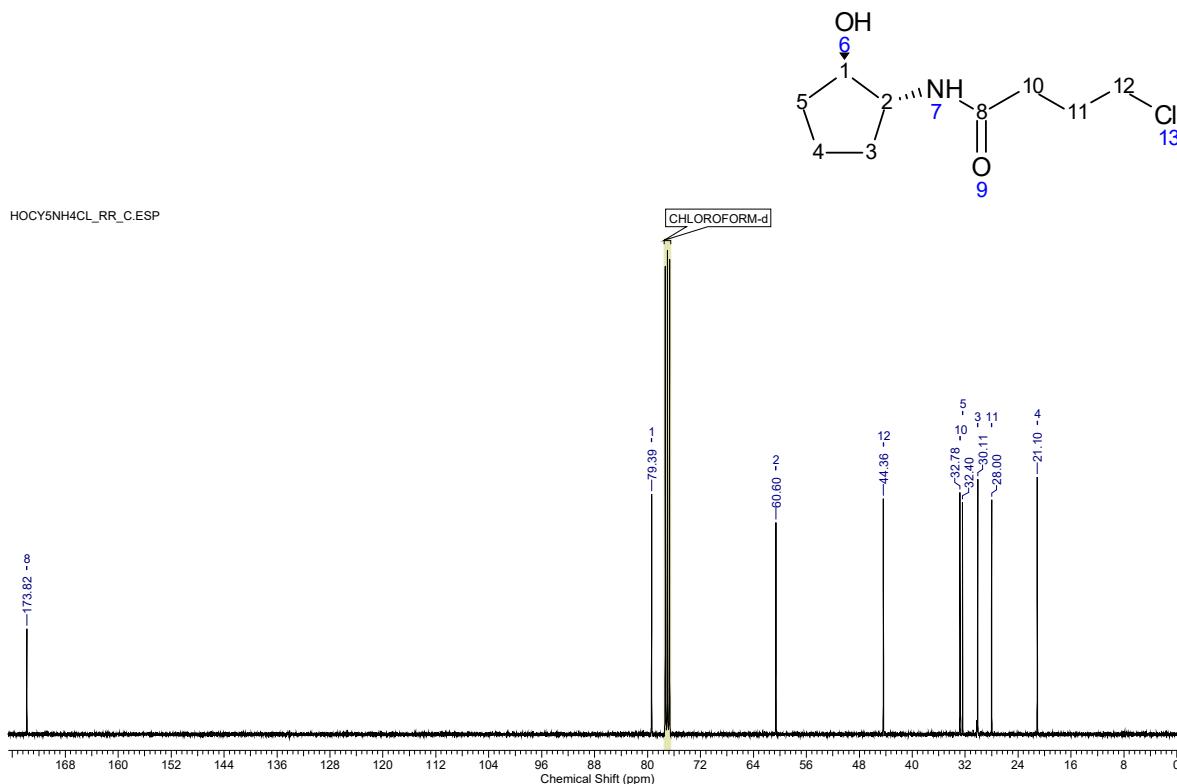
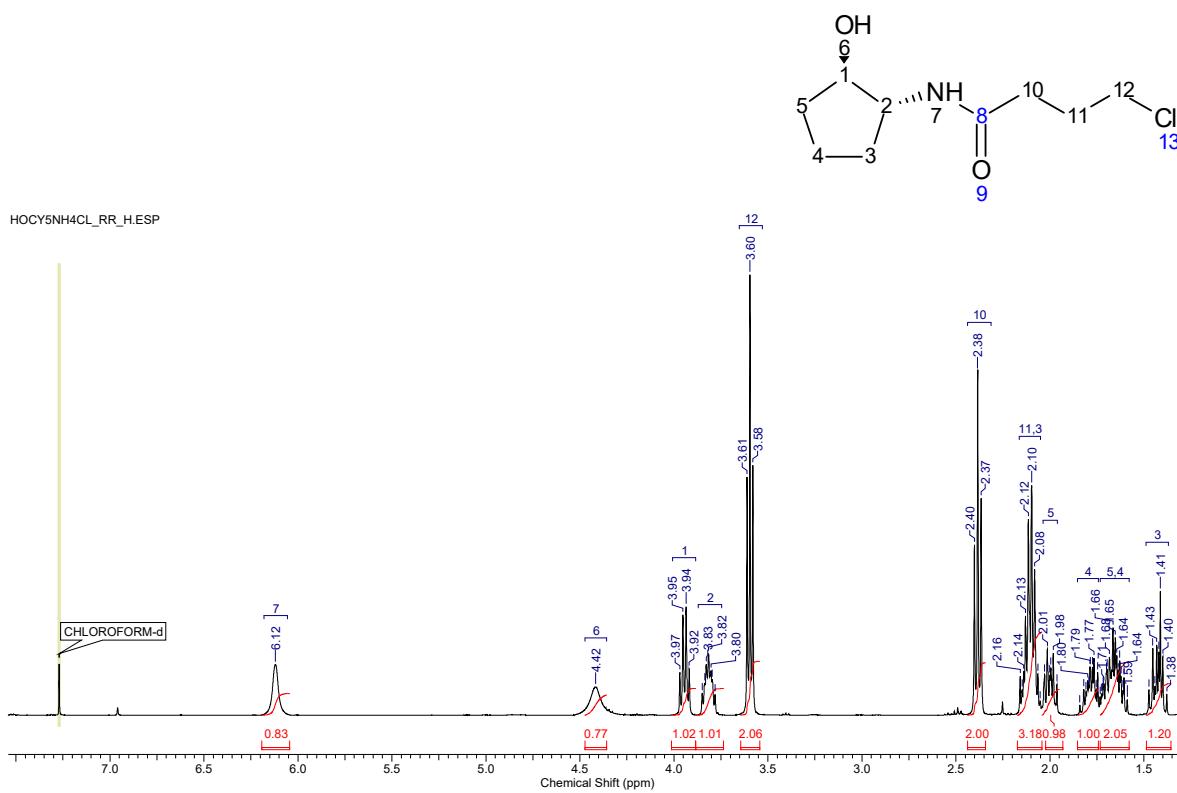
2.29 4-(4-(1-Cyclopropyl-6-fluoro-3-(methoxycarbonyl)-4-oxo-1,4-dihydroquinolin-7-yl)piperazin-1-yl)butanoic acid, trifluoroacetic acid salt 123



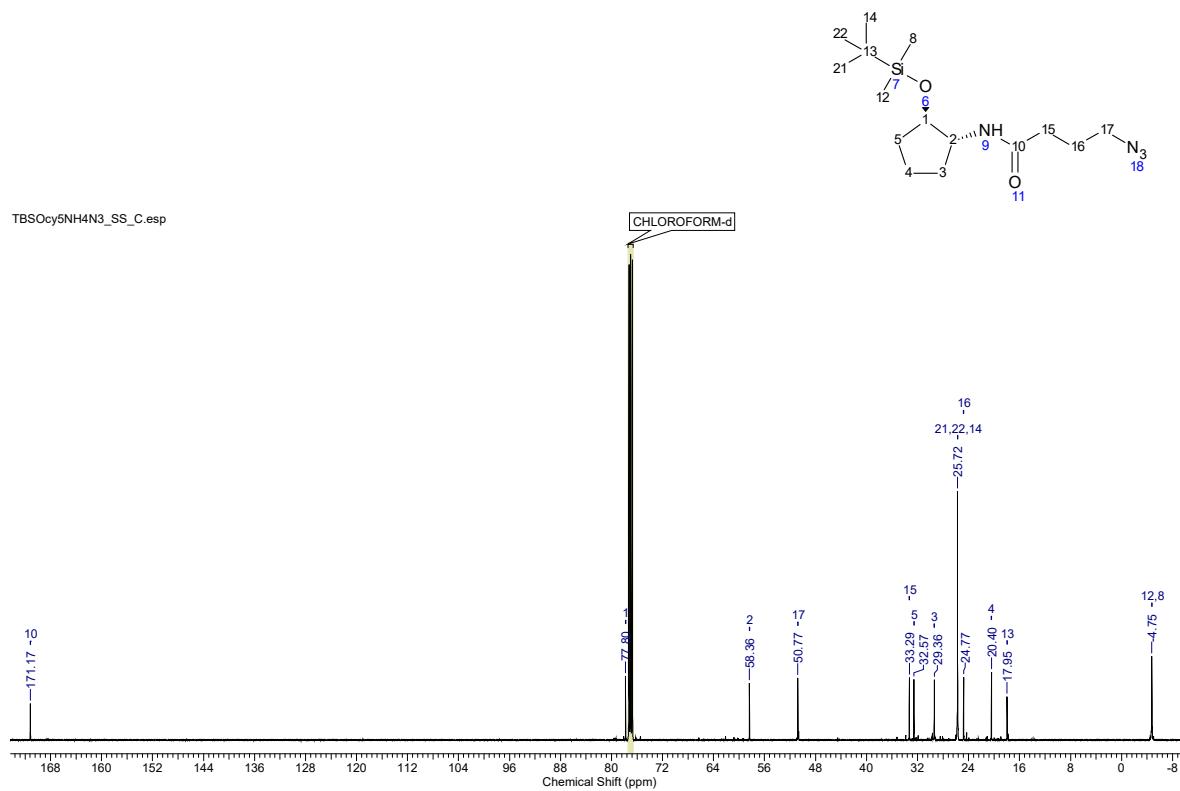
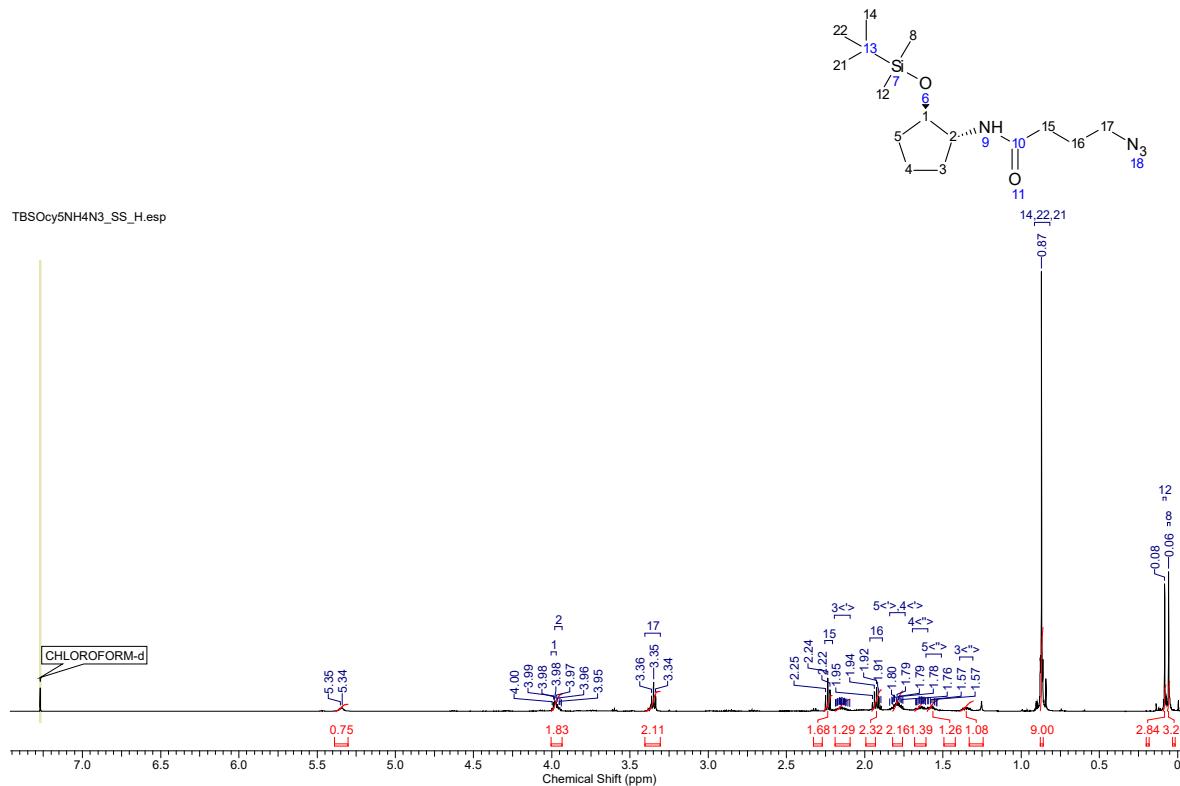
2.30 4-Chloro-*N*-((1*S*,2*S*)-2-hydroxycyclopentyl)butanamide 133



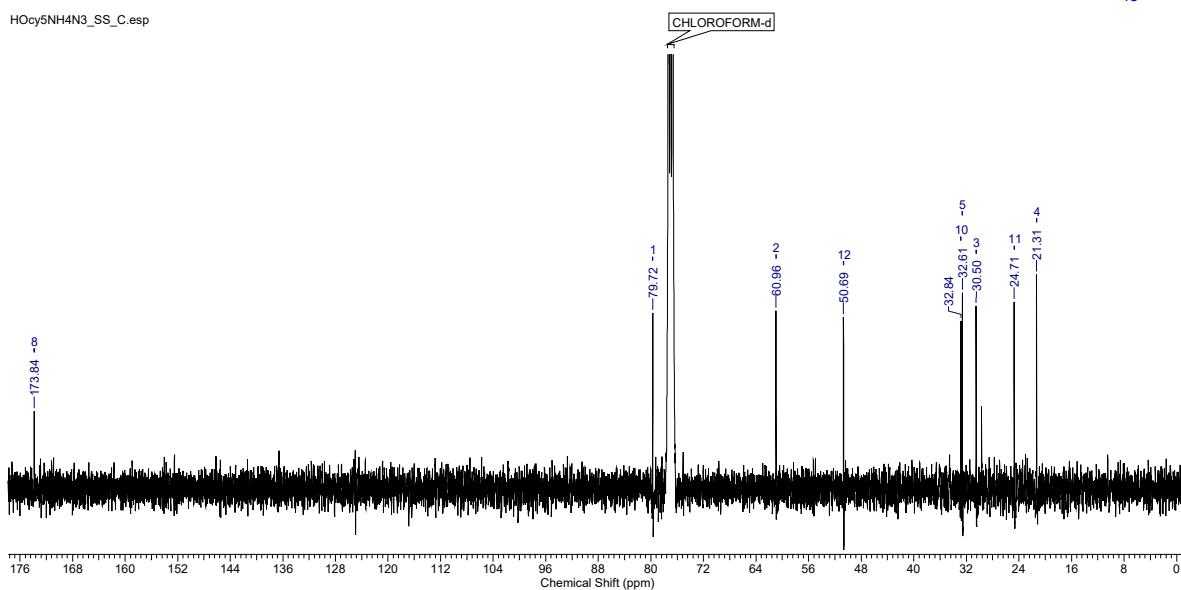
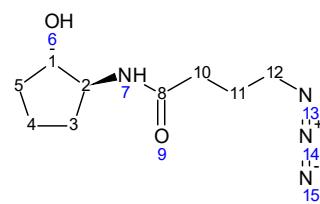
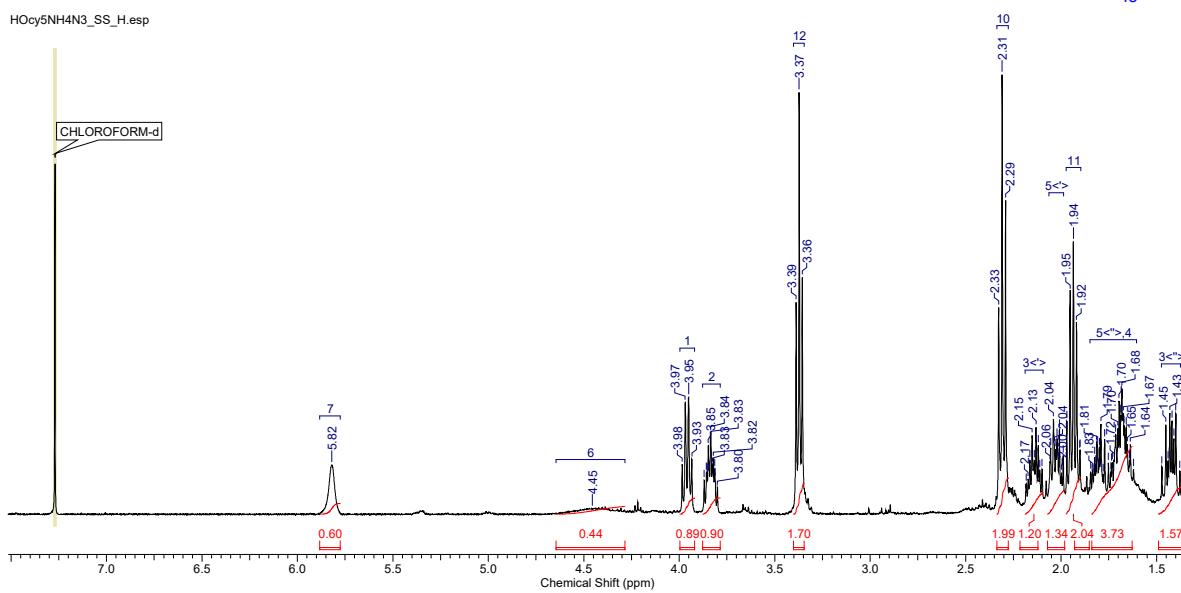
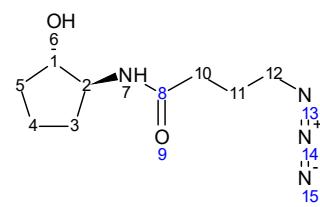
2.31 4-Chloro-*N*-(*1R,2R*)-2-hydroxycyclopentyl)butanamide 132



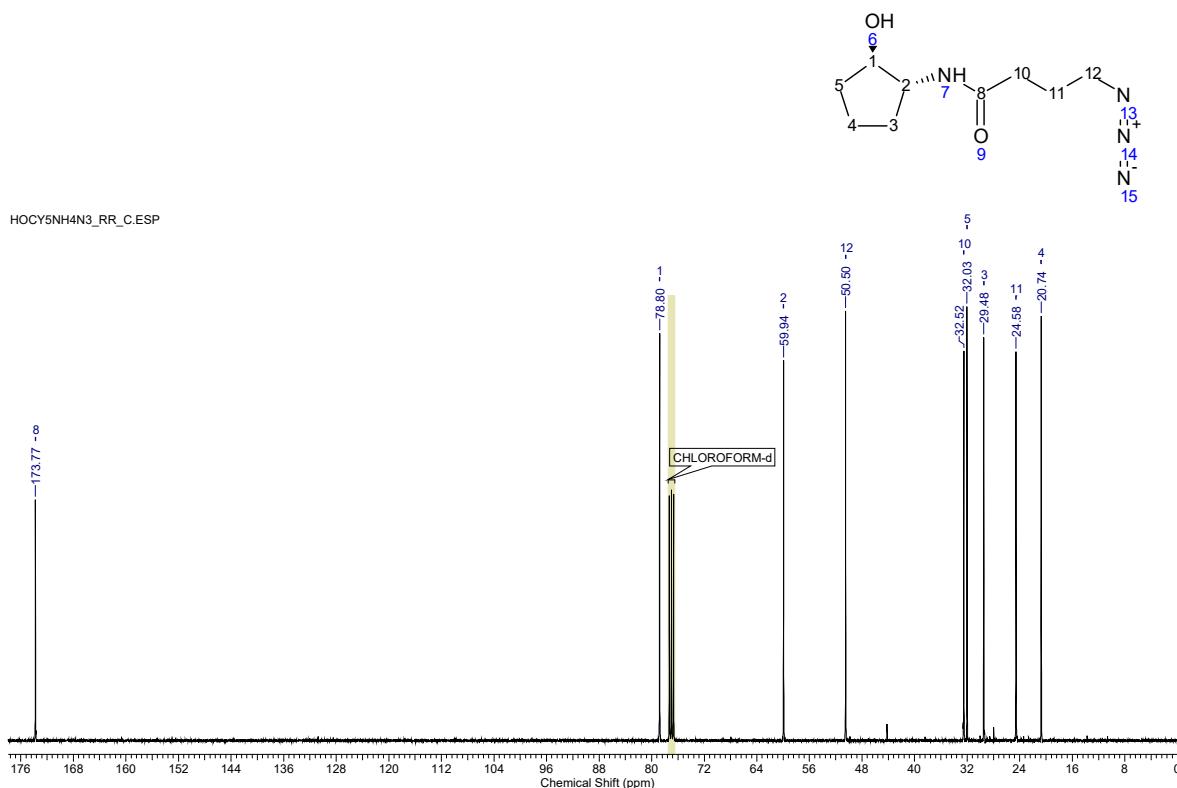
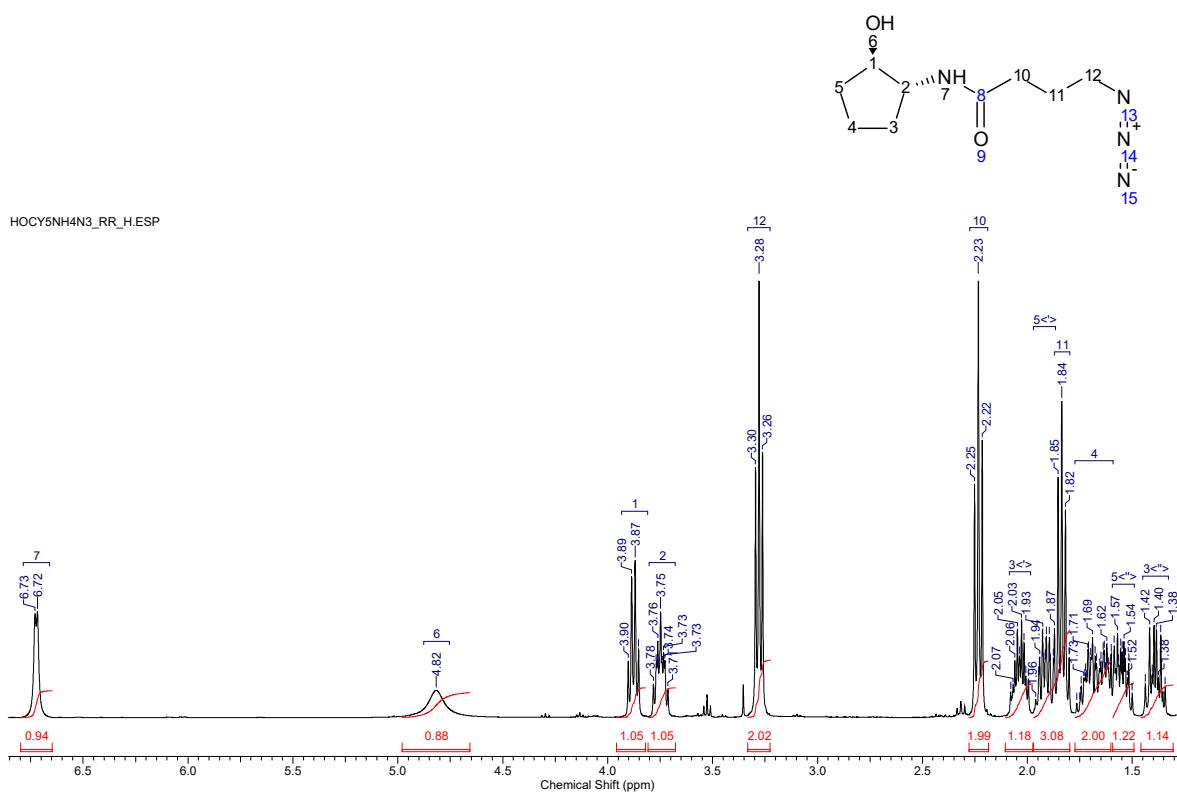
**2.32 4-Azido-*N*-((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclopentyl)butanamide
134**



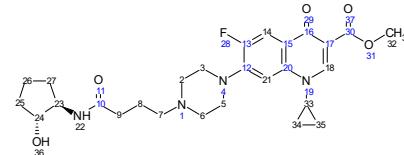
2.33 4-Azido-*N*-(*1S,2S*)-2-hydroxycyclopentyl)butanamide 136



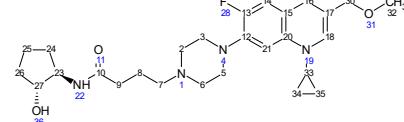
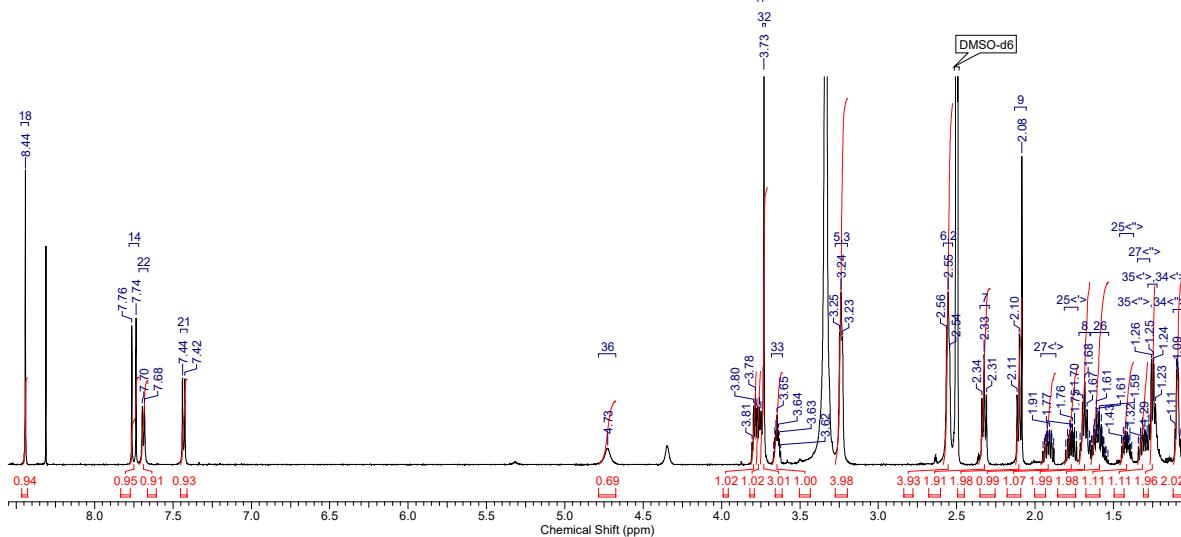
2.34 4-Azido-*N*-(*(1R,2R)*-2-hydroxycyclopentyl)butanamide 135



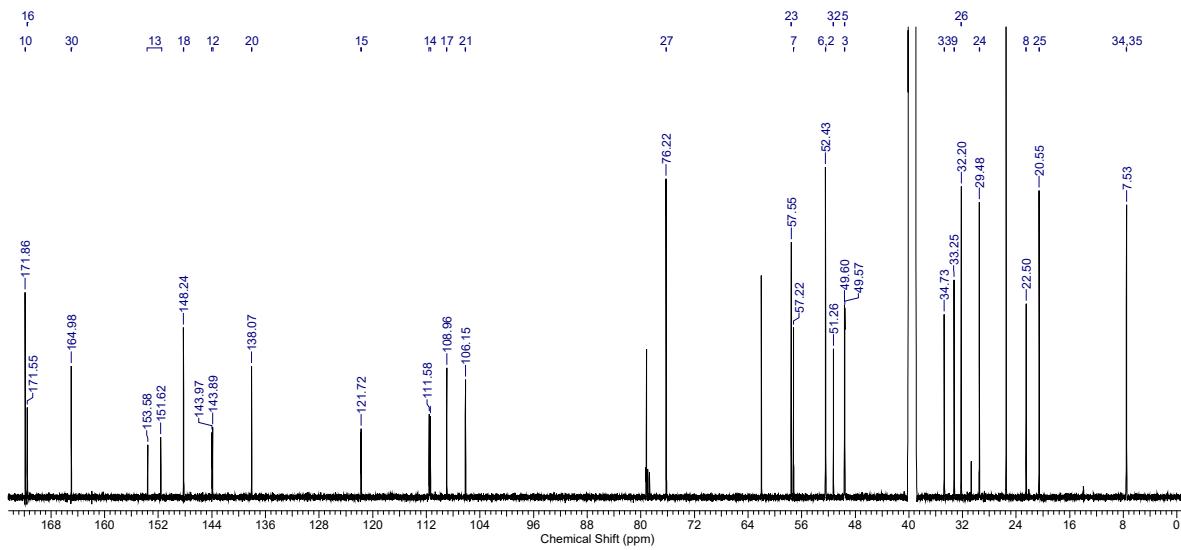
2.35 Methyl 1-cyclopropyl-6-fluoro-7-(4-((1*S*,2*S*)-2-hydroxycyclopentyl)amino)-4-oxobutyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 138



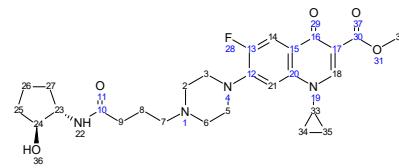
HOcy5NH4CipMe_SS_H.esp



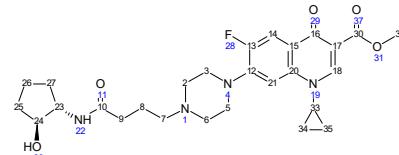
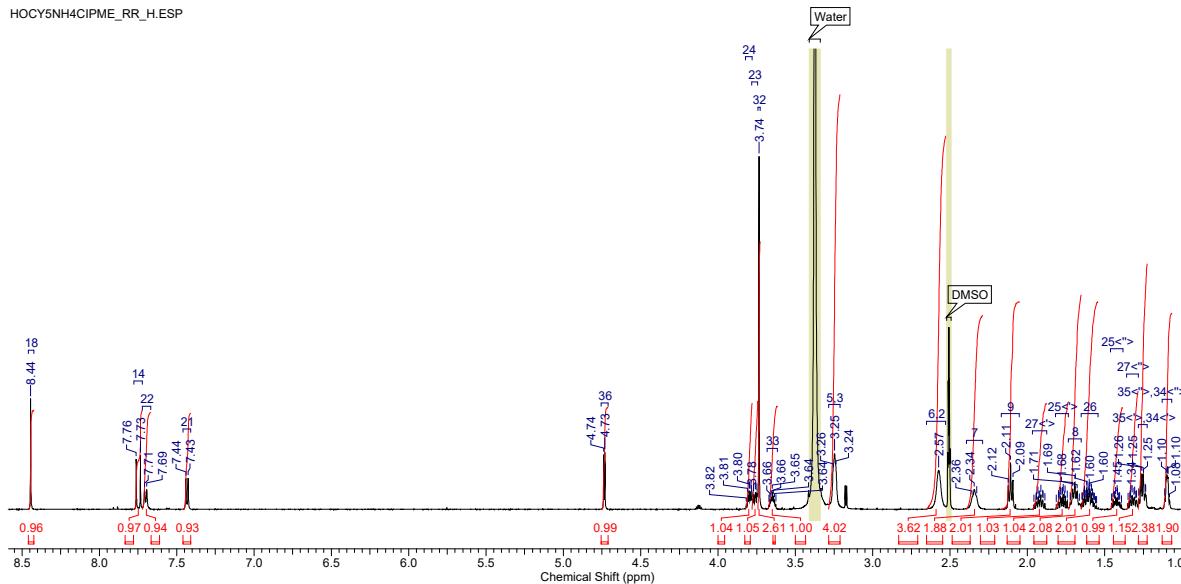
HOcy5NH4CipMe_SS_C.esp



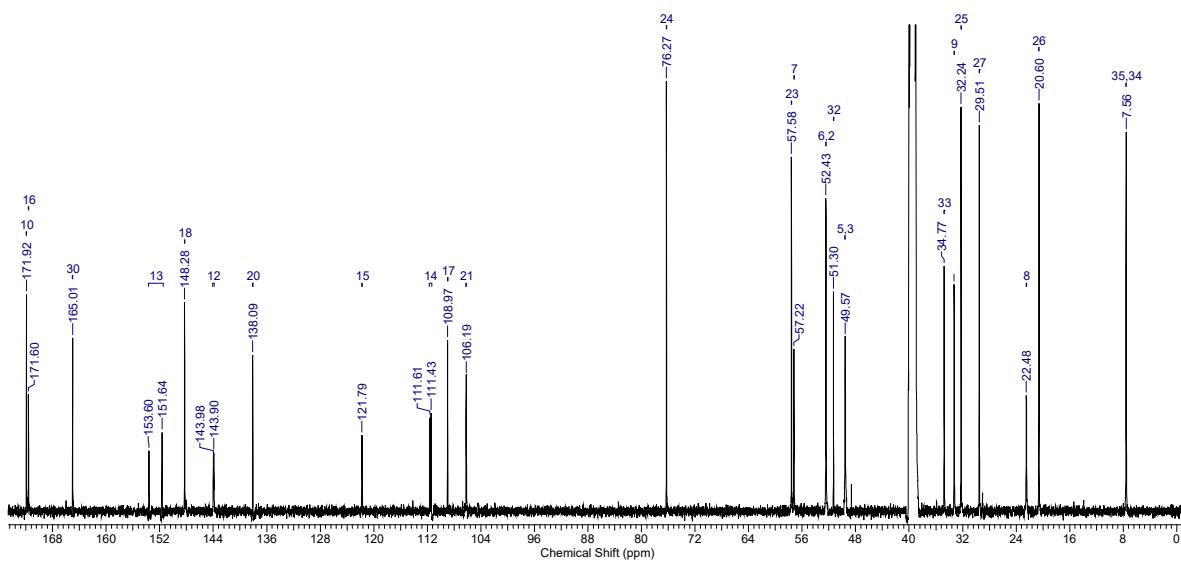
2.36 Methyl 1-cyclopropyl-6-fluoro-7-(4-((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-4-oxobutyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 137



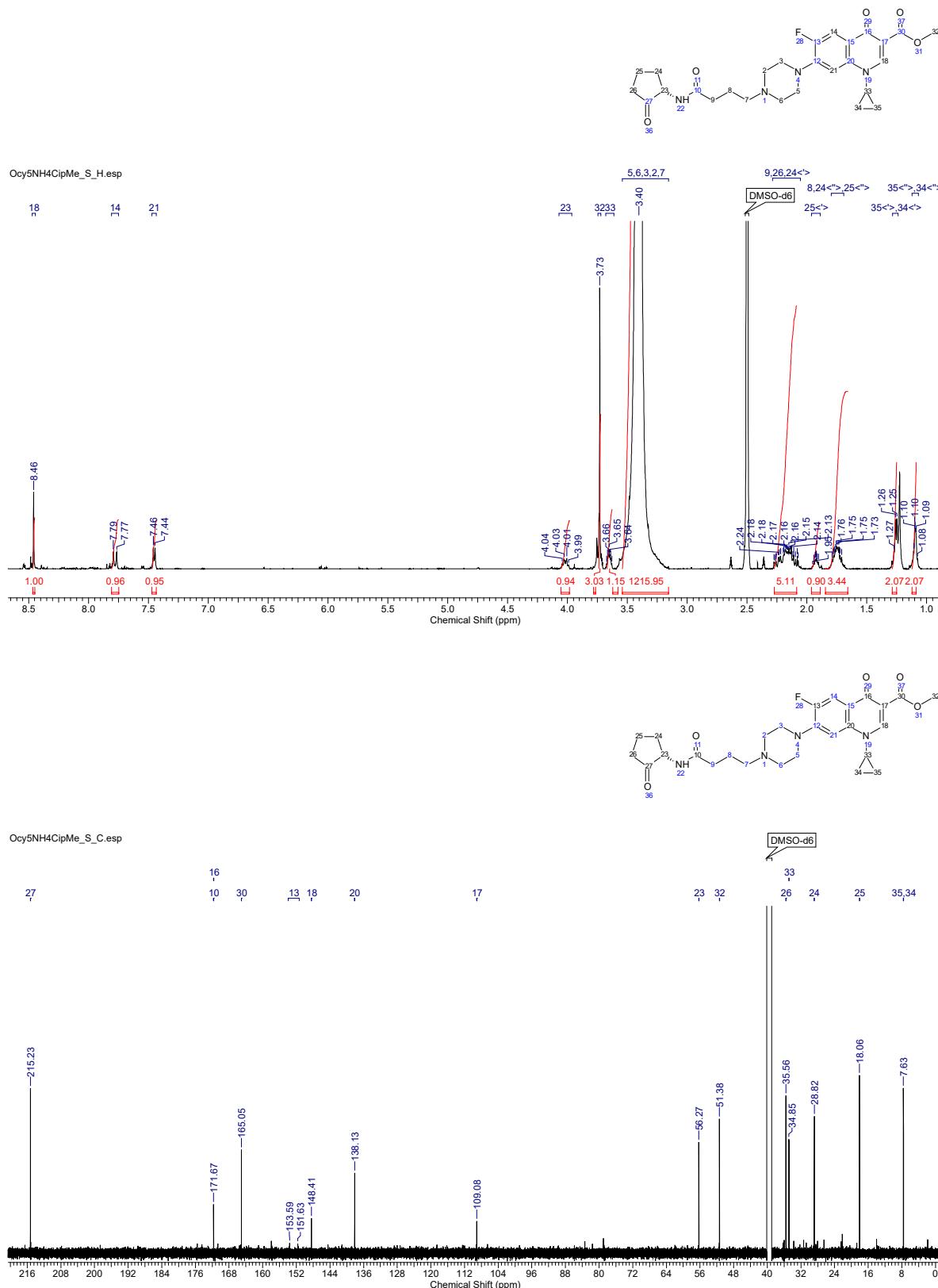
HO CY5 NH4 CIP ME_RR_H.ESP



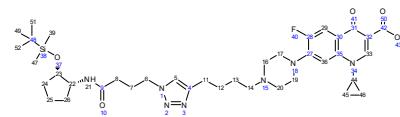
HOcy5NH4CipMe RR C.esp



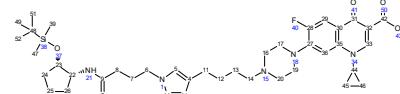
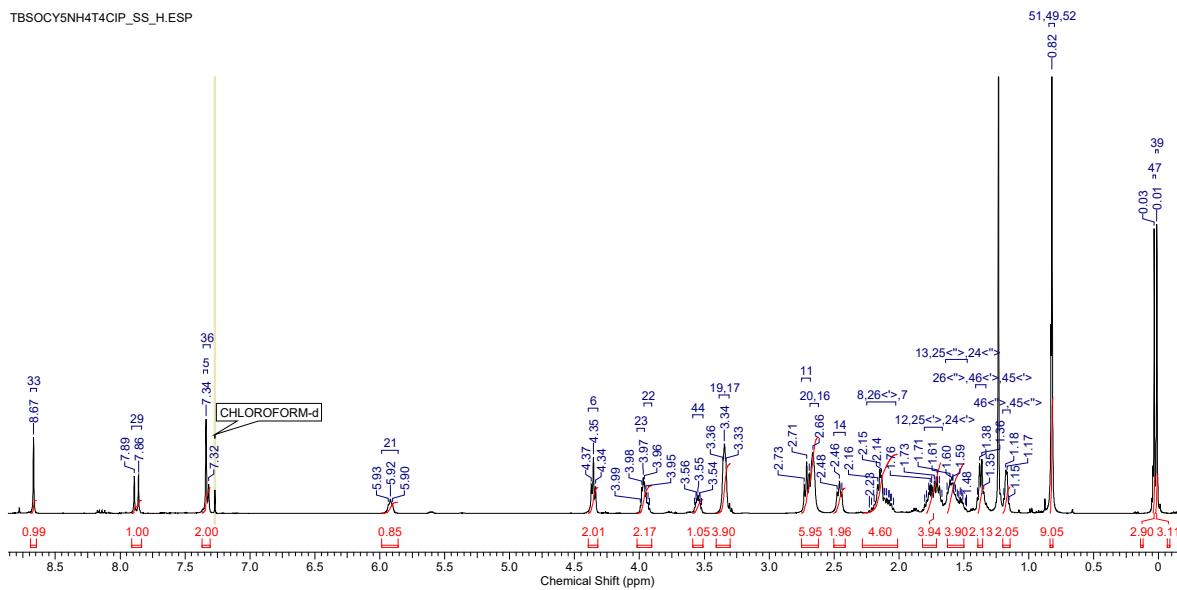
2.37 Methyl (S)-1-cyclopropyl-6-fluoro-4-oxo-7-(4-(4-oxo-4-((2-oxocyclopentyl)amino)butyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate 152



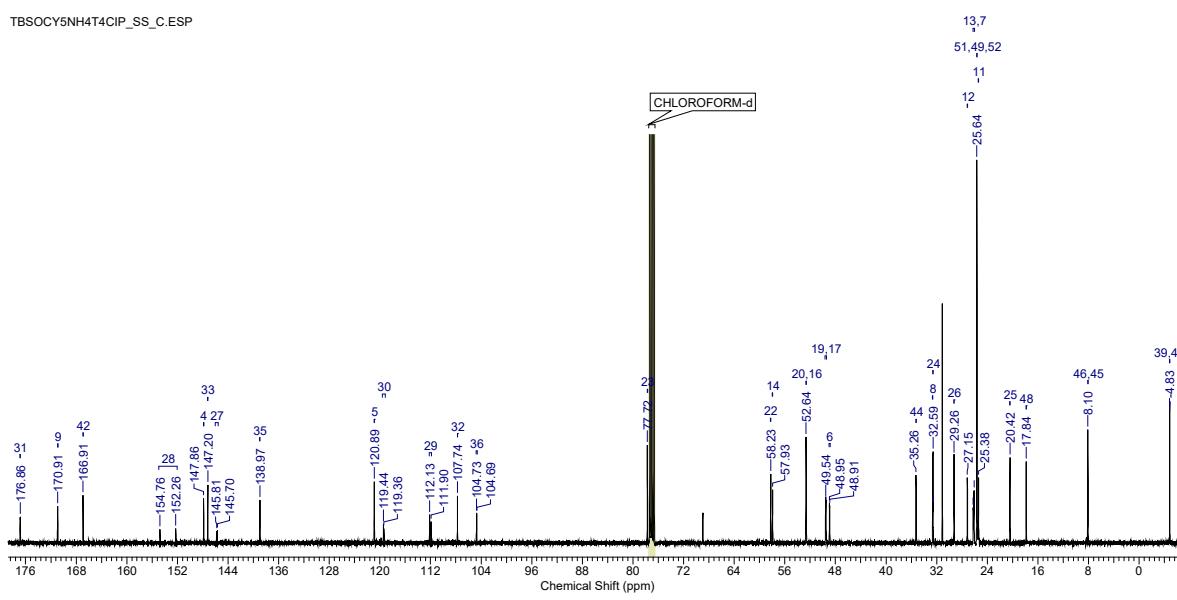
2.38 7-(4-(4-(1-(4-(((1*S*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)cyclopentyl)amino)-4-oxobutyl)-1*H*-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 140



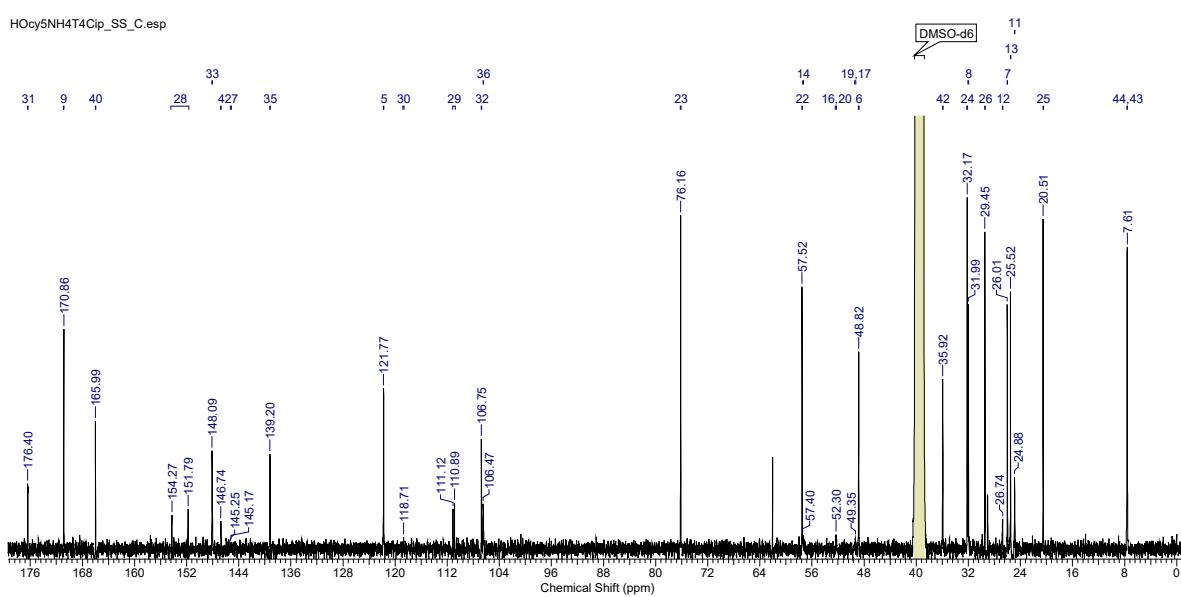
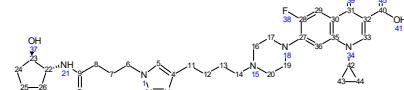
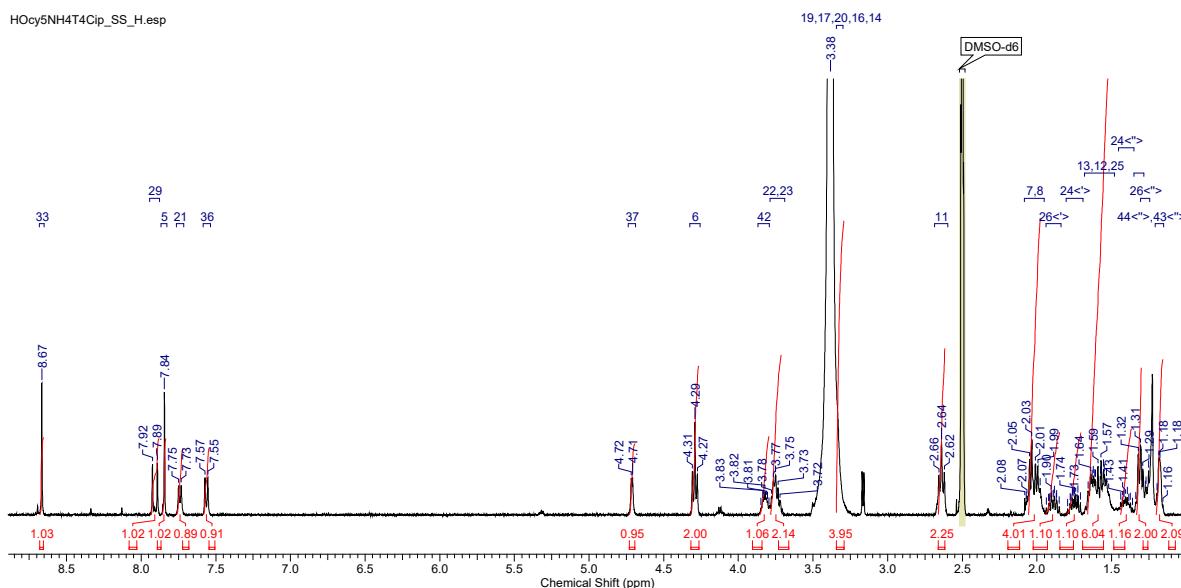
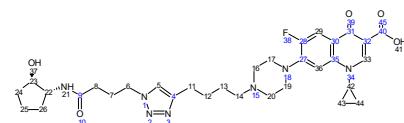
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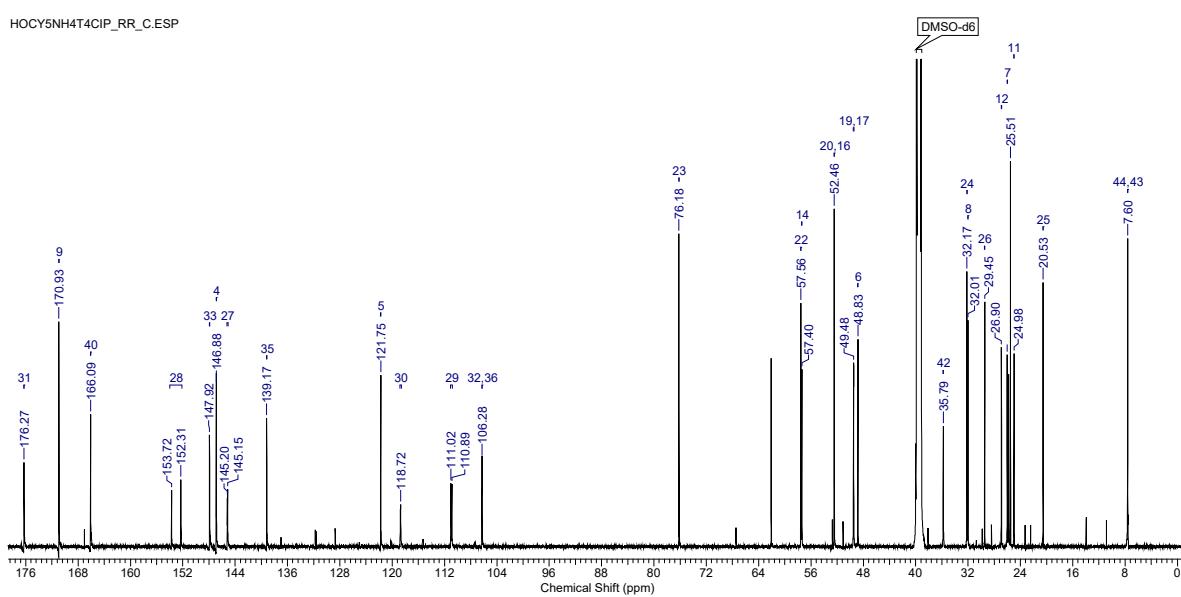
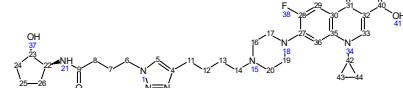
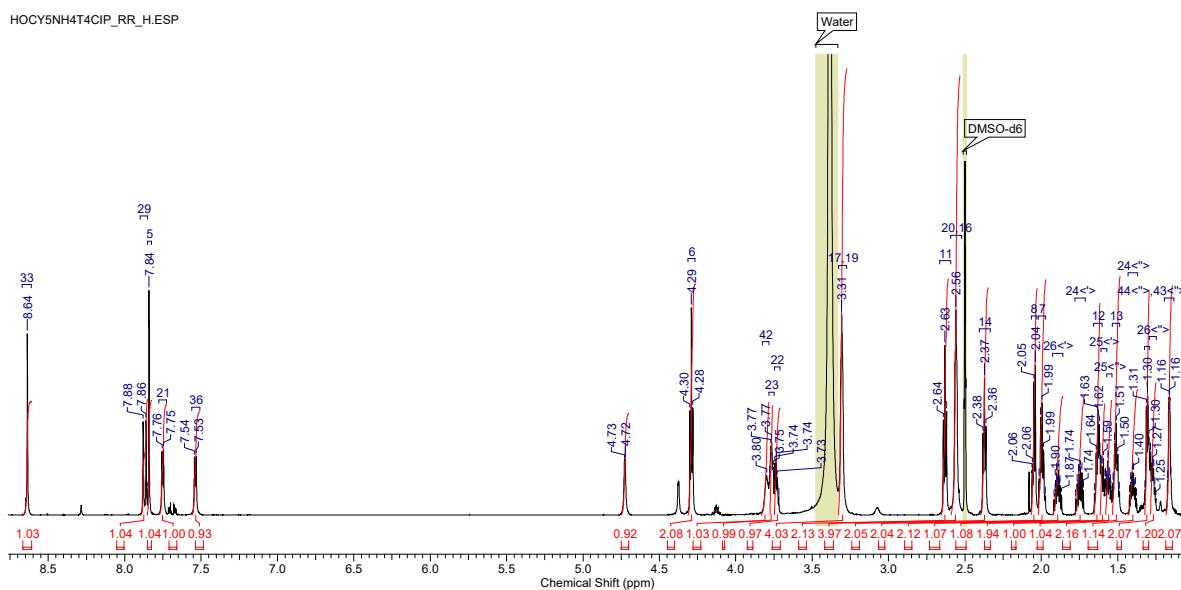
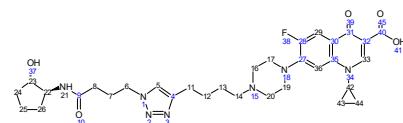
TBSOCY5NH4T4CIP SS C.ESP



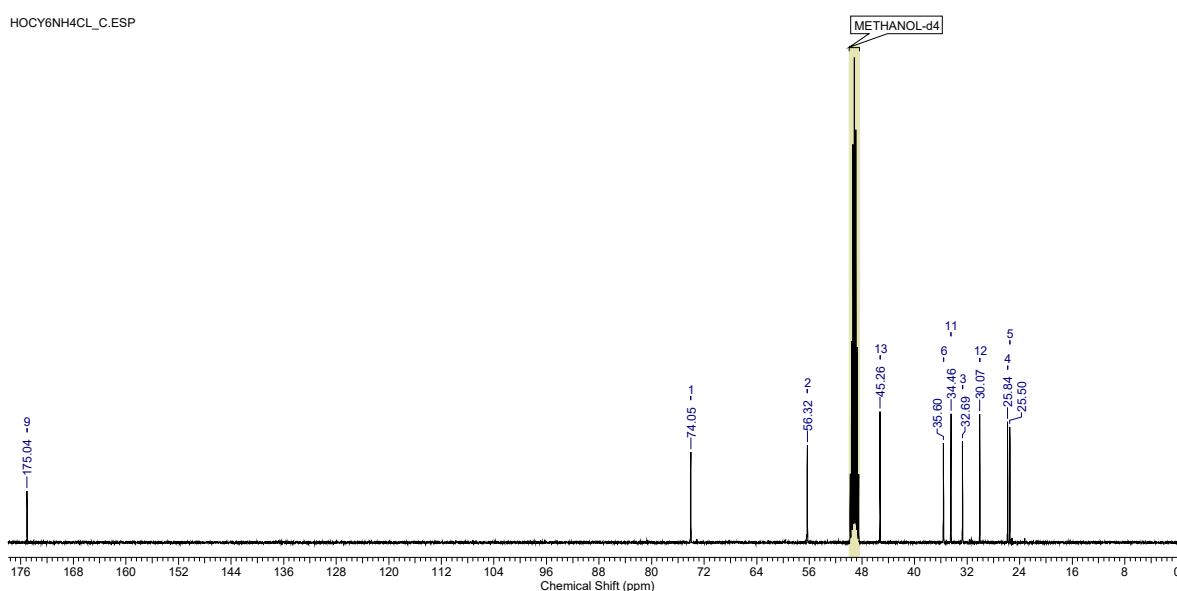
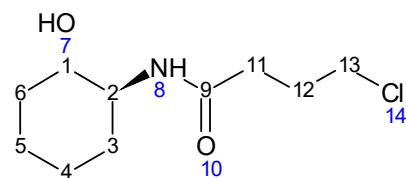
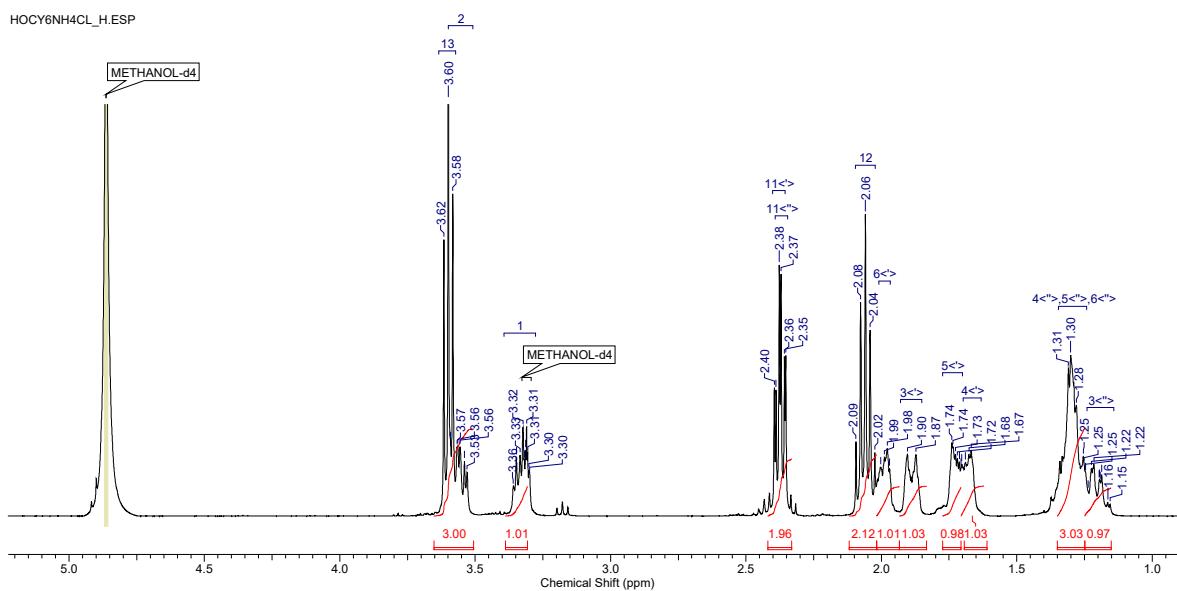
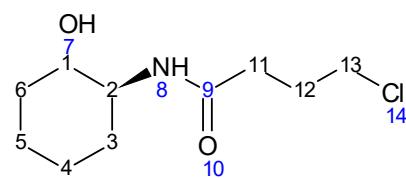
2.39 1-Cyclopropyl-6-fluoro-7-(4-(1-(4-(((1*S*,2*S*)-2-hydroxycyclopentyl)amino)-4-oxobutyl)-1*H*-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-4-oxo-1,4-dihydroquino-line-3-carboxylic acid 142



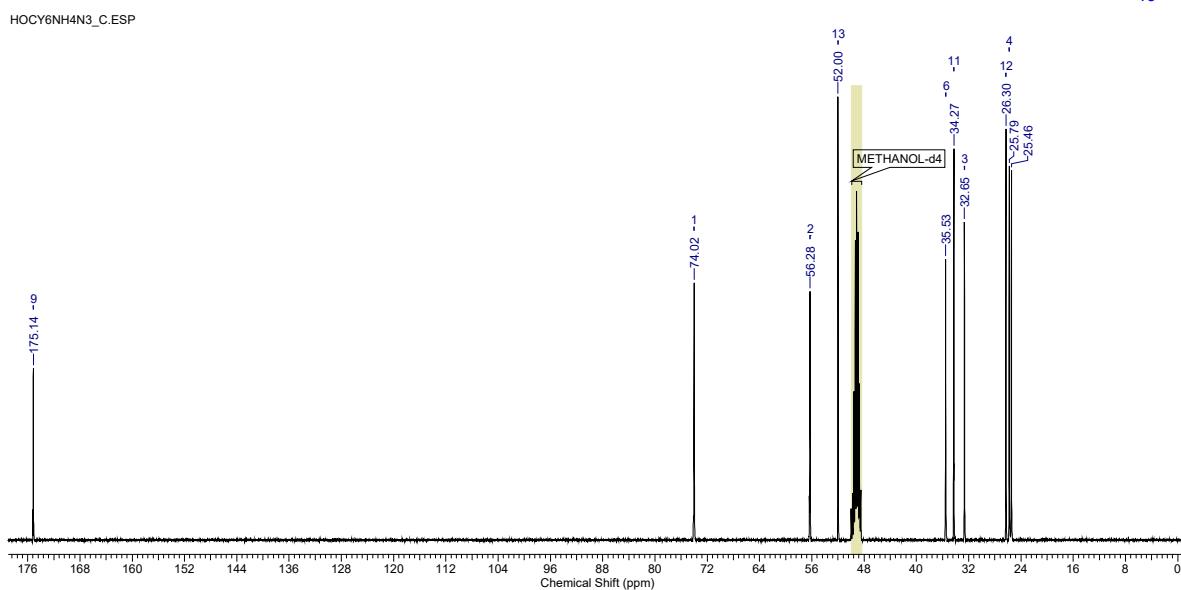
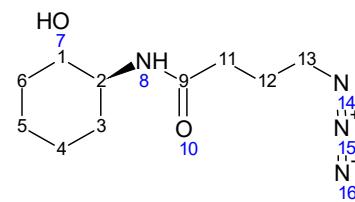
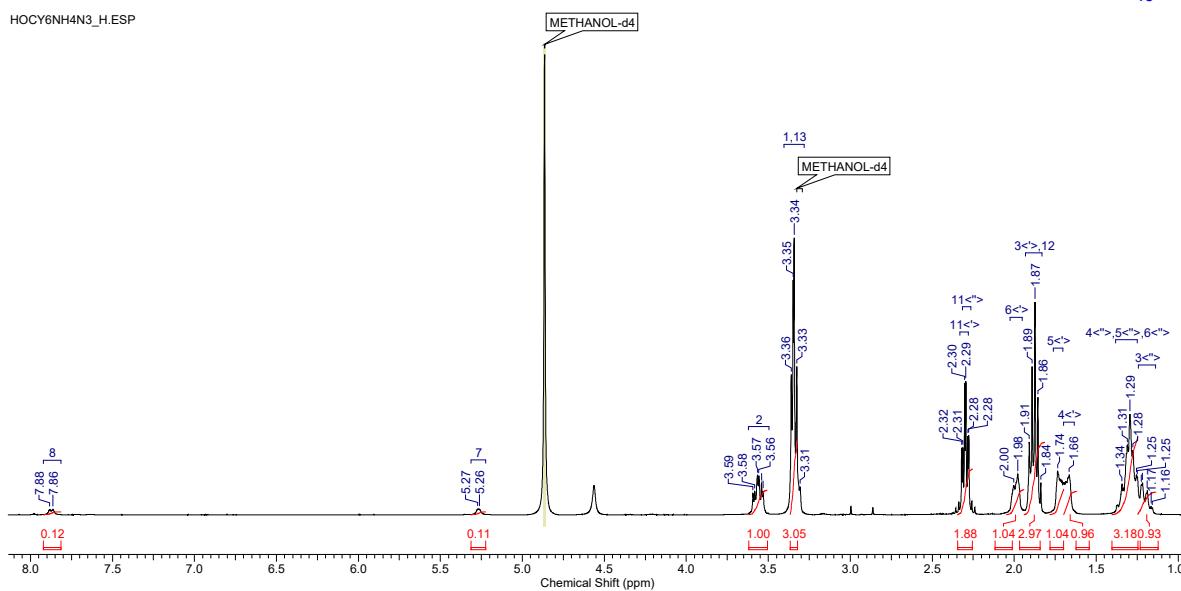
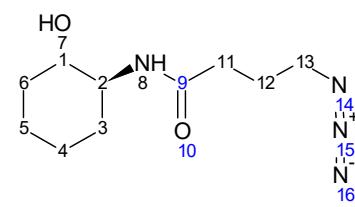
2.40 1-Cyclopropyl-6-fluoro-7-(4-(1-(4-(((1*R*,2*R*)-2-hydroxycyclopentyl)amino)-4-oxobutyl)-1*H*-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-4-oxo-1,4-dihydroquino-line-3-carboxylic acid 141



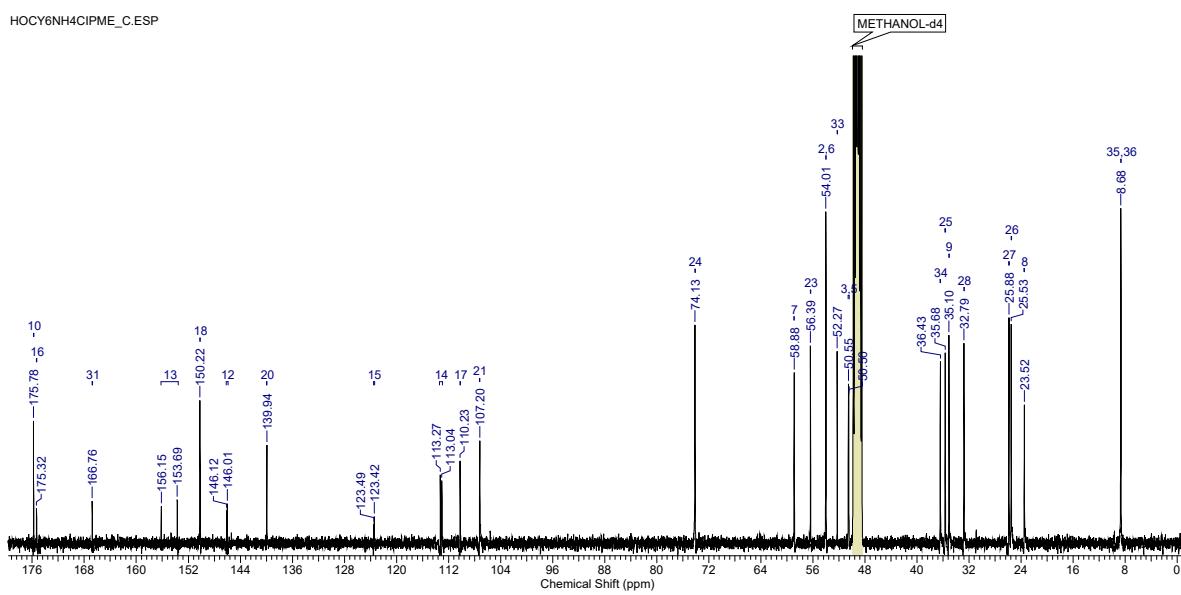
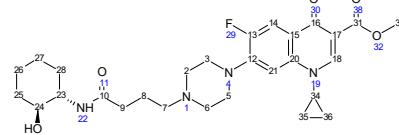
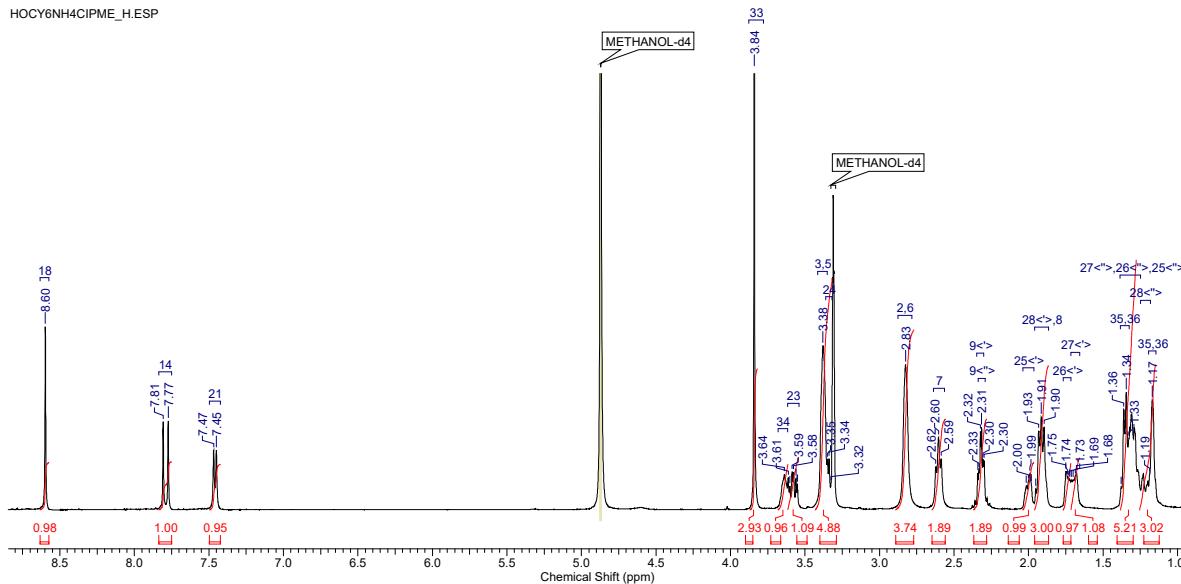
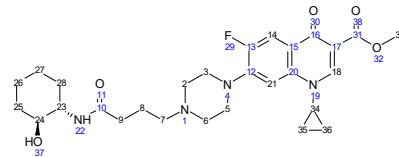
2.41 4-Chloro-*N*-((*trans*)-2-hydroxycyclohexyl)butanamide 145



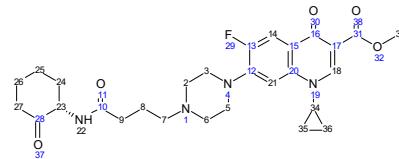
2.42 4-Azido-*N*-((*trans*)-2-hydroxycyclohexyl)butanamide 146



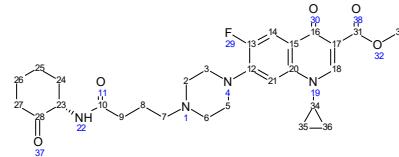
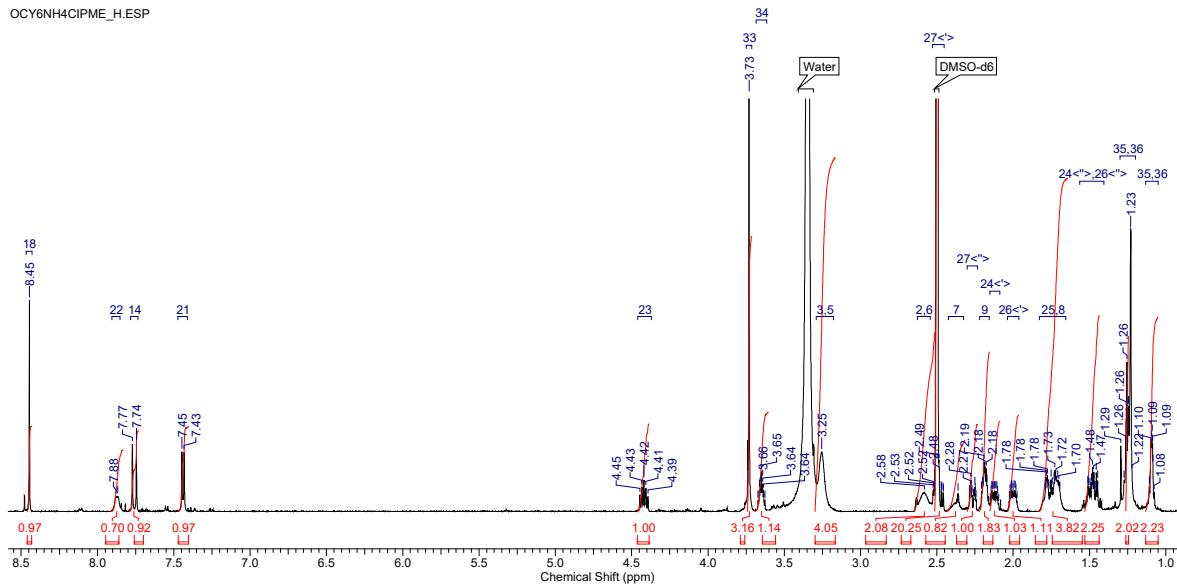
2.43 Methyl 1-cyclopropyl-6-fluoro-7-(4-((*trans*)-2-hydroxycyclohexyl)amino)-4-oxobutyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 147



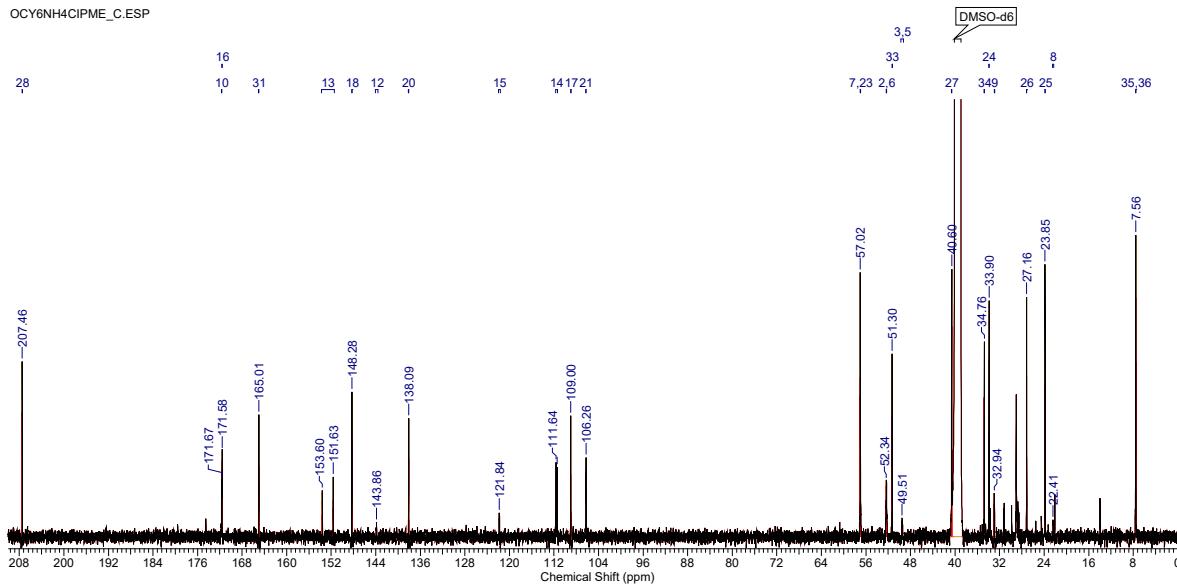
2.44 Methyl 1-cyclopropyl-6-fluoro-4-oxo-7-(4-(4-oxo-4-((2-oxocyclohexyl)amino)-butyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylate 148



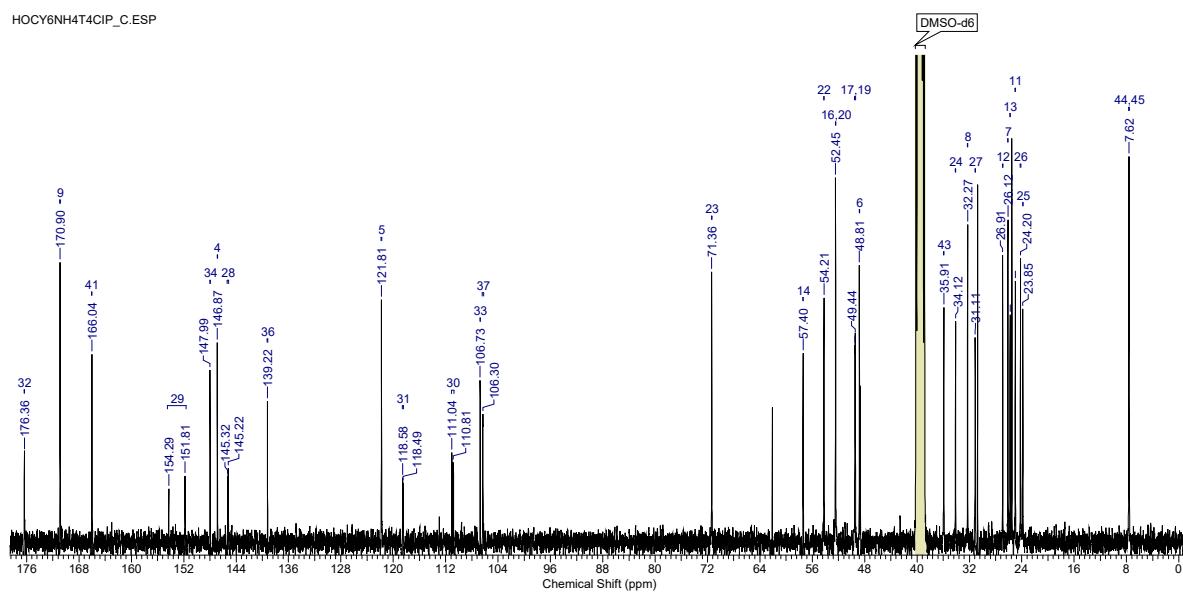
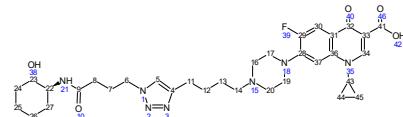
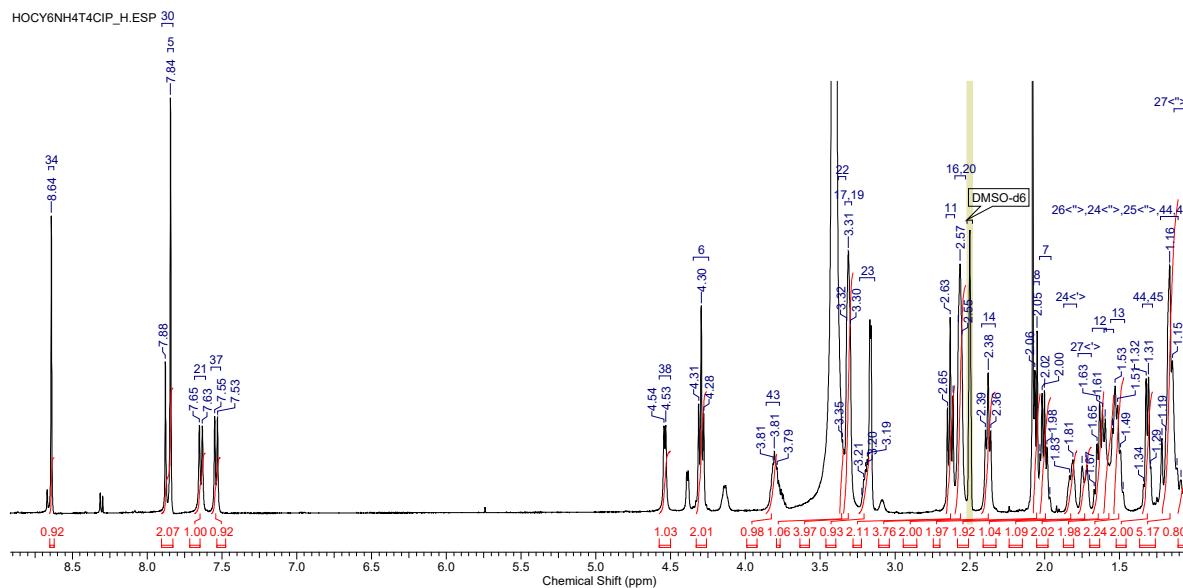
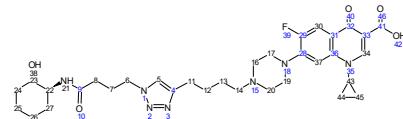
OCY6NH4CIPME_H.ESP



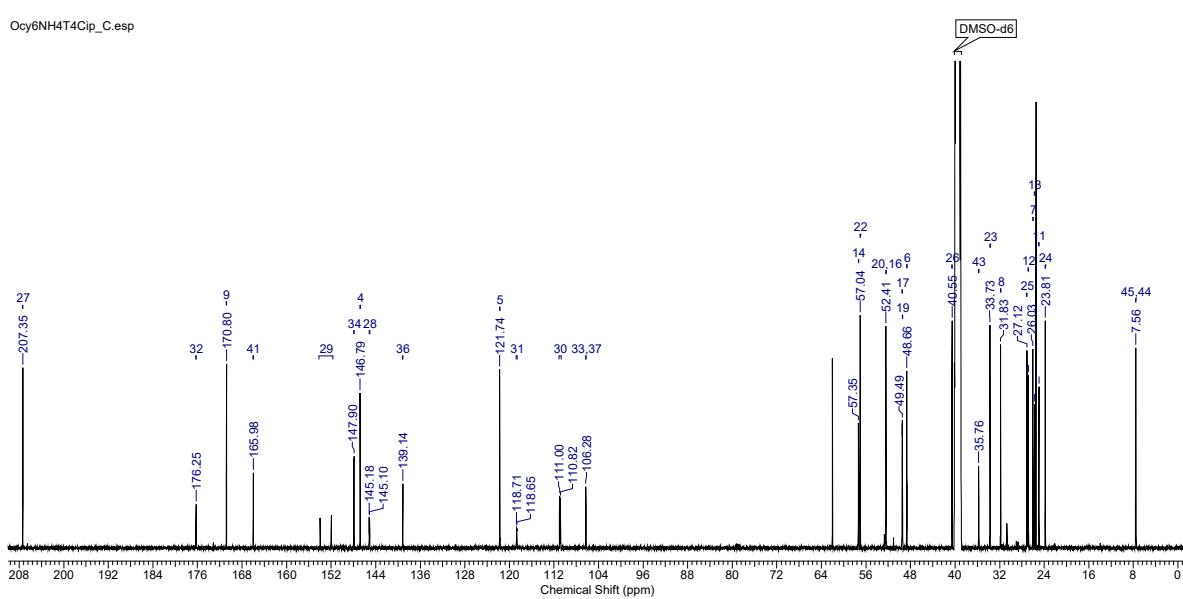
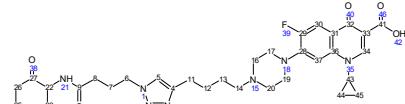
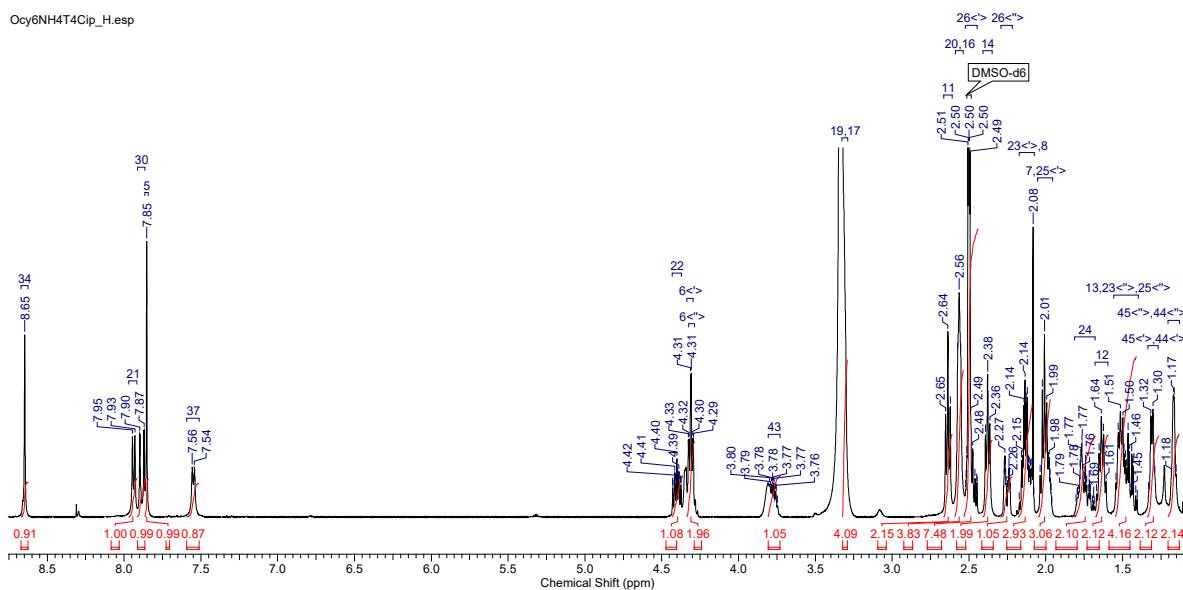
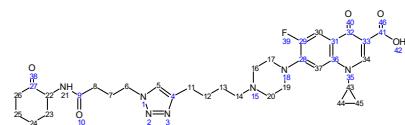
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2.45 1-Cyclopropyl-6-fluoro-7-(4-(1-(4-(((trans)-2-hydroxycyclohexyl)amino)-4-oxobutyl)-1*H*-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-4-oxo-1,4-dihydroquino-line-3-carboxylic acid 149



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

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