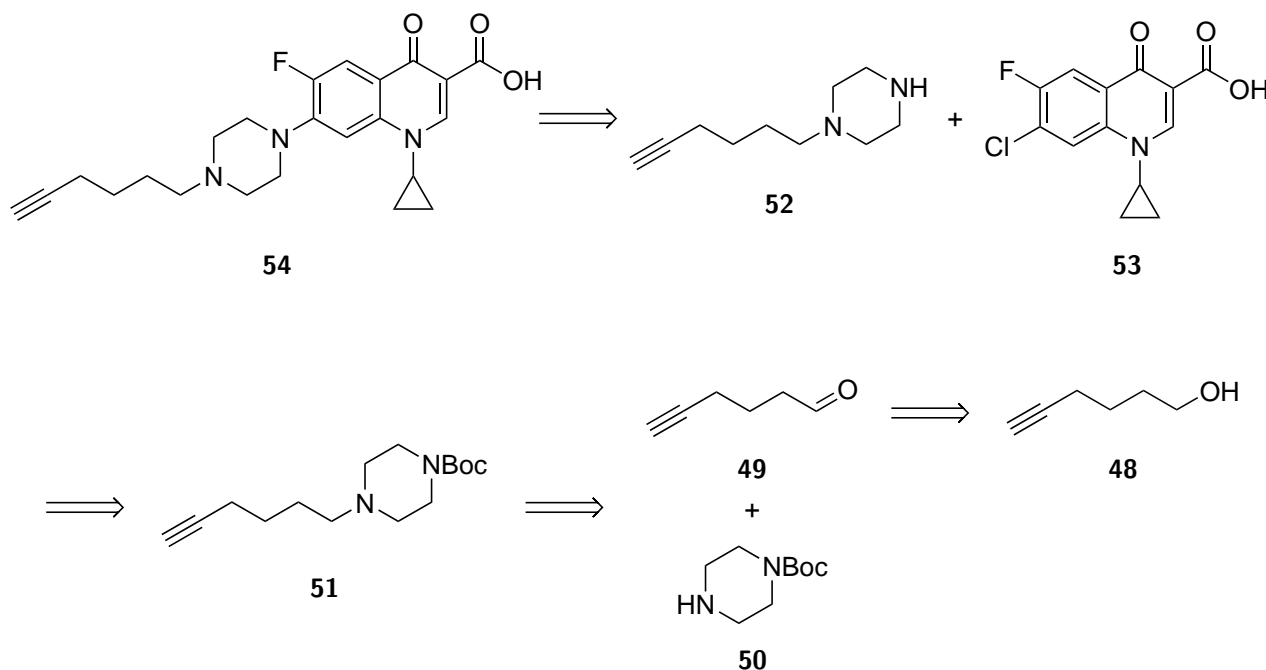


1 Antibiotic derivatives

1.1 Ciprofloxacin derivative

1.1.1 Retrosynthesis of ciprofloxacin derivative **54**

The retrosynthesis of ciprofloxacin derivative **54** is shown in Scheme 1. The derivative has an alkyne tail attached on the free piperazine N; it is more convenient to attach the alkyne chain to piperazine before coupling of the alkyl piperazine **52** to the ciprofloxacin core **53** as this method is more convergent. This can be achieved by reductive amination of hex-5-ynal **49** with 1-boc-piperazine **50** followed by deprotection to form the alkyl piperazine **52**. This method was found by Renau *et al.* to be "...superior to previous reports which involved alkylation of piperazine with an appropriate alkyl halide."^{1,2} S_NAr coupling of the piperazine derivative with ciprofloxacin precursor **53** leads to the final derivative **54**.

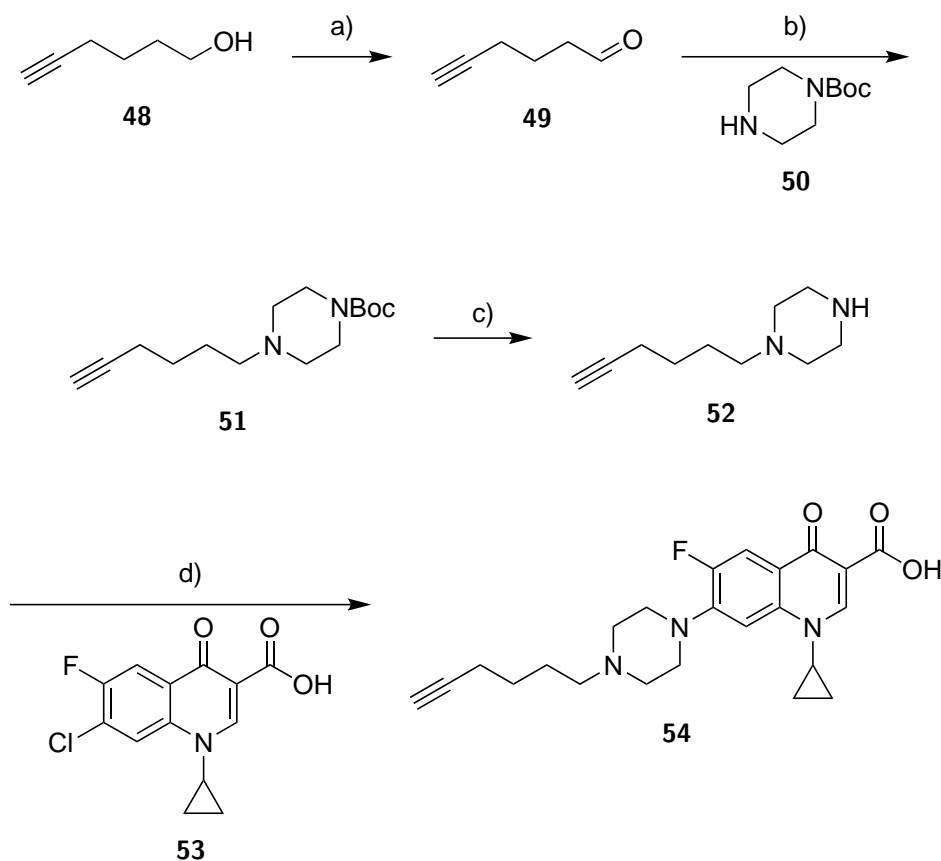


Scheme 1: The retrosynthesis of **54**.

1.1.2 Synthesis of ciprofloxacin derivative **54**

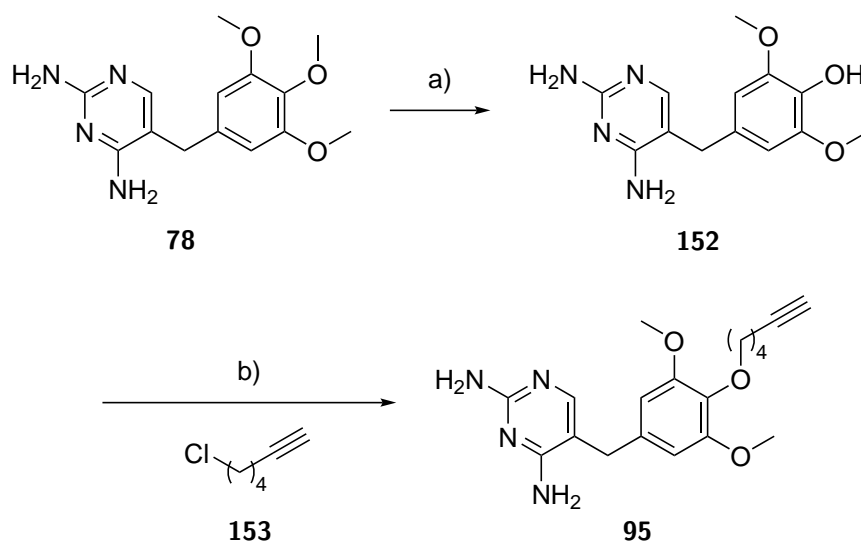
The synthesis of **54** follows the strategy followed by Renau *et al.*¹ Unlike the aldehydes and ketones used by Renau *et al.*,¹ hex-5-ynal **49** is not commercially available and so was successfully prepared by PCC oxidation of hex-5-ynol **48** according to the procedure described by Kocsis *et al.*³ Renau *et al.*¹ used sodium cyanoborohydride to facilitate the reductive amination of hex-5-ynal **49** and 1-Boc-piperazine **50**. However, it was decided to attempt this transformation using the less toxic sodium triacetoxyborohydride following a procedure reported by Abdel-Magid *et al.*⁴ This reaction yielded compound **51**, which was deprotected using TFA using the procedure described by Renau *et al.*¹ to give compound **52**. This was refluxed in MeCN with the commercially available ciprofloxacin precursor **53** according to the procedure described by Renau *et al.*,¹ however the reaction did not

proceed. Addition of NEt_3 did not lead to reaction, however it was found that refluxing in neat NEt_3 lead to conversion to the final ciprofloxacin derivative **54**.



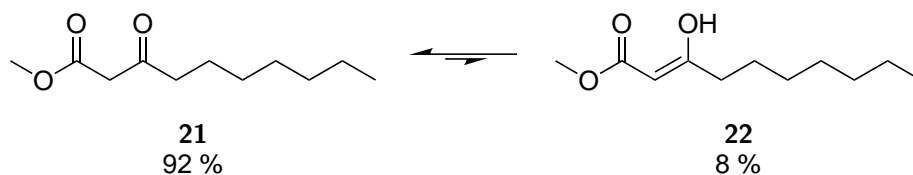
Scheme 2: The synthesis of **54**. a) Pyridinium chlorochromate, CH_2Cl_2 , r.t., 5 h, 72 %. b) $\text{NaBH}(\text{AcO})_3$, 1,2-dichloroethane, r.t., 10.5 h, 99 %. c) TFA, r.t., 1 h, 100 %. d) NEt_3 , reflux, 15 h, 21 %.

1.2 Trimethoprim derivative



Scheme 3: The synthesis of **95**.

1.3 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 % Et_2O /40-60 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, $\text{C(=O)CH}_2\text{C(=O)}$), 2.53 (t, J = 7.4 Hz, 2 H, $\text{C(=O)CH}_2\text{CH}_2$), 1.60 (quin, J = 7.1 Hz, 2 H, $\text{C(=O)CH}_2\text{CH}_2$), 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 ($\text{CH}_3\text{OC(=O)CH}_2\text{C(=O)}$), 167.3 ($\text{CH}_3\text{OC(=O)CH}_2\text{C(=O)}$), 51.7 (OCH_3), 48.5 ($\text{CH}_3\text{OC(=O)CH}_2\text{C(=O)}$), 42.5 ($\text{C(=O)CH}_2\text{CH}_2$), 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)

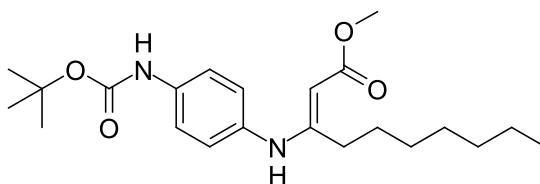
IR (neat) ν_{\max} / cm^{-1} = 2927.8 (C-H), 2856.3 (C-H), 1653.8 (C=C), 1629.2 (α,β unsaturated C=O)

^1H NMR (400 MHz, CDCl_3) δ / ppm = 12.02 (s, 1 H, COH), 4.99 (s, 1 H, C(=O)CH=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 ($\text{CH}_3\text{OC(=O)CH=COH}$), 172.7 ($\text{CH}_3\text{OC(=O)CH=COH}$), 88.2 ($\text{CH}_3\text{OC(=O)CH=COH}$), 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.^{5,6}

1.4 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)

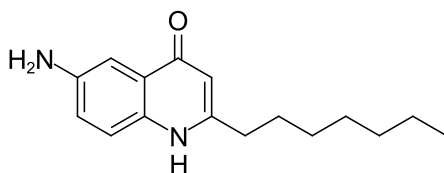
¹H NMR (400 MHz, CDCl₃) δ / ppm = 10.16 (s, 1 H, NH(C₇H₁₅)=C), 7.35 (d, J = 8.6 Hz, 2 H, *meta* to NHBoc), 7.02 (d, J = 8.7 Hz, 2 H, *meta* to enamine), 6.60 (br s, 1 H, NHBoc), 4.71 (s, 1 H, C=CH), 3.70 (s, 3 H, OCH₃), 2.23 (t, J = 7.7 Hz, 2 H, CH₂CH₂CH₂CH₂CH₂CH₂CH₃), 1.54 (s, 9 H, C(CH₃)₃), 1.40 (quin, J = 7.3 Hz, 2 H, CH₂CH₂CH₂CH₂CH₂CH₂CH₃), 1.33 - 1.16 (m, 8 H, CH₂CH₂CH₂CH₂CH₂CH₂CH₃), 0.86 (t, J = 7.1 Hz, 3 H, CH₂CH₂CH₂CH₂CH₂CH₂CH₃)

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.⁷

1.5 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 amorphous solid (121 mg, 0.468 mmol, 72 %).

mp $T / ^\circ\text{C} = 249$ (H_2O)

IR (neat) $\nu_{\text{max}} / \text{cm}^{-1} = 3336.5$ (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)

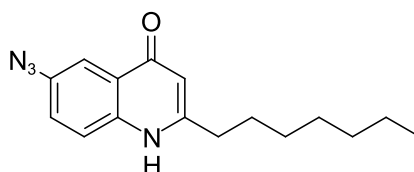
^1H NMR (400 MHz, DMSO-d_6) $\delta / \text{ppm} = 7.26$ (d, $J = 8.7$ Hz, 1 H, *meta* to NH_2), 7.15 (d, $J = 2.6$ Hz, 1 H, *ortho* to C(=O)), 6.95 (dd, $J = 2.7, 8.8$ Hz, 1 H, *para* to C(=O)), 5.74 (s, 1 H, *ortho* to CH_2), 5.16 (s, 2 H, NH_2), 2.52 (t, $J = 7.4$ Hz, 2 H, CCH_2), 1.64 (quin, $J = 7.6$ Hz, 2 H, CCH_2CH_2), 1.36 - 1.19 (m, 8 H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 0.86 (t, $J = 7.0$ Hz, 3 H, H_3)

^{13}C NMR (101 MHz, DMSO-d_6) $\delta / \text{ppm} = 176.7$ ($\text{C}(=\text{O})$), 151.7 (CCH_2), 145.1 (*para* to NH_2 or *ipso* to C(=O)), 132.4 (*ipso* to NH_2), 126.6 (*para* to NH_2 or *ipso* to C(=O)), 121.1 (*para* to C(=O)), 119.0 (*meta* to NH_2 and *meta* to C(=O)), 106.2 ($\text{CH}=\text{CCH}_2$), 105.9 (*ortho* to NH_2 and *ortho* to C(=O)), 33.6 (CCH_2), 31.6 ($\text{CH}_2\text{CH}_2\text{CH}_3$), 29.0 (CH_2), 29.0 (CH_2), 28.9 (CH_2), 22.5 (CH_2CH_3), 14.4 (CH_3)

HRMS (ESI^+) $m/z / \text{Da} = 259.1810$, $[\text{M}+\text{H}]^+$, $[\text{C}_{16}\text{H}_{23}\text{N}_2\text{O}]^+$ requires 259.1803

Spectroscopic data are consistent with the literature.⁷

1.6 6-Azido-2-heptylquinolin-4-ol **26**



6-Amino-2-heptylquinolin-4-ol **25** (50 mg, 0.194 mmol, 1 eq) was dissolved in HCl (conc., aq., 1.20 ml), water (1.80 ml) and MeOH (2.00 ml) and cooled to 0°C . A solution of NaNO_2 (16.0 mg, 0.232 mmol, 1.2 eq.) in water (0.300 ml) was added dropwise over 10 min and the mixture was stirred for 1 h. A solution of NaN_3 (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 % $\text{MeOH}/\text{CH}_2\text{Cl}_2$)

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

^1H NMR (400 MHz, MeOD) $\delta / \text{ppm} = 7.73$ (d, $J = 8.6$ Hz, 1 H, *ortho* to NH), 7.71 (d, $J = 2.8$ Hz, 1 H, *ortho* to N_3 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, CCH_2), 1.68 (quin, $J = 7.6$ Hz, 2 H, CCH_2CH_2), 1.28 - 1.39 (m, 4 H, $\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2$), 1.18 - 1.28 (m, 4 H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 0.85 (t, $J = 6.8$ Hz, 3 H, CH_3)

^{13}C NMR (101 MHz, MeOD) $\delta / \text{ppm} = 172.3$ ($\text{C}(=\text{O})$), 155.5 (NHCCH_2), 137.4 (CN_3), 135.6 (*para* to N_3), 124.6 (*para* to C(=O)), 124.1 (*ipso* to C(=O)), 120.7 (*meta* to N_3 and *meta* to C(=O)), 112.8 (*ortho* to N_3 and *ortho* to C(=O)), 107.0 (C(=O) CH), 33.3 (NHCCH_2), 31.2 ($\text{CH}_2\text{CH}_2\text{CH}_3$), 28.3 - 28.5 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 22.1 (CH_2CH_3), 14.0 (CH_3)

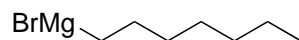
HRMS (ESI⁺) m/z / Da = ??, [M+H]⁺ found, [??]⁺ requires ??

get

Spectroscopic data are not consistent with the literature.⁷

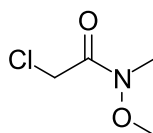
???

1.7 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.

1.8 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)

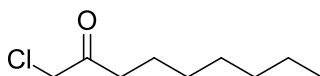
IR (neat) ν_{max} / cm⁻¹ = 3016.7 (C-H), 2966.4 (C-H), 2946.7 (C-H), 2827.7 (C-H), 1666.2 (C=O)

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.⁸

1.9 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 %).

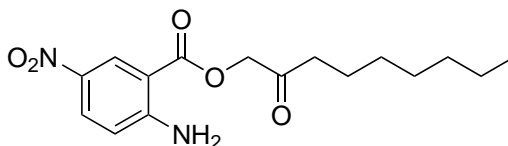
IR (neat) ν_{max} / cm⁻¹ = 2951.7 (C-H), 2925.0 (C-H), 2855.5 (C-H), 1720.4 (C=O)

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.⁸

1.10 2-Oxononyl 2-amino-5-nitrobenzoate **33**



5-Nitroanthranilic acid **32** (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)

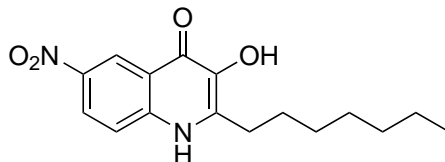
¹H NMR (400 MHz, DMSO-d₆) δ / ppm = 8.66 (d, J = 2.8 Hz, 1 H, *ortho* to C(=O)), 8.12 (dd, J = 2.8, 9.4 Hz, 1 H, *para* to C(=O)), 6.93 (d, J = 9.4 Hz, 1 H, *meta* to C(=O)), 5.05 (s, 2 H, OCH₂C(=O)), 2.49 (t, J = 7.4 Hz, 2 H, C(=O)CH₂CH₂), 1.52 (quin, J = 7.2 Hz, 2 H, C(=O)CH₂CH₂), 1.32 - 1.20 (m, 8 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.⁷

1.11 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)

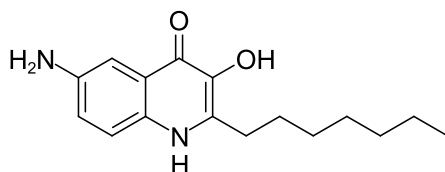
¹H NMR (400 MHz, DMSO-d₆) δ / ppm = 12.00 (s, 1 H, NH), 8.91 (d, J = 2.8 Hz, 1 H, *ortho* to C=O), 8.29 (dd, J = 2.7, 9.2 Hz, 1 H, *para* to C=O), 7.70 (d, J = 9.3 Hz, 1 H, *meta* to C=O), 2.75 (t, J = 7.7 Hz, 2 H, CCH₂), 1.67 (quin, J = 7.3 Hz, 2 H, CCH₂CH₂), 1.36 - 1.23 (m, 8 H, CH₂CH₂CH₂CH₂CH₂CH₃), 0.85 (t, J = 7.0 Hz, 3 H, CH₃)

¹³C NMR (101 MHz, DMSO-d₆) δ / ppm = 169.7 (C=O), 141.9 (*para* to NO₂), 140.7 (*ipso* to NO₂), 139.6 (*ipso* to OH), 137.3 (C=COH), 124.3 (*para* to C=O), 122.3 (*ortho* to NO₂ and *ortho* to C=O), 121.5 (*ipso* to C=O), 120.0 (*meta* to NO₂ and *meta* to C=O), 31.6 (CH₂CH₂CH₃), 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.⁷

1.12 6-Amino-2-heptyl-3-hydroxyquinolin-4(1*H*)-one **35**



6-Nitro-2-heptyl-3-hydroxyquinolin-4(1*H*)-one **34** (20 mg, 0.0658 mmol, 1 eq.) and PtO₂ (2 mg, 10 weight %) were stirred in MeOH (1 ml) under a H₂ atmosphere for 45 min at room temperature and pressure. The reaction mixture was then filtered through celite and the solvent was removed under vacuum to give a yellow-brown

amorphous solid (14.5 mg, 0.0529 mmol, 80 %).

mp (MeOH) $T / ^\circ\text{C} = 176$

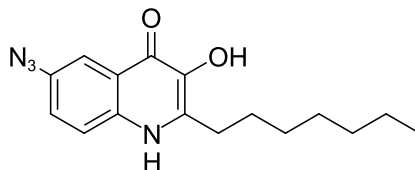
IR (neat) $\nu_{\text{max}} / \text{cm}^{-1} = 3000.00$ (O-H, br) 2925.41 (C-H), 2854.09 (C-H), 1613.43 (aromatic) 1555.29 (aromatic) 1504.47 (aromatic)

^1H NMR (400 MHz, MeOD) $\delta / \text{ppm} = 11.12$ (s, 1 H, NH), 7.47 (d, $J = 8.9$ Hz, 1 H, *meta* to C=O), 7.40 (d, $J = 2.4$ Hz, 1 H, *ortho* to C=O), 7.16 (dd, $J = 2.6, 9.0$ Hz, 1 H, *para* to C=O), 2.86 (t, $J = 7.5$ Hz, 2 H, CCH_2), 1.75 (quin, $J = 7.8$ Hz, 2 H, CCH_2CH_2), 1.48 - 1.22 (m, $J = 5.4$ Hz, 8 H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 0.89 (t, $J = 6.7$ Hz, 3 H, CH_3)

^{13}C NMR (101 MHz, MeOD) $\delta / \text{ppm} = 166.8$ ($\text{C}(=\text{O})$), 144.8 (*para* to NH_2 or *ipso* to $\text{C}(=\text{O})$), 140.5 (*ipso* to COH), 138.6 ($\text{C}=\text{COH}$), 132.6 (*ipso* to NH_2), 124.8 (*para* to NH_2 or *ipso* to $\text{C}(=\text{O})$), 123.8 (*para* to $\text{C}(=\text{O})$), 107.7 (*meta* to NH_2 and *meta* to $\text{C}(=\text{O})$), 106.4 (*ortho* to NH_2 and *ortho* to $\text{C}(=\text{O})$), 33.0 ($\text{CH}_2\text{CH}_2\text{CH}_3$), 29.5 - 31.0 ($\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2$), 23.8 (CH_2CH_3), 14.5 (CH_3)

HRMS (ESI^+) $m/z / \text{Da} = 275.1760$, $[\text{M}+\text{H}]^+$, $[\text{C}_{16}\text{H}_{23}\text{N}_2\text{O}_2]^+$ requires 275.1762 Spectroscopic data are not consistent with the literature.⁷ It is possible that Baker's product is a Zn adduct.

1.13 6-Azido-2-heptyl-3-hydroxyquinolin-4(1H)-one **36**



6-Amino-2-heptyl-3-hydroxyquinolin-4(1H)-one **35** (18.2 mg, 0.0664 mmol, 1 eq.) was dissolved in HCl (conc., aq., 0.8 ml) and MeOH (0.5 ml) at 0°C . NaNO_2 (5.0 mg, 0.0725 mmol, 1.09 eq.) in H_2O (0.2 ml) was added dropwise over 2 min and the mixture was stirred at 0°C for 50 min, during which time the solution turned from yellow to orange. NaN_3 (4.9 mg, 0.0754 mmol, 1.14 eq.) in H_2O (0.2 ml) was then added and the mixture was allowed to warm to r.t. and stirred for 4 h. The reaction mixture was then filtered to give a brown amorphous solid (5.5 mg, 0.0183 mmol, 28 %).

mp ($\text{H}_2\text{O}/\text{MeOH}$) $T / ^\circ\text{C} = \text{pending}$

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

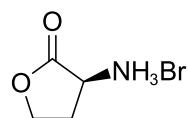
^1H NMR (400 MHz, DMSO-d_6) $\delta / \text{ppm} = 7.74$ (s, 1 H, *ortho* to C=O), 7.65 (d, $J = 6.9$ Hz, 1 H, *meta* to $\text{C}(=\text{O})$), 7.32 (d, $J = 7.4$ Hz, 1 H, *para* to $\text{C}(=\text{O})$), 2.75 (t, $J = 7.5$ Hz, 2 H, CCH_2), 1.67 (quin, $J = 6.4$ Hz, 2 H, CCH_2CH_2), 1.43 - 1.13 (m, 8 H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 0.85 (t, $J = 6.8$ Hz, 3 H, CH_3)

HRMS (ESI^+) $m/z / \text{Da} = \text{pending}$, $[\text{M}+\text{H}]^+$, $[\text{C}_{16}\text{H}_{21}\text{N}_4\text{O}_2]^+$ requires 301.1659

try?

Spectroscopic data are consistent with the literature.⁷

1.14 (*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 amorphous solid. 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) $\nu_{\text{max}} / \text{cm}^{-1} = 2972.1$ (N-H), 2877.5 (N-H), 1771.8 (C=O), 1585.1 (N-H bend), 1572.2 (N-H bend)

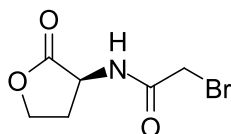
¹H NMR (400 MHz, DMSO-*d*₆) $\delta / \text{ppm} = 8.59$ (br s, 3 H, NH_3^+), 4.46 (dt, $J = 1.3, 8.9$ Hz, 1 H, OCHH), 4.37 (dd, $J = 8.8, 11.4$ Hz, 1 H, CHNH₃⁺), 4.29 (ddd, $J = 6.1, 8.8, 10.9$ Hz, 1 H, OCHH), 2.57 (dddd, $J = 1.2, 6.1, 8.9, 12.3$ Hz, 1 H, OCH₂CHH), 2.26 (dtd, $J = 9.0, 11.2, 12.2$ Hz, 1 H, OCH₂CHH)

¹³C NMR (101 MHz, DMSO-*d*₆) $\delta / \text{ppm} = 173.3$ (C=O), 66.2 (OCH₂), 47.8 (CHNH₃⁺), 27.0 (OCH₂CH₂)

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

The data are consistent with the literature.⁹

1.15 (*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 (4×10 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) $\nu_{\text{max}} / \text{cm}^{-1} = 3255.7$ (N-H), 3066.6 (C-H), 1763.0 (lactone C=O), 1658.0 (amide C=O), 1552.7 (N-H bend)

¹H NMR (400 MHz, CDCl₃) δ / 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)

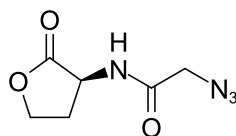
¹³C NMR (101 MHz, CDCl₃) δ / ppm = 174.6 (OC=O), 166.4 (C(=O)NH), 66.1 (OCH₂), 49.8 (CHNHC=O), 29.9 (OCH₂CH₂), 28.2 (O=CCH₂Br)

HRMS The compound does not ionise.

$[\alpha]_D^{20} / ^\circ 10^{-1} \text{cm}^2 \text{g}^{-1} = 27.0$ (c / g(100 ml)⁻¹ = 0.00740, CHCl₃)

The data are consistent with the literature.^{9,10}

1.16 (*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 / $^\circ\text{C}$ = 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)

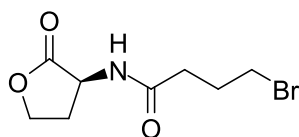
¹³C NMR (101 MHz, CDCl₃) δ / ppm = 174.9 (OC=O), 167.5 (C=ONH), 66.0 (OCH₂), 52.2 (O=CCH₂N₃), 48.9 (CHNHC=O), 29.7 (OCH₂CH₂)

HRMS The compound does not ionise.

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

The data are consistent with the literature.⁹

1.17 (*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 μL, 224 mg, 1.21 mmol, 1.10 eq.) was then added dropwise. The reaction mixture was stirred for 1 h, after which the CH₂Cl₂ was removed under vacuum. The aqueous phase was extracted with EtOAc (7×5 ml) and the combined organic layers were dried with MgSO₄. 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) $\nu_{\text{max}} / \text{cm}^{-1} = 3307.9$ (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)

¹H NMR (400 MHz, CDCl₃) $\delta / \text{ppm} = 6.31$ (br d, $J = 5.5$ Hz, 1 H, NH), 4.59 (ddd, $J = 6.2, 8.7, 11.5$ Hz, 1 H, CHNH), 4.48 (dt, $J = 1.2, 8.9$ Hz, 1 H, OCHH), 4.30 (ddd, $J = 5.8, 9.3, 11.3$ Hz, 1 H, OCHH), 3.49 (t, $J = 6.3$ Hz, 2 H, CH₂Br), 2.82 (dddd, $J = 1.3, 5.9, 8.7, 12.5$ Hz, 1 H, OCH₂CHH), 2.47 (t, $J = 7.3$ Hz, 2 H, C(=O)CH₂), 2.26 - 2.15 (m, 3 H, OCH₂CHH and CH₂CH₂Br)

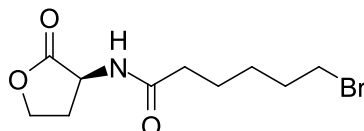
¹³C NMR (101 MHz, CDCl₃) $\delta / \text{ppm} = 175.4$ (OC=O), 172.3 (C(=O)NH), 66.1 (OCH₂), 49.3 (CHNHC=O), 33.9 (C(=O)CH₂), 33.1 (CH₂Br), 30.3 (OCH₂CH₂), 27.9 (C(=O)CH₂CH₂)

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.

1.18 (*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 NaHCO₃ (84.9 mg, 1.01 mmol, 1.84 eq.) were dissolved in CH₂Cl₂ (2 ml) and H₂O (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 CH₂Cl₂ was removed under vacuum. The mixture was then filtered, washed with H₂O (10 ml) and dried under high vacuum. **45** was obtained as white, needle-like crystals (101 mg, 0.362 mmol, 66 %).

mp $T / ^\circ\text{C} = 106$ (CH₂Cl₂/H₂O)

IR (neat) ν_{max} / 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)

^1H NMR (400 MHz, CDCl_3) δ / ppm = 6.09 (br d, J = 5.7 Hz, 1 H, NH), 4.57 (ddd, J = 5.9, 8.6, 11.6 Hz, 1 H, CHNH), 4.50 (dt, J = 1.3, 9.1 Hz, 1 H, OCHH), 4.31 (ddd, J = 5.9, 9.3, 11.3 Hz, 1 H, OCHH), 3.43 (t, J = 6.7 Hz, 2 H, CH_2Br), 2.88 (dddd, J = 1.3, 5.9, 8.6, 12.6 Hz, 1 H, OCH_2CHH), 2.30 (dt, J = 1.8, 7.5 Hz, 2 H, C(=O)CH_2), 2.16 (dtd, J = 8.9, 11.5, 12.5 Hz, 1 H, OCH_2CHH), 1.90 (quin, J = 7.2 Hz, 2 H, $\text{CH}_2\text{CH}_2\text{Br}$), 1.71 (quin, J = 7.6 Hz, 2 H, $\text{C(=O)CH}_2\text{CH}_2$), 1.59 - 1.46 (m, 2 H, $\text{C(=O)CH}_2\text{CH}_2\text{CH}_2$)

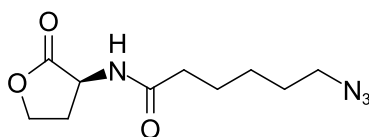
^{13}C NMR (101 MHz, CDCl_3) δ / ppm = 175.5 (OC=O), 173.3 (C(=O)NH), 66.1 (OCH_2), 49.3 (CHNHHC=O), 35.8 (CH_2Br), 33.5 (C(=O)CH_2), 32.3 ($\text{CH}_2\text{CH}_2\text{Br}$), 30.5 (OCH_2CH_2), 27.6 ($\text{C(=O)CH}_2\text{CH}_2$), 24.4 ($\text{C(=O)CH}_2\text{CH}_2\text{CH}_2$)

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.

1.19 (*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 $^{\circ}\text{C}$. 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 / $^{\circ}\text{C}$ = 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, OCHH), 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_2CHH), 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, $\text{C(=O)CH}_2\text{CH}_2\text{CH}_2$)

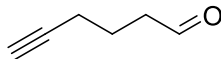
^{13}C NMR (101 MHz, CDCl_3) δ / ppm = 175.4 (OC=O), 172.2 (C(=O)NH), 66.1 (OCH_2), 51.2 (CH_2N_3), 49.4 (CHNHHC=O), 35.9 (C(=O)CH_2), 30.7 (OCH_2CH_2), 28.6 ($\text{CH}_2\text{CH}_2\text{N}_3$), 26.3 ($\text{C(=O)CH}_2\text{CH}_2$), 24.8 ($\text{C(=O)CH}_2\text{CH}_2\text{CH}_2$)

HRMS (ESI⁺) m/z / Da = 241.1289, [M+H]⁺, [C₁₀H₁₇N₄O₃]⁺ requires 241.1295

$[\alpha]_D^{26.6}$ / °10⁻¹cm²g⁻¹ = -16 (c / g(100 ml)⁻¹ = 0.208, MeOH)

The compound has not been reported previously.

1.20 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 %).

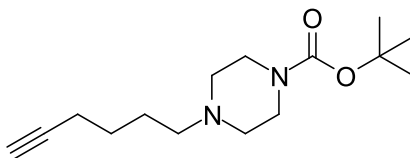
IR (neat) ν_{max} / cm⁻¹ = 3292.7 (alkyne C-H), 2943.3 (alkane C-H), 2830.9 (aldehyde C-H), 2728.6 (aldehyde C-H), 1720.3 (aldehyde C=O)

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 (HCC≡C), 42.4 (CH₂C(=O)), 20.7 (CH₂CH₂C(=O)), 17.6 (HC≡CCH₂)

Spectroscopic data are consistent with the literature.³

1.21 *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)

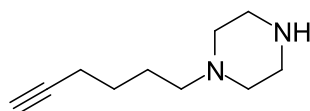
¹H NMR (400 MHz, CDCl₃) δ / ppm = 3.44 (t, J = 5.2 Hz, 4 H, CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 2.39 (t, J = 5.1 Hz, 4 H, CH₂CH₂CH₂N(CH₂)CH₂), 2.37 (t, J = 7.3 Hz, 2 H, CH₂CH₂CH₂N), 2.23 (dt, J = 2.7, 6.8 Hz, 2 H, HC≡CCH₂), 1.96 (t, J = 2.7 Hz, 1 H, HC≡C), 1.65 - 1.53 (m, 4 H, HC≡CCH₂CH₂CH₂), 1.47 (s, 9 H, CH₃)

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.

1.22 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)

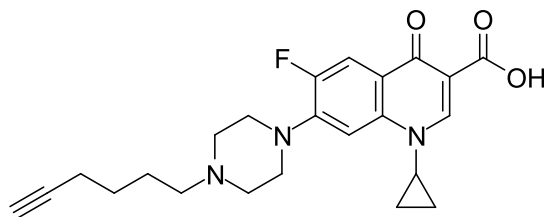
¹H NMR (400 MHz, CDCl₃) δ / ppm = 2.88 (t, J = 4.9 Hz, 4 H, CH₂CH₂CH₂N(CH₂CH₂)CH₂CH₂), 2.39 (m, 4 H, CH₂CH₂CH₂N(CH₂)CH₂), 2.31 (t, J = 7.1 Hz, 2 H, HC≡CCH₂CH₂CH₂CH₂N), 2.20 (dt, J = 2.7, 6.8 Hz, 2 H, HC≡CCH₂), 2.05 (br s, 1 H, NH), 1.93 (t, J = 2.7 Hz, 1 H, HC≡C), 1.65 - 1.48 (m, 4 H, HC≡CCH₂CH₂CH₂CH₂N)

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.

1.23 1-Cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **92**



7-Chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **53** (1.27 g, 4.51 mmol, 1 eq.), 1-(hex-5-yn-1-yl)piperazine **52** (1.5 g, 9.02 mmol, 2 eq.) and *N*-methyl-2-pyrrolidone (10 ml) were stirred in a microwave reactor at 115 °C for 24 h. The reaction mixture was cooled to r.t. and water (80 ml) was added. The mixture was stirred for 3 h and then filtered, and residue was washed with MeOH (50 ml). The resulting solid (0.571 g) was further purified by recrystallisation from EtOAc (50 ml). **92** 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(CH₂)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(CH₂)CH₂), 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≡CCH₂CH₂), 1.52 (quin, J = 7.4 Hz, 2 H, HC≡CCH₂CH₂), 1.29 - 1.36 (m, 2 H, NCH(CH₂)₂), 1.16 - 1.23 (m, 2 H, NCH(CH₂)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(CH₂)CH₂), 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.

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