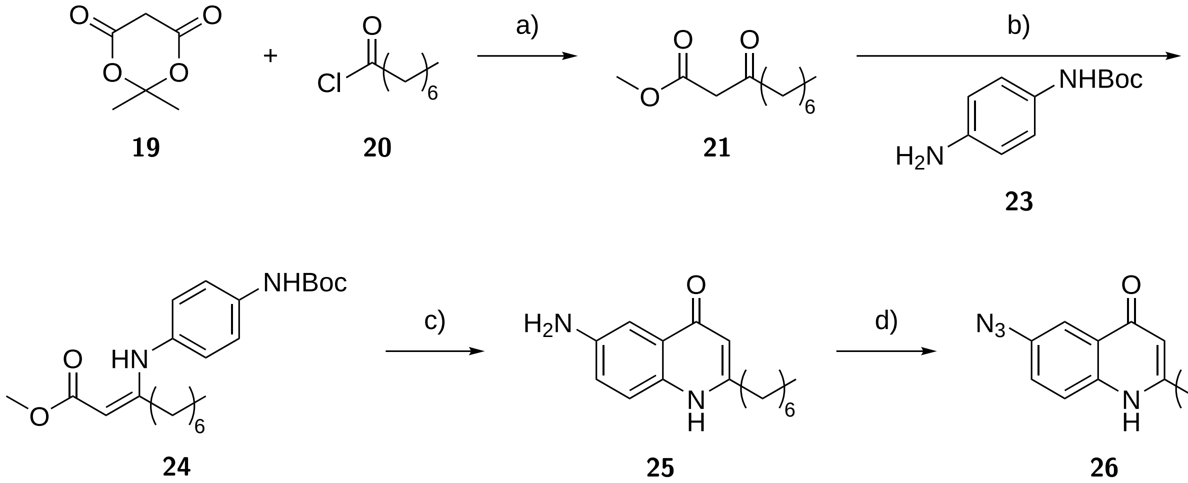
1 Autoinducer analogues

1.1 Synthesis of the HHQ derivative

The synthesis of HHQ analogue **26** is shown in Scheme 1 and follows a route devised by Baker.[1] Octonyl chloride **20** was be converted to β-ketoester **21** via a Meldrum's acid adduct.[2,3] The β-ketoester **21** was condensed with *N*-Boc-*p*-phenylenediamine **23** to form enamine **24**. The disappointing yield of this step was in part due to the reaction proceeding to an equilibrium state rather than to completion, and hence not all of the starting material being consumed. Starting materials can be recycled to improve the yield. Alternatively, Baker later found a higher-yielding reaction using a $ZrCl_4$ catalyst.

The enamine **24** was cyclised with polyphosphoric acid to form amino-HHQ **25** in good yield. The amine group of amino-HHQ **25** was converted to a diazo group by reaction with $NaNO_2$ and HCl, followed by displacement with NaN_3 to form the final azido-HHQ product **26**.[4]



Scheme 1: The synthesis of **26**. a) i) Pyridine, DCM, 0°C. ii) MeOH, reflux, 66 % over two steps. b) MeOH, reflux, 19 %. c) Polyphosphoric acid, 120°C, 72 %. d) i) $NaNO_2$, HCl, H_2O, 0 °C. ii) NaN_3, H_2O, r.t., 46.5 %.

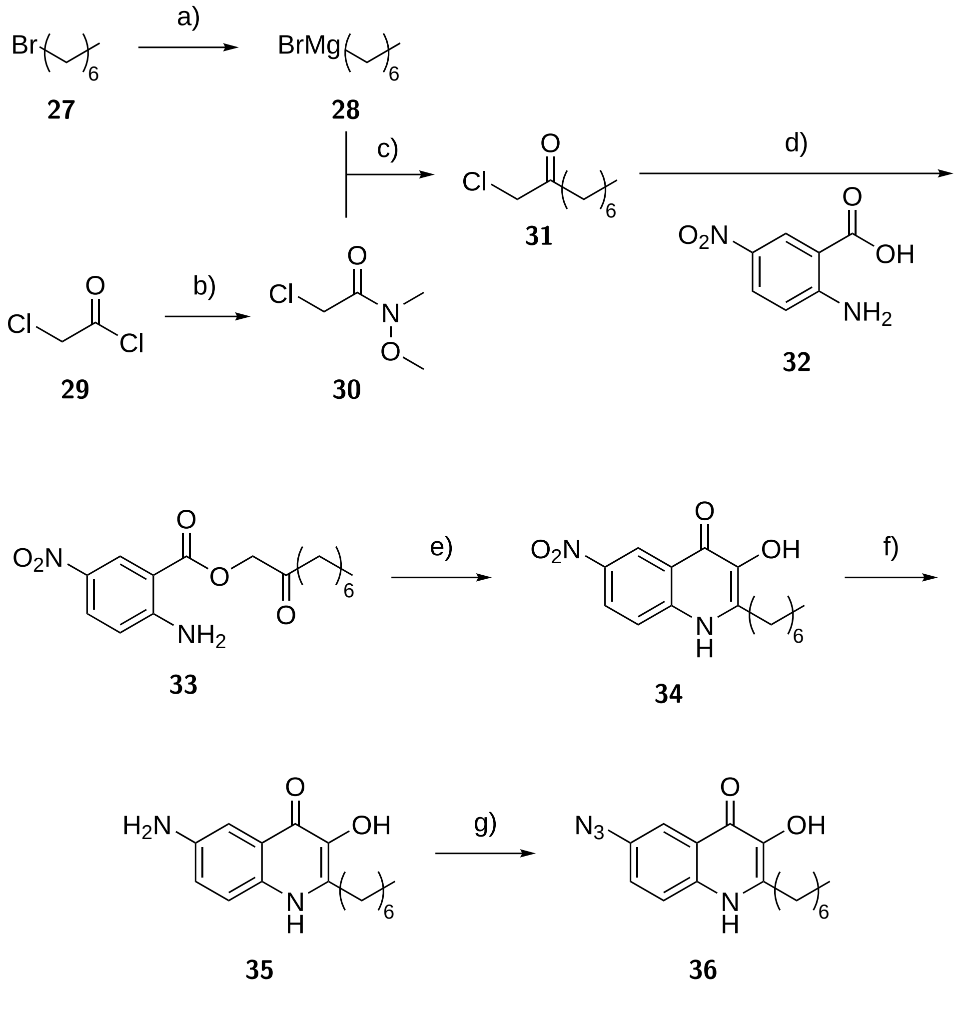
1.2 Synthesis of PQS derivative 36

The synthesis of PQS analogue **36** is shown in Scheme 2 and also follows a route devised by Baker.[1]The Weinreb amide **30** was prepared from chloroacetyl chloride, followed by attack with heptyl magnesium bromide **28** to form 1-chlorononan-2-one **31**. 5-Nitroanthranillic acid **32** was heated with K_2CO_3 to deprotonate the carboxylic acid, followed by addition of 1-chlorononan-2-one **31**. Cyclisation to form nitro-PQS **34** was attempted using Eaton's reagent as it has been reported to improve yields when compared with polyphosphoric acid,[5,6] however, this lead to production of a black powder side-product in addition to the desired product (see **??**). This proved difficult to separate out and thus lowered the yield of the desired quinolone. Cyclisation with polyphosphoric acid produced nitro-PQS **34** cleanly.[7]

Conditions for the reduction of the nitro group were then compared (see Table 1). Baker initially used Zn and HCl, however, this gave a yield over 100 % suggesting coordination of amino-PQS **35** to the Zn.[8] Reduction with $SnCl_2$ was then attempted, however, no product was detected by LCMS. Catalytic hydrogenation was then attempted. We determined that nitro-PQS **34** could not be reduced using H_2 and Pd/C at room temperature and pressure. However, increasing the pressure to 3 atm is sufficient to cause conversion to amino-PQS **35** in 4 h. Achieving 3 atm pressure of H_2 in a lab environment requires the use of a Parr hydrogenator, and it was found to be more convenient to use PtO_2 as a catalyst as this allows the reaction to proceed at room pressure and temperature.[9] Finally, amino-PQS **35** was converted to azido-PQS **36** by reaction with $NaNO_2$ and HCl to form diazo-PQS, followed by displacement of the diazo group using NaN_3 to give the azido-PQS **36**.[4]

Conditions	**Outcome**
$SnCl_2.2H_2O$, MeOH, r.t., 18 h	No reaction
H_2, Pd/C, MeOH, 3 atm, r.t., 4 h.	Product **35**, 100 % yield
H_2, PtO_2, MeOH, 1 atm, r.t., 45 min	Product **35**, 80 % yield

Table 1: Conditions attempted for the synthesis of **35**.

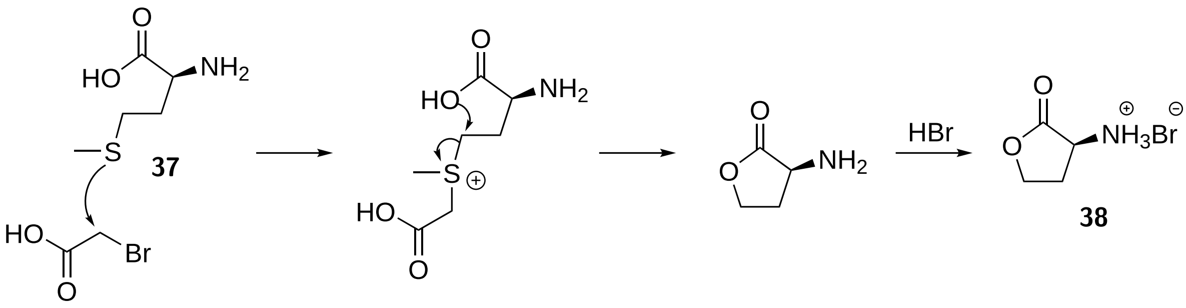


Scheme 2: The synthesis of **36**. a) Mg turnings, THF, r.t., 2 h then reflux, 2 h. b) *N*,*O*-dimethylhydroxyl amine hydrochloride, K_2CO_3, toluene, H_2O, - 5 °C to r.t., 30 min, 71 %. c) THF, 0 °C to r.t., 15 h, 96 %. d) **32**, K_2CO_3, DMF, 90 °C, 1 h, then **31**, r.t., 18 h, 100 %. e) Polyphosphoric acid, 90 °C, 5.5 h, 40 %. f) H_2, PtO_2, MeOH, 1 atm, r.t., 45 min, 80 %. g) i) $NaNO_2$, HCl, H_2O, 0 °C, 50 min. ii) NaN_3, H_2O, r.t., 4 h, 28 % over two steps.

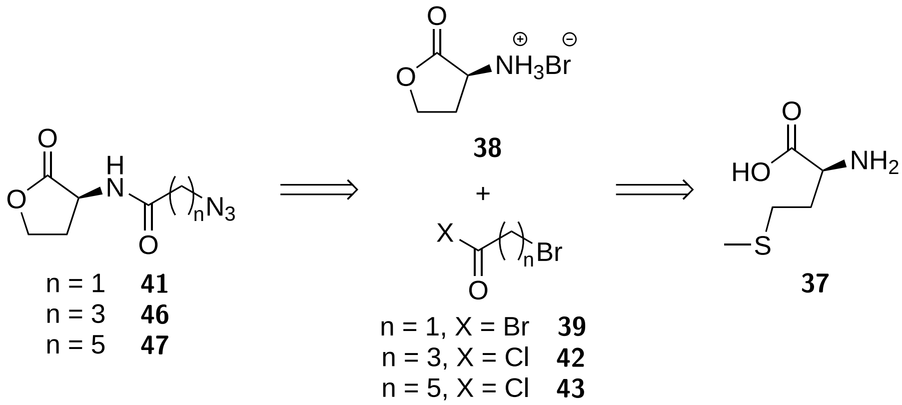
1.3 C_4-HSL derivatives

1.3.1 Retrosynthesis of C_4-HSL derivatives 41, 46 and 47

The azido analogue of C_4-HSL with a C_2 chain **41** (see **??**) has previously been prepared by Stacey *et al.*[10] It uses the cyclisation of L-methionine **37** using bromoacetic acid via the mechanism shown in Scheme 3 to form the homoserine lactone HBr salt **38**. This is then converted by a biphasic one-pot process to the azido-C_2 analogue **41** using bromoacetyl bromide **39** and NaN_3. It was hoped that this procedure could also be used to produce the azido-C_4 and C_6 chain analogues.



Scheme 3: The mechanism of formation of **38**.



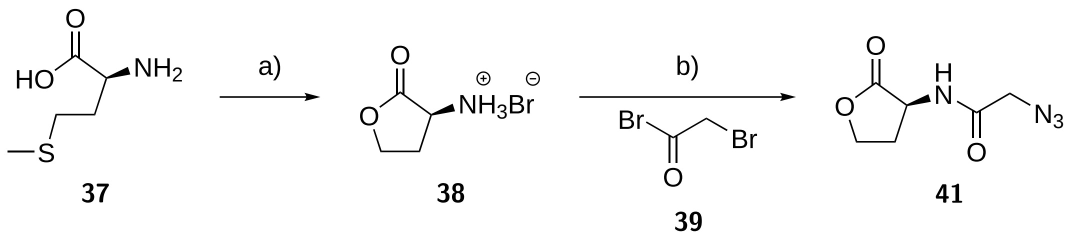
Scheme 4: The retrosynthesis of **41**, **46** and **47**.

1.3.2 Synthesis of C_4-HSL derivatives 41, 46 and 47

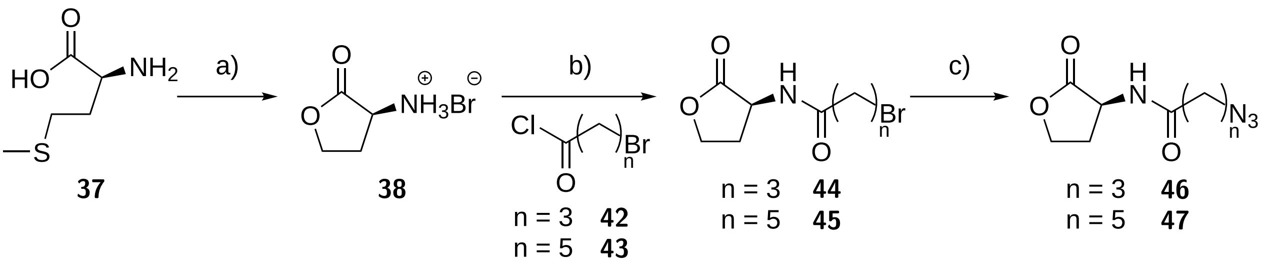
Homoserine lactone HBr salt **38** was synthesised using the procedure developed by Stacey *et al.*,[10] followed by conversion to the azido-C_2 analogue **41** (see Scheme 5). Attempts to convert homoserine lactone **37** to the azido-C_4 analogue using 4-bromobutyryl chloride **42** produced a complex mixture of products. This is likely to be because the S_N2 reaction where the azide anion displaces bromine is slower as the bromine atom being displaced is no longer next to a carbonyl group. Hence, this allows more side reactions to occur instead of the desired reaction. It was therefore decided that the conversion should be carried out as a two-step process, where a bromoacyl chain is first installed, followed by the S_N2 reaction with NaN_3 (see Scheme 6).

Reaction of the homoserine lactone HBr salt **38** with 4-bromobutyryl chloride **42** or 6-bromohexanoyl chloride **43** produced bromo-C_4 analogue **44** or bromo-C_6 analogue **45** respectively. Heating with NaN_3 in DMF converted bromo-C_6 analogue **45** to azido-C_6 analogue **47**.[2] It is hoped that the same conditions can be used to convert bromo-C_4 analogue **44** to azido-C_4 analogue **46** and this will be attempted shortly.

got from Bin Yu

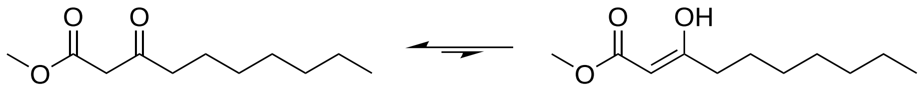


Scheme 5: The synthesis of **41**. a) Bromoacetic acid, *i*-PrOH:H_2O:AcOH (5:5:2), r.t., 18 h, 41 %. b) NaN_3, $NaHCO_3$, H_2O/CH_2Cl_2, r.t., 18 h, 41 %.



Scheme 6: The synthesis of **46** and **47**. a) Bromoacetic acid, *i*-PrOH:H_2O:AcOH (5:5:2), r.t, 18 h, 41 %. b) $NaHCO_3$, H_2O/CH_2Cl_2, r.t., 18 h, **44** : 80 %, **45** : 66 %. c) NaN_3, DMF, 100 °C, 5 h, **47** : 56 %.

1.4 Methyl 3-oxodecanoate 21/22



21 92 %

22 8 %

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 ^{1}H 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)

^{1}**H NMR** (400 MHz, $CDCl_3$) δ / ppm = 3.74 (s, 3 H, $OC\underline{H}_3$), 3.45 (s, 2 H, $C(=O)C\underline{H}_2C(=O)$), 2.53 (t, J = 7.4 Hz, 2 H, $C(=O)C\underline{H}_2CH_2$), 1.60 (quin, J = 7.1 Hz, 2 H, $C(=O)CH_2C\underline{H}_2$), 1.39 - 1.19 (m, 8 H, $C\underline{H}_2C\underline{H}_2C\underline{H}_2C\underline{H}_2CH_3$), 0.88 (t, J = 6.8 Hz, 3 H, $CH_2C\underline{H}_3$)

^{13}**C NMR** (101 MHz, $CDCl_3$) δ / ppm = 202.3 ($CH_3OC(=O)CH_2\underline{C}(=O)$), 167.3 ($CH_3O\underline{C}(=O)CH_2C(=O)$), 51.7 ($O\underline{C}H_3$), 48.5 ($CH_3OC(=O)\underline{C}H_2C(=O)$), 42.5 ($C(=O)\underline{C}H_2CH_2$), 31.3 ($\underline{C}H_2$), 28.7 ($\underline{C}H_2$), 28.6 ($\underline{C}H_2$), 23.1 ($\underline{C}H_2$), 22.2 ($\underline{C}H_2$), 13.6 ($CH_2\underline{C}H_3$)

Enol form 22

TLC R_f = 0.12 (5 % EtO_2/PE)

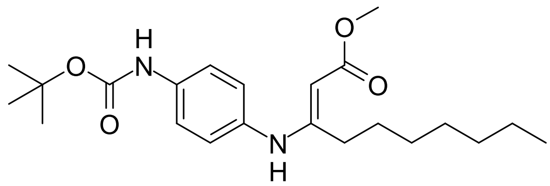
IR (neat) ν_{max} / cm^{-1} = 2927.8 (C-H), 2856.3 (C-H), 1653.8 (C=C), 1629.2 (α,β unsaturated C=O)

^{1}**H NMR** (400 MHz, $CDCl_3$) δ / ppm = 12.02 (s, 1 H, $CO\underline{H}$), 4.99 (s, 1 H, $C(=O)C\underline{H}=COH$), 3.73 (s, 3 H, $OC\underline{H}_3$), 2.20 (t, J = 7.4 Hz, 2 H, $COHC\underline{H}_2$), 1.76 - 1.72 (m, 2 H, $COHCH_2C\underline{H}_2$), 1.39 - 1.19 (m, 8 H, $C\underline{H}_2C\underline{H}_2C\underline{H}_2C\underline{H}_2CH_3$), 0.88 (t, J = 6.8 Hz, 3 H, $CH_2C\underline{H}_3$)

^{13}**C NMR** (101 MHz, $CDCl_3$) δ / ppm = 178.7 ($CH_3OC(=O)CH=\underline{C}OH$), 172.7 ($CH_3O\underline{C}(=O)CH=COH$), 88.2 ($CH_3OC(=O)\underline{C}H=COH$), 50.5 ($O\underline{C}H_3$), 37.9 ($COH\underline{C}H_2CH_2$), 34.6 ($\underline{C}H_2$), 31.2 ($\underline{C}H_2$), 29.0 ($\underline{C}H_2$), 25.9 ($\underline{C}H_2$), 22.3 ($\underline{C}H_2$), 13.6 ($CH_2\underline{C}H_3$)

Spectroscopic data are consistent with the literature.[2,3]

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



Methyl 3-oxodecanoate **21** (500 mg, 2.50 mmol, 1.00 eq.) and *O*-*tert*-butyl *N*-(4-aminophenyl)carbamate **90** (520 mg, 2.50 mmol, 1.00 eq.) were dissolved in MeOH (10 ml) and refluxed for 18 h. The solvent was removed under vacuum and the resulting residue was purified by column chromatography (SiO_2, gradient of 0 to 20 % Et_2O/40-60 P.E.). **24** was obtained as a white amorphous solid (0.169 mg, 0.480 mmol, 19 %).

TLC R_f = 0.30 (30 % Et_2O/40-60 P.E.)

mp T / °C = 78.8 (Et_2O/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)

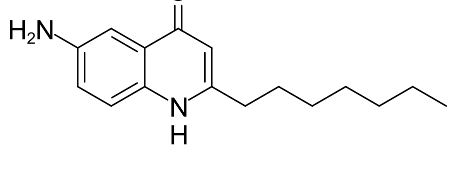
^{1}**H NMR** (400 MHz, $CDCl_3$) δ / ppm = 10.16 (s, 1 H, N$\underline{H}$C(C_7H_{15})=C), 7.35 (d, J = 8.6 Hz, 2 H, *meta* to NHBoc), 7.02 (d, J = 8.7 Hz, 2 H, *meta* to enamine), 6.60 (br s, 1 H, N$\underline{H}$Boc), 4.71 (s, 1 H, C=C$\underline{H}$), 3.70 (s, 3 H, OC$\underline{H}_3$), 2.23 (t, J = 7.7 Hz, 2 H, C$\underline{H}_2$$CH_2CH_2CH_2CH_2CH_2CH_3$), 1.54 (s, 9 H, C(C$\underline{H}_3$)$_3$), 1.40 (quin, J = 7.3 Hz, 2 H, CH_2C$\underline{H}_2$$CH_2CH_2CH_2CH_2CH_3$), 1.33 - 1.16 (m, 8 H, CH_2CH_2C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}_2$$CH_3$), 0.86 (t, J = 7.1 Hz, 3 H, $CH_2CH_2CH_2CH_2CH_2CH_2$C$\underline{H}_3$)

^{13}**C NMR** (101 MHz, $CDCl_3$) δ / ppm = 171.1 ($\underline{C}$(=O)CH=C), 164.3 (C(=O)CH=$\underline{C}$), 152.7 (O$\underline{C}$(=O)NH), 136.0 (*para* to NHBoc), 134.1 ($\underline{C}$NHBoc), 126.3 (*meta* to NHBoc), 119.1 (*ortho* to NHBoc), 83.8 (C(=O)$\underline{C}$H=C), 80.7 ($\underline{C}$(CH_3)$_3$), 50.2 (O$\underline{C}H_3$), 32.2 ($\underline{C}H_2$), 31.6 ($\underline{C}H_2$), 29.1 ($\underline{C}H_2$), 28.8 ($\underline{C}H_2$), 28.3 (C($\underline{C}H_3$)$_3$), 28.0 ($\underline{C}H_2$), 22.6 ($\underline{C}H_2$), 14.0 ($\underline{C}H_3$)

HRMS (ESI^+) m/z / Da = 391.2589, $[M+H]^+$, $[C_{22}H_{35}N_2O_4]^+$ requires 391.2591

Spectroscopic data are consistent with the literature.[1]

1.6 6-Amino-2-heptylquinolin-4-ol 25



Methyl (*E*)-3-((4-((*tert*-butoxycarbonyl)amino)phenyl)amino)dec-2-enoate **24** (168 mg, 0.649 mmol, 1 eq.) and polyphosphoric acid (5 g) were heated to 90 °C for 1 h. The reaction mixture was then poured into $NaHCO_3$ (sat., aq., 50 ml) cooled with ice. The precipitate was collected by vacuum filtration, washed with water (50 ml) and dried under high vacuum. **25** was obtained as a pale yellow powder (121 mg, 0.468 mmol, 72 %).

mp T / °C = 249 (H_2O)

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)

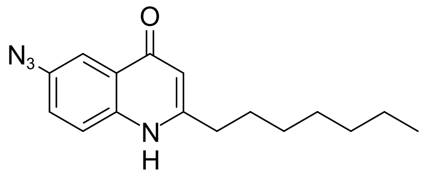
^{1}**H NMR** (400 MHz, DMSO-d$_6$) δ / ppm = 7.26 (d, J = 8.7 Hz, 1 H, *meta* to NH_2), 7.15 (d, J = 2.6 Hz, 1 H, *ortho* to C(=O)), 6.95 (dd, J = 2.7, 8.8 Hz, 1 H, *para* to C(=O)), 5.74 (s, 1 H, *ortho* to CH_2), 5.16 (s, 2 H, $N\underline{H}_2$), 2.52 (t, J = 7.4 Hz, 2 H, $C C\underline{H}_2$), 1.64 (quin, J = 7.6 Hz, 2 H, $CCH_2C\underline{H}_2$), 1.36 - 1.19 (m, 8 H, $C\underline{H}_2C\underline{H}_2C\underline{H}_2C\underline{H}_2CH_3$), 0.86 (t, J = 7.0 Hz, 3 H, $\underline{H}_3$)

^{13}**C NMR** (101 MHz, DMSO-d$_6$) δ / ppm = 176.7 ($\underline{C}$(=O)), 151.7 ($\underline{C}CH_2$), 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 ($\underline{C}H{=}CCH_2$), 105.9 (*ortho* to NH_2 and *ortho* to C(=O)), 33.6 ($C\underline{C}H_2$), 31.6 ($\underline{C}H_2CH_2CH_3$), 29.0 ($\underline{C}H_2$), 29.0 ($\underline{C}H_2$), 28.9 ($\underline{C}H_2$), 22.5 ($\underline{C}H_2CH_3$), 14.4 ($\underline{C}H_3$)

HRMS (ESI$^+$) m/z / Da = 259.1810, $[M+H]^+$, $[C_{16}H_{23}N_2O]^+$ requires 259.1803

Spectroscopic data are consistent with the literature.[1]

1.7 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 % MeoH/CH_2Cl_2)

IR (neat) ν_{max} / cm^{-1} = ??

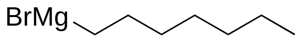
^{1}**H NMR** (400 MHz, MeOD) δ / ppm = 7.73 (d, J = 8.6 Hz, 1 H, *ortho* to NH), 7.71 (d, J = 2.8 Hz, 1 H, *ortho* to N_3 and *ortho* to C(=O)), 7.47 (dd, J = 8.9, 2.7 Hz, 1 H, *para* to C(=O)), 6.24 (s, 1 H, $C(=O)C\underline{H}$), 2.69 (t, J = 7.7 Hz, 2 H, $CC\underline{H}_2$), 1.68 (quin, J = 7.6 Hz, 2 H, $CCH_2C\underline{H}_2$), 1.28 - 1.39 (m, 4 H, $CCH_2CH_2C\underline{H}_2C\underline{H}_2$), 1.18 - 1.28 (m, 4 H, $C\underline{H}_2C\underline{H}_2CH_3$), 0.85 (t, J = 6.8 Hz, 3 H, $C\underline{H}_3$)

^{13}**C NMR** (101 MHz, MeOD) δ / ppm = 172.3 ($\underline{C}$(=O)), 155.5 ($NH\underline{C}CH_2$), 137.4 ($\underline{C}N_3$), 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 ($C(=O)\underline{C}H$), 33.3 ($NHC\underline{C}H_2$), 31.2 ($\underline{C}H_2CH_2CH_3$), 28.3 - 28.5 ($\underline{C}H_2\underline{C}H_2\underline{C}H_2CH_2CH_2CH_3$), 22.1 ($\underline{C}H_2CH_3$), 14.0 ($\underline{C}H_3$)

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

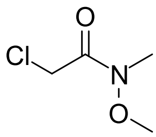
Spectroscopic data are not consistent with the literature.[1] ????

1.8 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.

1.9 2-Chloro-*N*-methoxy-*N*-methylacetamide 30



N,*O*-Dimethylhydroxyl amine hydrochloride (6.00 g, 61.5 mmol, 1 eq.) and toluene (75 ml) were added successively to a stirred solution of potassium carbonate (22.4 g, 162 mmol, 2.63 eq.) in water (75 ml) at 0 °C under argon. The mixture was cooled to - 5 °C and chloroacetyl chloride (5.88 ml, 73.8 mmol, 1.20 eq.) was added dropwise over 5 min. The mixture was allowed to warm to r.t. over 30 min, then the organic layer was separated and the aqueous layer was extracted with toluene (3×20 ml). The combined organic extracts were dried with $MgSO_4$ 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)

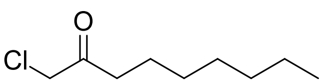
IR (neat) ν_{max} / cm^{-1} = 3016.7 (C-H), 2966.4 (C-H), 2946.7 (C-H), 2827.7 (C-H), 1666.2 (C=O)

^{1}**H NMR** (400 MHz, $CDCl_3$) δ / ppm = 4.20 (s, 2 H, $ClC\underline{H}_2C{=}O$), 3.71 (m, 3 H, $OC\underline{H}_3$), 3.18 (s, 3 H, $NC\underline{H}_3$)

^{13}**C NMR** (101 MHz, $CDCl_3$) δ / ppm = 167.4 (C=O), 61.6 ($O\underline{C}H_3$), 40.9 ($Cl\underline{C}H_2C{=}O$), 32.6 ($N\underline{C}H_3$)

Spectroscopic data are consistent with the literature.[11]

1.10 1-Chlorononan-2-one 31



2-Chloro-*N*-methoxy-*N*-methylacetamide (1.00 g, 7.26 mmol, 1 eq.) was added to a dry flask under argon. THF (20 ml) was added and the flask cooled to 0 °C. Heptyl magnesium bromide (~ 1 M, 15.0 ml, 15.0 mmol, 2.07

eq.) was added dropwise over 5 min, then the mixture was allowed to warm to r.t. and stirred for 15 h. The reaction mixture was then poured into HCl (aq., 2 N, 60 ml) at 0 °C and stirred for 10 min. The mixture was extracted with toluene (30 ml) and the aqueous layer discarded. The organic layer was washed with brine and dried with $MgSO_4$, and the solvent was removed by rotary evaporation. **31** was obtained as a colourless oil (1.23 g, 6.96 mmol, 96 %).

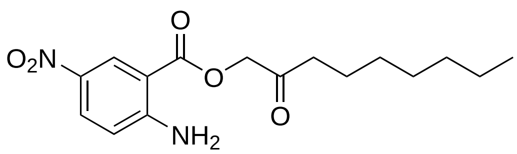
IR (neat) ν_{max} / cm^{-1} = 2951.7 (C-H), 2925.0 (C-H), 2855.5 (C-H), 1720.4 (C=O)

^{1}**H NMR** (400 MHz, $CDCl_3$) δ / ppm = 4.05 (s, 2 H, $ClC\underline{H}_2C(=O)$), 2.54 (t, J = 7.4 Hz, 2 H, $C(=O)C\underline{H}_2CH_2$), 1.59 (quin, J = 7.0 Hz, 2 H, $C(=O)CH_2C\underline{H}_2$), 1.34 - 1.21 (m, 8 H, $C\underline{H}_2C\underline{H}_2C\underline{H}_2C\underline{H}_2CH_3$), 0.87 (t, J = 6.8 Hz, 3 H, $C\underline{H}_3$)

^{13}**C NMR** (101 MHz, $CDCl_3$) δ / ppm = 202.6 ($\underline{C}(=O)$), 48.1 ($\underline{C}H_2Cl$), 39.6 ($C(=O)\underline{C}H_2CH_2$), 31.5 ($\underline{C}H_2CH_2 CH_3$), 28.9 ($\underline{C}H_2$), 28.9 ($\underline{C}H_2$), 23.5 ($C(=O)CH_2\underline{C}H_2$), 22.5 ($\underline{C}H_2CH_3$), 13.9 ($\underline{C}H_3$)

Spectroscopic data are consistent with the literature.[11]

1.11 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 Na_2HCO_3 (aq., 10 %, 50 ml) and ice (~ 20 g). The precipitate was collected by vacuum filtration, washed with water and dried under high vacuum. **33** was obtained as a yellow amorphous solid (0.674 g, 2.00 mmol, 100 %).

mp T / °C = 135 (H_2O)

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)

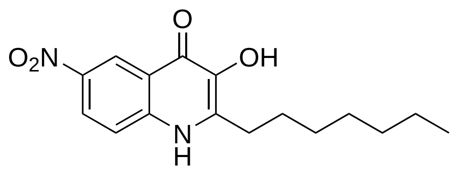
^{1}**H NMR** (400 MHz, DMSO-d_6) δ / ppm = 8.66 (d, J = 2.8 Hz, 1 H, *ortho* to C(=O)), 8.12 (dd, J = 2.8, 9.4 Hz, 1 H, *para* to C(=O)), 6.93 (d, J = 9.4 Hz, 1 H, *meta* to C(=O)), 5.05 (s, 2 H, $OC\underline{H}_2C(=O)$), 2.49 (t, J = 7.4 Hz, 2 H, $C(=O)C\underline{H}_2CH_2$), 1.52 (quin, J = 7.2 Hz, 2 H, $C(=O)CH_2C\underline{H}_2$), 1.32 - 1.20 (m, 8 H, $C\underline{H}_2C\underline{H}_2C\underline{H}_2C\underline{H}_2CH_3$), 0.86 (t, J = 6.8 Hz, 3 H, $C\underline{H}_3$)

^{13}**C NMR** (101 MHz, DMSO-d_6) δ / ppm = 204.4 ($OCH_2\underline{C}(=O)$), 165.6 ($\underline{C}(=O)O$), 156.3 (*ipso* to NH_2), 135.7 (*ipso* to NO_2), 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 ($O\underline{C}H_2C(=O)$), 38.3 ($C(=O)\underline{C}H_2CH_2$), 31.6 ($\underline{C}H_2CH_2CH_3$), 28.9 ($\underline{C}H_2$), 28.9 ($\underline{C}H_2$), 23.2 ($C(=O)CH_2\underline{C}H_2$), 22.5 ($\underline{C}H_2CH_3$), 14.4 ($\underline{C}H_3$)

HRMS (ESI^+) m/z / Da = 323.1610, $[M+H]^+$, $[C_{16}H_{23}N_2O_5]^+$ requires 323.1607

Spectroscopic data are consistent with the literature.[1]

1.12 6-Nitro-2-heptyl-3-hydroxyquinolin-4(1*H*)-one 34



2-Oxononyl 2-amino-5-nitrobenzoate (100 mg, 0.340 mmol, 1 eq.) and polyphosphoric acid (300 mg) were stirred for 5.5 h at 90 °C under argon. The mixture was then poured into $NaHCO_3$ (sat., aq., 50 ml) cooled on ice. The precipitate was collected by vacuum filtration, washed with water (50 ml) and dried under high vacuum. **34** was obtained as a yellow-brown amorphous solid (44 mg, 0.145 mmol, 43 %).

mp T / °C = 223 (H_2O, 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)

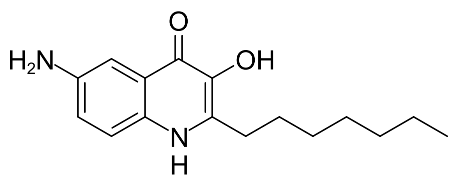
^{1}**H NMR** (400 MHz, DMSO-d_6) δ / ppm = 12.00 (s, 1 H, N$\underline{H}$), 8.91 (d, J = 2.8 Hz, 1 H, *ortho* to C=O), 8.29 (dd, J = 2.7, 9.2 Hz, 1 H, *para* to C=O), 7.70 (d, J = 9.3 Hz, 1 H, *meta* to C=O), 2.75 (t, J = 7.7 Hz, 2 H, $C\underline{H}_2$), 1.67 (quin, J = 7.3 Hz, 2 H, $CCH_2C\underline{H}_2$), 1.36 - 1.23 (m, 8 H, $C\underline{H}_2C\underline{H}_2C\underline{H}_2C\underline{H}_2CH_3$), 0.85 (t, J = 7.0 Hz, 3 H, $C\underline{H}_3$)

^{13}**C NMR** (101 MHz, DMSO-d_6) δ / ppm = 169.7 ($\underline{C}$=O), 141.9 (*para* to NO_2), 140.7 (*ipso* to NO_2), 139.6 (*ipso* to OH), 137.3 ($\underline{C}$=COH), 124.3 (*para* to C=O), 122.3 (*ortho* to NO_2 and *ortho* to C=O), 121.5 (*ipso* to C=O), 120.0 (*meta* to NO_2 and *meta* to C=O), 31.6 ($\underline{C}H_2CH_2CH_3$), 29.2 ($\underline{C}H_2$), 28.9 ($\underline{C}H_2$), 28.5 ($C\underline{C}H_2$), 28.1 ($CCH_2\underline{C}H_2$), 22.5 ($\underline{C}H_2CH_3$), 14.4 ($\underline{C}H_3$)

HRMS (ESI^+) m/z / Da = 305.1501, $[M+H]^+$, $[C_{16}H_{21}N_2O_4]^+$ requires 305.1500

Spectroscopic data are consistent with the literature.[1]

1.13 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 PtO_2 (2 mg, 10 weight %) were stirred in MeOH (1 ml) under a H_2 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 powder (14.5 mg, 0.0529 mmol, 80 %).

mp (MeOH) T / °C = 176

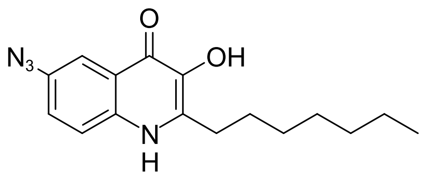
IR (neat) ν_{max} / cm^{-1} = 3000.00 (O-H, br) 2925.41 (C-H), 2854.09 (C-H), 1613.43 (aromatic) 1555.29 (aromatic) 1504.47 (aromatic)

^{1}**H NMR** (400 MHz, MeOD) δ / ppm = 11.12 (s, 1 H, N$\underline{H}$), 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, CC$\underline{H}_2$), 1.75 (quin, J = 7.8 Hz, 2 H, CCH$_2$C$\underline{H}_2$), 1.48 - 1.22 (m, J = 5.4 Hz, 8 H, C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}_2$CH$_3$), 0.89 (t, J = 6.7 Hz, 3 H, C$\underline{H}_3$)

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

HRMS (ESI$^+$) m/z / Da = 275.1760, [M+H]$^+$, [C$_{16}$H$_{23}$N$_2$O$_2$]$^+$ requires 275.1762 Spectroscopic data are not consistent with the literature.[1] It is possible that Baker's product is a salt as her ^{13}C NMR value for the carbon *ipso* to NH$_2$ is rather high.[12]

1.14 6-Azido-2-heptyl-3-hydroxyquinolin-4(1*H*)-one 36



6-Amino-2-heptyl-3-hydroxyquinolin-4(1*H*)-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$_2$O (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$_2$O (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 powder (5.5 mg, 0.0183 mmol, 28 %).

mp (H$_2$O/MeOH) T / °C = pending

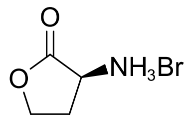
IR (neat) ν_{max} / cm^{-1} = pending

^{1}**H NMR** (400 MHz, DMSO-d$_6$) δ / ppm = 7.74 (s, 1 H, *ortho* to C=O), 7.65 (d, J = 6.9 Hz, 1 H, *meta* to C(=O)), 7.32 (d, J = 7.4 Hz, 1 H, *para* to C(=O)), 2.75 (t, J = 7.5 Hz, 2 H, CC$\underline{H}_2$), 1.67 (quin, J = 6.4 Hz, 2 H, CCH$_2$C$\underline{H}_2$), 1.43 - 1.13 (m, 8 H, C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}_2$CH$_3$), 0.85 (t, J = 6.8 Hz, 3 H, C$\underline{H}_3$)

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

Spectroscopic data are consistent with the literature.[1]

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



L-Methionine (3.04 g, 20.4 mmol, 1 eq.) and bromoacetic acid (3.08 g, 22.2 mmol, 1.09 eq.) were dissolved in *i*-PrOH (12.5 ml), H_2O (12.5 ml) and AcOH (5 ml). The reaction was refluxed for 15 h then concentrated under vacuum. The resulting brown oil was added to a mixture of *i*-PrOH (16 ml) and HBr (33 % in AcOH, 4 ml), causing the precipitation of a pale pink powder. The precipitate was collected by filtration and washed with *i*-PrOH (20 ml). The filtrate was concentrated under vacuum and precipitated again using the same procedure. The two crops of precipitate were combined. **38** was obtained as a pale pink amorphous solid (1.73 g, 9.50 mmol, 41 % yield).

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

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

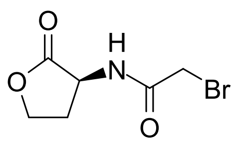
^{1}**H NMR** (400 MHz, DMSO-d$_6$) δ / ppm = 8.59 (br s, 3 H, N$\underline{H}_3^+$), 4.46 (dt, J = 1.3, 8.9 Hz, 1 H, OC$\underline{H}$H), 4.37 (dd, J = 8.8, 11.4 Hz, 1 H, C$\underline{H}$NH_3^+), 4.29 (ddd, J = 6.1, 8.8, 10.9 Hz, 1 H, OCH$\underline{H}$), 2.57 (dddd, J = 1.2, 6.1, 8.9, 12.3 Hz, 1 H, OCH_2C$\underline{H}$H), 2.26 (dtd, J = 9.0, 11.2, 12.2 Hz, 1 H, OCH_2CH$\underline{H}$)

^{13}**C NMR** (101 MHz, DMSO-d$_6$) δ / ppm = 173.3 ($\underline{C}$=O), 66.2 (O$\underline{C}H_2$), 47.8 ($\underline{C}$HNH_3^+), 27.0 (OC$H_2\underline{C}H_2$)

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

The data are consistent with the literature.[10]

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



(*S*)-3-Aminodihydrofuran-2(3*H*)-one hydrobromide **38** (100 mg, 0.549 mmol, 1.08 eq.) and $NaHCO_3$ (84.9 mg, 1.01 mmol, 2.00 eq.) were dissolved in CH_2Cl_2 (2 ml) and H_2O (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 CH_2Cl_2 was removed under vacuum. The aqueous phase was extracted with EtOAc (4×10 ml). The combined organic layers were dried with $MgSO_4$ and the solvent was removed under reduced pressure. **40** was obtained as white, needle-like crystals (88.0 mg, 0.396 mmol, 74 %).

mp T / °C = 132 (EtOAc)

IR (neat) ν_{max} / 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}**H NMR** (400 MHz, $CDCl_3$) δ / ppm = 6.94 (br s, 1 H, N$\underline{H}$), 4.57 (ddd, J = 11.7, 8.6, 5.9 Hz, 1 H, C$\underline{H}$NH), 4.51 (td, J = 9.2, 1.0 Hz, 1 H, OC$\underline{H}$H), 4.32 (ddd, J = 11.3, 9.4, 5.9 Hz, 1 H, OCH$\underline{H}$), 3.93 (s, 1 H, C$\underline{H}$HBr), 3.93 (s, 1 H, CH$\underline{H}$Br), 2.87 (dddd, J = 12.6, 8.6, 5.9, 1.3 Hz, 1 H, $OCH_2C\underline{H}H$), 2.22 (dtd, J = 12.6, 11.5, 11.5, 8.9 Hz, 1 H, $OCH_2CH\underline{H}$)

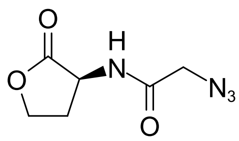
^{13}**C NMR** (101 MHz, $CDCl_3$) δ / ppm = 174.6 (O$\underline{C}$=O), 166.4 ($\underline{C}$(=O)NH), 66.1 ($O\underline{C}H_2$), 49.8 ($\underline{C}$HNHC=O), 29.9 ($OCH_2\underline{C}H_2$), 28.2 ($O{=}C\underline{C}H_2Br$)

HRMS The compound does not ionise.

$[\boldsymbol{\alpha}]_D^{20}$ / $°10^{-1}cm^2g^{-1}$ = 27.0 (c / $g(100\ ml)^{-1}$ = 0.00740 , $CHCl_3$)

The data are consistent with the literature.[10,13]

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



(3*S*)-2-Oxotetrahydrofuran-3-aminium bromide **38** (100 mg, 0.552 mmol, 1.08 eq.), NaN_3 (85.7 mg, 1.32 mmol, 2.61 eq.) and $NaHCO_3$ (84.9 mg, 1.01 mmol, 2.00 eq.) were dissolved in CH_2Cl_2 (2 ml) and H_2O (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 48 h, after which the CH_2Cl_2 was removed under vacuum. The aqueous phase was extracted with EtOAc (4×10 ml). The combined organic layers were dried with $MgSO_4$ 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 (N_3), 1782.9 (lactone C=O), 1661.4 (amide C=O), 1536.8 (N-H bend)

^{1}**H NMR** (400 MHz, $CDCl_3$) δ / ppm = 7.05 (br d, J = 6.5 Hz, 1 H, N$\underline{H}$), 4.64 (ddd, J = 11.6, 8.7, 6.8 Hz, 1 H, C$\underline{H}$NH), 4.48 (td, J = 9.1, 1.3 Hz, 1 H, OC$\underline{H}$H), 4.30 (ddd, J = 11.2, 9.2, 6.0 Hz, 1 H, OCH$\underline{H}$), 4.04 (s, 2 H, $C\underline{H_2}N_3$), 2.76 (dddd, J = 12.5, 8.8, 6.0, 1.4 Hz, 1 H, $OCH_2C\underline{H}H$), 2.25 (dtd, J = 12.5, 11.4, 11.4, 8.9 Hz, 1 H, $OCH_2CH\underline{H}$)

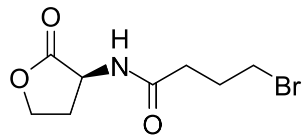
^{13}**C NMR** (101 MHz, $CDCl_3$) δ / ppm = 174.9 (O$\underline{C}$=O), 167.5 ($\underline{C}$=ONH), 66.0 ($O\underline{C}H_2$), 52.2 ($O{=}C\underline{C}H_2N_3$), 48.9 ($\underline{C}$HNHC=O), 29.7 ($OCH_2\underline{C}H_2$)

HRMS The compound does not ionise.

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

The data are consistent with the literature.[10]

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



(*S*)-3-Aminodihydrofuran-2(3*H*)-one hydrobromide **38** (200 mg, 1.10 mmol, 1.00 eq.) and $NaHCO_3$ (170 mg, 2.02 mmol, 1.84 eq.) were dissolved in CH_2Cl_2 (2 ml) and H_2O (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 CH_2Cl_2 was removed under vacuum. The aqueous phase was extracted with EtOAc (7×5 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 / °C = 105 (EtOAc)

IR (neat) ν_{max} / 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}**H NMR** (400 MHz, $CDCl_3$) δ / ppm = 6.31 (br d, J = 5.5 Hz, 1 H, N$\underline{H}$), 4.59 (ddd, J = 6.2, 8.7, 11.5 Hz, 1 H, C$\underline{H}$NH), 4.48 (dt, J = 1.2, 8.9 Hz, 1 H, OC$\underline{H}$H), 4.30 (ddd, J = 5.8, 9.3, 11.3 Hz, 1 H, OCH$\underline{H}$), 3.49 (t, J = 6.3 Hz, 2 H, C$\underline{H_2}$Br), 2.82 (dddd, J = 1.3, 5.9, 8.7, 12.5 Hz, 1 H, $OCH_2C\underline{H}H$), 2.47 (t, J = 7.3 Hz, 2 H, C(=O)C$\underline{H_2}$), 2.26 - 2.15 (m, 3 H, $OCH_2CH\underline{H}$ and $C\underline{H_2}CH_2Br$)

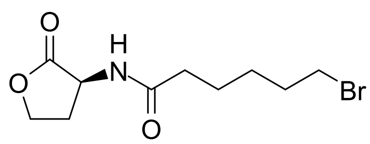
^{13}**C NMR** (101 MHz, $CDCl_3$) δ / ppm = 175.4 (O$\underline{C}$=O), 172.3 ($\underline{C}$(=O)NH), 66.1 (O$\underline{C}H_2$), 49.3 ($\underline{C}$HNHC=O), 33.9 (C(=O)$\underline{C}H_2$), 33.1 ($\underline{C}H_2$Br), 30.3 ($OCH_2\underline{C}H_2$), 27.9 ($C(=O)CH_2\underline{C}H_2$)

HRMS The compound does not ionise.

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

The compound has not been reported previously.

1.19 (*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 / °C = 106 (CH_2Cl_2/H_2O)

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)

^{1}**H NMR** (400 MHz, $CDCl_3$) δ / ppm = 6.09 (br d, J = 5.7 Hz, 1 H, N$\underline{\text{H}}$), 4.57 (ddd, J = 5.9, 8.6, 11.6 Hz, 1 H, C$\underline{\text{H}}$NH), 4.50 (dt, J = 1.3, 9.1 Hz, 1 H, OC$\underline{\text{H}}$H), 4.31 (ddd, J = 5.9, 9.3, 11.3 Hz, 1 H, OCH$\underline{\text{H}}$), 3.43 (t, J = 6.7 Hz, 2 H, C$\underline{\text{H}_2}$Br), 2.88 (dddd, J = 1.3, 5.9, 8.6, 12.6 Hz, 1 H, OCH_2C$\underline{\text{H}}$H), 2.30 (dt, J = 1.8, 7.5 Hz, 2 H, C(=O)C$\underline{\text{H}_2}$), 2.16 (dtd, J = 8.9, 11.5, 12.5 Hz, 1 H, OCH_2CH$\underline{\text{H}}$), 1.90 (quin, J = 7.2 Hz, 2 H, C$\underline{\text{H}_2}$$CH_2$Br), 1.71 (quin, J = 7.6 Hz, 2 H, C(=O)CH_2C$\underline{\text{H}_2}$), 1.59 - 1.46 (m, 2 H, C(=O)CH_2CH_2C$\underline{\text{H}_2}$)

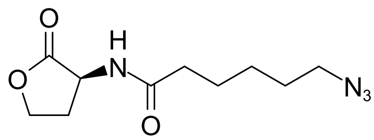
^{13}**C NMR** (101 MHz, $CDCl_3$) δ / ppm = 175.5 (O$\underline{\text{C}}$=O), 173.3 ($\underline{\text{C}}$(=O)NH), 66.1 (O$\underline{\text{C}}$$H_2$), 49.3 ($\underline{\text{C}}$HNHC=O), 35.8 ($\underline{\text{C}}$$H_2$Br), 33.5 (C(=O)$\underline{\text{C}}$$H_2$), 32.3 ($\underline{\text{C}}$$H_2CH_2$Br), 30.5 ($OCH_2$$\underline{\text{C}}$$H_2$), 27.6 (C(=O)$CH_2$$\underline{\text{C}}$$H_2$), 24.4 (C(=O)$CH_2$ $CH_2$$\underline{\text{C}}$$H_2$)

HRMS (ESI$^+$) m/z / Da = 278.0381, [M+H]$^+$, $[C_{10}H_{17}BrNO_3]^+$ requires 278.0386

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

The compound has not been reported previously.

1.20 (*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)

^{1}**H NMR** (400 MHz, $CDCl_3$) δ / ppm = 5.96 (d, J = 4.2 Hz, 1 H, N$\underline{\text{H}}$), 4.54 (ddd, J = 11.7, 8.6, 5.7 Hz, 1 H, C$\underline{\text{H}}$NH), 4.49 (td, J = 9.1, 1.0 Hz, 1 H, OC$\underline{\text{H}}$H), 4.30 (ddd, J = 11.3, 9.4, 5.8 Hz, 1 H, OCH$\underline{\text{H}}$), 3.29 (t, J = 6.9 Hz, 2 H, C$\underline{\text{H}_2}$$N_3$), 2.88 (dddd, J = 12.5, 8.6, 5.8, 1.1 Hz, 1 H, OCH_2C$\underline{\text{H}}$H), 2.28 (t, J = 7.5 Hz, 1 H, C(=O)C$\underline{\text{H}}$H), 2.28 (t, J = 7.4 Hz, 1 H, C(=O)CH$\underline{\text{H}}$), 2.14 (dtd, J = 12.3, 11.5, 11.5, 8.8 Hz, 1 H, OCH_2C$\underline{\text{H}}$H), 1.70 (quin, J = 7.6 Hz, 2 H, C$\underline{\text{H}_2}$$CH_2N_3$), 1.63 (quin, J = 7.2 Hz, 2 H, C(=O)CH_2C$\underline{\text{H}_2}$), 1.38 - 1.49 (m, 2 H, C(=O)CH_2CH_2C$\underline{\text{H}_2}$)

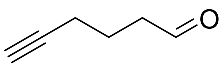
^{13}**C NMR** (101 MHz, $CDCl_3$) δ / ppm = 175.4 (O$\underline{\text{C}}$=O), 172.2 ($\underline{\text{C}}$(=O)NH), 66.1 (O$\underline{\text{C}}$$H_2$), 51.2 ($\underline{\text{C}}$$H_2N_3$), 49.4 ($\underline{\text{C}}$HNHC=O), 35.9 (C(=O)$\underline{\text{C}}$$H_2$), 30.7 ($OCH_2$$\underline{\text{C}}$$H_2$), 28.6 ($\underline{\text{C}}$$H_2CH_2N_3$), 26.3 (C(=O)$CH_2$$\underline{\text{C}}$$H_2$), 24.8 (C(=O)$CH_2$ $CH_2$$\underline{\text{C}}$$H_2$)

HRMS (ESI$^+$) m/z / Da = 241.1289, [M+H]$^+$, $[C_{10}H_{17}N_4O_3]^+$ requires 241.1295

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

The compound has not been reported previously.

1.21 Hex-5-ynal 49



Pyridinium chlorochromate (14.6 g, 68.1 mmol, 1.50 eq) and DCM (500 ml) were stirred at r.t. under argon. 5-hexyn-1-ol **48** (5.00 ml, 45.4 mmol, 1 eq.) was added and the reaction mixture was stirred for 5 h followed by addition of Et_2O (125 ml) and silica gel (62.5 g). The suspension was stirred for 1 h then filtered through a pad of silica (100 g) and washed with Et_2O. The solvent was removed by rotary evaporation. **49** was obtained as a pale yellow-green oil (4.72 g, 49.1 mmol, 72 %).

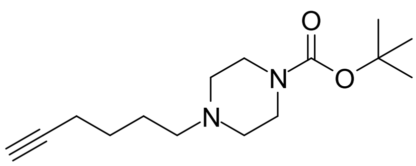
IR (neat) ν_{max} / cm^{-1} = 3292.7 (alkyne C-H), 2943.3 (alkane C-H), 2830.9 (aldehyde C-H), 2728.6 (aldehyde C-H), 1720.3 (aldehyde C=O)

^{1}**H NMR** (400 MHz, $CDCl_3$) δ / ppm = 9.80 (s, 1 H, C(=O)$\underline{H}$), 2.60 (t, J = 7.1 Hz, 2 H, C$\underline{H}_2$C(=O)H), 2.26 (dt, J = 2.6, 6.8 Hz, 2 H, HC≡CC$\underline{H}_2$), 1.98 (t, J = 2.7 Hz, 1 H, $\underline{H}$C≡C), 1.85 (quin, J = 7.0 Hz, 2 H, HC≡CCH$_2$C$\underline{H}_2$)

^{13}**C NMR** (101 MHz, $CDCl_3$) δ / ppm = 201.6 ($\underline{C}$(=O)), 83.1 (HC≡$\underline{C}$), 69.3 (H$\underline{C}$≡C), 42.4 ($\underline{C}$H$_2$C(=O)), 20.7 ($\underline{C}$H$_2$CH$_2$C(=O)), 17.6 (HC≡C$\underline{C}$H$_2$)

Spectroscopic data are consistent with the literature.[14]

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



Hex-5-ynal **49** (0.407 g, 4.24 mmol, 1.00 eq.) and *tert*-butyl piperazine-1-carboxylate (0.791 g, 4.24 mmol, 1.00 eq.) were stirred under a N_2 atmosphere in 1,2-dichloroethane (20 ml) for 2.5 h followed by addition of sodium triacetoxyborohydride (6.25 g, 29.5 mmol, 6.96 eq.) in four portions over 4 d. The mixture was stirred for a further day then $NaHCO_3$ (sat., aq., 120 ml) was added and the product extracted with EtOAc (2×100 ml). The solvent was dried over $MgSO_4$ and removed by rotary evaporation. **51** was obtained as a colourless liquid (1.12 g, 4.21 mmol, 99 %).

TLC R_f (10 % MeOH/CH_2Cl_2) = 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)

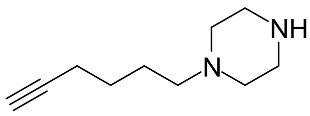
^{1}**H NMR** (400 MHz, $CDCl_3$) δ / ppm = 3.44 (t, J = 5.2 Hz, 4 H, $CH_2CH_2CH_2N(CH_2C\underline{H}_2)CH_2C\underline{H}_2$), 2.39 (t, J = 5.1 Hz, 4 H, $CH_2CH_2CH_2N(C\underline{H}_2)C\underline{H}_2$), 2.37 (t, J = 7.3 Hz, 2 H, $CH_2CH_2C\underline{H}_2N$), 2.23 (dt, J = 2.7, 6.8 Hz, 2 H, $HC{\equiv}CC\underline{H}_2$), 1.96 (t, J = 2.7 Hz, 1 H, $\underline{H}C{\equiv}C$), 1.65 - 1.53 (m, 4 H, $HC{\equiv}CCH_2C\underline{H}_2C\underline{H}_2$), 1.47 (s, 9 H, $C\underline{H}_3$)

^{13}**C NMR** (101 MHz, $CDCl_3$) δ / ppm = 154.7 ($N\underline{C}(=O)O$), 84.2 ($HC{\equiv}\underline{C}$), 79.6 ($\underline{C}(CH_3)_3$), 68.5 ($H\underline{C}{\equiv}C$), 60.4 ($CH_2CH_2\underline{C}H_2N$), 58.0 ($CH_2CH_2CH_2N(\underline{C}H_2)\underline{C}H_2$), 53.0 ($CH_2CH_2CH_2N(CH_2\underline{C}H_2)CH_2\underline{C}H_2$), 28.4 ($C(\underline{C}H_3)_3$), 26.3 ($\underline{C}H_2CH_2N$), 25.7 ($HC{\equiv}CCH_2\underline{C}H_2$), 18.3 ($HC{\equiv}C\underline{C}H_2$)

HRMS (ESI^+) m/z / Da = 267.2073, $[M+H]^+$, $[C_{15}H_{27}N_2O_2]^+$ requires 267.2064

The compound has not been reported previously.

1.23 1-(Hex-5-yn-1-yl)piperazine 52



tert-Butyl 4-(hex-5-yn-1-yl)piperazine-1-carboxylate **51** (763 mg, 2.86 mmol) was stirred in TFA (10 ml) at r.t. for 2 h. The TFA was removed under vacuum followed by co-evaporation with CH_2Cl_2 (2×20 ml). The oil was diluted with H_2O (10 ml) and the pH adjusted to 14 with NaOH (10 % aq.). This mixture was extracted with CH_2Cl_2 (2×20 ml) and the combined organic layers were dried over $MgSO_4$. The solvent was removed under vacuum and purified by column chromatography (SiO_2 $MeOH/CH_2Cl_2$ 3:7). **52** was obtained as a colourless liquid (476 mg, 2.86 mmol, 100 %).

TLC R_f (30 % $MeOH/CH_2Cl_2$) = 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)

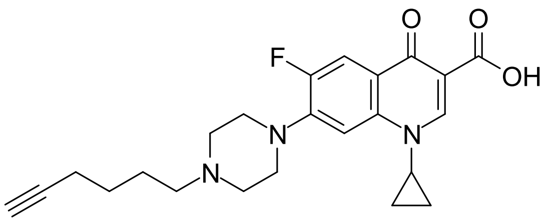
^{1}**H NMR** (400 MHz, $CDCl_3$) δ / ppm = 2.88 (t, J = 4.9 Hz, 4 H, $CH_2CH_2CH_2N(CH_2C\underline{H}_2)CH_2C\underline{H}_2$), 2.39 (m, 4 H, $CH_2CH_2CH_2N(C\underline{H}_2)C\underline{H}_2$), 2.31 (t, J = 7.1 Hz, 2 H, $HC{\equiv}CCH_2CH_2CH_2C\underline{H}_2N$), 2.20 (dt, J = 2.7, 6.8 Hz, 2 H, $HC{\equiv}CC\underline{H}_2$), 2.05 (br s, 1 H, $N\underline{H}$), 1.93 (t, J = 2.7 Hz, 1 H, $\underline{H}C{\equiv}C$), 1.65 - 1.48 (m, 4 H, $HC{\equiv}CCH_2C\underline{H}_2C\underline{H}_2$-$CH_2N$)

^{13}**C NMR** (101 MHz, $CDCl_3$) δ / ppm = 84.3 ($HC{\equiv}\underline{C}$), 68.4 ($H\underline{C}{\equiv}C$), 58.6 ($CH_2CH_2\underline{C}H_2N$), 54.5 ($CH_2CH_2CH_2N(\underline{C}H_2)\underline{C}H_2$), 46.0 ($CH_2CH_2CH_2N(CH_2\underline{C}H_2)CH_2\underline{C}H_2$), 26.4 ($CH_2\underline{C}H_2CH_2N$), 25.7 ($HC{\equiv}CCH_2\underline{C}H_2$), 18.3 ($HC{\equiv}C\underline{C}H_2$)

HRMS (ESI^+) m/z / Da = 167.1548, $[M+H]^+$, $[C_{10}H_{19}N_2]^+$ requires 167.1548

The compound has not been reported previously.

1.24 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-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 recrystalisation 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/CH_2Cl_2)

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)

^{1}**H NMR** (500 MHz, DMSO-d_6) δ / ppm = 15.12 (br s, 1 H, C(=O)O$\underline{H}$), 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, $NC\underline{H}(CH_2)_2$ and $CH_2CH_2CH_2N(CH_2C\underline{H}_2)CH_2CH_2$), 3.54 - 3.68 (br m, 2 H, $CH_2CH_2CH_2N(C\underline{H}_2)CH_2$), 3.45 (br. t, J = 11.6 Hz, 2 H, $CH_2CH_2CH_2N(CH_2CH_2)CH_2C\underline{H}_2$), 3.21 - 3.29 (br m, 2 H, $CH_2CH_2CH_2N(CH_2CH_2)CH_2C\underline{H}_2$), 3.11 - 3.20 (br m, 2 H, $CH_2CH_2CH_2N(CH_2)C\underline{H}_2$), 2.84 (t, J = 2.7 Hz, 1 H, $\underline{H}C{\equiv}C$), 2.24 (td, J = 7.0, 2.7 Hz, 2 H, $HC{\equiv}CC\underline{H}_2$), 1.83 (br. quin, J = 7.5 Hz, 2 H, $HC{\equiv}CCH_2CH_2C\underline{H}_2$), 1.52 (quin, J = 7.4 Hz, 2 H, $HC{\equiv}CCH_2C\underline{H}_2$), 1.29 - 1.36 (m, 2 H, $NCH(C\underline{H}H)_2$), 1.16 - 1.23 (m, 2 H, $NCH(CH\underline{H})_2$)

^{13}**C NMR** (126 MHz, DMSO-d_6) δ / ppm = 176.4 ($\underline{C}$(=O)CC(=O)OH), 165.8 ($\underline{C}$(=O)OH), 152.8 (d, J = 248.5 Hz, *ipso* to F), 148.2 ($\underline{C}$HCC(=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)$\underline{C}$C(=O)OH), 83.9 ($HC{\equiv}\underline{C}$), 71.8 ($H\underline{C}{\equiv}C$), 55.0 ($CH_2CH_2\underline{C}H_2N$), 50.5 ($CH_2CH_2CH_2N(\underline{C}H_2)\underline{C}H_2$), 46.3 ($CH_2CH_2CH_2N(CH_2\underline{C}H_2)CH_2\underline{C}H_2$), 36.0 ($N\underline{C}H(CH_2)_2$), 25.2 ($HC{\equiv}CCH_2\underline{C}H_2$), 22.3 ($HC{\equiv}CCH_2CH_2\underline{C}H_2$), 17.4 ($HC{\equiv}C\underline{C}H_2$), 7.6 ($NCH(\underline{C}H_2)_2$)

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

HRMS (ESI$^+$) m/z / Da = 412.2036, $[M+H]^+$, $[C_{23}H_{27}N_3O_3F]^+$ requires 412.2030

The compound has not been reported previously.

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Todo list