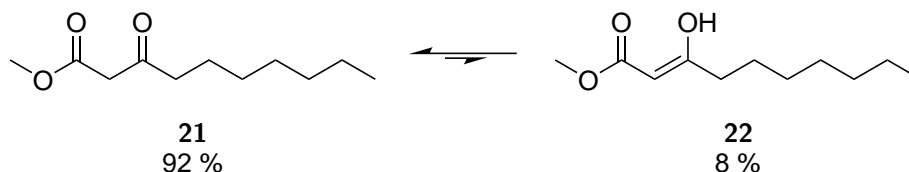


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0.1 Methyl 3-oxodecanoate **21**/**22**



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 Mg_2SO_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.) to give a tautomeric mixture of **21** and **22** as a colourless oil (8.34 g, 41.6 mmol, 66 %, 92 % **21** as determined by NMR).

Keto form **21**

TLC R_f = 0.12 (5 % EtO_2 /PE)

IR (neat) ν_{\max} / cm^{-1} = 2927.84 (C-H), 2856.26 (C-H), 1746.86 (ester C=O), 1716.70 (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, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.60 (quin, J = 7.1 Hz, 2 H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.39 - 1.19 (m, 8 H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 0.88 (t, J = 6.8 Hz, 3 H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$)

^{13}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 (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_3)

Enol form **22**

TLC R_f = 0.12 (5 % EtO_2 /PE)

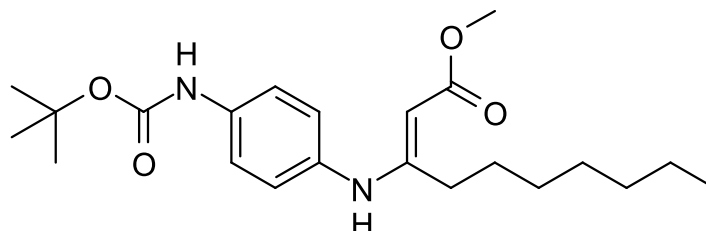
IR (neat) ν_{\max} / cm^{-1} = 2927.84 (C-H), 2856.26 (C-H), 1653.80 (C=C), 1629.21 (α,β unsaturated C=O)

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

^{13}C NMR (101 MHz, CDCl_3) δ / ppm = 178.7 ($\text{CH}_3\text{OC}(=\text{O})\text{CH}=\underline{\text{C}}\text{OH}$), 172.7 ($\text{CH}_3\text{OC}(=\text{O})\text{CH}=\text{COH}$), 88.2 ($\text{CH}_3\text{OC}(=\text{O})\underline{\text{C}}\text{H}=\text{COH}$), 50.5 ($\text{OC}\underline{\text{H}}_3$), 37.9 ($\underline{\text{C}}\text{H}_2$), 34.6 ($\underline{\text{C}}\text{H}_2$), 31.2 ($\underline{\text{C}}\text{H}_2$), 29.0 ($\underline{\text{C}}\text{H}_2$), 25.9 ($\underline{\text{C}}\text{H}_2$), 22.3 ($\underline{\text{C}}\text{H}_2$), 13.6 ($\underline{\text{C}}\text{H}_3$)

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

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



Methyl 3-oxodecanoate **21** (500 mg, 2.50 mmol, 1.00 eq.) and *tert*-butyl (4-aminophenyl)carbamate **124** (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 % $\text{Et}_2\text{O}/40\text{-}60$ P.E.) to give a white powder (0.169 mg, 0.480 mmol, 19 %).

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

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

IR (neat) ν_{max} / cm^{-1} = 3336.97 (N-H), 2927.71 (C-H), 2857.14 (C-H), 1723.71 (carbamate C=O), 1634.49 (α,β unsaturated C=O), 1610.73 (C=C), 1580.85 (N-H bend)

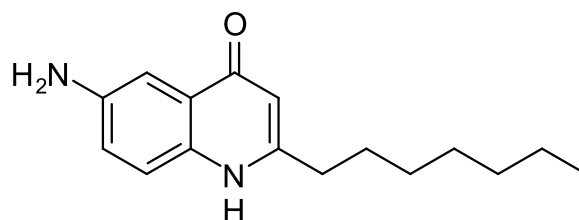
^1H NMR (400 MHz, CDCl_3) δ / ppm = 10.16 (s, 1 H, $\text{NH}\underline{\text{C}}(\text{C}_7\text{H}_{15})=\text{C}$), 7.35 (d, J = 8.6 Hz, 2 H, *meta* to NHBoc), 7.02 (d, J = 8.7 Hz, 2 H, *meta* to enamine), 6.60 (br s, 1 H, $\text{NH}\underline{\text{Boc}}$), 4.71 (s, 1 H, $\text{C}=\underline{\text{C}}\text{H}$), 3.70 (s, 3 H, $\text{OC}\underline{\text{H}}_3$), 2.23 (t, J = 7.7 Hz, 2 H, $\underline{\text{C}}\text{H}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.54 (s, 9 H, $\text{C}(\underline{\text{C}}\text{H}_3)_3$), 1.40 (quin, J = 7.3 Hz, 2 H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.33 - 1.16 (m, 8 H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 0.86 (t, J = 7.1 Hz, 3 H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$)

^{13}C NMR (101 MHz, CDCl_3) δ / ppm = 171.1 ($\underline{\text{C}}(=\text{O})\text{CH}=\text{C}$), 164.3 ($\text{C}(=\text{O})\text{CH}=\underline{\text{C}}$), 152.7 ($\text{OC}(=\text{O})\text{NH}$), 136.0 (*para* to NHBoc), 134.1 ($\underline{\text{C}}\text{NHBoc}$), 126.3 (*meta* to NHBoc), 119.1 (*ortho* to NHBoc), 83.8 ($\text{C}(=\text{O})\underline{\text{C}}\text{H}=\text{C}$), 80.7 ($\underline{\text{C}}(\text{CH}_3)_3$), 50.2 ($\text{OC}\underline{\text{H}}_3$), 32.2 ($\underline{\text{C}}\text{H}_2$), 31.6 ($\underline{\text{C}}\text{H}_2$), 29.1 ($\underline{\text{C}}\text{H}_2$), 28.8 ($\underline{\text{C}}\text{H}_2$), 28.3 ($\text{C}(\underline{\text{C}}\text{H}_3)_3$), 28.0 ($\underline{\text{C}}\text{H}_2$), 22.6 ($\underline{\text{C}}\text{H}_2$), 14.0 ($\underline{\text{C}}\text{H}_3$)

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

0.3 6-Amino-2-heptylquinolin-4-ol **25**

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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 to give a pale yellow powder (121 mg, 0.468 mmol, 72 %).

mp *T* / °C = 249 (H₂O)

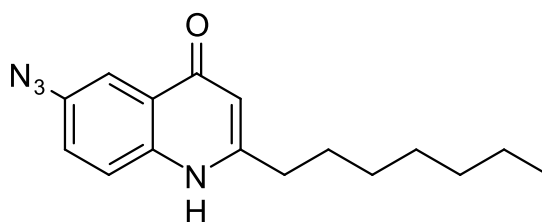
IR (neat) ν_{max} / cm⁻¹ = 3336.52 (N-H), 2926.47 (C-H), 2856.89 (C-H), 1723.88 (aromatic), 1634.48 (aromatic), 1610.84 (aromatic), 1583.26 (aromatic), 1519.06 (aromatic)

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, *para* to COH), 6.95 (dd, *J* = 2.7, 8.8 Hz, 1 H, *ortho* to COH), 5.74 (s, 1 H, *ortho* to OH), 5.16 (s, 2 H, NH₂), 2.52 (t, *J* = 7.4 Hz, 2 H, CH₂CH₂CH₂CH₂CH₂CH₂CH₃), 1.64 (quin, *J* = 7.6 Hz, 2 H, CH₂CH₂CH₂CH₂CH₂CH₂CH₃), 1.36 - 1.19 (m, 8 H, CH₂CH₂CH₂CH₂CH₂CH₂CH₃), 0.86 (t, *J* = 7.0 Hz, 3 H, CH₂CH₂CH₂CH₂CH₂CH₂CH₃)

¹³C NMR (101 MHz, DMSO-d₆) δ / ppm = 176.7 (C=O), 151.7 (CCH₂CH₂CH₂CH₂CH₂CH₂CH₃), 145.1 (CNH₂), 132.4 (*para* to NH₂), 126.6 (*para* to CH₂CH₂CH₂CH₂CH₂CH₂CH₃), 121.1 (*ortho* to NH₂ and *para* to COH), 119.0 (*meta* to NH₂ and *meta* to COH), 106.2 (*ortho* to NH₂ and *ortho* to COH), 105.9 (*ortho* to CH₂CH₂CH₂CH₂CH₂CH₂CH₃ and *ortho* to OH), 33.6 (CH₂), 31.6 (CH₂), 29.0 (CH₂), 29.0 (CH₂), 28.9 (CH₂), 22.5 (CH₂), 14.4 (CH₃)

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

0.4 6-Azido-2-heptylquinolin-4-ol **26**



6-Amino-2-heptylquinolin-4-ol **25** (50 mg, 0.194 mmol, 1 eq) was dissolved in HCl (conc., aq., 1.20 ml), water (1.80 ml) and MeOH (2.00 ml) and cooled to 0 °C. A solution of 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)

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

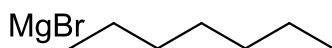
IR (neat) $\nu_{\text{max}} / \text{cm}^{-1} = ??$

^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 $\text{C}(=\text{O})$), 7.47 (dd, $J = 8.9, 2.7$ Hz, 1 H, *para* to $\text{C}(=\text{O})$), 6.24 (s, 1 H, $\text{C}(=\text{O})\text{CH}$), 2.69 (t, $J = 7.7$ Hz, 2 H, NHCCH_2), 1.68 (quin, $J = 7.6$ Hz, 2 H, $\text{NHCCH}_2\text{CH}_2$), 1.28 - 1.39 (m, 4 H, $\text{NHCCH}_2\text{CH}_2\text{CH}_2\text{CH}_2$), 1.18 - 1.28 (m, 4 H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 0.85 (t, $J = 6.8$ Hz, 3 H, 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 $\text{C}(=\text{O})$), 124.1 (*ipso* to $\text{C}(=\text{O})$), 120.7 (*meta* to N_3 and *meta* to $\text{C}(=\text{O})$), 112.8 (*ortho* to N_3 and *ortho* to $\text{C}(=\text{O})$), 107.0 ($\text{C}(=\text{O})\text{CH}$), 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)

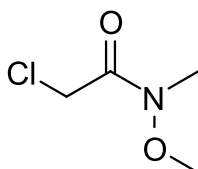
HRMS (ESI^+) $m/z / \text{Da} = ??$, $[\text{M}+\text{H}]^+$ found, $[??]^+$ requires ??

0.5 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.

0.6 2-Chloro-*N*-methoxy-*N*-methylacetamide 30



N,*O*-Dimethylhydroxyl amine hydrochloride (6.00 g, 61.5 mmol, 1 eq.) and toluene (75 mL) were added successively to a solution of potassium carbonate (22.4 g, 162 mmol, 2.63 eq.) in water (75 mL) at 0°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 four combined organic extracts were dried with MgSO_4 and the solvent was removed by rotary evaporation followed by high vacuum to give white, prism-like crystals (7.24 g, 52.6 mmol, 71 %).

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

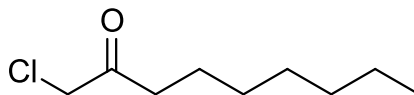
IR (neat) $\nu_{\text{max}} / \text{cm}^{-1} = 3016.69$ (C-H), 2966.38 (C-H), 2946.75 (C-H), 2827.73 (C-H), 1666.20 (C=O)

^1H NMR (400 MHz, CDCl_3) $\delta / \text{ppm} = 4.20$ (s, 2 H, $\text{ClCH}_2\text{C}(=\text{O})$), 3.71 (m, 3 H, OCH_3), 3.18 (s, 3 H, NCH_3)

^{13}C NMR (101 MHz, CDCl_3) δ / ppm = 167.4 (C=O), 61.6 (OCH_3), 40.9 ($\text{ClCH}_2\text{C=O}$), 32.6 (NCH_3)

Spectroscopic data are consistent with the literature.[?]

0.7 1-Chlorononan-2-one **31**



2-Chloro-*N*-methoxy-*N*-methylacetamide (1.00 g, 7.26 mmol, 1 eq.) was added to a dry flask under argon. THF (20 mL) was added and the flask cooled to 0 °C. Heptyl magnesium bromide (~ 1 M, 15.0 mL, 15.0 mmol, 2.07 eq.) was added dropwise over 5 min, then the mixture was allowed to warm to r.t. and stirred for 15 h. The reaction mixture was then poured into HCl (aq., 2 N, 60 mL) at 0 °C and stirred for 10 min. The mixture was extracted with toluene (30 mL) and the aqueous layer discarded. The organic layer was washed with brine and dried with MgSO_4 . The solvent was removed by rotary evaporation to give a colourless oil (1.23 g, 6.96 mmol, 96 %).

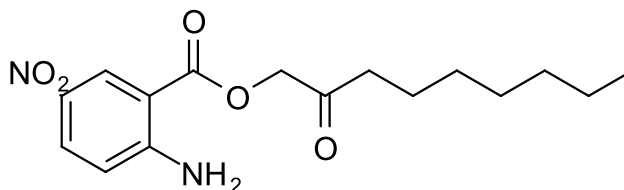
IR (neat) ν_{max} / cm^{-1} = 2951.65 (C-H), 2924.99 (C-H), 2855.46 (C-H), 1720.39 (C=O)

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

^{13}C NMR (101 MHz, CDCl_3) δ / ppm = 202.6 (C=O), 48.1 (CH_2Cl), 39.6 (C(=O)CH_2), 31.5 ($\text{CH}_2\text{CH}_2\text{CH}_3$), 28.9 (CH_2), 28.9 (CH_2), 23.5 ($\text{C(=O)CH}_2\text{CH}_2$), 22.5 (CH_2CH_3), 13.9 (CH_3)

Spectroscopic data are consistent with the literature.[?]

0.8 2-Oxononyl 2-amino-5-nitrobenzoate **33**



5-Nitroanthranilic acid (500 mg, 2.75 mmol, 1.38 eq.) and potassium carbonate (270 mg, 2.00 mmol, 1 eq.) were dissolved in DMF (5 ml). The mixture was heated under argon to 90 °C and stirred for 1 h then cooled to r.t.. 1-chlorononan-2-one **31** (353 mg, 2.00 mmol, 1 eq.) was added and the mixture was stirred for 15 h. The solution was poured into 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 to give a yellow powder (0.674 g, 2.00 mmol, 100 %).

mp T / °C = 135 (H_2O)

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

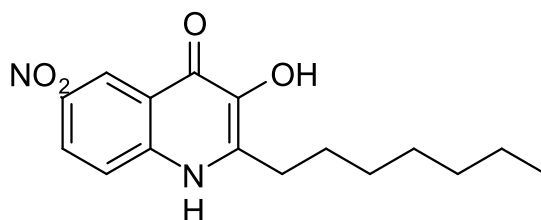
1703.91 (ketone C=O) 1626.14 (N-H bend) 1602.74 (aromatic) 1572.48 (N-O) 1506.58 (N-O)

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)CH₂CH₂CH₂CH₂CH₂CH₂CH₃), 1.52 (quin, J = 7.2 Hz, 2 H, C(=O)CH₂CH₂CH₂CH₂CH₂CH₂CH₃), 1.32 - 1.20 (m, 8 H, C(=O)CH₂CH₂CH₂CH₂CH₂CH₂CH₃), 0.86 (t, J = 6.8 Hz, 3 H, C(=O)CH₂CH₂CH₂CH₂CH₂CH₂CH₃)

¹³C NMR (101 MHz, DMSO-d₆) δ / ppm = 204.4 (OCH₂C(=O)), 165.6 (C(=O)O), 156.3 (C(NH₂)), 135.7 (CNO₂), 129.6 (*para* to C=O), 128.9 (*ortho* to C=O), 117.4 (*meta* to C=O), 107.5 (CC(=O)O), 68.8 (OCH₂C(=O)), 38.3 (CH₂), 31.6 (CH₂), 28.9 (CH₂), 28.9 (CH₂), 23.2 (CH₂), 22.5 (CH₂), 14.4 (CH₃)

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

0.9 6-Nitro-2-heptyl-3-hydroxyquinolin-4(1H)-one 34



2-Oxononyl 2-amino-5-nitrobenzoate (100 mg, 0.340 mmol, 1 eq.) and polyphosphoric acid (300 mg) were stirred for 5.5 h at 90 °C under argon. The mixture was then poured into 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 to give a yellow-brown powder (44 mg, 0.145 mmol, 43 %) which could be recrystallised from EtOAc to give yellow-brown plate-like crystals.

mp T / °C = 223 (H₂O)

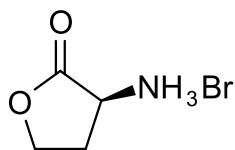
IR (neat) ν_{max} / cm⁻¹ = 3436.01 (N-H), 3000.00 (O-H, br), 2955.37 (C-H), 2925.76 (C-H), 2850.93 (C-H), 1648.18 (aromatic), 1606.05 (aromatic), 1570.67 (N-O), 1536.35 (N-O)

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, CH₂CH₂CH₂CH₂CH₂CH₂CH₃), 1.67 (quin, J = 7.3 Hz, 2 H, CH₂CH₂CH₂CH₂CH₂CH₂CH₃), 1.36 - 1.23 (m, 8 H, CH₂CH₂CH₂CH₂CH₂CH₂CH₃), 0.85 (t, J = 7.0 Hz, 3 H, CH₂CH₂CH₂CH₂CH₂CH₂CH₃)

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 (CCH₂CH₂CH₂CH₂CH₂CH₂CH₃), 120.0 (*meta* to NO₂ and *meta* to C=O), 31.6 (CH₂), 29.2 (CH₂), 28.9 (CH₂), 28.5 (CH₂), 28.1 (CH₂), 22.5 (CH₂), 14.4 (CH₃)

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

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



L-Methionine (3.04 g, 20.4 mmol, 1 eq.) and bromoacetic acid (3.08 g, 22.2 mmol, 1.09 eq.) were dissolved in *i*-PrOH (12.5 mL), 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 to give a pale pink powder (1.73 g, 9.50 mmol, 41 % yield).

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

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

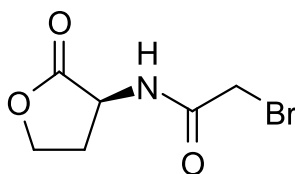
¹H NMR (400 MHz, DMSO-*d*₆) $\delta / \text{ppm} = 8.59$ (br s, 3 H, NH_3^+), 4.46 (dt, $J = 1.3, 8.9$ Hz, 1 H, OCH_2), 4.37 (dd, $J = 8.8, 11.4$ Hz, 1 H, CHNH_3^+), 4.29 (ddd, $J = 6.1, 8.8, 10.9$ Hz, 1 H, OCH_2), 2.57 (dddd, $J = 1.2, 6.1, 8.9, 12.3$ Hz, 1 H, OCH_2CH_2), 2.26 (dtd, $J = 9.0, 11.2, 12.2$ Hz, 1 H, OCH_2CH_2)

¹³C NMR (101 MHz, DMSO-*d*₆) $\delta / \text{ppm} = 173.3$ ($\text{C}=\text{O}$), 66.2 (OCH_2), 47.8 (CHNH_3^+), 27.0 (OCH_2CH_2)

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

The data are consistent with the literature.[?]

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



(*S*)-3-Aminodihydrofuran-2(3*H*)-one hydrobromide **38** (100 mg, 0.549 mmol, 1.08 eq.) and 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) and the combined organic layers were dried with MgSO₄. The solvent was removed under vacuum to give white, needle-like crystals (88.0 mg, 0.396 mmol, 74 %).

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

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

(N-H bend)

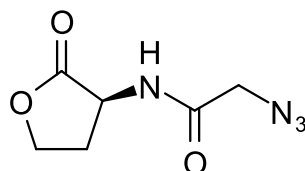
$^1\text{H NMR}$ (400 MHz, CDCl_3) δ / ppm = 6.95 (br d, 1 H, NH), 4.58 (ddd, $J = 5.9, 8.6, 11.7$ Hz, 1 H, CHNHC=O), 4.53 (dt, $J = 1.0, 9.2$ Hz, 1 H, OCH_2), 4.33 (ddd, $J = 5.9, 9.4, 11.3$ Hz, 1 H, OCH_2), 3.95 (d, $J = 1.3$ Hz, 2 H, $\text{C(=O)CH}_2\text{Br}$), 2.88 (dddd, $J = 1.3, 5.9, 8.6, 12.6$ Hz, 1 H, OCH_2CH_2), 2.24 (dtd, $J = 8.9, 11.5, 12.6$ Hz, 1 H, OCH_2CH_2)

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ / ppm = 174.6 (OC=O), 166.4 (C(=O)NH), 66.1 (OCH_2), 49.8 (CHNHC=O), 29.9 (OCH_2CH_2), 28.2 ($\text{O=CCH}_2\text{Br}$)

$[\alpha]_D^{20} / ^\circ 10^{-1} \text{cm}^2 \text{g}^{-1} = 27.0$ ($c / \text{g}(100 \text{ mL})^{-1} = 0.0074$, CHCl_3)

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

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



(3*S*)-2-Oxotetrahydrofuran-3-aminium bromide **38** (100 mg, 0.552 mmol, 1.08 eq.), 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 ($4 \times 10 \text{ mL}$) and the combined organic layers were dried with MgSO_4 . The solvent was removed under vacuum to give white, needle-like crystals (38.4 mg, 0.209 mmol, 41 %).

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

IR (neat) $\nu_{\text{max}} / \text{cm}^{-1} = 3283.47$ (N-H), 2923.28 (C-H), 2852.99 (C-H), 2129.69 (N_3), 1782.86 (lactone C=O), 1661.40 (amide C=O), 1536.81 (N-H bend)

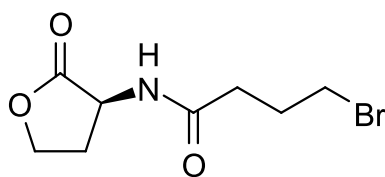
$^1\text{H NMR}$ (400 MHz, CDCl_3) δ / ppm = 7.07 (br d, $J = 5.1$ Hz, 1 H, NH), 4.65 (ddd, $J = 6.8, 8.7, 11.6$ Hz, 1 H, CHNHC=O), 4.49 (dt, $J = 1.3, 9.1$ Hz, 1 H, OCH_2), 4.31 (ddd, $J = 6.0, 9.2, 11.2$ Hz, 1 H, OCH_2), 4.05 (s, 2 H, $\text{C(=O)CH}_2\text{N}_3$), 2.77 (dddd, $J = 1.4, 6.0, 8.8, 12.5$ Hz, 1 H, OCH_2CH_2), 2.26 (dq, $J = 8.9, 11.8$ Hz, 1 H, OCH_2CH_2)

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ / ppm = 174.9 (OC=O), 167.5 (C=ONH), 66.0 (OCH_2), 52.2 ($\text{O=CCH}_2\text{N}_3$), 48.9 (CHNHC=O), 29.7 (OCH_2CH_2)

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

The data are consistent with the literature.[?]

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



(*S*)-3-Aminodihydrofuran-2(3*H*)-one hydrobromide **38** (200 mg, 1.10 mmol, 1.00 eq.) and NaHCO₃ (170 mg, 2.02 mmol, 1.84 eq.) were dissolved in CH₂Cl₂ (2 mL) and H₂O (2 mL). Bromobutyl chloride (140 μL, 224 mg, 1.21 mmol, 1.10 eq.) was then added dropwise. The reaction mixture was stirred for 1 h, after which the 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 to give white, needle-like crystals (219 mg, 0.878 mmol, 80 %).

mp *T* / °C = 105 (EtOAc)

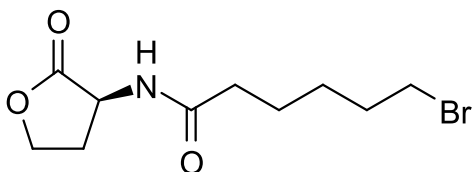
IR (neat) ν_{max} / cm⁻¹ = 3307.92 (N-H), 3073.85 (C-H), 2948.93 (C-H), 1773.66 (lactone C=O), 1643.46 (amide C=O), 1541.39 (N-H bend)

¹H NMR (400 MHz, CDCl₃) δ / 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, CHNH₂C=O), 4.48 (dt, *J* = 1.2, 8.9 Hz, 1 H, OCH₂), 4.30 (ddd, *J* = 5.8, 9.3, 11.3 Hz, 1 H, OCH₂), 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, OCH₂CH₂), 2.47 (t, *J* = 7.3 Hz, 2 H, C(=O)CH₂), 2.26 - 2.15 (m, 3 H, OCH₂CH₂ and C(=O)CH₂CH₂CH₂Br)

¹³C NMR (101 MHz, CDCl₃) δ / ppm = 175.4 (OC=O), 172.3 (C(=O)NH), 66.1 (OCH₂), 49.3 (CHNH₂C=O), 33.9 (C(=O)CH₂), 33.1 (CH₂Br), 30.3 (OCH₂CH₂), 27.9 (C(=O)CH₂CH₂CH₂Br)

$[\alpha]_D^{26.6}$ / °10⁻¹cm²g⁻¹ = - 78 (*c* / g(100 mL)⁻¹ = 0.08333, MeOH)

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



(*S*)-3-Aminodihydrofuran-2(3*H*)-one hydrobromide **38** (100 mg, 0.549 mmol, 1.00 eq.) and NaHCO₃ (84.9 mg, 1.01 mmol, 1.84 eq.) were dissolved in CH₂Cl₂ (2 mL) and H₂O (2 mL). Bromohexanoyl chloride (93.0 μL, 130 mg, 0.608 mmol, 1.11 eq.) was then added dropwise. The reaction mixture was stirred for 4 h, after which the CH₂Cl₂ was removed under vacuum. The mixture was then filtered, washed with H₂O (10 mL) and dried under high vacuum to give white, needle-like crystals (101 mg, 0.362 mmol, 66 %).

mp *T* / °C = 106 (CH₂Cl₂/H₂O)

IR (neat) ν_{max} / cm⁻¹ = 3300.30 (N-H), 3067.62 (C-H), 2937.37 (C-H), 2856.67 (C-H), 1784.83 (lactone C=O),

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

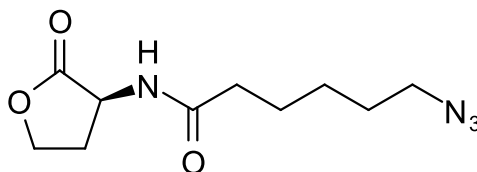
¹H NMR (400 MHz, CDCl₃) δ / ppm = 6.09 (br d, J = 5.7 Hz, 1 H, NH), 4.57 (ddd, J = 5.9, 8.6, 11.6 Hz, 1 H, CHNH₂C=O), 4.50 (dt, J = 1.3, 9.1 Hz, 1 H, OCH₂), 4.31 (ddd, J = 5.9, 9.3, 11.3 Hz, 1 H, OCH₂), 3.43 (t, J = 6.7 Hz, 2 H, C(=O)CH₂CH₂CH₂CH₂CH₂Br), 2.88 (dddd, J = 1.3, 5.9, 8.6, 12.6 Hz, 1 H, OCH₂CH₂), 2.30 (dt, J = 1.8, 7.5 Hz, 2 H, C(=O)CH₂CH₂CH₂CH₂CH₂Br), 2.16 (dtd, J = 8.9, 11.5, 12.5 Hz, 1 H, OCH₂CH₂), 1.90 (quin, J = 7.2 Hz, 2 H, C(=O)CH₂CH₂CH₂CH₂CH₂Br), 1.71 (quin, J = 7.6 Hz, 2 H, C(=O)CH₂CH₂CH₂CH₂CH₂Br), 1.59 - 1.46 (m, 2 H, C(=O)CH₂CH₂CH₂CH₂CH₂Br)

¹³C NMR (101 MHz, CDCl₃) δ / ppm = 175.5 (OC=O), 173.3 (C(=O)NH), 66.1 (OCH₂), 49.3 (CHNH₂C=O), 35.8 (C(=O)CH₂CH₂CH₂CH₂CH₂Br), 33.5 (C(=O)CH₂CH₂CH₂CH₂CH₂Br), 32.3 (C(=O)CH₂CH₂CH₂CH₂CH₂Br), 30.5 (OCH₂CH₂), 27.6 (C(=O)CH₂CH₂CH₂CH₂CH₂Br), 24.4 (C(=O)CH₂CH₂CH₂CH₂CH₂Br)

HRMS (ESI⁺) m/z / Da = 278.0381, [M+H]⁺, [C₁₀H₁₇BrNO₃]⁺ requires 278.0386

$[\alpha]_D^{26.6}$ / °10⁻¹cm²g⁻¹ = - 16 (c / g(100 mL)⁻¹ = 0.20833, MeOH)

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



(*S*)-6-Bromo-*N*-(2-oxotetrahydrofuran-3-yl)hexanamide (80 mg, 0.320 mmol, 1.00 eq.) and NaN₃ (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 CH₂Cl₂ (5 mL) and H₂O (5 mL). The aqueous phase was extracted twice more with CH₂Cl₂ (2 × 5 mL) and the organic layers were combined and dried over MgSO₄. The solvent was removed by rotary evaporation followed by high vacuum to give white, needle-like crystals (42.7 mg, 0.178 mmol, 56 %).

mp T / °C = 90.0 (CH₂Cl₂)

IR (neat) ν_{max} / cm⁻¹ = 3314.00 (N-H), 2931.56 (C-H), 2862.89 (C-H), 2095.06 (N₃), 1775.38 (lactone C=O), 1643.14 (amide C=O), 1547.90 (N-H bend)

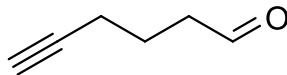
¹H NMR (400 MHz, CDCl₃) δ / ppm = 5.97 (br d, J = 4.2 Hz, 1 H, NH), 4.56 (ddd, J = 5.7, 8.6, 11.7 Hz, 1 H, CHNH₂C=O), 4.50 (dt, J = 1.0, 9.1 Hz, 1 H, OCH₂), 4.31 (ddd, J = 5.8, 9.4, 11.3 Hz, 1 H, OCH₂), 3.31 (t, J = 6.9 Hz, 2 H, CH₂N₃), 2.90 (dddd, J = 1.1, 5.8, 8.6, 12.5 Hz, 1 H, OCH₂CH₂), 2.30 (dt, J = 1.8, 7.4 Hz, 2 H, O=CCH₂), 2.15 (dtd, J = 8.8, 11.5, 12.3 Hz, 1 H, OCH₂CH₂), 1.72 (quin, J = 7.6 Hz, 2 H, O=CCH₂CH₂CH₂CH₂CH₂N₃), 1.65 (quin, J = 7.2 Hz, 2 H, O=CCH₂CH₂CH₂CH₂CH₂N₃), 1.46 (m, 2 H, O=CCH₂CH₂CH₂CH₂CH₂N₃)

¹³C NMR (101 MHz, CDCl₃) δ / ppm = 175.4 (OC=O), 172.2 (C(=O)NH), 66.1 (OCH₂), 51.2 (C(=O)CH₂CH₂CH₂CH₂CH₂N₃), 49.4 (CHNH₂C=O), 35.9 (C(=O)CH₂CH₂CH₂CH₂CH₂N₃), 30.7 (OCH₂CH₂), 28.6 (C(=O)CH₂CH₂CH₂CH₂CH₂N₃), 26.3 (C(=O)CH₂CH₂CH₂CH₂CH₂N₃), 24.8 (C(=O)CH₂CH₂CH₂CH₂CH₂N₃)

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 = 0.20833 , MeOH)

0.16 Hex-5-ynal **49**



Pyridinium chlorochromate (14.6 g, 68.1 mmol, 1.50 eq) and DCM (500 mL) were stirred at r.t. under argon. 5-hexyn-1-ol (5.00 mL, 45.4 mmol, 1 eq.) was added and the reaction mixture was stirred for 5 h followed by addition of 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 to give a pale yellow-green oil (4.72 g, 49.1 mmol, 72 %).

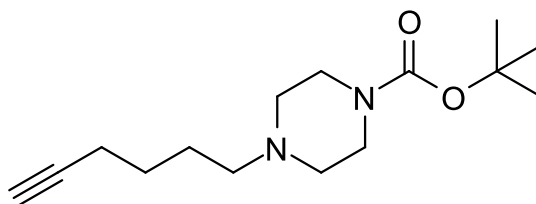
IR (neat) ν_{max} / cm⁻¹ = 3292.68 (alkyne C-H), 2943.26 (alkane C-H), 2830.88 (aldehyde C-H), 2728.56 (aldehyde C-H), 1720.29 (aldehyde C=O)

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≡CH₂), 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 (HC≡CCH₂CH₂CH₂C=O), 17.6 (HC≡CCH₂CH₂CH₂C=O)

Spectroscopic data are consistent with the literature.[?]

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



Hex-5-ynal **49** (0.407 g, 4.24 mmol, 1.00 eq.) and *tert*-butyl piperazine-1-carboxylate (0.791 g, 4.24 mmol, 1.00 eq.) were stirred under a 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 to give a colourless liquid (1.12 g, 4.21 mmol, 99 %).

TLC R_f (10 % MeOH/CH₂Cl₂) = 0.55

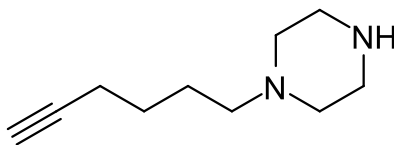
IR (neat) ν_{max} / cm⁻¹ = 3303.59 (alkyne C-H), 2939.96 (alkane C-H), 2865.23 (C-H), 2810.42 (C-H), 1691.29 (carbamate C=O)

^1H NMR (400 MHz, CDCl_3) δ / ppm = 3.44 (t, J = 5.2 Hz, 4 H, $\text{BocN}(\text{CH}_2)\text{CH}_2$), 2.39 (t, J = 5.1 Hz, 4 H, $\text{HC}\equiv\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2)\text{CH}_2$), 2.37 (t, J = 7.3 Hz, 2 H, $\text{HC}\equiv\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$), 2.23 (dt, J = 2.7, 6.8 Hz, 2 H, $\text{HC}\equiv\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$), 1.96 (t, J = 2.7 Hz, 1 H, $\text{HC}\equiv\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$), 1.65 - 1.53 (m, 4 H, $\text{HC}\equiv\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$), 1.47 (s, 9 H, CH_3)

^{13}C NMR (101 MHz, CDCl_3) δ / ppm = 154.7 ($\text{NC}(=\text{O})\text{O}$), 84.2 ($\text{HC}\equiv\text{C}$), 79.6 ($\text{C}(\text{CH}_3)_3$), 68.5 ($\text{HC}\equiv\text{C}$), 60.4 ($\text{HC}\equiv\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$), 58.0 ($\text{HC}\equiv\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2)\text{CH}_2$), 53.0 ($\text{BocN}(\text{CH}_2)\text{CH}_2$), 28.4 ($\text{C}(\text{CH}_3)_3$), 26.3 ($\text{HC}\equiv\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$), 25.7 ($\text{HC}\equiv\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$), 18.3 ($\text{HC}\equiv\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$)

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

0.18 1-(Hex-5-yn-1-yl)piperazine **52**



tert-Butyl 4-(hex-5-yn-1-yl)piperazine-1-carboxylate **51** (763 mg, 2.86 mmol) was stirred in TFA (10 mL) at r.t. for 2 h. The TFA was removed under vacuum followed by co-evaporation with 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) to give a colourless liquid (476 mg, 2.86 mmol, 100 %).

TLC R_f (30 % MeOH/ CH_2Cl_2) = 0.20

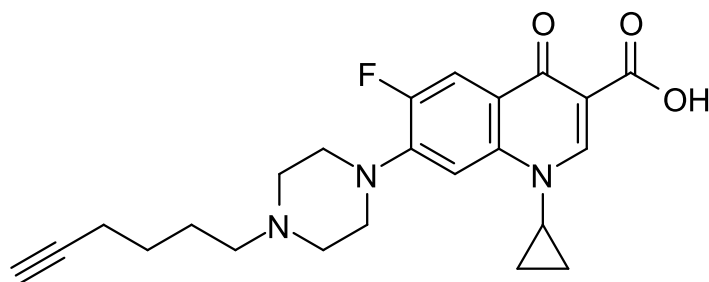
IR (neat) ν_{max} / cm^{-1} = 3295.87 (alkyne C-H), 2941.07 (alkane C-H), 2810.64 (alkane C-H), 1637.22 (N-H bend)

^1H NMR (400 MHz, CDCl_3) δ / ppm = 2.88 (t, J = 4.9 Hz, 4 H, $\text{HN}(\text{CH}_2)\text{CH}_2$), 2.39 (m, 4 H, $\text{HC}\equiv\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2)\text{CH}_2$), 2.31 (t, J = 7.1 Hz, 2 H, $\text{HC}\equiv\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$), 2.20 (dt, J = 2.7, 6.8 Hz, 2 H, $\text{HC}\equiv\text{CCH}_2$), 2.05 (br s, 1 H, NH), 1.93 (t, J = 2.7 Hz, 1 H, $\text{HC}\equiv\text{C}$), 1.65 - 1.48 (m, 4 H, $\text{HC}\equiv\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$)

^{13}C NMR (101 MHz, CDCl_3) δ / ppm = 84.3 ($\text{HC}\equiv\text{C}$), 68.4 ($\text{HC}\equiv\text{C}$), 58.6 ($\text{HC}\equiv\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$), 54.5 ($\text{HC}\equiv\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2)\text{CH}_2$), 46.0 ($\text{HN}(\text{CH}_2)\text{CH}_2$), 26.4 ($\text{HC}\equiv\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$), 25.7 ($\text{HC}\equiv\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$), 18.3 ($\text{HC}\equiv\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$)

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

0.19 1-Cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **54**



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

TLC R_f = 0.02 (10 % MeOH/CH₂Cl₂)

mp T / °C = 220 (MeOH, decomposes)

IR (neat) ν_{max} / cm⁻¹ = 3211.99 (alkyne C-H), 2459.32 (O-H), 1722.63 (carboxylic acid C=O), 1626.76 (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≡CCH₂CH₂CH₂), 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 = -121.82 (s, ciprofloxacin F)

HRMS (ESI⁺) m/z / Da = 412.2036, [M+H]⁺, [C₂₃H₂₇N₃O₃F]⁺ requires 412.2030