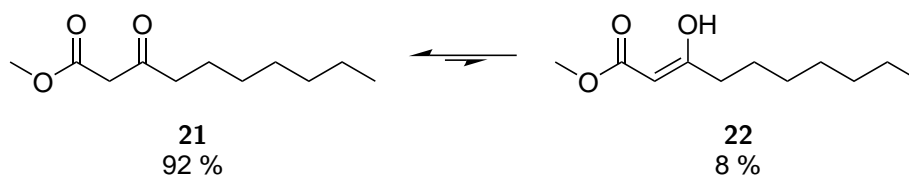


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## 0.1 Methyl 3-oxodecanoate **21/22**



Meldrum's acid (9.0 g, 63 mmol, 1 eq.) was dissolved in anhydrous  $\text{CH}_2\text{Cl}_2$  (150 mL) in an oven-dried flask and cooled to 0 °C. Pyridine (10.2 mL, 126 mmol, 2 eq.) was added dropwise over 20 min. Octanoyl chloride (11.7 mL, 69 mmol, 1.1 eq.) was then added and the mixture was stirred at 0 °C for a further 4 h. The mixture was allowed to warm to r.t., diluted with  $\text{CH}_2\text{Cl}_2$  (20 mL) and poured into a mixture of ice (~30 g) and HCl (2 N, 90 mL). The solution was washed with NaCl (sat., aq., 150 mL) and dried over  $\text{MgSO}_4$ . The solvent was removed under vacuum to give an orange-brown oil. The oil was refluxed in anhydrous MeOH (150 mL) for 5 h and the solvent was removed under vacuum. The resulting residue was purified by column chromatography ( $\text{SiO}_2$ , 5 %  $\text{Et}_2\text{O}$ /40-60 P.E.). A tautomeric mixture of **21** and **22** was obtained as a colourless oil (8.34 g, 41.6 mmol, 66 %, 92 % **21** as determined by  $^1\text{H}$  NMR).

### Keto form **21**

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

**IR** (neat)  $\nu_{\max}$  /  $\text{cm}^{-1}$  = 2927.8 (C-H), 2856.3 (C-H), 1746.9 (ester C=O), 1716.7 (ketone C=O)

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  / ppm = 3.74 (s, 3 H,  $\text{OCH}_3$ ), 3.45 (s, 2 H,  $\text{C}(=\text{O})\text{CH}_2\text{C}(=\text{O})$ ), 2.53 (t,  $J$  = 7.4 Hz, 2 H,  $\text{C}(=\text{O})\text{CH}_2\text{CH}_2$ ), 1.60 (quin,  $J$  = 7.1 Hz, 2 H,  $\text{C}(=\text{O})\text{CH}_2\text{CH}_2$ ), 1.39 - 1.19 (m, 8 H,  $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 0.88 (t,  $J$  = 6.8 Hz, 3 H,  $\text{CH}_2\text{CH}_3$ )

**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  / ppm = 202.3 ( $\text{CH}_3\text{OC}(=\text{O})\text{CH}_2\text{C}(=\text{O})$ ), 167.3 ( $\text{CH}_3\text{OC}(=\text{O})\text{CH}_2\text{C}(=\text{O})$ ), 51.7 ( $\text{OCH}_3$ ), 48.5 ( $\text{CH}_3\text{OC}(=\text{O})\text{CH}_2\text{C}(=\text{O})$ ), 42.5 ( $\text{C}(=\text{O})\text{CH}_2\text{CH}_2$ ), 31.3 ( $\text{CH}_2$ ), 28.7 ( $\text{CH}_2$ ), 28.6 ( $\text{CH}_2$ ), 23.1 ( $\text{CH}_2$ ), 22.2 ( $\text{CH}_2$ ), 13.6 ( $\text{CH}_2\text{CH}_3$ )

### Enol form **22**

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

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

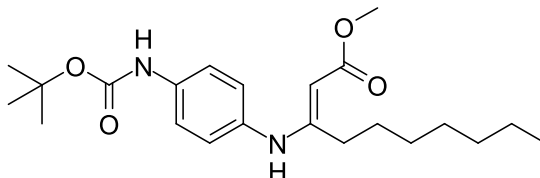
**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  / ppm = 12.02 (s, 1 H,  $\text{COH}$ ), 4.99 (s, 1 H,  $\text{C}(=\text{O})\text{CH}=\text{COH}$ ), 3.73 (s, 3 H,  $\text{OCH}_3$ ), 2.20 (t,  $J$  = 7.4 Hz, 2 H,  $\text{COHCH}_2\text{CH}_2$ ), 1.76 - 1.72 (m, 2 H,  $\text{COHCH}_2\text{CH}_2$ ), 1.39 - 1.19 (m, 8 H,  $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 0.88 (t,  $J$  = 6.8 Hz, 3 H,  $\text{CH}_2\text{CH}_3$ )

**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  / ppm = 178.7 ( $\text{CH}_3\text{OC}(=\text{O})\text{CH}=\text{COH}$ ), 172.7 ( $\text{CH}_3\text{OC}(=\text{O})\text{CH}=\text{COH}$ ), 88.2

(CH<sub>3</sub>OC(=O)CH=COH), 50.5 (OCH<sub>3</sub>), 37.9 (COHCH<sub>2</sub>CH<sub>2</sub>), 34.6 (CH<sub>2</sub>), 31.2 (CH<sub>2</sub>), 29.0 (CH<sub>2</sub>), 25.9 (CH<sub>2</sub>), 22.3 (CH<sub>2</sub>), 13.6 (CH<sub>2</sub>CH<sub>3</sub>)

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

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

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

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

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

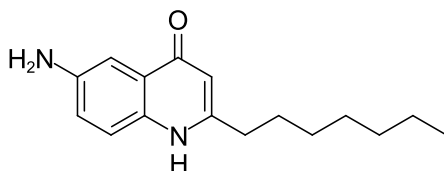
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  / ppm = 10.16 (s, 1 H, NH(C<sub>7</sub>H<sub>15</sub>)=C), 7.35 (d,  $J$  = 8.6 Hz, 2 H, *meta* to NHBoc), 7.02 (d,  $J$  = 8.7 Hz, 2 H, *meta* to enamine), 6.60 (br s, 1 H, NHBoc), 4.71 (s, 1 H, C=CH), 3.70 (s, 3 H, OCH<sub>3</sub>), 2.23 (t,  $J$  = 7.7 Hz, 2 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.54 (s, 9 H, C(CH<sub>3</sub>)<sub>3</sub>), 1.40 (quin,  $J$  = 7.3 Hz, 2 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.33 - 1.16 (m, 8 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 0.86 (t,  $J$  = 7.1 Hz, 3 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>)

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

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

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

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



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

**mp**  $T / ^\circ\text{C} = 249$  (H<sub>2</sub>O)

**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)

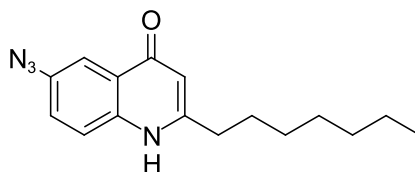
**<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta / \text{ppm} = 7.26$  (d,  $J = 8.7$  Hz, 1 H, *meta* to NH<sub>2</sub>), 7.15 (d,  $J = 2.6$  Hz, 1 H, *ortho* to C(=O)), 6.95 (dd,  $J = 2.7, 8.8$  Hz, 1 H, *para* to C(=O)), 5.74 (s, 1 H, *ortho* to CH<sub>2</sub>), 5.16 (s, 2 H, NH<sub>2</sub>), 2.52 (t,  $J = 7.4$  Hz, 2 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.64 (quin,  $J = 7.6$  Hz, 2 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.36 - 1.19 (m, 8 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 0.86 (t,  $J = 7.0$  Hz, 3 H, H<sub>3</sub>)

**<sup>13</sup>C NMR** (101 MHz, DMSO-*d*<sub>6</sub>)  $\delta / \text{ppm} = 176.7$  (C(=O)), 151.7 (CCH<sub>2</sub>), 145.1 (*para* to NH<sub>2</sub>), 132.4 (*ipso* to NH<sub>2</sub>), 126.6 (*para* to CH<sub>2</sub>), 121.1 (*para* to C(=O)), 119.0 (*meta* to NH<sub>2</sub> and *meta* to C(=O)), 106.2 (CH=CCH<sub>2</sub>), 105.9 (*ortho* to NH<sub>2</sub> and *ortho* to C(=O)), 33.6 (CCH<sub>2</sub>), 31.6 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 29.0 (CH<sub>2</sub>), 29.0 (CH<sub>2</sub>), 28.9 (CH<sub>2</sub>), 22.5 (CH<sub>2</sub>CH<sub>3</sub>), 14.4 (CH<sub>3</sub>)

**HRMS** (ESI<sup>+</sup>)  $m/z / \text{Da} = 259.1810$ , [M+H]<sup>+</sup>, [C<sub>16</sub>H<sub>23</sub>N<sub>2</sub>O]<sup>+</sup> requires 259.1803

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

#### 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 NaNO<sub>2</sub> (16.0 mg, 0.232 mmol, 1.2 eq.) in water (0.300 ml) was added dropwise over 10 min and the mixture was stirred for 1 h. A solution of NaN<sub>3</sub> (15.1 mg, 0.232 mmol, 1.2 eq.) in water (0.300 ml) was then added. The mixture was warmed to room temperature and stirred for a further 4 h. The resultant precipitate was filtered off and dried under reduced pressure. **26** was obtained as a pale cream amorphous solid (25.6 mg, 0.0900 mmol, 46.5 %).

**TLC**  $R_f = 0.40$  (5 % MeOH/CH<sub>2</sub>Cl<sub>2</sub>)

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

**<sup>1</sup>H 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<sub>3</sub> and *ortho* to C(=O)), 7.47 (dd,  $J = 8.9, 2.7$  Hz, 1 H, *para* to C(=O)), 6.24 (s, 1 H, C(=O)CH), 2.69 (t,  $J = 7.7$  Hz, 2 H, NHCCH<sub>2</sub>), 1.68 (quin,  $J = 7.6$  Hz, 2 H, NHCCH<sub>2</sub>CH<sub>2</sub>), 1.28 - 1.39 (m, 4 H, NHCCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 1.18 - 1.28 (m, 4 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 0.85 (t,  $J = 6.8$  Hz, 3 H, CH<sub>3</sub>)

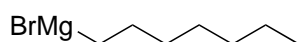
$^{13}\text{C}$  NMR (101 MHz, MeOD)  $\delta$  / ppm = 172.3 ( $\underline{\text{C}}(\text{=O})$ ), 155.5 ( $\text{NHC}\underline{\text{C}}\text{H}_2$ ), 137.4 ( $\underline{\text{C}}\text{N}_3$ ), 135.6 (*para* to  $\text{N}_3$ ), 124.6 (*para* to  $\text{C}(\text{=O})$ ), 124.1 (*ipso* to  $\text{C}(\text{=O})$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

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

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

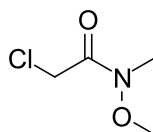
???

## 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 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  $\text{MgSO}_4$  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)

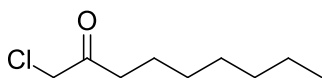
IR (neat)  $\nu_{\text{max}}$  /  $\text{cm}^{-1}$  = 3016.7 (C-H), 2966.4 (C-H), 2946.7 (C-H), 2827.7 (C-H), 1666.2 (C=O)

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  / ppm = 4.20 (s, 2 H,  $\text{ClCH}_2\text{C}=\text{O}$ ), 3.71 (m, 3 H,  $\text{OCH}_3$ ), 3.18 (s, 3 H,  $\text{NCH}_3$ )

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  / ppm = 167.4 (C=O), 61.6 ( $\text{OCH}_3$ ), 40.9 ( $\text{ClCH}_2\text{C}=\text{O}$ ), 32.6 ( $\text{NCH}_3$ )

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

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

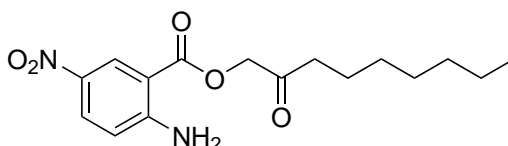
**IR** (neat)  $\nu_{max}$  / cm<sup>-1</sup> = 2951.7 (C-H), 2925.0 (C-H), 2855.5 (C-H), 1720.4 (C=O)

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

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

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

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

**mp**  $T$  / °C = 135 (H<sub>2</sub>O)

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

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

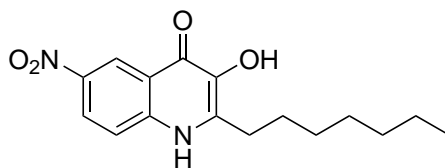
$\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 0.86 (t,  $J = 6.8$  Hz, 3 H,  $\text{CH}_3$ )

$^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  / ppm = 204.4 ( $\text{OCH}_2\text{C}(=\text{O})$ ), 165.6 ( $\text{C}(=\text{O})\text{O}$ ), 156.3 (*ipso* to  $\text{NH}_2$ ), 135.7 (*ipso* to  $\text{NO}_2$ ), 129.6 (*para* to  $\text{C}(=\text{O})$ ), 128.9 (*ortho* to  $\text{C}(=\text{O})$ ), 117.4 (*meta* to  $\text{C}(=\text{O})$ ), 107.5 (*ipso* to  $\text{C}(=\text{O})$ ), 68.8 ( $\text{OCH}_2\text{C}(=\text{O})$ ), 38.3 ( $\text{C}(=\text{O})\text{CH}_2\text{CH}_2$ ), 31.6 ( $\text{CH}_2\text{CH}_2\text{CH}_3$ ), 28.9 ( $\text{CH}_2$ ), 28.9 ( $\text{CH}_2$ ), 23.2 ( $\text{C}(=\text{O})\text{CH}_2\text{CH}_2$ ), 22.5 ( $\text{CH}_2\text{CH}_3$ ), 14.4 ( $\text{CH}_3$ )

HRMS ( $\text{ESI}^+$ )  $m/z$  / Da = 323.1610,  $[\text{M}+\text{H}]^+$ ,  $[\text{C}_{16}\text{H}_{23}\text{N}_2\text{O}_5]^+$  requires 323.1607

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

## 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  $\text{NaHCO}_3$  (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 ( $\text{H}_2\text{O}$ , EtOAc)

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

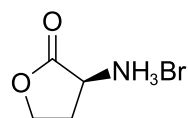
$^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  / ppm = 12.00 (s, 1 H,  $\text{NH}$ ), 8.91 (d,  $J = 2.8$  Hz, 1 H, *ortho* to  $\text{C}(=\text{O})$ ), 8.29 (dd,  $J = 2.7, 9.2$  Hz, 1 H, *para* to  $\text{C}(=\text{O})$ ), 7.70 (d,  $J = 9.3$  Hz, 1 H, *meta* to  $\text{C}(=\text{O})$ ), 2.75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

$^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  / ppm = 169.7 ( $\text{C}(=\text{O})$ ), 141.9 ( $\text{C}(\text{OH})$ ), 140.7 (*para* to  $\text{NO}_2$ ), 139.6 ( $\text{C}(\text{NO}_2)$ ), 137.3 ( $\text{CHC}(=\text{O})$ ), 124.3 (*ortho* to  $\text{NO}_2$  and *ortho* to  $\text{C}(=\text{O})$ ), 122.3 (*ortho* to  $\text{NO}_2$  and *para* to  $\text{C}(=\text{O})$ ), 121.5 ( $\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 120.0 (*meta* to  $\text{NO}_2$  and *meta* to  $\text{C}(=\text{O})$ ), 31.6 ( $\text{CH}_2$ ), 29.2 ( $\text{CH}_2$ ), 28.9 ( $\text{CH}_2$ ), 28.5 ( $\text{CCH}_2$ ), 28.1 ( $\text{CCH}_2\text{CH}_2$ ), 22.5 ( $\text{CH}_2\text{CH}_3$ ), 14.4 ( $\text{CH}_3$ )

HRMS ( $\text{ESI}^+$ )  $m/z$  / Da = 305.1501,  $[\text{M}+\text{H}]^+$ ,  $[\text{C}_{16}\text{H}_{21}\text{N}_2\text{O}_4]^+$  requires 305.1500

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

## 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), H<sub>2</sub>O (12.5 mL) and AcOH (5 mL). The reaction was refluxed for 15 h then concentrated under vacuum. The resulting brown oil was added to a mixture of *i*-PrOH (16 mL) and HBr (33 % in AcOH, 4 mL), causing the precipitation of a pale pink powder. The precipitate was collected by filtration and washed with *i*-PrOH (20 mL). The filtrate was concentrated under vacuum and precipitated again using the same procedure. The two crops of precipitate were combined. **38** was obtained as a pale pink amorphous solid (1.73 g, 9.50 mmol, 41 % yield).

**mp**  $T / ^\circ\text{C} = 242$  (*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)

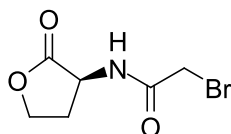
**<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta / \text{ppm} = 8.59$  (br s, 3 H,  $\text{NH}_3^+$ ), 4.46 (dt,  $J = 1.3, 8.9$  Hz, 1 H, OCHH), 4.37 (dd,  $J = 8.8, 11.4$  Hz, 1 H, CHNH<sub>3</sub><sup>+</sup>), 4.29 (ddd,  $J = 6.1, 8.8, 10.9$  Hz, 1 H, OCHH), 2.57 (dddd,  $J = 1.2, 6.1, 8.9, 12.3$  Hz, 1 H, OCH<sub>2</sub>CHH), 2.26 (dtd,  $J = 9.0, 11.2, 12.2$  Hz, 1 H, OCH<sub>2</sub>CHH)

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

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

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

## 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 NaHCO<sub>3</sub> (84.9 mg, 1.01 mmol, 2.00 eq.) were dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) and H<sub>2</sub>O (2 mL). Bromoacetyl bromide (44.0  $\mu\text{L}$ , 102 mg, 0.505 mmol, 1.00 eq.) was then added dropwise. The reaction mixture was stirred for 24 h, after which the CH<sub>2</sub>Cl<sub>2</sub> was removed under vacuum. The aqueous phase was extracted with EtOAc (4  $\times$  10 mL). The combined organic layers were dried with MgSO<sub>4</sub> and the solvent was removed under reduced pressure. **40** was obtained as white, needle-like crystals (88.0 mg, 0.396 mmol, 74 %).

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



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

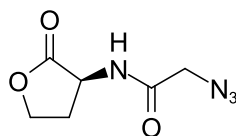
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  / ppm = 174.6 (OC=O), 166.4 (C(=O)NH), 66.1 (OCH<sub>2</sub>), 49.8 (CHNHC=O), 29.9 (OCH<sub>2</sub>CH<sub>2</sub>), 28.2 (O=CCH<sub>2</sub>Br)

**HRMS** The compound does not ionise.

$[\alpha]_D^{20}$  / °10<sup>-1</sup>cm<sup>2</sup>g<sup>-1</sup> = 27.0 ( $c$  / g(100 mL)<sup>-1</sup> = 0.00740, CHCl<sub>3</sub>)

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

## 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<sub>3</sub> (85.7 mg, 1.32 mmol, 2.61 eq.) and NaHCO<sub>3</sub> (84.9 mg, 1.01 mmol, 2.00 eq.) were dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) and H<sub>2</sub>O (2 mL). Bromoacetyl bromide (44.0  $\mu$ L, 102 mg, 0.505 mmol, 1.00 eq.) was then added dropwise. The reaction mixture was stirred for 48 h, after which the CH<sub>2</sub>Cl<sub>2</sub> was removed under vacuum. The aqueous phase was extracted with EtOAc (4  $\times$  10 mL). The combined organic layers were dried with MgSO<sub>4</sub> and the solvent was removed under reduced pressure. **41** was obtained as white, needle-like crystals (38.4 mg, 0.209 mmol, 41 %).

**mp**  $T$  / °C = 87 (EtOAc)

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

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

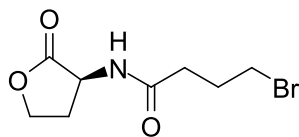
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  / ppm = 174.9 (OC=O), 167.5 (C=ONH), 66.0 (OCH<sub>2</sub>), 52.2 (O=CCH<sub>2</sub>N<sub>3</sub>), 48.9 (CHNHC=O), 29.7 (OCH<sub>2</sub>CH<sub>2</sub>)

**HRMS** The compound does not ionise.

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

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

### 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 NaHCO<sub>3</sub> (170 mg, 2.02 mmol, 1.84 eq.) were dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) and H<sub>2</sub>O (2 mL). Bromobutyryl chloride (140  $\mu$ L, 224 mg, 1.21 mmol, 1.10 eq.) was then added dropwise. The reaction mixture was stirred for 1 h, after which the CH<sub>2</sub>Cl<sub>2</sub> was removed under vacuum. The aqueous phase was extracted with EtOAc (7  $\times$  5 mL) and the combined organic layers were dried with MgSO<sub>4</sub>. 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)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta / \text{ppm} = 6.31$  (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, CH<sub>2</sub>Br), 2.82 (dddd,  $J = 1.3, 5.9, 8.7, 12.5$  Hz, 1 H, OCH<sub>2</sub>CHH), 2.47 (t,  $J = 7.3$  Hz, 2 H, C(=O)CH<sub>2</sub>), 2.26 - 2.15 (m, 3 H, OCH<sub>2</sub>CHH and CH<sub>2</sub>CH<sub>2</sub>Br)

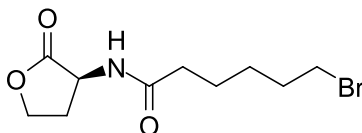
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta / \text{ppm} = 175.4$  (OC=O), 172.3 (C(=O)NH), 66.1 (OCH<sub>2</sub>), 49.3 (CHNHC=O), 33.9 (C(=O)CH<sub>2</sub>), 33.1 (CH<sub>2</sub>Br), 30.3 (OCH<sub>2</sub>CH<sub>2</sub>), 27.9 (C(=O)CH<sub>2</sub>CH<sub>2</sub>)

**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.

### 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 NaHCO<sub>3</sub> (84.9 mg, 1.01 mmol, 1.84 eq.) were dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) and H<sub>2</sub>O (2 mL) at r.t.. Bromohexanoyl chloride (93.0  $\mu$ L, 130 mg, 0.608 mmol, 1.11 eq.) was then added dropwise. The reaction mixture was stirred for 4 h, after which the CH<sub>2</sub>Cl<sub>2</sub> was removed under vacuum. The mixture was then filtered, washed with H<sub>2</sub>O (10 mL) and dried under high vacuum. **45** was obtained as white, needle-like crystals (101 mg, 0.362 mmol, 66 %).

**mp**  $T / ^\circ\text{C} = 106$  (CH<sub>2</sub>Cl<sub>2</sub>/H<sub>2</sub>O)

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

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

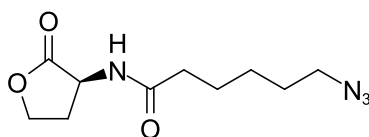
**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  / ppm = 175.5 ( $\text{OC=O}$ ), 173.3 ( $\text{C(=O)NH}$ ), 66.1 ( $\text{OCH}_2$ ), 49.3 ( $\text{CHNHC=O}$ ), 35.8 ( $\text{CH}_2\text{Br}$ ), 33.5 ( $\text{C(=O)CH}_2$ ), 32.3 ( $\text{CH}_2\text{CH}_2\text{Br}$ ), 30.5 ( $\text{OCH}_2\text{CH}_2$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

**HRMS** ( $\text{ESI}^+$ )  $m/z$  / 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 ( $c$  /  $\text{g(100 mL)}^{-1}$  = 0.208, MeOH)

The compound has not been reported previously.

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

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

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

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

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

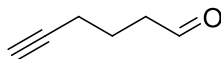
CH<sub>2</sub>CH<sub>2</sub>)

**HRMS** (ESI<sup>+</sup>)  $m/z$  / Da = 241.1289, [M+H]<sup>+</sup>, [C<sub>10</sub>H<sub>17</sub>N<sub>4</sub>O<sub>3</sub>]<sup>+</sup> requires 241.1295

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

The compound has not been reported previously.

### 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 Et<sub>2</sub>O (125 mL) and silica gel (62.5 g). The suspension was stirred for 1 h then filtered through a pad of silica (100 g) and washed with Et<sub>2</sub>O. The solvent was removed by rotary evaporation. **49** was obtained as a pale yellow-green oil (4.72 g, 49.1 mmol, 72 %).

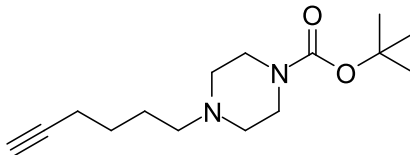
**IR** (neat)  $\nu_{max}$  / cm<sup>-1</sup> = 3292.7 (alkyne C-H), 2943.3 (alkane C-H), 2830.9 (aldehyde C-H), 2728.6 (aldehyde C-H), 1720.3 (aldehyde C=O)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  / ppm = 9.80 (s, 1 H, C(=O)H), 2.60 (t,  $J$  = 7.1 Hz, 2 H, CH<sub>2</sub>C(=O)H), 2.26 (dt,  $J$  = 2.6, 6.8 Hz, 2 H, HC≡CCH<sub>2</sub>), 1.98 (t,  $J$  = 2.7 Hz, 1 H, HC≡C), 1.85 (quin,  $J$  = 7.0 Hz, 2 H, HC≡CCH<sub>2</sub>CH<sub>2</sub>)

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  / ppm = 201.6 (C(=O)), 83.1 (HC≡C), 69.3 (HC≡C), 42.4 (CH<sub>2</sub>C(=O)), 20.7 (CH<sub>2</sub>CH<sub>2</sub>C(=O)), 17.6 (HC≡CCH<sub>2</sub>)

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

### 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 N<sub>2</sub> atmosphere in 1,2-dichloroethane (20 mL) for 2.5 h followed by addition of sodium triacetoxyborohydride (6.25 g, 29.5 mmol, 6.96 eq.) in four portions over 4 d. The mixture was stirred for a further day then NaHCO<sub>3</sub> (sat., aq., 120 mL) was added and the product extracted with EtOAc (2 × 100 mL). The solvent was dried over MgSO<sub>4</sub> and removed by rotary evaporation. **51** was obtained as a colourless liquid (1.12 g, 4.21 mmol, 99 %).

**TLC**  $R_f$  (10 % MeOH/CH<sub>2</sub>Cl<sub>2</sub>) = 0.55

**IR** (neat)  $\nu_{max}$  /  $\text{cm}^{-1}$  = 3303.6 (alkyne C-H), 2940.0 (alkane C-H), 2865.2 (C-H), 2810.4 (C-H), 1691.3 (carbamate C=O)

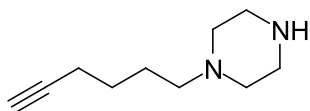
**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  / ppm = 3.44 (t,  $J$  = 5.2 Hz, 4 H,  $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)\text{CH}_2\text{CH}_2$ ), 2.39 (t,  $J$  = 5.1 Hz, 4 H,  $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2)\text{CH}_2$ ), 2.37 (t,  $J$  = 7.3 Hz, 2 H,  $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$ ), 2.23 (dt,  $J$  = 2.7, 6.8 Hz, 2 H,  $\text{HC}\equiv\text{CCH}_2$ ), 1.96 (t,  $J$  = 2.7 Hz, 1 H,  $\text{HC}\equiv\text{C}$ ), 1.65 - 1.53 (m, 4 H,  $\text{HC}\equiv\text{CCH}_2\text{CH}_2\text{CH}_2$ ), 1.47 (s, 9 H,  $\text{CH}_3$ )

**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  / 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 ( $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$ ), 58.0 ( $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2)\text{CH}_2$ ), 53.0 ( $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)\text{CH}_2\text{CH}_2$ ), 28.4 ( $\text{C}(\text{CH}_3)_3$ ), 26.3 ( $\text{CH}_2\text{CH}_2\text{N}$ ), 25.7 ( $\text{HC}\equiv\text{CCH}_2\text{CH}_2$ ), 18.3 ( $\text{HC}\equiv\text{CCH}_2$ )

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

The compound has not been reported previously.

## 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  $\text{CH}_2\text{Cl}_2$  ( $2 \times 20$  mL). The oil was diluted with  $\text{H}_2\text{O}$  (10 mL) and the pH adjusted to 14 with NaOH (10 % aq.). This mixture was extracted with  $\text{CH}_2\text{Cl}_2$  ( $2 \times 20$  mL) and the combined organic layers were dried over  $\text{MgSO}_4$ . The solvent was removed under vacuum and purified by column chromatography ( $\text{SiO}_2$  MeOH/ $\text{CH}_2\text{Cl}_2$  3:7). **52** was obtained as a colourless liquid (476 mg, 2.86 mmol, 100 %).

**TLC**  $R_f$  (30 % MeOH/ $\text{CH}_2\text{Cl}_2$ ) = 0.20

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

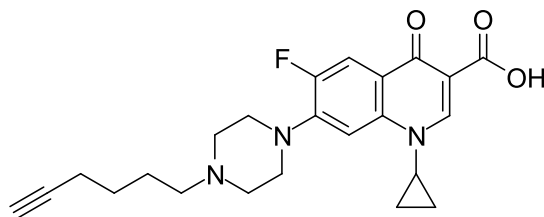
**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  / ppm = 2.88 (t,  $J$  = 4.9 Hz, 4 H,  $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)\text{CH}_2\text{CH}_2$ ), 2.39 (m, 4 H,  $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2)\text{CH}_2$ ), 2.31 (t,  $J$  = 7.1 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,  $\text{NH}$ ), 1.93 (t,  $J$  = 2.7 Hz, 1 H,  $\text{HC}\equiv\text{C}$ ), 1.65 - 1.48 (m, 4 H,  $\text{HC}\equiv\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$ )

**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  / ppm = 84.3 ( $\text{HC}\equiv\text{C}$ ), 68.4 ( $\text{HC}\equiv\text{C}$ ), 58.6 ( $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$ ), 54.5 ( $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2)\text{CH}_2$ ), 46.0 ( $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)\text{CH}_2\text{CH}_2$ ), 26.4 ( $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$ ), 25.7 ( $\text{HC}\equiv\text{CCH}_2\text{CH}_2$ ), 18.3 ( $\text{HC}\equiv\text{CCH}_2$ )

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

The compound has not been reported previously.

**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/CH<sub>2</sub>Cl<sub>2</sub>)

**mp**  $T$  / °C = 220 (MeOH, decomposes)

**IR** (neat)  $\nu_{max}$  / cm<sup>-1</sup> = 3212.0 (alkyne C-H), 2459.3 (O-H), 1722.6 (carboxylic acid C=O), 1626.8 (quinolone C=O)

**<sup>1</sup>H NMR** (500 MHz, DMSO-d<sub>6</sub>)  $\delta$  / ppm = 15.12 (br s, 1 H, C(=O)OH), 8.69 (s, 1 H, *ortho* to C(=O)OH), 7.96 (d,  $J$  = 13.0 Hz, 1 H, *ortho* to F), 7.61 (d,  $J$  = 7.6 Hz, 1 H, *meta* to F), 3.82 - 3.92 (m, 3 H, NCH(CH<sub>2</sub>)<sub>2</sub> and CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 3.54 - 3.68 (br m, 2 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 3.45 (br. t,  $J$  = 11.6 Hz, 2 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 3.21 - 3.29 (br m, 2 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 3.11 - 3.20 (br m, 2 H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 2.84 (t,  $J$  = 2.7 Hz, 1 H, HC≡C), 2.24 (td,  $J$  = 7.0, 2.7 Hz, 2 H, HC≡CCH<sub>2</sub>), 1.83 (br. quin,  $J$  = 7.5 Hz, 2 H, HC≡CCH<sub>2</sub>CH<sub>2</sub>), 1.52 (quin,  $J$  = 7.4 Hz, 2 H, HC≡CCH<sub>2</sub>CH<sub>2</sub>), 1.29 - 1.36 (m, 2 H, NCH(CH<sub>2</sub>)<sub>2</sub>), 1.16 - 1.23 (m, 2 H, NCH(CH<sub>2</sub>)<sub>2</sub>)

**<sup>13</sup>C NMR** (126 MHz, DMSO-d<sub>6</sub>)  $\delta$  / ppm = 176.4 (C(=O)CC(=O)OH), 165.8 (C(=O)OH), 152.8 (d,  $J$  = 248.5 Hz, *ipso* to F), 148.2 (CHCC(=O)OH), 143.7 (d,  $J$  = 11.1 Hz, *para* to C(=O)), 139.1 (*para* to F), 119.4 (d,  $J$  = 6.9 Hz, *ipso* to C(=O)), 111.2 (d,  $J$  = 22.5 Hz, *ortho* to F and *ortho* to C(=O)), 106.9 (*meta* to F and *meta* to C(=O)), 106.9 (C(=O)CC(=O)OH), 83.9 (HC≡C), 71.8 (HC≡C), 55.0 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N), 50.5 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>), 46.3 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>)CH<sub>2</sub>CH<sub>2</sub>), 36.0 (NCH(CH<sub>2</sub>)<sub>2</sub>), 25.2 (HC≡CCH<sub>2</sub>CH<sub>2</sub>), 22.3 (HC≡CCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 17.4 (HC≡CCH<sub>2</sub>), 7.6 (NCH(CH<sub>2</sub>)<sub>2</sub>)

**<sup>19</sup>F NMR** (376.45 MHz, MeOD)  $\delta$  / ppm = -121.8 (s, ciprofloxacin F)

**HRMS** (ESI<sup>+</sup>)  $m/z$  / Da = 412.2036, [M+H]<sup>+</sup>, [C<sub>23</sub>H<sub>27</sub>N<sub>3</sub>O<sub>3</sub>F]<sup>+</sup> requires 412.2030

The compound has not been reported previously.