Microwave and flow syntheses of *Pseudomonas* quinolone signal (PQS) and analogues

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Supplementary Experimental Section

1.1 General experimental details

Reactions were performed using oven-dried glassware apparatus under an atmosphere of nitrogen with anhydrous, freshly distilled solvents unless otherwise stated. Ethyl acetate was distilled from calcium hydride. Tetrahydrofuran was dried over Na wire and distilled from a mixture of lithium aluminium hydride and calcium hydride. Anhydrous 1-methyl-2-pyrrolidinone (NMP) was used as obtained from commercial sources. All other reagents were used as obtained from commercial sources.

Room temperature refers to ambient temperature. Temperatures of 0 ˚C were maintained using an ice-water bath. Reactions involving microwave irradiation were performed in 10 ml or 30 ml microwave tubes with clip lids using CEM Discover® microwave apparatus (internal temperature measurement). Reactions involving continuous flow-through conditions were carried out on the Uniqsis FlowSyn™ Continuous Flow Reactor.

Yields refer to chromatographically and spectroscopically pure compounds unless otherwise stated. All flash chromatography was carried out using slurry-packed Merck 9325 Keiselgel 60 silica gel. Were possible, reactions were monitored by thin layer chromatography (TLC) performed on commercially prepared glass plates precoated with Merck silica gel 60 F254 or aluminium oxide 60 F254. Visualisation was by the quenching of UV fluorescence (ν_{max} = 254 nm) or by staining with ceric ammonium

molybdate, potassium permanganate or Dragendorff 's reagent (0.08% w/v bismuth subnitrate and 2% w/v KI in 3 M aq. AcOH).

Infrared spectra were recorded neat on a Perkin-Elmer Spectrum One spectrometer with internal referencing. Selected absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}). The abbreviation "br" indicates a broad peak.

Melting points were obtained using a Büchi® melting point apparatus (model B-545) and are uncorrected.

Proton magnetic resonance spectra were recorded using an internal deuterium lock at ambient probe temperatures (unless otherwise stated) on the following instruments: Bruker DPX-400 (400 MHz), Bruker Avance 400 QNP (400 MHz), Bruker Avance 500 BB ATM (500 MHz) and Bruker Avance 500 Cryo Ultrashield (500 MHz). Chemical shifts (δ_H) are quoted in ppm, to the nearest 0.01 ppm, and are referenced to the residual non-deuterated solvent peak. Coupling constants (*J*) are reported in Hertz to the nearest 0.5 Hz. Data are reported as follows: chemical shift, integration, multiplicity [br, broad; s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; sept, septet; m, multiplet; or as a combination of these (*e.g.* dd, dt, *etc.*)], coupling constant(s) and assignment. Proton assignments were determined either on the basis of unambiguous chemical shift or coupling pattern, by patterns observed in 2D experiments (^1H-^1H COSY, HMBC and HMQC) or by analogy to fully interpreted spectra for related compounds.

Carbon magnetic resonance spectra were recorded by broadband proton spin decoupling at ambient probe temperatures (unless otherwise stated) using an internal deuterium lock on the following instruments: Bruker DPX-400 (100 MHz), Bruker Avance 400 QNP (100 MHz), Bruker Avance 500 BB ATM (125 MHz) and Bruker Avance 500 Cryo Ultrashield (125 MHz). Chemical shifts (δ_C) are quoted in ppm, to the nearest 0.1 ppm, and are referenced to the residual non-deuterated solvent peak. Where appropriate, coupling constants are reported in Hertz to the nearest 0.5 Hz and data are reported as for proton magnetic resonance spectra without integration. Assignments were supported by DEPT editing and determined either on the basis of unambiguous chemical shift or

coupling pattern, by patterns observed in 2D experiments (HMBC and HMQC) or by analogy to fully interpreted spectra for related compounds.

High resolution mass spectroscopy measurements were made by the EPSRC mass spectrometry service (Swansea) or recorded in-house using a Waters LCT Premier Mass Spectrometer or a Micromass Quadrapole-Time of Flight (Q-ToF) spectrometer. Mass values are reported within the error limits of ±5 ppm mass units. ESI = electrospray ionisation.

1.2 Abbreviations used

app = apparent

DIPEA = di*iso*propylethylamine

equiv = equivalents

hr = hour(s)

min = minute(s)

NMP = *N*-methylpyrrolidone (1-methyl-2-pyrrolidinone)

PQS = *Pseudomonas* quinolone signal (2-heptyl-3-hydroxyl-4(1*H*)-quinolone)

rt = room temperature

1.3 General experimental procedures

1.3.1 General procedure 1: preparation of α-chloro ketones

The appropriate Grignard reagent (1 N, 5.45 ml, 1.5 equiv) was added slowly to a solution of 2-chloro-*N*-methoxy-*N*-methylacetamide (0.5 g, 3.63 x 10^{-3} mol) in anhydrous THF (10 ml) under nitrogen at 0 ˚C over the course of 5 min. The reaction mixture was then allowed to stir at rt for 2 hr and toluene was added (15 ml). The reaction mixture was then poured onto HCl (10% aqueous solution) at 0 ˚C and stirred for 10 min. The aqueous and organic layers were separated and the organic layer was washed with brine (15 ml), dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude product was used in the subsequent step without further purification (or can be purified by column chromatography on SiO_2 if desired).

1.3.2 General procedure 2: preparation of PQS and analogues using microwave irridation

Di*iso*propylethylamine (1.2 equiv) and the appropiate α-chloro ketone (1.0 equiv) were added in sequence to a solution of the appropriate substituted anthranilic acid (0.15 g, 1.0 equiv) in anhydrous NMP (2.25 ml) contained in a 10 ml microwave vial. The solution was then heated under microwave irradiation to 200 ˚C for 30-60 min. The reaction mixture was then allowed to cool to rt and added to an ice/H_2O mix and left to settle for 20 min. The precipitate thus formed was then isolated by filtration, dried under high vacuum overnight and the crude product was purified by recrystallisation.

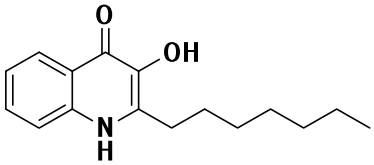
1.3.3 General procedure 3: preparation of PQS and an analogue under continuous flow conditions

Stock solution (**A**) of anthranilic acid (1.0 equiv) and *N,N*-di*iso*propylethylamine (1.0 equiv) in NMP at a concentration of (0.80 M) was prepared. Stock solution (**B**) was prepared using the appropriate α-chloro ketone (1.0 equiv) in NMP (0.80 M). Stock solutions/reagents were pumped from high-pressure pumps into a stainless steel coil reactor (5 ml) fitted with a 500 psi back pressure regulator at a flow rate of 1 ml/min at 220 ˚C. The heat exchanger was cooled to 40 ˚C by connecting it to a low pressure nitrogen line (<1 bar). The reaction mixture was collected by directing the flow reactor

output into a container of continuously stirring ice water (250 ml). After the total reaction mixture was passed through the steel coil reactor a final reactor wash of NMP was performed (7 ml, flow rate 5 ml/min). The product was collected by filtration of the aqueous suspension and purified by recrystallisation.

1.4 Experimental procedures

1.4.1 PQS



Prepared by general procedure 2 with 30 min heating time. The crude material was dried in a vacuum desiccator overnight and then recrystallised from EtOAc to give the title compound as a crystalline white solid (74%).

ν_{max} (neat)/cm^{-1} 3249 br (OH), 2949, 2924, 2849, (CH), 1639 (C=O); δ_H (400 MHz, d_6-DMSO); 11.42 (1H, br s, NH), 8.10 (1H, d, *J* 8.0 Hz, aryl CH), 8.00 (1H, br s, OH), 7.52-7.55 (2H, m, aryl CH), 7.19-7.24 (1H, m, aryl CH), 2.74 (2H, t, *J* 7.5 Hz NHCC$\underline{H}_2$), 1.68 (2H, quint, *J* 7.5 Hz NHCCH$_2$C$\underline{H}_2$), 1.20-1.40 (8H, m, 4 x CH$_2$), 0.86 (3H, t, *J* 7.0 Hz, CH$_3$); δ_C (125 MHz; d_6-DMSO) 168.9 (C=O), 137.9 (COH), 137.5 (CNH), 135.6 (CNH) 130.0 (CH), 124.6 (CH), 122.3 ($\underline{C}$C(=O)C(OH)), 121.6 (CH), 117.9 (CH), 31.3 (CH$_2$), 28.9 (CH$_2$), 28.6 (CH$_2$), 28.2 (CH$_2$), 27.9 (CH$_2$), 22.1 (CH$_2$), 14.0 (CH$_3$); **m.p.** 190-192 °C (EtOAc); lit 197-198 °C (EtOAc).[a]

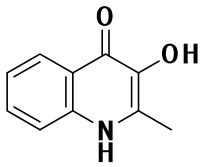
This data is in agreement with that previously reported [a]

[a] E. C. Pesci, J. B. J. Milbank, J. P. Pearson, S. McKnight, A. S. Kende, E. P. Greenberg and B. H. Iglewski, *Proc. Nat. Acad. Sci. U. S. A.*, 1999, **96**, 11229-11234.

1.4.2 PQS – preparation using the Uniqsis FlowSyn^{TM} continuous flow reactor

Prepared by general procedure 3, using anthranilic acid (2.125 g, 15.497 mmol, 1 equiv) and 1-chloro-2-nonanone (28) (2.738 g, 15.497 mmol, 1 equiv) This was recrystallised in EtOAc to yield PQS as a white powder, which was analytically pure (2.29 g, 8.8 mmol, 57%). Characterisation data is consistent with product obtained under microwave irradiation.

1.4.3 3-Hydroxy-2-methyl-quinolin-4(1*H*)-one **(10a)**



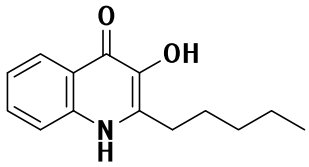
Prepared by general procedure 2 with 30 min heating time. The crude material was washed with water to remove residual NMP and dried in a vacuum oven at 100 °C for 12 hr to give an off white solid, no further purification was required (45%).

ν_{max} (neat)/cm^{-1}3249 br (OH), 1638 (C=O); δ_H (400 MHz, $CDCl_3$) 11.50 (1H, s, NH), 8.10 (1H, dd, *J* 8.0 Hz, 1.0 Hz, aryl CH), 8.05 (1H, br s, OH), 7.48-7.56 (2H, m, aryl CH), 7.20-7.40 (1H, m, aryl CH), 2.38 (3H, s, CH_3); δ_C (125 MHz; $CDCl_3$) 168.7 (C=O), 138.2 (COH), 137.4 (CHCNH), 131.7 ($CH_3\underline{C}NH$), 130.0 (CH), 124.6 (CH), 122.4 ($CH\underline{C}C=O$), 121.6 (CH), 117.7 (CH), 14.1 (CH_3); **m.p.** 290-295 °C (acetone); lit. 298-306 °C (dimethylformamide/acetone).[c]

This data is in agreement with that previously reported.[b]

[b] P. Hradil, J. Hlavac and K. Lemr, *J. Heterocycl. Chem.*, 1999, **36**, 141-144 and references therein.

1.4.4 1(*H*)-2-Pentyl-3-hydroxy quinolone **(10b)**

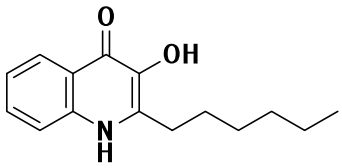


Prepared by general procedure 2 with 30 min heating time. The crude material was dried in a vacuum desiccator overnight and then recrystallised from EtOH to give the title compound as a crystalline off white solid (62%).

ν_{max} (neat)/cm^{-1} 3244 br (OH), 2955, 2924, 2857, 1640 (C=O), 1595, 1557, 1488, 1498; δ_H (400 MHz, d_6-DMSO) 11.39 (1H, s, NH), 8.10 (1H, d, *J* 8.5 Hz, aryl CH**)**, 7.54 (2H, app d, *J* 3.0 Hz, aryl CH), 7.25-7.19 (1H, m, aryl CH), 2.73 (2H, t, *J* 7.5 Hz, NHCC$\underline{H}_2$), 1.68 (2H, quint, *J* 7.5 Hz, NHCCH$_2$C$\underline{H}_2$), 1.37-1.30 (4H, m, 2 x CH$_2$), 0.88 (3H, t, *J* 7.0 Hz, CH$_3$); δ_C (125 MHz; d_6-DMSO) 168.9 (C=O), 137.8 (COH), 137.4 (C), 135.5 (C), 130.1 (CH), 124.6 (CH), 122.3 (C), 121.6 (CH), 117.8 (CH), 31.1 (CH$_2$), 28.1 (CH$_2$), 27.6 (CH$_2$), 22.0 (CH$_2$), 14.0 (CH$_3$); **HRMS** (ESI$^+$) *m/z* found $[M+H]^+$ 232.1347, $C_{14}H_{18}NO_2^+$ required 232.1338; **m.p.** 265 °C (dec; EtOH).

This synthesis of this compound has previously been reported (D. I. Pritchard, B. W. Bycroft, S. R. Chhabra and D. Hooi. Substitued 4-quinolones. PCT Int. Appl. WO/2002/047686, 2002).

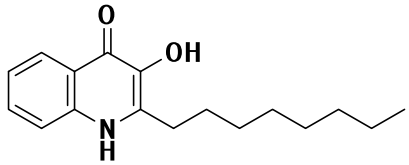
1.4.5 1(*H*)-2-Hexyl-3-hydroxy quinolone **(10c)**



Prepared by general procedure 2 with 30 min heating time. The crude material was dried in a vacuum desiccator overnight and then recrystallised from EtOH to give the title compound as a crystalline off white solid (56%).

ν_{max} (neat)/cm^{-1} 3241 br (OH), 2957, 2928, 2850, 1640 (C=O), 1595, 1557, 1488, 1498; δ_H (400 MHz, d_6-DMSO) 11.39 (1H, s, NH), 8.10 (1H, app dt, *J* 8.0 Hz, 1.0 Hz, aryl CH), 7.54 (2H, app d, *J* 3.0 Hz, aryl CH), 7.26-7.18 (1H, m, aryl CH), 2.73 (2H, t, *J* 7.5 Hz, NHCC$\underline{H_2}$), 1.67 (2H, quint, *J* 7.5 Hz, NHCCH$_2$C$\underline{H_2}$), 1.40-1.24 (6H, m, 3 x CH_2), 0.86 (3H, t, *J* 7.0 Hz, CH_3); δ_C (125 MHz; d_6-DMSO) 168.9 (C=O), 137.9 (COH), 137.4 (C), 135.5 (C), 130.0 (CH), 124.6 (CH), 122.3 (C), 121.6 (CH), 117.8 (CH), 31.1 (CH_2), 28.6 (CH_2), 28.2 (CH_2), 27.8 (CH_2), 22.1 (CH_2), 14.0 (CH_3); **HRMS** (ESI$^+$) *m/z* found [M+H]$^+$ 246.1500, $C_{15}H_{20}NO_2^+$ required 246.1494; **m.p.** 205-207 °C (EtOH).

1.4.6 1(*H*)-2-Octyl-3-hydroxy quinolone **(10d)**



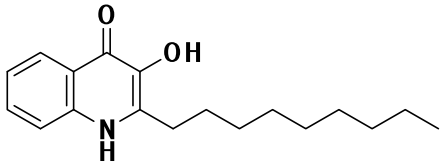
Prepared by general procedure 2 with 40 min heating time. The crude material was dried in a vacuum desiccator overnight and then recrystallised from EtOAc to give the title compound as a crystalline off white solid (62%).

ν_{max} (neat)/cm^{-1} 3243 br (OH), 2953, 2924, 2854, 1636 (C=O), 1597, 1558; δ_H (400 MHz, d_6-DMSO) 11.39 (1H, s, NH), 8.10 (1H, app dt , *J* 8.0 Hz, 1.0 Hz, aryl CH**)**, 7.53 (2H, app d, *J* 3.0 Hz, aryl CH), 7.26-7.18 (1H, m, aryl CH), 2.73 (2H, t, *J* 7.5 Hz, NHCC$\underline{H_2}$), 1.66 (2H, quint, *J* 7.5 Hz, NHCCH$_2$C$\underline{H_2}$), 1.40-1.20 (10H, m, 5 x CH_2), 0.86 (3H, t, *J* 7.0 Hz, CH_3); δ_C (125 MHz; d_6-DMSO) 169.3 (C=O), 138.2 (COH), 137.8 (C), 135.9 (C), 130.4 (CH), 124.9 (CH), 122.6 (C), 121.9 (CH), 118.2 (CH) 31.7 (CH_2), 29.5 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 28.6 (CH_2), 28.2 (CH_2), 22.5 (CH_2), 14.4 (CH_3); **HRMS** (ESI$^+$) *m/z* found [M+H]$^+$ 274.1787, $C_{17}H_{24}NO_2^+$ required 274.1807; **m.p.** 193-194 °C (EtOH).

1.4.7 1(*H*)-2-Octyl-3-hydroxy quinolone **(10d)** – preparation using the Uniqsis FlowSyn^{TM} continuous flow reactor

Prepared by general procedure 3, using anthranilic acid (0.115 g, 0.6 mmol, 1 equiv) and 1-chloro-2-decanone (0.083 g, 0.6 mmol, 1 equiv). Recrystallised in EtOAc to yield **10d** as an off white powder (0.11 g, 0.39 mmol, 65%). The product was determined to be approximately 90% pure by LCMS analysis (impurities could not be identified). Characterisation data is consistent with product obtained under microwave irradiation.

1.4.8 1(*H*)-2-Nonyl-3-hydroxy quinolone **(10e)**

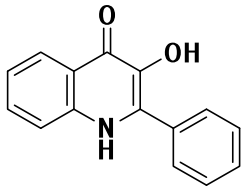


Prepared by general procedure 2 with 40 min heating time. The crude material was dried in a vacuum desiccator overnight and then recrystallised from EtOAc to give the title compound as a crystalline off white solid (45%).

ν_{max} (neat)/cm^{-1}3265 br (OH), 2950, 2924, 2852, 1638 (C=O), 1595, 1558; δ_H (400 MHz, d_6-DMSO) 11.39 (1H, s, NH), 8.10 (1H, d, *J* 8.0 Hz, aryl CH), 7.53 (2H, app d, *J* 3.5 Hz aryl CH), 7.26-7.18 (1H, m, aryl CH), 2.74 (2H, t, *J* 7.5 Hz, NHCC$\underline{H}_2$), 1.68 (2H, quint, *J* 7.5 Hz NHCCH$_2$C$\underline{H}_2$), 1.40-1.20 (12H, m, 6 x CH_2), 0.86 (3H, t, *J* 7.0 Hz, CH_3); δ_C (125 MHz; d_6-DMSO) 169.3 (C=O), 138.3 (COH), 137.8 (C), 135.9 (C), 130.4 (CH), 124.9 (CH), 122.6 (C), 121.9 (CH), 118.2 (CH), 31.7 (CH_2), 29.4 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 28.6 (CH_2), 28.2 (CH_2), 22.5 (CH_2), 14.4 (CH_3); **HRMS** (ESI$^+$) *m/z* found $[M+H]^+$ 288.2013, $C_{18}H_{26}NO_2^+$ required 288.1964; **m.p.** 184-187 °C (EtOAc).

This synthesis of this compound has previously been reported (D. I. Pritchard, B. W. Bycroft, S. R. Chhabra and D. Hooi. Substitued 4-quinolones. PCT Int. Appl. WO/2002/047686, 2002).

1.4.9 1-(*H*)-2-Phenyl-3-hydroxy-quinolone **(11a)**



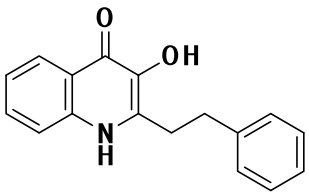
Prepared by general procedure 2 with 30 min heating time. The crude material was washed with water to remove residual NMP and dried in a vacuum oven at 100 °C for 12 hr to give an off white solid no further purification was required (65%).

ν_{max} (neat)/cm^{-1} 2937 br (OH), 1633 (C=O); δ_H (400 MHz, $CDCl_3$) 11.55 (1H, s, NH), 8.30 (1H, br s, OH), 8.16 (1H, dd, *J* 8.0 Hz, 1.5 Hz, aryl CH), 7.79-7.83 (2H, m, aryl CH), 7.72 (1H, d, *J* 8.0 Hz, aryl CH), 7.65-7.62 (4H, m, aryl CH), 7.28 (1H, ddd, *J* 8.0 Hz, 7.0 Hz, 1.5 Hz, aryl CH); δ_C (125 MHz; $CDCl_3$) 170.1 (C=O), 138.1 (COH), 137.8 (C), 132.4 (C), 131.5 (C), 130.6 (CH), 129.3 (CH), 128.4 (CH), 124.5 (CH), 122.0 (CH), 121.9 (C), 118.5 (CH), 118.4 (CH); **m.p.** 273-275 °C (acetone); lit. 278-281 °C (dimethylformamide/acetone).[b]

This data is in agreement with that previously reported.[c]

[c] P. Hradil, J. Hlavac and K. Lemr, *J. Heterocycl. Chem.*, 1999, **36**, 141-144 and references therein.

1.4.10 3-Hydroxy-2-phenylethylquinolin-4(1 *H*)-one **(11b)**

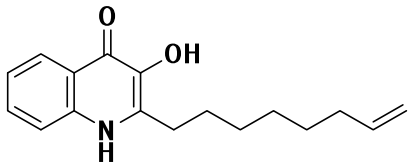


Prepared by general procedure 2 with 45 min heating time. The crude material was dried in a vacuum desiccator overnight and then recrystallised from acetone to give the title compound as a crystalline yellow solid (10%).

ν_{max} (neat)/cm^{-1} 3252 br (OH), 2916, 1637 (C=O), 1599, 1557; δ_H (400 MHz, d_6-DMSO) 11.47 (1H, s, NH), 8.10 (1H, d, *J* 8.0 Hz, aryl CH), 7.60-7.50 (2H, m, aryl CH), 7.34-7.18

(6H, m, aryl CH), 3.06-2.96 (4H, m, 2 x CH_2); δ_C (125 MHz; d_6-DMSO) 169.0 (C=O), 140.9 (C), 138.0 (C), 137.5 (C), 134.5 (C), 130.2 (CH), 128.5 (CH), 128.3 (CH), 126.2 (CH), 124.6 (CH), 122.4 (C), 121.6 (CH), 117.9 (CH), 33.5 (CH_2), 30.2 (CH_2); **HRMS** (ESI^+) *m/z* found $[M+H]^+$ 266.1171, $C_{17}H_{16}NO_2^+$ required 266.1181; **m.p.** 254-256 °C (acetone).

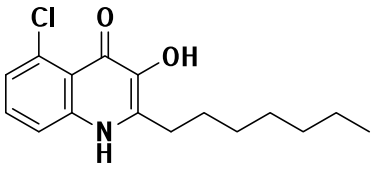
1.4.11 3-Hydroxy-2-(oct-7-enyl)quinolin-4(1H)-one **(12)**



Prepared by general procedure 2 with 40 min heating time. The crude material was dried in a vacuum desiccator overnight and then recrystallised from EtOAc to give the title compound as an off white solid (56%).

ν_{max} (neat)/cm^{-1} 3243 br (OH), 2929, 2853, 1637 (C=O), 1599, 1558; δ_H (400 MHz, d_6-DMSO) 11.40 (1H, s, NH), 8.10 (1H, d, *J* 8.0 Hz, aryl CH), 7.54 (2H, app d, *J* 3.0 Hz, aryl CH), 7.25-7.19 (1H, m, aryl CH), 5.84-5.73 (1H, m, C<u>H</u>=CH_2), 5.01-4.91 (2H, m, CH=C<u>H</u>$_2$), 2.73 (2H, t, *J* 7.5 Hz, NHCC<u>H</u>$_2$), 2.00 (2H, app q, *J* 6.5 Hz, C<u>H</u>$_2$CH=CH_2), 1.66 (2H, quint, *J* 7.5 Hz, NHCCH_2C<u>H</u>$_2$), 1.40-1.30 (6H, m, 3 x CH_2); δ_C (125 MHz; d_6-DMSO) 169.0 (C=O), 138.8 (<u>C</u>H=CH_2), 137.9 (COH), 137.5 (C), 135.6 (C), 130.1 (CH), 124.6 (CH), 122.3 (C), 122.3 (CH), 117.9 (CH) 114.8 (CH=<u>C</u>H_2), 33.2 (CH_2), 28.7 (CH_2), 28.4 (CH_2), 28.2 (CH_2), 28.2 (CH_2), 27.9 (CH_2); **HRMS** (ESI^+) *m/z* found $[M+H]^+$ 272.1636, $C_{17}H_{22}NO_2^+$ required 272.1651; **m.p.** 175-177 °C (EtOH).

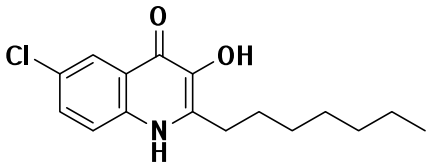
1.4.12 5-Chloro-2-heptyl-3-hydroxyquinolin-4-(1*H*)-one **(13a)**



Prepared by general procedure 2 with 60 min heating time. The crude material was dried in a vacuum desiccator overnight and then recrystallised from EtOAc to give the title compound as a white powder (64%).

ν_{max} (neat)/cm^{-1} 2952, 2923, 2857, 1655 (C=O), 1601, 1544, 1467, 1416; δ_H (400 MHz, d_6-DMSO) 11.50 (1H, br s, NH), 8.00 (1H, br s, OH), 7.50 (1H, dd, *J* 8.5 Hz, 1.5 Hz, aryl CH), 7.45-7.40 (1H, dd, *J* 8.5 Hz, 7.5 Hz, aryl CH), 7.20-7.17 (1H dd, *J* 7.5 Hz, 1.5 Hz, aryl CH), 2.71 (2H, t, *J* 7.5 Hz, NHCC$\underline{H}_2$), 1.66 (2H, quint, *J* 7.5 Hz, NHCCH$_2$C$\underline{H}_2$), 1.35-1.21 (8H, m, 4 x CH$_2$), 0.86 (3H, t, *J* 7.0 Hz, CH$_3$); δ_C (125 MHz; d_6-DMSO) 168.4 (C=O), 139.7 (COH), 139.3 (CH$\underline{C}$NH) 133.6 (CH), 131.5 (CH), 129.8 (CH), 124.0 (C), 117.8 (C), 117.5 (C), 31.3 (CH$_2$), 28.8 (CH$_2$), 28.5 (CH$_2$), 27.9 (CH$_2$), 27.7 (CH$_2$), 22.1 (CH$_2$), 14.0 (CH$_3$); **HRMS** (ESI$^+$) *m/z* found [M+H]$^+$ 294.1247, $C_{18}H_{21}NO_2Cl^+$ required 294.1265; **m.p.** 244-247 °C (EtOAc).

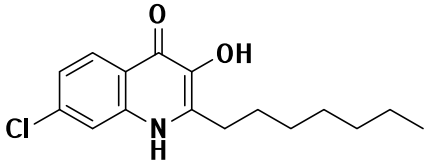
1.4.13 6-Chloro-2-heptyl-3-hydroxyquinolin-4-(1H)-one **(13b)**



Prepared by general procedure 2 with 45 min heating time. The crude material was dried in a vacuum desiccator overnight and then recrystallised from EtOAc to give the title compound as a crystalline white solid (68%).

ν_{max} (neat)/cm^{-1} 3237 br (OH), 2926, 2854, 1638 (C=O), 1555, 1460, 1407, 1368; δ_H (400 MHz, d_6-DMSO) 11.60 (1H br s, NH), 8.25 (1H, br s, OH), 8.03 (1H, dd, *J* 2.0 Hz, 1.0 Hz, aryl CH), 7.60-7.54 (2H, m, aryl CH), 2.73 (2H, t, *J* 7.5 Hz NHCC$\underline{H}_2$), 1.67 (2H, quint, *J* 7.5 Hz NHCCH$_2$C$\underline{H}_2$), 1.40-1.20 (8H, m, 4 x CH$_2$), 0.86 (3H, t, *J* 7.0 Hz CH$_3$); δ_C (125 MHz; d_6-DMSO) 167.8 (C=O), 138.3 (COH), 136.4 (CH$\underline{C}$NH), 135.8 (C), 130.2 (CH), 126.3 (C), 123.3 (CH), 123.25 (C), 120.4 (CH), 31.3 (CH$_2$), 28.9 (CH$_2$), 28.5 (CH$_2$), 28.2 (CH$_2$), 27.8 (CH$_2$), 22.1 (CH$_2$), 14.0 (CH$_3$); **HRMS** (ESI$^+$) *m/z* found [M+H]$^+$ 294.1241, $C_{16}H_{21}NO_2{}^{35}Cl^+$ required 294.1263; **m.p.** 261-266 °C (EtOAc).

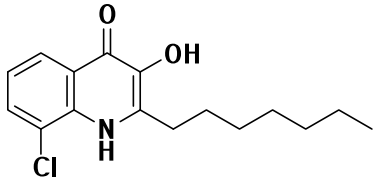
1.4.14 7-Chloro-2-heptyl-3-hydroxyquinolin-4-(1*H*)-one **(13c)**



Prepared by general procedure 2 with 30 min heating time. The crude material was dried in a vacuum desiccator overnight and then recrystallised from EtOAc to give the title compound as a crystalline white solid (48%).

ν_{max} (neat)/cm^{-1} 3248 br (OH), 2950, 2926, 2854, 1637 (C=O), 1564, 1551, 1467; δ_H (400 MHz, d_6-DMSO) 11.46 (1H, br s, NH), 8.20 (1H, br s, OH), 8.10 (1H, app br d, *J* 8.5 Hz, C(=O)CC<u>H</u>), 7.56 (1H, d, *J* 2.0 Hz, CClC<u>H</u>CNH), 7.23 (1H, dd, *J* 8.5 Hz, 2.0 Hz, C(=O)CCHC<u>H</u>), 2.72 (2H, t, *J* 7.0 Hz, NHCC<u>H</u>$_2$), 1.66 (2H, quint, *J* 7.0 Hz, NHCCH$_2$C<u>H</u>$_2$), 1.40-1.20 (8H, m, 4 x CH$_2$), 0.86 (3H, t, *J* 7.0 Hz, CH$_3$); δ_C (125 MHz; d_6-DMSO) 168.7 (C=O), 138.4 (COH), 137.9 (CH<u>C</u>NH) 136.0 (C), 134.7 (C), 127.0 (C), 122.0 (CH), 120.9 (CH), 116.8 (CH), 31.3 (CH$_2$), 28.8 (CH$_2$), 28.5 (CH$_2$), 28.2 (CH$_2$), 27.7 (CH$_2$), 22.1 (CH$_2$), 14.0 (CH$_3$); **HRMS** (ESI$^+$) *m/z* found [M+H]$^+$ 294.1243, $C_{16}H_{21}NO_2{}^{35}Cl^+$ required 294.1263; **m.p.** 264-269 °C (EtOAc).

1.4.15 8-Chloro-2-heptyl-3-hydroxyquinolin-4-(1*H*)-one **(13d)**

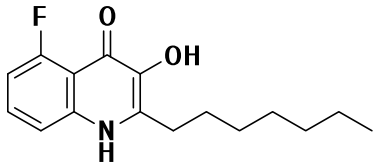


Prepared by general procedure 2 with 60 min heating time. The crude material was dried in a vacuum desicator overnight and then recrystallised from EtOAc to give the title compound as a crystalline white solid (29%).

ν_{max} (neat)/cm^{-1} 3170 br (OH), 2955, 2928, 2850, 1628 (C=O), 1564, 1517; δ_H (400 MHz, d_6-DMSO) 10.60 (1H, br s, NH), 8.30 (1H, br s, OH), 8.12 (1H, dd, *J* 8.0 Hz, 1.5 Hz, aryl CH), 7.74 (1H, dd, *J* 8.0, 1.5 Hz, aryl CH), 7.24 (1H, app t, *J* 8.0 Hz, aryl CH), 2.87 (2H, t, *J* 7.5 Hz NHCC<u>H</u>$_2$), 1.64 (2H, quint, *J* 7.5 Hz, NHCCH$_2$C<u>H</u>$_2$), 1.40-1.20 (8H, m, 4 x CH$_2$), 0.85 (3H, t, *J* 7.0 Hz, CH$_3$); δ_C (125 MHz; d_6-DMSO) 169.1 (C=O), 138.9 (COH),

137.5 (CCl<u>C</u>NH) 134.2 (C), 130.8 (C), 124.5 (C), 124.3 (CH), 123.3 (CH), 121.4 (CH), 31.7 (CH_2), 29.4 (CH_2), 29.0 (CH_2), 28.6 (CH_2), 28.1 (CH_2), 22.5 (CH_2), 14.4 (CH_3); **HRMS** (ESI^+) *m/z* found $[M+H]^+$ 294.1249, $C_{16}H_{21}NO_2{}^{35}Cl^+$ required 294.1263; **m.p.** 160-163 °C (EtOAc).

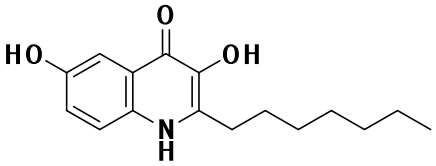
1.4.16 5-Fluoro-2-heptyl-3-hydroxyquinolin-4-(1*H*)-one **(13e)**



Prepared by general procedure 2 with 30 min heating time. The crude material was dried in a vacuum desicator overnight and then recrystallised from EtOAc to give the title compound as an off white powder (56%).

ν_{max} (neat)/cm^{-1} 2953, 2923, 2854, 1660 (C=O), 1623, 1561, 1484; δ_H (400 MHz, d_6-DMSO) 11.49 (1H, s, NH), 8.00 (1H, br s, OH), 7.46 (1H, app td, *J* 8.0 Hz, 5.0 Hz, aryl CH), 7.30 (1H, d, *J* 8.0 Hz, aryl CH), 6.88 (1H, ddd, *J* 12.0 Hz, 8.0 Hz, 1.0 Hz, aryl CH), 2.70 (2H, t, *J* 7.5 Hz, NHCC<u>H</u>$_2$), 1.66 (2H, quint, *J* 7.5 Hz, NHCCH$_2$C<u>H</u>$_2$), 1.40-1.20 (8H, m, 4 x CH_2), 0.85 (3H, t, *J* 7.0 Hz, CH_3); δ_C (125 MHz; d_6-DMSO) 167.8 (C=O), 160.4 (d, *J* 258 Hz, CF), 139.6 (d, *J* 5.0 Hz, CH<u>C</u>NH), 138.9 (COH), 134.2 (C), 130.3 (d, *J* 10.5 Hz, CH), 113.9 (d, *J* 10.5 Hz, CF<u>C</u>C(=O)), 112.1 (d, *J* 10.0 Hz, CH), 106.8 (d *J* 19.5 Hz, CH), 31.3 (CH_2), 28.8 (CH_2), 28.5 (CH_2), 28.0 (CH_2), 27.9 (CH_2), 22.1 (CH_2), 14.0 (CH_3); **HRMS** (ESI^+) *m/z* found $[M+H]^+$ 278.1539, $C_{16}H_{21}FNO_2{}^+$ required 278.3418; **m.p.** 280 °C (EtOAc).

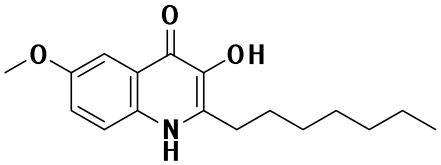
1.4.17 6-Hydroxy-2-heptyl-3-hydroxyquinolin-4-(1*H*)-one **(13f)**



Prepared by general procedure 2 with 30 min heating time. The crude material was dried in a vacuum desicator overnight and then recrystallised from acetone to give the title compound as a white powder (52%).

ν_{max} (neat)/cm^{-1} 3266 br (OH), 2958, 2921, 2853, 1613 (C=O), 1559, 1505, 1482; δ_H (400 MHz, d_6-DMSO) 11.27 (1H, s, NH), 9.47 (1H, br s, OH), 8.30 (1H, br s, OH), 7.42 (1H, d, *J* 9.0 Hz, aryl CH), 7.38 (1H, d, *J* 3.0 Hz, C(OH)C<u>H</u>CC(=O)), 7.07 (1H, dd, *J* 9.0 Hz, 3.0 Hz, aryl CH), 2.70 (2H, t, *J* 7.5 Hz, NHCC<u>H</u>$_2$), 1.66 (2H, quint, *J* 7.5 Hz, NHCCH$_2$C<u>H</u>$_2$), 1.40-1.20 (8H, m, 4 x CH$_2$), 0.85 (3H, t, *J* 7.0 Hz, CH$_3$); δ_C (125 MHz; d_6-DMSO) 167.8 (C=O), 152.4 (CH<u>C</u>OH) 136.9 (<u>C</u>OH), 134.8 (CH<u>C</u>NH) 131.6 (C), 123.5 (C), 121.1 (CH), 119.4 (CH), 106.2 (CH) 31.3 (CH$_2$), 28.9 (CH$_2$), 28.5 (CH$_2$), 28.2 (CH$_2$), 27.9 (CH$_2$), 22.1 (CH$_2$), 14.0 (CH$_3$); **HRMS** (ESI$^+$) *m/z* found [M+H]$^+$ 276.1588, $C_{16}H_{22}NO_3^+$ required 276.1600; **m.p.** 270 °C (acetone).

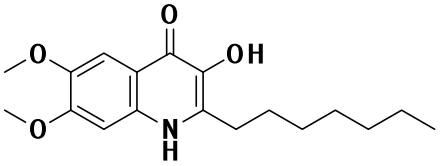
1.4.18 6 - Methoxy -2-heptyl-3-hydroxyquinolin-4-(1*H*)-one **(13g)**



Prepared by general procedure 2 with 30 min heating time. The crude material was dried in a vacuum desiccator overnight and then recrystallised from EtOH to give the title compound as a crystalline white solid (66%).

ν_{max} (neat)/cm^{-1} 3252 br (OH), 2929, 2854, CH, 1554, 1457; δ_H (400 MHz, d_6-DMSO) 11.40 (1H, br s, NH), 7.50 (1H, d, *J* 9.0 Hz, C<u>H</u>CHC(OCH$_3$)), 7.45 (1H, d, *J* 3.0 Hz, CHCHC(OCH$_3$)C<u>H</u>), 7.20 (1H, dd, *J* 9.0 Hz, 3.0 Hz, CHC<u>H</u>C(OCH$_3$)CH), 3.83 (3H, s, OCH$_3$), 2.72 (2H, t, *J* 7.5 Hz, NHCC<u>H</u>$_2$), 1.66 (2H, quint, *J* 7.5 Hz, NHCCH$_2$C<u>H</u>$_2$), 1.40-1.20 (8H, m, 4 x CH$_2$), 0.85 (3H, t, *J* 7.0 Hz, CH$_3$); δ_C (125 MHz; d_6-DMSO) 168.0 (C=O), 154.5 (<u>C</u>OCH$_3$), 137.4 (COH), 134.9 (C), 132.4 (C), 123.0 (C), 121.4 (CH), 119.7 (CH), 102.9 (CH), 55.3 (H$_3$CO), 31.2 (CH$_2$), 28.9 (CH$_2$), 28.5 (CH$_2$), 28.2 (CH$_2$), 27.9 (CH$_2$), 22.1 (CH$_2$), 14.0 (CH$_3$); **HRMS** (ESI$^+$) *m/z* found [M+H]$^+$ 290.1736, $C_{17}H_{24}NO_3^+$ required 290.1756; **m.p.** 217-220 °C (EtOH).

1.4.19 6,7-Dimethoxy-2-heptyl-3-hydroxyquinolin-4-(1*H*)-one **(14)**

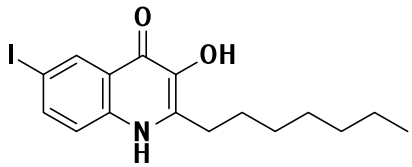


Prepared by general procedure 2 with 30 min heating time. The crude material was dried in a vacuum desiccator overnight and then recrystallised from EtOH to give the title compound as a white powder (54%).

ν_{max} (neat)/cm^{-1} 3239 br (OH), 2947, 2929, 2852, 1641 (C=O), 1604, 1552; δ_H (400 MHz, d_6-DMSO) 11.20 (1H, br s, NH), 7.39 (1H, s, C(=O)CC<u>H</u>) , 6.95 (1H, s, NHCC<u>H</u>), 3.85 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 2.69 (2H, t, *J* 7.5 Hz, NHCC<u>H</u>$_2$), 1.66 (2H, quint, *J* 7.5 Hz, NHCCH$_2$C<u>H</u>$_2$), 1.40-1.20 (8H, m, 4 x CH_2), 0.85 (3H, t, *J* 7.0 Hz, CH_3); δ_C (125 MHz; d_6-DMSO) 167.8 (C=O), 152.4 (<u>C</u>OCH_3), 145.9 (<u>C</u>OCH_3), 137.0 (COH), 133.6 (C), 133.3 (C), 116.1 (C), 103.3 (CH), 98.5 (CH), 55.6 (H_3CO), 55.5 (H_3CO), 31.3 (CH_2), 28.8 (CH_2), 28.5 (CH_2), 28.1 (CH_2), 27.9 (CH_2), 22.1, (CH_2), 14.0 (CH_3); **HRMS** (ESI$^+$) *m/z* found $[M+H]^+$ 220.1837, $C_{18}H_{26}NO_4^+$ required 220.1862; **m.p.** 268-271 °C (EtOH)

This synthesis of this compound has previously been reported (D. I. Pritchard, B. W. Bycroft, S. R. Chhabra and D. Hooi. Substitued 4-quinolones. PCT Int. Appl. WO/2002/047686, 2002).

1.4.20 6-Iodo-2-heptyl-3-hydroxyquinolin-4-(1H)-one **(13h)**



Prepared by general procedure 2 with 30 min heating time. The crude material was dried in a vacuum desiccator overnight and triturated in hot acetonitrile and filtered to give a purple solid (60%).

ν_{max} (neat)/cm^{-1} 3390 br (OH), 2925, 2854, 1649 (C=O), 1545, 1453, 1407, 1396; δ_H (400 MHz, d_6-DMSO) 11.52 (1H br s, NH), 8.35 (1H, d, *J* 2.0 Hz ,CC<u>H</u>CI), 8.31 (1H, br s, OH), 7.75 (1H, dd, *J* 8.8, 2.0 Hz, aryl CIC<u>H</u>CH), 7.33 (2H, d, *J* 8.8 Hz, CICHC<u>H</u>), 2.70 (2H, t, *J* 7.6 Hz NHCC<u>H_2</u>), 1.61-1.64 (2H, m, $NHCCH_2C\underline{H_2}$), 1.40-1.20 (8H, m, 4 x CH_2), 0.81 (3H, t, *J* 6.8 Hz CH_3); δ_C (125 MHz; d_6-DMSO) 167.5 (C=O), 138.4 (C), 137.89 (CH), 136.4 (C), 136.3 (C), 133.0 (CH), 124.3 (C), 120.3 (CH), 85.72 (<u>C</u>I), 31.2 (CH_2), 28.9 (CH_2), 28.5 (CH_2), 28.2 (CH_2), 27.8 (CH_2), 22.1 (CH_2), 14.0 (CH_3); **HRMS** (ESI^+) *m/z* found $[M+H]^+$ 386.0617, $C_{16}H_{21}NO_2I^+$ required 386.0632; **m.p.** 240-249 °C (acetonitrile).