Betti reaction enables efficient synthesis of 8-hydroxyquinoline inhibitors of 2-oxoglutarate oxygenases


Contents

Compound Characterisation .............................................................................................................. 3

General Procedure 1 for Betti-Type Amidoalkylation Reactions .................................................... 3

General Procedure 2 for the Synthesis of 8-Hydroxyquinolines .................................................. 3

NMR Spectra of compounds tested in cells ..................................................................................... 110

General Experimental for Biological Work ................................................................................... 116

AlphaScreen® activity assays ......................................................................................................... 116

KDM4C RapidFire™ Mass Spectrometry (RF-MS) assay ............................................................... 116

Non-denaturing ESI-MS studies14 ............................................................................................... 117

MALDI-TOF MS assays ............................................................................................................... 117

Viability analysis ......................................................................................................................... 118

Immunofluorescence assays ....................................................................................................... 118

Global histone analysis ............................................................................................................... 119

Immunoblotting .......................................................................................................................... 119

Supplementary Biochemical Data ............................................................................................... 121

ST1 .............................................................................................................................................. 121

SF1 .............................................................................................................................................. 122

SF2 .............................................................................................................................................. 123

SF3 .............................................................................................................................................. 124
Materials and Methods

Chemical Synthesis

All reactions involving moisture-sensitive reagents were carried out under a nitrogen atmosphere using standard vacuum line techniques and flame-dried glassware. Solvents were dried according to the procedure outlined by Grubbs and co-workers. Water was purified by an Elix® UV-10 system. All other solvents and reagents were used as supplied (analytical or HPLC grade). For workups, anhydrous MgSO₄ was used as drying agent. Thin layer chromatography was performed on aluminium plates coated with 60 F254 silica. Plates were visualised using UV light (254 nm), or 1% aq. KMnO₄. Flash column chromatography was performed on Kieselgel 60 silica on a glass column, or on a Biotage SP4 flash column chromatography platform. Melting points were recorded using a Gallenkamp Hot Stage apparatus. IR spectra were recorded using a Bruker Tensor 27 FT-IR spectrometer as thin films. Selected characteristic peaks are reported in cm⁻¹. NMR spectra were recorded using Bruker Avance spectrometers in the deuterated solvent stated. The field was locked by external referencing to the relevant residual proton resonance. Chemical shifts (δ) are reported in ppm and coupling constants (J) in Hz. Low-resolution mass spectra were recorded on either a VG MassLab 20-250 or a Micromass Platform 1 spectrometer. Accurate mass measurements were run using either a Bruker MicroTOF internally calibrated with polyalanine, or a Micromass GCT instrument fitted with a Scientific Glass Instruments BPX5 column (15 m × 0.25 mm) using amyl acetate as a lock mass, by the mass spectrometry service of the Chemistry Research Laboratory, University of Oxford, UK. All compounds were prepared as racemates except where explicitly stated.

Compound Characterisation

General Procedure 1 for Betti-Type Amidoalkylation Reactions

The requisite 8HQ (1.0 eq.), amide (1.0 eq.), and aldehyde (2.0 eq.) were stirred between 130 °C and 180 °C for 3 h. Toluene (5 mL) was added and the reaction mixture allowed to cool to room temperature (RT). The resulting precipitate was washed with toluene (3 × 5 mL), Et₂O (3 × 5 mL), and MeOH (3 x 5 mL) before being dried under reduced pressure to give the target compounds, typically without requirement for further purification other than crystallisation, unless specified otherwise.

General Procedure 2 for the Synthesis of 8-Hydroxyquinolines

A solution of the required 2-aminophenol (1 eq.) in HCl (6 N aq.) was stirred under reflux. The specified acrolein (1.5 eq.) was then slowly added dropwise; the resultant reaction mixture was stirred for another 2 h under reflux. After cooling to room temperature, the pH was adjusted to 7 with NaOH (6 N aq.). The aqueous reaction mixture was extracted three times with EtOAc; the combined organic layers were washed with brine, dried over anhydrous MgSO₄, and concentrated in vacuo. The crude product was purified via flash column chromatography (5 % - 20 % EtOAc, cyclohexane) to give the desired compound.
8-Hydroxyquinoline-4-carboxylic acid 4

S166 (1 g, 3.95 mmol) was dissolved in a solution of potassium hydroxide (5 g, 89.3 mmol) in water. The solvent was evaporated under reduced pressure. The residue was heated to above 300 °C with a heat gun until a colour change from off-white to dark yellow occurred. The residue was left to cool to room temperature and dissolved in water (200 mL). The pH was adjusted to 4.5 with aqueous hydrochloric acid and the solution was extracted with ethyl acetate (500 mL) three times. The combined organic layers were combined and dried over anhydrous Na2SO4 and the solvent was evaporated to give 4 (542 mg, 73 %) as a yellow solid.

mp 259 °C; νmax/cm⁻¹: 12539 (O-H); δH (400 MHz, DMSO-d6) 8.96 (1 H, d, J=4.5 Hz, Hα), 8.07 (1 H, d, J=8.0 Hz, Hε), 7.93 (1 H, d, J=4.5 Hz, Hβ), 7.54 (1 H, t, J=8.0 Hz, Hd), 7.15 (1 H, d, J=8.0 Hz, Hc); δC (100 MHz, DMSO-d6) 168.6 (C=O), 154.5, 148.6, 140.2, 137.3, 129.8, 126.2, 116.2, 112.4; m/z (ESI⁻) 188 ([M-H]⁻); HRMS (ESI⁻) C10H8NO3, ([M-H]⁻) requires 190.0499; found 190.0501.

N-((3,4-Dimethoxyphenyl)(8-hydroxyquinolin-7-yl)methyl)-3-methylbutanamide 5

Following general procedure 1, 8-hydroxyquinoline (290 mg, 2.0 mmol), isovaleramide (202 mg, 2.0 mmol) and 3,4-dimethoxybenzaldehyde (644 mg, 4.0 mmol) gave 5 (103 mg, 13 %) as a beige powder.

mp 193 °C; νmax/cm⁻¹: 3270 (NH), 2861 (OH), 1633 (C=O); δH (400 MHz, CDCl3) 8.69 - 8.80 (1 H, m, quinoline-Ar), 8.10 - 8.20 (1 H, m, quinoline-Ar), 7.40 - 7.50 (2 H, m, Ar), 7.32 - 7.38 (1 H, m, Ar), 7.18 - 7.23 (1 H, m, Ar), 6.96 - 7.01 (1 H, m, Ar), 6.77 - 6.83 (1 H, m, Ar), 6.72 - 6.77 (1 H, m, Ar), 6.55 (1 H, d, J=9.0 Hz, benzyl-H), 3.82 (3 H, s, OCH3), 3.81 (3 H, s, OCH3), 2.05 - 2.27 (3 H, m, Hb/c), 0.96 (6 H, dd, J=12.0, 6.0 Hz, CH3b); δC (100 MHz, CDCl3) 171.6 (C=O), 149.1, 149.0, 148.2, 138.3, 136.1, 134.3, 128.4, 127.7, 122.6, 121.9, 118.9, 118.0, 110.8, 110.5, 110.0 (OCH3), 55.8 (OCH3), 54.3 (benzyl-C), 46.3 (C8), 26.3 (C8), 22.5 (C8); m/z (ESI⁺) 393 ([M-H]⁺); HRMS (ESI⁺) C23H27N2O4, ([M+H]⁺) requires 395.1965; found 395.1969.
**7-[(4-Chlorophenyl)((3-hydroxypyridin-2-yl)amino)methyl]quinolin-8-ol** 6³

A solution of 8-hydroxyquinoline (2.9 g, 20 mmol), 4-chlorobenzaldehyde (2.8 g, 20 mmol), and 2-amino-4-hydroxypyridine (2.2 g, 20 mmol) in ethanol (50 mL) was stirred for 72 h at room temperature. The resulting precipitate was filtered, washed with EtOH, H₂O, and dried to give 6 (2.6 g, 34 %) as an off-white powder.

mp 189 °C; νmax/cm⁻¹ 3338 (OH); δH (400 MHz, DMSO-d₆) 8.80 - 8.91 (1 H, m, quinoline-Ar), 7.64 - 7.72 (1 H, m, quinoline-Ar), 7.51 - 7.57 (1 H, m, Ar), 7.46 - 7.50 (1 H, m, Ar), 7.30 - 7.44 (4 H, m, Ar), 6.81 - 6.93 (2 H, m, Ar); δC (100 MHz, DMSO-d₆) 150.3, 148.8, 148.8, 143.3, 140.1, 138.7, 137.6, 136.5, 131.4, 129.2, 128.5, 128.1, 127.8, 125.6, 122.2, 118.5, 118.0, 112.9, 53.0 (benzyl-C); m/z (ESI⁻) 376 ([M-H]⁻); HRMS (ESI⁺) C₂₁H₁₇O₂N₃Cl, ([M+H]+) requires 378.1004; found 378.0999.

**N-[(8-Hydroxyquinolin-7-yl)(phenyl)methyl]benzamide** 7⁴

Following general procedure 1, 8-hydroxyquinoline (290 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and benzaldehyde (406 µL, 4.0 mmol) gave 7 (295 mg, 42 %) as an off-white powder.

mp 190-192 °C; νmax/cm⁻¹ 3328 (NH), 3058 (OH), 1640 (C=O); δH (400 MHz, DMSO-d₆) 10.04 (1 H, br. s., NH), 9.17 - 9.33 (1 H, m, quinoline-Ar), 8.79 - 8.94 (1 H, m, quinoline-Ar), 8.24 - 8.38 (1 H, m, quinoline-Ar), 7.88 - 8.03 (2 H, m, quinoline-Ar), 7.66 - 7.77 (1 H, m, Ar), 7.51 - 7.61 (2 H, m, Ar), 7.39 - 7.51 (3 H, m, Ar), 7.28 - 7.38 (4 H, m, Ar), 7.24 (1 H, br. s., O-H), 7.02 (1 H, d, J=8.0 Hz, benzyl-H); δC (100 MHz, DMSO-d₆) 166.8 (C=O), 150.6, 149.2, 143.0, 138.9, 136.9, 135.3, 132.1, 129.1, 129.0, 128.5, 128.1, 127.8, 127.7, 125.2, 122.7, 118.2, 51.4 (benzyl-C); m/z (ESI+) 353 ([M-H]⁻, 100 %); HRMS (ESI⁺) C₂₃H₁₉N₂O₂, ([M+H]+) requires 355.1441; found 355.1434.
5-Chloro-7-[(3-methylthiophen-2-yl)pyrrolidin-1-yl]methyl]quinolin-8-ol 14

A mixture of 5-chloro-8-hydroxyquinoline (180 mg, 1 mmol), 3-methyl-2-thiophencarboxaldehyde (108 μL, 1 mmol), pyrrolidine (83 μL, 1 mmol), and triethylamine (140 μL, 1 mmol) was stirred in ethanol (15 mL) for 72 h at room temperature. The volume of the reaction mixture was reduced and the precipitate was filtered, washed with EtOH, H2O, and dried to give 14 (65 mg, 18 %) as a light-brown powder.

mp 148 °C; ν<sub>max</sub>/cm<sup>-1</sup> 3333 (OH); δ<sub>H</sub> (400 MHz, DMSO-d<sub>6</sub>) 10.47 (1 H, br. s., OH), 8.90 - 9.02 (1 H, m, quinoline-Ar), 8.37 - 8.56 (1 H, m, quinoline-Ar), 7.86 (1 H, s, Ar), 7.67 - 7.79 (1 H, m, Ar), 7.21 - 7.44 (1 H, m, Ar), 6.77 (1 H, m, Ar), 5.37 (1 H, s, benzyl-H), 2.38 - 2.52 (4 H, m, H<sub>a</sub>), 2.33 (3 H, s, CH<sub>3</sub>), 1.70 - 1.86 (4 H, m, H<sub>b</sub>); δ<sub>C</sub> (100 MHz, DMSO-d<sub>6</sub>) 149.7, 149.5, 141.0, 139.5, 143.6, 132.9, 129.9, 126.9, 126.3, 125.1, 124.5, 123.4, 119.2, 53.4 (benzyl-C), 23.6 (C<sub>b</sub>), 14.5 (thiophene-CH<sub>3</sub>); m/z (ESI<sup>+</sup>) 359 ([M+H]<sup>+</sup>); HRMS (ESI<sup>+</sup>) C<sub>19</sub>H<sub>20</sub>N<sub>2</sub>ClS, ([M+H]<sup>+</sup>) requires 359.0979; found 359.0969.

1,3-bis[(8-Hydroxyquinolin-7-yl)(phenyl)methyl]urea dihydrochloride 19

Following general procedure 1, 8-hydroxyquinoline (290 mg, 2.0 mmol), urea (60 mg, 1.0 mmol) and benzaldehyde (406 μL, 4.0 mmol) gave 19 (127 mg, 12 %) as an off-white powder. The solid was then stirred in a 4M HCl solution in dioxane for 1 h. The solvent was removed under reduced pressure to give the hydrochloride salt of 19 as an off-white powder in apparent quantitative yield.

mp 154 °C; ν<sub>max</sub>/cm<sup>-1</sup> 1748 (C=O); δ<sub>H</sub> (400 MHz, DMSO-d<sub>6</sub>) 8.88 - 9.02 (2 H, m, quinoline-Ar), 8.70 - 8.84 (2 H, m, quinoline-Ar), 8.18 - 8.47 (2 H, m, quinoline-Ar), 7.65 - 7.72 (2 H, m, Ar), 7.58 - 7.64 (2 H, m, Ar), 7.37 - 7.42 (8 H, m, Ar), 7.27 - 7.34 (4 H, m, Ar), 5.85 - 5.91 (2 H, m, benzyl-H); δ<sub>C</sub> (100 MHz, DMSO-d<sub>6</sub>) 151.5 (C=O), 150.2, 144.4, 144.0, 142.8, 138.1, 136.9, 129.8, 129.0, 127.7, 125.5, 124.4, 123.2, 121.0, 57.1 (benzyl-C); m/z (ESI<sup>+</sup>) 527 ([M+H]<sup>+</sup>); HRMS (ESI<sup>+</sup>) C<sub>33</sub>H<sub>23</sub>O<sub>2</sub>N<sub>4</sub>, ([M+H]<sup>+</sup>) requires 527.2078; found 527.2074.
2-Cyanobenzaldehyde (131 mg, 1 mmol) and sodium perborate tetrahydrate (615 mg, 4 mmol) were suspended in a mixture of water (10 mL) and ethanol (5 mL) inside a sealed vial and stirred at 100 °C for 10 minutes. The aqueous solution was extracted with Et<sub>2</sub>O three times and the combined organic fractions were concentrated under reduced pressure to give 21 as a white powder (115 mg, 77 %). This compound has previously been described using a different synthetic methodology.<sup>5</sup> mp 171 °C; ν<sub>max</sub>/cm<sup>-1</sup> 3339 (NH), 1697 (C=O); δ<sub>H</sub> (400 MHz, DMSO-<sub>d</sub>6) 8.87 (1 H, s, O<sub>H</sub>), 7.38 - 7.73 (4 H, m, Ar), 6.33 (1 H, d, J=9.0 Hz, NH), 5.87 (1 H, d, J=9.0 Hz, CH(OH)); δ<sub>C</sub> (100 MHz, DMSO-<sub>d</sub>6) 169.3 (C=O), 147.8, 132.9, 130.0, 124.5, 123.2, 78.9 (CH(OH)); m/z (ESI) 148 ([M-H]<sup>-</sup>); HRMS (ESI<sup>+</sup>) C<sub>8</sub>H<sub>7</sub>NNaO<sub>2</sub>, ([M+Na]<sup>+</sup>) requires 172.0369; found 172.0374.

Following general procedure 1, 5-chloro-8-hydroxyquinoline (144 mg, 1.0 mmol), and 21 (149 mg, 1.0 mmol) gave 22 (123 mg, 40 %) as a white powder. 22 was then stirred in a 4M HCl solution in dioxane for 1 h. The solvent was removed under reduced pressure to give the hydrochloride salt of 22 as a light-yellow powder in apparent quantitative yield.

mp 267 - 268 °C; ν<sub>max</sub>/cm<sup>-1</sup> 3177 (NH), 1657 (C=O); δ<sub>H</sub> (400 MHz, DMSO-<sub>d</sub>6) 9.06 (1 H, s, NH), 9.01 - 9.04 (1 H, m, quinoline-Ar), 8.37 - 8.61 (1 H, m, quinoline-Ar), 7.68 - 7.83 (2 H, m, Ar), 7.37 - 7.58 (3 H, m, Ar), 7.14 (1 H, s, Ar), 6.32 (1 H, s, benzyl-H); δ<sub>C</sub> (100 MHz, DMSO-<sub>d</sub>6) 170.8 (C=O), 151.0, 150.1, 148.7, 139.5, 134.1, 133.0, 132.5, 129.2, 126.2, 125.5, 124.3, 124.2, 123.9, 123.6, 119.9, 54.4 (benzyl-C); m/z (ESI) 309 ([M-H]<sup>-</sup>); HRMS (ESI<sup>+</sup>) C<sub>17</sub>H<sub>11</sub>CN<sub>2</sub>NaO<sub>2</sub>, ([M+Na]<sup>+</sup>) requires 333.0401; found 333.0391.
3-{Benzamido[5-chloro-8-hydroxyquinolin-7-yl]methyl}benzoic acid 23

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 3-formylenzoic acid (600 mg, 4.0 mmol) gave 12 (814 mg, 94 %) as a white powder.

mp 280 °C; νmax/cm⁻¹ 3324 (NH), 1693 (acid C=O), 1635 (amide C=O), 1633 (NH), 1599 - 1578 (quinoline-Ar); δH (400 MHz, DMSO-d6) 13.04 (1 H, br. s., CO₂H), 10.53 (1 H, br. s., NH), 9.43 - 9.42 (1 H, m, quinoline-Ar), 8.94 - 9.00 (1 H, m, quinoline-Ar), 8.65 - 8.52 (1 H, m, quinoline-Ar), 7.94 - 7.99 (2 H, m, Ar), 7.89 - 7.93 (2 H, m, Ar), 7.60 - 7.68 (1 H, m, Ar), 7.59 - 7.63 (1 H, m, Ar), 7.50 - 7.53 (3 H, m, Ar), 7.46 - 7.53 (3 H, m, Ar), 7.08 (1 H, d, J=8.5 Hz, benzyl-H); δC (100 MHz, DMSO-d6) 168.1 (acid C=O), 166.9 (amide C=O), 150.5, 150.1, 143.0, 139.5, 134.9, 133.4, 132.4, 131.7, 129.7, 129.2, 129.0, 128.8, 128.5, 127.4, 125.9, 125.4, 124.0, 119.5, 50.8 (benzyl-C); m/z (ESI⁻) 431 ([M-H]⁻); HRMS (ESI⁻) C₂₅H₁₉ClIN₃NaO₃, ([M+Na⁻]⁻) requires 455.0769; found 455.0753.

N-{[8-Hydroxyquinolin-7-yl](m-tolyl)methyl}benzamide 24

Following general procedure 1, 8-hydroxyquinoline (145 mg, 1.0 mmol), benzamide (121 mg, 1.0 mmol) and m-tolualdehyde (236 µL, 2.0 mmol) gave 24 (99 mg, 27 %) as a white powder.

mp 190 °C; νmax/cm⁻¹ 3321 (NH), 3056 (OH), 1639 (C=O); δH (400 MHz, DMSO-d6) 10.00 (1 H, br. s, NH), 9.12 - 9.31 (1 H, m, quinoline-Ar), 8.79 - 8.93 (1 H, m, quinoline-Ar), 8.24 - 8.37 (1 H, m, quinoline-Ar), 7.87 - 8.02 (2 H, m, quinoline-Ar), 7.65 - 7.79 (1 H, m, Ar), 7.50 - 7.58 (2 H, m, Ar), 7.41 - 7.50 (3 H, m, Ar), 7.10 - 7.23 (3 H, m, Ar), 7.04 (1 H, m, Ar), 6.99 (1 H, d, J=8.5 Hz, benzyl-H), 2.25 (3 H, s, CH₃); δC (100 MHz, DMSO-d6) 166.8 (C=O), 150.6, 149.2, 143.0, 138.9, 138.2, 136.9, 135.3, 132.1, 129.8, 129.1, 129.0, 128.7, 128.5, 128.3, 127.9, 125.3, 122.6, 118.2, 51.3 (benzyl-C), 22.0 (CH₃); m/z (ESI⁺) 367 ([M+H⁺], 100 %); HRMS (ESI⁺) C₂₄H₂₀N₂O₃, ([M+Na⁺]⁺) requires 391.1417; found 391.1401.
**N-((5-Chloro-8-hydroxyquinolin-7-yl)(m-tolyl)methyl)benzamide 25**

![Chemical structure of 25]

Following general procedure 1, 5-chloro-8-quinolinol (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and m-toluualdehyde (472 µL, 4.0 mmol) gave 25 (664 mg, 83 %) as a white powder.

mp 239-240 °C; ν\text{max}/\text{cm}^{-1} 3306 (NH), 1635 (C=O); δ\text{H} (400 MHz, DMSO-d$_6$) 10.40 (1 H, br. s., NH), 9.14 - 9.32 (1 H, m, quinoline-Ar), 8.91 - 9.02 (1 H, m, quinoline-Ar), 8.40 - 8.55 (1 H, m, quinoline-Ar), 7.90 - 8.00 (2 H, m, Ar), 7.87 (1 H, s, Ar), 7.66 - 7.77 (1 H, m, Ar), 7.52 - 7.60 (1 H, m, Ar), 7.45 - 7.51 (2 H, m, Ar), 7.19 - 7.26 (1 H, m, Ar), 7.10 - 7.18 (2 H, m, Ar), 7.04 - 7.10 (1 H, m, Ar), 6.99 (1 H, d, J=9.0 Hz, benzyl-H), 2.26 (3 H, s, CH$_3$); δ\text{C} (100 MHz, DMSO-d$_6$) 166.8 (C=O), 150.4, 150.0, 142.5, 139.5, 138.4, 135.1, 133.4, 132.2, 129.2, 128.6, 128.5, 127.7, 126.0, 125.8, 125.2, 123.8, 119.4, 50.9 (benzyl-C), 22.0 (CH$_3$); m/z (ESI) 401 ([M-H], 100 %); HRMS (ESI) C$_{34}$H$_{30}$ClN$_2$O$_2$, ([M-H]) requires 401.1062; found 401.1061.

**N-((8-Hydroxyquinolin-7-yl)(o-tolyl)methyl)benzamide 26**

![Chemical structure of 26]

Following general procedure 1, 8-hydroxyquinoline (290 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and o-toluualdehyde (463 µL, 4.0 mmol) gave 26 (324 mg, 88 %) as an off-white powder.

mp 196 °C; ν\text{max}/\text{cm}^{-1} 3302 (NH), 3057 (OH), 1638 (C=O); δ\text{H} (400 MHz, DMSO-d$_6$) 9.99 (1 H, br. s., NH), 9.05 - 9.21 (1 H, m, quinoline-Ar), 8.78 - 8.93 (1 H, m, quinoline-Ar), 8.22 - 8.39 (1 H, m, quinoline-Ar), 7.87 - 8.03 (2 H, m, quinoline-Ar), 7.49 - 7.60 (2 H, m, Ar), 7.36 - 7.49 (4 H, m, Ar), 7.08 - 7.29 (4 H, m, Ar), 7.04 (1 H, d, J=8.5 Hz, benzyl-H), 2.30 (3 H, s, CH$_3$); δ\text{C} (100 MHz, DMSO-d$_6$) 166.4 (C=O), 150.9, 149.1, 141.1, 138.8, 137.0, 136.9, 135.2, 132.1, 131.1, 129.0, 128.5, 128.4, 128.0, 127.8, 126.5, 124.5, 122.6, 117.8, 49.1 (benzyl-C), 19.7 (CH$_3$); m/z (ESI) 367 ([M-H], 100 %); HRMS (ESI$^+$) C$_{34}$H$_{30}$N$_2$NaO$_2$. ([M+Na]$^+$) requires 391.1417; found 391.1412.
N-((5-Chloro-8-hydroxyquinolin-7-yl)(o-tolyl)methyl)benzamide 27

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and o-tolualdehyde (463 µL, 4.0 mmol) gave 27 (627 mg, 64 %) as an off-white powder.

mp 217-218 °C; νmax/cm⁻¹ 3289 (NH), 1637 (C=O); δH (400 MHz, DMSO-d₆) 10.40 (1 H, br. s., NH), 9.09 - 9.24 (1 H, m, quinoline-Ar), 8.40 - 8.53 (1 H, m, quinoline-Ar), 7.90 - 7.97 (2 H, m, Ar), 7.68 - 7.75 (1 H, m, Ar), 7.64 (1 H, s, Ar), 7.50 - 7.56 (1 H, m, Ar), 7.42 - 7.49 (2 H, m, Ar), 7.12 - 7.27 (4 H, m, Ar), 7.04 (1 H, d, J=8.5 Hz, benzyl-H), 2.29 (3 H, s, CH₃); δC (100 MHz, DMSO-d₆) 166.5 (C=O), 150.7, 150.0, 140.5, 139.4, 136.9, 135.0, 133.4, 132.2, 131.2, 129.8, 128.4, 128.0, 127.9, 127.4, 126.7, 125.8, 125.2, 123.9, 119.0, 48.8 (benzyl-C), 19.6 (CH₃); m/z (ESI⁻) 401 ([M-H]⁻, 100 %); HRMS (ESI⁻) C₂₂H₁₉ClN₂O₂, ([M-H]⁻) requires 401.1062; found 401.1062.

N-((3-Bromophenyl)(5-chloro-8-hydroxyquinolin-7-yl)methyl)benzamide 28

Following general procedure, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 3-bromobenzaldehyde (468 µL, 4.0 mmol) gave 28 (789 mg, 84 %) as a white powder.

mp 233 - 235 °C; νmax/cm⁻¹ 3314 (NH), 1633 (C=O); δH (400 MHz, DMSO-d₆) 10.57 (1 H, br. s., NH), 9.30 - 9.38 (1 H, m, quinoline-Ar), 8.95 - 9.01 (1 H, m, quinoline-Ar), 8.46 - 8.52 (1 H, m, quinoline-Ar), 7.93 - 7.99 (2 H, m, Ar), 7.89 (1 H, s, Ar), 7.70 - 7.77 (1 H, m, Ar), 7.45 - 7.61 (5 H, m, Ar), 7.30 - 7.41 (2 H, m, Ar), 7.02 (1 H, d, J=9.0 Hz, benzyl-H); δC (100 MHz, DMSO-d₆) 166.5 (C=O), 150.1, 149.8, 144.9, 139.1, 134.5, 133.0, 132.0, 131.5, 130.5, 128.8, 128.1, 126.9, 126.9, 125.6, 124.8, 123.6, 122.2, 119.2, 50.3 (benzyl-C); m/z (ESI⁻) 465 ([M-H]⁻); HRMS (ESI⁻) C₂₃H₁₈BrClN₂O₂Na, ([M+Na]⁺) requires 488.9976; found 488.9970.
Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and biphenyl-3-carboxaldehyde (651 μL, 2.0 mmol) gave 29 (611 mg, 66 %) as a white powder. mp 211 °C; ν max/cm⁻¹ 3299 (NH), 1633 (C=O); δH (400 MHz, DMSO-d₆) 10.48 (1 H, br. s., NH), 9.29 - 9.41 (1 H, m, quinoline-Ar), 8.93 - 9.00 (1 H, m, quinoline-Ar), 8.43 - 8.51 (1 H, m, quinoline-Ar), 7.91 - 8.01 (3 H, m, Ar), 7.66 - 7.74 (2 H, m, Ar), 7.53 - 7.62 (4 H, m, Ar), 7.40 - 7.52 (5 H, m, Ar), 7.29 - 7.40 (2 H, m, Ar), 7.10 (1 H, d, J=9.0 Hz, benzyl-H); δC (100 MHz, DMSO-d₆) 167.0 (C=O), 150.4, 150.1, 143.2, 141.3, 141.0, 139.6, 135.1, 133.4, 132.3, 130.0, 129.8, 129.2, 128.5, 128.4, 127.6, 127.4, 127.3, 126.4, 126.0, 125.8, 123.9, 119.5, 51.2 (benzyl-C); m/z (FI⁺) 464 ([M⁺]); HRMS (FI⁺) C₂₉H₂₁ClN₂O₂, ([M⁺]) requires 464.1292; found 464.1292.

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and biphenyl-4-carboxaldehyde (729 mg, 4.0 mmol) gave 30 (604 mg, 65 %) as a white powder. 30 was then stirred in a 4M HCl solution in dioxane for 1 h. The solvent was removed under reduced pressure to give the hydrochloride salt of 30 as a bright-yellow powder in apparent quantitative yield.

mp 262 - 263 °C; ν max/cm⁻¹ 3305 (NH), 1634 (C=O); δH (400 MHz, DMSO-d₆) 9.32 - 9.40 (1 H, m, quinoline-Ar), 8.97 - 9.04 (1 H, m, quinoline-Ar), 8.51 - 8.61 (1 H, m, quinoline-Ar), 7.94 - 8.00 (3 H, m, Ar), 7.75 - 7.81 (1 H, m, Ar), 7.59 - 7.67 (4 H, m, Ar), 7.53 - 7.58 (1 H, m, Ar), 7.47 - 7.52 (2 H, m, Ar), 7.40 - 7.46 (4 H, m, Ar), 7.29 - 7.37 (1 H, m, Ar), 7.08 (1 H, d, J=8.5 Hz, benzyl-
H); δ_C (100 MHz, DMSO-d$_6$) 166.9 (C=O), 149.9, 149.7, 141.5, 140.7, 139.9, 138.8, 135.0, 134.4, 132.3, 129.8, 129.2, 128.7, 128.5, 128.3, 127.9, 127.7, 127.5, 126.6, 126.0, 124.0, 119.8, 50.8 (benzyl-C); m/z [ESI] 463 ([M-H]); HRMS [ESI$^+$] C$_{29}$H$_{21}$ClN$_2$NaO$_4$$_2$, ([M+Na]$^+$) requires 487.1184; found 487.1187.

**N-[(5-Chloro-8-hydroxyquinolin-7-yl)[3-phenoxyphenyl]methyl]benzamide 31**

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 3-phenoxybenzaldehyde (690 μL, 4.0 mmol) gave 31 (548 mg, 57 %) as an off-white powder.

mp 225 °C; $\nu_{max}$/cm$^{-1}$ 3307 (NH), 1638 (C=O); δ$_H$ (400 MHz, DMSO-d$_6$) 10.49 (1 H, br. s., NH), 9.21 - 9.35 (1 H, m, quinoline-Ar), 8.89 - 9.03 (1 H, m, quinoline-Ar), 8.40 - 8.54 (1 H, m, quinoline-Ar), 7.87 - 7.93 (2 H, m, Ar), 7.86 (1 H, s, Ar), 7.68 - 7.76 (1 H, m, Ar), 7.51 - 7.59 (1 H, m, Ar), 7.44 - 7.51 (2 H, m, Ar), 7.30 - 7.38 (3 H, m, Ar), 7.08 - 7.13 (2 H, m, Ar), 6.96 - 7.06 (4 H, m, Ar), 6.82 - 6.89 (1 H, m, Ar); δ_C (100 MHz, DMSO-d$_6$) 167.0 (C=O), 157.6, 157.1, 150.5, 150.1, 144.9, 139.5, 135.1, 133.4, 132.3, 130.9, 130.9, 129.2, 128.5, 128.4, 127.6, 125.9, 125.4, 124.4, 123.9, 123.1, 119.5, 118.0, 117.6, 50.7 (benzyl-C); m/z [ESI] 479 ([M-H]); HRMS [ESI$^+$] C$_{30}$H$_{21}$ClN$_2$NaO$_3$, ([M+Na]$^+$) requires 503.1133; found 503.1131.

**N-[(8-Hydroxy-5-nitroquinolin-7-yl)[3-phenoxyphenyl]methyl]benzamide 32**

Following general procedure 1, 5-nitro-8-hydroxyquinoline (380 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 3-phenoxybenzaldehyde (690 μL, 4.0 mmol) gave 32 (669 mg, 68 %) as a light-yellow powder.

mp 222 °C; $\nu_{max}$/cm$^{-1}$ 3294 (NH), 1634 (C=O); δ$_H$ (400 MHz, DMSO-d$_6$) 9.41 - 9.51 (1 H, m, quinoline-Ar), 9.15 - 9.23 (1 H, m, quinoline-Ar), 8.97 - 9.06 (1 H, m, quinoline-Ar), 8.78 (1 H, s, Ar), 7.85 - 7.98 (3 H, m, Ar), 7.53 - 7.59 (1 H, m, Ar), 7.46 - 7.53 (2 H, m, Ar), 7.31 - 7.42 (3 H, m, Ar), 7.07 - 7.18 (3 H, m, Ar), 6.97 - 7.03 (3 H, m, Ar), 6.85 - 6.94 (1 H, m, Ar); δ_C (100 MHz,
DMSO-$_d_6$ (C=O), 158.4, 157.2, 156.8, 149.4, 143.8, 137.2, 134.7, 134.6, 133.6, 132.0, 130.7, 130.5, 128.8, 128.7, 128.1, 125.8, 124.0, 123.8, 122.9, 122.2, 119.1, 117.9, 117.6, 50.4 (benzyl-C); m/z (Fl) 491 ([M]); HRMS (Fl) $C_{29}H_{21}N_3O_5$ ([M]) requires 491.1481; found 491.1247.

$N$-((5-Bromo-8-hydroxyquinolin-7-yl)[3-phenoxypyphenyl)methyl]benzamide 33

Following general procedure 1, 5-bromo-8-hydroxyquinoline (448 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 3-phenoxypybenzaldehyde (690 μL, 4.0 mmol) gave 33 (872 mg, 79 %) as a white powder.

mp 214 °C; $\nu_{max}/\text{cm}^{-1}$ 3294 (NH), 1636 (C=O); $\delta_{n}$ (400 MHz, DMSO-$_d_6$) 10.54 (1 H, br. s., NH), 9.24 - 9.38 (1 H, m, quinoline-Ar), 8.89 - 8.90 (1 H, m, quinoline-Ar), 8.35 - 8.49 (1 H, m, quinoline-Ar), 8.03 (1 H, s, Ar), 7.85 - 7.95 (2 H, m, Ar), 7.71 - 7.78 (1 H, m, Ar), 7.45 - 7.60 (4 H, m, Ar), 7.31 - 7.42 (2 H, m, Ar), 7.09 - 7.18 (2 H, m, Ar), 6.97 - 7.07 (3 H, m, Ar), 6.88 (1 H, d, $J$=8.0 Hz, benzyl-H); $\delta_{c}$ (100 MHz, DMSO-$_d_6$) 166.6 (C=O), 157.2, 156.8, 150.7, 149.7, 144.5, 139.4, 135.5, 134.7, 132.1, 131.9, 130.7, 130.6, 130.5, 128.1, 128.0, 126.8, 125.8, 124.0, 122.7, 119.2, 119.1, 109.0, 50.2 (benzyl-C); m/z (ESI$^+$) 525 ([M+H]$^+$); HRMS (ESI$^+$) $C_{29}H_{21}O_3N_2BrNa$, ([M+Na]$^+$) requires 547.0628; found 547.0606.

$N$-((5-Bromo-8-hydroxyquinolin-7-yl)[3-phenoxypyphenyl)methyl]-2-phenylacetamide 34

Following general procedure 1, 5-bromo-8-hydroxyquinoline (448 mg, 2.0 mmol), 2-phenylacetamide (270 mg, 2.0 mmol) and 3-phenoxypybenzaldehyde (690 μL, 4.0 mmol) gave 34 (873 mg, 81 %) as a white powder.

mp 212 °C; $\nu_{max}/\text{cm}^{-1}$ 3270 (NH), 1639 (C=O); $\delta_{n}$ (400 MHz, DMSO-$_d_6$) 10.48 (1 H, br. s., NH), 9.08 - 9.15 (1 H, m, quinoline-Ar), 8.92 - 8.97 (1 H, m, quinoline-Ar), 8.38 - 8.44 (1 H, m, quinoline-Ar), 7.87 (1 H, s, quinoline-Ar), 7.66 - 7.79 (1 H, m, Ar), 7.18 - 7.43 (7 H, m, Ar), 7.09 - 7.18 (1 H, m, Ar), 6.95 - 7.06 (4 H, m, Ar), 6.79 - 6.90 (1 H, m, Ar), 6.68 (1 H, d, $J$=8.5 Hz, benzyl-H), 3.57 (2 H, s, CH$_2$); $\delta_{c}$ (100 MHz, DMSO-$_d_6$) 170.0 (C=O), 157.1, 156.8, 150.4, 149.7, 144.5, 139.4, 136.7, 135.5, 130.6, 130.5,
Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 3-methyl-2-thiophenecarboxaldehyde (431 μL, 4.0 mmol) gave CCT1 (584 mg, 71%) as a white powder.

\[ \text{mp 223 °C; } \nu_{\text{max}}/\text{cm}^{-1} \text{ 3274 (NH), 1638 (C=O); } \delta_{\text{H}} \text{ (400 MHz, DMSO-} d_6 \text{) 10.53 (1 H, br. s., NH), 9.32 - 9.42 (1 H, m, quinoline-Ar), 8.95 - 9.01 (1 H, m, quinoline-Ar), 8.48 - 8.54 (1 H, m, quinoline-Ar), 7.89 - 7.97 (3 H, m, Ar), 7.70 - 7.78 (1 H, m, Ar), 7.51 - 7.59 (1 H, m, Ar), 7.44 - 7.51 (2 H, m, Ar), 7.25 - 7.32 (1 H, m, Ar), 7.18 (1 H, d, J=8.0 Hz, benzyl-H), 6.88 - 6.94 (1 H, m, Ar), 2.16 (3 H, s, CH₃); } \delta_{\text{C}} \text{ (100 MHz, DMSO-} d_6 \text{) 166.1 (C=O), 150.1, 149.7, 149.7, 139.5, 139.0, 134.6, 134.5, 133.0, 131.9, 131.0, 128.7, 128.7, 128.1, 126.9, 125.6, 125.2, 123.6, 118.8, 45.3 (benzyl-C), 14.0 (CH₃); } m/z \text{ (ESI) 407 ([M-H]); } \text{HRMS (ESI) } C_{22}H_{20}CIN_{2}O_{2}S, ([M-H] - 2) \text{ requires 407.0626; found 407.0613.} \]

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), 2-phenylacetamide (270 mg, 2.0 mmol) and 3-methyl-2-thiophenecarboxaldehyde (431 μL, 4.0 mmol) gave 35 (567 mg, 67%) as a white powder.

\[ \text{mp 181 °C; } \nu_{\text{max}}/\text{cm}^{-1} \text{ 3237 (NH), 1667 (C=O); } \delta_{\text{H}} \text{ (400 MHz, DMSO-} d_6 \text{) 10.44 (1 H, br. s., NH), 9.07 - 9.16 (1 H, m, quinoline-Ar), 8.89 - 9.02 (1 H, m, quinoline-Ar), 8.39 - 8.55 (1 H, m, quinoline-Ar), 7.68 - 7.77 (2 H, m, Ar), 7.18 - 7.35 (5 H, m, Ar), 6.87 - 6.90 (1 H, m, Ar), 6.84 (1 H, d, J=8.5 Hz, benzyl-H), 3.55 (2 H, s, CH₂), 2.11 (3 H, s, CH₃); } \delta_{\text{C}} \text{ (100 MHz, DMSO-} d_6 \text{) 169.7 (C=N), 149.9, 149.7, 139.4, 139.0, 136.8, 134.6, 133.0, 130.9, 129.4, 128.7, 126.8, 126.2, 125.5, 125.4, 123.6, 123.5, 118.9, 44.8} \]
(benzyl-\text{-C}), 42.5 (\text{CH}_3), 13.9 (\text{CH}_3); m/z (ESI) 421 ([M-H]); HRMS (ESI\textsuperscript{+}) \text{C}_{23}H_{30}Cl\text{N}_2\text{O}_2S, ([M+Na\textsuperscript{+}]) requires 445.0748; found 445.0731.

\textit{N-}\{(5-Chloro-8-hydroxyquinolin-7-yl)(3-methylthiophen-2-yl)methyl\}cyclohexanecarboxamide 36

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), cyclohexanecarboxamide (254 mg, 2.0 mmol) and 3-methyl-2-thiophenecarboxaldehyde (431 \mu L, 4.0 mmol) gave 36 (390 mg, 47 %) as an off-white powder.

mp 164 °C; \nu_{\max}/\text{cm}^{-1} 3297 (NH), 1640 (C=O); \delta_{\text{H}} (400 MHz, DMSO-\text{d}_6) 10.34 (1 H, br. s., NH), 8.90 - 8.99 (1 H, m, quinoline-Ar), 8.43 - 8.52 (1 H, m, quinoline-Ar), 7.72 - 7.76 (2 H, m, Ar), 7.19 - 7.25 (1 H, m, Ar), 6.79 - 6.90 (2 H, m, Ar and benzyl-\text{-H}), 2.21 - 2.32 (1 H, m, H\text{a}), 2.11 (3 H, s, \text{CH}_3), 1.57 - 1.76 (4 H, m, H\text{b/d}); \delta_{\text{C}} (100 MHz, DMSO-\text{d}_6) 175.1 (C=O), 150.2, 150.1, 140.5, 139.4, 134.6, 133.4, 131.3, 126.9, 125.9, 123.9, 123.7, 119.2, 44.5 (benzyl-\text{-C}), 30.4 (C\text{d}), 29.8 (C\text{b}), 26.2 (C\text{c}), 26.1 (C\text{d}), 14.3 (CH\text{\text{a}}); m/z (ESI\textsuperscript{+}) 413 ([M-H]); HRMS (ESI\textsuperscript{+}) \text{C}_{23}H_{30}Cl\text{N}_2\text{O}_2S, ([M+Na\textsuperscript{+}]) requires 437.1061; found 437.1051.

\textit{N-}\{(5-chloro-8-hydroxyquinolin-7-yl)(3-methylthiophen-2-yl)methyl\}cyclopropanecarboxamide 37

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), cyclopropanecarboxamide (170 mg, 2.0 mmol) and 3-methyl-2-thiophenecarboxaldehyde (431 \mu L, 4.0 mmol) gave 37 (312 mg, 42 %) as an off-white powder.

mp 202 °C; \nu_{\max}/\text{cm}^{-1} 3272 (NH), 1644 (C=O); \delta_{\text{H}} (400 MHz, DMSO-\text{d}_6) 10.41 (1 H, br. s., NH), 9.02 - 9.10 (1 H, m, quinoline-Ar), 8.91 - 8.99 (1 H, m, quinoline-Ar), 8.44 - 8.55 (1 H, m, quinoline-Ar), 7.77 (1 H, s, Ar), 7.68 - 7.75 (1 H, m, Ar), 7.19 - 7.28 (1 H, m, Ar), 6.92 (1 H, d, J=8.5 Hz) 6.82 - 6.88 (1 H, m, Ar), 2.13 (3 H, s, CH\text{\text{a}}), 1.65 - 1.80 (1 H, m, H\text{a}), 0.56 - 0.81 (4 H, m, H\text{b/d}); \delta_{\text{C}} (100 MHz, DMSO-\text{d}_6) 172.6 (C=O), 150.1, 150.1, 140.3, 139.4, 134.7, 133.4, 131.3, 127.9, 126.7, 125.9, 123.9, 123.9, 119.3,
45.0 \text{ (benzyl-C), 14.4 \text{ (CH}_3\text{), 14.2 \text{ (C}_\text{a})\text{, 7.4 \text{ (C}_\text{b})\text{; m/z (ESI\text{)} 371 ([M-H])}}; HRMS (ESI\text{)} \text{ C}_{19}\text{H}_{17}\text{ClN}_2\text{O}_2\text{S, ([M-H]) requires 371.0626; found 371.0625.}}

\text{N-((5-Chloro-8-hydroxyquinolin-7-yl)(4-methylthiophen-2-yl)methyl)benzamide 38}

\text{Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 4-methylthiophene-2-carboxaldehyde (492 \mu L, 4.0 mmol) gave 38 (382 mg, 47 \%) as a white powder.}}

mp 206 ^\circ \text{C; } \nu_{\max}/\text{cm}^{-1} 3313 \text{ (NH), 1632 (C=O); } \delta_{\text{H}} \text{ (400 MHz, DMSO-d}_6\text{) 10.50 (1 H, br. s., N\text{H}), 9.25 - 9.59 (1 H, m, quinoline-Ar), 8.89 - 9.03 (1 H, m, quinoline-Ar), 8.40 - 8.57 (1 H, m, quinoline-Ar), 8.00 (1 H, s, Ar), 7.91 - 7.97 (2 H, m, Ar), 7.70 - 7.77 (1 H, m, Ar), 7.52 - 7.59 (1 H, m, Ar), 7.45 - 7.52 (2 H, m, Ar), 7.14 (1 H, d, J=9.0 Hz, benzyl-H), 7.01 (1 H, s, Ar), 6.62 (1 H, s, Ar), 2.11 (3 H, s, CH}_3\text{); } \delta_{\text{C}} \text{ (100 MHz, DMSO-d}_6\text{) 166.6 (C=O), 150.3, 150.1, 146.3, 139.5, 137.6, 134.9, 133.4, 132.4, 129.2, 128.5, 128.2, 127.4, 126.0, 125.6, 124.0, 121.1, 119.5, 47.1 \text{ (benzyl-C), 16.3 \text{ (CH}_3\text{); m/z (ESI\text{)} 431 ([M+Na]+); HRMS (ESI\text{)}) C}_{22}\text{H}_{17}\text{ClN}_2\text{NaO}_2\text{S, ([M+Na]+) requires 431.0591; found 430.9132.}}

\text{N-((5-chloro-8-hydroxyquinolin-7-yl)(5-methylthiophen-2-yl)methyl)benzamide 39}

\text{Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 5-methylthiophene-2-carboxaldehyde (431 \mu L, 4.0 mmol) gave 39 (264 mg, 32 \%) as a white powder.}}

mp 213 ^\circ \text{C; } \nu_{\max}/\text{cm}^{-1} 3302 \text{ (NH), 1634 (C=O); } \delta_{\text{H}} \text{ (400 MHz, DMSO-d}_6\text{) 10.49 (1 H, br. s., NH), 9.30 - 9.48 (1 H, m, quinoline-Ar), 8.90 - 9.07 (1 H, m, quinoline-Ar), 8.41 - 8.57 (1 H, m, quinoline-Ar), 7.99 (1 H, s, Ar), 7.89 - 7.95 (2 H, m, Ar), 7.68 - 7.78 (1 H, m, Ar), 7.52 - 7.59 (1 H, m, Ar), 7.44 - 7.51 (2 H, m, Ar), 7.10 (1 H, d, J=9.0 Hz, benzyl-H), 6.49 - 6.67 (2 H, m, Ar), 2.37 (3 H, s, CH}_3\text{); } \delta_{\text{C}} \text{ (100 MHz, DMSO-d}_6\text{) 166.6 (C=O), 150.3, 150.1, 143.8, 139.5, 139.5, 134.9, 133.4, 132.3, 129.2, 128.5, 127.4, 126.5, 125.6, 124.0, 121.1, 119.5, 47.1 \text{ (benzyl-C), 16.3 \text{ (CH}_3\text{); m/z (ESI\text{)} 431 ([M+Na]+); HRMS (ESI\text{)}) C}_{22}\text{H}_{17}\text{ClN}_2\text{NaO}_2\text{S, ([M+Na]+) requires 431.0591; found 430.9132.}}
126.0, 125.8, 125.6, 124.0, 119.5, 47.1 (benzyl-C), 15.8 (CH₃); m/z (ESI⁻) 431 ([M+Na]⁺); HRMS (ESI⁺) C₁₂H₁₂ClIN₂NaO₂S, ([M+Na]⁺) requires 431.0591; found 431.0587.

**N-(Benzo[b]thiophen-2-yl)[5-chloro-8-hydroxyquinolin-7-yl]methylbenzamide 40**

![Diagram of 40]

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and benzo[b]thiohene-2-carboxaldehyde (649 mg, 4.0 mmol) gave 40 (273 mg, 31 %) as a white powder.

mp 267 - 268 °C; νmax/cm⁻¹ 3296 (NH), 1634 (C=O); δₜ (400 MHz, DMSO-d₆) 10.65 (1 H, br. s., NH), 9.55 - 9.68 (1 H, m, quinoline-Ar), 8.94 - 9.05 (1 H, m, quinoline-Ar), 8.47 - 8.60 (1 H, m, quinoline-Ar), 8.04 (1 H, s, Ar), 7.94 - 8.01 (3 H, m), 7.86 - 7.92 (1 H, m, Ar), 7.72 - 7.80 (2 H, m, Ar), 7.55 - 7.62 (1 H, m, Ar), 7.47 - 7.55 (2 H, m, Ar), 7.25 - 7.37 (2 H, m, Ar and benzyl-H), 7.10 (1 H, s, Ar); δc (100 MHz, DMSO-d₆) 166.8 (C=O), 150.6, 150.2, 147.4, 141.1, 139.9, 134.8, 133.5, 132.5, 129.3, 129.2, 128.6, 128.4, 127.4, 125.3, 125.1, 124.8, 124.4, 124.1, 123.2, 122.6, 119.7, 47.6 (benzyl-C); m/z (ESI⁻) 443 ([M-H]⁻); HRMS (ESI⁻) C₂₅H₁₆ClIN₂O₂S, ([M-H]⁻) requires 443.0626; found 443.0621.

**N-((3-Bromophenyl)[5-fluoro-8-hydroxyquinolin-7-yl]methylbenzamide 41**

![Diagram of 41]

Following general procedure 1, 5-fluoro-8-hydroxyquinoline (326 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 3-bromobenzaldehyde (468 μL, 4.0 mmol) gave 41 (543 mg, 61 %) as a white powder.

mp 208 °C; νmax/cm⁻¹ 3309 (NH), 1634 (C=O); δₜ (400 MHz, DMSO-d₆) 10.23 (1 H, br. s., NH), 9.27 - 9.33 (1 H, m, quinoline-Ar), 8.96 - 8.99 (1 H, m, quinoline-Ar), 8.42 - 8.48 (1 H, m, quinoline-Ar), 7.92 - 7.98 (2 H, m, Ar), 7.66 - 7.71 (1 H, m, Ar), 7.54 - 7.64 (2 H, m, Ar), 7.45 - 7.54 (4 H, m, Ar), 7.29 - 7.41 (2 H, m, Ar), 7.04 (1 H, d, J=9.0 Hz, benzyl-H); δc (100 MHz, DMSO-d₆) 166.6 (C=O), 150.1, 147.0, 145.0, 138.3, 134.6, 134.2, 132.0, 131.2, 130.4, 130.2, 129.7, 128.8, 128.1, 126.9, 123.6, 122.8,
122.2, 118.3, 110.5, 50.4 (benzyl-C); \( \delta \) (377 MHz, DMSO-d$_6$) -133.9 (CF); \( m/z \) (ESI$^+$) 451 ([M+H]$^+$); HRMS (ESI$^+$) $^{13}$C$_{23}$H$_{16}$BrFNaO$_2$, ([M+Na]$^+$) requires 473.0271; found 473.0254.

**N-((5-Chloro-8-methoxyquinolin-7-yl)(3-methylthiophen-2-yl)methyl)benzamide CCT2**

![CCT2 structure]

A solution of CCT1 (102 mg, 0.25 mmol), iodomethane (17 \( \mu \)L, 0.27 mmol), and potassium carbonate (69 mg, 0.5 mmol) in DMF (2 mL) was stirred for 16 h at room temperature. The reaction mixture was diluted with EtOAc (25 mL) and extracted with H$_2$O and brine. The organic layer was concentrated in vacuo and the crude product was purified via flash column chromatography to give CCT2 (51 mg, 97 %) as an off-white powder.

mp 129 °C; \( \nu_{max}/cm^{-1} \) 3275 (NH), 1632 (C=O); \( \delta \)H (400 MHz, CDCl$_3$) 8.73 - 8.93 (1 H, m, quinoline-Ar), 8.33 - 8.45 (1 H, m, quinoline-Ar), 7.70 - 7.80 (2 H, m, quinoline-Ar), 7.63 (1 H, s, Ar), 7.35 - 7.43 (2 H, m, Ar), 7.27 - 7.34 (2 H, m, Ar), 7.21 - 7.26 (1 H, m, Ar), 6.92 - 7.03 (2 H, m, Ar), 6.68 - 6.76 (1 H, m, Ar), 4.07 (3 H, s, OC$_2$H$_3$) 2.19 (3 H, s, CH$_3$); \( \delta \)C (100 MHz, CDCl$_3$) 166.4 (C=O), 152.6, 150.1, 143.3, 137.8, 135.0, 133.8, 133.7, 133.3, 131.9, 130.8, 128.7, 127.1, 126.2, 125.6, 123.2, 122.0, 62.8 (OCH$_3$), 48.4 (benzyl-C), 14.2 (CH$_3$); \( m/z \) (ESI$^+$) 423 ([M+H]$^+$); HRMS (ESI$^+$) $^{13}$C$_{23}$H$_{19}$ClN$_2$NaO$_2$, ([M+Na]$^+$) requires 445.0748; found 445.0828.

**3-Methyl-2-thiophenecarboxaldehyde S1**

![S1 structure]

A solution of diisobutylaluminium hydride (1M in hexanes, 29.2 mL, 29.2 mmol) was added dropwise to a stirring solution of 3-methylthiophene-2-carbonitrile (2.4 mL, 20.3 mmol) in chlorobenzene (60 mL) at 0 °C over a period of 20 min. The resulting mixture was stirred for one further hour at 0 °C and then diluted with CHCl$_3$ (100 mL). The mixture was shaken with 10 % HCl aq. for about 10 min and then extracted with CHCl$_3$. The combined organic layers were dried over anhydrous MgSO$_4$ and concentrated in vacuo. The crude product was purified via flash column chromatography (5 % EtOAc, 95 % cyclohexane) to give S1 as a light-yellow oil (4.55 g, 75 %). The synthesis of this compound has been described previously using a different methodology.⁶
\( \delta_n (400 \text{ MHz, CDCl}_3) 10.04 (1 \text{ H, s, CHO}), 7.63 (1 \text{ H, d, } J=5.0 \text{ Hz}), 6.97 (1 \text{ H, d, } J=5.0 \text{ Hz}), 2.58 (3 \text{ H, s, CH}_3); \delta_C (100 \text{ MHz, CDCl}_3) 182.4 (\text{CHO}), 147.4, 137.6, 134.3, 131.8, 14.2 (\text{CH}_3); m/z (\text{ESI}^+) 127 ([\text{M+H}]^+). \)

**N-([5-Chloro-8-hydroxyquinolin-7-yl][3-methylthiophen-2-yl)methyl]nicotinamide S2**

![Chemical structure](image)

3-Thiophenecarbonitrile (274 \( \mu \text{L, 3 mmol} \)) and sodium perborate tetrahydrate (1845 mg, 12 mmol) were suspended in a mixture of water (10 mL) and ethanol (5 mL) inside a sealed vial and stirred at 100 °C for 10 minutes. The aqueous solution was extracted with Et\(_2\)O three times and the combined organic fractions were concentrated under reduced pressure to afford S2 as a white powder (299 mg, 78 %). The synthesis of this compound has previously been described using a different methodology.\(^7\)

mp 185 °C; \( \delta_n (400 \text{ MHz, DMSO-}d_6) 8.08 - 8.16 (1 \text{ H, Ar}), 7.52 - 7.57 (1 \text{ H, Ar}), 7.45 - 7.50 (1 \text{ H, Ar}); \delta_C (100 \text{ MHz, DMSO-}d_6) 164.6 (\text{C=O}), 138.9, 129.9, 128.0, 127.4; m/z (\text{ESI}^-) 126 ([\text{M-H}]^-). \)

**[6,6'-Biquinoline]-8,8'-diol S3**

![Chemical structure](image)

Following general procedure 2, 3,3'-dihydroxybenzidine (2.2 g, 10 mmol) and acrolein (2 mL, 30 mmol) gave S3 (979 mg, 34 %) as a light-brown powder.

mp > 250 °C; \( \delta_n (400 \text{ MHz, DMSO-}d_6) 10.32 (2 \text{ H, br. s., OOH}), 8.70 - 9.01 (2 \text{ H, m, OOH}), 8.27 - 8.63 (2 \text{ H, m, Ar}), 7.87 (2 \text{ H, s, Ar}); \delta_C (100 \text{ MHz, DMSO-}d_6) 154.0, 148.6, 139.2, 137.7, 129.6, 122.9, 122.7, 116.5, 111.2; m/z (\text{ESI}^+) 289 ([\text{M+H}]^+); \text{HRMS (ESI}^+) \text{ C}_{18}\text{H}_{13}\text{O}_2\text{N}_2, ([\text{M+H}]^+) \text{ requires } 289.0972; \text{ found } 289.0966. \)

**3-Methylquinolin-8-ol S4**

![Chemical structure](image)

Following general procedure 2, 2-aminophenol (1.1 g, 10 mmol) and methacrolein (1.2 mL, 15 mmol) gave S4 (684 mg, 43 %) as a light-brown powder. The synthesis of this compound has previously been described using a different methodology.\(^8\)
mp 108 °C; \( \nu_{\text{max}} / \text{cm}^{-1} \) 3294 (OH); \( \delta \_H \) (400 MHz, DMSO-\( d_6 \)) 8.65 - 8.81 (1 H, m), 8.02 - 8.13 (1 H, m), 7.35 - 7.44 (1 H, m), 7.22 - 7.33 (1 H, m), 6.93 - 7.05 (1 H, m), 2.48 (3 H, s, \( CH_3 \)); \( \delta \_C \) (100 MHz, DMSO-\( d_6 \)) 153.8, 150.3, 137.3, 135.0, 131.4, 129.2, 128.0, 117.5, 110.9, 18.6 (\( CH_3 \)); m/z (ESI\(^+\)) 160 ([M+H]\(^+\)); HRMS (ESI\(^+\)) \( C_{10}H_{10}O \), ([M+H]\(^+\)) requires 160.0757; found 160.0754.

4-Methylquinolin-8-ol S5

![4-Methylquinolin-8-ol](image)

Following general procedure 2, 2-aminophenol (1.1 g, 10 mmol) and but-3-ene-2-one (1.2 mL, 15 mmol) gave S5 (938 mg, 59 %) as an off-white powder.

mp 140 °C; \( \delta \_H \) (400 MHz, DMSO-\( d_6 \)) 8.52 - 8.82 (1 H, m), 7.43 - 7.52 (2 H, m), 7.37 - 7.42 (1 H, m), 7.02 - 7.14 (1 H, m), 2.65 (3 H, s, \( CH_3 \)); \( \delta \_C \) (100 MHz, DMSO-\( d_6 \)) 154.0, 148.1, 144.8, 138.6, 129.0, 127.7, 122.9, 114.4, 111.3, 18.9 (\( CH_3 \)); m/z (ESI\(^+\)) 160 ([M+H]\(^+\)); HRMS (ESI\(^+\)) \( C_{10}H_{10}O \), ([M+H]\(^+\)) requires 160.0757; found 160.0754.

5-Methylquinolin-8-ol S6

![5-Methylquinolin-8-ol](image)

Following general procedure 2, 2-amino-4-methylphenol (1.0 g, 8.1 mmol) and acrolein (814 \( \mu L \), 12.2 mmol) gave S6 (1.00 g, 78 %) as a light-orange powder. The synthesis of this compound has previously been described using a different methodology.\(^{10}\)

mp 119 °C; \( \nu_{\text{max}} / \text{cm}^{-1} \) 3198 (OH); \( \delta \_H \) (400 MHz, methanol-\( d_4 \)) 8.54 - 8.74 (1 H, m), 8.11 - 8.30 (1 H, m), 7.29 - 7.42 (1 H, m), 7.03 - 7.15 (1 H, m), 6.78 - 6.94 (1 H, m), 2.42 (3 H, s, \( CH_3 \)); \( \delta \_C \) (100 MHz, methanol-\( d_4 \)) 151.1, 147.3, 138.8, 132.8, 128.0, 127.1, 124.2, 121.0, 109.9, 16.5 (\( CH_3 \)); m/z (ESI\(^+\)) 160 ([M+H]\(^+\)); HRMS (ESI\(^+\)) \( C_{10}H_{10}NO \), ([M+H]\(^+\)) requires 160.0757; found 160.0755.

6-Methylquinolin-8-ol S7

![6-Methylquinolin-8-ol](image)
Following general procedure 2, 2-amino-5-methylphenol (1.23 g, 10 mmol) and acrolein (1.0 mL, 15 mmol) gave S7 (620 mg, 39%) as an orange powder.

mp 88 °C; \( \delta_\text{H} \) (400 MHz, methanol-\( d_4 \)) 8.62 - 8.73 (1 H, m), 8.03 - 8.20 (1 H, m), 7.32 - 7.50 (1 H, m), 7.12 (1 H, s), 6.88 - 7.03 (1 H, m), 2.45 (3 H, s, CH\(_3\)); \( \delta_\text{C} \) (100 MHz, methanol-\( d_4 \)) 152.4, 146.9, 137.6, 137.3, 135.4, 129.2, 121.4, 116.8, 112.6, 20.6 (CH\(_3\)); \( m/z \) (ESI\(^+\)) 160 ([M+H]\(^+\)); HRMS (ESI\(^+\)) \( \text{C}_{10}\text{H}_{10}\text{ON} \), ([M+H]\(^+\)) requires 160.0757; found 160.0756.

5-Methoxyquinolin-8-ol S8

Following general procedure 2, 2-amino-4-methoxyphenol (1.0 g, 7.2 mmol) and acrolein (720 \( \mu \)L, 10.8 mmol) gave S8 (819 mg, 65%) as a light-brown powder.

mp 102 °C; \( \nu_{\text{max}}/\text{cm}^{-1} \) 3325 (OH); \( \delta_\text{H} \) (400 MHz, methanol-\( d_4 \)) 8.72 - 8.86 (1 H, m), 8.44 - 8.59 (1 H, m), 7.30 - 7.58 (1 H, m), 6.95 - 7.08 (1 H, m), 6.76 - 6.89 (1 H, m), 3.94 (3 H, s, OC\(_3\)H\(_3\)); \( \delta_\text{C} \) (100 MHz, methanol-\( d_4 \)) 148.2, 147.6, 146.3, 138.8, 130.8, 121.0, 120.4, 109.7, 104.6, 54.9 (OCH\(_3\)); \( m/z \) (ESI\(^+\)) 176 ([M+H]\(^+\));

8-Hydroxyquinoline-5-sulfonamide S9

Following general procedure 2, 2-aminophenol-4-sulfonamide (1.0 g, 5.3 mmol) and acrolein (534 \( \mu \)L, 8.0 mmol) gave S9 (499 mg, 42%) as a light-brown powder. The synthesis of this compound has previously been described using a different methodology.\(^{11}\)

mp 232 °C; \( \nu_{\text{max}}/\text{cm}^{-1} \) 1350 (S=O); \( \delta_\text{H} \) (400 MHz, DMSO-\( d_6 \)) 8.87 - 9.06 (2 H, m), 7.89 - 8.27 (1 H, m), 7.66 - 7.80 (1 H, m), 7.55 (2 H, br. s., SO\(_2\)NH\(_2\)), 7.06 - 7.22 (1 H, m); \( \delta_\text{C} \) (100 MHz, DMSO-\( d_6 \)) 158.0, 149.1, 139.0, 134.1, 129.7, 129.1, 124.9, 123.4, 109.8; \( m/z \) (ESI\(^+\)) 225 ([M+H]\(^+\)); HRMS (ESI\(^+\)) \( \text{C}_{10}\text{H}_{10}\text{N}_{2}\text{S} \), ([M-H]\(^-\)) requires 223.0183; found 223.0182. HRMS (ESI\(^+\)) \( \text{C}_{15}\text{H}_{15}\text{NO}_{2}\), ([M+H]\(^+\)) requires 176.0706; found 176.0703.
5-\{\text{Methanesulfonyl}\}quinolin-8-ol S10

Following general procedure 2, 3-amino-4-hydroxyphenylmethylsulphonate (1.0 g, 5.3 mmol) and acrolein (534 μL, 8.0 mmol) gave S10 (673 mg, 57 %) as a light-brown powder.

\[\text{mp } 203^\circ \text{C; } \nu_{\text{max}}/\text{cm}^{-1} 2920 (\text{OH}); \delta_H (400 \text{ MHz, DMSO-}d_6) 8.89 - 9.11 (2 \text{ H, m), 8.10 - 8.23 (1 H, m), 7.63 - 7.94 (1 H, m), 7.09 - 7.34 (1 H, m), 3.30 (3 H, s, SO}_2\text{CH}_3); \delta_C (100 \text{ MHz, DMSO-}d_6) 159.5, 149.5, 138.7, 133.2, 125.6, 125.6, 124.3, 110.4, 45.0 \text{ (SO}_2\text{CH}_3); m/z (\text{ESI}^+) 224 ([\text{M+H}]^+); \text{HRMS (ESI-)} \text{C}_{10}\text{H}_8\text{O}_3\text{NS, ([M-H]) requires } 222.0230; \text{found } 222.0229.\]

6-Chloroquinolin-8-ol S11

Following general procedure 2, 2-amino-5-chlorophenol (1.43 g, 10 mmol) and acrolein (1 mL, 15 mmol) gave S11 (1.3 g, 73 %) as an off-white powder. The synthesis of this compound has previously been described using a different methodology.\(^{13}\)

\[\text{mp } 154^\circ \text{C; } \nu_{\text{max}}/\text{cm}^{-1} 3324 (\text{OH}); \delta_H (400 \text{ MHz, DMSO-}d_6) 8.80 - 8.93 (1 \text{ H, m), 8.24 - 8.37 (1 H, m), 7.55 - 7.69 (1 H, m), 7.52 (1 H, s), 7.04 - 7.16 (1 H, m); } \delta_C (100 \text{ MHz, DMSO-}d_6) 155.2, 149.0, 137.8, 136.1, 132.0, 129.7, 123.4, 116.9, 112.5; m/z (\text{ESI}^+) 180 ([\text{M+H}]^+); \text{HRMS (ESI-)} \text{C}_{9}\text{H}_5\text{ONCl, ([M-H]) requires } 178.0065; \text{found } 178.0063.\]

6-Fluoroquinolin-8-ol S12

Following general procedure 2, 2-amino-5-fluorophenol (1.0 g, 7.9 mmol) and acrolein (788 μL, 11.8 mmol) gave S12 (785 mg, 61 %) as an orange-brown powder.

\[\text{mp } 135^\circ \text{C; } \nu_{\text{max}}/\text{cm}^{-1} 3063 (\text{OH}); \delta_H (400 \text{ MHz, methanol-}d_4) 8.47 - 8.78 (1 \text{ H, m), 7.91 - 8.22 (1 H, m), 7.21 - 7.52 (1 H, m), 6.85 - 6.96 (1 H, m), 6.71 - 6.85 (1 H, m); } \delta_C (100 \text{ MHz, methanol-}d_4) 162.5, 160.0, 155.2, 147.1, 136.2, 135.6, 129.3, 122.4; m/z (\text{ESI}^+) 164 ([\text{M+H}]^+); \text{HRMS (ESI-)} \text{C}_{9}\text{H}_5\text{ONF, ([M-H]) requires } 162.0361; \text{found } 162.0358.\]
4-Ethylquinolin-8-ol S13

Following general procedure 2, 2-aminophenol (1.1 g, 10 mmol) and 1-penten-3-one (1.5 mL, 15 mmol) gave S13 (1.23 g, 71 %) as a light-brown powder.

mp 102 °C; \( v_{\text{max}}/\text{cm}^{-1} \) 3297 (OH); \( \delta_{\text{H}} \) (400 MHz, DMSO-\( d_6 \)) 8.46 - 8.53 (1 H, m), 7.26 - 7.32 (1 H, m), 7.18 - 7.24 (1 H, m), 7.12 - 7.18 (1 H, m), 6.77 - 6.88 (1 H, m), 2.82 (2 H, q, \( J=7.5 \text{ Hz} \), CH\(_2\)); \( \delta_{\text{C}} \) (100 MHz, DMSO-\( d_6 \)) 154.3, 150.2, 148.3, 138.9, 128.2, 127.7, 120.8, 113.8, 111.2, 25.0 (CH\(_2\)), 14.4 (CH\(_3\)); m/z (ESI\(^+\)) 172 ([M-H]); HRMS (ESI\(^+\)) \( C_{11}H_{11}NO \), ([M+H]\(^+\)) requires 174.0913; found 174.0917.

5-Chloro-6-nitroquinolin-8-ol S14

Following general procedure 2, 2-amino-4-chloro-5-nitrophenol (1.89 g, 10 mmol) and acrolein (1 mL, 15 mmol) gave S14 (627 mg, 28 %) as a light-brown powder.

mp 186 °C; \( v_{\text{max}}/\text{cm}^{-1} \) 3087 (OH); \( \delta_{\text{H}} \) (400 MHz, DMSO-\( d_6 \)) 9.02 - 9.18 (1 H, m), 8.59 - 8.83 (1 H, m), 7.78 - 7.98 (1 H, m), 7.63 (1 H, s); \( \delta_{\text{C}} \) (100 MHz, DMSO-\( d_6 \)) 154.8, 151.9, 146.9, 140.3, 134.8, 126.5, 125.2, 111.5, 106.8; m/z (ESI\(^+\)) 225 ([M+H]\(^+\)); HRMS (ESI\(^+\)) \( C_{9}H_{5}ClN_{2}O_{3} \), ([M+H]\(^+\)) requires 225.0061; found 225.1019.

8-Hydroxy-2-methylquinoline-5-carboxylic acid S15

Following general procedure 2, 3-amino-4-hydroxybenzoic acid (3.2 g, 21.5 mmol) and crotonaldehyde (2.7 mL, 32.3 mmol) gave S15 (3.0 g, 69 %) as a light-brown powder.
δ_H (400 MHz, DMSO-d_6) 9.61 - 9.97 (1 H, m), 8.28 - 8.45 (1 H, m), 8.01 (1 H, m), 7.49 - 7.70 (1 H, m), 2.97 (3 H, s, CH_3); δ_C (100 MHz, DMSO-d_6) 167.4 (C=O), 157.9, 153.4, 142.6, 134.7, 130.6, 127.3, 126.2, 117.2, 114.4, 21.4 (CH_3); m/z [ESI+] 202 ([M-H]·).

5-Phenyquinolin-8-yl 4-methylbenzenesulfonate S16

A microwave vial was charged with S169 (33 mg, 0.1 mmol), phenylboronic acid (15 mg, 0.12 mmol), [1,1′-bis(di-tert-butylphosphino)ferrocene]dichloropalladium(II) (4 mg, 0.005 mmol), potassium carbonate (44 mg, 0.32 mmol), and dimethylacetamide (1 mL). The vial was sealed and the mixture was thoroughly degassed and subjected to an atmosphere of nitrogen gas. The reaction mixture was then stirred at 180 °C for 30 min under microwave irradiation before being diluted with EtOAc (10 mL) and extracted with H_2O and brine. The organic layer was dried over anhydrous MgSO_4 and concentrated in vacuo. The crude product was purified via flash column chromatography to give S16 (6 mg, 17 %) as an off-white solid.

The synthesis of this compound has previously been described using a different methodology.\textsuperscript{16}

mp 145 °C; ν_max/cm⁻¹ 1351 (S=O); δ_H (400 MHz, DMSO-d_6) 8.91 - 8.96 (1 H, m, Ar), 8.87 - 8.90 (1 H, m, Ar), 8.53 - 8.61 (1 H, m, Ar), 8.15 - 8.23 (1 H, m, Ar), 7.86 - 7.92 (2 H, m, Ar), 7.78 - 7.83 (2 H, m, Ar), 7.61 - 7.73 (1 H, m, Ar), 7.36 - 7.62 (5 H, m, Ar), 2.42 (3 H, s, CH_3); δ_C (100 MHz, DMSO-d_6) 152.3, 151.3, 146.0, 144.7, 139.0, 138.3, 134.4, 133.1, 130.4, 129.2, 128.8, 127.2, 127.0, 124.1, 123.1, 122.0, 21.6 (CH_3); m/z [ESI+] 376 ([M+H]^+); HRMS (ESI+) C_22H_18O_3NS, ([M+H]^+) requires 376.1002; found 376.0996.

5-[Furan-3-yl]quinolin-8-yl 4-methylbenzenesulfonate S17

A microwave vial was charged with S169 (33 mg, 0.1 mmol), 3-furanylboronic acid (13 mg, 0.12 mmol), [1,1′-bis(di-tert-butylphosphino)ferrocene]dichloropalladium(II) (4 mg, 0.005 mmol), potassium carbonate (44 mg, 0.32 mmol), and dimethylacetamide (1 mL). The vial was sealed and the mixture was thoroughly degassed and subjected to an atmosphere
of nitrogen gas. The reaction mixture was then stirred at 180 °C for 30 min under microwave irradiation before being diluted with EtOAc (10 mL) and extracted with H₂O and brine. The organic layer was dried over anhydrous MgSO₄ and concentrated in vacuo. The crude product was purified via flash column chromatography to give S17 (8 mg, 22 %) as an off-white solid. mp 132 °C; νmax/cm⁻¹ 1347 (S=O); δₜ (400 MHz, CDCl₃) 8.66 - 8.91 (1 H, m, Ar), 8.25 - 8.43 (1 H, m, Ar), 7.79 - 7.90 (2 H, m, Ar), 7.48 - 7.60 (3 H, m, Ar), 7.38 - 7.44 (1 H, m, Ar), 7.30 - 7.37 (1 H, m, Ar), 7.14 - 7.25 (2 H, m, Ar), 6.52 - 6.60 (1 H, m, Ar), 2.35 (3 H, s, CH₃); δC (100 MHz, CDCl₃) 150.4, 145.2, 144.6, 143.5, 141.3, 140.8, 134.5, 133.2, 130.5, 129.6, 128.9, 128.2, 126.6, 122.9, 122.3, 121.9, 112.0, 21.7 (CH₃); m/z (ESI⁺) 366 ([M+H]⁺); HRMS (ESI⁺) C₂0H₁₆O₄NS, ([M+H]⁺) requires 366.0795; found 366.0789.

4-Phenyquinolin-8-yl 4-methylbenzenesulfonate S18

A microwave vial was charged with S163 (33 mg, 0.1 mmol), phenylboronic acid (15 mg, 0.12 mmol), [1,1′-bis(di-tert-butylphosphino)ferrocene]dichloropalladium(II) (4 mg, 0.005 mmol), potassium carbonate (44 mg, 0.32 mmol), and dimethylacetamide (1 mL). The vial was sealed and the mixture was thoroughly degassed and subjected to an atmosphere of nitrogen gas. The reaction mixture was then stirred at 180 °C for 30 min under microwave irradiation before being diluted with EtOAc (10 mL) and extracted with H₂O and brine. The organic layer was dried over anhydrous MgSO₄ and concentrated in vacuo. The crude product was purified via flash column chromatography to give S18 (4 mg, 11 %) as an off-white solid. The synthesis of this compound has previously been described using a different methodology. mp 168 °C; νmax/cm⁻¹ 1375 (S=O); m/z (ESI⁺) 376 ([M+H]⁺); HRMS (ESI⁺) C₂₂H₂₆O₄NS, ([M+H]⁺) requires 376.1002; found 376.0997.

4-(Furan-3-yl)quinolin-8-yl 4-methylbenzenesulfonate S19

mp 110 °C; νmax/cm⁻¹ 1348 (S=O); m/z (ESI⁺) 366 ([M+H]⁺); HRMS (ESI⁺) C₂₀H₁₆O₄NS, ([M+H]⁺) requires 366.0795; found 366.0789.
A microwave vial was charged with S163 (33 mg, 0.1 mmol), 3-furanylboronic acid (13 mg, 0.12 mmol), [1,1′-bis(di-tert-butylphosphino)ferrocene]dichloropalladium(II) (4 mg, 0.005 mmol), potassium carbonate (44 mg, 0.32 mmol), and dimethylacetamide (1 mL). The vial was sealed and the mixture was thoroughly degassed and subjected to an atmosphere of nitrogen gas. The reaction mixture was then stirred at 180 °C for 30 min under microwave irradiation before being diluted with EtOAc (10 mL) and extracted with H₂O and brine. The organic layer was dried over anhydrous MgSO₄ and concentrated in vacuo. The crude product was purified via flash column chromatography to give S19 (6 mg, 16 %) as an off-white solid.

mp 107 °C; νmax/cm⁻¹ 1364 (S=O); δH (400 MHz, CDCl₃) 8.72 - 8.80 (1 H, m, Ar), 7.95 - 8.07 (1 H, m, Ar), 7.81 - 7.90 (2 H, m, Ar), 7.69 (1 H, s, Ar), 7.51 - 7.57 (2 H, m, Ar), 7.40 - 7.48 (1 H, m, Ar), 7.27 - 7.36 (1 H, m, Ar), 7.17 - 7.24 (2 H, m, Ar), 6.60 - 6.70 (1 H, m, Ar), 2.35 (3 H, s, CH₃);

δC (100 MHz, CDCl₃) 150.2, 145.6, 145.2, 143.9, 141.6, 133.2, 129.6, 128.9, 128.1, 126.2, 124.6, 122.7, 122.4, 121.6, 111.5, 21.8 (CH₃); m/z (ESI⁺) 366 ([M+H]⁺); HRMS (ESI⁺) C₂₀H₁₆O₄NS, ([M+H]⁺) requires 366.0795; found 366.0789.

5-Cyanoquinolin-8-yl 4-methylbenzenesulfonate S20

Prior to use, anhydrous dimethylacetamide was sparged with a gentle stream of nitrogen gas for 30 min. A 50 mM solution of sulphuric acid was prepared with 10 mL dimethylacetamide and 26.8 μL of concentrated H₂SO₄ and sparged with N₂ for 10 min. A microwave vial equipped with a magnetic follower was charged with palladium acetate (56 mg, 0.1 mmol) and XPhos (238 mg, 0.5 mmol). The vial was then sealed, subjected to an atmosphere of N₂ and filled with H₂SO₄ (2 mL, 50 mM in dimethyl acetamide). The catalyst mixture was then stirred at 80 °C for 30 min under microwave irradiation.

In parallel, a microwave vial equipped with a magnetic follower was charged with zinc dust (13.1 mg, 0.2 mmol), zinc cyanide (352 mg, 3 mmol) and S169 (1.67 g, 5 mmol). The vial was then sealed, subjected to an atmosphere of N₂ and filled with H₂SO₄ (2 mL, 50 mM in dimethyl acetamide). The catalyst mixture was then stirred at 80 °C for 30 min under microwave irradiation.

In parallel, a microwave vial equipped with a magnetic follower was charged with zinc dust (13.1 mg, 0.2 mmol), zinc cyanide (352 mg, 3 mmol) and S169 (1.67 g, 5 mmol). The vial was then sealed, subjected to an atmosphere of N₂ and 15 mL of dimethylacetamide were added. Then, the previously prepared catalyst solution was added (1 mL) and the reaction mixture was stirred for 45 min at 160 °C under microwave irradiation. The mixture was then diluted with EtOAc and extracted with H₂O and brine. The combined organic layers were dried over anhydrous MgSO₄ and concentrated in vacuo. The crude product was purified via flash column chromatography (15 % - 30 % EtOAc, cyclohexane) to give S20 (1.09 g, 67 %) as an off-white powder.

mp 119 °C; νmax/cm⁻¹ 2224 (nitrile); δH (400 MHz, CDCl₃) 8.83 - 8.91 (1 H, m, Ar), 8.39 - 8.46 (1 H, m, Ar), 7.86 - 7.92 (1 H, m, Ar), 7.78 - 7.83 (2 H, m, Ar), 7.58 - 7.65 (1 H, m, Ar), 7.52 - 7.57 (1 H, m, Ar), 7.20 - 7.26 (2 H, m, Ar), 2.35 (3 H, s, CH₃); δC (100
MHZ, CDCl₃) 152.2, 149.4, 145.8, 141.3, 133.9, 133.3, 133.0, 132.7, 131.8, 129.8, 129.6, 128.8, 124.0, 121.8, 21.8 (CH₃); m/z (ESI⁺) 325 ([M+H⁺]); HRMS (ESI⁺) C₁₁H₁₂O₃NaS, ([M+Na⁺]) requires 347.0461; found 347.0455.

8-Hydroxyquinoline-5-carbonitrile S21

A solution of S20 (162 mg, 0.5 mmol) in sodium hydroxide (1M aq., 0.5 mL), ethanol (3 mL) and H₂O (3 mL) was stirred under reflux for 1 h. The ethanol was removed in vacuo and the pH adjusted to 5. The precipitate was filtered and dried to give S21 (76 mg, 89 %) as a white solid.

mp 174 ºC; νmax/cm⁻¹ 3066 (OH), 2222 (nitrile); δH (400 MHz, DMSO-d₆) 8.91 - 9.08 (1 H, m) 8.35 - 8.50 (1 H, m) 7.95 - 8.19 (1 H, m) 7.31 - 7.66 (1 H, m) 7.02 - 7.31 (1 H, m); δC (100 MHz, DMSO-d₆) 159.3, 150.2, 138.5, 136.1, 133.5, 129.3, 124.9, 118.0, 112.3, 98.3; m/z (ESI⁺) 171 ([M+H⁺]); HRMS (ESI⁺) C₁₀H₅NO₂, ([M-H⁻]) requires 169.0407; found 169.0405.

5-(Furan-3-yl)quinolin-8-ol S22

A solution of S17 (445 mg, 1.2 mmol) in sodium hydroxide (1M aq., 3.66 mL), ethanol (7.5 mL) and H₂O (7.5 mL) was stirred under reflux for 2 h. The ethanol was removed in vacuo and the pH adjusted to 6.5. The precipitate was filtered and dried to give S22 (252 mg, 98 %) as an off-white solid.

mp 79 ºC; νmax/cm⁻¹ 3189 (OH); δH (400 MHz, CDCl₃) 8.71 - 8.81 (2 H, m, Ar), 8.41 - 8.50 (1 H, m, Ar), 8.22 - 8.35 (1 H, m, Ar), 7.42 - 7.52 (3 H, m, Ar), 7.25 - 7.32 (1 H, m, Ar), 6.97 - 7.09 (1 H, m, Ar); δC (100 MHz, CDCl₃) 151.4, 151.2, 148.3, 133.6, 131.0, 130.1, 128.9, 127.6, 127.4, 122.6, 121.8, 110.1; m/z (ESI⁺) 212 ([M+H⁺]); HRMS (ESI⁺) C₁₃H₁₂NO₂, ([M+H⁺]) requires 212.0706; found 212.0712.
Prior to use, anhydrous dimethylacetamide was sparged with a gentle stream of nitrogen gas for 30 min. A 50 mM solution of sulphuric acid was prepared with 10 mL dimethylacetamide and 26.8 μL of concentrated H₂SO₄ and sparged with N₂ for 10 min. A microwave vial equipped with a magnetic follower was charged with palladium acetate (56 mg, 0.1 mmol) and XPhos (238 mg, 0.5 mmol). The vial was then sealed, subjected to an atmosphere of N₂ and filled with H₂SO₄ (2 mL, 50 mM in dimethyl acetamide). The catalyst mixture is then stirred at 80 °C for 30 min under microwave irradiation.

In parallel, a microwave vial equipped with a magnetic follower was charged with zinc dust (13.1 mg, 0.2 mmol), zinc cyanide (352 mg, 3 mmol) and S163 (1.67 g, 5 mmol). The vial was sealed and subjected to an atmosphere of N₂ and 15 mL of dimethylacetamide were added. Then, the previously prepared catalyst solution was added (1 mL) and the reaction mixture was stirred for 45 min at 160 °C under microwave irradiation. The mixture was then diluted with EtOAc and extracted with H₂O and brine. The combined organic layers were dried over anhydrous MgSO₄ and concentrated in vacuo. The crude product was purified via flash column chromatography (15 % - 30 % EtOAc, cyclohexane) to give S23 (1.09 g, 23 %) as an off-white powder.

mp 115 °C; νmax/cm⁻¹ 2220 (nitrile); δH (400 MHz, CDCl₃) 8.81 - 8.93 (1 H, m, Ar), 7.98 - 8.12 (1 H, m, Ar), 7.71 - 7.84 (2 H, m, Ar), 7.60 - 7.69 (3 H, m, Ar), 7.16 - 7.25 (2 H, m, Ar), 2.36 (3 H, s, CH₃); δC (100 MHz, CDCl₃) 149.9, 146.0, 145.5, 141.8, 129.7, 128.9, 128.0, 127.0, 125.7, 124.3, 124.0, 120.8, 118.8, 115.2, 21.7 (CH₃); m/z (ESI⁺) 325 ([M+H]⁺); HRMS (ESI⁺) C₁₇H₁₂O₃N₂NaS, ([M+Na]⁺) requires 347.0461; found 347.0457.

8-Hydroxyquinoline-4-carbonitrile S24

A solution of S23 (343 mg, 1.1 mmol) in sodium hydroxide (1M aq., 1.1 mL), ethanol (6 mL) and H₂O (6 mL) was stirred under reflux for 1 h. The ethanol was removed in vacuo and the pH adjusted to 5. The precipitate was filtered and dried to give S24 (87 mg, 46 %) as a bright-yellow solid.
mp 200 °C; ν \(_{\text{max}}\) cm\(^{-1}\) 2235 (nitrile); δ\(_{\text{H}}\) (400 MHz, CDCl\(_3\)) 10.05 (1 H, s, CHO), 8.06 (1 H, s, Ar), 7.76 - 7.88 (2 H, m, Ar), 7.50 - 7.62 (1 H, m, Ar), 6.68 - 6.78 (2 H, m, Ar), 6.43 - 6.55 (1 H, m, Ar), 3.84 (6 H, s, CH\(_3\)); δ\(_{\text{C}}\) (100 MHz, CDCl\(_3\)) 192.3 (CHO), 161.2 (COCH\(_3\)), 142.0, 141.2, 136.8, 133.1, 129.4, 128.9, 128.1, 105.4, 99.9, 55.4 (OCH\(_3\)); m/z (ESI\(^+\)) 243 ([M+H\(^+\)]; HRMS (ESI\(^+\)) C\(_{15}\)H\(_{15}\)O\(_3\), ([M+H\(^+\)]) requires 243.1016; found 243.1011.

3'-Methoxy-[1,1'-biphenyl]-3-carbaldehyde S26\(^{17}\)

3-Formylphenylboronic acid (900 mg, 6 mmol), 3-bromoanisole (633 μL, 5 mmol), tetrakis(triphenylphosphine)palladium (0) (171 mg, 1.5 μmol) were mixed in dimethoxyethane (10 mL) inside a sealed vial. A 2 M aqueous solution of sodium carbonate (5 mL) was added, and the vial was purged with N\(_2\) three times. The mixture was stirred at 100 °C for 2.5 h under microwave irradiation. The reaction mixture was cooled to room temperature and diluted with EtOAc (200 mL). The organic layer was washed with water, a saturated aqueous solution of NH\(_4\)Cl, brine, and dried over anhydrous MgSO\(_4\). The solvent was removed under reduced pressure. The residue was subjected to flash column chromatography on silica gel using EtOAc/cyclohexane (20:8) as eluent to give S26 as a clear oil (634 mg, 52%).

δ\(_{\text{H}}\) (400 MHz, CDCl\(_3\)) 8.06 (1 H, s, Ar), 7.13 - 7.35 (1 H, m), 7.64 - 7.92 (1 H, m), 7.40 - 7.63 (1 H, m), 7.13 - 7.35 (1 H, m); δ\(_{\text{C}}\) (100 MHz, CDCl\(_3\)) 158.8, 148.1, 138.7, 131.3, 128.6, 126.8, 117.8, 114.4, 114.0; m/z (ESI\(^+\)) 171 ([M+H\(^+\)]; HRMS (ESI\(^+\)) C\(_{10}\)H\(_5\)ON\(_2\), ([M-H\(^-\)]) requires 169.0407; found 169.0406.

3',5'-Dimethoxy-[1,1'-biphenyl]-3-carbaldehyde S25

3-Formylphenylboronic acid (900 mg, 6 mmol), 1-bromo-3,5-dimethoxybenzene (1.09 g, 5 mmol), tetrakis(triphenylphosphine)palladium (0) (171 mg, 1.5 μmol) were mixed in dimethoxyethane (10 mL) inside a sealed vial. A 2 M aqueous solution of sodium carbonate (5 mL) was added, and the vial was purged with N\(_2\) three times. The mixture was stirred at 100 °C for 2.5 h under microwave irradiation. The reaction mixture was cooled to room temperature and diluted with EtOAc (200 mL). The organic layer was washed with water, a saturated aqueous solution of NH\(_4\)Cl, brine, and dried over anhydrous MgSO\(_4\). The solvent was removed under reduced pressure. The residue was subjected to flash column chromatography on silica gel using EtOAc/cyclohexane (20:8) as eluent to give S25 as a clear oil (634 mg, 52%).
under reduced pressure. The residue was subjected to flash column chromatography on silica gel using EtOAc/cyclohexane (20% / 80%) as eluent to give S26 (770 mg, 73%) as a clear oil.

δH (400 MHz, CDCl3) 10.06 (1 H, s, CHO), 8.05 - 8.10 (1 H, m, Ar), 7.79 - 7.88 (2 H, m, Ar), 7.54 - 7.62 (1 H, m, Ar), 7.33 - 7.43 (1 H, m, Ar), 7.17 - 7.22 (1 H, m, Ar), 7.12 - 7.17 (1 H, m, Ar), 6.91 - 6.97 (1 H, m, Ar), 3.86 (3 H, s, OC6H3); δC (100 MHz, CDCl3) 192.3 (CHO), 160.1 (COCH3), 141.9, 141.1, 136.9, 133.1, 130.1, 129.5, 128.2, 119.6, 113.4, 112.9, 55.3 (OCH3); m/z (ESI+) 213 ([M+H]+).

tert-Butyl (3'-formyl-[1,1'-biphenyl]-3-yl)carbamate S27

3-Formylphenylboronic acid (900 mg, 6 mmol), S185 (1.36 g, 5 mmol), tetrakis(triphenylphosphine)palladium (0) (171 mg, 1.5 μmol) were mixed in dimethoxyethane (10 mL) inside a sealed vial. A 2 M aqueous solution of sodium carbonate (5 mL) was added, and the vial was purged with N2 three times. The mixture was stirred at 100 °C for 2.5 h under microwave irradiation. The reaction mixture was cooled to room temperature and diluted with EtOAc (200 mL). The organic layer was washed with water, a saturated aqueous solution of NH4Cl, brine, and dried over anhydrous MgSO4. The solvent was removed under reduced pressure. The residue was subjected to flash column chromatography on silica gel using EtOAc/Cyclohexane (20:80) as eluent to give S27 (892 mg, 60%) as a clear oil.

mp 78 °C; νmax/cm-1 3339 (NH), 1693 (C=O); δH (400 MHz, CDCl3) 10.09 (1 H, s, CHO), 8.09 (1 H, s, Ar), 7.82 - 7.91 (2 H, m, Ar), 7.75 (1 H, s, Ar), 7.54 - 7.64 (1 H, m, Ar), 7.35 - 7.42 (1 H, m, Ar), 7.24 - 7.35 (2 H, m, Ar), 6.66 (1 H, br. s., NH), 1.54 (9 H, s, C(CH3)3); δC (100 MHz, CDCl3) 192.3 (CHO), 152.7, 141.9, 140.6, 139.1, 136.8, 133.2, 129.6, 129.4, 128.6, 128.4, 121.8, 118.0, 117.2, 80.7 (C(CH3)3), 28.3 (C(CH3)3); m/z (ESI+) 296 ([M-H]); HRMS (ESI+) C18H19NNaO3, ([M+Na]+) requires 320.1257; found 320.1245.

N-((5-Chloro-8-hydroxyquinolin-7-yl)(phenyl)methyl)benzamide S28

---

30
Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and benzaldehyde (406 µL, 4.0 mmol) gave 28 (662 mg, 85 %) as a white powder.

mp 244 °C; ν\textsubscript{max}/cm\textsuperscript{-1} 3330 (NH), 3063 (OH), 1636 (C=O); δ\textsubscript{H} (400 MHz, DMSO-\textit{d}\textsubscript{6}) 10.42 (1 H, br. s., NH), 9.19 - 9.33 (1 H, m, quinoline-Ar), 7.68 - 7.78 (1 H, m, Ar), 7.52 - 7.59 (1 H, m, Ar), 7.45 - 7.52 (2 H, m, Ar), 7.31 - 7.37 (4 H, m, Ar), 7.22 - 7.30 (1 H, m, Ar), 7.03 (1 H, d, J=8.5 Hz, benzyl-H); δ\textsubscript{C} (100 MHz, DMSO-\textit{d}\textsubscript{6}) 166.9 (C=O), 150.4, 150.1, 142.5, 139.5, 135.1, 133.4, 132.3, 129.3, 129.1, 128.5, 128.0, 127.9, 127.7, 125.9, 125.8, 123.9, 119.4, 50.9 (benzyl-C); m/z (ESI\textsuperscript{+}) 387 ([M-H]-, 100 %); HRMS (ESI\textsuperscript{+}) \textit{C}_{23}\textit{H}_{17}\textit{ClN}_{2}\textit{NaO}_{2}, ([M+Na]\textsuperscript{+}) requires 411.0871; found 411.0861.

\textit{N-((8-Hydroxyquinolin-7-yl)(p-toly)methyl)benzamide 29}

Following general procedure 1, 8-hydroxyquinoline (145 mg, 1.0 mmol), benzamide (121 mg, 1.0 mmol) and \textit{p}-tolualdehyde (236 µL, 2.0 mmol) gave 29 (60 mg, 16 %) as a white powder.

mp 173 °C; ν\textsubscript{max}/cm\textsuperscript{-1} 3308 (NH), 3048 (OH), 1640 (C=O); δ\textsubscript{H} (400 MHz, DMSO-\textit{d}\textsubscript{6}) 9.97 (1 H, br. s, NH), 9.16 - 9.22 (1 H, m, quinoline-Ar), 8.75 - 8.88 (1 H, m, quinoline-Ar), 8.68 - 8.83 (1 H, m, quinoline-Ar), 7.51 - 7.58 (2 H, m, Ar), 7.41 - 7.49 (3 H, m, Ar), 7.18 - 7.24 (1 H, m, Ar), 7.08 - 7.15 (3 H, m, Ar), 6.96 (1 H, d, J=8.5 Hz, benzyl-H), 2.25 (3 H, s, \textit{CH}_{3}); δ\textsubscript{C} (100 MHz, DMSO-\textit{d}\textsubscript{6}) 166.7 (C=O), 150.6, 149.2, 140.1, 138.9, 136.9, 136.7, 135.4, 132.1, 129.6, 129.1, 128.9, 128.5, 128.1, 127.8, 125.4, 122.6, 118.1, 51.1 (benzyl-C), 21.5 (\textit{CH}_{3}); m/z (ESI\textsuperscript{+}) 367 ([M-H]-, 100 %); HRMS (ESI\textsuperscript{+}) \textit{C}_{24}\textit{H}_{20}\textit{N}_{2}\textit{O}_{2}, ([M+Na]\textsuperscript{+}) requires 391.1417; found 391.1420.

\textit{N-((8-Hydroxyquinolin-7-yl)(naphthalen-1-yl)methyl)benzamide 30}

Following general procedure 1, 8-hydroxyquinoline (145 mg, 1.0 mmol), benzamide (121 mg, 1.0 mmol) and \textit{p}-tolualdehyde (236 µL, 2.0 mmol) gave 30 (150 mg, 37 %) as an off-white powder.
Following general procedure 1, 8-hydroxyquinoline (145 mg, 1.0 mmol), benzamide (121 mg, 1.0 mmol) and 2-naphthaldehyde (312 mg, 2.0 mmol) gave S31 (162 mg, 40%) as a white powder.

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 4-chlorobenzaldehyde (560 mg, 4.0 mmol) gave S32 (743 mg, 88%) as a white powder.
mp 267 - 269 °C; ν_{max}/cm^{-1} 3308 (NH), 2361 (OH), 1631 (C=O); δ_{HH} (400 MHz, DMSO-d_{6}) 10.49 (1 H, br. s., NH), 9.23 - 9.36 (1 H, m, quinoline-Ar), 8.91 - 9.04 (1 H, m, quinoline-Ar), 8.42 - 8.56 (1 H, m, quinoline-Ar), 7.91 - 7.98 (2 H, m, Ar), 7.85 (1 H, s, Ar), 7.70 - 7.77 (1 H, m, Ar), 7.52 - 7.59 (1 H, m, Ar), 7.45 - 7.52 (2 H, m, Ar), 7.38 - 7.43 (2 H, m, Ar), 7.30 - 7.37 (2 H, m, Ar), 6.99 (1 H, d, J=8.5 Hz, benzyl-H); δ_{CC} (100 MHz, DMSO-d_{6}) 166.9 (C=O), 150.5, 150.1, 141.4, 139.5, 135.0, 133.4, 132.5, 132.3, 130.0, 129.3, 128.5, 127.4, 125.9, 125.4, 119.5, 50.5 (benzyl-C); m/z (ESI') 867 ([2M+Na]'); HRMS (ESI) C_{23}H_{15}Cl_{2}N_{2}O_{2}, ([M-H]) requires 421.0516; found 421.

**([(3-Bromophenyl)(5-chloro-8-hydroxyquinolin-7-yl)methyl]urea S33**

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), urea (120 mg, 2.0 mmol) and 3-bromobenzaldehyde (234 μL, 2.0 mmol) gave S33 (470 mg, 58 %) as an off-white powder.

mp 183 °C; ν_{max}/cm^{-1} 3339 (NH), 1636 (C=O); δ_{HH} (400 MHz, DMSO-d_{6}) 10.47 (1 H, br. s., NH), 8.78 - 9.14 (1 H, m, quinoline-Ar), 8.35 - 8.61 (1 H, m, quinoline-Ar), 7.60 - 7.87 (2 H, m, Ar), 7.09 - 7.57 (6 H, m, Ar), 6.28 - 6.56 (1 H, m, benzyl-H), 5.55 - 5.87 (1 H, m, Ar); δ_{CC} (100 MHz, DMSO-d_{6}) 157.2 (C=O), 150.1, 139.6, 133.4, 131.5, 131.4, 130.6, 130.0, 127.0, 126.6, 126.2, 125.9, 123.9, 122.6, 119.7, 52.3 (benzyl-C); m/z (ESI') 404 ([M]+); HRMS (ESI') C_{17}H_{13}BrClIN_{2}O_{2}, ([M]+) requires 404.9880; found 404.0892.

**N-((4-Bromophenyl)(5-chloro-8-hydroxyquinolin-7-yl)methyl)benzamide S34**

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 4-bromobenzaldehyde (740 mg, 4.0 mmol) gave S34 (931 mg, 100 %) as an off-white powder.

mp 276 °C; ν_{max}/cm^{-1} 3316 (NH), 2946 (OH), 1630 (C=O); 691 (C-Br); δ_{HH} (400 MHz, DMSO-d_{6}) 10.49 (1 H, br. s., br. s., NH), 8.91 - 9.05 (1 H, m, quinoline-Ar), 8.42 - 8.56 (1 H, m, quinoline-Ar), 7.89 - 7.98 (2 H, m, Ar), 7.84 (1 H, s, m, Ar), 7.68 - 7.78 (1
H, m, Ar), 7.52 - 7.62 (3 H, m, Ar), 7.44 - 7.51 (2 H, m, Ar), 7.22 - 7.34 (2 H, m, Ar), 6.97 (1 H, d, J=8.5 Hz, benzyl-H); δC (100 MHz, DMSO-d6) 166.9 (C=O), 150.5, 150.1, 141.9, 139.5, 135.0, 133.4, 132.3, 132.2, 129.2, 128.5, 127.4, 125.9, 125.4, 124.0, 121.0, 119.5, 50.6 (benzyl-C); m/z (ESI) 467 ([M-H]-); HRMS (ESI+) C23H16BrClN2O2 (M+Na+) requires 490.9955; found 490.9944.

N-((5-Chloro-8-hydroxyquinolin-7-yl)(3-(trifluoromethyl)phenyl)methyl)benzamide S35

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 3-trifluoromethylbenzaldehyde (571 μL, 4.0 mmol) gave S35 (645 mg, 71%) as a white powder.

mp 219 - 222 °C; νmax/cm⁻¹ 3294 (NH), 1634 (C=O), 692 (C-Cl); δH (400 MHz, DMSO-d6) 10.58 (1 H, br. s., NH), 9.31 - 9.46 (1 H, m, quinoline-Ar), 8.94 - 9.01 (1 H, m, quinoline-Ar), 8.44 - 8.52 (1 H, m, quinoline-Ar), 7.91 - 7.99 (2 H, m, Ar), 7.88 (1 H, s, Ar), 7.45 - 7.77 (8 H, m, Ar), 7.09 (1 H, d, J=8.5 Hz, benzyl-H); δC (100 MHz, DMSO-d6) 167.0 (C=O), 150.6, 150.2, 143.9, 139.5, 134.9, 133.4, 132.4, 130.5, 130.2, 129.2, 128.5, 127.2, 126.0, 125.1, 124.8, 124.3, 124.0, 123.7, 119.7, 50.9 (benzyl-C); δF (377 MHz, DMSO-d6) -61.0 (CF3); m/z (ESI) 455 ([M-H]-); HRMS (ESI+) C24H16BrClF3N2O2 (M+Na+) requires 479.0745; found 479.0740.

N-((5-Chloro-8-hydroxyquinolin-7-yl)(3-fluorophenyl)methyl)benzamide S36

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 3-fluorobenzaldehyde (424 μL, 4.0 mmol) gave S36 (631 mg, 78%) as a white powder.

mp 234 °C; νmax/cm⁻¹ 3311 (NH), 1631 (C=O), 692 (C-Cl); δH (400 MHz, DMSO-d6) 10.53 (1 H, br. s., NH), 9.24 - 9.37 (1 H, m, quinoline-Ar), 8.91 - 9.02 (1 H, m, quinoline-Ar), 8.41 - 8.54 (1 H, m, quinoline-Ar), 7.90 - 8.00 (2 H, m, Ar), 7.86 (1 H, s, Ar), 7.65 - 7.78 (1 H, m, Ar), 7.45 - 7.61 (3 H, m, Ar), 7.34 - 7.44 (1 H, m, Ar), 7.07 - 7.24 (3 H, m, Ar), 7.03 (1 H, d, J=8.5 Hz, benzyl-
Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 3-(4-methylphenoxy)benzaldehyde (770 μL, 4.0 mmol) gave S37 (546 mg, 55 %) as a white powder.

mp 212 °C; \( \nu_{\text{max}}/\text{cm}^{-1} \) 3306 (NH), 1634 (C=O); \( \delta_H \) (400 MHz, DMSO-\( d_6 \)) 10.49 (1 H, br. s., NH), 9.17 - 9.35 (1 H, m, quinoline-Ar), 8.89 - 9.01 (1 H, m, quinoline-Ar), 8.37 - 8.58 (1 H, m, quinoline-Ar), 7.86 - 7.93 (2 H, m, Ar), 7.85 (1 H, s, Ar), 7.67 - 7.76 (1 H, m, Ar), 7.51 - 7.59 (1 H, m, Ar), 7.43 - 7.51 (2 H, m, Ar), 7.27 - 7.36 (1 H, m, Ar), 7.11 - 7.16 (2 H, m, Ar), 7.03 - 7.09 (1 H, m, Ar), 6.96 - 7.02 (2 H, m, Ar), 6.86 - 6.91 (2 H, m, Ar), 6.76 - 6.84 (1 H, m, Ar), 2.24 (3 H, s, CH\text{3}); \( \delta_C \) (100 MHz, DMSO-\( d_6 \)) 167.0 (C=O), 158.2, 154.6, 150.4, 150.1, 144.7, 139.5, 135.1, 133.6, 133.4, 132.3, 131.2, 129.1, 128.5, 127.6, 125.9, 125.6, 123.9, 122.6, 119.8, 119.5, 117.5, 117.0, 50.6 (benzyl-C), 21.1 (CH\text{3}); \( m/z \) (ESI\textsuperscript{+}) 493 ([M-H]); HRMS (ESI\textsuperscript{+}) \( C_{23}H_{21}ClF_2N_2NaO_3 \), ([M+Na\textsuperscript{+}) requires 517.1289; found 517.1276.

**N-((5-Chloro-8-hydroxyquinolin-7-yl)(3-(p-toloyloxy)phenyl)methyl)benzamide S38**
Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 3-(4-methoxy)phenoxybenzaldehyde (837 μL, 4.0 mmol) gave S38 (576 mg, 56 %) as a white powder.

mp 200-202 °C; νmax/cm⁻¹ 3274 (NH), 1633 (C=O); δ_H (400 MHz, DMSO-d$_6$) 10.47 (1 H, br. s., NH), 9.21 - 9.32 (1 H, m, Ar), 7.87 - 7.93 (2 H, m, Ar), 7.85 (1 H, s, Ar), 7.68 - 7.78 (1 H, m, Ar), 7.52 - 7.59 (1 H, m, Ar), 7.42 - 7.51 (2 H, m, Ar), 7.21 - 7.36 (1 H, m, Ar), 6.94 - 7.06 (5 H, m, Ar), 6.86 - 6.94 (2 H, m, Ar), 6.67 - 6.80 (1 H, m) 3.71 (3 H, s, C$_H$$_3$); δ_C (100 MHz, CDCl$_3$) 167.0 (C=O), 159.0, 156.4, 150.4, 150.1, 149.8, 144.7, 139.5, 135.1, 133.4, 132.3, 130.8, 129.1, 128.4, 127.6, 125.9, 125.6, 123.9, 122.2, 121.7, 119.5, 116.7, 116.2, 115.9, 56.2 (C$_H$$_3$), 50.6 (benzyl-C); m/z (ESI⁻) 509 ([M-H]⁻); HRMS (ESI⁻) C$_{30}$H$_{23}$ClN$_2$NaO$_4$, ([M+Na]⁺) requires 533.1239; found 533.1239.

N-((5-Chloro-8-hydroxyquinolin-7-yl)(p-tolyl)methyl)benzamide S39

Following general procedure 1, 5-chloro-8-quinolinol (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and p-tolualdehyde (472 μL, 4.0 mmol) gave S39 (686 mg, 85 %) as white powder.

mp 248-249 °C; νmax/cm⁻¹ 3310 (NH), 1634 (C=O); δ_H (400 MHz, DMSO-d$_6$) 10.39 (1 H, br. s., NH), 9.15 - 9.28 (1 H, m, quinoline-Ar), 8.91 - 9.01 (1 H, m, quinoline-Ar), 8.41 - 8.55 (1 H, m, quinoline-Ar), 7.90 - 7.97 (2 H, m, Ar), 7.86 (1 H, s, Ar), 7.68 - 7.75 (1 H, m, Ar), 7.51 - 7.58 (1 H, m, Ar), 7.44 - 7.51 (2 H, m, Ar), 7.19 - 7.26 (2 H, m, Ar), 7.10 - 7.17 (2 H, m, Ar), 6.98 (1 H, d, J=9.0 Hz, benzyl-H), 2.26 (3 H, s, CH$_3$); δ_C (100 MHz, DMSO-d$_6$) 166.8 (C=O), 150.3, 150.0, 139.5, 137.0, 135.2, 133.4, 132.2, 129.8, 129.1, 128.5, 128.0, 127.7, 126.2, 125.8, 123.8, 119.4, 50.7 (benzyl-C), 21.5 (CH$_3$); m/z (ESI⁺) 401 ([M-H]⁻), 100 %; HRMS (ESI⁺) C$_{30}$H$_{23}$ClN$_2$O$_2$, ([M-H]⁻) requires 401.1062; found 401.1061.

N-((5-Chloro-8-hydroxyquinolin-7-yl)(naphthalen-1-yl)methyl)benzamide S40
Following general procedure 1, 5-chloro-8-quinolinol (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 1-naphthaldehyde (544 µL, 4.0 mmol) gave S40 (541 mg, 62 %) as a white powder.

mp 229-230 °C; \( \nu_{\max } \text{cm}^{-1} \) 3234 (NH), 1630 (C=O); \( \delta_{H} \) (400 MHz, DMSO-\( d_6 \)) 10.54 (1 H, br. s., NH), 9.33 - 9.42 (1 H, m, quinoline-Ar), 8.45 - 8.51 (1 H, m, quinoline-Ar), 8.06 - 8.16 (1 H, m, Ar), 7.92 - 8.00 (3 H, m, Ar), 7.86 - 7.91 (1 H, m, Ar), 7.71 - 7.76 (1 H, m, Ar), 7.70 (1 H, s) 7.65 (1 H, d, \( J=8.5 \) Hz) 7.49 - 7.58 (3 H, m, Ar), 7.43 - 7.49 (3 H, m, Ar), 7.39 (1 H, m, Ar); \( \delta_{C} \) (100 MHz, DMSO-\( d_6 \)) 166.5 (C=O), 150.5, 150.1, 139.5, 138.1, 134.9, 134.4, 133.4, 132.3, 131.8, 129.6, 129.1, 128.8, 128.5, 128.0, 126.7, 126.2, 126.0, 125.6, 125.3, 123.9, 48.3 (benzyl-C); \( m/z \) (ESI) 437 ([M-H] \( - \) 100 %); HRMS (ESI) \( C_{27}H_{18}ClN_2O_2 \) requires 437.1062; found 437.1050.

\[ \text{N-((5-Chloro-8-hydroxyquinolin-7-yl)(naphthalen-2-yl)methyl)benzamide S41} \]

Following general procedure 1, 5-chloro-8-quinolinol (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 2-naphthaldehyde (312 mg, 4.0 mmol) gave S41 (654 mg, 75 %) as a white powder.

mp 263-266 °C; \( \nu_{\max } \text{cm}^{-1} \) 3367 (NH), 1654 (C=O); \( \delta_{H} \) (400 MHz, DMSO-\( d_6 \)) 10.49 (1 H, br. s., NH), 9.31 - 9.45 (1 H, m, quinoline-Ar), 8.91 - 9.04 (1 H, m, quinoline-Ar), 8.42 - 8.56 (1 H, m, quinoline-Ar), 7.96 - 8.02 (2 H, m, Ar), 7.84 - 7.93 (4 H, m, Ar), 7.80 (1 H, s, Ar), 7.69 - 7.76 (1 H, m, Ar), 7.43 - 7.61 (6 H, m, Ar), 7.19 (1 H, d, \( J=8.5 \) Hz, benzyl-H); \( \delta_{C} \) (100 MHz, DMSO-\( d_6 \)) 166.9 (C=O), 150.6, 150.1, 140.0, 139.6, 135.1, 133.6, 133.4, 133.0, 132.3, 129.2, 129.0, 128.7, 128.5, 128.3, 127.8, 127.2, 126.8, 126.7, 126.1, 125.9, 125.8, 123.9, 119.5, 51.2 (benzyl-C); \( m/z \) (ESI) 437 ([M-H] \( - \) 100 %); HRMS (ESI) \( C_{27}H_{18}ClN_2O_2 \) requires 437.1062; found 437.1061.

\[ \text{N-((5-Bromo-8-hydroxyquinolin-7-yl)(phenyl)methyl)benzamide S42} \]

![Diagram of S42](image-url)

Following general procedure 1, 5-bromo-8-quinolinol (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 1-naphthaldehyde (544 µL, 4.0 mmol) gave S42 (541 mg, 62 %) as a white powder.
Following general procedure 1, 5-bromo-8-hydroxyquinoline (448 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and benzaldehyde (406 µL, 4.0 mmol) gave S42 (620 mg, 72 %) as a white powder.

mp 246 - 247 °C; ν\text{max}/\text{cm}^{-1} 3263 (NH), 1638 (C=O); δ\text{H} (400 MHz, DMSO-d6) 10.46 (1 H, br. s., NH), 9.21 - 9.34 (1 H, m, quinoline-Ar), 8.89 - 8.98 (1 H, m, quinoline-Ar), 8.35 - 8.45 (1 H, m, quinoline-Ar), 8.03 (1 H, s, quinoline-Ar), 7.89 - 7.98 (2 H, m, Ar), 7.68 - 7.75 (1 H, m, Ar), 7.52 - 7.59 (1 H, m, Ar), 7.46 - 7.52 (2 H, m, Ar), 7.31 - 7.37 (4 H, m, Ar), 7.22 - 7.29 (1 H, m, Ar), 7.03 (1 H, d, J=8.5 Hz, benzyl-H); δ\text{C} (100 MHz, DMSO-d6) 166.9 (C=O), 151.0, 150.0, 142.5, 139.8, 135.8, 135.1, 132.3, 131.2, 129.3, 129.2, 128.5, 128.0, 127.9, 127.1, 126.6, 124.2, 109.3, 50.9 (benzyl-C); m/z (ESI\textsuperscript{+}) 431 ([M-H]); HRMS (ESI\textsuperscript{+}) C\textsubscript{23}H\textsubscript{16}BrN\textsubscript{2}O\textsubscript{2}, ([M-H]) requires 431.0401; found 431.0399.

(E)-N-(5-Chloro-8-hydroxyquinolin-7-yl)-3-phenyallyl)benzamide S43

\[
\text{\includegraphics{clipart.png}}
\]

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and trans-cinnamaldehyde (504 µL, 4.0 mmol) gave S43 (545 mg, 67 %) as a white powder.

mp 227 °C; ν\text{max}/\text{cm}^{-1} 3290 (NH), 1630 (C=O); δ\text{H} (400 MHz, DMSO-d6) 10.40 (1 H, br. s., NH), 9.07 - 9.25 (1 H, m, quinoline-Ar), 8.89 - 9.02 (1 H, m, quinoline-Ar), 8.37 - 8.56 (1 H, m, quinoline-Ar), 7.92 - 8.00 (2 H, m, Ar), 7.90 (1 H, s, Ar), 7.67 - 7.75 (1 H, m, Ar), 7.52 - 7.59 (1 H, m, Ar), 7.46 - 7.52 (2 H, m, Ar), 7.40 - 7.45 (2 H, m, Ar), 7.26 - 7.34 (2 H, m, Ar), 7.17 - 7.25 (1 H, m, Ar), 6.54 - 6.60 (2 H, m, Ar), 6.45 - 6.51 (1 H, m, benzyl-H); δ\text{C} (100 MHz, DMSO-d6) 166.5 (C=O), 150.3, 150.0, 139.6, 137.2, 135.1, 133.4, 132.2, 130.9, 130.0, 129.5, 129.2, 128.5, 128.4, 127.2, 125.8, 125.7, 123.8, 119.4, 50.0 (benzyl-C); m/z (ESI\textsuperscript{+}) 437 ([M+Na\textsuperscript{+}]); HRMS (ESI\textsuperscript{+}) C\textsubscript{25}H\textsubscript{19}ClN\textsubscript{2}O\textsubscript{2}Na, ([M+Na\textsuperscript{+}]) requires 437.1027; found 437.1019.

N-([1,1'-Biphenyl]-3-yl)(8-hydroxy-5-nitroquinolin-7-yl)methyl)benzamide S44

\[
\text{\includegraphics{clipart.png}}
\]

38
Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and biphenyl-3-carboxaldehyde (651 μL, 4.0 mmol) gave S44 (666 mg, 70 %) as a yellow powder.

mp 213 °C; νmax/cm⁻¹ 3283 (NH), 1633 (C=O); δn (400 MHz, DMSO-d₆) 9.40 - 9.62 (1 H, m, quinoline-Ar), 9.11 - 9.29 (1 H, m, quinoline-Ar), 8.93 - 9.07 (1 H, m, quinoline-Ar), 8.88 (1 H, s, quinoline-Ar), 7.92 - 8.03 (2 H, m, Ar), 7.84 - 7.91 (1 H, m, Ar), 7.72 (1 H, s, Ar), 7.53 - 7.65 (4 H, m, Ar), 7.28 - 7.37 (1 H, m, Ar), 7.07 (1 H, d, J=8.5 Hz, benzyl-H); δc (100 MHz, DMSO-d₆) 167.0 (C=O), 158.7, 149.8, 142.5, 141.4, 140.9, 137.7, 135.1, 135.0, 134.0, 132.3, 130.0, 129.8, 129.2, 128.9, 128.5, 127.6, 127.5, 126.6, 126.1, 124.7, 122.6, 51.3 (benzyl-C); m/z (ESI+) 476 ([M+H]+); HRMS (ESI+) C₂₉H₂₁N₃NaO₄, ([M+Na]+) requires 498.1424; found 498.1440.

N-((5-Chloro-8-hydroxyquinolin-7-yl)(4-phenoxyphenyl)methyl)benzamide S45

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 4-phenoxybenzaldehyde (700 μL, 4.0 mmol) gave S45 (573 mg, 60 %) as a white powder.

mp 222 °C; νmax/cm⁻¹ 3306 (NH), 1634 (C=O); δn (400 MHz, DMSO-d₆) 10.46 (1 H, br. s., NH), 9.23 - 9.36 (1 H, m, quinoline-Ar), 8.88 - 9.05 (1 H, m, quinoline-Ar), 8.40 - 8.57 (1 H, m, quinoline-Ar), 7.87 - 8.00 (3 H, m, Ar), 7.67 - 7.76 (1 H, m, Ar), 7.52 - 7.59 (1 H, m, Ar), 7.45 - 7.52 (2 H, m, Ar), 7.31 - 7.40 (4 H, m, Ar), 7.07 - 7.15 (1 H, m, benzyl-H), 6.93 - 7.04 (5 H, m, Ar); δc (100 MHz, DMSO-d₆) 166.8 (C=O), 157.5, 156.4, 150.4, 150.1, 139.5, 137.5, 135.1, 133.4, 132.3, 130.9, 129.8, 129.2, 128.5, 127.5, 126.0, 125.8, 124.3, 123.9, 119.5, 119.4, 50.5 (benzyl-C); m/z (FI) 480 ([M]); HRMS (FI) C₂₉H₂₂N₂O₄Cl, ([M]) requires 480.1241; found 480.1248.
Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 4-ethynylbenzaldehyde (260 mg, 4.0 mmol) gave S46 (430 mg, 52 %) as an off-white powder.

mp 228 °C; νmax/cm⁻¹ 3301 (NH), 1630 (C=O); δH (400 MHz, DMSO-d₆) 10.53 (1 H, br. s., NH), 9.23 - 9.45 (1 H, m, quinoline-Ar), 8.90 - 9.08 (1 H, m, quinoline-Ar), 8.40 - 8.57 (1 H, m, quinoline-Ar), 7.93 - 8.00 (2 H, m, Ar), 7.86 (1 H, s, Ar), 7.70 - 7.79 (1 H, m, Ar), 7.55 - 7.60 (1 H, m, Ar), 7.44 - 7.54 (4 H, m, Ar), 7.32 - 7.39 (2 H, m, Ar), 7.04 (1 H, d, J=9.0 Hz, benzyl-H), 4.18 (1 H, s, CH); δC (100 MHz, DMSO-d₆) 166.6 (C=O), 150.1, 149.7, 143.0, 139.1, 134.6, 133.0, 132.3, 132.0, 128.8, 128.1, 128.0, 127.1, 125.5, 125.0, 123.6, 130.9, 119.2, 83.8, 81.3, 50.4; m/z (ESI⁺) 413 ([M+H⁺]⁺); HRMS (ESI⁺) C₂₅H₁₇O₂N₂ClNa, ([M+Na⁺]) requires 435.0871; found 435.0866.

Following general procedure 1, 5-chloro-8-hydroxyquinoline (345 mg, 1.9 mmol), benzamide (233 mg, 1.9 mmol) and 3-ethynylbenzaldehyde (250 mg, 1.92 mmol) gave S47 (220 mg, 27 %) as an off-white powder.

mp 200 °C; νmax/cm⁻¹ 3297 (NH), 1637 (C=O); δH (400 MHz, DMSO-d₆) 10.55 (1 H, br. s., NH), 9.22 - 9.44 (1 H, m, quinoline-Ar), 8.92 - 9.05 (1 H, m, quinoline-Ar), 8.43 - 8.58 (1 H, m, quinoline-Ar), 7.92 - 7.99 (2 H, m, Ar), 7.89 (1 H, s, Ar), 7.70 - 7.77 (1 H, m, Ar), 7.54 - 7.60 (1 H, m, Ar), 7.47 - 7.54 (2 H, m, Ar), 7.34 - 7.45 (4 H, m, Ar), 7.02 (1 H, d, J=9.0 Hz, benzyl-H), 4.20 (1 H, s, CH); δC (100 MHz, DMSO-d₆) 166.6 (C=O), 150.1, 149.8, 142.7, 139.1, 134.5, 133.0, 132.0, 130.9, 130.6, 129.5, 128.6, 128.1, 126.9, 125.5, 125.0, 123.6, 122.2, 119.2, 83.9, 81.5, 50.4; m/z (ESI⁺) 413 ([M+H⁺]⁺); HRMS (ESI⁺) C₂₅H₁₇O₂N₂ClNa, ([M+Na⁺]) requires 435.0871; found 435.0867.
**N-((8-Hydroxyquinolin-7-yl)(phenyl)methyl)-3-methylbenzamide S48**

![Chemical Structure](image)

Following general procedure 1, 8-hydroxyquinoline (145 mg, 1.0 mmol), m-toluamide (135 mg, 1.0 mmol) and benzaldehyde (203 µL, 2.0 mmol) gave **S48** (80 mg, 22%) as a white powder.

mp 165 °C; \( \nu_{\text{max}}/\text{cm}^{-1} \) 3306 (NH), 3058 (OH), 1638 (C=O); \( \delta_{\text{H}} \) (400 MHz, DMSO-\( \text{d}_6 \)) 10.02 (1 H, br. s., NH), 9.12 - 9.25 (1 H, m, quinoline-Ar), 8.78 - 8.93 (1 H, m, quinoline-Ar), 8.18 - 8.44 (1 H, m, quinoline-Ar), 7.78 (1 H, s, quinoline-Ar), 7.68 - 7.75 (2 H, m, Ar), 7.52 - 7.58 (1 H, m, Ar), 7.41 - 7.46 (1 H, m, Ar), 7.30 - 7.36 (6 H, m, Ar), 7.24 (1 H, br. s, OH), 7.01 (1 H, d, J=9.0 Hz, benzyl-H), 2.30 - 2.42 (3 H, m, Me); \( \delta_{\text{C}} \) (100 MHz, DMSO-\( \text{d}_6 \)) 166.9 (C=O), 150.7, 149.2, 143.1, 138.9, 138.4, 136.9, 135.3, 132.7, 129.1, 129.0, 128.9, 128.5, 128.1, 127.9, 127.6, 125.7, 125.2, 118.2, 51.4 (benzyl-C), 21.8 (CH\(_3\)); \( m/z \) (ESI) 367 ([M-H], 100%); HRMS (ESI\( ^+ \)) C\(_{24}\)H\(_{20}\)N\(_2\)O\(_2\), ([M+Na\(^+\)]) requires 391.1417; found 391.1403.

**N-((8-Hydroxyquinolin-7-yl)(phenyl)methyl)-2-phenylacetamide S49**

![Chemical Structure](image)

Following general procedure 1, 8-hydroxyquinoline (290 mg, 2.0 mmol), 2-phenylacetamide (270 mg, 2.0 mmol) and benzaldehyde (406 µL, 4.0 mmol) gave **S49** (420 mg, 57%) as a white powder.

mp 207 °C; \( \nu_{\text{max}}/\text{cm}^{-1} \) 3307 (NH), 1634 (C=O); \( \delta_{\text{H}} \) (400 MHz, DMSO-\( \text{d}_6 \)) 9.95 (1 H, br. s., NH), 8.95 - 9.06 (1 H, m, quinoline-Ar), 8.81 - 8.88 (1 H, m, quinoline-Ar), 8.22 - 8.36 (1 H, m, quinoline-Ar), 7.50 - 7.59 (2 H, m, Ar), 7.39 - 7.45 (1 H, m, Ar), 7.14 - 7.35 (10 H, m, Ar), 6.70 (1 H, d, J=8.5 Hz, benzyl-H) 3.58 (2 H, s, CH\(_2\)); \( \delta_{\text{C}} \) (100 MHz, DMSO-\( \text{d}_6 \)) 170.3 (C=O), 150.4, 149.2, 143.2, 138.9, 137.3, 136.9, 129.9, 129.1, 129.0, 128.4, 127.9, 127.6, 127.2, 125.3, 122.6, 118.2, 50.9 (benzyl-C), 43.1 (CH\(_2\)); \( m/z \) (ESI) 367 ([M-H]); HRMS (ESI\( ^+ \)) C\(_{24}\)H\(_{19}\)N\(_2\)O\(_2\), ([M-H]) requires 367.1452; found 367.1444.
**N-((S-Chloro-8-hydroxyquinolin-7-yl)(phenyl)methyl)-2-phenylacetamide S50**

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), 2-phenylacetamide (270 mg, 2.0 mmol) and benzaldehyde (406 μL, 4.0 mmol) gave S50 (485 mg, 60 %) as a white powder.

mp 217 - 218 °C; ν_max/cm⁻¹ 3299 (NH), 1645 (C=O), 696 (C-Cl); δ_H (400 MHz, DMSO-d₆) 10.35 (1 H, br. s., NH), 9.00 - 9.13 (1 H, m, quinoline-Ar), 8.89 - 8.99 (1 H, m, quinoline-Ar), 8.40 - 8.52 (1 H, m, quinoline-Ar), 7.64 - 7.76 (2 H, m, Ar), 7.15 - 7.37 (10 H, m, Ar), 6.68 (1 H, d, J=8.5 Hz, benzyl-H), 3.58 (2 H, s, CH₂); δ_C (100 MHz, DMSO-d₆) 170.4 (C=O), 150.1, 142.5, 139.5, 137.2, 133.4, 129.9, 129.3, 129.1, 129.0, 127.9, 127.2, 127.1, 127.0, 126.1, 125.7, 123.8, 119.5, 50.7 (benzyl-C), 43.1 (CH₂); m/z (ESI⁻) 401 ([M-H]⁻); HRMS (ESI⁻) C₂₄H₂₁ClN₂O₂, ([M+Na]⁻) requires 425.1027; found 425.1024.

**N-((3-Bromophenyl)(5-chloro-8-hydroxyquinolin-7-yl)methyl)-3-fluorobenzamide S51**

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), 3-fluorobenzamide (278 mg, 2.0 mmol) and 3-bromobenzaldehyde (468 μL, 4.0 mmol) gave S51 (407 mg, 42 %) as a white powder.

mp 219 °C; ν_max/cm⁻¹ 3290 (NH), 1635 (C=O); δ_H (400 MHz, DMSO-d₆) 10.57 (1 H, br. s., NH), 9.32 - 9.43 (1 H, m, quinoline-Ar), 8.93 - 9.02 (1 H, m, quinoline-Ar), 8.43 - 8.55 (1 H, m, quinoline-Ar), 7.80 - 7.84 (1 H, m, Ar), 7.70 - 7.80 (3 H, m, Ar), 7.50 - 7.59 (2 H, m, Ar), 7.46 - 7.50 (1 H, m, Ar), 7.28 - 7.45 (3 H, m, Ar), 6.97 (1 H, d, J=8.5 Hz, benzyl-H); δ_C (100 MHz, DMSO-d₆) 165.6 (C=O), 164.0 (C-F), 150.5, 150.2, 145.0, 139.5, 137.2, 133.4, 131.6, 131.5, 131.4, 131.0, 130.6, 127.3, 127.2, 126.0, 125.0, 124.7, 124.0, 122.6, 119.6, 115.4, 41.0 (benzyl-C); m/z (ESI⁺) 483 ([M-H⁺]); HRMS (ESI⁺) C₂₃H₁₅BrClFN₂O₂, ([M+Na]⁺) requires 506.9882; found 506.9876.
**N-((8-Hydroxyquinolin-7-yl)(phenyl)methyl)-2-methylbenzamide S52**

Following general procedure 1, 8-hydroxyquinoline (145 mg, 1.0 mmol), o-toluamide (135 mg, 1.0 mmol) and benzaldehyde (203 µL, 2.0 mmol) gave S52 (206 mg, 56 %) as a white powder.

mp 170 °C; \( \nu_{\text{max}} / \text{cm}^{-1} \) 3292 (NH), 3060 (OH), 1643 (C=O); \( \delta \nu \) (400 MHz, DMSO-\( d_6 \)) 10.04 (1 H, br. s, NH), 9.15 - 9.32 (1 H, m, quinoline-Ar), 8.83 - 8.91 (1 H, m quinoline-Ar), 8.24 - 8.37 (1 H, m quinoline-Ar), 7.66 - 7.72 (1 H, m quinoline-Ar), 7.53 - 7.59 (1 H, m quinoline-Ar), 7.42 - 7.47 (1 H, m, Ar), 7.35 - 7.40 (3 H, m, Ar), 7.29 - 7.35 (3 H, m, Ar), 7.20 - 7.27 (3 H, m, Ar), 7.00 (1 H, d, J=9.0 Hz, benzyl-H), 2.29 (3 H, s, CH\(_3\)); \( \delta \)C (100 MHz, DMSO-\( d_6 \)) 169.4 (C=O), 150.5, 149.2, 143.2, 138.9, 136.9, 136.0, 131.1, 130.1, 129.2, 128.4, 128.0, 127.9, 127.7, 127.6, 126.3, 125.4, 122.7, 118.2, 50.9 (benzyl-C), 20.2 (CH\(_3\)); \( m/\text{z} \) (ESI) 367 ([M-H], 100 %); HRMS (ESI\(^+\)) C\(_{24}\)H\(_{20}\)N\(_2\)NaO\(_2\), ([M+Na\(^+\)] \( \text{requires} \) 391.1417; found 391.1404.

**N-((8-Hydroxyquinolin-7-yl)(phenyl)methyl)-4-methylbenzamide S53**

Following general procedure 1, 8-hydroxyquinoline (145 mg, 1.0 mmol), p-toluamide (135 mg, 1.0 mmol) and benzaldehyde (203 µL, 2.0 mmol) gave S53 (203 mg, 22 %) as a white powder.

mp 214-216 °C; \( \nu_{\text{max}} / \text{cm}^{-1} \) 3305 (NH), 3047 (OH), 1632 (C=O); \( \delta \nu \) (400 MHz, DMSO-\( d_6 \)) 10.04 (1 H, br. s, NH), 9.11 - 9.22 (1 H, m, quinoline-Ar), 8.82 - 8.89 (1 H, m, quinoline-Ar), 8.25 - 8.35 (1 H, m, quinoline-Ar), 7.83 - 7.88 (2 H, m, quinoline-Ar), 7.68 - 7.74 (1 H, m, Ar), 7.52 - 7.59 (1 H, m, Ar), 7.41 - 7.46 (1 H, m, Ar), 7.32 (2 H, s, Ar), 7.30 - 7.32 (2 H, m, Ar), 7.25 - 7.30 (2 H, m, Ar), 7.23 (1 H, br. s, O-H), 7.01 (1 H, d, J=9.0 Hz, benzyl-H), 2.35 (3 H, s, CH\(_3\)); \( \delta \)C (100 MHz, DMSO-\( d_6 \)) 166.65 (C=O), 150.6, 149.2, 143.1, 142.0, 138.9, 136.9, 132.5, 129.8, 129.6, 129.1, 128.5, 128.1, 127.9, 127.6, 125.3, 122.6, 118.2, 51.3 (benzyl-C), 21.8 (CH\(_3\)); \( m/\text{z} \) (ESI) 367 ([M-H], 100 %); HRMS (ESI\(^+\)) C\(_{24}\)H\(_{20}\)N\(_2\)NaO\(_2\), ([M+Na\(^+\)] \( \text{requires} \) 391.1417; found 391.1400.
**N-((5-Chloro-8-hydroxyquinolin-7-yl)(phenyl)methyl)-2-methylbenzamide S54**

Following general procedure 1, 5-chloro-8-quinolinol (359 mg, 2.0 mmol), o-toluamide (170 mg, 2.0 mmol) and benzaldehyde (406 µL, 4.0 mmol) gave S54 (445 mg, 55 %) as a white powder.

mp 213-215 °C; ν\textsubscript{max}/cm\textsuperscript{-1} 3284 (NH), 1637 (C=O), 730 (C-Cl); δ\textsubscript{H} (400 MHz, DMSO-d\textsubscript{6}) 10.44 (1 H, br. s., NH), 9.15 - 9.36 (1 H, m, quinoline-Ar), 8.90 - 9.03 (1 H, m, quinoline-Ar), 8.38 - 8.55 (1 H, m, quinoline-Ar), 7.86 (1 H, s, Ar), 7.68 - 7.77 (1 H, m, Ar), 7.29 - 7.42 (6 H, m, Ar), 7.20 - 7.29 (3 H, m, Ar), 6.99 (1 H, d, J=9.0 Hz, benzyl-H), 2.28 (3 H, s, CH\textsubscript{3}); δ\textsubscript{C} (100 MHz, DMSO-d\textsubscript{6}) 169.4 (C=O), 150.2, 150.1, 142.6, 139.6, 137.9, 136.0, 133.4, 131.2, 129.3, 127.9, 127.4, 126.4, 126.1, 125.8, 123.9, 119.5, 50.6 (benzyl-C), 20.2 (CH\textsubscript{3}); m/z (ESI\textsuperscript{-}) 401 ([M-H]-, 100 %); HRMS (ESI\textsuperscript{-}) C\textsubscript{24}H\textsubscript{18}ClN\textsubscript{2}O\textsubscript{2}, ([M-H]-) requires 401.1062; found 401.1067.

**N-((5-Chloro-8-hydroxyquinolin-7-yl)(phenyl)methyl)-3-methylbenzamide S55**

Following general procedure 1, 5-chloro-8-quinolinol (359 mg, 2.0 mmol), m-toluamide (170 mg, 2.0 mmol) and benzaldehyde (406 µL, 4.0 mmol) gave S55 (439 mg, 55 %) as a white powder.

mp 222-225 °C; ν\textsubscript{max}/cm\textsuperscript{-1} 3300 (NH), 1634 (C=O); δ\textsubscript{H} (400 MHz, DMSO-d\textsubscript{6}) \textsuperscript{1}H NMR 10.42 (1 H, br. s., NH), 9.15 - 9.27 (1 H, m, quinoline-Ar), 8.94 - 9.02 (1 H, m, quinoline-Ar), 8.43 - 8.53 (1 H, m, quinoline-Ar), 7.86 (1 H, s, Ar), 7.77 (1 H, s, Ar), 7.70 - 7.75 (2 H, m, Ar), 7.31 - 7.38 (6 H, m, Ar), 7.21 - 7.29 (1 H, m, Ar), 7.01 (1 H, d, J=8.5 Hz, benzyl-H), 2.23 - 2.43 (3 H, m, CH\textsubscript{3}); δ\textsubscript{C} (100 MHz, DMSO-d\textsubscript{6}) 166.9 (C=O), 150.4, 150.0, 142.5, 139.5, 138.4, 135.1, 133.4, 132.8, 129.3, 129.9, 128.9, 128.0, 127.9, 127.7, 126.0, 125.8, 125.7, 123.9, 119.4, 50.9 (benzyl-C), 21.8 (CH\textsubscript{3}); m/z (ESI\textsuperscript{-}) 401 ([M-H]-, 100 %); HRMS (ESI\textsuperscript{-}) C\textsubscript{24}H\textsubscript{18}ClN\textsubscript{2}O\textsubscript{2}, ([M-H]-) requires 401.1062; found 401.1068.
N-((5-Chloro-8-hydroxyquinolin-7-yl)(phenyl)methyl)-4-methylbenzamide S56

Following general procedure 1, 5-chloro-8-hydroxyquinolin (359 mg, 2.0 mmol), p-toluamide (170 mg, 2.0 mmol) and benzaldehyde (406 µL, 4.0 mmol) gave S56 (513 mg, 64 %) as white powder.

mp 237-240 °C; \( \nu_{\text{max}}/\text{cm}^{-1} \) 3321 (NH), 1634 (C=O); \( \delta_{\text{H}} \) (400 MHz, DMSO-\( d_6 \)) 10.41 (1 H, br. s., NH), 9.12 - 9.25 (1 H, m, quinoline-Ar), 7.80 - 7.93 (3 H, m, Ar), 7.65 - 7.77 (1 H, m, Ar), 7.31 - 7.35 (4 H, m, Ar), 7.23 - 7.31 (3 H, m, Ar), 7.02 (1 H, d, \( J=8.5 \) Hz, benzyl-H); \( \delta_{\text{C}} \) (100 MHz, DMSO-\( d_6 \)) 166.7 (C=O), 150.4, 150.0, 142.6, 142.4, 139.5, 133.4, 132.3, 129.7, 129.3, 128.5, 128.0, 127.9, 127.7, 126.0, 125.8, 123.9, 119.4, 50.9 (benzyl-C), 21.8 (CH\( _3 \)); \( m/z \) (ESI) 401 ([M-H], 100 %); HRMS (ESI) \( C_{24}H_{16}ClN_2O_2 \), ([M-H]) requires 401.1062; found 401.1062.

N-((5-Chloro-8-hydroxyquinolin-7-yl)(3-iodophenyl)methyl)benzamide S57

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 3-iodobenzaldehyde (928 mg, 4.0 mmol) gave S57 (659 mg, 64 %) as a white powder.

mp 226 - 228 °C; \( \nu_{\text{max}}/\text{cm}^{-1} \) 3300 (NH), 1632 (C=O), 692 (C-Cl); \( \delta_{\text{H}} \) (400 MHz, DMSO-\( d_6 \)) 10.54 (1 H, br. s., NH), 9.26 - 9.33 (1 H, m, quinoline-Ar), 8.94 - 8.99 (1 H, m, quinoline-Ar), 8.45 - 8.51 (1 H, m, quinoline-Ar), 7.90 - 7.97 (2 H, m, Ar), 7.87 (1 H, s, Ar), 7.68 - 7.76 (2 H, m, Ar), 7.61 - 7.66 (1 H, m, Ar), 7.53 - 7.59 (1 H, m, Ar), 7.46 - 7.52 (2 H, m, Ar), 7.35 - 7.40 (1 H, m, Ar), 7.13 - 7.19 (1 H, m, Ar), 6.96 (1 H, d, \( J=9.0 \) Hz, benzyl-H); \( \delta_{\text{C}} \) (100 MHz, DMSO-\( d_6 \)) 166.9 (C=O), 150.4, 150.2, 145.1, 139.5, 136.7, 136.4, 134.9, 133.4, 132.4, 131.6, 129.2, 128.5, 127.7, 127.3, 125.9, 125.3, 124.0, 119.6, 95.9, 50.5 (benzyl-C); \( m/z \) (ESI) 512 ([M-H]); HRMS (ESI') \( C_{24}H_{16}ClI_2N_2O_2 \), ([M+Na]) requires 536.9837; found 536.9825.
**N-((3-Bromophenyl)[8-hydroxy-5-nitroquinolin-7-yl]methyl)benzamide S58**

![Chemical structure](image)

Following general procedure 1, 8-hydroxy-5-nitroquinoline (380 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 3-bromobenzaldehyde (468 µL, 4.0 mmol) gave S58 (625 mg, 65 %) as a light-orange powder.

mp 264 °C; ν\textsubscript{max}/cm\textsuperscript{-1} 3287 (NH), 1635 (C=O); \(\delta\textsubscript{H}\) (400 MHz, DMSO-\(d_6\)) 9.38 - 9.55 (1 H, m, quinoline-Ar), 9.15 - 9.27 (1 H, m, quinoline-Ar), 8.94 - 9.06 (1 H, m, quinoline-Ar), 8.80 (1 H, s, quinoline-Ar), 7.83 - 8.00 (3 H, m, Ar), 7.53 - 7.60 (2 H, m, Ar), 7.46 - 7.53 (3 H, m, Ar), 7.38 - 7.43 (1 H, m, Ar), 7.30 - 7.37 (1 H, m, Ar), 6.97 (1 H, d, \(J=8.5\) Hz, benzyl-H); \(\delta\textsubscript{C}\) (100 MHz, DMSO-\(d_6\)) 166.9 (C=O), 158.9, 149.7, 144.6, 137.6, 134.8, 134.1, 132.4, 131.6, 131.1, 130.8, 129.2, 128.8, 128.5, 127.5, 126.2, 123.9, 122.8, 122.7, 50.8 (benzyl-C); \(m/z\) (ESI\textsuperscript{+}) 476 ([M-H]\textsuperscript{-}); HRMS (ESI\textsuperscript{+}) \(C_{23}H_{15}BrN_3O_4\) ([M-H]\textsuperscript{-}) requires 476.0251; found 476.0259.

**N-((3-Bromophenyl)[5-chloro-8-hydroxyquinolin-7-yl]methyl)-2-phenylacetamide S59**

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), 2-phenylacetamide (270 mg, 2.0 mmol) and 3-bromobenzaldehyde (468 µL, 4.0 mmol) gave S59 (456 mg, 47 %) as a white powder.

mp 169 °C; ν\textsubscript{max}/cm\textsuperscript{-1} 3273 (NH), 1638 (C=O), 694 (C-Cl); \(\delta\textsubscript{H}\) (400 MHz, DMSO-\(d_6\)) 10.48 (1 H, br. s., NH), 9.04 - 9.16 (1 H, m, quinoline-Ar), 8.91 - 9.00 (1 H, m, quinoline-Ar), 8.41 - 8.51 (1 H, m, quinoline-Ar), 7.65 - 7.76 (2 H, m, Ar), 7.39 - 7.53 (3 H, m, Ar), 7.16 - 7.35 (6 H, m, Ar), 6.65 (1 H, d, \(J=8.5\) Hz, benzyl-H), 3.37 (2 H, s, CH\(_2\)); \(\delta\textsubscript{C}\) (100 MHz, DMSO-\(d_6\)) 170.5 (C=O), 150.2, 145.3, 137.4, 137.1, 133.4, 131.6, 130.8, 130.3, 129.9, 129.0, 127.3, 127.1, 127.0, 126.8, 125.9, 125.3, 124.0, 122.6, 119.7, 50.3 (benzyl-C), 43.1 (CH\(_2\)); \(m/z\) (ESI\textsuperscript{+}) 481 ([M-H]\textsuperscript{-}); HRMS (ESI\textsuperscript{+}) \(C_{23}H_{15}BrClIN_2O_4\) ([M-H]\textsuperscript{-}) requires 479.0167; found 479.0157.
N-[(3-Bromophenyl)(5-chloro-8-hydroxyquinolin-7-yl)methyl]-4-chlorobenzamide S60

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), 4-chlorobenzamide (311 mg, 2.0 mmol) and 3-bromobenzaldehyde (468μL, 4.0 mmol) gave S60 (552 mg, 55 %) as a white powder. S60 was then stirred in a 4M HCl solution in dioxane for 1 h. The solvent was removed under reduced pressure to give the hydrochloride salt of S60 as a bright-yellow powder in quantitative yield.

mp 271 °C; νmax/cm⁻¹ 3302 (NH), 1635 (C=O); δH (400 MHz, DMSO-d₆) 9.36 - 9.48 (1 H, m, quinoline-Ar), 8.94 - 9.02 (1 H, m, quinoline-Ar), 8.44 - 8.57 (1 H, m, quinoline-Ar), 7.94 - 8.00 (2 H, m, Ar), 7.83 - 7.93 (1 H, m, Ar), 7.69 - 7.81 (1 H, m, Ar), 7.53 - 7.60 (2 H, m, Ar), 7.44 - 7.48 (1 H, m, Ar), 7.26 - 7.40 (2 H, m, Ar), 6.98 (1 H, d, J=8.5 Hz, benzyl-H); δC (100 MHz, DMSO-d₆) 165.9 (C=O), 150.2, 145.0, 139.1, 137.2, 134.1, 133.5, 131.6, 130.1, 130.6, 130.5, 129.3, 129.1, 127.4, 126.1, 125.5, 124.1, 119.8, 50.8 (benzyl-C); m/z (ESI⁺) 501 ([M+H]⁺); HRMS (ESI⁺) C₂₃H₁₅BrClN₂O₂, ([M+Na]⁺) requires 522.9586; found 522.9575.

N-[(3-Bromophenyl)(5-chloro-8-hydroxyquinolin-7-yl)methyl]-[1,1'-biphenyl]-4-carboxamide S61

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), biphenyl-4-carboxamide (394 mg, 2.0 mmol) and 3-bromobenzaldehyde (468μL, 4.0 mmol) gave S61 (718 mg, 66 %) as a white powder.

mp 236 °C; νmax/cm⁻¹ 3305 (NH), 1627 (C=O); δH (400 MHz, DMSO-d₆) 10.57 (1 H, br. s., NH), 9.31 - 9.43 (1 H, m, quinoline-Ar), 8.44 - 8.57 (1 H, m, quinoline-Ar), 7.94 - 8.00 (2 H, m, Ar), 8.01 - 8.09 (2 H, m, Ar), 7.83 - 7.93 (1 H, m, Ar), 7.69 - 7.81 (1 H, m, Ar), 7.53 - 7.60 (2 H, m, Ar), 7.44 - 7.48 (1 H, m, Ar), 7.28 - 7.35 (1 H, m, Ar), 7.03 (1 H, d, J=9.0 Hz, benzyl-H); δC (100 MHz, DMSO-d₆) 165.6 (C=O), 150.1, 150.2, 145.3, 144.0, 140.0, 139.5, 133.6, 133.4, 133.3, 131.6, 130.9, 129.9, 129.2, 129.0, 127.8, 127.5, 127.3, 126.0, 125.2, 124.0, 122.6, 119.6, 50.7 (benzyl-C); m/z (ESI⁺) 445 ([M+H]⁺); HRMS (ESI⁺) C₂₉H₁₉BrClN₂O₂, ([M+Na]⁺) requires 565.0289; found 565.0277.
Benzy[[(3-bromophenyl)[5-chloro-8-hydroxyquinolin-7-yl]methyl]carbamate S62

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzyl carbamate (302 mg, 2.0 mmol) and 3-bromobenzaldehyde (468 μL, 4.0 mmol) gave S62 (537 mg, 54 %) as a white powder.

mp 180 °C; \( \nu_{\text{max}} \) cm\(^{-1} \) 3305 (NH), 1684 (C=O); \( \delta_H \) (400 MHz, DMSO-\( \text{d}_6 \)) 10.55 (1 H, br. s., NH), 8.91 - 8.99 (1 H, m, quinoline-Ar), 8.49 - 8.57 (1 H, m, quinoline-Ar), 8.42 - 8.50 (1 H, s, Ar), 7.80 (1 H, s, Ar), 7.67 - 7.75 (1 H, m, Ar), 7.51 (1 H, s, Ar), 7.41 - 7.47 (1 H, m, Ar), 7.25 - 7.39 (6 H, m, Ar), 6.51 (1 H, d, J=9.5 Hz, benzyl-H), 5.08 (2 H, s, \( \text{CH}_2 \)); \( \delta_C \) (100 MHz, DMSO-\( \text{d}_6 \)) 156.6 (C=O), 150.2, 149.9, 145.5, 139.5, 137.7, 133.4, 131.6, 130.9, 129.1, 128.7, 126.8, 126.7, 125.9, 125.6, 124.0, 122.6, 119.8, 66.7 (\( \text{CH}_2 \)), 52.2 (benzyl-C); \( m/z \) (FI\(^+\)) 496 ([M]\(^+\)); HRMS (FI\(^+\)) \( \text{C}_{24}\text{H}_{18}\text{BrClN}_2\text{O}_3 \), ([M]\(^+\)) requires 496.0189; found 496.0206.

N-[(8-Hydroxy-5-nitroquinolin-7-yl)(phenyl)methyl]benzamide S63

Following general procedure 1, 5-nitroquinolin-8-ol (380 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and benzaldehyde (406 μL, 4.0 mmol) gave S63 (680 mg, 98 %) as an orange powder.

mp 259 - 261 °C; \( \nu_{\text{max}} \) cm\(^{-1} \) 3288 (NH), 1641 (C=O); \( \delta_H \) (400 MHz, DMSO-\( \text{d}_6 \)) 9.39 - 9.51 (1 H, m, quinoline-Ar), 9.12 - 9.23 (1 H, m, quinoline-Ar), 8.95 - 9.06 (1 H, m, quinoline-Ar), 8.80 (1 H, s, Ar), 7.91 - 7.98 (2 H, m, Ar), 7.84 - 7.91 (1 H, m, Ar), 7.52 - 7.59 (1 H, m, Ar), 7.45 - 7.52 (2 H, m, Ar), 7.33 - 7.41 (4 H, m, Ar), 7.23 - 7.33 (1 H, m, Ar), 7.01 (1 H, d, J=8.5 Hz, benzyl-H); \( \delta_C \) (100 MHz, DMSO-\( \text{d}_6 \)) 166.9 (C=O), 158.6, 149.9, 141.8, 137.7, 135.2, 135.0, 133.9, 132.3, 129.4, 129.2, 129.1, 128.5, 128.2, 128.1, 126.1, 124.6, 122.5, 51.0 (benzyl-C); \( m/z \) (ESI\(^+\)) 398 ([M-H], 100%); HRMS (ESI\(^+\)) \( \text{C}_{23}\text{H}_{18}\text{NaO}_{4} \), ([M+Na\(^+\)]) requires 422.1111; found 422.1101.
Following general procedure 1, 8-hydroxy-5-nitroquinoline (380 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and o-tolualdehyde (463 µL, 4.0 mmol) gave S64 (173 mg, 21%) as a brown powder.

mp 213 °C; \( \nu_{\text{max}}/\text{cm}^{-1} \) 3302 (NH), 1639 (C=O); 400 MHz, DMSO-\( d_6 \) 9.26 - 9.33 (1 H, m, quinoline-Ar), 9.15 - 9.23 (1 H, m, quinoline-Ar), 8.95 - 9.04 (1 H, m, quinoline-Ar), 8.62 (1 H, s, quinoline-Ar), 7.92 - 7.98 (2 H, m, Ar), 7.85 - 7.91 (1 H, m, Ar), 7.50 - 7.58 (1 H, m, Ar), 7.43 - 7.50 (2 H, m, Ar), 7.12 - 7.28 (4 H, m, Ar), 7.05 (1 H, d, J=8.5 Hz, benzyl-H), 2.31 (3 H, s, CH\(_3\)); 166.6 (C=O), 158.8, 149.9, 139.8, 137.6, 136.9, 134.9, 133.9, 132.3, 131.3, 129.1, 128.5, 128.3, 128.2, 127.9, 126.8, 126.1, 123.9, 122.6, 48.8 (benzyl-C), 19.6 (CH\(_3\)); m/z (ESI\(^{-}\)) 412 ([M-H]\(^{-}\); HRMS (ESI\(^{-}\)) C\(_{24}\)H\(_{19}\)N\(_3\)O\(_4\), ([M+Na\(^{+}\)]) requires 436.1268; found 436.1253.

Following general procedure 1, 8-hydroxy-5-nitroquinoline (380 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and m-tolualdehyde (472 µL, 4.0 mmol) gave S65 (556 mg, 67%) as a light-orange powder.

mp 217 °C; \( \nu_{\text{max}}/\text{cm}^{-1} \) 3271 (NH), 1636 (C=O); 400 MHz, DMSO-\( d_6 \) 9.31 - 9.47 (1 H, m, quinoline-Ar), 9.09 - 9.25 (1 H, m, quinoline-Ar), 8.94 - 9.05 (1 H, m, quinoline-Ar), 8.81 (1 H, s, quinoline-Ar), 7.91 - 7.99 (2 H, m, Ar), 7.85 - 7.91 (1 H, m, Ar), 7.52 - 7.58 (1 H, m, Ar), 7.45 - 7.52 (2 H, m, Ar), 7.22 - 7.28 (1 H, m, Ar), 7.14 - 7.21 (2 H, m, Ar), 7.06 - 7.12 (1 H, m, Ar), 6.98 (1 H, d, J=8.5 Hz, benzyl-H), 2.29 (3 H, s, CH\(_3\)); 166.9 (C=O), 158.5, 153.2, 149.9, 141.8, 138.5, 137.7, 135.2, 135.0, 133.9, 132.3, 129.3, 129.2, 129.1, 128.8, 128.5, 126.1, 125.4, 124.7, 122.5, 51.0 (benzyl-C), 22.0 (CH\(_3\)); m/z (ESI\(^{+}\)) 412 ([M+H]\(^{+}\); HRMS (ESI\(^{+}\)) C\(_{24}\)H\(_{19}\)N\(_3\)O\(_4\), ([M-H]\(^{-}\)) requires 412.1303; found 412.1307.
N-((8-Hydroxy-5-nitroquinolin-7-yl)(p-tolyl)methyl)benzamide S66

\[
\begin{align*}
\text{NO}_2 & \quad \text{N} \quad \text{OH} \\
\text{HO} & \quad \text{N} \quad \text{O} \\
\text{Me} & \quad \text{N} \quad \text{Me} \\
\end{align*}
\]

Following general procedure 1, 8-hydroxy-5-nitroquinoline (380 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and p-toluualdehyde (472 µL, 4.0 mmol) gave S66 (684 mg, 83%) as a light-orange powder.

mp 248 - 250 °C; \( \nu_{\text{max}}/\text{cm}^{-1} \) 3302 (NH), 1636 (C=O); \( \delta_\text{H} \) (400 MHz, DMSO-\( d_6 \)) 9.36 - 9.43 (1 H, m, quinoline-Ar), 9.13 - 9.20 (1 H, m, quinoline-Ar), 8.98 - 9.03 (1 H, m, quinoline-Ar), 8.79 (1 H, s, quinoline-Ar), 7.91 - 7.97 (2 H, m, Ar), 7.85 - 7.90 (1 H, m, Ar), 7.52 - 7.58 (1 H, m, Ar), 7.45 - 7.51 (2 H, m, Ar), 7.22 - 7.28 (2 H, m, Ar), 7.12 - 7.19 (2 H, m, Ar), 6.96 (1 H, \( J=8.5 \text{ Hz} \), benzyl-H), 2.27 (3 H, s, \( \text{CH}_3 \)); \( \delta_\text{C} \) (100 MHz, DMSO-\( d_6 \)) 166.9 (C=O), 158.5, 149.9, 141.8, 137.8, 137.7, 135.2, 135.1, 133.8, 132.3, 129.9, 129.1, 129.0, 128.5, 128.2, 126.1, 124.8, 122.5, 50.8 (benzyl-C), 21.5 (\( \text{CH}_3 \)); \( m/z \) (ESI) 412 ([M-H]); HRMS (ESI) \( C_{24}H_{18}N_3O_4 \) ([M-H]) requires 412.1303; found 412.1309.

\[ \text{N-} \quad \text{(8-Hydroxy-5-nitroquinolin-7-yl)(phenyl)methyl)-2-methylbenzamide S67} \]

\[
\begin{align*}
\text{NO}_2 & \quad \text{N} \quad \text{OH} \\
\text{HO} & \quad \text{N} \quad \text{O} \\
\text{Me} & \quad \text{N} \quad \text{Me} \\
\end{align*}
\]

Following general procedure 1, 8-hydroxy-5-nitroquinoline (380 mg, 2.0 mmol), \( o \)-toluamide (270 mg, 2.0 mmol) and benzaldehyde (406 µL, 4.0 mmol) gave S67 (669 mg, 81%) as a light-brown powder.

mp 244 - 246 °C; \( \nu_{\text{max}}/\text{cm}^{-1} \) 3278 (NH), 1636 (C=O); \( \delta_\text{H} \) (400 MHz, DMSO-\( d_6 \)) 9.39 - 9.47 (1 H, m, quinoline-Ar), 9.15 - 9.21 (1 H, m, quinoline-Ar), 8.99 - 9.05 (1 H, m, quinoline-Ar), 8.82 (1 H, s, quinoline-Ar), 7.84 - 7.92 (1 H, m, Ar), 7.31 - 7.43 (6 H, m, Ar), 7.22 - 7.30 (3 H, m, Ar), 6.95 (1 H, d, \( J=8.5 \text{ Hz} \), benzyl-H), 2.29 (3 H, s, \( \text{CH}_3 \)); \( \delta_\text{C} \) (100 MHz, DMSO-\( d_6 \)) 169.5 (C=O), 158.4, 149.9, 141.8, 137.8, 136.0, 135.2, 133.9, 131.2, 130.2, 129.4, 128.7, 128.1, 128.0, 126.4, 126.1, 124.8, 122.5, 50.8 (benzyl-C), 20.15 (\( \text{CH}_3 \)); \( m/z \) (ESI) 412 ([M-H]); HRMS (ESI) \( C_{24}H_{18}N_3O_4 \) ([M-H]) requires 412.1303; found 412.1303.
Following general procedure 1, 8-hydroxy-5-nitroquinoline (380 mg, 2.0 mmol), \textit{m}-toluamide (270 mg, 2.0 mmol) and benzaldehyde (406 µL, 4.0 mmol) gave 568 (261 mg, 32 %) as an orange powder.

Following general procedure 1, \textit{p}-toluamide (270 mg, 2.0 mmol) and benzaldehyde (406 µL, 4.0 mmol) gave 569 (563 mg, 68 %) as an orange powder.

\textit{N-}[(8-Hydroxy-5-nitroquinolin-7-yl)(phenyl)methyl]-3-methylbenzamide 568

\textit{N-}[(8-Hydroxy-5-nitroquinolin-7-yl)(phenyl)methyl]-4-methylbenzamide 569
**N-((8-Hydroxy-5-nitroquinolin-7-yl)(naphthalen-1-yl)methyl)benzamide S70**

Following general procedure 1, 8-hydroxy-5-nitroquinoline (380 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol), and 1-naphthaldehyde (544 µL, 4.0 mmol) gave S70 (532 mg, 59 %) as an off-white powder.

mp 237 °C; ν max/cm⁻¹ 3386 (NH), 1635 (C=O); δH (400 MHz, DMSO-d₆) 9.47 - 9.55 (1 H, m, quinoline-Ar), 9.19 - 9.24 (1 H, m, quinoline-Ar), 9.01 - 9.05 (1 H, m, quinoline-Ar), 8.71 (1 H, s, quinoline-Ar), 8.08 - 8.13 (1 H, m, Ar), 7.98 - 8.02 (1 H, m, Ar), 7.88 - 7.97 (4 H, m, Ar), 7.67 (1 H, d, J=8.5 Hz, benzyl-H), 7.51 - 7.60 (3 H, m, Ar), 7.45 - 7.51 (3 H, m, Ar), 7.39 - 7.43 (1 H, m, Ar); δC (100 MHz, DMSO-d₆) 165.8 (C=O), 157.8, 149.0, 136.8, 136.5, 134.1, 133.6, 133.1, 131.5, 131.0, 128.9, 128.4, 128.3, 128.2, 127.6, 126.7, 125.9, 125.4, 125.3, 124.9, 123.1, 122.9, 121.9, 47.3 (benzyl-C); m/z (ESI⁺) 448 ([M-H]⁺); HRMS (ESI⁺) C₁₇H₁₈N₃O₄, ([M-H]⁺) requires 448.1303; found 448.1301.

**N-((8-Hydroxy-5-nitroquinolin-7-yl)(naphthalen-2-yl)methyl)benzamide S71**

Following general procedure 1, 8-hydroxy-5-nitroquinoline (380 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol), and 2-naphthaldehyde (312 mg, 4.0 mmol) gave S71 (608 mg, 68 %) as an orange powder.

mp 216 - 217 °C; ν max/cm⁻¹ 3284 (NH), 1630 (C=O); δH (400 MHz, DMSO-d₆) 9.53 - 9.59 (1 H, m, quinoline-Ar), 9.19 - 9.23 (1 H, m, quinoline-Ar), 9.00 - 9.06 (1 H, m, quinoline-Ar), 8.86 (1 H, s, quinoline-Ar), 7.87 - 8.04 (6 H, m, Ar), 7.85 (1 H, s, Ar), 7.54 - 7.61 (2 H, m, Ar), 7.46 - 7.53 (5 H, m, Ar), 7.18 (1 H, d, J=8.5 Hz, benzyl-H); δC (100 MHz, DMSO-d₆) 166.1 (C=O), 158.0, 149.0, 138.5, 136.8, 134.1, 133.1, 132.8, 132.2, 131.5, 128.3, 128.3, 128.2, 127.9, 127.8, 127.6, 127.5, 126.3, 126.1, 126.0, 125.6, 125.3, 123.6, 121.8, 50.5 (benzyl-C); m/z (ESI⁺) 448 ([M-H]⁺); HRMS (ESI⁺) C₁₇H₁₈N₃O₄, ([M-H]⁺) requires 448.1303; found 448.1302.
**N-[(4-Bromophenyl)[8-hydroxy-5-nitroquinolin-7-yl]methyl]benzamide S72**

Following general procedure 1, 8-hydroxy-5-nitroquinoline (380 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 4-bromobenzaldehyde (740 mg, 4.0 mmol) gave S72 (643 mg, 67%) as a light-yellow powder.

mp 248 - 250 °C; νmax/cm⁻¹ 3222 (NH), 1637 (C=O); δH (400 MHz, DMSO-d₆) 9.39 - 9.52 (1 H, m, quinoline-Ar), 9.15 - 9.23 (1 H, m, quinoline-Ar), 8.98 - 9.04 (1 H, m, quinoline-Ar), 8.77 (1 H, s, quinoline-Ar), 7.86 - 7.98 (3 H, m, Ar), 7.53 - 7.59 (3 H, m, Ar), 7.45 - 7.52 (2 H, m, Ar), 7.29 - 7.36 (2 H, m, Ar), 6.95 (1 H, d, J=8.5 Hz, benzyl-H); δC (100 MHz, DMSO-d₆) 167.0 (C=O), 158.8, 149.8, 141.2, 137.6, 135.1, 134.9, 134.0, 132.4, 132.3, 130.5, 129.2, 128.9, 128.5, 126.2, 124.1, 122.7, 121.3, 50.7 (benzyl-C); m/z (ESI⁻) 476 ([M-H]⁻); HRMS (ESI⁻) C₂₃H₁₅BrN₃O₄ (M-H⁻) requires 476.0251; found 476.0247.

**N-[(4-Chlorophenyl)[8-hydroxy-5-nitroquinolin-7-yl]methyl]benzamide S73**

Following general procedure 1, 8-hydroxy-5-nitroquinoline (380 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 4-chlorobenzaldehyde (560 mg, 4.0 mmol) gave S73 (690 mg, 80%) as a light-yellow powder.

mp 246 - 249 °C; νmax/cm⁻¹ 3271 (NH), 1640 (C=O); δH (400 MHz, DMSO-d₆) 9.38 - 9.52 (1 H, m, quinoline-Ar), 9.14 - 9.24 (1 H, m, quinoline-Ar), 8.94 - 9.05 (1 H, m, quinoline-Ar), 8.78 (1 H, s, quinoline-Ar), 7.85 - 7.98 (3 H, m, Ar), 7.53 - 7.60 (1 H, m, Ar), 7.46 - 7.52 (2 H, m, Ar), 7.36 - 7.45 (4 H, m, Ar), 6.97 (1 H, d, J=8.5 Hz, benzyl-H); δC (100 MHz, DMSO-d₆) 167.0 (C=O), 158.8, 149.8, 140.8, 137.6, 135.1, 134.9, 134.0, 132.8, 132.4, 130.2, 129.3, 129.2, 128.9, 128.5, 126.2, 124.1, 122.7, 50.7 (benzyl-C); m/z (ESI⁻) 432 ([M-H]⁻); HRMS (ESI⁻) C₂₃H₁₅ClN₃O₄ (M-H⁻) requires 432.0757; found 476.0751.
Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and furfural (331μL, 4.0 mmol) gave \textbf{S74} (255 mg, 34 \%) as an off-white powder.

mp 245 °C; ν\textsubscript{max} /cm\textsuperscript{-1} 3309 (NH), 1639 (C=O), 691 (C-Cl); \textit{δ}\textsubscript{H} (400 MHz, DMSO-\textit{d}_6) 10.49 (1 H, br. s., NH), 9.32 - 9.42 (1 H, m, quinoline-Ar), 8.94 - 9.01 (1 H, m, quinoline-Ar), 8.45 - 8.53 (1 H, m, quinoline-Ar), 7.86 - 7.99 (3 H, m, Ar), 7.69 - 7.77 (1 H, m, Ar), 7.64 (1 H, s, Ar), 7.52 - 7.58 (1 H, m, Ar), 7.44 - 7.51 (2 H, m, Ar), 7.02 (1 H, d, J=8.5 Hz, benzyl-H), 6.37 - 6.44 (1 H, m, Ar), 6.08 - 6.15 (1 H, m, Ar); \textit{δ}\textsubscript{C} (100 MHz, DMSO-\textit{d}_6) 166.7 (C=O), 154.5, 150.6, 150.0, 143.6, 139.5, 134.8, 133.4, 132.4, 129.2, 128.5, 127.5, 126.1, 124.0, 123.7, 119.4, 111.4, 108.4, 45.6 (benzyl-C); m/z (ESI\textsuperscript{-}) 377 ([M-H]\textsuperscript{-}); HRMS (ESI\textsuperscript{+}) C\textsubscript{21}H\textsubscript{15}ClIN\textsubscript{2}NaO\textsubscript{3}, ([M+Na\textsuperscript{+}]\textsuperscript{+}) requires 401.0652; found 401.0663.

\textbf{N-((5-Chloro-8-hydroxyquinolin-7-yl)(furan-2-yl)methyl)benzamide S74}

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and furfural (331μL, 4.0 mmol) gave \textbf{S74} (255 mg, 34 \%) as an off-white powder.

mp 245 °C; ν\textsubscript{max} /cm\textsuperscript{-1} 3309 (NH), 1639 (C=O), 691 (C-Cl); \textit{δ}\textsubscript{H} (400 MHz, DMSO-\textit{d}_6) 10.49 (1 H, br. s., NH), 9.32 - 9.42 (1 H, m, quinoline-Ar), 8.94 - 9.01 (1 H, m, quinoline-Ar), 8.45 - 8.53 (1 H, m, quinoline-Ar), 7.86 - 7.99 (3 H, m, Ar), 7.69 - 7.77 (1 H, m, Ar), 7.64 (1 H, s, Ar), 7.52 - 7.58 (1 H, m, Ar), 7.44 - 7.51 (2 H, m, Ar), 7.02 (1 H, d, J=8.5 Hz, benzyl-H), 6.37 - 6.44 (1 H, m, Ar), 6.08 - 6.15 (1 H, m, Ar); \textit{δ}\textsubscript{C} (100 MHz, DMSO-\textit{d}_6) 166.7 (C=O), 154.5, 150.6, 150.0, 143.6, 139.5, 134.8, 133.4, 132.4, 129.2, 128.5, 127.5, 126.1, 124.0, 123.7, 119.4, 111.4, 108.4, 45.6 (benzyl-C); m/z (ESI\textsuperscript{-}) 377 ([M-H]\textsuperscript{-}); HRMS (ESI\textsuperscript{+}) C\textsubscript{21}H\textsubscript{15}ClIN\textsubscript{2}NaO\textsubscript{3}, ([M+Na\textsuperscript{+}]\textsuperscript{+}) requires 401.0652; found 401.0663.

\textbf{N-((5-Chloro-8-hydroxyquinolin-7-yl)(thiophen-2-yl)methyl)benzamide S75}

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 2-thiophenecarboxaldehyde (373 μL, 4.0 mmol) gave \textbf{S75} (205 mg, 26 \%) as a white powder.

mp 237 °C; ν\textsubscript{max} /cm\textsuperscript{-1} 3325 (NH), 1640 (C=O), 700 (C-Cl); \textit{δ}\textsubscript{H} (400 MHz, DMSO-\textit{d}_6) 10.53 (1 H, br. s., NH), 9.44 - 9.53 (1 H, m, quinoline-Ar), 8.96 - 9.01 (1 H, m, quinoline-Ar), 8.45 - 8.54 (1 H, m, quinoline-Ar), 8.00 (1 H, s, Ar), 7.91 - 7.97 (2 H, m, Ar), 7.70 - 7.78 (1 H, m, Ar), 7.53 - 7.59 (1 H, m, Ar), 7.42 - 7.53 (3 H, m, Ar), 7.20 (1 H, d, J=8.5 Hz, benzyl-H), 6.92 - 6.99 (1 H, m, Ar), 6.79 - 6.85 (1 H, m, Ar); \textit{δ}\textsubscript{C} (100 MHz, DMSO-\textit{d}_6) 166.7 (C=O), 150.3, 150.1, 146.5, 139.5, 134.9, 133.4, 132.4, 129.2, 128.5, 127.8, 127.3, 126.2, 126.1, 125.6, 124.0, 119.5, 47.0 (benzyl-C); m/z (ESI\textsuperscript{+}) 393 ([M-H\textsuperscript{-}]\textsuperscript{+}); HRMS (ESI\textsuperscript{+}) C\textsubscript{21}H\textsubscript{15}ClIN\textsubscript{2}NaO\textsubscript{3}S, ([M+Na\textsuperscript{+}]\textsuperscript{+}) requires 417.0435; found 417.0423.
**N-((5-Chloro-8-hydroxyquinolin-7-yl)(thiophen-3-yl)methyl)benzamide S76**

![Chemical structure](image)

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 3-thiophenecarboxaldehyde (373 μL, 4.0 mmol) gave **S76** (400 mg, 51 %) as an off-white powder.

mp 247 °C; ν\textsubscript{max}/cm\textsuperscript{-1} 3309 (NH), 1636 (C=O); δ\textsubscript{H} (400 MHz, DMSO-d\textsubscript{6}) 10.42 (1 H, br. s., NH), 9.24 - 9.36 (1 H, m, quinoline-Ar), 8.93 - 9.03 (1 H, m, quinoline-Ar), 8.39 - 8.55 (1 H, m, quinoline-Ar), 7.89 - 7.97 (3 H, m, Ar), 7.67 - 7.76 (1 H, m, Ar), 7.44 - 7.58 (4 H, m, Ar), 7.20 - 7.26 (1 H, m, Ar), 7.06 - 7.12 (1 H, m, Ar), 7.03 (1 H, d, J=9.0 Hz, benzyl-H); δ\textsubscript{C} (100 MHz, DMSO-d\textsubscript{6}) 166.7 (C=O), 150.1, 150.0, 143.5, 139.6, 135.1, 133.4, 132.2, 129.1, 128.5, 128.1, 127.5, 127.4, 126.2, 125.8, 123.8, 122.9, 119.4, 47.5 (benzyl-C); m/z (ESI) 393 ([M-H]); HRMS (ESI\textsuperscript{+}) C\textsubscript{21}H\textsubscript{15}ClIN\textsubscript{2}O\textsubscript{2}, ([M+Na]\textsuperscript{+}) requires 417.0435; found 417.0423.

**N-((5-Chloro-8-hydroxyquinolin-7-yl)(pyridin-2-yl)methyl)benzamide S77**

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 2-pyridinecarboxaldehyde (380 μL, 4.0 mmol) gave **S77** (235 mg, 30 %) as an off-white powder.

mp 196 - 198 °C; ν\textsubscript{max}/cm\textsuperscript{-1} 3306 (NH), 1646 (C=O); δ\textsubscript{H} (400 MHz, DMSO-d\textsubscript{6}) 10.46 (1 H, br. s., NH), 9.26 - 9.33 (1 H, m, quinoline-Ar), 8.94 - 8.99 (1 H, m, quinoline-Ar), 8.52 - 8.56 (1 H, m, quinoline-Ar), 8.44 - 8.49 (1 H, m, quinoline-Ar), 7.94 - 7.99 (2 H, m, Ar), 7.78 - 7.81 (1 H, m, Ar), 7.69 - 7.75 (1 H, m, Ar), 7.52 - 7.57 (1 H, m, Ar), 7.42 - 7.52 (3 H, m, Ar), 7.26 - 7.32 (1 H, m, Ar), 7.02 (1 H, d, J=8.0 Hz, benzyl-H); δ\textsubscript{C} (100 MHz, DMSO-d\textsubscript{6}) 166.8 (C=O), 160.7, 150.7, 149.9, 139.6, 137.9, 135.0, 133.3, 132.3, 129.2, 128.5, 128.3, 128.0, 125.9, 125.3, 123.9, 123.3, 122.8, 119.2, 52.8 (benzyl-C); m/z (ESI) 388 ([M-H]); HRMS (ESI\textsuperscript{+}) C\textsubscript{22}H\textsubscript{17}ClIN\textsubscript{2}O\textsubscript{2}, ([M+Na]\textsuperscript{+}) requires 390.1004; found 390.0997.
**N-((5-Chloro-8-hydroxyquinolin-7-yl)(pyridin-3-yl)methyl)benzamide 578**

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 3-pyridinecarboxaldehyde (366 μL, 4.0 mmol) gave 578 (495 mg, 63 %) as a white powder.

mp 266 - 227 °C; ν\text{max}/\text{cm}^{-1} 3309 (NH), 1638 (C=O); δ\text{H} (400 MHz, DMSO-d\text{6}) 10.57 (1 H, br. s., NH), 9.28 - 9.45 (1 H, m, quinoline-Ar), 8.88 - 9.02 (1 H, m, quinoline-Ar), 8.58 (1 H, s, quinoline-Ar), 8.43 - 8.53 (2 H, m, Ar), 7.85 - 8.02 (3 H, m, Ar), 7.65 - 7.81 (2 H, m, Ar), 7.44 - 7.62 (3 H, m, Ar), 7.29 - 7.41 (1 H, m, Ar), 7.02 (1 H, d, J=8.5 Hz, benzyl-H); δ\text{C} (100 MHz, DMSO-d\text{6}) 167.0 (C=O), 150.5, 150.2, 149.5, 149.1, 139.5, 137.8, 135.9, 134.9, 133.4, 132.4, 129.2, 128.5, 127.1, 126.0, 125.0, 124.5, 124.0, 119.7, 49.5 (benzyl-C); m/z (ESI\text{+}) 388 ([M-H]\text{+}); HRMS (ESI\text{+}) C\text{22}H\text{16}Cl\text{N}_3\text{O}_2, ([M+Na]\text{+}) requires 412.0823; found 412.0816.

**N-((5-Chloro-8-hydroxyquinolin-7-yl)(pyridin-4-yl)methyl)benzamide 579**

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 4-pyridinecarboxaldehyde (376 μL, 4.0 mmol) gave 579 (76 mg, 10 %) as a white powder.

mp 265 °C; ν\text{max}/\text{cm}^{-1} 3286 (NH), 1634 (C=O), 700 (C-Cl); δ\text{H} (400 MHz, DMSO-d\text{6}) 10.64 (1 H, br. s., NH), 9.31 - 9.41 (1 H, m, quinoline-Ar), 8.96 - 9.01 (1 H, m, quinoline-Ar), 8.52 - 8.56 (2 H, m, Ar), 8.46 - 8.51 (1 H, m, Ar), 7.92 - 7.99 (2 H, m, Ar), 7.81 (1 H, s) 7.71 - 7.78 (1 H, m, Ar), 7.54 - 7.60 (1 H, m, Ar), 7.44 - 7.53 (2 H, m, Ar), 7.30 - 7.35 (2 H, m, Ar), 7.01 (1 H, d, J=8.5 Hz, benzyl-H); δ\text{C} (100 MHz, DMSO-d\text{6}) 167.2 (C=O), 151.1, 150.8, 150.7, 150.2, 139.6, 134.8, 133.4, 132.4, 129.2, 128.5, 127.4, 126.1, 124.4, 124.1, 123.1, 119.6, 50.3 (benzyl-C); m/z (FI\text{+}) 389 ([M]\text{+}); HRMS (FI\text{+}) C\text{22}H\text{16}Cl\text{N}_3\text{O}_2, ([M]\text{+}) requires 389.0931; found 389.0926.
**N-((5-Chloro-8-hydroxyquinolin-7-yl)(5-hexylthiophen-2-yl)methyl)benzamide S80**

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 5-hexylthiophene-2-carboxaldehyde (771 μL, 4.0 mmol) gave S80 (331 mg, 35 %) as an off-white powder.

mp 145 °C; νmax/cm⁻¹ 3291 (NH), 1636 (C=O); δH (400 MHz, DMSO-d₆) 10.50 (1 H, br. s., NH), 9.36 - 9.51 (1 H, m, quinoline-Ar), 7.84 - 7.90 (1 H, m, Ar), 7.69 - 7.78 (1 H, m, Ar), 7.52 - 7.60 (1 H, m, Ar), 7.41 - 7.52 (2 H, m, Ar), 7.12 (1 H, d, J=8.5 Hz, benzyl-H), 6.52 - 6.68 (2 H, m, Ar), 2.61 - 2.75 (2 H, m, CH₂), 1.43 - 1.62 (2 H, m, CH₂), 1.10 - 1.37 (6 H, m), 0.73 - 0.90 (3 H, m, CH₃); δC (100 MHz, DMSO-d₆) 166.6 (C=O), 153.7, 151.0, 145.4, 143.6, 139.5, 134.9, 133.4, 132.4, 132.1, 129.2, 128.5, 127.4, 126.0, 125.6, 124.7, 124.0, 119.5, 47.1 (benzyl-C), 32.0, 31.8, 30.2, 29.0, 22.9, 14.8; m/z (Fl) 478 ([M⁺]; HRMS (Fl) C₂₇H₂₇ClN₂O₂S, ([M⁺]) requires 478.1486; found 478.1486.

**N-(Benzo[d]thiazol-2-yl)(5-chloro-8-hydroxyquinolin-7-yl)methyl)benzamide S81**

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and benzothiazole-2-carboxaldehyde (653 mg, 4.0 mmol) gave S81 (177 mg, 20 %) as an off-white powder.

mp 212 °C; νmax/cm⁻¹ 3255 (NH), 1640 (amide C=O); δH (400 MHz, DMSO-d₆) 10.79 (1 H, br. s., NH), 9.70 - 9.82 (1 H, m, quinoline-Ar), 9.46 - 9.57 (1 H, m, quinoline-Ar), 8.93 - 9.09 (1 H, m, quinoline-Ar), 8.47 - 8.58 (1 H, m, quinoline-Ar), 7.89 - 8.02 (4 H, m, Ar), 7.57 - 7.64 (1 H, m, Ar), 7.34 - 7.55 (5 H, m, Ar); δC (100 MHz, DMSO-d₆) 153.7 (C=O), 151.2, 150.3, 139.6, 135.7, 134.5, 134.1, 133.5, 132.8, 129.3, 128.6, 127.7, 127.2, 126.4, 124.3, 123.6, 123.2, 119.5, 50.3 (benzyl-C); m/z (ESI⁺) 444 ([M-H⁺); HRMS (ESI⁺) C₂₄H₁₆ClN₃NaO₂S, ([M+Na⁺]) requires 468.0544; found 468.0636.
$N\text{-}('5\text{-cyano}-8\text{-hydroxyquinolin}-7\text{-yl})(3\text{-methylthiophen}-2\text{-yl)methyl} \text{benzamide S82}$

Following general procedure 1, $\text{S82}$ (64 mg, 0.38 mmol), benzamide (46 mg, 0.38 mmol) and 3-methyl-2-thiophenecarboxaldehyde (81 μL, 0.76 mmol) gave $\text{S82}$ (130 mg, 86%) as a light-brown powder after purification via flash column chromatography (40 % - 60 % EtOAc, cyclohexane).

mp 202 °C; $\nu_{\text{max}}$/cm$^{-1}$ 3231 (NH), 1630 (C=O); δ$_{\text{H}}$ (400 MHz, DMSO-d$_6$) 9.30 - 9.41 (1 H, m, quinoline-Ar), 8.99 - 9.09 (1 H, m, quinoline-Ar), 8.43 - 8.51 (1 H, m, quinoline-Ar), 8.35 (1 H, s, quinoline-Ar), 7.90 - 7.98 (2 H, m, Ar), 7.82 - 7.87 (1 H, m, Ar), 7.53 - 7.61 (1 H, m, Ar), 7.45 - 7.52 (2 H, m, Ar), 7.28 - 7.32 (1 H, m, Ar), 7.17 (1 H, d, $J$=8.0 Hz, benzyl-H), 6.90 - 6.96 (1 H, m, Ar), 2.18 (3 H, s, CH$_3$); δ$_{\text{C}}$ (100 MHz, DMSO-d$_6$) 166.2 (C=O), 155.9, 150.5, 139.1, 138.0, 134.9, 134.5, 133.7, 132.0, 131.1, 128.8, 128.2, 128.1, 125.6, 125.0, 123.6, 123.8, 118.0, 97.9 (nitrite), 45.2 (benzyl-C), 14.0 (CH$_3$); m/z (ESI$^+$) 400 ([M+H]$^+$); HRMS (ESI$^+$) C$_{23}$H$_{18}$O$_2$N$_3$S, ([M+H]$^+$) requires 400.1114; found 400.1110.

$N\text{-}('5\text{-chloro}-8\text{-hydroxyquinolin}-7\text{-yl})(3\text{-methylthiophen}-2\text{-yl)methyl} \text{furan-2-carboxamide S83}$

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), 2-furancarboxamide (222 mg, 2.0 mmol) and 3-methyl-2-thiophenecarboxaldehyde (431 μL, 4.0 mmol) gave $\text{S83}$ (208 mg, 26%) as an off-white powder.

mp 157 °C; $\nu_{\text{max}}$/cm$^{-1}$ 3305 (NH), 1658 (amide C=O); δ$_{\text{H}}$ (400 MHz, DMSO-d$_6$) 10.51 (1 H, br. s., NH), 9.24 - 9.31 (1 H, m, quinoline-Ar), 8.92 - 9.00 (1 H, m, quinoline-Ar), 8.44 - 8.54 (1 H, m, quinoline-Ar), 7.83 - 7.93 (2 H, m, Ar), 7.67 - 7.78 (1 H, m, Ar), 7.24 - 7.30 (2 H, m, Ar), 7.09 (1 H, d, $J$=8.5 Hz, benzyl-H), 6.86 - 6.92 (1 H, m, Ar), 6.60 - 6.67 (1 H, m, Ar), 2.14 (3 H, s, CH$_3$); δ$_{\text{C}}$ (100 MHz, DMSO-d$_6$) 157.8 (C=O), 150.4, 150.1, 148.1, 146.3, 139.5, 135.1, 133.4, 131.3, 129.8, 129.1, 127.3, 126.0,
125.4, 124.0, 119.2, 115.0, 112.7, 45.1 (benzyl-C), 14.4 (CH₃); m/z (ESI⁺) 399 ([M+H]⁺); HRMS (ESI⁺) C₂₀H₁₅ClIN₂NaO₃S, ([M+Na]⁺) requires 421.0384; found 421.0370.

**N-[(5-Chloro-8-hydroxyquinolin-7-yl)[3-methylthiophen-2-yl]methyl]thiophene-3-carboxamide S84**

![Structure of S84](image)

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), S2 (254 mg, 2.0 mmol) and 3-methyl-2-thiophenecarbaldehyde (431 μL, 4.0 mmol) gave S84 (231 mg, 28 %) as an off-white powder.

mp 188 ºC; νmax/cm⁻¹ 3303 (NH), 1638 (C=O); δH (400 MHz, DMSO-d₆) 10.48 (1 H, br. s., NH), 9.08 - 9.20 (1 H, m, quinoline-Ar), 8.97 (1 H, s, quinoline-Ar), 8.42 - 8.56 (1 H, m, Ar), 8.31 (1 H, s, Ar), 7.87 (1 H, s, Ar), 7.69 - 7.78 (1 H, m, Ar), 7.59 (2 H, s, Ar), 7.23 - 7.30 (1 H, m, Ar), 7.11 (1 H, d, J=8.0 Hz, benzyl-H), 6.84 - 6.95 (1 H, m, Ar), 2.14 (3 H, s, CH₃); δC (100 MHz, DMSO-d₆) 162.0 (C=O), 150.5, 150.1, 139.8, 139.4, 137.9, 135.1, 133.4, 131.4, 130.3, 128.1, 127.5, 127.2, 126.0, 125.7, 124.0, 119.2, 45.4 (benzyl-C), 14.4 (CH₃); m/z (ESI⁺) 415 ([M+H]⁺); HRMS (ESI⁺) C₂₀H₁₅ClIN₂NaO₂S₂, ([M+Na]⁺) requires 437.0156; found 437.0141.

**N-[(5-Chloro-8-hydroxyquinolin-7-yl)[furan-3-yl]methyl]benzamide S85**

![Structure of S85](image)

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 3-furancarboxaldehyde (346 μL, 4.0 mmol) gave S85 (181 mg, 24 %) as a white powder.

mp 218 ºC; νmax/cm⁻¹ 3233 (NH), 1638 (C=O); δH (400 MHz, DMSO-d₆) 10.41 (1 H, br. s., NH), 9.20 - 9.26 (1 H, m, quinoline-Ar), 8.95 - 9.00 (1 H, m, quinoline-Ar), 8.46 - 8.51 (1 H, m, quinoline-Ar), 7.90 - 7.99 (3 H, m, Ar), 7.69 - 7.76 (1 H, m, Ar), 7.64 (1 H, s, Ar), 7.44 - 7.58 (4 H, m, Ar), 6.90 (1 H, d, J=8.5 Hz, benzyl-H), 6.52 (1 H, s, Ar); δC (100 MHz, DMSO-d₆) 166.3 (C=O), 149.7, 149.6, 144.1, 140.5, 139.2, 134.7, 133.0, 131.8, 128.7, 128.1, 126.9, 125.6, 125.4, 123.4, 119.0, 110.8, 43.6 (benzyl-C); m/z (ESI⁺) 379 ([M+H]⁺); HRMS (ESI⁺) C₂₄H₁₅ClIN₂NaO₃, ([M+Na]⁺) requires 401.0663; found 401.0652.
**N-[[3,3'-Bithiophen]-5-yl[5-chloro-8-hydroxyquinolin-7-yl]methyl]benzamide S86**

![Chemical structure](image)

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 3,3'-bithiophen-5-carboxaldehyde (777 mg, 4.0 mmol) gave S86 (373 mg, 39 %) as an off-white powder.

mp 213 °C; ν\textit{max}/cm\(^{-1}\) 3287 (NH), 1641 (C=O); δ\(\text{H}\) (400 MHz, DMSO-\(d_6\)) 10.57 (1 H, br. s., NH), 9.41 - 9.60 (1 H, s, Ar), 7.92 - 7.99 (2 H, m, Ar), 7.72 - 7.78 (1 H, m, Ar), 7.65 - 7.72 (2 H, m, Ar), 7.47 - 7.61 (4 H, m, Ar), 7.26 (1 H, s, Ar), 7.20 (1 H, d, \(J=8.5\) Hz, benzyl-H); δ\(\text{C}\) (100 MHz, DMSO-\(d_6\)) 166.7 (C=O), 150.5, 150.1, 147.4, 139.6, 137.6, 134.9, 133.4, 134.2, 129.2, 128.5, 127.6, 127.3, 127.2, 125.4, 125.2, 124.9, 120.1, 119.6, 47.2 (benzyl-C); \(m/z\) (ESI\(^+\)) 499 ([M+Na\(^+\)]; HRMS (ESI\(^+\)) C_{25}H_{17}ClIN_2O_2S_2, ([M+Na\(^+\)] requires 499.0312; found 499.0294.

**N-[[8-Hydroxy-2-methylquinolin-7-yl][3-methylthiophen-2-yl]methyl]benzamide S87**

Following general procedure 1, 8-hydroxyquinaldine (318 mg, 2 mmol), benzamide (242 mg, 2 mmol) and 3-methyl-2-thiophenecarboxaldehyde (431 μL, 4 mmol) gave S87 (264 mg, 34 %) as a light brown powder after purification via flash column chromatography (10 % - 20 % EtOAc, cyclohexane).

mp 189 °C; ν\textit{max}/cm\(^{-1}\) 3289 (NH), 1631 (C=O); δ\(\text{H}\) (400 MHz, DMSO-\(d_6\)) 9.27 - 9.38 (1 H, m, Ar), 8.16 - 8.22 (1 H, s, Ar), 7.89 - 7.96 (3 H, m, Ar), 7.64 - 7.72 (1 H, m, Ar), 7.50 - 7.60 (1 H, m, Ar), 7.42 - 7.47 (1 H, m, Ar), 7.26 (1 H, s, Ar), 7.20 (1 H, d, \(J=8.5\) Hz, benzyl-H); δ\(\text{C}\) (100 MHz, DMSO-\(d_6\)) 166.7 (C=O), 150.5, 150.1, 147.4, 139.6, 137.6, 134.9, 133.4, 134.2, 129.2, 128.5, 127.6, 127.3, 127.2, 125.4, 125.2, 124.9, 120.1, 119.6, 47.2 (benzyl-C); \(m/z\) (ESI\(^+\)) 389 ([M+H\(^+\)]; HRMS (ESI\(^+\)) C_{23}H_{21}O_2N_2S, ([M+H\(^+\)] requires 389.1318; found 389.1310.

---

60
Following general procedure 1, S4 (318 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 3-methyl-2-thiophenecarboxaldehyde (431 μL, 4.0 mmol) gave S88 (519 mg, 67 %) as a light-brown powder after purification via flash column chromatography (10 % - 20 % EtOAc, cyclohexane).

mp 160 °C; \( \nu_{\text{max}}/\text{cm}^{-1} \) 3274 (NH), 1636 (C=O); \( \delta_{\text{H}} \) (400 MHz, DMSO-\( d_6 \)) 10.05 (1 H, br. s, NH), 9.26 - 9.38 (1 H, m, quinoline-Ar), 8.67 - 8.80 (1 H, m, quinoline-Ar), 8.04 - 8.11 (1 H, m, quinoline-Ar), 7.88 - 7.96 (2 H, m, Ar), 7.68 - 7.76 (1 H, m, Ar), 7.51 - 7.56 (1 H, m, Ar), 7.43 - 7.50 (2 H, m, Ar), 7.31 - 7.37 (1 H, m, Ar), 7.20 - 7.27 (1 H, m, Ar), 7.11 - 7.18 (1 H, m, benzyl-H), 6.86 - 6.91 (1 H, m, Ar), 2.51 (3 H, s, quinoline-\( \text{CH}_3 \)), 2.16 (3 H, s, thiophene-\( \text{CH}_3 \)); \( \delta_{\text{C}} \) (100 MHz, DMSO-\( d_6 \)) 166.0 (C=O), 150.5, 150.3, 140.5, 136.8, 135.0, 134.7, 134.3, 131.7, 131.5, 130.8, 128.7, 128.6, 128.1, 127.1, 123.7, 123.3, 116.9, 45.6 (benzyl-C), 18.7 (quinoline-\( \text{CH}_3 \)), 14.1 (thiophene-\( \text{CH}_3 \)); m/z [ESI] 387 ([M-H] \(^-\)); HRMS (ESI\(^+\)) \( \text{C}_{23}\text{H}_{20}\text{N}_{2}\text{O}_{2}\text{S} \), ([M+Na\(^+\)] \(^+\)) requires 411.1138; found 411.1137.

Following general procedure 1, S5 (114 mg, 0.72 mmol), benzamide (87 mg, 0.72 mmol) and 3-methyl-2-thiophenecarboxaldehyde (155 μL, 4.0 mmol) gave S89 (142 mg, 51 %) as a light-brown powder after purification via flash column chromatography (10 % - 20 % EtOAc, cyclohexane).

mp 174 °C; \( \nu_{\text{max}}/\text{cm}^{-1} \) 3294 (NH), 1637 (C=O); \( \delta_{\text{H}} \) (400 MHz, DMSO-\( d_6 \)) 10.03 (1 H, br. s, NH), 9.27 - 9.42 (1 H, m, quinoline-Ar), 8.69 - 8.76 (1 H, m, quinoline-Ar), 7.90 - 7.98 (2 H, m, quinoline-Ar), 7.75 - 7.82 (1 H, m, Ar), 7.51 - 7.59 (2 H, m, Ar), 7.45 - 7.50 (2 H, m, Ar), 7.40 - 7.44 (1 H, m, Ar), 7.22 - 7.27 (1 H, m, Ar), 7.10 - 7.20 (1 H, m, benzyl-H), 6.87 - 6.93 (1 H, m, Ar), 2.67 (3 H, s, quinoline-\( \text{CH}_3 \)), 2.18 (3 H, s, thiophene-\( \text{CH}_3 \)); \( \delta_{\text{C}} \) (100 MHz, DMSO-\( d_6 \)) 166.1 (C=O), 150.6, 148.3, 145.0, 140.2, 138.1,
Following general procedure 1, S6 (159 mg, 1 mmol), benzamide (121 mg, 1 mmol) and 3-methyl-2-thiophenecarboxaldehyde (215 μL, 2.0 mmol) gave S90 (190 mg, 49 %) as an off-white powder after purification via flash column chromatography (10 % - 20 % EtOAc, cyclohexane).

mp 170 °C; ν\textsubscript{max}/cm\textsuperscript{-1} 3299 (NH), 1638 (C=O); \textdelta\textsubscript{H} (400 MHz, DMSO-\textit{d}_6) 9.84 (1 H, br. s., NH), 9.24 - 9.34 (1 H, m, quinoline-Ar), 8.81 - 8.95 (1 H, m, quinoline-Ar), 8.31 - 8.48 (1 H, m, quinoline-Ar), 7.85 - 8.02 (2 H, m, Ar), 7.58 - 7.64 (2 H, m, Ar), 7.51 - 7.57 (1 H, m, Ar), 7.43 - 7.50 (2 H, m, Ar), 7.21 - 7.27 (1 H, m, Ar), 7.11 - 7.18 (1 H, m, benzyl-H), 6.84 - 6.93 (1 H, m, Ar), 2.56 (3 H, s, quinoline-CH\textsubscript{3}), 2.17 (3 H, s, thiophene-CH\textsubscript{3}); \textdelta\textsubscript{C} (100 MHz, DMSO-\textit{d}_6) 166.1 (C=O), 148.3, 140.3, 138.7, 134.7, 133.5, 131.7, 130.8, 128.7, 128.1, 127.2, 127.0, 123.6, 123.3, 122.0, 45.6 (benzyl-C), 18.4 (quinoline-CH\textsubscript{3}), 14.1 (thiophene-CH\textsubscript{3}); m/z (ESI\textsuperscript{+}) 389 ([M+H]\textsuperscript{+}); HRMS (ESI\textsuperscript{+}) C\textsubscript{23}H\textsubscript{20}N\textsubscript{2}NaO\textsubscript{2}S, ([M+Na]\textsuperscript{+}) requires 411.1138; found 411.1142.

\textit{N}-((8-Hydroxy-5-methylquinolin-7-yl)(3-methylthiophen-2-yl)methyl)benzamide S90

Following general procedure 1, S7 (289 mg, 1.82 mmol), benzamide (220 mg, 1.82 mmol) and 3-methyl-2-thiophenecarboxaldehyde (392 μL, 3.64 mmol) gave S91 (403 mg, 57 %) as a light-brown powder after purification via flash column chromatography (10 % - 20 % EtOAc, cyclohexane).

mp 211 °C; ν\textsubscript{max}/cm\textsuperscript{-1} 2980 (NH), 1660 (C=O); \textdelta\textsubscript{H} (400 MHz, DMSO-\textit{d}_6) 8.96 - 9.03 (1 H, m, quinoline-Ar), 8.88 - 8.94 (1 H, m, quinoline-Ar), 8.26 - 8.38 (1 H, m, quinoline-Ar), 7.80 - 7.90 (2 H, m, Ar), 7.61 - 7.68 (2 H, m, Ar), 7.52 - 7.58 (1 H, m, Ar), 7.43 - 7.51 (2 H, m, Ar), 7.29 - 7.37 (1 H, m, Ar), 7.23 - 7.28 (1 H, m, benzyl-H), 6.81 - 6.90 (1 H, m, Ar), 3.18 (3 H, s, quinoline-CH\textsubscript{3}), 2.29 (3 H, s, thiophene-CH\textsubscript{3}); \textdelta\textsubscript{C} (100 MHz, DMSO-\textit{d}_6) 165.4 (C=O), 153.2, 149.4, 137.8, 137.5, 135.9, 135.0, 134.4, 132.1,

\textit{N}-((8-Hydroxy-6-methylquinolin-7-yl)(3-methylthiophen-2-yl)methyl)benzamide S91
132.0, 130.7, 129.0, 128.3, 127.7, 124.0, 123.7, 122.3, 118.0, 47.3 (benzyl-C), 15.9 (quinoline-CH$_3$), 14.3 (thiophene-CH$_3$); m/z (ESI$^+$) 389 ([M+H]$^+$); HRMS (ESI$^+$) C$_{23}$H$_{22}$O$_2$N$_2$S, ([M+H]$^+$) requires 389.1318; found 389.1310.

$N$-((8-Hydroxy-5-methoxyquinolin-7-yl)(3-methylthiophen-2-yl)methyl)benzamide S92

Following general procedure, S8 (146 mg, 0.83 mmol), benzamide (100 mg, 0.83 mmol) and 3-methyl-2-thiophenecarboxaldehyde (180 μL, 1.7 mmol) gave S92 (211 mg, 63%) as an off-white powder after purification via flash column chromatography (10% - 20% EtOAc, cyclohexane).

mp 254 °C; $\nu_{\text{max}}$/cm$^{-1}$ 3325 (NH), 1636 (C=O); $\delta$$_H$(400 MHz, DMSO-d$_6$) 9.53 (1 H, br. s., NH), 9.30 - 9.38 (1 H, m, quinoline-Ar), 8.82 - 8.95 (1 H, m, quinoline-Ar), 8.44 - 8.54 (1 H, m, quinoline-Ar), 7.89 - 7.96 (2 H, m, Ar), 7.53 - 7.61 (2 H, m, Ar), 7.45 - 7.52 (2 H, m, Ar), 7.39 (1 H, s, Ar), 7.22 - 7.27 (2 H, m, Ar), 6.85 - 6.92 (1 H, m, Ar), 3.92 (3 H, s, OC$_3$H$_3$), 2.20 (3 H, s, CH$_3$); $\delta$$_C$(100 MHz, DMSO-d$_6$) 166.1 (C=O), 149.3, 146.9, 143.8, 140.2, 138.7, 134.8, 134.5, 131.7, 130.9, 130.8, 128.7, 128.1, 123.8, 123.4, 121.6, 120.0, 105.6, 56.4 (OCH$_3$), 45.5 (benzyl-C), 14.1 (CH$_3$); m/z (ESI$^+$) 405 ([M+H]$^+$); HRMS (ESI$^+$) C$_{23}$H$_{20}$N$_2$O$_3$S, ([M+Na]$^+$) requires 427.1087; found 427.1082.

$N$-((4-Ethyl-8-hydroxyquinolin-7-yl)(3-methylthiophen-2-yl)methyl)benzamide S93

Following general procedure, S13 (277 mg, 1.6 mmol), benzamide (194 mg, 1.6 mmol) and 3-methyl-2-thiophenecarboxaldehyde (345 μL, 3.2 mmol) gave S93 (367 mg, 57%) as a light-brown powder after purification via flash column chromatography (10% - 20% EtOAc, cyclohexane).

mp 178 °C; $\nu_{\text{max}}$/cm$^{-1}$ 3280 (NH), 1638 (C=O); $\delta$$_H$(400 MHz, DMSO-d$_6$) 9.98 (1 H, br. s., NH), 9.26 - 9.40 (1 H, m, quinoline-Ar), 8.71 - 8.83 (1 H, m, quinoline-Ar), 7.90 - 7.98 (2 H, m, Ar), 7.73 - 7.80 (1 H, m, Ar), 7.58 - 7.64 (1 H, m, Ar), 7.51 - 7.57 (1 H, m, Ar), 7.40 - 7.50 (2 H, m, Ar), 7.23 - 7.29 (1 H, m, Ar), 7.15 (1 H, d, J=8.0 Hz, benzyl-H), 6.87 - 6.94 (1 H, m, Ar), 3.09 (2 H, q,
\[ J = 7.5 \text{ Hz}, \ CH_2CH_3, 2.18 \ (3 \ H, s, \ CH_3), 1.32 \ (3 \ H, t, J = 7.5 \text{ Hz}, \ CH_2CH_3); \delta_C \ (100 \text{ MHz, DMSO-}d_6) 166.1 \ (C=O), 150.7, 150.4, 148.5, 140.2, 138.3, 134.7, 134.4, 131.7, 128.6, 128.1, 127.2, 126.7, 124.0, 123.4, 120.9, 113.6, 45.6 \ (\text{benzyl-C}), 24.9 \ (\text{CH}_3CH), 14.5 \ (\text{CH}_3); \]

\[ \delta_C \ (100 \text{ MHz, DMSO-}d_6) 166.1 \ (C=O), 150.7, 150.4, 148.5, 140.2, 138.3, 134.7, 134.4, 131.7, 128.6, 128.1, 127.2, 126.7, 124.0, 123.4, 120.9, 113.6, 45.6 \ (\text{benzyl-C}), 24.9 \ (\text{CH}_3CH), 14.5 \ (\text{CH}_3); \]

\[ \text{δ}_C (100 \text{ MHz, DMSO-d}_6) 166.1 \ (C=O), 150.7, 150.4, 148.5, 140.2, 138.3, 134.7, 134.4, 131.7, 128.6, 128.1, 127.2, 126.7, 124.0, 123.4, 120.9, 113.6, 45.6 \ (\text{benzyl-C}), 24.9 \ (\text{CH}_3CH), 14.5 \ (\text{CH}_3); \]

\[ \text{m/z (ESI)} \ 401 \ (\text{[M-H]}); \ HRMS \ (ESI^+) \text{C}_{24}H_{23}O_2N_2S, (\text{[M+H]^+}) \text{ requires } 403.1475; \text{ found } 403.1469. \]

**N-((5-Chloro-8-hydroxyquinolin-7-yl)(3-methylthiophen-2-yl)methyl)-3-nitrobenzamide S94**

![Chemical structure of N-((5-Chloro-8-hydroxyquinolin-7-yl)(3-methylthiophen-2-yl)methyl)-3-nitrobenzamide S94](image)

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), 3-nitrobenzamide (332 mg, 2.0 mmol) and 3-methyl-2-thiohenecarboxaldehyde (431 μL, 4.0 mmol) gave **S94** (326 mg, 36 %) as an off-white powder.

mp 143 °C; \( \nu_{\text{max}} \text{ cm}^{-1} \) 3278 (NH), 1646 (C=O); \( \delta_H \ (400 \text{ MHz, DMSO-d}_6) \) 10.55 (1 H, br. s., NH), 9.69 - 9.79 (1 H, m, quinoline-Ar), 8.79 - 8.82 (1 H, m, quinoline-Ar), 8.46 - 8.54 (1 H, m, Ar), 8.29 - 8.44 (2 H, m, Ar), 7.86 (1 H, s, Ar), 7.77 - 7.83 (1 H, m, Ar), 7.68 - 7.76 (1 H, m, Ar), 7.66 - 7.67 (1 H, m, Ar), 7.17 (1 H, d, \( J = 8.0 \text{ Hz}, \text{benzyl-H})\), 6.86 - 6.98 (1 H, m, Ar), 2.16 (3 H, s, CH3); \( \delta_C \ (100 \text{ MHz, DMSO-d}_6) \) 166.4 (C=O), 150.3, 150.1, 139.4, 137.5, 135.2, 133.4, 131.7, 131.2, 130.8, 130.4, 129.8, 129.7, 129.1, 127.9,

\[ m/z (ESI) \ 929 \ (2M+Na)^{+}; \ HRMS \ (ESI^+) \text{C}_{22}H_{16}ClIN_2O_4S, (\text{[M+Na]^+}) \text{ requires } 476.0442; \text{ found } 476.0434. \]

**2-Chloro-N-((5-chloro-8-hydroxyquinolin-7-yl)(3-methylthiophen-2-yl)methyl)benzamide S95**

![Chemical structure of 2-Chloro-N-((5-chloro-8-hydroxyquinolin-7-yl)(3-methylthiophen-2-yl)methyl)benzamide S95](image)

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), 2-chlorobenzamide (311 mg, 2.0 mmol) and methyl 3-methyl-2-thiohenecarboxaldehyde (656 mg, 4.0 mmol) gave **S95** (290 mg, 33 %) as off-white powder.

mp 148 °C; \( \nu_{\text{max}} \text{ cm}^{-1} \) 3297 (NH), 1647 (C=O); \( \delta_H \ (400 \text{ MHz, DMSO-d}_6) \) 10.51 (1 H, br. s., NH), 9.49 - 9.57 (1 H, m, quinoline-Ar), 8.91 - 9.01 (1 H, m, quinoline-Ar), 8.45 - 8.54 (1 H, m, quinoline-Ar), 7.87 - 7.91 (1 H, m, Ar), 7.69 - 7.78 (1 H, m, Ar), 7.36 - 7.52 (4 H, m, Ar), 7.23 - 7.28 (1 H, m, Ar), 7.08 (1 H, d, \( J = 8.0 \text{ Hz}, \text{benzyl-H})\), 6.85 - 6.93 (1 H, m, Ar), 2.25 (3 H, s, CH3); \( \delta_C \ (100 \text{ MHz, DMSO-d}_6) \) 166.3 (C=O), 150.3, 150.1, 139.4, 137.5, 135.2, 133.4, 131.7, 131.2, 130.8, 130.4, 129.8, 129.7, 129.1, 127.9,
127.0, 126.0, 124.2, 124.0, 119.3, 45.4 (benzyl-\(\text{C}\)), 14.5 (\(\text{CH}_3\)); \(m/z\) (ESI) 441 ([M-H]); HRMS (ESI) \(\text{C}_{22}\text{H}_{17}\text{Cl}_2\text{N}_2\text{O}_2\text{S}\), ([M-H]) requires 441.0237; found 441.0233.

3-Chloro-\(N\)-(5-chloro-8-hydroxyquinolin-7-yl)(3-methylthiophen-2-yl)methyl)benzamide S96

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), 3-chlorobenzamide (311 mg, 2.0 mmol) and methyl 3-methyl-2-thiophencarboxaldehyde (656 mg, 4.0 mmol) gave S96 (266 mg, 30 %) as an off-white powder.

mp 172 °C; \(\nu_{\text{max}}/\text{cm}^{-1}\) 3300 (NH), 1642 (C=O); \(\delta_h\) (400 MHz, DMSO-\(\text{d}_6\)) 10.51 (1 H, br. s., NH), 9.42 - 9.50 (1 H, m, quinoline-Ar), 8.92 - 9.02 (1 H, m, quinoline-Ar), 8.46 - 8.53 (1 H, m, quinoline-Ar), 7.99 (1 H, s, Ar), 7.86 - 7.92 (1 H, m, Ar), 7.83 - 7.86 (1 H, m, Ar), 7.70 - 7.77 (1 H, m, Ar), 7.58 - 7.66 (1 H, m, Ar), 7.46 - 7.56 (1 H, m, Ar), 7.25 - 7.31 (1 H, m, Ar), 7.14 (1 H, d, \(J=8.0\) Hz, benzyl-H), 6.87 - 6.93 (1 H, m, Ar), 2.14 (3 H, s, \(\text{CH}_3\)); \(\delta_c\) (100 MHz, DMSO-\(\text{d}_6\)) 169.4 (C=O), 154.9, 154.4, 143.9, 143.8, 141.0, 139.5, 138.3, 137.8, 136.5, 135.7, 135.5, 132.5, 131.7, 131.5, 130.4, 129.6, 128.4, 123.6, 50.2 (benzyl-\(\text{C}\)), 18.7 (\(\text{CH}_3\)); \(m/z\) (ESI) 441 ([M-H]); HRMS (ESI) \(\text{C}_{22}\text{H}_{17}\text{Cl}_2\text{N}_2\text{O}_2\text{S}\), ([M-H]) requires 441.0237; found 441.0241.

\(N\)-(5-Chloro-8-hydroxyquinolin-7-yl)(3-methylthiophen-2-yl)methyl)-4-methoxybenzamide S97

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), 4-methoxybenzamide (302 mg, 2.0 mmol) and methyl 3-methyl-2-thiophencarboxaldehyde (431 \(\mu\)L, 4.0 mmol) gave S97 (339 mg, 39 %) as an off-white powder.

mp 163 - 164 °C; \(\nu_{\text{max}}/\text{cm}^{-1}\) 3305 (NH), 1637 (C=O); \(\delta_h\) (400 MHz, DMSO-\(\text{d}_6\)) 10.45 (1 H, br. s., NH), 9.14 - 9.19 (1 H, m, quinoline-Ar), 8.91 - 9.00 (1 H, m, quinoline-Ar), 8.45 - 8.53 (1 H, m, quinoline-Ar), 7.90 - 7.95 (2 H, m, Ar), 7.89 (1 H, s, Ar), 7.69 - 7.76 (1 H, m, Ar), 7.23 - 7.28 (1 H, m, Ar), 7.15 (1 H, d, \(J=8.0\) Hz, benzyl-H), 6.97 - 7.02 (2 H, m, Ar), 6.87 - 6.91 (1 H, m, Ar), 3.77 - 3.82 (3 H, m, thiophene-\(\text{CH}_3\)), 2.14 (3 H, s, \(\text{OCH}_3\)); \(\delta_c\) (100 MHz, DMSO-\(\text{d}_6\)) 165.9 (C=O), 162.6 (CO\(\text{CH}_3\)), 150.4, 150.0,
Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), thiophene-2-carboxamide (254 mg, 2.0 mmol) and methyl 3-methyl-2-thiophenecarboxaldehyde (431 μL, 4.0 mmol) gave S98 (179 mg, 22 %) as a white powder.

mp 172 °C; νmax/cm⁻¹ 3302 (NH), 1634 (C=O); δH (400 MHz, DMSO-d₆) 10.51 (1 H, br. s., NH), 9.31 - 9.40 (1 H, m, quinoline-Ar), 8.92 - 9.00 (1 H, m, quinoline-Ar), 8.43 - 8.56 (1 H, m, quinoline-Ar), 7.98 - 8.03 (1 H, m, Ar), 7.86 (1 H, s, Ar), 7.75 - 7.82 (1 H, m, Ar), 7.69 - 7.76 (1 H, m, Ar), 7.24 - 7.32 (1 H, m, Ar), 7.13 - 7.20 (1 H, m, Ar), 7.07 - 7.12 (1 H, m, Ar), 6.85 - 6.95 (1 H, m, Ar), 2.14 (3 H, s, CH₃); δC (100 MHz, DMSO-d₆) 161.2 (C=O), 150.5, 150.1, 140.1, 139.5, 139.4, 135.2, 133.4, 132.2, 131.4, 129.7, 128.8, 127.2, 126.0, 125.5, 124.1, 124.0, 119.2, 45.6 (benzyl-C), 14.4 (CH₃); m/z (ESI⁺) 415 ([M+H⁺]⁺); HRMS (ESI⁺) C₂₀H₁₆ClIN₂O₂S₂, ([M+H⁺]⁺) requires 415.0336; found 415.0330.

N-((5-Chloro-8-hydroxyquinolin-7-yl)(3-methylthiophen-2-yl)methyl)nicotinamide S99

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), nicotinamide (244 mg, 2.0 mmol) and 3-methyl-2-thiophenecarboxaldehyde (431 μL, 4.0 mmol) gave S99 (303 mg, 37 %) as an off-white powder.

mp 210 °C; νmax/cm⁻¹ 3173 (NH), 1667 (C=O); δH (400 MHz, DMSO-d₆) 10.54 (1 H, br. s., NH), 9.50 - 9.61 (1 H, m, quinoline-Ar), 9.04 - 9.07 (1 H, m, Ar), 8.94 - 9.00 (1 H, m, Ar), 8.69 - 8.74 (1 H, m, Ar), 8.45 - 8.55 (1 H, m, Ar), 8.20 - 8.30 (1 H, m, Ar), 7.86 (1 H, s, Ar), 7.69 - 7.79 (1 H, m, Ar), 7.46 - 7.58 (1 H, m, Ar), 7.26 - 7.32 (1 H, m, Ar), 7.16 (1 H, d, J=8.0 Hz, benzyl-H), 6.88 - 6.94 (1 H, m, Ar), 2.16 (3 H, s, CH₃); δC (100 MHz, DMSO-d₆) 165.1 (C=O), 152.3, 150.5, 150.1, 149.5, 139.5, 139.4, 136.2,
Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 6-(2-thienyl)-2-pyridinecarboxaldehyde (757 mg, 4.0 mmol) gave S100 (494 mg, 52 %) as an off-white powder.

mp 218 °C; νmax/cm⁻¹ 3294 (NH), 1650 (amide C=O); δH (400 MHz, DMSO-d₆) 10.50 (1 H, br. s., NH), 9.22 - 9.36 (1 H, m, quinoline-Ar), 8.03 (1 H, s, Ar), 7.91 - 8.00 (2 H, m, Ar), 7.88 (1 H, m, Ar), 7.77 - 7.85 (2 H, m, Ar), 7.68 - 7.75 (1 H, m, Ar), 7.47 - 7.67 (2 H, m, Ar), 7.24 - 7.32 (1 H, m, Ar), 7.09 - 7.21 (2 H, m, Ar), 6.93 - 7.04 (1 H, m, Ar); δC (100 MHz, DMSO-d₆) 160.2 (C=O), 158.6, 152.1, 150.8, 150.0, 145.2, 145.1, 139.6, 139.1, 138.9, 135.1, 137.4, 133.4, 132.5, 132.3, 129.5, 129.3, 128.3, 126.4, 123.9, 121.2, 119.2, 52.7 (benzyl-C); m/z [M⁺] 410 ([M+H⁺]; HRMS (ESI⁺) C₂₁H₁₆ClIN₃NaO₂S, ([M+Na⁺]) requires 321.0554; found 321.0527.

N-[(5-Chloro-8-hydroxyquinolin-7-yl)](6-(thiophen-2-y1)pyridin-2-yl)methyl)benzamide S100

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 6-(3-thienyl)-2-pyridinecarboxaldehyde (757 mg, 4.0 mmol) gave S101 (508 mg, 54 %) as an off-white powder.

mp 230 °C; νmax/cm⁻¹ 3299 (NH), 1634 (C=O); δH (400 MHz, DMSO-d₆) 10.60 (1 H, br. s., NH), 9.49 - 9.59 (1 H, m, quinoline-Ar), 8.89 - 9.10 (1 H, m, quinoline-Ar), 8.44 - 8.55 (1 H, m, quinoline-Ar), 8.03 (1 H, s, Ar), 7.92 - 8.00 (2 H, m, Ar), 7.71 - 7.77 (1 H, m, Ar), 7.54 - 7.61 (3 H, m, Ar), 7.47 - 7.53 (2 H, m, Ar), 7.31 - 7.39 (2 H, m, Ar), 7.24 - 7.30 (1 H, m, Ar), 7.21 (1 H, d, J=8.5 Hz, benzyl-H), 6.78 - 6.86 (1 H, m, Ar); δC (100 MHz, DMSO-d₆) 166.8 (C=O), 150.4, 150.1, 146.0, 143.4, 139.6, 134.8, 134.5,
133.5, 132.4, 130.0, 129.2, 128.5, 128.4, 127.4, 127.3, 126.1, 126.0, 125.2, 124.2, 124.1, 119.6, 47.2 (benzyl-C); m/z (EI+) 471 ([M]+); HRMS (EI+) C_{26}H_{18}ClN_{3}O_{2}S, ([M]+) requires 471.0808; found 471.0811.

\( N\)-(5-Chloro-8-hydroxyquinolin-7-yl)(5-phenylisoxazol-3-yl)methylbenzamide S102

\[
\text{Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 5-phenylisoxazole-3-carboxaldehyde (693 mg, 4.0 mmol) gave S102 (473 mg, 52 \%) as a white powder.}
\]

mp 235 °C; \( \nu_{\text{max}} \) cm\(^{-1} \) 3278 (NH), 1652 (C=O); \( \delta_{\text{H}} \) (400 MHz, DMSO-\( \text{d}_6 \)) 10.62 (1 H, br. s., NH), 9.47 - 9.59 (1 H, m, quinoline-Ar), 9.24 - 9.32 (1 H, m, quinoline-Ar), 8.96 - 9.03 (1 H, m, quinoline-Ar), 8.45 - 8.56 (1 H, m, Ar), 7.92 - 7.99 (2 H, m, Ar), 7.82 - 7.89 (2 H, m, Ar), 7.71 - 7.80 (1 H, m, Ar), 7.54 - 7.61 (1 H, m, Ar), 7.46 - 7.54 (5 H, m, Ar), 7.12 (1 H, d, \( J=8.5 \) Hz, benzyl-H), 7.07 (1 H, s, Ar); \( \delta_{\text{C}} \) (100 MHz, DMSO-\( \text{d}_6 \)) 170.1 (C=O), 166.9, 166.7, 165.7, 150.8, 150.1, 139.6, 134.7, 132.6, 131.3, 130.1, 129.2, 128.6, 128.5, 127.5, 126.5, 126.2, 124.1, 123.2, 119.5, 100.5, 45.0 (benzyl-C); m/z (EI+) 454 ([M-H]); HRMS (EI+) C_{26}H_{18}ClN_{3}O_{2}S, ([M+Na]+) requires 478.0929; found 478.0924.

\( N\)-(5-Chloro-8-hydroxyquinolin-7-yl)(4-phenyliothiophen-2-yl)methylbenzamide S103

\[
\text{Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 4-phenyliothiophene-2-carboxaldehyde (753 mg, 4.0 mmol) gave S103 (481 mg, 51 \%) as an off-white powder.}
\]

mp 237 °C; \( \nu_{\text{max}} \) cm\(^{-1} \) 3271 (NH), 1638 (C=O); \( \delta_{\text{H}} \) (400 MHz, DMSO-\( \text{d}_6 \)) 10.59 (1 H, br. s., NH), 9.42 - 9.62 (1 H, m, quinoline-Ar), 8.89 - 9.08 (1 H, m, quinoline-Ar), 8.39 - 8.55 (1 H, m, quinoline-Ar), 8.03 (1 H, s, Ar), 7.93 - 8.00 (2 H, m, Ar), 7.70 - 7.80 (2 H, m, Ar), 7.58 - 7.64 (2 H, m, Ar), 7.54 - 7.57 (1 H, m, Ar), 7.47 - 7.53 (2 H, m, Ar), 7.32 - 7.38 (2 H, m, Ar), 7.29 (1 H, s, Ar), 7.29 (1 H, s, Ar),
Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 5-phenylthiophene-2-carboxaldehyde (753 mg, 4.0 mmol) gave S104 (702 mg, 75 %) as a white powder.

mp 241 °C; \( \nu_{\text{max}}/\text{cm}^{-1} \) 3284 (NH), 1636 (C=O); \( \delta_{H} \) (400 MHz, DMSO-\( d_6 \)) 10.60 (1 H, br. s., NH), 9.42 - 9.64 (1 H, m, quinoline-Ar), 8.84 - 9.12 (1 H, m, quinoline-Ar), 8.39 - 8.58 (1 H, m, quinoline-Ar), 8.04 (1 H, s, Ar), 7.92 - 8.01 (2 H, m, Ar), 7.70 - 7.80 (1 H, m, Ar), 7.54 - 7.61 (3 H, m, Ar), 7.45 - 7.53 (2 H, m, Ar), 7.30 - 7.42 (3 H, m, Ar), 7.14 - 7.29 (2 H, m, Ar), 6.76 - 6.86 (1 H, m, Ar); \( \delta_{C} \) (100 MHz, DMSO-\( d_6 \)) 166.7 (C=O), 150.4, 150.1, 146.0, 143.4, 139.6, 134.5, 133.4, 132.4, 129.9, 129.2, 128.4, 127.4, 127.3, 126.1, 126.0, 125.2, 124.2, 124.0, 119.6, 47.2 (benzyl-C); \( m/z \) (ESI') 471 ([M+H]'); HRMS (ESI') \( \text{C}_{27}\text{H}_{19}\text{ClN}_{2}\text{O}_{2}\text{S}, ([M+Na]') \) requires 493.0748; found 493.0740.

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 5-phenyl-2-furaldehyde (689 mg, 4.0 mmol) gave S105 (508 mg, 56 %) as a white powder.

mp 238 °C; \( \nu_{\text{max}}/\text{cm}^{-1} \) 3290 (NH), 1635 (C=O); \( \delta_{H} \) (400 MHz, DMSO-\( d_6 \)) 10.56 (1 H, br. s., NH), 9.39 - 9.53 (1 H, m, quinoline-Ar), 8.93 - 9.02 (1 H, m, quinoline-Ar), 8.43 - 8.55 (1 H, m, quinoline-Ar), 7.91 - 8.01 (3 H, m, Ar), 7.69 - 7.78 (1 H, m, Ar), 7.61
- 7.68 (2 H, m, Ar), 7.53 - 7.59 (1 H, m, Ar), 7.45 - 7.52 (2 H, m, Ar), 7.33 - 7.43 (2 H, m, Ar), 7.19 - 7.30 (1 H, m, Ar), 7.07 (1 H, d, J=8.5 Hz, benzyl-H), 6.83 - 6.92 (1 H, m, Ar); δC (100 MHz, DMSO-d6) 166.8 (C=O), 154.3, 153.5, 150.7, 150.1, 139.5, 134.9, 133.4, 132.4, 131.1, 129.7, 129.2, 128.5, 128.3, 127.4, 126.1, 124.1, 124.0, 123.6, 119.4, 110.8, 107.4, 45.9 (benzyl-C); m/z (ESI+) 455 ([M+H]+); HRMS (ESI+) C27H19ClN2O3Na requires 477.0976; found 477.0961.

N-((5-Chloro-8-hydroxyquinolin-7-yl)(6-(3-nitrophenyl)pyridin-2-yl)methyl)benzamide S106

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 6-(3-nitrophenyl)-2-pyridin-2-ylcarboxaldehyde (912 mg, 4.0 mmol) gave S106 (584 mg, 71 %) as a white powder.

mp 243 °C; νmax/cm⁻¹ 3274 (NH), 1647 (C=O); δH (400 MHz, DMSO-d6) 10.54 (1 H, br. s., NH), 9.39 - 9.50 (1 H, m, quinoline-Ar), 9.14 - 9.26 (1 H, m, quinoline-Ar), 8.85 - 9.06 (1 H, m, quinoline-Ar), 8.50 - 8.62 (1 H, m, quinoline-Ar), 8.21 - 8.33 (1 H, m, Ar), 7.87 - 8.08 (6 H, m, Ar), 7.68 - 7.83 (1 H, m, Ar), 7.40 - 7.61 (4 H, m, Ar), 7.02 - 7.20 (1 H, m, Ar); δC (100 MHz, DMSO-d6) 167.0 (C=O), 166.8, 160.7, 159.2, 153.5, 153.4, 150.7, 150.0, 149.3, 140.9, 139.6, 139.5, 135.1, 134.7, 133.6, 132.5, 131.3, 129.7, 128.3, 128.0, 126.0, 123.9, 122.3, 120.9, 119.4, 52.8 (benzyl-C); m/z (ESI+) 509 ([M-H]+); HRMS (ESI+) C28H19ClN4NaO3 requires 533.0987; found 533.0979.

N-((5-Chloro-8-hydroxyquinolin-7-yl)(3-phenylisoxazol-5-yl)methyl)benzamide S107

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 3-phenylisoxazole-5-carboxaldehyde (693 mg, 4.0 mmol) gave S107 (450 mg, 49 %) as a white powder.

mp 260 °C; νmax/cm⁻¹ 3290 (NH), 1644 (C=O); δH (400 MHz, DMSO-d6) 10.75 (1 H, br. s., NH), 9.53 - 9.76 (1 H, m, quinoline-Ar), 8.90 - 9.10 (1 H, m, quinoline-Ar), 8.44 - 8.60 (1 H, m, quinoline-Ar), 7.95 - 8.02 (2 H, m, Ar), 7.93 (1 H, s, Ar); 7.83 - 7.91
Nat. Prod. Rep. 2023, 30, 71

(2 H, m, Ar), 7.73 - 7.80 (1 H, m, Ar), 7.55 - 7.64 (1 H, m, Ar), 7.42 - 7.54 (5 H, m, Ar), 7.13 - 7.23 (1 H, m, Ar), 6.94 (1 H, s, Ar);
\( \delta_c (100 \text{ MHz}, \text{DMSO}-d_6) 173.0 (\text{C=\text{N}}), 167.0 (\text{C=\text{O}}), 162.8, 151.0, 150.2, 139.6, 134.4, 133.5, 132.6, 131.1, 129.9, 129.2, 128.6, 127.5, 127.1, 126.5, 124.2, 122.1, 119.7, 102.1, 45.0 (\text{benzyl-}C); m/z (Ei+) 455 ([M]+); HRMS (Ei+) requires 455.1037; found 455.0306.

**N-((5-Fluoro-8-hydroxyquinolin-7-yl)(3-methylthiophen-2-yl)methyl)benzamide S108**

![N-((5-Fluoro-8-hydroxyquinolin-7-yl)(3-methylthiophen-2-yl)methyl)benzamide S108](image)

Following general procedure 1, 5-fluoro-8-hydroxyquinoline (326 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 3-methyl-2-thiophenecarboxaldehyde (431 \( \mu \)L, 4.0 mmol) gave S108 (305 mg, 39 %) as a light-brown powder.

mp 188 °C; \( \nu_{\text{max}}/\text{cm}^{-1} 3301 (\text{NH}), 1639 (\text{C=O}); \delta_h (400 \text{ MHz}, \text{DMSO}-d_6) 10.14 (1 H, br. s, NH), 9.25 - 9.36 (1 H, m, quinoline-Ar), 8.88 - 9.01 (1 H, m, quinoline-Ar), 8.38 - 8.47 (1 H, m, quinoline-Ar), 7.87 - 7.95 (2 H, m, Ar), 7.64 - 7.70 (1 H, m, Ar), 7.58 - 7.64 (1 H, m, Ar), 7.50 - 7.57 (1 H, m, Ar), 7.42 - 7.50 (2 H, m, Ar), 7.23 - 7.30 (1 H, m, Ar), 7.16 - 7.22 (1 H, m, benzyl-H), 6.89 (1 H, d, m, Ar), 2.17 (3 H, s, CH3); \( \delta_c (100 \text{ MHz}, \text{DMSO}-d_6) 166.5 (\text{C=O}), 150.2, 150.4, 147.4, 140.0, 135.0, 134.9, 132.2, 131.3, 130.0, 129.2, 129.1, 128.5, 124.4, 124.3, 124.0, 123.2, 110.9, 110.7, 45.8 (\text{benzyl-}C), 14.4 (\text{CH3}); m/z (ESi+) 391 ([M]+); HRMS (ESi+) C22H17FN5NaO8S, ([M+Na]+) requires 415.0873; found 415.0887.

**N-((5-Bromo-8-hydroxyquinolin-7-yl)(3-methylthiophen-2-yl)methyl)benzamide S109**

![N-((5-Bromo-8-hydroxyquinolin-7-yl)(3-methylthiophen-2-yl)methyl)benzamide S109](image)

Following general procedure 1, 5-bromo-8-hydroxyquinoline (448 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 3-methyl-2-thiophenecarboxaldehyde (431 \( \mu \)L, 4.0 mmol) gave S109 (186 mg, 21 %) as an off-white powder.

mp 152 °C; \( \nu_{\text{max}}/\text{cm}^{-1} 3304 (\text{NH}), 1639 (\text{C=O}); \delta_h (400 \text{ MHz}, \text{DMSO}-d_6) 10.53 (1 H, br. s., NH), 9.28 - 9.40 (1 H, m, quinoline-Ar), 8.89 - 8.98 (1 H, m, quinoline-Ar), 8.34 - 8.50 (1 H, m, quinoline-Ar), 8.06 (1 H, s, quinoline-Ar), 7.85 - 7.99 (2 H, m, Ar), 7.66 - 7.80 (1 H, m, Ar), 7.50 - 7.60 (1 H, m, Ar), 7.43 - 7.49 (2 H, m, Ar), 7.23 - 7.31 (1 H, m, Ar), 7.11 - 7.21 (1 H, m, benzyl-
Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 5-ethyl-2-thiophenecarboxaldehyde (500 μL, 4.0 mmol) gave S110 (362 mg, 43 %) as a light-brown powder.

mp 204 °C; \( \nu_{\text{max}} / \text{cm}^{-1} \) 3297 (NH), 1634 (C=O); \( \delta_H \) (400 MHz, DMSO-\( d_6 \)) 10.50 (1 H, br. s., NH), 9.39 - 9.49 (1 H, m, quinoline-Ar), 8.93 - 9.02 (1 H, m, quinoline-Ar), 8.45 - 8.53 (1 H, m, quinoline-Ar), 8.01 (1 H, s, quinoline-Ar), 7.90 - 7.96 (2 H, m, Ar), 7.69 - 7.78 (1 H, m, Ar), 7.52 - 7.59 (1 H, m, Ar), 7.43 - 7.52 (2 H, m, Ar), 7.12 (1 H, d, \( J=9.0 \) Hz, benzyl-H), 6.53 - 6.70 (2 H, m, Ar), 2.72 (2 H, q, \( J=7.5 \) Hz, CH\(_2\)), 1.17 (2 H, t, \( J=7.5 \) Hz, CH\(_3\)); \( \delta_C \) (100 MHz, DMSO-\( d_6 \)) 166.6 (C=O), 150.3, 150.1, 147.0, 143.5, 139.5, 134.9, 133.4, 132.4, 129.2, 128.5, 127.4, 126.0, 125.7, 125.6, 124.0, 119.5, 47.1 (benzyl-C), 23.7 (CH\(_2\)), 16.8 (CH\(_3\)); \( m/z \) (Fi) 422 ([M]+); HRMS (Fi) \( C_{23}H_{19}N_2O_2ClS, ([M]+) \) requires 422.0856; found 422.0865.

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 4,5-dimethylthiophene-2-carboxaldehyde (475 μL, 4.0 mmol) gave S111 (273 mg, 32 %) as an off-white powder.

mp 239 °C; \( \nu_{\text{max}} / \text{cm}^{-1} \) 3283 (NH), 1637 (C=O); \( \delta_H \) (400 MHz, DMSO-\( d_6 \)) 10.47 (1 H, br. s., NH), 9.26 - 9.45 (1 H, m, quinoline-Ar), 8.91 - 9.05 (1 H, m, quinoline-Ar), 8.39 - 8.56 (1 H, m, quinoline-Ar), 7.99 (1 H, s, Ar), 7.88 - 7.96 (2 H, m, Ar), 7.68 - 7.78 (1 H, m, Ar), 7.52 - 7.60 (1 H, m, Ar), 7.44 - 7.51 (2 H, m, Ar), 7.06 (1 H, d, \( J=8.5 \) Hz, benzyl-H), 6.47 (1 H, s) 2.22 (3 H, s, CH\(_3\)), 1.98 (3 H, s, CH\(_3\)); \( \delta_C \) (100 MHz, DMSO-\( d_6 \)) 166.6 (C=O), 150.2, 150.1, 141.1, 139.5, 134.9, 133.4, 133.1, 132.3, 129.2, 128.7,
Following general procedure 1, 5-bromo-8-hydroxyquinoline (448 mg, 2.0 mmol), 2-phenylacetamide (270 mg, 2.0 mmol) and 3-methyl-2-thiophenecarboxaldehyde (431 μL, 4.0 mmol) gave S112 (738 mg, 79%) as a white powder.

\[
\text{mp } 187 ^\circ \text{C; } \nu_{\text{max}}/\text{cm}^{-1} 3222 (\text{NH}), 1635 (\text{C}=\text{O}); \delta_{\text{H}} (400 \text{ MHz, DMSO-}d_6) 10.48 (1 \text{ H, br. s., NH}), 9.07 - 9.17 (1 \text{ H, m, quinoline-Ar}), 8.88 - 8.99 (1 \text{ H, m, quinoline-Ar}), 8.37 - 8.50 (1 \text{ H, s, quinoline-Ar}), 7.62 - 7.79 (1 \text{ H, m, Ar}), 7.17 - 7.36 (5 \text{ H, m, Ar}), 6.86 - 6.92 (1 \text{ H, m, Ar}), 6.83 (1 \text{ H, d, } J=8.0 \text{ Hz, benzyl-H}), 3.51 - 3.58 (2 \text{ H, m, C}_2\text{H}_5), 2.11 (3 \text{ H, s, C}_3\text{H}_3); \delta_{\text{C}} (100 \text{ MHz, DMSO-}d_6) 169.7 (\text{C}=\text{O}), 150.5, 149.4, 139.8, 139.2, 138.4, 135.7, 135.6, 134.6, 130.9, 129.8, 129.5, 129.4, 128.7, 126.8, 126.1, 123.9, 123.6, 108.8, 44.8 (\text{benzyl-C}), 42.5 (\text{C}_3\text{H}_5), 13.9 (\text{CH}_3); m/z (\text{ESI}^-) 465 ([M-H]^-); \text{HRMS (ESI)} C_{23}\text{H}_{19}\text{ClN}_2\text{NaO}_2\text{S}, ([\text{M+Na}]^-) \text{ requires 489.0243; found } 489.0242.
\]

\[\text{N-}((6\text{-Chloro-8-hydroxyquinolin-7-yl})(3\text{-methylthiophen-2-yl})\text{methyl})\text{benzamide S113}\]

Following general procedure 1, 5-bromo-8-hydroxyquinoline (448 mg, 2.0 mmol), 2-phenylacetamide (270 mg, 2.0 mmol) and 3-methyl-2-thiophenecarboxaldehyde (431 μL, 4.0 mmol) gave S113 (352 mg, 43%) as a light brown powder after purification via flash column chromatography (10% - 20% EtOAc, cyclohexane).

\[
\text{mp } 160 ^\circ \text{C; } \nu_{\text{max}}/\text{cm}^{-1} 3058 (\text{NH}), 1660 (\text{C}=\text{O}); \delta_{\text{H}} (400 \text{ MHz, DMSO-}d_6) 8.96 - 9.02 (1 \text{ H, m, quinoline-Ar}), 8.87 - 8.94 (1 \text{ H, m, quinoline-Ar}), 8.27 - 8.40 (1 \text{ H, m, quinoline-Ar}), 7.82 - 7.90 (2 \text{ H, m, Ar}), 7.61 - 7.69 (1 \text{ H, m, Ar}), 7.52 - 7.58 (1 \text{ H, m, Ar}), 7.44 - 7.51 (2 \text{ H, m, Ar}), 7.32 (1 \text{ H, d, } J=8.5 \text{ Hz, benzyl-H}), 7.24 - 7.28 (1 \text{ H, m, Ar}), 6.84 - 6.91 (1 \text{ H, m, Ar}), 2.29 (3 \text{ H, s, CH}_3); \delta_{\text{C}} (100 \text{ MHz, DMSO-}d_6) 165.4 (\text{C}=\text{O}), 153.2, 149.4, 137.9, 137.5, 135.9, 135.0, 134.4, 132.1, 132.0, 130.7, 129.0, 128.3, 127.7, 124.1,
\]
N-[(2,2'-Bithiophen]-5-yl(5-chloro-8-hydroxyquinolin-7-yl)methyl]benzamide S114

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 2,2'-bithiophen-5-carboxaldehyde (777 mg, 4.0 mmol) gave S114 (345 mg, 36 %) as a green-brown powder.

m/z (ESI⁻) 407 ([M-H]⁻); HRMS (ESI⁻) \(\text{C}_{22}\text{H}_{17}\text{O}_{2}\text{N}_{2}\text{ClNaS}, ([M+Na]⁻)\) requires 431.0592; found 431.0583.

N-((5-Chloro-8-hydroxyquinolin-7-yl)(3-methylthiophen-2-yl)methyl)isonicotinamide S115

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), isonicotinamide (244 mg, 2.0 mmol) and 3-methyl-2-thiophene-carboxaldehyde (431 µL, 4.0 mmol) gave S115 (415 mg, 51 %) as an off-white powder.

m/z (ESI⁺) 499 ([M+Na]⁺); HRMS (ESI⁺) \(\text{C}_{25}\text{H}_{17}\text{ClIN}_{2}\text{NaO}_{2}\text{S}_{2}, ([M+Na]⁺)\) requires 499.0312; found 499.0300.
122.3, 119.3, 45.9 (benzyl-\text{-}C), 14.4 (CH\text{)}_3; m/z (ESI\textsuperscript{+}) 817 ([2M-H\text{-}]); HRMS (ESI\textsuperscript{+}) C\textsubscript{23}H\textsubscript{19}ClIN\textsubscript{3}NaO\textsubscript{2}S, ([M+Na\textsuperscript{+}]) requires 432.0544; found 432.0531.

\textit{N-}((5-Chloro-8-hydroxyquinolin-7-yl)(4-methoxyphenyl)methyl)benzamide S116

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 4-methoxybenzaldehyde (486 µL, 4.0 mmol) gave S116 (662 mg, 79 \%) as a white powder.

mp 242 - 243 °C; \textit{v}\textsubscript{max}/cm\textsuperscript{-1} 3314 (NH), 1631 (C=O); \textit{δ}\textsubscript{H} (400 MHz, DMSO-\textit{d}_6) 10.36 (1 H, br. s., NH\text{)}, 9.15 - 9.25 (1 H, m, quinoline-Ar), 8.90 - 9.02 (1 H, m, quinoline-Ar), 8.39 - 8.55 (1 H, m, quinoline-Ar), 7.90 - 7.97 (2 H, m, Ar), 7.85 - 7.89 (1 H, m, Ar), 7.68 - 7.76 (1 H, m, Ar), 7.51 - 7.58 (1 H, m, Ar), 7.45 - 7.51 (2 H, m, Ar), 7.20 - 7.29 (2 H, m, Ar), 6.94 (1 H, d, J=8.5 Hz, benzyl-\text{-}H) 6.88 - 6.92 (2 H, m, Ar), 3.72 (3 H, s, O-CH\text{3}); \textit{δ}\textsubscript{C} (100 MHz, DMSO-\textit{d}_6) 166.8 (C=O), 159.2, 150.2, 150.0, 139.5, 135.2, 134.4, 133.4, 132.2, 129.2, 129.1, 128.4, 127.6, 126.3, 125.7, 123.8, 119.4, 114.7, 56.0 (O-CH\text{3}), 50.5 (benzyl-\text{-}C); m/z (ESI\textsuperscript{+}) 417 ([M-H\text{-}], 100 \%); HRMS (ESI\textsuperscript{+}) C\textsubscript{24}H\textsubscript{19}ClIN\textsubscript{3}NaO\textsubscript{3}, ([M+Na\textsuperscript{+}]) requires 441.0976; found 441.0963.

\textit{N-}((5-Chloro-8-hydroxyquinolin-7-yl)(3-(trifluoromethoxy)phenyl)methyl)benzamide S117

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 3-trifluoromethoxybenzaldehyde (535 µL, 4.0 mmol) gave S117 (682 mg, 72 \%) as a white powder.

mp 210 °C; \textit{v}\textsubscript{max}/cm\textsuperscript{-1} 3297 (NH), 1634 (C=O), 680 (C-Cl); \textit{δ}\textsubscript{H} (400 MHz, DMSO-\textit{d}_6) 10.56 (1 H, br. s., NH\text{)}, 9.29 - 9.40 (1 H, m, quinoline-Ar), 8.93 - 9.00 (1 H, m, quinoline-Ar), 8.42 - 8.53 (1 H, m, quinoline-Ar), 7.91 - 7.98 (2 H, m, Ar), 7.86 (1 H, s, Ar), 7.70 - 7.77 (1 H, m, Ar), 7.53 - 7.59 (1 H, m, Ar), 7.45 - 7.52 (3 H, m, Ar), 7.35 - 7.40 (1 H, m, Ar), 7.32 (1 H, s, Ar), 7.25 - 7.30 (1 H, m, Ar), 7.05 (1 H, d, J=9.0 Hz, benzyl-\text{-}H); \textit{δ}\textsubscript{C} (100 MHz, DMSO-\textit{d}_6) 167.0 (C=O), 150.6, 150.2, 149.4, 145.3, 139.5, 134.9,
7-{Amino(3-bromophenyl)methyl}-5-chloroquinolin-8-ol bis(2,2,2-trifluoroacetate) S118

Trifluoroacetic acid (83 μL, 1 mmol) was added dropwise to a stirring suspension of 159 (100 mg, 0.22 mmol) in CH$_2$Cl$_2$ (10 mL). After 30 min, the solvent was removed under reduced pressure. The residue was dried under vacuum to give S118 (118 mg, 100%) as a bright-yellow solid.

mp 107 °C; $\nu_{\text{max}}$/cm$^{-1}$ 1666 (C=O); $\delta_H$ (400 MHz, DMSO-d$_6$) 8.48 - 8.57 (1 H, m, NH$_3$), 7.88 (1 H, s, Ar), 7.77 - 7.83 (1 H, m, Ar), 7.73 - 7.76 (1 H, m, Ar), 7.54 - 7.61 (1 H, m, Ar), 7.35 - 7.47 (2 H, m, Ar), 7.11 - 7.28 (3 H, m, Ar), 6.06 (1 H, s, benzyl-H); $\delta_C$ (100 MHz, DMSO-d$_6$) 151.1, 150.6, 140.6, 139.6, 133.6, 132.3, 131.9, 130.8, 129.8, 129.1, 127.3, 126.2, 124.7, 122.8, 120.8, 120.0, 52.2 (benzyl-C), 21.9 (CF$_3$); $m/z$ (EI$^+$) 362 ([M]$^+$); HRMS (EI$^+$) C$_{16}$H$_{12}$BrClIN$_2$O, ([M]$^+$) requires 361.9822; found 361.9809.

$N$-{(3-Bromophenyl)(5-chloro-8-hydroxyquinolin-7-yl)methyl}-3-methoxybenzamide S119

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), 3-methoxybenzamide (302 mg, 2.0 mmol) and 3-bromobenzaldehyde (468 μL, 4.0 mmol) gave S119 (668 mg, 67 %) as a white powder.

mp 178 °C; $\nu_{\text{max}}$/cm$^{-1}$ 3306 (NH), 1634 (C=O); $\delta_H$ (400 MHz, DMSO-d$_6$) 10.55 (1 H, br. s., NH), 9.22 - 9.35 (1 H, m, quinoline-Ar), 8.92 - 9.03 (1 H, m, quinoline-Ar), 8.40 - 8.56 (1 H, m, quinoline-Ar), 7.85 (1 H, s, quinoline-Ar), 7.69 - 7.78 (1 H, m, Ar), 7.45 - 7.56 (4 H, m, Ar), 7.38 - 7.44 (1 H, m, Ar), 7.29 - 7.38 (2 H, m, Ar), 7.09 - 7.16 (1 H, m, Ar), 6.99 (1 H, d, J=8.5 Hz, benzyl-H), 3.81 (3 H, s, OCH$_3$); $\delta_C$ (100 MHz, DMSO-d$_6$) 166.6 (C=O), 160.0, 150.5, 150.2, 145.2, 139.5, 136.3, 133.4, 131.6, 130.9,
Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 3,4-dimethoxybenzaldehyde (444 mg, 4.0 mmol) gave **S120** (690 mg, 77 %) as a white powder.

mp 234 ⁰C; ν\text{max}/cm⁻¹ 3294 (NH), 1632 (C=O); δ\text{H} (400 MHz, DMSO-d₆) 10.37 (1 H, br. s., NH), 9.10 - 9.27 (1 H, m, quinoline-Ar), 8.88 - 9.02 (1 H, m, quinoline-Ar), 8.41 - 8.53 (1 H, m, quinoline-Ar), 7.88 - 7.95 (2 H, m, Ar), 7.86 (1 H, s, Ar), 7.65 - 7.76 (1 H, m, Ar), 7.51 - 7.58 (1 H, m, Ar), 7.44 - 7.51 (2 H, m, Ar), 7.02 (1 H, d, J=8.5 Hz, benzyl-H) 6.88 - 6.96 (2 H, m, Ar), 6.80 - 6.86 (1 H, m, Ar), 3.73 (3 H, s, OCH₃), 3.72 (3 H, s, OCH₃); δ\text{C} (100 MHz, DMSO-d₆) 166.4 (C=O), 149.9, 149.6, 149.2, 148.4, 139.1, 134.9, 134.5, 133.0, 131.8, 128.8, 128.1, 127.2, 126.0, 125.3, 123.4, 119.8, 118.9, 112.2, 111.7, 56.0 (2x OCH₃), 50.5 (benzyl-C); m/z (ESI⁺) 447 ([M-H]⁻); HRMS (ESI⁺) C₂₅H₂₁ClaN₂O₂, ([M+Na⁺] requires 471.1082; found 471.1076.

Following general procedure 1, 8-hydroxy-5-nitroquinoline (380 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 4-methoxybenzaldehyde (486 µL, 4.0 mmol) gave **S121** (459 mg, 53 %) as an orange powder.

mp 204 ⁰C; ν\text{max}/cm⁻¹ 3250 (NH), 1637 (C=O); δ\text{H} (400 MHz, DMSO-d₆) 9.31 - 9.45 (1 H, m, quinoline-Ar), 9.08 - 9.23 (1 H, m, quinoline-Ar), 8.92 - 9.06 (1 H, m, quinoline-Ar), 8.81 (1 H, s, quinoline-Ar), 7.91 - 7.97 (2 H, m, Ar), 7.84 - 7.90 (1 H, m, Ar), 7.51 - 7.57 (1 H, m, Ar), 7.45 - 7.51 (2 H, m, Ar), 7.25 - 7.33 (2 H, m, Ar), 6.88 - 6.96 (3 H, m, benzyl-H and Ar overlap), 3.72 (3 H, s, OCH₃); δ\text{C} (100 MHz, DMSO-d₆) 166.8 (C=O), 159.3, 158.4, 154.6, 149.9, 137.7, 135.1, 133.8, 133.7, 132.3, 129.5, 129.1,
128.9, 128.5, 126.1, 125.0, 114.7, 56.0 (OCH$_3$), 50.6 (benzyl-CH); $m/z$ (ESI$^+$) 428 ([M-H]$^-$); HRMS (ESI$^+$) C$_{24}$H$_{19}$N$_3$NaO$_5$,
([M+Na]$^+$) requires 452.1217; found 452.1212.

**N-((3,4-Dimethoxyphenyl)(8-hydroxyquinolin-7-yl)methyl)benzamide S122**

Following general procedure 1, 8-hydroxyquinoline (290 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 3,4-dimethoxybenzaldehyde (664 mg, 4.0 mmol) gave S122 (176 mg, 21%) as a white powder.

mp 174 °C; $\nu_{\text{max}}$/cm$^{-1}$ 3312 (NH), 1633 (C=O); $\delta_{\text{H}}$ (400 MHz, DMSO-d$_6$) 9.12 - 9.19 (1 H, m, quinoline-Ar), 8.81 - 8.90 (1 H, m, quinoline-Ar), 8.26 - 8.34 (1 H, m, quinoline-Ar), 7.88 - 7.96 (2 H, m, quinoline-Ar), 7.69 - 7.74 (1 H, m, Ar), 7.50 - 7.57 (2 H, m, Ar), 7.41 - 7.50 (3 H, m, Ar), 7.00 - 7.02 (1 H, m, benzyl-H), 6.87 - 6.94 (2 H, m, Ar), 6.79 - 6.85 (1 H, m, Ar), 7.31 (3 H, s, CH$_3$), 3.69 (3 H, s, CH$_3$); $\delta_{\text{C}}$ (100 MHz, DMSO-d$_6$) 166.7 (C=O), 150.5, 149.5, 149.1, 148.7, 138.9, 136.9, 135.5, 135.5, 132.6, 129.8, 129.1, 128.4, 128.4, 127.7, 125.6, 120.4, 118.1, 112.5, 112.3, 56.4 (OCH$_3$), 56.4 (OCH$_3$), 51.3 (benzyl-C); $m/z$ (ESI$^+$) 437 ([M+Na]$^+$); HRMS (ESI$^+$) C$_{25}$H$_{22}$N$_2$NaO$_4$, ([M+Na]$^+$) requires 437.1472; found 437.1467.

**N-((3,4-Dimethoxyphenyl)(8-hydroxyquinolin-7-yl)methyl)-2-phenylacetamide S123**

Following general procedure 1, 8-hydroxyquinoline (290 mg, 2.0 mmol), 2-phenylacetamide (270 mg, 2.0 mmol) and 3,4-dimethoxybenzaldehyde (644 mg, 4.0 mmol) gave S123 (445 mg, 52%) as a white powder.

mp 182 °C; $\nu_{\text{max}}$/cm$^{-1}$ 3292 (NH), 1638 (C=O); $\delta_{\text{H}}$ (400 MHz, DMSO-d$_6$) 9.93 (1 H, br. s, NH), 8.90 - 8.97 (1 H, m, quinoline-Ar), 8.81 - 8.88 (1 H, m, quinoline-Ar), 8.27 - 8.33 (1 H, m, quinoline-Ar), 7.50 - 7.57 (2 H, m, Ar), 7.39 - 7.43 (1 H, m, Ar), 7.25 - 7.32 (4 H, m, Ar), 6.86 - 6.91 (2 H, m, Ar), 6.80 - 6.85 (1 H, m, Ar), 6.66 - 6.70 (1 H, m, Ar), 6.64 (1 H, d, $J$=8.5 Hz, benzyl-H), 3.68 (3 H, s, OCH$_3$), 3.63 (3 H, s, OCH$_3$), 3.37 (2 H, s, CH$_2$); $\delta_{\text{C}}$ (100 MHz, DMSO-d$_6$) 173.1 (C=O), 170.2, 150.3, 149.5, 149.2, 148.6, 138.9, 137.4, 136.9, 135.7, 129.9, 129.0, 128.3, 127.2, 125.6, 122.6, 119.9, 118.1, 112.5, 111.7, 56.4 (OCH$_3$), 56.2 (OCH$_3$), 50.5 (benzyl-C); $m/z$ (ESI$^+$) 429 ([M+H]$^+$); HRMS (ESI$^+$) C$_{26}$H$_{23}$N$_2$NaO$_4$, ([M+Na]$^+$) requires 451.1628; found 451.1624.
N-((5-Chloro-8-hydroxyquinolin-7-yl)[3-methoxyphenyl]methyl)benzamide S124

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 3-methoxybenzaldehyde (487 µL, 4.0 mmol) gave S124 (635 mg, 76 %) as white powder. 255 was then stirred in a 4M HCl solution in dioxane for 1 h. The solvent was removed under reduced pressure to give the hydrochloride salt of S124 as a bright-yellow powder in quantitative yield. mp 250 °C; ν\textsubscript{max}/cm\textsuperscript{-1} 3288 (NH), 1641 (C=O); δ\textsubscript{H} (400 MHz, DMSO-d\textsubscript{6}) 10.13 (1 H, br. s, NH), 9.21 - 9.33 (1 H, m, quinoline-Ar), 8.95 - 9.03 (1 H, m, quinoline-Ar), 8.50 - 8.58 (1 H, m, quinoline-Ar), 7.91 - 7.98 (2 H, m, Ar), 7.90 (1 H, s, Ar), 7.72 - 7.81 (1 H, m, Ar), 7.51 - 7.58 (1 H, m, Ar), 7.44 - 7.50 (2 H, m, Ar), 7.21 - 7.31 (1 H, m, Ar), 7.00 (1 H, d, J=9.0 Hz, benzyl-H), 6.89 - 6.96 (2 H, m, Ar), 6.79 - 6.87 (1 H, m, Ar), 3.70 (3 H, s, OCH\textsubscript{3}); δ\textsubscript{C} (100 MHz, DMSO-d\textsubscript{6}) 166.9 (C=O), 160.2, 149.8, 149.6, 144.0, 138.7, 134.5, 132.3, 130.4, 129.2, 128.5, 128.0, 126.7, 126.0, 123.9, 120.3, 119.7, 114.2, 112.8, 55.9 (OCH\textsubscript{3}), 50.9 (benzyl-C); m/z (ESI\textsuperscript{+}) 419 ([M+H]\textsuperscript{+}); HRMS (ESI\textsuperscript{+}) C\textsubscript{24}H\textsubscript{20}ClN\textsubscript{2}O\textsubscript{3}, ([M+H]\textsuperscript{+}) requires 419.1157; found 419.1160.

N-((5-Chloro-8-hydroxyquinolin-7-yl)(2,4-dimethoxyphenyl)methyl)benzamide S125

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 2,4-dimethoxybenzaldehyde (664 mg, 4.0 mmol) gave S125 (464 mg, 52 %) as a white powder.

mp 186 - 187 °C; ν\textsubscript{max}/cm\textsuperscript{-1} 3306 (NH), 1636 (C=O); δ\textsubscript{H} (400 MHz, DMSO-d\textsubscript{6}) 10.18 (1 H, br. s., NH), 8.92 - 8.96 (1 H, m, quinoline-Ar), 8.87 - 8.92 (1 H, m, quinoline-Ar), 8.43 - 8.51 (1 H, m, quinoline-Ar), 7.87 - 7.93 (2 H, m, Ar), 7.66 - 7.73 (1 H, m, Ar), 7.55 (1 H, s, Ar), 7.48 - 7.53 (1 H, m, Ar), 7.41 - 7.47 (2 H, m, Ar), 7.07 - 7.12 (1 H, m, Ar), 7.01 (1 H, d, J=8.0 Hz, benzyl-H), 6.56 - 6.61 (1 H, m, Ar), 6.47 - 6.54 (1 H, m, Ar), 3.75 (3 H, s, OCH\textsubscript{3}), 3.73 (3 H, s, OCH\textsubscript{3}); δ\textsubscript{C} (100 MHz, DMSO-d\textsubscript{6}) 166.2
Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 1,4-benzodioxan-6-carboxaldehyde (657 mg, 4.0 mmol) gave S126 (549 mg, 63 %) as a white powder.

mp 226 °C; \( \nu_{\text{max}}/\text{cm}^{-1} \) 3282 (NH), 1631 (C=O); \( \delta_H \) (400 MHz, DMSO-\( d_6 \)) 10.40 (1 H, br. s., N\( H \)), 9.08 - 9.25 (1 H, m, quinoline-Ar), 8.84 - 9.04 (1 H, m, quinoline-Ar), 8.34 - 8.59 (1 H, m, quinoline-Ar), 7.82 - 8.04 (3 H, m, Ar), 7.64 - 7.78 (1 H, m, Ar), 7.39 - 7.60 (3 H, m, Ar), 6.90 (1 H, d, \( J=8.5 \text{ Hz} \), benzyl-H), 6.72 - 6.86 (3 H, m, Ar), 4.19 (4 H, s, CH(3)); \( \delta_C \) (100 MHz, DMSO-\( d_6 \)) 166.8 (C=O), 150.2, 150.0, 144.0, 143.3, 139.5, 135.6, 135.1, 133.4, 132.2, 129.1, 128.4, 127.5, 126.1, 125.7, 123.8, 120.9, 119.4, 117.8, 116.6, 64.9 (CH(3)), 50.4 (benzyl-C); \( m/z \) (ESI\( ^+ \)) 445 ([M+H\(^+ \)]); HRMS (ESI\( ^+ \)) \( C_{25}H_{19}ClIN_2\text{NaO}_4 \), ([M+Na\(^+ \)]\(^\pm \)) requires 469.0926; found 469.0917.

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and SD5 (634 mg, 2.6 mmol) gave S127 (513 mg, 49 %) as a white powder.

mp 239 °C; \( \nu_{\text{max}}/\text{cm}^{-1} \) 3298 (NH), 1633 (C=O); \( \delta_H \) (400 MHz, DMSO-\( d_6 \)) 10.50 (1 H, br. s., NH), 9.19 - 9.43 (1 H, m, quinoline-Ar), 8.88 - 9.02 (1 H, m, quinoline-Ar), 8.31 - 8.62 (1 H, m, quinoline-Ar), 7.90 - 8.04 (3 H, m, Ar), 7.68 - 7.76 (1 H, m, Ar), 7.66
(1 H, s, Ar), 7.52 - 7.59 (2 H, m, Ar), 7.46 - 7.52 (2 H, m, Ar), 7.40 - 7.45 (1 H, m, Ar), 7.32 - 7.39 (1 H, m, Ar), 7.07 (1 H, d, J=9.0 Hz, benzyl-H), 6.69 - 6.76 (2 H, m, Ar), 6.50 (1 H, s, Ar), 3.77 (6 H, s, OCH$_3$); δ$_C$ (100 MHz, DMSO-$d_6$) 167.0 (C=O), 161.7 (COCH$_3$), 150.4, 150.1, 143.1, 143.1, 141.1, 139.6, 135.3, 133.4, 132.3, 130.9, 129.2, 128.5, 127.4, 126.4, 126.0, 125.8, 123.9, 119.5, 105.8, 100.0, 56.1 (OCH$_3$), 51.2 (benzyl-C); m/z (EI$^+$) 524 ([M]$^+$); HRMS (EI$^+$) C$_{31}$H$_{25}$ClN$_2$O$_4$, ([M]$^+$) requires 524.1503; found 524.1511.

$N$-((5-Chloro-8-hydroxyquinolin-7-yl)(3'-methoxy-[1,1'-biphenyl]-3-yl)methyl)benzamide S128

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and S26 (770 mg, 3.6 mmol) gave S128 (497 mg, 50 %) as a white powder.

mp 208 °C; $\nu_{max}$/cm$^{-1}$ 3297 (NH), 1633 (C=O); δ$_H$ (400 MHz, DMSO-$d_6$) 10.49 (1 H, br. s., NH), 9.22 - 9.45 (1 H, m, quinoline-Ar), 8.81 - 9.05 (1 H, m, quinoline-Ar), 8.31 - 8.54 (1 H, m, quinoline-Ar), 7.88 - 7.99 (3 H, m, Ar), 7.64 - 7.75 (2 H, m, Ar), 7.52 - 7.58 (2 H, m, Ar), 7.46 - 7.52 (2 H, m, Ar), 7.40 - 7.46 (1 H, m, Ar), 7.30 - 7.39 (2 H, m, Ar), 7.02 - 7.21 (3 H, m, Ar), 6.87 - 6.96 (1 H, m, Ar), 3.78 (3 H, s, OCH$_3$); δ$_C$ (100 MHz, DMSO-$d_6$) 167.0 (C=O), 160.5 (COCH$_3$), 150.4, 150.1, 143.2, 142.5, 141.1, 139.6, 135.2, 132.3, 130.9, 129.9, 129.2, 128.5, 127.4, 126.4, 126.0, 125.8, 123.9, 119.5, 113.8, 113.2, 55.9 (OCH$_3$), 51.2 (benzyl-C); m/z (EI$^+$) 494 ([M]$^+$); HRMS (EI$^+$) C$_{30}$H$_{23}$ClN$_2$O$_3$, ([M]$^+$) requires 494.1397; found 494.1396.

$N$-((5-Chloro-8-hydroxyquinolin-7-yl)(3,4-dihydroxyphenyl)methyl)benzamide S129

To a solution of S120 (250 mg, 0.5 mmol) in CH$_2$Cl$_2$ (2 mL) at 0 °C was added a 1M solution of boron tribromide in CH$_2$Cl$_2$ (3 mL, 3 mmol). The reaction mixture was stirred for 30 min at 0 °C, allowed to warm to room temperature, and then stirred at room temperature for 24 h. The reaction mixture was quenched with MeOH (10 mL) and neutralised with a 1M aqueous
solution of NaOH. The precipitate was collected by filtration and dried under vacuum to give S129 as an off-white powder (210 mg, 100%).

$\text{mp decomposition } > 220^\circ \text{C;} \nu_{\text{max}}/\text{cm}^{-1} 3294 (\text{NH}), 1634 (\text{C}=\text{O}); \delta_{\text{H}} (400 \text{ MHz, DMSO-}d_6) 10.20 (1 \text{ H, br. s., NH}), 9.04 - 9.10 (1 \text{ H, m, quinoline-Ar}), 8.91 - 8.96 (1 \text{ H, m, quinoline-Ar}), 8.43 - 8.49 (1 \text{ H, m, quinoline-Ar}), 7.88 - 7.95 (3 \text{ H, m, Ar}), 7.67 - 7.72 (1 \text{ H, m, Ar}), 7.50 - 7.56 (1 \text{ H, m, Ar}), 7.42 - 7.49 (2 \text{ H, m, Ar}), 6.83 (1 \text{ H, d, } J=8.5 \text{ Hz, benzyl-H}), 6.50 - 6.56 (1 \text{ H, m, Ar}), 6.41 - 6.46 (1 \text{ H, m, Ar}), 6.36 - 6.41 (1 \text{ H, m, Ar}); \delta_{\text{C}} (100 \text{ MHz, DMSO-}d_6) 166.6 (\text{C}=\text{O}), 152.5, 151.1, 149.9, 149.9, 139.5, 135.4, 133.3, 132.0, 131.4, 129.1, 128.4, 127.8, 127.3, 125.5, 123.6, 119.1, 117.1, 107.9, 107.6, 51.1 (benzyl-C);

HRMS (FI$^+$) C$_{23}$H$_{17}$ClIN$_2$O$_4$, ([M]+) requires 420.0877; found 420.0883.

$\text{N-([5-Chloro-8-hydroxyquinolin-7-yl][3',5'-dihydroxy-[1,1'-biphenyl]-3-yl)methyl]benzamide S130}$

To a solution of S127 (200 mg, 0.38 mmol) in CH$_2$Cl$_2$ (8 mL) at 0 °C was added a 1M solution of boron tribromide in CH$_2$Cl$_2$ (2.3 mL, 2.3 mmol). The reaction mixture was stirred for 30 min at 0 °C, allowed to warm to room temperature, and then stirred at room temperature for 24 h. The reaction mixture was quenched with MeOH (10 mL) and neutralised with a 1M aqueous solution of NaOH. The solvent was removed under reduced pressure and the residue redissolved in CH$_2$Cl$_2$. The organic layer was washed with water, brine, and subsequently dried over anhydrous Na$_2$SO$_4$. Purification by flash column chromatography using CH$_2$Cl$_2$/MeOH (90:10) gave S130 (143 mg, 76 %) as an orange powder.

$\text{mp decomposition } > 230^\circ \text{C;} \nu_{\text{max}}/\text{cm}^{-1} 3206 (\text{OH}), 1597 (\text{C}=\text{O}); \delta_{\text{H}} (400 \text{ MHz, DMSO-}d_6) 9.16 - 9.50 (1 \text{ H, m, quinoline-Ar}), 8.83 - 9.14 (1 \text{ H, m, quinoline-Ar}), 8.41 - 8.67 (1 \text{ H, m, quinoline-Ar}), 7.95 (3 \text{ H, s, Ar}), 7.70 - 7.82 (1 \text{ H, m, Ar}), 7.51 - 7.58 (1 \text{ H, m, Ar}), 7.44 - 7.51 (2 \text{ H, m, Ar}), 7.35 - 7.42 (1 \text{ H, m, Ar}), 7.30 - 7.35 (2 \text{ H, m, Ar}), 7.20 - 7.26 (1 \text{ H, m, Ar}), 7.08 (1 \text{ H, d, } J=8.5 \text{ Hz, benzyl-H}), 6.43 - 6.48 (1 \text{ H, m, Ar}), 6.16 - 6.24 (1 \text{ H, m, Ar}); \delta_{\text{C}} (100 \text{ MHz, DMSO-}d_6) 167.0 (\text{C}=\text{O}), 1157.9 (\text{COH}), 156.0, 150.0, 149.7, 144.1, 142.1, 142.0, 138.9, 135.0, 134.3, 132.3, 129.2, 129.0, 128.8, 128.5, 128.1, 126.4, 126.0, 124.0, 119.7, 110.0, 103.2, 99.8, 50.8 (benzyl-C); A molecular ion could not be identified via the mass spectrometry techniques of ESI, EI or FI.
To a solution of S128 (160 mg, 0.31 mmol) in CH$_2$Cl$_2$ (10 mL) at 0 °C was added a 1M solution of boron tribromide in CH$_2$Cl$_2$ (0.97 mL, 0.97 mmol). The reaction mixture was stirred for 30 min at 0 °C, allowed to warm to room temperature, and then stirred at room temperature for 24 h. The reaction mixture was quenched with MeOH (10 mL) and neutralised with a 1M aqueous solution of NaOH. The solvent was removed under reduced pressure and the residue redissolved in CH$_2$Cl$_2$. The organic layer was washed with water, brine, and subsequently dried over anhydrous Na$_2$SO$_4$. Purification by flash column chromatography using CH$_2$Cl$_2$/MeOH (90:10) gave S131 (84 mg, 55 %) as a yellow powder.

mp decomposition > 180 °C; $\nu$_max/cm$^{-1}$ 3206 (NH), 1596 (C=O); $\delta$$_H$(400 MHz, DMSO-$d_6$) 9.26 - 9.42 (1 H, m, quinoline-Ar), 8.88 - 9.07 (1 H, m, quinoline-Ar), 8.46 - 8.64 (1 H, m, quinoline-Ar), 7.87 - 8.02 (3 H, m, Ar), 7.70 - 7.83 (1 H, m, Ar), 7.46 - 7.63 (5 H, m, Ar), 7.38 - 7.45 (1 H, m, Ar), 7.30 - 7.36 (1 H, m, Ar), 7.18 - 7.27 (1 H, m, Ar), 7.08 (1 H, d, J=8.5 Hz, benzyl-H) 6.92 - 7.02 (2 H, m, Ar), 6.67 - 6.81 (1 H, m, Ar); $\delta$$_C$(100 MHz, DMSO-$d_6$) 167.0 (C=O), 158.7, 149.8, 149.7, 142.9, 142.4, 141.4, 138.8, 135.1, 134.4, 132.3, 130.8, 129.9, 129.2, 128.5, 127.7, 127.2, 126.7, 126.3, 126.2, 126.0, 124.0, 119.8, 118.3, 115.4, 114.3, 51.1 (benzyl-C); $m/z$ (FI$^+$) 496 ([M$^+$]); HRMS (FI$^+$) C$_{29}$H$_{21}$ClN$_2$O$_4$, ([M$^+$]) requires 496.1190; found 496.1186.

 Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), 3-methoxybenzamide (302 mg, 2.0 mmol) and 3-methyl-2-thiophenecarboxaldehyde (431 μL, 4.0 mmol) gave S132 (129 mg, 15 %) as a light-brown powder.

mp 145 °C; $\nu$_max/cm$^{-1}$ 3291 (NH), 1640 (C=O); $\delta$$_H$(400 MHz, DMSO-$d_6$) 10.51 (1 H, br. s., NH), 9.24 - 9.39 (1 H, m, quinoline-Ar), 8.91 - 9.02 (1 H, m, quinoline-Ar), 8.43 - 8.59 (1 H, m, quinoline-Ar), 7.88 (1 H, s, Ar), 7.67 - 7.78 (1 H, m, Ar), 7.50 - 7.55 (1 H, m, Ar), 7.44 - 7.49 (1 H, m, Ar), 7.35 - 7.41 (1 H, m, Ar), 7.24 - 7.30 (1 H, m, Ar), 7.08 - 7.18 (2 H, m, Ar), 6.87 - 6.93 (1 H,
m, Ar), 3.80 (3 H, s, OCH₃), 2.15 (3 H, s, CH₃); δC (100 MHz, DMSO-d₆) 166.2 (C=O), 160.0, 150.5, 150.1, 139.8, 139.4, 137.6, 136.2, 135.0, 133.4, 131.4, 130.3, 127.3, 126.0, 125.5, 124.0, 120.8, 119.2, 118.0, 113.7, 56.2 (benzyl-C), 45.8 (OCH₃), 14.4 (CH₃); m/z (ESI) 437 ([M-H]⁻); HRMS (ESI⁺) C₂₃H₁₉ClN₂O₃S, ([M+Na]⁺) requires 461.0697; found 461.0699.

**N-((5-Chloro-8-hydroxyquinolin-7-yl)(3-cyanophenyl)methyl)benzamide S133**

![Chemical Structure](image)

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 3-formylbenzonitrile (524 mg, 4.0 mmol) gave S133 (548 mg, 66 %) as a white powder.

mp 226 - 228 °C; νmax/cm⁻¹ 3298 (NH), 1633 (C=O), 691 (C-Cl); δH (400 MHz, DMSO-d₆) 10.59 (1 H, br. s., NH), 9.28 - 9.38 (1 H, m, quinoline-Ar), 8.94 - 9.01 (1 H, m, quinoline-Ar), 8.45 - 8.52 (1 H, m, quinoline-Ar), 7.93 - 7.99 (2 H, m, Ar), 7.85 (1 H, s, Ar), 7.80 (1 H, s, Ar), 7.67 - 7.78 (3 H, m, Ar), 7.53 - 7.60 (2 H, m, Ar), 7.45 - 7.53 (2 H, m, Ar), 7.02 (1 H, d, J=8.5 Hz, benzyl-H); δC (100 MHz, DMSO-d₆) 167.0 (C=O), 150.6, 150.2, 144.0, 139.6, 134.8, 133.4, 133.2, 132.4, 131.9, 131.4, 130.7, 129.2, 128.5, 127.1, 126.1, 124.9 124.0, 119.7, 119.6, 112.3, 50.8 (benzyl-C); m/z (ESI⁺) 414 ([M+H]⁺); HRMS (ESI⁺) C₂₄H₁₇ClIN₃NaO₂S, ([M+Na]⁺) requires 436.0823; found 436.0815.

**N-((3-Acetylphenyl)(5-chloro-8-hydroxyquinolin-7-yl)methyl)benzamide S134**

![Chemical Structure](image)

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 3-acetylbenzaldehyde (524 mg, 4.0 mmol) gave S134 (476 mg, 55 %) as a white powder.

mp 192 °C; νmax/cm⁻¹ 3301 (NH), 1689 (acetyl C=O), 1633 (amide C=O), 692 (C-Cl); δH (400 MHz, DMSO-d₆) 10.53 (1 H, br. s., NH), 9.33 - 9.39 (1 H, m, quinoline-Ar), 8.94 - 8.99 (1 H, m, quinoline-Ar), 8.44 - 8.51 (1 H, m, quinoline-Ar), 7.92 - 7.98 (3 H, m, Ar), 7.87 - 7.91 (2 H, m, Ar), 7.69 - 7.76 (1 H, m, Ar), 7.60 - 7.66 (1 H, m, Ar), 7.45 - 7.57 (4 H, m, Ar), 7.08 (1 H, d, J=8.5 Hz, benzyl-H), 2.55 (3 H, s, CH₃); δC (100 MHz, DMSO-d₆) 198.7 (acetyl C=O), 167.0 (amide C=O), 150.5, 150.1, 143.1, 139.5, 137.8,
Methyl 3-(benzamido)[5-chloro-8-hydroxyquinolin-7-yl](methyl)benzoate S135

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and methyl 3-formylbenzoate (656 mg, 4.0 mmol) gave S135 (549 mg, 63 %) as a white powder.

mp 224 °C; ν_max/cm⁻¹ 3303 (NH), 1724 (ester C=O), 1636 (amide C=O); δ_H (400 MHz, DMSO-d₆) 10.54 (1 H, br. s., NH), 9.34 - 9.43 (1 H, m, quinoline-Ar), 8.92 - 9.01 (1 H, m, quinoline-Ar), 8.43 - 8.54 (1 H, m, quinoline-Ar), 7.93 - 7.97 (3 H, m, Ar), 7.84 - 7.90 (2 H, m, Ar), 7.70 - 7.76 (1 H, m, Ar), 7.62 - 7.66 (1 H, m, Ar), 7.46 - 7.60 (4 H, m, Ar), 7.08 (1 H, d, J=9.0 Hz, benzyl-H), 3.81 (3 H, s, CH₃); δ_C (100 MHz, DMSO-d₆) 167.0 (acid C=O), 167.0 (amide C=O), 150.5, 150.2, 143.3, 139.5, 134.9, 133.4, 133.1, 132.4, 130.6, 129.9, 129.2, 128.8, 128.5, 127.4, 126.0, 125.3, 124.0, 119.6 (benzyl-C), 53.1 (OCH₃), 50.9 (benzyl-C); m/z (ESI⁺) 469 ([M+Na]⁺); HRMS (ESI⁺) C_{25}H_{19}ClI_{2}N_{2}NaO_{4}, ([M+Na]⁺) requires 469.0926; found 469.0909.

N-[(5-Chloro-8-hydroxyquinolin-7-yl)(3-nitrophenyl)(methyl)benzamide S136

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 3-nitrobenzaldehyde (604 mg, 4.0 mmol) gave S136 (276 mg, 31 %) as a white powder.

mp 195 - 198 °C; ν_max/cm⁻¹ 3300 (NH), 1633 (C=O); δ_H (400 MHz, DMSO-d₆) 10.62 (1 H, br. s., NH), 9.38 - 9.50 (1 H, m, quinoline-Ar), 8.94 - 9.02 (1 H, m, quinoline-Ar), 8.44 - 8.53 (1 H, m, quinoline-Ar), 8.18 - 8.22 (1 H, m, Ar), 8.12 - 8.17 (1 H, m, Ar), 7.92 - 7.98 (2 H, m, Ar), 7.90 (1 H, s, Ar), 7.81 - 7.86 (1 H, m, Ar), 7.71 - 7.77 (1 H, m, Ar), 7.63 - 7.69 (1 H, m, Ar), 7.54 - 7.58 (1 H, m, Ar), 7.46 - 7.53 (2 H, m, Ar), 7.11 (1 H, d, J=9.0 Hz, benzyl-H); δ_C (100 MHz, DMSO-d₆) 167.1 (C=O), 150.6, 150.2,
N-((3-Bromophenyl)5-chloro-8-hydroxyquinolin-7-yl)methyl)-4-nitrobenzamide S137

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), 4-nitrobenzamide (332 mg, 2.0 mmol) and 3-bromobenzaldehyde (468 μL, 4.0 mmol) gave S137 (476 mg, 46 %) as a white powder.

mp 206 °C; νmax/cm⁻¹ 3315 (NH), 1640 (C=O); δH (400 MHz, DMSO-d6) 10.60 (1 H, br. s., NH), 9.50 - 9.71 (1 H, m, quinoline-Ar), 8.89 - 9.05 (1 H, m, quinoline-Ar), 8.42 - 8.55 (1 H, m, quinoline-Ar), 8.34 (2 H, d, J=8.5 Hz, α-H-NO₂), 8.17 (2 H, d, J=8.5 Hz, benzyl-H); δC (100 MHz, DMSO-d6) 165.4 (C=O), 150.6, 150.2, 150.0, 144.8, 140.5, 139.5, 133.4, 131.7, 131.1, 130.6, 130.1, 127.3, 127.1, 126.0, 124.8, 124.4, 124.1, 122.7, 119.6, 51.0 (benzyl-C); m/z [ESI⁺] 512 ([M+H⁺]); HRMS (ESI⁺) C23H15BrClN3NaO4 requires 533.9827; found 533.9815.

N-((5-Chloro-8-hydroxyquinolin-7-yl)(3-methylthiophen-2-yl)methyl)-4-nitrobenzamide S138

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), 4-nitrobenzamide (332 mg, 2.0 mmol) and 3-methyl-2-thiophenecarboxaldehyde (431 μL, 4.0 mmol) gave S138 (365 mg, 40 %) as a light-brown powder.

mp 194 °C; νmax/cm⁻¹ 3312 (NH), 1643 (C=O); δH (400 MHz, DMSO-d6) 10.57 (1 H, br. s., NH), 9.66 - 9.75 (1 H, m, quinoline-Ar), 8.93 - 9.03 (1 H, m, quinoline-Ar), 8.42 - 8.56 (1 H, m, quinoline-Ar), 8.24 - 8.36 (2 H, m, quinoline-Ar), 8.12 - 8.18 (2 H, m, Ar), 7.86 (1 H, s, Ar), 7.68 - 7.78 (1 H, m, Ar), 7.26 - 7.34 (1 H, m, Ar), 7.12 - 7.20 (1 H, m, Ar), 6.88 - 6.95 (1 H, m, Ar), 2.16 (3 H, s, CH₃); δC (100 MHz, DMSO-d6) 165.0 (C=O), 150.6, 150.2, 150.0, 140.4, 139.4, 135.2, 133.4, 131.4, 130.0, 129.8, 127.1,
Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), acetamide (118 mg, 2.0 mmol) and 3-bromobenzaldehyde (468 µL, 4.0 mmol) gave S139 (449 mg, 55 %) as a white powder.

mp 200 - 202 °C; ν$_{max}$/cm$^{-1}$ 3286 (NH), 1640 (C=O); δ$_{H}$ (400 MHz, DMSO-d$_6$) 10.48 (1 H, br. s., NH), 8.92 - 8.98 (1 H, m, quinoline-Ar), 8.45 - 8.50 (1 H, m, quinoline-Ar), 7.66 - 7.77 (2 H, m, Ar), 7.39 - 7.47 (2 H, m, Ar), 7.24 - 7.32 (2 H, m, Ar), 6.69 (1 H, d, J=9.0 Hz, benzyl-H), 1.93 - 1.99 (3 H, m, CH$_3$); δ$_{C}$ (100 MHz, DMSO-d$_6$) 169.6 (C=O), 150.2, 150.2, 145.6, 145.0, 139.5, 133.4, 131.6, 130.8, 130.2, 127.0, 126.8, 125.9, 125.6, 124.0, 122.6, 119.7, 50.1 (benzyl-C), 23.5 (CH$_3$); m/z (ESI$^-$) 402 ([M-H]$^-$); HRMS (ESI$^-$) C$_{18}$H$_{14}$BrClIN$_2$NaO$_2$, ([M+Na]$^+$) requires 426.9819; found 426.9810.

tert-Butyl ([3-bromophenyl][5-chloro-8-hydroxyquinolin-7-yl]methyl)carbamate S140

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), tert-butyl carbamate (234 mg, 2.0 mmol) and 3-bromobenzaldehyde (468 µL, 4.0 mmol) gave S140 (239 mg, 26 %) as a white powder.

mp 177 °C; ν$_{max}$/cm$^{-1}$ 3298 (NH), 1684 (C=O); δ$_{H}$ (400 MHz, DMSO-d$_6$) 10.49 (1 H, br. s., NH), 8.87 - 9.00 (1 H, m, quinoline-Ar), 8.38 - 8.53 (1 H, m, quinoline-Ar), 8.04 - 8.18 (1 H, m, quinoline-Ar), 7.84 (1 H, s, Ar), 7.62 - 7.75 (2 H, m, Ar), 7.49 (1 H, s, Ar), 7.37 - 7.45 (1 H, m, Ar), 7.22 - 7.35 (2 H, m, Ar), 6.46 (1 H, d, J=9.5 Hz, benzyl-H), 1.39 (9 H, s, C(CH$_3$)$_3$); δ$_{C}$ (100 MHz, DMSO-d$_6$) 171.5 (C=O), 150.1, 149.8, 146.0, 129.5, 133.4, 131.5, 130.7, 130.1, 126.9, 126.7, 126.0, 125.8, 123.9, 122.5, 119.7, 79.4 (C(CH$_3$)$_3$), 51.5 (benzyl-C), 29.0 (C(CH$_3$)$_3$); m/z (FI$^+$) 462 ([M]$^+$); HRMS (FI$^+$) C$_{21}$H$_{20}$BrClIN$_2$O$_3$, ([M]$^+$) requires 462.0346; found 462.0340.
**N-((8-Hydroxyquinolin-7-yl)(phenyl)methyl)pentanamide S141**

![Chemical Structure](image)

Following general procedure 1, 8-hydroxyquinoline (290 mg, 2.0 mmol), valeramide (202 mg, 2.0 mmol) and benzaldehyde (406 µL, 4.0 mmol) gave S141 (245 mg, 37%) as a beige powder.

mp 178 - 179 °C; ν\text{max}/\text{cm}^{-1} (DCM) 3334 (NH), 2957 (OH), 1645 (C=O); δ\text{H} (400 MHz, DMSO-\text{d}_6) 9.94 (1 H, br. s., NH), 8.81 - 8.88 (1 H, m, quinoline-Ar), 8.66 - 8.76 (1 H, m, quinoline-Ar), 8.26 - 8.33 (1 H, m, quinoline-Ar), 8.66 - 8.76 (1 H, m, quinoline-Ar), 8.26 - 8.33 (1 H, m, quinoline-Ar), 7.50 - 7.59 (2 H, m, Ar), 7.39 - 7.47 (1 H, m, Ar), 7.15 - 7.34 (5 H, m, Ar), 6.73 (1 H, d, J=9.0 Hz, benzyl-H), 2.18 - 2.28 (2 H, m, C\text{H}_2d), 1.51 (2 H, quin, J=7.5 Hz C\text{H}_2c), 1.26 (2 H, sxt, J=7.5 Hz C\text{H}_2b), 0.85 (3 H, t, J=7.5 Hz, C\text{H}_3a);

δ\text{C} (100 MHz, DMSO-\text{d}_6) 172.4 (C=O), 150.3, 149.2, 143.5, 138.9, 136.9, 129.1, 128.3, 127.9, 127.5, 127.3, 125.6, 118.2, 50.6 (benzyl-C), 35.9 (C\text{d}), 28.4 (C\text{c}), 22.7 (C\text{b}), 14.6 (C\text{a});

m/z (ESI-) 333 ([M-H]^{-}); HRMS (ESI-+ C_{22}H_{21}N_{2}O_{2}, ([M+Na]^+) requires 357.1573; found 357.1565.

**N-((8-Hydroxyquinolin-7-yl)(phenyl)methyl)-3-methylbutanamide S142**

![Chemical Structure](image)

Following general procedure 1, 5-chloro-8-quinolinol (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and o-tolualdehyde (463 µL, 4.0 mmol) gave S142 (627 mg, 64%) as an off-white powder.

mp 217-218 °C; ν\text{max}/\text{cm}^{-1} 3274 (NH), 1636 (C=O); δ\text{H} (400 MHz, DMSO-\text{d}_6) 10.40 (1 H, br. s., NH), 9.09 - 9.24 (1 H, m, quinoline-Ar), 8.88 - 9.01 (1 H, m, quinoline-Ar), 8.40 - 8.53 (1 H, m, quinoline-Ar), 7.90 - 7.97 (2 H, m, Ar), 7.68 - 7.75 (1 H, m, Ar), 7.64 (1 H, s, Ar), 7.50 - 7.56 (1 H, m, Ar), 7.42 - 7.49 (2 H, m, Ar), 7.12 - 7.27 (4 H, m, Ar), 7.04 (1 H, d, J=8.5 Hz, benzyl-H), 2.29 (3 H, s, CH\text{3}), δ\text{C} (100 MHz, DMSO-\text{d}_6) 166.5 (C=O), 150.7, 150.0, 140.5, 139.4, 136.9, 135.0, 133.4, 132.2, 131.2, 129.8, 128.4, 128.0, 127.9, 127.4, 126.7, 125.8, 125.2, 123.9, 119.0, 48.8 (benzyl-C), 19.6 (CH\text{3}); m/z (ESI-) 401 ([M-H]^{-}, 100%); HRMS (ESI-) C_{26}H_{28}ClN_{2}O_{2}, ([M-H]^{-}) requires 401.1062; found 401.1062.
N-[(3,4-Dimethoxyphenyl)[8-hydroxyquinolin-7-yl]methyl]pentanamide S143

Following general procedure 1, 8-hydroxyquinoline (290 mg, 2.0 mmol), valeramide (202 mg, 2.0 mmol) and 3,4-dimethoxybenzaldehyde (644 mg, 4.0 mmol) gave S143 (92 mg, 12 %) as an off-white powder.

mp 150 - 152 °C; δH (400 MHz, CDCl3) 8.71 - 8.85 (1 H, m, quinoline-Ar), 8.06 - 8.24 (1 H, m, quinoline-Ar), 7.40 - 7.50 (2 H, m, quinoline-Ar), 7.32 - 7.38 (1 H, m, Ar), 7.16 - 7.25 (1 H, m, Ar), 6.93 - 7.01 (1 H, m, Ar), 6.67 - 6.86 (2 H, m, Ar), 6.53 (1 H, d, J=9.0 Hz, benzyl-H), 3.83 (3 H, s, OCH3), 3.82 (3 H, s, OCH3), 2.30 (2 H, t, J=7.5 Hz, CH2), 1.67 (2 H, quin, J=7.5 Hz, CH2), 1.37 (2 H, sxt, J=7.5 Hz, CH2), 0.91 (3 H, t, J=7.5 Hz, CH3), δC (100 MHz, CDCl3) 172.3 (C=O), 149.0, 149.0, 148.2, 136.1, 134.3, 128.5, 127.6, 122.5, 121.9, 118.9, 118.0, 110.9, 110.5, 55.9 (OCH3), 55.8 (OCH3), 54.4 (benzyl-C), 36.7 (C6), 27.8 (C6), 22.4 (C6), 13.8 (C6); m/z (ESI) 393 ([M-H]); HRMS (ESI+) C23H27N2O4 (M+H)+ requires 395.1965; found 395.1973.

N-[(5-Chloro-8-hydroxyquinolin-7-yl)phenyl]methyl]pentanamide S144

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), valeramide (202 mg, 2.0 mmol) and benzaldehyde (406 μL, 4.0 mmol) gave S144 (636 mg, 84 %) as a white powder.

mp 205 °C; δH (400 MHz, DMSO-d6) 10.34 (1 H, br. s., NH), 8.89 - 9.00 (1 H, m, quinoline-Ar), 8.71 - 8.83 (1 H, m, quinoline-Ar), 8.39 - 8.53 (1 H, m, quinoline-Ar), 7.65 - 7.75 (2 H, m, Ar), 7.28 - 7.35 (2 H, m, Ar), 7.17 - 7.27 (3 H, m, Ar), 6.72 (1 H, d, J=9.0 Hz, benzyl-H), 2.23 (2 H, t, J=7.0 Hz, CH2), 1.51 (2 H, quin, J=7.0 Hz, CH2), 1.26 (2 H, sxt, J=7.0 Hz, CH2), 0.86 (3 H, t, J=7.0 Hz, CH3), δC (100 MHz, DMSO-d6) 172.5 (C=O), 150.1, 142.8, 139.5, 133.4, 129.3, 2x 127.8, 127.1, 126.4, 125.7, 123.8, 119.5, 50.3 (benzyl-C), 35.9 (C6), 28.4 (C6), 22.6 (C6), 14.6 (C6); m/z (ESI) 367 ([M-H]); HRMS (ESI) C21H21ClN2O4 (M+Na)+ requires 391.1184; found 391.1180.
Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), Valeramide (202 mg, 2.0 mmol) and 3-bromobenzaldehyde (468 μL, 4.0 mmol) gave S146 (786 mg, 88%) as an off-white powder.

mp 211 °C; νmax/cm⁻¹ 3250 (NH), 1639 (C=O), 688 (C-Cl); δH (400 MHz, DMSO-d6) 10.46 (1 H, br. s., NH), 8.90 - 9.01 (1 H, m, quinoline-Ar), 8.76 - 8.87 (1 H, m, quinoline-Ar), 8.39 - 8.54 (1 H, m, quinoline-Ar), 7.65 - 7.77 (2 H, m, Ar), 7.38 - 7.49 (2 H, m, Ar), 7.19 - 7.34 (2 H, m, Ar), 6.69 (1 H, d, J=8.5 Hz, benzyl-H), 2.24 (2 H, t, J=7.0 Hz, CH2(d)), 1.51 (2 H, quin, J=7.0 Hz CH2(b)), 1.26 (2 H, sxt, J=7.0 Hz CH2(a)), 0.86 (3 H, t, J=7.0 Hz CH3(b)); δC (100 MHz, DMSO-d6) 172.6 (C=O), 150.2, 145.6, 139.5, 133.4, 131.6, 130.7, 130.3, 127.0, 126.8, 125.8, 125.6, 123.9, 122.6, 119.6, 50.0 (benzyl-C), 35.8 (CH2(d)), 28.3 (CH2(a)), 22.6 (CH3(a)), 14.5 (CH3(b)); m/z (ESI) 445 ([M-H]⁻); HRMS (ESI⁻) C17H17BrClN2O₂, ([M-H]⁻) requires 445.0324; found 445.0318.
N-{(3-Bromophenyl)[5-chloro-8-hydroxyquinolin-7-yl]methyl}-3-methylbutanamide S147

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), isovaleramide (202 mg, 2.0 mmol) and 3-bromobenzaldehyde (468 μL, 4.0 mmol) gave S147 (722 mg, 81 %) as a white powder.

mp 212 °C; \( \nu_{\text{max}}/\text{cm}^{-1} \) 3206 (NH), 1658 (C=O), 684 (C-Cl); \( \delta_H \) (400 MHz, DMSO-\( d_6 \)) 10.45 (1 H, br. s., NH), 8.91 - 8.98 (1 H, m, quinoline-Ar), 8.78 - 8.87 (1 H, m, quinoline-Ar), 8.43 - 8.50 (1 H, m, quinoline-Ar), 7.65 - 7.76 (2 H, m, Ar), 7.40 - 7.46 (2 H, m, Ar), 7.21 - 7.33 (2 H, m, Ar), 6.70 (1 H, d, \( J=9.0 \) Hz, benzyl-H), 2.09 - 2.15 (2 H, m, \( CH_3k \)), 1.94 - 2.06 (1 H, m, \( CH_3b \)), 0.87 (6 H, m); \( \delta_C \) (100 MHz, DMSO-\( d_6 \)) 172.0 (C=O), 150.2, 145.6, 139.5, 133.4, 131.6, 130.7, 130.3, 127.0, 126.9, 125.8, 125.6, 124.0, 122.6, 119.6, 50.0 (benzyl-C), 45.4 (\( CH_3k \)), 26.6 (\( CH_3b \)), 23.1 (\( CH_3a \)); \( m/z \) (ESI\(^+\)) 447 ([M+H]\(^+\)); HRMS (ESI\(^+\)) \( C_{21}H_{19}BrClN_2O_2 \) \( ([\text{M}-H}]\) requires 445.0324; found 445.0313.

N-{(8-Hydroxyquinolin-7-yl)(phenyl)methyl}acetamide S148^a

Following general procedure 1, 8-hydroxyquinoline (290 mg, 2.0 mmol), acetamide (118 mg, 2.0 mmol) and benzaldehyde (406 μL, 4.0 mmol) gave S148 (316 mg, 54 %) as a white powder.

mp 197 °C; \( \nu_{\text{max}}/\text{cm}^{-1} \) 3305 (NH), 1644 (C=O); \( \delta_H \) (400 MHz, DMSO-\( d_6 \)) 9.97 (1 H, br. s., NH), 8.82 - 8.89 (1 H, m, quinoline-Ar), 8.74 - 8.81 (1 H, m, quinoline-Ar), 8.26 - 8.34 (1 H, m, quinoline-Ar), 7.50 - 7.58 (2 H, m, Ar), 7.56 - 7.45 (1 H, m, Ar), 7.24 - 7.31 (4 H, m, Ar), 7.61 - 7.23 (1 H, m, Ar), 6.72 (1 H, d, \( J=8.5 \) Hz, benzyl-H), 1.95 (3 H, s, \( CH_3 \)); \( \delta_C \) (100 MHz, DMSO-\( d_6 \)) 169.4 (C=O), 150.3, 149.2, 143.4, 138.9, 136.9, 129.1, 128.4, 127.9, 127.6, 127.3, 125.6, 122.6, 118.2, 50.7 (benzyl-C), 23.5 (\( CH_3 \)); \( m/z \) (ESI\(^+\)) 291 ([M-H]'); HRMS (ESI\(^+\)) \( C_{18}H_{18}IN_2NaO_2 \) \( ([\text{M}+\text{Na}]^+) \) requires 315.1104; found 315.1093.
N-[(5-Chloro-8-hydroxyquinolin-7-yl)[3-methylthiophen-2-yl]methyl)cyclobutanecarboxamide S149

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), cyclobutanecarboxamide (198 mg, 2.0 mmol) and 3-methyl-2-thiophenecarboxaldehyde (431 μL, 4.0 mmol) gave S149 (308 mg, 40 %) as a light-brown powder. mp 186 °C; νmax/cm⁻¹ 3270 (NH), 1640 (C=O); δH (400 MHz, CDCl₃) 10.41 (1 H, br. s., NH), 8.91 - 9.00 (1 H, m, quinoline-Ar), 8.59 - 8.69 (1 H, m, quinoline-Ar), 8.40 - 8.54 (1 H, m, quinoline-Ar), 7.64 - 7.77 (2 H, m, Ar), 7.18 - 7.26 (1 H, m, Ar), 6.78 - 6.92 (2 H, m, Ar), 3.05 - 3.23 (1 H, m, Hₐ), 2.11 (3 H, s, CH₃), 1.67 - 2.09 (6 H, m, Hb/c); δC (100 MHz, CDCl₃) 173.8 (C=O), 150.2, 150.1, 140.2, 135.3, 134.7, 133.4, 131.3, 127.8, 126.9, 125.9, 123.8, 119.2, 44.9 (benzyl-C), 25.7, 25.2, 18.7, 14.3 (CH₃); m/z (ESI⁻) 386 ([M-H]⁻); HRMS (ESI⁺) C₂₀H₁₉ClN₂O₂S, ([M+Na⁺]⁺) requires 409.0748; found 409.0733.

5-Chloro-7-(pyrrolidin-1-ylmethyl)quinolin-8-ol S150

A mixture of 5-chloro-8-hydroxyquinoline (180 mg, 1 mmol), paraformaldehyde (36.2 mg, 1.2 mmol), pyrrolidine (100 μL, 1.2 mmol), and triethylamine (170 μL, 1.2 mmol) was stirred in ethanol (15 mL) for 16 h under reflux. The volume of the reaction mixture was reduced and the precipitate was filtered, washed with EtOH, H₂O, and dried to give S150 (60 mg, 23 %) as a light-brown powder. mp 125 °C; δH (400 MHz, DMSO-d₆) 8.83 - 9.03 (1 H, m, quinoline-Ar), 8.30 - 8.64 (1 H, m, quinoline-Ar), 7.64 - 7.74 (1 H, m, quinoline-Ar), 7.62 (1 H, s, quinoline-Ar), 3.83 (2 H, s, benzyl-CH₂), 2.46 - 2.57 (4 H, m, Hₐ), 1.67 - 1.77 (4 H, m, Hb); δC (100 MHz, DMSO-d₆) 151.3, 149.4, 139.3, 132.7, 128.6, 125.2, 123.0, 122.1, 118.4, 54.2, 53.9, 23.7 (CH₂); m/z (ESI⁺) 263 ([M+H⁺]; HRMS (ESI⁺) C₁₄H₁₄O₂Cl, ([M+H⁺]⁺) requires 263.0946; found 263.0942.
5-Chloro-7-{morpholinomethyl}quinolin-8-ol S151

A mixture of 5-chloro-8-hydroxyquinoline (180 mg, 1 mmol), paraformaldehyde (36.2 mg, 1.2 mmol), morpholine (103 μL, 1.2 mmol), and triethylamine (170 μL, 1.2 mmol) was stirred in ethanol (15 mL) for 16 h under reflux. The volume of the reaction mixture was reduced and the precipitate was filtered, washed with EtOH, H₂O, and dried to give S151 (42 mg, 15 %) as an off-white powder.

mp 112 °C; ν_max/cm⁻¹ 3313 (OH); δ_H (400 MHz, DMSO-d₆) 8.73 - 9.06 (1 H, m, quinoline-Ar), 7.67 - 7.73 (1 H, m, quinoline-Ar), 7.65 (1 H, s, quinoline-Ar), 3.70 (2 H, s, benzyl-CH₂), 3.55 - 3.64 (4 H, m, H_b), 2.41 - 2.48 (4 H, m, H_a); δ_C (100 MHz, DMSO-d₆) 151.4, 149.4, 139.2, 132.9, 129.1, 125.4, 123.2, 120.9, 118.6, 66.7, (H_a), 56.4, 53.6; m/z (ESI⁺) 279 ([M+H]⁺); HRMS (ESI⁺) C₁₄H₁₆O₂N₂Cl, ([M+H]⁺) requires 279.0895; found 279.0891.

1-(4-{(5-Chloro-8-hydroxyquinolin-7-yl)methyl}piperazin-1-yl)ethan-1-one S152

A mixture of 5-chloro-8-hydroxyquinoline (180 mg, 1 mmol), paraformaldehyde (36.2 mg, 1.2 mmol), 1-acetylpiperazine (171 μL, 1.2 mmol), and triethylamine (170 μL, 1.2 mmol) was stirred in ethanol (15 mL) for 16 h under reflux. The volume of the reaction mixture was reduced and the precipitate was filtered, washed with EtOH, H₂O, and dried to give S152 (45 mg, 14 %) as a light-brown powder.

mp > 250 °C; ν_max/cm⁻¹ 1621 (C=O); δ_H (400 MHz, DMSO-d₆) 8.98 - 9.10 (1 H, m, quinoline-Ar), 8.52 - 8.69 (1 H, m, quinoline-Ar), 8.03 - 8.16 (1 H, m, quinoline-Ar), 7.80 - 7.92 (1 H, m, quinoline-Ar), 4.48 - 4.63 (2 H, m, benzyl-CH₂), 3.45 - 3.74 (4 H, m, H_b), 2.91 - 3.24 (4 H, m, H_a), 2.03 (3 H, s, CH₃); δ_C (100 MHz, DMSO-d₆) 169.0 (C=O), 153.4, 153.1, 149.4, 134.2, 131.3, 127.2, 124.6, 119.1, 113.3, 53.1 (C_b), 50.6 (C_a), 47.7 (benzyl-C), 21.5 (CH₃); m/z (ESI⁺) 320 ([M+H]⁺); HRMS (ESI⁺) C₁₄H₁₉O₂N₂Cl, ([M+H]⁺) requires 320.1160; found 320.1156.
tert-Butyl 4-[(5-Chloro-8-hydroxyquinolin-7-yl)methyl]piperazine-1-carboxylate S153

A mixture of 5-chloro-8-hydroxyquinoline (180 mg, 1 mmol), paraformaldehyde (36.2 mg, 1.2 mmol), 1-tert-butylpiperazine (224 mg, 1.2 mmol), and triethylamine (170 μL, 1.2 mmol) was stirred in ethanol (15 mL) for 16 h under reflux. The volume of the reaction mixture was reduced and the precipitate was filtered, washed with EtOH, H₂O, and dried to give S153 (79 mg, 21 %) as a light-brown powder.

mp 201 °C; νmax/cm⁻¹ 1701 (C=O); δH (400 MHz, DMSO-d₆) 8.83 - 9.06 (1 H, m, quinoline-Ar), 8.36 - 8.58 (1 H, m, quinoline-Ar), 7.67 - 7.77 (1 H, m, quinoline-Ar), 7.65 (1 H, s, benzyl-CH₂), 3.27 - 3.38 (4 H, m, Hb), 2.33 - 2.45 (4 H, m, Ha), 1.39 (9 H, s, C(CH₃)₃); δC (100 MHz, DMSO-d₆) 154.2 (C=O), 151.3, 149.4, 139.2, 132.9, 129.1, 125.4, 123.2, 121.0, 118.7, 79.2 (C₆), 55.9 (benzyl-CH₂), 52.9 (C₆), 28.5 (C(CH₃)₃); m/z (ESI⁺) 378 ([M+H]⁺); HRMS (ESI⁺) C₁₉H₂₅O₃N₃Cl, ([M+H]⁺) requires 378.1579; found 378.1574.

3-(Benzamido[5-chloro-8-hydroxyquinolin-7-yl]methyl)-N-(2-morpholinoethyl)benzamide S154

To a solution of 12 (217 mg, 0.5 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (96 mg, 0.5 mmol), hydroxybenzotriazole (81 mg, 0.6 mmol), and diisopropylethylamine (261 μL, 15 mmol) in DMF (10 mL) was added 4-(2-aminoethyl)morpholine (130 mg, 0.5 mmol). The reaction mixture was stirred for 16 h at 50 °C. The reaction mixture was then concentrated in vacuo and the resulting residue purified via flash column chromatography (0 % - 10 % MeOH, CH₂Cl₂, 1 % NH₄OH) to give S154 (160 mg, 59 %) as a white solid.

mp 144 °C; νmax/cm⁻¹ 3268 (NH), 1638 (C=O); δH (400 MHz, CDCl₃) 8.66 - 8.70 (1 H, m, quinoline-Ar), 8.34 - 8.41 (1 H, m, quinoline-Ar), 7.99 - 8.06 (1 H, m, quinoline-Ar), 7.75 - 7.83 (3 H, m, Ar), 7.51 - 7.58 (2 H, m, Ar), 7.37 - 7.50 (3 H, m, Ar), 7.30 - 7.36 (2 H, m, Ar), 7.24 - 7.30 (1 H, m, Ar), 7.19 (1 H, s, Ar), 6.81 - 6.94 (1 H, m, Ar), 6.68 (1 H, d, J=8.5 Hz, benzyl-H), 3.48 - 3.56 (4 H, m), 3.39 (2 H, q, J=6.0 Hz, H₆), 2.46 (2 H, t, J=6.0 Hz, H₆), 2.30 - 2.40 (4 H, m); δC (100 MHz, DMSO-d₆) 167.3, 166.6,
148.5, 141.5, 138.7, 135.1, 134.0, 131.8, 130.1, 128.9, 128.6, 127.7, 127.2, 126.1, 125.8, 122.8, 122.5, 121.1, 86.8, 55.9, 54.6, 53.2, 36.0; m/z (ESI') 545 ([M+H]+); HRMS (ESI') C30H30O4N4Cl, ([M+H]+) requires 545.1950; found 545.1945.

3-(Benzamido(5-chloro-8-hydroxyquinolin-7-yl)methyl)-N-(1-morphinopropan-2-yl)benzamide S155

To a solution of 12 (217 mg, 0.5 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (96 mg, 0.5 mmol), hydroxybenzotriazole (81 mg, 0.6 mmol), and diisopropylethylamine (261 μL, 15 mmol) in DMF (10 mL) was added 1-(morpholin-4-yl)propan-2-amine (72 mg, 0.5 mmol). The reaction mixture was stirred for 16 h at 50 °C. The reaction mixture was then concentrated in vacuo and the resulting residue purified via flash column chromatography (0 % - 10 % MeOH, CH2Cl2, 1 % NH3OH) to give S155 (193 mg, 69 %) as a white solid.

mp 216 °C; \( \nu_{\text{max}}/\text{cm}^{-1} \) 3393 (NH), 1638 (C=O); \( \delta_{\text{H}} \) (400 MHz, DMSO-\( \text{d}_6 \)) 10.48 (1 H, br. s., NH), 9.25 - 9.41 (1 H, m, quinoline-Ar), 8.91 - 9.05 (1 H, m, quinoline-Ar), 8.43 - 8.59 (1 H, m, quinoline-Ar), 8.11 - 8.27 (1 H, m, quinoline-Ar), 7.94 - 7.99 (2 H, m, Ar), 7.81 - 7.88 (2 H, m, Ar), 7.70 - 7.78 (2 H, m, Ar), 7.41 - 7.61 (4 H, m, Ar), 7.07 (1 H, d, \( J=8.5 \text{ Hz} \), benzyl-H), 4.12 - 4.23 (1 H, m, CH), 3.45 - 3.53 (4 H, m, OCH2), 2.33 - 2.43 (4 H, m, NCH2), 2.22 - 2.32 (2 H, m, CH2), 1.13 (3 H, d, \( J=6.5 \text{ Hz} \), CH3); \( \delta_{\text{C}} \) (100 MHz, DMSO-\( \text{d}_6 \)) 166.5 (C=O), 166.0 (C=O), 150.1, 149.7, 142.3, 142.3, 139.1, 135.6, 134.6, 133.0, 131.9, 130.3, 128.8, 128.1, 127.2, 127.0, 126.2, 125.6, 125.2, 123.5, 119.0, 66.7, 63.9, 53.9, 50.6, 42.6, 19.4 (CH3); m/z (ESI') 559 ([M+H]+); HRMS (ESI') C31H32O4N4Cl, ([M+H]+) requires 559.2107; found 559.2100.

3-(Benzamido(5-chloro-8-hydroxyquinolin-7-yl)methyl)-N-(2-morphinopropan-2-yl)benzamide S156

To a solution of 12 (217 mg, 0.5 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (96 mg, 0.5 mmol), hydroxybenzotriazole (81 mg, 0.6 mmol), and diisopropylethylamine (261 μL, 15 mmol) in DMF (10 mL) was added 2-
(morpholin-4-yl)propanamine (72 mg, 0.5 mmol). The reaction mixture was stirred for 16 h at 50 °C. The reaction mixture was then concentrated in vacuo and the resulting residue purified via flash column chromatography (0 % - 10 % MeOH, CH₂Cl₂, 1 % NH₄OH) to give S156 (211 mg, 75 %) as a white solid.

mp 196 °C; νmax/cm⁻¹ 3293 (NH), 1653 (C=O), 1635 (C=O); δn (400 MHz, DMSO-d₆) 10.50 (1H, br. s., NH), 9.28 - 9.42 (1H, m, quinoline-Ar), 8.92 - 9.07 (1H, m, quinoline-Ar), 8.44 - 8.56 (1H, m, quinoline-Ar), 8.23 - 8.36 (1H, m, quinoline-Ar), 7.93 - 8.00 (2H, m, Ar), 7.85 - 7.89 (1H, m, Ar), 7.82 (1H, s, Ar), 7.70 - 7.77 (2H, m, Ar), 7.39 - 7.61 (4H, m, Ar), 7.08 (1H, d, J=8.5 Hz, benzyl-H), 3.43 - 3.52 (4H, m, OCH₂), 3.29 - 3.42 (4H, m, NCH₂), 2.71 - 2.77 (1H, m, CH), 2.36 - 2.48 (2H, m, CH₂), 0.90 - 0.95 (3H, m, CH₃); δC (100 MHz, DMSO-d₆) 166.5 (C=O), 166.5 (C=O), 150.1, 149.7, 142.2, 139.1, 135.4, 134.6, 133.0, 131.9, 130.4, 128.9, 128.8, 127.2, 126.7, 126.1, 125.5, 125.2, 123.5, 119.1, 67.1, 58.6, 50.6, 49.0, 42.2, 12.8 (CH₃); m/z (ESI⁺) 559 ([M+H⁺]); HRMS (ESI⁺) C₉H₁₂O₂N₄Cl, ([M+H⁺]) requires 559.2107; found 559.2103.

3-(Benzamido(5-chloro-8-hydroxyquinolin-7-yl)methyl)-N-(2-morpholino-1-phenylethyl)benzamide S157

To a solution of 12 (217 mg, 0.5 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (96 mg, 0.5 mmol), hydroxybenzotriazole (81 mg, 0.6 mmol), and diisopropylethylamine (261 µL, 1.5 mmol) in DMF (10 mL) was added 2-(morpholin-4-yl)-1-phenylethylamine (103 mg, 0.5 mmol). The reaction mixture was stirred for 16 h at 50 °C. The reaction mixture was then concentrated in vacuo and the resulting residue purified via flash column chromatography (0 % - 10 % MeOH, CH₂Cl₂, 1 % NH₄OH) to give S157 (267 mg, 86 %) as a white solid.

mp 217 °C; νmax/cm⁻¹ 3271 (NH), 1637 (C=O); δn (400 MHz, DMSO-d₆) 10.49 (1H, br. s., NH), 9.27 - 9.42 (1H, m, quinoline-Ar), 8.93 - 9.04 (1H, m, quinoline-Ar), 8.73 - 8.86 (1H, m, quinoline-Ar), 8.45 - 8.57 (1H, m, quinoline-Ar), 7.93 - 8.01 (2H, m, Ar), 7.80 - 7.89 (4H, m, Ar), 7.70 - 7.77 (1H, m, Ar), 7.54 - 7.62 (1H, m, Ar), 7.44 - 7.53 (4H, m, Ar), 7.36 - 7.43 (2H, m, Ar), 7.27 - 7.34 (2H, m, Ar), 7.19 - 7.26 (1H, m, Ar), 7.08 (1H, d, J=8.5 Hz, benzyl-H), 3.42 - 3.57 (4H, m, OCH₂), 2.90 (1H, s, CH), 2.32 - 2.49 (4H, m, NCH₂); δC (100 MHz, DMSO-d₆) 165.5 (C=O), 166.4 (C=O), 162.8, 150.1, 149.7, 142.9, 142.3, 139.1, 135.4, 134.7, 133.0, 131.9, 130.5, 128.8, 128.7, 128.1, 127.9, 127.3, 127.2, 127.0, 126.3, 125.5, 125.2, 123.5, 119.1, 66.7, 63.8, 53.6, 50.7, 50.6; m/z (ESI⁺) 621 ([M+H⁺]); HRMS (ESI⁺) C₉H₁₂O₂N₄Cl, ([M+H⁺]) requires 621.2263; found 621.2258.
3-{Benzamido[5-chloro-8-hydroxyquinolin-7-yl]methyl}-N-{2-morpholino-2-phenylethyl}benzamide S158

To a solution of 12 (217 mg, 0.5 mmol), 1-ethyl-3-{3-dimethylaminopropyl}carbodiimide (96 mg, 0.5 mmol), hydroxybenzotriazole (81 mg, 0.6 mmol), and diisopropylethylamine (261 μL, 1.5 mmol) in DMF (10 mL) was added 2-(morpholin-4-yl)-2-phenylethan-1-amine (103 mg, 0.5 mmol). The reaction mixture was stirred for 16 h at 50 °C. The reaction mixture was then concentrated in vacuo and the resulting residue purified via flash column chromatography (0 % - 10 % MeOH, CH₂Cl₂, 1 % NH₄OH) to give S158 (310 mg, 100 %) as a white solid.

mp 201 °C; νₘₐₓ/cm⁻¹ 3297 (NH), 1640 (C=O); δ_H (200 MHz, CDCl₃) 8.75 - 8.86 (1 H, m, quinoline-Ar), 8.41 - 8.56 (1 H, m, quinoline-Ar), 8.02 - 8.11 (1 H, m, quinoline-Ar), 8.00 (2 H, s, Ar), 7.84 - 7.94 (2 H, m, Ar), 7.76 - 7.82 (1 H, m, Ar), 7.34 - 7.62 (8 H, m, Ar), 7.14 - 7.10 (4 H, m, Ar), 6.77 (1 H, d, J=8.5 Hz, benzyl-H), 4.50 (2 H, m, CH₂), 2.94 (4 H, m), 2.87 (4 H, m); m/z (ESI⁺) 621 ([M+H⁺]); HRMS (ESI⁺) C₃₆H₃₄O₄N₄Cl, ([M+H⁺]) requires 621.2263; found 621.2257.

N-((5-Amino-8-hydroxyquinolin-7-yl)(3-bromophenyl)methyl)benzamide S159

S58 (256 mg, 0.54 mmol) was suspended in ethanol (10 mL) and a 1M aqueous solution of sodium dithionite (5 mL) was added. The mixture was stirred under reflux for 16 h, cooled to room temperature and concentrated under reduced pressure. The residue was redissolved in CH₂Cl₂ and extracted with sodium bicarbonate. The organic layer was washed with brine and concentrated under reduced pressure to give S159 as a yellow powder (197 mg, 81 %).

mp 202 - 203 °C; νₘₐₓ/cm⁻¹ 3338 (NH), 1633 (C=O); δ_N (400 MHz, DMSO-d₆) 9.15 - 9.25 (1 H, m, quinoline-Ar), 8.95 (1 H, br. s., NH), 8.76 - 8.83 (1 H, m, quinoline-Ar), 8.43 - 8.56 (1 H, m, quinoline-Ar), 7.88 - 8.00 (2 H, m, Ar), 7.52 - 7.59 (1 H, m, Ar), 7.41 - 7.51 (5 H, m, Ar), 7.25 - 7.38 (2 H, m, Ar), 6.85 (1 H, d, J=8.0 Hz, benzyl-H), 6.76 (1 H, s, Ar), 5.33 (2 H, br. s., NH₂); δ_C (100 MHz, DMSO-d₆) 165.9 (C=O), 148.0, 145.2, 140.6, 138.3, 136.3, 134.3, 131.6, 131.3, 130.5, 129.8, 129.6, 128.2, 127.7,
126.6, 123.9, 121.6, 119.5, 117.9, 107.7, 50.8 (benzyl-\(\text{C}\)); \text{m/z } (\text{ESI}^-) 446 ([\text{M-H}^-]); \text{HRMS (ESI}^-_\text{C}_{23}\text{H}_{17}\text{BrN}_3\text{O}_2, ([\text{M-H}^-]) \text{ requires 446.0474; found 446.0499.}

5-Bromo-8-(2-(trimethylsilyl)ethoxy)quinolone S160

Diisopropylazodicarboxylate (740 \(\mu\)L, 3.6 mmol) was added dropwise to a stirring solution of 5-bromo-8-hydroxyquinoline (400 mg, 1.8 mmol), 2-trimethylsilylethanol (380 \(\mu\)L, 2.7 mmol), and triphenylphosphine (940 mg, 3.6 mmol) in tetrahydrofuran (4 mL) and toluene (4 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 16 h. The reaction mixture was concentrated \textit{in vacuo}. The crude product was purified via flash column chromatography (5 % - 50 % EtOAc, cyclohexane) to give S160 (455 mg, 78 %) as a light-yellow oil.

\(\delta\)H (400 MHz, CDCl\(_3\)) 8.74 - 8.91 (1 H, m, quinoline-Ar), 8.24 - 8.46 (1 H, m, quinoline-Ar), 7.47 - 7.71 (1 H, m, quinoline-Ar), 7.32 - 7.49 (1 H, m, quinoline-Ar), 6.63 - 6.91 (1 H, m, quinoline-Ar), 4.05 - 4.36 (2 H, m, CH\(_2\)), 1.24 - 1.37 (2 H, m, CH\(_2\)), -0.01 (9 H, s, Si(CH\(_3\))\(_3\)); \(\delta\)C (100 MHz, CDCl\(_3\)) 156.0, 151.2, 142.7, 136.9, 131.5, 129.8, 124.0, 112.9, 110.6, 68.0, 23.5, 19.0, 0.0 (Si(CH\(_3\))\(_3\)); \text{m/z} (\text{ESI}^+) 324 ([\text{M+H}^+]).

Quinoline-4,8-diol S161

Xanthurenic acid (5 g, 24.4 mmol) was suspended in diphenyl ether (50 mL) and stirred at 250 °C for 2.5 h. After the reaction mixture had cooled to room temperature, cyclohexane (250 mL) was added and the suspension was filtered. The precipitate was dried under reduced pressure to give S161 as a brown solid (3.9 g, 100 %).

mp 311 °C; \(\delta\)H (400 MHz, DMSO-d\(_6\)) 11.39 (1 H, br. s., OH), 10.74 (1 H, br. s., OH), 7.71 - 7.83 (1 H, m, Ar), 7.49 - 7.56 (1 H, m, Ar), 7.09 - 7.17 (1 H, m, Ar), 7.03 - 7.09 (1 H, m, Ar), 6.01 - 6.09 (1 H, m, Ar); \(\delta\)C (100 MHz, DMSO-d\(_6\)) 177.5, 147.6, 139.8, 131.4, 127.6, 124.0, 115.5, 115.1, 109.4; \text{m/z} (\text{ESI}^-) 160 ([\text{M-H}^-]).
4-Hydroxyquinolin-8-yl 4-methylbenzenesulfonate S162

\[
\text{OH} \\
\text{N} \\
\text{ OTs}
\]

S161 (3.94 g, 24.5 mmol) was dissolved in a 1M aqueous sodium hydroxide solution (25.7 mL). A solution of \( p \)-toluenesulfonyl chloride (4.67 g, 24.5 mmol) in acetone (7 mL) was added dropwise. The reaction mixture was stirred at room temperature for 3 h. Water (30 mL) was added and the precipitate was filtered and washed with water (40 mL) and acetone (40 mL) to give S162 as a light-brown powder (5.379 g, 70 %).

mp 255 °C; \( \delta_H \) (400 MHz, DMSO-\( d_6 \)) 11.47 (1 H, br. s., O\( \text{H} \)), 7.91 - 8.01 (1 H, m, Ar), 7.74 - 7.84 (2 H, m, Ar), 7.65 - 7.73 (1 H, m, Ar), 7.34 - 7.45 (3 H, m, Ar), 7.20 - 7.30 (1 H, m, Ar), 5.97 - 6.09 (1 H, m, Ar), 2.36 (3 H, s, Ar); \( \delta_C \) (100 MHz, DMSO-\( d_6 \)) 147.2, 140.6, 138.8, 133.8, 131.4, 130.9, 129.6, 128.1, 124.8, 124.7, 123.3, 110.2, 22.0 (\( \text{CCH}_3 \)); \( m/z \) (ESI) 314 ([M-H]);

4-Chloroquinolin-8-yl 4-methylbenzenesulfonate S163

\[
\text{Cl} \\
\text{N} \\
\text{ OTs}
\]

S162 (3.15 g, 10 mmol) and phosphorus oxychloride (25 mL, solvent) were stirred under reflux for 1 h. After cooling to room temperature, the reaction mixture was poured into a stirring mixture of ammonium hydroxide and ice. The precipitate was collected by filtration and washed with water to give S163 as a brown solid (2.98 g, 89 %).

mp 139 °C; \( \delta_H \) (400 MHz, DMSO-\( d_6 \)) 8.71 - 8.79 (1 H, m, Ar), 8.11 - 8.21 (1 H, m, Ar), 7.72 - 7.85 (4 H, m, Ar), 7.58 - 7.64 (1 H, m, Ar), 7.38 - 7.44 (2 H, m, Ar), 2.38 (3 H, s, \( \text{CH}_3 \)); \( \delta_C \) (100 MHz, DMSO-\( d_6 \)) 151.7, 146.5, 145.8, 142.7, 142.1, 132.9, 130.8, 129.2, 128.7, 127.9, 124.2, 124.0, 123.4, 22.0 (\( \text{CH}_3 \)); \( m/z \) (FAB) 333 ([M]+);

tert-Butyl 2-((8-(Tosyloxy)quinolin-4-yl)oxy)acetate S164

\[
\text{O} \\
\text{O} \\
\text{N} \\
\text{ OTs}
\]
A 60 % dispersion of sodium hydride in oil (47 mg, 7.8 mmol) was slowly added to a stirring solution of S162 (750 mg, 2.38 mmol) in DMF (15 mL) at room temperature. When hydrogen evolution had ceased, tert-butylbromoacetate was added to the solution and the reaction mixture was stirred for an additional 2 h at room temperature before being diluted with EtOAc and extracted with H₂O and brine. The organic layer was dried over anhydrous MgSO₄ and concentrated in vacuo. The crude product was purified via flash column chromatography (25 % - 50 % EtOAc, cyclohexane) to give S164 (745 mg, 73 %) as an off-white powder. mp 153 °C; δₜ (400 MHz, CDCl₃) 8.49 - 8.56 (1 H, m, quinoline-Ar), 8.05 - 8.14 (1 H, m, quinoline-Ar), 7.68 - 7.79 (2 H, m, Ar), 7.44 - 7.51 (1 H, m, Ar), 7.28 - 7.40 (1 H, m, Ar), 7.06 - 7.16 (2 H, m) 6.44 - 6.54 (1 H, m, Ar), 4.62 (2 H, s, CH₂), 2.27 (3 H, s, CH₃), 1.39 (9 H, s, C(CH₃)₃); δ_C (100 MHz, CDCl₃) 166.5 (C=O), 160.5, 151.3, 145.1, 142.4, 133.0, 129.4, 128.8, 125.2, 123.0, 122.7, 121.3, 101.5, 83.1, 66.7 (CH₃), 28.0 (C(CH₃)₃), 21.6 (CH₃); m/z (ESI⁺) 430 ([M+H⁺]⁺); HRMS (ESI⁺) C₂₂H₂₄NO₆S, ([M+H⁺]⁺) requires 430.1319; found 430.1323.

4-[(1H-Pyrazol-1-yl)quinolin-8-yl] 4-methylbenzenesulfonate S165

Pyrazole (336 mg, 5 mmol) and S163 (333 mg, 1 mmol) were stirred in toluene under reflux for 5 h. The reaction volume was reduced in vacuo and the mixture was left at room temperature. The crystals formed were collected by filtration to give S165 (226 mg, 62 %) as light-brown crystals. mp 141 °C; δₜ (400 MHz, CDCl₃) 8.76 - 8.86 (1 H, m), 8.07 - 8.22 (1 H, m), 7.82 - 7.87 (2 H, m), 7.77 - 7.81 (2 H, m), 7.54 - 7.63 (1 H, m), 7.43 - 7.52 (1 H, m), 7.34 - 7.39 (1 H, m), 7.15 - 7.23 (2 H, m), 6.50 - 6.57 (1 H, m), 2.34 (3 H, s, CH₃); δ_C (100 MHz, CDCl₃) 150.6, 145.6, 145.3, 144.2, 143.2, 142.7, 132.9, 131.3, 129.6, 128.8, 127.0, 124.1, 123.4, 123.2, 116.1, 108.4, 21.7 (CH₃); m/z (ESI⁺) 366 ([M+H⁺]⁺); 8-Sulfoquinoline-4-carboxylic acid S166
Fuming sulphuric acid (65 % SO₃, 1 mL) was added dropwise to 4-quinolinecarboxylic acid (1 g, 5.68 mmol) inside a 10 mL microwave vial. The vial was sealed and the reaction mixture heated at 200 °C in a sand bath for 2 h. The mixture was left to cool down to room temperature and water (5 mL) was added dropwise. The black residue was triturated with water until formation of a homogenous white powder occurred. The powder was collected by filtration and dried under reduced pressure to give S166 (886 mg, 61 %) as a white powder.

mp > 300 °C; νmax/cm⁻¹ 1721 (C=O); δH (400 MHz, DMSO-d₆) 9.50 (1 H, d, J=5.5 Hz, Hₐ), 8.82 (1 H, d, J=8.5 Hz, Hₑ), 8.49 (1 H, d, J=7.5 Hz, Hₐ), 8.43 (1 H, d, J=5.5 Hz, Hₑ) 8.05 (1 H, dd, J=8.5, 7.5 Hz, Hₑ); δC (100 MHz, DMSO-d₆) 166.5 (C=O), 148.5, 146.9, 138.8, 135.2, 133.3, 130.9, 126.7, 123.5; m/z (ESI⁻) 252 ([M-H]⁻); HRMS (ESI⁻) C₁₀H₇NO₂S, ([M+Na⁻]) requires 275.9937; found 275.9940.

8-((tert-Butyldimethylsilyloxy)-5-chloro-7-iodoquinoline S167

![Chemical structure of S167](image)

tert-Butyldimethylsilyl chloride (3.32 g, 22 mmol) was slowly added to a stirring solution of clioquinol (6.11 g, 20 mmol) and imidazole (1.43 g, 21 mmol) in CH₂Cl₂ (50 mL) at room temperature. The reaction mixture was stirred for 12 h, diluted with Et₂O (500 mL), washed with a 0.1 M aqueous solution of HCl (50 mL), water (100 mL), brine (100 mL) and dried over anhydrous MgSO₄. The solvent was subsequently evaporated under reduced pressure to give S167 (7.91 g, 94 %) as an off-white powder.

mp 81 °C; νmax/cm⁻¹ 1096 (Si-O); δH (400 MHz, CDCl₃) 8.69 - 8.94 (1 H, m, Ar), 8.32 - 8.59 (1 H, m, Ar), 7.95 (1 H, s, Ar), 7.40 - 7.59 (1 H, m, Ar), 1.14 (9 H, s, Si(CH₃)₂C(CH₃)₃), 0.38 (6 H, s, Si(CH₃)₂C(CH₃)₃); δC (100 MHz, CDCl₃) 153.2, 147.9, 139.8, 135.7, 133.1, 126.8, 122.2, 121.9, 85.2, 26.3 Si(CH₃)₂C(CH₃)₃, 19.6 Si(CH₃)₂C(CH₃)₃, -2.1 Si(CH₃)₂C(CH₃)₃; m/z (ESI⁺) 420 ([M+H⁺]); HRMS (ESI⁺) C₁₅H₂₁ClINOSi, ([M+H⁺]) requires 420.0042; found 420.0043.

5-Bromoquinolin-8-yl 4-methylbenzenesulfonate S168

![Chemical structure of S168](image)

5-Bromo-8-hydroxyquinoline (2.23 g, 10.0 mmol) was dissolved in a 1M aqueous sodium hydroxide solution (11.0 mL). A solution of p-toluenesulfonyl chloride (1.91 g, 11.0 mmol) in acetone (7 mL) was added dropwise. The reaction mixture was
stirred at room temperature for 3 h. Water (30 mL) was added and the precipitate was filtered and washed with water (40 mL) and acetone (40 mL) to give S168 as an off-white powder (3.08 g, 81%).

mp 134 °C; \( \nu_{\text{max}}/\text{cm}^{-1} \) 3305 (NH), 1369 (S=O); \( \delta_{H} \) (400 MHz, DMSO-\( d_{6} \)) 8.77 - 8.99 (1 H, m, Ar), 8.40 - 8.59 (1 H, m, Ar), 7.90 - 8.06 (1 H, m, Ar), 7.76 - 7.82 (2 H, m, Ar), 7.69 - 7.75 (1 H, m, Ar), 7.43 - 7.47 (1 H, m, Ar), 7.38 - 7.42 (2 H, m, Ar), 2.38 (3 H, s, CH\( _{3} \))]; \( \delta_{C} \) (100 MHz, DMSO-\( d_{6} \)) 152.7, 146.5, 145.5, 142.4, 135.9, 132.9, 130.9, 130.8, 129.3, 128.9, 124.8, 123.8, 120.5, 22.0 (CH\( _{3} \)); \( m/z \) (ESI\(^{+}\)) 378 ([M+H\(^{+}\)]; HRMS (ESI\(^{+}\)) \( C_{16}H_{12}BrNNaO_{3} \), ([M+Na\(^{+}\)] requires 399.9613; found 399.9606.

5-Chloroquino\( l\)-8-y\( l \) 4-methylbenzenesulfonate S169\(^{16}\)

![5-Chloroquino\( l\)-8-y\( l \) 4-methylbenzenesulfonate S169\(^{16}\)](image)

5-Chloro-8-hydroxyquinoline (1.8 g, 10 mmol) was dissolved in a 1M aqueous sodium hydroxide solution (10.5 mL). A solution of p-toluenesulfonyl chloride (1.91 g, 24.5 mmol) in acetone (4 mL) was added dropwise. The reaction mixture was stirred at room temperature for 3 h. Water (20 mL) was added and the precipitate was filtered and washed with water (20 mL) and acetone (20 mL) to give S169 as an off-white powder (2.76 g, 83%).

mp 133 °C; \( \delta_{H} \) (200 MHz, DMSO-\( d_{6} \)) 8.70 - 8.80 (1 H, m, quinoline-Ar), 8.10 - 8.29 (1 H, m, quinoline-Ar), 7.70 - 7.92 (4 H, m, Ar), 7.53 - 7.69 (1 H, m, Ar), 7.30 - 7.50 (2 H, m, Ar), 2.42 (3 H, s, CH\( _{3} \)); \( m/z \) (ESI\(^{+}\)) 334 ([M+H\(^{+}\)].

2-(Amino(phenyl)methyl)quinolin-8-ol S170\(^{4}\)

![2-(Amino(phenyl)methyl)quinolin-8-ol S170\(^{4}\)](image)

Phenyllithium (1.8 M in nBu\(_{2}\)O, 2.72 mL, 4.9 mmol) was slowly added to a stirring solution of 8-hydroxyquinoline-2-carbonitrile (446 mg, 2.45 mmol) in THF at -78 °C. The reaction was allowed to warm to RT over 2 h. After recooling the reaction mixture to -78 °C, EtOH (7 mL) was added dropwise followed by the addition of NaBH\(_{4} \) (110 mg, 2.9 mmol). The reaction mixture was allowed to warm to RT over 3 h. A solution of HCl (1 N in H\(_{2}\)O) was added dropwise until hydrogen evolution ceased. The mixture was treated with saturated aqueous NaHCO\(_{3}\) and then extracted three times with CHCl\(_{3}\). Combined organic layers were dried over anhydrous MgSO\(_{4}\), filtered and reduced to dryness. The organic residue was then recrystallised from toluene to give S170 as a bright-yellow solid (276 mg, 45%).
mp 149-151 °C; ν\text{max}/\text{cm}^{-1} 1244 (NH\text{\textsubscript{2}}); δ\text{H} (400 MHz, Acetone-\text{d}\textsubscript{6}) 8.23 (1 H, d, \textit{J}=8.5 Hz, 4-quinolinyl-H), 7.76 (1 H, d, \textit{J}=8.5 Hz, 3-quinolinyl-H), 7.54 - 7.60 (2 H, m, Ar), 7.38 - 7.47 (2 H, m, Ar), 7.32 - 7.37 (2 H, m, Ar), 7.23 - 7.33 (4 H, m, Ar), 7.07 - 7.14 (1 H, m, Ar), 6.07 (1 H, s), benzyl-H; δ\text{C} (100 MHz, Acetone-\text{d}\textsubscript{6}) 137.1, 128.7, 128.5, 128.1, 127.7, 127.6, 127.2, 126.7, 121.6, 118.3, 117.9, 110.4, 70.6 (benzyl-C); m/z (ESI\textsuperscript{+}) 251 ([M+H]\textsuperscript{+}, 100 %); HRMS (ESI) C\textsubscript{16}H\textsubscript{14}N\textsubscript{2}O, requires 250.1106; found 250.1110.

4-Methoxyquinolin-8-yl 4-methylbenzenesulfonate S171

Sodium hydride (60 % in oil, 190 mg, 4.76 mmol) was stirred with S162 (1000 mg, 3.17 mmol) in DMF (20 mL) at room temperature until H\textsubscript{2} evolution ceased. Methyl trifluoromethylsulfonate (347 μL) was slowly added under N\textsubscript{2}. After 2 h, the reaction mixture was poured into water (140 mL) and allowed to stand at room temperature overnight. The precipitate was collected by filtration and washed with water to give S171 as a white powder (298 mg, 29 %).

mp 147 °C; δ\text{H} (400 MHz, DMSO-\text{d}\textsubscript{6}) 8.09 - 8.19 (1 H, m, Ar), 7.79 - 7.84 (1 H, m, Ar), 7.72 - 7.77 (2 H, m, Ar), 7.45 - 7.52 (2 H, m, Ar), 7.27 - 7.33 (1 H, m, Ar), 7.17 - 7.23 (1 H, m, Ar), 6.03 - 6.08 (1 H, m, Ar), 3.90 (3 H, s, OCH\textsubscript{3}) 2.42 (3 H, s, CH\textsubscript{3}); δ\text{C} (100 MHz, DMSO-\text{d}\textsubscript{6}) 175.9 (COCH\textsubscript{3}), 148.7, 147.5, 131.7, 131.3, 130.9, 130.1, 129.6, 129.3, 127.5, 126.1, 124.0, 110.1, 45.7 (COCH\textsubscript{3}), 22.1 (CH\textsubscript{3}); m/z (ESI\textsuperscript{+}) 352 ([M+Na]\textsuperscript{+}).

4-Chloroquinolin-8-ol S172

S163 (1 g, 3 mmol) was stirred in an aqueous solution of sodium hydroxide (2M, 7.5 mL, 15 mmol) and ethanol (10 mL) under reflux for 1 h. The reaction mixture was diluted with water (50 mL) and neutralised with aqueous HCl to pH 7. The precipitate was collected by filtration to give S172 as a light-brown powder (374 mg, 69 %).

mp 144 °C; ν\text{max}/\text{cm}^{-1} 3154 (OH); δ\text{H} (400 MHz, DMSO-\text{d}\textsubscript{6}) 10.14 (1 H, br. s., OH), 8.67 - 8.87 (1 H, m, Ar), 7.67 - 7.82 (1 H, m, Ar), 7.49 - 7.65 (2 H, m, Ar), 7.07 - 7.31 (1 H, m, Ar); δ\text{C} (100 MHz, DMSO-\text{d}\textsubscript{6}) 154.8, 148.7, 142.1, 140.3, 129.9, 127.4, 122.9, 114.1, 113.6; m/z (FI\textsuperscript{+}) 179 ([M]\textsuperscript{+}).
5-Chloro-7-idoquinolin-8-yl 4-methylbenzenesulfonate S173

Clioquinol (6.11 g, 20.0 mmol) was dissolved in 1M aqueous sodium hydroxide solution (21.0 mL). A solution of p-toluenesulfonyl chloride (3.81 g, 21.0 mmol) in acetone (7 mL) was added dropwise. The reaction mixture was stirred at room temperature for 3 h. Water (30 mL) was added and the precipitate was collected by filtration, and washed with water (40 mL) and acetone (40 mL) to give S173 as an off-white powder (8.0 g, 87%).

mp 136 °C; νmax/cm⁻¹ 1137 (S=O); δH (400 MHz, DMSO-d6) 8.65 - 8.76 (1 H, m, Ar), 8.48 - 8.56 (1 H, m, Ar), 8.25 (1 H, s, Ar), 7.85 (2 H, d, J=8.0 Hz, SCHC), 7.66 - 7.77 (1 H, m, Ar), 7.47 (2 H, d, J=8.0 Hz, SCHC), 2.45 (3 H, s, CH3); δC (100 MHz, DMSO-d6) 152.5, 150.5, 148.3, 146.3, 142.3, 136.1, 135.2, 133.6, 130.6, 130.1, 129.4, 127.1, 124.5, 94.5, 22.1 (CH3); m/z (ESI⁻) 457 ([M-H]⁻); HRMS (ESI⁻) C16H11ClINaO3S, ([M+Na]⁻) requires 481.9085; found 481.9074.

4-Bromoquinolin-8-yl 4-methylbenzenesulfonate S174

S162 (3.07 g, 9.7 mmol) was added portionwise to a stirring solution of phosphorus oxybromide (8.39 g, 29.2 mmol) in CHCl₃ (15 mL). The mixture was heated under reflux for 4 h and poured into an ice/water slurry to decompose the excess phosphorus oxybromide. The CHCl₃ layer was separated and the aqueous layer adjusted to pH 6-7 with ammonium hydroxide and extracted with additional CHCl₃. The combined organic layers were washed with water and brine. The solvent was evaporated under reduced pressure to give S174 (2.53 g, 69 %) as a brown solid.

mp 138 °C; δH (400 MHz, CDCl₃) 8.47 - 8.66 (1 H, m, Ar), 7.97 - 8.26 (1 H, m, Ar), 7.78 - 7.92 (2 H, m, Ar), 7.46 - 7.74 (3 H, m, Ar), 7.07 - 7.35 (2 H, m, Ar), 2.41 (3 H, s, CH3); δC (100 MHz, DMSO-d6) 150.1, 145.5, 145.2, 142.5, 145.2, 142.5, 133.8, 133.0, 129.5, 129.2, 128.7, 127.1, 126.0, 125.9, 123.3, 21.7 (CH3); m/z (ESI⁺) 378 ([M+H]⁺); HRMS (ESI⁺) C16H13BrNO3S, ([M+H]⁺) requires 377.9794; found 377.9786.
**tert-Butyl (8-hydroxyquinolin-5-yl)carbamate S175**

Di-tert-butyl dicarbonate (2.4 g, 11 mmol) was added portionwise to a stirring solution of 5-amino-8-hydroxyquinoline dichloride (2.3 g, 10 mmol) and disopropylethylamine (5.2 mL, 30 mmol) in MeOH (20 mL) at room temperature. Stirring was continued overnight. The white precipitate formed was collected by filtration, washed with MeOH and water, and dried under reduced pressure to give **S175** (1.74 g, 67 %) as a white powder.

- **mp 188 °C; ν_max/cm⁻¹** 3229 (NH) 1680 (Boc C=O);
- δ_H (400 MHz, DMSO-d₆) 9.71 (1 H, s, Ar), 9.02 (1 H, br. s., NH), 8.75 - 8.90 (1 H, m, Ar), 8.19 - 8.40 (1 H, m, Ar), 7.48 - 7.65 (1 H, m, Ar), 7.20 - 7.44 (1 H, m, Ar), 6.90 - 7.15 (1 H, m, Ar), 1.46 (9 H, s, C(CH₃)₃);
- δ_C (100 MHz, DMSO-d₆) 155.4 (C=O), 151.9, 148.8, 139.1, 132.9, 125.5, 124.8, 122.3, 111.3, 79.6 (C(CH₃)₃), 29.0 (C(CH₃)₃);
- m/z (ESI⁺) 259 ([M-H]⁻); HRMS (ESI⁺) C₁₄H₁₆N₂NaO₃, ([M+Na]⁺) requires 283.1053; found 283.1053.

**5-Chloro-7-iodoquinolin-8-yl methanesulfonate S176**

Methanesulfonyl chloride (1 mL, 13 mmol) was added dropwise to a stirring solution of cloquinol (3.1 g, 10 mmol) and triethylamine (2.1 mL) in CH₂Cl₂ at 0 °C. The reaction mixture was warmed to room temperature and stirred for another 12 h before being washed with water, brine, and dried over anhydrous MgSO₄ and concentrated under reduced pressure. The crude product was purified by flash column chromatography using EtOAc/Cyclohexane (30:70) as eluent to give **S176** (3.06 g, 80 %) as a light-orange powder.

- **mp 177 °C; ν_max/cm⁻¹** 1347 (S=O); δ_H (400 MHz, DMSO-d₆) 8.96 - 9.19 (1 H, m, Ar), 8.44 - 8.72 (1 H, m, Ar), 8.29 (1 H, s, Ar), 7.63 - 8.01 (1 H, m, Ar), 3.89 (3 H, s, CH₃); δ_C (100 MHz, DMSO-d₆) 153.2, 148.3, 142.2, 135.9, 134.1, 130.0, 127.2, 124.7, 95.8, 42.2 (CH₃); m/z (ESI⁺) 406 ([M+Na]⁺); HRMS (ESI⁺) C₁₀H₇ClINaO₃S, ([M+Na]⁺) requires 405.8772; found 405.8767.

**5-Morpholinothiophene-2-carbaldehyde S177**

- **mp 177 °C; ν_max/cm⁻¹** 1347 (S=O); δ_H (400 MHz, DMSO-d₆) 8.96 - 9.19 (1 H, m, Ar), 8.44 - 8.72 (1 H, m, Ar), 8.29 (1 H, s, Ar), 7.63 - 8.01 (1 H, m, Ar), 3.89 (3 H, s, CH₃); δ_C (100 MHz, DMSO-d₆) 153.2, 148.3, 142.2, 135.9, 134.1, 130.0, 127.2, 124.7, 95.8, 42.2 (CH₃); m/z (ESI⁺) 406 ([M+Na]⁺); HRMS (ESI⁺) C₁₀H₇ClINaO₃S, ([M+Na]⁺) requires 405.8772; found 405.8767.
A solution of 5-bromothiophene-2-carboxaldehyde (1.2 mL, 10 mmol) and morpholine (2.6 mL, 30 mmol) in water (10 mL) was heated under reflux overnight. The reaction mixture was cooled to room temperature and extracted with CH$_2$Cl$_2$. The organic layer was washed with a saturated aqueous solution of NH$_4$Cl, brine, and concentrated under reduced pressure. The crude product was purified by flash column chromatography using MeOH/CH$_2$Cl$_2$ (5:95) to give S177 (1.22 g, 62 %) as a white powder.

mp 127 °C; $\nu_{\text{max}}$/cm$^{-1}$ 1637 (C=O); $\delta$(H) (400 MHz, CDCl$_3$) 9.57 (1 H, s, CHO), 7.50 (1 H, d, $J$=4.0 Hz, Ar), 6.13 (1 H, d, $J$=4.0 Hz, Ar), 3.80 - 3.87 (4 H, m, CH$_2$), 3.27 - 3.35 (4 H, m, CH$_2$); $\delta$(C) (100 MHz, CDCl$_3$) 180.0 ([CHO]), 167.9, 139.7, 128.2, 104.5, 65.9, 49.5; m/z (ESI$^+$) 199 ([M+H$^+$]); HRMS (ESI$^+$) C$_9$H$_{12}$NO$_2$S, ([M+H$^+$]) requires 199.0583; found 199.0587.

5-Chloro-7-iodoquinolin-8-yl trifluoromethanesulfonate S178

A solution of trifluoromethanesulfonic anhydride (4 mL, 24 mmol) in CH$_2$Cl$_2$ (10 mL) was added dropwise to a solution of clioquinol (6.11 g, 20 mmol) and pyridine (3.23 mL, 40 mmol) in CH$_2$Cl$_2$ (80 mL) at 0 °C. After complete addition, the mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was then diluted with Et$_2$O, quenched with 10 % aqueous HCl and washed successively with saturated aqueous NaHCO$_3$ and brine. The solvent was removed under reduced pressure to afford S178 (7.46 g, 85 %) as a white powder.

mp 92 °C; $\nu_{\text{max}}$/cm$^{-1}$ 1377 (S=O); $\delta$(H) (400 MHz, DMSO-d$_6$) 8.94 - 9.20 (1 H, m, Ar), 8.53 - 8.69 (1 H, m, Ar), 8.37 (1 H, s, Ar), 7.94 - 7.99 (1 H, m, Ar); $\delta$(C) (100 MHz, DMSO-d$_6$) 153.5, 147.6, 140.8, 136.1, 134.2, 131.5, 127.2, 125.3, 92.7; $\delta$(F) (377 MHz, DMSO-d$_6$) -71.9 (CF$_3$); m/z (FI$^+$) 437 ([M$^+$]); HRMS (FI$^+$) C$_{10}$H$_4$ClF$_3$INO$_3$S, ([M$^+$]) requires 436.8597; found 436.8598.

Methyl 8-hydroxyquinoline-4-carboxylate S179

4 (146 mg, 0.77 mmol) was dissolved in MeOH (10 mL). The solution was cooled to 0 °C. Thionyl chloride (67 μL, 0.92 mmol) was added dropwise. The reaction mixture was warmed to room temperature and left to stir for 2 h. The solvent was removed under reduced pressure to give S179 (156 mg, 100 %) as a bright-yellow powder.
mp 240 °C; $\nu_{\text{max}}$/cm$^{-1}$ 1725 (C=O); $\delta$$_{\text{H}}$ (400 MHz, DMSO-$d_6$) 9.06 (1 H, d, $J$=5.0 Hz, $H_1$), 8.07 - 8.14 (2 H, m, $H_{\text{b/e}}$), 7.67 (1 H, t, $J$=8.0 Hz), 7.34 (1 H, d, $J$=7.5 Hz, $H_c$), 3.17 (3 H, s, $CH_3$); $\delta$$_{\text{C}}$ (100 MHz, DMSO-$d_6$) 167.0 (C=O), 152.0, 146.6, 139.4, 136.1, 129.9, 125.7, 122.4, 115.5, 113.1, 48.6 (CH$_3$); $m/z$ (EI$^+$) 188 ([M$^+$]); HRMS (EI$^+$) C$_{11}$H$_9$NO$_3$, ([M$^+$]) requires 203.0582; found 203.0585.

**Quinoxalin-5-ol S180**

![Quinoxalin-5-ol](image)

2,3-Diaminophenol (1 g, 8.1 mmol) was dissolved in a mixture of sodium acetate (11 mL, 4 M aq.) and acetic acid (16 mL, 2 M aq.) and heated to 60 °C. In a second flask, a solution of sodium glyoxal bisulfite (2.25 g, 8.5 mmol) in H$_2$O (60 mL) was heated to 60 °C. The 2,3-diaminophenol solution was then transferred into the sodium glyoxal bisulfite solution with a pipette and stirred for 1 h at 60 °C. After cooling to room temperature, 1N NaOH aq. was used to adjust the pH to ~8. The resulting aqueous solution was then extracted with EtOAc, dried over anhydrous MgSO$_4$ and concentrated in vacuo. The crude product was purified via flash column chromatography (10 % - 50 % EtOAc, cyclohexane) to give S180 (553 mg, 47 %) as a brown powder.

mp 101 °C; $\delta$$_{\text{H}}$ (400 MHz, methanol-$d_4$) 8.32 - 8.91 (2 H, m), 7.52 - 7.61 (1 H, m), 7.38 - 7.47 (1 H, m), 7.02 - 7.12 (1 H, m); $\delta$$_{\text{C}}$ (100 MHz, methanol-$d_4$) 153.4, 145.1, 143.1, 142.8, 133.8, 130.9, 118.5, 111.8; $m/z$ (ESI$^+$) 147 ([M+H$^+$]); HRMS (ESI$^+$) C$_5$H$_5$ON$_2$, ([M-H$^-$]) requires 145.0407; found 145.0405.

**Methyl 2-((5-Chloroquinolin-8-yl)oxy)acetate S181**

![Methyl 2-((5-Chloroquinolin-8-yl)oxy)acetate](image)

A suspension of 5-chloro-8-hydroxyquinoline (900 mg, 5 mmol), methyl bromoacetate (574 µL, 6 mmol), and potassium carbonate (850 mg, 6 mmol) was stirred in a mixture of acetone (10 mL) and tetrahydrofuran (10 mL) for 16 h under reflux. The solvent was evaporated and the residue redissolved in a mixture of EtOAc and H$_2$O. The organic layer was extracted with H$_2$O and brine, dried over anhydrous MgSO$_4$ and concentrated in vacuo. The crude product was purified via flash column chromatography to give S181 (995 mg, 79 %) as an off-white solid.

mp 105 °C; $\nu_{\text{max}}$/cm$^{-1}$ 1771 (C=O); $\delta$H (400 MHz, DMSO-d$_6$) 8.92 - 9.05 (1 H, m, quinoline-Ar), 8.41 - 8.61 (1 H, m, quinoline-Ar), 7.69 - 7.80 (1 H, m, quinoline-Ar), 7.67 (1 H, s, quinoline-Ar), 7.10 - 7.21 (1 H, m, quinoline-Ar), 5.08 (2 H, s, OCH$_2$) 3.73
(3 H, s, CH3); δC (100 MHz, DMSO-d6) 169.4 (C=O), 153.3, 150.4, 140.5, 132.7, 127.1, 126.7, 123.6, 122.1, 110.8, 65.9 (OCH2), 52.4 (CH3); m/z (ESI+) 252 ([M+H]+); HRMS (ESI+) C12H11O3NCl, ([M+H]+) requires 252.0422; found 252.0417.

**Methyl 8-[2-Methoxy-2-oxoethoxy]quinoline-5-carboxylate S182**

![Methyl 8-[2-Methoxy-2-oxoethoxy]quinoline-5-carboxylate S182](image)

A solution of methyl 8-hydroxyquinoline-5-carboxylate (203 mg, 1 mmol), methyl bromoacetate (115 μL, 1 mmol), and potassium carbonate (170 mg, 1.2 mmol) in a mixture of acetone (2 mL) and THF (2 mL) was stirred at 100 °C for 2 h under microwave irradiation. The solvent was evaporated under reduced pressure and the residue was redissolved in EtOAc (10 mL) and water (10 mL). The organic layer was washed with brine, dried over anhydrous Na2SO4 and concentrated in vacuo.

The crude reaction product was purified via flash column chromatography (0 % - 10 % MeOH, CH2Cl2) to give S182 (264 mg, 96 %) as an off-white solid.

mp 151 °C; νmax/cm⁻¹ 1767 (C=O); δH (400 MHz, DMSO-d6) 9.19 - 9.40 (1 H, m, Ar), 8.82 - 9.04 (1 H, m, Ar), 8.13 - 8.29 (1 H, m, Ar), 7.56 - 7.81 (1 H, m, Ar), 7.03 - 7.36 (1 H, m, Ar), 5.17 (2 H, s, C\(\text{H}_2\)), 3.92 (3 H, s, C\(\text{H}_3\)), 3.75 (3 H, s, C\(\text{H}_3\)); δC (100 MHz, DMSO-d6) 169.1 (C=O), 166.5 (C=O), 157.7, 149.8, 139.7, 134.1, 132.6, 128.2, 123.8, 118.7, 108.9, 65.8 (CH2), 52.6 (OCH3), 52.5 (OCH3); m/z (ESI+) 276 ([M+H]+); HRMS (ESI+) C14H14O5N, ([M+H]+) requires 276.0867; found 276.0863.

**Methyl 8-Hydroxy-2-methylquinoline-5-carboxylate S183**

![Methyl 8-Hydroxy-2-methylquinoline-5-carboxylate S183](image)

Thionyl chloride (870 μL, 12 mmol) was added dropwise to a stirring suspension of S15 (2.03 g, 10 mmol) in methanol (50 mL) at 0 °C. The resulting mixture was brought to boiling and stirred for 16 h under reflux. After cooling to room temperature, the solvent was removed in vacuo to give S183 (2.2 g, 100 %) as a light-brown solid.

mp 228 °C; νmax/cm⁻¹ 1702 (C=O); δH (200 MHz, DMSO-d6) 9.44 - 9.80 (1 H, m, Ar), 8.22 - 8.45 (1 H, m, Ar), 7.80 - 8.08 (1 H, m, Ar), 7.39 - 7.63 (1 H, m), 3.91 (3 H, s, CH3), 2.93 (3 H, s, CH3); m/z (ESI+) 218 ([M+H]+); HRMS (ESI+) C12H12O3N, ([M+H]+) requires 218.0812; found 218.0809.
**Tert-Butyl (3-bromophenyl)carbamate S18**

![Chemical Structure](image)

Di-tert-butyl dicarbonate (2.18 g, 10 mmol) was added portionwise to a stirring solution of 3-bromoaniline (1088 μL, 10 mmol) in CH₂Cl₂ at room temperature. After 18 h the reaction mixture was poured into ice-cold water and extracted with CH₂Cl₂. The organic layer was washed with brine and dried over anhydrous MgSO₄. The solvent was removed under reduced pressure to give S18 (2.72 g, 100%) as a light-pink solid.

mp 78 °C; δₜₙ (400 MHz, DMSO-d₆) 9.56 (1 H, s, NH), 7.76 (1 H, s, Ar), 7.35 - 7.41 (1 H, m, Ar), 7.16 - 7.23 (1 H, m, Ar), 7.10 - 7.15 (1 H, m, Ar), 1.47 (9 H, s, C(CH₃)₃); δc (100 MHz, DMSO-d₆) 153.4 (C=O), 142.1, 131.5, 125.4, 121.1, 117.7, 80.4 (C(CH₃)₃), 28.9 (C(CH₃)₃); m/z (ESI-) 270 ([M-H]-).
NMR Spectra of compounds tested in cells

1H NMR of CCT1 in DMSO

[Image of 1H NMR spectrum of CCT1 in DMSO]

13C NMR of CCT1 in DMSO

[Image of 13C NMR spectrum of CCT1 in DMSO]
1H NMR of CCT2 in CDCl₃

13C NMR of CCT2 in CDCl₃
1H NMR of 27 in DMSO

13C NMR of 27 in DMSO
1H NMR of 28 in DMSO

13C NMR of 28 in DMSO
1H NMR of S85 in DMSO

13C NMR of S85 in DMSO
1H NMR of S120 in DMSO

13C NMR of S120 in DMSO
General Experimental for Biological Work

AlphaScreen® activity assays

KDM and PHD2 assays were carried out as previously reported. In brief, enzyme and inhibitor were pre-incubated in assay buffer (50 mM HEPES pH 7.5, 0.1 % w/v BSA and 0.01 % v/v Tween-20) for 15 min before initiation of the reaction with substrate containing sodium ascorbate (100 μM), ferrous ammonium sulphate (1 – 10 μM), peptide substrate and 2OG at or near the respective K_m concentrations (final assay volume of 10 μL) in 384-well white Proxiplates (Perkin Elmer). Reactions were quenched with 5 μL 30 mM EDTA and 5 μL ALPHA screen donor and acceptor beads (Protein A donor and streptavidin acceptor beads, pre-incubated with the required antibodies, final bead concentration 0.02 mg.mL^-1_) were added (Perkin Elmer). The sample was left in the dark for 1 hour before analysis using an EnVision™ 2104 Multilabel Reader (Perkin Elmer). Where necessary for inhibitor solubilisation, 1 % DMSO (final concentration) was included in the assay buffer. Data were normalised to a no-enzyme control.

KDM4C RapidFire™ Mass Spectrometry (RF-MS) assay

Inhibition of KDM4C activity was assessed by RapidFire™ MS as previously reported. Inhibition assays were performed using a 384-well plate format with polypropylene V-bottom plates (Greiner Bio One). 2-(N-Morpholino) ethanesulphonic acid (MES buffer) was from Thermo Fisher Scientific. The KDM4C H3-K9 trimethyl peptide substrate: ARTAQTARK(me3)STGGIA was synthesized by Peptide Protein Research Ltd (Hampshire, UK).

KDM4C enzyme (300 nM, 25 μL) in assay buffer (50 mM MES pH7.0) was transferred into each well of a 384-well polypropylene microplate. Titrations of compounds (0.1 μl) were transferred to each well and the enzyme incubated with compound for 15 minutes. Substrate mix (25 μl) consisting of FAS (20 μM), L-AA (200 μM), 2OG (20 μM) and peptide (20 μM) was dispensed into each well and the enzyme reaction progressed for 50 minutes. The enzyme reaction was stopped by addition of 5 μl of 10% formic acid and transferred to a RapidFire™ RF360 high-throughput sampling robot connected to an Agilent 6530 Accurate-Mass Quadrupole Time-of-Flight (Q-TOF) mass spectrometer operated in positive ion mode (Agilent, Wakefield, MA USA).

Samples were aspirated under vacuum for 400 ms, loaded onto a C4 SPE cartridge and buffer salts were removed by washing the cartridge with 0.1 % formic acid in water at a flow rate of 1.5 ml / min for 4.5 sec. Following the aqueous wash peptides were eluted onto the mass spectrometer with 85 % acetonitrile, 15 % deionised water containing 0.1 % formic acid at a flow rate of 1.25 ml / min for 4.5 seconds. The cartridge was re-equilibrated with water for 500 ms.

Ion chromatogram data was extracted for the +3 charge state for the substrate and the corresponding product and peak area data for extracted ion chromatograms were integrated using RapidFire™ Integrator software (Agilent, Wakefield, MA, USA) to determine % conversion. IC_{50} data were determined from nonlinear regression curve fit using GraphPad Prism 5.
Non-denaturing ESI-MS studies

PHD2 was desalted using a Bio-Spin 6 Column (Bio-Rad, Hemel Hempstead, U.K.) in 15 mM ammonium acetate (pH 7.5). The stock solution was diluted with the same buffer to a final concentration of 100 μM. Compounds at a 60 mM stock concentration in DMSO were further diluted in ammonium acetate to a concentration of 100 μM. MnSO₄ and 2OG were dissolved in MilliQ water at a concentration of 100 mM. This was then diluted with MilliQ water to give a final working concentration of 100 μM. The protein was mixed with Mn(II), compounds, and 2OG to give final concentrations of 15 μM PHD2, 15 μM Mn(II), and 15 μM compound and 15 μM 2OG. ESI-MS analysis was performed immediately without incubation.

Mass spectrometric data were acquired using a Q-TOF mass spectrometer (Q-TOF micro, Micromass, Altrincham, U.K.) interfaced with a NanoMate (Advion Biosciences, Ithaca, NY) with a chip voltage of 1.70 kV and a delivery pressure 0.5 psi. The sample cone voltage was typically 30 V with a source temperature of 60 °C and with an acquisition/scan time of 1 s/1 s. Calibration and sample acquisition were performed in the positive ion mode in the range of 2000-3700 m/z. The pressure at the interface between the atmospheric source and the high vacuum region was fixed at 6.30 mbar. External instrument calibration was achieved using a 2:1 mixture of myoglobin/trypsinogen. Data were processed with the MassLynx 4.0 (Waters).

MALDI-TOF MS assays

The PHD2 mass spectrometry-based activity assays were performed by determining the extent of hydroxylation of HIF-1αCODD peptide substrate (HIF-1α residues 556-574) by MALDI-TOF MS. The optimised hydroxylation assay involved incubation of PHD2 (1 μM) with inhibitor (1 % v/v in DMSO) in the presence of Fe(II) (10 μM), 2OG (60 μM), ascorbate (100 μM) and HIF-1αCODD 556-574 (50 μM) in HEPES (50 mM, pH 7.5) at 37 °C for 15 min. Reactions were quenched with formic acid (1 % v/v). Samples were prepared by mixing reaction mixture (1 μL) with α-cyano-4-hydrocinnamic acid (CHCA) solution (water: acetonitrile 1:1) (1 μL). Dose-response was assessed in 8-point triplicates. Data were analysed using GraphPad Prism® 5.04.

FIH activity assays were performed by determining the extent of hydroxylation of a synthetic ankyrin peptide (sequence: HLEVVKLLLEAGADVNAQDK) by matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry (MALDI-TOF MS) using a Waters® Micromass® MALDI micro MX™ mass spectrometer and MassLynx™ 4.1. The optimised hydroxylation assay involved incubation of FIH (50 nM) with inhibitor (1% v/v in DMSO) in the presence of Fe(II) (10 μM), 2OG (100 μM), ascorbate (2 mM) and synthetic ankyrin peptide (50 μM) in HEPES (50 mM, pH 7.5) at room temperature for 5 min. Reactions were quenched with formic acid (1% v/v). Samples were prepared by mixing reaction mixture (1μL) with α-cyano-4-hydrocinnamic acid solution (water: acetonitrile 1:1) (1 μL).

For inhibition assays, enzymes were pre-incubated with inhibitor for 5 min before initiation of the reaction with all other reagents. Data were normalised to both a no enzyme negative control and a no inhibitor positive control.
Viability analysis

Cell viability assays were carried out as previously reported. Cells were plated at 1500-3000 cells/well in 96 well plates and treated the next day with increasing doses of compound over 4 days and their viability assessed by standard MTS assays using Promega’s Cell Titer or Cell Titer-Glo reagents according to the manufacturer’s protocols. Absorbance at 490 nm and 650 nm (reference wavelength) or luminescence was measured by a Spectra Max (Molecular Devices) or a FluroStar Omega (BMG Biosciences) plate reader. Data were normalized to the untreated controls (100% viability). Each cell line was tested in 2-5 independent assays, each containing 4-8 replicates. IC50 values were calculated using DIVISA, a high-throughput software, developed in-house (EDM) (Girard et al, manuscript in preparation), for storing and analyzing drug sensitivity assays. Dose-response curves were plotted using a non-linear regression model and IC50s were determined from the fitted curves. The average IC50 derived from 2-5 independent assays, each containing 4-8 replicates is reported.

Immunofluorescence assays

Hela cells (8000 cells per well) were plated into 96-well plates one day prior to transfection. Cells were transiently transfected with full-length flag-tagged wild type (WT) KDM4A or H188A catalytically inactive (Mutant) KDM4A using Lipofectamine® 2000 as previously described (KDM4A plasmids were a kind gift from Prof. Yi Zhang). Transfection was carried out with cells at ~50 % confluency as judged using a Motic AE20 (Ted Pella) microscope. 2 hours prior to transfection media were exchanged for fresh media. DNA for transfection (0.1 μg per well) and transfection reagent (0.2 μL Lipofectamine® 2000 per well) were separately diluted in OptiMEM® and incubated at room temperature for 5 min. The two reagents were then mixed and left at room temperature for 10 min before adding dropwise to the cells. Transfected cells were dosed with compounds (in < 1% DMSO final concentration) 4hrs after transfection, and treated for 24hrs.

For MCF7 cells (no KDM overexpression), 5000 cells per well were seeded into 96 well plates one day prior to compound dosing. Both media and inhibitors were replaced every 24 h over 72 hrs.

After compound treatment, cells were washed with PBS, fixed with 4 % formaldehyde in PBS (15 min at RT), and washed (PBS, 2 x 10 min). Cells were permeabilised by incubation for 8 min at RT with 0.2 % Triton-X100 in PBS, washed (PBS, 3x, 30 min), and blocked with 5 % FBS in PBS (30 min, RT). Primary antibodies were diluted in blocking buffer (anti-H3K9me3 (Abcam – AB9909, dilution 1:500); anti-Flag (Sigma - Cat no. F3165-IMG, dilution 1:1000)), incubated with cells at room temperature (HeLa, 16 h; MCF7, 1 h), and subsequently washed (PBS, 3 x 10 min). Cells were then incubated (1 h, room temperature, dark) with secondary antibodies diluted in blocking buffer (Alexafluor 488 (Life Technologies - Cat. A11034, dilution 1:500); Alexafluor 594 (Life Technologies - Cat. A11032, dilution 1:500)), then washed with PBS (3 x 10 min), stained with DAPI (0.2 μg.mL-1) and washed with PBS (3 x 10 min) before visualisation. Cells were visualised using a Zeiss Axioobserver epifluorescence microscope with a 20 x objective. In Hela transfection assays, H3K9me3 levels of the transfected cells
(selected based on higher FLAG immunofluorescence than mock transfected cells) were quantitated, whereas in MCF7 cell assays, the global H3K9me3 levels of the cell population were quantitated.

**Global histone analysis**

Prepared cell (HEK293T) pellets were suspended in cooled hypotonic lysis buffer (10 mM Tris-HCl pH 8.0, 1 mM KCl, 1.5 mM MgCl₂, 1 mM dithiothreitol (DTT) and 1 mM phenylmethanesulfonylfluoride (PMSF), supplemented with 1x protease and phosphatase inhibitor and then incubated on a rotor at 4 °C for 30 minutes. The nuclei were pelleted by centrifugation at 10,000g for 10 min at 4 °C, and then the supernatant was removed. Pellets were resuspended in 400 μl 0.4 M ice-cold HCl. The sample was then centrifuged at 16,000 g for 10 min at 4 °C and the supernatant containing histones was transferred into a fresh tube. Following the above acid extraction method, approximately 400 μl of supernatant was added to the 15 mL falcon tube with 4 mL of acetone and then placed at -20 °C overnight for precipitation. The sample was centrifuged for 10 min at 2,500 g and at 4 °C. The supernatant was carefully discarded and the pellet was transferred into the fresh 1.5 ml tube. Three washes with ice-cold acetone were carried out by centrifugation at 16,000 g for 5 min and at 4 °C. The pellet was dried at room temperature. The appropriate volume of 0.1 % folic acid or H₂O (typically 100 μL) was added to dissolve the final pellet and the solution was stored at -20 °C.

Samples of histones were separated by reversed phase ultra-performance liquid chromatography (RP-UPLC) and analysed by electrospray ionisation time-of-flight mass spectrometry (ESI-TOF MS, Waters Acquity UPLC system, Waters LCT ESI-TOF MS). UPLC separation was carried out at a flow of 0.25 mL/min on a Waters BEH C4 reversed phase column (2.1 x 150 mm, 1.7μm particle size, 300 Å pore size) at 40 °C. The MS parameters settings were as follows: polarity mode: ES+; capillary voltage: 3,000 V; sample cone voltage: 35 V; extraction cone voltage: 2.5V; desolvation temperature: 250 °C; cone gas flow rate: 10 L/hour; desolvation gas flow (N2): 500 L/hour. The mass range were covered from 100 to 2000 m/z using MassLynx 4.1 software (Waters) and histones molecular weight and distribution were acquired using Maxent 1 with mass accuracy 70 ppm and continuum mode at the rate of 1 spectrum/s. Masses were confirmed using manual component analysis. Leu-Enkephalin was used as lock spray reagent for calibration of the mass spectrometer at the monoisotopic mass of 556.277 [M+H]⁺.

**Immunoblotting**

Cells were extracted using urea/SDS buffer (6.7 M urea, 10 mM Tris-HCl pH 6.8, 10% glycerol and 1% SDS) and processed for immunoblotting as described. The following primary antibodies were used for immunoblotting: mouse monoclonal HIF-1α antibody clone 54 (610958, BD Transduction Laboratories, 1:1000), rabbit polyclonal HIF-1α hydroxy-Pro402 antibody (07-1585, Millipore, 1:1000), rabbit monoclonal HIF-1α hydroxy-Pro564 antibody clone D43B5 (3434S, Cell Signaling, 1:500), mouse monoclonal HIF-1α hydroxy-Asn803 antibody (a kind gift from Dr M. K. Lee, Republic of Korea, 1:4000), mouse
monoclonal PHD2 antibody clone 76a\textsuperscript{37} (1:10) and β-actin/HRP (clone AC15, Abcam). HRP-conjugated swine polyclonal anti-rabbit IgG (P0399, Dako), and goat polyclonal anti-mouse IgG (P0447, Dako) were used as secondary antibodies.
**Supplementary Biochemical Data**

**ST1**

ST1 Activity of IOX1 against isolated recombinant 2OG oxygenases.

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>IC₅₀ (μM)</th>
<th>Enzyme</th>
<th>IC₅₀ (μM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KDM6B</td>
<td>0.12</td>
<td>KDM2A</td>
<td>10.3</td>
</tr>
<tr>
<td>KDM3A</td>
<td>0.17</td>
<td>PHD2</td>
<td>14.3</td>
</tr>
<tr>
<td>KDM4A</td>
<td>0.2</td>
<td>FIH</td>
<td>20.5</td>
</tr>
<tr>
<td>KDM4E</td>
<td>0.3</td>
<td>KDM5C</td>
<td>25</td>
</tr>
<tr>
<td>KDM4C</td>
<td>0.6</td>
<td>PHF8</td>
<td>37</td>
</tr>
<tr>
<td>KDM6A</td>
<td>1.0</td>
<td>BBOX1</td>
<td>196</td>
</tr>
<tr>
<td>Compound</td>
<td>Structure</td>
<td>In vitro IC₅₀ in μM (KDM4)</td>
<td>Cellular EC₅₀ in μM (KDM4A)</td>
</tr>
<tr>
<td>----------</td>
<td>-----------</td>
<td>-----------------------------</td>
<td>------------------------------</td>
</tr>
<tr>
<td>IOX1</td>
<td><img src="image" alt="IOX1 Structure" /></td>
<td>0.29 (KDM4A)</td>
<td>86</td>
</tr>
<tr>
<td>27</td>
<td><img src="image" alt="27 Structure" /></td>
<td>9 (KDM4C)</td>
<td>33</td>
</tr>
<tr>
<td>28</td>
<td><img src="image" alt="28 Structure" /></td>
<td>19 (KDM4E)</td>
<td>17</td>
</tr>
<tr>
<td>S85</td>
<td><img src="image" alt="S85 Structure" /></td>
<td>22 (KDM4E)</td>
<td>16</td>
</tr>
<tr>
<td>S120</td>
<td><img src="image" alt="S120 Structure" /></td>
<td>5 (KDM4E)</td>
<td>11</td>
</tr>
</tbody>
</table>

SF1 | Cellular activities in HeLa cells with transiently overexpressed KDM4A for selected compounds as determined by immunofluorescence-based analysis, alongside the activities against isolated recombinant KDM4s and KDM6B. Quantitation of H3K9me3 fluorescence levels in the KDM4A transfected cells was assessed by three independent biological repeats. Data points represent the mean for triplicate assays with standard error as error bars.
SF2

A. Studies on CCT1 enantiomers. (A) Resolution of CCT1 enantiomers using ultra performance liquid chromatography (UPLC) (multiple 10 µl injections on chiralpak IC column (4.6mm, 250 mm, 5 µm), isocratic heptane/isopropanol 3/1, flow rate 1 mL/min, column temperature 35°C). The separation was conducted by Dr Clarisse Lejeune at the Institut de Chimie de Substances Naturelles in Gif-sur-Yvette, France.

B. Activity of racemic CCT1 and resolved CCT1 enantiomers on isolated recombinant KDM4C.

<table>
<thead>
<tr>
<th>Compound</th>
<th>IC_{50}/µM (KDM4C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCT1 (racemic)</td>
<td>5 µM</td>
</tr>
<tr>
<td>CCT1a</td>
<td>6 µM</td>
</tr>
<tr>
<td>CCT1b</td>
<td>10 µM</td>
</tr>
</tbody>
</table>
SF3

A. Views of HeLa cells used in the immunofluorescence-based assay (Fig 5B) with transiently overexpressed KDM4A after compound treatment. CCT2 and IOX1 have little effect on cell numbers relative to the DMSO control at the tested concentrations. (B) Effects of CCT1, CCT2, and IOX1 on endogenous H3K9me3 levels in MCF7 cells after 72 h dosing as determined by immunofluorescence-based analysis. Data points represent the mean for triplicate assays with standard error as error bars. (C) Views of MCF7 cells grown in the presence of CCT1 and CCT2 for 72 h. (D) Effect of CCT1, CCT2, and IOX1 on MCF7 cell numbers after treatment for 72 h.
SF4
H2A

H2B
SF4 Mass spectrometry analysis of histones H2A, H2B, and H4 extracted from HEK293T cells after treatment with 30 μM of CCT1 for 24 h. Note the lack of effect on H2A, H2B, and H4 compared to H3 (see Fig. 5D).
The effect of CCT1 on the hypoxia-inducible factor (HIF) pathway. (A) Activity of CCT1, CCT2, and FG4592 against PHD2 as measured by AlphaScreen® assay. (B) Non-denaturing mass spectrometry analysis of equimolar amounts (15 μM each) of PHD2, Fe(II) and CCT1 in ammonium acetate buffer, 15 mM, pH 7.5. (C) Non-denaturing mass spectrometry analysis of (i) apo-PHD2 (15 μM); (ii) apo-PHD2 (15 μM), Fe(II) (7 μM); (iii) apo-PHD2 (15 μM), Fe(II) (7 μM), CCT1 (15 μM); (iv) apo-PHD2 (15 μM), Fe(II) (7 μM), CCT1 (78 μM). No binding for CCT1 or CCT2 was observed.
Immunoblot showing the upregulation of HIF-1α protein by CCT1, but not CCT2, in HeLa cells. (A) Immunoblot showing the upregulation of HIF-1α by CCT1 and the reversal of the effect by re-introducing Fe(II) in HeLa cells. A similar effect is observed with the iron chelator desferrioxamine (DFO), but not the PHD2 inhibitor FG4592. Compound concentration: DMSO: 1%, DFO: 250 μM, FG4592: 20 μM, CCT1: 20 μM. Total treatment for 22 hours – initial treatment with inhibitors and then add Fe(II) (ferric ammonium sulphate) at the 7th hour. (B) Immunoblot showing the inhibition of HIF-1α prolyl (CODD and NODD) and asparaginyl hydroxylation (CAD) in VHL-defective RCC4 cells by CCT1. (C) Reversal of the effect observed for (B) by re-introducing Fe(II) in HeLa cells. A similar effect is observed with the iron chelator desferrioxamine (DFO), but not the PHD2 inhibitor FG4592. Compound concentration: DMSO: 1%, DFO: 250 μM, FG4592: 20 μM, CCT1: 20 μM. Total treatment for 22 hours – initial treatment with inhibitors and then add Fe(II) (ferric ammonium sulphate) after 7 hours.
References


