There is interest in developing potent, selective, and cell-permeable inhibitors of human ferrous iron and 2-oxoglutarate (2OG) oxygenases for use in functional and target validation studies. The 3-component Betti reaction enables efficient one-step C-7 functionalisation of modified 8-hydroxyquinolines (BHQs) to produce cell-active inhibitors of KDM4 histone demethylases and other 2OG oxygenases; the work exemplifies how a template-based metallo-enzyme inhibitor approach can be used to give biologically active compounds.

The application of modern molecular biology techniques has led to the identification of a plethora of potential pharmaceutical targets. Applying efficient methods to validate these targets is an objective of academic and commercial research at the chemistry-biology-medicine interface, in many cases requiring both genetic and chemical approaches.1 We are interested in defining readily applicable methods for the synthesis of small molecules for use as functional probes for metallo-enzymes, in particular the 60-70 human ferrous iron and 2-oxoglutarate 1 (2OG)-dependent oxygenases. 2OG oxygenases play roles in all stages of protein biosynthesis in humans, including translation, splicing, and transcription.2 The reversible methylation of histones is of central importance in eukaryotic transcriptional regulation. The JmJC 2OG oxygenases are the largest family of histone lysyl demethylases (KDMs) with >15 human members grouped into 6 subfamilies (KDM2-7), some of which are anticancer targets.3

Defining the functions of the JmjC domains is challenging, in part because of the presence of multiple other domains in the JmJC-containing proteins, and in part because of redundancy. There is interest in developing inhibitors not only for specific 2OG oxygenases, but for specific enzyme sets, in order to up- or down-regulate expression of specific sets of genes.4 There are 6 human KDM4 enzymes, KDM4A-F (KDM4E/F being pseudogenes); their preferred substrates are histone 3 lysine 9 (H3K9) and histone 3 lysine 36 (H3K36) (for KDM4A-C only) N-tri- and dimethylated lysines (H3K9me3 being demethylated most efficiently).5 Although some 2OG oxygenase-selective inhibitors are reported,4 including for JmJC KDMs, no such
compounds are reported for the KDM4 subfamily, and there is little work on developing methods for generating inhibitors for different sets of 2OG oxygenases. We report that a modified Betti reaction is useful for efficient modification of 8-hydroxyquinoline templates for the generation of cell-active KDM4 and other 2OG oxygenase inhibitors.

Structural analyses reveal that 2OG oxygenase substrate binding sites vary considerably, but their Fe(II) and 2OG binding pockets are more conserved; during catalysis, 2OG binding is followed by substrate, then O2 (Fig. 1A). 2OG chelates to the metal in a bidentate manner via its keto and C-1 carboxylate; the 2OG binding site is thus attractive for targeting template inhibitors (Fig. 1B), with the substrate binding site offering a region into which selectivity-enabling side chains could extend. We recently reported that the 2OG analogue 8-hydroxyquinoline-5-carboxylic acid, IOX1, is a broad-spectrum 2OG oxygenase inhibitor active against enzymes including the JmJC KDMs (Fig. 1C, 2A, ST1). Some 7-substituted 8-hydroxyquinoline (8HQ) derivatives (e.g. 5 and 6, Fig. 2A) inhibit a 2OG oxygenase, the prolyl hydroxylase domain (PHD2), which is involved in transcription factor modification. IOX1 binds to the metal of 2OG oxygenases via its pyridinyl nitrogen and phenolic oxygen, and its C-5 carboxylate binds similarly to that of 2OG (Fig. 1C). We therefore considered 8HQ as a potential template for efficient modification to obtain 2OG oxygenase inhibitors.

Modelling of 8HQ inhibitors based on KDM4A structures indicates that modifications at C-7 of 8HQ will extend towards the substrate binding site (Fig. 4C). We considered methods for C-7 derivatisation and investigated the 3-component Betti reaction, which classically comprises C-α functionalisation of phenols via a Mannich-type process (Fig. 2B). Preliminary studies employed aromatic amides and aldehydes under high-temperature and solvent-free conditions to give e.g. 7 (Fig. 2C). Heating 8HQ 15, benzamidine, and benzoaldehyde 9 (180 °C, 3h) afforded a crude mixture; treatment with toluene precipitated the desired racem product 7 on cooling, with unreacted starting materials remaining in solution (Fig. 2A). In vitro activity assay results with 7 as an inhibitor of KDM4C/E (see below) encouraged further structure-activity relationship (SAR) studies employing commercial and synthetic aldehydes (prepared by nitrile reduction using disobutylaluminium hydride (supplementary information S1)), or amides using sodium perborate tetrahydrate with microwave irradiation (S2). Modified 8HQs were prepared from the requisite 2-amino phenols and acroleins via Skraup condensation (S3-S15); 4- and 5-substituted 8HQs and biphenyl-containing aldehydes were prepared via palladium-mediated cross-coupling (S16-S26). When conducting the Betti-type reaction at 130 °C, below which little product formation was observed, a wide variety of non-nucleophilic aromatic (S28-S73), heterocyclic (S74-S115), electron-rich (S116-S132), and –poor aldehydes (S133-S138), with primary amides, gave the desired 7-substituted 8HQs. Aliphatic amides, but not aliphatic aldehydes, yielded the desired products (S139-S149). Amines, instead of amides, can be used employing the standard Betti conditions (Fig. 3A, S150-S153). Reactions in the presence of nucleophiles, e.g. free alcohols or amines, did not yield the desired products; nucleophilic substituents were introduced after Betti reaction, e.g. amines by amide coupling involving the free acid 23 to give S154-S158 (Fig. 3D), and the nitro group was reduced to the free amine using sodium dithionite (S159). The conditions tolerate ‘bifunctional’ component urea 18 in a double Betti reaction to give 19 as a mixture of stereoisomers (Fig. 3B) and a 2-component process with both amide and aldehyde functionalities in the same molecule 21 to give 22 (Fig. 3C).
To validate the Betti approach for generation of inhibitors, we screened with KD4C/E, which act on methylated H3K9 (KD4C also acts on H3K36), and counter-screened against KDM6B, which acts on methylated H3K27. While some 7-substituted 8HQs inhibited both KDM4 and KDM6B, plotting potency vs. selectivity reveals a trend towards KD4C/E-selective compounds (Fig. 4A). SAR analysis suggested selectivity for KD4C/E over KDM6B may emerge from a combination of halogen substitution at the 8HQ C-5 position and modification at the meta-position of the aldehyde-derived component; e.g. comparing 24 and 25, or 26 and 27 (Fig. 4B). Note that bulky meta-substitution on the aldehyde Betti component is tolerated for KDM4, but not KDM6B inhibition, consistent with the relatively large 2OG substrate binding pocket for the KDM4s, compared to KDM6B (Fig. 4C/D). In contrast, alteration of the amide component did not lead to significant changes in activity (e.g. 35, 36, 37) (7-substituted 8HQs derived from a combination of both relatively large aldehydes and large amides were inactive, e.g. 34) (Fig. 4D).

Selected compounds displaying reasonable activity against isolated KDM4s were tested in an immunofluorescence (IF) assay using HeLa cells with transiently overexpressed KDM4A (SF1). Some compounds (27, 28, S85, S120 (SF1)) showed apparent inhibition as evidenced by increased H3K9me3 levels, with EC_{50} in the μM range, i.e. the compounds are more potent than IOX1. Racemic CCT1 was selected for further investigation as the resolved enantiomers displayed little difference in KDM4 inhibition (Fig. 5A, SF2A/B); with HeLa cells the CCT1 EC_{50} value was 9 μM, 10-fold more potent than IOX1 (EC_{50} = 86 μM), at a concentration range where catalytically inactive KDM4A showed no significant changes in H3K9me3 levels. The IF cell assays show a dose-dependent increase in H3K9me3 fluorescence and a corresponding decrease in cell numbers (SF3A/B/C/D) suggesting a narrow window between cellular effect and toxicity. The CCT1 analogue CCT2, in which the phenolic oxygen is methylated, was not cytotoxic, displayed no inhibition of isolated KDM4, and did not affect H3K9me3 levels in cells (Fig. 5A, SF3A/B/C/D). KDM4s are overexpressed in both breast and lung cancer cells;^{14} CCT1, but not CCT2, increased H3K9me3 levels in an MCF7 breast cancer cell line (EC_{50} = 12 μM) (SF3B). The effect of CCT1 and CCT2 on proliferation in some patient-matched cell lines, one derived from cancerous, the other from normal, lung tissue of the same patient was tested.^{15} CCT1 exerted a marked effect on the viability of the lung cancer cells (EC_{50} = 6 μM), whereas the non-cancer cells were relatively unaffected; CCT2 had little effect (Fig. 5C). Intact protein mass spectrometry indicated that histones H3.1 and H3.2 from HEK293T cells treated with CCT1 have an overall positive shift in mass, indicative of increased levels of post-translational modification compared to untreated cells (Fig. 5D); CCT1 manifested no effect on modifications to H2A, H2B, and H4 by this technique (SF4). Since histone methylation principally occurs on H3 proteins, the results support the proposal that CCT1 is a JmjC KDM inhibitor in cells. CCT1 (Fig. 5A) and some analogues (Fig. 4B/D) demonstrated selectivity for KDM4 against other isolated recombinant KDM subfamilies. The results with isolated enzymes indicate that CCT1 is selective for the JmjC KDMs over, at least some, other human 2OG oxygenases (Fig. 5A); in particular CCT1 was inactive against isolated recombinant hypoxia inducible transcription factor (HIF) prolyl hydroxylase PHD2 (MS-based assay: IC_{50} >100 μM; antibody-based AlphaScreen® assay: IC_{50} = 96 μM (Fig. 5A, SF5A)) under standard conditions, and non-denaturing mass spectrometry of PHD2 did not indicate binding of CCT1 (SF5B/C); similarly, CCT1 was inactive against isolated recombinant factor inhibiting HIF (FIH) (MS-based assay: IC_{50} >100 μM). HIF-α levels are regulated by PHD catalysis. Further studies revealed that the cell effects of CCT1 may not be solely due to ‘direct’ JmjC KDM inhibition. Treatment of HeLa cells with CCT1, but not CCT2, caused stabilisation of the hypoxia-inducible transcription factor HIF-1α (SF6A); treatment of Hep3b cells with CCT1, but not CCT2, caused stabilisation of HIF-1α, HIF-2a, and led to induction of PHD3 (Fig. 5E). The extent of HIF upregulation by CCT1 is comparable to that of the PHD2-selective inhibitor IOX2 (Fig. 5E). In renal cell carcinoma cells (RCC4), where HIF-1α is stabilised due to absence of functional Von-Hippel-Lindau (VHL) complex, all 3 identified sites of HIF-1α hydroxylation (two due to PHD catalysis and one due to catalysis by factor inhibiting HIF (FIH)) were reduced by CCT1, but not CCT2 (SF6C). The results suggest that PHD2, and to a lesser extent FIH, activities are inhibited by CCT1 in cells. Addition of Fe(II) to the media reversed the effects of CCT1 on HIF induction, as well as apparent PHD and FIH inhibition (SF6B/C). These results suggest that the effect of CCT1 on the hypoxic response pathway are, at least in part, related to Fe(II) availability in a cellular context.
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Betti reaction enables efficient synthesis of 8-hydroxyquinoline inhibitors of 2-oxoglutarate oxygenases

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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

![Chemical structure](image)

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; ν_max/cm⁻¹: 2539 (O-H); δ_H (400 MHz, DMSO-d₆): 8.96 (1 H, d, J=4.5 Hz, H_a), 8.07 (1 H, d, J=8.0 Hz, H_e), 7.93 (1 H, d, J=4.5 Hz, H_b), 7.54 (1 H, t, J=8.0 Hz, H_d), 7.15 (1 H, d, J=8.0 Hz, H_c); δ_C (100 MHz, DMSO-d₆): 168.6; m/z (ESI-) 188 ([M-H]⁻); HRMS (ESI⁺) C₁₀H₈N₂O₃, ([M+H⁺]) requires 190.0499; found 190.0501.

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

![Chemical structure](image)

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; ν_max/cm⁻¹: 3270 (NH), 2861 (OH), 1633 (C=O); δ_H (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, H₃b), 0.96 (6 H, dd, J=12.0, 6.0 Hz, CH₃a); δ_C (100 MHz, CDCl₃): 171.6 (C=O), 149.1, 149.0148.2, 138.3, 136.1, 134.3, 128.4, 127.7, 122.6, 121.9, 118.9, 118.0, 110.8, 110.5, 55.8 (OCH₃), 55.8 (OCH₃), 54.3 (benzyl-C), 46.3 (C₁), 26.3 (C₆), 22.5 (C₆); m/z (ESI-) 393 ([M-H]⁻); HRMS (ESI⁺) C₂₃H₂₇N₂O₄, ([M+H⁺]) requires 395.1965; found 395.1969.
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), 8.20 - 8.41 (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), 6.39 - 6.48 (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 7

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, 125.2, 122.7, 118.2, 51.4 (benzyl-C); m/z (ESI) 353 ([M-H], 100%); HRMS (ESI⁺) C₂₃H₁₉N₃O₂, ([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; νmax/cm⁻¹ 3333 (OH); δH(400 MHz, DMSO-d₆) 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), 7.63 - 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_a), 2.33 (3 H, s, C_H₃), 1.70 - 1.86 (4 H, m, H_b); δC(100 MHz, DMSO-d₆) 149.7, 149.5, 141.0, 139.5, 133.6, 132.9, 129.9, 126.3, 125.1, 124.5, 123.4, 119.2, 60.2 (C_a), 53.4 (benzyl-C), 23.6 (C_b), 14.5 (thiophene-CH₃); m/z (ESI⁺) 359 ([M+H⁺]); HRMS (ESI⁺) C₁₉H₂₀ON₂ClS, ([M+H⁺]) 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; νmax/cm⁻¹ 1748 (C=O); δH(400 MHz, DMSO-d₆) 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); δC(100 MHz, DMSO-d₆) 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⁺) 527 ([M+H⁺]); HRMS (ESI⁺) C₃₃H₂₂O₃N₄, ([M+H⁺]) requires 527.2078; found 527.2074.
3-Hydroxyisoindolin-1-one 21

2-Cyanobenzaldehyde (131 mg, 1.0 mmol) and sodium perborate tetrahydrate (615 mg, 4.0 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 give 21 as a white powder (115 mg, 77 %). This compound has previously been described using a different synthetic methodology.$^5$

mp 171 °C; $\nu_{\text{max}}$/cm$^{-1}$ 3339 (NH), 1697 (C=O); $\delta_H$ (400 MHz, DMSO-d$_6$) 8.87 (1 H, s, O$\text{H}$), 7.38 - 7.73 (4 H, m, Ar), 6.33 (1 H, d, $J$=9.0 Hz, N$\text{H}$), 5.87 (1 H, d, $J$=9.0 Hz, CH(OH)); $\delta_C$ (100 MHz, DMSO-d$_6$) 169.3 (C=O), 147.8, 132.9, 130.0, 124.5, 123.2, 78.9 (CH(OH)); m/z (ESI$^+$) 148 ([M-H]$^-$); HRMS (ESI$^+$) C$_8$H$_7$NNaO$_2$, ([M+Na]$^+$) requires 172.0369; found 172.0374.

3-(5-Chloro-8-hydroxyquinolin-7-yl)isoindolin-1-one hydrochloride 22

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; $\nu_{\text{max}}$/cm$^{-1}$ 3177 (NH), 1657 (C=O); $\delta_H$ (400 MHz, DMSO-d$_6$) 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); $\delta_C$ (100 MHz, DMSO-d$_6$) 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]$^-$); HRMS (ESI$^+$) C$_{17}$H$_{11}$ClN$_2$NaO$_2$, ([M+Na]$^+$) 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-formylbenzoic acid (600 mg, 4.0 mmol) gave 12 (814 mg, 94 %) as a white powder.

mp 280 °C; \( \nu_{\text{max}}/\text{cm}^{-1} \) 3324 (NH), 1693 (acid C=O), 1635 (amide C=O), 798 (C-Cl); \( \delta_{\text{H}} \) (400 MHz, DMSO-d\(_6\)) 13.04 (1 H, br. s., CO\(_2\)H), 10.53 (1 H, br. s., NH), 9.34 - 9.42 (1 H, m, quinoline-Ar), 8.94 - 9.00 (1 H, m, quinoline-Ar), 8.45 - 8.52 (1 H, m, quinoline-Ar), 7.94 - 7.99 (2 H, m, Ar), 7.83 - 7.88 (1 H, m, Ar), 7.69 - 7.76 (1 H, m, Ar), 7.59 - 7.63 (1 H, m, Ar), 7.53 - 7.58 (1 H, m, Ar), 7.46 - 7.53 (3 H, m, Ar), 7.08 (1 H, d, \( J = 8.5 \) Hz, benzyl-H); \( \delta_{\text{C}} \) (100 MHz, DMSO-d\(_6\)) 168.1 (acid C=O), 166.9 (amide C=O), 150.5, 150.1, 143.0, 139.5, 134.9, 133.4, 132.7, 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]\(^-\), 100 %); HRMS (ESI\(^+\)) C\(_{25}\)H\(_{19}\)ClIN\(_2\)O\(_3\), ([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; \( \nu_{\text{max}}/\text{cm}^{-1} \) 3321 (NH), 3056 (OH), 1633 (C=O); \( \delta_{\text{H}} \) (400 MHz, DMSO-d\(_6\)) 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, CH\(_3\)); \( \delta_{\text{C}} \) (100 MHz, DMSO-d\(_6\)) 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, 125.3, 122.6, 118.2, 51.3 (benzyl-C), 22.0 (CH\(_3\)); \( m/z \) (ESI\(^+\)) 367 ([M-H]\(^-\), 100 %); HRMS (ESI\(^+\)) C\(_{26}\)H\(_{21}\)N\(_2\)O\(_2\), ([M+Na\(^+\)]) requires 391.1417; found 391.1401.
**N-((5-Chloro-8-hydroxyquinolin-7-yl)(m-tolyl)methyl)benzamide 25**

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

mp 239-240 °C; ν\textsubscript{max}/cm\textsuperscript{-1} 3306 (NH), 1635 (C=O); δ\textsubscript{H} (400 MHz, DMSO-d\textsubscript{6}) 10.40 (1 H, br. s., NH), 9.14 - 9.32 (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), 7.49 - 7.60 (2 H, m, Ar), 7.36 - 7.49 (4 H, m, Ar), 7.04 (1 H, d, J=8.5 Hz, benzyl-H), 7.00 - 7.30 (1 H, m, Ar), 7.04 (1 H, d, J=8.5 Hz, benzyl-H), 2.30 (3 H, s, CH\textsubscript{3}); δ\textsubscript{C} (100 MHz, DMSO-d\textsubscript{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\textsubscript{3}); m/z (ESI+) 401 ([M-H] - 100 %); HRMS (ESI+) \textsubscript{C\textsubscript{24}H\textsubscript{18}ClN\textsubscript{2}O\textsubscript{2}, ([M-H] - 100 %) requires 401.1062; found 401.1061.

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

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

mp 196 °C; ν\textsubscript{max}/cm\textsuperscript{-1} 3302 (NH), 3057 (OH), 1638 (C=O); δ\textsubscript{H} (400 MHz, DMSO-d\textsubscript{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\textsubscript{3}); δ\textsubscript{C} (100 MHz, DMSO-d\textsubscript{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\textsubscript{3}); m/z (ESI+) 367 ([M-H] - 100 %); HRMS (ESI+) \textsubscript{C\textsubscript{24}H\textsubscript{18}N\textsubscript{2}O\textsubscript{2}, ([M+Na]\textsuperscript{+} 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-hydroxyquinolin (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; ν\text{max}/cm\textsuperscript{-1} 3289 (NH), 1637 (C=O); δ\textsubscript{H} (400 MHz, DMSO-d\textsubscript{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\textsubscript{3}); δ\textsubscript{C} (100 MHz, DMSO-d\textsubscript{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\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 401.1062.

**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; ν\text{max}/cm\textsuperscript{-1} 3314 (NH), 1633 (C=O); δ\textsubscript{H} (400 MHz, DMSO-d\textsubscript{6}) 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); δ\textsubscript{C} (100 MHz, DMSO-d\textsubscript{6}) 166.5 (C=O), 150.1, 149.8, 144.9, 139.1, 134.5, 133.0, 132.0, 131.2, 130.5, 130.2, 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\textsuperscript{+}) 465 ([M-H]); HRMS (ESI\textsuperscript{+}) C\textsubscript{26}H\textsubscript{20}BrClN\textsubscript{2}NaO\textsubscript{2}, ([M+Na\textsuperscript{+}]\textsuperscript{+}) requires 488.9976; found 488.9970.
\[ N-[(1,1'-\text{Biphenyl})-3-\text{yl}(5-\text{chloro}-8-\text{hydroxyquinolin}-7-\text{yl})\text{methyl}]\text{benzamide 29} \]

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; \( \nu_{\text{max}}/\text{cm}^{-1} \) 3299 (NH), 1633 (C=O); \( \delta_{\text{H}} \) (400 MHz, DMSO-\( d_6 \)) 10.48 - 10.1 (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); \( \delta_{\text{C}} \) (100 MHz, DMSO-\( d_6 \)) 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, 126.4, 126.0, 125.8, 123.9, 119.5, 51.2 (benzyl-C); \( m/z \) (FI\(^+\)) 464 ([M\(^+\)]\(^+\)); HRMS (FI\(^+\)) C\(_{29}\)H\(_{21}\)ClN\(_2\)O\(_2\), ([M\(^+\)]\(^+\)) requires 464.1292; found 464.1292.

\[ N-[(1,1'-\text{Biphenyl})-4-\text{yl}(5-\text{chloro}-8-\text{hydroxyquinolin}-7-\text{yl})\text{methyl}]\text{benzamide hydrochloride 30} \]

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; \( \nu_{\text{max}}/\text{cm}^{-1} \) 3305 (NH), 1634 (C=O); \( \delta_{\text{H}} \) (400 MHz, DMSO-\( d_6 \)) 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-
$\delta_C$ (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$^+$) 463.1484; found 463.1484.

$\delta$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$^+$) 503.1133; found 503.1133.

$N$-((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.

$\delta$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); $\delta_C$ (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$^+$) 503.1133; found 503.1133.

$N$-((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.

$\delta$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); $\delta_C$ (100 MHz,
DMSO-\text{d}_6 \text{ (C=O), 158.4, 157.2, 156.8, 149.4, 143.8, 137.2, 134.7, 134.6, 133.6, 132.0, 130.7, 128.9, 128.7, 128.1, 125.8, 124.0, 122.9, 122.2, 119.1, 117.9, 117.6, 50.4 \text{ (benzyl-C); m/z (FI) 491 ([M]); HRMS (FI) } C_{29}H_{21}N_3O_5, ([M]) \text{ requires 491.1481; found 491.1247.}

\text{N-([5-Bromo-8-hydroxyquinolin-7-yl][3-phenoxyphenyl)methyl]benzamide 33}

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

mp 214 °C; \nu_{\text{max}}/\text{cm}^{-1} 3294 (\text{NH}), 1636 (\text{C}=\text{O}); \delta_H (400 MHz, \text{DMSO-\text{d}_6}) 10.54 (1 \text{H, br. s., NH}), 9.24 - 9.38 (1 \text{H, m, quinoline-Ar}), 8.89 - 9.02 (1 \text{H, m, quinoline-Ar}), 8.35 - 8.49 (1 \text{H, m, quinoline-Ar}), 8.03 (1 \text{H, s, Ar}), 7.85 - 7.95 (2 \text{H, m, Ar}), 7.71 - 7.78 (1 \text{H, m, Ar}), 7.45 - 7.60 (4 \text{H, m, Ar}), 7.31 - 7.42 (2 \text{H, m, Ar}), 7.09 - 7.18 (2 \text{H, m, Ar}), 6.97 - 7.07 (3 \text{H, m, Ar}), 6.88 (1 \text{H, d, } J=8.0 \text{ Hz, benzyl-H}); \delta_C (100 MHz, \text{DMSO-\text{d}_6}) 166.6 (\text{C}=\text{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, 128.8, 128.1, 128.0, 126.8, 125.8, 124.0, 122.7, 119.2, 119.1, 109.0, 50.2 (\text{benzyl-C}); m/z (ESI^+^) 525 ([M+H]^+^); HRMS (ESI^+^) C_{29}H_{21}O_3N_3BrNa, ([M+Na]^+) requires 547.0628; found 547.0606.

\text{N-([5-Bromo-8-hydroxyquinolin-7-yl][3-phenoxyphenyl)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-phenoxybenzaldehyde (690 \mu L, 4.0 mmol) gave 34 (873 mg, 81 \%) as a white powder.

mp 212 °C; \nu_{\text{max}}/\text{cm}^{-1} 3270 (\text{NH}), 1639 (\text{C}=\text{O}); \delta_H (400 MHz, \text{DMSO-\text{d}_6}) 10.48 (1 \text{H, br. s., NH}), 9.08 - 9.15 (1 \text{H, m, quinoline-Ar}), 8.92 - 8.97 (1 \text{H, m, quinoline-Ar}), 8.38 - 8.44 (1 \text{H, m, quinoline-Ar}), 7.87 (1 \text{H, s, quinoline-Ar}), 7.66 - 7.79 (1 \text{H, m, Ar}), 7.18 - 7.43 (7 \text{H, m, Ar}), 7.09 - 7.18 (1 \text{H, m, Ar}), 6.95 - 7.06 (4 \text{H, m, Ar}), 6.79 - 6.90 (1 \text{H, m, Ar}), 6.68 (1 \text{H, d, } J=8.5 \text{ Hz, benzyl-H}), 3.57 (2 \text{H, s, CH}_2); \delta_C (100 MHz, \text{DMSO-\text{d}_6}) 170.0 (\text{C}=\text{O}), 157.1, 156.8, 150.4, 149.7, 144.5, 139.4, 136.7, 135.5, 130.6, 130.5,
N-((5-chloro-8-hydroxyquinolin-7-yl)(3-methylthiophen-2-yl)methyl)benzamide CCT1

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 3-methyl-2-thiophenecarboxaldehyde S1 (431 μL, 4.0 mmol) gave CCT1 (584 mg, 71%) as a white powder.

mp 223 °C; ν\textsubscript{max}/cm\textsuperscript{-1} 3274 (NH), 1638 (C=O); δ\textsubscript{H} (400 MHz, DMSO-\textit{d\textsubscript{6}}) 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, CH\textsubscript{3}); δ\textsubscript{C} (100 MHz, DMSO-\textit{d\textsubscript{6}}) 166.1 (C=O), 150.1, 149.7, 139.4, 139.0, 134.6, 134.5, 133.0, 131.9, 131.0, 128.7, 128.1, 126.9, 125.6, 125.2, 123.6, 118.8, 45.3 (benzyl-C), 14.0 (CH\textsubscript{3}); m/z (ESI\textsuperscript{+}) 407 (\[M-H\]\)); HRMS (ESI\textsuperscript{+}) C\textsubscript{21}H\textsubscript{16}ClN\textsubscript{2}O\textsubscript{2}S, (\[M-H\]\)) requires 407.0626; found 407.0613.

N-((5-Chloro-8-hydroxyquinolin-7-yl)(3-methylthiophen-2-yl)methyl)-2-phenylacetamide 35

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.

mp 181 °C; ν\textsubscript{max}/cm\textsuperscript{-1} 3237 (NH), 1667 (C=O); δ\textsubscript{H} (400 MHz, DMSO-\textit{d\textsubscript{6}}) 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, CH\textsubscript{2}), 2.11 (3 H, s, CH\textsubscript{3}); δ\textsubscript{C} (100 MHz, DMSO-\textit{d\textsubscript{6}}) 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, 123.6, 123.5, 118.9, 44.8
(benzyl-C), 42.5 (CH$_3$), 13.9 (CH$_3$); m/z (ESI) 421 ([M-H$^-$]); HRMS (ESI$^+$) C$_{23}$H$_{18}$ClN$_2$NaO$_2$S, ([M+Na$^+$]) requires 445.0748; found 445.0731.

**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 μL, 4.0 mmol) gave 36 (390 mg, 47 %) as an off-white powder.

mp 164 °C; ν$_{max}$/cm$^{-1}$ 3297 (NH), 1640 (C=O); δ$_H$ (400 MHz, DMSO-d$_6$) 10.34 (1 H, br. s., NH), 8.90 - 8.99 (1 H, m, quinoline-Ar), 8.72 - 7.76 (2 H, m, Ar), 7.19 - 7.25 (1 H, m, Ar), 6.79 - 6.90 (2 H, m, Ar and benzyl-H), 2.21 - 2.32 (1 H, m, H$_a$), 2.11 (3 H, s, CH$_3$), 1.57 - 1.76 (4 H, m, H$_b$), 1.05 - 1.42 (6 H, m, H$_c/d$); δ$_C$ (100 MHz, DMSO-d$_6$) 175.1 (C=O), 150.2, 150.1, 140.5, 134.9, 133.4, 131.3, 126.9, 125.9, 123.9, 123.7, 119.2, 44.5 (benzyl-C), 30.4 (C$_a$), 29.8 (C$_b$), 26.2 (C$_c$), 26.1 (C$_d$), 14.3 (CH$_3$); m/z (ESI) 413 ([M-H$^-$]); HRMS (ESI$^+$) C$_{23}$H$_{18}$ClN$_2$NaO$_2$S, ([M+Na$^+$]) requires 437.1061; found 437.1051.

**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 μL, 4.0 mmol) gave 37 (312 mg, 42 %) as an off-white powder.

mp 202 °C; ν$_{max}$/cm$^{-1}$ 3272 (NH), 1644 (C=O); δ$_H$ (400 MHz, DMSO-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$_3$), 1.65 - 1.80 (1 H, m, H$_a$), 0.56 - 0.81 (4 H, m, H$_b$); δ$_C$ (100 MHz, DMSO-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 (benzyl-C), 14.4 (CH3), 14.2 (C6), 7.4 (C6); m/z (ESI+) 371 ([M-H]-); HRMS (ESI+) C19H17ClN2O2S, ([M-H]-) requires 371.0626; found 371.0625.

**N-[(5-Chloro-8-hydroxyquinolin-7-yl)(4-methylthiophen-2-yl)methyl]benzamide 38**

![Chemical structure](image)

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 μL, 4.0 mmol) gave 38 (382 mg, 47%) as a white powder. mp 206 °C; νmax/cm⁻¹ 3313 (NH), 1632 (C=O); δH (400 MHz, DMSO-d6) 10.50 (1 H, br. s., NH), 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), 6.62 (1 H, s, Ar), 2.11 (3 H, s, CH3); δC (100 MHz, DMSO-d6) 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 (benzyl-C), 16.3 (CH3); m/z (ESI+) 431 ([M+Na]+); HRMS (ESI+) C22H17ClIN2O2NaS, ([M+Na]+) requires 431.0591; found 430.9132.

**N-[(5-chloro-8-hydroxyquinolin-7-yl)(5-methylthiophen-2-yl)methyl]benzamide 39**

![Chemical structure](image)

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 μL, 4.0 mmol) gave 39 (264 mg, 32%) as a white powder. mp 213 °C; νmax/cm⁻¹ 3302 (NH), 1634 (C=O); δH (400 MHz, DMSO-d6) 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), 6.62 - 6.67 (2 H, m, Ar), 2.37 (3 H, s, CH3); δC (100 MHz, DMSO-d6) 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,
126.0, 125.8, 125.6, 124.0, 119.5, 47.1 (benzyl-C), 15.8 (CH3); m/z (ESI) 431 ([M+Na]+); HRMS (ESI+) C22H17ClIN2NaO2S, ([M+Na]+) requires 431.0591; found 431.0587.

**N-(Benzo[b]thiophen-2-yl(5-chloro-8-hydroxyquinolin-7-yl)methyl)benzamide 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); δH (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, Ar), 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)methyl)benzamide 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); δH (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); δ1 (377 MHz, DMSO-d6) -133.9 (CF); m/z (ESI+) 451 ([M+H]+); HRMS (ESI+) C23H16BrFNO2, ([M+Na]+) requires 473.0271; found 473.0254.

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

![Chemical structure of CCT2](image)

A solution of CCT1 (102 mg, 0.25 mmol), iodomethane (17 μL, 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 H2O 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; νmax/cm⁻¹ 3275 (NH), 1632 (C=O); δH (400 MHz, CDCl3) 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, OCH3) 423 ([M+H]+); m/z (ESI+) 3275 (NH), 1632 (C=O); δH (400 MHz, CDCl3) 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, OCH3) 423 ([M+H]+); m/z (ESI+) 451 ([M+H]+); HRMS (ESI+) C23H16BrFNO2, ([M+Na]+) requires 473.0271; found 473.0254.

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

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 CHCl3 (100 mL). The mixture was shaken with 10 % HCl aq. for about 10 min and then extracted with CHCl3. The combined organic layers were dried over anhydrous MgSO4 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.
\(\delta_H\) (400 MHz, CDCl\(_3\)) 10.04 (1 H, s, CH\(_O\)), 7.63 (1 H, d, \(J=5.0\) Hz), 6.97 (1 H, d, \(J=5.0\) Hz), 2.58 (3 H, s, CH\(_3\)); \(\delta_C\) (100 MHz, CDCl\(_3\)) 182.4 (CHO), 147.4, 137.6, 134.3, 131.8, 14.2 (CH\(_3\)); \(m/z\) (ESI\(^+\)) 127 ([M+H]\(^+\)).

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

![Chemical Structure](image)

3-Thiophenecarbonitrile (274 \(\mu\)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; \(\delta_H\) (400 MHz, DMSO-\(d_6\)) 8.08 - 8.16 (1 H, m, Ar) 7.52 - 7.57 (1 H, m, Ar) 7.45 - 7.50 (1 H, m, Ar); \(\delta_C\) (100 MHz, DMSO-\(d_6\)) 164.6 (C=O), 138.9, 129.9, 128.0, 127.4; \(m/z\) (ESI\(^-\)) 126 ([M-H]\(^-\)).

**[6,6'-Biquinoline]-8,8'-dial 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; \(\delta_H\) (400 MHz, DMSO-\(d_6\)) 10.32 (2 H, br. s., OH), 8.70 - 9.01 (2 H, m), 8.27 - 8.63 (2 H, m), 7.87 (2 H, s), 7.46 - 7.73 (4 H, m); \(\delta_C\) (100 MHz, DMSO-\(d_6\)) 154.0, 148.6, 139.2, 137.7, 129.6, 122.9, 122.7, 116.5, 111.2; \(m/z\) (ESI\(^+\)) 289 ([M+H]\(^+\)); HRMS (ESI\(^+\)) \(C_{18}H_{13}O_2N_2\), ([M+H]\(^+\)) requires 289.0972; 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; $\nu_{\text{max}}$/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$_{10}$ON, ([M+H]$^+$) requires 160.0757; found 160.0754.

4-Methylquinolin-8-ol S5

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$_{10}$ON, ([M+H]$^+$) requires 160.0757; found 160.0754.

5-Methylquinolin-8-ol S6

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; $\nu_{\text{max}}$/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
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; $\delta_H$ (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$_3$); $\delta_C$ (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$^+$) C$_{10}$H$_{10}$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 μL, 10.8 mmol) gave S8 (819 mg, 65 %) as a light-brown powder.

mp 102 °C; $\nu_{max}/cm^{-1}$ 3325 (OH); $\delta_H$ (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$_3$); $\delta_C$ (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 μL, 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; $\nu_{max}/cm^{-1}$ 1350 (S=O); $\delta_H$ (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$_3$NH$_2$), 7.06 - 7.22 (1 H, m); $\delta_C$ (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$^+$) C$_{10}$H$_{12}$N$_2$S, ([M-H]$^-$) requires 223.0183; found 223.0182. HRMS (ESI$^+$) C$_{10}$H$_{10}$NO$_2$, ([M+H]$^+$) requires 176.0706; found 176.0703.
5-\{(Methylsulfonyl)quinolin-8-ol\} S10

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

mp 203 °C; \(\nu_{\text{max}}/\text{cm}^{-1}\) 2920 (OH); \(\delta_{\text{H}}\) (400 MHz, DMSO-\(d_6\)) 8.89 - 9.11 (2 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\(_2\)CH\(_3\)); \(\delta_{\text{C}}\) (100 MHz, DMSO-\(d_6\)) 159.5, 149.5, 138.7, 133.2, 132.3, 125.6, 125.6, 124.3, 110.4, 45.0 (SO\(_2\)CH\(_3\)); \text{m/z} (ESI\(^+\)) 224 ([M+H]\(^+\)); HRMS (ESI) \(\text{C}_{10}\text{H}_8\text{O}_3\text{NS}, ([M-H])\) requires 222.0230; 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.\(^{13}\)

mp 154 °C; \(\nu_{\text{max}}/\text{cm}^{-1}\) 3324 (OH); \(\delta_{\text{H}}\) (400 MHz, DMSO-\(d_6\)) 8.80 - 8.93 (1 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); \(\delta_{\text{C}}\) (100 MHz, DMSO-\(d_6\)) 155.2, 149.0, 137.8, 136.1, 132.0, 129.7, 123.4, 116.9, 112.5; \text{m/z} (ESI\(^+\)) 180 ([M+H]\(^+\)); HRMS (ESI) \(\text{C}_9\text{H}_5\text{ONCl}, ([M-H])\) requires 178.0065; 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.

mp 135 °C; \(\nu_{\text{max}}/\text{cm}^{-1}\) 3063 (OH); \(\delta_{\text{H}}\) (400 MHz, methanol-\(d_4\)) 8.47 - 8.78 (1 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); \(\delta_{\text{C}}\) (100 MHz, methanol-\(d_4\)) 162.5, 160.0, 155.2, 147.1, 136.2, 135.6, 129.5, 129.3, 122.4; \text{m/z} (ESI\(^+\)) 164 ([M+H]\(^+\)); HRMS (ESI) \(\text{C}_9\text{H}_5\text{ONF}, ([M-H])\) requires 162.0361; 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; \( \nu_{\text{max}}/\text{cm}^{-1} \) 3297 (OH); \( \delta_{\text{H}} \) (400 MHz, DMSO-\( \text{d}_6 \)) 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-\( \text{d}_6 \)) 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; \( \nu_{\text{max}}/\text{cm}^{-1} \) 3087 (OH); \( \delta_{\text{H}} \) (400 MHz, DMSO-\( \text{d}_6 \)) 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-\( \text{d}_6 \)) 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\(^{15}\)

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\textsubscript{n} (400 MHz, DMSO-\textsubscript{d}\textsubscript{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\textsubscript{3}); δ\textsubscript{c} (100 MHz, DMSO-\textsubscript{d}\textsubscript{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\textsubscript{3}); m/z (ESI\textsuperscript{+}) 202 ([M-H]\textsuperscript{−}).

5-Phenylquinolin-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\textsubscript{2}O and brine. The organic layer was dried over anhydrous MgSO\textsubscript{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\textsubscript{max}/cm\textsuperscript{−1} 1351 (S=O); δ\textsubscript{n} (400 MHz, DMSO-\textsubscript{d}\textsubscript{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), 7.71 - 7.78 (1 H, m, Ar), 7.36 - 7.62 (5 H, m, Ar), 2.42 (3 H, s, CH\textsubscript{3}); δ\textsubscript{c} (100 MHz, DMSO-\textsubscript{d}\textsubscript{6}) 152.3, 151.3, 146.0, 144.7, 139.0, 138.3, 134.4, 133.1, 130.4, 130.3, 129.2, 128.8, 127.2, 127.0, 124.1, 123.1, 122.0, 21.6 (CH\textsubscript{3}); m/z (ESI\textsuperscript{+}) 376 ([M+H]\textsuperscript{+}); HRMS (ESI\textsuperscript{+}) C\textsubscript{22}H\textsubscript{18}O\textsubscript{3}NS, ([M+H]\textsuperscript{+}) 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; δₙ (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); δₐ (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-Phenylquinolin-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; δₙ/cm⁻¹ 1375 (S=O); m/z (ESI⁺) 376 ([M+H]+); HRMS (ESI⁺) C₂₂H₁₈O₄NS, ([M+H]+) requires 376.1002; found 376.0997.

4-(Furan-3-yl)quinolin-8-yl 4-methylbenzenesulfonate S19
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, C₃H₃); 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.

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, C₃H₃); 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⁺) C₁₇H₁₂O₃NaS, ([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 °C; 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), 7.33 - 7.61 (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⁺) C₁₀H₅ON₂, ([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 °C; 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.
4-Cyanoquinolin-8-yl 4-methylbenzenesulfonate S23

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 H$_2$SO$_4$ and sparged with N$_2$ 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 N$_2$ and filled with H$_2$SO$_4$ (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 N$_2$ 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 H$_2$O and brine. The combined organic layers were dried over anhydrous MgSO$_4$ 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; $\nu_{max}$/cm$^{-1}$ 2220 (nitrile); $\delta$$_H$ (400 MHz, CDCl$_3$) 8.81 - 8.93 (1 H, m, Ar), 7.98 - 8.12 (1 H, m, Ar), 7.71 - 7.84 (2 H, m, Ar), 7.60 - 7.69 (3 H, m, Ar), 7.16 - 7.25 (2 H, m, Ar), 2.36 (3 H, s, CH$_3$); $\delta$$_C$ (100 MHz, CDCl$_3$) 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 (CH$_3$); m/z (ESI$^+$) 325 ([M+H$^+$]$^+$); HRMS (ESI$^+$) C$_{17}$H$_{12}$O$_3$N$_2$NaS, ([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 H$_2$O (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} /\text{cm}^{-1} 2235 (nitrile); δH (200 MHz, DMSO-\text{d}_6) 8.93 - 9.13 (1 H, m), 8.06 - 8.25 (1 H, m), 7.64 - 7.92 (1 H, m), 7.40 - 7.63 (1 H, m), 7.13 - 7.35 (1 H, m); δC (100 MHz, DMSO-\text{d}_6) 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_{11}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\textsubscript{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\textsubscript{4}Cl, brine, and dried over anhydrous MgSO\textsubscript{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 %).

δH (400 MHz, CDCl\textsubscript{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\textsubscript{3}I); δC (100 MHz, CDCl\textsubscript{3}) 192.3 (CHO), 161.2 (COCH\textsubscript{3}), 142.0, 141.2, 136.8, 133.1, 129.4, 128.9, 128.1, 105.4, 99.9, 55.4 (OCH\textsubscript{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 S2617

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\textsubscript{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\textsubscript{4}Cl, brine, and dried over anhydrous MgSO\textsubscript{4}. 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 S26 (770 mg, 73 %) as a clear oil.

δ \( \text{H} \) (400 MHz, CDCl\(_3\)) 10.06 (1 H, s, C\( \text{H} \)O), 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, OCH\(_3\)); δ \( \text{C} \) (100 MHz, CDCl\(_3\)) 192.3 (CHO), 160.1 (COCH\(_3\)), 141.9, 141.1, 136.9, 133.1, 129.5, 128.7, 128.2, 119.6, 113.4, 112.9, 55.3 (OCH\(_3\)); 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 \( \mu \)mol) 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 \( \text{N}_2 \) 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 \( \text{NH}_4\text{Cl} \), 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 (20:80) as eluent to give S27 (892 mg, 60 %) as a clear oil.

mp 78 °C; \( \nu_{\text{max}}/\text{cm}^{-1} \) 3339 (NH), 1693 (C=O); δ \( \text{H} \) (400 MHz, CDCl\(_3\)) 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(CH\(_3\))\(_3\)); δ \( \text{C} \) (100 MHz, CDCl\(_3\)) 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(CH\(_3\))\(_3\)), 28.3 (C(CH\(_3\))\(_3\)); m/z (ESI\(^-\)) 296 ([M-H]); HRMS (ESI\(^+\)) \( \text{C}_{31}\text{H}_{29}\text{NNaN}_{3} \), ([M+Na\(^+\]) requires 320.1257; found 320.1245.

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

\[ \text{N}-(5\text{-Chloro-8-hydroxyquinolin-7-yl})(\text{phenyl})\text{methyl} \text{benzamide S28}^* \]
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 S28 (662 mg, 85 %) as a white powder.

\[ mp \] 244 °C; \[ \nu_{\text{max}}/\text{cm}^{-1} \] 3330 (NH), 3063 (OH), 1636 (C=O); \[ \delta_{\text{H}} \] (400 MHz, DMSO-\(d_6\)) 10.42 (1 H, br. s., NH), 9.19 - 9.33 (1 H, m, quinoline-Ar), 7.92 - 7.94 (1 H, m, quinoline-Ar), 8.42 - 8.54 (1 H, m, quinoline-Ar), 7.90 - 8.01 (2 H, m, Ar), 7.87 (1 H, s, 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); \[ \delta_{\text{C}} \] (100 MHz, DMSO-\(d_6\)) 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\(^+\)) 387 ([M-H]\(^-\), 100 %); HRMS (ESI\(^+\)) \(C_{23}H_{17}ClN_2NaO_2\) requires 411.0871; found 411.0861.

**N-((8-Hydroxyquinolin-7-yl)(p-tolyl)methyl)benzamide S29**

Following general procedure 1, 8-hydroxyquinoline (145 mg, 1.0 mmol), benzamide (121 mg, 1.0 mmol) and \(p\)-tolualdehyde (236 µL, 2.0 mmol) gave S29 (60 mg, 16 %) as a white powder.

\[ mp \] 173 °C; \[ \nu_{\text{max}}/\text{cm}^{-1} \] 3308 (NH), 3048 (OH), 1640 (C=O); \[ \delta_{\text{H}} \] (400 MHz, DMSO-\(d_6\)) 9.97 (1 H, br. s, NH), 9.16 - 9.22 (1 H, m, quinoline-Ar), 8.85 - 8.88 (1 H, m, quinoline-Ar), 8.29 - 8.33 (1 H, m, quinoline-Ar), 7.90 - 7.97 (2 H, m, quinoline-Ar), 7.66 - 7.75 (1 H, m, 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, CH\(_3\)); \[ \delta_{\text{C}} \] (100 MHz, DMSO-\(d_6\)) 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 (CH\(_3\)); m/z (ESI\(^+\)) 367 ([M-H]\(^-\), 100 %); HRMS (ESI\(^+\)) \(C_{24}H_{20}N_2NaO_2\) ([M+Na]\(^+\)) requires 391.1417; found 391.1420.

**N-((8-Hydroxyquinolin-7-yl)(naphthalen-1-yl)methyl)benzamide S30**

Following general procedure 1, 8-hydroxyquinoline (145 mg, 1.0 mmol), benzamide (121 mg, 1.0 mmol) and \(p\)-tolualdehyde (236 µL, 2.0 mmol) gave S29 (60 mg, 16 %) as a white powder.
mp 208-210 °C; ν_{max}/cm^{-1} 3388 (NH), 3057 (OH), 1633 (C=O); δ_{H} (400 MHz, DMSO-d_{6}) 10.12 (1 H, br. s., NH), 9.28 - 9.42 (1 H, m, quinoline-Ar), 8.79 - 8.93 (1 H, m, quinoline-Ar), 8.24 - 8.37 (1 H, m, quinoline-Ar), 8.08 - 8.20 (1 H, m, quinoline-Ar), 7.91 - 8.01 (3 H, m, Ar), 7.84 - 7.90 (1 H, m, Ar), 7.67 (1 H, d, J=8.5 Hz, benzyl-H), 7.58 - 7.63 (1 H, m, Ar), 7.48 - 7.58 (4 H, m, Ar), 7.40 - 7.48 (4 H, m, Ar), 7.34 - 7.39 (1 H, m, Ar); δ_{C} (100 MHz, DMSO-d_{6}) 166.5 (C=O), 150.7, 149.2, 138.9, 138.7, 136.9, 135.1, 134.4, 132.1, 132.0, 129.6, 129.0, 128.6, 128.5, 128.2, 127.3, 126.2, 125.7, 124.7, 124.1, 122.7, 117.9, 48.5 (benzyl-C); m/z (ESI) 403 ([M-H]^{-}, 100 %); HRMS (ESI^+) C_{27}H_{21}N_{2}O_{2}, ([M+Na]^{+}) requires 427.1417; found 427.1408.

**N-((8-Hydroxyquinolin-7-yl)(naphthalen-2-yl)methyl)benzamide S31**

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.

mp 165 °C; ν_{max}/cm^{-1} 3305 (NH), 1636 (C=O); δ_{H} (400 MHz, CDCl_{3}) 8.68 - 8.78 (1 H, m, quinoline-Ar), 8.21 - 8.29 (1 H, m, quinoline-Ar), 7.88 - 7.98 (2 H, m, quinoline-Ar), 7.72 - 7.84 (4 H, m, Ar), 7.57 - 7.65 (2 H, m, Ar), 7.49 - 7.56 (1 H, m, Ar), 7.37 - 7.48 (6 H, m, Ar), 6.94 (1 H, d, J=8.5 Hz, benzyl-H); δ_{C} (100 MHz, DMSO-d_{6}) 166.5 (C=O), 154.2, 149.3, 148.3, 138.9, 138.4, 136.2, 134.5, 133.6, 132.7, 131.6, 128.8, 128.4, 128.1, 127.8, 127.6, 127.2, 126.1, 125.9, 125.4, 122.3, 122.0, 118.3, 55.6 (benzyl-C); m/z (ESI) 403 ([M-H]^{-}, 100 %); HRMS (ESI^+) C_{27}H_{21}N_{2}O_{2}, ([M+H]^{+}) requires 405.1598; found 405.1582.

**N-((5-Chloro-8-hydroxyquinolin-7-yl)(4-chlorophenyl)methyl)benzamide S32**

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\textsubscript{max}/cm\textsuperscript{-1} 3308 (NH), 2361 (OH), 1631 (C=O); δ\textsubscript{H} (400 MHz, DMSO-d\textsubscript{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, \textit{J}=8.5 Hz, benzyl-H); δ\textsubscript{C} (100 MHz, DMSO-d\textsubscript{6}) 166.9 (C=O), 150.5, 150.1, 141.4, 139.5, 135.0, 133.4, 132.5, 132.3, 130.0, 129.2, 128.5, 127.4, 125.9, 125.4, 119.5, 50.5 (benzyl-C); m/z (ESI\textsuperscript{+}) 867 ([2M+Na]\textsuperscript{+}); HRMS (ESI\textsuperscript{+}) C\textsubscript{23}H\textsubscript{15}Cl\textsubscript{2}N\textsubscript{2}O\textsubscript{2}, ([M-H]\textsuperscript{-}) requires 421.0516; found 421.

(N-(3-Bromophenyl)(5-chloro-8-hydroxyquinolin-7-yl)methyl)urea 533  

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 533 (470 mg, 58 %) as an off-white powder.

mp 183 °C; ν\textsubscript{max}/cm\textsuperscript{-1} 3339 (NH), 1636 (C=O); δ\textsubscript{H} (400 MHz, DMSO-d\textsubscript{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\textsubscript{C} (100 MHz, DMSO-d\textsubscript{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\textsuperscript{+}) 404 ([M]\textsuperscript{+}); HRMS (ESI\textsuperscript{+}) C\textsubscript{17}H\textsubscript{13}BrClIN\textsubscript{2}O\textsubscript{2}, ([M]\textsuperscript{+}) requires 404.9880; found 404.0892.

\textit{N-}(4-Bromophenyl)(5-chloro-8-hydroxyquinolin-7-yl)methyl)benzamide 534  

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 534 (931 mg, 100 %) as an off-white powder.

mp 276 °C; ν\textsubscript{max}/cm\textsuperscript{-1} 3316 (NH), 2946 (OH), 1630 (C=O); δ\textsubscript{H} (400 MHz, DMSO-d\textsubscript{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); δ C (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+) C13H16BrClN2O2, ([M+Na]+) requires 490.9955; found 490.9944.

\(N\)-(5-Chloro-8-hydroxyquinolin-7-yl)[3-(trifluoromethyl)phenyl]methylbenzamide 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; \(\nu_{max}/cm^{-1}\) 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); δ C (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−) C24H16BrClF3N2Na2O2, ([M+Na]+) requires 479.0745; found 479.0740.

\(N\)-(5-Chloro-8-hydroxyquinolin-7-yl)[3-fluorophenyl]methylbenzamide 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; \(\nu_{max}/cm^{-1}\) 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-
$H$); $\delta_C$ (100 MHz, DMSO-$d_6$) 167.0 (C=O), 150.5, 150.1, 139.5, 135.0, 133.4, 132.4, 131.4, 131.3, 129.2, 128.5, 127.4, 125.9, 125.4, 124.2, 124.0, 119.6, 114.8, 114.7, 144.6, 50.7 (benzyl-C); $\delta_H$ (377 MHz, DMSO-$d_6$) -113.0 (C-F); $m/z$ (ESI$^+$) 405 ([M-H$-$]); HRMS (ESI$^+$) $C_{23}H_{16}ClF_N2NaO2$, ([M+Na]$^+$) requires 429.0777; found 429.0770.

$N$-((5-Chloro-8-hydroxyquinolin-7-yl)(3-(p-tolyl)phenyl)methyl)benzamide S37

![Chemical structure of S37](image)

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; $\nu_{max}$/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$_3$); $\delta_C$ (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$_3$); $m/z$ (ESI$^+$) 493 ([M-H$-$]); HRMS (ESI$^+$) $C_{30}H_{23}ClN_2NaO_3$, ([M+Na]$^+$) requires 517.1289; found 517.1276.

$N$-((5-Chloro-8-hydroxyquinolin-7-yl)(3-(4-methoxyphenoxy)phenyl)methyl)benzamide S38

![Chemical structure of S38](image)
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); δH (400 MHz, DMSO-d₆) 10.47 (1 H, br. s., NH), 9.21 - 9.32 (1 H, m, 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, CH₃); δC (100 MHz, CDCl₃) 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 (benzyl-C); m/z (ESI⁻) 509 ([M-H]⁻); HRMS (ESI⁻) C30H23ClN2NaO₄, ([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); δH (400 MHz, DMSO-d₆) 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, CH₃); δC (100 MHz, DMSO-d₆) 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 (CH₃); m/z (ESI⁺) 401 ([M+H⁺], 100 %); HRMS (ESI⁺) C24H17ClN2O₂, ([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; νmax/cm⁻¹ 3234 (NH), 1630 (C=O); δH (400 MHz, DMSO-d₆) 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), 7.65 (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); δC (100 MHz, DMSO-d₆) 166.5 (C=O), 150.5, 150.1, 139.5, 138.1, 134.9, 133.4, 132.3, 131.8, 129.6, 129.1, 128.8, 128.5, 128.0, 127.4, 126.7, 126.2, 126.0, 125.6, 125.3, 123.9, 119.2, 48.3 (benzyl-C); m/z (ESI⁻) 437 ([M-H]⁻, 100 %); HRMS (ESI⁻) C₂₇H₁₈ClN₂O₂ ([M-H]⁻) requires 437.1062; found 437.1050.

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; νmax/cm⁻¹ 3367 (NH), 1654 (C=O); δH (400 MHz, DMSO-d₆) 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); δC (100 MHz, DMSO-d₆) 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⁻) C₂₇H₁₄ClN₂O₂ ([M-H]⁻) requires 437.1062; found 437.1061.

N-((5-Bromo-8-hydroxyquinolin-7-yl)(phenyl)methyl)benzamide S42
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; $\nu_{\text{max}}$/cm$^{-1}$ 3263 (NH), 1638 (C=O); $\delta_{\text{H}}$ (400 MHz, DMSO-$d_6$) 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); $\delta_{\text{C}}$ (100 MHz, DMSO-$d_6$) 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$^+$) 431 ([M-H]); HRMS (ESI$^+$) $C_{23}H_{16}BrN_2O_2$, ([M-H]) requires 431.0401; found 431.0399.

(E)-N-[1-(5-Chloro-8-hydroxyquinolin-7-yl)-3-phenylallyl]benzamide S43

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; $\nu_{\text{max}}$/cm$^{-1}$ 3290 (NH), 1630 (C=O); $\delta_{\text{H}}$ (400 MHz, DMSO-$d_6$) 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); $\delta_{\text{C}}$ (100 MHz, DMSO-$d_6$) 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$^+$) 437 ([M+Na$^+$]); HRMS (ESI$^+$) $C_{25}H_{19}ClN_2NaO_2$, ([M+Na$^+$]) requires 437.1027; found 437.1019.

N-[[1,1'-Biphenyl]-3-yl(8-hydroxy-5-nitroquinolin-7-yl)methyl]benzamide S44
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; \( \nu_{\text{max}}/\text{cm}^{-1} \) 3283 (NH), 1633 (C=O); \( \delta_{\text{H}} \) (400 MHz, DMSO-\( d_6 \)) 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), 7.38 - 7.52 (6 H, m, Ar), 7.28 - 7.37 (1 H, m, Ar), 7.07 (1 H, d, \( J=8.5 \) Hz, benzyl-\( H \)); \( \delta_{\text{C}} \) (100 MHz, DMSO-\( d_6 \)) 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, 128.4, 127.6, 127.5, 126.6, 126.1, 124.7, 122.6, 51.3 (benzyl-\( C \)); \( m/z \) (ESI\(^+\)) 476 ([M+H\(^+\)]\(^+\)); HRMS (ESI\(^+\)) \( C_{29}H_{21}N_3O_4 \), ([M+Na\(^+\)]\(^+\)) requires 498.1424; found 498.1440.

\( N-((5-\text{Chloro}-8-\text{hydroxyquinolin}-7-\text{yl})(4-\text{phenoxyphenyl})\text{methyl})\text{benzamide} \) 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; \( \nu_{\text{max}}/\text{cm}^{-1} \) 3306 (NH), 1634 (C=O); \( \delta_{\text{H}} \) (400 MHz, DMSO-\( d_6 \)) 10.46 (1 H, br. s., \( N\)H), 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); \( \delta_{\text{C}} \) (100 MHz, DMSO-\( d_6 \)) 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) \( C_{29}H_{21}N_3O_4Cl \), ([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; ν max/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; ν max/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, 128.8, 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

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

mp 165 °C; ν<sub>max</sub>/cm<sup>-1</sup> 3306 (NH), 3058 (OH), 1638 (C=O); δ<sub>H</sub> (400 MHz, DMSO-<sub>d</sub>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); δ<sub>C</sub> (100 MHz, DMSO-<sub>d</sub>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, 122.7, 118.2, 51.4 (benzyl-C), 21.8 (CH<sub>3</sub>); m/z (ESI) 367 ([M-H]<sup>-</sup>), (100 %); HRMS (ESI<sup>+</sup>) C<sub>24</sub>H<sub>20</sub>N<sub>2</sub>O<sub>2</sub>, ([M+Na]<sup>+</sup>) requires 391.1417; found 391.1403.

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

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; ν<sub>max</sub>/cm<sup>-1</sup> 3307 (NH), 1634 (C=O); δ<sub>H</sub> (400 MHz, DMSO-<sub>d</sub>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<sub>2</sub>); δ<sub>C</sub> (100 MHz, DMSO-<sub>d</sub>6) 167.3 (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, 127.2, 125.3, 122.6, 118.2, 50.9 (benzyl-C), 43.1 (CH<sub>2</sub>); m/z (ESI) 367 ([M-H]) ; HRMS (ESI<sup>+</sup>) C<sub>24</sub>H<sub>20</sub>N<sub>2</sub>O<sub>2</sub>, ([M+H]<sup>+</sup>) requires 367.1452; found 367.1444.
**N-[(5-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-d_{6}) 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, CH_{2}); δ_{C} (100 MHz, DMSO-d_{6}) 170.4 (C=O), 150.1, 142.5, 139.5, 137.2, 133.4, 129.9, 129.3, 129.1, 127.9, 127.2, 127.1, 127.0, 126.1, 125.7, 123.8, 119.5, 50.7 (benzyl-C), 43.1 (CH_{2}); m/z (ESI^{-}) 401 ([M-H]^{-}); HRMS (ESI^{-}) C_{24}H_{19}ClN_{2}O_{2}, ([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-d_{6}) 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-d_{6}) 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^{+}) C_{23}H_{13}BrClF_{2}N_{2}O_{2}, ([M+Na]^{+}) requires 506.9882; found 506.9876.
\textbf{N-\{(8-Hydroxyquinolin-7-yl)(phenyl)methyl\}-2-methylbenzamide S52}

![Image of compound 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.

\textbf{mp 170 °C; ν\textsubscript{max}/cm\textsuperscript{-1} 3292 (NH), 3060 (OH), 1643 (C=O); δ\textsubscript{H} (400 MHz, DMSO-\textit{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\textsubscript{3}); δ\textsubscript{C} (100 MHz, DMSO-\textit{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\textsubscript{3}); m/z (ESI) 367 ([M-H], 100 %); HRMS (ESI\textsuperscript{+}) C\textsubscript{24}H\textsubscript{20}N\textsubscript{2}NaO\textsubscript{2}, ([M+Na\textsuperscript{+}]\textsuperscript{+} requires 391.1417; found 391.1404.

\textbf{N-\{(8-Hydroxyquinolin-7-yl)(phenyl)methyl\}-4-methylbenzamide S53}

![Image of compound 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.

\textbf{mp 214-216 °C; ν\textsubscript{max}/cm\textsuperscript{-1} 3305 (NH), 3047 (OH), 1632 (C=O); δ\textsubscript{H} (400 MHz, DMSO-\textit{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\textsubscript{3}); δ\textsubscript{C} (100 MHz, DMSO-\textit{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\textsubscript{3}); m/z (ESI) 367 ([M-H], 100 %); HRMS (ESI\textsuperscript{+}) C\textsubscript{24}H\textsubscript{20}N\textsubscript{2}NaO\textsubscript{2}, ([M+Na\textsuperscript{+}]\textsuperscript{+} 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), α-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; νmax/cm⁻¹ 3284 (NH), 1637 (C=O), 730 (C–Cl); δH (400 MHz, DMSO-d₆) 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, CH₃); δC (100 MHz, DMSO-d₆) 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 (CH₃); m/z (ESI⁻) 401 ([M-H]⁻, 100 %); HRMS (ESI⁻) C₂₄H₁₈ClN₂O₂ ([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; νmax/cm⁻¹ 3300 (NH), 1634 (C=O); δH (400 MHz, DMSO-d₆) ¹H 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, CH₃); δC (100 MHz, DMSO-d₆) 166.9 (C=O), 150.4, 150.0, 142.5, 139.5, 138.4, 135.1, 133.4, 132.8, 129.3, 129.0, 128.9, 128.0, 127.9, 127.7, 126.0, 125.8, 125.7, 123.9, 119.4, 50.9 (benzyl-C), 21.8 (CH₃); m/z (ESI⁻) 401 ([M-H]⁻, 100 %); HRMS (ESI⁻) C₂₄H₁₈ClN₂O₂ ([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-hydroxyquinoline (359 mg, 2.0 mmol), p-tolualdehyde (170 mg, 2.0 mmol) and benzaldehyde (406 µL, 4.0 mmol) gave S56 (513 mg, 64 %) as white powder.

mp 237-240 ºC; \(\nu_{max}/\text{cm}^{-1}\) 3321 (NH), 13321 (NH); \(\delta_{H}\) (400 MHz, DMSO-\(d_6\)) 7.90 - 9.00 (1 H, m, quinoline-Ar), 8.90 - 9.00 (1 H, m, quinoline-Ar), 8.45 - 8.51 (1 H, m, quinoline-Ar), 7.90 - 7.97 (3 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); \(\delta_{C}\) (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⁺) \(C_{24}H_{19}ClI_N_2O_2\), ([M+H⁺] requires 536.9837; found 536.9825.

**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 ºC; \(\nu_{max}/\text{cm}^{-1}\) 3300 (NH), 1632 (C=O), 692 (C-Cl); \(\delta_{H}\) (400 MHz, DMSO-\(d_6\)) 7.90 - 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); \(\delta_{C}\) (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⁺) \(C_{24}H_{19}ClI_N_2O_2\), ([M+Na⁺] requires 536.9837; found 536.9825.
N-{(3-Bromophenyl)[8-hydroxy-5-nitroquinolin-7-yl]methyl}benzamide 558

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 558 (625 mg, 65 %) as a light-orange powder.

mp 264 °C; \( \nu_{\text{max}}/\text{cm}^{-1} \) 3287 (NH), 1635 (C=O); \( \delta_H \) (400 MHz, DMSO-\( \text{d}_6 \)) 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, \( J=8.5 \text{ Hz} \), benzyl-H); \( \delta_C \) (100 MHz, DMSO-\( \text{d}_6 \)) 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); \( \text{m/z} \) (ESI\(^+\)) 476 ([M-H]\(^-\)); HRMS (ESI\(^+\)) \( \text{C}_{23}\text{H}_{14}\text{BrN}_{3}\text{O}_4 \), ([M-H]\(^-\)) requires 476.0251; found 476.0259.

N-{(3-Bromophenyl)[5-chloro-8-hydroxyquinolin-7-yl]methyl}-2-phenylacetamide 559

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 559 (456 mg, 47 %) as a white powder.

mp 169 °C; \( \nu_{\text{max}}/\text{cm}^{-1} \) 3273 (NH), 1638 (C=O), 694 (C-Cl); \( \delta_H \) (400 MHz, DMSO-\( \text{d}_6 \)) 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, \( J=8.5 \text{ Hz} \), benzyl-H), 3.37 (2 H, s, \( \text{CH}_2 \)); \( \delta_C \) (100 MHz, DMSO-\( \text{d}_6 \)) 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 (\( \text{CH}_2 \)); \( \text{m/z} \) (ESI\(^+\)) 481 ([M-H]\(^-\)); HRMS (ESI\(^+\)) \( \text{C}_{23}\text{H}_{16}\text{BrClN}_{3}\text{O}_4 \), ([M-H]\(^-\)) requires 479.0167; found 479.0157.
Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), 4-chlorobenzamide (311 mg, 2.0 mmol) and 3-bromobenzaldehyde (468 μL, 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; \( \nu_{\text{max}}/\text{cm}^{-1} \) 3302 (NH), 1635 (C=O); \( \delta_{\text{H}} \) (400 MHz, DMSO-\( d_6 \)) 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), 7.49 - 7.53 (1 H, m, Ar), 7.44 - 7.48 (1 H, m, Ar), 7.26 - 7.30 (2 H, m, Ar), 6.98 (1 H, d, \( J=8.5 \) Hz, benzyl-H); \( \delta_{\text{C}} \) (100 MHz, DMSO-\( d_6 \)) 165.9 (C=O), 150.2, 145.0, 139.1, 137.2, 134.1, 133.5, 131.6, 130.1, 130.6, 130.5, 130.3, 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\(^+\)) C\(_{23}\)H\(_{15}\)BrCl\(_2\)N\(_2\)O\(_2\), ([M+Na\(^+\)]) requires 522.9586; found 522.9575.

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), biphenyl-4-carboxamide (394 mg, 2.0 mmol) and 3-bromobenzaldehyde (468 μL, 4.0 mmol) gave S61 (718 mg, 66 %) as a white powder. mp 236 °C; \( \nu_{\text{max}}/\text{cm}^{-1} \) 3305 (NH), 1627 (C=O); \( \delta_{\text{H}} \) (400 MHz, DMSO-\( d_6 \)) 10.57 (1 H, br. s., NH), 9.31 - 9.43 (1 H, m, quinoline-Ar), 8.44 - 8.52 (1 H, m, quinoline-Ar), 8.01 - 8.09 (2 H, m, Ar), 7.89 (1 H, s, Ar), 7.78 - 7.84 (2 H, m, Ar), 7.68 - 7.76 (3 H, m, Ar), 7.54 (1 H, s, Ar), 7.45 - 7.52 (3 H, m, Ar), 7.36 - 7.43 (2 H, m, Ar), 7.28 - 7.35 (1 H, m, Ar), 7.03 (1 H, d, \( J=9.0 \) Hz, benzyl-H); \( \delta_{\text{C}} \) (100 MHz, DMSO-\( d_6 \)) 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\(^+\)) C\(_{29}\)H\(_{20}\)BrClN\(_2\)O\(_2\), ([M+Na\(^+\)]) requires 565.0289; found 565.0277.
Benzyl(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 ⁰C; ν<sub>max</sub>/cm<sup>-1</sup> 3305 (NH), 1684 (C=O); δ<sub>H</sub> (400 MHz, DMSO-d<sub>6</sub>) 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, m, quinoline-Ar), 7.80 (1 H, s, Ar), 7.67 - 7.85 (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, CH<sub>2</sub>); δ<sub>C</sub> (100 MHz, DMSO-d<sub>6</sub>) 156.6 (C=O), 150.2, 149.9, 145.5, 139.5, 137.7, 133.4, 131.6, 130.9, 130.1, 130.2, 128.7, 126.8, 126.7, 126.0, 125.9, 125.6, 124.0, 122.6, 119.8, 66.7 (CH<sub>3</sub>), 52.2 (benzyl-C); m/z (EI<sup>+</sup>) 496 ([M]+); HRMS (EI<sup>+</sup>) C<sub>24</sub>H<sub>18</sub>BrClN<sub>2</sub>O<sub>3</sub>, ([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 ⁰C; ν<sub>max</sub>/cm<sup>-1</sup> 3288 (NH), 1641 (C=O); δ<sub>H</sub> (400 MHz, DMSO-d<sub>6</sub>) 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); δ<sub>C</sub> (100 MHz, DMSO-d<sub>6</sub>) 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<sup>+</sup>) 398 ([M-H], 100% ); HRMS (ESI<sup>+</sup>) C<sub>23</sub>H<sub>15</sub>BrN<sub>2</sub>O<sub>4</sub>, ([M+Na]<sup>+</sup> requires 422.1111; found 422.1101.
N-[(8-Hydroxy-5-nitroquinolin-7-yl)(o-tolyl)methyl]benzamide S64

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; νmax/cm⁻¹ 3302 (NH), 1639 (C=O); δH (400 MHz, DMSO-d6) 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, CH₃); δC (100 MHz, DMSO-d6) 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 (CH₃); m/z (ESI⁻) 412 ([M-H]⁻); HRMS (ESI⁻) C₂₄H₁₉N₃O₄Na, ([M+Na]+) requires 436.1268; found 436.1253.

N-[(8-Hydroxy-5-nitroquinolin-7-yl)(m-tolyl)methyl]benzamide S65

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; νmax/cm⁻¹ 3271 (NH), 1636 (C=O); δH (400 MHz, DMSO-d6) 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, CH₃); δC (100 MHz, DMSO-d6) 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 (CH₃); m/z (ESI⁻) 412 ([M-H]⁻); HRMS (ESI⁻) C₂₄H₁₉N₃O₄, ([M-H]⁻) requires 412.1303; found 412.1307.
Following general procedure 1, 8-hydroxy-5-nitroquinoline (380 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and p-tolualdehyde (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); \( \delta^H \) (400 MHz, DMSO-\( \text{d}_6 \)) 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, d, \( J=8.5 \) Hz, benzyl-H), 2.27 (3 H, s, CH\(_3\)); \( \delta^C \) (100 MHz, DMSO-\( \text{d}_6 \)) 166.9 (C=O), 158.5, 149.9, 141.8, 137.3, 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 (CH\(_3\)); \( m/z \) (ESI) 412 ([M-H]); HRMS (ESI) C\(_{24}\)H\(_{18}\)N\(_3\)O\(_4\) ([M-H]) requires 412.1303; found 412.1309.

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); \( \delta^H \) (400 MHz, DMSO-\( \text{d}_6 \)) 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, \( J=8.5 \) Hz, benzyl-H), 2.29 (3 H, s, CH\(_3\)); \( \delta^C \) (100 MHz, DMSO-\( \text{d}_6 \)) 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 (CH\(_3\)); \( m/z \) (ESI) 412 ([M-H]); HRMS (ESI) C\(_{24}\)H\(_{18}\)N\(_3\)O\(_4\) ([M-H]) requires 412.1303; found 412.1303.
N-{[(8-Hydroxy-5-nitroquinolin-7-yl)(phenyl)methyl]-3-methylbenzamide 568

![Chemical Structure]

Following general procedure 1, 8-hydroxy-5-nitroquinoline (380 mg, 2.0 mmol), m-toluamide (270 mg, 2.0 mmol) and benzaldehyde (406 µL, 4.0 mmol) gave 568 (261 mg, 32 %) as an orange powder.

mp 222 °C; ν max/cm⁻¹ 3293 (NH), 1636 (C=O); δn (400 MHz, DMSO-d₆) 9.35 - 9.41 (1 H, m, quinoline-Ar), 9.15 - 9.20 (1 H, m, quinoline-Ar), 8.99 - 9.03 (1 H, m, quinoline-Ar), 8.78 (1 H, s, quinoline-Ar), 7.85 - 7.92 (1 H, m, Ar), 7.76 (1 H, s, Ar), 7.70 - 7.75 (1 H, m, Ar), 7.33 - 7.40 (6 H, m, Ar), 7.26 - 7.32 (1 H, m, Ar), 6.99 (1 H, d, J=8.5 Hz, benzyl-H), 2.36 (3 H, s, C₃H₃); δc (100 MHz, DMSO-d₆) 167.0 (C=O), 158.6, 149.9, 141.8, 138.4, 137.7, 135.2, 135.0, 133.9, 132.9, 129.4, 129.1, 128.9, 128.2, 128.1, 126.1, 125.7, 124.7, 122.5, 51.0 (benzyl-C), 21.8 (CH₃); m/z (ESI⁻) 412 ([M-H]⁻); HRMS (ESI⁺) C₂₄H₂₀N₃NaO₄, ([M+Na⁺] requires 436.1268; found 436.1259.

N-{[(8-Hydroxy-5-nitroquinolin-7-yl)(phenyl)methyl]-4-methylbenzamide 569

![Chemical Structure]

Following general procedure 1, 8-hydroxy-5-nitroquinoline (380 mg, 2.0 mmol), p-toluamide (270 mg, 2.0 mmol) and benzaldehyde (406 µL, 4.0 mmol) gave 569 (563 mg, 68 %) as an orange powder.

mp 259 °C; ν max/cm⁻¹ 3229 (NH), 1638 (C=O); δn (400 MHz, DMSO-d₆) 9.32 - 9.40 (1 H, m, quinoline-Ar), 9.13 - 9.21 (1 H, m, quinoline-Ar), 8.96 - 9.04 (1 H, m, quinoline-Ar), 8.80 (1 H, s, quinoline-Ar), 7.83 - 7.90 (3 H, m, Ar), 7.33 - 7.40 (4 H, m, Ar), 7.25 - 7.32 (3 H, m, Ar), 7.01 (1 H, d, J=8.5 Hz, benzyl-H), 2.31 - 2.38 (3 H, m, CH₃); δc (100 MHz, DMSO-d₆) 166.8 (C=O), 158.6, 149.9, 142.2, 141.9, 137.7, 135.2, 133.9, 132.2, 129.7, 129.4, 129.1, 128.5, 128.2, 128.1, 126.1, 124.7, 122.5, 51.0 (benzyl-C), 21.8 (CH₃); m/z (ESI⁻) 412 ([M-H]⁻); HRMS (ESI⁺) C₂₄H₂₀N₃NaO₄, ([M+Na⁺] requires 436.1268; found 436.1254.
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.

**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 S71 (608 mg, 68 %) as an orange powder.

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

mp 237 °C; νmax/cm⁻¹ 3386 (NH), 1635 (C=O); δH (400 MHz, DMSO-d6) 9.47 - 9.55 (1 H, 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 (4 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, 133.9, 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⁻) C27H18N3O4, [(M-H)⁻] requires 448.1303; found 448.1301.

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; νmax/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⁻) C27H18N3O4, [(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⁻) C₂₃H₁₆BrN₃O₄, ([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, 121.3, 50.6 (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 S74 (255 mg, 34 %) as an off-white powder.

mp 245 °C; \( \nu_{\text{max}}/\text{cm}^{-1} \) 3309 (NH), 1639 (C=O), 691 (C-Cl); \( \delta_H \) (400 MHz, DMSO-\( d_6 \)) 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); \( \delta_C \) (100 MHz, DMSO-\( d_6 \)) 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-) 377 ([M-H]); HRMS (ESI-) \( C_{21}H_{15}ClIN_{2}NaO_{3} \), ([M+Na]+) requires 401.0652; found 401.0663.

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 S75 (205 mg, 26 %) as a white powder.

mp 237 °C; \( \nu_{\text{max}}/\text{cm}^{-1} \) 3325 (NH), 1640 (C=O), 700 (C-Cl); \( \delta_H \) (400 MHz, DMSO-\( d_6 \)) 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); \( \delta_C \) (100 MHz, DMSO-\( d_6 \)) 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, 126.1, 125.6, 124.0, 119.5, 47.0 (benzyl-C); \( m/z \) (ESI-) 393 ([M-H]); HRMS (ESI+) \( C_{21}H_{15}ClIN_{2}NaO_{2}S \), ([M+Na]+) requires 417.0435; found 417.0423.
**N-((5-Chloro-8-hydroxyquinolin-7-yl)(thiophen-3-yl)methyl)benzamide S76**

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), 710 (C-Cl); 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\textsuperscript{-}) 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\textsuperscript{+}) 388 ([M-H]); HRMS (ESI\textsuperscript{+}) C\textsubscript{22}H\textsubscript{17}ClIN\textsubscript{3}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; νmax/cm⁻¹ 3309 (NH), 1638 (C=O); δH (400 MHz, DMSO-d6) 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); δC (100 MHz, DMSO-d6) 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⁺) 388 ([M-H]⁻); HRMS (ESI+) C22H16ClN3O2, ([M+Na]⁺) 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; νmax/cm⁻¹ 3286 (NH), 1634 (C=O); δH (400 MHz, DMSO-d6) 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); δC (100 MHz, DMSO-d6) 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 (EI⁺) 389 ([M⁺]²); HRMS (EI⁺) C22H16ClN3O2, ([M⁺]²) 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), 8.92 - 9.02 (1 H, m, quinoline-Ar), 8.44 - 8.53 (1 H, m, quinoline-Ar), 8.00 (1 H, s, quinoline-Ar), 7.91 - 7.96 (1 H, m, 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, C₆H₄), 1.43 - 1.62 (2 H, m, C₆H₄), 1.10 - 1.37 (6 H, m), 0.73 - 0.90 (3 H, m, C₃H₇); δC (100 MHz, DMSO-d₆) 166.6 (C=O), 150.3, 150.1, 145.4, 145.6, 139.6, 139.5, 133.4, 132.4, 132.1, 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 478.1482; 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 benzo[d]thiazole-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⁻) C₂₄H₂₄ClN₃NaO₂S, ([M+Na]⁺) requires 468.0544; found 468.0636.
N-[(5-Cyano-8-hydroxyquinolin-7-yl)(3-methylthiophen-2-yl)methyl]benzamide S82

![Chemical Structure of Compound S82](image)

Following general procedure 1, S21 (64 mg, 0.38 mmol), benzamide (46 mg, 0.38 mmol) and 3-methyl-2-thiophenecarboxaldehyde (81 μL, 0.76 mmol) gave S82 (130 mg, 86 %) as a light-brown powder after purification via flash column chromatography (40 % - 60 % EtOAc, cyclohexane).

mp 202 °C; νmax/cm⁻¹ 3231 (NH), 1630 (C=O); δH (400 MHz, DMSO-d₆) 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, CH₃); δC (100 MHz, DMSO-d₆) 166.2 (C=O), 155.9, 150.5, 139.1, 138.0, 134.9, 134.5, 134.4, 133.7, 132.0, 131.1, 128.8, 128.2, 128.1, 125.6, 125.0, 123.0, 118.0, 97.9 (nitrile), 45.2 (benzyl-C), 14.0 (CH₃); m/z (ESI⁺) 400 ([M+H⁺]⁺); HRMS (ESI⁺) C₂₃H₁₈O₂N₃S, ([M+H⁺]⁺) requires 400.1114; found 400.1110.

N-[(5-Chloro-8-hydroxyquinolin-7-yl)(3-methylthiophen-2-yl)methyl]furan-2-carboxamide S83

![Chemical Structure of Compound S83](image)

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 S83 (208 mg, 26 %) as an off-white powder.

mp 157 °C; νmax/cm⁻¹ 3305 (NH), 1658 (amide C=O); δH (400 MHz, DMSO-d₆) 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, benzyll-H), 6.86 - 6.92 (1 H, m, Ar), 6.60 - 6.67 (1 H, m, Ar), 2.14 (3 H, s, CH₃); δC (100 MHz, DMSO-d₆) 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 (CH$_3$); m/z (ESI$^+$) 399 ([M+H$^+$]); HRMS (ESI$^+$) C$_{20}$H$_{15}$ClIN$_2$NaO$_2$S, ([M+Na$^+$]) requires 421.0384; found 421.0370.

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

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

mp 188 °C; $\nu_{\text{max}}$/cm$^{-1}$ 3303 (NH), 1638 (C=O); $\delta_H$ (400 MHz, DMSO-$d_6$) 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, CH$_3$); $\delta_C$ (100 MHz, DMSO-$d_6$) 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 (CH$_3$); m/z (ESI$^+$) 415 ([M+H$^+$]); HRMS (ESI$^+$) C$_{20}$H$_{15}$ClIN$_2$NaO$_2$S, ([M+Na$^+$]) requires 437.0156; found 437.0141.

$N$-((5-Chloro-8-hydroxyquinolin-7-yl)(furan-3-yl)methyl)benzamide S85

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 °C; $\nu_{\text{max}}$/cm$^{-1}$ 3323 (NH), 1638 (C=O); $\delta_H$ (400 MHz, DMSO-$d_6$) 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, CH$_3$); $\delta_C$ (100 MHz, DMSO-$d_6$) 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, 124.3, 119.0, 110.8, 43.6 (benzyl-C); m/z (ESI$^+$) 379 ([M+H$^+$]); HRMS (ESI$^+$) C$_{24}$H$_{15}$ClIN$_2$NaO$_2$, ([M+Na$^+$]) requires 401.0663; found 401.0652.
\(N\-\{(3,3’\-\text{Bithiophen})\-5\-\text{yl}(5\-\text{chloro}-8\-\text{hydroxyquinolin}-7\-\text{yl})\-\text{methyl}\}\text{benzamide S86}\)

\[
\begin{align*}
\text{Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 3,3’-bithiophen-5-carboxaldehyde (777 mg, 4.0 mmol) gave S86 (373 mg, 39 %) as an off-white powder.}
\end{align*}
\]

mp 213 °C; \(\nu_{\text{max}}/\text{cm}^{-1}\) 3287 (NH), 1641 (C=O); \(\delta_{\text{H}}\) (400 MHz, DMSO-\(\text{d}_6\)) 10.57 (1 H, br. s., NH), 9.41 - 9.60 (1 H, br. s., quinoline-Ar), 8.96 - 9.03 (1 H, m, quinoline-Ar), 8.46 - 8.55 (1 H, m, quinoline-Ar), 8.01 (1 H, s, 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), 7.42 - 7.47 (1 H, m, Ar), 7.26 (1 H, s, Ar), 7.20 (1 H, d, J=8.5 Hz, benzyl-H); \(\delta_{\text{C}}\) (100 MHz, DMSO-\(\text{d}_6\)) 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, 126.2, 125.4, 125.2, 124.0, 121.3, 120.4, 119.6, 47.2 (benzyl-C); \(m/z\) (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 499.0294.

\(N\-\{(8\-\text{Hydroxy}-2\-\text{methylquinolin}-7\-\text{yl})\-\text{methylthiophen-2-yl}\}\text{methyl}\text{benzamide S87}\)

\[
\begin{align*}
\text{Following general procedure 1, 8-hydroxyquinaldine (318 mg, 2 mmol), benzamide (242 mg, 2 mmol) and 3-methyl-2-thiophencarboxaldehyde (431 \(\mu\)L, 4 mmol) gave S87 (264 mg, 34 %) as a light brown powder after purification via flash column chromatography (10 % - 20 % EtOAc, cyclohexane).}
\end{align*}
\]

mp 189 °C; \(\nu_{\text{max}}/\text{cm}^{-1}\) 3289 (NH), 1631 (C=O); \(\delta_{\text{H}}\) (400 MHz, DMSO-\(\text{d}_6\)) 9.27 - 9.38 (1 H, m, quinoline-Ar), 8.16 - 8.22 (1 H, m, quinoline-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 - 7.49 (2 H, m, Ar), 7.36 - 7.41 (1 H, m, Ar), 7.22 - 7.27 (1 H, m, Ar), 7.11 - 7.19 (1 H, m, benzyl-H), 6.82 - 6.94 (1 H, m, Ar), 2.71 (3 H, s, quinoline-CH\(_3\)), 2.17 (3 H, s, thiophene-CH\(_3\)); \(\delta_{\text{C}}\) (100 MHz, DMSO-\(\text{d}_6\)) 166.7 (C=O), 157.5, 149.5, 140.4, 137.7, 136.6, 134.7, 134.3, 131.7, 130.8, 128.6, 128.1, 126.4, 125.9, 124.3, 123.3, 123.2, 117.4, 45.7 (benzyl-C), 25.2 (quinoline-CH\(_3\)), 14.1 (thiophene-CH\(_3\)); \(m/z\) (ESI\(^+\)) 389 ([M+H\(^+\)]; HRMS (ESI\(^+\)) \(\text{C}_{23}\text{H}_{19}\text{O}_2\text{N}_2\text{S}\), ([M+H\(^+\)]) requires 389.1318; found 389.1310.
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; ν\textsubscript{max}/cm\textsuperscript{-1} 3274 (NH), 1636 (C=O); δ\textsubscript{H} (400 MHz, DMSO-d\textsubscript{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-C\textsubscript{H\textsubscript{3}}), δ\textsubscript{C} (100 MHz, DMSO-d\textsubscript{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-CH\textsubscript{3}), 14.1 (thiophene-CH\textsubscript{3}); m/z [ESI\textsuperscript{+}] 387 ([M-H\textsuperscript{-}]), HRMS (ESI\textsuperscript{+}) \textit{C}_{23}\textit{H}_{20}\textit{N}_{2}\textit{O}_{2}\textit{S}, ([M+Na\textsuperscript{+}]) 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; ν\textsubscript{max}/cm\textsuperscript{-1} 3294 (NH), 1637 (C=O); δ\textsubscript{H} (400 MHz, DMSO-d\textsubscript{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-CH\textsubscript{3}), 2.18 (3 H, s, thiophene-CH\textsubscript{3}); δ\textsubscript{C} (100 MHz, DMSO-d\textsubscript{6}) 166.1 (C=O), 150.6, 148.3, 145.0, 140.2, 138.1,
N-[(8-Hydroxy-5-methylquinolin-7-yl)(3-methylthiophen-2-yl)methyl]benzamide S90

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; νmax/cm⁻¹ 3299 (NH), 1638 (C=O); δH (400 MHz, DMSO-d6) 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-CH3), 2.17 (3 H, s, thiophene-CH3); δC (100 MHz, DMSO-d6) 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-CH3), 14.1 (thiophene-CH3); m/z (ESI⁺) 389 ([M+H]+); HRMS (ESI⁺) C23H20N2NaO2S, ([M+Na]+) requires 411.1138; found 411.1142.

N-[(8-Hydroxy-6-methylquinolin-7-yl)(3-methylthiophen-2-yl)methyl]benzamide S91

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; νmax/cm⁻¹ 2980 (NH), 1660 (C=O); δH (400 MHz, DMSO-d6) 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-CH3), 2.29 (3 H, s, thiophene-CH3); δC (100 MHz, DMSO-d6) 165.4 (C=O), 153.2, 149.4, 137.8, 137.5, 135.9, 135.0, 134.4, 132.1,
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; νmax/cm⁻¹ 3325 (NH), 1636 (C=O); δH (400 MHz, DMSO-d₆) 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, OCH₃), 2.20 (3 H, s, CH₃); δC (100 MHz, DMSO-d₆) 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 (OCH₃), 45.5 (benzyl-C), 14.1 (CH₃); m/z [ESI⁺] 405 ([M+H⁺]); HRMS (ESI⁺) C₂₃H₂₀N₂O₃S, ([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; νmax/cm⁻¹ 3280 (NH), 1638 (C=O); δH (400 MHz, DMSO-d₆) 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,
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; νmax/cm⁻¹ 3278 (NH), 1646 (C=O); δH (400 MHz, DMSO-d₆) 10.55 (1 H, br. s., NH), 9.69 - 9.79 (1 H, m, quinoline-Ar), 8.74 - 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), 7.26 - 7.33 (1 H, m, Ar), 7.17 (1 H, d, J=8.0 Hz, benzyl-H), 6.98 (1 H, m, Ar), 2.16 (3 H, s, CH₃); δC (100 MHz, DMSO-d₆) 164.4 (C=O), 150.6, 150.2, 148.6, 139.4, 139.3, 136.0, 135.3, 135.1, 133.4, 131.4, 131.0, 127.1, 126.1, 125.2, 124.2, 124.1, 123.1, 119.3, 46.1 (benzyl-C), 14.4 (CH₃); m/z (ESI) 929 ([2M+Na]⁺); HRMS (ESI⁺) C₂₂H₁₆ClIN₃O₄S, ([M+Na]⁺) requires 476.0442; found 476.0434.

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; νmax/cm⁻¹ 3297 (NH), 1647 (C=O); δH (400 MHz, DMSO-d₆) 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 Hz, benzyl-H), 6.85 - 6.93 (1 H, m, Ar), 7.25 (3 H, s, CH₃); δC (100 MHz, DMSO-d₆) 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, 125.4, 124.2, 124.0, 119.3, 45.4 (benzyl-C), 14.5 (CH₃); m/z (ESI) 441 ([M-H]); HRMS (ESI) C_{22}H_{15}Cl_{2}N_{2}O_{3}S, ([M-H]) requires 441.0237; found 441.0233.

3-Chloro-4-((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-thiophenecarboxaldehyde (656 mg, 4.0 mmol) gave S96 (266 mg, 30 %) as an off-white powder.

mp 172 °C; ν_{max}/cm⁻¹ 3300 (NH), 1642 (C=O); δ_H (400 MHz, DMSO-d₆) 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, CH₃); δ_C (100 MHz, DMSO-d₆) 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, 128.4, 124.6, 123.6, 50.2 (benzyl-C), 18.7 (CH₃); m/z (ESI) 441 ([M-H]); HRMS (ESI) C_{22}H_{15}Cl_{2}N_{2}O_{3}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-thiophenecarboxaldehyde (431 μL, 4.0 mmol) gave S97 (339 mg, 39 %) as an off-white powder.

mp 163 - 164 °C; ν_{max}/cm⁻¹ 3305 (NH), 1637 (C=O); δ_H (400 MHz, DMSO-d₆) 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-CH₂), 2.14 (3 H, s, OCH₃); δ_C (100 MHz, DMSO-d₆) 165.9 (C=O), 162.6 (COCH₃), 150.4, 150.0,
140.1, 139.4, 134.9, 131.3, 130.4, 127.4, 127.0, 126.0, 125.8, 123.9, 119.2, 114.3, 114.2, 56.2 (benzyl-CH₃); m/z (ESI⁺) 899 ([2M+Na]⁺); HRMS (ESI⁺) C₃₂H₂₀ClIN₂O₃S, ([M+H]⁺) requires 439.0878; found 439.0241.

**N-((5-Chloro-8-hydroxyquinolin-7-yl)(3-methylthiophen-2-yl)methyl)thiophene-2-carboxamide 598**

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 598 (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-CH₃), 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 599**

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 599 (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,
135.2, 133.4, 131.4, 130.4, 127.1, 126.1, 125.2, 124.3, 124.1, 124.0, 119.3, 45.8 (benzyl-C), 14.4 (CH₃); m/z (ESI⁺) 410 ([M+H]⁺); HRMS (ESI⁺) C₂₁H₁₆ClIN₃NaO₂S, ([M+Na]⁺) requires 321.0554; found 432.0527.

N-[(5-Chloro-8-hydroxyquinolin-7-yl)6-(thiophen-2-yl)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-(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), 7.91 - 8.00 (2 H, m, Ar), 7.88 - 7.94 (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) 171.2 (C=O), 158.6, 152.1, 150.8, 150.0, 145.2, 145.1, 139.6, 139.1, 138.9, 135.1, 134.7, 133.4, 132.5, 132.3, 129.5, 129.3, 128.3, 126.4, 125.9, 123.9, 121.2, 119.2, 52.7 (benzyl-C); m/z (ESI⁺) 471 ([M⁺]⁺); HRMS (ESI⁺) C₂₆H₁₈N₃O₂S, ([M⁺]⁺) requires 471.0800; found 471.0800.

N-[(5-Chloro-8-hydroxyquinolin-7-yl)6-(thiophen-3-yl)pyridin-2-yl)methyl]benzamide S101

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 6-(3-thienyl)pyridine-2-carboxaldehyde (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 ([M]+); HRMS (EI+) C26H18ClN3O3S, ([M]+) requires 471.0808; found 471.0811.

\[ \text{N-[(5-Chloro-8-hydroxyquinolin-7-yl)[5-phenylisoxazol-3-yl]methyl]benzamide S102} \]

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; \( \nu_{\text{max}}/\text{cm}^{-1} \) 3278 (NH), 1652 (C=O); \( \delta_{\text{H}} \) (400 MHz, DMSO-\( d_6 \)) 10.62 (1 H, br. s., NH), 9.47 - 9.59 (1 H, m, quinoline-Ar), 8.96 - 9.03 (1 H, m, quinoline-Ar), 8.59 - 8.65 (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), 7.74 - 7.81 (2 H, m, Ar), 7.54 - 7.61 (1 H, m, Ar), 7.46 - 7.54 (5 H, m, Ar), 7.12 (1 H, d, \( J=8.5 \text{ Hz} \), benzyl-H), 7.07 (1 H, s, Ar); \( \delta_{\text{C}} \) (100 MHz, DMSO-\( d_6 \)) 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); \( m/z \) (ESI+) 454 ([M-H]); HRMS (ESI+) \( C_{26}H_{16}ClN_3O_3S, (\text{[M+Na]}^+) \) requires 478.0929; found 478.0924.

\[ \text{N-[(5-Chloro-8-hydroxyquinolin-7-yl)[4-phenylthiophen-2-yl]methyl]benzamide S103} \]

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

mp 237 °C; \( \nu_{\text{max}}/\text{cm}^{-1} \) 3271 (NH), 1638 (C=O); \( \delta_{\text{H}} \) (400 MHz, DMSO-\( d_6 \)) 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),
7.18 - 7.27 (2 H, m, Ar); δC (100 MHz, DMSO-d$_6$) 166.7 (C=O), 150.4, 150.1, 147.6, 141.8, 139.6, 135.9, 134.8, 133.4, 132.4, 129.7, 129.2, 128.5, 128.0, 127.2, 126.7, 126.1, 125.5, 124.8, 124.0, 121.0, 119.6, 47.3 (benzyl-C); m/z (EI) 470 ([M]+); HRMS (EI) C$_{27}$H$_{19}$ClN$_2$O$_2$S, ([M]+) requires 470.0856; found 470.0863.

**N-((5-Chloro-8-hydroxyquinolin-7-yl)(5-phenylthiophen-2-yl)methyl)benzamide S104**

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; ν$_{max}$/cm$^{-1}$ 3284 (NH), 1636 (C=O); δH (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); δC (100 MHz, DMSO-d$_6$) 166.7 (C=O), 150.4, 150.1, 146.0, 143.4, 139.6, 134.8, 134.5, 133.4, 132.4, 129.9, 129.2, 128.5, 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') C$_{27}$H$_{19}$ClN$_2$O$_2$S, ([M+Na]+) requires 493.0748; found 493.0740.

**N-((5-Chloro-8-hydroxyquinolin-7-yl)(5-phenylfuran-2-yl)methyl)benzamide S105**

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; ν$_{max}$/cm$^{-1}$ 3290 (NH), 1635 (C=O); δH (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); δ (100 MHz, DMSO-δ6) 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⁺) C_{27}H_{19}ClN_{2}NaO_{3}, ([M+Na⁺]) 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-pyridinecarboxaldehyde (912 mg, 4.0 mmol) gave **S106** (584 mg, 71 %) as a white powder.

mp 243 °C; ν_{max}/cm⁻¹ 3274 (NH), 1647 (C=O); δ_{H} (400 MHz, DMSO-δ6) 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); δ_{C} (100 MHz, DMSO-δ6) 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⁺) C_{28}H_{19}ClN_{4}NaO_{3}, ([M+H⁺]) 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; ν_{max}/cm⁻¹ 3290 (NH), 1644 (C=O); δ_{H} (400 MHz, DMSO-δ6) 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
(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); δC (100 MHz, DMSO-d6) 173.0 (C=N), 167.0 (C=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 (benzyl-C); m/z (EI+) 455 ([M]+); HRMS (EI+) C26H18ClN3O3, ([M]+) requires 455.1037; found 455.0306.

\textit{N}-(5-Fluoro-8-hydroxyquinolin-7-yl)(3-methylthiophen-2-yl)methylbenzamide S108

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 μL, 4.0 mmol) gave S108 (305 mg, 39 %) as a light-brown powder.

mp 188 °C; v\textsubscript{max}/cm\textsuperscript{-1} 3301 (NH), 1639 (C=O); δH (400 MHz, DMSO-d6) 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, Ar, benzyl-H), 6.89 (1 H, d, m, Ar), 2.17 (3 H, s, CH\textsubscript{3}); δC (100 MHz, DMSO-d6) 166.5 (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 (benzyl-C), 14.4 (CH\textsubscript{3}); m/z (ESI+) 391 ([M-H]-); HRMS (ESI+) C\textsubscript{22}H\textsubscript{17}FN\textsubscript{2}NaO\textsubscript{2}S, ([M+Na]+) requires 415.0873; found 415.0887.

\textit{N}-(5-Bromo-8-hydroxyquinolin-7-yl)(3-methylthiophen-2-yl)methylbenzamide S109

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 μL, 4.0 mmol) gave S109 (186 mg, 21 %) as an off-white powder.

mp 152 °C; v\textsubscript{max}/cm\textsuperscript{-1} 3304 (NH), 1639 (C=O); δH (400 MHz, DMSO-d6) 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.

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.
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.

mp 187 °C; νmax/cm⁻¹ 3222 (NH), 1635 (C=O); δH (400 MHz, DMSO-d6) 10.48 (1 H, br. s., NH), 9.07 - 9.17 (1 H, m, quinoline-Ar), 8.88 - 8.99 (1 H, m, quinoline-Ar), 8.37 - 8.50 (1 H, s, quinoline-Ar), 7.62 - 7.79 (1 H, m, Ar), 7.17 - 7.36 (5 H, m, Ar), 6.86 - 6.92 (1 H, m, Ar), 6.83 (1 H, d, J=8.8 Hz, benzyl-H), 3.51 - 3.58 (2 H, m, CH2), 2.11 (3 H, s, CH3); δC (100 MHz, DMSO-d6) 169.7 (C=O), 150.5, 149.7, 139.4, 139.3, 136.8, 135.5, 134.6, 130.9, 129.6, 129.5, 129.0, 128.7, 126.1, 123.9, 123.6, 108.8, 44.8 (benzyl-C), 42.5 (CH3), 13.9 (CH3); m/z (ESI⁻) 421 ([M-H]⁻); HRMS (ESI⁻) C23H19ClN2NaO2S, ([M+Na]⁻) requires 445.0748; found 445.0737.

N-((5-Bromo-8-hydroxyquinolin-7-yl)(3-methylthiophen-2-yl)methyl)-2-phenylacetamide S112

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.

mp 187 °C; νmax/cm⁻¹ 3222 (NH), 1635 (C=O); δH (400 MHz, DMSO-d6) 10.48 (1 H, br. s., NH), 9.07 - 9.17 (1 H, m, quinoline-Ar), 8.88 - 8.99 (1 H, m, quinoline-Ar), 8.37 - 8.50 (1 H, s, quinoline-Ar), 7.62 - 7.79 (1 H, m, Ar), 7.17 - 7.36 (5 H, m, Ar), 6.86 - 6.92 (1 H, m, Ar), 6.83 (1 H, d, J=8.8 Hz, benzyl-H), 3.51 - 3.58 (2 H, m, CH2), 2.11 (3 H, s, CH3); δC (100 MHz, DMSO-d6) 169.7 (C=O), 150.5, 149.7, 139.4, 139.3, 136.8, 135.5, 134.6, 130.9, 129.6, 129.5, 129.0, 128.7, 126.1, 123.9, 123.6, 108.8, 44.8 (benzyl-C), 42.5 (CH3), 13.9 (CH3); m/z (ESI⁻) 421 ([M-H]⁻); HRMS (ESI⁻) C23H19ClN2NaO2S, ([M+Na]⁻) requires 445.0748; found 445.0737.

N-((5-Bromo-8-hydroxyquinolin-7-yl)(3-methylthiophen-2-yl)methyl)-2-phenylacetamide S112

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.

mp 187 °C; νmax/cm⁻¹ 3222 (NH), 1635 (C=O); δH (400 MHz, DMSO-d6) 10.48 (1 H, br. s., NH), 9.07 - 9.17 (1 H, m, quinoline-Ar), 8.88 - 8.99 (1 H, m, quinoline-Ar), 8.37 - 8.50 (1 H, s, quinoline-Ar), 7.62 - 7.79 (1 H, m, Ar), 7.17 - 7.36 (5 H, m, Ar), 6.86 - 6.92 (1 H, m, Ar), 6.83 (1 H, d, J=8.8 Hz, benzyl-H), 3.51 - 3.58 (2 H, m, CH2), 2.11 (3 H, s, CH3); δC (100 MHz, DMSO-d6) 169.7 (C=O), 150.5, 149.7, 139.4, 139.3, 136.8, 135.5, 134.6, 130.9, 129.6, 129.5, 129.0, 128.7, 126.1, 123.9, 123.6, 108.8, 44.8 (benzyl-C), 42.5 (CH3), 13.9 (CH3); m/z (ESI⁻) 421 ([M-H]⁻); HRMS (ESI⁻) C23H19ClN2NaO2S, ([M+Na]⁻) requires 445.0748; found 445.0737.
123.7, 122.3, 118.0, 47.3 \text{(benzyl-C)}, 14.3 \text{(thiophene-CH$_3$)}; m/z (ESI$^-$) 407 ([M-H]); HRMS (ESI$^-$) C$_{22}$H$_{17}$O$_2$N$_2$ClNaS, ([M+Na]$^+$) requires 431.0592; found 431.0583.

$N$-\{(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.

mp 154 °C; $\nu_{\text{max}}$/cm$^{-1}$ 3291 (NH), 1635 (C=O); $\delta$$_{\text{H}}$ (400 MHz, DMSO-d$_6$) 10.62 (1 H, br. s., NH), 9.50 - 9.57 (1 H, m, quinoline-Ar), 8.95 - 9.03 (1 H, m, quinoline-Ar), 8.46 - 8.55 (1 H, m, quinoline-Ar), 8.02 (1 H, s, Ar), 7.91 - 7.98 (2 H, m, Ar), 7.70 - 7.80 (1 H, m, Ar), 7.54 - 7.60 (1 H, m, benzyl-H), 7.42 - 7.53 (3 H, m, Ar), 7.21 - 7.25 (1 H, m, Ar), 7.15 - 7.20 (1 H, m, Ar), 7.09 - 7.14 (1 H, m, Ar), 7.00 - 7.07 (1 H, m, Ar), 6.75 - 6.79 (1 H, m, Ar); $\delta$$_{\text{C}}$ (100 MHz, DMSO-d$_6$) 166.7 (C=O), 150.4, 150.2, 145.6, 139.6, 137.2, 136.7, 134.8, 133.5, 132.5, 129.2, 128.5, 127.2, 126.2, 126.1, 125.1, 124.8, 124.4, 124.1, 119.6, 47.1 (benzyl-C); m/z (ESI$^-$) 499 ([M+Na]$^+$); HRMS (ESI$^-$) C$_{25}$H$_{17}$ClIN$_2$NaO$_2$S$_2$, ([M+Na]$^+$) requires 499.0312; found 499.0300.

$N$-\{(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-thiophencarboxaldehyde (431 $\mu$L, 4.0 mmol) gave S115 (415 mg, 51%) as an off-white powder.

mp 120 °C; $\nu_{\text{max}}$/cm$^{-1}$ 3242 (NH), 1642 (C=O); $\delta$$_{\text{H}}$ (400 MHz, DMSO-d$_6$) 10.55 (1 H, br. s., NH), 9.59 - 9.70 (1 H, m, quinoline-Ar), 8.91 - 9.03 (1 H, m, quinoline-Ar), 8.66 - 8.78 (1 H, m, Ar), 8.43 - 8.56 (1 H, m, Ar), 7.81 - 7.88 (2 H, m, Ar), 7.69 - 7.80 (3 H, m, Ar), 7.25 - 7.32 (1 H, m, Ar), 7.15 (1 H, d, $J$=8.0 Hz, benzyl-H), 6.84 - 6.96 (1 H, m, Ar), 2.15 (3 H, s, CH$_3$); $\delta$$_{\text{C}}$ (100 MHz, DMSO-d$_6$) 165.1 (C=O), 151.0, 150.6, 150.2, 142.2, 141.8, 139.4, 139.3, 135.3, 133.4, 131.4, 127.1, 126.1, 125.0, 124.2, 124.1,
122.3, 119.3, 45.9 (benzyl-C), 14.4 (CH3); m/z (ESI-1) 817 ([2M-H]-); HRMS (ESI+) C32H3ClIN3Na2O5S, ([M+Na]+) requires 432.0544; found 432.0531.

*N*-(5-Chloro-8-hydroxyquinolin-7-yl)(4-methoxyphenyl)methylbenzamide 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; νmax/cm-1 3314 (NH), 1631 (C=O); δH (400 MHz, DMSO-d6) 10.36 (1 H, br. s., NH), 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-H) 6.88 - 6.92 (2 H, m, Ar), 3.72 (3 H, s, O-CH3); δC (100 MHz, DMSO-d6) 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-CH3), 50.5 (benzyl-C); m/z (ESI-) 417 ([M-H]-, 100%); HRMS (ESI-) C24H19ClIN3NaO3, ([M+Na]+) requires 441.0976; found 441.0963.

*N*-(5-Chloro-8-hydroxyquinolin-7-yl)(3-(trifluoromethoxy)phenyl)methylbenzamide 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; νmax/cm-1 3297 (NH), 1634 (C=O), 680 (C-Cl); δH (400 MHz, DMSO-d6) 10.56 (1 H, br. s., NH), 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-H); δC (100 MHz, DMSO-d6) 167.0 (C=O), 150.6, 150.2, 149.4, 145.3, 139.5, 134.9,
133.4, 132.4, 131.3, 129.2, 128.5, 127.3, 126.0, 125.1, 124.0, 120.3, 119.6, 50.6 (benzyl-C); δ_C (377 MHz, DMSO-d6) - 56.7 (CF3); m/z (ESI-) 495 ([M-H]-); HRMS (ESI+) C24H16ClF3N2NaO3, ([M+Na]+) requires 495.0694; found 495.0683.

7-(Amino(3-bromophenyl)methyl)-5-chloroquinolin-8-ol bis(2,2,2-trifluoroacetate) S118

![Chemical Structure Image](image)

Trifluoroacetic acid (83 μL, 1 mmol) was added dropwise to a stirring suspension of 159 (100 mg, 0.22 mmol) in CH2Cl2 (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; ν_max/cm⁻¹ 1666 (C=O); δ_H (400 MHz, DMSO-d6) 9.02 (3 H, br. s) 8.48 - 8.57 (1 H, m, NH3+), 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); δ_C (100 MHz, DMSO-d6) 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 (CF3); m/z (FI+) 362 ([M]+); HRMS (FI+) C16H12BrClIN2O, ([M]+) requires 361.9822; found 361.9809.

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

![Chemical Structure Image](image)

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; ν_max/cm⁻¹ 3306 (NH), 1634 (C=O); δ_H (400 MHz, DMSO-d6) 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, OCH3); δ_C (100 MHz, DMSO-d6) 166.6 (C=O), 160.0, 150.5, 150.2, 145.2, 139.5, 136.3, 133.4, 131.6, 130.9,
130.5, 130.4, 127.3, 127.3, 126.0, 125.1, 124.0, 122.6, 120.7, 119.6, 118.1, 113.8, 56.2 (OCH₃), 50.2 (benzyl-C); m/z (ESI⁺) 497 ([M+H⁺]); HRMS (ESI⁺) C₂₀H₂BrClN₂O₆, ([M+H⁺]) requires 497.0262; found 497.0249.

N-((5-Chloro-8-hydroxyquinolin-7-yl)(3,4-dimethoxyphenyl)methyl)benzamide S120

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 °C; νmax/cm⁻¹ 3294 (NH), 1632 (C=O); δₘ (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); 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⁺) C₂₅H₂₂ClN₂O₅ requires 471.1082; found 471.1076.

N-((8-Hydroxy-5-nitroquinolin-7-yl)(4-methoxyphenyl)methyl)benzamide S121

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 °C; νmax/cm⁻¹ 3250 (NH), 1637 (C=O); δₘ (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); δc (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 (OCH₃), 50.6 (benzyl-C); m/z (ESI⁻) 428 ([M-H]⁻); HRMS (ESI⁻) C₂₄H₁₉N₃NaO₅, ([M+Na]⁻) requires 452.1217; found 452.1212.

\[ \text{N-((3,4-Dimethoxyphenyl)(8-hydroxyquinolin-7-yl)methyl)benzamide S122} \]

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; ν<sub>max</sub>/cm⁻¹ 3312 (NH), 1633 (C=O); δ<sub>H</sub> (400 MHz, DMSO-d₆) 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), 3.71 (3 H, s, OCH₃), 3.69 (3 H, s, OCH₃), 3.37 (2 H, s, CH₂); δ<sub>C</sub> (100 MHz, DMSO-d₆) 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 (OCH₃), 56.4 (OCH₃), 51.3 (benzyl-C); m/z (ESI⁻) 437 ([M+Na]⁻); HRMS (ESI⁻) C₂₅H₂₂N₂NaO₄, ([M+Na]⁻) requires 437.1472; found 437.1467.

\[ \text{N-((3,4-Dimethoxyphenyl)(8-hydroxyquinolin-7-yl)methyl)-2-phenylacetamide S123} \]

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; ν<sub>max</sub>/cm⁻¹ 3292 (NH), 1638 (C=O); δ<sub>H</sub> (400 MHz, DMSO-d₆) 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, OCH₃), 3.63 (3 H, s, OCH₃), 3.37 (2 H, s, CH₂); δ<sub>C</sub> (100 MHz, DMSO-d₆) 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 (OCH₃), 56.2 (OCH₃), 50.5 (benzyl-C); m/z (ESI⁻) 429 ([M+H]⁻); HRMS (ESI⁻) C₂₆H₂₄N₂NaO₄, ([M+Na]⁻) requires 451.1628; found 451.1624.
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 124 (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 124 as a bright-yellow powder in quantitative yield.

mp 250 °C; \( \nu_{\text{max}}/\text{cm}^{-1} \) 3288 (NH), 1641 (C=O); \( \delta_H \) (400 MHz, DMSO-\( d_6 \)) 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, OCH₃); \( \delta_C \) (100 MHz, DMSO-\( d_6 \)) 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 (OCH₃), 50.9 (benzyl-C); m/z (ESI⁺) 419 ([M+H⁺]), HRMS (ESI⁺) \( \text{C}_{24}\text{H}_{20}\text{ClN}_2\text{O}_3 \) requires 419.1157; found 419.1160.

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 125 (464 mg, 52 %) as a white powder.

mp 186 - 187 °C; \( \nu_{\text{max}}/\text{cm}^{-1} \) 3306 (NH), 1636 (C=O); \( \delta_H \) (400 MHz, DMSO-\( d_6 \)) 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, OCH₃), 3.73 (3 H, s, OCH₃); \( \delta_C \) (100 MHz, DMSO-\( d_6 \)) 166.2.
(C=O), 160.8, 158.7, 150.6, 149.8, 139.4, 133.3, 132.0, 129.5, 129.0, 128.4, 127.9, 126.0, 125.6, 123.7, 122.3, 118.6, 105.2, 99.4, 56.5 (OCH₃), 56.1 (OCH₃), 46.6 (benzyl-C); m/z (ESI⁻) 895 ([2M-H]⁻); HRMS (ESI⁻) C₃₂H₂₃Cl₂N₂NaO₄ ([(M+Na)⁻] requires 471.1082; found 471.1079.

N-((5-Chloro-8-hydroxyquinolin-7-yl)(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)methyl)benzamide S126

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; v_max/cm⁻¹ 3282 (NH), 1631 (C=O); δ_H (400 MHz, DMSO-d₆) 10.40 (1 H, br. s., NH), 9.08 - 9.25 (1 H, m, 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 Hz, benzyl-H), 6.72 - 6.86 (3 H, m, Ar), 4.19 (4 H, s, CH₂); δ_C (100 MHz, DMSO-d₆) 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 (CH₃), 50.4 (benzyl-C); m/z (ESI⁻) 445 ([M+H]⁻); HRMS (ESI⁻) C₂₅H₂₁ClIN₂NaO₄ ([(M+Na)⁻] requires 469.0926; found 469.0917.

N-((5-Chloro-8-hydroxyquinolin-7-yl)(3',5'-dimethoxy-[1,1'-biphenyl]-3-yl)methyl)benzamide S127

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and S25 (634 mg, 2.6 mmol) gave S127 (513 mg, 49 %) as a white powder.

mp 239 °C; v_max/cm⁻¹ 3298 (NH), 1633 (C=O); δ_H (400 MHz, DMSO-d₆) 10.50 (1 H, br. s., NH), 9.19 - 9.43 (1 H, m, Ar), 8.88 - 9.02 (1 H, m, Ar), 8.31 - 8.62 (1 H, m, 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, OCH₃); δ_C (100 MHz, DMSO-d₆) 167.0 (C=O), 161.7 (COCH₃), 150.4, 150.1, 143.1, 143.1, 141.1, 139.6, 135.2, 133.4, 132.3, 129.9, 129.2, 128.5, 127.4, 126.4, 126.0, 125.8, 123.9, 119.5, 105.8, 100.0, 56.1 (OCH₃), 51.2 (benzyl-C); m/z (EI⁺) 524 ([M⁺]⁺); HRMS (EI⁺) C₃₁H₂₅ClN₂O₄, ([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; ν_max/cm⁻¹ 3297 (NH), 1633 (C=O); δ_H (400 MHz, DMSO-d₆) 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), 7.52 - 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, OCH₃); δ_C (100 MHz, DMSO-d₆) 167.0 (C=O), 160.5 (COCH₃), 150.4, 150.1, 143.2, 142.5, 141.1, 139.6, 135.2, 133.4, 132.3, 130.9, 129.9, 129.2, 128.5, 127.4, 126.4, 126.0, 125.8, 123.9, 119.5, 119.5, 113.8, 113.2, 55.9 (OCH₃), 51.2 (benzyl-C); m/z (EI⁺) 494 ([M⁺]⁺); HRMS (EI⁺) C₃₀H₂₃ClN₂O₃, ([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 CH₂Cl₂ (2 mL) at 0 °C was added a 1M solution of boron tribromide in CH₂Cl₂ (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%).

mp decomposition > 220 °C; \( \nu_{\text{max}} \text{cm}^{-1} \) 3294 (NH), 1634 (C=O); \( \delta_{\text{H}} \) (400 MHz, DMSO-d6) 10.20 (1 H, br. s., NH), 9.04 - 9.10 (1 H, m, quinoline-Ar), 8.91 - 8.96 (1 H, m, quinoline-Ar), 8.43 - 8.49 (1 H, m, quinoline-Ar), 7.88 - 7.95 (3 H, m, Ar), 7.67 - 7.72 (1 H, m, Ar), 7.50 - 7.56 (1 H, m, Ar), 7.42 - 7.49 (2 H, m, Ar), 6.83 (1 H, d, J=8.5 Hz, benzyl-H), 6.50 - 6.56 (1 H, m, Ar), 6.41 - 6.46 (1 H, m, Ar), 6.36 - 6.41 (1 H, m, Ar); \( \delta_{\text{C}} \) (100 MHz, DMSO-d6) 166.6 (C=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); \( m/z \) (ESI) 419 ([M-H]);

HRMS (ESI+) \( C_{23}H_{17}ClIN_{2}O_{4} \), ([M]+) requires 420.0877; found 420.0883.

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

To a solution of S127 (200 mg, 0.38 mmol) in \( \text{CH}_2\text{Cl}_2 \) (8 mL) at 0 °C was added a 1M solution of boron tribromide in \( \text{CH}_2\text{Cl}_2 \) (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 \( \text{CH}_2\text{Cl}_2 \). The organic layer was washed with water, brine, and subsequently dried over anhydrous \( \text{Na}_2\text{SO}_4 \). Purification by flash column chromatography using \( \text{CH}_2\text{Cl}_2/\text{MeOH} \) (90:10) gave S130 (143 mg, 76 %) as an orange powder.

mp decomposition > 230 °C; \( \nu_{\text{max}} \text{cm}^{-1} \) 3206 (OH), 1597 (C=O); \( \delta_{\text{H}} \) (400 MHz, DMSO-d6) 9.16 - 9.50 (1 H, m, quinoline-Ar), 8.83 - 9.14 (1 H, m, quinoline-Ar), 8.41 - 8.67 (1 H, m, quinoline-Ar), 7.95 (3 H, s, Ar), 7.70 - 7.82 (1 H, m, Ar), 7.51 - 7.58 (1 H, m, Ar), 7.44 - 7.51 (2 H, m, Ar), 7.35 - 7.42 (1 H, m, Ar), 7.30 - 7.35 (2 H, m, Ar), 7.20 - 7.26 (1 H, m, Ar), 7.08 (1 H, d, J=8.5 Hz, benzyl-H), 6.43 - 6.48 (1 H, m, Ar), 6.16 - 6.24 (1 H, m, Ar); \( \delta_{\text{C}} \) (100 MHz, DMSO-d6) 167.0 (C=O), 1157.9 (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.
**N-[(5-Chloro-8-hydroxyquinolin-7-yl)(3'-hydroxy-[1,1'-biphenyl]-3-yl)methyl]benzamide S131**

To a solution of S128 (160 mg, 0.31 mmol) in CH₂Cl₂ (10 mL) at 0 °C was added a 1M solution of boron tribromide in CH₂Cl₂ (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 CH₂Cl₂. The organic layer was washed with water, brine, and subsequently dried over anhydrous Na₂SO₄. Purification by flash column chromatography using CH₂Cl₂/MeOH (90:10) gave S131 (84 mg, 55 %) as a yellow powder.

mp decomposition > 180 °C; \( \nu_{\text{max}}/\text{cm}^{-1} \) 3206 (NH), 1596 (C=O); \( \delta_H \) (400 MHz, DMSO-\( \text{d}_6 \)) 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-\( \text{d}_6 \)) 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⁺) \( C_{29}H_{21}ClN_2O_4 \), ([M⁺]) requires 496.1190; found 496.1186.

**N-[(5-Chloro-8-hydroxyquinolin-7-yl)(3-methylthiophen-2-yl)methyl]-3-methoxybenzamide S132**

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

mp 145 °C; \( \nu_{\text{max}}/\text{cm}^{-1} \) 3291 (NH), 1640 (C=O); \( \delta_H \) (400 MHz, DMSO-\( \text{d}_6 \)) 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); δₛ (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⁺) C₂₃H₂₁ClN₂NaO₃S, ([M+Na]⁺) requires 461.0697; found 461.0699.

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

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.

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.

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

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.
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; \( \nu_{\text{max}}/\text{cm}^{-1} \) 3303 (NH), 1724 (ester C=O), 1636 (amide C=O), 696 (C-Cl); \( \delta_{\text{H}} \) (400 MHz, DMSO-\( d_6 \)) 10.54 (1 H, br. s., N\( \text{H} \)), 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, CH\( _3 \)); \( \delta_{\text{C}} \) (100 MHz, DMSO-\( d_6 \)) 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 (OCH\( _3 \)), 50.9 (benzyl-C); \( m/z \) (ESI\(^+\)) 469 ([M+Na\(^+\)]; HRMS (ESI\(^+\)) \( C_{25}H_{19}ClI\text{N}_2\text{NaO}_4 \), (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; \( \nu_{\text{max}}/\text{cm}^{-1} \) 3300 (NH), 1633 (C=O); \( \delta_{\text{H}} \) (400 MHz, DMSO-\( d_6 \)) 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); \( \delta_{\text{C}} \) (100 MHz, DMSO-\( d_6 \)) 167.1 (C=O), 150.6, 150.2,
148.8, 144.7, 139.5, 135.0, 134.8, 133.5, 132.5, 131.0, 129.2, 128.5, 127.2, 126.1, 124.7, 124.1, 123.1, 122.4, 119.7, 50.8 (benzyl-C); m/z (ESI) 432 ([M-H]); HRMS (ESI') C_{23}H_{16}ClN_{3}NaO_{4}, ([M+Na]') requires 456.0722; found 456.0712.

**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; ν_{max}/cm⁻¹ 3315 (NH), 1640 (C=O); δ_{H} (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); δ_{C} (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') C_{23}H_{16}BrClN_{3}NaO_{4}, ([M+Na]') 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; ν_{max}/cm⁻¹ 3312 (NH), 1643 (C=O); δ_{H} (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); δ_{C} (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,
126.1, 125.1, 124.4, 124.2, 124.1, 119.3, 46.0 (benzyl-C), 14.4 (CH₃); m/z (ESI−) 452 ([M-H]−); HRMS (ESI−) C₂₂H₁₄ClN₃NaO₄S, ([M+Na]⁺) requires 476.0442; found 476.0453.

N-((3-Bromophenyl)(5-chloro-8-hydroxyquinolin-7-yl)methyl)acetamide S139

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; νmax/cm⁻¹ 3286 (NH), 1640 (C=O); δH (400 MHz, DMSO-d₆) 10.48 (1 H, br. s., NH), 8.92 - 8.98 (1 H, m, quinoline-Ar), 8.84 - 8.90 (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, CH₃); δC (100 MHz, DMSO-d₆) 169.6 (C=O), 150.2, 150.2, 145.6, 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 (CH₃); m/z (ESI−) 402 ([M-H]−); HRMS (ESI−) C₁₈H₁₄BrClN₂NaO₂, ([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; νmax/cm⁻¹ 3298 (NH), 1684 (C=O); δH (400 MHz, DMSO-d₆) 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 (1 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(CH₃)₃); δC (100 MHz, DMSO-d₆) 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(CH₃)₃), 51.5 (benzyl-C), 29.0 (C(CH₃)₃); m/z (FI+) 462 ([M]+); HRMS (FI+) C₂₁H₂₂BrClN₂O₃, ([M]+) requires 462.0346; found 462.0340.
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; \( \nu_{\text{max}} / \text{cm}^{-1} \) (DCM) 3334 (NH), 2957 (OH), 1645 (C=O); \( \delta_h \) (400 MHz, DMSO-\( d_6 \)) 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), 7.50 - 7.59 (2 H, m, Ar), 7.15 - 7.47 (1 H, m, Ar), 7.12 - 7.27 (2 H, m, Ar), 7.04 (1 H, d, J=8.5 Hz, benzyl-H), 2.18 - 2.28 (2 H, m, \( \text{CH}_2 \)), 1.51 (2 H, quin, J=7.5 Hz C\( \text{H}_2 \)), 0.85 (3 H, t, J=7.5 Hz, C\( \text{H}_3 \)); \( \delta_c \) (100 MHz, DMSO-\( d_6 \)) 172.4 (C=O), 150.3, 149.2, 143.5, 138.9, 136.9, 129.1, 128.3, 127.9, 127.3, 126.5, 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\(^{-} \)) \( C_{22}H_{21}NO_2 \), ([M+Na\(^+ \)] requires 357.1573; found 357.1565.

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; \( \nu_{\text{max}} / \text{cm}^{-1} \) 3274 (NH), 1636 (C=O); \( \delta_h \) (400 MHz, DMSO-\( d_6 \)) 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, \( \text{CH}_3 \)); \( \delta_c \) (100 MHz, DMSO-\( d_6 \)) 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\( \text{b} \)); m/z (ESI\(^{+} \)) 401 ([M-H] \(^{+} \), 100 %); HRMS (ESI\(^{+} \)) \( C_{22}H_{28}ClN_2O_2 \), ([M-H] \(^{+} \)) requires 401.1062; found 401.1062.
**N-((3,4-Dimethoxyphenyl)(8-hydroxyquinolin-7-yl)methyl)pentanamide S143**

![Chemical structure of 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; \( \nu_{\text{max}} / \text{cm}^{-1} \) 3250 (NH), 2868 (OH), 1635 (C=O); \( \delta_{\text{H}} \) (400 MHz, CDCl\(_3\)) 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, \( J=9.0 \text{ Hz} \), benzyl-H), 3.83 (3 H, s, OCH\(_3\)), 3.82 (3 H, s, OCH\(_3\)), 2.30 (2 H, t, \( J=7.5 \text{ Hz} \), \text{C}_2H), 1.67 (2 H, quin, \( J=7.0 \text{ Hz} \), \text{CH}_2), 1.37 (2 H, sxt, \( J=7.5 \text{ Hz} \), \text{CH}_2), 0.91 (3 H, t, \( J=7.5 \text{ Hz} \), \text{CH}_3); \( \delta_{\text{C}} \) (100 MHz, CDCl\(_3\)) 172.3 (C=O), 149.0, 149.0, 148.2, 138.3, 136.1, 134.3, 128.5, 127.6, 122.5, 121.9, 118.9, 118.0, 110.9, 110.5, 55.9 (OCH\(_3\)), 55.8 (OCH\(_3\)), 54.4 (benzyl-C), 36.7 (C\(_d\)), 27.8 (C\(_d\)), 22.4 (C\(_b\)), 13.8 (C\(_a\)); \( m/z \) (ESI\(^{-}\)) 393 ([M-H]); HRMS (ESI\(^{-}\)) \( \text{C}_{23}\text{H}_{27}\text{N}_{2}\text{O}_{4} \), ([M-H]) requires 395.1965; found 395.1973.

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

![Chemical structure of S144]

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

mp 205 °C; \( \nu_{\text{max}} / \text{cm}^{-1} \) 3262 (NH), 1637 (C=O), 700 (C-Cl); \( \delta_{\text{H}} \) (400 MHz, DMSO-\( d_6 \)) 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, \( J=9.0 \text{ Hz} \), benzyl-H), 2.23 (2 H, t, \( J=7.0 \text{ Hz} \), \text{CH}_2), 1.51 (2 H, quin, \( J=7.0 \text{ Hz} \), \text{CH}_2), 1.26 (2 H, sxt, \( J=7.0 \text{ Hz} \), \text{CH}_2), 0.86 (3 H, t, \( J=7.0 \text{ Hz} \), \text{CH}_3); \( \delta_{\text{C}} \) (100 MHz, DMSO-\( d_6 \)) 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 (C\(_d\)), 28.4 (C\(_d\)), 22.6 (C\(_b\)), 14.6 (C\(_a\)); \( m/z \) (ESI\(^{+}\)) 367 ([M+H\(^{+}\)]) requires 391.1184; found 391.1180.
**N-((5-Chloro-8-hydroxyquinolin-7-yl)(phenyl)methyl)-3-methylbutanamide S145**

Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), isovaleramide (202 mg, 2.0 mmol) and benzaldehyde (406 μL, 4.0 mmol) gave S145 (534 mg, 73 %) as a white powder.

\[
\text{mp } 199 \, ^\circ\text{C}; \, \nu_{\text{max}}/\text{cm}^{-1} \ 3235 \ (\text{NH}), \ 1633 \ (\text{C}=\text{O}), \ 700 \ (\text{C}-\text{Cl}); \, \delta_{\text{H}} \ (400 \text{ MHz, DMSO-}d_6) \ 10.34 \ (1 \text{ H, br. s., NH}), \ 8.89 - 8.99 \ (1 \text{ H, m, quinoline-Ar}), \ 8.72 - 8.83 \ (1 \text{ H, m, quinoline-Ar}), \ 8.41 - 8.51 \ (1 \text{ H, m, quinoline-Ar}), \ 7.62 - 7.79 \ (2 \text{ H, m, Ar}), \ 7.17 - 7.36 \ (5 \text{ H, m, Ar}), \ 6.72 \ (1 \text{ H, d, } J=8.5 \text{ Hz, benzyl-H}), \ 2.09 - 2.13 \ (2 \text{ H, m, } CH_2\text{)}, \ 2.01 \ (1 \text{ H, m, } CH_3), \ 0.87 \ (6 \text{ H, dd, } J=8.0, 7.0 \text{ Hz, } 2\times CH_3\text{}); \, \delta_{\text{C}} \ (100 \text{ MHz, DMSO-}d_6) \ 171.9 \ (\text{C}=\text{O}), \ 150.1, \ 142.8, \ 139.5, \ 133.4, \ 129.2, \ 127.8, \ 127.8, \ 127.1, \ 126.4, \ 125.7, \ 123.8, \ 119.4, \ 50.3 \ (\text{benzyl-C}), \ 45.4 \ (CH_2\text{)}, \ 26.6 \ (CH_3), \ 23.2 \ (CH_3\text{}); \, m/z \ (\text{ESI}^-) \ 367 \ ([M-H]^-); \, \text{HRMS (ESI)}^- \ C_{21}H_{21}ClN_2O_2, ([M-H]^-) \text{ requires } 391.1184; \text{ found } 391.1180.
\]

**N-((3-Bromophenyl)(5-chloro-8-hydroxyquinolin-7-yl)methyl)pentanamide S146**

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.

\[
\text{mp } 211 \, ^\circ\text{C}; \, \nu_{\text{max}}/\text{cm}^{-1} \ 3250 \ (\text{NH}), \ 1639 \ (\text{C}=\text{O}), \ 688 \ (\text{C}-\text{Cl}); \, \delta_{\text{H}} \ (400 \text{ MHz, DMSO-}d_6) \ 10.46 \ (1 \text{ H, br. s., NH}), \ 8.90 - 9.01 \ (1 \text{ H, m, quinoline-Ar}), \ 8.76 - 8.87 \ (1 \text{ H, m, quinoline-Ar}), \ 8.39 - 8.54 \ (1 \text{ H, m, quinoline-Ar}), \ 7.65 - 7.77 \ (2 \text{ H, m, Ar}), \ 7.38 - 7.49 \ (2 \text{ H, m, Ar}), \ 7.19 - 7.34 \ (2 \text{ H, m, Ar}), \ 6.69 \ (1 \text{ H, d, } J=8.5 \text{ Hz, benzyl-H}), \ 2.24 \ (2 \text{ H, t, } J=7.0 \text{ Hz, } CH_2\text{)}, \ 1.51 \ (2 \text{ H, quin, } J=7.0 \text{ Hz } CH_2\text{)}, \ 1.26 \ (2 \text{ H, sxt, } J=7.0 \text{ Hz } CH_2\text{)}, \ 0.86 \ (3 \text{ H, t, } J=7.0 \text{ Hz } CH_2\text{}); \, \delta_{\text{C}} \ (100 \text{ MHz, DMSO-}d_6) \ 172.6 \ (\text{C}=\text{O}), \ 150.2, \ 145.6, \ 139.5, \ 133.4, \ 131.6, \ 130.7, \ 130.3, \ 127.0, \ 126.8, \ 125.8, \ 125.6, \ 123.9, \ 122.6, \ 119.6, \ 50.0 \ (\text{benzyl-C}), \ 35.8 \ (CH_2\text{)}, \ 28.3 \ (CH_3\text{)}, \ 22.6 \ (CH_3\text{)}, \ 14.5 \ (CH_3\text{}); \, m/z \ (\text{ESI}^-) \ 445 \ ([M-H]^-); \, \text{HRMS (ESI)}^- \ C_{21}H_{19}BrClN_2O_2, ([M-H]^-) \text{ requires } 445.0324; \text{ found } 445.0318.
\]
**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; νmax/cm⁻¹ 3206 (NH), 1658 (C=O); δH (400 MHz, DMSO-d6) 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, CH₂), 1.94 - 2.06 (1 H, m, CH₃); δC (100 MHz, DMSO-d6) 172.0 (C=O), 150.2, 145.6, 139.5, 133.4, 131.6, 130.7, 130.3, 127.0, 125.8, 125.6, 124.0, 122.6, 119.6, 50.0 (benzyl-C), 45.4 (CH₂), 26.6 (CH₃); m/z (ESI⁺) 447 ([M+H]⁺); HRMS (ESI+) C₂₁H₁₉BrClN₂O₂, ([M-H⁻]) requires 445.0324; found 445.0313.

**N-[(8-Hydroxyquinolin-7-yl)(phenyl)methyl]acetamide S148**

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; νmax/cm⁻¹ 3305 (NH), 1644 (C=O); δH (400 MHz, DMSO-d6) 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), 7.39 - 7.45 (1 H, m, Ar), 7.24 - 7.31 (4 H, m, Ar), 7.16 - 7.23 (1 H, m, Ar), 6.72 (1 H, d, J=8.5 Hz, benzyl-H), 1.95 (3 H, s, CH₃); δC (100 MHz, DMSO-d6) 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 (CH₃); m/z (ESI⁺) 291 ([M-H]⁻); HRMS (ESI⁺) C₁₃H₁₃IN₂NaO₂, ([M+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; ν\textsubscript{max}/cm\textsuperscript{-1} 3270 (NH), 1640 (C=O); δ\textsubscript{H} (400 MHz, CDCl\textsubscript{3}) 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, H\textsubscript{a}), 2.11 (3 H, s, CH\textsubscript{3}); δ\textsubscript{C} (100 MHz, CDCl\textsubscript{3}) 173.8 (C=O), 150.2, 150.1, 140.3, 139.4, 134.7, 133.4, 131.3, 127.8, 125.9, 125.8, 123.8, 119.2, 44.9 (benzyl-C), 25.7, 25.2, 18.7, 14.3 (CH\textsubscript{3}); m/z (ESI\textsuperscript{+}) 386 ([M-H]-); HRMS (ESI\textsuperscript{+}) C\textsubscript{20}H\textsubscript{19}ClN\textsubscript{2}O\textsubscript{2}S, ([M+Na]\textsuperscript{+}) 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, H\textsubscript{2}O, and dried to give S150 (60 mg, 23 %) as a light-brown powder.

mp 125 °C; δ\textsubscript{H} (400 MHz, DMSO-d\textsubscript{6}) 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-CH\textsubscript{2}), 2.46 - 2.57 (4 H, m, H\textsubscript{b}); δ\textsubscript{C} (100 MHz, DMSO-d\textsubscript{6}) 151.3, 149.4, 139.3, 132.7, 128.6, 125.2, 123.0, 122.1, 118.4, 54.2, 53.9, 23.7 (CH\textsubscript{2}); m/z (ESI\textsuperscript{+}) 263 ([M+H]\textsuperscript{+}); HRMS (ESI\textsuperscript{+}) C\textsubscript{14}H\textsubscript{16}ON\textsubscript{2}Cl, ([M+H]\textsuperscript{+}) 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; νmax/cm⁻¹ 3313 (OH); δH (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, Hb), 2.41 - 2.48 (4 H, m, Hα); δC (100 MHz, DMSO-d₆) 151.4, 149.4, 139.2, 152.9, 129.1, 125.4, 123.2, 120.9, 118.6, 66.7, (Hb), 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-acetlypiperazine (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; νmax/cm⁻¹ 1621 (C=O); δH (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, Hb), 2.91 - 3.24 (4 H, m, Hα), 2.03 (3 H, s, CH₃); δC (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 (Cβ), 50.6 (Cα), 47.7 (benzyl-C), 21.5 (CH₃); m/z (ESI⁺) 320 ([M+H]⁺); HRMS (ESI⁺) C₁₆H₁₉O₂N₃Cl, ([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), 3.71 (2 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 disopropylethylamine (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, 133.4, 131.8, 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-morpholinopropan-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 % NH₄OH) to give S155 (193 mg, 69 %) as a white solid.

mp 216 °C; νmax/cm⁻¹: 3393 (NH), 1638 (C=O); δH (400 MHz, DMSO-d₆) 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 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 Hz, CH₃); δC (100 MHz, DMSO-d₆) 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-morpholinopropyl)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; νₜₐₐₛ / cm⁻¹ 3293 (NH), 1653 (C=O), 1635 (C=O); δₚ (400 MHz, DMSO-d₆) 10.50 (1 H, br. s., NH), 9.28 - 9.42 (1 H, m, quinoline-Ar), 8.92 - 9.07 (1 H, m, quinoline-Ar), 8.44 - 8.56 (1 H, m, quinoline-Ar), 8.23 - 8.36 (1 H, m, quinoline-Ar), 7.93 - 8.00 (2 H, m, Ar), 7.85 - 7.89 (1 H, m, Ar), 7.82 (1 H, s, Ar), 7.70 - 7.77 (2 H, m, Ar), 7.39 - 7.61 (4 H, m, Ar), 7.08 (1 H, d, J=8.5 Hz, benzyl-H), 3.43 - 3.52 (4 H, m, OCH₂), 3.29 - 3.42 (4 H, m, NCH₂), 2.71 - 2.77 (1 H, m, CH), 2.36 - 2.48 (2 H, m, CH₂), 0.90 - 0.95 (3 H, 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, 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⁺) C₁₉H₂₂O₄N₂Cl, ([M+H⁺]) requires 559.2107; found 559.2103.

3-(Benzamido[5-chloro-8-hydroxyquinolin-7-yl)methyl]-N-(2-morpholin-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, 15 mmol) in DMF (10 mL) was added 2-(morpholin-4-yl)-1-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 S157 (267 mg, 86 %) as a white solid.

mp 217 °C; νₜₐₐₛ / cm⁻¹ 3271 (NH), 1637 (C=O); δₚ (400 MHz, DMSO-d₆) 10.49 (1 H, br. s., NH), 9.27 - 9.42 (1 H, m, quinoline-Ar), 8.93 - 9.04 (1 H, m, quinoline-Ar), 8.73 - 8.86 (1 H, m, quinoline-Ar), 8.45 - 8.57 (1 H, m, quinoline-Ar), 7.93 - 8.01 (2 H, m, Ar), 7.80 - 7.89 (4 H, m, Ar), 7.70 - 7.77 (1 H, m, Ar), 7.54 - 7.62 (1 H, m, Ar), 7.44 - 7.53 (4 H, m, Ar), 7.36 - 7.43 (2 H, m, Ar), 7.27 - 7.34 (2 H, m, Ar), 7.19 - 7.26 (1 H, m, Ar), 7.08 (1 H, d, J=8.5 Hz, benzyl-H), 3.42 - 3.57 (4 H, m, OCH₂), 2.90 (1 H, s, CH), 2.32 - 2.49 (4 H, m, NCH₂); δC (100 MHz, DMSO-d₆) 166.5 (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⁺) C₂₆H₂₄O₅N₄Cl, ([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-phenylethanolamine (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); δH (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 - 7.67 (8 H, m, Ar), 7.16 - 7.33 (4 H, m, Ar), 6.77 (1 H, d, J=8.5 Hz, benzyl-H), 3.60 (2 H, m, C₂H₂), 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)methylbenzamide 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); δH (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); δC (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-C); m/z (ESI) 446 ([M-H]−); HRMS (ESI) C_{23}H_{17}BrN_{3}O_{2}, ([M-H]−) requires 446.0474; found 446.0499.

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

\[
\text{S160} \quad \begin{array}{c}
\text{Br} \\
\text{O} \\
\text{TMS}
\end{array}
\]

Diisopropylazodicarboxylate (740 μL, 3.6 mmol) was added dropwise to a stirring solution of 5-bromo-8-hydroxyquinoline (400 mg, 1.8 mmol), 2-trimethylsilylethanol (380 μL, 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 \textit{S160} (455 mg, 78 %) as a light-yellow oil.

δ_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); δ_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); m/z (ESI+) 324 ([M+H]^+).

Quinoline-4,8-diol S161

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

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 \textit{S161} as a brown solid (3.9 g, 100 %).

mp 311 °C; δ_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); δ_C (100 MHz, DMSO-d_6) 177.5, 147.6, 139.8, 131.4, 127.6, 124.0, 115.5, 115.1, 109.4; m/z (ESI−) 160 ([M-H]−);
4-Hydroxyquinolin-8-yl 4-methylbenzenesulfonate S162\textsuperscript{19}

![Diagram of 4-Hydroxyquinolin-8-yl 4-methylbenzenesulfonate S162]

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; \(\delta\text{H} (400 MHz, \text{DMSO-d}_6)\) 11.47 (1 H, br. s., OH), 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); \(\delta\text{C} (100 MHz, \text{DMSO-d}_6)\) 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 (CH\textsubscript{3}); \textit{m/z} (ESI) 314 ([M-H]);

4-Chloroquinolin-8-yl 4-methylbenzenesulfonate S163\textsuperscript{19}

![Diagram of 4-Chloroquinolin-8-yl 4-methylbenzenesulfonate S163]

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; \(\delta\text{H} (400 MHz, \text{DMSO-d}_6)\) 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, CH\textsubscript{3}); \(\delta\text{C} (100 MHz, \text{DMSO-d}_6)\) 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 (CH\textsubscript{3}); \textit{m/z} (F\textsuperscript{+}) 333 ([M\textsuperscript{+}]);

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

![Diagram of tert-Butyl 2-((8-(Tosloyloxy)quinolin-4-yl)oxy)acetate S164]
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; δH (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); δC (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 (CH2), 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; δH (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); δC (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

100
Fuming sulphuric acid (65 % SO$_3$, 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; $\nu_{\text{max}}$/cm$^{-1}$ 1721 (C=O); $\delta_{\text{H}}$ (400 MHz, DMSO-d$_6$) 9.50 (1 H, d, $J$=5.5 Hz, $H_a$), 8.82 (1 H, d, $J$=8.5 Hz, $H_e$), 8.49 (1 H, d, $J$=7.5 Hz, $H_c$), 8.43 (1 H, d, $J$=5.5 Hz, $H_b$), 8.05 (1 H, dd, $J$=8.5, 7.5 Hz, $H_e$); $\delta_{\text{C}}$ (100 MHz, DMSO-d$_6$) 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$^+$) C$_{10}$H$_7$N$\text{NaO}_2$S, ([M+Na]$^+$) requires 275.9937; found 275.9940.

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

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

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 CH$_2$Cl$_2$ (50 mL) at room temperature. The reaction mixture was stirred for 12 h, diluted with Et$_2$O (500 mL), washed with a 0.1 M aqueous solution of HCl (50 mL), water (100 mL), brine (100 mL) and dried over anhydrous MgSO$_4$. The solvent was subsequently evaporated under reduced pressure to give S167 (7.91 g, 94 %) as an off-white powder.

mp 81 °C; $\nu_{\text{max}}$/cm$^{-1}$ 1096 (Si-O); $\delta_{\text{H}}$ (400 MHz, CDCl$_3$) 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(CH$_3$)$_2$C(CH$_3$)$_3$), 0.38 (6 H, s, Si(CH$_3$)$_2$C(CH$_3$)$_3$); $\delta_{\text{C}}$ (100 MHz, CDCl$_3$) 153.2, 147.9, 139.8, 135.7, 133.1, 126.8, 122.2, 121.9, 85.2, 26.3 Si(CH$_3$)$_2$C(CH$_3$)$_3$, 19.6 Si(CH$_3$)$_2$C(CH$_3$)$_3$, -2.1 Si(CH$_3$)$_2$C(CH$_3$)$_3$; $m/z$ (ESI$^+$) 420 ([M+H]$^+$); HRMS (ESI$^+$) C$_{15}$H$_{20}$ClINOSi, ([M+H]$^+$) requires 420.0042; found 420.0043.

5-Bromoquinolinol-8-yl 4-methylbenzenesulfonate S168

5-Bromoquinolinol-8-yl 4-methylbenzenesulfonate S168

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; $\nu_{\text{max}}$ cm$^{-1}$ 3305 (NH), 1369 (S=O); $\delta_{\text{H}}$ (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$_3$); $\delta_{\text{C}}$ (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$_3$S, ([M+Na]$^+$) requires 399.9613; found 399.9606.

**5-Chloroquinolin-8-yl 4-methylbenzenesulfonate S169**

![Chemical Structure](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; $\delta_{\text{H}}$ (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**

![Chemical Structure](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; $\nu_{\text{max}}$/cm$^{-1}$ 1244 (NH$_3$); $\delta_H$ (400 MHz, Acetone-$d_6$) 8.23 (1 H, d, $J$=8.5 Hz, 4-quinolinyl-$H$), 7.76 (1 H, d, $J$=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-$H$; $\delta_C$ (100 MHz, Acetone-$d_6$) 137.1, 128.7, 128.5, 128.1, 127.7, 127.6, 126.7, 121.6, 118.3, 117.9, 110.4, 70.6 (benzyl-C); $m/z$ (ESI$^+$) 251 ([M+H]$^+$, 100 %); HRMS (ESI) C$_{16}$H$_{14}$N$_2$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$_2$ evolution ceased. Methyl trifluoromethanesulfonate (347 µL) was slowly added under N$_2$. 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; $\delta_H$ (400 MHz, DMSO-$d_6$) 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$_3$) 2.42 (3 H, s, CH$_3$); $\delta_C$ (100 MHz, DMSO-$d_6$) 175.9 (COCH$_3$), 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$_3$), 22.1 (CH$_3$); $m/z$ (ESI$^+$) 352 ([M+Na]$^+$).

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; $\nu_{\text{max}}$/cm$^{-1}$ 3154 (OH); $\delta_H$ (400 MHz, DMSO-$d_6$) 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); $\delta_C$ (100 MHz, DMSO-$d_6$) 154.8, 148.7, 142.1, 140.3, 129.9, 127.4, 122.9, 114.1, 113.6; $m/z$ (F$^+$) 179 ([M]$^+$).
5-Chloro-7-idoquinolin-8-yl 4-methylbenzenesulfonate S17

![Chemical structure image]

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; \( \nu_{max} \) cm\(^{-1} \) 1376 (S=O); \( \delta_H \) (400 MHz, DMSO-\( d_6 \)) 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, SCHCH), 7.66 - 7.77 (1 H, m, Ar), 7.47 (2 H, d, \( J=8.0 \) Hz, SCHCH), 2.45 (3 H, s, C\( \text{H}_3 \)); \( \delta_C \) (100 MHz, DMSO-\( d_6 \)) 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 (C\( \text{H}_3 \)); \( m/z \) (ESI\(^+ \)) 457 ([M-H]); HRMS (ESI\(^+ \)) C\(_{16}\)H\(_{11}\)ClINaO\(_3\)S, ([M+Na\(^+ \)]) requires 481.9085; found 481.9074.

4-Bromoquinolin-8-yl 4-methylbenzenesulfonate S174

![Chemical structure image]

S162 (3.07 g, 9.7 mmol) was added portionwise to a stirring solution of phosphorus oxybromide (8.39 g, 29.2 mmol) in CHCl\(_3\) (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 CHCl\(_3\) layer was separated and the aqueous layer adjusted to pH 6-7 with ammonium hydroxide and extracted with additional CHCl\(_3\). 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; \( \delta_H \) (400 MHz, CDCl\(_3\)) 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, C\( \text{H}_3 \)); \( \delta_C \) (100 MHz, DMSO-\( d_6 \)) 150.1, 145.5, 145.2, 142.5, 133.8, 133.0, 129.5, 129.2, 128.7, 127.1, 126.0, 125.9, 123.3, 21.1 (CH\(_3\)); \( m/z \) (ESI\(^+ \)) 378 ([M+H\(^+ \)]); HRMS (ESI\(^+ \)) C\(_{16}\)H\(_{13}\)BrNO\(_3\)S, ([M+H\(^+ \)]) requires 377.9794; found 377.9786.
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 diisopropylethylamine (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; νmax/cm⁻¹ 3229 (NH) 1680 (Boc C=O); δH (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);

δC (100 MHz, DMSO-d₆) 155.4 (C=O), 151.9, 148.8, 139.1, 132.9, 125.5, 124.8, 112.3, 111.3, 79.6 (C(CH₃)₃), 29.0 (C(CH₃)₃);

m/z (ESI⁻) 259 ([M-H]⁻); HRMS (ESI⁻) C₁₄H₁₄N₂NaO₃, ([M+Na]⁻) requires 283.1053; found 283.1053.

Methanesulfonyl chloride (1 mL, 13 mmol) was added dropwise to a stirring solution of clioquinol (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; νmax/cm⁻¹ 1347 (S=O); δH (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); δC (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⁺) C₁₀H₁₀ClINaO₃S, ([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 S17 (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 S17

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 S17 (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), 7.74 - 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$_{16}$H$_4$ClF$_3$NO$_3$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; ν\textsubscript{max/cm}^{-1} 1725 (C=O); δ\textsubscript{H} (400 MHz, DMSO-d\textsubscript{6}) 8.07 - 8.14 (2 H, m, H\textsubscript{H}), 7.67 (1 H, t, J=8.0 Hz), 7.34 (1 H, d, J=7.5 Hz, H\textsubscript{C}), 3.17 (3 H, s, CH\textsubscript{3}); δ\textsubscript{C} (100 MHz, DMSO-d\textsubscript{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\textsubscript{3}); m/z (FI\textsuperscript{+}) 188 ([M]\textsuperscript{+}); HRMS (FI\textsuperscript{+}) C\textsubscript{11}H\textsubscript{9}NO\textsubscript{3}, ([M]\textsuperscript{+}) requires 203.0582; found 203.0585.

**Quinoxalin-5-ol S180\textsuperscript{25}**

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\textsubscript{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\textsubscript{4} and concentrated \textit{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; δ\textsubscript{H} (400 MHz, methanol-d\textsubscript{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); δ\textsubscript{C} (100 MHz, methanol-d\textsubscript{4}) 153.4, 145.1, 143.1, 142.8, 133.8, 130.9, 118.5, 111.8; m/z (ESI\textsuperscript{+}) 147 ([M+H]\textsuperscript{+}); HRMS (ESI\textsuperscript{+}) C\textsubscript{8}H\textsubscript{5}ON\textsubscript{2}, ([M-H]) requires 145.0407; found 145.0405.

**Methyl 2-((5-Chloroquinolin-8-yl)oxy)acetate S181\textsuperscript{26}**

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\textsubscript{2}O. The organic layer was extracted with H\textsubscript{2}O and brine, dried over anhydrous MgSO\textsubscript{4} and concentrated \textit{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; ν\textsubscript{max/cm}^{-1} 1771 (C=O); δH (400 MHz, DMSO-d6) 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\textsubscript{2}) 3.73
Methyl 8-{2-Methoxy-2-oxoethoxy}quinoline-5-carboxylate S182

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, CH₂), 3.92 (3 H, s, CH₃), 3.75 (3 H, s, CH₃); 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

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), 7.80 - 8.08 (1 H, m), 7.39 - 7.63 (1 H, m), 3.91 (3 H, s, OCH₃), 2.93 (3 H, s, CH₃); m/z (ESI⁺) 218 ([M+H]+); HRMS (ESI⁺) C₁₃H₁₂O₃N, ([M+H]+) requires 218.0812; found 218.0809.
tert-Butyl (3-bromophenyl)carbamate S18\(^{27}\)

![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 CH\(_2\)Cl\(_2\) at room temperature. After 18 h the reaction mixture was poured into ice-cold water and extracted with CH\(_2\)Cl\(_2\). The organic layer was washed with brine and dried over anhydrous MgSO\(_4\). The solvent was removed under reduced pressure to give S18 (2.72 g, 100 %) as a light-pink solid.

mp 78 °C; \(\delta\)\(_{H}\) (400 MHz, DMSO-\(d_6\)) 9.56 (1 H, s, N\(\text{H}\)), 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(CH\(_3\))\(_3\)); \(\delta\)\(_{C}\) (100 MHz, DMSO-\(d_6\)) 153.4 (C=O), 142.1, 131.5, 125.4, 121.1, 117.7, 80.4 (C(CH\(_3\))\(_3\)), 28.9 (C(CH\(_3\))\(_3\)); \(/m/z\) (ESI\(^+\)) 270 ([M-H]\^-).
NMR Spectra of compounds tested in cells

1H NMR of CCT1 in DMSO

13C NMR 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.\(^{28,29}\) In brief, enzyme and inhibitor were pre-incubated in assay buffer (50mM HEPES pH7.5, 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.\(^{28}\)

**KDM4C RapidFire™ Mass Spectrometry (RF-MS) assay**

Inhibition of KDM4C activity was assessed by RapidFire™ MS as previously reported.\(^{30}\) 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-α-A (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-1αC0DD 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-1αC0DD 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: HLEVKKLLLEAGADVNAQDK) 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. Doseresponse 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 × 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 76a³⁷ (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>IC_{50} (μM)</th>
<th>Enzyme</th>
<th>IC_{50} (μM)</th>
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<tr>
<td>KDM6B</td>
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<td>KDM2A</td>
<td>10.3</td>
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<tr>
<td>KDM3A</td>
<td>0.17</td>
<td>PHD2</td>
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<tr>
<td>KDM4A</td>
<td>0.2</td>
<td>FIH</td>
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<tr>
<td>KDM4E</td>
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<td>KDM5C</td>
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<tr>
<td>KDM4C</td>
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<td>PHF8</td>
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<td>KDM6A</td>
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SF1

<table>
<thead>
<tr>
<th>Compound</th>
<th>Structure</th>
<th>In vitro IC₅₀ in μM (KDM4)</th>
<th>Cellular EC₅₀ in μM (KDM4A)</th>
<th>In vitro IC₅₀ in μM (KDM6B)</th>
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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) 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>
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<tr>
<td>CCT1 (racemic)</td>
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<tr>
<td>CCT1α</td>
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</tr>
<tr>
<td>CCT1β</td>
<td>10 μM</td>
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</table>
SF3

A.

DMSO  
CCT1 50 μM  
CCT2 50 μM  
IOX1 50 μM

B.

![Graph showing relative fluorescence](image)

**SF3** Cellular activities of inhibitors. (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 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.
SF6 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 (C0DD and N0DD) 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


