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

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Contents

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.[1] 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 $MgSO_4$ 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. $KMnO_4$. 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 $\times$ 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

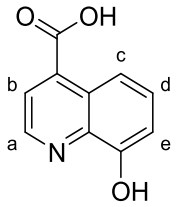
General Procedure 1 for Betti-Type Amidoalkylation Reactions

The requisite 8HQ (1.0 eq.), amide (1.0 eq.), and aldehyde (2.0 eq.) were stirred between 130 ^{o}C and 180 ^{o}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), Et_2O (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 $MgSO_4$, and concentrated *in vacuo*. The crude product was purified *via* flash column chromatography (5 % - 20 % EtOAc, cyclohexane) to give the desired compound.

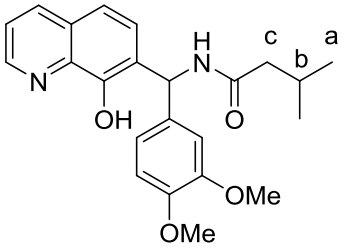
8-Hydroxyquinoline-4-carboxylic acid 4[2]



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 Na_2SO_4 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-d_6) 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-d_6) 168.6 (*C*=O), 154.5, 148.6, 140.2, 137.3, 129.8, 126.2, 123.2, 116.2, 112.4; *m*/*z* (ESI$^-$) 188 ([M-H]$^-$); HRMS (ESI$^+$) $C_{10}H_8NO_3$, ([M+H]$^+$) requires 190.0499; found 190.0501.

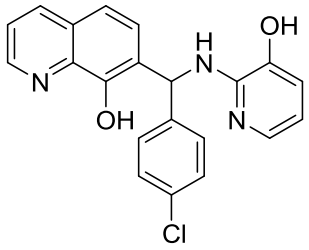
***N*-((3,4-Dimethoxyphenyl)(8-hydroxyquinolin-7-yl)methyl)-3-methylbutanamide 5[3]**



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, $CDCl_3$) 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, OCH_3), 3.81 (3 H, s, OCH_3), 2.05 - 2.27 (3 H, m, $H_{b/c}$), 0.96 (6 H, dd, J=12.0, 6.0 Hz, CH_{3a}); δ_C (100 MHz, $CDCl_3$) 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 (O*C*H$_3$), 55.8 (O*C*H$_3$), 54.3 (benzyl-*C*), 46.3 (C_c), 26.3 (C_b), 22.5 (C_a); *m*/*z* (ESI$^-$) 393 ([M-H]$^-$); HRMS (ESI$^+$) $C_{23}H_{27}N_2O_4$, ([M+H]$^+$) requires 395.1965; found 395.1969.

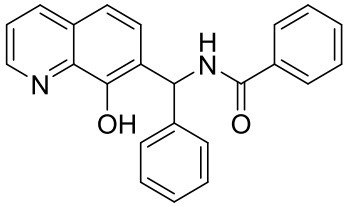
7-((4-Chlorophenyl)((3-hydroxypyridin-2-yl)amino)methyl)quinolin-8-ol 6[3]



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, H_2O, and dried to give **6** (2.6 g, 34 %) as an off-white powder.

mp 189 °C; ν_{max}/cm^{-1} 3338 (OH); δ_H (400 MHz, DMSO-d_6) 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*); δ_C (100 MHz, DMSO-d_6) 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$^+$) $C_{21}H_{17}O_2N_3Cl$, ([M+H]$^+$) requires 378.1004; found 378.0999.

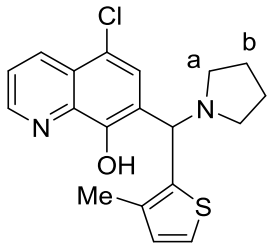
***N*-((8-Hydroxyquinolin-7-yl)(phenyl)methyl)benzamide 7[4]**



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; ν_{max}/cm^{-1} 3328 (NH), 3058 (OH), 1640 (C=O); δ_H (400 MHz, DMSO-d_6) 10.04 (1 H, br. s., N*H*), 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*); δ_C (100 MHz, DMSO-d_6) 166.8 (*C*=O), 150.6, 149.2, 143.0, 138.9, 136.9, 135.3, 132.1, 129.1, 129.0, 128.5, 128.1, 127.8, 127.7, 125.2, 122.7, 118.2, 51.4 (benzyl-*C*); *m/z* (ESI$^-$) 353 ([M-H]$^-$, 100 %); HRMS (ESI$^+$) $C_{23}H_{19}N_2O_2$, ([M+H]$^+$) requires 355.1441; found 355.1434.

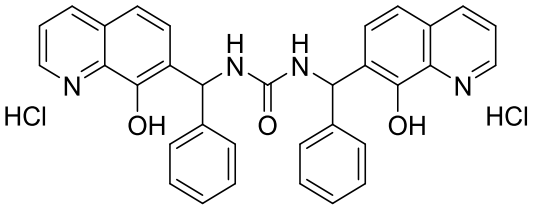
5-Chloro-7-((3-methylthiophen-2-yl)(pyrrolidin-1-yl)methyl)quinolin-8-ol 14



A mixture of 5-chloro-8-hydroxyquinoline (180 mg, 1 mmol), 3-methyl-2-thiophenecarboxaldehyde (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, H_2O, and dried to give **14** (65 mg, 18 %) as a light-brown powder.

mp 148 °C; ν_{max}/cm^{-1} 3333 (OH); δ_H (400 MHz, DMSO-d_6) 10.47 (1 H, br. s., O*H*), 8.90 - 9.02 (1 H, m, quinoline-*Ar*), 8.37 - 8.56 (1 H, m, quinoline-*Ar*), 7.86 (1 H, s, *Ar*), 7.67 - 7.79 (1 H, m, *Ar*), 7.21 - 7.44 (1 H, m, *Ar*), 6.77 (1 H, m, *Ar*), 5.37 (1 H, s, benzyl-*H*), 2.38 - 2.52 (4 H, m, H_a), 2.33 (3 H, s, CH_3), 1.70 - 1.86 (4 H, m, H_b); δ_C (100 MHz, DMSO-d_6) 149.7, 149.5, 141.0, 139.5, 133.6, 132.9, 129.9, 126.9, 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-*C*H$_3$); *m/z* (ESI$^+$) 359 ([M+H]$^+$); HRMS (ESI$^+$) $C_{19}H_{20}ON_2ClS$, ([M+H]$^+$) requires 359.0979; found 359.0969.

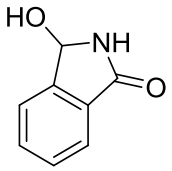
1,3-bis((8-Hydroxyquinolin-7-yl)(phenyl)methyl)urea dihydrochloride 19



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; ν_{max}/cm^{-1} 1748 (C=O); δ_H (400 MHz, DMSO-d_6) 8.88 - 9.02 (2 H, m, quinoline-*Ar*), 8.70 - 8.84 (2 H, m, quinoline-*Ar*), 8.18 - 8.47 (2 H, m, quinoline-*Ar*), 7.65 - 7.72 (2 H, m, *Ar*), 7.58 - 7.64 (2 H, m, *Ar*), 7.37 - 7.42 (8 H, m, *Ar*), 7.27 - 7.34 (4 H, m, *Ar*), 5.85 - 5.91 (2 H, m, benzyl-*H*); δ_C (100 MHz, DMSO-d_6) 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$^+$) $C_{33}H_{27}O_3N_4$, ([M+H]$^+$) requires 527.2078; found 527.2074.

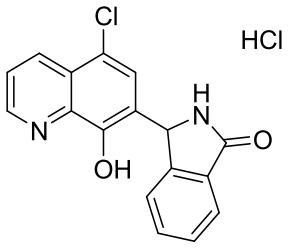
3-Hydroxyisoindolin-1-one 21



2-Cyanobenzaldehyde (131 mg, 1 mmol) and sodium perborate tetrahydrate (615 mg, 4 mmol) were suspended in a mixture of water (10 mL) and ethanol (5 mL) inside a sealed vial and stirred at 100 °C for 10 minutes. The aqueous solution was extracted with Et_2O 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; ν_{max}/cm^{-1} 3339 (NH), 1697 (C=O); δ_H (400 MHz, DMSO-d_6) 8.87 (1 H, s, O*H*), 7.38 - 7.73 (4 H, m, *Ar*), 6.33 (1 H, d, *J*=9.0 Hz, N*H*), 5.87 (1 H, d, *J*=9.0 Hz, C*H*(OH)); δ_C (100 MHz, DMSO-d_6) 169.3 (*C*=O), 147.8, 132.9, 130.0, 124.5, 123.2, 78.9 (*C*H(OH)); *m*/*z* (ESI$^-$) 148 ([M-H]$^-$); HRMS (ESI$^+$) $C_8H_7NNaO_2$, ([M+Na]$^+$) requires 172.0369; found 172.0374.

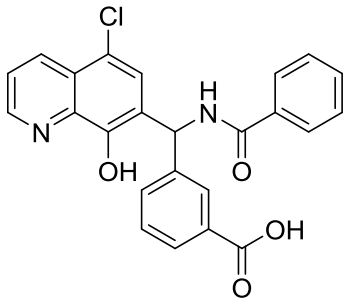
3-(5-Chloro-8-hydroxyquinolin-7-yl)isoindolin-1-one hydrochloride 22



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; ν_{max}/cm^{-1} 3177 (NH), 1657 (C=O); δ_H (400 MHz, DMSO-d_6) 9.06 (1 H, s, N*H*), 9.01 - 9.04 (1 H, m, quinoline-*Ar*), 8.37 - 8.61 (1 H, m, quinoline-*Ar*), 7.68 - 7.83 (2 H, m, *Ar*), 7.37 - 7.58 (3 H, m, *Ar*), 7.14 (1 H, s, *Ar*), 6.32 (1 H, s, benzyl-*H*); δ_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$^+$) $C_{17}H_{11}ClN_2NaO_2$, ([M+Na]$^+$) requires 333.0401; found 333.0391.

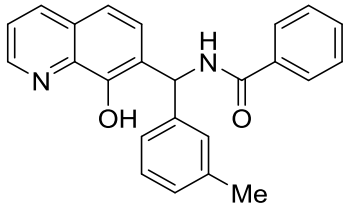
3-(Benzamido(5-chloro-8-hydroxyquinolin-7-yl)methyl)benzoic acid 23



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 ^{o}C; ν_{max}/cm^{-1} 3324 (NH), 1693 (acid C=O), 1635 (amide C=O), 695 (C-Cl); δ_H (400 MHz, DMSO-d_6) 13.04 (1 H, br. s., CO_2H), 10.53 (1 H, br. s., N*H*), 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*), 7.89 - 7.93 (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*); δ_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]$^-$); HRMS (ESI$^+$) $C_{25}H_{19}ClIN_2NaO_3$, ([M+Na]$^+$) requires 455.0769; found 455.0753.

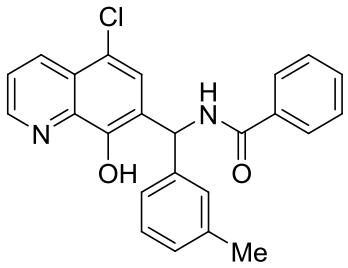
***N*-((8-Hydroxyquinolin-7-yl)(*m*-tolyl)methyl)benzamide 24**



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 ^{o}C; ν_{max}/cm^{-1} 3321 (NH), 3056 (OH), 1639 (C=O); δ_H (400 MHz, DMSO-d_6) 10.00 (1 H, br. s, N*H*), 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); δ_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 (*C*H$_3$); *m*/*z* (ESI$^-$) 367 ([M-H]$^-$, 100 %); HRMS (ESI$^+$) $C_{24}H_{20}N_2NaO_2$, ([M+Na]$^+$) requires 391.1417; found 391.1401.

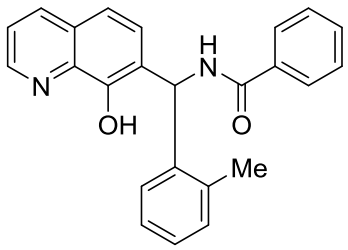
***N*-((5-Chloro-8-hydroxyquinolin-7-yl)(m-tolyl)methyl)benzamide 25**



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_{max}/cm^{-1} 3306 (NH), 1635 (C=O); δ_H (400 MHz, DMSO-d_6) 10.40 (1 H, br. s., N*H*), 9.14 - 9.32 (1 H, m, quinoline-*Ar*), 8.91 - 9.02 (1 H, m, quinoline-*Ar*), 8.40 - 8.55 (1 H, m, quinoline-*Ar*), 7.90 - 8.00 (2 H, m, *Ar*), 7.87 (1 H, s, *Ar*), 7.66 - 7.77 (1 H, m, *Ar*), 7.52 - 7.60 (1 H, m, *Ar*), 7.45 - 7.51 (2 H, m, *Ar*), 7.19 - 7.26 (1 H, m, *Ar*), 7.10 - 7.18 (2 H, m, *Ar*), 7.04 - 7.10 (1 H, m, *Ar*), 6.99 (1 H, d, *J*=9.0 Hz, benzyl-*H*), 2.26 (3 H, s, C*H*$_3$); δ_C (100 MHz, DMSO-d_6) 166.8 (*C*=O), 150.4, 150.0, 142.5, 139.5, 138.4, 135.1, 133.4, 132.2, 129.2, 129.1, 128.6, 128.6, 128.5, 127.7, 126.0, 125.8, 125.2, 123.8, 119.4, 50.9 (benzyl-*C*), 22.0 (*C*H$_3$); *m*/*z* (ESI$^-$) 401 ([M-H]$^-$, 100 %); HRMS (ESI$^-$) $C_{24}H_{18}ClN_2O_2$, ([M-H]$^-$) requires 401.1062; found 401.1061.

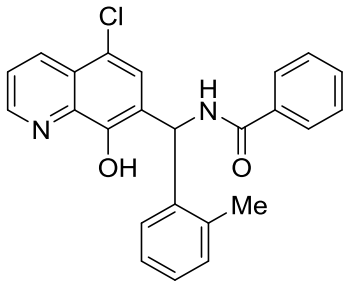
***N*-((8-Hydroxyquinolin-7-yl)(*o*-tolyl)methyl)benzamide 26**



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_{max}/cm^{-1} 3302 (NH), 3057 (OH), 1638 (C=O); δ_H (400 MHz, DMSO-d_6) 9.99 (1 H, br. s., N*H*), 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, C*H*$_3$); δ_C (100 MHz, DMSO-d_6) 166.4 (*C*=O), 150.9, 149.1, 141.1, 138.8, 137.0, 136.9, 135.2, 132.1, 131.1, 129.0, 128.5, 128.4, 128.0, 127.8, 126.5, 124.5, 122.6, 117.8, 49.1 (benzyl-*C*), 19.7 (*C*H$_3$); *m*/*z* (ESI$^-$) 367 ([M-H]$^-$, 100 %); HRMS (ESI$^+$) $C_{24}H_{20}N_2NaO_2$, ([M+Na]$^+$) requires 391.1417; found 391.1412.

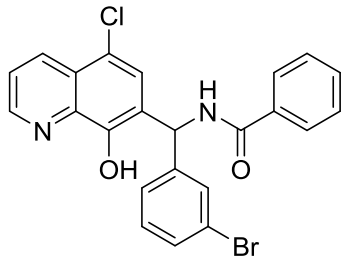
***N*-((5-Chloro-8-hydroxyquinolin-7-yl)(*o*-tolyl)methyl)benzamide 27**



Following general procedure 1, 5-chloro-8-quinolinol (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.

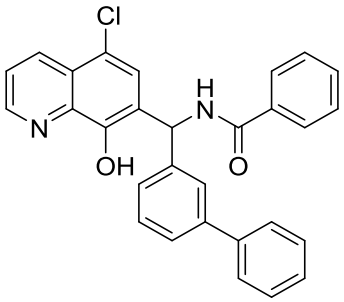
mp 217-218 °C; ν_{max}/cm^{-1} 3289 (NH), 1637 (C=O); δ_H (400 MHz, DMSO-d_6) 10.40 (1 H, br. s., N*H*), 9.09 - 9.24 (1 H, m, quinoline-*Ar*), 8.88 - 9.01 (1 H, m, quinoline-*Ar*), 8.40 - 8.53 (1 H, m, quinoline-*Ar*), 7.90 - 7.97 (2 H, m, *Ar*), 7.68 - 7.75 (1 H, m, *Ar*), 7.64 (1 H, s, *Ar*), 7.50 - 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, C*H*$_3$); δ_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 (*C*H$_3$); *m*/*z* (ESI$^-$) 401 ([M-H]$^-$, 100 %); HRMS (ESI$^-$) $C_{24}H_{18}ClN_2O_2$, ([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_{max}/cm^{-1} 3314 (NH), 1633 (C=O); 694 (C-Cl); δ_H (400 MHz, DMSO-d_6) 10.57 (1 H, br. s., N*H*), 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_C (100 MHz, DMSO-d_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$^-$) 465 ([M-H]$^-$); HRMS (ESI$^-$) $C_{23}H_{16}BrClN_2NaO_2$, ([M+Na]$^+$) requires 488.9976; found 488.9970.

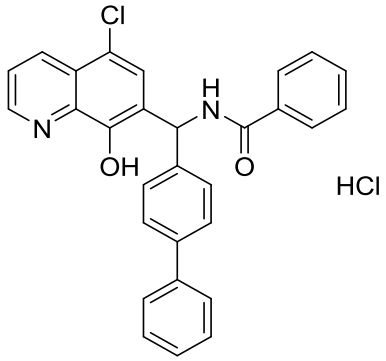
***N*-([1,1'-Biphenyl]-3-yl(5-chloro-8-hydroxyquinolin-7-yl)methyl)benzamide 29**



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 ^{o}C; ν_{max}/cm^{-1} 3299 (NH), 1633 (C=O); δ_H (400 MHz, DMSO-d_6) 10.48 (1 H, br. s., N*H*), 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*); δ_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$^+$) $C_{29}H_{21}ClN_2O_2$, ([M]$^+$) requires 464.1292; found 464.1292.

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

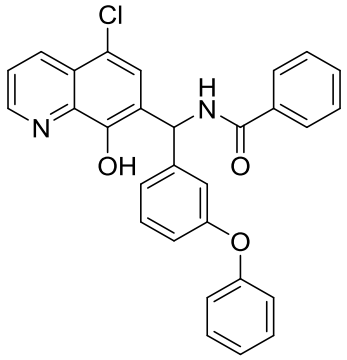


Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and biphenyl-4-carboxaldehyde (729 mg, 4.0 mmol) gave **30** (604 mg, 65 %) as a white powder. **30** was then stirred in a 4M HCl solution in dioxane for 1 h. The solvent was removed under reduced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

mp 262 - 263 ^{o}C; ν_{max}/cm^{-1} 3305 (NH), 1634 (C=O); δ_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-

H); δ_C (100 MHz, DMSO-d_6) 166.9 (*C*=O), 149.9, 149.7, 141.5, 140.7, 139.9, 138.8, 135.0, 134.4, 132.3, 129.8, 129.2, 128.7, 128.5, 128.3, 127.9, 127.7, 127.5, 126.6, 126.0, 124.0, 119.8, 50.8 (benzyl-*C*); *m/z* (ESI^-) 463 ($[M-H]^-$); HRMS (ESI^+) $C_{29}H_{21}ClN_2NaO_{42}$, ($[M+Na]^+$) requires 487.1184; found 487.1187.

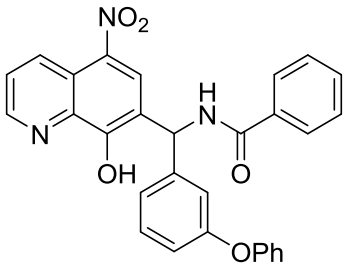
_N_-((5-Chloro-8-hydroxyquinolin-7-yl)(3-phenoxyphenyl)methyl)benzamide 31



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

mp 225 °C; ν_{max}/cm^{-1} 3307 (NH), 1638 (C=O); δ_H (400 MHz, DMSO-d_6) 10.49 (1 H, br. s., N*H*), 9.21 - 9.35 (1 H, m, quinoline-*Ar*), 8.89 - 9.03 (1 H, m, quinoline-*Ar*), 8.40 - 8.54 (1 H, m, quinoline-*Ar*), 7.87 - 7.93 (2 H, m, *Ar*), 7.86 (1 H, s, *Ar*), 7.68 - 7.76 (1 H, m, *Ar*), 7.51 - 7.59 (1 H, m, *Ar*), 7.44 - 7.51 (2 H, m, *Ar*), 7.30 - 7.38 (3 H, m, *Ar*), 7.08 - 7.13 (2 H, m, *Ar*), 6.96 - 7.06 (4 H, m, *Ar*), 6.82 - 6.89 (1 H, m, *Ar*); δ_C (100 MHz, DMSO-d_6) 167.0 (*C*=O), 157.6, 157.1, 150.5, 150.1, 144.9, 139.5, 135.1, 133.4, 132.3, 130.9, 130.9, 129.2, 128.5, 128.4, 127.6, 125.9, 125.4, 124.4, 123.9, 123.1, 119.5, 118.0, 117.6, 50.7 (benzyl-*C*); *m/z* (ESI^-) 479 ($[M-H]^-$); HRMS (ESI^+) $C_{30}H_{21}ClN_2NaO_3$, ($[M+Na]^+$) requires 503.1133; found 503.1131.

_N_-((8-Hydroxy-5-nitroquinolin-7-yl)(3-phenoxyphenyl)methyl)benzamide 32

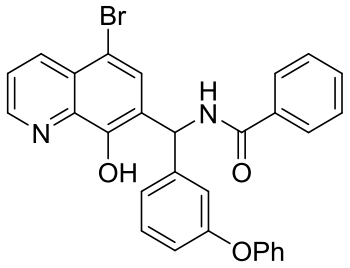


Following general procedure 1, 5-nitro-8-hydroxyquinoline (380 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 3-phenoxybenzaldehyde (690 µL, 4.0 mmol) gave **32** (669 mg, 68 %) as a light-yellow powder.

mp 222 °C; ν_{max}/cm^{-1} 3294 (NH), 1634 (C=O); δ_H (400 MHz, DMSO-d_6) 9.41 - 9.51 (1 H, m, quinoline-*Ar*), 9.15 - 9.23 (1 H, m, quinoline-*Ar*), 8.97 - 9.06 (1 H, m, quinoline-*Ar*), 8.78 (1 H, s, *Ar*), 7.85 - 7.98 (3 H, m, *Ar*), 7.53 - 7.59 (1 H, m, *Ar*), 7.46 - 7.53 (2 H, m, *Ar*), 7.31 - 7.42 (3 H, m, *Ar*), 7.07 - 7.18 (3 H, m, *Ar*), 6.97 - 7.03 (3 H, m, *Ar*), 6.85 - 6.94 (1 H, m, *Ar*); δ_C (100 MHz,

DMSO-d_6) 166.6 (*C*=O), 158.4, 157.2, 156.8, 149.4, 143.8, 137.2, 134.7, 134.6, 133.6, 132.0, 130.7, 130.5, 128.8, 128.7, 128.1, 125.8, 124.0, 123.8, 122.9, 122.2, 119.1, 117.9, 117.6, 50.4 (benzyl-*C*); *m*/*z* (FI) 491 ([M]); HRMS (FI) $C_{29}H_{21}N_3O_5$, ([M]) requires 491.1481; found 491.1247.

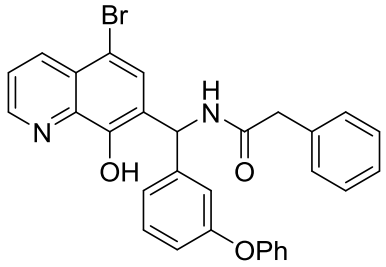
***N*-((5-Bromo-8-hydroxyquinolin-7-yl)(3-phenoxyphenyl)methyl)benzamide 33**



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

mp 214 °C; ν_{max}/cm^{-1} 3294 (NH), 1636 (C=O); δ_H (400 MHz, DMSO-d_6) 10.54 (1 H, br. s., N*H*), 9.24 - 9.38 (1 H, m, quinoline-*Ar*), 8.89 - 9.02 (1 H, m, quinoline-*Ar*), 8.35 - 8.49 (1 H, m, quinoline-*Ar*), 8.03 (1 H, s, *Ar*), 7.85 - 7.95 (2 H, m, *Ar*), 7.71 - 7.78 (1 H, m, *Ar*), 7.45 - 7.60 (4 H, m, *Ar*), 7.31 - 7.42 (2 H, m, *Ar*), 7.09 - 7.18 (2 H, m, *Ar*), 6.97 - 7.07 (3 H, m, *Ar*), 6.88 (1 H, d, *J*=8.0 Hz, benzyl-*H*); δ_C (100 MHz, DMSO-d_6) 166.6 (*C*=O), 157.2, 156.8, 150.7, 149.7, 144.5, 139.4, 135.5, 134.7, 132.1, 131.9, 130.7, 130.6, 130.5, 128.8, 128.1, 128.0, 126.8, 125.8, 124.0, 122.7, 119.2, 119.1, 109.0, 50.2 (benzyl-*C*); *m*/*z* (ESI$^+$) 525 ([M+H]$^+$); HRMS (ESI$^+$) $C_{29}H_{21}O_3N_2BrNa$, ([M+Na]$^+$) requires 547.0628; found 547.0606.

***N*-((5-Bromo-8-hydroxyquinolin-7-yl)(3-phenoxyphenyl)methyl)-2-phenylacetamide 34**

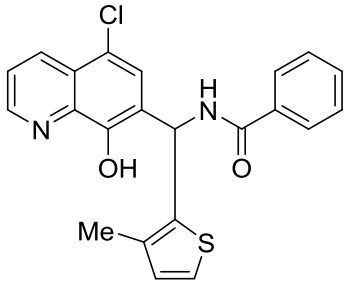


Following general procedure 1, 5-bromo-8-hydroxyquinoline (448 mg, 2.0 mmol), 2-phenylacetamide (270 mg, 2.0 mmol) and 3-phenoxybenzaldehyde (690 µL, 4.0 mmol) gave **34** (873 mg, 81 %) as a white powder.

mp 212 °C; ν_{max}/cm^{-1} 3270 (NH), 1639 (C=O); δ_H (400 MHz, DMSO-d_6) 10.48 (1 H, br. s., N*H*), 9.08 - 9.15 (1 H, m, quinoline-*Ar*), 8.92 - 8.97 (1 H, m, quinoline-*Ar*), 8.38 - 8.44 (1 H, m, quinoline-*Ar*), 7.87 (1 H, s, quinoline-*Ar*), 7.66 - 7.79 (1 H, m, *Ar*), 7.18 - 7.43 (7 H, m, *Ar*), 7.09 - 7.18 (1 H, m, *Ar*), 6.95 - 7.06 (4 H, m, *Ar*), 6.79 - 6.90 (1 H, m, *Ar*), 6.68 (1 H, d, *J*=8.5 Hz, benzyl-*H*), 3.57 (2 H, s, CH_2); δ_C (100 MHz, DMSO-d_6) 170.0 (*C*=O), 157.1, 156.8, 150.4, 149.7, 144.5, 139.4, 136.7, 135.5, 130.6, 130.5,

130.0, 129.4, 128.7, 126.8, 126.7, 126.0, 124.0, 123.9, 122.5, 119.0, 117.6, 117.3, 109.1, 49.9 (CH_2), 42.7 (benzyl-*C*); *m/z* (ESI^+) 539 ($[M+H]^+$); HRMS (ESI^+) $C_{30}H_{23}O_3N_2BrNa$, ($[M+Na]^+$) requires 561.0784; found 561.0759.

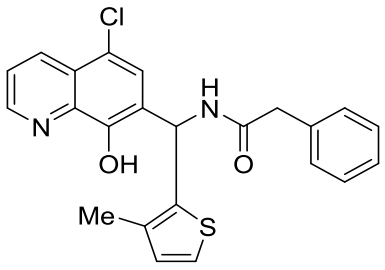
***N*-((5-chloro-8-hydroxyquinolin-7-yl)(3-methylthiophen-2-yl)methyl)benzamide CCT1**



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** (431µL, 4.0 mmol) gave **CCT1** (584 mg, 71 %) as a white powder.

mp 223 °C; ν_{max}/cm^{-1} 3274 (NH), 1638 (C=O); δ_H (400 MHz, DMSO- d_6) 10.53 (1 H, br. s., N*H*), 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_3); δ_C (100 MHz, DMSO- d_6) 166.1 (*C*=O), 150.1, 149.7, 139.5, 139.0, 134.6, 134.5, 133.0, 131.9, 131.0, 128.7, 128.7, 128.1, 126.9, 125.6, 125.2, 123.6, 118.8, 45.3 (benzyl-*C*), 14.0 (CH_3); *m/z* (ESI^-) 407 ($[M-H]^-$); HRMS (ESI^-) $C_{22}H_{16}ClN_2O_2S$, ($[M-H]^-$) requires 407.0626; found 407.0613.

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

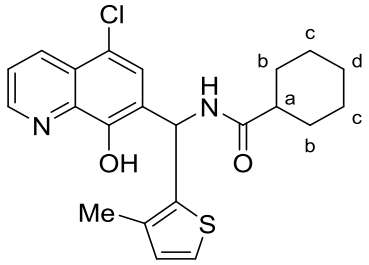


Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), 2-phenylacetamide (270 mg, 2.0 mmol) and 3-methyl-2-thiophenecarboxaldehyde (431 µL, 4.0 mmol) gave **35** (567 mg, 67 %) as a white powder.

mp 181 °C; ν_{max}/cm^{-1} 3237 (NH), 1667 (C=O); δ_H (400 MHz, DMSO-d_6) 10.44 (1 H, br. s., N*H*), 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_2), 2.11 (3 H, s, CH_3); δ_C (100 MHz, DMSO-d_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, 125.4, 123.6, 123.5, 118.9, 44.8

(benzyl-*C*), 42.5 (*C*H_2), 13.9 (*C*H_3); *m/z* (ESI$^-$) 421 ([M-H]$^-$); HRMS (ESI$^+$) $C_{23}H_{19}ClN_2NaO_2S$, ([M+Na]$^+$) requires 445.0748; found 445.0731.

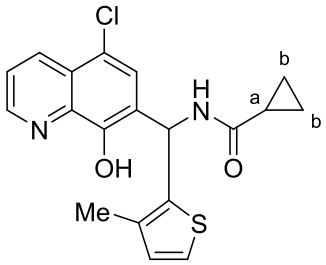
***N*-((5-Chloro-8-hydroxyquinolin-7-yl)(3-methylthiophen-2-yl)methyl)cyclohexanecarboxamide 36**



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 ^{o}C; ν_{max}/cm^{-1} 3297 (NH), 1640 (C=O); δ_H (400 MHz, DMSO-d_6) 10.34 (1 H, br. s., N*H*), 8.90 - 8.99 (1 H, m, quinoline-*Ar*), 8.65 - 8.74 (1 H, m, quinoline-*Ar*), 8.43 - 8.52 (1 H, m, quinoline-*Ar*), 7.72 - 7.76 (2 H, m, *Ar*), 7.19 - 7.25 (1 H, m, *Ar*), 6.79 - 6.90 (2 H, m, *Ar* and benzyl-*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, 139.4, 134.6, 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 (*C*H_3); *m/z* (ESI$^-$) 413 ([M-H]$^-$); HRMS (ESI$^+$) $C_{22}H_{23}ClN_2NaO_2S$, ([M+Na]$^+$) requires 437.1061; found 437.1051.

N-((5-chloro-8-hydroxyquinolin-7-yl)(3-methylthiophen-2-yl)methyl)cyclopropanecarboxamide **37**

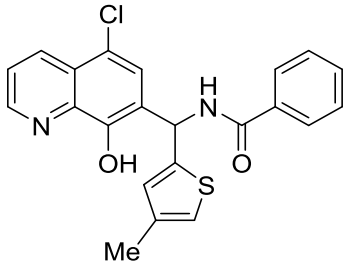


Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), cyclopropanecarboxamide (170 mg, 2.0 mmol) and 3-methyl-2-thiophenecarboxaldehyde (431µL, 4.0 mmol) gave **37** (312 mg, 42 %) as an off-white powder.

mp 202 ^{o}C; ν_{max}/cm^{-1} 3272 (NH), 1644 (C=O); δ_H (400 MHz, DMSO-d_6) 10.41 (1 H, br. s., N*H*), 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 (*C*H_3), 14.2 (*C*$_a$), 7.4 (*C*$_b$); *m/z* (ESI$^-$) 371 ([M-H]$^-$); HRMS (ESI$^-$) $C_{19}H_{17}ClN_2O_2S$, ([M-H]$^-$) requires 371.0626; found 371.0625.

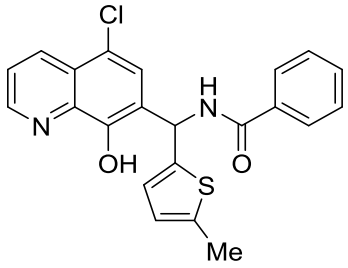
***N*-((5-Chloro-8-hydroxyquinolin-7-yl)(4-methylthiophen-2-yl)methyl)benzamide 38**



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; ν_{max}/cm^{-1} 3313 (NH), 1632 (C=O); δ_H (400 MHz, DMSO-d_6) 10.50 (1 H, br. s., N*H*), 9.25 - 9.59 (1 H, m, quinoline-*Ar*), 8.89 - 9.03 (1 H, m, quinoline-*Ar*), 8.40 - 8.57 (1 H, m, quinoline-*Ar*), 8.00 (1 H, s, *Ar*), 7.91 - 7.97 (2 H, m, *Ar*), 7.70 - 7.77 (1 H, m, *Ar*), 7.52 - 7.59 (1 H, m, *Ar*), 7.45 - 7.52 (2 H, m, *Ar*), 7.14 (1 H, d, *J*=9.0 Hz, benzyl-*H*), 7.01 (1 H, s, *Ar*), 6.62 (1 H, s, *Ar*), 2.11 (3 H, s, C*H*$_3$); δ_C (100 MHz, DMSO-d_6) 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 (*C*H_3); *m/z* (ESI$^+$) 431 ([M+Na]$^+$); HRMS (ESI$^+$) $C_{22}H_{17}ClIN_2NaO_2S$, ([M+Na]$^+$) requires 431.0591; found 430.9132.

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

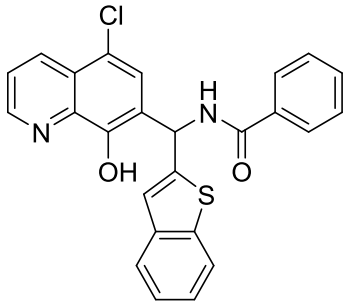


Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 5-methylthiophene-2-carboxaldehyde (431 µL, 4.0 mmol) gave **39** (264 mg, 32 %) as a white powder.

mp 213 °C; ν_{max}/cm^{-1} 3302 (NH), 1634 (C=O); δ_H (400 MHz, DMSO-d_6) 10.49 (1 H, br. s. , N*H*), 9.30 - 9.48 (1 H, m, quinoline-*Ar*), 8.90 - 9.07 (1 H, m, quinoline-*Ar*), 8.41 - 8.57 (1 H, m, quinoline-*Ar*), 7.99 (1 H, s, *Ar*), 7.89 - 7.95 (2 H, m, *Ar*), 7.68 - 7.78 (1 H, m, *Ar*), 7.52 - 7.59 (1 H, m, *Ar*), 7.44 - 7.51 (2 H, m, *Ar*), 7.10 (1 H, d, *J*=9.0 Hz, benzyl-*H*), 6.49 - 6.67 (2 H, m, *Ar*), 2.37 (3 H, s, C*H*$_3$); δ_C (100 MHz, DMSO-d_6) 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, 125.8, 125.6, 124.0, 119.5, 47.1 (benzyl-*C*), 15.8 (*C*H_3); *m/z* (ESI$^-$) 431 ([M+Na]$^+$); HRMS (ESI$^+$) $C_{22}H_{17}ClIN_2NaO_2S$, ([M+Na]$^+$) requires 431.0591; found 431.0587.

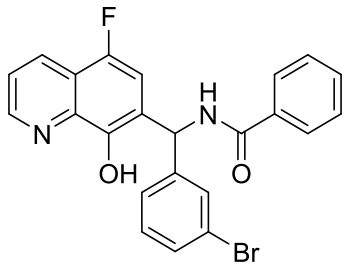
***N*-(Benzo[b]thiophen-2-yl(5-chloro-8-hydroxyquinolin-7-yl)methyl)benzamide 40**



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 ^{o}C; ν_{max}/cm^{-1} 3296 (NH), 1634 (C=O); δ_H (400 MHz, DMSO-d_6) 10.65 (1 H, br. s., N*H*), 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*); δ_C (100 MHz, DMSO-d_6) 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$^-$) $C_{25}H_{16}ClIN_2O_2S$, ([M-H]$^-$) requires 443.0626; found 443.0621.

***N*-((3-Bromophenyl)(5-fluoro-8-hydroxyquinolin-7-yl)methyl)benzamide 41**

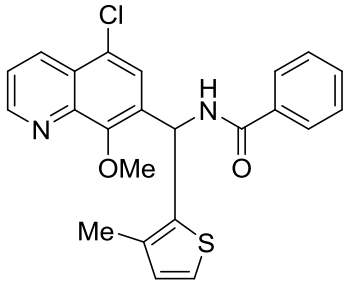


Following general procedure 1, 5-fluoro-8-hydroxyquinoline (326 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 3-bromobenzaldehyde (468 µL, 4.0 mmol) gave **41** (543 mg, 61 %) as a white powder.

mp 208 ^{o}C; ν_{max}/cm^{-1} 3309 (NH), 1634 (C=O); δ_H (400 MHz, DMSO-d_6) 10.23 (1 H, br. s., N*H*), 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*); δ_C (100 MHz, DMSO-d_6) 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*); δ_F (377 MHz, DMSO-d_6) -133.9 (*CF*); *m/z* (ESI$^+$) 451 ([M+H]$^+$); HRMS (ESI$^+$) $C_{23}H_{16}BrFN_2NaO_2$, ([M+Na]$^+$) requires 473.0271; found 473.0254.

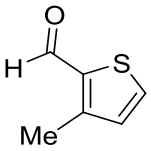
_N_-((5-Chloro-8-methoxyquinolin-7-yl)(3-methylthiophen-2-yl)methyl)benzamide CCT2



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 H_2O 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 ^oC; ν_{max}/cm^{-1} 3275 (NH), 1632 (C=O); δ_H (400 MHz, $CDCl_3$) 8.73 - 8.93 (1 H, m, quinoline-*Ar*), 8.33 - 8.45 (1 H, m, quinoline-*Ar*), 7.70 - 7.80 (2 H, m, quinoline-*Ar*), 7.63 (1 H, s, *Ar*), 7.35 - 7.43 (2 H, m, *Ar*), 7.27 - 7.34 (2 H, m, *Ar*), 7.21 - 7.26 (1 H, m, *Ar*), 6.92 - 7.03 (2 H, m, *Ar*), 6.68 - 6.76 (1 H, m, *Ar*), 4.07 (3 H, s, O*CH*$_3$) 2.19 (3 H, s, *CH*$_3$); δ_C (100 MHz, $CDCl_3$) 166.4 (*C*=O), 152.6, 150.1, 143.3, 137.8, 135.0, 133.8, 133.7, 133.3, 131.9, 130.8, 128.7, 127.1, 126.2, 125.6, 123.2, 122.0, 62.8 (O*C*H$_3$), 48.4 (benzyl-*C*), 14.2 (C*H*$_3$); *m/z* (ESI$^+$) 423 ([M+H]$^+$); HRMS (ESI$^+$) $C_{23}H_{19}ClN_2NaO_2S$, ([M+Na]$^+$) requires 445.0748; found 445.0828.

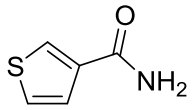
3-Methyl-2-thiophenecarboxaldehyde S1



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 $CHCl_3$ (100 mL). The mixture was shaken with 10 % HCl aq. for about 10 min and then extracted with $CHCl_3$. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was purified *via* flash column chromatography (5 % EtOAc, 95 % cyclohexane) to give **S1** as a light-yellow oil (4.55 g, 75 %). The synthesis of this compound has been described previously using a different methodology.[6]

δ_H (400 MHz, $CDCl_3$) 10.04 (1 H, s, C*H*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); δ_C (100 MHz, $CDCl_3$) 182.4 (*C*HO), 147.4, 137.6, 134.3, 131.8, 14.2 (*C*H_3); *m*/*z* (ESI^+) 127 ($[M+H]^+$).

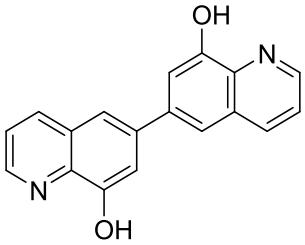
_N_-((5-Chloro-8-hydroxyquinolin-7-yl)(3-methylthiophen-2-yl)methyl)nicotinamide S2



3-Thiophenecarbonitrile (274 µL, 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_2O 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; δ_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*); δ_C (100 MHz, DMSO-d_6) 164.6 (*C*=O), 138.9, 129.9, 128.0, 127.4; *m*/*z* (ESI^-) 126 ($[M-H]^{+-}$).

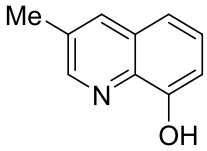
[6,6'-Biquinoline]-8,8'-diol S3



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; δ_H (400 MHz, DMSO-d_6) 10.32 (2 H, br. s., O*H*), 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); δ_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.

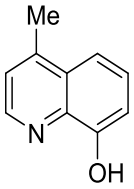
3-Methylquinolin-8-ol S4



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; ν_{max}/cm^{-1} 3294 (OH); δ_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); δ_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 (*C*H$_3$); *m/z* (ESI$^+$) 160 ([M+H]$^+$); HRMS (ESI$^+$) $C_{10}H_{10}ON$, ([M+H]$^+$) requires 160.0757; found 160.0754.

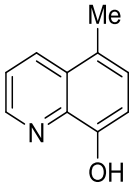
4-Methylquinolin-8-ol S5[9]



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; δ_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); δ_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 (*C*H$_3$); *m/z* (ESI$^+$) 160 ([M+H]$^+$); HRMS (ESI$^+$) $C_{10}H_{10}ON$, ([M+H]$^+$) requires 160.0757; found 160.0754.

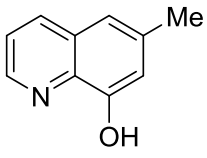
5-Methylquinolin-8-ol S6



Following general procedure 2, 2-amino-4-methylphenol (1.0 g, 8.1 mmol) and acrolein (814 µL, 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; ν_{max}/cm^{-1} 3198 (OH); δ_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); δ_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.

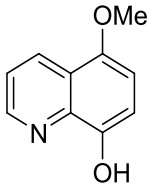
6-Methylquinolin-8-ol S7



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; δ_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); δ_C (100 MHz, methanol-d_6) 152.4, 146.9, 137.6, 137.3, 135.4, 129.2, 121.4, 116.8, 112.6, 20.6 (*C*H_3); *m/z* (ESI$^+$) 160 ([M+H]$^+$); HRMS (ESI$^+$) $C_{10}H_{10}ON$, ([M+H]$^+$) requires 160.0757; found 160.0756.

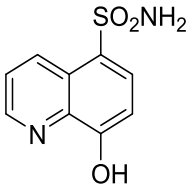
5-Methoxyquinolin-8-ol S8



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; ν_{max}/cm^{-1} 3325 (OH); δ_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, OCH_3); δ_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 (O*C*H$_3$); *m/z* (ESI$^+$) 176 ([M+H]$^+$);

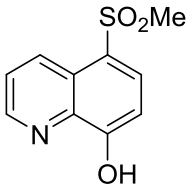
8-Hydroxyquinoline-5-sulfonamide S9



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; ν_{max}/cm^{-1} 1350 (S=O); δ_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_2NH_2), 7.06 - 7.22 (1 H, m); δ_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$^-$) $C_9H_7O_3N_2S$, ([M-H]$^-$) requires 223.0183; found 223.0182. HRMS (ESI$^+$) $C_{10}H_{10}NO_2$, ([M+H]$^+$) requires 176.0706; found 176.0703.

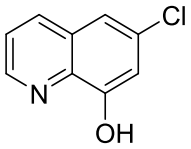
5-(Methylsulfonyl)quinolin-8-ol S10[12]



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; ν_{max}/cm^{-1} 2920 (OH); δ_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_2CH_3); δ_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_2CH_3); *m/z* (ESI$^+$) 224 ([M+H]$^+$); HRMS (ESI$^-$) $C_{10}H_8O_3NS$, ([M-H]$^-$) requires 222.0230; found 222.0229.

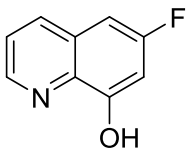
6-Chloroquinolin-8-ol S11



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; ν_{max}/cm^{-1} 3324 (OH); δ_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); δ_C (100 MHz, DMSO-d_6) 155.2, 149.0, 137.8, 136.1, 132.0, 129.7, 123.4, 116.9, 112.5; *m/z* (ESI$^+$) 180 ([M+H]$^+$); HRMS (ESI$^-$) C_9H_5ONCl, ([M-H]$^-$) requires 178.0065; found 178.0063.

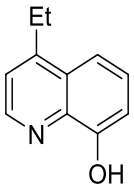
6-Fluoroquinolin-8-ol S12[14]



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; ν_{max}/cm^{-1} 3063 (OH); δ_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); δ_C (100 MHz, methanol-d_4) 162.5, 160.0, 155.2, 147.1, 136.2, 135.6, 129.5, 129.3, 122.4; *m/z* (ESI$^+$) 164 ([M+H]$^+$); HRMS (ESI$^-$) C_9H_5ONF, ([M-H]$^-$) requires 162.0361; found 162.0358.

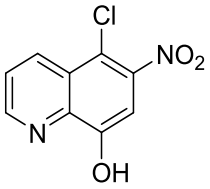
4-Ethylquinolin-8-ol S13



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; ν_{max}/cm^{-1} 3297 (OH); δ_H (400 MHz, DMSO-d_6) 8.46 - 8.53 (1 H, m), 7.26 - 7.32 (1 H, m), 7.18 - 7.24 (1 H, m), 7.12 - 7.18 (1 H, m), 6.77 - 6.88 (1 H, m), 2.82 (2 H, q, J=7.5 Hz, CH_2), 1.06 (3 H, t, J=7.5 Hz, CH_3); δ_C (100 MHz, DMSO-d_6) 154.3, 150.2, 148.3, 138.9, 128.2, 127.7, 120.8, 113.8, 111.2, 25.0 (*C*H$_2$), 14.4 (*C*H$_3$); *m*/*z* (ESI$^-$) 172 ([M-H]$^-$); HRMS (ESI$^+$) $C_{11}H_{11}NO$, ([M+H]$^+$) requires 174.0913; found 174.0917.

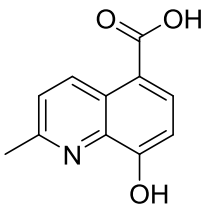
5-Chloro-6-nitroquinolin-8-ol S14



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; ν_{max}/cm^{-1} 3087 (OH); δ_H (400 MHz, DMSO-d_6) 9.02 - 9.18 (1 H, m), 8.59 - 8.83 (1 H, m), 7.78 - 7.98 (1 H, m), 7.63 (1 H, s); δ_C (100 MHz, DMSO-d_6) 154.8, 151.9, 146.9, 140.3, 134.8, 126.5, 125.2, 111.5, 106.8; *m*/*z* (ESI$^+$) 225 ([M+H]$^+$); HRMS (ESI$^+$) $C_9H_5ClN_2O_3$, ([M+H]$^+$) requires 225.0061; found 225.1019.

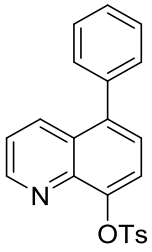
8-Hydroxy-2-methylquinoline-5-carboxylic acid S15[15]



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_H (400 MHz, DMSO-d_6) 9.61 - 9.97 (1 H, m), 8.28 - 8.45 (1 H, m), 8.01 (1 H, m), 7.49 - 7.70 (1 H, m), 2.97 (3 H, s, CH_3); δ_C (100 MHz, DMSO-d_6) 167.4 (*C*=O), 157.9, 153.4, 142.6, 134.7, 130.6, 127.3, 126.2, 117.2, 114.4, 21.4 (*C*H_3); *m/z* (ESI$^-$) 202 ([M-H]$^-$).

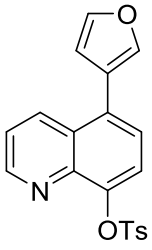
5-Phenylquinolin-8-yl 4-methylbenzenesulfonate S16



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_2O and brine. The organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was purified *via* flash column chromatography to give **S16** (6 mg, 17 %) as an off-white solid. The synthesis of this compound has previously been described using a different methodology.[16]

mp 145 °C; ν_{max}/cm^{-1} 1351 (S=O); δ_H (400 MHz, DMSO-d_6) 8.91 - 8.96 (1 H, m, *Ar*), 8.87 - 8.90 (1 H, m, *Ar*), 8.53 - 8.61 (1 H, m, *Ar*), 8.15 - 8.23 (1 H, m, *Ar*), 7.86 - 7.92 (2 H, m, *Ar*), 7.78 - 7.83 (2 H, m, *Ar*), 7.71 - 7.78 (1 H, m, *Ar*), 7.36 - 7.62 (5 H, m, *Ar*), 2.42 (3 H, s, CH_3); δ_C (100 MHz, DMSO-d_6) 152.3, 151.3, 146.0, 144.7, 139.0, 138.3, 134.4, 133.1, 130.4, 130.3, 129.2, 128.8, 127.2, 127.0, 124.1, 123.1, 122.0, 21.6 (*C*H_3); *m/z* (ESI$^+$) 376 ([M+H]$^+$); HRMS (ESI$^+$) $C_{22}H_{18}O_3NS$, ([M+H]$^+$) requires 376.1002; found 376.0996.

5-(Furan-3-yl)quinolin-8-yl 4-methylbenzenesulfonate S17

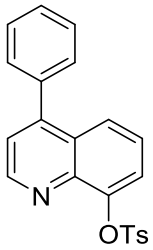


A microwave vial was charged with **S169** (33 mg, 0.1 mmol), 3-furanylboronic acid (13 mg, 0.12 mmol), [1,1'-bis(di-*tert*-butylphosphino)ferrocene]dichloropalladium(II) (4 mg, 0.005 mmol), potassium carbonate (44 mg, 0.32 mmol), and dimethylacetamide (1 mL). The vial was sealed and the mixture was thoroughly degassed and subjected to an atmosphere

of nitrogen gas. The reaction mixture was then stirred at 180 °C for 30 min under microwave irradiation before being diluted with EtOAc (10 mL) and extracted with H_2O and brine. The organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was purified *via* flash column chromatography to give **S17** (8 mg, 22 %) as an off-white solid.

mp 132 °C; ν_{max}/cm^{-1} 1347 (S=O); δ_H (400 MHz, $CDCl_3$) 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, C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 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 (*C*H$_3$); *m*/*z* (ESI$^+$) 366 ([M+H]$^+$); HRMS (ESI$^+$) $C_{20}H_{16}O_4NS$, ([M+H]$^+$) requires 366.0795; found 366.0789.

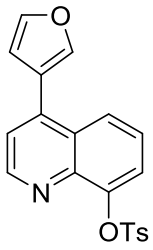
4-Phenylquinolin-8-yl 4-methylbenzenesulfonate S18



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 H_2O and brine. The organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was purified *via* flash column chromatography to give **S18** (4 mg, 11 %) as an off-white solid. The synthesis of this compound has previously been described using a different methodology.[16]

mp 168 °C; ν_{max}/cm^{-1} 1375 (S=O); *m*/*z* (ESI$^+$) 376 ([M+H]$^+$); HRMS (ESI$^+$) $C_{22}H_{18}O_3NS$, ([M+H]$^+$) requires 376.1002; found 376.0997.

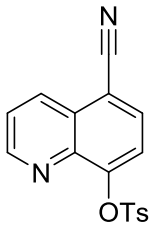
4-(Furan-3-yl)quinolin-8-yl 4-methylbenzenesulfonate S19



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 H_2O and brine. The organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was purified *via* flash column chromatography to give **S19** (6 mg, 16 %) as an off-white solid.

mp 107 °C; ν_{max}/cm^{-1} 1364 (S=O); δ_H (400 MHz, $CDCl_3$) 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, C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 150.2, 145.6, 145.2, 143.9, 141.6, 140.0, 133.2, 129.6, 128.9, 128.1, 126.2, 124.6, 122.7, 122.4, 121.6, 111.5, 21.8 (*C*H$_3$); *m/z* (ESI$^+$) 366 ([M+H]$^+$); HRMS (ESI$^+$) $C_{20}H_{16}O_4NS$, ([M+H]$^+$) requires 366.0795; found 366.0789.

5-Cyanoquinolin-8-yl 4-methylbenzenesulfonate S20



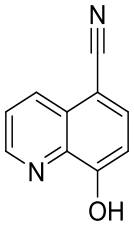
Prior to use, anhydrous dimethylacetamide was sparged with a gentle stream of nitrogen gas for 30 min. A 50 mM solution of sulphuric acid was prepared with 10 mL dimethylacetamide and 26.8 µL of concentrated H_2SO_4 and sparged with N_2 for 10 min. A microwave vial equipped with a magnetic follower was 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_2SO_4 (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 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_2O 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 **S20** (1.09 g, 67 %) as an off-white powder.

mp 119 °C; ν_{max}/cm^{-1} 2224 (nitrile); δ_H (400 MHz, $CDCl_3$) 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, C*H*$_3$); δ_C (100

MHz, $CDCl_3$) 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 (CH_3); *m/z* (ESI^+) 325 ($[M+H]^+$); HRMS (ESI^+) $C_{17}H_{12}O_3N_2NaS$, ($[M+Na]^+$) requires 347.0461; found 347.0455.

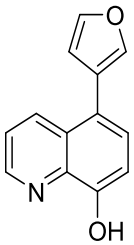
8-Hydroxyquinoline-5-carbonitrile S21



A solution of **S20** (162 mg, 0.5 mmol) in sodium hydroxide (1M aq., 0.5 mL), ethanol (3 mL) and H_2O (3 mL) was stirred under reflux for 1 h. The ethanol was removed *in vacuo* and the pH adjusted to 5. The precipitate was filtered and dried to give **S21** (76 mg, 89 %) as a white solid.

mp 174 ^oC; ν_{max}/cm^{-1} 3066 (OH), 2222 (nitrile); δ_H (400 MHz, DMSO-d_6) 8.91 - 9.08 (1 H, m) 8.35 - 8.50 (1 H, m) 7.95 - 8.19 (1 H, m) 7.73 - 7.86 (1 H, m) 7.02 - 7.31 (1 H, m); δ_C (100 MHz, DMSO-d_6) 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^-) $C_{10}H_5ON_2$, ($[M-H]^-$) requires 169.0407; found 169.0405.

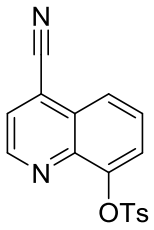
5-(Furan-3-yl)quinolin-8-ol S22



A solution of **S17** (445 mg, 1.2 mmol) in sodium hydroxide (1M aq., 3.66 mL), ethanol (7.5 mL) and H_2O (7.5 mL) was stirred under reflux for 2 h. The ethanol was removed *in vacuo* and the pH adjusted to 6.5. The precipitate was filtered and dried to give **S22** (252 mg, 98 %) as an off-white solid.

mp 79 ^oC; ν_{max}/cm^{-1} 3189 (OH); δ_H (400 MHz, $CDCl_3$) 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*); δ_C (100 MHz, $CDCl_3$) 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^+) $C_{13}H_{10}NO_2$, ($[M+H]^+$) requires 212.0706; found 212.0712.

4-Cyanoquinolin-8-yl 4-methylbenzenesulfonate S23

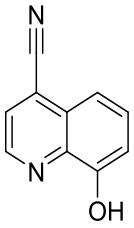


Prior to use, anhydrous dimethylacetamide was sparged with a gentle stream of nitrogen gas for 30 min. A 50 mM solution of sulphuric acid was prepared with 10 mL dimethylacetamide and 26.8 µL of concentrated H_2SO_4 and sparged with N_2 for 10 min. A microwave vial equipped with a magnetic follower was 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_2SO_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_2O 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; ν_{max}/cm^{-1} 2220 (nitrile); δ_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, C*H*$_3$); δ_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 (*C*H$_3$); *m/z* (ESI$^+$) 325 ([M+H]$^+$); HRMS (ESI$^+$) $C_{17}H_{12}O_3N_2NaS$, ([M+Na]$^+$) requires 347.0461; found 347.0457.

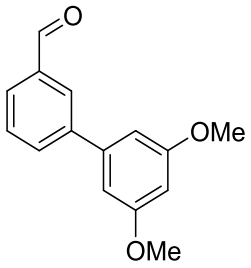
8-Hydroxyquinoline-4-carbonitrile S24



A solution of **S23** (343 mg, 1.1 mmol) in sodium hydroxide (1M aq., 1.1 mL), ethanol (6 mL) and H_2O (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_{max}/cm^{-1} 2235 (nitrile); δ_H (200 MHz, DMSO-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); δ_C (100 MHz, DMSO-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$^+$) $C_{10}H_5ON_2$, ([M-H]$^-$) requires 169.0407; found 169.0406.

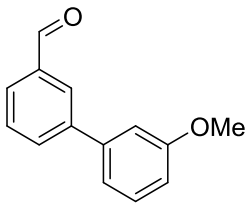
3',5'-Dimethoxy-[1,1'-biphenyl]-3-carbaldehyde S25



3-Formylphenylboronic acid (900 mg, 6 mmol), 1-bromo-3,5-dimethoxybenzene (1.09 g, 5 mmol), tetrakis(triphenylphosphine)palladium (0) (171 mg, 1.5 µmol) were mixed in dimethoxyethane (10 mL) inside a sealed vial. A 2 M aqueous solution of sodium carbonate (5 mL) was added, and the vial was purged with N_2 three times. The mixture was stirred at 100 °C for 2.5 h under microwave irradiation. The reaction mixture was cooled to room temperature and diluted with EtOAc (200 mL). The organic layer was washed with water, a saturated aqueous solution of NH_4Cl, brine, and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure. The residue was subjected to flash column chromatography on silica gel using EtOAc/cyclohexane (20:8) as eluent to give **S25** as a clear oil (634 mg, 52 %).

δ_H (400 MHz, $CDCl_3$) 10.05 (1 H, s, C*H*O), 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, C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 192.3 (*C*HO), 161.2 (*C*OCH$_3$), 142.0, 141.2, 136.8, 133.1, 129.4, 128.9, 128.1, 105.4, 99.9, 55.4 (O*C*H$_3$); *m/z* (ESI$^+$) 243 ([M+H]$^+$); HRMS (ESI$^+$) $C_{15}H_{15}O_3$, ([M+H]$^+$) requires 243.1016; found 243.1011.

3'-Methoxy-[1,1'-biphenyl]-3-carbaldehyde S26[17]

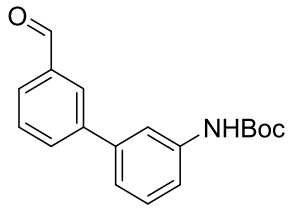


3-Formylphenylboronic acid (900 mg, 6 mmol), 3-bromoanisole (633µL, 5 mmol), tetrakis(triphenylphosphine)palladium (0) (171 mg, 1.5 µmol) were mixed in dimethoxyethane (10 mL) inside a sealed vial. A 2 M aqueous solution of sodium carbonate (5 mL) was added, and the vial was purged with N_2 three times. The mixture was stirred at 100 °C for 2.5 h under microwave irradiation. The reaction mixture was cooled to room temperature and diluted with EtOAc (200 mL). The organic layer was washed with water, a saturated aqueous solution of NH_4Cl, 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 **S26** (770 mg, 73 %) as a clear oil.

δ_H (400 MHz, $CDCl_3$) 10.06 (1 H, s, C*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_C (100 MHz, $CDCl_3$) 192.3 (*C*HO), 160.1 (*C*OCH_3), 141.9, 141.1, 136.9, 133.1, 130.1, 129.5, 128.7, 128.2, 119.6, 113.4, 112.9, 55.3 (O*C*H_3); *m/z* (ESI^+) 213 ($[M+H]^+$).

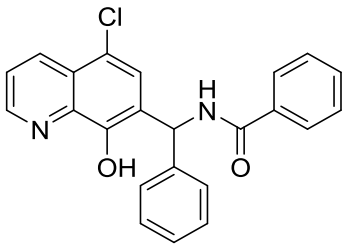
***tert*-Butyl (3'-formyl-[1,1'-biphenyl]-3-yl)carbamate S27**



3-Formylphenylboronic acid (900 mg, 6 mmol), **S185** (1.36 g, 5 mmol), tetrakis(triphenylphosphine)palladium (0) (171 mg, 1.5 µmol) were mixed in dimethoxyethane (10 mL) inside a sealed vial. A 2 M aqueous solution of sodium carbonate (5 mL) was added, and the vial was purged with N_2 three times. The mixture was stirred at 100 °C for 2.5 h under microwave irradiation. The reaction mixture was cooled to room temperature and diluted with EtOAc (200 mL). The organic layer was washed with water, a saturated aqueous solution of NH_4Cl, 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; ν_{max}/cm^{-1} 3339 (NH), 1693 (C=O); δ_H (400 MHz, $CDCl_3$) 10.09 (1 H, s, C*H*O), 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., N*H*), 1.54 (9 H, s, C(CH_3)$_3$); δ_C (100 MHz, $CDCl_3$) 192.3 (*C*HO), 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(*C*H_3)$_3$); *m/z* (ESI^-) 296 ($[M-H]^-$); HRMS (ESI^+) $C_{18}H_{19}NNaO_3$, ($[M+Na]^+$) requires 320.1257; found 320.1245.

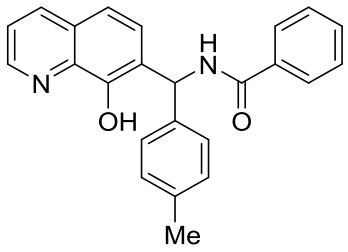
***N*-((5-Chloro-8-hydroxyquinolin-7-yl)(phenyl)methyl)benzamide S28[4]**



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; ν_{max}/cm^{-1} 3330 (NH), 3063 (OH), 1636 (C=O); δ_H (400 MHz, DMSO-d_6) 10.42 (1 H, br. s., N*H*), 9.19 - 9.33 (1 H, m, quinoline-*Ar*), 8.92 - 9.04 (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*); δ_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$^+$) $C_{23}H_{17}ClN_2NaO_2$, ([M+Na]$^+$) requires 411.0871; found 411.0861.

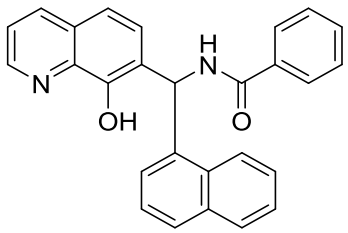
***N*-((8-Hydroxyquinolin-7-yl)(*p*-tolyl)methyl)benzamide S29**



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; ν_{max}/cm^{-1} 3308 (NH), 3048 (OH), 1640 (C=O); δ_H (400 MHz, DMSO-d_6) 9.97 (1 H, br. s, N*H*), 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, C*H*$_3$); δ_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 (*C*H$_3$); *m*/*z* (ESI$^-$) 367 ([M-H]$^-$, 100 %); HRMS (ESI$^+$) $C_{24}H_{20}N_2NaO_2$, ([M+Na]$^+$) requires 391.1417; found 391.1420.

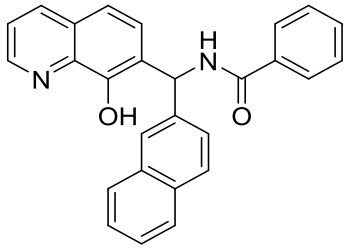
***N*-((8-Hydroxyquinolin-7-yl)(naphthalen-1-yl)methyl)benzamide S30**



Following general procedure 1, 8-hydroxyquinoline (145 mg, 1.0 mmol), benzamide (121 mg, 1.0 mmol) and 1-naphthaldehyde (272 µL, 2.0 mmol) gave **S30** (150 mg, 37 %) as an off-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., N*H*), 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, 128.6, 128.5, 128.2, 127.3, 126.6, 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$^+$) $C_{27}H_{20}N_2NaO_2$, ([M+Na]$^+$) requires 427.1417; found 427.1408.

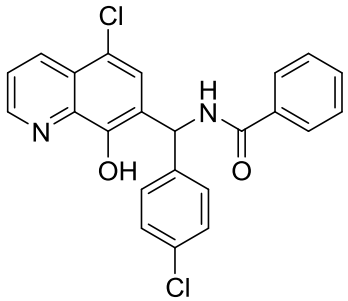
***N*-((8-Hydroxyquinolin-7-yl)(naphthalen-2-yl)methyl)benzamide S31**



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*), 8.14 - 8.20 (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, 128.6, 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$^+$) $C_{27}H_{21}N_2O_2$, ([M+H]$^+$) requires 405.1598; found 405.1582.

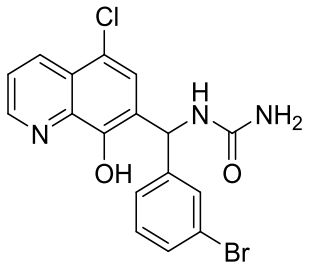
***N*-((5-Chloro-8-hydroxyquinolin-7-yl)(4-chlorophenyl)methyl)benzamide S32**



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_{max}/cm^{-1} 3308 (NH), 2361 (OH), 1631 (C=O); 691 (C-Cl); δ_H (400 MHz, DMSO-d_6) 10.49 (1 H, br. s. , N*H*), 9.23 - 9.36 (1 H, m, quinoline-*Ar*), 8.91 - 9.04 (1 H, m, quinoline-*Ar*), 8.42 - 8.56 (1 H, m, quinoline-*Ar*), 7.91 - 7.98 (2 H, m, *Ar*), 7.85 (1 H, s, *Ar*), 7.70 - 7.77 (1 H, m, *Ar*), 7.52 - 7.59 (1 H, m, *Ar*), 7.45 - 7.52 (2 H, m, *Ar*), 7.38 - 7.43 (2 H, m, *Ar*), 7.30 - 7.37 (2 H, m, *Ar*), 6.99 (1 H, d, *J*=8.5 Hz, benzyl-*H*); δ_C (100 MHz, DMSO-d_6) 166.9 (*C*=O), 150.5, 150.1, 141.4, 139.5, 135.0, 133.4, 132.5, 132.3, 130.0, 129.3, 129.2, 128.5, 127.4, 125.9, 125.4, 124.0, 119.5, 50.5 (benzyl-*C*); *m/z* (ESI$^+$) 867 ([2M+Na]$^+$); HRMS (ESI$^-$) $C_{23}H_{15}Cl_2N_2O_2$, ([M-H]$^-$) requires 421.0516; found 421.

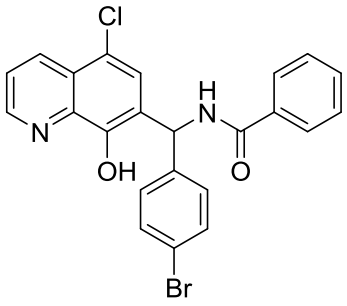
((3-Bromophenyl)(5-chloro-8-hydroxyquinolin-7-yl)methyl)urea S33



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

mp 183 °C; ν_{max}/cm^{-1} 3339 (NH), 1636 (C=O); δ_H (400 MHz, DMSO-d_6) 10.47 (1 H, br. s., N*H*), 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_C (100 MHz, DMSO-d_6) 157.2 (*C*=O), 150.1, 139.6, 133.4, 131.5, 131.4, 130.6, 130.0, 127.0, 126.6, 126.2, 125.9, 123.9, 122.6, 119.7, 52.3 (benzyl-*C*); *m/z* (FI$^+$) 404 ([M]$^+$); HRMS (FI$^+$) $C_{17}H_{13}BrClIN_3O_2$, ([M]$^+$) requires 404.9880; found 404.0892.

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

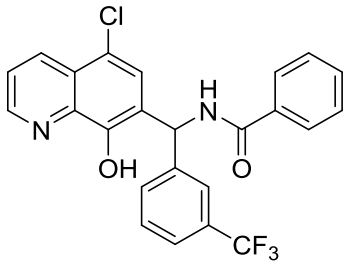


Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 4-bromobenzaldehyde (740 mg, 4.0 mmol) gave **S34** (931 mg, 100 %) as an off-white powder.

mp 276 °C; ν_{max}/cm^{-1} 3316 (NH), 2946 (OH), 1630 (C=O); 691 (C-Br); δ_H (400 MHz, DMSO-d_6) 10.49 (1 H, br. s. , br. s., N*H*), 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-d_6) 166.9 (*C*=O), 150.5, 150.1, 141.9, 139.5, 135.0, 133.4, 132.3, 132.2, 130.3, 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^+) $C_{23}H_{16}BrClN_2NaO_2$, ($[M+Na]^+$) requires 490.9955; found 490.9944.

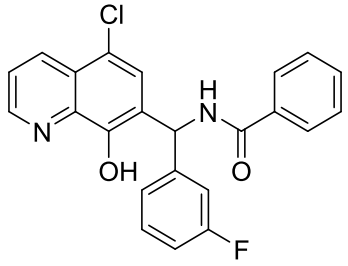
***N*-((5-Chloro-8-hydroxyquinolin-7-yl)(3-(trifluoromethyl)phenyl)methyl)benzamide S35**



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

mp 219 - 222 °C; ν_{max}/cm^{-1} 3294 (NH), 1634 (C=O), 692 (C-Cl); δ_H (400 MHz, DMSO-d_6) 10.58 (1 H, br. s., N*H*), 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-d_6) 167.0 (*C*=O), 150.6, 150.2, 143.9, 139.5, 134.9, 133.4, 132.4, 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*); δ_F (377 MHz, DMSO-d_6) -61.0 (CF_3); *m/z* (ESI^-) 455 ($[M-H]^-$); HRMS (ESI^+) $C_{24}H_{16}ClF_3N_2NaO_2$, ($[M+Na]^+$) requires 479.0745; found 479.0740.

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

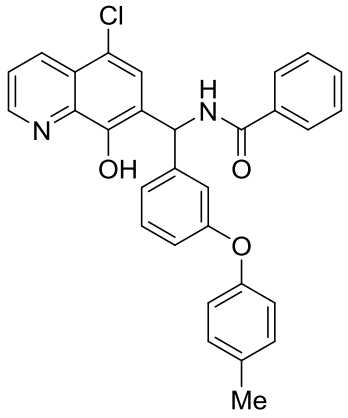


Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 3-fluorobenzaldehyde (424 µL, 4.0 mmol) gave **S36** (631 mg, 78 %) as a white powder.

mp 234 °C; ν_{max}/cm^{-1} 3311 (NH), 1631 (C=O), 692 (C-Cl); δ_H (400 MHz, DMSO-d_6) 10.53 (1 H, br. s., N*H*), 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); δ_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*); δ_F (377 MHz, DMSO-d_6) -113.0 (C*F*); *m*/*z* (ESI$^-$) 405 ([M-H]$^-$); HRMS (ESI$^+$) $C_{23}H_{16}ClFN_2NaO_2$, ([M+Na]$^+$) requires 429.0777; found 429.0770.

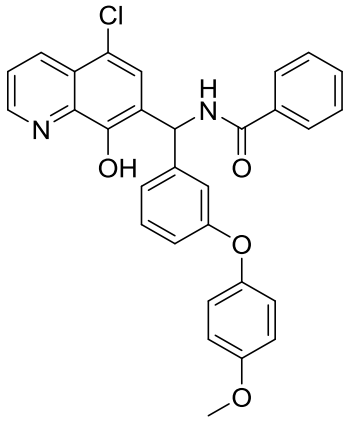
_N_-((5-Chloro-8-hydroxyquinolin-7-yl)(3-(p-tolyloxy)phenyl)methyl)benzamide S37



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 ^{o}C; ν_{max}/cm^{-1} 3306 (NH), 1634 (C=O); δ_H (400 MHz, DMSO-d_6) 10.49 (1 H, br. s., N*H*), 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); δ_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 (*C*H$_3$); *m*/*z* (ESI$^-$) 493 ([M-H]$^-$); HRMS (ESI$^+$) $C_{30}H_{23}ClN_2NaO_3$, ([M+Na]$^+$) requires 517.1289; found 517.1276.

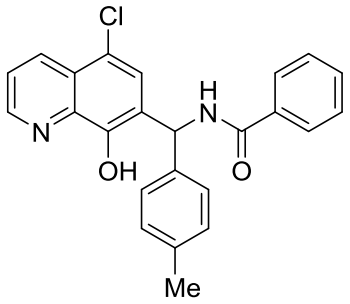
_N_-((5-chloro-8-hydroxyquinolin-7-yl)(3-(4-methoxyphenoxy)phenyl)methyl)benzamide S38



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; ν_{max}/cm^{-1} 3274 (NH), 1633 (C=O); δ_H (400 MHz, DMSO-d_6) 10.47 (1 H, br. s., N*H*), 9.21 - 9.32 (1 H, m, quinoline-*Ar*), 8.91 - 9.01 (1 H, m, quinoline-*Ar*), 8.42 - 8.52 (1 H, m, quinoline-*Ar*), 7.87 - 7.93 (2 H, m, *Ar*), 7.85 (1 H, s, *Ar*), 7.68 - 7.78 (1 H, m, *Ar*), 7.52 - 7.59 (1 H, m, *Ar*), 7.42 - 7.51 (2 H, m, *Ar*), 7.21 - 7.36 (1 H, m, *Ar*), 6.94 - 7.06 (5 H, m, *Ar*), 6.86 - 6.94 (2 H, m, *Ar*), 6.67 - 6.80 (1 H, m) 3.71 (3 H, s, C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 167.0 (*C*=O), 159.0, 156.4, 150.4, 150.1, 149.8, 144.7, 139.5, 135.1, 133.4, 132.3, 130.8, 129.1, 128.4, 127.6, 125.9, 125.6, 123.9, 122.2, 121.7, 119.5, 116.7, 116.2, 115.9, 56.2 (*C*H$_3$), 50.6 (benzyl-*C*); *m*/*z* (ESI$^-$) 509 ([M-H]$^-$); HRMS (ESI$^+$) $C_{30}H_{23}ClN_2NaO_4$, ([M+Na]$^+$) requires 533.1239; found 533.1239.

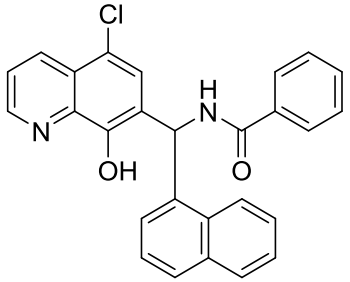
***N*-((5-Chloro-8-hydroxyquinolin-7-yl)(p-tolyl)methyl)benzamide S39**



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

mp 248-249 °C; ν_{max}/cm^{-1} 3310 (NH), 1634 (C=O); δ_H (400 MHz, DMSO-d_6) 10.39 (1 H, br. s., N*H*), 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, C*H*$_3$); δ_C (100 MHz, DMSO-d_6) 166.8 (*C*=O), 150.3, 150.0, 139.5, 137.0, 135.2, 133.4, 132.2, 129.8, 129.1, 128.5, 128.0, 127.7, 126.2, 125.8, 123.8, 119.4, 50.7 (benzyl-*C*), 21.5 (*C*H$_3$); *m*/*z* (ESI$^-$) 401 ([M-H]$^-$, 100 %); HRMS (ESI$^-$) $C_{24}H_{18}ClN_2O_2$, ([M-H]$^-$) requires 401.1062; found 401.1061.

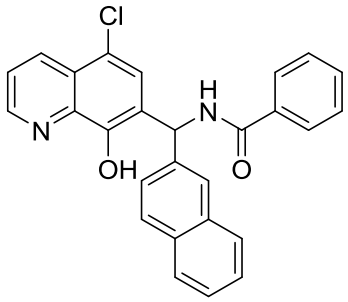
***N*-((5-Chloro-8-hydroxyquinolin-7-yl)(naphthalen-1-yl)methyl)benzamide S40**



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

mp 229-230 °C; ν_{max}/cm^{-1} 3234 (NH), 1630 (C=O); δ_H (400 MHz, DMSO-d_6) 10.54 (1 H, br. s., N*H*), 9.33 - 9.42 (1 H, m, quinoline-*Ar*), 8.94 - 9.01 (1 H, m, quinoline-*Ar*), 8.45 - 8.51 (1 H, m, quinoline-*Ar*), 8.06 - 8.16 (1 H, m, *Ar*), 7.92 - 8.00 (3 H, m, *Ar*), 7.86 - 7.91 (1 H, m, *Ar*), 7.71 - 7.76 (1 H, m, *Ar*), 7.70 (1 H, s) 7.65 (1 H, d, *J*=8.5 Hz) 7.49 - 7.58 (3 H, m, *Ar*), 7.43 - 7.49 (3 H, m, *Ar*), 7.39 (1 H, m, *Ar*); δ_C (100 MHz, DMSO-d_6) 166.5 (*C*=O), 150.5, 150.1, 139.5, 138.1, 134.9, 134.4, 133.4, 132.3, 131.8, 129.6, 129.1, 128.8, 128.5, 128.0, 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$^-$) $C_{27}H_{18}ClN_2O_2$, ([M-H]$^-$) requires 437.1062; found 437.1050.

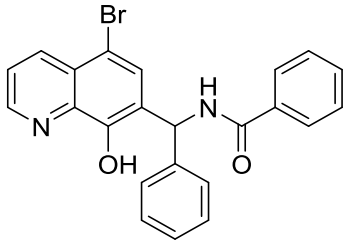
***N*-((5-Chloro-8-hydroxyquinolin-7-yl)(naphthalen-2-yl)methyl)benzamide S41**



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; ν_{max}/cm^{-1} 3367 (NH), 1654 (C=O); δ_H (400 MHz, DMSO-d_6) 10.49 (1 H, br. s. ,N*H*), 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*); δ_C (100 MHz, DMSO-d_6) 166.9 (*C*=O), 150.6, 150.1, 140.0, 139.6, 135.1, 133.6, 133.4, 133.0, 132.3, 129.2, 129.0, 128.7, 128.5, 128.3, 127.8, 127.2, 126.8, 126.7, 126.1, 125.9, 125.8, 123.9, 119.5, 51.2 (benzyl-*C*); *m*/*z* (ESI$^-$) 437 ([M-H]$^-$, 100 %); HRMS (ESI$^-$) $C_{27}H_{18}ClN_2O_2$, ([M-H]$^-$) requires 437.1062; found 437.1061.

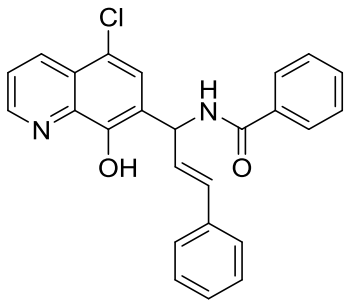
***N*-((5-Bromo-8-hydroxyquinolin-7-yl)(phenyl)methyl)benzamide S42**



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; ν_{max}/cm^{-1} 3263 (NH), 1638 (C=O); δ_H (400 MHz, DMSO-d_6) 10.46 (1 H, br. s., N*H*), 9.21 - 9.34 (1 H, m, quinoline-*Ar*), 8.89 - 8.98 (1 H, m, quinoline-*Ar*), 8.35 - 8.45 (1 H, m, quinoline-*Ar*), 8.03 (1 H, s, quinoline-*Ar*), 7.89 - 7.98 (2 H, m, *Ar*), 7.68 - 7.75 (1 H, m, *Ar*), 7.52 - 7.59 (1 H, m, *Ar*), 7.46 - 7.52 (2 H, m, *Ar*), 7.31 - 7.37 (4 H, m, *Ar*), 7.22 - 7.29 (1 H, m, *Ar*), 7.03 (1 H, d, *J*=8.5 Hz, benzyl-*H*); δ_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.

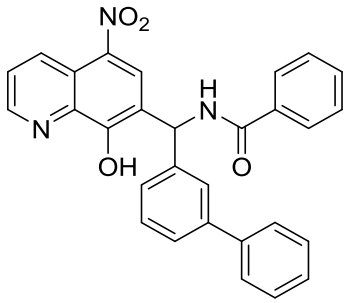
(*E*)-*N*-(1-(5-Chloro-8-hydroxyquinolin-7-yl)-3-phenylallyl)benzamide S43



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; ν_{max}/cm^{-1} 3290 (NH), 1630 (C=O); δ_H (400 MHz, DMSO-d_6) 10.40 (1 H, br. s., N*H*), 9.07 - 9.25 (1 H, m, quinoline-*Ar*), 8.89 - 9.02 (1 H, m, quinoline-*Ar*), 8.37 - 8.56 (1 H, m, quinoline-*Ar*), 7.92 - 8.00 (2 H, m, *Ar*), 7.90 (1 H, s, *Ar*), 7.67 - 7.75 (1 H, m, *Ar*), 7.52 - 7.59 (1 H, m, *Ar*), 7.46 - 7.52 (2 H, m, *Ar*), 7.40 - 7.45 (2 H, m, *Ar*), 7.26 - 7.34 (2 H, m, *Ar*), 7.17 - 7.25 (1 H, m, *Ar*), 6.54 - 6.60 (2 H, m, *Ar*), 6.45 - 6.51 (1 H, m, benzyl-*H*); δ_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.

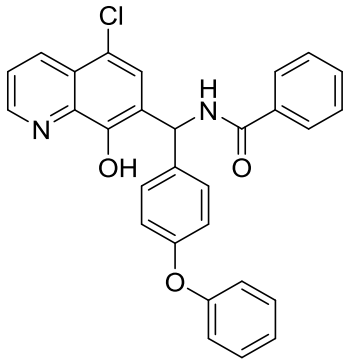
***N*-([1,1'-Biphenyl]-3-yl(8-hydroxy-5-nitroquinolin-7-yl)methyl)benzamide S44**



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; ν_{max}/cm^{-1} 3283 (NH), 1633 (C=O); δ_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*); δ_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$^+$) $C_{29}H_{21}N_3NaO_4$, ([M+Na]$^+$) requires 498.1424; found 498.1440.

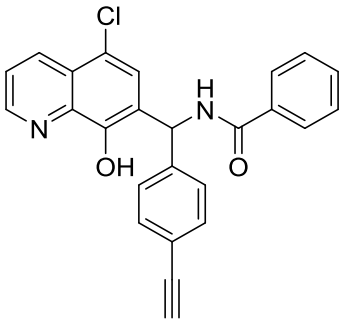
***N*-((5-Chloro-8-hydroxyquinolin-7-yl)(4-phenoxyphenyl)methyl)benzamide S45**



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

mp 222 °C; ν_{max}/cm^{-1} 3306 (NH), 1634 (C=O); δ_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*); δ_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) $C_{29}H_{21}N_2O_3Cl$, ([M]) requires 480.1241; found 480.1248.

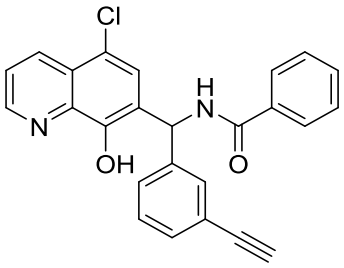
***N*-((5-Chloro-8-hydroxyquinolin-7-yl)(4-ethynylphenyl)methyl)benzamide S46**



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); δ_H (400 MHz, DMSO-d_6) 10.53 (1 H, br. s., N*H*), 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, C*H*); δ_C (100 MHz, DMSO-d_6) 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$^+$) $C_{25}H_{17}O_2N_2ClNa$, ([M+Na]$^+$) requires 435.0871; found 435.0866.

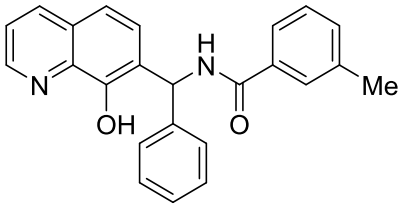
***N*-((5-Chloro-8-hydroxyquinolin-7-yl)(3-ethynylphenyl)methyl)benzamide S47**



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); δ_H (400 MHz, DMSO-d_6) 10.55 (1 H, br. s., N*H*), 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, C*H*); δ_C (100 MHz, DMSO-d_6) 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$^+$) $C_{25}H_{17}O_2N_2ClNa$, ([M+Na]$^+$) requires 435.0871; found 435.0867.

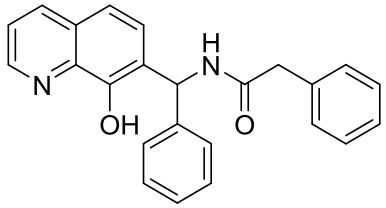
***N*-((8-Hydroxyquinolin-7-yl)(phenyl)methyl)-3-methylbenzamide S48**



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

mp 165 ^{o}C; ν_{max}/cm^{-1} 3306 (NH), 3058 (OH), 1638 (C=O); δ_H (400 MHz, DMSO-d_6) 10.02 (1 H, br. s., N*H*), 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, O*H*), 7.01 (1 H, d, *J*=9.0 Hz, benzyl-*H*), 2.30 - 2.42 (3 H, m, *Me*); δ_C (100 MHz, DMSO-d_6) 166.9 (*C*=O), 150.7, 149.2, 143.1, 138.9, 138.4, 136.9, 135.3, 132.7, 129.1, 129.0, 128.9, 128.5, 128.1, 127.9, 127.6, 125.7, 125.2, 122.7, 118.2, 51.4 (benzyl-*C*), 21.8 (*C*H$_3$); *m/z* (ESI$^-$) 367 ([M-H]$^-$, 100 %); HRMS (ESI$^+$) $C_{24}H_{20}N_2NaO_2$, ([M+Na]$^+$) requires 391.1417; found 391.1403.

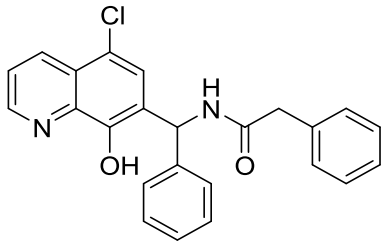
***N*-((8-Hydroxyquinolin-7-yl)(phenyl)methyl)-2-phenylacetamide S49**



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 ^{o}C; ν_{max}/cm^{-1} 3307 (NH), 1634 (C=O); δ_H (400 MHz, DMSO-d_6) 9.95 (1 H, br. s, N*H*), 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, C*H*$_2$); δ_C (100 MHz, DMSO-d_6) 170.3 (*C*=O), 150.4, 149.2, 143.2, 138.9, 137.3, 136.9, 129.9, 129.1, 129.0, 128.4, 127.9, 127.6, 127.2, 127.2, 125.3, 122.6, 118.2, 50.9 (benzyl-*C*), 43.1 (*C*H$_2$); *m/z* (ESI$^-$) 367 ([M-H]$^-$); HRMS (ESI$^-$) $C_{24}H_{19}N_2O_2$, ([M-H]$^-$) requires 367.1452; found 367.1444.

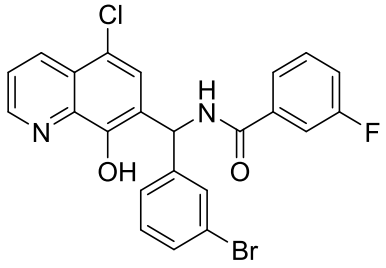
***N*-((5-Chloro-8-hydroxyquinolin-7-yl)(phenyl)methyl)-2-phenylacetamide S50[4]**



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., N*H*), 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, 129.0, 127.9, 127.2, 127.1, 127.0, 126.1, 125.7, 123.8, 119.5, 50.7 (benzyl-*C*), 43.1 (*C*H$_2$); *m/z* (ESI$^-$) 401 ([M-H]$^-$); HRMS (ESI$^-$) $C_{24}H_{19}ClN_2NaO_2$, ([M+Na]$^+$) requires 425.1027; found 425.1024.

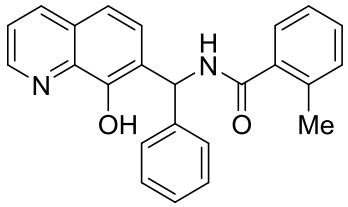
***N*-((3-Bromophenyl)(5-chloro-8-hydroxyquinolin-7-yl)methyl)-3-fluorobenzamide S51**



Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), 3-fluorobenzamide (278 mg, 2.0 mmol) and 3-bromobenzaldehyde (468µL, 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., N*H*), 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$^+$) $C_{23}H_{15}BrClFN_2NaO_2$, ([M+Na]$^+$) requires 506.9882; found 506.9876.

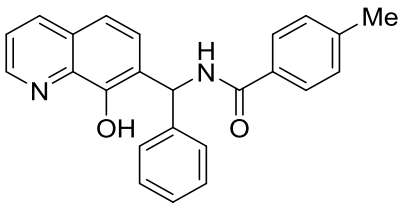
***N*-((8-Hydroxyquinolin-7-yl)(phenyl)methyl)-2-methylbenzamide S52**



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

mp 170 °C; ν_{max}/cm^{-1} 3292 (NH), 3060 (OH), 1643 (C=O); δ_H (400 MHz, DMSO-d_6) 10.04 (1 H, br. s, N*H*), 9.15 - 9.32 (1 H, m, quinoline-*Ar*), 8.83 - 8.91 (1 H, m quinoline-*Ar*), 8.24 - 8.37 (1 H, m quinoline-*Ar*), 7.66 - 7.72 (1 H, m quinoline-*Ar*), 7.53 - 7.59 (1 H, m quinoline-*Ar*), 7.42 - 7.47 (1 H, m, *Ar*), 7.35 - 7.40 (3 H, m, *Ar*), 7.29 - 7.35 (3 H, m, *Ar*), 7.20 - 7.27 (3 H, m, *Ar*), 7.00 (1 H, d, *J*=9.0 Hz, benzyl-*H*), 2.29 (3 H, s, CH_3); δ_C (100 MHz, DMSO-d_6) 169.4 (*C*=O), 150.5, 149.2, 143.2, 138.9, 136.9, 136.0, 131.1, 130.1, 129.2, 128.4, 128.0, 127.9, 127.7, 127.6, 126.3, 125.4, 122.7, 118.2, 50.9 (benzyl-*C*), 20.2 (*C*H$_3$); *m/z* (ESI$^-$) 367 ([M-H]$^-$, 100 %); HRMS (ESI$^+$) $C_{24}H_{20}N_2NaO_2$, ([M+Na]$^+$) requires 391.1417; found 391.1404.

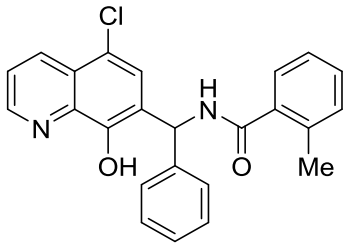
***N*-((8-Hydroxyquinolin-7-yl)(phenyl)methyl)-4-methylbenzamide S53**



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

mp 214-216 °C; ν_{max}/cm^{-1} 3305 (NH), 3047 (OH), 1632 (C=O); δ_H (400 MHz, DMSO-d_6) 10.04 (1 H, br. s, N*H*), 9.11 - 9.22 (1 H, m, quinoline-*Ar*), 8.82 - 8.89 (1 H, m, quinoline-*Ar*), 8.25 - 8.35 (1 H, m, quinoline-*Ar*), 7.83 - 7.88 (2 H, m, quinoline-*Ar*), 7.68 - 7.74 (1 H, m, *Ar*), 7.52 - 7.59 (1 H, m, *Ar*), 7.41 - 7.46 (1 H, m, *Ar*), 7.32 (2 H, s, *Ar*), 7.30 - 7.32 (2 H, m, *Ar*), 7.25 - 7.30 (2 H, m, *Ar*), 7.23 (1 H, br. s, O-*H*), 7.01 (1 H, d, *J*=9.0 Hz, benzyl-*H*), 2.35 (3 H, s, CH_3); δ_C (100 MHz, DMSO-d_6) 166.65 (*C*=O), 150.6, 149.2, 143.1, 142.0, 138.9, 136.9, 132.5, 129.8, 129.6, 129.1, 128.5, 128.1, 127.9, 127.6, 125.3, 122.6, 118.2, 51.3 (benzyl-*C*), 21.8 (*C*H$_3$); *m/z* (ESI$^-$) 367 ([M-H]$^-$, 100 %); HRMS (ESI$^+$) $C_{24}H_{20}N_2NaO_2$, ([M+Na]$^+$) requires 391.1417; found 391.1400.

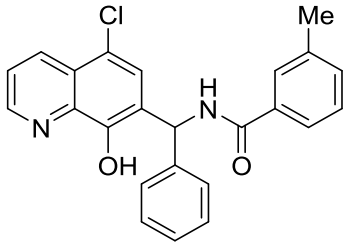
***N*-((5-Chloro-8-hydroxyquinolin-7-yl)(phenyl)methyl)-2-methylbenzamide S54**



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

mp 213-215 ^{o}C; ν_{max}/cm^{-1} 3284 (NH), 1637 (C=O), 730 (C-Cl); δ_H (400 MHz, DMSO-d_6) 10.44 (1 H, br. s., N*H*), 9.15 - 9.36 (1 H, m, quinoline-*Ar*), 8.90 - 9.03 (1 H, m, quinoline-*Ar*), 8.38 - 8.55 (1 H, m, quinoline-*Ar*), 7.86 (1 H, s, *Ar*), 7.68 - 7.77 (1 H, m, *Ar*), 7.29 - 7.42 (6 H, m, *Ar*), 7.20 - 7.29 (3 H, m, *Ar*), 6.99 (1 H, d, *J*=9.0 Hz, benzyl-*H*), 2.28 (3 H, s, CH_3); δ_C (100 MHz, DMSO-d_6) 169.4 (*C*=O), 150.2, 150.1, 142.6, 139.6, 137.9, 136.0, 133.4, 131.2, 130.2, 129.3, 127.9, 127.9, 127.4, 126.4, 126.1, 125.8, 123.9, 119.5, 50.6 (benzyl-*C*), 20.2 (*C*H$_3$); *m*/*z* (ESI$^-$) 401 ([M-H]$^-$, 100 %); HRMS (ESI$^-$) $C_{24}H_{18}ClN_2O_2$, ([M-H]$^-$) requires 401.1062; found 401.1067.

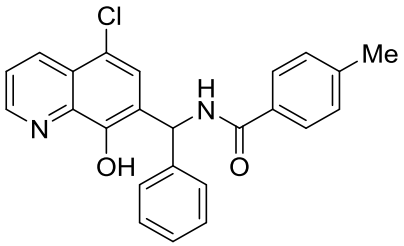
***N*-((5-Chloro-8-hydroxyquinolin-7-yl)(phenyl)methyl)-3-methylbenzamide S55**



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

mp 222-225 ^{o}C; ν_{max}/cm^{-1} 3300 (NH), 1634 (C=O); δ_H (400 MHz, DMSO-d_6) ^{1}H NMR 10.42 (1 H, br. s., N*H*), 9.15 - 9.27 (1 H, m, quinoline-*Ar*), 8.94 - 9.02 (1 H, m, quinoline-*Ar*), 8.43 - 8.53 (1 H, m, quinoline-*Ar*), 7.86 (1 H, s, *Ar*), 7.77 (1 H, s, *Ar*), 7.70 - 7.75 (2 H, m, *Ar*), 7.31 - 7.38 (6 H, m, *Ar*), 7.21 - 7.29 (1 H, m, *Ar*), 7.01 (1 H, d, *J*=8.5 Hz, benzyl-*H*), 2.23 - 2.43 (3 H, m, CH_3); δ_C (100 MHz, DMSO-d_6) 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 (*C*H$_3$); *m*/*z* (ESI$^-$) 401 ([M-H]$^-$, 100 %); HRMS (ESI$^-$) $C_{24}H_{18}ClN_2O_2$, ([M-H]$^-$) requires 401.1062; found 401.1068.

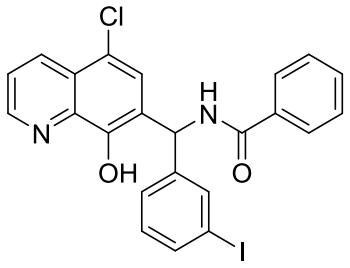
***N*-((5-Chloro-8-hydroxyquinolin-7-yl)(phenyl)methyl)-4-methylbenzamide S56**



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

mp 237-240 °C; ν_{max}/cm^{-1} 3321 (NH), 1634 (C=O); δ_H (400 MHz, DMSO-d_6) 10.41 (1 H, br. s., N*H*), 9.12 - 9.25 (1 H, m, quinoline-*Ar*), 8.90 - 9.00 (1 H, m, quinoline-*Ar*), 8.40 - 8.55 (1 H, m, quinoline-*Ar*), 7.80 - 7.93 (3 H, m, *Ar*), 7.65 - 7.77 (1 H, m, *Ar*), 7.31 - 7.35 (4 H, m, *Ar*), 7.23 - 7.31 (3 H, m, *Ar*), 7.02 (1 H, d, *J*=8.5 Hz, benzyl-*H*), 2.35 (3 H, s, CH_3); δ_C (100 MHz, DMSO-d_6) 166.7 (*C*=O), 150.4, 150.0, 142.6, 142.4, 139.5, 133.4, 132.3, 129.7, 129.3, 128.5, 128.0, 127.9, 127.7, 126.0, 125.8, 123.9, 119.4, 50.9 (benzyl-*C*), 21.8 (*C*H$_3$); *m*/*z* (ESI$^-$) 401 ([M-H]$^-$, 100 %); HRMS (ESI$^-$) $C_{24}H_{18}ClN_2O_2$, ([M-H]$^-$) requires 401.1062; found 401.1062.

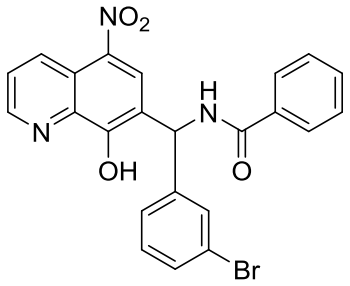
***N*-((5-Chloro-8-hydroxyquinolin-7-yl)(3-iodophenyl)methyl)benzamide S57**



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

mp 226 - 228 °C; ν_{max}/cm^{-1} 3300 (NH), 1632 (C=O), 692 (C-Cl); δ_H (400 MHz, DMSO-d_6) 10.54 (1 H, br. s., N*H*), 9.26 - 9.33 (1 H, m, quinoline-*Ar*), 8.94 - 8.99 (1 H, m, quinoline-*Ar*), 8.45 - 8.51 (1 H, m, quinoline-*Ar*), 7.90 - 7.97 (2 H, m, *Ar*), 7.87 (1 H, s, *Ar*), 7.68 - 7.76 (2 H, m, *Ar*), 7.61 - 7.66 (1 H, m, *Ar*), 7.53 - 7.59 (1 H, m, *Ar*), 7.46 - 7.52 (2 H, m, *Ar*), 7.35 - 7.40 (1 H, m, *Ar*), 7.13 - 7.19 (1 H, m, *Ar*), 6.96 (1 H, d, *J*=9.0 Hz, benzyl-*H*); δ_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$^+$) $C_{23}H_{16}ClIN_2NaO_2$, ([M+Na]$^+$) requires 536.9837; found 536.9825.

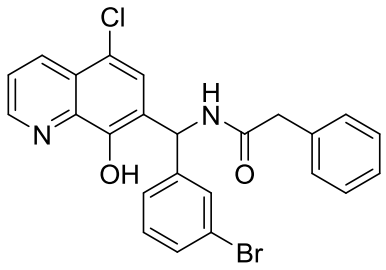
***N*-((3-Bromophenyl)(8-hydroxy-5-nitroquinolin-7-yl)methyl)benzamide S58**



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

mp 264 °C; ν_{max}/cm^{-1} 3287 (NH), 1635 (C=O); δ_H (400 MHz, DMSO-d_6) 9.38 - 9.55 (1 H, m, quinoline-*Ar*), 9.15 - 9.27 (1 H, m, quinoline-*Ar*), 8.94 - 9.06 (1 H, m, quinoline-*Ar*), 8.80 (1 H, s, quinoline-*Ar*), 7.83 - 8.00 (3 H, m, *Ar*), 7.53 - 7.60 (2 H, m, *Ar*), 7.46 - 7.53 (3 H, m, *Ar*), 7.38 - 7.43 (1 H, m, *Ar*), 7.30 - 7.37 (1 H, m, *Ar*), 6.97 (1 H, d, *J*=8.5 Hz, benzyl-*H*); δ_C (100 MHz, DMSO-d_6) 166.9 (*C*=O), 158.9, 149.7, 144.6, 137.6, 135.0, 134.8, 134.1, 132.4, 131.6, 131.1, 130.8, 129.2, 128.8, 128.5, 127.5, 126.2, 123.9, 122.8, 122.7, 50.8 (benzyl-*C*); *m*/*z* (ESI$^-$) 476 ([M-H]$^-$); HRMS (ESI$^-$) $C_{23}H_{15}BrN_3O_4$, ([M-H]$^-$) requires 476.0251; found 476.0259.

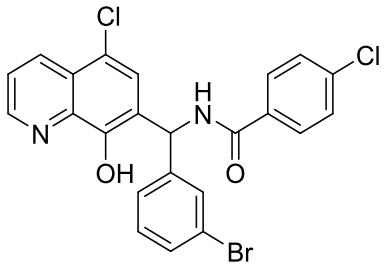
***N*-((3-Bromophenyl)(5-chloro-8-hydroxyquinolin-7-yl)methyl)-2-phenylacetamide S59**



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

mp 169 °C; ν_{max}/cm^{-1} 3273 (NH), 1638 (C=O), 694 (C-Cl); δ_H (400 MHz, DMSO-d_6) 10.48 (1 H, br. s., N*H*), 9.04 - 9.16 (1 H, m, quinoline-*Ar*), 8.91 - 9.00 (1 H, m, quinoline-*Ar*), 8.41 - 8.51 (1 H, m, quinoline-*Ar*), 7.65 - 7.76 (2 H, m, *Ar*), 7.39 - 7.53 (3 H, m, *Ar*), 7.16 - 7.35 (6 H, m, *Ar*), 6.65 (1 H, d, *J*=8.5 Hz, benzyl-*H*), 3.37 (2 H, s, CH_2); δ_C (100 MHz, DMSO-d_6) 170.5 (*C*=O), 150.2, 145.3, 137.4, 137.1, 133.4, 131.6, 130.8, 130.3, 129.9, 129.0, 127.3, 127.1, 127.0, 126.8, 125.9, 125.3, 124.0, 122.6, 119.7, 50.3 (benzyl-*C*), 43.1 (*C*H$_2$); *m*/*z* (ESI$^-$) 481 ([M-H]$^-$); HRMS (ESI$^-$) $C_{21}H_{17}BrClN_2O_2$, ([M-H]$^-$) requires 479.0167; found 479.0157.

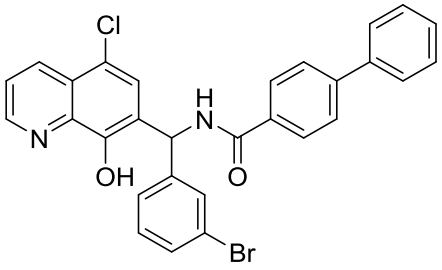
***N*-((3-Bromophenyl)(5-chloro-8-hydroxyquinolin-7-yl)methyl)-4-chlorobenzamide S60**



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

mp 271 °C; ν_{max}/cm^{-1} 3302 (NH), 1635 (C=O); δ_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 - 7.40 (2 H, m, *Ar*), 6.98 (1 H, d, *J*=8.5 Hz, benzyl-*H*); δ_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, 122.6, 119.8, 50.8 (benzyl-*C*); *m/z* (ESI$^+$) 501 ([M+H]$^+$); HRMS (ESI$^+$) $C_{23}H_{15}BrCl_2N_2NaO_2$, ([M+Na]$^+$) requires 522.9586; found 522.9575.

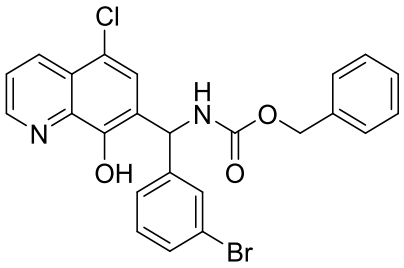
***N*-((3-Bromophenyl)(5-chloro-8-hydroxyquinolin-7-yl)methyl)-[1,1'-biphenyl]-4-carboxamide S61**



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

mp 236 °C; ν_{max}/cm^{-1} 3305 (NH), 1627 (C=O); δ_H (400 MHz, DMSO-d_6) 10.57 (1 H, br. s., N*H*), 9.31 - 9.43 (1 H, m, quinoline-*Ar*), 8.93 - 9.01 (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*); δ_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, 130.6, 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$^+$) $C_{29}H_{20}BrClN_2NaO_2$, ([M+Na]$^+$) requires 565.0289; found 565.0277.

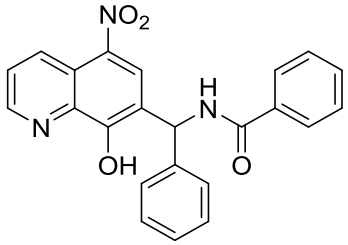
Benzyl((3-bromophenyl)(5-chloro-8-hydroxyquinolin-7-yl)methyl)carbamate S62



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 °C; ν_{max}/cm^{-1} 3305 (NH), 1684 (C=O); δ_H (400 MHz, DMSO-d_6) 10.55 (1 H, br. s. , N*H*), 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 - 7.75 (1 H, m, *Ar*), 7.51 (1 H, s, *Ar*), 7.41 - 7.47 (1 H, m, *Ar*), 7.25 - 7.39 (6 H, m, *Ar*), 6.51 (1 H, d, *J*=9.5 Hz, benzyl-*H*), 5.08 (2 H, s, CH_2); δ_C (100 MHz, DMSO-d_6) 156.6 (*C*=O), 150.2, 149.9, 145.5, 139.5, 137.7, 133.4, 131.6, 130.9, 130.1, 129.2, 128.8, 128.7, 126.8, 126.7, 125.9, 125.6, 124.0, 122.6, 119.8, 66.7 (*C*H$_2$), 52.2 (benzyl-*C*); *m*/*z* (FI$^+$) 496 ([M]$^+$); HRMS (FI$^+$) $C_{24}H_{18}BrClN_2O_3$, ([M]$^+$) requires 496.0189; found 496.0206.

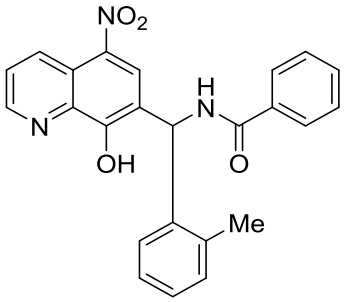
***N*-((8-Hydroxy-5-nitroquinolin-7-yl)(phenyl)methyl)benzamide S63**



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

mp 259 - 261 °C; ν_{max}/cm^{-1} 3288 (NH), 1641 (C=O); δ_H (400 MHz, DMSO-d_6) 9.39 - 9.51 (1 H, m, quinoline-*Ar*), 9.12 - 9.23 (1 H, m, quinoline-*Ar*), 8.95 - 9.06 (1 H, m, quinoline-*Ar*), 8.80 (1 H, s, *Ar*), 7.91 - 7.98 (2 H, m, *Ar*), 7.84 - 7.91 (1 H, m, *Ar*), 7.52 - 7.59 (1 H, m, *Ar*), 7.45 - 7.52 (2 H, m, *Ar*), 7.33 - 7.41 (4 H, m, *Ar*), 7.23 - 7.33 (1 H, m, *Ar*), 7.01 (1 H, d, *J*=8.5 Hz, benzyl-*H*); δ_C (100 MHz, DMSO-d_6) 166.9 (*C*=O), 158.6, 149.9, 141.8, 137.7, 135.2, 135.0, 133.9, 132.3, 129.4, 129.2, 129.1, 128.5, 128.2, 128.1, 126.1, 124.6, 122.5, 51.0 (benzyl-*C*); *m*/*z* (ESI$^-$) 398 ([M-H]$^-$, 100%); HRMS (ESI$^-$) $C_{23}H_{17}N_3NaO_4$, ([M+Na]$^+$) requires 422.1111; found 422.1101.

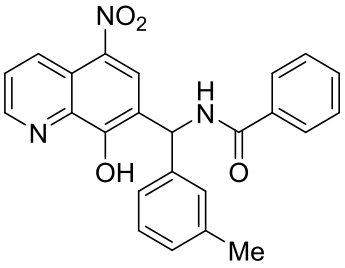
***N*-((8-Hydroxy-5-nitroquinolin-7-yl)(o-tolyl)methyl)benzamide S64**



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; ν_{max}/cm^{-1} 3302 (NH), 1639 (C=O); δ_H (400 MHz, DMSO-d_6) 9.26 - 9.33 (1 H, m, quinoline-*Ar*), 9.15 - 9.23 (1 H, m, quinoline-*Ar*), 8.95 - 9.04 (1 H, m, quinoline-*Ar*), 8.62 (1 H, s, quinoline-*Ar*), 7.92 - 7.98 (2 H, m, *Ar*), 7.85 - 7.91 (1 H, m, *Ar*), 7.50 - 7.58 (1 H, m, *Ar*), 7.43 - 7.50 (2 H, m, *Ar*), 7.12 - 7.28 (4 H, m, *Ar*), 7.05 (1 H, d, *J*=8.5 Hz, benzyl-*H*), 2.31 (3 H, s, C*H*$_3$); δ_C (100 MHz, DMSO-d_6) 166.6 (*C*=O), 158.8, 149.9, 139.8, 137.6, 136.9, 134.9, 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 (*C*H$_3$); *m/z* (ESI$^-$) 412 ([M-H]$^-$); HRMS (ESI$^+$) $C_{24}H_{19}N_3NaO_4$, ([M+Na]$^+$) requires 436.1268; found 436.1253.

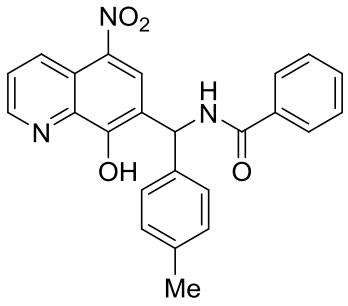
***N*-((8-Hydroxy-5-nitroquinolin-7-yl)(*m*-tolyl)methyl)benzamide S65**



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; ν_{max}/cm^{-1} 3271 (NH), 1636 (C=O); δ_H (400 MHz, DMSO-d_6) 9.31 - 9.47 (1 H, m, quinoline-*Ar*), 9.09 - 9.25 (1 H, m, quinoline-*Ar*), 8.94 - 9.05 (1 H, m, quinoline-*Ar*), 8.81 (1 H, s, quinoline-*Ar*), 7.91 - 7.99 (2 H, m, *Ar*), 7.85 - 7.91 (1 H, m, *Ar*), 7.52 - 7.58 (1 H, m, *Ar*), 7.45 - 7.52 (2 H, m, *Ar*), 7.22 - 7.28 (1 H, m, *Ar*), 7.14 - 7.21 (2 H, m, *Ar*), 7.06 - 7.12 (1 H, m, *Ar*), 6.98 (1 H, d, *J*=8.5 Hz, benzyl-*H*), 2.29 (3 H, s, C*H*$_3$); δ_C (100 MHz, DMSO-d_6) 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 (*C*H$_3$); *m/z* (ESI$^-$) 412 ([M-H]$^-$); HRMS (ESI$^-$) $C_{24}H_{18}N_3O_4$, ([M-H]$^-$) requires 412.1303; found 412.1307.

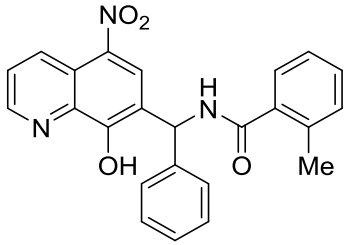
***N*-((8-Hydroxy-5-nitroquinolin-7-yl)(*p*-tolyl)methyl)benzamide S66**



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 ^{o}C; ν_{max}/cm^{-1} 3302 (NH), 1636 (C=O); δ_H (400 MHz, DMSO-d_6) 9.36 - 9.43 (1 H, m, quinoline-*Ar*), 9.13 - 9.20 (1 H, m, quinoline-*Ar*), 8.98 - 9.03 (1 H, m, quinoline-*Ar*), 8.79 (1 H, s, quinoline-*Ar*), 7.91 - 7.97 (2 H, m, *Ar*), 7.85 - 7.90 (1 H, m, *Ar*), 7.52 - 7.58 (1 H, m, *Ar*), 7.45 - 7.51 (2 H, m, *Ar*), 7.22 - 7.28 (2 H, m, *Ar*), 7.12 - 7.19 (2 H, m, *Ar*), 6.96 (1 H, d, *J*=8.5 Hz, benzyl-*H*), 2.27 (3 H, s, C*H*$_3$); δ_C (100 MHz, DMSO-d_6) 166.9 (*C*=O), 158.5, 149.9, 138.8, 137.7, 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 (*C*H$_3$); *m*/*z* (ESI$^-$) 412 ([M-H]$^-$); HRMS (ESI$^-$) $C_{24}H_{18}N_3O_4$, ([M-H]$^-$) requires 412.1303; found 412.1309.

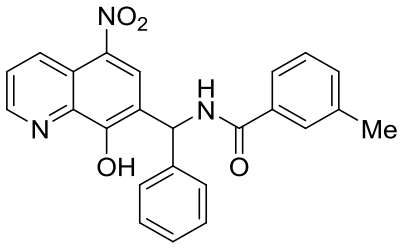
***N*-((8-Hydroxy-5-nitroquinolin-7-yl)(phenyl)methyl)-2-methylbenzamide S67**



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 ^{o}C; ν_{max}/cm^{-1} 3278 (NH), 1636 (C=O); δ_H (400 MHz, DMSO-d_6) 9.39 - 9.47 (1 H, m, quinoline-*Ar*), 9.15 - 9.21 (1 H, m, quinoline-*Ar*), 8.99 - 9.05 (1 H, m, quinoline-*Ar*), 8.82 (1 H, s, quinoline-*Ar*), 7.84 - 7.92 (1 H, m, *Ar*), 7.31 - 7.43 (6 H, m, *Ar*), 7.22 - 7.30 (3 H, m, *Ar*), 6.95 (1 H, d, *J*=8.5 Hz, benzyl-*H*), 2.29 (3 H, s, C*H*$_3$); δ_C (100 MHz, DMSO-d_6) 169.5 (*C*=O), 158.4, 149.9, 141.8, 137.8, 137.7, 136.0, 135.2, 133.9, 131.2, 130.2, 129.4, 128.7, 128.1, 128.1, 128.0, 126.4, 126.1, 124.8, 122.5, 50.8 (benzyl-*C*), 20.15 (*C*H$_3$); *m*/*z* (ESI$^-$) 412 ([M-H]$^-$); HRMS (ESI$^-$) $C_{24}H_{18}N_3O_4$, ([M-H]$^-$) requires 412.1303; found 412.1303.

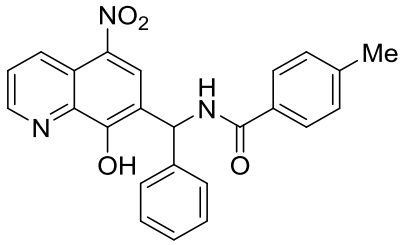
***N*-((8-Hydroxy-5-nitroquinolin-7-yl)(phenyl)methyl)-3-methylbenzamide S68**



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 **S68** (261 mg, 32 %) as an orange powder.

mp 222 ^{o}C; ν_{max}/cm^{-1} 3293 (NH), 1636 (C=O); δ_H (400 MHz, DMSO-d_6) 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, CH_3); δ_C (100 MHz, DMSO-d_6) 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 (*C*H$_3$); *m/z* (ESI$^-$) 412 ([M-H]$^-$); HRMS (ESI$^+$) $C_{24}H_{19}N_3NaO_4$, ([M+Na]$^+$) requires 436.1268; found 436.1259.

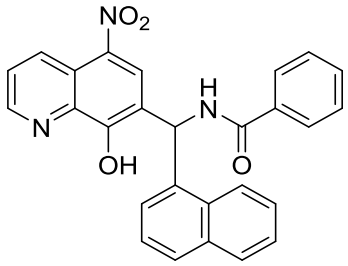
***N*-((8-Hydroxy-5-nitroquinolin-7-yl)(phenyl)methyl)-4-methylbenzamide S69**



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 **S69** (563 mg, 68 %) as an orange powder.

mp 259 ^{o}C; ν_{max}/cm^{-1} 3229 (NH), 1638 (C=O); δ_H (400 MHz, DMSO-d_6) 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, CH_3); δ_C (100 MHz, DMSO-d_6) 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 (*C*H$_3$); *m/z* (ESI$^-$) 412 ([M-H]$^-$); HRMS (ESI$^+$) $C_{24}H_{19}N_3NaO_4$, ([M+Na]$^+$) requires 436.1268; found 436.1254.

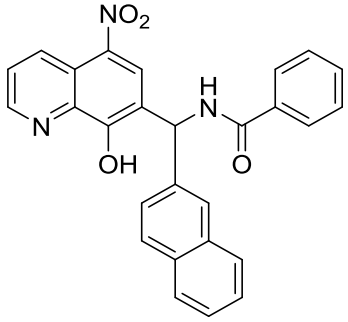
***N*-((8-Hydroxy-5-nitroquinolin-7-yl)(naphthalen-1-yl)methyl)benzamide S70**



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

mp 237 °C; ν_{max}/cm^{-1} 3386 (NH), 1635 (C=O); δ_H (400 MHz, DMSO-d_6) 9.47 - 9.55 (1 H, m, quinoline-*Ar*), 9.19 - 9.24 (1 H, m, quinoline-*Ar*), 9.01 - 9.05 (1 H, m, quinoline-*Ar*), 8.71 (1 H, s, quinoline-*Ar*), 8.08 - 8.13 (1 H, m, *Ar*), 7.98 - 8.02 (1 H, m, *Ar*), 7.88 - 7.97 (4 H, m, *Ar*), 7.67 (1 H, d, *J*=8.5 Hz, benzyl-*H*), 7.51 - 7.60 (4 H, m, *Ar*), 7.45 - 7.51 (3 H, m, *Ar*), 7.39 - 7.43 (1 H, m, *Ar*); δ_C (100 MHz, DMSO-d_6) 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$^-$) $C_{27}H_{18}N_3O_4$, ([M-H]$^-$) requires 448.1303; found 448.1301.

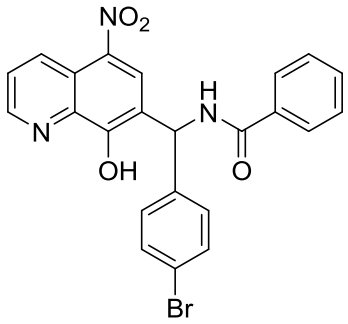
***N*-((8-Hydroxy-5-nitroquinolin-7-yl)(naphthalen-2-yl)methyl)benzamide S71**



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

mp 216 - 217 °C; ν_{max}/cm^{-1} 3284 (NH), 1630 (C=O); δ_H (400 MHz, DMSO-d_6) 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*); δ_C (100 MHz, DMSO-d_6) 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$^-$) $C_{27}H_{18}N_3O_4$, ([M-H]$^-$) requires 448.1303; found 448.1302.

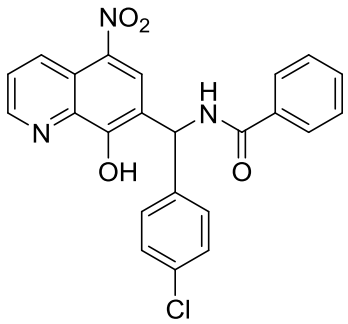
***N*-((4-Bromophenyl)(8-hydroxy-5-nitroquinolin-7-yl)methyl)benzamide S72**



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; ν_{max}/cm^{-1} 3222 (NH), 1637 (C=O); δ_H (400 MHz, DMSO-d_6) 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*); δ_C (100 MHz, DMSO-d_6) 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$^-$) $C_{23}H_{15}BrN_3O_4$, ([M-H]$^-$) requires 476.0251; found 476.0247.

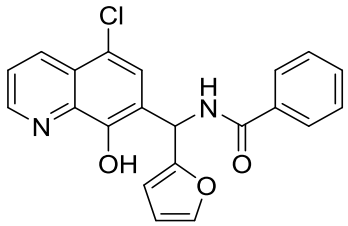
***N*-((4-Chlorophenyl)(8-hydroxy-5-nitroquinolin-7-yl)methyl)benzamide S73**



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; ν_{max}/cm^{-1} 3271 (NH), 1640 (C=O); δ_H (400 MHz, DMSO-d_6) 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*); δ_C (100 MHz, DMSO-d_6) 167.0 (*C*=O), 158.8, 149.8, 140.8, 137.6, 135.1, 134.9, 134.0, 132.8, 132.4, 130.2, 129.3, 129.2, 128.9, 128.5, 126.2, 124.1, 122.7, 50.6 (benzyl-*C*); *m*/*z* (ESI$^-$) 432 ([M-H]$^-$); HRMS (ESI$^-$) $C_{23}H_{15}ClN_3O_4$, ([M-H]$^-$) requires 432.0757; found 476.0751.

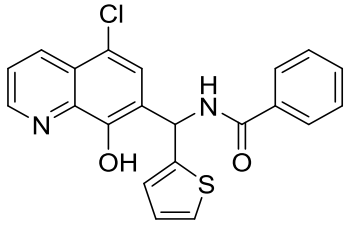
***N*-((5-Chloro-8-hydroxyquinolin-7-yl)(furan-2-yl)methyl)benzamide S74**



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

mp 245 °C; ν_{max}/cm^{-1} 3309 (NH), 1639 (C=O), 691 (C-Cl); δ_H (400 MHz, DMSO-d_6) 10.49 (1 H, br. s., N*H*), 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*); δ_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$^+$) $C_{21}H_{15}ClIN_2NaO_3$, ([M+Na]$^+$) requires 401.0652; found 401.0663.

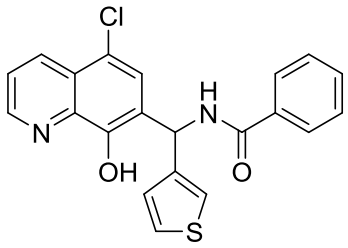
***N*-((5-Chloro-8-hydroxyquinolin-7-yl)(thiophen-2-yl)methyl)benzamide S75**



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

mp 237 °C; ν_{max}/cm^{-1} 3325 (NH), 1640 (C=O), 700 (C-Cl); δ_H (400 MHz, DMSO-d_6) 10.53 (1 H, br. s., N*H*), 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*); δ_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$^+$) $C_{21}H_{15}ClIN_2NaO_2S$, ([M+Na]$^+$) requires 417.0435; found 417.0423.

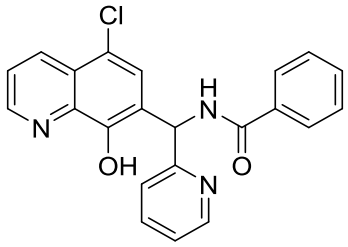
***N*-((5-Chloro-8-hydroxyquinolin-7-yl)(thiophen-3-yl)methyl)benzamide S76**



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 ^{o}C; ν_{max}/cm^{-1} 3309 (NH), 1636 (C=O), 710 (C-Cl); δ_H (400 MHz, DMSO-d_6) 10.42 (1 H, br. s., N*H*), 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_C (100 MHz, DMSO-d_6) 166.7 (*C*=O), 150.1, 150.0, 143.5, 139.6, 135.1, 133.4, 132.2, 129.1, 128.5, 128.1, 127.5, 127.4, 126.2, 125.8, 123.8, 122.9, 119.4, 47.5 (benzyl-*C*); *m/z* (ESI$^-$) 393 ([M-H]$^-$); HRMS (ESI$^+$) $C_{21}H_{15}ClIN_2NaO_2S$, ([M+Na]$^+$) requires 417.0435; found 417.0423.

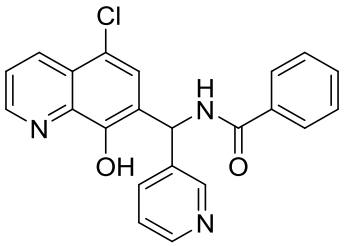
***N*-((5-Chloro-8-hydroxyquinolin-7-yl)(pyridin-2-yl)methyl)benzamide S77**



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 ^{o}C; ν_{max}/cm^{-1} 3306 (NH), 1646 (C=O); δ_H (400 MHz, DMSO-d_6) 10.46 (1 H, br. s., N*H*), 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_C (100 MHz, DMSO-d_6) 166.8 (*C*=O), 160.7, 150.7, 149.9, 139.6, 137.9, 135.0, 133.3, 132.3, 129.2, 128.5, 128.3, 128.0, 125.9, 125.3, 123.9, 123.3, 122.8, 119.2, 52.8 (benzyl-*C*); *m/z* (ESI$^-$) 388 ([M-H]$^-$); HRMS (ESI$^+$) $C_{22}H_{17}ClIN_3O_2$, ([M+H]$^+$) requires 390.1004; found 390.0997.

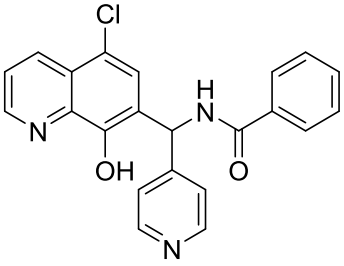
***N*-((5-Chloro-8-hydroxyquinolin-7-yl)(pyridin-3-yl)methyl)benzamide S78**



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 **S78** (495 mg, 63 %) as a white powder.

mp 266 - 227 °C; ν_{max}/cm^{-1} 3309 (NH), 1638 (C=O), 700 (C-Cl); δ_H (400 MHz, DMSO-d_6) 10.57 (1 H, br. s., N*H*), 9.28 - 9.45 (1 H, m, quinoline-*Ar*), 8.88 - 9.02 (1 H, m, quinoline-*Ar*), 8.58 (1 H, s, quinoline-*Ar*), 8.43 - 8.53 (2 H, m, *Ar*), 7.85 - 8.02 (3 H, m, *Ar*), 7.65 - 7.81 (2 H, m, *Ar*), 7.44 - 7.62 (3 H, m, *Ar*), 7.29 - 7.41 (1 H, m, *Ar*), 7.02 (1 H, d, *J*=8.5 Hz, benzyl-*H*); δ_C (100 MHz, DMSO-d_6) 167.0 (*C*=O), 150.5, 150.2, 149.5, 149.1, 139.5, 137.8, 135.9, 134.9, 133.4, 132.4, 129.2, 128.5, 127.1, 126.0, 125.0, 124.5, 124.0, 119.7, 49.5 (benzyl-*C*); *m*/*z* (ESI$^-$) 388 ([M-H]$^-$); HRMS (ESI$^+$) $C_{22}H_{16}ClN_3NaO_2$, ([M+Na]$^+$) requires 412.0823; found 412.0816.

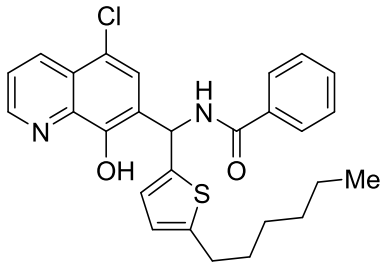
***N*-((5-Chloro-8-hydroxyquinolin-7-yl)(pyridin-4-yl)methyl)benzamide S79**



Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 4-pyridinecarboxaldehyde (376µL, 4.0 mmol) gave **S79** (76 mg, 10 %) as a white powder.

mp 265 °C; ν_{max}/cm^{-1} 3286 (NH), 1634 (C=O), 700 (C-Cl); δ_H (400 MHz, DMSO-d_6) 10.64 (1 H, br. s., N*H*), 9.31 - 9.41 (1 H, m, quinoline-*Ar*), 8.96 - 9.01 (1 H, m, quinoline-*Ar*), 8.52 - 8.56 (2 H, m, *Ar*), 8.46 - 8.51 (1 H, m, *Ar*), 7.92 - 7.99 (2 H, m, *Ar*), 7.81 (1 H, s) 7.71 - 7.78 (1 H, m, *Ar*), 7.54 - 7.60 (1 H, m, *Ar*), 7.44 - 7.53 (2 H, m, *Ar*), 7.30 - 7.35 (2 H, m, *Ar*), 7.01 (1 H, d, *J*=8.5 Hz, benzyl-*H*); δ_C (100 MHz, DMSO-d_6) 167.2 (*C*=O), 151.1, 150.8, 150.7, 150.2, 139.6, 134.8, 133.4, 132.4, 129.2, 128.5, 127.4, 126.1, 124.4, 124.1, 123.1, 119.6, 50.3 (benzyl-*C*); *m*/*z* (FI$^+$) 389 ([M]$^+$); HRMS (FI$^+$) $C_{22}H_{16}ClN_3O_2$, ([M]$^+$) requires 389.0931; found 389.0926.

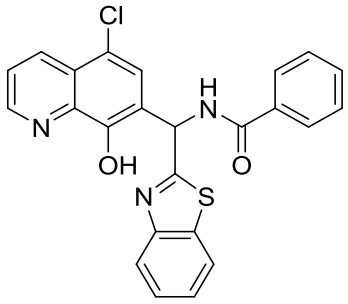
***N*-((5-Chloro-8-hydroxyquinolin-7-yl)(5-hexylthiophen-2-yl)methyl)benzamide S80**



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; ν_{max}/cm^{-1} 3291 (NH), 1636 (C=O); δ_H (400 MHz, DMSO-d_6) 10.50 (1 H, br. s., N*H*), 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, CH_2), 1.43 - 1.62 (2 H, m, CH_2), 1.10 - 1.37 (6 H, m), 0.73 - 0.90 (3 H, m, CH_3); δ_C (100 MHz, DMSO-d_6) 166.6 (*C*=O), 150.3, 150.1, 145.4, 134.6, 139.5, 134.9, 133.4, 132.4, 132.1, 129.2, 128.5, 127.4, 126.0, 125.6, 124.7, 124.0, 119.5, 47.1 (benzyl-*C*), 32.0, 31.8, 30.2, 29.0, 22.9, 14.8; *m/z* (FI) 478 ([M]$^+$); HRMS (FI) $C_{27}H_{27}ClN_2O_2S$, ([M]$^+$) requires 478.1482; found 478.1486.

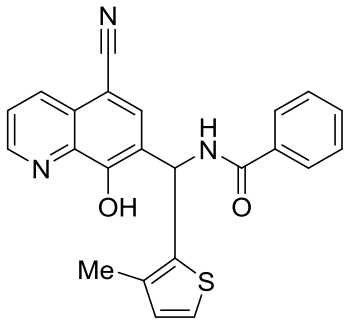
***N*-(Benzo[d]thiazol-2-yl(5-chloro-8-hydroxyquinolin-7-yl)methyl)benzamide S81**



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

mp 212 °C; ν_{max}/cm^{-1} 3255 (NH), 1640 (amide C=O); δ_H (400 MHz, DMSO-d_6) 10.79 (1 H, br. s., N*H*), 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*); δ_C (100 MHz, DMSO-d_6) 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$^+$) $C_{24}H_{16}ClIN_3NaO_2S$, ([M+Na]$^+$) requires 468.0544; found 468.0636.

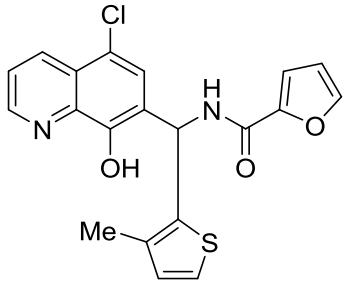
***N*-((5-Cyano-8-hydroxyquinolin-7-yl)(3-methylthiophen-2-yl)methyl)benzamide S82**



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; ν_{max}/cm^{-1} 3231 (NH), 2218 (nitrile), 1630 (C=O); δ_H (400 MHz, DMSO-d_6) 9.30 - 9.41 (1 H, m, quinoline-*Ar*), 8.99 - 9.09 (1 H, m, quinoline-*Ar*), 8.43 - 8.51 (1 H, m, quinoline-*Ar*), 8.35 (1 H, s, quinoline-*Ar*), 7.90 - 7.98 (2 H, m, *Ar*), 7.82 - 7.87 (1 H, m, *Ar*), 7.53 - 7.61 (1 H, m, *Ar*), 7.45 - 7.52 (2 H, m, *Ar*), 7.28 - 7.32 (1 H, m, *Ar*), 7.17 (1 H, d, *J*=8.0 Hz, benzyl-*H*), 6.90 - 6.96 (1 H, m, *Ar*), 2.18 (3 H, s, C*H*$_3$); δ_C (100 MHz, DMSO-d_6) 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, 123.8, 118.0, 97.9 (nitrile), 45.2 (benzyl-*C*), 14.0 (*C*H$_3$); *m*/*z* (ESI$^+$) 400 ([M+H]$^+$); HRMS (ESI$^+$) $C_{23}H_{18}O_2N_3S$, ([M+H]$^+$) requires 400.1114; found 400.1110.

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

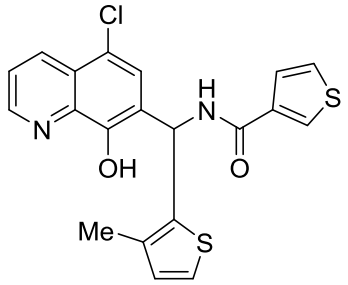


Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), 2-furancarboxamide (222 mg, 2.0 mmol) and 3-methyl-2-thiophenecarboxaldehyde (431µL, 4.0 mmol) gave **S83** (208 mg, 26 %) as an off-white powder.

mp 157 °C; ν_{max}/cm^{-1} 3305 (NH), 1658 (amide C=O); δ_H (400 MHz, DMSO-d_6) 10.51 (1 H, br. s., N*H*), 9.24 - 9.31 (1 H, m, quinoline-*Ar*), 8.92 - 9.00 (1 H, m, quinoline-*Ar*), 8.44 - 8.54 (1 H, m, quinoline-*Ar*), 7.83 - 7.93 (2 H, m, *Ar*), 7.67 - 7.78 (1 H, m, *Ar*), 7.24 - 7.30 (2 H, m, *Ar*), 7.09 (1 H, d, *J*=8.5 Hz, benzyl-*H*), 6.86 - 6.92 (1 H, m, *Ar*), 6.60 - 6.67 (1 H, m, *Ar*), 2.14 (3 H, s, C*H*$_3$); δ_C (100 MHz, DMSO-d_6) 157.8 (*C*=O), 150.4, 150.1, 148.1, 146.3, 139.5, 135.1, 133.4, 131.3, 129.8, 129.1, 127.3, 126.0,

125.4, 124.0, 119.2, 115.0, 112.7, 45.1 (benzyl-*C*), 14.4 (*C*H$_3$); *m*/*z* (ESI$^+$) 399 ([M+H]$^+$); HRMS (ESI$^+$) $C_{20}H_{15}ClIN_2NaO_3S$, ([M+Na]$^+$) requires 421.0384; found 421.0370.

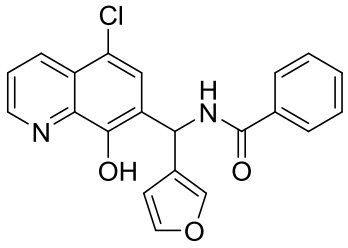
***N*-((5-Chloro-8-hydroxyquinolin-7-yl)(3-methylthiophen-2-yl)methyl)thiophene-3-carboxamide S84**



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 ^{o}C; ν_{max}/cm^{-1} 3303 (NH), 1638 (C=O); δ_H (400 MHz, DMSO-d_6) 10.48 (1 H, br. s., N*H*), 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, C*H*$_3$); δ_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 (*C*H$_3$); *m*/*z* (ESI$^+$) 415 ([M+H]$^+$); HRMS (ESI$^+$) $C_{20}H_{15}ClIN_2NaO_2S_2$, ([M+Na]$^+$) requires 437.0156; found 437.0141.

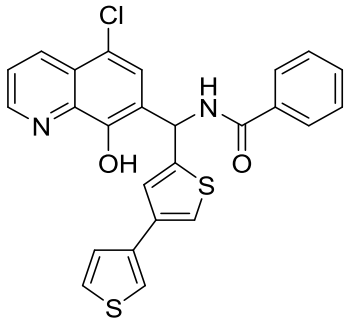
***N*-((5-Chloro-8-hydroxyquinolin-7-yl)(furan-3-yl)methyl)benzamide S85**



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 ^{o}C; ν_{max}/cm^{-1} 3323 (NH), 1638 (C=O); δ_H (400 MHz, DMSO-d_6) 10.41 (1 H, br. s., N*H*), 9.20 - 9.26 (1 H, m, quinoline-*Ar*), 8.95 - 9.00 (1 H, m, quinoline-*Ar*), 8.46 - 8.51 (1 H, m, quinoline-*Ar*), 7.90 - 7.99 (3 H, m, *Ar*), 7.69 - 7.76 (1 H, m, *Ar*), 7.64 (1 H, s, *Ar*), 7.44 - 7.58 (4 H, m, *Ar*), 6.90 (1 H, d, *J*=8.5 Hz, benzyl-*H*), 6.52 (1 H, s, *Ar*); δ_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, 125.4, 123.4, 119.0, 110.8, 43.6 (benzyl-*C*); *m*/*z* (ESI$^+$) 379 ([M+H]$^+$); HRMS (ESI$^+$) $C_{24}H_{15}ClIN_2NaO_3$, ([M+Na]$^+$) requires 401.0663; found 401.0652.

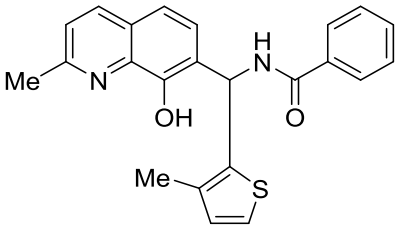
***N*-([3,3'-Bithiophen]-5-yl(5-chloro-8-hydroxyquinolin-7-yl)methyl)benzamide S86**



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

mp 213 °C; ν_{max}/cm^{-1} 3287 (NH), 1641 (C=O); δ_H (400 MHz, DMSO-d_6) 10.57 (1 H, br. s., N*H*), 9.41 - 9.60 (1 H, m, 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*), 7.92 - 7.99 (2 H, m, *Ar*), 7.72 - 7.78 (1 H, m, *Ar*), 7.65 - 7.72 (2 H, m, *Ar*), 7.47 - 7.61 (4 H, m, *Ar*), 7.42 - 7.47 (1 H, m, *Ar*), 7.26 (1 H, s, *Ar*), 7.20 (1 H, d, *J*=8.5 Hz, benzyl-*H*); δ_C (100 MHz, DMSO-d_6) 166.7 (*C*=O), 150.5, 150.1, 147.4, 139.6, 137.6, 137.3, 134.9, 133.4, 132.4, 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$^+$) $C_{25}H_{17}ClIN_2NaO_2S_2$, ([M+Na]$^+$) requires 499.0312; found 499.0294.

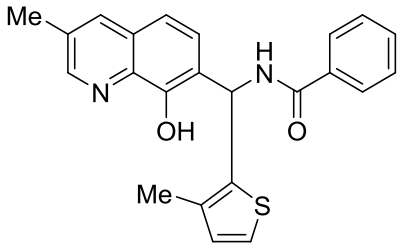
***N*-((8-Hydroxy-2-methylquinolin-7-yl)(3-methylthiophen-2-yl)methyl)benzamide S87**



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

mp 189 °C; ν_{max}/cm^{-1} 3289 (NH), 1631 (C=O); δ_H (400 MHz, DMSO-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); δ_C (100 MHz, DMSO-d_6) 166.1 (*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-*C*H$_3$), 14.1 (thiophene-*C*H$_3$); *m*/*z* (ESI$^+$) 389 ([M+H]$^+$); HRMS (ESI$^+$) $C_{23}H_{21}O_2N_2S$, ([M+H]$^+$) requires 389.1318; found 389.1310.

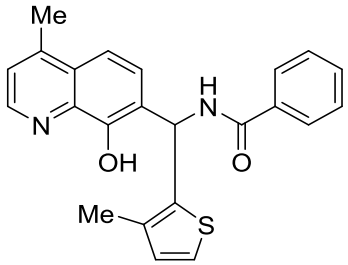
***N*-((8-Hydroxy-3-methylquinolin-7-yl)(3-methylthiophen-2-yl)methyl)benzamide S88**



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_{max}/cm^{-1} 3274 (NH), 1636 (C=O); δ_H (400 MHz, DMSO-d_6) 10.05 (1 H, br. s, N*H*), 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*H*$_3$), 2.16 (3 H, s, thiophene-C*H*$_3$); δ_C (100 MHz, DMSO-d_6) 166.0 (*C*=O), 150.5, 150.3, 140.5, 136.8, 135.0, 134.7, 134.3, 131.7, 131.5, 130.8, 128.7, 128.6, 128.1, 127.1, 123.7, 123.3, 116.9, 45.6 (benzyl-*C*), 18.7 (quinoline-*C*H$_3$), 14.1 (thiophene-*C*H$_3$); *m/z* (ESI$^-$) 387 ([M-H]$^-$); HRMS (ESI$^+$) $C_{23}H_{20}N_2NaO_2S$, ([M+Na]$^+$) requires 411.1138; found 411.1137.

***N*-((8-Hydroxy-4-methylquinolin-7-yl)(3-methylthiophen-2-yl)methyl)benzamide S89**

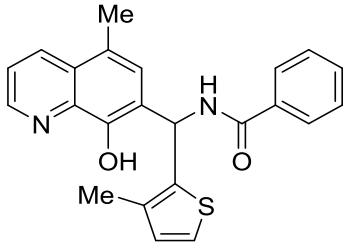


Following general procedure 1, **S5** (114 mg, 0.72 mmol), benzamide (87 mg, 0.72 mmol) and 3-methyl-2-thiophenecarboxaldehyde (155 µL, 4.0 mmol) gave **S89** (142 mg, 51 %) as a light-brown powder after purification *via* flash column chromatography (10 % - 20 % EtOAc, cyclohexane).

mp 174 °C; ν_{max}/cm^{-1} 3294 (NH), 1637 (C=O); δ_H (400 MHz, DMSO-d_6) 10.03 (1 H, br. s, N*H*), 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-C*H*$_3$), 2.18 (3 H, s, thiophene-C*H*$_3$); δ_C (100 MHz, DMSO-d_6) 166.1 (*C*=O), 150.6, 148.3, 145.0, 140.2, 138.1,

134.7, 134.4, 131.7, 130.8, 129.4, 128.6, 128.1, 126.6, 124.3, 123.4, 122.8, 114.0, 45.6 (benzyl-*C*), 18.8 (quinoline-*C*H_3), 14.1 (thiophene-*C*H_3); *m/z* (ESI$^-$) 387 ([M-H]$^-$); HRMS (ESI$^+$) $C_{23}H_{20}N_2NaO_2S$, ([M+Na]$^+$) requires 411.1138; found 411.1142.

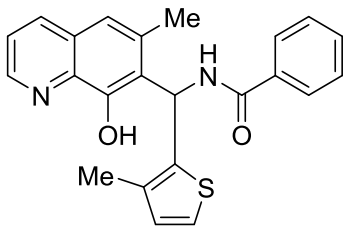
***N*-((8-Hydroxy-5-methylquinolin-7-yl)(3-methylthiophen-2-yl)methyl)benzamide S90**



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; ν_{max}/cm^{-1} 3299 (NH), 1638 (C=O); δ_H (400 MHz, DMSO-d_6) 9.84 (1 H, br. s., N*H*), 9.24 - 9.34 (1 H, m, quinoline-*Ar*), 8.81 - 8.95 (1 H, m, quinoline-*Ar*), 8.31 - 8.48 (1 H, m, quinoline-*Ar*), 7.85 - 8.02 (2 H, m, *Ar*), 7.58 - 7.64 (2 H, m, *Ar*), 7.51 - 7.57 (1 H, m, *Ar*), 7.43 - 7.50 (2 H, m, *Ar*), 7.21 - 7.27 (1 H, m, *Ar*), 7.11 - 7.18 (1 H, m, benzyl-*H*), 6.84 - 6.93 (1 H, m, *Ar*), 2.56 (3 H, s, quinoline-CH_3), 2.17 (3 H, s, thiophene-CH_3); δ_C (100 MHz, DMSO-d_6) 166.1 (*C*=O), 148.3, 140.3, 138.7, 134.7, 133.5, 131.7, 130.8, 128.7, 128.7, 128.1, 127.2, 127.0, 123.6, 123.3, 122.0, 45.6 (benzyl-*C*), 18.4 (quinoline-*C*H_3), 14.1 (thiophene-*C*H_3); *m/z* (ESI$^+$) 389 ([M+H]$^+$); HRMS (ESI$^+$) $C_{23}H_{20}N_2NaO_2S$, ([M+Na]$^+$) requires 411.1138; found 411.1131.

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

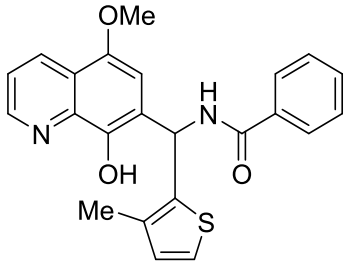


Following general procedure 1, **S7** (289 mg, 1.82 mmol), benzamide (220 mg, 1.82 mmol) and 3-methyl-2-thiophenecarboxaldehyde (392 µL, 3.64 mmol) gave **S91** (403 mg, 57 %) as a light-brown powder after purification *via* flash column chromatography (10 % - 20 % EtOAc, cyclohexane).

mp 211 °C; ν_{max}/cm^{-1} 2980 (NH), 1660 (C=O); δ_H (400 MHz, DMSO-d_6) 8.96 - 9.03 (1 H, m, quinoline-*Ar*), 8.88 - 8.94 (1 H, m, quinoline-*Ar*), 8.26 - 8.38 (1 H, m, quinoline-*Ar*), 7.80 - 7.90 (2 H, m, *Ar*), 7.61 - 7.68 (2 H, m, *Ar*), 7.52 - 7.58 (1 H, m, *Ar*), 7.43 - 7.51 (2 H, m, *Ar*), 7.29 - 7.37 (1 H, m, *Ar*), 7.23 - 7.28 (1 H, m, benzyl-*H*), 6.81 - 6.90 (1 H, m, *Ar*), 3.18 (3 H, s, quinoline-CH_3), 2.29 (3 H, s, thiophene-CH_3); δ_C (100 MHz, DMSO-d_6) 165.4 (*C*=O), 153.2, 149.4, 137.8, 137.5, 135.9, 135.0, 134.4, 132.1,

132.0, 130.7, 129.0, 128.3, 127.7, 124.0, 123.7, 122.3, 118.0, 47.3 (benzyl-*C*), 15.9 (quinoline-*C*H_3), 14.3 (thiophene-*C*H_3); *m/z* (ESI$^+$) 389 ([M+H]$^+$); HRMS (ESI$^+$) $C_{23}H_{21}O_2N_2S$, ([M+H]$^+$) requires 389.1318; found 389.1310.

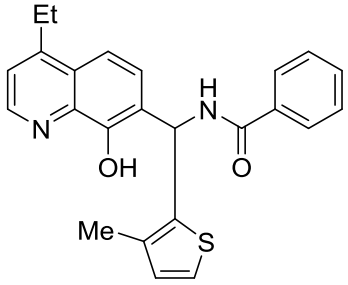
***N*-((8-Hydroxy-5-methoxyquinolin-7-yl)(3-methylthiophen-2-yl)methyl)benzamide S92**



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

mp 254 °C; ν_{max}/cm^{-1} 3325 (NH), 1636 (C=O); δ_H (400 MHz, DMSO-d_6) 9.53 (1 H, br. s., N*H*), 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, OCH_3), 2.20 (3 H, s, CH_3); δ_C (100 MHz, DMSO-d_6) 166.1 (*C*=O), 149.3, 146.9, 143.8, 140.2, 138.7, 134.8, 134.5, 131.7, 130.9, 130.8, 128.7, 128.1, 123.8, 123.4, 121.6, 120.0, 105.6, 56.4 (O*C*H_3), 45.5 (benzyl-*C*), 14.1 (*C*H_3); *m/z* (ESI$^+$) 405 ([M+H]$^+$); HRMS (ESI$^+$) $C_{23}H_{20}N_2NaO_3S$, ([M+Na]$^+$) requires 427.1087; found 427.1082.

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

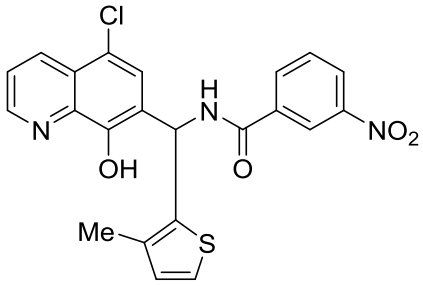


Following general procedure, **S13** (277 mg, 1.6 mmol), benzamide (194 mg, 1.6 mmol) and 3-methyl-2-thiophenecarboxaldehyde (345 µL, 3.2 mmol) gave **S93** (367 mg, 57 %) as a light-brown powder after purification *via* flash column chromatography (10 % - 20 % EtOAc, cyclohexane).

mp 178 °C; ν_{max}/cm^{-1} 3280 (NH), 1638 (C=O); δ_H (400 MHz, DMSO-d_6) 9.98 (1 H, br. s., N*H*), 9.26 - 9.40 (1 H, m, quinoline-*Ar*), 8.71 - 8.83 (1 H, m, quinoline-*Ar*), 7.90 - 7.98 (2 H, m, *Ar*), 7.73 - 7.80 (1 H, m, *Ar*), 7.58 - 7.64 (1 H, m, *Ar*), 7.51 - 7.57 (1 H, m, *Ar*), 7.40 - 7.50 (2 H, m, *Ar*), 7.23 - 7.29 (1 H, m, *Ar*), 7.15 (1 H, d, *J*=8.0 Hz, benzyl-*H*), 6.87 - 6.94 (1 H, m, *Ar*), 3.09 (2 H, q,

J=7.5 Hz, C*H*$_2$CH$_3$), 2.18 (3 H, s, C*H*$_3$), 1.32 (3 H, t, *J*=7.5 Hz, CH$_2$C*H*$_3$); δ_C (100 MHz, DMSO-d_6) 166.1 (*C*=O), 150.7, 150.4, 148.5, 140.2, 138.3, 134.7, 134.4, 131.7, 130.8, 128.6, 128.1, 127.2, 126.7, 124.0, 123.4, 120.9, 113.6, 45.6 (benzyl-*C*), 24.9 (*C*H$_2$CH$_3$), 14.5 (*C*H$_3$), 14.1 (CH$_2$*C*H$_3$); *m/z* (ESI$^-$) 401 ([M-H]$^-$); HRMS (ESI$^+$) $C_{24}H_{23}O_2N_2S$, ([M+H]$^+$) requires 403.1475; found 403.1469.

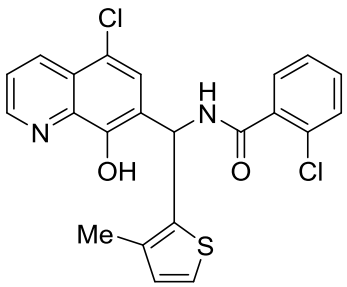
_N_-((5-Chloro-8-hydroxyquinolin-7-yl)(3-methylthiophen-2-yl)methyl)-3-nitrobenzamide S94



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 ^{o}C; ν_{max}/cm^{-1} 3278 (NH), 1646 (C=O); δ_H (400 MHz, DMSO-d_6) 10.55 (1 H, br. s., N*H*), 9.69 - 9.79 (1 H, m, quinoline-*Ar*), 8.92 - 9.01 (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*), 6.86 - 6.98 (1 H, m, *Ar*), 2.16 (3 H, s, C*H*$_3$); δ_C (100 MHz, DMSO-d_6) 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 (*C*H$_3$); *m/z* (ESI$^-$) 929 ([2M+Na]$^+$); HRMS (ESI$^+$) $C_{22}H_{16}ClIN_3O_4S$, ([M+Na]$^+$) requires 476.0442; found 476.0434.

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

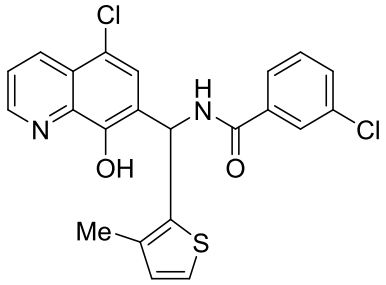


Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), 2-chlorobenzamide (311 mg, 2.0 mmol) and methyl 3-methyl-2-thiophenecarboxaldehyde (656 mg, 4.0 mmol) gave **S95** (290 mg, 33 %) as off-white powder.

mp 148 ^{o}C; ν_{max}/cm^{-1} 3297 (NH), 1647 (C=O); δ_H (400 MHz, DMSO-d_6) 10.51 (1 H, br. s., N*H*), 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*), 2.25 (3 H, s, C*H*$_3$); δ_C (100 MHz, DMSO-d_6) 166.3 (*C*=O), 150.3, 150.1, 139.4, 137.5, 135.2, 133.4, 131.7, 131.2, 130.8, 130.4, 129.8, 129.7, 129.1, 127.9,

127.0, 126.0, 125.4, 124.2, 124.0, 119.3, 45.4 (benzyl-*C*), 14.5 (*C*H$_3$); *m/z* (ESI$^-$) 441 ([M-H]$^-$); HRMS (ESI$^-$) $C_{22}H_{15}Cl_2N_2O_2S$, ([M-H]$^-$) requires 441.0237; found 441.0233.

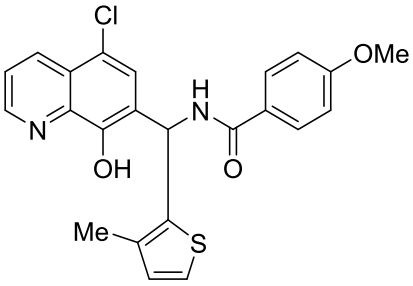
3-Chloro-*N*-((5-chloro-8-hydroxyquinolin-7-yl)(3-methylthiophen-2-yl)methyl)benzamide S96



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

mp 172 ^{o}C; ν_{max}/cm^{-1} 3300 (NH), 1642 (C=O); δ_H (400 MHz, DMSO-d_6) 10.51 (1 H, br. s., N*H*), 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, C*H*$_3$); δ_C (100 MHz, DMSO-d_6) 169.4 (*C*=O), 154.9, 154.4, 143.9, 143.8, 141.0, 139.5, 138.3, 137.8, 136.5, 135.7, 135.5, 132.5, 131.7, 131.5, 130.4, 129.6, 128.4, 128.4, 123.6, 50.2 (benzyl-*C*), 18.7 (*C*H$_3$); *m/z* (ESI$^-$) 441 ([M-H]$^-$); HRMS (ESI$^-$) $C_{22}H_{15}Cl_2N_2O_4S$, ([M-H]$^-$) requires 441.0237; found 441.0241.

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

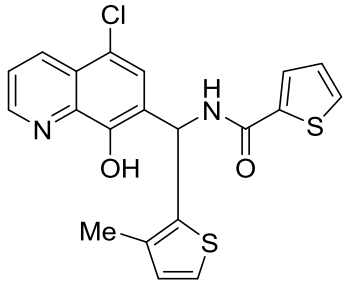


Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), 4-methoxybenzamide (302 mg, 2.0 mmol) and methyl 3-methyl-2-thiophenecarboxaldehyde (431 µL, 4.0 mmol) gave **S97** (339 mg, 39 %) as an off-white powder.

mp 163 - 164 ^{o}C; ν_{max}/cm^{-1} 3305 (NH), 1637 (C=O); δ_H (400 MHz, DMSO-d_6) 10.45 (1 H, br. s., N*H*), 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-C*H*$_3$), 2.14 (3 H, s, OC*H*$_3$); δ_C (100 MHz, DMSO-d_6) 165.9 (*C*=O), 162.6 (*C*OCH$_3$), 150.4, 150.0,

140.1, 139.4, 134.9, 133.4, 131.3, 130.4, 127.4, 127.0, 126.0, 125.8, 123.9, 123.9, 119.2, 114.3, 114.2, 56.2 (benzyl-*C*), 14.4 (*C*H_3); *m/z* (ESI$^+$) 899 ([2M+Na]$^+$); HRMS (ESI$^+$) $C_{23}H_{20}ClIN_2O_3S$, ([M+H]$^+$) requires 439.0878; found 439.0241.

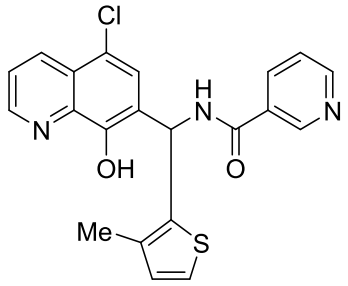
***N*-((5-Chloro-8-hydroxyquinolin-7-yl)(3-methylthiophen-2-yl)methyl)thiophene-2-carboxamide S98**



Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), thiophene-2-carboxamide (254 mg, 2.0 mmol) and methyl 3-methyl-2-thiophenecarboxaldehyde (431 µL, 4.0 mmol) gave **S98** (179 mg, 22 %) as a white powder.

mp 172 °C; ν_{max}/cm^{-1} 3302 (NH), 1634 (C=O); δ_H (400 MHz, DMSO-d_6) 10.51 (1 H, br. s., N*H*), 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, C*H*$_3$); δ_C (100 MHz, DMSO-d_6) 161.2 (*C*=O), 150.5, 150.1, 140.1, 139.5, 139.4, 135.2, 133.4, 132.2, 131.4, 129.7, 128.8, 127.2, 126.0, 125.5, 124.1, 124.0, 119.2, 45.6 (benzyl-*C*), 14.4 (*C*H_3); *m/z* (ESI$^+$) 415 ([M+H]$^+$); HRMS (ESI$^+$) $C_{20}H_{16}ClIN_2O_2S_2$, ([M+H]$^+$) requires 415.0336; found 415.0330.

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

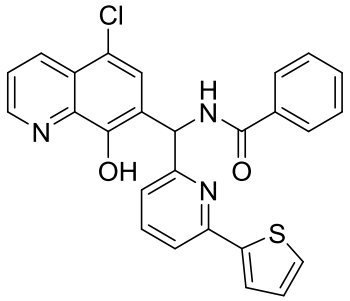


Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), nicotinamide (244 mg, 2.0 mmol) and 3-methyl-2-thiophenecarboxaldehyde (431 µL, 4.0 mmol) gave **S99** (303 mg, 37 %) as an off-white powder.

mp 210 °C; ν_{max}/cm^{-1} 3173 (NH), 1667 (C=O); δ_H (400 MHz, DMSO-d_6) 10.54 (1 H, br. s., N*H*), 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, C*H*$_3$); δ_C (100 MHz, DMSO-d_6) 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 (*C*H$_3$); *m*/*z* (ESI$^+$) 410 ([M+H]$^+$); HRMS (ESI$^+$) $C_{21}H_{16}ClIN_3NaO_2S$, ([M+Na]$^+$) requires 321.0554; found 432.0527.

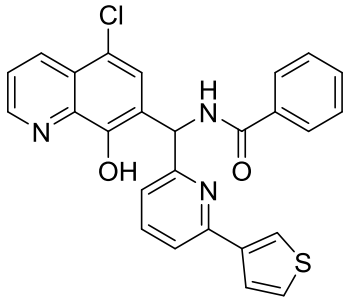
***N*-((5-Chloro-8-hydroxyquinolin-7-yl)(6-(thiophen-2-yl)pyridin-2-yl)methyl)benzamide S100**



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 ^{o}C; ν_{max}/cm^{-1} 3294 (NH), 1650 (amide C=O); δ_H (400 MHz, DMSO-d_6) 10.50 (1 H, br. s., N*H*), 9.22 - 9.36 (1 H, m, quinoline-*Ar*), 9.06 - 9.16 (1 H, m, quinoline-*Ar*), 8.92 - 9.02 (1 H, m, quinoline-*Ar*), 8.40 - 8.56 (1 H, m, quinoline-*Ar*), 7.91 - 8.00 (2 H, m, *Ar*), 7.88 (1 H, m, *Ar*), 7.77 - 7.85 (2 H, m, *Ar*), 7.68 - 7.75 (1 H, m, *Ar*), 7.47 - 7.67 (2 H, m, *Ar*), 7.24 - 7.32 (1 H, m, *Ar*), 7.09 - 7.21 (2 H, m, *Ar*), 6.93 - 7.04 (1 H, m, *Ar*); δ_C (100 MHz, DMSO-d_6) 160.2 (*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* (EI$^+$) 471 ([M]$^+$); HRMS (EI$^+$) $C_{26}H_{18}N_3O_2SCl$, ([M]$^+$) requires 471..0808; found 471.0800.

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

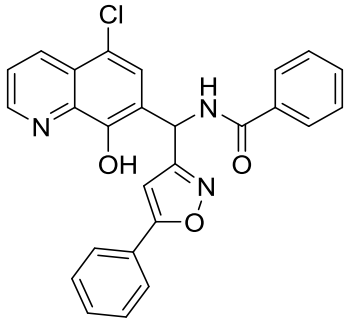


Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 6-(3-thienyl)pyridine-2-carboxaldehyde (757 mg, 4.0 mmol) gave **S101** (508 mg, 54 %) as an off-white powder.

mp 230 ^{o}C; ν_{max}/cm^{-1} 3299 (NH), 1634 (C=O); δ_H (400 MHz, DMSO-d_6) 10.60 (1 H, br. s., N*H*), 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*); δ_C (100 MHz, DMSO-d_6) 166.8 (*C*=O), 150.4, 150.1, 146.0, 143.4, 139.6, 134.8, 134.5,

133.5, 132.4, 130.0, 129.2, 128.5, 128.4, 127.4, 127.3, 126.1, 126.0, 125.2, 124.2, 124.1, 119.6, 47.2 (benzyl-*C*); *m*/*z* (EI^+) 471 ($[M]^+$); HRMS (EI^+) $C_{26}H_{18}ClN_3O_2S$, ($[M]^+$) requires 471.0808; found 471.0811.

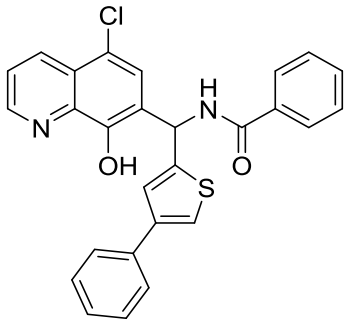
***N*-((5-Chloro-8-hydroxyquinolin-7-yl)(5-phenylisoxazol-3-yl)methyl)benzamide S102**



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; ν_{max}/cm^{-1} 3278 (NH), 1652 (C=O); δ_H (400 MHz, DMSO-d_6) 10.62 (1 H, br. s., N*H*), 9.47 - 9.59 (1 H, m, quinoline-*Ar*), 9.24 - 9.32 (1 H, m, quinoline-*Ar*), 8.96 - 9.03 (1 H, m, quinoline-*Ar*), 8.45 - 8.56 (1 H, m, *Ar*), 7.92 - 7.99 (2 H, m, *Ar*), 7.82 - 7.89 (2 H, m, *Ar*), 7.71 - 7.80 (1 H, m, *Ar*), 7.54 - 7.61 (1 H, m, *Ar*), 7.46 - 7.54 (5 H, m, *Ar*), 7.12 (1 H, d, *J*=8.5 Hz, benzyl-*H*), 7.07 (1 H, s, *Ar*); δ_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^+) $C_{26}H_{18}ClN_3NaO_3$, ($[M+Na]^+$) requires 478.0929; found 478.0924.

***N*-((5-Chloro-8-hydroxyquinolin-7-yl)(4-phenylthiophen-2-yl)methyl)benzamide S103**

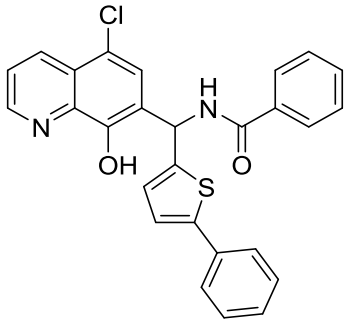


Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 4-phenylthiophene-2-carboxaldehyde (753 mg, 4.0 mmol) gave **S103** (481 mg, 51 %) as an off-white powder.

mp 237 °C; ν_{max}/cm^{-1} 3271 (NH), 1638 (C=O); δ_H (400 MHz, DMSO-d_6) 10.59 (1 H, br. s., N*H*), 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*); δ_C (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^+) $C_{27}H_{19}ClN_2O_2S$, ($[M]^+$) requires 470.0856; found 470.0863.

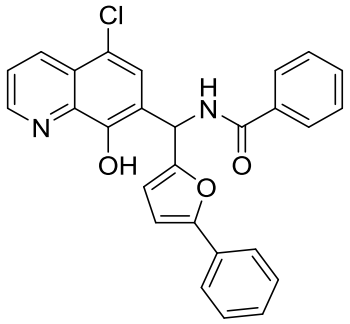
***N*-((5-Chloro-8-hydroxyquinolin-7-yl)(5-phenylthiophen-2-yl)methyl)benzamide S104**



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); δ_H (400 MHz, DMSO-d_6) 10.60 (1 H, br. s., N*H*), 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*); δ_C (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^+) $C_{27}H_{19}ClN_2NaO_2S$, ($[M+Na]^+$) requires 493.0748; found 493.0740.

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

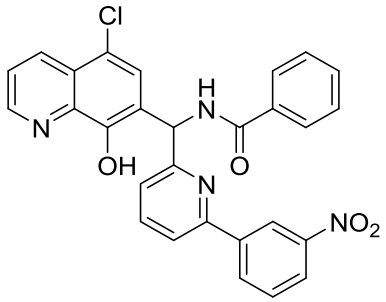


Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 5-phenyl-2-furaldehyde (689 mg, 4.0 mmol) gave **S105** (508 mg, 56 %) as a white powder.

mp 238 °C; ν_{max}/cm^{-1} 3290 (NH), 1635 (C=O); δ_H (400 MHz, DMSO-d_6) 10.56 (1 H, br. s., N*H*), 9.39 - 9.53 (1 H, m, quinoline-*Ar*), 8.93 - 9.02 (1 H, m, quinoline-*Ar*), 8.43 - 8.55 (1 H, m, quinoline-*Ar*), 7.91 - 8.01 (3 H, m, *Ar*), 7.69 - 7.78 (1 H, m, *Ar*), 7.61

- 7.68 (2 H, m, *Ar*), 7.53 - 7.59 (1 H, m, *Ar*), 7.45 - 7.52 (2 H, m, *Ar*), 7.33 - 7.43 (2 H, m, *Ar*), 7.19 - 7.30 (1 H, m, *Ar*), 7.07 (1 H, d, *J*=8.5 Hz, benzyl-*H*), 6.83 - 6.92 (1 H, m, *Ar*); δ_C (100 MHz, DMSO-d_6) 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$^+$) $C_{27}H_{19}ClN_2NaO_3$, ([M+Na]$^+$) requires 477.0976; found 477.0961.

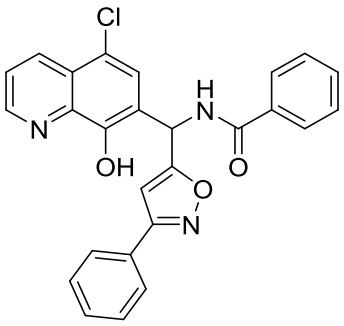
***N*-((5-Chloro-8-hydroxyquinolin-7-yl)(6-(3-nitrophenyl)pyridin-2-yl)methyl)benzamide S106**



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 ^{o}C; ν_{max}/cm^{-1} 3274 (NH), 1647 (C=O); δ_H (400 MHz, DMSO-d_6) 10.54 (1 H, br. s., N*H*), 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-d_6) 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$^-$) $C_{28}H_{19}ClN_4NaO_4$, ([M+H]$^+$) requires 533.0987; found 533.0979.

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

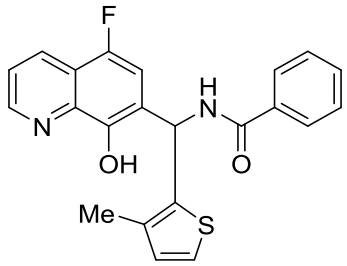


Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 3-phenylisoxazole-5-carboxaldehyde (693 mg, 4.0 mmol) gave **S107** (450 mg, 49 %) as a white powder.

mp 260 ^{o}C; ν_{max}/cm^{-1} 3290 (NH), 1644 (C=O); δ_H (400 MHz, DMSO-d_6) 10.75 (1 H, br. s., N*H*), 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*); δ_C (100 MHz, DMSO-d_6) 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^+) $C_{26}H_{18}ClN_3O_3$, ($[M]^+$) requires 455.1037; found 455.0306.

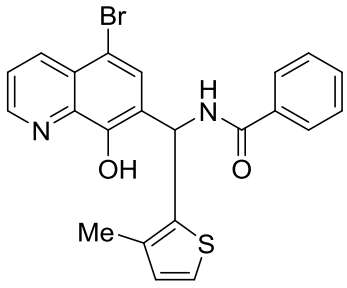
***N*-((5-Fluoro-8-hydroxyquinolin-7-yl)(3-methylthiophen-2-yl)methyl)benzamide S108**



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; ν_{max}/cm^{-1} 3301 (NH), 1639 (C=O); δ_H (400 MHz, DMSO-d_6) 10.14 (1 H, br. s, N*H*), 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_3); δ_C (100 MHz, DMSO-d_6) 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 (*C*H_3); *m/z* (ESI^-) 391 ($[M-H]^-$); HRMS (ESI^+) $C_{22}H_{17}FN_2NaO_2S$, ($[M+Na]^+$) requires 415.0873; found 415.0887.

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

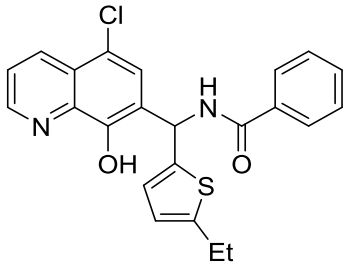


Following general procedure 1, 5-bromo-8-hydroxyquinoline (448 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 3-methyl-2-thiophenecarboxaldehyde (431 µL, 4.0 mmol) gave **S109** (186 mg, 21 %) as an off-white powder.

mp 152 °C; ν_{max}/cm^{-1} 3304 (NH), 1639 (C=O); δ_H (400 MHz, DMSO-d_6) 10.53 (1 H, br. s., N*H*), 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-

H), 6.90 (1 H, m, *Ar*), 2.15 (3 H, s, C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 166.5 (*C*=O), 151.1, 150.1, 139.9, 139.7, 135.9, 134.9, 132.3, 131.4, 130.8, 129.1, 128.5, 127.3, 126.2, 124.3, 124.0, 109.1, 45.7 (benzyl-*C*), 14.4 (*C*H$_3$); *m/z* (FI) 452 ([M]); HRMS (FI) $C_{22}H_{17}BrN_2O_2S$, ([M]) requires 452.0194; found 452.0199.

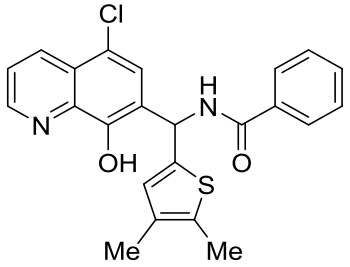
***N*-((5-Chloro-8-hydroxyquinolin-7-yl)(5-ethylthiophen-2-yl)methyl)benzamide S110**



Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 5-ethyl-2-thiophenecarboxaldehyde (500 µL, 4.0 mmol) gave **S110** (362 mg, 43 %) as a light-brown powder.

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

***N*-((5-Chloro-8-hydroxyquinolin-7-yl)(4,5-dimethylthiophen-2-yl)methyl)benzamide S111**

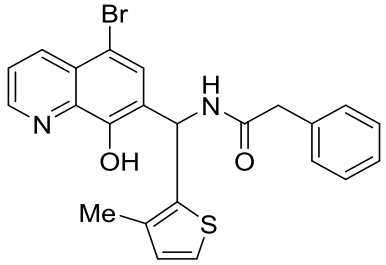


Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 4,5-dimethylthiophene-2-carboxaldehyde (475 µL, 4.0 mmol) gave **S111** (273 mg, 32 %) as an off-white powder.

mp 239 °C; ν_{max}/cm^{-1} 3283 (NH), 1637 (C=O); δ_H (400 MHz, DMSO-d_6) 10.47 (1 H, br. s., N*H*), 9.26 - 9.45 (1 H, m, quinoline-*Ar*), 8.91 - 9.05 (1 H, m, quinoline-*Ar*), 8.39 - 8.56 (1 H, m, quinoline-*Ar*), 7.99 (1 H, s, *Ar*), 7.88 - 7.96 (2 H, m, *Ar*), 7.68 - 7.78 (1 H, m, *Ar*), 7.52 - 7.60 (1 H, m, *Ar*), 7.44 - 7.51 (2 H, m, *Ar*), 7.06 (1 H, d, *J*=8.5 Hz, benzyl-*H*), 6.47 (1 H, s) 2.22 (3 H, s, C*H*$_3$), 1.98 (3 H, s, C*H*$_3$); δ_C (100 MHz, DMSO-d_6) 166.6 (*C*=O), 150.2, 150.1, 141.1, 139.5, 134.9, 133.4, 133.1, 132.3, 129.2, 128.7,

128.5, 127.4, 126.0, 125.6, 123.9, 119.4, 47.0 (benzyl-*C*), 14.2 (*C*H_3), 13.5 (*C*H_3); *m/z* (ESI$^-$) 421 ([M-H]$^-$); HRMS (ESI$^+$) $C_{23}H_{19}ClN_2NaO_2S$, ([M+Na]$^+$) requires 445.0748; found 445.0737.

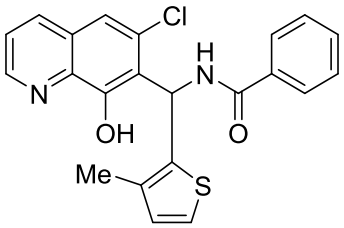
***N*-((5-Bromo-8-hydroxyquinolin-7-yl)(3-methylthiophen-2-yl)methyl)-2-phenylacetamide S112**



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; ν_{max}/cm^{-1} 3222 (NH), 1635 (C=O); δ_H (400 MHz, DMSO-d_6) 10.48 (1 H, br. s., N*H*), 9.07 - 9.17 (1 H, m, quinoline-*Ar*), 8.88 - 8.99 (1 H, m, quinoline-*Ar*), 8.37 - 8.50 (1 H, m, quinoline-*Ar*), 7.92 (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*=8.0 Hz, benzyl-*H*), 3.51 - 3.58 (2 H, m, CH_2), 2.11 (3 H, s, CH_3); δ_C (100 MHz, DMSO-d_6) 169.7 (*C*=O), 150.5, 149.7, 139.4, 139.3, 136.8, 135.5, 134.6, 130.9, 129.6, 129.5, 129.4, 128.7, 126.8, 126.1, 123.9, 123.6, 108.8, 44.8 (benzyl-*C*), 42.5 (*C*H_2), 13.9 (*C*H_3); *m/z* (ESI$^-$) 465 ([M-H]$^-$); HRMS (ESI$^+$) $C_{23}H_{19}BrN_2NaO_2S$, ([M+Na]$^+$) requires 489.0243; found 489.0242.

***N*-((6-Chloro-8-hydroxyquinolin-7-yl)(3-methylthiophen-2-yl)methyl)benzamide S113**

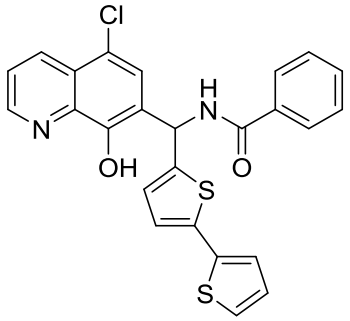


Following general procedure 1, **S11** (359 mg, 2 mmol), benzamide (242 mg, 2 mmol) and 3-methyl-2-thiophenecarboxaldehyde (431 µL, 4 mmol) gave **S113** (352 mg, 43 %) as a light brown powder after purification *via* flash column chromatography (10 % - 20 % EtOAc, cyclohexane).

mp 160 °C; ν_{max}/cm^{-1} 3058 (NH), 1660 (C=O); δ_H (400 MHz, DMSO-d_6) 8.96 - 9.02 (1 H, m, quinoline-*Ar*), 8.87 - 8.94 (1 H, m, quinoline-*Ar*), 8.27 - 8.40 (1 H, m, quinoline-*Ar*), 7.82 - 7.90 (2 H, m, *Ar*), 7.61 - 7.69 (1 H, m, *Ar*), 7.52 - 7.58 (1 H, m, *Ar*), 7.44 - 7.51 (2 H, m, *Ar*), 7.32 (1 H, d, *J*=8.5 Hz, benzyl-*H*), 7.24 - 7.28 (1 H, m, *Ar*), 6.84 - 6.91 (1 H, m, *Ar*), 2.29 (3 H, s, CH_3); δ_C (100 MHz, DMSO-d_6) 165.4 (*C*=O), 153.2, 149.4, 137.9, 137.5, 135.9, 135.0, 134.4, 132.1, 132.0, 130.7, 129.0, 128.3, 127.7, 124.1,

123.7, 122.3, 118.0, 47.3 (benzyl-*C*), 14.3 (thiophene-*C*H_3); *m/z* (ESI$^-$) 407 ([M-H]$^-$); HRMS (ESI$^+$) $C_{22}H_{17}O_2N_2ClNaS$, ([M+Na]$^+$) requires 431.0592; found 431.0583.

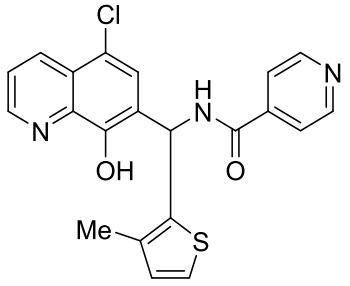
***N*-([2,2'-Bithiophen]-5-yl(5-chloro-8-hydroxyquinolin-7-yl)methyl)benzamide S114**



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 ^{o}C; ν_{max}/cm^{-1} 3291 (NH), 1635 (C=O); δ_H (400 MHz, DMSO-d_6) 10.62 (1 H, br. s., N*H*), 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*); δ_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, 120.2, 129.2, 128.5, 127.2, 126.2, 126.2, 125.1, 124.8, 124.4, 124.1, 119.6, 47.1 (benzyl-*C*); *m/z* (ESI$^+$) 499 ([M+Na]$^+$); HRMS (ESI$^+$) $C_{25}H_{17}ClIN_2NaO_2S_2$, ([M+Na]$^+$) requires 499.0312; found 499.0300.

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

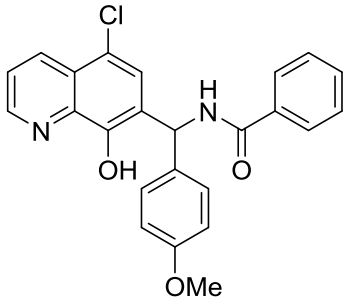


Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), isonicotinamide (244 mg, 2.0 mmol) and 3-methyl-2-thiophenecarboxaldehyde (431 µL, 4.0 mmol) gave **S115** (415 mg, 51 %) as an off-white powder.

mp 120 ^{o}C; ν_{max}/cm^{-1} 3242 (NH), 1642 (C=O); δ_H (400 MHz, DMSO-d_6) 10.55 (1 H, br. s., N*H*), 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); δ_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 (*C*H$_3$); *m/z* (ESI$^-$) 817 ([2M-H]$^-$); HRMS (ESI$^+$) $C_{21}H_{16}ClIN_3NaO_2S$, ([M+Na]$^+$) requires 432.0544; found 432.0531.

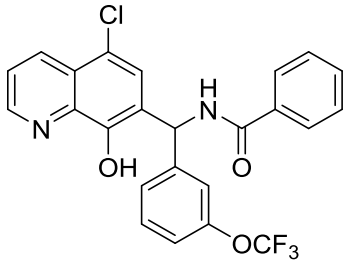
***N*-((5-Chloro-8-hydroxyquinolin-7-yl)(4-methoxyphenyl)methyl)benzamide S116**



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

mp 242 - 243 °C; ν_{max}/cm^{-1} 3314 (NH), 1631 (C=O); δ_H (400 MHz, DMSO-d_6) 10.36 (1 H, br. s., N*H*), 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-C*H*$_3$); δ_C (100 MHz, DMSO-d_6) 166.8 (*C*=O), 159.2, 150.2, 150.0, 139.5, 135.2, 134.4, 133.4, 132.2, 129.2, 129.1, 128.4, 127.6, 126.3, 125.7, 123.8, 119.4, 114.7, 56.0 (O-*C*H$_3$), 50.5 (benzyl-*C*); *m/z* (ESI$^-$) 417 ([M-H]$^-$, 100%); HRMS (ESI$^-$) $C_{24}H_{19}ClN_2NaO_3$, ([M+Na]$^+$) requires 441.0976; found 441.0963.

***N*-((5-Chloro-8-hydroxyquinolin-7-yl)(3-(trifluoromethoxy)phenyl)methyl)benzamide S117**

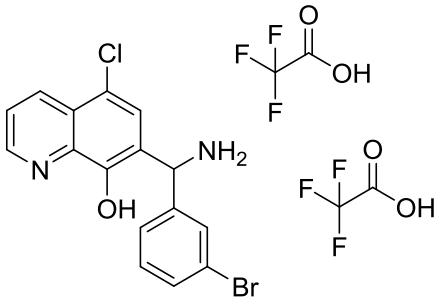


Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 3-trifluoromethoxybenzaldehyde (535 µL, 4.0 mmol) gave **S117** (682 mg, 72 %) as a white powder.

mp 210 °C; ν_{max}/cm^{-1} 3297 (NH), 1634 (C=O), 680 (C-Cl); δ_H (400 MHz, DMSO-d_6) 10.56 (1 H, br. s., N*H*), 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*); δ_C (100 MHz, DMSO-d_6) 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, 127.2, 126.0, 125.1, 124.0, 120.3, 119.6, 50.6 (benzyl-*C*); δ_F (377 MHz, DMSO-d_6) -56.7 (CF_3); *m/z* (ESI$^-$) 495 ([M-H]$^-$); HRMS (ESI$^+$) $C_{24}H_{16}ClF_3N_2NaO_3$, ([M+Na]$^+$) requires 495.0694; found 495.0683.

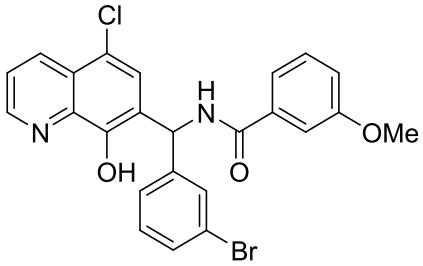
7-(Amino(3-bromophenyl)methyl)-5-chloroquinolin-8-ol bis(2,2,2-trifluoroacetate) S118



Trifluoroacetic acid (83 µL, 1 mmol) was added dropwise to a stirring suspension of **159** (100 mg, 0.22 mmol) in CH_2Cl_2 (10 mL). After 30 min, the solvent was removed under reduced pressure. The residue was dried under vacuum to give **S118** (118 mg, 100%) as a bright-yellow solid.

mp 107 °C; ν_{max}/cm^{-1} 1666 (C=O); δ_H (400 MHz, DMSO-d_6) 9.02 (3 H, br. s) 8.48 - 8.57 (1 H, m, NH_3^+), 7.88 (1 H, s, *Ar*), 7.77 - 7.83 (1 H, m, *Ar*), 7.73 - 7.76 (1 H, m, *Ar*), 7.54 - 7.61 (1 H, m, *Ar*), 7.35 - 7.47 (2 H, m, *Ar*), 7.11 - 7.28 (3 H, m, *Ar*), 6.06 (1 H, s, benzyl-*H*); δ_C (100 MHz, DMSO-d_6) 151.1, 150.6, 140.6, 139.6, 133.6, 132.3, 131.9, 130.8, 129.8, 129.1, 127.3, 126.2, 124.7, 122.8, 120.8, 120.0, 52.2 (benzyl-*C*), 21.9 (*C*F$_3$); *m/z* (FI$^+$) 362 ([M]$^+$); HRMS (FI$^+$) $C_{16}H_{12}BrClIN_2O$, ([M]$^+$) requires 361.9822; found 361.9809.

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

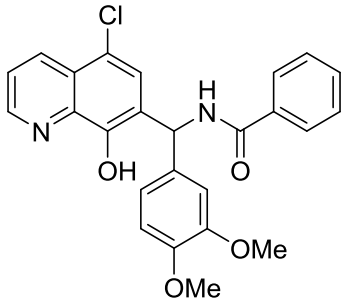


Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), 3-methoxybenzamide (302 mg, 2.0 mmol) and 3-bromobenzaldehyde (468 µL, 4.0 mmol) gave **S119** (668 mg, 67 %) as a white powder.

mp 178 °C; ν_{max}/cm^{-1} 3306 (NH), 1634 (C=O); δ_H (400 MHz, DMSO-d_6) 10.55 (1 H, br. s., N*H*), 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, OC*H*$_3$); δ_C (100 MHz, DMSO-d_6) 166.6 (*C*=O), 160.0, 150.5, 150.2, 145.2, 139.5, 136.3, 133.4, 131.6, 130.9,

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 (O*C*H$_3$), 50.2 (benzyl-*C*); *m/z* (ESI$^+$) 497 ([M+H]$^+$); HRMS (ESI$^+$) $C_{24}H_{19}BrClIN_2O_3$, ([M+H]$^+$) requires 497.0262; found 497.0249.

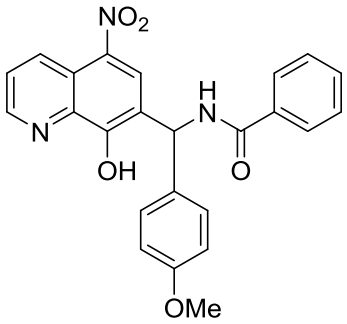
***N*-((5-Chloro-8-hydroxyquinolin-7-yl)(3,4-dimethoxyphenyl)methyl)benzamide S120**



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 ^{o}C; ν_{max}/cm^{-1} 3294 (NH), 1632 (C=O), 697 (C-Cl); δ_H (400 MHz, DMSO-d_6) 10.37 (1 H, br. s., N*H*), 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, OC*H*$_3$), 3.72 (3 H, s, OC*H*$_3$); δ_C (100 MHz, DMSO-d_6) 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 O*C*H$_3$), 50.5 (benzyl-*C*); *m/z* (ESI$^-$) 447 ([M-H]$^-$); HRMS (ESI$^-$) $C_{25}H_{21}ClN_2NaO_2$, ([M+Na]$^+$) requires 471.1082; found 471.1076.

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

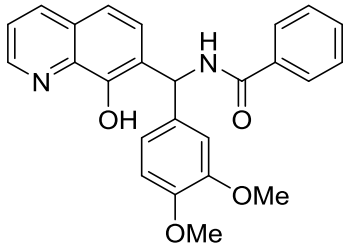


Following general procedure 1, 8-hydroxy-5-nitroquinoline (380 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 4-methoxybenzaldehyde (486 µL, 4.0 mmol) gave **S121** (459 mg, 53 %) as an orange powder.

mp 204 ^{o}C; ν_{max}/cm^{-1} 3250 (NH), 1637 (C=O); δ_H (400 MHz, DMSO-d_6) 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, OC*H*$_3$); δ_C (100 MHz, DMSO-d_6) 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, 122.4, 114.7, 56.0 (O*C*H$_3$), 50.6 (benzyl-*C*); *m/z* (ESI$^-$) 428 ([M-H]$^-$); HRMS (ESI$^+$) $C_{24}H_{19}N_3NaO_5$, ([M+Na]$^+$) requires 452.1217; found 452.1212.

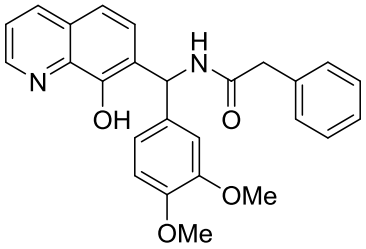
***N*-((3,4-Dimethoxyphenyl)(8-hydroxyquinolin-7-yl)methyl)benzamide S122**



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

mp 174 ^{o}C; ν_{max}/cm^{-1} 3312 (NH), 1633 (C=O); δ_H (400 MHz, DMSO-d_6) 9.12 - 9.19 (1 H, m, quinoline-*Ar*), 8.81 - 8.90 (1 H, m, quinoline-*Ar*), 8.26 - 8.34 (1 H, m, quinoline-*Ar*), 7.88 - 7.96 (2 H, m, quinoline-*Ar*), 7.69 - 7.74 (1 H, m, *Ar*), 7.50 - 7.57 (2 H, m, *Ar*), 7.41 - 7.50 (3 H, m, *Ar*), 7.00 - 7.02 (1 H, m, benzyl-*H*), 6.87 - 6.94 (2 H, m, *Ar*), 6.79 - 6.85 (1 H, m, *Ar*), 3.71 (3 H, s, C*H*$_3$), 3.69 (3 H, s, C*H*$_3$); δ_C (100 MHz, DMSO-d_6) 166.7 (*C*=O), 150.5, 149.5, 149.1, 148.7, 138.9, 136.9, 135.5, 135.5, 132.6, 129.8, 129.1, 128.4, 128.4, 127.7, 125.6, 120.4, 118.1, 112.5, 112.3, 56.4 (O*C*H$_3$), 56.4 (O*C*H$_3$), 51.3 (benzyl-*C*); *m/z* (ESI$^+$) 437 ([M+Na]$^+$); HRMS (ESI$^+$) $C_{25}H_{22}N_2NaO_4$, ([M+Na]$^+$) requires 437.1472; found 437.1467.

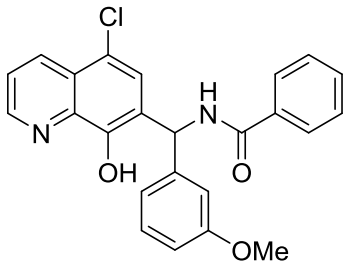
***N*-((3,4-Dimethoxyphenyl)(8-hydroxyquinolin-7-yl)methyl)-2-phenylacetamide S123**



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

mp 182 ^{o}C; ν_{max}/cm^{-1} 3292 (NH), 1638 (C=O); δ_H (400 MHz, DMSO-d_6) 9.93 (1 H, br. s, N*H*), 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, OC*H*$_3$), 3.63 (3 H, s, OC*H*$_3$), 3.37 (2 H, s, C*H*$_2$); δ_C (100 MHz, DMSO-d_6) 173.1 (*C*=O), 170.2, 150.3, 149.5, 149.2, 148.6, 138.9, 137.4, 136.9, 135.7, 129.9, 129.0, 128.3, 127.2, 125.6, 122.6, 119.9, 118.1, 112.5, 111.7, 56.4 (O*C*H$_3$), 56.2 (O*C*H$_3$), 50.5 (benzyl-*C*); *m/z* (ESI$^+$) 429 ([M+H]$^+$); HRMS (ESI$^+$) $C_{26}H_{24}N_2NaO_4$, ([M+Na]$^+$) requires 451.1628; found 451.1624.

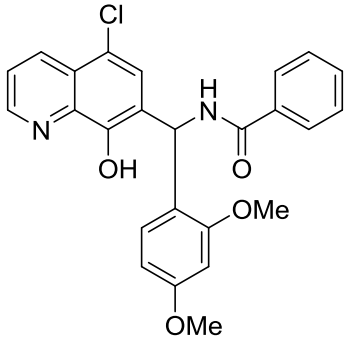
***N*-((5-Chloro-8-hydroxyquinolin-7-yl)(3-methoxyphenyl)methyl)benzamide S124**



Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 3-methoxybenzaldehyde (487 µL, 4.0 mmol) gave **S124** (635 mg, 76 %) as white powder. **255** was then stirred in a 4M HCl solution in dioxane for 1 h. The solvent was removed under reduced pressure to give the hydrochloride salt of **S124** as a bright-yellow powder in quantitative yield.

mp 250 °C; ν_{max}/cm^{-1} 3288 (NH), 1641 (C=O); δ_H (400 MHz, DMSO-d_6) 10.13 (1 H, br. s, N*H*), 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, OC*H*$_3$); δ_C (100 MHz, DMSO-d_6) 166.9 (*C*=O), 160.2, 149.8, 149.6, 144.0, 138.7, 135.1, 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 (O*C*H$_3$), 50.9 (benzyl-*C*); *m/z* (ESI$^+$) 419 ([M+H]$^+$); HRMS (ESI$^+$) $C_{24}H_{20}ClN_2O_3$, ([M+H]$^+$) requires 419.1157; found 419.1160.

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

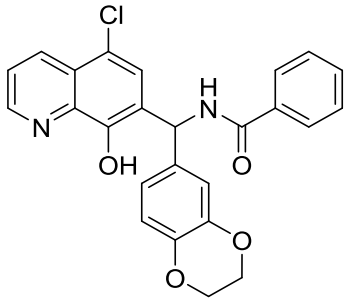


Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 2,4-dimethoxybenzaldehyde (664 mg, 4.0 mmol) gave **S125** (464 mg, 52 %) as a white powder.

mp 186 - 187 °C; ν_{max}/cm^{-1} 3306 (NH), 1636 (C=O); δ_H (400 MHz, DMSO-d_6) 10.18 (1 H, br. s., N*H*), 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, OC*H*$_3$), 3.73 (3 H, s, OC*H*$_3$); δ_C (100 MHz, DMSO-d_6) 166.2

(*C*=O), 160.8, 158.7, 150.6, 149.8, 139.4, 135.3, 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 (O*C*H$_3$), 56.1 (O*C*H$_3$), 46.6 (benzyl-*C*); *m/z* (ESI$^-$) 895 ([2M-H]$^-$); HRMS (ESI$^+$) $C_{25}H_{21}ClIN_2NaO_4$, ([M+Na]$^+$) requires 471.1082; found 471.1079.

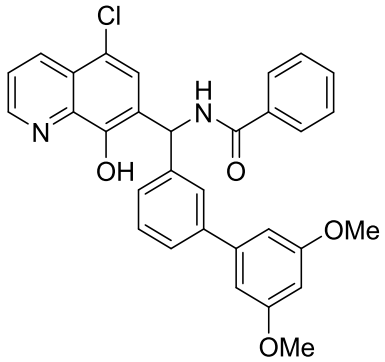
***N*-((5-Chloro-8-hydroxyquinolin-7-yl)(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)methyl)benzamide S126**



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 ^{o}C; ν_{max}/cm^{-1} 3282 (NH), 1631 (C=O); δ_H (400 MHz, DMSO-d_6) 10.40 (1 H, br. s., N*H*), 9.08 - 9.25 (1 H, m, quinoline-*Ar*), 8.84 - 9.04 (1 H, m, quinoline-*Ar*), 8.34 - 8.59 (1 H, m, quinoline-*Ar*), 7.82 - 8.04 (3 H, m, *Ar*), 7.64 - 7.78 (1 H, m, *Ar*), 7.39 - 7.60 (3 H, m, *Ar*), 6.90 (1 H, d, *J*=8.5 Hz, benzyl-*H*), 6.72 - 6.86 (3 H, m, *Ar*), 4.19 (4 H, s, C*H*$_2$); δ_C (100 MHz, DMSO-d_6) 166.8 (*C*=O), 150.2, 150.0, 144.0, 143.3, 139.5, 135.6, 135.1, 133.4, 132.2, 129.1, 128.4, 127.5, 126.1, 125.7, 123.8, 120.9, 119.4, 117.8, 116.6, 64.9 (*C*H$_2$), 50.4 (benzyl-*C*); *m/z* (ESI$^-$) 445 ([M+H]$^-$); HRMS (ESI$^+$) $C_{25}H_{19}ClIN_2NaO_4$, ([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**

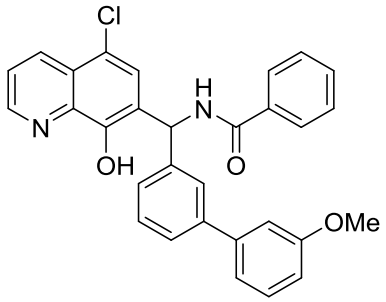


Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and **S25** (634 mg, 2.6 mmol) gave **S127** (513 mg, 49 %) as a white powder.

mp 239 ^{o}C; ν_{max}/cm^{-1} 3298 (NH), 1633 (C=O); δ_H (400 MHz, DMSO-d_6) 10.50 (1 H, br. s., N*H*), 9.19 - 9.43 (1 H, m, quinoline-*Ar*), 8.88 - 9.02 (1 H, m, quinoline-*Ar*), 8.31 - 8.62 (1 H, m, quinoline-*Ar*), 7.90 - 8.04 (3 H, m, *Ar*), 7.68 - 7.76 (1 H, m, *Ar*), 7.66

(1 H, s, *Ar*), 7.52 - 7.59 (2 H, m, *Ar*), 7.46 - 7.52 (2 H, m, *Ar*), 7.40 - 7.45 (1 H, m, *Ar*), 7.32 - 7.39 (1 H, m, *Ar*), 7.07 (1 H, d, *J*=9.0 Hz, benzyl-*H*), 6.69 - 6.76 (2 H, m, *Ar*), 6.50 (1 H, s, *Ar*), 3.77 (6 H, s, OCH_3); δ_C (100 MHz, DMSO-d_6) 167.0 (*C*=O), 161.7 (*C*OCH$_3$),150.4, 150.1, 143.1, 143.1, 141.1, 139.6, 135.2, 133.4, 132.3, 129.9, 129.2, 129.1, 128.5, 127.5, 127.4, 126.5, 126.0, 125.8, 123.9, 119.5, 105.8, 100.0, 56.1 (O*C*H$_3$), 51.2 (benzyl-*C*); *m*/*z* (EI$^+$) 524 ([M]$^+$); HRMS (EI$^+$) $C_{31}H_{25}ClN_2O_4$, ([M]$^+$) requires 524.1503; found 524.1511.

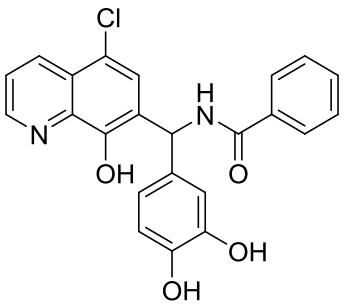
***N*-((5-Chloro-8-hydroxyquinolin-7-yl)(3'-methoxy-[1,1'-biphenyl]-3-yl)methyl)benzamide S128**



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

mp 208 °C; ν_{max}/cm^{-1} 3297 (NH), 1633 (C=O); δ_H (400 MHz, DMSO-d_6) 10.49 (1 H, br. s., N*H*), 9.22 - 9.45 (1 H, m, quinoline-*Ar*), 8.81 - 9.05 (1 H, m, quinoline-*Ar*), 8.31 - 8.54 (1 H, m, quinoline-*Ar*), 7.88 - 7.99 (3 H, m, *Ar*), 7.64 - 7.75 (2 H, m, *Ar*), 7.52 - 7.58 (2 H, m, *Ar*), 7.46 - 7.52 (2 H, m, *Ar*), 7.40 - 7.46 (1 H, m, *Ar*), 7.30 - 7.39 (2 H, m, *Ar*), 7.02 - 7.21 (3 H, m, *Ar*), 6.87 - 6.96 (1 H, m, *Ar*), 3.78 (3 H, s, OCH_3); δ_C (100 MHz, DMSO-d_6) 167.0 (*C*=O), 160.5 (*C*OCH$_3$),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, 119.9, 119.5, 113.8, 113.2, 55.9 (O*C*H$_3$), 51.2 (benzyl-*C*); *m*/*z* (EI$^+$) 494 ([M]$^+$); HRMS (EI$^+$) $C_{30}H_{23}ClN_2O_3$, ([M]$^+$) requires 494.1397; found 494.1396.

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

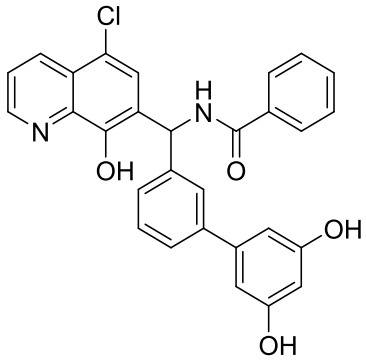


To a solution of **S120** (250 mg, 0.5 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added a 1M solution of boron tribromide in CH_2Cl_2 (3 mL, 3 mmol). The reaction mixture was stirred for 30 min at 0 °C, allowed to warm to room temperature, and then stirred at room temperature for 24 h. The reaction mixture was quenched with MeOH (10 mL) and neutralised with a 1M aqueous

solution of NaOH. The precipitate was collected by filtration and dried under vacuum to give **S129** as an off-white powder (210 mg, 100 %).

mp decomposition > 220 °C; ν_{max}/cm^{-1} 3294 (NH), 1634 (C=O); δ_H (400 MHz, DMSO-d_6) 10.20 (1 H, br. s., N*H*), 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*); δ_C (100 MHz, DMSO-d_6) 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 (FI$^+$) $C_{23}H_{17}ClIN_2O_4$, ([M]$^+$) requires 420.0877; found 420.0883.

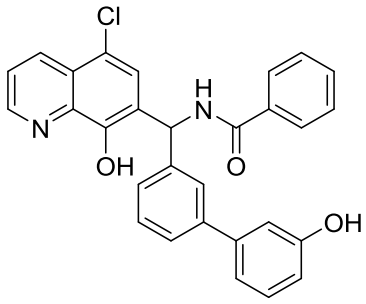
***N*-((5-Chloro-8-hydroxyquinolin-7-yl)(3',5'-dihydroxy-[1,1'-biphenyl]-3-yl)methyl)benzamide S130**



To a solution of **S127** (200 mg, 0.38 mmol) in CH_2Cl_2 (8 mL) at 0 °C was added a 1M solution of boron tribromide in CH_2Cl_2 (2.3 mL, 2.3 mmol). The reaction mixture was stirred for 30 min at 0 °C, allowed to warm to room temperature, and then stirred at room temperature for 24 h. The reaction mixture was quenched with MeOH (10 mL) and neutralised with a 1M aqueous solution of NaOH. The solvent was removed under reduced pressure and the residue redissolved in CH_2Cl_2. The organic layer was washed with water, brine, and subsequently dried over anhydrous Na_2SO_4. Purification by flash column chromatography using CH_2Cl_2/MeOH (90:10) gave **S130** (143 mg, 76 %) as an orange powder.

mp decomposition > 230 °C; ν_{max}/cm^{-1} 3206 (OH), 1597 (C=O); δ_H (400 MHz, DMSO-d_6) 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*); δ_C (100 MHz, DMSO-d_6) 167.0 (*C*=O), 1157.9 (*C*OH),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.

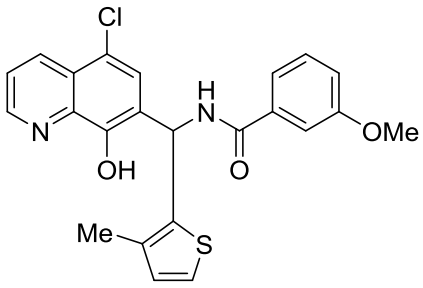
***N*-((5-Chloro-8-hydroxyquinolin-7-yl)(3'-hydroxy-[1,1'-biphenyl]-3-yl)methyl)benzamide S131**



To a solution of **S128** (160 mg, 0.31 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added a 1M solution of boron tribromide in CH_2Cl_2 (0.97 mL, 0.97 mmol). The reaction mixture was stirred for 30 min at 0 °C, allowed to warm to room temperature, and then stirred at room temperature for 24 h. The reaction mixture was quenched with MeOH (10 mL) and neutralised with a 1M aqueous solution of NaOH. The solvent was removed under reduced pressure and the residue redissolved in CH_2Cl_2. The organic layer was washed with water, brine, and subsequently dried over anhydrous Na_2SO_4. Purification by flash column chromatography using CH_2Cl_2/MeOH (90:10) gave **S131** (84 mg, 55 %) as a yellow powder.

mp decomposition > 180 °C; ν_{max}/cm^{-1} 3206 (NH), 1596 (C=O); δ_H (400 MHz, DMSO-d_6) 9.26 - 9.42 (1 H, m, quinoline-*Ar*), 8.88 - 9.07 (1 H, m, quinoline-*Ar*), 8.46 - 8.64 (1 H, m, quinoline-*Ar*), 7.87 - 8.02 (3 H, m, *Ar*), 7.70 - 7.83 (1 H, m, *Ar*), 7.46 - 7.63 (5 H, m, *Ar*), 7.38 - 7.45 (1 H, m, *Ar*), 7.30 - 7.36 (1 H, m, *Ar*), 7.18 - 7.27 (1 H, m, *Ar*), 7.08 (1 H, d, *J*=8.5 Hz, benzyl-*H*) 6.92 - 7.02 (2 H, m, *Ar*), 6.67 - 6.81 (1 H, m, *Ar*); δ_C (100 MHz, DMSO-d_6) 167.0 (*C*=O), 158.7, 149.8, 149.7, 142.9, 142.4, 141.4, 138.8, 135.1, 134.4, 132.3, 130.8, 129.9, 129.2, 128.5, 127.7, 127.2, 126.7, 126.3, 126.2, 126.0, 124.0, 119.8, 118.3, 115.4, 114.3, 51.1 (benzyl-*C*); *m/z* (FI$^+$) 496 ([M]$^+$); HRMS (FI$^+$) $C_{29}H_{21}ClN_2O_4$, ([M]$^+$) requires 496.1190; found 496.1186.

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

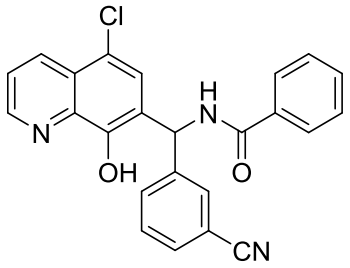


Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), 3-methoxybenzamide (302 mg, 2.0 mmol) and 3-methyl-2-thiophenecarboxaldehyde (431 µL, 4.0 mmol) gave **S132** (129 mg, 15 %) as a light-brown powder.

mp 145 °C; ν_{max}/cm^{-1} 3291 (NH), 1640 (C=O); δ_H (400 MHz, DMSO-d_6) 10.51 (1 H, br. s., N*H*), 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, OC*H*$_3$), 2.15 (3 H, s, C*H*$_3$); δ_C (100 MHz, DMSO-d_6) 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 (O*C*H$_3$), 14.4 (*C*H$_3$); *m/z* (ESI$^-$) 437 ([M-H]$^-$); HRMS (ESI$^+$) $C_{23}H_{19}ClN_2NaO_3S$, ([M+Na]$^+$) requires 461.0697; found 461.0699.

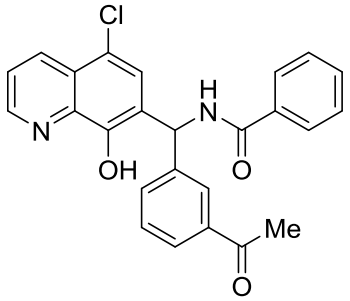
***N*-((5-Chloro-8-hydroxyquinolin-7-yl)(3-cyanophenyl)methyl)benzamide S133**



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.

mp 226 - 228 ^{o}C; ν_{max}/cm^{-1} 3298 (NH), 1633 (C=O), 691 (C-Cl); δ_H (400 MHz, DMSO-d_6) 10.59 (1 H, br. s., N*H*), 9.28 - 9.38 (1 H, m, quinoline-*Ar*), 8.94 - 9.01 (1 H, m, quinoline-*Ar*), 8.45 - 8.52 (1 H, m, quinoline-*Ar*), 7.93 - 7.99 (2 H, m, *Ar*), 7.85 (1 H, s, *Ar*), 7.80 (1 H, s, *Ar*), 7.67 - 7.78 (3 H, m, *Ar*), 7.53 - 7.60 (2 H, m, *Ar*), 7.45 - 7.53 (2 H, m, *Ar*), 7.02 (1 H, d, *J*=8.5 Hz, benzyl-*H*); δ_C (100 MHz, DMSO-d_6) 167.0 (*C*=O), 150.6, 150.2, 144.0, 139.6, 134.8, 133.4, 133.2, 132.4, 131.9, 131.4, 130.7, 129.2, 128.5, 127.1, 126.1, 124.9 124.0, 119.7, 119.6, 112.3, 50.8 (benzyl-*C*); *m/z* (ESI$^+$) 414 ([M+H]$^+$); HRMS (ESI$^+$) $C_{24}H_{16}ClIN_3NaO_2$, ([M+Na]$^+$) requires 436.0823; found 436.0815.

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

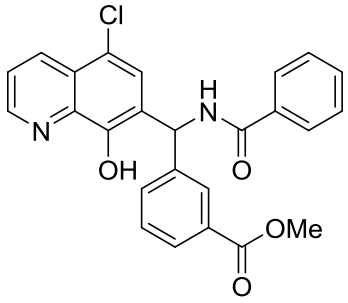


Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 3-acetylbenzaldehyde (524 mg, 4.0 mmol) gave **S134** (476 mg, 55 %) as a white powder.

mp 192 ^{o}C; ν_{max}/cm^{-1} 3301 (NH), 1689 (acetyl C=O), 1633 (amide C=O), 692 (C-Cl); δ_H (400 MHz, DMSO-d_6) 10.53 (1 H, br. s., N*H*), 9.33 - 9.39 (1 H, m, quinoline-*Ar*), 8.94 - 8.99 (1 H, m, quinoline-*Ar*), 8.44 - 8.51 (1 H, m, quinoline-*Ar*), 7.92 - 7.98 (3 H, m, *Ar*), 7.87 - 7.91 (2 H, m, *Ar*), 7.69 - 7.76 (1 H, m, *Ar*), 7.60 - 7.66 (1 H, m, *Ar*), 7.45 - 7.57 (4 H, m, *Ar*), 7.08 (1 H, d, *J*=8.5 Hz, benzyl-*H*), 2.55 (3 H, s, C*H*$_3$); δ_C (100 MHz, DMSO-d_6) 198.7 (acetyl *C*=O), 167.0 (amide *C*=O),150.5, 150.1, 143.1, 139.5, 137.8,

135.0, 133.4, 132.9, 132.4, 129.8, 129.2, 128.5, 128.4, 127.4, 127.1, 125.9, 125.5, 124.0, 119.5, 51.0 (benzyl-*C*), 27.7 (*C*H_3); *m/z* (ESI$^-$) 429 ([M-H]$^-$); HRMS (ESI$^+$) $C_{25}H_{19}ClIN_2NaO_3$, ([M+Na]$^+$) requires 453.0976; found 453.0975.

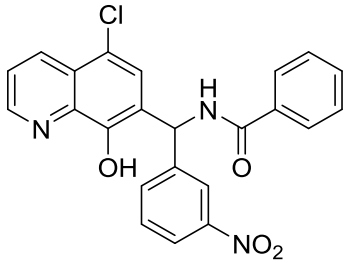
Methyl 3-(benzamido(5-chloro-8-hydroxyquinolin-7-yl)methyl)benzoate S135



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

mp 224 °C; ν_{max}/cm^{-1} 3303 (NH), 1724 (esther C=O), 1636 (amide C=O), 696 (C-Cl); δ_H (400 MHz, DMSO-d_6) 10.54 (1 H, br. s., N*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); δ_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, 128.6, 128.5, 127.4, 126.0, 125.3, 124.0, 119.6 (benzyl-*C*), 53.1 (O*C*H_3), 50.9 (benzyl-*C*); *m/z* (ESI$^+$) 469 ([M+Na]$^+$); HRMS (ESI$^+$) $C_{25}H_{19}ClIN_2NaO_4$, ([M+Na]$^+$) requires 469.0926; found 469.0909.

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

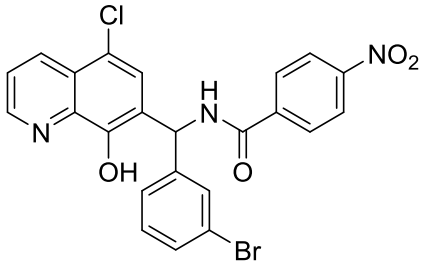


Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), benzamide (242 mg, 2.0 mmol) and 3-nitrobenzaldehyde (604 mg, 4.0 mmol) gave **S136** (276 mg, 31 %) as a white powder.

mp 195 - 198 °C; ν_{max}/cm^{-1} 3300 (NH), 1633 (C=O); δ_H (400 MHz, DMSO-d_6) 10.62 (1 H, br. s., N*H*), 9.38 - 9.50 (1 H, m, quinoline-*Ar*), 8.94 - 9.02 (1 H, m, quinoline-*Ar*), 8.44 - 8.53 (1 H, m, quinoline-*Ar*), 8.18 - 8.22 (1 H, m, *Ar*), 8.12 - 8.17 (1 H, m, *Ar*), 7.92 - 7.98 (2 H, m, *Ar*), 7.90 (1 H, s, *Ar*), 7.81 - 7.86 (1 H, m, *Ar*), 7.71 - 7.77 (1 H, m, *Ar*), 7.63 - 7.69 (1 H, m, *Ar*), 7.54 - 7.58 (1 H, m, *Ar*), 7.46 - 7.53 (2 H, m, *Ar*), 7.11 (1 H, d, *J*=9.0 Hz, benzyl-*H*); δ_C (100 MHz, DMSO-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$^+$) $C_{23}H_{16}ClN_3NaO_4$, ([M+Na]$^+$) requires 456.0722; found 456.0712.

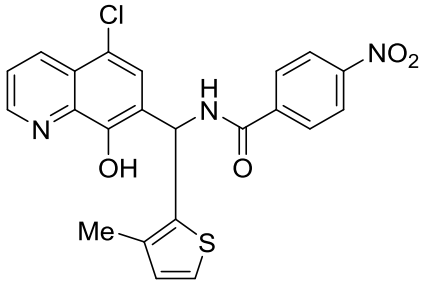
***N*-((3-Bromophenyl)(5-chloro-8-hydroxyquinolin-7-yl)methyl)-4-nitrobenzamide S137**



Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), 4-nitrobenzamide (332 mg, 2.0 mmol) and 3-bromobenzaldehyde (468µL, 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-d_6) 10.60 (1 H, br. s., N*H*), 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*-NO$_2$), 8.17 (2 H, d, *J*=8.5 Hz, *β*-*H*-NO$_2$), 7.81 (1 H, s, *Ar*), 7.69 - 7.77 (1 H, m, *Ar*), 7.53 (1 H, s, *Ar*), 7.46 - 7.51 (1 H, m, *Ar*), 7.25 - 7.44 (2 H, m, *Ar*), 6.98 (1 H, d, *J*=8.5 Hz, benzyl-*H*); δ_C (100 MHz, DMSO-d_6) 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$^+$) $C_{23}H_{15}BrClN_3NaO_4$, ([M+Na]$^+$) requires 533.9827; found 533.9815.

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

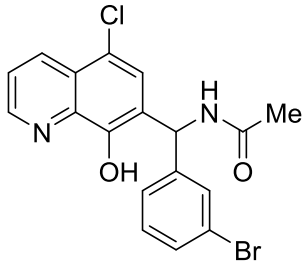


Following general procedure 1, 5-chloro-8-hydroxyquinoline (359 mg, 2.0 mmol), 4-nitrobenzamide (332 mg, 2.0 mmol) and 3-methyl-2-thiophenecarboxaldehyde (431 µL, 4.0 mmol) gave **S138** (365 mg, 40 %) as a light-brown powder.

mp 194 °C; ν_{max}/cm^{-1} 3312 (NH), 1643 (C=O); δ_H (400 MHz, DMSO-d_6) 10.57 (1 H, br. s., N*H*), 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, C*H*$_3$); δ_C (100 MHz, DMSO-d_6) 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 (*C*H$_3$); *m/z* (ESI$^-$) 452 ([M-H]$^-$); HRMS (ESI$^+$) $C_{22}H_{16}ClN_3NaO_4S$, ([M+Na]$^+$) requires 476.0442; found 476.0453.

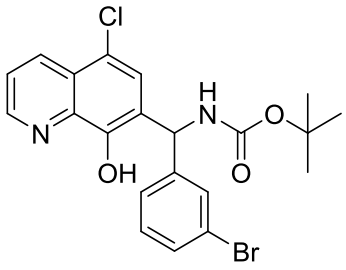
_N_-((3-Bromophenyl)(5-chloro-8-hydroxyquinolin-7-yl)methyl)acetamide S139



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 ^{o}C; ν_{max}/cm^{-1} 3286 (NH), 1640 (C=O); δ_H (400 MHz, DMSO-d_6) 10.48 (1 H, br. s., N*H*), 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, C*H*$_3$); δ_C (100 MHz, DMSO-d_6) 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 (*C*H$_3$); *m/z* (ESI$^-$) 402 ([M-H]$^-$); HRMS (ESI$^+$) $C_{18}H_{14}BrClIN_2NaO_2$, ([M+Na]$^+$) requires 426.9819; found 426.9810.

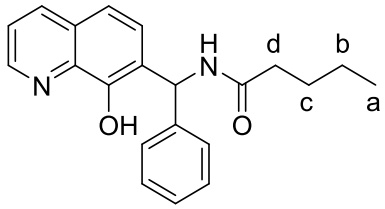
***tert*-Butyl ((3-bromophenyl)(5-chloro-8-hydroxyquinolin-7-yl)methyl)carbamate S140**



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

mp 177 ^{o}C; ν_{max}/cm^{-1} 3298 (NH), 1684 (C=O); δ_H (400 MHz, DMSO-d_6) 10.49 (1 H, br. s., N*H*), 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(C*H*$_3$)$_3$); δ_C (100 MHz, DMSO-d_6) 171.5 (*C*=O), 150.1, 149.8, 146.0, 129.5, 133.4, 131.5, 130.7, 130.1, 126.9, 126.7, 126.0, 125.8, 123.9, 122.5, 119.7, 79.4 (*C*(CH$_3$)$_3$), 51.5 (benzyl-*C*), 29.0 (C(*C*H$_3$)$_3$); *m/z* (FI$^+$) 462 ([M]$^+$); HRMS (FI$^+$) $C_{21}H_{20}BrClN_2O_3$, ([M]$^+$) requires 462.0346; found 462.0340.

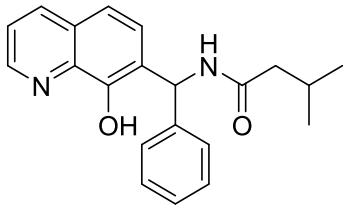
***N*-((8-Hydroxyquinolin-7-yl)(phenyl)methyl)pentanamide S141**



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

mp 178 - 179 °C; ν_{max}/cm^{-1} (DCM) 3334 (NH), 2957 (OH), 1645 (C=O); δ_H (400 MHz, DMSO-d_6) 9.94 (1 H, br. s., N*H*), 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*), 7.39 - 7.47 (1 H, m, *Ar*), 7.15 - 7.34 (5 H, m, *Ar*), 6.73 (1 H, d, *J*=9.0 Hz, benzyl-*H*), 2.18 - 2.28 (2 H, m, CH_{2d}), 1.51 (2 H, quin, *J*=7.5 Hz CH_{2c}), 1.26 (2 H, sxt, *J*=7.5 Hz CH_{2b}), 0.85 (3 H, t, *J*=7.5 Hz, CH_{3a}); δ_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, 127.5, 127.3, 125.6, 118.2, 50.6 (benzyl-*C*), 35.9 (C_d), 28.4 (C_c), 22.7 (C_b), 14.6 (C_a); *m*/*z* (ESI$^-$) 333 ([M-H]$^-$); HRMS (ESI$^+$) $C_{22}H_{21}N_2NaO_2$, ([M+Na]$^+$) requires 357.1573; found 357.1565.

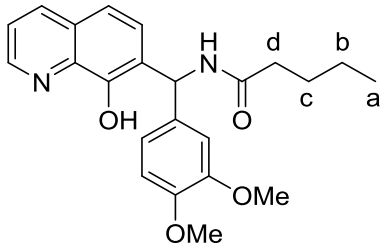
***N*-((8-Hydroxyquinolin-7-yl)(phenyl)methyl)-3-methylbutanamide S142**



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

mp 217-218 °C; ν_{max}/cm^{-1} 3274 (NH), 1636 (C=O); δ_H (400 MHz, DMSO-d_6) 10.40 (1 H, br. s., N*H*), 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_3); δ_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 (*C*H$_3$); *m*/*z* (ESI$^-$) 401 ([M-H]$^-$, 100 %); HRMS (ESI$^-$) $C_{24}H_{18}ClN_2O_2$, ([M-H]$^-$) requires 401.1062; found 401.1062.

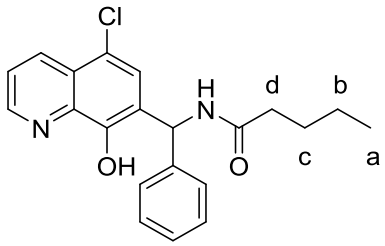
***N*-((3,4-Dimethoxyphenyl)(8-hydroxyquinolin-7-yl)methyl)pentanamide S143**



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

mp 150 - 152 °C; ν_{max}/cm^{-1} 3250 (NH), 2868 (OH), 1635 (C=O); δ_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 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 Hz, CH_{2d}), 1.67 (2 H, quin, *J*=7.5 Hz, CH_{2c}), 1.37 (2 H, sxt, *J*=7.5 Hz, CH_{2b}), 0.91 (3 H, t, *J*=7.5 Hz, CH_{3a}); δ_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 (O*C*H_3), 55.8 (O*C*H_3), 54.4 (benzyl-*C*), 36.7 (C_d), 27.8 (C_c), 22.4 (C_b), 13.8 (C_a); *m*/*z* (ESI$^-$) 393 ([M-H]$^-$); HRMS (ESI$^+$) $C_{23}H_{27}N_2O_4$, ([M+H]$^+$) requires 395.1965; found 395.1973.

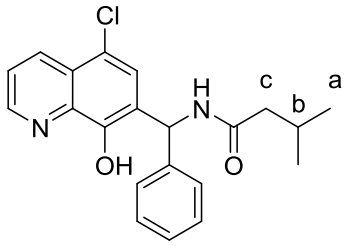
***N*-((5-Chloro-8-hydroxyquinolin-7-yl)(phenyl)methyl)pentanamide S144**



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

mp 205 °C; ν_{max}/cm^{-1} 3262 (NH), 1637 (C=O), 700 (C-Cl); δ_H (400 MHz, DMSO-d_6) 10.34 (1 H, br. s., N*H*), 8.89 - 9.00 (1 H, m, quinoline-*Ar*), 8.71 - 8.83 (1 H, m, quinoline-*Ar*), 8.39 - 8.53 (1 H, m, quinoline-*Ar*), 7.65 - 7.75 (2 H, m, *Ar*), 7.28 - 7.35 (2 H, m, *Ar*), 7.17 - 7.27 (3 H, m, *Ar*), 6.72 (1 H, d, *J*=9.0 Hz, benzyl-*H*), 2.23 (2 H, t, *J*=7.0 Hz, C$H_{2/d}$), 1.51 (2 H, quin, *J*=7.0 Hz, C$H_{2/c}$), 1.26 (2 H, sxt, *J*=7.0 Hz, C$H_{2/b}$), 0.86 (3 H, t, *J*=7.0 Hz, C$H_{2/a}$); δ_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_c), 22.6 (C_b), 14.6 (C_a); *m*/*z* (ESI$^-$) 367 ([M-H]$^-$); HRMS (ESI$^-$) $C_{21}H_{21}ClN_2NaO_2$, ([M+Na]$^+$) requires 391.1184; found 391.1180.

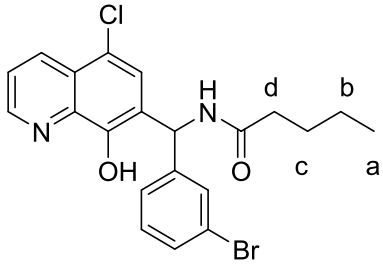
***N*-((5-Chloro-8-hydroxyquinolin-7-yl)(phenyl)methyl)-3-methylbutanamide S145**



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.

mp 199 °C; ν_{max}/cm^{-1} 3235 (NH), 1633 (C=O), 700 (C-Cl); δ_H (400 MHz, DMSO-d_6) 10.34 (1 H, br. s., N*H*), 8.89 - 8.99 (1 H, m, quinoline-*Ar*), 8.72 - 8.83 (1 H, m, quinoline-*Ar*), 8.41 - 8.51 (1 H, m, quinoline-*Ar*), 7.62 - 7.79 (2 H, m, *Ar*), 7.17 - 7.36 (5 H, m, *Ar*), 6.72 (1 H, d, *J*=8.5 Hz, benzyl-*H*), 2.09 - 2.13 (2 H, m, C$H_{2/c}$), 2.01 (1 H, m, CH_b), 0.87 (6 H, dd, *J*=8.0, 7.0 Hz, 2xC$H_{3/a}$); δ_C (100 MHz, DMSO-d_6) 171.9 (*C*=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 (benzyl-*C*), 45.4 (C$H_{2/c}$), 26.6 (CH_b), 23.2 (C$H_{3/a}$); *m/z* (ESI$^-$) 367 ([M-H]$^-$); HRMS (ESI$^-$) $C_{21}H_{21}ClN_2NaO_2$, ([M+Na]$^+$) requires 391.1184; found 391.1180.

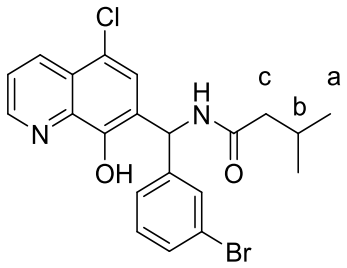
***N*-((3-Bromophenyl)(5-chloro-8-hydroxyquinolin-7-yl)methyl)pentanamide S146**



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.

mp 211 °C; ν_{max}/cm^{-1} 3250 (NH), 1639 (C=O), 688 (C-Cl); δ_H (400 MHz, DMSO-d_6) 10.46 (1 H, br. s., N*H*), 8.90 - 9.01 (1 H, m, quinoline-*Ar*), 8.76 - 8.87 (1 H, m, quinoline-*Ar*), 8.39 - 8.54 (1 H, m, quinoline-*Ar*), 7.65 - 7.77 (2 H, m, *Ar*), 7.38 - 7.49 (2 H, m, *Ar*), 7.19 - 7.34 (2 H, m, *Ar*), 6.69 (1 H, d, *J*=8.5 Hz, benzyl-*H*), 2.24 (2 H, t, *J*=7.0 Hz, C$H_{2/d}$), 1.51 (2 H, quin, *J*=7.0 Hz C$H_{2/c}$), 1.26 (2 H, sxt, *J*=7.0 Hz C$H_{2/b}$), 0.86 (3 H, t, *J*=7.0 Hz C$H_{3/a}$); δ_C (100 MHz, DMSO-d_6) 172.6 (*C*=O), 150.2, 145.6, 139.5, 133.4, 131.6, 130.7, 130.3, 127.0, 126.8, 125.8, 125.6, 123.9, 122.6, 119.6, 50.0 (benzyl-*C*), 35.8 (C$H_{2/d}$), 28.3 (C$H_{2/c}$), 22.6 (C$H_{2/b}$), 14.5 (C$H_{3/a}$); *m/z* (ESI$^-$) 445 ([M-H]$^-$); HRMS (ESI$^-$) $C_{21}H_{19}BrClN_2O_2$, ([M-H]$^-$) requires 445.0324; found 445.0318.

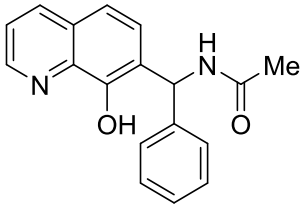
***N*-((3-Bromophenyl)(5-chloro-8-hydroxyquinolin-7-yl)methyl)-3-methylbutanamide S147**



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

mp 212 °C; ν_{max}/cm^{-1} 3206 (NH), 1658 (C=O), 684 (C-Cl); δ_H (400 MHz, DMSO-d_6) 10.45 (1 H, br. s., N*H*), 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, C$H_{2/c}$), 1.94 - 2.06 (1 H, m CH_b), 0.87 (6 H, m,); δ_C (100 MHz, DMSO-d_6) 172.0 (*C*=O), 150.2, 145.6, 139.5, 133.4, 131.6, 130.7, 130.3, 127.0, 126.9, 125.8, 125.6, 124.0, 122.6, 119.6, 50.0 (benzyl-*C*), 45.4 (*C*H$_{2/c}$), 26.6 (*C*H$_b$), 23.1 (*C*H$_{3/a}$); *m*/*z* (ESI$^+$) 447 ([M+H]$^+$); HRMS (ESI$^-$) $C_{21}H_{19}BrClN_2O_2$, ([M-H]$^-$) requires 445.0324; found 445.0313.

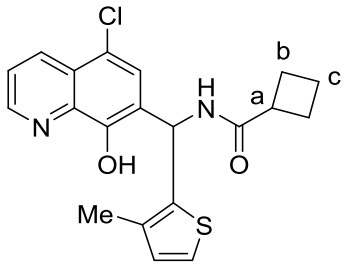
***N*-((8-Hydroxyquinolin-7-yl)(phenyl)methyl)acetamide S148[4]**



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; ν_{max}/cm^{-1} 3305 (NH), 1644 (C=O); δ_H (400 MHz, DMSO-d_6) 9.97 (1 H, br. s. , N*H*), 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, CH_3); δ_C (100 MHz, DMSO-d_6) 169.4 (*C*=O), 150.3, 149.2, 143.4, 138.9, 136.9, 129.1, 128.4, 127.9, 127.6, 127.3, 125.6, 122.6, 118.2, 50.7 (benzyl-*C*), 23.5 (*C*H$_3$); *m*/*z* (ESI$^-$) 291 ([M-H]$^-$); HRMS (ESI$^+$) $C_{18}H_{16}IN_2NaO_2$, ([M+Na]$^+$) requires 315.1104; found 315.1093.

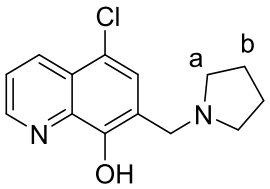
***N*-((5-Chloro-8-hydroxyquinolin-7-yl)(3-methylthiophen-2-yl)methyl)cyclobutanecarboxamide S149**



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_{max}/cm^{-1} 3270 (NH), 1640 (C=O); δ_H (400 MHz, $CDCl_3$) 10.41 (1 H, br. s., N*H*), 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_a), 2.11 (3 H, s, CH_3), 1.67 - 2.09 (6 H, m, $H_{b/c}$); δ_C (100 MHz, $CDCl_3$) 173.8 (*C*=O), 150.2, 150.1, 140.3, 139.4, 134.7, 133.4, 131.3, 127.8, 126.8, 125.9, 125.8, 123.8, 119.2, 44.9 (benzyl-*C*), 25.7, 25.2, 18.7, 14.3 (*C*H_3); *m*/*z* (ESI$^-$) 386 ([M-H]$^-$); HRMS (ESI$^+$) $C_{20}H_{19}ClN_2NaO_2S$, ([M+Na]$^+$) requires 409.0748; found 409.0733.

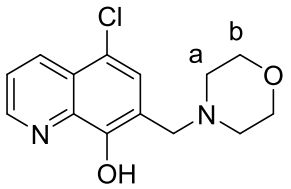
5-Chloro-7-(pyrrolidin-1-ylmethyl)quinolin-8-ol S150



A mixture of 5-chloro-8-hydroxyquinoline (180 mg, 1 mmol), paraformaldehyde (36.2 mg, 1.2 mmol), pyrrolidine (100 µL, 1.2 mmol), and triethylamine (170 µL, 1.2 mmol) was stirred in ethanol (15 mL) for 16 h under reflux. The volume of the reaction mixture was reduced and the precipitate was filtered, washed with EtOH, H_2O, and dried to give **S150** (60 mg, 23 %) as a light-brown powder.

mp 125 °C; δ_H (400 MHz, DMSO-d_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_2), 2.46 - 2.57 (4 H, m, H_b), 1.67 - 1.77 (4 H, m, H_a); δ_C (100 MHz, DMSO-d_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 (C_a); *m*/*z* (ESI$^+$) 263 ([M+H]$^+$); HRMS (ESI$^+$) $C_{14}H_{16}ON_2Cl$, ([M+H]$^+$) requires 263.0946; found 263.0942.

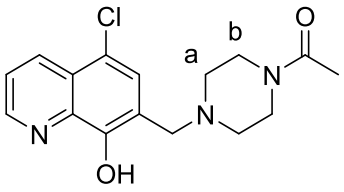
5-Chloro-7-(morpholinomethyl)quinolin-8-ol S151



A mixture of 5-chloro-8-hydroxyquinoline (180 mg, 1 mmol), paraformaldehyde (36.2 mg, 1.2 mmol), morpholine (103 µL, 1.2 mmol), and triethylamine (170 µL, 1.2 mmol) was stirred in ethanol (15 mL) for 16 h under reflux. The volume of the reaction mixture was reduced and the precipitate was filtered, washed with EtOH, H_2O, and dried to give **S151** (42 mg, 15 %) as an off-white powder.

mp 112 °C; ν_{max}/cm^{-1} 3313 (OH); δ_H (400 MHz, DMSO-d_6) 8.73 - 9.06 (1 H, m, quinoline-*Ar*), 8.35 - 8.55 (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-CH_2), 3.55 - 3.64 (4 H, m, H_b), 2.41 - 2.48 (4 H, m, H_a); δ_C (100 MHz, DMSO-d_6) 151.4, 149.4, 139.2, 132.9, 129.1, 125.4, 123.2, 120.9, 118.6, 66.7 , (H_a), 56.4, 53.6; *m/z* (ESI$^+$) 279 ([M+H]$^+$); HRMS (ESI$^+$) $C_{14}H_{16}O_2N_2Cl$, ([M+H]$^+$) requires 279.0895; found 279.0891.

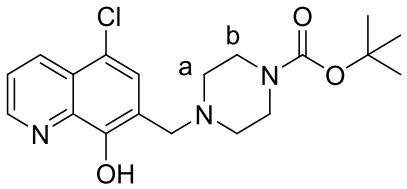
1-(4-((5-Chloro-8-hydroxyquinolin-7-yl)methyl)piperazin-1-yl)ethan-1-one S152



A mixture of 5-chloro-8-hydroxyquinoline (180 mg, 1 mmol), paraformaldehyde (36.2 mg, 1.2 mmol), 1-acetylpiperazine (171 µL, 1.2 mmol), and triethylamine (170 µL, 1.2 mmol) was stirred in ethanol (15 mL) for 16 h under reflux. The volume of the reaction mixture was reduced and the precipitate was filtered, washed with EtOH, H_2O, and dried to give **S152** (45 mg, 14 %) as a light-brown powder.

mp > 250 °C; ν_{max}/cm^{-1} 1621 (C=O); δ_H (400 MHz, DMSO-d_6) 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-CH_2), 3.45 - 3.74 (4 H, m, H_b), 2.91 - 3.24 (4 H, m, H_a), 2.03 (3 H, s, CH_3); δ_C (100 MHz, DMSO-d_6) 169.0 (*C*=O), 153.4, 153.1, 149.4, 134.2, 131.3, 127.2, 124.6, 119.1, 113.3, 53.1 (C_b), 50.6 (C_a), 47.7 (benzyl-*C*), 21.5 (*C*H$_3$); *m/z* (ESI$^+$) 320 ([M+H]$^+$); HRMS (ESI$^+$) $C_{16}H_{19}O_2N_3Cl$, ([M+H]$^+$) requires 320.1160; found 320.1156.

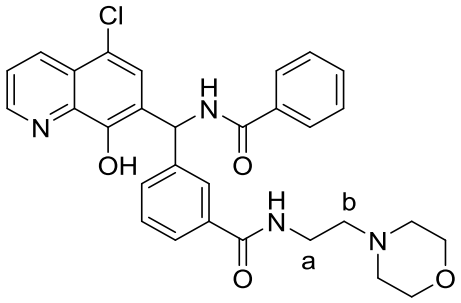
***tert*-Butyl 4-((5-Chloro-8-hydroxyquinolin-7-yl)methyl)piperazine-1-carboxylate S153**



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, H_2O, and dried to give **S153** (79 mg, 21 %) as a light-brown powder.

mp 201 °C; ν_{max}/cm^{-1} 1701 (C=O); δ_H (400 MHz, DMSO-d_6) 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, quinoline-*Ar*), 3.71 (2 H, s, benzyl-CH_2), 3.27 - 3.38 (4 H, m, H_b), 2.33 - 2.45 (4 H, m, H_a), 1.39 (9 H, s, C(CH_3)$_3$); δ_C (100 MHz, DMSO-d_6) 154.2 (*C*=O), 151.3, 149.4, 139.2, 132.9, 129.1, 125.4, 123.2, 121.0, 118.7, 79.2 (C_b), 55.9 (benzyl-*C*H$_2$), 52.9 (C_a), 28.5 (C(*C*H$_3$)$_3$); *m/z* (ESI$^+$) 378 ([M+H]$^+$); HRMS (ESI$^+$) $C_{19}H_{25}O_3N_3Cl$, ([M+H]$^+$) requires 378.1579; found 378.1574.

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

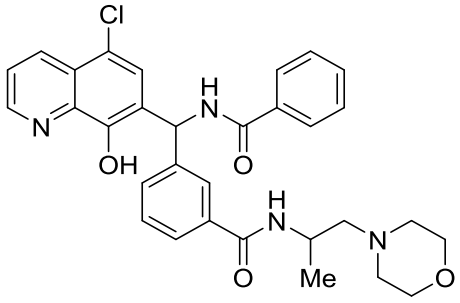


To a solution of **12** (217 mg, 0.5 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (96 mg, 0.5 mmol), hydroxybenzotriazole (81 mg, 0.6 mmol), and diisopropylethylamine (261 µL, 15 mmol) in DMF (10 mL) was added 4-(2-aminoethyl)morpholine (130 mg, 0.5 mmol). The reaction mixture was stirred for 16 h at 50 °C. The reaction mixture was then concentrated *in vacuo* and the resulting residue purified *via* flash column chromatography (0 % - 10 % MeOH, CH_2Cl_2, 1 % NH_4OH) to give **S154** (160 mg, 59 %) as a white solid.

mp 144 °C; ν_{max}/cm^{-1} 3268 (NH), 1638 (C=O); δ_H (400 MHz, $CDCl_3$) 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, H_a), 2.46 (2 H, t, *J*=6.0 Hz, H_b), 2.30 - 2.40 (4 H, m); δ_C (100 MHz, DMSO-d_6) 167.3, 166.6,

148.5, 141.5, 138.7, 135.1, 134.0, 133.4, 131.8, 130.1, 128.9, 128.6, 127.7, 127.2, 126.1, 125.8, 122.8, 122.5, 121.1, 86.8, 55.9, 54.6, 53.2, 36.0; *m/z* (ESI$^+$) 545 ([M+H]$^+$); HRMS (ESI$^+$) $C_{30}H_{30}O_4N_4Cl$, ([M+H]$^+$) requires 545.1950; found 545.1945.

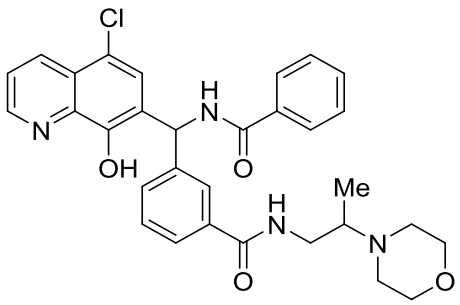
3-(Benzamido(5-chloro-8-hydroxyquinolin-7-yl)methyl)-N-(1-morpholinopropan-2-yl)benzamide S155



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, CH_2Cl_2, 1 % NH_4OH) to give **S155** (193 mg, 69 %) as a white solid.

mp 216 °C; ν_{max}/cm^{-1} 3393 (NH), 1638 (C=O); δ_H (400 MHz, DMSO-d_6) 10.48 (1 H, br. s., N*H*), 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, C*H*), 3.45 - 3.53 (4 H, m, OCH_2), 2.33 - 2.43 (4 H, m, NCH_2), 2.22 - 2.32 (2 H, m, CH_2), 1.13 (3 H, d, *J*=6.5 Hz, C*H*3); δ_C (100 MHz, DMSO-d_6) 166.5 (*C*=O), 166.0 (*C*=O), 150.1, 149.7, 142.3, 142.3, 139.1, 135.6, 134.6, 133.0, 131.9, 130.3, 128.8, 128.1, 127.2, 127.0, 126.2, 125.6, 125.2, 123.5, 119.0, 66.7, 63.9, 53.9, 50.6, 42.6, 19.4 (*C*H$_3$); *m/z* (ESI$^+$) 559 ([M+H]$^+$); HRMS (ESI$^+$) $C_{31}H_{32}O_4N_4Cl$, ([M+H]$^+$) requires 559.2107; found 559.2100.

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

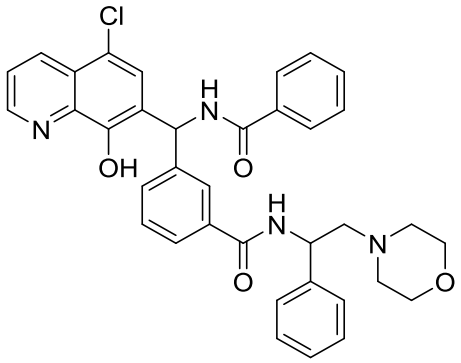


To a solution of **12** (217 mg, 0.5 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (96 mg, 0.5 mmol), hydroxybenzotriazole (81 mg, 0.6 mmol), and diisopropylethylamine (261 μL, 15 mmol) in DMF (10 mL) was added 2-

(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, CH_2Cl_2, 1 % NH_4OH) to give **S156** (211 mg, 75 %) as a white solid.

mp 196 °C; ν_{max}/cm^{-1} 3293 (NH), 1653 (C=O), 1635 (C=O); δ_H (400 MHz, DMSO-d_6) 10.50 (1 H, br. s., N*H*), 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, OCH_2), 3.29 - 3.42 (4 H, m, NCH_2), 2.71 - 2.77 (1 H, m, C*H*), 2.36 - 2.48 (2 H, m, CH_2), 0.90 - 0.95 (3 H, m, CH_3); δ_C (100 MHz, DMSO-d_6) 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, 128.1, 127.2, 126.7, 126.1, 125.5, 125.2, 123.5, 119.1, 67.1, 58.6, 50.6, 49.0, 42.2, 12.8 (*C*H_3); *m/z* (ESI$^+$) 559 ([M+H]$^+$); HRMS (ESI$^+$) $C_{31}H_{32}O_4N_4Cl$, ([M+H]$^+$) requires 559.2107; found 559.2103.

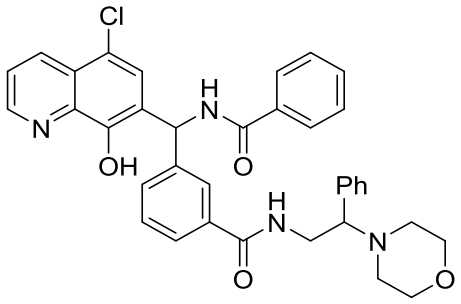
3-(Benzamido(5-chloro-8-hydroxyquinolin-7-yl)methyl)-N-(2-morpholino-1-phenylethyl)benzamide S157



To a solution of **12** (217 mg, 0.5 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (96 mg, 0.5 mmol), hydroxybenzotriazole (81 mg, 0.6 mmol), and diisopropylethylamine (261 µL, 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, CH_2Cl_2, 1 % NH_4OH) to give **S157** (267 mg, 86 %) as a white solid.

mp 217 °C; ν_{max}/cm^{-1} 3271 (NH), 1637 (C=O); δ_H (400 MHz, DMSO-d_6) 10.49 (1 H, br. s., N*H*), 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, OCH_2), 2.90 (1 H, s, C*H*), 2.32 - 2.49 (4 H, m, NCH_2); δ_C (100 MHz, DMSO-d_6) 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$^+$) $C_{36}H_{34}O_4N_4Cl$, ([M+H]$^+$) requires 621.2263; found 621.2258.

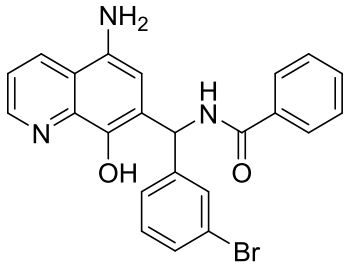
3-(Benzamido(5-chloro-8-hydroxyquinolin-7-yl)methyl)-N-(2-morpholino-2-phenylethyl)benzamide S158



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, 15 mmol) in DMF (10 mL) was added 2-(morpholin-4-yl)-2-phenylethan-1-amine (103 mg, 0.5 mmol). The reaction mixture was stirred for 16 h at 50 °C. The reaction mixture was then concentrated *in vacuo* and the resulting residue purified *via* flash column chromatography (0 % - 10 % MeOH, CH_2Cl_2, 1 % NH_4OH) to give **S158** (310 mg, 100 %) as a white solid.

mp 201 °C; ν_{max}/cm^{-1} 3297 (NH), 1640 (C=O); δ_H (200 MHz, $CDCl_3$) 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, CH_2), 2.94 (4 H, m), 2.87 (4 H, m); *m/z* (ESI$^+$) 621 ([M+H]$^+$); HRMS (ESI$^+$) $C_{36}H_{34}O_4N_4Cl$, ([M+H]$^+$) requires 621.2263; found 621.2257.

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

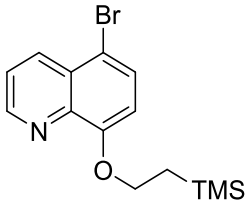


S58 (256 mg, 0.54 mmol) was suspended in ethanol (10 mL) and a 1M aqueous solution of sodium dithionite (5 mL) was added. The mixture was stirred under reflux for 16 h, cooled to room temperature and concentrated under reduced pressure. The residue was redissolved in CH_2Cl_2 and extracted with sodium 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; ν_{max}/cm^{-1} 3338 (NH), 1633 (C=O); δ_H (400 MHz, DMSO-d_6) 9.15 - 9.25 (1 H, m, quinoline-*Ar*), 8.95 (1 H, br. s., N*H*), 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., NH_2); δ_C (100 MHz, DMSO-d_6) 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^-) $C_{23}H_{17}BrN_3O_2$, ($[M-H]^-$) requires 446.0474; found 446.0499.

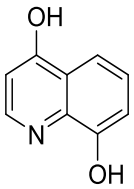
5-Bromo-8-(2-(trimethylsilyl)ethoxy)quinolone S160[18]



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 *in vacuo*. The crude product was purified *via* flash column chromatography (5 % - 50 % EtOAc, cyclohexane) to give **S160** (455 mg, 78 %) as a light-yellow oil.

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(*C*H_3)$_3$); *m/z* (ESI^+) 324 ($[M+H]^+$).

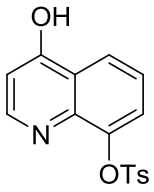
Quinoline-4,8-diol S161[19]



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

mp 311 °C; δ_H (400 MHz, DMSO-d_6) 11.39 (1 H, br. s., O*H*), 10.74 (1 H, br. s., O*H*), 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 ($[M-H]^-$);

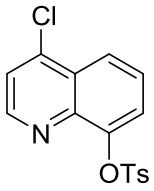
4-Hydroxyquinolin-8-yl 4-methylbenzenesulfonate S162[19]



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

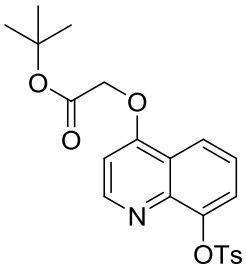
4-Chloroquinolin-8-yl 4-methylbenzenesulfonate S163[19]



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 ^{o}C; δ_H (400 MHz, DMSO-d_6) 8.71 - 8.79 (1 H, m, *Ar*), 8.11 - 8.21 (1 H, m, *Ar*), 7.72 - 7.85 (4 H, m, *Ar*), 7.58 - 7.64 (1 H, m, *Ar*), 7.38 - 7.44 (2 H, m, *Ar*), 2.38 (3 H, s, C*H*$_3$); δ_C (100 MHz, DMSO-d_6) 151.7, 146.5, 145.8, 142.7, 142.1, 132.9, 130.8, 129.2, 128.7, 127.9, 124.2, 124.0, 123.4, 22.0 (*C*H$_3$); *m*/*z* (FI$^+$) 333 ([M]$^+$);

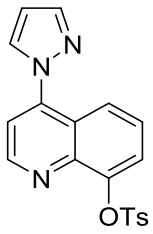
***tert*-Butyl 2-((8-(Tosyloxy)quinolin-4-yl)oxy)acetate S164**



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 H_2O and brine. The organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was purified *via* flash column chromatography (25 % - 50 % EtOAc, cyclohexane) to give **S164** (745 mg, 73 %) as an off-white powder.

mp 153 °C; δ_H (400 MHz, $CDCl_3$) 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, CH_2), 2.27 (3 H, s, CH_3), 1.39 (9 H, s, C(CH_3)$_3$); δ_C (100 MHz, $CDCl_3$) 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 (*C*H$_2$), 28.0 (C(*C*H$_3$)$_3$), 21.6 (*C*H$_3$); *m*/*z* (ESI$^+$) 430 ([M+H]$^+$); HRMS (ESI$^+$) $C_{22}H_{24}NO_6S$, ([M+H]$^+$) requires 430.1319; found 430.1323.

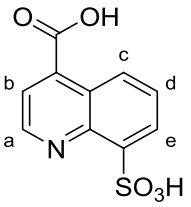
4-(1H-Pyrazol-1-yl)quinolin-8-yl 4-methylbenzenesulfonate S165[20]



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; δ_H (400 MHz, $CDCl_3$) 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, CH_3); δ_C (100 MHz, $CDCl_3$) 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 (C*H*$_3$); *m*/*z* (ESI$^+$) 366 ([M+H]$^+$);

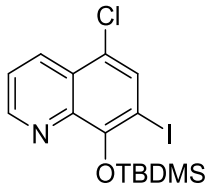
8-Sulfoquinoline-4-carboxylic acid S166[21]



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; ν_{max}/cm^{-1} 1721 (C=O); δ_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); δ_C (100 MHz, DMSO-d_6) 166.5 (*C*=O), 148.5, 146.9, 138.8, 135.2, 133.3, 130.9, 129.1, 126.7, 123.5; *m*/*z* (ESI$^-$) 252 ([M-H]$^-$); HRMS (ESI$^+$) $C_{10}H_7NNaO_2S$, ([M+Na]$^+$) requires 275.9937; found 275.9940.

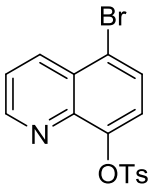
8-((*tert*-Butyldimethylsilyl)oxy)-5-chloro-7-iodoquinoline S167[22]



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_2Cl_2 (50 mL) at room temperature. The reaction mixture was stirred for 12 h, diluted with Et_2O (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; ν_{max}/cm^{-1} 1096 (Si-O); δ_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, $Si(CH_3)_2C(CH_3)_3$), 0.38 (6 H, s, $Si(CH_3)_2C(CH_3)_3$)); δ_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 $Si(CH_3)_2C(CH_3)_3$), 19.6 $Si(CH_3)_2C(CH_3)_3$), -2.1 $Si(CH_3)_2C(CH_3)_3$); *m*/*z* (ESI$^+$) 420 ([M+H]$^+$); HRMS (ESI$^+$) $C_{15}H_{20}ClINOSi$, ([M+H]$^+$) requires 420.0042; found 420.0043.

5-Bromoquinolin-8-yl 4-methylbenzenesulfonate S168

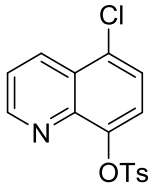


5-Bromo-8-hydroxyquinoline (2.23 g, 10.0 mmol) was dissolved in a 1M aqueous sodium hydroxide solution (11.0 mL). A solution of *p*-toluenesulfonyl chloride (1.91 g, 11.0 mmol) in acetone (7 mL) was added dropwise. The reaction mixture was

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; ν_{max}/cm^{-1} 3305 (NH), 1369 (S=O); δ_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, C*H*$_3$); δ_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 (*C*H$_3$); *m/z* (ESI$^+$) 378 ([M+H]$^+$); HRMS (ESI$^+$) $C_{16}H_{12}BrNNaO_3S$, ([M+Na]$^+$) requires 399.9613; found 399.9606.

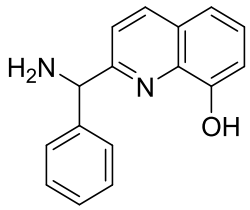
5-Chloroquinolin-8-yl 4-methylbenzenesulfonate S169[16]



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; δ_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, C*H*$_3$); *m/z* (ESI$^+$) 334 ([M+H]$^+$).

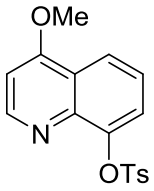
2-(Amino(phenyl)methyl)quinolin-8-ol S170[4]



Phenyllithium (1.8 M in nBu_2O, 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_2O) was added dropwise until hydrogen evolution ceased. The mixture was treated with saturated aqueous $NaHCO_3$ and then extracted three times with $CHCl_3$. Combined organic layers were dried over anhydrous $MgSO_4$, filtered and reduced to dryness. The organic residue was then recrystallised from toluene to give **S170** as a bright-yellow solid (276 mg, 45 %).

mp 149-151 °C; ν_{max}/cm^{-1} 1244 (NH_2); δ_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*); δ_C (100 MHz, Acetone-d_6) 137.1, 128.7, 128.5, 128.1, 127.7, 127.6, 127.2, 126.7, 121.6, 118.3, 117.9, 110.4, 70.6 (benzyl-*C*); *m/z* (ESI$^+$) 251 ([M+H]$^+$, 100 %); HRMS (ESI) $C_{16}H_{14}N_2O$, requires 250.1106; found 250.1110.

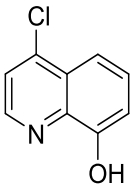
4-Methoxyquinolin-8-yl 4-methylbenzenesulfonate S171[19]



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 trifluoromethylsulfonate (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; δ_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); δ_C (100 MHz, DMSO-d_6) 175.9 (*C*OCH$_3$), 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 (CO*C*H$_3$), 22.1 (*C*H$_3$); *m/z* (ESI$^+$) 352 ([M+Na]$^+$).

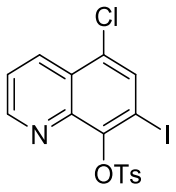
4-Chloroquinolin-8-ol S172[20]



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

mp 144 °C; ν_{max}/cm^{-1} 3154 (OH); δ_H (400 MHz, DMSO-d_6) 10.14 (1 H, br. s., O*H*), 8.67 - 8.87 (1 H, m, *Ar*), 7.67 - 7.82 (1 H, m, *Ar*), 7.49 - 7.65 (2 H, m, *Ar*), 7.07 - 7.31 (1 H, m, *Ar*); δ_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* (FI$^+$) 179 ([M]$^+$).

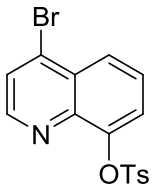
5-Chloro-7-iodoquinolin-8-yl 4-methylbenzenesulfonate S173[23]



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 ^{o}C; ν_{max}/cm^{-1} 1376 (S=O); δ_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, SC*H*CH), 7.66 - 7.77 (1 H, m, *Ar*), 7.47 (2 H, d, *J*=8.0 Hz, SCHC*H*), 2.45 (3 H, s, CH_3); δ_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*H_3); *m/z* (ESI$^-$) 457 ([M-H]$^-$); HRMS (ESI$^+$) $C_{16}H_{11}ClINNaO_3S$, ([M+Na]$^+$) requires 481.9085; found 481.9074.

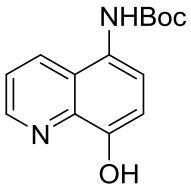
4-Bromoquinolin-8-yl 4-methylbenzenesulfonate S174[20]



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 ^{o}C; δ_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, CH_3); δ_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, 21.7 (*C*H_3); *m/z* (ESI$^+$) 378 ([M+H]$^+$); HRMS (ESI$^+$) $C_{16}H_{13}BrNO_3S$, ([M+H]$^+$) requires 377.9794; found 377.9786.

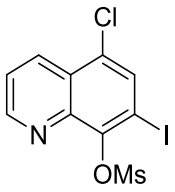
***tert*-Butyl (8-hydroxyquinolin-5-yl)carbamate S175**



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

mp 188 °C; ν_{max}/cm^{-1} 3229 (NH) 1680 (Boc C=O); δ_H (400 MHz, DMSO-d_6) 9.71 (1 H, s, *Ar*), 9.02 (1 H, br. s., N*H*), 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(C*H*$_3$)$_3$); δ_C (100 MHz, DMSO-d_6) 155.4 (*C*=O), 151.9, 148.8, 139.1, 132.9, 125.5, 124.8, 122.3, 111.3, 79.6 (*C*(CH$_3$)$_3$), 29.0 (C(*C*H$_3$)$_3$); *m/z* (ESI$^-$) 259 ([M-H]$^-$); HRMS (ESI$^+$) $C_{14}H_{16}N_2NaO_3$, ([M+Na]$^+$) requires 283.1053; found 283.1053.

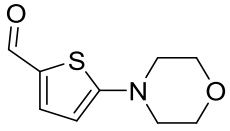
5-Chloro-7-iodoquinolin-8-yl methanesulfonate S176



Methanesulfonyl chloride (1 mL, 13 mmol) was added dropwise to a stirring solution of clioquinol (3.1 g, 10 mmol) and triethylamine (2.1 mL) in CH_2Cl_2 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 $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography using EtOAc/Cyclohexane (30:70) as eluent to give **S176** (3.06 g, 80 %) as a light-orange powder.

mp 177 °C; ν_{max}/cm^{-1} 1347 (S=O); δ_H (400 MHz, DMSO-d_6) 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. C*H*$_3$); δ_C (100 MHz, DMSO-d_6) 153.2, 148.3, 142.2, 135.9, 134.1, 130.0, 127.2, 124.7, 95.8, 42.2 (*C*H$_3$); *m/z* (ESI$^+$) 406 ([M+Na]$^+$); HRMS (ESI$^+$) $C_{10}H_7ClINNaO_3S$, ([M+Na]$^+$) requires 405.8772; found 405.8767.

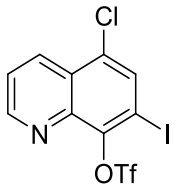
5-Morpholinothiophene-2-carbaldehyde S177[24]



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_2Cl_2. The organic layer was washed with a saturated aqueous solution of NH_4Cl, brine, and concentrated under reduced pressure. The crude product was purified by flash column chromatography using MeOH/CH_2Cl_2 (5:95) to give **S177** (1.22 g, 62 %) as a white powder.

mp 127 °C; ν_{max}/cm^{-1} 1637 (C=O); δ_H (400 MHz, $CDCl_3$) 9.57 (1 H, s, C*H*O), 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); δ_C (100 MHz, $CDCl_3$) 180.0 (*C*HO), 167.9, 139.7, 128.2, 104.5, 65.9, 49.5; *m*/*z* (ESI$^+$) 199 ([M+H]$^+$); HRMS (ESI$^+$) $C_9H_{12}NO_2S$, ([M+H]$^+$) requires 199.0583; found 199.0587.

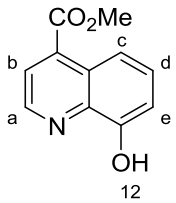
5-Chloro-7-iodoquinolin-8-yl trifluoromethanesulfonate S178



A solution of trifluoromethanesulfonic anhydride (4 mL, 24 mmol) in CH_2Cl_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_2Cl_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_2O, quenched with 10 % aqueous HCl and washed successively with saturated aqueous $NaHCO_3$ and brine. The solvent was removed under reduced pressure to afford **S178** (7.46 g, 85 %) as a white powder.

mp 92 °C; ν_{max}/cm^{-1} 1377 (S=O); δ_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*); δ_C (100 MHz, DMSO-d_6) 153.5, 147.6, 140.8, 136.1, 134.2, 131.5, 127.2, 125.3, 92.7; δ_F (377 MHz, DMSO-d_6) -71.9 (CF_3); *m*/*z* (FI$^+$) 437 ([M]$^+$); HRMS (FI$^+$) $C_{10}H_4ClF_3INO_3S$, ([M]$^+$) requires 436.8597; found 436.8598.

Methyl 8-hydroxyquinoline-4-carboxylate S179

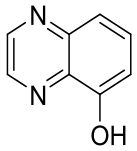


12

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_{max}/cm^{-1} 1725 (C=O); δ_H (400 MHz, DMSO-d_6) 9.06 (1 H, d, *J*=5.0 Hz, H_a), 8.07 - 8.14 (2 H, m, $H_{b/e}$), 7.67 (1 H, t, *J*=8.0 Hz), 7.34 (1 H, d, *J*=7.5 Hz, H_c), 3.17 (3 H, s, CH_3); δ_C (100 MHz, DMSO-d_6) 167.0 (*C*=O), 152.0, 146.6, 139.4, 136.1, 129.9, 125.7, 122.4, 115.5, 113.1, 48.6 (*C*H$_3$); *m/z* (FI$^+$) 188 ([M]$^+$); HRMS (FI$^+$) $C_{11}H_9NO_3$, ([M]$^+$) requires 203.0582; found 203.0585.

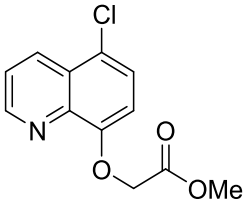
Quinoxalin-5-ol S180[25]



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_2O (60 mL) was heated to 60 °C. The 2,3-diaminophenol solution was then transferred into the sodium glyoxal bisulfite solution with a pipette and stirred for 1 h at 60 °C. After cooling to room temperature, 1N NaOH aq. was used to adjust the pH to ~8. The resulting aqueous solution was then extracted with EtOAc, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was purified *via* flash column chromatography (10 % - 50 % EtOAc, cyclohexane) to give **S180** (553 mg, 47 %) as a brown powder.

mp 101 °C; δ_H (400 MHz, methanol-d_4) 8.32 - 8.91 (2 H, m), 7.52 - 7.61 (1 H, m), 7.38 - 7.47 (1 H, m), 7.02 - 7.12 (1 H, m); δ_C (100 MHz, methanol-d_4) 153.4, 145.1, 143.1, 142.8, 133.8, 130.9, 118.5, 111.8; *m/z* (ESI$^+$) 147 ([M+H]$^+$); HRMS (ESI$^-$) $C_8H_5ON_2$, ([M-H]$^-$) requires 145.0407; found 145.0405.

Methyl 2-((5-Chloroquinolin-8-yl)oxy)acetate S181[26]

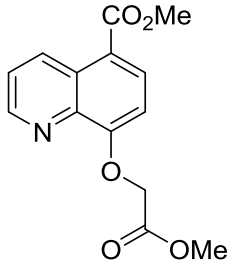


A suspension of 5-chloro-8-hydroxyquinoline (900 mg, 5 mmol), methyl bromoacetate (574 µL, 6 mmol), and potassium carbonate (850 mg, 6 mmol) was stirred in a mixture of acetone (10 mL) and tetrahydrofuran (10 mL) for 16 h under reflux. The solvent was evaporated and the residue redissolved in a mixture of EtOAc and H_2O. The organic layer was extracted with H_2O and brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was purified *via* flash column chromatography to give **S181** (995 mg, 79 %) as an off-white solid.

mp 105 °C; νmax/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, OCH2) 3.73

(3 H, s, CH3); δC (100 MHz, DMSO-d6) 169.4 (C=O), 153.3, 150.4, 140.5, 132.7, 127.1, 126.7, 123.6, 122.1, 110.8, 65.9 (OCH2), 52.4 (CH3); m/z (ESI+) 252 ([M+H]+); HRMS (ESI+) C12H11O3NCl, ([M+H]+) requires 252.0422; found 252.0417.

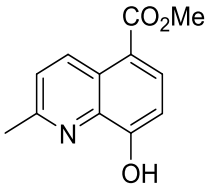
Methyl 8-(2-Methoxy-2-oxoethoxy)quinoline-5-carboxylate S182



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 Na_2SO_4 and concentrated *in vacuo*. The crude reaction product was purified *via* flash column chromatography (0 % - 10 % MeOH, CH_2Cl_2) to give **S182** (264 mg, 96 %) as an off-white solid.

mp 151 °C; ν_{max}/cm^{-1} 1767 (C=O); δ_H (400 MHz, DMSO-d_6) 9.19 - 9.40 (1 H, m, *Ar*), 8.82 - 9.04 (1 H, m, *Ar*), 8.13 - 8.29 (1 H, m, *Ar*), 7.56 - 7.81 (1 H, m, *Ar*), 7.03 - 7.36 (1 H, m, *Ar*), 5.17 (2 H, s, C*H*$_2$), 3.92 (3 H, s, C*H*$_3$), 3.75 (3 H, s, C*H*$_3$); δ_C (100 MHz, DMSO-d_6) 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 (*C*H$_2$), 52.6 (O*C*H$_3$), 52.5 (O*C*H$_3$); *m/z* (ESI$^+$) 276 ([M+H]$^+$); HRMS (ESI$^+$) $C_{14}H_{14}O_5N$, ([M+H]$^+$) requires 276.0867; found 276.0863.

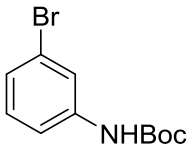
Methyl 8-Hydroxy-2-methylquinoline-5-carboxylate S183



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; ν_{max}/cm^{-1} 1702 (C=O); δ_H (200 MHz, DMSO-d_6) 9.44 - 9.80 (1 H, m), 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, OC*H*$_3$), 2.93 (3 H, s, C*H*$_3$); *m/z* (ESI$^+$) 218 ([M+H]$^+$); HRMS (ESI$^+$) $C_{12}H_{12}O_3N$, ([M+H]$^+$) requires 218.0812; found 218.0809.

***tert*-Butyl (3-bromophenyl)carbamate S184**[27]

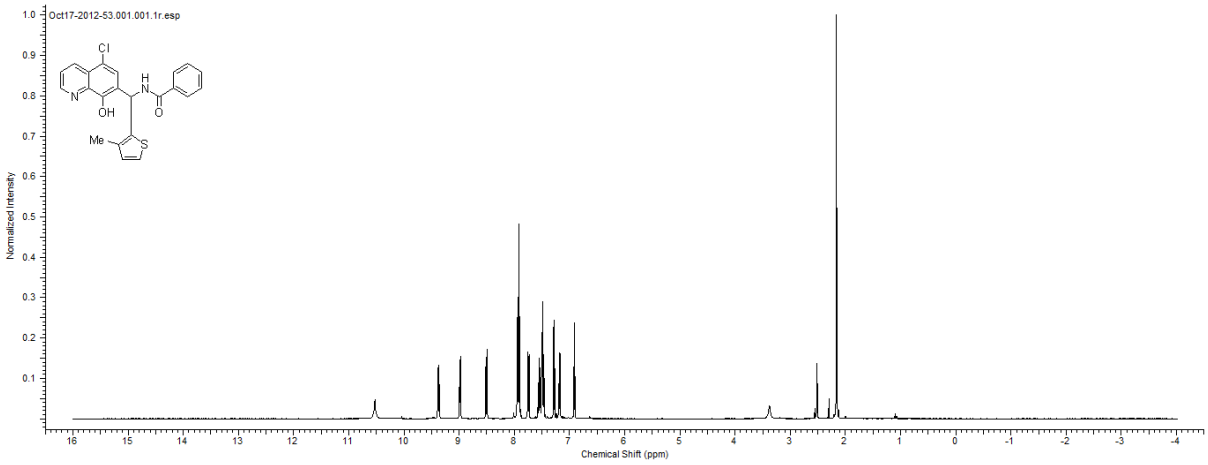


Di-*tert*-butyl dicarbonate (2.18 g, 10 mmol) was added portionwise to a stirring solution of 3-bromoaniline (1088 µL, 10 mmol) in CH_2Cl_2 at room temperature. After 18 h the reaction mixture was poured into ice-cold water and extracted with CH_2Cl_2. The organic layer was washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to give **S184** (2.72g, 100 %) as a light-pink solid.

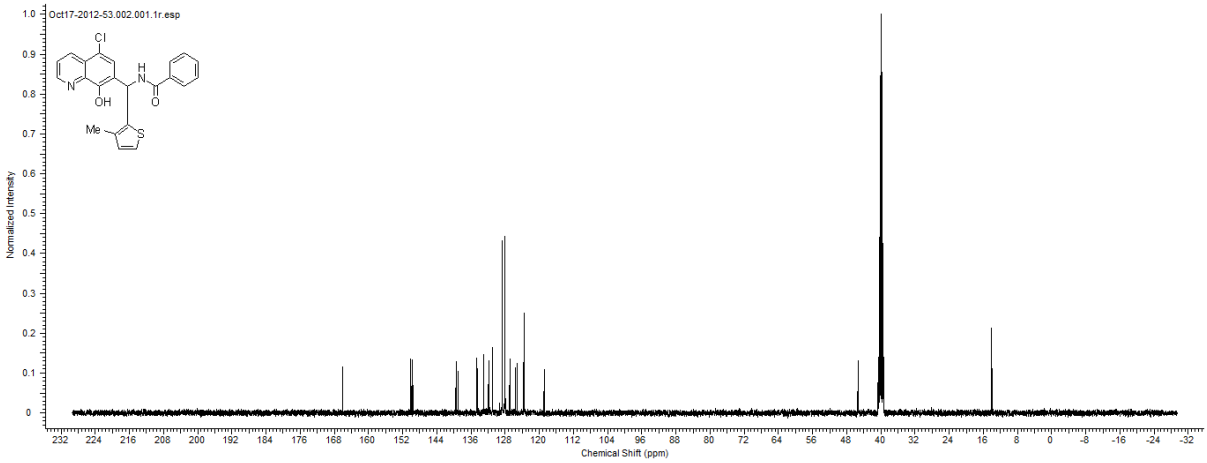
mp 78 °C; δ_H (400 MHz, DMSO-d_6) 9.56 (1 H, s, N*H*), 7.76 (1 H, s, *Ar*), 7.35 - 7.41 (1 H, m, *Ar*), 7.16 - 7.23 (1 H, m, *Ar*), 7.10 - 7.15 (1 H, m, *Ar*), 1.47 (9 H, s, C(CH_3)$_3$); δ_C (100 MHz, DMSO-d_6) 153.4 (*C*=O), 142.1, 131.5, 125.4, 121.1, 117.7, 80.4 (*C*(CH_3)$_3$), 28.9 (C(*C*H_3)$_3$); *m/z* (ESI$^-$) 270 ([M-H]$^-$).

NMR Spectra of compounds tested in cells

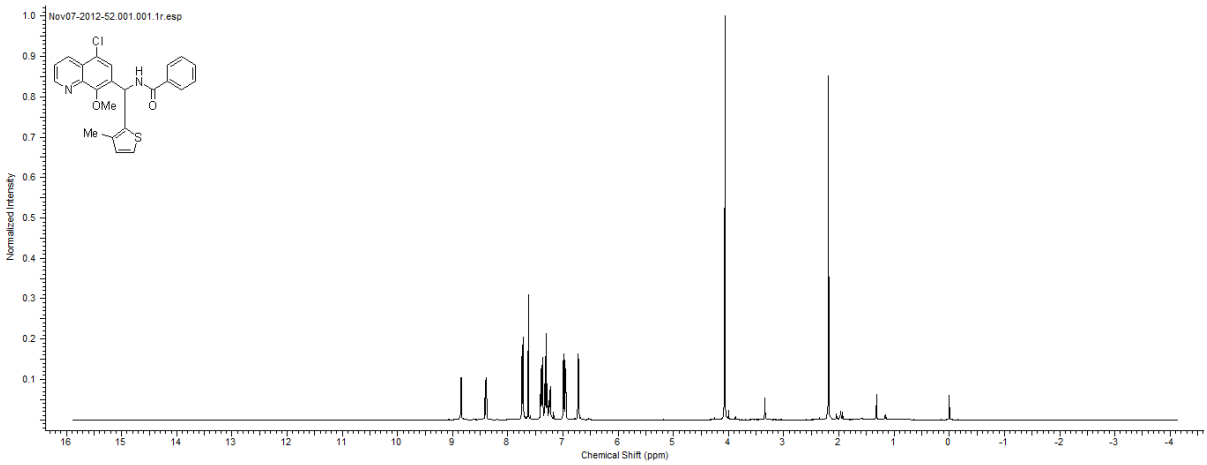
1H NMR of **CCT1** in DMSO



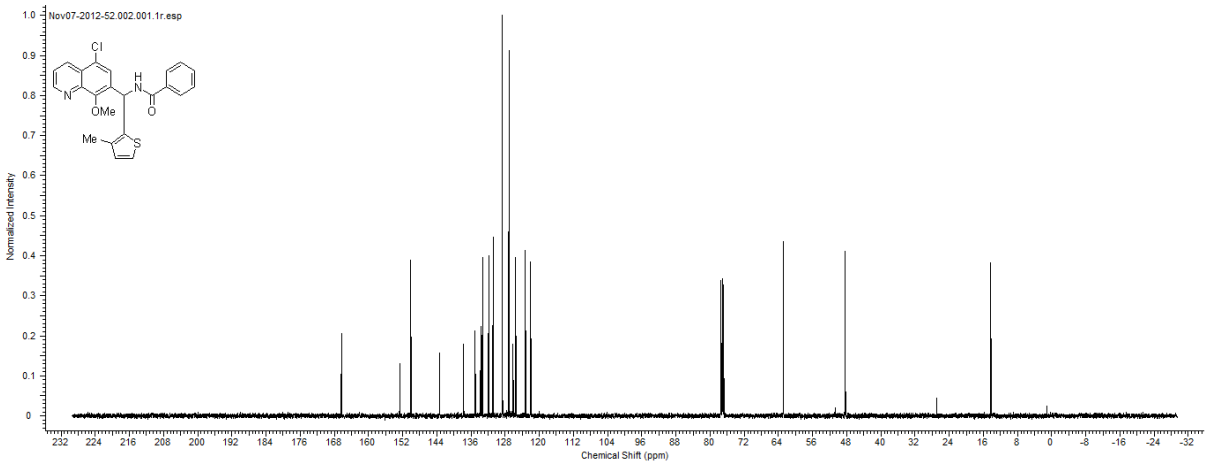
13C NMR of **CCT1** in DMSO



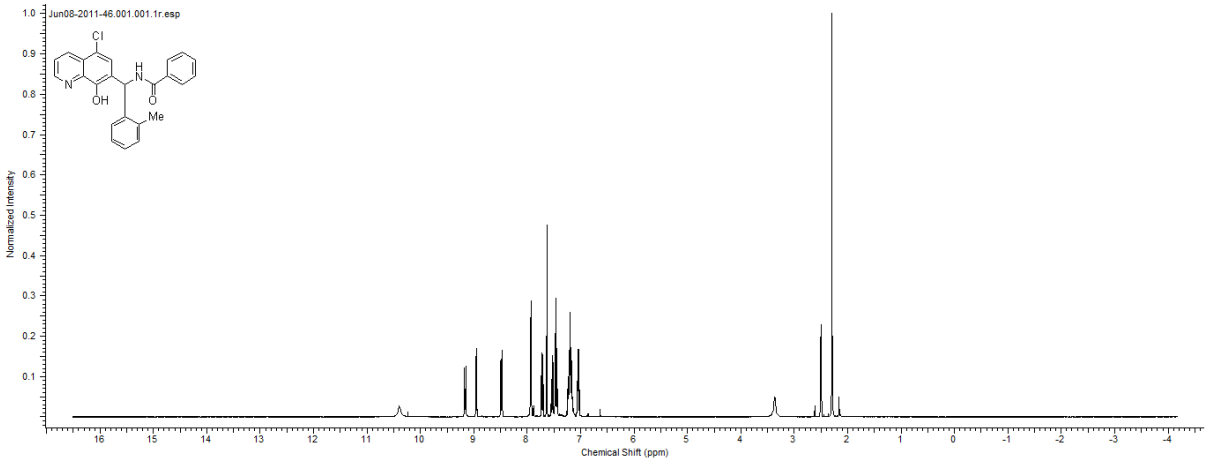
1H NMR of **CCT2** in $CDCl_3$



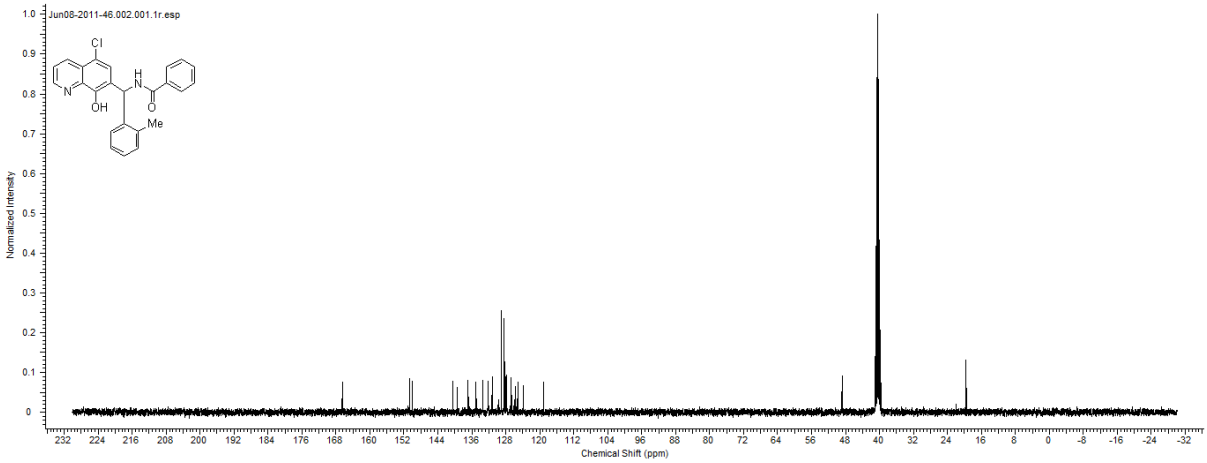
13C NMR of **CCT2** in $CDCl_3$



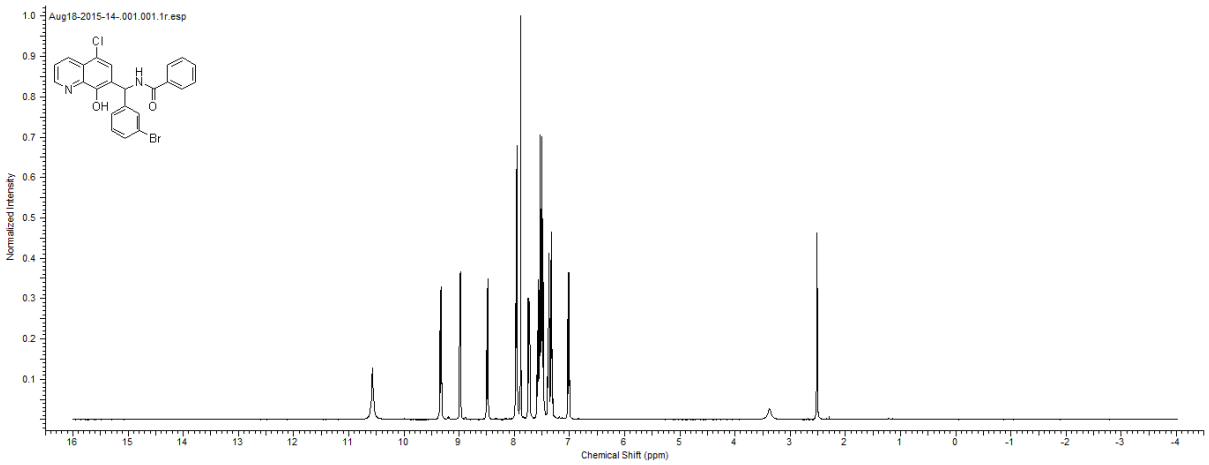
1H NMR of **27** in DMSO



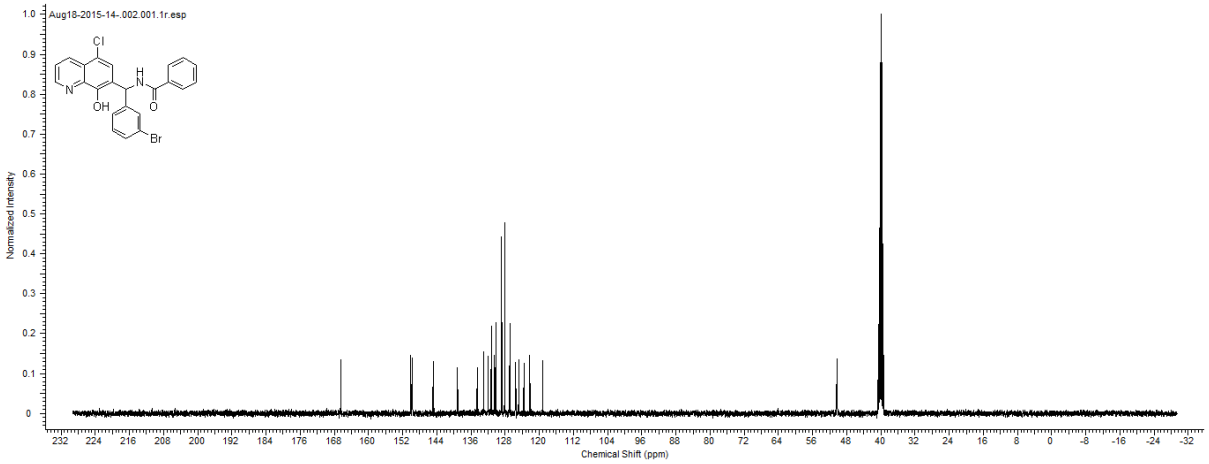
13C NMR of **27** in DMSO



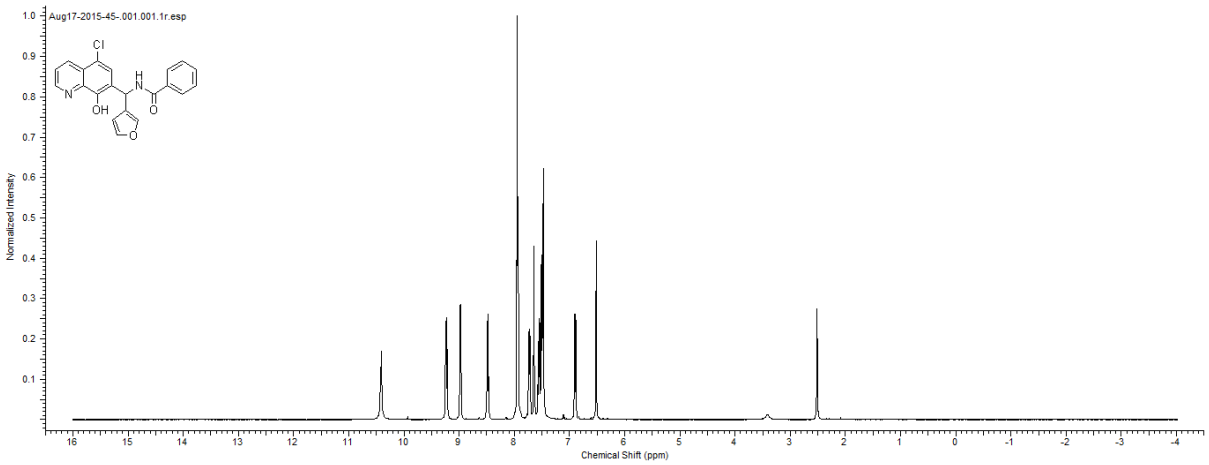
1H NMR of **28** in DMSO



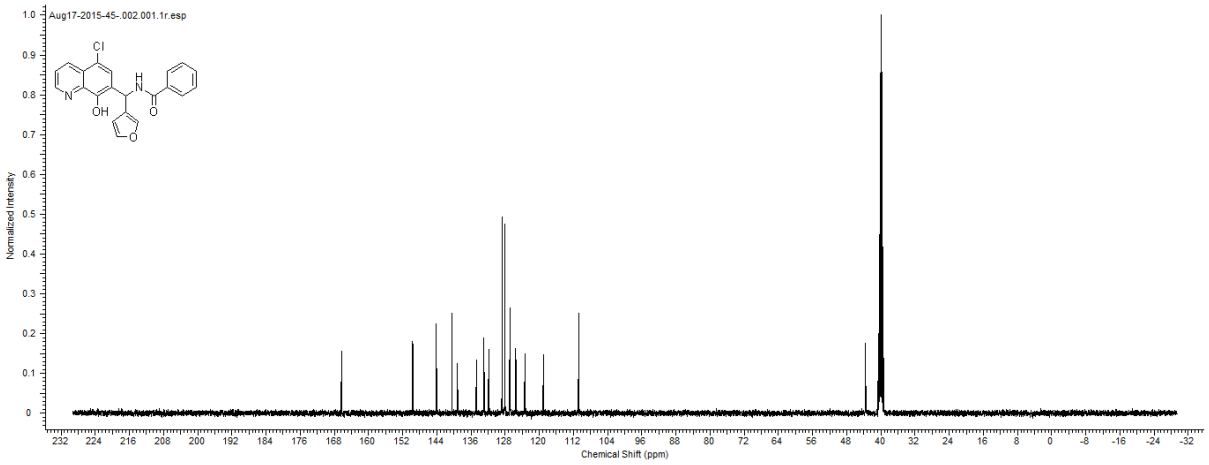
13C NMR of **28** in DMSO



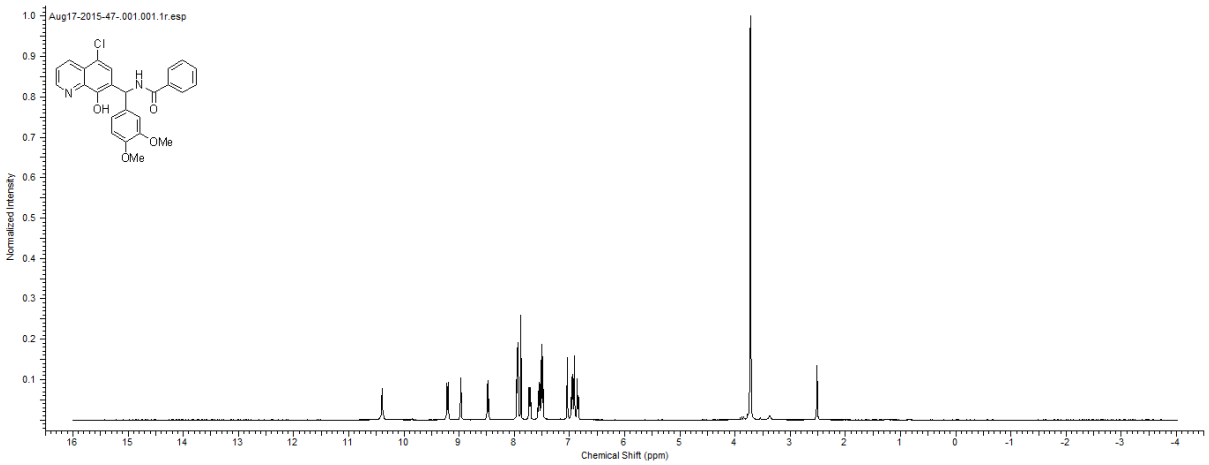
1H NMR of **S85** in DMSO



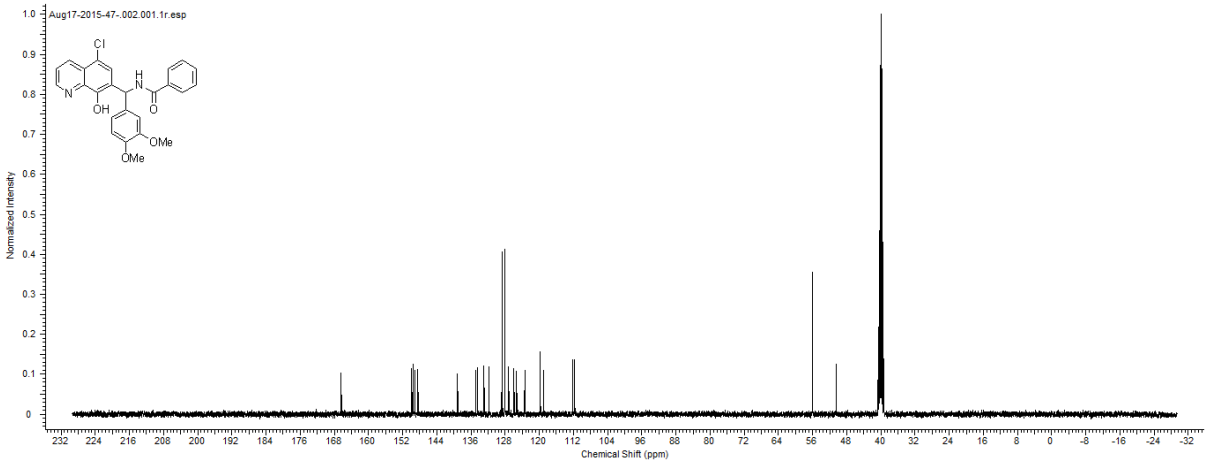
13C NMR of **S85** in DMSO



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-AA (200 μM), 2OG (20 μM) and peptide (20 μM) was dispensed into each well and the enzyme reaction progressed for 50 minutes. The enzyme reaction was stopped by addition of 5 μl of 10% formic acid and transferred to a RapidFire™ RF360 high-throughput sampling robot connected to an Agilent 6530 Accurate-Mass Quadrupole Time-of-Flight (Q-TOF) mass spectrometer operated in positive ion mode (Agilent, Wakefield, MA USA).

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

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

Non-denaturing ESI-MS studies[31]

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. $MnSO_4$ 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 myglobin/trypsinogen. Data were processed with the MassLynx 4.0 (Waters).

MALDI-TOF MS assays

The PHD2 mass spectrometry-based activity assays were performed by determining the extent of hydroxylation of HIF-1αCODD peptide substrate (HIF-1α residues 556-574) by MALDI-TOF MS.[32] The optimised hydroxylation assay involved incubation of PHD2 (1 μM) with inhibitor (1 % *v*/*v* in DMSO) in the presence of Fe(II) (10 μM), 2OG (60 μM), ascorbate (100 μM) and HIF-1αCODD $_{556\text{-}574}$ (50 μM) in HEPES (50 mM, pH 7.5) at 37 °C for 15 min. Reactions were quenched with formic acid (1 % *v*/*v*). Samples were prepared by mixing reaction mixture (1 μL) with α-cyano-4-hydrocinnamic acid (CHCA) solution (water: acetonitrile 1:1) (1 μL). Dose-response was assessed in 8-point triplicates. Data were analysed using GraphPad Prism® 5.04.

FIH activity assays were performed by determining the extent of hydroxylation of a synthetic ankyrin peptide (sequence: HLEVVKLLLEAGADVNAQDK) by matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry (MALDI-TOF MS) using a Waters® Micromass® MALDI micro MX™ mass spectrometer and MassLynx™ 4.1.[32] 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.[33] 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. IC_{50} 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 IC_{50}s were determined from the fitted curves. The average IC_{50} 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).[21, 34] 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 × 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 × 10 min), stained with DAPI (0.2 $\mu g.mL^{-1}$) 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 $MgCl_2$, 1mM dithiothreitol (DDT) and 1 mM phenylmethanesulfonylfluoride (PMSF), supplemented with 1x protease and phosphatase inhibitor and then incubated on a rotor at 4 ^{0}C for 30 minutes. The nuclei were pelleted by centrifugation at 10,000g for 10 min at 4 ^{0}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 ^{0}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 ^{0}C overnight for precipitation. The sample was centrifuged for 10 min at 2,500 g and at 4 ^{0}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 ^{0}C. The pellet was dried at room temperature. The appropriate volume of 0.1 % folic acid or H_2O (typically 100 µL) was added to dissolve the final pellet and the solution was stored at -20 ^{0}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 ^{0}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 ^{0}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 continnum 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.[35] 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),[36] mouse

monoclonal PHD2 antibody clone 76a[37] (1:10) and β-actin/HRP (clone AC15, Abcam). HRP-conjugated swine polyclonal anti-rabbit IgG (P0399, Dako), and goat polyclonal anti-mouse IgG (P0447, Dako) were used as secondary antibodies.

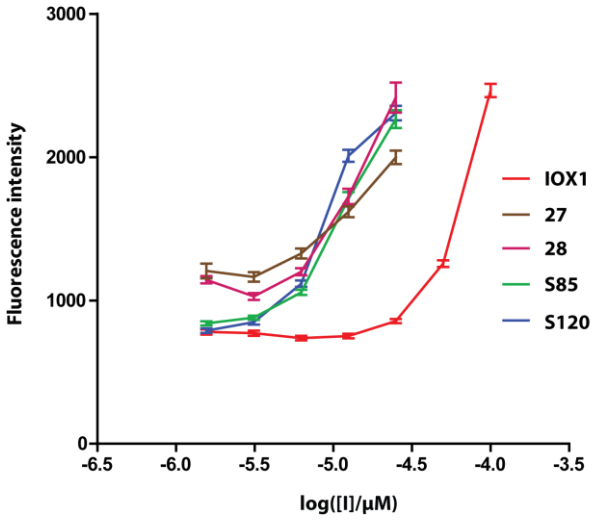
Supplementary Biochemical Data

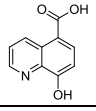
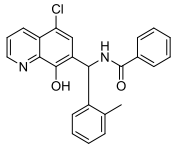
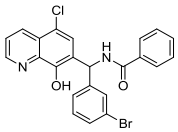
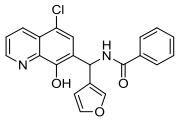
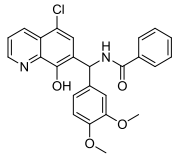
ST1

ST1 Activity of **IOX1** against isolated recombinant 2OG oxygenases.[38]

Enzyme	IC_{50}(μM)	Enzyme	IC_{50} (μM)
KDM6B	0.12	KDM2A	10.3
KDM3A	0.17	PHD2	14.3
KDM4A	0.2	FIH	20.5
KDM4E	0.3	KDM5C	25
KDM4C	0.6	PHF8	37
KDM6A	1.0	BBOX1	196

SF1

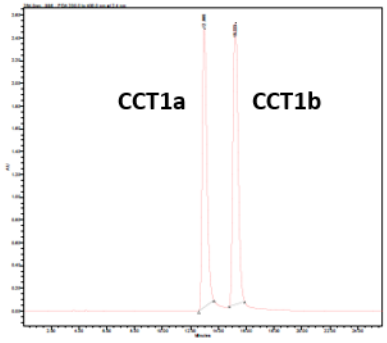


Compound	Structure	*In vitro* IC_{50} in µM (KDM4)	Cellular EC_{50} in µM (KDM4A)	*In vitro* IC_{50} in µM (KDM6B)
IOX1		0.29 (KDM4A)	86	0.12
27		9 (KDM4C)	33	123
28		19 (KDM4E)	17	433
S85		22 (KDM4E)	16	NI
S120		5 (KDM4E)	11	NI

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.

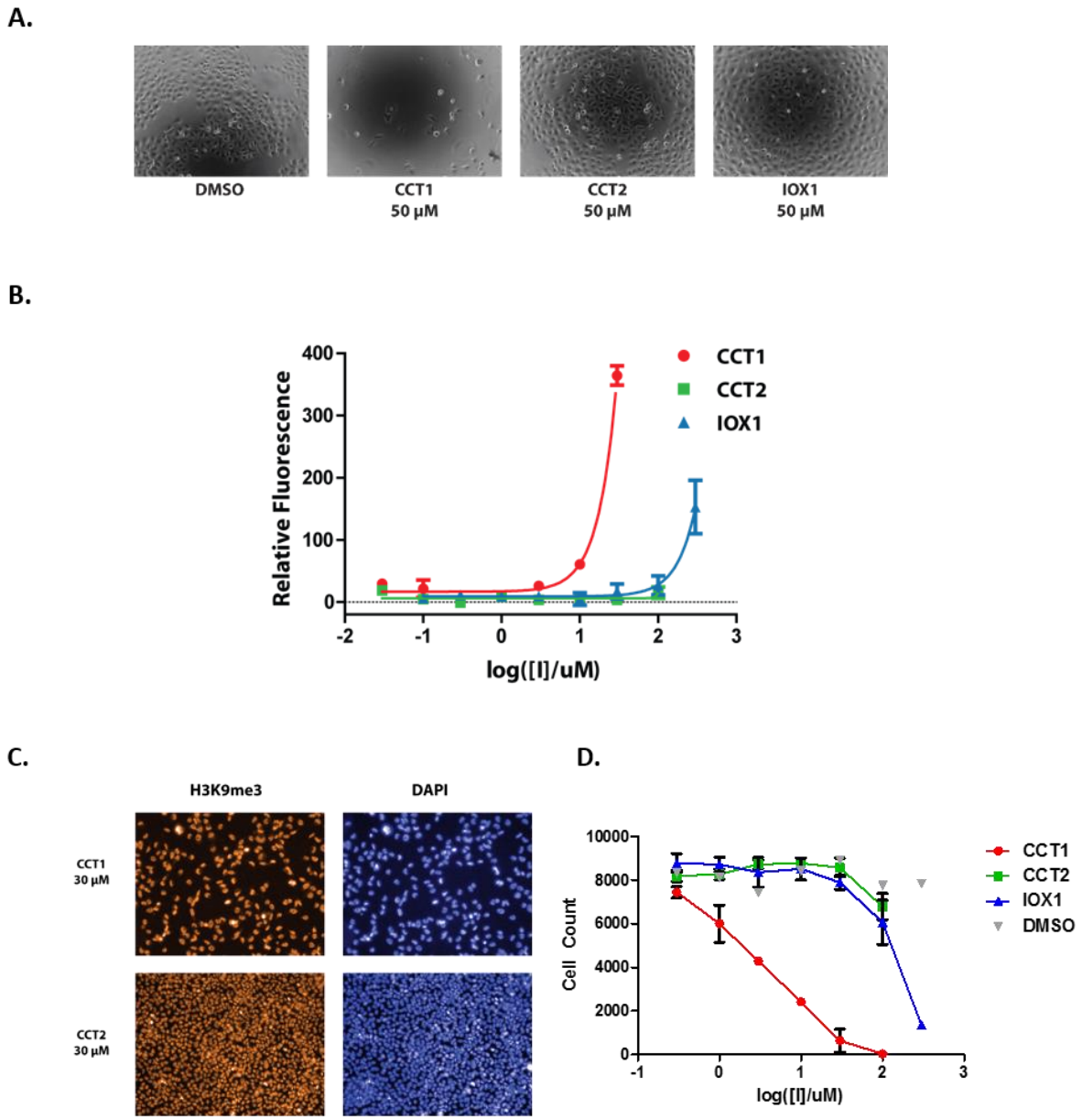


B.

Compound	IC_{50}/µM (KDM4C)
CCT1 (racemic)	5 µM
CCT1a	6 µM
CCT1b	10 µM

SF2 Studies on **CCT1** enantiomers.(A) Resolution of **CCT1** enantiomers using ultra performance liquid chromatography (UPLC) (multiple 10µl 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.

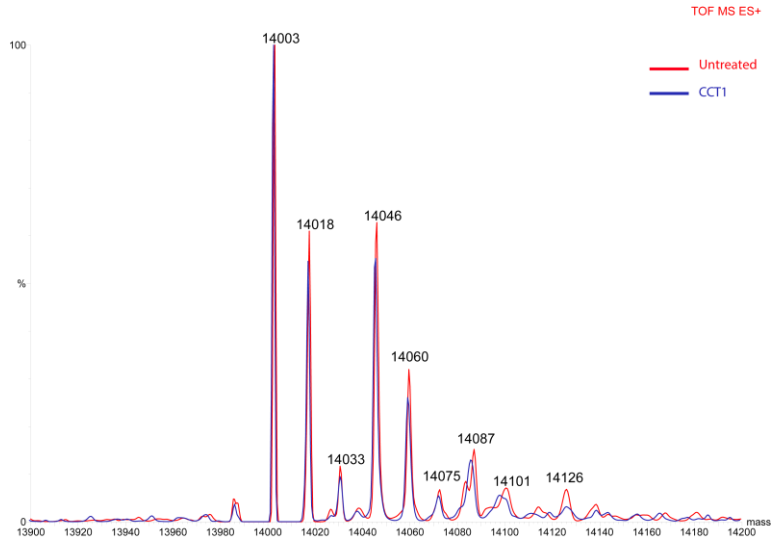
SF3



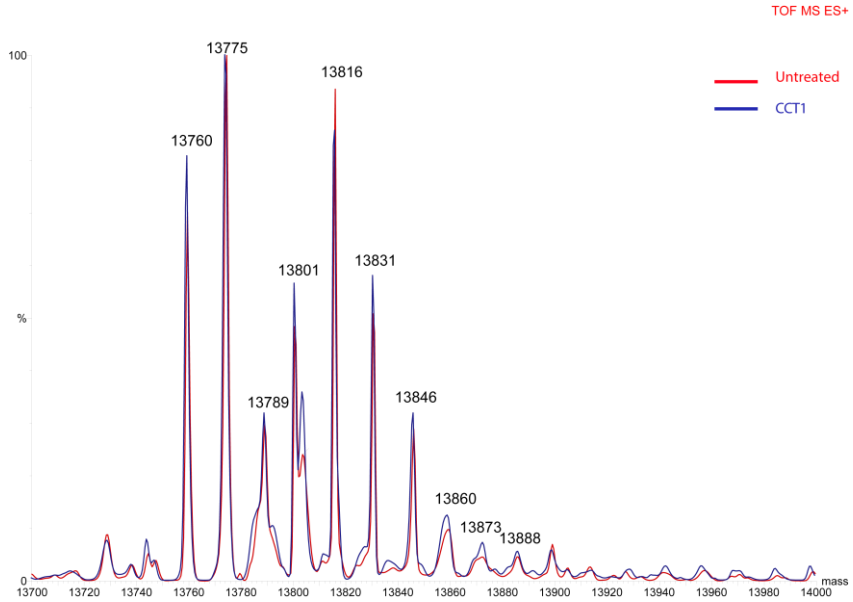
SF3 Cellular activities of inhibitors. (A) Views of HeLa cells used in the immunofluorescence-based assay (Fig 5B) with transiently overexpressed KDM4A after compound treatment. **CCT2** and **IOX1** have little effect on cell numbers relative to the DMSO control at the tested concentrations. (B) Effects 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

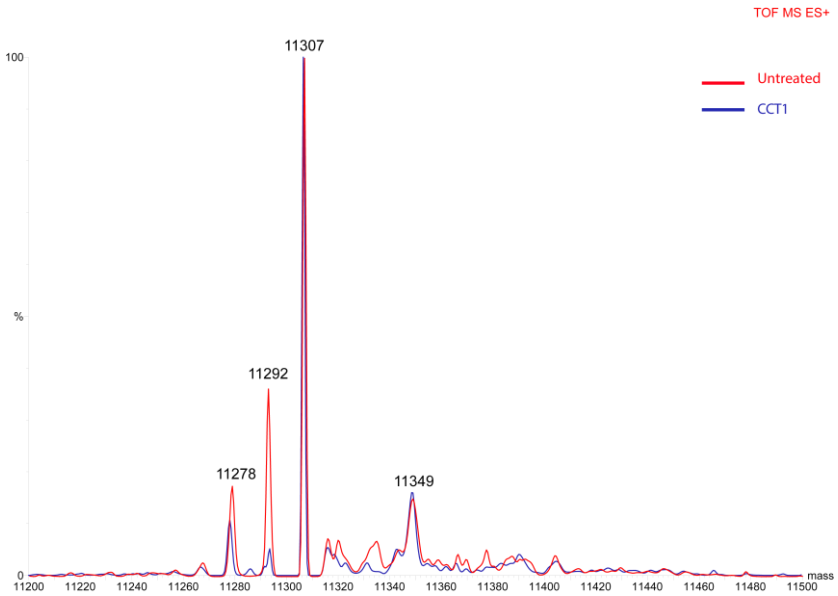
H2A


TOF MS ES+
Untreated
CCT1
100
%
0
14003
14018
14046
14060
14033
14087
14075
14101
14126
13900 13920 13940 13960 13980 14000 14020 14040 14060 14080 14100 14120 14140 14160 14180 14200
mass

H2B

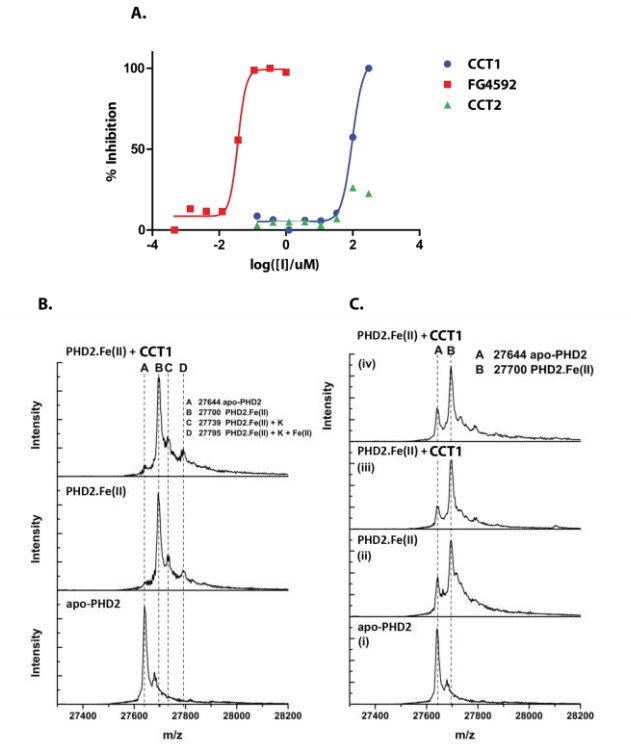

TOF MS ES+
Untreated
CCT1
100
%
0
13775
13816
13760
13801
13831
13789
13846
13860
13873
13888
13700 13720 13740 13760 13780 13800 13820 13840 13860 13880 13900 13920 13940 13960 13980 14000
mass

H4



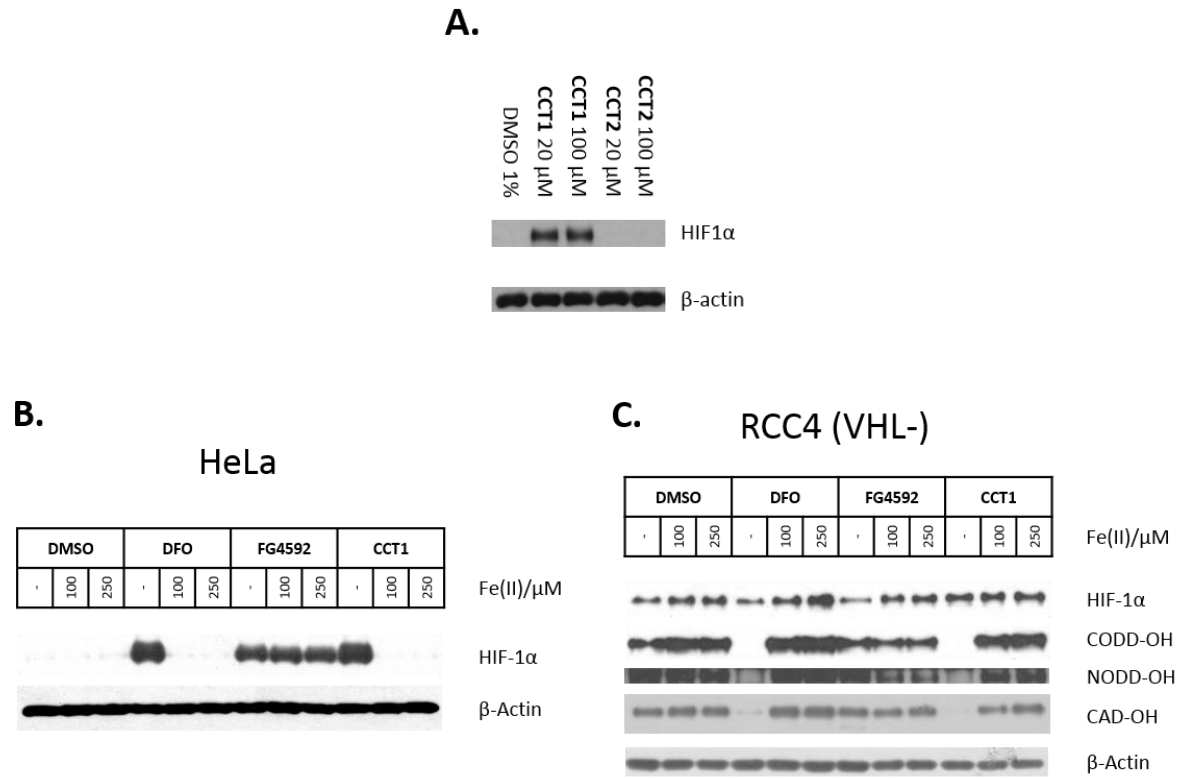
SF4 Mass spectrometry analysis of histones H2A, H2B, and H4 extracted from HEK293T cells after treatment with 30 µM of **CCT1** for 24 h. Note the lack of effect on H2A, H2B, and H4 compared to H3 (see Fig. 5D).

SF5



SF5 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



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 (CODD and NODD) and asparaginyl hydroxylation (CAD) in VHL-defective RCC4 cells by **CCT1**. (C) Reversal of the effect observed for (B) by re-introducing Fe(II) in HeLa cells. A similar effect is observed with the iron chelator desferrioxamine (DFO), but not the PHD2 inhibitor FG4592. Compound concentration: DMSO 1%, DFO: 250 μM, FG4592: 20 μM, **CCT1**: 20 μM. Total treatment for 22 hours – initial treatment with inhibitors and then add Fe(II) (ferric ammonium sulphate) after 7 hours.

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