Supporting Information

Lead optimization of 3-carboxyl-4(1H)-quinolones to deliver orally bioavailable antimalarials

Yiqun Zhang[1], Julie A Clark[1], Michele C. Connelly[1], Fangyi Zhu[1], Jaeki Min[1], W. Armand Guiguemde[1], Anupam Pradhan[2], Lalitha Iyer[3], Anna Furimsky[3], Jason Gow[3], Toufan Parman[3], Farah El Mazouni[4], Margaret A. Phillips[4], Dennis E. Kyle[2], Jon Mirsalis[3], and R. Kiplin Guy[1]*

[1] Department of Chemical Biology and Therapeutics, St Jude Children's Research Hospital, 262 Danny Thomas Place, Memphis, TN 38105, United States

[2] College of Public Health, University of South Florida, 13201 Bruce B. Downs Boulevard, MDC 56, Tampa, FL 33612, United States

[3]SRI International, 333 Ravenswood Avenue, Menlo Park, California 94025, United States

[4] UT Southwestern Medical Center at Dallas, 6001 Forest Park, Dallas, Texas 75390, United States

Table of Contents

Chemistry Procedures and Tabulated Data

General Consideration. 3,4-Methylenedioxphenyl boronic acid was bought from Boron Molecular, and other chemical reagents were from Acros, Aldrich, and Combi-Blocks. All materials were obtained from commercial suppliers and used without further purification. Thin layer chromatography was performed using silica gel 60 F254 plate from EMD. Purification of compounds was done by normal phase column chromatography (Biotage SP1). ^{1}H NMR, ^{13}C NMR spectra were recorded on a Bruker 400 MHz, chemical shifts were expressed in ppm relative to TMS used as an internal standard. Purity was estimated by chromotagraphic methods using an HPLC-MS (photodiode array, total ion count, and expected mass [m/z]) was obtained (Alliance HT, Micromass ZQ 4000 and RP-C18 Xterra column 5 μm, 6 mm × 50 mm [Waters]) or UPLC-MS (Acquity PDA detector, Acquity SQ detector and Acquity UPLC BEH-C18 column 1.7 μm, 2.1 × 50 mm [Waters]). FT-IR was recorded on a Thermo Niclet IR 100 FTIR. Compounds prepared in our laboratory were in 85-98% purity.

General procedure for synthesis of 8-13, 15-20. Quinolone derivatives **8-20** were synthesized as previous described,[12] except 7-methylthio quinolone derivatives **14**. Brifely, the intermediate 4(1H)-quinolone **6** were prepared from appropriate aniline **5** (15 mL) and 2-(ethoxymethylene)malonate (16.5 mmol), followed by Gould-Jacobs cyclization. Then, to the solution of **6** (6.5 mmol) in 6 mL 1,4-dioxane was added $POCl_3$ (7.8 mmol). The mixture was stirred at 120 °C for 1 hour. After cooling to room temperature, the reaction mixture was poured into ice water and then neutralized by aqueous K_2CO_3. The resulting 4-chloro quinoline derivatives were extracted by CH_2Cl_2, which were used for next step without purification. 4-Chloro quinoline derivatives were then treated with m-chloroperbenzoic acid (7.8 mmol) in 30 mL of $CHCl_3$ at room temperature for 4 hours to afford N-oxide 4-chloro-quinoline intermediate which then reacted with $POBr_3$ (7.2 mmoL) in 30 mL $CHCl_3$ at room temperature for 1 hour. The crude mixture was quenched by adding ice water and then neutralized by aqueous K_2CO_3. 2-Bromo-4-chloro-quinoline derivatives **7** were then extracted by CH_2Cl_2 and purified by flash chromatography.

The flask was charged with 2-bromo-4-chloro quinoline intermediate **7** (0.3 mmol), appopriate boronic acid (0.31 mmol), $Pd(PPh_3)_4$ (8.6 mg, 0.0075 mmol) in 2 mL of 1,4-dioxane. The flask was degassed three times. To the mixture was added the solution of $CsCO_3$ (0.195 g, 0.6 mmol) in 0.6 mL of H_2O. The flask was degassed again three times. The reaction mixture was stirred at 75 °C for 3 h. After being cooled to rt, the bottom aqueous layer was removed, and the organic layer was concentrated and purified by flash column chromatography to produce the intermediate compound ethyl 2-aryl-4-chloroquinoline-3-carboxylate.

The solution of ethyl 2-aryl-4-chloroquinoline-3-carboxylate intermediate (0.2 mmol) in 1 mL of AcOH/H_2O (9:1) was refluxed at 120 °C for 1 h. The reaction mixture was concentrated and neutralized by adding 5 drops of NH_4OH. Purification was performed by reverse-phase HPLC to produce the desired compounds **8-13, 15-20** (yields 10-77%). (Waters Xterra preparative C_{18} column, MeOH/H_2O, 10mM NH_4HCO_3).

General procedure for synthesis of 14.

Quinolone derivative **14** were synthesized as previous described with minor mortification.[34] To the solution of benzoyl chloride **22** (6.70 mmol) was added the solution of 3-methylthio Aniline **21** (8.04 mmol) in 10 mL toluene dropwise. After the reaction mixture was stirred at room temperature for 3 hours, solvents were evaporated to afford the crude amide product **23**, which was purified by flash column chromatography. Then, the amide **23** (4 mmol) in 10 mL of 1,4-dioxan was treated with PCl_5 (4 mmol). After refluxing at 110 ° for 1 hour, the solvent of the reaction mixture was evaporated under vacuum. The residues were re-dissolved in 5 mL of toluene and dropped into the solution of refresh prepared sodium diethyl malonate in 10 mL of toluene. The mixture was then refluxed at 110^{O} for 6 hours. The crude product **24** was purified by flash column chromatography. The compound **14** was prepared by the cyclization of **24** (0.7 mmol) in 1 mL of Ph_2O under 170 ºC for 4 hours. The reverse-phase HPLC was used to purify the desired compound **14** (total yield over 4 steps 4.9%).

General procedure for synthesis of 27-28.

To the solution of KOH (12 mmol) in 10 mL of water and 0.5 mL of EtOH was added quinolone ester **25**. After stirring at 75^{O}C for 40 hours, the reaction mixture was cooled to room temperature and neutralized by adding 2N HCl until pH reached to 7. The white solids were collected by filtration and washed by water twice. This crude product **26** was used for the next step without purification. Then, to the mixture of acid **26** (0.05 mmol) in 0.5 mL of DMF was added DPIEA (0.075 mmol) and HBTU (0.05 mmol). The mixture was stirred at rt for 30 min. After stirring at room temperature for 30 mins, appropriate alkyl alcohol or alkyl amine (0.150 mmol) was added into the reaction mixture. The mixture continued to stir at 40 ^{O}C for 2 hours. After the solvent was evaporated, the crude product **27-28** was purified by reverse-phase HPLC (yields 32-77%).

Ethyl 7-methoxy-4-oxo-2-(3-vinylphenyl)-1,4-dihydroquinoline-3-carboxylate 8d. 48% yield from intermediate **7**, ^{1}H NMR (400 MHz, MeOD) δ 8.18 (d, *J* = 9.5 Hz, 1H), 7.64 (d, *J* = 9.0 Hz, 1H), 7.59 – 7.43 (m, 1H), 7.10 – 7.01 (m, 1H), 6.82 (dd, *J* = 17.6, 11.0 Hz, 1H), 5.90 (d, *J* = 17.7 Hz, 1H), 5.36 (d, *J* = 11.0 Hz, 1H), 4.05 (q, *J* = 7.2 Hz, 1H), 3.92 (s, 1H), 0.97 (t, *J* = 7.2 Hz, 1H). ^{13}C NMR (101 MHz, MeOD) δ 176.58, 168.47, 165.18, 152.25, 143.06, 139.72, 137.17, 135.76, 130.19, 129.26, 128.58, 128.25, 126.98, 120.29, 116.69, 116.46, 115.90, 101.43, 100.26, 62.23, 56.30, 14.09. MS (ESI) cald C21H19NO4 for $[M+H]^{+}$, 350.13, found 350.21

Ethyl 2-([1,1'-biphenyl]-3-yl)-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate 8e. 56% yield from intermediate **7**, ^{1}H NMR (400 MHz, MeOD) δ 8.22 (d, *J* = 9.0 Hz, 1H), 7.90 (s, 1H), 7.79 – 7.59 (m, 2H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.46 (d, *J* = 7.3 Hz, 1H), 7.17 – 7.09 (m, 1H), 4.10 (q, *J* = 7.2 Hz, 1H), 3.97 (s, 1H), 1.00 (t, *J* = 7.2 Hz, 1H). ^{13}C NMR (101 MHz, MeOD) δ 176.34, 168.38, 165.05, 151.97, 143.19, 143.02, 141.24, 136.10, 130.72, 130.39, 130.11, 129.29, 128.38, 128.24, 128.09, 120.43, 117.02, 116.40, 101.43, 100.70, 62.23, 56.54, 14.36. MS (ESI) cald C25H21NO4 for $[M+H]^{+}$, 400.15, found 400.26

Ethyl 2-(3-ethoxyphenyl)-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate 8g. 34% yield from intermediate **7**, ^{1}H NMR (400 MHz, MeOD) δ 8.19 (d, *J* = 9.5 Hz, 1H), 7.49 – 7.39 (m, 1H), 7.18 – 7.03 (m, 3H), 4.10 (dq, *J* = 11.5, 7.0 Hz, 2H), 3.94 (s, 2H), 1.43 (t, *J* = 7.0 Hz, 2H), 1.02 (t, *J* = 7.2 Hz, 1H). ^{13}C NMR (101 MHz, MeOD) δ 176.57, 168.53, 165.16, 160.60, 152.18, 143.02, 136.53, 131.11, 128.22, 121.36, 120.26, 117.72, 116.44, 115.40, 100.23, 64.88, 62.25, 56.30, 15.10, 14.10. MS (ESI) cald C21H21NO5 for $[M+H]^{+}$, 368.14, found 368.22.

Ethyl 7-methoxy-4-oxo-2-(3-propoxyphenyl)-1,4-dihydroquinoline-3-carboxylate 8h. 65% yield from intermediate **7**, ^{1}H NMR (400 MHz, MeOD) δ 8.19 (d, *J* = 9.8 Hz, 1H), 7.45 (s, 1H), 7.19 – 7.04 (m, 3H), 4.09 (q, *J* = 7.1 Hz, 1H), 4.02 (t, *J* = 6.5 Hz, 1H), 3.94 (s, 2H), 1.84 (m, 1H), 1.05 (dt, *J* = 20.5, 7.3 Hz, 3H). ^{13}C NMR (101 MHz, MeOD) δ 176.56, 168.53, 165.14, 160.77, 152.14, 143.00, 136.49, 131.10, 128.20, 121.32, 120.24, 117.69, 116.42, 115.41, 100.21, 70.87, 62.24, 56.28, 23.60, 14.09, 10.83. MS (ESI) cald C22H23NO5 for $[M+H]^{+}$, 382.16, found 382.24

Ethyl 2-(3-isopropoxyphenyl)-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate 8i. 44% yield from intermediate **7**, ^{1}H NMR (400 MHz, MeOD) δ 8.19 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.50 – 7.39 (m, 1H), 7.19 – 7.02 (m, 3H), 4.69 (dt, *J* = 12.2, 6.1 Hz, 1H), 4.09 (q, *J* = 7.2 Hz, 1H), 3.95 (d, *J* = 5.5 Hz, 2H), 1.40 – 1.30 (m, 3H), 1.02 (t, *J* = 7.1 Hz, 1H). ^{13}C NMR (101 MHz, MeOD) δ 176.57, 168.50, 165.15, 159.54, 152.22, 143.00, 136.61, 131.14, 128.22, 121.26, 120.26, 118.87, 116.79, 116.64, 116.43, 100.23, 71.37, 62.22, 56.30, 22.31, 14.11. MS (ESI) cald C22H23NO5 for $[M+H]^{+}$, 382.16, found 382.24

Ethyl 2-(3-butoxyphenyl)-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate 8j. 36% yield from intermediate **7**, ^{1}H NMR (400 MHz, MeOD) δ 8.18 (d, *J* = 9.7 Hz, 1H), 7.44 (s, 1H), 7.18 – 7.03 (m, 2H), 4.07 (dt, *J* = 12.8, 6.8 Hz, 2H), 3.93 (d, *J* = 3.3 Hz, 2H), 1.86 – 1.72 (m, 1H), 1.60 – 1.47 (m, 1H), 1.01 (td, *J* = 7.3,

3.6 Hz, 3H). ^{13}C NMR (101 MHz, MeOD) δ 176.58, 168.55, 165.16, 160.78, 152.17, 143.03, 136.52, 131.12, 128.44, 128.22, 121.33, 120.26, 117.71, 116.44, 115.41, 114.58, 100.23, 69.04, 62.26, 56.30, 32.42, 20.31, 14.16, 14.11. MS (ESI) cald C23H25NO5 for $[M+H]^+$, 396.17, found 396.25

Ethyl 2-(3-isobutoxyphenyl)-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate 8k. 41% yield from intermediate **7**, ^{1}H NMR (400 MHz, MeOD) δ 8.18 (d, *J* = 9.7 Hz, 1H), 7.44 (t, *J* = 8.3 Hz, 1H), 7.12 (dd, *J* = 6.0, 2.7 Hz, 1H), 7.06 (dd, *J* = 6.8, 2.4 Hz, 1H), 4.08 (q, *J* = 7.2 Hz, 1H), 3.93 (s, 2H), 3.81 (d, *J* = 6.5 Hz, 1H), 2.16 – 2.01 (m, 1H), 1.10 – 0.97 (m, 5H). ^{13}C NMR (101 MHz, MeOD) δ 176.58, 168.57, 165.17, 160.88, 152.15, 143.04, 136.52, 131.13, 128.22, 121.34, 120.27, 117.69, 116.44, 115.46, 100.24, 75.76, 62.26, 56.30, 29.53, 19.52, 14.13. MS (ESI) cald C23H25NO5 for $[M+H]^+$, 396.17, found 396.25

Ethyl 2-(3-(benzyloxy)phenyl)-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate 8l. 48% yield from intermediate **7**, ^{1}H NMR (400 MHz, MeOD) δ 8.18 (d, *J* = 9.3 Hz, 1H), 7.45 (dd, *J* = 35.4, 6.6 Hz, 3H), 7.15 (dd, *J* = 56.3, 17.7 Hz, 3H), 5.19 (s, 1H), 4.06 (d, *J* = 7.2 Hz, 1H), 3.94 (s, 2H), 1.01 (t, *J* = 7.1 Hz, 1H). ^{13}C NMR (101 MHz, MeOD) δ 165.06, 160.36, 153.70, 150.16, 147.07, 138.38, 136.71, 131.32, 129.79, 129.27, 128.89, 128.32, 126.56, 121.95, 120.37, 118.07, 116.23, 100.58, 71.27, 62.22, 56.49, 14.36. MS (ESI) cald C26H23NO5 for $[M+H]^+$, 430.16, found 430.22

Ethyl 7-methoxy-4-oxo-2-(3-phenoxyphenyl)-1,4-dihydroquinoline-3-carboxylate 8m. Yield 77% from intermediate **7**. ^{1}H NMR (400 MHz, MeOD) δ 8.18 (d, *J* = 9.3 Hz, 1H), 7.53 (d, *J* = 7.7 Hz, 1H), 7.46 – 7.37 (m, 1H), 7.33 (d, *J* = 7.9 Hz, 1H), 7.20 (d, *J* = 7.5 Hz, 2H), 7.06 (d, *J* = 10.9 Hz, 2H), 4.09 (q, *J* = 7.2 Hz, 1H), 3.94 (s, 2H), 1.06 (t, *J* = 7.2 Hz, 1H). ^{13}C NMR (101 MHz, MeOD) δ 176.55, 168.36, 165.20, 159.22, 157.93, 151.51, 143.02, 136.99, 131.59, 131.18, 128.23, 125.22, 124.03, 121.46, 120.36, 120.29, 119.31, 116.67, 116.51, 100.24, 62.31, 56.31, 14.20. MS (ESI) cald C25H21NO5 for $[M+H]^+$, 416.14, found 416.21

Ethyl 7-methoxy-4-oxo-2-(3-(trifluoromethoxy)phenyl)-1,4-dihydroquinoline-3-carboxylate 8n. 62% yield from intermediate **7**, ^{1}H NMR (400 MHz, MeOD) δ 8.31 (d, *J* = 9.0 Hz, 1H), 8.20 (d, *J* = 9.0 Hz, 1H), 7.74 – 7.43 (m, 2H), 7.12 – 7.01 (m, 1H), 4.07 (q, *J* = 7.1 Hz, 1H), 3.95 (s, 2H), 1.01 (t, *J* = 7.2 Hz, 1H). ^{13}C NMR (101 MHz, MeOD) δ 176.50, 167.97, 165.28, 150.51, 143.02, 137.46, 131.91, 131.08, 128.35, 128.29, 123.98, 122.23, 120.40, 116.63, 100.31, 62.24, 56.33, 14.00. MS (ESI) cald C20H16F3NO5 for $[M+H]^+$, 408.10, found 408.20

Ethyl 2-(3-bromophenyl)-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate 8r. 24% yield from intermediate **7**, ^{1}H NMR (400 MHz, MeOD) δ 8.21 (d, *J* = 9.8 Hz, 1H), 7.80 (d, *J* = 8.9 Hz, 2H), 7.60 (s, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.11 (d, *J* = 7.4 Hz, 2H), 4.12 (q, *J* = 7.2 Hz, 2H), 3.96 (s, 3H), 1.07 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, MeOD) δ 176.31, 168.06, 165.16, 150.97, 150.55, 143.55, 143.14, 137.49, 134.62, 132.37, 131.93, 128.47, 128.36, 123.57, 120.44, 116.58, 100.63, 62.34, 56.53, 14.38. MS (ESI) cald C19H16BrNO4 for $[M+H]^+$, 402.03, found 402.13

Ethyl 2-(3-acetylphenyl)-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate 8s. 35% yield from intermediate **7**, ^{1}H NMR (400 MHz, MeOD) δ 8.21 (d, *J* = 8.9 Hz, 1H), 7.95 (s, 1H), 7.74 (s, 1H), 7.54 (t, *J* = 7.9 Hz, 1H), 7.33 (d, *J* = 7.7 Hz, 1H), 7.15 – 7.07 (m, 1H), 4.11 (q, *J* = 7.2 Hz, 1H), 3.97 (s, 2H), 2.65 (dt, *J* = 3.8, 1.9 Hz, 1H), 2.19 (s, 1H), 1.06 (t, *J* = 7.2 Hz, 2H). ^{13}C NMR (101 MHz, MeOD) δ 199.17, 176.55, 168.29, 165.25, 151.44, 143.12, 138.76, 135.90, 133.90, 131.32, 130.44, 129.22, 128.29, 120.37, 116.83, 116.58, 100.32, 62.31, 56.33, 26.83, 14.12. MS (ESI) cald C21H19NO5 for $[M+H]^+$, 366.13, found 366.16

Ethyl 7-methoxy-2-(3-(methylsulfonyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 8t. 28% yield from intermediate **7**, ^{1}H NMR (400 MHz, MeOD) δ 8.21 (t, *J* = 12.0 Hz, 1H), 7.94 (s, 1H), 7.86 (d, *J* = 7.7 Hz, 1H), 7.15 – 7.04 (m, 1H), 4.16 – 4.04 (m, 1H), 3.96 (s, 1H), 3.21 (s, 1H), 1.04 (t, *J* = 7.1 Hz, 1H). ^{13}C NMR (101 MHz, MeOD) δ 176.34, 168.38, 165.05, 151.96, 143.19, 143.02, 141.24, 136.10, 130.71, 130.38, 130.10,

129.29, 128.38, 128.23, 128.09, 120.43, 117.02, 116.40, 100.69, 62.22, 56.54, 14.36. MS (ESI) cald C20H19NO6S for $[M+H]^+$, 402.09, found 402.20

Ethyl 2-(3-(dimethylamino)phenyl)-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate 8v. 48% yield from intermediate **7**, ^{1}H NMR (400 MHz, MeOD) δ 8.19 (d, *J* = 9.5 Hz, 1H), 7.40 – 7.31 (m, 1H), 7.11 – 7.03 (m, 1H), 6.98 – 6.83 (m, 1H), 4.08 (q, *J* = 7.2 Hz, 1H), 3.94 (s, 2H), 3.01 (s, 3H), 1.02 (t, *J* = 7.2 Hz, 2H). ^{13}C NMR (101 MHz, MeOD) δ 176.25, 171.48, 168.10, 165.03, 151.82, 143.10, 140.87, 136.05, 130.60, 128.39, 124.69, 122.58, 120.52, 120.41, 116.87, 116.39, 100.68, 62.21, 56.58, 24.34, 14.42. MS (ESI) cald C21H22N2O4 for $[M+H]^+$, 367.16, found 367.22

Ethyl 2-(3-acetamidophenyl)-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate 8w. 55% yield from intermediate **7**, ^{1}H NMR (400 MHz, MeOD) δ 8.44 (d, *J* = 6.9 Hz, 1H), 8.21 (s, 1H), 8.12 (s, 1H), 7.36 (d, *J* = 6.9 Hz, 1H), 4.33 (d, *J* = 7.2 Hz, 1H), 4.20 (s, 1H), 3.49 (s, 1H), 1.28 (t, *J* = 7.2 Hz, 1H). ^{13}C NMR (101 MHz, MeOD) δ 176.25, 171.48, 168.10, 165.03, 164.19, 151.82, 143.11, 140.88, 136.06, 130.60, 128.39, 124.69, 122.59, 120.52, 120.42, 116.87, 116.39, 101.43, 100.68, 62.21, 56.58, 24.34, 14.42, 7.13. MS (ESI) cald C21H20N2O5 for $[M+H]^+$, 381.14, found 381.24

Ethyl 2-(3-hydroxyphenyl)-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate 8x. 36% yield from intermediate **7**, ^{1}H NMR (400 MHz, MeOD) δ 8.18 (d, *J* = 9.5 Hz, 1H), 7.35 (t, *J* = 8.2 Hz, 1H), 7.10 – 6.94 (m, 5H), 4.09 (q, *J* = 7.2 Hz, 2H), 3.93 (s, 3H), 3.36 (s, 1H), 1.02 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, MeOD) δ 176.58, 168.51, 165.14, 159.08, 152.42, 143.01, 136.56, 131.10, 128.22, 120.24, 120.18, 118.45, 116.52, 116.39, 116.12, 100.20, 62.24, 56.29, 14.07. MS (ESI) cald C19H17NO5 for $[M+H]^+$, 340.11, found 340.13

Ethyl 2-(3-(hydroxymethyl)phenyl)-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate 8y. 39% yield from intermediate **7**, ^{1}H NMR (400 MHz, MeOD) δ 8.20 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.64 – 7.45 (m, 4H), 7.08 (dd, *J* = 8.3, 1.9 Hz, 2H), 4.72 (s, 2H), 4.08 (q, *J* = 7.2 Hz, 2H), 3.94 (s, 3H), 1.02 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, MeOD) δ 175.85, 167.79, 164.43, 151.67, 143.23, 142.34, 134.69, 129.17, 129.05, 127.50, 127.34, 126.78, 119.52, 115.98, 115.69, 99.49, 63.81, 61.52, 55.56, 13.38. MS (ESI) cald C20H19NO5 for $[M+H]^+$, 354.13, found 354.15

Ethyl 2-(3,5-dimethoxyphenyl)-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate 8z. 62% yield from intermediate **7**, ^{1}H NMR (400 MHz, MeOD) δ 8.17 (d, *J* = 9.7 Hz, 1H), 7.06 (dd, *J* = 4.8, 2.5 Hz, 2H), 6.73 (d, *J* = 2.3 Hz, 2H), 6.67 (d, *J* = 2.3 Hz, 1H), 4.10 (q, *J* = 7.2 Hz, 2H), 3.93 (s, 3H), 3.84 (s, 6H), 1.04 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, MeOD) δ 176.56, 168.60, 165.16, 162.63, 143.03, 137.00, 128.21, 120.29, 116.44, 107.45, 103.17, 100.26, 62.31, 56.30, 56.13, 14.13. MS (ESI) cald C21H21NO6 for $[M+H]^+$, 384.14, found 384.18

Ethyl 2-(3-fluoro-5-methoxyphenyl)-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate 8aa. 73% yield from intermediate **7**, ^{1}H NMR (400 MHz, MeOD) δ 8.18 (d, *J* = 9.3 Hz, 1H), 7.10 – 7.02 (m, 2H), 7.01 – 6.88 (m, 3H), 4.12 (q, *J* = 7.2 Hz, 2H), 3.93 (s, 3H), 3.87 (s, 3H), 1.06 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, MeOD) δ 176.52, 168.22, 166.08, 165.24, 163.63, 162.97, 162.85, 143.00, 137.67, 128.24, 120.34, 116.58, 111.55, 111.52, 108.66, 108.42, 104.50, 104.24, 100.28, 62.33, 56.56, 56.32, 14.13. MS (ESI) cald C20H18FNO5 for $[M+H]^+$, 372.12, found 372.17

Ethyl 2-(benzo[d][1,3]dioxol-5-yl)-7-isopropoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate 9a. 46% yield from intermediate **7**, ^{1}H NMR (400 MHz, MeOD) δ 8.17 (d, *J* = 8.8 Hz, 1H), 7.04 (ddd, *J* = 27.5, 14.6, 7.9 Hz, 5H), 6.08 (s, 2H), 4.76 (dt, *J* = 12.1, 6.0 Hz, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 1.41 (d, *J* = 6.0 Hz, 6H), 1.11 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, MeOD) δ 176.59, 168.72, 163.37, 151.78, 151.09, 149.52, 143.03, 128.87, 128.27, 123.84, 119.92, 117.21, 116.56, 109.57, 109.52, 103.34, 101.90, 71.79, 62.30, 22.13, 14.25. MS (ESI) cald C22H21NO6 for $[M+H]^+$, 396.14, found 396.25

Ethyl 2-([1,1'-biphenyl]-3-yl)-7-isopropoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate 9b. 63% yield from intermediate **7**, ^{1}H NMR (400 MHz, MeOD) δ 8.21 (d, *J* = 8.6 Hz, 1H), 7.86 (dd, *J* = 4.7, 2.8 Hz, 2H), 7.74 – 7.30 (m, 8H), 7.06 (d, *J* = 8.7 Hz, 2H), 4.78 (dt, *J* = 12.1, 6.0 Hz, 1H), 4.08 (d, *J* = 7.1 Hz, 2H), 1.42 (d, *J* = 6.0 Hz, 7H), 0.96 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, MeOD) δ 176.61, 168.61, 163.44, 152.30, 143.17, 143.09, 141.24, 135.99, 130.51, 130.15, 130.02, 129.07, 128.35, 128.18, 128.07, 127.93, 120.07, 117.33, 101.97, 101.42, 71.81, 62.27, 22.13, 14.08. MS (ESI) cald C27H25NO4 for $[M+H]^+$, 428.18, found 428.29

Ethyl 7-isopropoxy-2-(3-methoxyphenyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 9c. 59% yield from intermediate **7**, ^{1}H NMR (400 MHz, MeOD) δ 8.19 (d, *J* = 8.8 Hz, 1H), 7.45 (d, *J* = 8.3 Hz, 1H), 7.15 (t, *J* = 5.2 Hz, 3H), 7.08 – 7.02 (m, 2H), 4.77 (dt, *J* = 12.1, 6.0 Hz, 1H), 4.09 (q, *J* = 7.1 Hz, 2H), 3.88 (s, 3H), 1.41 (d, *J* = 6.0 Hz, 6H), 1.02 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, MeOD) δ 176.57, 168.59, 163.40, 161.33, 152.16, 143.07, 136.61, 131.12, 128.31, 121.48, 120.03, 117.30, 117.17, 116.52, 114.85, 101.96, 71.80, 62.25, 56.02, 22.13, 14.10. MS (ESI) cald C22H23NO5 for $[M+H]^+$, 382.16, found 382.24

Ethyl 2-(benzo[d][1,3]dioxol-5-yl)-4-oxo-7-(trifluoromethoxy)-1,4-dihydroquinoline-3-carboxylate 10a. 63% yield from intermediate **7**, ^{1}H NMR (400 MHz, MeOD) δ 8.26 (d, *J* = 9.0 Hz, 1H), 7.46 (s, 1H), 7.25 (s, 1H), 7.05 – 6.97 (m, 2H), 6.89 (d, *J* = 7.9 Hz, 1H), 5.98 (s, 2H), 4.04 (q, *J* = 7.2 Hz, 2H), 1.00 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, MeOD) δ 176.19, 168.30, 153.51, 153.04, 151.30, 149.61, 142.20, 129.44, 128.64, 124.52, 123.95, 118.45, 117.50, 110.70, 109.63, 109.50, 103.41, 62.42, 14.24. MS (ESI) cald C20H14F3NO6 for $[M+H]^+$, 422.08, found 422.15

Ethyl 2-(3-methoxyphenyl)-4-oxo-7-(trifluoromethoxy)-1,4-dihydroquinoline-3-carboxylate 10b. 72% yield from intermediate **7**, ^{1}H NMR (400 MHz, MeOD) δ 8.40 (d, *J* = 9.0 Hz, 1H), 7.59 (s, 1H), 7.48 (t, *J* = 8.1 Hz, 1H), 7.37 (d, *J* = 8.9 Hz, 1H), 7.22 – 7.13 (m, 3H), 4.11 (q, *J* = 7.2 Hz, 2H), 3.88 (s, 3H), 1.03 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, MeOD) δ 176.22, 168.08, 161.38, 153.56, 153.28, 142.07, 136.24, 131.21, 129.52, 124.60, 123.11, 121.45, 120.55, 118.57, 117.49, 117.44, 114.83, 110.66, 62.39, 56.05, 14.09. MS (ESI) cald C20H16F3NO5 for $[M+H]^+$, 408.10, found 408.20

Ethyl 4-oxo-7-(trifluoromethoxy)-2-(3-(trifluoromethoxy)phenyl)-1,4-dihydroquinoline-3-carboxylate 10c. 66% yield from intermediate **7**, ^{1}H NMR (400 MHz, MeOD) δ 8.29 (d, *J* = 9.0 Hz, 1H), 7.64 – 7.40 (m, 5H), 7.27 (d, *J* = 9.0 Hz, 1H), 3.97 (q, *J* = 7.2 Hz, 2H), 0.90 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, MeOD) δ 176.17, 167.55, 153.66, 151.81, 150.54, 142.09, 137.18, 131.99, 129.59, 128.33, 124.74, 124.21, 123.19, 123.10, 122.24, 120.64, 120.54, 118.76, 117.98, 117.52, 110.72, 62.38, 13.99. MS (ESI) cald C20H13F6NO5 for $[M+H]^+$, 462.07, found 462.19

Ethyl 2-(benzo[d][1,3]dioxol-5-yl)-4-oxo-7-(trifluoromethyl)-1,4-dihydroquinoline-3-carboxylate 11a. 47% yield from intermediate **7**, ^{1}H NMR (400 MHz, MeOD) δ 8.46 (d, *J* = 8.5 Hz, 1H), 8.01 (s, 1H), 7.72 (s, 2H), 7.58 (s, 1H), 7.49 (s, 1H), 7.15 (d, *J* = 10.2 Hz, 1H), 7.01 (dd, *J* = 7.9, 5.3 Hz, 1H), 6.91 – 6.84 (m, 1H), 6.10 (s, 2H), 4.17 (q, *J* = 7.1 Hz, 2H), 1.09 (t, *J* = 5.8 Hz, 3H). ^{13}C NMR (101 MHz, MeOD) δ 176.21, 168.14, 166.69, 161.12, 153.13, 151.39, 150.47, 150.15, 149.64, 149.46, 140.80, 139.77, 130.18, 128.25, 124.02, 110.47, 109.66, 109.55, 109.53, 103.45, 103.12, 62.73, 62.47, 14.23. MS (ESI) cald C20H14F3NO5 for $[M+H]^+$, 406.08, found 406.20

Ethyl 2-(3-methoxyphenyl)-4-oxo-7-(trifluoromethyl)-1,4-dihydroquinoline-3-carboxylate 11b. 62% yield from intermediate **7**, ^{1}H NMR (400 MHz, MeOD) δ 8.48 (d, *J* = 8.4 Hz, 1H), 8.02 (s, 1H), 7.72 (d, *J* = 8.5 Hz, 1H), 7.49 (t, *J* = 8.2 Hz, 1H), 7.24 – 7.13 (m, 3H), 4.11 (q, *J* = 7.2 Hz, 2H), 3.88 (s, 3H), 1.04 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, MeOD) δ 176.20, 167.99, 161.39, 153.49, 140.79, 136.19, 135.51, 135.18, 131.24, 128.30, 128.18, 126.37, 121.49, 121.45, 117.93, 117.57, 117.53, 117.48, 114.88, 101.43, 62.43, 56.05, 14.09. MS (ESI) cald C20H16F3NO4 for $[M+H]^+$, 392.10, found 392.19

Ethyl 4-oxo-2-(3-(trifluoromethoxy)phenyl)-7-(trifluoromethyl)-1,4-dihydroquinoline-3-carboxylate 11c. 53% yield from intermediate **7**, ^{1}H NMR (400 MHz, MeOD) δ 8.49 (d, *J* = 8.5 Hz, 1H), 8.01 (s, 1H), 7.70 (d, *J* = 7.9 Hz, 2H), 7.59 (s, 1H), 7.44 – 7.40 (m, 1H), 7.37 (s, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 1.01 (td, *J* = 7.1, 4.4 Hz, 3H). ^{13}C NMR (101 MHz, MeOD) δ 167.48, 166.15, 160.84, 150.53, 148.92, 139.90, 137.24, 137.19, 134.09, 132.00, 131.82, 129.81, 129.07, 128.36, 124.25, 123.05, 122.84, 122.28, 121.63, 120.26, 114.26, 114.22, 62.41, 14.00. MS (ESI) cald C20H13F6NO4 for $[M+H]^+$, 446.07, found 446.18

Ethyl 2-(3-chlorophenyl)-4-oxo-7-(trifluoromethyl)-1,4-dihydroquinoline-3-carboxylate 11d. 44% yield from intermediate **7**, ^{1}H NMR (400 MHz, MeOD) δ 8.49 (d, *J* = 8.5 Hz, 1H), 8.01 (s, 1H), 7.76 – 7.54 (m, 5H), 4.13 (q, *J* = 7.2 Hz, 2H), 1.06 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, MeOD) δ 176.16, 167.57, 152.18, 140.83, 136.88, 136.58, 135.84, 135.61, 135.28, 131.82, 131.64, 129.45, 128.35, 128.30, 127.91, 126.35, 123.64, 121.64, 121.60, 117.92, 117.65, 62.46, 14.13, 13.92. MS (ESI) cald C19H13ClF3NO3 for $[M+H]^+$, 396.05, found 396.13

Ethyl 2-([1,1'-biphenyl]-3-yl)-7-hydroxy-4-oxo-1,4-dihydroquinoline-3-carboxylate 12a. 37% yield from intermediate **7**, ^{1}H NMR (400 MHz, MeOD) δ 8.55 (s, 1H), 8.14 (d, *J* = 8.6, 1H), 7.86 – 7.78 (m, 2H), 7.72 – 7.64 (m, 2H), 7.61 (t, *J* = 7.6, 1H), 7.54 (d, *J* = 7.6, 1H), 7.47 (t, *J* = 7.6, 2H), 7.38 (t, *J* = 7.4, 1H), 6.99 – 6.91 (m, 2H), 4.04 (q, *J* = 7.1, 2H), 0.93 (t, *J* = 7.1, 3H). ^{13}C NMR (101 MHz, MeOD) δ 176.69, 168.77, 164.16, 152.32, 143.33, 143.08, 141.27, 136.11, 130.43, 130.13, 129.91, 129.03, 128.41, 128.11, 128.07, 127.94, 119.36, 117.01, 116.19, 102.82, 62.21, 14.06. MS (ESI) cald C24H19NO4 for $[M+H]^+$, 386.13, found 386.18

Ethyl 7-hydroxy-4-oxo-2-(3-phenoxyphenyl)-1,4-dihydroquinoline-3-carboxylate 12b. 42% yield from intermediate **7**, ^{1}H NMR (400 MHz, MeOD) δ 8.11 (dd, *J* = 8.3, 1.0, 1H), 7.51 (td, *J* = 7.7, 0.9, 1H), 7.44 – 7.35 (m, 2H), 7.33 – 7.26 (m, 1H), 7.21 – 7.11 (m, 3H), 7.09 – 7.00 (m, 2H), 6.99 – 6.89 (m, 2H), 4.06 (q, *J* = 7.1, 2H), 1.03 (t, *J* = 7.1, 3H). ^{13}C NMR (101 MHz, MeOD) δ 176.64, 168.53, 163.73, 159.14, 157.98, 151.52, 143.21, 137.11, 131.50, 131.16, 128.43, 125.17, 124.06, 121.38, 120.32, 119.49, 119.37, 116.80, 116.13, 102.74, 62.26, 14.19. MS (ESI) cald C24H19NO5 for $[M+H]^+$, 402.13, found 402.20

Ethyl 2-([1,1'-biphenyl]-3-yl)-7-chloro-4-oxo-1,4-dihydroquinoline-3-carboxylate 13. 56% yield from intermediate **7**, ^{1}H NMR (400 MHz, MeOD) δ 8.29 (d, *J* = 8.7 Hz, 1H), 7.86 (s, 2H), 7.80 – 7.32 (m, 10H), 4.08 (q, *J* = 7.1 Hz, 2H), 0.97 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, MeOD) δ 176.43, 168.16, 153.11, 143.22, 141.82, 141.14, 140.24, 135.67, 130.57, 130.22, 130.16, 129.11, 128.57, 128.10, 128.06, 127.93, 126.48, 124.74, 119.14, 117.53, 62.39, 14.07. MS (ESI) cald C24H18ClNO3 for $[M+H]^+$, 404.10, found 404.20

Ethyl 2-(3-methoxyphenyl)-7-(methylthio)-4-oxo-1,4-dihydroquinoline-3-carboxylate 14. 28% yield from **24**,^{1}H NMR (400 MHz, MeOD) δ 8.14 (d, *J* = 8.7 Hz, 1H), 7.49 – 7.37 (m, 2H), 7.31 (d, *J* = 8.7 Hz, 1H), 7.14 (s, 3H), 4.07 (q, *J* = 7.1 Hz, 2H), 3.86 (s, 3H), 2.58 (s, 3H), 1.00 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, MeOD) δ 176.67, 168.43, 161.34, 152.26, 148.18, 141.66, 136.47, 131.16, 126.55, 123.99, 121.48, 117.25, 116.91, 114.87, 113.70, 62.31, 56.04, 14.71, 14.09. MS (ESI) cald C20H19NO4S for $[M+H]^+$, 370.10, found 370.16

Ethyl 2-(benzo[d][1,3]dioxol-5-yl)-5,7-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate 15a. 31% yield from intermediate **7**, ^{1}H NMR (400 MHz, MeOD) δ 7.16 (dd, *J* = 9.3, 1.9, 1H), 7.09 (dt, *J* = 3.9, 1.6, 2H), 7.02 – 6.92 (m, 2H), 6.07 (s, 2H), 4.13 (q, *J* = 7.1, 2H), 1.11 (t, *J* = 7.1, 3H). MS (ESI) cald C19H13F2NO5 for $[M+H]^+$, 374.08, found 374.17

Ethyl 5,7-difluoro-2-(3-methoxyphenyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 15b. 35% yield from intermediate **7**, ^{1}H NMR (400 MHz, MeOD) δ 7.50 – 7.43 (m, 1H), 7.22 – 7.12 (m, 4H), 6.99 (ddd, *J* = 11.7, 9.3, 2.4, 1H), 4.10 (q, *J* = 7.1, 2H), 3.87 (s, 3H), 1.04 (t, *J* = 7.1, 3H). ^{13}C NMR (101 MHz, MeOD) δ 175.32,

167.91, 161.35, 152.13, 135.82, 131.20, 121.42, 118.89, 117.41, 114.83, 101.95, 101.70, 101.43, 101.18, 62.42, 56.04, 14.11. MS (ESI) cald C19H15F2NO4 for $[M+H]^+$, 360.10, found 360.15

Ethyl 5,7-difluoro-4-oxo-2-(3-phenoxyphenyl)-1,4-dihydroquinoline-3-carboxylate 15c. 11% yield from intermediate **7**, ^{1}H NMR (400 MHz, MeOD) δ 7.53 (t, *J* = 8.4, 1H), 7.40 (t, *J* = 8.0, 2H), 7.31 (d, *J* = 7.9, 1H), 7.23 – 7.12 (m, 3H), 7.09 – 7.02 (m, 2H), 7.01 – 6.92 (m, 1H), 4.07 (q, *J* = 7.1, 2H), 1.06 (t, *J* = 7.1, 3H). ^{13}C NMR (101 MHz, MeOD) δ 175.27, 167.68, 167.17, 159.27, 157.86, 151.37, 136.13, 131.68, 131.20, 125.27, 123.95, 121.73, 120.38, 119.21, 102.06, 101.80, 101.79, 101.54, 101.30, 101.05, 62.50, 14.21. MS (ESI) cald C24H17F2NO4 for $[M+H]^+$, 422.11, found 422.28.

Ethyl 5,7-difluoro-4-oxo-2-(3-(trifluoromethoxy)phenyl)-1,4-dihydroquinoline-3-carboxylate 15d. 10% yield from intermediate **7**, ^{1}H NMR (400 MHz, MeOD) δ 7.73 – 7.64 (m, 1H), 7.62 – 7.57 (m, 1H), 7.57 – 7.50 (m, 2H), 7.19 – 7.11 (m, 1H), 7.00 (ddd, *J* = 11.6, 9.3, 2.3, 1H), 4.06 (q, *J* = 7.1, 2H), 1.01 (t, *J* = 7.1, 3H). ^{13}C NMR (101 MHz, MeOD) δ 175.20, 167.32, 164.88, 164.29, 150.52, 136.62, 132.01, 128.31, 124.27, 122.21, 120.62, 119.01, 113.51, 102.19, 101.94, 101.93, 101.67, 101.39, 101.18, 101.14, 62.44, 14.02. MS (ESI) cald C19H12F5NO4 for $[M+H]^+$, 414.07, found 414.21

Ethyl 2-(benzo[d][1,3]dioxol-5-yl)-6,7-dimethoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate 16a. 56% yield from intermediate **7**, ^{1}H NMR (400 MHz, DMSO) δ 11.75 (s, 1H), 7.43 (s, 1H), 7.18 – 7.00 (m, 4H), 6.13 (s, 2H), 4.02 (q, *J* = 7.1, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 1.02 (t, *J* = 7.1, 3H). ^{13}C NMR (101 MHz, DMSO) δ 172.43, 166.71, 153.25, 148.70, 147.34, 147.04, 147.00, 135.12, 127.45, 122.50, 118.45, 114.55, 108.44, 104.05, 101.73, 99.63, 60.10, 55.68, 55.55, 13.81. MS (ESI) cald C21H19NO7 for $[M+H]^+$, 398.12, found 398.27

Ethyl 2-([1,1'-biphenyl]-3-yl)-6,7-dimethoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate 16b. 62% yield from intermediate **7**,^{1}H NMR (400 MHz, DMSO) δ 11.95 (s, 1H), 7.99 – 7.34 (m, 10H), 7.16 (d, *J* = 6.5, 1H), 3.98 (q, *J* = 7.0, 2H), 3.87 (d, *J* = 2.7, 6H), 0.89 (t, *J* = 7.0, 3H). ^{13}C NMR (101 MHz, DMSO) δ 172.44, 166.64, 153.33, 147.47, 147.15, 140.41, 139.19, 135.20, 134.47, 129.32, 129.11, 128.25, 127.97, 127.10, 126.74, 126.45, 118.61, 114.67, 104.09, 99.68, 60.12, 55.71, 55.57, 13.60. MS (ESI) cald C26H23NO5 for $[M+H]^+$, 430.16, found 430.34

Ethyl 6,7-dimethoxy-2-(3-methoxyphenyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 16c. 62% yield from intermediate **7**, ^{1}H NMR (400 MHz, DMSO) δ 11.85 (s, 1H), 7.52 – 7.39 (m, 2H), 7.21 – 7.01 (m, 4H), 3.99 (q, *J* = 7.1, 2H), 3.87 (d, *J* = 3.2, 6H), 3.83 (s, 3H), 0.96 (t, *J* = 7.1, 3H). ^{13}C NMR (101 MHz, DMSO) δ 172.40, 166.56, 159.11, 153.29, 147.28, 147.12, 135.13, 129.87, 120.32, 118.56, 115.74, 114.57, 113.56, 104.05, 99.68, 60.10, 55.69, 55.56, 55.36, 13.67. MS (ESI) cald C21H21NO6 for $[M+H]^+$, 384.14, found 384.28

Ethyl 6,7-dimethoxy-4-oxo-2-(3-phenoxyphenyl)-1,4-dihydroquinoline-3-carboxylate 16d. 55% yield from intermediate **7**, ^{1}H NMR (400 MHz, DMSO) δ 11.88 (s, 1H), 7.57 (t, *J* = 8.0, 1H), 7.44 (t, *J* = 8.0, 3H), 7.31 (d, *J* = 7.7, 1H), 7.25 – 7.17 (m, 2H), 7.17 – 7.11 (m, 2H), 7.11 – 7.00 (m, 2H), 3.96 (q, *J* = 7.1, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 0.96 (t, *J* = 7.1, 3H). ^{13}C NMR (101 MHz, DMSO) δ 172.35, 166.41, 156.72, 156.00, 153.33, 147.18, 146.74, 135.59, 135.11, 130.51, 130.22, 124.03, 123.15, 119.99, 118.91, 118.61, 117.91, 114.53, 104.04, 99.69, 60.14, 55.70, 55.56, 13.68. MS (ESI) cald C26H23NO6 for $[M+H]^+$, 446.15, found 446.28

Ethyl 2-(benzo[d][1,3]dioxol-5-yl)-7-chloro-6-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate 17a. 22% yield from intermediate **7**, ^{1}H NMR (400 MHz, DMSO) δ 7.77 (s, 1H), 7.62 (s, 1H), 7.14 (d, *J* = 1.7, 1H), 7.06 (dt, *J* = 8.1, 4.9, 2H), 6.13 (s, 2H), 4.03 (q, *J* = 7.1, 2H), 3.95 (s, 3H), 1.02 (t, *J* = 7.1, 3H). ^{13}C NMR (101 MHz, DMSO) δ 172.40, 166.54, 157.70, 151.27, 148.79, 147.38, 146.73, 127.17, 124.51, 122.57, 120.49,

114.67, 110.99, 108.48, 105.40, 101.75, 60.22, 56.37, 13.81. MS (ESI) cald C20H16ClNO6 for $[M+H]^+$, 402.07, found 402.24

Ethyl 2-([1,1'-biphenyl]-3-yl)-7-chloro-6-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate 17b. 55% yield from intermediate **7**, ^{1}H NMR (400 MHz, DMSO) δ 12.13 (s, 1H), 7.94 – 7.82 (m, 2H), 7.79 (s, 1H), 7.77 – 7.71 (m, 2H), 7.69 – 7.62 (m, 2H), 7.59 – 7.47 (m, 3H), 7.44 (dd, *J* = 4.9, 3.7, 1H), 4.02 – 3.94 (m, 5H), 0.88 (t, *J* = 7.1, 3H). ^{13}C NMR (101 MHz, DMSO) δ 172.49, 166.21, 151.48, 148.66, 140.48, 139.08, 134.21, 133.87, 129.41, 129.12, 128.47, 128.02, 127.44, 127.12, 126.73, 126.47, 124.56, 120.13, 114.90, 105.48, 60.26, 56.41, 13.56. MS (ESI) cald C25H20ClNO4 for $[M+H]^+$, 434.11, found 434.31

Ethyl 7-chloro-6-methoxy-2-(3-methoxyphenyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 17c. 28% yield from intermediate **7**, ^{1}H NMR (400 MHz, DMSO) δ 12.05 (s, 1H), 7.78 (s, 1H), 7.63 (s, 1H), 7.48 (t, *J* = 8.1, 1H), 7.21 – 7.06 (m, 3H), 4.00 (q, *J* = 7.1, 2H), 3.96 (s, 3H), 3.82 (s, 3H), 0.95 (t, *J* = 7.1, 3H). ^{13}C NMR (101 MHz, DMSO) δ 172.42, 166.22, 159.15, 151.40, 148.59, 134.98, 134.02, 129.97, 127.34, 124.54, 120.32, 115.89, 114.75, 113.63, 105.42, 60.23, 56.38, 55.38, 13.64. MS (ESI) cald C20H18ClNO5 for $[M+H]^+$, 388.09, found 388.25

Ethyl 7-chloro-6-methoxy-4-oxo-2-(3-phenoxyphenyl)-1,4-dihydroquinoline-3-carboxylate 17d. 21% yield from intermediate **7**, ^{1}H NMR (400 MHz, DMSO) δ 12.08 (s, 1H), 7.77 (s, 1H), 7.59 (dd, *J* = 15.3, 7.2, 2H), 7.45 (dd, *J* = 11.3, 4.6, 2H), 7.33 (d, *J* = 7.6, 1H), 7.26 – 7.14 (m, 3H), 7.06 (d, *J* = 8.5, 2H), 3.97 (m, 5H), 0.96 (t, *J* = 7.1, 3H). ^{13}C NMR (101 MHz, DMSO) δ 172.43, 166.00, 156.81, 155.90, 151.50, 147.92, 135.30, 133.80, 130.62, 130.24, 127.46, 124.56, 124.10, 123.14, 120.13, 118.97, 117.89, 114.74, 105.43, 60.29, 56.40, 13.66. MS (ESI) cald C25H20ClNO5 for $[M+H]^+$, 450.10, found 450.25

Ethyl 2-(benzo[d][1,3]dioxol-5-yl)-6,7-dichloro-4-oxo-1,4-dihydroquinoline-3-carboxylate 18a. 11% yield from intermediate **7**, ^{1}H NMR (400 MHz, DMSO) δ 12.14 (s, 1H), 8.19 (s, 1H), 7.89 (s, 1H), 7.11 (ddd, *J* = 10.4, 9.8, 1.6, 3H), 6.15 (s, 2H), 4.05 (q, *J* = 7.1, 2H), 1.02 (t, *J* = 7.1, 3H). ^{13}C NMR (101 MHz, DMSO) δ 172.03, 165.81, 149.56, 149.15, 147.48, 138.65, 134.99, 126.78, 126.38, 124.23, 122.72, 120.59, 115.92, 108.59, 108.42, 101.88, 60.47, 13.77. MS (ESI) cald C19H13Cl2NO5 for $[M+H]^+$, 406.02, found 406.21

Ethyl 2-([1,1'-biphenyl]-3-yl)-6,7-dichloro-4-oxo-1,4-dihydroquinoline-3-carboxylate 18b. 10% yield from intermediate **7**, ^{1}H NMR (400 MHz, DMSO) δ 12.33 (s, 1H), 8.22 (s, 1H), 7.88 (d, *J* = 11.2, 3H), 7.80 – 7.33 (m, 7H), 3.97 (q, *J* = 7.1, 2H), 0.88 (t, *J* = 7.1, 3H). ^{13}C NMR (101 MHz, DMSO) δ 172.33, 140.82, 140.46, 140.34, 139.56, 135.38, 129.75, 129.53, 128.79, 128.41, 127.51, 127.13, 126.86, 126.78, 125.09, 116.23, 60.72, 13.98. MS (ESI) cald C24H17Cl2NO3 for $[M+H]^+$, 438.06, found 438.22

Ethyl 6,7-dichloro-2-(3-methoxyphenyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 18c. 19% yield from intermediate **7**, ^{1}H NMR (400 MHz, DMSO) δ 12.23 (s, 1H), 8.20 (s, 1H), 7.89 (s, 1H), 7.58 – 7.32 (m, 2H), 7.21 – 7.06 (m, 3H), 4.00 (q, *J* = 7.1, 2H), 3.82 (s, 3H), 0.95 (t, *J* = 7.1, 3H). ^{13}C NMR (101 MHz, DMSO) δ 171.96, 165.85, 159.58, 159.16, 134.85, 130.00, 126.70, 126.37, 124.45, 121.03, 120.30, 119.53, 118.50, 116.44, 116.06, 115.86, 113.62, 112.77, 60.38, 55.40, 13.62. MS (ESI) cald C19H15Cl2NO4 for $[M+H]^+$, 392.04, found 393.22

Ethyl 6,7-dichloro-4-oxo-2-(3-phenoxyphenyl)-1,4-dihydroquinoline-3-carboxylate 18d. 22% yield from intermediate **7**, ^{1}H NMR (400 MHz, DMSO) δ 12.27 (s, 1H), 8.20 (s, 1H), 7.88 (s, 1H), 7.59 (t, *J* = 7.9, 1H), 7.45 (dd, *J* = 11.2, 4.6, 2H), 7.34 (d, *J* = 7.6, 1H), 7.28 – 7.15 (m, 3H), 7.06 (d, *J* = 8.4, 2H), 3.98 (q, *J* = 7.0, 2H), 0.96 (t, *J* = 7.1, 3H). ^{13}C NMR (101 MHz, DMSO) δ 171.97, 170.78, 165.57, 159.71, 156.83, 155.88, 130.65, 130.25, 126.37, 124.45, 124.12, 123.11, 120.30, 118.98, 118.13, 117.86, 115.85, 112.36, 60.44, 13.65. MS (ESI) cald C24H17Cl2NO4 for $[M+H]^+$, 454.05, found 454.22

Ethyl 2-(benzo[d][1,3]dioxol-5-yl)-6-chloro-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate 19a. 23% yield from intermediate **7**, ^{1}H NMR (400 MHz, DMSO) δ 11.95 (s, 1H), 8.02 (d, *J* = 2.3, 1H), 7.26 (s, 1H), 7.09 (ddd, *J* = 9.8, 9.2, 1.7, 3H), 6.14 (s, 2H), 4.03 (q, *J* = 7.1, 2H), 3.95 (s, 3H), 1.02 (t, *J* = 7.1, 3H). ^{13}C NMR (101 MHz, DMSO) δ 174.12, 172.12, 166.23, 157.27, 148.93, 148.69, 147.40, 139.97, 127.12, 125.67, 122.58, 119.15, 118.85, 115.32, 108.49, 108.39, 101.81, 100.57, 60.29, 56.47, 13.79. MS (ESI) cald C20H16ClNO6 for $[M+H]^+$, 402.07, found 402.24

Ethyl 2-([1,1'-biphenyl]-3-yl)-6-chloro-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate 19b. 36% yield from intermediate **7**, ^{1}H NMR (400 MHz, DMSO) δ 12.13 (s, 1H), 8.06 (s, 1H), 7.93 – 7.81 (m, 2H), 7.74 (d, *J* = 7.9, 2H), 7.66 (t, *J* = 7.7, 1H), 7.59 – 7.37 (m, 4H), 7.28 (s, 1H), 4.06 – 3.88 (m, 5H), 0.89 (t, *J* = 7.1, 3H). ^{13}C NMR (101 MHz, DMSO) δ 172.14, 166.13, 157.35, 149.16, 140.45, 140.00, 139.10, 134.14, 129.38, 129.12, 128.51, 128.02, 127.07, 126.73, 126.44, 125.74, 119.33, 118.98, 115.47, 100.60, 60.30, 56.49, 13.58. MS (ESI) cald C25H20ClNO4 for $[M+H]^+$, 434.11, found 434.25

Ethyl 6-chloro-7-methoxy-2-(3-methoxyphenyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate **19c**. 29% yield from intermediate **7**, ^{1}H NMR (400 MHz, DMSO) δ 8.04 (s, 1H), 7.47 (t, *J* = 8.1, 1H), 7.28 (s, 1H), 7.13 (dt, *J* = 8.1, 4.3, 3H), 4.04 – 3.95 (m, 2H), 3.95 (s, 3H), 3.82 (s, 3H), 0.95 (t, *J* = 7.1, 3H). ^{13}C NMR (101 MHz, DMSO) δ 172.12, 166.16, 159.14, 157.28, 149.15, 140.15, 134.95, 129.94, 125.69, 120.29, 119.25, 119.00, 115.97, 115.33, 113.55, 100.77, 60.28, 56.48, 55.39, 13.65. MS (ESI) cald C20H18ClNO5 for $[M+H]^+$, 388.09, found 388.25

Ethyl 6-chloro-7-methoxy-4-oxo-2-(3-phenoxyphenyl)-1,4-dihydroquinoline-3-carboxylate 19d. 68% yield from intermediate **7**, ^{1}H NMR (400 MHz, DMSO) δ 12.08 (s, 1H), 8.02 (s, 1H), 7.56 (t, *J* = 8.0, 1H), 7.44 (dd, *J* = 11.3, 4.6, 2H), 7.32 (d, *J* = 7.7, 1H), 7.28 – 7.14 (m, 4H), 7.05 (d, *J* = 8.5, 2H), 4.08 – 3.87 (m, 5H), 0.95 (t, *J* = 7.1, 3H). ^{13}C NMR (101 MHz, DMSO) δ 171.98, 157.13, 156.69, 156.03, 130.45, 130.21, 125.63, 124.00, 123.13, 120.03, 118.89, 117.90, 60.21, 56.43, 13.67. MS (ESI) cald C25H20ClNO5 for $[M+H]^+$, 450.10, found 450.25

Ethyl 6-chloro-2-(3-chlorophenyl)-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate 19e. 45% yield from intermediate **7**, ^{1}H NMR (400 MHz, DMSO) δ 12.12 (s, 1H), 8.05 (s, 1H), 7.67 (d, *J* = 2.0 Hz, 2H), 7.63 – 7.55 (m, 1H), 7.55 – 7.48 (m, 1H), 7.24 (s, 1H), 4.01 (q, *J* = 7.0 Hz, 2H), 3.96 (s, 3H), 0.96 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 172.02, 165.72, 157.39, 147.78, 139.85, 135.34, 133.23, 130.60, 130.21, 127.96, 126.94, 125.72, 119.47, 118.99, 115.41, 100.51, 60.34, 56.49, 13.62. MS (ESI) cald C19H15Cl2NO4 for $[M+H]^+$, 392.04, found 392.14

Ethyl 2-(3-bromophenyl)-6-chloro-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate 19f. 66% yield from intermediate **7**, ^{1}H NMR (400 MHz, DMSO) δ 12.12 (s, 1H), 8.05 (s, 1H), 7.87 – 7.73 (m, 2H), 7.63 – 7.47 (m, 2H), 7.24 (s, 1H), 4.01 (q, *J* = 7.1 Hz, 2H), 3.96 (s, 3H), 0.96 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 172.02, 165.73, 157.39, 147.70, 139.85, 135.55, 133.11, 130.80, 130.73, 127.29, 125.72, 121.66, 119.46, 118.99, 115.41, 100.52, 60.35, 56.49, 13.65. MS (ESI) cald C19H15BrClNO4 for $[M+H]^+$, 438.00, found 438.06

Ethyl 6-chloro-2-(3-fluoro-5-methoxyphenyl)-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate 19g. 24% yield from intermediate **7**, ^{1}H NMR (400 MHz, DMSO) δ 12.10 (s, 1H), 8.04 (s, 1H), 7.25 (s, 1H), 7.09 (dd, *J* = 11.0, 2.2, 1H), 7.04 – 6.96 (m, 2H), 4.03 (q, *J* = 7.1, 2H), 3.95 (s, 3H), 3.84 (s, 3H), 0.99 (t, *J* = 7.1, 3H). ^{13}C NMR (101 MHz, DMSO) δ 172.05, 165.83, 163.83, 161.41, 160.77, 160.65, 157.39, 147.80, 139.90, 125.72, 119.45, 119.01, 115.34, 110.60, 107.44, 107.21, 103.45, 103.20, 100.61, 60.38, 56.51, 56.04, 13.64. MS (ESI) cald C20H17ClFNO5 for $[M+H]^+$, 406.08, found 406.20

Ethyl 2-(benzo[d][1,3]dioxol-5-yl)-6-fluoro-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate 20a. 31% yield from intermediate **7**, ^{1}H NMR (400 MHz, DMSO) δ 11.99 (s, 1H), 7.72 (d, *J* = 11.6, 1H), 7.30 (d, *J* = 7.4, 1H), 7.08 (ddd, *J* = 9.8, 9.1, 1.7, 3H), 6.14 (s, 2H), 4.02 (q, *J* = 7.1, 2H), 3.93 (s, 3H), 1.02 (t, *J* = 7.1, 3H). ^{13}C NMR (101 MHz, DMSO) δ 172.39, 166.48, 151.38, 151.24, 150.58, 148.79, 148.58, 148.14, 147.35, 137.71, 122.52, 118.17, 114.64, 109.85, 109.67, 108.42, 101.75, 60.20, 56.20, 13.80. MS (ESI) cald C20H16FNO6 for $[M+H]^+$, 386.10, found 386.24

Ethyl 2-([1,1'-biphenyl]-3-yl)-6-fluoro-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate 20b. 35% yield from intermediate **7**, ^{1}H NMR (400 MHz, DMSO) δ 12.10 (s, 1H), 7.89 (d, *J* = 7.7, 1H), 7.85 (s, 1H), 7.76 (t, *J* = 10.2, 3H), 7.66 (t, *J* = 7.7, 1H), 7.53 (dd, *J* = 14.8, 7.4, 3H), 7.42 (t, *J* = 6.8, 1H), 7.31 (d, *J* = 7.2, 1H), 4.03 – 3.96 (m, 2H), 3.95 (s, 3H), 0.89 (t, *J* = 7.1, 3H). ^{13}C NMR (101 MHz, DMSO) δ 172.43, 166.24, 151.42, 150.71, 148.77, 148.26, 140.45, 139.11, 137.40, 134.19, 129.37, 129.12, 128.45, 128.01, 127.08, 126.73, 126.45, 114.87, 109.99, 109.79, 101.64, 60.26, 56.24, 13.58. MS (ESI) cald C25H20FNO4 for $[M+H]^+$, 418.14, found 418.28

Ethyl 6-fluoro-7-methoxy-2-(3-methoxyphenyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate 20c. 56% yield from intermediate **7**, ^{1}H NMR (400 MHz, DMSO) δ 12.09 (s, 1H), 7.74 (d, *J* = 11.6, 1H), 7.47 (dd, *J* = 11.6, 4.7, 1H), 7.31 (d, *J* = 7.3, 1H), 7.19 – 7.04 (m, 3H), 3.99 (q, *J* = 7.1, 2H), 3.93 (d, *J* = 6.4, 3H), 3.82 (s, 3H), 0.95 (t, *J* = 7.1, 3H). ^{13}C NMR (101 MHz, DMSO) δ 172.39, 166.28, 159.12, 151.45, 151.32, 150.66, 148.80, 148.21, 137.62, 135.08, 129.90, 120.29, 118.26, 115.86, 114.69, 113.57, 109.90, 109.71, 101.86, 60.21, 56.21, 55.36, 13.65. MS (ESI) cald C20H18FNO5 for $[M+H]^+$, 372.12, found 372.23

Ethyl 6-fluoro-7-methoxy-4-oxo-2-(3-phenoxyphenyl)-1,4-dihydroquinoline-3-carboxylate 20d. 61% yield from intermediate **7**, ^{1}H NMR (400 MHz, DMSO) δ 12.06 (s, 1H), 7.74 (d, *J* = 11.5, 1H), 7.58 (t, *J* = 7.9, 1H), 7.45 (dd, *J* = 11.1, 4.3, 2H), 7.31 (t, *J* = 8.0, 2H), 7.24 – 7.13 (m, 3H), 7.06 (d, *J* = 7.9, 2H), 4.05 – 3.83 (m, 5H), 0.96 (t, *J* = 7.0, 3H). ^{13}C NMR (101 MHz, DMSO) δ 172.34, 166.05, 156.74, 155.96, 151.53, 151.39, 148.27, 148.15, 137.42, 135.37, 130.55, 130.22, 124.05, 123.12, 120.13, 118.92, 118.31, 118.26, 117.90, 114.69, 109.92, 109.73, 101.74, 60.27, 56.23, 13.66. MS (ESI) cald C25H20FNO5 for $[M+H]^+$, 434.13, found 434.23

Ethyl 6-fluoro-7-methoxy-4-oxo-2-(3-(trifluoromethoxy)phenyl)-1,4-dihydroquinoline-3-carboxylate 20e. 48% yield from intermediate **7**, ^{1}H NMR (400 MHz, DMSO) δ 12.14 (s, 1H), 7.81 – 7.66 (m, 2H), 7.65 – 7.57 (m, 2H), 7.55 (s, 1H), 7.26 (d, *J* = 7.3, 1H), 4.01 – 3.88 (m, 6H), 0.90 (t, *J* = 7.1, 3H). ^{13}C NMR (101 MHz, DMSO) δ 172.31, 165.73, 151.51, 148.11, 147.41, 137.30, 135.64, 130.89, 127.48, 122.78, 120.89, 118.41, 118.36, 114.82, 110.02, 109.83, 101.61, 99.50, 60.23, 56.27, 13.44. MS (ESI) cald C20H15F4NO5 for $[M+H]^+$, 426.09, found 426.22

Ethyl 6-fluoro-2-(3-fluorophenyl)-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate 20f. 36% yield from intermediate **7**, ^{1}H NMR (400 MHz, DMSO) δ 12.09 (s, 1H), 7.76 (d, *J* = 11.5, 1H), 7.62 (dt, *J* = 7.8, 6.8, 1H), 7.52 – 7.41 (m, 2H), 7.39 (d, *J* = 7.7, 1H), 7.27 (d, *J* = 7.3, 1H), 3.99 (q, *J* = 7.1, 2H), 3.94 (s, 3H), 0.94 (t, *J* = 7.1, 3H). ^{13}C NMR (101 MHz, DMSO) δ 172.34, 165.87, 162.94, 160.50, 151.62, 151.49, 150.77, 148.32, 147.55, 137.33, 135.67, 130.97, 130.89, 124.47, 118.34, 117.27, 117.06, 115.42, 115.19, 114.78, 110.00, 109.80, 101.63, 60.29, 56.26, 13.61. MS (ESI) cald C19H15F2NO4 for $[M+H]^+$, 360.10, found 360.15

Ethyl 2-(3-chlorophenyl)-6-fluoro-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate 20g. 29% yield from intermediate **7**, ^{1}H NMR (400 MHz, DMSO) δ 12.10 (s, 1H), 7.75 (d, *J* = 11.5, 1H), 7.69 – 7.63 (m, 2H), 7.63 – 7.55 (m, 1H), 7.51 (dt, *J* = 7.6, 1.3, 1H), 7.27 (d, *J* = 7.4, 1H), 4.00 (q, *J* = 7.1, 2H), 3.94 (s, 3H), 0.95 (t, *J* = 7.1, 3H). ^{13}C NMR (101 MHz, DMSO) δ 165.86, 151.62, 151.49, 148.33, 147.46, 137.34, 135.47, 133.23, 130.61, 130.16, 127.99, 126.97, 118.30, 114.79, 109.99, 109.80, 101.63, 60.31, 56.25, 13.64. MS (ESI) cald C19H15ClFNO4 for $[M+H]^+$, 376.07, found 376.17

Ethyl 2-(3-bromophenyl)-6-fluoro-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate 20h. 35% yield from intermediate **7**, ^{1}H NMR (400 MHz, DMSO) δ 12.09 (s, 1H), 7.88 – 7.70 (m, 3H), 7.63 – 7.45 (m, 2H), 7.27 (d, *J* = 7.3 Hz, 1H), 4.01 (q, *J* = 7.0 Hz, 2H), 3.95 (s, 3H), 0.96 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 172.28, 165.85, 151.59, 151.46, 150.75, 148.30, 147.36, 137.32, 135.66, 133.04, 130.79, 130.73, 127.30, 121.64, 118.34, 118.28, 114.77, 109.97, 109.78, 101.62, 60.30, 56.24, 13.66. MS (ESI) cald C19H15BrFNO4 for $[M+H]^+$, 420.02, found 422.11

Ethyl 6-fluoro-2-(3-fluoro-5-methoxyphenyl)-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate 20i. 20% yield from intermediate **7**, ^{1}H NMR (400 MHz, DMSO) δ 7.74 (d, *J* = 11.6, 1H), 7.30 (d, *J* = 7.4, 1H), 7.05 (dt, *J* = 11.0, 2.1, 1H), 6.97 (t, *J* = 4.8, 2H), 4.01 (q, *J* = 7.1, 2H), 3.93 (s, 3H), 3.83 (s, 3H), 0.98 (t, *J* = 7.1, 3H). ^{13}C NMR (101 MHz, DMSO) δ 172.28, 166.32, 163.79, 161.37, 160.68, 160.56, 151.39, 150.69, 148.25, 138.14, 118.47, 114.42, 110.54, 109.82, 109.63, 107.41, 107.18, 103.11, 102.86, 102.35, 60.22, 56.21, 55.97, 13.64. MS (ESI) cald C20H17F2NO5 for $[M+H]^+$, 390.11, found 390.18

Ethyl 2-(2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-6-fluoro-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate 20j. 28% yield from intermediate **7**, ^{1}H NMR (400 MHz, MeOD) δ 7.87 (d, *J* = 11.4, 1H), 7.62 (dt, *J* = 7.8, 7.1, 2H), 7.39 – 7.31 (m, 2H), 7.21 (d, *J* = 7.2, 1H), 7.19 – 7.08 (m, 3H), 4.08 (q, *J* = 7.1, 2H), 4.00 (s, 3H), 2.05 (s, 6H), 1.04 (t, *J* = 7.1, 3H). ^{13}C NMR (101 MHz, MeOD) δ 175.80, 168.41, 154.52, 154.39, 153.40, 151.99, 150.92, 150.64, 143.39, 141.87, 139.14, 136.80, 135.64, 132.57, 130.30, 130.09, 128.69, 128.54, 127.84, 119.85, 116.57, 111.33, 111.14, 102.11, 62.34, 57.03, 21.07, 14.26. MS (ESI) cald C27H24FNO4 for $[M+H]^+$, 446.17, found 446.24

Ethyl 2-(2'-chloro-[1,1'-biphenyl]-3-yl)-6-fluoro-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate 20k. 21% yield from intermediate **7**, ^{1}H NMR (400 MHz, DMSO) δ 7.75 (d, *J* = 11.6, 1H), 7.61 (dd, *J* = 19.4, 14.3, 4H), 7.47 (dd, *J* = 4.3, 2.0, 3H), 7.28 (d, *J* = 7.1, 1H), 4.05 – 3.85 (m, 5H), 0.87 (t, *J* = 7.1, 3H). ^{13}C NMR (101 MHz, DMSO) δ 172.40, 158.47, 155.57, 153.28, 149.18, 138.88, 138.78, 131.41, 131.17, 129.99, 129.67, 128.75, 128.56, 127.72, 127.51, 121.99, 114.66, 113.68, 112.29, 110.36, 109.89, 109.70, 105.59, 60.19, 56.20, 13.54. MS (ESI) cald C25H19ClFNO4 for $[M+H]^+$, 452.10, found 452.18

Ethyl 2-(3-(2,6-dimethylphenoxy)phenyl)-6-fluoro-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate 20l. 28% yield from intermediate **7**, ^{1}H NMR (400 MHz, DMSO) δ 8.36 (s, 0H), 7.72 (d, *J* = 11.7, 1H), 7.47 (t, *J* = 7.9, 1H), 7.28 (d, *J* = 7.4, 1H), 7.18 (d, *J* = 5.0, 3H), 7.15 – 7.07 (m, 1H), 6.94 – 6.81 (m, 2H), 3.90 (dd, *J* = 13.3, 5.8, 5H), 2.09 (s, 6H), 0.93 (t, *J* = 7.1, 3H). ^{13}C NMR (101 MHz, DMSO) δ 172.20, 157.03, 150.08, 148.12, 130.58, 130.23, 129.22, 125.51, 121.48, 118.57, 115.61, 113.89, 109.72, 109.53, 59.97, 56.14, 15.86, 13.66. MS (ESI) cald C27H24FNO5 for $[M+H]^+$, 462.16, found 462.26

Ethyl 2-(3-(4,5-dimethylthiazol-2-yl)phenyl)-6-fluoro-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate 20m. 22% yield from intermediate **7**, ^{1}H NMR (400 MHz, DMSO) δ 8.02 (s, 1H), 7.76 (d, *J* = 11.5 Hz, 1H), 7.68 – 7.56 (m, 1H), 7.31 (d, *J* = 7.1 Hz, 1H), 3.98 (m, *J* = 16.0, 8.9 Hz, 3H), 2.41 (s, 2H), 2.33 (s, 2H), 0.94 (t, *J* = 7.1 Hz, 2H). ^{1}H NMR (400 MHz, DMSO) δ 8.02 (s, 1H), 7.76 (d, *J* = 11.5 Hz, 1H), 7.68 – 7.56 (m, 2H), 7.31 (d, *J* = 7.1 Hz, 1H), 3.98 (dd, *J* = 16.0, 8.9 Hz, 5H), 2.41 (s, 3H), 2.33 (s, 3H), 0.94 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 172.38, 166.25, 160.82, 151.37, 150.73, 149.43, 148.86, 148.28, 133.52, 129.64, 129.15, 127.66, 127.17, 124.95, 118.40, 114.77, 109.93, 109.75, 101.95, 60.30, 56.23, 14.59, 13.63, 11.09. MS (ESI) cald C24H21FN2O4S for $[M+H]^+$, 453.12, found 453.06

Ethyl 2-(3-((4,5-dimethylthiazol-2-yl)methyl)phenyl)-6-fluoro-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate 20n. 24% yield from intermediate **7**, ^{1}H NMR (400 MHz, MeOD) δ 7.87 (d, *J* = 11.4 Hz, 1H), 7.51 (d, *J* = 11.0 Hz, 4H), 7.18 (d, *J* = 6.4 Hz, 1H), 4.30 (s, 2H), 4.00 (s, 3H), 3.95 (q, *J* = 7.2 Hz, 2H), 2.30 (d, *J* = 11.0 Hz, 6H), 0.90 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, MeOD) δ 175.77, 168.08, 166.90, 154.55, 154.41,

153.41, 152.05, 150.93, 148.61, 140.46, 139.03, 135.84, 132.08, 130.40, 129.67, 128.35, 128.02, 119.92, 119.86, 116.20, 111.40, 111.20, 102.05, 62.21, 57.05, 39.44, 14.30, 14.08, 11.07. MS (ESI) cald C25H23FN2O4S for $[M+H]^+$, 467.14, found 467.33

2-Morpholinoethyl 7-methoxy-4-oxo-2-(3-phenoxyphenyl)-1,4-dihydroquinoline-3-carboxylate 27a. 50% yield from acid intermediate **26**, ^{1}H NMR (400 MHz, MeOD) δ 8.17 (d, *J* = 9.0, 1H), 7.57 – 7.50 (m, 1H), 7.46 – 7.36 (m, 2H), 7.37 – 7.29 (m, 1H), 7.25 – 7.14 (m, 3H), 7.05 (dd, *J* = 14.3, 4.6, 4H), 4.29 (t, *J* = 5.5, 2H), 3.92 (s, 3H), 3.77 – 3.69 (m, 4H), 2.73 (t, *J* = 5.3, 2H), 2.63 (s, 3H). ^{13}C NMR (101 MHz, MeOD) δ 176.56, 167.94, 165.34, 159.23, 157.87, 151.84, 143.04, 136.75, 131.75, 131.23, 131.19, 128.23, 125.29, 124.09, 121.63, 120.38, 119.45, 116.78, 115.89, 100.31, 66.94, 62.15, 57.28, 56.36, 54.30. MS (ESI) cald C29H28N2O6 for $[M+H]^+$, 501.19, found 501.35

3-Morpholinopropyl 7-methoxy-4-oxo-2-(3-phenoxyphenyl)-1,4-dihydroquinoline-3-carboxylate 27b. 87% yield from acid intermediate **26**, ^{1}H NMR (400 MHz, MeOD) δ 8.18 (d, *J* = 8.8, 1H), 7.54 (t, *J* = 7.9, 1H), 7.47 – 7.37 (m, 2H), 7.32 (d, *J* = 7.7, 1H), 7.23 – 7.14 (m, 3H), 7.10 – 7.01 (m, 4H), 4.12 (t, *J* = 6.0, 2H), 3.92 (d, *J* = 2.8, 3H), 3.80 – 3.70 (m, 4H), 2.66 (br, 4H), 2.53 (t, *J* = 7.0, 2H), 1.79 (dd, *J* = 12.8, 6.3, 2H). ^{13}C NMR (101 MHz, MeOD) δ 176.56, 165.31, 159.19, 157.90, 152.19, 143.03, 137.03, 131.75, 131.22, 128.24, 125.26, 124.05, 121.61, 120.39, 119.40, 116.75, 115.86, 100.37, 66.82, 64.90, 56.86, 56.36, 54.38, 40.46, 25.38. MS (ESI) cald C30H30N2O6 for $[M+H]^+$, 515.21, found 515.37

2-(Dimethylamino)ethyl 7-methoxy-4-oxo-2-(3-phenoxyphenyl)-1,4-dihydroquinoline-3-carboxylate 27c. 32% yield from acid intermediate **26**, ^{1}H NMR (400 MHz, MeOD) δ 8.20 (d, *J* = 9.0, 1H), 7.59 – 7.50 (m, 1H), 7.46 – 7.33 (m, 4H), 7.20 (td, *J* = 9.4, 3.8, 4H), 7.11 – 7.02 (m, 5H), 4.48 – 4.40 (m, 2H), 3.94 (s, 3H), 2.86 (s, 3H), 2.80 (s, 5H). ^{13}C NMR (101 MHz, MeOD) δ 176.81, 167.59, 165.51, 159.23, 157.93, 143.11, 136.42, 131.80, 131.22, 131.19, 128.21, 125.27, 124.10, 121.84, 120.38, 119.43, 119.17, 117.05, 116.56, 100.42, 60.45, 57.24, 56.40, 56.31, 43.93. MS (ESI) cald C27H26N2O5 for $[M+H]^+$, 459.18, found 459.31

3-(Dimethylamino)propyl 7-methoxy-4-oxo-2-(3-phenoxyphenyl)-1,4-dihydroquinoline-3-carboxylate 27d. 62% yield from acid intermediate **26**, ^{1}H NMR (400 MHz, MeOD) δ 8.21 (d, *J* = 9.0, 1H), 7.54 (t, *J* = 7.9, 1H), 7.41 (t, *J* = 8.0, 2H), 7.32 (d, *J* = 7.6, 1H), 7.25 – 7.12 (m, 3H), 7.11 – 6.97 (m, 4H), 4.24 (t, *J* = 5.4, 2H), 3.92 (s, 3H), 3.25 (t, *J* = 6.3, 2H), 2.90 (s, 6H), 2.18 – 2.02 (m, 2H). ^{13}C NMR (101 MHz, MeOD) δ 176.86, 167.61, 165.43, 159.05, 158.05, 153.94, 142.81, 137.00, 131.69, 131.19, 128.36, 125.18, 124.11, 121.73, 120.41, 120.33, 119.53, 116.97, 114.28, 100.34, 65.05, 57.71, 56.39, 43.96, 24.47. MS (ESI) cald C28H28N2O5 for $[M+H]^+$, 473.20, found 473.33

6-(Dimethylamino)hexyl 7-methoxy-4-oxo-2-(3-phenoxyphenyl)-1,4-dihydroquinoline-3-carboxylate 27e. 68% yield from acid intermediate **26**, ^{1}H NMR (400 MHz, MeOD) δ 8.19 – 8.13 (m, 1H), 7.53 (t, *J* = 7.8, 1H), 7.44 – 7.37 (m, 2H), 7.35 – 7.29 (m, 1H), 7.23 – 7.14 (m, 3H), 7.09 – 7.01 (m, 4H), 4.03 (t, *J* = 6.3, 2H), 3.92 (s, 3H), 3.06 (dd, *J* = 9.4, 6.9, 2H), 2.84 (s, 6H), 1.74 – 1.60 (m, 2H), 1.56 – 1.42 (m, 2H), 1.40 – 1.20 (m, 4H). ^{13}C NMR (101 MHz, MeOD) δ 176.55, 165.24, 159.14, 157.92, 151.37, 143.07, 136.99, 131.70, 131.23, 128.15, 125.25, 124.09, 121.59, 120.32, 119.37, 116.64, 100.30, 66.14, 58.89, 56.35, 43.40, 29.16, 26.96, 26.41, 25.47. MS (ESI) cald C31H34N2O5 for $[M+H]^+$, 515.25, found 515.37

2-Morpholinoethyl 6-fluoro-7-methoxy-4-oxo-2-(3-phenoxyphenyl)-1,4-dihydroquinoline-3-carboxylate 28a. 51% yield from acid intermediate **26**, ^{1}H NMR (400 MHz, MeOD) δ 7.85 (d, *J* = 11.3, 1H), 7.59 – 7.49 (m, 1H), 7.41 (dd, *J* = 8.4, 7.6, 2H), 7.32 (d, *J* = 7.6, 1H), 7.23 – 7.13 (m, 4H), 7.06 (dd, *J* = 8.6, 0.9, 2H), 4.14 (t, *J* = 5.9, 2H), 4.00 (s, 3H), 3.81 (t, *J* = 4.7, 4H), 2.80 (s, 4H), 2.70 (t, *J* = 6.9, 2H), 1.88 (dd, *J* = 12.8, 6.4, 2H). ^{13}C NMR (101 MHz, MeOD) δ 175.81, 167.86, 159.19, 157.89, 154.70, 154.56, 153.56, 152.40, 151.08, 138.99, 136.90, 131.78, 131.23, 125.27, 124.05, 121.68, 120.39, 119.99, 119.93, 119.40, 115.18, 111.36, 111.16,

102.24, 101.42, 66.38, 64.94, 57.12, 57.00, 54.19, 40.45, 24.92. MS (ESI) cald C29H27FN2O6 for $[M+H]^+$, 519.19, found 519.24

3-Morpholinopropyl 6-fluoro-7-methoxy-4-oxo-2-(3-phenoxyphenyl)-1,4-dihydroquinoline-3-carboxylate 28b. 37% yield from acid intermediate **26**, ^{1}H NMR (400 MHz, MeOD) δ 7.87 (d, *J* = 11.1, 1H), 7.55 (t, *J* = 7.8, 1H), 7.41 (t, *J* = 7.4, 2H), 7.34 (d, *J* = 7.5, 1H), 7.26 – 7.14 (m, 4H), 7.06 (d, *J* = 7.7, 2H), 4.29 (d, *J* = 4.6, 2H), 4.00 (s, 3H), 3.73 (s, 4H), 2.72 (s, 2H), 2.62 (s, 4H). ^{13}C NMR (101 MHz, MeOD) δ 175.83, 167.79, 159.27, 157.85, 154.72, 154.59, 153.53, 151.68, 151.05, 139.06, 136.66, 131.79, 131.24, 125.31, 124.08, 121.68, 120.40, 119.81, 119.42, 115.55, 111.37, 111.17, 102.15, 66.97, 62.26, 57.29, 57.10, 54.33, 40.45. MS (ESI) cald C30H29FN2O6 for $[M+H]^+$, 533.20, found 533.26

2-(Pyrrolidin-1-yl)ethyl 6-fluoro-7-methoxy-4-oxo-2-(3-phenoxyphenyl)-1,4-dihydroquinoline-3-carboxylate 28c. 48% yield from acid intermediate **26**, ^{1}H NMR (400 MHz, DMSO) δ 8.16 (s, 1H), 7.76 (d, *J* = 11.6 Hz, 1H), 7.55 (t, *J* = 7.8 Hz, 1H), 7.44 (dd, *J* = 11.3, 4.6 Hz, 2H), 7.31 (dd, *J* = 16.3, 7.5 Hz, 2H), 7.19 (dd, *J* = 13.5, 4.0 Hz, 3H), 7.06 (d, *J* = 8.4 Hz, 2H), 4.18 (t, *J* = 5.4 Hz, 2H), 3.94 (s, 3H), 2.81 (s, 2H), 2.70 (s, 4H), 1.76 (s, 4H). ^{13}C NMR (101 MHz, DMSO) δ 172.24, 166.63, 163.30, 156.63, 156.05, 151.37, 151.24, 150.80, 148.35, 130.44, 130.20, 123.96, 123.19, 119.88, 118.83, 118.32, 118.26, 118.01, 113.50, 109.66, 109.47, 103.18, 61.78, 56.20, 53.30, 52.64, 22.88. MS (ESI) cald C29H27FN2O5 for $[M+H]^+$, 503.19, found 503.37

N-(3-Morpholinopropyl) 6-fluoro-7-methoxy-4-oxo-2-(3-phenoxyphenyl)-1,4-dihydroquinoline-3-carboxamide 28d. 56% yield from acid intermediate **26**, ^{1}H NMR (400 MHz, DMSO) δ 12.54 – 11.29 (m, 1H), 8.67 (s, 1H), 8.15 (d, *J* = 3.6 Hz, 1H), 7.78 (d, *J* = 11.6 Hz, 1H), 7.52 (t, *J* = 7.9 Hz, 1H), 7.48 – 7.37 (m, 2H), 7.35 – 7.24 (m, 2H), 7.16 (ddd, *J* = 10.7, 6.4, 2.0 Hz, 3H), 7.06 (d, *J* = 8.4 Hz, 2H), 3.93 (s, 3H), 3.54 (d, *J* = 4.0 Hz, 4H), 3.08 (d, *J* = 5.7 Hz, 2H), 2.30 (s, 4H), 2.20 (t, *J* = 6.9 Hz, 2H), 1.54 – 1.37 (m, 2H). ^{13}C NMR (101 MHz, DMSO) δ 173.82, 164.78, 163.19, 156.28, 155.98, 151.44, 151.31, 150.68, 149.25, 148.23, 136.98, 136.74, 130.09, 129.91, 123.67, 123.37, 119.53, 118.73, 118.54, 115.92, 110.02, 109.84, 101.44, 66.09, 56.20, 55.67, 53.20, 36.83, 25.69. MS (ESI) cald C30H30FN3O5 for $[M+H]^+$, 532.22, found 532.41

N-(2-(Pyrrolidin-1-yl)ethyl) 6-fluoro-7-methoxy-4-oxo-2-(3-phenoxyphenyl)-1,4-dihydroquinoline-3-carboxamide 28e. 51% yield from acid intermediate **26**, ^{1}H NMR (400 MHz, DMSO) δ 8.87 (s, 1H), 7.79 (d, *J* = 11.5 Hz, 1H), 7.50 (t, *J* = 7.9 Hz, 1H), 7.42 (dd, *J* = 11.2, 4.5 Hz, 2H), 7.32 (d, *J* = 6.3 Hz, 2H), 7.25 – 7.10 (m, 3H), 7.06 (d, *J* = 8.0 Hz, 2H), 3.93 (s, 3H), 3.26 (d, *J* = 5.3 Hz, 2H), 2.62 (d, *J* = 12.5 Hz, 5H), 1.74 (s, 4H). ^{13}C NMR (101 MHz, DMSO) δ 173.66, 165.48, 156.40, 155.89, 151.32, 151.19, 150.75, 148.30, 137.67, 130.07, 129.81, 123.57, 123.42, 119.39, 118.76, 118.44, 114.95, 109.67, 102.36, 56.19, 54.07, 53.34, 40.14, 39.93, 39.72, 39.51, 39.30, 39.09, 38.88, 37.23, 22.97. MS (ESI) cald C29H28FN3O4 for $[M+H]^+$, 502.21, found 502.36

N-(3-(Pyrrolidin-1-yl)propyl) 6-fluoro-7-methoxy-4-oxo-2-(3-phenoxyphenyl)-1,4-dihydroquinoline-3-carboxamide 28f. 49% yield from acid intermediate **26**, ^{1}H NMR (400 MHz, DMSO) δ 8.79 (s, 1H), 8.24 (s, 1H), 7.78 (d, *J* = 11.6 Hz, 1H), 7.51 (t, *J* = 7.9 Hz, 1H), 7.42 (t, *J* = 7.9 Hz, 2H), 7.31 (d, *J* = 7.5 Hz, 2H), 7.16 (dd, *J* = 20.0, 11.2 Hz, 3H), 7.06 (d, *J* = 8.3 Hz, 2H), 3.93 (s, 3H), 3.12 (d, *J* = 5.7 Hz, 2H), 2.70 (s, 4H), 2.61 (t, *J* = 7.1 Hz, 2H), 1.76 (s, 4H), 1.65 – 1.49 (m, 2H). ^{13}C NMR (101 MHz, DMSO) δ 173.76, 165.21, 156.27, 155.95, 151.37, 151.24, 150.67, 149.67, 148.23, 137.40, 137.06, 130.07, 129.86, 123.64, 123.36, 119.43, 118.67, 118.52, 115.57, 109.91, 109.72, 101.80, 56.18, 53.28, 52.64, 36.49, 27.04, 22.87. MS (ESI) cald C30H30FN3O4 for $[M+H]^+$, 516.22, found 516.41

2-Methoxyethyl 6-fluoro-7-methoxy-4-oxo-2-(3-phenoxyphenyl)-1,4-dihydroquinoline-3-carboxylate 28g. 48% yield from acid intermediate **26**, ^{1}H NMR (400 MHz, DMSO) δ 12.10 (s, 1H), 7.73 (dd, *J* = 11.4, 5.3, 1H), 7.56 (t, *J* = 7.6, 1H), 7.45 (dd, *J* = 11.1, 4.5, 2H), 7.31 (dd, *J* = 15.2, 6.9, 2H), 7.23 – 7.13 (m, 3H), 7.07 (d, *J* = 7.6, 2H), 4.10 – 3.99 (m, 2H), 3.94 (s, 3H), 3.15 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 172.28, 166.32,

156.70, 156.07, 151.44, 151.32, 150.70, 148.26, 135.68, 130.52, 130.21, 125.87, 125.23, 123.98, 123.14, 120.11, 118.85, 118.38, 118.32, 118.00, 114.33, 109.88, 109.69, 102.03, 69.39, 63.47, 57.96, 56.21. MS (ESI) cald C26H22FNO6 for $[M+H]^+$, 464.14, found 464.19

2-Hydroxyethyl 6-fluoro-7-methoxy-4-oxo-2-(3-phenoxyphenyl)-1,4-dihydroquinoline-3-carboxylate 28h. 34% yield from acid intermediate **26**, ^{1}H NMR (400 MHz, MeOD) δ 8.57 (s, 1H), 7.89 (d, *J* = 11.4 Hz, 1H), 7.55 (t, *J* = 8.0 Hz, 1H), 7.42 (t, *J* = 7.0 Hz, 2H), 7.36 (d, *J* = 7.5 Hz, 1H), 7.26 – 7.16 (m, 4H), 7.08 (d, *J* = 8.3 Hz, 2H), 4.18 – 4.12 (m, 2H), 4.02 (s, 3H), 3.61 (t, *J* = 4.9 Hz, 2H). ^{13}C NMR (101 MHz, MeOD) δ 175.82, 168.28, 159.24, 157.94, 154.58, 154.45, 153.44, 151.69, 150.96, 139.06, 136.76, 131.64, 131.18, 125.18, 124.08, 121.61, 120.40, 119.91, 119.85, 119.34, 115.97, 111.34, 111.15, 102.14, 67.78, 60.77, 57.07. MS (ESI) cald C25H20FNO6 for $[M+H]^+$, 450.13, found 450.25

Table S1. SAR of 7-Methoxy 4(1H)-quinolone derivatives 8a-aa

CMPD	SJNumber	Average EC_{50} K1 (µM)	Average EC_{50} C2B (µM)	Average EC_{50} D10 (µM)	Average EC_{50} D10_yDHOD (µM)	Average EC_{50} D10_yDHOD+PG (µM)
8a	SJ000311131	0.30 +/- 0.02	0.91 +/- 0.62	0.06 +/- 0.25	>15	0.07 +/- 0.01
8b	SJ000311166	0.82 +/- 0.07	>15	0.60 +/- 0.79	>15	>15
8c	SJ000311169	0.30 +/- 0.01	0.06 +/- 0.05	0.01 +/- 0.01	>15	<0.001
8d	SJ000311513	0.22 +/- 0.03	0.18 +/- 0.04	0.01 +/- 0.01	>15	<0.001
8e	SJ000311507	0.07 +/- 0.02	<0.001	<0.001	>15	<0.001
8f	SJ000311171	0.13 +/- 0.01	0.21 +/- 0.04	0.04 +/- 0.05	>15	<0.001
8g	SJ000311854	0.07 +/- 0.01	0.001 +/- 0.01	<0.001	>15	<0.001
8h	SJ000311850	0.02 +/- 0.01	<0.001	<0.001	>15	<0.001
8i	SJ000311502	0.16 +/- 0.03	<0.001	<0.001	>15	<0.001
8j	SJ000311851	0.03 +/- 0.01	<0.001	<0.001	>15	<0.001
8k	SJ000311505	0.04 +/- 0.01	<0.001	<0.001	>15	<0.001

8l	SJ000311501	0.08 +/- 0.01	<0.001	<0.001	>15	<0.001
8m	SJ000311901	0.03 +/- 0.01	<0.001	<0.001	>15	<0.001
8n	SJ000311853	0.11 +/- 0.01	<0.001	<0.001	>15	<0.001
8o	SJ000311167	0.22 +/- 0.02	>15	0.01 +/- 0.01	>15	<0.001
8p	SJ000311173	0.55 +/- 0.02	7.7 +/- 10	0.27 +/- 0.36	>15	2.1 +/- 2.5
8q	SJ000311162	0.18 +/- 0.02	>15	<0.001	>15	<0.001
8s	SJ000311510	0.13 +/- 0.05	1.8 +/- 1.5	<0.001	>15	0.41 +/- 0.24
8r	SJ000311511	1.45+/- 0.69	<0.001	1.0 +/- 0.05	>15	<0.001
8t	SJ000311504	21 +/- 8.0	6.3 +/- 2.5	>15	>15	>15
8u	SJ000311174	0.87 +/- 0.01	2.3 +/- 0.87	0.27 +/- 0.29	>15	0.41 +/- 0.32
8v	SJ000311509	0.95 +/- 0.12	0.02 +/- 0.02	0.27 +/- 0.33	>15	0.10 +/- 0.14
8w	SJ000311508	14 +/- 10	8.8 +/- 8.8	>15	>15	>15
8x	SJ000311498	>15	>15	>15	>15	>15
8y	SJ000311512	>15	>15	>15	>15	>15
8z	SJ000311499	0.26 +/- 0.06	0.01 +/- 0.01	0.02 +/- 0.25	>15	<0.001
8aa	SJ000311503	0.13 +/- 0.02	0.29 +/- 0.12	<0.001	>15	<0.001

Table S2. SAR of 4(1H)-quinolone derivatives 9-14

CMPD	SJNumber	Average EC_{50} K1 (µM)	Average EC_{50} C2B (µM)	Average EC_{50} D10 (µM)	Average EC_{50} D10_yDHOD (µM)	Average EC_{50} D10_yDHODH +PG (µM)
9a	SJ000358773	6.6 +/- 7.6E6	>15	>15	>15	>15
9b	SJ000358775	0.08 +/- 0.03	<0.001	<0.001	>15	<0.001
9c	SJ000358774	2.2 +/- 1.7	1.6 +/- 0.59	0.65 +/- 0.43	>15	0.42 +/- 0.02
10a	SJ000311864	>15	>15	>15	>15	>15
10b	SJ000311858	1.3 +/- 0.05	>15	>15	>15	>15
10c	SJ000311860	>15	5.8 +/- 1.1	4.9 +/- 1.5	>15	9.4 +/- 7.9
11a	SJ000311863	>15	>15	>15	>15	>15
11b	SJ000311857	3.4 +/- 0.91	>15	>15	>15	>15
11c	SJ000311859	>15	>15	>15	>15	3.3 +/- 0.36
11d	SJ000311855	>15	>15	>15	>15	>15
12a	SJ000520033	0.12 +/- 0.01	0.01 +/- 0.01	0.06 +/- 0.03	>15	0.02 +/- 0.01
12b	SJ000520034	0.18 +/- 0.04	0.22 +/- 0.08	0.06 +/- 0.58	>15	0.04 +/- 0.01
13	SJ000358776	0.38 +/- 0.13	<0.001	0.20 +/- 0.14	>15	<0.001

14	SJ000358771	0.28 +/- 0.05	5.1 +/- 0.02	1.3 +/- 1.2	>15	1.6 +/- 0.34

Table S3. SAR of 4(1H)-quinolone derivatives 15-20

CMPD	SJNumber	Average EC_{50} K1 (µM)	Average EC_{50} C2B (µM)	Average EC_{50} D10 (µM)	Average EC_{50} D10_yDHOD (µM)	Average EC_{50} D10_yDHOD+PG (µM)
15a	SJ000520043	0.04 +/- 0.01	>15	0.02 +/- 0.02	>15	0.01 +/- 0.01
15b	SJ000520044	0.06 +/- 0.01	>15	0.06 +/- 0.60	>15	0.05 +/- 0.03
15c	SJ000520048	0.01 +/- 0.01	1.2 +/- 0.04	0.01 +/- 0.01	>15	0.01 +/- 0.01
15d	SJ000520047	0.36 +/- 0.01	>15	0.33 +/- 0.18	>15	0.58 +/- 0.28
16a	SJ000515468	>15	>15	>15	>15	>15
16b	SJ000515469	0.38 +/- 0.13	0.03 +/- 0.01	0.35 +/- 0.26	>15	0.08 +/- 0.01
16c	SJ000515470	>15	>15	>15	>15	>15
16d	SJ000515471	1.5 +/- 0.72	0.47 +/- 0.20	1.4 +/- 0.21	>15	0.50 +/- 0.05
17a	SJ000515472	>15	>15	>15	>15	>15
17b	SJ000515473	>15	>15	>15	>15	>15

17c	SJ000515474	>15	1.5 +/- 0.62	>15	>15	6.9 +/- 5.4
17d	SJ000515475	>15	>15	>15	>15	>15
18a	SJ000515476	0.10 +/- 0.18	>15	0.14 +/- 0.03	>15	0.16 +/- 0.03
18b	SJ000515477	0.23 +/- 0.20	0.02 +/- 0.01	0.17 +/- 0.15	>15	0.04 +/- 0.01
18c	SJ000515478	0.54 +/- 0.17	>15	0.66 +/- 0.21	>15	0.34 +/- 0.16
18d	SJ000515479	0.05 +/- 0.02	>15	0.05 +/- 0.01	>15	0.05 +/- 0.01
19a	SJ000515480	0.03 +/- 0.01	0.05 +/- 0.01	0.03 +/- 0.01	>15	0.035 +/- 0.01
19b	SJ000515481	0.02 +/- 0.01	0.01 +/- 0.01	0.02 +/- 0.01	>15	0.004 +/- 0.01
19c	SJ000515482	0.06 +/- 0.01	0.12 +/- 0.03	0.05 +/- 0.06	>15	0.07 +/- 0.01
19d	SJ000515483	0.01 +/- 0.011	0.01 +/- 0.01	0.01 +/- 0.01	>15	0.002 +/- 0.01
19e	SJ000544646	0.17 +/- 0.01	0.11 +/- 0.14	0.13 +/- 0.05	>15	0.13 +/- 0.02
19f	SJ000544647	0.18 +/- 0.02	0.12 +/- 0.05	0.11 +/- 0.03	>15	0.11 +/- 0.02
19g	SJ000520051	0.03 +/- 0.01	0.03 +/- 0.01	0.02 +/- 0.13	>15	0.02 +/- 0.01
20a	SJ000520036	0.21 +/- 0.01	0.55 +/- 0.12	0.12+/- 0.07	>15	0.12 +/- 0.01
20b	SJ000520041	0.01 +/- 0.01	<0.001	0.01 +/- 0.01	>15	<0.001
20c	SJ000520037	0.09+/- 0.01	0.17 +/- 0.05	0.06 +/- 0.56	>15	0.05 +/- 0.01
20d	SJ000520050	0.01 +/- 0.01	0.01 +/- 0.01	0.01 +/- 0.01	>15	0.01 +/- 0.01
20e	SJ000520049	0.13 +/- 0.02	0.10 +/- 0.02	0.09 +/- 0.39	>15	0.09 +/- 0.01

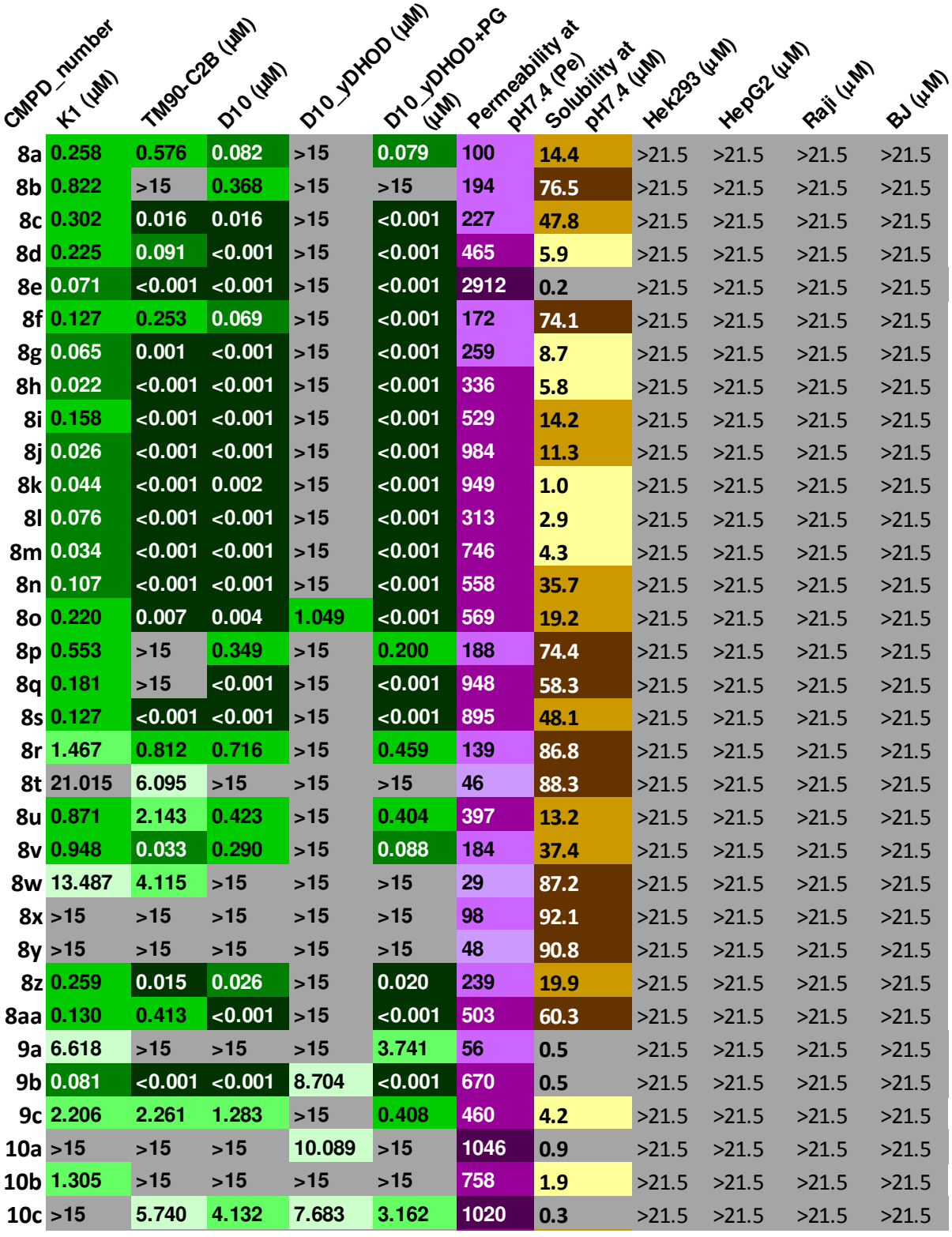
20f	SJ000520039	0.95 +/- 0.07	1.9 +/- 0.14	0.87 +/- 0.51	>15	1.1 +/- 0.09
20g	SJ000520040	0.08 +/- 0.1	0.20 +/- 0.07	0.05 +/- 0.02	>15	0.07 +/- 0.01
20h	SJ000544648	0.12 +/- 0.01	0.15 +/- 0.02	0.10 +/- 0.02	>15	0.11 +/- 0.01
20i	SJ000520038	0.04 +/- 0.01	0.05 +/- 0.01	0.03 +/- 0.03	>15	0.03 +/- 0.01
20j	SJ000520829	0.20 +/- 0.02	0.01 +/- 0.01	0.03 +/- 0.01	>15	0.01 +/- 0.000849
20k	SJ000520830	0.02+/- 0.01	<0.001	0.01 +/- 0.01	>15	<0.001
20l	SJ000520831	0.08 +/- 0.01	0.01 +/- 0.002	0.03 +/- 0.01	>15	0.01+/- 0.01
20m	SJ000544645	>15	>15	>15	>15	>15
20n	SJ000544643	0.29 +/- 0.04	0.08 +/- 0.01	0.19 +/- 0.04	>15	0.13 +/- 0.01

Table S4. SAR of 4(1H)-quinolone derivatives 27-28

CMPD	SJNumber	Average EC_{50} K1 (μM)	Average EC_{50} C2B (μM)	Average EC_{50} D10 (μM)	Average EC_{50} D10_yDHOD (μM)	Average EC_{50} D10_yDHOD+PG (μM)
27a	SJ000520183	0.53 +/- 0.05	0.11 +/- 0.07	0.22 +/- 0.07	>15	0.07 +/- 0.01
27b	SJ000520042	0.35 +/- 0.06	0.08 +/- 0.05	0.16 +/- 0.08	>15	0.09 +/- 0.04
27c	SJ000520184	0.64 +/- 0.01	0.45 +/- 0.14	0.34 +/- 0.10	>15	0.24 +/- 0.03
27d	SJ000520185	6.3 +/- 2.4	>15	>15	6.5 +/- 0.67	8.8 +/- 8.8
27e	SJ000520186	>15	>15	1.1 +/- 0.47	>15	0.66 +/- 0.09
28a	SJ000520827	0.82 +/- 0.23	0.04 +/- 0.01	0.15 +/- 0.01	>15	0.07 +/- 0.01
28b	SJ000520826	0.16 +/- 0.07	0.02 +/- 0.01	0.07 +/- 0.01	>15	0.04 +/- 0.01
28c	SJ000556728	0.52 +/- 0.26	0.18 +/- 0.06	0.19 +/- 0.07	>15	0.12 +/- 0.01
28d	SJ000556725	7.3 +/- 4.3	0.10 +/- 0.01	>15	>15	0.34 +/- 0.02
28e	SJ000556727	>15	1.8 +/- 1.5	>15	>15	8.5 +/- 9.1

28f	SJ000556726	>15	>15	>15	>15	>15
28g	SJ000520828	0.10 +/- 0.01	0.05 +/- 0.01	0.03 +/- 0.01	>15	0.03 +/- 0.01
28h	SJ000544644	0.42 +/- 0.19	0.11 +/- 0.01	0.22 +/- 0.01	>15	0.16 +/- 0.01

Figure S1. Heat map for Antimalarial activity, permeability and solubility of quinolone derivatives 8-20 and 27-28



CMPD_number	K1 (μM)	TM90-C2B (μM)	D10 (μM)	D10_yDHOD (μM)	D10_yDHOD+PG (μM)	Permeability at pH7.4 (Pe)	Solubility at pH7.4 (μM)	Hek293 (μM)	HepG2 (μM)	Raji (μM)	BJ (μM)
8a	0.258	0.576	0.082	>15	0.079	100	14.4	>21.5	>21.5	>21.5	>21.5
8b	0.822	>15	0.368	>15	>15	194	76.5	>21.5	>21.5	>21.5	>21.5
8c	0.302	0.016	0.016	>15	<0.001	227	47.8	>21.5	>21.5	>21.5	>21.5
8d	0.225	0.091	<0.001	>15	<0.001	465	5.9	>21.5	>21.5	>21.5	>21.5
8e	0.071	<0.001	<0.001	>15	<0.001	2912	0.2	>21.5	>21.5	>21.5	>21.5
8f	0.127	0.253	0.069	>15	<0.001	172	74.1	>21.5	>21.5	>21.5	>21.5
8g	0.065	0.001	<0.001	>15	<0.001	259	8.7	>21.5	>21.5	>21.5	>21.5
8h	0.022	<0.001	<0.001	>15	<0.001	336	5.8	>21.5	>21.5	>21.5	>21.5
8i	0.158	<0.001	<0.001	>15	<0.001	529	14.2	>21.5	>21.5	>21.5	>21.5
8j	0.026	<0.001	<0.001	>15	<0.001	984	11.3	>21.5	>21.5	>21.5	>21.5
8k	0.044	<0.001	0.002	>15	<0.001	949	1.0	>21.5	>21.5	>21.5	>21.5
8l	0.076	<0.001	<0.001	>15	<0.001	313	2.9	>21.5	>21.5	>21.5	>21.5
8m	0.034	<0.001	<0.001	>15	<0.001	746	4.3	>21.5	>21.5	>21.5	>21.5
8n	0.107	<0.001	<0.001	>15	<0.001	558	35.7	>21.5	>21.5	>21.5	>21.5
8o	0.220	0.007	0.004	1.049	<0.001	569	19.2	>21.5	>21.5	>21.5	>21.5
8p	0.553	>15	0.349	>15	0.200	188	74.4	>21.5	>21.5	>21.5	>21.5
8q	0.181	>15	<0.001	>15	<0.001	948	58.3	>21.5	>21.5	>21.5	>21.5
8s	0.127	<0.001	<0.001	>15	<0.001	895	48.1	>21.5	>21.5	>21.5	>21.5
8r	1.467	0.812	0.716	>15	0.459	139	86.8	>21.5	>21.5	>21.5	>21.5
8t	21.015	6.095	>15	>15	>15	46	88.3	>21.5	>21.5	>21.5	>21.5
8u	0.871	2.143	0.423	>15	0.404	397	13.2	>21.5	>21.5	>21.5	>21.5
8v	0.948	0.033	0.290	>15	0.088	184	37.4	>21.5	>21.5	>21.5	>21.5
8w	13.487	4.115	>15	>15	>15	29	87.2	>21.5	>21.5	>21.5	>21.5
8x	>15	>15	>15	>15	>15	98	92.1	>21.5	>21.5	>21.5	>21.5
8y	>15	>15	>15	>15	>15	48	90.8	>21.5	>21.5	>21.5	>21.5
8z	0.259	0.015	0.026	>15	0.020	239	19.9	>21.5	>21.5	>21.5	>21.5
8aa	0.130	0.413	<0.001	>15	<0.001	503	60.3	>21.5	>21.5	>21.5	>21.5
9a	6.618	>15	>15	>15	3.741	56	0.5	>21.5	>21.5	>21.5	>21.5
9b	0.081	<0.001	<0.001	8.704	<0.001	670	0.5	>21.5	>21.5	>21.5	>21.5
9c	2.206	2.261	1.283	>15	0.408	460	4.2	>21.5	>21.5	>21.5	>21.5
10a	>15	>15	>15	10.089	>15	1046	0.9	>21.5	>21.5	>21.5	>21.5
10b	1.305	>15	>15	>15	>15	758	1.9	>21.5	>21.5	>21.5	>21.5
10c	>15	5.740	4.132	7.683	3.162	1020	0.3	>21.5	>21.5	>21.5	>21.5

CMPD_number	K1 (µM)	TM90-C2B (µM)	D10 (µM)	D10_yDHOD (µM)	D10_yDHOD+PG (µM)	Permeability at pH7.4 (Pe)	Solubility at pH7.4 (µM)	Hek293 (µM)	HepG2 (µM)	Raji (µM)	BJ (µM)
11a	>15	>15	>15	>15	>15	530	24.4	>21.5	>21.5	>21.5	>21.5
11b	3.369	>15	>15	>15	>15	615	9.4	>21.5	>21.5	>21.5	>21.5
11c	>15	>15	>15	12.363	>15	1351	3.8	>21.5	>21.5	>21.5	>21.5
11d	>15	>15	>15	>15	>15	1168	11.7	>21.5	>21.5	>21.5	>21.5
12a	0.117	0.008	0.063	>15	0.026	846	7.2	>21.5	>21.5	>21.5	>21.5
12b	0.175	0.161	0.068	>15	0.044	706	1.2	>21.5	>21.5	>21.5	>21.5
13	0.380	<0.001	0.184	9.625	<0.001	514	2.2	>21.5	>21.5	>21.5	>21.5
14	0.277	4.878	1.549	>15	1.202	882	2.8	>21.5	>21.5	>21.5	>21.5
15a	0.038	>15	0.021	>15	0.015	153	25.3	>21.5	>21.5	>21.5	>21.5
15b	0.060	>15	0.090	>15	0.068	161	15.5	>21.5	>21.5	>21.5	>21.5
15c	0.011	1.662	0.008	>15	0.007	808	3.1	>21.5	>21.5	>21.5	>21.5
15d	0.365	>15	0.392	>15	0.536	808	16.9	>21.5	>21.5	>21.5	>21.5
16a	>15	>15	>15	>15	>15	70	45.4	>21.5	>21.5	>21.5	>21.5
16b	0.381	0.021	0.242	>15	0.076	1095	0.5	>21.5	>21.5	>21.5	>21.5
16c	>15	>15	>15	>15	>15	134	6.9	>21.5	>21.5	>21.5	>21.5
16d	1.502	0.351	1.131	>15	0.477	641	45.4	>21.5	>21.5	>21.5	>21.5
17a	>15	>15	>15	>15	>15	173	73.1	>21.5	>21.5	>21.5	>21.5
17b	>15	>15	>15	>15	>15	449	27.8	>21.5	>21.5	>21.5	>21.5
17c	>15	>15	>15	>15	>15	445	10.3	>21.5	>21.5	>21.5	>21.5
17d	>15	>15	>15	>15	>15	0	1.4	>21.5	>21.5	>21.5	>21.5
18a	0.102	>15	0.143	>15	0.143	0	1.2	>21.5	>21.5	>21.5	>21.5
18b	0.234	0.019	0.087	>15	0.040	221	27.2	>21.5	>21.5	>21.5	>21.5
18c	0.544	>15	0.576	>15	0.396	1199	0.2	>21.5	>21.5	>21.5	>21.5
18d	0.053	>15	0.037	>15	0.042	7	0.1	>21.5	>21.5	>21.5	>21.5
19a	0.026	0.055	0.031	>15	0.027	366	9.4	>21.5	>21.5	>21.5	>21.5
19b	0.017	0.004	0.013	>15	0.003	218	0.9	>21.5	>21.5	>21.5	>21.5
19c	0.063	0.123	0.084	>15	0.060	435	13.3	>21.5	>21.5	>21.5	>21.5
19d	0.004	0.004	0.004	>15	0.004	19	0.1	>21.5	>21.5	>21.5	>21.5
19e	0.175	0.146	0.124	>15	0.125	682	4.5	>21.5	>21.5	>21.5	>21.5
19f	0.179	0.136	0.114	>15	0.113	476	7.2	>21.5	>21.5	>21.5	>21.5
19g	0.028	0.021	0.025	>15	0.022	788	4.5	>21.5	>21.5	>21.5	>21.5
20a	0.213	0.404	0.128	>15	0.119	248	46.3	>21.5	>21.5	>21.5	>21.5
20b	0.008	<0.001	0.007	>15	0.004	250	3.7	>21.5	>21.5	>21.5	>21.5
20c	0.085	0.133	0.068	>15	0.055	287	8.5	>21.5	>21.5	>21.5	>21.5
20d	0.010	0.009	0.007	>15	0.008	557	4.3	>21.5	>21.5	>21.5	>21.5
20e	0.134	0.079	0.107	>15	0.084	571	17.4	>21.5	>21.5	>21.5	>21.5

CMPD_number	K1 (μM)	TM90-C2B (μM)	D10 (μM)	D10_yDHOD (μM)	D10_yDHOD+PG (μM)	Permeability at pH7.4 (Pe)	Solubility at pH7.4 (μM)	Hek293 (μM)	HepG2 (μM)	Raji (μM)	BJ (μM)
20f	0.955	4.580	0.863	>15	1.006	226	28.1	>21.5	>21.5	>21.5	>21.5
20g	0.083	0.274	0.061	>15	0.071	407	20.3	>21.5	>21.5	>21.5	>21.5
20h	0.117	0.153	0.095	>15	0.111	669	7.3	>21.5	>21.5	>21.5	>21.5
20i	0.038	0.048	0.042	>15	0.039	227	7.5	>21.5	>21.5	>21.5	>21.5
20j	0.199	0.004	0.027	>15	0.008	154	0.2	>21.5	>21.5	>21.5	>21.5
20k	0.022	<0.001	0.005	>15	<0.001	114	0.1	>21.5	>21.5	>21.5	>21.5
20l	0.077	0.003	0.024	>15	0.012	935	<0.2	>21.5	>21.5	>21.5	>21.5
20m	>15	>15	>15	>15	>15	175	5.7	>21.5	>21.5	>21.5	>21.5
20n	0.286	0.078	0.188	>15	0.122	734	4.0	>21.5	>21.5	>21.5	>21.5
27a	0.535	0.058	0.207	>15	0.078	833	19.2	>21.5	>21.5	>21.5	>21.5
27b	0.354	0.038	0.151	>15	0.063	884	15.8	>21.5	>21.5	>21.5	>21.5
27c	0.643	0.364	0.367	>15	0.263	1578	72.0	>21.5	>21.5	>21.5	>21.5
27d	6.291	1.595	>15	6.894	>15	1310	93.2	>21.5	>21.5	>21.5	>21.5
27e	>15	0.607	0.955	>15	0.703	1145	94.3	>21.5	>21.5	>21.5	>21.5
28a	0.821	0.035	0.155	>15	0.073	840	3.4	>21.5	>21.5	>21.5	>21.5
28b	0.163	0.021	0.073	>15	0.039	881	3.4	>21.5	>21.5	>21.5	>21.5
28c	0.523	0.169	0.191	>15	0.116	1023	52.3	>21.5	>21.5	>21.5	>21.5
28d	4.274	0.106	>15	>15	0.342	395	55.7	>21.5	>21.5	>21.5	>21.5
28e	>15	0.889	>15	>15	>15	330	57.1	>21.5	>21.5	>21.5	>21.5
28f	>15	>15	>15	>15	>15	5	51.8	>21.5	>21.5	>21.5	>21.5
28g	0.104	0.046	0.033	>15	0.029	1308	0.4	>21.5	>21.5	>21.5	>21.5
28h	0.418	0.107	0.227	>15	0.159	623	3.1	>21.5	>21.5	>21.5	>21.5
Atovaquone	0.015	>1.5015	0.016	>1.5	0.002						

EC50 (uM)	Permeability (Pe)	uSol (uM)	Cytotoxicity (uM)
<0.02	>1000	> 50	<1
0.02-0.1	300~1000	10~50	1~10
0.1~1	50~300	1~10	10~20
1~5	10~50	<1	>20
5-15	<10		
>15			

1) Data represent median EC_{50} values of parasite growth inhibition against a panel of *Plasmodium falciparum* strains, from replicate experiments, shown in a color gradient scale with darker squares indicating a higher antimalarial potency. The positive control for the antimalarial assay was atovaquone.

2) PAMPA passive permeability assay results at pH 7.4 are shown in a color gradient with darker purple squares indicating a higher permeability.

3) Aqueous solubility at pH 7.4 in isotonic buffer is shown in brown scale, as with darker squares indicating a higher solubility.

Table S5. PfDHOD inhibition assay.

Compound	IC_{50} (μm)
DSM1 (control)	0.042 (0.015 - 0.12)
8p	>100
20a	>30
20d	>100
20g	>100

Table S6. Plasma concentration of 20i in mouse after a single oral administration

Dose: 50 mg/kg		Dose: 200 mg/kg	
Time (hr)	Plasma Concentration (ng/mL)	Time (hr)	Plasma Concentration (ng/mL)
0.08	73.7 ± 19.74	0.08	269.72 ± 46.82
0.25	241.79 ± 54.11	0.25	619.35 ± 352.45
0.5	275.05 ± 86.94	0.5	592.01 ± 236.29
1	252.05 ± 47.95	1	536.44 ± 51.85
2	190.54 ± 55.64	2	423.51 ± 47.3
4	188.76 ± 34.01	4	344.75 ± 76.87
6	179.56 ± 87.99	6	415.87 ± 196.25
8	228.35 ± 15.11	8	481.29 ± 229.69
10	176.73 ± 77.79	10	344.64 ± 153.76
24	21.25	24	42.98

Table S7. Plasma concentration of 20g in mouse after a single oral administration

Dose: 50 mg/kg		Dose: 200 mg/kg	
Time (hr)	Plasma Concentration (ng/mL)	Time (hr)	Plasma Concentration (ng/mL)
0.08	1718.12 ± 1595.2	0.08	4329.54 ± 2100.28
0.25	12281.7 ± 2170.6	0.25	10101 ± 8418.03
0.5	14419.2 ± 2372.5	0.5	24783 ± 9857.04
1	11136.8 ± 2111.6	1	15424.7 ± 10570.76
2	4513.4 ± 1341.5	2	19371.6 ± 5527.17
4	2503.66 ± 1337.6	4	5601.5 ± 1170.14
6	1616.01 ± 738.71	6	3390.7 ± 470.11
8	1227.85 ± 384.53	8	5930.3 ± 4159.95
10	1648.64 ± 891.15	10	2289.5 ± 853.8
24	10	24	446.09 ± 416

Table S8. Plasma concentration of 20h in mouse after a single oral administration

Dose: 50 mg/kg		Dose: 200 mg/kg	
Time (hr)	Plasma Concentration (ng/mL)	Time (hr)	Plasma Concentration (ng/mL)
0.08	1240.05 ± 700.31	0.08	1952.12 ± 777.86
0.25	13079.2 ± 1094.5	0.25	10693.6 ± 2183.89
0.5	9057.87 ± 798.71	0.5	16137.1 ± 4160.57
1	7841.73 ± 577.84	1	16470.7 ± 3281.58
2	3966.48 ± 1663.76	2	11670.9 ± 1019.71
4	938.33 ± 189.06	4	6227.73 ± 1117.58
6	1120.35 ± 128.17	6	3333.5 ± 731.99
8	3277.41 ± 1418.83	8	2182.09 ± 873.51
10	882 ± 206.63	10	551.32 ± 374.66
24	< LLOQ	24	64.92 ± 89.53

[a]LLOQ: Lower Limit Of Quantification (5 ng/ml)

Table S9. Pharmacokinetic profiles of 8a, 8e, 8f, 8g, 8h, 8m, 20i, 20g, and 20h in mouse after a single oral administration.

Comound	Dose (mg/kg)	C_{max} (ng/mL)	T_{max} (hr)	AUC_{last} (hr·ng/mL)	$AUCl_{inf}$ (hr·ng/mL)	MRT_{last} (hr)	$t_{1/2}$ (hr)
8a	30	546	0.25	2112	2252	2.4	2.0
	200	1853	0.25	23533	23840	6.4	3.9
8e	30	92.6	2.0	661	676	5.2	4.2
	200	171	1.0	922	1702	3.6	7.1
8f	30	2817	0.25	2814	2837	1.1	1.3
	200	2046	0.08	2699	2757	2.4	1.6
8g	30	684	1.0	1797	1888	2.0	1.7
	200	883	1.0	3255	3759	2.7	2.6
8h	30	114	0.25	438	594	3.0	3.7
	200	684	1.0	1889	2935	2.7	6.2
8m	30	24	0.50	36	61	0.9	1.5
	200	167	0.25	376	437	2.8	1.2
20i	50	275 ± 50	0.5	3394 ± 377	3602	7.6	6.8
	200	619 ± 203	0.25	6965 ± 797	7376	7.5	6.6
20g	50	14419 ± 1370	0.5	47278 ± 4371	47313	4.6	2.5
	200	24783 ± 5691	0.5	103866 ± 9492	106770	4.9	4.5
20h	50	13079 ± 632	0.25	29684 ± 2205	31717	3.5	1.6
	200	16471 ± 1895	1	66752 ± 2333	67030	3.5	3

Table S10. Efficacy of quinolone compound 20g and 20h in *P. berghei* infected mice after 3 days of oral dosing.[a]

compound	dose (mg/kg)	% inhibition on day 6	Mice dead/Day died	Survival (days)
20g	10 × 3	2.32	4/8, 1/22	8-22
	30 × 3	57.2	1/8, 1/12, 1/16, 1/17, 1/22	8-22
20h	10 × 3	25.1	3/8, 1/9, 1/14	8-14
	30 × 3	22.4	1/6, 3/7, 1/8	6-8
Amodiaquine	30	100	1/15, 1/16, 1/17, 1/18, 1/23	15-23
infected controls	none	0	1/6, 2/7, 2/8	6-8

[a] The zero time point represents the day of infection; once daily oral dosing was performed at 72 hr, 96 hr and 120 hr post-infection. Five mice were dosed per group.

Table S11. Hammett Constants Used in Study.

Hammett Substituent Constants (σ) – Electronic Effects								
Substituent	**meta σ**	**para σ**	**Substituent**	**meta σ**	**para σ**	**Substituent**	**meta σ**	**para σ**
H	0	0	$C(O)C_6H_5$	0.34	0.43	NO_2	0.71	0.78
CH_3	-0.07	-0.17	$CO_2^{(-)}$	-0.10	0.00	$O^{(-)}$	-0.71	-1.00
CF_3	0.43	0.54	CO_2H	0.36	0.41	OH	0.12	-0.37
CCl_3	0.4	0.46	CO_2CH_3	0.32	0.39	OCH_3	0.12	-0.27
CH_2CH_3	-0.07	-0.15	$CO_2CH_2CH_3$	0.37	0.45	OCH_2CH_3	0.10	-0.24
$CH(CH_3)_2$	-0.07	-0.17	$CO_2C_6H_5$	0.37	0.44	O(*n*-C_4H_9)	0.10	-0.32
$CH_2CH_2CH_3$	-0.07	-0.13	$CONH_2$	0.28	0.36	O(C_6H_5)	0.25	-0.03
C_3H_5 (cyclopropyl)	-0.07	-0.21	$CONHCH_3$	0.35	0.36	OCF_3	0.40	0.35
nC_4H_9	-0.08	-0.16	$CON(CH_3)_2$	0.35	0.36	$OCOCH_3$	0.39	0.31
$C(CH_3)_3$	-0.10	-0.20	NH_2	-0.16	-0.66	$OC(O)C_6H_5$	0.21	0.13
nC_5H_{11} (n-pentyl)	-0.08	-0.16	$N^{(+)}H3$	0.86	0.6	SH	0.25	0.15
C_6H_5	0.06	-0.01	$NHCH_3$	-0.21	-0.7	SCH_3	0.15	0.00
c-C_6H_{11}	-0.15	-0.22	$NH(CH_2CH_3)$	-0.24	-0.61	SCH_2CH_3	0.18	0.03
$CH_2C_6H_5$	-0.08	-0.09	$NH(C_6H_5)$	-0.12	-0.40	SC_6H_5	0.23	0.07
CH_2OCH_3	0.02	0.03	$NHCOCH_3$	0.21	0.00	$SOCH_2CH_3$	0.52	0.49
$CH_2OC_6H_5$	0.03	0.04	$NHC(O)C_6H_5$	0.02	-0.19	$SO_3^{(-)}$	0.05	0.09
CH_2NH_2	0.15	0	$NHNH_2$	0.02	-0.55	SO_2CH_3	0.60	0.72
$CH_2^{(+)}NH_3$	0.3	0.3	NHOH	-0.04	-0.34	$SO_2CH_2CH_3$	0.60	0.72
1-pyrryl	0.47	0.37	$NHSO_2CH_3$	0.2	0.03	$SO_2C_6H_5$	0.61	0.70
2-thienyl	0.09	0.05	$NHSO_2C_6H_5$	0.16	0.01	SO_2CF_3	0.83	0.96
3-thienyl	0.03	-0.02	$N(CH_3)_2$	-0.21	-0.83	SO_2NH_2	0.46	0.57
2-benzthiazolyl	0.27	0.29	$N(CH_2CH_3)_2$	-.23	-0.90	F	0.34	0.06
CN	0.56	0.66	$N(C_6H_5)_2$	0.00	-0.22	Cl	0.37	0.23
C(O)H	0.36	0.44	$N^{(+)}(CH_3)_3$	0.88	0.82	Br	0.39	0.23
$COCH_3$	0.38	0.50	N_3	0.27	0.15	I	0.35	0.28

Table S12. Hansch Constants Used in Study.

Hansch-Fujita Constants (π) – hydrophobicity Taft Constants (E_s) – Steric Bulk								
Substituent	**π**	**E_s**	**Substituent**	**π**	**E_s**	**Substituent**	**π**	**E_s**
H	0	0	$C(O)C_6H_5$	1.05	--	NO_2	-0.28	2.52
CH_3	0.56	0.55	$CO_2^{(-)}$	-4.36	--	$O^{(-)}$	-3.87	--
CF_3	0.88	2.4	CO_2H	-0.32	--	OH	-0.67	0.55
CCl_3	1.31	3.3	CO_2CH_3	-0.01	--	OCH_3	-0.02	--
CH_2CH_3	1.02	1.31	$CO_2CH_2CH_3$	0.51	--	OCH_2CH_3	0.38	--
$CH(CH_3)_2$	1.55	1.71	$CO_2C_6H_5$	1.46	--	O(*n*-C_4H_9)	1.55	--
$CH_2CH_2CH_3$	1.55	1.43	$CONH_2$	-1.49	--	O(C_6H_5)	2.08	--
C_3H_5 (cyclopropyl)	1.14	2.21	$CONHCH_3$	-1.27	--	OCF_3	--	--
nC_4H_9	2.13	1.63	$CON(CH_3)_2$	-0.71	--	$OCOCH_3$	-0.64	--
$C(CH_3)_3$	1.98	2.78	NH_2	-1.23	0.61	$OC(O)C_6H_5$	1.46	--
nC_5H_{11} (n-pentyl)	2.67	--	$N^{(+)}H3$	-4.19	--	SH	0.39	1.07
C_6H_5	1.96	3.43	$NHCH_3$	-0.47	--	SCH_3	0.61	1.07
c-C_6H_{11}	2.51	--	$NH(CH_2CH_3)$	0.08	--	SCH_2CH_3	1.07	--
$CH_2C_6H_5$	2.01	1.51	$NH(C_6H_5)$	1.37	--	SC_6H_5	2.32	--
CH_2OCH_3	-0.78	1.43	$NHCOCH_3$	-0.97	4.00	$SOCH_2CH_3$	-1.04	--
$CH_2OC_6H_5$	1.66	--	$NHC(O)C_6H_5$	0.49	--	$SO_3^{(-)}$	-4.76	--
CH_2NH_2	-1.04	--	$NHNH_2$	-0.88	--	SO_2CH_3	-1.63	--
$CH_2^{(+)}NH_3$	-4.09	3.54	NHOH	-1.34	--	$SO_2CH_2CH_3$	-1.09	--
1-pyrryl	0.95	--	$NHSO_2CH_3$	-1.18	--	$SO_2C_6H_5$	0.27	--
2-thienyl	1.61	--	$NHSO_2C_6H_5$	0.45	--	SO_2CF_3	0.55	--
3-thienyl	1.81	--	$N(CH_3)_2$	0.18	--	SO_2NH_2	-1.82	--
2-benzthiazolyl	2.13	--	$N(CH_2CH_3)_2$	1.18	--	F	0.14	0.55
CN	-0.57	0.51	$N(C_6H_5)_2$	3.61	--	Cl	0.71	0.97
C(O)H	-0.65	--	$N^{(+)}(CH_3)_3$	-5.96	--	Br	0.86	1.16
$COCH_3$	-0.55	--	N_3	0.46	--	I	1.12	1.62

Figure S2. Experimental solubility vs predicted solubility of quinolone derivative following Yalkowsky and Banerjee's solubility equation.