Synthesis of Novel 2- and 8-Substituted 4-Amino-7-chloroquinolines and their *N*-Alkylated Coupling Products

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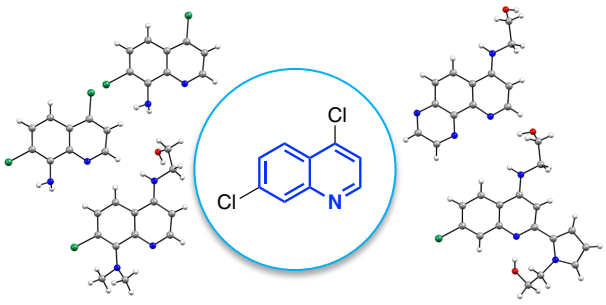
ABSTRACT

The synthesis of a series of 2- and 8-substituted 4-amino-7-chloroquinolines is presented. The chloro in the 7-position can be effectively substituted using amino alcohols to yield novel analogues of the antimalarial (hydroxy)chloroquine. Both short chain (2-aminoethanol) and long chain (5-[*N*-ethyl-*N*-(2-hydroxyethyl)amino]-2-aminopentane) coupling partners can be used. While ketone and nitro functionalities were found to be incompatible with the coupling conditions, electron-donating amino and dimethylamino substituents were tolerated. In addition to characterization in solution using multinuclear NMR spectroscopy and high-resolution mass spectrometry, single-crystal X-ray structures are presented of two 4,7-dichloroquinolines as well as three of the *N*-alkylated products including a unique species in which a pyrrole heterocycle formed at the 2-position of the quinoline sub-unit and a rare example of a 4-aza-1,10-phenanthroline.

KEYWORDS

chloroquine analogues; quinoline synthesis; X-ray crystallography

GRAPHICAL ABSTRACT



INTRODUCTION

Quinoline (benzo[*b*]pyridine) is a prominent pharmacophore, appearing in numerous biologically active synthetic molecules and natural products including prominent antimalarials such as the cinchona alkaloid quinine and the clinically critical drugs chloroquine and hydroxychloroquine (Figure 1).[1] Chloroquine was first prepared in the 1930s[2] and in the intervening years, analogues have emerged targeting resistance and the treatment of other ailments such as systemic lupus.[3] Of the analogues with intact quinoline moieties, many retain the 4-amino-7-chloro core of chloroquine (e.g., amodiaquine, piperaquine) while incorporating different functionality through the substituents at the 4-amino position; in other examples, alternative substituents on the quinoline unit itself are also present (e.g., mefloquine).[4] The persistent, global need for malaria treatment and expanded interest in chloroquine and its derivative for other applications[5] underpins the on-going importance of synthetic routes to novel quinoline-containing drug candidates.[6,7] In the context of repurposed compounds in particular, it is highly likely a new and potentially optimizable analogue could show improved efficacy for use in a new application. In this work, we present the synthesis and characterization of a library of novel substituted quinolines and demonstrate their utility for constructing chloroquine-like molecular scaffolds.

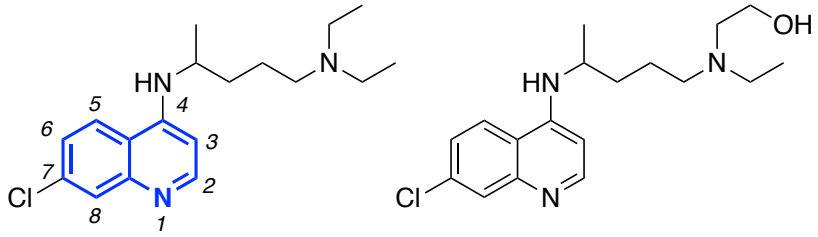


Figure 1. Antiviral compounds chloroquine (CQ) and hydroxychloroquine (HCQ). The quinoline (benzo[*b*]pyridine) sub-unit is highlighted in blue and the IUPAC numbering scheme indicated in italics.

MATERIALS AND METHODS

General Considerations

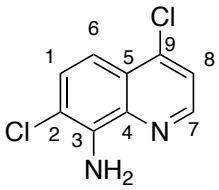
Air sensitive manipulations were carried out either in an N_2-filled glove box or using standard Schlenk techniques under Ar. All starting materials were purchased from commercial suppliers and used without further purification. When anhydrous and/or air-free conditions were employed, organic solvents were dried and distilled using appropriate drying agents. Distilled water was degassed prior to use. 1- and 2D NMR spectra were recorded on Bruker Avance 300 MHz, Bruker Avance 400 MHz, or Bruker Avance – III 500 MHz spectrometers. ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra were referenced to residual solvent peaks. Note: The numbering scheme used in the experimental section is solely for the purpose of assigning NMR resonances and should not be confused with the IUPAC numbering used in the manuscript discussion. High resolution mass spectra (HRMS) were recorded using a Bruker MicroOTOF-QIII.

Synthetic Procedures

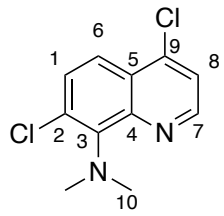
Preparation of 4,7-dichloro-8-nitroquinoline (1a): The following synthesis was adapted from literature.[8] A 250 mL round-bottom flask containing concentrated sulfuric acid (20 mL) was charged with 4,7-dichloroquinoline (3.02 g, 15.0 mmol). The mixture was left to stir for 10 min in an oil bath held at 40 ºC, at which point powdered sodium nitrate (1.16 g, 16.5 mmol, 1.1 equiv.) was added over a period of 15 min. The temperature of the oil bath was raised to 95 ºC and the solution left to stir. After 2 h, the solution was poured over ~200 g of ice. The precipitated product was filtered, washed with a dilute solution of sodium carbonate, then with water, and left to dry yielding a beige powder. Yield = 2.60 g (>98 %). ^{1}H NMR (500 MHz, $CDCl_3$, 22 ºC): δ 8.85-8.84 (d, J = 4.78 Hz, 1H; C_7), 8.29-

8.27 (d, J = 9.17 Hz, 1H; C_6), 7.70-7.68 (d, J = 9.18 Hz, 1H; C_1), 7.62-7.61 ppm (d, J = 4.79 Hz, 1H; C_8). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, 22 ºC): δ 152.9 (C_7), 143.1 (C_{Ar}), 141.2 (C_{Ar}), 128.5 (C_1), 127.1 (C_{Ar}), 126.8 (C_6), 125.7 (C_{Ar}), 123.2 (C_{Ar}), 123.2 (C_8) ppm. HR-MS (ESI-TOF/MS, m/z) calcd. for [M+H; M = $C_9H_4Cl_2N_2O_2$], 242.9723, found 242.9711.

Preparation of 4,7-dichloro-8-aminoquinoline (1b): The following synthesis was adapted from literature.[8] 4,7-Dichloro-8-nitroquinoline (3.01 g, 12.4 mmol) was added to a 250 mL round-bottom flask containing concentrated 50% aqueous acetic acid (45 mL). The mixture was left to stir for 10 min in an oil bath held at 90 ºC, at which point powdered iron (350 mesh) (2.11 g, 37.7 mmol) was slowly added over a period of 15 min. The mixture was left to stir for 1 h, then cooled slowly and diluted with 30 mL of distilled water forming a precipitate. The precipitate was isolated and subjected to Soxhlet extraction using diethyl ether. The organic extract was concentrated to dryness under reduced pressure. The resulting yellow powder was recrystallized from ethanol as pale yellow, needle-like crystals. Yield = 2.27 g (87 %). ^1H NMR (300 MHz, $CDCl_3$, 22 ºC): δ 8.63-8.59 (d, J = 4.73 Hz, 1H; C_7), 7.50-7.40 (m, 3H; C_{Ar}), 5.39 ppm (br s, 2H; -NH_2). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 22 ºC): δ 147.6 (C_7), 142.8 (C_{Ar}), 141.0 (C_{Ar}), 139.2 (C_{Ar}), 129.0 ($C_{1/6/8}$), 125.7(C_{Ar}), 121.7($C_{1/6/8}$), 115.6(C_{Ar}), 111.9 ($C_{1/6/8}$) ppm. HR-MS (ESI-TOF/MS, m/z) calcd. for [M+H; M = $C_9H_6Cl_2N_2$], 212.9981; found 212.9973.

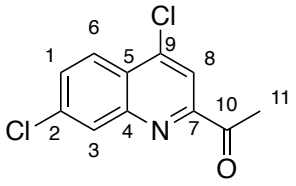


Preparation of 8-dimethylamino-4,7-dichloroquinoline (1c): A solution of 4,7-dichloro-8-aminoquinoline (1.01 g, 4.72 mmol) in *N*,*N*-dimethylformamide (10 mL) was added dropwise to a suspension of sodium



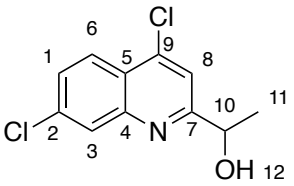
hydride (0.678 g, 28.3 mmol) also in *N*,*N*-dimethylformamide (10 mL). During the addition, the solution turned from a translucent yellow to a deep red. Iodomethane (1.75 mL, 28.6 mmol) was dissolved in *N*,*N*-dimethylformamide (5 mL) and added dropwise to the red suspension over a period of 30 min, during which the red colour changed to yellow, then brown. The resulting solution was left to stir overnight (14 h) and then quenched by addition of distilled water (50 mL). The mixture was extracted with dichloromethane (3 x 15 mL), the organic phase isolated, then washed with water (2 x 10 mL) and brine (1 x 10 mL). The isolated organic phase was then dried over solid $MgSO_4$, filtered, and reduced to dryness under vacuum. Brown oil. Yield = 1.10 g (97 %). ^{1}H NMR (300 MHz, $CDCl_3$, 22 ºC): δ 8.77-8.74 (d, J = 4.71 Hz, 1H; C_7), 7.88-7.83 (d, J = 9.22 Hz, 1H; C_6), 7.57-7.51 (d, J = 9.05 Hz, 1H; C_1), 7.44-7.40 (d, J = 4.61 Hz, 1H; C_8), 3.13 ppm (s, 6H, C_{10}). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, 22 ºC): δ 148.6 (C_7), 148.3 (C_{Ar}), 147.0 (C_{Ar}), 142.8 (C_{Ar}), 133.3 (C_{Ar}), 130.0 (C_6), 126.7 (C_{Ar}), 121.1 (C_1), 120.4 (C_8), 44.1 (C_{10}) ppm. HR-MS (ESI-TOF/MS, m/z) calcd. for [M+H; M = $C_{11}H_{10}Cl_2N_2$], 241.0294; found 241.0286.

Preparation of 2-acyl-4,7-dichloroquinoline (1d): A heat-dried Teflon-sealed flask was charged with potassium persulfate (21.8 g, 80.8 mmol), 4,7-dichloroquinoline (8.00 g, 40.4 mmol) and tetra(*n*-butyl)ammonium bromide (4.27 g, 13.4 mmol), followed by 1,2-dichloroethane (300 mL). To this solution, acetaldehyde (22.0 mL, 404 mmol) was added via pipette. The flask was then sealed and set to stir for 2 d in an oil bath heated to 40 ºC. After allowing to cool to room temperature, the mixture was washed with water (2 x 15 mL) and brine (2 x 15 mL). The organic phase was then concentrated via reduced pressure, and the crude organic mixture purified by column chromatography (silica; hexanes:acetone, 20:1). The organic fractions containing product were combined and concentrated



via reduced pressure. White powder. Yield 6.59 g (68 %). ^{1}H NMR (500 MHz, $CDCl_3$, 22 ºC): δ 8.21-8.20 (d, J = 2.10 Hz, 1H; C_6), 8.20-8.18 (d, J = 8.98, 1H; C_3), 8.16 (s, 1H; C_8), 7.68-7.65 (dd, J = 2.11, 8.99 Hz, 1H; C_1), 2.82 ppm (s, 3H; C_{11}). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, 22 ºC): δ 199.2 (C_{10}), 154.0 (C_{Ar}), 148.6 (C_{Ar}), 144.0 (C_{Ar}), 137.2 (C_{Ar}), 130.6 (C_1), 129.8 (C_6), 126.2 (C_{Ar}), 125.7 (C_3), 118.5 (C_8), 25.5 (C_{11}) ppm. HR-MS (ESI-TOF/MS, m/z) calcd. for [M+H; M = $C_{11}H_7Cl_2NO$], 239.9977; found 239.9969.

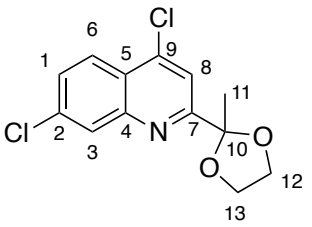
Preparation of 2-(1-hydroxy-ethane)-4,7-dichloroquinoline (1e): A 250 mL round-bottom flask was charged with 2-acyl-4,7-dichloroquinoline (2.00 g, 8.28 mmol), followed by 100 mL of methanol.



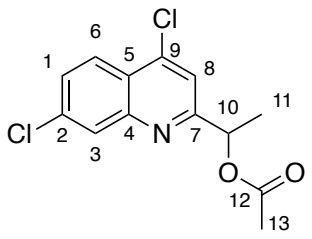
The resulting solution was cooled to 0 ºC and stirred for 15 min. Sodium borohydride (0.343 g, 9.067 mmol, 1.1 equiv.) was then added portion-wise over a period of 15 min. The solution was slowly brought to room temperature and allowed to stir overnight. To quench the reaction, distilled water (100 mL) and a drop of concentrated hydrochloric acid was added to the reaction mixture. The solution was allowed to stir for 15 min, then the methanol removed via reduced pressure. The residue was extracted with dichloromethane (2 x 15 mL). The combined organic fractions were washed with water (1 x 15 mL) and brine (1 x 15 mL). The resulting organic phase was then dried via reduced pressure to give a waxy amber solid. Yield = 1.270 g (64 %). ^{1}H NMR (300 MHz, $CDCl_3$, 22 ºC): δ 8.14-8.11 (d, J = 8.93 Hz, 1H; C_1), 8.08-8.05 (d, J = 1.89 Hz, 1H; C_3), 7.59-7.54 (dd, J = 1.89, 8.93, 1H; C_6), 7.47 (s, 1H; C_8), 5.03-4.96 (q, J = 6.64 Hz, 1H; C_{10}),4.54 (br s, 1H; -O*H*), 2.82 ppm (d, J = 6.65 Hz, 3H; C_{11}). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, 22 ºC): δ 164.7 (C_7), 147.7 (C_{Ar}), 143.6 (C_{Ar}), 137.0 (C_{Ar}), 128.5 (C_3), 128.2 (C_1), 125.7 (C_6), 124.2 (C_{Ar}), 118.5 (C_8),

69.0 (C_{10}), 24.1 ppm (C_{11}). HR-MS (ESI-TOF/MS, m/z) calcd. for [M+H; M = $C_{11}H_9Cl_2NO$], 242.0134; found 242.0125.

Preparation of 2-(1-ethylene acetal)-4,7-dichloroquinoline (1f): A round-bottom flask containing 75 mL of toluene was charged with 2-acyl-4,7-dichloroquinoline (1.00 g, 4.16 mmol), ethylene glycol (0.700 mL, 12.5 mmol) and *p*-toluenesulfonic acid monohydrate (0.079 g, 0.42 mmol). The flask was then outfitted with a Dean-Stark apparatus, and the solution heated to reflux overnight. Over this time, the yellow solution produced a green precipitate. After 14 h, the reaction vessel was cooled to ambient temperature and the solvent removed under reduced pressure. The crude product mixture was purified via column chromatography (neutral alumina, activated; 1:20 ethyl acetate:hexanes). Yellow powder. Yield = 0.287 g (24 %). ^{1}H NMR (300 MHz, $CDCl_3$, 22 ºC): δ 8.27-8.20 (d, J = 2.10 Hz, 1H; C_3), 8.16-8.11 (d, J = 9.53 Hz, 1H; C_6), 7.77, (s, 1H; C_8), 7.60-7.53 (dd, J = 2.11, 8.99 Hz, 1H; C_1), 4.18-4.08 (m, 2H; $C_{12/13}$), 3.99-3.89 (m, 2H; $C_{12/13}$) 1.78 ppm (s, 3H; C_{11}). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, 22 ºC): δ 163.0 (C_7), 149.0 (C_{Ar}), 143.5 (C_{Ar}), 136.5 (C_{Ar}), 136.7 (C_{Ar}), 129.2 (C_3), 128.8 (C_1), 125.4 (C_6), 124.4 (C_{Ar}), 118.3 (C_8), 108.5 (C_{10}), 65.3 ($C_{12+}C_{13}$), 25.3 ppm (C_{11}). HR-MS (ESI-TOF/MS, m/z) calcd. for [M+H; M = $C_{13}H_{11}Cl_2NO_2$], 284.0240; found 284.0219.



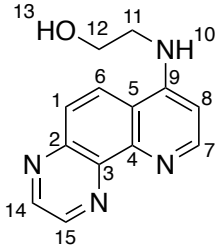
Preparation of 2-(1-ethyl ester)-4,7-dichloroquinoline (1g): In a dropping funnel containing 25 mL of dichloromethane, 2-(1-hydroxyethyl)-4,7-dichloroquinoline (1.20 g, 4.96 mmol), and anhydrous pyridine (0.600 mL, 7.45 mmol) were combined. Acetyl



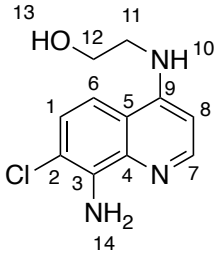
chloride (0.550 mL, 7.71 mmol) was dissolved in a 250 mL round-bottom flask containing 25 mL of dichloromethane and cooled to 0 ºC in an ice bath. The quinoline solution was added dropwise to the round-bottom flask over 30 min, then slowly warmed to room temperature. The solution was stirred for 2 h, then quenched with distilled water. The organic mixture was extracted with dichloromethane (3 x 15 mL), and the resulting organic mixture was washed with water (2 x 10 mL) and brine (1 x 10 mL). The isolated organic phase was dried with Mg_2SO_4, filtered, and the solvent removed under reduced pressure. The crude product was recrystallized from ethanol. White powder. Yield = 1.15 g (82 %). ^{1}H NMR (300 MHz, $CDCl_3$, 22 ºC): δ 8.15-8.10 (d, J = 8.87 Hz, 1H; C_1), 8.10-8.08 (d, J = 2.20, 1H; C_3), 7.59-7.53 (m, 2H; C_{6+8}), 6.02-5.94 (q, J = 6.73 Hz, 1H; C_{10}), 2.18 (s, 3H; C_{13}), 1.67-1.63 ppm (d, J = 6.70 Hz, 3H; C_{11}). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, 22 ºC): δ 170.4 (C_{12}), 162.2 (C_7), 148.9 (C_{Ar}), 143.5 (C_{Ar}), 136.8 (C_{Ar}), 128.8 (C_3), 128.6 (C_1), 125.5 (C_6), 124.3 (C_{Ar}), 118.6 (C_8), 73.3 (C_{10}), 21.4 (C_{11}), 20.8 (C_{13}) ppm. HR-MS (ESI-TOF/MS, m/z) calcd. for [M+H; M = $C_{13}H_{11}Cl_2NO_2$], 284.0240; found 284.0226.

General procedure for ethanolamine couplings (2a-e): To a 10 mL Telfon-stoppered flask, 1 mmol of substituted 4,7-dichloroquinoline (**1a-e**) was added, followed by 3 mmol of ethanolamine. The flask was degassed under vacuum while continuously sonicating it for 10 min. Then the flask was back-filled with Ar, sealed, and placed in an oil bath set to 170 °C for 24 h. The reaction mixture was then cooled to room temperature and the product isolated by column chromatography (silica gel, 1:9 (10% NH_4OH in MeOH):DCM as the mobile phase).

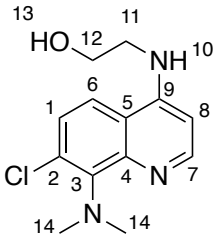
(2-(4-Aminopyrido)ethanol)[2,3-*f*]quinoxaline (2a): Substituted quinoline: **1a** (0.242 g, 0.996 mmol). Coupling partner: 2-aminoethanol (0.183 g, 3.16 mmol). Light yellow solid. Isolated Yield: 0.036 g (15 %). ^{1}H NMR (300 MHz, CD_3OD, 22 ºC): δ 9.05 (d, J = 2 Hz, 1H; C_{15}), 8.98 (d, J = 2 Hz, 1H; C_{14}), 8.61 (d, J = 5.61 Hz, 1H; C_7), 8.40 (d, J = 9.49 Hz, 1H; C_1), 7.90 (d, J = 9.49 Hz, 1H; C_6), 6.90 (d, J = 5.77 Hz, 1H; C_8), 3.88 (t, J = 5.84 Hz, 2H; C_{12}), 3.57 ppm (t, J = 5.83 Hz, 2H; C_{11}). ^{13}C{^{1}H} NMR (125 MHz, CD_3OD, 22 ºC): δ 153.1 (C_9), 151.3 (C_7), 146.9 (C_{14}), 146.4 (C_3), 145.6 (C_{15}), 144.9 (C_2), 142.0 (C_4), 125.3 (C_1), 125.2 (C_6), 118.8 (C_5), 103.3 (C_8), 60.8 (C_{12}), 46.4 ppm (C_{11}). HR-MS (ESI-TOF/MS, m/z) calcd. for [M+nH; M = $C_{13}H_{12}N_4O$], 241.1084; found 241.1077.



2-[(7-Chloro-8-aminoquinoline-4-yl)amino]ethanol (2b): Substituted quinoline: **1b** (0.213 g, 1.00 mmol). Coupling partner: 2-aminoethanol (0.183 g, 3.16 mmol). Brown solid. Isolated Yield: 0.054 g (23 %). ^{1}H NMR (500 MHz, CD_3OD, 22 ºC): δ 8.31 (d, J = 5.58 Hz, 1H; C_7), 7.30-7.28 (d, J = 9.08 Hz, 1H; C_6), 7.25-7.23 (d, J = 9.05 Hz, 1H; C_1), 6.54 (d, J = 5.57 Hz, 1H; C_8), 3.84 (t, J = 5.84 Hz, 2H; C_{12}), 3.48 ppm (t, J = 5.87 Hz, 1H; C_{11}). ^{13}C{^{1}H} NMR (125 MHz, CD_3OD, 22 ºC): δ 152.7 (C_9), 147.6 (C_7), 141.5 (C_3), 139.4 (C_4), 126.5 (C_1), 119.0 (C_2), 116.2 (C_5), 110.1 (C_6), 99.8 (C_8), 60.8 (C_{12}), 46.2 ppm (C_{11}). HR-MS (ESI-TOF/MS, m/z) calcd. for [M+nH; M = $C_{11}H_{12}N_3OCl$], 238.0742; found 238.0748.

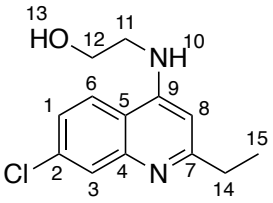


2-[(7-Chloro-8-dimethylaminoquinoline-4-yl)amino]ethanol (2c):

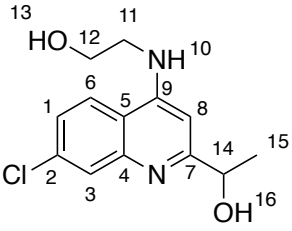


Substituted quinoline: **1c** (0.241 g, 1.00 mmol). Coupling partner: 2-aminoethanol (0.183 g, 3.16 mmol). Dark brown solid. Isolated Yield: 0.107 g (40 %). ^{1}H NMR (400 MHz, CD_3OD, 22 ºC): δ 8.40 (d, J = 5.66 Hz, 1H; C_7), 7.82 (d, J = 9.26 Hz, 1H; C_6), 7.34 (d, J = 9.13 Hz, 1H; C_1), 6.57 (d, J = 5.66 Hz, 1H; C_8), 3.84 (t, J = 5.87 Hz, 2H; C_{12}), 3.48 (t, J = 5.87 Hz, 1H; C_{11}), 2.98 ppm (s, 6H). ^{13}C{^{1}H} NMR (100 MHz, CD_3OD, 22 ºC): δ 153.4 (C_9), 150.4 (C_7), 147.8 (C_3), 146.3 (C_4), 134.8 (C_5), 127.6 (C_1), 120.0 (C_6), 119.8 (C_2), 99.8 (C_8), 60.8 (C_{12}), 46.4 (C_{11}), 43.4 ppm (C_{14}). HR-MS (ESI-TOF/MS, m/z) calcd. for [M+nH; M = $C_{13}H_{16}N_3OCl$], 266.1055; found 266.1051.

2-[(2-Ethyl-7-chloroquinoline-4-yl)amino]ethanol (2d): Substituted quinoline: **1d** (0.240 g, 1 mmol). Coupling partner: 2-aminoethanol (0.183 g, 3.16 mmol). Light brown oil. Isolated Yield: 0.029 g (12 %). ^{1}H NMR (400 MHz, CD_3OD, 22 ºC): δ 8.12 (d, J = 9.01 Hz, 1H; C_1), 7.78 (d, J = 2.13 Hz, 1H; C_3), 7.43 (dd, J = 8.99, 2.07 Hz, 1H; C_6), 6.59 (s, 1H; C_8), 3.86 (t, J = 5.61 Hz, 2H; C_{12}), 3.57 (t, J = 5.61 Hz, 2H; C_{11}), 2.84 (q, J = 7.66 Hz, 2H; C_{14}), 1.37 ppm (t, J = 7.67 Hz, 3H; C_{15}). ^{13}C{^{1}H} NMR (100 MHz, CD_3OD, 22 ºC): δ 165.7 (C_7), 154.3 (C_4), 147.3 (C_5), 137.6 (C_2), 126.1 (C_6), 125.2 (C_3), 124.4 (C_1), 117.3 (C_9), 98.7(C_8), 60.8 (C_{12}), 46.4 (C_{11}), 31.9 (C_{14}), 14.5 ppm (C_{15}). HR-MS (ESI-TOF/MS, m/z) calcd. for [M+H; M = $C_{13}H_{15}N_2OCl$], 251.0946; found 251.0962.



2-[(2-(1-Hydroxy-ethane)-7-chloroquinoline-4-yl)amino]ethanol (2e): Substituted quinoline: **1e** (0.242 g, 1.00 mmol). Coupling partner: 2-aminoethanol (0.183 g, 3.16 mmol). Light brown oil. Isolated Yield:



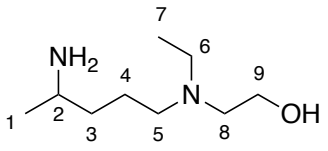
0.025 g (9 %). ^{1}H NMR (400 MHz, CD_3OD, 22 ºC): δ 8.08 (d, J = 9.11 Hz, 1H; C_1), 7.81 (d, J = 2.11 Hz, 1H; C_3), 7.39 (dd, J = 9.06, 2.14 Hz, 1H; C_6), 6.78 (s, 1H; C_8), 4.86 (q, J = 6.65 Hz, 1H; C_{14}), 3.86 (t, J = 5.81 Hz, 2H; C_{12}), 3.55 (t, J = 5.80 Hz, 2H; C_{11}), 1.51 ppm (d, J = 6.61 Hz, 3H; C_{15}). ^{13}C{^{1}H} NMR (100 MHz, CD_3OD, 22 ºC): δ 168.5 (C_7), 153.6 (C_4), 148.8 (C_5), 136.6 (C_2), 127.0 (C_3), 125.8 (C_6), 124.1 (C_1), 118.1 (C_9), 95.4 (C_8), 71.7 (C_{14}), 60.7 (C_{12}), 46.3 (C_{11}), 24.5 ppm (C_{15}). HR-MS (ESI-TOF/MS, m/z) calcd. for [M+H; M = $C_{13}H_{15}N_2O_2Cl$], 267.0895; found 267.0897.

2-[(2-(Pyrrole-1-ethanol)-7-chloroquinoline-4-yl)amino]ethanol (2f): This compound was isolated from reactions of both **1d** and **1e**. Isolated Yield from **1d**: 0.059 g (18 %). Yellow solid. Isolated Yield from **1e**: 0.018 g (5 %). ^{1}H NMR (400 MHz, CD_3OD, 22 ºC): δ 8.04 (d, J = 8.99 Hz, 1H; C_1), 7.79 (d, J = 2.14 Hz, 1H; C_3), 7.34 (dd, J = 2.17, 8.89 Hz, 1H; C_6), 6.97 (t, J = 1.86 Hz, 1H; C_{16}), 6.78 (s, 1H; C_8), 6.67 (q, J = 1.77 Hz, 1H; C_{15}), 6.21 (t, J = 1.80, 1H; C_{14}), 4.52 (t, J = 5.38 Hz, 2H; C_{17}), 3.96 (t, J = 5.29 Hz, 2H; C_{18}), 3.86 (t, J = 5.76 Hz, 2H; C_{12}), 3.53 ppm (t, J = 5.89, 2H; C_{11}). ^{13}C{^{1}H} NMR (100 MHz, CD_3OD, 22 ºC): δ 154.5 (C_7), 152.7 (C_4), 149.2 (C_5), 136.5 (C_2), 134.0 (C_{10}), 127.2 (C_{16}), 127.1(C_3), 125.4 (C_6), 123.9 (C_1), 117.6 (C_9), 113.3 (C_{15}), 109.5 (C_{14}), 98.4 (C_8), 64.5 (C_{18}), 60.8 (C_{12}), 50.7 (C_{17}), 46.3 ppm (C_{11}). HR-MS (ESI-TOF/MS, m/z) calcd. for [M+H; M = $C_{17}H_{18}N_3O_2Cl$], 332.1160; found 332.1173.

5-[*N*-Ethyl-*N*-(2-hydroxyethyl)amino]-2-pentanone (3): A 500 mL round bottom flask containing 100 mL xylenes and sodium chloride (42.0 g, 71.9 mmol) was charged with 5-chloro-2-pentanone (25.0 g, 207 mmol). After stirring at

room temperature for 5 min, 2-(ethylamino)ethanol (37.0 g, 415 mmol) was slowly added to the mixture. The reaction was heated in an oil bath held at 100 ºC for 2 h, then heated at reflux for 3 h. After letting the solution sit at room temperature overnight, the contents of the flask were passed through a filter. Anything remaining in the flask was sonicated with 30 mL of xylenes then passed through the filter. The filter cake was then washed with 60 mL of xylenes. The resulting oil filtrate was then reduced via vacuum, dissolved in dichloromethane (40 mL) and washed with water (3 x 30 ml) and brine (2 x 20 mL). The organic fraction was concentrated via low pressure. Amber oil. Yield = 15.1 g (42 %). ^{1}H NMR (300 MHz, $CDCl_3$, 22 ºC): δ 3.53-3.50 (t, J = 5.35 Hz, 2H; C_9), 2.58-2.50 (m, 4H; C_{6+8}), 2.46-2.41 (m, 4H; C_{3+5}), 2.13 (s, 3H; C_1), 1.76-1.66 (quintet, J = 7.11 Hz; C_4), 1.02-0.97 ppm (t, J = 7.11 Hz, 3H; C_7). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, 22 ºC): δ 208.8 (C_2), 58.6 (C_9), 55.1 (C_8), 52.5 (C_5), 47.2 (C_6), 41.3 (C_3), 30.1 (C_1), 21.3 (C_4), 11.8 (C_7) ppm. HR-MS (ESI-TOF/MS, m/z) calcd. for [M+H; M = $C_9H_{19}NO_2$], 174.1489; found 174.1490.

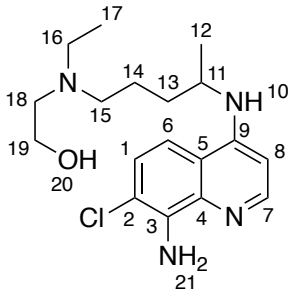
5-[*N*-Ethyl-*N*-(2-hydroxyethyl)amino]-2-aminopentane (4): 5-[*N*-Ethyl-*N*-(2-hydroxyethyl)amino]-2-pentanone (2.00 g, 11.5 mmol) was added to a glass sleeve containing saturated ammoniacal methanol (20 mL), and 10 % Pd/C (0.600 g). After allowing the suspension to stir at ambient pressure in a pressure reactor, hydrogen gas was added to the system until the pressure reached 1000 psi. The mixture was allowed to stir at room temperature for 24 h, then relieved of its pressure. The mixture was filtered, and then concentrated via reduced pressure. The resulting oil was then subjected to column chromatography, using 1:1 dichloromethane:[10%(v/v)NH_4OH/MeOH]. The relevant fractions were combined and concentrated. Brown oil. Yield = 1.42 g (70 %). ^{1}H NMR (300 MHz, CD_3OD, 22 ºC): δ 3.65-3.61 (t, J = 6.22 Hz, 2H; C_9), 2.96-2.85 (sextet, J = 6.35 Hz, 1H; C_2), 2.65-2.58 (q,



J = 7.10 Hz, 2H; C_6), 2.65-2.61 (t, J = 6.29 Hz, 2H; C_8), 2.53-2.48 (t, J = 7.47 Hz, 2H; C_5), 1.59-1.47 (m, 2H; C_4), 1.42-1.35 (m, 2H; C_3), 1.12-1.09 (d, J = 6.35 Hz, 3H; C_1), 1.08-1.01 ppm (t, J = 7.10 Hz, 3H; C_7). $^{13}C\{^1H\}$ NMR (75 MHz, CD_3OD, 22 ºC): δ 60.2 (C_9), 56.3 (C_8), 55.1 (C_5), 48.9 (C_6), 47.9 (C_2), 38.0 (C_3), 24.4 (C_4), 22.8 (C_1), 11.5 (C_7) ppm. Note: The numbering scheme shown here is used solely for the purpose of assigning the NMR and does not correspond to the manuscript discussion. HR-MS (ESI-TOF/MS, m/z) calcd. for [M+H; M = $C_9H_{22}N_2O$], 175.1805; found 175.1805.

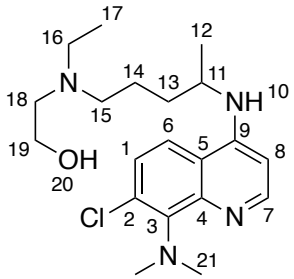
General procedure for hydroxychloroquine synthesis (5b-c): A 10 mL Telfon-stoppered flask was charged with 0.5 mmol of substituted 4,7-dichloroquinoline (**1b-c**) and 1.5 mmol of 5-[*N*-ethyl-*N*-(2-hydroxyethyl)amino]-2-aminopentane (**4**). The flask was degassed under vacuum while continuously sonicating it for 10 min. The flask was then back-filled with argon using standard Schlenk techniques, sealed, and placed in an oil bath set to 170 °C for 24 h. The reaction mixture was then cooled to room temperature and the product was isolated by column chromatography (silica gel, 1:9 (10% NH_4OH in MeOH):dichloromethane as the mobile phase).

***Rac*-2-[{4-[(7-chloro-8-aminoquinoline-4-yl)amino]pentyl}(ethyl)amino]ethanol (3b)**:Substituted quinoline: **1b** (0.107 g, 0.502 mmol). Coupling partner: **4** (0.261 g, 1.50 mmol). Dark brown oil. Isolated Yield: 0.046 g (26 %). ^1H NMR (500 MHz, CD_3OD, 22 ºC): δ 8.29 (d, J = 5.52 Hz, 1H; C_7), 7.37 (d, J = 9.02 Hz, 1H; C_6), 7.22 (d, J = 8.89 Hz, 1H; C_1), 6.52 (d, J = 5.67 Hz, 1H; C_8), 3.79 (sextet, J = 5.85 Hz, 1H; C_{11}), 3.62 (t, J = 6.32 Hz, 2H; C_{19}), 2.66-2.57 (m, 6H; $C_{15,16,18}$), 1.75-1.58 (m, 4H; $C_{13,14}$), 1.31 (d, J = 6.38 Hz, 3H; C_{12}), 1.05-1.02 ppm (t, J = 7.28 Hz,



3H; C_{17}). $^{13}C\{^{1}H\}$ NMR (125 MHz, CD_3OD, 22 ºC): δ 151.9 (C_9), 149.9 (C_7), 141.9 (C_3), 140.0 (C_4), 126.2 (C_1), 119.1 (C_2), 116.1 (C_5), 110.3 (C_6), 100.0 (C_8), 60.1 (C_{19}), 56.2 ($C_{15/16/18}$), 54.8 ($C_{15/16/18}$), 49.3 ($C_{15/16/18}$), 49.1 (C_{11}), 35.0 ($C_{13/14}$), 24.2 ($C_{13/14}$), 20.5 (C_{12}), 11.3 ppm (C_{17}). HR-MS (ESI-TOF/MS, m/z) calcd. for [M+H; M = $C_{18}H_{27}N_4OCl$], 351.1946; found 351.1940.

***Rac*-2-[{4-[(7-chloro-8-dimethylaminoquinoline-4-yl)amino]pentyl}(ethyl)amino]ethanol (3c)**: Substituted quinoline: **1c** (0.121 g, 0.502 mmol). Coupling partner: **4** (0.261 g, 1.50 mmol). Yellow-brown oil. Isolated Yield: 0.070 g (37 %). ^{1}H NMR (400 MHz, CD_3OD, 22 ºC): δ 8.37 (d, J = 5.79 Hz, 1H; C_7), 7.95 (d, J = 9.58 Hz, 1H; C_6), 7.36 (d, J = 9.58 Hz, 1H; C_1), 6.60 (d, J = 6.04 Hz, 1H; C_8), 3.82 (sextet, J = 5.77 Hz, 1H; C_{11}), 3.60 (t, J = 6.41 Hz, 2H; C_{19}), 2.98 (s, 6H; C_{21}), 2.62-2.49 (m, 6H; $C_{15,16,18}$), 1.78-1.56 (m, 4H; $C_{13,14}$), 1.32 (d, J = 6.44 Hz, 3H; C_{12}), 1.00 ppm (t, J = 7.31 Hz, 3H; C_{17}). $^{13}C\{^{1}H\}$ NMR (100 MHz, CD_3OD, 22 ºC): δ 153.0 (C_9), 150.0 (C_7), 147.5 (C_3), 145.9 (C_4), 135.1 (C_5), 127.6 (C_1), 120.2 (C_6), 119.9 (C_2), 100.0 (C_8), 60.4 (C_{19}), 56.3 ($C_{15/16/18}$), 54.8 ($C_{15/16/18}$), 49.8 (C_{11}), 49.0 ($C_{15/16/18}$), 43.1 (C_{21}), 35.0 ($C_{13/14}$), 24.4 ($C_{13/14}$), 20.4 (C_{12}), 11.5 ppm (C_{17}). HR-MS (ESI-TOF/MS, m/z) calcd. for [M+H; M = $C_{20}H_{31}N_4OCl$], 379.2259; found 379.2236.



X-Ray Crystallography Experimental Details

X-ray crystal structure data were collected from multi-faceted crystals of suitable size and quality, selected from a representative sample of crystals of the same habit using an optical microscope. Crystals were mounted on MiTeGen loops and data collection was carried out in a cold stream of nitrogen (150 K; Bruker D8 QUEST ECO). Diffractometer manipulations were carried out using

Bruker APEX3 software.[9] Structure solution and refinement were performed using XS[10] or XT[11] and XL[12] software, embedded within the OLEX2.[13] For each structure, the absence of additional symmetry was confirmed using ADDSYM incorporated in the PLATON program.[14]

Crystal structure data of 1a (CCDC 2211074): X-ray quality crystals were grown through the slow evaporation of chloroform at room temperature. Colourless blocks; $C_9H_4Cl_2N_2O_2$ 243.04 g/mol, triclinic, space group *P*-1; a = 7.0540(2) Å, b = 7.5470(2) Å, c = 9.4447(3) Å, α =100.5050(10), β = 102.1610(10)°, γ = 90.4390(10)°, V = 482.73(2) Å^3; Z = 2, ρ_{calcd} = 1.672 g cm^{-3}; crystal dimensions 0.670 x 0.350 x 0.150 mm; $2\theta_{max}$ = 66.904°; 20957 reflections, 3723 independent (R_{int} = 0.0241, intrinsic phasing; absorption coeff (μ = 0.649 mm^{-1}), absorption correction semi-empirical from equivalents (SADABS); refinement (against F_o^2) with SHELXTL V6.1, 136 parameters, 0 restraints, R_1 = 0.0449 ($I > 2\sigma$; 2809 reflections) and wR_2 = 0.1322 (all data), Goof = 1.028, residual electron density 0.34/−0.44 Å^{-3}.

Crystal structure data of 1b (CCDC 2211075): X-ray quality crystals were grown through the slow evaporation of methanol at room temperature. Yellow blocks; $C_9H_6Cl_2N_2$, 213.06 g/mol, monoclinic, space group $P2_1/n$; a = 13.883(3) Å, b = 3.8022(9) Å, c = 17.204(4) Å, α =90, β = 109.558(3)°, γ = 90°, V = 855.7(3) Å^3; Z = 4, ρ_{calcd} = 1.654 g cm^{-3}; crystal dimensions 0.312 x 0.085 x 0.077 mm; $2\theta_{max}$ = 61.406°; 17462 reflections, 2665 independent (R_{int} = 0.0351, intrinsic phasing; absorption coeff (μ = 0.702 mm^{-1}), absorption correction semi-empirical from equivalents (SADABS); refinement (against F_o^2) with SHELXTL V6.1, 136 parameters, 0 restraints, R_1 = 0.0352 ($I > 2\sigma$; 2248 reflections) and wR_2 = 0.1216 (all data), Goof = 1.067, residual

electron density 0.41/−0.26 $Å^{-3}$. The locations of hydrogen atoms were determined from the difference map, with the thermal parameters then fixed to neighbouring atoms.

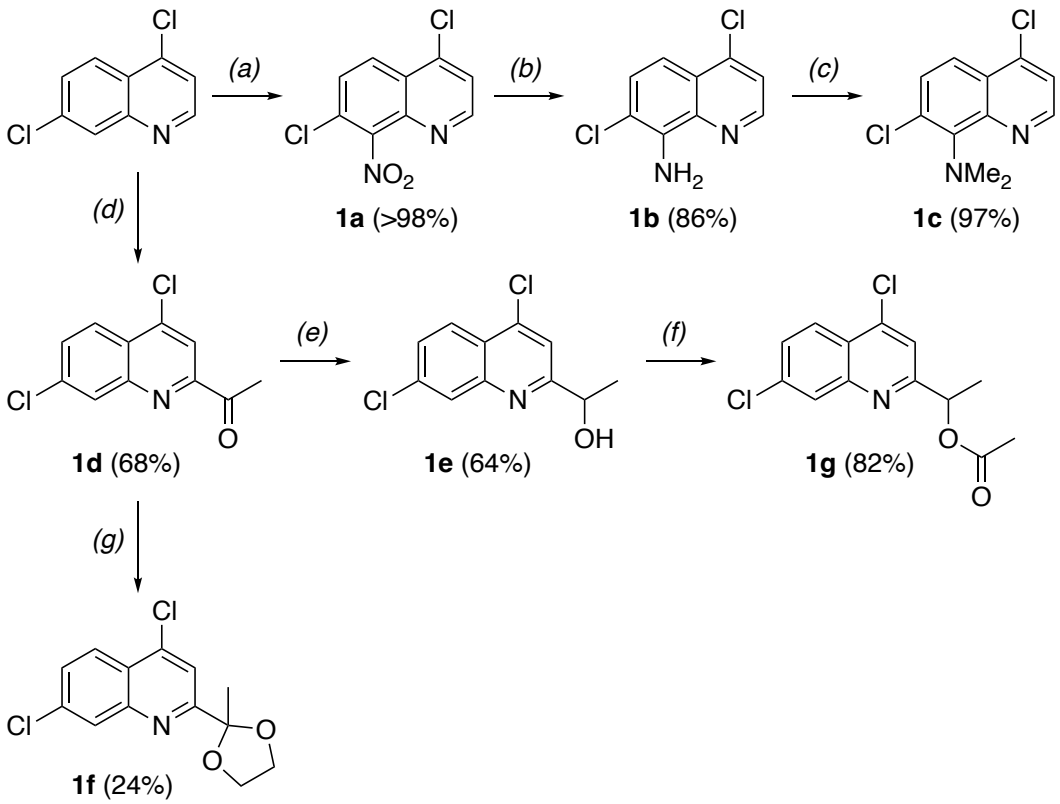
Crystal structure parameters for 2a (CCDC 2214095): X-ray quality crystals were grown through slow evaporation of a concentrated solution in methanol at room temperature. Yellow blocks; $C_{14}H_{16}N_4O_2$; 272.31 g/mol, monoclinic, space group $P2_1/n$; a = 7.359(2) Å, b = 9.9006(9) Å, c = 18.019(5) Å, β = 101.419(17)°, V = 1286.8(5) $Å^3$, Z = 4, ρ_{calcd} = 1.406 g cm^{-3}; crystal dimensions 0.491 × 0.205 × 0.107 mm; $2\theta_{max}$ = 56.564°; 41795 reflections, 3179 independent (R_{int} = 0.0246), dual space; absorption coeff (μ = 0.098 mm^{-1}), absorption correction semi-empirical from equivalents (SADABS); refinement (against F_o^2) with SHELXTL V6.1, 184 parameters, 0 restraints, R_1 = 0.0384 ($I > 2\sigma$; 3031 reflections) and wR_2 = 0.1141 (all data), Goof = 1.063, residual electron density 0.39/−0.21 $Å^{-3}$.

Crystal structure parameters for 2c (CCDC 2212313): X-ray quality crystals were grown through the slow evaporation of methanol at room temperature. Yellow plates; $C_{13}H_{16}ClN_3O$, 265.74 g/mol, triclinic, space group P-1; a = 7.964(2) Å, b = 9.0185(8) Å, c = 9.793(2) Å, α =81.250(9)°, β = 71.996(18)°, γ = 72.336(12)°, V = 636.0(3) $Å^3$; Z = 2, ρ_{calcd} = 1.388 g cm^{-3}; crystal dimensions 0.250 x 0.200 x 0.100 mm; $2\theta_{max}$ = 56.542°; 23461 reflections, 3116 independent (R_{int} = 0.0168, intrinsic phasing; absorption coeff (μ = 0.292 mm^{-1}), absorption correction semi-empirical from equivalents (SADABS); refinement (against F_o^2) with SHELXTL V6.1, 166 parameters, 0 restraints, R_1 = 0.0313 ($I > 2\sigma$; 2936 reflections) and wR_2 = 0.0894 (all data), Goof = 1.047, residual electron density 0.38/−0.36 $Å^{-3}$.

Crystal structure parameters for 2f (CCDC 2212314): X-ray quality crystals were grown through the slow evaporation of methanol at room temperature. Yellow-green blocks; $C_{34}H_{36}Cl_2N_6O_4$, 663.59 g/mol, triclinic, space group *P*-1; a = 11.099(3) Å, b = 12.089(3) Å, c = 13.139 Å, α =104.88(2)°, β = 91.59(2)°, γ = 111.68(2)°, V = 1568.4(8) Å^3; Z = 2, ρ_{calcd} = 1.405 g cm^{-3}; crystal dimensions 0.91 x 0.80 x 0.16 mm; $2\theta_{max}$ = 56.998°; 60082 reflections, 7801 independent (R_{int} = 0.0219, intrinsic phasing; absorption coeff (μ = 0.257 mm^{-1}), absorption correction semi-empirical from equivalents (SADABS); refinement (against F_o^2) with SHELXTL V6.1, 419 parameters, 0 restraints, R_1 = 0.0350 ($I > 2\sigma$; 7135 reflections) and wR_2 = 0.0975 (all data), Goof = 1.041, residual electron density 0.40/−0.21 Å^{-3}.

RESULTS AND DISCUSSION

Compared with derivatization of the alkylamino chain (e.g., as in hydroxychloroquine),[15–22] modifications of the quinoline core in the antimalarial medicinal chemistry literature have been comparably less explored,[23,24] with some focus on introducing trifluoromethyl groups as in mefloquine or improving known syntheses through the application of high-yielding continuous flow technologies.[25] We targeted two sites for quinoline ring-substitution starting from 4,7-dichloroquinoline: the 2- and 8- positions (note: the numbering refers to the IUPAC numbering illustrated in Figure 1). Of these, the 2-position is generally the more common site for functionalization of quinoline in general, in the literature.[26] Scheme 1 outlines our synthetic approach to accessing quinolines **1a**-**1g**.



406 **Scheme 1.** Synthetic pathways to access quinoline precursors with isolated yields in parentheses.
407 Conditions: (a) H_2SO_4, 10 min, 40 °C, followed by HNO_3, 2 h, 95 °C; (b) $Fe_{(s)}$, 50% (v/v) acetic
408 acid, 75 min, 90 °C; (c) iodomethane, sodium hydride, *N*,*N*-dimethylformamide, 16 h, 22 °C; (d)
409 $K_2S_2O_8$, [*n*Bu_4N]Br, acetaldehyde, 2 d, 40 °C; (e) $NaBH_4$, methanol, 16 h, 0 °C warmed to room
410 temperature, followed by HCl, 15 min, 0 °C; (f) anhydrous pyridine, acetyl chloride,
411 dichloromethane, 2 h, 0 °C warmed to room temperature; (g) ethylene glycol, *para*-toluene
412 sulfonic acid, toluene, Dean-Stark conditions.
413
414 Compounds **1a**-**1g** were characterized in solution using multinuclear NMR spectroscopy
415 and high-resolution mass spectrometry (HRMS). Substitution at either the 2- or 8- position could
416 thus be confirmed by disappearance of the ^{1}H NMR resonance attributed to a hydrogen nucleus at
417 these positions, and the inclusion of new functional groups through the appearance of new signals
418 with the appropriate integrations (with the exception of **1a** which presents no new H or C
419 resonances). In the case of **1a** and **1b**, single-crystals suitable for analysis by X-ray diffraction
420 were obtained by slow evaporation. The solid-state structure of these compounds is presented in
421 Figure 2. While most bond distances within the quinoline moiety were generally unaffected upon
422 reduction of the NO_2 moiety in **1a** to an NH_2 in **1b**, the C(7)-Cl(2) carbon chlorine bond distance
423 was observed to increase from 1.7173(14) Å to 1.7403(15) Å. Additionally, elongation of the C(4)-
424 C(5) carbon-carbon bond is evident [1.4268(19) Å in **1b** *cf.* 1.4094(18) Å in **1a**]. The most dramatic
425 change is in the bond distance separating C(6) and N(2), which contracts from 1.4681(16) Å in **1a**
426 to 1.3675(18) Å in **1b**, likely due to the stabilizing effect of nitrogen lone pair donation into the
427 electron deficient π-system of the dichloroquinoline.
428

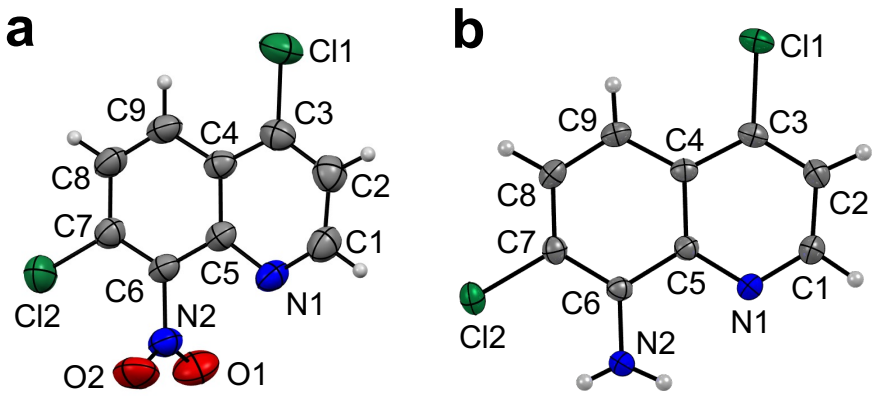
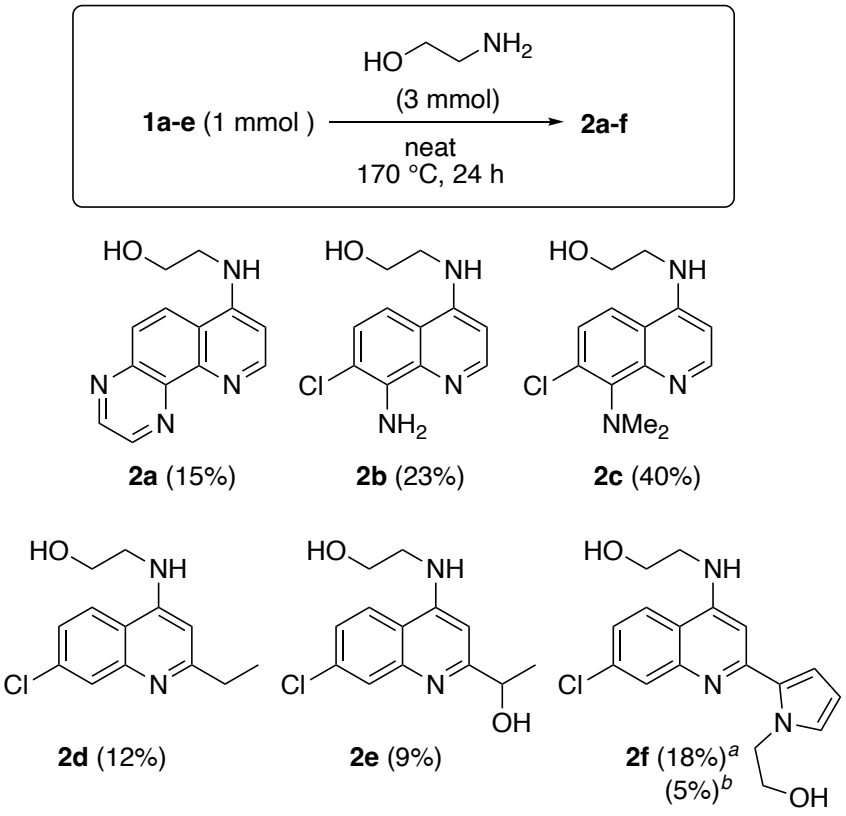


Figure 2. Solid-state structure of (a) **1a** and (b) **1b** with thermal ellipsoids shown at 50% probability levels. Hydrogen atom labels are omitted for clarity. Selected bond distances (Å) and angles (°): **1a** C(6)-N(2) 1.4681(16), C(1)-N(1) 1.312(2), C(5)-N(1) 1.3622(16), C(3)-Cl(1) 1.7253(15), C(7)-Cl(2) 1.7173(14); N(1)-C(5)-C(4) 124.39(12), N(1)-(C(5)-C(6) 117.99(11), N(2)-C(6)-C(7) 120.59(12), N(2)-C(6)-C(5) 117.06(12). **1b** C(6)-N(2) 1.3675(18), C(1)-N(1) 1.319(2), C(5)-N(1) 1.3652(18), C(3)-Cl(1) 1.7337(14), C(7)-Cl(2) 1.7403(15); N(1)-C(5)-C(4) 123.27(13), N(1)-(C(5)-C(6) 116.75(12), N(2)-C(6)-C(7) 123.08(13), N(2)-C(6)-C(5) 119.76(13).

With 4,7-dichloroquinolines **1a**-**1g** in hand, we next attempted reactions to install a hydroxychloroquine-like side chain. Prior to attempting direct coupling with 5-[*N*-ethyl-*N*-(2-hydroxyethyl)amino]-2-aminopentane, we first investigated thermal reactions in neat 2-aminoethanol using **1a**-**1e** (Scheme 2). Compounds **2a**-**2f** were synthesized by slightly modifying literature procedures for the synthesis of 4-(ethanolamino)-7-chloroquine.[27–30] We first optimized conditions for a small-scale synthesis of **2b** (0.3 mmol) during which it was found that a neat reaction with 4,7-dichloro-8-aminoquinoline at 130 °C only afforded a limited percentage conversion of ~10% by ^{1}H NMR spectroscopy. Increasing the temperature to 170 °C increased NMR conversion to 100%, suggesting improvements to product isolation could lead to higher

overall yields. The newly optimized set of conditions was then used to synthesize **2a**-**2f** on 1 mmol scales. Compounds **2a**-**2f** could be isolated in varying amounts (9-40% isolated yields). The crude reaction mixtures yielded thick, dark brown oils. Following purification, compounds **2a**-**2c** and **2f** were isolated as powders, while **2d** and **2e** were obtained as viscous oils. Of these five precursors, the reaction conditions proved compatible with isolation of a simple coupled product for **1b**, **1c** and **1e**. For substrates **1a** and **1d**, more complex – but no less interesting – transformations were observed. In the case of the acyl-substituted **1d**, the carbonyl group did not survive the reaction conditions and **2d** was isolated with an ethyl side chain in the 2-position. The reducing character of ethanolamines has been previously noted.[31] Interestingly, **2e** could be isolated with an intact secondary alcohol despite this being the presumed intermediate in the formation of **2d**. The yields of the coupling reaction rose with increasing electron-rich character of the quinoline as **2c**, containing a dimethylamino substituent on the quinoline, was isolated in the highest yield. Coupling products **2a**-**2f** were characterized in solution via multinuclear NMR and HRMS, and in the case of **2a**, **2c**, and **2f,** by single-crystal X-ray diffraction as well (*vide infra*).



464

465 **Scheme 2.** Thermal coupling of **1a**-**1e** with 2-ethanolamine. [a] From reaction of **1d**. [b] From reaction
466 of **1e**.

467

468 For **1a**, the NO_2 functionality reacted with a second equivalent of aminoethanol to form a
469 rare pyridoquinoxaline (4-aza-l,10-phenanthroline) framework[32–34] and 7-aminoethanol-4-aza-
470 1,10-phenanthroline (**2a**) was isolated. Conceivably, the nitro functional group is reduced to an
471 amine at high temperature, similar to the reduction observed in the reaction of **1d**. The so-oxidized
472 aminoethanol could then condense with this newly formed NH_2, followed by intramolecular attack
473 at the chloro-substituted 7-position to form the fused diazene moiety (see Supporting Information,
474 Figure S1). The thermal coupling of 2-aminoethanol with either **1d** or **1e** additionally returned an
475 appreciable amount of a quinoline bearing an *N*-substituted pyrrole (**2f**; 18% isolated yield from
476 **1d**, 5% from **1e**). The new heterocyclic functionality is connected to the C_2 carbon of the quinoline

by the α-carbon of the pyrrole. In each instance, TLC and ^{1}H NMR analysis of the crude reaction mixtures showed **2d/e** and **2f** to be the major components of the reaction mixtures, along with significant amounts of unreacted quinoline starting material. The formation of **2f** is not unprecedented[35] and could form through tautomerization of the imine likely to form initially through condensation of **1d** and 2-aminoethanol. **1d** could be formed at high temperature via dehydrogenation of **1e**. A proposed mechanism is provided as Figure S2.

Comparing the solid-state structures of **2c** and **2f** (Figure 3), the quinoline moieties are largely isostructural with the largest changes likely arising from the dimethylamino present on **2c**, like what is observed in the solid-state for **1a** and **1b** (*vide supra*). The C(7)-Cl(2) bond length is slightly shorter in **2f** (1.7413(12)/1.7390(14) Å; the asymmetric unit of **2f** contains two crystallographically distinct molecules) compared to in **2c** (1.7509(12) Å). The C-C bond connecting the aminoethanol and quinoline units are statistically indistinguishable (**2c**: 1.3524(13) Å, **2f**: 1.3530(14)/1.3463(14) Å). The torsional angle between the planes formed by the quinoline and pyrrole sub-units in **2f** (N(1)-C(1)-C(10)-N(2): 27.33(17)/29.71(16)°) is indicative of the potential for electronic communication between the two π-systems. This angle is a likely consequence of the intramolecular hydrogen bonding present between O(1) and N(1) which forms an intramolecular 8-membered ring. The hydrogen bonding environment shows an internuclear distance of O(1)-N(1) 2.6786(15)/2.6474(14) Å, and an angle of 173.0/174.4° for the O(1)-H(1)-N(1) bonding system. The fused ring system of **2a** seems to have little impact on the bond distances involving the pyridyl moiety containing the C(1) through C(5) carbons when compared to **2c**. For example, the C(3)-N(3) distance is 1.3501(12) Å in **2a** and 1.3524(13) Å in **2c**. The most dramatic change in this ring is found in the N(1)-C(5) bond, which elongates from 1.3562(12) Å (**2a**) to 1.3704(13) Å (**2c**). The shorter N(1)-C(5) bond length in **2a** could be indicative of an electron poor

environment, resulting from the π-extension at the C(6) and C(9) carbons. For comparison, the N(1)-C(5) bond found in the electron-poor quinoline **1a** is 1.3622(16) Å, which is longer than in **2a** by 0.006 Å. The bond distances in the C_6 ring moiety all increase in **2a** compared to **2c**, with the most notable difference in the C(6)-C(7) distances: 1.3831(15) Å in **2c** and 1.4095(13) Å in **2a**. Strong conjugation between the newly formed C_4N_2 ring and the quinoline section in **2a** is implied based on the N(2)-C(6) bond distance, which at 1.3592(13) Å is considerably shorter than either of the N(2)-C(6) distances in **2c** (1.4081(13) Å) or **1a** (1.4681(16) Å).

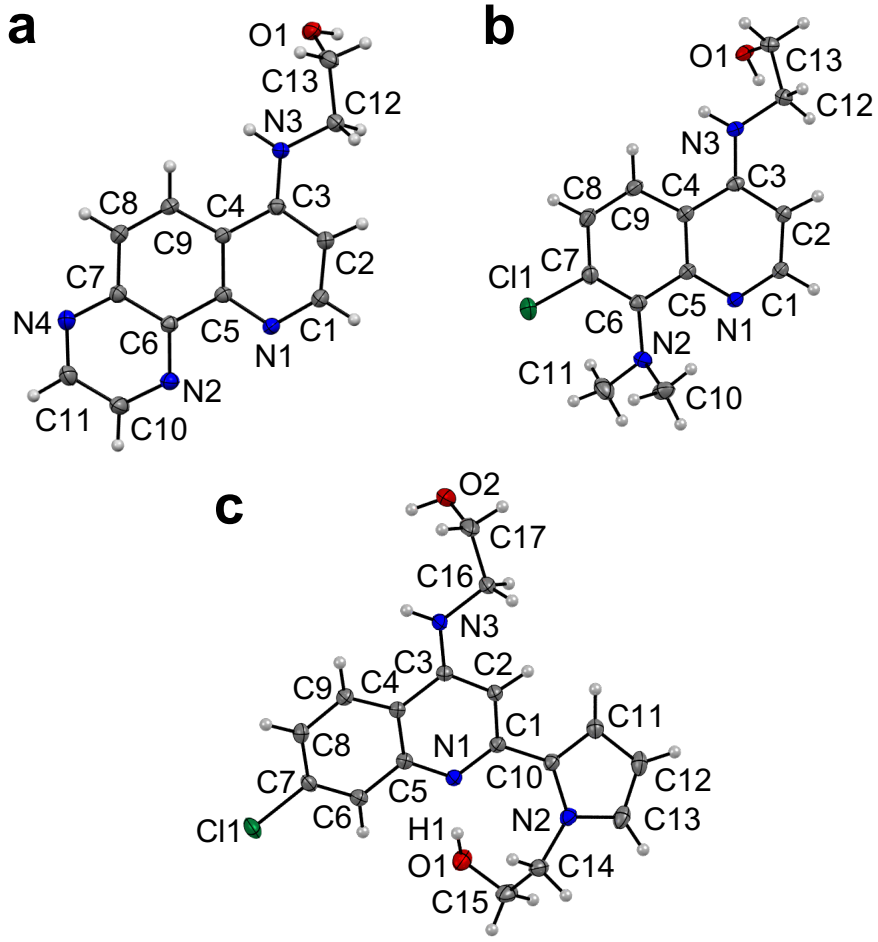
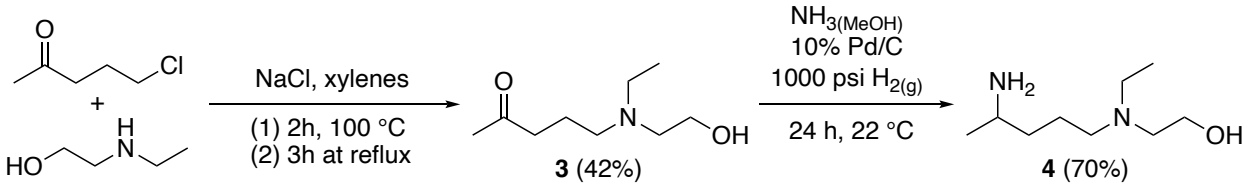


Figure 3. Solid-state structure of (a) **2a**, (b) **2c** and (c) **2f** with thermal ellipsoids shown at 50% probability levels. A co-crystallized methanol solvent molecule is omitted in (a) and only one of

two crystallographically distinct molecules of **2f** is shown in (c). Most hydrogen atom labels are also omitted for clarity. Selected bond distances (Å) and angles (°): **2c** C(6)-N(2) 1.4081(13), C(1)-N(1) 1.3226(14), C(5)-N(1) 1.3704(13), C(3)-N(3) 1.3524(13), C(7)-Cl(2) 1.7509(12); N(1)-C(5)-C(4) 122.86(9), N(1)-(C(5)-C(6) 116.88(9), N(2)-C(6)-C(5) 117.47(9), N(2)-C(6)-C(7) 125.45(10). **2a** C(1)-N(1) 1.331(1), C(5)-N(1) 1.356(1), C(3)-N(4) 1.350(1), C(6)-N(2) 1.359(1), C(7)-N(2) 1.320(1), C(8)-N(3) 1.320(2), C(9)-N(3) 1.363(1); N(1)-C(5)-C(4) 124.13(9), N(1)-C(5)-C(6) 117.32(8), N(2)-C(6)-C(5) 118.61(8), N(2)-C(6)-C(9) 121.31(9), C(6)-N(2)-C(7) 115.88(9), C(8)-N(3)-C(9) 115.61(9), N(3)-C(9)-C(10) 118.63(9). **2f** [distances/angles reported only for the crystallographically distinct molecule shown in (c)] C(7)-Cl(1) 1.7413(12), C(5)-N(1) 1.3679(15), C(1)-N(1) 1.3300(14), N(3)-C(3) 1.3530(14), C(1)-C(10) 1.4661(15), C(10)-N(2) 1.3820(14), C(13)-N(2) 1.3672(16), C(14)-N(2) 1.4630(15); N(1)-C(5)-C(4) 123.49(10), N(1)-C(5)-C(6) 116.78(10), C(10)-N(2)-C(14) 128.82(10), N(1)-C(1)-C(10)-N(2) 29.71(16).

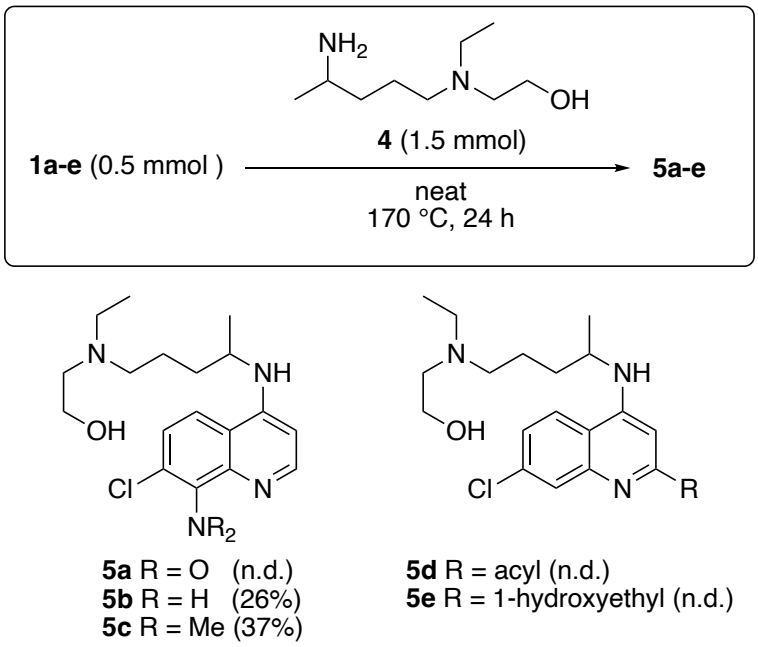
To access the *N*-substituent present in hydroxychloroquine, the coupling partner 5-[*N*-ethyl-*N*-(2-hydroxyethyl)amino]-2-aminopentane (**4**) was prepared via the ketone intermediate **3**, which was accessed via a modification to a published procedure (Scheme 3).[36] Briefly, 5-chloro-2-pentanone was reacted with 2-(ethylamino)ethanol in the presence of excess of sodium chloride in refluxing xylenes. Washing the crude product with water and extracting with dichloromethane gave **3** cleanly with no additional purification necessary. While this method of purification provided more modest yields (42%) compared to published procedures (99%),[36] the simplicity of the purification compared to the published route is attractive and leaves room for further optimization of the yield. To form **4**, compound **3** was reacted at room temperature with a saturated solution of freshly prepared, anhydrous, ammoniacal methanol in the presence of Pd/C under 1000

psi of $H_{2(g)}$, after Van Praet *et al*.[37] Column chromatography on silica using a mixture of ammonium hydroxide, methanol, and dichloromethane as eluent afforded **4** in high purity.



Scheme 3. Synthesis of the long chain coupling precursor 5-[*N*-ethyl-*N*-(2-hydroxyethyl)amino]-2-aminopentane (**4**) via a ketone intermediate (**3**).

The reaction conditions used for the synthesis of **2a-2e** were then replicated in the attempted synthesis of **5a-e** using **4** (Scheme 4). No product was isolated using **2a**, **2d** or **2e**, consistent with the observation that quinolines bearing electron-donating substituents are favored in these couplings. Indeed, of the two products successfully isolated (**5b** and **5c**) the dimethylamino containing quinoline **5c** was obtained in a higher yield. Crude reaction mixtures of compounds **5b** and **5c** were thick, black oils containing a number of unidentified species in addition to the isolable products. Column chromatography afforded **5b** and **5c** as viscous oils.



547

548 **Scheme 4.** Attempted thermal coupling reactions of **1a**-**1e** with 5-[*N*-ethyl-*N*-(2-
549 hydroxyethyl)amino]-2-aminopentane (**4**).

550

551 **CONCLUSION**

552 The synthesis and characterization of a series of seven 2- and 8-substituted 4-amino-7-
553 chloroquinolines is presented, along with six examples of their *N*-alkylated coupling products. The
554 high temperature reaction conditions led to the formation of unexpected and novel products
555 including a rare example of a 4-aza-1,10-phenanthroline sub-unit, and a pyrrolyl side chain. As the
556 chloroquine molecular motif is prominent in antimalarial and antiplasmodial compounds,[38] the
557 synthesis of novel congeners represents an area of interest for the treatment of emerging infectious
558 diseases.[39] The evaluation of the biological activity of this new compound library represents the
559 next logical step in this research direction.

560

AUTHOR STATEMENTS

Acknowledgements

Dr. Michael McDonald is thanked for collection of single-crystal X-ray data for **1b**.

Competing Interests Statement

The authors declare there are no competing interests.

Author Contributions

CRediT contributor roles for this manuscript were as follows: conceptualization (DN, KC, AF, DH); investigation and validation (DN, BS); methodology, visualization and writing – original draft (DN, BS, DH); writing – review & editing (DN, BS, KC, AF, DH); resources, project administration and supervision (DH); funding acquisition (KC, AF, DH).

Funding Statement

The following sources of funding are gratefully acknowledged: the Natural Sciences Engineering Research Council of Canada for an Alliance Grant (ALLRP 552044-20). Purchase of an X-Ray diffractometer was possible through support of the Canada Foundation for Innovation and Research Manitoba (#32146).

Data Availability Statement

The following files are available free of charge: Supporting Information File (PDF); Crystallographic Information Files (CIFs). Multinuclear NMR spectra and HRMS are provided as Supporting Information for each novel compound (PDF). CCDC 2211074, 2211075, 2214095, 2212313 and 2212314 contain the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/structures.

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