Antimalarials: Synthesis of 4-Aminoquinolines that Circumvent Drug Resistance in Malaria Parasites [1]

Dibyendu De, Larry D. Byers and Donald J. Krogstad*

Departments of Tropical Medicine and Chemistry, Tulane University, New Orleans, LA 70112

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The strategies described here have permitted the synthesis of a series of 4-aminoquinoline antimalarials. Substantive improvements over previous syntheses include nucleophilic substitution with neat amine rather than in phenol, regioselective reductive alkylation to convert the terminal primary amine (**12a-20a**) on the diaminoalkane side chain to a diethylamino group, and purification by column chromatography with basic alumina. The ^1H nmr spectra obtained after regioselective reductive alkylation with sodium borodeuteride (in comparison with sodium borohydride) demonstrated that this reductive alkylation proceeds *via* formation and subsequent reduction of the corresponding diamides *in situ*.

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Introduction.

The public health importance of malaria is difficult to overestimate, with more than 300 million clinical cases and 1 million deaths each year [2]. However, the most important antimalarial drug, chloroquine (Figure 1), has lost much of its value because of the widespread emergence of chloroquine-resistant *Plasmodium falciparum* [3]. To identify potential alternatives to chloroquine, a better understanding of the structure-activity relationships responsible for the antiplasmodial activity of chloroquine and other 4-aminoquinolines is essential. Although more than 300,000 compounds have been synthesized and tested thus far by the US Army Antimalarial Development Program [4], the structure-activity relationships responsible for aminoquinoline activity against chloroquine-susceptible and -resistant *P. falciparum* remain unknown [5]. Therefore, we synthesized a series of 4-aminoquinolines to define these structure-activity relationships. The biologic (antiplasmodial) activity of these aminoquinolines against chloroquine-susceptible and chloroquine-, mefloquine, and multiply-resistant *P. falciparum* is being reported in detail elsewhere [6].

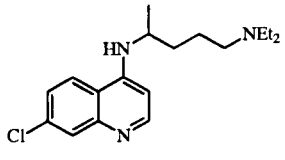
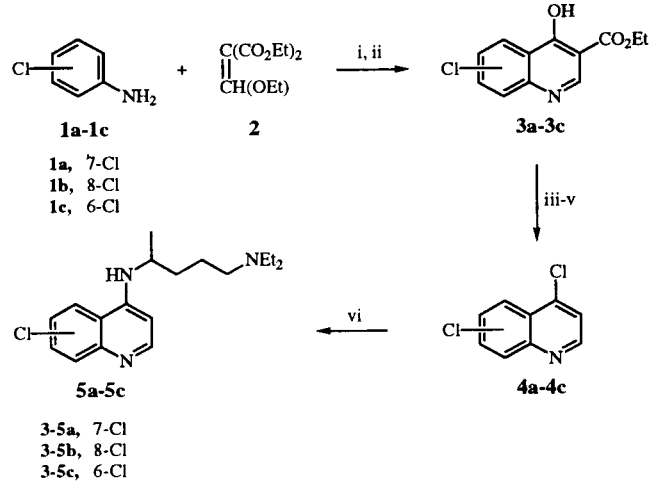


Figure 1. Chloroquine

Chemistry.

Aminoquinolines **5a-5c** were prepared using the method reported previously with several modifications (Scheme 1) [7]. Condensation of equimolar amounts of chloro-substituted anilines **1a-1c** with diethyl ethoxymethylenemalonate (**2**) yielded the corresponding *N*-substituted acrylates, which were then subjected to thermal cyclization in boiling phenyl ether to produce quinoline esters. After cyclization, the quinoline esters were purified by recrystallization to produce **3a-3c**. Alkaline hydrolysis of **3a-3c**, followed by decarboxylation and treatment with phosphorus oxychloride, produced **4a-4c** in excellent yields. Nucleophilic substitution of the chlorine atom at C-4 in neat 2-amino-5-diethylaminopentane at 150-170°, followed by the usual work-up, yielded a mixture of products [8]. Compounds **5a-5c** were purified from this crude mixture using basic alumina column chromatography [9].

Scheme 1

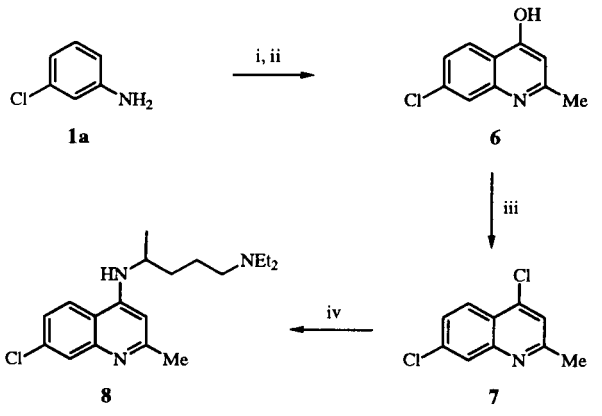


Reagents & conditions: i) 165°, 1.5 hours; ii) Ph_2O, reflux, 1 hour; iii) 2*N* NaOH, reflux, 1 hour; iv) Ph_2O, reflux, 1 hour; v) $POCl_3$, 100°; vi) 2-Amino-5-diethylaminopentane, 150-160°, 8-10 hours.

The preparation of **8** was accomplished in four steps, beginning with *m*-chloroaniline (Scheme 2) [10]. Briefly, acid catalyzed condensation of *m*-chloroaniline and ethyl acetoacetate, followed by thermal cyclization in boiling phenyl ether yielded a mixture of 7-chloro-4-hydroxy-2-methylquinoline and 5-chloro-4-hydroxy-2-methylquinoline. Several recrystallizations from 75% ethanol/water preferentially solubilized the 5-chloro isomer into the 75% ethanol/water, thus yielding the desired 7-chloro isomer, **6** as pure crystals. Treatment of **6** with phosphorus

oxychloride replaced the hydroxyl at C-4 with chlorine to provide **7**. The desired compound **8** was then obtained as a pure liquid from **7** (after nucleophilic substitution of the chlorine at C-4 with 2-amino-5-diethylaminopentane, followed by the usual work-up).

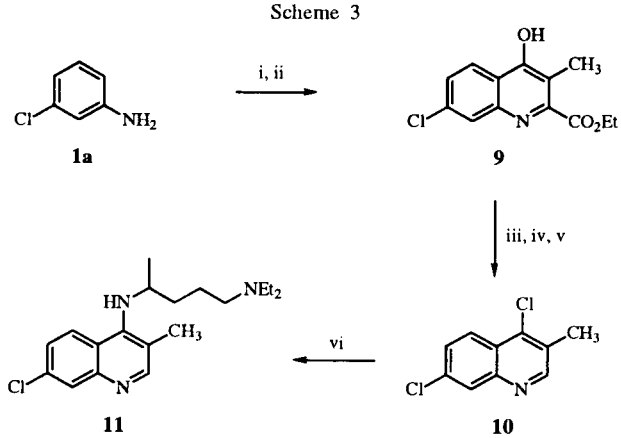
Scheme 2



Reagents & conditions; i) ethyl acetoacetate, catalytic HCl, 12 hours; ii) Ph_2O, 190°, 1 hour; iii) $POCl_3$; iv) 2-amino-5-diethylaminopentane, 145-155°, 10 hours.

Previous syntheses have used phenol as a solvent for the nucleophilic substitution reaction with the diaminoalkane [11]. In contrast, we obtained an improved yield by monitoring the progress of the reaction using thin-layer chromatography, eliminated phenol as a solvent by performing the nucleophilic substitution in neat 2-amino-5-diethylaminopentane at controlled temperature (145-155°) [12], and achieved better isolation of **11** from the crude mixture by purification with column chromatography using basic alumina (step vi in Scheme 3).

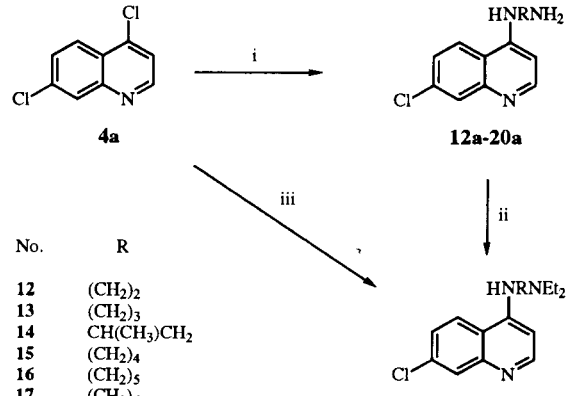
Scheme 3



Reagents and conditions: 1) diethyl oxalpropionate, catalytic HCl, 50°, 18 hours; ii) Ph_2O, 170-180°, 1 hour; iii) 2N NaOH, reflux, 1.5 hours; iv) Ph_2O, reflux; v) $POCl_3$, 100°, 1 hour; vi) 2-Amino-5-diethylaminopentane, 145-160°, 8 hours.

Because some of the diethylaminoalkyl amines required were not available commercially, we used a two step synthetic strategy for the preparation of **12-20** (Scheme 4). In the first step (step i, General Method A), equimolar amounts of **4a** were reacted with diaminoalkanes such as ethylenediamine to produce compounds such as **12a** in excellent yield [13]. The ^1H nmr and ms data confirmed these monomeric structures. In the second step (step ii, General Method A), regioselective reductive alkylation with sodium borohydride/acetic acid converted the terminal primary amines on the diaminoalkane side chains to diethylamines such as **12** in good yield [14]. Presumably, $Na[BH_3(OOCCH_3)]$ is the species formed by the sodium borohydride/acetic acid mixture which actually reacts with primary amines such as **12a** to produce the corresponding diamides *in situ* [15]. Subsequent reduction by sodium borohydride is then thought to convert the diamides to diethylamino groups, yielding **12-20**, respectively (Scheme 4). To test this hypothesis, reductive alkylation of **12a** was performed with sodium borodeuteride in the presence of acetic acid. The ^1H nmr spectrum of this compound **12d** revealed loss of the quartet (δ 2.62 ppm) due to the methylene protons of the two terminal diethyl groups. This result establishes that the sodium borohydride/acetic acid reduction proceeds by formation of the diamide *in situ*. The structures of compounds **12**, **13**, and **15** were further confirmed by a different single step synthesis from **4a** using commercially available diethylaminoalkyl amines (step iii, General Method B). The fact that compound **12** was identical by the ^1H nmr and ms data whether it was synthesized by Method A or B likewise supports the argument that the reductive alkylation step (step ii, Scheme 4) proceeds as we have proposed.

Scheme 4



No.	R
12	$(CH_2)_2$
13	$(CH_2)_3$
14	$CH(CH_3)CH_2$
15	$(CH_2)_4$
16	$(CH_2)_5$
17	$(CH_2)_6$
18	$(CH_2)_8$
19	$(CH_2)_{10}$
20	$(CH_2)_{12}$

Reagents and conditions: i) H_2NRNH_2, 120-150°, 2-4 hours; ii) $NaBH_4$, CH_3COOH, 55°, 12-16 hours; iii) H_2NRNEt_2, 135-150°.

Conclusions.

The ^1H nmr and ms studies presented here establish the identity of five aminoquinolines which have recently

been shown to be active against chloroquine-susceptible and -resistant *P. falciparum in vitro* and *in vivo* [6,16]. They also demonstrate convenient synthetic strategies which may be useful for the large scale preparation of these compounds, **12**, **13**, **14**, **19**, and **20**.

EXPERIMENTAL

Melting points were determined with a Thomas Hoover Melting Point Apparatus (Model 6406-K, Arthur Thomas - Philadelphia, PA), and are uncorrected. The ^{1}H nmr spectra were obtained with a General Electric Omega 500 MHz Spectrometer (Fremont, CA). The ^{1}H nmr signals are reported in parts per million (δ ppm), and are expressed as singlet (s), doublet (d), triplet (t), or multiplet (m). Coupling constants are expressed in hertz (Hz). Mass spectra were obtained with a Kratos Profile Mass Spectrometer (Manchester, UK). Elemental analyses (CHN) were performed by Atlantic Microlab, Inc., Norcross, GA. Thin layer chromatography was performed with silica gel F254 polyethylene-backed plates (EM Separations - Gibbstown, NJ) or aluminum oxide on polyester plates (layer thickness 200 μm, particle size <60 μm - Aldrich, Milwaukee, WI), and visualized with uv light, by staining with iodine vapors, or by spraying the thin layer chromatography plate with 2% aqueous potassium permanganate solution containing 1% sulfuric acid. Column chromatography was performed with activated basic alumina (Brockmann I, ~150 mesh, 58 Å - Aldrich). Freshly redistilled solvents (Curtin-Matheson - Houston, TX or Aldrich) were used for all isolation and purification procedures. Chemicals were purchased from Aldrich unless noted otherwise.

N^4-(6-Chloro-4-quinolinyl)-N^1,N^1-diethyl-1,4-pentanediamine (**5c**).

p-Chloroaniline (**1c**) (3.24 g, 25 mmoles) and diethyl ethoxymethylenemalonate (**2**) (6.9 ml, 34 mmoles) were mixed together and heated slowly to 110° for 45 minutes, liberating ethanol, which was evaporated under reduced pressure. Cooling to room temperature converted the resulting brownish oil to a semisolid, which was then suspended in hexane, triturated and recovered by filtration (95%, mp 64°). The solid anilide (2 g) was then suspended in boiling phenyl ether (80 ml), heated to reflux for 45 minutes to produce the quinoline ester, cooled to room temperature, diluted with petroleum ether and filtered. The resulting 3-carbethoxy-6-chloro-4-hydroxyquinoline (**3c**) was washed several times with ethyl acetate, and recrystallized from 70% ethanol (yield 60%, mp 308-310°, lit mp 308-310° [8b]). The product was then suspended in 2 *N* sodium hydroxide solution (100 ml), heated to reflux for 1.5 hours, charcoaled, filtered and neutralized with ice-cold 2 *N* aqueous hydrochloric acid. The solid precipitate (3-carboxy-6-chloro-4-hydroxyquinoline) was filtered, washed with water, and dried. This product was then suspended in boiling phenyl ether (80 ml) and allowed to reflux for 1 hour. After cooling to room temperature, the crystalline product was separated, filtered, washed several times with petroleum ether, and recrystallized from the ethanol/water mixture. The resultant 6-chloro-4-hydroxyquinoline (1.5 g, 7.57 mmoles) was then added to phosphorus oxychloride (6 ml) and heated at 140° for 1 hour. Upon completion of the reaction (as monitored by silica gel thin layer chromatography), excess phosphorus oxychloride was evaporated, cold aqueous 1 *N* sodium hydroxide solution was added (*p*H 8), and the precipitated solid was triturated, filtered, washed with water and dried. Recrystallization from chloroform/hexane (1:1) yielded pure **4c** (90%, mp 103°, lit mp 104-105° [8b]). A mixture of **4c** (0.5 g, 2.5 mmoles) and 2-amino-5-diethylaminopentane (1.2 ml, 6.2 mmoles) was heated initially at 100° for 2 hours with stirring, and subsequently at 150-160° for 5 hours with continued stirring to drive the reaction to completion. After cooling to 100°, excess amine was evaporated under reduced pressure, and the remaining material cooled to room temperature. Sodium hydroxide (1 *N*, 10 ml) was then added, and the organic product was extracted into methylene chloride, washed with water, dried over anhydrous sodium sulfate, and the solvent was evaporated to dryness *in vacuo*. The resulting reddish-brown, crude product was purified by column chromatography using basic alumina as the solid support and eluted with chloroform/petroleum ether (1:4) to yield **5c** (70%, mp 72-73°, lit mp 71-73° [8a]); ^{1}H nmr (deuteriochloroform, 500 MHz): δ 1.06 (t, 6H, J = 8.0, CH_3), 1.33 (d, 3H, J = 6.0, CH_3), 1.65-1.75 (m, 3H, CH_2, CH), 1.76-1.85 (m, 1H, CH), 2.53 (t, 2H, J = 5.0, NCH_2), 2.64 (q, 4H, J = 8.0, NCH_2), 3.66-3.76 (m, 1H, NCH), 5.58 (broad d, 1H, NH), 6.42 (d, 1H, J = 5.5, ArC_3-H), 7.53 (d, 1H, J = 9.0, ArC_6-H), 7.81 (s, 1H, ArC_5-H), 7.90 (d, 1H, J = 9.0, ArC_8-H), 8.51 (d, 1H, J = 5.5, ArC_2-H); ms: (70 eV, electron impact), m/z 319 (M^+), 321.

Anal. Calcd. for $C_{18}H_{26}ClN_3 \cdot H_2O$: C, 63.90; H, 8.28; N, 12.42. Found: C, 64.12; H, 8.46; N, 12.12.

N^4-(7-Chloro-4-quinolinyl)-N^1,N^1-diethyl-1,4-pentanediamine (**5a**).

A mixture of 4,7-dichloroquinoline (**4c**) (0.5 g, 2.5 mmoles) and 2-amino-5-diethylaminopentane (1.2 ml, 6.2 mmoles) was heated initially at 100° for 2 hours with stirring, and subsequently at 150-160° for 5 hours with continued stirring to drive the reaction to completion. Upon usual work-up, the desired product **5a** was obtained as a golden yellow oil following the procedure described for purification of **5c** (yield 80%); ^{1}H nmr (deuteriochloroform, 500 MHz): δ 1.02 (t, 6H, J = 8.5, CH_3), 1.31 (d, 3H, J = 7.0, CH_3), 1.59-1.69 (m, 3H, CH_2, CH), 1.74-1.80 (m, 1H, CH), 2.46 (t, 2H, J = 6.0, NCH_2), 2.55 (q, 4H, J = 7.5, NCH_2), 3.68-3.74 (m, 1H, NCH), 5.36 (broad d, 1H, NH), 6.41 (d, 1H, J = 5.5, ArC_3-H), 7.33 (dd, 1H, J = 9.0, 1.5, ArC_6-H), 7.71 (d, 1H, J = 9.0, ArC_5-H), 7.92 (d, 1H, J = 1.5, ArC_8-H), 8.50 (d, 1H, J = 5.5, ArC_2-H); ms: (70 eV, electron impact), m/z 319 (M^+), 321.

Anal. Calcd. for $C_{18}H_{26}ClN_3 \cdot 2HCl$: C, 54.96; H, 7.12; N, 10.68. Found: C, 54.72; H, 7.36; N, 10.41.

N^4-(8-Chloro-4-quinolinyl)-N^1,N^1-diethyl-1,4-pentanediamine (**5b**).

The starting material 4,8-dichloroquinoline (**4b**) for the synthesis of **5b** was prepared according to a previously published procedure [8b]. A mixture of **4b** (0.5 g, 2.5 mmoles) and 2-amino-5-diethylaminopentane (1.2 ml, 6.2 mmoles) was heated initially at 100° for 2 hours with stirring, and subsequently at 140-150° for 7 hours with continued stirring to drive the reaction to completion. Upon usual work-up, the desired product **5b** was obtained as a colorless powder following the procedure described for purification of **5c** (yield 85%). Recrystallization from petroleum ether yielded analytically pure **5b** (mp 122-123°, lit mp

122.9-123.5° [8a]); ^{1}H nmr (deuteriochloroform, 500 MHz): δ 1.06 (t, 6H, J = 8.5, CH_3), 1.34 (d, 3H, J = 6.5, CH_3), 1.65-1.72 (m, 3H, CH_2, CH), 1.78-1.85 (m, 1H, CH), 2.50-2.57 (m, 2H, NCH_2), 2.61 (q, 4H, J = 8.0, NCH_2), 3.70-3.77 (m, 1H, NCH), 5.43 (broad d, 1H, NH), 6.50 (d, 1H, J = 5.5, ArC_3-H), 7.32 (t, 1H, J = 9.0, ArC_6-H), 7.73 (dd, 2H, J = 9.0, 1.0, ArC_5-H, ArC_7-H), 8.63 (d, 1H, J = 5.5, ArC_2-H); ms: (70 eV, electron impact), m/z 319 (M^+), 321.

Anal. Calcd. for $C_{18}H_{26}ClN_3$: C, 67.50; H, 8.12; N, 13.12. Found: C, 67.54; H, 8.15; N, 13.07.

N^4-(7-Chloro-2-methyl-4-quinolinyl)-N^1,N^1-diethyl-1,4-pentanediamine (**8**).

Concentrated hydrochloric acid (0.5 ml) was added to a mixture of *m*-chloroaniline (**1a**) (2.67 ml, 25 mmoles) and ethyl acetoacetate (3.30 ml, 26 mmoles) and allowed to react overnight at room temperature. The mixture was then diluted with dichloromethane (50 ml), washed with water, and dried over sodium sulfate before evaporating the solvent *in vacuo*. The crude oily crotonate was suspended in boiling phenyl ether (80 ml), heated to reflux for 30 minutes, cooled to room temperature, diluted with petroleum ether and filtered. Repeated recrystallization of the mixture of products from 75% ethanol/water yielded **6** as pure crystals (yield 55%, mp 310-312°, lit mp 315-316° [10]). Compound **6** (1.80 g, 10 mmoles) was then added to phosphorus oxychloride (5 ml) and heated at 120° for 1 hour. Usual work-up as described for the preparation of **4c** yielded pure **7** (80% (petroleum ether), mp 101-102°, lit 103.5-104° [10]). A mixture of **7** (0.5 g, 2.5 mmoles) and 2-amino-5-diethylaminopentane (1.2 ml, 6.2 mmoles) was heated initially at 100° for 2 hours with stirring, and subsequently at 145-155° for 10 hours with continued stirring to drive the reaction to completion. After cooling to 100°, excess amine was evaporated under reduced pressure, and the remaining crude product cooled to room temperature. Upon usual work-up, the desired product **8** was obtained as a pure liquid following the procedure described for purification of **5c**; ^{1}H nmr (deuteriochloroform, 500 MHz): δ 1.04 (t, 6H, J = 8.5, CH_3), 1.32 (d, 3H, J = 6.0, CH_3), 1.60-1.68 (m, 3H, CH_2, CH), 1.72-1.77 (m, 1H, CH), 2.47 (t, 2H, J = 6.5, NCH_2), 2.55 (q, 4H, J = 8.0, NCH_2), 2.58 (s, 3H, CH_3), 3.72-3.79 (m, 1H, NCH), 5.17 (broad d, 1H, NH), 6.33 (s, 1H, ArC_3-H), 7.30 (d, 1H, J = 9.0, ArC_6-H), 7.65 (d, 1H, J = 9.0, ArC_5-H), 7.89 (s, 1H, ArC_8-H); ms: (70 eV, electron impact), m/z 333 (M^+), 335.

Anal. Calcd. for $C_{19}H_{28}ClN_3$•dioxalate•0.5H_2O: C, 52.72; H, 6.30; N, 8.03. Found: C, 52.92; H, 6.07; N, 7.71.

N^4-(7-Chloro-3-methyl-4-quinolinyl)-N^1,N^1-diethyl-1,4-pentanediamine (**11**).

The starting material 4,7-dichloro-3-methylquinoline (**10**) for the synthesis of **11** was prepared according to a previously published procedure [11]. A mixture of **10** (0.6 g, 2.8 mmoles) and 2-amino-5-diethylaminopentane (1.5 ml, 7.7 mmoles) was heated initially at 100° for 2 hours with stirring, and subsequently at 145-160° for 8 hours with continued stirring to drive the reaction to completion. After cooling to 100°, excess amine was evaporated under reduced pressure, and the remaining crude product cooled to room temperature. Upon usual work-up, the desired product **11** was obtained as a pure liquid following the procedure described for purification of **5c**; ^{1}H nmr (deuteriochloroform, 500 MHz): δ 0.97 (t, 6H, J = 8.0, CH_3), 1.15 (d, 3H, J = 6.0, CH_3), 1.48-1.62 (m, 4H, CH_2, CH), 2.35 (s, 3H, CH_3), 2.37 (t, 2H, J = 6.5, NCH_2), 2.48 (q, 4H, J = 8.0, NCH_2), 3.71-3.75 (m, 1H, NCH), 6.30 (broad d, 1H, NH), 7.38 (d, 1H, J = 9.0, ArC_6-H), 7.83 (d, 1H, J = 9.0, ArC_5-H), 7.88 (s, 1H, ArC_8-H), 8.41 (s, 1H, ArC_2-H); ms: (70 eV, electron impact), m/z 333 (M^+), 335.

Anal. Calcd. for $C_{19}H_{28}ClN_3$•dioxalate•0.5H_2O: C, 52.77; H, 6.30; N, 8.03. Found: C, 52.52; H, 6.03; N, 7.66.

N^2-(7-Chloro-4-quinolinyl)-N^1,N^1-diethyl-1,2-ethanediamine (**12**).

General Method A.

Step i: A mixture of 4,7-dichloroquinoline (**4a**) (1.98 g, 10.0 mmoles) and ethylenediamine (3.0 ml, 45 mmoles) was heated initially at 80° for 1 hour with stirring, subsequently at 135-145° for 3 hours with continued stirring to drive the reaction to completion, and then cooled to room temperature. Sodium hydroxide (1 *N*, 10 ml) was then added, and the organic product was extracted with ethyl acetate, washed with water, and dried over anhydrous sodium sulfate, before the solvent was evaporated *in vacuo*. The desired product **12a** was obtained as a pale yellow solid after trituration in petroleum ether (yield 90%). This semi-pure compound was used in the next step without further purification.

Step ii: A solution of **12a** (0.22 g, 1.0 mmole) in glacial acetic acid (10 ml) was cooled to 5° before adding sodium borohydride (0.6 g, 16.0 mmoles) carefully with slow stirring (vigorous reaction commenced upon addition of sodium borohydride). After complete addition the reaction mixture was stirred at room temperature for 1 hour and subsequently heated at 55° with continued stirring for 18 hours to drive the reaction to completion, and then cooled to room temperature. A chilled 35% sodium hydroxide solution was then added (*p*H ~8-9), and the organic product was extracted with dichloromethane (60 ml x 3), washed with water, and dried over anhydrous sodium sulfate, before the solvent was evaporated *in vacuo*. The resulting yellowish oil was purified by column chromatography using basic alumina as the solid support, and eluted with chloroform/petroleum ether (1:4) to yield **12** as a white powder. Single recrystallization from petroleum ether yielded colorless microcrystals (70%, mp 92°, lit mp 94-97° [7b]).

General Method B.

A mixture of 4,7-dichloroquinoline (**4a**) (10.1 g, 51 mmoles) and *N,N*-diethylethylenediamine (15 ml, 94 mmoles) was heated initially at 100° for 1 hour with stirring, and subsequently at 135-145° for 3 hours with continued stirring to drive the reaction to completion. After cooling to 100°, excess amine was evaporated under reduced pressure, and the remaining crude product cooled to room temperature. Sodium hydroxide (1*N*, 100 ml) was then added, and the organic product was extracted with methylene chloride, washed with water, and dried over anhydrous sodium sulfate, before the solvent was evaporated *in vacuo*. The resulting reddish-brown, crude product was purified by column chromatography using basic alumina as the solid support and eluted with chloroform/petroleum ether (1:4) to yield **12** as a white powder. Single recrystallization from petroleum ether yielded colorless microcrystals (85%, mp 92°); ^{1}H nmr (deuteriochloroform, 500 MHz): δ 1.10 (t, 6H, J = 7.5, CH_3), 2.62 (q, 4H, J = 7.0, NCH_2), 2.86 (t, 2H, J = 5.5, NCH_2), 3.28 (q, 2H, J = 4.0, NCH_2), 6.35 (bs, 1H, NH), 6.37 (d, 1H, J = 5.5, ArC_3-H), 7.38 (dd, 1H, J = 9.0, 1.5, ArC_6-H), 7.71 (d, 1H, J = 9.0, ArC_5-H),

7.96 (d, J = 1.5, 1H, ArC_8-H), 8.52 (d, 1H, J = 5.5, ArC_2-H); ms: (70 eV, electron impact), m/z 277 (M^+), 279.

Anal. Calcd. for $C_{15}H_{20}ClN_3$: C, 64.86; H, 7.21; N, 15.13. Found: C, 64.81; H, 7.30; N, 15.20.

N^2-(7-Chloro-4-quinolinyl)-N^1,N^1-di-(ethyl-1,1-d_2)-1,2-ethanediamine (**12d**).

The conditions employed for the preparation of this compound were those described in General Method A. However, sodium borodeuteride/acetic acid was used as regioselective reductive alkylating agent rather than sodium borohydride/acetic acid (yield 70% (petroleum ether), mp 105-106°); ^1H nmr (deuteriochloroform, 500 MHz): δ 1.06 (s, 6H, CH_3), 2.84 (t, 2H, J = 6.0, NCH_2), 3.26 (broad, 2H, NCH_2), 6.21 (bs, 1H, NH), 6.36 (d, 1H, J = 5.5, ArC_3-H), 7.38 (dd, 1H, J = 7.0, 1.5, ArC_6-H), 7.70 (d, 1H, J = 9.0, ArC_5-H), 7.94 (d, 1H, J = 1.5, ArC_8-H), 8.51 (d, 1H, J = 5.5, ArC_2-H).

N^3-(7-Chloro-4-quinolinyl)-N^1,N^1-diethyl-1,3-propanediamine (**13**).

The conditions employed for the preparation of this compound were those described in General Method B, (yield 90%, mp 58°, lit mp 55-57° [7]); ^1H nmr (deuteriochloroform, 500 MHz): δ 1.14 (t, 6H, J = 7.5, CH_3), 1.94-2.0 (m, 2H, CH_2), 2.69-2.76 (m, 6H, NCH_2), 3.43 (q, 2H, J = 5.5, NCH_2), 6.31 (d, 1H, J = 5.5, ArC_3-H), 7.35 (dd, 1H, J = 9.0, 2.0, ArC_6-H), 7.75 (d, 1H, J = 9.0, ArC_5-H), 7.95 (d, 1H, J = 2.0, ArC_8-H), 8.20 (bs, 1H, NH), 8.49 (d, 1H, J = 5.5, ArC_2-H); ms: (70 eV, electron impact), m/z 291 (M^+), 293.

Anal. Calcd. for $C_{16}H_{22}ClN_3$•3HCl: C, 47.88; H, 6.33; N, 10.47. Found: C, 48.08; H, 7.00; N, 10.48.

N^2-(7-Chloro-4-quinolinyl)-N^1,N^1-diethyl-1,2-propanediamine (**14**).

The conditions employed for the preparation of this compound were those described in General Method A, (yield 70%, as a colorless oil); ^1H nmr (deuteriochloroform, 500 MHz): δ 1.03-1.12 (m, 9H, CH_3), 2.40 (q, 2H, J = 5.5, NCH_2), 2.64 (q, 2H, J = 5.5, NCH_2), 2.93 (d, 2H, J = 7.5, NCH_2), 3.16-3.26 (m, 1H, NCH), 6.34 (d, 1H, J = 6.5, ArC_3-H), 6.49 (bs, 1H, NH), 7.37 (dd, 1H, J = 9.0, 2.0, ArC_6-H), 7.65 (d, 1H, J = 9.0, ArC_5-H), 7.95 (d, 1H, J = 2.0, ArC_8-H), 8.51 (d, 1H, J = 6.5, ArC_2-H); ms: (70 eV, electron impact) m/z 291 (M^+), 293.

Anal. Calcd. for $C_{16}H_{22}ClN_3$•2.0HCl: C, 52.60; H, 6.58; N, 11.50. Found: C, 52.22; H, 6.67; N, 11.42.

N^4-(7-Chloro-4-quinolinyl)-N^1,N^1-diethyl-1,4-butanediamine (**15**).

The conditions employed for the preparation of this compound were those described in General Method B (yield 80% as a colorless powder, mp 76°, lit mp 75-80° [7b]); ^1H nmr (deuteriochloroform, 500 MHz): δ 1.02 (t, 6H, J = 7.5, CH_3), 1.61-1.68 (m, 2H, CH_2), 1.78-1.85 (m, 2H, CH_2), 2.48 (t, 2H, J = 6.5, NCH_2), 2.55 (q, 4H, J = 7.5, NCH_2), 3.26 (q, 2H, J = 5.5, NCH_2), 6.01 (bs, 1H, NH), 6.33 (d, 1H, J = 5.0, ArC_3-H), 7.31 (dd, 1H, J = 9.0, 1.0, ArC_6-H), 7.70 (d, 1H, J = 9.0, ArC_5-H), 7.91 (d, 1H, J = 1.0, ArC_8-H), 8.50 (d, 1H, J = 5.0, ArC_2-H); ms: (70 eV, electron impact), m/z 305 (M^+), 307.

Anal. Calcd. for $C_{17}H_{24}ClN_3$•0.5H_2O: C, 64.70; H, 7.62; N, 13.30. Found: C, 64.20; H, 7.68; N, 13.20.

N^5-(7-Chloro-4-quinolinyl)-N^1,N^1-diethyl-1,5-pentanediamine (**16**).

The conditions employed for the preparation of this compound were those described in General Method A (yield 70% as a colorless powder, mp 74°); ^1H nmr (deuteriochloroform, 500 MHz): δ 1.02 (t, 6H, J = 7.5, CH_3), 1.40-1.48 (m, 2H, CH_2), 1.50-1.62 (m, 2H, CH_2), 1.76-1.85 (m, 2H, CH_2), 2.50 (t, 2H, J = 6.5, NCH_2), 2.59 (q, 4H, J = 7.5, NCH_2), 3.26 (q, 2H, J = 5.5, NCH_2), 5.55 (bs, 1H, NH), 6.39 (d, 1H, J = 5.0, ArC_3-H), 7.37 (dd, 1H, J = 9.0, 1.0, ArC_6-H), 7.65 (d, 1H, J = 9.0, ArC_5-H), 7.93 (d, 1H, J = 1.0, ArC_8-H), 8.52 (d, 1H, J = 5.0, ArC_2-H); ms: (70 eV, electron impact), m/z 319 (M^+), 321.

Anal. Calcd. for $C_{18}H_{26}ClN_3$•0.75H_2O: C, 64.67; H, 7.78; N, 12.57. Found: C, 64.43; H, 6.95; N, 12.65.

N^6-(7-Chloro-4-quinolinyl)-1,6-hexanediamine (**17a**).

This compound was prepared according to a previously published procedure (yield 90% (recrystallized from ethyl acetate), mp 137-138° [13]); ^1H nmr (deuteriochloroform + dimethyl sulfoxide-d_6, 500 MHz): δ 0.8-0.95 (m, 6H, CH_2), 1.13-1.21 (m, 2H, CH_2), 2.10 (t, 2H, J = 5.8, NCH_2), 2.72 (t, 2H, J = 4.4, NCH_2), 5.81 (d, 1H, J = 5.3, ArC_3-H), 6.36 (bs, 1H, NH), 6.75 (dd, 1H, J = 9.2, 1.0, ArC_6-H), 7.24 (d, 1H, J = 1.0, ArC_8-H), 7.62 (d, 1H, J = 9.2, ArC_5-H), 7.86 (d, 1H, J = 5.3, ArC_2-H).

N^6-(7-Chloro-4-quinolinyl)-N^1,N^1-diethyl-1,6-hexanediamine (**17**).

The conditions employed for the preparation of this compound were those described in General Method A (yield 75% as a colorless powder, mp 78°); ^1H nmr (deuteriochloroform, 500 MHz): δ 1.04 (t, 6H, J = 7.5, CH_3), 1.38-1.44 (m, 2H, CH_2), 1.46-1.59 (m, 4H, CH_2), 1.75-1.82 (m, 2H, CH_2), 2.49 (t, 2H, J = 6.5, NCH_2), 2.61 (q, 4H, J = 7.5, NCH_2), 3.32 (q, 2H, J = 5.5, NCH_2), 5.08 (bs, 1H, NH), 6.41 (d, J = 5.0, 1H, ArC_3-H), 7.36 (dd, 1H, J = 9.0, 1.0, ArC_6-H), 7.71 (d, 1H, J = 9.0, ArC_5-H), 7.96 (d, 1H, J = 1.0, ArC_8-H), 8.53 (d, 1H, J = 5.0, ArC_2-H); ms: (70 eV, electron impact), m/z 333 (M^+), 335.

Anal. Calcd. for $C_{19}H_{28}ClN_3$•0.25H_2O: C, 67.45; H, 8.28; N, 12.42. Found: C, 67.39; H, 8.45; N, 12.38.

N^8-(7-Chloro-4-quinolinyl)-N^1,N^1-diethyl-1,8-octanediamine (**18**).

The conditions employed for the preparation of this compound were those described in General Method A (yield 70% as a colorless powder, mp 77°); ^1H nmr (deuteriochloroform, 500 MHz): δ 1.03 (t, 6H, J = 7.5, CH_3), 1.22-1.50 (m, 10H, CH_2),1.72-1.80 (m, 2H, CH_2), 2.40 (t, 2H, J = 6.5, NCH_2), 2.55 (q, 4H, J = 7.5, NCH_2), 3.30 (q, 2H, J = 5.5, NCH_2), 4.96 (bs, 1H, NH), 6.42 (d, 1H, J = 5.0, ArC_3-H), 7.36 (dd, 1H, J = 9.0, 1.0, ArC_6-H), 7.66 (d, 1H, J = 9.0, ArC_5-H), 7.96 (d, 1H, J = 1.0, ArC_8-H), 8.53 (d, 1H, J = 5.0, ArC_2-H); ms: (70 eV, electron impact), m/z 361 (M^+), 363.

Anal. Calcd. for $C_{21}H_{32}ClN_3$•0.5H_2O: C, 67.92; H, 8.89; N, 11.32. Found: C, 68.07; H, 8.80; N, 11.34.

N^{10}-(7-Chloro-4-quinolinyl)-N^1,N^1-diethyl-1,10-decyldiamine (**19**).

The conditions employed for the preparation of this compound were those described in General Method A (yield 75% as a colorless powder, mp 68°); ^1H nmr (deuteriochloroform, 500 MHz): δ 1.02 (t, 6H, J = 7.5, CH_3), 1.22-1.41 (m, 10H, CH_2), 1.42-1.50 (m, 4H, CH_2), 1.70-1.82 (m, 2H, CH_2), 2.40 (t, 2H, J = 7.6, NCH_2), 2.52 (q, 4H, J = 7.5, NCH_2), 3.29 (q, 2H, J = 5.5, NCH_2), 4.98 (bs, 1H, NH), 6.42 (d, 1H, J = 5.5, ArC_3-H),

7.35 (dd, 1H, J = 8.0, 2.0, ArC_6-H), 7.65 (d, 1H, J = 9.0, ArC_5-H), 7.96 (d, 1H, J = 2.0, ArC_8-H), 8.53 (d, 1H, J = 5.0, ArC_2-H); ms: (70 eV, electron impact), m/z 389 (M^+), 391.

Anal. Calcd. for $C_{23}H_{36}ClN_3 \cdot 0.5H_2O$: C, 69.17; H, 9.27; N, 10.52. Found: C, 69.44; H, 9.36; N, 10.46.

N^{12}-(7-Chloro-4-quinolinyl)-N^1,N^1-diethyl-1,12-dodecyldiamine (**20**).

The conditions employed for the preparation of this compound were those described in General Method A (yield 75% as a colorless powder, mp 66°); ^1H nmr (deuteriochloroform, 500 MHz): δ 1.02 (t, 6H, J = 7.5, CH_3), 1.21-1.40 (m, 14H, CH_2), 1.41-1.50 (m, 4H, CH_2), 1.73-1.80 (m, 2H, CH_2), 2.40 (t, 2H, J = 8.5, NCH_2), 2.53 (q, 4H, J = 7.5, NCH_2), 3.27-3.34 (m, 2H, NCH_2), 4.95 (bs, 1H, NH), 6.43 (d, 1H, J = 5.5, ArC_3-H), 7.38 (dd, 1H, J = 7.5, 2.0, ArC_6-H), 7.65 (d, 1H, J = 9.0, ArC_5-H), 7.97 (d, 1H, J = 2.0, ArC_8-H), 8.54 (d, 1H, J = 5.0, ArC_2-H); ms: (70 eV, electron impact), m/z 417 (M^+), 419.

Anal. Calcd. for $C_{25}H_{40}ClN_3 \cdot 2.5H_2O$: C, 64.80; H, 9.50; N, 9.07. Found: C, 65.21; H, 9.31; N, 9.04.

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* Address correspondence to Dr. Krogstad at the Department of Tropical Medicine, SL-29, Tulane School of Public Health and Tropical Medicine, 1501 Canal St., New Orleans, LA 70112.

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