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Antimalarial Activity of Novel 5-Aryl-8-Aminoquinoline Derivatives

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In an attempt to separate the antimalarial activity of tafenoquine (**3**) from its hemolytic side effects in glucose-6-phosphate dehydrogenase (G6PD) deficiency patients, a series of 5-aryl-8-aminoquinoline derivatives was prepared and assessed for antimalarial activities. The new compounds were found metabolically stable in human and mouse microsomal preparations, with $t_{1/2} > 60$ min, and were equal to or more potent than primaquine (**2**) and **3** against *Plasmodium falciparum* cell growth. The new agents were more active against the chloroquine (CQ) resistant clone than to the CQ-sensitive clone. Analogues with electron donating groups showed better activity than those with electron withdrawing substituents. Compounds **4bc**, **4bd**, and **4be** showed comparable therapeutic index (TI) to that of **2** and **3**, with TI ranging from 5 to 8 based on IC_{50} data. The new compounds showed no significant causal prophylactic activity in mice infected with *Plasmodium berghei* sporozoites, but are substantially less toxic than **2** and **3** in mouse tests.

Introduction

Malaria is a life-threatening parasitic disease responsible for 300−500 million acute illnesses and 1−3 million deaths annually. The severity of the disease is illustrated by the fact that malaria kills approximately one child under the age of 5 years every 30 s, or 3000 per day.[1] Although many effective antimalarials have been developed so far, the extent of malaria infection is worsening, mainly due to the rapid spread of drug resistant malarial strains in many parts of the world.

The 8-aminoquinoline (8-AQ[a]) antimalarials,[2−4] such as pamaquine (**1**) and primaquine (**2**), have attracted much interest as chemotherapeutic and prophylactic agents against the liver stages of *Plasmodium vivax* and *Plasmodium falciparum* malarias (Figure 1). The 8-AQs are the only FDA approved drugs for the treatment of relapses in *Plasmodium* infections. However, the clinical value of this class is compromised by the toxic side effects, namely, methemoglobinemia and hemolytic anemia in patients with deficiency in glucose-6-phosphate dehydrogenase (G6PD) activity.[5,6]

G6PD plays a crucial role in the oxidant defense system of red blood cells. G6PD is required for the reduction of NADP to NADPH, which, in turn, is needed for the maintenance of glutathione in the reduced form (GSH). Because GSH works to remove the oxidant stress which leads to cell damage, the lack of G6PD activity enhances the sensitivity of the red cells to the oxidant assault.[7] It is generally believed that the metabolites of 8-AQ are the toxic species to erythrocytes, not parent compounds, at clinically relevant concentration.[8] The hemolytic toxicity and toxic metabolites identification of 8-AQ antimalarials have attracted broad interest among researchers in recent years.[9−13] However, the identities of the toxic species and the mechanism underlying hemotoxicity have remained unclear due to instability of the metabolites. In general, putative 5-hydroxy-8-aminoquinolines are thought to be responsible for the hemotoxic compounds.[9−13] These metabolites are capable of forming semiquinoneimine radical and iminoquinolinone under physiological conditions, leading to the subsequent generation of hydrogen peroxide and oxidative stress in erythrocytes[14] (Scheme 1). To avoid the quinoneimine metabolite formation and thus the hemolytic side effects, a series of derivatives of **2** were reported over the years.[3b,15−17] However, the new derivatives of **2** either lost antimalarial activity or retained both activity and hemolytic toxicity.

Tafenoquine (**3**) is a 5-phenoxyl derivative of primaquine. The drug is generally less toxic and has a longer plasma half-life (2−3 weeks) than **2**.[18] In addition, **3** has been shown to be at least 10 times more potent than **2**.[19−21] One of the reasons by which **3** is less toxic than the other 8-AQ derivatives is thought to be the resistance of the 5-(*m*-trifluoromethylphenyl) group to enzymatic cleavage to generate the phenolic metabolite which in turn forms the semiquinoneimine.[22] However, **3** also exhibited the toxic side effects of hemolysis and methemoglobinemia, although to a lesser extent than **2**.[18,19] The results suggest that the 3-trifluoromethylphenyloxyl group at the 5-position of **3** may be hydrolyzed to form an 8-iminoquinoline derivative (**3b** and **3b′**) in vivo as shown in Scheme 2. Indeed, extensive metabolic conversion of **3** to putative metabolites, **3b**−**c**, **3b′**−**c′**, in rat liver microsomes was reported.[22] However, no information is available on how this transformation occurs.

From the chemistry point of view, direct nucleophilic displacement of the 3-trifluoromethylphenyloxyl group at the 5-position of tafenoquine by water or other biological substances is not likely to take place until tafenoquine is metabolically oxidized to the corresponding 5-aryloxonium

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[a] Abbreviations: CQ, chloroquine; TQ, tafenoquine; PQ, primaquine; G6PD, glucose-6-phosphate dehydrogenase; 8-AQ, 8-aminoquinoline; EE, exoerythrocytic; MQ, mefloquine.

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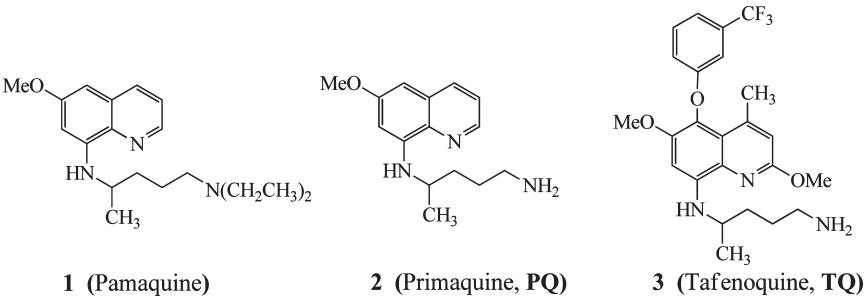
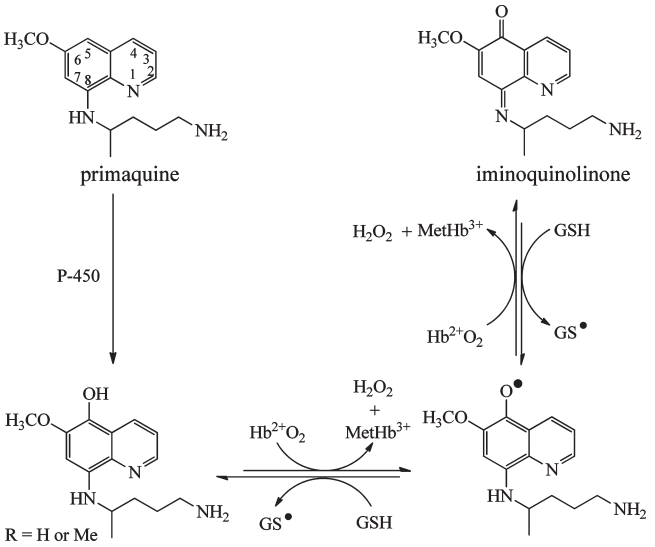


Figure 1. Chemical structures of 8-aminoquinoline antimalarials.

Scheme 1. Proposed Pathways for Free Radical, Hydrogen Peroxide, and Methemoglobin Production by PQ in the Erythrocyte (Adapted from ref 14)



quinoneimine (**3a**) as shown in Scheme 2. 5-Aryloxonium quinoneimine **3a** is expected to be hydrolyzed readily to the toxic quinoneimine **3b** and/or **3b′**. It is recognized that the antimalarial efficacy as well as the toxicity of 8-AQ antimalarials may be derived from the formation of quinoneimine metabolites.[8−14] However, there is no convincing evidence to substantiate this contention.

In this study, a series of new 5-aryl substituted 8-AQ derivatives **4** and **5** (Scheme 2) were designed, prepared, and tested in an attempt to probe the possibility of separating the antimalarial activity from the hemolytic toxicity of 8-AQ. The chemical structure of the new compounds **4** and **5** are almost identical to the corresponding 5-aryloxy analogues of **3**, except missing an oxygen atom at the 5-position of the quinoline ring. It is anticipated that the new compounds will retain the antimalarial activity of tafenoquine, if the parent molecule is the active species, and not the metabolites. As far as the new compounds are expected to be metabolically stable and generate no toxic semiquinoimine metabolites like that of **2** and **3**, they may be devoid of hemolytic side effects, if metabolites are responsible for the toxicity.

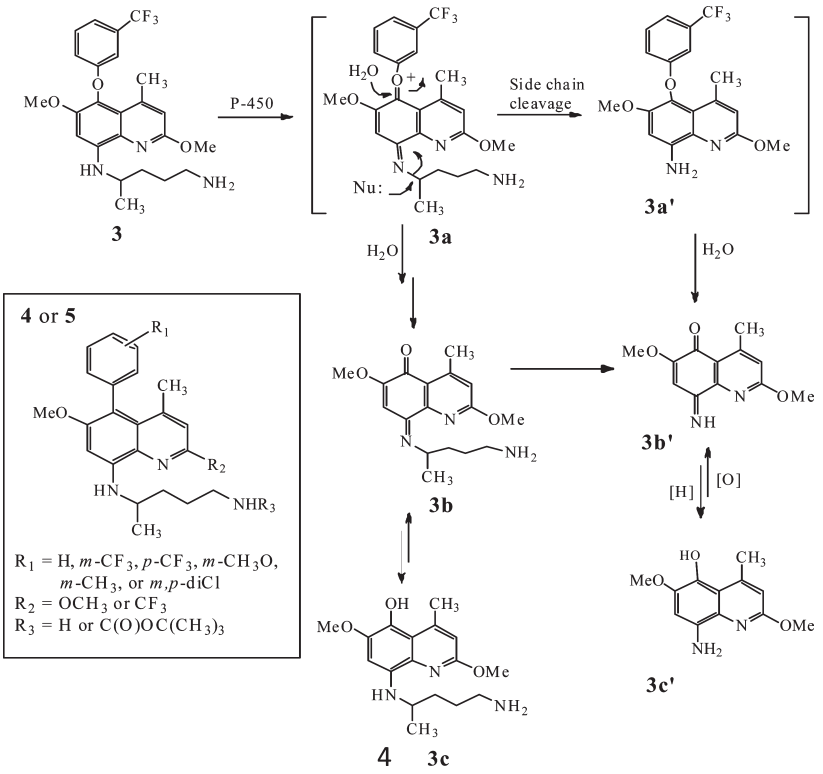
Chemistry

The new deoxo-tafenoquine analogues **4aa**−**4af**, **4ba**−**4be**, and **5bb**−**5be** were prepared as shown in Scheme 3. The procedure for the preparation of **3** was adapted to prepare the new compounds designed in this study.[23,24] Two subgroups of the new compounds were prepared with the substituent at the 2-position of the 8-AQ being either a 2-methoxy or 2-trifluoromethyl group. The Suzuki coupling reaction was used as the key step to introduce the aryl substituent at the 5-position of the 8-AQ ring, instead of displacement of the 5-chloro-8AQ with a phenolic nucleophile as in the synthesis of 5-aryloxy- analogues. Different intermediates, **8a** or **8b**, were used to prepare the two subclasses of the final products **4aa**−**af** and **4ba**−**be**. The intermediate 2,6-dimethoxy-4-methylquinoline (**8a**) was obtained by treatment of the commercially available starting material, 2-chloro-6-methoxy-4-methylquinoline (**6**), with sodium methoxide. The intermediate **8b** was prepared by annulations of commercially available *p*-anisidine (**7**) and 1,1,1-trifluoromethyl-2,4-pentanedione under the catalysis of polyphosphoric acid.

Although the annulation reaction may yield two isomeric products, 2-CF_3- and 4-CF_3-quinolines, the desired 2-CF_3 isomer was the predominant product of the reaction. The structure of **8b** was established by 2-D NMR data. The correlation between the 4-methyl-AQ singlet at 2.73 ppm and the 5-H-AQ singlet at 7.19 ppm as well as the correlation between the 5-H-AQ singlet at 7.19 ppm and the 6-OCH_3-AQ singlet (3.98 ppm) on NOESY are shown in Figure 2. Chlorination of **8a** and **8b** was achieved using sulfuryl chloride to give **9a** and **9b** in 73% and 79% yields, respectively. Subsequent nitration of **9a** and **9b** using phosphorus pentoxide and potassium nitrate gave 5-chloro-2,6-dimethoxy-4-methyl-8-nitroquinoline (**10a**) and 5-chloro-6-methoxy-4-methyl-8-nitro-2-trifluoromethyl-quinoline (**10b**) in 73% and 47% yield, respectively. Compound **10a** was a known compound. The newly synthesized **10a** was identical to the reported compound in NMR and melting point.[23,24] Compound **10b**, however, is a new compound. The position of the trifluoromethyl group at the 2-position and the nitro group at the 8-position were established by the correlation of the 4-methyl peak at 3.20 ppm and the carbon-8 carbon peak at 144.03 ppm on HMBC as shown in Figure 2.

The 5-aryl-2,6-dimethoxy-4-methyl-8-nitroquinolines **11aa**−**af** was prepared in good to excellent yield from 2-methoxy-5-chloro-8-aminoquinoline **10a** by Suzuki coupling reactions with a series of arylboronic acids.[24,25] 2-Trifluoromethylquinoline derivatives **10b**, under the same Suzuki coupling reaction conditions, gave slightly lower yields of **11ba**−**be**. It was noted that a phase transfer catalyst is essential for smooth Suzuki coupling reactions between **10a** and phenylboronic acid.[26] The yield of the reaction was poor and the majority of the starting material **10a** was recovered unchanged when no phase transfer catalyst was used. Furthermore, separation of the byproduct from the desired product by column chromatography was tedious and frustrating. However, when the reaction was carried out with a phase transfer catalyst,

Scheme 2. Proposed Metabolic Pathway of Tafenoquine (**3**) to Quinoneimines (**3b** and **3b′**)



tetrabutylammonium bromide (TBAB),[27,28] the yield of the desired product **11aa** improved and the byproduct formation decreased greatly. Catalytic hydrogenation of **11aa**−**11af** and **11ba**−**11be**, using palladium on activated carbon or slurry of Raney nickel in water, afforded the 8-aminoquinolines **12aa**−**12af** or **12ba**−**12be** in near quantitative yields. The amines obtained were pure enough for the next step reactions without further purification.

Incorporation of the amino-alkyl side chain to the 8-amino group of **12aa**−**af** and **12ba**−**be** was achieved by treatment of the 8-amino-AQ with either (i) 2-(4-iodopentyl)-1,3-isoindolinedione (**13**) and diisopropylamine[23] or (ii) 2-(4-oxopentyl)-1,3-isoindolinedione (**14**) and borane−pyridine complex.[24] Because the intermediate **13** and **14** were both unstable under basic or acidic conditions, the coupling reactions gave poor yields of **15aa**−**af** or **15ba**−**be** and numerous side products when a 1:1 ratio of the starting material and the reagent was used. However, moderate to excellent yields of the desired products **15aa**−**af** or **15ba**−**be** was obtained when excess iodide **13** or ketone **14** (>2 mol equiv) was added in small portions until the starting materials **12aa**−**af** or **12ba**−**be** was consumed.

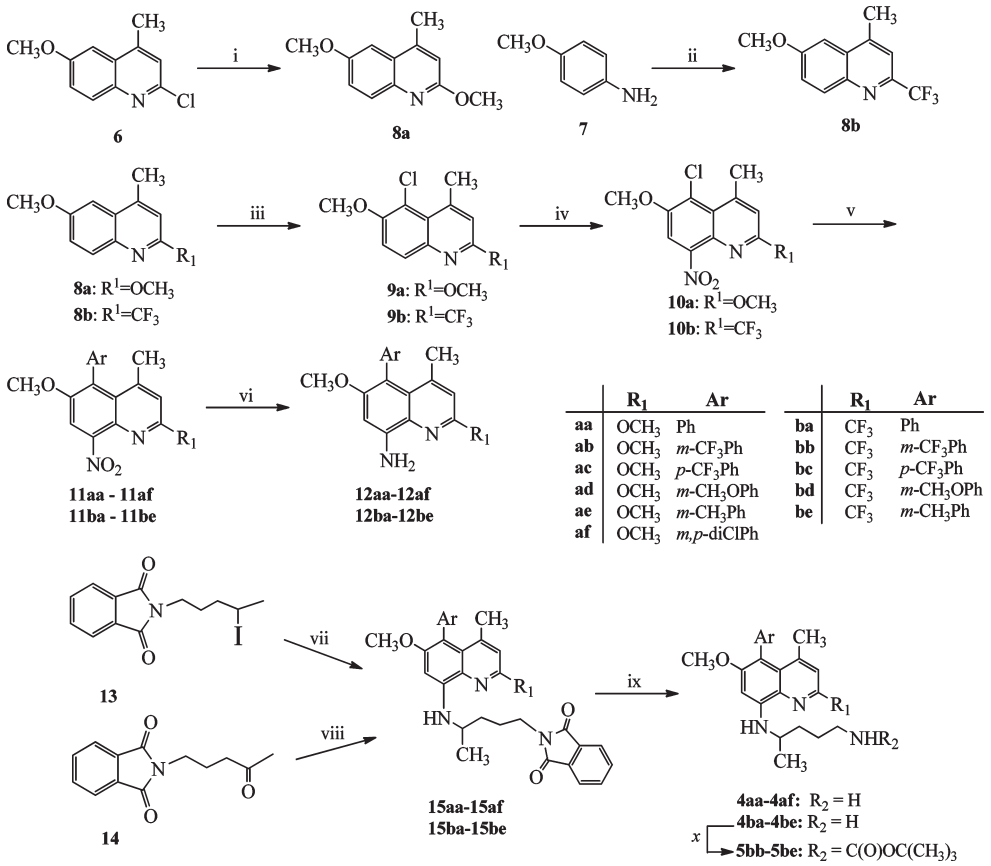
The final products, 2-methoxyquinoline compounds **4aa**−**af**, were obtained by treatment of **15aa**−**af** with hydrazine monohydrate to yield **4aa**−**af** as gummy oil which was converted to succinic acid salts. The succinic acid salts were purified by recrystallization from acetonitrile. Utilizing the same method, 2-trifluoromethylquinoline analogues **4ba**−**be** were obtained as a solid free base from **15ba**−**be**. Like the 8-AQ derivatives, i.e., **2** and **3**, the deoxo-TQ analogues, **4aa**−**af** and **4ba**−**be**, are gummy and the succinic acid salts are hygroscopic. Thus, good elemental analysis results were difficult to obtain without adjustment for H_2O or solvents, especially **4bb**−**bd**. The gummy and hygroscopic problems were solved by conversion of the final products to the crystalline carbamate derivatives **5bb**−**be**. With the side chain terminal amino group of **4bb**−**be** masked by t-Boc, all 4 carbamates **5bb**−**be** are crystalline, form no hydrate, and gave good elemental analysis results. The structures of all compounds were characterized by LC/MS, infrared (IR), ^{1}H- and ^{13}C- NMR spectrometry. Elemental analyses were performed only on final products.

Experimental Section

Melting points were determined in open capillary tubes on an OptiMelt melting point apparatus (Standard Research Systems, USA) and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded using Bruker Avance-300 and Bruker Avance 600 spectrometers (Bruker Instrument, Inc., Wilmington, DE). Chemical shifts are given in ppm (δ) relative to tetramethylsilane (TMS) as internal standard. Analytical thin-layer chromatography (TLC) was performed using HPLC-HLF normal phase 150 μm silica gel plates (Analtech, Newark, DE). Visualization of the developed chromatogram was performed with UV absorbance. Flash chromatography was conducted with silica gel 60 Å (200−400 mesh) from Sigma-Aldrich Co. Solvents and reagents obtained from commercial sources were used without purification, unless noted. Reactions were carried out under an inert atmosphere of nitrogen. Elemental analysis was performed by Atlantic Microlab, Inc. (Norcross, GA). Where analyses are indicated by symbols of the elements, the analytical results obtained were within ±0.4% of the theoretical values. An LC/UV−vis/ion trap mass spectrometer was employed for purity analysis and chromophore properties. The system consisted of an Agilent 1100 series LC-UV/vis system in line with a ThermoFinnigan (now Thermo Scientific; Waltham, MA) LCQ MS equipped with electrospray ionization (ESI) source. Samples were analyzed using shallow CH_3CN: 1% HCOOH/H_2O gradients at analytical flow rates. The purity of the final products was ≥ 95%.

2, 6-Dimethoxy-4-methyl-quinoline (8a). A 25% $NaOCH_3$/CH_3OH solution (55 mL, 240 mmol) was added to a solution of 2-chloro-6-methoxy-4-methylquinoline (**6**) (10 g, 48 mmol) in dry MeOH (120 mL). The resulting mixture was refluxed for

Scheme 3. Synthetic Scheme of Compounds **4aa**−**4af**, **4ba**−**4be**, and **5bb**−**5be**



	R_1	Ar		R_1	Ar
aa	OCH_3	Ph	ba	CF_3	Ph
ab	OCH_3	*m*-CF_3Ph	bb	CF_3	*m*-CF_3Ph
ac	OCH_3	*p*-CF_3Ph	bc	CF_3	*p*-CF_3Ph
ad	OCH_3	*m*-CH_3OPh	bd	CF_3	*m*-CH_3OPh
ae	OCH_3	*m*-CH_3Ph	be	CF_3	*m*-CH_3Ph
af	OCH_3	*m,p*-diClPh			

Reagents and conditions: (i) NaOMe, MeOH, reflux, 42 h; (ii) 1,1,1-trifluoromethyl-2,4-pentanedione, polyphosphoric acid, 120 °C, 40 h; (iii) SO_2C1_2, AcOH, 60 °C, 10 min to 3 h; (iv) P_2O_5, KNO_3, triethylphosphate, 35 °C, 30 min to 19 h; (v) $Pd(OAc)_2$, $ArB(OH)_2$, PPh_3, Na_2CO_3, tetrabutylammonium bromide, 1,2-dimethoxyethane, H_2O, reflux, 14−39 h or $Pd(PPh_3)_4$, $ArB(OH)_2$, Na_2CO_3, tetrabutylammonium bromide, 1, 2-dimethoxyethane, H_2O, reflux, 5−20 h; (vi) H_2, 10% Pd/C or Raney Ni, MeOH, or AcOEt, 2−24 h; (vii) **12aa**−**12af**, $(i\text{-}Pr)_2NH$, 27−49 h; (viii) **12ba**−**12be**, BH_3-pyridine, AcOH, 20−24 h; (ix) $NH_2NH_2 \cdot H_2O$, EtOH, 1−3 h; (x) $(t\text{-}Boc)_2O$, triethylamine, $CHC1_3$, 21−24 h.

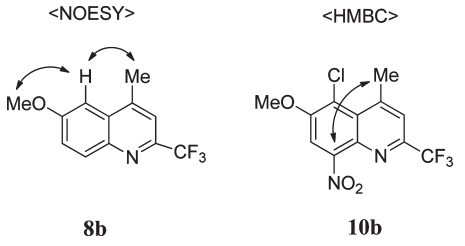


Figure 2. Determination of the structures of **8b** and **10b**.

19 h, followed by addition of another 22 mL of 25% CH_3ONa/CH_3OH solution (96 mmol) and refluxed for an additional 24 h. The reaction mixture was evaporated in vacuo to give a gum. Water (100 mL) was added to the gummy residue, and the pH of the suspension was adjusted to about 8 with 2N HCl. The aqueous solution was extracted with $CHCl_3$ (100 mL × 3), and the $CHCl_3$ extracts were combined, washed with brine, dried over Na_2SO_4, and concentrated in vacuo to dryness. The residue was purified with a silica gel column, eluted with 5% EtOAc/hexane, to give 9.2 g (94%) of the desired product **8a** as a colorless solid. ^{1}H NMR ($CDCl_3$): δ 7.77 (d, J = 9.1 Hz, 1H), 7.27 (dd, J = 9.1 and 2.8 Hz, 1H), 7.15 (d, J = 2.8 Hz, 1H), 6.74 (s, 1H), 4.02 (s, 3H), 3.91 (s, 3H), 2.58 (s, 3H). IR (neat): 1611, 1577, 1514, 1465, 1448, 1430, 1413, 1344, 1240, 1198, 1185, 1169, 1125, 1033, 987, 955, 918, 875, and 832 cm^{-1}. MS (ESI): m/z 204 $[M + 1]^+$.

6-Methoxy-4-methyl-2-trifluoromethyl-quinoline (8b). *p*-Anisidine (**7**) (10 g, 81 mmol) in polyphosphoric acid (60 g) was heated to 120 °C. 1,1,1-Trifluoromethyl-2,4-pentanedione (19 g, 122 mmol) was added dropwise with stirring and heated at 120 °C for 40 h. On cooling, the solution was diluted with H_2O (150 mL) and the viscous suspension was basified with 20% NaOH aqueous solution and extracted with $CHCl_3$ (150 mL × 3). The $CHCl_3$ extracts were combined, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified with a silica gel column, eluted with hexane/$CHCl_3$ (1: 3 v/v) mixed solvent, to give 14 g (69%) of the desired product (**8b**) as a yellow solid. ^{1}H NMR ($CDCl_3$): δ 8.11 (d, J = 9.3 Hz, 1H), 7.54 (s, 1H), 7.45 (dd, J = 9.3 and 2.7 Hz, 1H), 7.19 (d, J = 2.7 Hz, 1H), 3.98 (s, 3H), 2.73 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 159.0, 145.0, 142.8, 132.0, 130.0, 123.6, 123.0, 120.0, 117.6, 101.3, 55.5, 19.2. IR (neat): 1624, 1507, 1480, 1368, 1288, 1232, 1166, 1141, 1119, 1097, 1019, 927, 913, 871, and 841 cm^{-1}. MS (ESI): m/z 242 $[M + 1]^+$.

5-Chloro-2,6-dimethoxy-4-methyl-quinoline (9a). A solution of compound **8a** (9.0 g, 44 mmol) in glacial acetic acid (80 mL) was heated to 60 °C. To the solution, sulfuryl chloride (9.0 g, 66 mmol) in glacial acetic acid (20 mL) was added dropwise over 20 min. The resulting solution was stirred for 10 min at 60 °C and then poured into 50 mL of ice−water. The AcOH/H_2O mixture was evaporated to dryness under reduced pressure to give a crude product which was dissolved in 100 mL of H_2O, basified with 20% NaOH, and extracted with $CHCl_3$ (100 mL × 3). The combined $CHCl_3$ extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo to give 7.7 g (73%) of the desired product **9a** as a brown solid. ^{1}H NMR ($CDCl_3$): δ 7.76 (d, J = 9.2 Hz, 1H), 7.34 (d, J = 9.2 Hz, 1H), 6.71 (s, 1H), 4.01

(s, 3H), 3.98 (s, 3H), 2.97 (s, 3H). IR (neat): 1648, 1603, 1585, 1517, 1473, 1378, 1366, 1353, 1339, 1326, 1280, 1269, 1227, 1199, 1183, 1096, 1067, 1057, 1041, 872, and 822 cm^{-1}. MS (EI): m/z 237 $[M]^+$.

5-Chloro-6-methoxy-4-methyl-2-trifluoromethyl-quinoline (9b). Same method to prepare **9a** was used to prepare **9b** from **8b** (22 g, 91 mmol) and sulfuryl chloride (19 g, 137 mmol) to give crude solid product which was washed with hexane/$CHCl_3$ (1:3 v/v) mixed solvent several times to give 14 g (56%) of **9b** as a pale-yellow solid. The filtrate and the washing solutions were combined, evaporated to dryness in vacuo, and applied to a silica gel column. Upon elution with hexane and $CHCl_3$ (1:3 v/v) mixed solvent, additional desired product **9b** (6 g, 23%) was obtained. ^1H NMR ($CDCl_3$): δ 8.14 (d, J = 9.3 Hz, 1H), 7.56 (d, J = 9.3 Hz, 1H), 7.48 (s, 1H), 4.07 (s, 3H), 3.13 (s, 3H). IR (neat): 1508, 1468, 1434, 1382, 1373, 1271, 1187, 1175, 1130, 1114, 1091, 1050, 942, 920, 873, and 831 cm^{-1}. MS (EI): m/z 277 $[M]^+$.

5-Chloro-2,6-dimethoxy-4-methyl-8-nitro-quinoline (10a). Phosphorus pentoxide (15.7 g, 110 mmol) was added to a solution of **9a** (7.7 g, 32 mmol) in triethylphosphate (90 mL). The pale-yellow suspension was stirred for 1 h at rt and then heated to 35 °C. To the suspension, KNO_3 (6.6 g, 65 mmol) and MeOH (60 mL) were added successively and the resulting mixture was stirred and refluxed for 15 min. After cooling with an ice-bath, the crude product was collected, washed successively with H_2O (80 mL × 3) and MeOH (80 mL × 1), and dried under vacuum at 56 °C to give 7.4 g (73%) of the desired product, mp 200−201 °C (lit.[23,24] 199−200 °C). ^1H NMR ($CDCl_3$): δ 7.62 (s, 1H), 6.83 (s, 1H), 4.02 (s, 3H), 3.98 (s, 3H), 3.00 (s, 3H). IR (neat): 1606, 1534, 1518, 1467, 1375, 1352, 1321, 1272, 1193, 1174, 1063, 1054, 978, 895, 882, 860, and 780 cm^{-1}. MS (EI): m/z 282 $[M]^+$.

5-Chloro-6-methoxy-4-methyl-8-nitro-2-trifluoromethyl-quinoline (10b). Phosphorus pentoxide (23 g, 160 mmol) was added to a solution consisting of **9b** (13 g, 47 mmol) and triethylphosphate (100 mL). The pale-yellow suspension was stirred at rt for 1 h, heated to 35 °C, and followed by addition of KNO_3 (9.5 g, 95 mmol). The reaction mixture was stirred at 35 °C for additional 19 h and poured into an excess amount of ice−water (ca. 200 mL). The resulting slurry was kept at 4 °C for 1 h and the precipitates were collected. The crude product was dissolved in water (ca. 150 mL), basified with 20% NaOH, and extracted with $CHCl_3$ (100 mL × 3). The $CHCl_3$ extracts were combined, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by a silica gel column, eluted with hexane and $CHCl_3$ (1:3 v/v) mixed solvent, to give 7.2 g (47%) of the desired product **10b**. ^1H NMR ($CDCl_3$): δ 8.57 (s, 1H), 7.68 (s, 1H), 4.13 (s, 3H), 3.20 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 148.8, 146.6, 144.0, 130.2, 127.4, 126.3, 122.9, 120.0, 115.9, 62.9, 25.9. IR (neat): 1542, 1424, 1365, 1262, 1183, 1128, 1096, 1036, 981, 935, 896, and 859 cm^{-1}. MS (EI): m/z 320 $[M]^+$.

General Synthetic Procedure for 5-Aryl-2,6-dimethoxy-4-methyl-8-nitro-quinoline (11aa−af). Compound **10a** (4.2 g, 15 mmol) was dissolved in dry dimethoxyethane (126 mL). To the solution was added palladium acetate (0.25 g, 1.0 mmol), phenylboronic acid (2.4 g, 19 mmol), triphenylphosphine (0.6 g, 2.0 mmol), tetrabutylammonium bromide (1.0 g, 3.0 mmol), and Na_2CO_3 (3.2 g, 30 mmol) in H_2O (10 mL). The suspension was refluxed for 23 h, and additional tetrabutylammonium bromide (38.4 g, 2.4 mmol) was added. The mixture was further refluxed for 16 h and the solvents were evaporated to dryness in vacuo. A saturated aqueous solution of $NaHCO_3$ (50 mL) was added to the dry residue and the mixture was extracted with $CHCl_3$ (100 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The crude product was purified using a silica gel column, eluted with $CHCl_3$ and hexane (1:1 v/v) mixed solvent, to give 4.4 g (91%) of the desired product **11aa** as a pale-brown solid. ^1H NMR ($CDCl_3$): δ 7.05 (s, 1H), 7.44−7.42 (m, 3H), 7.26−7.21 (m, 2H), 6.67 (s, 1H), 3.99 (s, 3H), 3.77 (s, 3H), 1.80 (s, 3H). MS (EI): m/z 324 $[M]^+$.

2,6-Dimethoxy-4-methyl-8-nitro-5-(3-trifluoromethylphenyl)-quinoline (11ab). The same procedure was used to prepare **11ab**, using 3-trifluoromethylphenylboronic acid as the starting material. Yield: 99%. ^1H NMR ($CDCl_3$): δ 7.80 (d, J = 7.7 Hz, 1H), 7.64 (s, 1H), 7.57 (t, J = 7.7 Hz, 1H), 7.51 (s, 1H), 7.44 (d, J = 7.7 Hz, 1H), 6.71 (s, 1H), 4.00 (s, 3H), 3.75 (s, 3H), 1.76 (s, 3H). MS (EI): m/z 392 $[M]^+$.

2,6-Dimethoxy-4-methyl-8-nitro-5-(4-trifluoromethylphenyl)-quinoline (11ac). The title compound was prepared by the same procedure as described for the preparation of **11aa**, using 4-trifluoromethylphenylboronic acid as the starting material. Yield: 86%. ^1H NMR ($CDCl_3$): δ 7.71 (d, J = 8.0 Hz, 2H), 7.64 (s, 1H), 7.38 (d, J = 8.0 Hz, 2H), 6.71 (s, 1H), 3.99 (s, 3H), 3.78 (s, 3H), 1.79 (s, 3H). MS (EI): m/z 392 $[M]^+$.

2, 6-Dimethoxy-5-(3-methoxyphenyl)-4-methyl-8-nitro-quinoline (11ad). Compound **11ad** was prepared by the same general procedure using 3-methoxyphenylboronic acid as the starting material. Yield: 62%. ^1H NMR ($CDCl_3$): δ 7.64 (s, 1H), 7.38−7.32 (m, 1H), 6.99−6.96 (m, 1H), 6.83−6.81 (m, 1H), 6.79−6.78 (m, 1H), 6.68 (s, 1H), 3.99 (s, 3H), 3.83 (s, 3H), 3.79 (s, 3H), 1.88 (s, 3H). IR (neat): 1606, 1533, 1519, 1473, 1455, 1437, 1376, 1292, 1266, 1193, 1158, 1059, 1046, 775, and 700 cm^{-1}. MS (EI): m/z 354 $[M]^+$.

2, 6-Dimethoxy-4-methyl-5-(3-methylphenyl)-8-nitro-quinoline (11ae). The same general procedure was used to prepare **11ae** using 3-methylphenylboronic acid as the starting material. Yield: 64%. ^1H NMR ($CDCl_3$): δ 7.65 (s, 1H), 7.35−7.24 (m, 2H), 7.06 (s, 1H), 7.04 (s, 1H), 6.69 (s, 1H), 4.01 (s, 3H), 3.76 (s, 3H), 2.41 (s, 3H), 1.83 (s, 3H). IR (neat): 1604, 1535, 1442, 1371, 1345, 1324, 1196, 1159, 1064, 1049, 773, and 704 cm^{-1}. MS (ESI): m/z 339 $[M + 1]^+$.

5-(3,4-Dichlorophenyl)-2,6-dimethoxy-4-methyl-8-nitro-quinoline (11af). Compound **11af** was prepared by the same procedure using 3,4-dichlorophenylboronic acid as the starting material. Yield: 99%. ^1H NMR ($CDCl_3$): δ 7.63 (s, 1H), 7.53 (d, J = 8.2 Hz, 1H), 7.36 (d, J = 2.0 Hz, 1H), 7.10 (dd, J = 8.2 and 2.0 Hz, 1H), 6.73 (s, 1.0 H), 4.00 (s, 3H), 3.80 (s, 3H), 1.90 (s, 3H). IR (neat): 1606, 1532, 1373, 1273, 1193, 1166, 1068, 827, 793, and 697 cm^{-1}. MS (EI): m/z 392 $[M]^+$.

General Procedure for the Preparation of 5-Aryl-6-methoxy-4-methyl-8-nitro-2-trifluoro-methylquinoline (11ba−be). Suzuki coupling reaction as described for the synthesis of **11aa−af** was used to prepare compounds **11ba−be** from compound **10b** (2.0 g, 6.2 mmol) and an appropriate arylboronic acid.

6-Methoxy-4-methyl-8-nitro-5-phenyl-2-trifluoromethyl-quinoline (11ba). Compound **11ba** was obtained as dark-brown oil by the general procedure using phenylboronic acid as reagent. Yield: 73%. ^1H NMR ($CDCl_3$): δ 8.68 (s, 1H), 7.53−7.48 (m, 4H), 7.40−7.35 (m, 2H), 3.52 (s, 3H), 2.02 (s, 3H). IR (neat): 1539, 1431, 1362, 1269, 1201, 1187, 1139, 1038, 936, 847, 805, 762, and 754 cm^{-1}. MS (EI): m/z 362 $[M]^+$.

6-Methoxy-4-methyl-8-nitro-2-trifluoromethyl-5-(3-trifluoromethylphenyl)-quinoline (11bb). Compound **11bb** was obtained as a yellow solid by the same procedure using 3-trifluoromethylphenylboronic acid as reagent. Yield: 44%. ^1H NMR ($CDCl_3$): δ 8.75 (s, 1H), 7.83−7.81 (m, 1H), 7.71−7.53 (m, 4H), 3.53 (s, 3H), 1.99 (s, 3H). IR (neat): 1538, 1315, 1266, 1166, 1127, 1095, 1074, 1037, and 806 cm^{-1}. MS (EI): m/z 430 $[M]^+$.

6-Methoxy-4-methyl-8-nitro-2-trifluoromethyl-5-(4-trifluoromethylphenyl)-quinoline (11bc). The title compound was obtained as red oil by the same general procedure using 4-trifluoromethylphenyl-boronic acid as reagent. Yield: 62%. ^1H NMR ($CDCl_3$): δ 8.72 (s, 1H), 7.79 (d, J = 8.1 Hz, 2H), 7.55−7.50 (m, 3H), 3.53 (s, 3H), 2.01 (s, 3H). IR (neat): 1541, 1324, 1271, 1126, 1110, 1067, 1036, and 934 cm^{-1}. MS (ESI): m/z 431 $[M + 1]^+$.

6-Methoxy-5-(3-methoxyphenyl)-4-methyl-8-nitro-2-trifluoromethyl-quinoline (11bd). Compound **11bd** was obtained as yellow solid by the same procedure for the preparation of **11be** using 3-methoxyphenylboronic acid as reagent. Yield: 64%. ^1H NMR ($CDCl_3$): δ 8.67 (s, 1H), 7.53 (s, 1H), 7.44−7.39 (m, 1H),

7.07−7.04 (m, 1H), 6.92−6.91 (m, 2H), 3.86 (s, 3H), 3.57 (s, 3H), 2.10 (s, 3H). IR (neat): 1548, 1468, 1430, 1274, 1254, 1150, 1136, 1115, 1033, 916, 791, and 648 cm^{-1}. MS (EI): m/z 392 $[M]^+$.

6-Methoxy-4-methyl-5-(3-methylphenyl)-8-nitro-2-trifluoromethyl-quinoline (11be). Same method was used to prepare **11be**, using 3-methylphenylboronic acid as reagent. Yield: 78%. ^1H NMR ($CDCl_3$): δ 8.65 (s, 1H), 7.52 (s, 1H), 7.39 −7.31 (m, 2H), 7.18−7.15 (m, 2H), 3.53 (s, 3H), 2.43 (s, 3H), 2.04 (s, 3H). IR (neat): 1543, 1537, 1370, 1267, 1227, 1192, 1133, 1039, 1032, and 791 cm^{-1}. MS (EI): m/z 376 $[M]^+$.

General Procedure for the Preparation of 8-Amino-5-aryl-2,6-dimethoxy-4-methyl-quinoline (12aa−af). A solution of compound **11aa** (1.0 g, 3.1 mmol) in CH_3OH (200 mL) with a catalytic amount of 10% palladium on activated carbon (217 mg, 0.9 mmol) was hydrogenated under 50 psi pressure at rt for 2 h. The reaction mixture was filtered through a layer of Celite, and the yellow solution was evaporated in vacuo to give 0.9 g (99%) of the crude product **12aa**, which was pure enough for the next step reaction without further purification. Yield: 99%. ^1H NMR ($CDCl_3$): δ 7.35−7.31 (m, 3H), 7.27−7.24 (m, 2H), 6.77 (s, 1H), 6.59 (s, 1H), 4.92 (br s, 2H), 4.02 (s, 3H), 3.70 (s, 3H), 1.79 (s, 3H). MS (EI): m/z 294 $[M]^+$.

8-Amino-2,6-dimethoxy-4-methyl-5-(3-trifluoromethylphenyl)-quinoline (12ab). Compound **12ab** was prepared by catalytic reduction of **11ab** as described for the preparation of **12aa** except that the reduction was conducted under atmospheric pressure. Yield: 99%. ^1H NMR ($CDCl_3$): δ 7.61−7.45 (m, 4H), 6.75 (s, 1H), 6.52 (s, 1H), 4.97 (br s, 2H), 4.02 (s, 3H), 3.69 (s, 3H), 1.75 (s, 3H). MS (EI): m/z 362 $[M]^+$.

8-Amino-2,6-dimethoxy-4-methyl-5-(4-trifluoromethylphenyl)-quinoline (12ac). The title compound was prepared by catalytic reduction of **11ac**. Yield: 94%. ^1H NMR ($CDCl_3$): δ 7.62 (d, J = 7.8 Hz, 2H), 7.38 (d, J = 7.8 Hz, 2H), 6.77 (s, 1H), 6.62 (s, 1H), 4.02 (s, 3H), 3.69 (s, 3H), 1.77 (s, 3H). MS (ESI): m/z 363 $[M + 1]^+$.

8-Amino-2,6-dimethoxy-5-(3-methoxyphenyl)-4-methyl-quinoline (12ad). Compound **12ad** was prepared by the same procedure from **11ad**, except EtOAc was used as solvent. Yield: 99%. ^1H NMR ($CDCl_3$): δ 7.30−7.25 (m, 1H), 6.91−6.81 (m, 3H), 6.77 (s, 1H), 6.60 (s, 1H), 4.92 (br s, 2H), 4.01 (s, 3H), 3.81 (s, 3H), 3.71 (s, 3H), 1.86 (s, 3H). MS (EI): m/z 324 $[M]^+$.

8-Amino-2,6-dimethoxy-4-methyl-5-(3-methylphenyl)-quinoline (12ae). Compound **12ae** was prepared from **11ae** by the same procedure. Yield: 99%. ^1H NMR ($CDCl_3$): δ 7.29−7.24 (m, 1H), 7.17−7.14 (m, 1H), 7.09−7.07 (m, 2H), 6.78 (s, 1H), 6.60 (s, 1H), 4.77 (br s, 2H), 4.03 (s, 3H), 3.71 (s, 3H), 2.38 (s, 3H), 1.82 (s, 3H). MS (ESI): m/z 309 $[M + 1]^+$.

8-Amino-5-(3,4-dichlorophenyl)-2,6-dimethoxy-4-methyl-quinoline (12af). Compound **12af** was prepared by hydrogenation over a slurry of Raney nickel in water instead of palladium on activated carbon. Yield: 95%. ^1H NMR ($CDCl_3$): δ 7.44 (d, J = 8.2 Hz, 1H), 7.37 (d, J = 2.0 Hz, 1H), 7.12 (dd, J = 8.2 and 2.0 Hz, 1H), 6.74 (s, 1H), 6.64 (s, 1H), 4.99 (br s, 1H), 4.03 (s, 3H), 3.72 (s, 3H), 1.88 (s, 3H). MS (EI): m/z 362 $[M]^+$.

General Procedure for the Preparation of 8-Amino-5-aryl-6-methoxy-4-methyl-2-trifluoromethyl-quinoline (12ba−be). A solution of compound **11be** (1.7 g, 4.5 mmol) in EtOAc (80 mL) was subjected to hydrogenation, using 10% palladium on activated carbon (300 mg, 1.3 mmol) as catalyst under atmospheric pressure of H_2 gas for 18 h. The reaction mixture was filtered through a layer of Celite, and the yellow filtrate was evaporated to dryness under the reduced pressure. The residue was suspended in H_2O (100 mL), and the pH of the suspension was adjusted to 8 with NaOH aqueous solution. The mixture was extracted with $CHCl_3$ (100 mL × 3) and the combined extracts were combined, washed with brine, dried over Na_2SO_4, and concentrated in vacuo to give 1.6 g of the crude product, which was washed with a solvent mixture of 9% EtOAc in hexane to give 0.8 g (51%) of the desired product **12be** after drying. Additional amounts of compound **12be** (0.6 g, 35%) was recovered from the filtrate, using a silica gel column eluted with 20% EtOAc in hexane, to give **12be** in a combined total of 1.4 g (89%). ^1H NMR ($CDCl_3$): δ 7.44−7.15 (m, 6H), 4.38 (br s, 2H), 3.46 (s, 3H), 2.42 (s, 3H), 1.92 (s, 3H). IR (neat): 1636, 1471, 1385, 1370, 1257, 1164, 1139, 1107, 1005, 855, and 786 cm^{-1}. MS (ESI): m/z 347 $[M + 1]^+$.

8-Amino-6-methoxy-4-methyl-5-phenyl-2-trifluoromethyl-quinoline (12ba). Compound **12ba** was obtained by reduction of **11ba** according to the same procedure for the preparation of **12be**. Yield: 82%. ^1H NMR ($CDCl_3$): δ 7.47−7.45 (m, 4H), 7.37−7.36 (m, 2H), 7.16 (s, 1H), 3.44 (s, 3H), 1.91 (s, 3H). IR (neat): 1628, 1468, 1447, 1424, 1254, 1178, 1135, 1103, 1007, 936, 755, 739, and 704 cm^{-1}. MS (EI): m/z 332 $[M]^+$.

8-Amino-6-methoxy-4-methyl-5-(3-trifluoromethylphenyl)-2-trifluoromethyl-quinoline (12bb). The title compound was obtained by catalytic hydrogenation of **11bb**. Yield: 63%. ^1H NMR ($CDCl_3$): δ 7.75−7.73 (m, 1H), 7.65−7.53 (m, 3H), 7.49 (s, 1H), 7.18 (s, 1H), 4.36 (br s, 2H), 3.42 (s, 3H), 1.87 (s, 3H). IR (neat): 1628, 1471, 1351, 1324, 1313, 1252, 1156, 1127, 1103, 1001, 900, 856, and 808 cm^{-1}. MS (ESI): m/z 401 $[M + 1]^+$.

8-Amino-6-methoxy-4-methyl-5-(4-trifluoromethylphenyl)-2-trifluoromethyl-quinoline (12bc). Title compound was obtained as yellow solid from **11bc** by the same reduction procedure. The crude product was pure enough for the next reaction without further purification. ^1H NMR ($CDCl_3$): δ 8.23 (s, 1H), 7.73 (d, J = 6.9 Hz, 2H), 7.50 (d, J = 6.9 Hz, 2H), 7.49 (s, 1H), 3.42 (s, 3H), 1.89 (s, 3H). IR (neat): 1324, 1150, 1123, 1109, 1104, 1067, 836, 784, 770, 748, and 718 cm^{-1}. MS (ESI): m/z 401 $[M + 1]^+$.

8-Amino-6-methoxy-4-methyl-5-(3-methoxyphenyl)-2-trifluoromethyl-quinoline (12bd). The title compound was obtained by catalytic hydrogenation of **11bd**. Yield: 99%. ^1H NMR ($CDCl_3$): δ 7.45 (s, 1H), 7.39−7.34 (m, 1H), 7.16 (s, 1H), 7.01−6.90 (m, 3H), 4.38 (br s, 1H), 3.84 (s, 3H), 3.49 (s, 3H), 1.98 (s, 3H). IR (neat): 1470, 1252, 1177, 1150, 1136, 1102, 1032, 916, 860, 790, and 728 cm^{-1}. MS (ESI): m/z 363 $[M + 1]^+$.

General Procedure for the Preparation of 8-[(1-Methyl-4-phthalimido)-butyl]-amino-5-aryl-2,6-dimethoxy-4-methyl-quinoline (15aa−af). Compound **13** (1.9 g, 5.5 mmol) in *N*-methylpyrrolidinone (8 mL) was added dropwise a solution consist of compound **12aa** (1.6 g, 5.5 mmol) and diisopropylamine (0.4 g, 6.1 mmol) in 2 mL of *N*-methylpyrrolidinone. The resulting mixture was heated for 20 h at 80 °C. Additional amount of compound **13** (1.9 g, 5.5 mmol) and diisopropylamine (0.4 g, 6.1 mmol) were added slowly, and the reaction solution was heated for 8 more hours. After cooling to rt, the mixture was basified with 50 mL of 2N NaOH aqueous solution. The mixture was extracted with diethyl ether (100 mL × 3), and the combined ether extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by a silica gel column, eluted with 9% hexane in $CHCl_3$, to give 2.1 g (57%) of the desired product **15aa** as red oil.

8-[(1-Methyl-4-phthalimido)-butyl]-amino-2,6-dimethoxy-4-methyl-5-phenyl-quinoline (15aa). Yield: 57%. ^1H NMR ($CDCl_3$): δ 7.83−7.80 (m, 2H), 7.71−7.68 (m, 2H), 7.37−7.31 (m, 3H), 7.26−7.23 (m, 2H), 6.57 (s, 1H), 6.49 (s, 1H), 5.95 (d, J = 8.3 Hz, 1H), 3.99 (s, 3H), 3.78−3.70 (m, 3H), 3.70 (s, 3H), 1.92−1.71 (m, 4H), 1.77 (s, 3H), 1.33 (d, J = 6.3 Hz, 3H). MS (ESI): m/z 510 $[M + 1]^+$.

8-[(1-Methyl-4-phthalimido)-butyl]-amino-2,6-dimethoxy-4-methyl-5-(3-trifluoromethyl-phenyl)-quinoline (15ab). Compound **15ab** was prepared by the same procedure from **12ab** and **13**. Yield: 64%. ^1H NMR ($CDCl_3$): δ 7.85−7.79 (m, 2H), 7.73−7.69 (m, 2H), 7.60−7.58 (m, 1H), 7.51−7.46 (m, 3H), 6.60 (s, 1H), 6.47 (s, 1H), 6.01 (d, J = 8.5 Hz, 1H), 4.00 (s, 3H), 3.72 (s, 3H), 3.79−3.72 (m, 3H), 1.98−1.73 (m, 4H), 1.73 (s, 3H), 1.35 (d, J = 6.3 Hz, 3H). MS (ESI): m/z 578 $[M + 1]^+$.

8-[(1-Methyl-4-phthalimido)-butyl]-amino-2,6-dimethoxy-4-methyl-5-(4-trifluoromethyl-phenyl)-quinoline (15ac). The title compound was prepared by the same procedure from **12ac** and **13**. Yield: 85%. ^1H NMR ($CDCl_3$): δ 7.84−7.81 (m, 2H), 7.72−7.09 (m, 2H), 7.61 (d, J = 7.8 Hz, 2H), 7.38 (d, J = 7.8 Hz, 2H), 6.60 (s, 1H), 6.48 (s, 1H), 6.01 (d, J = 8.2 Hz, 1H), 4.00

(s, 3H), 3.79−0.68 (m, 3H), 3.72 (s, 3H), 2.03−1.62 (m, 4H), 1.72 (s, 3H), 1.35 (d, J = 6.3 Hz, 3H). MS (ESI): m/z 578 $[M + 1]^+$.

8-[(1-Methyl-4-phthalimido)-butyl]-amino-2,6-dimethoxy-4-methyl-5-(3-methoxyphenyl)-quinoline (15ad). The title compound was prepared by the same procedure from **12ad** and **13**. Yield: 55%. ^{1}H NMR ($CDCl_3$): δ 7.84−7.81 (m, 2H), 7.73−7.69 (m, 2H), 7.30−7.25 (m, 1H), 6.91−6.83 (m, 3H), 6.59 (s, 1H), 6.50 (s, 1H), 5.97 (d, J = 8.0 Hz, 1H), 4.00 (s, 3H), 3.82 (s, 3H), 3.82−3.73 (m, 3H), 3.73 (s, 3H), 2.00−1.66 (m, 4H), 1.97 (s, 3H), 1.35 (d, J = 6.3 Hz, 3H). MS (ESI): m/z 540 $[M + 1]^+$.

8-[(1-Methyl-4-phthalimido)-butyl]-amino-2,6-dimethoxy-4-methyl-5-(3-methylphenyl)-quinoline (15ae). The title compound was likewise prepared by the same method from **12ae** and **13.** Yield: 46%. ^{1}H NMR ($CDCl_3$): δ 7.85−7.80 (m, 2H), 7.73−7.69 (m, 2H), 7.29−7.06 (m, 4H), 6.58 (s, 1H), 6.50 (s, 1H), 5.95 (d, J = 7.6 Hz, 1H), 4.00 (s, 3H), 3.80−3.73 (m, 3H), 3.73 (s, 3H), 2.37 (s, 3H), 2.02−1.66 (m, 4H), 1.80 (s, 3H), 1.35 (d, J = 6.3 Hz, 3H). MS (ESI): m/z 524 $[M + 1]^+$.

8-[(1-Methyl-4-phthalimido)-butyl]-amino-2,6-dimethoxy-4-methyl-5-(3,4-dichlorophenyl)- quinoline (15af). The title compound was prepared by the same procedure from **12af** and **13**. Yield: 62%. ^{1}H NMR ($CDCl_3$): δ 7.84−7.81 (m, 2H), 7.71−7.68 (m, 2H), 7.45−7.42 (m, 1H), 7.38−7.36 (m, 1H), 7.14−7.10 (m, 1H), 6.62 (s, 1H), 6.48 (s, 1H), 6.04 (d, J = 8.4 Hz, 1H), 4.01 (s, 3H), 3.80−3.75 (m, 3H), 3.75 (s, 3H), 2.00−1.72 (m, 4H), 1.86 (s, 3H), 1.36 (d, J = 6.3 Hz, 3H). MS (EI): m/z 577 $[M]^+$.

General Procedure for the Preparation of 8-[(1-Methyl-4-phthalimido)-butyl]-amino-5-aryl-6-methoxy-4-methyl-2-trifluoromethyl-quinoline (15ba−be). Compound **12be** (0.8 g, 2.3 mmol) and borane−pyridine complex (0.8 g, 1.4 mmol) was added to a solution of compound **14** (0.8 g, 3.5 mmol) in glacial acetic acid (10 mL). The resulting mixture was stirred at rt for 2 h, and additional compound **14** (2.4 g, 11 mmol) was added. The solution was stirred at ambient temperature for 19 h and evaporated to dryness in vacuo. The residue was suspended in H_2O (100 mL), basified with NaOH aqueous solution and extracted with $CHCl_3$ (100 mL) 3 times. The combined extracts were washed with brine, dried over Na_2SO_4, and evaporated to dryness under reduced pressure. The residue was purified by a silica gel column, eluted with 20% EtOAc in hexane, to give 1.5 g (99%) of the desired product **15be** as yellow oil.

8-[(1-Methyl-4-phthalimido)-butyl]-amino-6-methoxy-4-methyl-5-(3-methylphenyl)-2-trifluoromethyl-quinoline (15be). Yield: 99%. ^{1}H NMR ($CDCl_3$): δ 7.82−7.80 (m, 2H), 7.69−7.67 (m, 2H), 7.35−7.09 (m, 6H), 4.85 (br d, J = 7.0 Hz, 1H), 3.76−3.71 (m, 3H), 3.38 (s, 1.5 H), 3.37 (s, 1.5H), 2.42 (s, 1.5H), 2.41 (s, 1.5H), 1.89 (s, 3H), 1.89−1.62 (m, 4H), 1.28 (d, J = 6.0 Hz, 3H). IR (neat): 1711, 1609, 1450, 1397, 1370, 1253, 1173, 1132, 1105, 756, and 719 cm^{-1}. MS (ESI): m/z 562 $[M + 1]^+$.

8-[(1-Methyl-4-phthalimido)-butyl]-amino-6-methoxy-4-methyl-5-phenyl-2-trifluoromethyl-quinoline (15ba). Compound **15ba** was obtained as yellow solid from **12ba** by the same procedure as described for the preparation of **15be**. Yield: 99%. ^{1}H NMR ($CDCl_3$): δ 7.83−7.80 (m, 2H), 7.69−7.67 (m, 2H), 7.46−7.44 (m, 3H), 7.35−7.34 (m, 2H), 7.19 (s, 1H), 7.10 (s, 1H), 4.59 (d, J = 8.4 Hz, 1H), 3.76−3.72 (m, 3H), 3.35 (s, 3H), 1.88 (s, 3H), 1.88−1.64 (m, 4H), 1.28 (d, J = 6.3 Hz, 3H). IR (neat): 1708, 1609, 1525, 1394, 1254, 1181, 1132, 1103, 757, and 717 cm^{-1}. MS (ESI): m/z 548 $[M + 1]^+$.

8-[(1-Methyl-4-phthalimido)-butyl]-amino-6-methoxy-4-methyl-2-trifluoromethyl-5-(3-trifluoromethylphenyl)-quinoline (15bb). Compound **15bb** was prepared from **12bb** and **14** by the same procedure. Purification of the title compound was difficult. Thus, the crude product was partially purified by silica gel column and used for the next step synthesis. ^{1}H NMR ($CDCl_3$): δ 7.84−7.57 (m, 8H), 7.23 (s, 1H), 7.11 (s, 1H), 4.56 (br d, J = 7.1 Hz, 1H), 3.78−3.71 (m, 3H), 3.33 (s, 3H), 1.84 (s, 3H), 1.84−1.57 (m, 4H), 1.29 (d, J = 6.2 Hz, 3H). IR (neat): 1712, 1610, 1397, 1371, 1321, 1255, 1168, 1128, 1105, 1071, 758, and 720 cm^{-1}. MS (ESI): m/z 616 $[M + 1]^+$.

8-[(1-Methyl-4-phthalimido)-butyl]-amino-6-methoxy-4-methyl-2-trifluoromethyl-5-(4-trifluoromethylphenyl)-quinoline (15bc). Compound **15bc** was prepared from **12bc** and **14** by the same procedure as described for the preparation of **15be**. Difficulty was encountered on purification of the title compound. The crude product was partially purified by silica gel column and used for the next synthesis without further purification. ^{1}H NMR ($CDCl_3$): δ 7.84−7.80 (m, 2H), 7.73−7.67 (m, 2H), 7.67−7.23 (m, 4H), 7.23 (s, 1H), 7.12 (s, 1H), 4.57 (br d, J = 8.7 Hz, 1H), 3.76−3.72 (m, 3H), 3.34 (s, 3H), 1.86 (s, 3H), 1.86−1.69 (m, 4H), 1.29 (d, J = 6.2 Hz, 3H). IR (neat): 1713, 1609, 1397, 1371, 1324, 1255, 1168, 1126, 1105, 1066, 934, and 721 cm^{-1}. MS (ESI): m/z 616 $[M + 1]^+$.

8-[(1-Methyl-4-phthalimido)-butyl]-amino-6-methoxy-5-(3-methoxy)-phenyl-4-methyl-2-trifluoromethyl-quinoline (15bd). The title compound **15bd** was obtained from **12bd** by the same procedure. Yield: 76%, ^{1}H NMR ($CDCl_3$): δ 7.83−7.79 (m, 2H), 7.70−7.67 (m, 2H), 7.35−7.33 (m, 1H), 7.19 (s, 1H), 7.10 (s, 1H), 7.00−6.89 (m, 3H), 4.58 (br. d, J = 8.4 Hz, 1H), 3.85 (s, 1.5 H), 3.83 (s, 1.5 H), 3.76−3.71 (m, 3H), 3.40 (s, 3H), 1.95 (s, 3H), 1.95−1.70 (m, 4H), 1.28 (d, J = 6.3 Hz, 3H). IR (neat): 1709, 1607, 1397, 1370, 1254, 1172, 1131, 1104, 755, and 719 cm^{-1}. MS (ESI): m/z 578 $[M + 1]^+$.

General Synthetic Procedure for 8-[(4-Amino-1-methyl)-butyl]-amino-5-aryl-2,6-dimethoxy-4-methyl-quinoline Succinate (4aa−af). A solution of compound **15aa** (1.6 g, 3.1 mmol) in EtOH (12 mL) was treated with an excess amount of hydrazine monohydrate (0.7 g, 13.2 mmol) and refluxed for 30 min. Upon cooling to rt, the precipitates were removed by suction filtration and washed with EtOH (5 mL × 4). The filtrate and the EtOH washing solutions were combined and concentrated to dryness. The crude product was dissolved in CH_2Cl_2 (50 mL), washed twice with 25 mL of 25% KOH, and subsequently once with water (25 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo to give an oil which was purified by a silica gel column, eluted with CH_2Cl_2 containing 2% of MeOH and 2% of triethylamine, to give 0.9 g of the desired product as yellow oil. The oil (540 mg, 1.4 mmol) was dissolved in CH_3CN (5 mL) and treated with a solution of succinic acid (168 mg, 1.4 mmol) in CH_3OH (1 mL) and CH_3CN (3 mL) mixed solvent to give 368 mg (41%) of **4aa** as a succinate salt.

8-[(4-Amino-1-methyl)-butyl]-amino-2,6-dimethoxy-4-methyl-5-phenyl-quinoline Succinate (4aa). Yield 41%; mp 156 °C. ^{1}H NMR (CD_3OD): δ 7.36−7.30 (m, 3H), 7.22−7.15 (m, 2H), 6.63 (s, 1H), 6.61 (s, 1H), 3.98 (s, 3H), 3.85−3.79 (m, 1H), 3.68 (s, 3H), 3.01−2.96 (m, 2H), 2.50 (s, 4H), 1.90−1.76 (m, 4H), 1.79 (s, 3H), 1.37 (d, J = 6.4 Hz, 3H). ^{13}C NMR (CD_3OD): δ 181.6, 160.3, 156.1, 149.8, 145.3, 141.5, 133.1, 133.1, 128.6, 128.6, 127.7, 126.0, 116.2, 115.2, 96.2, 57.7, 53.3, 41.3, 35.2, 35.1, 28.9, 26.4, 24.7, 21.3. IR (neat): 1592, 1577, 1533, 1467, 1450, 1394, 1373, 1337, 1207, 1185, 1158, 1053, 1038, 891, 857, 777, 756, and 706 cm^{-1}. MS (EI): m/z 379 $[M]^+$. Anal. ($C_{27}H_{35}N_3O_6$): C, H, N.

8-[(4-Amino-1-methyl)-butyl]-amino-2,6-dimethoxy-4-methyl-5-(3-trifluoromethylphenyl)-quinoline Succinate (4ab). Compound **4ab** was prepared from **15ab** by the same procedure except crude product was used to prepare the succinate salt without prior purification by column chromatography. Yield 46%; mp 154 °C. ^{1}H NMR (CD_3OD): δ 7.63−7.43 (m, 4H), 6.65 (s, 1H), 6.64 (s, 1H), 3.99 (s, 3H), 3.88−3.83 (m, 1H), 3.72 (s, 3H), 3.01−2.96 (m, 2H), 2.50 (s, 4H), 1.90−1.75 (m, 4H), 1.75 (s, 3H), 1.37 (d, J = 6.3 Hz, 3H). ^{13}C NMR (CD_3OD): δ 179.5, 160.3, 156.2, 148.9, 145.9, 142.7, 137.0, 132.9, 131.1, 130.7, 129.6, 129.4, 129.3, 127.8, 125.8, 124.4, 124.3, 116.6, 112.5, 95.0, 57.3, 53.4, 41.0, 34.9, 33.0, 25.7, 25.1, 21.3. IR (neat): 1640, 1598, 1536, 1474, 1430, 1394, 1374, 1338, 1325, 1308, 1230, 1210, 1162, 1121, 1084, 1073, 1051, 857, 838, 812, and 708 cm^{-1}. MS (EI): m/z 447 $[M]^+$. Anal. ($C_{28}H_{34}F_3N_3O_6 \cdot 0.1H_2O$): C, H, N, F.

8-[(4-Amino-1-methyl)-butyl]-amino-2,6-dimethoxy-4-methyl-5-(4-trifluoromethylphenyl)-quinoline Succinate (4ac). Compound **4ac** was prepared from **15ac** by the same procedure. Yield 32%;

mp 144 °C. ^{1}H NMR (CD_3OD): δ 7.65−7.62 (m, 2H), 7.40−.35 (m, 2H), 6.64−6.63 (m, 2H), 3.98 (s, 3H), 3.88−3.82 (m, 1H), 3.71 (s, 3H), 3.01−2.96 (m, 2H), 2.50 (s, 4H), 1.91−1.78 (m, 4H), 1.78 (s, 3H), 1.37 (d, J = 6.3 Hz, 3H). ^{13}C NMR (CD_3OD): δ 178.9, 160.3, 156.1, 149.1, 146.2, 145.8, 133.8, 133.7, 132.9, 130.0, 129.6, 128.0, 125.7, 125.4, 125.3, 124.4, 116.5, 112.8, 95.1, 57.3, 53.4, 41.0, 34.9, 32.4, 25.7, 25.1, 21.3. IR (neat): 1715, 1590, 1532, 1475, 1450, 1394, 1372, 1338, 1322, 1248, 1206, 1152, 1125, 1106, 1068, 1049, 1022, 894, 841, 810, 801, 753, and 609 cm^{-1}. MS (EI): m/z 447 $[M]^+$. Anal. ($C_{28}H_{34}F_3N_3O_6 \cdot 0.8H_2O$): C, H, N, F.

8-[(4-Amino-1-methyl)-butyl]-amino-2,6-dimethoxy-5-(3-methoxyphenyl)-4-methylquinoline Succinate (4ad). Compound **4ad** was prepared from **15ad** by the same procedure. Yield 46%; mp 164 °C. ^{1}H NMR (CD_3OD): δ 7.28−7.22 (m, 1H), 6.91−6.88 (m, 1H), 6.80−6.74 (m, 2H), 6.63 (s, 1H), 6.61 (s, 1H), 3.98 (s, 3H), 3.85−3.79 (m, 1H), 3.79 (s, 3H), 3.70 (s, 3H), 3.01−2.96 (m, 2H), 2.50 (s, 4H), 1.86−1.80 (m, 4H), 1.86 (s, 3H), 1.37 (d, J = 6.3 Hz, 3H). ^{13}C NMR (CD_3OD): δ 178.0, 159.1, 159.1, 158.8, 154.5, 148.3, 143.7, 141.2, 131.5, 128.0, 128.0, 124.4, 124.2, 124.2, 117.4, 117.4, 114.7, 113.5, 111.7, 111.5, 94.7, 56.2, 54.2, 51.8, 39.5, 33.4, 31.5, 24.1, 22.8, 19.8. IR (neat): 1638, 1597, 1535, 1468, 1449, 1393, 1371, 1337, 1283, 1218, 1154, 1081, 1051, 835, 806, 791, 788, 713, and 670 cm^{-1}. MS (EI): m/z 409 $[M]^+$. Anal. ($C_{28}H_{37}N_3O_7 \cdot 0.8H_2O$): C, H, N.

8-[(4-Amino-1-methyl)-butyl]-amino-2,6-dimethoxy-4-methyl-5-(3-methylphenyl)-quinoline Succinate (4ae). Compound **4ae** was prepared from **15ae** by the same procedure as described for the preparation of **4ab**. Yield 73%; mp 157 °C. ^{1}H NMR (CD_3OD): δ 7.24−7.19 (m, 1H), 7.14−7.12 (m, 1H), 7.02−6.95 (m, 2H), 6.63 (s, 1H), 6.60 (s, 1H), 3.98 (s, 3H), 3.85−3.79 (m, 1H), 3.68 (s, 3H), 3.00−2.96 (m, 2H), 2.50 (s, 4H), 2.35 (s, 3H), 1.90−1.79 (m, 4H), 1.79 (s, 3H), 1.36 (d, J = 6.3 Hz, 3H). ^{13}C NMR (CD_3OD): δ 179.4, 160.2, 155.9, 149.8, 145.0, 141.2, 138.0, 138.0, 133.6, 133.5, 133.0, 130.0, 130.0, 128.4, 128.3, 128.2, 125.9, 116.0, 115.3, 96.1, 57.6, 53.1, 40.9, 34.8, 32.9, 25.5, 24.6, 21.5, 21.2. IR (neat): 1638, 1597, 1473, 1450, 1393, 1372, 1337, 1213, 1154, 1083, 1053, 856, 836, 807, 785, 754, 715, and 685 cm^{-1}. MS (ESI): m/z 394 $[M + 1]^+$. Anal. ($C_{28}H_{37}N_3O_6$): C, H, N.

8-[(4-Amino-1-methyl)-butyl]-amino-5-(3,4-dichlorophenyl)-2,6-dimethoxy-4-methyl-quinoline succinate (4af). Compound **4af** was prepared from **15af** by the same procedure for **4ab** synthesis. Yield 37%; mp 115 °C. ^{1}H NMR (DMSO-d_6): δ 7.59−7.57 (m, 1H), 7.45−7.41 (m, 1H), 7.18−7.13 (m, 1H), 6.73 (s, 1H), 6.58 (s, 1H), 6.02 (br d, J = 8.8 Hz, 1H), 3.94 (s, 3H), 3.88−3.70 (m, 1H), 3.70 (s, 3H), 2.90−2.74 (m, 2H), 2.23 (s, 4H), 1.79 (s, 3H), 1.79−1.52 (m, 4H), 1.26 (d, J = 6.2 Hz, 3H). ^{13}C NMR (DMSO-d_6): δ 175.5, 158.3, 154.5, 147.3, 144.3, 140.7, 133.5, 133.4, 132.3, 132.3, 130.6, 130.2, 130.1, 129.6, 129.6, 129.3, 124.0, 115.3, 108.8, 93.3, 56.6, 52.8, 48.7, 47.1, 33.3, 32.6, 24.7, 24.4, 20.7. IR (neat): 1595, 1577, 1532, 1450, 1393, 1371, 1336, 1231, 1206, 1188, 1160, 1128, 1087, 1052, 1030, 828, 794, 757, 746, and 719 cm^{-1}. MS (ESI): m/z 448 $[M + 1]^+$. Anal. ($C_{27}H_{33}Cl_2N_3O_6 \cdot 0.5H_2O$): C, H, N, Cl.

General Synthetic Procedure for the Preparation of 8-[(4-Amino-1-methyl)-butyl]-amino-5-aryl-6-methoxy-4-methyl-2-trifluoromethyl-quinoline (4ba−be). A solution of compound **15be** (1.5 g, 2.7 mmol) in ethanol (15 mL) was treated with excess amount of hydrazine monohydrate (0.6 g, 11 mmol) and refluxed for 30 min. On cooling, the precipitates were removed by filtration and washed with EtOH (5 mL × 4). The EtOH washing solutions were combined and concentrated to dryness. The crude product was dissolved in $CHCl_3$ (100 mL), washed twice with 25 mL of 25% KOH aqueous solution, and followed twice with 25 mL of H_2O. The $CHCl_3$ layer was dried over Na_2SO_4 and concentrated in vacuo to give yellow oil which was purified by a silica gel column, eluted with a CH_2Cl_2 solution containing 5% of CH_3OH and 5% of Et_3N, to give 0.9 g (80%) of the desired product **4be** as yellow oil.

8-[(4-Amino-1-methyl)-butyl]-amino-6-methoxy-4-methyl-5-(3-methylphenyl)-2-trifluoromethyl-quinoline (4be). Yield: 80%. ^{1}H NMR ($CDCl_3$): δ 7.36−7.10 (m, 6H), 4.64 (br d, J = 7.5 Hz, 1H), 3.74−3.67 (m, 1H), 3.38 (s, 3H), 2.77−2.72 (m, 2H), 2.41 (s, 3H), 1.90 (s, 3H), 1.76−1.52 (m, 4H), 1.30 (d, J = 5.9 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 147.9, 147.7, 147.4, 142.8, 137.9, 137.5, 131.2, 128.4, 127.8, 127.7, 127.6, 116.2, 106.0, 60.0, 47.9, 42.1, 34.1, 29.9, 24.0, 21.4, 20.5. IR (neat): 1609, 1496, 1452, 1399, 1384, 1371, 1254, 1230, 1173, 1131, 1105, 1006, 945, 907, 855, 785, 760, 748, and 689 cm^{-1}. MS (ESI): m/z 432 $[M + 1]^+$. Anal. ($C_{24}H_{28}F_3N_3O \cdot 0.9H_2O$): C, H, N, F.

8-[(4-Amino-1-methyl)-butyl]-amino-6-methoxy-4-methyl-5-phenyl-2-trifluoromethyl-quinoline (4ba). Compound **4ba** was obtained as a brown oil from **15ba** by the same procedure as described for the preparation of **4be**. Yield 99%; mp 99 °C. ^{1}H NMR ($CDCl_3$): δ 7.46−7.44 (m, 3H), 7.36−7.33 (m, 2H), 7.23 (s, 1H), 7.11 (s, 1H), 4.65 (br d, J = 8.2 Hz, 1H), 3.74−3.68 (m, 1H), 3.36 (s, 3H), 2.77−2.73 (m, 2H), 1.88 (s, 3H), 1.70−1.55 (m, 4H), 1.30 (d, J = 6.3 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 147.9, 147.7, 147.3, 146.5, 146.0, 142.8, 138.0, 131.0, 130.5, 127.9, 127.7, 123.7, 120.9, 120.1, 116.2, 106.0, 59.9, 47.9, 42.1, 34.1, 30.1, 24.1, 20.6. IR (neat): 1611, 1450, 1371, 1255, 1177, 1132, 1105, 1003, 935, 852, 768, 745, and 706 cm^{-1}. MS (ESI): m/z 418 $[M + 1]^+$. Anal. ($C_{23}H_{26}F_3N_3O$): C, H, N, F.

8-[(4-Amino-1-methyl)-butyl]-amino-6-methoxy-4-methyl-2-trifluoromethyl-5-(3-trifluoromethylphenyl)-quinoline (4bb). The title compound was prepared from **15bb** by the same procedure as oil. Yield: 76%. ^{1}H NMR ($CDCl_3$): δ 7.73−7.57 (m, 4H), 7.26 (s, 1H), 7.13 (s, 1H), 4.64 (br d, J = 8.0 Hz, 1H), 3.73−3.71 (m, 1H), 3.34 (s, 3H), 2.79−2.74 (m, 2H), 1.92−1.57 (m, 4H), 1.85 (s, 3H), 1.31 (d, J = 6.3 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 148.1, 146.8, 142.9, 139.2, 134.1, 130.4, 129.5, 128.6, 127.6, 126.0, 124.8, 123.8, 122.4, 120.8, 120.2, 116.6, 107.0, 60.0, 48.1, 42.2, 34.3, 29.9, 24.6, 20.7. IR (neat): 1497, 1254, 1228, 1167, 1125, 1105, 1001, 806, and 749 cm^{-1}. MS (ESI): m/z 486 $[M + 1]^+$. Compound **4bb** is a gummy material that easily binds tightly with water and solvents. Several attempts were made to obtain satisfactory elemental analysis data but failed without adjustment for solvent content. It was converted to a t-Boc derivative, **5bb**, which is a crystalline material and gave satisfactory elemental analytical data.

8-[(4-Amino-1-methyl)-butyl]-amino-6-methoxy-4-methyl-2-trifluoromethyl-5-(4-trifluoromethylphenyl)-quinoline (4bc). Compound **4bc** was prepared from **15bc** by the same procedure. Yield: 29% in 3 steps from **11bc**, mp 145 °C. ^{1}H NMR ($CDCl_3$): δ 7.73 (d, J = 7.9 Hz, 2H), 7.51 (d, J = 7.9 Hz, 2H), 7.26 (s, 1H), 7.13 (s, 1H), 4.64 (br d, J = 8.4 Hz, 1H), 3.72−3.70 (m, 1H), 3.34 (s, 3H), 2.78−2.73 (m, 2H), 1.87 (s, 3H), 1.75−1.55 (m, 4H), 1.31 (d, J = 6.3 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 148.1, 148.0, 146.9, 142.9, 142.3, 131.2, 130.6, 130.1, 129.7, 125.0, 122.6, 120.7, 116.5, 107.0, 60.1, 48.2, 42.3, 34.4, 30.3, 24.6, 20.7. IR (neat): 1322, 1254, 1187, 1172, 1126, 1104, 1068, 1002, 934, 856, and 833 cm^{-1}. MS (ESI): m/z 486 $[M + 1]^+$. The compound **4bc** was a gummy material, which failed to give satisfactory elemental analysis results without adjustment for solvent content. It was converted to the t-Boc derivative, **5bc**, which is a crystalline material and gave good elemental analysis results after purification.

8-[(4-Amino-1-methyl)-butyl]-amino-6-methoxy-5-(3-methoxyphenyl)-4-methyl-2-trifluoromethyl-quinoline (4bd). Compound **4bd** was obtained as yellow oil from **15bd** by the same procedure described for the preparation of **4be**. Yield: 77%. ^{1}H NMR ($CDCl_3$): δ 7.39−7.34 (m, 1H), 7.27−7.12 (m, 2H), 7.01−6.90 (m, 3H), 4.65 (d, J = 8.2 Hz, 1H), 3.84 (s, 3H), 3.84−3.70 (m, 1H), 3.41 (s, 3H), 2.77−2.73 (m, 2H), 1.96 (s, 3H), 1.71−1.50 (m, 4H), 1.31 (d, J = 6.3 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 159.2, 147.3, 142.8, 139.4, 128.9, 123.2, 116.3, 116.2, 113.3, 106.2, 60.1, 55.3, 47.9, 42.2, 34.2, 30.1, 23.7, 20.5. IR (neat): 1608, 1585, 1498, 1479, 1451, 1371, 1254, 1174, 1131, 1105, 1047, 1003, 944, 858, 785, 753, and 689 cm^{-1}. MS (EI): m/z 447 $[M]^+$. The compound **4bd** was determined by LC-MS/MS to be about 95% pure. It was converted to t-Boc **5bd** which gave satisfactory elemental analytical results.

General Synthetic Procedure for 8-[(4-*tert*-Butoxycarbonylamino-1-methyl)-butyl]-amino-5-aryl-6-methoxy-4-methyl-2-trifluoromethyl-quinoline (5bb−be). Di-*tert*-butyl-dicarbonate (607 mg, 2.78 mmol) and triethylamine (282 mg, 2.78 mmol) were added to a solution of **4bb** (450 mg, 0.93 mmol) in chloroform (40 mL). The reaction mixture was stirred at rtfor 21 h and evaporated to dryness in vacuo. The residue was purified by a silica gel column, eluted with 20% of EtOAc in hexane, to give 540 mg (99%) of the desired product **5bb** as yellow solid.

8-[(4-*tert*-Butoxycarbonylamino-1-methyl)-butyl]-amino-6-methoxy-4-methyl-2-trifluoromethyl-5-(3-trifluoromethylphenyl)-quinoline (5bb). Yield: 99%, mp 53−57 °C. ^{1}H NMR ($CDCl_3$): δ 7.73-7.58 (m, 4H), 7.26 (s, 1H), 7.13 (s, 1H), 4.59−4.56 (m, 2H), 3.72 (m, 1H), 3.34 (s, 3H), 3.17−3.15 (m, 2H), 1.85 (s, 3H), 1.69−1.64 (m, 4H), 1.42 (s, 9H), 1.30 (d, J = 6.3 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 156.2, 148.1, 146.8, 142.8, 139.2, 134.1, 129.6, 128.6, 127.6, 126.0, 124.8, 123.9, 122.4, 120.8, 120.2, 116.7, 107.1, 79.5, 60.0, 48.3, 40.8, 34.2, 28.6, 27.2, 24.6, 20.8. IR (neat): 1256, 1168, 1164, 1127, 1107, 1074, 1004, 837, 808, and 793 cm^{-1}. MS (ESI): m/z 586 [M + 1]$^+$. Anal. ($C_{29}H_{33}F_6N_3O_3$): C, H, N, F.

8-[(4-*tert*-Butoxycarbonylamino-1-methyl)-butyl]-amino-6-methoxy-4-methyl-5-(4-trifluoro- methyl)-phenyl-2-trifluoromethyl-quinoline (5bc). Compound **5bc** was obtained as yellow solid from **4bc** by the same procedure as described for the preparation of **5bb**. Yield 99%; mp 53−58 °C. ^{1}H NMR ($CDCl_3$): δ 7.73 (d, J = 7.9 Hz, 2H), 7.50 (d, J = 7.9 Hz, 2H), 7.25 (s, 1H), 7.13 (s, 1H), 4.58−4.55 (m, 2H), 3.72−3.70 (m, 1H), 3.34 (s, 3H), 3.17−3.15 (m, 2H), 1.87 (s, 3H), 1.65−1.64 (m, 4H), 1.42 (s, 9H), 1.30 (d, J = 6.3 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 156.0, 147.9, 147.8, 146.6, 142.6, 142.1, 131.0, 130.3, 129.9, 129.5, 124.8, 125.0, 122.3, 120.0, 116.4, 106.8, 79.2, 59.9, 47.9, 40.6, 33.9, 28.4, 26.9, 24.3, 20.5. IR (neat): 1708, 1609, 1521, 1498, 1452, 1253, 1172, 1135, 1105, 860, 852, 834, and 737 cm^{-1}. MS (ESI): m/z 586 [M + 1]$^+$. Anal. ($C_{29}H_{33}F_6N_3O_3$): C, H, N, F.

8-[(4-*tert*-Butoxycarbonylamino-1-methyl)-butyl]-amino-6-methoxy-5-(3-methoxyphenyl)-4-methyl-2-trifluoromethyl-quinoline (5bd). Compound **5bd** was obtained in 93% yield from **4bd** as a yellow solid by the same general procedure, mp 62−66 °C. ^{1}H NMR ($CDCl_3$): δ 7.37−7.33 (m, 1H), 7.26−7.22 (m, 1H), 7.11 (s, 1H), 7.00−6.90 (m, 3H), 4.59−4.56 (m, 2H), 3.83 (s, 3H), 3.71 (m, 1H), 3.40 (s, 3H), 3.16 (m, 2H), 1.96 (s, 3H), 1.63−1.61 (m, 4H), 1.42 (s, 9H), 1.29 (d, J = 6.2 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 159.3, 156.2, 148.0, 147.8, 147.6, 142.9, 139.5, 131.0, 129.1, 123.9, 123.4, 121.1, 120.2, 116.4, 113.5, 106.3, 79.4, 60.4, 55.5, 48.0, 40.7, 34.1, 28.6, 27.1, 24.0, 20.8. IR (neat): 1499, 1286, 1238, 1155, 1113, 1084, 1048, 945, 790, 740, and 721 cm^{-1}. MS (ESI): m/z 548 [M + 1]$^+$. Anal. ($C_{29}H_{36}F_3N_3O_4$): C, H, N, F.

8-[(4-*tert*-Butoxycarbonylamino-1-methyl)-butyl]-amino-6-methoxy-4-methyl-5-(3-methylphenyl)-2-trifluoromethyl-quinoline (5be). Compound **5be** was prepared from **4be** in 69% yield as yellow solid by the same procedure, mp 58−62 °C. ^{1}H NMR ($CDCl_3$): δ 7.35−7.10 (m, 6H), 4.59−4.57 (m, 2H), 3.71−3.69 (m, 1H), 3.37 (s, 3H), 3.16−3.15 (m, 2H), 2.41 (s, 3H), 1.90 (s, 3H), 1.70−1.63 (m, 4H), 1.42 (s, 9H), 1.29 (d, J = 6.3 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 156.0, 147.9, 147.7, 147.4, 142.7, 137.9, 137.5, 137.5, 131.2, 128.4, 127.7, 127.6, 121.0, 120.1, 116.2, 106.1, 79.2, 60.0, 47.8, 40.6, 34.0, 28.4, 26.9, 24.0, 21.4, 20.6. IR (neat): 1699, 1610, 1520, 1498, 1455, 1397, 1384, 1370, 1254, 1170, 1134, 1106, 1007, 859, 841, and 784 cm^{-1}. MS (ESI): m/z 532 [M + 1]$^+$. Anal. ($C_{29}H_{36}F_3N_3O_3$): C, H, N, F.

Biological Studies. i. In Vitro Antimalarial Activity against *P. falciparum*. The in vitro assays were conducted using a modification of the technique of Desjardins et al.[29] and Chulay et al.[30] Two *P. falciparum* malaria parasite clones from CDC Indochina III (W-2), and CDC Sierra Leone I (D-6) were utilized in susceptibility testing. They were derived by direct visualization and micromanipulation from patient isolates.[31] The W-2 clone is susceptible to mefloquine (MQ) but resistant to CQ, sulfadoxine, pyrimethamine, and quinine, whereas the D-6 clone is naturally resistant to MQ but susceptible to CQ, sulfadoxine, pyrimethamine, and quinine. Test compounds were initially dissolved in DMSO and diluted 400-fold in RPMI 1640 culture medium supplemented with 25 mM Hepes, 32 mM $NaHCO_3$, and 10% Albumax I (Gibco BRL, Grand Island, NY). These solutions were subsequently serial diluted 2-fold with a Biomek 1000 (Beckman, Fullerton, CA) over 11 different concentrations. The parasites were exposed to serial dilutions of each compound for 48 h and incubated at 37 °C with 5% O_2, 5% CO_2, and 90% N_2 prior to the addition of [^{3}H]-hypoxanthine. After a further incubation of 18 h, parasite DNA was harvested from each microtiter well using Packard Filtermate 196 harvester (Meriden, CT) onto glass filters. Uptake of [^{3}H]-hypoxanthine was measured with a Packard Topcount scintillation counter. Concentration−response data were analyzed by a nonlinear regression logistic dose response model, and the IC_{50} values (50% inhibitory concentrations) for each compound were calculated.

ii. In Vitro Toxicity Assessment. Toxicity of the test compounds were assessed in the macrophage cell line RAW 264.7, which was obtained from the American Type Culture Collection and was cultured as previously described.[32] All steps of the experimental procedure were performed using a Biomek 2000 robot. The stock solution of the test drugs were prepared by dissolving in DMSO and serially diluted automatically by robot. Ninety-six-well plates were seeded each with 2.5×10^4 cells per well in 170 μL of culture media and incubated for approximately 12 h before the start of the assay. The following morning, cells were exposed to different drug concentrations, ranging from 0.29−48 μg/mL/well, and were incubated for additional 24 h. After incubation, the drugs were removed and 200 μL of fresh media was added to each well and incubated again for 24 more h to allow for recovery of the viable yet drug suppressed cells. The viability of the cells was assessed using the MTT (thiazolyl blue reduction) method as previously described.[33] Each assay plate includes the following 3 control wells: (a) background control, no cells and no drugs were added; (b) target control, cells added but no drugs; and (c) DMSO control, same as the target control, except the culture media contains 0.6% DMSO, which is the highest DMSO concentration among the wells with test drug and is not harmful to the macrophages. In the background control, the reading should be near zero while those in the target and the 0.6% DMSO controls, 100% cell survival are anticipated. The experimental results are not considered valid unless the results of all three controls are as expected. All experiments were run in duplicate, and the 50% inhibitory concentrations (IC_{50}s) were determined using GraphPad Prism (sigmoidal dose−response, variable slope).

iii. Causal Prophylactic Antimalarial Activity in Exoerythrocytic (EE) Mouse Model. The causal prophylactic activity of the new compounds were assessed in mice infected with sporozoites of *P. berghei* by intravenous inoculation, according to the method described earlier.[34]

iv. Metabolic Stability Test. Metabolic stability of the new compounds was assessed in the human and mouse microsomal preparations according to the procedure described.[34] Briefly, the metabolic stability assay was performed in a 96-well plate on a TECAN Genesis robotic sample processor following WRAIR SOP SP 01-02. Samples were analyzed by LC-MS/MS using fast LC gradient or isocratic methods. Parent drug was quantified using external calibration and plots of parent drug response vs amount.

Results and Discussion. i. In Vitro Antimalarial Activity. All new compounds prepared in this study (**4aa−af**, **4ba−be**, and **5bb−be**) were evaluated for their antimalarial activity against both CQ-susceptible (D6) and CQ-resistant clones (W2) of *P. falciparum* (Table 1). 8-Aminoquinoline antimalarials **2** and **3** were used as positive controls for the study. All new compounds showed moderate activity against both CQ-susceptible and CQ-resistant clones of *P. falciparum* with IC_{50} in the range of 1−3 μg/mL, which is comparable to or better than **2** and **3** (Table 1).

Table 1. In Vitro Growth Inhibitory Activity in *P falciparum* and Toxicity against Macrophage Cell Line

	metabolic stability $t_{1/2}$ (min)		EE *P. berghei* (mg/kg/day × 3)		*P. falciparum* (IC_{50}, μg/mL)		macrophage cell line	therapeutic index[a] (TI)	
compd[c]	human	mouse	MTD	MAD	D6	W2	(IC50, μg/mL)	D6	W2
4aa	> 60	> 60			3.2	1.3	1.9	0.59	1.46
4ab	> 60	> 60	> 480	> 480	2.7	1.3	1.3	0.48	1.0
4ac	> 60	> 60	> 480	> 480	2.2	1.3	1.2	0.54	0.92
4ad	> 60	> 60	> 480	> 480	2.8	0.8	3.1	1.11	3.87
4ae	> 60	> 60	960	960	1.3	0.7	1.9	1.46	2.71
4af	> 60	> 60	120	> 480	2.9	1.2	1.7	0.58	1.42
4ba	> 60	> 60	480	> 960	2.8	1.4	3.1	1.11	2.21
4bb	> 60	> 60			1.4	0.5	1.5	1.07	3.0
4bc	> 60	> 60			1.7	0.8	10.1	5.94	12.6
4bd	> 60	> 60			0.3	0.6	1.5	5.0	2.50
4be	> 60	> 60			0.2	0.9	1.8	9.0	2.0
5bb	18	18	> 960	> 960	1.1	2.8	> 48[b]	> 39.7	> 17
5bc	30	16	> 960	> 960	1.3	1.4	> 48[b]	> 36	> 34
5bd	9	8	> 960	> 960	0.3	0.6	> 80.2[b]	> 267	> 134
5be	13	11	> 960	> 960	0.2	0.9	> 48[b]	> 240	> 59
2	> 60	21	< 120[c]	60[c]	2.1	0.9	38.7	18.43	43
3	> 60	> 60	120[c]	7.5[c]	2.7	0.8	5.9	2.2	7.38

[a] TI, macrophage IC_{50}/*P. falciparum* IC_{50}; MTD, maximum tolerated dose; MAD, minimum active dose. [b] The compound was precipitated in media at the highest concentration. [c] Historical data of WRAIR.

Structure−activity relationship studies indicated that the antimalarial activity of the new compounds were affected significantly by the substituent on the 5-aryl ring as well as at the 2-position of 8-AQ. The new agents appear more active against the CQ-resistant clones W-2 than to the CQ-sensitive clone D-6. Electronic effects of the substituent on the 5-aryl ring influenced substantially the cell growth inhibitory activity. Compounds with electron donating groups (*m*-methoxyl or *m*-methyl) showed better activity than those with electron withdrawing substituents (*m*- or *p*-CF_3). Thus, compounds **4bd**, **4be**, **5bd**, and **5be** were more active than **4bb**, **4bc**, **5bb**, and **5bc**. Among the compounds tested, **4ae**, **4be**, and **5be** with *m*-methylphenyl substituents at the 5-position of the quinoline ring showed the best growth inhibitory activity in both clones of *P. falciparum*. Furthermore, compounds with a trifluoromethyl (CF_3) substituent at the 2-position of 8-aminoquinoline ring possess superior activity over those with a 2-methoxy group. In general, 2-trifluoromethyl-8-AQ derivatives (**4ba**−**be**) are 2−6-fold more active than the corresponding 2-methoxy-8-AQ analogues (**4aa**−**ae**).

The structures of the new compounds closely resemble to that of **3** and its analogues, except the oxygen atom at the 5-position of TQ was removed in the new compounds. Theoretically, with the 5-position blocked by a metabolically stable aryl group, the new compounds are not expected to produce toxic metabolites, quinone or quinoneimine. As hypothesized in the literature, if the metabolites responsible for toxicity are also responsible for the antimalarial activity then the new compounds would not be expected to exhibit antimalarial activity or hemolytic side effects. On the other hand, if the efficacy and toxicity of **3** are the effects of the parent drug and reactive metabolites, respectively, then the new compounds which showed antimalarial activity may not necessarily show hemolytic toxicity. This contention will be explored separately in other studies. The present report focused mainly on chemical synthesis, assessment of antimalarial efficacy in EE mouse model, *P. falciparum* cell culture, and toxicity in the mammalian macrophage cell line Raw 264.7.

ii. In Vitro Toxicity Assessment in Macrophage Cell Line RAW 264.7. Macrophage cell line Raw 264.7 was used to assess the general toxicity of the new 8-AQ derivatives **4aa**−**af**, **4ba**−**be**, and **5bb**−**be** synthesized in this study (Table 1). The results indicate that the concentration required for 50% growth inhibition (IC_{50}) against the macrophage cell line were in the range of 3−21 μmol/L for **4aa**−**af** and **4ba**−**be** vs 12.7 μmol/L and 149 μmol/L for **3** and **2**, respectively, indicating the new compounds are about equal to **3** but more toxic than **2**, based on weight or molar concentration. However, compounds **4bc**, **4bd**, and **4be**, the most active compounds of the new series, showed a comparable therapeutic index (TI) to that of **2** and **3**, with TI ranging from 5 to 8. The toxicity results are based on the growth inhibition of macrophage cell growth which is not relevant to the hemolytic toxicity but provide references to general toxicity of the test compounds. In mice efficacy tests, the new compounds are much less toxic and less active than **2** and **3**, with oral maximum tolerated dose (MTD) > 480−960 mg/kg, as compared to that of **2** (∼90 mg/kg) and **3** (∼60 mg/kg) (Table 1).

Hemolysis side effects associated with G6PD deficiency patients is the major concern of 8-AQ toxicity. However, there is no validated animal model available that can be used to predict this deadly toxicity. Currently, promising mice models are under development in several laboratories, including Walter Reed Army Institute of Research. Whether the new deoxo-TQ analogues prepared in this study are less hemolytic or not will have to wait until the validated model(s) are available.

iii. Causal Prophylactic Antimalarial Activity in EE Mouse Model. The new compounds **4ab**−**af**, **4ba**, and **5bb**−**be** were further tested for causal prophylactic activity in *P. berghei* sporozoites infected mouse model by oral administration and were found to be inactive up to 320 mg/kg per day for 3 days, except **4ae**, which showed weak activity at 320 mg/kg/day × 3 by oral, cured 1 out of 4 and delayed patency for 4 days 2 out of 4 mice. The weak activity of 8-AQ derivatives in exoerythrocytic mouse model was well documented.[21] Earlier efforts to develop new drugs effective against tissue schizonts and hypnozoites have been hampered by the difficulty in establishing an in vitro cell based model or a mouse model predictive for the exoerythrocytic stages of *P. falciparum* and *P. vivax*.[21] Extrapolating drug efficacy data from rodent models of malaria to primate models can be difficult to interpret due to interspecies differences in absorption, distribution, metabolism, and excretion. In addition, the rodent model may not be capable of distinguishing EE activity from blood stage activity because compounds with long half-life may result in a suppressive effect in the blood. Furthermore, a series of **3** analogues which showed radical curative activity in Rhesus were found inactive in causal prophylactic test in mice.[21] Consequently, developers of 8-AQ antimalarials have relied heavily on Rhesus monkeys infected with sporozoites of *P. cynomolgi* to confirm the antiparasitic activity among the drug candidates. Efficacy in the monkey model has a good correlation with efficacy against human *P. vivax* infection.[35,36] Similar difficulties were experienced in the

lead optimization of a new class of imidazolinedione derivatives which showed promising causal prophylactic and radical cure activity in Rhesus but showed no or very weak activity in the EE mouse model.[34,37,38] Thus, although the new deoxo-TQ analogues synthesized in this study showed poor efficacy in mice, it cannot be ruled out that they do possess good causal prophylactic and/or antihypnozoite activity in Rhesus monkey models.

iv. Metabolic Stability Test. Because metabolites were implied to play a role in the efficacy and hemolytic toxicity of 8-AQ antimalarials, metabolic stability of the new compounds were assessed in human and mouse microsomal preparations according to the published procedure.[34] The results indicated that compounds **4aa**−**af**, and **4ba**−**be** are, as expected, metabolically stable with $t_{1/2} > 60$ min. Compounds **5bb**−**be**, t-Boc of the corresponding **4bb**−**be**, are metabolically unstable with $t_{1/2} <$ 11 min, most likely due to hydrolysis of the t-Boc protecting group during the incubation. This contention was substantiated by the fact that the IC_{50} of **5bb**−**be** are about equal to the corresponding free base **4bb**−**be**. Under the same test, **2** was stable in human microsomes but was metabolically unstable in mouse microsomal preparations. This result may explain the fact that **2** exhibits good radical cure activity in Rhesus, and has been the drug of choice for radical cure for malaria relapse patients but showed only mediocre activity in the EE mouse model (Table 1). The results imply that the parent molecules of **2** and **3** may be the active species while the metabolites are responsible for hemolytic side effects. Because the new deoxo-TQ analogues prepared in this study are metabolically stable as expected and showed comparable in vitro blood stage activity as **2** and **3**, further assessments of the causal and radical cure activities of the new compounds in the Rhesus model and hemolytic side effects in a validated mouse model will be carried out and reported separately.

Conclusion

A series of 5-aryl-8-aminoquinoline derivatives was prepared in an attempt to search for compounds which retain the antimalarial activity of tafenoquine but are devoid of hemolytic toxicity in G6PD deficient patients. The new compounds appear to retain the activity of **2** and **3** against blood stage malaria *P. falciparum* and toxicity in macrophage cell culture, are metabolically stable in both human and mouse microsomal preparations, but lost both toxicity and causal prophylactic activity of **2** and **3** in mice test. The data suggested that the parent molecule of 8-AQ antimalarials is the active species against blood stage malarias, while metabolites are responsible for the toxicity and activity against tissue schizonts and hypnozoites in mouse model. However, because the 5-aryloxy-8-AQ antimalarials showed poor activity correlation between EE mouse and Rhesus monkey models,[21] the poor causal prophylactic activity of the new compounds in EE mouse model should not prevent it from further testing for radical curative activity in Rhesus model. Though well tolerated in mice, the hemolytic side effect of the new compounds has yet to be tested in a validated G6PD deficient mouse model which is currently under development.

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Supporting Information Available: Elemental analysis results of 5-aryl-8-aminoquinoline derivatives. This material is available free of charge via the Internet at http://pubs.acs.org.

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