Pergamon

SCIENCE DIRECT®

Bioorganic & Medicinal Chemistry 11 (2003) 4557–4568

BIOORGANIC & MEDICINAL CHEMISTRY

8-Quinolinamines and Their Pro Prodrug Conjugates as Potent Blood-Schizontocidal Antimalarial Agents☆

Suryanarayana Vangapandu†, Sandeep Sachdeva, Meenakshi Jain, Savita Singh, Prati Pal Singh, Chaman Lal Kaul and Rahul Jain*

National Institute of Pharmaceutical Education and Research, Sector 67, S.A.S. Nagar, Punjab 160 062, India

Received 2 June 2003; accepted 30 July 2003

Abstract—Synthesis and antimalarial activities of N^8-(4-amino-1-methylbutyl)-5-alkoxy-4-ethyl-6-methoxy-8-quinolinamines (**5**) and their pro prodrug analogues (**6**–**7**) prepared by covalently linking 5 to the redox-sensitive (**8**) and esterase-sensitive (**9**) linkers through the amide linkage are reported. The most effective 8-quinolinamines [**5c** ($R = C_5H_{11}$) and **5f** ($R = C_8H_{17}$)] have exhibited in vitro and in vivo biological efficacy superior to that of the standard drug chloroquine against both drug-sensitive and drug-resistant malaria strains. Analogues **6**–**7** were evaluated for in vivo blood-schizontocidal activity as potential pro prodrug models for the primary amino group containing 8-quinolinamines (**5**). The most effective pro prodrug analogue (**6c**) has displayed promising activities against drug-sensitive and drug-resistant strains of Plasmodia in vivo.

Introduction

Malaria caused by the protozoa of the genus *Plasmodium*, because of its prevalence, virulence and drug resistance, is the most serious and widespread parasitic disease, and that has an overwhelming impact on public health in developing regions of the world.[1–3] Attempts to control mosquito vector and the use of antimalarial drugs notwithstanding, there are yet some 2.5–3 million fatalities, mostly children and women annually from malaria.[4] Not clearly evident in the mortality statistics are the vast range of problems associated to the millions of cases suffering from morbidity derived from malaria infection. In part, the extent of the economic and public health problems originated from malaria has been related to difficulties in the chemotherapy of this protozoan disease.[5]

Depending upon their biological activities, currently available antimalarial drugs can be classified into two categories as blood-schizontocides and tissue-schizontocides.[6] All traditional blood-schizontocides exert their activity against the blood stages of the human malaria parasite. They are helpful in clearing the infected blood stages of *Plasmodium falciparum* malaria; the species responsible for approximately 95% of the mortality cases.[7] These drugs are thus used as suppressive agents, and the effectiveness of chloroquine, the cheap, mainstay blood-schizontocide for more than 50 years, is being undermined by the evolution of the resistant parasites.[8] Furthermore, the clinical usefulness of the many of the newly discovered blood-schizontocides like, mefloquine,[9] and artemisinin (recommended for use only in cerebral malaria cases),[10] is limited or restricted due to the emergence of *P. falciparum* resistant strains against them. On the other hand, 8-quinolinamines represents a typical tissue-schizontocidal agent, and the most important drug of this class primaquine exerts its action against the primary and secondary tissue forms of the *Plasmodium*. There are no reports of development of resistance against 8-quinolinamine class of compounds in the field, although reduction in sensitivity by *Plasmodium vivax* to primaquine is reported in the laboratory studies.[11] It is well known that primaquine suffers because of serious side effects and its toxicity limits its usefulness in both prophylactic and therapeutic applications. One of the most serious side effects is hemolytic anemia that is substantially enhanced in the individuals, who are genetically deficient in the glucose-6-phosphate dehydrogenase (G-6-PD) enzyme.[12] Furthermore, the efficacy of primaquine at dangerously toxic doses against asexual blood stages of the parasite precludes its use for the treatment of acute attack of malaria.

☆NIPER communication number 218.

*Corresponding author. Tel.: +91-172-214682; fax: +91-172-214692; e-mail: rahuljain@niper.ac.in

†Current address: Research Institute of Pharmaceutical Sciences, University of Mississippi, MS, USA.

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doi:10.1016/j.bmc.2003.07.003

Results and Discussion

Future research into 8-quinolinamines can be justified on the basis of several considerations: (i) 8-quinolinamines is the only class of compounds proven to be successful in the treatment of relapsing malaria; (ii) the 8-quinolinamines, such as primaquine is the only drug available to exhibit weak to high activity against majority of the stages including that of blood- and tissue-stages of the human malaria life cycle; (iii) the 8-quinolinamine, primaquine has been shown to possess efficacy against the drug-resistant strains of *P. falciparum*. This last factor coupled with the previous observation that 8-quinolinamines are effective against almost all of the stages of the parasite life cycle, underlines the potential of further analogue design in this class of compounds. However, as discussed earlier, primaquine cannot be used for the treatment of *P. falciparum* infections due to its activity at the toxic high doses. Thus, there is a need to modify the 8-quinolinamine class of antimalarial agents to enhance their efficacy against the asexual blood stages (blood-schizontocidal agents) of the malaria parasite. These modified compounds with increased blood-schizontocidal activity may be of immense therapeutic potential, provided they also exhibit potent activity against drug-resistant strains. In the past, we have described synthesis and potent tissue-schizontocidal activities of a series of 8-quinolinamines.[13] In continuation of our earlier work, this paper describes synthesis and potent in vitro and in vivo blood-schizontocidal activities against drug-resistant and drug-sensitive *Plasmodium* strains for a series of N^8-(4-amino-1-methylbutyl)-5-alkoxy-4-ethyl-6-methoxy-8-quinolinamines (**5a–f**).

As discussed earlier, although, primaquine has no clinical utility as a blood-schizontocide, the little activity it possesses against the erythrocytic form of the malaria parasite is derived from an oxidative stress mechanism.[14] It is well known that the hydroxylated metabolites of primaquine, stimulates the hexose monophosphate shunt, increases hydrogen peroxide and methemoglobin production, and decrease glutathione levels in the erythrocyte.[15,16] Unfortunately, this same peroxidant property of primaquine is speculated to be also responsible for its hemolytic side effect.[14] These observations indicates that metabolites of the 8-quinolinamines play an important role, and could be responsible for the toxic manifestations, which limits the usefulness of this class of antimalarials as potent blood-schizontocides. To validate this hypothesis, many putative metabolites of primaquine, which were previously isolated and characterized are synthesized, and evaluated for antimalarial activity. However, all of these compounds were found to be highly toxic and devoid of any activity, thereby confirming the hypothesis that metabolites of 8-quinolinamine class of compounds are responsible for toxic side effects.[17]

One approach towards improving the utility of such drugs is to develop prodrug analogues capable of selective release of the parent 8-quinolinamines. It is known that prodrug design comprises of approaches that helps at enhancing the efficacy and reducing the toxicity and unwanted effects of drugs by controlling their absorption, metabolism and distribution. However, various prodrug approaches applied to the 8-quinolinamine antimalarial agents indicates that a single chemical modification (as required in prodrugs) is not sufficient to achieve the desired alteration in the biological properties to enhance blood-schizontocidal activity.[18] Thus, to further increase the bio-efficacy of the 8-quinolinamines (**5**), an alternate 'double prodrug' or 'pro prodrug' approach can be applied. A pro prodrug, is a derivative, which undergoes two independent reactions in order to regenerate the parent drug. In the case of the pro prodrugs, the intermediate prodrug must be a chemically reactive entity, which rapidly undergoes a chemical conversion to release the parent drug under physiological conditions. However, this reactive prodrug is generated only after a biological step involving enzyme-catalyzed reaction/transformation on the chemically stable pro prodrug.[19]

The preliminary work on the concept of pro prodrug of amines was described by Cohen et al.[20] They demonstrated that various methyl substitutions present on the carboxylic acids **8** and **9** (Fig. 1) when converted to amides are interlocked in such a way (the 'trimethyl lock') that the side chain can exist only in a folded (cisoid) conformation. This results in immediate lactonization of the compounds to release the parent amines in the presence of an appropriate enzymatic trigger. This approach was further extended by Borchardt et al.[21,22] to successfully design and develop pro prodrugs of amines that are enzymatically converted (mediated by reductase and esterase enzymes) to hydroxyamide intermediates capable of rapidly undergoing lactonization step that leads to the release of amino group containing drug.

Malaria parasites are known to live in the hepatic cells as hypnozoites, become active periodically, and thus their maximum population is found in the liver at the time of their activation. Furthermore, it has been also found that the enzymes esterases and reductases are present in the liver at maximum levels. Therefore, we hypothesize that synthesis of 8-quinolinamine antimalarial drugs (**6–7**), where antimalarial analogues (**5**) are attached to a carrier molecule (pro prodrug anchor), may carry the drug molecule (**5**) to the site of action, where the drug may be released by the action of esterase or reductase enzymes present in the body. Thus, it is assumed that the biologically available esterases or reductases enzymes should convert the pro prodrug

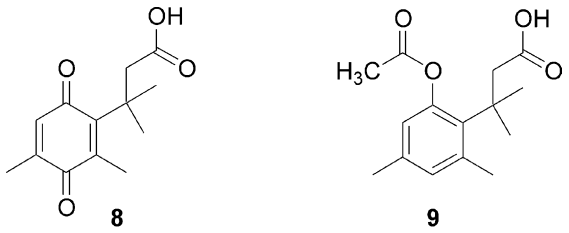


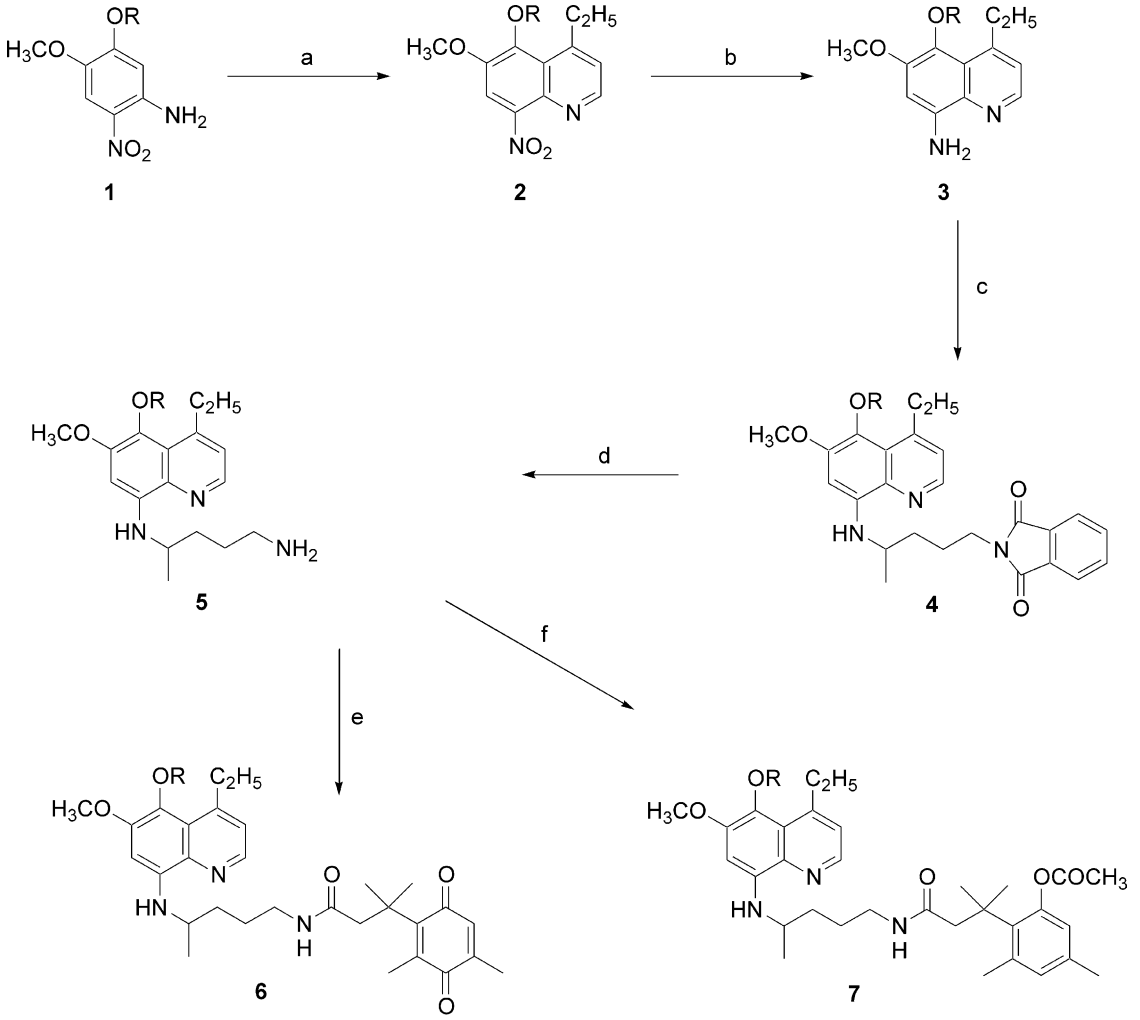
Figure 1.

analogues (**6**–**7**) attached to linkers (**8** and **9**) to the respective prodrugs and that followed by a spontaneous independent chemical modification should convert the intermediate prodrugs to the parent drugs (**5**) in vivo. Herein, we also describe the results of our study towards design, synthesis and biological activities of redox-sensitive (**6**) and esterase-sensitive (**7**) pro prodrug analogues of 8-quinolinamines (**5**).

Chemistry

For the synthesis of requisite intermediates, 5-alkoxy-4-ethyl-6-methoxy-8-nitroquinolines (**2a**–**f**), we first attempted the experimental procedure described earlier for the synthesis of 4-ethyl-5,6-dimethoxy-8-nitroquinoline that consists of reacting corresponding 3-alkoxy-4-methoxy-6-nitroaniline (**1**)[23,24] with ethyl vinyl ketone in the presence of arsenic acid and *ortho*-phosphoric acid. This method led to the formation of 8-nitroquinolines (**2**) in poor isolated yield (5–6%).[15] However, modifying the reaction conditions by replacement of ethyl vinyl ketone with 1-chloro-3-pentanone, and its subsequent addition in two equal portions to the well stirred homogenous mixture of 3-alkoxy-4-methoxy-6-nitroanilines (**1**) and *o*-phosphoric acid at 80 °C followed by the addition of arsenic(V) oxide provided the 5-alkoxy-4-ethyl-6-methoxy-8-nitroquinolines (**2a**–**f**) in excellent yield (Scheme 1).

Catalytic hydrogenation of 5-alkoxy-4-ethyl-6-methoxy-8-nitroquinolines (**2a**–**f**) in 95% ethyl alcohol with wet raney-nickel catalyst (T_1 grade) at 45 psi in a Parr hydrogenator for 45 min gave the corresponding 5-alkoxy-4-ethyl-6-methoxy-8-quinolinamines (**3a**–**f**) in quantitative yields. These 8-quinolinamines were found to be extremely hygroscopic and sensitive to atmosphere, and were used for subsequent reaction step without any further purification. Hence, condensation of 5-alkoxy-4-ethyl-6-methoxy-8-quinolinamines (**3a**–**f**) with 2-(4-bromopentyl)-1,3-isoindolinedione[25] in the presence of triethylamine at 120 °C for 24 h provided the corresponding 2-[4-(5-alkoxy-4-ethyl-6-methoxy-8-quinolylamino)pentyl]-1,3-isoindolinedione derivatives (**4a**–**f**). The latter compounds (**4a**–**f**) on hydrazinolysis with hydrazine hydrate in 95% ethyl alcohol at reflux temperature for 8 h afforded the requisite N^8-(4-amino-1-methylbutyl)-5-alkoxy-4-ethyl-6-methoxy-8-quinolinamine analogues (**5a**–**f**) in quantitative yield that upon



Scheme 1. (a) 1-Chloro-3-pentanone, 85% *o*-H_3PO_4, As_2O_5, 80 °C, 3 h; (b) Raney nickel, EtOH, H_2, 45 psi, 45 min; (c) 2-(4-bromopentyl)-1,3-isoindolinedione, Et_3N, 120 °C, 24 h; (d) $NH_2NH_2{\cdot}H_2O$, EtOH, reflux, 8 h; (e) 3-(2,4-dimethyl-3,6-dioxo-1,4-cyclohexadienyl)-3-methylbutanoic acid (**8**), DCC, DMAP, DCM, 4 h; (f) 3-(2,4-dimethyl-6-methylcarbonyloxyphenyl)-3-methylbutanoic acid (**9**), DCC, DMAP, DCM, 4 h.

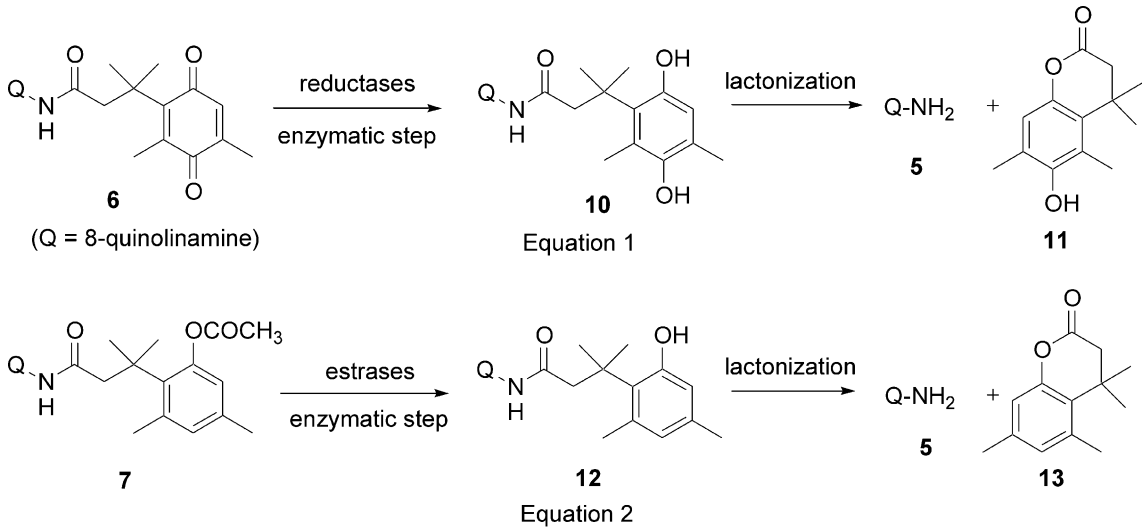


Figure 2.

treatment with anhydrous ethereal hydrogen chloride solution provided the corresponding hydrochloride salt.

The 8-quinolinamine pro-prodrugs conjugates (**6a**–**f**) were synthesized by the reaction of 8-quinolinamines (**5a**–**f**) with redox-sensitive linker, 3-(2,4-dimethyl-3,6-dioxo-1,4-cyclohexadienyl)-3-methylbutanoic acid[21] (**8**) in the presence of 1,3-dicyclohexylcarbodiimide (DCC) and catalytic amount of 4-(dimethylamino)pyridine (DMAP) in anhydrous dichloromethane at room temperature for 4 h in excellent yield. These pro prodrug conjugates involve a 'redox trigger' that controls the rate of hydroxyamide lactonization and the release of the drug in the presence of reductase enzymes. As described earlier, the reactivity of the hydroxyamide intermediates (**10**) is attributed to the presence of the 'trimethyl lock'[20] on the ring, which results in rapid lactonization followed by amide bond cleavage, producing the lactone (**11**) and the parent 8-quinolinamine compounds (**5**) (eq 1, Fig. 2).

Similarly, esterase-sensitive linker, 3-(2,4-dimethyl-6-methylcarbonyloxyphenyl)-3-methylbutanoic acid[22] (**9**) upon reaction with 8-quinolinamines (**5**) under reaction conditions described above for the synthesis of conjugates **6** provided the esterases-sensitive pro prodrug analogues (**7a**–**f**) in excellent yield. In this case, the chemically reactive hydroxyamides (**12**) obtained by esterases mediated enzymatic cleavage of the pro-prodrugs (**7**) results in spontaneous lactonization to release the drug (**5**) at near-physiological pH and temperature (eq 2, Fig. 2).

Biological activity

In vitro antimalarial activities of 8-quinolinamine compounds **5a**–**f** as IC_{50} values for the inhibition of chloroquine sensitive human *P. falciparum* strain are summarized in Table 1.[26] All six compounds displayed notably high activity against *P. falciparum* strain. The most effective compounds of the series **5c** ($R = C_5H_{11}$, $IC_{50} = 9.4$ ng/mL) and **5f** ($R = C_8H_{17}$, $IC_{50} = 9.7$ ng/mL) exhibited efficacy, which is superior to that of chloroquine with IC_{50} values of 13.12 ng/mL (Table 1).

All of the synthesized compounds were also tested for in vivo blood-schizontocidal activity against *Plasmodium berghei* infected mice model (Table 2).[27] Compounds **5c** ($R = C_5H_{11}$) and **5f** ($R = C_8H_{17}$) displayed highest activity from the series with 100% curative activity at a dose of 10 mg/kg. When tested at a further lower dose of 5 mg/kg, these two compounds were found to be active with all treated animals showing negative parasitaemia up to D + 7. However, by D + 28, some mice show negative and some mice show positive test result for parasitaemia. Of the remaining compounds, **5d** ($R = C_6H_{13}$) and **5e** ($R = C_7H_{15}$) are found to be curative at 25 mg/kg. At the same time, compounds **5a** ($R = C_3H_7$) and **5b** ($R = C_4H_9$) were found to be inactive at the maximum tested dose of 100 mg/kg. These results clearly demonstrated that the presence of an alkoxy group on the quinoline ring bearing less than five carbons is detrimental for biological activity.

From the pro prodrug analogues, compounds **6c**–**f** and **7c**–**f** have displayed potent efficacy with curative activity at various tested dose levels of 100, 50 and 25 mg/kg. Furthermore, compounds **6c**–**e** and **6c**–**e** when evaluated at the lower dose of 10 mg/kg, produced suppressive activity with all treated animals showing negative parasitaemia up to D + 7 indicating that these analogues are equipotent to chloroquine. However, compounds **6f** and

Table 1. In vitro sensitivity of chloroquine sensitive *P. falciparum* strain to the 8-quinolinamines (**5**)

No.	R	IC_{50} (ng/mL)
5a	C_3H_7	170.7
5b	C_4H_9	13.3
5c	C_5H_{11}	9.4
5d	C_6H_{13}	58.5
5e	C_7H_{15}	33.6
5f	C_8H_{17}	9.7
Chloroquine		13.12

Table 2. In vivo blood-schizontocidal antimalarial activity of the 8-quinolinamines (**5–7**) against *P. berghei* infection in mice (six mice per group)

No.	R	Dose (mg/kg/day×4, oral)				
		5	10	25	50	100
5a	C_3H_7	—	—	—	—	Inactive
5b	C_4H_9	—	—	—	—	Inactive
5c	C_5H_{11}	Active	Curative	Curative	Curative	Curative
5d	C_6H_{13}	—	Inactive	Curative	Curative	Curative
5e	C_7H_{15}	—	Active	Curative	Curative	Curative
5f	C_8H_{17}	Active	Curative	Curative	Curative	Curative
6a	C_3H_7	—	Inactive	Inactive	Inactive	Curative
6b	C_4H_9	—	Inactive	Curative	Curative	Curative
6c	C_5H_{11}	—	Active	Curative	Curative	Curative
6d	C_6H_{13}	—	Active	Curative	Curative	Curative
6e	C_7H_{15}	—	Active	Curative	Curative	Curative
6f	C_8H_{17}	—	Inactive	Curative	Curative	Curative
7a	C_3H_7	—	—	—	—	Inactive
7b	C_4H_9	—	—	Inactive	Curative	Curative
7c	C_5H_{11}	—	Active	Curative	Curative	Curative
7d	C_6H_{13}	—	Active	Curative	Curative	Curative
7e	C_7H_{15}	—	Active	Curative	Curative	Curative
7f	C_8H_{17}	—	Inactive	Curative	Curative	Curative

The term 'curative' indicates complete elimination of malaria parasites from the body, so that relapse cannot occur up to day D + 60. The term 'active' or minimum effective dose (MED) indicates that the treated animals show negative parasitaemia up to D + 7. However, by D + 28, some mice show negative and some mice show positive test result for parasitaemia. The term 'inactive' indicates that the treated animals show positive test result for parasitaemia either on D + 4 or D + 7 or on both D + 4 and D + 7.

7f ($R = C_8H_{17}$) were found to be inactive when tested at the lower dose of 10 mg/kg. Of the remaining compounds, **6a** ($R = C_3H_7$) was found to be curative at 100 mg/kg, but was found to be inactive at the next lower tested dose of 50 mg/kg. To our disappointment, none of the pro prodrug analogues were found to produce superior efficacy as compared to their 8-quinolinamine counterparts; though, pro prodrug analogues **6a** ($R = C_3H_7$) and **7a** ($R = C_3H_7$) of the quinolinamine counterpart **5a** ($R = C_3H_7$) that did not shown any activity in the *P. berghei* infected mice model were found to be curative at the preliminary tested dose of 100 mg/kg (Table 2).

The most effective analogues were selected for further in vivo bio-evaluation against *Plasmodium yoelii nigeriensis* (a strain resistant to almost all of the available antimalarial agents, and 100% mortality rate has been observed with this infection) and results are summarized in Table 3.[18] Quinolinamine analogues **5c** and **5f** have demonstrated curative activity at the initial tested dose of 100 mg/kg; however, compound **5f** was found to be superior amongst the two with curative activity at the lowest tested dose of 50 mg/kg. On the other hand, compounds **5d** and **5e** were found to be inactive at the preliminary tested dose of 100 mg/kg. From these results it can be concluded that compound **5f** ($R = C_8H_{17}$) is the most effective compound of the series as evident from the in vitro and in vivo activities against both *P. berghei* and *P. yoelii nigeriensis* strain.

Table 3. In vivo blood-schizontocidal antimalarial activity of the 8-quinolinamines (**5–7**) against drug resistant *P. yoelii nigeriensis* infection in mice (six mice per group)

No.	R	Dose (mg/kg/day×4, oral)	
		50	100
5c	C_5H_{11}	Active	Curative
5d	C_6H_{13}	—	Inactive
5e	C_7H_{15}	—	Inactive
5f	C_8H_{17}	Curative	Curative
6c	C_5H_{11}	Active	Curative
6d	C_6H_{13}	—	Active
6e	C_7H_{15}	Inactive	Curative
7c	C_5H_{11}	Inactive	Curative

The term 'curative' indicates complete elimination of malaria parasites from the body, so that relapse cannot occur up to day D + 60. The term 'active' or minimum effective dose (MED) indicates that the treated animals show negative parasitaemia up to D + 7, but show negative and positive test result for parasitaemia by D + 28.

On the other hand, pro prodrug analogues **6c** ($R = C_5H_{11}$), **6e** ($R = C_7H_{15}$) and **7c** ($R = C_5H_{11}$) have shown curative activity at the initial tested dose of 100 mg/kg. Further activity evaluation of compounds **6e** ($R = C_7H_{15}$) and **7c** ($R = C_5H_{11}$) at the lower tested dose of 50 mg/kg did not produce antimalarial effect. Whereas, compound **6c** ($R = C_5H_{11}$) was found to produce suppressive effects at the dose of 50 mg/kg, clearly indicating that it is the most potent compound from the pro prodrug series, and has produced antimalarial activity comparable to its 8-quinolinamine counterpart (**5c**).

Conclusions

In summary, some of the reported 8-quinolinamines have exhibited potent in vitro and in vivo antimalarial activities to warrant further investigation of the series. The pronounced in vivo efficacy of the analogue **5f** against *P. yoelii nigeriensis* strain is indicative of its potential use in the therapy of drug-resistant strains of *Plasmodium*. Although, 8-quinolinamine analogues (**5c–f**) themselves are potential clinically useful blood-schizontocides, the rationale for their use as eventual broad-

spectrum antimalarial agents can be justified provided they also display excellent tissue-schizontocidal activities. The basic sub-structure in our study is primaquine (clinically used radical curative drug); thus, we anticipate observing the same (as primaquine) or increased degree of tissue-schizontocidal activity for all of these molecules. Research efforts towards in vivo primate model testing of these compounds against the tissue (liver) stages of malaria parasite are currently underway in our laboratory. It is expected that the unique blend of broad-spectrum of antimalarial activity against blood stages, tissue stages, and resistant strains of the human malaria parasites may make these compounds very attractive for further antimalarial drug development.

On the other hand, many of the compounds from the pro prodrug series (**6**–**7**) have shown promising in vivo biological activity against drug-sensitive and drug-resistant malaria strains establishing the hypothetical assumption that the 8-quinolinamines could be converted to biologically effective redox-sensitive and esterase-sensitive pro prodrug analogues. Though, some of these analogues have displayed in vivo activities comparable to that of chloroquine, none of these pro prodrug analogues were found to possess activity comparable to the parent 8-quinolinamines. These pro prodrug compounds were designed and synthesized to detect bioreductive and bioesterase activation by endogenous enzymes present in the liver region to release the parent 8-quinolinamines (**5**). Many of these requirements are fulfilled, and some of the analogues have produced encouraging in vivo biological activities. Regardless of these promising and interesting results, we are of the opinion that attempts towards formation of pro prodrug analogues of 8-quinolinamines require additional studies to produce more efficacious antimalarial compounds.

Experimental

Melting points were recorded on Mettler DSC 851 or capillary melting point apparatus and are uncorrected. Both ^{1}H and ^{13}C NMR spectra were recorded on 300 MHz Bruker FT-NMR (Avance DPX300) spectrometer using tetramethylsilane as internal standard and the chemical shifts are reported in δ units. The sample concentration in each case was approximately 10 mg in chloroform-*d* (0.6 mL). Mass spectra were recorded on either GC–MS (Shimadzu QP 5000 spectrometer) auto sampler/direct injection (EI/CI) or HRMS (Finnigan Mat LCQ spectrometer) (APCI/ESI). Elemental analyses were recorded on Elementar Vario EL spectrometer. All chromatographic purification was performed with silica gel 60 (230–400 mesh), whereas all TLC (silica gel) development was performed on silica gel coated (Merck Kiesel 60 F254, 0.2 mm thickness) sheets. All chemicals were purchased from Aldrich Chemical Ltd (Milwaukee, WI, USA). Solvents used for the chemical synthesis acquired from commercial sources were of analytical grade, and were used without further purification unless otherwise stated.

General method for the synthesis of 5-alkoxy-4-ethyl-6-methoxy-8-nitroquinolines (2a–f)

A homogeneous mixture of 3-alkoxy-4-methoxy-6-nitroaniline (**1a**–**f**, 0.037 mol), 1-chloro-3-pentanone (0.020 mol) and *o*-phosphoric acid (85%, 15 mL) was placed in a three necked flask fitted with a thermometer and a dropping funnel. The reaction mixture was heated at 80 °C (internal) with mechanical stirring for 10 min. An additional quantity of 1-chloro-3-pentanone (0.020 mol) was added and stirring continued for another 10 min at 80 °C. Evolution of some hydrogen chloride gas was observed. Arsenic(V) oxide (0.029 mol) was then added at once to the reaction mixture and stirring was continued for 2.5 h at 80 °C. The dark colored reaction mixture was cooled, diluted with water (100 mL) and filtered. The filtrate was basified with 25% NH_4OH solution, extracted with dichloromethane (3×100 mL). Combined organic extracts were washed with brine solution (2×20 mL) and water (2×10 mL), and dried over sodium sulfate. The solvent was removed under vacuum to afford brown colored crude product. Purified by flash column chromatography using EtOAc/hexanes (20:80) to provide 5-alkoxy-4-ethyl-6-methoxy-8-nitroquinolines (**2a**–**f**) as low melting solid.

4-Ethyl-6-methoxy-8-nitro-5-propoxyquinoline (2a). Yield: 69%; mp 43–44 °C; ^{1}H NMR ($CDCl_3$) δ 8.76 (d, 1H, 2-Ar-H, $J=4.3$ Hz), 7.84 (s, 1H, 7-Ar-H), 7.27 (d, 1H, 3-Ar-H, $J=4.3$ Hz), 4.14 (t, 2H, OCH_2, $J=6.8$ Hz), 4.02 (s, 3H, OCH_3), 3.32 (m, 2H, CH_2), 1.90 (m, 2H, CH_2), 1.33 (t, 3H, CH_3, $J=7.4$ Hz), 1.06 (t, 3H, CH_3, $J=7.4$ Hz); ^{13}C NMR ($CDCl_3$) δ 150.6, 150.4, 147.9, 147.0, 144.7, 136.7, 123.9, 123.2, 112.4, 75.9, 57.2, 30.0, 23.3, 15.4, 10.5; ESIMS *m*/*z* 291 (M + 1); analysis for $C_{15}H_{18}N_2O_4$ (290.1), calcd, C, 62.06; H, 6.25; N, 9.65; found, C, 62.09; H, 6.21; N, 9.66.

5-Butoxy-4-ethyl-6-methoxy-8-nitroquinoline (2b). Yield: 68%; mp 51–52 °C; ^{1}H NMR ($CDCl_3$) δ 8.80 (d, 1H, 2-Ar-H, $J=4.3$ Hz), 7.86 (s, 1H, 7-Ar-H), 7.25 (d, 1H, 3-Ar-H, $J=4.3$ Hz), 4.11 (t, 2H, OCH_2, $J=6.8$ Hz), 4.0 (s, 3H, OCH_3), 3.35 (m, 2H, CH_2), 1.92 (m, 2H, CH_2), 1.50 (m, 2H, CH_2), 1.30 (t, 3H, CH_3, $J=7.4$ Hz), 1.00 (t, 3H, CH_3, $J=7.4$ Hz); ^{13}C NMR ($CDCl_3$) δ 150.5, 150.1, 148.0, 147.2, 144.5, 136.6, 123.5, 123.0, 112.1, 75.7, 57.2, 30.1, 28.4, 23.2, 15.3, 10.4; ESIMS *m*/*z* 305 (M + 1); analysis for $C_{16}H_{20}N_2O_4$ (304.3), calcd, C, 63.14; H, 6.62; N, 9.20; found, C, 63.19; H, 6.66; N, 9.28.

4-Ethyl-6-methoxy-8-nitro-5-pentoxyquinoline (2c). Yield: 80%; mp 47–48 °C; ^{1}H NMR ($CDCl_3$) δ 8.75 (d, 1H, 2-Ar-H, $J=4.4$ Hz), 7.84 (s, 1H, 7-Ar-H), 7.26 (d, 1H, 3-Ar-H, $J=4.4$ Hz), 4.14 (t, 2H, OCH_2, $J=6.8$ Hz), 4.02 (s, 3H, OCH_3), 3.30 (m, 2H, CH_2), 1.89 (m, 2H, CH_2), 1.46 (m, 4H, 2×CH_2), 1.33 (t, 3H, CH_3, $J=7.3$ Hz), 0.96 (t, 3H, CH_3, $J=7.0$ Hz); ^{13}C NMR ($CDCl_3$) δ 150.5, 150.4, 147.9, 146.9, 144.6, 136.6, 123.8, 123.1, 112.2, 74.4, 57.1, 29.6, 28.9, 28.4, 22.5, 15.4, 14.0; ESIMS *m*/*z* 319 (M + 1); analysis for $C_{17}H_{22}N_2O_4$ (318.2), calcd, C, 64.13; H, 6.97; N, 8.80; found, C, 64.18; H, 6.91; N, 8.85.

4 - Ethyl - 5 - hexoxy - 6 - methoxy - 8 - nitroquinoline (2d). Yield: 75%; mp 46–47 °C; ^{1}H NMR ($CDCl_3$) δ 8.62 (d, 1H, 2-Ar-H, J = 4.4 Hz), 7.74 (s, 1H, 7-Ar-H), 7.14 (d, 1H, 3-Ar-H, J = 4.4 Hz), 4.04 (t, 2H, OCH_2, J = 6.8 Hz), 3.92 (s, 3H, OCH_3), 3.2 (m, 2H, CH_2), 1.77 (m, 2H, CH_2), 1.41 (m, 2H, CH_2), 1.25 (m, 4H, 2×CH_2), 1.19 (t, 3H, CH_3, J = 7.4 Hz), 0.82 (t, 3H, CH_3, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 150.6, 147.9, 147.0, 144.7, 136.7, 123.9, 123.2, 112.3, 110.7, 74.5, 57.2, 31.7, 29.7, 29.0, 25.6, 22.7, 15.4, 14.1; EIMS m/z 332 (M^+); analysis for $C_{18}H_{24}N_2O_4$ (332.4), calcd, C, 65.04; H, 7.28; N, 8.43; found, C, 65.00; H, 7.22; N, 8.41.

4 - Ethyl - 5 - heptoxy - 6 - methoxy - 8 - nitroquinoline (2e). Yield: 63%; mp 41–42 °C; ^{1}H NMR ($CDCl_3$) δ 8.75 (d, 1H, 2-Ar-H, J = 4.4 Hz), 7.84 (s, 1H, 7-Ar-H), 7.26 (d, 1H, 3-Ar-H, J = 4.4 Hz), 4.17 (t, 2H, OCH_2, J = 6.8 Hz), 4.05 (s, 3H, OCH_3), 3.3 (m, 2H, CH_2), 1.90 (m, 2H, CH_2), 1.48 (m, 8H, 4×CH_2), 1.35 (t, 3H, CH_3, J = 7.3 Hz), 0.91 (t, 3H, CH_3, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 150.8, 150.5, 147.7, 146.6, 144.8, 136.4, 123.9, 123.2, 112.0, 74.3, 57.0, 31.7, 29.6, 29.6, 29.2, 25.8, 22.5, 15.4, 14.1; ESIMS m/z 347 (M + 1); analysis for $C_{19}H_{26}N_2O_4$ (346.4), calcd, C, 65.87; H, 7.56; N, 8.09; found, C, 65.82; H, 7.52; N, 8.14.

4-Ethyl-6-methoxy-8-nitro-5-octoxyquinoline (2f). Yield: 32%; mp 40–41 °C; ^{1}H NMR ($CDCl_3$) δ 8.75 (d, 1H, 2-Ar-H, J = 4.2 Hz), 7.84 (s, 1H, 7-Ar-H), 7.26 (d, 1H, 3-Ar-H, J = 4.2 Hz), 4.16 (t, 2H, OCH_2, J = 6.7 Hz), 4.04 (s, 3H, OCH_3), 3.32 (m, 2H, CH_2), 1.88 (m, 2H, CH_2), 1.60–1.35 (m, 10H, 5×CH_2), 1.32 (t, 3H, CH_3, J = 7.3 Hz), 0.93 (t, 3H, CH_3, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 150.4, 150.3, 147.8, 146.9, 144.6, 136.6, 123.8, 123.1, 112.3, 74.5, 57.1, 31.8, 30.0, 29.4, 29.3, 29.0, 25.9, 22.7, 15.3, 14.0; ESIMS m/z 361(M + 1); analysis for $C_{20}H_{28}N_2O_4$ (360.5), calcd, C, 66.64; H, 7.83; N, 7.77; found, C, 66.61; H, 7.87; N, 7.77.

General method for the synthesis of 5-alkoxy-4-ethyl-6-methoxy-8-quinolinamines (3a–f)

A solution of 5-alkoxy-4-ethyl-6-methoxy-8-nitroquinoline (**2a**–**f**, 6.6 mmol) in 95% ethyl alcohol (20 mL) was hydrogenated over raney nickel (T_1 grade) at 45 psi in a parr hydrogenator for 45 min. Catalyst was removed by filtration, and filtrate was evaporated under vacuum to afford 5-alkoxy-4-ethyl-6-methoxy-8-quinolinamine (**3a**–**f**) as dark colored oil.

4 - Ethyl - 6 - methoxy - 5 - propoxy - 8 - quinolinamine (3a). Yield: 94%; ^{1}H NMR ($CDCl_3$) δ 8.46 (d, 1H, 2-Ar-H, J = 4.2 Hz), 7.14 (d, 1H, 3-Ar-H, J = 4.2 Hz), 6.75 (s, 1H, 7-Ar-H), 4.58 (bs, 2H, NH_2), 3.92 (s, 3H, OCH_3), 3.87 (t, 2H, OCH_2, J = 6.9 Hz), 3.27 (m, 2H, CH_2), 1.87 (m, 2H, CH_2), 1.31 (t, 3H, CH_3, J = 7.3 Hz), 1.05 (t, 3H, CH_3, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 150.4, 149.8, 145.2, 141.0, 134.5, 134.4, 123.5, 122.3, 99.9, 75.8, 56.6, 28.6, 23.2, 14.2, 8.6; APCIMS m/z 261 (M + 1); analysis for $C_{15}H_{20}N_2O_2$ (260.3), calcd, C, 69.20; H, 7.74; N, 10.76; found, C, 69.45; H, 7.58; N, 10.80.

5-Butoxy-4-ethyl-6-methoxy-8-quinolinamine (3b). Yield: 72%; ^{1}H NMR ($CDCl_3$) δ 8.48 (d, 1H, 2-Ar-H, J = 4.2 Hz), 7.13 (d, 1H, 3-Ar-H, J = 4.2 Hz), 6.76 (s, 1H, 7-Ar-H), 4.58 (bs, 2H, NH_2), 3.94 (s, 3H, OCH_3), 3.87 (t, 2H, OCH_2, J = 6.9 Hz), 3.25 (m, 2H, CH_2), 1.81 (m, 4H, 2×CH_2), 1.31 (t, 3H, CH_3, J = 7.4 Hz), 0.95 (t, 3H, CH_3, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 149.5, 145.0, 141.3, 139.1, 134.2, 122.1, 122.1, 98.7, 97.2, 74.1, 56.5, 31.8, 30.1, 28.6, 15.4, 14.2; APCIMS m/z 275 (M + 1); analysis for $C_{16}H_{22}N_2O_2$ (274.3), calcd, C, 70.04; H, 8.08; N, 10.21; found, C, 70.16; H, 8.28; N, 10.35.

4 - Ethyl - 6 - methoxy - 5 - pentoxy - 8 - quinolinamine (3c). Yield: 92%; ^{1}H NMR ($CDCl_3$) δ 8.47 (d, 1H, 2-Ar-H, J = 4.2 Hz), 7.13 (d, 1H, 3-Ar-H, J = 4.2 Hz), 6.77 (s, 1H, 7-Ar-H), 4.57 (bs, 2H, NH_2), 3.93 (s, 3H, OCH_3), 3.88 (t, 2H, OCH_2, J = 6.9 Hz), 3.26 (m, 2H, CH_2), 1.84 (m, 2H, CH_2), 1.44 (m, 4H, 2×CH_2), 1.33 (t, 3H, CH_3, J = 7.4 Hz), 0.95 (t, 3H, CH_3, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 149.9, 145.3, 141.6, 139.5, 134.2, 122.1, 122.0, 98.8, 97.1, 74.4, 56.3, 31.9, 28.7, 25.7, 22.5, 15.4, 14.0; APCIMS m/z 289 (M + 1); analysis for $C_{17}H_{24}N_2O_2$ (288.4), calcd, C, 70.80; H, 8.39; N, 9.71; found, C, 70.55; H, 8.59; N, 9.56.

4 - Ethyl - 5 - hexoxy - 6 - methoxy - 8 - quinolinamine (3d). Yield, 95%; ^{1}H NMR ($CDCl_3$) δ 8.49 (d, 1H, 2-Ar-H, J = 4.2 Hz), 7.15 (d, 1H, 3-Ar-H, J = 4.2 Hz), 6.76 (s, 1H, 7-Ar-H), 4.55 (bs, 2H, NH_2), 3.92 (s, 3H, OCH_3), 3.87 (t, 2H, OCH_2, J = 6.9 Hz), 3.25 (m, 2H, CH_2), 1.81 (m, 4H, 2×CH_2), 1.44 (m, 4H, 2×CH_2), 1.31 (t, 3H, CH_3, J = 7.4 Hz), 0.95 (t, 3H, CH_3, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 149.6, 145.1, 141.5, 139.0, 134.0, 122.3, 122.0, 98.9, 97.0, 74.2, 56.5, 31.8, 30.0, 28.6, 25.7, 22.7, 15.5, 14.1; EIMS m/z 302 (M^+); analysis for $C_{18}H_{26}N_2O_2$ (302.4), calcd, C, 71.49; H, 8.67; N, 9.26; found, C, 71.23; H, 8.66; N, 9.30.

4 - Ethyl - 5 - heptoxy - 6 - methoxy - 8 - quinolinamine (3e). Yield: 98%; ^{1}H NMR ($CDCl_3$) δ 8.45 (d, 1H, 2-Ar-H, J = 4.2 Hz), 7.13 (d, 1H, 3-Ar-H, J = 4.2 Hz), 6.76 (s, 1H, 7-Ar-H), 4.57 (bs, 2H, NH_2), 3.93 (s, 3H, OCH_3), 3.88 (t, 2H, OCH_2, J = 6.9 Hz), 3.25 (m, 2H, CH_2), 1.84 (m, 4H, 2×CH_2), 1.47 (m, 6H, 3×CH_2), 1.33 (t, 3H, CH_3, J = 7.4 Hz), 0.92 (t, 3H, CH_3, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 150.6, 149.6, 145.1, 141.5, 134.1, 122.6, 122.3, 98.9, 74.2, 56.5, 31.8, 30.0, 29.7, 29.2, 28.6, 26.0, 22.7, 15.5, 14.1; APCIMS m/z 317 (M + 1); analysis for $C_{19}H_{28}N_2O_2$ (316.4), calcd, C, 72.12; H, 8.92; N, 8.85; found, C, 72.05; H, 8.99; N, 8.97.

4-Ethyl-6-methoxy-5-octoxy-8-quinolinamine (3f). Yield: 98%; ^{1}H NMR ($CDCl_3$) δ 8.45 (d, 1H, 2-Ar-H, J = 4.2 Hz), 7.15 (d, 1H, 3-Ar-H, J = 4.2 Hz), 6.77 (s, 1H, 7-Ar-H), 4.57 (bs, 2H, NH_2), 3.93 (s, 3H, OCH_3), 3.87 (t, 2H, OCH_2, J = 6.9 Hz), 3.25 (m, 2H, CH_2), 1.81 (m, 4H, 2×CH_2), 1.44 (m, 8H, 4×CH_2), 1.24 (t, 3H, CH_3, J = 7.4 Hz), 0.90 (t, 3H, CH_3, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 150.8, 149.9, 145.3, 141.6, 134.2, 122.8, 122.1, 98.8, 74.0, 56.4, 31.8, 30.1, 29.6, 29.1, 28.6, 26.2, 24.2, 22.9, 15.6, 14.0; APCIMS m/z 331 (M + 1); analysis for $C_{20}H_{30}N_2O_2$ (330.5), calcd, C, 72.69; H, 9.15; N, 8.48; found, C, 72.78; H, 9.30; N, 8.52.

General method for the synthesis of 2-[4-(5-alkoxy-4-ethyl - 6 - methoxy - 8 - quinolylamino)pentyl] - 1,3 - isoindolinediones (4a–f)

A mixture of 5-alkoxy-4-ethyl-6-methoxy-8-quinolinamine (**3a–f**, 6 mmol), 2-(4-bromopentyl)-1,3-isoindolinedione (6 mmol) and triethylamine (6 mmol) was heated at 120 °C with stirring for 4 h. An additional quantity of 2-(4-bromopentyl)-1,3-isoindolinedione (6 mmol) and triethylamine (6 mmol) was added and stirring continued with heating for another 4 h. A third aliquot of 2-(4-bromopentyl)-1,3-isoindolinedione (6 mmol) and triethylamine (6 mmol) was added and the reaction mixture stirred at 120 °C for additional 16 h. The dark brown reaction mixture was diluted with ethyl acetate (100 mL) and filtered. The filtrate was basified with 2 N NaOH solution and extracted with ethyl acetate (3×50 mL). The extract was washed once with water (20 mL), dried over sodium sulfate and concentrated to afford dark colored residue. Flash column chromatography on silica gel using EtOAc/hexanes (15:85) gave 2-[4-(5-alkoxy-4-ethyl-6-methoxy-8-quinolylamino)-pentyl]-1,3-isoindolinediones (**4a–f**) as viscous oil.

2-[4-(4-Ethyl-6-methoxy-5-propoxy-8-quinolylamino)pentyl]-1,3-isoindolinedione (4a). Yield: 79%; ^{1}H NMR ($CDCl_3$) δ 8.38 (d, 1H, 2-Ar-H, J = 4.4 Hz), 7.82 (m, 2H, Ar-H), 7.71 (m, 2H, Ar-H), 7.10 (d, 1H, 3-Ar-H, J = 4.4 Hz), 6.44 (s, 1H, 7-Ar-H), 6.07 (bs, 1H, NH), 3.96 (s, 3H, OCH_3), 3.87 (t, 2H, OCH_2, J = 6.9 Hz), 3.70 (m, 3H, N–CH and N–CH_2), 3.25 (m, 2H, CH_2), 1.78 (m, 6H, 3×CH_2), 1.3 (m, 6H, 2×CH_3), 1.04 (t, 3H, CH_3, J = 7.9 Hz); ^{13}C NMR ($CDCl_3$) δ 168.5, 151.1, 149.4, 145.1, 144.4, 142.0, 133.9, 132.3, 123.7, 123.2, 122.5, 98.9, 94.3, 70.3, 56.8, 48.0, 37.8, 34.0, 28.6, 24.7, 23.3, 20.7, 15.5, 10.6; APCIMS m/z 476 (M + 1); analysis for $C_{28}H_{33}N_3O_4$ (475.6), calcd, C, 70.71; H, 6.99; N, 8.84; found, C, 70.75; H, 6.93; N, 8.89.

2-[4-(5-Butoxy-4-ethyl-6-methoxy-8-quinolylamino)pentyl]-1,3-isoindolinedione (4b). Yield: 77%; ^{1}H NMR ($CDCl_3$) δ 8.40 (d, 1H, 2-Ar-H, J = 4.4 Hz), 7.85 (m, 2H, Ar-H), 7.70 (m, 2H, Ar-H), 7.14 (d, 1H, 3-Ar-H, J = 4.4 Hz), 6.45 (s, 1H, 7-Ar-H), 6.03 (bs, 1H, NH), 3.95 (s, 3H, OCH_3), 3.88 (t, 2H, OCH_2, J = 6.9 Hz), 3.71 (m, 3H, N–CH and N–CH_2), 3.24 (m, 2H, CH_2), 1.62 (m, 8H, 4×CH_2), 1.3 (m, 6H, 2×CH_3), 0.95 (t, 3H, CH_3, J = 7.9 Hz); ^{13}C NMR ($CDCl_3$) δ 168.4, 151.1, 149.5, 145.2, 144.3, 142.0, 133.8, 132.5, 123.7, 123.1, 122.6, 98.9, 94.4, 74.3, 56.9, 48.1, 38.0, 34.2, 30.1, 28.4, 28.3, 22.7, 20.8, 15.6, 14.1; APCIMS m/z 490 (M + 1); analysis for $C_{29}H_{35}N_3O_4$ (489.6), calcd, C, 71.14; H, 7.21; N, 8.58; found, C, 71.10; H, 7.24; N, 8.53.

2-[4-(4-Ethyl-6-methoxy-5-pentoxy-8-quinolylamino)pentyl]-1,3-isoindolinedione (4c). Yield: 67%; ^{1}H NMR ($CDCl_3$) δ 8.39 (d, 1H, 2-Ar-H, J = 4.4 Hz), 7.83 (m, 2H, Ar-H), 7.72 (m, 2H, Ar-H), 7.12 (d, 1H, 3-Ar-H, J = 4.4 Hz), 6.42 (s, 1H, 7-Ar-H), 6.10 (bs, 1H, NH), 3.92 (s, 3H, OCH_3), 3.85 (t, 2H, OCH_2, J = 6.9 Hz), 3.71 (m, 3H, N–CH and N–CH_2), 3.22 (m, 2H, CH_2), 1.62 (m, 10H, 5×CH_2), 1.3 (m, 6H, 2×CH_3), 0.95 (t, 3H, CH_3, J = 7.9 Hz); ^{13}C NMR ($CDCl_3$) δ 168.5, 151.2, 149.5, 145.1, 144.4, 142.0, 133.9, 132.3, 123.7, 123.2, 122.5, 98.9 94.3, 74.3, 56.8, 48.0, 38.0, 34.1, 30.1, 28.7, 28.3, 25.5, 22.7, 20.8, 15.6, 14.1; APCIMS m/z 504 (M + 1); analysis for $C_{30}H_{37}N_3O_4$ (503.6), calcd, C, 71.54; H, 7.40; N, 8.34; found, C, 71.50; H, 7.44; N, 8.30.

2-[4-(4-Ethyl-5-hexoxy-6-methoxy-8-quinolylamino)pentyl]-1,3-isoindolinedione (4d). Yield: 81%; ^{1}H NMR ($CDCl_3$) δ 8.38 (d, 1H, 2-Ar-H, J = 4.4 Hz), 7.85 (m, 2H, Ar-H), 7.7 (m, 2H, Ar-H), 7.14 (d, 1H, 3-Ar-H, J = 4.4 Hz), 6.44 (s, 1H, 7-Ar-H), 6.02 (bs, 1H, NH), 3.96 (s, 3H, OCH_3), 3.87 (t, 2H, OCH_2, J = 6.9 Hz), 3.72 (m, 3H, N–CH and N–CH_2), 3.24 (m, 2H, CH_2), 1.65 (m, 12H, 6×CH_2), 1.3 (m, 6H, 2×CH_3), 0.94 (t, 3H, CH_3, J = 7.9 Hz); ^{13}C NMR ($CDCl_3$) δ 168.5, 151.1, 149.5, 144.3, 142.1, 133.9, 132.3, 132.1, 123.7, 123.2, 122.4, 112.0, 94.3, 77.5, 77.3, 77.1, 76.6, 74.3, 56.8, 48.0, 38.0, 34.1, 31.8, 30.0, 28.6, 25.8, 22.7, 20.7, 15.5, 14.0; EIMS m/z 517 (M^+); analysis for $C_{31}H_{39}N_3O_4$ (517.7), calcd, C, 71.93; H, 7.59; N, 8.12; found, C, 71.90; H, 7.52; N, 8.11.

2-[4-(4-Ethyl-5-heptoxy-6-methoxy-8-quinolylamino)pentyl]-1,3-isoindolinedione (4e). Yield: 78%; ^{1}H NMR ($CDCl_3$) δ 8.39 (d, 1H, 2-Ar-H, J = 4.4 Hz), 7.82 (m, 2H, Ar-H), 7.71 (m, 2H, Ar-H), 7.10 (d, 1H, 3-Ar-H, J = 4.4 Hz), 6.44 (s, 1H, 7-Ar-H), 6.07 (bs, 1H, NH), 3.96 (s, 3H, OCH_3), 3.87 (t, 2H, OCH_2, J = 6.9 Hz), 3.75 (m, 3H, N–CH and N–CH_2), 3.25 (m, 2H, CH_2), 1.67 (m, 14H, 7×CH_2), 1.30 (m, 6H, 2×CH_3), 1.04 (t, 3H, CH_3, J = 7.9 Hz); ^{13}C NMR ($CDCl_3$) δ 168.6, 151.1, 149.6, 145.2, 144.4, 142.1, 133.9, 132.2, 123.5, 123.1, 122.7, 98.8, 94.2, 74.2, 56.6, 48.1, 38.2, 34.1, 33.5, 31.7, 30.1, 28.9, 28.5, 25.5, 22.9, 20.1, 15.6, 14.1; APCIMS m/z 532 (M + 1); analysis for $C_{32}H_{41}N_3O_4$ (531.7), calcd, C, 72.29; H, 7.77; N, 7.90; found, C, 72.25; H, 7.72; N, 7.91.

2-[4-(4-Ethyl-6-methoxy-5-octoxy-8-quinolylamino)pentyl]-1,3-isoindolinedione (4f). Yield: 75%; ^{1}H NMR ($CDCl_3$) δ 8.39 (d, 1H, 2-Ar-H, J = 4.4 Hz), 7.82 (m, 2H, Ar-H), 7.73 (m, 2H, Ar-H), 7.09 (d, 1H, 3-Ar-H, J = 4.4 Hz), 6.47 (s, 1H, 7-Ar-H), 6.07 (bs, 1H, NH), 3.95 (s, 3H, OCH_3), 3.88 (t, 2H, OCH_2, J = 6.9 Hz), 3.74 (m, 3H, N–CH and N–CH_2), 3.25 (m, 2H, CH_2), 1.66 (m, 16H, 8×CH_2), 1.30 (m, 6H, 2×CH_3), 1.06 (t, 3H, CH_3, J = 7.9 Hz); ^{13}C NMR ($CDCl_3$) δ 168.5, 151.1, 149.2, 145.0, 144.4, 142.2, 133.9, 132.1, 123.6, 123.1, 122.3, 98.9, 94.1, 74.3, 56.8, 48.1, 38.5, 34.1, 33.3, 31.4, 30.1, 28.7, 28.3, 25.5, 22.7, 21.9, 20.8, 15.7, 14.2; APCIMS m/z 546 (M + 1); analysis for $C_{33}H_{43}N_3O_4$ (545.7), calcd, C, 72.63; H, 7.94; N, 7.70; found, C, 72.61; H, 7.90; N, 7.71.

General method for the synthesis of N^8-(4-amino-1-methylbutyl)-5-alkoxy-4-ethyl-6-methoxy-8-quinolinamines (5a–f)

To a solution of 2-[4-(5-alkoxy-4-ethyl-6-methoxy-8-quinolylamino)pentyl]-1,3-isoindolinedione (**4a–f**, 4 mmol) in 95% ethyl alcohol (20 mL), was added hydrazine hydrate (100 mmol), and the reaction mixture was heated under reflux for 8 h. Solvent was removed

under reduced pressure and the residue was diluted with water (20 mL). The reaction mixture was basified with 8 N NaOH solution, extracted with chloroform (3×20 mL), and washed once with water (10 mL). Chloroform extracts were dried over sodium sulfate and concentrated under reduced pressure to yield N^8-(4-amino-1-methylbutyl)-5-alkoxy-4-ethyl-6-methoxy-8-quinolinamines (**5a–f**) as oil. Treatment with ethereal hydrochloric acid solution provided the requisite N^8-(4-amino -1-methylbutyl)-5-alkoxy-4-ethyl-6-methoxy-8-quinolinamines as their hydrochloride salts.

N^8-(4-Amino-1-methylbutyl)-4-ethyl-6-methoxy-5-propoxy-8-quinolinamine (5a). Yield: 96%; mp (salt) 107–112 °C (dec.); ^{1}H NMR (free base, $CDCl_3$) δ 8.38 (d, 1H, 2-Ar-H, J=4.3 Hz), 7.11 (d, 1H, 3-Ar-H, J=4.3 Hz), 6.44 (s, 1H, 7-Ar-H), 6.11 (bs, 1H, NH), 3.96 (s, 3H, OCH_3), 3.87 (t, 2H, OCH_2, J=6.9 Hz), 3.64 (m, 1H, N–CH), 3.25 (m, 4H, 2×CH_2), 1.80 (m, 8H, 2×CH_2 and NH_2), 1.32 (m, 6H, 2×CH_3), 1.05 (t, 3H, CH_3, J=7.9 Hz); ^{13}C NMR (free base, $CDCl_3$) δ 167.1, 151.2, 149.5, 144.4, 142.2, 134.1, 123.7, 122.4, 94.3, 75.8, 56.9, 51.5, 48.2, 34.9, 28.6, 27.7, 23.3, 20.7, 15.5, 10.6; APCIMS m/z 346 (M+1); analysis for $C_{20}H_{33}Cl_2N_3O_2$ (418.4), calcd, C, 57.41; H, 7.46; N, 10.03; found, C, 57.39; H, 7.41; N, 10.10.

N^8-(4-Amino-1-methylbutyl)-5-butoxy-4-ethyl-6-methoxy-8-quinolinamine (5b). Yield: 84%; mp (salt) 106–113 °C (dec.); ^{1}H NMR (free base, $CDCl_3$) δ 8.39 (d, 1H, 2-Ar-H, J=4.3 Hz), 7.13 (d, 1H, 3-Ar-H, J=4.3 Hz), 6.42 (s, 1H, 7-Ar-H), 6.10 (bs, 1H, NH), 3.97 (s, 3H, OCH_3), 3.89 (t, 2H, OCH_2, J=6.9 Hz), 3.64 (m, 1H, N–CH), 3.25 (m, 2H, CH_2), 2.75 (t, 2H, N–CH_2, J=6.9 Hz), 1.70 (m, 10H, 4×CH_2 and NH_2), 1.37 (m, 6H, 2×CH_3), 1.00 (t, 3H, CH_3, J=7.9 Hz); ^{13}C NMR (free base, $CDCl_3$) δ 167.0, 151.1, 149.4, 144.4, 142.0, 134.2, 123.5, 122.0, 94.1, 75.9, 56.7, 51.5, 48.0, 34.9, 28.1, 27.5, 23.3, 20.5, 15.5, 14.1, 10.5; APCIMS m/z 360 (M+1); analysis for $C_{21}H_{35}Cl_2N_3O_2$ (432.4), calcd, C, 58.32; H, 7.69; N, 9.71; found, C, 58.35; H, 7.72; N, 9.70.

N^8-(4-Amino-1-methylbutyl)-4-ethyl-6-methoxy-5-pentoxy-8-quinolinamine (5c). Yield: 96%; mp (salt) 86–89 °C (dec.); ^{1}H NMR (free base, $CDCl_3$) δ 8.37 (d, 1H, 2-Ar-H, J=4.3 Hz), 7.10 (d, 1H, 3-Ar-H, J=4.3 Hz), 6.41 (s, 1H, 7-Ar-H), 6.10 (bs, 1H, NH), 3.96 (s, 3H, OCH_3), 3.90 (t, 2H, OCH_2, J=6.9 Hz), 3.64 (m, 1H, N-CH), 3.22 (m, 2H, CH_2), 2.75 (t, 2H, N–CH_2, J=6.9 Hz), 1.62 (m, 12H, 5×CH_2 and NH_2), 1.30 (m, 6H, 2×CH_3), 0.95 (t, 3H, CH_3, J=7.9 Hz); ^{13}C NMR (free base, $CDCl_3$) δ 151.1, 149.5, 144.3, 142.1, 134.0, 132.2, 123.7, 122.3, 93.9, 74.2, 56.8, 48.2, 42.2, 34.2, 30.2, 29.7, 28.6, 28.2, 22.6, 20.7, 15.5, 14.0; APCIMS m/z 374 (M+1); analysis for $C_{22}H_{37}Cl_2N_3O_2$ (446.5), calcd, C, 59.59; H, 7.90; N, 9.41; found, C, 59.62; H, 7.93; N, 9.38.

N^8-(4-Amino-1-methylbutyl)-4-ethyl-5-hexoxy-6-methoxy-8-quinolinamine (5d). Yield: 94%; mp (salt) 76–79 °C (dec.); ^{1}H NMR (free base, $CDCl_3$) δ 8.40 (d, 1H, 2-Ar-H, J=4.3 Hz), 7.12 (d, 1H, 3-Ar-H, J=4.3 Hz), 6.44 (s, 1H, 7-Ar-H), 6.07 (bs, 1H, NH), 3.98 (s, 3H, OCH_3), 3.92 (t, 2H, OCH_2, J=6.9 Hz), 3.85 (m, 1H, N–CH), 3.28 (m, 2H, CH), 2.76 (t, 2H, N–CH_2, J=5.8 Hz), 1.63 (m, 14H, 6×CH_2 and NH_2), 1.35 (m, 6H, 2×CH_3), 0.94 (t, 3H, CH_3, J=7.95 Hz); ^{13}C NMR (free base, $CDCl_3$) δ 151.1, 149.6, 144.4, 142.0, 132.5, 130.9, 128.8, 123.7, 122.5, 94.4, 74.2, 68.2, 56.8, 48.2, 38.7, 31.8, 30.4, 28.9, 25.8, 22.9, 20.6, 15.5, 14.1; APCIMS m/z 388 (M+1); analysis for $C_{23}H_{39}Cl_2N_3O_2$ (460.5), calcd, C, 59.99; H, 8.97; N, 9.12; found, C, 59.95; H, 8.93; N, 9.10.

N^8-(4-Amino-1-methylbutyl)-4-ethyl-5-heptoxy-6-methoxy-8-quinolinamine (5e). Yield: 99%; mp (salt) 74–78 °C (dec.); ^{1}H NMR (free base, $CDCl_3$) δ 8.39 (d, 1H, 2-Ar-H, J=4.3 Hz), 7.11 (d, 1H, 3-Ar-H, J=4.3 Hz), 6.48 (s, 1H, 7-Ar-H), 6.10 (bs, 1H, NH), 3.99 (s, 3H, OCH_3), 3.85 (t, 2H, OCH_2, J=6.9 Hz), 3.64 (m, 1H, N–CH), 3.23 (m, 2H, CH_2), 2.74 (t, 2H, N–CH_2, J=6.9 Hz), 1.78 (m, 16H, 7×CH_2 and NH_2), 1.30 (m, 6H, 2×CH_3), 1.05 (t, 3H, CH_3, J=7.9 Hz); ^{13}C NMR (free base, $CDCl_3$) δ 151.0, 149.4, 144.3, 142.5, 134.2, 132.0, 123.4, 122.1, 94.2, 74.2, 56.5, 48.2, 42.1, 34.2, 31.9, 30.1, 30.9, 29.2, 28.6, 26.1, 22.7, 20.5, 15.5, 14.2; APCIMS m/z 402 (M+1); analysis for $C_{24}H_{41}Cl_2N_3O_2$ (474.5), calcd, C, 60.74; H, 8.28; N, 8.85; found, C, 60.62; H, 8.21; N, 8.92.

N^8-(4-Amino-1-methylbutyl)-4-ethyl-6-methoxy-5-octoxy-8-quinolinamine (5f). Yield: 84%; mp (salt) 70–72 °C (dec.); ^{1}H NMR (free base, $CDCl_3$) δ 8.36 (d, 1H, 2-Ar-H, J=4.3 Hz), 7.10 (d, 1H, 3-Ar-H, J=4.3 Hz), 6.43 (s, 1H, 7-Ar-H), 6.11 (bs, 1H, NH), 3.95 (s, 3H, OCH_3), 3.87 (t, 2H, OCH_2, J=6.9 Hz), 3.61 (m, 1H, N–CH), 3.24 (m, 2H, CH_2), 2.80 (t, 2H, N–CH_2, J=6.9 Hz), 1.65 (m, 18H, 8×CH_2 and NH_2), 1.29 (m, 6H, 2×CH_3), 0.89 (t, 3H, CH_3, J=7.9 Hz); ^{13}C NMR (free base, $CDCl_3$) δ 151.1, 149.7, 144.4, 141.8, 134.1, 132.5, 123.7, 122.5, 94.7, 74.3, 56.9, 50.7, 48.0, 40.2, 33.9, 31.9, 30.0, 29.3, 28.6, 26.1, 23.4, 22.7, 20.6, 15.5, 14.1; APCIMS m/z 416 (M+1); analysis for $C_{25}H_{43}Cl_2N_3O_2$ (488.6), calcd, C, 61.46; H, 8.45; N, 8.59; found, C, 61.32; H, 8.32; N, 8.63.

General method for the synthesis of N^1-[4-(5-alkoxy-4-ethyl-6-methoxy-8-quinolylamino)pentyl]-3-(2,4-dimethyl-3,6-dioxo-1,4-cyclo-hexadienyl)-3-methylbutan-amides (6a–f) and 2-{2-[4-(5-alkoxy-4-ethyl-6-methoxy-8-quinolylamino)pentyl-carbamoyl]-1,1-dimethylethyl}-3,5-dimethylphenyl acetates (7a–f)

To a mixture of 3-(2,4-dimethyl-3,6-dioxo-1,4-cyclohexadienyl)-3-methylbutanoic acid (**8**, 1.06 mmol) or 3-(2,4-dimethyl-6-methylcarbonyloxyphenyl)-3-methylbutanoic acid (9, 1.06 mmol) and N^8-(4-amino-1-methylbutyl)-5-alkoxy-4-ethyl-6-methoxy-8-quinolinamine (**5a–f**, 0.96 mmol) in anhydrous dichloromethane (15 mL), DCC (1.06 mmol) and DMAP (0.02 g) was added. The resulting reaction mixture was stirred for 4 h at room temperature under nitrogen atmosphere. Reaction mixture was filtered to remove the separated 1,3-dicyclohexylurea, and filtrate was evaporated under reduced pressure to provide crude product. Purified by flash

column chromatography on silica gel using methanol/chloroform (0.2:99.8) to yield N^1-[4-(5-alkoxy-4-ethyl-6-methoxy-8-quinolylamino)pentyl]-3-(2,4-dimethyl-3,6-dioxo-1,4-cyclo-hexadienyl)-3-methylbutanamide (**6a–f**) and 2-{2-[4-(5-alkoxy-4-ethyl-6-methoxy-8-quinolylamino)pentylcarbamoyl]-1,1-dimethylethyl}-3,5-dimethylphenyl acetates (**7a–f**) in excellent yields. Treatment with ethereal hydrochloric acid solution afforded the corresponding hydrochloride salt.

N^1-[4-(4-Ethyl-6-methoxy-5-propoxy-8-quinolylamino)pentyl]-3-(2,4-dimethyl-3,6-dioxo-1,4-cyclohexadienyl)-3-methylbutanamide (6a). Yield: 73%; mp (salt) 140–143 °C (dec.); ^{1}H NMR (free base, $CDCl_3$) δ 8.40 (d, 1H, 2-Ar-H, J = 4.3 Hz), 7.13 (d, 1H, 3-Ar-H, J = 4.3 Hz), 6.50 (s, 1H, Ar-H), 6.43 (s, 1H, 7-Ar-H), 5.55 (bs, 1H, NH), 4.22 (bs, 1H, NH), 3.96 (s, 3H, OCH_3), 3.86 (t, 2H, OCH_2, J = 6.9 Hz), 3.62 (m, 1H, CH), 3.49 (m, 2H, CH_2), 3.23 (m, 4H, 2×CH_2), 2.77 (s, 2H, CH_2), 2.17 (s, 3H, CH_3), 1.95 (s, 3H, CH_3), 1.75 (m, 6H, 3×CH_2), 1.38 (s, 6H, 2×CH_3), 1.28 (m, 6H, 2×CH_3), 1.05 (t, 3H, CH_3, J = 7.4 Hz); ESIMS m/z 564 (M + 1); analysis for $C_{33}H_{46}ClN_3O_5$ (600.2), calcd, C, 66.03; H, 7.55; N, 7.00; found, C, 66.24; H, 7.84; N, 7.22.

N^1-[4-(5-Butoxy-4-ethyl-6-methoxy-8-quinolylamino)pentyl]-3-(2,4-dimethyl-3,6-dioxo-1,4-cyclohexadienyl)-3-methylbutanamide (6b). Yield: 91%; mp (salt) 135–139 °C (dec.); ^{1}H NMR (free base, $CDCl_3$) δ 8.39 (d, 1H, 2-Ar-H, J = 4.2 Hz), 7.12 (d, 1H, 3-Ar-H, J = 4.2 Hz), 6.48 (s, 1H, Ar-H), 6.42 (s, 1H, 7-Ar-H), 5.60 (bs, 1H, NH), 4.12 (bs, 1H, NH), 3.97 (s, 3H, OCH_3), 3.89 (t, 2H, OCH_2, J = 6.9 Hz), 3.61 (m, 1H, CH), 3.23 (m, 4H, 2×CH_2), 2.76 (s, 2H, CH_2), 2.20 (s, 3H, CH_3), 1.95 (s, 3H, CH_3), 1.61 (m, 8H, 4×CH_2), 1.36 (s, 6H, 2×CH_3), 1.24 (m, 6H, 2×CH_3), 0.97 (t, 3H, CH_3, J = 6.9 Hz); APCIMS m/z 578 (M + 1); analysis for $C_{34}H_{48}ClN_3O_5$ (614.2), calcd, C, 66.48; H, 7.71; N, 6.84; found: C, 66.86; H, 7.67; N, 6.78.

N^1-[4-(4-Ethyl-6-methoxy-5-pentoxy-8-quinolylamino)pentyl]-3-(2,4-dimethyl-3,6-dioxo-1,4-cyclohexadienyl)-3-methylbutanamide (6c). Yield: 95%; mp (salt) 126–128 °C (dec.); ^{1}H NMR (free base, $CDCl_3$) δ 8.39 (d, 1H, 2-Ar-H, J = 4.3 Hz), 7.13 (d, 1H, 3-Ar-H, J = 4.3 Hz), 6.49 (s, 1H, Ar-H), 6.43 (s, 1H, 7-Ar-H), 5.57 (bs, 1H, NH), 4.10 (bs, 1H, NH), 3.96 (s, 3H, OCH_3), 3.88 (t, 2H, OCH_2, J = 6.8 Hz), 3.60 (m, 1H, CH), 3.24 (m, 4H, 2×CH_2), 2.73 (s, 2H, CH_2), 2.21 (s, 3H, CH_3), 1.94 (s, 3H, CH_3), 1.64 (m, 10H, 5×CH_2), 1.37 (s, 6H, 2×CH_3), 1.25 (m, 6H, 2×CH_3), 0.94 (t, 3H, CH_3, J = 6.8 Hz); APCIMS m/z 592 (M + 1); analysis for $C_{35}H_{50}ClN_3O_5$ (628.3), calcd, C, 66.90; H, 7.86; N, 6.68; found, C, 66.86; H, 7.67; N, 6.78.

N^1-[4-(4-Ethyl-5-hexoxy-6-methoxy-8-quinolylamino)pentyl]-3-(2,4-dimethyl-3,6-dioxo-1,4-cyclohexadienyl)-3-methylbutanamide (6d). Yield: 93%; mp (salt) 124–127 °C (dec.); ^{1}H NMR (free base, $CDCl_3$) δ 8.40 (d, 1H, 2-Ar-H, J = 4.4 Hz), 7.14 (d, 1H, 3-Ar-H, J = 4.4 Hz), 6.50 (s, 1H, Ar-H), 6.43 (s, 1H, 7-Ar-H), 5.51 (bs, 1H, NH), 4.11 (bs, 1H, NH), 3.95 (s, 3H, OCH_3), 3.87 (t, 2H, OCH_2, J = 6.7 Hz), 3.61 (m, 1H, CH), 3.23 (m, 4H, 2×CH_2), 2.75 (s, 2H, CH_2), 2.13 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 1.68 (m, 12H, 6×CH_2), 1.37 (s, 6H, 2×CH_3), 1.26 (m, 6H, 2×CH_3), 0.97 (t, 3H, CH_3, J = 7.9 Hz); APCIMS m/z 606 (M + 1); analysis for $C_{36}H_{52}ClN_3O_5$ (642.3), calcd, C, 67.32; H, 7.99; N, 6.54; found, C, 67.25; H, 7.90; N, 6.55.

N^1-[4-(4-Ethyl-5-heptoxy-6-methoxy-8-quinolylamino)pentyl]-3-(2,4-dimethyl-3,6-dioxo-1,4-cyclohexadienyl)-3-methylbutanamide (6e). Yield: 98%; mp (salt) 122–125 °C (dec.); ^{1}H NMR (free base, $CDCl_3$) δ 8.40 (d, 1H, 2-Ar-H, J = 4.2 Hz), 7.14 (d, 1H, 3-Ar-H, J = 4.2 Hz), 6.50 (s, 1H, Ar-H), 6.44 (s, 1H, 7-Ar-H), 5.56 (bs, 1H, NH), 4.12 (bs, 1H, NH), 3.97 (s, 3H, OCH_3), 3.85 (t, 2H, OCH_2, J = 6.8 Hz), 3.61 (m, 1H, CH), 3.21 (m, 4H, 2×CH_2), 2.74 (s, 2H, CH_2), 2.17 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 1.73 (m, 14H, 7×CH_2), 1.38 (s, 6H, 2×CH_3), 1.28 (m, 6H, 2×CH_3), 1.05 (t, 3H, CH_3, J = 7.3 Hz); APCIMS m/z 620 (M + 1); analysis for $C_{37}H_{54}ClN_3O_5$ (656.3), calcd, C, 67.71; H, 8.13; N, 6.40; found, C, 67.75; H, 8.20; N, 6.41.

N^1-[4-(4-Ethyl-6-methoxy-5-octoxy-8-quinolylamino)pentyl]-3-(2,4-dimethyl-3,6-dioxo-1,4-cyclohexadienyl)-3-methylbutanamide (6f). Yield: 57%; mp (salt) 121–123 °C (dec.); ^{1}H NMR (free base, $CDCl_3$) δ 8.40 (d, 1H, 2-Ar-H, J = 4.3 Hz), 7.13 (d, 1H, 3-Ar-H, J = 4.3 Hz), 6.50 (s, 1H, Ar-H), 6.43 (s, 1H, 7-Ar-H), 5.56 (bs, 1H, NH), 4.15 (bs, 1H, NH), 3.96 (s, 3H, OCH_3), 3.88 (t, 2H, OCH_2, J = 6.9 Hz), 3.62 (m, 1H, CH), 3.49 (m, 2H, CH_2), 3.23 (m, 2H, CH_2), 2.75 (s, 2H, CH_2), 2.21 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 1.73 (m, 16H, 8×CH_2), 1.38 (s, 6H, 2×CH_3), 1.28 (m, 6H, 2×CH_3), 0.89 (t, 3H, CH_3, J = 7.9 Hz); APCIMS m/z 634 (M + 1); analysis for $C_{38}H_{56}ClN_3O_5$ (670.4), calcd, C, 68.08; H, 8.26; N, 6.26; found, C, 68.12; H, 8.25; N, 6.35.

2-{2-[4-(4-ethyl-6-methoxy-5-propoxy-8-quinolylamino)-pentacarbamoyl]-1,1-dimethyl-ethyl}-3,5-dimethylphenyl acetate (7a). Yield: 99%; mp (salt) 124–129° (dec.); ^{1}H NMR (free base, $CDCl_3$) δ 8.52 (d, 1H, 2-Ar-H, J = 3.2 Hz), 7.30 (m, 1H, 3-Ar-H), 6.60 (s, 1H, Ar-H), 6.43 (s, 1H, Ar-H), 6.34 (s, 1H, 7-Ar-H), 5.62 (bs, 1H, NH), 4.65 (bs, 1H, NH), 3.91 (m, 2H, CH_2), 3.89 (s, 3H, OCH_3), 3.63 (m, 1H, CH), 3.42 (m, 2H, CH_2), 3.27 (m, 2H, CH_2), 2.60 (m, 2H, CH_2), 2.08 (m, 6H, 2×CH_3), 1.94 (s, 3H, CH_3), 1.78 (m, 2H, CH_2), 1.62 (m, 3H, CH_3), 1.31 (m, 7H, 2×CH_2 and CH_3), 1.14 (m, 6H, 2×CH_3), 1.05 (m, 3H, CH_3); APCIMS m/z 592 (M + 1); analysis for $C_{35}H_{50}ClN_3O_5$ (627.3); calcd, C, 66.91; H, 8.02; N, 6.69; found, C, 66.88; H, 8.22; N, 6.77.

2-{2-[4-(5-Butoxy-4-ethyl-6-methoxy-8-quinolylamino)-pentacarbamoyl]-1,1-dimethyl-ethyl}-3,5-dimethylphenyl acetate (7b). Yield: 85%; mp (salt): 133–137 °C (dec.); ^{1}H NMR (free base, $CDCl_3$) δ 8.55 (d, 1H, 2-Ar-H, J = 4.3 Hz), 7.31 (m, 1H, 3-Ar-H, J = 4.3 Hz), 6.62 (s, 1H, Ar-H), 6.41 (s, 1H, Ar-H), 6.37 (s, 1H, 7-Ar-H), 5.60 (bs, 1H, NH), 4.61 (bs, 1H, NH), 3.93 (m, 2H, OCH_2), 3.90 (s, 3H, OCH_3), 3.61 (m, 1H, CH), 3.40 (m, 2H, CH_2), 3.22 (m, 2H, CH_2), 2.65 (m, 2H, CH_2), 2.10 (m, 6H, 2×CH_3), 1.91 (s, 3H, CH_3), 1.73 (m, 2H, CH_2), 1.62 (m, 3H, CH_3), 1.33 (m, 9H, 3×CH_2 and CH_3), 1.12

(m, 6H, 2×CH_3), 1.08 (m, 3H, CH_3) APCIMS *m/z* 606 (M+1); analysis for $C_{36}H_{52}ClN_3O_5$ (641.3); calcd, C, 67.32; H, 8.16; N, 6.54; found, C, 67.22; H, 8.39; N, 6.55.

2-{2-[4-(-4-Ethyl-6-methoxy-5-pentoxy-8-quinolylamino)-pentacarbamoyl]-1,1-dimethyl-ethyl}-3,5-dimethylphenyl acetate (7c). Yield: 79%; mp (salt): 128–130 °C (dec.); ^{1}H NMR (free base, $CDCl_3$) δ 8.51 (d, 1H, 2-Ar-H, *J*=4.3 Hz), 7.25 (m, 1H, 3-Ar-H, *J*=4.3 Hz), 6.59 (s, 1H, Ar-H), 6.40 (s, 1H, Ar-H), 6.33 (s, 1H, 7-Ar-H), 5.66 (bs, 1H, NH), 4.63 (bs, 1H, NH), 3.89 (m, 2H, OCH_2), 3.85 (s, 3H, OCH_3), 3.62 (m, 1H, CH), 3.43 (m, 2H, CH_2), 3.24 (m, 2H, CH_2), 2.68 (m, 2H, CH_2), 2.13 (m, 6H, 2×CH_3), 1.93 (s, 3H, CH_3), 1.70 (m, 2H, CH_2), 1.61 (m, 3H, CH_3), 1.35 (m, 11H, 4×CH_2 and CH_3), 1.15 (m, 6H, 2×CH_3), 1.10 (m, 3H, CH_3) APCIMS *m/z* 620 (M+1); analysis for $C_{37}H_{54}ClN_3O_5$ (655.4); calcd, C, 67.71; H, 8.29; N, 6.40; found, C, 67.92; H, 8.52; N, 6.75.

2-{2-[4-(4-Ethyl-5-hexoxy-6-methoxy-8-quinolylamino)-pentacarbamoyl]-1,1-dimethyl-ethyl}-3,5-dimethylphenyl acetate (7d). Yield: 83%; mp (salt): 120–122 °C (dec.); ^{1}H NMR (free base, $CDCl_3$) δ 8.58 (d, 1H, 2-Ar-H, *J*=4.3 Hz), 7.29 (m, 1H, 3-Ar-H, *J*=4.3 Hz), 6.63 (s, 1H, Ar-H), 6.45 (s, 1H, Ar-H), 6.32 (s, 1H, 7-Ar-H), 5.61 (bs, 1H, NH), 4.60 (bs, 1H, NH), 3.91 (m, 2H, OCH_2), 3.87 (s, 3H, OCH_3), 3.62 (m, 1H, CH), 3.41 (m, 2H, CH_2), 3.24 (m, 2H, CH_2), 2.65 (m, 2H, CH_2), 2.15 (m, 6H, 2×CH_3), 1.93 (s, 3H, CH_3), 1.73 (m, 2H, CH_2), 1.60 (m, 3H, CH_3), 1.33 (m, 13H, 5×CH_2 and CH_3), 1.18 (m, 6H, 2×CH_3), 1.13 (m, 3H, CH_3) APCIMS *m/z* 634 (M+1); analysis for $C_{38}H_{56}ClN_3O_5$ (669.4); calcd, C, 68.09; H, 8.42; N, 6.27; found, C, 68.32; H, 8.82; N, 6.52.

2-{2-[4-(4-Ethyl-5-heptoxy-6-methoxy-8-quinolylamino)-pentacarbamoyl]-1,1-dimethyl-ethyl}-3,5-dimethylphenyl acetate (7e). Yield: 78%; mp (salt): 122–123 °C (dec.); ^{1}H NMR (free base, $CDCl_3$) δ 8.55 (d, 1H, 2-Ar-H, *J*=4.3 Hz), 7.28 (m, 1H, 3-Ar-H, *J*=4.3 Hz), 6.65 (s, 1H, Ar-H), 6.45 (s, 1H, Ar-H), 6.31 (s, 1H, 7-Ar-H), 5.62 (bs, 1H, NH), 4.61 (bs, 1H, NH), 3.91 (m, 2H, OCH_2), 3.88 (s, 3H, OCH_3), 3.60 (m, 1H, CH), 3.41 (m, 2H, CH_2), 3.24 (m, 2H, CH_2), 2.67 (m, 2H, CH_2), 2.13 (m, 6H, 2×CH_3), 1.95 (s, 3H, CH_3), 1.73 (m, 2H, CH_2), 1.60 (m, 3H, CH_3), 1.33 (m, 15H, 6×CH_2 and CH_3), 1.15 (m, 6H, 2×CH_3), 1.10 (m, 3H, CH_3) APCIMS *m/z* 648 (M+1); analysis for $C_{39}H_{58}ClN_3O_5$ (683.4); calcd, C, 68.45; H, 8.54; N, 6.14; found, C, 68.33; H, 8.80; N, 6.50.

2-{2-[4-(4-Ethyl-6-methoxy-5-octoxy-8-quinolylamino)-pentacarbamoyl]-1,1-dimethyl-ethyl}-3,5-dimethylphenyl acetate (7f). Yield: 89%; mp (salt): 125–127 °C (dec.); ^{1}H NMR (free base, $CDCl_3$) δ 8.52 (d, 1H, 2-Ar-H, *J*=4.3 Hz), 7.30 (m, 1H, 3-Ar-H, *J*=4.3 Hz), 6.63 (s, 1H, Ar-H), 6.44 (s, 1H, Ar-H), 6.31 (s, 1H, 7-Ar-H), 5.61 (bs, 1H, NH), 4.61 (bs, 1H, NH), 3.93 (m, 2H, OCH_2), 3.88 (s, 3H, OCH_3), 3.65 (m, 1H, CH), 3.41 (m, 2H, CH_2), 3.22 (m, 2H, CH_2), 2.65 (m, 2H, CH_2), 2.15 (m, 6H, 2×CH_3), 1.97 (s, 3H, CH_3), 1.75 (m, 2H, CH_2), 1.62 (m, 3H, CH_3), 1.35 (m, 17H, 7×CH_2 and CH_3), 1.12 (m, 6H, 2×CH_3), 1.08 (m, 3H, CH_3) APCIMS *m/z* 660 (M+1); analysis for $C_{40}H_{60}ClN_3O_5$ (697.4); calcd, C, 68.79; H, 8.66; N, 6.02; found, C, 68.93; H, 8.75; N, 6.33.

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26. **Assessment of in vitro susceptibility of an isolate of *Plasmodium falciparum* to the tested compounds**: Different drug dilutions [test compounds and chloroquine (positive control)] were prepared in complete RPMI (medium RPMI 1640 + 10% AB^+ human serum; CRPMI). 50 μL of each dilution was transferred to the respective well of a microtiter plate in triplicates. Parasitized erythrocytes (PE; mainly rings; 4% parasitaemia; 5% hematokrit) were added to each well. Volume in each well was made up to 200 μL with CRPMI. The plates were incubated at 37 °C in a candle jar. After 24–48 h of incubation, thin smears from each well were made and stained with Giemsa. The number of PE/10,000 cells was counted. Percent inhibition by the drug over the control (well which does not contain any drug) was plotted against the respective logarithmic concentration of the drug. Using non-linear regression analysis, the IC_{50} of the test compounds was then calculated.
27. **Blood-schizontocidal activity evaluation of potential antimalarial compounds against *P. berghei* (sensitive strain) and *P. yoelii nigeriensis* (resistant strain) infection in mice:** The method used for screening of the synthesized compounds for their blood-schizontocidal activity is based on a comparison of responses by groups of treated and control mice, six in each group, after infection with *P. berghei* or *P. yoelii nigeriensis*. Using a standard inoculum of *P. berghei* or *P. yoelii nigeriensis*, it is possible to produce a uniform disease that is fatal to 100% of untreated animals, within 6–8 days, with a mean survival time of 6.2 days. Test animals (Swiss mice of either sex, approximately 15–20 g and same age) were housed in metal-topped cages, given a standard laboratory diet and water ad libitum. In order to check factors such as changes in the infectivity of the strain or in the susceptibility of the host or to detect technical errors, a group of infected animals treated with chloroquine diphosphate at dose levels (8.0 mg/kg/day×4), producing definite increases in survival time is included as a positive control in every experiment. In each experiment, the test compounds were administered in graded doses of 100, 50, 25, 10 mg/kg. The compounds showing curative activity at 10 mg/kg were further selected for screening at lower doses. On day '0', groups of six mice each were inoculated intraperitoneally with 1×10^7 infected-erythrocytes from a donor mouse. Four hours later, mice were administered test compounds/chloroquine/vehicle, orally. A total of four doses were given orally on days D '0', D + 1, D + 2, and D + 3. The tail blood smears were made on day D + 4 and D + 7, stained with Giemsa and examined microscopically. The minimum dose that completely suppressed parasitaemia on days D + 4 and D + 7 was termed as minimum effective dose (MED), and the minimum dose that cleared the parasitaemia for up to 60 days was termed as curative dose (CD). The terms 'curative', 'active' and 'inactive' are used to describe the biological activities exhibited by the tested compounds. The term 'curative' indicates complete elimination of malaria parasites from the body, so that relapse cannot occur up to day D + 60. The term 'active' indicates that the treated animals show negative parasitaemia up to D + 7. However, by D + 28, some mice show negative and some mice may show positive test result for parasitaemia. The term 'inactive' indicates that the treated animals show positive test result for parasitaemia either on D + 4 or D + 7 or on both D + 4 and D + 7. The standard drug chloroquine has the MED of 8 mg/kg/day×4 (oral) and curative dose for the drug is 12 mg/kg/day×4 (oral) against *P. berghei* infected mice. On the other hand, chloroquine is found be ineffective against *P. yoelii nigeriensis* infection in mice up to the tested dose of 156 mg/kg/day×4 (oral).