# Synthesis and Antimalarial Activity of Side Chain Modified 4-Aminoquinoline Derivatives

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A new series of side-chain modified 4-aminoquinolines have been synthesized and found active against *P. falciparum* in vitro and *P. yoelli* in vivo. Compounds **6**, **11**, **12**, and **19** exhibited superior in vitro activity compared to chloroquine. Selected compounds **6**, **12**, and **19** exhibited significant suppression in the in vivo assay. These analogs form a complex with hematin and inhibit the $\beta$-hematin formation, suggesting that this class of compounds act on a heme polymerization target.

## Introduction

Malaria is the most common parasitic disease in tropical and subtropical regions, and worldwide 40% of the population lives in a malaria endemic area. According to the World Health Organization, it is estimated that a quantum of people living in areas at risk of malarial transmission is alarming, and approximately 1.0−3.0 million die due to nonavailability of proper treatment.[1] Malaria is caused by protozoan parasites of the genus *Plasmodium*, and *P. falciparum*, *vivax*, *malariae*, and *ovale* species are responsible for the spread of the disease in humans. In the past, quinoline-derived compounds were extensively studied for the development of new therapeutic agents that led to the development of some molecules, namely, pamaquine[2] and mepacrine[3] (Figure 1). The best compound that emerged from this endeavor is chloroquine (CQ[a]), which was discovered in the 1940s.[4] During the past six decades, CQ and other aminoquinolines have been the frontline antimalarial agents because of their therapeutic efficacy and lower cost.[5] However, development of resistance has severely limited the choice of available antimalarial drugs, which clearly highlights the urgent need of novel chemotherapeutic agents for the treatment of malaria.

The structure−activity relationship studies on 4-aminoquinoline antimalarial compounds suggest that the 7-chloro-4-aminoquinoline nucleus is obligatory for antimalarial activity, particularly, inhibition of $\beta$-hematin formation and accumulation of the drug at the target site.[6] It has been reported that when the 7-chloro group is replaced by an electron donor group like $NH_2$, $OCH_3$, and so on or an electron-withdrawing group like $NO_2$, the antimalarial activity is reduced due either to an increase or a decrease in the p$K_a$ of quinoline nitrogen atom (p$K_a$1). This suggests that 7-chloro is most suited for antiplasmodial activity of 4-aminoquinoline classes of compounds.[7] The importance of 4-aminopyridine (p$K_a$1) substructure for hematin binding and antimalarial activity was also supported by experimental and molecular modeling studies by Cheruku et al.[8] The role of carbon chain length in the aminoalkyl side chain has also been investigated, and the results suggest that both shortening (2−3 carbon atoms) and lengthening (10−12 carbon atoms) the carbon side chain in CQ leads to compounds that remain active against CQ-resistant strains of *P. falciparum*.[9] Similar results have been

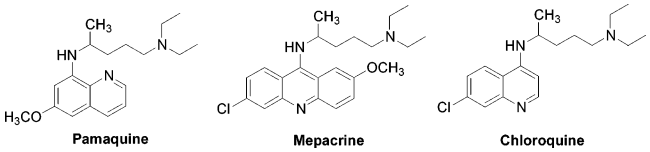


**Figure 1.** Structure of some clinically useful antimalarial agents.

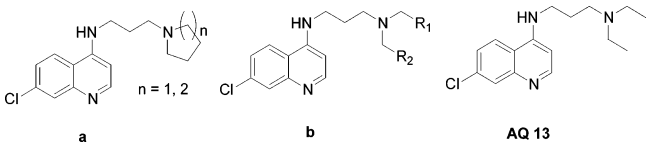


**Figure 2.** Structure of 4-aminoquinoline derivatives.

reported from this laboratory, suggesting that 4-aminoquinoline analogues with altered chain length exhibit promising activity against CQ sensitive strains of *P. falciparum* NF-54 in vitro and CQ resistant N-67 strain of *P. yoelii* in vivo.[10] Stocks et al. have shown that a series of short chain CQ derivatives, on replacement of the diethylamino function with the more metabolically stable side chain (*tert*-butyl) as well as heterocyclic ring (piperidyl, pyrrolidinyl, and morpholinyl, Figure 2a) modifications led to a substantial increase in the antimalarial activity.[11] Lately, Madrid et al. have replaced diethylamino (Figure 2b) functionality with one propyl group as constant with other bulky or aromatic rings and have found that some of these analogs are active against multiple drug resistant strains.[12] The dialkyl tertiary amino function of the lateral side chain is reportedly providing basic nitrogen (p$K_a$2), which helps in the accumulation of the drug in acidic food vacuoles, as well as in providing lipophilicity to the molecule, and minimally contributes to hematin binding.[7a,c,11,13] However, there is no report in the literature regarding the effect of complete removal of the basicity of tertiary nitrogen atom on the antimalarial activity. Recent evidence suggests that 4-aminoquinoline analogs of altered side chain such as $N^1$-(7-chloro-quinolin-4yl)-3-($N^3$,$N^3$-diethylamino) propylamine (AQ-13, Figure 2) show potential leads for the development of new drugs.[14]

These findings have given impetus to the thought that side chain modification is an attractive strategy for the development of antimalarial drugs with desirable activity profile. On the basis of this evidence we surmised that selectively modifying the pendent amino group with small heterocyclic systems (Figure 3, **4**−**33**) could modulate the antimalarial activity. In view of the fact that thiazolidin-4-one is a biologically privileged scaffold and well tolerated in human subjects[15a,b] as well as our interest

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[†] Division of Medicinal and Process Chemistry.
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[a] Abbreviations: CQ, chloroquine; DCC, *N*,*N*-dicyclohexylcarbodiimide; MIC, minimum inhibitory concentration.

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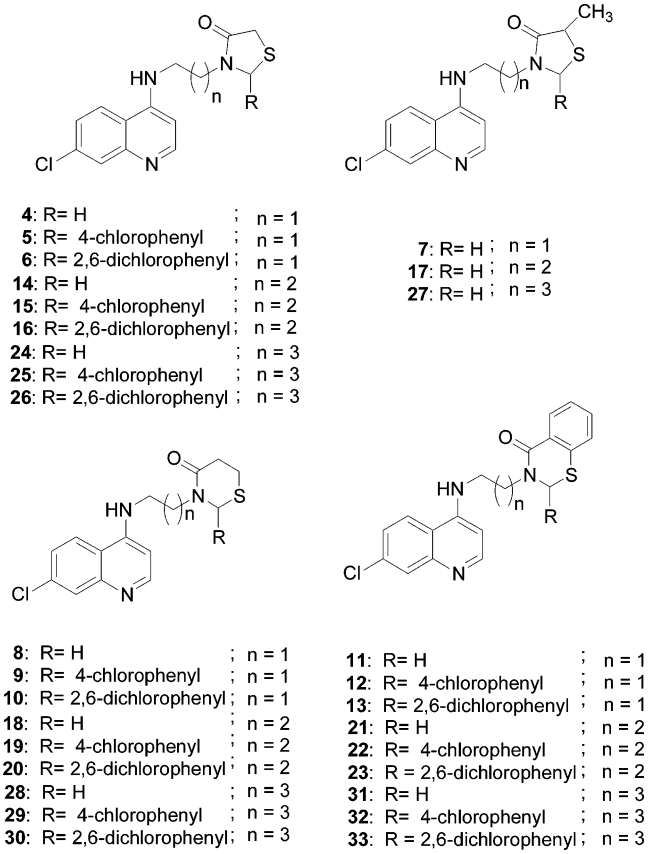


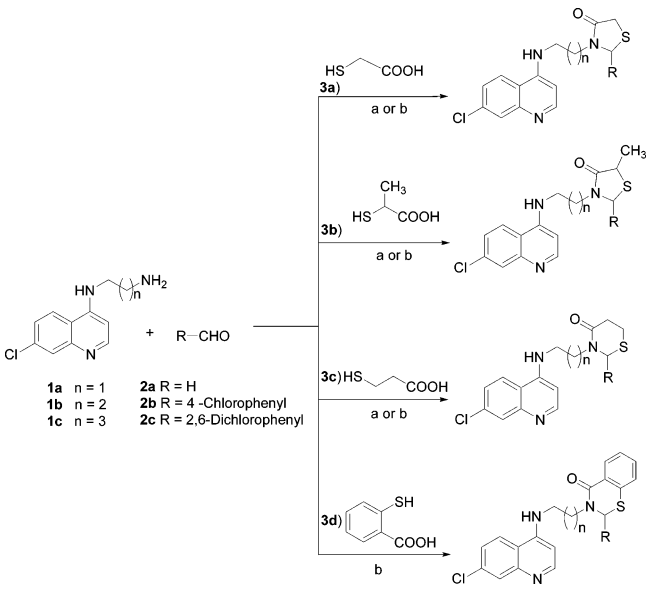

**Figure 3.** Structure of compounds **4**−**33**.

in the chemistry of thiazolidinones, we thought it would be appropriate to explore the antiplasmodial activity of derivatives having a thiazolidin-4-one nucleus at the terminal side chain amino group of 4-aminoquinoline. Furthermore, this type of modification would prevent dealkylation without adversely affecting the lipophilicity and antimalarial activity of the molecule as described in the literature.[11] For the present study, we have designed compounds wherein 7-chloro-4-aminoquinoline was not altered and modifications were carried out at the pendent amino group. The present study describes synthesis, biochemical studies, and antimalarial activity of this new series of compounds.

## Chemistry

The target compounds **4**−**33** were prepared as outlined in Scheme 1. The amino components (**1a**−**c**) used in the present study were prepared by aromatic nucleophilic substitution on 4,7-dichloroquinoline with excess of diaminoalkane in neat conditions with the simple standard workup procedure reported earlier from our laboratory.[10] The amino group can be transformed to the thiazolidin-4-one skeleton by the reaction of aldehyde and mercapto acid in the presence of a dehydrating agents, namely, molecular sieves, trimethyl orthoformate, and so on.[15a,b] However, an improved procedure reported from this laboratory in which *N*,*N*-dicyclohexylcarbodiimide (DCC) is used as a dehydrating agent to accelerate the intramolecular cyclization resulting in faster reaction and improved yields.[15c] The 4-aminoquinoline derivatives of 2-substituted thiazolidin-4-ones/[1,3]thiazinan-4-ones were obtained from the appropriate amine (**1a**−**c**), substituted aldehyde (**2a**−**c**), and mercapto acid (**3a**−**c**) in the presence of DCC in anhydrous THF at room temperature (Table 1). After completion of the reaction, which is usually 1.0 h, the desired products were obtained in excellent yields and purity.

**Scheme 1.** Synthesis of Compounds **4**−**33**[a]




[a] Reagents and conditions: (a) DCC, THF, room temperature; (b) toluene reflux.

In the case of thiazolidin-4-ones (**4**, **14**, and **24**), 5-methylthiazolidin-4-ones (**7**, **17**, and **27**), and [1,3]thiazinan-4-ones (**8**, **18**, and **28**) compounds, the aldehyde component is *p*-formaldehyde, which is insoluble in THF. Therefore, we have applied classical refluxing protocol wherein compounds were obtained by refluxing a mixture of the appropriate amine, *p*-formaldehyde, and mercapto acid in dry toluene at 120 °C for 20−24 h. The same reaction strategy was employed for the synthesis of 2-(unsubstituted/substituted)-2,3-dihydro-benzo[*e*][1,3]thiazin-4-one (**11**−**13**, **21**−**23**, and **31**−**33**) derivatives. Both analytical and spectral data of the synthesized compounds are in agreement with the structures of the synthesized compounds (**4**−**33**).

## Results and Discussion

All the compounds having modifications at the lateral amino group of the side chain (**4**−**33**) were evaluated for their antimalarial activity against the NF-54 strain of *P. falciparum* in vitro according to the procedure reported in the literature.[16a,b] The $IC_{50}$ values are calculated from experiments carried out in triplicate. Some of the selected compounds, which have shown activity comparable to CQ, were also evaluated against the N-67 strain of *P. yoelli* in Swiss mice. The in vitro activity data ($IC_{50}$) showed that these derivatives, having a nonbasic nitrogen atom at the side chain, showed remarkable antimalarial activity. This suggests that the modification at the lateral side chain nitrogen atom is very well tolerated for antimalarial activity.

Among the 30 compounds tested, nine compounds showed an $IC_{50}$ range between 0.013 and 0.98 $\mu$M, 10 compounds had an $IC_{50}$ range between 1.031 and 1.98 $\mu$M, and an $IC_{50}$ range between 2.144 and 2.917 $\mu$M was observed in five compounds. The remaining six compounds have shown $IC_{50}$ values above 3 $\mu$M, but not more than 7.15 $\mu$M. The difference in the $IC_{50}$ values can be attributed to factors such as number of carbon atoms in the side chain, ring size, and C-2 substitutions on the ring at distal amino group. In the **1a**−**c** amino component, introduction of the thiazolidin-4-one, [1,3]thiazinan-4-one, and 2,3-dihydro-benzo[*e*][1,3]thiazin-4-one ring system resulted in the molecules having moderate antimalarial activity. All the three types of heterocyclic substitutions, namely, thiazolidin-

**Table 1.** Biological and Biophysical Data of the Compounds (**4**−**33**)

| cmpd no. | $IC_{50}$[a] ($\mu$M) | MIC[b] ($\mu$M) | Log $P$[c] | p$K_a$[c] | Log $K$[d] | $IC_{50}$[e] ($\mu$M) |
|---|---|---|---|---|---|---|
| **4** | 2.144 ± 0.15 | 3.25 | 1.66 | 8.23 | 4.42 ± 0.01 | 0.98 ± 0.07 |
| **5** | 0.980 ± 0.07 | 1.20 | 4.59 | 8.23 | 5.25 ± 0.01 | 0.75 ± 0.15 |
| **6** | 0.039 ± 0.01 | 0.55 | 5.22 | 8.23 | 5.72 ± 0.01 | 0.46 ± 0.19 |
| **7** | 1.678 ± 0.07 | 3.11 | 2.89 | 8.23 | 4.56 ± 0.01 | 1.05 ± 0.12 |
| **8** | 2.917 ± 0.13 | 6.21 | 1.80 | 8.23 | 4.66 ± 0.02 | 0.99 ± 0.09 |
| **9** | 4.070 ± 0.17 | 4.62 | 4.73 | 8.23 | 5.54 ± 0.02 | 0.47 ± 0.04 |
| **10** | 3.271 ± 0.77 | 4.28 | 5.17 | 8.23 | 5.78 ± 0.01 | 0.45 ± 0.10 |
| **11** | 0.065 ± 0.01 | 0.68 | 3.61 | 8.23 | 4.51 ± 0.01 | 0.94 ± 0.04 |
| **12** | 0.013 ± 0.01 | 0.26 | 6.53 | 8.23 | 5.66 ± 0.02 | 0.24 ± 0.06 |
| **13** | 0.291 ± 0.03 | 5.88 | 6.83 | 8.23 | 5.77 ± 0.01 | 0.49 ± 0.09 |
| **14** | 1.650 ± 0.04 | 3.11 | 2.01 | 8.23 | 4.87 ± 0.01 | 0.96 ± 0.04 |
| **15** | 1.040 ± 0.08 | 1.16 | 4.94 | 8.23 | 5.36 ± 0.02 | 0.56 ± 0.18 |
| **16** | 0.138 ± 0.02 | 0.27 | 5.58 | 8.23 | 5.87 ± 0.01 | 0.39 ± 0.08 |
| **17** | 2.327 ± 0.05 | 5.65 | 2.55 | 8.23 | 4.12 ± 0.01 | 1.02 ± 0.07 |
| **18** | 1.810 ± 0.54 | 2.48 | 2.15 | 8.23 | 4.33 ± 0.02 | 0.96 ± 0.05 |
| **19** | 0.014 ± 0.01 | 0.28 | 5.08 | 8.23 | 5.27 ± 0.02 | 0.62 ± 0.12 |
| **20** | 6.154 ± 0.03 | 10.39 | 5.27 | 8.23 | 5.35 ± 0.01 | 0.88 ± 0.09 |
| **21** | 0.429 ± 0.02 | 1.30 | 3.96 | 8.23 | 4.62 ± 0.01 | 0.78 ± 0.15 |
| **22** | 1.031 ± 0.05 | 2.02 | 6.89 | 8.23 | 5.82 ± 0.03 | 0.46 ± 0.12 |
| **23** | 2.193 ± 0.10 | 9.45 | 6.93 | 8.23 | 6.01 ± 0.01 | 0.65 ± 0.04 |
| **24** | 2.647 ± 0.03 | 5.96 | 2.52 | 8.76 | 4.63 ± 0.02 | 0.91 ± 0.02 |
| **25** | 1.980 ± 0.04 | 4.08 | 4.68 | 8.76 | 5.55 ± 0.01 | 0.85 ± 0.03 |
| **26** | 3.031 ± 0.10 | 6.17 | 6.09 | 8.76 | 5.27 ± 0.02 | 0.64 ± 0.10 |
| **27** | 1.286 ± 0.08 | 5.73 | 3.06 | 8.76 | 4.58 ± 0.01 | 0.98 ± 0.07 |
| **28** | 1.812 ± 0.05 | 2.86 | 2.66 | 8.76 | 4.29 ± 0.01 | 0.89 ± 0.09 |
| **29** | 0.271 ± 0.02 | 0.54 | 5.59 | 8.76 | 4.88 ± 0.02 | 0.76 ± 0.05 |
| **30** | 7.153 ± 0.81 | 15.15 | 5.73 | 8.76 | 5.64 ± 0.01 | 0.58 ± 0.09 |
| **31** | 1.510 ± 0.07 | 2.51 | 4.47 | 8.76 | 4.78 ± 0.01 | 0.89 ± 0.10 |
| **32** | 1.272 ± 0.17 | 2.17 | 7.40 | 8.76 | 5.36 ± 0.01 | 0.95 ± 0.11 |
| **33** | 3.074 ± 0.17 | 13.81 | 7.39 | 8.76 | 5.64 ± 0.01 | 0.97 ± 0.03 |
| **CQ** | 0.106 ± 0.01 | 0.39 | 4.72 | 8.41 | 5.52 ± 0.02 | 0.40 ± 0.10 |

[a] $IC_{50}$ = 50% inhibitory concentration values ($\mu$M) against NF-54 strain of *P. falciparum* (data are expressed as means ± SD from at least three different experiments in duplicate). [b] MIC = minimum inhibiting concentration for the development of the ring stage parasite into the schizont stage during 40 h of incubation against NF-54 strain of *P. falciparum*. [c] Log $P$ and p$K_a$ values are calculated by Pallas software. [d] 1:1 (compound: hematin) complex formation in 40% aq. DMSO, 20 mM HEPES buffer, pH 7.5 at 25 °C (data are expressed as means ± SD from at least three different experiments in duplicate). [e] The $IC_{50}$ represents the millimolar equivalents of test compounds, relative to hemin, required to inhibit $\beta$-hematin formation by 50% (data are expressed as means ± SD from at least three different experiments in duplicate).

4-one, [1,3]thiazinan-4-one, and 2,3-dihydro-benzo[*e*][1,3]-thiazin-4-one ring systems, showed potent antimalarial activity, and in some cases the $IC_{50}$ values are comparable or better than CQ.

The compounds derived from the amino component **1a** with two-carbon atoms in the side chain, an increase in the ring size from five-membered (thiazolidin-4-one; **4**) to six-membered ([1,3]thiazinan-4-one; **8**) marginally reduces the antimalarial activity, but the introduction of an eight-membered ring system, 2,3-dihydro-benzo[*e*][1,3]thiazin-4-one with 4-chlorophenyl substitution on C-2 position (**12**; $IC_{50}$ = 0.013 $\mu$M), increases the antimalarial activity as compared to CQ ($IC_{50}$ = 0.106 $\mu$M). Introduction of 2,6-dichlorophenyl substitution on the thiazolidin-4-one ring system (**6**; $IC_{50}$ = 0.039 $\mu$M) results in a 2.7-fold higher antimalarial activity in comparison to CQ. However, an increase in the ring size from five-membered (**4**) to six-membered (**8**) reduces the antimalarial activity, whereas introduction of an eight-membered ring system 2,3-dihydro-benzo[*e*][1,3]thiazin-4-one (**11**) further increases the antimalarial activity as compared to **4** and **8**. Introduction of 4-chlorophenyl substitution at the C-2 position of five- (**5**) and eight-membered (**12**) rings causes a further increase in the antimalarial activity ($IC_{50}$ = 0.98 and 0.013 $\mu$M) in comparison to C-2 unsubstituted analogs (**4** and **11**; $IC_{50}$ = 2.144 and 0.065 $\mu$M).

Among the compounds obtained from the amino component **1b** with a three-carbon atom in the side chain, introduction of a thiazolidin-4-one ring system with 2,6-dichlorophenyl substitution at the C-2 position (**16**; $IC_{50}$ = 0.138 $\mu$M) was equipotent as compared to CQ. Also, modifications in the ring size from a five-membered to a six-membered ring with 4-chlorophenyl substitution at the C-2 position (**19**; $IC_{50}$ = 0.014 $\mu$M) shows an increased (8-fold) antiplasmodial activity as compared to CQ. 4-Chlorophenyl substitution on the C-2 position of five-membered **15** ($IC_{50}$ = 1.040 $\mu$M) and six-membered **19** ($IC_{50}$ = 0.014 $\mu$M) indicates an increased antiplasmodial activity as compared to the corresponding unsubstituted thiazolidin-4-one **14** ($IC_{50}$ = 1.650 $\mu$M) and [1,3]-thiazinan-4-one (**18**; $IC_{50}$ = 1.810 $\mu$M). 4-Chlorophenyl substitution on the C-2 position of 2,3-dihydro-benzo[*e*][1,3]thiazin-4-one (**22**; $IC_{50}$ = 1.031 $\mu$M) shows a lowering of antimalarial activity in comparison to unsubstituted 2,3-dihydro-benzo[*e*]-[1,3]thiazin-4-one (**21**; $IC_{50}$ = 0.429 $\mu$M).

Compounds derived from the amino component **1c** with a four-carbon atom in the side chain and 4-chlorophenyl substitution on the C-2 position of thiazolidin-4-one (**25**; $IC_{50}$ = 1.980 $\mu$M), [1,3]thiazinan-4-one (**29**; $IC_{50}$ = 0.271 $\mu$M), and 2,3-dihydro-benzo[*e*][1,3]thiazin-4-one (**32**; $IC_{50}$ = 1.272 $\mu$M) ring systems explicates an increased antimalarial activity in comparison to an unsubstituted ring system (**24**, **28**, and **31**; $IC_{50}$ = 2.647, 1.812, and 1.510 $\mu$M, respectively). 4-Chlorophenyl substitution at the C-2 position of [1,3]thiazinan-4-one (**29**) shows a 2.5-fold reduced antimalarial activity in comparison to CQ. In general, 2,6-dichlorophenyl substitution at the C-2 position (**20**, **23**, **26**, **30**, and **33**) shows a reduced antimalarial activity in comparison to the unsubstituted analog (**18**, **21**, **24**, **28**, and **31**).

All the compounds (**4**−**33**) were also evaluated for their antimalarial activity against the NF-54 strain of *P. falciparum* in vitro for the determination of minimum inhibitory concentration (MIC) values according to reported protocol,[16c] and the data is presented in Table 1. It is interesting that the MIC values of the test compounds are in accordance to their corresponding $IC_{50}$ values. Furthermore, there is reasonable correlation ($R^2$ = 0.69) between MIC and $IC_{50}$ values of the compounds.

The activity data (Table 1) suggest that three-carbon atoms in the side chain are appropriate for the antimalarial activity of compounds with six-membered rings (**18** and **19**), as an increase or decrease in carbon chain length results in reduced activity. The activity data further suggest that two carbon atoms in the side chain are best for the antimalarial activity in the case of eight-membered ring analogs (**11**, **12**, and **13**). This data suggest that the length of the side chain is also crucial for the activity of the compounds and has a correlation with the size of the heterocyclic ring.

Compounds with significant activity in vitro (**6**, **11**, **12**, **16**, **19**, and **29**) were selected for in vivo activity in Swiss mice against *P. yoelli* (N-67 strain). The mice were treated with compounds (30 mg/kg) intraperitoneally, once daily for four consecutive days, and their survival time and parasitaemia on day four were compared with those of control mice receiving saline (Table 2). These compounds showed significant activity against *P. yoelli* infections in mice. Compounds **6**, **12**, and **29** suppressed 76.08, 81.00, and 62.32% parasitaemia on day four compared to 100% suppression displayed by CQ. The mean survival time (MST) is also in accordance with inhibition data. The compelling antimalarial activity exhibited by the novel

**Table 2.** Data of In Vivo Antimalarial Activity against N-67 Strain of *Plasmodium yoelii* in Swiss Mice

| cmpd no. | % suppression on day 4[a] | mean survival time[b] (MST in days) ± SE |
|---|---|---|
| **6** | 76.08 | 14.6 ± 1.4 |
| **11** | 48.33 | 11.4 ± 1.4 |
| **12** | 81.00 | 15.2 ± 1.7 |
| **16** | 40.08 | 10.6 ± 1.2 |
| **19** | 23.50 | 12.0 ± 0.7 |
| **29** | 62.32 | 13.8 ± 0.9 |
| **CQ** | 99.99 | 20.00 ± 1.53 |
| control | | 10.1 ± 0.7 |

[a] Percent suppression = $[(C - T)/C] \times 100$; where $C$ = parasitaemia in control group and $T$ = parasitaemia in treated group. [b] MST calculated for the mice that died during the 28 day observation period, and the mice that survived beyond 28 days are excluded.

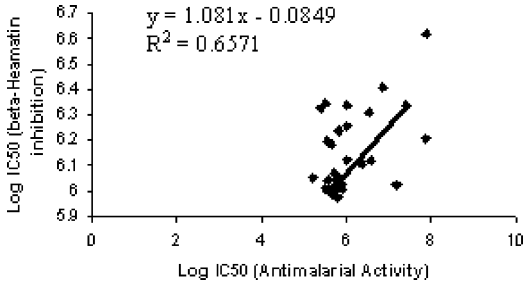



**Figure 4.** Correlation between antimalarial activity vs inhibition of $\beta$-hematin formation.

4-aminoquinoline derivatives described in the present study underscores their potential for further development as antimalarial drugs.

The antiplasmodial activity data clearly suggest that 7-chloro-4-aminoquinoline derivative(s) with a modified side chain having nonbasic nitrogen exhibit potent antimalarial activity. In spite of a major modification in the side chain, this series of compounds exhibits antimalarial activity by the same mode of action as that of CQ, namely, inhibition of hemozoin formation. It is tempting to infer from the data in Table 1 that all the active compounds bind with an association constant in the range 4.12−6.01 with hematin and form a complex. The Log $K$ values of hematin association constant highlighted the importance of C-2 substitution in the heterocyclic ring system of the side chain. In general, compounds that have 4-chlorophenyl and 2,6 dichlorophenyl substitution (lipophilic nature) at the C-2 position of the heterocyclic ring system of the side chain show very tight binding to hematin in comparison to unsubstituted analogs. It has been considered that the p$K_a$ of the tertiary nitrogen of the side chain as well as $\pi-\pi$ stacking interactions of the quinoline ring with the porphyrin ring system are the two important factors for hematin binding.[8a,11,13] However, Egan and Ncokazi have reported that the hydrophobic interactions dominated in hematin binding, whereas electrostatic ($\pi-\pi$) interaction play a trifling role for the 4-aminoquinoline antimalarial activity.[17] The present data suggest that the principle interaction might be hydrophobic as well as electrostatic interaction of the quinoline ring with the porphyrin ring system, and the p$K_a$2 of the tertiary nitrogen atom has no role in hematin binding.

All the compounds inhibited the $\beta$-hematin formation in a concentration-dependent manner. Furthermore, there is reasonable correlation between antimalarial activity and inhibition of $\beta$-hematin formation ($IC_{50}$ values; Figure 4) as reflected in the $R^2$ value of 0.651, thereby supporting that the mechanism of action of this class of compounds is similar to CQ. The most potent inhibitors were the compounds **6**, **12**, **16**, **19**, and **29**, with an inhibitory concentration ($IC_{50}$) of 0.24−0.76 $\mu$M. These five compounds were also found to be significantly active in the in vivo assay system.

It is generally believed that the p$K_a$1 and p$K_a$2 contribute to the overall antimalarial activity of 4-aminoquinoline-derived compounds. There is substantial evidence in the literature to support the role of p$K_a$1 for the hematin binding ($\pi-\pi$ interaction) that leads to the inhibition of hemozoin formation, whereas the role of p$K_a$2 for hematin binding is not clearly understood.[18] Among the 4-aminoquinoline derivative compounds having alkyl substitution at the amino group exhibit potent antimalarial activity, while unsubstituted derivatives are not reported to be active, suggesting, thereby, that lipophilicity and not basicity at this center has a direct bearing on the antimalarial activity. The modification carried out in the present study may affect the p$K_a$ values, which could have a cascading effect on the antimalarial activity. It is appropriate to mention here that the introduction of a heterocyclic ring system on the pendent amino group may affect the basicity of the ring nitrogen (p$K_a$1), therefore, we have calculated the p$K_a$ values of these compounds using Pallas.[19] The data presented in Table 1 clearly indicate that, in the present set of compounds, the side chain nitrogen is nonbasic and the p$K_a$ values of the quinoline ring nitrogen atom remain unaffected.

## Conclusion

The present study describes the synthesis and antiplasmodial activity of a novel series of 4-aminoquinoline derivatives with a nonbasic side chain nitrogen. All the compounds exhibit potent antiplasmodial activity in vitro, and a few are superior to chloroquine. Further, the in vivo results on selected compounds revealed that these compounds also show significant antimalarial activity in mice. The biochemical studies confirm that the mechanism of action is similar to that of chloroquine, as most of the compounds form an association complex with hematin and thereby inhibit hemozoin formation. The present findings are sufficient to establish that the basicity of the side chain nitrogen is not very essential for antiplasmodial activity of 4-aminoquinolines and opens new vistas for the designing of new antimalarial agents.

## Experimental Section

**General Synthetic Procedure for Compounds 4−33.** The appropriate amine (1.0 mmol) and aldehyde (2.0 mmol) were stirred in THF under ice-cold conditions for 5 min, followed by addition of the mercapto acid component (3.0 mmol). After 5 min, DCC (1.2 mmol) was added to the reaction mixture at 0 °C and the reaction mixture was stirred for an additional 50 min at room temp. DCU was removed by filtration, the filtrate was concentrated to dryness under reduced pressure, and the residue was taken up in chloroform. The organic layer was successively washed with 5% aq. sodium hydrogen carbonate and then finally with brine. The organic layer was dried over sodium sulfate, and the solvent was removed under reduced pressure to get a crude product that was purified by column chromatography on silica gel using chloroform−methanol.

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**Supporting Information Available:** Experimental procedures for the synthesis and analytical data of compounds **4**−**33** and the

protocols used for the biological as well as biophysical studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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