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Synthesis and antimalarial activity evaluation of some new 7-chloro-4-aminoquinolines with substituted ring at side chain

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Abstract

Some new 7-chloro-4-aminoquinoline derivatives with substituted ring at side chain were synthesized, characterized by their physical and spectral data and screened for *in vitro* antimalarial activity against a chloroquine sensitive strain of *P. falciparum* (3D7). All the compounds showed *in vitro* antimalarial activity at the tested dose which, however, was considerably less than that of the standard reference drug chloroquine. However, the compounds with 2-fluorophenyl (II_A), 4-methoxyphenyl (II_B), 3-hydroxyphenyl (II_C), furan-2-yl (II_D) substitution at 2- position of 1,3-thiazinan-4-one ring system attached with the terminal propyl side chain of 7-chloro-4-aminoquinoline nucleus showed comparatively better activity than that of the compounds with ethyl (II_E), (4-dimethylamino)phenyl (II_F), 3-methylthiophen-2-yl (II_G), at the side chain. The results clearly revealed that a bulky group with optimum lipophilicity at 1,3- thiazinan-4-one ring in the side chain might be required for antimalarial activity of 3-(3-(7-chloroquinolin-4-ylamino)propyl)-1,3-thiazinan-4-one derivatives.

Keywords: 4-aminoquinolines, Antimalarial, Bulky group, Lipophilicity.

Introduction

Despite over a hundred years of drug development, malaria remains one of the most devastating infectious diseases in the world, both from the point of view of mortality and morbidity and its worldwide occurrence in tropical and subtropical regions. According to the World Health Organization, it is estimated that approximately 40% of the world population lives in malaria endemic areas, with 300-500 million clinical cases and 1.5-2.7 million deaths per year globally, and up to 1 million of those deaths are among children younger than 5 years old [1-4]. Malaria is a life-threatening parasitic disease caused by protozoan parasites of the genus *Plasmodium*; and

P. falciparum, P. vivax, P. malariae, and *P. ovale* are four well known species of human malaria parasite [5]-[6] and more recently another species, *P. knowlesi* has been documented [7]. *Plasmodium falciparum* is the most widespread, and causing most severe and potentially fatal malaria [8]. Chloroquine (CQ), Fig.1 has remained the drug of choice for the malaria chemotherapy for decades, because it is an effective, less toxic and cheap drug [9]. The mechanism of action of CQ and its closely related 4-aminoquinoline antimalarial compounds involves formation of toxic drugs- Fe(III)protoporphyrin IX complexes (π-π complex) in the acidic (p^H 5.4) food vacuole of parasite, blocking the detoxification of heme [Fe(II)FPIX], produced as a toxic by-product of host hemoglobin degradation. This process is believed to prevent polymerization of heme into an insoluble compound, hemozoin (malaria pigment) by inhibiting parasitic heme polymerase; which ultimately leads to death of parasite [10-12]. The emergence and spread of resistance of malaria parasite, especially *P. falciparum* towards currently available drugs, especially chloroquine, has become a major health concern in the tropical and subtropical regions of the world and therefore, development of new chemotherapeutic agents is an urgent need to fight against malaria.

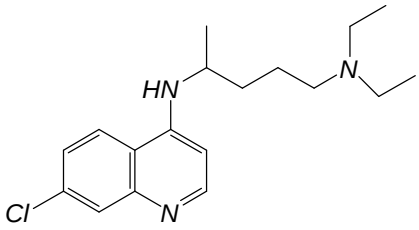


Figure 1. Chloroquine [1]

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 β-hematin formation and accumulation of the drug at the target site [10], [13]-[16]. The new series of compounds reported by Solomon *et al*. [17] with aromatic ring system at the side chain of 7-chloro-4-aminoquinoline nucleus are active against *P. falciparum (in vitro)* and *P. yoelli (in vivo)*. These compounds form a complex with hematin and inhibit the β-hematin formation which suggests that this class of compounds act on a heme polymerization target. Their observation that three-carbon atoms in the side chain are appropriate for the antimalarial activity of compounds with six-membered rings, while an increase or decrease in carbon chain length results in reduced activity suggesting 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.

These findings have given impetus to the concept that side chain modification is an attractive strategy for the development of new antimalarial drugs with desirable activity profile. Accordingly we presumed that selectively modifying the pendent amino group with small heterocyclic systems could modulate the antimalarial activity. Based on this fact, compounds were synthesized by modifications at the C-2 position of a six membered 1,3-thiazinan-4-one ring attached at the terminal propyl side chain of 7-chloro-4-aminoquinoline without making alteration in 7-chloro-4-aminoquinoline nucleus (Scheme 2). Accordingly, seven new derivatives of 3-(3-(7-chloroquinolin-4-ylamino)propyl)-2-substituted-1,3-thiazinan-4-one were prepared and screened for antimalarial activity.

Results and Discussion

Chemistry

In this study, seven new 3-(3-(7-chloroquinolin-4-ylamino)propyl)-1,3-thiazinan-4-one derivatives were synthesized. The intermediate (I) and all the products (II_{A-G}) were obtained in good yield and purity. The purity of all compounds was ascertained by TLC using various solvent combination of different polarity. The purified compounds were thereafter characterized by IR, ^{1}H-NMR, ^{13}C-NMR and Mass spectral methods, and elemental analysis. The spectral data are in agreement with the structure of the synthesized compounds.

All the compounds in chloroform exhibited three characteristic absorption maxima (λ_{max}) in the range between 220-450 nm. The shift of λ_{max} towards longer wavelength indicate the presence of strong chromophoric group such as quinoline structure, and C=O group in the molecule. The maxima in the lower wavelength range between 220-280 nm is due to the presence of substituted phenyl ring, and heteroaromatic ring system such as furan-2-yl as in II_D, thiophen-2-yl as in II_G. The infrared spectral data as depicted in experimental section showed characteristic absorption bands for >NH (3340-3435 cm^{-1}); C=O (1693-1734 cm^{-1}); C-N (1275-1398 cm^{-1}); C-Cl (1074-1097 cm^{-1}); $>CH_2$ (υ_{as}: 2976-2930 cm-^{1} & υ_s: 2819-1863 cm^{-1}), and aromatic C=C (1432-1657 cm^{-1}) stretching which confirms the anticipated structure of the synthesized compounds, II_A-II_G. The assignment of protons is fully supported by the characteristic chemical shift values for the 4-aminoquinoline nucleus as discussed in experimental section. The assignment of ^{13}C resonance for different carbon atoms of quinoline nucleus, $>CH_2$ group of side chain and C=O of 1,3-thiazinan-4-one ring system is in close agreement with the structures of the synthesized compounds. The prominent molecular ion peaks, $[M+H]^+$ for all the compounds are in accordance with the anticipated mass of II_{A-G}. The structures of synthesized compounds were further established by elemental analysis. The results of CHN analyses were within the acceptable limits of the calculated values. The elemental analyses data are shown in experimental section.

Antimalarial screening

Though, all the seven synthesized compounds showed antimalarial activity against chloroquine sensitive *P. falciparum* (3D7) strain at the tested dose, all the compounds were found to be much less potent than chloroquine. However, the compounds with 2-fluorophenyl (II_A), 4-methoxyphenyl (II_B), 3-hydroxyphenyl (II_C), furan-2-yl (II_D) substitution at 2- position of 1,3-thiazinan-4-one ring system attached with the terminal propyl side chain of 7-chloro-4-aminoquinoline nucleus showed comparatively better activity than that of the compounds with ethyl (II_E), 4-(dimethylamino)phenyl (II_F), 5-methylthiophen-2-yl (II_G), at the side chain. The results clearly revealed that a bulky group with optimum lipophilicity at 1,3-thiazinan-4-one ring in the side chain might be an important requirement for antimalarial activity of 3-(3-(7-chloroquinolin-4-ylamino)propyl)-1,3-thiazinan-4-one derivatives. The *in vitro* antimalarial activity data are shown in Table 1.

Table 1. *In vitro* antimalarial activity data[#]

Sl. No.	Comp. code	Dosage (µg/ml)	% Dead rings + trophozoites*
1	II_A	50	39.0
2	II_B	50	32.0
3	II_C	50	39.5
4	II_D	50	38.5
5	II_E	50	18.5
6	II_F	50	25.0
7	II_G	50	22.0
8	Chloroquine[@]	0.4	67.0

[#] Test strain: Chloroquine-sensitive *Plasmodium falciparum* (3D7); * Mean of two replicates and counted against 400 asexual parasites per replicate.; [@] Reference standard

The results of the present study can be correlated with the lipophilicity (i.e. LogP value) of compounds. The LogP value for all the synthesized compounds as obtained from 'Chem Draw Ultra 8.0 2004' software is shown in Table 2. The presence of a lipophilic bulky group at C-2 position of 1,3-thiazinan-4-one ring system seems to be important for the compounds to be active as antimalarial agents and perhaps it should be within a range of lipophilicity values. The compounds with 5-methylthiophen-2-yl substitution (LogP=6.15) and 4-(dimethylamino)phenyl (LogP=4.44) showed less activity than that of compounds with 2-fluorophenyl (LogP=4.31), 2-furyl (LogP=4.45) and 4-methoxyphenyl (LogP=4.03) substitution. Also it is important to note here that non-aromatic alkyl substitution (e.g. ethyl) with LogP=3.07 showed lowest activity in this series because of less lipophilicity than that of optimum. However, it is important to mention here that not only the lipophilicity, but also the basicity (p^{Ka}) of the molecule is important for a compound to be active as an antimalarial agent [17].

Table 2. Log P values[#] of synthesized compounds

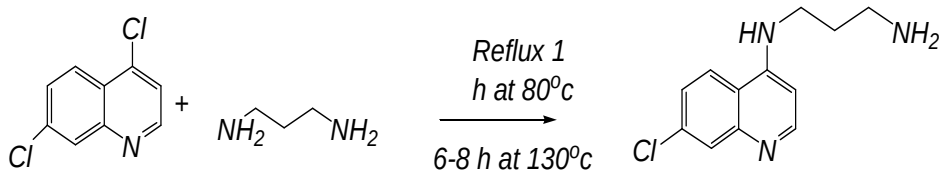
Sl. No.	**Comp. code**	**LogP**
1	II_A	4.31
2	II_B	4.03
3	II_C	3.77
4	II_D	4.45
5	II_E	3.07
6	II_F	4.44
7	II_G	6.15

[#] Log P values were obtained from Chem Draw Ultra 8.0 2004 Software.

Materials and Methods

1. Chemistry

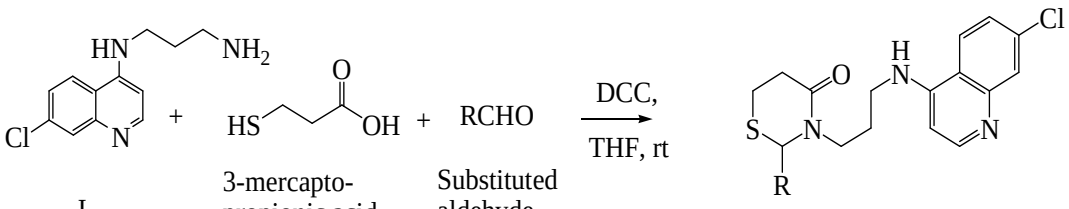
All chemicals and reagents were procured from Sigma-Aldrich Corporation (USA), Merck (Germany) or Spectrochem Pvt. Ltd. (India) and were used without further purification unless otherwise stated. 4,7-dichloroquinoline was obtained from M/s. Mangalam Drug & Organics, Mumbai, India. Melting points (mp) were taken in open capillaries on a Veego-MPI melting point apparatus and are uncorrected. The progress of reactions and purity of synthesized compounds were checked on silica gel-G TLC plate using various solvent combinations of different polarity. The spots were detected with iodine vapors on UV-light (254 nm). The UV-visible spectra (λ_{max}, nm) of synthesized compounds were obtained on Shimadzu UV-1700 UV-visible spectrophotometer. Infrared (IR) spectra were recorded on a FT-IR Perkin-Elmer Spectrum RX-I spectrometer.



4,7-dichloroquinoline *1,3-Diaminopropane*

N^1-(7-chloroquinolin-4-yl)propane-1,3diamine (I)

Scheme 1. Synthesis of intermediate, I (Step-I)



I

3-mercapto-propionic acid

Substituted aldehyde

3-(3-(7-chloroquinolin-4-ylamino)propyl)-2-substituted-1,3-thiazinan-4-one (II_{A-D})

Compound	R
II_A	2-fluorophenyl
II_B	4-methoxyphenyl
II_C	3-hydroxyphenyl
II_D	furan-2-yl
II_E	ethyl
II_F	4-(dimethylamino)phenyl
II_G	5-methylthiophen-2-yl

Scheme 2. Synthesis of target compounds, II_A-II_G (Step-II)

The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC-F 300 FT-NMR spectrometer using $CDCl_3$ as solvent. Chemical shifts (δ in ppm) are reported with tetramethylsilane (TMS) as an internal standard. Mass spectra were undertaken with a LC-MS Water 4000 ZQ instrument using atmospheric pressure ionization (API). Elemental microanalyses (CHN) were performed on a Perkin Elmer 2400 Series II CHNS/O analyzer and values were within the acceptable limits of the calculated values.

The intermediate reaction product (I), N^1-(7-chloroquinolin-4-yl)-propane-1,3-diamine (Scheme 1) was prepared according to the method reported by Madrid *et al*. [18,19,]. Seven derivatives (II_{A-G}) of 3-(3-(7-chloroquinolin-4-ylamino)propyl)-1,3-thiazinan-4-one were prepared as per the method designed by Solomon *et al*. [17]. The scheme of synthesis of I and II_{A-G} are outlined in Scheme 1 and Scheme 2 respectively.

N^1-(7-chloroquinolin-4-yl)propane-1,3-diamine ***(I)***

Yellowish white solid, 86% yield, mp: 96-98^{o}C, R_f: 0.25 (chloroform : methanol=1 :1); UV-visible spectrum (chloroform), λ_{max} (nm) : 270, 366, 412.5. IR (KBR), ν, cm^{-1} : 3422, 3382 (N-H str., -NH_2); 3312 (N-H str., >NH); 1352, 1286 (C-N str.); 1078 (Ar. C-Cl str). ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 1.82–1.86 (t, J=9.6 Hz, 2H, CH_2); 2.71–2.81 (t, J=19.2 Hz, 2H, CH_2); 3.20–3.32 (dd, J=9.6, 25.2 Hz, 2H, CH_2); 6.54–6.55 (d, J=5.6 Hz, 1H, quinoline-H_3); 7.25 (bs, 2H, NH_2), 7.51 (s, 1H, NH); 7.56–7.77 (dd, J=18.0, 18.0 Hz, quinoline-H_6); 7.89–7.90 (d, J=6.0 Hz, 1H, quinoline–H_5); 8.02–8.04 (d, J=9.2 Hz, 1H, quinoline–H_8); 8.22–8.29 (dd, J=5.2, 6.4 Hz, IH, quinoline- H_2). ^{13}C NMR (100MHz, $CDCl_3$), δ (ppm): 27.65 (CH_2), 39.38 (CH_2), 44.67 (CH_2); 109.54 (C-3, quinoline), 117.72 (C-4, quinoline); 124.48 (C-5, quinoline), 127.59 (C-6, quinoline); 134.26 (C-8, quinoline), 136.79 (C-7, quinoline C-Cl), 146.89 (C-8a, quinoline), 152.72 (C-2, quinoline), 151.53 (C-4, quinoline). MS (API), m/z (%): 236.72 (100), $[M+H]^+$. Anal. cacld. (%) for C_{12} H_{14} N_3Cl: C, 61.15; H, 5.99; N, 17.83; found (%): C, 61.42; H, 6.36; N, 12.99.

3-(3-(7-chloroquinolin-4-ylamino)propyl)-2-(2-fluorophenyl)-1,3-thiazinan-4-one ***(II_A)***

Light yellow gummy solid, 73% yield; R_f: 0.55 (chloroform : methanol=3:1); UV-visible spectrum (chloroform), λ_{max} (nm) : 262.0, 364.5, 428.0. IR spectrum (chloroform), υ, cm^{-1}: 3340 (N-H str., >NH); 1698 (C=O str.); 1371, 1275 (C-N str.); 1097 (Ar. C-Cl str.). ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 1.73–1.85 (t, 2H, J=17.4 Hz, CH_2), 2.57–2.61 (t, 2H, J=6.0 Hz, CH_2); 2.67–2.84 (m, 2H, CH_2); 3.16–3.37 (m, 2H, CH_2); 5.70 (s, 1H, NH), 6.22–6.23 (d, 1H, J=4.5 Hz, quinoline-H_3); 6.82–7.11 (m, 4H, C_6H_4–); 7.49–7.55 (dd 1H, J=8.7 Hz, 5.1 Hz, quinoline-H_6); 7.73–7.79 (dd 1H, J=7.5, 4.8 Hz, quinoline-H_5); 7.98–8.00 (d, 1H, J=6.9 Hz, quinoline-H_8); 8.23–8.24 (d, 1H, J=4.5 Hz, 2H quinoline). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 25.74 (CH_2), 29.59 (CH_2), 34.37 (CH_2), 39.85 (CH_2), 44.78 (CH_2), 55.73 (CH), 115.85 (C-2, quinoline), 116.58 (C-4a, quinoline), 123.07 (C-5, quinoline), 124.08, 124.64, 125.95, 126.63 (Ar-C), 127.63 (C-6, quinoline) 128.68 (Ar-C), 130.30 (C-8, quinoline), 132.67 (Ar-C), 136.37 (C-7, quinoline, C-Cl), 148.16 (C-8a, quinoline), 151.94 (C-2, quinoline), 158.28 (C-4, quinoline), 160.76 (C-F), 170.70 (C=O). MS (API), m/z (%): 430.2 (100), $[M+H]^+$; 431.1 (25.67), 432.1 (36.45), 433.2 (10.35). Anal. cacld. (%) for $C_{22}H_{21}N_3OSClF$: C, 61.46; H, 4.92; N, 9.77; found (%): C, 58.59 ; H, 5.65; N, 5.28.

3-(3-(7-chloroquinolin-4-ylamino)propyl)-2-(4-methoxyphenyl)-1,3-thiazinan-4-one ***(II_B)***
Light yellow gummy solid, 68% yield; R_f: 0.52 (chloroform : methanol=3:1); UV-visible spectrum (chloroform), λ_{max} (nm)**:** 277.0, 368.0, 442.0. IR spectrum (chloroform), υ, cm-^{1}: 3435 (N-H str., >NH); 1734 (C=O str.); 1304, 1296 (C-N str.); 1161, 1046 (υ_{as} & υ_s C-O-C str.); 1080 (Ar. C-Cl str.). ^{1}H NMR (300 MHz, $CDCl_3$, δ (ppm): 1.73–1.88 (m, 2H, CH_2), 2.59–2.64 (m, 2H, CH_2), 2.66–2.78 (m, 2H, CH_2), 3.11–3.17 (m, 2H, CH_2), 3.28–3.41 (m, 2H, CH_2), 3.72 (s, 1H, OCH_3), 5.43 (s, IH, NH), 6.24–6.26 (d, 1H, J=4.2 Hz, quinoline-H_3); 6.80–6.81 (m, 4H, C_6H_4-), 7.28–7.30 (d, 1H, J=1.2, 1.2 Hz, quinoline-H_6); 7.70–7.73 (d, 1H, J=10.2 Hz, quinoline-H_5); 7.89–7.91 (d, 1H, J=6.6 Hz, quinoline-H_8); 8.34–8.36 (d, 1H, J=4.2 Hz, quinoline-H_2). ^{13}C NMR (100 MHz, $CDCl_3$, δ (ppm) 25.59 (CH_2), 29.68 (CH_2), 33.92 (CH_2), 39.24 (CH_2), 44.35 (CH_2), 55.54 (OCH_3), 61.76 (CH_2), 113.95 (C-3, quinoline) 144.20 (2C), 117.49 (C-4a, quinoline), 122.20 (C-5, quinoline), 127.77 (C-5, quinoline), 124.34 (C-8, quinoline), 129.83 (2C), 131.99 (Ar-C), 135.13 (C-7, quinoline, C-Cl), 148.52 (C-8a, quinoline), 151.20 (C-2, quionline), 157.17 (C-4, quinoline), 159.59 (Ar-C), 170.78 (C=O). MS (API), m/z (%): 442.2 (100), $[M+H]^+$; 443.1 (27.45), 444.3 (42.75), 445.2 (10.80). Anal cacld. (%) for $C_{23}H_{24}N_3O_2SCl$: C, 62.50; H, 5.47; N, 9.51; found (%): C, 61.38; H, 6.94; N, 6.76.

3-(3-(7-chloroquinolin-4-ylamino)propyl)-2-(3-hydroxyphenyl)-1,3-thiazinan- 4-one ***(II_C)***
Light yellow gummy solid, 62% yield; R_f : 0.51 (chloroform : methanol=3:1); UV-visible spectrum (chloroform), λ_{max} (nm): 264.5, 388.0, 416.0. IR spectrum (chloroform), υ, cm-^{1}: 3530 (O-H str., bonded OH); 3430 (N-H str., >NH); 1310, 1283, (C-N str.), 1215 (C-O str.); 1083 (Ar. C-Cl.str.). ^{1}H NMR (300 MHz, $CDCl_3$, δ (ppm): 1.73–1.81 (m, 2H, CH_2), 2.63–2.66 (t, 2H, J=48 Hz, CH_2), 2.67–2.77 (m, 2H, CH_2), 3.62-3.66 (t, 2H, J=72 Hz, CH_2), 5.35 (s, 1H, NH), 6.20-6.21 (d, 1H, J=4.5 Hz, quinoline-H_3); 6.57–6.59 (d, 1H, J=5.7 Hz, C_6H_4–), 6.75–6.77 (d, 1H, J=6.0 Hz, C_6H_4–), 7.20–7.22 (d, 1H, J=3.9 Hz, quinoline-H_6), 7.78 (s, 1H, OH), 7.88–7.90 (d, 1H, J=6.6 Hz, quinoline-H_5), 8.19–8.20 (d, IH, J=4.2 Hz, quinoline-H_8), 8.46 (bs, 1H, quinoline-H_2). ^{13}C NMR (100 MHz, $CDCl_3$, δ (ppm): 24.85 (CH_2), 29.66 (CH_2), 33.74 (CH_2), 39.96 (CH_2), 45.13 (CH_2), 62.25 (CH_2), 113.86 (C-3, quinoline); 115.47 (2C), 116.58 (C-4a, quinoline) 121.75 (Ar-C), 122.48 (C-5, quinoline), 126.29 (C-5, quinoline), 129.90 (C-8, quinoline), 130.10 (Ar-C), 136.94 (C-7, quinoline, C-Cl), 139.80 (Ar-C), 147.58 (C-8a, quinoline), 152.41 (C-2, quinoline), 153.76 (C-4, quinoline), 158,14 (Ar-C), 171.25 (C=O). MS (API), m/z (%): 428.2 (100), $[M+H]^+$; 429.2 (27.45%), 433.2 (40.50), 433.1 (10.75). Anal. cacld. (%) for $C_{22}H_{21}N_3O_2SCl$: C, 61.74; H, 5.18; N, 9.82; found (%): C, 62.67; H, 7.16; N, 4.43.

3-(3-(7-chloroquinolin-4-ylamino)propyl)-2-(2-furyl)-1,3-thiazinan-4-one ***(II_D)***
Light yellow gummy solid, 65% yield ; R_f: 0.54 (chloroform : methanol=3:1); UV-visible spectrum (chloroform), λ_{max} (nm): 257.0, 364.0, 426.0. IR spectrum (chloroform), υ, cm^{-1}: 3432 (N-H str., >NH); (C=O str.); 1375,1305, (C-N str.); 1091 (Ar. C-Cl str.). ^{1}H NMR (300 MHz, $CDCl_3$, δ (ppm): 1.75–1.87 (m, 2H, CH_2), 2.52–2.55 (t, 2H, J=4.8 Hz, CH_2), 2.70–2.73 (m, 2H, CH_2), 3.64–3.78 (m, 2H, CH_2), 5.49 (s, 1H, NH), 6.18 (bs, 1H, CH), 6.09-6.12 (m, 2H, furan-2-yl); 6.22–623 (d, 1H, J=1.2 Hz, quinoline-H_3); 7.25 (bs, 1H, furan–2–yl), 7.29–7.32 (d, 1H, J=8.4 Hz, quinoline-H_6), 7.60 -7.62 (d, 1H, J=7.2 Hz, quinoline-H_5), 7.97–8.04 (d, 1H, J=18.3 Hz, quinoline-H_8); (bs, 1H, quinoline-H_2). ^{13}C NMR (100 MHz, $CDCl_3$, δ (ppm): 25.47 (CH_2), 27.15 (CH_2), 35.47 (CH_2), 39.39 (CH_2), 40.19 (CH_2), 67.78 (CH_2), 106.99 (C_3, furan-2-yl), 110.60 (C_4, furan-2-yl), 112.67 (C-3, quinoline); 119.78 (C-4a, quinoline), 121.70 (C-5, quinoline), 127.17 (C-6, quinoline), 138.66 (C-7, quinoline, C-Cl), 142.33 (C_5, furan-2-yl),

148.31 (C-8a, quinoline), 151.69 (C-2, quinoline), 152.25 (C_2, furan-2-yl), 154.95 (C-4, quinoline), 170.67 (C=O). MS (API), m/z (%): 402.1 (100), $[M+H]^+$; 403.1 (24.30), 404.1 (41.40), 405.1 (9.00). Anal. cacld. (%) for $C_{20}H_{20}N_3O_2SCl$: C, 59.77; H, 5.02; N, 10.46; found: C, 51.63; H, 6.11; N, 3.06.

3-(3-(7-chloroquinolin-4-ylamino)propyl)-2-ethyl-1,3-thiazinan- 4-one ***(II_E)***
Light yellow gummy solid in 74% yield ; R_f: 0.49 (chloroform : methanol=3:1); UV-visible spectrum (chloroform), λ_{max} (nm): 255.0, 350.0, 419.0. IR spectrum (chloroform), υ, cm^{-1}: 3422 (N-H str., >NH); 1719 (C= O str.); 1398, 1283 (C-N str.); 1074 (Ar. C-Cl str.). ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 0.96–0.98 (t, 3H, J=2.1 Hz, CH_3), 1.75–1.79 (m, 2H, CH_2), 1.91-1.96 (dd, 2H, J=5.1, 4.8 Hz, CH_2), 2.54–2.59 (m, 2H, CH_2), 2.60–2.77 (m, 2H, CH_2), 3.07–3.12 (dd, 2H, J=4.8, 4.8 Hz, CH_2), 3.65–3.68 (t, 2H, J=4.8 Hz, CH_2), 4.26–4.30 (t, 1H, J=5.4 Hz, CH), 6.35–6.37 (d, 1H, J=5.1 Hz, quinoline-H_3); 6.77 (bs, 1H, NH), 7.24–7.32 (dd, 1H, J=6.6, 17.7 Hz, quinoline-H_6); 7.88 (d, 1H, J=0.9 Hz, quinoline-H_5), 8.06 –8.09 (d, 1H, J=6.9 Hz, quinoline-H_8); 8.28–8.30 (d, 1H, J=4.8 Hz, quinoline-H_2). ^{13}C NMR (100 MHz, $CDCl_3$, δ (ppm): 11.45 (CH_3), 25.54 (CH_2), 27.78 (CH_2), 30.85 (CH_2), 36.07 (CH_2), 39.61 (CH_2), 40.56 (CH_2), 67.89(CH_2), 115.58 (C-3, quinoline), 120.87 (C-4a, quinoline), 123.90 (C-5, quinoline), 127.16 (C-6, quinoline), 138.62 (C-8, quinoline), 139.92 (C-7, quinoline, C-Cl), 143.97 (C-8a, quinoline), 154.52 (C-2, quinoline), 157.58 (C-4, quinoline), 170.41 (C=O). MS (API), m/z (%): 364.1 (100), $[M+H]^+$; 365.1 (22.95), 366.1 (41.25), 367.0 (8.72). Anal. cacld. (%) for $C_{18}H_{22}N_3OSCl$: C, 59.41; H, 6.09; N, 11.55; found (%): C, 52.13; H, 7371; N, 4.13.

*3-(3-(7-chloroquinolin-4-ylamino)propyl)-2-(4-(dimethylamino)phenyl)-1,3-thiazinan- 4-one****(II_F)***
Reddish yellow gummy solid, 69% yield; R_f: 0.56 (chloroform : methanol=3:1); UV-visible spectrum (chloroform), λ_{max} (nm): 279.0, 392.0, 447.0. IR spectrum (chloroform), υ, cm^{-1}: 3435 (N-H str., >NH); 1719 (C=O str.); 1336 (C-N str.), 1074 (Ar. C-Cl str.). ^{1}H NMR (300 MHz,$CDCl_3$), δ (ppm): 1.79–1.83 (t, 2H, J=5.4 Hz, CH_2), 2.50–2.57 (m, 2H, CH_2), 2.95 (s, 6H, NMe_2), 3.22-3.25 (t, 2H, J=4.5 Hz, CH_2), 3.30–3.47 (m, 2H, CH_2), 6.03 (bs, 1H, NH), 6.24–6.26 (d, 1H, J=6.3 Hz, quinoline-H_3), 6.67–6.69 (d, 1H, J=60 Hz, C_6H_4-), 6.86–6.88 (d, 1H, J=5.7 Hz, C_6H_4-), 7.26–7.28 (d, 1H, J=6.3 Hz, quinoline-H_6), 7.42–7.49 (dd, 1H, J=11.7, 3.3 Hz, quinoline-H_5), 7.79–7.87 (dd, 1H, J=5.7, 6.3 Hz, quinoline-H_8), 7.92–7.95 (t, 1H, J=5.1 Hz, quinoline-H_2). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 20.88 (C_4H_2SMe), 26.88 (CH_2), 29.57 (CH_2), 36.52 (CH_2), 40.07 (CH_2), 44.65 (CH_2), 63.53 (CH_2), 102.79 (C-3, quinoline), 120.71 (C-4a, quinoline), 122.32 (C-5, quinoline, 125.99 (2C), 129.61 (C-6, quinoline), 132.20 (C-8, quinoline), 136.75 (C-7, quinoline), C-Cl), 139.47 (C_5, thiophen-2-yl), 141.77 (C_2, thiophen-2-yl), 148.37 (C-8a, quinoline), 151.87 (C-2, quinoline); 156.24 (C-4, quinoline), 174.37 (C=O). MS (API), m/z (%): 455.2 (100), $[M+H]^+$; 456.2 (30.15), 457.2 (39.6), 458.2 (11.70). Anal cacld. (%) for $C_{24}H_{27}N_4OSCl$: C, 63.35; H, 5.98; N, 12.31; found (%): C, 58.92; H, 7.21; N, 5.36.

3-(3-(7-chloroquinolin-4-ylamino)propyl)-2-(5-methylthiophen-2-yl)-1,3-thiazinan- 4-one ***(II_G)***
Reddish yellow gummy solid, 66% yield ; R_f: 0.58 (chloroform : methanol=3:1); UV-visible spectrum (chloroform), λ_{max} (nm): 282.0, 381.5, 422.0. IR spectrum (chloroform), υ, cm^{-1}: 3435 (N-H str., >NH); 1719 (C=O str.); 1390, (C-N str.); 1077 (Ar. C-Cl. str). ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 1.66–1.77 (t, 2H, J = 9.3 Hz, CH_2), 2.25 (s, 3H, CH_3), 2.63–2.67 (t, 2H, J=4.8 Hz, CH_2), 2.79–2.82 (t, 2H, J=4.8 Hz, CH_2), 3.03–3.05 (d, 2H, J=5.4 Hz, CH_2), 3.44–3.3.47 (t, 2H, J = 4.5 Hz, CH_2), 6.38 (bs, 1H, NH), 6.60–6.69 (dd, 1H, J=7.8 Hz, 12.6 Hz, quinoline-H_3),

6.75 (s, 2H, thiophen-2-yl), 7.37–7.49 (dd, 2H, J=18.6, 6.0 Hz, 6H quinoline), 7.60–7.89 (dd, 1H, J = 29.1Hz, 36.0 Hz, quinoline-H_5), 8.04–8.15 (dd, 1H, J = 6.9, 24.0 Hz, quinoline-H_8), 8.21–8.69 (dd, 1H, J=22.5, 82.8 Hz, quinoline-H_2). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 25.38 (CH_2), 29.11(CH_2), 35.62 (CH_2), 39.80 (-NMe_2), 40.30 (CH_2), 66.72 (CH_2), 112.01 (C-3, quinoline), 116.20 (C-4a, quinoline), 115.51 (2C) 124.93 (C-5, quinoline), 127.43 (C-6, quinoline), 128.34 (C-8 quinoline), 131.75 (2C), 132.26 (C-7, quinoline C-Cl), 149.87 (C-8a, quinoline), 154.19 (C-2, quinoline), 157.63 (C-4, quinoline), 169.80 (C=O). MS (API), m/z (%): 432.1 (100), $[M+H]^+$; 433.1 (27.90), 434.2 (41.85), 435.2 (10.80). Anal. cacld. (%) for $C_{27}H_{27}N_4OSCl$: C, 58.29; H, 5.13; N, 9.73; found (%): C, 56.24; H, 6.50; N, 7.36.

Antimalarial screening

All the synthesized compounds were evaluated for *in vitro* antimalarial activity. Continuous culture of CQ-sensitive strain of *P. falciparum* (3D7) was maintained *in vitro* in O^+ human red blood cells diluted to 6% haematocrit in RPMI 1640 medium supplemented with 25 mM HEPES, 1% D-glucose, 0.23% sodium bicarbonate, gentamycin (40 µg/ml), amphotericin-B (0.25 µg/ml), and 10% human AB^+ serum [20]. Incubations were done at 37^0C and 5% CO_2 level in a modular incubator. D-sorbitol synchronized [21] 1% ring stage parasitaemia in 3% haematocrit was used for antimalarial assays using 96 well microtitre plate. A stock solution of 5 mg/ml of the test compound was prepared in DMSO and subsequent dilutions were made with incomplete RPMI in duplicate. All test compounds were assayed at a fixed dose of 50 µg/ml. Each test well of the microtitre plate contained 20 µl of the compound and 180 µl of 1% ring stage parasitaemia in 3% haematocrit. In addition, drug free negative control to assess the parasite growth and chloroquine diphosphate, at predetermined 50% inhibitory concentration (IC_{50}) dose, as positive control to assess the integrity of the assay were also maintained in duplicate in the microtitre plate. After 40 h of incubation the smears were prepared from each well, stained with 3% Giemsa and scanned under light microscope to ascertain percentage dead rings and trophozoites by examining a minimum of 400 asexual parasites.

Conclusion

The present investigation describes the synthesis and antimalarial activity of seven novel 7-chloro-4-aminoquinoline derivatives. The structures of the synthesized compounds were confirmed by physical, spectral, and analytical data. All the compounds at the tested dose exhibited antimalarial activity which was much inferior to the standard drug chloroquine. The results clearly demonstrated that a bulky group with optimum lipophilicity at 1,3-thiazinan-4-one ring system attached with the terminal propyl side chain of 7-chloro-4-aminoquinoline nucleus might be an important requirement for antimalarial activity of the prepared compounds.

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