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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis, antimalarial-, and antibacterial activity evaluation of some new 4-aminoquinoline derivatives

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Abstract Some new 4-aminoquinoline derivatives were synthesized, characterized by their analytical and spectral data (IR, ^{1}HNMR, ^{13}CNMR and MS), and screened for in vitro antimalarial activity against a chloroquine-sensitive strain of *Plasmodium falciparum* (3D7). Results clearly reveal that all the synthesized compounds possess in vitro antimalarial activity at the tested dose which, however, was considerably less than that of the standard reference drug, chloroquine. From results, it could be assumed that the presence of an aromatic bulky group with optimal lipophilicity at 1,3-thiazinan-4-one ring system might be an important requirement for the antimalarial activity of synthesized compounds, **6a–g**. In addition to the evaluation of antimalarial activity, the synthesized compounds were also screened for antibacterial activity against six different strains of Gram-positive (*Bacillus subtilis*, *Bacillus cereus*, and *Staphylococcus aureus*) and Gram-negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*). All the compounds at the tested doses were found to be active against all the tested organisms, but were less active as compared to the standard drug, ofloxacin. Results of antibacterial study indicate that aromatic bulky substituents have greater contributing effect than the aliphatic non-bulky group toward the antibacterial activity of the prepared 4-aminoquinoline derivatives.

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Introduction

Despite over a 100 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's 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 (Casteel, 2003; Farooq and Mahajan, 2004; Gillies, 2000; Wiesner *et al.*, 2003). This life-threatening parasitic disease is caused by protozoan parasites of the genus *Plasmodium*; *P. falciparum, P. vivax, P. malariae,* and *P. ovale* are four well-known species of human malaria parasite (Chiang *et al.*, 2006; http://www.rbm.who.int/) and more recently another species, *P. knowlesi* has been documented (White, 2008). *P. falciparum* is the most widespread and causing most severe and potentially fatal form of malaria (Talisuna *et al.*, 2004). 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 (Ridley, 2002). The emergence of resistance of malaria parasite, especially *P. falciparum* toward currently available drugs, especially chloroquine, has become a major health concern in the tropical and subtropical regions of the world; therefore, the development of new chemotherapeutic agents is an urgent need to fight against malaria.

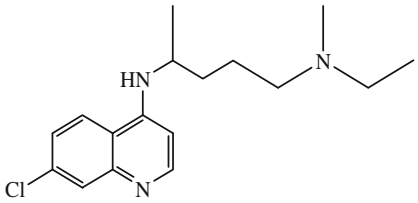


Fig. 1 Structure of chloroquine (CQ)

The structure–activity relationship studies on 4-aminoquinoline antimalarial compounds suggest that the 7-chloro-4-aminoquinoline nucleus is obligatory for antimalarial activity, which could be attributed mainly due to prevention of heme polymerization into an insoluble compound, hemozoin (malaria pigment) (Chou *et al.*, 1980; Dorn *et al.*, 1995; Egan and Marques, 1999; Foley and Tilley, 1998; Pandey *et al.*, 2001; Sullivan *et al.*, 1996) by inhibiting parasitic enzyme, particularly heme polymerase. This process ultimately leads to the death of parasite (Tilley *et al.*, 2001).

A new series of compounds with aromatic ring system at the side chain of 7-chloro-4-aminoquinoline nucleus was found active against *P. falciparum (*in vitro*)* and *P. yoelli (*in vivo*)* because of their direct action on heme polymerization target (Solomon *et al.*, 2007). It has been observed that three-carbon atoms in the side chain are appropriate for the antimalarial activity of compounds with terminal six-membered rings, while an increase or decrease in carbon chain length results in the decrease in activity, which indicates that the length of the side chain is crucial for the activity of compounds, along 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 selective modification at the pendent amino group with small heterocyclic systems could modulate the antimalarial activity. Based on this fact, proposed compounds were designed 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 1).

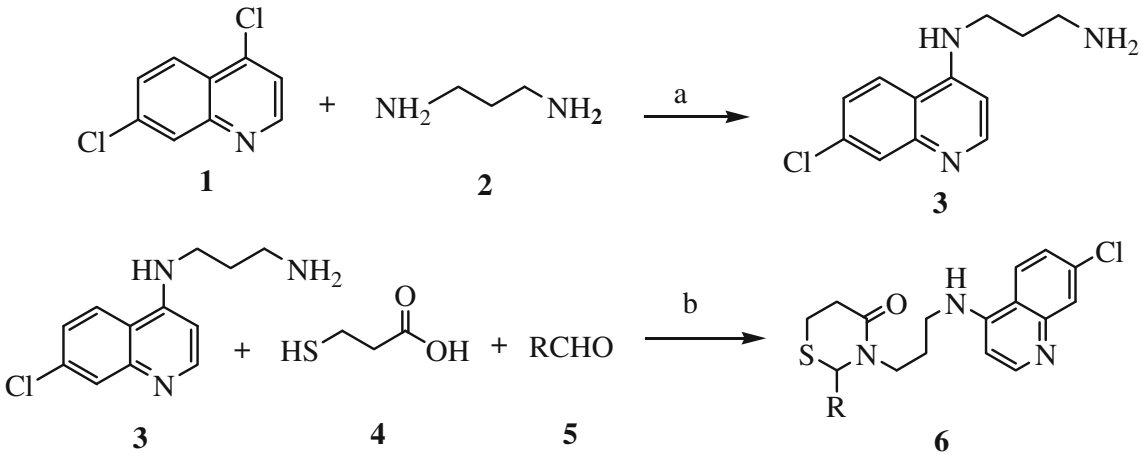
The incidence of microbial infections has been increasing worldwide over the past few decades because of widespread emergence of bacterial resistance toward the currently available beta-lactam antibiotics, quinolones, macrolides, etc. A matter of concern in the treatment of microbial infection is the limited number of efficacious antimicrobial agents, which clearly highlights the urgent need of novel antimicrobial agents (Goker *et al.*, 2002; He *et al.*, 2003). A large variety of synthetic compounds having therapeutic use in some other ailments possess antibacterial activities. On the basis of this premise, the synthesized compounds tested for antimalarial activity were also subjected to antibacterial activity screening.

In the present study, some new derivatives of 3-(3-(7-chloroquinolin-4-ylamino)propyl)-2-substituted-1,3-thiazinan-4-one were prepared and screened for antimalarial as well as antibacterial activities.

Experimental

Materials and methods

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



Scheme 1 Synthesis of compounds, **6a–g**. Reagents and conditions *a* Reflux for 1 h at 80 °C and 9 h at 130 °C, *b* DCC, THF, rt, 1 h

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 the 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. The ^{1}HNMR and ^{13}CNMR spectra were recorded on a Bruker AC-F 300 FT-NMR spectrometer using CDCl3 as solvent. Chemical shifts (δ in ppm) were reported with tetramethylsilane (TMS) as an internal standard. Mass spectra were undertaken using a LC–MS Water 4000 ZQ instrument by atmospheric pressure ionization (API). Elemental microanalyses (CHN) were performed on a Perkin Elmer 2400 Series II CHNS/O analyzer.

General method of synthesis, **6a–g**

The reaction intermediate N^1-(7-chloroquinolin-4-yl)-propane-1,3-diamine, **3** and target compounds, **6a–g** were prepared according to the following methods (Madrid *et al.*, 2004; Solomon *et al.*, 2005):

Step-I

A mixture of 4,7-dichloroquinoline, **1** (5 g, 25.18 mmol) and 1,3-diaminopropane, **2** (4.24 mL, 50.36 mmol) was heated slowly from room temperature to 80 °C over 1 h with stirring and subsequently at 130 °C for 9 h with continued stirring to drive the reaction to completion. Then, the reaction mixture was cooled to room temperature and taken up in dichloromethane (80 mL). The resulting mixture was washed with sodium hydroxide (1 M, 80 mL) and brine (a concentrated solution of sodium chloride, 80 mL) to give an aqueous layer, an organic layer, and a white coarse particulate precipitate. The organic layer was dried over anhydrous sodium sulfate, and solvent was removed under reduced pressure to obtain the product as a yellowish white solid. The precipitate from the wash was filtered and extracted in a Soxhlet extractor with dichloromethane for 24 h. The dichloromethane was then removed in vacuum to yield a second crop of the product as a yellowish white solid. TLC, melting point, and IR spectral analysis confirmed that the two solids were identical and pure so they were combined and used without further purification.

Step-II

N-(3-aminopropyl)-7-chloroquinolin-4-amine, **3** (1.0 mmol) and substituted aldehyde, **5** (2.0 mmol) were stirred in THF under ice-cold condition for 5 min, followed by the addition of 3-mercaptopropionic acid, **4** (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 60 min at room temperature. DCU (Dicyclohexylurea) was precipitated out and removed by filtration. The filtrate was concentrated under reduced pressure, and the residue was taken up in chloroform. The organic layer was successively washed with 5 % aqueous 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 the final product, **6a–g**. The synthetic routes for **3** and **6a–g** are outlined in Scheme 1.

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 % hematocrit in RPMI 1,640 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 (Trager and Jensen, 1976). Incubations were done at 37 °C and 5 % CO_2 level in a modular incubator. D-sorbitol synchronized (Lambros and Vanderberg, 1979) 1 % ring stage parasitemia in 3 % hematocrit 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 % hematocrit. In addition, drug-free negative control to assess the parasite growth and chloroquine diphosphate, at predetermined 50 % inhibitory concentration (IC50) 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.

Antibacterial screening

All the synthesized compounds were screened for antibacterial activity by Kirby–Bauer disk diffusion method (Hewitt, 2004; Collee *et al.*, 1989) against six different strains of Gram-positive and Gram-negative bacteria at two different tested doses, viz., 25 and 50 μg/disk. Three strains of Gram-positive bacteria—*Bacillus subtilis* [(ATCC 11774), *Bacillus cereus* (ATCC 10876), and *Staphylococcus*

aureus (ATCC BAA 1026), and three strains of Gram-negative bacteria—*Escherichia coli* (ATCC 10536)], *Klebsiella pneumoniae* (ATCC 33495), and *Pseudomonas aeruginosa* (ATCC 10662), were used for the study. All the bacterial strains were obtained from the National Collection of Industrial Microorganisms (NCIM), National Chemical Laboratory (Council of Scientific & Industrial Research), Pune, India. The cultures of bacteria were maintained in their appropriate agar slants at 4 °C throughout the study and used as stock cultures.

Freshly prepared and cooled (45–50 °C) medium of about 25 mL was inoculated aseptically with each standardized inoculum (0.5–1.0 mL) in a laminar air flow unit. The medium was then poured into previously sterilized petri-plate to occupy a depth of 4 mm. The plates were left at room temperature to allow solidification. Sterilized disk (6-mm diameter) of Whatman filter paper No. 2 impregnated with DMSO was used as negative control. Under aseptic condition, empty sterilized disks were impregnated with test drug solutions of two different doses (25–50 µg/disk) and with vehicle control, DMSO. After solvent evaporation, the dried disks were placed on the surface of the agar medium and the plates were left undisturbed for an hour at room temperature for pre-incubation diffusion to minimize the effects of variation in time between the applications of different solution. Ofloxacin was used as reference standard drug. After incubation of the plates at 37 ± 1 °C for 24 h, the diameters of the zones of complete inhibition surrounding each of the disk were measured including the diameter of the disk using a centimeter scale. Studies were performed in triplicate; mean values with standard deviation were calculated.

Results and discussion

In this study, new 3-(3-(7-chloroquinolin-4-ylamino)propyl)-1,3-thiazinan-4-one derivatives were synthesized. The intermediate, **3,** and target products, **6a–g,** were obtained in good yields and high 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}HNMR, ^{13}CNMR and Mass spectral data, and elemental analysis. The spectral data (Silverstein and Webster 2005) are in good agreement with the structure of the synthesized compounds.

Spectral and analytical data

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

Yellowish white solid, 86 % yield, mp: 96–98 °C, R_f: 0.25 (chloroform:methanol = 1:1); UV–Visible spectrum (chloroform), λ_{max} (nm): 270, 366, 412.5. IR (KBR), υ, 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}HNMR (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-H6); 7.89–7.90 (d, J = 6.0 Hz, 1H, quinoline-H5); 8.02–8.04 (d, J = 9.2 Hz, 1H, quinoline-H8); 8.22–8.29 (dd, J = 5.2, 6.4 Hz, 1H, quinoline-H2). ^{13}CNMR (100 MHz, $CDCl_3$), 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, ***6a***

Light yellow gummy solid, 73 % yield; R_f0.55 (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}HNMR (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}CNMR (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, ***6b***

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} and υ_{as} C–O–C str.); 1080 (Ar. C–Cl str.). ^{1}HNMR (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, 1H, 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}CNMR (100 MHz, $CDCl_3$, δ (ppm) 25.59 (CH2), 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, ***6c***

Light yellow gummy solid, 62 % yield; R_f0.51 (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}HNMR (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, 1H, J = 4.2 Hz, quinoline-H_8), 8.46 (bs, 1H, quinoline-H_2). ^{13}CNMR (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, ***6d***

Light yellow gummy solid, 65 % yield; R_f0.54 (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}HNMR (300 MHz, $CDCl_3$, δ (ppm): 1.75–1.87 (m, 2H, CH_2), 2.52–2.55 (t, 2H, J = 4.8 Hz, CH2), 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}CNMR (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 (C3, furan-2-yl), 110.60 (C4, 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 (C5, furan-2-yl), 148.31 (C-8a, quinoline), 151.69 (C-2, quinoline), 152.25 (C2, 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, ***6e***

Light yellow gummy solid, 74 % yield; R_f0.49 (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}CNMR (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, ***6f***

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}HNMR (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}CNMR (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 (C5, thiophen-2-yl), 141.77 (C2, 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, ***6g***

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.); 1,077 (Ar. C–Cl. str). ^{1}HNMR (300 MHz, CDCl3), 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 = 29.1 Hz, 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}CNMR (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.

All the compounds in chloroform exhibited three characteristic absorption maxima (λ_{max}) in the range between 220 and 450 nm. The shift of λ_{max} toward longer wavelength indicate the presence of strong chromophoric group such as quinoline ring, and C=O group in the molecule. The maxima in the lower wavelength range between 220 and 280 nm is due to the presence of substituted phenyl ring, and heteroaromatic ring system such as furan-2-yl (**6d**), thiophen-2-yl (**6g**). The infrared spectral data showed characteristic absorption bands for >NH (3,340–3,435 cm^{-1}); C=O (1,693–1,734 cm^{-1}); C–N (1,275–1,398 cm^{-1}); C–Cl (1,074–1,097 cm^{-1}); $>CH_2$ (υ_{as}: 2,976–2,930 cm^{-1} and υ_s: 2,819–1,863 cm^{-1}), and aromatic C=C (1,432–1,657 cm^{-1}) stretching which confirms the anticipated structure of the synthesized compounds, **6a**–**g**. The assignment of protons is fully supported by the characteristic chemical shift values for the 4-aminoquinoline nucleus. 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 **6a**–**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.

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 the standard drug, chloroquine. However, the compounds with 2-fluorophenyl (**6a**), 4-methoxyphenyl (**6b**), 3-hydroxyphenyl (**6c**), furan-2-yl (**6d**) 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 compounds with ethyl (**6e**), 4-(dimethylamino)phenyl (**6f**), 5-methylthiophen-2-yl (**6g**) moieties at the side chain. The results clearly reveal that a bulky group with optimal lipophilicity at 1,3-thiazinan-4-one ring in the side chain might be an important requirement for the antimalarial activity of prepared 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

Comp. code	Dosage (μg/mL)	% Dead rings + trophozoites[a]
6a	50	39.0
6b	50	32.0
6c	50	39.5
6d	50	38.5
6e	50	18.5
6f	50	25.0
6g	50	22.0
Chloroquine[b]	0.4	67.0

Test strain: *Chloroquine-sensitive P. falciparum* (3D7)

[a] Mean of two replicates and counted against 400 asexual parasites per replicate

[b] Reference standard

Antibacterial screening

The results depicted in Table 2 clearly reveal that all the synthesized compounds at the tested dose showed antibacterial activity and were equally active with some degree of variations, but were less active as compared to the standard drug, ofloxacin (5 μg/disk). However, no obvious difference in susceptibility was found between Gram-positive and Gram-negative bacterial strains for all the tested compounds. Among synthesized compounds, compounds with aromatic bulky substituents such as 2-fluorophenyl-(**6a**), 4-methoxyphenyl-(**6b**), 3-hydroxyphenyl-(**6c**), furan-2-yl (**6d**), 4- (dimethylamino)phenyl-(**6f**), 5-methylthiophen-2-yl (**6g**) were found to be more active than that of compound with aliphatic alkyl substituent (ethyl in **2e**) at C-2 position of 1,3-thiazinan ring system.

Correlation between antimalarial activity and lipophilicity (logP)

Furthermore, the antimalarial activity of the synthesized compounds was correlated with lipophilicity, i.e., logP values. The logP values of synthesized compounds obtained from Chem Draw Ultra 8.0 2004 software are shown in Table 3. The correlation study clearly demonstrate that compounds containing aromatic bulky (heavier) substituents such as **6g** (5-methylthiophen-2-yl, logP = 6.15) and **6f** (4-(dimethylamino)phenyl, logP = 4.44) possess slight higher lipophilicity (i.e., logP values) as compared to compounds that contain comparatively less bulkier substituents such as **6d** (2-furyl, logP = 4.45), **6a** (2-fluorophenyl, logP = 4.31), and **6b** (4-methoxyphenyl, logP = 4.03). As a consequence, a slight increased activity was seen for compounds (**6a**, **6b**) which possess comparatively lower

Table 2 Antibacterial activity data

Compd. code	Dose (μg/disk)	Diameter of zone of inhibition (mm ± SD)[a]					
		B. s ATCC 11774	B. c ATCC 10876	S. a ATCC BAA 1026	E. c ATCC 10536	K. p ATCC 33495	P. a ATTCC 10662
6a	50	23.66 ± 0.57	24.26 ± 0.28	23.93 ± 0.11	24.36 ± 0.32	24.16 ± 0.11	24.20 ± 0.20
	25	18.83 ± 0.28	14.26 ± 0.28	14.16 ± 0.15	14.33 ± 0.23	14.33 ± 0.30	14.06 ± 0.11
6b	50	23.30 ± 0.50	24.40 ± 0.20	24.06 ± 0.11	24.40 ± 0.20	24.20 ± 0.20	24.06 ± 0.11
	25	14.16 ± 0.28	14.33 ± 0.11	14.13 ± 0.11	14.23 ± 0.05	14.06 ± 0.11	14.33 ± 0.11
6c	50	23.83 ± 0.28	23.66 ± 0.28	24.06 ± 0.11	24.33 ± 0.11	24.20 ± 0.12	23.90 ± 0.36
	25	13.83 ± 0.28	14.06 ± 0.11	14.26 ± 0.23	13.93 ± 0.11	14.00 ± 0.20	13.86 ± 0.11
6d	50	23.50 ± 0.50	23.80 ± 0.20	24.20 ± 0.20	24.06 ± 0.11	24.13 ± 0.11	23.83 ± 0.28
	25	14.06 ± 0.11	14.16 ± 0.15	14.33 ± 0.11	14.00 ± 0.20	14.16 ± 0.15	13.73 ± 0.11
6e	50	23.16 ± 0.28	23.60 ± 0.20	23.06 ± 0.11	23.40 ± 0.10	23.13 ± 0.23	23.06 ± 0.11
	25	13.06 ± 0.11	13.53 ± 0.11	12.93 ± 0.11	13.66 ± 0.11	13.23 ± 0.05	13.46 ± 0.11
6f	50	23.66 ± 0.11	24.26 ± 0.23	23.86 ± 0.11	23.93 ± 0.11	24.06 ± 0.30	23.66 ± 0.11
	25	14.26 ± 0.30	14.00 ± 0.20	13.86 ± 0.11	14.26 ± 0.30	14.06 ± 0.30	13.73 ± 0.11
6g	50	23.93 ± 0.11	24.23 ± 0.20	23.93 ± 0.23	24.13 ± 0.23	23.93 ± 0.11	23.73 ± 0.11
	25	14.20 ± 0.20	13.93 ± 0.11	14.00 ± 0.20	14.20 ± 0.20	13.86 ± 0.11	13.86 ± 0.11
Ofloxacin[b]	5	20.66 ± 0.25	20.33 ± 0.57	21.66 ± 0.57	21.50 ± 0.50	20.33 ± 0.57	20.83 ± 0.28
DMSO[c]	–	Nil	Nil	Nil	Nil	Nil	Nil

B. s, Bacillus subtilis; B. c, Bacillus cereus; S. a, Staphylococcus aureus; *E. c*, *Escherichia coli*; *K. p, Klebsiella pneumoniae*; *P. a, Pseudomonas aeruginosa*

[a] Values are mean inhibition zone (mm ± SD) of three replicates

[b] Ofloxacin, 5 μg/disk was used as positive reference standard

[c] DMSO was used as vehicle control

Table 3 LogP values of synthesized compounds

Comp. code	R	LogP[a]
6a	2-Fluorophenyl-	4.31
6b	4-Methoxyphenyl-	4.03
6c	3-Hydroxyphenyl-	3.77
6d	Furan-2-yl-	4.45
6e	Ethyl-	3.07
6f	4-(Dimethylamino)phenyl-	4.44
6g	5-Methyl-thiophen-2-yl-	6.15

[a] Obtained using Chem Draw Ultra 8.0 2004 software

logP values than other compounds like **6f** and **6g**. Moreover, compound, **6e** with non-aromatic alkyl substitution (ethyl, logP = 3.07) showed lowest activity in this series, which could be attributed due to its very low logP value than that of optimum value. Form this study, it could be finally assumed that the presence of a lipophilic bulky group at C-2 position of 1,3-thiazinan-4-one ring system might be a requirement for the antimalarial activity of synthesized compounds, despite the lipophilicity of compound should be such that compound's activity-lipophilic property would be appropriately balanced (optimum). However, it is obvious that not only the lipophilicity but also the sufficient basicity (pKa) of the molecule (Solomon *et al.*, 2007) is another important requirement for the antimalarial activity of newly synthesized 4-aminoquinoline derivatives.

Conclusion

The present investigation describes the synthesis, antimalarial-, and antibacterial activity of some novel 4-aminoquinoline derivatives. The structures of the synthesized compounds were confirmed by spectral and analytical data. All the compounds at the tested dose exhibited antimalarial activity which was much inferior to the standard drug, chloroquine. Compounds were also found to be active against all the tested bacterial strains at the tested dose, but were less active as compared to the standard drug, ofloxacin. The results clearly demonstrate that the presence of a bulky group with optimal lipophilicity at 1,3-thiazinan-4-one ring system attached to the terminal propyl side chain of 7-chloro-4-aminoquinoline nucleus may be an important requirement for the antimalarial activity of synthesized compounds. Furthermore, aromatic bulky substituents have greater contributing effect than the aliphatic non-bulky group toward the antibacterial activity of 4-aminoquinoline derivatives.

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