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ORIGINAL ARTICLE

Synthesis, characterization and antimalarial activity of hybrid 4-aminoquinoline-1,3,5-triazine derivatives

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Abstract A novel series of hybrid 4-aminoquinolines-1,3,5-triazine were synthesized by means of aromatic nucleophilic displacement of chlorine atoms of 2,4,6-trichloro-1,3,5-triazine. Afforded title analogs were subsequently characterised by elemental analysis, FT-IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy and subjected to screening against chloroquine sensitive *RKL2* strain of *Plasmodium falciparum* in 96 well-microtitre plates. However, synthesized derivatives exhibit mild to moderate antimalarial activity and acute toxicity studies of the most active (**6a** and **6g**) compounds were shown to have no significant change in body insight and toxic sign.

1. Introduction

Multidrug resistant *Plasmodium* parasites are the biggest therapeutic challenge to health care in most malaria-endemic areas specifically tropical and sub-tropical areas (Kremsner and Krishna, 2004). Resistance to former first-line treatment, chloroquine and sulfadoxine-pyrimethamine is becoming most apparent in *Plasmodium falciparum* species (Marfurt et al., 2010). Moreover, it has rendered monotherapy for malaria useless in most parts of the world (Guidelines for the treatment of malaria, 2010). To improve efficacy and delayed onset of resistance, the World Health Organization began recommending the use of Artemisinin Combination Therapies (ACTs) since 2005 (Rogerson and Menendez, 2006). Currently, ACTs demonstrate excellent clinical efficacy, paradoxically the history of antimalarial chemotherapy predicts that it is a matter of time before parasitic resistance re-emerges (Ekland and Fidock, 2008). Nevertheless, safe and cost effective new antimalarial agents are urgently needed to treat malaria (Guerin et al., 2002).

One important pipeline approach is the new generation of hybrid molecules against both chloroquine sensitive and resistant strains of *P. falciparum* by diverse functionalization of

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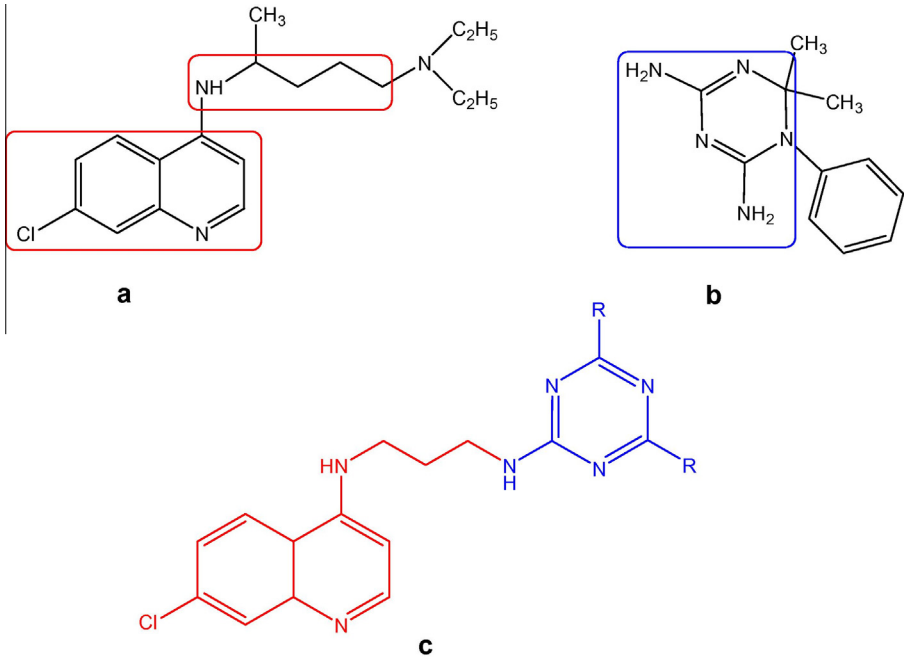


Figure 1 Structure of (a) chloroquine, (b) cycloguanil and (c) hybrid 4-aminoquinoline-1,3,5-triazine derivatives.

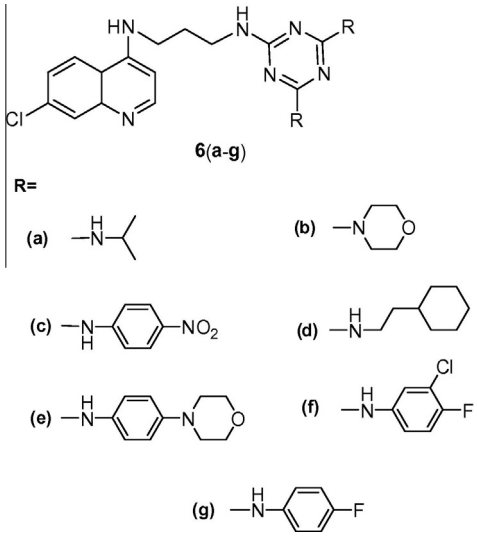


Figure 2 Hybrid 4-aminoquinoline-1,3,5-triazine derivatives (**6a**–**g**).

the lateral side chain of 4-aminoquinoline, such as isatin derivatives (Chiyanzu et al., 2005), β-carbolines (Gupta et al., 2008), the peroxide based trioxaquine derivatives (Singh et al., 2004) etc. The Structure activity relationships (SARs) of 4-aminoquinolines with propyl side chain [$-HN(CH_2)_3NH-$] exhibit most potent activity against chloroquine-susceptible *P. falciparum* (Kgokong et al., 2008). Encouraged by these observations and in continuation of our investigation in search of new and effective pharmacophores from 1,3,5-triazine (Singh et al., in press; Gahtori et al., 2009), we herein report a new series of hybrid 4-aminoquinoline-1,3,5-triazine (Fig. 1c), as a core bioactive lead fragment derived from chloroquine (Fig. 1a) and cycloguanil (Fig. 1b) to obtain seven novel hybrid 4-aminoquinoline-1,3,5-triazine derivatives (**6a–6g**) (Fig. 2).

2. Results

A series of hybrid 7-chloro-4-aminoquinoline substituted 1,3,5-triazines derivatives **6a–g** were synthesized, characterized and found in agreement with spectroscopic analysis. IR spectra of the all products **6a**–**g** nearer at 3350 cm^{-1} is due to the primary amino groups, where as the secondary –NH linker between 4-aminoquinoline and 1,3,5-triazine appears in the region 3214–3140 cm^{-1}. The strong absorption bands at 850–670 cm^{-1} confirm the existence of aromatic skeleton. The ^1H NMR spectrums report a signal corresponding to the quinolyl proton at 6.46–10.01 ppm. ^{13}C NMR of the carbon atom of 1,3,5-triazine was detected at 152.30–168.61 ppm. The tested compounds, **6e**, **6f** and **6g** have shown good in vitro antimalarial efficacy under similar experimental conditions with reference to the standard drug chloroquine.

2.1. Acute toxicity

The three active hybrid 4-aminoquinoline-1,3,5-triazine derivatives **6e**, **6f** and **6g**, were further tested for acute toxicity testing-Up and Down procedure (UDP) as recommended by the Organization for Economic Co-operation and Development (OECD) (Guidelines for the Testing of Chemicals, 2006). These test compounds at a test dose of 2000 mg/kg for 48 h intervals and serially for a total of 14 days have exhibited no significant changes in body weight and toxic signs.

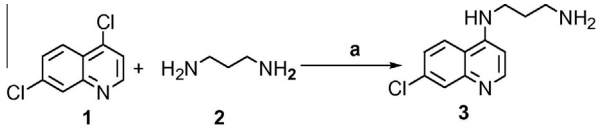
3. Discussion

The antimalarial screening result reflects that the compounds **6e**, **6f** and **6g** possessing aromatic group along with chloro,

fluoro and morpholino substitution have shown comparatively good in vitro antimalarial activity ranges from 47.5 to 56 in comparison to chloroquine under similar test conditions. Out of seven evaluated compounds, N^2,N^4-bis (3-chloro-4-fluorophenyl)-N^6-(3-(7chloroquinolin-4-ylamino) propyl)-1,3,5-triazine-2,4,6-triamine (**6f**) was found to be the most active against chloroquine sensitive strain and the cut off value (LD_{50} > 2000 mg/kg) for **6e**, **6f** and **6g** was recorded via oral administration proves its efficacy. These new hybrid series of 4-aminoquinoline-1,3,5-triazine were found to be less effective than chloroquine, however their in vitro results prove these new hybrids as a promising model for further optimization work in malarial chemotherapy.

4. Experimental

All commercially available solvents and reagents were of AR grade and used without further purification. Melting points were determined on a Veego, MPI melting point apparatus and are uncorrected. UV_{max} (DMSO) were recorded on Shimadzu UV-1700 and FT-IR (2.0 cm^{-1}, flat, smooth, abex) were taken on Perkin Elmer RX-I Spectrophotometer. ^1H NMR spectra were recorded on Bruker Avance II 400 NMR and ^{13}C NMR spectra on Bruker Avance II 100 NMR spectrometer in DMSO-d_6 using TMS as the internal standard. Mass spectra were obtained on VG-AUTOSPEC spectrometer equipped with electrospray ionization (ESI) sources. Elemental analysis was carried out on Vario EL-III CHNOS element or analyzer.



Scheme 1 Reagents and conditions: (a) Reflux/80 °C/1 h followed by reflux at 6–8 h at 120–130 °C.

4.1. Preparation of parasites

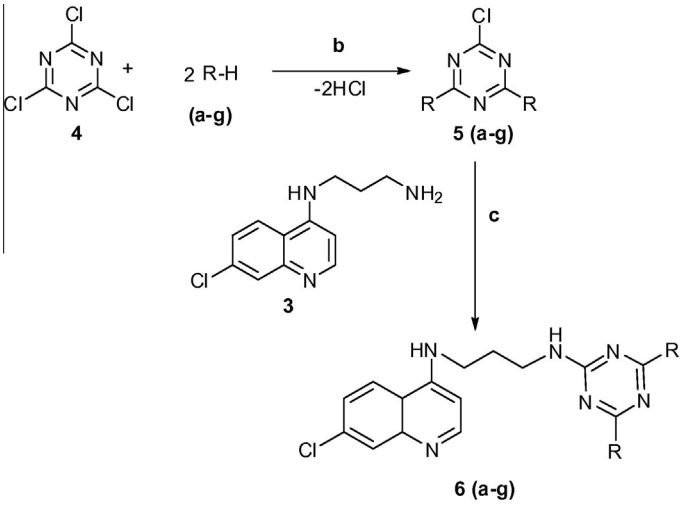
The chloroquine sensitive *RKL-2* strain (Raurkela, Orissa, India) of *P. falciparum* were routinely maintained in stock cultures in medium RPMI-1640 supplemented with 25 mmol HEPES, 1% D-glucose, 0.23% sodium bicarbonate and 10% heat inactivated human serum. The asynchronous parasites of *P. falciparum* were synchronized after 5% D-sorbitol treatment to obtain only the ring stage parasitized cells. For carrying out the assay, the initial ring stage parasitaemia of 0.8–1.5% at 3% hematocrit in a total volume of 200 μL of medium RPMI-1640 was uniformly maintained.

4.2. In vitro antimalarial efficacy test

The in vitro antimalarial assay was carried out according to microassay of Rieckmann et al. (1978) in 96 well-microtitre plates, with minor modifications. A stock solution of 5 mg/mL of each of the test samples was prepared in DMSO and subsequent dilutions were prepared with the culture medium. The test compounds in 20 μL volume concentration at 50 μg/mL in a duplicate well were incubated with parasitized cell preparation at 37 °C in a candle jar. After 36–40 h of incubation, the blood smears were prepared from each well and stained with Giemsa stain. The level of parasitemia in terms of % dead rings along with Schizonts was determined by counting a total of 100 asexual parasites (both live and alive) microscopically using chloroquine as the reference drug.

4.3. Synthesis and structural investigation

The desired compounds **3** and **6a**–**g** were synthesised by the synthetic protocols as outlined in Schemes 1 and 2, respectively. Synthesis of compound (**3**) was achieved by the nucleophilic substitution of 1,3-diaminopropane (**2**) at the 4-Cl atom of 4,7-dichloroquinoline (**1**). The synthesis of di-substituted 1,3,5-triazines **5**(**a**–**g**) were accomplished by the nucleophilic substitution of the Cl atom of the 1,3,5-triazines (**4**) with different primary amines (**a**–**g**) as shown in Fig. 2. Finally title analogs **6**(**a**–**g**) were synthesized by incorporating di-substituted



Scheme 2 Reagents and conditions: (a) R–H (a–g) distinguished amines, (b) 1,4 dioxane 0–5 °C 1 h, 40–45 °C 3 h, $KHCO_3$, (c) 1,4 dioxane 120–130 °C 5–6 h.

1,3,5-triazine moiety **5(a–g)** with the side chain attached to 4-aminoquinoline pharmacophore (**3**).

*4.4. Synthesis of N^1-(7-chloro-quinolin-4-yl)-propane-1,3-diamine (**3**)*

The compound **3** is prepared by the published procedure (De et al., 1997) to yield an off-white solid, characterized by the following physicochemical properties % yield: 83.2, mp: 77–78 °C; FTIR (cm^{-1}): 3346, 3333 ($_{sym.\ \&\ asym.}$ N–$H_{stretch}$, –NH_2), 3253 (N–$H_{stretch}$ > NH), 2987, 2893 (C–$H_{stretch}$, > CH_2), 2029, 1950, 1636, 1603, 1571 (N–H_{bend}), 1464, 1360, 1320, 1240, 1190 (C–$H_{stretch}$), 1090, 910, 850, 800, 760, 610; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.29–8.14 (m, 1H, quinolyl), δ 8.04–8.02 (d, 1H, J = 9.20 Hz, quinolyl), δ 7.90–7.89 (d, 1H, J = 6.00 Hz, quinolyl), δ 7.77–7.56 (dd, 1H, J = 18.00, 18.00 Hz, quinolyl), δ 7.51 (s, 2H, NH), δ 7.35–7.33 (d, 1H, J = 7.60 Hz, quinolyl), δ 7.25 (br s, 1H, NH), δ 6.55–6.08 (m, 2H, CH), δ 3.32–3.27 (t, 2H, J = 9.6 Hz, CH_2), δ 2.81–2.71 (t, 2H, J = 19.2 Hz, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ 176.94, 152.53, 150.75, 146.89, 136.79, 134.26, 127.59, 125.07, 117.72, 109.54, 103.24, 99.14, 44.67, 40.46, 37.95, 27.65, 25.07; Mass: 236.3 $[M+H]^+$.

*4.5. General procedure for the synthesis of di-substituted 1,3,5-triazine derivative **5a–g***

These derivatives were synthesized according to the published procedures (Thruston et al., 1951; Richard et al., 2007). Finally obtained reaction mixture was poured into crushed ice. The solid separated out was filtered, washed with water and recrystallized from different solvents to yield **5a–g**.

*4.5.1. 6-Chloro-N^2,N^4-di-isopropyl-1,3,5-triazine-2,4-diamine (**5a**)*

%Yield: 84.11, mp: 86–88 °C; FTIR (cm^{-1}): 2969.66 (C–$H_{stretch}$), 1582.26 (N–H_{bend}), 1324.20 (N–$H_{stretch}$, > NH), 1019.08 (C–$H_{bend\ out\ of\ plane}$); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.35 (d, J = 6.9 Hz, 12H, 4× CH_3), 2.04 (m, 2H, 2× CH), 3.42 (t, 2H, 2× NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.53, 47.35, 163.56, 168.96; Mass: 229.11 $(M+H)^+$; Anal. Calcd. for $C_9H_{16}ClN_5$: C, 47.06; H, 7.02; N, 30.49. Found: C, 47.04; H, 6.99; N, 30.50.

*4.5.2. 6-Chloro-2,4-dimorpholino-1,3,5-triazine (**5b**)*

%Yield: 73.32, mp: 132–135 °C; FTIR (KBr) cm^{-1} 2966.61, 1574.98–1451.24, 1362.21, 1116.51; H^1 NMR (400 MHz, $CDCl_3$) δ 3.70 (t, J = 4.9 Hz, 8H, 4× CH_2–N), 3.78 (t, 8H, 4× CH_2–O); C^{13} NMR (100 MHz, $CDCl_3$) 43.86, 66.56, 164.48, 169.69; Mass: 286.10 $(M+H)^+$; Anal. Calcd. for $C_{11}H_{16}ClN_5O_2$: C, 46.24; H, 5.64; N, 24.51. Found: C, 46.28; H, 5.58; N, 24.56.

*4.5.3. 6-Chloro-N^2,N^4-bis(4-nitrophenyl)-1,3,5-triazine-2,4-diamine (**5c**)*

%Yield: 84.16; mp: 86–88 °C; FTIR (cm^{-1}) 3055.70, 1548.28–1446.06, 1342.89, 1079.19; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (t, 4H, 4× ═CH–), 7.32 (t, 4H, 4× ═CH–), 3.62 (d, 2H, 2× –NH); ^{13}C NMR (100 MHz, $CDCl_3$) 126.23, 131.36 (Ar–C), 143.16 (Ar–C–NO_2), 148.26 (Ar–C–NH), 168.85 (Ar–C–Cl), 173.56 (Ar–C–N, s-triazine); Mass: 388.10 $(M+H)^+$; Anal. Calcd. for $C_{15}H_{10}ClN_7O_4$: C, 46.46; H, 2.60; N, 25.29. Found: C, 46.42; H, 2.62; N, 25.28.

*4.5.4. 6-Chloro-N^2,N^4-bis(2-cyclohexylethyl)-1,3,5-triazine-2,4-diamine (**5d**)*

%Yield: 95.12, mp: 145–147 °C; FTIR (cm^{-1}) 3058.50, 2964.12, 1549.12, 1446.06, 1342.89, 1076.11; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.62 (q, 4H, 2× –CH_2 ethyl), 2.62 (m, 2H, 2× –CH cyclohexyl), 1.48(m, 8H, –CH_2 cyclohexyl), 1.42 (m, 8H, –CH_2 cyclohexyl), 1.24 (t, 6H, 2×CH_3 ethyl); ^{13}C NMR (100 MHz, $CDCl_3$) 29.23, 25.26, 33.18 (cyclohexyl), 18.18, 52.12 (ethyl), 158.26 (Ar–C–NH), 169.65 (Ar–C–Cl), 172.16 (Ar–C–N, s-triazine); Mass: 367.25 $(M+H)^+$; Anal. Calcd. for $C_{19}H_{32}ClN_5$: C, 62.36; H, 8.81; N, 19.14. Found: C, 62.34; H, 8.90; N, 19.16.

*4.5.5. 6-Chloro-N^2,N^4-bis(4-morpholinylphenyl)-1,3,5-triazine-2,4-diamine (**5e**)*

%Yield: 85.22; mp: 108–110 °C; FTIR (cm^{-1}) 3057.70, 2965.12, 1549.18,1447.16, 1342.91, 1076.12, 974.13; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (t, 4H, 2× –CH), 6.75 (t, 2H, –CH), 6.65 (t, 4H, 2× –CH), 3.84 (m, 8H, –CH_2), 3.31(m, 8H, –CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) 71.23, 78.25 (C-morpholine), 113.46, 118.36, 128.26 (Ar–C), 168.85 (Ar–C–Cl), 172.24 (Ar–C–N, s-triazine); Mass: 468.18 $(M+H)^+$; Anal. Calcd. for $C_{23}H_{26}ClN_7O_2$: C, 59.03; H, 5.60; N, 20.95. Found: C, 59.05; H, 5.61; N, 20.95.

*4.5.6. 6-Chloro-N^2,N^4-bis(3-chloro-4-flurophenyl)-1,3,5-triazine-2,4-diamine (**5f**)*

%Yield: 91.86; mp: 152–155 °C; FTIR (cm^{-1}) 3052.32, 1549.58, 1453.25, 1345.91, 978.21; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 (d, 2H, 2× –CH), 6.54 (d, 2H, 2× –CH), 6.84 (d, 2H, 2× –CH), 4.66 (d, 2H, –NH); ^{13}C NMR (100 MHz, $CDCl_3$) 118.11, 122.13, 152.13 (Ar–C), 171.19 (Ar–C–Cl), 179.54 (Ar–C–N, s-triazine); Mass: 401.03 $(M+H)^+$; Anal. Calcd. for $C_{15}H_8Cl_3F_2N_5$: C, 44.75; H, 2.00; N, 17.39. Found: C, 44.74; H, 2.01; N, 17.40.

*4.5.7. 6-Chloro-N^2,N^4-bis(4-flurophenyl)-1,3,5-triazine-2,4-diamine (**5g**)*

%Yield: 88.86; mp: 143–145 °C; FTIR (cm^{-1}) 3054.72, 1548.58, 1448.25, 1342.91, 978.16; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, 4H, 2× –CH), 7.14 (d, 4H, 2× –CH), 4.84 (t, 2H, –NH); ^{13}C NMR (100 MHz, $CDCl_3$) 117.46, 118.11 (Ar–C), 153.43 (Ar–C–F), 172.89 (Ar–C–Cl), 181.24 (Ar–C–N, *s*-triazine); Mass: 334.10 $(M+H)^+$; Anal. Calcd. for $C_{15}H_{10}ClF_2N_5$: C, 53.99; H, 3.02; Cl, 10.62; F, 11.39; N, 20.99. Found: C, 54.00; H, 3.01; Cl, 10.64; F, 11.35; N, 20.98.

*4.6. General procedure for the synthesis of compounds (**6a–g**)*

A mixture of **3** (0.01 M) and **5a–g** (0.01 M) were dissolved in acetone (50 mL) and the reaction mixture was refluxed for 6–8 h. At a regular interval 10% sodium carbonate solution was added to neutralize hydrochloric acid evolved during the reaction. Then the reaction mixture was poured into crushed ice. The product separated was filtered, washed with water and recrystallized from ethanol (see Table 1).

Table 1 In vitro antimalarial activity of the synthesized compounds **6a**–**g**.

Compounds[a]	Antimalarial activity (% dead rings + schizonts[b])
6a	26.5
6b	17.0
6c	10.0
6d	8.5
6e	47.5
6f	56.0
6g	51.5
Chloroquine	50.5

[a] Dose for synthesized compounds 50 μg/ml whereas for chloroquine 0.4 μg/mL.
[b] Mean of two replicates counted against 100 asexual parasites per replicate.

*4.6.1. N^2-(3-(7-chloroquinolin-4-ylamino)propyl)-N^4,N^6-diisopropyl-1,3,5. triazine-2,4,6-triamine (**6a**)*
%Yield 64.86; mp: 184–186 °C; UV λ_{max} (DMSO): 334.0 nm; FTIR (cm^{-1}): 3251 (N–$H_{stretch}$, > NH), 2969 (C–$H_{stretch}$), 2872 (C–$H_{stretch}$, > CH2), 1554 (N–H_{bend}), 1461 (> C═C < stretch), 1383 ($_{Isopropyl\ group}$), 1364,1338, 1313 (C–$H_{stretch}$), 1243 (C–$H_{bending}$), 1167 (C–$H_{stretch}$), 1129, 1080 (C–$N_{stretch}$), 1018, 967, 891 (C–$H_{bend\ out\ of\ plane}$), 851, 805 (C–$H_{stretch\ out\ of\ plane}$), 761, 692 (C–$H_{bend\ out\ of\ plane}$), 557, 497; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.28–8.26 (d, 1H, *J* = 9.60 Hz, quinolyl), δ 7.75 (s, 1H,NH), δ 7.68–7.66 (d, 1H, *J* = 7.60 Hz, quinolyl), δ 7.57 (s, 1H, NH), δ 7.40–7.30 (d, 1H, *J* = 40.80 Hz, quinolyl), δ 6.47–6.39 (d, 1H, *J* = 32.00 Hz, Ar–H), δ 6.25–6.00 (d, 1H, *J* = 32.00 Hz, Ar–H), δ 4.38–4.14 (d, 1H, *J* = 96.80 Hz, CH), δ 3.98–3.96 (d, 2H, CH_2), δ 3.74 (s, 2H, CH_2), δ 3.39–3.27 (m, 2H, CH_2), δ 2.03–1.83 (d, 1H, *J* = 80.00 Hz, Isopropyl, CH_3), δ 1.69 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.61, 166.26, 165.40, 165.18, 164.93, 164.56, 152.29, 150.55, 149.51, 133.83, 127.90, 124.50, 124.44, 117.95, 99.17, 99.02, 42.49, 42.28, 42.06, 41.29, 40.56, 40.35, 40.14, 39.93, 39.51, 39.31, 38.14, 28.48, 26.90, 23.15, 22.74, 22.62, 22.38; Mass: 429.28 $(M+H)^+$; Anal. Calcd. for $C_{21}H_{29}ClN_8$: C, 58.80; H, 6.81; N, 26.12 Found: C, 58.69; H, 6.63; N, 26.34.

*4.6.2. N^2-(3-(7-chloroquinolin-4-ylamino)propyl)-4,6-dimorpholino-1,3,5. triazine-2-amine (**6b**)*
%Yield: 73.0; mp: 207–209 °C; UV λ_{max} (DMSO): 337.0 nm; FTIR (cm^{-1}): 3354 (N–$H_{stretch}$, > NH), 2959 (C–$H_{stretch}$, > CH_2), 2853 (C–$H_{stretch}$), 1583 (N–H_{bend}), 1541 (C═$O_{stretch}$), 1481 (> C═C < ring stretch), 1441, 1361, 1330, 1303, 1286, 1255, 1213 (C–$H_{in\ plane\ bend}$), 1136 (C–$H_{stretch}$), 1110, 1067 (C–$N_{stretch}$), 1005 (C–$O_{stretch}$), 906, 855 (C–$H_{stretch\ out\ of\ plane}$), 805, 765 (C–$H_{bend\ out\ of\ plane}$),737, 639 (C–$H_{bend}$), 544; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.33–8.32 (d, 1H, *J* = 4.80 Hz, quinolyl), δ 8.29–8.27 (d, 1H, *J* = 8.80 Hz, quinolyl), δ 8.23–8.21 (d, 1H, *J* = 8.80 Hz, quinolyl, δ 7.75 (br s, 1H, NH), δ 741–7.39 (d, 1H, *J* = 9.60 Hz, quinolyl), δ 7.33 (br s, 1H, NH), δ 6.90–6.88 (d, 1H, *J* = 7.60 Hz, Ar–H), δ 6.46–6.44 (d, 1H, *J* = 8.80 Hz, quinolyl), δ 6.40–6.39 (d, 1H, *J* = 6.40 Hz, morpholine CH), δ 6.31 (br s, 1H, morpholine NH), δ 3.55 (s, 1H, CH), δ 3.39–3.32 (d, 2H, CH_2), δ 2.47 (s, 2H, CH_2), δ 2.036–1.828 (m, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.17, 165.17, 152.34, 150.54, 150.48, 149.55, 133.81, 127.93, 124.65, 124.44, 117.94, 99.19, 99.06, 66.51, 66.35, 43.70, 43.64, 43.48, 40.36, 40.16, 39.95, 39.74, 39.53, 39.32, 28.34, 26.88; Mass: 485.2 $(M+H)^+$; Anal. Calcd. for $C_{23}H_{29}ClN_8O_2$, C, 56.96; H, 6.03; N, 23.10, Found: C, 57.00; H, 6.01; N, 22.98.

*4.6.3. N^2-(3-(7-Chloroquinolin-4ylamino)propyl)-N^4,N^6-bis(4-nitrophenyl)-1,3,5-triazine -2,4,6-triamine (**6c**)*
%Yield: 66.67; mp: 230–232 °C; UV λ_{max} (DMSO): 373.0 nm; FTIR (cm^{-1}): 3214 (N–$H_{stretch}$, > NH), 2923 (C–$H_{stretch}$, > CH_2), 1580 (N–H_{bend}), 1530, 1494 (> C═C < ringstretch), 1418 (C–O–H_{bend}), 1369, 1301 (C═$O_{stretch}$), 1245, 1177, 1135 (C–$H_{stretch}$), 1108, 899, 847 (C–$H_{stretch\ out\ of\ plane}$), 804, 750 (C–$H_{bend\ out\ of\ plane}$), 691 (C–$H_{bend}$), 628,492; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.01–9.93 (d, 2H, *J* = 33.20 Hz, quinolyl –H), δ 9.68–9.60 (d, 2H, *J* = 30.00 Hz, quinolyl –H), δ 8.53 (s,1H, NH), δ 8.33–8.26 (d, 1H, *J* = 26.80 Hz, quinolyl), δ 8.11–8.05 (d, 1H, *J* = 21.20 Hz, quinolyl), δ 7.92–7.74 (d, 1H, *J* = 69.20 Hz, quinolyl), δ 7.42–7.37 (d, 1H, *J* = 21.20 Hz, quinolyl), δ 7.12–7.07 (d, 1H, *J* = 20.80 Hz, quinolyl), δ 6.71 (s, 1H, NH), δ 6.58–6.47 (d, 1H, *J* = 45.20 Hz, Ar–H), δ 5.84–5.83 (d, 2H, *J* = 56.40 Hz, CH_2), δ 3.52–3.38 (d, 2H, CH_2), δ 2.03–1.92 (d, 2H, *J* = 41.20 Hz,; ^{13}C NMR (100 MHz, DMSO-d_6): δ 152.31, 151.03, 149.45, 134.02, 127.91, 124.55, 117.92, 99.22, 40.56, 40.37, 40.16, 39.95, 39.75, 39.54, 39.33; Mass: 587.2 (4.45) $(M+H)^+$, 324.1 (100), 397.1 (72.64) 399.1 (49.09). Anal. Calcd. for $C_{27}H_{23}ClN_{10}O_4$: C, 55.25; H, 3.95; N, 23.86, Found: C, 55.23; H, 3.91; N, 23.89.

*4.6.4. N^2-(3-(7-Chloroquinolin-4-ylamino)propyl)-N^4,N^6-bis(2-cyclohexylethyl)-1,3,5-triazine-2,4,6-triamine (**6d**)*
%Yield: 65.53; mp: 252–254 °C; UV λ_{max} (DMSO): 269.0 nm; FTIR (cm^{-1}): 3242 (N–$H_{stretch}$, > NH), 2924 (C–$H_{stretch}$, > CH_2), 2852 (C–$H_{stretch}$), 2872, 2364, 1579 (N–H_{bend}), 1463 ($_{n\text{-}hexene}$), 1364, 1201, 1135 (C–$H_{stretch}$), 899, 851 (C–$H_{stretch\ out\ of\ plane}$), 808, 598; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32–8.24 (d, 1H, *J* = 30.40 Hz, quinolyl), δ 8.03 (d, 1H, *J* = 2.08 Hz, quinolyl), δ 7.75–7.55 (d, 1H, *J* = 80.00 Hz, quinolyl), δ 7.39–7.23 (d, 1H, *J* = 64.00 Hz, cyclohexyl), δ 6.46–6.40 (d, 1H, *J* = 26.00 Hz, Ar–H), δ 3.58 (s, 2H, CH_2), δ 2.50–2.46 (d, 1H, CH), δ 1.63 (s, 2H, CH_2), δ 1.43 (s, 1H, NH), δ 1.43–1.13 (d, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ 152.30, 150.60, 133.94, 127.79, 124.58, 117.90, 99.22, 40.70, 40.43, 40.23, 40.02, 39.81, 39.60, 39.39, 39.18, 36.28; Mass: 551.4 (5.25) $(M+H)^+$, 381 (100%), 397.1 (78.04), 399 (53.07); Anal. Calcd. for $C_{31}H_{45}ClN_8$: C, 65.88; H, 8.03; N, 19.83. Found: C, 65.70; H, 8.09; N, 19.98.

*4.6.5. N^2-(3-(7-Chloroquinolin-4-ylamino)propyl)-N^4,N^6-bis(4-morpholinophenyl)-1,3,5-triazine-2,4,6-triamine (**6e**)*
%Yield: 58.33; mp: 258–260 °C; UV λ_{max} (DMSO): 260.5 nm; FTIR (cm^{-1}): 3294 (N–$H_{stretch}$, > NH), 2922 (C–$H_{stretch}$, > CH_2), 2853 (C–$H_{stretch}$), 1579 (N–H_{bend}), 1451 (> C═C < stretch), 1367, 1207, 1136 (C–$H_{stretch}$), 852 (C–$H_{stretch\ out\ of\ plane}$), 807, 645 (C–$H_{bend}$); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.37 (d, 1H, quinolyl), δ 8.28–8.25 (d, 1H, *J* = 12.00 Hz, quinolyl), δ 7.74 (d, 1H, quinolyl), δ 7.45 (d, 1H, quinolyl), δ 6.83 (s, 1H, morpholine), δ 6.48 (d, 1H, Ar–H), δ 3.71 (s, 2H, CH_2), δ 3.43 (s, 2H, CH_2), δ 2.99 (s, 1H, NH), δ 2.48 (s, 1H, NH), δ 2.07–2.03 (d, 2H, phenyl); ^{13}C NMR (100 MHz, DMSO-d_6): δ152.31, 127.91, 124.55, 40.58,

40.37, 40.16, 39.95, 39.75, 39.54, 39.33; Mass: 667.2 (3.06) $(M+H)^+$, 353.3 (100), 381.3 (61.98), 711.6 (4.26); Anal. Calcd. for $C_{35}H_{39}ClN_{10}O_2$: C, 63.01; H, 5.89; N, 20.99. Found: C, 63.10; H, 6.01; N, 20.74.

*4.6.6. N^2-(3-(7chloroquinolin-4-ylamino)propyl)-N^4,N^6-bis(3-chloro-4-fluorophenyl)-1,3,5-triazine-2,4,6-triamine (**6f**)*

%Yield: 46.78; mp: 202–204 °C; UV λ_{max} (DMSO): 262.0 nm; FTIR (cm^{-1}): 3413, 3271 (N–$H_{stretch}$ > NH), 3106 (C–$H_{stretch}$), 2929 (C–$H_{stretch}$, > CH_2), 1581 (N–H_{bend}), 1493 (> C=C < $_{stretch}$), 1415, 1259, 1210, 1135 (C–$H_{stretch}$), 1054 (C–$N_{stretch}$), 870 (C–$H_{stretch\ out\ of\ plane}$), 807, 699 (C–$H_{bend\ out\ of\ plane}$), 653 (C–$H_{bend}$), 576, 554, 513; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.53–8.34 (d, 1H, J = 78.00 Hz, quinolyl), δ 8.30–8.28 (d, 1H, J = 9.20 Hz, quinolyl), δ 8.09 (s, 1H, quinolyl), δ 8.02 (s, 1H, quinolyl), δ 7.75–7.73 (d, 1H, J = 8.80 Hz, quinolyl), δ 7.71–7.68 (d, 1H, J = 13.60 Hz, quinolyl), δ 7.61 (s, 2H, NH), δ 7.42–7.39 (d, 1H, J = 10.40 Hz, quinolyl), δ 7.34–7.33 (d, 1H, J = 4.40 Hz, quinolyl), δ 7.28–7.20 (m, 1H, quinolyl), δ 6.46 (s, 2H, phenyl), δ 3.41–3.36 (d, 2H, J = 19.20 Hz, CH_2), δ 2.47 (s, 1H, NH), δ 1.16–0.787 (d, 2H, J = 151.20 Hz, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ166.03, 164.35, 164.19, 153.92, 151.52, 151.17, 151.10, 150.06, 148.15, 137.99, 136.58, 134.42, 126.83, 124.80, 124.36, 121.47, 120.38, 119.39, 119.21, 117.68, 116.93, 116.72, 99.04, 40.74, 40.36, 40.15, 39.94, 39.73, 39.52, 39.32, 38.51, 28.17; Mass: 601.1 $(M+H)^+$; Anal. Calcd. for $C_{27}H_{21}Cl_3F_2N_8$: C, 53.88; H, 3.52; N, 18.62. Found: C, 54.00; H, 3.11; N, 18.48.

*4.6.7. N^2-(3-(7-chloroquinolin-4-ylamino)propyl)-N^4,N^6-bis(4-fluorophenyl)-1,3,5-triazine-2,4,6-triamine (**6g**)*

%Yield: 55.56; mp: 183–185 °C; UV λ_{max} (DMSO): 261.0 nm; FTIR (cm^{-1}): 3265 (N–$H_{stretch}$, > NH), 3108, 2930 (C–$H_{stretch}$, > CH_2), 1617, 1582 (N–H_{bend}), 1502, 1415, 1209, 1154 (C–$H_{stretch}$), 984, 832 (C–$H_{stretch\ out\ of\ plane}$), 787 (C–$H_{bend\ out\ of\ plane}$), 542, 510; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.81–8.72 (d, 1H, J = 35.60 Hz, quinolyl), δ 8.55–8.52 (d, 1H, J = 14.00 Hz, quinolyl), δ 8.40–8.36 (d, 1H, J = 12.40 quinolyl), δ 7.88 (s, 1H, quinolyl), δ 7.73–7.66 (d, 1H, J = 30.80 Hz, quinolyl), δ 7.52–7.50 (d, 1H, J = 6.80 Hz, quinolyl), δ 7.20–7.17 (d, 1H, J = 13.20 Hz, quinolyl), δ 7.14–7.11 (d, 1H, J = 10.80 Hz, quinolyl), δ 7.07 (s, 2H, NH), δ 7.04–7.00 (m, 1H, quinolyl), δ 6.30 (s, 2H, phenyl), δ 6.62–6.60 (d, 1H, J = 5.60 Hz, phenyl), δ 3.72 (s, 1H, NH), δ 3.47–3.46 (d, 2H, J = 2.40 Hz, CH_2), δ 3.43–3.40 (dd, 2H, J = 4.00,5.60 Hz, CH_2), δ 2.47 (s, 1H, NH), δ 2.04–1.97 (d, 2H, J = 27.20 Hz, CH_2), δ 1.15 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.12, 164.46, 164.35, 156.54, 153.44, 147.03, 143.55, 137.09, 136.35, 125.91, 125.71, 124.16, 123.58, 123.10, 121.99, 116.83, 115.76, 115.53, 115.29, 115.08, 98.95, 95.87, 41.01, 40.58, 40.37, 40.16, 39.95, 39.53, 39.32, 38.20, 28.05; Mass: 533.2 (33.19) $(M+H)^+$, 377.2 (100), 535.2 (13.62), 536.2 (3.97); Anal. Calcd. for $C_{27}H_{23}ClF_2N_8$: C, 60.85; H, 4.35; N, 21.02. Found: C, 60.60; H, 4.51; N, 20.98.

5. Conclusion

On close perlustration and analysis, all the target compounds exhibit mild to moderate degrees of parasite inhibition. But, none of the compounds proved to be as effective as lead, although it contains 1,3,5-traizine and 4-aminoquinoline which already proved be an effective pharmacophore present in clinically used drugs such as cycloguanil and chloroquine, respectively. The present study illustrates that the existence of these two active pharmacophoric groups could not translate hybrid molecules into potent antimalarials. In the light of the above, our further studies are in progress to explain the plausible mechanism lying behind this untoward activity.

However, it can be concluded that this class of compounds will certainly hold a great promise by effective pharmacomodulation toward pursuit to discover a novel class of antimalarial agents to substitute expensive ACTs in the near future.

Conflict of interest

Authors declare no conflict of interest.

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References

Chiyanzu, I., Clarkson, C., Smith, P.J., Lehman, J., Gut, J., Rosenthal, P.J., Chibale, K., 2005. Design, synthesis and antiplasmodial evaluation in vitro of new 4-aminoquinoline isatin derivatives. Bioorg. Med. Chem. 13, 3249–3261.

De, D., Byers, L.D., Krogstad, D.J., 1997. Antimalarials: synthesis of 4-aminoquinolines that circumvent drug resistance in malaria parasites. J. Het. Chem. 34, 315–320.

Ekland, E.H., Fidock, D.A., 2008. In vitro evaluations of antimalarial drugs and their relevance to clinical outcomes. Int. J. Parasitol. 38, 743–747.

Gahtori, P., Das, A., Bhatt, H., 2009. Synthesis and antibacterial assessment of N-[4-(4-substituted phenyl)-1,3-thiazol-2-yl]-1,3,5-triazin-2-amine. Indian J. Pharm. Sci. 71, 79–82.

Guerin, P.J., Olliaro, P., Nosten, F., Druilhe, P., Laxminarayan, R., Binka, F., Kilama, W.L., Ford, N., White, N.J., 2002. Current status of control, diagnosis, treatment, and a proposed agenda for research and development. Lancet Infect. Dis. 2, 564–573.

Guidelines for the Testing of Chemicals, Test No. 425, 2006. Acute Oral Toxicity: Up-and-Down Procedure, Organization for Economic Co-operation and Development (OECD), pp. 1–27.

Guidelines for the treatment of malaria, 2nd edition, 2010. WHO Press: Geneva.

Gupta, L., Srivastava, K., Singh, S., Puri, S.K., Chauhan, P.M.S., 2008. Synthesis of 2-[3-(7-Chloro-quinolin-4-ylamino)-alkyl]-1-(substituted phenyl)-2,3,4,9-tetrahydro-1H-b-carbolines as a new class of antimalarial agents. Bioorg. Med. Chem. Lett. 18, 3306–3309.

Kgokong, Joseph L., Matsabisa, Gilbert M., Smith, Peter P., Breytenbach, Jaco C., 2008. N,N-Bis(trifluoromethylquinolin-4-yl)diamino Alkanes: Synthesis and Antimalarial Activity. Med. Chem. 4, 438–445.

Kremsner, P.G., Krishna, S., 2004. Antimalarial combinations. Lancet 364, 285–294.

Marfurt, J., Smith, T.A., Hastings, I.M., Müller, I., Sie, A., Oa, O., Avizor, M., Reeder, J.C., Beck, H.P., Genton, B., 2010. Plasmodium falciparum resistance to anti-malarial drugs in Papua New

Guinea: evaluation of a community-based approach for the molecular monitoring of resistance. Malar. J. 9, 8.

Richard, T., Christopher, A.W., Sivaram, P., Saxena, U., 2007. Methods and compositions of novel triazine compounds United States Patent. 7173032.

Rieckmann, K.H., Sax, L.J., Campbell, G.H., Mrema, J.E., 1978. Drug sensitivity of Plasmodium falciparum: an in vitro microtechnique. Lancet 1, 22–23.

Rogerson, S.J., Menendez, C., 2006. Treatment and prevention of malaria in pregnancy: opportunities and challenges. Expert Rev. Anti Infect. Ther. 4, 687–702.

Singh, C., Malik, H., Puri, S.K., 2004. Synthesis of new 6-alkylvinyl/arylalkylvinyl substituted 1,2,4-trioxanes active against multidrug-resistant malaria in mice. Bioorg. Med. Chem. 12, 1177–1182.

Singh, U.P., Singh, R.K., Bhat, H.R., Subhashchandra, Y.P., Kumar, V., Kumawat, M.K., Gahtori, P., in press. Synthesis and antibacterial evaluation of series of novel tri-substituted-s-triazine derivatives. Med. Chem. Res., doi: 10.1007/s00044-010-9446-7.

Thruston, J.T., Dudley, J.R., Kaiser, D.W., Henbleikner, I., Schaefer, F.C., Holm-Hensen, D., 1951. Chloride derivatives I aminochloros-triazines. J. Am. Chem. Soc. 73, 2981–2983.