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ORIGINAL ARTICLE

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

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KEYWORDS

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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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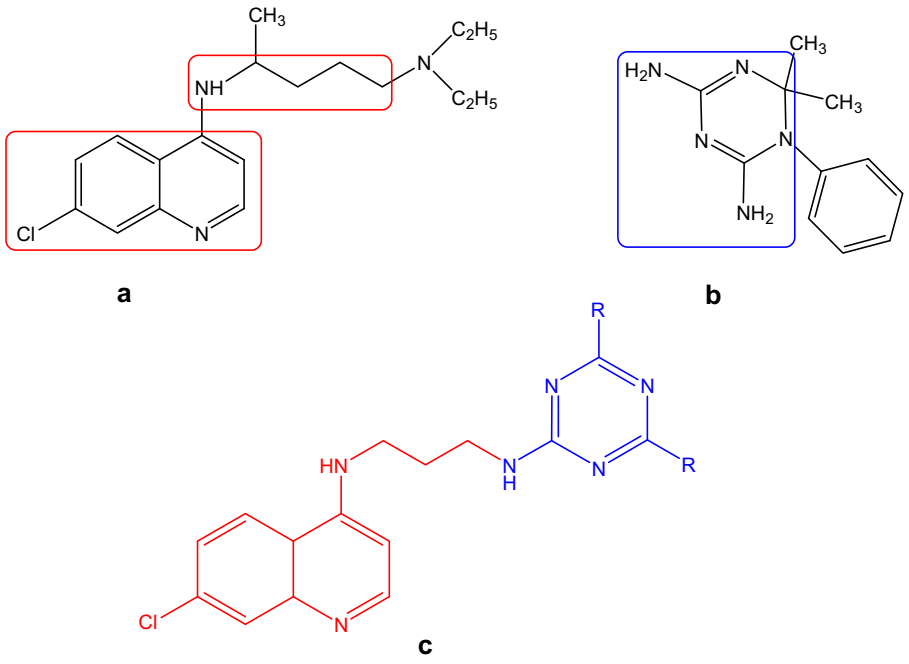

Figure 1 Structure of (a) chloroquine, (b) cycloguanil and (c) hybrid 4-aminoquinoline-1,3,5-triazine derivatives.

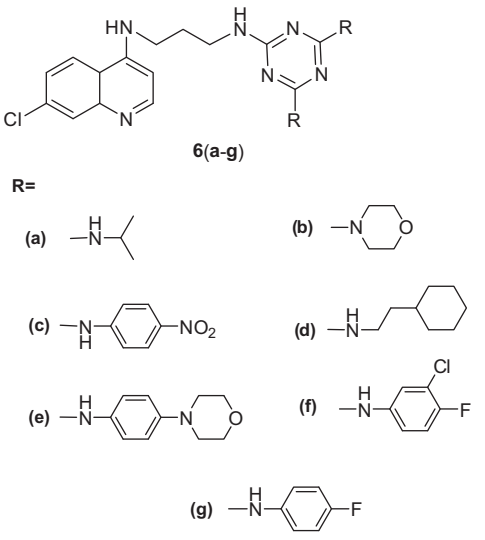

Figure 2 Hybrid 4-aminoquinoline-1,3,5-triazine derivatives (**6a**–**g**).

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,

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