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Synthesis and evaluation of new diaryl ether and quinoline hybrids as potential antiplasmodial and antimicrobial agents

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ABSTRACT

Synthesis and bioevaluation of new diaryl ether hybridized quinoline derivatives as antiplasmodial, antibacterial and antifungal agents is reported. It was encouraging to discover that several compounds displayed 2–3 folds better efficacy than chloroquine in chloroquine-resistant K1 strain of *Plasmodium falciparum*. Further, a few members of the library displayed good antibacterial efficacy against gram positive strains of bacteria but none of the compounds displayed any significant antifungal activity.

Malaria continues to be one of the most widespread of all the infectious diseases. The recent WHO report in 2011 estimated more than 216 million clinical cases of malaria and approximately 655,000 deaths in 2010, which in itself reflect the magnitude of the disease.[1,2] Amongst all the malaria causing Plasmodium species, *Plasmodium falciparum* is considered to be the deadliest. Unfortunately there is now widespread resistance of this parasite to most of the available antimalarial chemotherapy including chloroquine (CQ), mefloquine, amodaquine, pyrimethamine, sulphadoxine, atovaquone, etc. Fortunately artemisinin or its derivatives which have the propensity to kill the parasite rapidly were considered to be an effective alternative. As a consequence WHO advocated for combinations of artemisinin with other antimalarial drugs to treat malaria in all the endemic areas. However recent report of decreasing efficacy of artemisinin in the malaria endemic areas has not only send the alarm bells ringing but has justified the continued search for the new chemotherapeutic agents in this area.[3]

As assimilated in a recent review the search for new antimalarial agents concentrate around reoptimizing the use of existing antimalarials, repurposing of drugs used to treat other diseases, chemically modifying the existing antimalarials, natural product leads, large scale screening of diverse chemical libraries or parasite-genome based target approach.[4] Although large scale screening of the chemical libraries by GSK, Novartis has offered several chemical starting points for the medicinal chemists to work upon,[5] most of the literature pertaining to the medicinal chemistry programs during last decade concentrate on chemically modifying the existing antiplasmodial agents. It is well known that amongst all the antimalarials present in clinics, CQ is the cheapest and is considered to be safe for use even among pregnant women. Possibly, these attributes provided impetus to introduce changes in this molecule in many ways which included altering the length and nature of the side chain at 4-position, investigating more hydrophobic side chains or by dimerizing the two quinoline units by linkers of variable nature and length.[6] Whereas limited success was achieved through these strategies, after the invent of DU1302[7] more efforts were directed towards the construction of quinoline-based hybrids. There are several reviews[8] on the topic and based on a critical analysis of the structural profiles, these hybrids quinolines can be divided into four major classes illustrated in Figure 1. Significantly, though no clinical candidate is obtained, there is considerable interest to explore the potential of this approach for obtaining antimalarials.[9]

In a medicinal chemistry program directed towards designing new antimalarials we envisaged synthesis and antiplasmodial evaluation of a new quinoline-based hybrid containing diarylether

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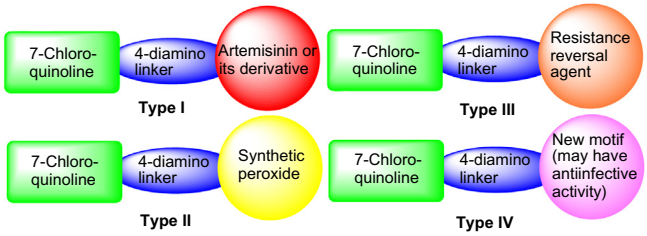


Figure 1. Major classes of quinoline-based hybrid compounds reported during the last decade.

and guanidine unit. Whereas rational to introduce diarylether was based on the prior knowledge that Triclosan, a diarylether is a well established antibacterial agent with mild in vitro antiplasmodial effect,[10] the incorporation of guanidine was based on the presence of this subunit in several antimalarial drugs (Fig. 2). It has also been shown that the guanidine group can bind to the *Pf*DHFR via hydrogen bonding.[11] Accordingly, we prepared new quinoline-based hybrids using some robust chemistry and evaluated their antiplasmodial effect in chloroquine sensitive and chloroquine resistant *P. falciparum* strains. We describe herein the details of results of this study.

The synthesis of diaryl ether framework commenced with the coupling of 2-fluoronitrobenzene or 4-fluoronitrobenzene with 2,5-dichlorophenol **1**{**1**} or 4-methoxyphenol **1**{**2**} in the presence of K_2CO_3 in DMF at room temperature (rt) to afford the diarylethers **2**{**1**,**2**}. Reducing the nitro group in **2**{**1**,**2**} with Fe–AcOH proceeded smoothly to furnish the respective substituted anilines **3**{**1**,**2**} in quantitative yields. Subsequent treatment of **3**{**1**,**2**} with different aryl isothiocyanates in DMF gave the corresponding thioureides **4**{**1**–**2**,**1**–**2**,**1**–**3**} in 65–90% yields, as outlined in Scheme 1. Thiourea derivatives **4**{**1**–**2**,**1**–**2**,**1**–**3**} were transformed to their corresponding guanidine derivatives **5**{**1**,**2**,**1**–**2**,**1**–**3**,**1**–**3**} by reacting with different 4-quinolinamines in the presence of $HgCl_2$ and Et_3N in DMF at rt.

Synthesis of another series of diarylether based hybrids is outlined in Scheme 2. In the first step the 4-hydroxy benzaldehyde was reacted either with 2- or 4-fluoronitrobenzenes in the presence of K_2CO_3 in DMF as medium to prepare the benzaldehydes **6**{**1**,**2**}. The Morita–Baylis–Hillman (MBH) reaction of **6**{**1**,**2**} with methyl acrylate in the presence of DABCO under neat conditions followed by successive acetylation and $NaBH_4$-mediated reduction in S_N2' fashion afforded **9**{**1**,**2**} as E-isomer exclusively. Chemoselective reduction of the nitro functionality with Fe–AcOH in **9**{**1**,**2**} afforded the substituted anilines **10**{**1**,**2**}, which upon treatment with different aryl isothiocyanates in DMF at rt furnished thioureides **11**{**1**–**2**,**1**–**3**} in 65–85% yields. These thioureides were then transformed to the respective guanidine derivatives **12**{**1**,**1**,**1**–**5**},

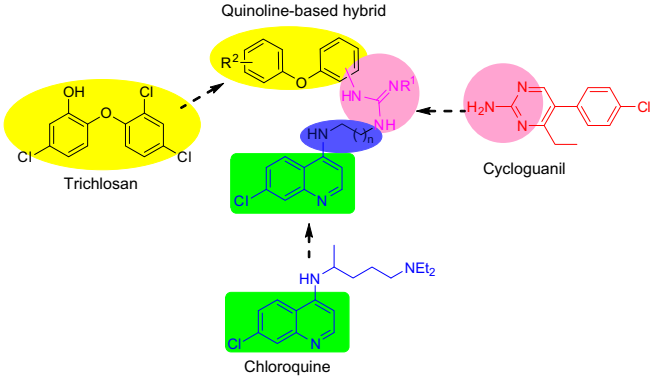
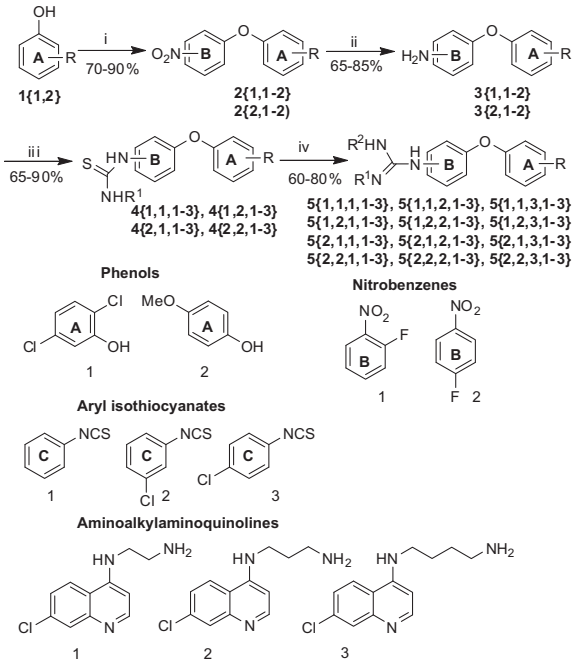
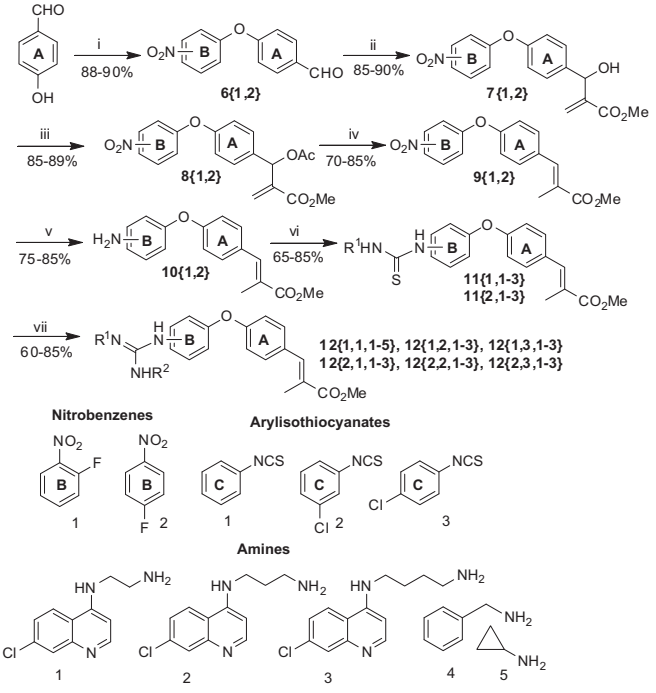


Figure 2. Design for the quinoline-based hybrid compounds.



Scheme 1. Reagents and conditions: (i) 2-fluoronitrobenzene or 4-fluoronitrobenzene (1.0 equiv), K_2CO_3 (1.5 equiv), DMF, rt, 3–6 h; (ii) Fe (5.0 equiv), AcOH, 90 °C, 20–40 min; (iii) R^1NCS (1.2 equiv), DMF, rt, 2–4 h; (iv) R^2NH_2 (0.8 equiv), $HgCl_2$ (1.0 equiv), Et_3N (5.0 equiv), DMF, rt, 2–3 h.



Scheme 2. Reagents and conditions: (i) 2-fluoronitrobenzene or 4-fluoronitrobenzene (1.0 equiv), K_2CO_3 (1.5 equiv), DMF, rt, 3–6 h; (ii) methyl acrylate (1.1 equiv), DABCO (0.5 equiv), rt, 72 h; (iii) AcCl (1.5 equiv), pyridine (1.3 equiv), CH_2Cl_2, 0 °C–rt, 30 min; (iv) $NaBH_4$ (1.0 equiv), MeOH, 0 °C–rt, 30 min; (v) Fe (5.0 equiv), AcOH, 90 °C, 20–40 min; (vi) R^1NCS (1.2 equiv), DMF, rt, 2–4 h; (vii) R^2NH_2 (0.8 equiv), $HgCl_2$ (1.0 equiv), Et_3N (5.0 equiv), DMF, rt, 2–3 h.

12{**1**,**2**–**3**,**1**–**3**} and **12**{**2**,**1**–**3**,**1**–**3**} by reacting them with different primary amines in the presence of $HgCl_2$ as shown in Scheme 2.

A total of 58 guanidine derivatives were synthesized and assessed for their in vitro antiplasmodial efficacy against CQ-sensitive (3D7) and CQ-resistant (K1) strain of *P. falciparum*.[12]