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Synthesis of new 4-aminoquinolines and quinoline–acridine hybrids as antimalarial agents

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ABSTRACT

Despite emergence of resistance to CQ and other 4-aminoquinoline drugs in most of the endemic regions, research findings provide considerable support that there is still significant potential to discover new affordable, safe, and efficacious 4-aminoquinoline antimalarials. In present study, new side chain modified 4-aminoquinoline derivatives and quinoline–acridine hybrids were synthesized and evaluated in vitro against NF 54 strain of *Plasmodium falciparum*. Among the evaluated compounds, compound **17** (MIC = 0.125 μg/mL) was equipotent to standard drug CQ (MIC = 0.125 μg/mL) and compound **21** (MIC = 0.031 μg/mL) was four times more potent than CQ. Compound **17** showed the curative response to all the treated swiss mice infected with CQ-resistant N-67 strain of *Plasmodium yoelii* at the doses 50 mg/kg and 25 mg/kg for four days by intraperitoneal route and was found to be orally active at the dose of 100 mg/kg for four days. The promising antimalarial potency of compound **17** highlights the significance of exploring the privileged 4-aminoquinoline class for new antimalarials.

Despite the extensive research efforts, malaria continues to exert the tremendous burden on the health and economies of developing countries. It is estimated that 40% population of the world is exposed to the malaria, killing more than 2 million people every year.[1] Malaria caused by *Plasmodium falciparum* is the most fatal and accounts for 95% mortality.[2] Since the discovery of natural product quinine, structural modifications of its quinoline pharmacophore led to the development of most effective antimalarial agents namely chloroquine (CQ, **1**), amodiaquine (AQ, **2**), and mefloquine (**3**) (Fig. 1).[3,4] The wide-spread resistance to 4-aminoquinolines and antifolates has seriously limited the therapeutic options. Therefore, there is urgency to develop new affordable, safe, and efficacious antimalarilas.[5] Although the resistance to CQ and related 4-aminoquinoline antimalarial drugs has emerged; designing new antimalarial based on the quinoline pharmacophore has distinct advantages due to unique pharmacological effect of 4-aminoquinoline drugs.[6]

During the erythrocyte stage, malaria parasite invade the red blood cell of human host, digest and degrade a huge amount of hemoglobin as a source of amino acids, consequently releasing toxic heme as a by product.[7] Heme detoxification crucial for parasite survival is a unique non-enzymatic efficient process characterized by conversion of free heme into non-toxic crystalline pigment hemozoin.[8] CQ and other related drugs block the heme detoxification process, thus substantial build up of heme lead to the parasite death.[9] Despite the persistent heavy drug pressure of CQ for several decades, the delayed emergence of resistance to CQ is considered due to the complexity of digestive vacuole environment and the immutable nature of heme target. Multiple point mutations in *P. falciparum* chloroquine resistance transporter protein (*pfcrt*) conferred resistance to CQ characterized by the substantially reduced accumulation of CQ level in food vacuole. Interaction of CQ with *pfcrt* induces resistance very slowly to *P. falciparum* owing to the complexity in amino acid substitutions in pfcrt.[10]

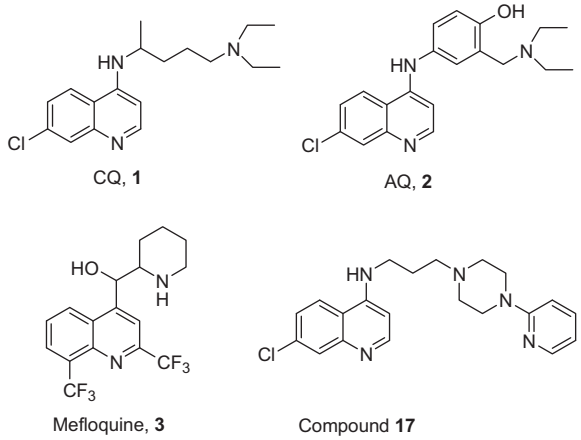

Figure 1. Structures of CQ (**1**), AQ (**2**), mefloquine (**3**), and target compound **17**.

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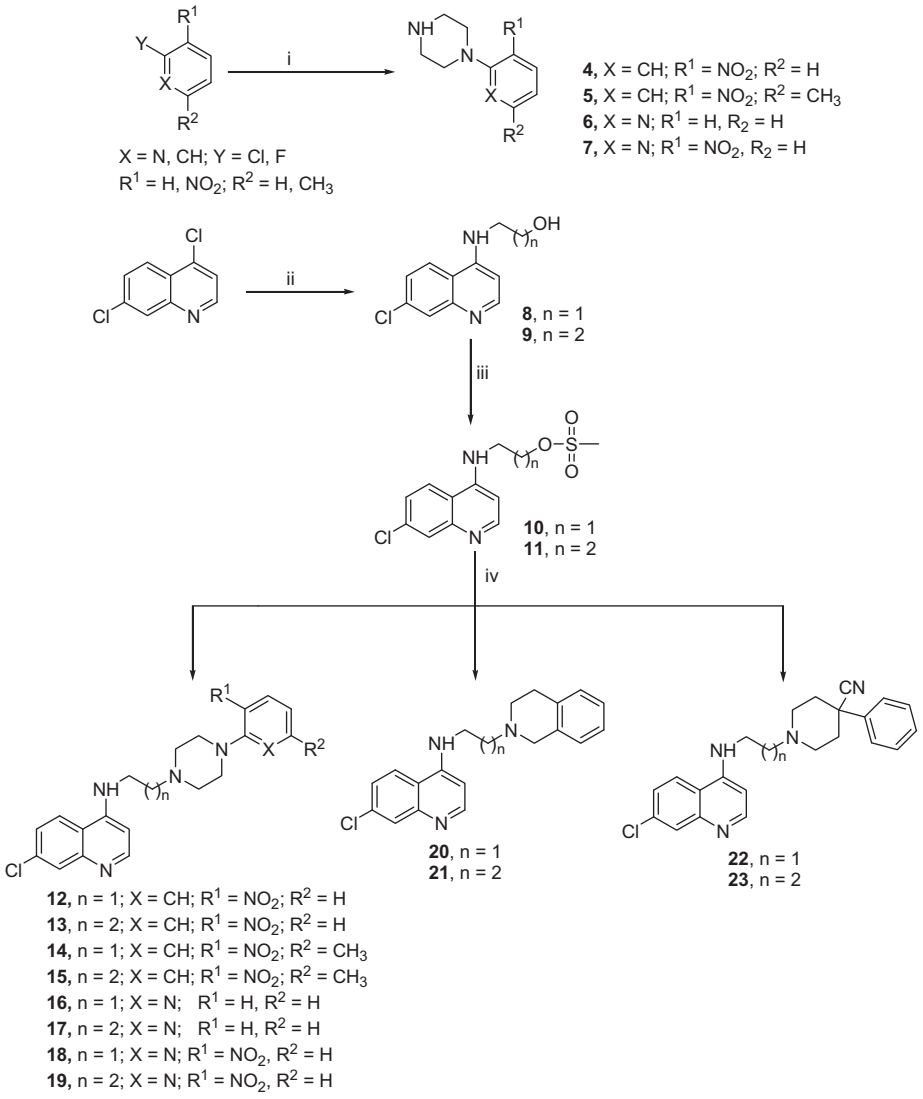
The structure–activity relationship studies on CQ–Heme binding have been explored in order to identify the key structural requirement for designing the new antimalarial agents. It was well established that the 7-chloro-4-aminoquinoline nucleus is quintessential for the inhibition of heme polymerization and parasite growth.[11] Moreover, the basic nature of the side chain is crucial for accumulation of drug within the acidic food vacuole of the parasite.[12] Several studies demonstrated that various structurally diverse modifications in the side chain of CQ were well tolerated for the antimalarial activity. Systematic variation of the branching and basicity of the side chain of CQ yielded the new 4-aminoquinoline derivatives exhibiting excellent potency against CQ-sensitive and CQ-resistant strains.[13] Replacement of diethylamino function of CQ with *tert*-butyl or cyclic amines such as piperidine, morpholine furnished the metabolically stable potent antimalarials.[14,15] Incorporation of guanidines,[16] and intramolecular hydrogen-bonding motif like α-aminocresols[17] in the side chain produced the new potential antimalarials. More recently, the 4-aminoquinoline carrying dimethylaminomethyl substituted phenyl ring, phenylequine (PQ) has been identified as potent antimalarial.[18]

To overcome the resistance, the bulky bisquinolines were designed embodying the hypothesis that steric hindrance would not allow drug efflux by the proteinaceous transporter.[19,20] Though bisquinolines such as Ro 47-7737[20] and other piperaquine, hydroxypiperaquine and dichloroquinazine[21] exhibited promising antimalarial efficacy but toxic liabilities ruled out their development as drug candidate. In addition, bisacridine derivatives with di-, tri-, and tetramine linker have been investigated for their effect on the antimalarial activity.[22] Hybridization of the 4-aminoquinoline and 9-amino acridine with 1,2,4-trioxanes produced the antimalarials exhibiting the low nM potency.[23]

As part of research program devoted to the synthesis of nitrogen heterocycles as antimalarials, our group has identified potential quinoline-based antimalarials.[24] In view of this background, we have synthesized the side chain modified 4-aminoquinolines and quinoline–acridine hybrids and screened in vitro against NF 54 strain of *P. falciparum*. Selected compounds were also subjected to in vivo study against CQ-resistant strain of *Plasmodium yoelii*.

New side chain modified 4-aminoquinoline derivatives (**12–23**) were synthesized by a synthetic route as described in Scheme 1. Starting compounds, substituted aryl/heteroaryl piperazines (**4–7**) were synthesized by aromatic nucleophilic substitution reaction of aryl/heteroaryl substrates with piperazine under appropriate reaction conditions, depending upon the nature of substrates.



Scheme 1. Reagents and conditions: (i) piperazine, THF, 0 °C to rt, 3 h; (ii) 2-amino ethanol or 3-amino-propan-1-ol, *n*-butanol, 100 °C, 8 h; (iii) methanesulfonyl chloride, dry pyridine, 0 °C, 3 h; (iv) amines, NMP, MW, 30 s.