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Synthesis of chiral chloroquine and its analogues as antimalarial agents

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ABSTRACT

In this investigation, we describe a new approach to chiral synthesis of chloroquine and its analogues. All tested compounds displayed potent activity against chloroquine sensitive as well as chloroquine resistant strains of *Plasmodium falciparum* in vitro and *Plasmodium yoelii* in vivo. Compounds *S*-**13b**, *S*-**13c**, *S*-**13d** and *S*-**13i** displayed excellent in vitro antimalarial activity with an IC_{50} value of 56.82, 60.41, 21.82 and 7.94 nM, respectively, in the case of resistant strain. Furthermore, compounds *S*-**13a**, *S*-**13c** and *S*-**13d** showed in vivo suppression of 100% parasitaemia on day 4 in the mouse model against *Plasmodium yoelii* when administered orally. These results underscore the application of synthetic methodology and need for further lead optimization.

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1. Introduction

Malaria is a protozoan disease of wide occurrence. It is caused by five species of the genus *Plasmodium*, the most lethal form being *Plasmodium falciparum*. According to World Health Organization, it is estimated that 3.4 billion people are at risk and 90% of all malaria deaths occur in sub-Saharan Africa.[1] Drugs with quinoline scaffold (Fig. 1) have huge significance as antimalarial agents. However, the emergence of chloroquine resistant parasite strains has led to renewed interest in development of antimalarial agents based on chloroquine.[2] Chloroquine (CQ), a 4-aminoquinoline has been in clinical use for more than five decades and it is administered as racemate. It is generally accepted that stereochemistry of a molecule not only affects the pharmacodynamic profile but changes the pharmacokinetic property of a drug molecule. Although there is no difference in the activity of CQ enantiomers in the case of CQ sensitive strain, in vitro studies have indicated that (*S*)-CQ is more active than (*R*)-CQ against CQ resistant strain. The plasma protein binding of chloroquine and hydroxychloroquine in human is enantioselective. The (*S*)-enantiomers of both drugs showed more binding to plasma proteins than their respective enantiomers.[3] The antimalarial activity of the two enantiomers of chloroquine has been studied in mice, and it is observed that (*S*)-CQ is more active than the other isomer and also toxicity (LD_{50}) is lower for the (*S*)-enantiomer in the mouse model.[4,5] Later, Fu and coworkers[6] studied in vitro activity of (*S*)- and (*R*)-enantiomers of chloroquine and found that (*S*)-CQ is more active than (*R*)-CQ in CQ resistant strain. There is little information available in the literature on the activity of chiral chloroquine analogues against the CQ-R strains of *P. falciparum*, possibly because of the non availability of chirally pure chloroquine. This background led us to design new generic methodology for chiral synthesis of chloroquine and its analogues.

During the literature search, it was observed that there are only two approaches for the synthesis of chiral chloroquine using glutamic acid and pyroglutamic acid as starting materials.[7,8] There are limitations associated with these methods viz., the reaction involves the conversion of carboxylic acid group to methyl which is a low yielding step, secondly, only methyl group could be introduced at the chiral center. In order to optimize substituent group at the chiral carbon, it is important to have a methodology that enables introduction of alkyl/aralkyl substitution at this centre. In the light of these observations, we have developed a new method that involves the homologative olefination for the synthesis of chiral side chain, using L and D-alanine, respectively, as shown in Scheme 1. In the present study, we have designed compounds wherein 7-chloro-4-aminoquinoline scaffold as well as carbon chain length was not altered; modifications were carried out only at the pendant amino group (Fig. 2). The diethylamine function of CQ is replaced by metabolically more stable alkyl amine groups, namely secondary or tertiary terminal nitrogens. The present study

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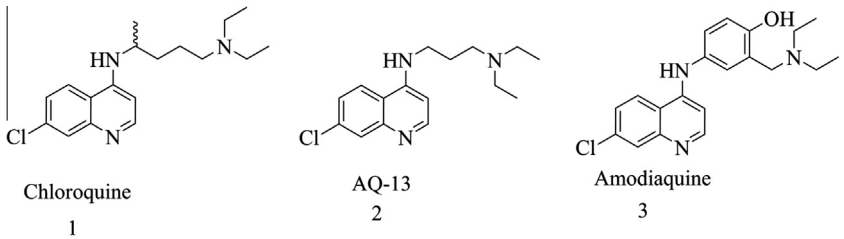


Figure 1. Structures of some 4-aminoquinolines having antimalarial activity.

describes synthesis, biophysical studies, and antimalarial activity of new series of compounds.

2. Chemistry

The target compounds were prepared as outlined in Scheme 1. The compounds having either (*S*)- or (*R*)-configuration at the chiral carbon in the side chain of chloroquine were synthesized from L- and D-alanine, respectively. The alanine methyl ester (**2**) was prepared by adding thionyl chloride to a suspension of amino acid in methanol and stirring the reaction mixture at 0 °C to room temperature.[9] Compound **2** was converted to the corresponding Boc derivative (**3**) by di-*tert*-butylpyrocarbonate in DCM with 2 equiv of triethylamine.[10] Boc protected methyl ester was subjected to the DIBAL-H (diisobutylaluminum hydride) mediated reduction at −78 °C in dry THF to obtain the Boc protected aldehyde (**4**).[11] The aldehyde obtained was highly prone to epimerization and

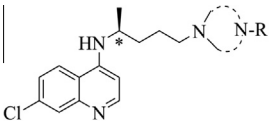
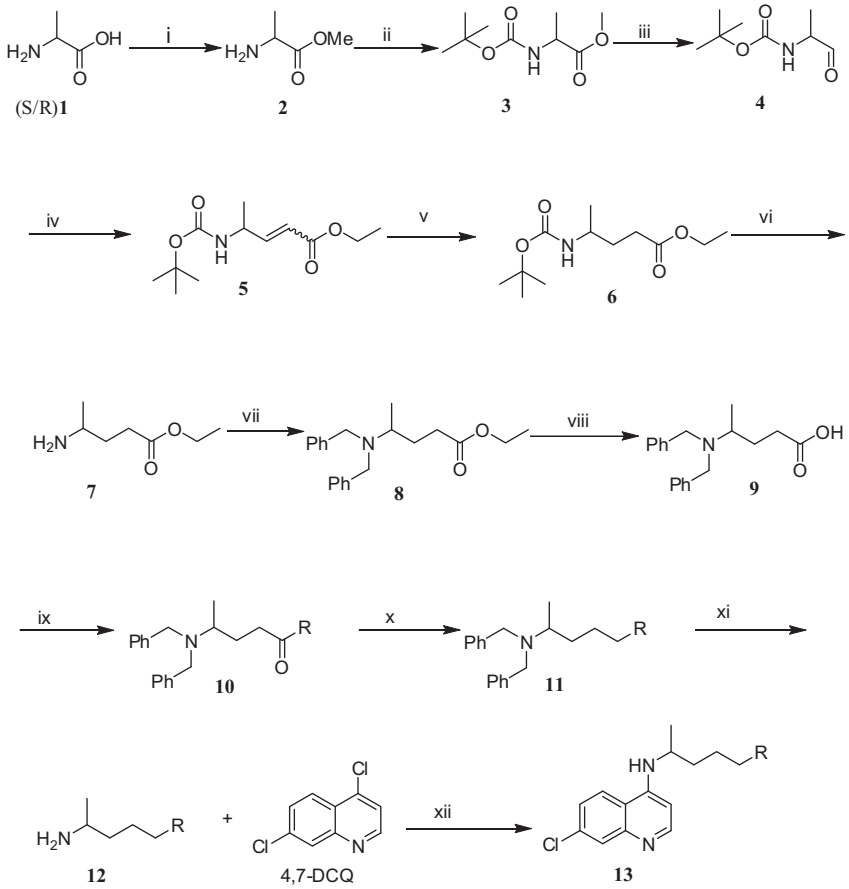


Figure 2. The general structure of the synthesized compounds (R= diethylamine, morpholine, pyrrolidine, methylpiperazine, piperidine, dimethylamine, *tert*-butylamine, ethyl methylamine, dioctylamine).



R = a. Diethylamine; b. Morpholine; c. Pyrrolidine; d. methyl piperazine; e. Piperidine; f. Dimethylamine; g. t-Butylamine; h. Ethyl methylamine; i. Dioctylamine.

Scheme 1. Synthesis of compounds (*S*-**13a–i** and *R*-**14a–i**). Reagents and conditions: (i) thionyl chloride, methanol, 0 °C, 3 h; (ii) $(Boc)_2O$, triethyl amine, DCM, 0 °C, 2 h; (iii) DIBAL-H, Dry THF, −78 °C, 3 h; (iv) $Ph_3PCHCOOEt$, dry DCM, 0 °C to rt, 4 h; (v) Pd/C, methanol, H_2, 30 psi, rt, 2 h; (vi) 15% HCl/dioxane; (vii) BnBr, K_2CO_3, acetonitrile, reflux, 4 h; (viii) LiOH, THF/water, 0 °C to rt; (ix) NMM, IBCF, amines a–i, −10 °C, 3 h; (x) LAH, dry THF, reflux, 4 h; (xi) Pd/C, methanol, H_2, 60 psi, rt, 5 h; (xii) phenol, 140 °C, 12 h.

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