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Antiplasmodial activity of new 4-aminoquinoline derivatives against chloroquine resistant strain

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ABSTRACT

Emergence and spread of multidrug resistant strains of *Plasmodium falciparum* has severely limited the antimalarial chemotherapeutic options. In order to overcome the obstacle, a set of new side-chain modified 4-aminoquinolines were synthesized and screened against chloroquine-sensitive (3D7) and chloroquine-resistant (K1) strains of *P. falciparum*. The key feature of the designed molecules is the use of methylpiperazine linked α, β^3- and γ-amino acids to generate novel side chain modified 4-aminoquinoline analogues. Among the evaluated compounds, **20c** and **30** were found more potent than CQ against K1 and displayed a four-fold and a three-fold higher activity respectively, with a good selectivity index (SI = 5846 and 11,350). All synthesized compounds had resistance index between 1.06 and >14.13 as against 47.2 for chloroquine. Biophysical studies suggested that this series of compounds act on heme polymerization target.

1. Introduction

Malaria is a tropical disease caused by Apicomplexan parasite *Plasmodium falciparum* severely affecting human well being. It is estimated that about 1 million deaths occur annually, mostly children under five years of age.[1,2] High morbidity is associated with the failure of the established chemotherapies due to emergence of drug resistant *P. falciparum* against most of the antimalarial drugs.[3] Although, chloroquine (CQ) and other related 4-aminoquinolines (Fig. 1) have played important role during the past five decades drug resistance to CQ has been a major problem in malaria eradication programme. So, the search for novel, affordable, and structurally diverse drugs has become an urgent need to eradicate this parasitic disease. Early biochemical studies carried out to understand the mechanism of CQ resistance have led to two seminal findings namely, a mutation in the *P. falciparum* CQ-resistance transporter (PfCRT) gene resulting in rapid efflux of CQ from the intracellular loci. Secondly and more importantly study by Ridley et al.[4] has established that drug resistance is compound specific. This has fueled research activity towards modifying CQ side chain so as to obtain molecules active against CQ-resistant parasite.

Several modifications have been done in the side chain of chloroquine and studied in detail. It has been found that shortening of the chain length or incorporation of intramolecular hydrogen-bonding motif in the side chain significantly increases the antimalarial activity.[4–6] While replacement of 4-position nitrogen atom of the 7-chloro-4-aminoquinoline by oxygen and sulfur significantly decreases the basicity of the quinonyl nitrogen which leads to reduced antimalarial activity.[7] Earlier in our research group we have also explored some specific modifications by introducing, guanidine, tetramethylguandine, and thiazolidin-4-one and substituted thiourea moieties at the side chain. Some of these compounds exhibited superior in vitro activity and significant suppression of parasitemia in the in vivo assay as compared to chloroquine. Based on the limited SAR-studies it was inferred that basicity of the quinoline ring nitrogen (pKa1) and side chain nitrogen (pKa2) played an important role for the antimalarial activity.[8] Inspired by these observations, in this study we have synthesized a set of compounds with specific modifications to CQ that are predicated to be relevant for activity against chloroquine resistant parasites. The diversity in the synthesized compounds has been generated through variations in the side chain of CQ. Initially we have selected alanine and synthesized various amides (Scheme 1). Compound having *N*-methylpiperzine as a pendant group showed improved activity against CQ-R strain. We further preferred variety of α-amino acids by keeping the pendant group with

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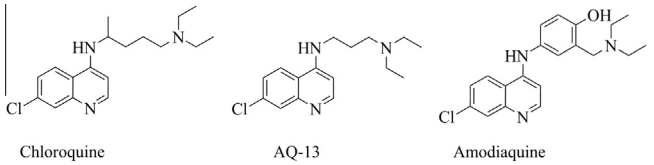
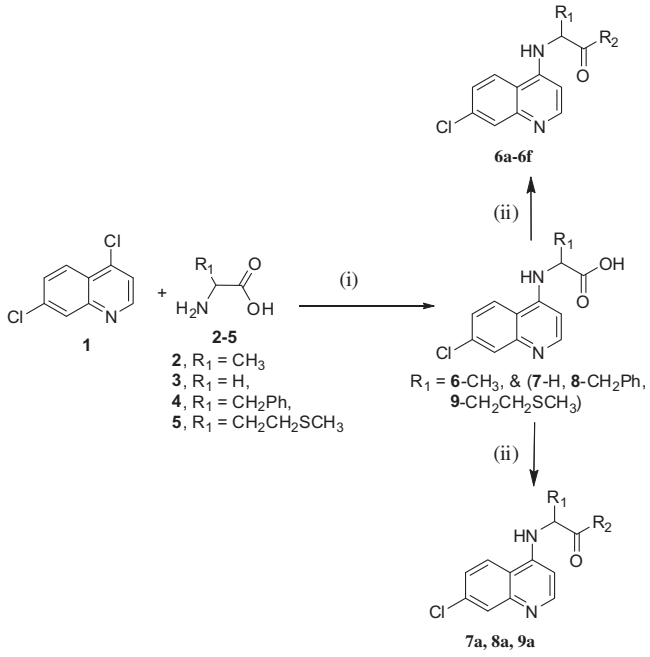


Figure 1. Structures of CQ and related 4-aminoquinolines having antimalarial activity.

N-methylpiperzine. We have found that some of them exhibited promising antimalarial activity than CQ in the case of CQ-R strain. Additionally we have also investigated the effect of chain length variation between 2 and 4 carbon atoms via homologation of α-amino acids to get corresponding β^3 and γ-amino acids. The results are described in the present communication.

2. Chemistry

4,7-Dichloroquinoline (**1**), was fused with an excess of alanine (**2**) in the presence of phenol at 140 °C to afford the compound (**6**).[9] The obtained Compound (**6**) was coupled with different amines using DCC, HOBt protocol taking DMF as solvent at 0 °C to afford (**6a–6f**).[10] A similar approach was utilized for some selected α-amino acids viz. glycine (**3**), phenylalanine (**4**), methionine (**5**) directly fused to 4,7-Dichloroquinoline to get **7–9** in good yields followed by coupling with *N*-methylpiperzine to afford **7a**, **8a**, and **9a** as shown in Scheme 1. We have observed poor yields in the case of remaining α-amino acids. Therefore, in order to get the desired final products **14a–14j** we have opted for different synthetic strategy. The route is delineated in Scheme 2. Synthesis of compounds **20a–20c** involve prior preparation of β-amino acids followed by their conversion to piperazine amides and after deprotection they were finally fused with 4,7-Dichloroquinoline as



Compound No	R_1	R_2
(6a)	CH_3	N-Methylpiperzine
(6b)	CH_3	N^1,N^1-diethylpropane-1,3-diamine
(6c)	CH_3	1-phenylpiperazine
(6d)	CH_3	N^1,N^1-dimethylpropane-1,3-diamine
(6e)	CH_3	2-(piperidin-1-yl) ethanamine
(6f)	CH_3	N^1,N^1-diethylethane-1,2-diamine
(7a)	H	N-Methylpiperzine
(8a)	CH_2Ph	N-Methylpiperzine
(9a)	$CH_2CH_2SCH_3$	N-Methylpiperzine

Scheme 1. Synthesis of compounds (**6a–6f**, **7a**, **8a**, & **9a**); Reagents and conditions: (i) Phenol, 140 °C; (ii) Amines, (a) *N*-methylpiperazine; (b) N^1,N^1-diethylpropane-1,3-diamine; (c) 1-phenylpiperazine; (d) N^1,N^1-dimethylpropane-1,3-diamine; (e) 2-(piperidin-1-yl) ethanamine; (f) N^1,N^1-diethylethane-1,2-diamine, DCC; HOBt, DMF, 0 °C.