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Design, synthesis and antiplasmodial activity of novel imidazole derivatives based on 7-chloro-4-aminoquinoline

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ABSTRACT

A series of short chain 4-aminoquinoline-imidazole derivatives have been synthesized in one pot two step multicomponent reaction using van leusen standard protocol. The diethylamine function of chloroquine is replaced by substituted imidazole derivatives containing tertiary terminal nitrogen. All the synthesized compounds were screened against the chloroquine sensitive (3D7) and chloroquine resistant (K1) strains of *Plasmodium falciparum*. Some of the compounds (**6**, **8**, **9** and **17**) in the series exhibited comparable activity to CQ against K1 strain of *P. falciparum*. All the compounds displayed resistance factor between 0.09 and 4.57 as against 51 for CQ. Further, these analogues were found to form a strong complex with hematin and inhibit the β-hematin formation, therefore these compounds act *via* heme polymerization target.

1. Introduction

Malaria still remains a serious health problem to human beings around the world, mostly sub-Saharan African countries are at much higher risk [1]. As per WHO report 3.2 billion people remain at risk of malaria. In 2015 alone, there were an estimated 212 million new cases of malaria and 429,000 deaths. Most among them are children younger than 5 years [2]. Among the protozoan parasites (*P. falciparum*, *vivax*, *ovale, malariae* and *knowlesi*) of the genus *Plasmodium, P. falciparum* is the most prevalent and virulent in human, and contributes maximum number of deaths compared to other *Plasmodium* species [3]. Over the last 60 years the use of quinine has declined owing to the development of synthetic 4-aminoquinolines such as chloroquine (CQ) (Fig. 1). Among several quinoline based antimalarials, CQ is the most effective and widely used drug in malaria chemotherapy because of its rapid onset of action, good tolerability and low cost [4]. However, emergence and wide-spread of drug resistance to CQ and many other drugs, including primaquine, pyrimethamine and mefloquine (Fig. 1) has increased the burden of mortality rate quite abnormally in the last few years [5]. So, there is an urgent need of new chemical entities active against drug resistant parasites. However, despite emergence of drug resistance CQ scaffold still could be a good choice for further chemical modifications, owing to its excellent efficacy, limited host toxicity and affordability [6]. Subsequently, literature survey on 4-aminoquinolines clearly suggested that antimalarial activity, particularly inhibition of β-hematin formation and accumulation of the drug at the target site, resides in 4-aminoquinoline core [7]. Accordingly, a number of new 4-aminoquinoline analogues with enhanced activity against CQ-R strain have been developed by conducting synthetic modification of the CQ side chain [8,9]. However, in recent years various strategies have been employed to circumvent the drug resistant. The 4-aminoquinoline hybridization is one quite attractive strategy which has been recently introduced in the medicinal chemistry and drug discovery process [10,11]. Moreover, chemotherapeutic agents derived from Schiff's base have occupied a unique place in the field of medicinal chemistry [12]. Further, incorporation of bioactive functionalities in the side chain of 4-aminoquinoline emerged as promising strategies to construct the molecules with enhanced activity against drug-resistant *P. falciparum* and also with improved metabolic stability [13]. Recently, Campiani *et al.* synthesized Clotrimazole (CLT) analogues [14] and subsequently prepared hybrid of the 4-aminoquinoline with the clotrimazole-like pharmacophore [15] in which imidazole ring of CLT behaves as a Fe(III) axial ligand and inhibit β-hematin formation and reported promising *in vitro* (against both sensitive and resistant strain) and *in vivo* antimalarial activities. On the other hand, various imidazole-based compounds have shown good coordination properties and are able to form stable

Abbreviations: CQ, chloroquine; DMF, dimethylformamide; TOSMIC, Toluenesulfonylmethyl isocyanide

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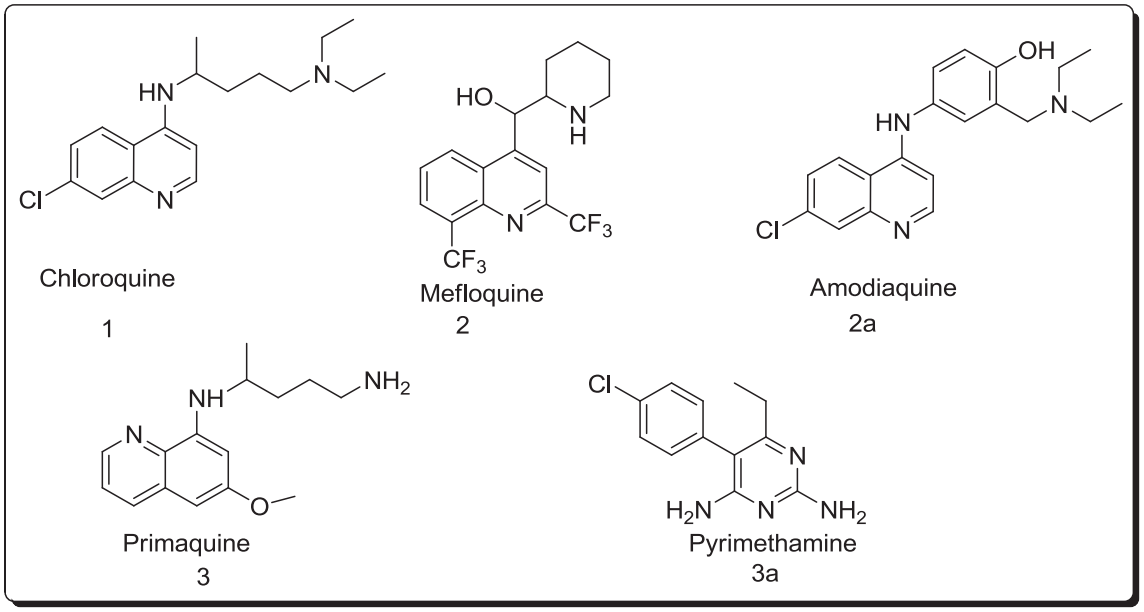

Fig. 1. Structures of some molecules having antimalarial activity.

complexes with several metal ions inhibitors [13].

Previously from our laboratory we introduced biologically privileged thiazolidine-4-one ring system in the side chain in order to enhance the lipophilicity (Fig. 2a). These analogues showed remarkable activity against CQ-sensitive strain (NF-54) of *P. falciparum in vitro* and CQ-resistant strain (N-67) of *P. yoelii in vivo* [16]. Later, we reported the synthesis of chiral chloroquine and its analogues by incorporating different acyclic/cyclic amines in the side chain of CQ (Fig. 2a). These chiral chloroquine analouges exhibited superior activity against both *in vitro* (3D7 & K1 strains) and *in vivo* (N-67 strain) studies [17]. Encouraged by these results, we envisaged that incorporation of biological privileged motif such as imidazole (with ability to coordinate with the heme) in the side chain of 4-aminoquinoline pharmacophore would lead to develop the new antimalarial agents active against CQ-R strain of *P. falciparum*. Based on the above fact and in the continuation of our ongoing antimalarial programme, herein we report the one-pot two step

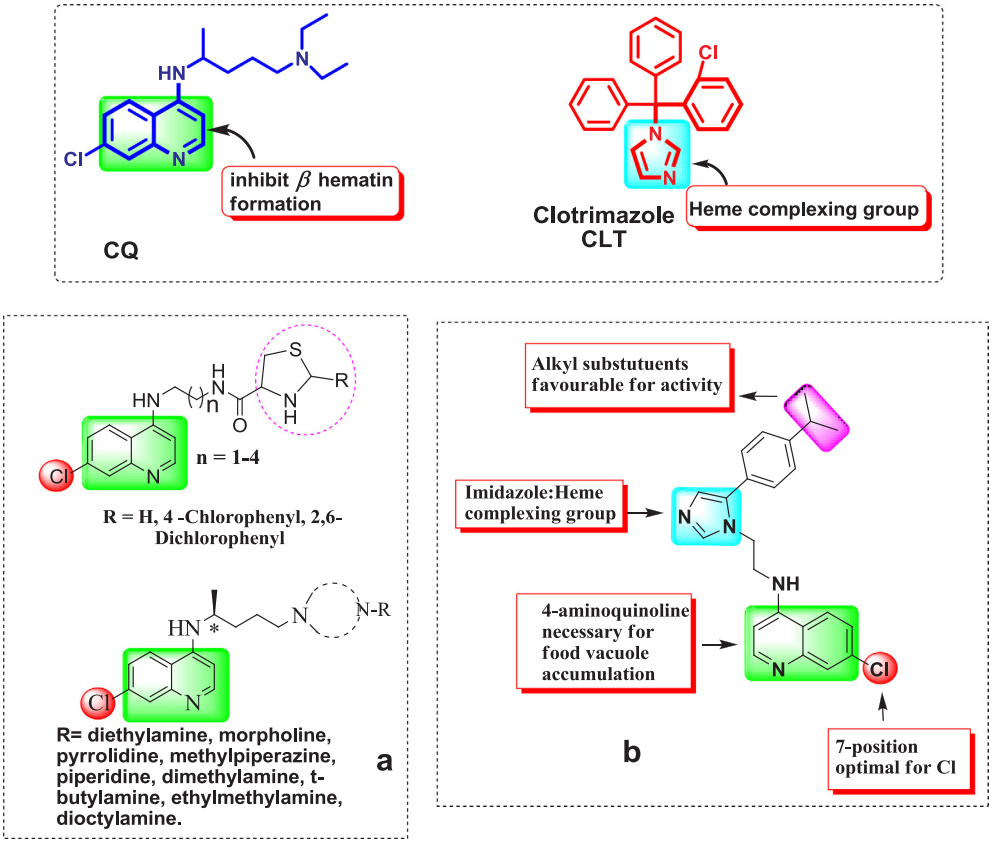

Fig. 2. (a) Previously reported 4-aminoquinolines from this laboratory. (b) Designed 4-aminoquinoline imidazole Prototype.