Novel 4-aminoquinoline analogues as antimalarial agents: A review

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ABSTRACT

Malaria remains the world’s most devastating human parasitic infection, afflicting 500 million people and causing from 1.7-2.5 million deaths each year globally. 4-aminoquinoline drugs are highly effective and rapidly acting agents against asexual erythrocytic stages of malaria parasites mainly P. vivax and P. falciparum responsible for life threatening clinical manifestations and severity of the disease. However, development of resistance of malaria parasites, especially P. falciparum towards CQ (the most potent and less toxic 4-aminoquinoline drug) has limited its use in the treatment of malaria. The present review article depicted the antimalarial activity of novel series of 4-aminoquinoline structural analogues against different CQ-sensitive as well as CQ-resistant strains of Plasmodium species especially P. falciparum.

Keywords: Malaria, CQ-resistant P. falciparum, 4-Aminoquinolone analogs.

INTRODUCTION

Malaria remains the world’s most devastating human parasitic infection, afflicting 500 million people and causing from 1.7-2.5 million deaths each year globally [1]. Human malaria is caused by protozoan parasites of the genus Plasmodium, P. falciparum, P. vivax, P. malariae, and P. ovale are four well known species of human malaria parasite [2], [3] and more recently another species, P. knowlesi has been documented [4]. Infection with P. falciparum causes the most severe and potentially fatal form of malaria, which preferentially affects children less than 5 years age, pregnant woman, and non immune individuals. Since 1960, transmission of malaria has risen in most regions of the world where malaria is endemic; chloroquine (CQ) -resistant and multi-drug resistant strains of P. falciparum have spread and the degree of drug resistance has increased. Nearly all antimalarial drugs were developed because of their action against asexual erythrocytic forms of malaria parasites that cause clinical illness. 4-aminoquinoline drugs are
highly effective and rapidly acting agents against asexual erythrocytic stages of malaria parasites (mainly *P. vivax* and *P. falciparum*). The most effective drug among hundreds of synthesized 4-aminoquinolines is CQ. It is still potent drug in malaria chemotherapy in most regions of the world where malaria is endemic and where sensitivity to the drug remains [5]. However, because of emergence and spread of resistance of malaria parasites, especially *P. falciparum* towards CQ has severely limited its use in the treatment of malaria. Most recently, CQ-resistant strains of *P. vivax* has been documented. Amodiaquine (AQ) and hydroxychloroquine were found to be effective as alternative drugs to CQ-resistant *P. falciparum* strain but these are less effective as compared to CQ; and AQ is more toxic too [6]. Research on the structure activity relationship studies on CQ and related 4-aminoquinoline drugs continues in an effort to develop new, effective antimalarial agents with improved activity profile against parasites that can be used successfully against CQ- and multi-drug resistant strains of *P. falciparum*.

4-aminoquinoline based antimalarials

Solomon & coauthors [7] reported the synthesis of a new series of side-chain modified 4-aminoquinolines (1) and found active against *P. falciparum* in vitro and *P. yoelii* in vivo. These analogs form a complex with hematin and inhibit the β-hematin formation, suggesting that this class of compounds act on a heme polymerization target.

Madrid and coworkers [8] synthesized a library of ring-substituted 4-aminoquinoline compounds (2) and evaluated their antimalarial activity against chloroquine (CQ) -sensitive strain, 3D7 and -resistant strain, W2 of *Plasmodium falciparum*. Substituted quinoline rings other than the 7-chloroquinoline ring of chloroquine were found to have significant activity against the drug-resistant strain of *P. falciparum*.

Solomon and coworkers [9] synthesized a new series of 4-aminoquinoline derivatives (3) and evaluated their activity against a CQ-sensitive strain, NF-54 in *in vitro* and CQ-resistant N-67 strain of *Plasmodium yoelii* *in vivo*. All the analogs form a complex with hematin and inhibit the β-hematin formation, suggesting that this class of compounds act on a heme polymerization target.
Ridley and coauthors [10] reported the synthesis of a new series of 4-aminoquinoline analogs (4) with shortened side chain which retained activity against CQ-resistant strain of *Plasmodium falciparum*. The reported compounds differed from CQ only in the nature of side chain attached to the 4-aminoquinoline moiety.

![Image of compound 4](image)

Madrid and coworkers [11] reported the development of an efficient method for producing libraries of 4-aminoquinolines variant in the side chain portion of the molecule (5). The effects of these substitutions were evaluated by screening this library for activity against *P. falciparum*.

![Image of compound 5](image)

Sparatore & coauthors [12] synthesized a new series of quinolizidinyl and quinolizidinylalkyl derivatives of 7-chloro-4-aminoquinoline (6). Among all the synthesized compounds some of the quinolizidine derivatives were 5 to 10 times more active than chloroquine on the chloroquine-resistant strain.

![Image of compound 6](image)

Freitag and his group [13] synthesized a novel series of N-[3-(4{3-[97-chloroquinolin-4-yl]amino}propyl)]piperazine-1-yl]propyl]carboxamides (7) by the parallel acylation with polymer-bound carboxylic acids opened straightforward method and evaluated their activity against a CQ-sensitive strain and a CQ-resistant mutant. Most of the novel structures exhibited activity against both strains in the lower nanomolar range, four novel compounds showed at least four fold increase in the ratio of inhibition of CQ-resistant to sensitive strains over CQ itself.

Ryckebusch and coauthors [14] reported the design and synthesis of new series of N1-(7 chloro-4-quinolyl)-1, 4-bis (3-aminopropyl) piperazine derivatives (8) and evaluated their antimalarial activity against a chloroquine-resistant strain of *Plasmodium falciparum*. All the compounds were also tested for cytotoxicity upon a human diploid embryonic lung cell line (MRC-5 cells) using...
the colorimetric MTT assay. Most of the synthesized compounds were reported with high activities and reduced cytotoxicities.

Musonda and coauthors [15] synthesized a novel series of first generation 4-aminoquinoline containing 2,4,5-trisubstituted aminoxazoles (9) and evaluated their in vitro antimalarial activity against two strains of the *Plasmodium falciparum*. They reported that a number of compounds significantly more potent than the standard drug chloroquine.

De and coworkers [16] studied structure-activity relationships (SARs) for antiplasmodial activity among 7-substituted-4-aminoquinolines (10). They found that 7-iodo- and 7-bromo-aminoquinolines with diaminoalkane side chains [-HN(CH₂)₂NEt₂, -HN(CH₂)₃NEt₂, or –HNCHMeCH₂NEt₂] were as active as the corresponding 7-chloro-4-aminoquinolines against both chloroquine-susceptible and –resistant *Plasmodium falciparum* (IC₅₀s of 3-12nM).

Delarue and coauthors [17] reported a new series of 4-anilinoquinolines (11) with two proton-accepting side chains and many of them were found to be active against both chloroquine-sensitive and resistant strains of *P. falciparum* strains in vitro.
A set of novel 4-aminoquinoline Mannich base derivatives (12) was reported by Raynes & coauthors [18] with their antimalarial activity. Seven alkyl Mannich base derivatives were screened and were found to be active against both chloroquine-susceptible (HB-3) and chloroquine-resistant (K1) strains of *Plasmodium falciparum in vitro*.

A novel series of isoquine and related amodiaquine analogues (13) were reported by O’Neill and coauthors [19]. These analogues were obtained by interchanging the 3’ hydroxyl and the 4’ Mannich side-chain function of amodiaquine. Several analogues displayed potent antimalarial activity against both CQ–sensitive and -resistant strains of *P. falciparum in vitro*.

Delarue-Cochin and coauthors [20] reported a new series of amodiaquine (AQ) analogues as antimalarial agents (14). Among the compounds synthesized, new amino derivatives of AQ displayed a notable *in vitro* and *in vivo* antimalarial activity and best selectivity index towards the most CQ-resistant strain K1.
O’Neill and coworkers [21] reported some novel tebuquine analogues (15) with their antimalarial activity. These novel tebuquine analogues were designed by replacing the 4-hydroxyl function of tebuquine with either fluorine or hydrogen and with tert-butyl or diethylamino substitution in the side chain.

The Effect of substitution of fluorine atom on the antimalarial activity of tebuquine (16) was studied by O’Neill and coauthors [22]. A novel synthetic route was developed for the synthesis of fluorotebuquine which was active against the CQ-resistant K1 strain of Plasmodium falciparum. O’Neill and coauthors [23] reported that fluorinated analogs (17) showed similar in vitro antimalarial activity to amodiaquine against the chloroquine-resistant K1 and CQ-sensitive T9-96 strain of Plasmodium falciparum.

Miroshnikova and coworkers [24] reported a new series of isotebuquine analogues and their N’-oxides with a hydroxy group in meta rather than in para position to the amino group of the aniline moiety (18). The new derivatives exhibited promising in vitro antimalarial activity against both CQ-sensitive (D6) and CQ-resistant (W2) strain of P. falciparum. with IC_{50} in the range of 0.3-120 ng/mL.
Kesten and coauthors [25] reported synthesis and antimalarial effects of 4-[(7-chloro-4-quinolinyl)-amino]-2-[(diethylamino)-methyl]-6-alkylphenols and their N’-oxides (19).

Werbel and coauthors (26) studied a quantitative structure-activity relationships of tebuquine and synthesized a series of related 5-[(7-chloro-4-quinolinyl)-amino]-3-[(alkylamino)-methyl]-1, 1”-biphenyl]-2-ols and Nω-oxides (20) and reported their antimalarial efficacy.

CONCLUSION

The present review article summarizes the in vitro and in vivo antimalarial screening of novel series of 4-aminoquinoline structural analogues against different CQ-sensitive as well as CQ-resistant strains of \textit{Plasmodium} species especially \textit{P. falciparum}. The structure-activity relationship studies on new 4-aminoquinoline antimalarial compounds suggest that the 7-chloro-4-aminoquinoline nucleus is obligatory for antimalarial activity, particularly, inhibition of \(\beta\)-hematin formation and accumulation of the drug at the target site. Thus, further research on above mentioned novel derivatives of chloroquine, amodiaquine and tebuquine can be continued for the development of new and effective antimalarial against which may fight against CQ-resistant and multi-drug resistant strains of \textit{P. falciparum}.

REFERENCES