4-aminoquinolines: An Overview of Antimalarial Chemotherapy

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Abstract

Malaria is a major health problem and Plasmodium falciparum strain resistance to existing antimalarials drugs made the current approach inadequate for treatment of malaria. Drug development directed against malaria is generally targeting blood schizonts. However, to prevent relapse, tissue schizontocides are recommended to clean residual infection in the tissues. In spite of the available drugs, malarial chemotherapy is still insufficient and therefore new strategies are being explored to fill the gaps. The new approaches are being used to generate new compounds as well as combinations of drugs for development of effective and safe antimalarial therapy. This review discusses the recent developments in 4-aminoquinoline derived new analogs and insight into design and development of new antimalarials.

Keywords: Antimalarial; 4-aminoquinoline; Quinine; Chloroquine; Drug resistance

Introduction

Malaria remains as one of the most devastating diseases of the developing world concentrated mainly in tropical regions. Despite the huge advances in our understanding of the disease, it continues to be one of the greatest causes of serious illness and death in the world. Approximately 156 species of plasmodium infect various vertebrates, but only four; P. falciparum, P. malariae, P. vivax and P. ovale are known to infect humans. Among these, P. falciparum is the cause of most severe and life threatening malaria in human beings. Endemic maps indicate that P. falciparum and P. vivax account for 95% of malarial infections [1-4]. P. falciparum is found throughout tropical Africa, Asia and Latin America while P. vivax is found worldwide in tropical and some temperate zones [5,6]. P. falciparum is remarkable for its high case of fatality rate causing 2-3 million deaths worldwide, particularly children, and a further 300-500 million cases occur each year [7]. Malaria is transmitted by the bite of an infected anopheles mosquito and is characterized by periodic chills, high fever, nausea, and vomiting. The role played by the host immune system in resistance and healing of the disease is well established, however the strategies involving the development of vaccine against malaria is inadequate [8]. Currently chemotherapy of malaria depends on several drugs, yet proper treatment is not in sight. Even though the available drugs have the ability to cure malaria infection and control the spread. There are several limitations which includes left over infection leading to relapse, toxicity to the host and development of resistance.

Resistance of plasmodia to antimalarial drugs is now recognized as one of the major problems in the treatment of malaria. This rapidly increasing resistance of P. falciparum malaria parasites to most commonly used drugs such as quinine, chloroquine (CQ), proguanil and pyrimethamine has made the chemotherapy ineffective. Moreover, new and more expensive chemotherapeutic agents, such as mefloquine and halofantrine are also showing resistance. Alternative strategies to control malaria infection include vector control and development of vaccines, remain inadequate [8]. Therefore, to meet the new challenges development of novel molecules with better therapeutic potential and safety is a very high priority task. So far, malaria control has relied largely on a small number of chemically related drugs, belonging to three classes of compounds: Quinoline and its related analogs (quinine, CQ, amodiaquine, primaquine, mefloquine, and halofantrine), the artemisinin and its derivatives (artemisinin, artesunate, arteether, dihydroartemisinin), the antifolate compounds (pyrimethamine, proguanil, chlorcyclizoguanil, dapsone, and sulfadoxine), and most recently, the hydroxynaphthoquinone atovaquone (Figure 1) [9,10].

Challenges in Drug Development

The success of malaria chemotherapy depends on thorough understanding of the interaction among the three major components, namely human host, antimalarial drugs and malaria parasite (Figure 2). The challenge in antimalarial drug development arises in consideration of malaria life cycle. This contains two hosts (Human host and Mosquitoes) and five main stages in life cycle. Once the human host is
infected, malaria parasite induces 'pathological condition'. It is a disease caused by multiplication of parasites in repeated cycles of growth of the parasite Plasmodium in the erythrocyte. Immune response induces the protective mechanism in the host is in response to parasitic invasion. Malaria symptoms can develop as soon as 6–8 days after being bitten by an infected Anopheles mosquito, or as late as several months after departure from a malaria endemic area. The effectiveness of an antimalarial drug depends, principally on the interactions between antimalarial drug and malaria parasite, i.e., 'selective toxicity' and 'drug resistance', and between antimalarial drug and host, the compatibility i.e., 'pharmacokinetics' and 'pharmacodynamics'. The ideal antimalarials are drugs which are selective and show curative activity without or minimal toxicity to the host [11,12]. The development of new antimalarials requires prior knowledge of life cycle of the parasite and drug action of existing chemotherapy.

**Malaria Life Cycle**

The life cycle of plasmodia has five stages that include both sexual and asexual mode of reproduction in two hosts, namely a mosquito and a human (Figure 3). During a blood meal, a malaria-infected female Anopheles mosquito injects sporozoites into the human host. These sporozoites then migrate to the liver where they transform,
multiply, and mature into tissue schizonts, which eventually rupture, releasing merozoites into the blood stream. To avoid the host’s immune system, they invade erythrocytes. After the initial replication in the liver, the parasites undergo asexual multiplication in the erythrocytes (erythrocytic stage). In every cycle, schizonts get ruptured with erythrocytes and releases new merozoites into the blood stream, which in turn again invade the new erythrocytes. Before this stage the infected individual may not have any symptoms, once RBCs get ruptured, the host immune system get exposed to parasite factors in turn stimulates to release cytokines and results in the symptoms like fever and chills.

In case of *P. vivax* and *P. ovale*, a dormant, hypnozoite stage remains in the liver and causes relapses by invading the bloodstream, weeks to years later. After a number of asexual life cycles, Some merozoites develop into sexual erythrocytic forms (gametocytes). When an Anopheles mosquito ingests male and female gametocytes during a blood meal from an infected host, fertilization takes place in the gut of the mosquito forming zygotes. The zygotes become elongated and invade the gut wall of the mosquito developing into oocysts. These oocysts grow, rupture, and release sporozoites. These invade the mosquito’s salivary gland, and the mosquito is then ready to transmit the disease during the next blood meal [13-15].

Antimalarial agents are classified by the stages of the malaria life cycle that are targeted by the drug. Blood schizonticides acting on the asexual intraerythrocytic stages of the parasites. Tissue schizonticides kill hepatic schizonts, and thus prevent the invasion of erythrocytes, acting in a causally prophylactic manner. Hypnozoitocides kill persistent intrahepatic stages of *P. vivax* and *P. ovale*, thus preventing relapses from these dormant stages. Gametocytocides destroy intraerythrocytic sexual forms of the parasites and prevent transmission from human to mosquito. As there are no dormant liver stages in *P. vivax* and *P. ovale*, a combination of blood schizonticides and tissue schizonticides is required [5,6].

**Chemotherapeutic Approaches**

Drug development directed against malaria is generally targeting blood schizonts. However, to prevent relapse tissue schizontocides are recommended to clean residual infection in the tissues. In spite of the available drugs, malarial chemotheraphy is still inadequate and therefore new strategies are being explored to fill the gaps. The new approaches are being used to generate new compounds as well as combinations of drugs for development of effective and safe antimalarial therapy. This review discusses the recent developments in new analogs of existing drugs, especially 4-aminoquinolines derived antimalarials.

**Combination therapy**

Owing to rapid spreading of disease as well as emergence of resistance new strategies are being explored. Among various such approaches combination therapy offers several advantages. The combination therapy has also been recommended by World Health Organization (WHO) for the effective treatment of malaria. As information on pharmacokinetics of antimalarials have become increasingly available, it is appropriate to reexamine current recommendations for effective treatment and prophylaxis. In addition, antimalarial formulations and dosage forms can be improved [16]. This approach is to optimize therapy with existing agents. New dosing regimens or formulations may optimize activity. Combination therapies, including newer agents (e.g., artemisinin derivatives, atovaquone) and new combinations of older agents (e.g., amodiaquine/sulfadoxine/pyrimethamine, chlorproguanil/dapsone), are under study as first-line therapies for Africa and other tropical areas with widespread drug resistance [17,18]. The use of combination antimalarial therapy offers two important potential advantages. First, the combination improves the antimalarial efficacy with additive or, preferably, synergistic effect. In the case of both the artemisinin derivatives and atovaquone, the new agents have had unacceptable failure rates when used as single agents to treat falciparum malaria but they have been highly effective in combination with other established antimalarials. Second, and probably most important in the use of combination therapy is slow down the progression of parasite resistance to the new agents. This latter factor is a key consideration as we attempt to develop new therapies that will retain activity for a long period. Ideally, a combination regimen that prevents resistance development should include at least two agents against which parasite resistance has not yet developed and which have similar pharmacokinetics, so that low blood levels of a single agent will not be present. No such ideal regimen is currently available, although chlorproguanil/dapsone/artsunate may prove to fit this description. Alternatively, the combination of a short-acting, highly potent compound and a longer-acting agent may prove effective, if the initial decrease in parasite burden is so great as to limit subsequent resistance development to the long-acting agent (e.g., artesunate/mefloquine) [19].

**New analogs of existing drugs**

Improving upon the antimalarial chemotherapy profile of existing compounds by chemical modifications has been a rewarding approach. This approach does not require development of knowledge of the mechanism of action or the therapeutic target of the agents that used for combination therapy. Indeed, this approach was responsible for optimizing the activity and selectivity of existing antimalarials even against resistant strains. For example, CQ, primaquine and mefloquine were discovered through chemical strategies to improve upon quinine [20]. More recently, 4-aminoquinoline derivatives that are closely related to CQ appear to offer the great potency even against CQ-resistant strains of parasites [21,22]. A related compound, pyronaridine (Figure 4), was developed in China and is now undergoing extensive clinical trials in other areas [23]. An 8-aminoquinoline derivative, tafenoquine (Figure 4), offers improved activity against hepatic-stage parasites over that of the parent compound, primaquine [24], and is effective for antimalarial chemoprophylaxis [25]. Since halofantrine use is limited by toxicity, the analog lumezantrine was developed and now a component of the new combination co-artemether (artemether/lumezantrine) [26]. New folate antagonists [27] and new endoperoxides related to artemisinin [28,29] are also under study.

**Development of Aminoquinolines Derived Antimalarials**

4-Aminoquinolines derivatives were the first class of compounds used for the successful treatment of malaria and drugs of choice for the present time also. In the 18th century, the first attempt of successful treatment of malaria was made with use of the bark of cinchona trees [30]. Gomes et al. in 1810 extracted the cinchona bark but after a decade, active ingredient of quinine (Figure 5) was isolated and made Malaria as first disease for which a pure compound was used for the treatment [31]. The structure elucidation and different synthetic routes have come up in near 19th century. In 1856, chemist William Henry Perkins set out to synthesize quinine. His efforts resulted not in quinine (the first total synthesis was accomplished later in 1944), but rather in the first synthetic textile dye called “mauve”. Paul Ehrlich noticed that methylene blue (1) was particularly effective in staining malaria parasites (Figure 5). He rationalized that this dye might also be selectively toxic to the parasite [30]. In 1891, Ehrlich and Guttmann cured two malaria patients with methylene blue (1), which became the first synthetic drug ever used in therapy. Although it was not used further at that time, methylene blue...
constituted the basis for the development of synthetic antimalarials. In the 1920s, chemists at Bayer in Germany started to modify the structure of methylene blue (1). A key modification was the replacement of one methyl by a dialkylaminoalkyl side chain to give compound 2.

Subsequently, this side chain was connected with different heterocyclic systems such as the quinoline system, yielding the first synthetic antimalarial drug, plasmochin (3, also known as plasmoquine or pamaquine) in the year 1925. However, under clinical evaluation, this drug displayed multiple side effects, and was therefore not widely used. The congeneric primaquine (4), introduced in 1952, was better tolerated, making it the main representative of the class of 8-aminoquinoline derived anti-malarials. Connection of the diethylaminoisopentylamino side chain with an acidine heterocycle yielded mepacrine (5, also known as quinacrine), which was introduced in 1932 for prophylaxis and treatment of malaria [30-33].

A major success with the drug-design strategy was achieved in 1934 with the introduction of a diethylaminisopentlamino side chain into position 4 of a 7-chloroquinoline, yielding a compound named resochin by the German inventors (later known as chloroquine (6). However, after initial trials, resochin was regarded as too toxic for use in humans and ignored for a decade. In 1936, the structurally closely related sontoquin (7, later known as nivaquine) was prepared in the Bayer laboratories and tested in Germany. Resochin (CQ) was re-evaluated in 1943 and was found safe for human subjects. After the World War II, CQ became the foundation of malaria therapy for at least four decades [30-33] and most successful drug in clinical use till date [34-36].

Mode of action of 4-aminoquinoline derivatives

Mode of action of 4-aminoquinoline classes of compounds is still a matter of debate despite the overwhelming importance. Various theories have been proposed and reviewed [1,37-39]. The consensus points out that CQ interacts with the parasite’s ability to digest haemoglobin. During its erythrocytic stages, the parasite consumes large quantities of haemoglobin from its host cell, either for the purpose of amino acid supply, or simply to create space inside the erythrocyte. Haemoglobin is shuttled to vesicles to a specialized organelle called digestive vacuole (DV). A number of facts relating to the drugs action are now widely accepted. Based on these facts several hypotheses have been raised.

Early biochemical studies demonstrated that CQ was able to inhibit DNA and RNA synthesis [40-42]. However, interaction of CQ with DNA does not explain the antimalarial activity and the selective toxicity of this compound. Some other mechanisms have been proposed, but they would call for higher drug concentrations than what can be achievable in vivo and not generally regarded as convincing options [1]. These include inhibition of protein synthesis; inhibition of digestive vacuole (DV) lipase, and aspartic protease [1,37-39].

A clue to the mechanism of action of CQ came from the observation that it is active only against the erythrocytic stages of malaria parasites. The next phase of research concentrated on the feeding process of the parasites, where CQ could able to inhibit the haemoglobin degradation. Uptake of haemoglobin and its metabolism by a series of proteases in food vacuole of the parasite strengthen the hypothesis [43-45]. Thus, the 4-aminoquinoline derived drugs have been proposed that selectively target the haemoglobin degradation which is a specific to parasites [46]. The free heme, which is toxic to parasite, released from the haemoglobin degradation and a series of proteases involved were drawn more attention of the researchers (Figure 6) [47-49].

The plasmodial enzymes involved in digestion of haemoglobin have attracted much attention as possible targets for antimalarial drug design. When hemereleased from haemoglobin get converted into ferric form, which is highly toxic to vacuolar proteases and damaging to parasite membranes. Interestingly, parasite has a unique non-enzymatic heme detoxification mechanism, in which heme released from parasite digestion is converted to an insoluble polymer, called hemozoin. It is microscopically visible in the DV as malaria pigments [50].
4-Aminoquinoline derived drugs are known to inhibit the hematin formation by complexing with ferriprotochlorophyrin IX (FPIX) thereby prevents its polymerization into hemoglobin, which results into parasite death. Crystallographic information of the structure of the CQ–FP complex is not available. Most NMR and molecular modeling studies [36,51] show a face-to-face π staggering of the porphyrin and quinoline systems, although a structure showing an edge-to-face complex with the ring nitrogen atom sitting above the ring iron center has also been reported [52]. Very recently, structure determination by NMR spectroscopy showed CQ sitting in a central position over the outermost porphyrin rings of a FPIX–CQ 4:2 complex [53]. Most researchers assume that the buildup of noncrystalline FPIX, either in its free form or as a FPIX–CQ complex, finally kills the parasite. The precise mechanism by which this toxic effect is exerted remains to be elucidated [35,54]. According to a recent theory, the FPIX–CQ complex acts on a yet to be undefined membrane target, thereby either impairing the membrane function directly, or triggering the release of Ca²⁺ ions, resulting in the premature fusion of the transport vesicles shuttling haemoglobin to the DV. In these prematurely fused vesicles, haemoglobin is no longer properly degraded [55]. This hypothesis is supported by an independently conducted study that demonstrated the inhibition of macromolecule endocytosis by more than 40% and the accumulation of transport vesicles in the parasite cytosol upon the addition of CQ to late ring-stage parasites.

Since FPIX is a potential target for 4-aminoquinolines and related antimalarials, a number of studies have investigated the nature of FP binding to 4-aminoquinolines. Structure of heme, hemoglobin and their structural similarity with synthetic FPIX have been well documented (Figure 6). An important difference between monomeric heme (including heme aggregates) and hemoglobin is their differential solubility in organic and aprotic solvents and in sodium dodecyl sulphate (SDS) and mildly alkaline bicarbonate solutions. This property may be useful in specific estimation of hemoglobin and β-hematin formation inhibition assay [47-49].

Considerable evidence has accumulated in recent years that antimalarial drugs such as CQ act by forming complexes with FP, the hydroxoo or aqua complex of Ferriprotochlorophyrin IX (Fe(III) FP), derived from parasite proteolysis of host haemoglobin. Studies by Dorn et al. confirmed that CQ forms a complex with the μ-oxo dimeric form of FP with a stoichiometry of 1 CQ : 2 μ-oxo dimmers. They have supported the enzymatic mechanism of hemepolymerization in vivo [56-60]. Considerable data supports the hypothesis that hematin is the target of 4-aminoquinoline class of compounds [61]. 4-AQ are weak bases and are expected to accumulate in an acidic food vacuole to many folds. Recently Egan et al. have shown that CQ, amodiaquine and quinine can inhibit synthetic β-hematin formation by direct interaction [62]. As discussed earlier, UV, NMR, mass, crystallography and molecular modeling studies also support the complex formation [36,51]. The isothermal titration calorimeter (ITC) is also used to explain the mechanism.

Mechanisms of resistance

The indiscriminate use of CQ has led to the development of resistant malaria strains. They are almost spread over the entire malaria-endangered area. Today, more than 80% of wild isolates are resistant to CQ [55]. The need to understand the mechanisms of action of the 4-AQ antimalarials is urgent as levels of resistance to these drugs is on increase. This information is also highly useful for the design and development of drugs against CQ-resistant strain of malaria. Resistance to CQ is more likely to involve more than one gene and altered drug transport rather than changes at site of drug action.

In CQ-resistant strains, the drug is apparently removed from its putative locus of action, the digestive food vacuole (Figure 7). The main cause of CQ resistance is a matter of intense research and debate. Mutation in the transporter gene ‘pfcrt’ is the main culprit in which codes for a protein called the chloroquine resistance transporter (PfCRT). Because there is not much else of significance inside the DV worthy transport, it has been proposed that the physiological role of this protein is the transport of amino acids or small peptides resulting from the degradation of haemoglobin into the cytoplasm [63]. All CQ-resistant strains have a threonine residue in place of lysine at position 76 of the protein. In wild-type CRT, this positively charged side chain is thought to prevent access of the dicationic form of CQ to the substrate binding area of the transporter. The K76T mutation replaces the positively charged side chain by a neutral moiety, and thereby allows access of the CQ di-cation to the transporter, which then decreases the concentration of CQ in the DV considerably (Figure 7).

The K76T mutation is accompanied by up to 14 more amino acid replacements, which are thought to restore the physiological function of the transporter, as, an engineered strain carrying only the K76T mutation is not viable [64-66]. Interestingly, a CQ-resistant strain kept under continuous drug pressure with halofantrine (Figure 1) shows a S163R mutation that renders this strain halofantrine resistant but restores susceptibility to CQ, most probably through re-emergence of the cation-repelling positive charge in the substrate binding area of the transporter [64,67]. This is in agreement with the fact that CQ resistance can be reversed in vitro by several compounds of which verapamil (8) is the prototype (Figure 8). The common molecular feature of these so-called CQ resistance reversers are two lipophilic aromatic residues and a basic aminoaalkyl side chain. It is believed that the ary1 residues interact with a lipophilic pocket in the substrate binding site of the CRT, while the protonated amino group restores the positive charge that repels the CQ di-cation. The underlying molecular scaffold for CQ resistance reversers, resembles a variety of molecules including certain H1-antihistaminic agents (chlorpheniramine 9) and neuroleptics [68-71]. Recent results suggest that this mutation plays a compensatory role in CQ-resistant isolates under CQ pressure and may also have some fine tuning effects on the degree of CQ resistance. Efforts to design new reversers of CQ resistance are underway [61]. Thus, although CQ appears to already have failed as a first-line antimalarial in most of the world, this inexpensive, rapid acting, well-tolerated antimalarial may be resurrected by combination with effective resistance reversers.

An explanation of CQ resistance, focuses on the enzyme glutathione reductase (GR), which might be another target of the CQ–FPIX complex [35]. Considerably elevated glutathione levels are found
in CQ-resistant strains, leading to the theory that a combination of CQ with a glutathione reductase inhibitor might overcome resistance. A dual drug consisting of a quinoline derivative [62] and a GR inhibitor (10) showed activity against various CQ-resistant strains that was superior to the parent quinoline, but failed to produce a radical cure in P. berghei-infected mice [72]. The presumed role of glutathione in CQ resistance could also be the rationale behind the recently renewed interest in methylene blue (1), which is known to inhibit GR [73].

However, very recent results showed that methylene blue and CQ are antagonistic in vitro [74]. In light of these results; it is not surprising that a clinical trial showed no advantage in using a combination of methylene blue and CQ over CQ monotherapy in an area with a high probability of CQ resistance.

Modifications of 4-aminoquinoline derived scaffold

4-aminoquinoline derived antimalarial constitute in major class of available antimalarial drugs broadly in clinical use. Much work has been invested in the structural modification on the 4-aminoquinoline scaffold, resulting in a large number of derivatives. Excellent reviews have described these efforts in depth. Three different structural modifications are able to overcome CQ resistance (Figure 9): 1) The elongation, or more important, the shortening of the diaminoalkyl side chain; 2) The introduction of lipophilic aromatic moieties into the side chain; and 3) The dimerization of two 4-aminoquinolines by a linker of variable nature and length. Figure 9 depicts the side chain modification on the 4-AQ and relative structure activity relationship.

For the sake of clarity, the discussion is organized as following sub headings (a) modification on 4-aminoquinoline-nucleus (b) modification on side chain analogs (c) modification on side chain dialkylaminomethyl-phenol and d) Bisquinoine analogs.

Modifications on 4-aminoquinoline nucleus

The core nucleus, 4-aminoquinoline is an essential for antimalarial activity and several attempts have been made on modifying the side chain on the quinoline ring. The reason being that intact 4-AQ is required in hematin binding and for antimalarial activity [75]. Several studies report, the modification on the 4-AQ nucleus leads to loss of activity with the exceptions of chloroquine-N-oxide [76]. In literature it is evident that 7-halo substituted 4-aminoquinoline derivatives are more active than unsubstituted analogs [77]. Further Vippagunta et al. and other groups suggested that 7-chloro-4-aminoquinoline is essential for inhibition of β-hematin formation and optimal for antimalarial activity [75]. This evidence is further supported by Egan et al. for obligatory nucleus in the inhibition of β-hematin formation. Other electron donor groups like NH2 or OCH3 in the place of 7-chloro group reduces the hematin association constant and weakens inhibition of β-hematin formation, thus finally reduces the antimalarial activity. Whereas electron withdrawing group like NO2 reduces the accumulation in the DV and show weaker inhibition of β-hematin formation and antimalarial activity.

Side chain modifications

The diaminoalkyl side chain of 4-AQ derived antimalarials plays significant role in modulation of the activity. It is considered that, side chain would provide and modulate the required pharmacokinetic properties for drug transport as well as basicity for accumulation in the DV. Thus several reports depict the alteration, or more importantly the shortening, of the dialkyl side chain for the activity against CQ resistant strains [77,78]. A CQ derivative with a shortened side chain is AQ13 (Figures 10 and 11). It retains activity against CQ-resistant parasites (IC50=59 nm versus 315 pm for CQ), but there is a clear correlation between the susceptibility of different isolates toward AQ13 (11) and CQ, pointing to some degree of cross-resistance. A recently completed dose-dependent trial in healthy volunteers suggests that the adverse effects of AQ13 may not be different from those of CQ and that higher
The hits need to pass through pharmacology and toxicology filters to find the most promising candidates. In the same line various analogs (12) of AQ13 with potent antimalarial activities have been developed. Extensive investigations were done by several research groups on the modification of side chain to determine the appropriate length and size. Stock et al. showed that the replacement of the diethylamino function with a metabolically stable ‘Bu group (F2bu; 13) led to a 20-fold increase in the potency against the CQR strain [80]. Iwaniuk et al. introduced a linear dibasic side chain (14) with good improvement in the activity [81].

Sergherart et al. have synthesized a series of 4-aminoquinoline based sulfonamide library bearing a common piperazine linker. The most effective analog (Figures 10 and 15) shows that 100 fold better activity than CQ [82]. Further, in one more study, they have synthesized \( \text{N'(7-chloro-4-quinyl)-1,4-bis(3-aminopropyl) piperazine derivatives} \) and screened them against CQ resistant strain of \( P. falciparum \). All these compounds showed higher selectivity index than CQ and one of the compounds (X=CO) (16) showed 5-fold higher selectivity index and was 5 fold more active than CQ [83]. In another series, eleven compounds displayed higher selectivity index than CQ, among these one of the compounds (17) cured mice infected by \( P. berghei \) [84]. Musonda et al. have reported a new series of 4-aminoquinoline derivatives from Ugi reaction and found these analogs were active against both CQ resistant and sensitive strains of \( P. falciparum \), with the best compound (18) showing an IC\(_{50}\) value of 73 nM against a resistant strain [85].

Pyrrolizidinyl moiety at the pendant nitrogen (19) was recently reported by Sparatore et al. has showed a promising antimalarial activity for further development. There are different research groups have reported potent antimalarial activity by introducing a aromatic group (20) in the side chain as well as lengthening the diaminoalkyl side chain of 4-aminoquinolines (21).

Manohar et al. reported class of hydrid molecules of 4-aminoquinolines and pyrimidine (Figure 11); 22-39) as antimalarials. All compounds were screened for \textit{in vitro} antimalarial activity against chloroquine (CQ)-sensitive (D6) and chloroquine (CQ)-resistant (W2) strains of \( P. falciparum \) [86].

Out of the derivatives synthesized, 11 compounds (26, 27, 30, 31, and 33-39) have shown better antimalarial activity (IC\(_{50}\)=0.005−0.03 μM) against the CQ sensitive strain. 12 compounds (27-31, and 33-39) displayed better antimalarial activity (IC\(_{50}\)=0.01−0.21 μM) against the CQ-resistant strains of \( P. falciparum \). Generally hydrid derivatives showed roughly 1.6-2.0 fold increase in activity compared to pyrrolizidine in case of drug resistant strains. Most active compounds found to be 34 and 38.

Bhat et al. reported series of hybrid 4-aminoquinolines-1,3,5-triazines (Figure 12); 40-46) and screened against chloroquine sensitive RKL2 strain of \( P. falciparum \) in 96 well-microtiter plates. However, synthesized derivatives exhibited mild to moderate antimalarial activity with no toxicity signs [87].

Kumar et al. reported the modified 4-aminoquinoline derivatives–acridine hybrids (Figure 13); 47-64) as potential compounds to overcome the resistance of \( P. falciparum \) to aminoquinoline and related antimalarial drugs. All the synthesized derivatives were evaluated for antimalarial activity against NF 54 strain of \( P. falciparum \) [88]. Compounds 47 and 48 with ethyl and propyl chain exhibited MIC value of 10 μg/mL. Further, methyl group on phenyl derivatives lead to corresponding compounds 49 and 50 with no antimalarial activity. Derivative 51 with ethyl linker attached to the 1-pyridin-2-yl piperazine had MIC of 10 μg/mL, however 52 propyl linker resulted in remarkable improvement in antimalarial potency with MIC value of 0.125 μg/mL.

doses of AQ13 over CQ may be necessary to produce similar blood levels and AUC values [79]. Several options have come up with AQ13 success and variation have been made on the lateral amino group of the AQ13.
Compound 55 with ethyl linker attached to the tetrahydroisoquino-line exhibited MIC value of 2 lg/mL and replacement with propyl linker (56) led the excellent antimalarial potency with MIC value of 0.031 lg/mL. Compound 57 with ethyl linker attached to the 4-phenyl-piperidine-4-carbonitrile showed MIC value of 10 lg/mL, while addition of one methylene unit resulted in compound 58 with excellent activity. Data analysis revealed that propyl linker was favorable for the antimalarial activity. All other derivatives were showed moderate antimalarial activity.

Modifications on AQ side chain of dialkylaminomethylphenol

Enhancement of lipophilicity of the side chain by the incorporation of an aromatic structure resulted in amodiaquine (AQ) (Figure 14); 65 with certain degree of cross resistance to CQ activity. However, the therapeutic value of amodiaquine is significantly decreased by the biotransformation of its p-aminophenol moiety into a quinonimine (66), a severe hepatotoxic intermediate by complexing (nucleophilic attack by thiol groups) with proteins. Moreover, amodiaquine-protein complexes (67) are highly immunogenic, leading to life-threatening agranulocytosis. To overcome these adverse effects, several anilinoquinolines have been developed to prevent the undesirable formation of toxic quinoninines and improved antimalarial activity. One of the modifications is the exchange of the positions of the hydroxy and diethylaminoethyl groups on the phenyl ring. The resulting isquinoine (69) is not bioactivated and therefore does not lead to hepatotoxicity [85] with significantly improved activity against CQ-resistant strains. Furthermore, to improve upon the rapid biotransformation by oxidative dealkylation in the body, tert-butylamino group is replaced the diethylamino moiety, resulting tert-butylisouquinoline (70). It promises a new generation of affordable, well tolerated and effective antimalarial agents that is devoid of any cross-resistance to the chemically related CQ and amodiaquine.

Sergherart et al. have synthesized a series of 4-anilinoquinolines (Figure 15); 71-73) with two proton accepting side chains of varying length, which help these dicatonic moieties in their likely interaction with carboxylate groups of haem. From this study, they concluded that structural features of 4-anilinoquinoline, can help in circumventing cross resistance with CQ [62]. In continuation as mentioned earlier, they have synthesized prodrg of 4-anilinoquinolines derivatives (Figures 8 and 10) in which metabolically labile ester linkage of GR inhibitor was combined to amino and hydroxy functionality of amodiaquine [72].

Bisquinoline analogs

Bisquinolines were introduced to overcome CQ-resistance by connecting two 4-aminoquinoline moieties through linkers of various length and chemical nature. The activity of such bisquinolines against CQ-resistant strains has been explained by their steric bulk, which prevents them from fitting into the substrate binding site of PfCRT. Alternatvely, the bisquinolines may be more efficiently trapped in the acidic DV because of their four positive charges. On this basis bulky bisquinoline compounds were synthesized and evaluated for their antimalarial activity. The most advanced representative of the bisquinolines, piperaquine (Figure 16); 74 was developed in 1960s and heavily used in China. Widespread resistance has developed in areas where piperaquine has been extensively used. However there are indications of cross-resistance with dihydroartemisinin (Figure 1). This significant finding made to develop the combination of piperaquine and dihydroartemisinin (named Euartekin) and entered phase II clinical trials [89]. Of the several bisquinoline analogs developed, the compound (WR 268,268) (Figure 16); 75 has shown potent in vivo activity against P. berghei [90]. For this reason, compound 75 underwent preclinical studies at Hoffman-LaRoche Ltd, and was found to be a good inhibitor of hematin polymerization, but its photocotoxicity precluded its further development. tris- and tetraquinolines (Figure 16); 76, 77) also developed by attaching 4-amino group to tri- and tetramacrocycles (cyclams) ring system. However, these derivatives are extruded with difficulty by proteaceous transporter with the aim of reducing CQ resistance. The results suggest that increased rigidity by cyclization, yields molecules that were not more active in CQ sensitive strains but very potent against resistant strains and were also non-toxic [91].

Compounds Active against Other Diseases

A third approach to antimalarial chemotherapy is to identify agents that are developed or marketed as treatments for other diseases. These compounds might act against orthologs of their targets in other systems or by different mechanisms against malaria parasites. This strategy further named as ‘piggy back’ approach which is cost effective when a molecular target present in parasites is being pursued for other (commercial) indications as it indicates the identification of chemical starting points. The advantage of these compounds is that, whatever is the mechanism of action, they have already been developed for a human indication, so will be quite inexpensive to develop as antimalarials. Specific examples of this approach include the antimalarial screening of lead series of Histone-deacetylase inhibitors [92], which were originally developed for cancer chemotherapy, and cysteine protease inhibitors that are being developed for osteoporosis. It should be noted that structure–activity relationships emerging from the parasite assays are unlikely to be the same as those observed for the original indication. It is therefore likely that optimized clinical candidates emerging from this strategy will be disease-specific. In many cases, however, drugs may be quite inexpensive to produce and may be available as inexpensive antimalarials, especially after patents have expired, as has been the case with some antibiotics. Folate antagonists, tetracyclines and other antibiotics were developed for their antibacterial properties and were later found to be active against malaria parasites [93]. Iron chelators, which are used to treat iron overload syndromes, have documented antimalarial efficacy [94]. These examples suggest that it is appropriate
to screen new antimicrobial agents and other available compounds as antimalarial drugs. This approach is facilitated by the presence of high-throughput assays for potential antimalarials. In the case of protein farnesyltransferases, development efforts have been led to viable anticancer therapies, however expedited the consideration of these targets for antimalarial chemotherapy [95].

Conclusion

It is apparent from the forgoing discussion that 4-aminoquinoline continues to occupy center stage in search of a new viable alternative to CQ for successfully controlling malaria. The 7-chloro-4-aminoquinoline structural requirements for antimalarial activity are summarized below:

- The inter-nitrogen distance between the quinoline nitrogen (pKα1) and tertiary alkylation nitrogen (pK, 2) plays an essential role in activity.
- Diprotonated forms are essential for pharmacological action.
- 7-Chloro-4-aminoquinoline is required for inhibition of β-hematin formation.
- The role of carbon chain length in the aminalkyl side chain by shortening (2-3 carbon atoms) and lengthening (10-12 carbon atoms) leads to improve the active against CQ-resistant strains of P. falciparum.
- Modification on pendant amino group leads to improved activity.
- Bisquinoquine analogues are also active against CQ-resistant parasites in vivo.

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