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4-Aminoquinolines as Antimalarial Agents: A Review of A Medicinal Chemistry Perspective

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Abstract: Malaria is a potentially fatal parasitic disease brought on by five Plasmodium species, including *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium malariae*, and *Plasmodium knowlesi*. The fast emergence of *P. falciparum* resistance to currently available treatments has increased health concerns in developing countries. The growth in resistance emphasizes the need for a novel, secure, and cost-effective antimalarial drug that can treat malaria resistant to multiple antimalarial drugs. Therefore, it has become crucial to create new therapeutic approaches to deal with the rise of parasites resistant to artemisinin. For the treatment of *P. falciparum* malaria in children living in areas with moderate to high transmission, as established by WHO, the malaria vaccine RTS, S has been authorized. The WHO recommends that governments consider this immunization against a human parasite when deciding the optimum subnational combination of measures for maximum impact. The current research synthesizes numerous 4-aminoquinoline derivatives successfully treating malaria and its diverse etiological species.Additionally crucial to the management and prevention of malaria are antibiotics. Effective and well-tolerated antimalarial medications include tetracycline and chloramphenicol, chloroquine, primaquine, pamaquine, and artemisinins are some of the drugs used to treat malaria; however, numerous new compounds have proven to be even more efficient. This review, based on literature reports, will give medicinal chemists ideas for new malaria drugs to develop. In addition, this review will help search for new antimalarial drug leads in the future.

Key words: Malaria; 4-Aminoquinoline; RTS,S Malaria Vaccine; Artemisinin

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1.1 INTRODUCTION

The parasitic disease malaria, which can be fatal, is spread by mosquitoes called Anopheles. Human malaria is brought on by a genus of parasitic worms called Plasmodium. Five distinct Plasmodium species exist. In contrast to *P. falciparum* and *P. vivax*, responsible for the vast majority of fatal cases, *P. ovale* and *P. malariae* cause a less severe form of malaria that is rarely fatal. A zoonotic species from Southeast Asia called *P. knowlesi* can infect humans in addition to causing malaria in macaques[1-15]. According to the WHO report 2021, between 2000 and 2020, 10.6 million malaria mortality and 1.7 billion malaria cases were prevented worldwide. The WHO African Region avoided the majority of cases (82%) and fatalities (95%), followed by the WHO South-East Asia Region (cases 10%, deaths 2%)[16]. Other factors that affect malaria transmission or sicknesses, such as rising socioeconomic status, malnutrition, infrastructure, housing, and urbanization, could have decreased cases and fatalities in addition to malaria interventions. In all areas where falciparum malaria is endemic, artemisinin-based combination therapy (ACTs) is indicated. Over the past 20 years, antimalarial medicines (ACTs) have been essential in lowering malaria, with artemether-lumefantrine being the most commonly used ACT in Africa. The advent of *Plasmodium falciparum* parasites that are resistant to artemisinin has reduced the efficacy of numerous ACTs in Southeast Asia. Even worse, newly discovered artemisinin-resistant parasites are appearing in Africa, according to recent findings from Rwanda and Northern Uganda. If artemesinin activity were to disappear, the efficacy of companion drugs like lumefantrine would be hampered; the disappearance of both ACT components may have catastrophic effects across the continent. It has become crucial to create new therapeutic approaches to deal with the rise of parasites resistant to artemisinin[17]. In 2020, it was expected that 170 million cases and 938000 deaths would have been prevented, compared to the estimated burden, if case incidence and fatality rates continued at 2000 levels, despite major malaria services disruptions during the COVID-19 epidemic. For treating *P. falciparum* malaria in children living in areas with moderate to high transmission, as established by WHO, the malaria vaccine RTS, S has been authorized. The WHO recommends that governments consider this immunization against a human parasite when deciding the optimum subnational combination of measures for maximum impact[16]. The following is a description of the available antimalarial medications for both treatment and prevention:

1.1 Malaria Life Cycle

Malaria in humans has a complicated life cycle with two stages. The mosquito vector goes through both the asexual stage, which affects people, and the sexual stage, during which the male and female gametes unite and produce sporozoites[18] (Figure 1).

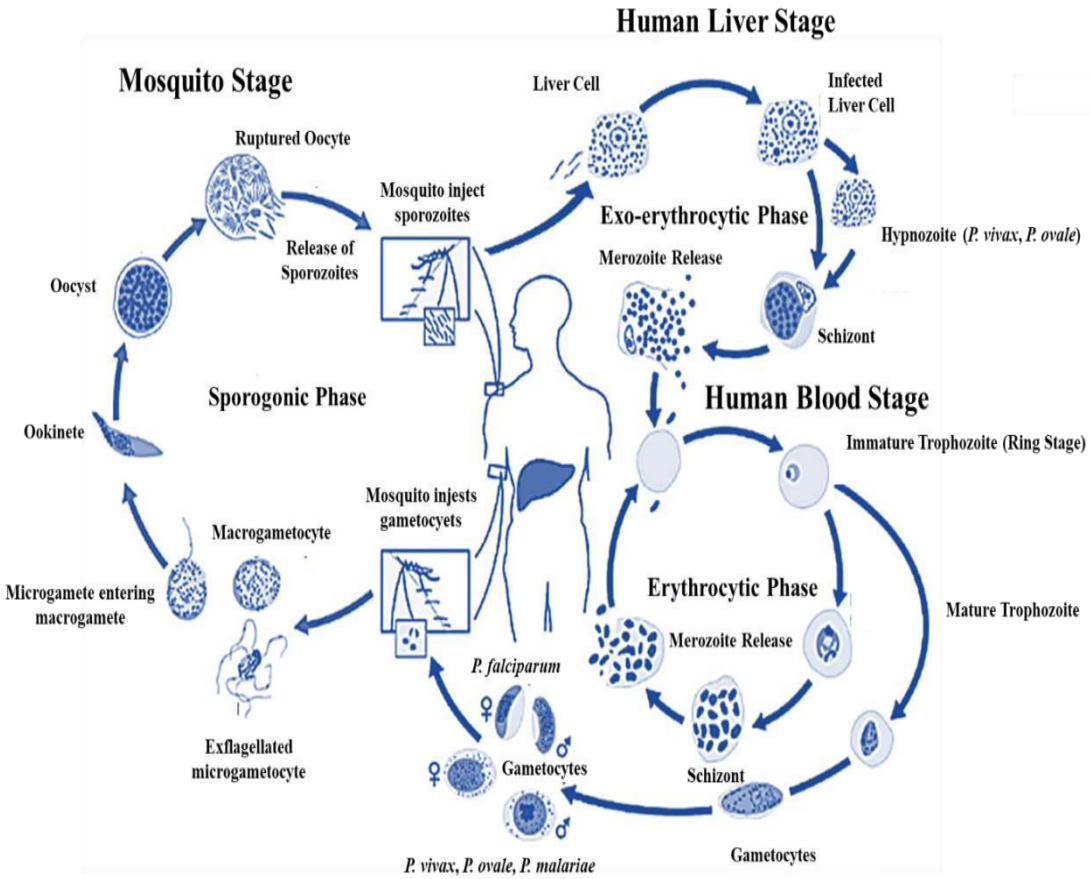


Fig 1: Life cycle of Plasmodium species[18,19]

1.2 Chemotherapeutic Approaches

There are typically three classes of medications available to treat malaria, and each is categorized based on how effectively it combats the various stages of the parasite's life cycle found in human hosts: trophozoites and schizonts in red blood cells, schizonts in the liver, and gametocytes in red blood cells. Mefloquine, chloroquine, quinine, halofantrine, sulfadoxine, dapsone, tetracyclines, amodiaquine, atovaquone, and artemisinin are medications used to treat blood stages (trophozoite/schizont). Primaquine, proguanil, lumefantrine, and pyrimethamine are liver-schizont medications. Chloroquine, artemisinin, amodiaquine, and quinine are the gametocyte medications. Gametocytes and hypnozoites can both be killed by primaquine[20] (Table 1).

Table 1: Chemical classification of the currently used antimalarial drugs[20]

Chemical class	Examples
A. 4-aminoquinolines	Chloroquine, Hydroxychloroquine, Amodiaquine
B. 8-aminoquinolines	Primaquine, Tafenoquine, Bulaquine
C. Arylamino alcohols	Quinine
D. Methanols i. 4-quinoline methanol ii. 9-phenanthrene methanol	 Mefloquine Halofantrine, Lumefantrine
E. Biguanides	Proguanil
F. Diaminopyrimidines	Pyrimethamine
G. Antimalarial endoperoxides	Artesunate, Artemether, Arteether
H. Hydroxynaphthoquinone	Atovaquone
I. Benzonaphthyridine derivative	Pyronaridine
J. Antibiotics	Tetracycline, Doxycycline, Clindamycin, Azithromycin

1.3 Mechanism of Action of currently available antimalarial drugs

The proposed mechanism of action of the currently available drugs for the treatment of malaria is given in Table 2[20].

Table 2: Mechanism of Action of currently available antimalarial drugs[20]

S. No.	Name of Drug	Mechanism of action
1.	Chloroquine	▪ Inhibits plasmodial heme polymerase ▪ Toxic drug-heme complex formation ▪ Intravascular pH alteration
2.	Quinine	(Same as Chloroquine)
3.	Artesunate Artemether Arteether	▪ Activated by heme/ molecular iron to produce carbon-centred free radicals ▪ Membrane damage by free radical
4.	Mefloquine	▪ Formation of toxic substance with heme ▪ Damages membrane and other components ▪ Causes swelling of food vacuole
5.	Halofantrine	▪ Concentrates in parasites and combines with ferriprotoporphyrin IX, leading to membrane damage
6.	Atovaquone	▪ Inhibits parasite mitochondrial electron transport chain (complex III)
7.	Pyronaridine	▪ Inhibits vacuolar degradation, leading to impaired haemoglobin degradation
8.	Sulfadoxine - Pyrimethamine	▪ Acts against the parasite dihydrofolate reductase enzyme
9.	Primaquine	▪ May get converted to electrophiles that act as redox mediators
10.	Proguanil	▪ Selective inhibition of the bi-functional dihydrofolate reductase-thymidylate synthetase of Plasmodium.
11.	Halofantrine	▪ Concentrates in parasites and combines with ferriprotoporphyrin IX, leading to membrane damage

1.4 Development of Aminoquinoline drug from Quinine

Treatment and chemoprophylaxis for acute or uncomplicated falciparum malaria and vivax malaria usually use antimalarials containing Quinine structural derivatives (Figure 2). Unfortunately, the quick establishment of resistance has severely restricted their usage alone. Still, combined with drugs from the same class or other drugs, they have been proven useful in treating acute and severe instances of chloroquine- or multidrug-resistant *P. falciparum* infection[21,22].

1.5 Folate antagonists

These substances prevent the synthesis of parasitic pyrimidines and, as a result, prevent the production of parasitic DNA. Antifolates can be divided into two groups: I dihydrofolate reductase (DHFR) inhibitors, which include biguanides and diaminopyrimidines like pyrimethamine, trimethoprim, proguanil, and chlorproguanil; and (ii) dihydropteroate synthase (DHPS) inhibitors, which include sulphonamides and sulfones like sulfadoxine, sulfalene, and dapsone[23].

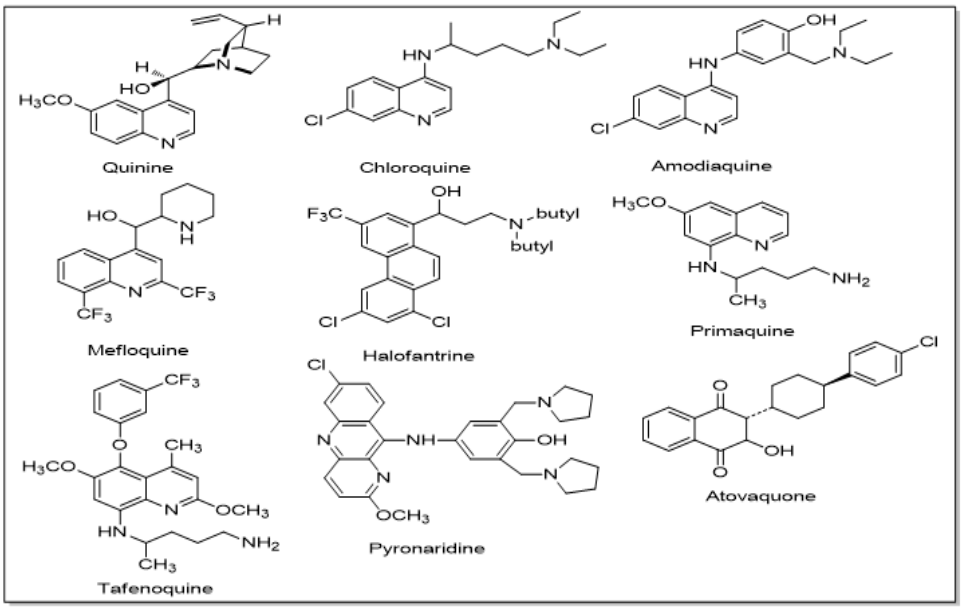


Fig 2: The chemical structures of antimalarial medicines based on quinoline

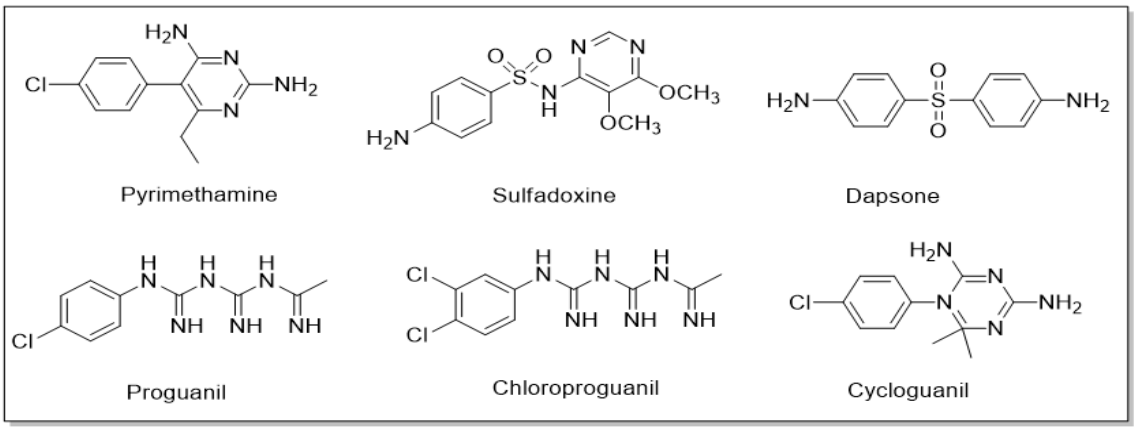


Fig 3: Folate antagonist's chemical structure

1.6 *Artemisinin and its derived substances*

The drug artemisinin, which has a quick onset of action and is efficient against multidrug-resistant *P. falciparum* strains, is found in sweet wormwood (Artemisia annua). Artemisinin-based drugs (including its derivatives) are currently acknowledged as the most significant novel antimalarials for treating severe malaria (Figure 4). Dihydroartemisinin (DHA), artemether, arteether (oil-soluble ethers), artesunate (water-soluble hemisuccinate), and artelinic acid are among the derivatives of artemisinin. These compounds are all cyclic endoperoxides or sesquiterpene lactones[24,25].

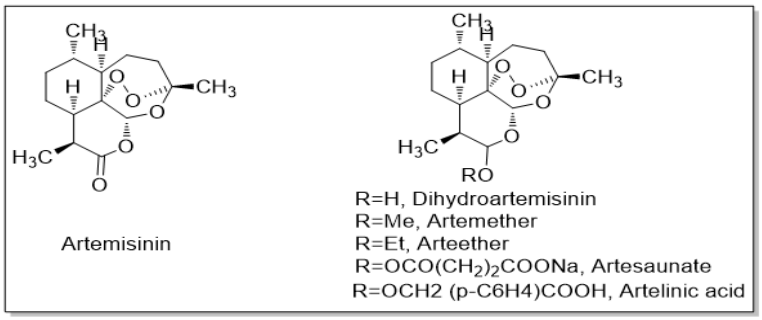


Fig 4: Artemisinin and its derivative's chemical structures

Haem, produced when the Plasmodium parasite digests haemoglobin, reductively activates artemisinin and other peroxide antimalarials to make them parasiticidal. The carbon-centred free radicals produced by this irreversible redox process cause alkylation of proteins and heme, as well as proteins and enzymes[22].

1.7 Antibiotics

Additionally crucial to the management and prevention of malaria are antibiotics. Effective and well-tolerated antimalarial medications include tetracycline and chloramphenicol. Tetracycline is used as a preventative against *P. falciparum*, as are its equivalents, doxycycline, azithromycin, and clindamycin (Figure 5). However, they are known to impede translation by reversibly binding to the 30S subunit and distorting it such that the charged tRNA anticodons do not line up appropriately with the codons of the tRNA[22- 24].

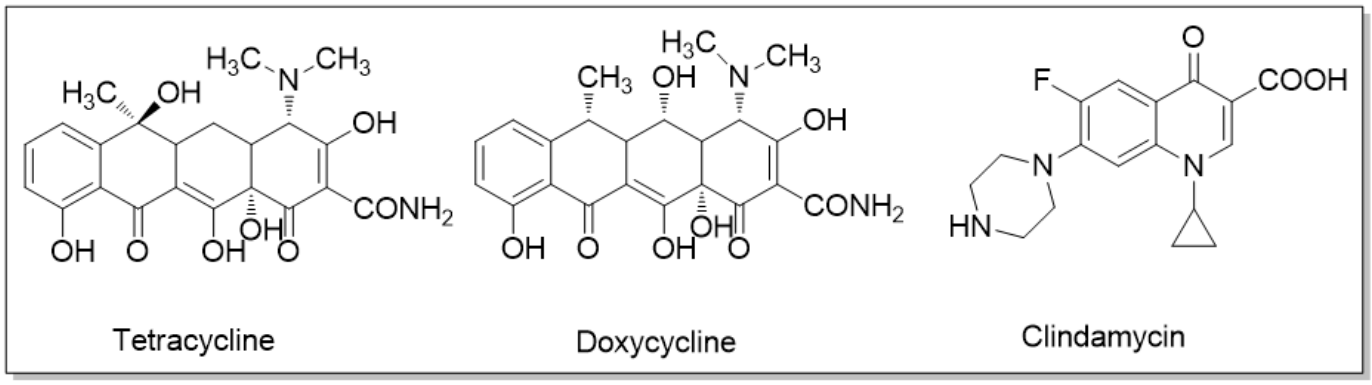


Fig 5: Antimalarial antibiotic's chemical structures

Numerous efforts have been made in recent years to define the synthesis of safe, potent, and efficient drugs to treat malaria. As a result, chemists worldwide have developed antimalarial medications with heterocyclic moieties, including pyrimidine, 4-aminoquinolines, and triazoles. In this study, the authors looked at the relationship between the structure and activity of a variety of newly synthesized 4-aminoquinoline chemical entities and documented their production process and antimalarial potential.

1.8 Challenges in Drug Development

The interactions between an antimalarial drug and the malaria parasite, such as "selective toxicity" and "drug resistance," as well as the compatibility between an antimalarial drug and the host, such as "pharmacokinetics" and "pharmacodynamics," are what determine an antimalarial drug's effectiveness. The best antimalarials are selective, exhibit curative action, and do so with little to no host toxicity. According to the WHO, resistance to antimalarials is the ability of a parasite strain to persist and proliferate despite the administration and absorption of a medication given in doses that are equivalent to or higher than those typically recommended but within the subject's tolerance, with the qualification that the form of the drug that is active against the parasite must be able to access the parasite or the infected red blood cell for the duration required for its normal action. The parasites that cause malaria show a variety of antimalarial drug susceptibilities. This range is explained by several distinct phenomena, such as acquired resistance, strain-specific innate resistance (for example, the asexual liver stages of *P. vivax* from the island of New Guinea against primaquine), and species-specific innate resistance (for example, asexual blood stages of *P. falciparum* lack susceptibility to primaquine, whereas those of *P. vivax* appear to be sensitive to it)[3,10]. Several variables affect the prevalence, frequency, and rate of resistance development[3]. (i) *Pharmaco-Biological Factors:* Pharmacological factors, such as the drug's pharmacokinetic and pharmacodynamic properties and inherent potential to produce resistance, might affect the rate at which resistance develops. (ii) *Epidemiological Factors:* When a mosquito captures male and female gametocytes during a blood meal, self-fertilization between the gametocytes occurs, which is one factor in developing resistance. The mutations carried by the parasites that follow and are passed on to the next person are determined by such reassortment (s). (iii) *Operational and behavioural factors:* How individuals use antimalarial medications significantly impacts the level of selective drug pressure; several behaviours expose parasites

to insufficient or subtherapeutic drug levels, which promote the development of resistance. Developing drug resistance in Plasmodium species towards all antimalarial drugs is challenging in Antimalarial Drug Development. Therefore, there is an urgent need to develop a new effective antimalarial drug in front of researchers of the world[3].

1.9 Medicinal Chemistry and Antimalarial activity

An exhaustive assessment of numerous reputable scientific publications and other significant instructional books was done to identify current developments in the field of antimalarials. The literature survey study aims to find information about many kinds of 4-aminoquinoline-containing chemical structures and the methods used in their creation. Singh and co-authors[26] have revealed twelve unique 1, 2-diamino propane side chain modified 4-aminoquinoline Mannich bases (Scheme 01) (Figure 6). With MICs ranging from 15.6 to 125 g/mL, all substances demonstrated antimalarial efficacy against the *Plasmodium falciparum* (3D7) chloroquine-sensitive strain. In addition, the chloroquine-sensitive strain of *Plasmodium falciparum* was found to be moderately responsive to two of these compounds, 7-chloro-N-(1-(3-(dibenzylamino)-1-p-tolylpropylamino) quinoline-4-amine and 7-chloro-N-(1-(3-(dibenzylamino)-1-(4-methoxyphenyl)propylamino (3D7).

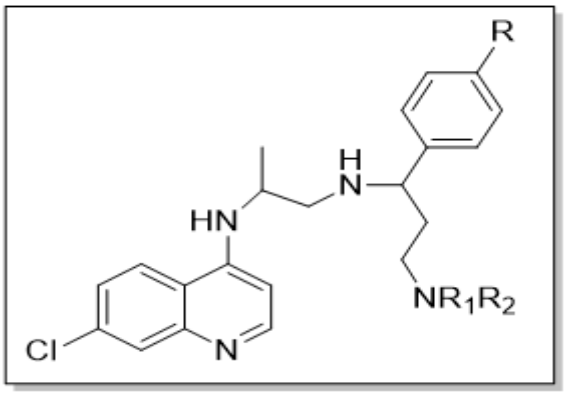
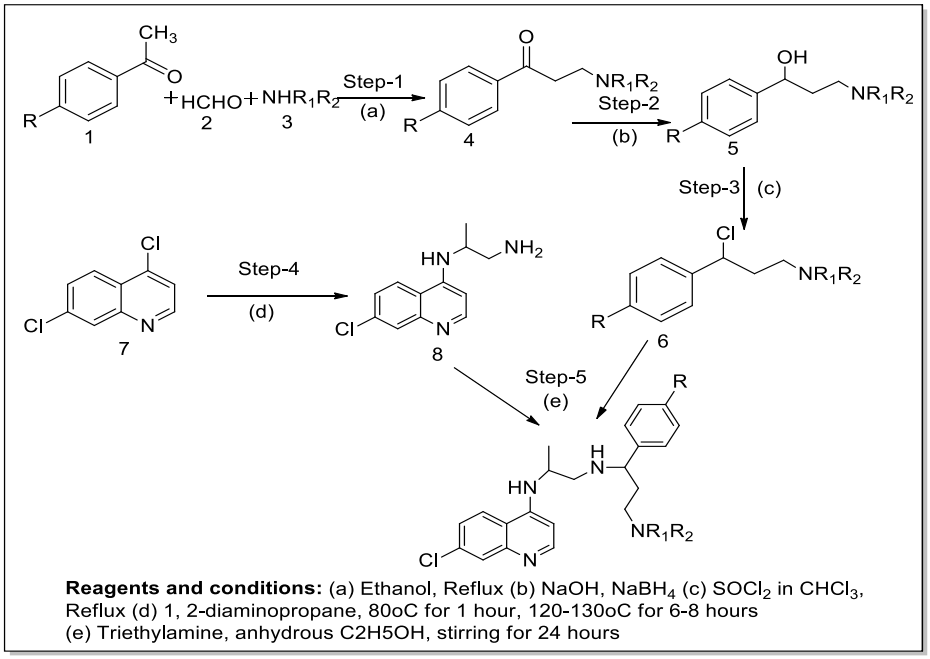


Figure 6



Scheme 01: Modified side chain of 1,2-diamino propane with 4-Aminoquinoline Mannich bases

The derivatives of 3-(3-(7-chloroquinolin-4-ylamino)propyl)-1,3-thiazinan-4-one synthesized by Kumawat and colleagues[27] were tested *in vitro* against the RKL-2 strain of the chloroquine-sensitive *Plasmodium falciparum*. According to the authors, when compared to the standard, the majority of the synthesized compounds displayed mild to moderate parasite susceptibilities. However, in comparison to the other medicines examined, they discovered that 3-(3-(7-chloroquinolin-4-ylamino)propyl)-2-(4-bromophenyl)-1,3-thiazinan-4-one (Figure 7 & Scheme 2) exhibited somewhat superior antimalarial activity.

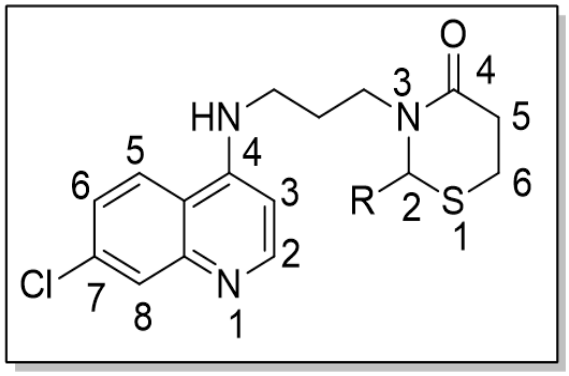
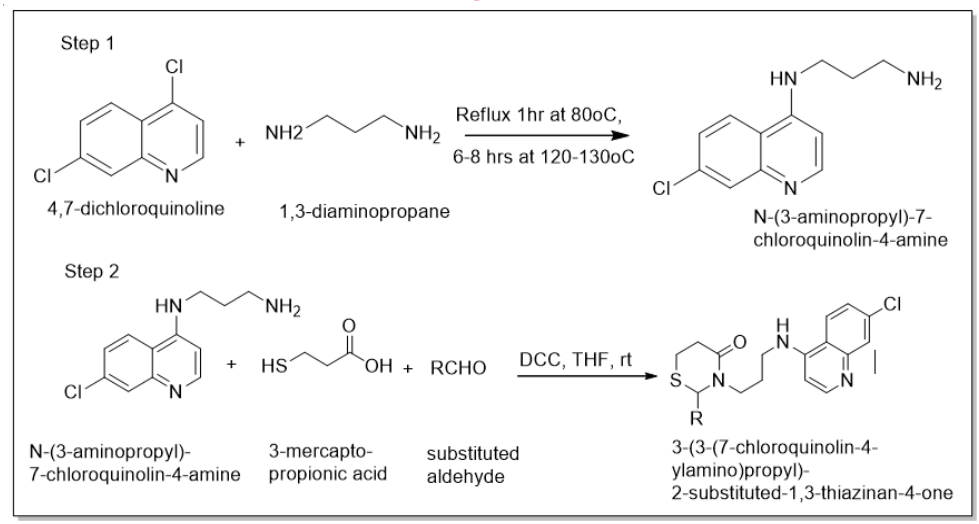
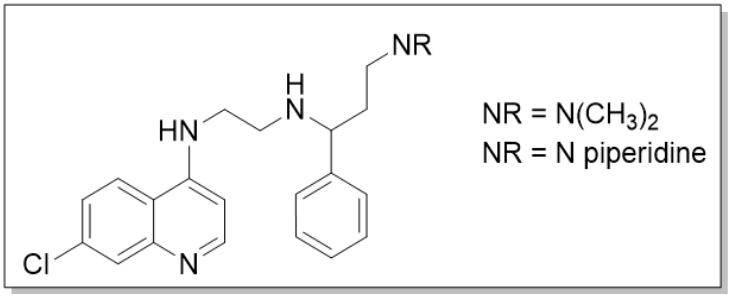


Figure 7

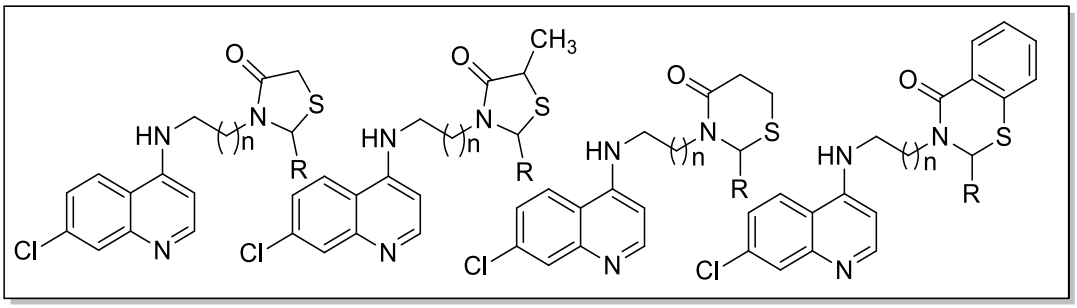


Scheme 02: Derivatives of 1,3-thiazinan-4-one



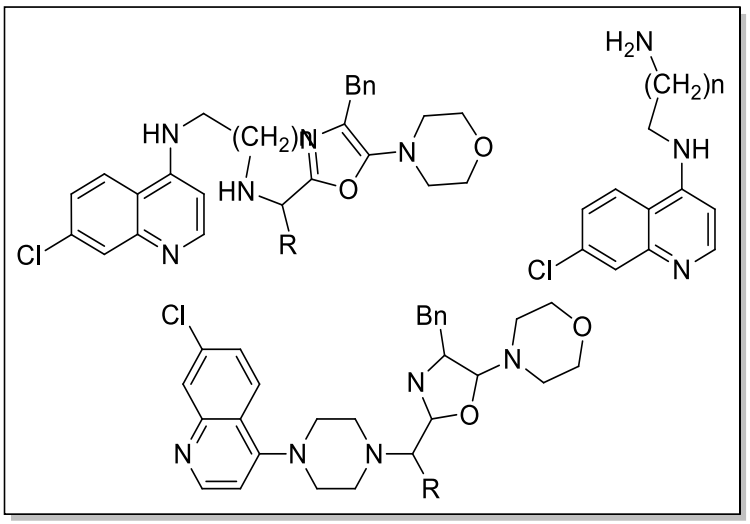
Wenzel and associates[28] described new medicines with dual organic and organometallic bases and 4-aminoquinoline (Figure 8). With IC_{50} and IC_{90} values (low nM range), some compounds from this class of dual medicines have demonstrated strong antimalarial activity.

Figure 8



A new class of 4-aminoquinolines with side-chain modifications (Figure-09) created and published by Solomon and co-authors[29] were found to be effective against Plasmodium yoelli in vivo and Plasmodium falciparum in vitro. Because these analogues bind to hematin and prevent the synthesis of hematin, this family of drugs likely works to inhibit heme polymerization.

Figure-09



Musonda and co-authors[30] developed a novel series of aminoxazoles (Figure-10) that comprise 2,4,5-trisubstituted 4-aminoquinolines and examined their antimalarial effectiveness in vitro against two Plasmodium falciparum strains. They found a variety of substances that were significantly more potent than the common medication, chloroquine.

Figure-10

Freitag and co-authors[31] developed several new derivatives of chloroquinolin-4-amine using a straightforward parallel acylation with carboxylic acids bound to polymers (Figure-11). They tested their effectiveness against a sensitive strain of chloroquine (CQ) and a resistant mutant of CQ. Four compounds showed a four times increase in the ratio of strains of chloroquine-resistant to sensitive inhibition when compared to CQ alone, and most of the novel structures were active against both strains in the nanomolar range.

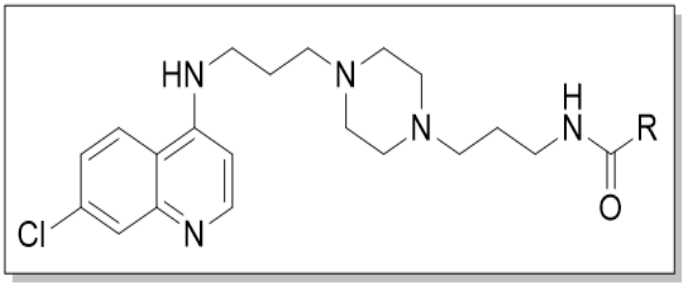
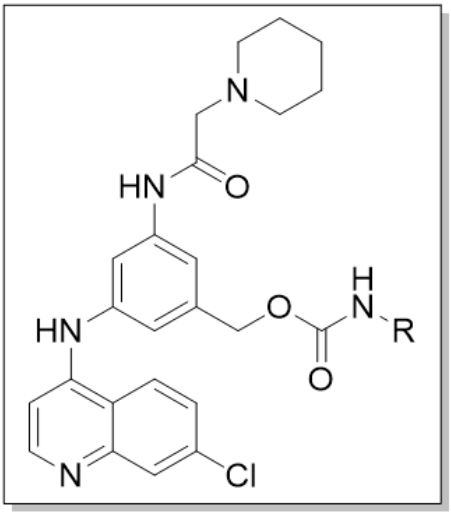
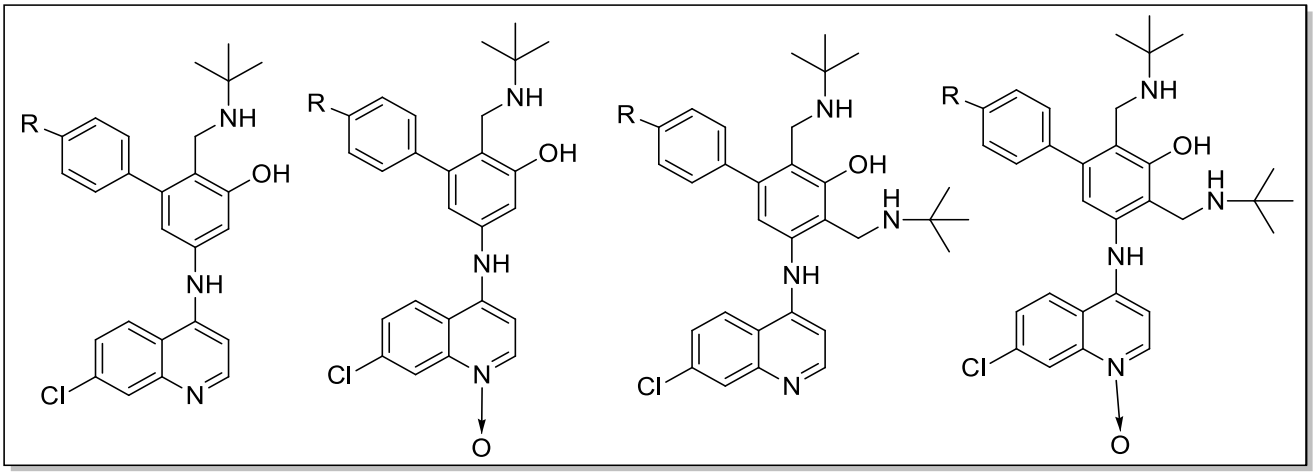


Figure-11



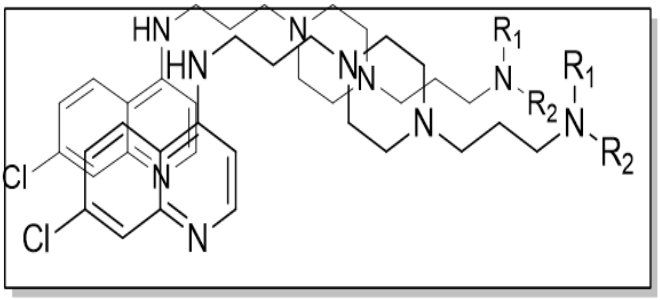
Delarue-Cochin and colleagues[32] tested the antimalarial activity and cytotoxicity of 4-anilinoquinolines (Figure-12) in MRC-5 cells. Most of the 17 compounds had low nanomolar activity in vitro and minimal cytotoxicity against both strains. Following that, two drugs were examined in mice infected with Plasmodium berghei and found acceptable in vivo activity.

Figure-12



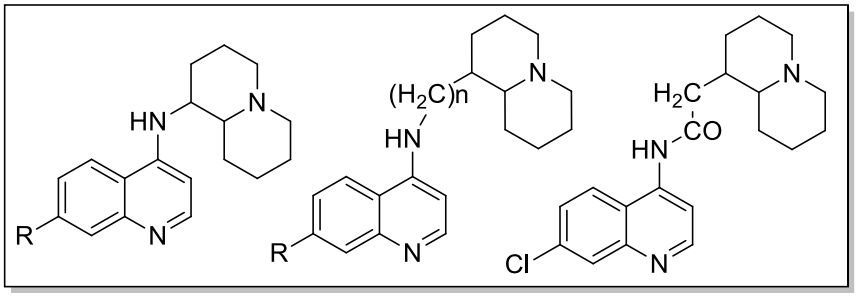
Miroshnikova and colleagues[33] reported synthesizing many isotebuquine derivatives (Figure-13). In addition, the novel Mannich bases were very effective against chloroquine-sensitive (D6) and chloroquine-resistant P. falciparum clones, with IC_{50}s ranging from 0.3 to 120 g/mL.

Figure-13



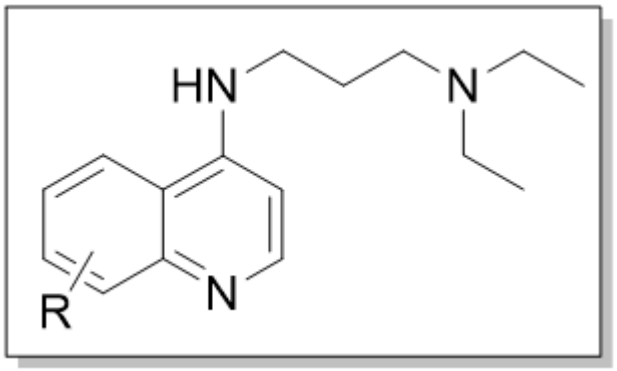
A variety of N1-(7 chloro-4-quinolyl)-1, 4-bis (3-aminopropyl) piperazine compounds (Figure-14) were developed by Ryckebusch and colleagues[34] and tested for antimalarial efficacy against a chloroquine-resistant Plasmodium falciparum strain. Using the colourimetric MTT assay, the cytotoxicity of each drug was evaluated against a human diploid embryonic lung cell line (MRC-5 cells). The majority of the synthetic compounds had high activity and low cytotoxicity, it was discovered.

Figure-14



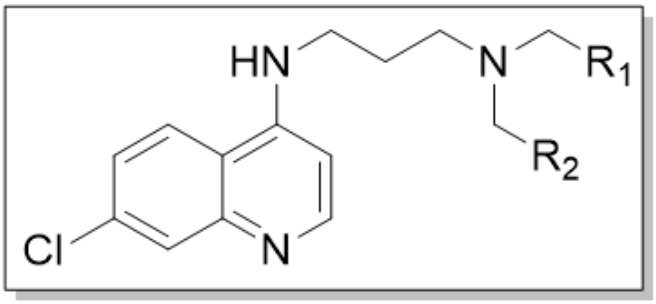
Numerous 7-chloro-4-aminoquinoline quinolizidinylalkyl and quinolizidinyl derivatives of this compound were produced by Sparatore and co-authors[35] (Figure-15). The substances were all antimalarial in nature. Some quinolizidine compounds were five to ten folds more effective than CQ against the chloroquine-resistant strain.

Figure-15



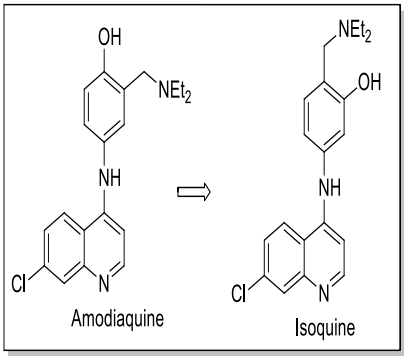
A library of ring-substituted 4-aminoquinoline compounds (Figure-16) was developed by Madrid and colleagues[36] and evaluated for antimalarial activity against Plasmodium falciparum sensitive and resistant to chloroquine. In addition to the 7-chloroquinoline ring of chloroquine, substituted quinoline rings were discovered to have significant efficacy against the drug-resistant strain of P. falciparum.

Figure-16



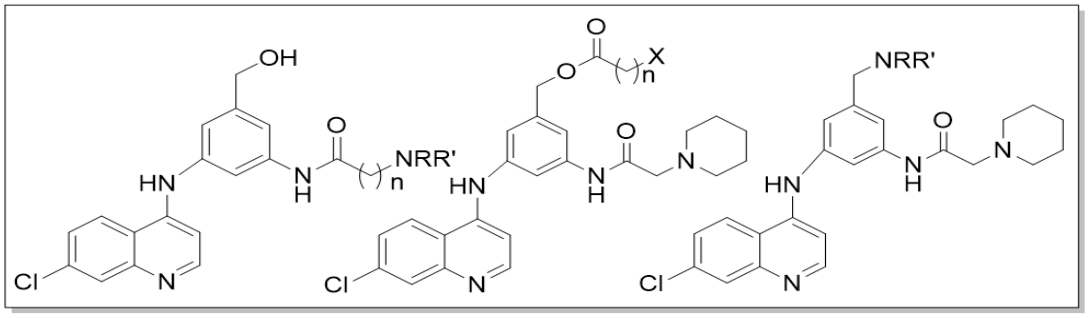
According to the description of creating a workable technique for creating libraries of 4-aminoquinolines with diverse side chains by Madrid and collaborators[37] (Figure-17). The consequences of these alterations were assessed by checking this library's P. falciparum activity.

Figure-17



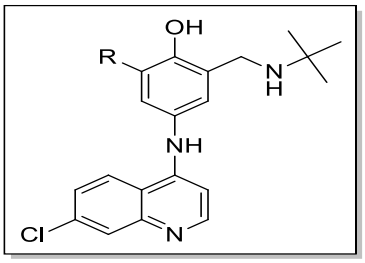
O'Neill and coauthors described a unique family of isoquine and associated amodiaquine analogues[38] (Figure 18). These analogues were created by switching the amodiaquine's 3' hydroxyl and 4' Mannich side-chain functions. Several analogues exhibited potent antimalarial activity when tested in vitro against P. falciparum isolates that were both CQ-sensitive and CQ-resistant.

Figure 18



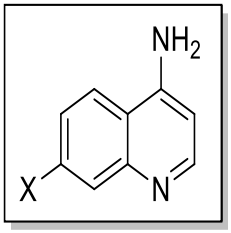
Delarue and associates[39], who created a novel family of 4-anilinoquinolines (Figure 19) with two proton-accepting side chains, discovered that several of these compounds were efficient in vitro against P. falciparum strains.

Figure-19



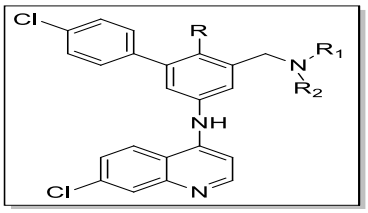
A group of new 4-aminoquinoline Mannich base derivatives with antimalarial activity (Figure 20) was presented by Raynes and co-authors[40]. Amodiaquine (AQ) had its 3'-diethylamino group replaced with a group of 3'-tert-butylamino, and the side chain of 4'-hydroxyanilino had an aliphatic hydrocarbon added to the 5' position.

Figure-20



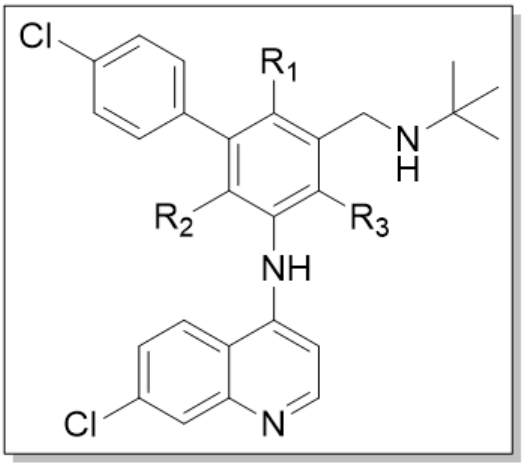
Studying the structure-activity correlations of 4-aminoquinolines with seven alterations for antiplasmodial efficacy was done by De and colleagues[41] (Figure-21).

Figure-21



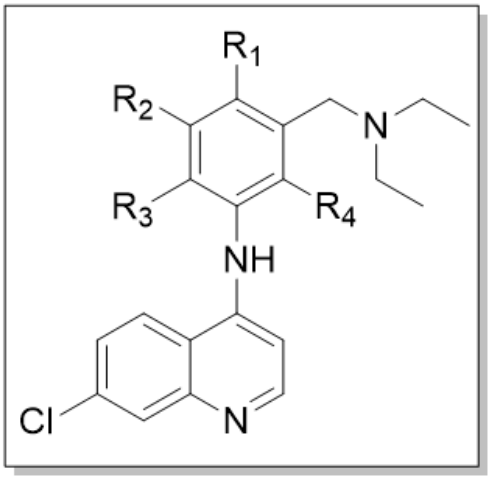
O'Neill and co-authors[42] reported on certain new tebuquine analogues' antimalarial activity (Figure-22). These new tebuquine analogues were made by changing the 4-OH function of tebuquine to fluorine or hydrogen and the side chain to tert-butyl or NH $(C_2H_5)_2$.

Figure-22



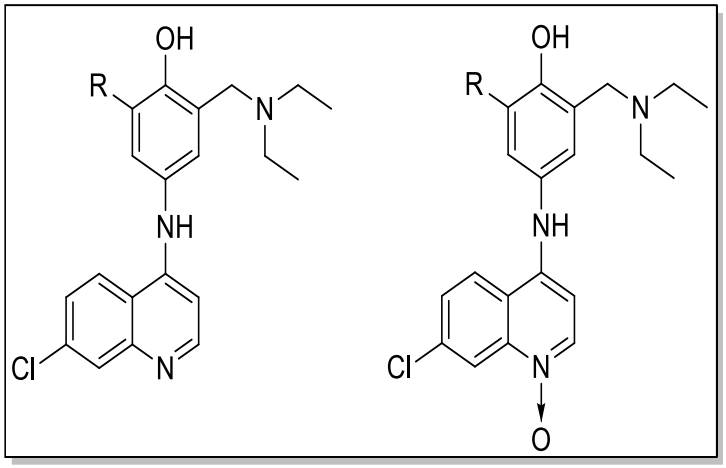
O'Neill and co-authors[43] studied the antimalarial properties of tebuquine's 4-OH-anilino side chains that had fluorine atoms swapped in them (Figure-23).

Figure-23



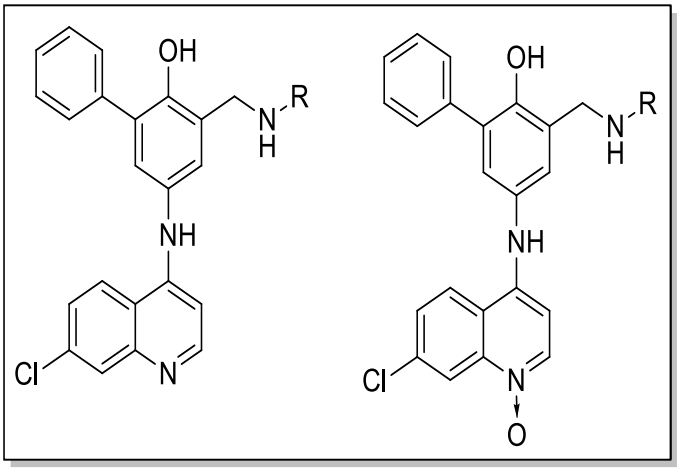
According to O'Neill and coauthors[44], resistant strains of chloroquine- K1 and sensitive strains of CQ- T9-96 of Plasmodium falciparum showed equal in vitro antimalarial activity to fluorinated analogues (Figure 24) as compared to amodiaquine.

Figure-24



The creation of 4-[(7-chloro-4-quinolinyl)-amino]-2[(diethylamino)methyl]-6-alkylphenols and N'-oxides with their antimalarial activity by Kesten and co-authors[45] (Figure-25).

Figure-25



Tebuquine was examined for its quantitative structure-activity connections by Werbel and co-authors[46], who also created several similar 5-[(7-chloro-4-quinolinyl)-amino]-3-[(alkylamino)-methyl] Biphenyl-1, 1' and N'-oxides (Figure 26) and documented their capacity to combat malaria.

Figure-26

1.10 Structure-Activity Relationship Studies of 4-Aminoquinolines

The key elements to take into account when creating 4-aminoquinoline derivatives that are active against chloroquine-resistant parasites are summarised in **Figure 27**.

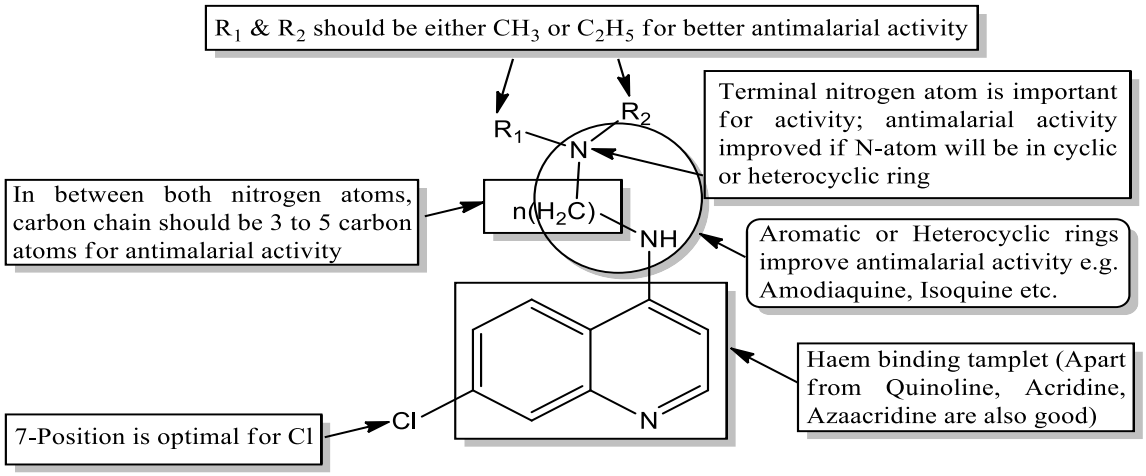


Fig 27: SAR of 4-Aminoquinoline derivatives

1.11 Aminoquinoline Resistance

In 1959, resistance to the effects of chloroquine was first documented in South America, followed by South-East Asia. Since then, resistance has expanded across the world's *P. falciparum* endemic regions. The discovery that chloroquine resistance emerged several years after its widespread usage has been cited to support the theory that it has a multigenic origin resulting from broad and persistent pharmacological pressure on parasite populations. According to biochemical investigations, chloroquine-resistant *P. falciparum* isolates collect less drug than their sensitive counterparts. Chloroquine is a diprotic weak base that accumulates in acidic compartments, as explained. The feeding vacuole of the parasite is acidic (pH 5.0), and based on the pH gradient between this compartment and the extracellular environment, standard Hasselbach calculations predict that chloroquine should accumulate 60,000-fold.

Consequently, drug resistance may arise from any mechanism that lowers drug accumulation. This may entail an increase in efflux, a decrease in absorption, or a mix of the two. Several plausible reasons exist for the changed absorption rate, including changes in transmembrane pH in resistant parasites, altered membrane permeability features, and, ironically, an efflux pump working prior to the cytosolic appearance of medication.

1.12 Drug Disposition

1.12.1 Chloroquine

Depending on the formulation supplied, chloroquine is readily absorbed from the gastrointestinal system and has a bioavailability between 80 and 90% after oral treatment. Peak plasma concentrations are reached 1 to 3.5 hours after intake. However, timeframes and concentrations are extremely dose-dependent.

1.13 Amodiaquine

Human amodiaquine metabolism has been extensively researched. However, due to a substantial first-pass impact, amodiaquine has limited bioavailability despite its high absorption from the digestive tract. The major plasma metabolite of DESAQ is its N-deethylated metabolite. DESAQ has been demonstrated to be as effective as amodiaquine against chloroquine-sensitive parasites in vitro.

1.14 Future Work

Since it is known that 4-aminoquinolines, including amodiaquine and chloroquine, may bind to FPIX, this fact gives a chemotherapeutic target for the further rational design of pharmacological analogues. Using de novo computer techniques and three-dimensional QSAR analysis (for example, comparative molecular-field analysis, COMFA), it may be possible to design novel drug compounds based on their capacity to bind to heme within the acidic food vacuole of the parasite. Again, this is something that can be done through the use of comparative molecular-field analysis.

2. CONCLUSION

We gathered a list of various aromatic and heterocyclic compounds with antimalarial activity in this article since we are interested in medicinal and organic chemistry. However, according to applied chemistry, selective heterocyclic scaffolds may be useful in creating a fresh antimalarial scaffold. The prevalence of heterocyclic moieties and the possibility of unfavourable effects with the method of action are two causes. This review paper focused on the medicinal chemistry and antimalarial potential of 4-aminoquinoline scaffolds. Chloroquine, primaquine, pamaquine, and artemisinins are some drugs used to treat malaria; however, numerous new compounds have proven even more efficient. This material will be helpful in the future in the search for new antimalarial drug leads.

3. ACKNOWLEDGEMENTS

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1.15 Competing interests

For this paper, the authors say they have no competing interests.

4. AUTHOR CONTRIBUTION STATEMENT

Dr. Bhupendra Singh and Dr. Mukesh Kumar Kumawat prepared the original draft of the review. Mr. Manoj Kumar Sharma, Dr. Narender Yadav provided valuable inputs towards the designing of the manuscript. All authors read and approved the final version of the manuscript.

5. CONFLICT OF INTEREST

Conflict of interest declared none.

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