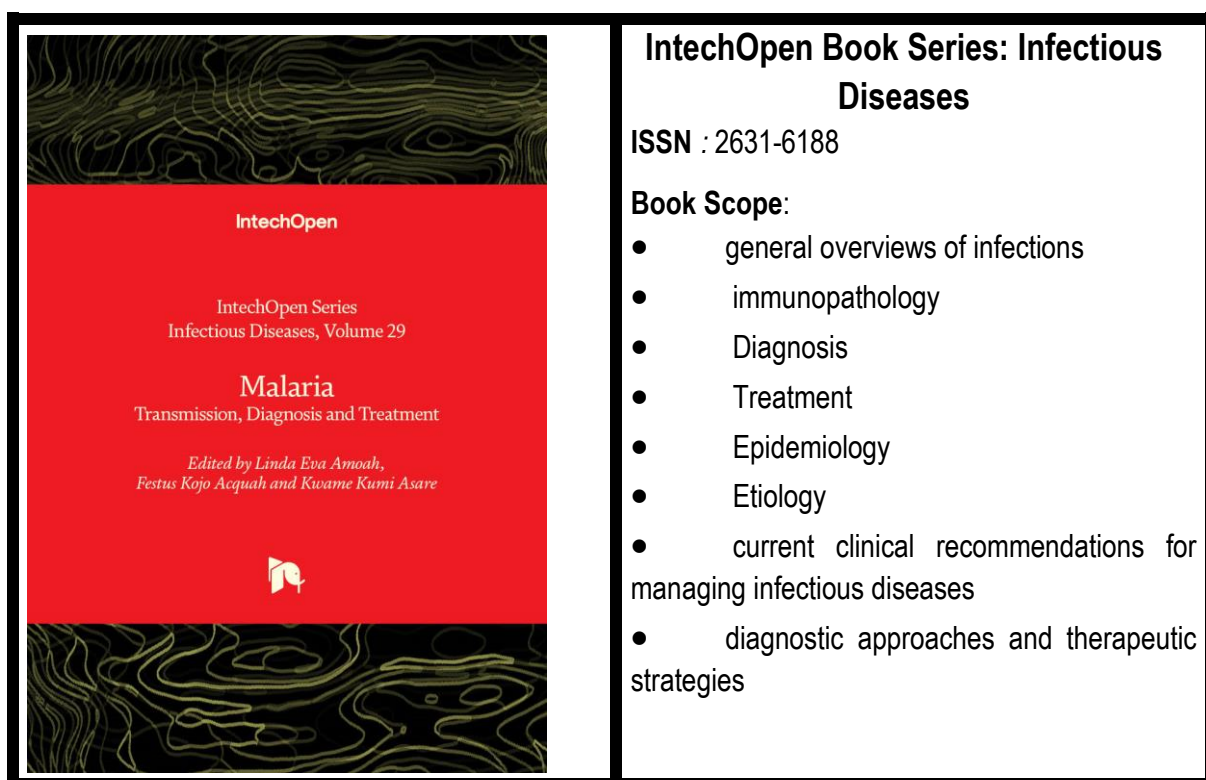


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Antimalarial Drugs with Quinoline Nucleus and Analogs. In Malaria-Transmission, Diagnosis and Treatment.

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Antimalarial Drugs with Quinoline Nucleus and Analogs

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Abstract

Quinoline core antimalarials are a major class used for the management of uncomplicated malaria in combination with artemisinin derivatives. Moreover, despite its adverse effects, Quinine remains the reference molecule in the treatment of cerebral malaria due to *Plasmodium falciparum*. This class also contains molecules such as Mefloquine used in the prevention of malaria. In addition, synthetic derivatives are more manageable with greater therapeutic margins and fewer adverse effects. They have an interest in avoiding the spread of resistance, especially with derivatives possessing gametocytocidal activities. With the presence of a chloroquine-resistant strain of *Plasmodium*, the use of synthetic derivatives as monotherapy is prohibited to avoid the spread of resistance in this class. In this chapter, we propose to present the class of antimalarials with a quinoline nucleus under its pharmacochemical aspects as well as the prospects for its development to preserve and improve the effectiveness of its representatives in the management of malaria.

Keywords: quinoline, *Plasmodium*, antiprotozoal, antimalarial, chloroquine resistance

1. Introduction

Malaria is one of the deadliest parasitic diseases. Global mortality from this disease has increased in recent years due to the impact of Covid-19. Indeed, since 2020, the WHO has reported more than 600,000 deaths each year, the majority of which occur in Africa and tropical regions [1]. This mosquito-borne parasitosis affects millions of people each year, with significant socio-economic consequences [2].

The therapeutic arsenal used to prevent and treat malaria mainly comprises, on the one hand, antimalarials with a quinoline nucleus and, on the other hand, artemisinin and its derivatives. All antimalarials work by interfering with the life cycle of plasmodium in the human body. They can target different stages of the parasite cycle, such as the reproduction of the parasite in the red blood cells, they are called erythrocytes schizonticides or their development in the liver, in the case of tissue schizonticides.

Antimalarial drugs with quinoline patterns and analogs constitute a homogeneous class of antiparasitic-antiprotozoal drugs. They are mostly of natural or synthetic origin. They proceed by blocking the growth of parasites of the genus *Plasmodium*, the causative agents of paludism or Malaria. They are used in the treatment of uncomplicated malaria and severe malaria. Quinine is an essential drug for the treatment of cerebral malaria because truly little resistance has been reported [2, 3].

From the point of view of their chemical constitution, they all have in their respective molecules the quinoline nucleus or a similar tricyclic unit.

Over time, the malaria parasite has developed resistance to certain antimalarials, in this case chloroquine. This has led to the appearance and proliferation of chloroquine-resistant strains of *Plasmodium* [4, 5]. This resistance has limited the effectiveness of these drugs in certain regions of the world, forcing the development of new therapeutic options.

Thus, the challenge for pharmacochemists has been to develop effective antimalarials on these resistant strains and to protect their effectiveness, in particular by drug combinations.

Finding effective treatments for malaria is therefore a global public health priority.

Understanding the chemistry and pharmacology of this class of drugs is essential to improving their efficacy and developing new therapeutic agents.

This chapter aims on the one hand to present the chemical aspects of quinoline core antimalarial drugs and their structural analogs; and on the other hand, to highlight the link that exists between the structural elements and their mechanisms of action or even their therapeutic implications, justifying their current use in the treatment of malaria.

2. Natural prototype: quinine

2.1 Structure and origin

2.1.1 Structure

Quinine is a 4-methanol quinoline derivative. It is characterized by the presence of four asymmetric carbons in its structure. Therefore, two forms are distinguished: the levogyre form and the dextrorotatory form. Only the levogyre form (quinine, **Figure 1**) has antimalarial properties. The dextrorotatory form (quinidine) has essentially antiarrhythmic properties. Quinine and quinidine are distinguished from each other based on methanolic carbon stereochemistry [2, 3].

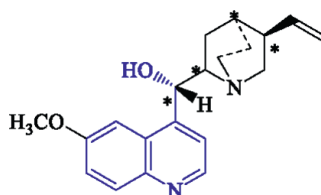


Figure 1.
Quinine (Quinimax®).

Quinine has a heterocyclic structure comprising four rings, two of which are aromatic in nature at the quinoline level and two in the bicyclic amine called quinuclidine. The presence of these rings gives quinine good hydrophobicity.

2.1.2 Origin

Quinine is an alkaloid extracted with quinidine, Cinchonine and Cinchonidine from cinchona bark of Peru in the form of sulfate. For the other salts: Quinine base released by treatment with NaOH then salified (Hydrohydrate, formate) [2, 6, 7].

2.2 Spectrum of action and limits of use

2.2.1 Action spectrum

Specificity: Quinine primarily targets the erythrocytic stage of the malaria parasite's life cycle and may not be effective against other stages (such as the liver stage). It is a fast-acting erythrocytic schizonticide acting on the endoerythrocytic forms of all Plasmodium species (*P. falciparum*, *P. vivax*, *P. malariae* and *P. ovale*). However, it is inactive on mature gametocytes of *P. falciparum* [2, 6].

2.2.2 Usage limits

- Limitation

The synthesis of quinine is long and expensive. Thus, it is not very profitable, so the quinine marketed is mainly extractive origin.

Quinine has a narrow therapeutic window. Indeed, the effective plasma concentration is between 2 and 5 µg/ml. In addition, the toxic concentration is around 7 µg/ml. Hence, the need to repeat the doses three times a day [8–11].

- Side effects

Quinine is an antimalarial drug with a long history of use. While it has been effective in treating malaria, it does have limitations and side effects, here are some of the associated aspects:

The most common side effects are:

- Gastrointestinal effects: this drug can cause nausea, vomiting, and abdominal pain.
- Cardiovascular effects: Quinine has been associated with cardiac arrhythmias and can have negative effects on the heart, especially when administered intravenously in high doses.
- Cinchonism: Quinine can cause a condition called cinchonism, characterized by symptoms such as tinnitus (ringing in the ears), headache, dizziness, and visual disturbances.

- Retinopathy: Prolonged use of chloroquine, particularly at high doses, may lead to retinopathy, which can affect vision [6].
- Reasons that led to the development of synthesis derivatives to overcome these drawbacks

The development of synthetic derivatives of antimalarial drugs was driven by several reasons, including the need to overcome limitations and improve the therapeutic properties of existing antimalarials. Here are some key reasons:

- Enhancing efficacy: Many natural antimalarial compounds, such as quinine from the cinchona tree, exhibited therapeutic properties but had limitations in terms of their efficacy. Hemisynthesis and synthesis of derivatives allowed modifications of the chemical structure to enhance the potency and effectiveness against malaria parasites [12–14].
- Overcoming resistance: The emergence of drug resistance in malaria parasites, particularly to drugs like chloroquine, necessitated the development of new compounds. By modifying the chemical structure through hemisynthesis and synthesis, researchers aimed to create derivatives with improved efficacy against drug-resistant strains of the malaria parasite [2, 9, 10].
- Improving safety and tolerability: Some natural antimalarial compounds may have significant side effects or toxicity when used at effective doses. Hemisynthesis and synthesis allowed for the modification of the chemical structure to retain antimalarial activity while reducing adverse effects or improving the drug's safety profile [8, 13].
- Pharmacokinetic properties: Hemisynthesis and synthesis of derivatives also focused on improving the pharmacokinetic properties of antimalarial drugs. This includes factors such as bioavailability, distribution in the body, metabolism, and elimination. Optimization of these properties can enhance the drug's efficacy and patient compliance [4, 14].

By exploring hemisynthesis and synthesis techniques, researchers can modify the chemical structure of natural antimalarial compounds to address these factors, ultimately leading to the development of more effective, safer, and commercially viable antimalarial drugs.

- Key points

Quinine is a natural molecule used in levogyre form.

It has a basic character due to the presence of its nitrogen atoms. This character is used for the preparation of water-soluble salts which can be administered intravenously.

Adverse effects are often dose-dependent. Moreover, the chemical synthesis of quinine is difficult and expensive. Hence the need to develop synthetic derivatives [2, 3, 6, 7].

3. Synthetic derivatives

This part is dedicated to the presentation of the different classes of quinoline antimalarial drugs according to their chemical structure.

3.1 Classification

Quinoline antimalarial drugs can be classified into several categories according to their chemical structure.

This classification is based on substituents on quinoline and the number of cycles. Indeed, there are four chemical series:

- 4-methanol quinolines (**Figure 2**)
- 4-amino quinolines (**Figure 3**)
- 8-amino quinolines (**Figure 4**)
- Tricyclic analogs (**Figure 5**)

3.2 Structures

Here are some of the major classes of quinoline antimalarial drugs and some examples of drugs in each class [3, 6–8, 15].

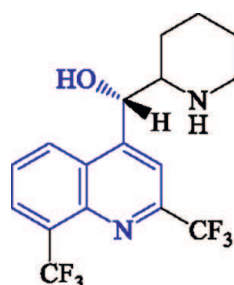
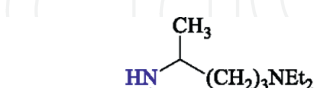
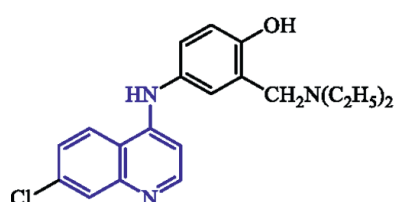


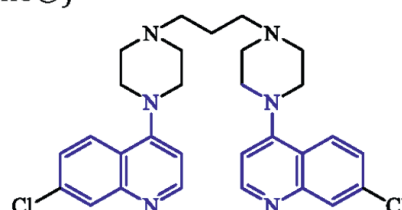
Figure 2.
Mefloquine (Lariam®).



Chloroquine (Nivaquine®)



Amodiaquine (Flavocine®)



Piperaquine (Eurartesim®)

Figure 3.
4-Aminoquinolines antimalarial.

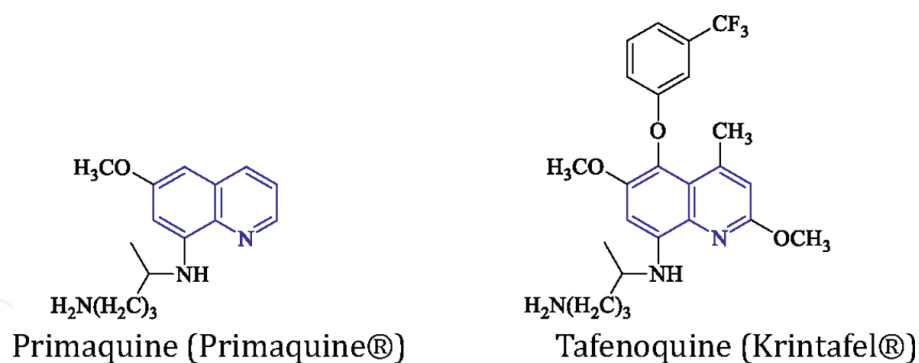


Figure 4.
8-Aminoquinolines antimalarial.

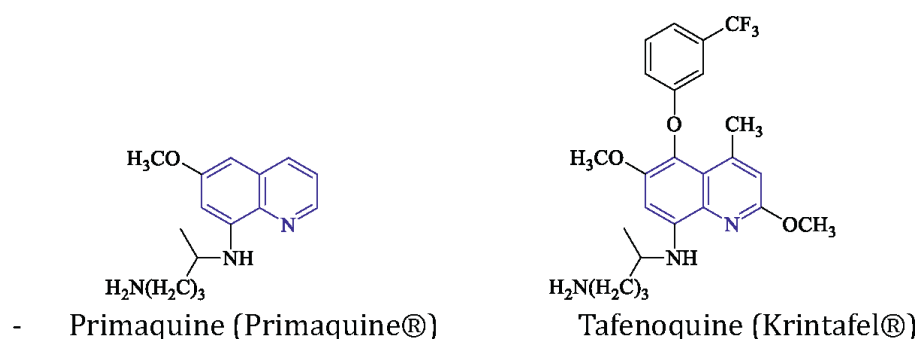


Figure 5.
Antimalarial agents with tricyclic nucleus.

3.2.1 4-Methanol quinolines

Mefloquine is a synthetic quinoline attached to a piperidine ring at the level of the methanolic chain at 4. In addition, we note the presence of two trifluoromethyl groups on the quinoline in position 2 and 8. All these ring and substituents make it possible to preserve the lipophilicity of the molecule.

3.2.2 4-Aminoquinolines

Chloroquine is an aminoquinoline derivative with an aliphatic diethylamine side chain on the amine at position 4. Amodiaquine has in its structure a diaminoalkyl side chain with a phenolic group. Piperaquine is a bisquinoline whose linker chain on the amines in position 4 has two piperazines.

3.2.3 8-Aminoquinolines

Tafenoquine (**Figure 4**) is a prodrug whose active form, obtained after metabolism, is quinone Tafenoquine. Primaquine has a Quinoline nucleus carrying a methoxyl group at 6 like quinine and an amine at 8. The side chain on this amine is aliphatic in nature with a terminal primary amine. Tafenoquine is distinguished by the presence in position 5 of the quinoline, a phenolic group carrying a trifluoromethyl.

3.2.4 Tricyclic analogs

- Lumefantrine (**Figure 5**) is a derivative with a fluorene nucleus, while pyronaridine is a 8-Azaacridine's derivative. Pyronaridine (**Figure 5**) is actually a 4-aminoquinoline fused to a pyridine. The side chain on the amine carries a phenolic ring doubly substituted by a methyl pyrrolidine chain. Lumefantrine is a synthetic aryl amino-alcohol compound that is structurally related to chloroquine by the presence of a butylamine chain [6, 15, 16].

4. Pharmacochemical aspects

4.1 Mechanism of action

8-Aminoquinolines, such as primaquine and tafenoquine, act primarily against the hypnozoite (dormant) forms of the *Plasmodium* parasite in the liver, making them particularly effective against the latent form of malaria caused by *Plasmodium vivax* and *Plasmodium ovale* [8, 12].

The precise mechanism of action of 8-aminoquinolines is not fully understood, but they are thought to interfere with the metabolism of heme, a molecule essential for parasite survival. 8-Aminoquinolines cause toxic heme buildup in parasites, which leads to oxidative damage and parasite death [12].

In contrast, other classes of antimalarials with a quinoline core, such as 4-aminoquinolines and quinine, have a different mechanism of action. They act primarily by inhibiting the polymerization of heme to hematozin, which leads to toxic accumulation of free heme in the parasites. This disrupts the metabolism of the parasite and ultimately leads to its death [8, 9].

4.2 Pharmacotherapeutic activity of the quinolines antimalarial

This chapter presents the exploration of the relationship between the chemical structure of quinoline antimalarial drugs and their pharmacological activity. The relationship between the chemical structure of quinoline antimalarial drugs and their pharmacological activity is complex and multifaceted. However, there are some general structural features that contribute to their antimalarial activity [2, 5, 7, 8, 12, 16]. Here are some key aspects.

4.2.1 Indispensable structural elements

- Quinoline core (**Figure 6**): Quinoline is a heterocyclic aromatic compound that forms the core structure of many antimalarial drugs, such as chloroquine and quinine.

Quinine works by binding to 18S ribosomal RNA, which is essential for parasite protein synthesis. This interaction disrupts the function of ribosomal RNA, thus inhibiting the normal protein synthesis of the parasite and leading to its death [2, 8, 17].

More specifically, the quinoline core of quinine is involved in π - π interactions with specific nucleotide bases of 18S ribosomal RNA. These π - π interactions involve the pi (π) electrons from the aromatic rings of the quinoline nucleus and the pi (π) electrons

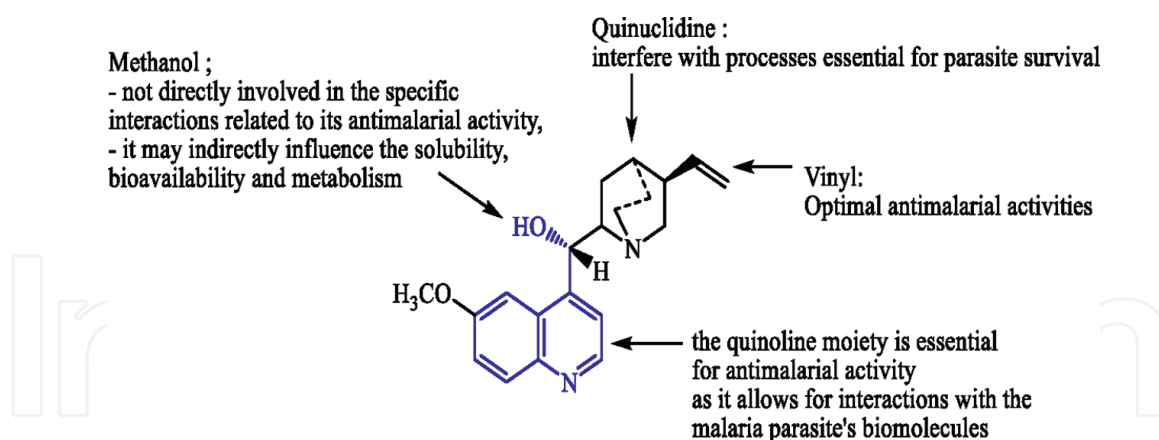


Figure 6.
Summary of SAR of quinine.

from the nucleotide bases of RNA. This pi- π bond stabilizes the bond between quinine and ribosomal RNA, thus promoting the inhibition of protein synthesis [2, 8, 16].

Additionally, the quinoline core of quinine can form hydrogen bonds with specific residues of ribosomal RNA, thereby enhancing the ligand-receptor interaction [2, 8, 16].

- The vinyl group (**Figure 6**) and the quinuclidine ring of quinine play a key role by causing its antimalarial activities. The vinyl group is involved in interactions with the ion channels of the parasite, while the quinuclidine ring allows binding to specific proteins or receptors of the parasite. The stereochemistry of the quinuclidine ring is also important for quinine activity. In fact, the vinyl group, allows quinine to interact with specific cellular targets of the malaria parasite, such as the ion channels present in the membranes of the parasite. These interactions can disrupt ion flow and other vital processes within the parasite, leading to its death or inability to grow and reproduce [6].
- The quinuclidine ring (**Figure 6**), which is a cyclic structure containing a nitrogen atom, also confers antimalarial properties to quinine. This structure is important for the binding of quinine to certain specific parasite proteins or receptors. For example, quinuclidine can bind to parasite proteins involved in ion transport, pH regulation, and other processes essential for parasite survival. Furthermore, the quinuclidine ring of quinine also contributes to its stereochemistry, which means that its spatial configuration is important for its antimalarial activity. Studies have shown that the specific configuration of certain atoms in the quinuclidine ring is crucial for the interaction of quinine with its cellular targets and for its antimalarial efficacy [6, 13].
- The methanol group (**Figure 6**) is a substituent present in the structure of quinine. It is not directly involved in the specific interactions between quinine and the cellular targets of the malaria parasite. These interactions are mainly mediated by other parts of the quinine molecule, such as the quinuclidine ring and the vinyl group [6, 13].

However, the presence of the methanol group can have an impact on the solubility of quinine in biological solvents and pharmaceutical formulations. Good solubility of quinine is essential so that it can be well absorbed in the body after administration

and reach the desired sites of action. Solubility can also affect the release rate and distribution of quinine in tissues.

Furthermore, the methanol moiety may also be involved in the metabolic reactions of quinine in the body. Quinine undergoes metabolism and elimination processes in the liver and kidneys, and functional groups such as methanol may play a role in these processes [6, 12, 13].

Overall, the presence of four cycles in quinoline and quinuclidine nucleus allows this molecule to increase the hydrophobicity of the molecule as well as good crossing of the blood-brain barrier. This particularity is relevant in the treatment of cerebral malaria [6, 12, 13].

In some national therapeutic protocols for the management of malaria, Quinine by IV infusion is used to manage severe malaria. In pregnant women, Quinine *per os* is used first [12].

4.2.2 4-methanolquinoline series

- Molecular simplification of quinuclidine

The addition of trifluoromethyl groups (**Figure 7**) to mefloquine was carried out with the aim of improving its antimalarial activity and increasing its lipophilicity, which promotes its penetration into cells infected by the parasite responsible for malaria (*Plasmodium*). Trifluoromethyl groups may influence the interaction of mefloquine with its specific cellular targets, such as ion channels, receptors, or enzymes involved in parasite metabolism [6, 12]. It has increased potency against chloroquine-resistant strains of malaria and has a prolonged half-life compared to quinine.

Regarding the potential CNS toxicity of mefloquine, trifluoromethyl groups may play a role in this property. Mefloquine can cross the blood-brain barrier and bind to receptors in the brain, which can cause neurological side effects in some individuals. Trifluoromethyl groups can influence the affinity of mefloquine for these receptors and thus modulate its effect on the central nervous system [6, 12, 13].

4.2.3 Aminoquinolines

Aminoquinoline derivatives, such as chloroquine and amodiaquine, have an amino group attached to the quinoline ring. This amino group is thought to be crucial for the drugs' antimalarial activity. It helps in the accumulation of the drug within the parasite's acidic digestive vacuole, disrupting its physiological processes [12, 13].

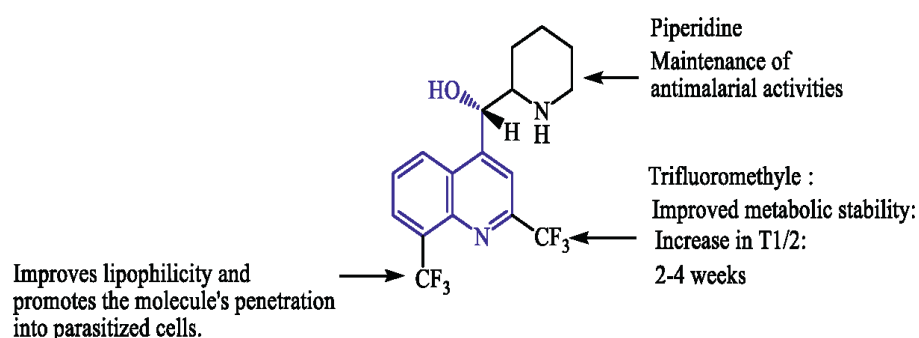


Figure 7.
Summary of SAR of mefloquine.

- The chlorine atom of chloroquine (**Figure 8**) is responsible for several key interactions with the biological target, namely the malaria parasite. These interactions are mainly mediated by chemical bonds and intermolecular forces between chlorine and the specific components of the parasite [6, 13].
- More precisely, the chlorine atom of chloroquine is involved in interactions with the nucleic acid of the parasite, in particular DNA. It binds to nucleobases, thereby disrupting the structure and function of parasitic DNA. This DNA disruption leads to damage at the genetic level, preventing the replication of the parasite and ultimately leading to its death [6].
- In addition, the chlorine atom of chloroquine can also interact with other cellular components of the parasite, such as proteins essential for its survival. These additional interactions contribute to the effectiveness of chloroquine as an antimalarial agent [12, 13].

It should be noted that the precise mechanisms by which chloroquine interacts with *Plasmodium* are complex and are still the subject of extensive research. However, it is well established that the presence of the chlorine atom in the structure of chloroquine is crucial for its antimalarial activity by specifically targeting the parasite and disrupting its vital processes [6, 12, 13].

- Basicity and ionization: The basicity of the nitrogen atom in the quinoline ring in chloroquine affects the molecule's ability to interact with acidic compartments, including the nutrient vacuole of the malaria parasite. Indeed, it is an antimalarial with a quinoline nucleus having a weak base character, allowing the trapping of ions in the acid vacuole of the parasite and preventing the phenomenon of efflux [6, 12, 13].
- The tertiary amine of the diamino alkyl chain gives chloroquine basic properties, which facilitates its diffusion through the cell membranes of the parasite when it is in non-ionized form. Moreover, in ionized form under the acidic conditions of the food vacuole, this tertiary amine plays a crucial role in the inhibition of the formation of β -hematin by ionic interaction and in the accumulation of the molecule within *Plasmodium* [6, 12, 13].

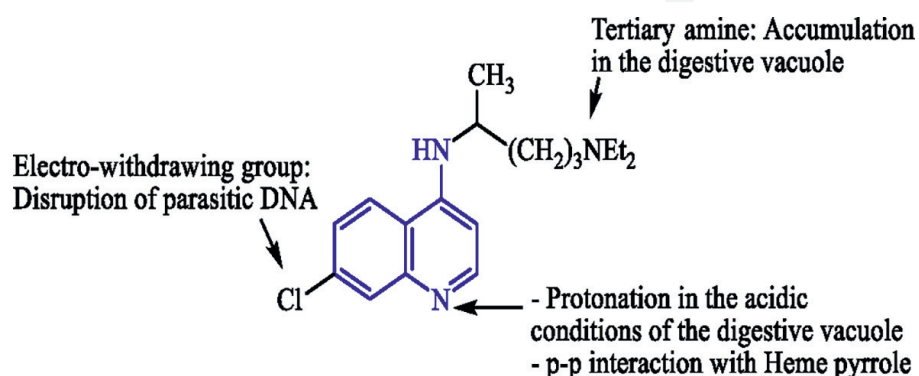


Figure 8.
Summary of SAR of chloroquine.

The main limit of the use of chloroquine was the appearance and development of resistance in many parts of the world, particularly in areas with high levels of malaria transmission. *Plasmodium falciparum* strains with mutations in the chloroquine target protein, known as *P. falciparum* chloroquine resistance transporter (PfCRT), are less susceptible to the drug's action [2, 9–11].

In short, the first two molecules obtained by pharmacomodulation of the basic structure of Quinine with the aim of having on the one hand molecules of easy chemical access, and on the other hand more manageable molecules with a wide therapeutic margin were Mefloquine and Chloroquine [2].

Indeed, it appeared that Mefloquine exhibited increased neurotoxicity, and a long half-life and was sold at a high cost. This led to the decline of the 4-methanol-quinoline series [2].

Chloroquine was less toxic than Quinine. However, the emergence of chloroquine drug-resistant *P. falciparum* has also shown the limit of this series of 4-aminoquinolines. Thus, other pharmacomodulations were undertaken in this last series, with the aim of improving antimalarial activity on gametocytes, intrahepatic forms and reducing toxicity [2, 11].

Since then, two main modulations have been undertaken by pharmacochemists on the structure of chloroquine. One at the diaminoalkyl chain, the other at the position of the amine function.

4.3 Structural modifications of the quinoline structures and its antimalaria potency

Structural modifications have been made to chloroquine to improve its antimalarial activity against resistant strains or enhance its pharmacokinetic properties. Here are some examples.

4.3.1 Incorporation of an aromatic ring into the diaminoalkyl chain

The introduction of side chain modifications of chloroquine may enhance its antimalarial activity. Indeed, the cyclization of the butyl side chain to a phenyl-like aryl chain results in the synthesis of Amodiaquine, which exhibits increased potency against resistant strains of malaria. In addition, this derivative also has a reduced toxicity compared to chloroquine [4, 16].

4.3.2 Changing the length of the aminoalkyl chain

The incorporation of the nitrogen of the aminoalkyl chain in a piperazine cycle, associated with the duplication of the 7-chloroquinoline motif, led to the production of Piperaquine.

Piperaquine (**Figure 3**) is a bisquinoline derivative containing two quinoline rings linked by a piperazine linker. The presence of its six nitrogen atoms, would allow a better accumulation in the digestive vacuole by protonation. It has improved pharmacokinetic properties and is effective against chloroquine-resistant strains due to its stability against efflux [16].

4.3.3 Displacement of the diaminoalkyl chain in position 8

Primaquine (**Figure 9**) is an 8-aminoquinoline derivative, currently used for the treatment of *Plasmodium vivax* and *Plasmodium ovale* malaria. Interestingly, it is

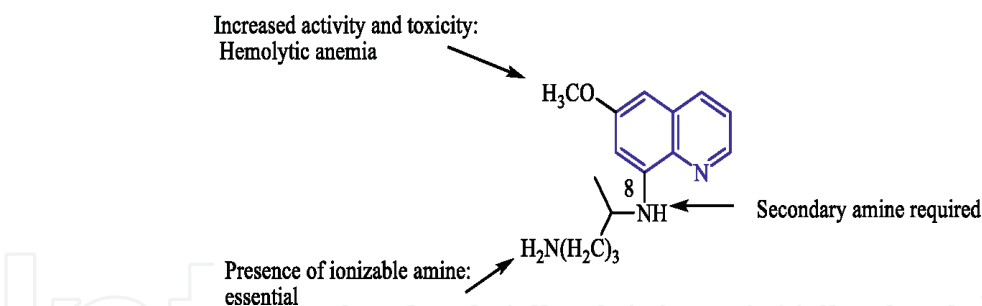


Figure 9.
Summary of SAR on primaquine.

active on *Plasmodium falciparum* gametocytes and active on hepatic hypnozoite forms and has been used for malarial prophylaxis [4, 16].

Tafenoquine is structurally related to primaquine and is approved for the prevention of relapse of *Plasmodium vivax* malaria, when co-administered with chloroquine. It exhibits potent activity against *Plasmodium vivax* and *Plasmodium falciparum*, including drug-resistant strains. Tafenoquine has a long half-life, allowing for a single-dose treatment option [4, 16].

4.3.4 Isosteric replacements

Replacing the quinoline ring with tricyclic isosteres such as a pyridoquinoline (Aza-acridine) or fluorene ring in compounds like pyronaridine and lumefantrine (**Figure 5**) has led to increased antimalarial activity. The presence of these isosteric nuclei gives these molecules special features in terms of their mechanism of action [2, 4, 13, 16, 18].

- The pyronaridine is an aminoalkoxy derivative having an aza-acridine core that would act as a facilitator of pi-pi interactions, helping to block the biopolymerization of β -hematin into hemozoin, and thus facilitating the accumulation of toxic hematin in the digestive vacuole of the parasite [2, 4, 13, 16, 18].
- The fluorene ring of lumefantrine would play a key role by increasing the solubility of the molecule in lipids, which facilitates its incorporation into the membranes of the parasites responsible for malaria. This interaction with parasitic membranes contributes to its accumulation in fatty tissue and prolongs the half-life of lumefantrine to 4–6 days [2, 4, 13, 16, 18].
- The aminoalkyl alcohol side chain of Lumefantrine would have the ability to associate with heme, a hemoglobin degradation molecule. The interaction between lumefantrine and heme disrupts the process of heme degradation, leading to toxic accumulation of heme in the parasite and thus causing its death. This molecule exhibits improved pharmacokinetic properties, such as better absorption and a longer half-life than chloroquine. It is used in combination with artemether as a first-line treatment for uncomplicated malaria [2, 4, 13, 16, 18].

These examples highlight the successful application of structural modifications to the chloroquine scaffold to improve antimalarial activity and overcome drug resistance.

In summary, RSA studies have shown that the quinoline nucleus contributes to the onset and maintenance of antimalarial activity, by contributing to the inhibition of the formation of hemozoin from the heme of parasitized erythrocytes.

The increase in the number of nitrogen atoms will contribute to better activity on resistant *Plasmodium* strains.

4.4 Principles of combinations of antimalarials based on artemisinin derivatives

Quinoline derivatives have been widely used in combination therapies for the treatment of malaria.

The antimalarial combination refers to the use of two or more antimalarial drugs with different mechanisms of action to treat malaria. This approach is used to improve the effectiveness of treatment, delays the development of drug resistance and improves the speed of remission of patients.

Indeed, when two or more drugs with different mechanisms of action are used together, the likelihood of a parasite acquiring resistance to all drugs simultaneously is greatly reduced. It is thus more difficult for resistant strains to emerge and spread in the population. Artemisinin derivatives have a short half-life, which means they are eliminated quickly from the body. By combining them with quinoline derivative drugs with a longer half-life, the selection pressure on the parasites is reduced, thus limiting the emergence of resistance. In addition, by using combinations, the effectiveness of quinoline drugs can be preserved for a longer time [6, 12].

- **Synergistic action:** The drugs in the combination work together, enhancing their individual activities and improving overall antimalarial efficacy. Synergy occurs when the combined action of the drugs is greater than the sum of their individual effects. This synergistic interaction can lead to increased parasite killing, faster clearance of the infection, and improved treatment outcomes.

This is the case with artemisinin derivatives. Artemisinin derivatives have a rapid and powerful action against the parasites responsible for malaria. They quickly reduce the parasite load in the blood, which can quickly relieve symptoms and prevent serious complications. By combining quinoline drugs with other antimalarials, the overall efficacy is enhanced by attacking the parasites at different stages of their life cycle, leading to better parasite clearance and improved treatment outcomes. Combination antimalarials have shown higher efficacy in the treatment of uncomplicated malaria compared to monotherapy [6, 12].

- **Broadening activity spectrum:** Combination therapies can extend coverage against different species of *Plasmodium* parasites. Certain quinoline derivatives, such as Amodiaquine are effective against certain species like *Plasmodium falciparum*, while primaquine, is more active against *Plasmodium vivax* and artemisinin derivatives are particularly effective against the early stages of the parasite. By combining drugs with complementary activity profiles, the treatment can effectively target multiple malaria species, providing broader coverage and improving the chances of elimination of the parasite [6, 12].
- **Reduced treatment failure rates:** By using drugs with different pharmacokinetic properties, the combination can provide longer-lasting effects and maintain

effective drug levels in the body, improving treatment outcomes and reducing the risk of recurrent infections [6, 12].

The mechanisms of action of combination antimalarials involving quinoline drugs can vary depending on the specific drugs used. However, some common mechanisms include [6, 12]:

- Artemether-lumefantrine: This combination therapy consists of artemether, an artemisinin derivative, and lumefantrine, a quinoline derivative. It is widely used as a first-line treatment for uncomplicated malaria caused by *Plasmodium falciparum*.
- Dihydroartemisinin-piperaquine: This combination therapy involves dihydroartemisinin, an artemisinin derivative, and piperaquine, a bisquinoline derivative. It combines the rapid action of artemisinin with the longer-lasting effect of piperaquine. The combination is effective against drug-resistant strains of malaria and has been widely used as a first-line treatment.

Overall, combination antimalarials, including those involving quinoline drugs, provide increased efficacy, delayed development of drug resistance, synergistic effects, and a broader spectrum of activity. These advantages make them valuable in the treatment of uncomplicated malaria, improving patient outcomes and helping to combat the challenges posed by drug-resistant malaria strains. Despite some particular side effects limiting their use such as risk of mental confusion, vertigo, hallucination with Mefloquine; hematological disorders and liver toxicity with Amodiaquine; or even allergic manifestations such as skin erythema or photosensitization with quinine, antimalarials with a quinoline nucleus retain a place of choice in the treatment of malaria.

5. New directions in the medicinal chemistry of quinoline core antimalarials

In the area of the medicinal chemistry of quinoline core antimalarials, several advances have been made. Their objective is to improve the efficacy, safety of use and sustainably preserve these drugs from resistance. Here are some examples of notable advances:

- Development of new antimalarial derivatives: By carrying out specific structural modifications, researchers have obtained new derivatives with a quinoline nucleus with improved antimalarial activities. These modifications consisted of the introduction of atoms or functional groups on the quinoline nucleus in order to improve the antimalarial activity [19, 20].
- Combinatorial approach: Pharmacochemists are exploring how to use the chemical library and combinatorial chemistry to generate a wide range of quinoline core compounds and select those that show promising antimalarial activity. This chemoinformatics approach has led to faster discovery of new antimalarial drug candidates [4, 5, 13, 19, 20].
- Anti-resistance strategies: among the strategies for circumventing resistance to current antimalarials, some researchers propose designing compounds capable of targeting several metabolic pathways in *Plasmodium* [2, 20];

- Treatment personalization approach: The objective sought by adopting a personalized medicine approach is to identify the genetic markers of *Plasmodium* allowing the identification of the optimal treatment for each individual, taking into account the effectiveness of the drugs and the factors related to resistance [21].
- Optimization of pharmacokinetic properties: In order to ensure a sufficient concentration of the drug in infected tissues and to reduce side effects, pharmacologists are working to improve the pharmacokinetic characteristics of antimalarials with a quinoline core, such as bioavailability, tissue distribution and half-life [13, 14].

These advances in the medicinal chemistry of quinoline antimalarials offer new perspectives for the development of more effective, safer and longer-lasting treatments for malaria. It should be noted, however, that research in this area is constantly evolving and new discoveries and innovations are likely to occur in the future.

6. Conclusion

Antimalarial drugs with quinoline patterns and analogs are a major class of antimalarial whose importance in the management of all forms of malaria has not diminished since the discovery of quinine in 1820.

The use of early quinoline core antimalarials such as chloroquine and mefloquine was associated with certain drawbacks, which motivated the development of other synthetic derivatives. Here are some of these disadvantages:

- Parasite resistance: Over time, the malaria parasite has developed resistance to certain antimalarials with a quinoline core, including chloroquine. This resistance has limited the effectiveness of these drugs in certain regions of the world, forcing the development of new therapeutic options.
- Some adverse effects specific to certain molecules limit their use in certain circumstances. Early quinoline core antimalarials showed adverse effects in some patients. For example, chloroquine can cause gastrointestinal upset, visual disturbances, and heart problems in some people. Mefloquine is also associated with side effects such as neuropsychiatric disorders, dizziness and sleep disturbances.

These disadvantages led to the research and development of new synthetic derivatives of antimalarials, such as amodiaquine, piperaquine, and pyronaridine, showing increased efficacy against malaria and better tolerance in many patients. These new therapeutic options contributed to improving the management of malaria and dealing with emerging parasitic resistance.

The quinoline nucleus remains essential for obtaining the antimalarial activities of the representatives of this class. It is necessary to respect the national protocol for the fight against malaria which proposes effective therapeutic combinations considering the characteristics of resistance specific to each population.

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