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CLINICAL REVIEW

A Review on the Importance of the Quinoline Ring in the Preparation of New Antimalarial Drugs

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ABSTRACT

Malaria is a problem whose history exceeds the length of human life on earth. This disease is caused by a plasmodium protozoan in red blood cells and is transmitted through the bite of an infected female Anopheles mosquito and causes fever and chills. Many drugs have been mentioned for this disease, but the newest one is artemisinin.

According to the statistics of the World Health Organization, malaria is being transmitted in more than 104 countries of the world. Currently, there are many problems to fight this disease and to control and eliminate it, one of the most important of which is the resistance of the parasite to the malaria drugs available in the market. Therefore, it is necessary to find an alternative drug with a new structure and a different mechanism of action. For this reason, scientists and researchers have focused on heterocyclic rings. With the aim of finding new drugs with a different mechanism of action compared to existing drugs. to synthesize various derivatives and investigate their antimalarial activities on different stages of parasite growth. Meanwhile, the compounds with quinolone ring with different substitutions in different positions of the ring showed a good effect on the blood, liver and sexual stages of the parasite. Therefore, considering the affinity of these compounds on the different growth stages of the malaria parasite as a guide combination for Finding new antimalarial drugs with different mechanism of action were further evaluated and investigated.

In this review article, considering the importance of this issue, we introduced some quinolone derivatives with antimalarial effect.

KEYWORDS

Decoquinate; Quinolone ring; Antimalarial; Endochin; *Plasmodium falciparum*

INTRODUCTION

Malaria is an acute or chronic infectious disease caused by a single-celled parasite of the genus Plasmodium. This disease is endemic in many African, Asian, and American countries, and despite the control of the disease in recent years, due to various reasons, such as: the number of carriers, the resistance of carriers to insecticides, the resistance of Plasmodium parasite to existing drugs, the warming trend of Korea, the transmission season. long and finally the social, cultural and economic factors of the involved countries, this disease remains as a health problem at the global level [1-3]. According to the statistics of the World Health Organization, 198 million people contracted malaria and 584,000 deaths occurred in 2013 [4]. Five types of malaria parasites cause disease in humans, which are: *Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale, Plasmodium malariae and Plasmodium novelzi*. The deadliest type of malaria is Plasmodium falciparum. Mortality caused by Plasmodium falciparum cerebral malaria, especially in children under five years of age, susceptible adults, and pregnant women, is considered the main cause of death in these vulnerable groups [4]. Eradication of the World Health Organization is up to 2050. Today, the incidence of this disease is increasing due to the emergence of resistance to existing drugs and insecticides, and the acquisition of new effective drugs that lead to radical treatment or are effective in prevention and lead to epidemic control is a part of the programs of Jahfani Health Organization in Hazafani. It is the eradication of malaria. Unfortunately, one of the most important reasons for the lack of success in the malaria eradication program so far, in the first step is parasite resistance to chloroquine as the cheapest and best anti-malarial drug and resistance to inexpensive insecticides such as D.D.T. Also, during the following years, parasites, especially Plasmodium falciparum, have become resistant to other anti-malarial drugs, and in the absence of a new effective drug, they have faced a serious problem in controlling this disease. These reasons make the need to find an alternative medicine unavoidable. During the parasite's life cycle, the Anopheles mosquito inoculates Plasmodium sporozoites into humans, which are the initiators of human infection (Figure 1) [3]. These sporozoites enter the liver cells through the bloodstream. In the liver, after the tissue schizonts mature, the merozoites are released and enter the blood stream and then enter the red blood cells. Then, by forming a ring, they become a trophozoite and finally a bloody schizont. Next, by tearing red blood cells, schizonts enter the bloodstream and infect other red blood cells. Some of these blood schizonts become gametocytes. By feeding the mosquito with infected human blood, sex cells are introduced into the mosquito's body and the life cycle of the parasite begins. Only parasites inside the erythrocyte cause clinical disease. Repeated cycles of infection can lead to severe disease by infecting a large number of erythrocytes.

The effective drug chloroquine was used as a strong blood schizonticide from 1940 AD in the treatment and prevention of malaria in all types of diseases; But due to the emergence of resistance in the early 1960s, its use for Plasmodium falciparum has decreased. The reason for this early resistance is due to monotherapy, drug pressure resulting from frequent and inappropriate use of chloroquine, long time of its use and high doses used in prophylaxis. Today, it is known that resistance to chloroquine in Plasmodium falciparum is caused by mutations in the vital transporter genes ˙fCRT and ˙fMDRT, which are the cause of reducing the concentration of chloroquine in the target tissue [5]. With the emergence of cross-resistance between Amodiaquine and Mefloquine and Chloroquine, all of which are antimalarial derivatives with quinoline active core, the above problems were added (Figure 2). On the other hand, the tissue schizonticide drug primaquine and the blood schizonticide artemisinin with gametocidal effect in epidemic control are considered ideal targets in malaria elimination (Figure 2); But

unfortunately, the resistance to artemisinin and tolerance to primaquine is also increasing and it is inevitable to find new effective drugs. The emergence of the above problems prompted researchers to develop new analogs with different action mechanisms.

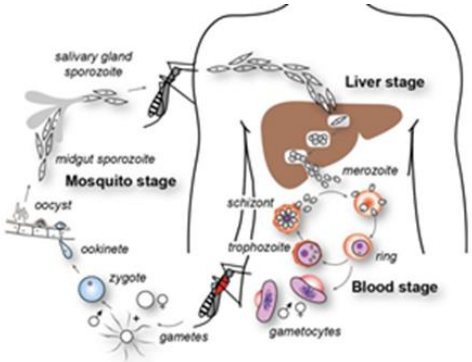

Figure 1: Malaria parasite life cycle (http://jcb.rupress.org/content/198/6/961/F1.large.jpg)

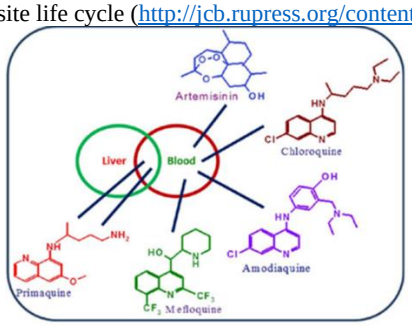

Figure 2: Common antimalarial drugs effective on the blood and liver stages of the malaria parasite.

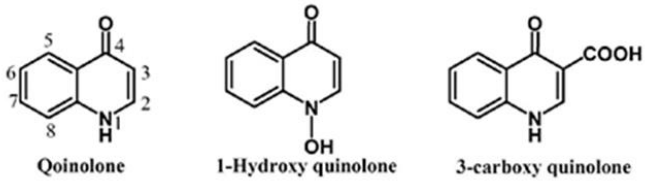

Figure 3: The structure of quinolone analogues design and synthesis.

In one of the solutions, the quinoline ring was replaced with other heteroaromatic rings and new analogues were synthesized and the effect of these new compounds on the malaria parasite was evaluated in vitro and in vivo. One of these active heteroaromatic structures is the quinolone ring (Figure 3). Compounds with a quinolone ring such as Endochin (Endochin 1) (Figure 4) were effective against the malaria parasite [6]. The lack of activity of this compound in in vivo conditions prompted researchers to obtain more effective derivatives by making changes in its structure. In this direction, the replacement of the aliphatic substitution of indochine in the 3rd region with aromatic substitutions and the substitution of halogen atoms in the 5th or 6th ring region led to the strengthening of the antimalarial effect in these derivatives [7-9]. Also, compounds with the simple structure of 1-hydroxyquinolone (Figure 3) were used as another template for the synthesis of new quinolone analogs [10]. By replacing the aromatic groups in the 2nd ring region of hydroxyquinolone, they obtained effective compounds against malaria in vitro and in vivo [10-12]. Next, the antimalarial activity of compounds with 3-carboxyquinolone structure (Figure 3) and research on this structure led to the effective drug DQ (Decoquinate) (Figure 6) with remarkable activity on different stages of the parasite [13- 17].

Introduction Of Quinolone Structure

Quinolone or 4-hydroxyquinoline is a common structure in quinolone antibiotics. A number of quinolone derivatives have been synthesized and have shown various anticancer [18], antiviral [19], antibacterial [20] and antioxidant [21] effects. The effect of compounds containing the heterocycle quinolone ring with antibacterial effect has been evaluated by a number of research groups on the malaria parasite, and many of these derivatives have shown a very good effect against different stages of haematological, hepatic, and gamy parasites [2]. It seems that these compounds have a different mechanism of action compared to existing antimalarial drugs; Therefore, according to the importance of the subject and the importance of presenting the research works in the form of review articles [23], this article introduces a number of compounds containing the quinolone ring and effective against malaria.

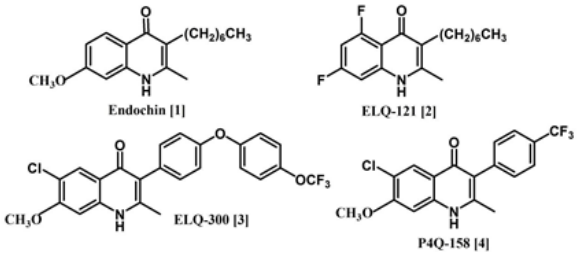

Figure 4: Structure of compounds 1-4 [7-9].

Endochin and its Analogues

The activity of combined endochin with quinoline structure was proposed against avian malaria in 1948 [6]. This combination was effective on both the blood and liver stages of the parasite. Further research showed that endochin affects the parasite's CYPbc1 complex with a different mechanism of action than common antimalarial drugs [20]. Unfortunately, in vivo studies on human malaria confirmed the inactivity of this compound. Research showed that this compound is easily metabolized and deactivated by CYP450 enzymes [24,25]. However, endochin (1) was chosen as the lead compound and various analogs of it were synthesized by researchers and against the malaria parasite. were evaluated (Figure 4). Winter and his colleagues optimized some indochine analogs. One of the most effective compounds (2) is ELQ-121 with fluorine substitutions in positions 5 and 7 of the quinolone ring. This compound has IC50 = 0.1 nM was more effective against D6 (chloroquine-sensitive strain) and Dd2 (chloroquine-resistant strain) strains of Plasmodium falciparum than endochin with IC50 = 4 nM against these two strains. Another advantage of this compound is its stability against CYP450 enzymes [23]. Nilsen and his colleagues synthesized some quinolone-3-diaryl ether derivatives and compound (3) ELQ-300 with chlorine atom substitution at position 6 and trifluoromethoxy diphenyl ether-4 substitution at position 3 of the quinolone ring. instead of the normal heptyl chain in Endochin, in addition to metabolic stability with IC50 = 1.7 nM against strain W2 (chloroquine-resistant strain) and IC50 = 1.8 nM against strain TM90-C2B (atvaquone-resistant strain) in comparison with chloroquine. IC50 = 126 nM and IC50 = 2.96 nM against W2 and TM90-(C2B) strains showed a much higher potency [7]. This compound also showed a high potency at a concentration of 0.1 nM with a complete stop of the development of stages I and II of gametocytes. Compound (3) ELQ-300 is also active with IC50 = 1.79 nM against stage IV gametocytes in *in vivo* studies.

It showed EC50 = 0.02 (mg/kg/day) against Plasmodium Yoelii, and at a dose of 0.3 mg/kg/day, within 30 days after infection in infected mouse models, parasitism was completely eradicated. The most important point about this combination is the lack of cross-resistance with atovaquone and high selectivity for Parasite respiratory bc1

complex with SI ≥20000. Considering the mentioned merits, this compound is under formulation to be examined in clinical phases [8].

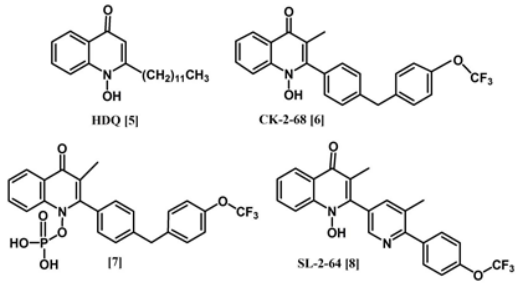

Figure 5: Structure of compounds 8-5 [10-12].

Lacrue and his colleagues synthesized some quinolone analogs and investigated their effect on the liver stage of *Plasmodium berghei*. In analog (4) P4Q-158, chlorine atom is substituted in position 6 of the quinolone ring and in position 3 of this ring. Trifluorotoluene is a substitute for normal heptyl in endochin. Examining the in vitro activity of this compound with IC50 = 3.07 nM against the liver stage of the parasite *Plasmodium berghei* indicates the strong antimalarial activity of this compound. On the other hand, examining the in vivo activity of this compound against the liver stage of *Plasmodium berghei* at a dose of 10 mg/kg, showed a survival rate higher than 60% in comparison with untreated mice. Endochin and the displacement of the 3-position chain with the aromatic part have affected the improvement of the antimalarial activity of these derivatives (Figure 4).

The compound Hydroxy-2-dodecyl-(1-4-hydro)-quinolone HDQ [5] is considered a multi-purpose inhibitory compound that inhibits the ubiquinone oxidoreductase enzyme NADH and the bc1 complex in the respiratory chain of Plasmodium falciparum, it is definitely a more effective combination than a single target inhibitor (Figure 5). The use of such compounds delays the onset of drug resistance [10]. Having these advantages, HDQ was considered by the researchers as another guide compound. As a result, various analogs were synthesized from it, and some of the most important analogs are mentioned below.

By substituting (trifluoromethoxy) benzyl instead of normal dodecyl in position 2 of the HDQ compound, the active compound (6) 68CK-2- was obtained. In vitro studies of this compound, IC50 = 31 nM against 3D7 strain (chloroquine sensitive strain) of *Plasmodium falciparum* and in vivo studies at a concentration of 20 mg/kg showed the complete elimination of *Plasmodium berghei* parasites in mice. According to the proper activity of the CK-2-68 compound, the prodrug [7] of this compound was also prepared in the phosphate form at the 1 position of the quinolone ring.

In examining the activity against Plasmodium falciparum microgametocytes, both of these compounds showed IC50 ~ 10nM [10-12]. These compounds are also effective in oxidoreductase enzyme NADH: Ubiquinone Plasmodium falciparum with IC50 = 16 nM inhibit.

Nixon and his colleagues introduced other analogs of HDQ. The compound SL-2-64(8) with ((-4-trifluoromethoxy)-phenyl)-pyridine substitution at the 2-position of the quinolone ring showed activity like some common antimalarial drugs against Plasmodium falciparum strain 3D7. In vivo studies of this compound in a mouse model 3D7 strain showed ED50 = 3.3 mg/kg and like in vivo activity of artemether with ED50 = 1.3 mg/kg on the same strain. The presence of the pyridine ring in SL-2-64 leads to an increase in aqueous solubility and a decrease in lipophilicity in this compound in comparison with the analogues (6) of CK-2-68 and its prodrug [7].

According to the appropriate results Obtained for compound SL-2-64, this analogue based on medicines for Malaria Venture (MMV) is listed [10].

Certainly, the methyl substitution in position 3 of the hydroxyquinoline ring and the aliphatic substitution in position 2 with an aromatic group in comparison with the original drugHDQ (Figure 5). Combination of ICI56-780 [9] (MMV) is listed [10].

Certainly, the methyl substitution in position 3 of the hydroxyquinoline ring and the replacement of the aliphatic substitution in position 2 with an aromatic group are responsible for increasing the antimalarial activity in these compounds compared to the original drug HDQ (Figure 5).

The composition of ICI56-780 [9] has the structure of 3 Carboxyquinolone (Figure 6) with its antimalarial activity prompted researchers to focus on carboxyl quinolone derivatives as new antimalarial drugs [13]. Zhang and his colleagues by derivatizing this compound into analog [10] were obtained by substituting methoxyphenyl in position two in the quinolone ring. This combination IC50 = 0.31 μM against K1 strain (chloroquine resistant strain) and IC50 = 0.10 μM against Plasmodium falciparum strain 3D7 [14]. Dacruz and his colleagues by screening method to the antioxidative drug decoquinate [11]. DQ was obtained as an effective substance on the liver stages of Plasmodium falciparum. The interesting point of this compound is its effect on different stages of malaria parasite in vitro (with IC50 = 6.2 nM on the liver stage, IC50 = 10 nM on the blood stage and IC50 = 36 nM on the sexual stage) [15]. With such effectiveness, the DQ compound has the necessary tools of the MMV foundation to obtain next-generation drugs for the eradication of malaria [16]. Another advantage of this compound is its effect on the bc1 complex of *Plasmodium falciparum*. In addition, this compound did not show cross-resistance with atovaquone [15,17], the special activity of the DQ compound on different stages of the parasite is due to the substitution of aliphatic ether groups in the 6- and 7-positions of the 3-carboxyquinolone ring. Despite all these merits mentioned for this compound, weak water solubility and fast metabolism are among its disadvantages. By eliminating these disadvantages, we can hope to create a new generation of antimalarial drugs in the design and manufacture of new derivatives inspired by this compound.

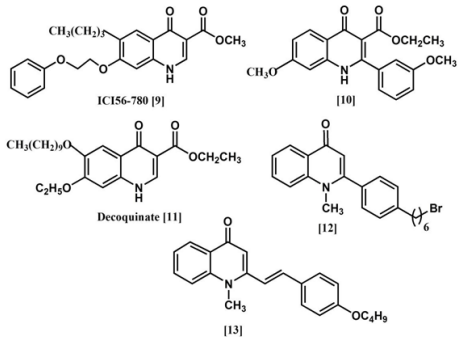

Figure 6: The structure of compounds 9-13 [13-15,26].

The special activity of DQ composition on different stages of the parasite is caused by the substitution of groups Aliphatic ethers in the 6th and 7th positions of the 3-carboxyquinolone ring are known. Despite all these advantages mentioned for this compound, its weak water solubility and fast metabolism are among its disadvantages. By removing these disadvantages, we can hope to create a new generation of anti-malarial drugs in the design and manufacture of new derivatives inspired by this combination.

Wube and his colleagues synthesized new derivatives of -(1H)-4 quinolones with different substitutions in the 1st and 2nd position of the ring. Derivatives with phenylalkyl substitution in position 2 of the ring significantly increased their antimalarial potency against *Plasmodium falciparum* [26]. On the other hand, the substitution of bromine on the end part of the alkyl chain improved the antimalarial activities of these derivatives. Compound [12] has these substitutions with IC50 = 0.09 μM and SI = 73.33 (L-6/NF54) it was the strongest derivative synthesized by this group.

Of course, compound [13] with IC50-0./47 μM and SI(L-6/NF54)-342/89 showed a higher selectivity compared to the Chloroquine NF 54 sensitive strain in *Plasmodium falciparum*. These compounds having a simple structure can be used as new guide compounds.

CONCLUSION

Parasite resistance to existing drugs is the biggest problem in the prevention, control, elimination and finally eradication of malaria, and in the absence of a suitable alternative drug, obtaining a new, safe, affordable drug with low toxicity and effective on strains Resistance to common drugs is a big challenge against malaria. In this regard and considering the importance of the subject, this review article deals with the introduction of new effective compounds against malaria, sometimes with a different mechanism of action from common drugs. The importance of the presence of quinolone rings in fluoroquinolone antimicrobial compounds is not hidden from anyone. The use of quinolone core by research groups was also used in the synthesis of various compounds and its antibacterial, anti-cancer, anti-viral, anti-parasitic, etc. activities were proven. Recent research on the antimalarial activity of the quinolone nucleus showed that some of its derivatives have a strong effect on the different stages of the malaria parasite, including the blood, liver, and sexual stages. Some of these effective compounds have a different mechanism of action compared to common drugs. Considering the problem of drug resistance, the merits of the quinolone core and the positive results obtained, we can hope for a new effective drug in the malaria eradication program. Of course, provided if it is focused on the low solubility of quinolone derivatives and its metabolic instability and solves this problem.

DATA AVAILABILITY

All the required data will be available upon request to the corresponding author.

CONSENT

Written informed consent was obtained from each participant.

AUTHORS' CONTRIBUTIONS

All authors contributed equally to the reported work, in the concept and design of the research, execution, data collection, analysis, and interpretation and engaged in the drafting and critical review of the paper.

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CONFLICTS OF INTEREST

There are no conflicts of interest.

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