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Review article

Quinoline hybrids and their antiplasmodial and antimalarial activities

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ABSTRACT

Malaria, in particular infection with *P. falciparum* (the most lethal of the human malaria parasite species, responsible for nearly one million deaths every year), is one of the most devastating and common infectious disease throughout the world. Beginning with quinine, quinoline containing compounds have long been used in clinical treatment of malaria and remained the mainstays of chemotherapy against malaria. The emergence of *P. falciparum* strains resistant to almost all antimalarials prompted medicinal chemists and biologists to study their effective replacement with an alternative mechanism of action and new molecules. Combination with variety of quinolines and other active moieties may increase the antiplasmodial and antimalarial activities and reduce the side effects. Thus, hybridization is a very attractive strategy to develop novel antimalarials. This review aims to summarize the recent advances towards the discovery of antiplasmodial and antimalarial hybrids including quinoline skeleton to provide an insight for rational designs of more active and less toxic quinoline hybrids antimalarials.

Contents

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1. Introduction

Malaria is one of the most widespread and deadliest diseases that resulted in 212 million clinical cases and 429,000 deaths in 2015 alone, especially among children (in Africa, 78% of deaths apply to children under the age of five) and pregnant women according to the World Health Organization (WHO) 2016 report [1,2]. Malaria is usually caused by protozoan parasites of the genus *Plasmodium* including *P. falciparum, P. vivax, P. malariae, P. ovale* and *P. knowlesi* species of human malaria parasite. In particular, *P. falciparum* is the most fatal one, which is responsible for 95% of the case of death.

The life cycle of malaria parasites is rather complex. Hereinto, the erythrocytic stage is responsible for the diverse symptoms caused by infection. In order to maintain osmotic stability and to provide space for the intracellular parasite, parasites ingest and digest more than 70% of host hemoglobin as an amino acid source inside erythrocytes. It is known that hemoglobin degradation and hemozoin formation are essential for parasite survival, making these processes important targets for antimalarials development. Heme detoxification into hemozoin was believed to be the main target of quinoline antimalarials and remained one of the most attractive drug development targets [3].

Quinoline and its derivatives, exhibited diverse of activities such as antimalarial, antibiotic, antituberculosis, anti-HIV, antiplasmodial, antitumor and anti-inflammatory properties, are emerged as an important class of bioactive heterocyclic compounds in the field of pharmaceuticals [4–8]. Quinoline-containing antimalarials, such as quinine (**QN**), chloroquine (**CQ**), amodiaquine (**AQ**), mefloquine (**MQ**) and primaquine (**PQ**) (Fig. 1) are mainstays of chemotherapy against malaria which have long been used in clinical. Among them, **CQ** has been used in the treatment as well as prophylaxis of almost all forms of malaria owing to its highly effective, safe, well-tolerated and reasonably low cost. **CQ** acts against the malaria parasites by blocking haemozoin formation through π-π stacking of the 4-aminoquinoline core to the heme ring system or by docking into grooves on the haemozoin crystal and preventing further crystal growth. The toxic haematins then leave the digestive vacuole and enter into the parasite cytosol where oxidative membrane damage is induced [9].

The human malaria parasite *P. falciparum* is able to regulate its genes and results in strains resistant to almost all the antimalarials, especially toward **CQ**. Resistance to **CQ** is associated with mutations in the gene encoding the digestive vacuole membrane protein *P. falciparum* **CQ** resistance transporter (PfCRT), which appears to result in reduced drug concentration at the target without altering the target itself. In this case, the target remains vulnerable and the organism is susceptible to drug action if access and binding to the target can be achieved [3].

To overcome the drug resistance, great efforts have been undertaken to modify the launched antimalarials and to discover entirely novel structures. Numerous of studies revealed that modification of the basic amine side chain of quinoline-contained antimalarials can keep activities against drug-resistant *P. falciparum* strains, but it has generally been assumed that changes to the quinoline nucleus itself will not. In fact, modification of the ring system affects the p*K*a of nitrogen both in the quinoline ring and in the side-chain as well as other physical parameters such as lipophilicity, sterics, and

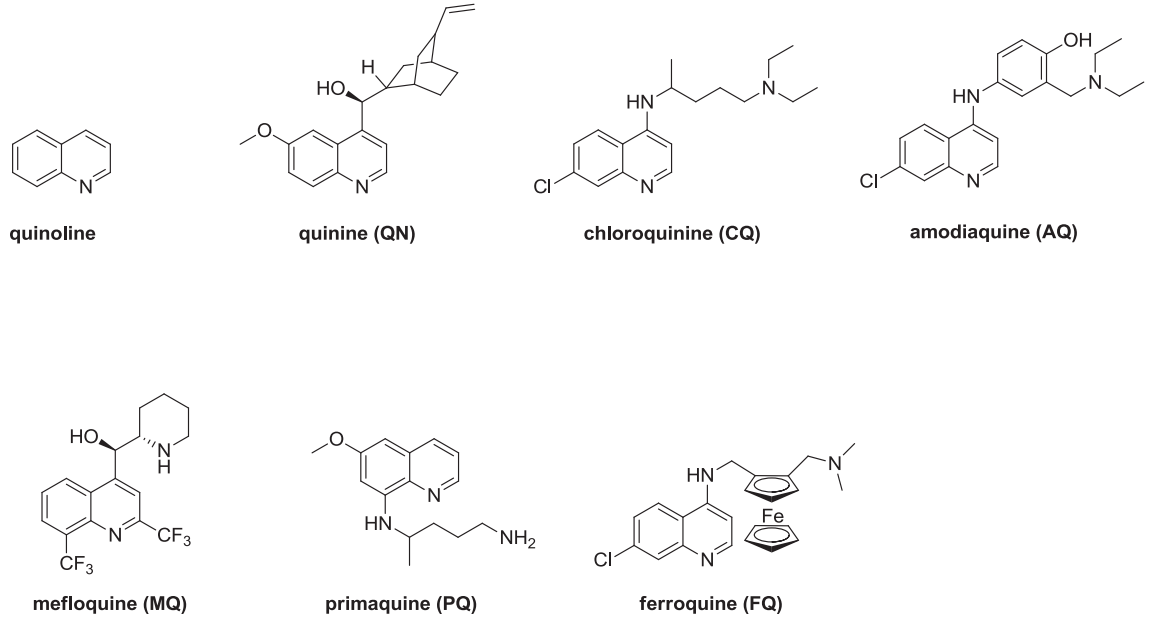

Fig. 1. Structures of quinoline and common quinoline-contained antimalarials.