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Mini-review

A comprehensive review on synthetic approach for antimalarial agents

Ajay Kumar [a, *], Deepika Paliwal [a], Deepika Saini [a], Aman Thakur [a], Shilpy Aggarwal [b], Dhirender Kaushik [a]

[a] Institute of Pharmaceutical Sciences, Kurukshetra University, Kurukshetra 136119, India
[b] R.K.S.D (PG) College, Kaithal, Haryana, India

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ABSTRACT

Malaria has emerged as a major health problem worldwide after the appearance of resistant strains of *Plasmodium falciparum* to the most of antimalarial drugs. The development of resistance by the parasite against first line as well as second line antimalarial drugs has drawn attention to develop new drugs to alleviate the disease burden. Therefore, there is a great need for new antimalarial drugs with improved attributes over older therapies. This review is primarily addressed to description of the recent advances in the synthesis of heterocyclic compound as antimalarial agents which can facilitate the development of more potent and effective antimalarial agents.

1. Introduction

Malaria is a lethal and widespread infectious parasitic diseases mainly affecting people from developing countries like Central- and South-America, Asia, and Sub-Saharan Africa [1,2]. According to the World Health Organization (WHO), approximately 250 million clinical cases of malaria occur every year [3]. About 1.1–2.7 million people in tropical and subtropical regions die of malaria every year, with most of the deaths occurring in children under 5 years of age in sub-Saharan Africa [4–7]. Additionally, pregnant women and newborns have reduced immunity, and therefore are vulnerable to severe complications of malaria infection and disease [8,9]. In India, over the past two decades, malaria incidence has been fluctuating between 2 and 3 million cases per year [10,11]. India contributes 40% of all cases outside Africa. In 1972, *Plasmodium falciparum* incidence was 9.3%, which increased to 43.4% in 1991 [12].

Malaria is primarily caused by four species of the protozoan parasite *Plasmodium*: *P. falciparum*, *Plasmodium vivax*, *Plasmodium malariae*, and *Plasmodium ovale*, which are transmitted by over 70 species of *Anopheles* mosquitoes [13,14]. These parasite species, occur sympatrically both in human populations and within infected individuals with *P. falciparum* and *P. vivax* being the predominant species [15–17]. Approximately 80% of all malaria cases and 90% of malaria-attributed deaths occur in Africa are caused by *P. falciparum*. Outside of Africa, *P. vivax* is the most widespread species, occurring largely in Asia, including the Middle East and the Western Pacific, and in Central and South America. This parasite species causes a relatively less lethal form of the disease compared with *P. falciparum* [18,19].

Today when many mosquito vectors are resistant to insecticides [20,21], and an effective vaccine is not yet available [22], chemoprophylaxis/chemotherapy remains the principal means of combating malaria. The chemotherapy of malaria basically involves killing of the asexual parasites and providing supportive therapy to the host to boost its immune system.

The development of resistance by the parasite against first line as well as second line antimalarial drugs has drawn attention to develop new drugs to alleviate the disease burden. Therefore, there is a great need for new antimalarial drugs with improved attributes over older therapies. These new medicines need to be orally active, rapidly efficacious, safe in all age groups, including children and pregnant women, and inexpensive to produce [23]. This review was compiled to focus on recent progress in the synthesis of important active antimalarial compounds published mostly during last ten years.

* Corresponding author.
E-mail address: ajkumar@kuk.ac.in (A. Kumar).

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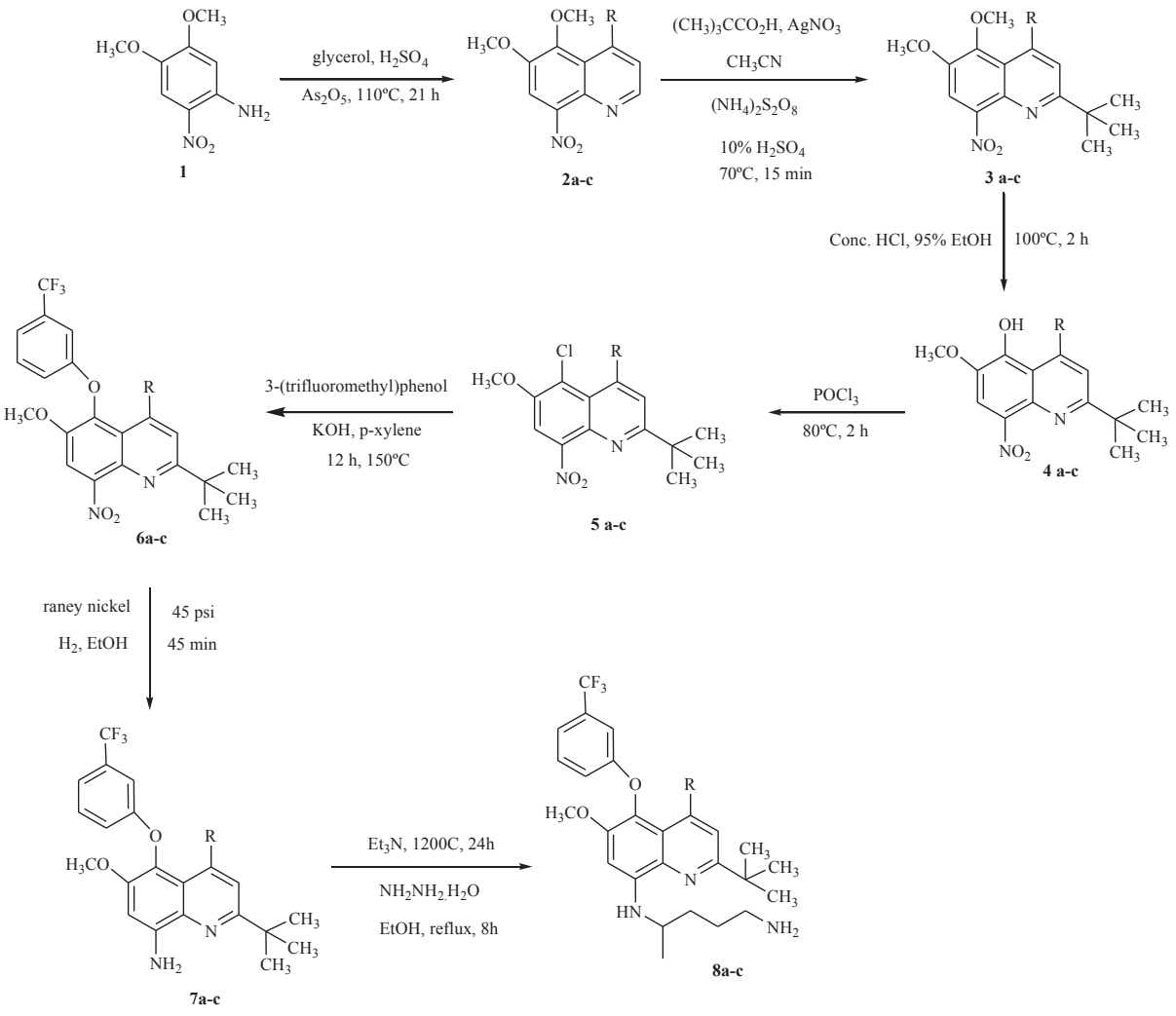
2. Various synthetic procedures of antimalarial agents

2.1. Heterocyclic compounds containing one nitrogen atom

2.1.1. Synthesis of quinoline and its derivatives

Quinoline containing compounds have long been used for the treatment of malaria, beginning with quinine, which is a 4,6-substituted quinoline. Systematic modification of quinine led to diverse quinoline antimalarial drugs [24–26] with diverse substitutions around the quinoline ring. One of the first drugs to be prepared was the potent and inexpensive chloroquine (CQ) [27–29], which is a 7-chloroquinoline with an amino substituent at position 4. The other known drugs from this family include: amodiaquine, piperaquine, prima-quine, and mefloquine. The understanding of the mode of action of quinoline based antimalarials has increased in the recent years, but remains incomplete [30–34]. The drugs from this group mostly act during the blood stages of the parasite's life cycle but some target the hepatic stages as well [35,36]. Unfortunately, the design and subsequent synthesis of new antimalarials are hindered by the fact that the mechanism of resistance is not fully understood [37].

Jain et al. have reported a class of 8-quinolinamine analogs which showed potent antimalarial compounds. Title compound **8** was synthesized using procedures reported earlier [38,39] starting from 4,5-dimethoxy-2-nitroaniline **1** upon direct ring-alkylation via a silver catalyzed radical oxidative decarboxylation of trimethylacetic acid by ammonium persulfate in CH_3CN and 10% H_2SO_4 at 80 °C efficiently produced 4-alkyl-2-tert-butyl-5,6-dimethoxy-8-nitroquinolines **3a–c** in good yields (Scheme 1). Selective demethylation of the 5-methoxy group with conc. hydrochloric acid in 95% ethyl alcohol at 100 °C for 2 h easily afforded 4-alkyl-2-tert-butyl-6-methoxy-8-nitro-5-quinolinols **4a–c** in excellent yields. Reaction of the later compounds **24a–c** with phosphorous oxychloride at 80 °C for 2 h produced 4-alkyl-2-tert-butyl-5-chloro-6-methoxy-8-nitroquinolines **5a–c** in quantitative yields. Chloro derivatives **5a–c** upon reaction with 3-(trifluoromethyl) phenol in the presence of potassium hydroxide pellets in *p*-xylene at 150 °C for 12 h afforded 4-alkyl-2-tertbutyl-6-methoxy-8-nitro-5-(3-trifluoromethylphenoxy)-quinolines **6a–c** in good yields. The later compounds **6a–c** were then efficiently converted to requisite N-8-(4-amino-1-methylbutyl)-4-alkyl-2-tert-butyl-6-methoxy-5-(3-trifluoromethylphenoxy)-8-quinolinamines **8a–c** in three steps using the procedure reported earlier [40], and finally isolated as hydrochloride salts for their biological evaluation by treatment with etheral hydrochloric acid solution. The synthesized compounds were tested for their *in vitro* antimalarial activity against chloroquine sensitive and resistant *P. falciparum* strains whereas; *in vivo* screening was performed against *Plasmodium berghei*



Scheme 1.