European Journal of Medicinal Chemistry 122 (2016) 635–646

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Research paper

Synthesis and biological evaluation of a series of non-hemiacetal ester derivatives of artemisinin

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ARTICLE INFO

Article history:
Received 25 May 2016
Received in revised form
11 July 2016
Accepted 12 July 2016
Available online 14 July 2016

Keywords:
Artemisinin
Malaria
Plasmodium falciparum
Cancer
Ester

ABSTRACT

In an attempt to improve the efficacy and stability of current, clinically used artemisinins, a series non-hemiacetal ester derivatives of artemisinin were synthesized and evaluated for their *in vitro* antiplasmodial and anticancer activities as well as cytotoxicities. These esters were synthesized through the reaction of acid anhydrides, or acid chlorides with artemisinin derived alcohol. *In vitro* antiplasmodial activity assessments were conducted against intraerythrocytic NF54 and Dd2 *Plasmodium falciparum* strains. Cytotoxicities were assessed, using normal human fetal lung fibroblast (WI-38) and Chinese hamster ovarian (CHO) mammalian cell lines, while anticancer activities were tested by using panels with three cell lines, consisting of renal (TK10), melanoma (UACC62) and breast (MCF7) cancer cells. Most compounds were found active against the breast cancer cell line. Since antiplasmodial activities for most compounds were found comparable only to that of artesunate, this study did not yield any esters with significantly improved antimalarial efficacies, nor did it deliver any promising antitumor hits. However, from the outcomes of this study, compounds with good safety profiles and increased thermal stabilities, compared to the clinically used artemisinins, were identified. The benzoate derivative **11** was found to have antimalarial activity, comparable to that of dihydroartemisinin and was it subsequently identified as a candidate for further investigation in the urgent search for new, safe and effective antimalarial drugs.
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1. Introduction

Malaria is an infectious, treatable and manageable disease that is transmitted to humans through the bite of an infected female *Anopheles* mosquito [1,2]. The disease is prevalent in tropical and sub-tropical areas, specifically in sub-Saharan Africa, South-East Asia and the Eastern Mediterranean region. In 2014 alone, 214 million malaria cases were reported, the majority of which (88%) were in the World Health Organization (WHO) African region. Ninety percent (90%) of the 438 000 malaria related deaths had occurred in the WHO African Region, with most of these fatalities having been children under the age of five. The WHO reported a 48% decline in malaria mortalities between 2000 and 2015, of which 90% still were among African children. Despite this decrease in malaria fatalities, children under 5 years of age remain the group that is the most vulnerable to malaria [2].

Five species of the genus, *Plasmodium* (*P.*), namely, *Plasmodium falciparum, Plasmodium vivax, Plasmodium malariae, Plasmodium ovale and Plasmodium knowlesi* are responsible for malaria infections in humans [2]. *P. falciparum* accounts for high cases of morbidity and mortality, while *P. vivax* infections, although rarely life threatening, has consequential morbidity implications, since it has the ability to develop in the *Anopheles* mosquito at low temperatures and to develop into a dormant liver stage [2–4]. As evidenced by the statistics, the life threatening effects of malaria can be dire, especially if the infection is caused by *P. falciparum*, which may either be uncomplicated, or severe. The importance of treating uncomplicated *P. falciparum* malaria is necessitated by its risk of developing into life threatening, severe malaria.

The recent progress being made in reducing malaria infections and fatalities can be attributed to effective prevention and treatment interventions. The key prevention interventions include vector control and chemoprevention. Insecticide treated mosquito nets (ITNs) and indoor residual spraying (IRS) are used as vector control methods, aimed at reducing the transmission of parasites

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http://dx.doi.org/10.1016/j.ejmech.2016.07.027
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from humans to mosquitoes and then back to humans. Chemoprevention is particularly effective in pregnant women, infants and children, as it diminishes blood-stage infection in humans. Other chemoprevention programs include intermittent preventive treatments during pregnancy (IPTp), intermittent preventive treatments for infants (IPTi) and seasonal malaria chemo-prevention (SMC), which is achieved by the administration of either sulfadoxine-pyrimethamine alone, or a combination of amodiaquine and sulfadoxine-pyrimethamine [2]. The artemisinins currently are the lifeline of antimalarial treatments, as these clinically used drugs have the highest efficacies against the malaria parasites. They remain the mainstay of antimalarial chemotherapies, mainly because they are active against all *Plasmodium* species that infect humans. The artemisinins are effective against a wide range of the life stages of the parasites, including the asexual blood and gametocyte stages of *Plasmodium* [5–7]. In addition to their potency, rapid action, as well as their broad antiplasmodial spectrum against the malarial parasite, the artemisinins also show good tolerability and no serious adverse drug reactions [8].

The WHO recommended artemisinin-based combination therapies (ACTs), which involve the administration of the artemisinins in combination with other, longer acting antimalarial drugs, aimed at ensuring constantly persistent antimalarial action in the course of treatment of uncomplicated malaria. This strategy had been necessitated to prevent parasite recrudescence, which occurs as a consequence of the short pharmacological half-lives of the artemisinins, when used in monotherapy [5,9,10]. Owing to the ACTs, artemisinins have continued to elude *P. falciparum* drug resistance until recently, when the emergence of resistance at the boarder of Thai-Cambodia was reported [11]. Since the parasite is continually evolving and adapting to its environment, it ultimately develops drug resistance and are the artemisinins no exception. The emergence of resistance against the artemisinins and the spread thereof pose a serious global health threat and risk to the ultimate goal of eradicating malaria [2,12]. This growing emergence of drug resistance has led to the inception of counter measures to try and ensure that the artemisinins, especially, remain effective against malaria [10,13]. Increased dosages of artemisinin regimens have been suggested as a means to combat the reduced sensitivity of the parasite, by either increasing the dosage frequency of the drugs, or by increasing the concentration of the artemisinins in ACTs [10]. An increase in the dosage of the artimisinins, however, is a cause of great concern, since literature reports on animal studies suggest that neurotoxicity is one of the consequences of administering artemisinin at high doses [14,15]. Neurotoxicity of artemisinins in humans remains a grey area, with only a few isolated cases being reported [16]. However, it is well documented that DHA, the principal metabolite of current, clinically used artemisinins (Fig. 1), is linked to their neurotoxicity [17,18]. This necessitates finding ways to ensure that new artemisinins remain the effective mainstay in malaria chemotherapies, but also that the progress made is not marred by any adverse side effects of the new derivatives.

A crucial starting point in the strategy to develop new derivatives is to maintain the endoperoxide bridge (O-1 – O-2), which is responsible for the antimalarial activity of artemisinin, notwithstanding the fact that the effectiveness of artemisinin is hindered by its poor solubility in both oil and water, as well as its poor efficacy upon oral administration [19]. Although the water soluble ester derivative of artemisinin, i.e. artesunate, currently is the golden standard among all antimalarial drugs in terms of its efficacy, it quickly metabolizes into DHA, following oral administration [20]. New ester derivatives, with truncated artemisinin scaffold, therefore are worth investigating as potential alternatives.

During this research, new ester derivatives were synthesized based upon the hypothesis that the truncation of an artemisinin scaffold would preserve the endoperoxide pharmacophore so that there is no loss in antimalarial activity, but rather a possible improvement in efficacy. Since all current, clinically used artemisinins are metabolized into DHA as a result of the D-ring, the contraction of this six-membered ring into a five-membered ring, with the C-10 carbon being rendered exocyclic, might eliminate the formation of DHA upon metabolism. Such truncation may thus also result in derivatives with improved stability, because of the elimination of the hemiacetal in the DHA structure. The synthesis and *in vitro* biological activities outcomes of the newly prepared esters are reported on.

2. Results

2.1. Chemistry

Adopting the method reported by Lin et al. [21], the synthesis of glycal **2** was achieved in a good yield (95%). The conversion of **2** into the halohydrin **3** also accomplished a good yield (90%), when using a literature adapted method [19]. Compounds **4** and **5** were successfully synthesized in good yields (91% and 72%, respectively) by applying and slightly modifying methods from the literature [22]. These compounds were isolated as epimeric mixtures, following purification through silica gel column chromatography. The esters **6**–**18** were prepared in moderate to good yields (43–78%) through the reaction of **5** with either an acid anhydride, or an acid chloride. Purification through silica gel column chromatography and/or recrystallization afforded the target compounds as epimeric mixtures. Attempts to isolate the crystals through recrystallization for single isomer identification, using X-ray diffraction (XRD), proved futile.

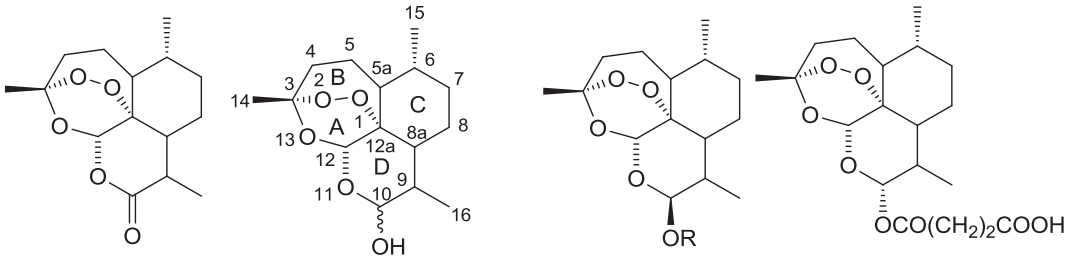

Fig. 1. Structures of artemisinin and its clinically used derivatives The artemisinins class comprises artemisinin and its oil-soluble semi-synthetic derivatives dihydroartemisinin, artemether and arteether, and water-soluble, artesunate.

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