European Journal of Medicinal Chemistry 95 (2015) 230–239

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

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

Preliminary communication

Synthesis and *in vitro* antiplasmodial evaluation of 7-chloroquinoline–chalcone and 7-chloroquinoline–ferrocenylchalcone conjugates

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ARTICLE INFO

Article history:
Received 31 January 2015
Received in revised form
18 March 2015
Accepted 19 March 2015
Available online 20 March 2015

Keywords:
7-Chloroquinoline
Chalcone
Ferrocenylchalcone
Antiplasmodial activity
IC_{50} value

ABSTRACT

The manuscript describes the synthesis of novel amide tethered 7-chloroquinoline–chalcone and 7-chloroquinoline–ferrocenylchalcone bifunctional hybrids and their evaluation as antimalarial agents against W2 resistant strain of *Plasmodium falciparum*. The antiplasmodial activity of 7-chloroquinoline–ferrocenylchalcones was found to be less than their corresponding simple chalcone conjugates. The presence of a methoxy substituent at *para* position of ring B on chalcones and longer alkyl chain length markedly improved the antiplasmodial profiles of the synthesized scaffolds with the most potent of the test compound exhibiting an IC_{50} value of 17.8 nM.

1. Introduction

Malaria poses a major public health threat, especially in developing countries, where it has huge economic and social costs, with an estimated 207 million cases of infection and 627,000 deaths worldwide in 2012 [1]. In Africa alone, ~90% of malaria deaths occur, with the vast majority of them being young children under the age of five years [2]. Among Plasmodium species that cause disease in humans, *Plasmodium falciparum* is most fatal and responsible for majority of deaths. The major obstacle in the control of malaria is resistance of *P. falciparum* to common antimalarials including quinolines, antifolates, and artemisinin and its semi synthetic derivatives, potentially limiting the ability of artemisinin-based combination therapy (ACT) to contribute importantly to control and eventually eradicate the disease [3–8]. Thus, the synthesis of new antimalarials with the ability to overcome *P. falciparum* resistance is an urgent priority.

Since the discovery of quinine, the quinoline based drugs continued as the mainstay in the fight against malaria for many years. Among quinolines, chloroquine (CQ) has immense significance and extensively utilized in malaria chemotherapy due to its excellent clinical efficacy, limited host toxicity, simple and cost effective synthesis [9]. Unfortunately, emergence of resistant strains of *P. falciparum* to CQ led to its replacement by ACTs for the treatment of falciparum malaria [10,11]. However, recent studies have revealed that the resistance to CQ seems compound specific [12], and certain synthetic modifications around the quinoline nucleus have yielded many quinolines active against CQ-resistant parasites [13–17].

The quinoline hybridization strategy may allow us to circumvent quinoline resistance. The strategy involves covalently linking a quinoline nucleus with other drugs to result in a single hybrid molecule with improved efficacy compared to the parent drugs [18–21]. The potential of the hybridization strategy in malaria chemotherapy can be exemplified with the recent success of ferroquine (FQ) (7-chloroquinoline–ferrocene conjugate) and trioxaquine (7-chloroquinoline–trioxane conjugate). The hybrid FQ is an organometallic molecule active against CQ-sensitive as well as CQ-resistant strains of *P. falciparum* [22,23], and it has recently completed phase IIb clinical trials for the treatment of malaria [24]. Based on the success of FQ, a variety of ferrocenyl analogues of CQ have been synthesized [23,25] due to its favourable properties such as stability in aqueous and aerobic media and lipophilicity to

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http://dx.doi.org/10.1016/j.ejmech.2015.03.045
0223-5234/

enhance penetration into cellular membranes. In addition to inhibition of hemozoin formation, ferrocene was shown to create oxidative stress due to the redox property of the ferrocene (Fe^{2+})/ferricinium (Fe^{3+}) system, generating reactive oxygen species *via* a Fenton-like reaction in the parasite digestive vacuole, resulting in parasite death [26].

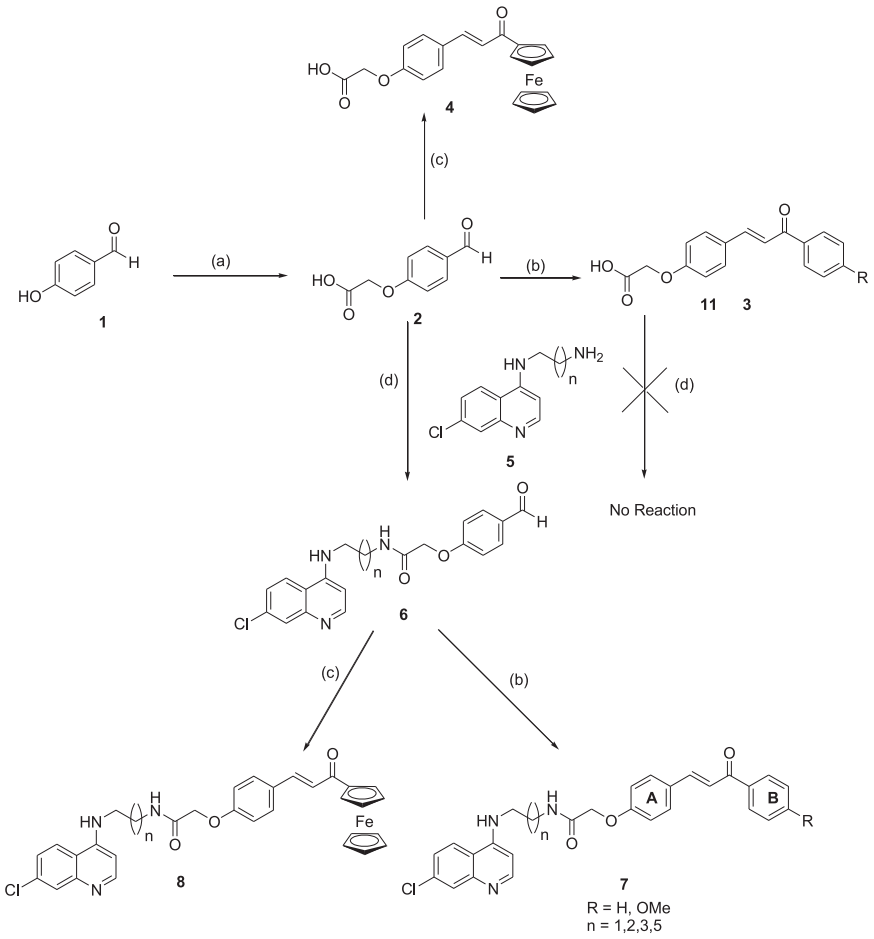
Chalcones represent key structural motifs among biologically active molecules, and they are key intermediates for combinatorial assembly of heterocyclic scaffolds. Synthetic manoeuvring of chalcones or their isolation from natural sources are being investigated because of their many relevant properties including antioxidant, antitumour, anti-inflammatory, antibacterial, and antiprotozoan activities [27,28]. The discovery of the oxygenated chalcone Licochalcone A as a potential antimalarial agent [29] encouraged researchers to design and synthesize variably functionalized chalcones and to assess their antimalarial efficacies. The antimalarial potential of chalcones is augmented by their ability to inhibit both plasmodial aspartate and cysteine proteases [30], which are potential novel chemotherapeutic targets [31]. Continuing our efforts in the synthesis of molecular conjugates and their antimalarial evaluation [32], we now describe the synthesis and characterization of amide tethered 7-chloroquinoline–chalcones and 7-chloroquinoline–ferrocenyl chalcones. The introduction of an amide as linker is based on its hydrogen bonding abilities, as this has been shown to enhance antimalarial efficacy against both CQ-sensitive and CQ-resistant strains of *P. falciparum* [33].

2. Result and discussion

2.1. Synthetic chemistry

The synthetic methodology involved an initial base-promoted treatment of 4-hydroxybenzaldehyde **1** with bromoacetic acid in water as solvent under refluxing conditions for 4–5 h to yield (4-Formyl-phenoxy)-acetic acid **2**. The aldol condensation of **2** with substituted acetophenones afforded the substituted chalcones **3** and **4**. These precursors were then utilized to provide an access to the desired amide tethered 7-chloroquinoline–chalcone conjugates. However, no significant reaction was observed, possibly because of the poor solubility of these chalcones in DMF. The approach was thus refined, with an initial DCC-HOBt promoted coupling of **2** with 4-diamino-7-chloroquinolines **5** having varied spacer length, to yield the corresponding amide **6**. Aldol condensation of **6** with varied acetophenones at room temperature for 0.5–2 h yielded the desired conjugates **7** and **8** in good to excellent yields (Scheme 1).

The structures of the synthesized conjugates were assigned on



Reagent and conditions: (a) $BrCH_2COOH$, H_2O, reflux, 3-5 h; (b) 40% KOH, Acetophenone/4-Methoxyacetophenone, EtOH, rt, 0.5-2 h; (c) 40% KOH, Acetylferrocene, EtOH, rt, 0.5-2 h; (d) **5**, HOBt, DCC, Et_3N, DCM:DMF (20:80) mix., rt, 10-12 h

Scheme 1. Synthesis of amide-tethered 7-chloroquinoline chalcone conjugates **7a**–**7h** and 7-chloroquinoline ferrocenylchalcone conjugates **8a**–**8d**.