European Journal of Medicinal Chemistry 57 (2012) 259–267

Contents lists available at SciVerse ScienceDirect

European Journal of Medicinal Chemistry

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

Original article

The design, synthesis, *in silico* ADME profiling, antiplasmodial and antimycobacterial evaluation of new arylamino quinoline derivatives

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ARTICLE INFO

Article history:
Received 23 May 2012
Received in revised form
29 August 2012
Accepted 30 August 2012
Available online 7 September 2012

Keywords:
Antiplasmodial
Antimycobacterial
Arylamino quinoline tetrazoles
Physico-chemical properties

ABSTRACT

A series of new arylamino quinoline derivatives was designed based on the quinine and mefloquine scaffolds and evaluated *in vitro* for antiplasmodial and antimycobacterial activities. A number of these compounds exhibited significant activity against the drug-sensitive 3D7 and drug-resistant K1 strains of *Plasmodium falciparum*. Furthermore, two compounds, **4.12b** and **4.12d**, also showed 94 and 98% growth inhibitory activity against non-replicating and replicating *Mycobacterium tuberculosis* strains, respectively.

1. Introduction

Malaria and tuberculosis (TB) are ancient diseases that continue to have devastating impact on mankind, killing over 2.5 million people annually [1]. The recent widespread emergence of multi-drug resistant (MDR) strains of *Plasmodium falciparum* and *Mycobacterium tuberculosis* to clinically available drugs puts further impetus to the urgent need for the discovery of new and effective antimalarial and anti-TB agents with novel mechanisms of action. The TB problem is further exacerbated by extensively drug-resistant (XDR) and totally drug-resistant (TDR) forms [1b]. Compounds containing the quinoline scaffold exhibit a wide-spectrum of biological actions, including antiviral [2], anticancer [3], antibacterial [4], antifungal [5] and anti-inflammatory activities [6]. The diarylquinoline drug, TMC 207 (**1**) (Fig. 1), currently in phase IIB TB clinical trials, is active against drug-sensitive and drug-resistant *M. tuberculosis*, and has a bactericidal effect against dormant tubercle *bacilli* [7,8]. Moreover, this compound functions by inhibiting ATP synthase subunit C, an energy source for the bacterium [9], thus exhibiting a new mechanism of action. The majority of the quinoline-based antimalarial drugs, including the arylamino alcohols, have been shown to possess moderate anti-TB activity [10–12].

Members of the arylamino alcohol family of quinolines, which includes quinine (**2**) and mefloquine (**3**), possess potent activity against multi-drug resistant *P. falciparum* [13]. The mechanism of action of these drugs against the plasmodial parasite is not clearly understood. However, recent studies [14,15] suggest that these compounds exert their activity through (i) π-stacking of the quinoline ring with the porphyrin ring of haeme moieties (green), (ii) coordination with the iron centre of haeme *via* alkoxide formation on the benzylic alcohol (red), and (iii) intermolecular hydrogen-bonding interactions with the propionate side-chain of haeme (blue) (Fig. 2; for interpretation of the references to colour in this figure, the reader is referred to the web version of this article).

Recently, Egan and co-workers described the coordinating ability of various nitrogen donor ligands such as imidazoles, pyridines and amines, which contain sp^2 hybridized nitrogen(s), with haeme [15].

Abbreviations: ADME, adsorption, distribution, metabolism and excretion; ATP synthase, adenosine triphosphate synthase; CQ, chloroquine; IC_{50}, 50% inhibitory concentration; MIC_{90}, 90% minimum inhibitory concentration; MABA, microplate Alamar blue assay; MCR, multi-component reactions; LORA, low oxygen recovery assay; PLS, partial least square; SAR, structure activity relationship; $TMSN_3$, trimethylsilane azide.

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http://dx.doi.org/10.1016/j.ejmech.2012.08.047

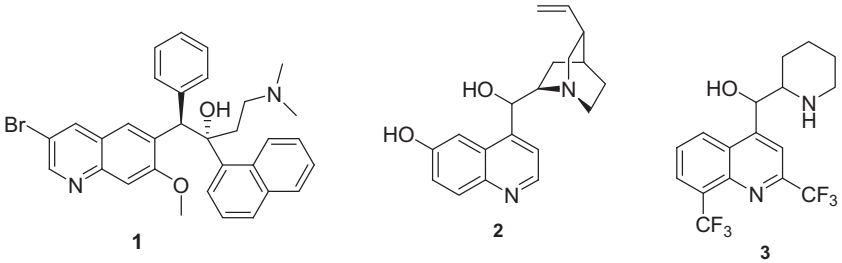

Fig. 1. TMC 207 (**1**), quinine (**2**) and mefloquine (**3**).

The above studies prompted us to investigate whether the introduction of *N*-donor atoms on arylamino quinolines enhances antiplasmodial and/or antimycobacterial activity. In designing the new arylamino quinoline derivatives, the *O*-donor hydroxyl group was replaced with an *N*-donor tetrazole ring that contains sp^2 hybridized nitrogen atoms, while the heterocyclic ring systems containing a basic nitrogen in quinine and mefloquine were in turn replaced by various tertiary amines (Fig. 3). The ability of the tetrazole ring to coordinate with the iron centre of haeme was exploited by Roman et al. [16] in the design of haeme oxygenase inhibitors, and by Adachi et al. [17] in ligand binding studies of tetrazole–myoglobin complexes, justifying the use of this heterocyclic system in our work. The substituent on the tetrazole ring was limited to the *t*-butyl isocyanide (a cleavable isocyanide) and hydrogen atom, the result of the de-*tert*-butylation of the former.

Herein, we describe the synthesis, *in silico* ADME profiling and biological evaluation of a series of new arylamino quinoline derivatives.

2. Results and discussion

2.1. Synthesis

The first step in the synthesis of the designed arylamino quinoline derivatives involved the respective synthesis of the quinine and mefloquine nuclei, *i.e.* 6-methoxyquinoline-4-carbaldehyde (**4.8**) and 2,8-bis(trifluoromethyl)quinoline-4-carbaldehyde (**4.11**). Preparation of **4.8** (Scheme 1) commenced with the four-step synthesis of 4-bromo-6-methoxyquinoline (**4.7**) according to the procedure described by Daines et al. [18]. Treatment of **4.7**, and 4-bromo-2,8-*bis*(trifluoromethyl)quinoline prepared from commercially available alcohol precursor, with 2-equivalents of *n*-BuLi at −78 °C and subsequent formylation by DMF to afford the corresponding aldehydes **4.8** and **4.11** in 86 and 29% yields, respectively [19].

With the desired nuclei (**4.8** and **4.11**) in hand, the modified $TMSN_3$-Ugi MCR procedure described by Dömling et al. [20] and Mayer et al. [21] was followed. The quinoline aldehydes (**4.8** and **4.11**) were allowed to react at ambient temperature with various commercially available secondary amines and *t*-butyl isocyanide in the presence of $TMSN_3$ in anhydrous MeOH for 24 h to obtain the desired target compounds, **4.12a**–**f** and **4.13a**–**b**, in low to excellent yields after column chromatographic purification. Post-modification (de-*tert*-butylation) of these compounds then furnished the de-*tert*-butylated compounds, **4.14a**–**f**, in low yields after purification (Scheme 2, Table 1). The purity of all synthesized compounds was determined to be >95% by HPLC. Post-modification of the mefloquine derivatives was not attempted due to the insufficient amounts obtained of the precursor compounds. All the intermediates and target compounds were characterized fully by analytical and spectroscopic techniques.

2.2. In silico profiling

The small series of the synthesized arylamino quinoline derivatives was profiled *in silico* for various physico-chemical properties of interest such as aqueous solubility, metabolic stability, and blood–brain barrier (BBB) permeation using Volsuf+ software [22]. Mefloquine and its derivatives accumulate in the central nervous system (CNS) [23], while quinine has been shown to have dose-related CNS effects following excessive infusion or from accumulation following oral administration [24]. Therefore, designing compounds with reduced permeation through the BBB is likely of importance in avoiding adverse CNS effects. Figs. 4 and 5 show predicted aqueous solubility (log S) of arylamino quinoline derivatives plotted against the predicted *n*-octanol–water partition coefficient (log D) at pH 5.0 and 7.5, and 2D PLS plots of metabolic stability and BBB permeation, respectively. In the 2D PLS plots the blue and the red zones indicate good and poor predicted properties, respectively, while the block dots represents a dataset of compounds that the program is built on [25] (For interpretation of the references to colour, the reader is referred to the web version of this article.). At both pH 5 and 7.5, the majority of the de-*tert*-

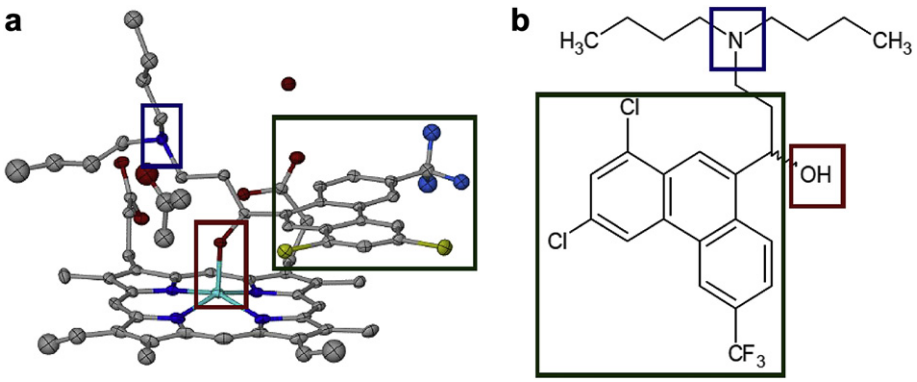

Fig. 2. (a) Crystal structure of the haeme-halofantrine complex; and (b) highlighted halofantrine structural features responsible for the interaction with the haeme (reproduced from Ref. [14]).