Biomedicine & Pharmacotherapy 65 (2011) 313–316

Available online at ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com/en

Original article

4-aminoquinoline analogues and its platinum (II) complexes as antimalarial agents

Nicolli Bellotti de Souza [b], Arturene M.L. Carmo [a], Davi C. Lagatta [b], Márcio José Martins Alves [c], Ana Paula Soares Fontes [a], Elaine Soares Coimbra [b], Adilson David da Silva [a], Clarice Abramo [b,*]

[a] Departamento de Química, ICE, Universidade Federal de Juiz de Fora, Campus Universitário, 36036-900 Juiz de Fora, Minas Gerais, Brazil
[b] Departamento de Parasitologia, Microbiologia e Imunologia, ICB, Universidade Federal de Juiz de Fora, Campus Universitário, Rua José Lourenço Kelmer, s/n, 36036-900 Juiz de Fora, Minas Gerais, Brazil
[c] Departamento de Saúde Coletiva, Faculdade de Medicina, Universidade Federal de Juiz de Fora, Campus Universitário, 36036-900 Juiz de Fora, Minas Gerais, Brazil

ARTICLE INFO

Article history:
Received 1 February 2011
Accepted 1 March 2011
Available online 30 May 2011

Keywords:
Antimalarial activity
Plasmodium berghei
Quinoline
Platinum (II) complexes

ABSTRACT

The high incidence of malaria and drug-resistant strains of *Plasmodium* have turned this disease into a problem of major health importance. One of the approaches used to control it is to search for new antimalarial agents, such as quinoline derivates. This class of compounds composes a broad group of antimalarial agents, which are largely employed, and inhibits the formation of β-haematin (malaria pigment), which is lethal to the parasite. More specifically, 4-aminoquinoline derivates represent potential sources of antimalarials, as the example of chloroquine, the most used antimalarial worldwide. In order to assess antimalarial activity, 12 4-aminoquinoline derived drugs were obtained and some of these derivatives were used to obtain platinum complexes platinum (II). These compounds were tested *in vivo* in a murine model and revealed remarkable inhibition of parasite multiplication values, whose majority ranged from 50 to 80%. In addition they were not cytotoxic. Thus, they may be object of further research for new antimalarial agents.

1. Introduction

Human malaria is caused by mainly four species of the genus *Plasmodium*. *Plasmodium falciparum*, which is responsible for over 90% of global malaria [1] and is the most virulent species, causes severe malaria and very high rates of morbidity and mortality [2]. Besides, it has become increasingly resistant to known chemotherapeutic agents [3]. Malaria consists in one of the world's biggest public health problems and represents one of the major infectious diseases that afflicts human kind nowadays [4,5] in more than 109 countries in Africa, Asia and Latin America [6], causing over 500 million clinical cases and one to three million deaths per year [4,7].

For many years, malaria treatment has relied on a narrow variety of drugs. Moreover, resistance to both chloroquine and alternative drugs has been reported [8,9]. In this scenery, chemotherapy has been the mainstay of malaria control [1] and combinations have been used to improve efficacy and delay onset of resistance [10], but they present lower abundance and high cost [3]. Therefore, there is a compelling and urgent need for research and development of new antimalarial agents, preferentially with novel mechanism of action [11,12]. Most of the current efforts have relied on *de novo* drug design and chemical modification of existing antimalarials [13].

"Quinoline-containing compounds" are classical antimalarials and have long been used to combat malaria, representing a major part of the armory against it [14,15]. They compose a very versatile group of compounds considering effectiveness against malaria and its synthesis is easy and cheap. They are well tolerated, presenting low levels of cytotoxicity [16]. Their action is based on interfering with the heme detoxification process of the parasite [17]. Furthermore, one group that has attracted interest is the 4-aminoquinoline derivates. They exert potent activity against chloroquine-resistant *P. falciparum* strains by bearing different basic moieties. Therefore, efforts must be urgently held to develop aminoquinoline analogues, since drug development has provided modifications of existing agents [18,19]. Changes in the structure can lead to new compounds and this hampers the onset of parasite resistance, considering the matters mentioned before.

The current goal is to synthesize a new series of 4-amino-7-chloroquinoline derivatives (Scheme 1) using 4,7-dichloroquinoline linked together with a series of diaminealkyne and diaminedialkyne. These fragments are considered able to interact with membrane lipids, also to be transported into the cytoplasm and possibly, to interfere with the lipid or polyamine transport or

* Corresponding author. Tel.: +55 32 2102 3219; fax: +55 32 2102 3216.
E-mail addresses: nicollisouza@yahoo.com.br (N.B. de Souza), clarice.abramo@ufjf.edu.br (C. Abramo).

0753-3322/$ – see front matter © 2011 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.biopha.2011.03.003

metabolism of the parasite [23,24]. We have also obtained platinum (II) complexes from these derivatives. Metal complexes have attracted considerable attention in recent years and can be used as a strategy to enhance biological activity and overcome resistance. Organic ligants with various transition metals have demonstrated antiparasitic activities [17–22].

2. Experimental

2.1. Materials and methods

2.1.1. Antimalarial activity

2.1.1.1. Animals. For the *in vivo* tests, Swiss albino adult mice, 6–8 weeks of age and weighting 20–22 g, were used. These animals were obtained from Center for Biology of Reproduction, in Federal University of Juiz de Fora (process in Ethic Committee number 063/2007-CEEA).

2.1.2. In vivo antimalarial activity evaluation

The animals, randomly distributed in groups of four mice each, were infected with 1×10^6 *Plasmodium berghei* infected red blood cells (NK65 strain) by intraperitoneal route on day 1. The drugs were diluted in dimethyl sulfoxide 5% plus water, providing an aqueous suspension.

Using the 4-day suppressive test [25], treatment was performed daily by oral route (0.1 mL for each mouse) for four consecutive days. Two control groups were used; one receiving the standard antimalarial drug chloroquine and the second one was not treated. Test groups were treated with the compounds **5**-**16** and chloroquine at dosages of 10 mg/kg and/or 25 mg/kg each.

Treatments started on the day of infection. Giemsa stained blood smears were made on day 5, 7 and 9 and then examined by microscopy to assess the percentage parasitaemia.

2.2. Percentage of inhibition of parasite multiplication

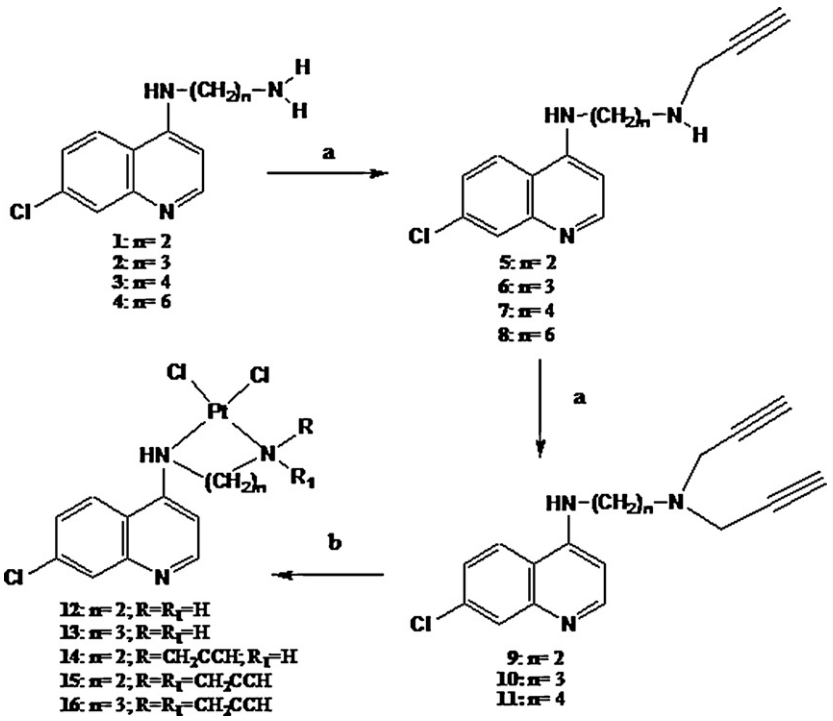
The antimalarial activity of the drugs was established on the basis of average parasitaemia of each group. The percent inhibition of parasite multiplication was calculated using treated group compared with untreated group, by means of the following formula [26]: $[(A - B)/A] \times 100$, where A = parasitaemia in the control (untreated) group and B = parasitaemia in the test group. Results were expressed as a percentage of parasitaemia.

2.3. Cytotoxicity evaluation

The cytotoxicity against mammalian cells expressed as cell viability was assayed on mice peritoneal macrophages. Swiss albino mice received thioglycolate 4%. After 72 h, the cells were harvested and cultivated on a 96-well plate and incubated at 37 °C in a 5% CO_2 atmosphere for 24 h. After this, the compounds were added and the plate was incubated at 37 °C in 5% CO_2 atmosphere for 48 h. Then, the viability of the macrophages was determined with the colorimetric 3-(4,5 dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide (MTT; Sigma) method. After 2 h, the reaction was interrupted by the addition of a solution composed by hydrochloric acid and isopropanol and absorbance at 570 nm was measured in an Elisa reader. Each assay was performed in triplicate.

2.4. Chemicals

The 4-amino-7-chloroquinoline derivatives were treated with 2 eq. of propargyl bromide and K_2CO_3 in EtOH at 0 °C for 72 h producing compounds **5**-**8** in 50 to 60% yield (Scheme 1). The addition of 4 eq. of propargyl bromide in the same conditions led to compounds **9**-**11** in 50 to 60% yield. Finally, the platinum (II) complexes **12**-**16** were synthesized by reacting K_2PtCl_4 and the intermediates **1**, **2**, **5** and **9** respectively, at 80–90% yield (Scheme 1). The compounds were well characterized by ^{1}H NMR, ^{13}C NMR, IR, elemental analyses and mass spectra CG MS.



Scheme 1. Reagents and conditions: a: propargyl bromide, K_2CO_3, EtOH, 25 °C, 48 h, 50 to 60%; b: K_2PtCl_4, 24 to 48 h, 25 °C, 70 to 80%.