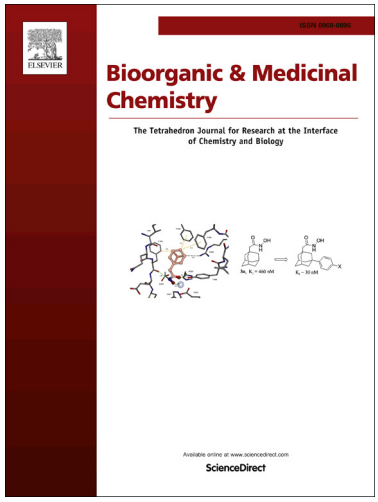
Accepted Manuscript



Anti-*Plasmodium falciparum* activity of quinoline-sulfonamide hybrids

Luiz C.S. Pinheiro, Núbia Boechat, Maria de Lourdes G. Ferreira, Carlos C.S. Júnior, Antônio M.L. Jesus, Milene M.M. Leite, Nicolli B. Souza, Antoniana U. Krettli

PII: S0968-0896(15)00550-7
DOI: http://dx.doi.org/10.1016/j.bmc.2015.06.056
Reference: BMC 12412

To appear in: *Bioorganic & Medicinal Chemistry*

Received Date: 29 April 2015
Revised Date: 12 June 2015
Accepted Date: 20 June 2015

Please cite this article as: Pinheiro, L.C.S., Boechat, N., Ferreira, d.L.G., Júnior, C.C.S., Jesus, A.M.L., Leite, M.M.M., Souza, N.B., Krettli, A.U., Anti-*Plasmodium falciparum* activity of quinoline-sulfonamide hybrids, *Bioorganic & Medicinal Chemistry* (2015), doi: http://dx.doi.org/10.1016/j.bmc.2015.06.056

Bioorganic & Medicinal Chemistry
journal homepage: www.elsevier.com

Anti-*Plasmodium falciparum* activity of quinoline-sulfonamide hybrids

Luiz C. S. Pinheiro[a] , Núbia Boechat[a *] , Maria de Lourdes G. Ferreira[a] , Carlos C. S. Júnior[a, b] , Antônio M. L. Jesus[a] , Milene M. M. Leite[a] , Nicolli B. Souza[c] and Antoniana U. Krettli[c,d,*]

[a] *Departamento de Síntese de Fármacos, Instituto de Tecnologia em Fármacos, Farmanguinhos - FIOCRUZ, Rua Sizenando Nabuco 100, Manguinhos, Rio de Janeiro, RJ, 21041-250, Brazil.*
[b] *Programa de Pós Graduação em Farmacologia e Química Medicinal, Instituto de Ciências Biomédicas, Universidade Federal do Rio de Janeiro, Rio de Janeiro, RJ, Brazil.*
[c] *Centro de Pesquisas René Rachou, CPqRR - FIOCRUZ, Belo Horizonte, MG, 30190-002, Brazil.*
[d] *Programa de Pós Graduação em Medicina Molecular. Faculdade de Medicina. Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brazil.*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
malaria
quinoline
sulfonamide
hybrids
Plasmodium falciparum

ABSTRACT

Fifteen quinoline-sulfonamide hybrids, with a 7-chloroquinoline moiety connected by a linker group to arylsulfonamide moieties with different substituents in the 4-position were synthesized and assayed against *P. falciparum*. The compounds displayed high schizonticidal blood activity *in vitro*, with IC_{50} values ranging from 0.05 to 1.63 µM, in the anti-HPR2 assay against clone W2-chloroquine-resistant; ten of them showed an IC_{50} (ranging from 0.05 to 0.40 µM) lower than that of chloroquine and sulfadoxine. Among them, two compounds inhibited *P. berghei* parasitemia by 47 and 49% on day 5 after mice inoculation. The most active, in vivo, hybrid **13** is considered to be a new prototype for the development of an antimalarial drug against chloroquine-resistant parasites.

1. Introduction

The World Health Organization (WHO) estimates that approximately 3.2 billion people in 97 countries and territories in tropical and subtropical regions are at risk of acquiring malaria, and 1.2 billion are at high risk. Approximately 198 million cases of malaria occurred globally in 2013, leading to 584 000 deaths[1]. The difficulty in controlling the mosquito vector or developing an effective vaccine, in addition to the spread of antimalarial drug resistant parasites, makes the development of antimalarial drugs the main strategy to control the disease[2].

Due to the high parasitic resistance exhibited by *P. falciparum* to most available drugs, monotherapy is no longer used to treat malaria. The WHO recommends the use of artemisinine-combined therapies (ACTs) to treat simple and severe falciparum malaria, using artemether plus lumefantrine; artesunate plus amodiaquine or mefloquine; artesunate plus sulfadoxine-pyrimethamine; or dihydrortemisinin plus piperaquine, among other ACTs[3].

The combined therapy with the simultaneous use of two or more drugs with different modes of action aims to prevent or delay the onset of drug resistance. In addition, it is often more effective if a mutant parasite resistant to one of the drugs emerges during the course of the infection, allowing the other drug to kill the parasite[3]. Non-artemisinin based therapies include sulfadoxine-pyrimethamine plus chloroquine (CQ) or amodiaquine.

In the recent literature, several new antimalarial compounds have been described, however quinoline derivatives are still the dominate class[4-9]. A new generation of hybrids antimalarial drugs instead of combined drugs has the advantages of a lower risk of drug-drug adverse interactions and greater treatment adherence[10-11]. Synthetic hybrid compounds designed to increase the efficacy of quinoline derivatives include chalcone-chloroquinoline **(I)**[12], AZT-CQ **(II)**[13], quinine-dihydroartemisinin **(III)**[14] and artesunate-mefloquine (MEFAS **IV**)[15]; some of these have reached the stage of clinical trials[16].

In our previous search for new drugs against malaria, the importance of 2-(trifluoromethyl)[1,2,4]triazolo[1,5-

* Corresponding authors. Tel.: +55-21-3977-2456; fax: +55-21-2560-2518
e-mail: boechat@far.fiocruz.br; and akrettli@cpqrr.fiocruz.br