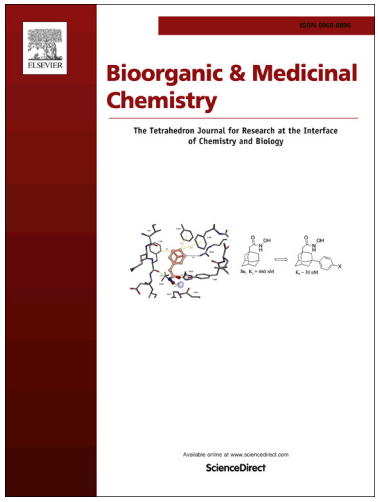
Accepted Manuscript



Synthesis, biological profiling and mechanistic studies of 4-aminoquinoline-based heterodimeric compounds with dual trypanocidal-antiplasmodial activity

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PII: S0968-0896(15)00047-4
DOI: http://dx.doi.org/10.1016/j.bmc.2015.01.031
Reference: BMC 12034

To appear in: *Bioorganic & Medicinal Chemistry*

Received Date: 14 December 2014
Revised Date: 16 January 2015
Accepted Date: 19 January 2015

Please cite this article as: Sola, I., Castellà, S., Viayna, E., Galdeano, C., Taylor, M.C., Gbedema, S.Y., Pérez, B., Victòria Clos, M., Jones, D.C., Fairlamb, A.H., Wright, C.W., Kelly, J.M., Muñoz-Torrero, D., Synthesis, biological profiling and mechanistic studies of 4-aminoquinoline-based heterodimeric compounds with dual trypanocidal-antiplasmodial activity, *Bioorganic & Medicinal Chemistry* (2015), doi: http://dx.doi.org/10.1016/j.bmc.2015.01.031

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

Synthesis, biological profiling and mechanistic studies of 4-aminoquinoline-based heterodimeric compounds with dual trypanocidal-antiplasmodial activity

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Molecular hybridization
Trypanocidal agents
Antimalarial agents
Trypanothione reductase inhibitors
Inhibitors of β-haematin formation
Brain permeability

ABSTRACT

Dual submicromolar trypanocidal-antiplasmodial compounds have been identified by screening and chemical synthesis of 4-aminoquinoline-based heterodimeric compounds of three different structural classes. In *Trypanosoma brucei,* inhibition of the enzyme trypanothione reductase seems to be involved in the potent trypanocidal activity of these heterodimers, although it is probably not the main biological target. Regarding antiplasmodial activity, the heterodimers seem to share the mode of action of the antimalarial drug chloroquine, which involves inhibition of the haem detoxification process. Interestingly, all of these heterodimers display good brain permeabilities, thereby being potentially useful for late stage human African trypanosomiasis. Future optimization of these compounds should focus mainly on decreasing cytotoxicity and acetylcholinesterase inhibitory activity.

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1. Introduction

Human African trypanosomiasis (HAT or sleeping sickness), one of the 17 so-called neglected tropical diseases, and malaria have an enormous health and socioeconomic impact in the developing world.[1-3] Notwithstanding a wide-scale reduction in the number of infected people over recent years due to public health campaigns, HAT and malaria are still leading causes of morbidity and death and of loss of productivity especially in sub-Saharan Africa.[1,4-6] Malaria annually kills more than 600,000 people.[3] The numbers dying from trypanosomiasis have recently been reduced to around 10,000, but the disease retains the potential for major epidemic outbreaks, and it has a devastating impact on domestic livestock.

HAT and malaria are caused by protozoan parasites of the genera *Trypanosoma* and *Plasmodium*, which are transmitted to humans through the bite of blood-feeding infected tsetse flies and female *Anopheles* mosquitoes, respectively. The most common form of HAT in humans, accounting for nearly 95% of cases, is caused by *Trypanosoma brucei gambiense*, which results in a chronic infection that can last for years. A less common form of the disease with a more acute clinical presentation is caused by the subspecies *Trypanosoma brucei rhodesiense.* In the case of malaria, five species of *Plasmodium* can cause the disease, *Plasmodium falciparum* being the most common and deadly.

HAT begins with a hemolymphatic stage, where the parasite multiplies within the blood, lymph and subcutaneous tissue, and which is characterized by the appearance of nonspecific symptoms such as fever and headache. Invasion of the central nervous system (CNS) by the parasite, after crossing the blood–brain barrier (BBB), leads to the late-stage meningoencephalitic disease. This gives rise to severe neurological symptoms such as psychiatric, motor and sleep disturbances and loss of consciousness. Without treatment, this results in coma and death.

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