Bioorganic Chemistry 105 (2020) 104280

Contents lists available at ScienceDirect

Bioorganic Chemistry

journal homepage: www.elsevier.com/locate/bioorg

Synthesis and anti-parasitic activity of *N*-benzylated phosphoramidate Mg^{2+}-chelating ligands

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ARTICLE INFO

Keywords:
N-benzylated phosphoramidate esters
Fosmidomycin analogues
Antimalarial
Anti-trypanosmal

ABSTRACT

A series of *N*-benzylated phosphoramidate esters, containing a 3,4-dihydroxyphenyl Mg^{2+}-chelating group, has been synthesised in five steps as analogues of fosmidomycin, a *Plasmodium falciparum* 1-deoxy-1-D-xylulose-5-phosphate reductoisomerase (*Pf*DXR) inhibitor. The 3,4-dihydroxyphenyl group effectively replaces the Mg^{2+}-chelating hydroxamic acid group in fosmidomycin. The compounds showed very encouraging anti-parasitic activity with IC_{50} values of 5.6–16.4 μM against *Plasmodium falciparum* parasites and IC_{50} values of 5.2 – 10.2 μM against *Trypanosoma brucei brucei (T.b.brucei)*. Data obtained from *in silico* docking of the ligands in the *Pf*DXR receptor cavity (3AU9)[5] support their potential as PfDXR inhibitors.

1. Introduction

Malaria remains a major health challenge in the developing world [1] and the accelerated emergence of resistance to available drugs [2] calls for sustained attention to the discovery of novel antimalarial agents. *Plasmodium falciparum* 1-deoxy-1-D-xylulose-5-phosphate reductoisomerase (*Pf*DXR) has been validated as a target for therapeutic intervention [3–5]. 1-Deoxy-D-xylulose-5-phosphate (DOXP), the natural substrate for the *Pf*DXR enzyme [6], contains a phosphoric acid group and an α-hydroxycarbonyl chelating moiety, which interact, respectively, with a phosphate-binding site and a Mg^{2+} co-factor in the enzyme active site [5]. Fosmidomycin **1** and its *N*-acetyl derivative FR900098 **2** (Fig. 1) are effective *Pf*DXR inhibitors [3], but their clinical use is precluded by problems associated with recrudescence and rapid *in vivo* clearance [7–9]. Researchers have consequently explored other phosphonic acid analogues [10,11]. The location of vacant hydrophobic pockets adjacent to the *Pf*DXR active site [12–14] has led our own [14–18] and other groups to develop potential *Pf*DXR inhibitors containing hydrophobic moieties to enhance binding within the receptor cavity. Haemers *et al.* [19], for example, have reported the preparation of a series of FR900098 derivatives, which contain hydrophobic α-aryl substituents and which exhibited encouraging inhibition of *Escherichia coli* DXR and the *Plasmodium falciparum* parasite; the most active of these was the 3,4-dichlorophenyl derivative **3** which exhibited submicromolar IC_{50} values. Attention has also been given to the preparation of "reverse" fosmidomycin analogues in which the hydroxamate Mg^{2+}-chelating moiety is replaced by an *N*-methylhydroxamic acid group [17,18,20], while Deng *et al.* [13]. have reported a potent DXR inhibitor (IC_{50} = 1.4 μM) containing an *N*-hydroxy-2-pyrdinone Mg^{2+}-chelating moiety.

Another parasitic infection endemic to regions of the African continent, Nagana (African cattle sleeping sickness), is due to *Trypanosoma brucei brucei* (*T. brucei brucei*) for which Tsetse flies (*Glossina*) serve as the vector [21]. There have been substantial improvements in the control of the disease but currently used drugs are few in number and susceptible to resistance [22]. *Trypanosoma brucei gambiense*, the parasite generally responsible for human African trypanosomiasis (HAT) is carried by animals [23]. Reports on the identification of potential *T. brucei brucei* enzyme targets [22] have yet to include DXR.

In this communication, we describe the synthesis of a series of novel, *N*-benzylated phosphoramidate ester derivatives of the generalised phosphoramidic acid **4**, their anti-parasitic activity against *P.falciparum* and trypanosomal targets, and exploratory *in silico* studies of the *Pf*DXR binding potential of the corresponding mono-deprotonated phosphoramidic acids.

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https://doi.org/10.1016/j.bioorg.2020.104280
Received 29 May 2020; Received in revised form 11 September 2020; Accepted 12 September 2020
Available online 17 September 2020