Bioorganic & Medicinal Chemistry 19 (2011) 1321–1327

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

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

Synthesis and evaluation of phosphonated *N*-heteroarylcarboxamides as DOXP-reductoisomerase (DXR) inhibitors

Taryn Bodill [c], Anne C. Conibear [a], Gregory L. Blatch [b,c], Kevin A. Lobb [a,c], Perry T. Kaye [a,c,*]

[a] Department of Chemistry, Rhodes University, Grahamstown 6140, South Africa
[b] Biomedical Biotechnology Research Unit and Department of Biochemistry, Rhodes University, Grahamstown 6140, South Africa
[c] Centre for Chemico- and Biomedicinal Research, Rhodes University, Grahamstown 6140, South Africa

ARTICLE INFO

Article history:
Received 22 September 2010
Revised 22 November 2010
Accepted 25 November 2010
Available online 2 December 2010

Keywords:
Anti-malarial
Phosphonates
DOXP-reductoisomerase
Enzyme inhibitors
In silico docking
Saturation Transfer Difference NMR

ABSTRACT

The diethyl esters and disodium salts of a range of heteroarylcarbamoylphosphonic acids have been prepared and evaluated as analogues of the highly active DOXP-reductoisomerase (DXR) inhibitor, fosmidomycin. Computer-simulated docking studies, Saturation Transfer Difference (STD) NMR analysis and enzyme inhibition assays have been used to explore enzyme-binding and -inhibition potential, while in silico analysis of the DXR active site has highlighted the importance of including a well-parameterised metal co-factor in docking studies and has revealed the availability of an additional binding pocket to guide future drug design.

1. Introduction

Malaria continues to be an enormous health-threat in the developing world. Treatment is compounded by the phenomenon of drug resistance, and the development of novel therapeutics has become a research priority.[1–3] *Plasmodium falciparum* (*Pf*) is the parasite responsible for the most dangerous form of human malaria, and the enzyme, 1-deoxy-1-D-xylulose-5-phosphate (**1**; Fig. 1) reductoisomerase (*Pf*DXR) has recently been validated as a target for the design of potential antimalarial drugs.[4,5] This enzyme is involved in a parasite-specific, isoprenoid biosynthetic DOXP/MEP pathway, for which the natural product, fosmidomycin **2**,[6,7] and its acetyl analogue, FR900098 **3**,[6,7] have been shown to act as inhibitors. Fosmidomycin **2** was isolated from *Streptomyces lavendulae* in the 1970s and found to have antibiotic and herbicidal properties.[5,6,8,9] The DOXP/MEP pathway has also been found in several pathogenic species such as *Helicobacter pylori, Mycobacterium tuberculosis*, *Escherichia coli (Ec)* and *P. falciparum* but, since it is not found in humans, it has obvious potential as a target for chemotherapy.[8] In humans, fosmidomycin **2** has been shown to be active against uncomplicated *P. falciparum* malaria, but its efficacy as a clinical drug is compromised by poor absorption, short plasma half-life and the high observed rate of recrudescence.[7,8] Nevertheless, the high levels of DXR inhibition exhibited by fosmidomycin **2** and FR900098 **3** have made these compounds particularly promising leads for the development of novel and effective antimalarials.[7] Although few of the DXR inhibitors described in the literature have been more effective than fosmidomycin, they provide useful structure–activity relationships to guide the design of new inhibitors. Deng et al. have highlighted the importance of a metal-coordinating group, especially nitrogen- and oxygen-containing functionalities which are able to bind to the hard Mg^{2+} ion.[10] The phosphonate moiety of fosmidomycin **2** is more biologically stable than the corresponding phosphate of DOXP **1** and the importance of the double negative charge on the phosphonate group has also been demonstrated.[11,12]

In our laboratories, attention has been given to designing and synthesising fosmidomycin **2** analogues as potential DXR inhibitors, and we have recently reported[9] the synthesis of a series of phosphonated *N*-phenylcarboxamides **4**. We now describe: (i) the preparation of novel *N*-heteroarylamino-2-oxoethylphosphonate esters **8a–e** and the disodium salts **11a–e** of the corresponding phosphonic acids **9a–e** (Scheme 1); (ii) the use of *Ec*DXR in STD NMR ligand-binding and enzyme inhibition studies; (iii) the results of in silico ligand-docking studies; and (iv) progress in the topological analysis of the enzyme active site.

2. Results and discussion

2.1. Chemistry

Deng et al.[10] have highlighted the role of metal-coordinating groups (especially nitrogen- or oxygen-containing functionalities)

* Corresponding author. Tel.: +27 46 6037030; fax: +27 46 6225109.
E-mail address: P.Kaye@ru.ac.za (P.T. Kaye).

0968-0896/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmc.2010.11.062