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Synthesis of *N*-Substituted phosphoramidic acid esters as "reverse" fosmidomycin analogues

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ABSTRACT

An efficient synthetic pathway to a series of novel "reverse" fosmidomycin analogues has been developed, commencing from substituted benzylamines. In these analogues, the fosmidomycin hydroxamate moiety is reversed and the tetrahedral methylene carbon adjacent to the phosphonate moiety is replaced by a nitrogen atom bearing different benzyl groups. The resulting phosphonate esters were designed as potential antimalarial "pro-drugs".

1. Introduction

The phosphonic acid derivatives Fosmidomycin **1** and its *N*-acetyl analogue FR900098 are active inhibitors of the *Plasmodium falciparum* 1-deoxy-D-xylulose-5-phosphate reductase (*Pf*DXR) enzyme [1] – an established antimalarial target [2]. The therapeutic value of these compounds is, however, limited by their rapid *in vivo* clearance and the recrudescence associated with their use [3,4] and attention has turned to the development of novel analogues. Brücher et al. [5] have reported the preparation of promising ligands **2** (Fig. 1) which exhibit high inhibitory potency against *Pf*DXR. In addition to a 'reversed' arrangement of the hydroxamate moiety, these compounds contain an α-phenyl substituent capable of occupying the hydrophobic pocket adjacent to the *Pf*DXR active-site.

Our own research has focussed on developing ligands which exploit such hydrophobic binding opportunities [6–8] and, more particularly, on phosphoramidic acid derivatives **3** in which the hydrophobic aryl group is attached to nitrogen rather than to a tetrahedral sp^3 carbon (as in compound **2**), thus obviating chirality issues. Although the phosphonic acid moiety is expected to bind to the *Pf*DXR phosphate binding-site, phosphonate esters have, in fact, been shown to be effective *Pf*DXR inhibitors [5]. The use of ester derivatives as pro-drugs would be expected not only to delay exposure of the phosphoramidic acid moiety to premature decomposition, but also to decrease the overall polarity of the ligands, possibly mitigating the unacceptably rapid clearance exhibited by fosmidomycin itself. Recent reports [9,10] reflect the potential of aryl and dialkyl phosphoramidate pro-drugs as hepatitis C virus inhibitors. In this communication, we now report on our attempts to access the *N*-aryl compounds **3** and the eventual synthesis of a range of *N*-benzylated phosphoramidate ester derivatives **4** as "reverse" fosmidomycin analogues.

2. Results and discussion

In designing the synthesis of the *N*-aryl phosphoramidic acid analogues (**3**), compound **5** was identified as a critical intermediate and several approaches to this compound were explored (Scheme 1). In ***Approach I***, ethyl 3-bromopropanoate **7**, obtained by acid-catalysed esterification of 3-bromopropanoic acid **6** [11–13] (Scheme 1), was reacted with aniline and NaH in dry THF to furnish compound **8** which contains the desired bimethylene linking group

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