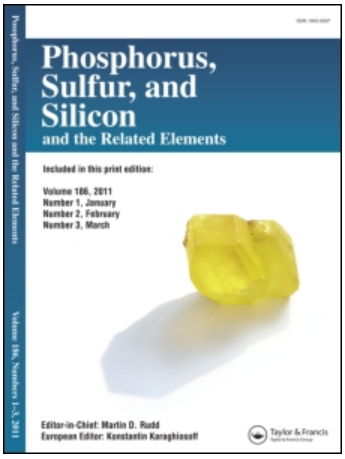

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Synthesis of Novel Bisphosphonate Inhibitors of Phosphoglycerate Kinase (3-PGK) (E.C.2.7.2.3)

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SYNTHESIS OF NOVEL BISPHOSPHONATE INHIBITORS OF PHOSPHOGLYCERATE KINASE (3-PGK) (E.C.2.7.2.3)

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Abstract Novel, aromatic bisphosphonates have been synthesised as non-systematic analogues of 1,3-*bis*phosphoglyceric acid (1,3-BPG). These incorporate non-scissile α-halo and α-methylene phosphonates and have submicromolar K_i values for 3-PGK.

Keywords: halogenation, isopolar, isosteric, spectrophotometric assay, aromatic.

INTRODUCTION

3-PGK converts 1,3-*Bis*phosphoglycerate (1,3-BPG) into 3-phosphoglyceric acid (3-PGA), forming ATP. In a minor alternative process, 1,3-BPG is converted into 2,3-BPG by *bis*phosphoglycerate mutase, (BPGM), and this is then hydrolysed to 3-PGA by 2,3-BPG phosphatase. The selective inhibition of the kinase but not of the mutase is a significant medical target. Crystallographic analysis of these two enzymes shows that the active site of 3-PGK [1] is larger than that of BPGM.[2, 3] Thus, it should be possible to identify inhibitors of 3-PGK which are excluded from the site of the mutase. We have synthesised 'non-systematic' inhibitors whose structures are generally based on 1,3-BPG and are 1,4- or 1,5-bisphosphonates with an aromatic spacer.

SYNTHESIS AND RESULTS

Our need for isopolar and isosteric mimics of bisphosphates calls for synthesis of a range of bisphosphonates and their monochloro, dichloro, monofluoro and difluoromethylene analogues. We have used pyridine and benzene as the aromatic spacer and are working on use of pyrrole and thiophene cores. All the bisphosphonic acids are made as their tetraalkyl esters and deprotected using trimethylsilylbromide or 6N hydrochloric acid. They are purified and tested as their cyclohexylammonium salts. The testing of the bisphosphonic acids was carried out using 3-PGK isolated from human blood and the K_i values were obtained spectrophotometrically by monitoring NAD^+ at 340 nm for the back reaction. The general order of the results was checked by a luminometric assay for the forward reaction. The α-chloro and fluoromethylene bisphosphonates tested showed submicromolar K_i values. The K_i values for the α-hydroxy and methylene phosphonates were around 100μM.
These results clearly show good leads on strong, competitive inhibitors for 3-PGK. Routes to the dichloro and difluoromethylene phosphonates have now been established. Also, routes are being investigated to bisphosphonates with thiophene and pyrrole cores.

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