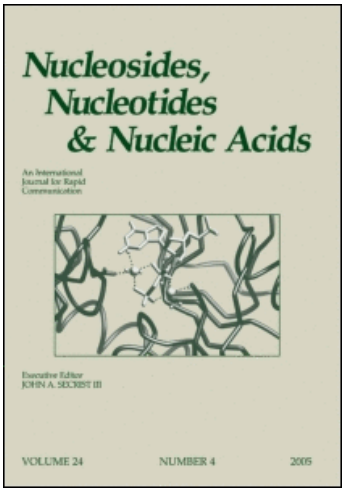

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PHOSPHORAMIDATE DERIVATIVES OF 2′,5′-DIDEOXYADENOSINE AS POTENTIAL INHIBITORS OF THE EDHF PHENOMENON

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▫ *P-site inhibitors of adenyl cyclase, such as the dideoxynucleosides 2′,3′-ddA and 2′,5′-ddA, have been shown to attenuate EDHF phenomenon in rabbit arteries and veins. In order to present the dideoxynucleosides as pre-activated nucleotides and bypass the kinase, as well as to prevent their metabolism to dideoxyinosine by adenosine deaminase, the aryloxyphosphoramidate approach has been successfully applied, initially on the 2′,3′-ddA. In the present work a new series of 2′,5′-ddA phosphoramidates has been synthesized, representing the first example of phosphoramidate protide not at the 5′-position.*

Keywords EDHF Phenomenon, Phosphoramidate, Protide

INTRODUCTION

The phosphoramidate approach, conceived by McGuigan et al.[1] involves the addition to nucleoside derivatives of a phosphate moiety shielded by hydrophobic groups, generating lipophilic pro-drugs that readily enter the cell to free the mononucleotides, by passing the first step of kinase-mediated activation. This strategy (already applied with success to nucleoside derivatives supporting antiviral and anticancer activity) has been recently addressed to P-site inhibitors of adenylyl cyclase, such as the dideoxyadenosine nucleosides 2′,3′-ddA and 2′,5′-ddA, which have been shown to attenuate the EDHF (endothelium-derived hyperpolarizing factor) phenomenon in rabbit arteries and veins. The phenyl methoxyalaninyl phosphoramidate derivative of 2′,3′-ddA (2′,3′-ddA-PMAPh) has already shown enhanced inhibitory activity compared to the parent nucleoside itself.[2]

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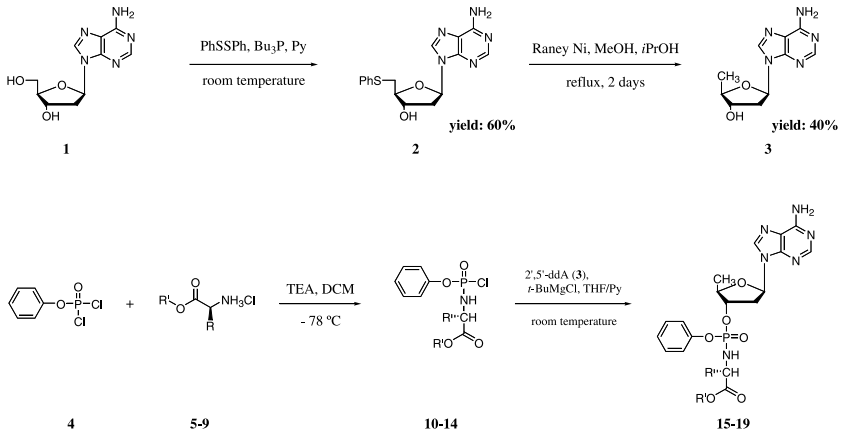
Knowing that the addition of phosphate groups at the 3′-site enhances the ability of ddA nucleosides to inhibit adenylyl cyclase, a new series of 2′,5′-ddA phosphoramidates has been synthesized, using different amino acids (glycine, L-alanine, L-phenylalanine) containing alternative ester moieties (methyl and benzyl groups). These represent the first example of phosphoramidate protide not at the 5′-position. A similar approach has recently been presented with SATE protection.[3]

The synthetic pathway involves firstly the preparation of 2′,5′-dideoxyadenosine by a two-step reaction: conversion of 2′-deoxyadenosine (**1**) to the 5′-phenylthio derivative (**2**), followed by Raney nickel hydrogenation to afford compound (**3**) in 40% yield.[4]

The target structures (**15–19**) were obtained following the phosphoramidate approach mainly developed in our laboratories.[5]

The synthesis involved stoichiometric treatment of aryloxyphosphorodichloridates with the carboxy-protected amino acids in the presence of TEA. 2′,5′-ddA (**3**) was then coupled with the appropriate phosphorochloridate (**10–14**) in the presence of 1.4 equivalents of *t*-BuMgCl in THF/Py at room temperature (Scheme 1).

The inhibitory effect on the EDHF phenomenon was evaluated by electrophysiological tests performed on iliac arteries obtained from NZW rabbits. Initial results showed that the lipophilic phosphoramidate 2′,3′-ddA-PMAPh had enhanced activity as an inhibitor of the EDHF phenomenon of *ca.* 7-fold compared to its parent nucleoside 2′,3′-ddA. IC_{50} values for 2′,3′-ddAdo and 2′,3′-ddA-PMAPh were estimated as 86.2 μM and 12.6 μM, respectively. 2′,5′-ddA is more potent than 2′,3′-ddA by 1.3-fold and its phosphoramidate derivative 2′,5′-ddA-PMAPh is *ca.* 107-fold more potent than the parent nucleoside and *ca.* 21-fold more potent than 2′,3′-ddA-PMAPh. IC_{50} values for 2′,5′-ddA and 2′,5′-ddA-PMAPh were estimated as 64.4 μM and 0.6 μM, respectively.



SCHEME 1

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