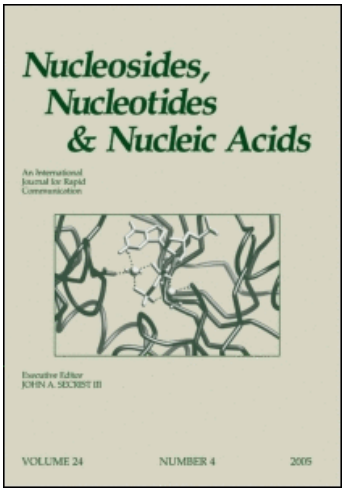

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Non-inhibition of Acetylcholinesterase by *cyclo*Sal Nucleotides

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ABSTRACT

An acetylcholinesterase (AChE) assay based on the Rappaport method was established to investigate the behaviour of several *cyclo*Sal nucleotides against AChE from *electrophorus electricus* and human sources (purified enzymes). AChE is a physiologically essential enzyme as it catalyzes the hydrolysis of the neurotransmitter acetylcholine. No inhibition was observed in any of the cases.

Key Words: AChE; *cyclo*Sal; Inhibition; Pronucleotides.

INTRODUCTION

The *cyclo*Sal pronucleotide system has been developed for a selective intracellular delivery of therapeutically active nucleoside monophosphates (NMPs) and has already been applied on different nucleoside analogues successfully leading to improved biological activities.[1] The introduction of different substitution patterns in the aryl moiety of the *cyclo*Sal nucleotides allows a fine-tuning of the stability

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of the pronucleotides.[2] As *cyclo*Sal nucleotides belong to the class of reactive organophosphates, they may inhibit cholinesterases irreversibly by reaction with the serine residue of the catalytic triade in the active site (*suicide mechanism*). Especially an inhibition of acetylcholinesterase (AChE) would cause serious side effects as this enzyme plays physiologically an essential role catalyzing the hydrolysis of the neurotransmitter acetylcholine. Therefore, investigations had to be carried out concerning a possible interaction of AChE with *cyclo*Sal nucleotides.

RESULTS

An AChE assay was established based on the known Rappaport procedure.[3] It was based on a photometrical monitoring of the enzymatic reaction in the presence of different concentrations of the possible inhibitor. Two types of AChE were used for the assay, purified human AChE as well as purified AChE from *electrophorus electricus* (Sigma^{TM}). A variety of *cyclo*Sal nucleotides was investigated to determine possible structural influences on their behaviour towards AChE. Therefore, 3-methyl-*cyclo*Sal derivatives of the monophosphates of 2′,3′-dideoxy-2′,3′-didehydrothymidine (d4T), (*E*)-5-(2-bromovinyl)-2′-deoxyuridine (BVDU), 2′,3′-dideoxy-3′-azidothymidine (AZT), 5-fluoro-2′-deoxyuridine (FdU), 2′-deoxythymidine (dT), 2′-deoxyguanosine (dG), acyclovir, penciclovir, ganciclovir, T-penciclovir and T-ganciclovir have been used for the experiments. Furthermore, derivatives of *cyclo*Sal d4T monophosphate bearing different substitution patterns in the aryl moiety including substituents in the benzyl position[2] were investigated. Separation of the diastereomeric mixtures of some of the *cyclo*Sal nucleotides (R_P and S_P configuration) by preparative HPLC allowed to determine possible stereochemical influences. The structural variations which were encountered using the described test compounds are summarized in Fig. 1.

However, none of the *cyclo*Sal nucleotides described above showed inhibitory activity towards both AChEs used in this study. This result clearly proves that the *cyclo*Sal nucleotides can *not* act as suicide inhibitors of AChE.

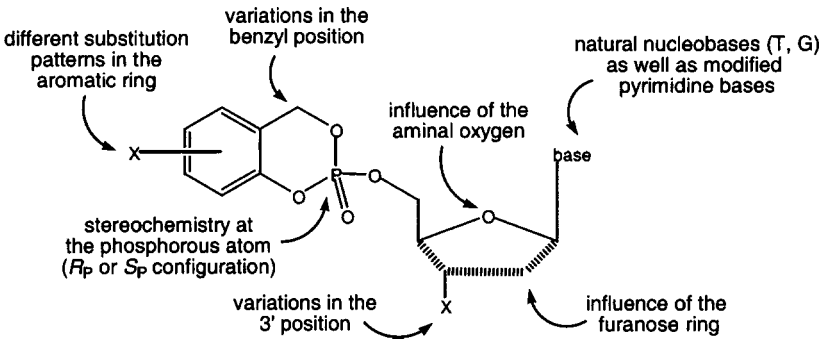

Figure 1. Structural variations encountered for the AChE assay, shown on the prototype of a *cyclo*Sal-nucleotide.

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