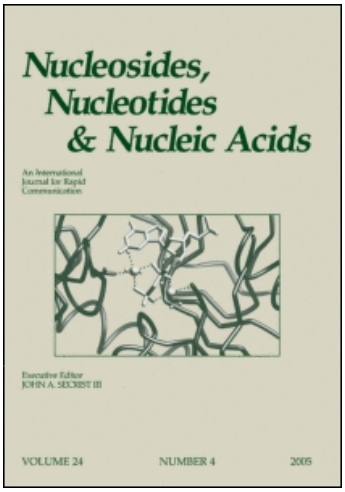

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Prodrugs of Ara-CMP and Ara-AMP with a *S*-Acyl-2-thioethyl (SATE) Biolabile Phosphate Protecting Group: Synthesis and Biological Evaluation

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PRODRUGS OF ARA-CMP AND ARA-AMP WITH A *S*-ACYL-2-THIOETHYL (SATE) BIOLABILE PHOSPHATE PROTECTING GROUP: SYNTHESIS AND BIOLOGICAL EVALUATION

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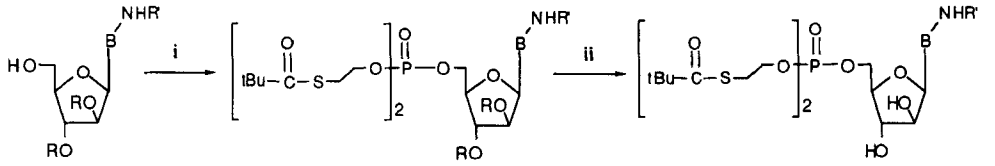
ABSTRACT. The bis(*S*-pivaloyl-2-thioethyl) phosphotriesters of Ara-C and Ara-A were synthesized as potential bioreversible mononucleotide prodrugs. Some N- and O-acylated derivatives were also prepared with the aim to modify the lipophilicity of the title pronucleotides. Compounds were tested for their antitumor/antiviral activity against a variety of tumor cells and viruses.

Long-term chemotherapy with Ara-C in patients with acute leukemia may result in development of resistant cell populations. A similar induction of cellular resistance was observed after treatment with Ara-A in patients with HSV infection. Several cellular mechanisms have been proposed for the decreased intracellular Ara-NuTP level which results in a lowered *in vitro* and *in vivo* efficacy of both Ara-C and Ara-A: i) suppression of the activity of kinases which phosphorylate the nucleoside analogs to their corresponding NuMP; ii) increased activation of deaminases; iii) decreased nucleoside uptake by the cells.

The pronucleotide approach uncovered a new valuable strategy in order to overcome some of these cellular resistance mechanisms. Among the prodrugs of bio-active mononucleotides, mononucleoside phosphotriester derivatives incorporating biolabile phosphate protections such as *S*-acyl-2-thioethyl (SATE) groups have proved to be very

effective[1]. We decided to undertake the synthesis of bis(*S*-pivaloyl-2-thioethyl) phosphotriester derivatives of Ara-C and Ara-A in order to explore the potential of this pronucleotide approach in the bioactive arabinonucleoside series. In addition, some N- and O-acylated prodrugs were synthetized with the aim to study the effect of increased lipophilicity on their biological activity.

Chemistry. The synthesis of the phosphotriesters **5a-b**, **6-7a** and **8a-b** was carried out starting from the suitable silylated or acylated nucleosides according to a published procedure[1]. Final deprotection of silyl groups was performed with $Et_3N{\cdot}3HF$ giving **9a-b** and **10-11a** in overall yields of 60-80% over two steps. For all new compounds high-field multinuclear NMR and mass spectroscopies were consistent with the structures.



1a-b: R = TBDMS; R' = H
2a: R = TBDMS; R' = acetyl
3a: R = TBDMS; R' = stearoyl
4a: R = acetyl; R' = acetyl
4b: R = acetyl; R' = H

5a-b: R = TBDMS; R' = H
6a: R = TBDMS; R' = acetyl
7a: R = TBDMS; R' = stearoyl
8a: R = acetyl; R' = acetyl
8b: R = acetyl; R' = H

9a-b: R' = H
10a: R' = acetyl
11a: R' = stearoyl

a: B = cytosin-1-yl; **b:** B = adenin-9-yl

(i) bis(*S*-pivaloyl-2-thioethyl) *N,N*-diisopropylphosphoramidite, tetrazole, THF, tBuOOH; (ii) $NEt_3{\cdot}3HF$, THF.

Biology. The deprotected compounds **9-11** as well as some intermediates were tested for their antitumor/antiviral activity against a variety of sensitive and resistant tumor cells and viruses. In the case of **9a** the drug only partially overcame the resistance problem[2], suggesting an increased activation of non-specific phosphorylases or a decreased Ara-CTP incorporation into the cellular DNA in Ara-C resistant cell lines. **9b** showed increased activity against a variety of wild-type and resistant viruses, as compared with Ara-A, but in some cases it strongly impaired cell growth. Details on both synthesis and biological activity will be published elsewhere.

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