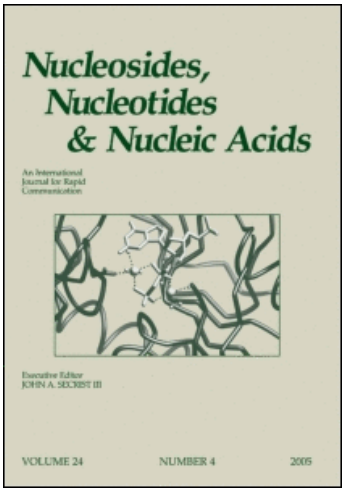

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A New Cyclic Phosphoramidate D4T Prodrug Approach *cyclo*Amb-D4T-Phosphoramidates

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A NEW CYCLIC PHOSPHORAMIDATE D4T PRODRUG APPROACH *CYCLO*AMB-D4T-PHOSPHORAMIDATES

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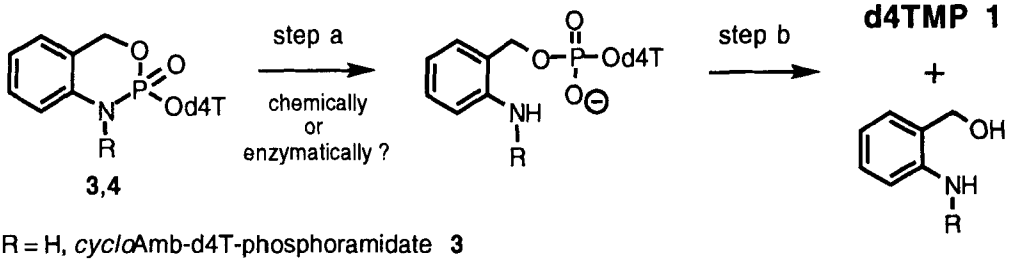
Abstract: A new potential phosphoramidate prodrug approach for d4T **1** is described. In hydrolyses studies the *cyclo*Amb-d4T-phosphoramidates **2** and **3** proved to deliver d4TMP following a tandem reaction.

Here we present the synthesis and some properties of a new potential pro-nucleotide approach as neutral prodrug of d4TMP **1** of the antivirally active nucleoside analogue d4T **2**. As for the previously reported *cyclo*Sal-NMPs[1], the ***cyclo*aminobenzyl-d4T**-phosphoramidates **3** and **4** (*cyclo*Amb-d4T-phosphoramidate, Scheme 1) were designed to release the nucleotide **1** *selectively* by controlled, chemically induced hydrolysis following a tandem mechanism. The concept involves a sucessive, coupled cleavage of the amidate- and the benzylester of the phosphoramidate based on the different stabilities of these bonds.

Scheme 1: The proposed hydrolysis pathway of *cyclo*Amb-d4T-phosphoramidates **3,4**



R = H, *cyclo*Amb-d4T-phosphoramidate **3**

R = CH_3, *cyclo*-(*N*-methyl)-Amb-d4T-phosphoramidate **4**

*Cyclo*Amb-d4T-phosphoramidate **3** was synthesized using phosphorus(V)-chemistry. In contrast to the P(III)-chemistry use in the case of the *cyclo*Sal-NMPs, here we preferred the P(V)-reagents due to the reactivity of the amino-group in 2-aminobenzyl alcohol. D4T was

Table: PCs, log*P* and chemical hydrolysis half-lives in phosphate buffer

Compounds	PC 1-octanol/PB	log*P* 1-octanol/PB	$t_{1/2}$ in 25 mM PB at pH 7.3 [h]
d4T **2**	0.15	-0.82	--
3 (fast-diastereomer)	1.9	0.28	60.7
3 (slow-diastereomer)	2.3	0.36	41.5
4	2.4	0.38	< 3% in 100 h
*cyclo*Sal-d4TMP	1.9	0.28	4.6

converted to the phosphorusdichloridate with $P(O)Cl_3$ in the presence of triethylamine (TEA) in dry THF at -10°C. By further treatment with a solution of 2-aminobenzyl alcohol and TEA in THF, the cyclic phosphoramidate **3** was obtained in 38% yield. *Cyclo*-(*N*-methyl)-Amb-d4T-phosphoramidate **4** could not be prepared by this approach. Here, again P(III)-chemistry lead to the successful isolation of the amidate diester: *N*-Methyl-aminobenzyl alcohol was reacted with phosphorus trichloride in the presence of TEA to yield the cyclic chlorophosphoramidite. In the following "one-pot" reaction, d4T was treated with this cyclic chlorophosphoramidite in the presence of diisopropylethylamine (DIPEA) to obtain the *cyclo*-(*N*-methyl)-Amb-d4T-phosphoramidite which was subsequently oxidizied with *t*-butylhydroperoxide (TBHP) to give the title compound **4** in 17% yield.

The partition coefficients (PC) in 1-octanol/phosphate buffer (PB), pH 6.8 are a qualitative estimation of the lipophilic properties of *cyclo*Amb-d4T-phosphoramidates **3** and **4**. The PCs of **3** and **4** were by a factor 12-16 higher relative to d4T **2** and in the same order of magnitude as the corresponding *cyclo*Sal-d4TMP (Table).

As a first model for the physiological milieu, *cyclo*Amb-d4T-phosphoramidates **3** and **4** were hydrolyzed in 25 mM phosphate buffer, pH 7.3 at 37°C. The chemical hydrolyses were followed by means of HPLC. Under these conditions, *cyclo*Amb-d4T-phosphoramidate **3** was degraded with a $t_{1/2}$ of about 50 h. In contrast, the *N*-methylated *cyclo*-Amb-d4T-phosphoramidate **4** showed less than 3% degradation within 100 h. In comparison to *cyclo*Sal-d4TMP[1], the half-lives were increased by a factor 9-13 for the *cyclo*Amb-d4T-phosphoramidate **3**, while *cyclo*-(*N*-methyl)-Amb-d4T-phosphoramidate **4** showed scarcely degradation. Antiviral cell tests of **3** and **4** are in progress.

Reference

1. Meier, C.; Lorey, M.; De Clercq, E.; Balzarini, J.; *J. Med. Chem.* **1998**, *41*, 1417-1427; Meier, C.; *Synlett* **1998**, 233-242.