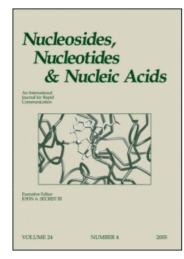
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Synthesis, Stability, and Biological Evaluation of 1,3-Dihydrobenzo[*c*]furan Analogue of d4T and Its SATE Pronucleotide

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Synthesis, Stability, and Biological Evaluation of 1,3-Dihydrobenzo[c]furan Analogue of d4T and Its SATE Pronucleotide

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ABSTRACT

The anti-HIV activity and stability studies of 1,3-dihydrobenzo[c]furan analogue of d4T are reported. The corresponding mononucleoside phosphotriester derivative bearing a *S*-pivaloyl-2-thioethyl (*t*BuSATE) group, as biolabile phosphate protection, is also studied.

Key Words: 1,3-Dihydrobenzo[c]furane; d4T; SATE pronucleotide.

In order to improve the physico-chemical parameters of 2',3'-didehydro-3'-deoxythymidine (d4T), we have recently reported the synthesis of its 1,3-dihydro-

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Scheme 1. Reagents and conditions: (i) Ref. 1; (ii) bis(S-pivaloyl-2-thioethyl) N,N-diisopropyl phosphoramidite, 1H-tetrazole, CH₃CN then tBuOOH, toluene.

Table 1. Chemical stability and lipophilicity of nucleoside 2 compared to d4T.

Compounds		2	d4T
t _{1/2}	pH 7.3	34 days	6 days
	pH 2.0	31 days	5 days
	pH 1.2	18 days	3 days
Log P ^a		0.55	-0.77

^aLog P determinations were performed using log P dB 4.5 calculations (ACD, Canada).

benzo[c]furan derivative (BcFT).^[1,2] Briefly, starting from the readily available phthalaldehyde **1**, the enantiomerically pure nucleosides **2** and **3** were obtained in 8% overall yield (Sch. 1).

The chemical hydrolysis of nucleoside 2 and d4T gives rise to the formation of thymine but BcFT was more stable than d4T in all the studied buffers (Table 1). As expected, the introduction of a benzene ring on the sugar residue increases the liphophilicity of the resulting structure.

The possibility to improve the anti-HIV efficiency of nucleoside analogues **2** and **3** using a pronucleotide approach was evaluated. Thus, the mononucleoside phosphotriesters **4** and **5** (Scheme) incorporating the *S*-pivaloyl-2-thioethyl (*t*BuSATE) group as biolabile phosphate protection were synthesised according to a previously published method. [3]

Compounds 2–5 were evaluated for their inhibitory effects on the replication of HIV-1 in human T4-lymphoblastoid cells, CEM-SS and MT-4. All compounds were found to be inactive at concentration up to $100\,\mu\text{M}$.

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