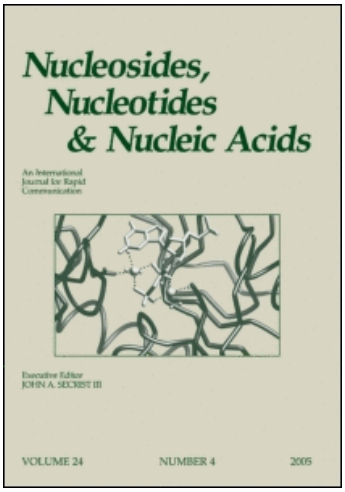

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SYNTHESIS AND ANTI-HIV ACTIVITY OF MODIFIED 2',3'-DIDEOXY-3'-FLUORO PYRIMIDINE NUCLEOSIDES

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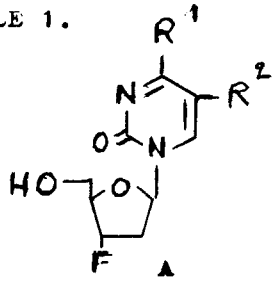
ABSTRACT - Among the 2',3'-dideoxy-3'-fluoro pyrimidine nucleosides modified at C-4 and C-5 several congeners have been identified which show a selective inhibition of HIV-1 replication in vitro.

A series of 2',3'-dideoxy-3'-fluoro pyrimidine nucleosides has been synthesized, starting from 3'-deoxy-3'-fluoro-thymidine(FLT), 2',3'-dideoxy-3'-fluoro-uridine(FUdR) and 2',3'-dideoxy-3'-fluoro-5-ethyl-uridine, respectively. The oxygen at C-4 in FLT and in FUdR was replaced by sulfur[1] to give the corresponding 4-thio analogues which were transformed into the mercapto, hydroxylamino and 2-pyrimidinone[2] derivatives. The bromination of 5'-O-acetyl-2',3'-dideoxy-3'-fluoro-5-ethyluridine under radically conditions and subsequently elimination with triethylamine gave after deblocking the 5-vinyl and the (E)-5-(2-bromovinyl) derivatives. We compared the in vitro activity against HIV-1 of the new nucleosides(TABLE 1, column A). The 4-thio analogue of FLT is the most effective and selective inhibitor in this series, requiring a dose of 1 μM for a 50% protection of MT-4 cells against the cytopathic effect of HIV-1 [3]. Furthermore, we have examinated the susceptibility of both the HIV-1 reverse transcriptase and the cellular DNA-polymerases α and β to the inhibition by the

TABLE 1.



A

A : The anti-HIV activity and cytotoxicity of the fluoro nucleosides in MT-4 cells

B : Inhibition of HIV-reverse transcriptase and of cellular DNA-polymerases (conc. for 50% inhibition in μ M) by the corresponding 5'-O-triphosphates

				B		
R^1	R^2	ED_{50} (μ M)	CD_{50} (μ M)	HIV-1 reverse transcr.	α-polymerase	β-polymerase
OH	$CH=CH_2$	2,4	6	0,025	20	0,8
OH	CH=CHBr	30	300	0,015	10	2
SH	H	15	130			
SCH_3	H	ineffect.	50			
NHOH	H	100	100			
NH_2	CH_3	2	190	0,6	200	1
NHOH	CH_3	110	300			
H	CH_3	7	300	3,6	80	57
SH	CH_3	1	480	0,2	140	7
OH	CH_3	0,03	11	0,05	200	2,2
OH	H	0,275	75	0,07	200	3
OH	CH_2CH_3	500	500	7,5	10	4

5'-O-triphosphates of the most potent 3'-fluoro nucleosides in this series(TABLE 1, column B).

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