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## Nucleosides, Nucleotides and Nucleic Acids

Publication details, including instructions for authors and subscription information:

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### Synthesis and Anti-HIV Activity of Modified 2',3'-Dideoxy-3'-Fluoro Pyrimidine Nucleosides

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**To cite this Article** Von Janta-Lipinski, M. , Gaertner, K. , Schildt, J. , Matther, E. , Scholz, D. and Langon, P.(1991) 'Synthesis and Anti-HIV Activity of Modified 2',3'-Dideoxy-3'-Fluoro Pyrimidine Nucleosides', *Nucleosides, Nucleotides and Nucleic Acids*, 10: 1, 651 – 652

**To link to this Article:** DOI: 10.1080/07328319108046561

**URL:** <http://dx.doi.org/10.1080/07328319108046561>

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

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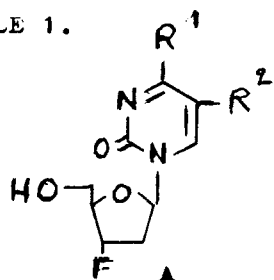
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**ABSTRACT** - Among the 2',3'-dideoxy-3'-fluoro pyrimidine nucleosides modified at C-4 and C-5 several congeners have been identified which show a selective inhibition of HIV-1 replication in vitro.

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<sup>1</sup> to give the corresponding 4-thio analogues which were transformed into the mercapto, hydroxylamino and 2-pyrimidinone<sup>2</sup> 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  $\mu$ M for a 50% protection of MT-4 cells against the cytopathic effect of HIV-1<sup>3</sup>. Furthermore, we have examined the susceptibility of both the HIV-1 reverse transcriptase and the cellular DNA-polymerases  $\alpha$  and  $\beta$  to the inhibition by the

TABLE 1.



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  $\mu$  M) by the corresponding 5'-O-triphosphates

R <sup>1</sup>	R <sup>2</sup>	A		B		
		ED <sub>50</sub> ( $\mu$ M)	CD <sub>50</sub> ( $\mu$ M)	HIV-1 reverse transcr.	$\alpha$ -poly- merase	$\beta$ -poly- merase
OH	CH=CH <sub>2</sub>	2,4	6	0,025	20	0,8
OH	CH=CHBr	30	300	0,015	10	2
SH	H	15	130			
SCH <sub>3</sub>	H	ineffect.	50			
NHOH	H	100	100			
NH <sub>2</sub>	CH <sub>3</sub>	2	190	0,6	200	1
NHOH	CH <sub>3</sub>	110	300			
H	CH <sub>3</sub>	7	300	3,6	80	57
SH	CH <sub>3</sub>	1	480	0,2	140	7
OH	CH <sub>3</sub>	0,03	11	0,05	200	2,2
OH	H	0,275	75	0,07	200	3
OH	CH <sub>2</sub> CH <sub>3</sub>	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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