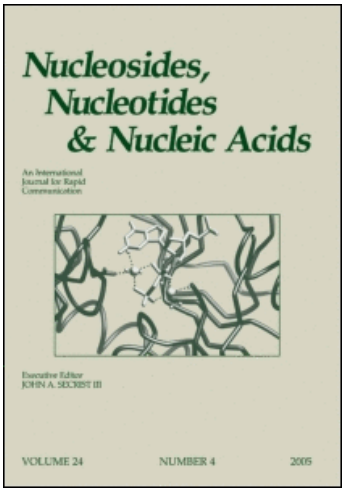

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Sugar and Base-Modified 2',3'-Dideoxynucleosides as Potential Anti-Aids Drugs

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SUGAR- AND BASE-MODIFIED 2',3'-DIDEOXYNUCLEOSIDES AS POTENTIAL ANTI-AIDS DRUGS

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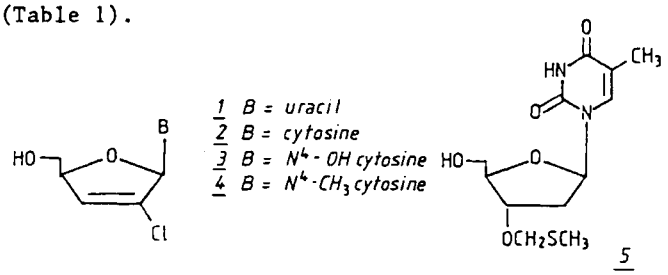
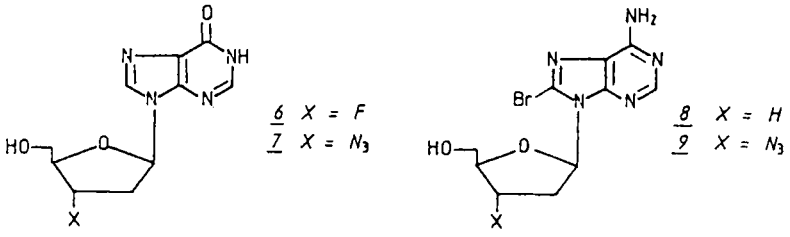
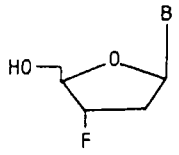
Several 2',3'-dideoxynucleosides have proven to be effective against HIV-1 in cell culture. The 2',3-unsaturated analogues dideoxycytidinene (D4C) and dideoxythymidinene (D4T) are among the most potent and selective inhibitors of HIV-1 replication in vitro. However, 2',3'-didehydro-2',3'-dideoxynucleosides are relatively unstable. A chlorine substituent at the 2'-position increases the stability, and, therefore, some 2'-chloro-2',3'-didehydro-2',3'-dideoxynucleosides were synthesized and evaluated for anti-HIV-1 activity.

Likewise, 3'-fluoro-2',3'-dideoxyuridine and -thymidine are known to be potent and selective anti-HIV-1 agents, and some modifications were introduced in the base with the aim to obtain compounds with increased selectivity. Finally, 3'-azido- and 3'-fluoro-2',3'-dideoxyinosine, 2',3'-dideoxy-8-bromoadenosine and 3'-azido-2',3'-dideoxy-8-bromoadenosine were synthesized, and their anti-HIV-1 activity was determined.

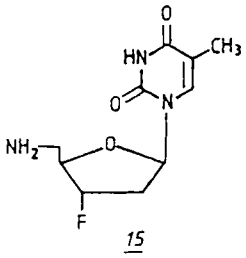
Of all these new 2',3'-dideoxynucleoside analogues, compound 10 (3'-fluoro-2',3'-dideoxy-5-chlorouridine, FddClUrd) offers the greatest promise as a potential anti-AIDS drug, as it achieved a selectivity index > 1000 (Table 1).







10 B = 5-chlorouracil
11 B = 5-bromouracil
12 B = 5-iodouracil
13 B = 5-methylcytosine
14 B = O4-methyluracil



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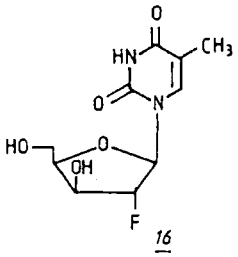

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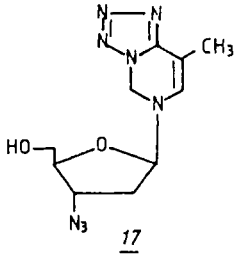

17

TABLE 1. ANTI-HIV-1 ACTIVITY IN MT-4 CELLS

Compound	ED_{50} (μM)	CD_{50} (μM)	S.I.
1	> 500	> 500	-
2	> 500	> 500	-
3	> 500	> 500	-
4	> 500	> 500	-
5	> 500	> 500	-
6	222	818	3.7
7	> 8	15	< 2
8	484 ± 171	> 500	-
9	> 500	409 ± 53	-
10	0.38 ± 0.06	535 ± 41	1408
11	0.41 ± 0.16	24 ± 18	59
12	0.16 ± 0.11	2.2 ± 2.0	13.6
13	1.7 ± 0.8	7.7 ± 5.6	4.5
14	46 ± 14	348 ± 190	7.6
15	> 500	> 500	-
16	> 500	> 500	-
17	8.5 ± 0.3	39.0 ± 1.4	4.6
ddAdo	6.4	890	139
AzddAdo	5	10	2
FddThd	0.001	0.197	197
FddUrd	0.04	16	400

ED_{50} : 50 % effective dose; CD_{50} : 50 % cytotoxic dose; S.I. : selectivity index (ratio of CD_{50} to ED_{50}).