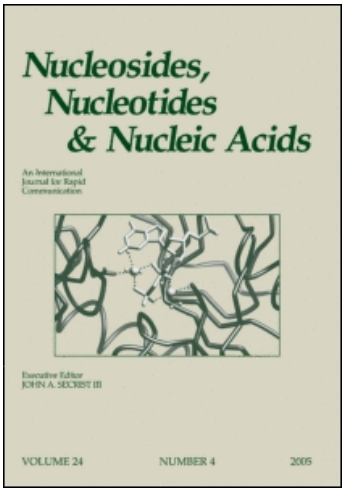

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ANTI-HIV-1 ACTIVITY OF 2',3'-DIDEOXYNUCLEOSIDE ANALOGUES : STRUCTURE-ACTIVITY RELATIONSHIP

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ABSTRACT - Among the purine and pyrimidine 2',3'-dideoxynucleosides, 2',3'-didehydro-2',3'-dideoxynucleosides, 3'-azido-2',3'-dideoxynucleosides and 3'-fluoro-2',3'-dideoxynucleosides, several congeners have been identified which achieve a potent and selective inhibition of HIV-1 replication in vitro.

The finding that 3'-azido-2',3'-dideoxythymidine (AzddThd, azidothymidine, AZT)[1] and various 2',3'-dideoxynucleosides such as 2',3'-dideoxycytidine (ddCyd), 2',3'-dideoxyadenosine (ddAdo), 2',3'-dideoxyguanosine (ddGuo), 2',3'-dideoxyinosine (ddIno) and 2',3'-dideoxythymidine (ddThd),[2] are able to inhibit the replication of human immunodeficiency virus type 1 (HIV-1) at concentrations well below the toxicity threshold for the host cells has prompted the search for new 2',3'-dideoxynucleoside analogues that may be equally, if not more, potent and/or selective in their anti-HIV-1 activity than their parent compounds. This search has yielded various 2',3'-unsaturated and 3'-substituted 2',3'-dideoxynucleoside analogues,[3] 2'- and 3'-substituted 2',3'-dideoxyadenosine,[4] 5-substituted 2',3'-dideoxycytidines,[5] 5-substituted pyrimidine 3'-azido-2',3'-dideoxynucleosides[6] as well as pyrimidine and purine 3'-azido- and 3'-fluoro-2',3'-dideoxynucleosides.[7] In addition to these compounds, various other 2',3'-dideoxynucleoside analogues have recently been synthesized and examined for their anti-HIV-1 activity in our laboratory. It would seem timely, therefore, to review the 2',3'-dideoxynucleosides from a structure-function viewpoint and to determine the structural requirements they have to fulfil to achieve optimal activity against HIV-1.

Unless stated otherwise, all compounds were examined in the same cell system (human MT-4 cells infected with the HTLV-III_B strain of HIV-1) following a cytopathogenicity assay based on cell viability (measured by trypan blue exclusion).[8] For all compounds, the 50 % effective dose (ED_{50}, or dose required to protect 50 % of the HIV-1-infected cells against destruction) and 50 % cytotoxic dose (CD_{50}, or dose required to reduce the viability of uninfected cells by 50 %) were determined in parallel, and the selectivity index (SI) was defined as the ratio of CD_{50} to ED_{50}.

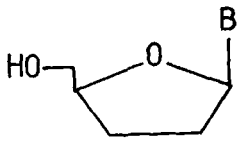
2',3'-DIDEOXYNUCLEOSIDES

From a comparative study of the inhibitory effects of ddAdo, ddGuo, ddIno, ddCyd and ddThd on HIV-1 replication in ATH8 cells,[2] ddCyd emerged as the most potent inhibitor; it was also the most cytotoxic. Our own results confirm these findings, in that of all 2',3'-dideoxynucleosides that were examined,[9-12] ddCyd was both the most potent HIV-1 inhibitor and most cytotoxic agent (Table 1). In addition to ddCyd, ddAdo, ddGuo and ddIno which had been previously recognized as potent and selective inhibitors of HIV-1 replication,[2] we also found ddDAPR[11] and ddThd[9,12] to be highly effective inhibitors : ddThd proved clearly more active as an inhibitor of HIV-1 replication in MT-4 cells[9,12] than ATH8 cells,[2] which underscores the importance of the host cell line in anti-HIV activity determinations. While 5-fluoro-2',3'-dideoxycytidine (FddCyd) proved equally potent and selective as ddCyd, no anti-HIV-1 activity was observed with the 5-methyl and 5-bromo substituted ddCyd derivatives.[5] The 5-aza analogue of ddCyd was cytotoxic at antivirally active concentrations.[5] In contrast with ddAdo, the 8-bromo substituted ddAdo did not prove active against HIV-1 in MT-4 cells (Table 1). Also, the pyrrolo [2,3-d]pyrimidine 2',3'-dideoxynucleosides did not reveal much selectivity in their anti-HIV-1 action.[13]

2',3'-DIDEHYDRO-2',3-DIDEOXYNUCLEOSIDES

The potent and selective anti-HIV-1 effects of the 2',3'-unsaturated derivatives of ddCyd [2',3'-dideoxycytidinene (ddeCyd, also referred to as ddddCyd or D4C)] and ddThd [2',3'-dideoxythymidinene (ddeThd, also referred to as ddddThd or D4T)] were first mentioned by Balzarini *et al.*[14] and Baba *et al.*[9], respectively. Selective inhibition of HIV-1 by both D4C and D4T has been observed in varying cell culture systems, including ATH8

TABLE 1. ANTI-HIV-1 ACTIVITY OF 2',3'-DIDEOXYNUCLEOSIDES

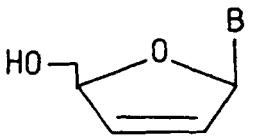


	Potency ED_{50} (μM)	Cytotoxicity CD_{50} (μM)	Selectivity SI
B = Uracil[†,ǂ]	210	> 625	> 3
	48		> 13
Thymine[†,ǂ]	6	> 625	> 104
	0.2		> 3125
5-Ethyluracil[ǂ]	> 625	> 625	...
Cytosine[†]	0.3	40	120
	0.06	37	616
Adenine[†,§]	6.4	890	139
	2.5		356
Guanine[§]	7.6	486	64
2,6-Diaminopurine[¶]	3.6	404	112
Hypoxanthine	10	> 500	> 50
8-Bromoadenine	484	> 500	> 1
"Tubercidin"[Π]	> 25	33	< 1.3
"Toyocamycin"[Π]	8.5	54	6.3
"Sangivamycin"[Π]	64	242	3.8

†, §, ¶, ǂ, Π : see references 9, 10, 11, 12 and 13, respectively.

cells,[15] MT-4 cells[9,16] and peripheral blood mononuclear (PBM) cells.[17,18] While D4C and D4T are almost as potent and selective in their inhibitory effects on HIV-1 as their 2',3'-saturated counterparts ddCyd and ddThd, the 2',3'-unsaturated derivatives of ddUrd, ddAdo, ddGuo and ddDAPR are virtually inactive against HIV-1, and so are the 2',3'-unsaturated 2',3'-dideoxyribosides of the pyrrolo[2,3-d]pyrimidines (Table 2). It would be interesting to see how 5-substituted analogues of D4C and D4T behave as anti-HIV-1 agents.

TABLE 2. ANTI-HIV-1 ACTIVITY OF 2',3'-DIDEHYDRO-2',3'-DIDEOXYNUCLEOSIDES



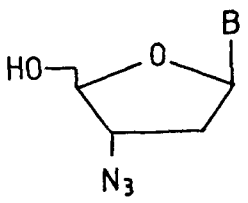
	Potency ED_{50} (μM)	Cytotoxicity CD_{50} (μM)	Selectivity SI
B = Uracil†	> 125	27	< 0.2
Thymine†	0.01	1.2	120
Cytosine†	0.13	7.9	61
Adenine¶	> 5	19	< 3.4
Guanine§	> 5	11	< 2.2
2,6-Diaminopurine¶	> 5	15	< 3
"Tubercidin"Π	205	> 1250	> 6.1
"Toyocamycin"Π	14	44	3.1
"Sangivamycin"Π	> 125	625	< 5

†, §, ¶, Π : see references 9, 10, 11 and 13, respectively.

3'-AZIDO-2',3'-DIDEOXYNUCLEOSIDES

The remarkable activity of AzddThd against HIV-1 has been widely confirmed,[1,6,8,12,19] and its vitro potency has not been excelled by any other 3'-azido analogues. From a series of 3'-azido analogues of pyrimidine 2',3'-dideoxynucleosides examined by Lin et al.[6] for their activity against HIV-1 in PBM cells, AzddThd emerged as the most potent, followed (in order of decreasing potency) by the 3-(3-oxy-1-propenyl derivative of AzddThd, AzddUrd, AzddBrUrd, AzddFCyd, AzddIUrd, AzddCyd, AzddFUrd, and others. While AzddThd is the most potent of all 3'-azido analogues that have been compared for their anti-HIV-1 activity in MT-4 cells (Table 3), it should be recognized that, in addition to AzddThd, several other 3'-azido analogues, i.e. AzddUrd[12] and AzddMeCyd[7], exhibit a marked selectivity against HIV-1. Also, several 3'-azido analogues of purine 2',3'-di-

TABLE 3. ANTI-HIV-1 ACTIVITY OF 3'-AZIDO-2',3'-DIDEOXYNUCLEOSIDES



B =	Potency ED_{50} (μM)	Cytotoxicity CD_{50} (μM)	Selectivity SI
Uracil[ǂ]	0.36	244	677
Thymine[†]	0.006	3.5	583
	0.004	20	5000
5-Ethyluracil[ǂ]	64	418	6.5
Cytosine[ǂ]	7.6	160	21
5-Methylcytosine[Φ]	1.8	1000	555
N^4-Methylcytosine[Φ]	605	> 1000	> 1.6
N^4,5-Dimethylcytosine[Φ]	17.3	> 1000	> 58
N^4-Hydroxyl-5-methylcytosine[Φ]	1.5	92	61
Adenine[Ω]	5	10	2
Guanine[§]	1.4	190	136
2,6-Diaminopurine[Σ]	0.3	44	147
Hypoxanthine	> 8	15	< 2
8-Bromoadenine	> 500	409	< 1

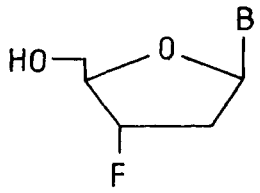
Ω, Φ, †, §, ǂ, Σ : see references 4, 7, 9, 10, 12 and 20, respectively.

deoxynucleosides, i.e. AzddGuo[10] and AzddDAPR,[20] are remarkably selective in their anti-HIV-1 action (Table 3). To the extent that AzddDAPR is deaminated intra- or extracellularly, its anti-HIV activity may be mediated by AzddGuo. It is also noteworthy that AzddDAPR is more active against HIV-1 than its parent, ddDAPR (Table 1). This contrasts sharply with ddAdo and ddIno which become virtually inactive against HIV-1 following conversion to their 3'-azido forms AzddAdo and AzddIno (Tables 1 and 3).

3'-FLUORO-2',3'-DIDEOXYNUCLEOSIDES

From the studies of Herdewijn et al.[3] it has become evident that not only a 3'-azido but also a 3'-fluoro substituent is compatible with anti-

TABLE 4. ANTI-HIV-1 ACTIVITY OF 3'-FLUORO-2',3'-DIDEOXYNUCLEOSIDES

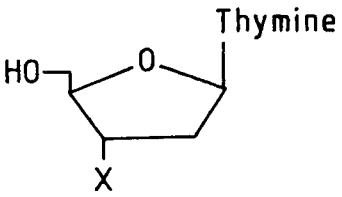


B =	Potency ED_{50} (μM)	Cytotoxicity CD_{50} (μM)	Selectivity SI
Uracil[ǂ]	0.04	16	400
Thymine[ǂ]	0.001	0.197	197
5-Ethyluracil[ǂ]	330	> 625	> 1.9
Cytosine[ǂ]	16	26	1.6
5-Iodouracil	0.16	2.17	13.6
5-Bromouracil	0.41	24	59
5-Chlorouracil	0.38	535	1408
5-Methylcytosine	1.7	7.7	4.5
O^4-Methyluracil	46	348	7.6
Adenine[Ω]	50	557	11
Guanine[Σ]	2.4	237	96
2,6-Diaminopurine[Σ]	4.5	360	80
Hypoxanthine	222	818	3.7

Ω, ǂ, Σ : see references 4, 12 and 20, respectively.

HIV-1 activity. In fact, FddThd (Table 4) is more potent an inhibitor of HIV-1 replication than is AzddThd (Table 3). FddThd is also more cytotoxic, so that its selectivity index is somewhat inferior to that of AzddThd. Other 3'-fluoro analogues such as FddUrd,[12] FddGuo[20] and FddDAPR[20] demonstrate a selectivity against HIV-1 that is quite comparable to that of their 3'-azido counterparts (Tables 3 and 4). Of particular interest is the marked selectivity shown by the 3'-fluoro analogue of 2',3'-dideoxy-5-chlorouridine (FddClUrd). With a selectivity index of 1400, FddClUrd emerged as the most selective HIV-1 inhibitor among the 3'-fluoro-2',3'-dideoxynucleosides that have been synthesized to date.

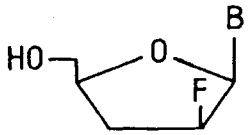
TABLE 5. ANTI-HIV-1 ACTIVITY OF 3'-SUBSTITUTED-2',3'-DIDEOXYTHYMIDINE ANALOGUES*



X =	Potency ED_{50} (μM)	Cytotoxicity CD_{50} (μM)	Selectivity SI
H	100	> 2000	> 20
N_3	2.4	45	19
F	1.4	15	10
Cl	> 500	> 500	...
Br	> 500	180	< 0.4
I	> 500	> 500	...
OMe	> 100	88	< 0.9
OEt	> 100	> 100	...
OCH_2COONa	> 100	> 100	...
OSO_2CH_3	> 100	> 100	...
SEt	> 100	100	< 1
SCH_2CH_2OH	> 100	> 100	...
SCN	> 100	> 100	...
$OC(S)OMe$	> 500	398	< 1
$OC(S)OC_6H_5$	> 250	> 250	...
OCH_2SCH_3	> 500	> 500	...
$SC(O)CH_3$	27	29	1.1
$S-)_2$	16	34	2.1
$SC_6H_4CH_3$	> 100	116	< 1.2
$NHC(O)C_6H_5$	> 500	> 500	...
CN	> 16	30	< 1.9

* Compounds down to dotted line were evaluated in ATH8 cells (ref. 3); others in MT-4 cells (ref. 7).

TABLE 6. ANTI-HIV-1 ACTIVITY OF 2'-FLUORO-ARA-2',3'-DIDEOXYNUCLEOSIDES



	Potency ED_{50} (μM)	Cytotoxicity CD_{50} (μM)	Selectivity SI
B = Thymine	> 500	> 500	...
Cytosine	9.8	117	12
Adenine[Ω]	35	> 625	> 18
5-Methylcytosine	> 500	> 500	...
2,6-Diaminopurine	> 100	> 100	...

Ω : see reference 4.

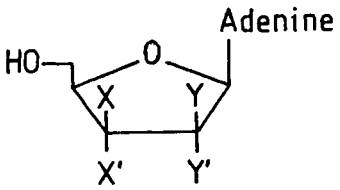
3'-SUBSTITUTED-2',3'-DIDEOXYTHYMIDINES

In addition to an azido or fluoro group, various other substituents have been introduced in the 3'-position of 2',3'-dideoxythymidine.[3,7] Most, if not all, substitutions appeared to abrogate the anti-HIV-1 activity of the parent compound (Table 5). Thus, 3'-chloro-, 3'-bromo-, 3'-thiocyano-, 3'-cyano-,[21] 3'-methoxy-2',3'-dideoxythymidine and various other 3'-substituted ddThd analogues are devoid of selective anti-HIV-1 activity, and so are the ddThd analogues with substituent groups linked to the 3'-carbon atom *via* an oxygen, sulfur or sulfonyl bridge (Table 5).

2'-FLUORO-ARA-2',3'-DIDEOXYNUCLEOSIDES

Several 2',3'-dideoxynucleosides with a fluorine "up" in the 2'-position have been synthesized. Two of these derivatives (FaraddAdo[22] and FaraddCyd) were found to selectively inhibit HIV-1 replication (Table 6). In our cell system, FaraddAdo was less potent than ddAdo[4] (Tables 1 and 6). Marquez *et al.*[22] in their cell system (ATH8 cells) did not see much difference in the anti-HIV-1 activity of the two compounds. According to J.S. Driscoll (personal communication), the hypoxanthine counterpart of FaraddAdo, FaraddIno, would also be a potent and selective anti-HIV-1 agent.

TABLE 7. ANTI-HIV-1 ACTIVITY OF VARIOUS 2'- OR 3'-AZIDO, 2'- OR 3'-FLUORO, AND 2'- OR 3'-AMINO SUBSTITUTED 2',3'-DIDEOXYADENOSINES*



X	X'	Y	Y'	Potency ED_{50} (μM)	Cytotoxicity CD_{50} (μM)	Selectivity SI
H	H	H	H	6.2	889	148
H	H	H	N_3	215	> 625	> 2.9
H	H	N_3	H	55	625	11.4
H	N_3	H	H	5	10	2
N_3	H	H	H	> 625	551	< 0.9
H	H	H	F	> 625	> 625	...
H	H	F	H	35	> 625	> 18
H	F	H	H	50	557	11.1
F	H	H	H	221	> 625	> 2.8
H	H	H	NH_2	> 400	220	< 0.5
H	H	NH_2	H	> 2000	> 500	...
H	NH_2	H	H	> 400	104	< 0.26
NH_2	H	H	H	> 2000	> 500	...

* : data taken from references 4 and 23.

2'- OR 3'-AZIDO, -FLUORO- OR -AMINO-2',3'-DIDEOXYADENOSINES

Starting from 2',3'-dideoxyadenosine, a structure-function analysis was worked out based on the positioning ("up" or "down") of the azido, fluoro or amino groups at C-2 or C-3 of the sugar moiety.[4,23] None of the azido, fluoro or amino derivatives proved more selective in their anti-HIV-1 activity than the parent compound ddAdo. The amino derivatives were totally inactive irrespective of their positioning. For the azido and fluoro analogues, only two positions appeared compatible with anti-HIV-1 activity. These were "up" at C-2 and "down" at C-3. Most selective was

FaraddAdo with the fluorine "up" at C-2, and most potent (and also most toxic) was AzddAdo with the azido "down" at C-3 (Table 7). These compounds may serve as guidelines for the synthesis of new congeners, i.e. with modifications in the heterocycle, that may be superior in potency and/or selectivity to the parent compounds.

CARBOCYCLIC 2',3'-DIDEOXYNUCLEOSIDES

Various carbocyclic analogues of nucleosides in which the sugar moiety is replaced by a cyclopentyl or cyclopentenyl ring are known to be effective antiviral agents: i.e. neplanocin A, cyclopentyl cytosine (carbodine), cyclopentenyl cytosine, carbocyclic 3-deazaadenosine, and the carbocyclic analogues of 2'-deoxythymidine, 5-iodo-2'-deoxyuridine, (E)-5-(2-bromovinyl)-2'-deoxyuridine and (E)-5-(2-bromovinyl)-2'-deoxycytidine. In this perspective, it appeared attractive to examine whether the carbocyclic analogues of 2',3'-dideoxynucleosides may be endowed with selective anti-HIV-1 activity. This did not appear to be the case for the carbocyclic analogues of ddAdo, ddThd and AzddThd.[24] Nor did the enantiomerically pure carbocyclic AzddThd [(+)C-AZT][25] show any anti-HIV-1 activity (our unpublished data). Also, the 2',3'-dideoxycyclopentenyl derivatives of adenine and cytosine failed to show anti-HIV-1 activity.[26] The only carbocyclic 2',3'-dideoxynucleoside which has been reported to inhibit HIV-1 replication is carbovir, the carbocyclic analogue of 2',3'-didehydro-2',3'-dideoxyguanosine (C-ddeGuo)[27] : the anti-HIV-1 potency and selectivity of this compound would be similar to those of ddCyd.

CONCLUSION

Several 2',3'-dideoxynucleosides, 2',3'-didehydro-2',3'-dideoxynucleosides, 3'-azido- and 3'-fluoro-2',3'-dideoxynucleosides have been recognized as potent and selective inhibitors of HIV-1 replication in cell culture. Foremost among those compounds that because of their *in vitro* anti-HIV-1 activity should be pursued for their *in vivo* potential as anti-AIDS drugs are, besides AzddThd, ddCyd and ddAdo which have already entered the clinic, the following congeners : ddThd, ddDAPR, ddeCyd, ddeThd, AzddUrd, AzddMeCyd, AzddGuo, AzddDAPR, FddUrd, FddThd, FddClUrd, FddGuo, FddDAPR and C-ddeGuo. These compounds inhibit HIV-1 *in vitro* at a concentration which is by 2 or 3 orders of magnitude lower than their cytotoxic concentration, thus achieving a selectivity index comparable to that of AzddThd.

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