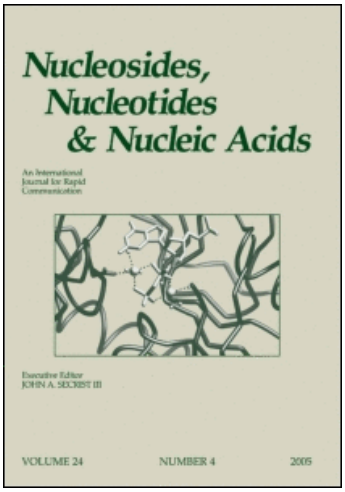

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COMPARATIVE EFFICACY OF NUCLEOSIDE ANALOGUES AGAINST AFRICAN SWINE FEVER VIRUS "IN VITRO"

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Abstract. A comparative study on the "in vitro" activity of various nucleoside analogues has been carried out on the Lisbona 60 strain of ASFV adapted to VERO cells. ß-D-xylofuranosyl-adenine and ß-D-lyxofuranosyl-guanine emerged as the compounds endowed with the most favourable selectivity index.

INTRODUCTION

African swine fever virus (ASFV) is the agent of an important desease of wild and domestic pigs that threatens the swine industry of many European, African and South American countries. So far, no effective means of eradication have been found, and the control of the desease is still confined to recognition, quarantine, slaughter and decontamination procedures.

Recently, (S)-HPMPA and other wide spectrum antiviral compounds have been found active on ASFV "in vitro" [1,2]. Therefore, we deemed interesting to test a larger number of nucleoside analogues.

As most of the compounds tested in the present study were described by different investigators using different virus strains, different cell lines and different assay procedures, we examined to what extent the anti-ASFV activity of the compounds correlated with their inhibitory effect on other DNA viruses, namely HSV-1 and vaccinia virus, using the same type of assay (PRT) and the same type of cell culture.

EXPERIMENTAL

Plaque reduction tests were performed according to Collins and Bauer [3] in VERO cell monolayers. The plaque counts obtained in treated cultures were expressed as percentage of untreated controls and plotted against the logarithm of drug concentrations. Dose-response lines were drawn by linear regression technique and 50% inhibitory concentrations (ID_{50}) were calculated.

For drug toxicity tests VERO cell were seeded at a concentration of $2x10^4$ cells/well in growth medium and allowed to adhere to the surface overnight at 37°C in a CO_2-humidified incubator. New growth medium containing serial dilutions of the drugs was then added. After incubation for 4 days, the cultues were harvested, trypsinized, resuspended in maintenance medium and counted in a hemocytometer. Number of cells in untreated cultures was $2x10^5$/well. Variation between duplicate samples was less than 10%.

Abbreviations used: HSV-1, Herpes simplex virus type 1; BVDU, E-5-(2-bromovinyl)-2'-deoxyuridine; 5'-NH2-TdR, 5'-amino-2',5'-dideoxythymidine; AIU, 5'-amino-2',5'-dideoxy-5-iodouridine; 3'-NH2-TdR, 3'-amino-2',3'-dideoxyxythymidine; 3'-N3-UdR, 3'-azido-2',3'-dideoxyuridine; AZT, 3'-azido-2',3'dideoxythimidine; d4T, 3'-deoxythimidin-2'-ene; ara-U, ara-T, ara-C and ara-A, ß-D-arabinofuranosyl-uracil,-thymine,-cytosine,-adenine; FMAU, 1-(2'fluoro-2'-deoxy-ß-D-arabinofuranosyl)-5-methyluracil; FIAC, 1-(2'-fluoro-2'-deoxy-ß-D-arabinofuranosyl)5-iodocytosine; 5'-NH2-FMAU, 1-(2'-fluoro-2'-deoxy-5'-amino-ß-D-arabinofuranosyl)5methyluracil; 5'-deoxy-FIAC, 1-(2',5,dideoxy-2'-fluoro-ß-D-arabinofuranosyl)-5-iodocytosine; 5'-SH-FIAC, 1-(2'-deoxy-2'-fluoro-5'-thio-ß-D-arabinofuranosyl)5-iodocytosine; 5'-deoxy-FAC, 1-(2',5'-dideoxy-2'-fluoro-ß-D-arabinofuranosyl)cytosine; ß-lyxo-U, ß-lyxo-T, ß-lyxo-G, ß-lyxo-A, ß-D-lyxofuranosyl-uracil, -thymine, -guanine, -adenine; α-lyxo-A, α-D-lyxofuranosyl-adenine; ß-xylo-U, ß-xylo-T, ß-xylo-C, ß-xylo-G, and ß-xylo-A, ß-D-xylofuranosyl-uracil, -thymine, -cytosine, -guanine, adenine; SKP-I-12, 9-(trans-4-hydroxy-2-buten-1-yl)adenine; SKP-I-14, 9-(trans-4-hydroxy-2-buten-1-yl)guanine; ACG, 9-(2-hydroxyethoxymethyl)guanine; PAA, phosphonoacetic acid.

RESULTS AND DISCUSSION

Due to the fact that compounds with a same or a very close ID_{50} for uninfected cells might possess quite different maxi-

TABLE. Effect of various nucleoside analogues on ASFV

COMPOUND	MNTD[a] (μM)	PLAQUE REDUCTION[b]: ID_{50} (μM)[c]			MNTD/ ID_{50} ASFV
		HSV-1	Vaccinia	ASFV	
BVDU	67	0.05	22	15	4
5'-NH_2-TdR	≥ 829	25	> 829	> 829	1
AIU	50	35	> 566	150	< 1
3'-NH_2-TdR	≥ 829	≥ 829	420	535	1
3'-N_3-UdR	12.3	> 790	> 790	> 790	< 1
AZT	6.5	> 750	187	23	< 1
d4T	50	800	> 800	892	< 1
ara-U	400	9.0	> 400	> 400	≤ 1
ara-T	85	0.6	9	5.5	15
ara-C	0.6	1.0	1.3	1.3	< 1
ara-A	20	40	60	150	< 1
FMAU	1.5	0.1	0.3	0.2	7
FIAC	7.5	0.1	0.7	6.3	1
5'-NH_2-FMAU	7.3	7.0	6.3	5.6	1
5'-deoxy-FIAC	300	> 500	> 500	> 500	< 1
5'-SH-FIAC	300	> 500	> 500	> 500	< 1
5'-deoxy-FAC	150	> 400	> 400	> 400	< 1
ß-Lyxo-U	≥ 2000	> 2000	> 2000	1000	> 2
ß-Lyxo-T	≥ 1900	> 1900	> 1900	1900	≥ 1
ß-Lyxo-G	≥ 1700	220	1500	40	> 42
ß-Lyxo-A	≥ 1900	> 1900	> 1900	250	> 8
α-Lyxo-A	935	1900	935	200	5
ß-Xylo-U	255	800	500	64	4
ß-Xylo-T	960	> 1900	> 1900	> 1900	< 1
ß-Xylo-C	16	50	60	20	< 1
ß-Xylo-G	110	150	110	110	1
ß-Xylo-A	7.5	0.7	0.4	0.1	75
SKP-I-12	600	> 2400	> 2400	> 1200	1
SKP-I-14	1000	135	> 2100	> 1200	< 1
ACG	300	0.1	> 500	100	3
PAA	250	60	180	200	1

[a] MNTD: maximum non toxic dose

[b] number of plaques in untreated controls: 136 (HSV-1);185 (Vaccinia);178 (ASFV)

[c] ID_{50} : dose capable of inhibiting plaque formation by 50%

mum non toxic doses, we preferred to use the latter to define the cytotoxicity of the test compounds. Nevertheless, the values shown in the table are in good agreement with those reported previously [4-10]. The only significant exception was AIU which showed a toxicity at least four times higher than that reported by Cheng et al. on VERO cells [11]. It should be noted, however, that these Authors carried out cytotoxicity tests on an initial cell number which was 100 times higher than that used in the present study. Therefore a possible explanation for the above discrepancy could be that the cytotoxicity of AIU is inversely related to the initial cell density, as seems to be the case for d4T in H9 cells[12].

Also in agreement with previous results are the 50% inhibitory doses of the compounds when tested on the reference viruses. In decreasing order of potency ACG BVDU araT FIAC araU confirmed their selective and specific antiherpes activity. These compounds, in fact, were significantly active neither on vaccinia nor on ASFV.

The only compound which showed the same degree of activity on the three viruses was FMAU.

Among the compounds active on ASFV ß-xylo-A was both potent and selective, while ß-lyxo-G was also selective but not very potent.

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