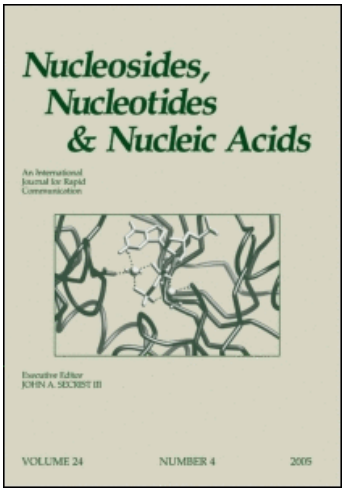

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ANTI-HERPES ACTIVITIES OF ISONUCLEOSIDE ANALOGUES WITH VARIABLE BASES AT THE 2' POSITION

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Abstract. We examined eight isonucleoside analogues, which have variable bases at the 2' position of deoxyribose, for anti-herpes virus activities *in vitro*. Six of the eight compounds showed anti-herpes activity.

RESULTS AND DISCUSSION

Recently, Tino *et al.* reported on a series of novel branched-chain sugar isonucleoside analogues with strong anti-herpes activities *in vitro* and in animals.[1] These isonucleoside analogues have variable bases at the 2' position. We have also examined similar isonucleoside analogues with variable bases at the 2' position for anti-herpes activities *in vitro*. These compounds were synthesized in the laboratory of Dr. A. Matsuda. The chemical details are shown in Fig. 1 and Table 1.

We examined anti-HSV-1 (KOS strain) activity of the eight AKA series compounds by MTT method in the NC-37 cell line derived from human B-cells. This method was described by Takeuchi *et al.*[2] The results are shown in Table 1. In these experiments only AKA 4-47-1 and AKA 4-48-1 showed anti-HSV-1 activity. Since NC-37 cell line was susceptible to HSV-1 but

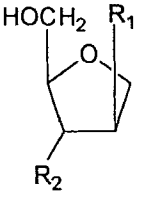

FIG. 1. The common chemical structure of AKA series compounds.

TABLE 1
Inhibitory effects of the AKA series compounds on the replication of HSV-1(KOS) in NC-37 cells

Compound	R_1	R_2	EC_{50}[a] (μg/ml)	CC_{50}[b] (μg/ml)
AKA 4-47-1	guanine	OH	0.84 ± 0.5	≥ 100
AKA 4-48-1	guanine	CH_2OH	1.63 ± 1.5	58.67 ± 5.1
AKA 3-84-1	adenine	OH	> 43.44	43.44 ± 2.3
AKA 4-5-1	adenine	CH_2OH	> 16.44	16.44 ± 3.8
AKA 4-4-1	diaminopurine	OH	> 87.63	87.63 ± 6.3
AKA 4-13-1	diaminopurine	CH_2OH	> 79.70	79.70 ± 6.3
AKA 5-6-1	cytosine hydrochloride	OH	> 100	> 100
AKA 4-76-1	cytosine hydrochloride	CH_2OH	> 38.82	38.82 ± 3.8
ACV			0.041	> 100

All data represent mean values (± SD) for at least five separate experiments.
[a]Fifty percent effective concentration, based on the inhibition of HSV-1-induced cytopathic effect in NC-37 cells.
[b]Fifty percent cytotoxic concentration, based on the impairment of viability of mock-infected NC-37 cells.

not to HSV-2, we developed a new test system for screening of anti-HSV activity using RPMI 8226 cell line derived from human myeloma. When the NC-37 cells were used for the anti-HSV assay, only AKA 4-47-1 and AKA 4-48-1 showed anti-HSV-1 activity; on the other hand, when RPMI 8226 cells were used, AKA 3-84-1, AKA 4-5-1, AKA 4-13-1 and AKA 5-6-1 showed inhibitory activity to HSV-1 as well as HSV-2 in addition to the two compounds cited above (Table 2).

We selected AKA 4-47-1 and AKA 4-48-1 as the most effective anti-HSV compounds and examined their anti-HSV-2 and -VZV activity using the human embryo cell line (MRC-5, HEL-9). Antiviral activity was judged by the MTT method, developed by Sudoh *et al.*[3] The anti-VZV (CaQu strain) activity was judged by the plaque reduction method following Baba *et al.*[4] As shown in Table 3, both compounds had an EC_{50} of 2 to 3 μg/ml against HSV-2 and VZV, except for AKA 4-47-1, which had an EC_{50} of 29.7 μg/ml against VZV. The EC_{50} values of AKA 4-47-1 and AKA 4-48-1 against HSV-2 were 16 and 165 times higher in MRC-5 than RPMI 8226 cells.

We examined the anti-herpes activities of eight isonucleoside analogues with variable bases at the 2' position. Especially (2*R*)-1,4-anhydro-2-deoxy-2-*C*-(guanine-9-yl)-D-arabitol (AKA 4-47-1) and (2*R*,3*R*)-1,4-anhydro-2,3-dideoxy-2-*C*-(guanine-9-yl)-3*C*-hydroxymethyl-D-arabitol (AKA 4-48-1) showed potent anti-HSV-1 and -HSV-2 activity, and the EC_{50} values

TABLE 2

Antiviral activity of AKA series compounds in RPMI 8226 cells

Compound	EC_{50}[a] (μg/ml)			CC_{50}[b] (μg/ml)
	HSV-1(KOS)	HSV-1(A4D)[c]	HSV-2(G)	
AKA 4-47-1	0.074 ± 0.025	> 90.43	0.21 ± 0.19	90.43
AKA 4-48-1	0.050 ± 0.015	> 79.89	0.019 ± 0.008	79.89
AKA 3-84-1	1.105 ± 0.298	17.019 ± 6.427	0.331 ± 0.17	52.64
AKA 4-5-1	0.348 ± 0.060	> 20.978	0.127 ± 0.037	20.62
AKA 4-4-1	> 73.29			73.29
AKA 4-13-1	4 ± 0	> 50	7.103 ± 5.40	53.92
AKA 4-76-1	> 44.09			44.09
AKA 5-6-1	1.224 ± 0.878	> 50	5.536 ± 4.999	55.46
ACV	0.074 ± 0.019	> 66.85	0.041 ± 0.013	66.85

All data represent mean values (± SD) for at least three times separate experiments.
[a]Fifty percent effective concentration, based on the inhibition of HSV-1- or -HSV-2-induced cytopathic effect in RPMI 8226 cells.
[b]Fifty percent cytotoxic concentration, based on the impairment of viability of mock-infected RPMI 8226 cells.
[c]ACV-resistant HSV-1 strain.

TABLE 3

Antiviral efficacy of AKA 4-47-1 and AKA 4-48-1

Compound	Virus	Cell	EC_{50}[a] (μg/ml)	CC_{50}[b] (μg/ml)
AKA 4-47-1	HSV-2 (G strain)	MRC-5	3.36	> 100
	VZV (CaQu strain)	HEL	29.67 ± 2.87	> 100
AKA 4-48-1	HSV-2 (G strain)	MRC-5	3.16	> 100
	VZV (CaQu strain)	HEL	2.66 ± 0.73	> 100
ACV	HSV-2 (G strain)	MRC-5	1.22	> 10
	VZV (CaQu strain)	HEF	1.8	> 10

[a,b]See footnotes a and b to Tables 1 and 2.

were comparable with that of ACV. The EC_{50} of AKA 4-47-1 was lower than that of AKA 4-48-1. Neither AKA 4-47-1 nor AKA 4-48-1 were effective against the ACV-resistant HSV-1 strain. AKA 4-48-1 was the same compound which had been previously reported as BMS-181,164 by Tino *et al.*,[1] AKA 4-48-1 (BMS-181,164) showed activity against HSV-1, HSV-2 and VZV. In this study we demonstrated that AKA 4-47-1, in which the R_2 of AKA 4-48-1 was changed from CH_2OH to OH, had comparable antiviral activities (Tables 1, 2 and 3). Neither compound had activity against the ACV-resistant HSV-1 strain A4D (Table 2).

(2*R*)-2-*C*-(adenine-9-yl)-1,4-anhydro-2-deoxy-D-arabitol (AKA 3-84-1), (2*R*,3*R*)-2-*C*-(adenine-9-yl)-1,4-anhydro-2,3-dideoxy-3-*C*-hydroxymethyl-D-arabitol (AKA 4-5-1), (2*R*,3*R*)-1,4-anhydro-2-*C*-(2,6-diaminopurine-9-yl)-2,3-dideoxy-3-*C*-hydroxymethyl-D-arabitol (AKA 4-13-1) and (2*R*,3*R*)-1,4-anhydro-2-*C*-(cytosine-1-yl)-2,3-dideoxy-3-*C*-hydroxymethyl-D-arabitol hydrochloride (AKA 5-6-1) also showed anti-HSV-1 and -HSV-2 activity.

Of these compounds, only AKA 3-84-1 was inhibitory against ACV-resistant HSV-1 replication. The latter did not show antiviral activity in NC-37 cells but showed activity in RPMI 8226 against the KOS strain (HSV-1) (Tables 1 and 2). It is known that araA also does not show anti-herpes activity in NC-37 but shows activity in RPMI 8226 cells [2] (our unpublished data). The reason for this differential behavior is not known but perhaps some step in the cellular phosphorylation of AKA 3-84-1 as well as araA takes place in RPMI 8226 but not in NC-37.

In summary, for the isonucleoside analogues examined here, the anti-HSV activity declined in the order of guanine > adenine > diaminopurine > cytosine hydrochloride. As to the R_2 substituent, CH_2OH provided stronger activity than OH.

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