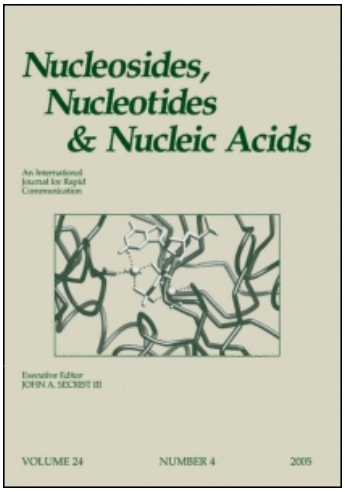

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ANTI-HIV-1 ACTIVITIES OF 1,3-DIOXOLANE GUANINE AND 2,6-DIAMINOPURINE DIOXOLANE

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ABSTRACT DXG and its prodrug DAPD have been demonstrated to be effective inhibitors of HIV-1 in various cells. The EC_{50}s for DXG were 0.032 μM in CBMCs and 0.05 μM in MT-4 cells, which were generally equipotent as 3TC. 3TC-resistant, but not AZT-resistant, HIV-1 had minimum diminished sensitivity to the compounds. Both DXG and DAPD were non-toxic to cells up to 500 μM.

(-)-β-D-1,3-dioxolane guanine (DXG) and (-)-β-D-2,6-diaminopurine dioxolane (DAPD) are purine nucleoside analogs. *In vivo*, DAPD is quickly converted into DXG mediated by adenosine deaminase[1] and can be considered as a prodrug for DXG. Both compounds were previouslyreported to have anti-viral activities[1,2]. We report detailed evaluation of anti-HIV-1 efficacy and cytotoxicity for the compounds.

Inhibition of HIV-1 in various cells. The anti-HIV-1 efficacy of DXG and DAPD was assessed in cord blood mononuclear cells (CBMCs) and cell lines. Table 1 shows the 50% effective concentrations (EC_{50}) tested with HIV-1_{IIIB}. The EC_{50}s for DXG were 0.032 μM in CBMCs and 0.05 μM in MT-4 cells. These values were generally equipotent as 3TC, but approximately 5-fold higher than the EC_{50}s determined for AZT. Generally, the efficacy of DAPD was 5- to 20-fold less than DXG in the various cells tested.

Susceptibility of drug-resistant HIV-1. A number of drug-resistant strains of HIV-1 were tested for their sensitivity to DXG and DAPD. The results indicate that both 3TC-resistant recombinant virus (Table 2) and clinical strains (data not shown) had minimum (about 2-5-fold) cross resistance to DXG and DAPD. However, AZT-resistant HIV-1 remained sensitive to these compounds.

TABLE 1. Inhibitory effects of DXG and DAPD on HIV-1_{IIIB}

	EC_{50} (μM)[a] in MT-2 cell			
Cell	DXG	DAPD	3TC	AZT
CBMC	0.032	0.9	0.015	0.005
MT-4	0.05	0.95	0.06	0.015
MT-2	0.045	0.2	0.22	0.01
Jurkat	0.34	1.37	ND[b]	0.011
H9	0.06	0.075	ND	0.031

[a] The average of two or more experiments. [b] ND = not determined

TABLE 2. Sensitivity of drug-resistant HIV-1 to DXG and DAPD

	EC_{50} (μM)[a] in MT-2 cell			
HXB2-D	DXG	DAPD	3TC	AZT
wt	0.18	3.3	0.3	0.023
K65R	0.91	17.2	8.1	0.033
M184V	0.75	ND[b]	>100	0.02
41L/70R/215Y/219Q	0.22	6.4	0.86	0.45

[a] The average of two or more experiments. [b] ND = not determined

Cytotoxicity. DXG and DAPD were tested for their effect on proliferation of CBMCs and cell lines (Molt-4, HT-1080, HSF, U-145, and HepG2) by [^{3}H]-thymidine uptake. Both compounds were non-toxic to these cells at concentrations up to 500 μM which was the highest concentrations tested.

Viral resistance. *In vitro* selection of HIV-1 resistance to DXG and DAPD is in progress. In a 2-month selection, which is ongoing, neither consistent mutation in the RT gene nor decreased sensitivity to DXG and DAPD, as well as to other nucleoside analogs, has been observed for the selected viruses.

Summary. DXG and its prodrug DAPD had efficacy against both wild-type and drug-resistant HIV-1 variants, with minimum decreased sensitivity to 3TC-resistant virus. Furthermore, the compounds had remarkably low cytotoxicity. Thus, our study demonstrated that DXG and DAPD should be pursued as anti-HIV-1 agents.

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