

This article was downloaded by:

On: 26 January 2011

Access details: *Access Details: Free Access*

Publisher *Taylor & Francis*

Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



## Nucleosides, Nucleotides and Nucleic Acids

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t713597286>

### Anti-HIV-1 Activities of 1,3-Dioxolane Guanine and 2,6-Diaminopurine Dioxolane

Zhengxian Gu<sup>a</sup>; Mark A. Wainberg<sup>b</sup>; Paul Nguyen-ba<sup>a</sup>; Lucille L'Heureux<sup>a</sup>; Jean-Marc De Muys<sup>a</sup>; Robert F. Rando<sup>a</sup>

<sup>a</sup> BioChem Therapeutics Inc., Laval, Quebec <sup>b</sup> McGill University AIDS Center, Jewish General Hospital, Montreal, Quebec, Canada

**To cite this Article** Gu, Zhengxian , Wainberg, Mark A. , Nguyen-ba, Paul , L'Heureux, Lucille , De Muys, Jean-Marc and Rando, Robert F.(1999) 'Anti-HIV-1 Activities of 1,3-Dioxolane Guanine and 2,6-Diaminopurine Dioxolane', *Nucleosides, Nucleotides and Nucleic Acids*, 18: 4, 891 — 892

**To link to this Article:** DOI: 10.1080/15257779908041594

**URL:** <http://dx.doi.org/10.1080/15257779908041594>

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: <http://www.informaworld.com/terms-and-conditions-of-access.pdf>

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

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

Zhengxian Gu,<sup>1\*</sup> Mark A. Wainberg,<sup>2</sup> Paul Nguyen-Ba,<sup>1</sup> Lucille L'Heureux,<sup>1</sup> Jean-Marc de Muys<sup>1</sup> and Robert F. Rando<sup>1</sup>

<sup>1</sup>BioChem Therapeutics Inc., 275 Amand-Frappier, Laval, Quebec H7V 4A7,

<sup>2</sup>McGill University AIDS Center, Jewish General Hospital, 3755 Cote Ste-Catherine,  
Montreal, Quebec H3T 1E2, Canada

**ABSTRACT** DXG and its prodrug DAPD have been demonstrated to be effective inhibitors of HIV-1 in various cells. The EC<sub>50</sub>s for DXG were 0.032  $\mu$ M in CBMCs and 0.05  $\mu$ M 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  $\mu$ M.

(-)- $\beta$ -D-1,3-dioxolane guanine (DXG) and (-)- $\beta$ -D-2,6-diaminopurine dioxolane (DAPD) are purine nucleoside analogs. *In vivo*, DAPD is quickly converted into DXG mediated by adenosine deaminase<sup>1</sup> and can be considered as a prodrug for DXG. Both compounds were previously reported to have anti-viral activities<sup>1,2</sup>. 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<sub>50</sub>) tested with HIV-1<sub>MB</sub>. The EC<sub>50</sub>s for DXG were 0.032  $\mu$ M in CBMCs and 0.05  $\mu$ M in MT-4 cells. These values were generally equipotent as 3TC, but approximately 5-fold higher than the EC<sub>50</sub>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<sub>IIIb</sub>**

| Cell   | EC <sub>50</sub> (μM) <sup>a</sup> in MT-2 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 <sup>b</sup> | 0.011 |
| H9     | 0.06  | 0.075 | ND              | 0.031 |

<sup>a</sup> The average of two or more experiments. <sup>b</sup> ND = not determined

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

| HXB2-D            | EC <sub>50</sub> (μM) <sup>a</sup> in MT-2 cell |                 |      |       |
|-------------------|---|-----------------|------|-------|
|                   | 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 <sup>b</sup> | >100 | 0.02  |
| 41L/70R/215Y/219Q | 0.22  | 6.4             | 0.86 | 0.45  |

<sup>a</sup> The average of two or more experiments. <sup>b</sup> 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 [<sup>3</sup>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.

## REFERENCES

1. Rajagopalan, P.; Boudinot, F. D.; Chu, C. K.; Tennant, B. C.; Baldwin, B. H.; Schinazi. *Antiviral Chem. Chemother.*, **1996**, 7, 65-70.
2. Siddiqui, M. N.; Brown, W. L.; Nguyen-Ba, N. Dixit, D. M.; Mansour, T. S. *Bioorg. Med. Chem. Lett.*, **1993**, 3, 1543-1546.