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(*R*)-9-(2-Phosphonylmethoxypropyl)-2,6-diaminopurine [(*R*)-PMPDAP]: a potent anti-retrovirus agent *in vitro* and *in vivo*

J. Balzarini[1], A. Holy[2], L. Naesens[1] and E. De Clercq[1]
[1]*Rega Institute for Medical Research, Katholieke Universiteit Leuven, B-3000 Leuven, Belgium and* [2]*Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Sciences, 16610 Praha 6, Czechoslovakia*

The (*S*)- and (*R*)-enantiomers of the acyclic nucleoside phosphonate derivative 9-(2-phosphonylmethoxypropyl)-2,6-diaminopurine (PMPDAP) were evaluated for their antiviral activity. Neither of the PMPDAP enantiomers proved effective against herpes simplex virus type 1 or type 2 [50% effective concentration ($EC_{50}$): > 100 μM]. However, both compounds proved highly effective in inhibiting human immunodeficiency virus (HIV) replication in MT-4 and CEM cells. (*R*)-PMPDAP inhibited HIV-induced cytopathicity in MT-4 cells at an $EC_{50}$ of 0.17 μM. Its $EC_{50}$ for inhibition of C3H/3T3 cell transformation by Moloney murine sarcoma virus (MSV) was 0.67 μM. (*S*)-PMPDAP was 15- to 50-fold less inhibitory to HIV-1, HIV-2 and MSV than its (*R*)-enantiomer. When evaluated for its inhibitory effect on MSV-induced tumor formation in NMRI mice, (*R*)-PMPDAP, administered as a single dose of 2, 5, 10 or 20 mg/kg at 4 h prior to infection, afforded a dose-dependent protection against MSV-induced tumor development and therewith associated mortality. The *in vivo* antiretroviral activity of (*R*)-PMPDAP was at least 5- to 10-fold superior over that of 9-(2-phosphonylmethoxyethyl)adenine (PMEA) when evaluated under similar experimental conditions. Moreover, (*R*)-PMPDAP proved less toxic than PMEA both *in vitro* (cell culture) and *in vivo* (mice). In conclusion, (*R*)-PMPDAP should be considered as a prime candidate drug for further development for the treatment of retrovirus infections (i.e. AIDS).

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**Activity of BRL47923 and its Oral Prodrug, SB203657A Against a Rauscher Murine Leukaemia Virus Infection in Mice.** R.M.Perkins[1], S.Barney[1], R.Wittrock[1], P.H.Clark[1], R.Levin[1], D.M.Lambert[1], S.R. Petteway[1], H.Serafinowska[2], S.Bailey[2], S.M.Jackson[2], M.R.Harnden[2], R.J.Ashton[2], D.Sutton[2], J.J.Harvey[3], A.G.Brown[2]. SmithKline Beecham Pharmaceuticals, King of Prussia, USA[1], and Epsom, UK[2]. Clinical Research Centre, Harrow, UK[3].

BRL47923, 9-[2-(phosphonomethoxy)ethoxy]adenine is a novel acyclic nucleotide analogue with selective anti-retroviral activity. The $IC_{50}$ against HIV-1 replication in human peripheral blood lymphocytes was 0.2μM. BRL47923 inhibits Rauscher murine leukaemia virus (RMLV) replication in D56 S+ L- cells with an $IC_{50}$ of 4μM and a 50% cell inhibitory concentration($CD_{50}$) of >346μM. Comparible results for AZT were $IC_{50}$ = 0.004 μM; $CD_{50}$ = 13.9μM. In RMLV-infected mice, we have previously demonstrated that either BRL47923 or AZT (0.4mmol/kg), administered subcutaneously, twice daily throughout the experiment, resulted in 86% and 84% inhibition of splenomegaly, respectively. Here we present a dose response study with BRL47923 and AZT and data on the efficacy of an oral form, SB203657A, in the RMLV model. Mice were infected intraperitoneally with RMLV and dosed as above with either BRL47923 or AZT at 0.4, 0.13, 0.04. or 0.013 mmoles/kg, starting at the time of infection. Mice were sacrificed 14 days post-infection and spleen weights, spleen virology, and viraemia were determined. At each dose level, BRL47923 and AZT gave comparable inhibition of splenomegaly; even at the lowest dose, 64% inhibition was achieved for BRL47923. Similar inhibitory effects were seen on viraemia. Pharmacokinetic studies demonstrated that BRL47923 had poor oral bioavailability (1-2%) in mice. A prodrug strategy was therefore adopted to develop an oral form of BRL47923. Following bioavailability studies on a large number of derivatives, SB203657A was selected as the preferred prodrug for *in vivo* efficacy studies. In mice the oral bioavailability of BRL47923 from a single 0.2mmol/kg dose of SB203657A was 50% with peak BRL47923 levels of 20μM. SB203657A was shown to effectively inhibit RMLV-induced splenomegaly and viraemia, in a dose-dependent manner.