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Differential Inhibitory Effects of the (*S*)- and (*R*)-Enantiomers of 9-(3-Fluoro-2-Phosphonylmethoxypropyl)Purine Derivatives on Retrovirus Replication *in vitro* and *in vivo*

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Recently, we reported on the selective activity of several 9-[(2*RS*)-3-fluoro-2-phosphonylmethoxypropyl]purine derivatives against a broad spectrum of retroviruses [including human immunodeficiency virus type 1 (HIV-1) and type 2 (HIV-2), and Moloney murine sarcoma virus (MSV)] but not other RNA or DNA viruses (J. Balzarini *et al.*, Proc. Natl. Acad. Sci. USA **88**, 4961-4965, 1991). We have now synthesized the (*S*)- and (*R*)-enantiomers of the FPMP derivatives of adenine (FPMPA), 2,6-diaminopurine (FPMPDAP), 2-monoaminopurine (FPMPMAP) and guanine (FPMPG). The (*S*)-enantiomer of FPMPA was 30- to 50-fold more inhibitory to HIV-1 and HIV-2 replication in MT-4 cells and MSV-induced transformation of C3H/3T3 cells than (*R*)-FPMPA [50% effective concentration (EC_{50}): 2.1-2.7 μM *versus* 64->100 μM]. In contrast, the (*R*)- and (*S*)-enantiomers of FPMPDAP and FPMPG were almost equally inhibitory to HIV (EC_{50}: 1.4-6.1 μM). (*S*)- and (*R*)-FPMPMAP were without any inhibitory effect at 100 μM. While (*R*)-FPMPA did not inhibit MSV-induced tumor formation in newborn NMRI mice, (*S*)-FPMPA proved highly effective and equally inhibitory as 9-(2-phosphonylmethoxyethyl)adenine (PMEA) in this animal model. The reason(s) for the differential behavior of the (*S*)- and (*R*)-enantiomers of FPMPA, FPMPDAP and FPMPG as retrovirus inhibitors warrant further investigation.

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SELENOORGANIC COMPOUNDS USEFUL AS ANTI-HIV INHIBITORS

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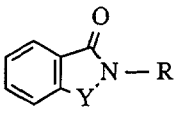
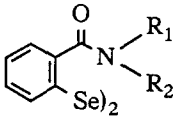
Some benzisoselenazolones (I, Y = Se), (BISA) and diaryldiselenides (II) were found to display activity - in the μM range - in HIV-1 infected CEM Cl13 cells. The corresponding benzisothiazolones (I, Y = S) were either of lower activity or completely inactive in the test system. Cytotoxicity of the sulfur analogs tended to be higher than in the case of the selenium derivatives.

(I) 

(II) 

These compounds were also found to inactivate HIV-1 protease in test system using the fluorogenic substrate Suc-TLNFPIS-4MCA (Ph.H. Hirel et al., Antiviral Chem. Chemother. (1990), 1,9-15). However the observed inactivation can be prevented by increasing quantities of β-mercaptoethanol. The latter result has excluded the HIV-1 protease inhibition as a possible mechanism of action.