Oral Session II

Synthesis, In Vitro Evaluation

7

Potent and selective anti-retrovirus activity of 9-(*RS*)-(3-fluoro-2-phosphonylmethoxypropyl)purine derivatives

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The 9-(*RS*)-(3-fluoro-2-phosphonylmethoxypropyl) derivatives of adenine (A) and 2,6-diaminopurine (DAP), designated FPMPA and FPMPDAP, are markedly inhibitory to Moloney murine sarcoma virus (MSV), simian immunodeficiency virus (SIV), human immunodeficiency virus type 1 (HIV-1) and type 2 (HIV-2), but not other RNA viruses or DNA viruses [i.e. herpes simplex virus type 1 (HSV-1)]. In this respect, FPMPA and FPMPDAP are more selective antiretroviral agents than 9-(2-phosphonylmethoxyethyl)adenine (PMEA) and its 2,6-diaminopurine derivative PMEDAP. Due to their lack of toxicity at doses as high as 1 gram/kg, both FPMPA and FPMPDAP also achieve a markedly higher therapeutic index in suppressing MSV-induced tumor formation in newborn mice than PMEA and PMEDAP. Also, FPMPA and FPMPDAP are more than 20-fold less inhibitory to human bone marrow cells than PMEA. The diphosphorylated derivative of FPMPA is a potent and selective inhibitor of HIV-1 reverse transcriptase but not HSV-1 DNA polymerase or DNA polymerase α. FPMPA acts as a DNA chain terminator in the DNA polymerisation reaction catalysed by HIV-1 reverse transcriptase.