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Synthesis and HIV-1 Reverse Transcriptase Inhibition of 3'-Azido-3',5'-Dideoxythymidine 5'-Methylphosphonic Acid Diphosphate G. A. Freeman*†, J. L. Rideout†, and W. H. Miller≠. Burroughs Wellcome Co.,†Division of Organic Chemistry and ≠Division of Experimental Therapy, 3030 Cornwallis Rd., Research Triangle Park, N. C. U.S.A.

Synthesis of 3'-azido-3'-deoxythymidine-5'-phosphonate was accomplished by a five-step reaction sequence. The 5'-hydroxyl of AZT was converted to the 5'-aldehyde utilizing a Moffit oxidation. Wittig reaction of the aldehyde gave a phosphinoylvinyl intermediate which could be selectively reduced to the 5'-phosphonate with diimide in the presence of the 3'-azido group. Two-step deprotection of the diphenyl phosphonate gave AZT phosphonate. AZT phosphonate is inactive against HIV-1. Conversion of AZT phosphonate to the 5'-deoxy-5'-methylphosphonic acid diphosphate analog was accomplished in order to examine the triphosphate analog as a HIV-1 RT inhibitor. The results indicate the lack of activity of AZT phosphonate against HIV-1 was at least partially explained by demonstrating that the 5'-deoxy-5'-methylphosphonic acid diphosphate analog was much weaker alternate substrate for HIV-1 reverse transcriptase compared to AZT 5'-triphosphate.

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Broad-Spectrum Antiviral Activity of Polyoxometalates Against Human Immunodeficiency Virus and other Enveloped Viruses

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A large variety of polyoxometalates were evaluated, and found active, against a broad range of enveloped RNA and DNA viruses: retroviruses [human immunodeficiency virus (HIV-1, HIV-2), simian immunodeficiency virus (SIV), murine sarcoma virus (MSV), rhabdoviruses [i.e. vesicular stomatitis virus (VSV)], arenaviruses (Junin, Tacaribe), ortho- and paramyxoviruses [influenza A and B, respiratory syncytial virus (RSV)] and herpesviruses [herpes simplex virus (HSV), cytomegalovirus (CMV)]. For example, $K_{13}[Ce(S\ W_{11}O_{39})_2]$ (JM1590) inhibited the cytopathicity of SIV at an EC_{50} of 0.05 μg/ml, while it was toxic to the host cells only at a CC_{50} of 200 μg/ml, thus exhibiting a selectivity index of 4000. The polyoxometalates inhibited giant cell (syncytium) formation if added to co-cultures of persistently HIV-1-infected (HUT-78) cells with uninfected MOLT-4 cells. Within the range of concentrations that were inhibitory to HIV cytopathicity, polyoxometalates inhibited HIV binding to the cells as well as HIV reverse transcriptase activity. According to "time of addition" experiments, their anti-HIV action may be attributed to inhibition of virus-cell binding.