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Low Molecular Weight Difluoroketones That Are Inhibitors of HIV-1 Protease and With Antiviral Activities *In Vitro*. H. Sham, D. Betebenner, N. Wideburg, W. Kohlbrenner, D. Norbeck, J. Erickson and J. Plattner, Abbott Laboratories, Anti-infective Division, Abbott Park, Illinois 60064-3500 U.S.A.

Human immunodeficiency virus type-1 (HIV-1) is a retrovirus that is the causative agent of acquired immunodeficiency syndrome (AIDS). The *gag* and *pol* genes of HIV-1 encode the viral structural and replicative enzymes that are translated as polyprotein precursors. The polyproteins are proteolytically processed by the action of a virus encoded protease. The activity of the protease is essential for the formation of mature and fully infectious virions of HIV-1. Thus, the HIV-1 protease has become an important target for the design of antiviral agents for AIDS. We have designed and synthesized a novel series of low molecular weight (M.W. <600) difluoroketones with good inhibitory potency against HIV-1 protease (IC_{50} ranges from 4.7-54 nM) starting from phenylalaninol. Some of these difluoroketones showed antiviral activities in a CPE assay using the MT-4 cell line. Because of their small size, these difluoroketones have potential of being orally bioavailable.

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Antiviral Activity of 5'-Modified Analogs of AZT Against HIV-1 and 2
G. A. FREEMAN,* J. L. RIDEOUT, M. H. ST. CLAIR, G. B. ROBERTS and P. A. SHERMAN
Burroughs Wellcome Co., Res. Tri. Park, N.C.

Synthesis of an analog of AZT homologated by one methylene unit at the 5'-position and two pairs of 5'-C-substituted, methyl and phenyl, diastereomers from the 5'-aldehyde of AZT will be presented. The phenyl diastereomers were separated by HPLC. The methyl diastereomers were not resolved. Screening these compounds against HIV-1 and 2 in MT4 cells and HIV-1 in PBLs demonstrated inactivity against both viruses. In addition, screening against VZV in MRC5 cells and HCMV in HFF demonstrated no antiviral activity. No detectable enzyme substrate activity for these analogs was found with either H9 cytosolic thymidine kinase or VZV thymidine kinase. Lack of formation of the monophosphates of these analogs is a possible explaination for the antiviral inactivity.