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Lipophilic Phosphorus Prodrugs for the Antiviral Agent PMEA

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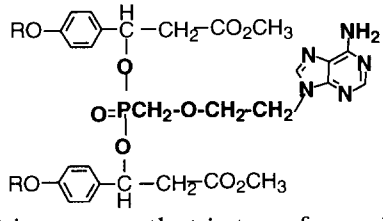
We have synthesized a series of lipophilic phosphorus prodrugs of the antiviral agent PMEA in order to improve bioavailability. These prodrugs are based on a class of phospho-esters which undergo degradation via an elimination reaction following the unmasking of a para-hydroxy group.[1]The general structure of these prodrugs is shown below as 1:



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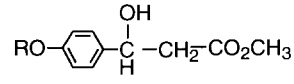

2

where RO is a group that is transformed enzymatically or spontaneously to a hydroxy group. Refluxing PMEA or PMEA·HCl with oxalyl chloride in CH_2Cl_2 and a catalytic amount of dimethylformamide yielded PMEA dichloride, which in the presence of triethylamine and 1-methylimidazole reacted with **2** to give the prodrugs. Details on the synthesis and in vitro anti-retroviral activity of these prodrugs will be presented. [1]Antiviral Research 17, Suppl. 1:77, Abstract 66 (1992). Supported by NIAID SBRI grant 1-R43-AI33758-01.

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Superantigen Toxic Shock Syndrome Toxin-1 (TSST-1) Enhances the Replication of HIV-1 in Peripheral Blood Mononuclear Cells: Implication of a New Anti-HIV-1 Assay *In Vitro.*

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The prime target for human immunodeficiency virus type 1 (HIV-1) is peripheral blood mononuclear cells (PBMCs), in particular, $CD4^+$ T-lymphocytes. It has been shown that activation of PBMCs is required for effective production of HIV-1. Superantigens potently activate PBMCs by binding to the MHC class II molecules expressed on their surface. We have investigated whether the superantigen toxic shock syndrome toxin-1 (TSST-1) is able to bring about high-level of HIV-1 production in virus-infected PBMCs through their activation. PBMCs were obtained from healthy donors, infected with HIV-1, and cultured in the presence of various concentrations of TSST-1. After 6-9 days, the culture supernatants were collected and examined for their p24 antigen levels. Macromolecular synthesis and cell viability were also determined. TSST-1 could activate PBMCs at a concentration of 10-100 pg/ml. The cells proliferated well and produced much higher level of HIV-1 as compared to those in the absence of TSST-1. Mechanism studies suggest that the enhanced production of HIV-1 in TSST-1-activated PBMCs is in part attributed to the induction of TNF-α by the superantigen. Thus, the infections with superantigen producing bacteria may play an important role in the production of HIV-1 in AIDS patients. Evaluation of compounds for their anti-HIV-1 activity in superantigen-activated PBMCs may be useful and, it is now in progress.