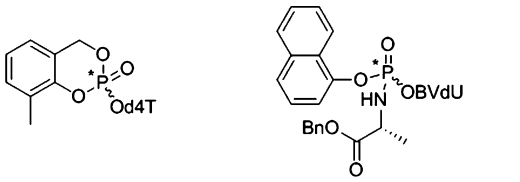
with respect to the configuration at the phosphorus center. The mixtures of diastereomers can only be separated in limited cases and in addition to this, the diastereomers have different antiviral activity, toxicity and hydrolysis stabilities (see below) (Meier, 2002; Congiatu et al., 2006). For this reason developing strategies to synthesize isomerically pure pronucleotides is very mandatory. Here, we present new diastereoselective syntheses of pronucleotides by using a convergent strategy and a linear strategy. Both strategies are based on the use of chiral auxiliaries. We could synthesize for the first time 3-methyl-*cyclo*Sal-nucleotides as well as several nucleoside arylphosphoramidates with very high diastereoselectivities. Beside the antiviral activity, biophysical properties will be presented and discussed in dependence on the different chirality at the phosphate.



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L-β-1-(5-Bromovinyl-2-hydroxymethyl-1,3-dioxolanyl) Uracil (L-Bhdu) Prevents Varicella-Zoster Virus Replication in Fibroblasts, Skin Organ Culture, and Scid-Hu Mice with Human Skin Xenografts

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The αα-herpesvirus varicella-zoster virus (VZV) causes chickenpox and shingles. Current treatments are acyclovir, valaciclovir (VACV), famciclovir and brivudin (Europe). Vaccines are also approved that lower the incidence of primary and recurrent infections. Additional antiviral compounds with increased potency and specificity are needed to treat VZV and for strains resistant to the existing drugs. L-BHDU (MW 319.1) had anti-VZV activity in pilot studies. We evaluated L-BHDU in 3 models of VZV replication: primary human foreskin fibroblasts (HFFs), skin organ culture (SOC) and in SCID-Hu mice with skin xenografts. In HFFs, 100 μM L-BHDU was noncytotoxic over 3 days, and the antiviral effects of 2 μM treatment were reversible. Virus replication was measured by bioluminescence imaging of the VZV-BAC-Luc strain. The EC_{50} in HFFs was ~0.03 μM and in SOC was <0.1 μM. In mouse studies, L-BHDU in DMSO was administered by oral gavage once daily for 7 days, or 3 mg/mL VACV was added to drinking water, starting 2 dpi. Groups (n = 5) were given 8, 15, or 150 mg/kg/day L-BHDU, and all doses significantly reduced VZV growth compared to VACV or DMSO. VACV was not effective and the group lost >20% of body weight, suggesting mice were averse to the drug in water. L-BHDU and DMSO caused moderate weight loss, which did not correspond to dose, and mortality was 1/8 in the DMSO group and 1/5 in the 8 mg/kg/day group. Mouse organs were harvested 2 h after the last dose. C_{max} values in the human skin xenografts were 0.7 ± 0.1 and 11.3 ± 1.1 for the 8 and 150 mg/kg/day doses, respectively. Comparison of concentration ratios of tissue to plasma indicated saturation of uptake at the higher dose. To determine the phase of VZV replication blocked by L-BHDU, virus proteins were evaluated by immunoblot and all were reduced in treated HFFs. The effects of drug on VZV genome copy number will be measured by quantitative PCR. L-BHDU was effective and well tolerated in mice, therefore it has potential as a novel anti-VZV agent.

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Synthesis and Antiviral Evaluation of Alkoxyalkyl Esters of (*R*)-[2-(Phosphonomethoxy)propyl]-Nucleosides

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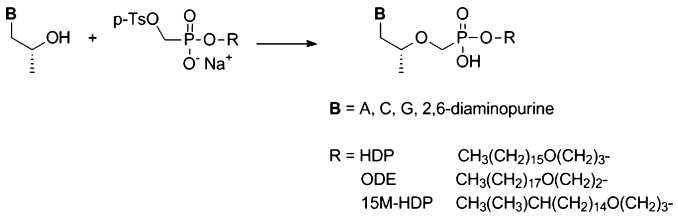
PMPA, (9-(*R*)-[2-(phosphonomethoxy)propyl]adenine, tenofovir), administered orally as its disoproxil fumarate prodrug, is a potent anti-HIV therapy used most often in combination with other antiretroviral drugs. We previously reported the synthesis of a lipophilic tenofovir prodrug, hexadecyloxypropyl 9-(*R*)-[2-(phosphonomethoxy)propyl]adenine (HDP-(*R*)-PMPA, CMX157), that was more potent than tenofovir versus in vitro replication of HIV, and was orally bioavailable in rats. Encouraged by these results, we have synthesized several more alkoxyalkyl esters in the PMP-series. We first prepared hexadecyloxypropoyl (HDP), octadecyloxyethyl (ODE) and 15-methyl-hexadecyloxypropyl (15M-HDP) esters of p-toluenesulfonyloxymethylphosphonate. These synthons reacted with hydroxypropyl derivatives of adenine, cytosine, 6-*O*-benzylguanine and 2,6-diaminopurine to afford alkoxyalkyl monoesters of (*R*)-PMPA, (*R*)-PMPC, (*R*)-PMPG and (*R*)-PMPDAP, respectively. The antiviral activity of the new compounds was evaluated in PBMCs. The octadecyloxyethyl ester of (*R*)-PMPA proved slightly more potent (EC_{50} = 1 nM) than the HDP ester. However, because the cytotoxicity of ODE-PMPA also increased, the selectivity index (CC_{50}/EC_{50}) was less than observed with the HDP ester. The most active compounds were ODE-(*R*)-PMPDAP and ODE-(*R*)-PMPG with EC_{50} values of 0.3–2 nM. The HDP and 15M-HDP-esters of (*R*)-PMPG were also highly active. ODE-(*R*)-PMPC was not active against HIV.



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