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Synthesis and antiviral evaluation of 2-amino-6-carbamoylpurine dioxolane nucleoside derivatives and their phosphoramidates prodrugs

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ABSTRACT

The synthesis of 9-(β-D-1,3-dioxolan-4-yl)2,6-diaminopurine nucleoside phosphoramidate prodrugs as well as various 2-amino-6-carbamoylpurine dioxolane derivatives and their phosphoramidates prodrugs is reported. Their ability to block HIV and HBV replication along with their cytotoxicity toward HepG2, human lymphocyte, CEM and Vero cells was also assessed.

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1. Introduction

Nucleoside reverse transcriptase inhibitors (NTRI) are the backbone in fixed dose combinations now called highly active antiretroviral therapy (HAART) for human immunodeficiency virus type 1 (HIV-1).[1] Despite the effectiveness of these drugs, resistance can result from their long-term use and latent toxicity remains an issue.[2] Therefore, studies on novel nucleoside analogs with improved efficacy, resistance profile and safety are continuously needed to improve clinical outcome. Among all the modified nucleosides prepared over the years, β-D-1,3-dioxolan-4-yl nucleosides appeared to be a very promising family. Therefore, 9-(β-D-1,3-dioxolan-4-yl)2,6-diaminopurine (DAPD) **1**, a prodrug of 9-(β-D-1,3-dioxolan-4-yl)guanine (DXG, **2**), was evaluated for the treatment of HIV-1 infected persons in phase 2 clinical studies. However, the study was abandoned due to slow enrollment and high dosing regimens (500 mg twice a day). Over the years of nucleoside analog development, two main approaches have been utilized to improve the potency of a compound and potentially decrease the administered dose: (A) formation of a monophosphate prodrug to bypass the rate limiting first phosphorylation step.[3,4] For instance, (−)-β-D-(2*R*,4*R*)-1,3-dioxolane-2-amino-6-aminopropyl purine nucleoside phosphoramidate prodrug **4** displayed submicromolar activities against HBV and HIV while its corresponding nucleoside **3** was devoid of activity (Fig. 1).[5] (B) Conversion of hydrophilic functional groups (such as amino or hydroxy) into corresponding lipophilic groups (such as amides or esters) in order to improve cell penetration. Thus, L-1,3-dixolane-cytidine (L-OddC) bearing a fatty acid group at its N^4-position demonstrated significantly improved antitumor activity (170-fold) in vitro when compared to the parent nucleoside.[6] Fatty acyl derivatives of (−)-2′,3′-dideoxy-3′-thiacytidine (3TC) and (−)-2′,3′-dideoxy-5-fluoro-3′-thiacytidine [(−)-FTC] were 36- and 24-fold, respectively, more potent against HIV when compared to 3TC and (−)-FTC.[7]

Herein, we combine both approaches to potentially improve the antiviral potency of DAPD. Thus, we report the synthesis and antiviral evaluation of DAPD phosphoramidate prodrugs as well as their 2-amino-6-carbamoylpurine derivatives as a potential strategy to increase intracellular delivery of DXG-TP.

2. Results and discussion

We first envisaged to prepare the desired 2-amino-6-carbamoylpurine dioxolane nucleoside phosphoramidate prodrugs **10a–i** from DAPD in a 2 steps sequence by (1) formation of the phosphoramidate prodrug **5**; (2) introduction of the carbamoyl

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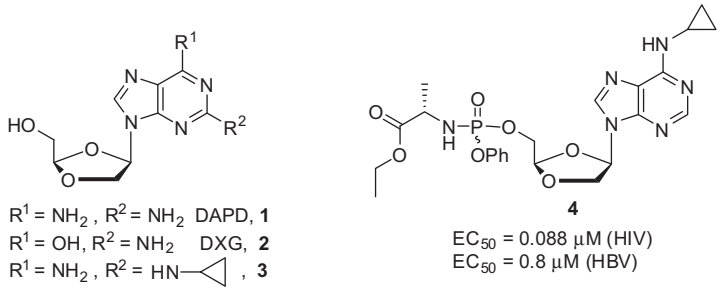
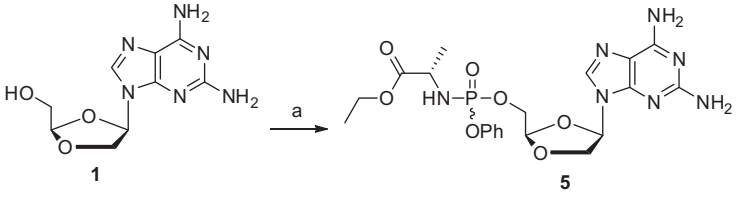


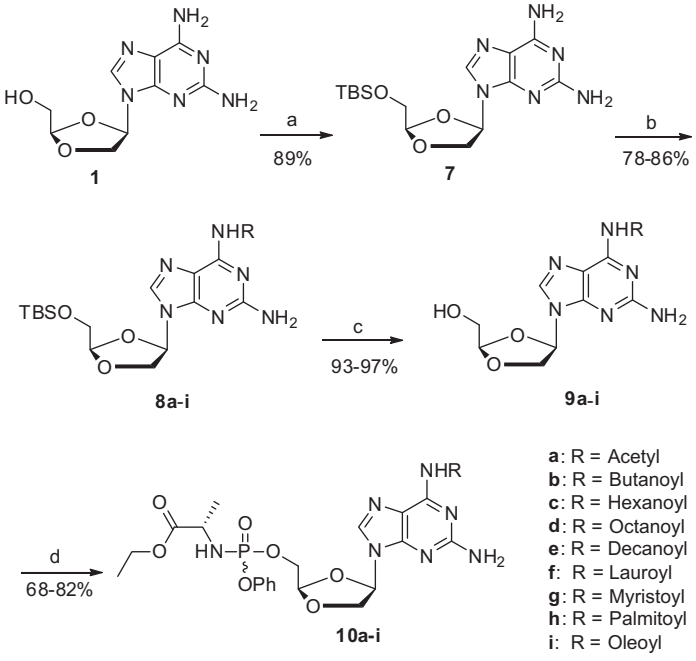
Figure 1.

moiety. However, reaction of DAPD **1** with phosphoramidate chloride **6**[8] in the presence of *t*-BuMgCl afforded DAPD prodrug **5** in only 45% yield (Scheme 1). To further complicate this approach, acylation reactions with **5** would either proceed to only about 50% or when forced gave a substantial amount of the N^2,N^6-diacylated product. These low yields combined with the difficulty of purifying **5** using repeated tedious silica gel column chromatography lead us to design an alternative sequence which also allowed us to prepare and evaluate the 2-amino-6-carbamoylpurine dioxolanes **9a–i** (Scheme 2).

Thus, DAPD **1** was reacted with *t*-butyldimethylsilyl chloride (TBSCl) in the presence of imidazole in pyridine to give 5′-*O*-TBS-2,6-diaminopurine dioxolane **7** in 89% yield. With **7** in hand, its chemoselective N^6-acylation was investigated using oleoyl chloride as the model system for optimization (Table 1). Interestingly, the reaction of **7** with oleoyl chloride (1.1 equiv) in the presence of pyridine (entry 2), DMAP (entry 4), Et_3N (entry 6), imidazole (entry 7) or their combination (entries 3 and 5) lead to the formation of 5′-*O*-TBS-2-amino-6-oleoylpurine dioxolane **8i** in poor to moderate yields along with N^2,N^6-diacylated DAPD in ca. 5–25% yields. On the other hand, treatment of **7** with oleic acid chloride (1.1 equiv) in the presence of *N*-methylimidazole (entry 1),[9] provided the desired compound **8i** in 80% yield with less than 5% of the N^2,N^6-diacylated byproduct. Using these optimized conditions, compound **7** was reacted with a variety of acyl chlorides to give the corresponding 5′-*O*-TBS-2-amino-6-carbamoylpurine



Scheme 1. Reagents and reaction conditions: (a) (EtOAlaNH)P(=O)(OPh)Cl **6**, *t*-BuMgCl, THF, −78 °C then rt, 8 h.



Scheme 2. Reagents and reaction conditions: (a) TBSCl, imidazole, pyridine, 0 °C then rt, 12 h; (b) RCl, NMI, CH_2Cl_2, 0 °C then rt, 12 h; (c) Et_3N–3HF, THF, rt, 12 h; (d) (NHAlaOEt)P(=O)(OPh)Cl **6**, NMI, −78 °C then rt, 8–12 h.

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