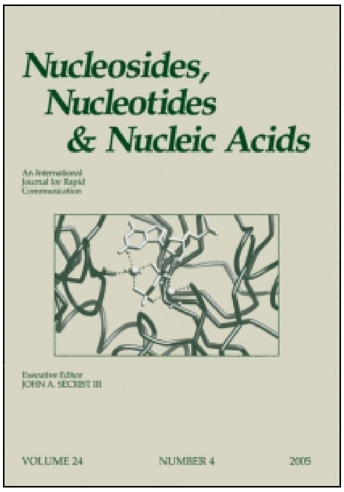

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Design, Enantiopure Synthesis, and Biological Evaluation of Novel ISO-D-2',3'-Dideoxy-3'-Fluorothianucleoside Derivatives as a bioisostere of Lamivudine

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DESIGN, ENANTIOPURE SYNTHESIS, AND BIOLOGICAL EVALUATION OF NOVEL ISO-D-2′,3′-DIDEOXY-3′-FLUOROTHIANUCLEOSIDE DERIVATIVES AS A BIOISOSTERE OF LAMIVUDINE

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□ *Novel iso D-2′,3′-dideoxythianucleoside derivatives* ***1–3*** *were designed and asymmetrically synthesized to search for new anti-HIV agents. Final compounds* ***1–3*** *were evaluated against a variety of viruses including HIV-1 and 2. Only cytosine analog* ***3*** *showed a potent anti-VSV activity (EC_{50} = 9.43 μg/mL). This result implies that iso 2′,3′-dideoxy sugar templates might play a role of a sugar surrogate of nucleosides for the development of anti-RNA virus agent.*

Keywords Anti-HIV agents; 2′-3′-dideoxy sugar templates; anti-VSV activity; sulfur participation

INTRODUCTION

Although 2′,3′-ddNs (2′,3′-dideoxynucleosides) such as zidovudine,[1] didanosine,[2] zalcitabine,[3] and stavudine[4] have been launched as drugs for the treatment of AIDS patients, these nucleosides have several drawbacks such as easy cleavage of their glycosidic bond under acidic conditions similar to a gastric environment and catabolism by several enzymes. Lamivudine (3TC)[5] also has been clinically used for the treatment of AIDS and HBV (hepatitis B virus) infection. Structural characteristics of lamivudine are that there is no hydroxyl substituent at both its 2′- and 3′-positions

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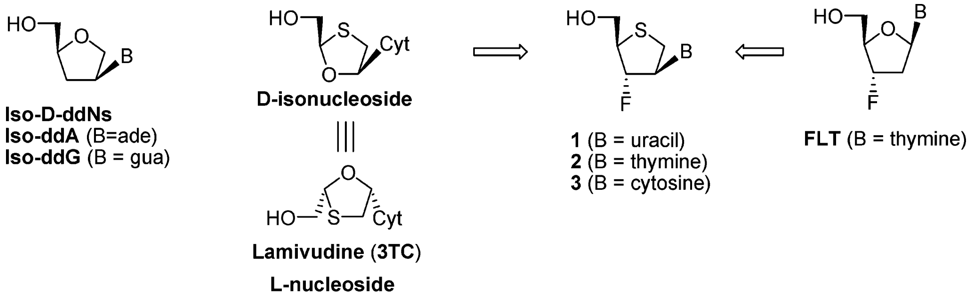
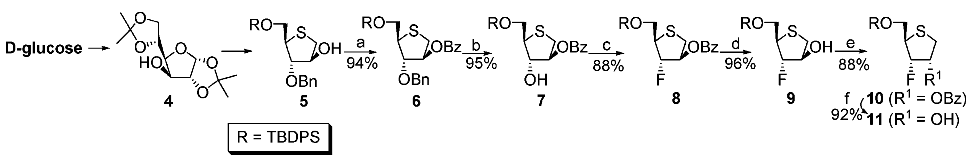


FIGURE 1 The rationale for the design of the desired nucleosides **1–3**.

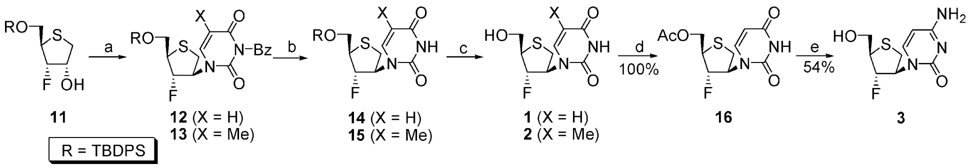
like 2′,3′-ddN analogues and are two heteroatoms on the ring of its sugar moiety. In addition, lamivudine belongs to L-nucleoside unlike other anti-AIDS drugs. Isonucleosides[6] in which their base is moved into C2′ position from anomeric position have been synthesized and among them, iso-ddA and iso-ddG were found to be active against HIV-1 (Figure 1). Isonucleosides were known to possess the intrinsic metabolic advantages such as resistance to ADA and enhanced stability of glycosidic bond under acidic and enzymatic conditions.[6,7]

On the other hand, many functional groups have been replaced with a fluorine atom in view of bioisosterism because many nucleosides fluorinated at their sugar ring such as 2′-F-ddA,[8] 2′-F-ara-ddC,[9] and FLT were found to exhibit significant antiviral activities. Furthermore, it is worthy to note that L-nucleoside analogues such as lamivudine can be considered as iso D-nucleoside analogue.

On the basis of these findings, it was interesting to design and synthesize iso D-2′,3′-dideoxythianucleoside derivatives with a 3′-fluoro substituent and to evaluate them against various viruses because CH-F group might act as a bioisostere of sugar ring oxygen of lamivudine and/or as a hydrogen bonding acceptor at the active site of their target enzyme, and because the D-sugar skeleton of iso D-2′,3′-dideoxythianucleosides resembles L-1,3-oxathiolane ring of lamivudine. Here, we wish to report the asymmetric synthesis and biological activities of novel fluorinated iso D-2′,3′-dideoxythianucleosides **1–3**.



SCHEME 1 Reagents and conditions: (a) BzCl, DMAP, pyridine, 88°C, 3 hours; (b) BCl_3, CH_2Cl_2, −78°C, 40 minutes; (c) DAST, CH_2Cl_2, −10°C, 30 minutes; (d) 1 M NaOMe, CH_2Cl_2, MeOH, rt, 4 hours; (e) BzOH, PPh_3, DEAD, THF, 60°C, 5 hours; (f) 1 M NaOMe, MeOH, CH_2Cl_2, rt, 7 hours.



SCHEME 2 Reagents and conditons: (a) N^3-benzoyl uracil or N^3-benzoyl thymine, PPh_3, DEAD, THF, rt, overnight, 62% for **12**, 66% for **13**; (b) 1 M NaOMe, MeOH, CH_2Cl_2, rt, 6 hours, 82% for **14**, overnight, 94% for **15**; (c) 1 M TBAF, THF, rt, 2 hours, 97% for **1**, 98% for **2**; (d) Ac_2O, pyridine, rt, overnight; (e) i) 1,2,4-triazole, $POCl_3$, pyridine, rt, overnight; ii) 1,4-dioxane, 28% NH_4OH, rt, overnight; iii) NH_3, MeOH, rt, overnight.

CHEMISTRY

A strategy for the synthesis of glycone of iso-D-2′,3′-dideoxy-3′-fluorothianucleosides **1–3** is outlined in Scheme 1. It was envisioned that 1,4-anhydro-4-thioarabitol **5** derived from D-glucose via 1,2;5,6-di-*O*-isopropylidene-D-glucofuranose (**4**) could be an appropriate intermediate to synthesize D-4-fluorothiophen-3-ol **11**, which could be condensed with pyrimidine bases to afford lamivudine analogs **1–3**.

Diacetone glucose (**4**) was derived from D-glucose by the known one-pot synthesis method reported by Moravcova and his coworkers.[10] Compound **4** was converted into 1,4-anhydro-4-thioarabitol **5** according to the known procedure developed by Yoshimura and his coworkers over ten steps.[11] Benzoylation of compound **5** with benzoyl chloride, DMAP and pyridine at elevated temperature (88°C) gave the corresponding benzoate **6** in 94% yield. Debenzylation of **6** with BCl_3 at –78°C gave **7**. Fluorination of **7** with DAST gave the fluorinated compound **8** in 88% yield with the desired "α" stereochemistry through double inversion mechanism by the nucleophilic participation of the ring sulfur atom.[12,13] Removal of benzoyl group of **8** using catalytic amounts of 1 M NaOMe in MeOH gave the corresponding alcohol **9** in nearly quantitative yield, which was used for coupling with benzoic acid under Mitsunobu conditions. During Mitsunobu reaction the nucleophilic participation of sulfur atom occurred only to the extent of 3~5%. The major product **10** which underwent a single inversion was formed in 88% yield with its epimer (3~5%) at 3-position. The structures of major and minor product, **10** and its epimer, were confirmed by comparing ^{1}H NMR data of the corresponding alcohols generated from each epimers after debenzoylation with those of compound **9**. Debenzoylation of **10** afforded the glycosyl donor **11**.

Synthesis of pyrimidine nucleoside analogs **1–3** is illustrated in Scheme 2. Coupling of **11** with N^3-benzoyluracil and N^3-benzoylthymine, PPh_3 and DEAD gave the desired β–nucleosides **12** (62%) and **13** (66%), respectively. It is worthy to note that the participation of sulfur atom did not occur at all during coupling of glycosyl donor **11** with nucleobases. Deprotection of *N*-benzoyl group with 1 M NaOMe produced TBDPS-protected compounds **14** and **15** in 82% and 94% yield, respectively. Finally, treatment of **14** and **15** with TBAF gave the desired final compounds **1** and **2**, respectively. Compound **1** was converted into lamivudine analog, cytosine nucleoside **3** via acetylation of the hydroxyl group followed by successive three conventional steps (1,2,4-triazole, $POCl_3$, pyridine; 1,4-dioxane, NH_4OH; NH_3, MeOH)[14] in overall 54% yield.

BIOLOGICAL RESULTS

Antiviral activities of all iso D-2′,3′-dideoxy-3′-fluorothianucleoside derivatives **1–3** synthesized as a bioisostere of lamivudine were measured against a variety of viruses such as HIV type 1 and 2, EMCV, Cox. B3, VSV, and HSV type 1 and 2. EC_{50} of compounds **1** and **2** exceeded 100 μg/mL and also did not show any cytotoxicity up to 100 μg/mL at all tested cells such as MT4, HeLa, and Vero cells. On the other hand, cytosine nucleoside derivative **3** exhibited potent anti-VSV actitivity ($EC_{50} = 9.43$ μg/mL) with high cytotoxicity ($CC_{50} = 14.54$ μg/mL) in HeLa cell, but was inactive against the other viruses and not cytotoxic. It is very interesting that cytosine nucleoside analog **3** designed as a bioisostere of lamvudine showed anti-VSV activity instead of the expected anti-HIV activity. It is worthy to note that **3** classified into ddNs exhibited potent anti-VSV activity because VSV belongs to RNA virus.

CONCLUSION

We have designed and synthesized novel iso D-2′,3′-dideoxythianucleoside derivatives **1–3** as a bioisostere of lamivudine to search for new anti-HIV agents. Among compounds tested, only cytosine analog **3** showed potent anti-VSV activity even if it pertains to ddNs classification and VSV is RNA virus. This observation implies that iso D-2′,3′-dideoxy sugar templates might act as a sugar surrogate of nucleosides for the development of anti-RNA virus agent. Information about participation of sulfur atom during fluorination reaction using DAST and Mitsunobu reaction will be of great help in synthesizing sulfur-containing compounds.

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