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SYNTHESES AND ANTIVIRAL ACTIVITIES OF 1,3-DIOXOLANYL-, 1,3-OXATHIOLANYL- AND 1,3-DITHIOLANYLNUCLEOSIDES WITH 2-HYDROXYMETHYL SUBSTITUENTS

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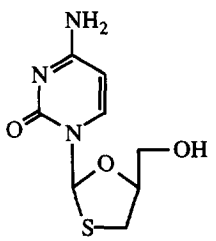
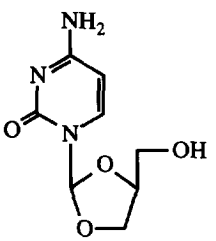
Abstract: Novel 1,3-dioxolanyl-, 1,3-oxathiolanyl- and 1,3-dithiolanylnucleosides with 2-hydroxymethyl substituents (**1a-4b**) were each synthesized with good yields through the condensation of dinucleophiles (oxygen and/or sulfur) with 1,3-dibenzoxy-2-propanone methyl ketal as a key step. © 1997 Elsevier Science Ltd.

Recently, several nucleosides possessing more than one heteroatom in the sugar ring have been reported to exhibit good antiviral activity.[1-4] Among these, (-)-**L**-β-1,3-oxathiolanylcytosine (3TC, Lamivudine) has been approved for the treatment of AIDS and will soon be approved by the Food and Drug Administration (FDA) for anti-HBV agent.[5,6]

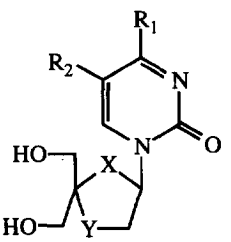
Lamivudine is the first **L**-nucleoside to be approved by FDA and is much less cytotoxic than its enantiomer, **D**-isomer. Another **L**-nucleoside, (-)-**L**-β-1,3-dioxolanylcytosine (L(-)OddC) was found to be highly potent against HIV and HBV as well as highly cytotoxic and is being developed as an anticancer agent.[7,8]



Lamivudine



L(-)OddC

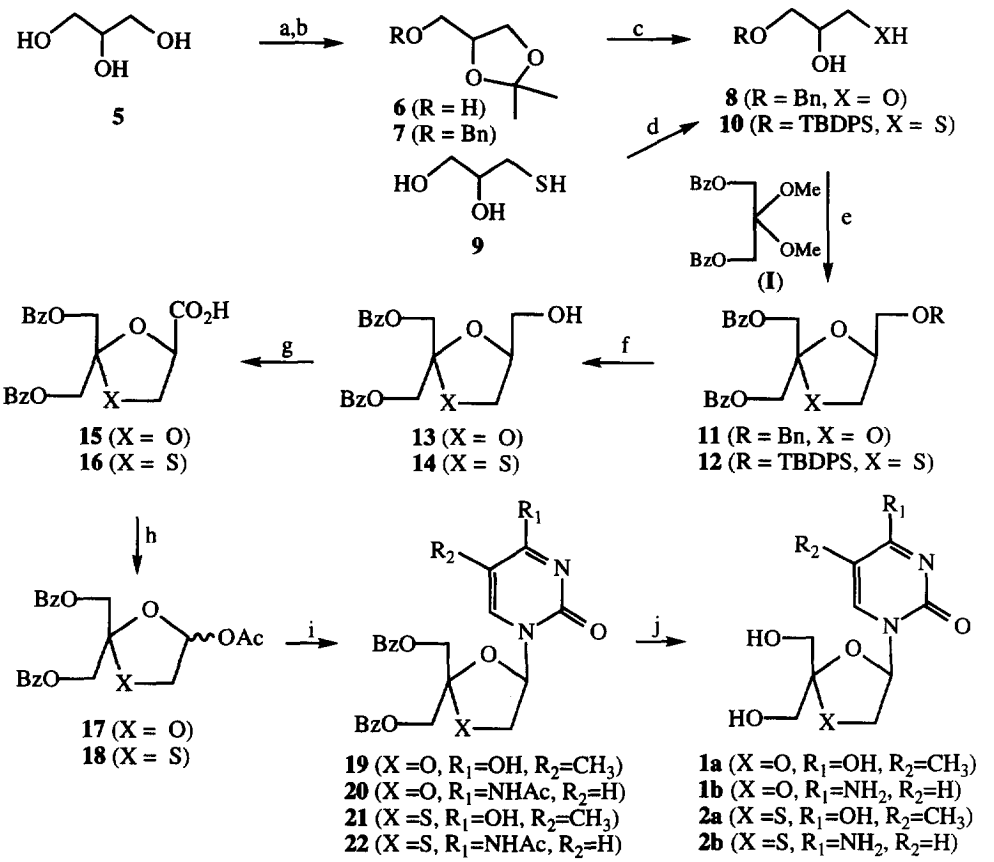


1a (X=O, Y=O, R_1=OH, R_2=CH_3)
1b (X=O, Y=O, R_1=NH_2, R_2=H)
2a (X=O, Y=S, R_1=OH, R_2=CH_3)
2b (X=O, Y=S, R_1=NH_2, R_2=H)
3a (X=S, Y=O, R_1=OH, R_2=CH_3)
3b (X=S, Y=O, R_1=NH_2, R_2=H)
4a (X=S, Y=S, R_1=OH, R_2=CH_3)
4b (X=S, Y=S, R_1=NH_2, R_2=H)

For structure-activity relationship study, substituents are bonded onto the dioxolane or oxathiolane ring, and a comparison is made between the biological activity of the new compound with that of its parent. Therefore, we decided to synthesize 2-hydroxymethyl analogues of 1,3-dioxolanyl- and 1,3-oxathiolanyl nucleosides, since oxetanocin A[9] and its ring-enlarged analogues[10] showed good antiviral activity.

A concurrent investigation of synthesis of 4'-thio analogues of 4'-hydroxymethyl-3'-oxa- and 3'-thianucleosides and a comparsion of the antiviral activities of each were carried out, since 4'-thionucleosides, possessing hetero atoms such as oxygen or sulfur atom at the 3'-position were reported to show good to excellent antiviral activity.[11-13]

Scheme 1[a]



Reagents[a] : a) $CH_3C(OMe)_2CH_3$, cHCl, RT, 15 h, 87%. b) NaH, BnBr, DMF, RT, 15 h, 98%. c) cHCl, MeOH, reflux, 1 h, 77%. d) t-BDPSCl, imidazole, THF, RT, 30 min, 86%. e) cat. p-TsOH, toluene, reflux, 76% for **13**, 53% for **14**. f) H_2, 10% Pd/C, RT, 15 h 78% for **15**, n-Bu_4NF, THF, RT, 20 min, 86% for **16**. g) PDC, DMF, 45-50°C, 15 h h) $Pb(OAc)_4$, pyridine, THF, 0°C to RT, 30 min, 50% from **15** for **19**,49% from **16** for **20**. i) persilylated bases, TMSOTf, 1,2-DCE, -20°C to RT, 2 h, 74% for **19**, 46% for **20**, 69% for **21**, 55% for **22**. j) NaOMe, CH_2Cl_2, RT, 30 min, 97% for **1a**, 95% for **1b**, 80% for **2a**, 99% for **2b**.

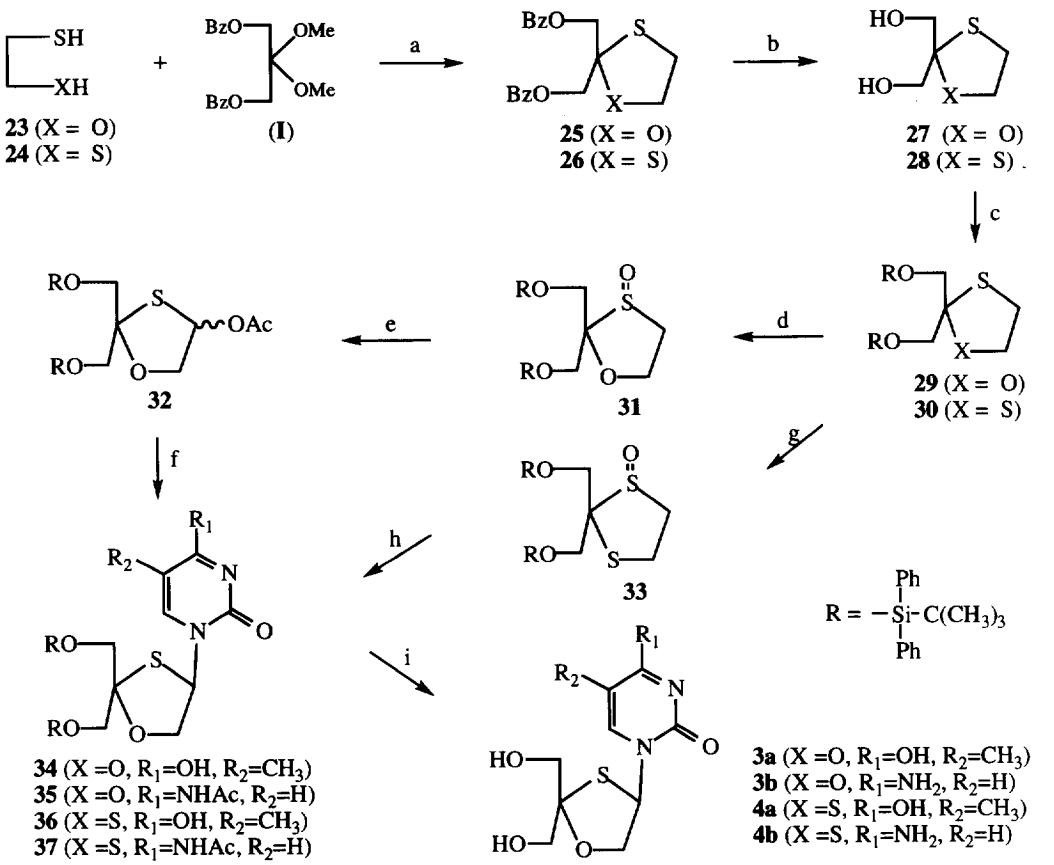
This paper describes the syntheses and antiviral activities of racemic 1,3-dioxolanyl-, 1,3-oxathiolanyl- and 1,3-dithiolanylnucleosides (**1a-4b**) with 2-hydroxymethyl substituents through the condensation reaction of dinucleophiles (oxygen and/or sulfur) with 1,3-dibenzoxy-2-propanone methyl ketal. In order to produce the target nucleosides (**1a-2b**), sugar acetate was first synthesized and then condensed with heterocyclic bases. (Scheme 1).

1,2-Diol of **DL**-glycerin (**5**) was protected as acetonide (**6**) and underwent benzylation to produce a benzyl derivative (**7**). The isopropylidene group of **7** was removed under acidic conditions to yield the diol **8**. The another dinucleophile **10** was synthesized from 3-mercapto-1,2-propanediol (**9**) after treatment with tert-butyldiphenylsilyl chloride in DMF. The intermediates **8** and **10** were condensed with 1,3-dibenzoxy-2-propanone methyl ketal (**I**) in the presence of catalytic amount of acid to give 3'-oxa- and 3'-thiasugars **11** and **12**, respectively. 1,3-Dibenzoxy-2-propanone methyl ketal (**I**) could be readily synthesized from 1,3-dihydroxypropane-2-one dimer. Treatment of 1,3-dihydroxypropane-2-one dimer with trimethyl orthoformate and p-TsOH yielded the ketal derivative (82%), which was benzoylated using NaH and benzoyl chloride to give the intermediate (**I**) in an 89% yield. Compounds **11** and **12** were deprotected using H_2 in Pd/C and n-Bu_4NF to yield the alcohol derivatives **13** and **14**, respectively. Treatment of **13** and **14** with pyridinium dichromate (PDC) in DMF[14] produced acid derivatives **15** and **16**, which underwent oxidative decarboxylation with lead tetraacetate to give the key intermediates **17** and **18**, respectively. Lewis acid (TMSOTf) catalyzed the condensation of the sugar **17** with persilylated bases (thymine and N-acetylcytosine) in 1,2-dichloroethane at room temperature and yielded the protected 3'-oxanucleosides **19** and **20**. 3'-Thianucleosides **21** and **22** were similarly prepared. Protecting groups of the 3'-oxa- and 3'-thianucleosides were removed using sodium methoxide in CH_2Cl_2 to afford the final nucleosides **1a-2b**.[15,16]

Syntheses of racemic 1,3-oxathiolanyl- and 1,3-dithiolanyl nucleosides (**3a-4b**) with 2-hydroxymethyl group were accomplished utilizing a Pummerer rearrangement[17] of the sulfoxide as a key step and are described in detail in Scheme 2. Dinucleophiles, 2-mercaptoethanol (**23**) and 1,2-ethanedithiol (**24**) were condensed with methyl ketal (**I**) in the presence of a catalytic amount of p-TsOH to give 1,3-oxathiolane ring (**25**) and 1,3-dithiolane ring (**26**) in 73% yields, respectively. Treatment of benzoates (**25** and **26**) with methanolic ammonia yielded diol derivatives (**27** and **28**) which were protected with t-butyldiphenyl silyl group to give **29** and **30**, respectively. The sulfur atom of compound **29** was oxidized to sulfoxide **31** by treating with m-CPBA at 0 °C. A Pummerer rearrangement of sulfoxide was utilized to synthesize the sugar acetate ready for the condensation with pyrimidine bases.[17] Thus, treatment of sulfoxide **31** with sodium acetate and acetic anhydride at 120 °C produced acetate **32** in a 34% yield.

Condensation reactions of **32** with persilylated pyrimidine bases such as thymine and N-acetylcytosine in 1,2-dichloroethane, which used TMSOTf as a Lewis acid catalyst at room temperature, yielded the protected nucleosides **34** and **35** in 38% to 49% yields. On the other hand, the production of 1,3-dithiolanyl nucleosides by a direct condensation reaction of sulfoxide with persilylated pyrimidine bases, through a Pummerer type rearrangement, was utilized instead of preparing a sugar acetate like 1,3-oxathiolanyl nucleosides **34** and **35**.[18,19] Thus, compound **30** was oxidized to sulfoxide **33** by treating with m-CPBA in methylene chloride at -78 °C. Reaction of sulfoxide **33** with persilylated pyrimidine bases such as thymine and N-acetylcytosine in 1,2-dichloroethane, using TMSOTf as a Lewis acid catalyst at 50 °C, yielded the protected nucleosides **36** and **37** in 53% to 86% yields. Silyl groups of protected nucleosides **34-37** were removed using tetrabutylammonium fluoride to give **3a-4b**.[20,21] The silyl groups remained intact at room temperature and were only removed under conditions of elevated temperature (45 °C) and a longer reaction time (15 h).

Scheme 2[a]



Reagents[a]: a) p-TsOH, toluene, reflux, 3 h, 73%. b) NH_3, MeOH, RT, 3 d, 88%.
c) t-BDPSCl, imidazole, THF, RT, 40 min, 89%. d) mCPBA, CH_2Cl_2, 0°C, 30 min.
e) NaOAc, Ac_2O, reflux, 3 days, 34%. f) persilylated bases, TMSOTf, 1,2-DCE, -20°C to RT, 2 h, 49% for **34**, 38% for **35**. g) mCPBA, CH_2Cl_2, -78°C, 1 h, 75%.
h) persilylated bases, TMSOTf, 1,2-DCE, -20°C to 50°C, 18-48 h, 61% for **36**, 86% for **37**.
i) n-Bu_4NF, THF, 45°C, 15 h, 90% for **3a**, 70% for **3b**, 74% for **4a**, 86% for **4b**.

It was interesting to note that the silyl and acetate groups were removed simultaneously using tetrabutylammonium fluoride in the cases of **35** and **37**.

Antiviral assay against several viruses such as HIV, HSV-1, HSV-2, poliovirus and VSV were performed on the final nucleosides **3a-4c**. Most compounds did not show any significant antiviral activity except compound **1b**, which only exhibited a weak anti-HIV activity in MT-4 cells. It is presumed that a lack of recognition by kinases due to intramolecular hydrogen bonding between two hydroxyl groups, disallowing the formation of

triphosphates, may be responsible for an absence of antiviral activity. Our laboratory is now testing the affinity of **1a-4b** to the kinases and synthesizing the triphospahtes of **1a-4b** to test against HIV-1 to determine if an absence of antiviral activity is due to a lack of recognition by kinases. The results will soon be published elsewhere.

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15. Compound **1b**: white solid, mp 202-205°C; MS *m/e* 243 (M^+); UV (MeOH) λ_{max} 270 nm (ε 8,000) (pH 7); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.87 (d,1 H, J = 6.6 Hz, H-6), 7.21 (br s, 1 H, NH_a), 7.09 (br

s, 1 H, NH_b), 6.24 (dd, 1 H, *J* = 3.2, 5.8 Hz, 1'-H), 5.72 (d, 1 H, *J* = 6.3 Hz, H-5), 5.08 (t, 1 H, J = 5.9 Hz, OH), 4.97 (t, 1 H, J = 5.6 Hz, OH), 4.44 (dd, 1 H, J = 6.0, 9.0 Hz, 2'-H_a), 3.90 (dd, 1 H, J = 3.3, 9.0 Hz, 2'-H_b), 3.37-3.54 (m, 4 H, 2 X $C\underline{H}_2$-OH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 165..69, 155.29, 140.93, 112.18, 93.97. 82.30, 70.48, 61.91, 61.59. Normal sugar numbering system was used for the interpretation of ^1H NMR. Calcd for $C_9H_{13}N_3O_5$: C, 44.40; H, 5.35; N, 17.28. Found: C, 44.00; H, 5.27; N, 17.04.

16. Compound **2b**: white solid, mp 201-205 °C; MS *m/e* 258 (M+); UV (MeOH) λ_{max} 270 nm (ε 7,500) (pH 7); ^1H NMR (DMSO-d_6, 400 MHz) δ 7.84 (d,1 H, *J* = 7.6 Hz, H-6), 7.24 (br s, 2 H, NH_2), 6.31 (t, 1 H, *J* = 5.6 Hz, 1'-H), 5.73 (d, 1 H, *J* = 7.6 Hz, H-5), 5.23 (br s, 1 H, OH), 5.16 (br s, 1 H, OH), 3.71 (d, 1 H, J = 12.0 Hz, $C\underline{H}_a$-OH), 3.63 (d, 1 H, J = 11.2 Hz, $C\underline{H}_b$-OH), 3.60 (d, 1 H, J = 11.2 Hz, $C\underline{H}_c$-OH), 3.33-3.47 (m, 2 H, 2'-H_a, $C\underline{H}_d$-OH), 2.96 (dd, 1 H, J = 11.6 Hz, 2'-H_b); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 165.59, 154.66, 140.84, 97.34, 94.17, 87.17, 64.42, 63.95, 36.11. Calcd for $C_9H_{13}N_3O_4S$: C, 41.70; H, 5.02; N, 16.22. Found: C, 41.39; H, 4.95; N, 15.86.

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20. Compound **3b**: white solid, mp 201-205 °C; MS *m/e* 259 (MH+); UV (MeOH) λ_{max} 270 nm (ε 8,500) (pH 7); ^1H NMR (DMSO-d_6, 400 MHz) δ 7.93 (d,1 H, *J* = 3.2 Hz, H-6), 7.18 (br s, 1 H, NH_a), 7.10 (br s, 1 H, NH_b), 6.21 (d, 1 H, *J* = 4.8 Hz, 1'-H), 5.73 (d, 1 H, *J* = 3.2 Hz, H-5), 5.23 (t, 1 H, J = 6.0 Hz, OH), 5.11 (dd, 1 H, J = 5.2, 6.8 Hz, OH), 4.33 (d, 1 H, J = 11.2 Hz, 2'-H_a), 4.25 (dd, 1 H, J = 4.8, 10.8 Hz, 2'-H_b), 3.80 (dd, 1 H, J = 4.8, 11.6 Hz, $C\underline{H}_a$OH); 3.63-3.67 (m, 2 H, $C\underline{H}_b$OH, $C\underline{H}_c$OH); 3.39 (dd, 1 H, J = 6.8, 12.0 Hz, $C\underline{H}_d$OH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 165.39, 155.21, 140.04, 100.51, 94.53. 74.70, 63.07, 62.62, 61.79. Calcd for $C_9H_{13}N_3O_4S$: C, 41.70; H, 5.02; N, 16.22. Found: C, 41.90; H, 5.27; N, 16.04.

21. Compound **4b**: white solid, mp 200-204 °C; MS *m/e* 275 (M+); UV (MeOH) λ_{max} 270 nm (ε 9,000) (pH 7); ^1H NMR (DMSO-d_6, 300 MHz) δ 8.16 (d,1 H, *J* = 7.6 Hz, H-6), 7.19 (br s, 1 H, NH_a), 7.11 (br s, 1 H, NH_b), 6.44 (pseudo t, 1 H, *J* = 2.7, 4.7 Hz, 1'-H), 5.73 (d, 1 H, *J* = 7.6 Hz, H-5), 5.49 (t, 1 H, J = 5.5 Hz, OH), 5.31 (t, 1 H, J = 5.7 Hz, OH), 3.81 (d, 2 H, J = 5.1 Hz, $C\underline{H}_2$OH), 3.53-3.67 (m, 3 H, 2'-H_a, $C\underline{H}_2$OH); 3.30-3.40 (m, 1 H, 2'-H_b). Calcd for $C_9H_{13}N_3O_3S_2$: C, 39.27; H, 4.73; N, 15.27. Found: C, 39.67; H, 4.95; N, 15.66.

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