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Il Farmaco 57 (2002) 993–997

IL FARMACO

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Synthesis of oxathiolane imidazole nucleosides

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Received 27 April 2002; received in revised form 4 May 2002; accepted 25 May 2002

Abstract

Nucleosides have been of great interest since their strong antiviral activities were discovered. 1,3-Oxathiolane ring system has been known for many years, but it is in recent years that the ring has been used as the sugar ring in nucleoside analogs (Synthesis (1991) 1046; J. Am. Chem. Soc. 113 (1991) 9377; Tetrahedron Lett. 35 (1994) 4739). Besides, bredinin is a natural nucleoside antibiotic with imidazole moiety and there are some other studies reported on nucleosides with the imidazole group (Biorg. Med. Chem. 7 (1999) 481; Biorg. Med. Chem. 7 (1999) 1617; Nucleosides Nucleotides 18 (1999) 331). These findings make the imidazole group interesting as the base of a nucleoside. In this study, in order to find out the structure–activity relationships of L-oxathiolanyl nucleosides, L-oxathiolanyl imidazole nucleosides **7** and **8** were synthesized, via novel intermediates **2**–**6**, which were then tested for anti-HIV activity (Antivir. Res. 1–11 (1994) 25) in human peripheral blood mononuclear (PBM) cells, the synthesized nucleosides did not show significant activity up to 100 μM against HIV-1.

Keywords: Nucleosides; Oxathiolane; Imidazole; Synthesis; Antiviral activity

1. Introduction

Belleau et al. reported the synthesis and anti-HIV activity of an unnatural class of nucleosides, (±)-BCH-189 in which C-3′ position had been replaced by a sulfur atom [1]. It was of interest to synthesize the pure enantiomers of BCH-189 (Fig. 1), since it was being tested clinically on patients with AIDS. Chu et al. synthesized (+)-BCH-189 starting from D-mannose [2], but this synthesis had many steps and consequently the yield was low. Chu et al. in another study, obtained this same compound from 1,6-thioanhydro-D-galactose by a more efficient and shorter route [3], which enabled the examination of the structure-activity relationships of the [1,3]oxathiolanyl nucleosides as anti-HIV agents. In general, β-D isomers of nucleosides were found to be the biologically active isomers, but when the four possible isomers of BCH-189 were evaluated the L-like nucleoside was more potent than the D-like nucleoside [4,5].

In this study the L-like nucleosides, 1-(2-hydroxymethyl-α-L-[1,3]oxathiolan-5-yl)imidazole 4-carboxamide (**7**) and 1-(2-hydroxymethyl-β-L-[1,3]oxathiolan-5-yl)imidazole 4-carboxamide (**8**) were synthesized via novel intermediates **2**–**6** and evaluated for anti-HIV activity in human peripheral blood mononuclear (PBM) cells infected with HIV-1 strain LAI the synthesized nucleosides did not show significant activity up to 100 μM against HIV-1.

2. Chemistry

(2*R*, 5*R*)-5-Hydroxy-[1,3]oxathiolane-2-carboxylic acid-(L) menthyl ester (**1**), prepared by the method given by Jin et al. [6], was treated with HCl/MeOH to give menthyl 5-methoxy-[1,3]oxathiolane-2-carboxylate (**2**)

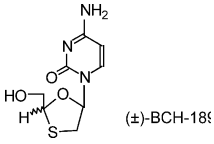

Fig. 1.

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0014-827X/02/$ - see front matter
PII: S0014-827X(02)01287-9

[7]. Compound **2** in THF (tetrahydrofurane) was reduced with LAH (lithium aluminium hydride) in THF to 5-methoxy-2-hydroxymethyl-[1,3]oxathiolane (**3**) [8]. A solution of **3** and pyridine in CH_2Cl_2 was treated with benzoyl chloride to obtain 5-methoxy-2-benzoylmethyl-[1,3]oxathiolane (**4**) [3,7]. Imidazole 4-carboxylic acid methyl ester was heated with $(NH_4)_2SO_4$ and HMDS (hexamethyldisilazane) and after removal of HMDS, **4** in CH_2Cl_2 and TMSOTf (trimethylsilyl triflate) was added to this residue to give methyl 1-(2-benzoyloxymethyl-β (and α)-L-[1,3]oxathiolan-5-yl)imidazole 4-carboxylate (**5** and **6**, respectively) [4,7]. Compound **5** (or **6**) in saturated NH_3/MeOH was stirred at 90 °C to gain 1-(2-hydroxymethyl-β (or α)-L-[1,3]oxathiolan-5-yl)imidazole 4-carboxamide (**7** or **8**, respectively).

3. Experimental

M.p.s were determined on a Mel-temp II melting point apparatus in open capillaries and are uncorrected. Elemental analyses were performed by Atlantic Microlab Inc., Norcross, GA. ^1H and ^{13}C NMR spectra were obtained on a Bruker AMX spectrophotometer at 400 MHz, using Me_4Si as the internal standard and $CDCl_3$ as the solvent. FAB MS were recorded on a Micromass Autospec high resolution mass spectrometer. Optical rotations were determined on a JASCO DIP-370 Digital Polarimeter. UV spectra were determined on a Beckman DU 650 spectrophotometer. TLC was performed on Uniplates (silica gel) purchased from Analtech Co. Column chromatography was performed using either Silica Gel-60 (220–440 mesh) for flash chromatography or Silica Gel G (TLC grade > 440 mesh) vacuum flash column chromatography.

3.1. Menthyl 5-methoxy-[1,3]oxathiolane-2-carboxylate (2) [7]

(2*R*, 5*R*)-5-hydroxy-[1,3]oxathiolane-2-carboxylic acid-(L) menthyl ester (2.71 mmol, 780 mg) which was prepared according to the method given by Jin et al. [6] was treated with HCl/MeOH solution (1%, 3.6 ml) at room temperature (r.t.) for 3 h. The mixture was quenched with 0.7 ml of pyridine and concentrated to dryness under reduced pressure. Residue was purified by silicagel column chromatography (5:95 EtOAc–C_6H_{14}) to give **2**, a yellow oil, as a mixture of α and β anomers: ^1H NMR ($CDCl_3$): δ 5.59, 5.52 (2 × s, 2H, H-2), 4.78–4.68 (m, 1H, H-5), 3.53, 3.43 (2 × s, 3H, CH_3O), 3.27–3.07 (m, 2H, H-4), 1.70–1.01 (m, 9H, H-menthyl), 1–0.96 (m, 7H, H of CH–$(CH_3)_2$), 0.85–0.82 (s, 3H, CH_3 of menthyl). ^{13}C NMR ($CDCl_3$): δ 169.49 (C=O), 107.97 (CH_3O), 55.78, 47.40, 41.07, 37.78, 34.52, 31.77, 26.39, 23.61, 22.37, 21.15, 16.50 (C–oxathiolane and menthyl). FAB-MS, *m/z* 303 $[M+H]^+$, 165, 139, 119, 83. *Anal.* Calc. for $C_{15}H_{26}O_4S$: C, 59.57; H, 8.67. Found: C, 59.59; H, 8.70%.

3.2. 5-Methoxy-2-hydroxymethyl-[1,3]oxathiolane (3) [8]

To a suspension of LAH (1.602 mmol, 60.88 mg) and 13 ml of THF was added dropwise a solution of **2** (0.801 mmol, 241.8 mg) in 7 ml of THF and stirred under nitrogen for 2 h in ice bath. Then LAH was quenched with 50 ml of MeOH and the mixture was filtered through Celite pad, evaporated to dryness under reduced pressure, and purified by silica gel column chromatography (20:80 EtOAc–C_6H_{14}) to give **3**, a yellow oil, as a mixture of α and β anomers: ^1H NMR ($CDCl_3$): δ 5.49–5.33 (m, 2H, H-2 and H-5), 3.89–3.76 (m, 2H, H-2′), 3.44, 3.41 (2 × s,3H,CH_3), 3.26–3.07 (m, 2H, H-4), 2.43, 2.09 (2 × s, 1H, OH). ^{13}C NMR ($CDCl_3$): δ 106.82 (CH_3), 84.55 (CH_2–OH), 64.32, 55.32, 38.52 (C–oxathiolane). *Anal.* Calc. for $C_5H_{10}O_3S$: C, 39.98; H, 6.71. Found: C, 39.99; H, 6.79%.

3.3. 5-Methoxy-2-benzoyloxymethyl-[1,3]oxathiolane (4) [3,7]

A solution of **3** (1.798 mmol, 270 mg) and 0.5 ml of pyridine in 6 ml of CH_2Cl_2 was treated with BzCl (2.158 mmol, 0.25 ml) at 0 °C and the mixture was stirred at r.t. for 1 h. The reaction mixture was quenched with ice while stirring for another 20 min, washed with H_2O, saturated $NaHCO_3$ and brine, dried on $MgSO_4$ and purified by silica gel column chromatography (10:90 EtOAc–C_6H_{14}) to give **4**, a yellow oil. ^1H NMR ($CDCl_3$): δ 8.18–7.44 (m, 5H, H-phenyl), 5.64–5.41 (m, 2H, H-2 and H-5), 4.56–4.41 (m, 2H, H-2′), 3.44, 3.42 (2 × s, 3H, CH_3), 3.24–3.09 (m, 2H, H-4). ^{13}C NMR ($CDCl_3$): δ 165.94, 165.91 (C=O), 134.43, 133.07, 130.64, 129.63, 128.76 (C–phenyl), 107.44, 106.43 (CH_3), 83.03, 80.96 (CH_2OBz), 66.02, 55.17, 37.95, 37.63 (C–oxathiolane). FAB-MS *m/z*: 255 $[M+H]^+$, 223, 195, 105. *Anal.* Calc. for $C_{12}H_{14}O_4S \cdot 0.1C_6H_{14}$: C, 57.56; H, 5.90. Found: C, 57.38, H, 5.50%.

3.4. Methyl 1-(2-benzoyloxymethyl-β-L-[1,3]oxathiolan-5-yl)imidazole 4-carboxylate (5) and methyl 1-(2-benzoyloxymethyl-α-L-[1,3]oxathiolan-5-yl)imidazole 4-carboxylate (6) [4,7]

A mixture of imidazole 4-carboxylic acid methyl ester (1.966 mmol, 247.95 mg), $(NH_4)_2SO_4$ (9.93 mg) and HMDS (10 ml) was heated at 140 °C for 18 h. HMDS was removed in vacuo. First, **4** (1.966 mmol, 500 mg) in 20 ml of CH_2Cl_2, and then TMSOTf (1.6 ml) was added to the residue. The mixture was stirred at r.t. for 6 h,

then poured into saturated $NaHCO_3$ and stirred for 30 min. Aqueous layer was washed with CH_2Cl_2 and combined organic layers were washed with H_2O, dried on $MgSO_4$, filtered through Celite pad, evaporated and purified by PTLC (0.5% MeOH–$CHCl_3$). The bottom spot was collected to give compound **5** as an oil which was crystallized with MeOH–ether to give white solid (70 mg, 20.1%): m.p. 80–81 °C; UV (MeOH) λ_{max} 230.5 nm. $[\alpha]_D^{25}$ −34.19° (c, 1.60, MeOH); ^{1}H NMR ($CDCl_3$): δ 8.07–8.03 and 7.49–7.45 (m, 5H, H-phenyl), 7.79 (s, 1H, H-5) 7.62–7.58 (m, 1H, H-2), 7.12–7.11 (d, $J = 4.93$ Hz, 1H, H-1′), 5.80 (dd, $J = 4.2$ Hz, 1H, H-4′), 4.57 (dd, $J = 6.3$ Hz, 1H, H-5′), 4.47 (dd, $J = 4.1$ Hz, 1H, H-5′), 3.88 (s, 3H, CH_3), 3.75 (dd, $J = 5.2$ Hz, 1H, H-2′), 3.28 (dd, $J = 4.5$ Hz, 1H, H-2′). ^{13}C NMR ($CDCl_3$): δ 166.00, 160.77 (C=O), 139.87, 138.32, 133.50, 129.24, 128.58, 127.38 (C–phenyl and imidazole), 88.30 (CH_3), 84.19 (CH_2OBz), 64.66, 51.79, 39.86 (C–oxathiolane). FAB-MS m/z: 349 $[M+H]^+$. *Anal.* Calc. for $C_{16}H_{16}N_2O_5S \cdot 0.1$MeOH: C, 55.00; H, 4.70, N, 7.97. Found: C, 55.39, H, 4.69, N, 8.01%.

The upper spot was collected to give compound **6** as an oil which was crystallized with MeOH–ether to give white solid (45 mg, 12.9%): m.p. 71–73 °C; UV (MeOH) λ_{max} 232 nm. $[\alpha]_D^{25}$ +30.79° (c, 1.00, MeOH); ^{1}H NMR ($CDCl_3$): δ 8.19 (s, 1H, H-5), 8.09–8.07 and 7.62–7.58 (m, 5H, H-phenyl), 7.78 (s, 1H, H-2), 6.82 (dd, $J = 3.6$ Hz, 1H, H-1′), 5.57 (dd, $J = 3.5$ Hz, 1H, H-4′), 4.77 (dd, $J = 5.3$ Hz, 1H, H-5′), 4.70 (dd, $J = 3.5$ Hz, 1H, H-5′), 3.87 (s, 3H, CH_3), 3.72 (dd, $J = 5.3$ Hz, 1H, H-2′), 3.20 (dd, $J = 3.5$ Hz, 1H, H-2′). ^{13}C NMR ($CDCl_3$): δ 166.04, 160.59 (C=O), 137.26, 133.42, 129.78, 129.41, 128.53, (C–phenyl and imidazole), 88.30 (CH_3), 84.19 (CH_2OBz), 64.66, 51.79, 39.86 (C–oxathiolane). FAB-MS m/z: 349 $[M+H]^+$. *Anal.* Calc. for $C_{16}H_{16}N_2O_5S$: C, 55.16; H, 4.63, N, 8.04. Found: C, 55.42, H, 4.75, N, 7.99%.

*3.5. 1-(2-Hydroxymethyl-β-L-[1,3]oxathiolan-5-yl)imidazole 4-carboxamide (7) and 1-(2-hydroxymethyl-α-L-[1,3]oxathiolan-5-yl)imidazole 4-carboxamide (**8**)*

Compound **5** was dissolved in saturated NH_3/MeOH (5 ml) and stirred 12 h in sealed bomb at 90 °C. After reaction all solvent evaporated to dryness and coevaporated with MeOH to give crude compound **7** which is purified by silica gel column chromatography ($CHCl_3$–MeOH, 9:1), (35 mg, 76.1%): m.p. 164–166 °C; UV (H_2O) λ_{max} 231.0 (ε 73 641) 276.5 (ε 14 762) (pH 2), 202.5 (ε 10 903) 238.5 (ε 13 152) (pH 7), 210.5 (ε 10 277) 239.0 (ε 12 510) (pH 11); $[\alpha]_D^{25}$ −64.74° (c 0.37, MeOH); ^{1}H NMR ($CDCl_3$): δ 8.22 (s, 1H, H-5), 7.97 (s, 1H, H-2), 7.85 and 7.64 (2s, 2H, NH_2), 6.84 (t, $J = 3.6$ Hz, 1H, H-1′), 5.47 (t, 1H, H-4′), 5.21 (t, $J = 3.5$ Hz, 2H, H-5′), 3.73 (bs, 1H, OH) 3.55 (m, $J = 5.3$ Hz, 1H, H-2′), 3.21 (m, 1H, H-2′). ^{13}C NMR ($CDCl_3$): δ 161.48 (C=O), 139.21, 138.98, 133.27, 133.13, 124.62, 124.55, 88.24, 87.30, 87.28, 87.18, 64.66. FAB-MS m/z: 230 $[M+H]^+$. *Anal.* Calc. for $C_8H_{11}N_3O_3S$: C, 41.91; H, 4.84; N, 18.33. Found: C, 41.86; H, 4.98; N, 18.13%.

Compound **6** was dissolved in saturated NH_3/MeOH (5 ml) and stirred 12 h in sealed bomb at 90 °C. After reaction all solvent evaporated to dryness and coevaporated with MeOH to give crude compound **8** which is purified by silica gel column chromatography ($CHCl_3$–MeOH, 9:1), (20 mg, 43.5%): m.p. 173–175 °C; UV (H_2O) λ_{max} 207.0 (ε 24 044) 237.0 (ε 9154) (pH 2), 207.5 (ε 15 624) 238.5 (ε 22 125) (pH 7), 207.0 (ε 10 297) 237.0 (ε 13 658) (pH 11); $[\alpha]_D^{25}$ 31.78° (c 0.78, MeOH); ^{1}H NMR ($CDCl_3$): δ 7.97 (s, 1H, H-5), 7.94 and 7.92 (2s, 2H, NH_2), 7.84 (s, 1H, H-2), 6.95 (t, $J = 3.6$ Hz, 1H, H-1′), 5.47 (t, 1H, H-4′), 5.17 (t, $J = 3.5$ 2H, H-5′), 3.54 (m, 1H, OH) 3.23 (m, $J = 5.3$ Hz, 1H, H-2′), 3.20 (m, 1H, H-2′). ^{13}C NMR ($CDCl_3$): δ 163.38 (C=O), 140.52, 134.03, 130.61, 129.98, 90.12, 88.28, 65.48. FAB-MS m/z: 230 $[M+H]^+$. *Anal.* Calc. for $C_8H_{11}N_3O_3S \cdot$MeOH: C, 41.79.; H, 5.05; N 17.83. Found: C, 41.74; H, 5.02; N, 17.64%.

4. Antiviral assay

Human PBM cells (obtained from Atlanta Red Cross) were isolated by Ficoll–Hypaque discontinuous gradient centrifugation from healthy seronegative donors. Cells were stimulated with phytohemagglutinin A (Difco, Sparks, MD) for 2–3 days prior to use. HIV-1/LAI obtained from the Centers for Disease Control and Prevention (Atlanta, GA) was used as the standard reference virus for the antiviral assays. Infections were done in bulk for 1 h, either with 100 $TCID_{50}/1 \times 10^7$ cells for a flask (T25) assay or with 200 $TCID_{50}/6 \times 10^5$ cells/well for a 24 well plate assay. Cells were added to a plate or flask containing a 10-fold serial dilution of the test compound. Assay medium was RPMI-1640 supplemented with heat inactivated 16% fetal bovine serum, 1.6 mM L-glutamine, 80 IU/ml penicillin, 80 μg/ml streptomycin, 0.0008% DEAE-Dextran, 0.045% sodium bicarbonate, and 26 IU/ml recombinant interleukin-2 (Chiron Corp, Emeryville, CA). AZT was used as a positive control for the assay. Untreated and uninfected PBM cells were grown in parallel at equivalent cell concentrations as controls. The cell cultures were maintained in a humidified 5% CO_2–air at 37 °C for 5 days and supernatants were collected for reverse transcriptase (RT) activity.

Supernatants were centrifuged at 12,000 rpm for 2 h to pellet the virus. The pellet was solubilized with vortexing in 100 μl virus solubilization buffer containing 0.5% Triton X-100, 0.8 M NaCl, 0.5 mM phenylmethylsulfonyl fluoride, 20% glycerol, and 0.05 M Tris, pH 7.8.

Ten microliters of each sample were added to 75 μl RT reaction mixture (0.06 M Tris, pH 7.8, 0.012 M $MgCl_2$, 0.006 M dithiothreitol, 0.006 mg/ml poly $(rA)_n$ oligo $(dT)_{12-18}$, 96 microg/ml dATP, and 1 μM of 0.08 mCi/ml ^{3}H-thymidine triphosphate (Moravek Biochemicals, Brea, CA) and incubated at 37 °C for 2 h. The reaction was stopped by the addition of 100 μl 10% trichloroacetic acid containing 0.05% sodium pyrophosphate. The acid insoluble product was harvested onto filter paper using a Packard Harvester (Meriden, CT), and the RT activity was read on a Packard Direct Beta Counter (Meriden, CT). The RT results were expressed in counts per minute (CPM) per milliliter. The antiviral 50% effective concentration (EC_{50}) and 90% effective concentration (EC_{90}) were determined from the concentration-response curve using the median effect method [7].

4.1. Cytotoxicity assays

The compounds were evaluated for their potential toxic effects on uninfected PHA-stimulated human PBM cells, in CEM (T-lymphoblastoid cell line obtained from American Type Culture Collection, Rockville, MD.) and Vero (African green monkey kidney) cells. PBM cells were obtained from whole blood of healthy seronegative donors (HIV-1 and hepatitis B virus) by single-step Ficoll-Hypaque discontinous gradient centrifugation. Log phase Vero, CEM and PHA-stimulated human PBM cells were seeded at a density of 5×10^3, 2.5×10^3 and 5×10^4 cells/well, respectively. All of the cells were plated in 96-well cell culture plates containing ten-fold serial dilutions of the test drug. The cultures were incubated for 3, 4, and 5 days for Vero, CEM, and PBM cells, respectively in a humidified 5% CO_2–air at 37 °C. At the end of incubation, MTT tetrazolium dye solution (Cell titer 96®, Promega, Madison, WI) was added to each well and incubated overnight. The reaction was stopped with stop solubilization solution (Promega, Madison, WI). The plates were incubated for 5 h to ensure that the formazan crystals were dissolved. The plates were read at a wavelength of 570 nm using an ELISA plate reader (Bio-tek instruments, Inc., Winooski, VT, Model # EL 312e). The 50% inhibition concentration (IC_{50}) was determined from the concentration–response curve using the median effect method [7].

As a result of this antiviral assay, compounds **7** and **8** did not show significant activity up to 100 μM against HIV-1. The compounds were found out to be toxic in the various mammalian cells up to 100 μM (Fig. 1).

5. Results and discussion

Compounds **7** and **8** were synthesized as described in Section 2 and Scheme 1.

Structures of the novel compounds were determined by the elemental analyses and their formulae were confirmed by UV, ^{1}H and ^{13}C NMR and MS spectrometric data.

In the ^{1}H NMR spectrum of compound **2**, the signals of the CH_3O group were observed at 3.43 and 3.53 ppm as two singlets due to two anomers, α and β; and the signals due to menthyl group were observed at 1.70–1.01, 1.00–0.96 and 0.85–0.82 ppm. These signals disappeared in the ^{1}H NMR spectrum of compound **3** and signals at 3.89–3.76 ppm due to methylene and 2.43 and 2.09 ppm due to the OH group were observed which confirmed the reduction of compound **2**. In the ^{1}H NMR spectrum of compound **4**, the signal due to OH group disappeared and the signal due to benzoyl group appeared at 8.18–7.44 ppm. In the ^{1}H NMR spectrum of compound **5** (and compound **6**) the signals due to C_2–H and C_5–H of the imidazole moiety could be observed at 7.62–7.58 (7.78; **6**) and 7.79 (8.19; **6**) ppm; the protons of the oxathiolane moiety were observed as a doublet for CH_2–*CH*–O at 7.12–7.11 (as a double doublet at 6.82; **6**); and another double doublet for S–CH at 5.80 (5.57; **6**); as two double doublets for S–CH_2 at 3.75 and 3.28 (at 3.72 and 3.20; **6**) and as two double doublets for *CH_2*–OBz at 4.57 and 4.47 (4.77 and 4.70; **6**) ppm. These protons absorbed as double doublets because of the rigidity of the ring. The protons of S–CH_2 and *CH_2*–OBz were diastereotropic and therefore gave peaks at different values which splits each other. In the ^{1}H NMR spectra of the compounds **7** and **8**, the peaks due to CH_3 and phenyl were replaced by the NH_2 (at 7.85 and 7.64 ppm; **7** and 7.94 and 7. 92 ppm; **8** as two singlets) and OH (at 3.73 ppm as a broad singlet; **7** and 3.54 ppm as a multiplet; **8**) peaks.

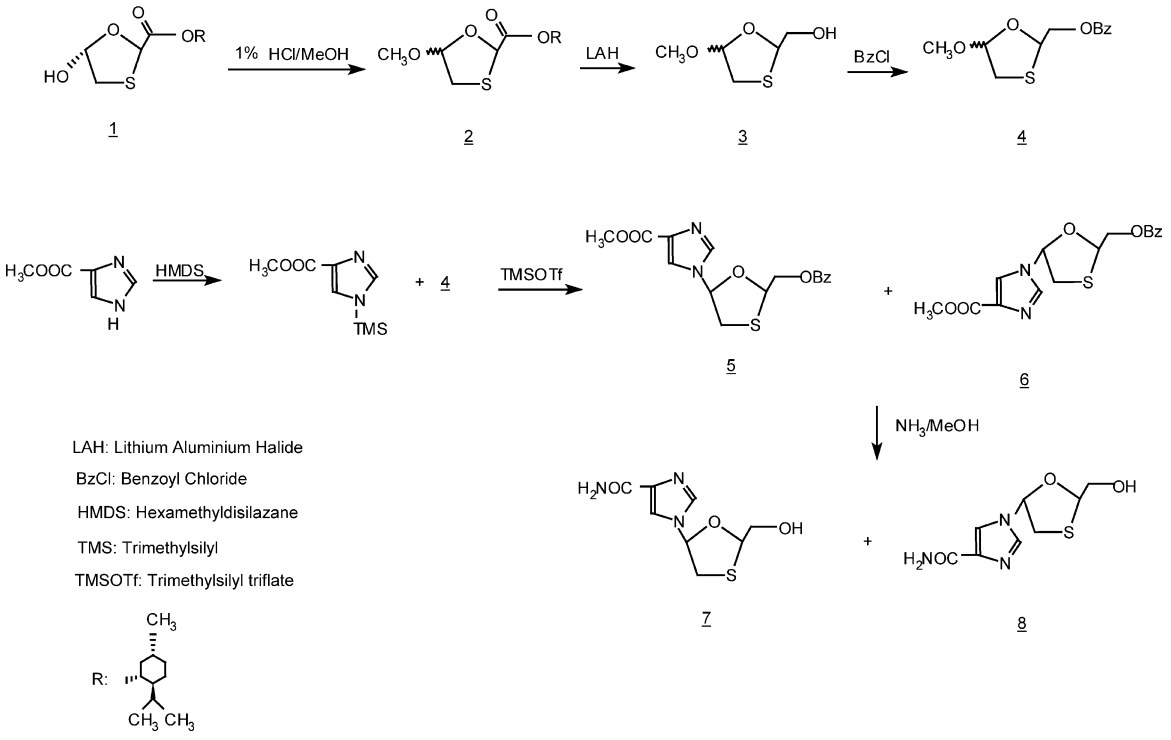
The structures of the synthesized compounds were also confirmed by the data provided by ^{13}C NMR spectra; the peaks due to the entering groups could be observed, while the peaks due to the leaving groups disappeared in the spectra.

The FAB-MS spectra of the synthesized compounds showed the $[M+H]^+$ peaks, but in the spectrum of compound **3**, the compound fragmented so fast, that the mentioned peak could not be observed.

Optical rotations of β and α anomers **5**, **6** and **7**, **8** were determined to be −34.19, +30.79 and −64.74, +31.78°, respectively. Since the β and α anomers are both mixtures of the two enantiomers which could not be separated by column chromatography, they do not rotate the plane polarized light equally.

In the uv spectra of compounds **5**, **6**, **7** and **8**, the λ_{max} were determined to be 230.5, 232, 231 and 207 nm, respectively.

In this study, novel oxathiolane imidazole nucleosides were synthesized with the expectation of gaining compounds with anti-HIV activity. Compounds **7** and **8** were tested for anti-HIV activity in human PBM cells,



Scheme 1.

and they were found not to possess significant activity up to 100 μM against HIV-1. Nucleosides always have been challenging structures with anti-HIV activity and structural modification of **7** and **8** may still lead to promising compounds.

Acknowledgements

A. Kocabalkanli acknowledges the support of the NATO Science Fellowship Program of The Scientific and Technical Research Council of Turkey (TUBITAK) and extends her special thanks to Dr C.K.Chu for his collaboration. R.F. Schinazi is supported in part by the Department of Veterans Affairs and NIH grant AI-32351 and AI-41980.

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