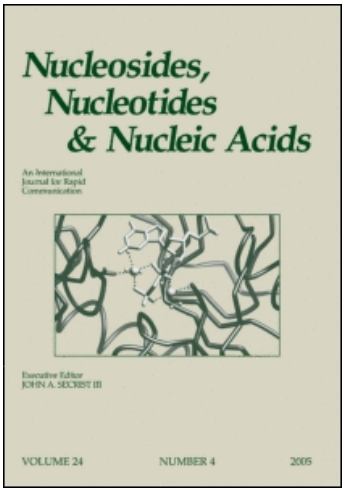

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Synthetic Nucleosides and Nucleotides. XXX.[1] Synthesis and Antiviral Activity of 3'-Azido, 2',3'-Unsaturated and 2',3'-Dideoxy Derivatives of E-5-Styryl-2'-Deoxyuridine on Human Immunodeficiency Virus

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SYNTHETIC NUCLEOSIDES AND NUCLEOTIDES. XXX.[1] SYNTHESIS AND ANTIVIRAL ACTIVITY OF 3'-AZIDO, 2',3'-UNSATURATED AND 2',3'-DIDEOXY DERIVATIVES OF *E*-5-STYRYL-2'-DEOXYURIDINE ON HUMAN IMMUNODEFICIENCY VIRUS*

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Abstract: Some new 3'-azido, 2',3'-unsaturated and 2',3'-dideoxy 5-styryl analogs of deoxyuridine-related compounds have been synthesized and evaluated against human immunodeficiency virus *in vitro*. Among these compounds, 3'-azido-2',3'-dideoxy-5-*E*-styryluridine (**6**) and 2',3'-dideoxy-*E*-5-styryluridine (**9**) were found to be active, with ED_{50} values of 5 and 10 μg/ml respectively.

The human immunodeficiency virus type 1 (HIV-1) is now recognized as the pathogenic retrovirus of the acquired immunodeficiency syndrome (AIDS).[2] Although 3'-azido-3'-deoxythymidine (AZT) inhibits the replication of this virus and has been proved useful in the treatment of AIDS patients,[3] some problems such as short half-life in the body[4] and bone marrow suppression[5] have been reported. Therefore, there is an urgent need for other compounds that are equally potent but more selective in their anti-HIV-1 activity. AZT is known to exert its activity as a triphosphate by inhibiting the HIV-1 reverse transcriptase.[6] However, the triphosphate of AZT may also inhibit host cellular DNA polymerases, especially in β and γ-type.[7,8] Thus, AZT may exhibit side effects. Now, it is desired to synthesize new compounds which inhibit retroviral reverse transcriptase more efficiently and more selectively than host cellular DNA polymerases.

In our previous paper, we reported that a hydrophobic group at the 5-position of araUTP could increase the affinity of the analog to DNA polymerase α, based on experiments using several 5-alkylated araUTPs.[9] We also reported that araUTPs

* This paper is dedicated to the memory of late Professor Tohru Ueda.

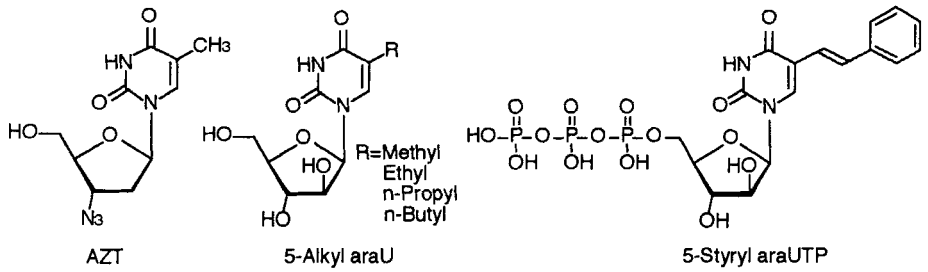


FIG. 1

modified with strongly hydrophobic styryl groups at the 5-position showed potent inhibitory effects on DNA polymerase α and herpesviral DNA polymerase.[10,11] On the other hand, 2'-deoxyUMPs modified with styryl groups at the 5-position showed remarkable inhibitory effects on eukaryotic thymidylate synthase.[12] These studies prompted us to synthesize a series of 2',3'-dideoxypyrimidine nucleosides substituted with the styryl group at 5-position in the hope that they would exhibit better antiviral activities on HIV replication.

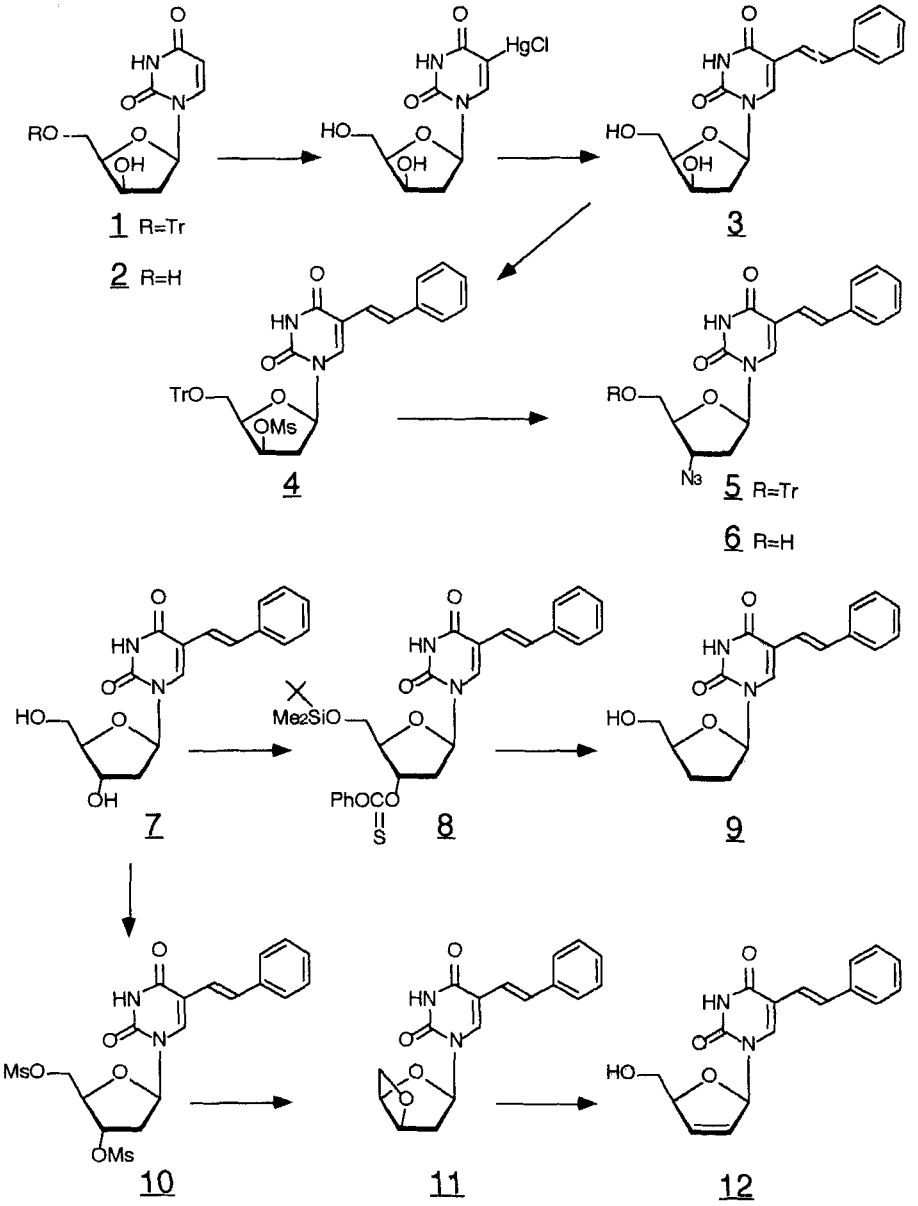
SYNTHESIS

The synthesis of new nucleosides (**3**, **6**, **9** and **12**) is outlined in SCHEME 1.

For the synthesis of uracil nucleosides substituted with styryl groups at the 5-position of the uracil ring, a method *via* organopalladium intermediates is applicable.[13] In a previous study, we used successfully this method for the synthesis of several arabinofuranosyluracil nucleosides modified with styryl groups at the 5-position.[10] In a similar manner , 2'-deoxy-5-styryllyxofuranosyluracil (**3**) was obtained by the following method. In this study, 2'-deoxylyxofuranosyluracil (**2**) was first converted to its mercurated derivative by treatment with mercuric acetate and sodium chloride,[14] followed by reaction with styrene in the presence of lithium tetrachloropalladate as a catalyst in methanol.

The protection of **3** with trityl chloride in pyridine followed by reaction with methanesulfonyl chloride afforded compound (**4**). Nucleophilic displacement of the mesyloxy group in **4** with azide ion gave the corresponding crude 3'-azido-3'-deoxy derivative (**5**), and then the 5'-*O*-trityl group of **5** was removed by treatment with 75% acetic acid at 90° for 1.5 h to give pure **6** in 51% yield from **2**.

After protection of (**7**)[13] with a *t*-butyldimethylsilyl group, the 5'-silylated derivative was then converted to the 3'-thionocarbonate (**8**). Compound **8** was treated with excess tri-*n*-butyltin hydride[15] to give the 2',3'-dideoxy derivative, and then removal of the silyl



SCHEME 1

group with fluoride ion gave 2',3'-dideoxy-5-styryluridine (**9**) as a glass. Unsaturated derivative (**12**) was synthesized from **7** essentially by the method of Horwitz et al.[16] Compound (**7**) was treated with methanesulfonyl chloride in pyridine to give bis-mesylate (**10**). Reaction of **10** with aqueous sodium hydroxide gave the oxetane (**11**). Elimination reaction of **11** by treatment with potassium *t*-butoxide in dimethyl sulfoxide (DMSO) at room temperature yielded 2',3'-dideoxy-2',3'-didehydro derivative (**12**) in 67% yield. The proton nuclear magnetic resonance (^{1}H-NMR) data of the compounds indicated that configurations of the olefinic protons on the styryl substituent of these nucleosides were assigned *trans*, since the vinylic protons had a coupling constant of J=16.2~16.5 Hz, as reported by Bigge et al.[13]

BIOLOGICAL ACTIVITIES

The anti-HIV-1 activity of the compounds **3**, **6**, **7**, **9** and **12** were tested using HIV-1 (Kenya) infected human MOLT 4 cells.[17] Among these compounds, 3'-azido-2',3'-dideoxy-*E*-5-styryluridine (**6**) and 2',3'-dideoxy-*E*-5-styryluridine (**9**) were found to be active, with ED_{50} values of 5 and 10 μg/ml respectively. The other compounds **3**, **7** and **12** were found to be essentially inactive. Only a few studies have been reported on the anti-HIV activity of pyrimidine nucleosides bearing bulky groups at the C-5 position of the pyrimidine ring. First, Chu et al. reported that 3'-azido-5-(2-bromovinyl)-2',3'-dideoxyuridine did not show any anti-HIV-1 activity at 100 μM.[18] Lin et al. reported that 5-bromovinyl and 5-carboxyvinyl analogs of 2',3'-dideoxyuridine were inactive against Moloney murine leukemia virus.[19] In contrast to their results, in our study, nucleosides **6** and **9** bearing a styryl group at C-5 of the uracil ring showed moderate anti-HIV-1 activity, while AZT showed significant anti-HIV-1 activity, with an ED_{50} value of 0.02 μg/ml under the same assay conditions. Probably, dideoxyuridine analogs substituted with a styryl group at the C-5 position may be poorer substrates for cellular deoxyribonucleoside kinases than AZT. The detailed kinetic analysis for the phosphorylation of 5-styryl-2',3'-dideoxyuridines and the inhibitory effects of their 5'-triphoshates on reverse transcriptase and cellular DNA polymerases will be reported elsewhere.

EXPERIMENTAL

Melting points were determined on a Yanaco Model MP-3 apparatus and are uncorrected. UV spectra were recorded on a Shimadzu UV-160A recording spectrophotometer. NMR spectra were obtained on a JEOL GSX-400 NMR spectrometer with tetramethylsilane as an internal standard.

1-(2-Deoxy-β-D-lyxofuranosyl)-*E*-5-styryluracil (3)

A suspension of **1**[20] (25.8 g, 54.8 mmol) in 175 ml of 80% acetic acid was heated at 80° for 1 h. The solvent was evaporated *in vacuo*, and then the residue was dissolved in a mixture of 200 ml of chloroform–water (1:1). The aqueous layer was evaporated and the residue was chromatographed on a column of silica gel (70 g) with chloroform–methanol (5:1) as eluting solvent. After evaporation of the combined fractions, the crude product of **2** (10.4 g, 45.6 mmol, 83%) was obtained as a white solid, and used directly without further purification in the next step. The product (**2**) (9.1 g, 40 mmol) was dissolved in 40 ml of water. To this solution was added the solution of 13.4 g(42 mmol) of mercuric acetate in 58 ml of water, and the mixture was stirred for 1 day at 50°. After the reaction mixture was allowed to stand to room temperature, the precipitates were collected by filtration and washed with 75 ml of 0.16 M aqueous sodium chloride, 75 ml of ethanol and finally with 50 ml of ether. Crude 1-(2-deoxy-1-β-D-lyxofuranosyl)-5-chloromercuriuracil (11.7 g, 25.2 mmol, 63%) was obtained as a white solid. The well dried mercuri derivative (11.7 g) was suspended in 140 ml of methanol, and then 12 ml (105 mmol) of styrene and 260 ml of methanolic solution of 0.1 M lithium tetrachloropalladate were added. After being refluxed for 1 day, the reaction mixture was filtered, and the filtrate was bubbled with hydrogen sulfide for 2 min. The resulting precipitates were filtered off, and the solvent was evaporated. The residue was chromatographed on a column of silica gel (120 g). Elution was performed with chloroform–methanol (14:1). After evaporation of the combined fractions, the resulting gummy residue was crystallized from methanol to give **3** as a colorless crystal. 1.15 g (14%). mp 83—86°. UV (MeOH), λmax 313 nm (ε, 18500). ^{1}H-NMR (DMSO-d_6+D_2O) δ: 1.9–2.0 (m, 1H, H-2'), 2.5–2.6 (m, 1H, H-2'), 3.7–3.9 (m, 3H, H-4' and 5'), 4.28 (m, 1H, H-3'), 6.09 (d, 1H, H-1', J=7.9 Hz), 6.86 (d, 1H, vinylic, J=16.2 Hz), 7.2–7.5 (m, 5H, aromatic), 7.25 (d, 1H, vinylic, J=16.2 Hz), 8.25 (s, 1H, H-6). *Anal.* Calcd for $C_{17}H_{18}N_2O_5 \cdot 0.3CH_3OH$: C, 61.12; H, 5.69; N, 8.24. Found: C, 61.30; H, 5.39; N, 7.97.

1-(2-Deoxy-3-*O*-methanesulfonyl-5-*O*-trityl-β-D-lyxofuranosyl)-*E*-5-styryluracil (4)

A mixture of **3** (0.70 g, 2.12 mmol) and trityl chloride (0.70 g, 2.5 mmol) in pyridine (15 ml) was heated at 80° for 1.5 h. The reaction mixture was cooled in an ice bath, and then methanesulfonyl chloride (0.4 ml) was added. The mixture was stirred for 1 day at room temperature. After the addition of water (0.5 ml), the solvent was removed *in vacuo* and the residue was dissolved in ethyl acetate (30 ml) and washed with brine. The organic layer was dried ($MgSO_4$) and evaporated to dryness *in vacuo*. The residue was

chromatographed on a column of silica gel (50 g), using chloroform–ethyl acetate (2:1) as an eluent. The fractions containing nucleoside derivative were combined and evaporated to dryness to give 1.13 g of crude mesylate (**4**) (1.74 mmol, 82%), which was used in the next step without further purification.

3'-Azido-2',3'-dideoxy-*E*-5-styryluridine (6)

A mixture of **4** (1.13 g, 1.74 mmol) and sodium azide (0.45 g) in DMF (50 ml) was heated at 80° for 2 h with stirring. The solvent was removed *in vacuo* and the residue was chromatographed on a column of silica gel with chloroform–ethyl acetate (3:1). The fractions containing compound (**5**) were combined and evaporated to dryness. Detritylation of **5** was carried out by heating with in 24 ml of 80% acetic acid–dioxane (5:1) for 2 h at reflux temperature. The mixture was evaporated *in vacuo*. The residue was dissolved in chloroform and applied to a column of silica gel (40 g). The column was washed with chloroform and elution was performed with chloroform-ethyl acetate (3:1). After evaporation of the combined fractions, the residual syrup was treated with benzene–ether to give a white solid of **6**. 382 mg (1.07 mmol, 62%). UV (MeOH), λmax 313 nm (ε 18000). IR (KBr); 2100 cm^{-1} (N_3). ^{1}H-NMR (DMSO-d_6+D_2O) δ: 2.3–2.5 (m, 2H, H-2'), 3.6–3.9 (m, 3H, H-4' and 5'), 4.46 (m, 1H, H-3'), 6.13 (dd, 1H, H-1', J=5.6 Hz), 6.90 (d, 1H, vinylic, J=16.5 Hz), 7.5–7.5 (5H, m, aromatic), 7.38 (d, 1H, vinylic, J=16.5 Hz), 8.21 (s, 1H, H-6). *Anal.* Calcd for $C_{17}H_{17}N_5O_4 \cdot 1/4C_6H_6$: C, 59.27; H, 4.97; N, 18.68. Found: C, 59.47; H, 4.71; N, 18.94.

2',3'-Dideoxy-*E*-5-styryluridine (9)

A solution of 2'-deoxy-*E*-5-styryluridine (**7**)[13] (0.8 g, 2.4 mmol) and imidazole (0.33 g, 5 mmol) in 20 ml of dimethylformamide was treated with 0.40 g (2.7 mmol) of *t*-butyldimethylsilyl chloride, and the mixture was stirred at room temperature for 3 h. The reaction was quenched with addition of methanol (1 ml). After evaporation of the solvent, the residue was chromatographed on a column of silica gel (50 g). Elution was performed with chloroform–methanol (19:1). After evaporation of the combined fractions, the residue was dissolved in 10 ml of acetonitrile. To this solution was added 4-(dimethylamino)pyridine (1.22 g, 10 mmol) and phenyl chlorothionocarbonate (0.5 ml, 3.6 mmol), and the mixture was stirred at room temperature for 6 h. The reaction mixture was diluted with 50 ml of ethyl acetate, and then it was extracted with brine. The organic layer was washed with 2% aqueous sulfuric acid, saturated hydrogen bicarbonate and brine, dried ($MgSO_4$), and then evaporated to dryness. The crude product **8** (0.93 g, 1.6 mmol, 67%) was obtained as a yellow solid, and directly used without further purification in the next step. To a solution of **8** (0.93 g) in dry xylene (20 ml) was added a catalytic amount

of 2,2'-azobisisobutyronitrile (AIBN) and 3.0 ml (11.1 mmol) of tri-*n*-butyltin hydride. The mixture was heated at 90° for 1 h. The reaction mixture was diluted with 100 ml of *n*-hexane, and applied to a column of silica gel (50 g). The column was washed with *n*-hexane, and elution was performed with *n*-hexane–ethyl acetate (2:1). After evaporation of the combined fractions, residual material (0.28 g) was dissolved in tetrahydrofuran (20 ml) and treated with 0.8 ml of tetrabutylammonium fluoride in tetrahydrofuran (1 M solution). The solution was stirred for 1 h at room temperature, and the solvent was evaporated . The residue was chromatographed on a column of silica gel (40 g). Elution was performed with chloroform–methanol (19:1). The fractions containing nucleoside were combined and the solvent was removed to give **9** as a glass. 0.11 g (0.35 mmol, 22% from **8**). UV (MeOH), λmax 313 nm (ε 17400). ^{1}H-NMR (DMSO-d_6+D_2O) δ: 1.92 (m, 2H, H-3'), 2.07 (broad s, 1H, H-2'), 2.3–2.4 (m, 1H, H-2'), 3.5–3.9 (m, 2H, H-5'), 4.10 (m, 1H, H-4'), 6.06 (dd, 1H, H-1'), 6.90 (d, 1H, vinylic, J=16.5 Hz), 7.2–7.5 (m, 6H, aromatic and vinylic), 8.43 (s, 1H, H-6). *Anal.* Calcd for $C_{17}H_{18}N_2O_4$: C, 64.96; H, 5.77; N, 8.91. Found: C, 64.71; H, 5.74; N, 8.64.

2'-Deoxy-3',5'-di-*O*-methanesulfonyl-*E*-5-styryluridine (10)

To a suspension of **7** (0.6 g, 1.82 mmol) in pyridine (12 ml) was added methanesulfonyl chloride (0.60 ml, 7.8 mmol), and the mixture was stirred for 2 h at room temperature. The mixture was then poured onto vigorously stirred ice–water mixture. After stirring for 0.5 h, the precipitate was collected by filtration and washed with water. The product was crystallized from hot benzene–ethanol to give **10** as colorless crystals. 0.80 g (1.6 mmol, 90%). mp 165–168°. UV (MeOH), λmax 313 nm. ^{1}H-NMR (DMSO-d_6) δ: 2.5 (m, 2H, H-2'), 3.23 (s, 6H, SO_2CH_3), 4.3–4.5 (m, 3H, H-4' and 5'), 5.28 (m, 1H, H-3'), 6.19 (dd, 1H, H-1', J=7.0 Hz), 6.84 (d, 1H, vinylic, J=16.5 Hz), 7.1–7.4 (m, 5H, aromatic), 7.43 (d, 1H, vinylic, J=16.2 Hz), 7.81 (s, 1H, H-6), 11.6 (s, 1H, NH). *Anal.* Calcd for $C_{19}H_{22}N_2O_9S_2 \cdot 1/3C_6H_6$: C, 49,39; H, 4.56; N, 5.45. Found: C, 49.21; H, 4.72; N, 5.47.

1-(3,5-Anhydro-2-deoxy-β-D-*threo*-pentofuranosyl)-*E*-5-styryluracil (11)

To a suspension of **10** (0.70 g, 1.44 mmol) in dioxane (10 ml) was added aqueous 0.6 N NaOH (30 ml), and the mixture was heated at reflux temperature for 0.5 h. The mixture was evaporated and the residue was triturated with water (20 ml). The precipitates were collected by filtration and washed with water. The precipitates were crystallized from hot benzene–ethanol to give **11** as pale yellow crystals. 0.40 g (1.28 mmol, 89 %). mp 187—191°. UV (MeOH), λmax 313 nm. ^{1}H-NMR (DMSO-d_6+D_2O) δ: 2.5–2.7 (m, 2H, H-2'), 4.11 (broad s, 1H, H-4'), 4.74 (dd, 1H, H-5'), 4.98 (broad s, 1H, H-5'), 5.54 (dd,

1H, H-3'), 6.55 (d, 1H, H-1', J=8.1 Hz), 6.90 (d, 1H, vinylic, J=16.2 Hz), 7.2–7.5 (m, 6H, aromatic and vinylic), 8.48 (s, 1H, H-6). *Anal.* Calcd for $C_{17}H_{16}N_2O_4 \cdot 0.1C_6H_6$: C, 66.03; H, 5.23; N, 8.75. Found: C, 65.91; H, 5.22; N, 8.98.

2',3'-Dideoxy-2',3'-didehydro-*E*-5-styryluridine (12)

A mixture of **11** (0.46 g, 1.47 mmol) and potassium *t*-butoxide (0.50 g, 4.46 mmol) in DMSO (10 ml) was stirred at room temperature for 1 h. The mixture was neutralized with acetic acid, and then poured onto water (150 ml) with crushed ice. After stirring for 0.5 h, the precipitate was collected by filtration and washed with water. The precipitate was triturated with methanol and filtered from the insoluble materials. The filtrate was chromatographed on a column of silica gel (40 g) with chloroform–methanol (14:1). After evaporation of the combined fraction, the residue was crystallized from ethanol to give **12** as pale yellow crystals. 307 mg (0.98 mmol, 67%). mp 105—109°. UV (MeOH), λmax 313 nm (ε 16000). ^{1}H-NMR (DMSO-d_6+D_2O) δ: 3.69 (m, 2H, H-5'), 4.86 (broad s, 1H, H-4'), 5.98 (broad s, 1H, H-3'), 6.46 (broad s, 1H, H-2'), 6.85 (d, 1H, vinylic, J=16.5 Hz), 6.89 (broad s, 1H, H-1'), 7.2–7.5 (m, 6H, aromatic and vinylic, 8.21 (s, 1H, H-6). *Anal.* Calcd for $C_{17}H_{16}N_2O_4 \cdot 2/3H_2O$: C, 62.96; H, 5.39; N, 8.64. Found: C, 63.26; H, 5.35; N, 8.40.

Antiviral Evaluation in Human MOLT 4 Cells

The evaluation of test compounds for anti-HIV-1 activity was carried out as the method described by Inoue et al.[17]

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