Synthesis of New Cyclic and Acyclic 5-Halouridine Derivatives as Potential Antiviral Agents

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Abstract: The synthesis of new cyclic and acyclic nucleoside analogues was achieved by alkylation of 5-halogenated 6-(2,4-dichlorophenoxymethyl)pyrimidine-2,4-dione following the Vorbrüggen coupling procedure. Nucleoside analogues of the 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine (HEPT)-type were obtained as well as analogues of ganciclovir, acyclovir, and ribonucleosides. All compounds were tested against a variety of viruses. Three of the new compounds were potent and selective anti-HIV-1 inhibitors.

Key words: bioorganic chemistry, drugs, antiviral agents, nucleosides, glycosylation

Nucleoside analogues are an important class of chemotherapeutics that are used as antiviral or antitumor agents in the clinic. The main mechanism of action of these compounds is an inhibition of DNA-replicating enzymes. However, to exert their biological activity, these compounds have to be converted into their corresponding nucleoside triphosphates by cellular enzymes such as kinases. Despite their toxic side effects[1,2] and the risk of developing resistance after prolonged treatment,[3] eight nucleoside analogues like 3′-azido-3′-deoxythymidine (AZT) (**1**), 2′,3′-dideoxyinosine (ddI) (**2**), L-3′-thiacytidine (3TC) (**3**), and abacavir (ABC) (**4**) are nowadays used as anti-HIV agents to improve the quality of life of AIDS patients. Nucleoside analogues may be modified in the glycone as in **1**–**3** or in the glycone and the aglycone part as in **4** compared to naturally occurring nucleosides (Figure 1).

In addition, at least one nucleoside analogue is always included in multiple-drug therapies as in the highly active antiretroviral therapy (HAART) strategy. However, the alarming expectations concerning the spread and the increasing number of people infected by this disease demonstrate the need for further and more potent drugs. 5-Substituted cyclic and acyclic nucleosides, for example, (5*E*)-bromovinyl-2′-deoxyuridine (BVDU) (**5**) or even 5-halogenated heterocycles like 5-fluorouracil (5-FU) (**6**) have been shown to exhibit interesting chemotherapeutic, biochemical, and biophysical properties (Figure 1).[4] Thus, new methods for the convenient synthesis of 5-halouracil derivatives are of current interest in nucleoside chemistry.

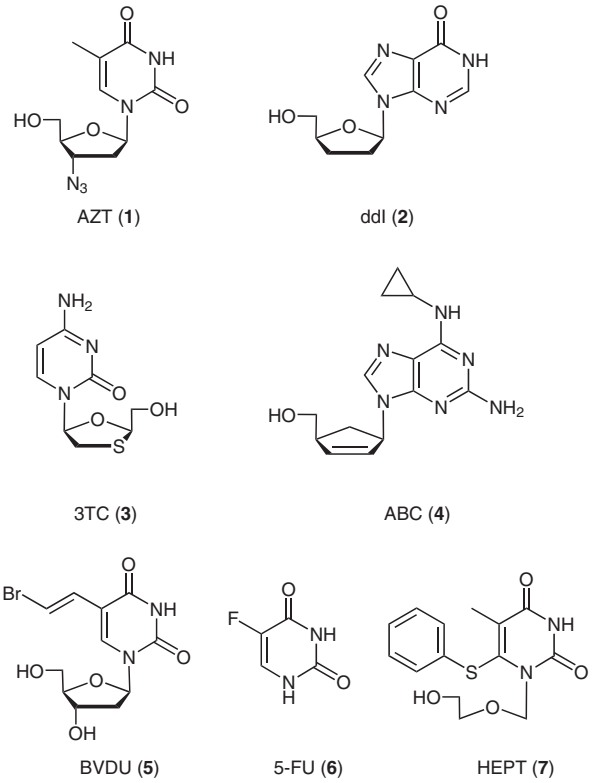

Figure 1 Structural formulas of clinically used nucleoside analogues **1**–**5** as well as 5-fluorouracil (**6**) and HEPT (**7**)

Another very interesting class of antiviral active derivatives are the 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine (HEPT) compounds **7**, which showed selective anti-HIV-1 activity (Figure 1).[5] Here we report on new nucleobase and nucleoside analogues bearing halogen atom at C-5 and an aryloxymethyl residue in the 6-position of the uracil pyrimidine ring system.

The key reaction in our strategy for the synthesis of new nucleoside analogues is based on the alkylation of silylated heterocycles following the Vorbrüggen procedure.[6] However, first 6-[(2,4-dichlorophenoxy)methyl]pyrimidine-2,4(1*H*,3*H*)-dione (**8**) was synthesized in high yield by condensation of ethyl-4-(2,4-dichlorophenoxy)-3-oxobutanoate (**9**) with thiourea in the presence of sodium

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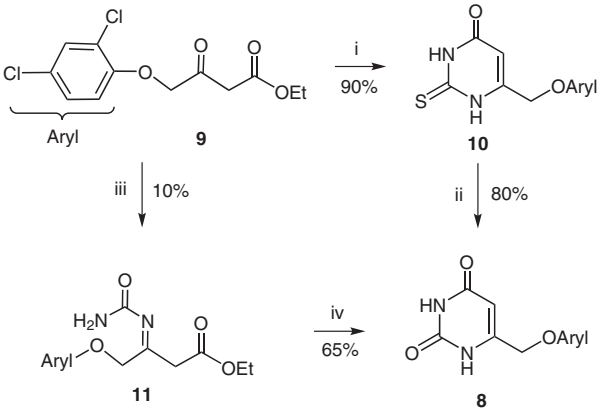
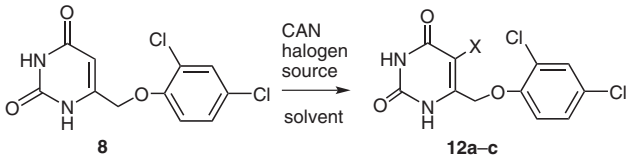
ethoxide to give 6-(2,4-dichlorophenoxymethyl)-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one (**10**),[7] and then desulfurization with (10%) aqueous chloroacetic acid yielding the target molecule **8**.[8] The same compound was available in poor yield by condensation of **9** with urea in the presence of concentrated hydrochloric acid in absolute ethanol to give **11** and cyclization with 2 N sodium hydroxide to yield **8** (Scheme 1).[9]



Scheme 1 Synthesis of **8**. *Reagents and conditions*: (i) 1. thiourea, NaOEt, reflux, 24 h, 2. aq 30% HCl; (ii) 10% $ClCH_2CO_2H$ in H_2O, reflux, 24 h; (iii) urea, EtOH–HCl, r.t., 5–7 d; (iv) 1. aq 2 N NaOH, 95 °C, 1 h, 2. concd HCl.

Next, three halogenated pyrimidine analogues were prepared by halogenation of uracil derivative **8** using different halogen sources and ceric ammonium nitrate (CAN) at 70 °C or 80 °C. Iodination of 6-modified uracil derivative **8** takes place in the presence of CAN and elemental iodine in methanol at 70 °C to give 5-iodouracil **12a**. In addition, chlorination of uracil derivative **8** by LiCl/CAN in acetonitrile–AcOH as solvent at 80 °C for 24 hours gave 5-chlorouracil **12b**. Bromination took place by treatment of pyrimidine **8** with LiBr/CAN in methanol at 70 °C to yield 5-bromouracil **12c** (Table 1).[10]

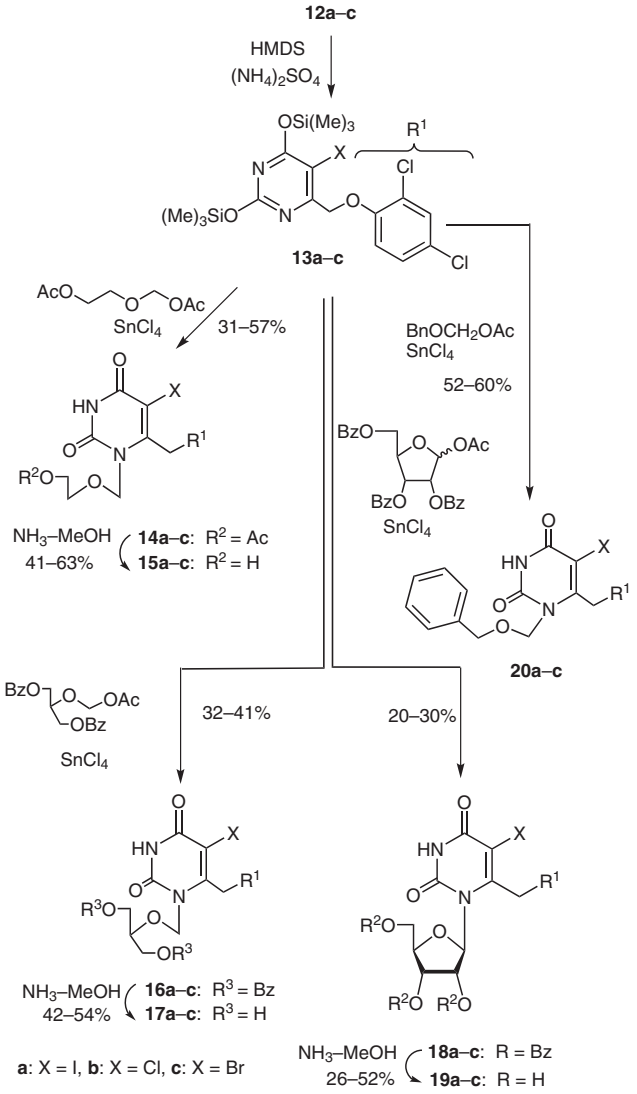
Table 1 5-Halogenation of 6-(2,4-Dichlorophenyloxymethyl)uracil (**8**)



12	X	Solvent	Halogen source	Yield
a	I	MeOH	I_2	72%
b	Cl	MeCN–AcOH	LiCl	65%
c	Br	MeOH	LiBr	46%

The bis(trimethylsilyl) derivatives **13a–c**, obtained from the silylation of **12a–c** with hexamethyldisilazane (HMDS) and a catalytic amount of ammonium sulfate, were reacted with 2-acetoxyethyl acetoxymethyl ether, 2-(acetoxymethoxy)propanediyl-1,3-dibenzoate, and benzyloxymethyl acetate.[11] These reactions were carried out in anhydrous acetonitrile with tin(IV) chloride as a catalyst.

The same procedure was applied to 2,3,5-tri-*O*-benzoate-β-D-ribofuranose-1-acetate leading to the protected β-ribofuranosyl nucleoside **18a–c** (Scheme 2). Finally, the deprotected compounds **15a–c**, **17a–c** and **19a–c** were obtained by cleavage of the ester blocking group with methanolic ammonia. The products were purified by silica gel column chromatography. All new nucleoside analogues and pyrimidine analogues were fully characterized by analytical methods like ^{1}H NMR, ^{13}C NMR, and elemental analysis.



Scheme 2 Synthesis of acyclic 5-halogenated uracil nucleoside analogues **15**–**20**

The newly prepared compounds were tested for their biological activity against various viruses. All compounds failed to exhibit any antiviral effect against feline corona virus (FIPV), feline herpes virus, para-influenza-3-virus, reovirus, sindbis virus, cocksackie virus B4, punta toro vi-

rus, herpes virus type-1 (KOS), herpes virus-type-2 (G), herpes simplex virus-1 TK$^-$ KOS ACV^r, vaccinia virus, vesicular stomatitis virus, respiratory syncytial virus, influenza A H1N1 subtype, influenza A H3N2 subtype, and influenza B. Most compounds also proved to be inactive against HIV-1 and HIV-2 in T-lymphocytes (CEM/0-cells). However, compounds **20a–c** showed significant and highly selective inhibitory potency against HIV-1 while they proved to be inactive against HIV-2.[12] The activity found was in the low- and submicromolar range, respectively (**20a**: EC_{50} = 0.16 μM, **20b**: EC_{50} = 5.6 μM and **20c**: EC_{50} = 0.83 μM). Maybe this selective HIV-1 activity can be explained by the resemblance of compounds **20a–c** with the HEPT structure. Interestingly, compounds **20a** and **20c** were found to be 10-fold more active as compared to HEPT (**7**) (EC_{50} = 7.5 μM).[13]

In summary, we have prepared efficiently new 6-alkylated 5-halogenated uracil nucleobases and nucleoside analogues. Some of these compounds showed promising selective anti-HIV-1 activity. Further work focusing on analogues of **20** is currently under investigation in our laboratories.

Melting points were taken on an Apotec apparatus and are uncorrected. IR spectra were recorded on an Avatar 370 FT- IR spectrometer. NMR spectra were recorded with Bruker AMX400 and Bruker and Bruker DRX 500 Fourier-transform spectrometers. All ^{1}H and ^{13}C NMR chemical shifts (δ) are quoted in ppm and calibrated with respect to solvent signals. ESI mass spectra were taken on a Finnigan Thermo Quest MAT 95XL spectrometer. Merck precoated 60 F_{254} plates with a 0.2 mm layer of silica gel were used for TLC. For column chromatography, Merck silica gel 60 (230–400) mesh was used. All reactions were carried out under dry N_2, except for the synthesis of **8** and **12a–c**. Petroleum ether (PE) refers to the fraction boiling in the range 40–60 °C.

6-(2,4-Dichlorophenoxymethyl)-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one (10)

Thiourea (8.90 g, 117 mmol) and ethyl 4-(2,4-dichlorophenoxy)-3-oxobutanoate (**9**; 13.4 g, 45.95 mmol) were added to a solution of Na (2.70 g, 117 mmol) in EtOH (100 mL) and refluxed under anhyd conditions for 24 h. The reaction product was evaporated in vacuum and the residue was dissolved in H_2O (200 mL), acidified with aq 30% HCl and the precipitate was collected by filtration, dried at 60–70 °C, and recrystallized from a mixture of DMF and H_2O (5:1); yield: 12.5 g (90%); crystalline, colorless solid; mp 318–320 °C.

^{1}H NMR (DMSO-d_6/TMS): δ = 5.00 (s, 2 H, CH_2Oaryl), 6.01 (s, 1 H, CH), 7.20–7.80 (m, 3 H_{aryl}), 11.03 (br s, 2 H, 2 NH).

^{13}C NMR (DMSO-d_6/TMS): δ = 65.5, 103.1, 115.7, 122.9, 125.9, 128.6, 129.8, 151.3, 152.1, 161.1, 176.3.

MS (ESI$^-$): *m*/*z* = 302.0 [M]$^+$.

Anal. Calcd for $C_{11}H_8Cl_2N_2O_2S$ (301.97): C, 43.58; H, 2.66; N, 9.24. Found: C, 43.66; H, 2.59; N, 9.30.

Ethyl 4-(2,4-Dichlorophenoxy)-3-ureidobutanoate (11)

Finely powdered urea (8.00 g, 133 mmol) was added to a mixture of **9** (35.8 g, 123 mmol) dissolved in absolute EtOH (2.5 mL) containing concd HCl (0.5 mL). The mixture was stored in a desiccator over concd H_2SO_4 under a membrane pump vacuum for 7 d to obtain a dry product **11**, which was recrystallized from EtOH; yield: 4.30 g (10%); white crystals; mp 150–152 °C.

^{1}H NMR (DMSO-d_6/TMS): δ = 1.21 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3), 4.13 (q, *J* = 7.1 Hz, 2 H, CH_2CH_3), 5.22 (s, 2 H, CH_2), 5.32 (s, 2 H, CH_2Oaryl), 6.94–7.60 (m, 3 H_{aryl}), 10.13 (s, 2 H, NH).

^{13}C NMR (DMSO-d_6/TMS): δ = 14.10, 33.86, 61.20, 67.10, 116.67, 121.02, 126.01, 127.68, 129.29, 149.96, 154.26, 166.07, 166.94.

MS(ESI$^-$): *m*/*z* = 333.0 [M]$^+$.

Anal. Calcd for $C_{13}H_{14}Cl_2N_2O_4$ (333.17): C, 46.87; H, 4.24; N, 8.41. Found: C, 46.94; H, 4.18; N, 8.49.

6-[(2,4-Dichlorophenoxy)methyl]pyrimidine-2,4(1*H*,3*H*)-dione (8)

Method A: A mixture of **10** (1.95 g, 6.48 mmol) and chloroacetic acid (3.10 g, 32.81 mmol) in H_2O (30 mL) was refluxed for 24 h and cooled to r.t. The formed precipitate was collected by filtration, washed with H_2O (2 × 20 mL), dried, and recrystallized from a mixture of DMF and H_2O (5:1); yield: 1.50 g (80%); fine colorless crystals; mp 278–280 °C.

^{1}H NMR (DMSO-d_6/TMS): δ = 4.80 (s, 2 H, CH_2Oaryl), 5.55 (s, 1 H, CH), 7.10–7.70 (m, 3 H_{aryl}), 11.11 (br s, 2 H, 2 NH).

^{13}C NMR (DMSO-d_6/TMS): δ = 65.5, 98.0, 115.3, 122.6, 125.4, 128.1, 129.4, 150.6, 151.2, 151.8, 163.8.

MS (ESI$^-$): *m*/*z* = 286.0 [M]$^+$.

Anal. Calcd for $C_{11}H_8Cl_2N_2O_3$ (287.10): C, 46.02; H, 2.81; N, 9.76. Found: C, 46.10; H, 2.76; N, 9.85.

Method B: The crude product **11** was added to a solution of aq 2 N NaOH (30 mL) at 95 °C with stirring. The clear solution was cooled to 65 °C and carefully acidified while stirring by slow addition of concd HCl. The product precipitated immediately, collected by filtration, and dried. Compound **8** was obtained as colorless powder of a high degree of purity in 65% yield.

6-(2,4-Dichlorophenoxymethyl)-5-iodo-2-oxo-2,3-dihydro-1*H*-pyrimidinon-4-one (12a)

A mixture of uracil derivative **8** (0.38 g, 1.34 mmol), I_2 (0.20 g, 0.80 mmol), CAN (0.37 g, 0.67 mmol), and MeOH (8 mL) was stirred at 70 °C for 24 h. The product precipitated and was filtered from the hot solvent, washed with Et_2O (10 mL), dried, and crystallized from MeOH; yield: 0.40 g (72%); colorless solid; mp 255–257 °C.

^{1}H NMR (DMSO-d_6/TMS): δ = 5.03 (s, 2 H, CH_2Oaryl), 7.30–7.70 (m, 3 H_{aryl}), 11.10 (br s, 2 H, 2 NH).

^{13}C NMR (DMSO-d_6/TMS): δ = 71.4, 74.9, 116.2, 123.3, 126.1, 128.6, 129.8, 150.5, 151.0, 152.6, 162.0.

MS (ESI$^-$): *m*/*z* = 412.0 [M – 1].

Anal. Calcd for $C_{11}H_7Cl_2IN_2O_3$ (412.99): C, 31.99; H, 1.71; N, 6.78. Found: C, 32.06; H, 1.66; N, 6.87.

5-Chloro-6-(2,4-dichlorophenoxymethyl)-2-oxo-2,3-dihydro-1*H*-pyrimidinon-4-one (12b)

A mixture of the uracil derivative **8** (0.31 g, 1.07 mmol), LiCl (0.54 g, 1.28 mmol), CAN (1.17 g, 2.14 mmol), and MeCN–AcOH (1:1.8 mL) was stirred at 80 °C for 18 h. The solvent was evaporated. After coevaporation with EtOH–H_2O (2:1, 3 × 10 mL) gave a colorless powder that was crystallized from EtOH; yield: 0.20 g (65%); colorless solid; mp 266–268 °C.

^{1}H NMR (DMSO-d_6/TMS): δ = 4.81 (s, 2 H, CH_2Oaryl), 7.11–7.48 (m, 3 H_{aryl}), 11.00 (br s, 2 H, 2 NH).

^{13}C NMR (DMSO-d_6/TMS): δ = 65.6, 107.2, 115.4, 124.3, 126.2, 128.4, 129.8, 145.8, 150.2, 152.6, 160.1

MS (ESI$^-$): *m*/*z* = 320.0 [M – 1].

Anal. Calcd for $C_{11}H_7Cl_3N_2O_3$ (321.54): C, 41.09; H, 2.19; N, 8.71. Found: C, 41.17; H, 2.11; N, 8.81.

5-Bromo-6-(2,4-dichlorophenoxymethyl)-2-oxo-2,3-dihydro-1*H*-pyrimidinon-4-one (12c)
A mixture of uracil derivative **8** (0.38 g, 1.34 mmol), LiBr (0.14 g, 1.61 mmol), CAN (1.47 g, 2.68 mmol), and MeOH (8 mL) was stirred at 70 °C for 24 h. Workup as for **12b** gave a colorless powder that was recrystallized from EtOH; yield: 0.23 g (46%); white solid; mp 247–249 °C.

^{1}H NMR (DMSO-d_6/TMS): δ = 4.90 (s, 2 H, CH_2Oaryl), 7.10–7.50 (m, 3 H_{aryl}), 11.11 (br s, 2 H, 2 NH).

^{13}C NMR (DMSO-d_6/TMS): δ = 67.7, 97.7, 116.3, 123.3, 126.2, 128.3, 129.8, 147.6, 150.5, 152.6, 160.4.

MS (ESI$^-$): *m*/*z* = 366.0 [M – 1].

Anal. Calcd for $C_{11}H_7BrCl_2N_2O_3$ (365.99): C, 36.10; H, 1.93; N, 7.65. Found: C, 36.19; H, 1.85; N, 7.74.

Nucleosides 14, 16, 18, 20; General Procedure
A suspension of uracils **12a**–**c** (0.01 mol) and $(NH_4)_2SO_4$ (10 mg) in HMDS (40 mL) was stirred under reflux for 4 h. The excess of HMDS was evaporated under reduced pressure to give bis(trimethylsilyl) compounds **13a**–**c**. A solution of protected cyclic and acyclic aglycone part (0.01 mol) in anhyd MeCN (60 mL) and $SnCl_4$ (2 mL) was added to **13a**–**c** and the mixture was stirred at –30 ° for 24 h. After addition of pyridine (4 mL), the mixture was filtered to remove the inorganic materials. The filtrate was diluted with $CHCl_3$ (100 mL). The organic layers were washed with a aq sat. $NaHCO_3$ (150 mL), followed by aq 1 N HCl (150 mL), then brine (100 mL), and finally H_2O (50 mL), dried (Na_2SO_4), and then the filtrate was concentrated to dryness under reduced pressure. The products **14a**–**c**, **16a**–**c**, **18a**–**c**, and **20a**–**c** were separated by silica gel column chromatography (gradient of EtOAc–PE). Each protected nucleoside was dissolved in MeOH saturated with ammonia and stirred for 2 d at r.t. Then, the solution was concentrated to dryness and the residue was recrystallized from MeOH to give nucleosides **15a**–**c**, **17a**–**c**, and **19a**–**c** as colorless solids.

1-[(2-Acetoxyethoxy)methyl]-6-(2,4-dichlorophenoxymethyl)-5-iodouracil (14a)
Yield: 1.80 g (34%); mp 130–132 °C.

^{1}H NMR (DMSO-d_6/TMS): δ = 2.14 (s, 3 H, $COCH_3$), 4.10 (t, *J* = 3.7 Hz, 2 H, HOCH_2), 4.35 (t, *J* = 3.7 Hz, 2 H, CH_2O), 5.60 (s, 2 H, CH_2Oaryl), 5.75 (s, 2 H, OCH_2N), 7.63–7.90 (m, 3 H_{aryl}), 12.12 (br s, 1 H, NH).

^{13}C NMR (DMSO-d_6/TMS): δ = 21.0, 63.2, 66.9, 71.4, 73.7, 83.1, 117.2, 123.6, 128.6, 129.9, 149.7, 151.5, 160.9, 170.6.

MS (ESI$^-$): *m*/*z* = 528.0 [M – 1].

Anal. Calcd for $C_{16}H_{15}Cl_2IN_2O_6$ (529.11): C, 36.32; H, 2.86; N, 5.29. Found: C, 36.39; H, 2.95; N, 5.36.

1-[(2-Acetoxyethoxy)methyl]-5-chloro-6-(2,4-dichlorophenoxymethyl)uracil (14b)
Yield: 2.50 g (57%); mp 144–146 °C.

^{1}H NMR (DMSO-d_6/TMS): δ = 2.10 (s, 3 H, $COCH_3$), 3.95 (t, *J* = 3.8 Hz, 2 H, HOCH_2), 4.31 (t, *J* = 3.8 Hz, 2 H, CH_2O), 5.45 (s, 2 H, CH_2Oaryl), 5.61 (s, 2 H, OCH_2N), 7.61–7.91 (m, 3 H_{aryl}), 12.20 (br s, 1 H, NH).

^{13}C NMR (DMSO-d_6/TMS): δ = 20.9, 63.2, 64.7, 67.0, 73.6, 112.2, 117.3, 123.6, 126.7, 128.7, 129.9, 145.4, 150.8, 152.2, 158.9, 170.6.

MS (ESI$^-$): *m*/*z* = 437.0 [M – 1].

Anal. Calcd for $C_{16}H_{15}Cl_3N_2O_6$ (437.66): C, 43.91; H, 3.45; N, 6.40. Found: C, 43.99; H, 3.53; N, 6.32.

1-[(2-Acetoxyethoxy)methyl]-5-bromo-6-(2,4-dichlorophenoxymethyl)uracil (14c)
Yield: 1.50 g (31%); mp 148–150 °C.

^{1}H NMR (DMSO-d_6/TMS): δ = 2.00 (s, 3 H, $COCH_3$), 3.81 (t, *J* = 3.7 Hz, 2 H, HOCH_2), 4.20 (t, *J* = 3.7 Hz, 2 H, CH_2O), 5.35 (s, 2 H, CH_2Oaryl), 5.60 (s, 2 H, OCH_2N), 7.10–7.51 (m, 3 H_{aryl}), 11.95 (br s, 1 H, NH).

^{13}C NMR (DMSO-d_6/TMS): δ = 21.2, 63.4, 67.5, 68.4, 74.5, 104.4, 117.4, 125.5, 128.4, 129.0, 130.9, 147.3, 151.1, 152.1, 158.9, 171.2.

MS (ESI$^-$): *m*/*z* = 482.0 [M – 1].

Anal. Calcd for $C_{16}H_{15}BrCl_2N_2O_6$ (482.11): C, 39.86; H, 3.14; N, 5.81. Found: C, 39.78; H, 3.23; N, 5.90.

6-(2,4-Dichlorophenoxymethyl)-1-(2-hydroxyethoxymethyl]-5-iodouracil (15a)
Yield: 2.00 g (41%); mp 154–156 °C.

^{1}H NMR (DMSO-d_6/TMS): δ = 3.70 (t, *J* = 3.7 Hz, 2 H, HOCH_2), 3.60 (t, *J* = 3.7 Hz, 2 H, CH_2O), 4.70 (br s, 1 H, OH), 5.40 (s, 2 H, CH_2Oaryl), 5.50 (s, 2 H, OCH_2N), 7.30–7.80 (m, 3 H_{aryl}), 12.00 (br s, 1 H, NH).

^{13}C NMR (DMSO-d_6/TMS): δ = 60.2, 70.9, 70.7, 71.5, 73.9, 82.9, 117.3, 123.6, 126.7, 128.7, 129.9, 149.8, 151.4, 152.4.

MS (ESI$^-$): *m*/*z* = 487.0 [M – 1].

Anal. Calcd for $C_{14}H_{13}Cl_2IN_2O_5$ (487.07): C, 34.52; H, 2.69; N, 5.75. Found: C, 34.60; H, 2.61; N, 5.84.

5-Chloro-6-(2,4-dichlorophenoxymethyl)-1-(2-hydroxyethoxymethyl]uracil (15b)
Yield: 2.50 g (63%); mp 165–167 °C.

^{1}H NMR (DMSO-d_6/TMS): δ = 3.60 (t, *J* = 3.7 Hz, 2 H, HOCH_2), 3.50 (t, *J* = 3.7 Hz, 2 H, CH_2O), 4.64 (br s, 1 H, OH), 5.29 (s, 2 H, CH_2Oaryl), 5.40 (s, 2 H, OCH_2N), 7.32–7.72 (m, 3 H_{aryl}), 12.20 (br s, 1 H, NH).

^{13}C NMR (DMSO-d_6/TMS): δ = 60.2, 64.8, 70.9, 73.7, 112.0, 117.4, 123.6, 126.8, 128.7, 129.9, 145.5, 150.7, 152.2, 158.9.

MS (ESI$^-$): *m*/*z* = 394.0 [M – 1].

Anal. Calcd for $C_{14}H_{13}Cl_3N_2O_5$ (395.62): C, 42.50; H, 3.31; N, 7.08. Found: C, 42.59; H, 3.23; N, 7.17.

5-Bromo-6-(2,4-dichlorophenoxymethyl)-1-(2-hydroxyethoxymethyl]uracil (15c)
Yield: 1.90 g (43%); mp 170–172 °C.

^{1}H NMR (DMSO-d_6/TMS): δ = 3.67 (t, *J* = 3.7 Hz, 2 H, HOCH_2), 3.55 (t, *J* = 3.8 Hz, 2 H, CH_2O), 4.62 (br s, 1 H, OH), 5.30 (s, 2 H, CH_2Oaryl), 5.45 (s, 2 H, OCH_2N), 7.31–7.74 (m, 3 H_{aryl}), 12.11 (br s, 1 H, NH).

^{13}C NMR (DMSO-d_6/TMS): δ = 60.2, 67.3, 70.9, 73.9, 103.6, 117.3, 123.6, 126.7, 128.7, 129.9, 147.1, 151.0, 152.3, 159.2.

MS (ESI$^-$): *m*/*z* = 440.0 [M – 1].

Anal. Calcd for $C_{14}H_{13}BrCl_2N_2O_5$ (440.07): C, 38.21; H, 2.98; N, 6.37. Found: C, 38.30; H, 2.90; N, 6.46.

2-{[6-(2,4-Dichlorophenoxymethyl)-5-iodo-2,4-dioxo-1-pyrimidinyl]methoxy}-1,3-propanediyl Dibenzoate (16a)
Yield: 2.40 g (33%); mp 96–98 °C.

^{1}H NMR (DMSO-d_6/TMS): δ = 4.12–4.42 (m, 5 H, 2 CH_2 and CH), 5.11 (s, 2 H, CH_2Oaryl), 5.50 (s, 2 H, OCH_2N), 7.10–7.82 (m, 13 H_{aryl}), 12.20 (br s, 1 H, NH).

^{13}C NMR (DMSO-d_6/TMS): δ = 64.1, 71.4, 73.4, 74.8, 83.4, 117.1, 123.6, 126.7, 128.5, 129.1, 129.4, 129.5, 129.9, 133.8, 149.3, 151.6, 152.2, 160.7, 165.7.

MS (ESI$^-$): *m*/*z* = 725.0 [M – 1].

Anal. Calcd for $C_{29}H_{23}Cl_2IN_2O_8$ (725.31): C, 58.02; H, 3.20; N, 3.86. Found: C, 48.11; H, 3.11; N, 3.96.

5-Chloro-2-{[6-(2,4-dichlorophenoxymethyl)-2,4-dioxo-1-pyrimidinyl]methoxy}-1,3-propanediyl Dibenzoate (16b)
Yield: 2.60 g (41%); mp 105–107 °C.

^{1}H NMR (DMSO-d_6/TMS): δ = 4.26–4.51 (m, 5 H, 2 CH_2 and CH), 5.10 (s, 2 H, CH_2Oaryl), 5.55 (s, 2 H, OCH_2N), 7.11–7.91 (m, 13 H_{aryl}), 11.98 (br s, 1 H, NH).

^{13}C NMR (DMSO-d_6/TMS): δ = 64.1, 64.7, 65.2, 73.2, 74.8, 117.2, 123.6, 126.8, 128.6, 129.1, 129.4, 129.5, 129.9, 133.8, 145.0, 150.9, 152.1, 158.6, 165.7.

MS (ESI$^-$): *m*/*z* = 634.0 [M – 1].

Anal. Calcd for $C_{29}H_{23}Cl_3N_2O_8$ (633.86): C, 54.95; H, 3.66; N, 4.42. Found: C, 54.82; H, 3.71; N, 4.49.

5-Bromo-2-{[6-(2,4-dichlorophenoxymethyl)-2,4-dioxo-1-pyrimidinyl]methoxy}-1,3-propanediyl Dibenzoate (16c)
Yield: 2.20 g (32%); mp 146–148 °C.

^{1}H NMR (DMSO-d_6/TMS): δ = 4.51–4.80 (m, 5 H, 2 CH_2 and CH), 5.41 (s, 2 H, CH_2Oaryl), 5.80 (s, 2 H, OCH_2N), 7.30–8.03 (m, 13 H_{aryl}), 11.94 (br s, 1 H, NH).

^{13}C NMR (DMSO-d_6/TMS): δ = 64.1, 67.2, 73.3, 74.8, 104.1, 117.2, 123.6, 126.8, 128.6, 129.1, 129.4, 129.5, 129.9, 133.8, 146.6, 151.1, 152.2, 159.0, 165.7.

MS (ESI$^-$): *m*/*z* = 678.0 [M – 1].

Anal. Calcd for $C_{29}H_{23}BrCl_2N_2O_8$ (678.31): C, 51.35; H, 3.42; N, 4.13. Found: C, 51.44; H, 3.35; N, 4.20.

6-(2,4-Dichlorophenoxymethyl)-1-[2-hydroxy-1-(hydroxymethyl)ethoxymethyl]-5-iodouracil (17a)
Yield: 2.20 g (42%); mp 155–157 °C.

^{1}H NMR (DMSO-d_6/TMS): δ = 3.31–3.50 (m, 5 H, 2 CH_2 and CH), 4.49 (m, 2 H, OH), 5.35 (s, 2 H, CH_2Oaryl), 5.40 (s, 2 H, OCH_2N), 7.20–7.61 (m, 3 H_{aryl}), 11.88 (br s, 1 H, NH).

^{13}C NMR (DMSO-d_6/TMS): δ = 61.1, 71.6, 73.3, 81.1, 82.6, 117.3, 123.6, 126.7, 128.7, 129.9, 150.0, 151.4, 152.4, 160.9.

MS (ESI$^-$): *m*/*z* = 517.1 [M – 1].

Anal. Calcd for $C_{15}H_{15}Cl_2IN_2O_6$ (517.10): C, 34.84; H, 2.92; N, 5.42. Found: C, 34.89; H, 2.88; N, 5.49.

5-Chloro-6-(2,4-dichlorophenoxymethyl)-1-[2-hydroxy-1-(hydroxymethyl)ethoxymethyl]uracil (17b)
Yield: 2.30 g (54%); mp 138–140 °C.

^{1}H NMR (DMSO-d_6/TMS): δ = 3.41–3.70 (m, 5 H, 2 CH_2 and CH), 4.82 (m, 2 H, OH), 5.51 (s, 2 H, CH_2Oaryl), 5.69 (s, 2 H, OCH_2N), 7.45–7.89 (m, 3 H_{aryl}), 12.10 (br s, 1 H, NH).

^{13}C NMR (DMSO-d_6/TMS): δ = 61.1, 64.8, 73.2, 81.2, 111.7, 117.4, 123.6, 126.8, 128.7, 129.9, 145.7, 150.7, 152.2, 159.0.

MS (ESI$^-$): *m*/*z* = 427.1 [M – 1].

Anal. Calcd for $C_{15}H_{15}Cl_3N_2O_6$ (425.65): C, 42.33; H, 3.55; N, 6.58. Found: C, 42.39; H, 3.49; N, 6.64.

5-Bromo-6-(2,4-dichlorophenoxymethyl)-1-[2-hydroxy-1-(hydroxymethyl)ethoxymethyl]uracil (17c)
Yield: 2.50 g (53%); mp 158–160 °C.

^{1}H NMR (DMSO-d_6/TMS): δ = 3.39–3.64 (m, 5 H, 2 CH_2 and CH), 4.81 (m, 2 H, OH), 5.50 (s, 2 H, CH_2Oaryl), 5.62 (s, 2 H, OCH_2N), 7.44–7.81 (m, 3 H_{aryl}), 12.30 (br s, 1 H, NH).

^{13}C NMR (DMSO-d_6/TMS): δ = 61.1, 67.4, 73.3, 81.2, 103.3, 117.3, 123.6, 126.8, 128.7, 129.9, 147.4, 151.0, 152.3, 159.3.

MS (ESI$^-$): *m*/*z* = 471.0 [M – 1].

Anal. Calcd for $C_{15}H_{15}BrCl_2N_2O_6$ (470.10): C, 38.32; H, 3.22; N, 5.96. Found: C, 38.38; H, 3.18; N, 5.90.

1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-6-(2,4-dichlorophenoxymethyl)-5-iodouracil (18a)
Yield: 1.90 g (22%); mp 130–132 °C.

^{1}H NMR (DMSO-d_6/TMS): δ = 4.42–4.59 (m, 2 H, H-5′,5″), 4.62–4.79 (m, 1 H, H-4′), 4.92 (s, 2 H, CH_2Oaryl), 6.02–6.21 (m, 2 H, H-2′, H-3′), 6.61 (d, *J* = 2.5 Hz, 1 H, H-1′), 7.20–7.92 (m, 18 H_{aryl}), 12.03 (br s, 1 H, NH).

^{13}C NMR (DMSO-d_6/TMS): δ = 64.0, 66.2, 70.9, 71.4, 74.3, 79.6, 86.5, 116.3, 125.0, 128.8, 129.3, 129.4, 129.9, 130.0, 130.2, 130.3, 131.0, 133.4, 133.7, 133.8, 133.9, 148.9, 151.3, 159.3, 165.5, 165.9.

MS (ESI$^-$): *m*/*z* = 857.0 [M – 1].

Anal. Calcd for $C_{37}H_{27}Cl_2IN_2O_{10}$ (857.43): C, 51.83; H, 3.17; N, 3.27. Found: C, 51.74; H, 3.20; N, 3.33.

1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-5-chloro-6-(2,4-dichlorophenoxymethyl)uracil (18b)
Yield: 2.3 g (30%); mp 136–138 °C.

^{1}H NMR (DMSO-d_6/TMS): δ = 4.50–4.58 (m, 2 H, H-5′,5″), 4.71–4.82 (m, 1 H, H-4′), 5.21 (s, 2 H, CH_2Oaryl), 6.11–6.23 (m, 2 H, H-2′, H-3′), 6.62 (d, *J* = 2.5 Hz, 1 H, H-1′), 7.31–7.98 (m, 18 H_{aryl}), 12.19 (br s, 1 H, NH).

^{13}C NMR (DMSO-d_6/TMS): δ = 63.4, 65.5, 70.3, 73.8, 78.3, 86.7, 116.2, 123.3, 126.2, 128.6, 128.8, 128.9, 129.1, 129.5, 129.7, 129.9, 133.7, 134.0, 134.2, 149.5, 152.6, 159.1, 164.9, 165.1, 165.8.

MS (ESI$^-$): *m*/*z* = 764.0 [M – 1].

Anal. Calcd for $C_{37}H_{27}Cl_3N_2O_{10}$ (765.98): C, 58.02; H, 3.55; N, 3.66. Found: C, 58.10; H, 3.62; N, 3.72.

1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-5-bromo-6-(2,4-dichlorophenoxymethyl)uracil (18c)
Yield: 1.70 g (20%); mp 123–125 °C.

^{1}H NMR (DMSO-d_6/TMS): δ = 4.41–4.59 (m, 2 H, H-5′,5″), 4.60–4.71 (m, 1 H, H-4′), 5.01 (s, 2 H, CH_2Oaryl), 6.01–6.19 (m, 2 H, H-2′, H-3′), 6.60 (d, *J* = 2.6 Hz, 1 H, H-1′), 7.20–7.99 (m, 18 H_{aryl}), 12.10 (br s, 1 H, NH).

^{13}C NMR (DMSO-d_6/TMS): δ = 60.1, 63.3, 67.7, 70.2, 73.9, 78.3, 86.9, 116.2, 123.3, 126.2, 128.6, 128.7, 128.9, 129.1, 129.5, 129.7, 129.8, 129.9, 133.7, 134.0, 134.2, 152.6, 159.2, 164.8, 165.2, 165.9.

MS (ESI$^-$): *m*/*z* = 810.0 [M – 1].

Anal. Calcd for $C_{37}H_{27}BrCl_2N_2O_{10}$ (810.43): C, 54.83; H, 3.36; N, 3.46. Found: C, 54.75; H, 3.28; N, 3.53.

6-(2,4-Dichlorophenoxymethyl)-1-(β-D-ribofuranosyl)-5-iodouracil (19a)
Yield: 1.50 g (28%); mp 108–110 °C.

^{1}H NMR (DMSO-d_6/TMS): δ = 3.57–3.73 (m, 2 H, H-5′,5″), 4.08–4.15 (m, 1 H, H-4′), 4.45–4.48 (m, 1 H, H-3′), 4.49–4.53 (m, 1 H, H-2′), 4.59 (t, *J* = 5.6 Hz, 1 H, OH), 4.90 (s, 2 H, CH_2Oaryl), 5.10 and 5.0 (2 d, *J* = 5.8 Hz, 2 H, 2 × OH), 5.12 (s, 1 H, CH uracil), 6.10 (d, *J* = 2.7 Hz, 1 H, H-1′), 7.20–7.68 (m, 3 H_{aryl}), 11.87 (br s, 1 H, NH).

^{13}C NMR (DMSO-d_6/TMS): δ = 62.6, 70.5, 71.7, 84.9, 89.9, 105.9, 116.0, 123.2, 126.0, 128.5, 129.1, 131.5, 133.6, 150.4, 152.6.

MS (ESI$^-$): *m*/*z* = 544.9 [M – 1].

Anal. Calcd for $C_{16}H_{15}Cl_2IN_2O_7$ (545.11): C, 35.25; H, 2.77; N, 5.14. Found: C, 35.31; H, 2.69; N, 5.22.

5-Chloro-6-(2,4-dichlorophenoxymethyl)-1-(β-D-ribofuranosyl)uracil (19b)
Yield: 2.50 g (55%); mp 183–185 °C.

^{1}H NMR (DMSO-d_6/TMS): δ = 3.46–3.66 (m, 2 H, H-5′,5″), 3.69–3.72 (m, 1 H, H-4′), 4.07–4.15 (m, 1 H, H-3′), 4.49–4.53 (m, 1 H, H-2′), 4.62 (t, *J* = 5.6 Hz, 1 H, OH), 4.92 (s, 2 H, CH_2Oaryl), 5.13 and 5.00 (2 d, *J* = 5.8 Hz, 2 H, 2 × OH), 6.11 (d, *J* = 2.7 Hz, 1 H, H-1′), 7.21–7.62 (m, 3 H_{aryl}), 11.95 (br s, 1 H, NH).

^{13}C NMR (DMSO-d_6/TMS): δ = 62.5, 65.5, 70.4, 71.0, 84.9, 89.1, 106.9, 116.1, 123.2, 126.2, 128.6, 129.9, 145.4, 149.7, 152.5.

MS(ESI$^-$): *m*/*z* = 453.2 [M – 1].

Anal. Calcd for $C_{16}H_{15}Cl_3N_2O_7$ (453.66): C, 42.36; H, 3.33; N, 6.18. Found: C, 42.44; H, 3.40; N, 6.27.

5-Bromo-6-(2,4-dichlorophenoxymethyl)-1-(β-D-ribofuranosyl)uracil (19c)
Yield: 1.30 g (26%); mp 96–98 °C.

^{1}H NMR (DMSO-d_6/TMS): δ = 3.40–3.63 (m, 2 H, H-5′,5″), 3.69–3.73 (m, 1 H, H-4′), 4.07–4.14 (m, 1 H, H-3′), 4.48–4.53 (m, 1 H, H-2′), 4.61 (t, *J* = 5.6 Hz, 1 H, OH), 4.91 (s, 2 H, CH_2Oaryl), 5.11 and 5.00 (2 d, *J* = 5.8 Hz, 2 H, 2 × OH), 6.07 (d, *J* = 2.5 Hz, 1 H, H-1′), 7.00–7.62 (m, 3 H_{aryl}), 11.88 (br s, 1 H, NH).

^{13}C NMR (DMSO-d_6/TMS): δ = 62.5, 65.2, 70.4, 71.1, 84.9, 89.3, 97.3, 116.1, 123.3, 126.2, 128.6, 129.1, 129.9, 147.1, 152.6.

MS (ESI$^-$): *m*/*z* = 499.1 [M – 1].

Anal. Calcd for $C_{16}H_{15}BrCl_2N_2O_7$ (498.11): C, 38.58; H, 3.04; N, 5.62. Found: C, 38.65; H, 3.12; N, 5.71.

1-(Benzyloxymethyl)-6-(2,4-dichlorophenoxymethyl)-5-iodouracil (20a)
Yield: 2.80 g (52%) mp 145–147 °C.

^{1}H NMR (DMSO-d_6/TMS): δ = 4.40 (s, 2 H, CH_2Ph), 5.20 (s, 2 H, CH_2Oaryl), 5.22 (s, 2 H, OCH_2N), 7.10–7.42 (m, 8 H_{aryl}), 12.10 (br s, 1 H, NH).

^{13}C NMR (DMSO-d_6/TMS): δ = 70.8, 71.4, 73.6, 83.1, 116.2, 123.5, 126.6, 127.7, 128.5, 128.6, 128.7, 129.9, 137.6, 149.6, 151.4, 152.3, 160.8.

MS (ESI$^-$): *m*/*z* = 533.0 [M – 1].

Anal. Calcd for $C_{19}H_{15}Cl_2IN_2O_4$ (533.14): C, 42.80; H, 2.84; N, 5.25. Found: C, 42.89; H, 2.77; N, 5.31.

1-(Benzyloxymethyl)-5-chloro-6-(2,4-dichlorophenoxymethyl)uracil (20b)
Yield: 2.60 g (59%); mp 198–200 °C.

^{1}H NMR (DMSO-d_6/TMS): δ = 4.52 (s, 2 H, CH_2Ph), 5.21 (s, 2 H, CH_2Oaryl), 5.44 (s, 2 H, OCH_2N), 7.12–7.71 (m, 8 H_{aryl}), 12.08 (br s, 1 H, NH).

^{13}C NMR (DMSO-d_6/TMS): δ = 64.8, 70.9, 73.5, 112.2, 117.2, 123.6, 126.7, 127.7, 128.0, 128.5, 128.7, 129.9, 137.6, 145.3, 150.6, 152.2, 158.8.

MS (ESI$^-$): *m*/*z* = 442.0 [M – 1].

Anal. Calcd for $C_{19}H_{15}Cl_3N_2O_4$ (441.69): C, 51.67; H, 3.42; N, 6.34. Found: C, 51.70; H, 3.48; N, 6.41.

1-(Benzyloxymethyl)-5-bromo-6-(2,4-dichlorophenoxymethyl)uracil (20c)
Yield: 2.90 g (60%); mp 165–168 °C.

^{1}H NMR (DMSO-d_6/TMS): δ = 4.41 (s, 2 H, CH_2Ph), 5.20 (s, 2 H, CH_2Oaryl), 5.38 (s, 2 H, OCH_2N), 7.21–7.65 (m, 8 H_{aryl}), 11.95 (br s, 1 H, NH).

^{13}C NMR (DMSO-d_6/TMS): δ = 67.3, 70.9, 73.6, 116.4, 117.2, 123.6, 126.7, 127.8, 128.0, 128.5, 128.7, 129.9, 137.7, 146.9, 150.6, 152.3, 159.8.

MS (ESI$^-$): *m*/*z* = 486.9 [M – 1].

Anal. Calcd for $C_{19}H_{15}BrCl_2N_2O_4$ (486.14): C, 46.94; H, 3.11; N, 5.76. Found: C, 46.99; H, 3.06; N, 5.83.

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References

(1) Richman, D. D.; Fischl, M. A.; Grieco, M. H.; Gottieb, M. S.; Volberding, P. A.; Lasin, O. L.; Leedon, J. M.; Groopman, J. E.; Mildran, D.; Hirsch, M. S.; Jackson, G. G.; Durack, D. T.; Lehrman, N. S.and the AZT Collaborative Working Group*N. Engl. J. Med.* **1987**, *317*, 192.
(2) Yarchoan, R.; Mitsuya, H.; Thamas, R. V.; Pluda, J.; Hartman, N. R.; Perno, C. F.; Marczyck, K. S.; Allain, J. P.; Johns, D. G.; Broder, S. *Science* **1989**, *245*, 412.
(3) Larder, B. A.; Darby, G.; Richman, D. V. *Science* **1989**, *243*, 1731.
(4) (a) Roy-Burman, P. *Analogues of Nucleic Acid Components*; Springer-Verlag: New York, **1970**. (b) Goodman, L. In *Basic Principles in Nucleic Acid Chemistry*, Vol. 1; Ts'V, P. O. P., Ed.; Academic Press: New York, **1974**, 146. (c) Uesugi, S.; Ikehara, M. *Chem. Pharm. Bull.* **1978**, *26*, 3040.
(5) (a) Baba, M.; De Clercq, E.; Tanaka, H.; Ubasawa, M.; Takashima, H.; Sekiya, K.; Nitta, I.; Umezu, K.; Walker, R. T.; Mori, S.; Ito, M.; Shigeta, S.; Miyasaka, T. *Mol. Pharmacol.* **1993**, *39*, 805. (b) Pontkis, R.; Benhida, R.; Aubertin, A. M.; Grierson, D. S.; Monneret, C. *J. Med. Chem.* **1997**, *40*, 1845. (c) Kim, D. K.; Gam, J.; Kim, Y. W.; Lim, J.; Kim, H. T.; Kim, K. H. *J. Med. Chem.* **1997**, *40*, 2363.
(6) (a) Niedballa, U.; Vorbrüggen, H. *J. Org. Chem.* **1974**, *39*, 3654. (b) Niedballa, U.; Vorbrüggen, H. *J. Org. Chem.* **1976**, *41*, 2084. (c) Vorbrüggen, H.; Krolikiewiecz, K.; Bennua, B. *Chem. Ber.* **1981**, *114*, 1234.
(7) (a) Andersen, G. W.; Halverstadt, I. F.; Miller, W. H.; Roblin, R. O. Jr. *J. Am. Chem. Soc.* **1945**, *67*, 2197. (b) Eltelbani, E. M.; Elshehry, M. F.; Nawwar, G. A. M. *Monatsh. Chem.* **2008**, *139*, 685.
(8) Johnson, T. B.; Ambelang, J. C. *J. Am. Chem. Soc.* **1938**, *60*, 2941.
(9) Donleavy, J. J.; Kise, M. A. *Org. Synth. Coll. Vol. II*; Wiley: New York, **1943**, 422; *Org. Synth.* **1937**, *17*, 63.
(10) Asakura, J.-I.; Robins, M. J. *J. Org. Chem.* **1990**, *55*, 4928.
(11) Jourdan, F.; Laduree, D.; Robba, M. *J. Heterocycl. Chem.* **1994**, *31*, 305.

(12) All new compounds were evaluated concerning their ability to inhibit the replication of HIV in T-lymphocytes cells. Briefly, a CEM cell suspension was infected with HIV-1 or HIV-2. The mutant thymidine kinase-deficient CEM cell cultures were only infected with HIV-2. Then, 100 μL of the infected cell suspensions was transferred into 96-well microtiter plate wells and mixed with 100 μL of the appropriate dilutions of the test compounds. After 4–5 days, giant cell formation was recorded microscopically in the HIV-infected cell cultures.

(13) Balzarini, J.; Karlsson, A.; De Clercq, E. *Mol. Pharmacol.* **1993**, *44*, 694.