Synthesis and Biological Activities of Novel *s*-Triazine Bridged Dinucleoside Analogs

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A series of novel dinucleosides linked by *s*-triazine were synthesized via the nucleophilic substitution reaction of amino nucleoside and cyanuric chloride in THF/H_2O. The biological activities of these novel dinucleoside analogs against HIV-RT, HeLa and A-549 cell lines *in vitro* were evaluated.

Keywords dinucleoside, *s*-triazine, HIV-RT inhibition, cyanuric chloride

Introduction

The synthesis of nucleoside analogs has been the hot topic in the past decades due to their potential application as anticancer and antiviral therapeutic agents.[1] To meet the ever-growing requirements in the discovery of new drugs, various modifications on the heterocyclic bases and/or the sugar moiety have been approached,[2] such as heterocyclic-sugar nucleosides,[3] spirocyclic nucleosides,[4] two-headed nucleosides,[5] dinucleosides,[6] *etc*. Among them, the chemically modified dinucleoside analogs have attracted great attentions because of their promising biological activities and potential applications as a building block for preparing backbone-modified oligonucleotides for DNA repair or mutation in functional genomics.[7] Furthermore, the most modification of dinucleotides focused on the replacement of the phosphate linkage in order to improve the affinity, stability, resistance, and membrane permeability or cellular uptake,[8] and the dinucleoside analogs linked by thioacetamido,[9] guanidinium,[10] carbonate[11] and butadiynyl group[12] have been reported. Recently, a new type of dinucleoside analogs linked by heterocycle[13] have also been synthesized. These dinucleoside analogs could be regarded as a special "triple headed" dinucleoside sharing one base, and would exhibit selective affinity to DNA by simultaneous and synergitic interaction and recognition with three complementary bases.[14]

s-Triazine derivatives are of broad range of biological activity[15] and the triazine scaffold provides a basis for the design of biologically relevant molecule.[16] Nucleoside analogs containing an *s*-triazine moiety, such as Decitabine (aza-dCyd) (**A**) and Vidaza (aza-Cyd) (**B**) (Figure 1), have been approved by FDA to be used in clinic as anticancer agents.

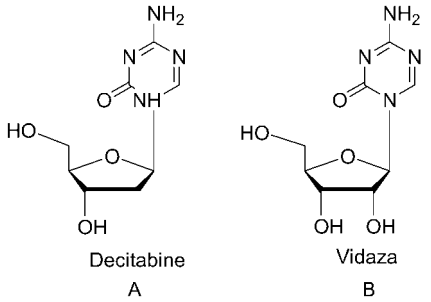

Figure 1 Structure of nucleoside analogs having *s*-triazine analogs.

From the above points of view, we envisaged to connect two nucleoside moieties with an *s*-triazine ring because such "triple headed" dinucleoside sharing *s*-triazine would be beneficial to simultaneously building and recognizing three complementary bases via base pairing rules.[17,5] In this paper, a series of novel "triple headed" dinucleoside analogs (**1**) have been conveniently synthesized by stepwise nucleophilic substitutions of amino nucleosides with cyanuric chloride as shown in Scheme 1. Their biological activities against HIV-RT, and HeLa and A-549 cell lines were also preliminarily evaluated.

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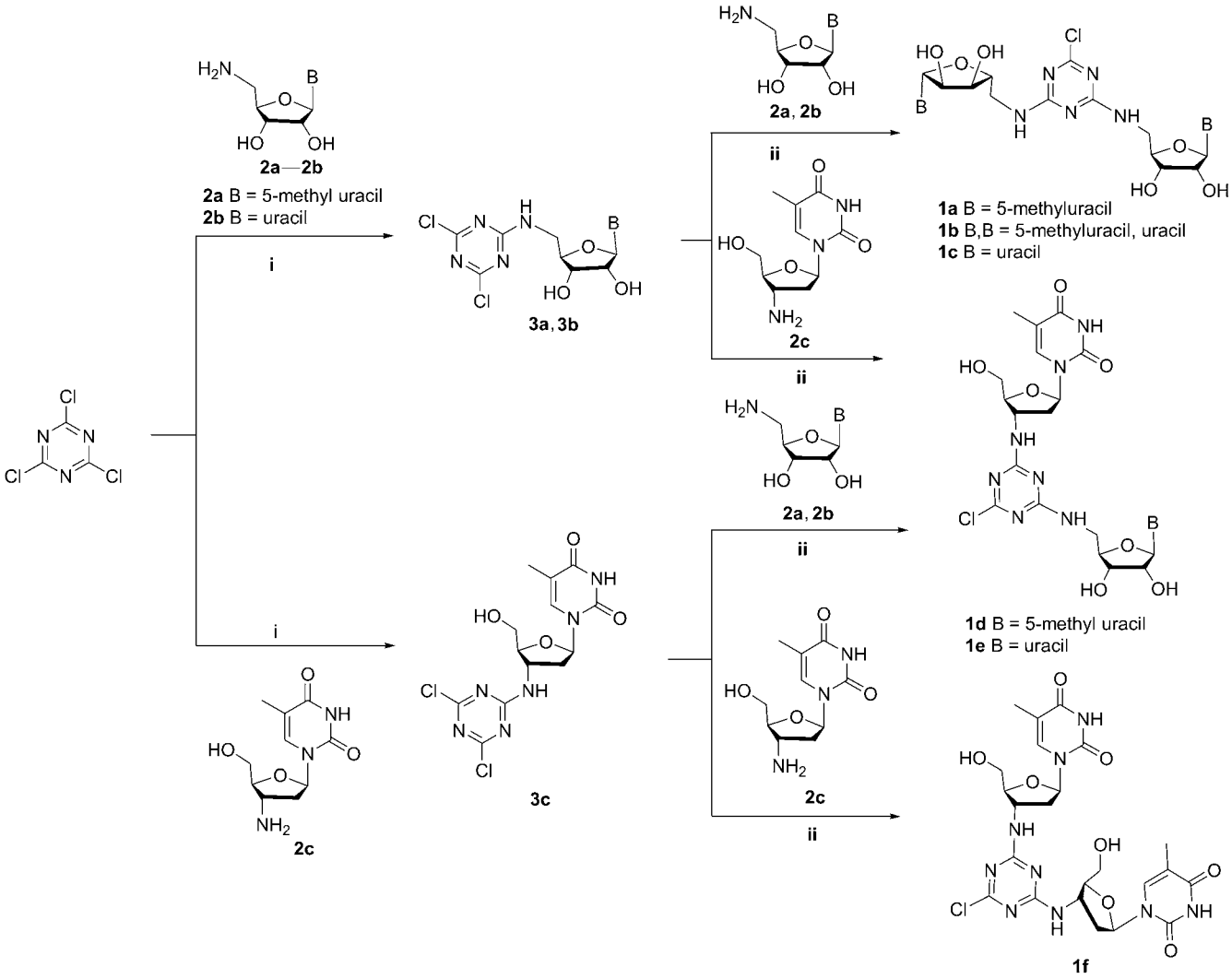
Scheme 1



Reagents and conditions: (i) DIPEA, THF/H_2O, 0 ℃; (ii) DIPEA, THF/ H_2O, 55 ℃.

Experimental

Materials and instruments

Melting points were measured on a SGW$^{@}$X-4 micro melting point apparatus and uncorrected. Optical rotations were determined on a SGW$^{@}$-1 automatic polarimeter. ^{1}H NMR and ^{13}C NMR spectra were measured on an RT-NMR Bruker AVANCE 400 (400 MHz) and an RT-NMR Bruker AVANCE 600 (600 MHz) NMR spectrometer using tetramethylsilane (Me_4Si) as an internal standard. Mass spectra (MS) and high resolution mass spectra (HRMS) were carried out on an FTICR-MS (Ionspec 7.0T) mass spectrometer with electrospray ionization (ESI). The optical densities for examining the activity of HIV-RT inhibition was measured on a BioRad Model 3550 microplate spectrophotometer. Anticancer activity was evaluated using MTT assay. Thin-layer chromatography (TLC) was performed on precoated plates (Qingdao GF254) with detection by UV light or with phosphomolybdic acid in EtOH/H_2O followed by heating. Column chromatography was performed using SiO_2 (Qingdao 200—300 mesh or 300—400 mesh). Solvents were distilled and dried immediately prior to use.

General procedure for the synthesis of compounds 3a—3c

To a solution of **2c** (1.2 g, 5.0 mmol) and cyanuric chloride (1.8 g, 10.0 mmol) in THF (30 mL) was added *N*,*N*-diisopropylethlamine (DIPEA) (1.0 mL, 6.0 mmol) under nitrogen atmosphere at 0 ℃. The reaction was monitored by TLC [$V(CH_2Cl_2)$ ∶ $V(CH_3OH)$ = 4 ∶ 1]. After the reaction is completed, the solvent was evaporated and the residue was applied on column chromatography with the eluent of CH_2Cl_2 and CH_3OH (V ∶ V = 20 ∶ 1) to get compound **3c** (330 mg, 85%). Similarly, nucleoside analogs **3a** and **3b** were synthesized from nucleosides **2a** and **2b** in yields of 64% and 35%, respectively.

3a: White solid, 64%; m.p. 174—176 ℃; ^{1}H NMR

(DMSO-d_6, 400 MHz) δ: 1.73 (s, 3H, CH_3), 3.44—3.59 (m, 2H, CH_2-5'), 3.82—3.88 (m, 2H, CH-2', CH-3'), 4.06 (s, 1H, H-4'), 5.16 (s, 1H, OH), 5.35 (s, 1H, OH), 5.66 (d, J=5.88 Hz, 1H, CH-1'), 7.41 (s, 1H, CH-6), 9.24—9.27 (m, 1H, NH), 11.30 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 12.83, 43.93, 71.65, 72.88, 82.14, 89.24, 110.59, 137.47, 151.62, 164.50, 166.56, 169.50, 170.364; HRMS calcd for $C_{13}H_{14}Cl_2N_6O_5$ 404.0402, found 404.0398.

3b: White solid, 35%; m.p. 132—134 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.57 (s, 2H, CH_2-5'), 3.89—3.92 (m, 2H, CH-2', CH-3'), 4.12 (s, 1H, CH-4'), 5.29 (s, 1H, OH), 5.47 (s, 1H, OH), 5.63 (d, J=8.04 Hz, 1H, CH-5), 5.72 (d, J=5.56 Hz, 1H, CH-1'), 7.69 (d, J=8.04 Hz, 1H, CH-6), 9.32 (s, 1H, NH), 11.38 (s, 1H, NH); ^{13}C NMR (CD_3OD, 100 MHz) δ: 43.24, 71.51, 73.69, 82.33, 91.88, 102.01, 142.12, 150.50, 151.26, 165.01, 166.80, 169.91, 170.59; HRMS calcd for $C_{12}H_{12}Cl_2N_6O_5$ 390.0746, found 390.0713.

3c: White solid, 85%; m.p. 233—235 ℃; ^{1}H NMR (DMSO-d_6, 600 MHz) δ: 1.79 (s, 3H, CH_3), 2.21—2.36 (m, 2H, CH_2-2'), 3.62—3.69 (m, 2H, CH_2-5'), 3.94—3.96 (q, J=5.40, 11.40 Hz, 1H, CH-3'), 4.49—4.55 (m, 1H, CH-4'), 6.20 (t, J=10.20, 21.00 Hz, 1H, CH-1'), 7.78 (s, 1H, CH-6), 9.54 (d, J=10.8 Hz, 1H, NH), 11.31 (s, 1H, NH-3); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 12.23, 36.56, 51.47, 61.37, 83.58, 84.05, 109.48, 136.13, 150.35, 163.71, 164.96, 168.54, 169.32; HRMS calcd for $C_{13}H_{14}Cl_2N_6O_4$ 388.0453, found 388.0428.

General procedure for the synthesis of compounds (1a—1f)

To a solution of **3c** (300 mg, 0.8 mmol) in THF (30 mL) was added DIPEA and amino nucleoside derivative **2a** (297 mg, 1.2 mmol). The mixture was stirred at 55 ℃ for 2 h, and water (1 mL) was added. The reaction progress was monitored by TLC [V(CH_2Cl_2) ∶ V(CH_3OH)=20∶1]. After the solvent was evaporated under reduced pressure, the residue was submitted to column chromatography [V(CH_2Cl_2) ∶ V(CH_3OH) = 20∶1] to afford the dinucleoside derivative **1d** (250 mg, 53%). Following the same procedure, the dinucleoside derivatives **1a**—**1c** and **1f** were prepared.

1a: White solid, 30%; m.p. 230 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.76 (s, 6H, CH_3), 3.45—3.52 (m, 4H, CH-5'), 3.89—3.94 (m, 4H, CH-2', CH-3'), 4.07 (s, 2H, CH-4'), 5.13 (s, 1H, OH), 5.18 (s, 1H, OH), 5.37 (s, 2H, OH), 5.72 (s, 1H, CH-1'), 5.74 (s, 1H, CH-1'), 7.40—7.45 (m, 2H, H-6), 8.00—8.10 (m, 2H, NH), 11.31 (s, 2H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 12.74, 43.13, 71.68, 72.92, 82.60, 82.9, 88.86, 110.55, 137.34, 151.66, 164.49, 166.60, 169.24, 169.80; HRMS calcd for $C_{23}H_{28}ClN_9O_{10}$ 625.1649, found 625.1614.

1b: White solid, 33%; m.p. 214—216 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.84 (s, 3H, CH_3), 3.59—3.60 (m, 4H, CH_2-5'), 3.99—4.00 (m, 4H, CH-2', CH-3'), 4.15—4.18 (m, 2H, CH-4'), 5.19—5.29 (m, 2H, OH), 5.43—5.50 (m, 2H, OH), 5.67—5.70 (m, 1H, CH-1'), 5.79—5.81 (m, 2H, CH-1', CH-5), 7.48—7.52 (m, 1H, CH-6), 7.69—7.79 (m, 1H, CH-6), 8.07—8.16 (m, 2H, NH), 11.4 (s, 2H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 11.93, 42.31, 48.56, 70.62, 70.82, 71.88, 72.10, 81.91, 82.07, 87.55, 87.91, 101.93, 109.68, 136.41, 141.16, 150.74, 150.81, 162.97, 163.65, 165.56, 167.84, 168.25; HRMS calcd for $C_{22}H_{26}ClN_9O_{10}$ 611.1490, found 611.1452.

1c: White solid, 34%; m.p. 192—194 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.47—3.53 (m, 4H, CH_2-5'), 3.90—3.93 (m, 4H, CH-3', CH-4'), 4.08 (s, 2H, CH-2'), 5.15 (s, 1H, OH), 5.19 (s, 1H, OH), 5.40 (s, 2H, OH), 5.59—5.63 (m, 2H, CH-5), 5.72—5.74 (m, 2H, CH-1'), 7.92—7.98 (m, 2H, CH-6), 8.02—8.05 (m, 2H, NH), 11.33 (s, 2H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 43.30, 71.61, 73.14, 73.40, 82.97, 89.23, 102.81, 142.03, 151.59, 163.83, 166.54, 169.20, 169.81; HRMS calcd for $C_{21}H_{24}ClN_9O_{10}$ 597.1334, found 597.1364.

1d: White solid, 53%; m.p. 188—190 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.76—1.79 (m, 6H, CH_3), 2.19—2.31 (m, 2H, CH_2-2'), 3.54—3.67 (m, 5H, CH_2-5', CH-2'), 3.88—3.96 (m, 2H, CH-3'), 4.05 (q, J=5.60, 11.60 Hz, 1H, CH-4'), 4.46—4.49 (m, 1H, CH-4'), 5.74 (d, J=6.00 Hz, 1H, CH-1'), 6.22—6.25 (m, 1H, CH-1'), 7.37—7.46 (m, 1H, H-6), 7.73—7.83 (m, 1H, H-6), 11.28 (d, J=8.00 Hz, 1H, NH), 11.34 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 11.93, 12.18, 36.50, 41.96, 51.05, 61.56, 70.54, 71.88, 81.90, 83.48, 84.64, 87.31, 109.32, 109.68, 136.18, 136.40, 150.34, 150.80, 163.68, 163.74, 164.95, 165.57, 167.83; HRMS calcd for $C_{23}H_{28}ClN_9O_9$ 609.1698, found 609.1673.

1e: White solid, 44%; m.p. 182—184 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.78 (s, 3H, CH_3), 2.20—2.27 (m, 2H, CH_2-2' (AZT)), 3.46—3.65 (m, 4H, CH_2-5'), 4.07 (s, 1H, CH-4'), 4.41—4.48 (m, 1H, CH-4'), 5.09—5.15 (m, 2H, CH-3'), 5.41 (d, J=5.80 Hz, 1H, CH-2'), 5.61 (m, 1H, CH-5), 5.72 (d, J=5.92 Hz, 1H, CH-1'), 6.14 (m, 1H, CH-1'), 7.61—7.82 (m, 2H, CH-6), 11.26 (d, J=7.36 Hz, 1H, NH), 11.34 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 168.35, 166.02, 165.49, 164.24, 163.59, 151.20, 150.92, 141.63, 136.70, 110.05, 102.40, 88.50, 85.08, 84.04, 82.43, 72.64, 71.17, 61.95, 51.33, 42.69, 37.04, 12.63; HRMS calcd for $C_{22}H_{26}ClN_9O_9$ 595.1541, found 595.1535.

1f: White solid, 51%; m.p. 250 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.72 (s, 3H, CH_3), 2.19 (s, 2H, CH_2-2'), 3.59 (s, 2H, CH_2-5'), 3.83 (s, 1H, H-4'), 4.42 (s, 1H, H-3'), 5.02 (d, J=7.74, 1H, OH), 6.15 (s, 1H, H-1'), 7.66 (s, 1H, H-6), 8.31 (d, J=5.84 Hz, 1H, NH), 11.25 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 13.03, 37.73, 51.72, 62.37, 84.90, 85.61, 110.38, 137.02, 151.27, 164.54, 165.77, 168.75, 169.07; HRMS calcd for $C_{23}H_{28}ClN_9O_8$ 593.1749, found 593.1723.

Biological activity assay

Antitumor activity[18]

The cytotoxicity of the compounds was evaluated

using HeLa (human cervical cancer cell line) and A-549 (human lung adenocarcinoma epithelial cell line) cell lines by the modified Mosmann's protocol as follows: Briefly, cells (10^4 cells per well) were plated in 96-well culture plates and cultured overnight at 37 ℃ in a 5% CO_2 humidified incubator. Compounds were added to the wells at final concentrations of 1, 10, and 100 μmol/L. Control wells were prepared by the addition of DMEM. Wells containing DMEM without cells were used as blanks. The plates were incubated at 37 ℃ in a 5% CO_2 incubator for 48 h. Upon completion of the incubation, stock MTT dye solution (10 μL, 5 mg/mL) was added to each well. After 4 h incubation, the supernatant was removed and DMSO (100 mL) was added to solubilize the MTT. The optical density of each well was measured on a microplate spectrophotometer at a wavelength of 570 nm. The inhibition rate was calculated according to the formula: $(OD_{control} - OD_{treated})/ODcontrol \times 100\%$.

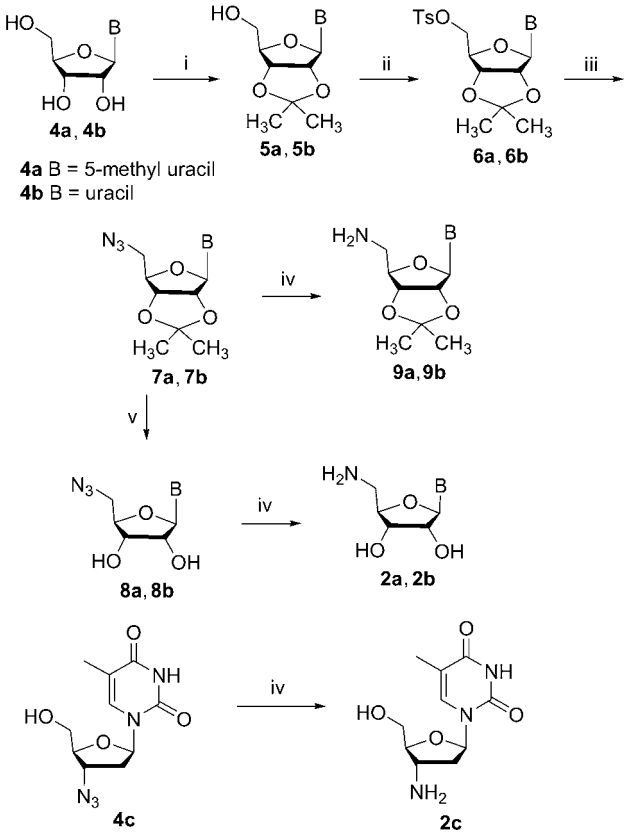
HIV-RT kit assay

The HIV-RT inhibition assay was performed by using an RT assay kit (Roche), and the procedure for assaying RT inhibition was performed as described in the kit protocol. Briefly, the reaction mixture consists of template/primer complex, 2'-deoxy-nucleotide-5'-triphosphates (dNTPs) and reverse transcriptase (RT) enzyme in the lysis buffer with or without inhibitors. After 1 h incubation at 37 ℃ the reaction mixture was transferred to streptavidin-coated microtitre plate (MTP). The biotin labeled dNTPs that are incorporated in the template due to the activity of RT were bound to streptavidin. The unbound dNTPs were washed using wash buffer and antidigoxigenin-peroxidase (DIG-POD) was added in MTP. The DIG-labeled dNTPs incorporated in the template were bound to anti-DIG-POD antibody. The unbound anti-DIG-POD was washed and the peroxide substrate (ABST) was added to the MTP. A colored reaction product was produced during the cleavage of the substrate catalyzed by a peroxide enzyme. The absorbance of the sample was determined at OD 405 $nmol \cdot L^{-1}$ using microtiter plate ELISA reader. The resulting color intensity is directly proportional to the actual RT activity. The percentage inhibitory activity of RT inhibitors was calculated by comparing to a sample that does not contain an inhibitor. The percentage inhibition was calculated by formula as given below: Inhibition = 100% − [($OD_{405\ nm}$ with inhibitor/$OD_{405\ nm}$ without inhibitor) × 100%].

Results and discussion

The requisite raw materials **2** (amino nucleosides) were synthesized from commercially available nucleosides 5-methyl uridine (**4a**) and uridine (**4b**) according to the literature procedure,[19] and compound **2c** was prepared from azidothymidine (**4c**) via the reduction of azido, as shown in Scheme 2.

Scheme 2



Reagents and conditions: (i) acetone, H_2SO_4, r.t.; (ii) TsCl, pyridine, r.t.; (iii) NaN_3, DMF, 80 ℃; (iv) PPh_3, H_2O or Pt/C (10%), H_2; (v) TFA/H_2O (90%), r.t.

The nucleophilic substitution of cyanuric chloride was mainly carried out in THF solution.[20] At first, the 2,3-propylidene protected nucleoside (**9a**) was used as the starting material for approaching the preparation of the dinucleoside, and the successive two-step substitutions were carried out smoothly and provided the corresponding dinucleoside analog **11a** as shown in Scheme 3. However, the following deprotection of 2,3-propylidene could not proceed well under the conventional condition, which gave the desired product in a poor yield less than 10%. Then, we tried to use compound **2a** without protective group as the starting material for the synthesis of the dinucleosides. After careful examination on various conditions, the reaction was found to undergo smoothly in THF solution containing a small amount of H_2O by improving the solubility of compounds **2**, and could directly afford the desired dinucleosides **1** as shown in Scheme 1. Thus, the solution of **2a** in THF with minimal water was stirred at ice bath for 10 min, then cyanuric chloride and *N*,*N*-diisopropylethylamine (DIPEA) were added and was stirred for another 30 min to afford the corresponding monosubstitution product **3a** in 63% yield (Scheme 1). The disubstituted **1a** was obtained in 30% upon treatment of **2a** with **3a** in presence of DIPEA at 55 ℃. Under the

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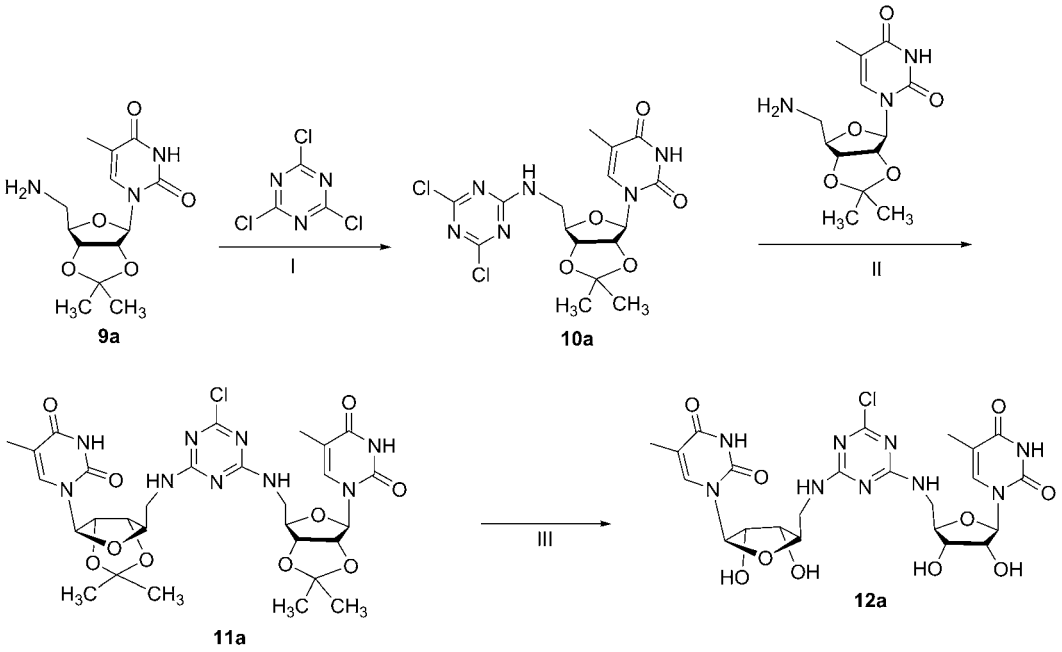
Scheme 3



Reagents and conditions: (i) DIPEA, THF, 0 ℃; (ii) DIPEA, THF, 55 ℃; (iii) TFA/H_2O (90%).

same conditions, the dinucleoside analogs **1b—1f** were synthesized. It should be mentioned that the synthesis of such trinucleoside analog connected with triazine was also attempted, but no desired product was obtained, possibly due to the lower reactivity of the chlorine on triazine in compound **1** and their steric effect.[12]

HIV-1 reverse transcriptase (RT) inhibitory and antitumor activities of nucleoside analogs **1** and **3** were evaluated. Their cytotoxicity was examined using HeLa (human cervical cancer cell) and A-549 (human lung adenocarcinoma epithelial cell) by the modified Mosmann's protocol[18] and the results are summarized in Table 1. It could be seen from Table 1 that some of the compounds **1** showed good inhibitory activities against the HeLa and A-549, for instance, compounds **1c** and **1e** exhibited inhibitory activity to HeLa cells with the IC_{50} of 8.6 and 10.5 μmol•L^{-1}, respectively. Moreover, the intermediates **3**, which would be regarded as "double headed" nucleoside analogs, gave a high selectivity against HeLa cells. However, compounds **1** and **3** displayed very weak activity against HIV-RT incomparison to the control AZT.

Table 1 Anticancer activities of nucleoside analogs **1** and **3** against HeLa and A-549 cells

Compound	IC_{50}/(μmol•L^{-1})	
	A-549	HeLa
1a	74.2±1.0	48.2±0.2
1b	>100	>100
1c	60.0±1.3	8.6±0.3
1d	>100	52.7±0.8
1e	20.8±1.4	10.5±0.2
1f	>100	>100
3a	>100	32.5±0.9
3b	>100	41.6±0.8
3c	>100	77.9±0.8

Conclusions

In summary, we have synthesized a series of novel *s*-triazine linked "triple headed" dinucleoside analogs **1** by stepwise substitutions of unprotected nucleosides with cyanuric chloride. Some of the compounds, such as **1c** and **1e**, showed good *in vitro* inhibitory activity against human cervical cancer cell (HeLa), but none of them exhibited anti-HIV-RT activity. The further synthesis and biological study for the similar novel heterocycle-linked dinucleoside analogs are underway in this laboratory.

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