

Article

Synthesis of Novel Homo-*N*-Nucleoside Analogs Composed of a Homo-1,4-Dioxane Sugar Analog and Substituted 1,3,5-Triazine Base Equivalents

Qiang Yu ¹, Dirk Schwidom ², Alexander Exner ² and Per Carlsen ^{1,*}

¹ Department of Chemistry, Norwegian University of Science and Technology (NTNU), N-7491 Trondheim, Norway; E-mail: qiang.yu@chem.ntnu.no (Q. Y.)

² Socrates exchange student: Department of Chemistry, University of Hamburg, D-20146 Hamburg, Germany

* Author to whom correspondence should be addressed. E-mail: per.carlsen@chem.ntnu.no; Fax: +47 73594256.

Received: 7 November 2008; in revised form: 21 November 2008 / Accepted: 3 December 2008 /

Published: 10 December 2008

Abstract: Enantioselective syntheses from dimethyl tartrate of 1,3,5-triazine homo-*N*-nucleoside analogs, containing a 1,4-dioxane moiety replacing the sugar unit in natural nucleosides, were accomplished. The triazine heterocycle in the nucleoside analogs was further substituted with combinations of NH₂, OH and Cl in the 2,4-triazine positions.

Keywords: 1,3,5-Triazine; 1,4-Dioxane; Nucleoside analogue; Heterocycle; Homo-*N*-nucleoside; Nucleoside analogs.

Introduction

Nucleoside analogs represent a potentially important class of medicinal active agents that have found uses in antitumor and antiviral drugs [1]. However, some drugs such as AZT [2-3], ddI [3], 3TC [4], are rapidly becoming less effective due to the developing drug resistance. Multi-drug resistance is a serious problem also for chemo- and anticancer therapy. In addition some drugs exhibit a variety of

side effects. Therefore, it is desirable to develop new, active nucleoside analogs for application in medicine.

It is interesting to note that purines, amino derivatives of 1,3,5-triazines (also named *s*-triazines) and substituted guanines were found in the Orgueil meteorite [5-6]. The presence of *s*-triazines was interesting, since the various 1,3,5-triazines can be formed from hydrogen cyanide, ammonia and water, components believed to be plentiful in the primordial soup. Triazines may therefore have been abundant on early Earth [7]. The interesting question therefore arises as to what extent these triazines have played a role in the evolution of the original RNA [8].

The 1,3,5-triazine heterocyclic system is today found in a number of bioactive molecules such as herbicides and pharmaceutical products [9]. Various triazine substituted molecules exhibit diverse biological activities, having thus been reported as potentially cardiotoxic [10-11], anti-HIV [12-13], antitumor [14] and anticancer agents [15]. Some triazines have found clinical applications. Hexamethylmelamine (HMM) has for example been used as antitumor agents [16]. Therefore nucleoside analogues containing triazines as the nucleic base equivalents are interesting subjects to study [17-18].

In the solid state 2-amino-4,6-dichloro-1,3,5-triazine form a ribbon structure of hydrogen bonded dimers [19]. Triazine oligomers were shown to self-assemble in duplex-strand structures [20]. Amino substituted triazine based oligomers and cyclic receptor molecules have also been studied [21]. Like the natural complementary pyrimidine and purine nucleic bases forming associates through hydrogen bonds as observed in the nucleic acid structures, amino and hydroxyl substituted triazines can self-assemble into supramolecular structures through the formation of hydrogen bonds [22-23]. A typical example of such associates is sketched in Figure 1. In addition, it has been observed that triazine derivatives, for example 2,6-diamino-1,3,5-triazines, may function as purine mimics and can recognize pyrimidines, forming associates with for example uracils or thymines through hydrogen bonding [24-26], Figure 2.

Figure 1. Interaction between NH₂ and OH substituted triazines.

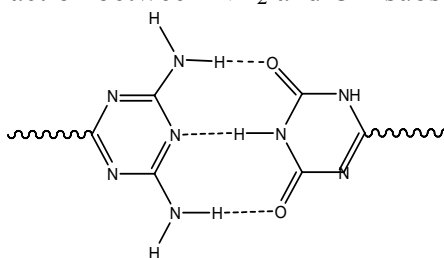
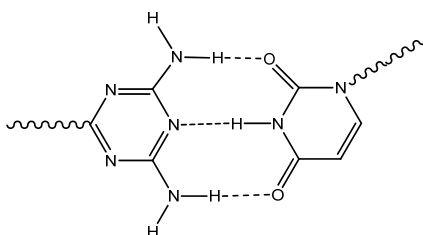
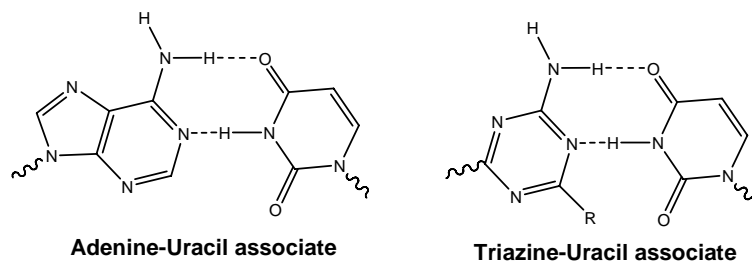


Figure 2. Interaction between triazine and uracil structures.



Monoaminotriazine nucleoside analogs also represent interesting structures, as they may mimic adenines, forming associates with uracil analogs, Figure 3.

Figure 3. Interaction between nucleic bases (adenine-uracil) and monoaminotriazine derivatives with uracil.

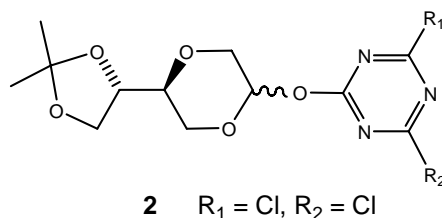


These observations suggest the use of triazine nucleoside analogs as leads for the development of new nucleoside and nucleotide analogs for medicinal application. Considering the potential applications of the 1,3,5-triazine based systems, surprisingly few triazine nucleoside analogs or triazine glycosides have been reported in the literature [27-31]. For these reasons we found it viable to initial a study of the synthesis of triazine based nucleoside analogs.

Results and Discussion

Rather than applying the five-membered sugars found in the natural nucleosides, we targeted on the application of the more robust and more flexible sugar analogs containing the 1,4-dioxane moiety, for example compound **1**, whose synthesis has been reported in a previous publication [32]. Compound **1**, containing an unnatural sugar analog may also prove to be robust in biologic systems, as enzymes may not find pathways to convert the unnatural nucleoside system. The synthesis of the triazine *O*-nucleoside analogs **2**, in which a 1,4-dioxane sugar moiety was connected to a dichloro substituted triazine ring system via an ether linkage at the anomeric position (Figure 4) was thus the initial synthetic goal.

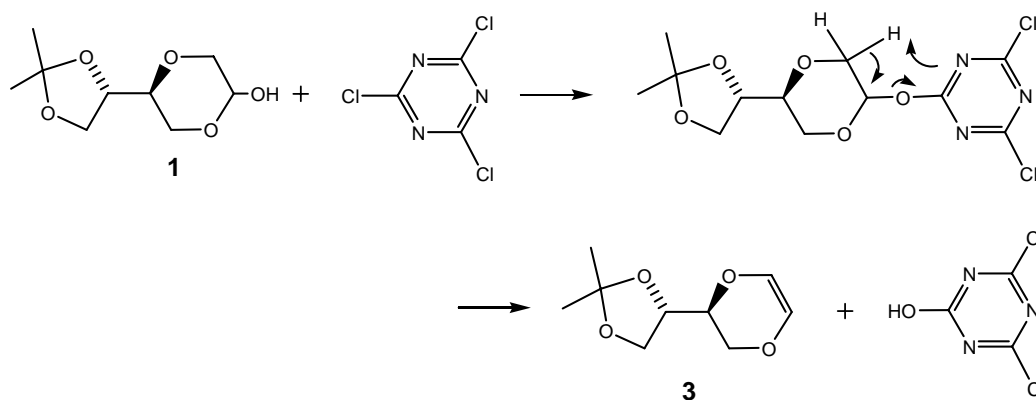
Figure 4. Triazine nucleoside analogs.



Preparation of this structure was attempted from the 1,4-dioxane sugar analog **1**, by its reaction with 2,4,6-trichlorotriazine. However, all attempts failed to give the desired product, as formation of the elimination product **3** always predominated (Scheme 1). This was surprising, as triazine glycosides are known [30]. However, in the 1,4-dioxane system, the CH₂-group neighboring the anomeric -OH group may here actually facilitate an elimination reaction pathway, providing instead product **3**, which was

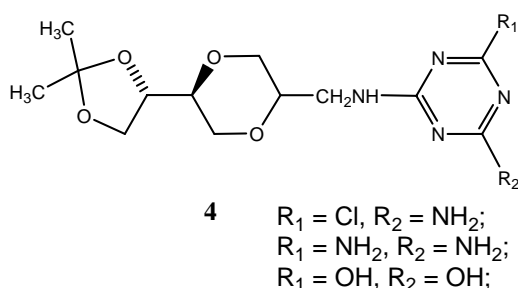
isolated and the structure confirmed by NMR spectroscopy. As a spin-off of this observation, we are currently exploring the possible use of chlorotriazine as an elimination reagent for the formation of alkenes from alcohols.

Scheme 1. Reaction of 1,4-dioxane sugar analog **1** with 2,4,6-trichlorotriazine.



The observed instability of the triazine *O*-nucleoside analog **2** (Scheme 1), prompted us to design the potentially more stable triazine homo-*N*-nucleoside analogs, **4** (Figure 5). *N*-glycosidic nucleoside analogs represent a known, well established class of stable modified nucleosides [33-37]. For increased stability, the linking ether group was thus replaced by the corresponding $-\text{CH}_2\text{-NH}-$ linker. This was expected to result in a conformationally more flexible but also a chemically and biologically more stable structure. Hence, the alternative structures **4**, became the new targets. Nucleophilic, aromatic substitution readily takes place with chlorosubstituted triazines. Therefore, we could conveniently adopt a general synthetic procedure in which variously substituted chlorotriazines were reacted with for example the amino sugar analogues **5** (Scheme 2).

Figure 5. Structure of triazine homo-*N*-nucleoside analogs.

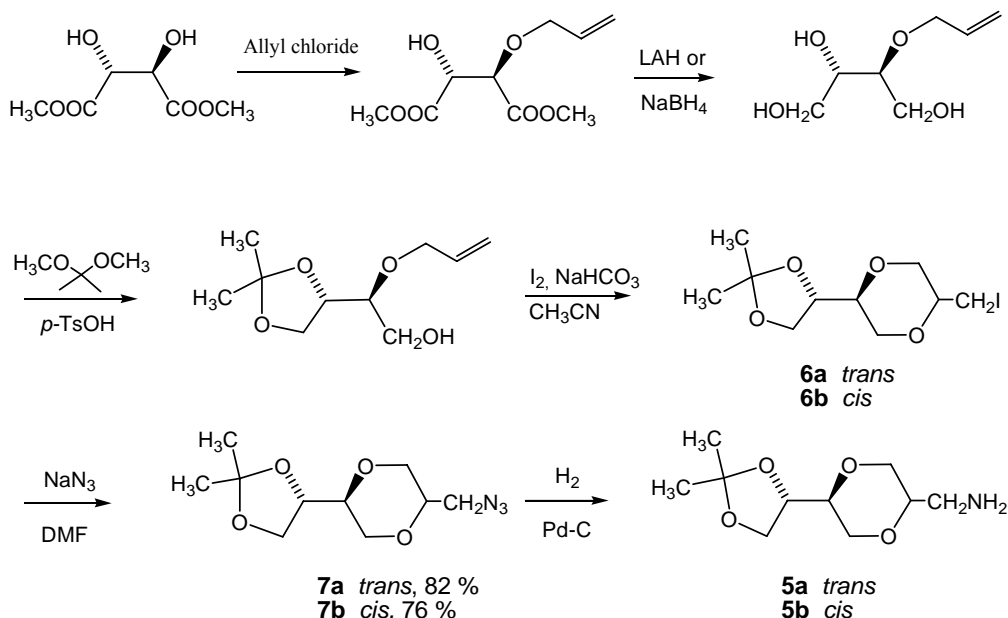


For the purpose of constructing triazine nucleoside analogs that may function as complementary bases to the naturally occurring bases, controlled substitution in the 2- and 4-positions of the triazine heterocyclic system was investigated. Thus, the triazine may be substituted with various combinations of H, OH and NH_2 groups. The combinations that included H were not prepared, but instead chloro substituted triazines were used. Chloro-substituted purine and pyrimidine systems have also found uses in medicinal chemistry. The OH- / NH_2 substituted triazine may correspond to the nucleobases

cytosine and guanine, while the OH / OH combination corresponds to uracil and thymine. It has previously been reported that such triazine systems may form hydrogen bond with the complementary natural bases [38].

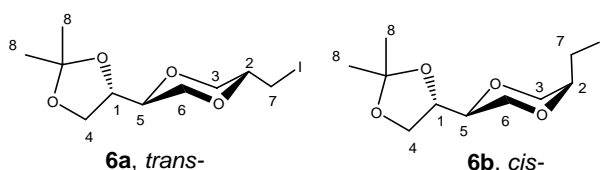
The enantiomerically pure homo amino sugar analogs **5a** and **5b** were readily prepared from iodides **6a** and **6b** by the reaction with sodium azide in DMF [39-40], to give azides **7a** and **7b** in 76 and 82 % yields, respectively. Subsequent hydrogenolysis of the azides using Pd-C as the catalyst readily provided the corresponding amines **5a** and **5b**, respectively, in essentially quantitative yields. Iodides **6** were obtained from (2*R*,3*R*)-dimethyl tartrate as previously reported [41] according to the reaction sequence shown in Scheme 2. Product **6** was isolated as an approximately 1:1 diastereomeric mixture of *trans*-**6a** and *cis*-**6b**. The application of the tartrates as starting materials, readily available from the chiral pool, conveniently allow for the synthesis of all the possible stereoisomers of the target molecules.

Scheme 2. Synthesis of homo amino-1,4-dioxane *pseudo*-sugar **5a** and **5b**.



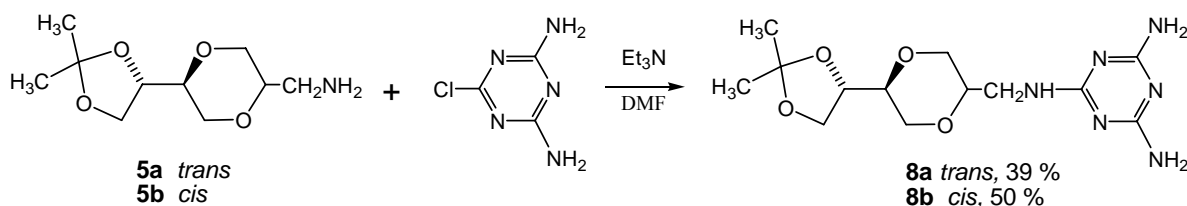
Structures **6a** and **6b** were established by NMR spectroscopy. Thus, product **6a** exhibited a large H-2/H-3 coupling constant (10.2 Hz), which was in agreement with an axial H-2 proton. The corresponding coupling constant (3.6 Hz) observed for compound **6b** was in agreement with the corresponding *cis*-isomer configuration (Figure 6).

Figure 6. Molecular structures **6a** and **6b**.



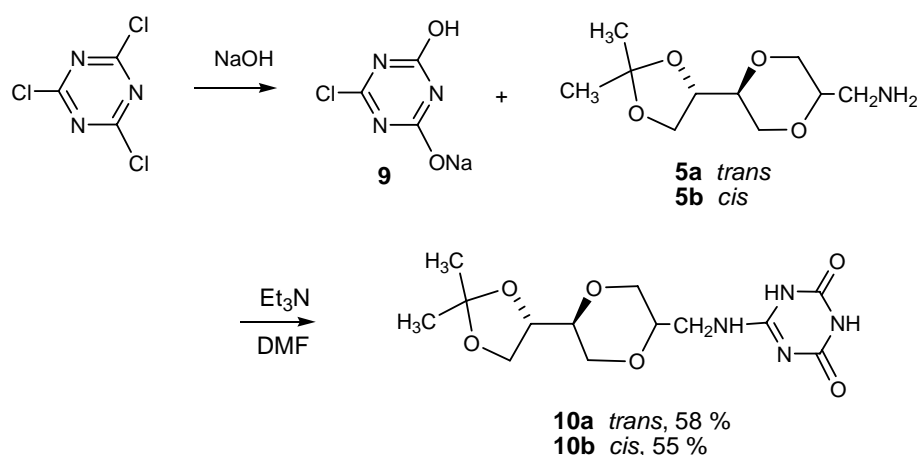
The 3,5-diaminotriazine homo-*N*-nucleoside analogs **8a** and **8b** were prepared by the reaction of the amino sugar analogs **5a** and **5b** respectively with 2-chloro-4,6-diaminotriazine in DMF in the presence of triethylamine. Thus, *trans*-amine **5a** afforded the desired diamino triazine homo-*N*-nucleoside analog **8a** in 39 % yield. The corresponding *cis*-triazine homo-*N*-nucleoside **8b** was obtained in 50 % isolated yield (Scheme 3).

Scheme 3. Synthesis of diaminotriazine homo-*N*-nucleoside analogues **8a** and **8b**.



For the purpose of mimicking the thymine and uracil bases, the 2,4-dihydroxy substituted triazine systems were also prepared. The 2-chloro-4,6-dihydroxy-1,3,5-triazine was readily prepared according to a known procedure [42] from commercial available 2,4,6-trichlorotriazine by treatment in an aqueous sodium hydroxide solution. This provided the monosodium salt of 2-chloro-4,6-dihydroxy-1,3,5-triazine **9**, which was further coupled with **5a** in DMF in the presence of triethylamine to provide triazine nucleoside analogue **10a** in 58 % isolated yield. The *cis*- triazine nucleoside analogue **10b** was similarly prepared from **5b** in 55 % isolated yield (Scheme 4).

Scheme 4. Synthesis of triazine homo-*N*-nucleoside analogue **10a** and **10b**.

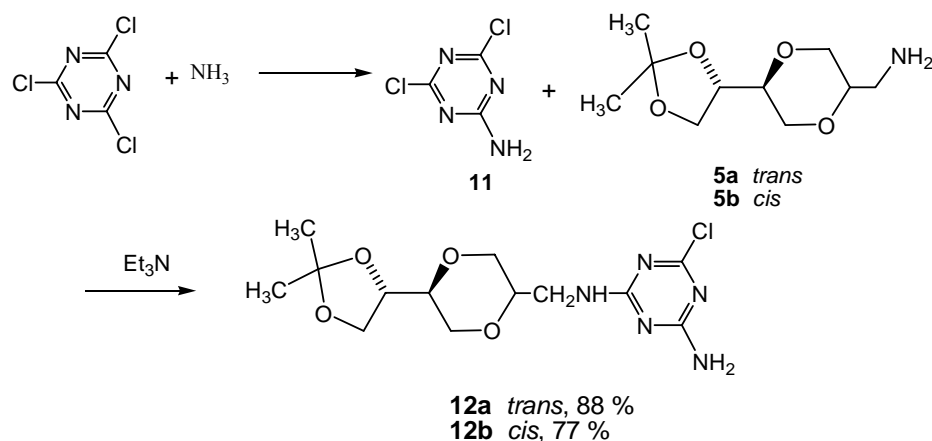


Monoaminotriazine nucleoside analogues were also of interest, as they may mimic adenines, forming associates with for example uracil analogs (Figure 3). Thus for further structural variations of the triazine *N*-nucleoside analogs, **5a** and **5b**, respectively, were coupled with 2,4-dichloro-6-aminotriazine (**11**), which was obtained from 2,4,6-trichlorotriazine by treatment with ammonia at 0 °C [43]. Products **12a** and **12b** were obtained in 88 % and 77 % isolated yields (Scheme 5).

Interestingly, a chromatographically pure sample of **12a** was observed to exhibit an exchange effects in the $^1\text{H-NMR}$ spectra. When the $^1\text{H-NMR}$ of **12a** was recorded at 25 °C in CDCl_3 , the spectra exhibited the presence of two series of signals ascribed to two different structures in a 5:8 ratio.

However, these signals collapsed into a single set of signals when the temperature of the sample exceeded 50 °C. In the course of this process, the chemical shifts also changed. Product **12b** exhibited a similar behavior.

Scheme 5. Synthesis 2-chloro-4-amino triazine homo-*N*-nucleoside analogues **12a** and **12b**.



The observed temperature effects on the NMR spectra of **12** is not yet clear, but may be rationalized in terms of dimerization of **12** or due to the presence of rotamers. Aminotriazines may form complexes through hydrogen bond formation. In this respect it is also worthwhile to note that a number of possible tautomers of the aminotriazine system may play a role in for example dimer formation. Triazine systems have been observed to exhibit rotational isomerism [44-47]. For the present system, **12**, there are several rotatable bonds. One of these, the triazine-NH bond, may be associated with a high rotational barrier, for example due to a possible, partial C-N double bond character, as the result of tautomer formation. An initial, though rudimentary conformational analysis, using theoretical molecular mechanics calculations (ChemModel/MMX), indicated the presence of rotamers and several low-energy conformations. Due to a number of possible rotatable bonds and the dimensional limitations associated with the applied method, we can not here point to distinct structures related to the transformations observed in the NMR experiments. These aspects of the properties of products **12a** and **12b** have so far not been further pursued.

Conclusions

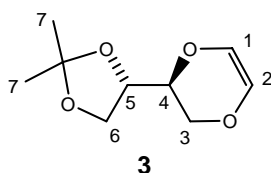
In conclusion, optically active homo-*N*-nucleoside analogs containing a 1,3,5-triazine base equivalent, were synthesized from dimethyl tartrate. The triazines, including the 2,4-diamino substituted, the dihydroxy substituted and chloro-amino 2,4-disubstituted triazines, were linked to the homo-1,4-dioxane sugar analog moiety via a CH₂NH linker. Biologic screening of the prepared nucleoside analogs is now in progress.

Experimental

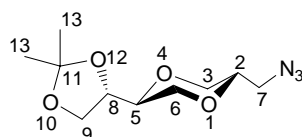
General

NMR spectra were recorded on Bruker Avance DPX 400 instruments. Chemical shifts are reported in ppm using TMS as the internal standard in CDCl_3 or relative to 2.50 ppm for ^1H and 39.99 ppm for ^{13}C in $\text{DMSO}-d_6$ or 3.31 ppm for ^1H and 49.15 ppm for ^{13}C in CD_3OD . Structural assignments were based on ^1H , ^{13}C , DEPT135 and 2D spectra, COSY, HSQC, HMBC, NOESY. EI-Mass and ESI spectra were recorded on a Finnigan MAT 95XL spectrometer. IR spectra of the solid products were obtained on a Thermo Nicolet FT-IR Nexus spectrometer equipped with a Smart Endurance reflection cell. Silica gel Kieselgel 60G (Merck) was used for Flash Chromatography. The solvents were purified by standard methods. The preparations of **6a** and **6b** were described in the previous paper [41].

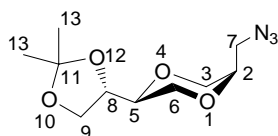
(5*S*)-5-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-6-dihydro-1,4-dioxane (**3**). To compound **1** (0.66 g, 3.2 mmol) in dry THF (12 mL) was added sodium hydride (101 mg, 4.2 mmol) and the mixture was stirred for 10 min. at room temperature. 2,4,6-Trichloro-1,3,5-triazine (0.80 g, 6.2 mmol) was then added to the mixture, which was refluxed for 4 hours. The mixture was concentrated and purified by flash chromatography by using a mixture of diethyl ether and *n*-hexane (1:3) as eluent to provide product **3** (0.1 g, 17 %). ^1H -NMR (400 MHz, CDCl_3) δ 1.38 (d, $J = 0.4$ Hz, 3H, H-7), 1.45 (d, $J = 0.4$ Hz, 3H, H-7), 3.84 (dd, $J = 11.2$ Hz, 7.2 Hz, 1H, H-3), 3.89 (dd, $J = 8.4$ Hz, 6.8 Hz, 1H, H-6), 3.96-4.0 (m, 1H, H-4), 4.04-4.10 (m, 2H, H-3 and H-6), 4.27 (dt, $J = 5.2$ Hz, 6.8 Hz, 1H, H-5), 5.99 (d, $J = 3.4$ Hz, 1H, H-2), 6.04 (d, $J = 3.4$ Hz, 1H, H-1) ppm. ^{13}C -NMR (100 MHz, CDCl_3) δ 25.3, 26.2, 65.0, 65.3, 73.3, 74.3, 109.9, 126.5, 126.8 ppm.



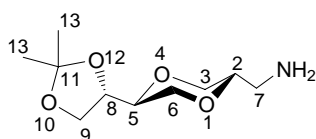
(2*S*,5*S*)-2-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-5-azidomethyl-1,4-dioxane (**7a**). To the solution of **6a** (1.30 g, 4 mmol) in DMF, sodium azide (1.41 g, 22 mmol) was added. The mixture was stirred overnight at 80 °C. The mixture was concentrated under reduced pressure and the residue was extracted with chloroform. The filtrate was concentrated and the residue purified by flash chromatography using a mixture of ethyl ether and *n*-hexane (1:2) as eluent to give product **7a** (yield 0.79, 82 %). ^1H -NMR (400 MHz, CDCl_3) δ 4.06 (dt, 1H, $J = 6.8$ Hz, 5.6 Hz, H-8), 3.97 (dd, 1H, $J = 8.4$ Hz, 6.0 Hz, H-9 eq), 3.85 (dd, 1H, $J = 11.6$ Hz, 2.4 Hz, H-3 eq), 3.79 (dd, 1H, $J = 8.4$ Hz, 7.2 Hz, H-9 ax), 3.77 (dd, 1H, $J = 11.2$ Hz, 2.4 Hz, H-6 eq), 3.76-3.69 (m, 1H, H-2), 3.61 (ddd, 1H, $J = 2.0$ Hz = 5.2 Hz, H-5), 3.53 (dd, 1H, $J = 11.2$ Hz, 7.6 Hz, H-6 ax), 3.48 (dd, 1H, $J = 11.6$ Hz, 10.4 Hz, H-3 ax), 3.26 (d, 2H, $J = 5.2$ Hz, H-7), 1.43 (d, 3H, $J = 0.4$ Hz, H-13), 1.36 (d, 3H, $J = 0.4$ Hz, H-13). ^{13}C -NMR (100 MHz, CDCl_3) δ 109.9, 75.5, 75.1, 74.0, 68.6, 67.5, 65.2, 51.6, 26.4, 25.4. IR (neat): 2984, 2866, 2096, 1448, 1370, 1292 cm^{-1} . HRMS (m/z , ESI): for $\text{C}_{10}\text{H}_{17}\text{N}_3\text{O}_4$ $[\text{M}+\text{Na}]^+$; Calcd. 266.1116; Found 266.1108.

**7a**

(2*S*,5*R*)-2-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-5-azidomethyl-1,4-dioxane (**7b**). The *trans*-compound **7b** was prepared by following the same procedure as described for **7a**. Product **7b** was obtained as a colorless oil (0.73 g, 75.8 %). ¹H-NMR (400 MHz, CDCl₃) δ 4.34 (dd, 1H, *J* = 13.6 Hz, 6.8 Hz, H-8), 4.04 (dd, 1H, *J* = 8.4 Hz, 6.4 Hz, H-3 eq), 3.82-3.76 (m, 3H, H-2, H-6), 3.75 (dd, 1H, *J* = 8.4 Hz, 6.8 Hz, H-3 ax), 3.70 (dd, 1H, *J* = 6.8 Hz, 12 Hz, H-9 ax), 3.69-3.61 (m, 1H, H-7), 3.66 (dd, 1H, *J* = 6.8 Hz, *J* = 1.6 Hz, H-9 eq), 3.63 (dd, 1H, *J* = 3.2 Hz, *J* = 6.4 Hz, H-5), 3.37-3.32 (m, 1 H, H-7), 1.44 (d, 3H, *J* = 0.4 Hz, H-13), 1.38 (d, 3H, *J* = 0.4 Hz, H-13) ppm. ¹³C-NMR (100 MHz, CDCl₃) δ 110.0, 74.9, 74.0, 71.9, 65.8, 65.3, 63.2, 45.0, 26.6, 25.6 ppm. HRMS (*m/z*, ESI): for C₁₀H₁₇N₃O₄ (M+Na⁺), Calcd. 266.1116, found 266.1115.

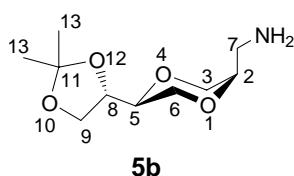
**7b**

(2*S*,5*S*)-2-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-5-aminomethyl-1,4-dioxane (**5a**). To compound **7a** (90.1 mg, 0.365 mmol) dissolved in MeOH (5 mL) was added Pd-C (5 % Pd, 13.4 mg, 0.2 mol %). The suspension was stirred for 2.5 hours under a hydrogen atmosphere (1.8 – 2.0 bar), until TLC indicated complete conversion. The catalyst was removed by filtration and the filtrate was concentrated to dryness. The resulting residue was dissolved in 1 mL MeOH, and filtered through a plug of Celite, which was then washed five times with MeOH (2 mL). The combined filtrates were evaporated to give a colorless oil as product. The yield was 80.4 mg (0.371 mmol, 99 %) product. It became solid after standing a couple of days. The ¹H-NMR (400 MHz, CDCl₃) δ 4.06 (dt, 1H, *J* = 6.8 Hz, 6.4 Hz, H-8), 3.97 (dd, 1H, *J* = 8.4 Hz, 6.8 Hz, H-9eq), 3.85 (dd, 1H, *J* = 11.6 Hz, 2.4 Hz, H-3 eq), 3.79 (dd, 1H, 8.0 Hz, 7.2 Hz, H-9 ax), 3.74 (dd, 1H, *J* = 10.8 Hz, 2.0 Hz, H-6 eq), 3.62-3.55 (m, 2H, H-2, H-5), 3.52 (dd, 1H, *J* = 10.8 Hz, 10.4 Hz, H-6 ax), 3.41 (dd, 1H, *J* = 11.6 Hz, 10.4 Hz, H-3 ax), 2.78 (dd, 1H, *J* = 13.2 Hz, 4.0 Hz, H-7), 2.69 (dd, 1H, *J* = 13.2 Hz, 8.4 Hz, H-7), 2.57 (broad s, 2H, NH₂), 1.43 (d, 3H, *J* = 0.4 Hz, H-13), 1.36 (d, 3H, *J* = 0.4 Hz, H-13) ppm. ¹³C-NMR (100 MHz, CDCl₃) δ 109.7, 75.9, 75.6, 75.2, 69.1, 67.4, 65.2, 42.7, 26.4, 25.4 ppm. HRMS (*m/z*, ESI): for C₁₀H₁₇N₃O₄ (M+H⁺), calcd. 218.1392, found 218.1389.

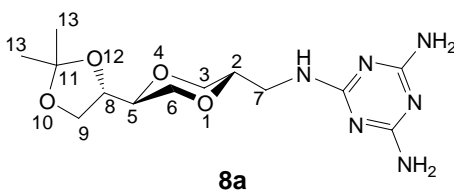
**5a**

(2*S*,5*R*)-2-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-5-aminomethyl-1,4-dioxane (**5b**). The *cis*- compound **5b** was prepared by following the same method as for synthesis of **5a**. ¹H-NMR (400 MHz, CDCl₃) δ 4.38 (ddd, 1H, *J* = 6.8 Hz, 6.8 Hz, 6.8 Hz, H-8), 4.04 (dd, 1H, *J* = 8.4 Hz, 6.8 Hz, H-9 eq), 3.76 (d, 2H,

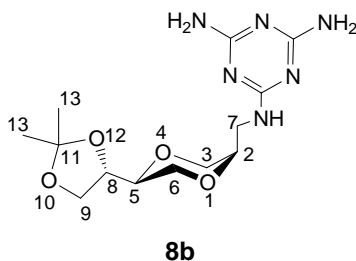
$J = 4.4$ Hz, H-3), 3.73 (dd, 1H, $J = 8.0$ Hz, $J = 7.2$ Hz, H-5), 3.68-3.58 (m, 4 H, H-9 ax, H-6, H-2), 3.10 (dd, 1H, $J = 13.2$ Hz, 8.8 Hz, H-7), 2.79 (dd, 1H, $J = 13.2$ Hz, 4.4 Hz, H-7), 2.42 (bs, 2H, NH₂), 1.44 (d, 3H, $J = 0.4$ Hz, H-13), 1.38 (d, 3H, $J = 0.4$ Hz, H-13) ppm. ¹³C-NMR (100 MHz, CDCl₃): δ 109.8, 74.6, 74.4, 73.9, 65.8, 65.5, 63.2, 41.1, 26.6, 25.5 ppm. IR (neat): 2990, 2864, 1625, 1450, 1434, 1376, 1367, 1122, 1022, 979 cm⁻¹. HRMS (m/z , ESI): for C₁₀H₁₇N₃O₄ (M+H⁺), calcd. 218.1392, found 218.1394.



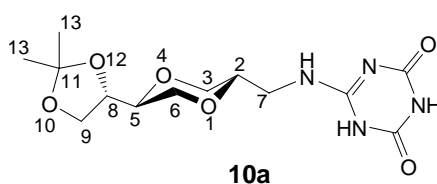
2,4-Diamino-6-[[[(2S,5S)-2-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]-1,4-dioxan-5-yl]methylamino]-1,3,5-triazine (8a). To a solution of **5a** (244 mg, 1.12 mmol) and triethylamine (0.16 mL, 1.15 mmol) in DMF (16 mL) was added 2-chloro-4,6-diaminotriazine (80 mg, 0.55 mmol). The mixture was heated at 80 °C and stirred overnight. The solution was evaporated under high vacuum and the residue was purified by column chromatography using gradient eluent systems [dichloromethane and methanol (20:1); dichloromethane and methanol (10:1)]. Product **8a** was obtained as a white solid in 39 % yield. ¹H-NMR (400 MHz, CDCl₃) δ 6.40 (t, 1H, $J = 6$ Hz, NH), 6.06 (s, 2H, NH₂), 5.95 (s, 2H, NH₂), 3.96-4.01 (m, 1H, H-8), 3.89 (dd, 1H, $J = 8.2$ Hz, 6.6 Hz, H-9), 3.79 (dd, 1H, $J = 11.6$, 2.6 Hz, H-3), 3.72 (dd, 1H, $J = 8.2$ Hz, 7.0 Hz, H-9), 3.67 (dd, 1H, $J = 11.2$ Hz, 2 Hz, H-6), 3.52-3.58 (m, 1H, H-2), 3.44-3.48 (m, 1H, H-5), 3.30-3.37 (m, 1H, H-6), 3.21-3.29 (m, 2H, H-3, H-7), 3.08-3.15 (m, 1H, H-3), 1.30 (s, 3H, H-13), 1.24 (s, 3H, H-13) ppm. ¹³C-NMR (100 MHz, CDCl₃) δ 167.0, 166.4, 108.4, 74.5, 73.6, 69.1, 66.6, 64.3, 41.0, 26.1, 25.3 ppm. IR (neat): 3353, 3130, 2983, 1633, 1608, 1537, 1455, 1108, 1048 cm⁻¹. HRMS (m/z , ESI): for C₁₃H₂₂N₆O₄ (M+H⁺), calcd. 327.1780, found 327.1780.



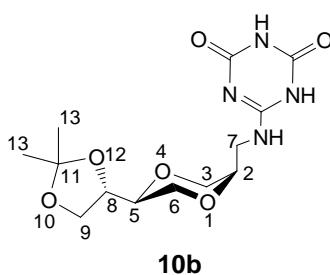
2,4-Diamino-6-[[[(2S,5R)-2-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]-1,4-dioxan-5-yl]-methylamino]-1,3,5-triazine (8b). *cis*-Compound **8b** was prepared in 50 % yield from **5b** by following the same method as for the synthesis of **8a**. ¹H-NMR (400 MHz, CDCl₃) δ 6.34 (t, 1H, $J = 6$ Hz, NH), 5.43 (s, 4H, NH₂), 4.35 (ddd, 1H, $J = 6.8$ Hz, 6.8 Hz, 6.8 Hz, H-8), 4.01 (dd, 1H, $J = 8.4$ Hz, 6.4 Hz, H-9), 3.59-3.82 (m, 7H, H-9, H-2, H-3, H-5, H-6), 3.47-3.54 (m, 2H, H-7), 1.43 (s, 3H, H-13), 1.37 (s, 3H, H-13) ppm. ¹³C-NMR (100 MHz, CDCl₃) δ 167.5, 167.2, 166.8, 109.9, 74.5, 74.0, 72.1, 65.8, 65.3, 63.2, 40.0, 26.6, 25.4 ppm. IR (neat) 3342, 3168, 2983, 1539, 1449, 1122, 1065 cm⁻¹. HRMS (m/z , ESI): for C₁₃H₂₂N₆O₄ (M+H⁺), calcd. 327.1780, found 327.1787.



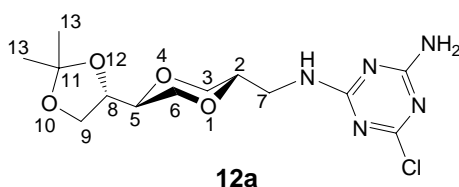
2,4-Dihydroxy-6-[[*(2S,5S)*-2-[[*(4S)*-2,2-dimethyl-1,3-dioxolan-4-yl]-1,4-dioxan-5-yl]methylamino]-1,3,5-triazine (**10a**). To compound **5a** (88 mg, 0.41 mmol) and triethylamine (0.08 mL, 0.58 mmol) in DMF (10 mL) was added the monosodium salt of 2-chloro-4,6-dihydroxy-1,3,5-triazine (**9**, 127 mg, 0.62 mmol). The mixture was heated at 80 °C and stirred overnight. The solvent was evaporated under high vacuum and the residue was purified by flash chromatography using a mixture of dichloromethane and methanol (10:1) as eluent. The product **10a** (67 mg) was obtained in 43 % yield. ¹H-NMR (400 MHz, CDCl₃) δ 10.40 (broad s, 2H, OH), 7.02 (s, 1H, NH), 4.00 (ddd, 1H, *J* = 6.8 Hz, 6.8 Hz, 6.8 Hz, H-8), 3.90 (dd, 1H, *J* = 8.2 Hz, 6.6 Hz, H-9), 3.80 (dd, 1H, *J* = 11.6 Hz, 2.4 Hz, H-3), 3.71-3.76 (m, 2H, H-9, H-6), 3.57-3.61 (m, 1H, H-2), 3.46-3.50 (m, 1H, H-5), 3.17-3.44 (m, 4H, H-6, H-3, H-7), 1.30 (s, 3H, H-13), 1.24 (s, 3H, H-13) ppm. ¹³C-NMR (100 MHz, CDCl₃) δ 156.5, 108.5, 74.4 (C-5 and C-8), 72.8, 68.1, 66.7, 64.3, 40.9, 26.1, 25.3 ppm. IR (neat) 3090, 2983, 1720, 1628, 1490, 1131, 1061 cm⁻¹. HRMS (*m/z*, ESI), for C₁₃H₂₀N₄O₆ (M+H⁺), calcd. 329.1461, found 329.1469.



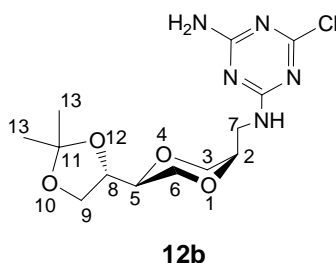
2,4-Dihydroxy-6-[[*(2S,5R)*-2-[[*(4S)*-2,2-dimethyl-1,3-dioxolan-4-yl]-1,4-dioxan-5-yl]-methylamino]-1,3,5-triazine (**10b**). *cis*-Compound **10b** was prepared from **5b** by following the same method as for the synthesis of **10a**. ¹H-NMR (400 MHz, CDCl₃) δ 10.62 (broad s, 1H, OH), 10.48 (broad s, 1H, OH), 6.90 (s, 1H, NH), 4.24 (ddd, 1H, *J* = 6.4 Hz, 6.4 Hz, 6.4 Hz, H-8), 3.94 (dd, 1H, *J* = 8.4 Hz, 6.8 Hz, H-9), 3.72 (dd, 1H, *J* = 8 Hz, 6.8 Hz, H-9), 3.48-3.69 (m, 7H, H-5, H-6, H-3, H-2, H-7), 3.36-3.42 (m, 1H, H-7), 1.31 (s, 3H, H-13), 1.27 (s, 3H, H-13) ppm. ¹³C-NMR (100 MHz, CDCl₃) δ 156.3, 149.9, 108.5, 73.8, 73.5, 70.1, 64.8, 64.7, 61.9, 39.3, 26.4, 25.3 ppm. IR (neat) 3126, 2985, 1741, 1588, 1121, 1060 cm⁻¹. HRMS (*m/z*, ESI), for C₁₃H₂₀N₄O₆ (M+H⁺), calcd. 329.1461, found 329.1462.



2-Chloro-4-amino-6-[[[(2*S*,5*S*)-2-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-1,4-dioxan-5-yl]-methyl-amino]-1,3,5-triazine (**12a**). To compound **5a** (40 mg, 0.18 mmol) and triethylamine (0.04 mL, 0.29 mmol) in DMF (6 mL) was added 2,4-dichloro-6-amino-1,3,5-triazine (**11**, 31 mg, 0.19 mmol). The mixture was stirred at room temperature overnight. The DMF was evaporated under high vacuum and the residue was purified by flash chromatography using a mixture of dichloromethane and methanol (20:1) as the eluent. The product (53 mg) was obtained in 88 % yield. $^1\text{H-NMR}$ (400 MHz, CDCl_3 , 25 $^\circ\text{C}$) δ 1.36, 1.43 (s, $2 \times \text{CH}_3$ for both rotamers), 3.25-3.32 (m), 3.37-3.46 (m), 3.48-3.61 (m), 3.65-3.82 (m), 3.86-3.93 (m), 4.03-4.08 (m), 5.20-5.40 (broad, 2H, NH_2 , for both rotamers), 5.83 (t, NH), 6.14 (t, NH) ppm. $^1\text{H-NMR}$ (400 MHz, CDCl_3 , 50 $^\circ\text{C}$) δ 5.71 (broad s, 1H, NH), 5.19 (broad s, 2H, NH_2), 4.03-4.08 (m, 1H), 3.95 (dd, 8.2, $J = 6.6$ Hz, 1H), 3.85-3.88 (m, 1H), 3.81 (dd, $J = 8.2$, $J = 7.0$ Hz, 1H,), 3.74 (dd, $J = 10.6$ and $J = 1.4$ Hz, 1H), 3.65-3.71 (m, 1H), 3.48-3.60 (m, 3H), 3.40 (dd, $J = 11.4$ and 10.6 Hz, 1H), 3.26-3.32 (m, 1H), 1.413, 1.412, 1.342, 1.341 (6H, $2 \times \text{CH}_3$) ppm. $^{13}\text{C-NMR}$ (100 MHz, CDCl_3 , 50 $^\circ\text{C}$) δ 25.3, 26.3, 41.8, 65.1, 67.5, 68.9, 73.6, 75.1, 75.3, 109.8, 166.5, 167.3, 169.8. IR (neat) 3392, 3265, 3119, 2983, 1655, 1576, 1485, 1103, 1056 cm^{-1} . HRMS (m/z , ESI), for $\text{C}_{13}\text{H}_{20}\text{ClN}_5\text{O}_4$ ($\text{M}+\text{H}^+$), calcd. 346.1282, found 346.1283.



2-Chloro-4-amino-6-[[[(2*S*,5*R*)-2-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-1,4-dioxan-5-yl]-methyl-amino]-1,3,5-triazine (**12b**) *cis*-Compound **12b** was prepared by following the same method as for synthesis of **12a**. $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 1.37, 1.44 (s, $2 \times \text{CH}_3$ for both rotamers), 3.49-3.55(m), 3.57-3.67(m), 3.75-3.86(m), 3.99-4.06 (m, 1H, for both rotamers), 4.31-4.36 (m, 1H, for both rotamers), 5.3-5.9 (broad, 2H, NH_2 , for both rotamers), 6.02, 6.11 (1H, NH, for both rotamers) ppm. $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 25.2, 25.3, 26.4, 26.5, 62.6, 62.9, 65.4, 65.48, 65.52, 65.6, 70.9, 71.3, 74.0, 74.4, 166.1, 166.3, 166.6, 167.0, 169.2 ppm. IR (neat) 3327, 3270, 3171, 2983, 1646, 1563, 1482, 1123, 1065 cm^{-1} . HRMS (m/z , ESI), for $\text{C}_{13}\text{H}_{20}\text{ClN}_5\text{O}_4$ ($\text{M}+\text{H}^+$), calcd. 346.1282, found 346.1295.



Acknowledgements

The authors wish to thank the Norwegian Research Council, NFR, for financial support. We also thank Professor E. Uggerud, University of Oslo, for performing mass spectrometric measurements.

References

1. Li, F.; Maag, H.; Alfredson, T. Prodrugs of nucleoside analogues for improved oral absorption and tissue targeting. *J. Pharm. Sci.* **2007**, *97*, 1109-1134.
2. Adrian, R.; Murakami, E.; Basavapathruni, A.; Vaccaro, J. A.; Ulrich, D.; Chu, C. K.; Schinazi, R. F.; Anderson, K. S. Probing the molecular mechanisms of AZT drug resistance mediated by HIV-1 reverse transcriptase using a transient kinetic analysis. *Biochemistry* **2003**, *42*, 8831-8841.
3. Ren, J.; Esnouf, R.M.; Hopkins, A.L.; Jones, E.Y.; Kirby, I.; Keeling, J.; Ross, C.K.; Larder, B. A.; Stuart, D.I.; Stammers, D.K. 3'-Azido-3'-deoxythymidine drug resistance mutations in HIV-1 reverse transcriptase can induce long range conformational changes. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 9518-9523.
4. Feng, J.Y.; Anderson, K.S. Mechanistic Studies Examining the Efficiency and Fidelity of DNA Synthesis by the 3TC-Resistant Mutant (184V) of HIV-1 Reverse Transcriptase. *Biochemistry* **1999**, *38*, 9440-9448.
5. Hayatsu, H. Orgueil Meteorite: Organic Nitrogen Contents. *Science* **1964**, *146*, 1291-1293.
6. Hayatsu, R.; Studier, M.H.; Moore, L.P.; Anders, E. Purines and triazines in the Murchison meteorite. *Geochim. Cosmochim. Acta* **1975**, *39*, 471-488.
7. Minard, R.D.; Hatcher, P.G.; Gourley, R.C.; Matthews, C.N. Structural investigations of hydrogen cyanide polymers: new insights using TMAH thermochemolysis/GC-MS, Origins of life and evolution of the biosphere. *J. International Soc. Study Orig. Life* **1998**, *28*, 461-473.
8. Hysell, M.; Siegel, J.S.; Tor, Y. Synthesis and stability of exocyclic triazine nucleosides. *Org. Biomol. Chem.* **2005**, *3*, 2946-295
9. Blotny, G. Recent applications of 2,4,6-trichloro-1,3,5-triazine and its derivatives in organic synthesis. *Tetrahedron* **2006**, *62*, 9507-9522.
10. Kosary, J.; Kasztreiner, E.; Rablaczky, G.; Kurthy, M. Synthesis and cardiotoxic activity of 2,4-diamino-1,3,5-triazines. *Eur. J. Med. Chem.* **1989**, *24*, 97-99.
11. Hargreaves, R.B.; McLoughlin, B.J.; Mills, S.D. Thiadiazine, oxadiazine and triazine derivatives, and pharmaceutical compositions containing them. *Eur. Pat. Appl.* **1983**, EP 85227
12. Kukla, M.J.; Ludovici, D.W.; Janssen, P.A.J.; Heeres, J.; Moereels, H.E.L. Preparation and anti-HIV activity of substituted diamino-1,3,5-triazine derivatives. *Eur. Pat. Appl.* **1998**, EP 834507.
13. De Corte, B.; De Jonge, M.R.; Heeres, J.; Janssen, P.A.J.; Koymans, L.M.H.; Kukla, M.J.; Ludovici, D.W.; Van Aken Koen, J.A. Preparation of 2,4-disubstituted triazine derivatives as anti - HIV agents. *PCT Int. Appl. WO 2000027828*, **2000**.
14. Brzozowski, Z.; Saczewski, F.; Gdaniec, M. Synthesis, structural characterization and antitumor activity of novel 2,4-diamino-1,3,5-triazine derivatives. *Eur. J. Med. Chem.* **2000**, *35*, 1053-1064.
15. An, H.; Chamakura, V.; Chen, H.; Hong, Z. Solid phase synthesis and combinatorial library of nucleosides as potential antiviral and anticancer agents. *PCT Int. Appl.*, **2003**, WO 2003051898.
16. Ames, M.M. Hexamethylmelamine: pharmacology and mechanism of action. *Cancer treatment rev.* **1991**, *18, Suppl. A*, 3-14.

17. Varaprasad, C.V.; Habib, Q.; Li, D.Y.; Huang, J. Synthesis of novel exocyclic amino nucleosides by parallel solid-phase combinatorial strategy. *Tetrahedron* **2003**, *59*, 2297-2307.
18. Gaubert, G.; Gosselin, G.; Eriksson, S.; Vita, A.; Maury, G. Unnatural enantiomers of 5-azacytidine analogues: syntheses and enzymatic properties. *Nucleosides Nucleotides Nucleic Acids* **2001**, *20*, 837-840.
19. Archer, E. A.; Goldberg, N.T.; Lynch, V.; Krische, M.J. Nanostructured Polymer Duplexes via the Covalent Casting of 1-Dimensional H-Bonding Motifs: A New Strategy for the Self-Assembly of Macromolecular Precursors. *J. Am. Chem. Soc.* **2000**, *122*, 5006-5007.
20. Archer, E.A.; Cauble, D.F.; Lynch, V.; Krische, M.J. Synthetic duplex oligomers: optimizing interstrand affinity through the use of a non-covalent constraint. *Tetrahedron* **2002**, *58*, 721-725.
21. Löwik, D.W.P.M.; Lowe, C.R. Synthesis of macrocyclic, triazine-based receptor molecules. *Eur. J. Org. Chem.* **2001**, *15*, 2825-2839.
22. Choi, I.S.; Li, X.; Simanek, E.E.; Akaba, R.; Whitesides, G.M. Self-Assembly of Hydrogen-Bonded Polymeric Rods Based on the Cyanuric Acid Melamine Lattice. *Chem. Mat.* **1999**, *11*, 684-690.
23. Shiki, Y.; Takashi, K.; Akihide, K. Melamine-barbiturate/cyanurate binary organogels possessing rigid azobenzene-tether moiety. *Langmuir* **2005**, *21*, 11048-11052.
24. Kunz, M.J.; Hayn, G.; Saf, R.; Binder, W.H. Hydrogen-bonded supramolecular poly(ether ketones). *J. Polym. Sci., A: Polym. Chem.* **2004**, *42*, 661-674.
25. Asanuma, H.; Ban, T.; Gotoh, S.; Hishiya, T.; Komiyama, M. Precise recognition of nucleotides and their derivatives through hydrogen bonding in water by poly(vinyldiaminotriazine). *Supramol. Sci.* **1998**, *5*, 405-410.
26. Nie, L.; Ma H.; Li X.; Sun M.; Xiong S. Recognition of thymine by triazine fluorescent probe through intermolecular multiple hydrogen bonding. *Biopolymers* **2003**, *72*, 274-281.
27. Jochims, J.C.; Von V., Hubertus; W.G. Barriers to hindered rotation around the N-glycosidic bond, I. N-Glucopyranosides. *Chem. Ber.* **1978**, *111*, 1693-1708.
28. Chen, H.; Dai, Z.; Su, X.; Fu, L.; Qu, F. Synthesis of 2,4-dioxohexahydro-1,3,5-triazine glucosides. *J. Wuhan Univ. Nat. Sci. Ed.* **1999**, *45*, 168-170.
29. Simmonds, R.J.; Stevens, M.F.G. Triazines and related products. Part 25. Methods for the attachment of sugar residues to cytotoxic 1,3,5-triazines. *J. Chem. Soc., Perkin Trans. 1, Org. Bioorg. Chem.* **1982**, *8*, 1821-1825.
30. Huchel, U.; Schmidt, C.; Schmidt, R.R. Anomeric O-alkylation. Part 16. Synthesis of hetaryl glycosides and their glycosyl donor properties. *Eur. J. Org. Chem.* **1998**, *7*, 1353-1360.
31. Niedballa, U.; Vorbruggen, H. A general synthesis of N-glycosides. V. Synthesis of 5-azacytidines. *J. Org. Chem.* **1974**, *39*, 3672-3674.
32. Yu, Q.; Carlsen, P. Synthesis of Novel, Optically Active Uridine Analog Containing a 1,4-Dioxane Sugar Moiety. Synthesis of the Corresponding Dinucleotide. *Nucleos. Nucleot. Nucleic Acids*. Submitted.
33. Hossain, N.; Blaton, N.; Peeters, O.; Rozenski, J.; Herdewijn, P.A. Synthesis of homo-N-nucleosides, a series of C1' branched-chain nucleosides. *Tetrahedron* **1996**, *52*, 5563-5578.

34. Hossain, N.; Hendrix, C.; Lescrinier, E.; Van Aerschot, A.; Busson, R.; De Clercq, E.; Herdewijn, P. Homo-N - nucleosides : incorporation into oligonucleotides and antiviral activity. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1465-1468.
35. Franzyk, H.; Rasmussen, J.H.; Mazzei, R.A.; Jensen, S.R. Synthesis of carbocyclic homo - N - nucleosides from iridoids. *Eur. J. Org. Chem.* **1998**, *12*, 2931-2935.
36. Chun, M.W.; Kim, J.H.; Kim, M.J.; Kim, B.R.; Jeong, L.S. Synthesis of homo-N-nucleoside with 1,2,4-triazole-3-carboxamide. *Nucleos. Nucleot. Nucleic Acids* **2005**, *24*, 979-981.
37. Saladino, R.; Ciambecchini, U.; Hanessian, S. Synthesis of 1'- homo-N-nucleosides from hexitols. *Eur. J. Org. Chem.* **2003**, *22*, 4401-4405.
38. Asanuma, H.; Ban, T.; Gotoh, S.; Hishiya, T.; Komiyama, M. Precise recognition of nucleotides and their derivatives through hydrogen bonding in water by poly(vinyldiaminotriazine). *Supramol. Sci.* **1998**, *5*, 405-410.
39. Appeldoorn, C.C.M.; Joosten, J.A.F.; Ait el Maate, F.; Dobrindt, U.; Hacker, J., Liskamp, R.J.; Khan, A.; Pieters, R.J. Novel multivalent mannose compounds and their inhibition of the adhesion of type 1 fimbriated uropathogenic E. coli. *Tetrahedron Asymmetry* **2005**, *16*, 361-372.
40. Rye, C.S.; Withers, S.G. Synthesis and evaluation of potential inhibitors of chondroitin AC Lyase from Flavobacterium heparinum. *J. Org. Chem.* **2002**, *67*, 4505-4512.
41. Yu, Q.; Carlsen, P. Enantioselective Synthesis of Homo-N-Nucleosides Containing a 1,4-Dioxane Sugar Analog. *Molecules*, **2008**, *13*, 2962-2974.
42. Horrobin, B.S. The hydrolysis of some chloro-1,3,5-triazines: Mechanism: Structure and Reactivity. *J. Chem. Soc.* **1963**, 4130-4145.
43. Baliani, A.; Bueno, G. J.; Stewart, M. L.; Yardley, V., Brun, R.; Barrett, M. P.; Gilbert, L. H. Design and Synthesis of a Series of Melamine-based Nitroheterocycles with Activity against Trypanosomatid Parasites. *J. Med. Chem.* **2005**, *48*, 5570-5575.
44. Katritzky, A.R.; Oniciu, D.C.; Ghiviriga, I.; Barcock, R.A. 4,6-Bis- and 2,4,6-tris-(N,N-dialkylamino)-s-triazines: synthesis, NMR spectra and restricted rotations. *J. Chem. Soc. Perkin Trans. 2: Phys. Org. Chem.* **1995**, *4*, 785-792.
45. Katritzky, A.R.; Ghiviriga, I.; Steel, P.J.; Oniciu, D.C. Restricted rotations in 4,6-bis- and 2,4,6-tris(N,N-dialkylamino)-s-triazines. *J. Chem. Soc. Perkin Trans. 2: Phys. Org. Chem.* **1996**, *3*, 443-447.
46. Amm, M.; Platzer, N.; Guilhem, J.; Bouchet, J.; Volland, J. Structural and conformational study of substituted triazines by 15N NMR and x-ray analysis. *Mag. Res. Chem.* **1998**, *36*, 587-596.
47. Birkett, H.E.; Harris, R. K.; Hodgkinson, P.; Carr, K.; Charlton, M.H.; Cherryman, J.C.; Chippendale, A.M; Glover, R.P. NMR studies of exchange between triazine rotamers. *Mag. Res. Chem.* **2000**, *38*, 504-511.

Sample Availability: Samples of selected compounds are available from the authors.