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

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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 extend 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 cardiotonic [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 NH$_2$ and OH substituted triazines.

![Figure 1. Interaction between NH$_2$ and OH substituted triazines.](image1)

**Figure 2.** Interaction between triazine and uracil structures.

![Figure 2. Interaction between triazine and uracil structures.](image2)
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-trichloritriazine. 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 \( \text{CH}_2 \)-group neighboring the anomeric \(-\text{OH}\) 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 –CH2-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 NH2 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- / NH2 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 (2R,3R)-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.

![Scheme 2](image)

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 \(^\circ\)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 \(^1\)H-NMR spectra. When the \(^1\)H-NMR of 12a was recorded at 25 \(^\circ\)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-dioxoane 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 CDCl₃ or relative to 2.50 ppm for ¹H and 39.99 ppm for ¹³C in DMSO-d₆ or 3.31 ppm for ¹H and 49.15 ppm for ¹³C in CD₃OD. Structural assignments were based on ¹H, ¹³C, 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].

(5S)-5-[(4S)-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, CDCl₃) 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 = 12.2 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 = 3.4Hz, 1H, H-2), 6.04 (d, J = 3.4 Hz, 1H, H-1) ppm. ¹³C-NMR (100 MHz, CDCl₃) δ 25.3, 26.2, 65.0, 65.3, 73.3, 74.3, 109.9, 126.5, 126.8 ppm.

(2S,5S)-2-[(4S)-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 purified by flash chromatography using a mixture of diethyl ether and n-hexane (1:2) as eluent to give product 7a (yield 0.79, 82 %). ¹H-NMR (400 MHz, CDCl₃) 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 = 12.2 Hz, 2.4 Hz, H-6 eq), 3.76-3.69 (m, 1H, H-2), 3.61 (dd, 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). ¹³C-NMR (100 MHz, CDCl₃) 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 C₁₀H₁₇N₃O₄ [M+Na]^⁺; Calcd. 266.1116; Found 266.1108.
(2S,5R)-2-[(4S)-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, 8.4 Hz, H-8), 4.04 (dd, 1H, J = 5.6 Hz, 8.4 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, 1H, 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.

(2S,5S)-2-[(4S)-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, 6.8 Hz, H-8), 3.97 (dd, 1H, J = 8.4 Hz, 6.8 Hz, H-9 eq), 3.85 (dd, 1H, J = 11.6 Hz, 2.4 Hz, H-3 eq), 3.79 (dd, 1H, J = 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.
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. 

$^1$H-NMR (400 MHz, CDCl$_3$) δ 6.40 (t, 1H, $J = 6$ Hz, NH), 6.06 (s, 2H, NH$_2$), 5.95 (s, 2H, NH$_2$), 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-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, CDCl$_3$) 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 C$_{13}$H$_{22}$N$_6$O$_4$ (M+H$^+$), calcd. 327.1780, found 327.1780.
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 triethyl amine (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 = 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,5S)-2-[(4S)-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. 1H-NMR (400 MHz, CDCl3, 25 °C) δ 1.36, 1.43 (s, 2 × CH3 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, NH2, for both rotamers), 5.83 (t, NH), 6.14 (t, NH) ppm. 1H-NMR (400 MHz, CDCl3, 50 °C) δ 5.71 (broad s, 1H, NH), 5.19 (broad s, 2H, NH2), 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 × CH3) ppm. 13C-NMR (100 MHz, CDCl3, 50 °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 C13H20ClN5O4 (M+H⁺), calcd. 346.1282, found 346.1283.

cis-Compound 12b was prepared by following the same method as for synthesis of 12a. 1H-NMR (400 MHz, CDCl3) δ 1.37, 1.44 (s, 2 × CH3 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, NH2, for both rotamers), 6.02, 6.11 (1H, NH, for both rotamers) ppm. 13C-NMR (100 MHz, CDCl3) 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 C13H20ClN5O4 (M+H⁺), calcd. 346.1282, found 346.1295.

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

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