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NOVEL SERINOLIC MELAMINES AS POTENTIAL PERIPHERAL GROUPS IN DENDRITIC CHEMISTRY

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ABSTRACT. A rapid access to elaborated *N*-substituted 2,4,6-triamino-*s*-triazines (*melamines*), seen as potential non-symmetric peripheral groups in dendritic chemistry, is reported. It consists of the highly selective amination of cyanuric chloride by some *C*-substituted 2-aminopropane-1,3-diols (*serinols* as *"open chain serinolic unit"*), their cyclic acetals (*O*,*O*-protected forms as amino-1,3-dioxanes, *"closed chain serinolic unit"*) and piperazine as linker. All results are fully supported by IR, DNMR and MS data.

Keywords: *s-triazine, serinols, amination, restricted rotation*

INTRODUCTION

Subsequent to our recent findings in the synthesis [1-5], structure [1-5] and use [6-8] of elaborated *N*-substituted 2,4,6-triamino-*s*-triazines (*melamines*) based on the versatile nucleophilicity of *C*-substituted 2-aminopropane-1,3-diols (*serinols*) against cyanuric chloride, we now report the preliminary results in a combined new approach, resumed in Scheme 1. Both theoretic [9] and/or synthetic [10] recent advances in dendrimers' chemistry called attention on *non-symmetric peripheral groups, providing different sites for further nanoscale manipulation* of these architectures.

In this context, we considered of interest two new *N*-substituted **TARGET MELAMINES** based on serinols (Scheme 1) possessing:

i) A basic site as *closed chain serinolic unit*, *e.g.* of type enantiomerically pure (4*S*,5*S*)-amino-1,3-dioxane (**1a** and **1b**).

ii) An *open-chain serinolic unit*, *e.g.* of type **TRIS (THAM)**.

iii) An appropriate, non sophisticated and widely used dendritic linker, *e.g.* piperazine, able to connect cores [10, 11], generations [12] or both [13].

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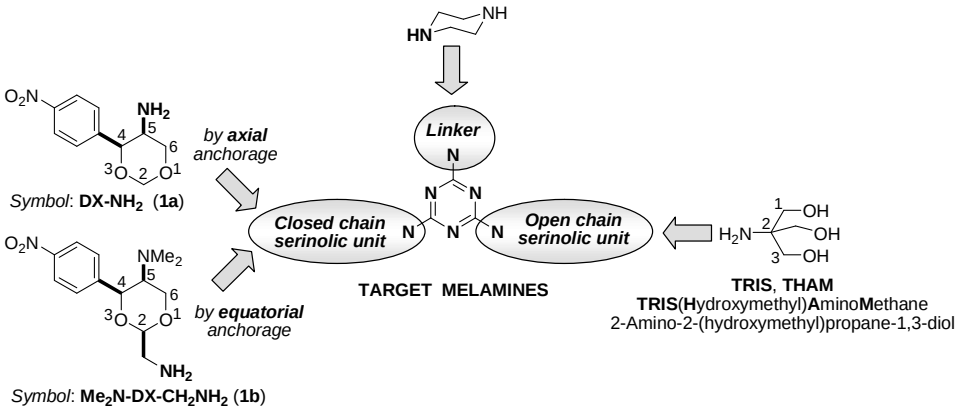
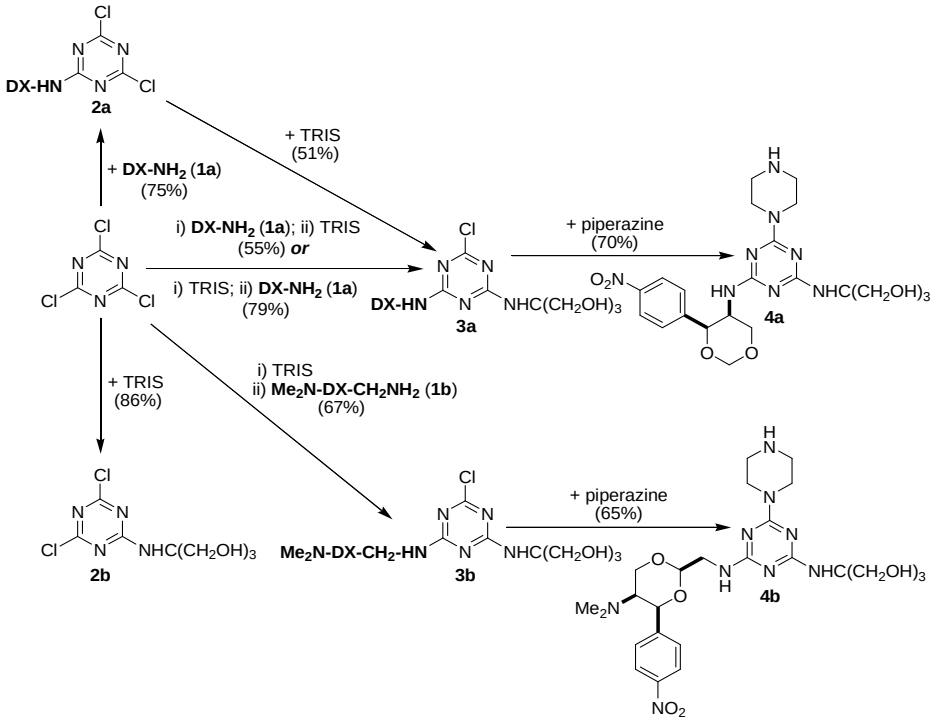


Scheme 1

RESULTS AND DISCUSSION

The chemistry we have developed is depicted in Scheme 2 while reaction conditions are listed in Table 1. Compounds **3a**, **3b**, **4a** and **4b** are new ones.



Scheme 2

Table 1. Reaction conditions for the synthesis of compounds **2b**, **3a**, **3b**, **4a** and **4b**

No.	Conditions			
	Molar ratios	Solvent	Time (hrs.)	*T* (^{o}C)
2a	1.03 (**1a**) : 1.03 (Base)* : 1.00 (C.C.)**	THF	24	0 → r.t.
2b	1.00 (TRIS) : 1.00 (Base) : 1.00 (C.C.)	THF	24	-15 → r.t.
3a	1.00 (TRIS) : 1.00 (Base) : 1.00 (**2a**)	THF	17	reflux
3a	1.03 (**1a**) : 1.03 (Base) : 1.00 (C.C.) ⏭	THF	24	0 → r.t.
	⏭1.00 (TRIS) : 1.00 (Base) : 1.00 (***2a***)***	THF	15	reflux
3a	1.00 (TRIS) : 1.00 (Base) : 1.00 (C.C.) ⏭	THF	24	-15 → r.t.
	⏭ 1.00 (**1a**) : 1.00 (Base) : 1.00 (***2b***)	THF	9	reflux
3b	1.00 (TRIS) : 1.00 (Base) : 1.00 (C.C.) ⏭	THF	24	-15 → r.t.
	⏭ 1.00 (**1b**) : 1.00 (Base) : 1.00 (***2b***)	THF	96	r.t.
4a	4.00 (piperazine) : 1.00 (Base) : 1.00 (**3a**)	1,4-dioxane	9	reflux
4b	4.00 (piperazine) : 1.00 (Base) : 1.00 (**3b**)	1,4-dioxane	9	reflux

*Throughout anh. K_2CO_3; **C. C.: Cyanuric Chloride ****Italicised*: intermediates not isolated in the one-pot (⏭) procedure (Scheme 2)

The synthesis and stereochemistry of the starting amino-1,3-dioxanes **1a** and **1b** (Scheme 1) we discussed in detail previously [1, 14]. They were used as pure enantiomeric (4*S*,5*S*-**1a**), (2*R*,4*S*,5*S*-**1b**) forms.

Monoamination of cyanuric chloride by TRIS occurred slowly with high selectivity. In fact, the yield obtained in the case of the resulted **2b** refers rather to its direct isolation by simple crystallisation than to the very clean reaction revealed by the TLC monitoring.

The same clear evolution was observed during the preparation of the dichloroamino-*s*-triazine **2a** whose synthesis and stereochemistry we described elsewhere [1]. Treatment of the isolated **2a** with TRIS required 17 hrs. in refluxing THF in order to afford compound **3a** in 51% yield after flash column chromatography, hence a 38% overall yield with respect to cyanuric chloride.

Two alternative one-pot protocols were envisaged for the preparation of **3a**, account being taken on the expected lower nucleofilicity of TRIS, more solvated in THF, in comparison with the amino-1,3-dioxane **1a**:

a) Amination of cyanuric chloride with **1a** then with TRIS (15 hrs. in refluxing THF) was performed without isolation of the intermediate **2a**. Chlorodiamino-*s*-triazine **3a** was obtained with a higher overall yield (55%, after flash column chromatography).

b) Amination of cyanuric chloride was firstly carried out with TRIS followed by **1a**, without isolation, this time, of the intermediate **2b**. **3a** was prepared in 79% yield and isolated by simple crystallisation.

Besides obvious benefits when one-pot synthesis was applied, the above results observed in the case of **3a** confirmed our anticipations that TRIS should be, like it or not, the first nucleophile in this chemistry.

We also note that, despite the presence of three hydroxymethyl groups *vs.* but one amino in TRIS, we detected no product of a competitive alkoxylation *vs.* amination in the depicted conditions when accessing compounds **2b** or **3a** [15].

We next used this know-how in the preparation of the chlorodiamino-*s*-triazine **3b**.

Previous findings of us evidenced the non-selective interaction between equimolar amounts of cyanuric chloride and the amino-1,3-dioxane **1b** as oligomerisations and *N*-demethylation [1]. Therefore, the single option we had consisted of the use, again, of TRIS as the first nucleophile with respect to cyanuric chloride, followed by **1b**, in a one-pot procedure. **3b** was obtained simply, in 67% overall yield, in much milder conditions than **3a**.

Particularly, one must observe that amino-1,3-dioxanes **1a**, **1b** were both anancomeric structures because of their overwhelmingly one-sided conformational equilibriums due to *p*-nitrophenyl ring located at C-4 in equatorial position (A value ≈ 11.93 kJ/mol) [16]. It was by far greater than A values of C-5 amino (5.15 – 7.10 kJ/mol) in **1a** or C-5 dimethylamino (6.40 – 8.80 kJ/mol) group in **1b** [16].

On the other hand, the expected equatorial linkage of the C-2 aminomethyl group in **1b** (A value up to 7.50 kJ/mol) *vs.* the rigid C-5 axial amino one in **1a** crucially discriminated the nucleofilicity as of **1b** greater than that of **1a** in amination conditions.

Finally, the target melamines **4a**, **4b** were prepared according to our standard procedure [2]: it consisted of adding portionwise the clorodiamino-*s*-triazines **3a**, **3b** to an excess of piperazine dissolved in a refluxing 1,4-dioxanic K_2CO_3 suspension. As expected, due to their basicity and polarity, melamines **4a**, **4b** could not be eluted on silica gel. Thus, after complete removal of 1,4-dioxane, they were isolated by direct crystallisation from cooled water which completely discarded the excess of piperazine. Subsequent crystallisations from appropriate solvents provided pure analytical samples of **4a** and **4b**. Nevertheless, we were suspicious that the quantitative results in the synthesis of melamines **4a** and **4b** disclosed rather their partial solubility in water than the yield of aminations which occurred quantitatively with regard to the complete disappearance of the starting **3a**, **3b** (TLC monitoring).

Except **2b**, total NMR assignment of new compounds **3a**, **3b**, **4a** and **4b** took into account their complex four terms diastereomerism, occurring at room temperature, promoted by the restricted rotation about the C(*s*-triazine)-N(exocyclic) bonds following the normal lpN→π(*s*-triazine) conjugation (Scheme 3) [17]. A typical example is given in Figure 1.

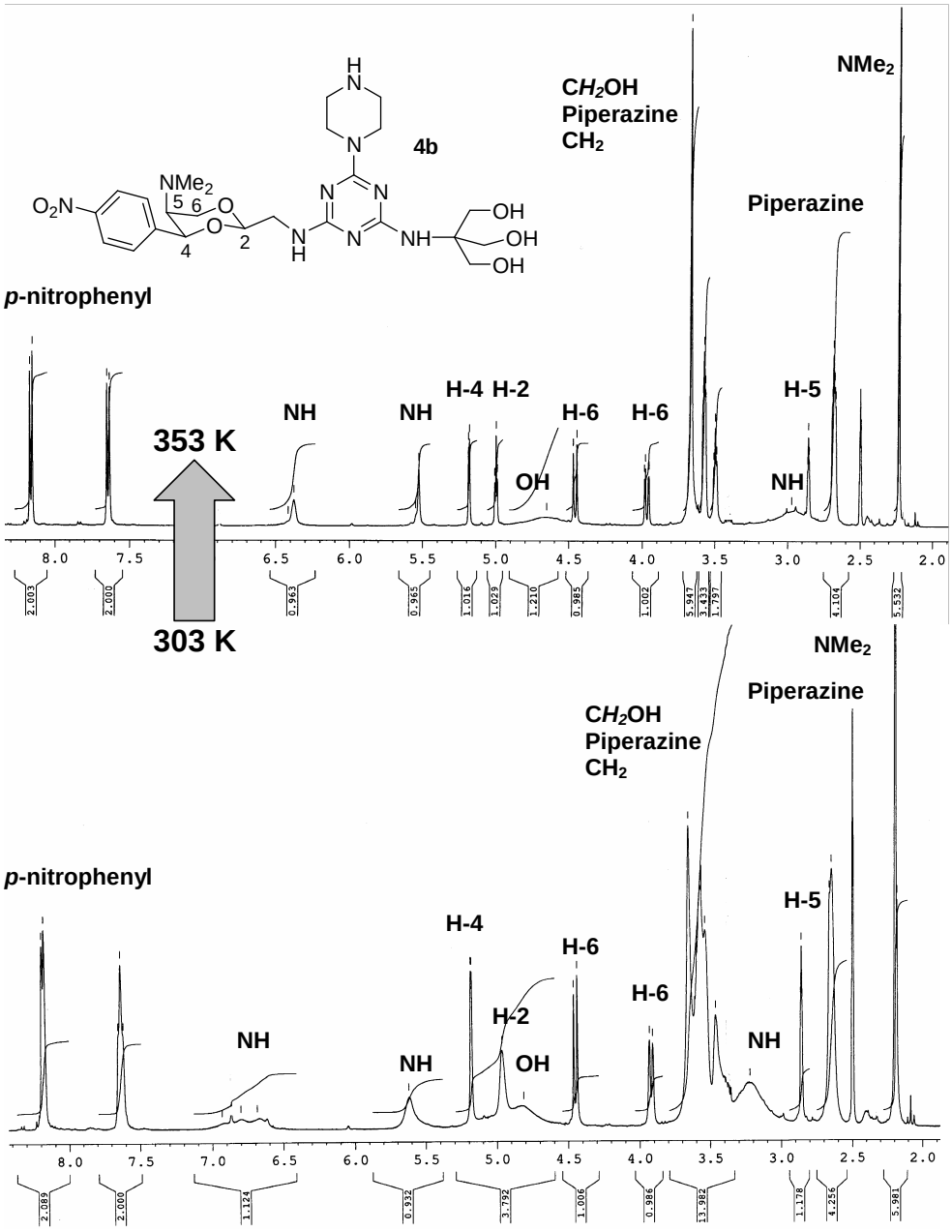
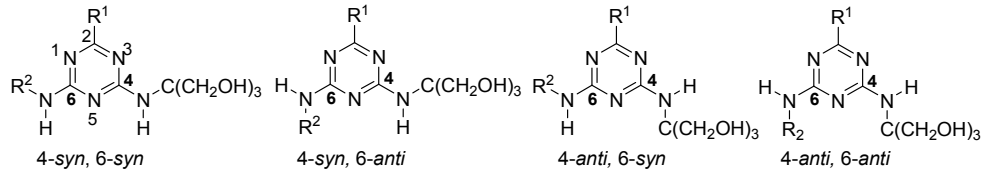


Figure 1. ^{1}H DNMR evolution of compound **4b** on 500 MHz timescale ([D_6]-DMSO)



R^1 = Cl: R^2 = **DX** (**3a**), **Me_2N-DX-CH_2** (**3b**)
R^1 = piperazin-1-yl: R^2 = **DX** (**4a**), **Me_2N-DX-CH_2** (**4b**)

Scheme 3

For the present discussion, introducing for the first time rotational phenomena in *N*-substituted amino-*s*-triazines as a competition between an *open-chain unit* (*e.g.* TRIS) and a *closed chain unit* (Scheme 1), we will limit it to some preliminary remarks only:

a) As shown in Figure 1, upon heating, at 353 K melamine **4b** reached complete flexibility with respect to the bonds C(*s*-triazine)-N(exocyclic). It involved both serinolic units, the *open-chain* (TRIS) and the *closed chain* one (**Me_2N-DX-CH_2NH**).

b) In the same ^{1}H DNMR conditions, melamine **4a** displayed some residual decoalescence of the signals assigned to protons *p*-nitrophenyl and H-5-e (see **EXPERIMENTAL PART**). It was but almost completely deblocked at 353 K. This nuanced difference between ^{1}H DNMR behaviours of the two serinolic melamines we rationalised recently as steric hindrance in the transition state of the rotational phenomena: it was less crowded in the case of the equatorial anchorage of the amino-1,3-dioxane **1b** on **4b** than the axial one of **1a** on **4a** [1].

c) If the *s*-triazine ring was more π-defficient, *e.g.* due to the presence of the electro-withdrawing chlorine atom linked at C-2 (precursors **3a**, **3b**), the bond order C(*s*-triazine)-N(exocyclic) obviously increased. Hence, the frozen rotamerism about these connections was better exhibited by the chlorodiamino-*s*-triazines **3a** and **3b** (Scheme 3, Figure 2). At 353 K, **3b** was a completely freely rotating structure meanwhile for **3a** one can appreciate two different speed rotational motions:

- the *open-chain serinolic unit* as a freely rotating fragment about the bond C(*s*-triazine)-N(TRIS).

- the *closed chain serinolic unit* in a slow exchange status with respect to rotation regarding the bond C(*s*-triazine)-N(axial-**DX**), mediating unequal populations of rotamers.

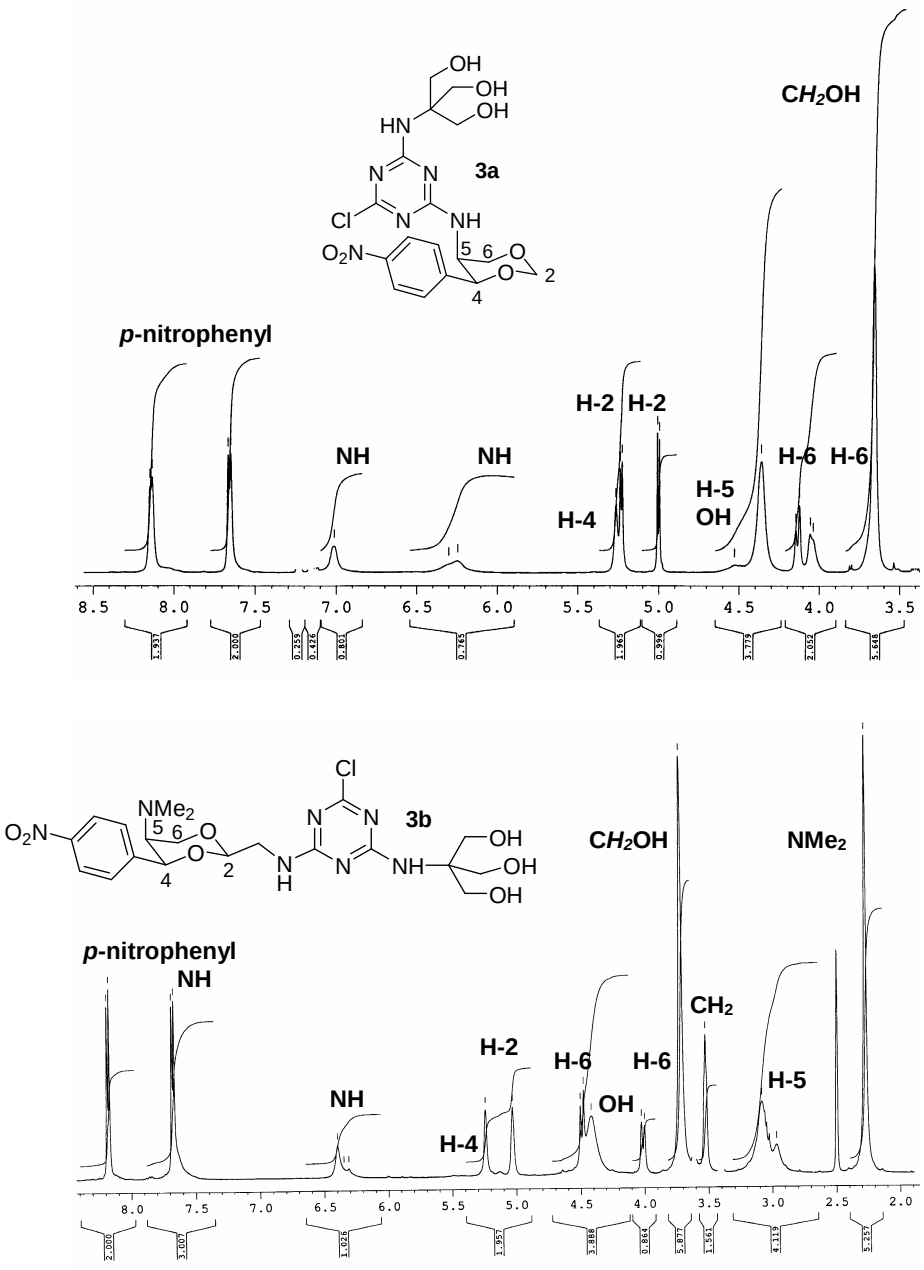


Figure 2. ^{1}H NMR spectra ok compounds 3a and 3b **(**353 K, 500 MHz, [D_6]DMSO)

CONCLUSIONS

Elaborated *N*-substituted melamines with *open-chain* vs. *closed chain serinolic units* together with a piperazin-1-yl fragment were available rapidly by applying one-pot procedures on cyanuric chloride. The first nucleophile replacing the *s*-triazine chlorine should be to most solvated one, hence the less reactive. The existence of a piperazin-1yl group recommends our compounds as attractive building-blocks in iterativesynthesis directed to dendritic structures. Restricted rotations about the partial double bonds C(*s*-triazine)-N(exocyclic) were encountered. They can be modulated by i) the *open vs. closed chain* nature of the two serinolic fragments substituting amino functionality in melamines and ii) axial vs. equatorial anchorage of the *closed chain serinolic unit* on the *s*-triazine skeleton. The full report on the observed phenomena and other representative examples are in progress.

EXPERIMENTAL SECTION

General. Melting points are uncorrected; they were carried out on ELECTROTHERMAL® instrument. Conventional NMR spectra were recorded on a Brucker® AM 300 instrument operating at 300 and 75 MHz for ^{1}H and ^{13}C nuclei respectively. A Brucker® DMX500 instrument was used for ^{1}H DNMR Experiments. All NMR spectra were measured in anhydrous commercially available deuteriated solvents. No $SiMe_4$ was added; chemical shifts were measured against the solvent peak. All chemical shifts (δ values) are given throughout in ppm; all coupling patterns ($^{n}J_{H,H}$ values) are given throughout in Hz.TLC was performed by using aluminium sheets with silica gel 60 F_{254} (Merck®); flash column chromatography was conducted on Silica gel Si 60 (40–63 μm, Merck®). IR spectra were performed on a Perkin-Elmer® Paragom FT-IR spectrometer. Only relevant absorptions are listed [throughout in cm^{-1}: weak (w), medium (m) or (s) strong]. Microanalyses were performed on a Carlo Erba® CHNOS 1160 apparatus. Mass spectra (MS) were recorded on a Brucker® Esquire Instrument. Specific rotations were measured on a Polamat A® Karl Zeiss Jena Instrument.

Note 1

Specific abbreviations used in description of NMR spectra: *p*-NPh (*p*-nitrophenyl), DX (1,3-dioxane ring of type **DX-NH_2** or **Me_2N-DX-CH_2NH_2**), pip. (piperazin-1-yl), *s*-T (*s*-triazine).

Note 2

The NMR description of compounds exhibiting frozen rotamers at room temperature was made by considering them as one global structure. Multiple values as chemical shifts and coupling constants for the same labelled

^{1}H or ^{13}C position means mixture of rotamers, as described in Scheme 3. Some specific abbreviations were used: bd (broad doublet) and bm (broad multiplet).

2,4-Dichloro-6-{[(1,3-dihydroxy-2-(hydroxymethyl)prop-2-yl]amino}-*s*-triazine (2b) (86%) white crystalline powder, mp 164–165 °C (direct trituration from Et_2O). [Found C 30.89, H 4.12, N 20.66; $C_7Cl_2H_{10}N_4O_3$ (269.09) requires C 31.24, H 3.75, N 20.82%). R_f (50% ligroin/acetone) = 0.80. IR (KBr): ν = 3372 (s), 3094 (s), 2957 (m), 2899 (m), 1751 (w), 1690 (w), 1563 (s), 1413 (s), 1332 (m), 1232 (m), 1161 (m), 1075 (m), 1051 (m), 1016 (m), 958 (m), 858 (m), 797 (m), 638 (w), 605 (w) cm^{-1}. ^{1}H NMR (300 MHz, [D_6]DMSO) δ_H = 8.05 (s, 1 H, NH), 4.60 (bs, 3 H, CH_2OH) 3.62 (s, 6 H, CH_2OH) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO) δ_C = 168.8, 168.2 (2 C, C-2, -4, *s*-T), 165.3 (1 C, C-6, *s*-T), 64.0 (1 C, C-2, TRIS), 58.3 (3 C, CH_2OH, TRIS) ppm. MS (DCI, +200 eV, NH_3): *m/z* (%) = 269 (100) [M^+], 210 (12),192 (20), 140 (25), 122 (33), 104 (62), 88 (90).

*Typical procedure for the synthesis of compounds **3a** and **3b** in a one-pot procedure*. *Preparation of compound **3a**.*

To anh. K_2CO_3 (1.38 g, 100%, 10 mmol) suspended in anh. THF (100 mL), TRIS (1.21 g 100%, 10 mmol) was added with vigorous stirring. The resulted suspension was cooled at -15 °C when cyanuric chloride (1.84 g, 100%, 10 mmol) as clear anh. THF (25 mL) solution was rapidly injected. The reaction mixture was let gently to reach room temperature and was kept as such for additional 24 hrs. with stirring. After this period, TLC monitoring indicated the intermediate 2,4-dichloro-6-{[1,3-dihydroxy-2-(hydroxymethyl)prop-2-yl]amino}-*s*-triazine **2b** as a single spot (eluent acetone: ligroin 2:1, R_f = 0.80). Freshly prepared (4*S*,5*S*)-4-(4- nitrophenyl)-1,3-dioxane (**1a**) (2.24 g 100%, 10 mmol and anh. K_2CO_3 (1.38 g, 100%, 10 mmol) were added and the reaction mixture was heated at reflux (65 °C) for 9 hrs (TLC monitoring, eluent toluene : isopropanol 2:1 v/v, R_f = 0.75). When **1a** and **2b** were detected in small traces only, the reaction mixture was cooled at room temperature. Minerals were filtered off and well washed with anh. THF. The organic filtrate was evaporated under reduced pressure to dryness and the resulted oil was twice crystallised from THF/Et_2O at -20 °C affording 3.61 g **3a** (79% yield with respect to cyanuric chloride). Optional purification of **3a**: column chromatography, eluent toluene : isopropanol 2:1 v/v.

2-Chloro-4-{[1,3-dihydroxy-2-(hydroxymethyl)prop-2-yl]amino}-6-{[(4*S*, 5*S*)-4-(4-nitrophenyl)-1,3-dioxan-5-yl]amino}-*s*-triazine (3a) (79%) white crystalline powder, mp 109.0 – 110.2 °C (flash column chromatography, eluent toluene: *i*-PrOH 2:1 v/v R_f = 0.70 or ligroin : acetone 1.5:2 v/v R_f = 0.60). [Found: C, 45.04; H, 4.55; N, 18.18; $C_{17}H_{21}ClN_6O_7$ (456.116) requires: C, 44.69;

H, 4.63; N, 18.40%]. IR ν_{max} (KBr) = 3369 (s), 2950 (m), 2865 (m), 1586 (s), 1519 (s), 1418 (m), 1387 (m), 1347 (s), 1243 (m), 1175 (s), 1096 (s), 1026 (s), 967 (m), 852 (w), 804 (m), 743 (m), 711 (m), 593 (w) cm^{-1}. ^{1}H NMR (500 MHz, [D_6]DMSO, 303 K) δ_H = 8.18, 8.14 (2 H, 2 × d, $^3J_{H,H}$ = 8.5, 9.5 Hz resp., H-3, -5, *p*-NPh), 7.67, 7.64 (2 H, 2 × d, $^3J_{H,H}$ = 8.5, 9.0 Hz resp., H-2, -6, *p*-NPh), 7.52, 7.50 (1 H, 2 × d, $^3J_{H,H}$ = 9.5, 9.5 Hz resp., DX-N*H*), 6.57, 6.50, 6.27, 6.21 (1 H, 4 × bs, TRIS-N*H*), 5.29, 5.25 (1 H, 2 × s, H-4-a, DX), 5.22 (1 H, d, $^2J_{H,H}$ = 6.0 Hz, H-2-e, DX), 4.98, 4.95 (1 H, d, s resp., $^2J_{H,H}$ = 6.0 Hz, H-2-a, DX), 4.66, 4.50 – 4.46 (3 H, t, m resp., $^3J_{H,H}$ = 5.5 Hz, CH_2O*H*), 4.36, 4.34, 4.32, 4.30 (1 H, 4 × d, $^3J_{H,H}$ = 10.0, 10.5, 10.5, 9.0 Hz resp., H-5-e, DX), 4.13 – 3.94 (2 H, m, H-6-e, -a, DX), 3.68 – 3.58 (6 H, m, C*H*$_2$OH) ppm ; ^{1}H NMR (500 MHz, [D_6]DMSO, 353 K) δ_H = 8.14 (2 H, bd, $^3J_{H,H}$ = 7.5 Hz, H-3, -5, *p*-NPh), 7.65 (2 H, d, $^3J_{H,H}$ = 7.5 Hz, H-2, -6, *p*-NPh), 7.01(1 H, bs, DX-N*H*), 6.30, 6.24 (1 H, 2 × bs, TRIS-N*H*), 5.27 (1 H, bs, H-4-a, DX), 5.23 (1 H, d, $^2J_{H,H}$ = 6.0 Hz, H-2-e, DX), 5.00, 4.95 (1 H, d, $^2J_{H,H}$ = 6.0 Hz, H-2-a, DX), 4.53, 4.36 (3 H, 2 × bs, CH_2O*H*), 4.36 (1 H, bs, H-5-e, DX), 4.14 (1 H, d, $^2J_{H,H}$ = 11.5 Hz, H-6-e, DX), 4.05 (1 H, bd, $^2J_{H,H}$ = 9.5 Hz, H-6-a, DX), 3.66 (6 H, bs, C*H*$_2$OH) ppm ; ^{13}C NMR (75 MHz, [D_6]DMSO, 298 K) δ_C = 167.8, 167.6 (1 C, C-2, *s*-T), 165.4, 165.2, 165.0, 164.9 (2 C, C-4, -6, *s*-T), 147.1 (1 C, C-4, *p*-NPh), 146.6 (1 C, C-1, *p*-NPh), 127.7, 127.6, 127.4 (2 C, C-3, -5, *p*-NPh), 123.4, 123.2 (2 C, C-2, -6, *p*-NPh), 93.8 (1 C, C-2, DX), 78.6, 78.1, 78.0 (1 C, C-4, DX), 70.3, 69.9 (1 C, C-6, DX), 62.4, 62.3, 62.1 (3 C, CH_2OH), 60.1, 59.6, 59.4 (1 C, C-2, TRIS), 49.7, 49.3, 49.2 (1 C, C-5, DX) ppm. MS (DCI positive, 200 eV, isobutane), m/z (rel. int. %): 513[M^+ + $HC(CH_3)_3$ – 2 H] (20), 495 [M^+] (< 10), 457 (100), 421 (< 10), 225 (< 10), 140 (10), 104 (< 10), 93 (< 10). $[\alpha]_D^{20}$ = -31.0 (0.5% THF).

2-Chloro-4-{[1,3-dihydroxy-2-(hydroxymethyl)prop-2-yl]amino}-6-{[(2*R*, 4*S*,5*S*)-5-(dimethylamino)-4-(4-nitrophenyl)-1,3-dioxan-2-yl]methylamino}-*s*-triazine (3b) (67%) yellow crystalline powder, mp 138.0 – 140.5 °C (flash column chromatography, eluent ligroin : acetone 1:2.5 v/v, R_f = 0.50). [Found: C, 47.04; H, 5.15; N, 18.89; $C_{20}H_{28}ClN_7O_7$ (513.174) requires: C, 46.74; H, 5.49; N, 19.08%]. IR ν_{max} (KBr) = 3369 (s), 2945 (m), 2876 (m), 1583 (s), 1520 (s), 1460 (m), 1412 (m),1348 (s), 1154 (m), 1113 (m), 1054 (s), 1014 (m), 852 (w), 804 (m), 710 (m), 570 (w) cm^{-1}. ^{1}H NMR (500 MHz, [D_6]DMSO, 303 K) δ_H = 8.20 (2 H, d, $^3J_{H,H}$ = 7.8 Hz, H-3, -5, *p*-NPh), 8.00, 7.94, 7.92 (1 H, 3 × t, $^3J_{H,H}$ = 4.8, 6.0, 6.0 Hz resp., DX-N*H*), 7.67 (2 H, d, $^3J_{H,H}$ = 7.5 Hz, H-2, -6, *p*-NPh), 6.64, 6.60, 6.56, 6.28 (1 H, 4 × s, TRIS-N*H*), 5.25, 5.23 (1 H, 2 × bs, H-4-a, DX), 5.02 – 4.98 (1 H, m, H-2-a, DX), 4.68 (1 H, t, $^3J_{H,H}$ = 5,5 Hz, CH_2O*H*), 4.57 – 4.48 (2 H, m, CH_2O*H*), 4.57 – 4.48 (1 H, m, H-6-e, DX), 3.97, 3.95 (1 H, 2 × bs, H-6-a, DX), 3.68 – 3.65, 3.61 – 3.58 (6 H,

2 × m, C*H*$_2$OH), 3.49 – 3.46 (2 H, m, C*H*$_2$NH), 2.93 (1 H, bs, H-5-e, DX), 2.23 (6 H, bs, NMe$_2$) ppm ; ^{1}H NMR (500 MHz, [D$_6$]DMSO, 353 K) δ_H = 8.18 (2 H, d, $^3J_{H,H}$ = 8.5 Hz, H-3, -5, *p*-NPh), 7.68 (2 H, d, $^3J_{H,H}$ = 8.5 Hz, H-2, -6, *p*-NPh), 7.68 (1 H, bs, DX-N*H*), 6.39 (1 H, bs, TRIS-N*H*), 5.24 (1 H, bs, H-4-a, DX), 5.03 (1 H, bs, H-2-a, DX), 4.49 (1 H, d, $^2J_{H,H}$ = 12.0 Hz, H-6-e, DX), 4.42 (3 H, bs, CH$_2$O*H*), 4.01 (1 H, d, $^2J_{H,H}$ = 12.0 Hz, H-6-a, DX), 3.72 (6 H, s, C*H*$_2$OH), 3.53 (2 H, s, C*H*$_2$NH), 2.97 (1 H, s, H-5-e, DX), 2.27 (6 H, s, NMe$_2$) ppm ; ^{13}C NMR (75 MHz, [D$_6$]DMSO, 298 K) δ_C = 168.2, 167.7 (1 C, C-2, *s*-T), 165.7, 165.2 (2 C, C-4, -6, *s*-T), 146.7 (2 C, C-1, -4, *p*-NPh),126.9 (2 C, C-3, -5, *p*-NPh), 123.2 (2 C, C-2, -6, *p*-NPh), 99.2 (1 C, C-2, DX), 80.5 (1 C, C-4, DX), 67.4, 65.3, 64.4 (1 C, C-6, DX), 62.5, 62.4, 59.6 (3 C, CH$_2$OH), 60.2, 60.0 (1 C, C-2, TRIS), 58.5 (1 C, C-5, DX), 44.6, 44.2 (1 C, CH$_2$NH), 43.7 (2 C, NMe$_2$) ppm. MS (DCI positive, 200 eV, isobutane), m/z (rel. int. %): 514 [M$^+$ + 1] (25), 310 (< 5), 292 (< 5), 278 (5), 241 (< 5), 178 (100), 166 (<5), 140 (20), 116 (11), 104 (20), 87 (18), 73 (<5). $[\alpha]_D^{25}$ = +137.8 (0.5% THF).

*Typical procedure for the synthesis of compounds **4a** and **4b**. Preparation of compound **4a***.

Anh. piperazine (1.137 g, 13.2 mmol) was dissolved in anh. 1,4-dioxane (75 mL) then anh. K_2CO_3 (0.455 g, 3.29 mmol) was added. The resulted suspension was heated at reflux (102 °C) with vigorous stirring. At this temperature, 2-chloro-4-{[1,3-dihydroxy-2-(hydroxymethyl)prop-2-yl]amino}-6-{[(4*S*,5*S*)-4-(4-nitrophenyl)-1,3-dioxan-5-yl]amino}-*s*-triazine **3a** (1.500 g, 3.29 mmol) as anh. 1,4-dioxane (25 mL) solution was added portionwise as 5 mL each 2 hrs. After the addition of each portion, within 2 hrs., TLC monitoring indicated the complete absence of the starting **3a** (eluent toluene : isopropanol 2:1 v/v). The reaction mixture was cooled at room temperature when minerals were filtered off and well washed with anh. 1,4-dioxane (optionally, anh. THF). The organic filtrate was evaporated to dryness under reduced pressure to yield an oily residue (2.158 g). This was taken with cooled water (20 mL) with vigorous stirring to provide a yellowish suspension. The solid was filtered off, well washed with cooled water then dried at room temperature. Supplementary crystallisation from ether at -20 °C provided the pure product **4a** (1.170 g, 70% yield with respect to **3a**).

1-{4-{[1,3-dihydroxy-2-(hydroxymethyl)prop-2-yl]amino}-6-{[(4*S*,5*S*)-4-(4-nitrophenyl)-1,3-dioxan-5-yl]amino}-*s*-triazin-2-yl}piperazine (4a) (70%) yellowish crystalline powder, mp 119 – 124 °C (Et_2O). [Found: C, 50.03; H, 5.88; N, 21.95; $C_{21}H_{30}N_8O_7$ (506.22) requires: C, 49.80; H, 5.97; N, 22.12%]. IR ν_{max} (KBr) = 3392 (m), 2493 (m), 2856 (m), 1549 (s), 1504 (s), 1446 (m), 1346 (s), 1273 (m) 1174 (m), 1105 (m), 1025 (m), 872 (w), 852 (w), 809 (m), 744 (w), 711 (w), 584 (w) cm^{-1}. ^{1}H NMR (500 MHz, [D$_6$]DMSO, 303 K) δ_H = 8.18, 8.12 (2 H, 2 × bd, $^3J_{H,H}$ = 7.0, 5.5 Hz resp., H-3, -5, *p*-NPh), 7.64, 7.62 (2 H,

2 × d, $^3J_{H,H}$ = 9.0, 9.0 Hz resp., H-2, -6, *p*-NPh), 5.92, 5.81 (1 H, bs, d, $^3J_{H,H}$ = 6.5 Hz, DX-N*H*), 5.57, 5.49 (1 H, 2 × bs, TRIS-N*H*), 5.28 - 5.21 (2 H, m, H-2-e, H-4-a, DX), 4.96 (1 H, d, $^2J_{H,H}$ = 6.0 Hz, H-2-a, DX), 4.43 - 4.24 (1 H, bm, H-5-e, DX), 4.09 – 3.97 (2 H, bm, H-6-e, -a, DX), 3.59 (6 H, bm, C*H*$_2$OH), 3.45 (7 H, bs, CH$_2$O*H*, H-2, -6, pip.), 2.64 – 2.60 (5 H, bm, H-3, -5, NH, pip.) ppm ; ^{1}H NMR (500 MHz, [D$_6$]DMSO, 353 K) δ_H = 8.12 (2 H, d, $^3J_{H,H}$ = 8.5 Hz, H-3, -5, *p*-NPh), 7.63 (2 H, d, $^3J_{H,H}$ = 8.5 Hz, H-2, -6, *p*-NPh), 5.61 (1 H, d, $^3J_{H,H}$ = 9.5 Hz, DX-N*H*), 5.43 (1 H, s, TRIS-N*H*), 5.23 (2 H, s, d, $^2J_{H,H}$ = 5.8 Hz, H-4-a, H-2-e, DX), 5.00 (1 H, d, $^2J_{H,H}$ = 5.8 Hz, H-2-a, DX), 4.40 (1 H, bd, $^3J_{H,H}$ = 9.5 Hz, H-5-e, DX), 4.11 (1 H, d, $^2J_{H,H}$ = 11.0 Hz, H-6-e, DX), 4.02 (1 H, d, $^2J_{H,H}$ = 11.0 Hz, H-6-a, DX), 3.62 (6 H, s, C*H*$_2$OH), 3.46 (4 H, t, $^3J_{H,H}$ = 5.0 Hz, H-2, -6, pip.), 3.30 (3 H, bs, CH$_2$O*H*), 2.65 (5 H, s, t, $^3J_{H,H}$ = 5.0 Hz, H-3, -5, NH, pip.) ppm; ^{13}QC NMR (75 MHz, [D$_6$]DMSO, 298 K) δ_C = 165.5, 165.4, 165.2, 165.0 (2 C, C-4, -6, *s*-T), 164.2 (1 C, C-2, *s*-T), 146.9 (2 C, C-1, -4, *p*-NPh), 127.4, 127.1 (2 C, C-3, -5, *p*-NPh), 123.3, 123.1 (2 C, C-2, -6, *p*-NPh), 93.9 (1 C, C-2, DX), 78.8, 78.4 (1 C, C-4, DX), 70.7, 70.5 (1 C, C-6, DX), 61.3, 61.0 (4 C, C-2, CH$_2$OH, TRIS), 48.8 (1 C, C-5, DX), 45.4 (2 C, C-2, -6, pip.), 43.9 (2 C, C-3, -5, pip.) ppm. MS (DCI positive, 200 eV, isobutane), m/z (rel. int. %): 563 [M$^+$ + HC(CH$_3$)$_3$ - 2] (< 10), 507 [M$^+$ + 1] (100), 489 (10), 477 (10), 404 (10), 282 (15), 225 (10), 208 (35), 178 (25), 165 (12), 115 (< 10), 104 (20), 87 (75). $[\alpha]_D^{20}$ = -16.0 (0.5% THF).

1-{4-{[1,3-dihydroxy-2-(hydroxymethyl)prop-2-yl]amino}-6-{[(2*R*,4*S*,5*S*)-5-(dimethylamino)-4-(4-nitrophenyl)-1,3-dioxan-2-yl]methylamino}-*s*-triazin-2-yl}piperazine (4b) (65%) yellow crystalline powder, mp 145 – 147 °C (Et_2O) [Found: C, 50.97; H, 6.88; N, 22.05; $C_{24}H_{37}N_9O_7$ (563.282) requires: C, 51.15; H, 6.62; N, 22.37%]. IR ν_{max} (KBr) = 3298 (m), 2940 (m), 2858 (m), 1551 (s), 1515 (s), 1446 (s),1347 (s), 1297 (m), 1151 (m), 1112 (m), 1054 (m), 1015 (m), 852 (m), 809 (m), 710 (w), 578 (w) cm^{-1}. ^{1}H NMR (500 MHz, [D$_6$]DMSO, 303 K) δ_H = 8.18 (2 H, d, $^3J_{H,H}$ = 7.5 Hz, H-3, -5, *p*-NPh), 7.64, 7.63 (2 H, 2 × d, $^3J_{H,H}$ = 9.0 Hz, H-2, -6, *p*-NPh), 6.93, 6.80, 6.69 (1 H, 3 × bs, DX-N*H*), 5.62 (1 H, bs, TRIS-N*H*), 5.19 (1 H, d, $^3J_{H,H}$ = 2.5 Hz, H-4-a, DX), 4.97 (1 H, bs, H-2-a, DX), 4.81 (3 H, bs, CH$_2$O*H*), 4.45 (1 H, d, $^2J_{H,H}$ = 11.3 Hz, H-6-e, DX), 3.92 (1 H, d, $^2J_{H,H}$ = 11.3 Hz, H-6-a, DX), 3.66 - 3.54 (10 H, bm, C*H*$_2$OH, H-2, -6, pip.), 3.40 (2 H, bs, C*H*$_2$NH), 3.22 (1 H, bs, NH, pip.), 2.86 (1 H, dd, $^3J_{H,H}$ = 2.5 Hz, H-5-e, DX), 2.66 (4 H, m, H-3, -5, pip.), 2.20, 2.18 (6 H, m, NMe$_2$) ppm ; ^{1}H NMR (500 MHz, [D$_6$]DMSO, 353 K) δ_H = 8.17 (2 H, d, $^3J_{H,H}$ = 8.5 Hz, H-3, -5, *p*-NPh), 7.64 (2 H, d, $^3J_{H,H}$ = 8.5 Hz, H-2, -6, *p*-NPh), 6.41 (1 H, bs, DX-N*H*), 5.53 (1 H, bs, TRIS-N*H*), 5.19 (1 H, d, $^3J_{H,H}$ = 3.0 Hz, H-4-a, DX), 5.00 (1 H, dd, $^3J_{H,H}$ = 4.5 Hz, H-2-a, DX), 4.65 (3 H, bs, CH$_2$O*H*), 4.46 (1 H, d, $^2J_{H,H}$ = 12.5 Hz, H-6-e, DX), 3.97 (1 H, dd, $^2J_{H,H}$ = 12.5 Hz, $^3J_{H,H}$ = 3.0 Hz, H-6-a, DX), 3.66 (6 H, s, C*H*$_2$OH), 3.57 (4 H, t, $^3J_{H,H}$ = 4.3 Hz, H-2, -6,

pip.), 3.50 (2 H, dd, $^3J_{H,H}$ = 4.5 Hz, C*H*$_2$NH), 2.97 (1 H, bs, NH, pip.), 2.86 (1 H, dd, $^3J_{H,H}$ = 2.8 Hz, H-5-e, DX), 2.68 (4 H, m, H-3, -5, pip.), 2.23 (6 H, s, NMe_2) ppm ; ^{13}C NMR (75 MHz, [D_6]DMSO, 298 K) δ_C = 165.8 (1 C, C-4, -6, *s*-T), 164.4 (1 C, C-2, *s*-T), 148.8 (1 C, C-4, *p*-NPh), 146.5 (1 C, C-1, *p*-NPh), 126.9, 125.3, 123.1 (4 C, C-2, -3, -5, -6, *p*-NPh), 99.6 (1 C, C-2, DX), 80.0 (1 C, C-4, DX), 65.3, (1 C, C-6, DX), 64.3 (3 C, CH_2OH), 61.4, 61.3 (1 C, C-2, TRIS), 58.4 (1 C, C-5, DX), 46.3, 46.1 (2 C, C-2, -6, pip.), 45.8 (2 C, C-3, -5, pip.), 44.3 (1 C, CH_2NH), 43.7 (2 C, NMe_2) ppm. MS (DCI positive, 200 eV, isobutane), m/z (rel. int. %): 620 [M^+ + $HC(CH_3)_3$ - 2] (< 10), 564 [M^+ + 1] (65), 449 (28), 380 (55), 300 (10), 282 (15), 221 (< 10), 178 (100), 165 (25), 148 (10), 104 (45), 87 (35). $[\alpha]_D^{25}$ = +140.8 (0.5% THF).

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