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TO WHAT EXTENT THE NMR "MOBILE PROTONS" ARE RELEVANT FOR RESTRICTED ROTATIONAL STEREOCHEMISTRY PHENOMENA?

A CASE IN AMINO-*s*-TRIAZINE SERIES

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ABSTRACT. The use of the so-called NMR "mobile protons" in investigation of restricted rotational phenomena about partial double bonds, *i.e.* C^{sp2}(*s*-triazine)-N(exocyclic), is examined in the case of twelve highly elaborated amino-*s*-triazines.

Keywords: *amino-s-triazines, NMR, restricted rotation, serinols*

INTRODUCTION

The ^{1}H NMR assignment of the so-called "mobile (exchangeable, labile) protons" X*H* (X = N, O, S, etc.) is usually achieved by taking into account the crucial influence of the solvent (hydrogen bond donor or acceptor), heteroatom (X), temperature and molecular environment [1a]. Hydrogen bond acceptor solvents, *e.g.* [D_6]DMSO, allow, by their chelatizing aptitude, detection of vicinal couplings $^3J_{H,H}$ in A_nX systems (n = 1, 2) of type >C*H*-N*H*- and >C*H*-O*H*. In contrast, in hydrogen bond acceptor solvents, *e.g.* $CDCl_3$, these "mobile protons" are observed much upfield and their broad shaped signals are somehow "classical", for example in the case of NH groups, due also to the quadrupolar moment of the isotope ^{14}N (I = 1) [1].

Higher temperatures increase the X*H* intra- or intermolecular mobility. For complex molecular environments, the correct significance of the "mobile protons" ^{1}H NMR location is still a challenging task [1b, 1c].

In the above context, the aim of this study is to present the synthesis and rotational stereochemistry about the C^{sp2}-N partial double bonds in some elaborated amino-*s*-triazines possessing a plethora of "mobile protons" together with their versatile role in evaluation of this dynamic behaviour.

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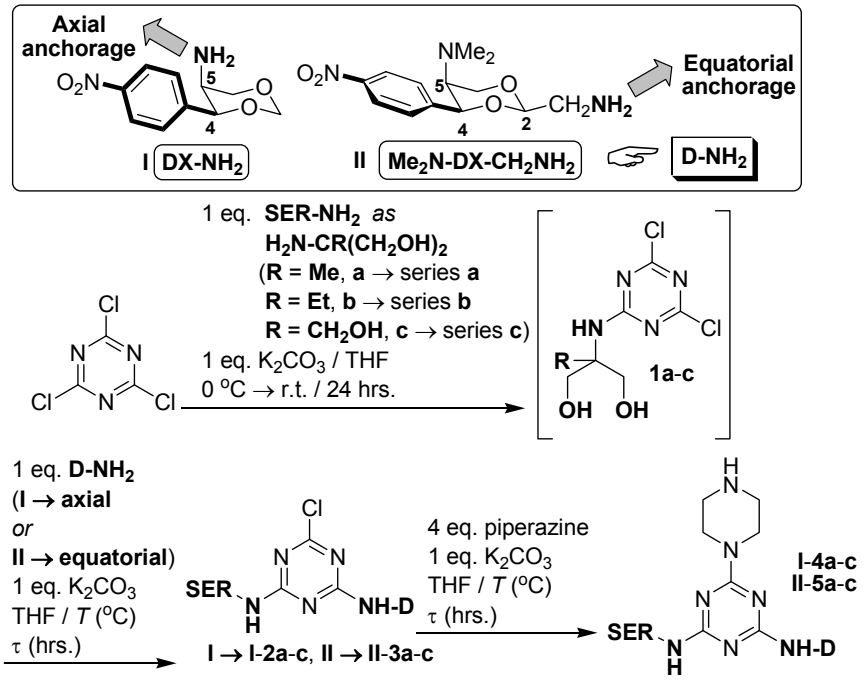
RESULTS AND DISCUSSION

Synthesis

The chemistry of the performed reactions is resumed in *Scheme 1*. Quantitative data are listed in *Table 1*.



Scheme 1

Except our earlier results [2] on this topic, no similar approach was reported so far. All compounds are new ones.

Thus, by successive three highly selective aminations of cyanuric chloride with amino-nucleophiles of type *C*-substituted 2-aminopropane-1,3-diol (**SER-NH$_2$**, "*serinol*", **a**-**c**), we accessed the *N*-unsymmetrically substituted triamino-*s*-triazines ("*melamines*") **I-4a**-**c** and **II**-**5a**-**c**. They can be seen as novel building-blocks for further iterative synthesis. This account was performed in the presence of piperazine, a widely recognised dendritic linker [3].

The use of tandem two-type serinolic amino-nucleophiles (**a**-**b** and **I**, **II**) needs the comments below:

i) C-2-substituted serinols (**SER-NH$_2$**, **a** "*Methylserinol*", **b** "*Ethylserinol*" and **c** TRIS), were designed to play the role of an "*open-chain*" *N*-ligand in the target melamines. The first step-amination, carried out with **a**-**c,** occurred quantitatively in a very clean but slow evolution, due most likely to solvation effects diminishing their nucleophilicity.

Table 1. Reaction conditions and quantitative results in the synthesis of compounds **I**-**2a**-**c**, **II**-**3a**-**c**, **I**-**4a**-**c** and **II**-**5a**-**c** (*Scheme 1*)

No.[a]	**SER-NH (R)**	**D-NH** (**I** *or* **II**)	*T* (°C) / τ (hrs.)	Yield (%)[b]
I-**2a**	Me	**DX-NH** (**I**)	reflux / 16	80
I-**2b**	Et		reflux / 22	66
I-**2c**	CH_2OH		reflux / 12	84
II-**3a**	Me	**Me_2N-DX-CH_2NH** (**II**)	-10 → r.t. / 24 reflux / 14	83
II-**3b**	Et		-10 → r.t. / 24 reflux / 16	42
II-**3c**	CH_2OH		-10 → r.t. / 24 reflux / 12	95
I-**4a**	Me	**DX-NH** (**I**)	r.t. /10[c]	80
I-**4b**	Et		r.t. / 24	84
I-**4c**	CH_2OH			86
II-**5a**	Me	**Me_2N-DX-CH_2NH** (**II**)		71
II-**5b**	Et			67
II-**5c**	CH_2OH			81

[a] The synthesis and stereochemistry of intermediates **1a**-**c** we reported elsewhere [2a];
[b] In case of compounds **I**-**2a**-**c** and **II**-**3a**-**c** as isolated global yields, after two-steps synthesis; in case of melamines **I**-**4a**-**c** and **II**-**5a**-**c** as isolated yields, after one-step synthesis.
[c] Time required by the slow addition, portionwise, of chlorodiamino-*s*-triazine to a four fold molar excess of piperazine (see **EXPERIMENTAL SECTION**).

ii) *Mutatis-mutandis*, enantiopure amino-1,3-dioxanes **D-NH_2**, **I** and **II**, should be seen as "*closed-chain*" *N*-ligands. They were readily available by our "sulphuric acetalisation" methodology [2b,2d] applied to the corresponding (1*S*,2*S*)-2-amino-1-(4-nitrophenyl)propane-1,3-diols ("*Threo-p-nitrophenylserinols*"). **I** and **II** were used in the second step-amination. In the case of nucleophile **II**, precautions against side reactions, *i.e.* amination by *N*-demethylation, required milder conditions [2b, 4].

iii) The selective attachment of the third nucleophile was accomplished based on our previously reported procedure [2a], consisting of the portionwise addition of chlorodiamino-*s*-triazines **I**-**2a**-**c** and **II**-**3a**-**c** (10 hrs. at room temperature) to a four fold molar amount of piperazine. Melamines **I**-**4a**-**c** and **II**-**5a**-**c** were purified by column chromatography on partially deactivated silica gel.

Rotational stereochemistry phenomena

Brief overview of our problem

Starting from the well-known herbicide ATRAZINE®, 2-chloro-4-ethylamino-6-isopropylamino-*s*-triazine structural assignment [5], the elucidation of rotational diastereomers of *N*-substituted amino-*s*-triazines, in solution, is a quite difficult task [6]. They are issued from the lpN(exocyclic) → π (deficient *s*-triazine) delocalisation determining an increased order of bonds C(*s*-triazine)-

N(exocyclic). In addition to NMR and 2D-^{1}H,^{1}H NMR techniques [6], in investigating this phenomenon, computational methods [6a, 6g] including DFT approaches [2a, 2b] are also of interest. Usually, these studies focused on (un)symmetrically *N*-substituted melamines [6] by means of (VT) NMR at low temperature. In contrast, apart from ATRAZINE®, minor attention was paid to *N*,*N*'-substituted-2-chloro-4,6-diamino-*s*-triazines concerning their dynamic behaviour [5b, 6a-c], limited to *symmetric* 2-chloro-4,6-bis(*N*,*N*-dialkylamino) derivatives only.

Some introductory structural observations on our *unsymmetrically N*-substituted amino-*s*-triazines are mandatory.

The serinolic "*open-chain*" site, containing a variable number of geminal hydroxymethyl groups, is *a priori* seen as the most solvated region of the molecule while the amino-1,3-dioxanic "*closed-chain*" units, **I** and **II**, are anancomeric structures due to the overwhelmingly one-sided conformational equilibria, by the adoption of an equatorial position by the C-4'-*p*-nitrophenyl ring (*i.e.*, anancomerising group) [7]. However, their amino-anchorage to the *s*-triazine is essentially different, either *axial* (in **I**-**2a**-**c** and **I**-**4a**-**c**) or *equatorial* (in **II**-**3a**-**c** and **II**-**5a**-**c**).

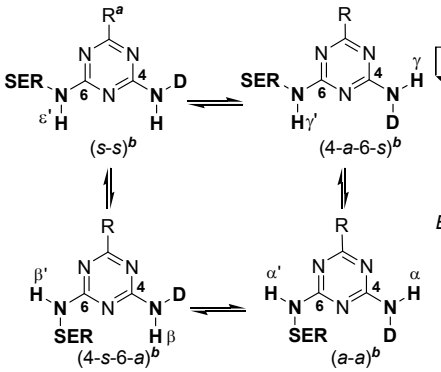
As expected, the increased bond order of bonds C(*s*-triazine)-N(exocyclic) in our compounds creating restricted rotation, determined their NMR rather complicate appearance, at room temperature (*e.g.* a "sugar like" aspect). Indeed, depending on the π-deficiency of the *s*-triazine ring, higher in chlorodiamino-*s*-triazines than in melamines, and in an idealised topological model, four stereoisomers are possible (*Scheme 2*). Each of them can be generated by a single rotation / (frozen) equilibrium (a step-by-step interconversion).

Next, since the intimate rotational status of these four species was very different in the above two series, **I**-**2** and **II**-**3** *vs.* **I**-**4** and **II**-**5**, they will be discussed separately, in the decreasing order of *s*-triazine π-deficiency.

Rotational stereochemistry phenomena in chlorodiamino-s-triazines

As predicted, at *room temperature*, chlorodiamino-*s*-triazines **I**-**2a**-**c** and **II**-**3a**-**c** consisted of mixtures of four frozen rotamers (*Scheme 2*). Their abundance could be evaluated by means of ^{1}H NMR resonance of protons D-N*H* (α, β, γ) and SER-N*H* (α', β', γ'), the best separated, hence the single ones indicative for rotational behaviour. [D_6]DMSO was the only appropriate NMR solvent in all investigations (*Table 2*, *Table 3*).

In series **I**-**2**, the individual assignment of rotamers starts from the 2D-^{1}H,^{1}H-NOESY chart of compound **I**-**2a** (*Figure 1*, *Scheme 2*) disclosing dipolar interactions between the proton SER-N*H* (6.46 ppm, signal γ') and the *p*-nitrophenyl ring of the axially anchored D-NH moiety in rotamer **I**-**2a** (4-*a*-6-*s*), hence a "*trans*" relationship between the *N*,*N*'-ligands (*Table 2*).

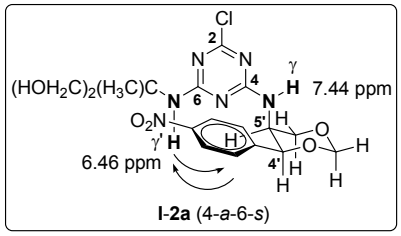


R = Cl

Axial anchorage of **D** *N*-ligand in	Content of blocked rotamers (%)[c]			
	a-a	4-*s*-6-*a*	4-*a*-6-*s*	*s-s*
I-2a	62.0	19.5	16.5	2.0
I-2b	56.5	19.5	16.0	8.0
I-2c	52.0	23.0	18.0	7.0

Equatorial anchorage of **D** *N*-ligand in	*s-s*	4-*s*-6-*a*	4-*a*-6-*s*	*a-a*
II-3a	62	19	19	-
II-3b	67	18	15	-
II-3c	57	21	22	-

[a]R = Cl, in series **I-2**, **II-3**; piperazin-1-yl in series **I-4**, **II-5**
[b]Descriptors *s* (*syn*) and a (*anti*) are used with respect to orientation of "*open-chain*" **SER**inolic and "*closed-chain* "**D**ioxanic *N*-ligands *vs*. **R**.
[c]Throughout percentages deduced from the ^{1}H NMR spectra performed at room temperature in [D$_6$]DMSO using signals of the *indicative protons* D-N*H* (α, β, γ) and SER-N*H* (α', β', γ', ε') (see *Table 2*, *Table 3*).



Scheme 2

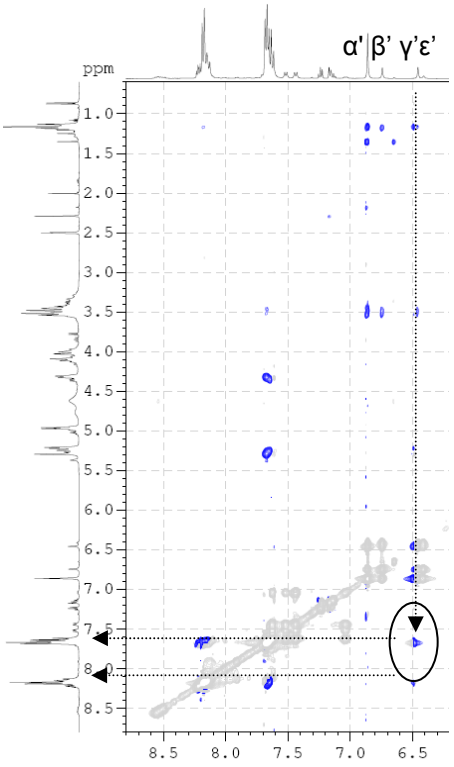


Figure 1. 2D-^{1}H,^{1}H-NOESY chart of compound **I-2a** (500 MHz, [D$_6$]DMSO)

The "*trans*" analogue **I-2a** (4-*s*-6-*a*) was deduced logically, since its incidence was comparable. The major rotamer **I-2a** (*a*-*a*) was preliminarily established by considering the two closed SER-N*H* δ values, signals α' and β', in their *anti* local environment: 6.74 ppm in **I-2a** (4-*s*-6-*a*, signal β') and 6.86 ppm in **I-2a** (*a*-*a*), signal α' (*Table 2*). If so, in the *syn* local environments, rotamers **I-2a** (4-*a*-6-*s*), **I-2a** (*s*-*s*), the δ values of protons SER-N*H* are also very related, 6.46 (signal γ') and 6.41 (signal ε') respectively. It is to note that compound **I-2a** was the single case that made possible the rotamerism recognition based on NOESY Experiment.

Table 2. Relevant ^{1}H NMR data of restricted rotation about C(*s*-triazine)- N(exocyclic) bonds in compounds **I-2a-c**: *axial anchorage of the 1,3-dioxane N-ligand*

No.	*T* (K)	Indicative protons	Discriminating δ_H (ppm) values and multiplicity $^3J_{H,H}$ (Hz)[a] in blocked rotamers			
			a-a	4-*s*-6-*a*	4-*a*-6-*s*	*s-s*
			α[b] α'	β β'	γ γ'	ε ε'
I-2a	**298**	D-N*H*	7.62 (d, 10.0)	7.52 (d, 9.5)	7.44 (d, 9.5)	-[c]
		SER-N*H*	6.86 (s)	6.74 (s)	6.46[d] (s)	6.41 (bs)
		OH	4.95, 4.75 (2×bs)			
	353	D-N*H* 7.01 (bs); SER-N*H* 6.51, 6.41 (2×bs); OH 4.50 (bs)				
I-2b	**303**	D-N*H*	7.62 (d, 9.0)	7.52 (d, 9.5)	7.46 (d, 10.0)	-
		SER-N*H*	6.77 (s)	6.64 (s)	6.34 (s)	6.33 (bs)
		OH	4.72-4.68 (m, 5.5), 4.56 (dd, 6.0), 4.52 (dd, 5.8), 4.47 (dd, 5.3)			
	353	D-N*H* 7.02 (bs); SER-N*H* 6.43, 6.31 (2×bs); OH 4.37 (bs)				
I-2c	**303**	D-N*H*	7.53, 7.52, 7.49[e]			
		SER-N*H*	6.57 (s)	6.50 (s)	6.27 (s)	6.21 (bs)
		OH	4.51 - 4.58 (m, 6.0)			
	353	D-N*H* 7.01 (bs); SER-N*H* 6.30, 6.24 (2×bs); OH 4.53, 4.36 (2×bs)				
Final rotational status of I-2a-c *i) slow free rotation about bond C-4(s-triazine)-NH (**D** N-ligand)* *ii) slow exchange about bond C-6(s-triazine)-NH (**SER** N-ligand)*						

[a]As ^3J(ax-N*H*-*H*-5-e) in **D** *N*-ligand, ^3J(CH_2*OH*) in **SER** *N*-ligand, also supported by the 2D-^{1}H, ^{1}H-COSY Charts.
[b]Relevant peaks for (VT) ^{1}H NMR analysis (*Scheme 2*, *Figure 3*).
[c]Rotamers not found on the D-N*H* zone of the spectrum: the corresponding abundance was adopted from the SER-N*H* signal, ε'.
[d]Deduced from the 2D-^{1}H,^{1}H-NOESY Experiment (*Figure 1*).
[e]Not assignable as overlapped signals.

Therefore, in order to validate this assignment for the entire series **I-2** and to predict the rotamerism occurrence in series **II-3** (*Table 3*), computational methods were applied to compounds **I-2a** (*axially* anchored) and **II-3a** (*equatorially* anchored) (*Table 4*).

Thus, by optimisation of rotational stereoisomers (*a-a*) and (*s-s*) of compounds **I-2a** and **II-3a** at B3LYP/6-311++G** level of theory and taking into account the effect of solvent (DMSO), we found out that:

i) In compounds **I-2a-c**, in agreement with ^{1}H NMR data, frozen stereoisomers **I-2a-c** (*a-a*) were indeed dominant while **I-2a-c** (*s-s*) should be the minor ones.

ii) In contrast, in series **II**-**3**, if the 1,3-dioxanic *N*-ligand was *equatorially* amino-linked to *s*-triazine, the less crowded rotamers **II**-**3a**-**c** (*s*-*s*) were, this time, the major species.

If so, regardless the type of anchorage of **D** *N*-ligand (*Table 2*, *Table 3*, *Table 4*) in each series, the most polar rotamer, hence the highest solvated, was dominant, displaying the most deshielded indicative protons SER-N*H* and D-N*H* as well. Surprisingly, in spite of opposite incidence of the major stereoisomer, **I**-**2** (*a*-*a*) *vs.* **II**-**3** (*s*-*s*), overall, the rotameric content was similar in the two series (*Scheme 2*).

Table 3. Relevant ^{1}H NMR data of restricted rotation about C(*s*-triazine)-N(exocyclic) bonds in compounds **II**-**3a**-**c**: *equatorial anchorage of the 1,3-dioxane N-ligand*

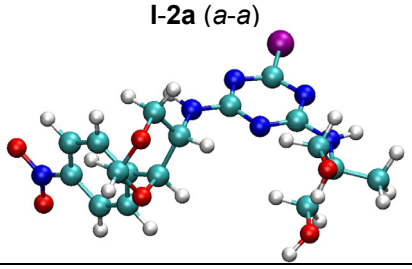
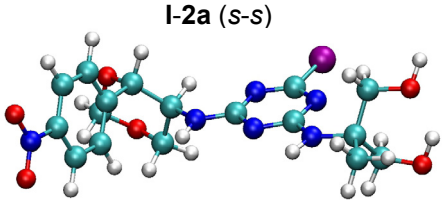
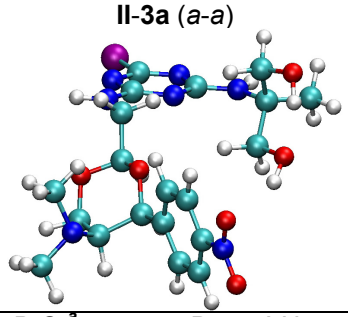
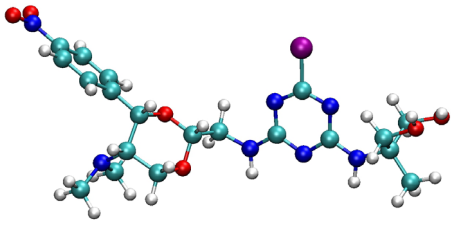
No.	*T* (K)	Indicative protons	Discriminating δ_H (ppm) values and multiplicity $^{3}J_{H,H}$ (Hz)[a] in blocked rotamers			
			s-*s*	4-*s*-6-*a*	4-*a*-6-*s*	*a*-*a*
			α[b] α'	β β'	γ γ'	ε[c] ε'
II-**3a**	**298**	D-N*H*	8.03 (dd, 6.0)	7.91 (dd, 6.0)	7.89 (dd, 6.0)	-
		SER-N*H*	6.92 (s)	6.82 (s)	6.80 (s)	-
		OH	4.80 (dd, 5.8), 4.67 (dd, 5.8), 4.66 (dd, 6.0)			
	353	D-N*H* 7.48 (bs); SER-N*H* 6.58, 6.45 (2×bs); OH 4.52 (bs)				
II-**3b**	**298**	D-N*H*	8.05 (dd, 5.5)	7.91 (dd, 6.3)	7.88 (dd, 6.3)	-
		SER-N*H*	6.83 (s)	6.75 (s)	6.71 (s)	-
		OH	4.81 (dd, 5.5, 6.5), 4.76 (dd, 5.5), 4.64 – 4.60 (m, 5.8)			
	353	D-N*H* 7.50 (bs); SER-N*H* 6.47, 6.39 (2×bs); OH 4.53 (bs)				
II-**3c**	**303**	D-N*H*	8.01 (dd, 4.8)	7.94 (dd, 6.5)	7.92 (dd, 6.5)	-
		SER-N*H*	6.64 (s)	6.60 (s)	6.56 (s)	-
		OH	4.68 (dd, 5.5), 4.56 (dd, 5.5), 4.53 – 4.48 (m, 5.5)			
	353	D-N*H* 7.60 (bs); SER-N*H* 6.40, 6.31 (2×bs); OH 4.42 (bs)				
Final rotational status of II-3a-c *i) slow free rotation about bond C-4(s-triazine)-NH (**D** N-ligand)* *ii) slow exchange about bond C-6(s-triazine)-NH (**SER** N-ligand)*						

[a]As ^{3}J(eq-CH_2-N*H*) in **D** *N*-ligand, ^{3}J(CH_2O*H*) in **SER** *N*-ligand, also supported by the 2D-^{1}H, ^{1}H-COSY Charts.
[b]Relevant peaks for (VT) ^{1}H NMR analysis (*Scheme 2*).
[c]Rotamers not found on the NH zone of the spectra.

^{1}H NMR data in *Tables 2* and *3* also deserved supplementary comments with respect to their accuracy (*Figure 2*).

The anticipated number of rotamers was not ^{1}H NMR observed in all cases, *e.g.* terms **II-3a-c** (*a-a*) were throughout absent (*Table 3*) as well as D-N*H* signals of **I-2a-c** (*s-s*) (*Table 2*). It was ^{13}C NMR spectra, which revealed, for almost all positions, distinct peaks for each rotameric environment (see **EXPERIMENTAL SECTION**).

Table 4. Bond orders (B.O.), dipole moments μ (D), ZPE corrected relative energies ΔH_{0K} (kJ/mol) and relative free energies ΔG_{298} (kJ/mol) of blocked rotamers (*a-a*) and (*s-s*) of compounds **I-2a** and **II-3a**.

Axial anchorage of the 1,3-dioxane N-ligand									
I-2a (*a-a*)					**I-2a** (*s-s*)				
									
Equatorial anchorage of the 1,3-dioxane N-ligand									
II-3a (*a-a*)					**II-3a** (*s-s*)				
									
B.O.[a]		D	ΔH_0 K	ΔG_{298}	B.O.		D	ΔH_0 K	ΔG_{298}
C(4)-N<	C(6)-N<				C(4)-N<	C(6)-N<			
B3LYP/6-311++G* / CPCM / DMSO[b]									
I-2a (*a-a*)					**I-2a** (*s-s*)				
1.23	1.25	**4.84**	0.00	**0.00**	1.22	1.24	**2.07**	2.93	**3.14**
II-3a (*a-a*)					**II-3a** (*s-s*)				
1.24	1.25	**7.81**	0.00	**1.38**	1.24	1.24	**11.63**	1.38	**0.00**

[a] Wiberg bond order calculated within the NBO (Natural Bonding Orbital) analysis.
[b] The effect of solvent took into account by using the implicit solvent method CPCM (Conductor-like Polarizable Continuum Model) implemented in Gaussian 09.

In both series **I**-**2** and **II**-**3**, protons N*H* were strongly chelatized by DMSO since clear ^{3}J coupling patterns through nitrogen, ax-N*H*-C*H*-5-*e* (*Table 2*) and eq–CH_2-N*H*- (*Table 3*) were detectable respectively and fully confirmed by the 2D-^{1}H,^{1}H-COSY Charts. Hence, they were not "mobile" at all as their lifetime of the spin state, τ_1 was greater than 0.1 sec. in compounds **I**-**2a**-**c** and greater than 0.15 sec. in **II**-**3a**-**c** [1a]. No broadening of the NH lines due to $^{1}J(^{14}$N-H) heterocoupling was observed [1c]. Particularly, the magnitude of vicinal coupling ax-N*H*-C*H*-5-*e* (*Table 2*, 9-10 Hz) we considered rather stereospecific [2b] for a preferred "s-*trans*-out" spatial arrangement between *s*-triazinyl and 1,3-dioxan-*c*-5-yl units with respect to the axial bond C-5-N (*Scheme 2*) [2b].*

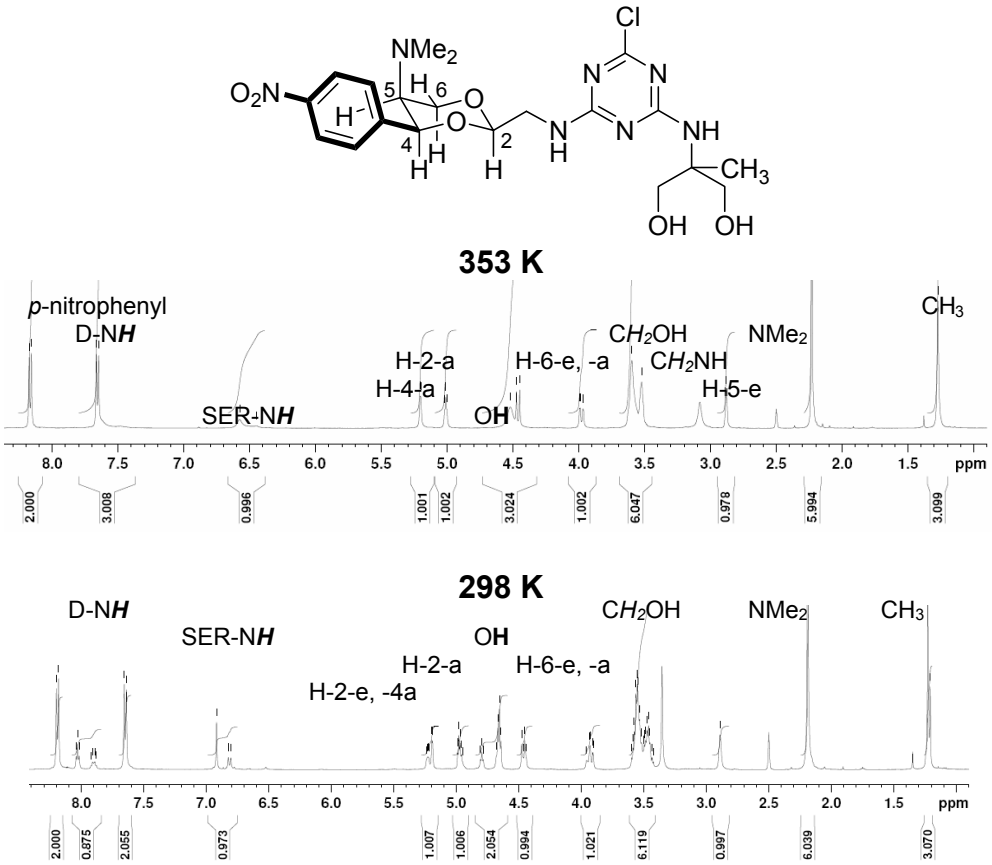


Figure 2. ^{1}H NMR evolution of compound **II**-**3a** (500 MHz time scale, [D_6]DMSO)

* Calculated as $\tau_1 > J^{-1}$ (sec.) where *J* is the vicinal coupling constant >C*H*-N*H*-, ~ 9.5 Hz in **I**-**2a**-**c** (*Table 2*) and ~ 6.5 Hz in **II**-**3a**-**c** (*Table 3*).

The same was valid for hydroxyl protons who displayed typical (overlapped) dd signals in all rotamers, $^{3}J(CH_2\text{-}OH) \sim 5.5$ Hz, except compound **I-2a** (*Table 2*). As one can observe, hydroxyl protons were less sensitive to the distinct rotameric ambiances, hence not useful for their quantitative evaluation.

On heating up to 80 °C, VT ^{1}H NMR spectra disclosed many successive coalescences, consistent with a complex dynamic evolution. Therefore, three hypotheses simplifying the problem, we had to adopt in the following:

i) By intercalation of the *s*-triazine ring, the two *N,N'*-ligands were "sufficiently remote" for a certain signal NH exhibited by each of them, D-N*H* (α, β, γ) or SER-N*H* (α', β', γ') be relevant for the rotational behaviour of the group to which this signal belongs, **D** or **SER**, only (*Figure 3*).

ii) Regardless series, **I-2** or **II-3**, completely de-blocking of a certain rotamer (*Scheme 2*) was mandatory to the equilibria involving, distinctly, its two *N*-ligands, **SER** and **D**. However, the final status of the entire molecule, as a wholly free rotating structure, required the validation of all fourth pathways.

iii) The consecutive nature of the four equilibria (*Scheme 2*) was disclosed as the succession in which the coalescences of NH signals ("indicative protons") appeared (*Figure 3*).

Accordingly, one can reach the preliminary conclusion that our *N,N'*-unsimmetrically substituted chlorodiamino-*s*-triazines could be but partially deblocked, with respect to **D** *N*-ligand about bonds C(4)(*s*-triazine)-N(exocyclic) only (*Figure 3*). This acquired *local rotational status* (*Table 2*, *Table 3*)

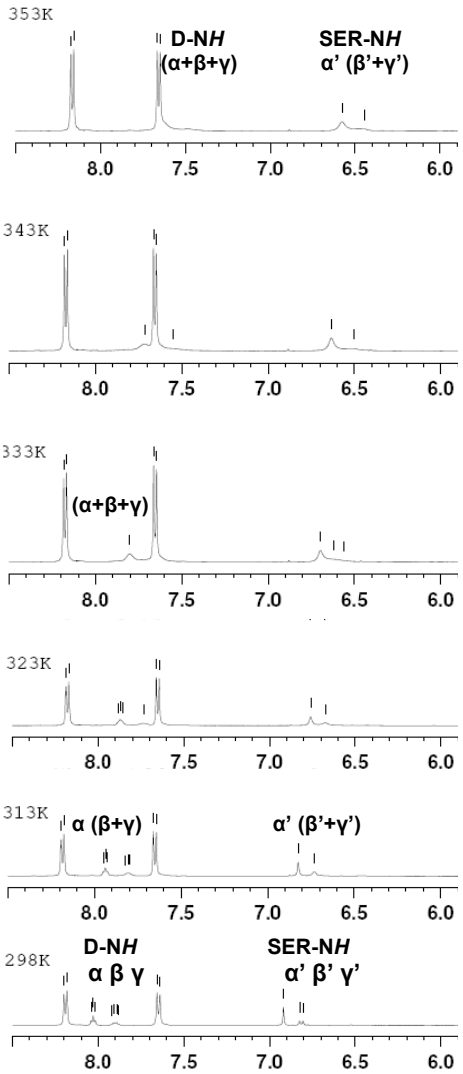


Figure 3. VT ^{1}H NMR spectra of compound **II-3a** on 500 MHz time scale ([D_6]DMSO)

we entitled "*slow free rotation*" (see the later discussion) while the **SER** *N*-ligand, more solvated at room temperature, displayed, at 80 °C, a typical *slow exchange status between unequally populated sites* [1a].

Furthermore, since computational data (*Table 4*) predicted the same bond order concerning C(*s*-triazine)-N(exocyclic) connections, it followed that the above delay in the dynamic behaviour of the two *N*-ligands was dictated mainly by solvation and not by electronic effects.

If so, we calculated the so-called "*temperature gradients*" $[\Delta\delta(NH)/\Delta T]\times10^3$ of protons NH for the major rotational diastereomer in series **I**-**2** and **II**-**3** (*Table 5*) [1b].

Table 5. Temperature gradients of protons NH of compounds **I**-**2a**-**c** and **II**-**3a**-**c**

Compd. (as major rotamer)	T (K)	δ_H (ppm) (T, K)		$[\Delta\delta(NH)/\Delta T]\times10^3$ (ppb/K)[a]	
		D-N*H*	SER-N*H*	D-N*H*	SER-N*H*
I-**2a** (*a*-*a*)	298	7.62	6.86	-11.1	-8.2
	353	7.01	6.41[b]		
I-**2b** (*a*-*a*)	303	7.62	6.77	-12.0	-6.8
	353	7.02	6.43		
I-**2c** (*a*-*a*)	303	-	6.57	-	-6.6
	353		6.24		
II-**3a** (*s*-*s*)	298	8.03	6.92	-10.0	-6.2
	353	7.48	6.58		
II-**3b** (*s*-*s*)	298	8.05	6.83	-10.0	-6.5
	353	7.50	6.47		
II-**3c** (*s*-*s*)	303	8.01	6.64	-8.2	-4.8
	353	7.60	6.40		

[a] Calculated as $[\delta(NH)_{353\,K} - \delta(NH)_{r.t.}] / (353 - T_{r.t.})$;
[b] At 353 K, in all cases, as signal displayed by the major SER-NH rotational site.

Thus, as recently Simanek observed in the case of elaborated amino-*s*-triazines [8], although temperature gradient is usually applied to peptides and proteins [1b], it is generally accepted and indicative that if this coefficient is more negative than -4 ppb/K in aqueous solution, the NH group was, initially, exposed to solvent and not involved in intramolecular hydrogen bonds. Conversely, a temperature gradient less negative than -4 ppb/K indicates the NH protons being, primarily, involved in intramolecular hydrogen bonding.

Our temperature gradients (*Table 5*) were consistent with the below assignments:

i) Although, at room temperature, D-N*H* protons were by far more chelated by the solvent, upon heating, they faster "escaped" from the solvent cage, in agreement with the *slow free rotating status* reached by these "*closed-chain*" *N*-ligands. The D-N*H*-solvation in our chlorodiamino-*s*-triazines was not dependent on the type of **D**-anchorage, *axial* or *equatorial*.

ii) In the "*open-chain*" SER-NH part, the NH protons less interacted with the solvent, presumably because of an intramolecular >NH…OH- partial association, clearly observed in the case of TRIS derivatives **I**-**2c** and **II**-**3c**.

To conclude, the late deblocking of the **SER** *N*-ligand was due to solvation of its OH protons and not to NH. Moreover, NH signals change progressively, from "amide type protons" (r.t.) to authentic "amine protons" upon heating up to 353 K.

In the end, we note the above "unsynchronised" **D** *vs.* **SER** evolution" to be completely different with respect to that of *symmetrically N*,*N*'-substituted chlorodiamino-*s*-triazines with the same *N*-ligands, previously reported by us. Thus, if the *N,N'*-identical ligands were serinols **a**-**c** (*Scheme 1*) a complete but slow rotational mobility (a single mediated structure) was observed at 353 K ($\Delta G^{\neq}$ = 68.10 – 69.22 kJ/mol). In contrast, if *N*,*N*'-identical ligands **I** or **II** were present (*Scheme 1*), a single mediated structure (slow rotation, $\Delta G\neq$ 71.20 kJ/mol) was found only in the case of the double equatorial **D** linkage of **II** [2b].

Rotational stereochemistry phenomena in melamines

Keeping in mind the above findings, melamines **I**-**4a**-**c** and **II**-**5a**-**c** were examined following the same algorithm (*Table 6*, *Table 7*, *Figure 4*).

By replacing the *s*-triazine C-2-chlorine atom with a bulky and strong releasing substituent, piperazine, the π-deficiency of *s*-triazine ring obviously decreased. However, *at room temperature*, essentially unlike from other simpler melamines [6], rotamerism was still existent. Moreover, the independent rotational evolution of the two *N*-ligands was once more revealed, since the number of broad singlets, D-N*H vs.* SER-N*H*, was not the same (*Table 6*)[**]. Therefore, the rotational situation of our melamines, at room temperature, we assigned as a *slow exchange between unequally populated sites* [1a]. Once again, since but in one case, compound **I**-**4c**, the 2D-^{1}H,^{1}H-COSY chart detected some ^{3}J(ax-N*H*-C*H*-5-e) coupling patterns, the D-N*H* and SER-N*H* lines width we associated to the above slow motion and not to a $^{1}J(^{14}$N-H) heterocoupling.

Another interesting feature we observed concerning the "mobile protons", OH and NH of piperazine, Pip-N*H*. In the less hydroxylated compounds **I**-**4a**, **I**-**4b**, **II**-**5a** **II**-**5b**, these protons exhibited a unique broad singlet, suggesting a rapid intermolecular exchange defining a mediated environment, -CH_2O*H* ⇆ *H*N-Pip. Hence, an important intermolecular interaction of these melamines we had to suppose, *e.g.* a polymeric self-assembly. If so, in the case of TRIS based melamines **I**-**4c** and **I**-**5c**, it is very likely that the *internal* association of its three geminal hydroxymethyl groups prevailed against the alternative one, *external*, that with NH of piperazine.

[**] The number of these broad NH singlets is not indicative at all for the number of rotational sites because in the case of compound **I**-**4c** only the 2D-^{1}H,^{1}H-COSY chart clearly exhibited an ax-N*H*-C*H*-5-e ^{3}J coupling; it disclosed four rotamers displaying the two broad D-N*H* singlets.

Table 6. Relevant ^{1}H NMR data of restricted rotation about C(*s*-triazine)-N(exocyclic) bonds in melamines **I**-**4a**-**c** and **II**-**5a**-**c**

No.		Discriminating δH (ppm) values and multiplicity 3JH,H (Hz)a			
	T (K)	D-NH	SER-NH	Pip-NH	OH
Axial anchorage of the 1,3-dioxane N-ligand					
I-4a	**298**	5.80, 5.70 (2×bs)	5.56 (bs)	4.77 (bs)	
	Tc	5.59 (313, bs)	-	-	
	363	5.49 (d, 9.5)	5.43 (s)	4.54 (bs)	
I-4b	**298**	5.81, 5.68 (2×bs)	5.55, 5.44 (2×bs)	4.74 (bs)	
	Tc	5.65 (313, bs)	5.44 (313, bs)	-	
	363	5.52 (d, 9.5)	5.35 (s)	4.54 (bs)	
I-4c	**293**	5.92, 5.81 (2×bs)	5.57, 5.49 (2×bs)	3.45 (bs)	2.63 (s)
	Tc	5.77 (313, bs)	5.48 (313, bs)	-	-
	353	5.61 (d, 9.5)	5.43 (s)	-	2.68 (s)
Equatorial anchorage of the 1,3-dioxane N-ligand					
II-5a	**298**	6.77, 6.60 (2×bs)	5.71, 5.60 (2×bs)	4.84 (bs)	
	Tc	6.49 (323, bs)	5.62 (323, bs)		
	353	6.27 (bdd as bt, 5.5)	5.55 (s)	4.66 (bs)	
II-5b	**298**	6.82, 6.58 (2×bs)	5.59 (bs)	4.77 (bs)	
	Tc	5.51 (323, bs)	-	-	
	353	6.29 (bdd as bt, 5.5)	5.46 (s)	4.68 (bs)	
II-5c	**303**	6.93, 6.80, 6.69 (3×bs)	5.62 (bs)	3.60 (bs)	4.81 (bs)
	Tc	6.60 (323, bs)	-	-	
	353	6.38 (bs)	5.53 (s)	-	4.65 (bs)
Final rotational status of I-4a-c and II-5a-c					
Fast free rotation about bonds C-4(s-triazine)-NH (D ligand), C-6(s-triazine)-NH (SER ligand) and C-2(s-triazine)-N (Pip. Ligand)					

[a] As ^{3}J(ax-N*H*-C*H*-5-e) in **D** *N*-ligand, ^{3}J(CH_2O*H*) in **SER** *N*-ligand in series **I**-**4**; as ^{3}J(eq-CH_2-N*H*) in **D** *N*-ligand, ^{3}J(CH_2O*H*) in **SER** *N*-ligand in series **II**-**5**.

On heating up to 80-90 °C, all our melamines could be completely "activated" about all connections C(*s*-triazine)-N(exocyclic) reaching a *fast free rotation status* as a single mediated structure.

Table 7. Maximum temperature gradients of protons NH of compounds **I**-**4a**-**c** and **II**-**5a**-**c**

Compd.	*T* (K)	Relevant δ_H (ppm)			$[\Delta\delta(NH)/\Delta T]\times10^3$ (ppb / K)		
		D-N*H*	SER-N*H*	Pip-N*H*	D-N*H*	SER-N*H*	Pip-N*H*
I-**4a**	298	5.80	5.56 [a]	4.77	-4.8	-2.0	-3.5
	363	5.49	5.43	4.54			
I-**4b**	298	5.81	5.55	4.74	-4.5	-3.1	-3.1
	363	5.52	5.35	4.54			
I-**4c**	298	5.92	5.57	3.45	-5.6	-2.5	-
	353	5.61	5.43	-			
II-**5a**	298	6.77	5.71	4.84	-9.1	-2.9	-3.3
	353	6.27	5.55	4.66			
II-**5b**	298	6.82	5.59	4.77	-9.6	-2.4	-1.6
	353	6.29	5.46	4.68			
II-**5c**	303	6.93	5.62	-	-11.0	-1.8	-
	353	6.38	5.53	-			

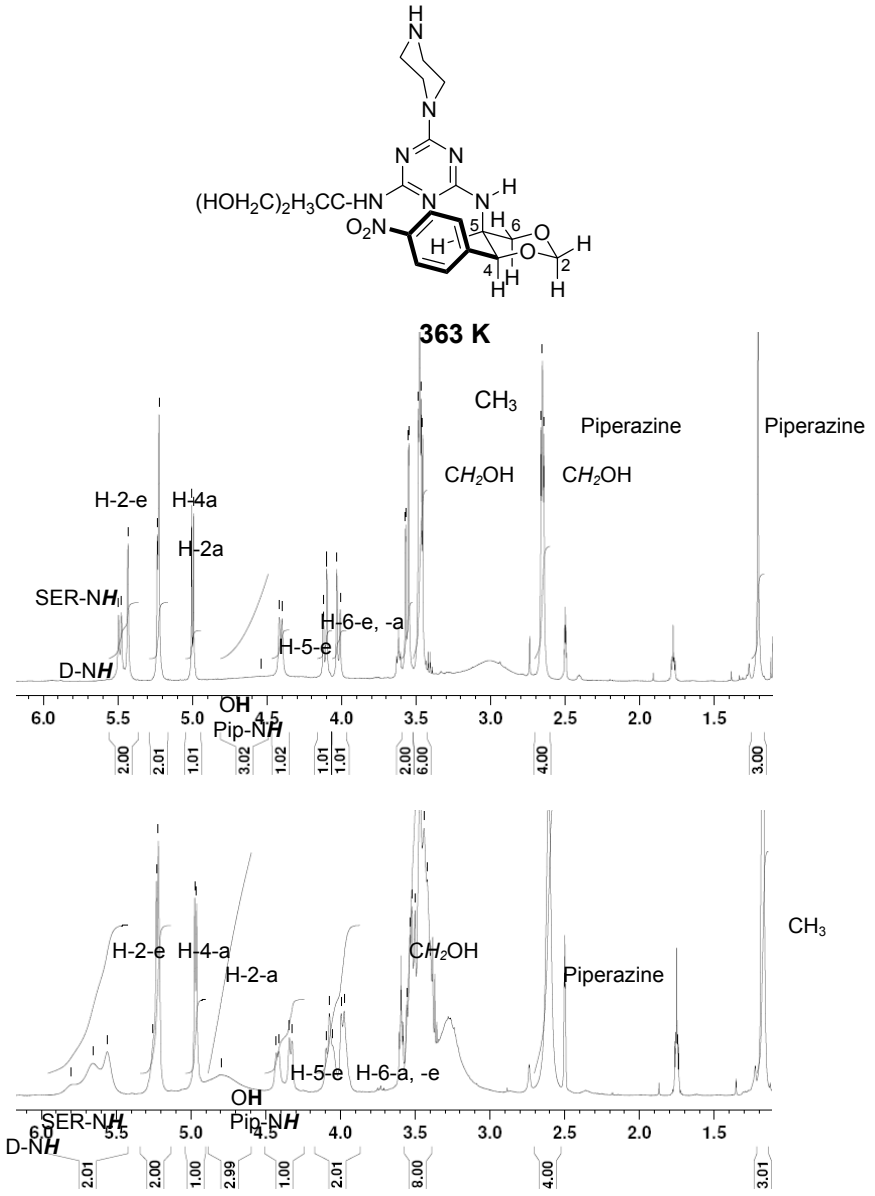
[a] At r.t., in all cases, as signal displayed by the most deshielded broad singlet, D-N*H* or SER-N*H* proton respectively.

Their dynamic evolution can be subjected to the below comments:

i) If different slow exchanging rotameric sites were initially detected for each **D** and **SER** *N*-ligand, the coalescence was reached, however, almost simultaneously by the two fragments. Higher T_c values (+10 K) were observed for melamines **II**-**5a**-**c** against **I**-**4a**-**c** in agreement with the more solvated ground states of equatorially anchored derivatives (*Table 7*).

ii) The final *fast free rotation* status acquired by all melamines was nicely supported by the line-shape analysis of signals D-N*H* (sharp doublet or broad triplet) and SER-N*H* (sharp singlet) (*Figure 4*). Undoubtedly, one cannot assign this line-width as to belong to "exchangeable" protons. In contrast, OH and Pip-N*H* signals, as unique broad lines, were fully consistent with the mobility of these protons involved in a fast exchange with the solvent in a molecular unique mediated environment.

iii) Temperature gradients (*Table 7*) crucially discriminated between amino-1,3-dioxane anchorages, *axial* or *equatorial vs.* solvent, melamines **II**-**5c** being, at room temperature, by far more D-N*H*…O=SMe_2 solvated. That is, the slow turning *equatorial* amino-linkage to the *s*-triazine ring was sterically less crowded, facilitating the access of DMSO to this connection. In the SER-N*H* and Pip-N*H* counterparts, the $\Delta\delta(NH)/\Delta T$ values, much less negative than -4, confirmed our earlier assignment, namely the intermolecular $CH_2OH \leftrightarrows H$-Pip interchange in the case of *methyl*- (**a**) and *ethylserinol* (**b**) based melamines.



CONCLUSIONS

A rapid and efficient access to highly elaborated enantiopure melamines based on serinols was described. To the title report question,our answer consists of considering (i) primarily, the NH protons, involved in partial double

bonds, as very relevant for distribution of rotamers, dynamic behavior and sterically conditioned relationships with the solvent; (ii) the OH protons, indicative for solvation effects as intra- -OH…HO- or intermolecular -OH…HN< associations determining the stability of ground states.

EXPERIMENTAL SECTION

General. Melting points are uncorrected; they were carried out on ELECTROTHERMAL® instrument. Conventional NMR spectra were recorded on a Bruker® AM300 instrument operating at 300 and 75 MHz for ^{1}H and ^{13}C nuclei respectively. VT NMR experiments were performed on a Bruker® DMX500 instrument. All NMR spectra were measured in anhydrous commercially available deuteriated solvents. The ^{13}C NMR description of compounds exhibiting frozen rotamers at room temperature was made by considering them as one global structure. Multiple δ_C values for the same-labelled position means mixture of rotamers. Some specific abbreviations were used: bd (broad doublet) and bm (broad multiplet), *p*-NPh (*p*-nitrophenyl).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®). All visualisations were realised in UV at 254 nm. 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 Bruker® Esquire Instrument. Specific rotations were measured on a POLAMAT® Karl-Zeiss Jena instrument. Full characterisation and synthesis of compounds **I** and **II** we reported in detail elsewhere [2b].

*Typical procedure for the synthesis of compounds **I-2a-c** and **II-3a-c**. Preparation of compound **I-2c***

To anh. K_2CO_3 (1.512 g, 100%, 10.944 mmol) suspended in anh. THF (100 ml), solid 2-amino-2-(hydroxymethyl)propane-1,3-diol (TRIS, 1.325 g, 10.944 mmol) was added with vigorous stirring. The resulted suspension was cooled at -15 °C when cyanuric chloride (2.018 g, 10.944 mmol) as clear anh. THF (25 ml) solution was injected rapidly. 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 **1c** as a single spot (eluent acetone : ligroin 2:1, R_f = 0.80). Freshly prepared (4*S*,5*S*)-5-amino-4-(4-nitrophenyl)-1,3-dioxane (**I**, **DX-NH$_2$**) (2.452 g, 100%, 10.944 mmol) and anh. K_2CO_3 (1.512 g, 100%, 10.944 mmol) were added and the reaction mixture was heated at reflux (65 °C) for 12 hrs. (TLC monitoring, eluent toluene : isopropanol 2:1, R_f = 0.80). When **I** and **1c** 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 to provide 5.222 g crude product. This was purified by column chromatography on silica gel (eluent toluene : isopropanol 2:1) affording 4.110 g compound **I-2c** (84 % yield with respect to cyanuric chloride).

2-Chloro-6-{[1,3-dihydroxy-2-(methyl)prop-2-yl]amino}-4-{[(4*S*,5*S*)-4-(4-nitrophenyl)-1,3-dioxan-5-yl]amino}-*s*-triazine I-2a (80 %) yellowish crystalline powder, mp 107-118 °C (flash column chromatography, eluent toluene : isopropanol, 2:1 v/v). [Found: C 45.98, H 5.11, N 18.80; $C_{17}H_{21}ClN_6O_6$ (440.12) requires: C 46.32, H 4.80, N 19.06%]. R_f 0.86 (66% toluene/ isoporpanol). IR $\nu_{max.}$ (KBr) 3320 (s), 2946 (m), 2867 (m), 1581 (s), 1520 (s), 1411 (m), 1347 (s), 1242 (m), 1175 (s), 1094 (s), 1027 (s), 966 (m), 852 (m), 804 (s), 744 (m), 711 (m), 592 (w) cm^{-1}. ^1H NMR (500 MHz, [D_6]DMSO, 353 K)**:** δ_H 1.12 (3 H, s, CH_3), 3.48-3.57 (4 H, m, C*H*$_2$OH), 4.03 (1 H, d, $^2J_{H,H}$=11.0 Hz, H-6-a D-NH), 4.14 (1 H, d, $^2J_{H,H}$=11.5 Hz, H-6-e D-NH), 4.37 (1 H, d, $^3J_{H,H}$=9.0 Hz, H-5-e D-NH), 4.50 (2 H, bs, OH), 5.00 (1 H, d, $^2J_{H,H}$=6.0 Hz, H-2-a D-NH), 5.23 (1 H, d, $^2J_{H,H}$=6.0 Hz, H-2-e D-NH), 5.28 (1 H, s, H-4-a D-NH), 6.41, 6.51 (1 H, 2×bs SER-N*H*), 7.01 (1 H, bs D-N*H*), 7.66 (2 H, d, $^3J_{H,H}$=8.5 Hz, H-2, -6 *p*-NPh), 8.14 (2 H, d, $^3J_{H,H}$=7.0 Hz, H-3, -5 *p*-NPh) ppm; ^{13}C NMR (125 MHz, [D_6]DMSO, 298 K): δ_C 18.7, 18.8, 19.0, 19.4 (1 C, CH_3), 49.3, 49.5, 49.8 (1 C, C-5 D-NH), 58.8, 59.0 (1 C, C-2 SER-NH), 63.4, 63.5, 63.6, 63.7, 63.8 (2 C, CH_2-OH), 69.7, 70.1, 70.2, 70.5 (1 C, C-6 D-NH), 77.9, 78.2, 78.4, 78.8 (1 C, C-4 D-NH), 93.88, 93.94, 94.0, 94.2 (1 C, C-2 D-NH), 123.3, 123.5, 123.6, 123.8 (2 C, C-2, -6 *p*-NPh), 127.4, 127.5, 127.6, 127.9 (2 C, C-3, -5 *p*-NPh), 146.7, 146.76, 146.78 (1 C, C-1 *p*-NPh), 147.17, 147.21, 147.24 (1 C, C-4 *p*-NPh), 164.9, 165.1, 165.3, 165.4, 165.6 (2 C, C-4, -6 *s*-triazine), 167.76, 167.82, 167.9, 168.2 (1 C, C-2 *s*-triazine) ppm. MS (ESI+), *m/z* (rel. int. %) 463.1 [M+Na^+] (7.5), 443.1 [M^++2] (38), 441.3 [M^++H] (100), 315.1 (10). $[\alpha]_D^{25}$=-46 (0.5 % DMSO).

2-Chloro-6-{[1-hydroxy-2-(hydroxymethyl)but-2-yl]amino}-4-{[(4*S*,5*S*)-4-(4-nitrophenyl)-1,3-dioxan-5-yl]amino}-*s*-triazine I-2b (66 %) yellowish crystalline powder, mp 97-102 °C (flash column chromatography, eluent toluene : isopropanol, 2:1 v/v). [Found: C 47.35, H 5.25, N 18.79; $C_{18}H_{23}ClN_6O_6$ (454.14) requires: C 47.53, H 5.10, N 18.48%]. R_f 0.83 (66% toluene/*i*-PrOH). IR $\nu_{max.}$ (KBr) 3372 (s), 2972 (m), 2864 (m), 1587 (s), 1521 (s), 1414 (m), 1346 (s), 1242 (m), 1175 (s), 1095 (s), 1028 (s), 966 (m), 852 (m), 804 (m), 745 (w), 711 (m), 582 (w) cm^{-1}. ^1H NMR (500 MHz, [D_6]DMSO, 353 K): δ_H 0.72 (3 H, t, $^3J_{H,H}$=7.3 Hz, CH_3), 1.70 (2 H, bq, $^3J_{H,H}$=7.2 Hz, C*H*$_2$-CH_3), 3.50 (2 H, d, $^2J_{H,H}$=11.0 Hz, C*H*$_2$-OH), 3.59 (2 H, bd, $^2J_{H,H}$=8.5 Hz, C*H*$_2$OH), 4.02 (1 H, d, $^2J_{H,H}$=11.0 Hz, H-6-a D-NH), 4.14 (1 H, d, $^2J_{H,H}$=11.5 Hz, H-6-e D-NH), 4.37 (3 H, bs, H-5-e D-NH, OH), 5.00 (1 H, d, $^2J_{H,H}$=6.5 Hz, H-2-a D-NH), 5.23 (1 H, d, $^2J_{H,H}$=6.0 Hz, H-2-e D-NH), 5.28 (1 H, s, H-4-a D-NH), 6.31, 6.43 (1 H, 2×bs

SER-N*H*), 7.02 (1 H, bs D-N*H*), 7.65 (2 H, d, $^3J_{H,H}$=7.5 Hz, H-2, -6 *p*-NPh), 8.14 (2 H, bd, $^3J_{H,H}$=6.0 Hz, H-3, -5 *p*-NPh) ppm; ^{13}C NMR (125 MHz, [D$_6$]DMSO, 298 K): δ_C 7.8, 7.9 (1 C, CH_3), 22.1, 22.5, 23.0, 23.1 (1 C, CH_2-CH_3), 49.3, 49.37, 49.4, 49.9 (1 C, C-5 D-NH), 60.9 (1 C, C-2 SER-NH), 61.2, 61.3, 61.4, 61.5 (2 C, CH_2OH), 70.07, 70.1, 70.2, 70.5 (1 C, C-6 D-NH), 78.2, 78.4, 78.5, 78.8 (1 C, C-4 D-NH), 93.89, 93.94 (1 C, C-2 D-NH), 123.2, 123.3, 123.4, 123.6, (2 C, C-2, -6 *p*-NPh), 127.6, 127.7, 127.9, 128.0 (2 C, C-3, -5 *p*-NPh), 146.7, 146.8, (1 C, C-1 *p*-NPh), 147.1, 147.17, 147.22 (1 C, C-4 *p*-NPh), 164.7, 164.99, 165.04, 165.3, 165.4, 165.7 (2 C, C-4, -6 *s*-triazine), 167.8 (1 C, C-2 *s*-triazine) ppm. MS (ESI+), *m/z* (rel. int. %) 493.1 [M+K$^+$] (9), 477.1 [M+Na$^+$] (18), 457.1 [M$^+$+2] (35), 455.1 [M$^+$+H] (100), 438.2 (11), 437.2 (54), 419.2 (41). $[\alpha]_D^{25}$=-34 (0.5 % DMSO).

2-Chloro-6-{[1,3-dihydroxy-2-(hydroxymethyl)prop-2-yl]amino}-4-{[(4*S*, 5*S*)-4-(4-nitrophenyl)-1,3-dioxan-5-yl]amino}-*s*-triazine I-2c (84 %) yellowish crystalline powder, mp 200-205 °C (flash column chromatography, eluent toluene : isopropanol, 2:1 v/v). [Found: C 45.01, H 4.39, N 18.59; $C_{17}H_{21}ClN_6O_7$ (456.12) requires: C 44.69, H 4.63, N 18.40%]. R_f 0.80 (66% toluene/*i*-PrOH). IR $\nu_{max.}$ (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, 353 K): δ_H 3.66 (6 H, bs, C*H*$_2$OH), 4.05 (1 H, bd, $^2J_{H,H}$=9.5 Hz, H-6-a D-NH), 4.14 (1 H, d, $^2J_{H,H}$=11.5 Hz, H-6-e D-NH), 4.36 (1 H, bs, H-5-e D-NH), 4.36, 4.53 (3 H, 2×bs, OH), 5.00 (1 H, d, $^2J_{H,H}$=6.0 Hz, H-2-a D-NH), 5.23 (1 H, d, $^2J_{H,H}$=6.0 Hz, H-2-e D-NH), 5.27 (1 H, bs, H-4-a, D-NH), 6.24, 6.30 (1 H, 2×bs SER-N*H*), 7.01 (1 H, bs D-N*H*), 7.65 (2 H, d, $^3J_{H,H}$=8.0 Hz, H-2, -6 *p*-NPh), 8.14 (2 H, bd, $^3J_{H,H}$=7.0 Hz, H-3, -5 *p*-NPh) ppm; ^{13}C NMR (75 MHz, [D$_6$]DMSO, 298 K): δ_C 49.2, 49.3, 49.7 (1 C, C-5 D-NH), 59.4, 59.6, 60.1 (1 C, C-2 SER-NH), 62.1, 62.3, 62.4 (3 C, CH_2OH), 69.9, 70.3 (1 C, C-6 D-NH), 78.0, 78.1, 78.6 (1 C, C-4 D-NH), 93.8 (1 C, C-2 D-NH), 123.2, 123.4 (2 C, C-2, -6 *p*-NPh), 127.4, 127.6, 127.7 (2 C, C-3, -5 *p*-NPh), 146.6 (1 C, C-1 *p*-NPh), 147.1 (1 C, C-4 *p*-NPh), 164.9, 165.0, 165.2, 165.4 (2 C, C-4, -6 *s*-triazine), 167.6, 167.8 (1 C, C-2 *s*-triazine) ppm. MS (CI, isobutane) *m/z* (rel. int. %) 513 [M$^+$ +HC(CH$_3$)$_3$-2 H] (20), 495 [M+K$^+$] (9), 457 [M$^+$] (100), 421 (10), 225 (11),140(10). $[\alpha]_D^{25}$=-36 (0.5 % DMSO).

2-Chloro-6-{[1,3-dihydroxy-2-(methyl)prop-2-yl]amino}-4-{[(2*R*,4*S*,5*S*)-5-(dimethylamino)-4-(4-nitrophenyl)-1,3-dioxan-2-yl]methylamino}-*s*-triazine II-3a (83 %) yellowish crystalline powder, mp 126-134 °C (flash column chromatography, eluent toluene : ethanol, 1:5 v/v). [Found: C 47.95, H 5.51, N 19.39; $C_{20}H_{28}ClN_7O_6$ (497.18) requires: C 48.24, H 5.67, N 19.69%]. R_f 0.80 (17% toluene/EtOH). IR $\nu_{max.}$ (KBr) 3382 (s), 3276 (s), 2941 (m), 2878 (m), 1587 (s), 1521 (s), 1462 (m), 1412 (m), 1349 (s), 1153 (m), 1113 (m), 1057 (s),

852 (w), 804 (m), 753 (w), 709 (m), 571 (w) cm^{-1}. ^{1}H NMR (500 MHz, [D_6]DMSO, 353 K)**:** δ_H 1.27 (3 H, s, CH_3), 2.23 [6 H, s, $N(CH_3)_2$], 2.88 (1 H, dd as t, $^3J_{H,H}$=3.0 Hz, H-5-e D-NH), 3.52 (2 H, bs, C*H*$_2$-NH), 3.60 (4 H, bs, C*H*$_2$OH), 3.98 (1 H, dd, $^3J_{H,H}$=2.0 Hz, $^2J_{H,H}$=12 Hz, H-6-a D-NH), 4.46 (1 H, d, $^2J_{H,H}$=12.0 Hz, H-6-e D-NH), 4.52 (2 H, bs, OH), 5.01 (1 H, dd as t, $^3J_{H,H}$=4.3 Hz, H-2-a D-NH), 5.20 (1 H, d, $^3J_{H,H}$=2.0 Hz, H-4-a D-NH), 6.45, 6.58 (1 H, 2×bs SER-N*H*), 7.48 (1 H, bs, CH_2N*H*), 7.66 (2 H, d, $^3J_{H,H}$=8.5 Hz, H-2, -6 *p*-NPh), 8.17 (2 H, d, $^3J_{H,H}$=9.0 Hz, H-3, -5 *p*-NPh) ppm; ^{13}C NMR (125 MHz, [D_6]DMSO, 298 K): δ_C 18.8, 19.0 (1 C, CH_3), 43.8 [2 C, $N(CH_3)_2$], 44.3, 44,4, 44,8 (1 C, CH_2NH), 58.46, 58.51 (1 C, C-5 D-NH), 58.98, 59.04 (1 C, C-2 SER-NH), 63.5, 63.6, 63.6, 63.9 (2 C, CH_2OH), 64.4, 64.6 (1 C, C-6 D-NH), 80.05, 80.12, 80.3 (1 C, C-4 D-NH), 99.0, 99.2, 99.5 (1 C, C-2 D-NH), 123.3 (2 C, C-2, -6 *p*-NPh), 127.1 (2 C, C-3, -5 *p*-NPh), 146.7 (1 C, C-1 *p*-NPh), 148.8, 148.9 (1 C, C-4 *p*-NPh), 165.0, 165.3, 165.6, 165.85, 165.91 (2 C, C-4, -6 *s*-triazine), 167.88, 167.93, 168.4 (1 C, C-2 *s*-triazine) ppm. MS (ESI+), *m/z* (rel. int. %) 537.2 [M+K^+] (2), 520.1 [M+Na^+] (3.5), 500.2 [M^++3], 498.1 [M^++H] (100), 462.2 (7), 273.2 (7), 208.0 (11), 182.2 (17). $[\alpha]_D^{25}$=+147 (0.5 % DMSO).

2-Chloro-6-{[1-hydroxy-2-(hydroxymethyl)but-2-yl]amino}-4-{[(2*R*,4*S*, 5*S*)-5-(dimethylamino)-4-(4-nitrophenyl)-1,3-dioxan-2-yl]methylamino}-*s*-triazine II-3b (42 %) yellowish crystalline powder, mp 110-115 °C (flash column chromatography, eluent diethyl ether : ethanol : water, 0.5:8:1 v/v/v). [Found: C 48.98, H 5.81, N 19.39; $C_{21}H_{30}ClN_7O_6$ (511.19) requires: C 49.27, H 5.91, N 19.15%]. R_f 0.73 (5% Et_2O/84% EtOH/H_2O). IR $\nu_{max.}$ (KBr) 3275 (s), 2971 (m), 2881 (m), 1591 (s), 1521 (s), 1464 (m), 1411 (s), 1349 (s), 1154 (m), 1117 (m), 1059 (s), 852 (w), 802 (m), 752 (w), 708 (m), 570 (w) cm^{-1}. ^{1}H NMR (500 MHz, [D_6]DMSO, 353 K): δ_H 0.779, 0.784 (3 H, 2×t, $^3J_{H,H}$=7.5 Hz, CH_3), 1.79 (2 H, q, $^3J_{H,H}$=7.3 Hz, C*H*$_2$CH$_3$), 2.27 [6 H, s, $N(CH_3)_2$], 2.97 (1 H, bs, H-5-e D-NH), 3.51-3.54 (2 H, m, C*H*$_2$-OH), 3.56 (2 H, dd as t, $^3J_{H,H}$=3.0 Hz, C*H*$_2$NH), 3.67 (2 H, 2×d as t, $^2J_{H,H}$=11.0, 12.5 Hz, C*H*$_2$OH), 4.00 (1 H, d, $^2J_{H,H}$=11.5 Hz, H-6-a D-NH), 4.49 (1 H, d, $^2J_{H,H}$=12.5 Hz, H-6-e D-NH), 4.53 (2 H, bs, OH), 5.01 (1 H, dd as t, $^3J_{H,H}$=4.5 Hz, H-2-a D-NH), 5.24 (1 H, bs, H-4-a D-NH), 6.39, 6.47 (1 H, 2×bs SER-N*H*), 7.50 (1 H, bs, CH_2N*H*), 7.67 (2 H, d, $^3J_{H,H}$=8.5 Hz, H-2, -6 *p*-NPh), 8.17 (2 H, d, $^3J_{H,H}$=9.0 Hz, H-3, -5 *p*-NPh) ppm; ^{13}C NMR (125 MHz, [D_6]DMSO, 298 K): δ_C 7.9, 7.96, 8.01, 8.1 (1 C, CH_3), 22.2, 22.3, 22.6, 23.0, 23.1 (1 C, *C*H$_2$-CH$_3$), 43.8 [2 C, $N(CH_3)_2$], 44.2, 44.4, 44.8 (1 C, CH_2NH), 58.6 (1 C, C-5 D-NH), 60.9, 61.0, 61.1, 61.2, (1 C, C-2 SER-NH), 61.46, 61.51, 61.65, 61.71 (2 C, CH_2OH), 64.4, 64.6 (1 C, C-6 D-NH), 80.0, 80.1, 80.3 (1 C, C-4 D-NH), 99.1, 99.3, 99.6 (1 C, C-2 D-NH), 123.4 (2 C, C-2, -6 *p*-NPh), 127.1 (2 C, C-3, -5 *p*-NPh), 146.8 (1 C, C-1 *p*-NPh), 148.6, 148.8 (1 C, C-4 *p*-NPh), 165.0, 165.2, 165.6, 165.8, 165.9, 166.0, (2 C, C-4, -6 *s*-triazine), 167.3, 167.9, 168.3 (1 C, C-2 *s*-triazine) ppm. MS (ESI+), *m/z* (rel. int. %) 515.4 [M^++4] (8), 514.4 [M^++3], 512.4 [M^++H] (100), 498.4 (4). $[\alpha]_D^{25}$=+128 (0.5 % DMSO).

2-Chloro-6-{[1,3-dihydroxy-2-(hydroxymethyl)prop-2-yl]amino}-4-{[(2*R*, 4*S*,5*S*)-5-(dimethylamino)-4-(4-nitrophenyl)-1,3-dioxan-2-yl]methylamino}-*s*-triazine II-3c (95 %) yellowish crystalline powder, mp 138-140 °C (flash column chromatography, eluent ligroin : acetone, 1:4 v/v). [Found: C 47.08, H 5.55, N 19.38; $C_{20}H_{28}ClN_7O_7$ (513.17) requires: C 46.74, H 5.49, N 19.08%]. R_f 0.80 (20% ligroin/acetone)**.** IR $\nu_{max.}$ (KBr) 3369 (s), 2945 (m), 2878 (m), 1583 (s), 1520 (s), 1412 (m), 1348 (s), 1299 (m), 1154 (m), 1113 (m), 1054 (s), 1014 (m), 852 (w), 804 (m), 710 (m), 597 (w) cm^{-1}. ^{1}H NMR (500 MHz, [D_6]DMSO, 353 K): δ_H 2.28 [6 H, s, N(CH_3)$_2$], 2.97 (1 H, bs, H-5-e D-NH), 3.53 (2 H, s, C*H*$_2$-NH), 3.72 (6 H, s, C*H*$_2$OH), 4.01 (1 H, d, $^2J_{H,H}$=11.5 Hz, H-6-a D-NH), 4.42 (3 H, bs, OH), 4.49 (1 H, d, $^2J_{H,H}$=12.5 Hz, H-6-e D-NH), 5.03 (1 H, bs, H-2-a D-NH), 5.24 (1 H, bs, H-4-a D-NH), 6.31, 6.40 (1 H, 2×bs SER-N*H*), 7.60 (1 H, bs CH_2N*H*), 7.68 (2 H, d, $^3J_{H,H}$=8.5 Hz, H-2, -6 *p*-NPh), 8.18 (2 H, d, $^3J_{H,H}$=8.5 Hz, H-3, -5 *p*-NPh) ppm; ^{13}C NMR (75 MHz, [D_6]DMSO, 298 K): δ_C 43.7 [2 C, N(CH_3)$_2$], 44.2, 44.6 (1 C, CH_2NH), 58.5 (1 C, C-5 D-NH), 59.6, 60.0, 60.2 (1 C, C-2 SER-NH), 62.4, 62.5 (3 C, CH_2OH), 64.4, 65.3, 67.4 (1 C, C-6 D-NH), 80.5 (1 C, C-4 D-NH), 99.2 (1 C, C-2 D-NH), 123.2 (2 C, C-2, -6 *p*-NPh), 126.9 (2 C, C-3, -5 *p*-NPh), 146.7 (2 C, C-1, -4 *p*-NPh), 165.2, 165.7 (2 C, C-4, -6 *s*-triazine), 167.7, 168.2 (1 C, C-2 *s*-triazine) ppm. MS (CI, isobutane), *m/z* (rel. int. %) 514 [M^++H] (25) 278 (5), 178 (100), 140 (18), 116(11), 104 (21), 87 (18). $[\alpha]_D^{25}$=+157 (0.5 % DMSO).

*Typical procedure for the synthesis of compounds **I-4a-c** and **II-5a-c**. Preparation of compound **I-4c***

At room temperature and with vigorous stirring, anh. K_2CO_3 (0.604 g, 4.377 mmol) was suspended in a solution obtained by dissolving anh. piperazine (1.504 g, 17.508 mmol) in anh. THF (125 mL). To this suspension, chlorodiamino-*s*-triazine **I-2c** (2.000 g, 4.377 mmol) was added portionwise (5 equal portions, 0.400 g **I-2c** / portion, each 2 hours). After each addition and within 2 hours, TLC monitoring indicated the completion of reaction as follows: total consumption of **I-2c** (eluent toluene : isopropanol = 2:1 v/v, R_f = 0.8, visualisation in UV 254 nm) and formation of **I-4c** (eluent ethanol : aq. NH_3 25% = 9:1 v/v, R_f = 0.76, double visualisation: UV 254 nm then I_2 bath). After addition, the reaction mixture was stirred at room temperature for 24 hrs. Minerals were filtered off and well-washed with anh. THF. The combined THF solution was evaporated under reduced pressure to yield 2.900 g crude material which was separated by column chromatography on silica gel (eluent ethanol : aq. NH_3 25% = 9:1 v/v, R_f = 0.76, double visualisation: UV 254 nm then I_2 bath). The isolated **I-4c**, 2.267 g was taken with anh. THF (2 mL) then diethyl ether was added and the resulted fine yellow suspension was stirred at room temperature for 1 hr. After cooling at -20 °C for 12 hrs., filtering off, washing with could diethyl ether and drying 1.910 g pure **I-4c** were obtained (86% yield with respect to **I-2c**).

1-{6-{[1,3-Dihydroxy-2-(methyl)prop-2-yl]amino}-4-{[(4*S*,5*S*)-4-(4-nitrophenyl)-1,3-dioxan-5-yl]amino}-*s*-triazin-2yl}-piperazine I-4a (80 %) yellowish crystalline powder, mp 123-133 °C (flash column chromatography, eluent ethanol : aq. NH_3 25% 9:1 v/v). [Found: C 51.55, H 5.80, N 23.03; $C_{21}H_{30}N_8O_6$ (490.23) requires: C 51.42, H 6.16, N 22.84%]. R_f 0.77 (90% ethanol/aq. NH_3 25%). IR ν_{max} (KBr) 3400 (s), 2922 (m), 2855 (s), 1548(s), 1501 (s), 1444 (s), 1346 (s), 1274 (m), 1174 (m), 1106 (m), 1056 (m), 1027 (m), 875 (w), 852 (w), 810 (m), 744 (w),711 (m), 583 (w) cm^{-1}. ^1H NMR (500 MHz, [D_6]DMSO, 363 K): δ_H 1.21 (3 H, s, CH_3), 2.65 (4 H, t, $^3J_{H,H}$=5.0 Hz, H-3, -5 Piperazine), 3.47 (2 H, d, $^2J_{H,H}$=10.5 Hz, CH_2OH), 3.48 (4 H, t, $^3J_{H,H}$=5.0 Hz, H-2, -6 Piperazine), 3.56 (2 H, d, $^2J_{H,H}$=10.5 Hz, CH_2OH), 4.02 (1 H, d, $^2J_{H,H}$=11.0 Hz, H-6-a D-NH), 4.11 (1 H, dd, $^3J_{H,H}$=1.5 Hz, $^2J_{H,H}$ = 11.5 Hz, H-6-e D-NH), 4.41 (1 H, d, $^3J_{H,H}$ = 9.0 Hz, H-5-e D-NH), 4.54 (3 H, bs, OH, Pip-N*H*), 5.00 (1 H, d, $^2J_{H,H}$=6.5 Hz, H-2-a D-NH), 5.225 (1 H, s, H-4-a D-NH), 5.230 (1 H,d, $^2J_{H,H}$=5.5 Hz, H-2-e D-NH), 5.43 (1 H, s SER-N*H*), 5.49 (1 H, d, $^3J_{H,H}$=9.5 Hz D-N*H*), 7.62 (2 H, d, $^3J_{H,H}$=9.0 Hz, H-2, -6 *p*-NPh), 8.11 (2 H, d, $^3J_{H,H}$=8.5 Hz, H-3, -5 *p*-NPh) ppm; ^{13}C NMR (125 MHz, [D_6]DMSO, 298 K): δ_C 19.2 (1 C, CH_3), 44.2, 44.3 (2 C, C-3, -5 Piperazine), 45.8, 45.9, 46.0 (2 C, C-2, -6 Piperazine), 48.8, 48.9 (1 C, C-5 D-NH), 57.9 (1 C, C-2 SER-NH), 64.6, 64.9 (2 C, CH_2OH), 70.5, 70.6, 70.8, 71.0 (1 C, C-6 D-NH), 78.5, 78.6, 78.9, 79.0 (1 C, C-4 D-NH), 93.9, 94.0, 94.1 (1 C, C-2 D-NH), 123.2, 123.5 (2 C, C-2, -6 *p*-NPh), 127.4, 127.6 (2 C, C-3, -5 *p*-NPh), 147.0, 147.1 (2 C, C-1, -4 *p*-NPh), 164.17, 164.22, 164.3, 164.5 (1 C, C-2 *s*-triazine), 165.3, 165,4 (2 C, C-4, -6 *s*-triazine) ppm. MS (ESI+), *m/z* (rel. int. %) 491.2 [M^++H] (100), 403.2 (22), 208.0 (29). $[\alpha]_D^{25}$=+28 (0.5 % DMSO).

1-{6-{[1-Hydroxy-2-(hydroxymethyl)but-2-yl]amino}-4-{[(4*S*,5*S*)-4-(4-ni- trophenyl)-1,3-dioxan-5-yl]amino}-*s*-triazin-2-yl}-piperazine I-4b (84 %) yellowish crystalline powder, mp 125-130 °C (flash column chromatography, eluent ethanol : aq. NH_3 25% 9:1 v/v). [Found: C 51.99, H 6.22, N 21.95; $C_{22}H_{32}N_8O_6$ (504.24) requires: C 52.37, H 6.39, N 22.21%]. R_f 0.66 (90% ethanol/aq. NH_3 25%). IR ν_{max} (KBr) 3401 (s), 2966 (m), 2856 (s), 1552 (s), 1500 (s), 1445 (s), 1346 (s), 1174 (m), 1106 (m), 1061 (m), 1026 (m), 873 (w), 852 (w), 809 (m), 744 (w), 710 (w), 583 (w) cm^{-1}. ^1H NMR (500 MHz, [D_6]DMSO, 363 K): δ_H 0.74 (3 H, t, $^3J_{H,H}$ = 7.3 Hz, CH_3), 1.73, 1.74 (2 H, 2×q, $^3J_{H,H}$=7.5 Hz, CH_2CH$_3$), 2.69 (4 H, t, $^3J_{H,H}$=5.0 Hz, H-3, -5 Piperazine), 3.49-3.51 (6 H, m, CH_2OH, H-2, -6 Piperazine), 3.56 (2 H, d, $^2J_{H,H}$=10.5 Hz, CH_2OH), 4.02 (1 H, d, $^2J_{H,H}$=11.5 Hz, H-6-a D-NH), 4.12 (1 H, dd, $^3J_{H,H}$=1.5 Hz, $^2J_{H,H}$ = 11.5 Hz, H-6-e D-NH), 4.41 (1 H, d, $^3J_{H,H}$ = 9.0 Hz, H-5-e D-NH), 4.54 (3 H, bs, OH, Pip-N*H*), 5.00 (1 H, d, $^2J_{H,H}$=6.5 Hz, H-2-a D-NH), 5.23 (1 H, d, $^2J_{H,H}$=5.5 Hz, H-2-e D-NH), 5.24 (1 H, s, H-4a D-NH), 5.35 (1 H, s SER-N*H*), 5.52 (1 H, d, $^3J_{H,H}$=9.5 Hz D-N*H*), 7.62 (2 H, d, $^3J_{H,H}$=8.0 Hz, H-2, -6 *p*-NPh), 8.10 (2 H, d, $^3J_{H,H}$=8.5 Hz, H-3, -5 *p*-NPh) ppm; ^{13}C NMR (125 MHz, [D_6]DMSO, 298 K): δ_C 8.1 (1 C, CH_3), 23.4, 23.46, 23.54 (1 C, *C*H$_2$CH$_3$), 43.5, 44.0 (2 C, C-3, -5 Piperazine),

45.45, 45.55, 45.64, 45.7 (2 C, C-2, -6 Piperazine), 48.8, 48,9 (1 C, C-5 D-NH), 60.2 (1 C, C-2 SER-NH), 62.5, 62.9 (2 C, CH_2OH), 70.5, 70,6 70.8, 70.9 (1 C, C-6 D-NH), 78.5, 78.95, 79.04 (1 C, C-4 D-NH), 93.9, 94.0 94.1 (1 C, C-2 D-NH), 123.2, 123.5 (2 C, C-2, -6 *p*-NPh), 127.3, 127.6 (2 C, C-3, -5 *p*-NPh), 147.0, 147.1 (2 C, C-1, -4 *p*-NPh), 164.5 (1 C, C-2 *s*-triazine), 165.4, 165.6 (2 C, C-4, -6 *s*-triazine) ppm. MS (ESI+), *m/z* (rel. int. %) 505.3 [M^++H] (100), 403.2 (25), 224.0 (12), 208.0 (37). $[\alpha]_D^{25}$=+42 (0.5 % DMSO).

1-{6-{[1,3-Dihydroxy-2-(hydroxymethyl)prop-2-yl]amino}-4-[(4*S*,5*S*)-4-(4-nitrophenyl)-1,3-dioxan-5-yl]amino}-*s*-triazin-2-yl}-iperazine I-4c (86 %) yellowish crystalline powder, mp 146-157 °C (flash column chromatography, eluent ethanol : aq. NH_3 25% 9:1 v/v). [Found: C 50.11, H 5.88, N 21.90; $C_{21}H_{30}N_8O_7$ (506.22) requires: C 49.80, H 5.97, N 22.12%]. R_f 0.71 (90% ethanol/aq. NH_3 25%). IR ν_{max} (KBr) 3392 (m), 2943 (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, 353 K): δ_H 2.65 (3 H, t, $^3J_{H,H}$=4.8 Hz, H-3, -5 Piperazine), 2.68 (3 H, s, OH), 3.46 (4 H, t, $^3J_{H,H}$=5.0 Hz, H-2, -6 Piperazine), 3.62 (6 H, s, CH_2OH), 4.02 (1 H, d, $^2J_{H,H}$=11.0 Hz, H-6-a D-NH), 4.11 (1 H, $^2J_{H,H}$=11.0 Hz, H-6-e D-NH), 4.40 (1 H, bd, $^3J_{H,H}$ = 7.5 Hz, H-5-e D-NH), 5.00 (1 H, d, $^2J_{H,H}$=6.5 Hz, H-2-a D-NH), 5.22 (1 H, s, H-4-a D-NH), 5.23 (1 H, d, $^2J_{H,H}$=5.5 Hz, H-2-e D-NH), 5.43 (1 H, s SER-N*H*), 5.61 (1 H, d, $^3J_{H,H}$=9.5 Hz D-N*H*), 7.63 (2 H, d, $^3J_{H,H}$=9.0 Hz, H-2, -6 *p*-NPh), 8.12 (2 H, d, $^3J_{H,H}$=8.0 Hz, H-3, -5 *p*-NPh) ppm; ^{13}QC NMR (75 MHz, [D_6]DMSO, 298 K): δ_C 43.9 (2 C, C-3, -5 Piperazine), 45.4 (3 C, C-2, -6 Piperazine), 48.8 (1 C, C-5 D-NH), 61.0, 61.3 (4 C, C-2, CH_2OH, SER-NH), 70.5, 70.7 (1 C, C-6 D-NH), 78.4, 78,8 (1 C, C-4 D-NH), 93.9 (1 C, C-2 D-NH), 123,1, 123,3 (2 C, C-2, -6 *p*-NPh), 127.1, 127.4 (2 C, C-3, -5 *p*-NPh), 146.9 (2 C, C-1, -4 *p*-NPh), 164.2 (1 C, C-2 *s*-triazine), 165.0, 165.2, 165.4, 165.5 (2 C, C-4, -6 *s*-triazine) ppm. MS (DCI positive, 200 eV, isobutane), *m/z* (rel. int. %) 563 [M^++$HC(CH_3)_3$-2 H] (9), 507 [M^++H] (100), 489 (10), 477 (10), 404 (10),282 (5), 225 (10), 115 (8), 104 (20), 87 (75). $[\alpha]_D^{25}$=+24 (0.5 % DMSO).

1-{6-{[1,3-Dihydroxy-2-(methyl)prop-2-yl]amino}-4-{[(2*R*,4*S*,5*S*)-5-(dimethylamino)-4-(4-nitrophenyl)-1,3-dioxan-2-yl]methylamino}-*s*-triazin-2-yl}-piperazine II-5a (71 %) yellowish crystalline powder, mp 118-123 °C (flash column chromatography, eluent ethanol : aq. NH_3 25% 9:1 v/v). [Found: C 52.88, H 7.07, N 22.85; $C_{24}H_{37}N_9O_6$ (547.29) requires: C 52.64, H 6.81, N 23.02%]. R_f 0.57 (90% ethanol/aq. NH_3 25%). IR ν_{max} (KBr) 3295 (s), 2932 (s), 2860 (s), 1670 (m), 1548 (s), 1516 (s), 1444 (s), 1348 (s), 1296 (m), 1151 (m), 1113 (m), 1055 (m), 1016 (m), 852 (m), 809 (m), 710 (m), 668 (w), 572 (w) cm^{-1}. ^{1}H NMR (500 MHz, [D_6]DMSO, 353 K): δ_H 1.27 (3 H, s, CH_3), 2.23 [6 H, s, $N(CH_3)_2$], 2.69 (4 H, t, $^3J_{H,H}$=4.8 Hz, H-3, -5 Piperazine), 2.86 (1 H, dd as t, $^3J_{H,H}$=2.8 Hz, H-5-e D-NH), 3.496 (2 H, dd as t, $^3J_{H,H}$=4.5 Hz, CH_2NH), 3.504 (2 H, d, $^2J_{H,H}$=10.0 Hz, CH_2OH), 3.58 (4 H, t, $^3J_{H,H}$=5.3 Hz, H-2, -6 Piperazine), 3.60

(2 H, d, $^2J_{H,H}$=10.5 Hz, C*H*$_2$OH), 3.96 (1 H, dd, $^2J_{H,H}$=12.5 Hz, $^3J_{H,H}$=3.0 Hz, H-6-a D-NH), 4.46 (1 H, d, $^2J_{H,H}$=12.0 Hz H-6-e), 4.66 (3 H, bs, OH, Pip-N*H*), 4.99 (1 H, dd as t, $^3J_{H,H}$=4.8 Hz, H-2-a D-NH), 5.18 (1 H, d, $^3J_{H,H}$=3.5 Hz, H-4-a D-NH), 5.55 (1 H, s SER-N*H*), 6.27 (1 H, bdd as bt, $^3J_{H,H}$=5.5 Hz D-N*H*), 7.64 (2 H, d, $^3J_{H,H}$=8.5 Hz, H-2, -6 *p*-NPh), 8.16 (2 H, d, $^3J_{H,H}$=8.5 Hz, H-3, -5 *p*-NPh) ppm; ^{13}C NMR (125 MHz, [D$_6$]DMSO, 298 K): δ_C 19.3 (1 C, CH$_3$), 43.8 [2 C, N(CH$_3$)$_2$], 44.4 (2 C, C-3, -5 Piperazine), 45.87, 45.94, 46.03 (3 C, C-2, -6 Piperazine, CH$_2$NH), 58.0 (1 C, C-2 SER-NH), 58.5, 58.6 (1 C, C-5 D-NH), 64.4, 64.5, 64.6 (2 C, CH$_2$OH), 64.88, 64.92, 65.3 (1 C, C-6 D-NH), 80.1, 80.2 (1 C, C-4 D-NH), 99.8, 99.9 (1 C, C-2 D-NH), 123.19, 123.24 (2 C, C-2, -6 *p*-NPh), 127.0 (2 C, C-3, -5 *p*-NPh), 146.7 (1 C, C-1 *p*-NPh), 148.9 (1 C, C-4 *p*-NPh), 164.7 (1 C, C-2 *s*-triazine), 165.9 (2 C, C-4, -6 *s*-triazine) ppm. MS (ESI+), *m/z* (rel. Int. %) 548.3 [M$^+$+H] (100), 543.3 (8), 295.2 (10), 217.1 (15), 154.1 (10), 120.1 (3). $[\alpha]_D^{25}$= +145 (0.5 % DMSO).

1-{6-{[1-Hydroxy-2-(hydroxymethyl)but-2-yl]amino}-4-{[(2*R*,4*S*,5*S*)-5-(dimethylamino)-4-(4-nitrophenyl)-1,3-dioxan-2-yl]methylamino}-*s*-tri-azin-2-yl}-piperazine II-5b (67 %) yellowish crystalline powder, mp 112-118 °C (flash column chromatography, eluent ethanol : aq. NH$_3$ 25% 9:1 v/v). [Found: C 53.55, H 7.17, N 22.22; C$_{25}$H$_{39}$N$_9$O$_6$ (561.30) requires: C 53.46, H 7.00, N 22.45%]. R_f 0.70 (90% ethanol/aq. NH$_3$ 25%). IR ν_{max} (KBr) 3392 (s), 2939 (s), 2856 (s), 1553 (s), 1514 (s), 1446 (s), 1348 (s), 1298 (m), 1151 (m), 1113 (m), 1055 (s), 1011 (m), 852 (m), 710 (m), 573 (w) cm^{-1}. ^{1}H NMR (500 MHz, [D$_6$]DMSO, 353 K): δ_H 0.79, 0.80 (3 H, 2×t, $^3J_{H,H}$ = 7.5 Hz, CH$_3$), 1.80, 1.81 (2 H, 2×q, $^3J_{H,H}$=7.5 Hz, C*H*$_2$CH$_3$), 2.23 [6 H, s, N(CH$_3$)$_2$], 2.70 (4 H, t, $^3J_{H,H}$=4.8 Hz, H-3, -5 Piperazine), 2.86 (1 H, dd as t, $^3J_{H,H}$=2.3 Hz, H-5-e D-NH), 3.50 (2 H, dd as t, $^3J_{H,H}$=4.5 Hz, C*H*$_2$NH), 3.51-3.62 (8 H, m, C*H*$_2$OH, H-2, -6 Piperazine), 3.96 (1 H, dd, $^2J_{H,H}$=12.5 Hz, $^3J_{H,H}$=3.0 Hz, H-6-a D-NH), 4.46 (1 H, d, $^2J_{H,H}$=12.5 Hz, H-6-e D-NH), 4.68 (3 H, bs, OH, Pip-N*H*), 4.99 (1 H, dd as t, $^3J_{H,H}$ = 4.8 Hz, H-2-a D-NH), 5.18 (1 H, d, $^3J_{H,H}$=3.0 Hz, H-4-a D-NH), 5.46 (1 H, s SER-N*H*), 6.29 (1 H, bdd as bt, $^3J_{H,H}$=5.5 Hz D-N*H*), 7.64 (2 H, d, $^3J_{H,H}$=8.5 Hz, H-2, -6 *p*-NPh), 8.16 (2 H, d, $^3J_{H,H}$=9.0 Hz, H-3, -5 *p*-NPh) ppm; ^{13}C NMR (125 MHz, [D$_6$]DMSO, 298 K): δ_C 8.3 (1 C, CH$_3$), 23.5, 23.6 (1 C, *C*H$_2$CH$_3$), 43.8 [2 C, N(CH$_3$)$_2$], 44.3 (2 C, C-3, -5 Piperazine), 45.8, (3 C, C-2, -6 Piperazine, CH$_2$NH), 58.6 (1 C, C-5 D-NH), 60.4 (1 C, C-2 SER-NH), 62.8, 63.4 (1 C, C-6 D-NH), 64.5 (2 C, CH$_2$OH), 80.1, 80.3 (1 C, C-4 D-NH), 99.8, 100.1 (1 C, C-2 D-NH), 123.2 (2 C, C-2, -6 *p*-NPh), 127.0 (2 C, C-3, -5 *p*-NPh), 146.7 (1 C, C-1 *p*-NPh), 148.93, 148.95 (1 C, C-4 *p*-NPh), 164.7 (1 C, C-2 *s*-triazine), 165.9, 166.0 (2 C, C-4, -6 *s*-triazine) ppm. MS (ESI+), *m/z* (rel. Int. %) 562.3 [M$^+$+H] (100), 548.3 (10), 302.2 (15), 281.7 (25), 208.0 (13), 143.1 (7). $[\alpha]_D^{25}$=+136 (0.5 % DMSO).

1-{6-{[1,3-Dihydroxy-2-(hydroxymethyl)prop-2-yl]amino}-4-{[(2*R*,4*S*,5*S*)-5-(dimethylamino)-4-(4-nitrophenyl)-1,3-dioxan-2-yl]methylamino}-*s*-triazin-2-yl}-piperazine II-5c (81 %) yellowish crystalline powder, mp 140-145 °C (flash

column chromatography, eluent ethanol : aq. NH_3 25% 9:1 v/v). [Found: C 50.98, H 6.77, N 22.55; $C_{24}H_{37}N_9O_7$ (563.28) requires: C 51.15, H 6.62, N 22.37%]. R_f 0.57 (90% ethanol/aq. NH_3 25%). IR ν_{max} (KBr) 3298 (s), 2940 (s), 2858 (s), 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, 353 K): δ_H 2.23 [6 H, s, $N(CH_3)_2$], 2.69 (4 H, t, $^3J_{H,H}$=4.8 Hz, H-3, -5 Piperazine), 2.86 (1 H, dd as t, $^3J_{H,H}$=2.8 Hz H-5-e.), 3.50 (2 H, dd as t, $^3J_{H,H}$=4.8 Hz, CH_2NH), 3.57 (4 H, t, $^3J_{H,H}$=4.3 Hz, H-2, -6 Piperazine), 3.66 (6 H, s, CH_2OH), 3.97 (1 H, dd, $^2J_{H,H}$=12.5 Hz, $^3J_{H,H}$=3.0 Hz, H-6-a D-NH), 4.46 (1 H, d, $^2J_{H,H}$=12.5 Hz H-6-e D-NH), 4.65 (3 H, bs, OH), 5.00 (1 H, dd as t, $^3J_{H,H}$=4.5 Hz, H-2-a D-NH), 5.19 (1 H, d, $^3J_{H,H}$=3.0 Hz, H-4-a D-NH), 5.53 (1 H, s SER-N*H*), 6.38 (1 H, bs D-N*H*), 7.64 (2 H, d, $^3J_{H,H}$=8.5 Hz, H-2, -6 *p*-NPh), 8.17 (2 H, d, $^3J_{H,H}$=8.5 Hz, H-3, -5 *p*-NPh) ppm; ^{13}C NMR (75 MHz, [D_6]DMSO, 298 K): δ_C 43.7 [2 C, $N(CH_3)_2$], 44.3 (2 C, C-3, -5 Piperazine), 45.8, 46.1, 46.3 (3 C, C-2, -6, Piperazine, CH_2NH), 58.4 (1 C, C-5 D-NH), 61.3, 61.4 (1 C, C-2 SER-NH), 64.3 (3 C, CH_2OH), 65.3 (1 C, C-6 D-NH), 80.0 (1 C, C-4 D-NH), 99.6 (1 C, C-2 D-NH), 123.1 (2 C, C-2, -6 *p*-NPh), 126.9 (2 C, C-3, -5 *p*-NPh), 146.5 (1 C, C-1 *p*-NPh), 148.8 (1 C, C-4 *p*-NPh), 164.4 (1 C, C-2 *s*-triazine), 165.8 (2 C, C-4, -6 *s*-triazine) ppm. MS (DCI positive, 200 eV, isobutane), *m/z* (rel. Int. %) 620 [M^++$HC(CH_3)_3$-2 H] (5),564 [M^++1] (65), 449 (28), 380 (55), 300 (10), 282 (15), 221 (5), 178 (100), 165 (25), 148 (10), 104 (45), 87 (35). $[\alpha]_D^{25}$=+137 (0.5 % DMSO).

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