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Serinolic amino-*s*-triazines: iterative synthesis and rotational stereochemistry phenomena as *N*-substituted derivatives of 2-aminopropane-1,3-diols

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ABSTRACT

The iterative synthesis of 2,4,6-triamino-*s*-triazines (*melamines*), precursors and dendritic structures, by amination of cyanuric chloride with *C*-1 versus *C*-2-substituted 2-aminopropane-1,3-diols (*serinols*), is comparatively examined. The stereochemistry of the resulting serinolic amino-*s*-triazines, issued from the restricted rotation about the newly created C(*s*-triazine)–N< bonds, is for the first time discussed in terms of (pro)diastereomerism based on DNMR and DFT calculation data.

1. Introduction

The synthesis of highly elaborated *N*-substituted triamino-*s*-triazines (*melamines*) is, nowadays, a part of supramolecular chemistry as dendrimers,[1] macrocycles[2] and molecular tectonics.[3] Among suitable amines able to provide *s*-triazine dendritic structures, as defined by Tomalia,[4] little attention was paid to *C*-substituted *serinols* (2-aminopropane-1,3-diols) as there are only three papers, which dealt with their reactivity with cyanuric chloride.[5] The resulting simple melamines and their serinolic amino-*s*-triazine precursors were claimed, as early as 1979, as antitumour[5a] or antibacterial compounds.[5b] In dendrimer chemistry, the exploitation of some serinols, mentioned in Scheme 1, is of interest as cores,[6a–c] branch cells,[6d] linkers[6d] and peripheral groups.[6d,e]

Aiming to expand our previous expertise in (masked) serinols' nucleophilic anchorage on π-deficient systems,[7a–g] we obtained some insight in testing amination of cyanuric chloride with the use of two typical terms of this family, **A** and **E** (Scheme 1).

The preliminary promising findings[7f,g] encouraged us to broaden the investigations to a variety of *C*-2-(**A**–**C**) and *C*-1-(**D**, **E**)-substituted serinols (Scheme 1). Hence, we herein report our results in two main areas:

(i) A comparative study of reactivity using five commercial serinols **A**–**E** with cyanuric chloride, in order to access melamines and dendritic structures.
(ii) Since in *N*-substituted melamines' and several precursors' chemistry, recent DNMR, X-ray and computational data,[8] ours included,[7e–g,8d] established hindered rotation about C(*s*-triazine)–N(exocyclic) bonds, we were also interested in examining these phenomena in serinolic amino-*s*-triazines class. Indeed, extension of this structural concept rapidly disseminated the relevance of melamines based anticancer drugs, dyes and self-assembly architectures.[8c,9]

2. Results and discussion

2.1. Synthesis of serinolic amino-*s*-triazines

Starting from serinols **A**–**E** (Scheme 1), we first developed the chemistry summarised in Scheme 2 while the results are collected in Table 1.

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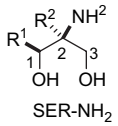
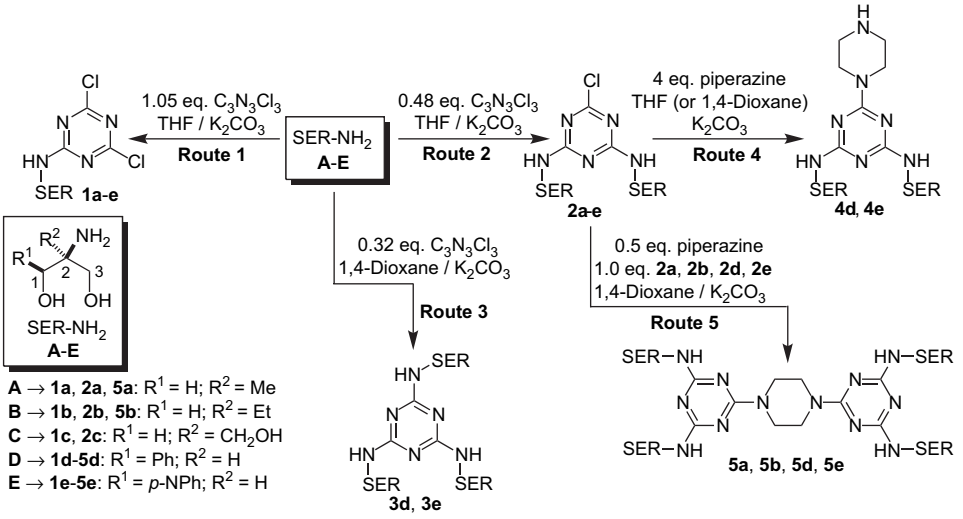


SER-NH$_2$
A–E

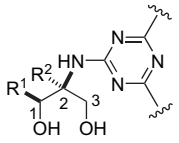
	2-aminopropane-1,3-diol R^1	R^2	Trivial name
	H	H	*Serinol*[6c, 6d]
	C-2-substituted serinols		
A	H	Me	*"Methylserinol"*
B	H	Et	*"Ethylserinol"*
C	H	CH_2OH	*TRIS, THAM*[6b, 6e]
	C-1-substituted serinols		
D	Ph	H	(1*S*,2*S*)-*"Threo-phenylserinol"*
E	***p*-NPh**	H	(1*S*,2*S*)-*"Threo-**p-N**itro**Ph**enylserinol"*

Scheme 1.



Scheme 2.

Table 1
Results and conditions in the synthesis of serinolic amino-*s*-triazines **1**–**5** (Scheme 2)



1a, 2a, 5a: R^1 = H; R^2 = Me
1b, 2b, 5b: R^1 = H; R^2 = Et
1c, 2c: R^1 = H; R^2 = CH_2OH
1d-5d: R^1 = Ph; R^2 = H
1e-5e: R^1 = *p*-NPh; R^2 = H

Route	Molar ratios	*T* (°C) (time, h)	Main and by-products, yields (%) and isolation: direct crystallisation (d.c.) or flash column chromatography on silica gel (c.c.)
1	1.00 (**A**–**E**) 1.05 ($C_3N_3Cl_3$)	(i) (−10)→0 (2) (ii) rt (24–48)	**1a**, 45 (d.c.); **1b**, 58 (c.c.); **1c**, 86 (d.c.); **1d** [83][a]+**2d** [9] (c.c.); **1e**, 61 (c.c.)
2	2.1 (**A**–**E**) 1.0 ($C_3N_3Cl_3$)	(i) (−10)→0 (12) (ii) 40 (24) (iii) 65 (24)	**2a**, 92 (d.c.); **2b**, 61 (c.c.); **2c**, 47 (d.c.)
		(i) (−10)→0 (2) (ii) rt (24–48)	**2d** [83]+**3d** [8] (c.c.); **2e**, 65 (c.c.)
	2.0 (**A**–**E**) 1.0 ($C_3N_3Cl_3$)	(i) (−78)→rt (12) (ii) rt (24)	**2a**, 60 (d.c.); **2d**, 96 (d.c.); **2e**, 88 (d.c.)
3	3.15 (**D**, **E**) 1.00 ($C_3N_3Cl_3$)	(i) rt (24) (ii) 101 (60)	**3d** [75]+**2d** [23] (c.c.); **3e** [46]+**2e** [16] (c.c.)
4	4 (piperazine) 1 (**2d**, **2e**)	65 (12)	**4d**, 75 (d.c.); **4e**, 84 (d.c.)
5	0.5 (piperazine) 1.0 (**2a**, **2b**, **2d**, **2e**)	101 (24)	**5a**, 50 (c.c.); **5b**, 67 (c.c.); **5d**, 60 (c.c.); **5e**, 69 (c.c.)

[a] In square brackets: partial conversions of cyanuric chloride into the depicted compounds, calculated based on effective amounts isolated by column chromatography on silica gel.

Since our approach was a comparative one, all the syntheses were carried out under the same conditions, in THF (or 1,4-dioxane) in the presence of potassium carbonate as proton scavenger. DMSO-d_6 was throughout the solvent for NMR monitoring.

Initial experiments were directed towards the unexplored reaction between equimolar amounts of **A**–**E** and cyanuric chloride (Route 1) since compounds **1a**–**c** were only mentioned in the literature as non-isolated intermediates in antitumour melamines'

syntheses.[5a] Although TLC control and NMR spectra of crude **1a–e** indicated in all cases clean and almost quantitative reactions, pure analytical samples were difficult to obtain. Compounds **1a–c** were slightly contaminated with competitively alkoxylated *s*-triazines meanwhile the by-products found in crude products **1d**, **1e** were the corresponding chlorodiamino-*s*-triazines: small traces of **2e** in **1e** but significant amounts of **2d** in **1d**. Therefore, data in Route 1 (Table 1, **1a–e**) disclose rather yields of purifications than of reactions. To summarise, as amino nucleophiles against cyanuric chloride, *C*-2-substituted serinols **A–C** appeared less reactive than *C*-1-substituted ones **D**, **E**. Two explanations, (i) better solvated nucleophiles **A–C** versus **D**, **E** in THF and (ii) steric hindrance as tertiary carbon in **A–C** versus secondary carbon in **D**, **E** bearing the amino group, were plausible at this stage of our study.

Synthesis of serinolic chlorodiamino-*s*-triazines **2a–e** in a one-pot procedure (Scheme 2, Route 2, Table 1) better illustrated the difference in reactivity of the above nucleophiles **A–C** versus **D**, **E**.

Reactions of cyanuric chloride with 2 mol equiv of **A–C**, affording series **2a–c**, reached completion only in refluxing THF. Apparently, they worked well in the case of methylserinol **A** only, providing compound **2a** in 92% yield. In fact, the lower yield in the synthesis of the ethyl analogue **2b** (61%) was due to loss of material during its purification by column chromatography (imposed mainly by the side compounds present in the commercial starting material **B**). Next, despite its excellent TLC and NMR appearance, the crude TRIS derivative **2c** was a sticky mass, very difficult to handle during work-up by crystallisation or column chromatography. Actually, this was but one of the major drawbacks against persisting in the use of TRIS **C** in the present chemistry (see Section 4, compound **2c**).

If performed with phenylserinolic nucleophiles **D**, **E**, the double amination yielded the expected **2d**, **2e** (Route 2), under much milder conditions, similar to those used in the monosubstitution step (Route 1). Compounds **2d**,[5c] **2e**[5b] were previously mentioned in the literature but the NMR assignment was reported only for **2d**. Phenylserinol **D** showed again higher reactivity than **E**, as proved by the noticeable amounts of triserinolic-*s*-triazine **3d** (8%) accompanying the desired **2d**.

The double amination carried out under cryogenic conditions (Table 1) was a pivotal improvement in the synthesis of compounds **2d**, **2e** since this protocol routinely allowed their direct isolation, as pure analytical samples, by simple crystallisation when very small traces of the corresponding intermediates **1d**, **1e** were completely eliminated. In this context, we note the recently claimed as clean synthesis of **2d** (86% yield) under PTC conditions if 18-crown-6 was used as a catalyst (48 h, 0–25 °C, K_2CO_3/toluene).[5c] However, the product prepared by this method needed purification by column chromatography.

Unsurprisingly, cryogenic conditions were unsuitable for *C*-2-substituted serinols' **A–C** manipulation, as shown by the lower yield (60%) obtained in the synthesis of **2a**.

The attempt to one-pot preparation of *N*-substituted 2,4,6-triamino-1,3,5-triazines (*melamines*) based entirely on serinols and cyanuric chloride (Scheme 2, Route 3, Table 1) critically discriminated the nucleophilicity of our two series of reagents **A–C** versus **D**, **E**.

C-2-Substituted serinols **A–C** gave no isolable (if formed) melamine but reaction mixtures with complex NMR spectra of the crude material. In the case of ethylserinol **B**, the reaction product (if the desired one), exhibited both high retention on silica gel and instability. Even higher was the instability of the isolated crude reaction mixture starting from TRIS **C** (NMR monitoring).

In contrast, the successful synthesis of melamines **3d**, **3e** evidenced clear differences in nucleophilicity between phenylserinols **D**, **E**. The best result as 75% level of conversion of cyanuric chloride (**3d**) was obtained if **D** was used as a nucleophile. The *p*-nitro-analogue **E** afforded **3e** in 46% level of conversion to indicate that the substitution of the reminder chlorine in the precursor **2e** was problematic. Indeed, in an alternative experiment aiming at **3e** (not depicted in Scheme 2), the reaction between isolated **2e** and 1.03 mol equiv of **E** (22 h in refluxing 1,4-dioxane) occurred in 54% yield.

In summary, serinolic melamines were directly obtainable with medium to satisfactory yields based only on phenylserinols **D**, **E**. The enantiomerically pure **3d** and **3e** can be seen as valid candidates for dendrimeric cores. They have, three times, two types of hydroxyl sites (primary and secondary), available for further selective manipulation against electrophiles as we have previously pointed out.[7h,i,10]

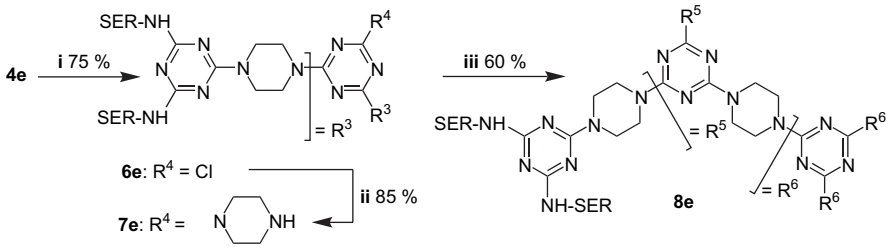
With complete series **2a–e** available, we next envisaged their mono-anchorage on piperazine, a widely used linker in melamine dendritic chemistry, as connecting cores,[1b,f,h,11a] generations[1e,g,i,11b] or both.[1c,j,11c,d] In spite of the simplicity of previously described direct methodologies[1c,e,i,11b] (no protecting–deprotecting step), in our hands, they worked properly only in the case of the target compounds **4e** and, with restrictions, **4d** (Scheme 2, Route 4, Table 1, see Section 4). Essentially, selectivity was ensured by adding portionwise chloro-*s*-triazines **2d**, **2e** (0.2 equiv each 60 min) in refluxing THF (or 1,4-dioxane) containing 4 equiv of anhyd piperazine. After this period, TLC monitoring indicated, in each case, complete absence of the starting **2d**, **2e**. Indeed, due to their polarity and basicity, compounds **4** could not be eluted on silica gel. Fortunately, crude **4d**, **4e** required no sophisticated purification since they were recovered pure after several washings with cold water, which completely discarded the excess of piperazine and the small traces of double melamines **5d**, **5e** (Scheme 2, Route 5). In contrast, compounds of type **4** (if formed), starting from **2a–c**, rapidly decomposed during the work-up. In fact, **4d** also slowly decomposed on storage.

In contrast, serinolic chlorodiamino-*s*-triazines **2a**, **2b**, **2d** and **2e** simply underwent dimerisation through the piperazine linker (Scheme 1, Route 5, Table 1) to give double melamines **5a**, **5b**, **5d** and **5e** in satisfactory yields. They were all stable structures and could be purified by column chromatography, when an important retention on silica gel was observed. Series **5** was also seen as valid cores for dendritic synthesis.

Critical analysis of the above results compelled us to continue a convergent strategy towards dendritic structures using only *p-nitrophenylserinol* **E** derivatives (Schemes 1 and 3).[7g]

We reiterated a second double connection of **4e** to an *s*-triazine unit in a single step, under cryogenic conditions, accessing compound **6e** in a clean reaction. According to TLC monitoring, crude **6e** contained only very small traces of much less polar side products, easily removable by flash column chromatography on silica gel, presumably issued from the statistical 1 versus 4 nucleophilic competition, amination versus alkoxylation, respectively, in **4e**. We note dramatically decreased yields of **6e** (15–20%) in non-cryogenic conditions (e.g., from −10 °C to rt during 12 h and then 36 h at rt). Next, we obtained the dendron **7e** reacting the second piperazine linker with **6e** in good yield. The synthetic protocol was as for the melamine **4e** although the reaction was slower requiring higher temperature.

Finally, the G-2 dendrimer **8e** was prepared in a one-pot synthesis. Systematic TLC control of the reaction from −78 °C to refluxing THF exposed spot-to-spot transformations in different polar eluents and combinations thereof, dichloromethane, chloroform, acetone and ethanol. When no more evolution was detected, THF was replaced by 1,4-dioxane. The reaction was stopped whilst some thermal decomposition was observed. The crude product was easily purified by two successive crystallisations from ethanol then from isopropanol. The comparative TLC control of mother liquors versus final remainder crystalline solid exhibited the latter as a single spot ($CHCl_3$/EtOH 2:1 v/v) with a very small R_f, around 0.10. Thus, **8e** was rapidly obtainable in five linear steps in 27% overall yield.



i: 0.49 eq. $C_3N_3Cl_3$ / 1.00 eq. anh. K_2CO_3 / THF / 12 hrs. (from −78 °C to r.t.) / 72 hrs. (r.t.).
ii: 4.00 eq. piperazine / 1.00 eq. anh. K_2CO_3 / 1,4-dioxane / 12 hrs. (reflux).
iii: 0.33 eq. $C_3N_3Cl_3$ / 1.00 eq. anh. K_2CO_3 / THF /12 hrs. (from −78 °C to r.t.) / 24 hrs. (reflux) / 1,4-dioxane / 24 hrs. (reflux).

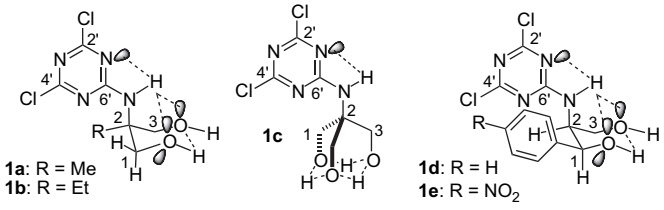
Scheme 3.

2.2. Rotational stereochemistry phenomena in serinolic amino-*s*-triazines

We gradually analysed the stereochemistry of our compounds' account being taken on *the number of increasing serinolic groups*, keeping in mind the leading concept, discussed in the literature since 1995,[8] namely the restricted rotation about C(*s*-triazine)–N< partial double bonds in amino-*s*-triazines. In our approach, they have been optimally seen as (pro)stereogenic axes creating (pro)-diastereomerism, recently pointed out as such by us.[8d] This intrinsic feature appears scarcely mentioned in the case of dendritic amino-*s*-triazines,[1b,c,h] usually by referring to specialised DNMR investigations.[9]

2.2.1. *Monoserinolic aminodichloro-s-triazines* ***1a–e***

We first inspected the NMR data of the simplest title compounds supporting comments, listed in Supplementary data (Table I, Scheme 4).



Scheme 4.

In all derivatives **1a–e**, *s*-triazine carbons C-2′, -4′ were found diastereotopic ($\Delta\delta$=0.5–0.7 ppm), consistent with the hindered rotation about C-6′–N(serinol) bond. It was an authentic prostereogenic axis. Fluctuations of diastereotopicity were negligible as we were unable to discriminate any influence of the serinolic site.

In ^{1}H NMR spectra, in the presence of the diatropic *s*-triazine ring, we basically differentiated series **1a–c** against **1d**, **1e** starting from the δNH(**1a–c**)<δNH(**1d**, **1e**) dissimilarity (Table I in Supplementary data). Then we alleged that the more deshielded 'exchangeable' protons NH were in a hydrogen bond acceptor solvent, such as DMSO-d_6,[1b,8c] more solvation as well as double bond character of the connection C-6′–N< had been expected.[12,†]

In this approach, the tertiary nature of serinolic carbon C-2 in **1a–c** appeared to disturb coplanarity required by the lpN(serinol)→π(*s*-triazine) conjugation in addition to internal chelation of the amide type proton NH. In fact, previously reported UV data of compounds **1a–c** considered their hydroxymethylated sites being solvated as six-membered hydrogen bond aggregates.[5a] When they were seen by us as chair conformers, δ values of protons NH in **1a** (8.39 ppm) and **1b** (8.27 ppm) compared with **1c** (8.05 ppm) suggested their implication in a deshielding trifurcated hydrogen bonding in environments **1a** and **1b**. In **1c**, a preferred internal aggregation involving three geminal hydroxymethyl groups only might be envisaged. Next, the decreasing order of pK_a values of starting aminodiols **A** (8.78), **B** (8.80), **C**(8.24)[5a] we correlated with:

(i) A reduced lpN(serinol)→π(*s*-triazine) donating ability as **1a**≈**1b**>**1c**.
(ii) A diminished C-6′–N< double bond character involving protons NH as **1a**≈**1b**>**1c**.
(iii) The downfield location of the corresponding δNH values as **1a**>**1b**>**1c** (Table I in Supplementary data).

Phenylserinolic *s*-triazines **1d**, **1e** were derivatives of the less basic amines, **D** (pK_a=7.81±0.1) and **E** (pK_a=7.14±0.1).[‡] However, taking into account the secondary nature of aliphatic carbon C-2, hence a sterically less disturbed conjugated lpN→π relationship, the important downfield resonance of protons NH, promoted by solvation in DMSO-d_6 (8.93 ppm in **1d**, 9.42 ppm in **1e**) was also due to the withdrawing σ field effect and anisotropy of the C-1 benzene ring in a similar chair six-membered chelate representation as in series **1a–c**.

Therefore, at this stage, we could only presume that more C(*s*-triazine)–N(serinol) double bond character exists in *C*-1-substituted serinolic amino-*s*-triazine **1d**, **1e** than in the corresponding *C*-2-substituted derivatives **1a–c**, although we failed to provide evidence by DNMR. On heating in DMSO-d_6, all **1a–e** underwent irreversible transformation that we rather associated to thermal decomposition. Confirmation was obtained when diserinolic chlorodiamino-*s*-triazines **2a–e** were investigated.

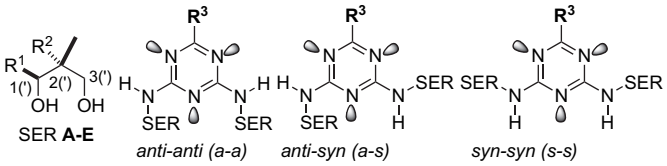
2.2.2. *Diserinolic amino-s-triazines* ***2a–e, 4d*** *and* ***4e***

Our analysis was based on ^{1}H NMR spectroscopy (Table 2, Table II in Supplementary data) met in conjunction with DFT computational data (Table 3).

† Following solvation, from a hydrogen bond donor solvent ($CDCl_3$) to a hydrogen acceptor one (DMSO-d_6), the deshielding of exchangeable protons NH in series **1a–c** was illustrated by compound **1a** (8.39 ppm in DMSO-d_6 but 6.52 ppm in $CDCl_3$); next, the sharp NH doublets in **1d**, **1e** ($^3J_{H,H}$=9.0–9.4 Hz) denoted their τ_1 (the life time of the spin state), defined as $\tau_1 > J^{-1}$, more than 0.11 s; that is, in **1d**, **1e**, protons NH were not quite exchangeable but located in a chelatizing environment.[12]

‡ Calculated using Advanced Chemistry Development (ACD/Labs) Software V8.14 for Solaris (© 1994–2007 ACD/Labs); in this approach, pK_a values of **A–C** are **A** (8.90±0.29), **B** (8.86±0.29) and **C** (7.78±0.29).[5d]

Table 2
Relevant ^{1}H NMR spectroscopic data of restricted rotation about C(*s*-triazine)–N(′)< bonds in compounds **2a–e**, **4d** and **4e**



R^3 = Cl **2a:** R^1 = H, R^2 = Me; **2b:** R^1 = H, R^2 = Et; **2c:** R^1 = H, R^2 = CH_2OH
2d: R^1 = Ph, R^2 = H; **2e:** R^1 = *p*-NPh, R^2 = H
R^3 = piperazin-1-yl **4d:** R^1 = Ph, R^2 = H; **4e:** R^1 = *p*-NPh, R^2 = H

No.	Solvent	*T* (K)	Indicative protons	Discriminating δ (ppm) values in rotamers				Content of blocked rotamers (%)[a]		
				(*a*-*a*)	(*a*-*s*)≡(*s*-*a*)		(*s*-*s*)	(*a*-*a*)	(*a*-*s*)≡(*s*-*a*)	(*s*-*s*)
2a	DMSO-d_6	298	N(′)H	6.41	6.66	6.74	6.78	4	46	50
			O(′)H	5.19	4.82	4.65	4.65			
		353		6.43 [br s, N(′)H]; 4.52 [br s, O(′)H]→Single mediated structure $\Delta G^{\neq}$=68.10 kJ/mol						
2b	DMSO-d_6	303	N(′)H	6.31	6.55	6.67	6.65	4	36	60
			O(′)H	4.81	4.81	4.61	4.61			
		353		6.37 [br s, N(′)H]; 4.46 [br s, O(′)H]→Single mediated structure $\Delta G^{\neq}$=68.35 kJ/mol						
2c	DMSO-d_6	298	N(′)H	6.29	6.52	6.57	6.50	(i) 6[b]	70	24
			O(′)H	5.20	4.82	4.57	4.51	(ii) 6	65	29
								(iii) 7	62	31
		353		6.30 [br s, N(′)H]; 4.43 [br s, O(′)H]→Single mediated structure $\Delta G^{\neq}$=69.22 kJ/mol						
2d	DMSO-d_6	298	N(′)H[c]	7.05	7.01	6.81	6.71	43	44	13
			1(′)-OH	5.35	5.43	5.53	5.54			
	THF-d_8	298	NH	6.52	6.45	6.32	6.22	36	50	14
	DMSO-d_6	353		6.64, 6.45 [2 br s, N(′)H]; 5.23, 5.11 [2 br s, 1(′)-OH]→Partially deblocked structure						
2e	DMSO-d_6	293	N(′)H	7.07	7.10	6.88	6.82	51	38	11
			1(′)-OH	5.61	5.72	5.80	5.83			
			p-NPh	8.13	8.21	8.00	8.13			
				7.58	7.64	7.45	7.54			
	THF-d_8	298	N(′)H	6.75	6.75	6.51	6.41	45	39	16
	DMSO-d_6	353		6.74, 6.51 [2 br s, N(′)H]; 5.59, 5.45 [2 br s, 1(′)-OH]→Partially deblocked structure						
4d	DMSO-d_6	298	N(′)H	5.81	5.67	5.81	5.67	25	50	25
		353		5.77, 5.63 [2 br s, N(′)H]; 5.25, 4.94 [2 br s, 1(′)-H]→Partially decomposed structure						
4e	DMSO-d_6	298	N(′)H[d]	5.73	5.64	5.73	5.69	25	50	25
			p-NPh	8.18, 8.14, 8.10, 7.98 (≈1:1:1:1)				25	50	25
				7.62, 7.53, 7.47 (≈2:1:1)						
		353		5.55 [br s, N(′)H]; 5.55 [br s, 1(′)-OH]→Single mediated structure $\Delta G^{\neq}$=66.52 kJ/mol						

[a] Averaged values using signals of protons N(′)H, O(′)H [or 1(′)-OH], *p*-NPh (**2e**, **4e**) and connectivity N(′)H/2(′)-H found in the 2D ^{1}H,^{1}H-COSY experiments in **2d**, **2e**, **4d** and **4e** (298 and 353 K).
[b] Averaged values according to dilution test of the NMR sample: (i) standard (0.18 M)→(ii) 1/3 (0.06 M)→(iii) 1/9 (0.02 M).
[c] Doublets ($^3J_{H,H}$=8.7–9.4 Hz) in **2d**, **2e**, denoting that protons N(′)H were not quite exchangeable at rt but located in a chelatizing environment.
[d] Deduced from 2D ^{1}H,^{1}H-NOESY experiment.

2.2.2.1. Analysis of frozen equilibria. As expected, at room temperature, on 75, 300, 400 and 500 MHz NMR timescales, each of the chlorodiamino-*s*-triazines **2a–e** and melamines **4d**, **4e** displayed four anisochronous environments, consistent with three diastereomers, arising from the restricted rotation about two C(*s*-triazine)–N(′)(**A–E**) bonds (frozen equilibriums), actually two stereogenic axes. From here on, we will discuss this stereochemistry in terms of the usual nomenclature of these rotamers: *anti-anti* (*a*-*a*), *anti-syn* (*a*-*s*) and *syn-syn* (*s*-*s*) (SER groups and R^3 substituent as references, Table 2).[8c–f]

Upon heating (293–353 K), in ^{1}H NMR spectra run on 400 or 500 MHz timescale, chlorodiamino-*s*-triazines **2a–c** containing two *C*-2-substituted serinolic side chains **A–C** and melamine **4e** reached the fast exchange status between unequally populated sites[12] as freely rotating structures (Table 2, Fig. 1, compound **2b**) meanwhile none of the chlorodiamino-*s*-triazines **2d**, **2e** based on *C*-1-substituted serinols **D**, **E** were totally deblocked. At 353 K, they displayed a slow exchange status between unequal populated sites (Table 2, Fig. 1, compound **2e**).

At room temperature, statistic rotameric abundance has been noticed just in melamines **4d** and **4e**, which could be assigned by 2D ^{1}H,^{1}H-NOESY experiment in the case of **4e** only (Table 2).

Therefore, we considered it to be of interest to investigate all series **2a–e**, **4d** and **4e**. Except our recent findings,[8d] no similar study in chlorodiamino-*s*-triazines was previously reported.

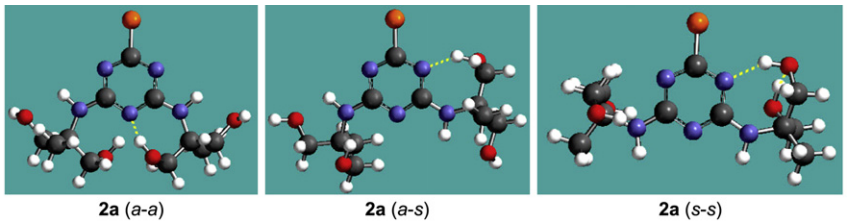
Firstly, we calculated the composition of frozen equilibria using signals of what from here on are named *the indicative protons* N(′)H, O(′)H [1(′)-OH in **2d**, **2e**] and *p*-NPh (in **2e**, **4e**). They were the best separated, providing very comparable results (Table 3). Only percentages of statistically twice favoured rotamers **2a–e** (*a*-*s*)≡**2a–e** (*s*-*a*) could be unambiguously established so far, exhibiting different resonances of equal intensity for the indicative protons.

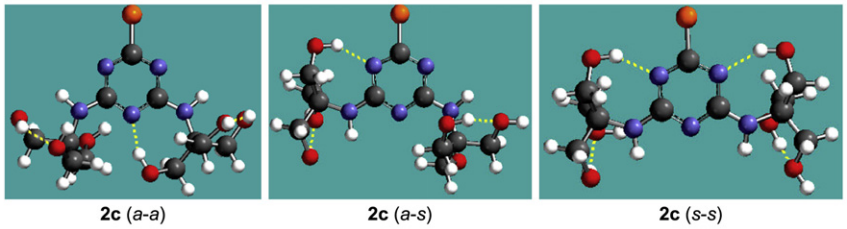
Because of the failure in differentiating by means of NMR the environments (*s*-*s*) versus (*a*-*a*) in chloro derivatives **2a–e**, we applied computational methods on selected compounds **2a**, **2c** and **2e** (Table 3). Their lowest energy conformers, generated by Spartan'04 with the MMFF force field, have been subjected to full geometry optimisation at the B3LYP/6-31G(d) level of theory. Further, the effect of solvent (DMSO) has been taken into account by performing SCRF calculation with COSMO (CPCM) option implemented in Gaussian 98.[13]

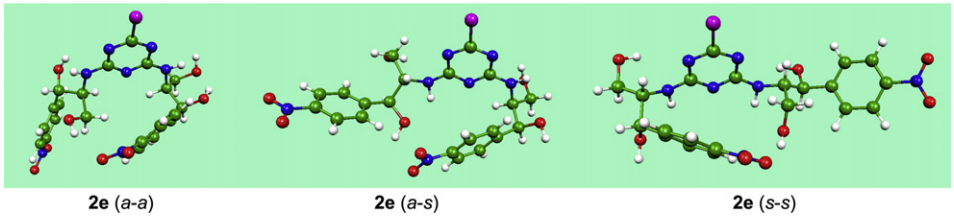
Calculations predicted a major and opposite incidence of rotamers (*a*-*a*) versus (*s*-*s*) in the two series, **2a–c** against **2d**, **2e** (Table 3).

In **2a–c**, the (*s*-*s*)+(*a*-*s*) spatial arrangements of the *C*-2-substituted serinolic sites were highly dominant. We were confident that solvation and dipolar interactions with the solvent were

Table 3
Relative energies (Δ*E*, kJ/mol), solvation energies (Δ*G*, kJ/mol) and dipole moments (*μ*, D) of the blocked rotamers of compounds **2a**, **2c** and **2e** versus their ^{1}H NMR abundance







No.	Gas phase[a]			Solution (DMSO)[b]		
	Relative energy (Δ*E*, kJ/mol)			Relative energy (Δ*E*, kJ/mol)		
	Dipole moment (*μ*, D)			Solvation Energy (Δ*G*, kJ/mol)		
				Dipole moment (*μ*, D)		
				Assigned ^{1}H NMR abundance (DMSO-d_6) (%)[c]		
	(*a*-*a*)	(*a*-*s*)	(*s*-*s*)	(*a*-*a*)	(*a*-*s*)	(*s*-*s*)
2a	6.61	8.68	0.00	8.12	8.33	0.00
				−18.81	−20.19	−20.31
	3.32	4.05	4.44	4.18	4.98	5.68
				5	30	65
2c	15.26	12.56	0.00	20.45	13.83	0.00
				−27.42	−31.14	−30.05
	5.96	6.49	6.22	7.24	7.76	7.61
				9[d]	49[d]	42[d]
2e	0.00	4.59	8.71	0.00	0.88	7.61
				−0.92	−5.18	−3.09
	6.68	9.47	10.95	7.96	11.59	13.52
				63	24	13

[a] B3LYP/6-31G(d) implemented in Gaussian 98.
[b] CPCM (COSMO COnductor-like Screening MOdel)//B3LYP/6-31G(d) (COSMO) implemented in Gaussian 98.
[c] Abundances corrected for symmetry since rotamer (*a*-*s*) is twice favoured; e.g., for **2a** the ^{1}H NMR deduced abundances were 50% (*s*-*s*), 46% (*a*-*s*≡*s*-*a*) and 4% (*a*-*a*) (Table 2); ratio corrected for symmetry: 50:23:4=(*s*-*s*)/(*a*-*s*)/(*a*-*a*), respectively; corrected abundances: 65% (*s*-*s*), 30% (*a*-*s*), 5% (*a*-*a*).
[d] Averaged and corrected for symmetry values, following successive dilutions, see Table 2.

responsible for this occurrence (Table 3). Thus, compound **2c**, possessing six hydroxymethyl groups able to ensure maximum solvation in DMSO-d_6, had a maximum content of rotamer (*a*-*s*) according to NMR data (Table 2). However, by successive dilution of the NMR sample, 1→1/3→1/9, the (*a*-*s*) abundance of **2c** decreased (70%→62%) while just another one, with similar dipole moment and solvation energy (Table 3), assigned as **2c** (*s*-*s*), increased (24%→31%). No effect of dilution was observed for the methyl (**2a**) or ethyl (**2b**) tetrahydroxymethyl derivatives.

Consistent with the calculations in the case of **2e**, rotamers **2d** and **2e** (*a*-*a*)+(*a*-*s*), having a bulky hydrophobic phenyl ring at C-1(′) were the major ones. Their predicted free energy of solvation was much smaller in comparison to those of **2a**–**c**. The percentages of **2d** and **2e** (*a*-*a*), suggesting a rather internal chelation between the two phenylserinolic sites, were slightly influenced by the polarity of the solvent, decreasing from DMSO-d_6 to THF-d_8 (Table 2). It was accepted that the (*a*-*a*) disposal adopted by **2d**, **2e** would also reduce steric hindrance between the three aromatic units.

If so, a ^{1}H NMR evaluation of the indicative protons N(′)H and O(′)H, this time as *syn* versus *anti* location, was performed for all compounds **2a**–**e**.

We ascertained that rotamers **2a**–**c** (*s*-*s*) exhibited the most deshielded N(′)H signals based on global solvation effects and dipole moments of these molecules. Conversely, in **2d**, **2e**, we ascertained rotamers (*a*-*a*) as providing the most downfield environment for the protons N(′)H. They were positioned towards the close strong dipole moment created by the remainder *s*-triazine chlorine,[1h,8d] deshielded by the vicinal anisotropic phenyl rings and

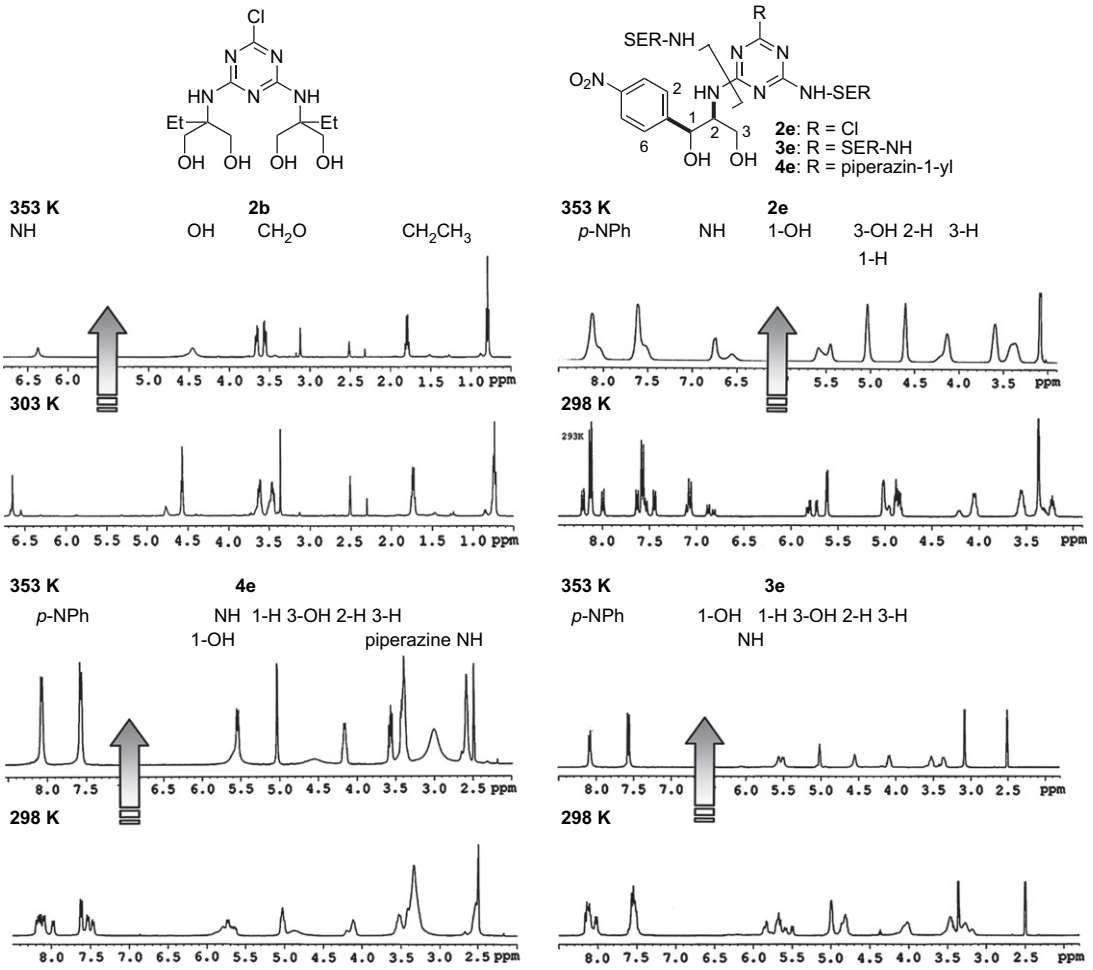


Figure 1. ^{1}H DNMR evolution of compounds **2b**, **2e**, **3e** and **4e** [DMSO-d_6, rt to 353 K on 400 MHz timescale (**2e**, **3e**, **4e**) and on 500 MHz timescale (**2b**)].

involved in two identically oriented intramolecular hydrogen bonds with the lone pairs of triazine nitrogens N-1′, -3′. To resume, δN(′)H(*s*-*s*)>δN(′)H(*a*-*a*) in series **2a**–**c** but δN(′)H(*a*-*a*)>δN(′)H(*s*-*s*) in **2d**, **2e**.

Once rotamers of type (*s*-*s*) and (*a*-*a*) established as such, the resonance of the indicative protons in the *syn* sites of rotamers (*s*-*a*) was found rather similar to that of isochronous ones, revealed by the rotamers (*s*-*s*): δN(′)H(*s*-*a*)≈δN(′)H(*s*-*s*) and δO(′)H(*s*-*a*)≈δO(′)H(*s*-*s*). The same remark applied mutatis-mutandis for the protons N(′)H and O(′)H of the *anti* sites of rotamers (*a*-*s*): δN(′)H(*a*-*s*)≈δN(′)H(*a*-*a*) and δO(′)H(*a*-*s*)≈δO(′)H(*a*-*a*).

2.2.2.2. Analysis of dynamic equilibria. Next, the different DNMR behaviour of diserinolic chlorodiamino-*s*-triazines **2a**–**c** versus **2d**, **2e** (Table 2, Fig. 1), in comparison with melamine **4e** (Fig. 1), we attempted to explain starting from the above assignments. We suspected that the opposite rotameric distributions actually disclosed dissimilar ground states of the two series of molecules.

As a representative example, the ^{1}H DNMR evolution of compound **2b** to a freely rotating structure at 353 K (Fig. 1)[§], showed, progressively, three non-synchronised '*internal clocks*'[14] [CH_2O, N(′)*H* and O(′)*H*] each exhibiting its own domain of coalescence. With the use of resonances of protons N(′)H, we estimated the barriers to rotation as free enthalpies of activation $\Delta G^{\neq}$, restricted to rotamers (*a*-*s*) in series **2a**–**c** and **4e** (Eq. 1), by application of Eyring equations (Eqs. 2 and 3).[12,14]

$$\mathbf{2a}\text{–}\mathbf{c},\ \mathbf{4e}(a\text{-}s) \underset{k_{-c}}{\overset{k_c}{\leftrightarrows}} \mathbf{2a}\text{–}\mathbf{c},\ \mathbf{4e}(a\text{-}a) \underset{k_c}{\overset{k_{-c}}{\leftrightarrows}} \mathbf{2a}\text{–}\mathbf{c},\ \mathbf{4e}(s\text{-}a) \tag{1}$$

$$k_c \approx k_{-c} = 2.22\Delta\nu \left[s^{-1}\right] \tag{2}$$

$$\Delta G^{\neq} = 19.14 T_c (10.32 + \log T_c/k_c) [\mathrm{J/mol}] \tag{3}$$

where T_c (K) is the coalescence temperature, $\Delta\nu$ (Hz) is the frequency separation between two analysed signals at room temperature belonging, in the absence of an exchange, to two equally populated sites and k_c (s^{-1}) is the rate constant of the first order-kinetically exchange dynamic process occurring at T_c.

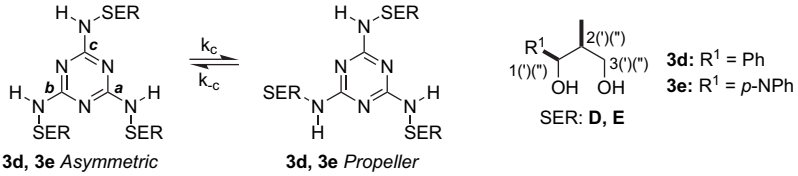
The results are collected in Table II in Supplementary data.

The obtained $\Delta G^{\neq}$ values for diserinolic chlorodiamino-*s*-traizines **2a**–**c** were credible since they were smaller or comparable with those previously determined for three more conjugated and crowded lpN→π 2-chloro-4,6-bis(dialkylamino)-*s*-triazines (alkyl: *n*-octyl, *n*-Bu, *i*-Pr) on ^{13}C NMR 75 MHz timescale, 75.15–65.33 kJ/mol (in $C_2D_2Cl_4$ or $CDCl_3$).[8b]

Some intrinsic limits, which operated the present analysis must be pointed out:

[§] In all hereafter discussed figures, labelling of isochronous positions as (′) or (″) was omitted for reasons of simplicity. The ^{1}H DNMR evolution was throughout resumed.

Table 4
Relevant ^{1}H NMR spectroscopic data of restricted rotation about C(*s*-triazine)–N(′)(″)< bonds in triserinolic-*s*-triazines **3d** and **3e**



3d, 3e *Asymmetric* **3d, 3e** *Propeller*

No.	Solvent	*T* (K)	Indicative protons	Discriminating δ (ppm) values in rotamers		Content of blocked rotamers (%)[a]	
				Asymmetric	*Propeller*	*Asymmetric*	*Propeller*
3d	DMSO-d_6	298	N(′)(″)H[b]	5.78; 5.66; 5.54	5.66	75	25
		353		5.53 [d, $^3J_{H,H}$=5.6 Hz, N(′)(″)H]→Single mediated structure			
				$\Delta G_a^{\neq}$=67.7, $\Delta G_b^{\neq}$=65.3, $\Delta G_c^{\neq}$=64.3 kJ/mol			
3e	DMSO-d_6	298	N(′)(″)H	5.67; 5.60; 5.51	5.67	75	25
			1(′)(″)-OH	5.84; 5.67; 5.67	5.84		
	THF-d_8	298	N(′)(″)H	6.28; 5.81; 5.81	5.81	47	53
	DMSO-d_6	353		5.50 [d, $^3J_{H,H}$=8.4 Hz, N(′)(″)H]→Single mediated structure			
				$\Delta G_a^{\neq}$=69.8, $\Delta G_b^{\neq}$=70.2, $\Delta G_c^{\neq}$=68.1 kJ/mol			

[a] Averaged values calculated using the best separated signals of protons N(′)(″)H [and 1(′)(″)-OH in **3e**] and their connectivity with 2(′)(″)-H found in the 2D ^{1}H,^{1}H-COSY experiments (298 and 353 K, respectively).
[b] Doublets ($^3J_{H,H}$=6.8–9.4 Hz) denote that protons N(′)(″)H were not quite exchangeable but located in a chelatizing environment.

(i) We used DNMR parameters of the classically entitled 'exchangeable protons' because we had to opt for the N(′)H signals of rotamers (*a*-*s*), the best separated (Table 2). Their final spectral shape (353 K, Fig. 1) might also refer to a fast exchange with the hydrogen bond acceptor solvent, obscuring their relevance in rotational phenomena. That is, the progressive shielding of protons N(′)H when passing from 'amide character' (room temperature) to 'amine character' (freely rotating structure, 353 K) was both expected and observed. Nevertheless, except melamine **4e**, in none of spectra of **2a**–**c** ranged the final N(′)H resonance (353 K) out of its domain of values at room temperature but very close to the initial N(′)H chemical shift in the frozen (*a*-*a*) environment.
(ii) Points of coalescences were difficult to establish properly. Similarly for other serinolic structures reported by us, domains of coalescences were rather observed in ^{1}H DNMR spectra.[7a–c,g]
(iii) Barriers to rotation $\Delta G^{\neq}$ in Table 2 (Table II in Supplementary data) do not refer to a three terms dynamic equilibrium (*a*-*a*)⇆(*a*-*s*)⇆(*s*-*s*), albeit each interconversion was a first order reaction, because the rotameric populations were unequal in series **2a**–**c** (Table 2).[13] In our simplified model (Eq. 1), they should be seen as to describe only the rotational diastereomers (*a*-*s*)≡(*s*-*a*) of **2a**–**c** reaching complete flexibility at 353 K, e.g., a rapid topomerisation (*a*-*s*)⇆(*s*-*a*), most probably via the rotamer (*a*-*a*), hence $k_c \approx k_{-c}$.

With these premises, the $\Delta G^{\neq}$ values of **2a**–**c** were rather identical for tetrahydroxymethyl derivatives **2a**, **2b**. Their ground states consisted at least of 50% occurrence of rotamers (*s*-*s*) and 35% (*s*-*a*) to accomplish solvation requirements (Tables 2 and 3). The presence of six hydroxymethyl groups in **2c** turned the contents of solvated rotamers to at least 62% (*s*-*a*) and not more than 31% (*s*-*s*), causing a slightly greater barrier to rotation ($\approx$+1 kJ/mol). Hence, at room temperature, for chlorodiamino-*s*-triazines **2a**–**c** based on *C*-2-substituted serinols, we believe that it was solvation, which imposed a more (*s*-*s*) in **2a**, **2b** or less (*a*-*s*) in **2c** crowded spatial arrangements. This stereochemistry appeared distorted since conflicted, as well as the C-2 tertiary aliphatic carbon vicinity, with the coplanarity mandatory to lpN(′)(**A**–**C**)→π(*s*-triazine) delocalisation. Upon heating, steric hindrance associated to a weak double bond character of C(*s*-triazine)–N(′)(**A**–**C**) junctions prevailed against solvation, these molecules becoming freely rotating structures.

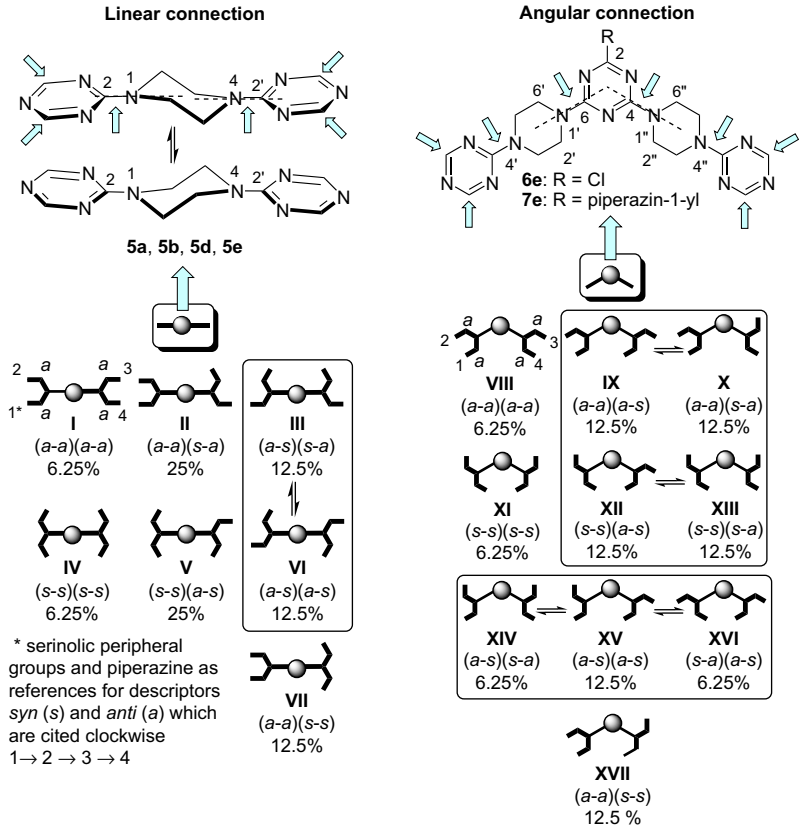
The DNMR results for **2d**, **2e** (Table 2, Fig. 1), showing that none of them could be completely deblocked in the same conditions, one can motivate electronically by the higher double bond character, at least in rotamers (*a*-*a*), of their C(*s*-triazine)–N(′)(**D**, **E**) links adjacent to a secondary aliphatic carbon. In more hydrophobic **2d**, **2e**, their weaker solvation obeyed conjugation as lpN(′)(**D**, **E**)→π (*s*-triazine), best realised in the less congested rotamers (*a*-*a*)+(*a*-*s*), which dictated the composition of the ground state. The alternative hypothesis that, in fact, more crowded transition states with respect to ground states of **2d**, **2e** versus **2a**–**c** were basically responsible for their different DNMR evolution, we had to exclude when examined two supplementary crowded compounds, melamines **4d** and **4e**.

At 293 K, although the less π-deficient *s*-triazines **4d** and **4e** still were statistical mixtures of rigid Ar–N< rotamers, in ^{1}H DNMR experiments (Fig. 1), only **4e** reached a totally freely rotating status, meanwhile **4d** partially decomposed. The $\Delta G^{\neq}$ barrier of **4e** (Table 2, Table II in Supplementary data) was smaller in comparison to those of **2a**–**c** to evidence the electronic and not steric influence of piperazin-1-yl strong donor substituent in **4e**. As expected, the energetic barrier to rotation of our well solvated tetrahydroxy derivative **4e** in DMSO-d_6 was much higher than those previously found for other less polar *N*-substituted melamines containing piperidin-1-yl or piperazin-1-yl groups (60.4–60.6 kJ/mol in MeOH-d_4).[9b] In our case, however, separation of piperazin-1-yl peaks of **4e** was poor, preventing any pertinent assignment of rotamerism about C(*s*-triazine)–N(piperazine) bond.

2.2.3. *Triserinolic melamines **3d** and **3e***

The ^{1}H NMR spectroscopic data supporting the specific rotamerism of melamines **3d**, **3e**, constructed entirely from phenylserinolic units, are listed in Table 4 and in Supplementary data (Table III).

At room temperature, compounds **3d**, **3e** consisted of a mixture of two rigid rotational diastereomers about bonds ***a***–***c***, namely *Asymmetric* (axis ***a***, ***c*** prostereogenic, ***b*** stereogenic) and *Propeller*, (axis ***a***–***c*** stereogenic).[8c] Their assignment was based again on indicative protons N(′)(″)H (**3d**, **3e**) and 1(′)(″)-OH (**3e**). In DMSO-d_6, the rotameric ratio was statistic for both compounds, 75:25 *Asymmetric* versus *Propeller* (Table 4). In the case of melamine **3e** only, an important shifting of this percentage to the less polar C_3 symmetric rotamer **3e** *Propeller* in THF-d_8 was detected.



Scheme 5.

^{1}H DNMR explorations [298–353 K, on 400 MHz timescale, (Table III in Supplementary data), Fig 1, compound **3e**] made possible, by application of Eyring equations, to estimate for each melamine, three barriers to rotation $\Delta G^{\neq}_{\boldsymbol{a}-\boldsymbol{c}}$ about C(*s*-triazine)–N(′)(″)< bonds ***a***–***c***. In this purpose, we used, successively, the combined three pairs of signals N(′)(″)H in the *Asymmetric* rotamers.

From rotational point of view, melamines **3d**, **3e** were comparable since we found almost the same $\Delta G_{\boldsymbol{a}}^{\neq} > \Delta G_{\boldsymbol{b}}^{\neq} > \Delta G_{\boldsymbol{c}}^{\neq}$ decreasing order of values. We ascertained the lowest energetic barrier, $\Delta G_{\boldsymbol{c}}^{\neq}$, as being related to the sterically less hindered transition state when SER-NH group **D** or **E** rotates out of plane about bond ***c***.[8c] If so, $\Delta G^{\neq}$ values of the more crowded **3e** $\Delta G_{\boldsymbol{a}}^{\neq} \approx \Delta G_{\boldsymbol{b}}^{\neq} > \Delta G_{\boldsymbol{c}}^{\neq}$ were all higher than those of **3d** and, unsurprisingly, more important than that of already discussed piperazine analogue **4e** (66.52 kJ/mol, Table 2, Fig. 1).

In the end, we note the magnitude of rotational barriers (64.3–70.2 kJ/mol) of serinolic melamines **3d**, **3e** and **4e**, due to stabilisation by solvation of their ground states in DMSO-d_6 combined with congested transition states, compared to other reported results for simpler *N*-alkylmelamines such as tris(dialkylamino)-*s*-triazines (alkyl: *i*-Pr, *n*-Bu 55.52–62.69 kJ/mol in $CDCl_3$)[8b] and tris(methylamino)-*s*-triazine (57.05–62.66 kJ/mol in acetone-d_6 and DMF-d_6).[8c]

2.2.4. Serinolic double melamines and dendritic structures

We synthesised two types of double melamines, *linearly connected* by a piperazine linker **5a**, **5b**, **5d**, **5e** (Scheme 2) and *angularly connected* by an *s*-triazine core **6e**, **7e** (Scheme 3). At room temperature, their ^{1}H NMR spectra run on 300 and 400 MHz timescale, exhibiting mainly broad multiplets, we associated with populations of conformers about C(*s*-triazine)–N(serinol) and C(*s*-triazine)–N(piperazine) partial double bonds, generating *peripheral* and *internal* frozen rotamerism, respectively, including piperazine chair–chair ring flipping.[¶] Blocked conformers were also detected in ^{13}C NMR spectra on 75 MHz timescale when, mostly in **5d**, **5e**, **6e** and **7e**, more than one signal was identified for some serinolic homo- or enantiotopic positions with respect to a freely rotating structure (see Section 4).

Since the type of construction, *linear* or *angular* was very relevant in *peripheral* versus *internal* rotational specific phenomena of the title compounds, their analysis had to be done separately (Scheme 5).

To our knowledge no similar distinction in melamines' complex rotational phenomena was reported so far.

*2.2.4.1. Linearly connected double melamines **5a**, **5b**, **5d** and **5e**.* Theoretically, frozen rotamerism in this series comprised seven **I**–**VII** linear conformers (Scheme 5). If statistic, their incidence could be predicted mathematically. They were generated by six restricted rotations, about four peripheral C(*s*-triazine)–N(serinol) and two internal C(*s*-triazine)–N(piperazine) bonds, N-1–C-2 and N-4–C-2′.

With respect to the newly created internal restricted rotations, just conformers **III** versus **VI** were related as diastereomers since only in **III** and **VI** was the axis C-2–C-2′, issued from the statistic colinearity N-1–C-2–N-4–C-2′, stereogenic. It was prostereogenic in blocked rotamers **II** and **V** and C_s symmetric in **I**, **IV** and **VII**, hence a free internal rotation of these conformers would result in topomerisations.

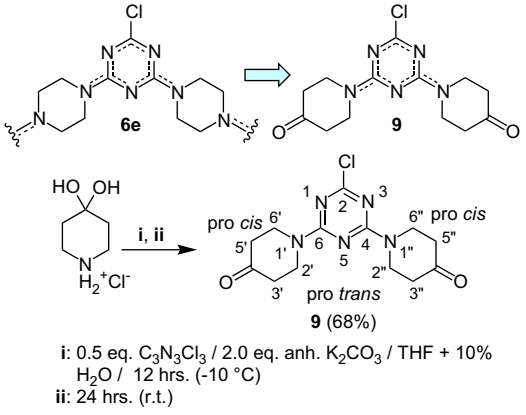
[¶] The stable sp^2 hybridisation of piperazine nitrogens connected to an *N,N′*-disubstituted (e.g., diallyl) diamino-*s*-triazine ring is already well documented[9a,b] being supported both by DNMR and X-ray data.

On increasing the temperature, on 400 MHz timescale, each double melamine **5a**, **5b**, **5d**, **5e** afforded, at 353 K, a unique mediated structure. Coalescences occurred anyhow differently, until 323 K for **5a**, **5b** and up to 333 K in the case of **5d**, **5e**. Once again, rigid amino-*s*-triazine rotamers of *C*-2-substituted serinols **A**–**C** were easily deblocked than their *C*-1-substituted analogues, **D**, **E**. The resonance of piperazine protons displayed throughout, at 293–298 K, but a unique broad singlet progressively converted into a sharp one at 353 K.

We note the very comparable ^{1}H DNMR evolution of **5e** with respect to its precursor **4e** (Table 2, Fig. 1) concerning mainly NH and serinolic *p*-NPh groups. This observation allowed us to assume a similar peripheral rotational barrier in **5e**, $\Delta G^{\neq} \approx 66.5$ kJ/mol about the C(*s*-triazine)–N(serinol **E**) bonds.

*2.2.4.2. Angularly connected melamines **6e**, **7e** and **8e**.* The *angularly connected* compounds **6e** and **7e** implied a different approach (Scheme 5).

In G-1 dendron **6e**, one could anticipate ten rotamers, **VIII**–**XVII** arising from eight restricted rotations. Depending on the *syn*/*anti* orientations of the termini **E** serinolic groups, the internal partial double bonds N-1′–C-6 and N-1″–C-4 were two (pro)stereogenic axes, creating diastereomeric relationships between conformers **IX**–**X**, **XII**–**XIII** and **XIV**–**XV**–**XVI**. Indeed, in **6e**, the *s*-triazine core was of type rigid 2-chloro-4,6-bis(dialkylamino)-*s*-triazine whose rotational Ar–N< $\Delta G^{\neq}$ barriers are known to be high enough, ranging between 74.22 and 75.17 kJ/mol.[8b] However, in our case, the 4,6-bis(dialkylamino) group was tied together in a six-membered saturated heterocycle whose aza positions N-4′(″) were also involved in partial double bonds with peripheral *s*-triazines units, as in precursor **4e** (Table 2). Since we found no similar example in the literature, we tried a 'simulation' of this situation consisting of a simpler but comparable *s*-triazine with the core of G-1 dendron **6e**, namely the *s*-triazine moiety linked doubly to two piperazine rings (Scheme 5), by replacing the latter with two piperidone units (Scheme 6).



Scheme 6.

Hence, compound **9** was prepared with a satisfactory yield by treatment of cyanuric chloride with 4-piperidone hydrate hydrochloride (Scheme 6) under mild conditions.[15,|]

In NMR spectra of **9** (293–303 K), positions 2′(″) versus 6′(″) and 3′(″) versus 5′(″) (Scheme 6, Fig. 2) were identified diastereotopic, two (partially overlapped) ^{1}H A_2X_2 systems, in various solvents,

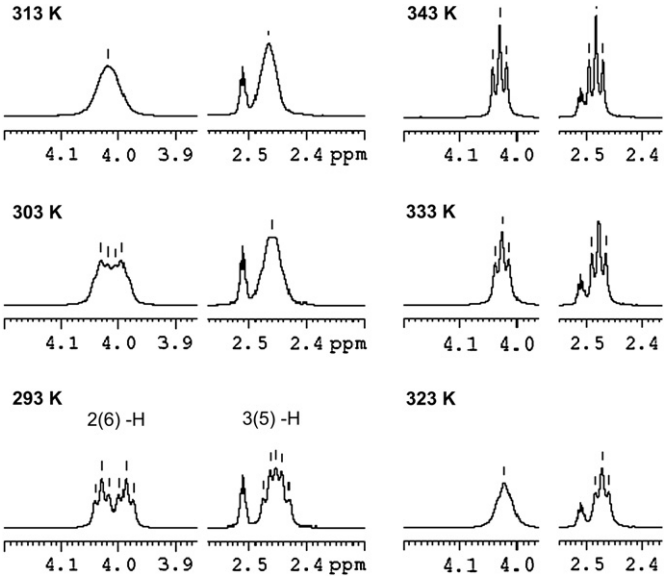


Figure 2. ^{1}H DNMR spectra of compound **9** (DMSO-d_6, 293–343 K on 500 MHz timescale).

DMSO-d_6, THF-d_8 and $CDCl_3$ ($\Delta\delta$=0.02–0.04 ppm (^{1}H) and 0.1–0.3 ppm (^{13}C)).

Normally, diastereotopicity observed in diketone **9** was caused by the restricted rotations about C(*s*-triazine)–N(piperidone) bonds N-1′–C-6 and N-1″–C-4, in fact, two prostereogenic axes (pro *cis*/pro *trans* as descriptors with respect to chlorine atom as reference, Scheme 6). They layed on the plane of positions C-6′–C-2′–N-5–C-2″–C-6″ following lpN(piperidone)→π(*s*-triazine) delocalisation.

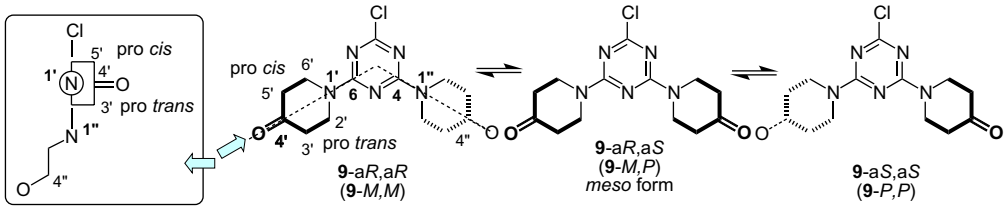
Indeed, compound **9** was rapidly deblocked in DMSO-d_6 on ^{1}H 500 MHz timescale (293–343 K, Fig. 2). Eyring calculations, using ^{1}H resonances of positions 2′(″) versus 6′(″) ($T_{coales.}$=313 K) and 3′(″) versus 5′(″) ($T_{coales.}$=308 K), gave the $\Delta G^{\neq}$ barrier to rotation of **9** to be 67.05±0.27 kJ/mol. It was smaller by far with respect to those of two known open normal chain 2-chloro-4,6-bis(di-*n*-alkylamino)-*s*-triazines (*n*-Bu, 74.22 kJ/mol, *n*-octyl 75.17 kJ/mol) but comparable if the alkyl chain was branched (*i*-Pr, 65.33 kJ/mol).[8b]

Obviously, the $\Delta G^{\neq}$ value of **9** could not be mutatis-mutandis extrapolated, as an internal rotational barrier, to dendron **6e**, whose ^{1}H DNMR separation (298–353 K) in the zone of piperazine signals, as in **4e** (Fig. 1), was poor. It provided, however, at least an idea about the dynamic behaviour of the core C(*s*-triazine)–N< connections in **6e**. In addition, in piperazine linkers of **6e**, some distortions and, presumably, the incidence of previously invoqued transannular interactions in this type of internal linkages we had also to presume.[1i,11d,14]

Furthermore, as shown in Figure 2, no geminal anisochrony was detected in the model compound **9** at room temperature but, according to 2D ^{1}H,^{1}H-COSY chart, mediated vicinal couplings $^3J_{H,H} \approx 7$ Hz between non-equivalent triplets, consistent with the fast chair–chair flipping of piperidone rings. This spectral appearance was reasonably kept in ^{1}H DNMR spectra of **9**, performed in THF-d_8 by lowering of the temperature. No (de)coalescence was observed. Its *N*-substituted rotationally Ar–N< rigid piperidone rings were flipping still at 193 K. Nevertheless, as depicted in Scheme 7, this double chair–chair as 'rear-front' inversion we considered as to be a peculiar one, a global enantiomeric interconvertion between C_2 symmetric chiral conformers **9**-a*R*,a*R*⇆**9**-a*S*,a*S* via a C_s symmetric *meso* form **9**-a*R*,a*S*.

That is, because of the increased order of bonds N-1′–C-6 and N-1″–C-4 in **9**, these two axes were not only prostereogenic with

[|] To our knowledge, the use of piperidone, generated in situ under carefully controlled mild conditions, was not previously reported as useful nucleophile with respect to cyanuric chloride, presumably because of its known instability as a free base.[15]



Scheme 7.

respect to blocked rotamerism (pro *cis*/pro *trans*), but also stereogenic (a*R*/a*S*) from conformation chirality's point of view.

The same double 'rear-front' inversion, implying this time twice lpN→π conjugated two piperazine rings, we expected to occur in all rigid rotational diastereomers **VIII**–**XVII** of dendron **6e** as well (Scheme 5). At room temperature, this motion created additional 3 conformation relationships in each of the 10 configuration enantiomerically pure (*S*,*S*,*S*,*S*) species **VIII**–**XVII**, disclosing 30 predictable diastereomers of **6e** (Table 5).

In turn, at peripheral level of angular **6e**, as in linear **5e**, again a good ^{1}H DNMR similitude of *p*-NPh and NH groups' behaviour versus precursor **4e** (Fig. 1) prompted as to presume an energetic barrier $\Delta G^{\neq} \approx 66.5$ kJ/mol about C(*s*-triazines)–N(serinol **E**) bonds (Table 5).

Replacement of chlorine in **6e** by a piperazin-1-yl group considerably simplified analysis of the resulted G-1 dendron **7e** because its core became a free rotating melamine [like tris(dialkylamino)-*s*-triazine, tris-morpholino and tris-piperidino hetero-analogues] with known rotational Ar–N< $\Delta G^{\neq}$ values much smaller, around 60 kJ/mol.[8b,c,9b] Consequently, at room temperature, the number of possible rotamers of **7e** would be reduced, from 10 to 6 (Scheme 5) since they were generated by the remaining peripheral *anti*/*syn* frozen rotamerism only (Table 6).

In the case of free internal diastereomeric rotations, one can also be observed that they induced local topomerisations at peripheral level, in melamine like **4e** fragments of **7e**, as (*a*-*s*)⇆(*s*-*a*).

^{1}H DNMR exploration of **7e** (293–353 K) evidenced the same dynamic transformations already seen in the case of melamine **4e** (Fig. 1). Only deblocking about C(*s*-triazine)–N(serinol **E**) bonds we recognised and assigned once more as peripheral $\Delta G^{\neq} \approx 66.5$ kJ/mol. No spectral modifications reliable to piperazines inducing internal rotamerism were noticeable.

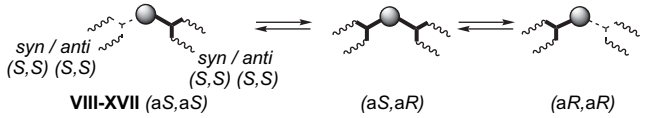
In the present discussion, we had to use for several times, as comparable term, the statistical rotamerism of melamine **4e** (Table 2, Fig. 1). As one can see in Figure 3, regardless of the type of connection, linear or angular, all more elaborated derivatives containing **4e** motif, **5e**, **6e**, **7e**, displayed the same four sensibly equal intense and partially overlapped AA′XX′ systems of the termini *p*-NPh groups.

We believe that this common spectral appearance was relevant only for **4e** possessing one pair of termini serinolic **E** units as 25% (*a*-*a*), 50% (*a*-*s*), 25% (*s*-*s*) percentages of its rotamers. If two peripheral pairs of **E** were present (**5e**–**7e**), statistics referred, this time, to the content of a specific local arrangement, for example, (*a*-*a*), but disseminated in all possible linear arrangements (25%), **I**–**VII** or angular **VIII**–**XVII** (Scheme 5), and not to an effective existence in the mixtures of rotamer **I** (or **VIII**) (*a*-*a*) (*a*-*a*) in 25% occurrence, respectively.

Finally, the essential spectral data confirming the structure of dendrimer **8e** are presented in Figure 4 and in Supplementary data (Figs. I and II).

^{1}H DNMR spectra (Fig. 4) validated the dynamic behaviour about C(*s*-triazine)–N(exocyclic) links and, by comparison with the intermediates **4e**, **6e**, **7e** (Figs. 1, 3) in the aromatic region, a statistic occurrence of the peripheral rotamerism. In the 2D ^{1}H,^{1}H-COSY chart at 353 K, we distinguished the piperazine linkers as G-1 (broad singlet at 3.80 ppm) and G-2 (3.73–3.50 ppm).

Table 5
Conformational 'rear-front' diastereomeric equilibria in frozen rotamers of **6e**



Frozen Rotamer (Scheme 5)	Axis N-1′–C-6		Axis N-1″–C-4	
	In rotational diastereomerism	In axial chirality	In rotational diastereomerism	In axial chirality
VIII, **XI**, **XVII**	Prostereogenic	Stereogenic	Prostereogenic	Stereogenic
IX, **X**, **XII**, **XIII**	Prostereogenic		Stereogenic	
XIV, **XV**, **XVI**	Stereogenic		Stereogenic	

Table 6
Internal rotational relationships in dendron **7e** (Scheme 5)

	Free rotation		Number of Rotamers
	About axis N-1′–C-6	About axis N-1″–C-4	
VIII, **XI**, **XVII**	Topomerisation	Topomerisation	3 Rotamers
IX⇆**X**	Topomerisation	Diastereomeric rotation	1 Mediated rotamer
XII⇆**XIII**	Topomerisation	Diastereomeric rotation	1 Mediated rotamer
XIV⇆**XV**⇆**XVI**	Diastereomeric rotation	Diastereomeric rotation	1 Mediated rotamer

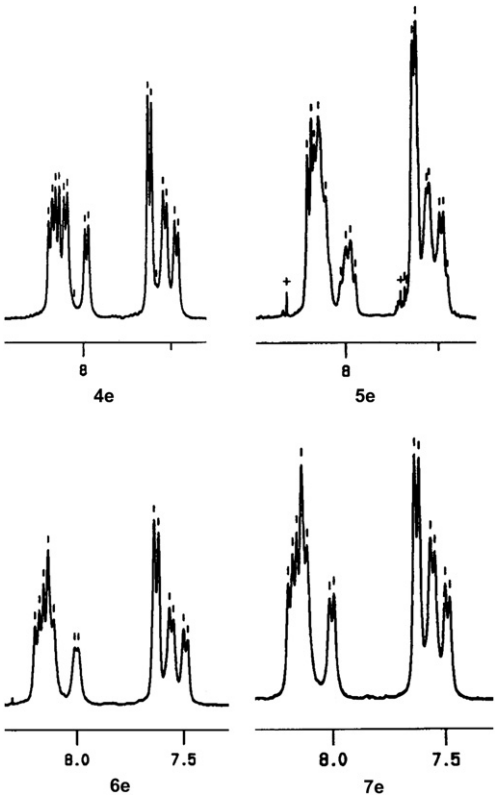


Figure 3. ^{1}H NMR spectra of *p*-nitrophenyl groups in compounds **4e**, **5e**, **6e** and **7e**.

In the QC NMR spectrum (Fig. I in Supplementary data), no trace of signal to be assigned to the starting material **7e** has been detected. The broad line shape of C^{sp^3} nuclei we associated with (i) slow exchange dynamic process on 75 MHz timescale and (ii) size of the molecule.[1a]

In the MS spectrum (MALDI, Fig. II in Supplementary data), for $C_{174}H_{204}N_{72}O_{48}$ (M=4072), one can recognise the base peak as $(M+Na^{+}-3H_2O)$.

No spectral evidence consistent with the epimerisation of the initial absolute configuration 1*S*,2*S* of *p*-nitrophenylserinol **E** was found. That is, both NMR and MS spectra suggested that **8e** was pure within detection limits of these techniques.

Compound **8e** was soluble in 1,4-dioxane, DMSO and THF, sparingly soluble in MeOH, EtOH and *i*-PrOH, and insoluble in water. Its peculiar behaviour in cyclic voltametry, in agreement with the complex internal versus peripheral rotamerism, was reported by us in detail recently.[16]

2.3. Biological impact of diserinolic chlorodiamino-*s*-triazines

Following literature methodology,[17] we consider of interest to also differentiate our two series of *s*-triazines, based on *C*-1 or *C*-2-substituted serinols, i.e., from a potential herbicidal activity point of view.

In this purpose, we evaluated diserinolic chlorodiamino-*s*-triazines **2a**–**e** using seeds of *Cucumis sativus* and *Raphanus sativus*. Upon treatment, the mean (±SD) values on inhibition of their root length were determined and compared to that of control. The results are collected in Table 7.

The preliminary data showed compounds **2a**–**c** exhibiting higher inhibition (including complete) effect in comparison with **2d**, **2e**. The most active was the methylserinol derivative **2a**.

Hence, we decided a better evaluation of **2a**, for example, against well-known Atrazine® (2-chloro-6-ethylamino-4-isopropylamino-*s*-triazine). Both influence on germination and root length were relatively tested (Table 8).

Compound **2a** exhibited comparable inhibition effect on root length as Atrazine®. It was anyhow less efficient on inhibition of germination.

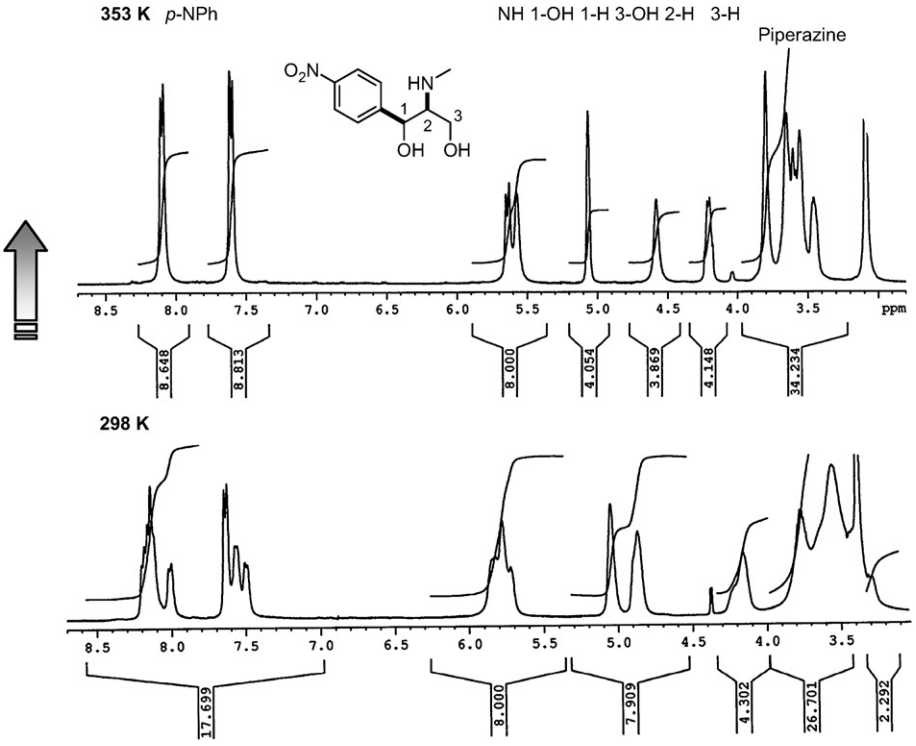


Figure 4. ^{1}H DNMR evolution of compound **8e** (DMSO-d_6 on 400 MHz timescale).

Table 7
Percent inhibitions of root length of *Cucumis sativus* and *Raphanus sativus* in response to different concentrations of compounds **2a–e** compared with that of control

Tested species	Concn (mM)	Root length				
		2a	**2b**	**2c**	**2d**	**2e**
Cucumis sativus	0.50	70±6.4	68±5.8	66±5.4	56±3.7	54±4.3
	0.75	93±4.5	90±3.3	89±4.2	77±3.2	76±2.5
	1.00	100±0.0	100±0.0	100±0.0	92±1.3	90±1.7
Raphanus Sativus	0.50	72±4.6	69±3.8	67±3.5	61±6.5	59±7.4
	0.75	94±1.8	92±2.4	90±2.1	79±5.7	76±2.6
	1.00	100±0.0	100±0.0	100±0.0	93±1.9	91±2.3

Table 8
Percent inhibitions of germination and root length of *Cucumis sativus* and *Raphanus sativus* in response to different concentrations of compound **2a** as compared to those of Atrazine®

Tested species	Concn (mM)	Germination		Root length	
		2a	Atrazine®	**2a**	Atrazine®
Cucumis sativus	0.50	59±5.4	62±4.2	68±4.4	69±6.5
	0.75	86±2.7	89±2.5	88±3.9	91±3.3
	1.00	100±0.0	100±0.0	—	—
Raphanus Sativus	0.50	67±4.9	71±5.6	73±6.7	74±6.2
	0.75	88±3.3	90±2.4	91±5.2	93±5.8
	1.00	100±0.0	100±0.0	—	—

3. Conclusion

Amino-*s*-triazines and (dendritic) melamines based on commercial *C*-1(**A**–**C**)- and *C*-2(**D**, **E**)-substituted 2-amino-1,3-propanediols (*serinols*) were obtained in medium to good yields by iterative amination of cyanuric chloride. The selectivity of chlorine replacement depended on the starting aminodiol, *C*-1-substituted serinols **D**, **E** being more reactive as amino nucleophile than *C*-2-substituted ones **A**–**C**. Selectivity, including largely favoured amination versus alkoxylation in **D**, **E** series of derivatives, has been improved significantly using cryogenic conditions. Dendritic chemistry can be developed using serinol **E**, other results being decided mainly by the stability of some key intermediates. At room temperature, all series of serinolic amino-*s*-triazines revealed frozen rotamerism about C(*s*-triazine)–N< bonds. In diserinolic chlorodiamino-*s*-triazines series, it was influenced by different factors (i) in the series of **A**–**C** derivatives by solvation and dipolar interactions in opposition with Ar–N< double bond character, (ii) in the series **D**, **E** by steric accommodation to favour lpN(serinol)→π(*s*-triazine) delocalisation. Regardless complexity of rotamerism, amino-*s*-triazines derivatives were easier deblocked if based on *C*-1-substituted serinols. Restricted rotations in double melamines and dendrons showed the relevance of internal against peripheral rotamerism in linearly versus angularly build molecules creating exacerbated (pro)diastereomerism and axial chirality. The herbicidal activity of some *N*-substituted diserinolic chlorodiamino-*s*-triazines was tested and evidenced comparable effect with respect to Atrazine®.

4. Experimental section

4.1. 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. ^{1}H DNMR spectra were performed on a Brucker® AM 400 instrument operating at 400 and 100 MHz for ^{1}H and ^{13}C nuclei, respectively with each step 10 K increasing temperature. Compound **2b** was also examined on 500 MHz timescale (Brucker® DMX500 instrument). All NMR spectra were measured in anhydrous commercially available deuterated solvents. No $SiMe_4$ was added; chemical shifts were measured against the solvent peak. All chemical shifts (δ values) are given throughout in parts per million; all coupling patterns ($^nJ_{H,H}$ values) are given throughout in hertz. NMR description of compounds exhibiting three ore more 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 Tables 3 and 6. Some specific abbreviations were used: br d (broad doublet), br dd (broad doublet of doublets), br t (broad triplet) and br m (broad multiplet). 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 as follows: FAB Spectra on a JEOL® AX 500 Instrument equipped with a DEC DA 5000 computer and ionisation realised with a FAB JEOL® Cannon (fascicle of Xenon accelerated under 4 kV/10 μA); MALDI Spectra on Micromass TOF-SpecE MALDI® Instrument equipped with a time flying analyser and a nitrogen pulsed laser (337 nm); ESI spectra on a Brucker® Esquire Instrument with ions trapping in electrospray mode. Computational details: the lowest energy conformers generated by Spartan'04 with the MMFF force field have been subjected to the full geometry optimisation at the B3LYP/6-31G(d) level of theory. Further, the effect of solvent (DMSO) has been taken into account by performing SCRF calculation with COSMO[13] (CPCM) option in Gaussian 98.[13a]

4.2. Typical procedure for the synthesis of compounds 1a–e (Scheme 2, Route 1, Table 1)

4.2.1. *Preparation of compound **1c***

In a dry THF (30 mL) suspension of TRIS **C** (0.60 g, 5 mmol) and anhyd K_2CO_3 (0.69 g, 5 mmol) cooled at −10 °C, cyanuric chloride (0.97 g, 5.25 mmol) as dry THF (40 mL) solution, also cooled at −10 °C, was injected portionwise, with vigorous stirring, within 2 h. The reaction mixture was let to reach room temperature until completion of the reaction (about 24 h, TLC monitoring). After filtering off and washing minerals well with dry THF (30 mL), the combined filtrate was evaporated under reduced pressure to dryness affording the crude product **1c**, which was crystallised from dry ether at −20 °C. Yield 86% (1.152 g **1c**). Routine scale up of the synthesis: 15 mmol TRIS.

*4.2.1.1. 2,4-Dichloro-6-(1,3-dihydroxy-2-methylprop-2-ylamino)-s-triazine (**1a**).* Yield 45%, white crystalline powder, mp 139.6–140.5 °C (direct trituration from MeOH). Anal. Calcd for $C_7Cl_2H_{10}N_4O_2$ (253.09): C, 33.22; H, 3.98; N, 22.14. Found: C, 33.42; H, 4.30; N, 21.98. R_f (80% toluene/isopropanol)=0.66. IR (KBr): ν=3352 (s), 3220 (s), 3133 (s), 3082 (s), 2976 (s), 1702 (s), 1604 (s), 1563 (s), 1517 (s), 1470 (s), 1333 (s), 1227 (s), 1161 (s), 1019 (s), 976 (m), 950 (m), 856 (m), 795 (m) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C): δ=1.26 (s, 3H, CH_3), 3.57 (d, $^2J_{H,H}$=10.9 Hz, 2H, 1-H, 3-H), 3.62 (d, $^2J_{H,H}$=10.9 Hz, 2H, 1-H, 3-H), 4.92 (br s, 2H, 2×OH), 8.39 (s, 1H, NH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6, 25 °C): δ=18.4 (1C, CH_3), 60.4 (1C, C-2), 63.0 (2C, C-1, -3), 165.2 (1C, C-6, *s*-triazine), 168.3, 168.8 (2C, C-2, -4, *s*-triazine) ppm. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ=1.33 (s, 3H, CH_3), 2.93 (br s, 2H, 2×OH), 3.76 (d, $^2J_{H,H}$=11.5 Hz, 2H, 1-H, 3-H), 3.90 (d, $^2J_{H,H}$=11.5 Hz, 2H, 1-H, 3-H),

6.52 (s, 1H, NH) ppm. MS (CI, +200 eV, *i*-BuH): *m*/*z* (%)=253 (100) [M^+], 219 (18), 117 (13), 99 (10).

*4.2.1.2. 2,4-Dichloro-6-[1-hydroxy-2-(hydroxymethyl)but-2-yl-amino]-s-triazine (**1b**).* Yield 58%, white crystalline powder, mp 99.8–101.5 °C (flash column chromatography; eluent toluene/isopropanol, 4:1). Anal. Calcd for $C_8Cl_2H_{12}N_4O_2$ (267.11): C, 35.97; H, 4.53; N, 20.97. Found: C, 36.25; H, 4.19; N, 21.29. R_f (80% toluene/isopropanol)=0.70. IR (KBr): ν=3382 (s), 3260 (s), 3144 (s), 2972 (s), 2884 (s), 1707 (s), 1596 (s), 1570 (s), 1527 (s), 1402 (s), 1327 (s), 1233 (s), 1163 (s), 1068 (s), 1050 (s), 1021 (m), 852 (m), 800 (s), 782 (m), 535 (w) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 25 °C): δ=0.78 (t, 3H, $^3J_{H,H}$=7.5 Hz, 4-H), 1.72 (q, $^3J_{H,H}$=7.5 Hz, 2H, 3-H), 3.51 (d, $^2J_{H,H}$=10.9 Hz, 2H, 1-H, CH_2OH), 3.69 (d, $^2J_{H,H}$=10.9 Hz, 2H, 1-H, CH_2OH), 4.58 (br s, 2H, 2×OH), 8.27 (s, 1H, NH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6, 25 °C): δ=7.54 (1C, C-4), 21.7 (1C, C-3), 59.6 (1C, C-2), 62.9 (2C, C-1, CH_2OH), 165.1 (1C, C-6, *s*-triazine), 168.2, 168.9 (2C, C-2, -4, *s*-triazine) ppm. MS (CI, +200 eV, *i*-BuH): *m*/*z* (%)=267 (100) [M^+], 233 (33), 208 (25), 199 (15), 120 (43), 113 (15), 87 (18), 73 (28), 61 (10).

*4.2.1.3. 2,4-Dichloro-6-[1,3-dihydroxy-2-(hydroxymethyl)prop-2-ylamino]-s-triazine (**1c**).* Yield 86%, white crystalline powder, mp 164–165 °C (direct trituration from Et_2O). Anal. Calcd for $C_7Cl_2H_{10}N_4O_3$ (269.09): C, 31.24; H, 3.75; N, 20.82. Found: C, 30.89; H, 4.12; N, 20.66. 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}. ^1H NMR (300 MHz, DMSO-d_6, 25 °C): δ=3.62 [s, 6H, 2×(1-H), 2×(3-H), CH_2OH], 4.60 (br s, 3H, 1-OH, 3-OH, CH_2OH), 8.05 (s, 1H, NH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6, 25 °C): δ=58.3 (3C, C-1, C-3, CH_2OH), 64.0 (1C-2), 165.3 (1C, C-6, *s*-triazine), 168.2, 168.8 (2C, C-2, -4, *s*-triazine) ppm. MS (DCI, +200 eV, NH_3): *m*/*z* (%)=269 (100) [M^+], 210 (12), 192 (20), 140 (25), 122 (33), 104 (62), 88 (90).

*4.2.1.4. 2,4-Dichloro-6-[(1S,2S)-1,3-dihydroxy-1-phenylprop-2-ylamino]-s-triazine (**1d**).* Yield 83%, white crystalline powder, mp 128.5–128.9 °C (flash column chromatography; eluent toluene/isopropanol, 4:1). Anal. Calcd for $C_{12}Cl_2H_{12}N_4O_2$ (315.16): C, 45.73; H, 3.84; N, 17.78. Found: C, 45.39; H, 4.10; N, 18.05. R_f (80% toluene/isopropanol)=0.65. IR (KBr): ν=3238 (s), 2969 (m), 2888 (m), 1610 (s), 1566 (s), 1501 (s), 1420 (s), 1358 (s), 1236 (s), 1166 (s), 1058 (s), 1041 (m), 966 (w), 870 (w), 845 (m), 797 (s), 698 (m), 557 (w) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 25 °C): δ=3.39 [ddd, $^2J_{H,H}$=10.5 Hz, $^3J_{H,H}$=6.5 Hz, 1H, 1×(3-H)], 3.56 [ddd, $^2J_{H,H}$=10.5 Hz, $^3J_{H,H}$=5.0, 5.5 Hz, 1H, 1×(3-H)], 4.20 (dddd, $^3J_{H,H}$=5.5, 6.0, 6.5, 9.4 Hz, 1H, 2-H), 4.82 (d, $^3J_{H,H}$=4.5 Hz, 1H, 1-H), 4.84 (br s, 1H, 3-OH), 5.55 (d, $^3J_{H,H}$=4.5 Hz, 1H, 1-OH), 7.22–7.37 (m, 5H, Ph), 8.93 (d, $^3J_{H,H}$=9.4 Hz, 1H, NH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6, 25 °C): δ=59.8 (1C, C-2), 60.4 (1C, C-3), 71.0 (1C, C-1), 126.8 (2C, CH, Ph), 127.4 (1C, CH, Ph), 128.1 (2C, CH, Ph), 143.1 (1C, C-1, Ph), 166.1 (1C, C-6, *s*-triazine), 168.6, 169.3 (2C, C-2, -4, *s*-triazine) ppm. MS (FAB+, 3-nitrobenzylalcohol): *m*/*z* (%)=315 (100) [M^+], 297 (30), 279 (20), 267 (20), 245 (15), 235 (15), 219 (30), 207 (25), 192 (15), 178 (15), 167 (35). $[\alpha]_D^{20}$ +43.3 (*c* 0.55, MeOH).

*4.2.1.5. 2,4-Dichloro-6-[(1S,2S)-1,3-dihydroxy-1-(4-nitrophenyl)-prop-2-ylamino]-s-triazine (**1e**).* Yield 61%, yellowish crystalline powder, mp 184–185 °C (flash column chromatography; eluent toluene/isopropanol, 4:1). Anal. Calcd for $C_{12}Cl_2H_{11}N_5O_4$ (360.16): C, 40.02; H, 3.08; N, 19.45. Found: C, 40.35; H, 2.88; N, 19.15. R_f (80% toluene/isopropanol)=0.80. IR (KBr): ν=3255 (s), 2889 (s), 1573 (s), 1516 (s), 1412 (s), 1350 (s), 1240 (s), 1165 (s), 1070 (s), 1025 (s), 959 (w), 845 (s), 796 (s), 726 (m), 648 (w), 546 (w) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 25 °C): δ=3.87 [dd, $^2J_{H,H}$=10.6 Hz, $^3J_{H,H}$=6.8 Hz, 1H, 1×(3-H)], 4.08 [dd, $^2J_{H,H}$=10.6 Hz, $^3J_{H,H}$=6.0 Hz, 1H, 1×(3-H)], 4.65 (ddd, $^3J_{H,H}$=6.0, 6.8, 9.0 Hz, 1H, 2-H), 4.81 (br s, 1H, 3-OH), 5.46 (d, $^3J_{H,H}$=3.4 Hz, 1H, 1-H), 6.28 (br s, 1H, 1-OH), 8.05 (d, $^3J_{H,H}$=8.7 Hz, 2H, 2-, 6-H, *p*-NPh), 8.62 (d, $^3J_{H,H}$=8.7 Hz, 2H, 3-, 5-H, *p*-NPh), 9.42 (d, $^3J_{H,H}$=9.0 Hz, 1H, NH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6, 25 °C): δ=59.3 (1C, C-2), 60.3 (1C, C-3), 70.3 (1C, C-1), 123.3 (2C, C-2, -6, *p*-NPh), 128.0 (2C, C-3, -5, *p*-NPh), 146.9 (1C, C-1, *p*-NPh), 151.3 (1C, C-4, *p*-NPh), 166.0 (1C, C-6, *s*-triazine), 168.7, 169.2 (2C, C-2, -4, *s*-triazine) ppm. MS (FAB+, glycerol): *m*/*z* (%)=360 (20) [M^+], 315 (<10), 285 (<10), 277 (100), 245 (<10), 223 (10), 215 (<10), 207 (10). $[\alpha]_D^{20}$ +13.2 (*c* 0.2, MeOH).

4.3. Typical procedure for the synthesis of compounds 2a–e (Scheme 2, Route 2, Table 1)

*4.3.1. Preparation of compound **2e***

To a dry THF (75 mL) solution containing (1*S*,2*S*)-2-amino-1-(4-nitrophenyl)-1,3-propanediol **E** (4.24 g, 20 mmol), anhyd K_2CO_3 (2.76 g, 20 mmol) was added with vigorous stirring then cooled at −78 °C when cyanuric chloride (1.84 g, 10 mmol) as dry THF(70 mL) solution was injected rapidly. The reaction mixture was let very gently to reach room temperature (about 18 h) then kept with stirring until completion of the reaction (about 24 h, TLC monitoring). After filtering off and washing minerals well with dry THF (100 mL), the combined filtrate was evaporated under reduced pressure to dryness affording the crude product **2e**, which was directly triturated with dry ether (25 mL) at −20 °C to give pure **2e** (4.72 g, 88% yield). Two different TLC system eluents (toluene/isopropanol, 4:1 and chloroform/ethanol, 4:1) indicated chromatographic purity of **2e** as a single spot.

*4.3.1.1. 2-Chloro-4,6-bis(1,3-dihydroxy-2-methylprop-2-ylamino)-s-triazine (**2a**).* Yield 92%, white crystalline powder, mp 169.9–170.3 °C (direct trituration from Et_2O). Anal. Calcd for $C_{11}ClH_{20}N_5O_4$ (321.76): C, 41.06; H, 6.26; N, 21.77. Found: C, 40.88; H, 6.55; N, 21.98. R_f (80% toluene/isopropanol)=0.55. IR (KBr): ν=3270 (s), 3103 (s), 2983 (s), 1625 (s), 1555 (s), 1391 (s), 1205 (s), 1075 (s), 1041 (s), 959 (m), 860 (w), 802 (m), 737 (m), 604 (w) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 25 °C): δ=1.22 (s, 6H, 2×CH_3), 3.50–3.70 [m, 8H, 2×(1-, 1′-, 3-, 3′-H)], 4.65, 4.82, 5.19 (3×br s, 4H, 4×OH), 6.41, 6.66, 6.74, 6.78 (4×br s, 2H, N-, N′-H) ppm. ^1H NMR (400 MHz, DMSO-d_6, 80 °C): δ=1.22 (s, 6H, 2×CH_3), 3.55 (d, $^2J_{H,H}$=10.8 Hz, 4H, 1-, 1′- 3-, 3′-H), 3.61 (d, $^2J_{H,H}$=10.8 Hz, 4H, 1-, 1′-, 3-, 3′-H), 4.52 (br s, 4H, 4×OH), 6.43 (br s, 2H, N-, N′-H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6, 25 °C): δ=18.7 (2C, 2×CH_3), 58.5, 58.7 (2C, C-2, -2′), 63.4, 63.8 (4C, C-1, -1′, -3, -3′), 164.6, 165.0, 165.3 (2C, C-4, -6, *s*-triazine), 167.2 (1C, C-2, *s*-triazine) ppm. MS (CI, +200 eV, NH_3): *m*/*z* (%)=322 (100) [M^+], 288 (13), 140 (5), 88 (5).

*4.3.1.2. 2-Chloro-4,6-bis[1-hydroxy-2-(hydroxymethyl)but-2-ylamino]-s-triazine (**2b**).* Yield 61%, white crystalline powder, mp 116.5–117.6 °C (flash column chromatography; eluent toluene/isopropanol, 2:1). Anal. Calcd for $C_{13}ClH_{24}N_5O_4$ (349.82): C, 44.64; H, 6.91; N, 20.02. Found: C, 44.45; H, 7.11; N, 19.90. R_f (66% toluene/isopropanol)=0.55. IR (KBr): ν=3397 (s), 3296 (s), 2964 (m), 2885 (m), 1585 (s), 1431 (m), 1406 (m), 1201 (w), 1063 (m), 1038 (m), 801 (m), 630 (w), 520 (w) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 25 °C): δ=0.76 [t, $^3J_{H,H}$=7.2 Hz, 6H, 3×(4-, 4′-H)], 1.75 [q, $^3J_{H,H}$=7.2 Hz, 4H, 2×(3-, 3′-H)], 3.48 (dd, $^2J_{H,H}$=10.5 Hz, $^3J_{H,H}$=5.6 Hz, 4H, 1-, 1′-H, CH_2OH), 3.65 (dd, $^2J_{H,H}$=10.5 Hz, $^3J_{H,H}$=5.6 Hz, 4H, 1-, 1′-H, CH_2OH), 4.61, 4.81 (2×dd, $^3J_{H,H}$=5.9, 5.9 Hz, 4H, 4×OH), 6.31, 6.55, 6.65, 6.67 (4×br s, 2H, N-, N′-H) ppm. ^1H NMR (400 MHz, DMSO-d_6, 80 °C): δ=0.79 [t, $^3J_{H,H}$=7.5 Hz, 6H, 3×(4-, 4′-H)], 1.79 [q, $^3J_{H,H}$=7.5 Hz, 4H, 2×(3-, 3′-H)], 3.56 (dd, $^2J_{H,H}$=10.8 Hz, $^3J_{H,H}$=5.8 Hz, 4H, 1-, 1′-H,

CH_2OH), 3.66 (dd, $^2J_{H,H}$=10.8 Hz, $^3J_{H,H}$=5.8 Hz, 4H, 1-, 1′-H, CH_2OH), 4.46 (br s, 4H, 4×OH), 6.37 (br s, 2H, N-, N′-H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6, 25 °C): δ=7.7, 7.8, 8.0 (2C, C-4, -4′), 22.4, 23.0 (2C, C-3, -3′), 60.9, 61.0, 61.2, 61.3, 61.6 (6C, C-1, -1′, C-2, -2′, 2×CH_2OH), 164.5, 165.0, 165.2 (2C, C-4, -6, *s*-triazine), 167.1, 167.2 (1C, C-2, *s*-triazine) ppm. MS (FAB+, 3-nitrobenzylalcohol): *m*/*z* (%)=350 (33) [M$^+$], 245 (45), 219 (20), 165 (20).

*4.3.1.3. 2-Chloro-4,6-bis[1,3-dihydroxy-2-(hydroxymethyl)prop-2-ylamino]-s-triazine (**2c**).* Yield 47%, white crystalline powder, mp 86–88 °C (direct trituration from acetone/ligroin). Anal. Calcd for $C_{11}ClH_{20}N_5O_6$ (353.76): C, 37.34; H, 5.70; N, 19.80. Found: C, 36.99; H, 5.25; N, 20.04. R_f (75% acetone/ligroin)=0.30. IR (KBr): non-depositable on KBr, insoluble in appropriate IR solvents. ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C): δ=3.65 [s, 12H, 2×(1-, 1′-, 3-, 3′-H, CH_2OH)], 4.51, 4.57, 4.82, 5.20 (4×t, $^3J_{H,H}$=5.2, 6.0, 6.0 Hz, respectively, br s at 5.20 ppm, 6H, 6×OH), 6.29, 6.50, 6.52, 6.57 (4×br s, 2H, N-, N′-H) ppm. ^{1}H NMR (400 MHz, DMSO-d_6, 80 °C): δ=3.70 [s, 12H, 2×(1-, 1′-, 3-, 3′-H, CH_2OH)], 4.43 (br s, 6H, 6×OH), 6.30 (br s, 2H, N-, N′-H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6, 25 °C): δ=59.8, 59.9, 60.3 (6C, C-1, -1′, -3, -3′, 2×CH_2OH), 62.0, 62.3, 62.4 (2C, C-2, -2′), 164.6, 165.1 (2C, C-4, -6, *s*-triazine), 167.1 (1C, C-2, *s*-triazine) ppm. MS (FAB+, glycerol): *m*/*z* (%)=354 (90) [M$^+$], 336 (20), 320 (23), 306 (10), 262 (53), 250 (25), 232 (15), 223 (25), 217 (100), 201 (25), 192 (35).

*4.3.1.4. 2-Chloro-4,6-bis[(1S,2S)-1,3-dihydroxy-1-phenylprop-2-ylamino]-s-triazine (**2d**).* Yield 96%, white crystalline powder, mp 78–80 °C (flash column chromatography; eluent toluene/isopropanol, 3:1 or direct trituration from Et$_2$O/ligroin, Table 1). Anal. Calcd for $C_{21}ClH_{24}N_5O_4$ (445.90): C, 56.57; H, 5.42; N, 15.71. Found: C, 56.44; H, 5.61; N, 15.99. R_f (75% toluene/isopropanol)=0.30. IR (KBr): ν=3308 (s), 3029 (s), 2929 (m), 2873 (m), 1729 (w), 1581 (s), 1528 (s), 1496 (s), 1454 (s), 1419 (s), 1291 (m), 1128 (m), 1042 (m), 988 (m), 803 (m), 756 (w), 700 (s), 571 (m) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C): δ=3.31–3.38 (m, 2H, 3-, 3′-H), 3.48–3.61 (m, 2H, 3-, 3′-H), 4.07–4.14 (br m, 2H, 2-, 2′-H), 4.82–4.89 (m, 2H, 1-, 1′-H), 4.78, (dd, $^3J_{H,H}$=4.9, 4.9 Hz, 2H, 3-, 3′-OH), 5.35, 5.43, 5.53, 5.54 (4×d, $^3J_{H,H}$=5.7, 5.7, 4.9, 3.4 Hz, respectively, 2H, 1-, 1′-OH), 6.71, 6.81, 7.01, 7.05 (4×d, $^3J_{H,H}$=9.0, 9.1, 9.4, 9.0 Hz, respectively, 2H, N-, N′-H), 7.10–7.40 (m, 10H, Ph) ppm. ^{1}H NMR (400 MHz, DMSO-d_6, 80 °C): δ=3.38 (ddd, $^2J_{H,H}$=10.5 Hz, $^3J_{H,H}$=5.2, 5.2 Hz, 2H, 3-, 3′-H), 3.56 (dd, $^2J_{H,H}$=10.5 Hz, $^3J_{H,H}$=6.2 Hz, 2H, 3-, 3′-H), 4.12–4.18 (m, 2H, 2-, 2′-H), 4.46 (br s, 2H, 3-, 3′-OH), 4.89 (s, 2H, 1-, 1′-H), 5.11, 5.23 (2×br s, 2H, 1-, 1′-OH), 6.45, 6.64 (2×br s, 2H, N-, N′-H), 7.14–7.33 (m, 10H, Ph) ppm. ^{13}C NMR (75 MHz, DMSO-d_6, 25 °C): δ=58.0, 58.1, 58.2 (2C, C-2, -2′), 60.4, 60.6 (2C, C, C-3, -3′), 70.2, 70.3, 70.5 (2C, C-1, -1′), 126.5, 126.55, 126.61, 127.0, 127.2, 128.06, 128.10, 128.6, 129.2 (10C, CH, Ph), 143.6, 143.67, 143.73 (2C, C-1, -1′, Ph), 165.4, 165.6, 166.0 (2C, C-4, -6, *s*-triazine), 167.7, 168.2 (1C, C-2, *s*-triazine) ppm. MS (FAB+, 3-nitrobenzylalcohol): *m*/*z* (%)=446 (40) [M$^+$], 391 (55), 338 (15), 279 (15), 235 (15), 219 (20), 167 (33). $[\alpha]_D^{20}$ −3.0 (*c* 0.5, THF).

*4.3.1.5. 2-Chloro-4,6-bis[(1S,2S)-1,3-dihydroxy-1-(4-nitrophenyl)-prop-2-ylamino]-s-triazine (**2e**).* Yield 88%, yellowish crystalline powder, mp 137.9–138.6 °C (flash column chromatography; eluent toluene/isopropanol, 3:1 or direct trituration from Et$_2$O, Table 1). Anal. Calcd for $C_{21}ClH_{22}N_7O_8$ (535.90): C, 47.07; H, 4.14; N, 18.30. Found: C, 46.95; H, 4.41; N, 18.18. R_f (75% toluene/isopropanol)=0.75. IR (KBr): ν=3338 (s), 2942 (w), 2885 (w), 1579 (s), 1516 (s), 1417 (m), 1348 (s), 1130 (m), 1109 (m), 1068 (m), 1014 (m), 987 (m), 854 (m), 804 (m), 726 (w), 701 (m), 566 (w) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C): δ=3.23 (dd, $^2J_{H,H}$=9.8 Hz, $^3J_{H,H}$=4.9 Hz, 2H, 3-, 3′-H), 3.55 (br d, $^3J_{H,H}$=6.4 Hz, 2H, 3-, 3′-H), 4.05, 4.21 (2×br d, $^3J_{H,H}$=6.0, 6.8 Hz, respectively, 2H, 2-, 2′-H), 4.83–4.90 (m, 2H, 3-, 3′-OH), 4.97–5.02 (br m, 2H, 1-, 1′-H), 5.61, 5.72, 5.80, 5.83 (4×d, $^3J_{H,H}$=5.3, 5.3, 4.9, 5.3 Hz, respectively, 2H, 1-, 1′-OH), 6.82, 6.88, 7.07, 7.10 (4×d, $^3J_{H,H}$=9.0, 9.4, 9.1, 8.3 Hz, respectively, 2H, N-, N′-H), 7.45, 7.54, 7.58, 7.64 (4×d, $^3J_{H,H}$=8.6, 8.7, 8.7, 8.7 Hz, respectively, 4H, 2-, 2′-, 6-, 6′-H, *p*-NPh), 8.00, 8.13, 8.21 (3×d, $^3J_{H,H}$=8.7, 8.7, 8.7 Hz, respectively, 2H, 3-, 3′-, 5-, 5′-H, *p*-NPh) ppm. ^{1}H NMR (400 MHz, DMSO-d_6, 80 °C): δ=3.37–3.42 (br m, 2H, 3-, 3′-H), 3.59 (br s, 2H, 3-, 3′-H), 4.13 (br s, 2H, 2-, 2′-H), 4.61 (br s, 2H, 3-, 3′-OH), 5.03 (s, 2H, 1-, 1′-H), 5.45, 5.59 (2×br s, 2H, 1-, 1′-OH), 6.51, 6.74 (2×br s, 2H, N-, N′-H), 7.56 (br m, 4H, 2-, 2′-, 6-, 6′-H, *p*-NPh), 8.09 (br m, 4H, 3-, 3′-, 5-, 5′-H, *p*-NPh) ppm. ^{13}C NMR (75 MHz, DMSO-d_6, 25 °C): δ=57.3, 57.6 (2C, C-2, -2′), 60.5, 60.6 (2C, C-3, -3′), 69.9, 70.0, 70.1 (2C, C-1, -1′), 122.9, 123.1, (4C, C-2, -2′ -6, -6′, *p*-NPh), 127.7, 127.9 (4C, C-3, -3′, -5, -5′, *p*-NPh), 146.6 (2C, C-1, -1′, *p*-NPh), 151.9, 152.0, 152.2 (2C, C-4, -4′, *p*-NPh), 165.26, 165.34, 165.9 (2C, C-4, -6, *s*-triazine), 167.6, 168.0 (1C, C-2, *s*-triazine) ppm. MS (FAB+, 3-nitrobenzylalcohol): *m*/*z* (%)=536 (40) [M$^+$], 520 (<10), 355 (<10), 335 (<10), 273 (<10), 261 (40), 245 (100), 230 (10), 213 (15), 192 (10), 176 (15), 165 (13). MS (FAB+, glycerol): *m*/*z* (%)=536 (90), 520 (25), 502 (17), 488 (<10), 461 (<10), 446 (<10), 427 (<10), 413 (<10), 402 (<10), 383 (40), 369 (25), 341 (12), 315 (10), 301 (12), 285 (20), 277 (100), 263 (915), 251 (11), 245 (22), 230 (21), 225 (68), 214 (28), 203 (27). $[\alpha]_D^{20}$ −8.37 (*c* 1, DMSO); −28.4 (*c* 0.05, MeOH).

4.4. Typical procedure for the synthesis of compounds 3d and 3e (Scheme 2, Route 3, Table 1)

*4.4.1. Preparation of compound **3d***

To a dry 1,4-dioxane (50 mL) solution containing (1*S*,2*S*)-2-amino-1-phenyl-1,3-propanediol **D** (1.00 g, 5.98 mmol) and cyanuric chloride (0.350 g, 1.90 mmol), anhyd K_2CO_3 (0.828 g, 6.00 mmol) was added with vigorous stirring. The resulted suspension was first kept at room temperature for 24 h when TLC monitoring indicated formation of a mixture containing the unreacted **D**, intermediate **2d** and the desired **3d** in traces. The reaction mixture was then heated at reflux until TLC control (dichloromethane/ethanol 4:1 v/v) showed no more evolution (about 60 h) and then cooled at room temperature. After filtering off and washing minerals well with dry 1,4-dioxane (50 mL), the combined filtrate was evaporated under reduced pressure to dryness yielding the crude reaction mixture, which was submitted to column chromatography on silica gel. The following fractions were isolated using gradient of eluents: intermediate **2d** (0.192 g, 23% partial conversion of cyanuric chloride, eluent dichloromethane/ethanol 4:0.75 v/v) and the desired **3d** (0.820 g, 75% conversion of cyanuric chloride, eluent dichloromethane/ethanol 3.25:1 v/v).

*4.4.1.1. 2,4,6-Tris[(1S,2S)-1,3-dihydroxy-1-phenylprop-2-ylamino]-s-triazine (**3d**).* Yield 75%, white crystalline powder, mp 104–108 °C (flash column chromatography; dichloromethane/ethanol, 3.25:1). Anal. Calcd for $C_{30}H_{36}N_6O_6$ (576.65): C, 62.49; H, 6.29; N, 14.57. Found: C, 62.79; H, 5.95; N, 14.88. R_f (80% dichloromethane/ethanol)=0.60. IR (KBr): ν=3400 (s), 2937 (w), 2834 (w), 1562 (s), 1509 (s), 1451 (m), 1197 (w), 1162 (w), 1053 (m), 810 (m), 701 (m) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C): δ=3.32 (d, $^3J_{H,H}$=4.1 Hz, 3H, 3-, 3′-, 3″-H), 3.41 (s, 3H, 3-, 3′-, 3″-H), 3.94, 4.06 (br s, 3H, 2-, 2′-, 2″-H), 4.74 (br s, 3H, 3-, 3′-, 3″-OH), 4.88 (s, 3H, 1-, 1′-, 1″-H), 5.48 (d, $^3J_{H,H}$=4.9 Hz, 3H, 1-, 1′-, 1″-OH), 5.54, 5.66, 5.78 (3×d, $^3J_{H,H}$=6.8, 6.8, 7.5 Hz, respectively, 3H, N-, N′-, N″-H), 7.20–7.60 (m, 15H, Ph) ppm. ^{1}H NMR (400 MHz, DMSO-d_6, 80 °C): δ=3.37 (dd, $^2J_{H,H}$=10.5 Hz, $^3J_{H,H}$=5.2 Hz, 3H, 3-, 3′-, 3″-H), 3.51 (dd, $^2J_{H,H}$=10.5 Hz, $^3J_{H,H}$=6.6 Hz, 3H, 3-, 3′-, 3″-H), 4.05 (dddd, $^3J_{H,H}$=5.8, 5.8, 5.8, 6.0 Hz, 3H, 2-, 2′-, 2″-H), 4.46 (br s, 3H, 3-, 3′-, 3″-OH), 4.88 (d, $^3J_{H,H}$=3.6 Hz, 3H, 1-, 1′-, 1″-H), 5.26 (br s, 3H, 1-, 1′-, 1″-OH), 5.53 (d, $^3J_{H,H}$=5.6 Hz, 3H, N-, N′-, N″-H), 7.19 (dd, $^3J_{H,H}$=7.2, 7.2 Hz, 3H,

Ph), 7.27 (dd, $^3J_{H,H}$=7.2, 7.2 Hz, 6H, Ph), 7.34 (d, $^3J_{H,H}$=7.2 Hz, 6H, Ph) ppm. QC NMR (75 MHz, DMSO-d_6, 25 °C): δ=57.4 (3C, C-2, -2′, -2″), 60.8 (3C, C-3, -3′, -3″), 70.2, 70.5 (3C, C-1, -1′, -1″), 126.5 (6C, CH, Ph), 127.0 (3C, CH, Ph), 128.1 (6C, CH, Ph), 144.1 (3C, C-1, Ph) 165.5, 165.7, 165.9 (3C, C-2, -4, -6, *s*-triazine) ppm. MS (FAB+, glycerol): *m*/*z* (%)=577 (100) [M$^+$], 559 (20), 459 (15), 427 (15), 145 (15), 128 (20), 105 (30), 91 (50), 79 (20). $[\alpha]_D^{20}$ +59.4 (*c* 0.2, MeOH).

*4.4.1.2. 2,4,6-Tris[(1S,2S)-1,3-dihydroxy-1-(4-nitrophenyl)prop-2-ylamino]-s-triazine (**3e**).* Yield 46%, yellowish crystalline powder, mp 149–151 °C (flash column chromatography; dichloromethane/ethanol, 9:1). Anal. Calcd for $C_{30}H_{33}N_9O_{12}$ (711.64): C, 50.63; H, 4.67; N, 17.71. Found: C, 50.88; H, 5.01; N, 17.55. R_f (90% dichloromethane/ethanol)=0.30. IR (KBr): ν=3400 (s), 2839 (w), 2886 (w), 1581 (s), 1516 (s), 1437 (m), 1348 (s), 1108 (w), 1069 (w), 854 (w), 811 (w), 570 (w) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C): δ=3.28–3.48 [m, 6H, 2×(3-, 3′-, 3″-H)], 4.03 (br s, 3H, 2-, 2′-, 2″-H), 4.82 (br s, 3H, 3-, 3′-, 3″-OH), 5.00 (s, 3H, 1-, 1′-, 1″-H), 5.51, 5.60, 5.67 (3×d, $^3J_{H,H}$=8.7, 7.9, 9.4 Hz, respectively, 3H, N-, N′-, N″-H), 5.67, 5.84. (2×d, $^3J_{H,H}$=9.4, 5.3 Hz, respectively, 3H, 1-, 1′-, 1″-OH), 7.55–7.58 (m, 6H, 2-, 2′-, 2″-, 6-, 6′-, 6″-H, *p*-NPh), 8.02–8.17 (m, 6H, 3-, 3′-, 3″-, 5-, 5′-, 5″-H, *p*-NPh) ppm. ^{1}H NMR (400 MHz, DMSO-d_6, 80 °C): δ=3.35 (d, $^3J_{H,H}$=4.0 Hz, 3H, 3-, 3′-, 3″-H), 3.52 (dd, $^2J_{H,H}$=10.4 Hz, $^3J_{H,H}$=5.6 Hz, 3H, 3-, 3′-, 3″-H), 4.08 (ddd, $^3J_{H,H}$=3.0, 4.4, 8.6 Hz, 3H, 2-, 2′-, 2″-H), 4.54 (br s, 3H, 3-, 3′-, 3″-OH), 5.00 (s, 3H, 1-, 1′-, 1″-H), 5.50 (d, $^3J_{H,H}$=8.6 Hz, 3H, N-, N′-, N″-H), 5.55 (br s, 3H, 1-, 1′-, 1″-OH), 7.56 (d, $^3J_{H,H}$=8.6 Hz, 6H, 2-, 2′-, 2″-, 6-, 6′-, 6″-H, *p*-NPh), 8.08 (d, $^3J_{H,H}$=8.6 Hz, 6H, 3-, 3′-, 3″-, 5-, 5′-, 5″-H, *p*-NPh) ppm. ^{13}C NMR (75 MHz, DMSO-d_6, 25 °C): δ=56.4, 57.0 (3C, C-2, -2′-, 2″), 60.5, 60.8 (3C, C-3, -3′, -3″), 69.8 (3C, C-1, -1′, -1″), 123.1 (6C, C-2, -2′, -2″, -6, -6′, -6″, *p*-NPh), 127.6 (6C, C-3, -3′, -3″, -5, -5′, -5″, *p*-NPh), 146.6 (3C, C-1, -1′, -1″, *p*-NPh), 152.4 (3C, C-4, -4′, -4″, *p*-NPh), 165.6, 165.9 (3C, C-2, -4, -6, *s*-triazine) ppm. MS (FAB+, glycerol): *m*/*z* (%)=712 (75) [M$^+$], 696 (40), 680 (15), 667 (10), 645 (12), 559 (20), 543 (15), 529 (10), 517 (10), 461 (30), 406 (10), 390 (15), 369 (100), 315 (20), 307 (10). $[\alpha]_D^{20}$ +15.5 (*c* 0.2, MeOH).

4.5. Typical procedure for the synthesis of compounds 4d and 4e (Scheme 2, Route 4, Table 1)

*4.5.1. Preparation of compound **4e***

To a dry 1,4-dioxane (optionally dry THF, Note 1, 100 mL) solution containing anhyd piperazine (1.600 g, 18.66 mmol), anhyd K_2CO_3 (0.643 g, 4.66 mmol) was added with vigorous stirring. The resulted suspension was heated at reflux when 2-chloro-4,6-bis[(1*S*,2*S*)-1,3-dihydroxy-1-(4-nitrophenyl)-prop-2-ylamino]-*s*-triazine **2e** (2.500 g, 4.66 mmol) as dry 1,4-dioxane (optionally dry THF, 25 mL) solution was injected portionwise as 6.25 mL/portion each 60 min. After each addition, within 60 min, TLC monitoring indicated only the complete absence of **2e** [R_f (75% toluene/isopropanol)=0.75]. Compound **4e** could not be eluted on silica gel. Finally, the reaction mixture was kept at reflux for 3 h and then cooled at room temperature. After filtering off and washing minerals well with dry 1,4-dioxane (optionally dry THF, 50 mL), the combined filtrate was evaporated under reduced pressure to dryness yielding the crude reaction mixture, which was taken with cooled water (40 mL, NOTE 2) with vigorous stirring for 2 h. The suspension was filtered off at room temperature and very washed well with cooled water. The protocol was repeated using 50 mL of water to give compound **4e** (2.293 g, 84% yield, NOTE 3). Note 1: THF instead of 1,4-dioxane for the synthesis of **4d**. Note 2: since **4d** showed much higher solubility in water than **4e**, for its successful isolation, this volume was calculated as only 10% excess with respect to solubility of unreacted piperazine in water at theoretically quantitative conversion of **2d** into **4d**. The protocol for removal of piperazine was made at 0 °C. Note 3: CARE! Compound **4d** was unstable on storage, i.e., drying at room temperature.

*4.5.1.1. 1-{4,6-Bis[(1S,2S)-1,3-dihydroxy-1-phenylprop-2-ylamino]-s-triazin-2-yl}piperazine (**4d**).* Yield 75%, yellowish crystalline powder, mp 70–72 °C (H_2O). Anal. Calcd for $C_{25}H_{33}N_7O_4$ (495.58): C, 60.59; H, 6.71; N, 19.78. Found: C, 60.88; H, 7.01; N, 19.55. IR (KBr): ν=3368 (s), 2936 (s), 2864 (s), 1547 (s), 1503 (s), 1448 (s), 1366 (m), 1276 (m), 1056 (m), 809 (m), 701 (m), 585 (w) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C): δ=2.64 (br s, 5H, 3-, 5-H-e, -a piperazine, NH-piperazine), 3.39–3.51 [br m, 8H, 2-, 6-H-e, -a piperazine, 2×(3-, 3′-H)], 4.08 (br s, 2H, 2-, 2′-H), 4.94 (br s, 4H, 1-, 1′-H, 3-, 3′-OH), 5.67–5.81 (br m, 4H, N-, N′-H, 1-, 1′-OH), 7.34 (br s, 10H, Ph) ppm. ^{1}H NMR (400 MHz, DMSO-d_6, 80 °C): δ=2.74 (br s, 5H, 3-, 5-H-e, -a, piperazine, NH-piperazine), 3.45–3.57 (br m, 6H, 2-, 6-H-e, -a, piperazine, 3-, 3′-H), 4.14–4.53 (br m, 6H, 1-, 1′-OH, 3-, 3′-OH, 2-, 2′-H), 4.94, 5.09, 5.25 (3×br s, 2H, 1-, 1′-H), 5.63, 5.77 (2×br s, 2H, N-, N′-H), 7.21–7.37 (br m, 10H, Ph) ppm. QC NMR (75 MHz, DMSO-d_6, 25 °C): δ=44.0 (2C, C-3, -5, piperazine), 45.7 (2C, C-2, -6, piperazine), 57.4, 57.6 (2C, C-2, -2′), 60.9 (2C, C-3, -3′), 70.3 (2C, C-1, -1′), 126.5 (4C, CH, Ph), 127.0 (2C, CH, Ph), 128.1 (4C, CH, Ph), 144.1 (2C, C-1, Ph), 164.52 (1C, C-2, *s*-triazine), 165.54, 165.7 (2C, C-4, -6, *s*-triazine) ppm. MS (DIC, isobutane): *m*/*z* (%)=496 (100) [M$^+$], 282 (75), 256 (15), 238 (45), 156 (30), 154 (22), 141 (25), 115 (15), 107 (30), 93 (38). $[\alpha]_D^{20}$ +5.8 (*c* 2.0, DMSO).

*4.5.1.2. 1-{4,6-Bis[(1S,2S)-1,3-dihydroxy-1-(4-nitrophenyl)prop-2-ylamino]-s-triazin-2-yl}piperazine (**4e**).* Yield 84%, yellow crystalline powder, mp 158–160 °C (H_2O). Anal. Calcd for $C_{25}H_{31}N_9O_8$ (585.58): C, 51.28; H, 5.34; N, 21.53. Found: C, 51.44; H, 5.55; N, 21.55. IR (KBr): ν=3401 (s), 2858 (s), 1513 (s), 1444 (s), 1347 (s), 1275 (m), 1109 (w), 1068 (m), 1015 (m), 855 (w), 809 (s), 702 (w), 542 (w) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C): δ=2.52 (s, 5H, 3-, 5-H-e, -a, piperazine, NH-piperazine), 3.33–3.42 (br m, 6H, 3-, 3′-H, 2-, 6-H-e, -a, piperazine), 3.51–3.62 (br m, 2H, 3-, 3′-H), 4.12–4.20 (br m, 2H, 2-, 2′-H), 4.87 (br s, 2H, 3-, 3′-OH), 5.00, 5.03 (2×s, 2H, 1-, 1′-H), 5.64, 5.69, 5.73 (3×d, $^3J_{H,H}$=8.8, 9.6, 8.8 Hz, respectively, 2H, N-, N′-H), 5.92 (br s, 2H, 1-, 1′-OH), 7.47, 7.53, 7.62 (3×d, $^3J_{H,H}$=8.0, 8.0, 8.4 Hz, respectively, 4H, 2-, 2′-, 6-, 6′-H, *p*-NPh), 7.98, 8.10, 8.14, 8.18 (4×d, $^3J_{H,H}$=8.0, 8.4, 8.0, 8.0 Hz, respectively, 4H, 3-, 3′-, 5-, 5′-H, *p*-NPh) ppm. ^{1}H NMR (400 MHz, DMSO-d_6, 80 °C): δ=2.59 (s, 5H, 3-, 5-H-e, piperazine, NH-piperazine), 3.42 (m, 6H, 2-, 6-H-e, -a, 3-, 3′-H, piperazine), 3.58 (dd, $^2J_{H,H}$=10.4 Hz, $^3J_{H,H}$=7.2 Hz, 2H, 3-, 3′-H), 4.17 (dd, $^3J_{H,H}$=3.6, 8.4 Hz, 2H, 2-, 2′-H), 4.56 (br s, 2H, 3-, 3′-OH), 5.04 (d, $^3J_{H,H}$=2.4 Hz, 2H, 1-, 1′-H), 5.55 (d, $^3J_{H,H}$=8.4 Hz, 4H, 1-, 1′-OH, N-, N′-H), 7.58 (d, $^3J_{H,H}$=8.0 Hz, 4H, 2-, 2′-, 6-, 6′-H, *p*-NPh), 8.08 (d, $^3J_{H,H}$=8.0 Hz, 4H, 3-, 3′-, 5-, 5′-H, *p*-NPh) ppm. QC NMR (75 MHz, DMSO-d_6, 25 °C): δ=43.9 (2C, C-3, -5, piperazine), 45.8 (2C, C-2, -6, piperazine), 56.7, 57.1, 57.3, 57.4 (2C, C-2, -2′), 60.8 (2C, 3C-3, -3′), 70.0 (2C, C-1, -1′), 122.9, 123.2 (4C, C-2, -2′, -6, -6′, *p*-NPh)], 127.1, 127.6 (4C, C-3, -3′, -5, -5′, *p*-NPh), 146.46, 146.54 (2C, C-1, -1′, *p*-NPh), 152.7 (2C, C-4, -4′, *p*-NPh), 164.2, 164.4 (3C, C-2, *s*-triazine), 165.6, 165.8 (2C, C-4, -6, *s*-triazine) ppm. MS (FAB+, 3-nitrobenzylalcohol): *m*/*z* (%)=586 (50) [M$^+$], 570 (<10), 496 (<10), 460 (22), 433 (18), 417 (<10), 403 (<10), 391 (20), 371 (15), 338 (45), 245 (15), 235 (30), 219 (40), 178 (18), 165 (40). $[\alpha]_D^{20}$ −2.8 (*c* 2.0, DMSO).

4.6. Typical procedure for the synthesis of compounds 5a, 5b, 5d and 5e (Scheme 2, Route 5, Table 1)

*4.6.1. Preparation of compound **5d***

To a dry 1,4-dioxane (25 mL) solution containing 2-chloro-4,6-bis[(1*S*,2*S*)-1,3-dihydroxy-1-phenylprop-2-ylamino]-*s*-triazine **2d** (0.760 g, 1.70 mmol) and anhyd piperazine (0.070 g, 0.80 mmol), anhyd K_2CO_3 (0.234 g, 1.70 mmol) was added with vigorous

stirring. The resulted suspension was heated at reflux until TLC control (chloroform/ethanol 2.5:1 v/v) showed no more evolution of reaction (about 24 h) then cooled at room temperature. After filtering off and washing minerals well with dry 1,4-dioxane (25 mL), the combined filtrate was evaporated under reduced pressure to dryness yielding the crude reaction mixture, which was submitted to column chromatography on silica gel. The following fractions were isolated: unreacted **2d** (0.111 g, 14% recovering with respect to the initial amount) then the desired **5d** (0.433 g, 60% yield, calculated by neglecting the amount of the recovered starting material **2d**).

*4.6.1.1. 1,4-Bis[4,6-bis(1,3-dihydroxy-2-methylprop-2-ylamino)-s-triazin-2-yl]piperazine (**5a**).* Yield 50%, white crystalline powder, mp 245.2–246.8 °C (flash column chromatography; chloroform/methanol, 2.5:1). Anal. Calcd for $C_{26}H_{48}N_{12}O_8$ (656.74): C, 47.55; H, 7.37; N, 25.59. Found: C, 47.85; H, 6.99; N, 25.38. R_f (71% chloroform/methanol)=0.75. IR (KBr): ν=3404 (s), 3329 (s), 2935 (s), 2854 (s), 1586 (s), 1543 (s), 1508 (s), 1354 (m), 1262 (m), 1186 (w), 1127 (w), 1049 (s), 1016 (m), 806 (m) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 25 °C): δ=1.24 (s, 12H, 4×CH_3), 3.30–3.36 [br m, 8H, 2×(1-, 1′-, 3-, 3′-H)], 3.47 [br m, 8H, 2×(1-, 1′-, 3-, 3′-H)], 3.57–3.64 (br m, 8H, piperazine), 4.87 (br s, 8H, 8×OH), 5.66 [m, 4H, 2×(N-, N′-H)] ppm. ^1H NMR (400 MHz, DMSO-d_6, 80 °C): δ=1.28 (s, 12H, 4×CH_3), 3.52 [d, $^2J_{H,H}$=10.6 Hz, 8H, 2×(1-, 1′-, 3-, 3′-H)], 3.62 [d, $^2J_{H,H}$=10.6 Hz, 8H, 2×(1-, 1′-, 3-, 3′-H)], 3.67 (s, 8H, piperazine), 4.68 (br s, 8H, 8×OH), 5.53 [br s, 4H, 2×(N-, N′-H)] ppm. ^{13}C NMR (75 MHz, DMSO-d_6, 25 °C): δ=19.2 (4C, 4×CH_3), 42.9 (4C, piperazine), 57.8 [4C, 2×(C-2, -2′)], 64.5 [8C, 2×(C-1, -1′, -3, -3′)], 164.3 (2C, C-2, -2′, *s*-triazine), 165.5 (4C, C-4, -4′, -6, -6′, *s*-triazine) ppm. MS (FAB+, glycerol): *m*/*z* (%)=657 (30) [M^+], 639 (25), 442 (100), 428 (30), 391 (30), 373 (20), 334 (25), 315 (30), 286 (80), 271 (40), 233 (25), 223 (60), 207 (30).

*4.6.1.2. 1,4-Bis{4,6-bis[1-hydroxy-2-(hydroxymethyl)but-2-ylamino]-s-triazin-2-yl}piperazine (**5b**).* Yield 67%, white crystalline powder, mp 148–149 °C (flash column chromatography; chloroform/methanol, 4:1). Anal. Calcd for $C_{30}H_{56}N_{12}O_8$ (712.85): C, 50.55; H, 7.92; N, 23.58. Found: C, 50.77; H, 8.10; N, 23.88. R_f (80% chloroform/methanol)=0.50. IR (KBr): ν=3379 (s), 2938 (s), 1736 (w), 1561 (s), 1492 (s), 1439 (s), 1261 (s), 1058 (s), 1009 (m), 983 (m), 809 (m), 620 (w) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 25 °C): δ=0.75 (t, $^3J_{H,H}$=6.3 Hz, 12H, 4×CH_3), 1.77 [d, $^3J_{H,H}$=6.3 Hz, 8H, 4×(3-, 3′-H)], 3.37 [br s, 8H, 2×(1-, 1′-H, CH_2OH)], 3.54–3.56 [br s, 8H, 2×(1-, 1′-H, CH_2OH)], 3.62 (br m, 8H, piperazine), 4.66, 4.84, 5.09 (3×br s, 8H, 8×OH), 5.55 [m, 4H, 2×(N-, N′-H)] ppm. ^1H NMR (400 MHz, DMSO-d_6, 80 °C): δ=0.80 (t, $^3J_{H,H}$=7.5 Hz, 12H, 4×CH_3), 1.81 [q, $^3J_{H,H}$=7.5 Hz, 8H, 4×(3-, 3′-H)], 3.56 [d, $^2J_{H,H}$=10.8 Hz, 8H, 2×(1-, 1′-, CH_2OH)], 3.61 [d, $^2J_{H,H}$=10.8 Hz, 8H, 2×(1-, 1′-H, CH_2OH)], 3.65 (s, 8H, piperazine) 4.67 (br s, 8H, 8×OH), 5.44 [br s, 4H, 2×(N-, N′-H)] ppm. ^{13}C NMR (75 MHz, DMSO-d_6, 25 °C): δ=8.1 (4C, 4×CH_3), 23.4 [4C, 2×(C-3, -3′)], 41.7 (4C, piperazine), 60.2, 62.5 [4C, 2×(C-2, -2′)], 63.1, 63.4 [8C, 2×(C-1, -1′, CH_2OH)], 165.4 (6C, C-2, -2′, -4, -4′, -6, -6′, *s*-triazine) ppm. MS (FAB+, glycerol): *m*/*z* (%)=713 (100) [M^+], 695 (75), 681 (30), 663 (25), 611 (40), 357 (20), 343 (37), 325 (20), 305 (20), 277 (72), 241 (20), 221 (30).

*4.6.1.3. 1,4-Bis{4,6-bis[(1S,2S)-1,3-dihydroxy-1-phenylprop-2-ylamino]-s-triazin-2-yl}piperazine (**5d**).* Yield 60%, white crystalline powder, mp 131.0–132.8 °C (flash column chromatography; chloroform/ethanol, 2.5:1). Anal. Calcd for $C_{46}H_{56}N_{12}O_8$ (905.02): C, 61.05; H, 6.24; N, 18.57. Found: C, 61.39; H, 6.11; N, 18.29. R_f (71% chloroform/ethanol)=0.55. IR (KBr): ν=3368 (s), 2926 (m), 2879 (m), 1547 (s), 1495 (s), 1438 (s), 1361 (m), 1266 (m), 1028 (m), 1007 (m), 809 (m), 700 (m), 573 (w) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 25 °C): δ=3.42 [br s, 4H, 2×(3-, 3′-H)], 3.55 [s, 12H, 8H, piperazine, 2×(3-, 3′-H)], 4.05, 4.19 [2×br s, 4H, 2×(2-, 2′-H)], 4.81 [br s, 4H, 2×(3-, 3′-OH)], 4.95 [br s, 4H, 2×(1-, 1′-H)], 5.52 [br s, 4H, 2×(1-, 1′-OH)], 5.74, 5.86 [2×br s, 4H, 2×(N-, N′-H)], 6.90–7.60 (m, 20H, Ph) ppm. ^1H NMR (400 MHz, DMSO-d_6, 80 °C): δ=3.42 [dd, $^2J_{H,H}$=8.8 Hz, $^3J_{H,H}$=4.2 Hz, 4H, 2×(3-, 3′-H)], 3.53 [s, 12H, 8H, piperazine, 2×(3-, 3′-H)], 4.11 [m, 4H, 2×(2-, 2′-H)], 4.47 [br s, 4H, 2×(3-, 3′-OH)], 4.91 [br s, 4H, 2×(1-, 1′-H)], 5.25 [br s, 4H, 2×(1-, 1′-OH)], 5.60 [d, $^3J_{H,H}$=7.6 Hz, 4H, 2×(N-, N′-H)], 7.18 (dd, $^3J_{H,H}$=7.2, 7.2 Hz, 4H, Ph), 7.27 (dd, $^3J_{H,H}$=7.4, 7.4 Hz, 8H, Ph), 7.35 (d, $^3J_{H,H}$=7.6 Hz, 8H, Ph) ppm. ^{13}C NMR (75 MHz, DMSO-d_6, 25 °C): δ=42.7 (4C, piperazine), 57.4, 57.7 [4C, 2×(C-2, -2′)], 60.5, 60.8 [4C, 2×(C-3, -3′)], 70.2, 70.3, 70.5 [4C, 2×(C-1, -1′)], 126.5 (8C, Ph), 126.9, 127.1 (4C, Ph), 128.1 (8C, Ph), 144.1, 143.7 [4C, 2×(C-1, -1′, Ph)], 164.6 (2C, C-2, -2′, *s*-triazine), 165.7, 165.9 (4C, C-4, -4′, -6, -6′, *s*-triazine) ppm. MS (ESI+): *m*/*z* (×10^{-6})=927.6 (0.60) [M+Na^+], 905.7 [MH^+] (1.2), 887.6 [M^+−18] (0.02), 647.6 (0.2), 619.6 (0.22), 591 (0.1). $[\alpha]_D^{20}$ +3.7 (*c* 0.5, THF).

*4.6.1.4. 1,4-Bis{4,6-bis[(1S,2S)-1,3-dihydroxy-1-(4-nitrophenyl)prop-2-ylamino]-s-triazin-2-yl}piperazine (**5e**).* Yield 69%, yellow crystalline powder, mp 121.3–123.0 °C (flash column chromatography; dichloromethane/methanol, 6.3:1). Anal. Calcd for $C_{46}H_{52}N_{16}O_{16}$ (1085.01): C, 50.92; H, 4.83; N, 20.65. Found: C, 51.25; H, 5.11; N, 20.29. R_f (86% dichloromethane/methanol)=0.50. IR (KBr): ν=3369 (s), 2926 (m), 1546 (s), 1517 (s), 1439 (s), 1346 (s), 1272 (m), 1069 (m), 1007 (m), 809 (m), 701 (w) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 25 °C): δ=3.40 [br s, 12H, 8H, piperazine, 2×(3-, 3′-H)], 3.55 [s, 4H, 2×(3-, 3′-H)], 4.15 [br s, 4H, 2×(2-, 2′-H)], 4.86 [s, 4H, 2×(3-, 3′-OH)], 5.05 [br s, 4H, 2×(1-, 1′-H)], 5.77 [d, $^3J_{H,H}$=8.3 Hz, 4H, 2×(N-, N′-H)], 5.79 [d, $^3J_{H,H}$=4.9 Hz, 2×(1-, 1′-OH)], 7.47, 7.56, 7.63 [3×d, $^3J_{H,H}$=7.6, 10.4, 9.2 Hz, respectively, 8H, 2×(2-, 2′-, 6-, 6′-H, *p*-NPh)], 7.99, 8.15, 8.19 [3×d, $^3J_{H,H}$=10.8, 8.4, 8.4 Hz, respectively, 8H, 2×(3-, 3′-, 5-, 5′-H, *p*-NPh)] ppm. ^1H NMR (400 MHz, DMSO-d_6, 80 °C): δ=3.44 [s, 12H, 8H, piperazine, 2×(3-, 3′-H)], 3.57 [m, 4H, 2×(3-, 3′-H)], 4.18 [dd, $^3J_{H,H}$=3.6, 8.2 Hz, 4H, 2×(2-, 2′-H)], 4.57 [br s, 4H, 2×(3-, 3′-OH)], 5.06 [s, 4H, 2×(1-, 1′-H)], 5.58 [br s, 4H, 2×(1-, 1′-OH)], 5.62 [d, $^3J_{H,H}$=8.2 Hz, 4H, 2×(N-, N′-H)], 7.60 [d, $^3J_{H,H}$=7.4 Hz, 8H, 2×(2-, 2′-, 6-, 6′-H, *p*-NPh)], 8.09 [d, $^3J_{H,H}$=7.4 Hz, 8H, 2×(3-, 3′-, 5-, 5′-H, *p*-NPh)] ppm. ^{13}C NMR (75 MHz, DMSO-d_6, 25 °C): δ=42.5 (4C, piperazine), 56.7, 57.1 [4C, 2×(C-2, -2′)], 60.8, 60.9 [4C, 2×(C-3, -3′)], 70.0 [4C, 2×(C-1, -1′)], 123.2 [8C, 2×(C-2, -2′, -6, -6′, *p*-NPh)], 127.6 [8C, 2×(C-3, -3′, -5, -5′, *p*-NPh)], 146.6 [4C, 2×(C-1, -1′, *p*-NPh)], 152.5, 152.6 [4C, 2×(C-4, -4′, *p*-NPh)], 164.4 (2C, C-2, -2′, *s*-triazine), 165.6 (4C, C-4, -4′, -6, -6′, *s*-triazine) ppm. MS (MALDI+): *m*/*z* (%)=1085.4 [M^+] (25), 877.0 (10), 578.3 (27), 381.2 (48), 212.0 (100). $[\alpha]_D^{20}$ −35.7 (*c* 0.1, MeOH).

*4.6.2. Preparation of compound **6e** (Scheme 3)*

To a dry THF (100 mL) solution containing 1-{4,6-bis[(1*S*,2*S*)-1,3-dihydroxy-1-(4-nitrophenyl)prop-2-ylamino]-*s*-triazin-2-yl}-piperazine **4e** (2.318 g, 3.96 mmol), anhyd K_2CO_3 (0.546 g, 3.96 mmol) was added with vigorous stirring. In the resulted suspension, cooled at −78 °C, cyanuric chloride (0.363 g, 1.932 mmol) was rapidly injected as dry THF (15 mL) solution. The reaction mixture was let very gently to reach room temperature (20–24 h) and then kept at this temperature for additional 48 h. After filtering and washing minerals with dry THF (50 mL), the combined filtrate was evaporated under vacuum to dryness yielding the crude product **6e**, which was purified by column chromatography on silica gel (eluent chloroform/ethanol, 3:1 v/v). Yield 75% (1.858 g **6e**).

*4.6.2.1. 2-Chloro-4,6-bis{4-{4,6-bis[(1S,2S)-1,3-dihydroxy-1-(4-nitrophenyl)-prop-2-ylamino]-s-triazin-2-yl}piperazin-1-yl}-s-triazine (**6e**).* Yield 75%, yellow crystalline powder, mp 179–183 °C (flash column chromatography; chloroform/ethanol, 3:1). Anal. Calcd for

$C_{53}ClH_{60}N_{21}O_{16}$ (1282.64): C, 49.63; H, 4.71; N, 22.93. Found: C, 50.01; H, 4.77; N, 23.12. R_f (75% chloroform/ethanol)=0.25. IR (KBr): ν=3401 (m), 2878 (m), 1764 (w), 1720 (w), 1566 (s), 1491 (s), 1440 (s), 1347 (s), 1273 (m), 1231 (m), 1164 (w), 1108 (w), 1068 (w), 999 (m), 978 (m), 809 (w), 702 (w), 530 (w) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 25 °C): δ=3.53 (br s, 16H, 2×piperazine), 3.58 [m, 8H, 4×(3-, 3′-H)], 4.16, 4.21 [2×br s, 4H, 2×(2-, 2′-H)], 4.86 [br s, 4H, 2×(3-, 3′-OH)], 5.05 [s, 4H, 2×(1-, 1′-H)], 5.70, 5.76, 5.84 [3×br s, 8H, 2×(N-, N′-H), 2×(1-, 1′-OH)], 7.49, 7.56, 7.63 [3×d, $^3J_{H,H}$=7.2, 8.0, 8.4 Hz, respectively, 8H, 2×(2-, 2′-, 6-, 6′-H, *p*-NPh)], 8.00, 8.12, 8.15, 8.19 [4×d, $^3J_{H,H}$=7.2, 8.0, 8.8, 10.4 Hz, respectively, 8H, 2×(3-, 3′-, 5-, 5′-H, *p*-NPh)] ppm. ^1H NMR (400 MHz, DMSO-d_6, 80 °C): δ=3.38–3.44 [m, 4H, 2×(3-, 3′-H)], 3.59–3.61 [m, 12H, piperazine 2′-, 2″-, 6′-, 6″-H-a, -e, 2×(3-, 3′-H)], 3.63 (s, 8H, piperazine 3′-, 3″-, 5′-, 5″-H-a, -e), 4.20 [dddd, $^3J_{H,H}$=4.7, 4.8, 7.0, 8.7 Hz, 4H, 2×(2-, 2′-H)], 4.58 [br s, 4H, 2×(3-, 3′-OH)], 5.06 [s, 4H, 2×(1-, 1′-H)], 5.57 [br s, 4H, 2×(1-, 1′-OH)], 5.67 [d, $^3J_{H,H}$=8.7 Hz, 4H, 2×(N-, N′-H)], 7.60 [d, $^3J_{H,H}$=7.6 Hz, 8H, 2×(2-, 2′-, 6-, 6′-H, *p*-NPh)], 8.09 [d, $^3J_{H,H}$=7.6 Hz, 8H, 2×(3-, 3′-, 5-, 5′-H, *p*-NPh)] ppm. QC NMR (75 MHz, DMSO-d_6, 25 °C): δ=42.4 (4C, piperazine C-3, -3′, -5, -5′), 43.2 (4C, piperazine C-2, -2′, -6, -6′), 56.7, 57.1, 57.5 [4C, 2×(C-2, -2′)], 60.8 [4C, 2×(C-3, -3′)], 70.1 [4C, 2×(C-1, -1′)], 122.9, 123.1 [8C, 2×(C-2, -2′, -6, -6′, *p*-NPh)], 127.6 [8C, 2×(C-3, -3′, -5, -5′, *p*-NPh)], 146.5 [4C, 2×(C-1, -1′, *p*-NPh)], 152.4 [4C, 2×(C-4, -4′, *p*-NPh)], 164.1 (6C, C-2′, -2″, -4′, -4″, -6′, -6″, *s*-triazine), 165.6 (2C, C-4, -6, *s*-triazine), 169.1 (1C, C-2, *s*-triazine) ppm. MS (ESI+): m/z (×10^{-5})=1320.5 [M+K^+] (1.1), 1304.5 [M+Na^+] (1.1), 1282.6 [M^+] (1.1), 647.6 (0.5), 619.6 (0.8). $[\alpha]_D^{20}$ −5.9 (*c* 2, DMSO).

4.6.3. Preparation of compound **7e** (Scheme 3)

To a dry 1,4-dioxane (100 mL) solution containing anhyd piperazine (0.350 g, 4.052 mmol), anhyd K_2CO_3 (0.140 g, 1.013 mmol) was added with vigorous stirring. The resulted suspension was heated at reflux when 2-chloro-4,6-bis{4-{4,6-bis[(1*S*,2*S*)-1,3-dihydroxy-1-(4-nitrophenyl)prop-2-ylamino]-*s*-triazin-2-yl}piperazin-1-yl}-*s*-triazine **6e** (1.300 g, 1.013 mmol) as dry 1,4-dioxane (50 mL) solution was injected portionwise as 12.50 mL/portion each 3 h. After each addition, within 3 h, TLC monitoring indicated only the complete absence of **6e** [R_f (75% chloroform/ethanol)=0.25]. Compound **7e** could not be eluted on silica gel. Finally, the reaction mixture was kept at reflux for 3 h and then cooled at room temperature. After filtering off and washing minerals well with dry 1,4-dioxane (50 mL), the combined filtrate was evaporated under reduced pressure to dryness yielding the crude reaction mixture, which was taken with cooled water (50 mL) with vigorous stirring for 2 h. The resulted suspension was filtered off at room temperature and washed very well with cooled water. The recovered solid was taken with HCl 5% (50 mL, final *p*H=0.5) and vigorous stirring for 30 min, then cooled at 0 °C and filtered off at this temperature. The solid material was then taken carefully, at room temperature, with 5% aq K_2CO_3 (50 mL, final *p*H=10), stirred for additional 30 min and then filtered off. After washing well with water to neutrality and drying, 1.148 g pure **7e** were obtained (85% yield).

4.6.3.1. 1-{4,6-Bis{4-{4,6-bis[(1S,2S)-1,3-dihydroxy-1-(4-nitrophenyl)-prop-2-ylamino]-s-triazin-2-yl}piperazin-1-yl}-s-triazin-2-yl}piperazine (**7e**).

Yield 85%, yellow crystalline powder, mp 187–191 °C (H_2O). Anal. Calcd for $C_{57}H_{69}N_{23}O_{16}$ (1332.32): C, 51.39; H, 5.22; N, 24.18. Found: C, 51.27; H, 4.98; N, 24.12. IR (KBr): ν=3104 (s), 2858 (m), 1518 (s), 1439 (s), 1347 (s), 1268 (s), 1179 (w), 1109 (w), 1068 (w), 1001 (s), 809 (m), 702 (w), 541 (w) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 25 °C): δ=2.67 (br s, 5H, piperazine 3-, 5-H-e, -a, NH-piperazine), 3.47 [br s, 4H, 2×(3-, 3′-H)], 3.54 [br s, 8H, 2′-, 2″-, 6′-, 6″-H-e, -a, piperazine], 3.60 [br s, 16H, 2×(3-, 3′-H), 2-, 6-H-e, -a, piperazine 3′-, 3″-, 5′-, 5″-H-e, -a, piperazine], 4.03–4.14 [br m, 4H, 2×(2-, 2′-H)], 4.86 [br s, 4H, 2×(3-, 3′-OH)], 5.04 [s, 4H, 2×(1-, 1′-H)], 5.73–5.87 [br m, 8H, 2×(N-, N′-H), 2×(1-, 1′-OH)], 7.49, 7.55, 7.63 [3×d, $^3J_{H,H}$=7.6, 8.0, 8.0 Hz, respectively, 8H, 2×(2-, 2′-, 6-, 6′-H, *p*-NPh)], 8.00, 8.12, 8.15, 8.19 [4×d, $^3J_{H,H}$=8.0, 8.4, 9.2, 10.0 Hz, respectively, 8H, 2×(3-, 3′-, 5-, 5′-H, *p*-NPh)] ppm. ^1H NMR (400 MHz, DMSO-d_6, 80 °C): δ=2.72 (br s, 5H, piperazine 3-, 5-H-e, -a, NH-piperazine), 3.44 [m, 4H, 2×(3-, 3′-H)], 3.53 (br s, 8H, 2′-, 2″-, 6′-, 6″-H-e, -a, piperazine), 3.59 [s, 16H, 2×(3-, 3′-H), 2-, 6-H-e, -a, piperazine 3′-, 3″-, 5′-, 5″-H-e, -a, piperazine], 4.19 [ddd, $^3J_{H,H}$=4.0, 8.0, 8.5 Hz, 4H, 2×(2-, 2′-H)], 4.59 [br s, 4H, 2×(3-, 3′-OH)], 5.06 [d, $^3J_{H,H}$=2.4 Hz, 4H, 2×(1-, 1′-H)], 5.62 [d, $^3J_{H,H}$=8.5 Hz, 8H, 2×(N-, N′-H), 2×(1-, 1′-OH)], 7.59 [d, $^3J_{H,H}$=7.8 Hz, 8H, 2×(2-, 2′-, 6-, 6′-H, *p*-NPh)], 8.09 [d, $^3J_{H,H}$=7.8 Hz, 8H, 2×(3-, 3′-, 5-, 5′-H, *p*-NPh)] ppm. QC NMR (75 MHz, DMSO-d_6, 25 °C): δ=42.8 (8C, C-2′, -2″, -3′, -3″, -5′, -5″, -6′, -6″, piperazine), 44.1 (2C, C-3, -5, piperazine), 45.9 (2C, C-2, -6, piperazine), 56.7, 57.1, 57.4 [4C, 2×(C-2, -2′)], 60.9 [4C, 2×(C-3, -3′)], 70.0 [4C, 2×(C-1, -1′)], 123.1 [8C, 2×(C-2, -2′, -6, -6′, *p*-NPh)], 127.6 [8C, 2×(C-3, -3′, -5, -5′, *p*-NPh)], 146.5 [4C, 2×(C-1, -1′, *p*-NPh)], 152.4, 152.5 [4C, 2×(C-4, -4′, *p*-NPh)], 164.4 (2C, *s*-triazine), 164.9 (1C, *s*-triazine), 165.0 (2C, *s*-triazine), 165.7 (3C, *s*-triazine), 165.9 (1C, *s*-triazine) ppm. MS (ESI+): m/z (×10^{-6})=1370.5 [M−1+K^+] (0.1), 1354.6 [M−1+Na^+] (0.22), 1333.0 [M^+] (0.95). $[\alpha]_D^{20}$ −8.2 (*c* 2, DMSO).

4.6.4. Preparation of compound **8e** (Scheme 3)

To a dry THF (40 mL) solution containing 1-{4,6-bis{4-{4,6-bis[(1*S*,2*S*)-1,3-dihydroxy-1-(4-nitrophenyl)-prop-2-ylamino]-*s*-triazin-2-yl}-piperazin-1-yl}-*s*-triazin-2-yl}-piperazine **7e** (1.278 g, 0.959 mmol), anhyd K_2CO_3 (0.132 g, 0.959 mmol) was added with vigorous stirring. In the resulted suspension, cooled at −78 °C, cyanuric chloride (0.057 g, 0.313 mmol) was rapidly injected as dry THF (10 mL) solution. The reaction mixture was let very gently to reach room temperature (12 h), kept at this temperature for additional 24 h and then refluxed 24 h. Since TLC monitoring (chloroform/ethanol 2:1) still indicated transformations, the reaction mixture was evaporated under vacuum to dryness. The solid residue was taken with dry 1,4-dioxane (50 mL) then refluxed with careful TLC monitoring until a single major spot (R_f around 0.1) was observed (about 24 h). After filtering and washing minerals with dry 1,4-dioxane (50 mL) at room temperature, the combined filtrate was evaporated under vacuum to dryness yielding the crude product **8e**. This was taken with boiling ethanol (10 mL) and crystallised by cooling at −20 °C. The same procedure was repeated using boiling isopropanol (10 mL). Yield 60% (0.774 g **8e**).

4.6.4.1. 2,4,6-Tris{4-{4,6-bis{4-{4,6-bis[(1S,2S)-1,3-dihydroxy-1-(4-nitrophenyl)prop-2-ylamino]-s-triazin-2-yl}piperazin-1-yl}-s-triazin-2-yl}piperazin-1-yl}-s-triazine (**8e**).

Yield 60%, yellow crystalline powder, mp around 220 °C (*i*-PrOH). Anal. Calcd for $C_{174}H_{204}N_{72}O_{48}$ (4071.98): C, 51.32; H, 5.05; N, 24.77. Found: C, 50.98; H, 5.38; N, 25.09. IR (KBr): ν=3394 (s), 2862 (m), 1523 (s), 1435 (s), 1347 (s), 1258 (s), 998 (s), 808 (m) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 25 °C): δ=3.20–3.90 [br m, 96H, 72×(G-1, -2, piperazine), 12×(3-, 3′-H)], 4.22 [br s, 12H, 6×(2-, 2′-H)], 4.92 [br s, 12H, 6×(3-, 3′-OH)], 5.11 [br s, 12H, 6×(1-, 1′-H)], 5.83 [br s, 24H, 6×(N-, N′-H), 6×(1-, 1′-OH)], 7.63–7.67 [br m, 24H, 6×(2-, 2′-, 6-, 6′-H, *p*-NPh)], 8.06–8.19 [br m, 24H, 6×(3-, 3′-, 5-, 5′-H, *p*-NPh)] ppm. ^1H NMR (400 MHz, DMSO-d_6, 80 °C): δ=3.45 [s, 12H, 6×(3-, 3′-H)], 3.50–3.73 [m, 60H, 6×8(G-2, piperazine), 6×(3-, 3′-H)], 3.80 [br s, 24H, 3×8(G-1, piperazine)], 4.21 [m, 12H, 6×(2-, 2′-H)], 4.58 [br s, 12H, 6×(3-, 3′-OH)], 5.06 [s, 12H, 6×(1-, 1′-H)], 5.57 [s, 12H, 6×(1-, 1′-OH)], 5.64 [d, $^3J_{H,H}$=8.4 Hz, 12H, 6×(N-, N′-H)], 7.60 [d, $^3J_{H,H}$=7.8 Hz, 24H, 6×(2-, 2′-, 6-, 6′-H, *p*-NPh)], 8.09 [d, $^3J_{H,H}$=7.8 Hz, 24H, 6×(3-, 3′-, 5-, 5′-H, *p*-NPh)] ppm. QC NMR (75 MHz, DMSO-d_6, 25 °C): δ=42.4 (36C, G-1, -2, piperazine), 56.3, 56.9 [12C, 6×(C-2, -2′)], 61.0 [12C, 6×(C-3, -3′)], 69.5 [12C, 6×(C-1, -1′)], 122.6 [24C, 6×(C-2, -2′,

-6, -6′, *p*-NPh)], 127.1 [24C, 6×(C-3, -3′, -5, -5′, *p*-NPh)], 146.0 [12C, 6×(C-1, -1′, *p*-NPh)], 152.0 [12C, 6×(C-4, -4′, *p*-NPh)], 163.9, 164.5, 165.1 (30C, *s*-triazine) ppm. MS (MALDI+): *m*/*z* (%)=4039 [M+Na^+−$3H_2O$] (100), 4036 [M^+−36] (98), 4020 (75), 1332 (68). $[\alpha]_D^{20.8}$ −6.3 (*c* 2, DMSO).

4.6.5. Synthesis of compound ***9*** *(Scheme 5)*

To a 10% v/v aq in THF suspension (100 mL) containing cyanuric chloride (0.922 g, 5 mmol) and anhyd K_2CO_3 (2.762 g, 20 mmol), cooled at −15 °C, solid piperidone hydrate hydrochloride (1.536 g, 10 mmol) was added slowly and portionwise within 12 h with vigorous stirring and keeping temperature to not exceed −10 °C. The mixture was then allowed to reach very slowly room temperature and was kept as such for additional 24 h. until TLC monitoring showed completion of reaction (eluent: ligroin/acetone 1.5:1 v/v, single spot, R_f=0.70). The reaction mixture was filtered off, minerals were washed well with dichloromethane (50 mL) and then dichloromethane (75 mL) was added to the filtrate with stirring. The organic layer was separated from the aqueous one and then washed several times with water (×50 mL) to neutrality. After drying over anhyd Na_2SO_4, and filtering off, the organic solution was evaporated to dryness under vacuum. The solid residue was crystallised from dry ether (5 mL) at −20 °C to yield 1.053 g pure **9** (68% yield).

*4.6.5.1. 2-Chloro-4,6-bis(4-oxopiperidin-1-yl)-s-triazine (**9**).* Yield 68%, white crystalline powder, mp 189–190 °C (Et_2O). Anal. Calcd for $C_{13}H_{16}ClN_5O_2$ (309.75): C, 50.41; H, 5.21; N, 22.61. Found: C, 50.59; H, 5.45; N, 22.24. R_f (60% ligroin/acetone)=0.70. IR (KBr): *ν*=3007 (w), 2974 (w), 2900 (w), 1714 (s), 1592 (s), 1492 (s), 1450 (s), 1367 (m), 1331 (m), 1231 (s), 1211 (s), 1016 (m), 982 (m), 967 (m), 827 (m), 793 (m), 753 (w), 685 (w), 556 (w), 497 (w) cm^{-1}. ^1H NMR (500 MHz, THF-d_8, 30 °C): *δ*=2.44 [br t, 4H, 3′(5′)-, 3″(5″)-, H-e, -a], 2.45 [br t, 4H, 5′(3′)-, 5″(3″)-, H-e, -a], 4.10 (t, 8H, $^3J_{H,H}$=6.5 Hz, 2′-, 2″-, 6′-, 6″-H-e, -a) ppm. ^1H NMR (500 MHz, THF-d_8, 10 °C): *δ*=2.41 [t, 4H, $^3J_{H,H}$=6.3 Hz, 3′(5′)-, 3″(5″)-H-e, -a], 2.43 [t, 4H, $^3J_{H,H}$=6.3 Hz, 5′(3′)-, 5″(3″)-H-e, -a], 4.07 [t, 4H, $^3J_{H,H}$=5.8 Hz, 2′(6′)-, 2″(6″)-H-e, -a], 4.08 [t, 4H, $^3J_{H,H}$=5.8 Hz, 6′(2′)-, 6″(2″)-H-e, -a] ppm. QC NMR (125 MHz, THF-d_8, 25 °C): *δ*=40.3, 40.6 (4C, C-3′, -3″, -5′, -5″), 42.6, 42.7 (4C, C-2′, -2″, -6′, -6″), 165.2 (2C, C-4, -6, *s*-triazine), 170.3 (1C, C-2, *s*-triazine), 205.1 (2C, C-4′, -4″) ppm. ^1H NMR (500 MHz, DMSO-d_6, 70 °C): *δ*=2.48 (t, 8H, $^3J_{H,H}$=6.3 Hz, 8H, 3′-, 3″-, 5′-, 5″-H-e, -a), 4.03 (t, 8H, $^3J_{H,H}$=6.3 Hz, 2′-, 2″-, 6′-, 6″-H-e, -a) ppm. MS (EI, 70 eV): *m*/*z* (%)=309 [M^+−1] (100), 281 (58), 253 (78), 240 (70), 225 (40), 197 (33), 184 (29), 70 (37).

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Supplementary data

Tables I–III and Figures I and II are provided. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.06.071.

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