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FIRST SYNTHESIS, ROTAMERISM AND HERBICIDAL EVALUATION OF SUBSTITUTED *s*-TRIAZINES WITH SERINOLIC FRAGMENTS (I): OPEN-CHAIN STRUCTURES

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ABSTRACT. First series of melamines and precursors, starting from commercially *C*-substituted-2-amino-1,3-propanediols (pharmaceutical chemistry nomenclature as *serinols*) in reaction with cyanuryl chloride is reported. The diastereomerism generated by the more or less restricted rotation about the C^{sp2}(*s*-triazine)-N<(*serino*l) bond in this series is for the first time discussed along with a preliminary herbicidal evaluation of some representative terms.

INTRODUCTION

The chemistry of highly elaborated *N*-substituted triamino-*s*-triazines (*melamines*) is, nowadays, a part of supramolecular chemistry as dendrimers, tectons and macrocycles[1]. In the last decade, the knowledge focused on their use as antiangiogenic, anticancer or antimicrobial agents[2a-d]. They also led to new generation of herbicides and highly specific enzyme inhibitors[2e].

Among the suitable amines to provide interesting architectures, almost no attention was paid to *C*-substituted-2-amino-1,3-propanediols (the so called *serinols*): to our knowledge there are only two papers dealing with their reactivity against cyanuryl chloride[3,4]. On the other hand, according to Katritzky and Ghiviriga recent findings, in *N*-substituted melamines as well as in their precursors, more or less hindered rotamerism phenomena are encountered with respect to the C^{sp2}(*s*-triazine)-N<(exocyclic) bond[5-7]. Extension of this concept rapidly disseminated the chemistry of melamine based anticancer drugs and dyes[8-11].

Starting from our previous expertise in the domain of *C*-substituted serinols chemistry[12,13], we got some insight on testing their versatile nucleophilicity against cyanuryl chloride. Thus, the aim of this preliminary communication is to report the synthesis and some properties of the first series of substituted *s*-triazines, including melamines, bearing serinolic fragments.

RESULTS AND DISCUSSION

1. Synthesis

The compounds under study were prepared following the synthetic pathway depicted in **Scheme 1**. It started from the commercially available serinols **1a-e**; the chiral serinols **1d, e** were used as pure 1*S*,2*S* enantiomers. Since the "dimeric" melamines **4b-e** were the target series, a convergent synthetic strategy was straightforward.

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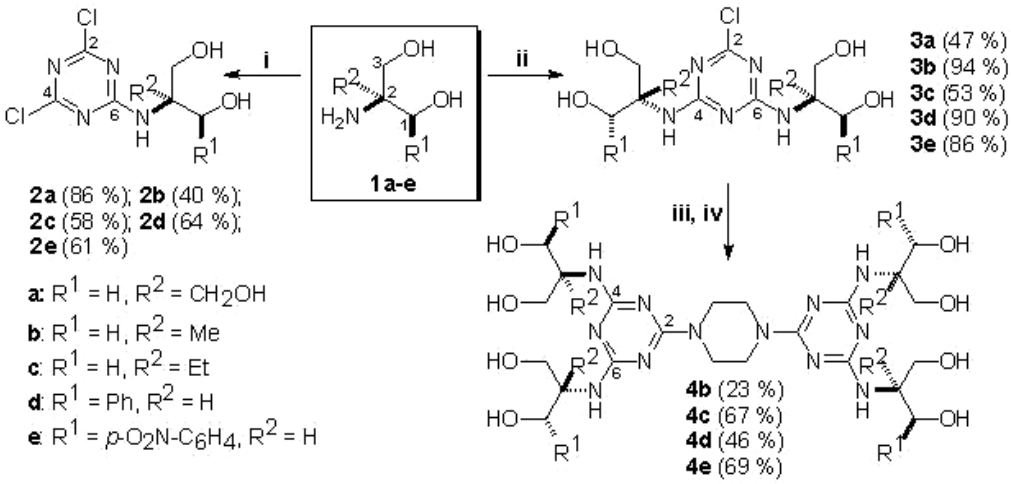


i: 1.05 eq. $C_3N_3Cl_3$ / 1.05 eq. anh. K_2CO_3 / THF / from 0 ^oC (12 hrs.) to r.t. (24-48 hrs); **ii:** 0.49 eq. $C_3N_3Cl_3$ / 1.00 eq. anh. K_2CO_3 / THF / from r.t. (12-24 hrs.) to 40-60 ^oC (12-24 hrs); **iii:** 0.49 eq. piperazine hexahydrate + 1.15 eq. HCl / *i*-PrOH (80 ^oC); **iv:** 0.49 eq. piperazine hydrochloride / 2.00 eq. anh. K_2CO_3/ 1,4-dioxane / reflux 24-72 hrs.

Scheme 1

i) The *first nucleophilic replacement of chorine in cyanuryl chloride* yielded the series **2a-e**. The preliminary results indicated this synthesis to be not quite of routine. Except the TRIS® (α,α,α-trimethylolaminomethane) derivative **2a**, all other compounds required isolation by flash column chromatography since, in the crude reaction mixture, the TLC monitoring revealed, besides unreacted starting materials, some traces of the disubstituted products **3a-e** together with traces of other side products. These by products originated presumably from the competitive statistic replacement of chlorine by the hydroxyl groups[14]. Serious complications also arose from the retention of the products on silica gel. However, our work up (*e.g. s*-triazines **2d**, **2e**) is only apparently a "drawback": indeed, this behavior is already very well documented as useful methodology to access silica gel HPLC chiral *s*-triazines selectors for enantiomeric separation[15]. Accordingly, our yields were calculated as isolated amounts after flash column chromatography.

ii) Hence, the *second nucleophilic substitution of chlorine* was performed starting directly from **1a-e** in a one pot process. This option appeared correct, as shown by the yields obtained in the cases of compounds **3b**, **3d** or **3e** which were isolated by simple crystallization. Under identical conditions, pure **3a** was obtained only as a gummy solid despite repeated crystallizations.

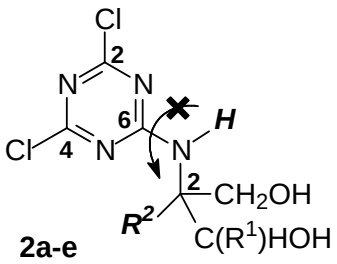
iii, iv) The *last s-triazine chlorine* was replaced by using piperazine as nucleophile to give the compounds **4b-e**. At this stage, we readily concluded that the hygroscopic piperazine should be preliminarily converted into its anhydrous hydrochloride. Next, upon treatment with the triazines **3** in refluxing 1,4-dioxane, the corresponding free base was *in situ* re-generated by the excess of proton scavenger:

the anhydrous potassium carbonate. Only this protocol was successful in order to avoid the formation of monosubstituted piperazines as side-products. However, in the case of the *s*-triazine **3a**, the TLC monitoring of the reaction indicated unpredictable decomposition; in contrast, starting from **3b-e**, the coupling was clean enough to afford the expected **4b-e** with satisfactory yields. These yields refer again to isolated products after flash column chromatography when the previously mentioned retentions on silica gel were observed.

2. Stereochemistry and rotameric behavior

At room temperature, all the series **2-4** exhibited peculiar stereochemistry consistent throughout with the hindered rotation about the C^{sp2}(*s*-triazine)-N<(exocyclic) bond. The supporting NMR study, in all cases, was carried out in DMSO-d_6 only.

2.1. 6-Amino-2,4-dichloro-*s*-triazines bearing one serinolic fragment: compounds **2a-e (Scheme 1, Scheme 2)**



Scheme 2

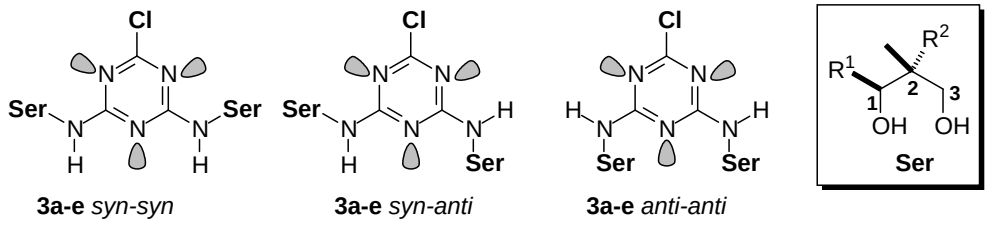
In the case of compounds **2a-e**, the ^{1}H NMR spectra performed at room temperature located the N*H* protons as the most deshielded and "rigid": 8.05 ppm (**2a**), 8.39 ppm (**2b**), 8.26 ppm (**2c**), 9.14 ppm (**2d**), 9.02 ppm (**2e**); yet, the 2D-^{1}H,^{1}H-COSY Experiment of the phenylserinols derivatives **2d** and **2e** (R^1 = Ph, *p*-O_2N-C_6H_4, R^2 = H) evidenced a significant coupling pattern between the proton N*H* (as clear doublets, ^3J=9.1-9.4 Hz) and H-2 from the aliphatic motif. In the ^{13}C NMR spectra, the triazinic carbons C-2, -4 were found diastereotopic (two different signals around 161 ppm) in agreement with a hindered rotation about C-6-N(serinol) bond. The ^{13}C diastereotopicity between positions 2, 4 (Δδ values, ppm) was independent on the type of serinol: 0.5-0.7 ppm.

By increasing the temperature (up to 80 ^{o}C in DMSO-d_6), the ^{13}C NMR spectra reached no coalescence of the discussed signals, but some decomposition of the investigated compounds was observed.

2.2. 4,6-Diamino-2-chloro-*s*-triazines bearing two serinolic fragment: compounds **3a-e (Scheme 1, Scheme 3)**

For the present communication, discussion is constrained to the results obtained by ^{1}H NMR analysis at room temperature.

Thus, the same hindered rotation was twice found in the series **3a-e** to proof the combined effect of the two amino groups (+M) with the (-M) effect of the remaining chlorine atom. If so, the rotation barrier $\Delta G^{\neq}$ in series **3a-e** should be higher than those previously discussed in the literature in the case of 2-chloro-4,6-bis(dialkylamino)-*s*-triazines, 50.6-75.4 kJ/mol[8-10]. Symmetry considerations establish the compounds **3a-e** to exist as three diastereomers (blocked rotamers), discriminated by the stereochemical descriptors previously proposed by Ghiviriga[7]: *syn* (*s*) and *anti* (*a*) (the Serinol group and the C-2 chlorine atom as references, **Scheme 3**)



3a-e *syn-syn* **3a-e** *syn-anti* **3a-e** *anti-anti*

Scheme 3

At room temperature, the analysis of the ^{1}H NMR spectra disclosed, in each case, the presence of all three stereoisomers (**Table 1**).

The assignments were based on the well separated peaks displayed by the N*H* protons: sharp singlets in **3a-c** and typical doublets (^3J=9.1-9.4 Hz) in the cases of **3d** and **3e**. The stereochemistry as (*s*-*s*), (*s*-*a* ≡ *a*-*s*) and (*a*-*a*) was established starting from the rotamers of type **3**(*a*-*s*) since, besides twice statistically favored, they revealed unambiguously two different with equal intensity environments for the two serinolic groups, including the N*H* and O*H* protons. Therefore, in connection to this observed stereochemistry, we considered as pertinent the following two factors:

Table 1

Relevant ^{1}H NMR data and contribution of the blocked rotamers in the series **3a-e** (DMSO-d_6, 293 K)

Compound	Rotamers (averaged %) according to N*H* and O*H* signals			δ_{NH} (ppm)		
	(*s*-*s*)	(*s*-*a*)	(*a*-*a*)	(*s*-*s*)	(*s*-*a*)	(*a*-*a*)
3a	24[a]	70	6	6.50	6.50 6.58	6.29
	29[b]	64	7			
	32[c]	62	6			
3b	49[a]	48	3	6.78	6.75 6.66	6.41
	50[b]	45	5			
3c	61	35	4	6.70	6.70 6.59	6.34
3d	44	45	11	7.03	6.99 6.80	6.69
3e	51	39	10	7.07	7.10 6.88	6.82

[a]standard sample; [b]dilution as 1/3; [c]dilution as 1/9

a) The steric hindrance between the serinolic groups related to their C-1 (or C-2) substitution (**Scheme 3**, **Table 1**).

b) The solvation interactions required by the chelating DMSO-d_6.

Calculations in **Table 1** were made by means of the signals of the protons N*H* and O*H*. It must be observed that in rotamers of type **3**(*a*-*a*) the resonance of the protons N*H* was found throughout upfield, in agreement with the weakest character of double bond of the linkage C^{sp2}(*s*-triazine)-N<(exocyclic). This assignment should be plausible since the steric hindrance conflicts with the coplanarity mandatory to the **Ser**-NH-C(N)=N- sequence (**Scheme 3**).

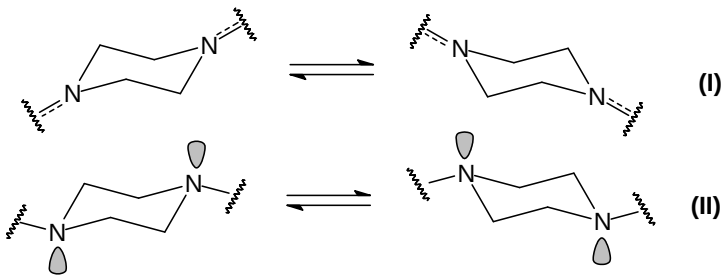
In the case of **3a**, possessing six hydroxyl groups, the strongest solvation interactions were expected. Thus, successive dilution showed a decreasing proportion of the rotamer **3a**(*s*-*a*) whilst the proportion of the less hindered rotamer **3a**(*s*-*s*) increased; probably because, in this latter case, the exposure of the hydroxyl groups to chelation was more favored.

By replacing one hydroxymethyl group with methyl (**3b**) or ethyl (**3c**), the resulted *s*-triazines were nearly an equimolar mixture of (*s*-*s*) + (*s*-*a*) rotamers (**3b**) or slightly dominant (*s*-*s*) rotamers (**3c**). No effect on stereochemistry was found following dilution, but the importance of the substitution at C-2 (methyl *vs.* ethyl) was evidenced.

The *s*-triazines **3d**, **3e** were also mainly (*s*-*s*) + (*s*-*a*) rotamers; however, the presence of a bulky substituent on the serinolic chain (to interact with the triazine skeleton) promoted the noteworthy occurrence of rotamers of type **3**(*a*-*a*).

2.3. "Dimeric" melamines: compounds **4b-e** (**Scheme 1**, **Scheme 4**, **Scheme 5**)

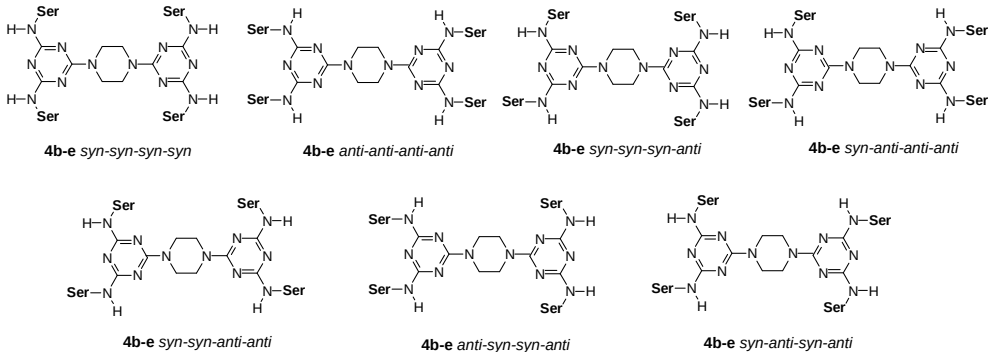
Based on literature data[8,9], we expected that the "dimeric" melamines **4b-e** possessing three donating (+M) ligands be free rotating structures ($\Delta G^{\neq}$=59.3±1 kJ/mol in the range 315-325 K) with a mobile piperazine ring (chair-chair ring **I** and / or double pyramidal inversion **II**, **Scheme 4**).



Scheme 4

The same stereochemical analysis as in the series **3a-e** provided this time seven rotamers (**Scheme 5**, the serinol and piperazine groups as references; *syn* and *anti* descriptors are cited clockwise).

Obviously, it was not viable to assign a preferred arrangement by mean of NMR methods. Indeed, the NMR spectra carried out at room temperature had a very complex appearance and by far ambiguous (**Figure 1**, 293 K, compound **4e** considered as an illustrative example): it was hazardous to ascertain whether the signals belong to a blocked multicomponent mixture of rotamers (overlapped peaks ?)



Scheme 5

or a slow exchange between anisochronous sites occurring at room temperature. Moreover, on the 75 MHz ^{13}C NMR time scale, we only detected a single set of signals.

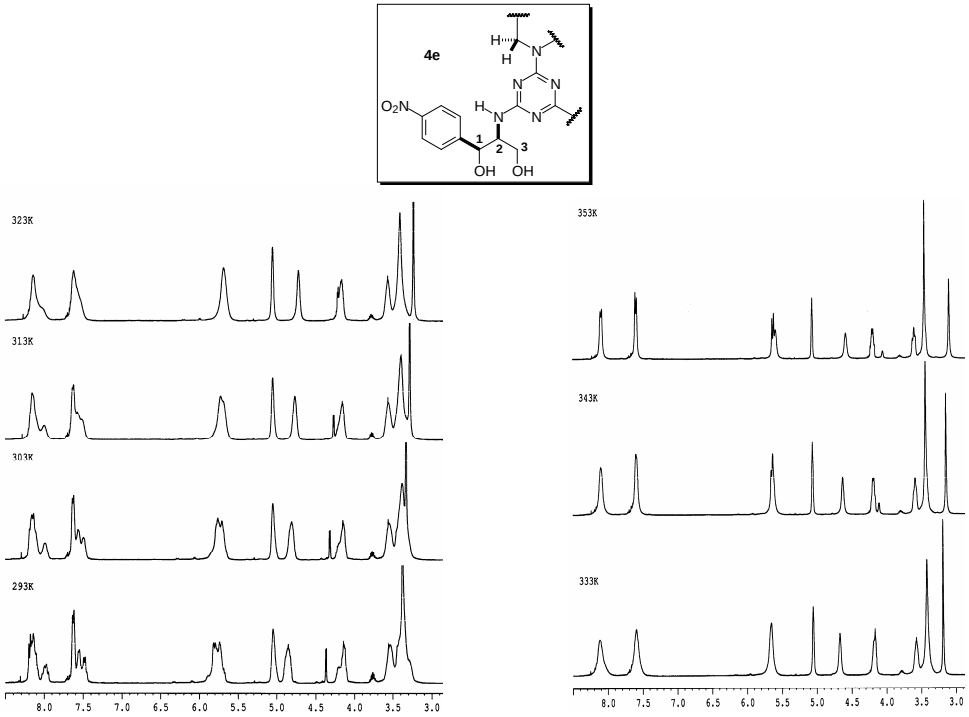


Figure 1: ^{1}H DNMR of the compound **4e** (400 MHz, DMSO-d_6); at 353 K from left to right, δ (ppm): 8.09 (2 H, d, H-Ar); 7.60 (2 H, d, H-Ar); 5.62 (1 H, d, N*H*); 5.58 (1 H, bs, O*H*-sec.); 5.06 (1 H, s, H-1); 4.57 (1 H, bs, O*H*-prim.); 4.18 (1 H, ddd, H-2); 3.59 (1 H, m, H-3); 3.44 (3 H, s, H-3 + 2 H-piperazine).

In contrast, the ^{1}H NMR spectra run by progressive increasing the temperature (**Figure 1**) permitted to observe the general coalescence at about 333 K and a single mediated structure at 353 K. The overlapped multiplet of N*H* protons was shifted upfield, from 5.80 ppm (293 K) to a clear unique doublet (^{3}J=9.2 Hz) at 5.62 ppm (353 K). That is, even at 80 ^{o}C, we avoided to consider the N*H* resonance as a typical "amine mobile proton". In addition, the 2D-^{1}H,^{1}H-COSY Experiment at 353 K located all the other expected coupling patterns including the piperazine protons. They exhibited just a sharp singlet: no diastereotopicity due to the vicinity of (1*S*,2*S*)-serinolic chains was detected (**Figure 1**, 353 K).

3. Herbicidal evaluation

Following literature methodology[16], the herbicidal activity of the series **3a-e** was evaluated by using seeds of *Cucumis sativus* and *Raphanus sativus*. Upon treatment with the compounds **3a-e**, the mean (±SD) values on the inhibition of root length were determined. They are collected in **Table 2**.

Table 2

Percent inhibitions of root length of *Cucumis sativus* and *Raphanus sativus* in response to different concentrations of the compounds **3a-e** compared to that of control

Tested species		**Root length**				
Conc.		**3a**	**3b**	**3c**	**3d**	**3e**
Cucumis	0.50 mM	66 ± 5.4	70 ± 6.4	68 ± 5.8	56 ± 3.7	54 ± 4.3
sativus	0.75 mM	89 ± 4.2	93 ± 4.5	90 ± 3.3	77 ± 3.2	76 ± 2.5
	1.00 mM	100 ± 0.0	100 ± 0.0	100 ± 0.0	92 ± 1.3	90 ± 1.7
Raphanus	0.50 mM	67 ± 3.5	72 ± 4.6	69 ± 3.8	61 ± 6.5	59 ± 7.4
Sativus	0.75 mM	90 ± 2.1	94 ± 1.8	92 ± 2.4	79 ± 5.7	76 ± 2.6
	1.00 mM	100 ± 0.0	100 ± 0.0	100 ± 0.0	93 ± 1.9	91 ± 2.3

As indicated by the preliminary data, compounds **3a-c** exhibited higher inhibition (including complete) effect in comparison with **3d**, **3e**. Although no reference compound was used along with the synthesized compounds, they already appeared active at 5×10^{-4} M as compared, in similar conditions, with Atrazine® (>> 10^{-4}M)[16a].

CONCLUSIONS

As shown by our preliminary results, the *C*-substituted-2-amino-1,3-propanediols react with cyanuryl chloride to afford amino-*s*-triazines in medium to good yields. Selectivity of the first and second chlorine replacement is complete, with respect to the polyfunctionality of the starting serinol. At room temperature, all *C*-substituted chloro-*s*-triazines with a serinolic NH group and serinols based melamines are blocked rotamers due to the partial double bond character of the C^{sp2}-N(serinol) site. The herbicidal activity in this class of *s*-triazines was tested. The full report of our findings is under consideration for the near future.

EXPERIMENTAL

General

Melting points were uncorrected; they were carried out on Electrothermal® instrument. Current NMR spectra were recorded on Brucker® AM 300 instrument operating at 300 and 75 MHz for ^{1}H and ^{13}C nuclei respectively. The ^{1}H DNMR spectra were run on Brucker® AM 400 instrument operating at 400 MHz for ^{1}H nuclei with each step 10 K increasing the temperature. No $SiMe_4$ was added; chemical shifts were measured against the solvent peak. All chemical shifts (δ values) are given throughout in ppm; all coupling patterns ($^{n}J_{H,H}$ values) are given throughout in Hz. TLC was performed by using aluminium sheets with silica gel 60 F_{254} (Merck®); flash column chromatography was conducted on Silica gel Si 60 (40–63 μm, Merck®). IR spectra were performed on a Perkin-Elmer® 16 PC FT-IR spectrometer. Only relevant absorptions are listed [throughout in cm^{-1}: weak (w), medium (m) or (s) strong]. Mass spectrum (MS) was recorded on an ATI-Unicam Automass® apparatus, fitted (or not) with a GC-mass coupling (high-resolution J&W column, 30 m, 0.25 mm ID, flow rate: 1.2 mL min^{-1}).

For the present preliminary communication, only the synthetic pathway **2b →3b→4b** is listed below:

2,4-Dichloro-6-(1,3-dihydroxy-2-methylprop-2-yl)-amino-*s*-triazine (2b): (40 %) white crystalline powder; m.p.=141.0-142.5 °C (flash column chromatography, eluent toluene : *i*-Pr-OH 4:1 v/v); [Found: C, 33.11; H, 4.25; N, 21.89. $C_7H_{10}N_4Cl_2O_2$ requires C, 33.22; H, 3.98; N, 22.13 %]; IR (ν_{max}, KBr) 3351 (s), 3220 (s), 2894 (s), 1702 (m), 1604 (s), 1563 (s), 1517 (s), 1333 (s), 1161 (s), 1066 (m), 1019 (s), 950 (w), 856 (m), 795 (w) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6, 293 K): 8.39 (1 H, s, N*H*), 4.84 (2 H, bs, O*H*), 3.62 (2 H, d, ^{2}J=10.9 Hz, CH_2), 3.55 (2 H, d, ^{2}J =10.9 Hz, CH_2), 1.26 (3 H, s, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6, 293 K): 168.8 (1 C, C-Cl), 168.3 (1 C, C-Cl), 165.2 (1 C, C-N), 62.5 (2 C, C-OH), 60.4 (1 C, C-q), 18.4 (1 C, CH_3); MS (CI, 200 eV); m/z (rel. int. %): 253 (100) [M^+], 219 (20), 117 (15), 99 (10).

2-Chloro-4,6-bis(1,3-dihydroxy-2-methylprop-2-yl)-amino-*s*-triazine (3b): (94 %) white crystalline powder; m.p.=169.0-170.3 °C (Et_2O); [Found: C, 40.96; H, 6.55; N, 21.69. $C_{11}H_{20}N_5ClO_4$ requires C, 41.07; H, 6.27; N, 21.77 %]; IR (ν_{max}, KBr) 3269 (s), 3103 (s), 2983 (s), 1625 (m), 1555 (s), 1391 (s), 1205 (s), 1161 (s), 1075 (s), 1041 (s), 959 (w), 802 (m), 737 (w) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6, 293 K): 6.78 (2 H, s, N$H_{s\text{-}s}$), 6.75 (1 H, s, N$H_{s\text{-}a}$), 6.66 (1 H, s, N$H_{s\text{-}a}$), 6.41 (2 H, s, N$H_{a\text{-}a}$), 5.20 (4 H, bs, O$H_{a\text{-}a}$), 4.82 (2 H, bs, O$H_{s\text{-}a}$), 4.65 (6 H, bs, 2 × O$H_{s\text{-}a}$, 4 × O$H_{s\text{-}s}$), 3.55 (24 H, m, C$H_{2s\text{-}s,\ s\text{-}a,\ a\text{-}a}$), 1.24 and 1.22 (18 H, s, C$H_{3s\text{-}s,\ s\text{-}a,\ a\text{-}a}$); ^{13}C NMR (75 MHz, DMSO-d_6, 293 K): 167.2 (3 C, C-Cl), 165.3, 165.0 and 164.6 (6 C, C-N), 63.8, 63.4 and 63.1 (12 C, C-OH), 58.7 and 58.5 (6 C, C-q), 18.7 (6 C, CH_3); MS (CI, 200 eV); m/z (rel. int. %): 322 (100) [M^+], 288 (10), 88 (5).

1,4-Bis[4,6-bis(1,3-dihydroxy-2-methylprop-2-yl)-amino-*s*-triazin-2-yl]-pipe-razine (4b): (23 %) white crystalline powder; m.p.=245-246 °C (flash column chromatography, eluent $CHCl_3$: MeOH 2.5:1.0 v/v); [Found: C, 47.88; H, 6.99; N, 25.50. $C_{26}H_{48}N_{12}O_8$

requires C, 47.55; H, 7.37; N, 25.59 %]. IR (ν_{max}, KBr) 3404 (s), 3329 (s), 2935 (s), 2854 (s), 1586 (m), 1543 (s), 1390 (m), 1354 (m), 1262 (m), 1185 (w), 1049 (s), 1016 (m), 983 (w), 806 (m) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6, 293 K): 5.66 (4 H, bs, N*H*), 4.87 (8 H, bs, O*H*), 3.64-3.47 (24 H, m, CH_2), 1.25 (12 H, s, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6, 293 K): 165.5 (2 C, C-N), 165.3, 164.3 (4 C, C-N), 63.4, (8 C, C-OH), 52.0 (4 C, C-q), 19.2 (4 C, CH_3); ^{1}H NMR (400 MHz, DMSO-d_6, 353 K): 5.53 (4 H, s, N*H*), 4.68 (8 H, bs, O*H*), 3.67 (8 H, s, CH_2 piperazine), 3.62 (8 H, d, ^{2}J=10.8 Hz, CH_2), 3.52 (8 H, d, ^{2}J=10.4 Hz, CH_2), 1.28 (12 H, s, CH_3); MS (FAB^+); m/z (rel. int. %): 657 [M^+] (22), 442 (100), 286 (80), 223 (60).

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