FIRST SYNTHESIS, ROTAMERISM AND HERBICIDAL EVALUATION OF SUBSTITUTED *s*-TRIAZINES WITH SERINOLIC FRAGMENT

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

Introduction

The chemistry of highly elaborated *N*-substituted triamino-*s*-triazines (*melamine*) 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 melamine, bearing a serinolic fragment.

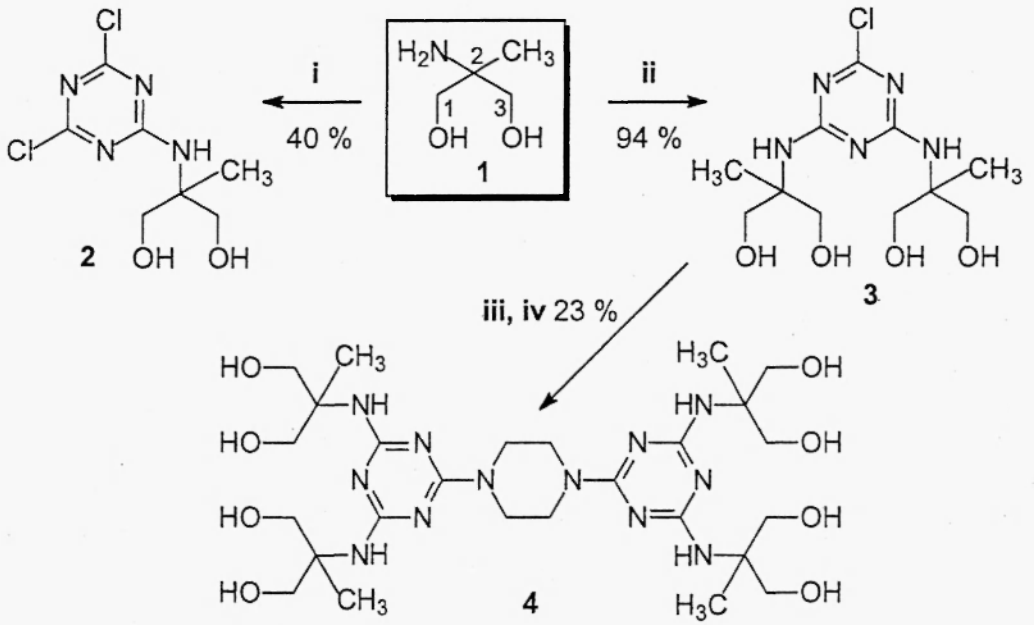
Results and Discussions

1. Synthesis

The compounds under study were prepared following the synthetic pathway depicted in **Scheme-1**. It started from the commercially available serinol **1** 2-amino-2-methyl-1,3-propanediol. Since the "dimeric" melamines **4** was the target compound, a convergent synthetic strategy was straightforward.

i) The *first nucleophilic replacement of chorine in cyanuryl chloride* yielded the compound **2**. The initial results indicated this synthesis to be not quite of routine since **2** already required isolation by flash column chromatography. Indeed, in the crude reaction mixture, the TLC monitoring revealed, besides the unreacted starting material, some traces of the disubstituted product **3** 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 product on silica gel. However, our work up is only apparently a "drawback": this behaviour is already very well documented as useful methodology to access silica gel HPLC chiral *s*-

triazines selectors for enantiomeric separation (15). Accordingly, our yield was calculated as isolated amounts after flash column chromatography.



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

Scheme-1

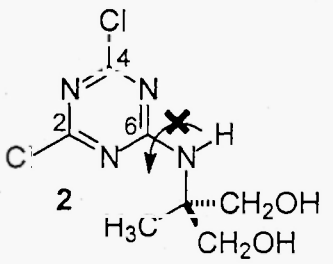
ii) Hence, the *second nucleophilic substitution of chlorine* was performed starting directly from **1** in a one pot process. This option appeared correct, as shown by the yield obtained in the case of compound **3** which was isolated by simple crystallisation.

iii, iv) The *last s-triazine chlorine* was replaced by using piperazine as nucleophile to give the compounds **4**. At this stage, we readily concluded that the hygroscopic piperazine should be preliminarily converted into its anhydrous hydrochloride. Next, upon treatment with the triazine **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 piperazine as side-products. However, the TLC monitoring of the reaction indicated unpredictable decomposition. The yield refers again to the isolated product after flash column chromatography when the previously mentioned retentions on silica gel were encountered.

2. Stereochemistry and Rotameric Behaviour

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

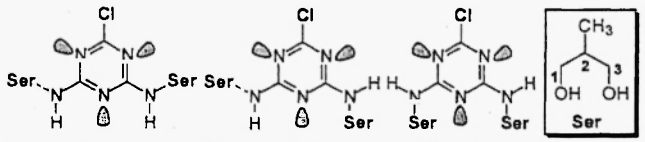
In the case of compound **2** (**Scheme-1, Scheme-2**), the ^{1}H NMR spectrum performed at room temperature located the N*H* proton as the most deshielded: 8.39 ppm. In the ^{13}C NMR spectrum, the



Scheme-2

triazinic carbons C-2, -4 were found diastereotopic, as two different signals at 168.8 and 168.3 ppm, in agreement with a hindered rotation about C-6-N(serinol) bond. By increasing the temperature (up to 80 °C in DMSO-d_6), the ^{13}C NMR spectra reached no coalescence of the discussed signals, but some decomposition of the investigated compound was observed.

The same hindered rotation was twice exhibited by the triazine **3** to proof the combined effect of the two amino groups (+M) with the (-I) effect of the remaining chlorine atom. If so, its rotation barrier $\Delta G^{\neq}$ should be higher than that 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 **3** to exist as three diastereomers (blocked rotamers), discriminated by the stereochemical descriptors previously proposed by Ghiviriga (7): *syn* (*s*) and *anti* (*a*) (the **Ser**inol group and the C-2 chlorine atom as references, **Scheme-3**)



3 *syn-syn* **3** *syn-anti* **3** *anti-anti*

Scheme-3

Indeed, at room temperature, the analysis of the ^1H NMR spectra of **3** disclosed the presence of all three stereoisomers (**Table-1**).

Table-1: Relevant ^1H NMR data and contribution of the blocked rotamers of the compound **3** (DMSO-d_6, 293 K)

Rotamers (averaged %) according to N*H* signals			**δ_{NH} (ppm)**		
3 (*s-s*)	**3** (*s-a*)	**3** (*a-a*)	(*s-s*)	(*s-a*)	(*a-a*)
49[a]	48	3	6.78	6.75	6.41
50[b]	45	5		6.66	

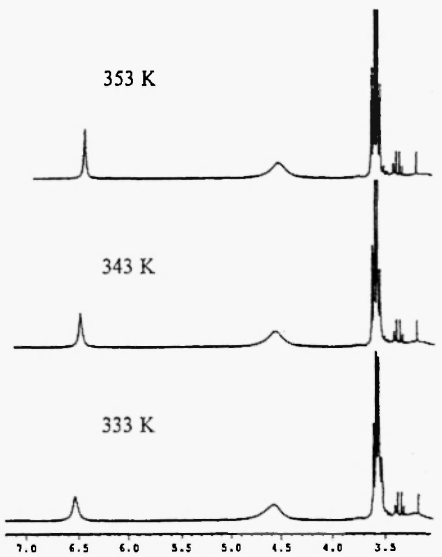
[a]standard sample; [b]dilution as 1/3

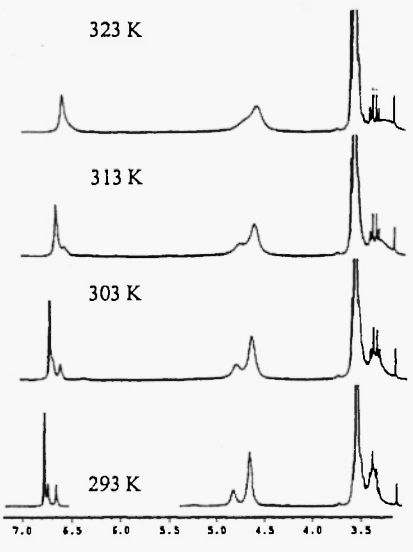
The assignments were based on the well separated peaks displayed by the N*H* protons as distinct singlets (**Figure-1**, 293 K). The stereochemistry as (*s-s*), (*s-a* = *a-s*) and (*a-a*) was established starting from the rotamer **3** (*a-s*) since, besides twice statistically favoured, it revealed unambiguously two different with equal intensity environments for the N*H* protons. Therefore, in connection to this observed stereochemistry, we considered as pertinent the following two factors:

a) The steric hindrance between the serinolic groups related to C-1 substitution (**Scheme-3, Table11**).

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*. It must be observed that in rotamers of





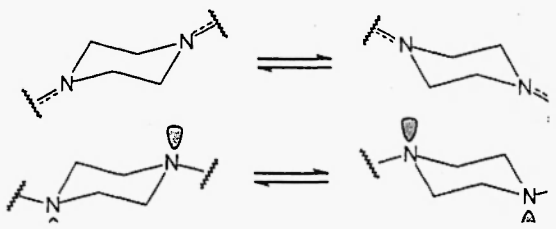
Details of the ^1H DNMR spectrum of the compound 3 (400 MHz, DMSO-d_6; from downfield to upfield: N*H*, O*H*, CH_2OH

Figure-1

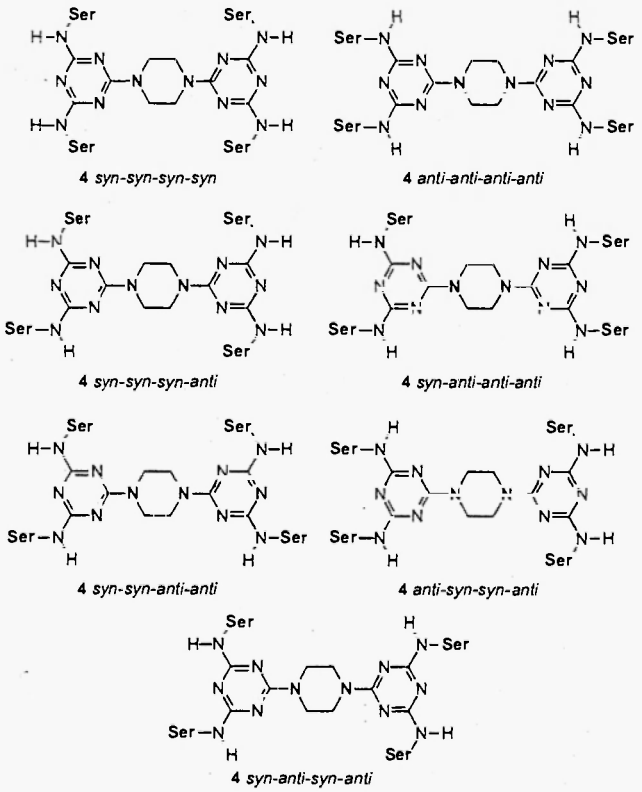
type **3** (*a-a*), the resonance of the protons N*H* was found upfield, in agreement with the weakest character of double bond of the linkage C^{sp2}(*s*-triazine)-N<(serinol). This assignment should be plausible since the steric hindrance conflicts with the coplanarity mandatory to the Ser-NH-C(N)=N- sequence (**Scheme-3**).

The ^{1}H DNMR spectrum of the compound **3** run progressively at higher temperatures (**Figure-1**, 293 → 353 K) revealed the free rotation of the serinolic fragments up to 333 K. The N*H* resonances were shifted upfield, from 6.78-6.41 ppm to an unique broad singlet located at 6.43 ppm. Upon heating, the unsolvable multiplet of the diastereotopic methylene protons, at 293 K, became gradually the typical AX system at 3.61 and 3.54 ppm respectively (^2J=10.8 Hz).

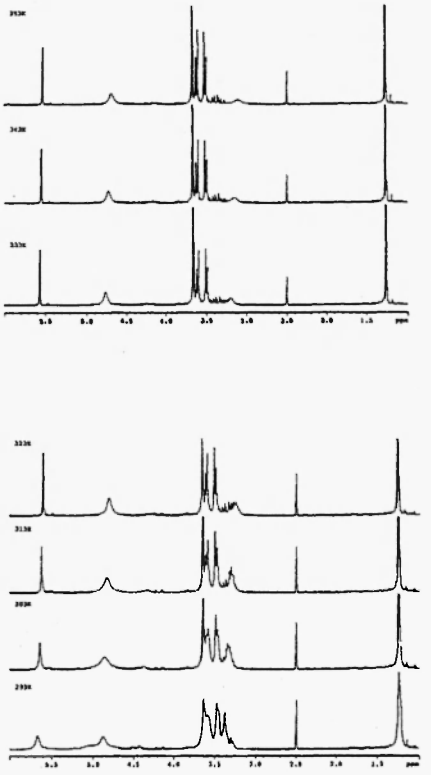
Based on literature data (8,9), we expected that the "dimeric" melamine **4** possessing three donating (+M) ligands be a free rotating structure ($\Delta G^{\neq}$=59.3±1 kJ/mol in the range 315-325 K) with a mobile piperazine ring as chair-chair ring **I** and / or double pyramidal inversion **II** (**Scheme-4**). On the other hand, the same stereochemical analysis as above (**Scheme-3**) provided this time seven rotamers (**Scheme-5**, the serinol and piperazine groups are the references; *syn* and *anti* descriptors are cited clockwise).



Scheme-4



Scheme-5



^{1}H DNMR of the compound 4 (400 MHz, DMSO-d_6) at 353 K; from downfiled to upfield, δ (ppm), *J* (Hz): 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, ^2J=10.6 Hz, CH_2OH), 3.52 (8 H, d, ^2J=10.6 Hz, CH_2OH), 1.28 (12 H, s, CH_3).

Figure-2

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-2**, 293 K): it was hazardous to ascertain whether the signals belong to a blocked multicomponent mixture of rotamers (overlapped peaks ?) 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.

In contrast, the ^{1}H NMR spectra recorded by progressive increasing the temperature (**Figure-2**) permitted to observe the general coalescence at about 313 K and a single mediated structure at 353 K. The broad singlet of N*H* protons was shifted upfield, from 5.66 ppm (293 K) to a clear sharp signal at 5.53 ppm (353 K) meanwhile the peaks of the hydroxyl protons, dispersed at room temperature between 5.25-4.40 ppm, displayed the typical broad singlet at 4.68 ppm (353 K).

3. Herbicidal evaluation

Following literature methodology (16), the herbicidal activity of the compound **3** was evaluated by using seeds of *Cucumis sativus* and *Raphanus sativus* and compared with that of Atrazine®. Upon treatment with **3** and Atrazine®, the mean (±SD) values on the inhibition of germination and 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 compound **3** as compared to those of Atrazine®

Tested species	Conc.	Germination		Root length	
		3	**Atrazine®**	**3**	**Atrazine®**
Cucumis sativus	0.50 mM	59 ± 5.4	62 ± 4.2	68 ± 4.4	69 ± 6.5
	0.75 mM	86 ± 2.7	89 ± 2.5	88 ± 3.9	91 ± 3.3
	1.00 mM	100 + 0.0	100 ± 0.0	-	-
Raphanus Sativus	0.50 mM	67 ± 4.9	71 ± 5.6	73 ± 6.7	74 ± 6.2
	0.75 mM	88 ± 3.3	90 ± 2.4	91 ± 5.2	93 ± 5.8
	1.00 mM	100 ± 0.0	100 + 0.0	-	-

As indicated by the introductory data, the new compound **3** exhibited comparable inhibition effect (including complete) with respect to the structurally related Atrazine®.

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, the synthetic pathway **2** →**3**→**4** is listed below:

2,4-Dichloro-6-(1,3-dihydroxy-2-methylprop-2-yl)-amino-*s*-triazine (2): (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}□ □□R (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-Chioro-4,6-bis(1,3-dihydroxy-2-methylprop-2-yl)-amino-*s*-triazine (3): (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}□ □□R (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$H_{s\text{-}o}$, 4 × O$H_{s\text{-}s}$), 3.55 (24 H, m, $CH_{2\,s\text{-}s,\,s\text{-}a,\,a\text{-}a}$), 1.24 and 1.22 (18 H, s, $CH_{3\,s\text{-}s,\,s\text{-}a,\,a\text{-}a}$); ^{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]-piperazine (4): (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}□ □□R (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}□ □□R (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, ^2J=10.6 Hz, CH_2), 3.52 (8 H, d, ^2J=10.6 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).

Conclusions

As shown by our preliminary results, 2-amino-2-methyl-propane-1,3-diol reacted with cyanuryl chloride to afford substituted *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, the corresponding chloro-*s*-triazines with a serinolic NH group and serinol based melamine are blocked rotamers due to the partial double bond character of the C^{sp2}(*s*-triazine)-N(serinol) site. The herbicidal activity in this class of *s*-triazines was tested and revealed comparable with Atrazine®. The full report of our findings is under consideration for the near future.

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