STUDIA UBB CHEMIA, LXI, 4, 2016 (p. 69 - 84)
(RECOMMENDED CITATION)

4-AMINOPIPERIDINE BASED NEW AMINO-*s*-TRIAZINES AS POTENTIAL DENDRITIC BUILIDING-BLOCKS

ANA-MARIA ŢICALĂ[a], DAN PORUMB[a], CARMEN SĂCĂLIȘ[a]* AND MIRCEA DARABANTU[a]*

ABSTRACT. Starting from commercial 4-aminopiperidine, three new amino-*s*-triazines, seen as potential dendritic building-blocks, were synthesised by chemoselective S_N2-Ar amination of cyanuric chloride. A three steps synthetic sequence, (i) Boc-chemoselective *N*-protection of 4-aminopiperidine → (ii) amination of cyanuric chloride → (iii) deprotection, yielded a novel potential dendritic central unit, 2,4,6-tris[(piperidin-4-yl)amino]-*s*-triazine.

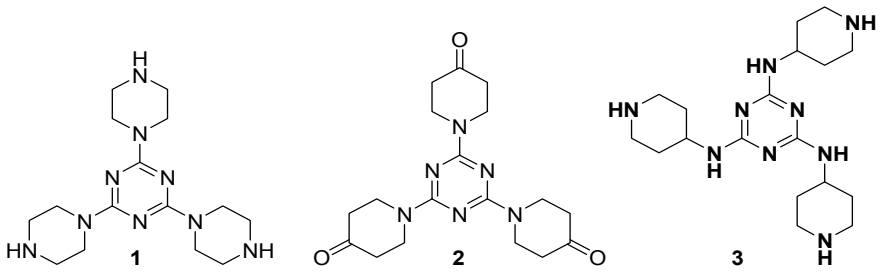
Keywords: *4-aminopiperidine, S_N2-Ar amination, dendritic cores, melamines*

INTRODUCTION

N,N'N"-substituted melamines are well-known building-blocks in the construction of dendritic systems [1] as early as 2000 [1a] when Simanek and co-workers reported the access to the first dendrimer, encompassing *s*-triazine rings as branch-cells and cores, obtained by iterative chemoselective S_N2-Ar amination of cyanuric chloride. During elaboration of these arborescent architectures, the need of *meta*-trivalent and C_3 symmetric central building-blocks, such as 2,4,6-tris(piperazin-1-yl)-*s*-triazine **1** (Scheme 1) was revealed [2]. Melamine **1** can be easily prepared by amination of cyanuric chloride with commercial *N*-(*tert*-butoxy- carbonyl)piperazine, followed by the removal of Boc protecting groups [2a].

In continuation of our efforts in a similar direction, we previously reported the synthesis and stereodynamic behaviour of a new potential dendritic building-block, 2,4,6-tris(4-oxopiperidin-1-yl)-*s*-triazine **2** (Scheme 1) [3]. Compound **2** is readily available by amination in of cyanuric chloride with the use of the ethylene ketal of 4-piperidone and final acidolysis of the 1,3-dioxolane rings.

[a] *Babeş-Bolyai University, Faculty of Chemistry and Chemical Engineering, Department of Chemistry 11 Arany Jànos st., RO-400028, Cluj-Napoca, Romania*
* *Corresponding authors: cbatiu@chem.ubbcluj.ro, darab@chem.ubbcluj.ro*



Scheme 1

Subsequent to the above findings, the aim of the present work is to account on the first synthesis of an identically *N,N',N"*-substituted melamine built from 4-aminopiperidine through its primary amino group, namely 2,4,6-tris[(piperidin-4-yl)amino]-*s*-triazine **3** (Scheme 1), together with that of its main precursors. Last but not least, it is worth mentioning that, recently, series of 4-aminopiperidine-linked amino-*s*-triazines were described as well and evaluated for *in vitro* anti-HIV activity with very promising results [4].

RESULTS AND DISCUSSION

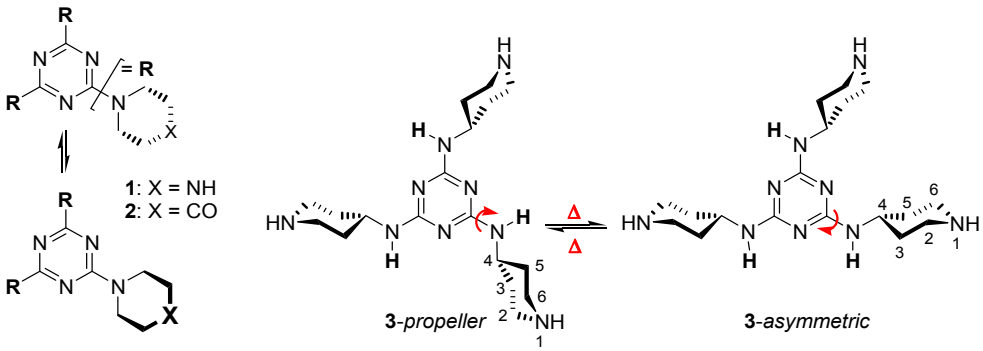
1. Structural premises

Previously reported *N,N',N"*-substituted melamines **1** and **2** are statistically C_3-symmetric owing to the chair ⇆ chair flipping of piperazine or 4-piperidone rings (Scheme 2). On the other hand, due to the p(N-exocyclic)→π(*s*-triazine) extended conjugation, the well-documented partial double bond character of the C(*s*-triazine)-N(exocyclic) linkages [5] promotes, at room temperature, hindered rotation about these connexions [3b, 3c]. In terms of DNMR, this feature is defined as "slow exchange status between (un)equally populated sites" [6], i.e., in the case of melamines **1** and **2**, a slow topomerisation. Upon heating up to 80-90 °C, these C_3-symmetric melamines reach a fast freely rotating status about all bonds C(*s*-triazine)-N(exocyclic) (single mediated structures) in a rapid topomerisation [3b].

In the target melamine **3** (Scheme 2), since the anchorage of the 4-aminopiperidine units to the *s*-triazine ring is realised *via* the primary amino group, the abovementioned stereodynamism implies, in a topological idealized model, the existence of two interchangeable rotational diastereomers, **3**-*propeller* and **3**-*asymmetric* [5i] from which only the first one is C_3-symmetric. Conversely, in both rotamers, the piperidine rings should be anancomeric* due to the presence

* According to the definition from Ref. [6b] "Fixed in a single conformation either by geometric constraints or because of an overwhelmingly on-sided conformational equilibrium"

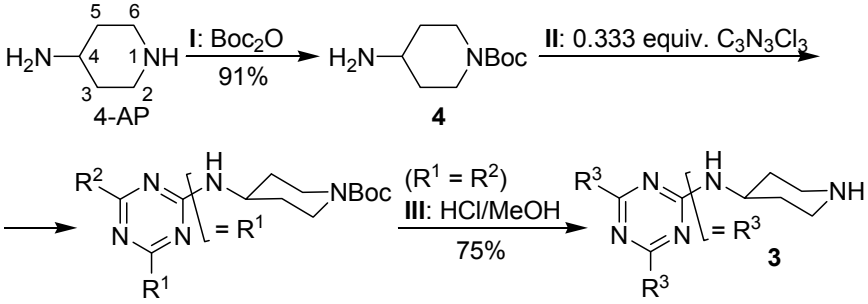
in position C-4-eq of a bulky (*s*-triazin-2, -4, -6-triyl)amino ligand. Finally, as a result of the same p(N-exocyclic)→π(*s*-triazine) extended delocalisation, pyramidal inversion and proton interchange should involve, primarily, the piperidine nitrogen.



Scheme 2

2. Synthesis

With the above premises in mind, we have obtained melamine **3** in three steps **I**-**III** (Scheme 3). Though 1-Boc-4-aminopiperidine **4** is commercial (CAS Number 87120-72-7, GC purity ≥ 96.5%) [7], we decided to prepare this compound by applying a patented [8] simple methodology (**I**). While the



5a (68%*): R^2 = Cl
5b (21%): $R^1 = R^2$

*Partial conversions of cyanuric chloride into the depicted compounds, based on the effective amounts of material isolated after column chromatography

Key

I: 1.020 equiv. Boc_2O, 1.005 equiv. TEA, H_2O : 1,4-dioxane (9:5 v/v) / 2-4 °C (1 h) / r.t. (12 h) / N_2
II: 0.333 equiv. cyanuric chloride, 0.333 equiv. K_2CO_3, 1,4-dioxane / r.t. (24 h) / reflux (88 h) / N_2
III: 20.328 equiv. HCl (aq. 6 N HCl), MeOH / 0-1 °C (70 min) / 0 °C (2 h) / r.t. (3 h) / 40 °C (15 h) / N_2 / aq. NaOH 10%, 0 °C, pH = 14

Scheme 3

synthetic protocol was reproducible, our work-up to isolate crude product **4** had to be different with respect to the cited literature. In our hands, the extraction of the organic material with ethyl acetate followed by concentration under mild conditions and predicted slow crystallisation [8], afforded a mixture of compounds with a GC-MS composition as 66.5% **4** (1-Boc-4-NH_2 derivative) and 33.5% an additionally *N*-acetylated analogue of **4**, 1-Boc-4-NH-Ac (transamidation product, not depicted in Scheme 3).

Replacement by us of ethyl acetate with chloroform provided crude compound **4** only (≥ 97% GC-MS purity).

Concerning the utility of this preliminary chemoselective *N*-protection step, we note that the previous use of 4-aminopiperidine in melamine dendritic chemistry, playing the role of linker, is already documented [1b, 9c]. However, this role refers to the free diamine only. Thus, by exploiting the higher basicity and nucleophilicity of the secondary amino group against the primary one, two distinct chloro-diamino-*s*-triazine dendrons can be attached to 4-aminopiperidine. This strategy was based on Simanek and co-workers' "relative reactivity maps" [9a, 9b, 9d, 9e] of several (aza)alicyclic (di)amines against cyanuric chloride. In the case of 4-aminopiperidine, one can approximate the pK_b of the primary amino-group as being comparable with that of isopropyl amine (3.37) and that of the secondary amino-group similar with that of piperidine itself (2.78) [10].

Furthermore (**II**), amination of cyanuric chloride with three molar equivalents of **4** afforded, constantly, the mixture of two compounds, chloro-diamino-s-triazine **5a** (major) and melamine **5b** (minor), separable by column chromatography. In spite of various conditions used (solvent: 1,4-dioxane, THF or toluene; proton scavenger: K_2CO_3 or DIPEA), neither global conversion of cyanuric chloride (~85%) nor chemoselectivity (**5a**:**5b** ~3:1) could be improved. One reason for these results consists of the conformational nature of our amino-nucleophile, a real rigid "back-bone" which did not allow an appropriate steric arrangement, mandatory to the S_N2-Ar process[♦] (see later discussion in Section 3). No similar examples were reported so far (including as well the case of simple but flipping cyclohexylamine [11] in reaction with cyanuric chloride [12]), except our previous data concerning other saturated six-membered and anancomeric amino-heterocycles, e.g. amino-1,3-dioxanes [13a-c] and 4,4'-bipiperidine [3c, 13d].

Final deprotection (**III**) of **5a** in a 6N HCl aq. / MeOH medium gave the expected *N*,*N*',*N*''-substituted melamine **3** (Scheme 3) with a good yield. In this purpose, we followed, with minor modifications, the previously published procedure of Simanek and co-workers [2a]. As other piperidine ring systems, earlier reported by us [3, 13c, 13d], melamine **3** required storage under inert atmosphere in order to avoid its carbonation.

♦ Indeed, the same total amination of cyanuric chloride performed with flipping 1-Boc-piperazine, provides the corresponding melamine in high yield (90-93%), during 20 h in refluxing THF [2a].

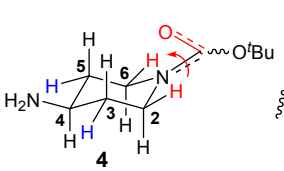
3. *Structural investigations based on (VT) ^{1}H-NMR*

The identity of all compounds under consideration was fully confirmed by routine analysis (see EXPERIMENTAL SECTION). In such doing, we were particularly interested in the moderate reactivity of our amino-nucleophile **4** supported by the experimental conditions, depicted in Scheme 3. Next, since (VT) NMR is, by far, the optimal option in order to investigate the specific stereodynamism of amino-*s*-triazines [3, 5, 9b, 13], we adopted as well this technique for the present discussion (Table 1).

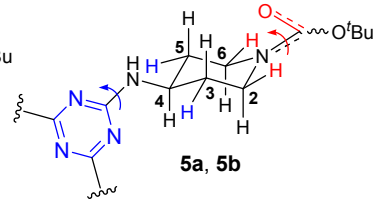
The (VT) ^{1}H-NMR data in are mandatory to several comments:

a) The anancomeric nature of compounds **4**, **5a**, **5b** and **3** was supported by important ^{1}H geminal anisochronies at piperidine positions C-2(6) and C-3(5), expressed as $\Delta\delta_H = \delta_{H\text{-}eq}\text{-}\delta_{H\text{-}ax}>0$ values. Regardless the NMR solvent ($CDCl_3$ or DMSO-d_6) and temperature (r.t. or 353 K), in compounds **4**, **5a**, and **5b** geminal anisochrony was much higher in positions C-2(6), α-located against the carbamate group (around 1 ppm!), than in positions C-3(5) (0.32-0.66 ppm) [14]. Upon heating at 353 K, no reached flexibility of the piperidine ring skeleton, as δ_H mediating $\delta_{H\text{-}eq} \leftrightarrows \delta_{H\text{-}ax}$ values, was observed.

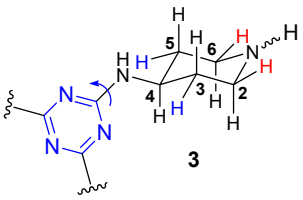
Table 1. Relevant (VT) ^{1}H-NMR δ_H values of compounds **4**, **5a**, **5b** and **3** on 400 MHz time scale



4



5a, **5b**



3

No.	Solvent	δ_H (ppm)[a]						
		T (K)	H-3, -5 (ax)	H-3, -5 (eq)	H-2, -6 (ax)	H-2, -6 (eq)	H-4 (ax)	NH[b]
4	$CDCl_3$	298	1.29	1.75	1.89	2.78	2.72	3.98
	DMSO-d_6	298	1.22	1.66	2.72	3.82	3.04	3.39
	DMSO-d_6	353	1.30	1.69	2.82	3.81	2.50	3.43
5a	$CDCl_3$	298	1.27	1.93	2.88	4.00	3.88	5.31 5.53 5.65 6.11
	DMSO-d_6	298	1.30	1.76	2.82	3.87	3.87	7.45 7.77 7.79 7.91
	DMSO-d_6	353	1.40	1.80	2.87	3.90	3.87	7.44 7.55

No.	Solvent	δ_H (ppm)[a]						
		T (K)	H-3, -5 (ax)	H-3, -5 (eq)	H-2, -6 (ax)	H-2, -6 (eq)	H-4 (ax)	NH[b]
5b	$CDCl_3$	298	1.32	1.93	2.86	3.98	3.88	4.84 4.95
	DMSO-d_6	298	1.30	1.71	2.75	3.91	3.88	6.27 6.41 6.51
	DMSO-d_6	353	1.36	1.80	2.82	3.91		6.70 6.13
3[c]	D_2O+DCl	298	-0.31	0.02	0.91 1.02	1.25	1.85 2.15	-

[a] Labelling of topological equivalent positions as (‘) and (“) was omitted for reasons of simplicity.
[b] When multiple δ_H values are collected, they refer to detection of different stereoisomeric species issued from the rotational diastereomerism about C(*s*-triazine)-N(exocyclic) partial double bond (see discussion).
[c] As protonated form; the D_2O resonance (at 4.79 ppm) was taken as reference signal.

Particularly, the ^{1}H-NMR spectra of our amino-nucleophile **4** at room temperature not only that fully confirmed all above but also allowed the assignment, based on the stereospecific homocoupling ($^nJ_{H,H}$) patterns in the sequence C-2(6)-C-3(5)-C-4, of the equatorial position of the amino-group (Figure 1).

b) The presence of the carbamate group (>N-CO-O^{t}Bu), with a well-documented magnetic anisotropy [15], had two major consequences:

(i) the occurrence, at room temperature, of a slow rotational motion about the partial double-bond in the amide sequence >N-(C=O)- $\leftrightarrow$ >N$^+$=(C-O$^-$)-, unable, however, to induce any chemical non-equivalence between proximal protons H-2-eq vs. H-6-eq or carbons C-2 vs.C-6. That is, the electronic effect of the O^{t}Bu fragment, acting as EDG (or ERG), was concurrent against the effective existence of the above partial-double bond.

(ii) the carbamate group was responsible for the observed geminal $\Delta\delta_H$ anisochrony, and, in tandem with the *s*-triazinylamino unit equatorial location (compounds **5a** and **5b**), determined the rigidity of the piperidine rings.

c) At room temperature, compound **5a** displayed an expected three terms frozen rotational equilibrium of type *a*(*nti*) $\leftrightarrows$ *s*(*yn*) about the partial double bonds C(*s*-triazine)-N(exocyclic) (Chart 1). Discrimination between rotameric species was made founded on the different proximity of the best separated (“indicative”) protons, NH, with respect to the dipole moment of the bond C-2(*s*-triazine)-Cl, i.e. this link was considered a strong deshielding factor (“dipole rule” [3, 13, 16], Table 1). The rotameric occurrence was non statistic♥ but dependent on the ability of the solvent to act as a hydrogen bond acceptor [5i],

♥ (%)**5a** (*a*-*a*) = **5a** (*s*-*s*) = 25, (%)**5a** (*a*-*s*) = 50 [the (*a*-*s*) arrangement is, statistically, twice favored]

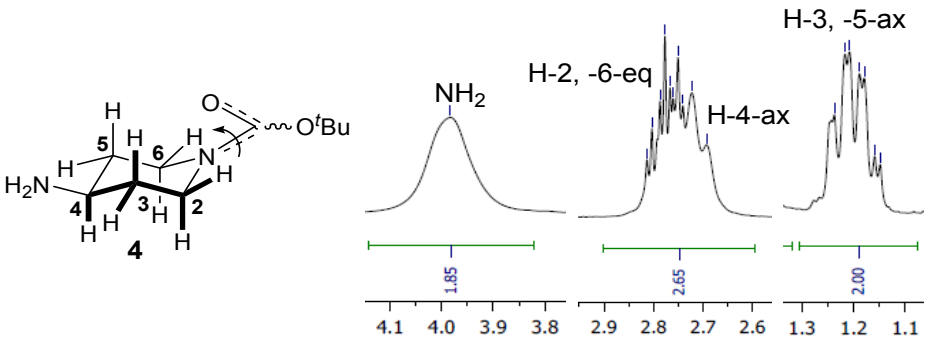
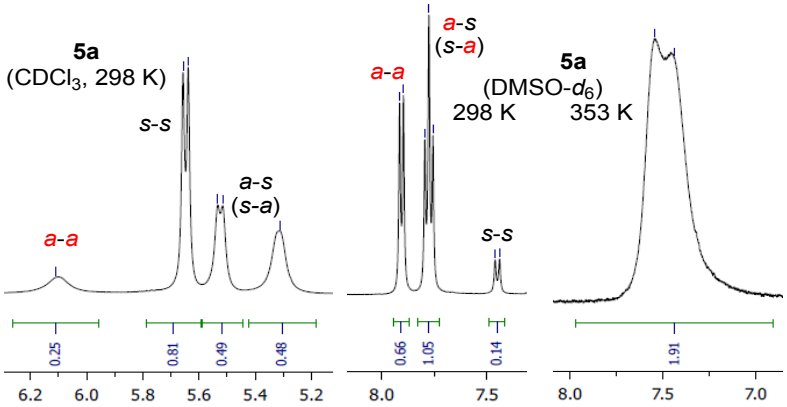
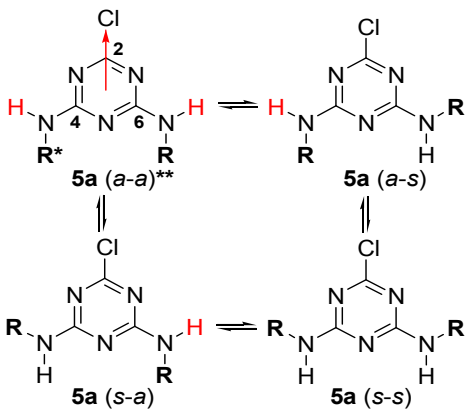


Figure 1. Details from the ^{1}H-NMR spectrum (400 MHz, $CDCl_3$, 298 K) of compound **4** (crude product): 3.98 (2H, br s, NH_2), 2.78 (2H, ddd, $^{2}J_{gem}$~8.9 Hz, $^{3}J_{cis\text{-}eq\text{-}ax}$~$^{3}J_{trans\text{-}eq\text{-}eq}$=4.3 Hz, H-2, -6-eq), 2.72 (1H, br dd app. br t, $^{3}J_{trans\text{-}ax\text{-}ax}$=11.6 Hz, H-4-ax), 1.19 (2H, dddd, $^{2}J_{gem}$~$^{3}J_{trans\text{-}ax\text{-}ax}$~$^{3}J_{trans\text{-}ax\text{-}ax}$=11.7 Hz, $^{3}J_{cis\text{-}ax\text{-}eq}$=3.8 Hz, H-3, -5-ax) ppm.





	Occurrence (%)		
Rotamer	$CDCl_3$	DMSO-d_6	TG (ppb/K)[a]
(*a*-*a*)	12	36	-7.45
(*a*-*s*)	48	57	-5.27, -4.91
(*s*-*s*)	40	7	-0.91

[a]Calculated as $[(\delta_H^{298\ K} - \delta_H^{353\ K})/(298\ K - 353\ K)]\times10^3$<0 ($\delta_H$ values taken from Table 1)

*1-*tert*-butoxycarbonylpiperidin-4-yl unit
Chlorine atom and the *N*-ligand **R as references for descriptors *a*(*nti*) and *s*(*yn*) [3, 5i, 13]

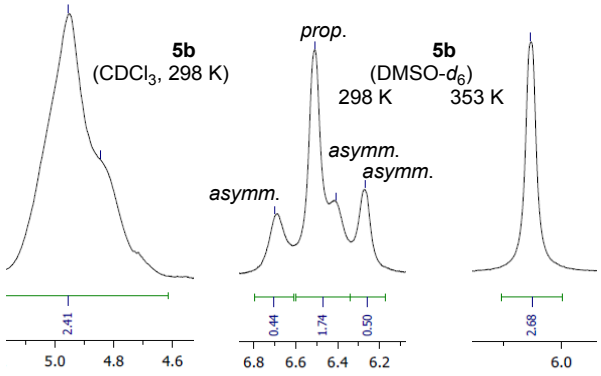
Chart 1

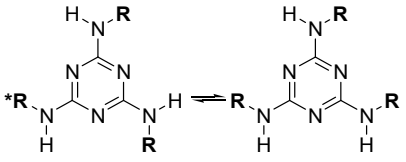
DMSO (ε = 46.7) against chloroform (ε = 4.81). In order to better evaluate this behaviour, we used Temperature Gradients (TGs) of the "indicative" NH protons. Though the use of this parameter is suitable for amide –N(H)–C(=O)– ↔ –N^+(H)=C(–O^-)– protons of peptides and proteins [17] in D_2O, it can also be applied to amino-*s*-triazines, –N(H)–C(=N–)– ↔ –N^+(H)=C(–N^-–)– as recommended by Simanek and Moreno [9c]. Following this extrapolation, if TG values of "amidine-like" protons in amino-*s*-triazines are more negative than -4 ppb/K in strong hydrogen bond acceptor solvents, such as DMSO-d_6 [5i], the NH groups are exposed to the solvent rather than forming intramolecular hydrogen bonds. Conversely, a TG value less negative than -4 ppb/K discloses that the NH group preferentially forms intramolecular hydrogen bonds at room temperature. As one can see (Chart 1), besides the normal aptitude for binding of the carbamate units of **5a**, the contribution to solvation of NH groups, Me_2S=O…H…N<, was also significant. Indeed, 95% of the rotameric species of **5a** had TGs more negative than -4 ppb/K in conjunction with the adopted *anti-anti* and *anti-syn* arrangements of the *N*-Boc piperidine arms. Upon heating at 353 K, compound **5a** could be near totally deblocked (Chart 1) with respect to the connexions C(*s*-triazine)-N(exocyclic), however not, as already mentioned, concerning the rigidity of the piperidine ring (Table 1).

d) Similar concepts applied in the case of melamine **5b** (Chart 2). At room temperature, both the expected rotational diastereomers, **5b**-*propeller* (C_3-symmetric) and **5b**-*asymmetric* could be ^{1}H detected in a ratio completely different than statistics (25% *propeller* against 75% *asymmetric*) in DMSO-d_6 only. Except for one arm of the *asymmetric* rotamer (TG -2.55 ppb/K, Chart 2), all other arrangements exhibited TGs (much) less negative than -4 ppb/K. Upon heating, melamine **5b** reached the almost free rotational status in the region C(*s*-triazine)-N (exocyclic).

CONCLUSIONS

Starting from 4-aminopiperidine, we have developed the synthesis of a new *N,N',N"*-substituted melamine possessing piperidin-4-yl units as *N*-ligands, together with its foremost precursors. Indeed, the 1-Boc-piperidin-4-yl unit *N*,*N*'-substituting a chloro-diamino-*s*-triazine, can be seen as an useful building-block in dendritic melamines construction. The synthetic feasibility of these compounds is crucially influenced, mainly in the third amination step, by the rigid conformation and significant solvation of the reaction partners, namely 1-Boc-4-NH_2 piperidine and *C*-substituted *s*-triazines with 1-Boc-piperidin-4-ylamino units. The inherent occurrence of the rotational diastereomerism about the partial double bonds C(*s*-triazine)-N(exocyclic) revealed a non-statistic content of frozen or slowly exchangeable rotamers, hence a new opening route towards structural diversity.





	Occurrence (%)		
Rotamer	$CDCl_3$	DMSO-d_6	TG (ppb/K)[a]
propeller	-	47	-6.90
asymmetric	-	53	-2.55, -5.10, -10.36

[a]Calculated as $[(\delta_H^{298\ K} - \delta_H^{353\ K})/(298\ K - 353\ K)]\times 10^3 < 0$ (δ_H values taken from Table 1)

*1-*tert*-butoxycarbonylpiperidin-4-yl unit
**Terminology adopted from Ref. [5i]

Chart 2

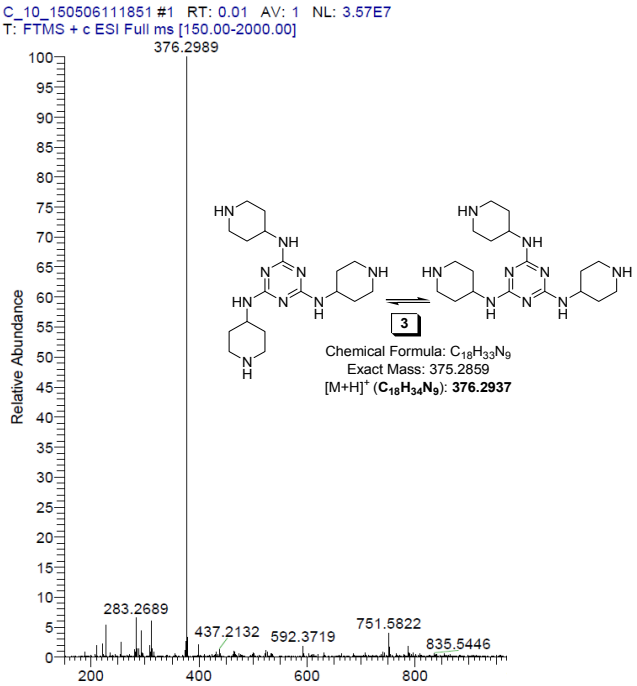


Figure 2. HRMS spectrum (ESI) of compound **3**

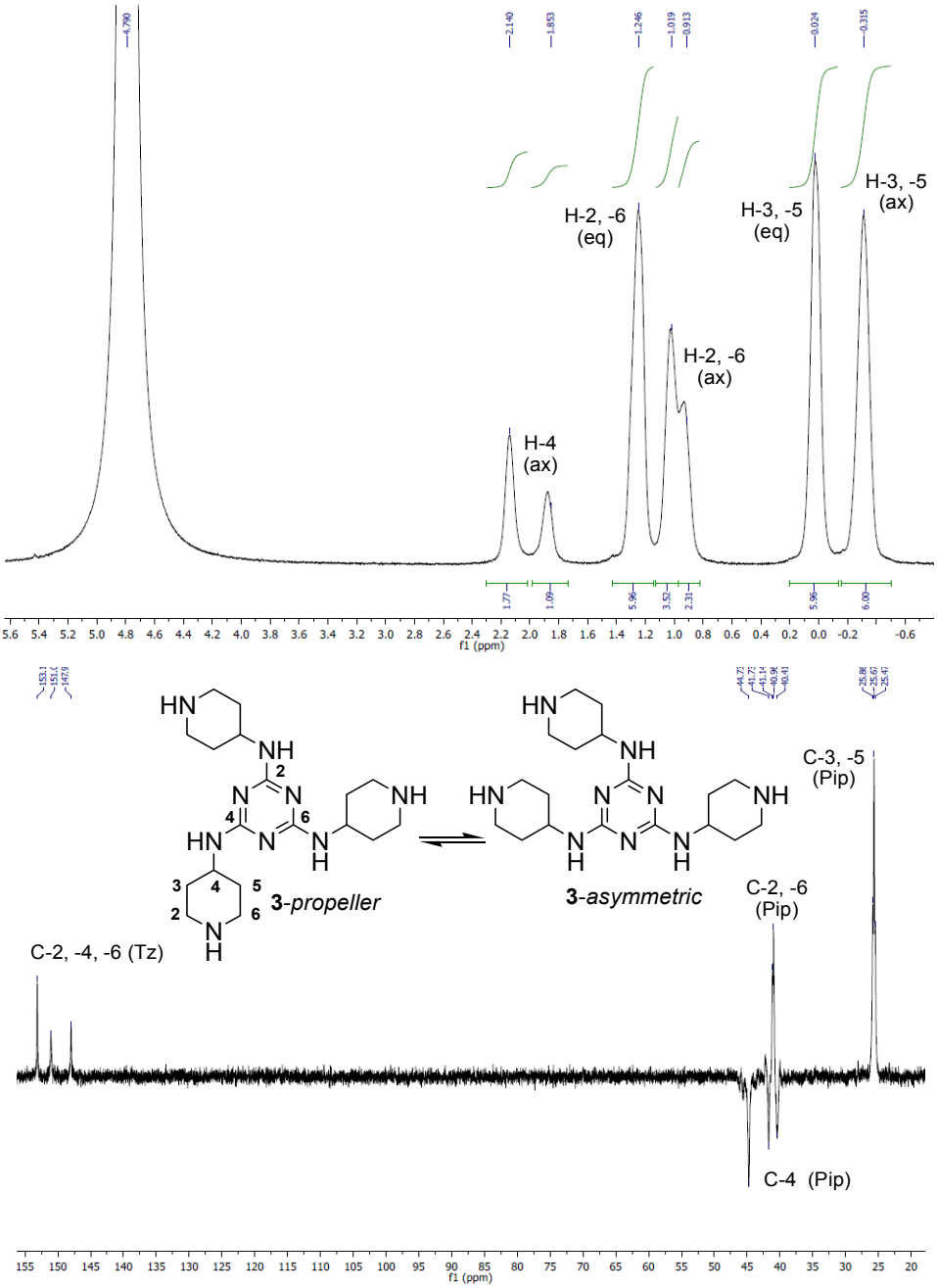


Figure 3. ^{1}H-and ^{13}C-J_{mod}-NMR spectra (400 MHz, D_2O+DCl, pH = 0.5-1, 298 K) of compound **3**. The protonated forms of **3** should be deduced implicitly.

EXPERIMENTAL SECTION

General. All reagents and solvents were of commercial quality and required no purification prior to use. Melting points were carried out on an ELECTROTHERMAL® instrument and were not corrected. TLC monitoring was performed by using aluminium sheets with silica gel 60 F_{254} (Merck®) (visualisation in UV at λ=254 nm except compound **4**, in I_2 bath). Column chromatography was conducted on Silica gel Si 60 (0.063-0.200 mm, Merck®). IR spectra were recorded on a JASCO® FT-IR 6100 Spectrometer. Only relevant absorption maxima are listed, throughout, in cm^{-1}: s (strong), m (medium) and w (weak). NMR spectra were recorded on Bruker® AM 400 instruments operating at 400 and 100 MHz for ^1H and ^{13}C nuclei, respectively. All chemical shifts (δ values) are given in parts per million (ppm); all homocoupling patterns ($^nJ_{H,H}$ values) are given in Hertz. No TMS was added, chemical shifts were measured against the solvent residual peak. In the NMR descriptions, some specific abbreviations were used: "br s" (broad singlet), "br d" (broad doublet), "br m" (broad multiplet), "br dd app. br t" (broad doublet of doublets appearance as broad triplet), Pip (Piperidine) and Tz (*s*-Triazine). GC-MS spectra were recorded on a Gas Chromatograph with Mass Spectrometer Shimadzu® QP 2010 PLUS. Mass spectra were carried out on a LTQ ORBITRAP® XL (Thermo Scientific) instrument which was externally calibrated using the manufacturer's ESI(+) calibration mix. The samples were introduced into the spectrometer by direct infusion.

Preparation of 4-amino-1-tert-butoxycarbonylpiperidine **4** (crude product). Under inert atmosphere, to a cooled (0 °C) dioxane / water (5 : 9 v/v) solution, 4-aminopiperidine (1.526 g, 1.60 mL, 14.93 mmol) was added with vigorous stirring at 0 °C. A cooled (0 °C) solution obtained by dissolving di-*tert*-butyldicarbonate (Boc_2O) (3.431 g, 15.24 mmol) and trimethylamine (TEA) (1.504 g, 2.06 mL, 15.01 mmol) in 1,4-dioxane (4 mL) was then added dropwise over 1 h at max. 2-4 °C. Next, the reaction mixture was let to reach the room temperature and left to stir for additional 12 h. 1,4-Dioxane was gently removed under reduced pressure and the remaining aqueous phase was extracted with chloroform (6 x 30 mL). The combined organic solution was dried over Na_2SO_4, filtered off and then evaporated in vacuum to dryness. The resulted oily residue slowly solidified in time (48-72 h) to provide crude compound **4** (2.721 g, with 97% GC purity, 91% yield with respect to 4-aminopiperidine). White solid. M.p. 50-52 °C (lit. [8] 47-52 °C). R_f (isopropanole : 25% aq. NH_3 = 9 : 1 v/v) = 0.64. IR (KBr) ν_{max} 3351 (w), 2979 (m), 2935 (m), 2862 (m), 2680 (w), 2576 (w), 2220 (w), 1694 (s), 1562 (m), 1531 (m), 1423 (s), 1392 (m), 1366 (m), 1284 (m), 1150 (s), 1043 (w) cm^{-1}. ^1H- and 2D-^1H,^1H-COSY-NMR (400 MHz, $CDCl_3$, 298 K) δ_H 1.19 (2H, dddd, $^2J_{H,H}$~$^3J_{H,H}$~$^3J_{H,H}$=11.7 Hz, $^3J_{H,H}$=3.8 Hz, H-3, -5-ax), 1.40 (s, 9H, *t*Bu), 1.75

(2H, d, $^2J_{H,H}$=12.4 Hz, H-3, -5-eq), 1.89 (2H, s, H-2, -6-ax), 2.72 (1H, br dd app. br t, $^3J_{H,H}$=11.6 Hz, Hz, H-4-ax), 2.78 (2H, ddd, $^2J_{H,H}$=8.9 Hz, $^3J_{H,H}$=4.3 Hz, H-2, -6-eq), 3.98 (2H, br s, NH_2) ppm. ^{13}C-J_{mod}-NMR (100 MHz, $CDCl_3$, 298 K) δ_C 28.5 (Me), 32.4 (C-3, -5), 35.4 (C-2, -6), 48.9 (C-4), 79.6 [*C*(Me)$_3$], 154.9 (C=O) ppm. ^{1}H-RMN (400 MHz, DMSO-d_6, 298 K) δ_H 1.07, 1.22 (2H: br ddd, $^2J_{H,H}$~$^3J_{H,H}$~$^3J_{H,H}$=11.1 Hz; br dd, $^2J_{H,H}$~$^3J_{H,H}$=9.8 Hz, H-3, -5-ax), 1.38 (9H, s, ^{t}Bu), 1.66 (2H, d, $^2J_{H,H}$=12.0 Hz, H-3, -5-eq), 2.72 (2H, br d, $J_{H,H}$=10.0 Hz, H-2, -6-ax), 3.04 (2H, br s, H-4-ax), 3.39 (2H, br s, NH_2), 3.82 (2H, br d, $^2J_{H,H}$=10.8 Hz, H-2, -6-eq) ppm. ^{1}H-RMN (400 MHz, DMSO-d_6, 353 K) δ_H 1.13, 1.30 (2H: br ddd, $^2J_{H,H}$~$^3J_{H,H}$~$^3J_{H,H}$=10.9, Hz; br dd, $^2J_{H,H}$~$^3J_{H,H}$=11.2 Hz, H-3, -5-ax), 1.41 (9H, s, ^{t}Bu), 1.69 (2H, d, $^2J_{H,H}$=12.8 Hz, H-3, -5-eq), 2.50 (2H, br s, H-4-ax), 2.82 (2H, br dd app. br t, $J_{H,H}$=12.0 Hz, H-2, -6-ax), 3.43 (2H, br s, NH_2), 3.81 (2H, br d, $^2J_{H,H}$=12.0 Hz, H-2, -6-eq) ppm. HRMS-ESI(+) (rel. int. %) *m*/*z*: 201.1591 (7) $[M+H]^+$. $[M+H]^+$ calcd. for $C_{10}H_{20}N_2O_2$, 201.1525.

Preparation of compounds **5a** *and* **5b.** At room temperature and under inert atmosphere, into a 1,4-dioxane (10 mL) solution containing cyanuric chloride (0.455 g, 2.47 mmol), anhyd. K_2CO_3 (1.047 g, 7.53 mmol) was suspended with vigorous stirring. A 1,4-dioxane (30 mL) solution containing 4-amino-1-*tert*-butoxycarbonylpiperidi-ne **4** (1.538 g as 97 % GC-MS purity, 1.492 g 100%, 7.49 mmol) was added dropwise over 1 h. After additional 24 h of stirring at room temperature, TLC monitoring (eluent acetone : ligroin : chloroform = 2:1:3 v/v/v) indicated the incomplete consumption of cyanuric chloride and formation of compounds **5a** (major) and **5b** (minor). Therefore, the reaction mixture was refluxed for 88 h, i.e., until TLC monitoring indicated no more evolution of the amination process. The reaction mixture was evaporated to dryness under reduced pressure and the solid residue was taken with distilled water (30 mL) with stirring, at room temperature. The resulted suspension was filtered off and well washed with distilled water to the complete removal of minerals. After drying at room temperature, the crude material (1.738 g) was purified by column chromatography on silica gel (eluent acetone : ligroin : chloroform= 2:1:3 v/v/v) to give 0.853 g pure compound **5a** (68% partial conversion of cyanuric chloride) as the first fraction. Next elution afforded 0.355 g compound **5b** (21% partial conversion of cyanuric chloride).

2-Chloro-4,6-bis(1-tert-butoxycarbonylpiperidin-4-ylamino)-s-triazine **5a.** White solid. M.p. 177-179 °C. R_f (acetone : ligroin : chloroform = 2:1:3 v/v/v) = 0.75. IR (KBr) ν_{max} 3357 (m), 3256 (m), 2976 (m), 2931 (m), 2846 (w), 1698 (s), 1678 (s), 1576 (s), 1534 (s), 1425 (s), 1365 (s), 1240 (m), 1175 (s), 1143 (s), 969 (w), 806 (w) cm^{-1}. ^{1}H- and 2D-^{1}H,^{1}H-COSY-NMR (400 MHz, $CDCl_3$, 298 K) δ_H 1.27-1.43 (22H, br m, 2×^{t}Bu, H-3, -3', -5, -5'-ax), 1.93 (4H, br s, H-3, -3', -5, -5'-eq), 2.88 (4H, d, $J_{H,H}$=10.8 Hz, H-2, -2', -6, -6'-ax), 3.87 (2H, br m, H-4,

-4'-ax), 4.00 (4H, br s, H-2, -2', -6, -6'-eq), 5.31, 5.52, 5.65, 6.11 (0.48H, br s; 0.49H, d, $^3J_{H,H}$=6.8 Hz; 0.81H, $^3J_{H,H}$=7.6 Hz; 0.25H, br s; NH) ppm. ^{13}C-J_{mod}-NMR (100 MHz, $CDCl_3$, 298 K) δ_C 28.5 (Me), 31.6, 31.7, 32.0, 32.2 (C-3, -3', -5, -5', Pip), 42.6 (C-2, -2', -6, -6', Pip), 48.0, 48.1, 48.2, 48.5 (C-4, -4', Pip), 79.8, 79.9 [*C*(Me)$_3$], 154.7, 154.8 (C=O), 164.4, 165.0, 165.2 (C-4, -6, Tz), 168.6, 169.5 (C-2, Tz) ppm. ^{1}H-NMR (400 MHz, DMSO-d_6, 298 K) δ_H 1.30 (4H, br dd app. br t, $^2J_{H,H}\sim^3J_{H,H}$=11.6 Hz, H-3, -3', -5', -5'-ax), 1.39 (18H, s, 2×*t*Bu), 1.76 (4H, br dd app. br q, $^2J_{H,H}$=10.1 Hz, H-3, -3', -5, -5'-eq), 2.82 (4H, br s, H-2, -2', -6, -6'-ax), 3.87 (6H, br s, H-4, -4'-ax, H-2, -2', -6, -6'-eq), 7.45, 7.77, 7.79, 7.91 (0.14H, d, $^3J_{H,H}$=8.0 Hz; 0.52H, $^3J_{H,H}$=7.6 Hz; 0.52H, $^3J_{H,H}$=7.6 Hz; 0.66H, $^3J_{H,H}$=7.2 Hz; NH) ppm. ^{1}H- and 2D-^{1}H,^{1}H-COSY-NMR (400 MHz, DMSO-d_6, 353 K) δ_H 1.40 (4H, br t, $^2J_{H,H}\sim^3J_{H,H}$=12.8 Hz, H-3, -3', -5, -5'-ax), 1.42 (18H, s, 2×*t*Bu), 1.80 (4H, br d, $^2J_{H,H}$=10.4 Hz, Hz, H-3, -3', -5, -5'-eq), 2.87 (4H, br dd app. br t, $^2J_{H,H}\sim^3J_{H,H}$=11.6 Hz, H-2, -2', -6, -6'-ax), 3.87 (2H, br s, H-4, -4'-ax), 3.90 (4H, br s, H-2, -2', -6, -6'-eq), 7.44, 7.55 (2H, 2×br s, NH) ppm. HRMS-ESI(+) (rel. int. %) *m*/*z*: 512.2767 (100) $[M+H]^+$. $[M+H]^+$ calcd. for $C_{23}H_{39}ClN_7O_4$, 512.2752.

2,4,6-Tris(1-tert-butoxycarbonylpiperidin-4-ylamino)-s-triazine **5b**. White solid. M.p. 182-184 °C. R_f (acetone : ligroin : chloroform = 2:1:3 v/v/v) = 0.45. IR (KBr) ν_{max} 3340 (w), 2977 (m), 2930 (m), 2853 (w), 1704 (s), 1577 (m), 1504 (s), 1423 (s), 1365 (m), 1238 (m), 1161 (s), 870 (w), 813 (w), 769 (w) cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$, 298 K) δ_H 1.32 (6H, br s, H-3, -3', -3", -5, -5', -5"-ax), 1.43 (27H, s, 3×*t*Bu), 1.93 (6H, br s, H-3, -3', -3", -5, -5', -5"-eq), 2.86 (6H, br s, H-2, -2', -2", -6, -6', -6"-ax), 3.88 (3H, br s, H-4, -4', -4"-ax), 3.98 (6H, br s, H-2, -2', -2", -6, -6', -6"-eq), 4.84, 4.95 (3H, 2×br s, NH) ppm. ^{13}C-J_{mod}-NMR (100 MHz, $CDCl_3$, 298 K) δ_C 28.5 (Me), 32.3 (C-3, -3', -3", -5, -5', -5", Pip), 47.3, 47.4, 48.1 (C-4, -4', -4", Pip), 79.7 [*C*(Me)$_3$], 154.9 (C=O) ppm. ^{1}H-NMR (400 MHz, DMSO-d_6, 298 K) δ_H 1.30 (6H, br s, H-3, -3', -3", -5, -5', -5"-ax), 1.39 (27H, s, 3×*t*Bu), 1.71 (6H, br d, $^2J_{H,H}$=10.0 Hz, H-3, -3', -3", -5, -5', -5"-eq), 2.75 (6H, br s, H-2, -2', -2", -6, -6', -6"-ax), 3.88 (3H, br s, H-4, -4', -4"-ax), 3.91 (6H, br s, H-2, -2', -2", -6, -6', -6"-eq), 6.27, 6.41, 6.51, 6.70 (3H, 4×br s, NH) ppm. ^{1}H- and 2D-^{1}H,^{1}H-COSY-NMR (400 MHZ, DMSO-d_6, 353 K) δ_H 1.37 (6H, dddd, $^2J_{H,H}\sim^3J_{H,H}\sim^3J_{H,H}$=12.0 Hz, $^3J_{H,H}$=3.2 Hz, H-3, -3', -3", -5, -5', -5"-ax), 1.42 (27H, s 3×*t*Bu), 1.80 (6H, dd, $^2J_{H,H}$=10.0 Hz, $^3J_{H,H}$=2.4 Hz, H-3, -3', -3", -5, -5', -5"-eq), 2.83 (6H, dd app. t, $^2J_{H,H}\sim^3J_{H,H}$=11.4 Hz, H-2, -2', -2", -6, -6', -6"-ax), 3.88 (3H, br s, H-4, -4', -4"-ax), 3.91 (6H, br s, H-2, -2', -2", -6, -6', -6"-eq), 6.13 (3H, br s, NH) ppm. HRMS-ESI(+) (rel. int. %) *m*/*z*: 676.4528 (100) $[M+H]^+$, 620.3900. (9) $[M+H-C_4H_8]^+$. $[M+H]^+$ calcd. for $C_{33}H_{58}N_9O_6$, 676.4510. $[M+H-C_4H_8]^+$ calcd. for $C_{29}H_{50}N_9O_6$, 620.3884.

Preparation of 2,4,6-tris(piperidin-4-ylamino)-s-triazine **3.** Under inert atmosphere and vigorous stirring, to a suspension of 2,4,6-tris(1-*tert*-butoxycarbonylpiperidin-4-ylamino)-*s*-triazine **5b** (0.350 g, 0.518 mmol) in cooled (0 °C) methanol (5 mL), a 6N HCl solution (1.8 mL, 10.53 mmol pure HCl) was added dropwise over 70 min. keeping the temperature at 0-1 °C. The resulted slurry was stirred at 0 °C for 2 h and then allowed to reach the room temperature over 3 h. The reaction mixture was slowly heated at 40 °C for 15 h. After this period, TLC monitoring (eluent : acetone : ligroin : chloroform = 2:1:3 v/v/v) indicated the complete consumption of **5b** and formation of the desired compound **3** (eluent EtOH : 25% aq. NH_3 = 1:9 v/v**)** as a single spot. The reaction mixture was evaporated under reduced pressure to the complete removal of methanol. The remaining solution was diluted with distilled water (2 mL), cooled at 0 °C for 1 h then carefully made alkaline with a 10% NaOH aq. soln. to pH = 14. The resulted suspension was cooled at 0 °C for 24 h then filtered off. The organic solid was well-washed with cooled (0 °C) and distilled water to the complete removal of minerals and dried in vacuum at room temperature to yield 0.145 g compound **3** (75% yield with respect to **5b**). White solid. M.p. 340-342 °C. R_f (EtOH : 25% aq. NH_3 = 1:9 v/v) = 0.15. IR (KBr) ν_{max} 3278 (m), 2947 (w), 2914 (w), 2813 (w), 2739 (w), 1588 (m), 1517 (s), 1385 (m), 1353 (m), 1178 (w), 860 (w), 811 (m) cm^{-1}. ^{1}H- and 2D-^{1}H,^{1}H-COSY-NMR (400 MHz, D_2O+DCl, 298 K) -0.33 (6H, br s, H-3, -3', -3", -5, -5', -5"-ax), 0.02 (6H, br s, H-3, -3', -3", -5, -5', -5"-eq), 0.91, 1.02 (6H, 2×br s, H-2, -2', -2", -6', -6', -6"-ax), 1.25 (6H, br s, H-2, -2', -2", -6, -6', -6"-eq), 1.85, 2.14 (3H, 2×br s, H-4, -4', -4"-ax) ppm. ^{13}C-J_{mod}-NMR (100 MHz, D_2O+DCl, 298 K) δ_C 25.5, 25.7, 25.9 (C-3, -3', -3", -5, -5', -5", Pip), 40.4, 41.7, 43.7 (C-4, -4', -4", Pip), 40.96, 41.14 (C-2, -2', -2", -6, -6', -6", Pip), 148.0, 151, 153.1 (C-2, -4, -6, Tz) ppm. HRMS-ESI(+) (rel. int. %) *m*/*z*: 376.2989 (100) $[M+H]^+$. $[M+H]^+$ calcd. for $C_{18}H_{34}N_9$, 376.2937.

ACKNOWLEDGMENTS

The financial support from a Grant provided by the Research Council Romania (project PN-II-ID-PCE-2011-3-0128) is gratefully acknowledged.

REFERENCES AND NOTES

[1]. a) W. Zhang, E.E. Simanek, *Org. Lett.*, **2000**, *2*, 843; b) M. B. Steffensen, E.E. Simanek, *Angew. Chem. Int. Ed.*, **2004**, *43*, 5178; c) E. Hollink, E.E. Simanek, *Org. Lett.*, **2006**, *8*, 2293; d) H. Crampton, E. Hollink, L.M. Perez, E.E. Simanek, *New J. Chem.*, **2007**, *31*, 1283; e) A. Chouai, E.E. Simanek, *J. Org. Chem.*, **2008**, *73*, 2357; f) J. Lim, E.E. Simanek, *Org. Lett.*, **2008**, *10*, 201; g) A.E. Enciso, F. Ramirez-Crescencio, M. Zeiser, R. Redón, E.E. Simanek, *Polym. Chem.*, **2015**, *6*, 5219; h) R.S. Sreeperumbuduru, Z.M. Abid, K.M. Claunch, H.-H. Chen, S.M. McGillivray, E.E. Simanek, *RSC Adv.*, **2016**, *6*, 8806.

[2]. a) A. Chouai, V.J. Venditto, E.E. Simanek, *Org. Synth.*, **2009**, *86*, 141; b) A. Chouai, V.J. Venditto, E.E. Simanek, *Org. Synth.*, **2009**, *86*, 151.

[3]. a) F. Popa, I. Simioanca, M. Pintea, M. Fazekas, L. Gratecap, C. Berghian, C. Batiu, M. Darabantu, *Studia UBB Chemia*, **2008**, *LIII(4)*, 5; b) F. Popa, P. Lameiras, E. Henon, O. Moldovan, A. Martinez, C. Batiu, Y. Ramondenc, M. Darabantu, *Can. J. Chem.*, **2011**, *89*, 1207; c) F. Popa, P. Lameiras, O. Moldovan, M. Tomoaia-Cotisel, E. Henon, A. Martinez, C. Sacalis, A. Mocanu, Y. Ramondenc, M. Darabantu, *Tetrahedron*, **2012**, *68*, 8945; d) O. Moldovan, P. Lameiras, I. Nagy, T. Opruta, F. Popa, C. Antheaume, Y. Ramondenc, M. Darabantu, *Tetrahedron*, **2013**, *69*, 2199.

[4]. a) X. Chen, P. Zhan, C. Pannecouque, J. Balzarini, E. De Clercq, X. Liu, *Eur. J. Med. Chem.*, **2012**, *51*, 60; b) X. Chen, P. Zhan, Z. Cheng, C. Meng, S. Shao, C. Pannecouque, E. De Clercq, X. Liu, *Bioorg. and Med. Chem.*, **2012**, *20*, 3856.

[5]. a) T. Drakenberg, S. Forsen, *Chem. Commun.*, **1971**, *21*, 1404; b) S.S. Mirvish, P. Gannett, D.M. Babcook, D. Williamson, S.C. Chen, D.D. Weisenburger, *J. Agric. Food Chem.*, **1991**, *39*, 1205; c) I. Willner, J. Rosengaus, Y. J. Eichen, *Phys. Org. Chem.*, **1993**, *6*, 29; d) A.R. Katritzky, I. Ghiviriga, D.C. Oniciu, A. Barkock, *J. Chem. Soc., Perkin Trans. 2*, **1995**, *4*, 785; e) A.R. Katritzky, I. Ghiviriga, P.G. Steel, D.C. Oniciu, *J. Chem. Soc., Perkin Trans. 2*, **1996**, *3*, 443; f) P. Amm, N. Platzer, J. Guilhem, J.P. Bouchet, J.P. Volland, *Magn. Reson. Chem.*, **1998**, *36*, 587; g) H.E. Birkett, R.K. Harris, P. Hodgkinson, K. Carr, M.H. Charlton, J.C. Cherryman, A.M. Chippendale, R.P. Glover, *Magn. Reson. Chem.*, **2000**, *38*, 504; h) M. Amm, N. Platzer, J.P. Bouchet, J.P. Volland, *Magn. Reson. Chem.*, **2001**, *39*, 77; i) I. Ghiviriga, D.C. Oniciu, *Chem. Commun.*, **2002**, *22*, 2718; j) H.E. Birkett, J.C. Cherryman, A.M. Chippendale, J.O.S. Evans, R.K. Harris, M. James, I.J. King, G. Mc Pherson, *Magn. Reson. Chem.*, **2003**, *41*, 324.

[6]. a) F. Friebolin, *Basic one- and two dimensional NMR spectroscopy*, VCH Verlagsgesellschaft: Weinheim, New York, **1991**, p. 93, 263-291; b) E.L. Eliel, H.S. Wilen, *Stereochemistry of the Organic Compounds*, John Wiley & Sons, New York, **1994**, p. 642, 1191

[7]. http://www.sigmaaldrich.com/Graphics/COfAInfo/SigmaSAPQM/SPEC/64/640042/640042-BULK_____ALDRICH__.pdf.

[8]. a) F. Himmelsbach, G. Dahmann, T. von Ruden, T. Metz (Dr. Karl Thomas GmbH) **1998**, *US Pat. US5821240A1*, Mar.5, **1997** / Oct.13, **1998**, App. No. US 08/811,907; b) F. Himmelsbach, G. Dahmann, T. von Ruden, T. Metz (Dr. Karl Thomas GmbH) **1999***, US Pat. US5977102A1*, Mar.5, **1997** / Nov.2, **1999**, App. No. US 08/812,002; c) D. Xiao, Y. Zhu, Y. Hu, H. Wang, Y. Liu, J. Li, D. Sun, Z. Wang, Y. Wei, Z. Wang, G. Tang, L. Jing (Centaurus Biopharma Co.,Ltd.) **2012**, *WO2012/103806A1*, Jan.31, **2012**/Aug.9, 2012. App. No. PCT/CN2012/070800.

[9]. a) M.B. Steffensen, E.E. Simanek, *Org. Lett.*, **2003**, *5*, 2359; b) K.X. Moreno, E.E. Simanek, *Tetrahedron Lett.*, **2008**, *49*, 1152; c) X.K. Moreno, E.E. Simanek, *Macromolecules*, **2008**, *41*, 4108; d) M.A. Mintzer, L.M. Perez, E.E. Simanek, *Tetrahedron Lett.*, **2010**, *51*, 1631; e) E.E. Simanek, H. Abdou, S. Lalwani, J. Lim, M. Mintzer, V.J. Venditto, B. Vittur, *Proc. R. Soc. A*., **2010**, *466*, 1445.

[10]. H.K. Hall, *J. Am. Chem. Soc.*, **1957**, *79*, 5441.

[11]. For the conformational analysis of cyclohexylamine (aminocyclohexane) by means of (VT) ^{1}H-, ^{13}C- or ^{15}N-NMR and computational methods see a) H. Booth, M. L. Jozefowicz, *J. Chem. Soc. Perkin 2*, **1976**, 895; b) H. –J. Schneider, V. Hoppen, *J. Org. Chem.*, **1978**, *43*, 3866; c) G. W. Buchanan, V.L. Webb, *Tetrahedron Lett.*, **1983**, *24*, 4519.

[12]. *See for example* a) J.T. Thurston, J.R. Dudley, D.W. Kaiser, I. Hechenbleikner, F.C. Schaefer, D. Holm-Hansen, *J. Am. Chem. Soc.*, **1951**, *73*, 2981; b) K.N. Sarmah, N.K. Sarmah, K.B. Kurmi, T.V. Patel, *Adv. Appl. Sci. Res.*, **2012**, *3*, 459.

[13]. a) M. Fazekas, M. Pintea, P. Lameiras, A. Lesur, C. Berghian, I. Silaghi-Dumitrescu, N. Plé, M. Darabantu, *Eur. J. Org. Chem.*, **2008**, *14*, 2473; b) O. Moldovan, P. Lameiras, E. Hénon, F. Popa, A. Martinez, D. Harakat, C. Sacalis, Y. Ramondenc, M. Darabantu, *Centr. Eur. J. Chem.*, **2012**, *10*, 1119; c) O. Moldovan, I. Nagy, P. Lameiras, C. Antheaume, C. Sacalis, M. Darabantu, *Tetrahedron: Asymmetry*, **2015**, *26*, 683; d) C. Morar, G. Turdean, A. Bende, P. Lameiras, C. Antheaume, L. M. Muresan, M. Darabantu, *Compt. Rend. Chim.*, **2016**, http://dx.doi.org/10.1016/j.crci.2016.07.002.

[14]. For the relevance of this α-geminal anisochrony versus a carbamate group in anancomeric 1-Boc-4-NH_2 piperidine, see the ^{1}H-NMR analysis of flipping non-symmetrically N-substituted-N-Boc piperazines in J. Lim, G.M. Pavan, O. Annunziata, E.E. Simanek, *J. Am. Chem.Soc.*, **2012**, *134*, 1942.

[15]. W.E. Stewart, T.H. Siddall, *Chem. Rev.*, **1970**, *70*, 517.

[16]. a) J. Lim, E.E. Simanek, *Mol. Pharm.*, **2005**, *2*, 273; b) M. Pintea, M. Fazekas, P. Lameiras, I. Cadis, C. Berghian, I. Silaghi-Dumitrescu, F. Popa, C. Bele, N. Plé, M. Darabantu, *Tetrahedron*, **2008**, *64*, 8851.

[17]. H. Kessler, *Angew. Chem., Int. Ed. Engl.*, **1982**, *21*, 512.