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SYNTHESIS OF NOVEL *N*-SUBSTITUTED AMPHIONIC MELAMINES WITH THE TANDEM 4-(1-CARBOXY-*n*-ALKOXY)PHENYL / 4-(*n*-OCTYLOXY)PHENYL UNITS AS POTENTIAL DENDRITIC BUILDING-BLOCKS

STEFANIA IONESCU-ZINCA[a], PEDRO LAMEIRAS[b], DAN PORUMB[a], EMESE GÁL[c] AND MIRCEA DARABANTU[a*]

ABSTRACT. Starting from etheric type derivatives of 4-aminophenol, namely (4-aminophenoxy)acetic acid or 4-(4-aminophenoxy)butyric acid and 4-(*n*-octyloxy)aniline, we report herein two routes of access to two novel *N*-substituted amphionic melamines with the tandem 4-(1-carboxy-*n*-alkoxy) phenyl/4-(*n*-octyloxy)phenyl units against the piperazin-1-yl group, as a basic site. The successful S_N2-Ar aminations of cyanuric chloride performed with these amine-nucleophiles are discussed in terms of chemoselectivity, mainly in the third step of the synthesis, implying piperazine as such or its *N*-Boc-mono-protected form. The amphionic nature of the targeted melamines was fully confirmed both in solution (VT-NMR) and in the solid state (IR).

Keywords: *(4-aminophenoxy)acetic acid, 4-(4-aminophenoxy)butyric acid, amphionic melamines, N-Boc-piperazine, 4-(n-octyloxy)aniline*

INTRODUCTION

The inclusion of (4-aminophenoxy)alkanoic acid motifs, acetic or butyric, in the structure of bioactive compounds such as antisickling agents [1], anti-*Helicobacter pylori* agents [2], inhibitors of the cellular checkpoint kinase [3], antimalarial [4], analgesic, antipyretic and anti-inflammatory agents [5] is already well-documented.

[a] *Babeş-Bolyai University*, *Department of Chemistry*, *11 Arany Janos str.*, *RO-400028, Cluj-Napoca*, *Romania*
[b] *University of Reims Champagne-Ardenne, ICMR, UMR 7312, BP 1039, 51687 Reims, France*
[c] *Babeş-Bolyai University*, *Department of Chemistry and Chemical Engineering*, *Hungarian Line of Study*, *11 Arany János St.*, *400028 Cluj-Napoca*, *Romania*
***** *Corresponding author: darab@chem.ubbcluj.ro*

It was our Laboratory the first who reported, recently, the use of these aryl-amino acids in organic materials chemistry as well [6] (Chart1): primary, as precursors of novel *N*-substituted melamines (2,4,6-triamino-1,3,5-triazines) [6a] and then the propensity of the tripodands thus obtained to act, by simple acid-base neutralization, as anionic *meta*-trivalent central building-blocks in G-2 dendritic melamines' elaboration [6b]. This type of ionic macromolecules exhibited a noticeably supramolecular behaviour tailoring a "shell-to-shell" pre-organisation in solution, able to endorse subsequent self-assembly into large homogeneously packed spherical nano-aggregates [6, 7].

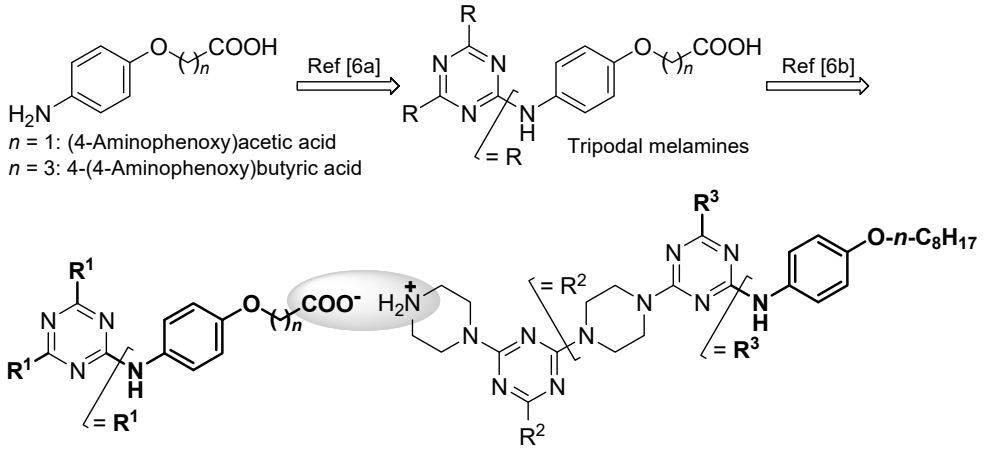


Chart 1. Previous use of (4-aminophenoxy)alkanoic acids and 4-(*n*-octyloxy)aniline in G-2 ionic construction of dendritic melamines

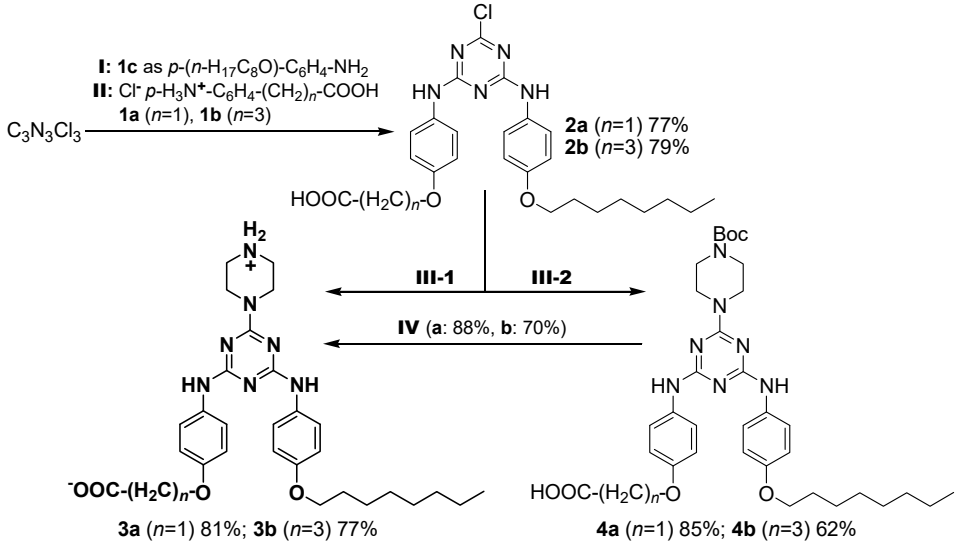
In the above context (Chart 1), so far, we utilised merely 4-(*n*-octyloxy)aniline (a "traditional" starting material for mesogenic *N*-substituted Schiff-bases [8]) playing the role of unique dendritic peripheral unit. In fact, later reports focused on organic materials area evidenced this "fatty" *p*-alkoxyaniline becoming, along the years, a well-recognised component for macromolecules fabrication [9], for example mesogenic supramolecular perylene bisimide assemblies with a number of 2-amino-4,6-bis[(4-*n*-alkoxy)phenylamino]-*s*-triazines [9a], amphiphilic azobenzene-containing linear-dendritic block copolymers [9b] and G-0 monomeric or dimeric dendritic liquid crystals with photochromic azobenzene mesogens [9c].

Accordingly, in continuation of our previous findings [6, 7], we envisaged to enlarge this topic by investigating the synthesis of novel *N*-substituted melamines with the tandem 4-(1-carboxy-*n*-alkoxy)phenyl/4-(*n*-octyloxy)phenyl units, seen as prospective G-0 dendrons.

RESULTS AND DISCUSSION

1. Synthesis (Scheme 1)

Chlorodiamino-*s*-triazines **2a** and **2b** were prepared in two clean-chemoselective S_N2-Ar consecutive aryl aminations of cyanuric chloride by applying a one-pot mild conditions manipulation (**I+II**). In our hands, 4-(*n*-octyloxy)aniline **1c** had to be the first amine-nucleophile (**I**, Eq. 1) because this commercial compound appeared to us sensitive to light and UV irradiation during TLC control (λ=254 nm), i.e, the dichloroamino-*s*-triazine intermediate (not depicted in Scheme 1) was even not isolated.



I $R^1\text{-}NH_2$ (**1c**) + $C_3N_3Cl_3$ + $NaHCO_3$ → $R^1\text{-}NH\text{-}C_3N_3Cl_2$ + NaCl + CO_2 + H_2O (1)

II $HOOC\text{-}R^2\text{-}NH_3^+Cl^-$ (**1a** *or* **1b**) + K_2CO_3 → $KOOC\text{-}R^2\text{-}NH_2$ + KCl + CO_2 + H_2O (2)

$KOOC\text{-}R^2\text{-}NH_2$ + $R^1\text{-}NH\text{-}C_3N_3Cl_2$ + AcONa → $R^1\text{-}NH\text{-}C_3N_3Cl\text{-}NH\text{-}R^2\text{-}COONa$ + AcOH + KCl (3)

$R^1\text{-}NH\text{-}C_3N_3Cl\text{-}NH\text{-}R^2\text{-}COONa$ + AcOH → $R^1\text{-}NH\text{-}C_3N_3Cl\text{-}NH\text{-}R^2\text{-}COOH$ (**2a** *or* **2b**) + AcONa (4)

Step	Products	Conditions
I	*not isolated*	1.0 equiv **1c**, acetone, 0-5 °C (2 h) / 1.0 equiv $NaHCO_3$, H_2O, 0-5 °C / rt (24 h) / N_2
II	**2a**, **2b**	1.0 equiv **1a** (or **1b**), 1.0 equiv K_2CO_3, H_2O, 0-5 °C / 1.0 equiv AcONa, H_2O, 0-5 °C (0.5 h) / rt (24 h) / N_2
III-1	**3a**, **3b**	6.00 equiv piperazine, 6×(0.16 equiv **2a** or **2b** added every 2 h), THF / rt (24 h) / 1.0 equiv K_2CO_3 / AcOH, pH=6-6.5
III-2	**4a**, **4b**	2.25 equiv Boc-piperazine, 1.00 equiv K_2CO_3,THF / rt (24 h) / 55-60 °C (48 h) / AcOH, pH~6 / N_2
IV	**3a**, **3b**	3M aq HCl, 1,4-dioxane, rt (48 h) / 50-55 °C (5 h) / 25% aq NH_3, pH=6-6.5

Scheme 1

Furthermore, (4-aminophenoxy)alkanoic acids, as free bases, were released *in situ* from their hydrochlorides **1a** (*n*=1) and **1b** (*n*=3) (**II**, Eq. 2). The need to isolate the crude products, **2a** and **2b**, in neutral form by adding, in this purpose, sodium acetate, we discussed earlier (**II**, Eq. 3, 4 [6a]). Finally, the global (**I+II**) yields in the synthesis of **2a** (77%) and **2b** (79%), as pure analytical products, refer rather to their expeditious purification by simple crystallization from boiling isopropanol, than the intimate evolution of the reactions (TLC survey).

The mono-attachment of piperazine to **2a** and **2b** (**III-1**) was more problematic than we expected. Thus, inspired from our previous expertise (6b, 10), the portionwise addition of **2a** or **2b** to a 300% molar excess of piperazine, at room temperature, yielded the targeted melamines, **3a** and **3b**, with excellent NMR appearance. Only careful inspection of their HRMS spectra divulged very discrete peaks assigned to the symmetrically di-substituted piperazine-1,4-diyl byproduct. In similar attempts, reported by Simanek and co-workers [11], the use of larger piperazine molar excesses, 400 [11a] or even 500% [11b], were mentioned. Indeed, in our present cases (Scheme 1), only a 500% molar surplus of piperazine ensured a 100% chemoselectivity of the non-symmetric S_N2-Ar amination processes, **2a**→**3a** and **2b**→**3b**. In spite of this improvement, compounds **3a** and **3b** could be isolated, in pure analytical state, only if column chromatography on de-activated silica-gel followed by crystallization from boiling isopropanol were applied (see EXPERIMENTAL SECTION).

Therefore, we also considered a two steps alternative strategy, by employing *N*-Boc-piperazine (**III-2**) with subsequent deprotection (**IV**). To our surprise, ^{1}H NMR (rather than TLC) monitoring of the reactions between equimolar amounts of **2a** (or **2b**) and *N*-Boc-piperazine revealed, in each case, even after 48 h (at rt), still the incidence of unconsumed starting materials, **2a** (14%) or **2b** (42%). As shown in Scheme 1, a 125 % molar excess of *N*-Boc-piperazine was required for both aminations, **2a**→**4a** and **2b**→**4b**, reached completion upon long time of heating (55-60 ^{o}C, 48 h) with discrepant yields, 85% (**4a**) and 62% (**4b**). A plausible explanation for this unexpected low reactivity of Boc-piperazine in comparison with piperazine itself in our conditions might arise from i) manifestation of a transannular effect occurring in EWG-*N*-substituted piperazines (previously noticed by Lai and co-workers [12a, 12b], then by our Laboratory [10a]) against ii) a reduced aptitude as leaving-group of the remaining *s*-triazine chlorine in compounds **2a** and **2b** in S_N2-Ar amination conditions. Despite of all above, we note *N*-Boc-piperazine being reported [13] as a useful S_N complete amination reagent versus highly *C*-electrophilic halo-compounds, cyanuric chloride [13a] and 2,4,6-tris (bromomethyl)-benzene [13b].

The successful removal of Boc-*N*-protecting group from **4a** and **4b** (**IV**) was also mandatory to a long time reaction and heating, with satisfactory (70%, **3b**) to good yields (85%, **3a**). To resume, the global yields were **1a**→**3a** 62% (57% via **4a**) and **1b**→**3b** 61% (34% via **4b**).

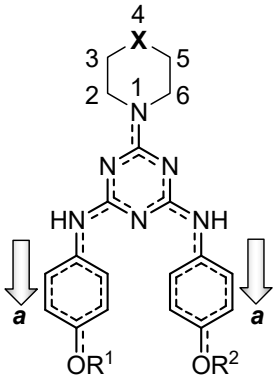
All new compounds **2**-**4a**(**b**) provided analytical and spectral data in full agreement with the proposed structures.

2. Structural assignments

2.1. *In solution* (Table 1)

The amphionic nature of melamines **3a** and **3b** in solution was established with the help of NMR data. However, their relevance could be evaluated by comparison with those of precursors **2a**, **2b** and known melamine analogs **3c**

Table 1. Comparative 1D-^{1}H and 2D-^{1}H-DOSY NMR data of compounds **3a** and **3b** against their 4-aminophenol (**3c**) and 4-(*n*-octyloxy)aniline (**3d**) based analogs on ^{1}H 500 MHz timescale in DMSO-d_6



anti-anti

3a-d

X = $^+$**NH$_2$**

a: R^1 = CH_2-COO^-, R^2 = *n*-C_8H_{17}

b: R^1 = $(CH_2)_3$-COO^-, R^2 = *n*-C_8H_{17}

X = **NH**

c: R^1 = R^2 = H (our Ref [10c])

d: R^1 = R^2 = *n*-C_8H_{17} (our Ref [6b])

No.	*T* (K)	1D-^{1}H NMR: δ_H (ppm)[a]			M (g mol^{-1})	2D-^{1}H-DOSY NMR[a]	
		Piperazin-1-yl -4-ium		-C*H*$_2$-COO$^-$		*D*(μm^2 s^{-1})	d_H (nm)
		H-2, -6	H-3, -5				
3a	298	3.80	2.94	4.47 (4.65 in **2a**)[b]	549.66	164.4	1.33
	363	3.74	2.85	4.56 (4.60 in **2a**)		-	-
3b	298	3.87	3.08	2.38 (2.38 in **2b**)	577.72	162.2	1.35
	363	3.90	3.09	2.38 (2.39 in **2b**)		-	-
		Piperazin-1-yl					
3c	298	3.63	2.69	-	379.42	152.0	1.44
	363	3.65	2.73			-	-
3d	298	3.66	2.70	-	603.84	191.0	1.14
	363	3.67	2.74			-	-

[a]As 5 mM solutions; [b]As 28 mM solution

(based on 4-aminophenol, [10c]) and **3d** (based on 4-(*n*-octyloxy)aniline, [6b]) only. One must observe that all four melamines **3a**-**d** belong to the same family of extended p→π delocalised systems, inducing the well-known rotational diastereomerism of type *a* (*anti*)/*s* (*syn*) about the partial double bonds >N(exocyclic)⁻⁻⁻C(*s*-triazine) [14].* On the ^{1}H NMR 500 MHz timescale, this stereo-dynamism was exposed by the spectral shape defined as "slow exchange status between unequally populated sites" [15].

At room temperature, the existence of a protonated, at N-4, piperazine-1-yl ligand (>NH_2^+ as EWG) determined a noticeable deshielding ($\Delta\delta_H$~+0.30 ppm, downfield resonances) of the adjacent methylenes, H-3, -5, in **3a** and **3b** vs. **3c** and **3d**. An identical but weaker influence was observed for protons H-2, -6 ($\Delta\delta_H$~+0.20 ppm). On heating at 90 °C, the magnetic environment did not changed significantly, the shifting to lower fields being $\Delta\delta_H$~+0.23 ppm (H-3, -5) and $\Delta\delta_H$~+0.16 ppm (H-2, -6) in **3a**, **3b** vs. **3c**, **3d**, to prove, in addition, the cationic stability of the piperazin-1-yl-4-ium ligand.

The presence of the carboxylate (COO^-) counterpart could be indirectly attributed as well. Thus, in the case of melamine **3a** only, a shielding (upfield resonances) of the α-located –CH_2–(C=O)– protons was observed as the result of the COOH (EWG in **2a**)→COO^- (EDG, ERG in **3a**) deprotonation. A related diagnosis, issued from an aliphatic carboxyl group ionisation thus promoting ^{1}H higher field absorptions of proximal (α and β) methylene protons, was earlier reported by Sierra and co-workers [16] in the case of some G-2 PAMAM ionic dendrimers (–COO^- H_3N^+–) obtained by direct –COOH + H_2N– neutralisation in $CDCl_3$.

No fluctuation as $\pm\Delta\delta_C$ (COOH vs. COO^-) was detectable in the whole series **2**-**4a**(**b**) on the 125 MHz ^{13}C NMR timescale.

Somehow predictably, DOSY charts of compounds **3a**-**d** did not allowed a direct correlation between *D* values by means of hydrodynamic diameters (d_H) (Table 1) and the molecular size [6b, 7, 17]. Hydrodynamic diameters d_H were calculated from the hydrodynamic radii (r_H) by applying the Stokes-Einstein equation (Eq. 1).

$$\text{(Eq. 1)} \quad D = \frac{k\,T}{6\,\pi\,\eta\,r_H} \times 10^{-9}$$

where *k* is the Boltzmann's constant (1.38×10^{-23} j K^{-1}), η is the dynamic viscosity (2.00×10^{-3} kg m^{-1} s^{-1}) of DMSO at *T* (298 K) and r_H (nm) is the hydrodynamic radius.

*In Table 1, solely the (*a*-*a*) rotamer is illustrated (as the more stable type of stereoisomer, according to preceding DFT calculation of our Laboratory [6b, 7, 10c]).

DOSY data disclosed that, although the biggest in size, melamine **3d** displaced a minimum volume of solvent (d_H 1.14 nm) due, most likely, to its isolated as independent molecular species in solution. By contrast, aggregation through multiple H-bonding interactions (compound **3c**, d_H 1.44 nm) or by simple electrostatic attractions (compounds **3a**, **3b**, d_H 1.33 and 1.35 nm respectively) suggested incipient supramolecular aptitudes, as we reported previously for other melamines based on 4-aminophenol derivatives [6b, 7, 10c, 18].

2.2. *In the solid state* (Figure 1)

IR spectra (KBr) completed the above attributions, limited, this time, to the carboxyl group's behavior (Figure 1). Thus, the bands located at 1712 (**2a**) and 1702 cm^{-1} (**2b**) we ascribed to the $\nu_{C=O}$ stretch in the carboxylic (COOH) groups, classically associated as dimers [19]. These absorptions were significantly shifted

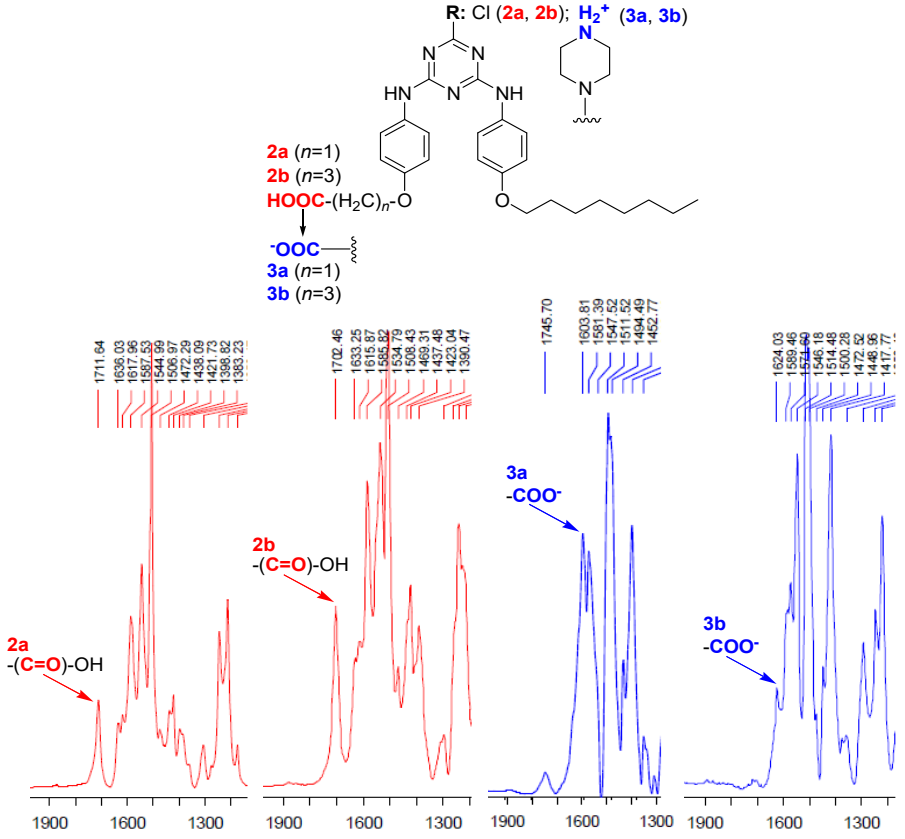


Figure 1. Comparative details from IR spectra (KBr) of chlorodiamino-*s*-triazines **2a** and **2b** versus amphionic melamines **3a** and **3b**

downfield, →1604 (in **3a**) and →1624 cm^{-1} (in **3b**) consistent with their carboxylate (COO^-) environment. Other relevant bands denoting polymeric H-bonding intermolecular associations of compounds **2a** (1636, 1618 cm^{-1}) and **2b** (1633, 1617 cm^{-1}) were completely absent in the IR spectra of amphionic melamines **3a** and **3b**. Nonetheless, the stretching (ν_{NH}, 3000-2700 cm^{-1}) or deformation (δ_{NH}, 1620-1560 cm^{-1}) bands of the protonated $>NH_2^+$ group of the piperazin-1-yl-4-ium ligand [20] could not be definitely identified due to the overlapping in the above regions between the absorptions of the piperazine methylenes (ν_{CH2}), carbonyl bonds ($\nu_{C=O}$) in the COO^- groups, aryl ($\nu_{C=C}$) and *s*-triazine ($\nu_{C=N}$) bonds.

CONCLUSIONS

In summary, two novel amphionic *N,N',N''*-substituted melamines with 4-(1-carboxylate-*n*-alkoxy)phenyl, 4-(*n*-octyloxy)phenyl and piperazin-1-yl-4-ium ligands were obtained by S_N2-Ar chemoselective aminations of cyanuric chloride. The chemoselective non-symmetric attachment of the piperazine ligand was achieved by using a large molar excess (500%) of this diamine-nucleophile, rather than its *N*-Boc mono-protected form. NMR and IR data had to complement each other in supporting the amphionic structure of the above melamines. (VT)-^{1}H NMR chemical shifts proved the piperazin-1-yl-4-ium cationic nature of this ligand together with its thermal stability as such in solution meanwhile IR (KBr) ν-stretch bands evidenced the existence, in the solid state, of carboxylate groups.

EXPERIMENTAL SECTION

All reagents and solvents were of commercial quality and required no purification prior to use.

Melting points were carried out on a KSP1N instrument and are not corrected.

Microanalyses were performed on a Carlo Erba CHNOS 1160 apparatus.

TLC monitoring was performed by using aluminium sheets with silica gel 60 F254. (Merck) (visualisation under UV at λ=254 nm, optionally on an 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 (in cm^{-1}) are listed throughout as being s (strong), m (medium) or w (weak).

NMR spectra were recorded on a Bruker AM 500 instrument operating at 500 or 125 MHz for ^{1}H 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 (Hz). No TMS was added: chemical shifts were measured against the solvent peak, taken as reference signal. In the NMR descriptions, some specific abbreviations were used: tt (triplet of triplets), qu (quartet), qui (quintet), sx (sextet), sept (septet), oct (octet), td (triplet of doublets), T (*s*-Triazine), PZ (piperazin-1-yl). In the NMR assignment of nuclei as "α", "β" and "γ" refers to their increased vicinity with respect to the carboxyl (COOH) group on the *n*-butanoic chain. Designation of topologic equivalent positions of ^{1}H and ^{13}C nuclei as (’), (’’) etc. was omitted for reasons of simplicity

HRMS spectra were obtained on an 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.

Typical procedure for the synthesis of compounds **2a** *and* **2b***; preparation of compound* **2a** (**I**+**II**, Scheme 1)

Under inert atmosphere, to cyanuric chloride (1.304 g 99%, 1.291 g 100%, 7.00 mmol) suspended in acetone (20 mL), a solution obtained by dissolving (4-*n*-octyloxy)aniline (1.581 g 98%, 1.549 g 100%, 7.00 mmol) in acetone (40 mL) was slowly (2 h) added at 0-5 °C with vigorous stirring to provide, in the end, a deep purple solution. At this moment, a solution obtained by dissolving anhyd $NaHCO_3$ (0.588 g, 7.00 mmol) in distilled water (10 mL) was injected dropwise during 15 min, keeping the temperature between 0-5 °C. The reaction mixture was let to reach the room temperature for the next 24 h. During this time, an abundant crystallisation temporarily occurred. The re-formed solution was again cooled at 0-5 °C when a solution obtained by dissolving (4-amino)phenoxyacetic acid hydrochloride (1.425 g, 7.00 mmol) in distilled water (6 mL) was added dropwise followed, immediately, by anhyd K_2CO_3 (0.967 g, 7.00 mmol) dissolved in distilled water (3.5 mL). After 30 min, anhyd AcONa (0.574 g, 7.00 mmol) dissolved in distilled water (1.50 mL) was injected dropwise. After that, the reaction mixture was let to reach again the room temperature and was stirred for additional 24 h when a second rich crystallization was observed. TLC control (eluent *n*-hexane/EtOH 1:1 v/v) indicated formation of compound **2a** as a single spot. The suspension, having pH=6-6.5, was poured on ice (150 g), stirred 2 h, then kept at 0 °C for 24 h and, finally, filtered off. The crude washed and dried material (3.400 g) was crystallized from boiling *i*-PrOH (30 mL) to give pure compound **2a** (2.695 g, 77% yield with respect to cyanuric chloride).

2-Chloro-4-[4-(carboxymethoxy)phenyl]amino-6-[(4-n-octyloxy)phenyl]amino-s-triazine **2a**. White solid. Mp 179.5-180 °C (*i*-PrOH). R_f (*n*-hexane/EtOH 1:1 v/v)=0.50. Elemental analysis calcd. (%) for $C_{25}H_{30}ClN_5O_4$: C 60.05, H 6.05, N 14.01; found: C 60.38, H 5.91, N 13.88. IR (KBr) ν_{max} 3295 (w), 2957 (w), 2937 (m), 2922 (m), 2853 (w), 1712 (m), 1588 (s), 1545 (m), 1507 (s), 1438 (m), 1422 (m), 1245 (m), 1212 (m), 1081 (w), 999 (w), 824 (w), 795 (w) cm^{-1}. ^{1}H and 2D-^{1}H,^{1}H-COSY NMR (500 MHz, 28 mM in DMSO-d_6, 298 K) δ_H 0.86 (3H, t, $^{3}J_{H,H}$=7.0 Hz, Me), 1.26-1.33 (8H, m, 4×CH_2, *n*-octyl), 1.40 (2H, tt app. qui, $^{3}J_{H,H}$=7.3 Hz, CH_2, *n*-octyl), 1.69 (2H, tt app. qui, $^{3}J_{H,H}$=7.0 Hz, OCH_2CH_2, *n*-octyl), 3.93 (2H, t,$^{3}J_{H,H}$=6.0 Hz, OCH_2, *n*-octyl), 4.65 (2H, s, OCH_2), 6.88 (4H, d, $^{3}J_{H,H}$=8.5 Hz, H-3, -5, Ph), 7.48, 7.49 and 7.65 (4H, d, $^{3}J_{H,H}$=7.0 Hz;

d, $^3J_{H,H}$=7.0 Hz; bs, H-2, -6, Ph), 9.88, 9.98, 10.06 and 10.08 (2H, 2×bs, 2×s, NH), 12.99 (1H, bs, COOH) ppm. ^{1}H and 2D-^{1}H,^{1}H-COSY NMR (500 MHz, 28 mM in DMSO-d_6, 363 K) δ_H 0.88 (3H, t, $^3J_{H,H}$=7.0 Hz, Me), 1.28-1.36 (8H, m, 4×CH_2, *n*-octyl), 1.44 (2H, tt app. qui, $^3J_{H,H}$=7.3 Hz, CH_2, *n*-octyl), 1.72 (2H, tt app. qui, $^3J_{H,H}$=7.0 Hz, OCH_2CH_2, *n*-octyl), 3.97 (2H, t,$^3J_{H,H}$=6.5 Hz, OCH_2, *n*-octyl), 4.60 (2H, s, OCH_2), 6.87 (2H, d, $^3J_{H,H}$=9.0 Hz, H-3, -5, Ph), 6.89 (2H, d, $^3J_{H,H}$=8.5 Hz, H-3, -5, Ph), 7.50 (2H, d, $^3J_{H,H}$=8.5 Hz, H-2, -6, Ph), 7.52 (2H, d, $^3J_{H,H}$=9.0 Hz, H-2, -6, Ph), 9.62 and 9.64 (2H, 2×s, NH) ppm. 2D-^{1}H-DOSY NMR (500 MHz, 5 mM in DMSO-d_6, 298 K) *D* 185.8 μm^2 s^{-1}. DEPT-^{13}C NMR (125 MHz, 28 mM in DMSO-d_6, 298 K) δ_C 14.5 (Me), 22.6, 26.1, 29.17, 29.23 and 29.3 (5×CH_2, *n*-octyl), 31.7 (OCH_2CH_2, *n*-octyl), 65.2 (OCH_2, *n*-octyl), 68.1 (OCH_2), 114.6 (C-3, -5, Ph), 122.7, 123.02, 123.04, 123.08, 123.09 and 123.3 (C-2, -6, Ph), 131.6 and 132.2 (C-1, Ph), 154.6 and 155.6 (C-4, Ph), 164.19, 164.21, 164.24, 164.4, 164.46,164.47,164.49 and 164.50 (C-4, -6, T), 168.3, 168.7 and 168.8 (C-2, T), 170.7 (COOH) ppm. HRMS (APCI) (rel. int. %) *m*/*z*: 500.2058 (100) $[M+H]^+$. $[M+H]^+$ calcd. for $C_{25}H_{31}ClN_5O_4$: 500.2065.

2-Chloro-4-[4-(3-carboxypropoxy)phenyl]amino-6-[(4-n-octyloxy)phenyl]amino-s-triazine **2b**. 2.280 g (79% yield starting from 1.018 g 99%, 1.008 g 100% cyanuric chloride).White solid. Mp 164.9-165.0 ºC (*i*-PrOH). R_f (*n*-hexane/EtOH 3:1 v/v)=0.60. Elemental analysis calcd. (%) for $C_{27}H_{34}ClN_5O_4$: C 61.41, H 6.49, N 13.26; found: C 61.18, H 6.71, N 12.89. IR (KBr) ν_{max} 3369 (w), 3280 (w), 3112 (m), 2259 (m), 2924 (m), 2853 (m), 1702 (m), 1616 (m), 1535 (s), 1508 (s), 1437 (m), 1390 (m), 1296 (s), 1261 (s), 1041 (m), 1015 (m), 998 (m), 828 (m), 793 (m), 598 (w), 520 (w) cm^{-1}. ^{1}H and 2D-^{1}H,^{1}H-COSY NMR (500 MHz, 5 mM in DMSO-d_6, 298 K) δ_H 0.85 (3H, t, $^3J_{H,H}$=6.8 Hz, Me), 1.25-1.34 (8H, m, 4×CH_2, *n*-octyl), 1.40 (2H, tt app. qui, $^3J_{H,H}$=7.3 Hz, CH_2, *n*-octyl), 1.68 (2H, tt app. qui, $^3J_{H,H}$=7.0 Hz, OCH_2CH_2, *n*-octyl), 1.93 (2H, tt app. qui, $^3J_{H,H}$=6.9 Hz, H-β), 2.38 (2H, t, $^3J_{H,H}$=7.3 Hz, H-α), 3.93 (2H, t,$^3J_{H,H}$=6.5 Hz, OCH_2, *n*-octyl), 3.96 (2H, t, $^3J_{H,H}$=6.5 Hz, H-γ), 6.88 (4H, d, $^3J_{H,H}$=7.5 Hz, H-3, -5, Ph), 7.31, 7.47, 7.48 and 7.66 (4H, bs; d, $^3J_{H,H}$=7.5 Hz; d, $^3J_{H,H}$=5.5 Hz; bs, H-2, -6, Ph), 9.86, 9.97 and 10.05 (2H, 2×bs, s, NH), 12.13 (1H, bs, COOH) ppm. ^{1}H and 2D-^{1}H,^{1}H-COSY NMR (500 MHz, 5 mM in DMSO-d_6, 363 K) δ_H 0.88 (3H, t, $^3J_{H,H}$=7.0 Hz, Me), 1.28-1.38 (8H, m, 4×CH_2, *n*-octyl), 1.44 (2H, tt app. qui, $^3J_{H,H}$=7.1 Hz, CH_2, *n*-octyl), 1.72 (2H, tt app. qui, $^3J_{H,H}$=7.0 Hz, OCH_2CH_2, *n*-octyl), 1.97 (2H, tt app. qui, $^3J_{H,H}$=6.9 Hz, H-β), 2.39 (2H, t, $^3J_{H,H}$=7.3 Hz, H-α), 3.97 (2H, t,$^3J_{H,H}$=6.5 Hz, OCH_2, *n*-octyl), 4.00 (2H, t, $^3J_{H,H}$=6.5 Hz, H-γ), 6.87 (2H, d, $^3J_{H,H}$=9.0 Hz, H-3, -5, Ph), 6.88 (2H, d, $^3J_{H,H}$=9.5 Hz, H-3, -5, Ph), 7.50 (2H, d, $^3J_{H,H}$=8.5 Hz, H-2, -6, Ph), 7.51 (2H, d, $^3J_{H,H}$=8.5 Hz, H-2, -6, Ph), 9.62 (2H, s, NH) ppm. 2D-^{1}H-DOSY NMR (500 MHz, 5 mM in DMSO-d_6, 298 K) *D* 171.0 μm^2 s^{-1}. DEPT-^{13}C NMR (125 MHz, 5 mM in DMSO-d_6, 298 K) δ_C 14.4 (Me), 22.6 (CH_2, *n*-octyl), 24.8 (C-β), 26.0, 29.17, 29.21 and 29.3 (4×CH_2, *n*-octyl), 30.6 (C-α), 31.7 (OCH_2CH_2, *n*-octyl), 67.2 and 67.3 (OCH_2, *n*-octyl), 68.1 and 68.2 (C-γ), 114.8 and 115.0 (C-3, -5, Ph), 122.5, 123.1, 123.2 and 123.4 (C-2, -6, Ph), 131.6, 131.8 and 132.1 (C-1, Ph),155.3 and 155.6 (C-4, Ph), 163.7, 164.2 and 164.5 (C-4, -6, T), 168.2 and 168.7 (C-2, T), 174.6 (COOH) ppm. HRMS (APCI) (rel. int. %) *m*/*z*: 528.2407 (100) $[M+H]^+$. $[M+H]^+$ calcd. for $C_{27}H_{35}ClN_5O_4$: 528.2378.

Typical procedure for the synthesis of compounds **3a** *and* **3b***; preparation of compound* **3b** (**III-1**, Scheme 1)

Under inert atmosphere, at room temperature and with vigorous stirring, to a THF (25 mL) solution containing anhyd piperazine (0.987 g 99%, 0.977 g 100%, 11.34 mmol), solid compound **2b** (1.000 g, 1.89 mmol) was added as six equal portions every 2 h. After each of these periods, TLC monitoring indicated the complete consumption of the starting material **2b** (eluent *n*-hexane/EtOH 3:1 v/v) and formation of the desired melamine **3b** as a major spot (eluent EtOH/25% aq NH_3 9:0.3 v/v). The reaction mixture was treated with solid anhyd K_2CO_3 (0.261 g, 1.89 mmol) and then evaporated, under vacuum, to dryness. At room temperature, the solid residue was taken with distilled water (25 mL) and then AcOH was added dropwise to the resulted solution to adjust its pH to 6-6.5 when crude compound **3b** precipitated. After cooling the resulted suspension at 0 °C for 12 h, the crude product **3b** (0.990 g) was isolated by filtration. This material was purified by column chromatography on silica gel (eluent EtOH/25% aq NH_3 9:0.3 v/v) to give a single fraction (0.920 g). Supplementary recrystallization of the last one from boiling *i*-PrOH (10 mL) afforded pure compound **3b** (0.840 g, 77% yield with respect to **2b**).

1-{4-[4-(Carboxymethoxy)phenyl]amino-6-[(4-n-octyloxy)phenyl]amino-s-triazin-2-yl}-piperazine **3a**. 1.157 g (81% yield starting from 1.300 g **2a**). White solid. Mp 252-253 °C (*i*-PrOH). R_f (EtOH/25% aq NH_3 9:1 v/v)=0.70. Elemental analysis calcd. (%) for $C_{29}H_{39}N_7O_4$: C 63.37, H 7.15, N 17.84; found: C 62.98, H 7.22, N 17.79. IR (KBr) ν_{max} 3190 (m), 2956 (s), 2925 (s), 2854 (m), 2620 (w), 1745 (w), 1604 (s), 1581 (s), 1494 (s), 1453 (m), 1418 (s), 1335 (m), 1306 (m), 1245 (s), 1223 (s), 1045 (w), 828 (m), 802 (m) cm^{-1}. ^1H and 2D-^1H,^1H-COSY NMR (500 MHz, 5 mM in DMSO-d_6, 298 K) δ_H 0.86 (3H, t, $^3J_{H,H}$=7.0 Hz, Me), 1.26-1.34 (8H, m, 4×CH_2, *n*-octyl), 1.40 (2H, tt app. qui, $^3J_{H,H}$=7.3 Hz, CH_2, *n*-octyl), 1.68 (2H, tt app. qui, $^3J_{H,H}$=6.9 Hz, OCH_2CH_2, *n*-octyl), 2.94 (4H, bs, H-3, -5, PZ), 3.80 (4H, bs, H-2, -6, PZ), 3.91 (2H, t,$^3J_{H,H}$=6.5 Hz, OCH_2, *n*-octyl), 4.47 (2H, s, OCH_2), 6.79 (2H, d, $^3J_{H,H}$=9.0 Hz, H-3, -5, Ph), 6.83 (2H, d, $^3J_{H,H}$=9.0 Hz, H-3, -5, Ph), 7.56 (4H, bs, H-2, -6, Ph), 8.97 (2H, bs, NH) ppm. ^1H and 2D-^1H,^1H-COSY NMR (500 MHz, 5 mM in DMSO-d_6, 363 K) δ_H 0.88 (3H, t, $^3J_{H,H}$=6.8 Hz, Me), 1.27-1.38 (8H, m, 4×CH_2, *n*-octyl), 1.43 (2H, tt app. qui, $^3J_{H,H}$=7.1 Hz, CH_2, *n*-octyl), 1.71 (2H, tt app. qui, $^3J_{H,H}$=6.9 Hz, OCH_2CH_2, *n*-octyl), 2.85 (4H, t, $^3J_{H,H}$=4.8 Hz, H-3, -5, PZ), 3.74 (4H, t, $^3J_{H,H}$=5.0 Hz, H-2, -6, PZ), 3.95 (2H, t,$^3J_{H,H}$=6.5 Hz, OCH_2, *n*-octyl), 4.56 (2H, s, OCH_2), 6.83 (2H, d, $^3J_{H,H}$=9.0 Hz, H-3, -5, Ph), 6.84 (2H, d, $^3J_{H,H}$=9.0 Hz, H-3, -5, Ph), 7.55 (2H, d, $^3J_{H,H}$=10.0 Hz, H-2, -6, Ph), 7.57 (2H, d, $^3J_{H,H}$=9.5 Hz, H-2, -6, Ph), 8.56 and 8.58 (2H, 2×s, NH) ppm. 2D-^1H-DOSY NMR (500 MHz, 5 mM in DMSO-d_6, 298 K) *D* 164.4 μm^2 s^{-1}. DEPT-^{13}C NMR (125 MHz, 20 mM in DMSO-d_6, 298 K) δ_C 14.5 (Me), 22.6, 26.1, 29.2 and 29.3 (4×CH_2, *n*-octyl), 31.7 (OCH_2CH_2, *n*-octyl), 41.6 (C-2, -6, PZ), 43.7 (C-3, -5, PZ), 66.5 (OCH_2, *n*-octyl), 68.0 (OCH_2), 114.6 (C-3, -5, Ph), 122.1 and 123.0 (C-2, -6, Ph), 133.6 (C-1, Ph), 154.0 and 154.4 (C-4, Ph), 164.5 and 165.1 (C-2, -4, -6, T), 171.7 (COO^-) ppm. HRMS (ESI) (rel. int. %) *m*/*z*: 572.2991 $[M+Na]^+$ (5), 550.3176 (100) $[M+H]^+$. $[M+Na]^+$ calcd. for $C_{29}H_{39}N_7NaO_4$: 572.2961; $[M+H]^+$ calcd. for $C_{29}H_{40}N_7O_4$: 550.3142.

1-{4-[4-(3-Carboxypropoxy)phenyl]amino-6-[(4-n-octyloxy)phenyl]amino-s-triazin-2-yl}-piperazine **3b**. White solid. Mp 178.1-179.0 °C (*i*-PrOH). R_f (EtOH/25% aq. NH_3 9:0.3 v/v)=0.75. Elemental analysis calcd. (%) for $C_{31}H_{43}N_7O_4$: C 64.45, H 7.50, N 16.97; found: C 64.77, H 7.81, N 17.11. IR (KBr) ν_{max} 3392 (m), 2928 (m), 2851 (w), 1624 (w), 1572 (s), 1514 (s), 1418 (s), 1294 (m), 1248 (m), 1222 (s), 1130 (w), 957 (w), 827 (w), 804 (w), 594 (w) cm^{-1}. ^1H and 2D-^1H,^1H-COSY NMR (500 MHz, 5 mM in DMSO-d_6, 298 K) δ_H 0.86 (3H, t, $^3J_{H,H}$=7.0 Hz, Me), 1.26-1.33 (8H, m, 4×CH_2, *n*-octyl), 1.40 (2H, tt app. sx, $^3J_{H,H}$=6.9 Hz, CH_2, *n*-octyl), 1.67 (2H, tt app. qui, $^3J_{H,H}$=6.9 Hz, OCH_2CH_2, *n*-octyl), 1.92 (2H, tt app. qui, $^3J_{H,H}$=6.9 Hz, H-β), 2.38 (2H, t, $^3J_{H,H}$=7.3 Hz, H-α), 3.08 (4H, bs, H-3, -5, PZ), 3.87 (4H, bs, H-2, -6, PZ), 3.91 (2H, t,$^3J_{H,H}$=6.8 Hz, OCH_2, *n*-octyl), 3.94 (2H, t, $^3J_{H,H}$=6.8 Hz, H-γ), 6.835 (2H, d, $^3J_{H,H}$=9.0 Hz, H-3, -5, Ph), 6.842 (2H, d, $^3J_{H,H}$=8.5 Hz, H-3, -5, Ph), 7.56 (4H, bs, H-2, -6, Ph), 9.01 (2H, 2×bs, NH) ppm. ^1H and 2D-^1H,^1H-COSY NMR (500 MHz, 5 mM in DMSO-d_6, 363 K) δ_H 0.88 (3H, t, $^3J_{H,H}$=6.8 Hz, Me), 1.29-1.38 (8H, m, 4×CH_2, *n*-octyl), 1.43 (2H, tt app. qui, $^3J_{H,H}$=7.0 Hz, CH_2, *n*-octyl), 1.71 (2H, tt app. qui, $^3J_{H,H}$=6.9 Hz, OCH_2CH_2, *n*-octyl), 1.96 (2H, tt app. qui, $^3J_{H,H}$=6.8 Hz, H-β), 2.38 (2H, t, $^3J_{H,H}$=7.3 Hz, H-α), 3.09 (4H, t, $^3J_{H,H}$=5.0 Hz, H-3, -5, PZ), 3.90 (4H, t, $^3J_{H,H}$=5. 0 Hz, H-2, -6, PZ), 3.95 (2H, t,$^3J_{H,H}$=6.5 Hz, OCH_2, *n*-octyl), 3.98 (2H, t, $^3J_{H,H}$=6.5 Hz, H-γ), 6.83 (2H, d, $^3J_{H,H}$=9.0 Hz, H-3, -5, Ph), 6.84 (2H, d, $^3J_{H,H}$=9.0 Hz, H-3, -5, Ph), 7.536 (2H, d, $^3J_{H,H}$=9.0 Hz, H-2, -6, Ph), 7.544 (2H, d, $^3J_{H,H}$=9.0 Hz, H-2, -6, Ph), 8.64 (2H, 2×bs, NH) ppm. 2D-^1H-DOSY NMR (500 MHz, 5 mM in DMSO-d_6, 298 K) *D* 162.2 μm^2 s^{-1}. DEPT-^{13}C NMR (125 MHz, 20 mM in DMSO-d_6, 298 K) δ_C 14.6 (Me), 22.7 (CH_2, *n*-octyl), 24.9 (C-β), 26.1, 29.25 and 29.33 (3×CH_2, *n*-octyl), 30.7 (C-α), 31.8 (OCH_2CH_2, *n*-octyl), 40.6 (C-2, -6, PZ), 43.2 (C-3, -5, PZ), 67.3 (OCH_2, *n*-octyl), 68.1 (C-γ), 114.77 and 114.82 (C-3, -5, Ph), 122.4(C-2, -6, Ph), 133.4 and 133.6 (C-1, Ph),154.3, 154.5 and 154.6 (C-4, Ph), 164.6 and 165.2 (C-2, -4, -6, T), 174.8 (COO^-) ppm. HRMS (ESI) (rel. int. %) *m*/*z*: 600.3301 (7) $[M+Na]^+$, 578.3486 (100) $[M+H]^+$. $[M+Na]^+$ calcd. for $C_{31}H_{43}N_7NaO_4$: 600.3274; $[M+H]^+$ calcd. for $C_{31}H_{44}N_7O_4$: 578.3455.

Typical procedure for the synthesis of Boc-N-protected forms of compounds **3a** *and* **3b***; preparation of compound* **4a** (**III-2**, Scheme 1)

At room temperature, under inert atmosphere and with vigorous stirring, in a THF (25 mL) solution containing compound **2a** (1.000 g, 2.00 mmol), anhyd K_2CO_3 (0.276 g, 2.00 mmol) was suspended. To this suspension, Boc-piperazine (0.855 g 98%, 0.838 g 100%, 4.50 mmol) as THF (3 mL) solution was injected and the reaction mixture was stirred at room temperature for 24 h. Since after this period TLC monitoring still revealed the presence of the unreacted starting material **2a** (eluent *n*-hexane/EtOH 1:1 v/v), the reaction mixture was heated at 55-60 °C for additional 48 h, then evaporated, under vacuum, to dryness. The solid residue was taken with distilled water (20 mL) and the pH of the resulted solution was adjusted to pH~6 with AcOH when crude compound **4a** precipitated. After complete crystallization at 0 °C for 24 h, filtering off and drying, the crude material (1.125 g) was purified by crystallization from boiling *i*-PrOH (2.5 mL) to provide pure compound **4a** (1.100 g, 85% yield with respect to **2a**).

{1-{4-[4-(Carboxymethoxy)phenyl]amino-6-[(4-n-octyloxy)phenyl]amino-s-triazin-2-yl}-4-tertbutoxycarbonyl}-piperazine **4a**. White solid. Mp 240.6-241.0 ºC (*i*-PrOH). R_f (*n*-hexane/EtOH 1:1.5 v/v)=0.75. Elemental analysis calcd. (%) for $C_{34}H_{47}N_7O_6$: C 62.85, H 7.29, N 15.09; found: C 63.02, H 7.41, N 14.93. IR (KBr) ν_{max} 3328 (w), 2930 (m), 2855 (m), 1700 (m), 1623 (m), 1602 (m), 1544 (s), 1513 (s), 1500 (s), 1420 (s), 1238 (m), 1173 (m), 1009 (w), 829 (m), 801 (w), 598 (w), 515 (w) cm^{-1}. ^1H and 2D-^1H,^1H-COSY NMR (500 MHz, 32 mM in DMSO-d_6, 298 K) δ_H 0.86 (3H, t, $^3J_{H,H}$=6.8 Hz, Me, *n*-octyl), 1.26-1.32 (8H, m, 4×CH_2, *n*-octyl), 1.39-1.43 (2H, m, CH_2, *n*-octyl), 1.43 (9H, s, Me, Boc),1.68 (2H, tt app. qui, $^3J_{H,H}$=6.9 Hz, OCH_2CH_2, *n*-octyl), 3.39 (4H, s, H-3, -5, PZ), 3.71 (4H, s, H-2, -6, PZ), 3.91 (2H, t,$^3J_{H,H}$=6.5 Hz, OCH_2, *n*-octyl), 4.39 and 4.40 (2H, s, OCH_2), 6.79 (2H, d, $^3J_{H,H}$=9.0 Hz, H-3, -5, Ph), 6.83 (2H, d, $^3J_{H,H}$=8.5 Hz, H-3, -5, Ph), 7.57 (4H, bs, H-2, -6, Ph), 8.96 (2H, bs, s, NH), ppm. ^1H and 2D-^1H,^1H-COSY NMR (500 MHz, 32 mM in DMSO-d_6, 363 K) δ_H 0.89 (3H, t, $^3J_{H,H}$=7.0 Hz, Me, *n*-octyl), 1.29-1.38 (8H, m, 4×CH_2, *n*-octyl), 1.40-1.45 (2H, m, CH_2, *n*-octyl), 1.45 (9H, s, Me, Boc), 1.71 (2H, tt app. qui, $^3J_{H,H}$=6.9 Hz, OCH_2CH_2, *n*-octyl), 3.42 (4H, dd, $^3J_{H,H}$=4.5 Hz, H-3, -5, PZ), 3.73 (4H, t, $^3J_{H,H}$=5.3 Hz, H-2, -6, PZ), 3.95 (2H, t,$^3J_{H,H}$=6.5 Hz, OCH_2, *n*-octyl), 4.37 and 4.38 (2H, s, OCH_2), 6.81 (2H, ddd app. dt, $^3J_{H,H}$=9.5 Hz, $^4J_{H,H}$~$^5J_{H,H}$=2.4 Hz, H-3, -5, Ph), 6.83 (2H, ddd app. dt, $^3J_{H,H}$=9.5 Hz, $^3J_{H,H}$~$^4J_{H,H}$=2.4 Hz, H-3, -5, Ph), 7.53 (2H, d, $^3J_{H,H}$=9.0 Hz, H-2, -6, Ph), 7.56 (2H, dd, $^3J_{H,H}$=7.0 Hz, $^4J_{H,H}$=2.0 Hz, H-2, -6, Ph), 8.54 and 8.59 (2H, 2×s, NH) ppm. 2D-^1H-DOSY NMR (500 MHz, 5 mM in DMSO-d_6, 298 K) *D* 153.1 $\mu m^2\ s^{-1}$. DEPT-^{13}C NMR (125 MHz, 32 mM in DMSO-d_6, 298 K) δ_C 14.5 (Me, *n*-octyl), 22.6, 26.1, (2×CH_2, *n*-octyl), 28.5 and 28.6 (Me, Boc), 29.2, 29.26 and 29.27 (3×CH_2, *n*-octyl), 31.7 (OCH_2CH_2, *n*-octyl), 43.1 (C-3, -5, PZ), 44.1 and 44.4 (C-2, -6, PZ), 66.8 (OCH_2, *n*-octyl), 68.0 (OCH_2), 79.6 (Cq, Boc), 114.62 and 114.64 (C-3, -5, Ph), 122.0 and 123.0 (C-2, -6, Ph), 133.5 and 133.6 (C-1, Ph), 154.1 and 154.3 (C-4, Ph), 154.4 (>CO-N<, carbamate), 164.5 and 165.1 (C-2, -4, -6, T), 171.5 and 171.6 (COOH) ppm. HRMS (ESI) (rel. int. %) *m*/*z*: 726.2779 $[M-H+2K]^+$ (100), 688.3220 $[M+K]^+$ (98), 650.3660 $[M+H]^+$ (72), 626.2251 $[(M+K)-CH_4-H_2-CO_2]^+$ (19). $[M-H+2K]^+$ calcd. for $C_{34}H_{46}K_2N_7O_6$: 726.2784; $[M+K]^+$ calcd. for $C_{34}H_{47}KN_7O_6$: 688.3225; $[M+H]^+$ calcd. for $C_{34}H_{48}N_7O_6$: 650.3666; $[(M+K)-CH_4-H_2-CO_2]^+$ calcd. for $C_{32}H_{41}KN_7O_4$: 626.2857.

{1-{4-[4-(3-Carboxypropoxy)phenyl]amino-6-[(4-n-octyloxy)phenyl]amino-s-triazin-2-yl}-4-tertbutoxycarbonyl}-piperazine **4b**. 0.800 g (62% yield starting from 1.000 g **2b**). White solid. Mp 196.5-197.0 ºC (MeOH). R_f (*n*-hexane/EtOH 1:1.5 v/v) = 0.80. Elemental analysis calcd. (%) for $C_{36}H_{51}N_7O_6$: C 63.79, H 7.58, N 14.46; found: C 64.02, H 7.73, N 14.29. IR (KBr) ν_{max} 3399 (m), 3250 (m), 2929 (m), 2854 (m), 1736 (m), 1701 (m), 1678 (m), 1572 (s), 1514 (s), 1496 (s), 1431 (s), 1420 (s), 1240 (s), 1172 (m), 1011 (w), 829 (w), 738 (w) cm^{-1}. ^1H and 2D-^1H,^1H-COSY NMR (500 MHz, 28 mM in DMSO-d_6, 298 K) δ_H 0.86 (3H, t, $^3J_{H,H}$=6.8 Hz, Me, *n*-octyl), 1.26-1.34 (8H, m, 4×CH_2, *n*-octyl), 1.37-1.42 (2H, m, CH_2, *n*-octyl), 1.42 (9H, s, Me, Boc), 1.68 (2H, tt app. qui, $^3J_{H,H}$=6.9 Hz, OCH_2CH_2, *n*-octyl), 1.92 (2H, tt app. qui, $^3J_{H,H}$=6.9 Hz, H-β), 2.37 (2H, t, $^3J_{H,H}$=7.3 Hz, H-α), 3.38 (4H, bs, H-3, -5, PZ), 3.71 (4H, bs, H-2, -6, PZ), 3.91 (2H, t,$^3J_{H,H}$=6.8 Hz, OCH_2, *n*-octyl), 3.94 (2H, t, $^3J_{H,H}$=6.5 Hz, H-γ), 6.83 (2H, d,

$^3J_{H,H}$=9.0 Hz, H-3, -5, Ph), 6.84 (2H, d, $^3J_{H,H}$=8.5 Hz, H-3, -5, Ph), 7.57 (4H, bs, H-2, -6, Ph), 8.96 (2H, bs, NH) ppm. ^{1}H and 2D-^{1}H,^{1}H-COSY NMR (500 MHz, 28 mM in DMSO-d_6, 363 K) δ_H 0.88 (3H, t, $^3J_{H,H}$=6.8 Hz, Me, *n*-octyl), 1.29-1.36 (8H, m, 4×CH_2, *n*-octyl), 1.38-.45 (2H, m, CH_2, *n*-octyl), 1.45 (9H, s, Me, Boc), 1.71 (2H, tt app. qui, $^3J_{H,H}$=6.9 Hz, OCH_2CH_2, *n*-octyl), 1.96 (2H, tt app. qui, $^3J_{H,H}$=6.8 Hz, H-β), 2.36 (2H, t, $^3J_{H,H}$=7.3 Hz, H-α), 3.42 (4H, t, $^3J_{H,H}$=5.3 Hz, H-3, -5, PZ), 3.73 (4H, t, $^3J_{H,H}$=5.3 Hz, H-2, -6, PZ), 3.95 (2H, t,$^3J_{H,H}$=6.5 Hz, OCH_2, *n*-octyl), 3.99 (2H, t, $^3J_{H,H}$=6.5 Hz, H-γ), 6.84 (2H, d, $^3J_{H,H}$=9.0 Hz, H-3, -5, Ph), 6.85 (2H, d, $^3J_{H,H}$=9.0 Hz, H-3, -5, Ph), 7.55 (2H, d, $^3J_{H,H}$=8.5 Hz, H-2, -6, Ph), 7.56 (2H, d, $^3J_{H,H}$=9.0 Hz, H-2, -6, Ph), 8.58 (2H, s, NH) ppm. 2D-^{1}H-DOSY NMR (500 MHz, 5 mM in DMSO-d_6, 298 K) *D* 169.4 $\mu m^2 s^{-1}$. DEPT-^{13}C NMR (125 MHz, 28 mM in DMSO-d_6, 298 K) δ_C 14.5 (Me, *n*-octyl), 22.6 (CH_2, *n*-octyl), 24.9 (C-β), 26.1 (CH_2, *n*-octyl), 28.5 and 28.6 (Me, Boc), 29.2 and 29.3 (2×CH_2, *n*-octyl), 30.7 (C-α), 31.7 (OCH_2CH_2, *n*-octyl), 43.1 (C-3, -5, PZ), 44.0 and 44.1 (C-2, -6, PZ), 67.2 (OCH_2, *n*-octyl), 68.0 (C-γ), 79.6 (Cq, Boc), 114.65 and 114.71 (C-3, -5, Ph), 122.1 (C-2, -6, Ph), 133.55, 133.58 and 133.7 (C-1, Ph),154.1 and 154.3 (C-4, Ph), 154.4 (>CO-N<, carbamate), 164.5 and 165.1 (C-2, -4, -6, T), 174.7 (COOH) ppm. HRMS (ESI) (rel. int. %) *m*/*z*: 722.3607 (19) $[M-H+2Na]^+$, 700.3789 (56) $[M+Na]^+$, 678.3973 (100) $[M+H]^+$, 600.3265 $[M+H-CH_4-H_2O-CO_2]^+$ (18). $[M-H+2Na]^+$ calcd. for $C_{36}H_{50}N_7Na_2O_6$: 722.3618; $[M+Na]^+$ calcd. for $C_{36}H_{51}N_7NaO_6$: 700.3799; $[M+H]^+$ calcd. for $C_{36}H_{52}N_7O_6$ 678.3979; $[M+H-CH_4-H_2O-CO_2]^+$ calcd. for $C_{34}H_{46}N_7O_3$: 600.3662.

Typical procedure for Boc N-protecting group removal from compounds **4a** *and* **4b**; *alternative route towards compounds* **3a** *and* **3b** (**IV**, Scheme 1)

At room temperature, to a 1,4-dioxane (5 mL) solution containing Boc-derivative **4b** (0.715 g, 1.055 mmol), 3M aq HCl (2.5 mL) was added and then the reaction mixture was stirred in these conditions for 48 h. Since after this period TLC still revealed the presence of the unreacted starting material **4b** (eluent *n*-hexane/EtOH 1:1.5 v/v) together with the desired **3b** (eluent EtOH/25% aq NH_3 9:0.3 v/v), the reaction mixture was heated at 50-55 °C for 5 h. After that, at room temperature, the pH of the solution was adjusted to 6-6.5 with 25% aq NH_3. Evaporation under vacuum to dryness of the resulted suspension provided a solid residue which was taken with distilled water (25 mL). After complete crystallization at 0 °C for 24 h, filtering off and drying, the crude compound **3b** (0.540 g) was purified by crystallization from boiling *i*-PrOH (5 mL) to give the pure melamine (0.426 g, 70% yield with respect to **4b**). Following the same protocol, starting from Boc-derivative **4a** (0.700 g, 1.077 mmol), melamine **3a** was obtained (0.520 g, 88% yield with respect to **4a**).

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