SOLUTION- AND SOLID-PHASE SYNTHESIS OF COMBINATORIAL LIBRARIES OF TRISUBSTITUTED 1,3,5-TRIAZINES

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Abstract - A general synthesis of trisusbstituted 1,3,5-triazines of types (**4**) and (**5**) by condensation of amidines (**2**) and thiouronium salts (**3**) with dimethyl cyanoiminodithiocarbonate (**1**) was first established in solution (*Scheme 1*). Further investigations were directed toward a multidirectional cleavage procedure of the 2-alkylsulfinyl intermediates with different nucleophiles to form highly substituted 1,3,5-triazines of type (**8**) and (**9**). This methodology was successfully transferred onto solid support taking advantages of a sulfur-based safety catch linkage, using the polymer-bound thiouronium salt (**11**) (*Scheme 3*). In addition, other compounds libraries were chemoselectively generated on solid support in good to excellent yields combining both solution- and solid-phase synthesis, starting from a resin-bound thiol (**15**) and cyanuric chloride (**16**) (*Scheme 4*).

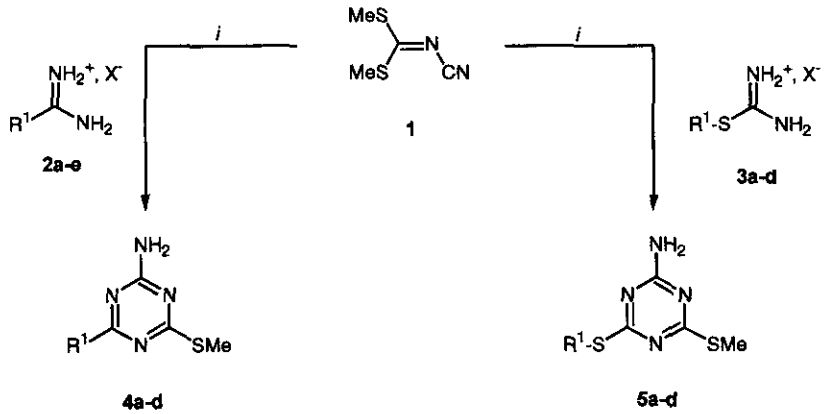
INTRODUCTION

The richness of the pharmacopeia in compounds containing heterocyclic system is the basis of a continuing search for simple, mild and more versatile processes towards these key structural elements. The introduction of combinatorial chemistry approaches in medicinal chemistry field to accelerate the drug discovery process has stimulated considerable efforts to find rapid and efficient access to a variety of classes of heterocycles. Thus, in the course of our investigations toward the development of a potentially valuable strategy for the combinatorial production of versatile heterocycles,[1-3] we report herein facile solution- and solid-phase approaches towards

2-alkylthio-1,3,5-triazines (**4**, **5**, **13** and **18**), and their subsequent conversion into substituted 1,3,5-triazines (**8**, **9**, **14** and **19**). Our first and second strategies, respectively performed in solution and on solid support, efficiently combine the reaction of dimethyl cyanoiminodithiocarbonate with amidines (**2a-d**) and thiouronium salts of type (**3a-d**) and (**11**) to form the 2-alkylthio-1,3,5-triazine skeleton, which undergoes nucleophilic displacement of the 2-alkylthio group with various nucleophiles.[2,4,5] The third approach combines both solution- and solid-phase chemistry through the successive substitution of cyanuric chloride (**16**),[6-10] followed by nucleophilic displacement of the 2-alkylthio group of triazines with various nucleophiles in a final step.

RESULTS AND DISCUSSION

The successful production of multigeneration compounds libraries by solution-phase chemistry heavily depends on the choice of the high-yielding reactions for each individual step, as well as on the carefully choice of the strategies for the chemical inactivation, and on the separation of highly reactive reagents. An example of an efficient solution-phase synthesis suitable for a multigeneration compounds library based on the 2-alkylthio-1,3,5-triazine template is outlined in *Scheme 1*.



i : EtOH, DIPEA, rt-65°C

Scheme 1

Ketene dithioacetal derivatives have been used for several decades to prepare polyfunctionalized heterocycles.[11-15] In a straightforward manner analogous to a previously described reaction,[16] reaction of dimethyl cyanoiminodithiocarbonate (**1**) with amidines (**2a-d**)

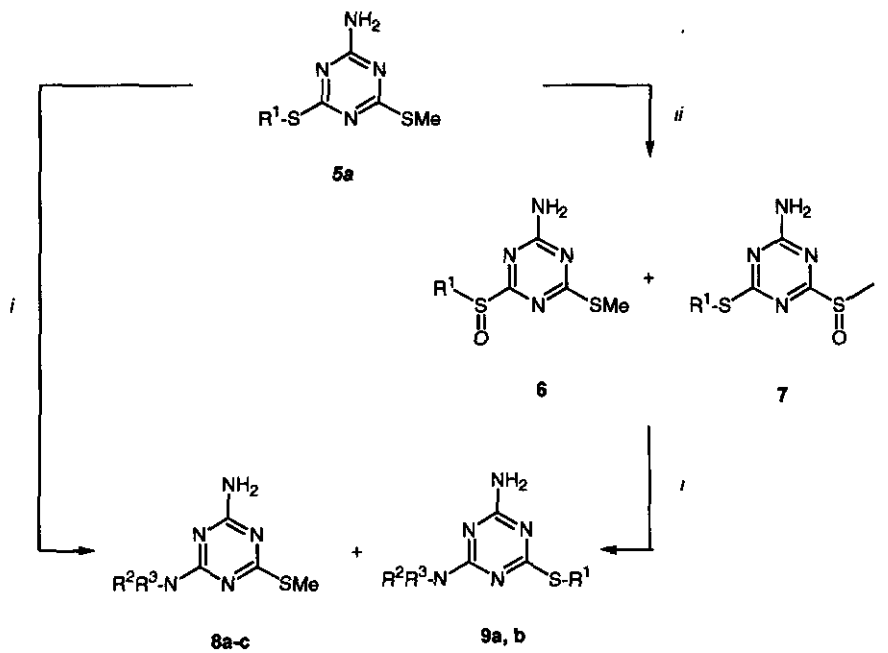
(DIPEA) in ethanol (EtOH) at 65°C gave the corresponding trisubstituted-1,3,5-triazines (**4a-d**) and (**5a-d**) in good yields (*Scheme 1, Table 1*). The required bis-nucleophilic thiouronium salts of type (**3a-d**) were easily accessible from thiourea and a large variety of alkyl halides in excellent yields.[16-18]

	R	Amidine	Thiouronium salt	Product	Yield [%]
1	Ph	**2a**		**4a**	89
1	4-Cl-C_6H_4	**2b**		**4b**	90
1	H_2NOC-C_6H_4	**2c**		**4c**	96
1	3-O_2N-C_6H_4	**2d**		**4d**	91
1	C_6H_{13}		**3a**	**5a**	70
1	4-Cl-$C_6H_4CH_2$		**3b**	**5b**	74
1	$C_6H_5CH_2$		**3c**	**5c**	65
1	3-indolyl		**3d**	**5d**	64

Table 1: *Synthesis of trisubstituted triazines (**4a-d**) and (**5a-d**)*

As already reported,[19] compounds of type (**5**) react directly with amines in dioxane at 85°C to afford mixtures of the corresponding 2- and 4-amino analogues (**8a-b**) and (**9a-b**), respectively (*Method C*) (*Scheme 2, Table 2*). At this stage purification by flash chromatography (FC) on silica gel led to the pure compounds. When substitution is performed with 2-*N,N'*-dimethylaminoethylamine, the corresponding 2-amino derivative (**8c**) is isolated exclusively. Moreover, we observed that previous oxidation of the alkylthiotriazine (**5a**) with 1.5 eq of 3-chloroperbenzoic acid (*m*-CPBA) gave a mixture of the corresponding alkylsulfinyl-substituted triazines of types (**6**) and (**7**) which were easily separated. Subsequent treatment with amines and purification by FC, afforded products (**8b**) and (**9b**) in moderate yields (*Method D*) (*Table 2*). In the scope of our research aiming at the design of efficient processes for combinatorial and parallel synthesis of libraries of heterocyclic compounds, the aforementioned sequence appeared ideally suited for a solid-phase production. Thus, when resin-bound thiouronium salt (**11**), prepared by reaction of thiourea with commercially available *Merrifield* resin (**10**) (1.8 mmol/g),[1,2,20] was reacted with dimethyl cyanoiminodithiocarbonate (**1**) in the presence of DIPEA in *N,N*-dimethylacetamide (DMA) at 80°C, the corresponding polymer-bound alkylthiotriazine (**12**) was obtained (*Scheme 3*). The formation of the resin-

bound compounds was followed by ATR/FT-IR (attenuated total reflexion method).[21]



i : R^2R^3NH, dioxane, 85°C ; *ii* : *m*-CPBA (1.5 eq), CH_2Cl_2, 0°C-rt

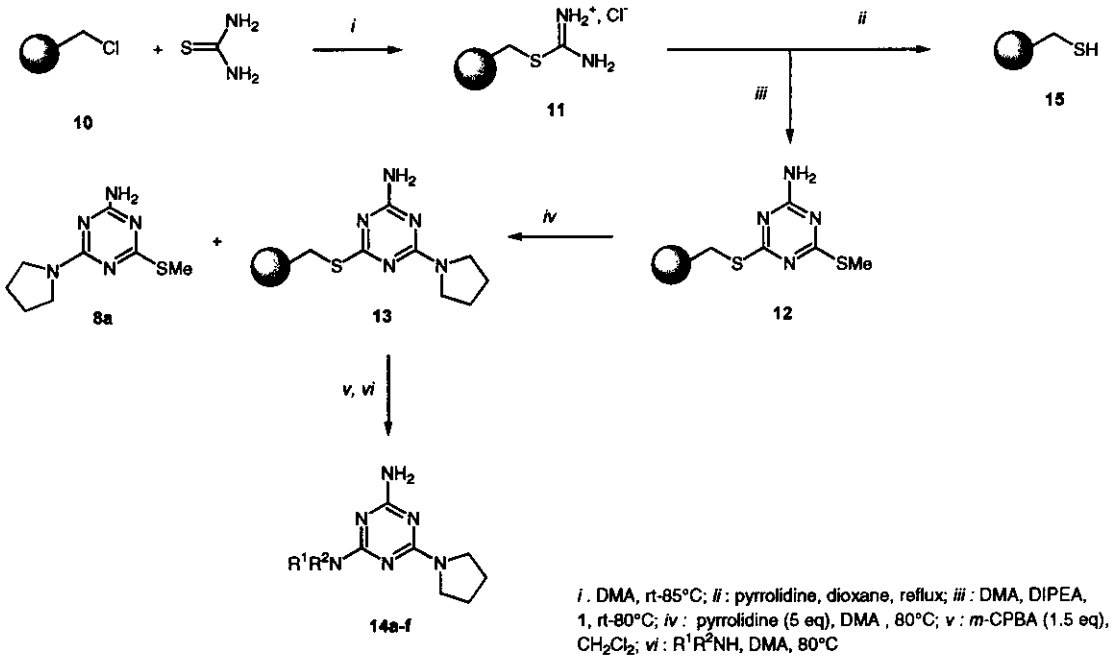
Scheme 2

	Method	Amine	Product	Yield [%]
5a	C	pyrrolidine	**8a, 9a**	55/33
5a	C	$MeNH_2$	**8b, 9b**	55/38
5a	D	$MeNH_2$	**8b, 9b**	20/23
5a	C	$Me_2N(CH_2)_2NH_2$	**8c**	73

Table 2: *Synthesis of trisubstituted triazines (**8a-c**) and (**9a-b**)*

As a key step in the sequence, the polymer-bound alkylthiotriazine (**12**) was treated with 5 eq of pyrrolidine in DMA to form a 1 : 1 mixture of 4-amino-2-methylthio-4-(pyrrolidin-1-yl)-1,3,5-triazine (**8a**) and pyrrolo-polymer-bound alkylthiotriazine (**13**), which was easily separated by filtration. Compound (**8a**) was isolated in high purity without any further purification. Sulfur oxidation of **13** with 1.2 eq of *m*-CPBA in CH_2Cl_2 to form the intermediate alkylsulfinyl derivative

and subsequent cleavage with various amines gave a second generation of 1,3,5-triazines (**14**) (*Scheme 3*). Compounds (**14a-f**) (*Table 3*) were purified by FC.



Scheme 3

This synthetic strategy clearly demonstrates the key strength of solid-phase chemistry over solution-phase synthesis, since triazine (**13**) remained attached to the resin and could be directly used in the next substitution step, while compound (**8a**) is obtained in a pure form by filtration of the resin. Nevertheless, the potential of this solid-phase approach is restricted to reactive amines (3,5-dichloroaniline does not react with the oxidized **13**). In order to explore in depth the potential of a *S*-atom as a safety catch linker towards generation of highly functionalized triazines libraries and to overcome the issues described above, we combined both solution- and solid-phase chemistry to develop a new and facile access to trisubstituted 1,3,5-triazines of type (**19**) based on previously described successive substitution of cyanuric chloride.[4-6] Treatment of cyanuric chloride (**16**) with 3,5-dichloroaniline in acetone at -20°C in the presence of 2N NaOH gave the pure 2-(3,5-dichloroanilino)-4,6-dichloro-1,3,5-triazine (**17b**) (*Scheme 4*). Substitution of the second chlorine with a resin-bound thiol (**15**) in DMA in the

presence of DIPEA at 40°C afforded the key polymer-bound alkylthiotriazine (**18b**).

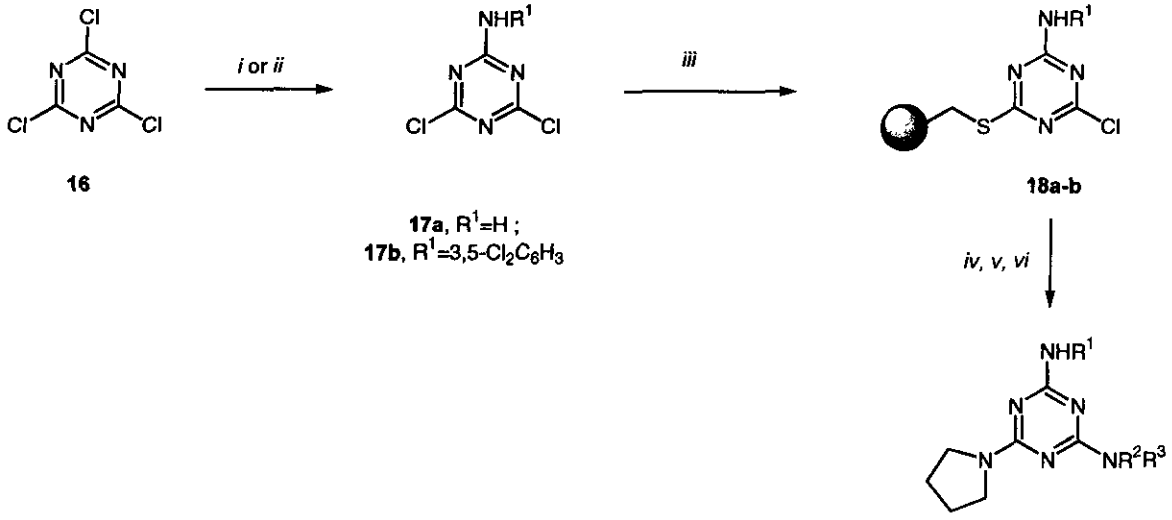
	Amine	Product
13	piperidine	**14a**
13	cyclohexylamine	**14b**
13	2,2,2-trifluoroethylamine	**14c**
13	3,4,5-trimethoxybenzylamine	**14d**
13	4-chlorobenzylamine	**14e**
13	4-methoxyaniline	**14f**
13	3,5-dichloroaniline	no reaction

Table 3: *Synthesis of trisubstituted triazines (**14a-f**).*

The anchoring thiol resin (**15**) was easily accessible by treatment of the polymer-bound thiouronium salt (**11**) with pyrrolidine in refluxing dioxane. The third chlorine atom was then substituted with various amines in DMA at 45°C in the presence of DIPEA. Additionally, to introduce a new element of diversity, the same procedure was repeated using 2-amino-4,6-dichloro-1,3,5-triazine (**17a**). Finally, the *S*-atom of **18a, b** was selectively oxidized with *N*-phenylsulfonyl-3-phenyloxaziridine[22] followed by treatment with pyrrolidine to yield a third generation of pure 1,3,5-triazines (**19a-h**) in good yields (*Scheme 4, Table 4*). *N*-Phenylsulfonyl-3-phenyloxaziridine was selected as reagent of choice in term of selectivity, purity and reaction work-up. Compared to other existing approaches, our combination of both solution- and solid-phase process was found to be in our hands the most valuable access towards polyfunctionalized 1,3,5-triazines, allowing introduction of poorly reactive amines in high yield and with high purity.

CONCLUSION

These approaches featured thiouronium salts as a useful source of masked sulfur and can be considered as a potent demonstration of a sulfur-based safety-catch linkage strategy for the traceless synthesis of heterocyclic compounds on solid supports. These new and facile solution- and solid-phase approach gave access to various libraries of highly substituted triazines in good yields and high purity.



Scheme 4

	R^1	Amine	Product	Yield [%] [a]
16	H	3,4,5-trimethoxybenzylamine	**19a**	67
16	H	benzylamine	**19b**	70
16	H	isopropylmethylamine	**19c**	85
16	H	4-fluorobenzylamine	**19d**	42
16	3,5-$Cl_2C_6H_3$	3,4,5-trimethoxybenzylamine	**19e**	29
16	3,5-$Cl_2C_6H_3$	benzylamine	**19f**	31
16	3,5-$Cl_2C_6H_3$	isopropylmethylamine	**19g**	42
16	3,5-$Cl_2C_6H_5$	4-fluorobenzylamine	**19h**	31

a) calculation based on the relative loading of the resin evaluated by elemental analysis

Table 4: *Synthesis of trisubstituted triazines (**19a-f**).*

ACKNOWLEDGEMENTS

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EXPERIMENTAL PART

All reactions which require air- or moisture-sensitive reactants and solvents were carried out in oven- or flame-dried glassware under a positive pressure of dry Ar. Reaction solvents and liquidreagents were purified before use or purchased in abs. quality. Anal. TLC : 2.5 x 10 cm precoated TLC plates, SiO_2 *60F-254*, layer thickness 0.25 mm (*E. Merck & Co.*, Darmstadt, Germany). Flash chromatography (FC):[23] *E. Merck* SiO_2 60 (70-230 Mesh ASTM). ATR/FT-IR: *Nicolet-7199 FT-IR* spectrometer; solids in KBr pellets, liquids as thin films ; characteristic bands in cm^{-1}. ^{1}H-NMR Spectra: *Bruker-AC-250* apparatus, at 250 MHz; in DMSO-d_6 or $CDCl_3$; TMS as internal standard ; chemical shift of signal centers and ranges in ppm (δ), *J* in Hz. EI-MS: *Finnigan MS9-AEI* or *Mat90* ; m/z (rel.). HRMS Spectra: *Mat95* GC/MS apparatus.

Thiouronium salts (**3a-d**),[2] 2-amino-4,6-dichloro-1,3,5-triazine (**17a**),[24] and *N*-phenylsulfonyl-3-phenyloxaziridine,[22] were prepared following literature procedures.

General Procedures: *Method A*: To a stirred mixture of amidine (**2**) (1.1 mmol) and dimethyl cyanodithioiminocarbonate (**1**) (0.162 g, 1 mmol) in EtOH (5 mL) under Ar at rt, DIPEA (377 mL, 2.2 mmol) was added. The mixture was warmed to 65°C for several hours, cooled to rt, and H_2O (5 mL) was added. The suspension was filtered and washed with an equimolar mixture of EtOH/H_2O affording **3**, without any further purification.

Method B: To a stirred mixture of thiouronium salt (**3**) (1.1 mmol) and dimethyl cyanoiminodithiocarbonate (**1**) (0.162 g, 1 mmol) in EtOH (5 mL) under Ar at rt, DIPEA (377 mL, 2.2 mmol) was added. The mixture was warmed up to 65°C for several hours, cooled to rt and poured onto ice, H_2O, and EtOAc. The organic layer was washed with brine, and evaporated. The residue was purified by FC (SiO_2).

Method C: A mixture of triazine (**5**) (1 mmol) and excess of amine R^2R^3NH in dioxane (3 mL) was stirred for several hours at 85°C. After comsumption of **5**, the mixture was cooled to rt, poured into water, and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and evaporated. The residue was purified by FC (SiO_2) as indicated in the corresponding description yielding to **8** and **9**.

Method D: To a stirred solution of 1 mmol of triazines (**5**) in DCM (3 mL) was added *m*-CPBA (0.258 g, 1.5 mmol) under Ar at 0°C. After stirring at rt for 2 h, the reaction was poured into sat. aq $NaHCO_3$ and extracted with EtOAc. The organic phase was washed with brine, dried over $MgSO_4$ and the solvent was evaporated. To a solution of the residue in dioxane (3 mL) was added 1.2 mmol of amine. The reaction was stirred at rt or warmed at 85°C for several hours and poured onto ice, water and EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and the solvent was evaporated. The residue was chromatographed on SiO_2 as indicated yielding to **8** and **9**.

Method E: 2-Alkylthio-4-amino-6-(pyrrolidin-1-yl)-1,3,5-triazine resin (**13**) (6 g, 6 mmol) was washed with DCM (2 x 20 mL). Then DCM (25 mL) and *m*-CPBA (1.55 g, 9 mmol) were added and the suspension was stirred at rt for 2 h under Ar. The solvent was sucked off and the resin was washed with DCM (4 x 20 mL). The oxidation with *m*-CPBA was repeated once for 15 h. The solvent was filtered off and the resin was successively washed with DCM (4 x 30 mL), dioxane (3 x 30 mL), isopropyl alcohol (3 x 30 mL), dioxane (3 x 30 mL), pentane (2 x 30 mL), and dried over MgSO4 under high vacuum. The alkylsulfinyltriazine resin was divided in portion (0.200 g, 0.2 mmol) and dry dioxane (2 mL) was added followed by the desired amine (3 eq). The suspension was shaken at 80°C for 15 h under Ar. This eluate and one subsequent wash with dioxane (2 mL) were collected and combined, and the solvent removed. The residue was chromatographed on SiO_2 eluting with DCM/MeOH (10 : 1) affording **14a-f**.

Method F: To the resin (**18a**) (0.192 g, 0.25 mmol) were added amine (0.625 mmol), DIPEA (0.215 mL, 1.25 mmol) and DMA (1.5 mL). After stirring at 45°C for 17 h, the resin was washed successively with DMA (2 x 5 mL), isopropyl alcohol (5 mL), and finally DCM (3 x 5 mL). The resin was then treated with *N*-phenylsulfonyl-3-phenyloxaziridine (0.075 g, 0.288 mmol) and DCM (2.5 mL) for 14 h at rt. The oxidized resin was washed with DCM (5 mL), isopropyl alcohol (5 mL), and dioxane (2 x 5 mL). A solution of pyrrolidine (0.041 mL, 0.50 mmol) in dioxane (2.5 mL) was added to the resin and the mixture was shaken for 6 h at 60°C. The combined filtrates were lyophylized to yield **19a-h** in high purity.

4-Amino-2-methylthio-6-phenyl-1,3,5-triazine (**4a**): According to *Method A* with **1** (0.292 g, 2 mmol), **2a** (0.264 g, 2.2 mmol): 0.25 g (89 %) of **4a** as colorless crystals (CH_3CN-H_2O); mp 174-176°C. NMR (250 MHz, DMSO-d_6): 8.35-8.30 (m, 2 H, arom.); 7.60-7.50 (m, 3 H, arom. and NH_2); 2.52 (s, 3 H, aliph.). IR (KBr): 3386w, 3162w, 1632m, 1519s, 778m, 700m. HRMS:

Calcd for $C_{10}H_{10}N_4S$: 218.0626. Found: 218.0626.

4-Amino-6-(4-chlorophenyl)-2-methylthio-1,3,5-triazine (**4b**): According to *Method A* with **1** (0.292 g, 2 mmol), **2b** (0.621 g, 2.2 mmol): 0.454 g (90 %) of **4b** as colorless crystals (CH_3CN-H_2O); mp 219-221°C. NMR (250 MHz, DMSO-d_6): 8.27 (d, *J*=8, 2 H, arom.); 7.65 (s, NH_2); 7.58 (d, *J*=8, 2 H, arom.); 2.49 (s, 3 H, aliph.). IR (KBr): 3477w, 3159w, 1659m, 1505s, 848m, 800m. HRMS: Calcd for $C_{10}H_9N_4ClS$: 252.0236. Found: 252.0234.

4-Amino-6-(4-carbamoylphenyl)-2-methylthio-1,3,5-triazine (**4c**): According to *Method A* with **1** (0.292 g, 2 mmol), **2c** (0.649 g, 2.2 mmol): 0.501 g (96 %) of **4c** as colorless crystals crystals (CH_3CN-H_2O); mp >260°C. NMR (250 MHz, DMSO-d_6): 8.28 (d, *J*=8, 2 H, arom.); 7.65 (s, NH_2); 7.57 (d, *J*=8, 2 H, arom.); 2.49 (s, 3 H, aliph.). IR (KBr): 3395w, 3192w, 1653m, 1513s, 828m, 800m. HRMS: Calcd for $C_{11}H_{11}N_5OS$: 261.0684. Found: 261.0683.

4-Amino-2-methylthio-6-(3-nitrophenyl)-1,3,5-triazine (**4d**): According to *Method A* with **1** (0.292 g, 2 mmol), **2d** (0.443 g, 2.2 mmol): 0.478 g (91 %) of **4d** as colorless crystals crystals (CH_3CN-H_2O); mp 231-232°C. NMR (250 MHz, DMSO-d_6): 9.10-9.00 (m, 1 H, arom.); 8.75-8.65 (m, 1 H, arom.); 8.50-8.40 (m, 1 H, arom.); 7.90-7.80 (m, 1 H, arom. and NH_2); 2.54 (s, 3 H, aliph.). IR (KBr): 3444w, 3170w, 1652m, 1522s, 1347m, 828m, 712m. HRMS: Calcd for $C_{10}H_9N_5O_2S$: 263.0477. Found: 263.0484.

6-Amino-2-hexylthio-4-methylthio-1,3,5-triazine (**5a**): According to *Method B* with **1** (5.84 g, 40 mmol), **3a** (10.6 g, 44 mmol): 7.22 g (70 %) of **5a** as colorless crystals crystals (CH_3CN-H_2O); mp 68-69°C. NMR (250 MHz, DMSO-d_6): 7.47 (s, NH_2); 3.01 (t, *J*=6.6, 2 H, aliph.); 2.41 (s, 3 H, aliph.); 1.65-1.55 (m, 2 H, aliph.); 1.40-1.20 (m, 6 H, aliph.); 0.90 (t, *J*=6.2, 3 H, aliph.). IR (KBr): 3397w, 3211w, 1642m, 1515s, 847m, 802m. HRMS: Calcd for $C_{10}H_{18}N_4S_2$: 258.0973. Found: 258.0974.

6-Amino-2-(4-chlorobenzylthio)-4-methylthio-1,3,5-triazine (**5b**): According to *Method B* with **1** (0.292 g, 2 mmol), **3b** (0.451 g, 2.2 mmol): 0.44 g (74 %) of **5b** as colorless crystals crystals (CH_3CN-H_2O); mp 131-133°C. NMR (250 MHz, DMSO-d_6): 7.58 (s, NH_2); 7.50-7.35 (m, 4 H, arom.); 4.32 (s, 2 H, aliph.); 2.41 (s, 3 H, aliph.). IR (KBr): 3456w, 3201w, 1632m, 1513s, 848m, 800m. HRMS: Calcd for $C_{11}H_{11}N_4ClS_2$: 298.0114. Found: 298.0109.

6-Amino-2-benzylthio-4-methylthio-1,3,5-triazine (**5c**): According to *Method B* with **1** (0.292 g, 2 mmol), **3c** (0.446 g, 2.2 mmol): 0.343 g (65 %) of **5c** as colorless crystals (CH_3CN-H_2O); mp 138-139°C. NMR (250 MHz, DMSO-d_6): 7.58 (s, NH_2); 7.40-7.25 (m, 5 H, arom.); 4.35 (s, 2 H, aliph.); 2.42 (s, 3 H aliph.). IR (KBr): 3451w, 3201w, 1638m, 1513s, 785m, 705m. HRMS: Calcd for $C_{11}H_{12}N_4S_2$: 264.0503. Found: 264.0503.

6-Amino-2-(1H-indol-3-ylmethylthio)-4-methylthio-1,3,5-triazine (**5d**): According to *Method B* with **1** (0.292 g, 2 mmol), **3d** (0.702 g, 2.2 mmol): 0.370 g (64 %) of **5d** as yellowish crystals (CH_3CN-H_2O); mp 185-187°C. NMR (250 MHz, DMSO-d_6): 11.63 (s, NH); 7.70-7.65 (m, 1 H, arom.); 7.50-7.45 (m, 1 H, arom.); 7.39 (s, NH_2); 7.20-7.10 (m, 3 H, arom.); 2.42 (s, 3 H, aliph.). IR (KBr): 3440w, 3185w, 1647m, 1518s, 743m. HRMS: Calcd for $C_{12}H_{11}N_5S_2$: 289.0456. Found: 289.0459.

6-Amino-2-hexylsulfinyl-4-methylthio-1,3,5-triazine (**6**): According to *Method B* with **5a** (0.20 g, 0.775 mmol): 0.106 g (50 %) of **6** as colorless crystals (CH_3CN-H_2O); mp 125-128°C. NMR (250 MHz, DMSO-d_6): 8.07 (br s, NH_2); 3.05-2.90 (m, 2 H, aliph.); 2.48 (s, 3 H, aliph.); 1.75-1.70 (m, 1 H, aliph.); 1.55-1.50 (m, 1 H, aliph.); 1.45-1.20 (m, 6 H, aliph.); 0.90 (t, *J*=6.2, 3 H, aliph.). IR (KBr): 3352w, 3208w, 1652m, 1481s, 1058m, 8.37w. HRMS: Calcd for $C_{10}H_{18}N_4OS_2$: 274.0922. Found: 274.0921.

6-Amino-2-hexylthio-4-methysulfinyl-1,3,5-triazine (**7**): According to *Method B* with **5a** (0.2 g, 0.775 mmol): 0.106 g (50 %) of **7** as colorless crystals (CH_3CN-H_2O); mp 160-161°C. NMR (250 MHz, DMSO-d_6): 8.07 (br s, NH_2); 3.01 (t, *J*=6.6, 2 H, aliph.); 2.81 (s. 3 H, aliph.); 1.65-1.55 (m, 2 H, aliph.); 1.40-1.20 (m, 6 H, aliph.); 0.90 (t, *J*=6.2, 3 H, aliph.). IR (KBr): 3420w, 3199w, 1661m, 1481s, 1060m. HRMS: Calcd for $C_{10}H_{19}N_4OS_2$ (M^++H): 275.1000. Found: 275.0999.

6-Amino-2-hexylthio-4-(pyrrolidin-1-yl)-1,3,5-triazine (**8a**): According to *Method C* with **5a** (0.20 g, 0.775 mmol): 0.130 g (55 %) of **8a** as colorless crystals (MeOH); mp 100-102°C. NMR (250 MHz, DMSO-d_6): 6.72 (s, NH_2); 3.40-3.35 (m, 4 H, aliph.); 2.98 (t, *J*=6.6, 2 H, aliph.); 1.85-1.80 (m, 4 H, aliph.); 1.65-1.55 (m, 2 H, aliph.); 1.40-1.20 (m, 6 H, aliph.); 0.90(t, *J*=6.2, 3 H, aliph.). IR (KBr): 3356w, 3182w, 1648m, 1538s, 604m. HRMS: Calcd for $C_{13}H_{23}N_5S$: 281.1674. Found: 281.1669.

6-Amino-4-methylamino-2-hexylthio-1,3,5-triazine (**8b**): According to *Method C* with **5a** (1.0 g,

3.87 mmol) : 0.52 g (55 %) of **8b**: According to *Method D* with **5a** (0.50 g, 1.92 mmol): 0.09 g (20 %) of **8b** as colorless crystals (MeOH); mp 119-120°C. NMR (250 MHz, DMSO-d_6): 7.10-6.95 (m, NH); 6.75 (br s, NH_2); 2.96 (q, *J*=6.9, 2 H, aliph.); 2.75-2.65 (m, 3 H, aliph.); 1.60-1.50 (m, 2 H, aliph.); 1.40-1.20 (m, 6 H, aliph.); 0.90 (t, *J*=6.2, 3 H, aliph.). HRMS: Calcd for $C_{10}H_{19}N_5S$: 241.1361. Found: 241.1358.

6-Amino-4-(2-dimethylaminoethylamino)-2-hexylthio-1,3,5-triazine (**8c**): According to *Method C* with **5a** (0.20 g, 0.775 mmol): 0.115 g (50 %) of **8c** as colorless crystals (MeOH); mp 109-112°C. NMR (250 MHz, DMSO-d_6): 7.10-6.95 (m, NH); 6.61 (br s, NH_2); 3.35-3.25 (m, 2 H, aliph.); 2.98 (t, *J*=6.7, 2 H, aliph.); 2.30 (t, *J*=6.8, 2 H, aliph.); 2.14 (s, 3 H, aliph.); 1.60-1.50 (m, 2 H, aliph.); 1.40-1.20 (m, 6 H, aliph.); 0.90 (t, *J*=6.2, 3 H, aliph.). IR (KBr): 3356w, 3153w, 1656m, 1483s, 807m. HRMS: Calcd for $C_{13}H_{27}N_6S$ (M^++H): 299.2018. Found: 299.2018.

6-Amino-2-hexylthio-4-(pyrrolidin-1-yl)-1,3,5-triazine (**9a**): According to *Method C* with **5a** (0.20 g, 0.775 mmol) : 0.06 g (33 %) of **9a** as colorless crystals (MeOH); mp 172-174°C. NMR (250 MHz, DMSO-d_6): 6.72 (s, NH_2); 3.40-3.35 (m, 4 H, aliph.); 2.36 (s, 3 H, aliph.); 1.85-1.80 (m, 4 H, aliph.). IR (KBr): 3339w, 3176w, 1659m, 1545s, 604m. HRMS: Calcd for $C_8H_{13}N_5S$: 211.0892. Found: 211.0891.

6-Amino-2-hexylthio-4-methylamino-1,3,5-triazine (**9b**): According to *Method C* with **5a** (1.0 g, 3.87 mmol) : 0.254 g (38 %) of **9b**. According to *Method D* with **5a** (0.5 g, 1.92 mmol): 0.09 g (23 %) of (**9b**) as colorless crystals (MeOH); mp 173-175°C. NMR (250 MHz, DMSO-d_6): 7.10-6.95 (m, NH); 6.75 (br s, NH_2); 2.67 (t, *J*=4.8, 3 H, aliph.); 2.33 (s, 3 H, aliph.). IR (KBr): 3442w, 3191w, 1638m, 1467s, 804m. HRMS: Calcd for $C_5H_9N_5S$: 171.0579. Found: 171.0576.

Polymer-bound thiouronium salt (**11**). A mixture of *Merrifield* resin (100 g, 1.80 mmol/g), thiourea (68.5 g, 900 mmol), and DMA (1 L) was shaken at 85°C for 20 h and then washed with isopropyl alcohol (1 x 5 min), dioxane (2 x 4 min), dioxane-H_2O (1 : 1, 6 x 4 min), DMA (3 x 4 min) and isopropyl alcohol (5 x 3 min) at rt using an automated washing station. Drying under high vacuum for 20 h afforded polymer-bound thiouronium salt (**11**): 92 % of conversion based on elemental analysis. IR: 3040s, 2920s, 1640s, 1500m, 1450s, 750m, 700s. Anal. Found: N, 4.33; S, 5.21.

Polymer-bound alkylthiotriazine (**12**): To a suspension of resin (**11**) (48 g, 71 mmol) in dry DMA

(400 mL), dimethyl cyano-dithioiminocarbonate (**1**) (12.5 g, 85 mmol) and DIPEA (18.3 mL, 107 mmol) were successively added. After 72 h shaking at 80°C under Ar, the solvent was sucked off and the resin washed using an automated washing station with DMA (5 x 3 min), isopropyl alcohol (5 x 2 min), DMA (5 x 3 min), isopropyl alcohol (5 x 2 min), and dried under high vacuum. 50 g of **12**, 73 % of conversion according to elemental analysis. IR: 3480w, 3320w, 3020w, 1660m, 1600m, 1505s, 1493s, 1451s, 1296m, 1258m, 948m, 844m, 802m, 757m, 696s. Anal. Found: N, 5.21; S, 6.96.

Pyrrolo-polymer-bound alkylthiotriazine (**13**): To a suspension of resin (**12**) (15 g, 15 mmol) in DMA (230 mL), pyrrolidine (6.2 mL, 75 mmol) was added. After 72 h shaking at 80°C under Ar, the solvent was sucked off and the resin washed using an automated washing station with DMA (3 x 3 min), isopropyl alcohol (3 x 3 min), and dried under high vacuum. Resin was treated a second time with pyrrolidine for 72 h at 80°C under Ar, washed and dried as described for **12**. 13 g of **13**: 50 % conversion according to decrease in molecular weight (elemental analysis). Evaporation of the combined washings furnished pure compound (**8a**) (1.6 g, 50 %). **13**; IR: 3024w, 2921m, 2949m, 1630m, 1602m, 1539s, 1504s, 1492s, 1450m, 1298m, 757m, 696s. Anal. Found: N, 4.04; S, 4.20.

2-Amino-4-(piperidin-1-yl)-6-(pyrrolidin-1-yl)-1,3,5-triazine (**14a**): According to *Method E* with piperidine to yield **14a**. Pale yellowish solid (MeOH); mp 135-137°C. ^{1}H-NMR (250 MHz, DMSO-d_6): 6.18 (br s, NH_2); 3.71 (t, J = 5, 4 H, aliph.); 3.51-3.45 (m, 4 H, aliph.); 1.92-1.85 (m, 4 H, aliph.); 1.71-1.63 (m, 2 H, aliph.); 1.54-1.48 (m, 4 H, aliph.). HRMS: *Calcd for* $C_{12}H_{20}N_6$: 248.1749. Found: 248.1752.

2-Amino-4-(cyclohexylamino)-6-(pyrrolidin-1-yl)-1,3,5-triazine (**14b**): Prepared similarly to **14a**, performing cleavage with cyclohexylamine. Brownish crystals (MeOH); mp 116-118°C. ^{1}H-NMR (250 MHz, DMSO-d_6): 6.08 (br s, NH_2); 3.49-3.35 (m, 5 H, aliph.); 1.82-1.52 (m, 10 H, aliph.); 1.24-1.10 (m, 4 H, aliph.). HRMS: Calcd for $C_{13}H_{22}N_6$: 262.1906. Found: 262.1904.

2-Amino-6-(pyrrolidin-1-yl)-4-(2,2,2-trifluoroethylamino)-1,3,5-triazine (**14c**): Prepared similarly to **14a**, performing cleavage with 2,2,2-trifluoroethylamine. Yellowish crystals (MeOH); mp 183-185°C. ^{1}H-NMR (250 MHz, DMSO-d_6): 6.20 (br s, NH_2); 4.10-3.95 (m, 2 H, aliph.); 3.51-3.45 (m, 4 H, aliph.); 1.92-1.85 (m, 4 H, aliph.). HRMS: Calcd for $C_9H_{13}N_6F_3$: 262.1154. Found: 262.1154.

2-Amino-6-(pyrrolidin-1-yl)-4-(3,4,5-trimethoxybenzylamino)-1,3,5-triazine (**14d**): Prepared similarly to **14a**, performing cleavage with 3,4,5-trimethoxybenzylamine. Brownish crystals (MeOH); mp 139-140°C. ^{1}H-NMR (250 MHz, DMSO-d_6): 6.96 (t, *J*=7.5, NH); 6.63 (s, 2 H arom.); 6.10 (br s, NH_2); 4.33 (d, *J*=6.2, 2 H, aliph.); 3.73 (s, 6 H, aliph.); 3.62 (s, 3 H, aliph.); 3.51-3.45 (m, 4 H, aliph.); 1.92-1.85 (m, 4 H, aliph.). HRMS: Calcd for $C_{17}H_{24}N_6O_3$: 360.1910. Found: 360.1907.

2-Amino-4-(4-chlorobenzylamino)-6-(pyrrolidin-1-yl)-1,3,5-triazine (**14e**): Prepared similarly to **14a**, performing cleavage with 4-chlorobenzylamine. Yellowish oil. ^{1}H-NMR (250 MHz, DMSO-d_6): 7.40-7.25 (m, 4 H, arom.); 7.12 (br s, NH); 6.10 (br s, NH_2); 4.36 (d, *J*=6.2, 2 H, aliph.); 3.51-3.45 (m, 4 H, aliph.); 1.92-1.85 (m, 4 H, aliph.). HRMS: Calcd for $C_{14}H_{17}N_6Cl$: 304.1203. Found: 304.1198.

2-Amino-4-(4-methoxyanilino)-6-(pyrrolidin-1-yl)-1,3,5-triazine (**14f**): Prepared similarly to **14a**, performing cleavage with with 4-methoxyaniline. Yellowish oil. ^{1}H-NMR (250 MHz, DMSO-d_6): 8.63 (s, NH); 7.61 (d, *J*=9.0, 2 H, arom.); 6.73 (d, *J*=9.2, 2 H, arom.); 6.20 (br s, NH_2); 3.63 (s, 3 H, aliph.); 3.51-3.45 (m, 4 H, aliph.); 1.92-1.85 (m, 4 H, aliph.). HRMS: Calcd for $C_{14}H_{18}N_6O$: 286.1542. Found: 286.1543.

Polymer-bound thiol (**15**): A mixture of polymer-bound thiouronium salt (**11b**) (92 g, 2.1 mmol/g) and dioxane:pyrrolidine (4 : 1, 900 mL) was stirred at 110°C for 2 h and then washed and dried as described for **12**. 65.3 g of thiol resin (**15**): 88 % of conversion based on elemental analysis. IR: 3040w, 2940s, 2860w, 1620w, 1520s, 1500s, 1460s, 1430s, 1020s, 830s, 770m, 700s. Anal. Found: S, 9.27.

4-(3,5-Dichloroanilino)-2,6-dichloro-1,3,5-triazine (**17b**): According to literature,[25] a finely divided suspension was prepared by adding water (175 mL) into a stirred solution of cyanuric chloride (**16**) (15.0 g, 79.7 mmol) in acetone (150 mL). After cooling to -20°C a solution of 3,5-dichloroaniline (13.3 g, 79.7 mmol) in acetone (150 mL) then a 2 N NaOH solution (40 mL) were added dropwise to the suspension. The mixture was stirred for 2 h at 0°C. Acetone was then evaporated. The precipitate was filtered off, washed with water and dried over $MgSO_4$. 23.8 g (96 %) of **17b** were isolated as colorless crystals (MeOH); mp 139-141°C. ^{1}H-NMR (250 MHz, DMSO-d_6): 11.45 (s, NH); 7.75 (m, 2 H, arom.); 7.45 (m, 1 H, arom.). HRMS: Calcd for $C_9H_4N_4Cl_4$: 307.9190. Found: 307.9186.

Polymer-bound 2-alkylthio-4-amino-6-chloro-1,3,5-triazine (**18a**): The resin (**15**) (4.0 g, 11.2 mmol) was washed with DMA (3 x 15 mL) at 40°C. 2-Amino-4,6-dichloro-1,3,5-triazine (**17a**)[24] (2.17 g, 13.2 mmol), DIPEA (2.45 mL, 14 mmol) and DMA (15 mL) were added and the mixture was shaken 40°C for 18 h. The polymer-bound triazine (**18a**) was washed successively at 40°C with DMA (15 mL), isopropyl alcohol (15 mL), DMA (15 mL), isopropyl alcohol (15 mL) and hexane (15 mL). The resin was dried at 50°C under high vacuum: 6.23 g of **18a**, 72 % of conversion based on elemental analysis. Anal. Found: N, 9.34; Cl, 5.42; S, 6.70.

Polymer-bound 2-alkylthio-4-(3,5-dichloroanilino)-6-chloro-1,3,5-triazine (**18b**): The resin (**18b**) was prepared following the same procedure as described for **18a** starting from the resin (**15**) (4.0 g, 11.2 mmol), triazine (**17b**) (5.49 g, 14.0 mmol), DIPEA (2.45 mL, 14 mmol) and DMA (15 mL): 5.91 g of **18b**, 53 % of conversion based on elemental analysis. Anal. Found: N, 6.07; S, 6.33; Cl, 9.93.

2-Amino-4-(3,4,5-trimethoxybenzylamino)-6-(pyrrolidin-1-yl)-1,3,5-triazine (**19a**): According to *Method F* using 3,4,5-trimethoxybenzylamine (0.123 g, 0.625 mmol) as amine: 0.060 g (67 %) of **19a** was obtained as colorless crystals (MeOH); mp 177-178°C. ^{1}H-NMR (250 MHz, DMSO-d_6): 6.99-6.89 (m, NH); 6.61 (s, NH_2); 6.21-5.98 (m, 2 H, arom.); 4.30 (d, *J*=6.3, 2 H, aliph.); 3.70 (s, 3 H, aliph.); 3.43-3.28 (m, 4 H, aliph.); 1.86-1.71 (m, 4 H, aliph.). HRMS: Calcd for $C_{17}H_{24}N_6O_3$: 360.1910. Found: 360.1907.

2-Amino-4-benzylamino-6-(pyrrolidin-1-yl)-1,3,5-triazine (**19b**): According to *Method F* using benzylamine (0.067 g, 0.625 mmol) as amine: 0.047 g (70 %) of **19b** were obtained as yellowish crystals (MeOH); mp 140-142°C. ^{1}H-NMR (250 MHz, DMSO-d_6): 7.30 - 6.95 (m, NH, NH_2, 3 H, arom.); 6.24-5.92 (m, 2H, arom.); 4.41 (d, *J* = 6.1, 2 H, aliph.); 3.47-3.31 (m, 4 H, aliph.); 1.93-1.71 (m, 4 H, aliph.). HRMS: Calcd for $C_{14}H_{18}N_6$: 270.1593. Found: 270.1590.

2-Amino-4-(isopropylmethylamino)-6-(pyrrolidin-1-yl)-1,3,5-triazine(**19c**): According to *Method F* using isopropylmethylamine (0.046 g, 0.625 mmol) as amine: 0.05 g (85 %) of **19c** were obtained as colorless crystals (MeOH); mp 137-139°C. ^{1}H-NMR (250 MHz, DMSO-d_6): 6.07 (s, NH_2); 4.98 (sept, *J* = 6.7, 1 H, aliph.); 3.49-3.34 (m, 4 H, aliph.); 2.82 (s, 3 H, aliph.); 1.92-1.72 (m, 4 H, aliph.); 1.06 (d, *J* = 6.7, 6 H, aliph.). HRMS: Calcd for $C_{11}H_{20}N_6$: 236.1749. Found: 236.1754.

2-Amino-4-(4-fluorobenzylamino)-6-(pyrrolidin-1-yl)-1,3,5-triazine (**19d**): According to *Method F* using 4-fluorobenzylamine (0.078 g, 0.625 mmol) as amine: 0.030 g (42 %) of **19d** were obtained as yellowish crystals (MeOH); mp 148-150°C. ^{1}H-NMR (250 MHz, DMSO-d_6): 7.38-7.25 (m, NH, 1 H, arom.); 7.16-7.00 (m, NH_2, 1 H, arom.); 6.23-6.00 (m, 2 H, arom.); 4.37 (d, *J*=6.1, 2 H, aliph.); 3.49-3.30 (m,4 H, aliph.); 1.86-1.75 (m, 4 H, aliph.). HRMS: Calcd for $C_{14}H_{17}N_6F$: 288.1499. Found: 288.1498.

2-(3,5-dichloroanilino)-4-(3,4,5-trimethoxybenzylamino)-6-(pyrrolidin-1-yl)-1,3,5-triazine (**19e**): According to *Method F* using 3,4,5-trimethoxybenzylamine (0.123 g, 0.625 mmol) as amine: 0.037 g (29 %) of **19e** were obtained as yellowish crystals (MeOH); mp 109-111°C. ^{1}H-NMR (250 MHz, DMSO-d_6): 9.50-9.24 (m, NH); 8.01-7.90 (m, 2 H, arom.); 7.64-7.51 (m, 1 H, arom.); 7.00-7.09 (m, 1 H, arom.); 6.73-6.58 (m, 1 H, arom, NH); 4.49-4.33 (m, 2 H, aliph.); 3.70 (s, 3 H, aliph.); 3.61 (s, 3 H, aliph.); 3.57 (s, 3 H, aliph.); 3.3.54-3.48 (m, 4 H, aliph.); 2.00-1.80 (m, 4 H, aliph.). HRMS: Calcd for $C_{23}H_{26}N_6O_3Cl_2$: 504.1443. Found: 504.1442.

2-Benzylamino-4-(3,5-dichloroanilino)-6-(pyrrolidin-1-yl)-1,3,5-triazine (**19f**): According to *Method F* using benzylamine (0.067 g, 0.625 mmol) as amine: 0.032 g (31 %) of **19f** were obtained as yellowish crystals (MeOH); mp 127-129°C. ^{1}H-NMR (250 MHz, DMSO-d_6): 9.44-9.25 (m, NH); 7.99-7.87 (m, 2 H, arom.); 7.65-7.00 (m, NH, 6 H, arom.); 4.59-4.41 (m, 2 H, aliph.); 3.57-3.46 (m, 4 H, aliph.); 1.96-1.80 (m, 4 H, aliph.). HRMS: Calcd for $C_{20}H_{20}N_6Cl_2$: 414.1127. Found: 414.1129.

2-(3,5-dichloroanilino)-4-isopropylmethylamino-6-(pyrrolidin-1-yl)-1,3,5-triazine (**19g**): As described in *Method F* using isopropylmethylamine (0.046 g, 0.625 mmol) as amine: 0.040g (42 %) of **19g** were isolated as colorless crystals (MeOH); mp 125-128°C. ^{1}H-NMR (250 MHz, DMSO-d_6): 9.43-9.39 (s, NH); 8.01-7.94 (m, 2 H, arom.); 7.09-7.06 (m, 1 H, arom.); 5.06-4.93 (m, 1 H, aliph.); 3.57-3.43 (m, 4 H, aliph.); 2.92 (s, 3 H, aliph.); 1.98-1.85 (m, 4 H, aliph.); 1.13 (d, *J*=6.2, 6 H, aliph.). HRMS: Calcd for $C_{17}H_{22}N_6Cl_2$: .380.1283. Found: 380.1286.

2-(3,5-dichloroanilino)-4-(4-fluorobenzylamino)-6-(pyrrolidin-1-yl)-1,3,5-triazine (**19h**): According to *Method F* using 4-fluorobenzylamine (0.078 g, 0.625 mmol) as amine: 0.034 g (31 %) of **19h** were obtained as yellowish crystals (MeOH); mp 117-119°C. ^{1}H-NMR (250 MHz, DMSO-d_6): 9.45-9.30 (m, NH); 7.99-7.78 (m, 2 H, arom.); 7.02-7.72 (m, 5 H, arom., NH); 4.53-4.40 (m, 2 H,

aliph.); 3.55-3.38 (m, 4 H, aliph.); 1.95-1.80 (m, 4 H, aliph.). HRMS: Calcd for $C_{20}H_{19}N_6FCl_2$: 432.1032. Found: 432.1025.

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