Synthesis and Antimalarial-Activity Evaluation of Tetraoxane–Triazine Hybrids and Spiro[piperidine-4,3′-tetraoxanes]

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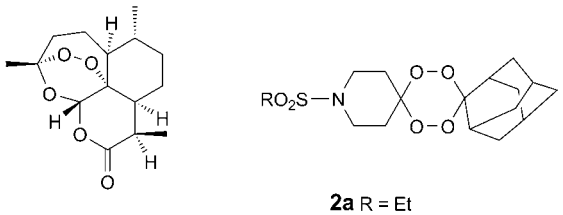
A series of tetraoxane–triazine hybrids and spiro[piperidine-4,3′-tetraoxanes] have been synthesized, and all the compounds were screened for *in vitro* antimalarial activity against chloroquine-sensitive (D6) and chloroquine-resistant (W2) strains of *Plasmodium falciparum*. Most of the spiro[piperidine-4,3′-tetraoxanes] exhibited moderate to good antimalarial activities, and two compounds have shown good antimalarial activity with IC_{50} values in the range of 0.30 to 0.70 μM against both the strains with high selectivity index and no cytotoxicity towards mammalian kidney cell line.

Introduction. – Artemisinin (**1**) and its semi-synthetic derivatives such as artemether, arteether, and artisunate belong to the endoperoxide class of compounds, and these compounds have been used for the treatment of *P. falciparum*-related infections where traditional antimalarial remedies such as chloroquine and mefloquine have lost their efficacy [1]. Mechanistic studies revealed that the presence of a peroxide bridge is essential for the activity of these compounds [2–5], and this key structural feature led to the quest to discover other synthetically accessible peroxides as potential antimalarial agents [3][4]. The subsequent studies identified tetraoxanes, **2**, as a new class of antimalarials, and some of these compounds have shown very promising activities [6–11] (*Fig. 1*). These compounds such as artemisinin exert their activity due to their ability to form radical species under physiological conditions and thus stop the hemozoin formation [12]. Recent studies confirmed that introduction of a basic moiety in the trioxane and tetraoxane pharmacophore can improve the antimalarial activity of these compounds [13][14].

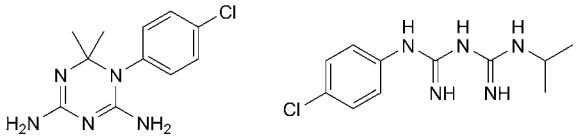


1 **2a** R = Et **2b** R = cyclopropyl

Fig. 1. *Endoperoxide-based antimalarials*

The dihydrofolate reductase (DHFR) is another target that has been subject of intense study in malaria research, and substituted *s*-triazine derivatives have been

widely studied against DHFR. This class of compounds also possess a broad range of biological activities such as antitumor, anticancer, cytotoxicity, anti-inflammatory, antibacterial, antifungal, antimalarial, antitrypanosomal, anti-AIDS, *etc.*, and played an important role in the development of medicinal chemistry [15–20]. All the biologically active *s*-triazine derivatives are obtained from commercially available, inexpensive reagents such as melamine, cyanuric chloride, and cyanuric acid. Cycloguanil (**3**), a triazine-based antimalarial drug and a metabolite of the antimalarial drug chloroguanide (**4**), inhibits dihydrofolate reductase (DHFR) domain of *P. falciparum* and *P. berghei* [21–30] (*Fig. 2*). Inhibition of cellular DHFR reduces the source of tetrahydrofolates, which eventually leads to cell death as a result of deficient DNA biosynthesis. Cycloguanil also affects proliferating human blood mononuclear cells when studied *in vitro* [31], and has a potent inhibitory effect on *Toxoplasma gondii* when combined with a non-inhibitory concentration of sulfadiazine [28].



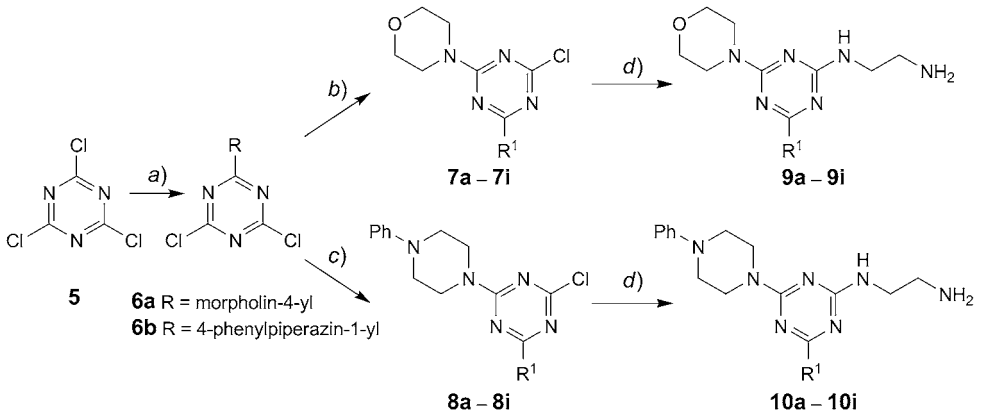
3 **4**

Fig. 2. *Dihydrofolate reductase inhibitors*

To overcome the drug resistance, the concept of hybrid molecules has been introduced recently, and some of these hybrids have entered the clinical trials [32]. As a part of ongoing work towards the development of novel antimalarials [33–36], we report herein synthesis and antimalarial activity of tetraoxane–triazine conjugates and spiro[piperidine-4,3′-tetraoxanes].

Results and Discussion. – *Chemistry.* Keeping in mind the numerous biological applications of triazine derivatives and antimalarial activities of tetraoxanes, we designed tetraoxane–triazine conjugates **12a**–**12i**, **13a**–**13i**, in anticipation that this kind of hybrid molecules may exhibit better antimalarial activity, and may solve the problem of drug resistance, as these hybrids contain two different antimalarially active pharmacophores with different targets. We initiated our work by synthesizing the known compounds **6a** and **6b** using cyanuric chloride (**5**) as a starting material (*Scheme 1*) [37–40]. It is important to mention here that **5** at 0° with aliphatic amines/aromatic amines undergoes nucleophilic substitution reactions to give monoamino-triazines in high and diamino-triazines in low yield. The second Cl-atom of monoamino-triazines undergoes nucleophilic substitution reactions with aliphatic amines/aromatic amines at room temperature to give diamino-triazines as major products while triamino-triazines are formed in low yield. The Cl-atom of diamino-triazines undergoes nucleophilic substitution reactions with substituted amines at higher temperature. The reaction of 1 mol of amine with compound **5** at 0° in the presence of anhydrous K_2CO_3 led to the formation of compounds **6a** and **6b** in moderate-to-good yields (*Scheme 1*). Subsequent reaction of 1 mol of amine with compounds **6a** and **6b** at room temperature in the presence of anhydrous K_2CO_3 gave

Scheme 1



7a	R^1 = morpholin-4-yl	**9a**	R^1 = morpholin-4-yl
7b, **8a**	R^1 = piperidin-1-yl	**9b**, **10a**	R^1 = piperidin-1-yl
7c, **8b**	R^1 = cyclohexylamino	**9c**, **10b**	R^1 = cyclohexylamino
7d, **8c**	R^1 = 4-phenylpiperazin-1-yl	**9d**, **10c**	R^1 = 4-phenylpiperazin-1-yl
7e, **8d**	R^1 = 4-MeC_6H_4NH	**9e**, **10d**	R^1 = 4-MeC_6H_4NH
7f, **8e**	R^1 = 2-MeC_6H_4NH	**9f**, **10e**	R^1 = 2-MeC_6H_4NH
7g, **8g**	R^1 = 4-^{i}PrC_6H_4NH	**9g**, **10g**	R^1 = 4-^{i}PrC_6H_4NH
7h, **8h**	R^1 = 4-$MeOC_6H_4NH$	**9h**, **10h**	R^1 = 4-$MeOC_6H_4NH$
7i, **8i**	R^1 = 3,5-$(MeO)_2C_6H_3NH$	**9i**, **10i**	R^1 = 3,5-$(MeO)_2C_6H_3NH$
8f	R^1 = 4-EtC_6H_4NH	**10f**	R^1 = 4-EtC_6H_4NH

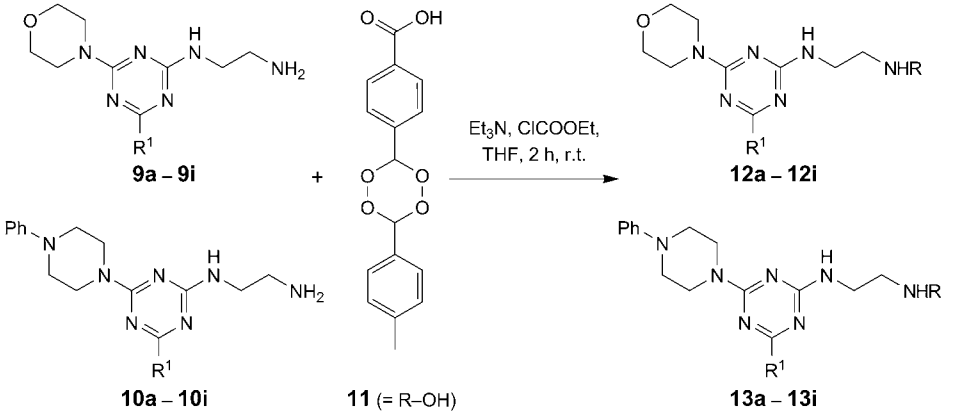
a) RX, K_2CO_3, THF, 0°, 3 h. *b*) R^1X, K_2CO_3, THF, 3 h, room temperature, with **6a**. *c*) R^1X, K_2CO_3, THF, 3 h, room temperature, with **6b**. *d*) Ethylenediamine, K_2CO_3, THF, 60°, 3 h.

compounds **7a**–**7i** and **8a**–**8i**, respectively, in moderate-to-good yields (*Scheme 1*). The third nucleophilic reaction was carried out by reacting compounds **7a**–**7i** and **8a**–**8i**, respectively, with excess of ethylenediamine in the presence of K_2CO_3 in THF at 60°. After usual workup and purification, all the synthesized compounds **9a**–**9i** and **10a**–**10i** were characterized spectroscopically. Finally, compounds **9a**–**9i** and **10a**–**10i** were reacted with compound **11** [33] in the presence of Et_3N and ClCOOEt in THF at room temperature for 2 h to give compounds **12a**–**12i** and **13a**–**13i**, respectively, in good-to-moderate yields (*Scheme 2*).

The spiro[piperidine-4,3′-tetraoxanes] were prepared in anticipation that the N-atom of the piperidinone ring will help the tetraoxane to accumulate more in the acidic food vacuole of the parasite, and, thus, these compounds will exhibit improved antimalarial activities. With these aims in mind, we started our synthesis with the preparation of compounds **15a** and **15b** [41][42] as outlined in *Scheme 3*. Reaction of **15a** and **15b** with different substituted ketones/aldehydes in presence of 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP), methyltrioxorhenium (MTO), and an Et_2O solution of HBF_4 led to the formation of desired the compounds **16a**–**16m** and **17a**–**17h**, respectively in moderate yields (*Scheme 3*) [43].

Biological Activity. In vitro *Antimalarial Activity.* All the synthesized compounds, **12a**–**12i** and **13a**–**13i**, were screened for antimalarial activity against D6 (chloroquine-

Scheme 2



9a	R^1 = morpholin-4-yl
9b, **10a**	R^1 = piperidin-1-yl
9c, **10b**	R^1 = cyclohexylamino
9d, **10c**	R^1 = 4-phenylpiperazin-1-yl
9e, **10d**	R^1 = 4-MeC_6H_4NH
9f, **10e**	R^1 = 2-MeC_6H_4NH
9g, **10g**	R^1 = 4-^{i}PrC_6H_4NH
9h, **10h**	R^1 = 4-MeOC_6H_4NH
9i, **10i**	R^1 = 3,5-$(MeO)_2C_6H_3$NH
10f	R^1 = 4-EtC_6H_4NH

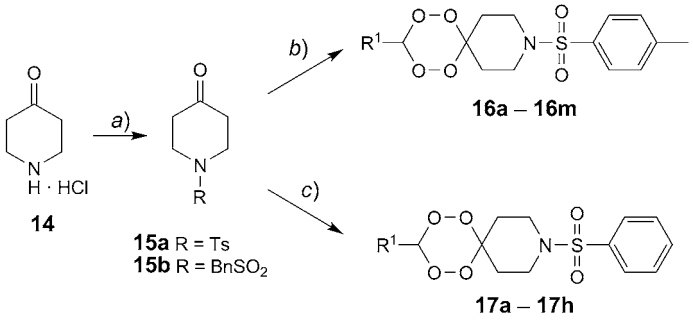
12a	R^1 = morpholin-4-yl
12b, **13a**	R^1 = piperidin-1-yl
12c, **13b**	R^1 = cyclohexylamino
12d, **13c**	R^1 = 4-phenylpiperazin-1-yl
12e, **13d**	R^1 = 4-MeC_6H_4NH
12f, **13e**	R^1 = 2-MeC_6H_4NH
12g, **13g**	R^1 = 4-^{i}PrC_6H_4NH
12h, **13h**	R^1 = 4-MeOC_6H_4NH
12i, **13i**	R^1 = 3,5-$(MeO)_2C_6H_3$NH
13f	R^1 = 4-EtC_6H_4NH

sensitive) and W2 (chloroquine-resistant) strains of *P. falciparum*, and for cytotoxicity towards mammalian kidney cells (*Vero* cells) up to a highest concentration of 12.5 μM in an *in vitro* assay. Chloroquine and artemisinin were used as standard drugs for antimalarial activity, and doxorubicin was used as standard drug for cytotoxicity. The *in vitro* antimalarial activity was determined on the basis of plasmodial LDH activity as an index of plasmodial growth [44] and expressed as IC_{50} values. Selectivity index (*SI*) of antimalarial activity was calculated based on the cytotoxicity to mammalian cells. Most of the compounds were inactive except compounds **12b**, **12e**, and **12i**. These compounds exhibited moderate antimalarial activities with IC_{50} values in the range of 2.74 – 5.45 (D6) and 2.13 – 5.43 μM (W2) (*Table*).

Some spiro[piperidine-4,3′-tetraoxanes] have shown very good-to-moderate antimalarial activities. Two compounds, **16a** (R^1 = 4-Me–C_6H_9) and **17a** (R^1 = 4-Me–C_6H_4), exhibited good activities against both strains of *P. falciparum* with IC_{50} values in the range of 0.30 – 0.70 (D6) and 0.20 – 0.83 μM (W2) with high *SI*s. Compounds **16b**, **16c**, **17c**, and **17h** with (R^1 = Ph, 4-Me–C_6H_4, 2-Me–C_6H_4, 4-MeO–C_6H_4, resp.) exhibited moderate-to-good antimalarial activities with IC_{50} values in the range of 1.48 – 4.90 (D6) and 1.40 – 7.36 μM (W2). All other compounds were found to be inactive up to tested concentration (25 μM) with no clear SAR.

Conclusions. – We have successfully synthesized two new series of substituted triazine–tetraoxane hybrids and spiro[piperidine-4,3′-tetraoxanes]. Some of the

Scheme 3



16a	R^1 = –CH_2CH_2–CH(Me)–CH_2CH_2–
16b	R^1 = Ph
16c, **17a**	R^1 = 4-MeC_6H_4
16d, **17b**	R^1 = 3-MeC_6H_4
16e, **17c**	R^1 = 2-MeC_6H_4
16f, **17d**	R^1 = 4-EtC_6H_4
16g, **17e**	R^1 = 4-PrC_6H_4
16h, **17f**	R^1 = 4-^{i}PrC_6H_4
16i, **17g**	R^1 = 4-^{t}BuC_6H_4
16j, **17h**	R^1 = 4-$MeOC_6H_4$
16k	R^1 = 4-FC_6H_4
16l	R^1 = 4-BrC_6H_4
16m	R^1 = 3-BrC_6H_4

a) TsCl or benzenesulfonyl chloride, K_2CO_3, $CHCl_3/H_2O$ 1 : 1, 4 h, r.t. *b*) Aldehyde/ketone, H_2O_2, $HBF_4 \cdot Et_2O$, 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP), methyltrioxorhenium ($MeReO_3$, MTO), 2 h, room temperature, with **15a**. *c*) Aldehyde/ketone, H_2O_2, $HBF_4 \cdot Et_2O$, 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP), methyltrioxorhenium (MTO), 2 h, room temperature, with **15b**.

Table. In vitro *Antimalarial Activities of Tetraoxane–Triazine Hybrid and Spiro[piperidine-4,3′-tetraoxanes]*

Compound	*P. f*[a]) (D6) [μM]	*SI*[b])	*P. f* (W2) [μM]	*SI*	Cytotoxicity (*Vero* cell)
12b	5.43	> 1.5	5.43	> 1.5	NC[c])
12e	5.23	> 1.5	3.76	> 2.1	NC
12i	2.74	> 2.6	2.13	> 3.4	NC
16a	0.70	> 17	0.83	> 14.4	NC
16b	1.51	> 8.4	1.40	> 9.0	NC
16c	2.09	> 5.6	1.89	> 6.2	NC
17a	0.30	> 39.7	> 0.20	> 59.5	NC
17c	1.48	> 8.2	1.71	> 7.1	NC
17h	4.90	> 2.4	7.36	> 1.6	NC
Chloroquine	0.035		0.22		NC
Artemisinin	0.015		0.013		NC

[a]) *P. f* = *Plasmodium falciparum*.[b]) *SI* = Selectivity index. [c]) NC = No cytotoxicity.

compounds have shown promising *in vitro* antimalarial activities without showing any cytotoxicity against *Vero* cells. Out of 56 compounds under study, two compounds, **16a** and **17a**, have shown good activities against both strains of *P. falciparum* with high *SI*. Further derivatization of the most active analogs is under progress, and results will be published in due course.

D.S.R. thanks the *Department of Science and Technology* (SR/S1/OC-08/2008), New Delhi, India, for financial support, and USIC-CIF, University of Delhi for NMR data. *N. K.* is thankful to *CSIR*, New Delhi, for the award of junior and senior research fellowships. *United States Department of Agriculture* (USDA), Agricultural Research Service Specific Cooperative Agreement No. 58-6408-2-0009, is also acknowledged for partial support of this work. Mr. *John Trott* is acknowledged for his excellent technical assistance in the screening of biological activity at NCNPR, University of Mississippi, USA.

Experimental Part

General. All chemicals used in the syntheses were purchased from *Sigma–Aldrich* and were used as such. TLC was used to monitor the progress of the reactions. The compounds were purified by silica-gel column chromatography (CC; SiO_2; *Merck*, India). M.p.: melting-point apparatus *SRS EZ 120*; uncorrected. IR Spectra (KBr, film): *Perkin-Elmer FT-IR* spectrophotometer and the values are expressed as ν_{max} in cm^{-1}. ^{1}H-NMR Spectra: *Bruker 320 Spectrospin* spectrometer at 300 MHz and *Jeol spectospin ECX400* at 400 MHz.^{13}C-NMR Spectra: 75.5 and 100 MHz, resp., with TMS as internal standard; the chemical-shift values on δ scale [ppm] and the coupling constants (J) in Hz. MS: *Waters micro mass LCT* mass spectrometer/data system. Elemental analyses: *Carlo Erba Model EA-1108* elemental analyzer, and data of C, H, and N are within $\pm 0.4\%$ of calculated values.

Synthesis and Characterization of the Compounds. Synthesis of **6a** *and* **6b** [37–40]. *2,4-Dichloro-6-(morpholin-4-yl)-1,3,5-triazine* (**6a**). Yield: 75.3%. M.p. 166°. IR (KBr): 3110, 2970, 2861, 1922, 1585, 1479, 1232, 992. ^{1}H-NMR (400 MHz, $CDCl_3$): 3.68 (*t*, $J = 5.1$, 2 NCH_2CH_2O); 3.82 (*t*, $J = 5.1$, 2 NCH_2CH_2O).^{13}C-NMR (100 MHz, $CDCl_3$): 44.3; 66.2; 163.8; 170.2. ESI-MS: 235.1 (100, $[M+H]^+$), 237.1 (63).

2,4-Dichloro-6-(4-phenylpiperazin-1-yl)-1,3,5-triazine (**6b**). Yield: 76%. M.p. 165°. IR (film): 2902, 2818, 1599, 1569, 1494, 1445, 1312, 1255, 1230, 1003, 980, 912, 758. ^{1}H-NMR (400 MHz, $CDCl_3$): 3.19–3.25 (*m*, 2 NCH_2CH_2NPh); 3.95–3.98 (*m*, 2 NCH_2CH_2NPh); 6.88–6.98 (*m*, 3 arom. H); 7.27–7.31 (*m*, 2 arom. *H*). ^{13}C-NMR (100 MHz, $CDCl_3$): 43.4; 49.3; 116.7; 120.5; 129.2; 157.0; 164.3; 169.7. ESI-MS: 310.0 (100, $[M+H]^+$), 312.2 (64).

General Procedure for the Synthesis of **7b**–**7i** *and* **8a**–**8i**, *Examplified by the Preparation of 4,4′-(6-Chloro-1,3,5-triazine-2,4-diyl)dimorpholine* (*=2-Chloro-4,6-di(morpholin-4-yl)-1,3,5-triazine*; **7a**). Morpholine (1.85 g, 21.2 mmol) was added to a suspension of **6a** (5 g, 21.2 mmol) in THF (30 ml) at r.t., followed by K_2CO_3 (8.80 g, 63.8 mmol). The mixture was stirred at r.t. for 3–4 h. Then, the mixture was filtered to remove K_2CO_3, and excess of solvent was evaporated under vacuum. The residue thus obtained was dissolved in 30 ml of $CHCl_3$ and washed with sat. brine. The $CHCl_3$ layer was dried (Na_2SO_4), and excess of solvent was removed under vacuum to give crude product, which was purified by CC (SiO_2; AcOEt/hexane) to yield **7a** (4.12 g, 68%). White solid. M.p. 175° ([45]: 173°). IR (film): 2979, 2966, 2852, 1604, 1567, 1493, 1448, 1361, 1305, 1269, 1206, 1181, 1117, 1062, 977, 955, 797. ^{1}H-NMR (400 MHz, $CDCl_3$): 3.65–3.68 (*m*, 4 – NCH_2CH_2O); 3.70–3.81 (*m*, 4 NCH_2CH_2O). ^{13}C-NMR (100 MHz, $CDCl_3$): 43.8; 66.6; 164.4; 169.6. ESI-MS: 286.7 (100, $[M+H]^+$), 288.8 (32).

2-Chloro-4-(morpholin-4-yl)-6-(piperidin-1-yl)-1,3,5-triazine (**7b**). Yield: 68%. M.p. 145° ([46]: 140–142°). IR (film): 2935, 2855, 1567, 1493, 1445, 1309, 1237, 1116, 975, 799. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.54–1.57 (*m*, 4 H), 1.64–1.65 (*m*, 2 H); 3.58–3.88 (*m*, 12 H).^{13}C-NMR (100 MHz, $CDCl_3$): 24.6; 25.8; 43.8; 44.6; 66.6; 164.5; 169.5. ESI-MS: 284.1 (100, $[M+H]^+$), 286.2 (31).

4-Chloro-N-*cyclohexyl-6-(morpholin-4-yl)-1,3,5-triazin-2-amine* (**7c**). Yield: 62%. M.p. 193°. IR (film): 3347 (NH), 2923, 2852, 1583, 1537, 1503, 1441, 1247, 989, 792. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.09–1.46 (*m*, 4 H); 1.56–1.76 (*m*, 6 H); 1.89–2.03 (*m*, 2 H); 3.63–3.89 (*m*, 8 H).^{13}C-NMR (100 MHz,

$CDCl_3$): 24.5; 25.5; 32.5; 32.2; 43.7; 49.2; 49.5; 66.6; 164.6; 169.1. ESI-MS: 298.1 (100, $[M+H]^+$), 300.2 (32).

2-Chloro-4-(morpholin-4-yl)-6-(4-phenylpiperazin-1-yl)-1,3,5-triazine (**7d**). Yield: 58%. M.p. 133°. IR (film): 2963, 2856, 1567, 1494, 1444, 1309, 1231, 1115, 1004, 978, 798. ^{1}H-NMR (400 MHz, $CDCl_3$): 3.19 (*t*, *J* = 5.0, 2 NCH_2CH$_2$NPh); 3.71 – 3.72 (*m*, 2 NCH$_2$CH_2NPh); 3.79 – 3.80 (*m*, 2 NCH$_2$CH_2O); 3.86 – 3.94 (*m*, 2 NCH_2CH$_2$O); 6.88 – 6.95 (*m*, 3 arom. H); 7.25 – 7.30 (*m*, 2 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 43.3; 43.8; 49.5; 66.5; 66.7; 116.6; 120.5; 129.2; 151.0; 164.3; 169.6. ESI-MS: 361.2 (100, $[M+H]^+$), 363.2 (32).

4-Chloro-N-*(4-methylphenyl)-6-(morpholin-4-yl)-1,3,5-triazin-2-amine* (**7e**). Yield: 61%. M.p. 212° ([47]: 205 – 207°). IR (film): 3277 (NH), 2924, 1560, 1530, 1491, 1442, 1278, 1110, 979, 794, 731. ^{1}H-NMR (400 MHz, $CDCl_3$): 2.32 (*s*, *Me*–C_6H_4); 3.68 – 3.75 (*m*, 2 NCH_2CH$_2$O); 3.76 – 3.82 (*m*, 2 NCH$_2$CH_2O); 7.08 (br. *s*, NH); 7.12 (*d*, *J* = 7.8, 2 arom. H); 7.35 (*d*, *J* = 7.8, 2 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 20.8; 44.0; 66.5; 120.7; 129.4; 133.7; 135.0; 165.5; 169.2. ESI-MS: 306.1 (100, $[M+H]^+$), 308.1 (34).

4-Chloro-N-*(2-methylphenyl)-6-(morpholin-4-yl)-1,3,5-triazin-2-amine* (**7f**). Yield: 59%. M.p. 151° ([47]: 146 – 150°). IR (film): 3234 (NH), 2966, 2857, 1573, 1526, 1497, 1242, 1115, 981, 754, 730. ^{1}H-NMR (400 MHz, $CDCl_3$): 2.28 (*s*, *Me*–C_6H_4); 3.61 – 3.88 (*m*, 2 NCH_2CH_2O); 6.88 (br. *s*, NH); 7.06 – 7.10 (*m*, 2 arom. H); 7.19 – 7.27 (*m*, 2 arom. H). ESI-MS: 306.1 (100, $[M+H]^+$), 308.2 (34).

4-Chloro-6-(morpholin-4-yl)-N-*[4-(propan-2-yl)phenyl]-1,3,5-triazin-2-amine* (**7g**). Yield: 60%. M.p. 157°. IR (film): 3283 (NH), 2961, 2863, 1576, 1530, 1514, 1422, 1248, 1115, 981, 732. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.22 (*d*, *J* = 6.8, *Me*$_2$C*H*); 2.85 – 2.90 (*m*, Me$_2$C*H*); 3.68 – 3.78 (*m*, 2 NCH_2CH$_2$O); 3.79 – 3.89 (*m*, 2 NCH$_2$CH_2O); 7.18 (*d*, *J* = 8.4, 2 arom. H); 7.25 (br. s, NH); 7.40 (*d*, *J* = 8.4, 2 arom. H). ESI-MS: 334.1 (100, $[M+H]^+$), 336.2 (30).

4-Chloro-N-*(4-methoxyphenyl)-6-(morpholin-4-yl)-1,3,5-triazin-2-amine* (**7h**). Yield: 68%. M.p. 153° ([47]: 146 – 150°). IR (film): 3285 (NH), 2921, 1579, 1532, 1510, 1422, 1243, 1114, 1033, 981, 798. ^{1}H-NMR (400 MHz, $CDCl_3$): 3.70 – 3.74 (*m*, 2 NCH_2CH$_2$O); 3.82 (*s*, MeO); 3.83 – 3.88 (*m*, 2 NCH$_2$CH_2O); 6.85 (*d*, *J* = 6.8, 2 arom. H); 7.35 (*d*, *J* = 6.8, 2 arom. H); 7.04 – 7.18 (br. *s*, NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 44.0; 55.5; 66.5; 114.1; 122.6; 130.5; 156.4; 164.0; 164.5. ESI-MS: 322.1 (100, $[M+H]^+$), 324.2 (31).

4-Chloro-N-*(3,5-dimethoxyphenyl)-6-(morpholin-4-yl)-1,3,5-triazin-2-amine* (**7i**). Yield: 67%. M.p. 168°. IR (film): 3323 (NH), 2934, 2862, 1587, 1530, 1461, 1207, 1155, 1061, 824, 797, 671. ^{1}H-NMR (300 MHz, $CDCl_3$): 3.72 – 3.75 (*m*, 2 NCH_2CH$_2$O); 3.78 (*s*, 2 MeO); 3.82 – 3.86 (*m*, 2 NCH$_2$CH_2O); 6.22 – 6.24 (*m*, 1 arom. H); 6.74 – 6.75 (*m*, 2 arom. H); 7.17 (br. *s*, NH). ^{13}C-NMR (75.5 MHz, $CDCl_3$): 44.0; 55.2; 66.4; 95.9; 98.9; 138.8; 160.8; 163.7; 164.5; 169.3. ESI-MS: 352.1 (100, $[M+H]^+$), 354.2 (33).

2-Chloro-4-(4-phenylpiperazin-1-yl)-6-(piperidin-1-yl)-1,3,5-triazine (**8a**). Yield: 57%. M.p. 148°. IR (film): 2929, 2854, 1573, 1529, 1494, 1227, 987, 732. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.09 – 1.37 (*m*, 3 H); 1.38 – 1.47 (*m*, 2 H); 1.55 – 1.78 (*m*, 3 H); 1.92 – 2.04 (*m*, 2 H); 3.13 – 3.29 (*m*, 2 NCH_2CH$_2$NPh); 3.78 – 3.97 (*m*, 2 NCH$_2$CH_2NPh); 6.88 – 6.95 (*m*, 3 arom. H); 7.26 – 7.30 (*m*, 2 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 24.6; 25.5; 32.5; 33.2; 43.3; 49.2; 116.6; 120.4; 129.2; 151.0; 164.5; 169.6; 169.0. ESI-MS: 359.2 (100, $[M+H]^+$), 361.2 (32).

4-Chloro-N-*cyclohexyl-6-(4-phenylpiperazin-1-yl)-1,3,5-triazin-2-amine* (**8b**). Yield: 53%. M.p. 95°. IR (nujol): 3296, 2923, 2854, 1505, 1416, 1383, 1300, 1283, 1227, 1155, 1010, 921, 806, 761. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.54 – 1.66 (*m*, 7 H); 3.18 – 3.20 (*m*, 4 H); 3.73 – 3.76 (*m*, 2 NCH_2CH$_2$NPh); 3.93 – 3.94 (*m*, 2 NCH$_2$CH_2NPh); 6.87 – 6.95 (*m*, 2 arom. H); 7.25 – 7.30 (*m*, 3 arom. H, NH). ESI-MS: 373.2 (100, $[M+H]^+$), 375.1 (31).

2-Chloro-4,6-bis(4-phenylpiperazin-1-yl)-1,3,5-triazine (**8c**). Yield: 49%. M.p. 195°. IR (film): 3059, 2963, 2902, 2818, 1569, 1445, 1312, 1255, 1230, 1194, 1153, 1045, 980, 912. ^{1}H-NMR (400 MHz, $CDCl_3$): 3.19 – 3.25 (*m*, 4 NCH_2CH$_2$NPh); 3.95 – 3.98 (*m*, 4 NCH$_2$CH_2NPh); 6.88 – 6.98 (*m*, 6 arom. H); 7.27 – 7.31 (*m*, 4 arom. H). ESI-MS: 436.2 (100, $[M+H]^+$), 438.2 (33).

4-Chloro-N-*(4-methylphenyl)-6-(4-phenylpiperazin-1-yl)-1,3,5-triazin-2-amine* (**8d**). Yield: 48%. M.p. 102°. IR (film): 3249 (NH), 2920, 2851, 1577, 1512, 1493, 1445, 1229, 980, 730. ^{1}H-NMR (400 MHz, $CDCl_3$): 2.33 (*s*, *Me*–C_6H_4); 3.23 – 3.24 (*m*, 2 NCH_2CH$_2$NPh); 3.95 – 4.10 (*m*, 2 NCH$_2$CH_2NPh); 6.91 – 7.04 (*m*, 3 arom. H); 7.14 – 7.16 (*d*, *J* = 8.2, 2 arom. H); 7.27 – 7.31 (*m*, 2 arom. H, NH); 7.38 (*d*, *J* = 8.2, 2 arom. H). ESI-MS: 381.2 (100, $[M+H]^+$), 383.2 (33).

4-Chloro-N-*(2-methylphenyl)-6-(4-phenylpiperazin-1-yl)-1,3,5-triazin-2-amine* (**8e**). Yield: 51%. M.p. 143°. IR (film): 3391 (NH), 2922, 2381, 2207, 1620, 1574, 1494, 1232, 906, 755, 731. ^{1}H-NMR (400 MHz, $CDCl_3$): 2.36 (*s*, *Me*–C_6H_4); 3.19 – 3.45 (*m*, 2 NCH_2CH$_2$NPh); 3.91 – 4.40 (*m*, 2 NCH$_2$CH_2NPh); 6.92 – 7.12 (*m*, 2 arom. H); 7.16 – 7.26 (*m*, 4 arom. H); 7.28 – 7.58 (*m*, 4 arom. H). ESI-MS: 381.1 (100, $[M+H]^+$), 383.1 (32).

4-Chloro-N-*(4-ethylphenyl)-6-(4-phenylpiperazin-1-yl)-1,3,5-triazin-2-amine* (**8f**). Yield: 48%. M.p. 137°. IR (film): 3271 (NH), 2964, 2927, 1574, 1514, 1230, 982, 912, 743. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.21 (*t*, *J* = 7.5, *Me*CH$_2$); 2.60 – 2.64 (*q*, *J* = 7.5, MeCH_2); 3.15 – 3.26 (*m*, 2 NCH_2CH$_2$NPh); 3.91 – 4.05 (*m*, 2 NCH$_2$CH_2NPh); 6.90 – 6.96 (*m*, 3 arom. H); 7.05 (br. *s*, NH); 7.15 – 7.19 (*m*, 2 arom. H); 7.28 – 7.30 (*m*, 2 arom. H); 7.41 – 7.45 (*m*, 2 arom. H). ESI-MS: 395.2 (100, $[M+H]^+$), 397.2 (32).

4-Chloro-6-(4-phenylpiperazin-1-yl)-N-*[4-(propan-2-yl)phenyl]-1,3,5-triazin-2-amine* (**8g**). Yield: 53%. M.p. 197°. IR (film): 3279 (NH), 2959, 1576, 1513, 1492, 1421, 1232, 980. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.25 (*d*, *J* = 6.0, *Me*$_2$CH); 2.88 – 2.92 (*sept.*, *J* = 4.0, Me$_2$C*H*); 3.31 – 3.42 (*m*, 2 NCH_2CH$_2$NPh); 4.15 – 4.39 (*m*, 2 NCH$_2$CH_2NPh); 7.21 – 7.23 (*m*, 4 arom. H); 7.38 – 7.43 (*m*, 5 arom. H, NH). ESI-MS: 409.2 (100, $[M+H]^+$), 411.2 (32).

4-Chloro-N-*(4-methoxyphenyl)-6-(4-phenylpiperazin-1-yl)-1,3,5-triazin-2-amine* (**8h**). Yield: 47%. M.p. 185°. IR (film): 3278 (NH), 2919, 1578, 1508, 1232, 981, 757. ^{1}H-NMR (400 MHz, $CDCl_3$): 3.20 (*t*, *J* = 5.0, 2 NCH_2CH$_2$NPh); 3.81 (*s*, MeO); 3.95 – 3.99 (*m*, 2 NCH$_2$CH_2NPh); 6.88 – 6.95 (*m*, 5 arom. H); 7.25 – 7.30 (*m*, 2 arom. H); 7.39 – 7.41 (*m*, 3 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 43.5; 49.2; 55.5; 114.1; 116.7; 120.5; 122.6; 129.2;130.6; 151.0; 156.4; 164.6; 166.0. ESI-MS: 397.3 (100, $[M+H]^+$), 399.2 (33).

4-Chloro-N-*(3,5-dimethoxyphenyl)-6-(4-phenylpiperazin-1-yl)-1,3,5-triazin-2-amine* (**8i**). Yield: 49%. M.p. 162°. IR (film): 3391 (NH), 2922, 2851, 1588, 1392, 1154, 1063, 989, 909, 731. ^{1}H-NMR (400 MHz, $CDCl_3$): 3.21 – 3.29 (*m*, 2 NCH_2CH$_2$NPh); 3.78 (*s*, 2 MeO); 4.04 – 4.12 (*m*, 2 NCH$_2$CH_2NPh); 6.22 – 6.24 (*m*, 1 arom. H); 6.76 – 6.78 (*m*, 2 arom. H); 6.97 – 7.10 (*m*, 4 arom. H); 7.29 – 7.33 (*m*, 1 arom. H, NH). ESI-MS: 427.2 (100, $[M+H]^+$), 429.2 (32).

General Procedure for the Synthesis of Compounds **9a** – **9i** *and* **10a** – **10i**, *Exemplified by the Preparation of* N-*[4,6-Di(morpholin-4-yl)-1,3,5-triazin-2-yl]ethane-1,2-diamine* (**9a**). Ethylenediamine (0.210 g, 3.50 mmol) was added to a suspension of **7a** (1.0 g, 3.50 mmol) in THF (10 ml) at r.t., followed by the addition of K_2CO_3 (1.45 g, 10.5 mmol). The mixture was stirred at 60° for 3 – 4 h. Then, the mixture was filtered to remove K_2CO_3 and excess of solvent was evaporated under vacuum. The residue thus obtained was dissolved in 30 ml of $CHCl_3$ and washed with brine. The $CHCl_3$ layer was dried (Na_2SO_4) and excess of solvent was removed under vacuum to give a crude product, which was purified by CC (SiO_2; AcOEt/hexane) to yield **9a** (346 mg, 32%). White solid. M.p. 221°. IR (nujol): 3346 (NH), 3232 (NH_2), 2924, 2854, 1602, 1550, 1490, 1363, 1290, 1263, 1111, 1021, 857, 802. ^{1}H-NMR (400 MHz, (D_6)DMSO): 2.37 (br. *s*, NHCH$_2$CH_2NH_2); 2.49 (*t*, *J* = 6.9, NHCH_2CH$_2$NH$_2$); 2.89 – 3.09 (*m*, 4 NCH_2CH$_2$O); 3.44 – 3.49 (*m*, 4 NCH$_2$CH_2O); 6.58 (br. *s*, NH). ^{13}C-NMR (100 MHz, (D_6)DMSO): 41.4; 43.2; 43.7; 66.0; 164.8; 165.8. ESI-MS: 310.2 ($[M+H]^+$).

N-*[4-(Morpholin-4-yl)-6-(piperidin-1-yl)-1,3,5-triazin-2-yl]ethane-1,2-diamine* (**9b**). Yield: 35%. M.p. 159°. IR (film): 3408 (NH, NH_2), 2856, 1608, 1571, 1518, 1480, 1461, 1435, 1390, 1284, 1247, 1116, 1025, 913. ^{1}H-NMR (400 MHz, (D_6)DMSO): 0.85 – 0.87 (*m*, 2 H); 1.19 – 1.25 (*m*, 4 H); 1.55 – 1.80 (*m*, 4 H); 3.33 – 3.45 (*m*, 4 H); 3.51 – 3.52 (*m*, 4 H); 3.70 – 3.73 (*m*, 4 H); 4.07 – 4.10 (*m*, 2 H); 5.83 (br. *s*, NH). ^{13}C-NMR (100 MHz, (D_6)DMSO): 24.5; 25.6; 43.7; 44.5; 66.6; 163.9; 164.5; 169.5. ESI-MS: 308.2 (15, $[M+H]^+$).

N-*(2-Aminoethyl)*-N′-*cyclohexyl-6-(morpholin-4-yl)-1,3,5-triazine-2,4-diamine* (**9c**). Yield: 27%. Liquid. IR (film): 3309 (NH, NH_2), 2927, 2853, 1635, 1582, 1525, 1279, 1114, 757. ^{1}H-NMR (400 MHz, (D_6)DMSO): 1.07 – 1.29 (*m*, 4 H); 1.51 – 1.65 (*m*, 4 H); 1.78 – 1.89 (*m*, 4 H); 2.80 – 3.67 (*m*, 15 H). ESI-MS: 322.2 (18, $[M+H]^+$).

N-*[4-(Morpholin-4-yl)-6-(4-phenylpiperazin-1-yl)-1,3,5-triazin-2-yl]ethane-1,2-diamine* (**9d**). Yield: 23%. M.p. 101°. IR (film): 3340 (NH, NH_2), 2928, 2853, 1708, 1549, 1508, 1445, 1272, 1115, 1025, 811. ^{1}H-NMR (400 MHz, (D_6)DMSO): 3.09 – 3.25 (*m*, 8 H); 3.44 – 3.78 (*m*, 15 H); 6.76 – 6.78 (*m*, 1 arom. H); 6.93 – 6.95 (*m*, 2 arom. H); 7.18 – 7.22 (*m*, 2 arom. H). ESI-MS: 385.3 (24, $[M+H]^+$).

N-*(2-Aminoethyl)*-N′-*(4-methylphenyl)-6-(morpholin-4-yl)-1,3,5-triazine-2,4-diamine* (**9e**). Yield: 21%. M.p. 166°. IR (nujol): 3264 (NH, NH_2), 2923, 2854, 1577, 1552, 1512, 1462, 1377, 1351, 1110, 806.

^{1}H-NMR (400 MHz, (D_6)DMSO): 2.21 (*s*, *Me*–C_6H_4); 2.49–2.66 (*m*, NHCH_2CH_2NH_2); 3.22–3.24 (br. *s*, NH_2); 3.54–3.65 (*m*, 2 NCH_2CH_2O); 6.84 (br. *s*, NH); 7.02 (*d*, *J* = 8.2, 2 arom. H); 7.56 (*d*, *J* = 8.2, 2 arom. H); 8.78–8.93 (br. *s*, N*H*–C_6H_4Me). ESI-MS: 330.2 (19, $[M+H]^+$).

N-*(2-Aminoethyl)*-N′*-(2-methylphenyl)-6-(morpholin-4-yl)-1,3,5-triazine-2,4-diamine* (**9f**). Yield: 24%. M.p. 170°. IR (nujol): 3398 (NH), 3331 (NH_2), 2923, 2854, 1681, 1496, 1378, 1149, 1017, 921, 828, 806, 757, 691. ^{1}H-NMR (400 MHz, (D_6)DMSO): 2.23 (*s*, *Me*–C_6H_4); 2.48–2.66 (*m*, NHCH_2CH_2NH_2); 3.20–3.26 (br. *s*, NH_2); 3.56–3.67 (*m*, 2 NCH_2CH_2O); 7.06 (*d*, *J* = 8.2, 2 arom. H); 7.58 (*d*, *J* = 8.2, 2 arom. H); 8.80–8.93 (br. *s*, 1 arom. H, N*H*–C_6H_4Me). ESI-MS: 330.2 (17, $[M+H]^+$).

N-*(2-Aminoethyl)-6-(morpholin-4-yl)*-N′*-[4-(propan-2-yl)phenyl]-1,3,5-triazine-2,4-diamine* (**9g**). Yield: 26%. M.p. 173°. IR (nujol): 3274 (NH, NH_2), 2924, 1596, 1305, 1111, 1068, 1025, 831, 807, 722. ^{1}H-NMR (400 MHz, (D_6)DMSO): 1.21 (*d*, *J* = 6.8, *Me*$_2$CH); 2.78–2.89 (*m*, Me$_2$C*H*, NCH_2CH_2NH_2); 3.31–3.39 (*m*, 2 NCH_2CH_2O); 3.53–3.72 (*m*, 2 NCH_2CH_2O); 7.15 (*d*, *J* = 8.1, 2 arom. H); 7.67 (*d*, *J* = 8.1, 2 arom. H); 8.87–9.02 (br. *s*, NH, *H*N–C_6H_4^{i}Pr). ^{13}C-NMR (100 MHz, (D_6)DMSO): 24.0; 38.9; 43.3; 66.0; 119.4; 126.0; 138.2; 141.3; 164.0; 165.1. ESI-MS: 358.2 (18, $[M+H]^+$.

N-*(2-Aminoethyl)*-N′*-(4-methoxyphenyl)-6-(morpholin-4-yl)-1,3,5-triazine-2,4-diamine* (**9h**). Yield: 27%. M.p. 150°. IR (nujol): 3263 (NH, NH_2), 2923, 2854, 1601, 1581, 1505, 1435, 1278, 1116, 1029, 1012, 895, 828, 805. ^{1}H-NMR (400 MHz, (D_6)DMSO): 2.43–2.45 (*m*, NHCH_2CH_2NH_2); 2.63 (*t*, *J* = 5.9, NHCH_2CH_2NH_2); 2.95–3.29 (*m*, 2 NCH_2CH_2O, NH_2); 3.56–3.61 (*m*, 2 NCH_2CH_2O); 3.65 (*s*, MeO); 6.77 (*d*, *J* = 6.8, 2 arom. H); 7.54 (*d*, *J* = 6.8, 2 arom. H); 8.67–8.83 (br. *s*, NH, N*H*–C_6H_4OMe). ^{13}C-NMR (100 MHz, (D_6)DMSO): 43.3; 55.1; 66.1; 113.6; 121.0; 133.6; 154.6; 164.0; 165.7. ESI-MS: 346.2 (20, $[M+H]^+$).

N-*(2-Aminoethyl)*-N′*-(3,5-dimethoxyphenyl)-6-(morpholin-4-yl)-1,3,5-triazine-2,4-diamine* (**9i**). Yield: 23%. M.p. 104°. IR (nujol): 3292 (NH, NH_2), 2924, 2854, 1595, 1458, 1377, 1152, 1067, 1023, 807, 757. ^{1}H-NMR (400 MHz, (D_6)DMSO): 2.48–2.49 (*m*, NHCH_2CH_2NH_2); 3.24–3.40 (*m*, 2 NCH_2CH_2O, NH_2); 3.58–3.66 (*m*, 2 NCH_2CH_2O); 3.68 (*s*, 2 MeO); 6.08 (*s*, 1 arom. H); 6.95–7.11 (*m*, 1 arom. H); 7.71–7.89 (*m*, 1 arom. H); 8.97–9.10 (br. *s*, NH, N*H*–C_6H_3(OMe)$_2$). ESI-MS: 376.2 (19, $[M+H]^+$).

N-*[4-(4-Phenylpiperazin-1-yl)-6-(piperidin-1-yl)-1,3,5-triazin-2-yl]ethane-1,2-diamine* (**10a**). Yield: 29%. M.p. 122°. IR (film): 3297 (NH, NH_2), 2933, 2852, 1526, 1445, 1371, 1271, 1231, 998, 808, 756. ^{1}H-NMR (400 MHz, (D_6)DMSO): 1.44–1.57 (*m*, 6 H); 2.48–2.68 (*m*, NHCH_2CH_2NH_2); 3.10–3.26 (*m*, CH_2NCH_2); 3.41–3.52 (*m*, 2 NCH_2CH_2NPh); 3.64–3.77 (*m*, 2 NCH_2CH_2NPh); 6.54–6.69 (br. *s*, NH); 6.78–6.86 (*m*, 1 arom. H); 6.94–6.96 (*m*, 2 arom. H); 7.19–7.23 (*m*, 2 arom. H). ESI-MS: 383.3 (25, $[M+H]^+$).

N-*(2-Aminoethyl)*-N′*-cyclohexyl-6-(4-phenylpiperazin-1-yl)-1,3,5-triazine-2,4-diamine* (**10b**). Yield: 27%. M.p. 98°. IR (nujol): 3297, 2922, 2853, 1538, 1455, 1374, 1231, 1140, 1015, 982, 930, 810, 760, 693. ^{1}H-NMR (400 MHz, (D_6)DMSO): 1.09–1.19 (*m*, 6 H); 1.53–1.79 (*m*, 6 H); 2.48–2.49 (*m*, NHCH_2CH_2NH_2); 2.71–2.82 (*m*, NHCH_2CH_2NH_2); 3.09–3.30 (*m*, 2 NCH_2CH_2NPh); 3.73–3.76 (*m*, 2 NCH_2CH_2NPh); 6.76–6.80 (*m*, NH, N*H*–cyclohexyl); 6.94–6.96 (*m*, 2 arom. H); 7.18–7.22 (*m*, 2 arom. H). ^{13}C-NMR (100 MHz, (D_6)DMSO): 24.9; 32.7; 42.4; 48.4; 115.9; 119.2; 129.0; 151.1; 164.6; 166.0. ESI-MS: 397.3 (23, $[M+H]^+$).

N-*[4,6-Bis(4-phenylpiperazin-1-yl)-1,3,5-triazin-2-yl]ethane-1,2-diamine* (**10c**). Yield: 24%. M.p. 113°. IR (nujol): 3263 (NH, NH_2), 2921, 2726, 1651, 1622, 1538, 1455, 1377, 1289, 1228, 1015, 927, 742. ^{1}H-NMR (400 MHz, (D_6)DMSO): 2.62–2.65 (*m*, NHCH_2CH_2NH_2); 3.10–3.25 (*m*, 4 NCH_2CH_2NPh); 3.71–3.84 (*m*, 4 NCH_2CH_2NPh); 6.74–6.78 (*m*, 2 arom. H, NH); 6.92–6.94 (*m*, 4 arom. H); 7.17–7.21 (*m*, 4 arom. H). ESI-MS: 460.3 (27, $[M+H]^+$).

N-*(2-Aminoethyl)*-N′*-(4-methylphenyl)-6-(4-phenylpiperazin-1-yl)-1,3,5-triazine-2,4-diamine* (**10d**). Yield: 21%. M.p. 115°. IR (nujol): 3292 (NH, NH_2), 2920, 2726, 1463, 1377, 1325, 1267, 1232, 1152, 1002, 912, 756. ^{1}H-NMR (400 MHz, (D_6)DMSO): 1.92 (br. *s*, NH_2); 2.30 (*s*, *Me*–C_6H_4); 3.20–3.54 (*m*, 2 NCH_2CH_2NPh, NHCH_2CH_2NH_2); 3.94–4.09 (*m*, 2 NCH_2CH_2NPh); 6.85–6.96 (*m*, 3 arom. H); 7.10–7.12 (*m*, 2 arom. H); 7.21–7.30 (*m*, 2 arom. H); 7.36–7.43 (*m*, 2 arom. H); 8.11 (br. *s*, N*H*–C_6H_4Me, NH). ESI-MS.: 405.3 (18, $[M+H]^+$).

N-*(2-Aminoethyl)*-N′*-(2-methylphenyl)-6-(4-phenylpiperazin-1-yl)-1,3,5-triazine-2,4-diamine* (**10e**). Yield: 19%. M.p. 131°. IR (film): 3417 (NH, NH_2), 2938, 1704, 1504, 1434, 1245, 1174, 1158, 1028, 753.

^{1}H-NMR (400 MHz, (D_6)DMSO): 1.92 (br. *s*, NH_2); 2.30 (*s*, *Me*–C_6H_4); 3.20–3.54 (*m*, NHCH_2CH_2NH_2, 2 NCH_2CH_2NPh); 3.94–4.09 (*m*, 2 NCH$_2$CH_2NPh); 6.85–6.96 (*m*, 3 arom. H); 7.10–7.12 (*m*, 2 arom. H); 7.21–7.30 (*m*, 2 arom. H); 7.36–7.43 (*m*, 2 arom. H); 8.11 (br. *s*, *H*N–C_6H_4Me, NH). ESI-MS: 405.3 (24, $[M+H]^+$).

N-*(2-Aminoethyl)*-N′-*(4-ethylphenyl)-6-(4-phenylpiperazin-1-yl)-1,3,5-triazine-2,4-diamine* (**10f**). Yield: 30%. M.p. 139°. IR (nujol): 3297 (NH, NH_2), 2924, 2854, 1547, 1505, 1436, 1227, 1155, 1010, 921, 761. ^{1}H-NMR (400 MHz, (D_6)DMSO): 1.12 (*t*, *J* = 7.5, *Me*CH$_2$); 2.46–2.52 (*m*, NHCH$_2$CH_2NH_2); 2.61–2.66 (*m*, MeCH_2, NHCH_2CH$_2$NH$_2$); 3.21–3.25 (*m*, 2 NCH$_2$CH_2NPh); 3.75–3.90 (*m*, 2 NCH$_2$CH_2NPh); 6.74–6.84 (*m*, 2 arom. H); 6.94 (*d*, *J* = 7.3, 2 arom. H); 6.96–7.03 (*m*, 1 arom. H); 7.17–7.21 (*m*, 2 arom. H); 7.59 (*d*, *J* = 7.3, 2 arom. H); 8.77–8.92 (br. *s*, N*H*–C_6H_4Et, NH). ^{13}C-NMR (100 MHz, (D_6)DMSO): 15.8; 27.5; 39.9; 48.4; 115.9; 119.5; 127.5; 128.9; 136.5; 138.2; 151.1; 164.1; 166.0. ESI-MS: 419.8 (27, $[M+H]^+$).

N-*(2-Aminoethyl)-6-(4-phenylpiperazin-1-yl)*-N′-*[4-(propan-2-yl)phenyl]-1,3,5-triazine-2,4-diamine* (**10g**). Yield: 28%. M.p. 165°. IR (nujol): 3313, 2922, 2726, 2370, 1686, 1585, 1537, 1463, 1455, 1377, 1258, 1114, 1008, 722. ^{1}H-NMR (400 MHz, (D_6)DMSO): 1.23 (*d*, *J* = 6.8, *Me*$_2$CH); 2.86–2.89 (*m*, NHCH_2CH_2NH_2, Me$_2$C*H*); 3.13–3.39 (*m*, 2 NCH_2CH$_2$NPh); 3.54–4.11 (*m*, 2 NCH$_2$CH_2NPh); 6.88–6.91 (*m*, 1 arom. H); 6.96 (*d*, *J* = 8.2, 2 arom. H); 7.16 (*d*, *J* = 8.2, 2 arom. H); 7.26–7.31 (*m*, 2 arom. H); 7.45–7.47 (*m*, 2 arom. H); 8.87 (br. *s*, *H*N–C_6H_4^{i}Pr, NH). ESI-MS: 433.2 (30, $[M+H]^+$).

N-*(2-Aminoethyl)*-N′-*(4-methoxyphenyl)-6-(4-phenylpiperazin-1-yl)-1,3,5-triazine-2,4-diamine* (**10h**). Yield: 23%. M.p. 162°. IR (film): 3403 (NH, NH_2), 2919, 1575, 1520, 1479, 1232, 1165, 995, 980, 751. ^{1}H-NMR (400 MHz, (D_6)DMSO): 2.48–2.49 (*m*, NHCH$_2$CH_2NH_2); 2.70–2.73 (*t*, *J* = 5.1, NCH_2CH$_2$NH$_2$); 3.13–3.41 (*m*, 2 NCH_2CH$_2$NPh); 3.70 (*s*, MeO); 3.79–3.92 (*m*, 2 NCH$_2$CH_2NPh); 6.77–6.82 (*m*, 3 arom. H); 6.96 (*d*, *J* = 7.8, 2 arom. H); 7.19–7.23 (*m*, 2 arom. H); 7.60 (*d*, *J* = 7.8, 2 arom. H); 8.71–8.97 (br. *s*, N*H*–C_6H_4OMe, NH). ESI-MS: 421.2 (25, $[M+H]^+$).

N-*(2-Aminoethyl)*-N′-*(3,5-dimethoxyphenyl)-6-(4-phenylpiperazin-1-yl)-1,3,5-triazine-2,4-diamine* (**10i**). Yield: 21%. M.p. 90°. IR (film): 3271, 2964, 2929, 1575, 1514, 1421, 1231, 982, 831, 758. ^{1}H-NMR (400 MHz, (D_6)DMSO): 2.45–2.67 (*m*, NHCH_2CH_2NH$_2$); 3.11–3.21 (*m*, 2 NCH_2CH$_2$NPh); 3.66 (*s*, 2 MeO); 3.74–3.82 (*m*, 2 NCH$_2$CH_2NPh); 6.03 (*s*, 1 arom. H); 6.74–6.77 (*m*, 1 arom. H); 6.93–7.05 (*m*, 4 arom. H); 7.16–7.20 (*m*, 2 arom. H); 8.83–8.99 (br. *s*, N*H*–C_6H_3(OMe)$_2$, NH). ESI-MS: 451.3 (28, $[M+H]^+$).

General Procedure for the Synthesis of Compounds **12a**–**12i** *and* **13a**–**13i**, *Exemplified by the Preparation of* N-*(2-{[4,6-Di(morpholin-4-yl)-1,3,5-triazin-2-yl]amino}ethyl)-4-[6-(4-methylphenyl)-1,2,4,5-tetroxan-3-yl]benzamide* (**12a**). Compound **11** (100 mg, 0.33 mmol) was dissolved in 10 ml of THF, and Et_3N (40 mg, 0.66 mmol) was added. After 15 min, ClCOOEt (36 mg, 0.33 mmol) was added, the mixture was stirred for 30 min, and **9a** (204 mg, 0.66 mmol) was added. The mixture was stirred for 2 h, and the progress of the reaction was monitored by TLC. After completion of the reaction, the product was extracted with $CHCl_3$. The layer was dried (Na_2SO_4), and the solvent was removed under vacuum, and the crude product was purified by CC (SiO_2; AcOEt/hexane). Yield of **12a**: 36 mg (19%). M.p. 158°. IR (film): 3346 (NH), 2854, 1713 (C=O), 1502, 1257, 1112, 1006, 858, 807, 752. ^{1}H-NMR (400 MHz, $CDCl_3$): 2.39 (*s*, Me); 3.50–3.71 (*m*, NHCH_2CH_2NHCO, 4 NCH_2CH_2O); 5.37 (br. *s*, NH); 6.88 (*s*, OCHO); 6.94 (*s*, OCHO), 7.23 (*d*, *J* = 8.2, 2 arom. H); 7.38 (*d*, *J* = 8.2, 2 arom. H); 7.51 (*d*, *J* = 8.2, 2 arom. H);7.67 (br. *s*, CONH); 7.72 (*d*, *J* = 8.2, 2 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 21.5; 39.5; 42.9; 43.7; 66.8; 107.2; 108.4; 127.4; 127.8; 129.5; 133.6; 137.2; 141.8; 164.9; 166.8. ESI-MS: 594.2 (38, $[M+H]^+$). Anal. calc. for $C_{29}H_{35}N_7O_7$ (593.63): C 58.67, H 5.94, N 16.52; found: C 58.89, H 5.69, N 16.85.

4-[6-(4-Methylphenyl)-1,2,4,5-tetroxan-3-yl]-N-*(2-{[4-(morpholin-4-yl)-6-(piperidin-1-yl)-1,3,5-triazin-2-yl]amino}ethyl)benzamide* (**12b**). Yield: 17%. M.p. 159°. IR (film): 3408 (NH), 2856, 1608, 1571, 1518, 1461, 1390, 1247, 1116, 980, 745. ^{1}H-NMR (300 MHz, (D_6)DMSO): 1.18–1.25 (*m*, 6 H); 1.56–1.65 (*m*, 4 H); 2.40 (*s*, Me); 3.34–3.52 (*m*, 4 H); 3.72–3.80 (*m*, 4 H); 4.04–4.11 (*m*, 4 H); 6.94–6.98 (*m*, 2 OCHO); 7.20 (*d*, *J* = 7.8, 2 arom. H); 7.67–7.70 (*d*, *J* = 7.8, 2 arom. H); 7.76–8.07 (*m*, 4 arom. H); 8.65 (br. *s*, CONH); 9.96 (br. *s*, NH). ESI-MS: 592.2 (36, $[M+H]^+$). Anal. calc. for $C_{30}H_{37}N_7O_6$ (591.66): C 60.90, H 6.30, N 16.57; found: C 61.22, H 6.12, N 16.79.

N-*(2-{[4-(Cyclohexylamino)-6-(morpholin-4-yl)-1,3,5-triazin-2-yl]amino}ethyl)-4-[6-(4-methylphenyl)-1,2,4,5-tetroxan-3-yl]benzamide* (**12c**). Yield: 17%. M.p. 176°. IR (film): 3340 (NH), 2897, 2855, 1713

(C=O), 1527, 1360, 1262, 1161, 1115, 1006, 910, 809, 759, 732. ^{1}H-NMR (300 MHz, (D_6)DMSO): 1.11–1.20 (*m*, 6 H); 1.53–1.78 (*m*, 5 H); 2.36 (*s*, Me); 3.11–3.58 (*m*, 8 H); 3.92–3.99 (*m*, 5 H); 7.06 (*s*, OCHO); 7.13 (*s*, OCHO); 7.28–7.32 (*m*, 2 arom. H); 7.39–7.49 (*m*, 2 arom. H); 7.79–8.00 (*m*, 4 arom. H); 8.63–8.69 (br. *s*, CONH); 9.94–10.07 (br. *s*, NH). ^{13}C-NMR (100 MHz, (D_6)DMSO): 18.8; 21.1; 21.4; 24.9; 25.4; 31.9; 32.6; 43.1; 66.1; 107.3; 107.4; 127.4; 128.0; 129.1; 129.3; 129.6; 129.7; 143.0; 164.8; 167.0; 167.4; 192.6; 192.9. ESI-MS: 606.3 (34, $[M+H]^+$). Anal. calc. for $C_{31}H_{39}N_7O_6$ (605.68): C 61.47, H 6.49, N 16.19; found: C 61.76, H 6.21, N 16.51.

4-[6-(4-Methylphenyl)-1,2,4,5-tetroxan-3-yl]-N-*(2-{[4-(morpholin-4-yl)-6-(4-phenylpiperazin-1-yl)-1,3,5-triazin-2-yl]amino}ethyl)benzamide* (**12d**). Yield: 18%. M.p. 158°. IR (film): 3338 (NH), 2854, 1708 (C=O), 1528, 1438, 1363, 1262, 1232, 1160, 1115, 1006, 759. ^{1}H-NMR (300 MHz, (D_6)DMSO): 2.35 (*s*, Me); 3.06–3.93 (*m*, 20 H); 6.73–6.82 (*m*, 2 arom. H); 6.91–7.08 (*m*, 1 arom H, OCHO); 7.15–7.23 (*m*, 1 arom. H, 2 OCHO); 7.42–7.48 (*m*, 2 arom. H); 7.75–7.83 (*m*, 2 arom. H); 7.89–8.10 (*m*, 4 arom. H); 8.58–8.69 (br. *s*, CONH); 9.90–10.00 (br. *s*, NH). ESI-MS: 669.3 (39, $[M+H]^+$). Anal. calc. for $C_{35}H_{40}N_8O_6$ (668.74): C 62.86, H 6.03, N 16.76; found: C 62.58, H 6.31, N 16.98.

N-*[2-({4-[(4-Methylphenyl)amino]-6-(morpholin-4-yl)-1,3,5-triazin-2-yl}amino)ethyl]-4-[6-(4-methylphenyl)-1,2,4,5-tetroxan-3-yl]benzamide* (**12e**). Yield: 16%. M.p. 175°. IR (film): 3327 (NH), 2963, 2924, 2248, 1704 (C=O), 1515, 1360, 1261, 1112, 1023, 910, 734. ^{1}H-NMR (300 MHz, (D_6)DMSO): 2.35 (*s*, Me); 2.42 (*s*, *Me*–C_6H_4); 3.33–3.64 (*m*, 2 NCH_2CH_2O, NHCH_2CH_2NHCO); 7.05 (*s*, OCHO); 7.13 (*s*, OCHO); 7.30 (*d*, *J* = 7.8, 2 arom. H); 7.46 (*d*, *J* = 7.8, 2 arom. H); 7.56 (*d*, *J* = 8.1, 2 arom. H); 7.64 (*d*, *J* = 8.1, 2 arom. H); 7.97–8.03 (*m*, 4 arom. H); 8.63 (br. *s*, CONH); 8.81–8.96 (br. s, N*H*–C_6H_4Me, NH). ^{13}C-NMR (100 MHz, (D_6)DMSO): 20.4; 21.2; 39.9; 65.9; 106.8; 107.6; 119.7; 127.8; 127.9; 128.0; 129.5; 133.3; 137.9; 141.6; 164.2; 165.8. ESI-MS: 614.2 (32, $[M+H]^+$). Anal. calc. for $C_{32}H_{35}N_7O_6$ (613.66): C 62.63, H 5.75, N 15.98; found: C 62.35, H 5.47, N 16.30.

N-*[2-({4-[(2-Methylphenyl)amino]-6-(morpholin-4-yl)-1,3,5-triazin-2-yl}amino)ethyl]-4-[6-(4-methylphenyl)-1,2,4,5-tetroxan-3-yl]benzamide* (**12f**). Yield: 17%. M.p. 181°. IR (film): 3276 (NH), 2925, 2852, 1697 (C=O), 1508, 1460, 1231, 1158, 1010, 754. ^{1}H-NMR (300 MHz, (D_6)DMSO): 2.36 (*s*, *Me*–C_6H_4); 2.43 (*s*, Me); 3.34–3.65 (*m*, 2 NCH_2CH_2O, NHCH_2CH_2NHCO); 7.07 (*s*, OCHO); 7.11 (*s*, OCHO); 7.31 (*d*, *J* = 7.8, 2 arom. H); 7.47 (*d*, *J* = 7.8, 2 arom. H); 7.57 (*d*, *J* = 8.1, 2 arom. H); 7.64 (*d*, *J* = 8.1, 2 arom. H); 7.97–8.01 (*m*, 4 arom. H); 8.65 (br. *s*, CONH); 8.83–8.97 (br. *s*, N*H*–C_6H_4Me, NH). ESI-MS: 614.2 (35, $[M+H]^+$). Anal. calc. for $C_{32}H_{35}N_7O_6$ (613.66): C 62.63, H 5.75, N 15.98; found: C 62.41, H 5.99, N 15.69.

4-[6-(4-Methylphenyl)-1,2,4,5-tetroxan-3-yl]-N-*(2-{[4-(morpholin-4-yl)-6-{[4-(propan-2-yl)phenyl]amino}-1,3,5-triazin-2-yl]amino}ethyl)benzamide* (**12g**). Yield: 18%. M.p. 154°. IR (film): 3326 (NH), 2960, 1704 (C=O), 1505, 1418, 1275, 1115, 1023, 755. ^{1}H-NMR (300 MHz, (D_6)DMSO): 1.10 (*d*, *J* = 6.6, Me_2CH); 2.35 (*s*, Me); 2.70–2.79 (*m*, Me_2C*H*); 3.15–3.62 (*m*, 2 NCH_2CH_2O, NHCH_2CH_2NHCO); 6.94–7.25 (*m*, 2 OCHO); 7.25 (*d*, *J* = 7.2, 2 arom. H); 7.34 (*d*, *J* = 7.5, 2 arom. H); 7.42 (*d*, *J* = 7.2, 2 arom. H); 7.55–7.61 (*m*, 2 arom. H); 7.74–7.80 (*m*, 2 arom. H); 7.85–8.08 (*m*, 2 arom. H); 8.62–8.70 (br. *s*, CONH); 8.81–8.96 (br. *s*, NH); 9.90–10.02 (br. *s*, N*H*–C_6H_4Me). ^{13}C-NMR (100 MHz, (D_6)DMSO): 20.8; 24.1; 38.9; 40.1; 66.3; 106.8; 107.8; 119.5; 126.0; 127.9; 128.0; 129.5; 132.9; 134.1; 138.1; 141.1; 145.6; 163.8; 166.0. ESI-MS: 642.3 (38, $[M+H]^+$). Anal. calc. for $C_{34}H_{39}N_7O_6$ (641.72): C 63.64, H 6.13, N 15.28; found: C 63.36, H 6.35, N 15.39.

N-*[2-({4-[(4-Methoxyphenyl)amino]-6-(morpholin-4-yl)-1,3,5-triazin-2-yl}amino)ethyl]-4-[6-(4-methylphenyl)-1,2,4,5-tetroxan-3-yl]benzamide* (**12h**). Yield: 15%. M.p. 143°. IR (film): 3338 (NH), 2926, 2857, 1702 (C=O), 1540, 1508, 1244, 1026, 809, 732. ^{1}H-NMR (300 MHz, (D_6)DMSO): 2.36 (*s*, Me); 3.29–3.65 (*m*, 2 NCH_2CH_2O, NHCH_2CH_2NHCO); 3.69 (*s*, MeO); 6.80–6.83 (*m*, 2 OCHO); 7.27 (*d*, *J* = 7.8, 2 arom. H); 7.39 (*d*, *J* = 7.8, 2 arom. H); 7.59 (*d*, *J* = 7.8, 2 arom. H); 7.78–7.84 (*m*, 4 arom. H); 7.88–8.03 (*m*, 2 arom. H); 8.60–8.84 (br. *s*, CONH, NH); 9.95–10.00 (br. *s*, N*H*–C_6H_4OMe). ESI-MS: 630.2 (37, $[M+H]^+$).

N-*[2-({4-[(3,5-Dimethoxyphenyl)amino]-6-(morpholin-4-yl)-1,3,5-triazin-2-yl}amino)ethyl]-4-[6-(4-methylphenyl)-1,2,4,5-tetroxan-3-yl]benzamide* (**12i**). Yield: 16%. M.p. 154°. IR (film): 3338 (NH), 2924, 1702 (C=O), 1591, 1508, 1447, 1358, 1266, 1172, 1153, 809. ^{1}H-NMR (300 MHz, (D_6)DMSO): 2.31 (*s*, Me); 3.10–3.95 (*m*, 2 NCH_2CH_2O, NHCH_2CH_2NHCO, 2 MeO); 6.02 (*s*, 1 arom. H); 7.01 (*s*, OCHO); 7.09 (*s*, OCHO); 7.26 (*d*, *J* = 7.8, 2 arom. H); 7.42 (*d*, *J* = 7.8, 2 arom. H); 7.60 (*d*, *J* = 7.8, 2 arom. H); 7.75–

7.94 (*m*, 4 arom. H); 8.62 (br. *s*, CONH); 8.84–9.01 (br. *s*, NH); 9.90–10.03 (br. *s*, N*H*–$C_6H_3(OMe)_2$). ^{13}C-NMR (100 MHz, (D_6)DMSO): 21.3; 43.3; 66.1; 97.5; 106.8; 107.6; 128.0; 129.6; 137.3; 142.2; 160.2; 166.0. ESI-MS: 660.2 (35, $[M+H]^+$).

4-[6-(4-Methylphenyl)-1,2,4,5-tetroxan-3-yl]-N-*(2-{[4-(4-phenylpiperazin-1-yl)-6-(piperidin-1-yl)-1,3,5-triazin-2-yl]amino}ethyl)benzamide* (**13a**). Yield: 18%. M.p. 129°. IR (film): 3340 (NH), 2930, 2852, 1702 (C=O), 1530, 1499, 1270, 1231, 1153, 808. ^{1}H-NMR (300 MHz, (D_6)DMSO): 1.44–1.57 (*m*, 6 H); 2.36 (*s*, Me); 3.10–3.90 (*m*, 16 H); 6.77–6.81 (*m*, 2 H); 6.94–7.13 (*m*, 2 OCHO); 7.19–7.24 (*m*, 2 arom. H); 7.28–7.32 (*m*, 2 arom. H); 7.40–7.48 (*m*, 2 arom. H); 7.79–7.84 (*m*, 2 arom. H); 7.89–8.10 (*m*, 3 arom. H); 8.64–8.71 (br. *s*, CONH); 9.95–10.06 (br. *s*, NH). ESI-MS: 667.3 (37, $[M+H]^+$). Anal. calc. for $C_{36}H_{42}N_8O_5$ (666.77): C 64.85, H 6.35, N 16.81; found: C 64.55, H 6.65, N 16.51.

N-*(2-{[4-(Cyclohexylamino)-6-(4-phenylpiperazin-1-yl)-1,3,5-triazin-2-yl]amino}ethyl)-4-[6-(4-methylphenyl)-1,2,4,5-tetroxan-3-yl]benzamide* (**13b**). Yield: 16%. M.p. 145°. IR (film): 3388 (NH), 2929, 1708 (C=O), 1523, 1364, 1222, 1011, 758. ^{1}H-NMR (300 MHz, (D_6)DMSO): 1.24–1.91 (*m*, 10 H); 2.37 (*s*, 3 H); 3.10–3.78 (*m*, 13 H); 6.79–7.83 (*m*, 4 H); 6.97–7.05 (*m*, 2 OCHO); 7.22–7.43 (*m*, 4 arom. H); 7.80–8.12 (*m*, 6 arom. H); 8.62–8.68 (br. *s*, CONH); 9.96–10.07 (br. *s*, NH). ^{13}C-NMR (100 MHz, (D_6)DMSO): 18.8; 21.1; 21.1; 21.4; 24.9; 32.6; 43.1; 66.1; 105.8;107.3; 107.4; 126.2; 127.9; 128.0; 129.1; 129.3; 129.4; 129.7; 131.0; 137.4; 141.5; 143.0; 145.3; 167.4; 192.7. ESI-MS: 681.3 (40, $[M+H]^+$).

N-*(2-{[4,6-Bis(4-phenylpiperazin-1-yl)-1,3,5-triazin-2-yl]amino}ethyl)-4-[6-(4-methylphenyl)-1,2,4,5-tetroxan-3-yl]benzamide* (**13c**). Yield: 16%. M.p. 152°. IR (film): 3338 (NH), 2924, 1702 (C=O), 1508, 1439, 1267, 1231, 1004, 759. ^{1}H-NMR (300 MHz, (D_6)DMSO): 2.36 (*s*, 3 H); 3.33–3.84 (*m*, 4 NHCH_2CH_2NPh, NHCH_2CH_2N); 6.89–6.95 (*m*, 4 arom. H); 7.05 (*s*, OCHO); 7.13 (*s*, OCHO); 7.25–7.48 (*m*, 4 arom. H); 7.67–7.70 (*m*, 2 arom. H); 7.79–7.98 (*m*, 6 arom. H); 8.23–8.25 (*m*, 2 arom. H); 8.65–8.71 (br. *s*, CONH); 9.94–10.07 (br. *s*, NH). ^{13}C-NMR (100 MHz, (D_6)DMSO): 25.4; 43.2; 59.5; 66.1; 105.8; 107.3; 107.4; 126.2; 127.7; 127.9; 128.0; 129.1; 129.4; 129.7; 131.0; 131.2; 137.4; 141.5; 156.3; 164.9; 165.8; 192.6. ESI-MS: 744.3 (45, $[M+H]^+$). Anal. calc. for $C_{41}H_{45}N_9O_5$ (643.85): C 66.20, H 6.10, N 16.95; found: C 66.42, H 6.31, N 16.75.

N-*[2-({4-[(4-Methylphenyl)amino]-6-(4-phenylpiperazin-1-yl)-1,3,5-triazin-2-yl}amino)ethyl]-4-[6-(4-methylphenyl)-1,2,4,5-tetroxan-3-yl]benzamide* (**13d**).Yield: 17%. M.p. 137°. IR (film): 3227 (NH), 2925, 1702 (C=O), 1577, 1544, 1365, 1281, 1232, 1159, 1012, 808, 758. ^{1}H-NMR (300 MHz, (D_6)DMSO): 2.23 (*s*, *Me*–C_6H_4); 2.36 (*s*, Me); 3.14–3.96 (*m*, 2 NCH_2CH_2NPh, NHCH_2CH_2NHCO); 6.79–6.82 (*m*, 1 arom. H); 6.97–7.15 (*m*, 2 arom. H, 2 OCHO); 7.19–7.32 (*m*, 4 arom. H); 7.39–7.42 (*m*, 2 arom. H); 7.58–7.66 (*m*, 4 arom. H); 7.78–7.84 (*m*, 2 arom. H); 7.90–8.02 (*m*, 2 arom. H); 8.63–8.61 (br. *s*, CONH); 9.25 (br. *s*, NH); 9.95–10.06 (br. *s*, N*H*–C_6H_4 Me). ESI-MS: 689.3 (39, $[M+H]^+$).

N-*[2-({4-[(2-Methylphenyl)amino]-6-(4-phenylpiperazin-1-yl)-1,3,5-triazin-2-yl}amino)ethyl]-4-[6-(4-methylphenyl)-1,2,4,5-tetroxan-3-yl]benzamide* (**13e**). Yield: 15%. M.p. 148°. IR (film): 3390 (NH), 2915, 1600, 1578, 1528, 1494, 1231, 1130, 980, 799, 756. ^{1}H-NMR (300 MHz, (D_6)DMSO): 2.36 (*s*, 2 Me); 3.14–3.96 (*m*, 2 NCH_2CH_2NPh, NHCH_2CH_2NHCO); 6.79–6.82 (*m*, 1 arom. H); 6.97–7.11(*m*, 2 arom. H, 2 OCHO); 7.19–7.32 (*m*, 2 arom. H); 7.39–7.42 (*m*, 4 arom. H); 7.58–7.66 (*m*, 4 arom. H); 7.78–7.84 (*m*, 2 arom. H); 7.90–8.02 (*m*, 2 arom. H); 8.65 (br. *s*, CONH); 9.25 (br. *s*, NH); 9.95–10.05 (br. *s*, N*H*–C_6H_4 Me). ESI-MS: 689.3 (23, $[M+H]^+$). Anal. calc. for $C_{38}H_{40}N_8O_5$ (688.77): C 66.26, H 5.85, N 16.27; found: C 66.46, H 5.65, N 16.57.

N-*[2-({4-[(4-Ethylphenyl)amino]-6-(4-phenylpiperazin-1-yl)-1,3,5-triazin-2-yl}amino)ethyl]-4-[6-(4-methylphenyl)-1,2,4,5-tetroxan-3-yl]benzamide* (**13f**). Yield: 16%. M.p. 135°. IR (film): 3315 (NH), 2963, 1702 (C=O), 1508, 1420, 1364, 1232, 1159, 1011, 758. ^{1}H-NMR (300 MHz, (D_6)DMSO): 1.12 (*t*, *J* = 7.5, *Me*CH_2); 2.36 (*s*, Me); 2.44–2.53 (*m*, MeCH_2); 3.14–3.84 (*m*, 2 NCH_2CH_2NPh, NHCH_2CH_2NHCO); 6.77–6.82 (*m*, 1 arom. H); 6.96–6.98 (*m*, 2 arom. H); 7.05–7.12 (*m*, 2 OCHO); 7.19–7.32 (*m*, 4 arom. H); 7.39–7.48 (*m*, 2 arom. H); 7.64–7.72 (*m*, 2 arom. H); 7.78–7.84 (*m*, 2 arom. H); 7.91–8.04 (*m*, 4 arom. H); 8.68–8.75 (br. *s*, CONH); 8.86–9.01 (br. *s*, NH); 9.99–10.05 (br. *s*, N*H*–C_6H_4Et). ESI-MS: 703.3 (41, $[M+H]^+$).

4-[6-(4-Methylphenyl)-1,2,4,5-tetroxan-3-yl]-N-*(2-{[4-(4-phenylpiperazin-1-yl)-6-{[4-(propan-2-yl)phenyl]amino}-1,3,5-triazin-2-yl]amino}ethyl)benzamide* (**13g**). Yield: 18%. M.p. 133°. IR (film): 3314 (NH), 2959, 1702 (C=O), 1508, 1419, 1365, 1232, 1159, 1012, 927, 732. ^{1}H-NMR (300 MHz, (D_6)DMSO): 1.16 (*d*, *J* = 6.9, Me_2CH); 2.35 (*s*, Me); 2.76–2.85 (*sept.*, Me_2C*H*); 3.14–3.84 (*m*, 2 NCH_2CH_2NPh,

NHCH_2CH_2NHCO); 6.77–6.82 (*m*, 1 arom. H); 6.96 (*d*, *J* = 7.8, 2 arom. H); 7.04 (*s*, OCHO); 7.11 (*s*, OCHO); 7.20–7.32 (*m*, 4 arom. H); 7.39–7.48 (*m*, 4 arom. H); 7.64 (*d*, *J* = 7.8, 2 arom. H); 7.78–7.84 (*m*, 2 arom. H); 7.91–8.00 (*m*, 2 arom. H); 8.33–8.69 (br. *s*, CONH); 8.96 (br. *s*, NH); 9.95–10.05 (br. *s*, N*H*–C_6H_4^{i}Pr). ESI-MS: 717.3 (46, $[M+H]^+$). Anal. calc. for $C_{40}H_{44}N_8O_5$ (716.83): C 67.02, H 6.19, N 15.63; found: C 67.22, H 6.39, N 15.42.

N-*[2-({4-[(4-Methoxyphenyl)amino]-6-(4-phenylpiperazin-1-yl)-1,3,5-triazin-2-yl}amino)ethyl]-4-[6-(4-methylphenyl)-1,2,4,5-tetroxan-3-yl]benzamide* (**13h**). Yield: 16%. M.p. 171° IR (film): 3327 (NH), 2925, 2853, 1699 (C=O), 1505, 1445, 1232, 1159, 1035, 928, 760. ^{1}H-NMR (300 MHz, (D_6)DMSO): 2.36 (*s*, Me); 3.13–3.47 (*m*, 2 NCH_2CH_2NPh, NHCH_2CH_2NHCO); 3.70 (*s*, MeO); 3.82 (*m*, 2 NCH_2CH_2NPh); 6.77–6.82 (*m*, 1 arom. H); 6.96–7.12 (*m*, 2 arom. H, 2 OCHO); 7.19–7.24 (*m*, 4 arom. H); 7.28–7.33 (*m*, 2 arom. H); 7.40–7.52 (*m*, 2 arom. H); 7.61–7.67 (*m*, 2 arom. H); 7.79–7.84 (*m*, 2 arom. H); 7.93–8.02 (*m*, 2 arom. H); 8.67–8.78 (br. *s*, CONH); 8.94 (br. *s*, NH); 9.94–10.05 (br. *s*, N*H*–C_6H_4OMe). ESI-MS: 705.3 (38, $[M+H]^+$).

N-*[2-({4-[(3,5-Dimethoxyphenyl)amino]-6-(4-phenylpiperazin-1-yl)-1,3,5-triazin-2-yl}amino)ethyl]-4-[6-(4-methylphenyl)-1,2,4,5-tetroxan-3-yl]benzamide* (**13i**). Yield: 18%. M.p. 138°. IR (film): 3346 (NH), 2932, 1707 (C=O), 1593, 1508, 1448, 1232, 1152, 913, 808, 742. ^{1}H-NMR (300 MHz, (D_6)DMSO): 2.35 (*s*, Me); 3.14–3.85 (*m*, 2 NCH_2CH_2NPh, NHCH_2CH_2NHCO, 2 MeO); 6.07 (*s*, 1 arom. H); 6.77–6.82 (*m*, 2 arom. H); 6.97–7.12 (*m*, 2 arom. H, 2 OCHO); 7.20–7.25 (*m*, 2 arom. H); 7.30 (*d*, *J* = 8.1, 2 arom. H); 7.46 (*d*, *J* = 7.8, 2 arom. H); 7.64 (*d*, *J* = 8.1, 2 arom. H); 7.91–8.02 (*m*, 3 arom. H); 8.65 (br. *s*, CONH); 8.90–9.06 (br. *s*, NH); 10.05 (br. *s*, N*H*–C_6H_3(OMe)$_2$). ESI-MS: 735.3 (43, $[M+H]^+$).

General Procedure for the Synthesis of Compounds **16a**–**16m** *and* **17a**–**17h**, *Exemplified by the Preparation of 3-(4-Methoxyphenyl)-9-[(4-methylphenyl)sulfonyl]-1,2,4,5-tetraoxa-9-azaspiro[5.5]undecane* (**16j**). A mixture of **15a** (800 mg, 3.15 mmol), 30% H_2O_2 (0.71 ml, 6.31 mmol), and methyltrioxorhenium (MTO; 0.79 mg, 0.003 mmol) in 50 ml of 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP) was stirred for 2 h at r.t. and 4-MeO–C_6H_4CHO (860 mg, 6.31 mmol) was added to the mixture, followed by the addition of 54% Et_2O soln. of HBF_4 (511 mg, 3.15 mmol). The mixture was stirred for an additional h at r.t. After completion of the reaction (TLC), $CHCl_3$ was added to the mixture, and the layer was washed with sat. $NaHSO_3$ soln. followed by sat. soln. of $NaHCO_3$. The $CHCl_3$ layer was then dried (Na_2SO_4), and solvent was evaporated under reduced pressure. The crude product was then purified by CC (SiO_2, $CHCl_3$/hexane) to give **16j**. Yield: 266 mg (20%). M.p. 176°. IR (film): 2925, 2854, 1611, 1517, 1465, 1345, 1333, 1255, 1164, 1078, 1039, 993, 963. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.87 (*t*, *J* = 5.7, NCH$_2$CH_2); 2.44 (*s*, Me); 2.65 (*t*, *J* = 5.7, NCH$_2$CH_2); 3.13 (*t*, *J* = 5.7, NCH_2CH$_2$); 3.21 (*t*, *J* = 5.7, NCH_2CH$_2$); 3.81 (*s*, MeO); 6.56 (*s*, OCHO); 6.89 (*d*, *J* = 8.1, 2 arom. H); 7.32–7.34 (*m*, 4 arom. H); 7.64 (*d*, *J* = 8.1, 2 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 21.5; 29.7; 31.1; 42.0; 43.1; 55.3; 105.7; 108.0; 114.1; 123.1; 127.6; 129.2; 129.8; 132.9; 143.9; 161.8. HR-ESI-MS: 421.3566 (M^+, $C_{20}H_{23}NO_7S^+$; calc. 421.1195).

12-Methyl-3-[(4-methylphenyl)sulfonyl]-7,8,15,16-tetraoxa-3-azadispiro[5.2.5.2]hexadecane (**16a**). Yield: 36%. M.p. 197°. IR (film): 2956, 2925, 1331, 1232, 1156, 1039, 993, 811, 729. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.88–1.80 (*m*, 14 H); 2.43 (*s*, 3 H); 2.56–2.60 (*m*, 2 H); 3.03–3.16 (*m*, 4 H); 7.30 (*d*, *J* = 8.1, 2 arom. H); 7.61 (*d*, *J* = 8.1, 2 arom. H). ESI-MS: 398.2 (18, $[M+H]^+$). Anal. calc. for $C_{19}H_{27}O_6S$ (397.49): C 57.41, H 6.85; found: C 57.66, H 6.49.

9-[(4-Methylphenyl)sulfonyl]-3-phenyl-1,2,4,5-tetraoxa-9-azaspiro[5.5]undecane (**16b**). Yield: 26%. M.p. 178°. IR (film): 3033, 2926, 2858, 1721, 1599, 1494, 1459, 1360, 1333, 1234, 1165, 1079, 1040, 994, 965. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.88 (*t*, *J* = 5.7. NCH$_2$CH_2); 2.43 (*s*, Me); 2.66 (*t*, *J* = 5.7, NCH$_2$CH_2); 3.13 (*t*, *J* = 5.7, NCH_2CH$_2$); 3.22 (*t*, *J* = 5.7, NCH_2CH$_2$); 6.63 (*s*, OCHO); 7.28–7.50 (*m*, 7 arom. H); 7.63–7.66 (*m*, 2 arom. H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): 21.5; 29.7; 31.1; 42.0; 43.1; 106.0; 108.1; 127.4; 127.6; 128.8; 129.8; 130.8; 131.3; 132.9; 143.9. ESI-MS: 392.1 (24, $[M+H]^+$). Anal. calc. for $C_{19}H_{21}NO_6S$ (391.44): C 58.30, H 5.41, N 3.58; found: C 58.61, H 5.72, N 3.40.

3-(4-Methylphenyl)-9-[(4-methylphenyl)sulfonyl]-1,2,4,5-tetraoxa-9-azaspiro[5.5]undecane (**16c**). Yield: 32%. M.p. 171°. IR (film): 2950, 2924, 1458, 1345, 1331, 1232, 1181, 1156, 1077, 1039, 1017, 995, 729. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.87 (*t*, *J* = 6.0, NCH$_2$CH_2); 2,36 (*s*, Me); 2.43 (*s*, Me); 2.65 (*t*, *J* = 6.0, NCH$_2$CH_2); 3.12 (*t*, *J* = 6.0, NCH_2CH$_2$); 3.22 (*t*, *J* = 6.0, NCH_2CH$_2$); 6.59 (*s*, OCHO); 7.18–7.22 (*m*, 2 arom. H); 7.28–7.41 (*m*, 4 arom. H); 7.63–7.66 (*m*, 2 arom. H). HR-ESI-MS: 405.2570 (75, M^+, $C_{20}H_{23}NO_6S^+$; calc. 405.1246).

3-(3-Methylphenyl)-9-[(4-methylphenyl)sulfonyl]-1,2,4,5-tetraoxa-9-azaspiro[5.5]undecane (**16d**). Yield: 27%. M.p. 151°. IR (film): 2928, 2865, 1597, 1466, 1358, 1334, 1235, 1167, 1081, 1040, 993, 964, 936. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.85 (*t*, *J* = 5.7, NCH_2CH_2); 2.35 (*s*, Me); 2.43 (*s*, Me); 2.63 (*t*, *J* = 5.7, NCH_2CH_2); 3.10 (*t*, *J* = 5.7, NCH_2CH_2); 3.20 (*t*, *J* = 5.7, NCH_2CH_2); 6.59 (*s*, OCHO); 7.18–7.27 (*m*, 2 arom. H); 7.28–7.41 (*m*, 4 arom. H); 7.63–7.66 (*m*, 2 arom. H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): 21.2; 29.7; 31.1; 42.0; 43.1; 105.9; 108.2; 124.6; 127.6;127.9; 128.6; 129.8; 132.1; 132.9; 138.9; 138.7; 143.9. HR-ESI-MS: 405.2080 (85, M^+, $C_{20}H_{23}NO_6S^+$; calc. 405.1246).

3-(2-Methylphenyl)-9-[(4-methylphenyl)sulfonyl]-1,2,4,5-tetraoxa-9-azaspiro[5.5]undecane (**16e**). Yield: 27%. M.p. 167°. IR (film): 2924, 2845, 1610, 1358, 1202, 1018, 1007, 911, 835, 797. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.88 (*t*, *J* = 5.7, NCH_2CH_2); 2.36 (*s*, Me); 2.38 (*s*, Me); 2.65 (*t*, *J* = 5.7, NCH_2CH_2); 3.15 (*t*, *J* = 5.7, NCH_2CH_2); 3.25 (*t*, *J* = 5.7, NCH_2CH_2); 6.58 (*s*, OCHO); 7.18–7.28 (*m*, 3 arom. H); 7.38–7.41 (*m*, 1 arom. H); 7.52–7.64 (*m*, 2 arom. H); 7.76–7.78 (*m*, 2 arom. H). ESI-MS: 406.3 (30, $[M+H]^+$).

3-(4-Ethylphenyl)-9-[(4-methylphenyl)sulfonyl]-1,2,4,5-tetraoxa-9-azaspiro[5.5]undecane (**16f**). Yield: 32%. M.p. 181°. IR (film): 2928, 1600, 1458, 1331, 1232, 1156, 1077, 1039, 993, 833, 729. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.21 (*t*, *J* = 7.5, $MeCH_2$); 1.87 (*t*, *J* = 5.7, NCH_2CH_2); 2.43 (*s*, Me); 2.61–2.69 (*m*, 4 H); 3.12 (*t*, *J* = 6.0, NCH_2CH_2); 3.22 (*t*, *J* = 5.7, NCH_2CH_2); 6.59 (*s*, OCHO); 7.20 (*d*, *J* = 8.1, 2 arom. H); 7.28–7.34 (*m*, 4 arom. H); 7.63–7.66 (*d*, *J* = 8.1, 2 arom. H). ESI-MS: 420.1 (55, $[M+H]^+$). Anal. calc. for $C_{21}H_{25}NO_6S$ (419.49): C 60.13, H 6.01, N 3.34; found: C 59.85, H 6.35, N 3.63.

9-[(4-Methylphenyl)sulfonyl]-3-(4-propylphenyl)-1,2,4,5-tetraoxa-9-azaspiro[5.5]undecane (**16g**). Yield: 21%. M.p. 168°. IR (film): 2929, 2363, 1653, 1542, 1522, 1459, 1360, 1156, 1018, 909, 792. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.88 (*t*, *J* = 7.2, $MeCH_2CH_2$); 1.55–1.67 (*m*, $MeCH_2CH_2$); 1.86 (*t*, *J* = 5.7, NCH_2CH_2); 2.43 (*s*, Me); 2.56–2.66 (*m*, $MeCH_2CH_2$, NCH_2CH_2); 3.12 (*t*, *J* = 5.7, NCH_2CH_2); 3.22 (*t*, *J* = 5.7, NCH_2CH_2); 6.59 (*s*, OCHO); 7.18 (*d*, *J* = 8.1, 2 arom. H); 7.25–7.33 (*m*, 4 arom. H); 7.63 (*d*, *J* = 8.1, 2 arom. H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): 13.7; 21.5; 24.3; 29.7; 30.3; 31.1; 37.9; 42.0; 43.1; 105.9; 108.2; 127.4; 127.6; 128.2; 128.9; 129.8; 133.0; 143.9; 146.4. ESI-MS: 434.1 (60, $[M+H]^+$). Anal. calc. for $C_{22}H_{27}NO_6S$ (433.52): C 60.95, H 6.28, N 3.23; found: C 60.62, H 6.04, N, 3.40.

9-[(4-Methylphenyl)sulfonyl]-3-[4-(propan-2-yl)phenyl]-1,2,4,5-tetraoxa-9-azaspiro[5.5]undecane (**16h**). Yield: 27%. M.p. 178° IR (film): 2951, 1602, 1369, 1017, 1018, 1002, 922, 756. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.21 (*d*, *J* = 6.9, Me_2CH); 1.85–1.89 (*m*, NCH_2CH_2); 2.43 (*s*, Me); 2.65–2.67 (*m*, NCH_2CH_2); 2.86–2.95 (*sept.*, Me_2CH), 3.12 (*t*, *J* = 5.7, NCH_2CH_2); 3.22 (*t*, *J* = 5.7, NCH_2CH_2); 6.59 (*s*, OCHO); 7.23–7.34 (*m*, 6 arom. H); 7.63–7.66 (*m*, 2 arom. H). ESI-MS: 434.1 (25, $[M+H]^+$).

*3-[4-(*tert*-Butyl)phenyl]-9-[(4-methylphenyl)sulfonyl]-1,2,4,5-tetraoxa-9-azaspiro[5.5]undecane* (**16i**). Yield: 40%. M.p. 196°. IR (film): 2959, 2925, 2855, 1345, 1331, 1232, 1181, 1156, 1077, 1039, 994, 965. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.29 (*s*, Me_3C); 1.87 (*t*, *J* = 5.7, NCH_2CH_2); 2.43 (*s*, Me); 2.65 (*t*, *J* = 5.7, NCH_2CH_2); 3.12 (*t*, *J* = 5.7, NCH_2CH_2); 3.22 (*t*, *J* = 5.7, NCH_2CH_2); 6.60 (*s*, OCHO); 7.30–7.34 (*m*, 4 arom. H); 7.40–7.45 (*m*, 2 arom. H); 7.63–7.66 (*m*, 2 arom. H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): 21.5; 29.7; 31.1; 34.8; 42.0; 43.1; 105.8; 108.0; 125.7; 127.7; 127.2; 127.6; 127.9; 129.8; 132.9; 143.8; 154.7. ESI-MS: 448.2 (100, $[M+H]^+$). Anal. calc. for $C_{23}H_{29}NO_6S$ (447.54): C 61.72, H 6.53, N 3.13; found: C 61.91, H 6.88, N 3.35.

3-(4-Fluorophenyl)-9-[(4-methylphenyl)sulfonyl]-1,2,4,5-tetraoxa-9-azaspiro[5.5]undecane (**16k**). Yield: 40%. M.p. 175°. IR (film): 3038, 2926, 2857, 1601, 1460, 1328, 1232, 1077, 1038, 1015, 993. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.87 (*t*, *J* = 5.7, NCH_2CH_2); 2.43 (*s*, Me); 2.61–2.69 (*m*, NCH_2CH_2); 3.12 (*t*, *J* = 5.7, NCH_2CH_2); 3.22 (*t*, *J* = 5.7, NCH_2CH_2); 6.59 (*s*, OCHO); 7.20 (*d*, *J* = 8.1, 2 arom. H); 7.28–7.34 (*m*, 4 arom. H); 7.63 (*d*, *J* = 8.1, 2 arom. H). ESI-MS: 410.1 (22, $[M+H]^+$). Anal. calc. for $C_{19}H_{20}FNO_6S$ (409.43): C 55.74, H 4.92, N 3.42; found: C 55.53, H 4.74, N, 3.66.

3-(4-Bromophenyl)-9-[(4-methylphenyl)sulfonyl]-1,2,4,5-tetraoxa-9-azaspiro[5.5]undecane (**16l**). Yield: 27%. M.p. 167°. IR (film): 2922, 2847, 1611, 1357, 1212, 1018, 1017, 911, 835, 797. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.87 (*t*, *J* = 5.7, NCH_2CH_2); 2.44 (*s*, Me); 2.63 (*t*, *J* = 5.7, NCH_2CH_2); 3.12 (*t*, *J* = 5.7, NCH_2CH_2); 3.22 (*t*, *J* = 5.7, NCH_2CH_2); 6.59 (*s*, OCHO); 7.26–7.39 (*m*, 4 arom. H); 7.53–7.66 (*m*, 4 arom. H). ESI-MS: 471.0 (100, $[M+H]^+$), 472.1 (95). Anal. calc. for $C_{19}H_{20}BrNO_6S$ (470.33): C 48.52, H 4.29, N 2.98; found: C 48.73, H 4.49, N 3.18.

3-(3-Bromophenyl)-9-[(4-methylphenyl)sulfonyl]-1,2,4,5-tetraoxa-9-azaspiro[5.5]undecane (**16m**). Yield: 23%. M.p. 147°. IR (film): 2963, 2862, 1722, 1597, 1573, 1468, 1427, 1358, 1263, 1236, 1164, 1079,

1021, 935. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.80 (*t*, *J* = 5.7, NCH_2CH_2); 2.37 (*s*, Me); 2.56 (*t*, *J* = 5.7, NCH_2CH_2); 3.05 (*t*, *J* = 5.7, NCH_2CH_2); 3.15 (*t*, *J* = 5.7, NCH_2CH_2); 6.52 (*s*, OCHO); 7.19–7.27 (*m*, 5 arom. H); 7.45–7.59 (*m*, 3 arom. H). Anal. calc. for $C_{19}H_{20}BrNO_6S$ (470.33): C 48.52, H 4.29, N 2.98; found: C 48.52, H 4.29, N, 2.98.

3-(4-Methylphenyl)-9-(phenylsulfonyl)-1,2,4,5-tetraoxa-9-azaspiro[5.5]undecane (**17a**). Yield: 26%. M.p. 178°. IR (film): 3069, 2961, 2930, 2868, 1612, 1445, 1330, 1233, 1162, 1077, 1039, 993. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.88 (*t*, *J* = 5.7, NCH_2CH_2); 2.42 (*s*, Me); 2.65 (*t*, *J* = 5.7, NCH_2CH_2); 3.15 (*t*, *J* = 5.7, NCH_2CH_2); 3.25 (*t*, *J* = 5.7, NCH_2CH_2); 6.58 (*s*, OCHO); 7.18–7.28 (*m*, 3 arom. H); 7.38–7.41 (*m*, 2 arom. H); 7.52–7.64 (*m*, 2 arom. H); 7.76–7.78 (*m*, 2 arom. H). HR-ESI-MS: 391.9906 (M^+, $C_{19}H_{21}NO_6S^+$; calc. 391.1090).

3-(3-Methylphenyl)-9-(phenylsulfonyl)-1,2,4,5-tetraoxa-9-azaspiro[5.5]undecane (**17b**). Yield: 31%. M.p. 143°. IR (film): 3029, 2927, 2866, 1466, 1447, 1360, 1334, 1268, 1235, 1171, 1097, 1081, 1042, 1015, 991. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.89 (*t*, *J* = 5.7, NCH_2CH_2); 2.42 (*s*, Me); 2.66 (*t*, *J* = 5.7, NCH_2CH_2); 3.15 (*t*, *J* = 5.7, NCH_2CH_2); 3.25 (*t*, *J* = 5.7, NCH_2CH_2); 6.81 (*s*, OCHO); 7.18–7.34 (*m*, 4 arom. H); 7.52–7.64 (*m*, 3 arom. H); 7.76–7.79 (*m*, 2 arom. H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): 18.8; 29.9; 31.1; 42.0; 43.6; 105.9; 126.2; 127.5; 129.2; 130.8; 131.0; 133.0. HR-ESI-MS: 391.2341 (M^+, $C_{19}H_{21}NO_6S^+$; calc. 391.1090).

3-(2-Methylphenyl)-9-(phenylsulfonyl)-1,2,4,5-tetraoxa-9-azaspiro[5.5]undecane (**17c**). Yield: 23%. M.p. 163°. IR (film): 2922, 2852, 1637, 1363, 1217, 1018, 1003, 804, 775. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.87 (*t*, *J* = 5.4, NCH_2CH_2); 2.42 (*s*, Me); 2.65 (*t*, *J* = 5.4, NCH_2CH_2); 3.13 (*t*, *J* = 5.4, NCH_2CH_2); 3.23 (*t*, *J* = 5.4, NCH_2CH_2); 6.81 (*s*, OCHO); 7.18–7.34 (*m*, 4 arom. H); 7.52–7.64 (*m*, 3 arom. H); 7.76–7.79 (*m*, 2 arom. H). ESI-MS: 392.1 (24, $[M+H]^+$). Anal. calc. for $C_{19}H_{21}NO_6S$ (391.44): C 58.30, H 5.41, N 3.58; found: C 58.51, H 5.66, N 3.76.

3-(4-Ethylphenyl)-9-(phenylsulfonyl)-1,2,4,5-tetraoxa-9-azaspiro[5.5]undecane (**17d**). Yield: 33%. M.p. 150°. IR (film): 3069, 2961, 1930, 1868, 1612, 1445, 1329, 1272, 1233, 1162, 1077, 1039, 993. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.21 (*t*, *J* = 6.0, $MeCH_2$); 1.88 (*m*, NCH_2CH_2); 2.64–2.66 (*m*, NCH_2CH_2, $MeCH_2$); 3.15–3.42 (*m*, 2 NCH_2CH_2); 6.59 (*s*, OCHO); 7.21–7.30 (*m*, 4 arom. H); 7.54–7.61 (*m*, 3 arom. H); 7.76–7.78 (*m*, 2 arom. H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): 15.3; 28.8; 29.7; 31.1; 42.0; 43.1; 105.8; 108.2; 127.5; 128.3; 129.2; 133.0; 136.0; 148.0. HR-ESI-MS: 405.8187 (78, M^+, $C_{20}H_{23}NO_6S^+$; calc. 405.1246).

9-(Phenylsulfonyl)-3-(4-propylphenyl)-1,2,4,5-tetraoxa-9-azaspiro[5.5]undecane (**17e**). Yield: 26%. M.p. 142°. IR (film): 2954, 2870, 1446, 1332, 1233, 1168, 1077, 1040, 994, 897, 740. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.91 (*t*, *J* = 7.5, $MeCH_2CH_2$); 1.56–1.67 (*m*, $MeCH_2CH_2$); 1.87 (*t*, *J* = 5.7, NCH_2CH_2); 2.58 (*t*, *J* = 7.5, $MeCH_2CH_2$); 2.65 (*t*, *J* = 5.7, NCH_2CH_2); 3.15 (*t*, *J* = 5.7, NCH_2CH_2); 3.25 (*t*, *J* = 5.7, NCH_2CH_2); 6.59 (*s*, OCHO); 7.18 (*d*, *J* = 8.1, 2 arom. H); 7.28 (*d*, *J* = 8.1, 2 arom. H); 7.51–7.64 (*m*, 3 arom. H); 7.76–7.78 (*m*, 2 arom. H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): 13.6; 24.2; 29.7; 31.1; 37.8; 42.0; 43.1; 105.8; 108.2; 127.4; 127.5; 128.8; 129.2; 133.0; 136.0; 146.4. HR-ESI-MS: 419.8205 (M^+, $C_{21}H_{25}NO_6S^+$; calc. 419.1403).

9-(Phenylsulfonyl)-3-[4-(propan-2-yl)phenyl]-1,2,4,5-tetraoxa-9-azaspiro[5.5]undecane (**17f**). Yield: 21%. M.p. 167°. IR (film): 2956, 2925, 1459, 1331, 1233, 1161, 1076, 1039, 1015, 992, 965. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.23 (*d*, *J* = 6.9, Me_2CH); 1.88 (*t*, *J* = 5.7, NCH_2CH_2); 2.66 (*t*, *J* = 5.7, NCH_2CH_2); 2.88–2.95 (*sept.*, Me_2CH); 3.15 (*t*, *J* = 5.7, NCH_2CH_2); 3.25 (*t*, *J* = 5.7, NCH_2CH_2); 6.59 (*s*, OCHO); 7.23–7.32 (*m*, 4 arom. H); 7.52–7.64 (*m*, 3 arom. H); 7.76–7.79 (*m*, 2 arom. H). ESI-MS: 420.14 (100, $[M+H]^+$).

*3-[4-(*tert*-Butyl)phenyl]-9-(phenylsulfonyl)-1,2,4,5-tetraoxa-9-azaspiro[5.5]undecane* (**17g**). Yield: 22%. M.p. 173°. IR (film): 2959, 2925, 2852, 1607, 1457, 1360, 1170, 1080, 1041, 994. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.29 (*s*, Me_3C); 1.88 (*t*, *J* = 5.7, NCH_2CH_2); 2.66 (*t*, *J* = 5.7, NCH_2CH_2); 3.15 (*t*, *J* = 5.7, NCH_2CH_2); 3.25 (*t*, *J* = 5.7, NCH_2CH_2); 6.60 (*s*, OCHO); 7.30–7.33 (*m*, 2 arom. H); 7.40–7.45 (*m*, 3 arom. H); 7.54–7.62 (*m*, 2 arom. H); 7.76–7.79 (*m*, 2 arom. H). ESI-MS: 434.1 (85, $[M+H]^+$). Anal. calc. for $C_{22}H_{27}NO_6S$ (433.52): C 60.95, H 6.28, N 3.23; found: C 61.17, H 6.44, N 3.21.

3-(4-Methoxyphenyl)-9-(phenylsulfonyl)-1,2,4,5-tetraoxa-9-azaspiro[5.5]undecane (**17h**). Yield: 21%. M.p. 180°. IR (film): 2924, 2850, 1610, 1517, 1359, 1333, 1309, 1256, 1170, 1080, 1041, 991. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.87 (*t*, *J* = 5.7, NCH_2CH_2); 2.65 (*t*, *J* = 5.7, NCH_2CH_2); 3.15 (*t*, *J* = 5.7, NCH_2CH_2); 3.25 (*t*, *J* = 5.7, NCH_2CH_2); 3.81 (*s*, MeO); 6.55 (*s*, OCHO); 6.88 (*d*, *J* = 8.7, 2 arom. H); 7.30 (*d*, *J* = 8.7, 2 arom. H); 7.53–7.64 (*m*, 3 arom. H); 7.76–7.79 (*m*, 2 arom. H). ^{13}C-NMR (75.5 MHz,

$CDCl_3$): 29.8; 31.1; 42.1; 43.1; 55.3; 105.6; 108.0; 114.2; 123.08; 127.5; 129.2; 129.2; 133.0; 136.1; 161.9. HR-ESI-MS: 407.6611 (M^+, $C_{19}H_{21}NO_7S^+$; calc. 407.1039).

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Received January 12, 2012