

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].

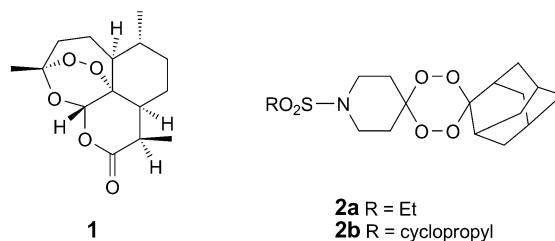


Fig. 1. Endoperoxide-based antimalarials

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].

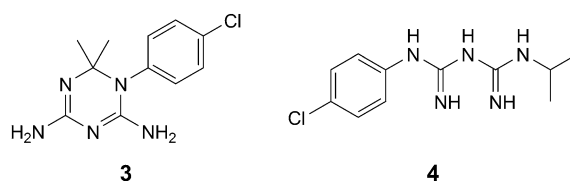
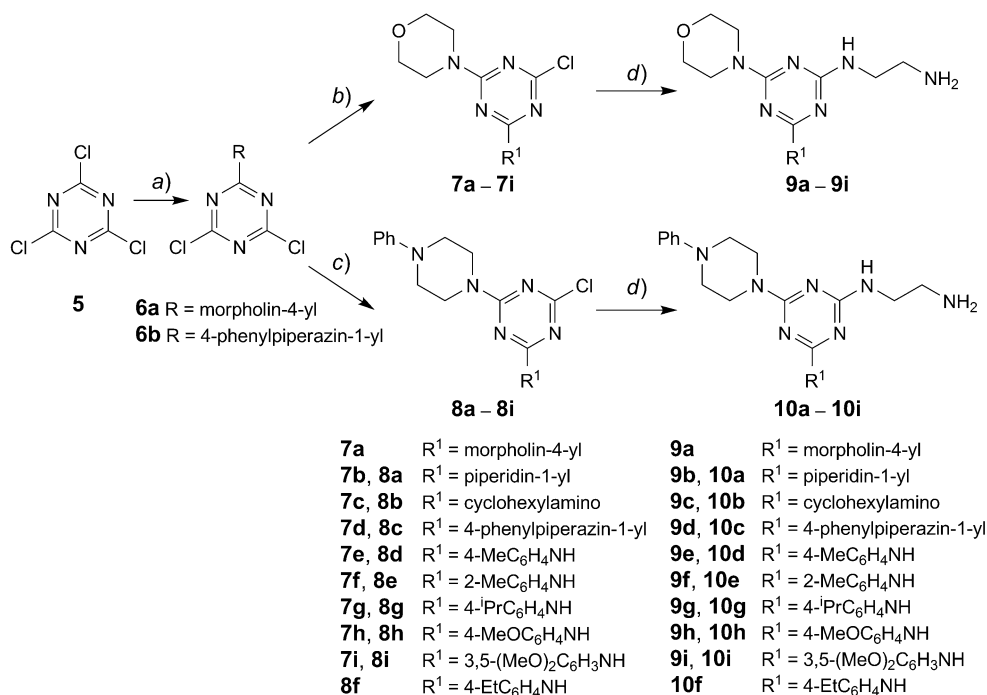


Fig. 2. Dihydrofolate reductase inhibitors

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 K₂CO₃ 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 K₂CO₃ gave

Scheme 1



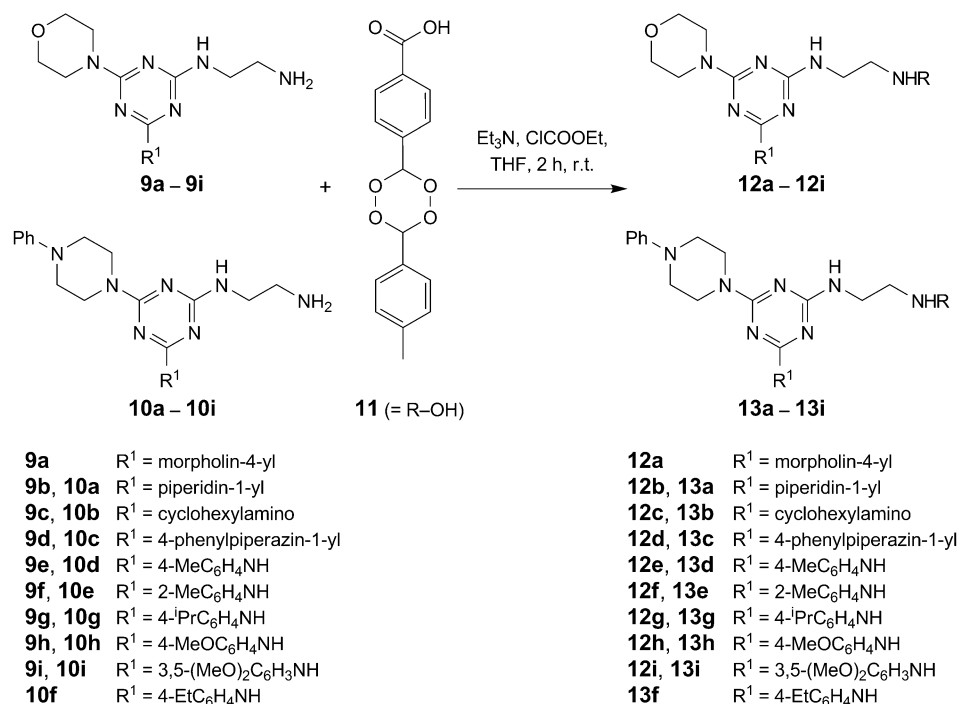
a) RX, K₂CO₃, THF, 0°, 3 h. b) R¹X, K₂CO₃, THF, 3 h, room temperature, with **6a**. c) R¹X, K₂CO₃, THF, 3 h, room temperature, with **6b**. d) Ethylenediamine, K₂CO₃, THF, 60°, 3 h.

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 K₂CO₃ 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 Et₃N 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 Et₂O solution of HBF₄ 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

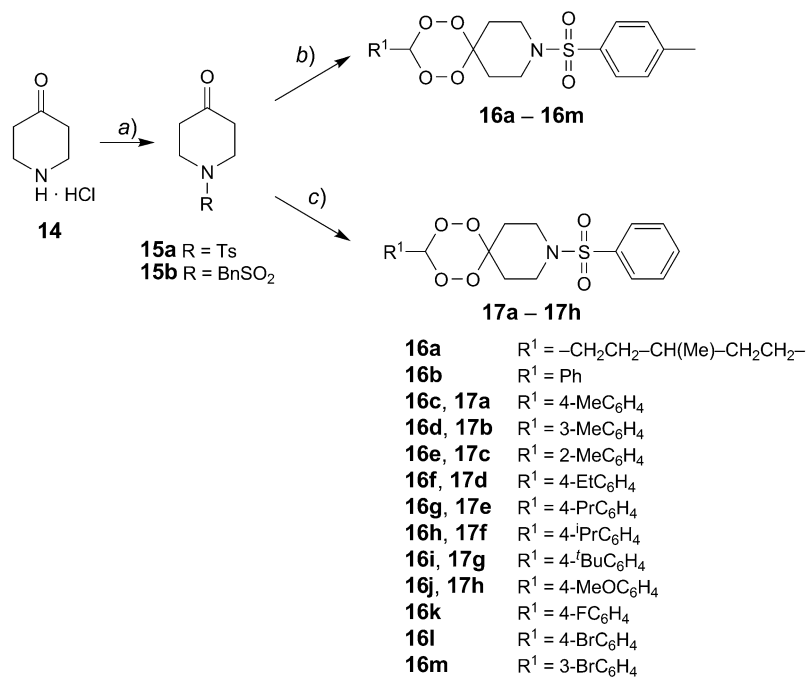


sensitive) and W2 (chloroquine-resistant) strains of *P. falciparum*, and for cytotoxicity towards mammalian kidney cells (*Vero* cells) up to a highest concentration of $12.5\ \mu\text{M}$ in an *in vitro* assay. Chloroquine and artemisinin were used as standard drugs for antimalarial activity, and 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 $2.74\text{--}5.45$ (*D6*) and $2.13\text{--}5.43\ \mu\text{M}$ (*W2*) (*Table*).

Some spiro[piperidine-4,3'-tetraoxanes] have shown very good-to-moderate antimalarial activities. Two compounds, **16a** ($\text{R}^1 = \text{4-Me-C}_6\text{H}_9$) and **17a** ($\text{R}^1 = \text{4-Me-C}_6\text{H}_4$), exhibited good activities against both strains of *P. falciparum* with IC_{50} values in the range of $0.30\text{--}0.70$ (*D6*) and $0.20\text{--}0.83\ \mu\text{M}$ (*W2*) with high *SI*s. Compounds **16b**, **16c**, **17c**, and **17h** with ($\text{R}^1 = \text{Ph}$, $\text{4-Me-C}_6\text{H}_4$, $\text{2-Me-C}_6\text{H}_4$, $\text{4-MeO-C}_6\text{H}_4$, resp.) exhibited moderate-to-good antimalarial activities with IC_{50} values in the range of $1.48\text{--}4.90$ (*D6*) and $1.40\text{--}7.36\ \mu\text{M}$ (*W2*). All other compounds were found to be inactive up to tested concentration ($25\ \mu\text{M}$) 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



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; SiO₂; *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 $\nu_{\max}$ in cm⁻¹. ¹H-NMR Spectra: *Bruker 320 Spectrospin* spectrometer at 300 MHz and *Jeol spectospin ECX400* at 400 MHz. ¹³C-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. ¹H-NMR (400 MHz, CDCl₃): 3.68 (*t*, *J* = 5.1, 2 NCH₂CH₂O); 3.82 (*t*, *J* = 5.1, 2 NCH₂CH₂O). ¹³C-NMR (100 MHz, CDCl₃): 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. ¹H-NMR (400 MHz, CDCl₃): 3.19–3.25 (*m*, 2 NCH₂CH₂NPh); 3.95–3.98 (*m*, 2 NCH₂CH₂NPh); 6.88–6.98 (*m*, 3 arom. H); 7.27–7.31 (*m*, 2 arom. H). ¹³C-NMR (100 MHz, CDCl₃): 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, Exemplified 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 K₂CO₃ (8.80 g, 63.8 mmol). The mixture was stirred at r.t. for 3–4 h. Then, the mixture was filtered to remove K₂CO₃, and excess of solvent was evaporated under vacuum. The residue thus obtained was dissolved in 30 ml of CHCl₃ and washed with sat. brine. The CHCl₃ layer was dried (Na₂SO₄), and excess of solvent was removed under vacuum to give crude product, which was purified by CC (SiO₂; 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. ¹H-NMR (400 MHz, CDCl₃): 3.65–3.68 (*m*, 4 – NCH₂CH₂O); 3.70–3.81 (*m*, 4 NCH₂CH₂O). ¹³C-NMR (100 MHz, CDCl₃): 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. ¹H-NMR (400 MHz, CDCl₃): 1.54–1.57 (*m*, 4 H), 1.64–1.65 (*m*, 2 H); 3.58–3.88 (*m*, 12 H). ¹³C-NMR (100 MHz, CDCl₃): 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. ¹H-NMR (400 MHz, CDCl₃): 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). ¹³C-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. $^1\text{H-NMR}$ (400 MHz, CDCl_3): 3.19 (*t*, $J = 5.0$, 2 $\text{NCH}_2\text{CH}_2\text{NPh}$); 3.71–3.72 (*m*, 2 $\text{NCH}_2\text{CH}_2\text{NPh}$); 3.79–3.80 (*m*, 2 $\text{NCH}_2\text{CH}_2\text{O}$); 3.86–3.94 (*m*, 2 $\text{NCH}_2\text{CH}_2\text{O}$); 6.88–6.95 (*m*, 3 arom. H); 7.25–7.30 (*m*, 2 arom. H). $^{13}\text{C-NMR}$ (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. $^1\text{H-NMR}$ (400 MHz, CDCl_3): 2.32 (*s*, $\text{Me}-\text{C}_6\text{H}_4$); 3.68–3.75 (*m*, 2 $\text{NCH}_2\text{CH}_2\text{O}$); 3.76–3.82 (*m*, 2 $\text{NCH}_2\text{CH}_2\text{O}$); 7.08 (*br. s*, NH); 7.12 (*d*, $J = 7.8$, 2 arom. H); 7.35 (*d*, $J = 7.8$, 2 arom. H). $^{13}\text{C-NMR}$ (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. $^1\text{H-NMR}$ (400 MHz, CDCl_3): 2.28 (*s*, $\text{Me}-\text{C}_6\text{H}_4$); 3.61–3.88 (*m*, 2 $\text{NCH}_2\text{CH}_2\text{O}$); 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. $^1\text{H-NMR}$ (400 MHz, CDCl_3): 1.22 (*d*, $J = 6.8$, Me_2CH); 2.85–2.90 (*m*, Me_2CH); 3.68–3.78 (*m*, 2 $\text{NCH}_2\text{CH}_2\text{O}$); 3.79–3.89 (*m*, 2 $\text{NCH}_2\text{CH}_2\text{O}$); 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. $^1\text{H-NMR}$ (400 MHz, CDCl_3): 3.70–3.74 (*m*, 2 $\text{NCH}_2\text{CH}_2\text{O}$); 3.82 (*s*, MeO); 3.83–3.88 (*m*, 2 $\text{NCH}_2\text{CH}_2\text{O}$); 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). $^{13}\text{C-NMR}$ (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. $^1\text{H-NMR}$ (300 MHz, CDCl_3): 3.72–3.75 (*m*, 2 $\text{NCH}_2\text{CH}_2\text{O}$); 3.78 (*s*, 2 MeO); 3.82–3.86 (*m*, 2 $\text{NCH}_2\text{CH}_2\text{O}$); 6.22–6.24 (*m*, 1 arom. H); 6.74–6.75 (*m*, 2 arom. H); 7.17 (*br. s*, NH). $^{13}\text{C-NMR}$ (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. $^1\text{H-NMR}$ (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 $\text{NCH}_2\text{CH}_2\text{NPh}$); 3.78–3.97 (*m*, 2 $\text{NCH}_2\text{CH}_2\text{NPh}$); 6.88–6.95 (*m*, 3 arom. H); 7.26–7.30 (*m*, 2 arom. H). $^{13}\text{C-NMR}$ (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. $^1\text{H-NMR}$ (400 MHz, CDCl_3): 1.54–1.66 (*m*, 7 H); 3.18–3.20 (*m*, 4 H); 3.73–3.76 (*m*, 2 $\text{NCH}_2\text{CH}_2\text{NPh}$); 3.93–3.94 (*m*, 2 $\text{NCH}_2\text{CH}_2\text{NPh}$); 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. $^1\text{H-NMR}$ (400 MHz, CDCl_3): 3.19–3.25 (*m*, 4 $\text{NCH}_2\text{CH}_2\text{NPh}$); 3.95–3.98 (*m*, 4 $\text{NCH}_2\text{CH}_2\text{NPh}$); 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. $^1\text{H-NMR}$ (400 MHz, CDCl_3): 2.33 (*s*, $\text{Me}-\text{C}_6\text{H}_4$); 3.23–3.24 (*m*, 2 $\text{NCH}_2\text{CH}_2\text{NPh}$); 3.95–4.10 (*m*, 2 $\text{NCH}_2\text{CH}_2\text{NPh}$); 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. ¹H-NMR (400 MHz, CDCl₃): 2.36 (s, Me-C₆H₄); 3.19–3.45 (m, 2 NCH₂CH₂NPh); 3.91–4.40 (m, 2 NCH₂CH₂NPh); 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. ¹H-NMR (400 MHz, CDCl₃): 1.21 (t, J = 7.5, MeCH₂); 2.60–2.64 (q, J = 7.5, MeCH₂); 3.15–3.26 (m, 2 NCH₂CH₂NPh); 3.91–4.05 (m, 2 NCH₂CH₂NPh); 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. ¹H-NMR (300 MHz, CDCl₃): 1.25 (d, J = 6.0, Me₂CH); 2.88–2.92 (sept., J = 4.0, Me₂CH); 3.31–3.42 (m, 2 NCH₂CH₂NPh); 4.15–4.39 (m, 2 NCH₂CH₂NPh); 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. ¹H-NMR (400 MHz, CDCl₃): 3.20 (t, J = 5.0, 2 NCH₂CH₂NPh); 3.81 (s, MeO); 3.95–3.99 (m, 2 NCH₂CH₂NPh); 6.88–6.95 (m, 5 arom. H); 7.25–7.30 (m, 2 arom. H); 7.39–7.41 (m, 3 arom. H). ¹³C-NMR (100 MHz, CDCl₃): 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. ¹H-NMR (400 MHz, CDCl₃): 3.21–3.29 (m, 2 NCH₂CH₂NPh); 3.78 (s, 2 MeO); 4.04–4.12 (m, 2 NCH₂CH₂NPh); 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 K₂CO₃ (1.45 g, 10.5 mmol). The mixture was stirred at 60° for 3–4 h. Then, the mixture was filtered to remove K₂CO₃ and excess of solvent was evaporated under vacuum. The residue thus obtained was dissolved in 30 ml of CHCl₃ and washed with brine. The CHCl₃ layer was dried (Na₂SO₄) and excess of solvent was removed under vacuum to give a crude product, which was purified by CC (SiO₂; AcOEt/hexane) to yield **9a** (346 mg, 32%). White solid. M.p. 221°. IR (nujol): 3346 (NH), 3232 (NH₂), 2924, 2854, 1602, 1550, 1490, 1363, 1290, 1263, 1111, 1021, 857, 802. ¹H-NMR (400 MHz, (D₆)DMSO): 2.37 (br. s, NHCH₂CH₂NH₂); 2.49 (t, J = 6.9, NHCH₂CH₂NH₂); 2.89–3.09 (m, 4 NCH₂CH₂O); 3.44–3.49 (m, 4 NCH₂CH₂O); 6.58 (br. s, NH). ¹³C-NMR (100 MHz, (D₆)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, NH₂), 2856, 1608, 1571, 1518, 1480, 1461, 1435, 1390, 1284, 1247, 1116, 1025, 913. ¹H-NMR (400 MHz, (D₆)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). ¹³C-NMR (100 MHz, (D₆)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, NH₂), 2927, 2853, 1635, 1582, 1525, 1279, 1114, 757. ¹H-NMR (400 MHz, (D₆)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, NH₂), 2928, 2853, 1708, 1549, 1508, 1445, 1272, 1115, 1025, 811. ¹H-NMR (400 MHz, (D₆)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, NH₂), 2923, 2854, 1577, 1552, 1512, 1462, 1377, 1351, 1110, 806.

¹H-NMR (400 MHz, (D₆)DMSO): 2.21 (s, Me–C₆H₄); 2.49–2.66 (m, NHCH₂CH₂NH₂); 3.22–3.24 (br. s, NH₂); 3.54–3.65 (m, 2 NCH₂CH₂O); 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, NH–C₆H₄Me). 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 (NH₂), 2923, 2854, 1681, 1496, 1378, 1149, 1017, 921, 828, 806, 757, 691. ¹H-NMR (400 MHz, (D₆)DMSO): 2.23 (s, Me–C₆H₄); 2.48–2.66 (m, NHCH₂CH₂NH₂); 3.20–3.26 (br. s, NH₂); 3.56–3.67 (m, 2 NCH₂CH₂O); 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, NH–C₆H₄Me). 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, NH₂), 2924, 1596, 1305, 1111, 1068, 1025, 831, 807, 722. ¹H-NMR (400 MHz, (D₆)DMSO): 1.21 (d, *J* = 6.8, Me₂CH); 2.78–2.89 (m, Me₂CH, NCH₂CH₂NH₂); 3.31–3.39 (m, 2 NCH₂CH₂O); 3.53–3.72 (m, 2 NCH₂CH₂O); 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, HN–C₆H₄iPr). ¹³C-NMR (100 MHz, (D₆)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, NH₂), 2923, 2854, 1601, 1581, 1505, 1435, 1278, 1116, 1029, 1012, 895, 828, 805. ¹H-NMR (400 MHz, (D₆)DMSO): 2.43–2.45 (m, NHCH₂CH₂NH₂); 2.63 (t, *J* = 5.9, NHCH₂CH₂NH₂); 2.95–3.29 (m, 2 NCH₂CH₂O, NH₂); 3.56–3.61 (m, 2 NCH₂CH₂O); 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, NH–C₆H₄OMe). ¹³C-NMR (100 MHz, (D₆)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, NH₂), 2924, 2854, 1595, 1458, 1377, 1152, 1067, 1023, 807, 757. ¹H-NMR (400 MHz, (D₆)DMSO): 2.48–2.49 (m, NHCH₂CH₂NH₂); 3.24–3.40 (m, 2 NCH₂CH₂O, NH₂); 3.58–3.66 (m, 2 NCH₂CH₂O); 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, NH–C₆H₃(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, NH₂), 2933, 2852, 1526, 1445, 1371, 1271, 1231, 998, 808, 756. ¹H-NMR (400 MHz, (D₆)DMSO): 1.44–1.57 (m, 6 H); 2.48–2.68 (m, NHCH₂CH₂NH₂); 3.10–3.26 (m, CH₂NCH₂); 3.41–3.52 (m, 2 NCH₂CH₂NPh); 3.64–3.77 (m, 2 NCH₂CH₂NPh); 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. ¹H-NMR (400 MHz, (D₆)DMSO): 1.09–1.19 (m, 6 H); 1.53–1.79 (m, 6 H); 2.48–2.49 (m, NCH₂CH₂NH₂); 2.71–2.82 (m, NHCH₂CH₂NH₂); 3.09–3.30 (m, 2 NCH₂CH₂NPh); 3.73–3.76 (m, 2 NCH₂CH₂NPh); 6.76–6.80 (m, NH, NH–cyclohexyl); 6.94–6.96 (m, 2 arom. H); 7.18–7.22 (m, 2 arom. H). ¹³C-NMR (100 MHz, (D₆)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, NH₂), 2921, 2726, 1651, 1622, 1538, 1455, 1377, 1289, 1228, 1015, 927, 742. ¹H-NMR (400 MHz, (D₆)DMSO): 2.62–2.65 (m, NHCH₂CH₂NH₂); 3.10–3.25 (m, 4 NCH₂CH₂NPh); 3.71–3.84 (m, 4 NCH₂CH₂NPh); 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, NH₂), 2920, 2726, 1463, 1377, 1325, 1267, 1232, 1152, 1002, 912, 756. ¹H-NMR (400 MHz, (D₆)DMSO): 1.92 (br. s, NH₂); 2.30 (s, Me–C₆H₄); 3.20–3.54 (m, 2 NCH₂CH₂NPh, NHCH₂CH₂NH₂); 3.94–4.09 (m, 2 NCH₂CH₂NPh); 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, NH–C₆H₄Me, 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, NH₂), 2938, 1704, 1504, 1434, 1245, 1174, 1158, 1028, 753.

¹H-NMR (400 MHz, (D₆)DMSO): 1.92 (br. s, NH₂); 2.30 (s, Me–C₆H₄); 3.20–3.54 (m, NHCH₂CH₂NH₂, 2 NCH₂CH₂NPh); 3.94–4.09 (m, 2 NCH₂CH₂NPh); 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, HN–C₆H₄Me, 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, NH₂), 2924, 2854, 1547, 1505, 1436, 1227, 1155, 1010, 921, 761. ¹H-NMR (400 MHz, (D₆)DMSO): 1.12 (t, *J* = 7.5, MeCH₂); 2.46–2.52 (m, NHCH₂CH₂NH₂); 2.61–2.66 (m, MeCH₂, NHCH₂CH₂NH₂); 3.21–3.25 (m, 2 NCH₂CH₂NPh); 3.75–3.90 (m, 2 NCH₂CH₂NPh); 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, NH–C₆H₄Et, NH). ¹³C-NMR (100 MHz, (D₆)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. ¹H-NMR (400 MHz, (D₆)DMSO): 1.23 (d, *J* = 6.8, Me₂CH); 2.86–2.89 (m, NHCH₂CH₂NH₂, Me₂CH); 3.13–3.39 (m, 2 NCH₂CH₂NPh); 3.54–4.11 (m, 2 NCH₂CH₂NPh); 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, HN–C₆H₄iPr, 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, NH₂), 2919, 1575, 1520, 1479, 1232, 1165, 995, 980, 751. ¹H-NMR (400 MHz, (D₆)DMSO): 2.48–2.49 (m, NHCH₂CH₂NH₂); 2.70–2.73 (t, *J* = 5.1, NCH₂CH₂NH₂); 3.13–3.41 (m, 2 NCH₂CH₂NPh); 3.70 (s, MeO); 3.79–3.92 (m, 2 NCH₂CH₂NPh); 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, NH–C₆H₄OMe, 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. ¹H-NMR (400 MHz, (D₆)DMSO): 2.45–2.67 (m, NHCH₂CH₂NH₂); 3.11–3.21 (m, 2 NCH₂CH₂NPh); 3.66 (s, 2 MeO); 3.74–3.82 (m, 2 NCH₂CH₂NPh); 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, NH–C₆H₃(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 Et₃N (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 CHCl₃. The layer was dried (Na₂SO₄), and the solvent was removed under vacuum, and the crude product was purified by CC (SiO₂; 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. ¹H-NMR (400 MHz, CDCl₃): 2.39 (s, Me); 3.50–3.71 (m, NHCH₂CH₂NHCO, 4 NCH₂CH₂O); 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). ¹³C-NMR (100 MHz, CDCl₃): 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 C₂₉H₃₅N₇O₇ (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. ¹H-NMR (300 MHz, (D₆)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 C₃₀H₃₇N₇O₆ (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. ¹H-NMR (300 MHz, (D₆)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). ¹³C-NMR (100 MHz, (D₆)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 C₃₁H₃₉N₇O₆ (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. ¹H-NMR (300 MHz, (D₆)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 C₃₅H₄₀N₈O₆ (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. ¹H-NMR (300 MHz, (D₆)DMSO): 2.35 (*s*, Me); 2.42 (*s*, Me–C₆H₄); 3.33–3.64 (*m*, 2 NCH₂CH₂O, NHCH₂CH₂NHCO); 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*, NH–C₆H₄Me, NH). ¹³C-NMR (100 MHz, (D₆)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 C₃₂H₃₅N₇O₆ (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. ¹H-NMR (300 MHz, (D₆)DMSO): 2.36 (*s*, Me–C₆H₄); 2.43 (*s*, Me); 3.34–3.65 (*m*, 2 NCH₂CH₂O, NHCH₂CH₂NHCO); 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*, NH–C₆H₄Me, NH). ESI-MS: 614.2 (35, [*M* + H]⁺). Anal. calc. for C₃₂H₃₅N₇O₆ (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. ¹H-NMR (300 MHz, (D₆)DMSO): 1.10 (*d*, *J* = 6.6, Me₂CH); 2.35 (*s*, Me); 2.70–2.79 (*m*, Me₂CH); 3.15–3.62 (*m*, 2 NCH₂CH₂O, NHCH₂CH₂NHCO); 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*, NH–C₆H₄Me). ¹³C-NMR (100 MHz, (D₆)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 C₃₄H₃₉N₇O₆ (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. ¹H-NMR (300 MHz, (D₆)DMSO): 2.36 (*s*, Me); 3.29–3.65 (*m*, 2 NCH₂CH₂O, NHCH₂CH₂NHCO); 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*, NH–C₆H₄OMe). 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. ¹H-NMR (300 MHz, (D₆)DMSO): 2.31 (*s*, Me); 3.10–3.95 (*m*, 2 NCH₂CH₂O, NHCH₂CH₂NHCO, 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*, NH–C₆H₃(OMe)₂). ¹³C-NMR (100 MHz, (D₆)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. ¹H-NMR (300 MHz, (D₆)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 C₃₆H₄₂N₈O₅ (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. ¹H-NMR (300 MHz, (D₆)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). ¹³C-NMR (100 MHz, (D₆)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. ¹H-NMR (300 MHz, (D₆)DMSO): 2.36 (*s*, 3 H); 3.33–3.84 (*m*, 4 NHCH₂CH₂NPh, NHCH₂CH₂N); 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). ¹³C-NMR (100 MHz, (D₆)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 C₄₁H₄₅N₉O₅ (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. ¹H-NMR (300 MHz, (D₆)DMSO): 2.23 (*s*, Me–C₆H₄); 2.36 (*s*, Me); 3.14–3.96 (*m*, 2 NCH₂CH₂NPh, NHCH₂CH₂NHCO); 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*, NH–C₆H₄ 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. ¹H-NMR (300 MHz, (D₆)DMSO): 2.36 (*s*, 2 Me); 3.14–3.96 (*m*, 2 NCH₂CH₂NPh, NHCH₂CH₂NHCO); 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*, NH–C₆H₄ Me). ESI-MS: 689.3 (23, [*M* + H]⁺). Anal. calc. for C₃₈H₄₀N₈O₅ (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. ¹H-NMR (300 MHz, (D₆)DMSO): 1.12 (*t*, *J* = 7.5, MeCH₂); 2.36 (*s*, Me); 2.44–2.53 (*m*, MeCH₂); 3.14–3.84 (*m*, 2 NCH₂CH₂NPh, NHCH₂CH₂NHCO); 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*, NH–C₆H₄Et). 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. ¹H-NMR (300 MHz, (D₆)DMSO): 1.16 (*d*, *J* = 6.9, Me₂CH); 2.35 (*s*, Me); 2.76–2.85 (*sept.*, Me₂CH); 3.14–3.84 (*m*, 2 NCH₂CH₂NPh,

NHCH₂CH₂NHCO); 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*, NH–C₆H₄Pr). ESI-MS: 717.3 (46, [*M* + H]⁺). Anal. calc. for C₄₀H₄₄N₈O₅ (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. ¹H-NMR (300 MHz, (D₆)DMSO): 2.36 (*s*, Me); 3.13–3.47 (*m*, 2 NCH₂CH₂NPh, NHCH₂CH₂NHCO); 3.70 (*s*, MeO); 3.82 (*m*, 2 NCH₂CH₂NPh); 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*, NH–C₆H₄OMe). 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. ¹H-NMR (300 MHz, (D₆)DMSO): 2.35 (*s*, Me); 3.14–3.85 (*m*, 2 NCH₂CH₂NPh, NHCH₂CH₂NHCO, 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*, NH–C₆H₃(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% H₂O₂ (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–C₆H₄CHO (860 mg, 6.31 mmol) was added to the mixture, followed by the addition of 54% Et₂O soln. of HBF₄ (511 mg, 3.15 mmol). The mixture was stirred for an additional h at r.t. After completion of the reaction (TLC), CHCl₃ was added to the mixture, and the layer was washed with sat. NaHSO₃ soln. followed by sat. soln. of NaHCO₃. The CHCl₃ layer was then dried (Na₂SO₄), and solvent was evaporated under reduced pressure. The crude product was then purified by CC (SiO₂, CHCl₃/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. ¹H-NMR (400 MHz, CDCl₃): 1.87 (*t*, *J* = 5.7, NCH₂CH₂); 2.44 (*s*, Me); 2.65 (*t*, *J* = 5.7, NCH₂CH₂); 3.13 (*t*, *J* = 5.7, NCH₂CH₂); 3.21 (*t*, *J* = 5.7, NCH₂CH₂); 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). ¹³C-NMR (100 MHz, CDCl₃): 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*⁺, C₂₀H₂₃NO₇S⁺; 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. ¹H-NMR (300 MHz, CDCl₃): 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 C₁₉H₂₇O₆S (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. ¹H-NMR (300 MHz, CDCl₃): 1.88 (*t*, *J* = 5.7, NCH₂CH₂); 2.43 (*s*, Me); 2.66 (*t*, *J* = 5.7, NCH₂CH₂); 3.13 (*t*, *J* = 5.7, NCH₂CH₂); 3.22 (*t*, *J* = 5.7, NCH₂CH₂); 6.63 (*s*, OCHO); 7.28–7.50 (*m*, 7 arom. H); 7.63–7.66 (*m*, 2 arom. H). ¹³C-NMR (75.5 MHz, CDCl₃): 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 C₁₉H₂₁NO₆S (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. ¹H-NMR (300 MHz, CDCl₃): 1.87 (*t*, *J* = 6.0, NCH₂CH₂); 2.36 (*s*, Me); 2.43 (*s*, Me); 2.65 (*t*, *J* = 6.0, NCH₂CH₂); 3.12 (*t*, *J* = 6.0, NCH₂CH₂); 3.22 (*t*, *J* = 6.0, NCH₂CH₂); 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*⁺, C₂₀H₂₃NO₆S⁺; 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. ¹H-NMR (300 MHz, CDCl₃): 1.85 (t, *J* = 5.7, NCH₂CH₂); 2.35 (s, Me); 2.43 (s, Me); 2.63 (t, *J* = 5.7, NCH₂CH₂); 3.10 (t, *J* = 5.7, NCH₂CH₂); 3.20 (t, *J* = 5.7, NCH₂CH₂); 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). ¹³C-NMR (75.5 MHz, CDCl₃): 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*⁺, C₂₀H₂₃NO₆S⁺; 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. ¹H-NMR (300 MHz, CDCl₃): 1.88 (t, *J* = 5.7, NCH₂CH₂); 2.36 (s, Me); 2.38 (s, Me); 2.65 (t, *J* = 5.7, NCH₂CH₂); 3.15 (t, *J* = 5.7, NCH₂CH₂); 3.25 (t, *J* = 5.7, NCH₂CH₂); 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. ¹H-NMR (300 MHz, CDCl₃): 1.21 (t, *J* = 7.5, MeCH₂CH₃); 1.87 (t, *J* = 5.7, NCH₂CH₂); 2.43 (s, Me); 2.61–2.69 (m, 4 H); 3.12 (t, *J* = 6.0, NCH₂CH₂); 3.22 (t, *J* = 5.7, NCH₂CH₂); 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 C₂₁H₂₅NO₆S (419.49): C 60.13, H 6.01, N 3.34; found: C 59.85, H 6.35, N 3.63.

9-[4-(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. ¹H-NMR (300 MHz, CDCl₃): 0.88 (t, *J* = 7.2, MeCH₂CH₂CH₃); 1.55–1.67 (m, MeCH₂CH₂CH₃); 1.86 (t, *J* = 5.7, NCH₂CH₂); 2.43 (s, Me); 2.56–2.66 (m, MeCH₂CH₂CH₃, NCH₂CH₂); 3.12 (t, *J* = 5.7, NCH₂CH₂); 3.22 (t, *J* = 5.7, NCH₂CH₂); 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). ¹³C-NMR (75.5 MHz, CDCl₃): 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 C₂₂H₂₇NO₆S (433.52): C 60.95, H 6.28, N 3.23; found: C 60.62, H 6.04, N 3.40.

9-[4-(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. ¹H-NMR (300 MHz, CDCl₃): 1.21 (d, *J* = 6.9, Me₂CH); 1.85–1.89 (m, NCH₂CH₂); 2.43 (s, Me); 2.65–2.67 (m, NCH₂CH₂); 2.86–2.95 (sept., Me₂CH); 3.12 (t, *J* = 5.7, NCH₂CH₂); 3.22 (t, *J* = 5.7, NCH₂CH₂); 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. ¹H-NMR (300 MHz, CDCl₃): 1.29 (s, Me₃C); 1.87 (t, *J* = 5.7, NCH₂CH₂); 2.43 (s, Me); 2.65 (t, *J* = 5.7, NCH₂CH₂); 3.12 (t, *J* = 5.7, NCH₂CH₂); 3.22 (t, *J* = 5.7, NCH₂CH₂); 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). ¹³C-NMR (75.5 MHz, CDCl₃): 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 C₂₃H₂₉NO₆S (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. ¹H-NMR (300 MHz, CDCl₃): 1.87 (t, *J* = 5.7, NCH₂CH₂); 2.43 (s, Me); 2.61–2.69 (m, NCH₂CH₂); 3.12 (t, *J* = 5.7, NCH₂CH₂); 3.22 (t, *J* = 5.7, NCH₂CH₂); 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 C₁₉H₂₀FNO₆S (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. ¹H-NMR (300 MHz, CDCl₃): 1.87 (t, *J* = 5.7, NCH₂CH₂); 2.44 (s, Me); 2.63 (t, *J* = 5.7, NCH₂CH₂); 3.12 (t, *J* = 5.7, NCH₂CH₂); 3.22 (t, *J* = 5.7, NCH₂CH₂); 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 C₁₉H₂₀BrNO₆S (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. $^1\text{H-NMR}$ (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 $\text{C}_{19}\text{H}_{20}\text{BrNO}_6\text{S}$ (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. $^1\text{H-NMR}$ (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^+ , $\text{C}_{19}\text{H}_{21}\text{NO}_6\text{S}^+$; 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. $^1\text{H-NMR}$ (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). $^{13}\text{C-NMR}$ (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^+ , $\text{C}_{19}\text{H}_{21}\text{NO}_6\text{S}^+$; 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. $^1\text{H-NMR}$ (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 $\text{C}_{19}\text{H}_{21}\text{NO}_6\text{S}$ (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. $^1\text{H-NMR}$ (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). $^{13}\text{C-NMR}$ (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^+ , $\text{C}_{20}\text{H}_{23}\text{NO}_6\text{S}^+$; 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. $^1\text{H-NMR}$ (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). $^{13}\text{C-NMR}$ (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^+ , $\text{C}_{21}\text{H}_{25}\text{NO}_6\text{S}^+$; 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. $^1\text{H-NMR}$ (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. $^1\text{H-NMR}$ (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 $\text{C}_{22}\text{H}_{27}\text{NO}_6\text{S}$ (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. $^1\text{H-NMR}$ (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). $^{13}\text{C-NMR}$ (75.5 MHz,

CDCl₃): 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*⁺, C₁₉H₂₁NO₇S⁺; calc. 407.1039).

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Received January 12, 2012