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Synthesis and antitumor evaluation of a novel series of triaminotriazine derivatives

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Abstract—A series of triaminotriazine derivatives (compounds **5a**–**f**, **6a**–**x**, and **7a**–**g**) was designed, synthesized, and evaluated for their inhibition activities to colorectal cancer (CRC) cell lines (HCT-116 and HT-29). Most of the synthesized compounds demonstrated moderate anti-proliferatory effects on both HCT-116 and HT-29 cell lines at the concentration of 10 μM. The inhibitory activities against HCT-116 and HT-29 cell lines were discussed to develop the structure–activity relationships of this new series. Compounds **6l** and **6o** exhibited prominent inhibition activities toward HCT-116, with IC_{50}s of 0.76 and 0.92 μM, respectively. The in vivo antitumor studies and pharmacokinetics of compound **6l** showed that it might be a promising new hit for further development of antitumor agents.

1. Introduction

Triazines have been widely studied due to its broad range of biological activities, such as anti-microbial effects,[1] Erm (erythromycin-resistance methylase) methyltransferase inhibition,[2] anti-trypanosomal activity,[3] VLA-4 (integrin very late antigen-4) antagonism,[4] estrogen receptor modulation,[5] and cytotoxic activity.[6] Hexamethylmelamine (HMM) **1** (Fig. 1) was discovered as an effective agent against breast, lung, and ovarian cancers, but unfortunately it causes many severe adverse effects, including nausea, vomiting, abdominal cramps, and anorexia.[7] Recently, more studies based on the triazine scaffold toward antitumor activity have been carried out.[8–10] Compound **2** (Fig. 1) was reported by Moon et al.[8] as a microtubule destabilizing entity with potent growth inhibition against U937 cells

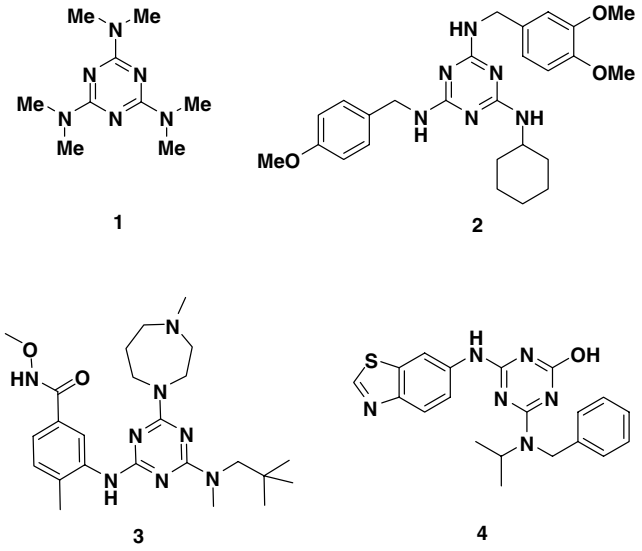

Figure 1. Reported triaminotriazine compounds with antitumor activity.

Keywords: Antitumor; Triazine derivatives; Inhibitor; Colorectal cancer.
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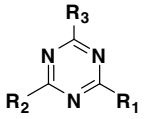
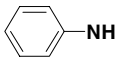
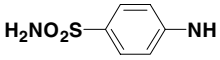
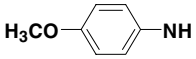
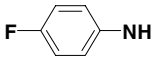
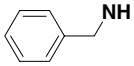
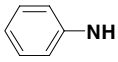
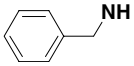
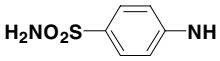
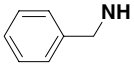
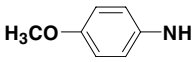
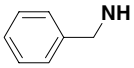
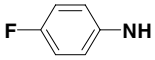
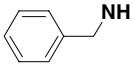
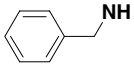
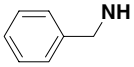
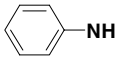
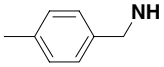
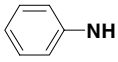
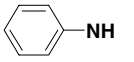
(GI_{50} = 1 μM). Leftheris et al.[9] found compound **3** as a potent inhibitor of p38 MAP kinase with oral activities. Compound **4** was recently investigated by Baindur et al.[10] as potent VEGF-R2 (KDR) tyrosine kinase inhibitor. From the reported structures, we notice that it is a common feature for compounds to exhibit antitumor activities by introducing structural units of various arylamino groups into the triazine scaffold.

Based on the above findings and the availability of abundant tri-substituted 1,3,5-triazine compounds in our in-house collection, we were intrigued to screening our compounds on selected targets, especially some tumor cell lines. One of the exciting screening results is that compound (4,6-bis(*N*-morpholino)-[1,3,5]triazin-2-yl)-phenylamine (**5a**, Table 1) exhibited moderate inhibition activity toward HT-29 (one of the cell lines of colorectal cancer), with 80.5% inhibition at the concentration of 10 μM. Nowadays, colorectal cancer (CRC) has become one of the major cancers that threaten people's lives. The American Cancer Society estimates that there will be about 106,680 new cases of colon cancer and 41,930 new cases of rectal cancer in 2006 in the United States, and they will cause about 55,170 deaths.[11] Though the death rate from colorectal cancer has been going down for the past 15 years, there

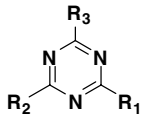
Table 1. Chemical structures of compounds **5a**–**f** and **6a**–**g**, and their inhibitory effects on the growth of tumor cell lines

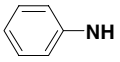
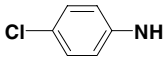
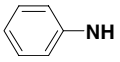
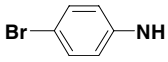
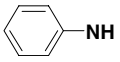
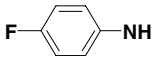
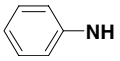
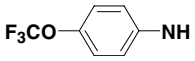
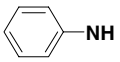
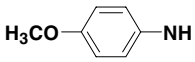
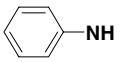
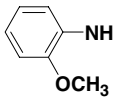
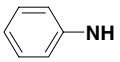
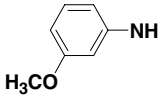
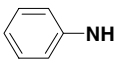
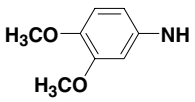
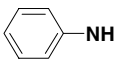
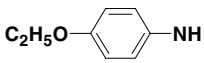
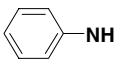
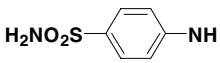
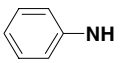
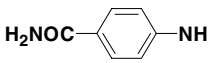
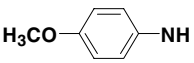
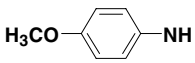
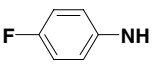
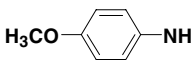


Compound	R_1	R_2	R_3	%Inhibition at 10 μM[a]	
				HT-29	HCT-116
5a				80.5	44.9
5b				NI[b]	NI[b]
5c				74.2	6.9
5d				80.2	NI[b]
5e				5.2	NI[b]
5f				NI[b]	NI[b]
6a				90.5	48.7
6b				68.6	NI[b]
6c				88.4	20.1
6d				87.1	10.1
6e				50.0	NI[b]
6f				75.3	15.7
6g				85.0	81.3

[a] Values are means of three determinations and deviation from the mean is <10% of the mean value.
[b] NI, no inhibition.

Table 2. Chemical structures of compounds **6h–x** and their inhibitory effects on the growth of tumor cell lines



Compound	R_1	R_2	R_3	%Inhibition at 10 μM[a]	
				HT-29	HCT-116
6h				87.1	51.7
6i				89.7	77.7
6j				90.0	60.1
6k				87.3	63.4
6l				100	81.4
6m				89.3	78.3
6n				87.4	82.6
6o				76.4	84.7
6p				87.5	64.1
6q				80.4	96.2
6r				87.8	85.8
6s				80.6	53.3
6t				82.3	NI[b]
6u				85.5	62.0
6v				54.1	71.1
6w				81.4	79.2
6x				83.2	69.0

[a] Values are means of three determinations and deviation from the mean is <10% of the mean value.
[b] NI, no inhibition.

is a continuing urgent need to develop new potent chemical agents.[11,12] The finding of compound **5a** prompted us to undertake a study of the in vitro inhibition activities of triazine derivatives substituted by subunits of morpholino and arylamino toward CRC cell lines, HCT-116 and HT-29. Rita Menicagli et al.[6] had reported 2,4,6-tris(*N*-morpholino)-1,3,5-triazine and several 2-alkyl-4,6-bis(*N*-morpholino)-[1,3,5]triazines, with negligible cytotoxic activities against leukemia cell lines, L1210 and HL60, and glioma cell line C6, but no (4,6-bis(*N*-morpholino)-[1,3,5]triazin-2-yl)-arylamines and 6-morpholino-*N*,*N*′-diaryl-[1,3,5]triazine-2,4-diamines have been considered.

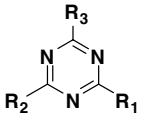
Herein, the design, synthesis, and biological activities of a series of novel *N*-morpholino triaminotriazine derivatives (**5a–f**, **6a–x**, and **7a–g**) are reported. The cellular activities in relative colorectal tumor cell lines (HCT-116 and HT-29) were examined and discussed to develop the preliminary structure–activity relationships (SAR) of this series. Most of the compounds exhibited moderate inhibitory potency against the HCT-116 and HT-29 cell lines at the concentration of 10 μM. Significantly, four compounds (**6g**, **6l**, **6o**, and **6q**) showed higher inhibition activities against the proliferation of the HCT-116 cell lines. The in vivo antitumor studies and pharmacokinetics of compound **6l** showed that it might be a promising new hit for further development of antitumor agents.

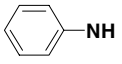
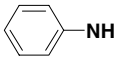
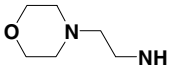
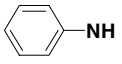
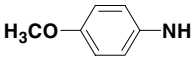
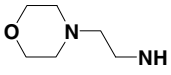
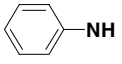
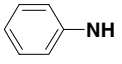
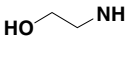
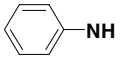
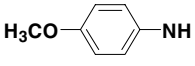
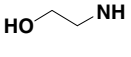
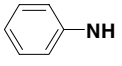
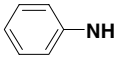
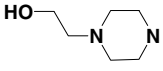
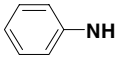
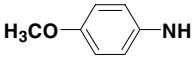
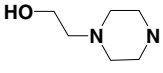
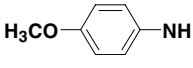
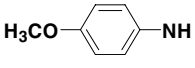
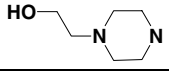
2. Materials and methods

2.1. Chemistry

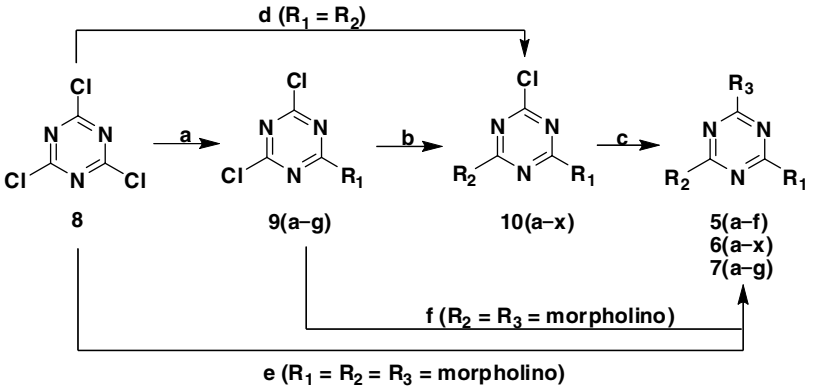
2.1.1. Design of analogues of triazine compounds. Based on the structural feature of the screening hit **5a**, 12 compounds (**5b–f** and **6a–g**, Table 1) were designed and synthesized for the first round. Keeping the two morpholino groups of **5a**, we obtained compounds **5b–e** by introducing different electronic substituents to the para position of the phenyl ring of **5a**, or substituting the phenyl ring of **5a** with benzyl. Substitution of the anilino group of **5a** with morpholino gave the tris(*N*-morpholino)-1,3,5-triazine (**5f**). Replacing one of the morpholino units of compounds **5a–e** with benzylamino, *p*-methylbenzylamino or anilino unit, the corresponding mono-*N*-morpholino substituted triazine derivatives (**6a–g**) were obtained. According to the bioassay results of the first round, we further designed and synthesized compounds **6h–x** (Table 2), using 6-morpholino-*N*,*N*′-diphenyl-[1,3,5]triazine-2,4-diamine (**6g**) as the benchmark compound. Compounds **6h–r** were obtained by introducing various steric, electronic, and hydrophobic groups to one of the phenyl rings of **6g**. Compounds **6s–x** were prepared by introducing various substituents to both of the phenyl rings of **6g**. Displacing the morpholino unit of the potent compounds **6** with the desired amines, we synthesized compounds **7a–g** (Table 3).

Table 3. Chemical structures of compounds **7a–g** and their inhibitory effects on the growth of tumor cell lines



Compound	R_1	R_2	R_3	%Inhibition at 10 μM[a]	
				HT-29	HCT-116
7a				23.4	30.1
7b				74.6	NI[b]
7c				33.9	NI[b]
7d				13.7	NI[b]
7e				76.1	22.0
7f				77.3	19.0
7g				49.3	NI[b]

[a] Values are means of three determinations and deviation from the mean is <10% of the mean value.
[b] NI, no inhibition.



Scheme 1. Synthetic procedures of target compounds **5**–**7**. Reagents and conditions: (a) R_1H, Na_2CO_3, acetone, 0 °C, 3 h; (b) R_2H, K_2CO_3 or NaOH, acetone, rt, 5–12 h; (c) morpholine or 4-(2-aminoethyl)morpholine or ethanolamine or *N*-(2-hydroxyethyl)piperazine, K_2CO_3, DMF, rt; (d) 2 equiv R_1H, Na_2CO_3, acetone, 0 °C–rt, 3–8 h; (e) 6 equiv morpholine, acetone; (f) 4 equiv morpholine, acetone.

2.1.2. Synthetic methods. Scheme 1 depicts the sequence of reactions that led to the preparation of compounds **5a**–**f**, **6a**–**x**, and **7a**–**g**, using cyanuric chloride (**8**) as the starting material. In general, treatment of commercially available arylamine with **8** through chloride displacement formed derivatives **9**, which were then reacted with 4 equiv morpholine to give compounds **5a**–**e**. **8** was reacted with 6 equiv morpholine to produce the tris(*N*-morpholino)-1,3,5-triazine (**5f**). Cyanuric chloride (**8**) reacted with 2 equiv arylamine in the presence of Na_2CO_3 in acetone to afford compounds **10e, 10g**, and**10s**. Compounds **9** were substituted by various arylamines to produce derivatives **10a**–**d**, **10f**, **10h**–**r**, and**10t**–**x**. Subsequent coupling of **10** with the desired amines under basic conditions formed the corresponding triaminotriazines **6a**–**x** and**7a**–**g**.

3. Results and discussion

3.1. Analogue synthesis

In total, 36 compounds (**5b**–**f**, **6a**–**x**, and **7a**–**g**) were designed and synthesized based on the structural feature of the screening hit **5a**, and their chemical structures are shown in Tables 1–3. These compounds were synthesized through the routes outlined in Scheme 1, and the details of synthetic procedures and structural characterizations are described in Section 5.

3.2. Biological activities

Compounds **5a**–**f**, **6a**–**x**, and **7a**–**g** were evaluated and analyzed by the sulforhodamine B (SRB, Sigma) assay[13] for their inhibitory activities toward CRC cell lines (HCT-116 and HT-29). For the primary assay, the percent inhibitions of the compounds at the concentration of 10 μM against HCT-116 and HT-29 were measured. The results are summarized in Tables 1–3. The details for bioassay procedures are described in Section 5.

As shown in Table 1, the initial compound **5a** exhibited potential inhibition activities toward HT-29 and HCT-116, with 80.5% and 44.9% inhibition at the concentration of 10 μM, respectively. Introducing substituents to the para position of the phenyl ring of **5a** (compounds **5b**–**d**) did not improve the inhibition activities. Substitution of the anilino unit of **5a** with benzylamino (**5e**) or morpholino (**5f**) resulted in a complete loss of inhibitory activities to both HCT-116 and HT-29. These findings indicate that the anilino group of compound **5a** plays an important role in the potent inhibition activities of the CRC cell lines. The mono-*N*-morpholino substituted triazine derivatives (**6a**–**e**) presented more potent inhibitory effects against HT-29 than their corresponding 4,6-bis(*N*-morpholino)-[1,3,5]triazine derivatives (**5a**–**e**). Among them, compounds **6a**, **6c**, and **6d** were a little more active than the initial compound **5a**, with 90.5%, 88.4%, and 87.1% inhibition against HT-29 at 10 μM, respectively. Dianilino derivative (**6g**) showed more potent activity against HT-29 and a large improved inhibitory activity against HCT-116 in comparison with **5a**, with 85% and 81.3% inhibition at 10 μM, respectively. Thus, compound **6g** was chosen as the benchmark compound for subsequent optimization studies.

The inhibitory activities of the second round of compounds **6h**–**x** against HCT-116 and HT-29 were tested and the results are summarized in Table 2. Compounds **6h**–**r**, which retained the morpholino group and one of the anilino units of **6g**, were first investigated. Halogen (F, Cl, and Br) substituted derivatives (**6h**–**j**) demonstrated improved activities toward HT-29. However, their inhibition activities toward HCT-116 were decreased. Electron-donating groups substituted on the phenyl ring of **6g** produced excellent to good anti-proliferatory potencies against HT-29. For instance, compounds **6l** (4-OCH_3), **6m** (2-OCH_3), **6n** (3-OCH_3), and **6p** (4-OCH_2CH_3) exhibited high inhibition activity toward HT-29, with 100%, 89.3%, 87.4%, and 87.5% inhibition at 10 μM, respectively. The similar potency of compounds **6l**–**n** indicates that a methoxy substituent walking on the phenyl ring had little impact on the inhibition potency to both HCT-116 and HT-29. Synergistic increase in activity was not found for the two methoxy-substituted derivative (**6o**) toward HT-29, but was found in its activity against HCT-116, with 84.7% inhibition at 10 μM. The sulfanilamide derivative (**6q**) and

p-aminobenzamide derivative (**6r**) exhibited the high inhibitory activities against HCT-116, with 96.2% and 85.8% inhibition at 10 μM, respectively. Among the second round of compounds, four compounds (**6l**, **6n**, **6q**, and **6r**) exhibited significant inhibitory potency against both HT-29 and HCT-116.

Compounds (**6s**–**x**), with substituents on both of the two phenyl rings of **6g**, showed similar inhibition potency with the benchmark compound **6g**. However, they were all less active than the *p*-methoxy analogue (**6l**). Decreased potency toward HCT-116 was observed throughout this subseries of compounds, and the *p*-fluoro derivative (**6t**) proved to be virtually inactive against HCT-116 at 10 μM.

Table 3 lists the biological results of derivatives **7a**–**g**, which were designed based on the potent inhibitors of **6g** and **6l**. All these compounds showed decreased inhibitory activities toward both HCT-116 and HT-29, and a few of them proved to have completely lost inhibitory activity. These results suggest the morpholino subunit directly introduced to the 1,3,5-triazine nuclear is an important determinant of inhibitory activity toward both HCT-116 and HT-29.

To determine the exact potency of the compounds that exhibited significant inhibition toward HCT-116 or HT-29 at 10 μM, ten compounds (**6g**–**i**, **6l**, **6n**, **6o**, **6q**–**s**, and **6v**) were further investigated in concentration–response studies, and the results are summarized in Table 4. Compounds **6g**–**i**, **6l**, **6n**, and **6r**–**s** were tested for their IC_{50}s (the compound concentration required for 50% growth inhibition of tumor cells) against HT-29. Most of these compounds showed moderate growth inhibition activities with IC_{50}s ranging from 8.1 to 39 μM. Compound **6r** (IC_{50} = 8.1 μM), which was most prominent in this series of compounds against HT-29, was nearly four times more active than the benchmark compound **6g** (IC_{50} = 31 μM). Compounds **6g**, **6l**, **6o**, **6q**–**r**, and **6v** were tested for their IC_{50}s against HCT-116. Most of them proved to be potent inhibitors with IC_{50} values below 5 μM, except compounds **6r** and **6v**. Among them, compounds **6l** (IC_{50} = 0.76 μM) and **6o** (IC_{50} = 0.92 μM) were the optimal ones, which were five times more active relative to the benchmark compound **6g** (IC_{50} = 4.7 μM). Compound **6l**, which was the most potent one in vitro against HCT-116, was chosen as the representative one of this class of triaminotriazines to undertake a study of its pharmacokinetic properties and in vivo antitumor activities.

Table 4. Determination of IC_{50} values of selected compounds of **6** on the growth of CRC cell line

Compound	IC_{50}[a] (μM)	
	HT-29	HCT-116
6g	31	4.7
6h	37	ND[b]
6i	25	ND[b]
6l	30	0.76
6n	39	ND[b]
6o	ND[b]	0.92
6q	ND[b]	2.0
6r	8.1	9.6
6s	100	ND[b]
6v	ND[b]	120

[a] Values are means of three determinations and deviation from the mean is <10% of the mean value.
[b] ND, not determined.

3.3. Pharmacokinetic properties and in vivo antitumor activity of 6l

The pharmacokinetic (PK) properties of **6l** were assessed in Sprague–Dawley rats. The details of procedures are described in Section 5. The orally administered **6l** was found to be rapidly absorbed from the gastrointestinal tract. The mean peak concentration (C_{max}) was 1.29 μg/mL achieved at 15 min after oral administration. By comparing with intravenous data, the oral bioavailability (F) of **6l** was 30.9%. The elimination half-lives ($T_{1/2}$) of **6l** by oral and intravenous administration were 1.16 and 1.09 h, respectively, while the mean resident times (MRT) were 1.88 and 1.06 h, respectively. The distribution volume (V_d) and clearance (CL) of intravenous **6l** were 2.11 and 1.36 L/h/kg, respectively.

When evaluated for antitumor efficacy in a sarcoma 180 mice model, compound **6l** demonstrated modest tumor inhibitory activity with 40.7% inhibition at a dose of 200 mg/kg/day. The detailed experimental data are shown in Table 5.

4. Conclusions

A series of triaminotriazine derivatives (**5**–**7**) was designed and synthesized, based on the screening hit **5a**. All the compounds were evaluated for their growth inhibition activities to colorectal tumor cell lines, HCT-116 and HT-29. 6-Morpholino-*N*,*N*′-diphenyl-[1,3,5]triazine-2,4-diamine (**6g**) was discovered from the first subseries of triazine derivatives with potent anti-prolif-

Table 5. In vivo experimental data of compound **6l**[a]

Group	Dose (mg/kg)	Mice (*n*) Initial/end	Body weight (g) Initial/end	Tumor weight (g) $X \pm SD$	Inhibition rate (%)	*P*
Control	—	20/20	18.6/29.4	1.50 ± 0.52	—	—
6l	100	10/10	18.5/29.3	1.65 ± 0.42	nc[b]	nc[b]
6l	200	10/10	18.6/27.3	0.89 ± 0.44	40.7	<0.05

[a] The in vivo experiment was carried out in the mice sarcoma 180 model, using intraperitoneal (ip) treatment. For other detailed procedures, please see Section 5.1.2.
[b] nc, not calculated.

erative activities against both HCT-116 and HT-29. Using **6g** as the benchmark compound, structural modification led to a series of compounds (**6h–x**), which demonstrated significant anti-proliferatory effects at the concentration of 10 μM. Among them, compounds **6l** and **6o** exhibited prominent activities to HCT-116, with IC_{50}s of 0.76 and 0.92 μM, respectively, which were five times more active than the benchmark compound **6g**. Compound **6r** was the most prominent derivative against HT-29, which was nearly four times more active than the benchmark compound **6g**. The preliminary in vivo antitumor studies and pharmacokinetics studies on compound **6l** showed that it might be promising for the development of new antitumor agents. Further investigations are in progress for understanding the mechanism of action of this novel class of triaminotriazine compounds.

5. Experimental

5.1. Biology

5.1.1. Cell growth inhibition assay. Two human colorectal cell lines, HCT-116 and HT-29, obtained from American Type Culture Collection (Rockville, MD) were used for the cell proliferation assay. Cells were maintained in RPMI-1640 medium supplemented with 10% (v/v) fetal bovine serum, 2 mmol/L glutamine, 100 U/mL penicillin, and 100 μg/mL streptomycin (Gibco, Grand Island, NY, USA) in a highly humidified atmosphere of 95% air with 5% CO_2 at 37 °C. The growth inhibition was analyzed by the sulforhodamine B (SRB, Sigma) assay.[13] Briefly, the cells were seeded at 6000 cells/well in 96-well plates (Falcon, CA, USA) and allowed to attach overnight. The cells were treated in triplicate with grade concentrations of compounds at 37 °C for 72 h. Then, they were fixed with 10% trichloroacetic acid and incubated for 60 min at 4 °C. Then, the plates were washed and dried. SRB solution (0.4% w/v in 1% acetic acid) was added and the culture was incubated for an additional 15 min. After the plates were washed and dried, bound stain was solubilized with Tris buffer, and the optical densities were read on the plate reader (model VERSA Max, Molecular Devices) at 515 nm (A_{515}). The growth inhibitory rate (GIR) of treated cells was calculated by the following Eq. (1),

$$\mathrm{GIR}(\%) = [1 - (A_{515}\ \text{treated}/A_{515}(\text{control}))] \times 100\% \quad (1)$$

The results were also expressed as IC_{50} (the compound concentration required for 50% growth inhibition of tumor cells), which was calculated by the Logit method. The mean IC_{50} was determined from the results of three independent tests.

5.1.2. In vivo tumor growth inhibition assay. Female KM mice (6–8 weeks of age) were used to study the inhibition of tumor growth in vivo.[14] The use of lab animals was in accordance with guidelines of Experimental Animal Association of China (certificate number: SYXK [Shanghai] 2003-0029). Well-grown sarcoma 180 cells ($1–2 \times 10^6$/mL) were subcutaneously implanted into the axilla of mice on Day 0, and mice were randomly grouped (20 mice/group for control, and 10 mice/group for drug-treated group) on Day 1. Intraperitoneal (ip) treatment of the drug-treated groups was then administered once daily for 7 days, with 200 mg/kg of **6l**, which was suspended in 0.5% CMC. Animals were sacrificed 24 h after the last administration, and mice and tumor weights were measured. The rate of inhibition of tumor growth in vivo was calculated using the following formula: growth inhibition (%) = (average tumor weight of control group − average tumor weight of test group)/average tumor weight of control group × 100%.

5.2. Pharmacokinetics

Pharmacokinetic animal experiments were conducted according to protocols approved by the Review Committee of Animal Care and Use at the Shanghai Institute of Materia Medica (Shanghai, China).[15] Six male Sprague–Dawley rats (~250 g; Shanghai Laboratory Animals Co., Shanghai, China) were housed in two rat cages ($48 \times 29 \times 18$ cm^3) and maintained in an air-conditioned rat room. Animals were allowed to acclimatize for one week prior to experiments. Rats were given a single oral dose (by gavage) of **6l** at 10 mg/kg (suspended in 0.5% CMC-Na); or a single intravenous dose at 2 mg/kg [dissolved in a solvent containing PEG400 and cremophor (100:15, v/v)], and serial blood samples (0.22–0.25 mL; 0, 5, 15, 30 min, 1, 2, 4, 6, and 8 h) were collected in heparinized tubes from the orbital sinus under light ether anesthesia. The blood samples were centrifuged, and the plasma was frozen at −70 °C until use.

To determine the plasma concentration of **6l**, 50 μL of the thawed rat plasma sample were extracted with 1 mL EtOAc by vortex-mixing for 5 min and then centrifuging at 16,060*g* for 5 min. The upper organic phase (850 μL) was removed and dried at 35 °C under a stream of nitrogen. The residue was reconstituted in 50 μL of an LC mobile phase and centrifuged at 13,000 rpm for 5 min. The supernatant (10 μL) was used for LC–MS/MS analysis. The LC–MS/MS system consisted of a Thermo Finnigan TSQ Quantum triple-quadrupole mass spectrometer (Thermo Finnigan, San Jose, CA, USA) interfaced via an electrospray ionization probe with a Surveyor series liquid chromatography system, an MS pump, and an autosampler (Thermo Finnigan). The Xcalibur software (Version 1.3) was used to control the LC–MS/MS system, as well as for data acquisition and processing (Thermo Finnigan, San Jose, CA, USA). Chromatographic separations were achieved on a 5-μm Zorbax SB-C_{18} column (50×2.1 mm id; Agilent Technologies, Chadds Ford, PA, USA) maintained at 25 °C. A 0.2-μm filter (Upchurch Scientific, Oak Harbor, WA, USA) was used before the analytical column. The LC mobile phase was CH_3CN/H_2O (636:364 v/v, containing a mass fraction of 0.02% $HCOONH_4$) at a flow rate of 0.2 mL/min for an isocratic elution. The mass spectrometer was operated in the positive ion electrospray ionization and multiple-reaction monitoring modes for **6l**. The instrument parameters were optimized for the analyte to maximize generation of the protonated molecules and to efficiently produce the characteristic

fragment ions. The precursor-to-product ion transitions *m/z* 379 → 250 for **6l** were monitored with a scan time of 0.2 s per transition. The peak widths of the precursor and product ions were maintained at 0.7 U.

To determine the pharmacokinetics of **6l**, concentration-time data were analyzed by noncompartmental methods using Kinetica™ 2000 software package (version 3.0, InnaPhase Corp. Philadelphia, PA, USA). The peak concentration (C_{max}) and the time taken to achieve peak concentration (T_{peak}) were obtained directly from the data without interpolation. The terminal elimination half-life ($t_{1/2}$) was calculated using the relationship 0.693/k, where k is the elimination rate constant. The area unde r concentration-time curve up to the last measurable time point ($AUC_{0\rightarrow t}$) was calculated by the trapezoidal rule. The oral bioavailability (F) of orally administered **6l** was calculated by the following equation:

$$F = \frac{AUC_{oral} \times Dose_{intravenous}}{AUC_{intravenous} \times Dose_{oral}} \times 100\% \qquad (2)$$

All results were expressed as arithmetic mean ± standard deviation (SD).

5.3. Chemistry

The reagents (chemicals) were purchased from Shanghai Chemical Reagent Company, Lancaster, and Acros, and used without further purification. The type of analytical thin-layer chromatography (TLC) was HSGF 254 (0.15–0.2 mm thickness, Yantai Huiyou Company, China). Yields were not optimized. Melting points were measured in capillary tube on a SGW X-4 melting point apparatus without correction. Nuclear magnetic resonance (NMR) spectra were recorded on a Brucker AMX-300 NMR (TMS as IS). Chemical shifts were reported in parts per million (ppm, δ) downfield from tetramethylsilane. Proton coupling patterns were described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (br). Low- and high-resolution mass spectra (LRMS and HRMS) were given with electric (EI) produced by Finnigan MAT-95 mass spectrometer.

5.3.1. General procedures for the preparations of intermediates 9 are described as those for (4,6-dichloro-[1,3,5]triazin-2-yl)-phenyl-amine (9a).

5.3.1.1. (4,6-Dichloro-[1,3,5]triazin-2-yl)phenylamine (9a). To a solution of cyanuric chloride (**8**, 1.0 g, 5.4 mmol) in acetone (15 mL) at 0 °C were added Na_2CO_3 (5.4 mmol) and aniline (0.49 mL, 5.4 mmol). The resulting mixture was stirred at 0 °C for 2 h and then for another 2 h at room temperature. The solvent was removed under reduced pressure and ice water (20 mL) was added. The solid was collected by vacuum filtration, washed with water (3× 20 mL), dried in vacuo, and purified by flash chromatography on silica gel (EtOAc/petroleum ether 1:10) to afford the title compound as a white solid (1.22 g, 93% yield). Mp 136–138 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61 (s, 1H), 7.57 (d, J = 8.1 Hz, 2H), 7.43 (t, J = 8.1 Hz, 2H), 7.25 (t, J = 7.8 Hz, 2H). LRMS (EI) *m/z* 241 (M^+), 239 (100%).

5.3.2. General procedures for the preparations of 5b–e are described as those for 5b.

5.3.2.1. 4-(4,6-Bis(*N*-morpholino)-[1,3,5]triazin-2-ylamino)-benzenesulfonamide (5b). To a solution of 4-(4,6-dichloro-1,3,5-triazin-2-ylamino)benzenesulfonamide (**9b**, 250 mg, 0.78 mmol) in acetone (10 mL) was added morpholine (0.27 mL, 3.12 mmol). The reaction mixture was stirred at room temperature for 5 h. The solvent was removed under reduced pressure and ice water (20 mL) was added. The solid was collected by vacuum filtration, washed with water (3× 20 mL), dried in vacuo, and purified by flash chromatography on silica gel to afford **5b** as a white solid (300 mg, 92% yield). Mp > 300 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.84 (d, J = 9.0 Hz, 2H), 7.71 (t, J = 8.7 Hz, 2H), 3.71 (m, 8H), 3.64 (m, 8H). LRMS (EI) *m/z* 421 (M^+), 391 (100%); HRMS (EI) *m/z* calcd for $C_{17}H_{23}N_7O_4S$ (M^+) 421.1532, found 421.1529.

5.3.2.2. (4,6-Bis(*N*-morpholino)-[1,3,5]triazin-2-yl)-(4-methoxyphenyl)-amine (5c). Compound **5c** was prepared from 4,6-dichloro-*N*-(4-methoxyphenyl)-1,3,5-triazin-2-amine (**9c**) and morpholine using a procedure similar to that described for the preparation of **5b** as a white solid. Yield: 96%; mp 206–207 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.55 (d, J = 9.0 Hz, 2H), 6.84 (t, J = 8.7 Hz, 2H), 3.60–3.70 (m, 19H). LRMS (EI) *m/z* 372 (M^+, 100%); HRMS (EI) *m/z* calcd for $C_{18}H_{24}N_6O_3$ (M^+) 372.1910, found 372.1906.

5.3.2.3. (4,6-Bis(*N*-morpholino)-[1,3,5]triazin-2-yl)-(4-fluorophenyl)-amine (5d). Compound **5d** was prepared from 4,6-dichloro-*N*-(4-fluorophenyl)-1,3,5-triazin-2-amine (**9d**) and morpholine using a procedure similar to that described for the preparation of **5b** as a white solid. Yield: 95%; mp 199–200 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48 (m, 2H), 7.01 (t, J = 8.4 Hz, 2H), 3.71–3.81 (m, 16H). LRMS (EI) *m/z* 360 (M^+, 100%); HRMS (EI) *m/z* calcd for $C_{17}H_{21}FN_6O_2$ (M^+) 360.1710, found 360.1709.

5.3.2.4. Benzyl-(4,6-bis(*N*-morpholino)-[1,3,5]triazin-2-yl)-amine (5e). Compound **5e** was prepared from *N*-benzyl-4,6-dichloro-1,3,5-triazin-2-amine (**9e**) and morpholine using a procedure similar to that described for the preparation of **5b** as a white solid. Yield: 92%; mp 160–161 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.36 (t, J = 6.6 Hz, 1H), 7.17–7.29 (m, 5H), 4.40 (d, J = 6.3 Hz, 2H), 3.55–3.61 (m, 16H). LRMS (EI) *m/z* 356 (M^+, 100%); HRMS (EI) *m/z* calcd for $C_{18}H_{24}N_6O_2$ (M^+) 356.1961, found 356.1950.

5.3.3. Procedures for 2,4,6-tris(*N*-morpholino)-1,3,5-triazine (5f).

An ice-cooled solution of cyanuric chloride (**8**, 300 mg, 1.63 mmol) in acetone (8 mL) was treated with morpholine (0.85 mL, 9.76 mmol). The reaction temperature was gradually raised to 40 °C until the complete disappearance of the cyanuric chloride. The solvent was removed under reduced pressure and 30 mL water was added to the residue. The precipitate was filtered, washed with water (3× 20 mL), and dried to afford compound **5f** as a white solid (525 mg, 96%). Mp 267 °C. ^{1}H NMR (300 M, $CDCl_3$): δ 3.69–3.78 (m, 24H). LRMS

(EI) *m/z* 336 (M^+, 100%); HRMS (EI) *m/z* calcd for $C_{15}H_{24}N_6O_3$ (M^+) 336.1910, found 336.1910.

5.3.4. General procedures for the preparations of intermediates 10, except for 10e, 10g, and 10s, are described as those for 10a.

5.3.4.1. *N*-Benzyl-6-chloro-*N*′-phenyl-[1,3,5]triazine-2,4-diamine (10a). To a solution of **9a** (500 mg, 2.07 mmol) in acetone (10 mL) were added K_2CO_3 (286 mg, 2.07 mmol) and benzylamine (144 μL, 2.07 mmol). The resulting mixture was stirred at room temperature for 5 h. The solvent was removed under reduced pressure and ice water (20 mL) was added. The solid was collected by vacuum filtration, washed with water (3× 20 mL), dried in vacuo, and purified by flash chromatography on silica gel (EtOAc/petroleum ether 1:5) to give **10a** as a white solid (530 mg, 82% yield). Mp 173–175 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.55 (d, J = 8.1 Hz, 2H), 7.21–7.36 (m, 7H), 7.00 (t, J = 8.1 Hz, 1H), 4.49(s, 1H). LRMS (EI) *m/z* 311 (M^+, 100%).

5.3.5. General procedures for the preparations of intermediates 10e, 10g, and 10s are described as those for 10g.

5.3.5.1. 6-Chloro-*N*,*N*′-diphenyl-[1,3,5]triazine-2,4-diamine (10g). To a solution of cyanuric chloride (**8**, 500 mg, 2.7 mmol) in acetone (10 mL) at 0 °C were added Na_2CO_3 (575 mg, 5.4 mmol) and aniline (494 μL, 5.4 mmol). The resulting mixture was stirred at 0 °C for 2 h and then at room temperature for an additional 5 h. The solvent was removed under reduced pressure and ice water (20 mL) was added. The solid was collected by vacuum filtration, washed with water (3× 20 mL), dried in vacuo, and purified by flash chromatography on silica gel (EtOAc/petroleum ether 1:5) to afford **10g** as a white solid (694 mg, 86% yield). Mp 197 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.76 (s, 4H), 7.35 (t, J = 7.5 Hz, 4H), 7.10 (t, J = 7.5 Hz, 2H). LRMS (EI) *m/z* 297 (M^+, 100%).

5.3.6. General procedures for the preparations of target compounds 6 are described as those for 6a.

5.3.6.1. *N*-Benzyl-6-morpholino-*N*′-phenyl-[1,3,5]triazine-2,4-diamine (6a). To a solution of **10a** (250 mg, 0.80 mmol) in acetone (10 mL) at room temperature was added morpholine (140 μL, 1.6 mmol). The reaction mixture was stirred at room temperature for 3 h. The solvent was removed under reduced pressure and ice water (20 mL) was added. The solid was collected by vacuum filtration, washed with water (3× 20 mL), dried in vacuo, and purified by flash chromatography on silica gel to give **6a** as a white solid in 93% yield. Mp 121–123 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.53 (d, J = 8.7 Hz, 2H), 7.25–7.34 (m, 7H), 7.01 (t, J = 7.2 Hz, 1H), 6.87 (s, 1H), 5.31 (br s, 1H), 4.61 (d, J = 5.7 Hz, 2H), 3.69–3.77 (m, 8H). LRMS (EI) *m/z* 362 (M^+, 100%); HRMS (EI) *m/z* calcd for $C_{20}H_{22}N_6O$ (M^+) 362.1855, found 362.1867.

5.3.6.2. 4-(4-Benzylamino-6-morpholino-[1,3,5]triazin-2-ylamino)-benzenesulfonamide (6b). Compound **6b** was prepared from 4-(4-(benzylamino)-6-chloro-1,3,5-triazin-2-ylamino)benzenesulfonamide (**10b**) and morpholine using a procedure similar to that described for the preparation of **6a** as a white solid. Yield: 92%; mp 205–206 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.89 (d, J = 8.7 Hz, 1H), 7.75 (d, J = 8.7 Hz, 1H), 7.63 (m, 2H), 7.17–7.31 (m, 5H), 4.46 (d, J = 12 Hz, 2H), 3.59–3.66 (m, 8H). LRMS (EI) *m/z* 441 (M^+, 100%); HRMS (EI) *m/z* calcd for $C_{20}H_{23}N_7O_3S$ (M^+) 441.1583, found 441.1591.

5.3.6.3. *N*-Benzyl-*N*′-(4-methoxyphenyl)-6-morpholino-[1,3,5]triazine-2,4-diamine (6c). Compound **6c** was prepared from *N*-benzyl-6-chloro-*N*′-(4-methoxyphenyl)-1,3,5-triazine-2,4-diamine (**10c**) and morpholine using a procedure similar to that described for the preparation of **6a** as a white solid. Yield: 95%; mp 152–153 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40 (d, J = 9.0 Hz, 2H), 7.26–7.33 (m, 5H), 6.83 (d, J = 9.0 Hz, 2H), 6.75 (br s, 1H), 5.27 (br s, 1H), 4.59 (d, J = 5.7 Hz, 2H), 3.68–3.78 (m, 11H). LRMS (EI) *m/z* 392 (M^+, 100%); HRMS (EI) *m/z* calcd for $C_{21}H_{24}N_6O_2$ (M^+) 392.1961, found 392.1962.

5.3.6.4. *N*-Benzyl-*N*′-(4-fluorophenyl)-6-morpholino-[1,3,5]triazine-2,4-diamine (6d). Compound **6d** was prepared from *N*-benzyl-6-chloro-*N*′-(4-fluorophenyl)-1,3,5-triazine-2,4-diamine (**10d**) and morpholine using a procedure similar to that described for the preparation of **6a** as a white solid. Yield: 95%; mp 143–144 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45 (m, 2H), 7.25–7.33 (m, 5H), 6.96 (t, J = 8.7 Hz, 2H), 6.78 (s, 1H), 5.28 (t, J = 5.7 Hz, 1H), 4.59 (d, J = 6.0 Hz, 2H), 3.69–3.76 (m, 8H). LRMS (EI) *m/z* 380 (M^+, 100%); HRMS (EI) *m/z* calcd for $C_{20}H_{21}FN_6O$ (M^+) 380.1761, found 380.1753.

5.3.6.5. *N*,*N*′-Dibenzyl-6-morpholino-[1,3,5]triazine-2,4-diamine (6e). Compound **6e** was prepared from *N*,*N*′-dibenzyl-6-chloro-1,3,5-triazine-2,4-diamine (**10e**) and morpholine using a procedure similar to that described for the preparation of **6a** as a white solid. Yield: 92%; mp 135–136 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.23–7.31 (m, 10H), 5.17 (br s, 2H), 4.57 (d, J = 5.7 Hz, 4H), 3.66–3.73 (m, 8H). LRMS (EI) *m/z* 376 (M^+), 73 (100%); HRMS (EI) *m/z* calcd for $C_{21}H_{24}N_6O$ (M^+) 376.2012, found 376.2016.

5.3.6.6. *N*-(4-Methylbenzyl)-6-morpholino-*N*′-phenyl-[1,3,5]triazine-2,4-diamine (6f). Compound **6f** was prepared from *N*-benzyl-6-chloro-*N*′-*p*-tolyl-1,3,5-triazine-2,4-diamine (**10f**) and morpholine using a procedure similar to that described for the preparation of **6a** as a white solid. Yield: 91%; mp 80–85 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.73 (d, J = 7.8 Hz, 1H), 7.63 (d, J = 8.1 Hz, 1H), 7.22 (m, 4H), 7.11 (d, J = 8.1 Hz, 2H), 6.89 (t, J = 7.2 Hz, 1H), 4.42 (d, J = 13.2 Hz, 2H), 3.60–3.67 (m, 8H), 2.25 (s, 3H). LRMS (EI) *m/z* 376 (M^+, 100%); HRMS (EI) *m/z* calcd for $C_{21}H_{24}N_6O$ (M^+) 376.2012, found 376.2010.

5.3.6.7. 6-Morpholino-*N*,*N*′-diphenyl-[1,3,5]triazine-2,4-diamine (6g). Compound **6g** was prepared from 6-chloro-*N*,*N*′-diphenyl-1,3,5-triazine-2,4-diamine (**10g**) and morpholine using a procedure similar to that described for the preparation of **6a** as a white solid. Yield: 96%; mp 195–197 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55 (d, J = 7.8 Hz, 4H), 7.32 (t, J = 6.8 Hz, 4H), 7.05 (t, J = 7.8 Hz, 2H), 6.88 (s, 2H), 3.82 (t, J = 4.8 Hz, 4H), 3.75 (t, J = 4.8 Hz, 4H). LRMS (EI) *m/z* 348

(M^+, 100%); HRMS (EI) *m/z* calcd for $C_{19}H_{20}N_6O$ (M^+) 348.1699, found 348.1699.

5.3.6.8. *N*-(4-Chlorophenyl)-6-morpholino-*N*′-phenyl-[1,3,5]triazine-2,4-diamine (6h). Compound **6h** was prepared from 6-chloro-*N*-(4-chlorophenyl)-*N*′-phenyl-1,3,5-triazine-2,4-diamine (**10h**) and morpholine using a procedure similar to that described for the preparation of **6a** as a white solid. Yield: 96%; mp 226 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55 (d, J = 7.8 Hz, 4H), 7.50 (d, J = 6.6 Hz, 2H), 7.33 (t, J = 7.8 Hz, 2H), 7.27 (dd, J = 7.2 and 1.5 Hz, 2H), 7.08 (t, J = 7.2 Hz, 1H), 7.02 (br s, 2H), 3.74–3.84 (m, 8H). LRMS (EI) *m/z* 382 (M^+, 100%); HRMS (EI) *m/z* calcd for $C_{19}H_{19}ClN_6O$ (M^+) 382.1309, found 382.1304.

5.3.6.9. *N*-(4-Bromophenyl)-6-morpholino-*N*′-phenyl-[1,3,5]triazine-2,4-diamine (6i). Compound **6i** was prepared from *N*-(4-bromophenyl)-6-chloro-*N*′-phenyl-1,3,5-triazine-2,4-diamine (**10i**) and morpholine using a procedure similar to that described for the preparation of **6a** as a white solid. Yield: 97%; mp 227–228 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.73 (m, 4H), 7.43 (d, J = 9.0 Hz, 2H), 7.29 (t, J = 7.8 Hz, 2H), 6.98 (t, J = 7.5 Hz, 1H), 3.65–3.74 (m, 8H). LRMS (EI) *m/z* 426 (M^+, 100%); HRMS (EI) *m/z* calcd for $C_{19}H_{19}BrN_6O$ (M^+) 426.0804, found 426.0790.

5.3.6.10. *N*-(4-Fluorophenyl)-6-morpholino-*N*′-phenyl-[1,3,5]triazine-2,4-diamine (6j). Compound **6j** was prepared from 6-chloro-*N*-(4-fluorophenyl)-*N*′-phenyl-1,3,5-triazine-2,4-diamine (**10j**) and morpholine using a procedure similar to that described for the preparation of **6a** as a white solid. Yield: 96%; mp 210–211 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54 (dd, J = 8.7 & 1.2 Hz, 2H), 7.48 (m, 2H), 7.31 (t, J = 8.4 Hz, 2H), 6.97–7.08 (m, *3*H), 6.96 (s, 1H), 6.91 (s, 1H), 3.72–3.83 (m, 8H). LRMS (EI) *m/z* 366 (M^+, 100%); HRMS (EI) *m/z* calcd for $C_{19}H_{19}FN_6O$ (M^+) 366.1604, found 366.1602.

5.3.6.11. 6-Morpholino-*N*-phenyl-*N*′-(4-trifluoromethoxyphenyl)-[1,3,5]triazine-2,4-diamine (6k). Compound **6k** was prepared from 6-chloro-*N*-phenyl-*N*′-(4-(trifluoromethoxy)phenyl)-1,3,5-triazine-2,4-diamine (**10k**) and morpholine using a procedure similar to that described for the preparation of **6a** as a white solid. Yield: 93%; mp 178–180 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.85 (d, J = 9.0 Hz, 2H), 7.72 (d, J = 7.8 Hz, 2H), 7.28 (m, 4H), 6.97 (t, J = 7.5 Hz, 1H), 3.64–3.85 (m, 8H). LRMS (EI) *m/z* 432 (M^+, 100%); HRMS (EI) *m/z* calcd for $C_{20}H_{19}F_3N_6O_2$ (M^+) 432.1522, found 432.1521.

5.3.6.12. *N*-(4-Methoxyphenyl)-6-morpholino-*N*′-phenyl-[1,3,5]triazine-2,4-diamine (6l). Compound **6l** was prepared from 6-chloro-*N*-(4-methoxyphenyl)-*N*′-phenyl-1,3,5-triazine-2,4-diamine (**10l**) and morpholine using a procedure similar to that described for the preparation of **6a** as a white solid. Yield: 94%; mp 198–200 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55 (d, J = 7.6 Hz, 2H), 7.45 (d, J = 7.2 Hz, 2H), 7.30 (t, J = 7.6 Hz, 2H), 7.05 (t, J = 7.6 Hz, 1H), 6.91 (s, 1H), 6.88 (d, J = 6.8 Hz, 2H), 6.81 (s, 1H), 3.81 (m, 7H), 3.75 (t, J = 4.8 Hz, 4H). LRMS (EI) *m/z* 378 (M^+, 100%); HRMS (EI) *m/z* calcd for $C_{20}H_{22}N_6O_2$ (M^+) 378.1804, found 378.1875.

5.3.6.13. *N*-(2-Methoxyphenyl)-6-morpholino-*N*′-phenyl-[1,3,5]triazine-2,4-diamine (6m). Compound **6m** was prepared from 6-chloro-*N*-(2-methoxyphenyl)-*N*′-phenyl-1,3,5-triazine-2,4-diamine (**10m**) and morpholine using a procedure similar to that described for the preparation of **6a** as a white solid. Yield: 90%; mp 162–163 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.13 (br s, 1H), 7.74 (br s, 1H), 7.70 (d, J = 8.1 Hz, 2H), 7.26 (t, J = 8.1 Hz, 2H), 7.05 (d, J = 3.6 Hz, 2H), 6.92–6.98 (m, 2H), 3.86 (s, 3H), 3.73 (m, 4H), 3.66 (m, 4H). LRMS (EI) *m/z* 378 (M^+), 347 (100%); HRMS (EI) *m/z* calcd for $C_{20}H_{22}N_6O_2$ (M^+) 378.1804, found 378.1800.

5.3.6.14. *N*-(3-Methoxyphenyl)-6-morpholino-*N*′-phenyl-[1,3,5]triazine-2,4-diamine (6n). Compound **6n** was prepared from 6-chloro-*N*-(3-methoxyphenyl)-*N*′-phenyl-1,3,5-triazine-2,4-diamine (**10n**) and morpholine using a procedure similar to that described for the preparation of **6a** as a white solid. Yield: 94%; mp 164 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.75 (d, J = 7.5 Hz, 2H), 7.43 (s, 1H), 7.27 (m, 3H), 7.17 (t, J = 8.1 Hz, 1H), 6.96 (t, J = 7.5 Hz, 1H), 6.55 (d, J = 7.5 Hz, 1H), 3.65–3.75 (m, 11H). LRMS (EI) *m/z* 378 (M^+, 100%); HRMS (EI) *m/z* calcd for $C_{20}H_{22}N_6O_2$ (M^+) 378.1804, found 378.1792.

5.3.6.15. *N*-(3,4-Dimethoxyphenyl)-6-morpholino-*N*′-phenyl-[1,3,5]triazine-2,4-diamine (6o). Compound **6o** was prepared from 6-chloro-*N*-(3,4-dimethoxyphenyl)-*N*′-phenyl-1,3,5-triazine-2,4-diamine (**10o**) and morpholine using a procedure similar to that described for the preparation of **6a** as a white solid. Yield: 96%; mp 132–135 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.53 (d, J = 7.6 Hz, 2H), 7.30 (t, J = 7.6 Hz, 2H), 7.23 (s, 1H), 7.04 (t, J = 7.2 Hz, 1H), 6.95 (dd, J = 8.4 and 2.4 Hz, 2H), 6.91 (s, 1H), 6.82 (d, J = 8.4 Hz, 1H), 3.87 (s, 3H), 3.82 (m, 7H), 3.73 (t, J = 5.2 Hz, 4H). LRMS (EI) *m/z* 408 (M^+, 100%); HRMS (EI) *m/z* calcd for $C_{21}H_{24}N_6O_3$ (M^+) 408.1910, found 408.1917.

5.3.6.16. *N*-(4-Ethoxyphenyl)-6-morpholino-*N*′-phenyl-[1,3,5]triazine-2,4-diamine (6p). Compound **6p** was prepared from 6-chloro-*N*-(3-ethoxyphenyl)-*N*′-phenyl-1,3,5-triazine-2,4-diamine (**10p**) and morpholine using a procedure similar to that described for the preparation of **6a** as a white solid. Yield: 95%; mp 174–175 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.74 (d, J = 7.8 Hz, 2H), 7.59 (d, J = 9.0 Hz, 2H), 7.27 (t, J = 7.8 Hz, 2H), 6.95 (t, J = 7.2 Hz, 1H), 6.85 (d, J = 9.0 Hz, 2H), 3.98 (q, J = 6.9 Hz, 2H), 3.64–3.73 (m, 8H), 1.31 (t, J = 6.9 Hz, 3H). LRMS (EI) *m/z* 392 (M^+, 100%); HRMS (EI) *m/z* calcd for $C_{21}H_{24}N_6O_2$ (M^+) 392.1961, found 392.1958.

5.3.6.17. 4-(4-Morpholino-6-phenylamino-[1,3,5]triazin-2-ylamino)-benzenesulfonamide (6q). Compound **6q** was prepared from 4-(4-chloro-6-(phenylamino)-1,3,5-triazin-2-ylamino)benzenesulfonamide (**10q**) and mor-

pholine using a procedure similar to that described for the preparation of **6a** as a white solid. Yield: 90%; mp 245–248 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.95 (d, J = 8.7 Hz, 2H), 7.78 (d, J = 8.7 Hz, 2H), 7.74 (d, J = 8.7 Hz, 2H), 7.29 (t, J = 7.6 Hz, 2H), 7.00 (t, J = 7.6 Hz, 1H), 3.79 (t, J = 4.8 Hz, 4H), 3.68 (t, J = 4.8 Hz, 4H). LRMS (EI) m/z 427 (M^+, 100%); HRMS (EI) m/z calcd for $C_{19}H_{21}N_7O_3S$ (M^+) 427.1427, found 427.1411.

5.3.6.18. 4-(4-Morpholino-6-phenylamino-[1,3,5]triazin-2-ylamino)-benzamide (6r). Compound **6r** was prepared from *N*-(4-(aminooxycarbonyl)phenyl)-6-chloro-*N*-phenyl-1,3,5-triazine-2,4-diamine (**10r**) and morpholine using a procedure similar to that described for the preparation of **6a** as a white solid. Yield: 87%; mp 222–223 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.78–7.85 (m, 5H), 7.73 (d, J = 8.1 Hz, 2H), 7.30 (t, J = 8.1 Hz, 2H), 7.18 (s, 1H), 6.99 (t, J = 7.5 Hz, 1H), 3.66–3.76 (m, 8H). LRMS (EI) m/z 391 (M^+, 100%); HRMS (EI) m/z calcd for $C_{20}H_{21}N_7O_2$ (M^+) 391.1757, found 391.1741.

5.3.6.19. *N*,*N*′-Bis(4-methoxyphenyl)-6-morpholino-[1,3,5]triazine-2,4-diamine (6s). Compound **6s** was prepared from 6-chloro-*N*,*N*′-bis(4-methoxyphenyl)-1,3,5-triazine-2,4-diamine (**10s**) and morpholine using a procedure similar to that described for the preparation of **6a** as a white solid. Yield: 96%; mp 192–193 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42 (d, J = 8.7 Hz, 4H), 6.86 (d, J = 8.7 Hz, 4H), 6.78 (s, 2H), 3.72–3.80 (m, 14H). LRMS (EI) m/z 408 (M^+, 100%); HRMS (EI) m/z calcd for $C_{21}H_{24}N_6O_3$ (M^+) 408.1910, found 408.1904.

5.3.6.20. *N*-(4-Fluorophenyl)-*N*′-(4-methoxyphenyl)-6-morpholino-[1,3,5]triazine-2,4-diamine (6t). Compound **6t** was prepared from 6-chloro-*N*-(4-fluorophenyl)-*N*′-(4-methoxyphenyl)-1,3,5-triazine-2,4-diamine (**10t**) and morpholine using a procedure similar to that described for the preparation of **6a** as a white solid. Yield: 93%; mp 200–201 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47 (m, 2H), 7.41 (d, J = 9.0 Hz, 2H), 6.70 (t, J = 8.7 Hz, 2H), 6.87 (d, J = 9.3 Hz, 2H), 6.82 (s, 1H), 6.77 (s, 1H), 3.71–3.81 (m, 11H). LRMS (EI) m/z 396 (M^+, 100%); HRMS (EI) m/z calcd for $C_{20}H_{21}FN_6O_2$ (M^+) 396.1710, found 396.1710.

5.3.6.21. *N*-(4-Fluorophenyl)-6-morpholino-*N*′-(4-trifluoromethoxyphenyl)-[1,3,5]triazine-2,4-diamine (6u). Compound **6u** was prepared from 6-chloro-*N*-(4-fluorophenyl)-*N*′-(4-(trifluoromethoxy)phenyl)-1,3,5-triazine-2,4-diamine (**10u**) and morpholine using a procedure similar to that described for the preparation of **6a** as a white solid. Yield: 89%; mp 198–199 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55 (d, J = 9.3 Hz, 2H), 7.47 (m, 2H), 7.15 (d, J = 8.7 Hz, 2H), 7.01 (t, J = 9.0 Hz, 2H), 6.88 (s, 1H), 6.80 (s, 1H), 3.73–3.82 (m, 8H). LRMS (EI) m/z 450 (M^+, 100%); HRMS (EI) m/z calcd for $C_{20}H_{18}F_4N_6O_2$ (M^+) 450.1427, found 450.1441.

5.3.6.22. *N*-(4-Methylsulfanylphenyl)-6-morpholino-*N*′-*p*-tolyl-[1,3,5]triazine-2,4-diamine (6v). Compound **6v** was prepared from 6-chloro-*N*-(4-methylsulfanylphenyl)-*N*′-*p*-tolyl-1,3,5-triazine-2,4-diamine (**10v**) and morpholine using a procedure similar to that described for the preparation of **6a** as a white solid. Yield: 97%; mp 230–231 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.70 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 8.1 Hz, 2H), 7.20 (d, J = 8.7 Hz, 2H), 7.07 (t, J = 8.4 Hz, 2H), 3.63–3.71 (m, 8H), 2.43 (s, 3H), 2.24 (s, 3H). LRMS (EI) m/z 408 (M^+, 100%); HRMS (EI) m/z calcd for $C_{21}H_{24}N_6OS$ (M^+) 408.1732, found 408.1735.

5.3.6.23. *N*-(3,4-Dimethoxyphenyl)-*N*′-(4-methylsulfanylphenyl)-6-morpholino-[1,3,5]triazine-2,4-diamine (6w). Compound **6w** was prepared from 6-chloro-*N*-(3,4-dimethoxyphenyl)-*N*′-(4-methylsulfanylphenyl)-1,3,5-triazine-2,4-diamine (**10w**) and morpholine using a procedure similar to that described for the preparation of **6a** as a white solid. Yield: 95%; mp 124–126 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.70 (d, J = 6.3 Hz, 2H), 7.41 (s, 1H), 7.16–7.20 (m, 3H), 6.86 (d, J = 9.0 Hz, 2H), 3.63–3.71 (m, 14H), 2.43 (s, 3H). LRMS (EI) m/z 454 (M^+, 100%); HRMS (EI) m/z calcd for $C_{22}H_{26}N_6O_3S$ (M^+) 454.1787, found 454.1790.

5.3.6.24. 4-(4-(4-Methoxyphenylamino)-6-morpholino-1,3,5-triazin-2-ylamino)benzenesulfonamide (6x). Compound **6x** was prepared from 4-(4-chloro-6-(4-methoxyphenylamino)-1,3,5-triazin-2-ylamino)benzenesulfonamide (**10x**) and morpholine using a procedure similar to that described for the preparation of **6a** as a white solid. Yield: 94%; mp 257–258 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.91 (d, J = 7.2 Hz, 2H), 7.68 (d, J = 8.7 Hz, 2H), 7.57 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 7.2 Hz, 2H), 3.73 (m, 7H), 3.65 (m, 4H). LRMS (EI) m/z 457 (M^+, 100%); HRMS (EI) m/z calcd for $C_{20}H_{23}N_7O_4S$ (M^+) 457.1532, found 457.1522.

5.3.7. General procedures for the preparations of compounds 7 are described as those for 7a.

5.3.7.1. *N*-(2-Morpholinoethyl)-*N*′,*N*″-diphenyl-[1,3,5]triazine-2,4,6-triamine (7a). To a solution of 6-chloro-*N*,*N*′-diphenyl-1,3,5-triazine-2,4-diamine (**10g**, 250 mg, 0.84 mmol) in acetone (10 mL) at room temperature were added 2-(4-morpholino)ethylamine (110 μL, 0.84 mmol) and K_2CO_3 (116 mg, 0.84 mmol). The reaction mixture was stirred at room temperature for 5 h. The solvent was removed under reduced pressure and ice water (20 mL) was added. The resulting mixture was extracted with ethyl acetate (3× 15 mL). The combined extracts were washed with brine (3× 10 mL), dried over anhydrous sodium sulfate, filtered, concentrated, and purified by flash chromatography on silica gel to afford **7a** as a white solid (270 mg, 82% yield). Mp 167–168 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59 (m, 4H), 7.34 (t, J = 7.5 Hz, 4H), 7.07 (t, J = 7.2 Hz, 2H), 6.96 (s, 2H), 5.58 (t, J = 6.0 Hz, 1H), 3.74 (t, J = 4.8 Hz, 4H), 3.55 (q, J = 5.7 Hz, 2H), 2.59 (t, J = 6.0 Hz, 2H), 2.50 (t, J = 4.8 Hz, 4H). LRMS (EI) m/z 391 (M^+), 279 (100%); HRMS (EI) m/z calcd for $C_{21}H_{25}N_7O$ (M^+) 391.2121, found 391.2120.

5.3.7.2. *N*-(4-Methoxyphenyl)-*N*′-(2-morpholinoethyl)-N″-phenyl-[1,3,5]triazine-2,4,6-triamine (7b). Compound

7b was prepared from 6-chloro-*N*-(4-methoxyphenyl)-*N*′-phenyl-1,3,5-triazine-2,4-diamine (**10l**) and 2-(4-morpholino)ethylamine using a procedure similar to that described for the preparation of **7a** as a white solid. Yield: 88%; mp 147–148 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.57 (d, J = 7.5 Hz, 2H), 7.45 (d, J = 7.5 Hz, 2H), 7.30 (t, J = 8.7 Hz, 2H), 7.04 (t, J = 7.2 Hz, 2H), 6.89 (br s, 1H), 6.87 (d, J = 9.0 Hz, 2H), 6.85 (br s, 1H), 5.54 (t, J = 6.0 Hz, 1H), 3.81 (s, 3H), 3.71 (t, J = 4.8 Hz, 4H), 3.51 (q, J = 5.7 Hz, 2H), 2.56 (t, J = 5.4 Hz, 2H), 2.47 (t, J = 4.5 Hz, 4H). LRMS (EI) *m*/*z* 421 (M^+), 309 (100%); HRMS (EI) *m*/*z* calcd for $C_{22}H_{27}N_7O_2$ (M^+) 421.2226, found 421.2211.

5.3.7.3. 2-(4,6-Bis(phenylamino)-[1,3,5]triazin-2-ylamino)ethanol (7c). Compound **7c** was prepared from 6-chloro-*N*,*N*′-diphenyl-1,3,5-triazine-2,4-diamine (**10g**) and 2-aminoethanol using a procedure similar to that described for the preparation of **7a** as a white solid.Yield: 85%; mp 182–183 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.80 (d, J = 8.1 Hz, 4H), 7.25 (t, J = 7.8 Hz, 4H), 6.94 (t, J = 7.5 Hz, 2H), 3.54 (t, J = 6.0 Hz, 2H), 3.38 (q, J = 5.7 Hz, 2H). LRMS (EI) *m*/*z* 322 (M^+), 304 (100%); HRMS (EI) *m*/*z* calcd for $C_{17}H_{18}N_6O$ (M^+) 322.1542, found 322.1540.

5.3.7.4. 2-(4-(4-Methoxyphenylamino)-6-(phenylamino)-1,3,5-triazin-2-ylamino)ethanol (7d). Compound **7d** was prepared from 6-chloro-*N*-(4-methoxyphenyl)-*N*′-phenyl-1,3,5-triazine-2,4-diamine (**10l**) and 2-aminoethanol using a procedure similar to that described for the preparation of **7a** as a white solid. Yield: 84%; mp 173–174 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55 (d, J = 8.7 Hz, 4H), 7.42 (d, J = 9.0 Hz, 2H), 7.31 (t, J = 7.5 Hz, 2H), 7.06 (t, J = 7.5 Hz, 1H), 6.86 (t, J = 8.7 Hz, 2H), 6.79 (s, 1H), 6.70 (s, 1H), 5.45 (t, J = 5.4 Hz, 1H), 3.78–3.82 (m, 5H), 3.58 (q, J = 5.1 Hz, 2H). LRMS (EI) *m*/*z* 352 (M^+, 100%); HRMS (EI) *m*/*z* calcd for $C_{18}H_{20}N_6O_2$ (M^+) 352.1648, found 352.1631.

5.3.7.5. 2-(4-(4,6-Bis(phenylamino)-1,3,5-triazin-2-yl) piperazin-1-yl)ethanol (7e). Compound **7e** was prepared from 6-chloro-*N*,*N*′-diphenyl-1,3,5-triazine-2,4-diamine (**10g**) and 2-(piperazin-1-yl)ethanol using a procedure similar to that described for the preparation of **7a** as a white solid. Yield: 71%; mp 151–152 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.57 (d, J = 9.0 Hz, 4H), 7.33 (t, J = 8.4 Hz, 4H), 7.06 (t, J = 7.2 Hz, 2H), 6.98 (s, 2H), 3.88 (t, J = 5.1 Hz, 4H), 3.69 (t, J = 5.7 Hz, 2H), 2.90 (s, 1H), 2.56–2.63 (m, 6H). LRMS (EI) *m*/*z* 391 (M^+), 291 (100%); HRMS (EI) *m*/*z* calcd for $C_{21}H_{25}N_7O$ (M^+) 391.2121, found 391.2096.

5.3.7.6. 2-(4-(4-(4-Methoxyphenylamino)-6-(phenylamino)-1,3,5-triazin-2-yl)piperazin-1-yl)ethanol (7f). Compound **7f** was prepared from 6-chloro-*N*-(4-methoxyphenyl)-*N*′-phenyl-1,3,5-triazine-2,4-diamine (**10l**) and 2-(piperazin-1-yl)ethanol using a procedure similar to that described for the preparation of **7a** as a white solid. Yield: 68%; mp 84–86 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54 (d, J = 8.7 Hz, 2H), 7.44 (d, J = 6.6 Hz, 2H), 7.30 (t, J = 8.1 Hz, 2H), 7.03 (t, J = 7.8 Hz, 1H), 7.03 (s, 1H), 6.93 (s, 1H), 6.86 (d, J = 7.2 Hz, 2H), 3.87 (t, J = 5.1 Hz, 4H), 3.80 (s, 3H), 3.69 (t, J = 5.7 Hz, 2H), 3.00 (s, 2H), 2.58–2.64 (m, 6H). LRMS (EI) *m*/*z* 421 (M^+), 321 (100%); HRMS (EI) *m*/*z* calcd for $C_{22}H_{27}N_7O_2$ (M^+) 421.2226, found 421.2201.

5.3.7.7. 2-(4-(4,6-Bis(4-methoxyphenylamino)-1,3,5-triazin-2-yl)piperazin-1-yl)ethanol (7g). Compound **7g** was prepared from 6-chloro-*N*,*N*′-bis(4-methoxyphenyl)-1,3,5-triazine-2,4-diamine (**10s**) and 2-(piperazin-1-yl)ethanol using a procedure similar to that described for the preparation of **7a** as a white solid. Yield: 75%; mp 149–151 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44 (d, J = 9.3 Hz, 4H), 6.86 (d, J = 9.0 Hz, 4H), 3.84 (m, 10H), 3.68 (t, J = 6.8 Hz, 2H), 2.54–2.61 (m, 6H). LRMS (EI) *m*/*z* 451 (M^+), 352 (100%); HRMS (EI) *m*/*z* calcd for $C_{23}H_{29}N_7O_3$ (M^+) 451.2332, found 451.2305.

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