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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and characterization of new *s*-triazine bearing benzimidazole and benzothiazole derivatives as anticancer agents

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Abstract Two new series of *s*-triazine derivatives appended with benzimidazole (**15a–h**) and benzothiazole derivatives (**16a–h**) are synthesized, and structure–activity relationships on anticancer activity of these **15a–h** and **16a–h** were probed. In vitro inhibitory activity against the growth of six cancer cell lines, viz., MCF-7, MDAMB-231, PC-3, DU-145, HT-29 and HGC-27 was evaluated for synthesized analogues. Among the two series of compounds, derivatives containing benzimidazole scaffold were found to be relatively potent over benzothiazole analogues. In accordance with our previous observation, within benzimidazole derivatives, tri-substituted *s*-triazine derivatives were found to be more potent over di-substituted derivatives irrespective of cell lines. Structure–activity relationships provided useful insights into these classes of compounds and paved the way to design novel analogues with more potency.

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Keywords *s*-Triazine benzimidazole derivatives · *s*-Triazine benzothiazole derivatives · Anticancer activity · Structure–activity relationships

Introduction

Cancer is the most deadly disease, and finding remedies for it is at the forefront of many scientists around the globe. In this context, *s*-triazine scaffold has attracted the attention of many researchers for its therapeutic potential (Sathiakumar *et al.*, 2011) and ease of functionalization on it (Blotny 2006; Therrien 2010). For example, these compounds possess potent antiprotozoal (Klenke *et al.*, 2001), antimalarial (Manohar *et al.*, 2010; Melato *et al.*, 2008), antiviral (Maga *et al.*, 2011; Mahajan *et al.*, 2009; Maarouf *et al.*, 2012; Xiong *et al.*, 2008; Kalyan *et al.*, 2004; Ludovicia *et al.*, 2001), anticancer (Baindur *et al.*, 2005; Chua *et al.*, 1999; Leftheris *et al.*, 2004; Manohar *et al.*, 2010; Moon *et al.*, 2002; Sun *et al.*, 2010; Zheng *et al.*, 2007), antimicrobial (Bhat *et al.*, 2013; Khan *et al.*, 2013; McKay *et al.*, 2006; Patel *et al.*, 2013, 2012a, b; Raval *et al.*, 2011; Singh *et al.*, 2011; Srinivas *et al.*, 2005, 2006; Desai *et al.*, 2008), antituberculosis (Patel *et al.*, 2013; Sunduru *et al.*, 2010). Recently, the *s*-triazine derivatives were extensively investigated for anticancer activity with a particular target to mTOR/PI3K pathway (Menear *et al.*, 2009; Peterson *et al.*, 2011, Poulsen *et al.*, 2012; Richard *et al.*, 2010; Tanneeru *et al.*, 2012; Venkatesan *et al.*, 2010; Verheijen *et al.*, 2010; Wurz *et al.*, 2012; Zask *et al.*, 2010; Zhang *et al.*, 2011). Considering the potent bioactivities of compounds possessing an *s*-triazine core, we became interested to synthesize new *s*-triazine derivatives as antibacterial and anticancer agents. Recently, we have reported *s*-triazine analogues appended with substituted

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benzoxazoles as anticancer agents (Kumar *et al.*, 2013). In continuation to the previous work, we herein report newer *s*-triazine derivatives appended with benzimidazole and benzothiazole derivatives in place of benzoxazole derivatives. Synthesized compounds were screened against six types of cancer cells (MCF-7, MDAMB-231, PC-3, DU-145, HT-29 and HGC-27), and their potential as anticancer agents were assessed. Some of them were found to be more potent than compounds reported in our previous report (Kumar *et al.*, 2013).

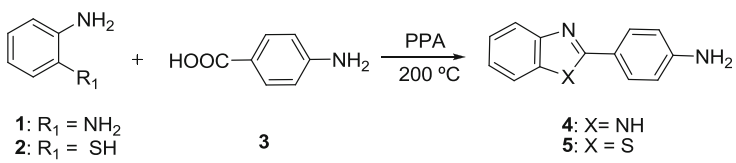
Chemistry

Common synthetic strategy was followed to make desired tri-substituted derivatives by sequential nucleophilic replacement of each chlorine atom on cyanuric chloride with: (a) aniline derivatives and benzyl amine; (b) substituted benzimidazoles and substituted benzothiazole; (c) morpholine. Initially, benzimidazole and benzothiazole derivatives (**4** and **5**; Scheme 1) were prepared in gram quantities according to the published procedure (Chua *et al.*, 1999). Compound **4** was synthesized by condensation reaction between benzene-1,2-diamine (**1**) and *p*-amino benzoic acid (**3**) using polyphosphoric acid (PPA) at 200 °C. Similarly, compound **5** was synthesized by condensation of 2-aminobenzenethiol (**2**) with *p*-amino benzoic acid (**3**) in polyphosphoric acid (PPA) at same temperature (Scheme 1). Mono-substituted triazine derivatives (**10–12** and **14**) were prepared as per the recent report (Kumar *et al.*, 2013; Zheng *et al.*, 2007; Hunter *et al.*, 1994; McKay *et al.*, 2006; Maga *et al.*, 2011) involving a nucleophilic substitution reaction between cyanuric chloride (**6**) and various amines such as aniline (**7**), *p*-methoxy aniline (**8**), *p*-fluoro aniline (**9**) and benzyl amine (**13**) in the presence of base, diisopropylethylamine (DIPEA) (Scheme 2). Milder reaction conditions need to be maintained to get desired mono-substitution on cyanuric chloride. These mono-substituted triazine derivatives were taken further in making di- and tri-substituted triazine derivatives. Second nucleophilic substitution reaction was carried out on mono-substituted triazine derivatives (**10–12** and **14**) with using benzimidazole (**4**) and benzothiazole derivatives (**5**) in the presence of K_2CO_3 and THF at 70–80 °C temperature to get compounds **15a–d** and **16a–d** (Scheme 3). Tri-substituted triazine derivatives (**15e–h**) were synthesized by reacting morpholine **17** with di-substituted triazines (**15a–d**) in the presence of K_2CO_3 and DMF at 100 °C. Similarly, compounds **16e–h** were synthesized from **16a–d**, respectively (Scheme 4). All the synthesized compounds were purified using silica gel column chromatography and characterized by spectroscopic techniques.

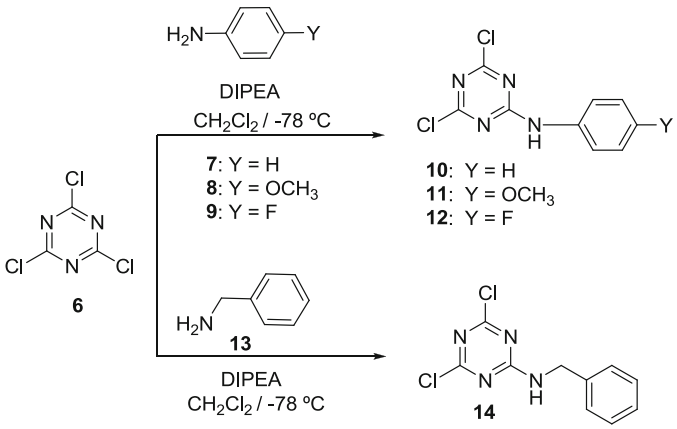
Biology

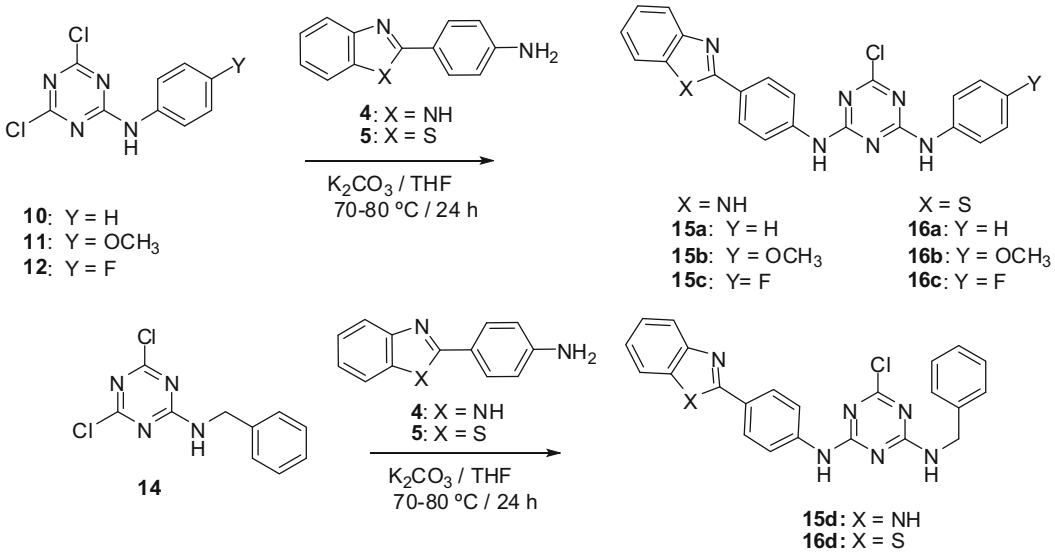
The anticancer activities of all the synthesized compounds were evaluated by MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide] method using six cancer cell lines, viz., MCF-7, MDAMB-231 (breast cancer), PC-3, DU-145, HT-29 (colon cancer) and HGC-27 (gastric cancer). The effect of compounds on the cell viability for each cell line after exposure to different concentrations is depicted in Fig. 1, and their respective IC_{50} values are presented in Table 1. As discussed above, two series of compounds were synthesized: benzimidazole derivatives and benzothiazole derivatives. Within these two series of compounds, there exist di-substituted (**15a–d** and **16a–d**) and tri-substituted derivatives (**15e–h** and **16e–h**) (di- or tri-substitution w.r.t. cyanuric chloride). The major difference in di- and tri-substituted derivatives is the absence and presence of morpholine ring, respectively, on *s*-triazine ring. Compounds **15a**, **15c**, **15e**, **15g**, **15h** and **16d** were found to be more potent when screened against MCF-7 cell lines. Among the active compounds, **15e** is most potent. Remaining synthesized compounds were inactive. In case of MDMAB-231 cell lines, compound **15e** and **15g** were found to be more potent with IC_{50} value of 8.3 ± 1.9 and 10.3 ± 0.2, respectively. Compounds **15a**, **15c**, **15f** and **15h** are moderately active in MDMAB-231 cell lines, whereas remaining compounds (**15b**, **15d**, **16a–h**) were inactive. Structure–activity relationships of **15e–h** demonstrates that substitution with 'H' and 'F' on aniline group favours activity as both have similar size. But in case of **15f** and **15h**, 'OCH_3' on aniline and benzylamine group present, respectively, on triazine ring, and this relatively disfavours the activity. When all these 16 compounds were screened against PC-3 cancer cell lines, only compound **15g** was active with IC_{50} value of 13.5 ± 0.5. Compounds **15f–h** were active (IC_{50} values: 18.6 ± 0.4; 10.7 ± 1.7; 20.3 ± 1.6, respectively) against

Scheme 1 Synthesis of compounds **4–5**



Scheme 2 Synthesis of compounds **10**–**12** and **14**



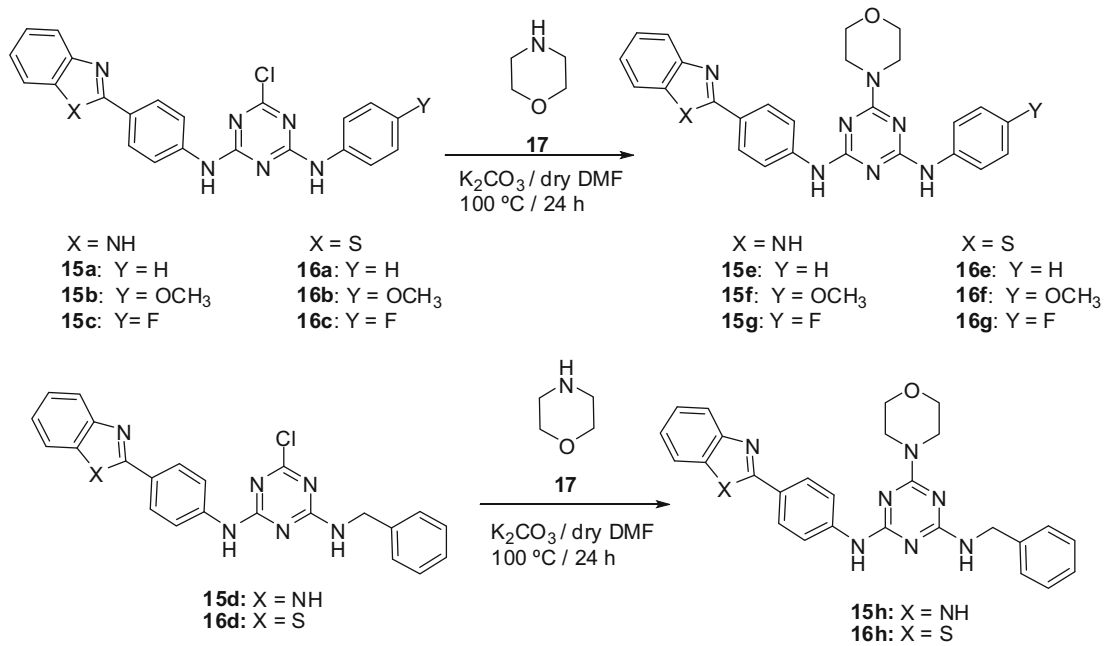


Scheme 3 Synthesis of compounds **15a**–**d** and **16a**–**d**

DU-145 cell lines. In case of HT-29 cancer cell lines, compounds **15e** and **15g** were found to be more potent and compounds **15a**, **15c** and **15h** are moderately active. In case of HGC-27 cell line, **15a** and **15e**–**h** were found to be active and remaining were inactive. Among the screened 16 compounds, benzimidazole derivatives (**15a**–**h**) were found to be more potent over benzothiazole (**16a**–**h**). The difference between them is –NH– versus –S– group, and this reflected hugely in anticancer activity. Among benzimidazole derivatives (**15a**–**h**), tri-substituted derivatives (**15e**–**h**) were found to be relatively more potent over di-substituted derivatives (**15a**–**d**); the difference lies in the presence and absence of morpholine group. This observation reinforces the previous conclusions presented in recent report from our group (Kumar *et al.*, 2013), indicating the presence of morpholine has significant impact on anticancer activity of these compounds.

Conclusion

In conclusion, two series of *s*-triazine derivatives bearing benzimidazole and benzothiazole were synthesized as anticancer agents. All the synthesized compounds were screened against six cancer cell lines. Among the two series of compounds, derivatives containing benzimidazole scaffold were found to be relatively potent over benzothiazole analogues. This unusual behaviour is a subject of our future work along with molecular mechanistic studies. In accordance with our previous observation, within benzimidazole derivatives, tri-substituted *s*-triazine derivatives were found to be more potent over di-substituted derivatives irrespective of cell lines. Structure–activity relationships in these classes of compounds laid foundations to develop more potent compounds as leads for cancer chemotherapy. Focus of our future work includes synthesis



Scheme 4 Synthesis of compounds **15e–h** and **16e–h**

of more derivatives of *s*-triazine with benzimidazoles to evaluate their potential anticancer agents.

Experimental section

General procedure for synthesis of di-substituted triazines (15a–d and 16a–d)

To a solution of mono-substituted triazine derivatives **10–14** (1 mmol) in dry THF was added K_2CO_3 (2.5 mmol), and the reaction mixture was stirred for 5 min at room temperature, **4** or **5** (1 mmol) was added to the reaction mixture and stirred for 24 h at reflux temperature. After completion of the reaction K_2CO_3 was decanted and the THF was removed, water was added and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, concentrated and purified by using silica gel column chromatography to give the desired di-substituted *s*-triazines.

*N^2-(4-(1H-benzo[d]imidazol-2-yl)phenyl)-6-chloro-N^4-phenyl-1,3,5-triazine-2,4-diamine (**15a**)*

Yield: 85 %; Light red solid; mp 188–190 °C; IR (KBr) *v* max: 3853, 3735, 2927, 2360, 1600, 1514, 1430, 1314, 1290, 1188 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.1 (brs, 1H, NH), 7.9 (d, $J = 8.0$ Hz, 1H, ArH), 7.6 (m, 5H, ArH), 7.38 (t, $J = 8.0$ Hz, 4H, ArH), 7.1 (m, 3H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO d_6): δ 164.5 (C, *s*-triazine), 163.9 (C, *s*-triazine-C), 163.8 (C, *s*-triazine-C), 162.4 (C, N=C–NH), 149.9 (C_{Ar}), 143.7 (C_{Ar}), 141.6 (C_{Ar}), 139.7 (C_{Ar}), 128.3 (C_{Ar}), 127.7 (C_{Ar}), 124.8 (C_{Ar}), 124.5 (C_{Ar}), 121.9 (C_{Ar}), 120.1 (C_{Ar}), 119.5 (C_{Ar}), 119.2 (C_{Ar}), 118.9 (C_{Ar}), 110.5 (C_{Ar}); Mass (ESI–MS): *m/z* 414 $[M + H]^+$. HRMS calcd for $C_{22}H_{16}ClN_7O$ 414.13641 Found: 414.13452.

*N^2-(4-(1H-benzo[d]imidazol-2-yl)phenyl)-6-chloro-N^4-(4-methoxyphenyl)-1,3,5-triazine-2,4-diamine (**15b**)*

Yield: 89 %; Light red solid; mp 195–197 °C; IR (KBr) *v* max: 3390, 3291, 3112, 2925, 1732, 1614, 1575, 1552, 1505, 1476, 1279, 1187, 1109, 1030 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.07 (m, 3H, ArH), 7.9 (s, 1H, ArH), 7.6 (m, 4H, ArH), 7.29 (s, 2H, ArH), 6.90 (s, 2H, ArH), 3.82 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO d_6): δ 163.8 (C, *s*-triazine), 163.3 (C, *s*-triazine), 163.2 (C, *s*-triazine), 160.7 (C, N=C–NH), 157.8 (C_{Ar}), 155.3 (C_{Ar}), 150.7 (C_{Ar}), 139.7 (C_{Ar}), 137.9 (C_{Ar}), 126.5 (C_{Ar}), 123.3 (C_{Ar}), 122.3 (C_{Ar}), 121.5 (C_{Ar}), 119.5 (C_{Ar}), 113.9 (C_{Ar}), 113.0 (C_{Ar}), 54.6 (C, O–CH_3); Mass (ESI–MS): *m/z* 444 $[M + H]^+$. HRMS calcd for $C_{23}H_{18}ClN_7O$ 444.13341 Found: 444.13252.

*N^2-(4-(1H-benzo[d]imidazol-2-yl)phenyl)-6-chloro-N^4-(4-fluorophenyl)-1,3,5-triazine-2,4-diamine (**15c**)*

Yield: 83 %; Light red solid; mp 191–193 °C; IR (KBr) *v* max: 3404, 3270, 3059, 2924, 1609, 1617, 1575, 1506, 1450, 1410, 1314, 1276, 1210, 1157, 1044, 1016 cm^{-1}; ^1H

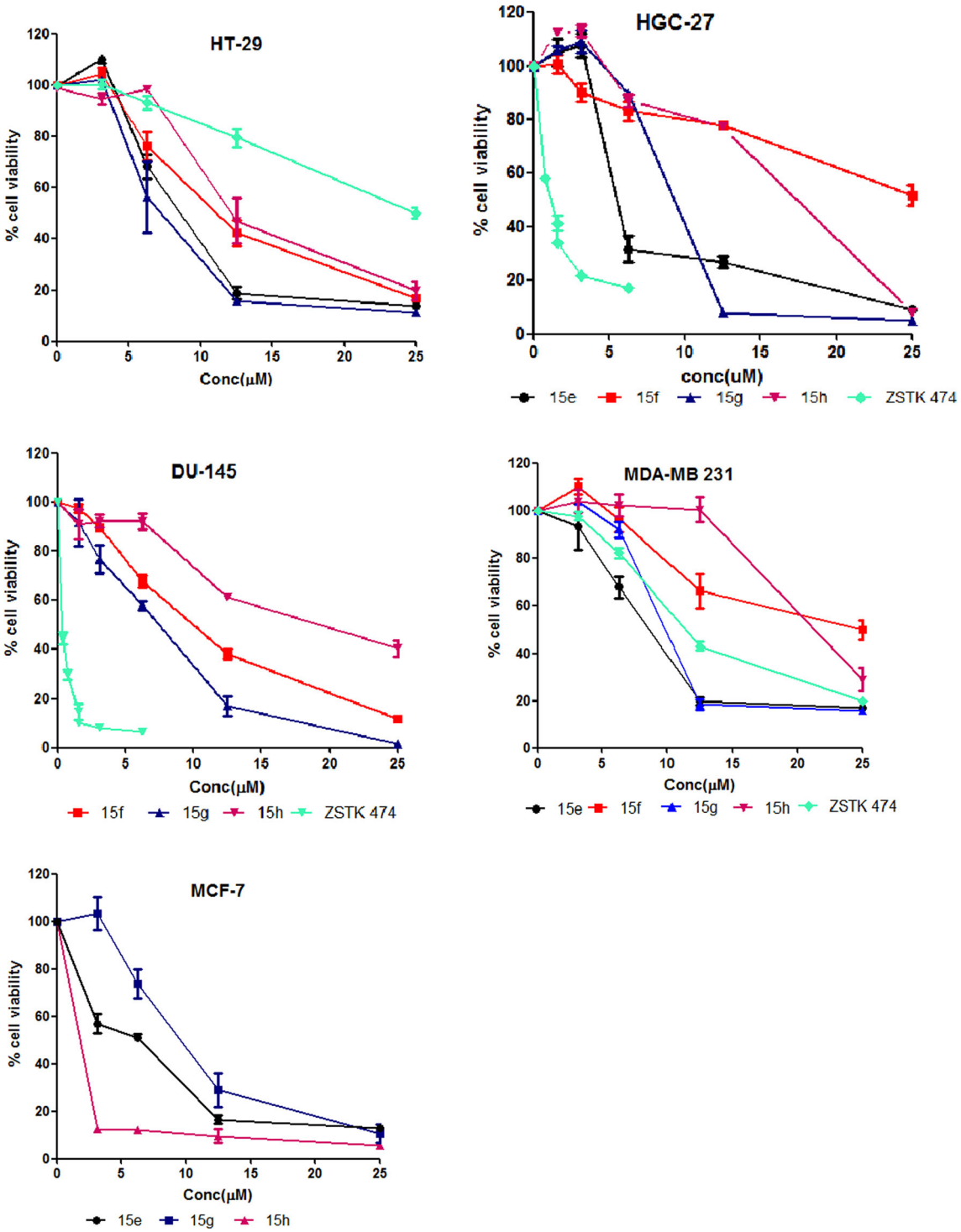
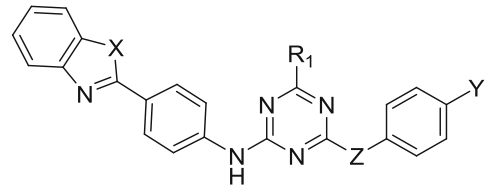


Fig. 1 Dose response curve of *s*-triazine derivatives on human cancer cell lines determined by MTT assay after 48-h treatment

NMR (300 MHz, $CDCl_3$): δ 9.43 (brs, 1H, NH), 9.17 (brs, 1H, NH), 8.13 (d, $J = 9.4$ Hz, 2H, ArH), 8.04 (d, $J = 8.5$ Hz, 2H, ArH), 7.77 (t, $J = 8.5$, 5.6 Hz, 1H, ArH), 7.69 (m, 2H, ArH), 7.58 (m, 1H, ArH), 7.31 (m, 2H, ArH), 7.04 (t, $J = 8.5$ Hz, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO d_6): δ 162.79 (C, *s*-triazine), 162.71 (C, *s*-triazine), 162.5 (C, *s*-triazine), 158.9 (C, N=C–NH), 155.6 (C_{Ar}), 149.6 (C_{Ar}), 136.7 (C_{Ar}), 133.1 (C_{Ar}), 125.8

Table 1 Chemical structures of compounds **13a–h** and their inhibitory effects on the growth of human cancer cell lines



Compound	X	Y	Z	R_1	IC_{50} (μM)					
					MCF-7[a]	MDAMB-231[b]	PC-3[c]	DU-145[d]	HT-29[e]	HGC-27[f]
15a	NH	H	–NH–	Cl	12.1 ± 2.6	19.9 ± 0.66	NA	NA	22.2 ± 2.9	11.1 ± 3.8
15b	NH	OCH_3	–NH–	Cl	NA	NA	NA	NA	NA	NA
15c	NH	F	–NH–	Cl	15.1 ± 1.3	17.4 ± 0.2	NA	NA	16.0 ± 1.15	NA
15d	NH	H	–NH–CH_2–	Cl	NA	NA	NA	NA	NA	NA
16a	S	H	–NH–	Cl	NA	NA	NA	NA	NA	NA
16b	S	OCH_3	–NH–	Cl	NA	NA	NA	NA	NA	NA
16c	S	F	–NH–	Cl	NA	NA	NA	NA	NA	NA
16d	S	H	–NH–CH_2–	Cl	14.7 ± 098	NA	NA	NA	NA	NA
15e	NH	H	–NH–		4.8 ± 0.5	8.3 ± 1.1	NA	NA	9.8 ± 0.4	15.1 ± 0.2
15f	NH	OCH_3	–NH–		NA	25.1 ± 0.13	NA	18.6 ± 0.4	11.5 ± 1.6	24.6 ± 0.8
15g	NH	F	–NH–		9.5 ± 1.6	10.3 ± 0.2	13.5 ± 0.5	10.7 ± 1.7	8.3 ± 0.77	9.2 ± 0.03
15h	NH	H	–NH–CH_2–		7.02 ± 3.9	18.6 ± 3.1	NA	20.3 ± 1.6	15.6 ± 2.2	16.7 ± 0.01
16e	S	H	–NH–		NA	NA	NA	NA	NA	NA
16f	S	OCH_3	–NH–		NA	NA	NA	NA	NA	NA

Table 1 continued

Compound	X	Y	Z	R_1	IC_{50} (μM)					
					MCF-7[a]	MDAMB-231[b]	PC-3[c]	DU-145[d]	HT-29[e]	HGC-27[f]
16g	S	F	–NH–		NA	NA	NA	NA	NA	NA
16h	S	H	–NH–CH_2–		NA	NA	NA	NA	NA	NA
ZSTK474 (Yaguch *et al.*, 2006)					ND**	10.8 ± 0.2	11.7 ± 1.2	0.25 ± 0.06	25.1 ± 1.1	1.11 ± 0.05

* NA—not active (compounds showing less than 50 % cytotoxicity up to 100 μM concentration)

** ND—not determined

[a] MCF-7 (breast cancer ER +ve), [b] MDA-MB 231 (TNBC), [c] PC3 (prostate), [d] DU145 (prostate), [e] HT 29 (colon cancer), [f] HGC-27 (gastric cancer)

(C_{Ar}), 122.0 (C_{Ar}), 121.8 (C_{Ar}), 121.7 (C_{Ar}), 121.2 (C_{Ar}), 119.0 (C_{Ar}), 113.9 (C_{Ar}), 113.8 (C_{Ar}), 113.5 (C_{Ar}), 113.2 (C_{Ar}); Mass (ESI–MS): *m/z* 432 $[M + H]^+$. HRMS calcd for $C_{22}H_{15}ClFN_7$ 432.11343 Found: 432.11254.

*N^2-(4-(1H-benzo[d]imidazol-2-yl)phenyl)-N^4-benzyl-6-chloro-1,3,5-triazine-2,4-diamine (**15d**)*

Yield: 92 %; Light red solid; mp 194–196 °C; IR (KBr) *v* max: 3854, 3734, 3640, 3367, 3260, 3116, 2926, 2852, 2371, 1610, 1575, 1451, 1410, 1353, 1247, 1192, 1120, 1060 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.1 (brs, 1H, NH), 7.9 (d, $J = 8.0$ Hz, 1H, ArH), 7.6 (m, 5H, ArH), 7.38 (t, $J = 8.0$ Hz, 4H, ArH), 7.1 (m, 3H, ArH), 4.5 (m, 2H, Ar–CH_2); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO d_6): δ 168.0 (C, *s*-triazine), 165.5 (C, *s*-triazine), 163.4 (C, *s*-triazine), 151.3 (C, NH–C=N), 139.9 (C_{Ar}), 138.6 (C_{Ar}), 138.0 (C_{Ar}), 128.0 (C_{Ar}), 127.2 (C_{Ar}), 126.8 (C_{Ar}), 126.6 (C_{Ar}), 126.5 (C_{Ar}), 123.8 (C_{Ar}), 121.7 (C_{Ar}), 119.7 (C_{Ar}), 114.3 (C_{Ar}), 44.0 (C, Ph–CH2–NH–); Mass (ESI–MS): *m/z* 428 $[M + H]^+$. HRMS calcd for $C_{23}H_{18}ClN_7$ 428.13850 Found: 428.13700.

*N^2-(4-(benzo[d]thiazol-2-yl)phenyl)-6-chloro-N^4-phenyl-1,3,5-triazine-2,4-diamine (**16a**)*

Yield: 88 %; Grey solid; mp 150–152 °C; IR (KBr) *v* max: 3838, 3735, 3392, 3274, 2924, 1601, 1570, 1507, 1496, 1412, 1225, 1181, 988, 966, 836, 802, 756 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.01 (m, 5H, ArH), 7.92 (d, $J = 8.1$ Hz, 2H, ArH), 7.81 (d, $J = 7.6$ Hz, 1H, ArH), 7.66 (d, $J = 7.6$ Hz, 1H, ArH) 7.48 (t, $J = 7.6$, Hz, 1H, ArH), 7.37 (m, 3H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO d_6): δ 165.8 (C, *s*-triazine), 163.8 (C, *s*-triazine), 163.6 (C, *s*-triazine), 162.0 (C, S–C=N), 150.0 (C_{Ar}), 141.8 (C_{Ar}), 141.5 (C_{Ar}), 128.5 (C_{Ar}), 127.7 (C_{Ar}), 125.0 (C_{Ar}), 124.6 (C_{Ar}), 120.6 (C_{Ar}), 120.3 (C_{Ar}), 120.1 (C_{Ar}), 110.6 (C_{Ar}); Mass (ESI–MS): *m/z* 431$[M + H]^+$. HRMS calcd for $C_{22}H_{15}ClN_6S$ 431.08402 Found: 431.08357.

*N^2-(4-(benzo[d]thiazol-2-yl)phenyl)-6-chloro-N^4-(4-methoxyphenyl)-1,3,5-triazine-2,4-diamine (**16b**)*

Yield: 91 %; Grey solid; mp 156–158 °C; IR (KBr) *v* max: 3854, 3735, 3397 3274, 3060, 2927, 2360, 1601, 1573, 1508, 1411, 1227, 1180, 1034, 829, 755 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.07 (m, 3H, ArH), 7.9 (s, 1H, ArH), 7.6 (m, 4H, ArH), 7.38 (s, 2H, ArH), 6.9 (s, 2H, ArH), 3.8 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO d_6): δ 166.8 (C, *s*-triazine), 166.2 (C, *s*-triazine), 162.3 (C, *s*-triazine), 153.4 (C, S–C=N), 134.0 (C_{Ar}), 127.2 (C_{Ar}), 125.7 (C_{Ar}), 124.4 (C_{Ar}), 123.4 (C_{Ar}), 123.2 (C_{Ar}), 122.5 (C_{Ar}), 122.1 (C_{Ar}), 121.1 (C_{Ar}), 120.2 (C_{Ar}), 119.9 (C_{Ar}), 113.3 (C_{Ar}), 113.2 (C_{Ar}), 113.1 (C_{Ar}), 54.8 (O–CH_3); Mass

(ESI–MS): *m/z* 460 $[M]^+$. HRMS calcd for $C_{23}H_{17}ClN_6OS$ 461.09458 Found: 461.09507.

*N^2-(4-(benzo[d]thiazol-2-yl)phenyl)-6-chloro-N^4-(4-fluorophenyl)-1,3,5-triazine-2,4-diamine (**16c**)*

Yield: 85 %; Grey solid; mp 155–157 °C; IR (KBr) ν max: 3853, 3393, 3274, 3058, 2924, 1613, 1573, 1505, 1410, 1314, 1227, 1014, 967, 832, 863, 756, 726, 550, 508 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.01 (m, 5H, ArH), 7.9 (d, $J = 8.0$ Hz, 1H, ArH), 7.6 (m, 2H), 7.44 (t, $J = 8.0$ Hz, 1H, ArH), 7.38 (t, $J = 8.0$ Hz, 1H, ArH), 7.1 (m, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO d_6): δ 166.7 (C, *s*-triazine), 153.4 (C, S–C=N), 140.9 (C_{Ar}), 134.0 (C_{Ar}), 127.4 (C_{Ar}), 127.2 (C_{Ar}), 125.7 (C_{Ar}), 124.4 (C_{Ar}), 123.1 (C_{Ar}), 122.1 (C_{Ar}), 121.1 (C_{Ar}), 120.4 (C_{Ar}), 120.0 (C_{Ar}), 115.0 (C_{Ar}), 114.7 (C_{Ar}), 114.4 (C_{Ar}); Mass (ESI–MS): *m/z* 449 $[M + H]^+$. HRMS calcd for $C_{22}H_{14}ClFN_6S$ 449.07460 Found: 449.07486.

*N^2-(4-(benzo[d]thiazol-2-yl)phenyl)-N^4-benzyl-6-chloro-1,3,5-triazine-2,4-diamine (**16d**)*

Yield: 87 %; Grey solid; mp 222–224 °C; IR (KBr) ν max: 3839, 3735, 3264, 3217, 3056, 2832, 2780, 1699, 1628, 1578, 1530, 1393, 1240, 1227, 796, 758, 726, 549, 534 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.93 (d, $J = 8.1$ Hz, 2H, ArH), 7.88 (d, $J = 8.1$ Hz, 2H, ArH), 7.80 (s, 1H), 7.73 (m, 1H, ArH), 7.42 t, $J = 7.6$ 1H, ArH), 7.3 (m, 5H, ArH) 7.1 (m, 1H, ArH), 4.5 (m, 2H, Ar–CH_2); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO d_6): δ 165.6 (C, *s*-triazine), 162.4 (C, *s*-triazine), 162.1 (C, *s*-triazine), 150.0 (C, S–C=N), 141.6 (C_{Ar}), 138.7 (C_{Ar}), 128.3 (C_{Ar}), 127.8 (C_{Ar}), 127.2 (C_{Ar}), 126.8 (C_{Ar}), 125.0 (C_{Ar}), 124.8 (C_{Ar}), 124.6 (C_{Ar}), 119.8 (C_{Ar}), 119.6 (C_{Ar}), 119.4 (C_{Ar}), 119.1 (C_{Ar}), 110.6 (C_{Ar}), 43.9 (C, Ph–CH_2–NH–); Mass (ESI–MS): *m/z* 445 $[M + H]^+$. HRMS calcd for $C_{23}H_{17}ClN_6S$ 445.09967 Found: 445.09997.

General procedure for synthesis of tri-substituted triazines (15e–h and 16e–h)

To a solution of di-substituted *s*-triazine derivatives **15a–d** and **16a–d** (1 mmol) in dry DMF, was added K_2CO_3 (2.5 mmol), and the reaction mixture was stirred for 5 min, at room temperature. Morpholine **17** (1 mmol) was added to the reaction mixture and stirred at 24 h at reflux temperature. After completion of the reaction K_2CO_3 was decanted and the DMF was removed, water was added and extracted with EtOAc. The organic layer was dried over Na_2SO_4 concentrated and purified by using silica gel column chromatography to give the desired tri-substituted triazine derivatives in quantitative yields.

*N^2-(4-(1H-benzo[d]imidazol-2-yl)phenyl)-6-morpholino-N^4-phenyl-1,3,5-triazine-2,4-diamine (**15e**)*

Yield: 89 %; Light red solid; mp 182–184 °C; IR (KBr) *v* max: 3459, 3284, 3208, 2947, 2860, 1593, 1559, 1483, 1419, 1305, 1274, 1232, 1108, 1027, 804, 737 cm^{-1}; ^1H NMR (300 MHz, DMSO d_6): δ 9.58 (brs, 1H, NH), 8.01 (d, $J = 9.0$ Hz, 2H, ArH), 7.82 (brs, 1H, NH), 7.74 (d, $J = 9.0$ Hz, 2H, ArH), 7.57 (d, $J = 8.0$ Hz, 2H, ArH), 7.47 (brs, 1H, NH), 7.34 (t, $J = 8.0$, 7.0 Hz, 3H, ArH), 7.10 (m, 1H, ArH), 6.84 (s, 2H, ArH), 3.85 (t, $J = 5.0$ Hz, 4H, O–CH_2), 3.77 (t, $J = 5.0$, 4.0 Hz, 4H, N–CH_2); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO d_6): δ 164.6 (C, *s*-triazine), 164.1 (C, *s*-triazine), 164.0 (C, *s*-triazine), 151.4 (C, NH–C=N), 143.8 (C_{Ar}), 141.8 (C_{Ar}), 139.9 (C_{Ar}), 134.9 (C_{Ar}), 128.4 (C_{Ar}), 126.8 (C_{Ar}), 123.2 (C_{Ar}), 122.1 (C_{Ar}), 122.0 (C_{Ar}), 121.5 (C_{Ar}), 119.6 (C_{Ar}), 118.4 (C_{Ar}), 111.0 (C_{Ar}), 66.0 (2C, CH_2–O–CH_2), 43.4 (2C, CH_2–N–CH_2); Mass (ESI–MS): *m/z* 465 $[M + H]^+$. HRMS calcd for $C_{26}H_{24}N_8O$ 465.21458 Found: 465.21463.

*N^2-(4-(1H-benzo[d]imidazol-2-yl)phenyl)-N^4-(4-methoxyphenyl)-6-morpholino-1,3,5-triazine-2,4-diamine (**15f**)*

Yield: 92 %; Light red solid; mp 168–170 °C; IR (KBr) *v* max: 3276, 2958, 2922, 2853, 2366, 1541, 1491, 1420, 1239, 1181, 1110, 1023, 805, 744 cm^{-1}; ^1H NMR (300 MHz, DMSO d_6): δ 8.47 (brs, 1H, NH), 8.11 (d, $J = 8.4$ Hz, 2H, ArH), 7.85 (d, $J = 8.4$ Hz, 2H, ArH), 7.70 (s, 2H, ArH), 7.57 (d, $J = 8.7$ Hz, 2H, ArH), 7.49 (brs, 1H, ArH), 7.19 (m, 2H, ArH), 6.87 (d, $J = 8.6$ Hz, 2H, ArH), 3.83 (s, 4H, O–CH_2), 3.80 (s, 3H, OCH_3), 3.75 (s, 3H, N–CH_2); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO d_6): δ 164.6 (C, *s*-triazine), 163.8 (C, *s*-triazine), 163.7 (C, *s*-triazine), 154.4 (C, NH–C=N), 151.4 (C_{Ar}), 141.7 (C_{Ar}), 141.6 (C_{Ar}), 132.6 (C_{Ar}), 126.6 (C_{Ar}), 122.8 (C_{Ar}), 121.6 (C_{Ar}), 121.3 (C_{Ar}), 119.3 (C_{Ar}), 119.2 (C_{Ar}), 113.3 (C_{Ar}), 110.7 (C_{Ar}), 65.9 (2C, CH_2–O–CH_2), 54.9 (C, O–CH_3), 43.3 (2C, CH_2–N–CH_2); Mass (ESI–MS): *m/z* 495 $[M + H]^+$. HRMS calcd for $C_{27}H_{26}N_8O_2$ 495.22515 Found: 495.22378.

*N^2-(4-(1H-benzo[d]imidazol-2-yl)phenyl)-N^4-(4-fluorophenyl)-6-morpholino-1,3,5-triazine-2,4-diamine (**15g**)*

Yield: 84 %; Light red solid; mp 178–180 °C; IR (KBr) *v* max: 3422, 3283, 3190, 2964, 2922, 2855, 1609, 1578, 1542, 1498, 1429, 1265, 1210, 1111, 1014, 899, 744 cm^{-1}; ^1H NMR (300 MHz, DMSO d_6): δ 12.48 (brs, 1H, NH), 8.99 (brs, 1H, NH), 8.86 (brs, 1H, NH), 8.10 (d, $J = 7.8$ Hz, 2H, ArH), 7.90 (d, $J = 7.8$ Hz, 3H, ArH),

7.69 (m, 3H, ArH), 7.48 (s, 1H, ArH), 7.18 (m, 2H, ArH), 7.02 (t, $J = 7.8$, 9.0 Hz, 2H, ArH), 3.83 (t, 4H, O–CH_2), 3.74 (t, 4H, N–CH_2); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO d_6): δ 164.6 (C, *s*-triazine), 163.8 (C, *s*-triazine), 158.9 (C, *s*-triazine), 151.4 (C, NH–C=N), 143.7 (C_{Ar}), 141.7 (C_{Ar}), 136.1 (C_{Ar}), 134.8 (C_{Ar}), 126.6 (C_{Ar}), 123.1 (C_{Ar}), 121.8 (C_{Ar}), 121.6 (C_{Ar}), 121.3 (C_{Ar}), 119.4 (C_{Ar}), 118.2 (C_{Ar}), 114.8 (C_{Ar}), 114.5 (C_{Ar}), 110.8 (C_{Ar}), 65.9 (2C, CH_2–O–CH_2), 43.3 (2C, CH_2–N–CH_2); Mass (ESI–MS): *m/z* 483 $[M + H]^+$. HRMS calcd for $C_{26}H_{23}FN_8O$ 483.20516 Found: 483.20503.

*N^2-(4-(1H-benzo[d]imidazol-2-yl)phenyl)-N^4-benzyl-6-morpholino-1,3,5-triazine-2,4-diamine (**15h**)*

Yield: 86 %; Light red solid; mp 166–168 °C; IR (KBr) *v* max: 3297, 2961, 2921, 2855, 1497, 1430, 1275, 1112, 1023, 807, 745 cm^{-1}; ^{1}H NMR (300 MHz, DMSO d_6): δ 8.1 (d, $J = 9.0$ Hz, 1H, ArH), 7.7 (d, $J = 9.0$ Hz, 1H, ArH), 7.5 (d, $J = 8.0$ Hz, 1H, ArH), 7.34 (t, $J = 8.0$ Hz, 2H, ArH), 7.18 (m, 3H, ArH), 6.90 (m, 3H, ArH), 6.81 (s, 2H, ArH), 4.5 (m, 2H, Ar–CH_2), 3.83 (s, 4H, O–CH_2), 3.75 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO d_6): δ 164.5 (C, *s*-triazine), 163.8 (C, *s*-triazine), 151.5 (C, *s*-triazine), 145.3 (C, NH–C=N), 140.1 (C_{Ar}), 127.8 (C_{Ar}), 127.8 (C_{Ar}), 127.1 (C_{Ar}), 126.8 (C_{Ar}), 126.7 (C_{Ar}), 126.6 (C_{Ar}), 126.5 (C_{Ar}), 126.2 (C_{Ar}), 122.5 (C_{Ar}), 121.4 (C_{Ar}), 119.0 (C_{Ar}), 65.9 (2C, CH_2–O–CH_2), 48.4 (C, Ph–CH_2–NH–), 43.1 (2C, CH_2–N–CH_2); Mass (ESI–MS): *m/z* 478 $[M + H]^+$. HRMS calcd for $C_{27}H_{26}N_8O$ 479.23023 Found: 479.23049.

*N^2-(4-(benzo[d]thiazol-2-yl)phenyl)-6-morpholino-N^4-phenyl-1,3,5-triazine-2,4-diamine (**16e**)*

Yield: 90 %; Grey solid; mp 149–151 °C; IR (KBr) *v* max: 3394, 3296, 2922, 2852, 2365, 2345, 1497, 1410, 1312, 1226, 1178, 1111, 965, 754 cm^{-1}; ^{1}H NMR (300 MHz, DMSO d_6): δ 9.10 (brs, 1H, NH), 8.69 (brs, 1H, NH), 8.13 (d, $J = 9.0$ Hz, 2H, ArH), 7.97 (d, $J = 9.0$ Hz, 2H, ArH), 7.81 (m, 2H, ArH), 7.70 (m, 2H, ArH), 7.59 (m, 1H, ArH), 7.32 (m, 3H, ArH), 7.00 (t, $J = 7.1$ Hz, 1H, ArH), 3.85 (t, $J = 5.0$ Hz, 4H, O–CH_2), 3.75 (t, $J = 5.0$ Hz, 4H, N–CH_2); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO d_6): δ 164.6 (C, *s*-triazine), 164.0 (C, *s*-triazine), 163.9 (C, *s*-triazine), 151.4 (C, S–C=N), 143.8 (C_{Ar}), 141.7 (C_{Ar}), 139.8 (C_{Ar}), 134.8 (C_{Ar}), 128.3 (C_{Ar}), 126.7 (C_{Ar}), 123.2 (C_{Ar}), 122.0 (C_{Ar}), 121.9 (C_{Ar}), 121.4 (C_{Ar}), 120.1 (C_{Ar}), 118.5 (C_{Ar}), 118.4 (C_{Ar}), 110.9 (C_{Ar}), 65.9 (2C, CH_2–O–CH_2), 43.3 (2C, CH_2–N–CH_2); Mass (ESI–MS): *m/z* 482 $[M + H]^+$. HRMS calcd for $C_{26}H_{23}N_7OS$ 482.17576 Found: 482.17597.

*N^2-(4-(benzo[d]thiazol-2-yl)phenyl)-N^4-(4-methoxyphenyl)-6-morpholino-1,3,5-triazine-2,4-diamine (**16f**)*

Yield: 82 %; Grey solid; mp 153–155 °C; IR (KBr) ν max: 3394, 3310, 3058, 2957, 2899, 2853, 1601, 1496, 1411, 1241, 1179, 1112, 1024, 966, 828, 804 cm^{-1}; ^{1}H NMR (300 MHz, DMSO d_6): δ 9.03 (brs, 1H, NH), 8.54 (brs, 1H, NH), 7.99 (m, 4H, ArH), 7.94 (d, $J = 6.6$ Hz, 2H, ArH), 7.60 (d, $J = 8.8$ Hz, 2H, ArH), 7.48 (t, $J = 7.4$, 6.6 Hz, 1H, ArH), 7.38 (t, $J = 7.4$, 6.6 Hz, 2H, ArH), 6.86 (d, $J = 8.8$ Hz, 2H, ArH), 3.83 (s, 4H, O–CH_2), 3.80 (s, 3H, OCH_3), 3.75 (s, 4H, N–CH_2); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO d_6): δ 167.1 (C, *s*-triazine), 163.7 (C, *s*-triazine), 164.6 (C, *s*-triazine), 153.6 (C, S–C=N), 154.4 (C_{Ar}), 143.2 (C_{Ar}), 134.0 (C_{Ar}), 132.6 (C_{Ar}), 127.3 (C_{Ar}), 126.0 (C_{Ar}), 125.7 (C_{Ar}), 124.5 (C_{Ar}), 122.1 (C_{Ar}), 121.5 (C_{Ar}), 119.3 (C_{Ar}), 65.9 (2C, CH_2–O–CH_2), 54.8 (C, O–CH_3), 43.3 (2C, CH_2–N–CH_2); Mass (ESI–MS): *m/z* 512 $[M + H]^+$. HRMS calcd for $C_{27}H_{25}N_7O_2S$ 512.18632 Found: 512.18488.

*N^2-(4-(benzo[d]thiazol-2-yl)phenyl)-N^4-(4-fluorophenyl)-6-morpholino-1,3,5-triazine-2,4-diamine (**16g**)*

Yield: 89 %; Grey solid; mp 152–154 °C; IR (KBr) *v* max: 3398, 3296, 2922, 2852, 2367, 2345, 1576, 1498, 1409, 1222, 966, 831, 757 cm^{-1}; ^{1}H NMR (300 MHz, DMSO d_6): δ 8.57 (brs, 1H, NH), 8.30 (brs, 1H, NH), 8.12 (d, $J = 8.1$ Hz, 2H, ArH), 7.86 (d, $J = 8.1$ Hz, 2H, ArH), 7.70 (d, $J = 7.7$ Hz, 2H, ArH), 7.64 (s, 1H, ArH), 7.49 (brs, 1H, NH), 7.31 (t, $J = 7.3$, 7.7 Hz, 2H, ArH), 7.19 (m, 2H, ArH), 7.01 (t, $J = 7.3$ Hz, 1H, ArH), 3.85 (s, 4H, O–CH_2), 3.76 (s, 4H, N–CH_2); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO d_6): δ 167.0 (C, *s*-triazine), 164.5 (C, *s*-triazine), 163.8 (C, *s*-triazine), 153.6 (C, S–C=N), 142.8 (C_{Ar}), 134.1 (C_{Ar}), 127.4 (C_{Ar}), 126.2 (C_{Ar}), 126.0 (C_{Ar}), 124.6 (C_{Ar}), 122.2 (C_{Ar}), 121.6 (C_{Ar}), 119.8 (C_{Ar}), 119.4 (C_{Ar}), 114.7 (C_{Ar}), 114.6 (C_{Ar}), 114.4 (C_{Ar}), 114.3 (C_{Ar}), 65.9 (2C, CH_2–O–CH_2), 43.1 (2C, CH_2–N–CH_2); Mass (ESI–MS): *m/z* 500 $[M + H]^+$. HRMS calcd for $C_{26}H_{22}FN_7OS$ 500.18342 Found: 500.18108.

*N^2-(4-(benzo[d]thiazol-2-yl)phenyl)-N^4-benzyl-6-morpholino-1,3,5-triazine-2,4-diamine (**16h**)*

Yield: 85 %; Grey solid; mp 158–160 °C; IR (KBr) *v* max: 3291, 3186, 3058, 2957, 2920, 2851, 1667, 1575, 1478, 1249, 1176, 1114, 965, 697 cm^{-1}; ^{1}H NMR (300 MHz, DMSO d_6): δ 8.14 (d, $J = 9.0$ Hz, 1H, ArH), 7.78 (d, $J = 9.0$ Hz, 1H, ArH), 7.52 (d, $J = 8.0$ Hz, 1H, ArH), 7.34 (t, $J = 8.0$ Hz, 2H, ArH), 7.16 (m, 3H, ArH), 6.93 (m, 3H, ArH), 6.85 (s, 2H, ArH), 4.50 (m, 2H, Ar–CH_2), 3.83

(s, 4H, O–CH_2), 3.75 (s, 4H, N–CH_2); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO d_6): δ 167.1 (C, *s*-triazine), 165.5 (C, *s*-triazine), 164.6 (C, *s*-triazine), 163.9 (C, S–C=NH), 153.6 (C_{Ar}), 140.2 (C_{Ar}), 134.0 (C_{Ar}), 127.9 (C_{Ar}), 127.4 (C_{Ar}), 127.2 (C_{Ar}), 126.7 (C_{Ar}), 126.3 (C_{Ar}), 126.1 (C_{Ar}), 125.4 (C_{Ar}), 124.7 (C_{Ar}), 121.7, 119.1 (C_{Ar}), 65.9 (2C, CH_2–O–CH_2), 43.2 (2C, CH_2–N–CH_2), 43.0 (C, Ph–CH_2–NH–); Mass (ESI–MS): *m/z* 496 $[M + H]^+$. HRMS calcd for $C_{27}H_{25}N_7OS$ 496.19141 Found: 496.19017.

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