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Original article

Synthesis and antileishmanial activity of novel 2,4,6-trisubstituted pyrimidines and 1,3,5-triazines

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ABSTRACT

A series of 2,4,6-trisubstituted pyrimidines and 1,3,5-triazines have been synthesized and screened for their *in vitro* and *in vivo* antileishmanial activity against *Leishmania donovani*. Among all, 14 compounds have shown promising inhibition of **80–100%** at 10 μg/ml against promastigotes and IC_{50} in the range of **0.89–9.68** μg/ml against amastigotes. Three compounds **13**, **32** and **33** with good selectivity index (S.I.) were screened for their *in vivo* activity in golden hamsters (*Mesocricetus auratus*) infected with MHOM/IN/80/Dd_8 strain of *L. donovani* and have shown moderate *in vivo* inhibition of **48–56%** at a dose of 50 mg/kg × 5, i.p. route for 5 days.

1. Introduction

Leishmaniasis, a parasitic disease caused by protozoal species of the genus *Leishmania* is transmitted by the bite of more than 30 different species of sand flies [1]. This disease is currently prevalent in four continents, being endemic in 88 countries. The most severe form, visceral leishmaniasis (VL), known as kala-azar, is nearly always fatal if not treated. It is estimated that about half a million people die annually with visceral leishmaniasis and over 350 million people live at risk of this infection [2]. In spite of this, AIDS and other immunosuppressive conditions have also enhanced the risk of Leishmania–HIV co-infected people and contributed to the appearance of new severe clinical forms of the disease [3]. The current chemotherapy to the leishmaniasis still poses a serious problem. The drugs of first choice are pentavalent antimonial compounds, which were developed before 1960, and in general, require long-term treatment and have severe side effects. But leishmania parasites have developed resistance to these antimonials since 1990s [4]. Presently, amphotericin B and the oral anticancer drug miltefosine are considered to be the best second-line therapeutic solutions. Nevertheless, they do not represent a safe treatment in all clinical cases [5]. So, there is an urgent need to develop safer, cheaper and more effective chemotherapy.

Dihydrofolate reductase (DHFR) has successfully been used as a drug target in the area of parasitic diseases. But most of the clinically used DHFR inhibitors show less selectivity for leishmanial enzymes [6]. This is due to the over expression of the gene pteridine reductase (PTR1) in some leishmanial mutants. This PTR1 has ability to provide reduced pterins and folates and has the potential to act as a by-pass or modulator of DHFR inhibition. Thus to stop the folate biosynthesis that is essential for the survival of leishmania, both PTR1 and DHFR have to be inhibited [7]. Selective inhibitors of PTR1 or a single inhibitor that acts on both enzymes would constitute a rational approach for new antileishmanial agents. Earlier, pyrimidines were synthesized and evaluated as inhibitors of leishmanial and trypanosomal dihydrofolate reductase [8], while triazine class of compounds being the inhibitors of DHFR [9–11] have also been identified as potential antileishmanial agents [12,13]. Based on these observations we have designed and synthesized a class of hybrid molecules having pyrimidine along with triazine moiety and substituted pyrimidines.

As our ongoing research devoted to the synthesis of diverse heterocycles as anti-infective agents, we had previously reported antiparasitic activity in substituted pyrimidines, pyridines, triazines, and quinolines [12–22]. This communication describes the synthesis and *in vitro*, *in vivo* antileishmanial activity of 2,4,6-trisubstituted pyrimidines and 1,3,5-triazines.

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2. Chemistry

To synthesize the 2,4,6-trisubstituted-1,3,5-triazine compounds (**8**–**29**), substituted acetophenone was reacted with CS_2 in the presence of NaH in dry THF, followed by methylation with methyl iodide [23] to yield corresponding 3,3-bis-methylsulfanyl-1-(substituted-phenyl)-propenones (**1**, **2**). The compounds **1**, **2** were cyclized with guanidine hydrochloride in the presence of sodium hydride in DMF [24] to obtain corresponding 4-(substituted-phenyl)-6-methylsulfanyl-pyrimidin-2-ylamines (**3**, **4**). Compounds **3**, **4** were further reacted with cyanuric chloride (2,4,6-trichloro-1,3,5-triazine) in the presence of K_2CO_3 in dry THF to obtain the corresponding (4,6-dichloro-[1,3,5]triazin-2-yl)-[4-(substituted-phenyl)-6-methylsulfanyl-pyrimidin-2-yl]-amines (**5**, **6**), which were subjected to nucleophilic substitution with different amines (Table 1) to afford the final targeted compounds (Scheme 1).

To synthesize 2,4,6-trisubstituted pyrimidines, **3** was oxidized to corresponding sulfone 4-(methylsulfonyl)-6-(3,4,5-trimethoxyphenyl)pyrimidin-2-amine (**7**) in the presence of *m*-chloroperoxybenzoic acid (2.5 equiv) in dry DCM. The sulfone **7** was subjected to nucleophilic substitution with various amines (Table 1) in closed steel vessel to yield targeted compounds **30**–**36** [24]. All the synthesized compounds were well characterized by spectroscopic methods such as IR, mass, NMR and elemental analyses.

3. Biological activities

3.1. Materials and methods

3.1.1. Antipromastigote activity

The *Leishmania donovani* promastigotes (MHOM/IN/80/Dd_8; originally obtained from Imperial College, London) were transfected with firefly luciferase gene and the transfectants were maintained in medium 199 (Sigma Chemical Co., USA) supplemented with 10% foetal calf serum (GIBCO) and 1% penicillin (50 U/ml), streptomycin (50 μg/ml) solution (Sigma) under pressure of G418 (Sigma). The *in vitro* effect of the compounds on the growth of promastigotes was assessed by monitoring the luciferase activity of viable cells after treatment. The transgenic promastigotes of late log phase were seeded in 5×10^5/100 μl medium 199 in 96-well flat-bottomed microtiter (MT) plates (CELLSTAR) and incubated for 72 h in medium alone or in the presence of serial dilutions of drugs (1–10 μg/ml) in DMSO [25]. Parallel dilutions of DMSO were used as controls. After incubation, an aliquot (50 μl) of promastigote suspension was aspirated from each well of a 96-well plate and mixed with an equal volume of Steady Glo® reagent (Promega) and luminescence was measured by a luminometer. The values were expressed as relative luminescence unit (RLU). The inhibition of parasitic growth is determined by comparison of the luciferase activity of drug treated parasites with that of untreated controls by the general formula:

$$\text{Percentageinhibition} = \frac{N - n \times 100}{N}$$

where N is average relative luminescence unit (RLU) of control wells and n is average RLU of treated wells.

3.1.2. Antiamastigote activity

In vitro activity: For assessing the activity of compounds against the amastigote stage of the parasite, mouse macrophage cell line (J774A.1) infected with promastigotes expressing luciferase firefly reporter gene was used. Cells were seeded in a 96-well plate (1.5×10^4 cells/100 μl/well) in RPMI-1640 containing 10% foetal calf serum and the plates were incubated at 37 °C in a CO_2 incubator. After 24 h, the medium was replaced with fresh medium containing stationary phase promastigotes (2.25×10^5/100 μl/well). Promastigotes invade the macrophage and are transformed into amastigotes. The test material in appropriate concentrations (0.25–10 μg/ml) in complete medium was added after replacing the previous medium and the plates were incubated at 37 °C in a CO_2 incubator for 72 h. After incubation, the drug containing medium was decanted and 50 μl PBS was added in each well and mixed with an equal volume of Steady Glo® reagent. After gentle shaking for 1–2 min, the reading was taken in a luminometer [25]. The inhibition of parasitic growth is determined by comparison of the luciferase activity of drug treated parasites with that of untreated controls as described above.

In vivo activity: The *in vivo* leishmanicidal activity was determined in golden hamsters (*Mesocricetus auratus*) infected with MHOM/IN/80/Dd_8 strain of *L. donovani* obtained through the courtesy of P.C.C. Garnham, Imperial College, London (UK). For *in vivo* evaluation of compounds, the method of Beveridge [26] as modified by Bhatnagar et al. [27] and Gupta et al. [28] was employed. Golden hamsters (of either sex) weighing 40–45 g were infected intracardially with 1×10^7 amastigotes per animal. Pretreatment spleen biopsy in all the animals was carried out to assess the degree of infection. The animals with +1 infection (5–15 amastigotes/100 spleen cell nuclei) were included in the chemotherapeutic trials. The infected animals are randomized into several groups on the basis of their parasitic burdens. Four to six animals were used for each test sample. Drug treatment by i.p. route is initiated after 2 days of biopsy and continued for 10 consecutive days. Post-treatment biopsies are done on day 7 of the last drug administration and amastigote counts are assessed by Giemsa staining. Intensity of infection in both, treated and untreated animals, as also the initial count in treated animals is compared and the efficacy is expressed in terms of percentage inhibition (PI) using the following formula:

$$\text{PI} = 100 - (\text{ANAT} \times 100/\text{INAT} \times \text{TIUC})$$

where PI is the percentage inhibition of amastigotes' multiplication; ANAT is Actual Number of amastigotes in treated animals; INAT is Initial Number of amastigotes in treated animals and TIUC is Times Increase of parasites in untreated control animals.

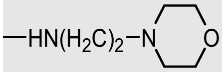
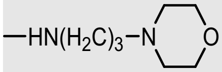
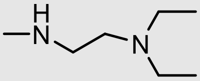
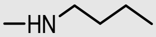
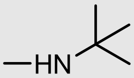
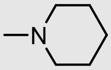
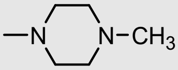
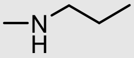
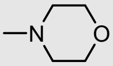
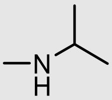
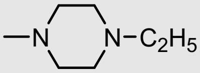
3.1.3. Data analysis

IC_{50} was calculated by Probit analysis [29]. Compounds with more than 15 μg/ml IC_{50} were considered as inactive while compounds with IC_{50} between 15 and 5 μg/ml were considered as moderately active and less than 5 μg/ml are highly active compounds.

3.1.4. Cytotoxicity assay

The cell viability was determined using the MTT assay. J774A.1 cell line was maintained in RPMI medium (Sigma), supplemented with 10% foetal calf serum and 40 mg/ml gentamycin. Exponentially growing cells (1×10^4 cells/100 μl/well) were incubated with different drug concentrations for 72 h and were incubated at 37 °C in a humidified mixture of CO_2 and 95% air in an incubator. Stock solutions of compounds were initially dissolved in DMSO and further diluted with fresh complete medium. After incubation, 25 μl of MTT reagent (5 mg/ml) in PBS medium, followed by syringe filtration were added to each well and incubated at 37 °C for 2 h. At the end of the incubation period, the supernatant was removed by tilting plate completely without disturbing cell layer and 150 μl of pure DMSO are added to each well. After 15 min of shaking the readings were recorded as absorbance at 544 nm on a microplate reader. The cytotoxic effect was expressed as 50% lethal dose, i.e., as

Table 1
Antileishmanial *in vitro* activity against luciferase–promastigote system.

R_2	Comp. no. ($R_1 = OCH_3$)	% Inhibition at 10 μg/ml promastigote	Comp. no. ($R_1 = H$)	% Inhibition at 10 μg/ml promastigote	Comp. no.	% Inhibition at 10 μg/ml promastigote
	**8**	42.5	**19**	NI	**30**	68.5
	**9**	75.2	**20**	35.2	**31**	46.9
	**10**	NI	**21**	94.7	**32**	95.10
	**11**	75.5	**22**	78.6	**33**	84.4
	**12**	95.8	**23**	NI	–	–
	**13**	90.8	**24**	53.8	**34**	88
	**14**	99.5	**25**	99.8	**35**	63.88
	**15**	86.7	**26**	85.6	–	–
	**16**	80.8	**27**	90.5	**36**	43.90
	**17**	94.5	**28**	NI	–	–
	**18**	100	**29**	NI	–	–
Pentamidine®[a]						
SSG® (**sodium stibogluconate**)[b]						

NI: no inhibition.

[a] Pentamidine shows 85–90% inhibition against promastigotes at 0.5 μg/ml.

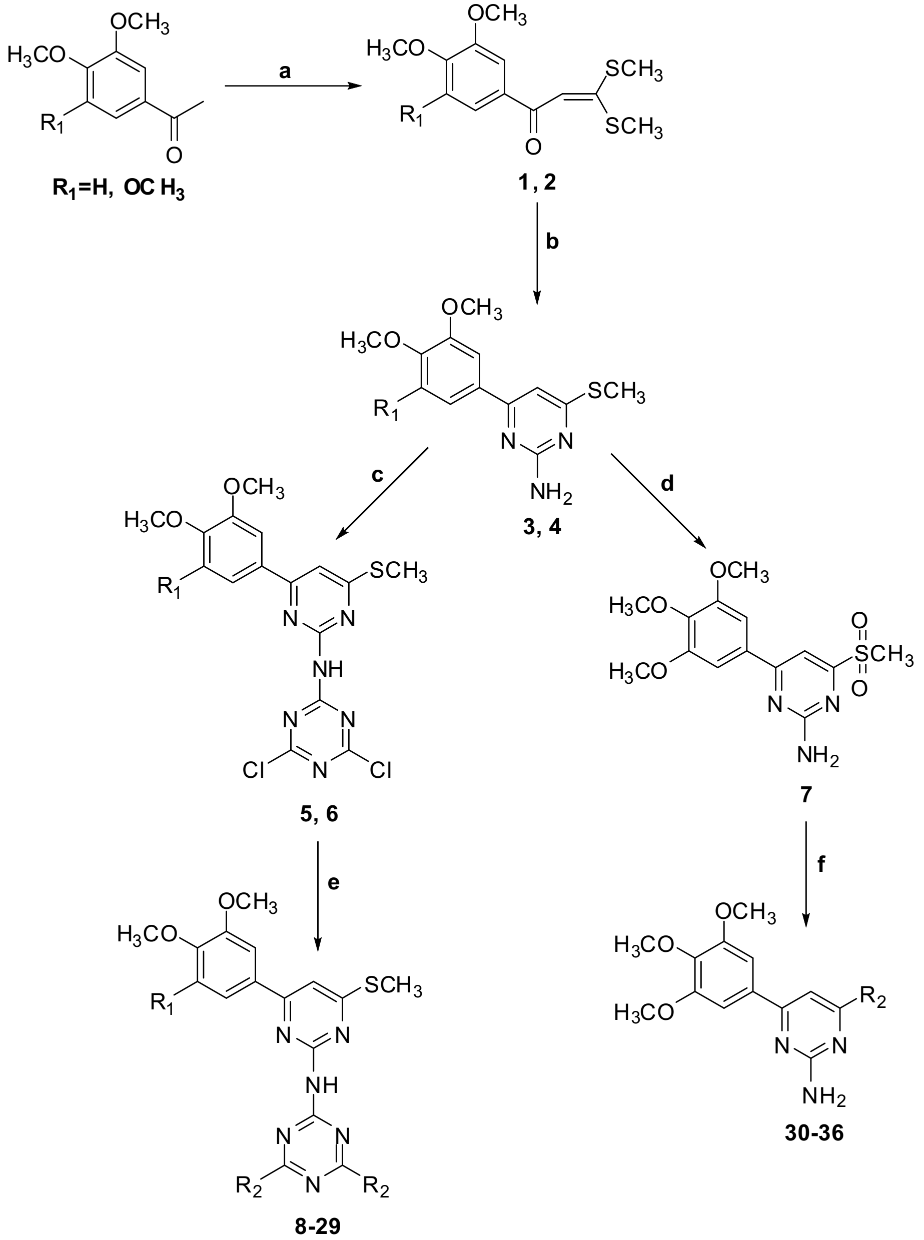
[b] **SSG** shows 40–50% inhibition against promastigotes at 940 μg/ml.

the concentration of a compound which provoked a 50% reduction in cell viability compared to cell in culture medium alone. IC_{50} values were estimated through the preformed template as described by Huber and Koella [30].

4. Results and discussion

Biological activity of 2,4,6-trisubstituted-1,3,5-triazines (**8**–**29**) and pyrimidines (**30**–**36**) hasve shown encouraging results against *L. donovani*. The percentage inhibition of these compounds against promastigotes has been given in Table 1. Among all twenty-nine synthesized compounds, fourteen compounds have shown more than 80% inhibition at 10 μg/ml against promastigotes and were further screened against amastigote model. Their IC_{50}, CC_{50} and S.I. values have been given in Table 2.

Among all tested fourteen compounds, four compounds (**13**, **14**, **17** and **25**) have shown IC_{50} in the range of **0.8–2.0 μg/ml** and five compounds (**12**, **18**, **21**, **26** and **33**) in the range of 2.0–5.0 μg/ml



Scheme 1. Reagents and conditions: (a) CS_2, NaH, MeI, THF, 0 °C to reflux; (b) guanidine hydrochloride, NaH, DMF, reflux; (c) cyanuric chloride, K_2CO_3, THF, reflux; (d) *m*-CPBA, DCM, 0 °C to rt; (e) various amines, K_2CO_3, THF, reflux; (f) different amines, THF, 100 °C, in closed steel vessel.

against amastigotes. Compound **25** consisting of 3,4-dimethoxyphenyl group at the fourth position of pyrimidine and *N*-methylpiperazine at the 4,6 position of 1,3,5-triazine has shown the lowest IC_{50} of 0.89 μg/ml and has the maximum S.I. (selectivity index) value of 40.71, which is several folds better than the standard drugs (**pentamidine**, **SSG**). While compound **13** having 3,4,5-trimethoxyphenyl group at the fourth position of pyrimidine and piperidine at the 4,6 position of 1,3,5-triazine showed IC_{50} of 1.80 μg/ml with less cytotoxicity value of CC_{50} 51.67 μg/ml in comparison to compound **25**. Similarly compounds **32** and **33** consisting of 3,4,5-trimethoxyphenyl group at the fourth position and *N*,*N*-diethylethylenediamine and butylamine at the sixth position of pyrimidine respectively, showed IC_{50} of 5.12, 4.99 μg/ml and cytotoxicity (CC_{50}) of 81.52 and 49.93 μg/ml. Due to their lower cytotoxicity and better selectivity index (28.70, 15.92 and 10.00), compounds **13**, **32** and **33** were screened for *in vivo* antileishmanial activity in golden hamsters (*M. auratus*) infected with MHOM/IN/80/Dd_8 strain of *L. donovani*. Compounds **13**, **33** have shown above moderate percentage inhibition of 56.58 and 54.10 respectively, while compound **32** has shown moderate inhibition of 48.46%. Structure–activity relationship (SAR) shows that the 3,4,5-trimethoxyphenyl group at the fourth position of pyrimidine ring incorporated with 1,3,5-triazine enhances the antileishmanial activity.

In conclusion, compounds **13**, **25**, **32** and **33** have shown better selectivity index in comparison to **pentamidine** and **sodium stibogluconate**. As a consequence of the above results and considerations, these hybrid molecules can be served as promising prototypes for the development of potent antileishmanial agents.

5. Experimental

IR spectra were recorded on Beckman Aculab-10, Perkin Elmer 881 and FTIR Shimadzu 8201PC spectrophotometers either on KBr

Table 2
In vitro (against MQ amastigotes) and *in vivo* antileishmanial activity.

Comp. no.	*In vitro* antiamastigote activity IC_{50} (μg/ml)	Cytotoxicity against J774A.1 cell lines CC_{50} (μg/ml)	S.I. (selectivity index) CC_{50}/IC_{50}	*In vivo* % inhibition 50 mg/kg × 5, i.p. for 5 days in hamsters[a]
12	2.97	9.80	3.29	ND
13	1.80	51.67	28.70	56.58
14	1.34	16.54	12.34	ND
15	ND	1.46	–	ND
16	7.02	10.85	1.54	ND
17	1.04	1.90	1.82	ND
18	4.56	27.36	6.00	ND
21	4.88	42.01	8.60	ND
25	0.89	36.24	40.71	ND
26	2.27	14.34	6.31	ND
27	9.68	23.85	2.46	ND
32	5.12	81.52	15.92	48.46
33	4.99	49.93	10.00	54.10
34	7.09	10.45	1.47	ND
Pentamidine®	12.11	31.31	2.58	84.10 (20 mg/kg)
SSG®	53.62	297	5.53	92 (40 mg/kg)

[a] The *in vivo* leishmanicidal activity was determined in golden hamsters (*Mesocricetus auratus*) infected with MHOM/IN/80/Dd_8 strain of *L. donovani*. ND: not done.

discs or in neat. Nuclear magnetic resonance (NMR) spectra were recorded on either Bruker Avance DRX-300 MHz or Bruker DPX 200 FT spectrometer using TMS as an internal reference. FAB mass spectra were recorded on JEOL SX 102/DA 6000 mass spectrometer using Argon/Xenon (6 kV, 10 mA) as the FAB gas. Chemical analysis was carried out on Carlo-Erba-1108 instrument. The melting points were recorded on an electrically heated melting point apparatus and are uncorrected.

*5.1. General procedure for the synthesis of compounds **1**, **2***

The mixture, 1 equiv of substituted acetophenone and 1 equiv of carbondisulfide in dry THF, was added dropwise to an ice-cold stirred suspension of NaH (2 equiv) in dry THF over a period of 30 min. The reaction mixture was stirred at room temperature for 4 h. Methyl iodide (2.5 equiv) was added in excess to the reaction mixture at 0 °C for 5 min. The reaction mixture was stirred additionally for 12 h at room temperature. The solvent was removed under reduced pressure and the resultant residue was dissolved in chloroform. The organic phase was washed with water (three times), dried over anhydrous Na_2SO_4. The solution was concentrated and crystallized from $CHCl_3$–hexane to afford the respective compounds **1**, **2** yielding in the range of 75–80%.

*5.1.1. 3,3-Bis-methylsulfanyl-1-(3,4,5-trimethoxyphenyl)-propenone (**1**)*

Yield: 80%; mp 136–139 °C; FAB-MS: 315 (M + 1); IR (KBr): 3029, 2855, 1691, 1615, 1575, 1495, 1372 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): 6.82 (s, 2H), 6.25 (s, 1H), 3.85 (s, 6H), 3.79 (s, 3H), 2.52 (s, 3H), 2.46 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 184.75, 166.54, 153.01, 141.46, 134.80, 109.22, 105.28, 60.94, 56.31, 17.38, 15.15. Anal. Calcd for $C_{14}H_{18}O_4S_2$: C, 53.48; H, 5.77. Found: C, 53.62; H, 5.73.

*5.1.2. 1-(3,4-Dimethoxyphenyl)-3,3-bis-methylsulfanyl-propenone (**2**)*

Yield: 75%; mp 118–121 °C; FAB-MS: 285 (M + 1); IR (KBr): 3033, 2865, 1695, 1612, 1574, 1493, 1370 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.61 (d, 1H, $J = 2.86$ Hz), 7.51 (dd, 1H, $J = 2.78$, 8.45 Hz), 6.88 (d, 1H, $J = 8.32$ Hz), 6.78 (s, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 2.58 (s, 3H), 2.54 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 184.43, 166.15, 152.24, 149.06, 132.30, 123.31, 121.32, 110.63, 109.89, 109.27, 56.02, 55.94, 17.34, 15.11. Anal. Calcd for $C_{13}H_{16}O_3S_2$: C, 54.90; H, 5.67. Found: C, 54.81; H, 5.59.

*5.2. General procedure for the synthesis of compounds **3**, **4***

To a suspension of NaH (1.5 equiv) and compounds **1**, **2** (1 equiv) in dry DMF was added guanidine hydrochloride (1.5 equiv). The reaction mixture was refluxed with stirring for 12 h. The solvent was removed under vacuum and the resultant residue was purified by using column chromatography to obtain the respective compounds **3**, **4** yielding in the range of 60–70%.

*5.2.1. 4-Methylsulfanyl-6-(3,4,5-trimethoxyphenyl)-pyrimidin-2-ylamine (**3**)*

Yield: 65%; mp 112–115 °C; FAB-MS: 308 (M + 1); IR (KBr): 3448, 3341, 3211, 3002, 2934, 2833, 1637, 1558, 1422,1348, 1225, 1128, 1008, 820 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): 7.19 (s, 2H), 6.88 (s, 1H), 5.08 (br-s, 2H), 3.94 (s, 6H), 3.89 (s, 3H), 2.55 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 171.60, 162.96, 162.41, 153.36, 140.04, 132.72, 104.73, 104.19, 60.96, 56.24, 12.42. Anal. Calcd for $C_{14}H_{17}N_3O_3S$: C, 54.71; H, 5.57; N, 13.67. Found: C, 54.68; H, 5.69; N, 13.46.

*5.2.2. 4-(3,4-Dimethoxyphenyl)-6-methylsulfanyl-pyrimidin-2-ylamine (**4**)*

Yield: 63%; mp 107–110 °C; FAB-MS: 277 (M + 1); IR (KBr): 3387, 3319, 3195, 2929, 2837, 1644, 1550, 1516, 1426,1344, 1262, 1133, 1025, 795 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): 7.60 (d, 1H, $J = 2.89$ Hz), 7.53 (dd, 1H, $J = 2.93$, 8.38 Hz), 6.95 (s, 1H) 6.91 (S, 1H), 5.09 (br-s, 2H), 3.99 (s, 3H), 3.95 (s, 3H), 2.56 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 171.38, 162.91, 162.44, 151.04, 149.07, 129.89, 120.01, 110.82, 109.83, 104.13, 55.98, 12.45. Anal. Calcd for $C_{13}H_{15}N_3O_2S$: C, 56.30; H, 5.45; N, 15.15. Found: C, 56.51; H, 5.38; N, 15.09.

*5.3. General procedure for the synthesis of compounds **5**, **6***

The solution of compounds **3**, **4** (1 equiv) in dry THF was added dropwise to an ice-cold mixture of cyanuric chloride (1.5 equiv) and K_2CO_3 (2 equiv) in dry THF. The reaction mixture was stirred at room temperature for 1 h and then refluxed with stirring for 8 h. The reaction mixture was filtered and solvent was evaporated under vacuum to dryness. The solid mass was purified by using column chromatography within a day to afford respective compounds **5**, **6** yielding in the range of 70–75%.

*5.3.1. (4,6-Dichloro-[1,3,5]triazin-2-yl)-[4-methylsulfanyl-6-(3,4,5-trimethoxyphenyl)-pyrimidin-2-yl]-amine (**5**)*

Yield: 72%; mp > 200 °C (decomposes); FAB-MS: 455 (M + 1); IR (KBr): 3238, 3032, 2963, 2849, 1607, 1560, 1514, 1397, 1267, 1152, 1006, 831 cm^{-1}; ^{1}H NMR (300 MHz, 75% $CDCl_3$ + 25% CD_3OD): 7.42 (s, 2H), 7.00 (s, 1H), 4.06 (s, 6H), 4.00 (s, 3H), 2.66 (s, 3H). ^{13}C NMR (75 MHz, 75% $CDCl_3$ + 25% CD_3OD): 184.49, 176.33, 169.49, 158.91, 158.36, 157.58, 155.45, 130.04, 112.96, 112.08, 64.76, 60.68, 16.86. Anal. Calcd for $C_{17}H_{16}Cl_2N_6O_3S$: C, 44.84; H, 3.54; N, 18.46. Found: C, 44.73; H, 3.43; N, 18.37.

*5.3.2. (4,6-Dichloro-[1,3,5]triazin-2-yl)-[4-(3,4-dimethoxyphenyl)-6-methylsulfanyl-pyrimidin-2-yl]-amine (**6**)*

Yield: 70%; mp > 200 °C (decomposes); FAB-MS: 425 (M + 1); IR (KBr): 3367, 3173, 3082, 2926, 2838, 1602, 1574, 1518, 1432, 1237, 1157, 1157, 1015, 848 cm^{-1}; ^{1}H NMR (300 MHz, 75% $CDCl_3$ + 25% CD_3OD): 7.63 (d, 1H, $J = 2.84$ Hz), 7.53 (dd, 1H, $J = 2.87$, 8.32 Hz), 6.98 (s, 1H) 6.90 (S, 1H), 4.06 (s, 3H), 4.02 (s, 3H), 2.63 (s, 3H). ^{13}C NMR (75 MHz, 75% $CDCl_3$ + 25% CD_3OD): δ (ppm) 184.53, 176.12, 169.58, 159.10, 158.40, 157.22, 155.51, 129.24, 113.70, 112.39, 107.52, 59.91, 17.57. Anal. Calcd for $C_{16}H_{14}Cl_2N_6O_2S$: C, 45.19; H, 3.32; N, 19.76. Found: C, 45.15; H, 3.26; N, 19.81.

5.4. General procedure for the synthesis of compounds 8–29

The mixture of compounds **5**, **6** (1 equiv), different amines (2 equiv) listed in Table 1, and K_2CO_3 (2 equiv) in dry THF was refluxed for 8 h. The reaction mixture was filtered and the solvent was evaporated under vacuum. The solid residue was purified with column chromatography using silica gel as adsorbent to obtain respective compounds **8**–**29** in good yield.

5.4.1. N^2-(4-(Methylthio)-6-(3,4,5-trimethoxyphenyl)pyrimidin-2-yl)-N^4,N^6-bis(2-morpholinoethyl)-1,3,5-triazine-2,4,6-triamine (**8**)

Yield: 67%; mp 164–167 °C; FAB-MS: 643 (M + 1); IR (KBr): 3385, 2922, 2855, 1593, 1351, 1119, 861, 765 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.27 (s, 2H), 7.11 (s, 1H), 6.09 (br-s, 2H), 5.56 (br-s, 1H), 3.94 (s, 6H), 3.90 (s, 3H), 3.74–3.69 (m, 8H), 3.49–3.46 (m, 4H), 2.69 (s, 3H), 2.54–2.43 (m, 12H). ^{13}C NMR (50 MHz, $CDCl_3$): 172.35, 166.53, 164.02, 163.01, 158.40, 153.82, 140.81, 132.50, 107.86, 104.92, 67.28, 61.38, 57.67, 56.71, 53.76, 37.42, 12.94. Anal. Calcd for $C_{29}H_{42}N_{10}O_5S$: C, 54.19; H, 6.59; N, 21.79. Found: C, 54.21; H, 6.47; N, 21.63.

5.4.2. N^2-(4-(Methylthio)-6-(3,4,5-trimethoxyphenyl)pyrimidin-2-yl)-N^4,N^6-bis(3-morpholinopropyl)-1,3,5-triazine-2,4,6-triamine (**9**)

Yield: 65%; mp 135–137 °C; FAB-MS: 671 (M + 1); IR (KBr): 3401, 3260, 2931, 2853, 1575, 1475, 1348, 1126, 813, 759 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.30 (s, 2H), 7.13 (s, 1H), 6.46 (br-s, 2H), 5.67 (br-s, 1H), 3.96 (s, 6H), 3.92 (s, 3H), 3.75–3.70 (m, 8H), 3.49–3.44 (m, 4H), 2.65 (s, 3H), 2.48–2.36 (m, 12H), 1.76 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$): 172.55, 167.76, 165.39, 163.05, 157.97, 153.79, 140.78, 132.39, 108.14, 104.87, 67.27, 61.35, 57.02, 56.62, 54.02, 39.85, 26.31, 13.07. Anal. Calcd for $C_{31}H_{46}N_{10}O_5S$: C, 55.50; H, 6.91; N, 20.88. Found: C, 55.37; H, 7.02; N, 20.79.

5.4.3. N^2,N^4-Bis(2-(diethylamino)ethyl)-N^6-(4-(methylthio)-6-(3,4,5-trimethoxyphenyl)pyrimidin-2-yl)-1,3,5-triazine-2,4,6-triamine (**10**)

Yield: 57%; mp 105–108 °C; FAB-MS: 615 (M + 1); IR (KBr): 3406, 2934, 2850, 1595, 1349, 1125, 762 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.26 (s, 2H), 7.10 (s, 1H), 6.07 (br-s, 2H), 5.64 (br-s, 1H), 3.94 (s, 6H), 3.89 (s, 3H), 3.45 (m, 4H), 2.69 (s, 3H), 2.60–2.50 (m, 12H), 1.01 (t, 12H, $J = 7.08$ Hz). ^{13}C NMR (50 MHz, $CDCl_3$): 172.32, 166.60, 163.96, 163.01, 158.50, 153.77, 140.66, 132.59, 107.81, 104.84, 61.34, 56.66, 52.06, 47.16, 38.59, 12.96, 11.85. Anal. Calcd for $C_{29}H_{46}N_{10}O_3S$: C, 56.65; H, 7.54; N, 22.78. Found: C, 56.58; H, 7.47; N, 22.61.

5.4.4. N^2,N^4-Dibutyl-N^6-(4-(methylthio)-6-(3,4,5-trimethoxyphenyl)pyrimidin-2-yl)-1,3,5-triazine-2,4,6-triamine (**11**)

Yield: 70%; mp 125–127 °C; FAB-MS: 529 (M + 1); IR (KBr): 3406, 2957, 2861, 1593, 1349, 1124, 818, 755 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.20 (s, 2H), 7.07 (s, 1H), 5.97 (br-s, 2H), 5.13 (br-s, 1H), 3.92 (s, 6H), 3.90 (s, 3H), 3.26 (m, 4H), 2.67 (s, 3H), 1.33–1.25 (m, 8H), 0.88–0.85 (m, 6H). ^{13}C NMR (50 MHz, $CDCl_3$): 172.46, 166.56, 163.99, 163.40, 158.86, 156.78, 140.53, 132.87, 107.79, 104.94, 61.32, 56.63, 40.84, 32.06, 20.43, 14.18, 13.01. Anal. Calcd for $C_{25}H_{36}N_8O_3S$: C, 56.80; H, 6.86; N, 21.20. Found: C, 56.97; H, 6.62; N, 21.11.

5.4.5. N^2,N^4-Di-*tert*-butyl-N^6-(4-(methylthio)-6-(3,4,5-trimethoxyphenyl)pyrimidin-2-yl)-1,3,5-triazine-2,4,6-triamine (**12**)

Yield: 78%; mp 109–111 °C; FAB-MS: 529 (M + 1); IR (KBr): 3405, 2959, 2856, 1597, 1363, 1114, 816, 761 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.31 (s, 2H), 7.17 (s, 1H), 5.63 (br-s, 1H), 5.50 (br-s, 2H) 3.99 (s, 6H), 3.92 (s, 3H), 2.67 (s, 3H), 1.47 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$): 174.31, 166.68, 165.25, 164.49, 158.36, 155.11, 142.18, 133.56, 110.19, 106.26, 63.89, 59.34, 31.84, 15.62. Anal. Calcd for $C_{25}H_{36}N_8O_3S$: C, 56.80; H, 6.86; N, 21.20. Found: C, 56.74; H, 6.69; N, 21.24.

5.4.6. N-(4-(Methylthio)-6-(3,4,5-trimethoxyphenyl)pyrimidin-2-yl)-4,6-di(piperidin-1-yl)-1,3,5-triazin-2-amine (**13**)

Yield: 84%; mp 113–115 °C; FAB-MS: 553 (M + 1); IR (KBr): 3430, 2927, 2852, 1591, 1386, 1124, 1018, 806, 753 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.28 (s, 2H), 7.10 (s, 1H), 5.29 (br-s, 1H), 3.96 (s, 6H), 3.92 (s, 3H), 3.81 (m, 8H), 2.68 (s, 3H), 1.69–1.59 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$): 170.17, 163.84, 162.40, 161.12, 156.84, 152.10, 139.14, 131.07, 107.64, 104.81, 61.14, 56.41, 44.14, 25.73, 23.63, 12.51. Anal. Calcd for $C_{27}H_{36}N_8O_3S$: C, 58.67; H, 6.57; N, 20.27. Found: C, 58.73; H, 6.49; N, 20.31.

5.4.7. 4,6-Bis(4-methylpiperazin-1-yl)-N-(4-(methylthio)-6-(3,4,5-trimethoxyphenyl)pyrimidin-2-yl)-1,3,5-triazin-2-amine (**14**)

Yield: 72%; mp 185–188 °C; FAB-MS: 583 (M + 1); IR (KBr): 3440, 3113, 2923, 2836, 1571, 1492, 1388, 1121, 1004, 819, 745 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.28 (s, 2H), 7.11 (s, 1H), 5.31 (br-s, 1H), 3.95 (s, 6H), 3.91 (s, 3H), 3.89–3.86 (m, 8H), 2.66 (s, 3H), 2.47–2.43 (m, 8H), 2.35 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$): 170.27, 163.95, 162.44, 161.23, 156.66, 152.40, 139.26, 130.99, 107.44, 104.82, 61.15, 56.43, 55.03, 46.12, 42.98, 12.23. Anal. Calcd for $C_{27}H_{38}N_{10}O_3S$: C, 55.65; H, 6.57; N, 24.04. Found: C, 55.73; H, 6.49; N, 24.11.

5.4.8. N^2-(4-(Methylthio)-6-(3,4,5-trimethoxyphenyl)pyrimidin-2-yl)-N^4,N^6-dipropyl-1,3,5-triazine-2,4,6-triamine (**15**)

Yield: 67%; mp 155–158 °C; FAB-MS: 501 (M + 1); IR (KBr): 3269, 2961, 2872, 1599, 1460, 1328, 1126, 813, 755 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.25 (s, 2H), 7.09 (s, 1H), 5.89 (br-s, 2H), 5.13 (br-s, 1H), 3.94 (s, 6H), 3.91 (s, 3H), 3.28 (m, 4H), 2.68 (s, 3H), 1.50 (m, 4H), 0.89 (m, 6H). ^{13}C NMR (50 MHz, $CDCl_3$): 170.80, 164.89, 162.28, 161.70, 157.12, 152.10, 138.91, 131.15, 107.36, 104.58, 60.94, 56.25, 42.52, 22.79, 12.61, 11.43. Anal. Calcd for $C_{23}H_{32}N_8O_3S$: C, 55.18; H, 6.44; N, 22.38. Found: C, 55.27; H, 6.39; N, 22.16.

5.4.9. N-(4-(Methylthio)-6-(3,4,5-trimethoxyphenyl)pyrimidin-2-yl)-4,6-dimorpholino-1,3,5-triazin-2-amine (**16**)

Yield: 69%; mp 161–163 °C; FAB-MS: 557 (M + 1); IR (KBr): 3427, 2925, 2851, 1600, 1480, 1422, 1326, 1252, 1005, 855 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.25 (s, 2H), 7.11 (s, 1H), 5.37 (br-s, 1H), 3.94 (s, 6H), 3.90 (s, 3H), 3.84 (m, 8H), 3.74–3.72 (m, 8H), 2.63 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): 172.08, 165.75, 164.14, 162.97, 158.27, 153.82, 141.13, 132.58, 107.98, 105.30, 67.17, 61.34, 56.89, 44.07, 12.74. Anal. Calcd for $C_{25}H_{32}N_8O_5S$: C, 53.94; H, 5.79; N, 20.13. Found: C, 53.77; H, 5.89; N, 20.15.

5.4.10. N^2,N^4-Diisopropyl-N^6-(4-(methylthio)-6-(3,4,5-trimethoxyphenyl)pyrimidin-2-yl)-1,3,5-triazine-2,4,6-triamine (**17**)

Yield: 71%; mp 128–130 °C; FAB-MS: 501 (M + 1); IR (KBr): 3272, 2968, 2931, 1569, 1399, 1328, 1124, 1004, 814, 727 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.29 (s, 2H), 7.10 (s, 1H), 5.41 (br-s, 1H), 4.93 (br-s, 2H), 3.95 (s, 6H), 3.90 (s, 3H), 3.49–3.46 (m, 2H), 2.65 (s, 3H), 1.24–1.16 (m, 12H). ^{13}C NMR (50 MHz, $CDCl_3$): 172.34, 165.79, 163.77, 162.98, 158.53, 153.75, 140.78, 132.61, 107.53, 104.97, 61.33, 56.62, 42.81, 23.04, 12.97. Anal. Calcd for $C_{23}H_{32}N_8O_3S$: C, 55.18; H, 6.44; N, 22.38. Found: C, 55.04; H, 6.58; N, 22.29.

5.4.11. 4,6-Bis(4-ethylpiperazin-1-yl)-N-(4-(methylthio)-6-(3,4,5-trimethoxyphenyl)pyrimidin-2-yl)-1,3,5-triazin-2-amine (**18**)

Yield: 69%; mp 168–170 °C; FAB-MS: 611 (M + 1); IR (KBr): 3408, 2967, 2860, 1596, 1414, 1389, 1118, 844, 765 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.25 (s, 2H), 7.10 (s, 1H), 5.39 (br-s, 1H), 3.94 (s, 6H), 3.90 (m, 11H), 2.65 (s, 3H), 2.48–2.45 (m, 12H), 1.12 (t, 6H, *J* = 7.03 Hz). ^{13}C NMR (50 MHz, CDCl$_3$): 171.94, 165.56, 164.13, 162.91, 158.36, 153.79, 140.95, 132.68, 107.98, 105.12, 61.35, 56.85, 53.04, 52.81, 43.43, 12.73, 12.28. Anal. Calcd for $C_{29}H_{42}N_{10}O_3S$: C, 57.03; H, 6.93; N, 22.93. Found: C, 56.97; H, 6.82; N, 22.75.

5.4.12. N^2-*(4-(3,4-Dimethoxyphenyl)-6-(methylthio)pyrimidin-2-yl)-*N^4,N^6-*bis(2-morpholinoethyl)-1,3,5-triazine-2,4,6-triamine (**19**)*

Yield: 62%; mp 102–104 °C; FAB-MS: 613 (M + 1); IR (KBr): 3468, 2964, 2821, 1592, 1459, 1350, 1114, 764 cm^{-1}; ^{1}H NMR (200 MHz, 95% CDCl$_3$ + 5% CD$_3$OD): *δ* (ppm) 7.63 (m, 2H), 7.14 (s, 1H), 6.94 (d, 1H, *J* = 8.50 Hz), 3.96 (s, 3H), 3.94 (s, 3H), 3.57–3.50 (m, 4H), 2.65 (s, 3H), 2.55 (m, 4H), 2.49 (m, 8H). ^{13}C NMR (50 MHz, 95% CDCl$_3$ + 5% CD$_3$OD): 176.34, 170.19, 167.07, 162.03, 160.05, 155.77, 153.43, 133.64, 124.83, 115.32, 114.61,111.30, 71.02, 61.67, 60.24, 59.70, 57.65, 16.88. Anal. Calcd for $C_{28}H_{40}N_{10}O_4S$: C, 54.88; H, 6.58; N, 22.86. Found: C, 54.62; H, 6.44; N, 22.79.

5.4.13. N^2-*(4-(3,4-Dimethoxyphenyl)-6-(methylthio)pyrimidin-2-yl)-*N^4,N^6-*bis(3-morpholinopropyl)-1,3,5-triazine-2,4,6-triamine (**20**)*

Yield: 64%; mp 115–118 °C; FAB-MS: 641 (M + 1); IR (KBr): 3282, 2933, 2847, 1594, 1400, 1348, 1114, 810, 762 cm^{-1}; ^{1}H NMR (200 MHz, 95% CDCl$_3$ + 5% CD$_3$OD): *δ* (ppm) 7.62 (m, 2H), 7.13 (s, 1H), 6.95 (d, 1H, *J* = 8.51 Hz), 3.97 (s, 3H), 3.94 (s, 3H), 3.74 (t, 8H, *J* = 4.07 Hz), 3.57 (m, 4H), 2.64 (s, 3H), 2.48 (m, 12H), 1.77 (m, 4H). ^{13}C NMR (50 MHz, 95% CDCl$_3$ + 5% CD$_3$OD): 172.54, 166.32, 163.28, 161.54, 158.19, 151.73, 149.43, 129.67, 120.83, 111.30, 110.58, 107.20, 66.91, 56.86, 56.30, 53.80, 39.33, 26.19, 13.05. Anal. Calcd for $C_{30}H_{44}N_{10}O_4S$: C, 56.23; H, 6.92; N, 21.86. Found: C, 56.09; H, 6.94; N, 21.98.

5.4.14. N^2,N^4-*Bis(2-(diethylamino)ethyl)-*N^6-*(4-(3,4-dimethoxyphenyl)-6-(methylthio)pyrimidin-2-yl)-1,3,5-triazine-2,4,6-triamine (**21**)*

Yield: 68%; mp 125–127 °C; FAB-MS: 585 (M + 1); IR (KBr): 3278, 2967, 2930, 1568, 1403, 1341, 1303, 1138, 812, 760 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$): *δ* (ppm) 7.60 (m, 2H), 7.09 (s, 1H), 6.91 (d, 1H, *J* = 8.53 Hz), 6.32 (br-s, 2H), 5.68 (br-s, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 3.40 (m, 4H), 2.66 (s, 3H), 2.53–2.50 (m, 12H), 0.99 (t, 12H, *J* = 7.05 Hz). ^{13}C NMR (50 MHz, CDCl$_3$): 171.98, 166.63, 164.01, 162.98, 158.61, 151.65, 149.47, 129.87, 120.76, 111.24, 110.49, 107.22, 56.32, 52.11, 47.18, 38.70, 11.99, 11.34. Anal. Calcd for $C_{28}H_{44}N_{10}O_2S$: C, 57.51; H, 7.58; N, 23.95. Found: C, 57.72; H, 7.55; N, 24.03.

5.4.15. N^2,N^4-*Dibutyl-*N^6-*(4-(3,4-dimethoxyphenyl)-6-(methylthio)pyrimidin-2-yl)-1,3,5-triazine-2,4,6-triamine (**22**)*

Yield: 79%; mp 138–140 °C; FAB-MS: 499 (M + 1); IR (KBr): 3275, 2931, 2853, 1576, 1401, 1347, 1136, 1022, 810, 759 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$): *δ* (ppm) 7.60 (m, 2H), 7.08 (s, 1H), 6.92 (d, 1H, *J* = 8.47 Hz), 6.07 (br-s, 2H), 5.12 (br-s, 1H), 3.96 (s, 3H), 3.94 (s, 3H), 3.28 (m, 4H), 2.65 (s, 3H), 1.39–1.25 (m, 8H), 0.89–0.85 (m, 6H). ^{13}C NMR (50 MHz, CDCl$_3$): 172.14, 166.54, 163.89, 163.31, 158.78, 151.57, 149.47, 130.08, 120.76, 111.23, 110.59, 107.30, 56.36, 40.85, 32.10, 20.44, 14.19, 13.03. Anal. Calcd for $C_{24}H_{34}N_8O_2S$: C, 57.81; H, 6.87; N, 22.47. Found: C, 57.69; H, 6.76; N, 22.43.

5.4.16. N^2,N^4-*Di-*tert*-butyl-*N^6-*(4-(3,4-dimethoxyphenyl)-6-(methylthio)pyrimidin-2-yl)-1,3,5-triazine-2,4,6-triamine (**23**)*

Yield: 74%; mp 100–102 °C; FAB-MS: 499 (M + 1); IR (KBr): 3393, 2962, 2854, 1589, 1402, 1347, 1152, 1020, 805, 763 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$): *δ* (ppm) 7.76 (m, 2H), 7.21 (s, 1H), 6.93 (d, 1H, *J* = 8.46 Hz), 5.64 (br-s, 1H), 5.48 (br-s, 2H), 4.02 (s, 3H), 3.95 (s, 3H), 2.64 (s, 3H), 1.45 (s, 18H). ^{13}C NMR (50 MHz, CDCl$_3$): 172.57, 166.11, 163.98, 163.18, 157.05, 151.91, 149.61, 129.42, 120.62, 111.17, 110.49, 108.18, 56.39, 29.02, 13.15. Anal. Calcd for $C_{24}H_{34}N_8O_2S$: C, 57.81; H, 6.87; N, 22.47. Found: C, 57.74; H, 6.92; N, 22.56.

5.4.17. N-*(4-(3,4-Dimethoxyphenyl)-6-(methylthio)pyrimidin-2-yl)-4,6-di(piperidin-1-yl)-1,3,5-triazin-2-amine (**24**)*

Yield: 68%; mp 174–176 °C; FAB-MS: 523 (M + 1); IR (KBr): 3276, 2927, 2851, 1582, 1478, 1328, 1130, 1021, 802, 757 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$): *δ* (ppm) 7.61 (m, 2H), 7.10 (s, 1H), 6.90 (d, 1H, *J* = 8.46 Hz), 5.36 (br-s, 1H), 3.97 (s, 3H), 3.94 (s, 3H), 3.82–3.80 (m, 8H), 2.63 (s, 3H), 1.67–1.60 (m, 12H). ^{13}C NMR (50 MHz, CDCl$_3$): 171.54, 165.59, 164.15, 162.71, 158.50, 151.68, 149.46, 130.04, 120.86, 111.18, 110.48, 107.31, 56.56, 44.56, 26.25, 25.35, 12.71. Anal. Calcd for $C_{26}H_{34}N_8O_2S$: C, 59.75; H, 6.56; N, 21.44. Found: C, 59.91; H, 6.52; N, 21.28.

5.4.18. N-*(4-(3,4-Dimethoxyphenyl)-6-(methylthio)pyrimidin-2-yl)-4,6-bis(4-methylpiperazin-1-yl)-1,3,5-triazin-2-amine (**25**)*

Yield: 71%; mp 105–108 °C; FAB-MS: 553 (M + 1); IR (KBr): 3431, 2927, 2853, 2797, 1591, 1514, 1347, 1142, 1003, 807, 763 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$): *δ* (ppm) 7.64 (m, 2H), 7.14 (s, 1H), 6.94 (d, 1H, *J* = 8.39 Hz), 5.33 (br-s, 1H), 3.96 (s, 3H), 3.94 (s, 3H), 3.92–3.89 (m, 8H), 2.61 (s, 3H), 2.49 (m, 8H), 2.35 (s, 6H). ^{13}C NMR (50 MHz, CDCl$_3$): 176.00, 169.46, 168.15, 166.82, 162.16, 155.81, 153.41, 133.71, 124.95, 115.28, 114.74, 111.31, 60.52, 58.98, 50.10, 47.01, 16.65. Anal. Calcd for $C_{26}H_{36}N_{10}O_2S$: C, 56.50; H, 6.57; N, 25.34. Found: C, 56.43; H, 6.54; N, 25.29.

5.4.19. N^2-*(4-(3,4-Dimethoxyphenyl)-6-(methylthio)pyrimidin-2-yl)-*N^4,N^6-*dipropyl-1,3,5-triazine-2,4,6-triamine (**26**)*

Yield: 66%; mp 155–157 °C; FAB-MS: 471 (M + 1); IR (KBr): 3264, 2958, 2853, 1546, 1401, 1354, 1141, 1027, 835, 763 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$): *δ* (ppm) 7.62 (m, 2H), 7.09 (s, 1H), 6.92 (d, 1H, *J* = 8.49 Hz), 5.98 (br-s, 2H), 5.11 (br-s, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 3.46–3.27 (m, 4H), 2.65 (s, 3H), 1.49 (m, 4H), 0.89–0.85 (m, 6H). ^{13}C NMR (50 MHz, CDCl$_3$): 172.53, 166.07, 165.84, 164.29, 158.24, 151.89, 149.32, 131.43, 120.75, 111.20, 110.54, 107.23, 56.39, 42.93, 23.24, 13.04, 11.86. Anal. Calcd for $C_{22}H_{30}N_8O_2S$: C, 56.15; H, 6.43; N, 23.81. Found: C, 56.07; H, 6.41; N, 23.79.

5.4.20. N-*(4-(3,4-Dimethoxyphenyl)-6-(methylthio)pyrimidin-2-yl)-4,6-dimorpholino-1,3,5-triazin-2-amine (**27**)*

Yield: 70%; mp 185–188 °C; FAB-MS: 527 (M + 1); IR (KBr): 3426, 2953, 2841, 1593, 1478, 1350, 1111, 1023, 805, 769 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$): *δ* (ppm) 7.68 (m, 2H), 7.12 (s, 1H), 6.90 (d, 1H, *J* = 8.47 Hz), 5.35 (br-s, 1H), 3.96 (s, 3H), 3.94 (s, 3H), 3.85–3.82 (m, 8H), 3.75–3.70 (m, 8H), 2.60 (s, 3H). ^{13}C NMR (50 MHz, CDCl$_3$): 171.84, 165.78, 164.14, 162.88, 158.21, 151.89, 149.52, 129.85, 120.92, 111.15, 110.64, 107.45, 67.22, 56.64, 44.08, 12.81. Anal. Calcd for $C_{24}H_{30}N_8O_4S$: C, 54.74; H, 5.74; N, 21.28. Found: C, 54.51; H, 5.69; N, 21.42.

5.4.21. N^2-*(4-(3,4-Dimethoxyphenyl)-6-(methylthio)pyrimidin-2-yl)-*N^4,N^6-*diisopropyl-1,3,5-triazine-2,4,6-triamine (**28**)*

Yield: 70%; mp 141–143 °C; FAB-MS: 471 (M + 1); IR (KBr): 3310, 2946, 2853, 1583, 1439, 1347, 1327, 1130, 1015, 815, 753 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$): *δ* (ppm) 7.58 (m, 2H), 7.08 (s, 1H), 6.91 (d, 1H, *J* = 8.13 Hz), 5.52 (br-s, 1H), 5.07 (br-s, 2H), 3.94 (s, 3H), 3.92 (s, 3H), 3.48–3.46 (m, 2H), 2.66 (s, 3H), 1.24–1.14 (m, 12H). ^{13}C NMR (50 MHz, CDCl$_3$): 172.19, 165.73, 163.54, 162.78, 158.51, 153.72, 140.77, 132.66, 111.23, 107.31, 56.78, 42.76, 23.28, 13.08. Anal. Calcd for $C_{22}H_{30}N_8O_2S$: C, 56.15; H, 6.43; N, 23.81. Found: C, 56.32; H, 6.39; N, 23.86.

5.4.22. N-*(4-(3,4-Dimethoxyphenyl)-6-(methylthio)pyrimidin-2-yl)-4,6-bis(4-ethylpiperazin-1-yl)-1,3,5-triazin-2-amine (**29**)*

Yield: 68%; mp 164–166 °C; FAB-MS: 581 (M + 1); IR (KBr): 3428, 2966, 2814, 1563, 1444, 1395, 1253, 1161, 1013, 810, 760 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$): *δ* (ppm) 7.69 (m, 2H), 7.14 (s, 1H), 6.94 (d, 1H, *J* = 8.43 Hz), 5.38 (br-s, 1H), 3.97 (s, 3H), 3.94 (s, 3H), 3.91–3.89 (m, 8H), 2.63 (s, 3H), 2.53–2.43 (m, 12H), 1.24–1.10 (m, 6H). ^{13}C NMR (50 MHz, $CDCl_3$): 175.97, 169.41, 168.05, 166.86, 162.10, 155.75, 153.40, 133.79, 124.91, 115.21, 114.64, 111.37, 60.50, 56.84, 56.69, 47.09, 16.68, 15.75. Anal. Calcd for $C_{28}H_{40}N_{10}O_2S$: C, 57.91; H, 6.94; N, 24.12. Found: C, 57.63; H, 7.12; N, 24.09.

5.5. *General procedure for the synthesis of compound **7***

To an ice-cold solution of compound **3** (1 equiv) in dry DCM was added *m*-CPBA (2.5 equiv) solution in dry DCM through dropping funnel for 30 min, after the addition of *m*-CPBA, the reaction mixture was left to stir at r.t. for 1 h. After stirring a saturated solution of $NaHCO_3$ was added to the reaction mixture and allowed to stir vigorously for 30 min. The organic layer was separated and washed twice with water and dried over anhydrous Na_2SO_4. The solution was concentrated and purified with column chromatography to afford compound **7** in the range of 72–75%.

5.5.1. *4-(Methylsulfonyl)-6-(3,4,5-trimethoxyphenyl)pyrimidin-2-amine (**7**)*

Yield: 73%; mp 126–128 °C; FAB-MS: 340 (M + 1); IR (KBr): 3438, 3326, 3208, 3052, 2934, 1638, 1562, 1434, 1347, 1226, 1125, 1004, 816 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): 7.18 (s, 2H), 6.86 (s, 1H), 5.06 (br-s, 2H), 3.96 (s, 6H), 3.90 (s, 3H), 3.21 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 171.62, 162.97, 162.38, 153.35, 140.04, 132.67, 104.58, 104.26, 60.98, 56.32, 38.63. Anal. Calcd for $C_{14}H_{17}N_3O_5S$: C, 49.55; H, 5.05; N, 12.38. Found: C, 49.61; H, 5.02; N, 12.35.

5.6. *General procedure for the synthesis of compounds **30**–**36***

The solution of compound **7** (1 equiv) and different amines (1 equiv) listed in Table 1 in dry THF was heated in closed steel vessel at 100 °C for 12 h. The solvent was removed under vacuum and the resultant residue was dissolved in $CHCl_3$ (100 ml). The organic phase was washed with H_2O (three times), dried over anhydrous Na_2SO_4. The solution was concentrated and purified with column chromatography to afford compounds **30**–**36** in good yields.

5.6.1. N^4-*(2-Morpholinoethyl)-6-(3,4,5-trimethoxyphenyl)pyrimidine-2,4-diamine (**30**)*

Yield: 67%; mp 179–181 °C; FAB-MS: 390 (M + 1); IR (KBr): 3405, 3328, 3185, 2928, 2849, 1659, 1574, 1466, 1377, 1260, 1119, 859, 805 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.16 (s, 2H), 6.13 (s, 1H), 5.42 (s, 1H), 4.93 (br-s, 2H), 3.95 (s, 6H), 3.89 (s, 3H), 3.76–3.71 (m, 4H), 3.48–3.41 (m, 2H), 2.62 (t, 2H, J = 5.98 Hz), 2.48 (t, 4H, J = 7.52 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): 164.43, 164.03, 163.35, 153.63, 140.04, 134.19, 104.59, 91.61, 67.26, 61.28, 57.36, 56.64, 54.51, 53.71, 37.70. Anal. Calcd for $C_{19}H_{27}N_5O_4$: C, 58.60; H, 6.99; N, 17.98. Found: C, 58.56; H, 6.92; N, 17.93.

5.6.2. N^4-*(3-Morpholinopropyl)-6-(3,4,5-trimethoxyphenyl)pyrimidine-2,4-diamine (**31**)*

Yield: 62%; mp 138–140 °C; FAB-MS: 404 (M + 1); IR (KBr): 3431, 3336, 3224, 2933, 2863, 1634, 1574, 1506, 1457, 1312, 1122, 861, 805 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.14 (s, 2H), 6.07 (s, 1H), 5.76 (s, 1H), 4.91 (br-s, 2H), 3.94 (s, 6H), 3.89 (s, 3H), 3.75 (t, 4H, J = 5.96 Hz), 3.48–3.42 (m, 2H), 2.49 (t, 6H, J = 7.49 Hz), 1.84–1.76 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): 164.66, 164.28, 163.48, 153.63, 140.02, 134.49, 104.64, 91.44, 67.40, 61.29, 57.52, 56.65, 54.13, 40.84, 25.93. Anal. Calcd for $C_{20}H_{29}N_5O_4$: C, 59.54; H, 7.24; N, 17.36. Found: C, 59.62; H, 7.19; N, 17.33.

5.6.3. N^4-*(2-(Diethylamino)ethyl)-6-(3,4,5-trimethoxyphenyl)pyrimidine-2,4-diamine (**32**)*

Yield: 64%; mp 143–145 °C; FAB-MS: 376 (M + 1); IR (KBr): 3410, 3356, 3204, 2968, 2829, 1650, 1577, 1508, 1470, 1375, 1206, 1125, 860, 808 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.15 (s, 2H), 6.12 (s, 1H), 5.52 (s, 1H), 4.85 (br-s, 2H), 3.93 (s, 6H), 3.88 (s, 3H), 3.41–3.38 (m, 2H), 2.71–2.53 (m, 6H), 1.04 (t, 6H, J = 7.12 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): 164.53, 164.05, 163.47, 153.62, 139.82, 134.47, 104.48, 91.56, 61.30, 56.62, 51.76, 47.01, 38.94, 11.90. Anal. Calcd for $C_{19}H_{29}N_5O_3$: C, 60.78; H, 7.79; N, 18.65. Found: C, 60.69; H, 7.72; N, 18.57.

5.6.4. N^4-*Butyl-6-(3,4,5-trimethoxyphenyl)pyrimidine-2,4-diamine (**33**)*

Yield: 72%; mp 135–137 °C; FAB-MS: 333 (M + 1); IR (KBr): 3432, 3317, 3215, 2958, 2868, 1648, 1580, 1458, 1387, 1316, 1229, 1129, 856, 801 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.16 (s, 2H), 6.11 (s, 1H), 5.09 (s, 1H), 4.93 (br-s, 2H), 3.96 (s, 6H), 3.93 (s, 3H), 3.39–3.33 (m, 2H), 1.67–1.58 (m, 2H), 1.51–1.38 (m, 2H), 0.98 (t, 3H, J = 7.53 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 162.87, 162.22, 160.98, 152.02, 138.45, 133.10, 102.87, 89.78, 59.66, 55.02, 39.89, 30.24, 18.81, 12.53. Anal. Calcd for $C_{17}H_{24}N_4O_3$: C, 61.43; H, 7.28; N, 16.86. Found: C, 61.52; H, 7.23; N, 16.81.

5.6.5. *4-(Piperidin-1-yl)-6-(3,4,5-trimethoxyphenyl)pyrimidin-2-amine (**34**)*

Yield: 68%; mp 134–136 °C; FAB-MS: 345 (M + 1); IR (KBr): 3474, 3349, 3193, 2933, 2853, 1629, 1572, 1506, 1409, 1329, 1284, 1124, 876, 797 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.14 (s, 2H), 6.28 (s, 1H), 4.86 (br-s, 2H), 3.96 (s, 6H), 3.90 (s, 3H), 3.65 (t, 4H, J = 4.56 Hz), 1.73–1.64 (m, 6H). ^{13}C NMR (50 MHz, $CDCl_3$): 164.52, 163.92, 163.12, 153.67, 139.98, 134.90, 104.77, 90.82, 61.30, 56.72, 45.59, 26.04, 25.13. Anal. Calcd for $C_{18}H_{24}N_4O_3$: C, 62.77; H, 7.02; N, 16.27. Found: C, 62.70; H, 6.94; N, 16.32.

5.6.6. *4-(4-Methylpiperazin-1-yl)-6-(3,4,5-trimethoxyphenyl)pyrimidin-2-amine (**35**)*

Yield: 73%; mp 149–151 °C; FAB-MS: 360 (M + 1); IR (KBr): 3477, 3305, 3187, 2933, 2841, 1626, 1573, 1506, 1406, 1304, 1235, 1127, 867, 797 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.14 (s, 2H), 6.27 (s, 1H), 4.89 (br-s, 2H), 3.95 (s, 6H), 3.89 (s, 3H), 3.69 (t, 4H, J = 4.52 Hz), 2.49 (t, 4H, J = 4.46 Hz), 2.36 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): 162.99, 162.24, 161.22, 151.73, 138.10, 132.82, 102.81, 88.81, 59.36, 54.77, 53.19, 44.59, 42.38. Anal. Calcd for $C_{18}H_{25}N_5O_3$: C, 60.15; H, 7.01; N, 19.48. Found: C, 60.18; H, 7.08; N, 19.43.

5.6.7. *4-Morpholino-6-(3,4,5-trimethoxyphenyl)pyrimidin-2-amine (**36**)*

Yield: 68%; mp 133–135 °C; FAB-MS: 347 (M + 1); IR (KBr): 3462, 3354, 3215, 2965, 2835, 1622, 1576, 1505, 1406, 1330, 1253, 1124, 882, 796 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.12 (s, 2H), 6.24 (s, 1H), 4.84 (br-s, 2H), 3.94 (s, 6H), 3.88 (s, 3H), 3.79 (t, 4H, J = 4.47 Hz), 3.64 (t, 4H, J = 4.44 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): 165.33, 164.49, 163.23, 153.69, 140.06, 134.77, 104.68, 90.60, 67.03, 61.32, 56.69, 44.76. Anal. Calcd for $C_{17}H_{22}N_4O_4$: C, 58.95; H, 6.40; N, 16.17. Found: C, 58.91; H, 6.47; N, 16.22.

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