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Synthesis of 2,4,6-trisubstituted pyrimidine and triazine heterocycles as antileishmanial agents

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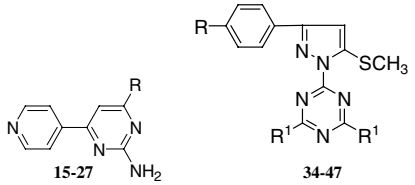
Abstract—A series of 2,4,6 trisubstituted pyrimidines and triazines have been synthesized and screened for its in vitro antileishmanial activity profile in promastigote model. Nine compounds have shown >94% inhibition against promastigotes at a concentration of 10 μg/mL.

1. Introduction

Leishmaniasis is caused by different species belonging to the genus *Leishmania*, a protozoan which is transmitted to humans by the bite of an insect vector, phlebotomine sandfly. Leishmaniasis has an overwhelming impact on the global public health and is endemic in many tropical and subtropical regions of the world. It affects around 12 million people of the world and 350 million are estimated to be prone to the disease, of which around 1.7 million people will be infected each year.[1–3] Infection by various strains of Leishmania causes a wide spectrum of disease in humans, with many different clinical manifestations, that is, cutaneous, mucocutaneous and visceral. Visceral form of Leishmaniasis, commonly known as Kala-azar, is caused by the parasite *Leishmania donovani*, which affects 61 out of the 88 countries worldwide. It attacks the phagocytic cells of the spleen, liver, and bone marrow, and is fatal in more than 90% of the untreated cases.[4]

There is still no effective vaccine for Kala-azar and chemotherapy remains the most effective control measure. The drugs for the treatment of leishmaniasis are sodium stibogluconate (Pentostam) and meglumine antimonate (Glucantime), despite the fact that they exhibit renal and cardiac toxicity. Although new drugs, that is, amphotericin B and its lipid complex are quite effective but they are expensive and out of the reach of poor people.[2,5] Newly introduced first orally active drug miltefosine, a phosphocholine analogue, is quite effective presenting severe gastrointestinal problems and also shows teratogenic effects and cannot be used in the pregnant women.[6,7] The search for new drugs continues, with bisphosphonates, for example, residronate and pamidronate. It is also known that these drugs also contribute to increased co-infections leishmaniasis-AIDS. No treatment has proven effective in achieving radical cure of visceral leishmaniasis when it is associated with HIV infection. Therefore, development of more effective and safer chemotherapeutic agents for treating Leishmanias remains desirable.[8]



15-27 34-47

Compounds of both synthetic and natural origin comprising a diverse group of chemical structures have been reported as antileishmanial agents. These include mostly

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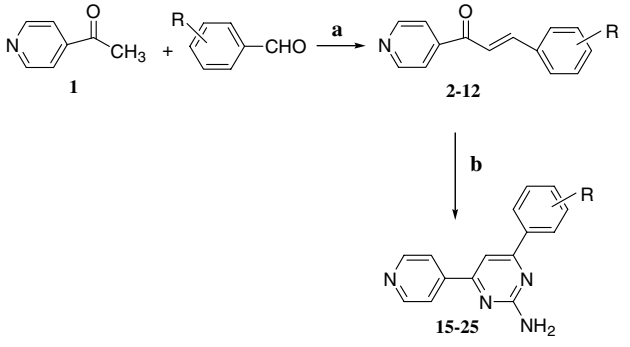
the nitrogen heterocycles as quinolines,[9] acridines,[10] phenothiazines,[11] pyrimidines,[12] purines,[13] bis-benzamidines,[14] pyrazolo[3,4-*b*]pyridine,[15] benzothiazoles,[16] triazines,[17] and imidazolidine.[18] Other classes of compounds include buparvaquone-oxime,[19] chalcones,[20] quinines,[21] amino acid esters and amides,[22] amino alcohols,[23] alkyl phospholipids,[24] ether phospholipids,[25] sulfanilamides,[26] artemisinin,[27] and certain Platinum complexes.[28]

Dihydrofolate reductase (DHFR) is an important target site in most of the parasitic diseases. Most of the clinically used DHFR inhibitors show less selectivity for leishmanial enzymes.[29] This is due to the fact that the gene for pteridine reductase (PTR1) is amplified in some leishmanial mutants. PTR1 can reduce pterins and folates and therefore act as a bypass for DHFR inhibition. This implies that antifolate drugs must simultaneously target both DHFR and PTR1 to be successful antileishmanials.[30] A number of compounds having pyrimidine and triazine moiety are reported to be potent inhibitors of PTR1 in Leishmania.[17,31] Pyridine, pyrimidine, and triazine class of compounds are previously reported to be potential antileishmanial agents. Based on these observations we hypothesized and synthesized hybrid derivatives having both pyridine with pyrimidine moiety and pyrazole with triazine moiety. The synthesized compounds can act as an inhibitor of PTR1 as well as an inhibitor of DHFR and thus can act as potential antileishmanial agents.

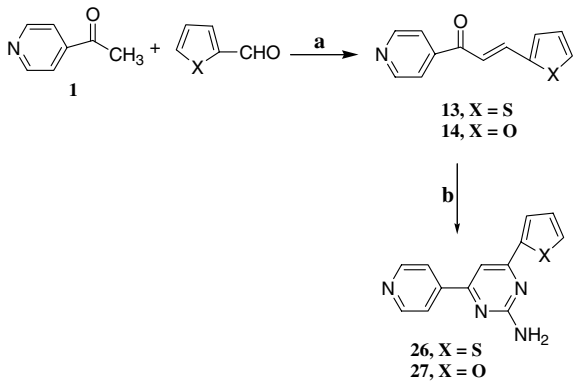
As part of our ongoing program devoted to the synthesis of diverse heterocycles as anti-infective agents,[32] we had previously reported antiparasitic activity in substituted pyrimidines, pyridines, triazines, and quinolines.[33] This communication describes the synthesis of 2,4,6-substituted pyrimidines and triazines as antileishmanial agents.

2. Chemistry

To synthesize the 2,4,6-trisubstituted pyrimidine compounds (**15**–**27**), 4-acetylpyridine was reacted with different aldehydes in 10% aq NaOH and methanol to yield the corresponding chalcones **2**–**14**.[34] The chalcones **2**–**14** were further cyclized with guanidine hydrochloride in the presence of sodium isopropoxide (synthesized in situ by adding sodium metal in isopropanol) to afford the 2,4,6-trisubstituted pyrimidines **15**–**25** (Scheme 1) and **26**, **27** (Scheme 2).



Scheme 1. Reagents and conditions: (a) 10% aq NaOH, methanol, 0 °C rt, 30 min; (b) Guanidine·HCl, sodium isopropoxide, isopropanol, reflux, 8 h.



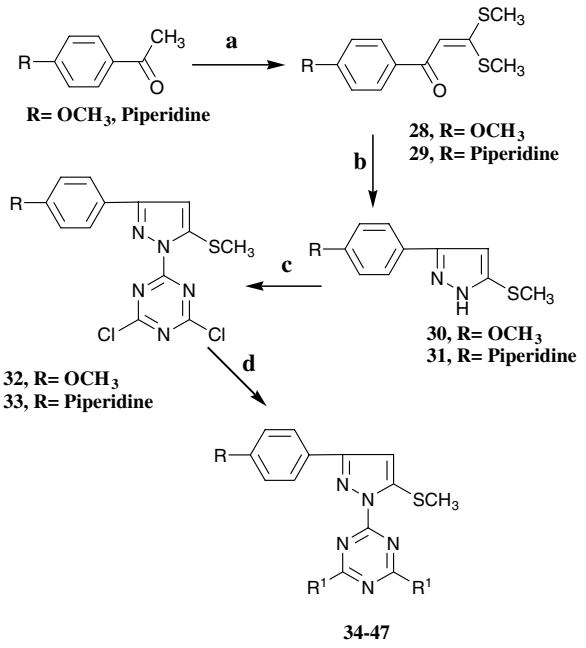
Scheme 2. Reagents and conditions: (a) 10% aq NaOH, methanol, 0 °C rt, 30 min; (b) Guanidine·HCl, sodium isopropoxide, isopropanol, reflux, 8 h.

To synthesize the 2,4,6-trisubstituted triazine compounds (**34**–**47**), substituted acetophenone was reacted with CS_2 in presence of NaH followed by methylation with methyl iodide[35,36] to yield corresponding 3,3-bismethylsulfanyl-1-(substituted-phenyl)-propenone (**28**, **29**). The compounds **28**, **29** were cyclized with hydrazine hydrate[37,38] in methanol to obtain corresponding 5-methylsulfanyl-3-(substituted-phenyl)-1H-pyrazole (**30**, **31**). The compounds **30**, **31** were further reacted with cyanuric chloride (2,4,6-trichloro-1,3,5-triazine) in presence of K_2CO_3 in dry THF to yield corresponding 2,4-dichloro-6-[5-methylsulfanyl-3-(substituted-phenyl)-pyrazol-1-yl]-[1, 3,5]-triazine (**32**, **33**), which were subjected to nucleophilic substitution with different amines to afford the final targeted compounds **34**–**47** (Scheme 3).

3. Antileishmanial activity

The *L. donovani* promastigotes (MHOM/IN/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% fetal calf serum (GIBCO) and 1% penicillin (50 U/ml), streptomycin (50 μg/ml) solution (Sigma) under pressure of G418 (Sigma).[39]

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 at 5×10^5/100 μl medium 199 well 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.[40] Parallel dilutions of DMSO were used as controls. After incubation, an aliquot (50 μl) of promastigote suspension was aspirated



Scheme 3. Reagents and conditions: (a) CS_2, NaH, MeI, THF, 0 °C reflux; (b) $NH_2NH_2{\cdot}H_2O$, MeOH, reflux; (c) cyanuric chloride, K_2CO_3, THF, reflux; (d) Various amines, K_2CO_3, THF, reflux.

from each well of a 96-well plate and mixed with an equal volume of stready Glo$^{(R)}$ reagent (Promega) and luminescence was measured by a luminometer. The values were expressed as relative luminescence unit (RLU).

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

Where N is average relative luminescence unit (RLU) of control wells; n is average RLU of treated wells.

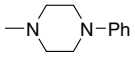
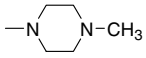
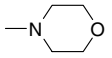
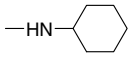
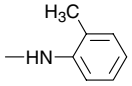
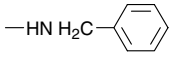
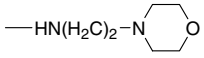
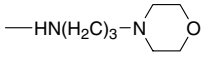
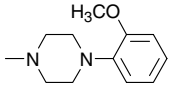
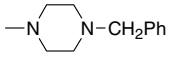
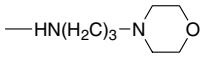
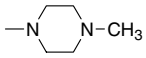
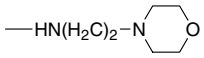
4. Results and discussion

The in vitro biological activities of trisubstituted pyrimidines and triazines have shown encouraging results (Tables 2 and 3) against promastigotes of *L donovani*.

The compound **15** having R as phenyl group exhibited ~80% inhibition at a concentration of 10μg/mL. Substitution of methoxy group at para position on the phenyl ring (**16**) slightly increased the activity having an inhibition of ~85%.

Disubstitution of the phenyl ring with methoxy group (**17**, **18**, **19**) further increased the activity and compound **19** has shown 98% and 89% inhibition at a concentration of 10 and 5 μg/mL, respectively. Trisubstitution of the methoxy group on the phenyl ring (**20**, **21**) completely diminished the activity. Substitution of methyl group on phenyl ring (**22**) increased the activity, whereas substitution of thiomethyl group (**23**) and chloro group (**25**) completely diminished the activity. Disubstitution of methyl group (**24**) further increased the activity and the compound **24** has shown 98% and 94% inhibition at a concentration of 10 and 5 μg/mL, respectively.

Table 1.

Compound	R	R_1
34	OCH_3	
35	OCH_3	
36	OCH_3	
37	OCH_3	
38	OCH_3	
39	OCH_3	
40	OCH_3	
41	OCH_3	
42	OCH_3	
43	OCH_3	
44	OCH_3	
45		
46		
47		

Compounds **26** and **27** having heterocyclic groups as furan and thiophene exhibited a sharp reduction in activity.

The compound **34** having methoxy group as R and phenylpiperazine as R_1 has shown no inhibition, while by substituting R_1 with methylpiperazine (**35**) has shown increase in inhibition noticeably by 96%, 85%, and 69% at 10, 5, and 2 μg/mL, respectively. Substitution of R_1 with morpholine(**36**) further increased the inhibition by 98%, 97%, and 72% at 10, 5, and 2 μg/mL, respectively, and with piperidine(**37**) the inhibition increased further at lower concentrations by 98%, 94%, 78%, and 73% at 10, 5, 2, and 1 μg/mL, respectively. While by substituting R_1 with cyclohexylamine(**38**) decreased the inhibition by 88% and 87% at 10 and 5 μg/mL, respectively, and with *o*-toulidine (**39**) and

Table 2.

Compound	R	% inhibition	
		10 μg/mL	5 μg/mL
15	H	80.5	NI
16	4-OMe	85.2	NI
17	2,5-DiOMe	94.0	62.7
18	2,3-DiOMe	88.2	NI
19	3,5-DiOMe	98.3	89.4
20	2,4,5-TriOMe	NI	—
21	3,4,5-TriOMe	NI	—
22	4-Me	95.8	68.4
23	4-SMe	NI	—
24	3,4-DiMe	98.2	94.0
25	4-Cl	NI	—
26	—	19.7	NI
27	—	69.6	NI

NI, no inhibition.

Table 3.

Compound	% inhibition[a]			
	10 μg/mL	5 μg/mL	2 μg/mL	1 μg/mL
34	NI	—	—	—
35	96.2	85.1	69.4	18.6
36	98.4	97.3	72.4	36.4
37	98.9	94.4	78.1	73.2
38	88.1	87.4	NI	NI
39	21.5	24.5	NI	NI
40	66.3	59.0	NI	NI
41	94.4	93.0	NI	NI
42	100	88.8	71.2	24.5
43	NI	—	—	—
44	16.5	16.26	NI	NI
45	NI	—	—	—
46	NI	—	—	—
47	NI	—	—	—

NI, no inhibition.

[a] Pentamidine shows 100% inhibition at dose 10, 5, 2 μg/mL and 95% inhibition at 1 μg/mL.[39,40]

benzylamine (**40**) the inhibition decreased drastically. The compound with same R and with *N*-ethylaminomorpholine as R_1 (**41**) has shown a little increase in inhibition by 94% and 93% at 10 and 5 μg/mL, respectively, and with *N*-propylaminomorpholine as R_1 (**42**) has shown remarkable increase by 100% inhibition at 10 μg/mL and 88%, 71% at 5 and 2 μg/mL, respectively. Substitution of R1 with *o*-methoxyphenylpiperazine (**43**) and benzylpiperazine (**44**) decreased the inhibition drastically. The compounds (**45**, **46**, and **47**) also have shown the decrease in inhibition by substituting R with piperidine in compounds **35**, **41**, and **42**, respectively.

5. Conclusion

Leishmaniasis is a disease of developing countries. The majority of antileishmanial chemotherapy relies on antimonials and benzamidines, which are highly toxic. Therefore, development of more effective and safer chemotherapeutic agents for treating Leishmaniasis remains desirable. There is also lack of interest among Pharmaceutical industry in the discovery of new antileishmanial agent due to a lack of financial incentive. The synthesized trisubstituted pyrimidines and triazines have shown good in vitro activity. These compounds are new lead in antileishmanial chemotherapy. These compounds can be very useful for further optimization work in antileishmanial chemotherapy.

6. Experimental

IR spectra were recorded on Beckman Aculab-10, Perkin Elmer 881 and FTIR 8210 PC, Schimadzu spectrophotometers either on KBr discs or in neat. Nuclear magnetic resonance (NMR) spectra were recorded on either Bruker Avance DRX-300 MHz or Bruker DPX 200 FT spectrometers 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.

6.1. General procedure for the synthesis of compounds 2–14

Method A: 1 equiv of 4-acetyl pyridine was added dropwise to a cooled solution of 10% NaOH, 1.0 equiv of liquid aldehydes over a period of 30 min. The solution was maintained at 0 °C for an hour and then was allowed to stir at room temperature. After some time, a solid started separating out. The solution was further stirred for about 1 h. The solid was filtered out and recrystallized from methanol or ethanol to afford crystals of the chalcone having yield in the range 60–75%.

Method B: In case of solid aldehydes, the aldehydes (1 equiv) were first dissolved in a minimum quantity of ethanol or methanol (approx 25 ml) and then 10% NaOH solution (approx 100 ml) was added to it to give a clear solution. The solution was cooled up to 0 °C and 1 equiv of 4-acetyl pyridine was added dropwise to it, in around 30 min. The solution was maintained at 0 °C for 1 h and then was allowed to stir at room temperature. After some time, a solid started separating out. This was stirred for about an hour. The solid was filtered out and recrystallized from methanol or ethanol to give crystals of the chalcone having yield in the range 50–60%.

6.1.1. 3-Phenyl-1-pyridin-4-yl-propenone (2). The compound was synthesized using the method A. Yield: 75%; mp 172–174 °C; MS: 210 (M+1); IR (KBr) 3521, 1956, 1673, 1595, 1411, 1225 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 8.84 (d, 2H, $J = 6.0$ Hz), 8.01 (d, 2H, $J = 7.8$ Hz), 7.86 (d, 1H, $J = 15.1$ Hz), 7.76 (d, 2H, $J = 6.0$ Hz), 7.44–7.40 (m, 3H), 7.36 (d, 1H, $J = 15.1$ Hz). Anal. Calcd for $C_{14}H_{11}NO$: C, 80.36; H, 5.30; N, 6.69. Found: C, 80.56; H, 5.53; N, 6.78.

6.1.2. 3-(4-Methoxy-phenyl)-1-pyridin-4-yl-propenone (3). The compound was synthesized using the method A. Yield: 67%; mp 104–106 °C; MS: 240 (M+1); IR

(KBr) 3420, 1946, 1683, 1598, 1489, 1411, 1257 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 8.83 (d, 2H, $J = 6.1$ Hz), 7.89 (d, 2H, $J = 8.6$ Hz), 7.82 (d, 1H, $J = 15.4$ Hz), 7.75 (d, 2H, $J = 6.1$ Hz), 7.37 (d, 1H, $J = 15.4$ Hz), 6.92 (d, 2H, $J = 8.6$ Hz), 3.88 (s, 3H, OMe). Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.54; H, 5.59; N, 5.71.

6.1.3. 3-(2,5-Dimethoxy-phenyl)-1-pyridin-4-yl-propenone (4). The compound was synthesized using the method B. Yield: 67%; mp 128–130 °C; MS: 270 (M+1); IR (KBr) 3299, 1956, 1685, 1597, 1456, 1411, 1259 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 8.85 (d, 2H, $J = 6.0$ Hz), 7.82 (d, 1H, $J = 15.4$ Hz), 7.77 (d, 2H, $J = 6.0$ Hz), 7.39 (d, 1H, $J = 15.4$ Hz), 7.36 (s, 1H), 7.24 (d, 1H, $J = 7.2$ Hz), 6.76 (d, 1H, $J = 7.2$ Hz), 3.88 (s, 3H, OMe), 3.85 (s, 3H, OMe). Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.58; H, 5.86; N, 4.97.

6.1.4. 3-(2,3-Dimethoxy-phenyl)-1-pyridin-4-yl-propenone (5). The compound was synthesized using the method B. Mp 134–136 °C; MS: 270 (M+1); IR (KBr) 3291, 1934, 1686, 1588, 1454, 1418, 1255 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 8.85 (d, 2H, $J = 6.1$ Hz), 7.50 (d, 1H, $J = 7.2$ Hz), 7.82 (d, 1H, $J = 15.1$ Hz), 7.81 (d, 2H, $J = 6.1$ Hz), 7.03 (d, 1H, $J = 7.3$ Hz), 7.38 (d, 1H, $J = 15.1$ Hz), 7.12 (t, 1H, $J = 5.2$ Hz), 3.93 (s, 3H, OMe), 3.79 (s, 3H, OMe). Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.59; H, 5.36; N, 5.45.

6.1.5. 3-(3,5-Dimethoxy-phenyl)-1-pyridin-4-yl-propenone (6). The compound was synthesized using the method B. Mp 116–118 °C; MS: 270 (M+1); IR (KBr) 3286, 1952, 1678, 1596, 1445, 1411, 1250 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 8.88 (d, 2H, $J = 6.0$ Hz), 7.84 (d, 1H, $J = 14.8$ Hz), 7.76 (d, 2H, $J = 6.0$ Hz), 7.56 (s, 1H), 7.40 (d, 1H, $J = 14.8$ Hz), 6.97 (s, 2H), 3.90 (s, 6H, OMe). Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.59; H, 5.36; N, 5.45.

6.1.6. 1-Pyridin-4-yl-3-(2,4,5-trimethoxy-phenyl)-propenone (7). The compound was synthesized using the method B. Yield: 67%; mp 160–162 °C; MS: 300 (M+1); IR (KBr) 3282, 1939, 1689, 1598, 1468, 1420, 1232 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 8.82 (d, 2H, $J = 5.9$ Hz), 7.84 (d, 1H, $J = 15.6$ Hz), 7.72 (d, 2H, $J = 5.9$ Hz), 7.64 (s, 1H), 7.37 (d, 1H, $J = 15.6$ Hz), 6.72 (s, 1H), 3.96 (s, 3H, OMe), 3.92 (s, 3H, 2OMe). Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.72; N, 4.68. Found: C, 67.98; H, 5.94; N, 4.91.

6.1.7. 1-Pyridin-4-yl-3-(3,4,5-trimethoxy-phenyl)-propenone (8). The compound was synthesized using the method B. Yield: 67%; mp 194–196 °C; MS: 300 (M+1); IR (KBr) 3278, 1943, 1687, 1596, 1457, 1445, 1245 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 8.79 (d, 2H, $J = 6.0$ Hz), 7.82 (d, 1H, $J = 15.2$ Hz), 7.70 (d, 2H, $J = 6.0$ Hz), 7.37 (d, 1H, $J = 15.2$ Hz), 7.30 (s, 2H), 3.98 (s, 3H, 2OMe), 3.95 (s, 3H, OMe). Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.72; N, 4.68. Found: C, 68.47; H, 5.98; N, 4.31.

6.1.8. 1-Pyridin-4-yl-3-*p*-tolyl-propenone (9). The compound was synthesized using the method A. Yield: 76%; mp 138–140 °C; MS: 224 (M+1); IR (KBr) 3290, 1967, 1689, 1598, 1492, 1412, 1238 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 8.84 (d, 2H, $J = 6.0$ Hz), 7.84 (d, 1H, $J = 15.6$ Hz), 7.74 (d, 2H, $J = 6.0$ Hz), 7.54 (d, 2H, $J = 8.2$ Hz), 7.37 (d, 1H, $J = 15.6$ Hz), 7.24 (d, 2H, $J = 8.2$ Hz), 2.39 (s, 3H); Anal. Calcd for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.82; H, 5.62; N, 6.42.

6.1.9. 3-(4-Methylsulfanyl-phenyl)-1-pyridin-4-yl-propenone (10). The compound was synthesized using the method A. Yield: 70%; mp 94–96 °C; MS: 256 (M+1); IR (KBr) 3412, 1956, 1682, 1595, 1415, 1225 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 8.83 (d, 2H, $J = 6.1$ Hz), 7.82 (d, 1H, $J = 14.9$ Hz), 7.76 (d, 2H, $J = 6.1$ Hz), 7.55 (d, 2H, $J = 8.6$ Hz), 7.38 (d, 1H, $J = 14.9$ Hz), 7.26 (d, 2H, $J = 8.6$ Hz), 2.52 (s, 3H); Anal. Calcd for $C_{15}H_{13}NOS$: C, 70.56; H, 5.13; N, 5.49. Found: C, 70.74; H, 5.34; N, 5.34.

6.1.10. 3-(3,4-Dimethyl-phenyl)-1-pyridin-4-yl-propenone (11). The compound was synthesized using the method A. Yield: 67%; mp 168–170 °C; MS: 238 (M+1); IR (KBr) 3392, 1952, 1687, 1597, 1424, 1249 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 8.84 (d, 2H, $J = 6.0$ Hz), 7.89 (d, 2H, $J = 7.8$ Hz), 7.83 (d, 1H, $J = 15.2$ Hz), 7.74 (d, 2H, $J = 6.0$ Hz), 7.51 (s, 1H), 7.40 (d, 1H, $J = 15.2$ Hz), 7.29 (d, 2H, $J = 7.8$ Hz), 2.37 (s, 3H), 2.34 (s, 3H). Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 81.24; H, 6.09; N, 5.68.

6.1.11. 3-(4-Chloro-phenyl)-1-pyridin-4-yl-propenone (12). The compound was synthesized using the method B. Yield: 68%; mp 205–207 °C; MS: 244 (M+1); IR (KBr) 3297, 1948, 1684, 1598, 1489, 1257 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 8.85 (d, 2H, $J = 6.1$ Hz), 7.86 (d, 1H, $J = 15.6$ Hz), 7.75 (d, 2H, $J = 6.1$ Hz), 8.09 (d, 2H, $J = 8.6$ Hz), 7.38 (d, 1H, $J = 15.6$ Hz), 7.52 (d, 2H, $J = 8.6$ Hz). Anal. Calcd for $C_{14}H_{10}ClNO$: C, 69.00; H, 4.14; N, 5.75. Found: C, 68.74; H, 4.32; N, 5.44.

6.1.12. 1-Pyridin-4-yl-3-thiophen-2-yl-propenone (13). The compound was synthesized using the method A. Yield: 60%; mp 98–100 °C; MS: 216 (M+1); IR (KBr) 3292, 2932, 1948, 1682, 1445, 1250 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 8.84 (d, 2H, $J = 6.1$ Hz), 7.86 (d, 1H, $J = 14.9$ Hz), 7.80 (d, 1H, $J = 3.8$ Hz), 7.74 (d, 2H, $J = 6.1$ Hz), 7.48 (d, 1H, $J = 4.6$ Hz), 7.40 (d, 1H, $J = 14.8$ Hz), 7.14 (t, 1H, $J = 4.5$ Hz). Anal. Calcd for $C_{12}H_9NOS$: C, 66.95; H, 4.21; N, 6.51. Found: C, 66.68; H, 4.369; N, 6.27.

6.1.13. 3-Furan-2-yl-1-pyridin-4-yl-propenone (14). The compound was synthesized using the method A. Yield: 65%; mp 125–127 °C; MS: 200 (M+1); IR (KBr) 3286, 1952, 1678, 1596, 1445, 1411, 1250 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 8.86 (d, 2H, $J = 6.0$ Hz), 7.88 (d, 1H, $J = 15.2$ Hz), 7.74 (d, 2H, $J = 6.0$ Hz), 7.58 (d, 1H, $J = 3.9$ Hz), 7.40 (d, 1H, $J = 15.2$ Hz),

6.88 (d, 1H, J = 4.4 Hz), 6.65 (t, 1H, J = 4.4 Hz). Anal. Calcd for $C_{12}H_9NO_2$: C, 72.35; H, 4.55; N, 7.03. Found: C, 72.57; H, 4.37; N, 7.36.

6.2. General procedure for the synthesis of compounds 15–27

To a solution of 1.1 equiv of guanidine hydrochloride in 50 mL isopropanol, 1.1 equiv of sodium metal was added. The reaction mixture was refluxed for 2 h and then different chalcones (2–14, 1.0 equiv) were added to it and refluxed for 8 h. The solvent was removed from the reaction mixture under reduced pressure. Water was added and the aqueous phase was extracted with chloroform. The organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by crystallization from methanol or ethanol or sometimes by column chromatography on silica gel (2% Methanol in chloroform) to afford the pure compounds.

6.2.1. 4-Phenyl-6-pyridin-4-yl-pyrimidin-2-ylamine (15). Yield: 70%; mp 176–178 °C; MS: 249 (M+1), IR (KBr) 3387, 2993, 1668, 1511, 1451, 1257 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 8.75 (d, 2H, J = 5.9 Hz), 8.09 (d, 2H, J = 7.8 Hz), 7.90 (d, 2H, J = 5.9 Hz), 7.520-7.49 (m, 3H), 7.45 (s, 1H), 5.28 (s, 2H, NH_2). ^{13}C ($CDCl_3$, 50 MHz): 167.4, 164.2, 164.0, 150.9, 145.4, 137.6, 131.2, 129.3, 127.6, 121.5, 104.7. Anal. Calcd for $C_{15}H_{12}N_4$: C, 72.56; H, 4.87; N, 22.57. Found: C, 72.38; H, 4.56; N, 22.74.

6.2.2. 4-(4-Methoxy-phenyl)-6-pyridin-4-yl-pyrimidin-2-ylamine (16). Yield: 68%; mp 128–130 °C; MS: 279 (M+1), IR (KBr) 3410, 2986, 1664, 1524, 1442, 1262 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 8.77 (d, 2H, J = 6.0 Hz), 8.04 (d, 2H, J = 8.8 Hz), 7.89 (d, 2H, J = 6.0 Hz), 7.45 (s, 1H), 7.03 (d, 2H, J = 8.8 Hz), 5.21 (s, 2H, NH_2), 3.88 (s, 3H, OMe). ^{13}C ($CDCl_3$, 50 MHz): 167.4, 164.4, 163.9, 162.9, 150.4, 145.5, 129.9, 128.6, 121.0, 114.0, 104.2, 55.4. Anal. Calcd for $C_{16}H_{14}N_4O$: C, 69.05; H, 5.07; N, 20.13. Found: C, 69.28; H, 5.23; N, 20.32.

6.2.3. 4-(2,5-Dimethoxy-phenyl)-6-pyridin-4-yl-pyrimidin-2-ylamine (17). Yield: 67%; mp 194–196 °C; MS: 309 (M+1), IR (KBr) 3415, 2998, 1648, 1520, 1451, 1248 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 8.78 (d, 2H, J = 5.9 Hz), 7.89 (d, 2H, J = 5.9 Hz), 7.52 (s, 1H), 7.44 (s, 1H), 7.22 (d, 1H, J = 6.8 Hz), 6.71 (d, 1H, J = 6.8 Hz), 5.17 (s, 2H, NH_2), 3.84 (s, 3H, OMe), 3.82 (s, 3H, OMe). ^{13}C ($CDCl_3$, 50 MHz): 167.4, 164.6, 163.9, 162.2, 161.9, 152.9, 146.1, 128.3, 121.6, 116.9, 116.3, 113.7, 107.9, 56.9, 56.3. Anal. Calcd for $C_{17}H_{16}N_4O_2$: C, 66.22; H, 5.23; N, 18.17. Found: C, 66.44; H, 5.42; N, 18.45.

6.2.4. 4-(2,3-Dimethoxy-phenyl)-6-pyridin-4-yl-pyrimidin-2-ylamine (18). Yield: 65%; mp 162–164 °C; MS: 309 (M+1); IR (KBr) 3399, 2993, 1662, 1518, 1455, 1257 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 8.76 (d, 2H, J = 6.1 Hz), 7.90 (d, 2H, J = 6.1 Hz), 7.72 (s, 1H), 7.42 (d, 1H, J = 8.2 Hz), 7.18 (t, 1H, J = 6.8 Hz), 7.02 (d, 1H, J = 8.4 Hz), 5.26 (s, 2H, NH_2), 3.93 (s, 3H, OMe), 3.77 (s, 3H, OMe). ^{13}C ($CDCl_3$, 50 MHz): 167.4, 164.2, 163.9, 162.3, 161.9, 150.5, 146.3, 145.7, 122.8, 122.4, 121.4, 120.6, 116.4, 106.7, 57.2, 56.7. Anal. Calcd for $C_{17}H_{16}N_4O_2$: C, 66.22; H, 5.23; N, 18.17. Found: C, 66.38; H, 5.38; N, 18.35.

6.2.5. 4-(3,5-Dimethoxy-phenyl)-6-pyridin-4-yl-pyrimidin-2-ylamine (19). Yield: 70%; mp 130–132 °C; MS: 309 (M+1); IR (KBr) 3387, 2993, 1668, 1511, 1451, 1257 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 8.77 (d, 2H, J = 5.9 Hz), 7.89 (d, 2H, J = 5.9 Hz), 7.67 (s, 1H), 7.54 (s, 1H), 6.95 (s, 2H), 5.28 (s, 2H, NH_2), 3.87 (s, 6H, OMe). ^{13}C ($CDCl_3$, 50 MHz): 167.2, 164.7, 164.2, 161.8, 161.2, 150.4, 145.4, 139.3, 121.2, 107.9, 105.2, 57.3. Anal. Calcd for $C_{17}H_{16}N_4O_2$: C, 66.22; H, 5.23; N, 18.17. Found: C, 66.38; H, 5.44; N, 18.38.

6.2.6. 4-Pyridin-4-yl-6-(2,4,5-trimethoxy-phenyl)-pyrimidin-2-ylamine (20). Yield: 72%; mp 176–178 °C; MS: 339 (M+1); IR (KBr) 3428, 2981, 1654, 1509, 1458, 1254 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 8.75 (d, 2H, J = 6.1 Hz), 7.90 (d, 2H, J = 6.1 Hz), 7.83 (s, 1H), 7.65 (s, 1H), 6.61 (s, 1H), 5.24 (s, 2H, NH_2), 3.97 (s, 3H, OMe), 3.93 (s, 6H, 2OMe). ^{13}C ($CDCl_3$, 50 MHz): 167.2, 164.6, 163.9, 157.1, 155.8, 154.6, 147.3, 144.3, 121.6, 118.9, 114.2, 107.6, 98.3, 57.2, 57.0, 56.6. Anal. Calcd for $C_{18}H_{18}N_4O_3$: C, 63.89; H, 5.36; N, 16.56. Found: C, 63.74; H, 5.49; N, 16.68.

6.2.7. 4-Pyridin-4-yl-6-(3,4,5-trimethoxy-phenyl)-pyrimidin-2-ylamine (21). Yield: 74%; mp 206–208 °C; MS: 339 (M+1); IR (KBr) 3396, 2990, 1666, 1515, 1452, 1256 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 8.77 (d, 2H, J = 6.2 Hz), 7.91 (d, 2H, J = 6.2 Hz), 7.41 (s, 1H), 7.31 (s, 2H), 5.28 (s, 2H, NH_2), 3.98 (s, 6H, OMe), 3.92 (s, 3H, OMe). ^{13}C ($CDCl_3$, 50 MHz): 167.1, 164.8, 163.9, 157.2, 155.6, 154.4, 140.8, 134.6, 121.6, 105.1, 104.7, 61.4, 56.8. Anal. Calcd for $C_{18}H_{18}N_4O_3$: C, 63.89; H, 5.36; N, 16.56. Found: C, 63.68; H, 5.14; N, 16.34.

6.2.8. 4-Pyridin-4-yl-6-*p*-tolyl-pyrimidin-2-ylamine (22). Yield: 75%; mp 182–184 °C; MS: 263 (M+1); IR (KBr) 3387, 2993, 1668, 1511, 1451, 1257 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 8.75 (d, 2H, J = 6.1 Hz), 7.98 (d, 2H, J = 7.9 Hz), 7.88 (d, 2H, J = 6.1 Hz), 7.45 (s, 1H), 7.31 (d, 2 H, J = 7.9 Hz), 5.39 (s, 2H, NH_2), 2.42 (s, 3H, Me). ^{13}C ($CDCl_3$, 50 MHz): 167.3, 164.2, 163.8, 150.9, 145.5, 141.7, 134.8, 129.9, 127.5, 121.5, 104.4, 21.9. Anal. Calcd for $C_{16}H_{14}N_4$: C, 73.26; H, 5.38; N, 21.36. Found: C, 73.32; H, 5.61; N, 21.59.

6.2.9. 4-(4-Methylsulfanyl-phenyl)-6-pyridin-4-yl-pyrimidin-2-ylamine (23). Yield: 72%; mp 184–186 °C; MS: 295 (M+1), IR (KBr) 3407, 2987, 1672, 1532, 1462, 1262 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 8.77 (d, 2H, J = 6.1 Hz), 8.02 (d, 2H, J = 8.6 Hz), 7.88 (d, 2H, J = 6.1 Hz), 7.46 (s, 1H), 7.35 (d, 2H, J = 8.6 Hz), 5.28 (s, 2H, NH_2), 2.54 (s, 3H, SMe). ^{13}C ($CDCl_3$, 50 MHz): 167.3, 164.3, 163.9, 151.2, 145.8, 142.8, 134.4, 127.8, 126.4, 121.4, 104.2, 18.7. Anal. Calcd for $C_{16}H_{14}N_4S$: C, 65.28; H, 4.79; N, 19.03. Found: C, 65.44; H, 4.59; N, 19.23.

6.2.10. 4-(3,4-Dimethyl-phenyl)-6-pyridin-4-yl-pyrimidin-2-ylamine (24). Yield: 68%; mp 182–184 °C; MS: 277 (M+1); IR (KBr) 3428, 2968, 1654, 1526, 1458, 1257 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 8.75 (d, 2H, $J = 6.1$ Hz), 7.94 (d, 2H, $J = 6.1$ Hz), 7.80 (d, 1H, $J = 7.9$ Hz), 7.47 (s, 1H), 7.37 (s, 1H), 7.25 (d, 1H, $J = 7.9$ Hz), 5.46 (s, 2H, NH_2), 2.36 (s, 3H), 2.34 (s, 3H). ^{13}C ($CDCl_3$, 50 MHz): 167.2, 164.1, 163.9, 150.8, 145.4, 141.6, 134.7, 129.8, 127.4, 121.4, 104.4, 20.3, 20.1. Anal. Calcd for $C_{17}H_{16}N_4$: C, 73.89; H, 5.84; N, 20.27. Found: C, 73.68; H, 5.61; N, 20.45.

6.2.11. 4-(4-Chloro-phenyl)-6-pyridin-4-yl-pyrimidin-2-ylamine (25). Yield: 72%; mp 242–244 °C; MS: 283 (M+1); IR (KBr) 3426, 2976, 1662, 1518, 1454, 1260 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 8.75 (d, 2H, $J = 6.0$ Hz), 8.02 (d, 2H, $J = 7.9$ Hz), 7.92 (d, 2H, $J = 6.0$ Hz), 7.46 (d, 2H, $J = 7.9$ Hz), 7.41 (s, 1H), 5.26 (s, 2H, NH_2). ^{13}C ($CDCl_3$, 50 MHz): 167.4, 164.6, 163.9, 155.9, 145.6, 135.2, 134.4, 130.2, 128.8, 121.2, 104.4. Anal. Calcd for $C_{15}H_{11}ClN_4$: C, 63.72; H, 3.92; N, 19.82. Found: C, 63.98; H, 3.67; N, 19.65.

6.2.12. 4-Pyridin-4-yl-6-thiophen-2-yl-pyrimidin-2-yl-amine (26). Yield: 65%; mp Decomposes at 210 °C; MS: 255 (M+1); IR (KBr) 3412, 2989, 1654, 1522, 1456, 1248 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 8.76 (d, 2H, $J = 6.0$ Hz), 7.91 (d, 2H, $J = 6.0$ Hz), 7.76 (d, 1H, $J = 3.8$ Hz), 7.48 (d, 1H, $J = 4.6$ Hz), 7.41 (s, 1H), 7.15 (t, 1H, $J = 4.5$ Hz). ^{13}C ($CDCl_3$, 50 MHz): 167.2, 164.2, 163.8, 151.3, 145.4, 144.2, 128.1, 125.8, 123.2, 121.2, 104.6. Anal. Calcd for $C_{13}H_{10}N_4S$: C, 61.40; H, 3.96; N, 22.03. Found: C, 61.64; H, 4.18; N, 22.41.

6.2.13. 4-Furan-2-yl-6-pyridin-4-yl-pyrimidin-2-yl-amine (27). Yield: 62%; mp Decomposes at 220 °C; MS: 239 (M+1), IR (KBr) 3416, 2979, 1654, 1518, 1456 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 8.75 (d, 2H, $J = 6.0$ Hz), 7.88 (d, 2H, $J = 6.0$ Hz), 7.76 (d, 1H, $J = 3.8$ Hz), 7.41 (s, 1H), 6.98 (d, 1H, $J = 4.6$ Hz), 6.72 (t, 1H, $J = 4.5$ Hz). ^{13}C ($CDCl_3$, 50 MHz): 167.3, 164.2, 163.6, 154.1, 151.3, 145.4, 142.1, 121.2, 110.9, 105.1, 104.6. Anal. Calcd for $C_{13}H_{10}N_4O$: C, 65.54; H, 4.23; N, 23.52. Found: C, 65.68; H, 4.08; N, 23.24.

6.3. General procedure for the synthesis of compounds 28, 29. The mixture, 1 equiv of phenyl-substituted actophenone 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 for 1 h at room temperature and then refluxed for 4 h. The methyl iodide (2.5 equiv) was added in excess by cooling the reaction mixture during 5 min and was allowed to stir for 1 h at room temperature. Further the reaction mixture was refluxed with stirring for 12 more hours. 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 with $CHCl_3$-hexane to afford the respective compounds **28**, **29** yielding in the range of 80–90%.

6.3.1. 1-(4-Methoxy-phenyl)-3,3-bis-methylsulfanyl-propenone (28). Yield: 96%; mp 90 °C; FAB-MS: 255 (M+1); IR(KBr): 3059, 3012, 2918, 2843, 1693, 1610, 1598, 1473, 1344, 831 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (pap) 7.91 (d, 2H, $J = 8.84$ Hz, Are-H), 6.93 (d, 2H, $J = 8.84$ Hz, Are-H), 6.75 (s, 1H, =CH), 3.86 (s, 3H, OCH_3), 2.55 (s, 3H,SCH_3), 2.52 (s, 3H, SCH_3); Anal. Calcd for $C_{12}H_{14}O_2S_2$: C, 56.66; H, 5.55. Found: C, 56.78; H, 5.52.

6.3.2. 3,3-Bis-methylsulfanyl-1-(4-piperidin-1-yl-phenyl)-propenone (29). Yield: 72%; mp 110 °C; FAB-MS: 308 (M+1); IR(KBr): 3011, 2928, 1658, 1596, 1517, 1470, 1355, 833 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.85 (d, 2H, $J = 8.63$ Hz, Ar-H), 6.86 (d, 2H, $J = 8.63$ Hz, Ar-H), 6.76 (s, 1H, =CH), 3.31 (t, 4H, $J = 4.70$ Hz, NCH_2), 2.54 (s, 3H,SCH_3), 2.50 (s, 3H, SCH_3), 1.65-1.56 (m, 6H, CH_2); Anal. Calcd for $C_{16}H_{21}NOS_2$: C, 62.50; H, 6.88; N, 4.56. Found: C, 62.71; H, 6.93; N, 4.59.

6.4. General procedure for the synthesis of compounds 30, 31

The solution of compounds **28**, **29** (1 equiv) and hydrazine hydrate (1.2 equiv) in MeOH was refluxed for 4 h. The solvent was removed under reduced pressure to give solid residue which was dissolved in $CHCl_3$ and washed with water (three times), dried over anhydrous Na_2SO_4, concentrated, and crystallized with $CHCl_3$-hexane to obtain respective compounds **30**, **31** yielding in the range of 65–70%.

6.4.1. 3-(4-Methoxy-phenyl)-5-methylsulfanyl-1H-pyrazole (30). Yield: 68%; mp 113–115 °C; FAB-MS: 221 (M+1); IR(KBr): 3456, 3111, 3022, 2933, 2868, 1611, 1505, 1459, 1328, 831 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.55 (d, 2H, $J = 8.77$ Hz, Ar-H), 6.93 (d, 2H, $J = 8.77$ Hz, Ar-H), 6.46 (s, 1H, pyrazole-H), 3.83 (s, 3H, OCH_3), 2.52 (s, 3H, SCH_3); Anal. Calcd for $C_{11}H_{12}N_2OS$: C, 59.97; H, 5.49; N, 12.72. Found: C, 59.86; H, 5.57; N, 12.75.

6.4.2. 1-[4-(5-Methylsulfanyl-1H-pyrazol-3-yl)-phenyl]-piperidine (31). Yield: 65%; m.p. 134-136 °C; FAB-MS: 274 (M + 1); IR(KBr): 3451, 3031, 2907, 1618, 1580, 1490, 1371, 833 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.47 (d, 2H, $J = 8.78$ Hz, Ar-H), 6.94 (d, 2H, $J = 8.78$ Hz, Ar-H), 6.41 (s, 1H, pyrazole-H), 3.22 (t, 4H, $J = 4.75$ Hz, NCH_2), 2.52 (s, 3H, SCH_3), 1.71–1.62 (m, 6H, CH_2); Anal. Calcd for $C_{15}H_{19}N_3S$: C, 65.90; H, 7.00; N, 15.37. Found: C, 65.95; H, 7.16; N, 15.42.

6.5. General procedure for the synthesis of compounds 32, 33

The solution of compound **30**, **31** (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 dissolved in

$CHCl_3$, washed with water (three times) dried over anhydrous Na_2SO_4, concentrated, and purified with column chromatography to afford respective compounds **32**, **33** yielding in the range of 70–80%.

6.5.1. 2,4-Dichloro-6-[3-(4-methoxy-phenyl)-5-methylsulfanyl-pyrazol-1-yl]-[1,3,5]triazine (32)

Yield: 82%; mp 186 °C; FAB-MS: 368 (M+1); IR(KBr): 3005, 2967, 2934, 2841, 1610, 1519, 1464, 1385, 846 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.55 (d, 2H, J = 8.82 Hz, Ar-H), 6.93 (d, 2H, J = 8.82 Hz, Ar-H), 6.49 (s, 1H, pyrazole-H), 3.86 (s, 3H, OCH_3), 2.58 (s, 3H, SCH_3); Anal. Calcd for $C_{14}H_{11}Cl_2N_5OS$: C, 45.66; H, 3.01; N, 19.02. Found: C, 45.73; H, 3.15; N, 19.13.

6.5.2. 2,4-Dichloro-6-[5-methylsulfanyl-3-(4-piperidin-1-yl-phenyl)-pyrazol-1-yl]-[1,3,5]triazine (33)

Yield: 45%; mp 178 °C; FAB-MS: 421 (M+1); IR(KBr): 3035, 2947, 1623, 1575, 1497, 1365, 835 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.74 (d, 2H, J = 8.71 Hz, Ar-H), 6.91 (d, 2H, J = 8.71 Hz, Ar-H), 6.48 (s, 1H, pyrazole-H), 3.24 (t, 4H, J = 4.74 Hz, NCH_2), 2.54 (s, 3H, SCH_3), 1.69–1.57 (m, 6H, CH_2); Anal. Calcd for $C_{18}H_{18}Cl_2N_6S$: C, 45.66; H, 3.01; N, 19.02. Found: C, 45.73; H, 3.15; N, 19.13.

6.6. General procedure for the synthesis of compounds 34–47

The mixture of compounds **32**, **33** (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 dissolved in $CHCl_3$, washed with water (three times), dried over anhydrous Na_2SO_4. The solution was concentrated and purified with column chromatography using silica-gel as adsorbent to obtain respective compounds **34–47** in good yield.

6.6.1. 2-[3-(4-Methoxy-phenyl)-5-methylsulfanyl-pyrazol-1-yl]-4,6-bis-(4-phenyl-piperazin-1-yl)-[1,3,5]triazine (34). Yield: 98%; mp 198–200 °C; FAB-MS: 620 (M+1); IR(KBr): 3000, 2963, 2898, 2862, 1589, 1496, 1426, 1357, 838 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.88 (d, 2H, J = 8.32 Hz, Ar-H), 7.32 (d, 2H, J = 8.32 Hz, Ar-H), 7.00-6.87 (m, 10H, Ar-H), 6.40 (s, 1H, pyrazole-H), 4.14-4.06 (m, 8H, NCH_2), 3.85 (s, 3H, OCH_3), 3.28–3.21 (m, 8H, NCH_2), 2.55 (s, 3H, SCH_3), ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 165.40, 162.89, 160.54, 154.04, 151.67, 144.96, 129.66, 128.04, 120.77, 117.09, 103.14, 55.71, 49.88, 43.86, 18.30; Anal. Calcd for $C_{34}H_{37}N_9OS$: C, 65.89; H, 6.02; N, 20.34. Found: C, 65.97; H, 6.23; N, 20.51.

6.6.2. 2-[3-(4-Methoxy-phenyl)-5-methylsulfanyl-pyrazol-1-yl]-4,6-bis-(4-methyl-piperazin-1-yl)-[1,3,5]triazine (35). Yield: 65%; mp 168–170 °C; FAB-MS: 496 (M+1); IR(KBr): 3000, 2963, 2898, 2862, 1589, 1496, 1426, 1357, 838 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.88 (d, 2H, J = 8.30 Hz, Ar-H), 6.95 (d, 2H, J = 8.30 Hz, Ar-H), 6.41 (s, 1H, pyrazole-H), 4.10–3.95 (m, 8H, NCH_2), 3.85 (s, 3H, OCH_3), 2.62–2.45 (m, 11H, NCH_2, SCH_3), 2.32 (s, 6H, NCH_3), ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 165.50, 162.84, 160.50, 153.98, 144.95, 128.01, 114.29, 103.10, 55.28, 46.61, 43.87, 18.28; Anal. Calcd for $C_{24}H_{33}N_9OS$: C, 58.16; H, 6.71; N, 25.43. Found: C, 58.24; H, 6.67; N, 25.59.

6.6.3. 2-[3-(4-Methoxy-phenyl)-5-methylsulfanyl-pyrazol-1-yl]-4,6-di-morpholin-4-yl-[1,3,5]triazine (36). Yield: 57%; mp 223–225 °C; FAB-MS: 470 (M+1); IR(KBr): 3045, 2969, 2914, 2857, 1584, 1500, 1425, 1383, 834 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.86 (d, 2H, J = 8.80 Hz, Ar-H), 6.94 (d, 2H, J = 8.80 Hz, Ar-H), 6.40 (s, 1H, pyrazole-H), 3.98–3.87 (m, 8H, OCH_2), 3.84 (s, 3H, OCH_3), 3.82–3.78 (m, 8H, NCH_2), 2.55 (s, 3H, SCH_3), ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 165.47, 162.80, 160.54, 154.04, 144.91, 127.98, 114.29, 103.12, 67.18, 55.67, 44.49, 18.20; Anal. Calcd for $C_{22}H_{27}N_7O_3S$: C, 56.27; H, 5.80; N, 20.88. Found: C, 56.43; H, 5.91; N, 20.79.

6.6.4. 2-[3-(4-Methoxy-phenyl)-5-methylsulfanyl-pyrazol-1-yl]-4,6-di-piperidin-1-yl-[1,3,5]triazine (37). Yield: 81%; mp 170 °C; FAB-MS: 466 (M+1); IR(KBr): 3000, 2929, 2853, 1595, 1498, 1422, 1399, 835 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.87 (d, 2H, J = 8.61 Hz, Ar-H), 6.93 (d, 2H, J = 8.61 Hz, Ar-H), 6.38 (s, 1H, pyrazole-H), 3.90–3.86 (m, 8H, NCH_2), 3.83 (s, 3H, OCH_3), 2.51 (s, 3H, SCH_3), 1.67–1.53 (m, 12H, CH_2), ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 165.15, 162.86, 160.33, 153.58, 144.68, 127.96, 114.19, 102.73, 55.65, 44.97, 26.26, 25.23, 18.28; Anal. Calcd for $C_{24}H_{31}N_7OS$: C, 61.91; H, 6.71; N, 21.06. Found: C, 61.89; H, 6.53; N, 21.27.

6.6.5. *N,N′*-Dicyclohexyl-6-[3-(4-methoxy-phenyl)-5-methylsulfanyl-pyrazol-1-yl]-[1,3,5]triazine-2,4-diamine (38). Yield: 65%; mp 112–114 °C; FAB-MS: 494 (M+1); IR(KBr): 3429, 3007, 2929, 2852, 1592, 1497, 1381, 836 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.86 (d, 2H, J = 8.44 Hz, Ar-H), 6.93 (d, 2H, J = 8.44 MHz, Ar-H), 6.37 (s, 1H, pyrazole-H), 4.12–3.98 (m, 2H, CH), 3.83 (s, 3H, OCH_3), 2.50 (s, 3H, SCH_3), 2.14–1.90 (m, 4H, CH_2), 1.75–1.62 (m, 4H, CH_2), 1.42–1.17 (m, 12H, CH_2), ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 165.66, 162.62, 160.45, 154.06, 145.39, 128.19, 125.30, 114.17, 103.13, 55.64, 33.68, 25.94, 25.15, 18.32; Anal. Calcd for $C_{26}H_{35}N_7OS$: C, 63.26; H, 7.15; N, 19.86. Found: C, 63.41; H, 7.07; N, 19.83.

6.6.6. 6-[3-(4-Methoxy-phenyl)-5-methylsulfanyl-pyrazol-1-yl]-*N,N′*-di-o-tolyl-[1,3,5]triazine-2,4-diamine (39). Yield: 81%; mp 182–184 °C; FAB-MS: 510 (M+1); IR(KBr): 3227, 3011, 2965, 2915, 2835, 1613, 1581, 1498, 1424, 834 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.87 (d, 2H, J = 8.74 Hz, Ar-H), 7.25–7.07 (m, 6H, Ar-H), 6.94 (d, 2H, J = 8.74 Hz, Ar-H), 6.36 (s, 1H, pyrazole-H), 3.84 (s, 3H, OCH_3), 2.52 (s, 3H, SCH_3), 2.32 (s, 6H, Ar-CH_3), ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 165.64, 163.00, 160.66, 154.65, 146.21, 136.27, 130.90, 128.28,

126.79, 114.30, 103.62, 55.71, 18.62, 18.14; Anal. Calcd for $C_{28}H_{27}N_7OS$: C, 65.99; H, 5.34; N, 19.24. Found: C, 66.08; H, 5.29; N, 19.39.

6.6.7. *N,N′*-Dibenzyl-6-[3-(4-methoxy-phenyl)-5-methylsulfanyl- pyrazol-1-yl]-[1,3,5]triazine-2,4-diamine (40). Yield: 65%; mp 168–170 °C; FAB-MS: 510 (M+1); IR(KBr): 3276, 3029, 2922, 2835, 1590, 1496, 1428, 1379, 835 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.86 (d, 2H, $J = 8.35$ Hz, Ar-H), 7.38–7.28 (m, 10H, Ar-H), 6.93 (d, 2H, $J = 8.35$ Hz, Ar-H), 6.38 (s, 1H, pyrazole-H), 4.66–4.58 (m, 4H, NCH_2), 3.83 (s, 3H, OCH_3), 2.48 (s, 3H, SCH_3), ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 165.59, 162.72, 160.53, 154.15, 145.71, 139.12, 128.88, 128.15, 127.98, 127.60, 114.34, 103.25, 55.71, 45.25, 18.26; Anal. Calcd for $C_{28}H_{27}N_7OS$: C, 65.99; H, 5.34; N, 19.24. Found: C, 65.94; H, 5.47; N, 19.21.

6.6.8. 6-[3-(4-Methoxy-phenyl)-5-methylsulfanyl-pyrazol-1-yl]-*N,N′*-bis-(2-morpholin-4-yl-ethyl)-[1,3,5]triazine-2,4-diamine (41). Yield: 40%; mp 78 °C; FAB-MS: 556 (M+1); IR(KBr): 3296, 3012, 2953, 2855, 1591, 1498, 1426, 1380, 839 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.86 (d, 2H, $J = 8.74$ Hz, Ar-H), 6.94 (d, 2H, $J = 8.74$ Hz, Ar-H), 6.39 (s, 1H, pyrazole-H), 3.84 (s, 3H, OCH_3), 3.75–3.69 (m, 8H, OCH_2), 3.52–3.49 (m, 4H, NCH_2), 2.64–2.53 (m, 12H, NCH_2), 2.52 (s, 3H, SCH_3), ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 166.28, 162.68, 160.53, 154.25, 145.38, 128.22, 114.21, 103.34, 67.31, 57.61, 55.68, 53.74, 37.43, 18.25; Anal. Calcd for $C_{26}H_{37}N_9O_3S$: C, 56.20; H, 6.71; N, 22.69. Found: C, 56.37; H, 6.87; N, 22.81.

6.6.9. 6-[3-(4-Methoxy-phenyl)-5-methylsulfanyl-pyrazol-1-yl]-*N,N′*-bis-(3-morpholin-4-yl-propyl)-[1,3,5]triazine-2,4-diamine (42). Yield: 65%; mp 152–154 °C; FAB-MS: 584 (M+1); IR(KBr): 3266, 3015, 2927, 2814, 1588, 1496, 1426, 1378, 835 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.85 (d, 2H, $J = 8.45$ Hz, Ar-H), 6.93 (d, 2H, $J = 8.45$ Hz, Ar-H), 6.38 (s, 1H, pyrazole-H), 3.84 (s, 3H, OCH_3), 3.77–3.66 (m, 8H, OCH_2), 3.55–3.43 (m, 4H, NCH_2), 2.58–2.38 (m, 15H, SCH_3, NCH_2), 1.81–1.79 (m, 4H, CH_2), ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 166.34, 162.53, 160.46, 154.03, 145.32, 128.12, 114.21, 103.14, 67.38, 57.71, 55.66, 54.14, 40.51, 25.85, 18.26; Anal. Calcd for $C_{28}H_{41}N_9O_3S$: C, 57.61; H, 7.08; N, 21.59. Found: C, 57.75; H, 7.13; N, 21.67.

6.6.10. 2-[3-(4-Methoxy-phenyl)-5-methylsulfanyl-pyrazol-1-yl]-4,6-bis-[4-(2-methoxy-phenyl)-piperazin-1-yl]-[1,3,5]triazine (43). Yield: 88%; mp 158–160 °C; FAB-MS: 680 (M+1); IR(KBr): 3001, 2948, 2907, 2828, 1586, 1499, 1425, 1378, 836 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.88 (d, 2H, $J = 8.57$ Hz, Ar-H), 7.04–6.88 (m, 10H, Ar-H), 6.41 (s, 1H, pyrazole-H), 4.20–4.08 (m, 8H, NCH_2), 3.91 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.15–3.04 (m, 8H, NCH_2), 2.54 (s, 3H, SCH_3), ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 165.34, 162.90, 160.46, 153.90, 152.73, 144.88, 141.55, 128.01, 123.74, 121.47, 118.84, 114.26, 103.00, 55.69, 51.26, 44.46, 18.29; Anal. Calcd for $C_{36}H_{41}N_9O_3S$: C, 63.60; H, 6.08; N, 18.54. Found: C, 63.59; H, 6.16; N, 18.66.

6.6.11. 2,4-Bis-(4-benzyl-piperazin-1-yl)-6-[3-(4-methoxy-phenyl)-5-methylsulfanyl-pyrazol-1-yl]-[1,3,5]triazine (44). Yield: 85%; mp 176–178 °C; FAB-MS: 648 (M+1); IR(KBr): 3027, 2934, 2906, 2862, 1588, 1496, 1422, 1399, 845 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.85 (d, 2H, $J = 8.61$ Hz, Ar-H), 7.33–7.29 (m, 10H, Ar-H), 6.92 (d, 2H, $J = 8.61$ Hz, Ar-H) 6.37 (s, 1H, pyrazole-H), 3.90–3.85 (m, 8H, NCH_2), 3.83 (s, 3H, OCH_3), 3.55 (s, 4H, NCH_2), 2.51–2.42 (m, 11H, SCH_3, NCH_2), ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 165.53, 162.78, 160.36, 153.89, 151.76, 144.87, 129.64, 128.72, 127.99, 127.60, 114.26, 102.91, 63.53, 55.68, 53.37, 44.23, 18.24; Anal. Calcd for $C_{36}H_{41}N_9OS$: C, 66.74; H, 6.38; N, 19.46. Found: C, 66.81; H, 6.41; N, 19.37.

6.6.12. 6-[5-Methylsulfanyl-3-(4-piperidin-1-yl-phenyl)-pyrazol-1-yl]-*N,N′*-bis-(3-morpholin-4-yl-propyl)-[1,3,5]-triazine-2,4-diamine (45). Yield: 60%; mp 62 °C; FAB-MS: 638 (M+1); IR(KBr): 3314, 2936, 2853, 2815, 1589, 1500, 1435, 1379, 808 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.77 (d, 2H, $J = 8.06$ Hz, Ar-H), 6.93 (d, 2H, $J = 8.06$ Hz, Ar-H) 6.36 (s, 1H, pyrazole-H), 3.72–3.68 (m, 8H, OCH_2), 3.52–3.45 (m, 4H, NCH_2), 2.77 (t, 4H, $J = 6.67$, NCH_2), 2.50–2.36 (m, 15H, SCH_3, NCH_2), 1.81–1.64 (m, 10H, CH_2), ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 166.21, 162.27, 154.33, 152.62, 145.13, 127.59, 115.95, 103.03, 67.24, 57.19, 54.06, 50.26, 40.66, 29.01, 26.02, 24.65, 18.20; Anal. Calcd for $C_{32}H_{48}N_{10}O_2S$: C, 60.35; H, 7.60; N, 21.99. Found: C, 60.39; H, 7.62; N, 21.91.

6.6.13. 6-[5-Methylsulfanyl-3-(4-piperidin-1-yl-phenyl)-pyrazol-1-yl]-*N,N′*-bis-(2-morpholin-4-yl-ethyl)-[1,3,5]triazine-2,4-diamine (46). Yield: 70%; mp 75–78 °C; FAB-MS: 610 (M+1); IR(KBr): 3300, 2933, 2836, 2814, 1590, 1500, 1456, 1382, 808 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.71 (d, 2H, $J = 8.02$ Hz, Ar-H), 6.87 (d, 2H, $J = 8.02$ Hz, Ar-H) 6.30 (s, 1H, pyrazole-H), 3.75–3.66 (m, 8H, OCH_2), 3.50–3.43 (m, 4H, NCH_2), 3.19–3.15 (m, 4H, NCH_2), 2.57–2.31 (m, 15H, SCH_3, NCH_2), 1.92–1.76 (m, 6H, CH_2), ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 166.24, 162.55, 154.62, 152.73, 143.68, 127.73, 115.93, 103.28, 67.29, 57.61, 53.76, 50.29, 37.54, 26.07, 24.69, 18.23; Anal. Calcd for $C_{30}H_{44}N_{10}O_2S$: C, 59.19; H, 7.28; N, 23.01. Found: C, 59.43; H, 7.35; N, 23.23.

6.6.14. 2,4-Bis-(4-methyl-piperazin-1-yl)-6-[5-methylsulfanyl-3-(4-piperidin-1-yl-phenyl)-pyrazol-1-yl]-[1,3,5]triazine (47). Yield: 50%; mp 68–70 °C; FAB-MS: 550 (M+1); IR(KBr):2936, 2855, 2800, 1659, 1583, 1502, 1426, 1379, 806 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.80 (d, 2H, $J = 8.54$ Hz, Ar-H), 6.95 (d, 2H, $J = 8.54$ Hz, Ar-H) 6.38 (s, 1H, pyrazole-H), 3.57–3.49 (m, 12H, NCH_2), 2.60 (t, 8H, $J = 5.00$, NCH_2), 2.52 (s, 3H, SCH_3), 2.35 (s, 6H, N-CH_3), 1.82–1.67 (m, 6H, CH_2), ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 165.24, 162.75, 154.23, 152.62, 144.60, 127.51, 116.02, 102.93, 55.23, 52.85, 46.52, 43.97, 26.06, 24.68, 18.23; Anal. Calcd for $C_{28}H_{40}N_{10}S$: C, 61.28; H, 7.35; N, 25.52. Found: C, 61.47; H, 7.32; N, 25.57.

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